UNIVERSITÄT BAYREUTH

Totalsynthese natürlicher Lactone und Lactame mit antibiotischer Aktivität

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

im Fach Chemie

an der Fakultät für Biologie, Chemie und Geowissenschaften der

Universität Bayreuth

vorgelegt von

Manuel Georg Schriefer

geboren in Pegnitz

Bayreuth 2023

UNIVERSITÄT
BAYREUTH

Totalsynthese natürlicher Lactone und Lactame mit antibiotischer Aktivität

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

im Fach Chemie

an der Fakultät für Biologie, Chemie und Geowissenschaften der

Universität Bayreuth

vorgelegt von

Manuel Georg Schriefer

geboren in Pegnitz

Bayreuth 2023

Die vorliegende Arbeit wurde in der Zeit von Dezember 2019 bis Januar 2023
am Lehrstuhl für Organische Chemie I der Universität Bayreuth
unter Betreuung von Herrn Prof. Dr. Rainer Schobert angefertigt.

Vollständiger Abdruck der von der Fakultät für Biologie, Chemie, und Geowissenschaften der Universität Bayreuth genehmigten Dissertation zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften (Dr. rer. nat.).

Dissertation eingereicht am:	18.01.2023
Zulassung durch die Promotionskommission:	25.01.2023
Wissenschaftliches Kolloquium:	17.05.2023

Amtierender Dekan: Prof. Dr. B. Westermann

Prüfungsausschuss:

Prof. Dr. Rainer Schobert	(Gutachter)
Prof. Dr. Matthias Breuning	(Gutachter)
Prof. Dr. Rhett Kempe	(Vorsitz)
Prof. Dr. Stephan Schwarzinger	(Prüfer)

NIHIL TAM DIFFICILE EST, QUIN QUAERENDO INVESTIGARI POSSIT.

NICHTS IST SO SCHWIERIG, DASS ES NICHT ERFORSCHT WERDEN KÖNNTE.

TERENZ

Inhaltsverzeichnis

Abkürzungsverzeichnis

In den Formelbildern und im Text werden folgende Abkürzungen verwendet:

Å	Ångstrom (0.1 nm)
Ac	Acetyl
acac	Acetylaceton
AD-Mix	*asymmetric dihydroxylation*-Mix
Ala	Alanin
aq.	wässrig
Äquiv.	Äquivalente
atm	Atmosphäre (Einheit)
ATP	Adenosintriphosphat
Aux*	chirales Auxiliar
BACE-1	Beta-Sekretase
9-BBN	9-Borabicyclo[3.3.1]nonan
BINAP	2,2'–Bis(diphenylphosphino)–1,1'–binaphthyl
BLNAR	β-Lactamase negativer, Ampicillin resistenter Erreger
BLPACR	β-Lactamase-produzierender Amoxicillin-Clavulanat-resistenter Erreger
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOP	Benzotriazolyloxytris(dimethylamino)phosphoniumhexafluorophosphat
CBS	Corey-Bakshi-Shibata(-Reduktion)
CDI	Carbonyldiimidazol
CM	Kreuzmetathese (*cross metathesis*)
Cy	Cyclohexyl
Δ	Erhitzen auf Siedehitze
DA	Diels-Alder
DABCO	1,4-Diazabicyclo[2.2.2]octan
DB	Doppelbindung
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCE	Dichlorethan
DCC	Dicyclohexylcarbodiimid
DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinon
DEAD	Diethylazodicarboxylat
$(DHQD)_2PHAL$	Hydrochinidin-1,4-phthalazindiyl-diether
DIBAL	Di-*iso*-butylaluminiumhydrid
DIPEA	Diisopropylethylamin (Hünig-Base)
DIPT	Diisopropyltartrat
DKR	Dynamisch kinetische Racematspaltung
DMAP	4-(*N*,*N*-Dimethylamino)pyridin
DMF	Dimethylformamid
DMM	Dimethoxymethan

DMSO	Dimethylsulfoxid
DMP	Dess-Martin-Periodinan
DNA	Desoxyribonukleinsäure (*deoxyribonucleic acid*)
d.r.	Diastereomerenverhältnis (*diastereomeric ratio*)
DTBP	Di-*tert*-Butylperoxid
EDA	Ethyldiazoacetat
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid
ee	Enantiomerenüberschuss (*enantiomeric excess*)
ESKAPE	Nosokomiale Infektions-auslösende *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*
FGI	funktionelle Gruppen-Transformation (*functional group interconversion*)
Gen.	Generation
GPCR	G-Protein gekoppelte Rezeptoren
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorphosphat
HIF	Hypoxie-induzierter Faktor
HKR	hydrolytisch kinetische Racematspaltung
HOAt	1-Hydroxy-7-azabenzotriazol
HOBt	1-Hydroxybenzotriazol
HPLC	Hochleistungsflüssigchromatographie (*high performance liquid chromatography)*
HRMS	Hochaufgelöste Massenspektrometrie (*high resoluting mass spectrometry*)
HSP90	*heat shock protein 90*
HTS	Hochdurchsatzscreening (*high-throughput-screening*)
HWE	Horner-Wadsworth-Emmons
i	*iso*
IBX	Iodoxybenzoesäure
IC_{50}	Konzentration, um 50% des *targets* zu inhibieren
Ile	Isoleucin
IMDA	intramolekulare Diels-Alder
IPCF	*iso*-Propylchlorformiat
Kat.	Katalysator
KHMDS	Kaliumhexamethyldisilazid
K_i	Dissoziationskonstante
LDA	Lithiumdiisopropylamid
LiHMDS	Lithiumhexamethyldisilazid
LLS	längste lineare Sequenz
*m*CPBA	*meta*-Chlorperbenzoesäure (*meta-chloroperoxybenzoic acid*)
Me	Methyl
MEM	2-Methoxyethoxymethyl
MIC	Minimale Hemmkonzentration (*minimum inhibitory concentration*)
MOM	Methoxymethyl
MoOPH	*Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*

MRSA	Methicillin-resistente *Staphylococcus aureus*
MS	Molsieb
n	*normal*
NBS	*N*-Bromsuccinimid
NHK	Nozaki-Hiyama-Kishi
NMR	Magnetresonanzspektroskopie (*nuclear magnetic resonance*)
NMO	*N*-Methylmorpholin-*N*-oxid
NOESY	Nuklear-Overhauser-Effekt-Spektroskopie (*nuclear Overhauser effect* spectroscopy)
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PPO	Propylenoxid
PPTS	Pyridinium-*para*-toluolsulfonat
PRSP	Penicillin-resistente *Streptococcus pneumoniae*
PS	Polystyrol
*p*TsOH	*para*-Toluolsulfonsäure
quant.	quantitativ
RCAM	Ringschließende Alkin-Metathese (*ring closing alkyne metathesis*)
RCM	Ringschließende Metathese (*ring closing metathesis*)
RNA	Ribonukleinsäure (*ribonucleic acid*)
RT	Raumtemperatur
S_N	Nucleophile Substitution
Suc	Succinyl
t	*tert*
TASF	*tris(dimethylamino)sulfonium difluorotrimethylsilicate*
TBAF	Tetrabutylammoniumfluorid
TBAI	Tetrabutylammoniumiodid
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxid
TBS	*tert*-Butyldimethylsilyl
TCE	Trichlorethyl
TES	Triethylsilyl
Tf	Trifluormethansulfonyl (*Triflyl*)
TFA	Trifluoressigsäure (*Trifluoroacetic acid*)
TFAA	Trifluoressigsäureanhydrid (*Trifluoroacetic acid anhydride*)
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPST	Triisopropylsilylthiol
TMS	Trimethylsilyl
TMSCN	Trimethylsilylcyanid
TMSE	Trimethylsilylethyl
Trt	Trityl

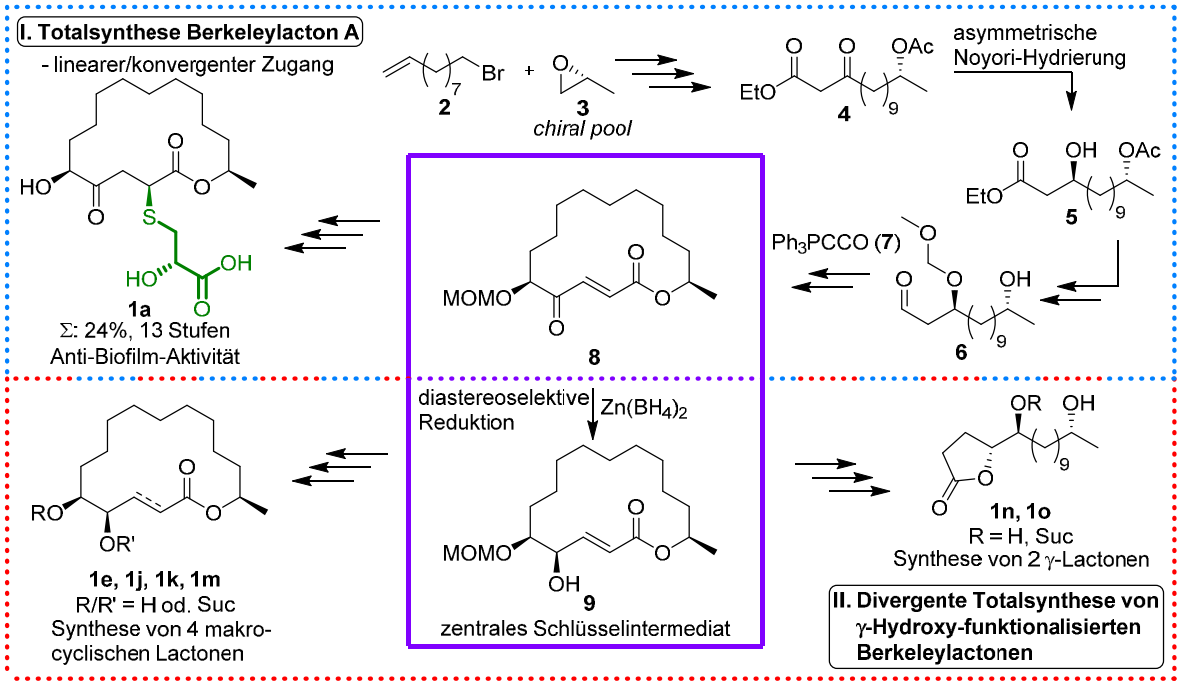
Ts	Tosyl
TsDPEN	*N*-Tosyl-1,2-diphenyl-1,2-ethylendiamin
ü.N.	über Nacht
Val	Valin
VEGFR	vaskulär endothelialer Wachstumsfaktor (*vascular endothelial growth factor*)
VRE	Vacomycin-resistente Enterokokken
XRD	Röntgenbeugung (*X-ray diffraction*)

Zusammenfassung

Im Zuge dieser Dissertation wurden drei Teilbereiche behandelt, welche die Gemeinsamkeit hatten, antibiotisch wirksame Naturstoffe synthetisch zugänglich zu machen. Während der Arbeiten konnten neue Synthesekonzepte bezüglich der divergenten Synthese von Macroliden, der *N*-Glykosylierung von 3-Acyl-Tetramsäuren und der Bildung von 3-(α-Aminoalkyl)-verbrückten Glykosiden erarbeitet werden. Konkret wurden die Berkeleylactone A (**1a**), E (**1e**), J (**1j**), K (**1k**), M (**1m**), N (**1n**) und O (**1o**) totalsynthetisiert sowie Kibdelomycin (**10**) formal synthetisiert (SCHEMA 1 u. 2). Die besondere Motivation für die Synthese antibiotischer Wirkstoffe bestand darin, der bereits herrschenden Antibiotikaresistenz-Krise entgegen-zuwirken.

Das erste Projekt umfasste die Totalsynthese von Berkeleylacton A (**1a**, SCHEMA 1, oben). Hierbei wurde ein neuer Syntheseweg zum Macrolid **8** entwickelt. Die Stereoinformation des Lactons **8** stammt zum einen aus dem *chiral pool* [(*R*)-PPO (**3**)], zum anderen aus einer asymmetrischen Noyori-Hydrierung (→ **5**). Die makrocyclische Struktur wurde in einer Domino-Wittig-Reaktion mit dem kumulierten Ylid **7** generiert. Für die finale Darstellung des Berkeleylactons A (**1a**) wurde eine *Thia*-Michael-Addition mit einer Thiol-Seitenkette (**1a**, grün) gewählt. Neben der sehr effizienten Synthese (24%, 13 Stufen) konnten auch noch die starken Anti-Biofilm-Eigenschaften gegenüber den gefährlichen Pathogenen *S. aureus* und *C. albicans* aufgezeigt werden. Infektionen durch diese treten häufig in Zusammenhang mit Implantationen auf und haben eine hohe Mortalität, was eine Behandlung mit Antibiotika wie z.B. Berkeleylacton A (**1a**) notwendig macht.

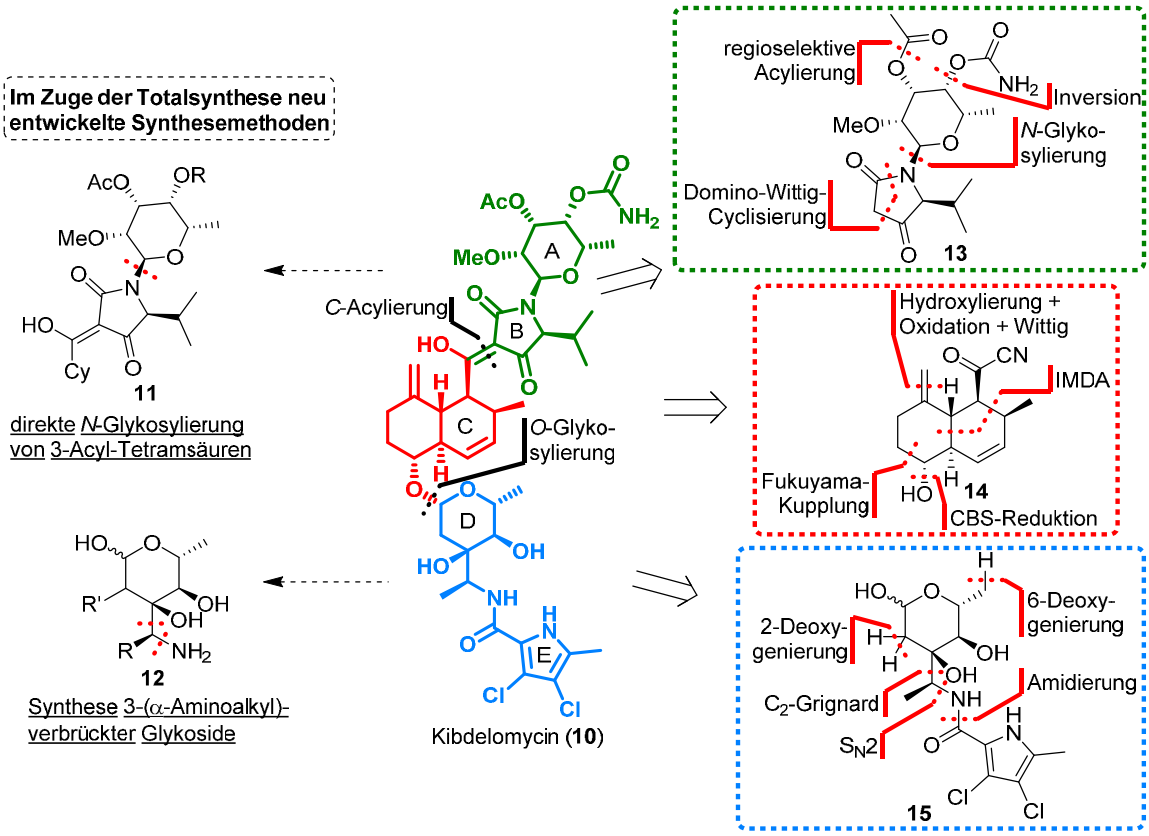
Der zweite Teil, eng verknüpft mit der Totalsynthese von Berkeleylacton A (**1a**), beschäftigte sich mit der divergenten Synthese sechs neu entdeckter Berkeleylactone (SCHEMA 1, unten). Hierfür wurde das Makrolacton **8** diastereoselektiv zum zentralen Schlüsselintermediat **9** reduziert, welches als Ausgangsstoff für alle weiteren Transformationen hin zu den diversen Naturstoffen diente. Alle synthetisierten Berkeleylactone in dieser Arbeit wiesen das γ-Hydroxy-Ester-Motiv auf. Ausgehend vom Schlüsselintermediat **9** wurden durch FGI und eine spezielle Schutzgruppen-Strategie vier verschieden substituierte Makrolactone erhalten. Ein Problem bereitete dabei insbesondere der spontane Acyl-*shift* der Succinyl-Gruppen. Darüber hinaus wurde durch Ringkontraktion noch ein Weg zu den γ-Lactonen **1n** und **1o** geschaffen. Aufgrund der strukturellen Nähe der makrocyclischen Vertreter zu Berkeleylacton A (**1a**) wäre auch hier eine Untersuchung bezüglich der Anti-Biofilm-Aktivität interessant.



SCHEMA 1. Die ersten beiden Teilprojekte mit der Totalsynthese von Berkeleylacton A (**1a**) und der divergenten Synthese γ-Hydroxy-funktionalisierter Berkeleylactone.

Im dritten Projekt wurde eine formale Totalsynthese von Kibdelomycin (**10**) erarbeitet, einem potenten Antibiotikum mit einem neuartigen Wirkmechanismus, weswegen der Naturstoff als potenzieller Wirkstoffkandidat vorgesehen ist (SCHEMA 2). Die komplexe Struktur mit vielen funktionellen Gruppen, konzentriert auf kleinstem Raum, erschwerte die Synthese derartig, dass die synthetische Darstellung nahezu 15 Jahre nicht gelang. Während der Projektarbeiten wurden jedoch drei Totalsynthesen publiziert, was dazu führte, eine formale Totalsynthese anzustreben. Dabei sollte, wie auch ursprünglich geplant, Kibdelomycin (**10**) in die drei Fragmente **13**, **14** und **15** geteilt werden, welche in einer konvergenten Synthese zum Schluss durch *O*-Glykosylierung sowie *C*-Acylierung zusammengefügt werden sollten. **13** und **15** stellen dabei die Derivate der unnatürlichen Zucker Amykitanose (grün) und Amycolose (blau) dar. Diese wurden allesamt aus natürlich vorkommenden Zuckern hergestellt, wobei die Schlüsselschritte als rote Retrosynthese-Schnitte in SCHEMA 2 abgebildet sind. Es gilt anzumerken, dass der Aufbau der Stereozentren in den Glykosiden ausschließlich durch diastereoselektive Reaktionen (Inversion, C_2-Grignard, *N*-Glykosylierung) oder unter Verwendung der darin vorkommenden funktionellen Gruppe (S_N2) realisierbar war. Zudem waren für die *N*-acylierte Amycolose **15** partielle Deoxygenierungen essentiell. Das Gerüst des zentralen Decalin-Fragments **14** wurde durch eine intramolekulare Diels-Alder-Reaktion (IMDA) aufgebaut, wobei die funktionellen Gruppen noch durch CBS-Reduktion und Wittig-Olefinierung eingeführt wurden. Die Synthesearbeiten zu den einzelnen Bausteinen machten es

notwendig, neue Synthesekonzepte zu erarbeiten. Dazu zählten die *N*-Glykosylierung von 3-Acyl-Tetramsäuren (vgl. **11**) sowie der Aufbau 3-(α-Aminoalkyl)-verbrückter Glykoside (vgl. **12**). Insgesamt wurden im letzten Projekt sowohl ein alternativer Zugang zu Kibdelomycin (**10**) als auch neue Synthesemethoden im Bereich der Tetramsäure- und Zuckerchemie entwickelt.



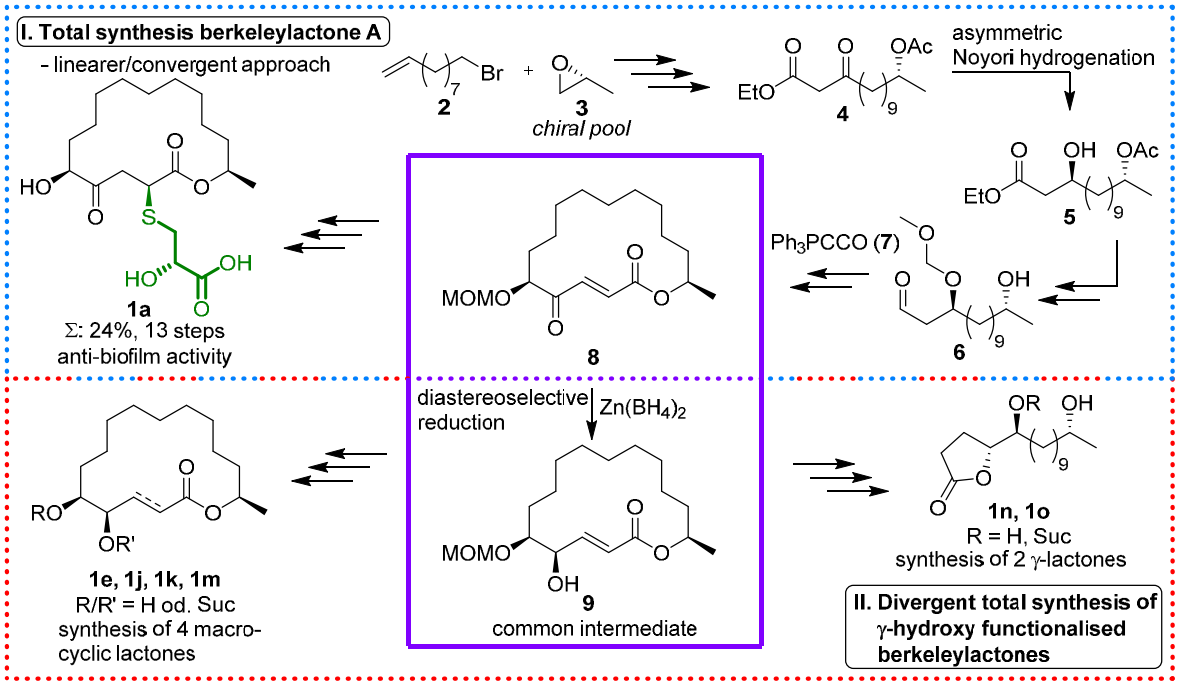
SCHEMA 2. Ergebnisse während der formalen Totalsynthese von Kibdelomycin (**10**).

Summary

During the dissertation, three research topics were investigated that had in common the synthetic accessibility of natural products that can be used as antibiotic agents. Throughout this work, new synthetic concepts were developed regarding the divergent synthesis of macrolides, the *N*-glycosylations of 3-acyl tetramic acids and the accessibility of 3-(α-aminoalkyl)-bridged glycosides. In concrete terms, berkeleylactones A (**1a**), E (**1e**), J (**1j**), K (**1k**), M (**1m**), N (**1n**) and O (**1o**) were synthesised and kibdelomycin (**10**) was formally synthesised (SCHEME 3 and 4). The primary motivation for the synthesis of antibiotic agents was to combat the current antibiotic resistance crisis.

The first project concerned the total synthesis of berkeleylactone A (**1a**, SCHEME 3, top). In this context, a new synthetic pathway to the macrolide **8** was established. The stereoinformation of lactone **8** derives on the one hand from the chiral pool [(R)-PPO (**3**)], and on the other hand from an asymmetric Noyori hydrogenation (→ **5**). The macrocyclic structure was formed in a domino-Wittig reaction with the cumulated ylide **7**. A *thia*-Michael addition with a thiol side chain (**1a**, green) was chosen for the final preparation of the berkeleylactone A (**1a**). In addition to the very efficient synthesis (24%, 13 steps), the strong anti-biofilm properties against *S. aureus* and *C. albicans*, which are responsible for a large number of infections, could also be demonstrated. These infections frequently occur in association with implantations and have a high mortality, which would necessitate treatment with antibiotics such as berkeleylactone A (**1a**).

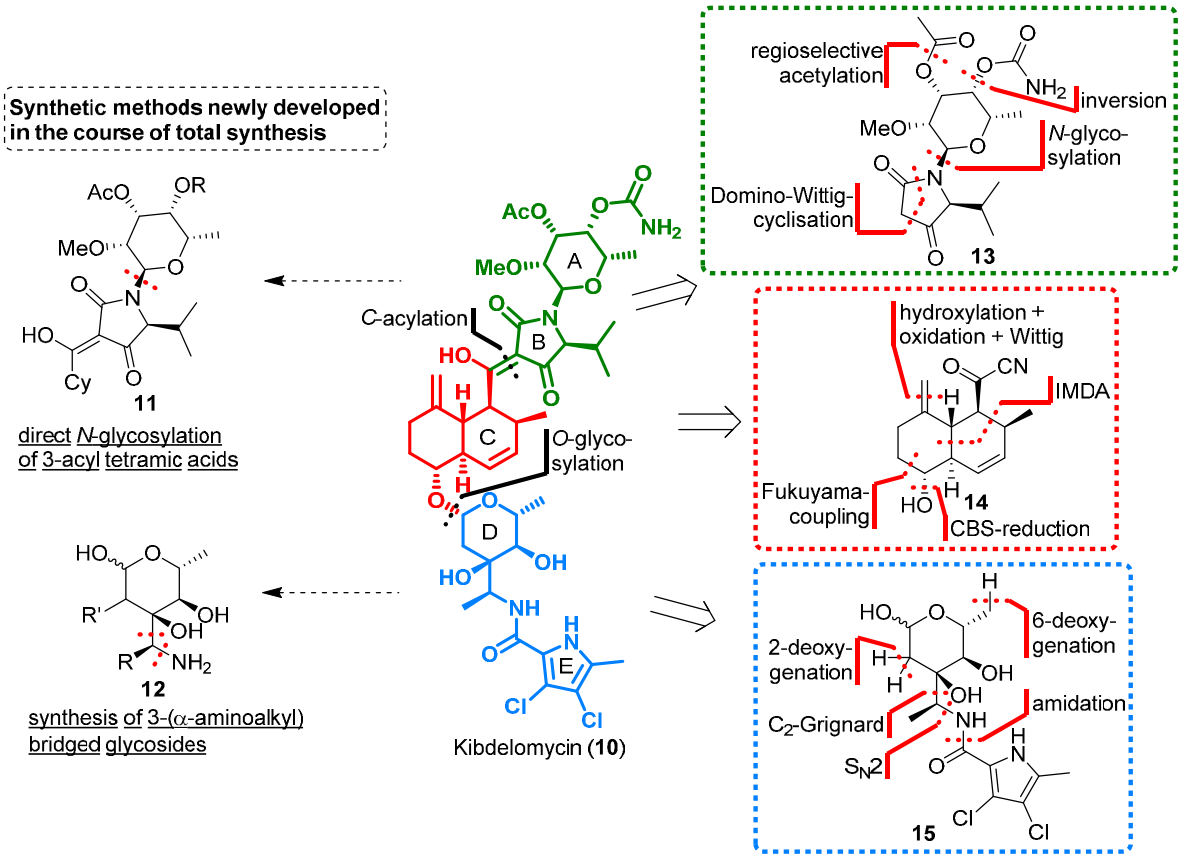
The second part, closely linked to the total synthesis of berkeleylactone A (**1a**), dealt with the divergent synthesis of six different, newly discovered berkeleylactones (SCHEME 3, bottom). For this purpose, the macrolactone **8** was diastereoselectively reduced to the common intermediate **9**, which was used as the starting material for all further transformations to the various natural products. All berkeleylactones synthesised in this work had the γ-hydroxy ester motif. Starting from the common intermediate **9**, four differently substituted macrolactones were obtained by FGI and a special protecting group strategy. Problems were caused in particular by the spontaneous acyl-shift of the succinyl groups. In addition, a pathway to the γ-lactones **1n** and **1o** was opened up by ring contraction. Due to the structural proximity of the macrocyclic representatives to berkeleylactone A (**1a**), an investigation of the anti-biofilm activity might be interesting here as well.



SCHEME 3. The first two projects with the total synthesis of berkeleylactone A (**1a**) and the divergent synthesis of γ-hydroxy-functionalised berkeleylactones.

In the third project, a formal total synthesis of kibdelomycin (**10**) was developed, a potent antibiotic with a novel mode of action which is the reason why the natural product is a potential drug candidate (SCHEME 4). The complex structure with a high number of functional groups concentrated in an exceedingly small space made the synthesis so difficult that the synthetic preparation was not possible for almost 15 years. During the course of the project, however, three total syntheses were published, which led to the aim of a formal total synthesis. As originally planned, kibdelomycin (**10**) was to be divided into three fragments **13**, **14** and **15** and finally assembled in a convergent synthesis by *O*-glycosylation and *C*-acylation. **13** and **15** represent derivatives of the unusual sugars amykitanose (green) and amycolose (blue). All of these were prepared from naturally occurring sugars, with the key steps shown as red retrosynthetic cuts in SCHEME 4. It should be noted that the construction of the stereogenic centers in the glycosides was feasible only by diastereoselective reactions (inversion, C_2-Grignard, *N*-glycosylation) or using the functional groups occurring in them (S_N2). In addition, partial deoxygenations were essential for the *N*-acylated amycolose **15**. The backbone of the central decalin fragment **14** was constructed in an intramolecular Diels-Alder reaction, and the functional groups were further introduced by CBS reduction and Wittig olefination. The synthetic studies towards the individual building blocks made it necessary to design new synthetic concepts. These included the *N*-glycosylation of 3-acyl tetramic acids (*cf.* **11**) and the construction of 3-(α-aminoalkyl)-bridged glycosides (*cf.* **12**). Overall, the final project involved

the development of an alternative approach to kibdelomycin (**10**) and new synthetic methods in the field of tetramic acid as well as sugar chemistry.



SCHEME 4. Results during the formal synthesis of kibdelomycin (**10**).

1 Einleitung

1.1 Antibiotikaresistenz-Krise

Die bereits aktuell herrschende Antibiotikaresistenz-Krise resultiert aus im Wesentlichen fünf Ursachen.[1] (1) Ein Problem stellt der übermäßige Gebrauch durch nicht regulierte Abgabe an Patienten dar. Dabei ist bekannt, dass die Einnahmemenge von diversen Antibiotika mit deren Resistenzentwicklung korreliert.[2] Die Entstehung der Resistenzen ist dabei auf den Gen-Transfer zwischen den Mikroorganismen oder zufällige Mutationen zurückzuführen. (2) Eng verbunden mit der übermäßigen Einnahme ist auch der Einsatz in der Landwirtschaft. Dabei ist der Grund für den Einsatz meist nicht die Anwendung gegen Infektionen, sondern die Steigerung des Tierwachstums. Das Resultat daraus ist das Vorhandensein von Antibiotika in Nahrungsmitteln, die Übertragung resistenter Keime davon auf den Menschen, aber auch die Verteilung von ausgeschiedenen Antibiotika-Rückständen in der Umwelt. (3) Ein weiterer Grund ist eine häufig falsch angewendete Antibiotikatherapie, bezogen auf Dauer, Art des Antibiotikums oder gar Indikation. Die letzten beiden Gründe für das Entstehen der Krise sind eher ökonomischer und administrativer Natur. (4) Einerseits zeigte sich, dass Antibiotika-forschung, -produktion und -vertrieb für große Pharmaunternehmen keine gewinnbringenden Geschäftsfelder mehr sind. (5) Zum anderen sind Zulassungsverfahren bürokratisch und auf-wendig. Dass diese Krise ein großes Problem darstellt, wird durch die Annahmen deutlich, im Jahr 2050 könnten durch antibiotikaresistente Keime die meisten krankheitsbedingten Todesfälle zu Stande kommen und das globale Bruttoinlandsprodukt sinke um mindestens 1%.[3] Dabei wird die Auswirkung auf weniger entwickelte Länder deutlich stärker sein als auf jetzige Industrienationen. Lösungsansätze, um gegen die Krise vorzugehen bzw. sie einzudämmen, existieren bereits.[3,4] Dazu zählen einerseits die Medikation gezielter zu verabreichen, die Infektionen von Beginn an zu verhindern oder Diagnosen genauer stellen zu können. Andererseits ist auch eine pharmazeutische Herangehensweise mit der Entwicklung neuer Antibiotika sowie der Verwendung von Kombi-Präparaten und Adjuvantien notwendig.

1.2 Makrocyclische Lactone und Wirkstoffe

Die wahrscheinlich wichtigste Klasse der Lactone bezüglich Bioaktivität sind Makrolactone, auch Macrolide genannt. Diese zählen zu den makrocyclischen Wirkstoffen, welche außerdem noch Makrolactame und cyclische Peptide einschließen.[5] Die Gemeinsamkeit aller ist eine Ringgröße von zwölf oder größer.[6] Ein wesentlicher Vorteil makrocyclischer Wirkstoffe gegenüber den acyclischen ist die verringerte Anzahl möglicher Konformationen durch weniger frei drehbare Bindungen und die bessere Vororganisation der Struktur in der Nähe der Bindungsstellen. Diese Rigidität hat zur Folge, dass die Bindungsaffinität sowie -selektivität zunimmt. Darüber hinaus wird postuliert, dass dadurch auch die orale Bioverfügbarkeit erhöht sein kann.[7] Wird die *drug-likeness* vieler klinisch verwendeter makrocyclischer Wirkstoffe betrachtet, fällt auf, dass diese aufgrund des Brechens vieler Lipinski-Regeln eigentlich nicht gegeben wäre.[8] Vor allem wegen der größeren Gerüststrukturen der Makrocyclen wird das für Medikamente maximal akzeptierte Molekulargewicht von 500 $g \cdot mol^{-1}$ selten eingehalten. Dennoch sind Makrocyclen gerade wegen der Schnittstelle zwischen den üblich verwendeten kleinen Molekülen und Makromolekülen interessant. Da die Komplexität der Synthese von makrocyclischen Wirkstoffen, vor allem im Hinblick auf den Ringschluss, häufig hoch ist, wird wenn möglich auf eine biotechnologische Produktion zurückgegriffen und in wenigen weiteren Syntheseschritten das Zielmolekül hergestellt.

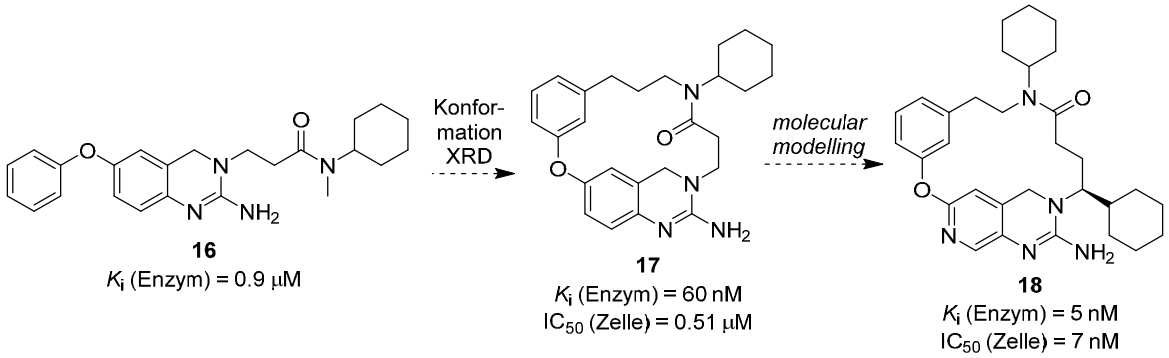
1.2.1 Biologische Wirkung und *targets* von Makrocyclen

Ein wesentlicher Grund für die Synthese, aber auch die Isolation makrocyclischer Wirkstoffe ist deren biologische Aktivität und die damit verbundenen verschieden adressierbaren *targets* im Körper bzw. im zu bekämpfenden Mikroorganismus. Im menschlichen Organismus seien vor allem Enzym-Inhibitionen, Interaktionen mit G-Protein gekoppelten Rezeptoren und die Inhibition von Protein-Protein-Wechselwirkungen zu nennen.[6] Als Wirkmechanismus gegen Bakterien und Pilze ist vor allem die Hemmung der Proteinbiosynthese sowie die Einlagerung in die Zellmembran bekannt. Sämtliche übergeordnete Mechanismen werden im Folgenden an einem dazugehörigen Beispiel erläutert.

1.2.1.1 Enzym-Inhibitoren

Ein anschauliches Beispiel für rationales Wirkstoffdesign von acyclischen *hits* im *high-throughput-screening* (HTS) hin zu makrocyclischen Leitstrukturen ist der BACE-1-Inhibitor **18**.[9] BACE-1 (Beta-Sekretase) ist eine Protease, welche im Zusammenhang mit der Entstehung von Alzheimer steht und dadurch ein interessantes *target* ist, um ebendieses zu bekämpfen.

Huang *et al.* identifizierten das Amid **16** mit einem K_i von 0.9 µM als potenziellen Inhibitor der Protease BACE-1, in welcher es in einer hufeisenförmigen Konformation vorlag (SCHEMA 5). Bei dem naheliegenden Ringschluss (→ **17**) führte das bereits zu einem deutlich verbesserten K_i (60 nM), wohingegen der IC_{50} (0.51 µM) bezogen auf die Inhibition von BACE-1 in einer Alzheimer-Zelllinie noch nicht zufriedenstellend war. Durch molekulare Modellierung wurde herausgefunden, dass ein weiterer hydrophober Cyclohexyl-Rest (→ **18**) eine weitere Verbesserung mit sich bringen sollte. Diese machte sich durch einen verringerten K_i (5 nM) und deutlich verringerten IC_{50} (7 nM) bemerkbar.



SCHEMA 5. Design eines BACE-1-Inhibitors durch Huang *et al.*[6,9]

1.2.1.2 G-Protein gekoppelte Rezeptoren sowie Integrine

G-Protein gekoppelte Rezeptoren (GPCRs) und Integrine sind als Membranproteine auch für die Signalübertragung aus dem extrazellulären Raum in das Cytosol verantwortlich und eines der häufigsten *targets*, weswegen 30 – 40% der am Markt erhältlichen Medikamente GPCRs ansteuern.[6,10] Da im Gegensatz zu den vorher vorgestellten Proteasen nur wenige Kristallstrukturen bekannt sind, muss vor allem auf das HTS statt molekularer Modellierung zurückgegriffen werden. Ein großer Vorteil von GPCR-basierten Therapeutika ist, dass kein Durchtritt der Zellmembran notwendig ist. Dies wurde bei dem Motilin-Rezeptor-Antagonisten **19** ausgenutzt (ABB. 1).[11] Der natürliche Botenstoff Motilin steht im direkten Zusammenhang mit der Bewegung des Darminhalts. Eine Steuerung davon kann für die Medikation von Erkrankungen im gastrointestinalen Trakt hilfreich sein.

Ein Integrin-ansteuerndes Wirkstoffmolekül ist das Pentapeptid Cilengitid (**20**, ABB. 1). Dieses zeigt antagonistische Wirkung gegenüber dem in Tumorzellen hochregulierten und dem für Angiogenese verantwortlichen αvβ3-Rezeptor im subnanomolaren Bereich.[12] Die Phase III-Studie von Merck erreichte allerdings nicht die erwünschten Ziele.[13]

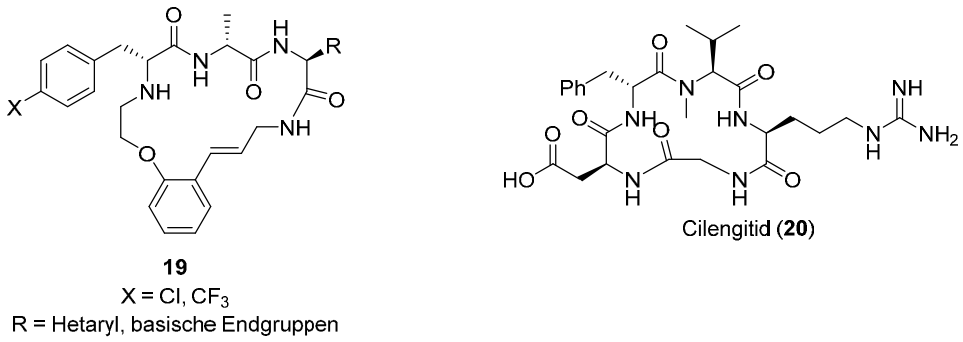
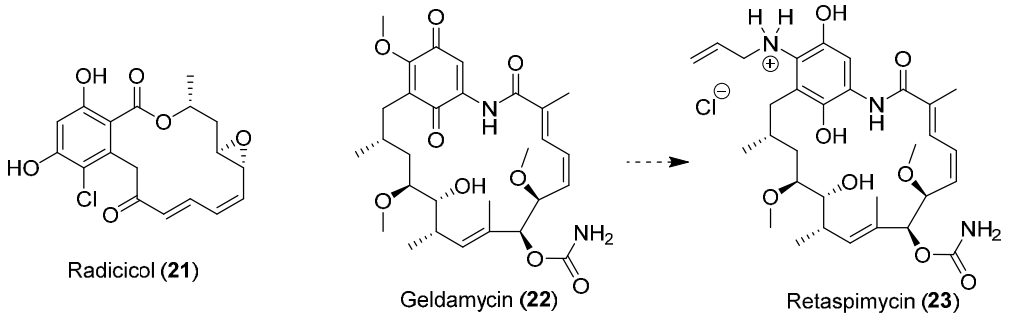


ABBILDUNG 1. Wirkstoffe auf der Basis der Modulation von GPCRs und Integrinen.

1.2.1.3 Inhibition von Protein-Protein-Wechselwirkungen

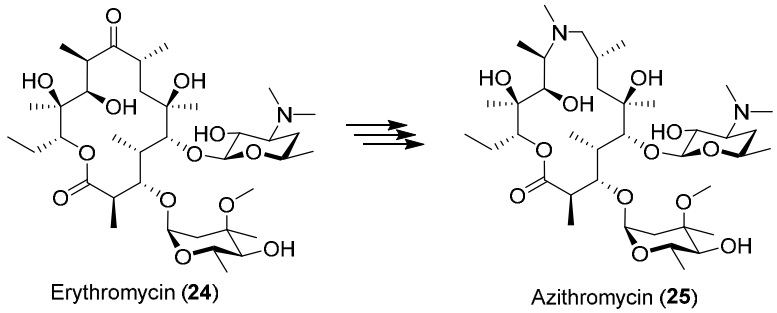
Bezogen auf die jüngere Vergangenheit zeigte sich, dass in der Inhibition von Protein-Protein-Wechselwirkungen das größte Wachstumspotential steckt.[6] Hierbei können Makrocyclen ihre Stärken ausnutzen, vor allem da sie sich durch ihre relativ feste Konformation gut an komplementär geformte Proteine über große Flächen von bis zu mehreren 100 Å^2 anlagern können und somit die Interaktion zwischen Proteinen verhindern. Ein *target* hiervon ist das *heat-shock-protein 90* (HSP90), vor allem in Bezug auf antitumorale Wirkungen. HSP90 lagert sich unter anderem an HIF-1α oder VEGFR an und verhindert deren zellulären Abbau.[14,15] HIF-1α und VEGFR lösen die krebstypischen zellulären Eigenschaften wie Hypoxie oder Angiogenese aus.[14,16] Die makrocyclischen Inhibitoren des HSP90 sind mit Geldamycin (**22**) oder Radicicol (**21**) auch in der Natur zu finden (SCHEMA 6). Da diese allerdings physiologische Nachteile mit sich brachten, musste der von Geldamycin (**22**) abgeleitete Wirkstoff IPI-504/Retaspimycin (**23**) entwickelt werden, welcher bereits im klinischen Stadium ist.



SCHEMA 6. Darstellung dreier HSP90-Inhibitoren.[14]

1.2.1.4 Hemmung der Proteinbiosynthese

Primäre *targets* für moderne Antibiotika sind immer noch das Binden an die 30S- oder 50S-Untereinheit von bakteriellen Ribosomen und die damit einhergehende Unterbindung der Proteinbiosynthese. Für die macrolidischen Antibiotika der Erythromycin-Klasse, aber auch für andere Proteinbiosynthese-Hemmer, wurde 2001 von Schlünzen *et al.* die exakte Bindungsstelle durch Röntgenkristallstrukturanalyse der Co-Kristalle von Ribosom und Antibiotikum aufgeklärt.[17] Interessant dabei war die Tatsache, dass trotz der strukturellen Divergenz verschiedener Proteinbiosynthese-Hemmer die gleiche Bindungstasche, jedoch mit unterschiedlichen Positionen genutzt wird. Als Wirkmolekül ist Erythromycin (**24**) in der 23S ribosomalen RNA am Eingang eines Tunnels lokalisiert, durch welchen ein neu gebildetes Peptid anfangs geschoben werden muss. Aufgrund der Anlagerung des Macrolids durch intermolekulare Wechselwirkung ausgehend vom Desosamin (oberes Zuckerfragment) und einigen H-Brücken am Makrocyclus verengt sich dieser Durchgang auf etwa die Hälfte (10 Å), wodurch nach der Synthese eines sieben- bis neungliedrigen Peptids keine weitere Translokation mehr möglich ist. Da Erythromycin (**24**) säurelabil ist, war eine orale Gabe nur sehr eingeschränkt möglich, was dazu veranlasste, verbesserte Erythromycin-abgeleitete Antibiotika zu entwickeln.[18] Am stärksten davon am Markt vertreten ist womöglich Azithromycin (**25**), welches in wenigen Stufen aus im Tonnen-Maßstab biotechnologisch herstellbaren Erythromycin (**24**) synthetisiert werden kann (SCHEMA 7).[18,19] Neben der höheren oralen Verfügbarkeit hat Azithromycin (**25**) gegenüber Erythromycin (**24**) Verbesserungen in den Bereichen Plasmahalbwertszeit und -proteinbindung, Toxizität sowie Aktivität.



SCHEMA 7. Entwicklung und Synthese von Erythromycin (**24**) hin zu Azithromycin (**25**).

1.2.1.5 Einlagern in die Zellmembran

Die klinisch relevanten, hauptsächlich topisch angewendeten Antimykotika Nystatin (**26**) und Amphotericin B (**27**), aber auch das vor allem in der Lebensmittelindustrie eingesetzte

Natamycin (**28**), gehören zu der Wirkstoffklasse der Polyen-Makrolactone (ABB. 2).[20] Alle weisen einen amphiphilen Charakter auf, zum einen durch einen lipophilen Polyen-Teil, zum anderen durch einen hydrophilen Gegenspieler. Es ist gut erforscht, dass sich Amphotericin B (**27**) an Ergosterol in der Phospholipid-Doppelschicht einer mykotischen Zelle anlagert und Kanäle bildet, die zum erhöhten Efflux von kleinen Kationen (K^+, Ca^{2+}, Mg^{2+}) beitragen.[21,22] Die Annahme, der osmotische Stress sei für das Absterben der Zelle verantwortlich, war lange Zeit anerkannt. Allerdings haben neuere Forschungsergebnisse gezeigt, dass nicht zwingend der Efflux von kleinen Kationen verantwortlich für den Zelltod sein muss.[21,23]

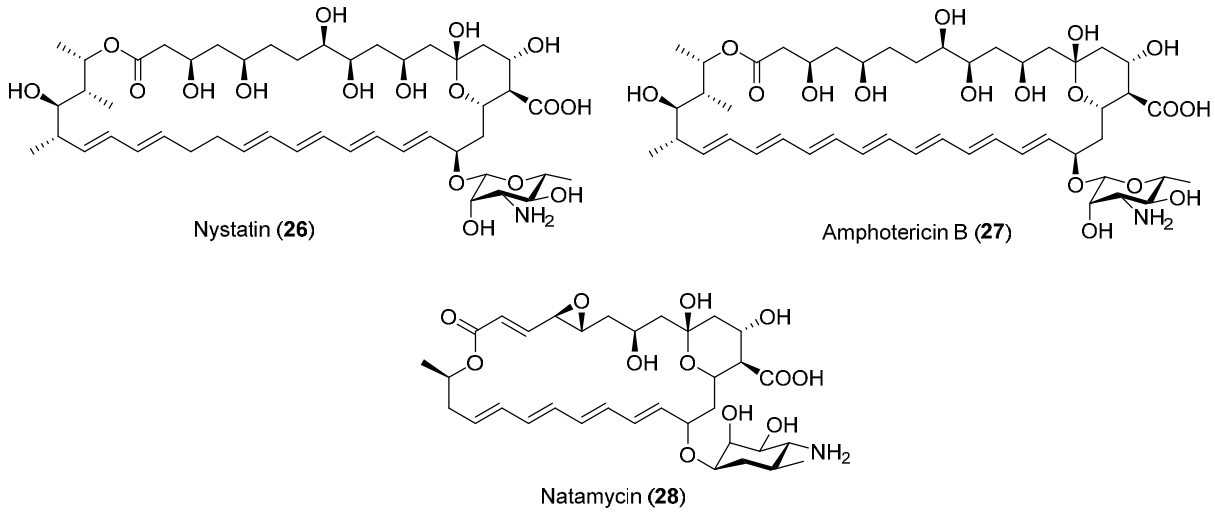
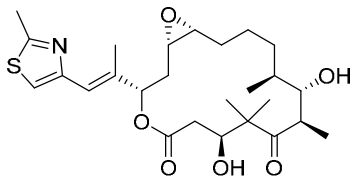


ABBILDUNG 2. Bekannte Polyen-Macrolide mit antimykotischer Wirkung.

1.2.1.6 Nicht klassifizierbare Wirkmechanismen

Aufgrund der strukturellen Komplexität der häufig von Bioorganismen produzierten Makrocyclen sind auch gänzlich andere, einzigartige Wirkmechanismen bekannt. Als macrolidischer Vertreter kann das Epothilon A (**29**, ABB. 3) genannt werden, welches die Depolymerisation der Microtubuli hemmt.[24] Hierbei wird angenommen, dass das Binden von Epothilon A (**29**) an Tubulin eine strukturelle Veränderung des Proteingerüsts auslöst, welches sowohl die Anlagerung von weiterem Tubulin begünstigt als auch die Depolymerisation verhindert. Dies führt auf Dauer zur Apoptose.



Epothilon A (**29**)

ABBILDUNG 3. Das Microtubuli-stabilisierende Makrolacton Epothilon A (**29**).

1.2.2 Synthese von Makrocyclen

Für die Synthese von Makrocyclen sind vor allem C-C- und C-Heteroatom-Bindungsknüpfungen, meist unter Hochverdünnung, bekannt.[6] Auch eher exotische Synthesemethoden wie Ringerweiterungen durch beispielsweise (Grob-)Fragmentierung oder Umlagerungen sind bekannt, wenn auch nicht anwendbar auf allgemeine Problemstellungen der Makrocyclisierung.[25] In ABBILDUNG 4 sind die retrosynthetischen Schnitte des Großteils der totalsynthetisierten Makrocyclen gezeigt, welche im Folgenden noch an bekannten Naturstoffsynthesen genauer vorgestellt werden.

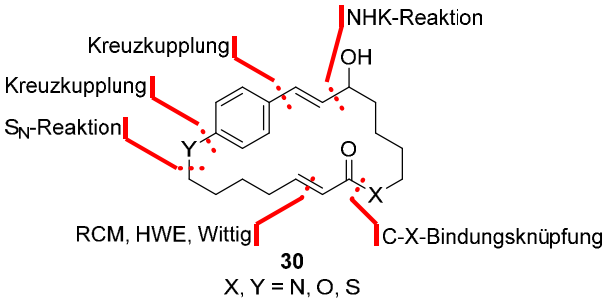


ABBILDUNG 4. Standardmäßig anwendbare Protokolle für Makrocyclisierungen.

1.2.2.1 C-C-Bindungsknüpfung

Während vor Jahrzehnten der Anfang der C-C-verknüpfenden Makrocyclisierungen mit Olefinierungen wie HWE- oder Wittig-Reaktion gemacht wurde, sind diese heute weitestgehend von katalytischen Verfahren wie Ringschlussmetathese (RCM) oder Kreuzkupplungen abgelöst worden. Viele Cyclisierungsreaktionen wurden ursprünglich für den Aufbau linearer Moleküle entwickelt und erst später zu Ringschlussreaktionen umgewidmet. In ABBILDUNG 5 sind bekannte Naturstoffe mit deren ringschließenden Schlüsselreaktionen gezeigt. Am Beispiel von Amphidinolacton A (**31**) können zwei verschiedene Verfahren gezeigt werden; zum einen die Nozaki-Hiyama-Kishi-Reaktion (NHK).[26] Neben dem Aufbau des Macrolids macht es die NHK-Reaktion auch möglich, den Allylalkohol in **31** diastereoselektiv zu

synthetisieren. Während in diesem Beispiel ein Allylalkohol dargestellt wurde, können durch die NHK-Reaktionen zwischen Allyl(pseudo)halogeniden und Aldehyden oder Ketonen auch Homoallylalkohole aufgebaut werden.[27] Zum anderen wurde eine RCM zweier terminaler Doppelbindungen zum Aufbau des 13-gliedrigen Rings ebenfalls von Mohapatra *et al.* genutzt.[28] Die RCM ist aus diversen Gründen weder aus der präparativen noch industriellen organischen Chemie wegzudenken.[29] Für Metathese sprechen die hohe Atomökonomie, milde Reaktionsbedingungen, die Toleranz einer Vielzahl funktioneller Gruppen und mit Ausnahme ihrer Oxidationsempfindlichkeit relativ stabile Katalysatoren. Zudem besteht auch die Möglichkeit, selektiv *E*- und *Z*-Alkene aufzubauen.[30] Neben der RCM ist aber auch die RCAM mit dem Ringschluss von Alkinen bekannt.[29,31] Pionierarbeit leistete dabei die Arbeitsgruppe um Fürstner.[31,32]

Übergangsmetall-katalysierte Kreuzkupplungen werden häufig dann angewendet, wenn Biaryl-, Aryl/Alkenyl- oder Alkenyl/Alkenyl-Strukturmotive auftreten, wie z.B. im Rutamycin B (**32**, ABB. 5).[33] Höchste Selektivität und mildeste Bedingungen zeigen dabei die Stille-, Heck-, Sonogoshira-, Tsuji-Trost- und Suzuki-Miyaura-Reaktion, wobei letztere drei auch sp- bzw. sp^3-hybridisierte Kohlenstoffe mit sp^2-Kohlenstoffen kuppeln können.

Bei makrocyclisierenden C-C-Verknüpfungen kann beobachtet werden, dass diese überproportional häufig in der Nähe von oder an Doppelbindungen stattfinden, ebenso bei der Phosphor-basierten HWE- und Wittig-Reaktion. Nachteilig hierbei ist die geringere Atomökonomie verglichen mit katalytischen Reaktionen. Nicolaou *et al.* verwendete eine HWE-Ringschlussreaktion für die Darstellung des Amphoteronolid B (**34**), das strukturverwandt zu den in 1.2.1.5 vorgestellten Nystatin (**26**) und Amphotericin (**27**) ist.[34] Eine modifizierte Domino-Wittig-Reaktion wurde von Schmidt *et al.* verwendet, um ein ω-Hydroxyaldehyd in Form eines glykosidischen Halbacetals zum Macrolid Aspicilin (**33**) mit Hilfe des kumulierten Ylids **7** zu überführen.[35]

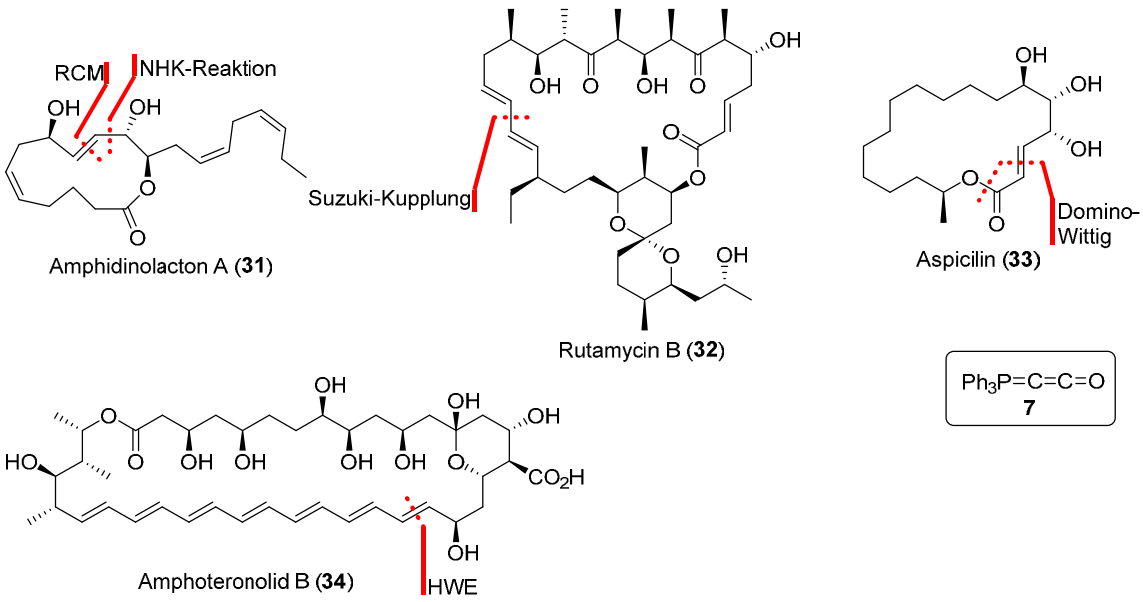


ABBILDUNG 5. Makrocyclische Naturstoffe, die durch ringschließende C-C-Verknüpfung aufgebaut wurden.

1.2.2.2 C-Heteroatom-Bindungsknüpfung

C-Heteroatom-Bindungsknüpfungen umfassen vor allem das Feld von Veresterung, Amidierung und Veretherung. Vorteilig hierbei ist der Fakt, dass die meisten Verknüpfungen ohne aufwendige Transformation der Edukte stattfinden kann, da z.B. Macrolide bzw. Makrolactame aus Hydroxy- bzw. Aminocarbonsäuren in einem Schritt aufgebaut werden können. In ABBILDUNG 6 sind die etablierten Makrolactonisierungen gezeigt.[36] Mit Ausnahme der Mitsunobu-Makrolactonisierung machen es sich alle zum Ziel, intermediär aktivierte Carbonylverbindungen zu bilden. Bei der Yamamoto- (→ **35**) und Yamaguchi-Makrolactonisierung (→ **38**) geschieht dies durch ein gemischtes Anhydrid, die Corey-Nicolaou-Makrolactonisierung (→ **36**) nutzt einen Thioester und die Lactonisierung nach Mukaiyama (→ **37**) eine Acyloxypyridinium-Spezies.[37,38] Keck entwickelte die Bedingungen einer Steglich-Veresterung (→ **39**) weiter und in der Mitsunobu-Makrolactonisierung (→ **40**) wird ein Azodicarboxylat wie DEAD (**46**) verwendet, um in diesem Fall die freie Hydroxy-Gruppe in eine Abgangsgruppe zu überführen, was an einen klassischen S_N2-Mechanismus angelehnt ist.[39] Durch diese Methoden wurden die Naturstoffe (±)-Zearalenon (**36**), Gloeosporon (**37**), Epothilon C (**38**) und Colletodiol (**39**) hergestellt.[38,40]

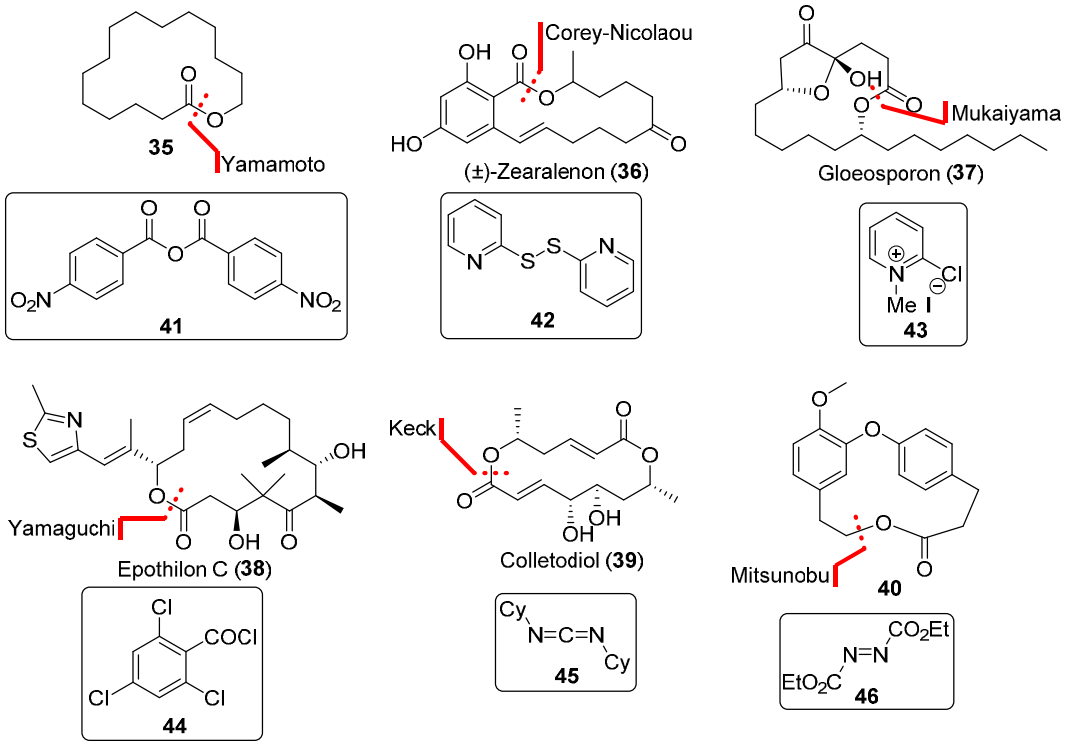
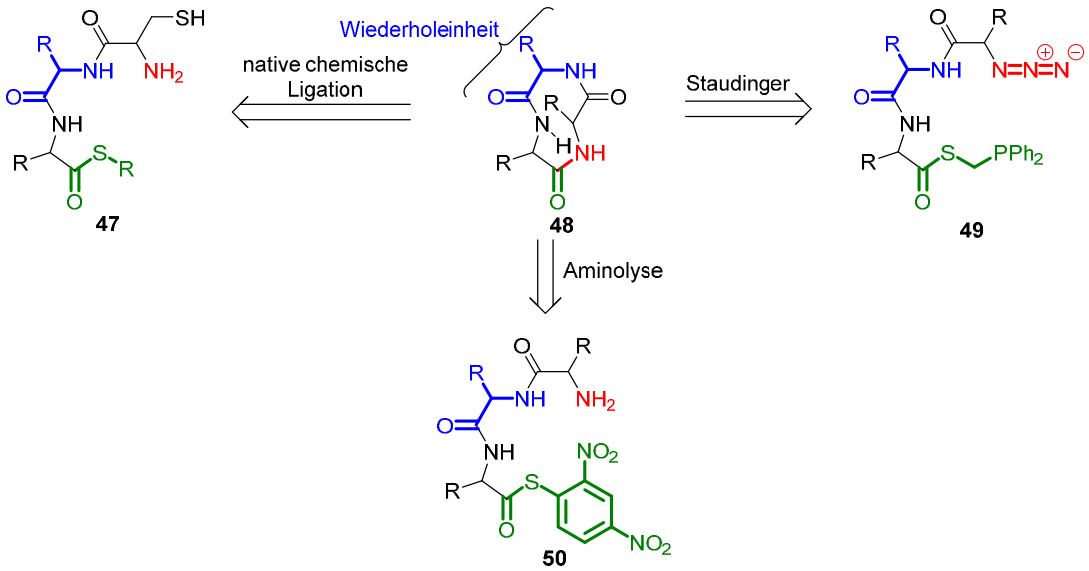


ABBILDUNG 6. Synthese der Makrocyclen **35** – **40** durch bekannte Makrolactonisierungen.

Neben Makrolactonisierungen sind insbesondere für den Aufbau cyclischer Peptide Makrolactamisierungen entscheidend.[41] Dabei spielen aus der Peptidchemie bekannte Verfahren wie native chemische Ligation, Aminolyse aktivierter Thioester oder die Staudinger-Ligation (SCHEMA 8), aber auch Amidierungen durch Aktivierungsreagenzien wie BOP eine Rolle.



SCHEMA 8. Möglichkeiten zum Aufbau cyclischer Peptide.

Zuletzt gibt es auch noch die Möglichkeit, makrocyclische Ether (oder Amine) durch beispielsweise Ullmann-Reaktion oder SN-Reaktionen aufzubauen. Als Beispiel für die Verwendung einer Ullmann-Kupplung wäre die Synthese des Biarylethers **51** zu nennen (ABB. 7) .[42] Eine Williamson-Makroveretherung wurde in der Synthese von Macrocidin A (**52**) angewendet.[43]

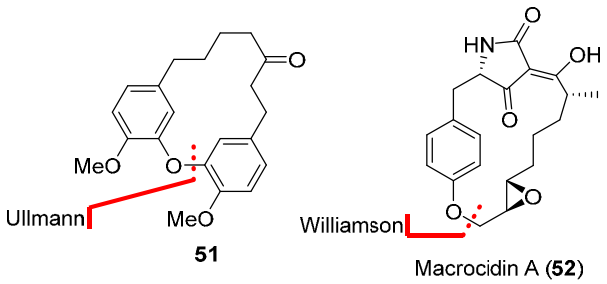


ABBILDUNG 7. Durch Ullmann-Kupplung und Williamson-Makroveretherung dargestellte Arylether.

1.2.3 A26771B (53) und Berkeleylactone A – R (1a – 1r)

1.2.3.1 Isolation und biologische Wirkung

Michel *et al.* isolierten 1977 erstmals A26771B (**53**) aus dem Pilz *Penicillium turbatum* (ABB. 8).[44] Im Gegensatz zu den Epipolythiopiperazindion-Metaboliten der A26771-Reihe besitzt A26771B (**53**) einen 16-gliedrigen Makrocyclus sowie einen γ-Oxo-α,β-ungesättigten Ester und eine in δ-Position acylierte Bernsteinsäure. Während die Strukturaufklärung mittels NMR-Spektroskopie gelang, konnte die absolute Stereokonfiguration aufgrund fehlender Kristallstruktur erst 1980 mittels Totalsynthese ausgehend von enantiomerenreiner D-Glucose bestimmt werden.[45]

40 Jahre später isolierten Stierle *et al.* neben A26771B (**53**) die Berkeleylactone A – H (**1a -1h**) aus einer Co-Kultur von *Penicillium fuscum* (Sopp) Raper & Thom und *Penicillium camembertii/clavigerum* Thom, welche aus der extremen Umgebung der Berkeley-Grube, einer aufgelassenen Kupfermine, entnommen wurden (ABB. 8).[46] Interessant hierbei ist, dass die axenischen Kulturen die neuen Naturstoffe nicht produzierten. Weitere vier Jahre später wurden sieben neue Berkeleylactone I – O (**1i -1o**) von der gleichen Arbeitsgruppe entdeckt. Dieses Mal wurden sie aus dem Produzenten von A26771B (**53**) *Penicillium turbatum* isoliert.[47] Dies hängt damit zusammen, dass einige Berkeleylactone Zwischenstufen in der Biosynthese von A26771B (**53**) sind.[48] Strukturell bestehen die Berkeleylactone A – M aus einem 16-gliedrigen Macrolid-Cyclus. Die α,β-Position der 16-gliedrigen Naturstoffe ist in den meisten ungesättigt, die γ-Position immer in Form eines Carbonyls oder einer Hydroxy-Gruppe oxidiert. In δ-Position sitzt mit Ausnahme von Berkeleylacton L (**1l**) immer eine (veresterte) Hydroxygruppe.

Die Berkeleylactone C, D, F, H und I (**1c**, **1d**, **1f**, **1h, 1i**) besitzen noch an anderen Positionen im Macrolid-Rückgrat Hydroxy-Gruppen. Neue Strukturmotive besitzen die Berkeleylactone A und B (**1a**, **1b**) mit deren Thioether. Die Berkeleylactone N und O (**1n**, **1o**) sind strukturverwandte γ-Lactone. Ende 2022 veröffentlichten Cowled *et al.* weitere sieben Berkeleylactone (darunter: **1p** – *epi*-**1r**), welche ähnlich zu den Berkeleylactonen C, D und I (**1c**, **1d**, **1i**) sind, allerdings die γ,δ-Dihydroxy-α,β-ungesättigte Ester-Gruppe als Funktionalität tragen.[49]

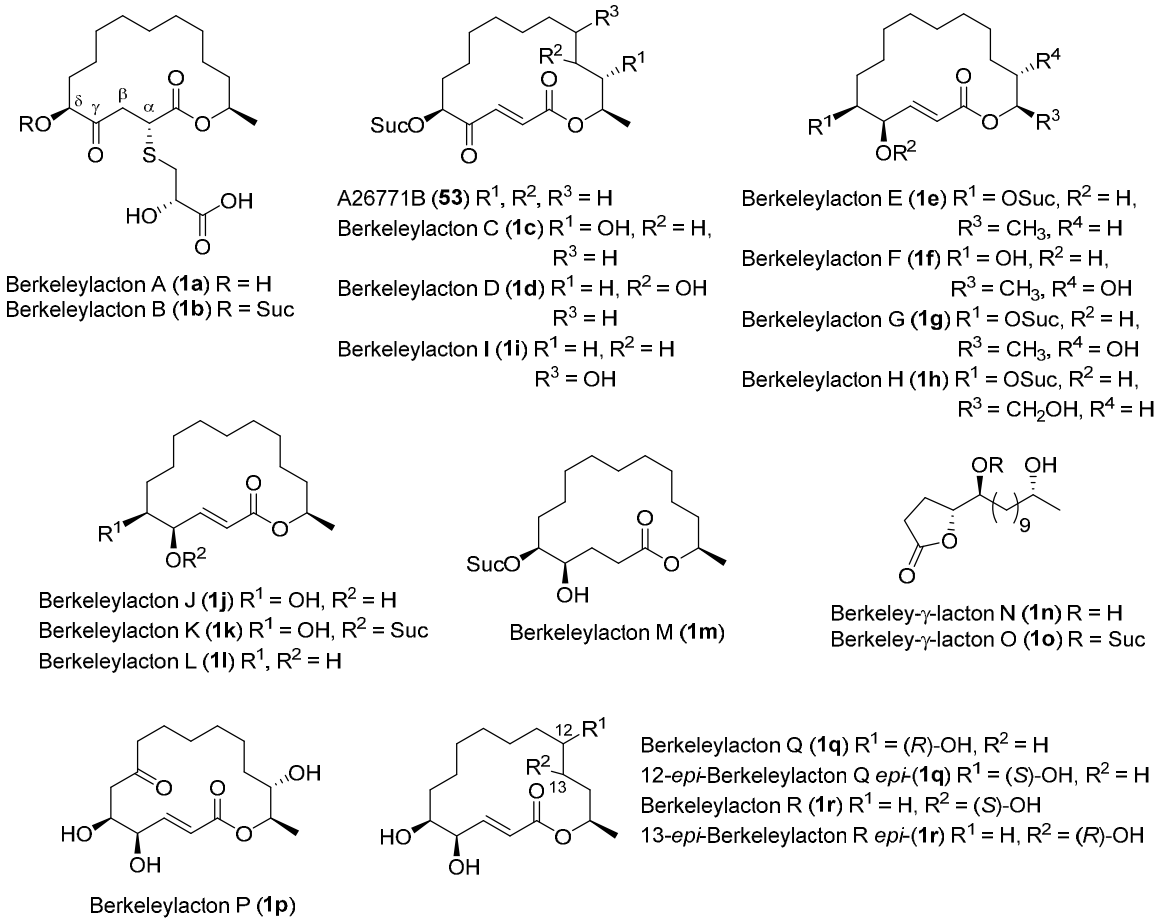


ABBILDUNG 8. Strukturen von A26771B (**53**) und den Berkeleylactonen A – R (**1a – 1r**). Suc = Succinyl.

Im Zuge der Isolation der Berkeleylactone in den Jahren 2017 und 2021 untersuchten Stierle *et al.* aufgrund der strukturellen Nähe zum bekannten Antibiotikum A26771B (**53**) deren antibiotische Eigenschaften gegenüber einigen Bakterien und Pilzen (Tabelle 1).[46,47] Vor allem Berkeleylacton A (**1a**) zeigte sehr geringe MICs gegenüber Gram-positiven Erregern. Bemerkenswert ist, dass Berkeleylacton A (**1a**) auch eine höhere Wirkung auf MRSA-Stämme hat im Vergleich zu anderen, nicht Penicillin-abgeleiteten Antibiotika (Vancomycin, Erythromycin, Clindamycin, Levofloxacin, Doxycyclin; nicht in Tabelle 1 gezeigt). Bei Vorhandensein einer γ-Oxo-Funktionalität kann ein positiver Effekt auf die biologische

Aktivität beobachtet werden, da die 2021 entdeckten Berkeleylactone I – O (**1i** – **1o**) sich meist als nur sehr schwach antibiotisch erwiesen.

Tabelle 1. Angabe der minimalen Hemm-Konzentration (MIC) von A26771B (**53**) und den neu isolierten Berkeleylactonen **1a** - **1o** gegenüber ausgewählten Bakterien- und Pilz-Stämmen.[46,47]

	Staphylococcus aureus µM (µg/mL)	*Streptococcus pyogenes* µM (µg/mL)	*Candida glabrata* µM (µg/mL)	*Bacillus subtilis* µM (µg/mL)	*Candida albicans* µM (µg/mL)	*Bacillus anthracis* µM (µg/mL)
53	8 (3)	125 (48)	125 (48)	32 (12)	250 (96)	16 (6)
1a	2 (1)	8 (3)	16 (6)	32 (13)	64 (26)	8 (3)
1b	8 (4)	250 (119)	64 (31)	64 (31)	>250 (>119)	16 (8)
1c	16 (6)	64 (26)	64 (26)	64 (26)	125 (50)	16 (6)
1d	32 (13)	125 (50)	>1000 (>400)	250 (100)	>1000 (>400)	64 (26)
1e	125 (45)	>250 (>90)	>250 (>90)	>250 (>90)	>250 (>90)	>250 (>90)
1f	64 (19)	500 (150)	>1000 (>300)	>1000 (>300)	>1000 (>300)	250 (75)
1g	64 (24)	>125 (>50)	>125 (>50)	>125 (>50)	>125 (>50)	64 (24)
1h	>250 (>100)	>250 (>100)	>250 (>100)	>250 (>100)	>250 (>50)	>250 (>100)
1i	32 (13)	250 (100)	>500 (>200)	125 (50)	>500 (>200)	64 (26)
1j	250 (71)	>250 (>71)	>250 (>71)	>250 (>71)	>250 (>71)	250 (>71)
1k	125 (40)	>250 (>90)	>250 (>90)	125 (40)	>250 (>90)	250 (>90)
1l	125 (33)	250 (67)	>250 (>67)	125 (33)	>250 (>67)	125 (>67)
1m	>500 (>45)	>500 (>45)	>500 (>45)	>500 (>45)	>500 (>45)	>500 (>45)
1n	500 (143)	16 (5)	>500 (>143)	>500 (>143)	>500 (>143)	>500 (>143)
1o	500 (193)	>500 (193)	500 (193)	500 (193)	125 (48)	>500 (193)

Tiefere Einblicke in die Struktur-Wirkungsbeziehungen von vor allem Berkeleylacton A (**1a**) gaben Malatinský *et al.*, indem sie die biologische Aktivität Berkeleylacton A-naher Substanzen bestimmten.[50] Auch hierbei wurde ausgehend von der Macrolid-Struktur ein deutlicher Einfluss auf die Wirkung erkannt. Ebenso entscheidend war aber auch die γ-Oxo-α,β-ungesättigte Ester-Gruppe. Ein Thioether hingegen bewirkte nur eine höhere metabolische Stabilität, was die hohe Wirksamkeit von Berkeleylacton A (**1a**) begründen könnte. Überraschenderweise zeigte im Zuge der Derivatisierung ein auf das Grundsystem heruntergebrochenes 16-gliedriges Makrolactam mit γ-Oxo-α,β-ungesättigter Amid-Gruppe die höchste Inhibition von *Staphylococcus aureus*.

Während die biosynthetischen Wege für A26771B (**53**) und einige Berkeleylactone bereits bekannt sind, gibt es bis heute kaum Erkenntnisse über das zelluläre *target* der Naturstoffe in Mikroorganismen.[48,49,51] Stierle *et al.* untersuchten Berkeleylacton A (**1a**) hinsichtlich der Fähigkeit, die bakterielle Proteinbiosynthese zu hemmen, wie es andere Macrolide tun.[46] Allerdings fanden sie keinerlei Hinweis, dass der Wirkstoff darauf Einfluss nimmt. Dies brachte sie zur Annahme, es müsse ein anderer Wirkmechanismus vorherrschen.

1.2.3.2 Totalsynthesen von A26771B (53)

Zur Darstellung von A26771B (**53**) sind bis ins Jahr 2023 22, häufig formale, Totalsynthesen veröffentlicht worden (Tabelle 2). [45,52–74] Ausgewählte, wiederkehrende Schlüsselschritte sowie Ringschlussmethoden sind in ABBILDUNG 9 gezeigt. Auffällig dabei ist, dass sich einige wenige Reaktionen bei sehr vielen Synthesen wiederfinden. Hierzu zählen die RCM an teils ähnlichen Stellen, die Ringöffnung von (*R*)-PPO (**3**), die Achmatowicz-Reaktion, die chemoselektive Oxidation eines Allylalkohols und diverse Makrolactonisierungen. Dennoch wählten viele Gruppen A26771B (**53**), um daran neu entwickelte Methoden auf die Naturstoffsynthese zu übertragen und mit anderen vergleichbar zu sein.

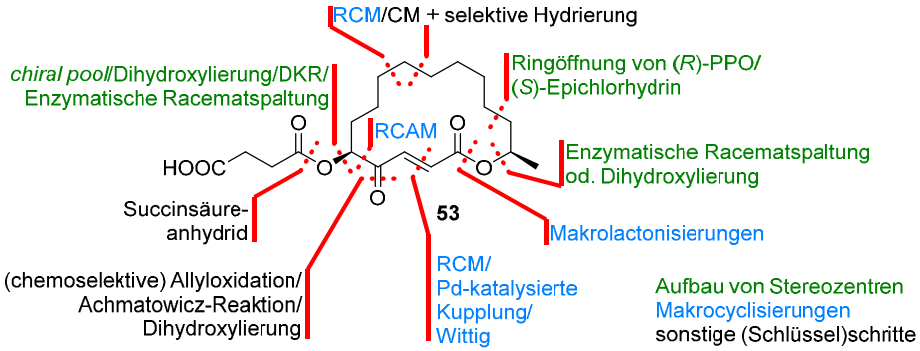


ABBILDUNG 9. Wichtige retrosynthetische Schnitte der literaturbekannten (asymmetrischen) Synthesen von A26771B (**53**). [45,52–74]

Tabelle 2 zeigt alle veröffentlichten Synthesen zu A26771B (**53**) seit 1979, wobei in chronologischer Reihenfolge die Ausbeuten und Länge der längsten linearen Sequenz zu den jeweiligen Autoren zugeordnet wurden. Um innerhalb der enantioselektiven Synthesen besser vergleichen zu können, wurden nur deren Daten angegeben. Zudem haben zwei Gruppen (Saha, Reddy) nicht die Vorgabe einer formalen Totalsynthese erreicht. Es gilt anzumerken, dass innerhalb der ersten zehn Jahre nach der Entdeckung von A26771B (**53**) fast ausschließlich stereounselektive Synthesen publiziert wurden, während danach mit einer Ausnahme nur noch enantioselektive Totalsynthesen veröffentlicht wurden. In frühen Jahren war vor allem die bloße Naturstoffsynthese Ziel der Arbeiten, wohingegen ab den 2000er Jahren eine immer höhere Effizienz sowie eine Verringerung der Stufenzahl zu beobachten war.

Tabelle 2. Veröffentlichte Totalsynthesen von A26771B (**53**) bis ins Jahr 2023. Zur besseren Vergleichbarkeit wurden nur Stufenanzahl und Ausbeuten für asymmetrische Synthesen angegeben.

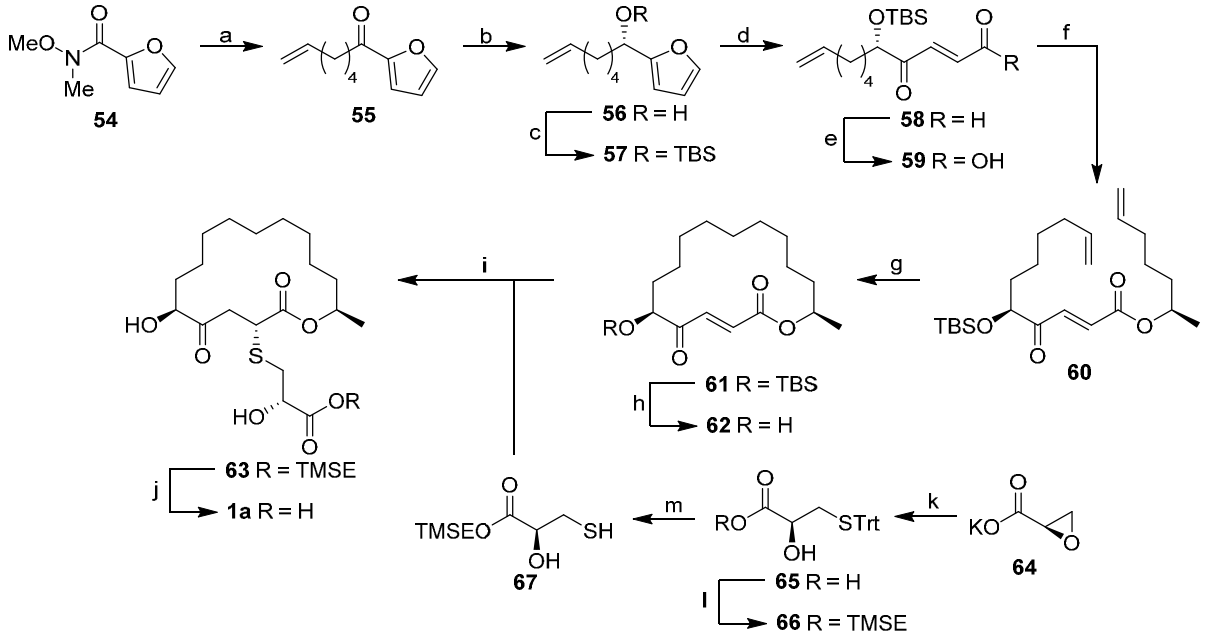
Autor/Arbeitsgruppe	Jahr	Stufen (längste lineare Sequenz)	Ausbeute
Hase[a,b]	1979[52]		
Tatsuta	1980[45], 1982[53]	21	4.4%
Asaoka[a]	1980[54], 1982[55]		
Fujisawa[a]	1983[56]		
Trost[a]	1983[57]		
Schobert/Bestmann[a]	1985[58]		
Hesse[a]	1987[59]		
Ichimoto	1988[60,61]	16	1.6%[c]
Quinkert	1991[62]	21	2.9%
Baldwin[a]	1992[63]		
Keinan	1993[64]	11	4.1%
		12	6.6%
Nagarajan	1999[65]	12	1.9%
Kobayashi	2000[66]	11	6.2%
Chang	2001[67]	10	2.9%
Blechert	2006[68]	11	17.3%
Reddy	2012[69]	10	14.3%[c]
Fürstner	2013[70]	8	25%
Chattopadhyay	2014[71]	18	9.1%
Shaw	2015[72]	13	13.7%
Chatterjee	2018[73]	10	16.6%
Saha	2022[74]	18	1.3%[d]

[a] keine enantioselektive Totalsynthese; [b] Darstellung des A26771B-Methylesters; [c] nicht von kommerziell erhältlichen Edukten startend; [d] anders als publiziert keine formale Totalsynthese per Definition.

1.2.3.3 Totalsynthese von Berkeleylacton A (1a)

Im Gegensatz zu A26771B (**53**) wurde das Berkeleylacton A (**1a**) nur einmal im Jahr 2019 von Ferko *et al.* synthetisiert (SCHEMA 9).[75] Dabei wurde mit der Weinreb-Keton-Synthese gestartet, die zur Darstellung des Furans **55** verwendet wurde. Nach stereoselektiver CBS-Reduktion und TBS-Schützung (→ **57**) wurde in der Achmatowicz-Reaktion der Aldehyd **58** hergestellt. Anschließende Pinnick-Oxidation und Steglich-Veresterung mit (*R*)-Hept-6-en-2-ol führte zum Vorläufer für die RCM (→ **60**). Ebendieser wurde mit 20 Mol-% des Grubbs-Katalysators der ersten Generation umgesetzt, woraufhin sich *one pot* die chemoselektive Hydrierung der isolierten Doppelbindung anschloss (→ **61**). Es folgte die Silylentschützung des sekundären Alkohols (→ **62**). Ausgehend vom (*R*)-Kaliumglycidat (**64**) wurde in drei Stufen mittels Epoxid-Öffnung, Veresterung und Tritylentschützung der Ester **67** erhalten, welcher in einer *Thia*-Michael-Addition mit **62** zum Macrolid **63** umgesetzt wurde. Nach saurer

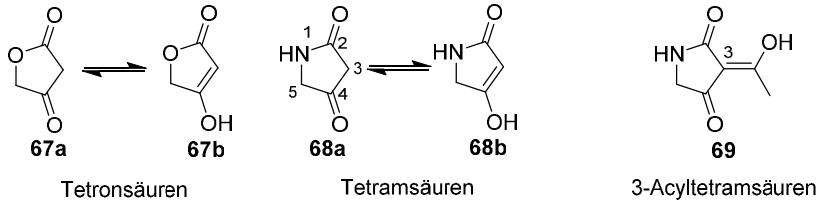
TMSE-Entschützung wurde Berkeleylacton A (**1a**) in 9.5% Ausbeute über zehn Stufen erhalten. Insgesamt wurde bei dieser Synthese auf bereits bestehende A26771B-Synthesen aufgebaut.[67]



SCHEMA 9. Totalsynthese von Berkeleylacton A (**1a**) nach Ferko *et al*.[75]
Reagenzien und Bedingungen: a) Hex-5-en-1-ylmagnesiumbromid, THF, 0 °C → RT, 82%; b) (*R*)-CBS (35 Mol-%), $BH_3{\cdot}Me_2S$, THF, −40 °C, 4 h, 88%, 99% *ee*; c) TBSCl, Imidazol, DMAP, DMF, 0 °C → RT, 5 h, 93%; d) NBS, $NaHCO_3$, AcMe, H_2O, −50 °C, 5 h, dann Pyridin, $NaHCO_3$, RT, 2.5 h, 69%; e) $NaClO_2$, Amylen, Phosphatpuffer, *t*BuOH, H_2O, 4 h, 98%; f) (*R*)-Hept-6-en-2-ol, DCC, DMAP, CH_2Cl_2, 0 °C → RT, 2 h, 67%; g) Grubbs-Kat. 1.Gen. (25 Mol-%), CH_2Cl_2, RT, 4.5 h, dann PtO_2, H_2 (1 atm), RT, 4 h, 45%; h) TFA, CH_2Cl_2, 0 °C → 4 °C, 24 h, 89%; i) NEt_3 (20 Mol-%), CH_2Cl_2, RT, 2 h, 85%, *d.r.* 16:1; j) TFA, CH_2Cl_2, 0 °C, 15 h, 92%, *d.r.* >20:1; k) TrtSH, NaH, THF, 0 °C → RT, 14 h, 73%; l) TMSEOH, DCC, DMAP, CH_2Cl_2, 0 °C, 18.5 h, 23%; m) Et_3SiH, TFA, CH_2Cl_2, 30 min, 73%.

1.3 Wirkstoffe mit Tetramsäure-Motiv

Neben den bisher hauptsächlich behandelten Lactonen bzw. Makrolactonen spielen als bioaktive Moleküle Lactame eine ebenso wichtige Rolle. Im Folgenden sollen die Lactam-abgeleiteten Tetramsäuren mit ihrem Pyrrolidin-2,4-dion-Gerüst bezüglich ihrer Eigenschaften, biologischen Wirkung und Synthese vorgestellt werden. Namensgebend für Tetramsäuren waren die zuvor bekannten strukturnahen Tetronsäuren (**67a**, **67b**) mit einem Lacton-Motiv. Sowohl Tetron- als auch Tetramsäuren wurden von Anschütz *et al.* im frühen 20. Jahrhundert untersucht und es wurden für die Tetramsäuren die in SCHEMA 10 gezeigten tautomeren Strukturen (**68a**, **68b**) vorgeschlagen.[76,77] Die hierzu postulierte Synthese einer Tetramsäure stellte sich jedoch später als Irrtum heraus.[78] Weitaus häufiger als die Pyrrolidin-2,4-dione kommen an 3-Position acylierte Tetramsäuren **69** in der Natur vor.

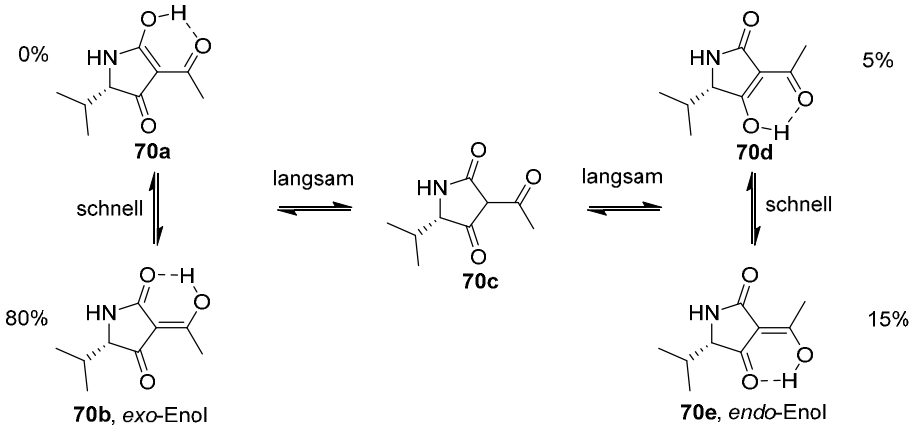


SCHEMA 10. Tautomere Strukturen des Grundgerüsts von Tetram- und Tetronsäuren.[76,77]

1.3.1 Eigenschaften und biologische Wirkung von Tetramsäuren

Die bis heute sowohl aus terrestrischen als auch marinen Quellen, vor allem aber Pilzen (61%), Actinobacteria (19%) und Cyanobakterien (16%, Stand 2020), extrahierten Tetramsäuren lassen sich grob in sieben Klassen einteilen: Makrocyclische Tetramsäuren, *N*-acylierte Tetramsäuren, 3-Decalinoyltetramsäuren, 3-Spirotetramsäuren, α-Cyclopiazonsäure-Tetramsäuren, 3-Acyl-Tetramsäuren sowie Oligoenoyltetramsäuren, wobei die drei erstgenannten 50% der Isolationen (Stand 2020) ausmachten.[79,80] Dennoch gilt zu beachten, dass die meisten Vertreter in den benannten Klassen ebenfalls ein 3-Acyl-Tetramsäure-Motiv (vgl. SCHEMA 10) enthalten.[81,82] 3-Acyl-Tetramsäuren können im Allgemeinen in vier tautomeren Formen vorliegen, welche in SCHEMA 11 gezeigt sind.[83,84] Anders als zuvor angenommen, wurde durch NMR-Experimente sowie Kristallstrukturen bewiesen, dass die *exo*-Enol-Form **70b** in Tetramsäuren am häufigsten vorliegt. Die Umwandlung zwischen *exo*- und *endo*-Form **70e** verläuft aufgrund der nötigen Drehung der mit dem Ring an 3-Position verbundenen Acyl-Gruppe langsam und ist daher mittels NMR beobachtbar. Unter Umständen verläuft die Umwandlung über eine Trioxo-Zwischenstufe **70c**.[84] Dahingegen sind die Tautomere **70a**/**70b**

und **70d**/**70e** schnell ineinander überführbar. Der Anteil der verschiedenen Tautomere ist auch in direkter Abhängigkeit zum verwendeten Lösungsmittel.



SCHEMA 11. Mögliche tautomere Formen von 3-Acetyl-5-isopropylpyrrolidin-2,4-dion (**70**).[84]

Folgen der Tautomerie sind die guten Chelatisierungseigenschaften von Tetramsäuren, z.B. erkennbar an den zahlreichen Komplexen der Tenuazonsäure (**71**/M-**71**).[80,85] Die Metallkomplexe können zum einen für die Wirkung notwendig sein, zum anderen kann auch erst die Komplexbildung im Organismus die Wirkung auslösen. Für letzteres ist Macrocidin A (**52**, vgl. ABB. 7) zu nennen, wobei dessen herbizide Aktivität unter anderem durch dessen Fe-Komplexierung in Schädlingspflanzen ausgelöst wird.[86] Für ersteres wäre die Harziansäure (**72**) anzuführen (ABB. 10), welche nur als Zn^{2+}-Komplex biologische Aktivität zeigt.[87] Ein weiterer Wirkmechanismus von Tetramsäuren kann, wie bei den Tetronsäuren, aufgrund der strukturellen Ähnlichkeit zu Phosphaten die Inhibition von Phosphatasen und Kinasen sein.[80,88] Bekannt sind Tetramsäuren dabei vor allem für deren cytotoxische, antibakterielle, antifungale und antivirale Eigenschaften.[79,81]

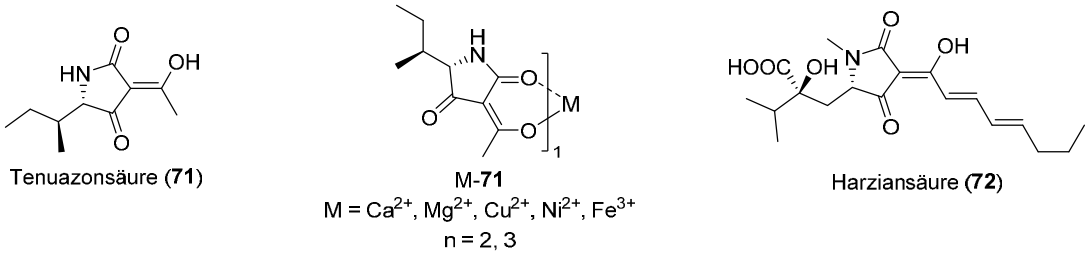


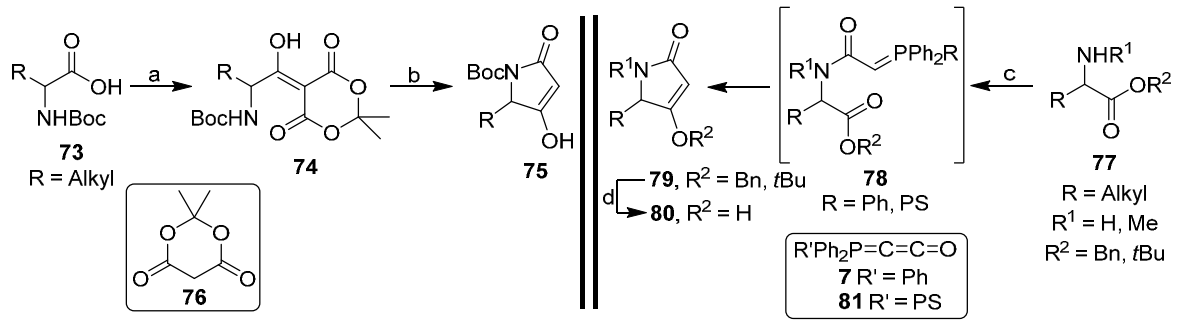
ABBILDUNG 10. Tenuazonsäure (**71**) dessen Metallkomplexe M-**71** und Harziansäure (**72**).

Biosynthetisch gesehen sind für den Aufbau von Tetramsäuren zumeist hybride Polyketidsynthasen und nicht-ribosomale Peptidsynthetasen unter der Verwendung von α-Aminosäuren verantwortlich.[89] Darüber hinaus sind aber auch noch etliche andere für die Biosynthese von Tetramsäuren entscheidende Enzyme, wie Aldolasen oder Diels-Alderasen, literaturbekannt.[90]

1.3.2 Synthesemethoden für Tetramsäuren und 3-Acyl-Tetramsäuren

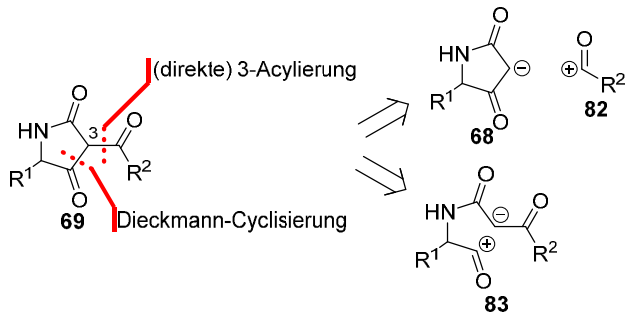
Aufgrund diverser biologischer Eigenschaften, die den Einsatz in Medikamenten ermöglichen, ist der synthetische Zugang zu (3-Acyl-)Tetramsäuren interessant. Dieser wurde wegen einer Fehlinterpretation von Anschütz *et al.* erst deutlich später als 1909 gefunden wurde.[77,78,91] Die Synthesewege zu Tetramsäuren können nochmals zwischen 3-H_2-Tetramsäuren (kein weiterer Substituent an 3-Position außer H) und 3-Acyl-Tetramsäuren unterschieden werden.

Für 3-H_2-Tetramsäuren sind im Wesentlichen zwei Methoden bekannt, welche sich auf sämtliche Problemstellungen bei der Darstellung anwenden lassen. Zunächst wurde eine Synthese unter Verwendung von *N*-Boc-geschützten α-Aminosäuren **73** und Meldrumsäure (**76**) von Jouin *et al.* bekannt.[92] Sie wurde dahingehend verbessert, zur Herstellung des Meldrumsäure-Addukts **74** statt des ungewöhnlichen IPCF-Kupplungsreagenzes auch DCC oder EDC·HCl zu verwenden (SCHEMA 12, links).[92–95] Die darauf folgende thermische Umlagerung führt zu *N*-Boc-geschützten Tetramsäuren **75**. Eine weitere Möglichkeit besteht darin, α-Aminoester **77** mit Ketenylidentriphenylphosphoran (**7**) bzw. mit dessen PS-gebundenen Derivat **81** umzusetzen (SCHEMA 12, rechts).[96–98] In einem weiteren Schritt, je nach Wahl der Schutzgruppe der Carbonsäure (Bn od. *t*Bu), können die 4-*O*-Alkyltetramsäuren **79** hydrogenolytisch oder sauer zu den 3-H_2-Tetramsäuren **80** entschützt werden. Beide Methoden haben die identische Länge bei hohen Ausbeuten und führen nicht zur Racemisierung der α-Amino-Gruppe. Am Ende unterscheiden sich beide Sequenzen vorrangig durch die Möglichkeit einer unterschiedlichen *N*-Substitution (Boc bzw. H/Alkyl).



SCHEMA 12. Möglichkeiten der Darstellung von 3-H_2-Tetramsäuren.[92–98]
Reagenzien und Bedingungen: a) IPCF/DCC/EDC·HCl, Meldrumsäure (**76**), DMAP, CH_2Cl_2, −5 °C – RT, 30 min – ü.N.; b) EtOAc, Δ, 30 min; c) **7**/**81**, PhMe/Xylol/THF, 60 °C – Δ, 10 h – 12 h; d) R = *t*Bu: TFA, RT, 3 h, R = Bn: H_2, Pd/C, MeOH, RT, 2 h.

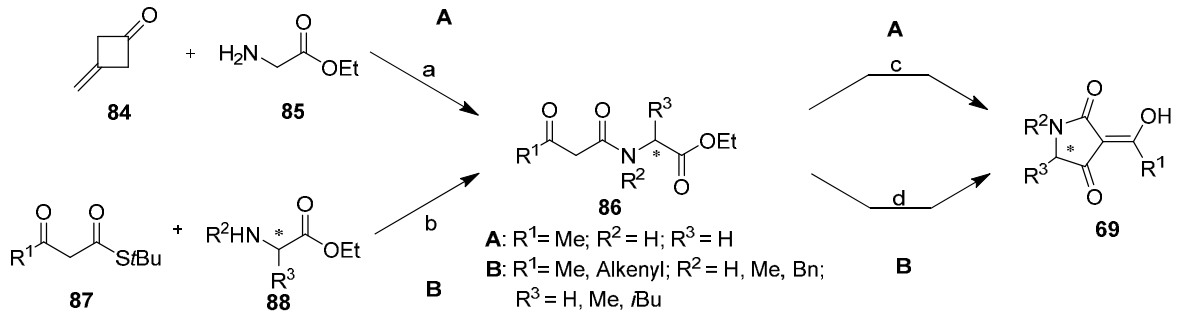
Für die Synthese von 3-Acyl-Tetramsäuren **69** wird wiederum zwischen zwei grundlegenden Möglichkeiten unterschieden (SCHEMA 13). Bekannt sind zum einen direkte 3-Acylierungen mit einer Übertragung eines Acylrestes **82** an 3-Position von 3-H_2-Tetramsäuren **68**. Zum anderen sind ebenso Dieckmann-artige Esterkondensationen (vgl. **83**) möglich. Der Unterschied beider Methoden besteht insbesondere darin, inwiefern und mit welcher Carbonylfunktionalität (einfaches Carbonyl bzw. β-Ketoamid) der Rest R^2 in die Tetramsäure eingeführt werden soll.



SCHEMA 13. Retrosynthetische Betrachtung der 3-Acyl-Tetramsäuredarstellung und die daraus resultierenden Synthone.

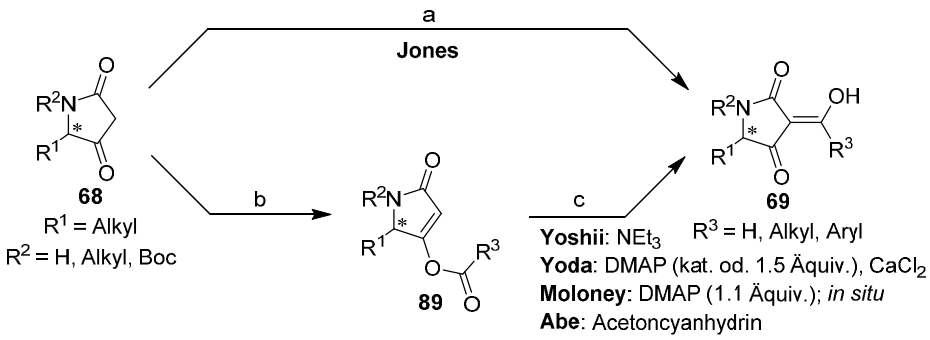
Die als Lacey-Dieckmann-Cyclisierung bekannt gewordene Methode startete ursprünglich ausgehend von Diketen (**84**) und einem α-Aminoester **85**, welche zunächst in das β-Ketoamid **86** überführt wurden (SCHEMA 14, Weg **A**).[91] Durch Baseneinwirkung mittels NaOEt wurde der Ring zur Tetramsäure **69** geschlossen. Probleme bei der Synthese waren zum einen, dass enantiomerenreine α-Aminoester unter den stark basischen Bedingungen racemisieren konnten. Zum anderen war auf der Basis von Diketen (**84**) lediglich ein Acetyl-Substituent an 3-Position möglich. Ley *et al.* verbesserten die Methode, indem der Aufbau des Amids **86** anstatt von

Diketen (**84**) ausgehend von einem β-Ketothioester **87** erfolgte (SCHEMA 14, Weg **B**).[99] Dadurch konnten die Substituenten an 3-Position variiert werden. Für die abschließende Cyclisierung wurden drei Methoden gefunden, bei denen keine ungewollte Racemisierung auftrat. Es war möglich, unter Baseneinwirkung von NaOMe oder KO*t*Bu (in MeOH bzw. *t*BuOH, 5 min, RT) den Ring zu schließen oder besonders mild via TBAF.



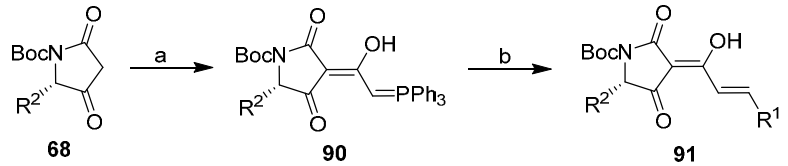
SCHEMA 14. Die von Lacey entwickelte Cyclisierung (Weg **A**) und Verbesserung von Ley (Weg **B**).[91,99] *Reagenzien und Bedingungen*: a) EtOH, <5 °C → RT, 1 h, 87%; b) CF_3COOAg, 4 Å MS, THF, RT, 15 min – 20 h; c) NaOMe, Δ, 3 h, 76%; d) TBAF, THF, RT – Δ, 30 min – 24 h od. KO*t*Bu, *t*BuOH, RT, 30 min, 35 – 92%.

Die zweite in SCHEMA 13 beschriebene Möglichkeit ist die Verknüpfung einer Tetramsäure mit einem Acyl-Rest. Neben der direkten 3-Acylierung von 3-H_2-Tetramsäuren **68** mit Carbonsäurechloriden unter Einwirkung stöchiometrischer Mengen Lewissäure (z.B. $BF_3 \cdot OEt_2$) nach Jones sind auch noch Verfahren mit weniger reaktiven Reagenzien bekannt (SCHEMA 15).[100] Hierzu zählen sämtliche Varianten, welche zunächst ein 4-*O*-Acyl-Derivat **89** darstellen und dieses entweder *in situ* oder in einer weiteren Stufe zur 3-Acyl-Tetramsäure **69** umlagern. Ursprünglich entwickelt von Yoshii[101] mit der am Anfang stehenden Veresterung zur 4-*O*-Acyl-Tetramsäure **89** unter Steglich-Bedingungen, wurde die Methode der darauffolgenden Umlagerung zur 3-Acyl-Tetramsäure **69** durch weitere Arbeitsgruppen aufgrund situationsbedingter Probleme verbessert. Hierbei wären insbesondere Yoda[102] und Moloney[103] zu nennen, aber auch Abe.[104] Die ausschlaggebenden Unterschiede in den Reaktionsbedingungen sind in SCHEMA 15 (Reaktionspfeil c) zu finden. Vor der eigentlichen Methodenentwicklung durch Yoshii berichtete bereits van der Baan über die Darstellung einer Tetramsäure mittels 4-*O*-Acyl-Umlagerung.[105]



SCHEMA 15. Möglichkeiten der 3-Acylierung von 3-H_2-Tetramsäuren **68**.
Reagenzien und Bedingungen: a) R^3COCl, $BF_3{\cdot}OEt_2$, ($MeNO_2$), 75 °C – 100 °C, 1 h – ü.N.; b) z.B. R^3COOH, DCC, DMAP, CH_2Cl_2, RT; c) siehe Abbildung.

Die neueste Entwicklung direkter 3-Acylierungen von 3-H_2-Tetramsäuren **68** sind wiederum in der Arbeitsgruppe Schobert zu finden (SCHEMA 16).[106] Diese entwickelte die Strategie, eine Tetramsäure **68** mit Ketenylidentriphenylphosphoran (**7**) zum Ylen **90** umzusetzen, welches im weiteren Verlauf durch eine Wittig-Reaktion mit einem Aldehyd ein Alken **91** bilden kann. Dies ermöglicht die Darstellung von 3-Enoyltetramsäuren **91**, wobei die neu entstandene Doppelbindung auch mittels Hydrierung entfernt werden kann.



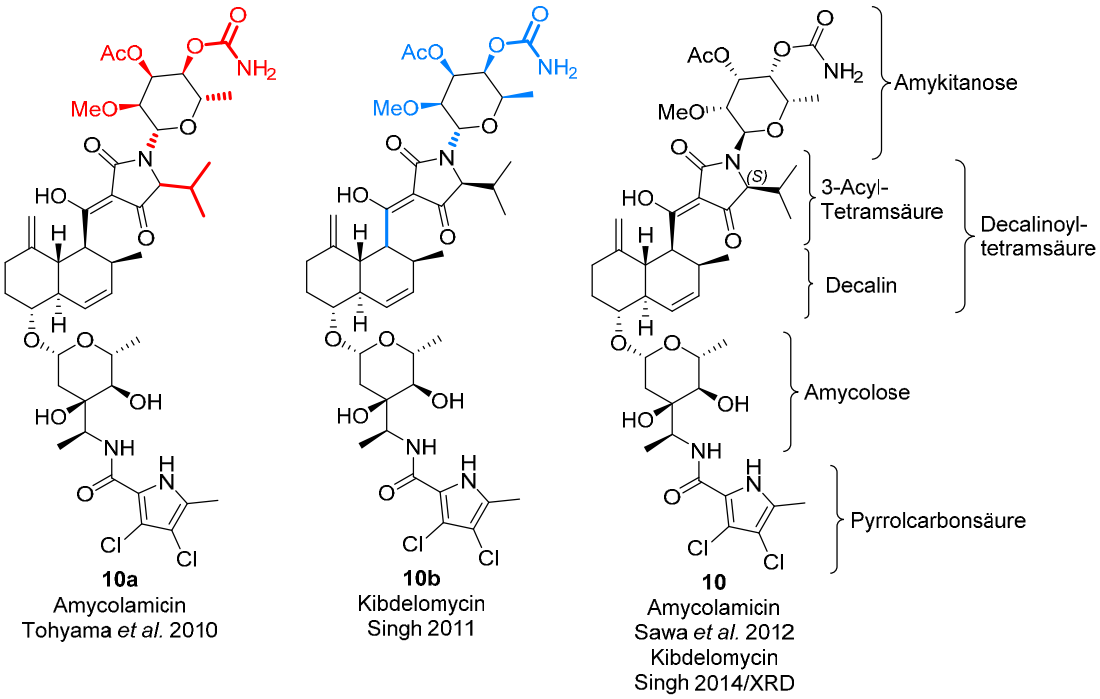
SCHEMA 16. Darstellung von 3-Enoyltetramsäuren **91** nach dem Schobert-Protokoll.[106]
Reagenzien und Bedingungen: a) Ph_3PCCO (**7**), THF, Δ, 16 h, 98% – 99%; b) KO*t*Bu, THF, Δ, 20 min; dann R^1CHO, THF, Δ, 6 h, 62% – 84%.

1.4 Kibdelomycin

1.4.1 Isolation und biologische Wirkung von Kibdelomycin

Die Isolation und Strukturaufklärung von Kibdelomycin (**10**) bzw. dem strukturgleichen Amycolamicin war ein jahrelanger, interessanter Prozess. In einem japanischen Patent aus dem Jahr 2008/2009, in dem das erste Mal die Isolation von Amycolamicin aus dem Bakterium *Amycolatopsis* sp. MK575-fF5 beschrieben wurde, war auch bereits die ausgezeichnete antibiotische Aktivität gegenüber (resistenten) Bakterien bekannt.[107] Trotz der Angabe eines Strukturvorschlags im Patent wurde noch keinerlei Stereoinformation bekannt gegeben. Im Jahr 2010 untersuchte eine aus demselben Forschungszentrum wie die Patentschrift-Ersteller stammende Gruppe die Biosynthese der Amycolose, eine mit dem Decalin-Gerüst *O*-glykosidisch verknüpfte Hexopyranose (vgl. ABB. 11).[108] Dieser an 3-Position α-Aminoethyl-verbrückte Zucker stellte bis dahin ein absolutes Novum dar. Es wurde mittels Verfütterungs-experimenten von ^{13}C-markiertem Pyruvat herausgefunden, dass dieser α-Aminoethyl-Rest durch ein Thiamin-Pyrophosphat-abhängiges Enzym in Form von Pyruvat an die eigentliche Hexose angebracht worden sein muss. Im Zuge dieser Entdeckungen wurde darüber hinaus die stereochemische Form des Amycolamicins (**10a**) angegeben (ABB. 11, links). Nicht bekannt war bis dahin das in der 3-Acyl-Tetramsäure liegende Stereozentrum. Von einer von Merck stammenden Arbeitsgruppe um Singh wurde im Jahr 2009 ein Patent über die Isolation antibiotischer Naturstoffe angemeldet.[109] Mit der Veröffentlichung des Patents parallel zu einem Zeitschriftenaufsatz im Jahr 2011 wurde das durch eine neuartige Screening-Methode aus *Kibdelsporangium* sp. MA 7385 isolierte und zu Amycolamicin (**10a**) ähnliche Kibdelomycin (**10b**, ABB. 11, Mitte) bekannt gegeben.[110] Es unterschied sich durch die Konfiguration der Methyl-Gruppe in der Amykitanose (oberes Zucker-Fragment). Zudem blieb ein Stereozentrum am Decalin-Gerüst unbestimmt. Den nächsten Schritt vorwärts machte ein Jahr später wieder die japanische Gruppe, welche durch über NMR-Spektroskopie und HRMS hinausgehende Analysemethoden die derzeitig anerkannte Struktur von Amycolamicin (**10**) herausfanden (ABB. 11, rechts).[111] Die Unterschiede zur ursprünglichen Form **10a** wurden dazu in ABB. 11 rot gekennzeichnet. Durch chemischen Abbau konnten manche Fragmente zusätzlich analysiert werden. Vom Methyl-Anomer der *N*-acylierten Amycolose wurde eine Kristallstruktur angefertigt und bestätigte dessen Struktur. Mittels Periodat-Spaltung und saurer Hydrolyse konnte das in der Tetramsäure (*S*)-konfigurierte Valin gefunden werden. Die revidierte, absolute Stereokonfiguration der Amykitanose wurde durch den Vergleich der Drehwerte eines Amykitanose-Abbauprodukts mit dem komplementären synthetischen Derivat bestimmt. Die höchste Aussagekraft lieferte die Arbeitsgruppe um Singh, indem sie 2014 Co-

Kristallstrukturen von Kibdelomycin (**10**) mit bakterieller Gyrase B bzw. Topoisomerase IV anfertigten.[112] Dabei musste wiederum die ursprünglich angenommene Struktur von Kibdelomycin (**10b**) revidiert werden (vgl. ABB. 11, blau). Durch XRD-Analyse war die fehlende Stereokonfiguration am Decalin-Gerüst bekannt und es wurde ersichtlich, dass Amycolamicin und Kibdelomycin (**10**) dieselbe Verbindung sind. Strukturell besitzt Kibdelomycin (**10**) zwei Zucker, eine hoch funktionalisierte 6-Deoxytalose, genannt Amykitanose, welche *N*-glykosidisch mit einer 3-Acyl-Tetramsäure verknüpft ist. Diese Tetramsäure hat ihren Ursprung in L-Valin und ist mit einem Decalin-Rest verbunden. Dieser ist durch eine glykosidische Bindung mit der Amycolose verbunden, eine 3-(α-Aminoethyl)-2,6-dideoxyhexopyranose. Die in der Ethyl-Verbrückung sitzende Amino-Gruppe ist mit einer Pyrrolcarbonsäure acyliert. Zusätzlich ist noch Kibdelomycin A bekannt, die an der Pyrrolcarbonsäure demethylierte Form des Kibdelomycins.[113]



10a
Amycolamicin
Tohyama *et al.* 2010

10b
Kibdelomycin
Singh 2011

10
Amycolamicin
Sawa *et al.* 2012
Kibdelomycin
Singh 2014/XRD

ABBILDUNG 11. Verschiedene Strukturannahmen für Amycolamicin und dem strukturgleichen Kibdelomycin (**10**).[108,110–112]

Gut untersucht wurde auch die antibiotische Aktivität vom Kibdelomycin (**10**).[110,111,113,114] Wie andere bekannte Antibiotika der Gyrase-Hemmer-Klasse (ABB. 12) verhindert es negatives *supercoiling* und greift damit direkt in die Raumorientierung der DNA ein. Da die Gyrase ein bakterielles Enzym ist, kann diese selektiv als *target* für antibiotische Wirkstoffe hergenommen werden. Während Fluorchinolone wie Ciprofloxacin (**94**) den beim notwendigen DNA-Doppelstrangbruch entstehenden Enzym-DNA-Komplex stabilisieren und somit die DNA-

Synthese inhibieren, wirken Aminocumarine wie Novobiocin (**92**) in der ATPase-Kavität der ATP-abhängigen Gyrase B und haben schließlich denselben Effekt.[115] Für Kibdelomycin (**10**) wurde schon früh ein zu den Aminocumarinen ähnlicher Wirkmechanismus erkannt. Allgemein wirkt Kibdelomycin (**10**) äußerst gut gegen Gram-positive Bakterien (*S. aureus*, *Streptococcus pneumoniae*, …), selbst bei deren resistenten Erregern (MRSA, VRE, PRSP, ESKAPE), aber auch gegen wenige Gram-negative Bakterien (*Haemophilius influenzae* sowie dessen resistente Formen: BLNAR, BLPACR). Insbesondere aufgrund der hohen Bioaktivität und keinen bekannten Kreuzresistenzen zu anderen Antibiotika ist Kibdelomycin (**10**) als Wirkstoff bzw. als Leitstruktur ein interessanter Kandidat.

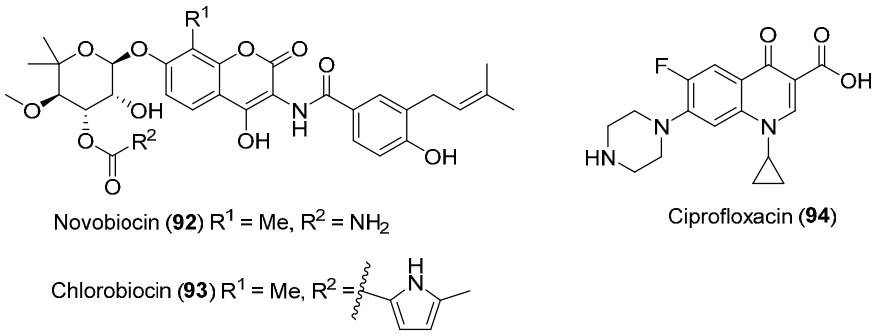


ABBILDUNG 12. Strukturen der Aminocumarin-Antibiotika Novobiocin (**92**) und Chlorobiocin (**93**) sowie Ciprofloxacin (**94**).

Nachdem Singh *et al.* bereits 2012 eine starke Inhibition (IC_{50} = 9 – 60 nM) von bakterieller Gyrase (*S. aureus*, *E. coli*), aber auch eine Hemmung der Topoisomerase IV (*S. aureus*, *E. coli*; IC_{50} = 500 – 29000 nM) gefunden haben, wollten sie in weiteren Studien das exakte molekulare *target* sowie den Bindungsmechanismus finden.[112,113] Hierfür wurden Co-Kristallstrukturen von Gyrase B und Topoisomerase IV mit Kibdelomycin (**10**) und Novobiocin (**92**) aufgenommen. Die Co-Kristallstruktur mit Novobiocin wurde aufgenommen, um einen strukturellen Vergleich mit einem bekannten ATPase-inhibierenden Gyrase-Hemmer ziehen zu können. In ABBILDUNG 13 ist die Gegenüberstellung der beiden Enzym-Ligand-Komplexe zu sehen. Die in diesem Fall gewählte Gyrase B ist in Abhängigkeit der Hydrophobie (Octanol/H_2O) der einzelnen Aminosäuren visualisiert (grün ― hydrophob, rot ― hydrophil).[116] Die Gemeinsamkeit beider Wirkstoffe besteht darin, in die ATP-Bindungstasche (mittiges Loch) einzudringen und das Binden von ATP zu verhindern. Der restliche Teil des Kibdelomycins (**10**, links) liegt in Richtung links oben auf der flexiblen Oberseite der Gyrase B auf. Novobiocin (**92**, rechts) hingegen verläuft strukturell tendenziell nach rechts unten.

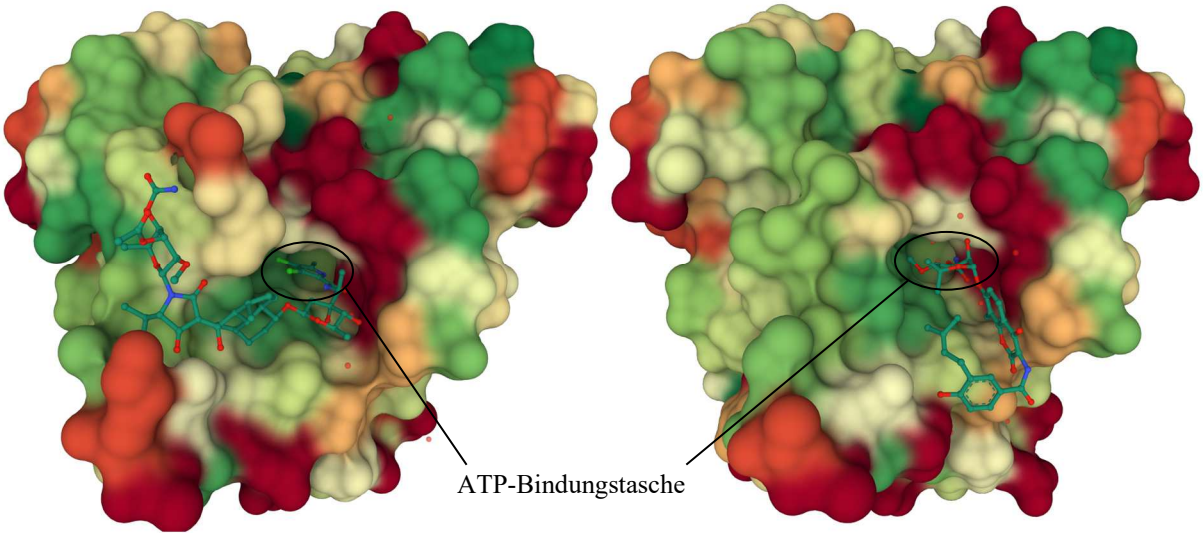


ABBILDUNG 13. Co-Kristallstrukturen von Gyrase B (*S. aureus*) mit Kibdelomycin (**10**, links) bzw. Novobiocin (**92**, rechts). Darstellung der Hydrophophie (Octanol/H_2O; grün: hydrophob; rot: hydrophil) auf den Moleküloberflächen.[112,117,118] Gut erkennbar ist dabei die Penetration der ATP-Bindungstasche (mittiges Loch) bei beiden Wirkstoffen sowie die neuartige Hufeisen-förmige Enzym-Ligand-Bindung des Kibdelomycins (**10**) in einem ganz neuen Bereich der Gyrase.

In Bezug auf die intermolekularen Kräfte sind für die hohe Bindungsaffinität strukturell gesehen vor allem die Tetramsäure-Einheit sowie das Amycolose-Fragment verantwortlich (ABB. 14).[112] Bei der *N*-acylierten Amycolose sind vor allem die hydrophoben Wechselwirkungen der Chloride des Pyrrolamids und der daneben liegenden Methyl-Gruppe mit dem apolaren Teil der Bindungstasche sowie das Pyrrol-*N* und das Amid-*O* mit deren H-Brücken entscheidend. Ebenso wird der sekundäre freie Alkohol in der Hexose durch eine H-Brücke fixiert. Das daran verknüpfte Decalin tritt nur durch van-der-Waals-Wechselwirkungen mit den in der Nähe liegenden apolaren Aminosäuren (Ala, Ile, Val) in Erscheinung. Die wiederum am Decalin gebundene Tetramsäure bildet auf einem sehr kleinen Raum viele verschiedene Wechselwirkungen aus. Zu nennen wären hierbei ausgehend von allen drei im Tetramsäure-Motiv vorkommenden Sauerstoffen H-Brücken sowie mögliche hydrophobe und ionische Wechselwirkungen. Die *N*-glykosylierte Amykitanose sitzt an einem sehr flexiblen Teil des Proteins, wodurch intermolekulare Kräfte nicht genau bekannt sind. Dennoch hat dieser obere Teil des Moleküls einen weiteren wichtigen Effekt für den dualen Wirkmechanismus von Kibdelomycin (**10**), indem es durch das Aufliegen auf der äußeren Oberfläche die für die Aktivität des Enzyms notwendige Gyrase B-Dimerisierung erschwert. Bei Kibdelomycin (**10**) ist dementsprechend nicht nur das Blockieren der ATP-Bindungstasche wie bei vielen anderen Gyrase-Hemmern, sondern noch ein weiterer Effekt für dessen antibiotische Wirkung verantwortlich. Dieser duale Mechanismus spielt auch eine große Rolle für das Ausbleiben von Kreuzresistenzen gegenüber beispielsweise Novobiocin (**92**).

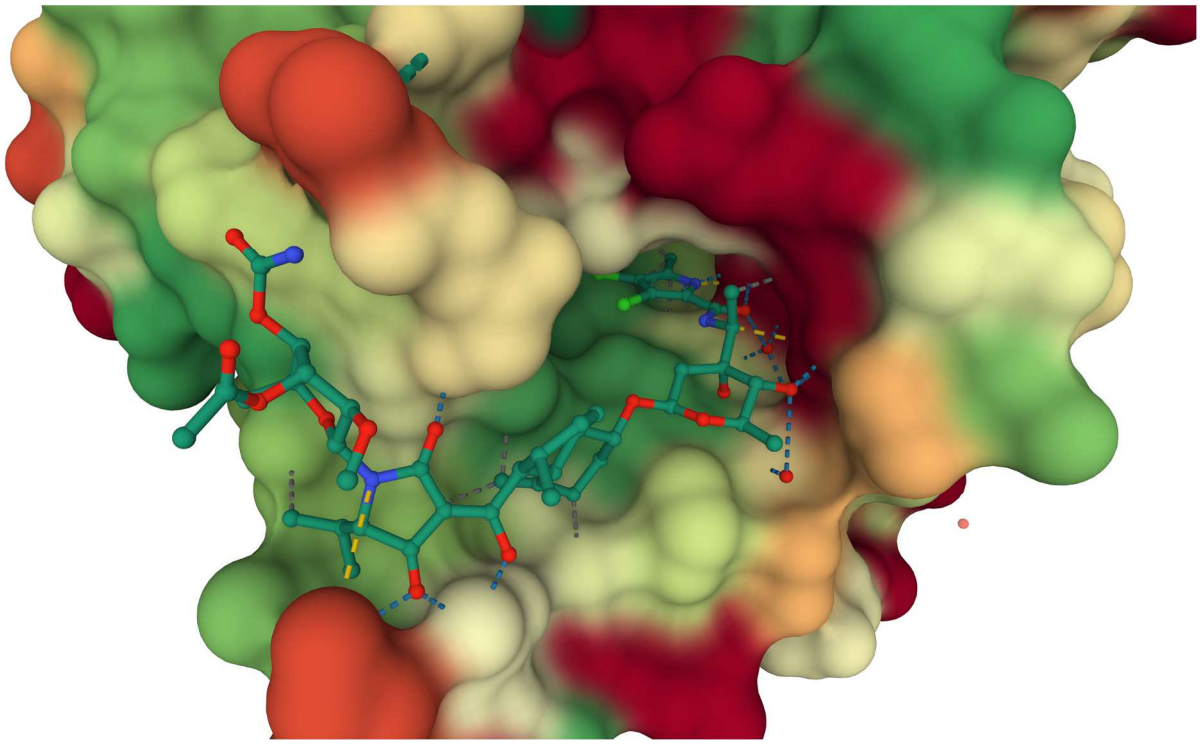
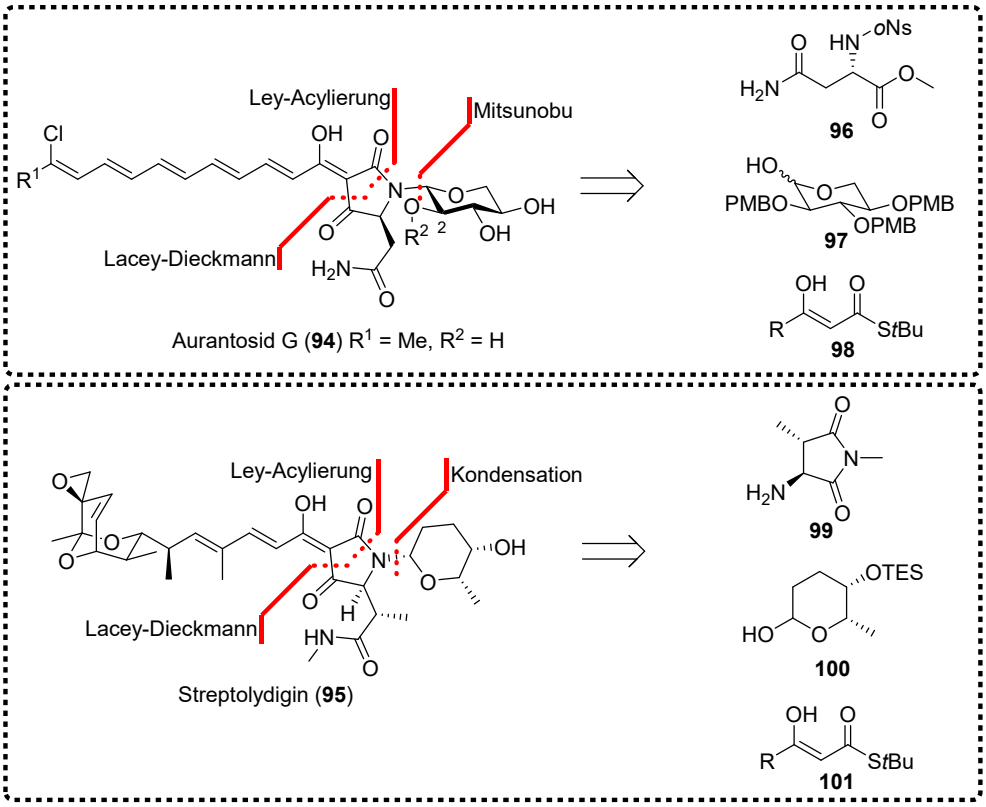


ABBILDUNG 14. Co-Kristallstrukturen von Gyrase B (*S. aureus*) und Kibdelomycin (**10**) mit den nicht-kovalenten Wechselwirkungen: ionisch (gelb gestrichelt), H-Brückenbindungen (blau gestrichelt), hydrophobe Wechselwirkungen/van der Waals (grau gestrichelt). Darstellung der Hydrophophie (Octanol/H_2O; grün: hydrophob; rot: hydrophil) auf den Molekülоberflächen.[112,118] Auffällig sind die wenigen Wechselwirkungen ausgehend vom Amykitanose-Fragment (linke Molekülseite).

1.4.2 Natürliche *N*-glykosylierte 3-Acyl- sowie Decalinoyltetramsäuren und deren Darstellung

Während Decalinoyltetramsäuren einen sehr großen Teil der bekannten Tetramsäure-Naturstoffe ausmachen, sind für *N*-glykosylierte Tetramsäuren kaum Beispiele bekannt. Genannt werden können die strukturell ähnlichen Aurantoside und Rubroside sowie Streptolydigin (**95**).[119] Noch seltener in der Literatur vorzufinden sind Totalsynthesen ebensolcher Naturstoffe. Hierbei sind nur insgesamt zwei Beispiele von Aurantosid G (**94**) und Streptolydigin (**95**) bekannt (SCHEMA 17).[120,121] Aurantosid G (**94**) ist der strukturell einfachste Vertreter der Aurantosid-Klasse. Andere Aurantoside besitzen ein ausgedehnteres (chloriertes) konjugiertes Doppelbindungssystem (R^1 = Alkenyl) oder weitere in 2-Position glykosylierte Zucker (R^2 = Glykosid, SCHEMA 17). Die *N*-Glykosylierung der Tetramsäure-Einheit war bei beiden Synthesen eine Schlüsselreaktion. Die darauffolgenden Schritte der Cyclisierung zur Tetramsäure waren mit *N*-Acylierung nach Ley und Lacey-Dieckmann-Cyclisierung identisch. Für die *N*-Glykosylierung mit den Aminosäure-Fragmenten **96** bzw. **99** hingegen wurden verschiedene Wege gewählt. In der Synthese des Aurantosid G (**94**) wurde in einer Mitsunobu-

Reaktion das Sulfonamid **96** mit dem geschützten Glykosid **97** gekuppelt, aber vorerst das falsche Anomer erhalten. Dieses wurde im Laufe der Synthese noch in das richtige überführt. Bei der Streptolydigin-Synthese wurde sich zu Nutze gemacht, die natürliche Aminosäure erst zum Asparaginsäure-abgeleiteten Succinimid **99** umzusetzen, welches dann bereits in einer simplen Kondensation mit dem Zucker **100** reagierte.



SCHEMA 17. Retrosynthese der Tetramsäure-Einheit von Aurantosid (**94**) und Streptolydigin (**95**).[120,121]

Für die Synthese von Decalinoyltetramsäuren wurden bereits oft biomimetische Verfahren zum Aufbau des Decalin-Gerüsts in Form einer intramolekularen Diels-Alder-Reaktion (IMDA) angewendet. Als Beispiel wären hier unter anderem Hymenosetin (**102**) und die Spirotetramsäure Spiroscytalin (**103**) zu nennen (ABB. 15).[122,123]

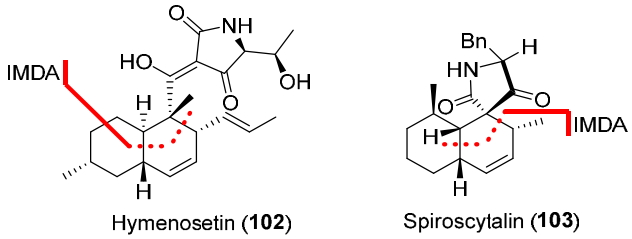
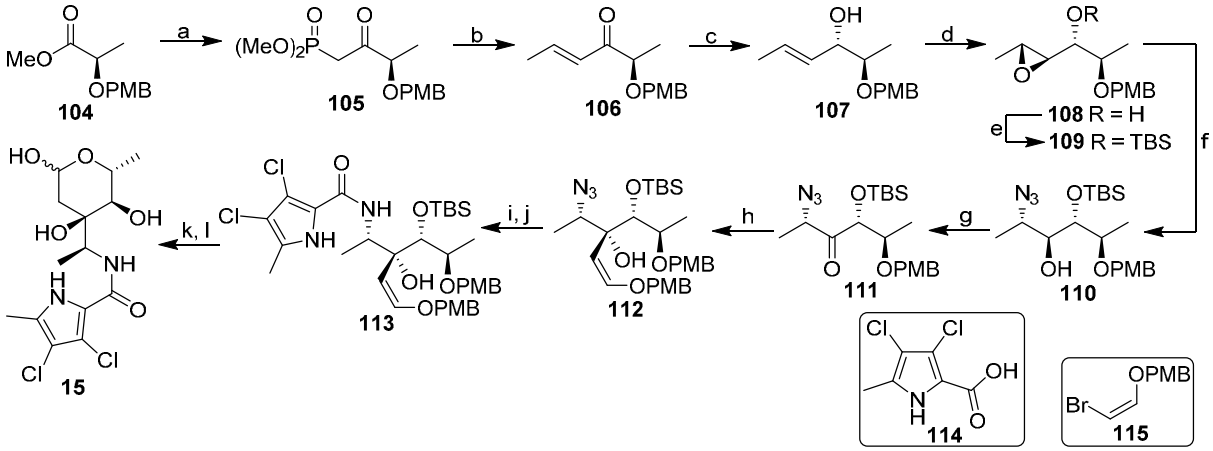


ABBILDUNG 15. Retrosynthese der Decalin-Einheit von Hymenosetin (**102**) und Spiroscytalin (**103**).[122,123]

1.4.3 Synthetische Arbeiten zu Kibdelomycin

1.4.3.1 Synthese des *N*-acylierten Amycolose-Fragments 15

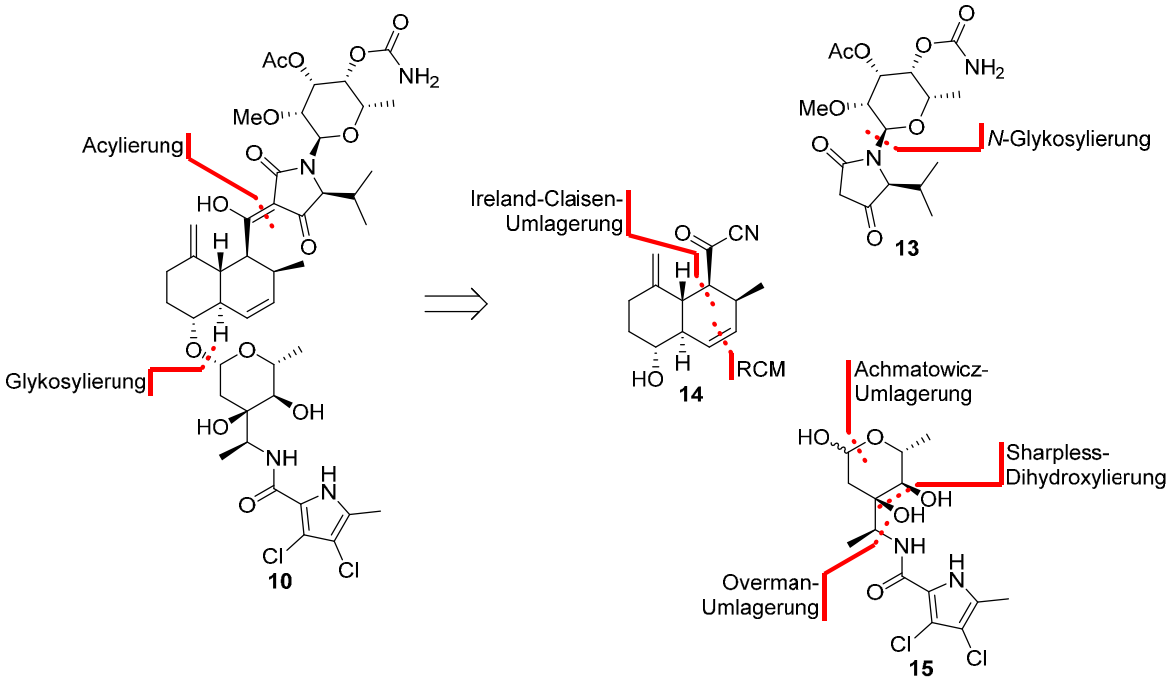
Die ersten synthetischen Arbeiten zu einem Kibdelomycin-Fragment wurden durch Meguro *et al.* bekannt.[124] Diese synthetisierten in zwölf Stufen die *N*-acylierte Amycolose **15** ausgehend vom PMB-geschützten Milchsäuremethylester (**104**, SCHEMA 18). Die Sequenz wurde durch einen nucleophilen Angriff eines deprotonierten Methylphosphonats an Ester **104** gestartet, um das β-Ketophosphonat **105** darzustellen. Dieses wurde in einer HWE-Olefinierung zum α,β-ungesättigten Keton **106** umgesetzt, welches diastereoselektiv zum Allylalkohol **107** reduziert wurde. Die asymmetrische Sharpless-Epoxidierung führte in lediglich 56% Ausbeute zum Epoxid **108** nach Abtrennung des zweiten unerwünschten Diastereomers. TBS-Schützung der freien Hydroxy-Gruppe und Öffnung des Epoxids mit NaN_3 lieferte das Azid **110**. Der Alkohol wurde einer DMP-Oxidation unterzogen und das resultierende Keton **111** mit dem lithiierten Enolether **115** angegriffen. Das Pyrrolamid **113** wurde mittels Freisetzung des Amins durch Staudinger-Reaktion und anschließender Amidierung gewonnen. Die finalen Stufen waren die saure Entschützung der beiden PMB-Gruppen sowie die Abspaltung der TBS-Gruppe mit TBAF. Insgesamt wurde hierbei eine Gesamtausbeute von 13% über zwölf Stufen erzielt. Darüber hinaus wurde auch noch eine Synthese der beiden Methyl-Anomere der *N*-acylierten Amycolose (**15**) gezeigt (nicht abgebildet).



SCHEMA 18. Erster synthetischer Zugang zur *N*-acylierten Amycolose **15**.[124]
Reagenzien und Bedingungen: a) $(MeO)_2P(O)Me$, *n*BuLi, THF, −78 °C → RT, 24 h, 98%; b) MeCHO, LiCl, DIPEA, THF, 0 °C, 24 h, 89%; c) $Zn(BH_4)_2$, THF, −20 °C, 2.5 h, 77%; d) TBHP, (−)–DIPT, $Ti(OiPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 56%; e) TBSCl, Imidazol, DMAP, CH_2Cl_2, 0 °C → RT, 4 h, quant.; f) NaN_3, $Me_3N{\cdot}HCl$, aq. EtOH, 100 °C, 7 d, 57%; g) DMP, Pyridin, CH_2Cl_2, RT, 1 h, 99%; h) *t*BuLi, **115**, dann **111**, Et_2O, −78 °C, 30 min, 84%; i) nBu_3P, MeOH, RT, 12 h; j) **114**, EDC·HCl, HOBt, NEt_3, CH_2Cl_2, 0 °C → RT, 2 h, 96% (2 Stufen); k) TFA, CH_2Cl_2, −20 °C → RT, 3 h, 83%; l) TBAF, THF, RT, 12 h, 94%.

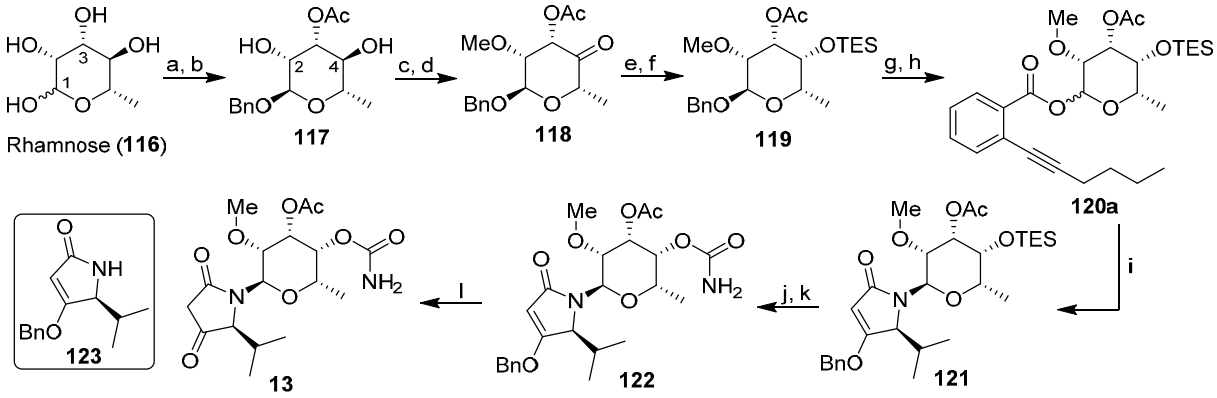
1.4.3.2 Totalsynthese von Kibdelomycin (10) nach Yang *et al.*

Die erste Totalsynthese Kibdelomycins (**10**) stammt von Yang *et al.* und wurde im Dezember 2021 veröffentlicht.[125] Es wurde eine konvergente Synthesestrategie gewählt und das Molekül **10** in die drei Hauptfragmente **13**, **14**, und **15** geteilt (SCHEMA 19). Für das Zusammenfügen der Teile war letztlich die Glykosylierung des Decalins **14** mit der *N*-acylierten Amycolose **15** und darauffolgende 3-Acylierung der 3-H_2-Tetramsäure **13** mit dem Acylcyanid notwendig.



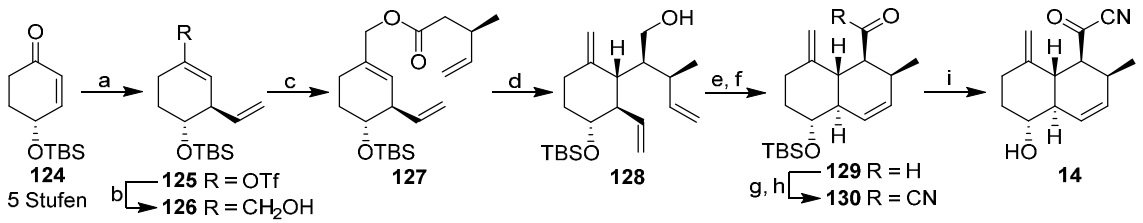
SCHEMA 19. Retrosynthese des Kibdelomycins (**10**) nach Yang *et al.*[125]

Für die Synthese der *N*-glykosylierten Tetramsäure **13** wurde L-Rhamnose (**116**) als Edukt genutzt und zunächst an der anomeren Position Benzyl-geschützt sowie an 3-Position regioselektiv acetyliert (→ **117**, SCHEMA 20).[125] Daraufhin wurde die 4-Position regioselektiv oxidiert und die 2-Position methyliert (→ **118**). Das Keton **118** wurde diastereoselektiv reduziert und Silyl-geschützt, was die an 4-Position invertierte Talose-abgeleitete Verbindung **119** lieferte. Durch hydrogenolytische Abspaltung der anomeren Benzylgruppe und Steglich-Veresterung wurde der Benzoesäureester **120a** erhalten. Unter Au-Katalyse konnte die 4-*O*-Benzyltetramsäure **123** mit dem aktivierten Zucker **120a** glykosyliert werden. Nach TES-Entschützung wurde die Carbaminsäure **122** gebildet. Die letzte Stufe stellte die Benzyl-Entschützung der alkylierten Tetramsäure dar (→ **13**).



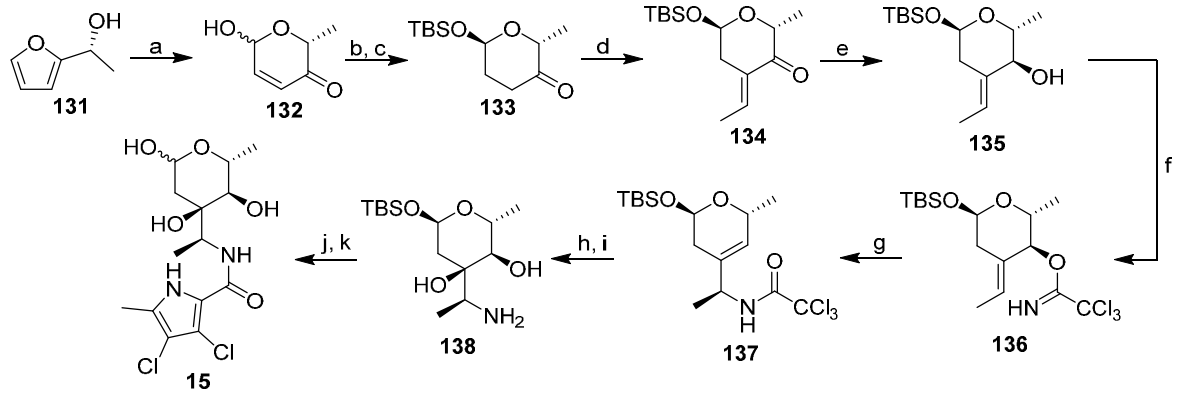
SCHEMA 20. Synthese der *N*-glykosylierten Tetramsäure **13**.[125]
Reagenzien und Bedingungen: a) BnOH, NH_2SO_3H, 80 °C, 21 h, 82%, α/β 7.7:1; b) AcCl, $MoO_2(acac)_2$, 2,4,6-Collidin, 1,4-Dioxan, 0 °C → RT, 4 h, 79%; c) [(Neocuproin) $Pd(OAc)]_2(OTf)_2$, 2,6-Diisopropylphenol, O_2, MeCN, 50 °C, 20 h, 78%; d) Me_3OBF_4, Protonenschwamm, CH_2Cl_2, 0 °C → RT, 12 h, 70%; e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −20 °C, 30 min, 76%; f) TESOTf, Pyridin, CH_2Cl_2, 0 °C, 2 h, 95%; g) H_2, Pd/C, EtOAc, RT, 19 h; h) 2-(Hex-1-in-1-yl)-benzoesäure, DCC, DMAP, CH_2Cl_2, 0 °C → RT, 4 h, 65% (2 Stufen); i) **123**, PPh_3AuNTf_2, PhMe, 40 °C, ü.N., 64%; j) $LiBF_4$, MeCN, H_2O, 4 °C, 36 h; k) Trichloracetylisocyanat, CH_2Cl_2, 0 °C → RT, 1 h, dann NEt_3, MeOH, 0 °C → RT, 2 h, 78% (2 Stufen); l) H_2, Pd/C, EtOAc, 2 h, 96%.

Die Synthese des Decalin-Fragments **14** wurde ausgehend vom literaturbekannten Cyclohexanon **124** gestartet, welches zuvor über fünf Stufen hergestellt wurde (SCHEMA 21).[125] Mittels einer vinylogen Grignard-Addition und dem Abfangen mit dem Comins-Reagenz wurde das Triflat **125** erhalten. Dieses wurde mittels Stille-Kupplung zum primären Alkohol **126** umgesetzt und zur Verbindung **127** verestert. Durch Ireland-Claisen-Umlagerung und anschließender Reduktion wurde der Alkohol **128** erhalten. Ringschlussmetathese der monosubstituierten Olefine und Parikh-Doering-Oxidation des primären Alkohols führten zum Aldehyd **129**, welcher mit TMSCN zum Cyanohydrin überführt und schlussendlich durch IBX zum Acylcyanid **130** oxidiert wurde. TBS-Entschützung lieferte das Decalin-Fragment **14**.



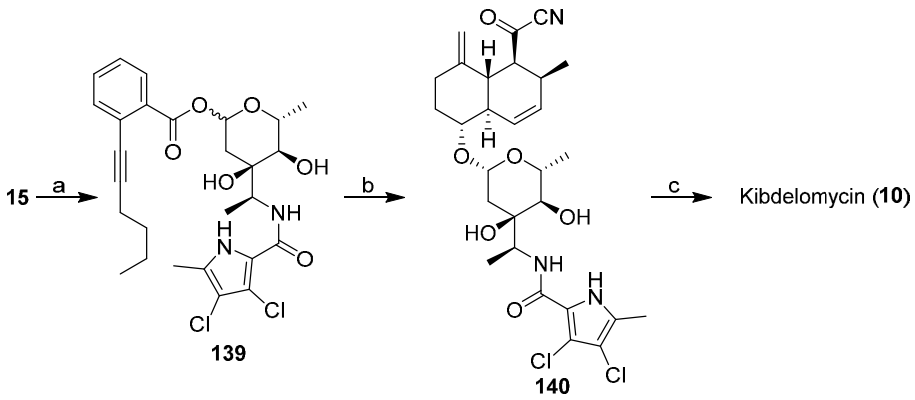
SCHEMA 21. Synthese des Decalin-Fragments **14**.[125]
Reagenzien und Bedingungen: a) CuI, Me_2S, VinylMgBr, THF, −78 °C, 3 h, dann Comins-Reagenz, RT, 18 h, 68%; b) $Pd(PPh_3)_4$, LiCl, nBu_3SnCH_2OH, THF, 70 °C, 3 h, 87%; c) (*R*)-3-Methylpent-4-ensäure, EDC·HCl, DMAP, NEt_3, CH_2Cl_2, RT, 5 h, 92%; d) TBSOTf, NEt_3, CH_2Cl_2, −78 °C, 30 min, RT, 30 min, dann 55 °C, 60 h, dann DIBAL, 0 °C → RT, 2 h, 85%; e) Grubbs-Kat. 2. Gen., CH_2Cl_2, Δ, 3 h, 92%; f) SO_3·Pyridin, NEt_3, DMSO, CH_2Cl_2, RT, 3 h, 77%; g) TMSCN, NEt_3, CH_2Cl_2, 0 °C → RT, 12 h, dann NH_4F, EtOH, 0 °C, 2 h, 84%; h) IBX, EtOAc, 80 °C, 2 h, 83%; i) $LiBF_4$, MeCN, H_2O, 96%.

Die *N*-acylierte Amycolose **15** wurde gänzlich anders synthetisiert als bereits vorher von Meguro *et al.*[125] Begonnen wurde ausgehend vom Furylethanol **131**, welcher in einer Achmatowicz-Reaktion zum Pyran **132** umgelagert, danach anomer TBS-geschützt und hydriert wurde (→ **133**, SCHEMA 22). Anschließend wurde in einer Aldol-Kondensation das α,β-ungesättigte Keton **134** dargestellt, welches diastereoselektiv zum Alkohol **135** reduziert wurde. Installation eines Trichloracetimidats (→ **136**) und Overman-Umlagerung führten zum Allylamid **137**. Die dreifach substituierte Doppelbindung wurde in einer asymmetrischen Sharpless-Dihydroxylierung in ein Diol überführt. Durch DIBAL wurde das Trichloracetat abgenommen und das Amin **138** freigesetzt, aus welchem mittels Amidierung und anomerer TBS-Entschützung die *N*-acylierte Amycolose **15** synthetisiert wurde.



SCHEMA 22. Synthese der *N*-acylierten Amycolose **15**.[125]
Reagenzien und Bedingungen: a) NBS, $NaHCO_3$, NaOAc, THF, H_2O, 0 °C, 1 h; b) TBSOTf, DIPEA, CH_2Cl_2, −78 °C, 1 h, 70% (2 Stufen); c) H_2, Pd/C, EtOAc, RT, ü.N., quant., α:β 4/1; d) KHMDS, PhMe, −78 °C, 1 h dann $ZnBr_2$, THF, 1 h, dann MeCHO, −78 °C → 0 °C, 1 h, dann TFAA, Pyridin, dann DBU, 0°C → −20 °C, 1 h, 90%; e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h, 69%; f) CCl_3CN, DBU, CH_2Cl_2, 0 °C, ü.N.; g) K_2CO_3, *p*-Xylol, Δ, 8 h; h) $K_2OsO_4 \cdot 2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH, H_2O, RT, 1 d, 44% (3 Stufen); i) DIBAL, PhMe, −78 °C, 1 h; j) **114**, EDC·HCl, HOBt, NEt_3, CH_2Cl_2, 0 °C → RT, ü.N., 57% (2 Stufen); k) HCl aq., THF, RT, 3 h, 83%.

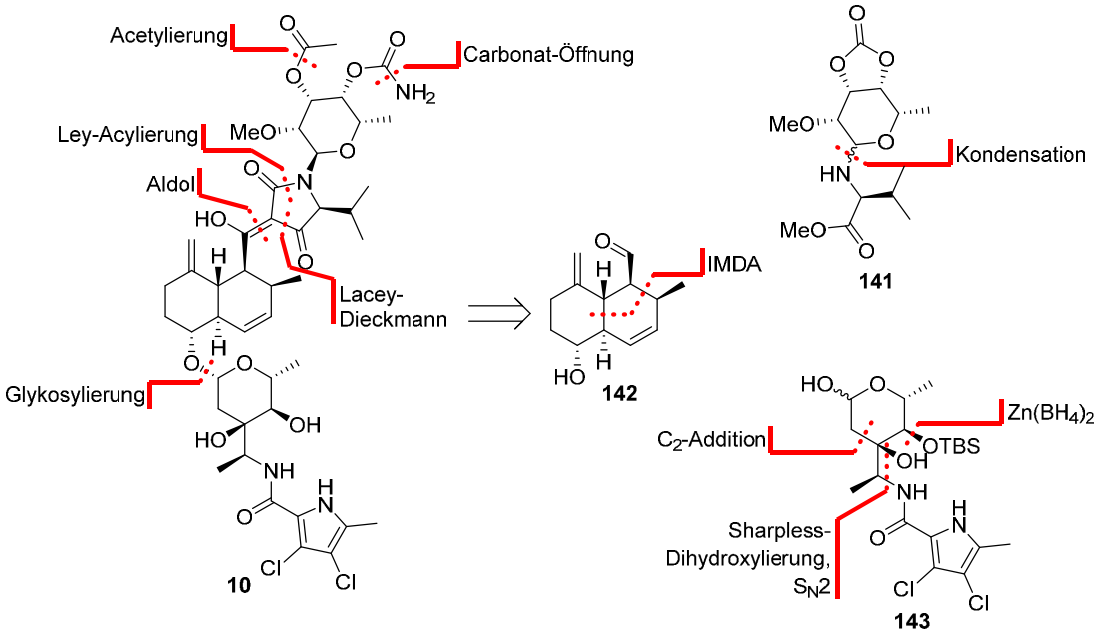
Die finalen Schritte bestanden darin, die einzelnen Fragmente zusammenzufügen (SCHEMA 23).[125] Dafür wurde ähnlich zur *N*-Glykosylierung der Benzoesäureester **139** der *N*-Acyl-Amycolose **15** hergestellt, welcher mit dem Decalin-Fragment **14** unter Au-Katalyse und Zusatz von $Gd(OTf)_3$ hauptsächlich zum β-Anomer **140** (β/α 4:1) reagierte. Der letzte Schritt war die bis dato unbekannte Möglichkeit einer direkten 3-Acylierung der 3-*H*$_2$-Tetramsäure **13** mit dem Acylcyanid **140** durch HOAt und NEt_3 zum Kibdelomycin·NEt_3-Addukt. Für analytisch reines Kibdelomycin (**10**) wurde diese Substanz noch mit 0.01N HCl behandelt und mittels präparativer HPLC aufgereinigt.



SCHEMA 23. Letzte Schritte zur Synthese von Kibdelomycin (**10**).[125]
Reagenzien und Bedingungen: a) 2-(Hex-1-in-1-yl)-benzoesäure, EDC·HCl, DMAP, CH_2Cl_2, 0 °C → RT, 3 h, 80%, α/β 1:2; b) **14**, PPh_3AuOTf, $Gd(OTf)_3$, 4 Å MS, PhMe, MeCN, −78 °C, 7 h, 67%, α/β 1:4; c) **13**, HOAt, NEt_3, CH_2Cl_2, 35 °C, 3 d; (42% Kibdelomycin·NEt_3, 8% Kibdelomycin, NMR-Ausbeute).

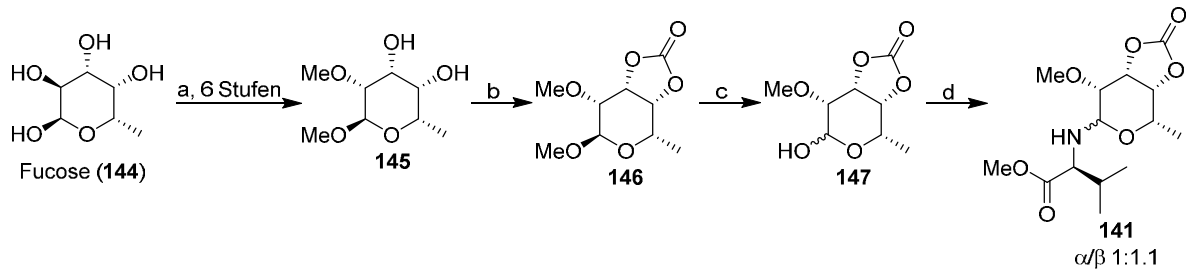
1.4.3.3 Totalsynthese von Kibdelomycin (10) nach Meguro *et al.*

Die wenige Wochen nach der Erstsynthese publizierte Totalsynthese von Meguro *et al.* zeichnet sich ebenfalls durch die konvergente Syntheseplanung aus, wenn auch noch wesentlich mehr Modifikationen nach dem Zusammenfügen der einzelnen Fragmente **141**, **142** und **143** verglichen mit Yang *et al.* durchzuführen waren (SCHEMA 24).[126] Die *N*-Acyl-Amycolose **143** wurde *O*-glykosidisch mit dem Decalin-Fragment **142** verknüpft, woraufhin aus dessen Aldehyd-Funktion ein β-Ketothioester mittels Aldol-Reaktion generiert wurde. Die Synthese des Amykitanose-Bausteins **141** zeichnete sich durch die Kondensation der Methyl-veresterten Aminosäure mit dem korrespondierenden Zucker aus. Dieses Aminoglykosid **141** musste durch Ley-Acylierung mit dem vorher benannten β-Ketothioester in ein β-Ketoamid überführt werden, welches zur 3-Acyl-Tetramsäure nach Lacey-Dieckmann cyclisiert wurde (vgl. retrosynthetische Schnitte SCHEMA 24). Ab diesem Punkt waren noch weitere Syntheseschritte am Amykitanose-Fragment in Form einer Öffnung des Carbonats und Acetylierung notwendig. Die Schlüsselschritte der Synthesen der einzelnen Fragmente hoben sich von denen von Yang *et al.* deutlich ab. Der Decalin-Baustein wurde durch eine IMDA aufgebaut. Bei der Synthese der *N*-acylierten Amycolose **143** wurde weitgehend dem von dieser Arbeitsgruppe veröffentlichten und in 1.4.3.1 beschriebenen Protokoll gefolgt.



SCHEMA 24. Retrosynthese der Kibdelomycin-Synthese nach Meguro *et al.*[126]

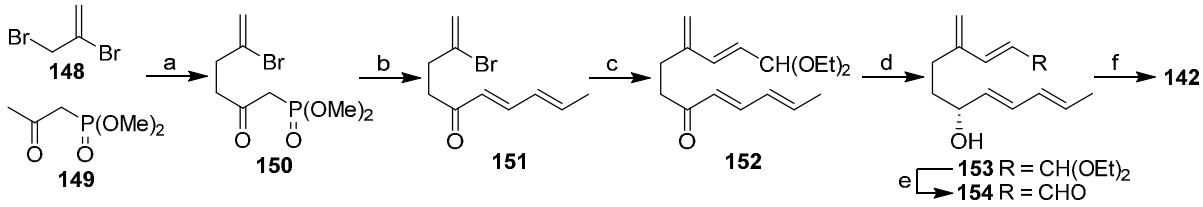
Für die Darstellung des Amykitanose-Fragments **141** wurde zunächst die Synthese von Sawa *et al.*[111] bzw. Takagi *et al.*[127] beginnend von wenig preiswerter L-Fucose (**144**) adaptiert (SCHEMA 25). Sawa *et al.* nutzten die Synthese der Talose **145** 2012 zur Strukturaufklärung der Amykitanose in Amycolamicin. Die doppelt methylierte Talose **145** wurde mit CDI zum Carbonat **146** umgesetzt, welches nach anomerer Entschützung (→ **147**) mit L-Valin-methylester kondensiert wurde (→ **141**).[126]



SCHEMA 25. Synthese des Glykosid-Fragments **141**.[126]
Reagenzien und Bedingungen: a) Ref.[111,127]; b) CDI, Imidazol, THF, 0 °C → RT, 12 h, 79%; c) $TiBr_4$, CH_2Cl_2, EtOAc, 0 °C → RT, 15 h, 80% (α/β 94:6, NMR); d) L-Val-OMe, PPTS, CH_2Cl_2, RT, 2 d, 91% (α/β 48:52, NMR).

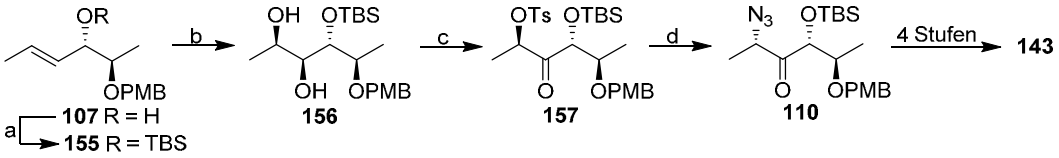
SCHEMA 26 zeigt die Synthese des Decalin-Fragments **142**.[126] Zunächst wurde das Phosphonat **149** an terminaler Stelle mit dem Allylbromid **148** alkyliert. Durch HWE-Reaktion mit Crotonaldehyd wurde das α,β,γ,δ-ungesättigte Keton **151** aufgebaut, welches in einer Heck-Kupplung mit Acroleindiethylacetal in das Tetraen **152** überführt wurde. CBS-Reduktion baute

stereoselektiv die Hydroxy-Gruppe auf (→ **153**). Durch saure Hydrolyse des Acetals wurde das Aldehyd **154** freigesetzt, welches in einer IMDA zum Decalin **142** umgesetzt wurde.



SCHEMA 26. Synthese des Decalin-Fragments **142**.[126]
Reagenzien und Bedingungen: a) **149**, NaH, THF, 0 °C, 1.5 h, dann *n*BuLi, 1 h, dann **148**, −40 °C, 1 h; b) LiBr, NEt_3, THF, RT, 1 h, dann (*E*)-2-Butenal, 6 h, 51% (2 Stufen, *E*/*Z* 19:1); c) Acroleindietyhlacetal, $Pd(OAc)_2$, K_2CO_3, DMF, 40 °C, 3 d, 76%, *E*/*Z* 16:1; d) (*S*)-Me-CBS-Kat. (2 Äquiv.), BH_3·THF, THF, −78 °C → −40 °C, 3 h, 95%, 96% *ee*; e) HCl aq., THF, 0 °C, 30 min; f) Et_2AlCl, CH_2Cl_2, −20 °C → 0 °C, 9 h, 71% (2 Stufen).

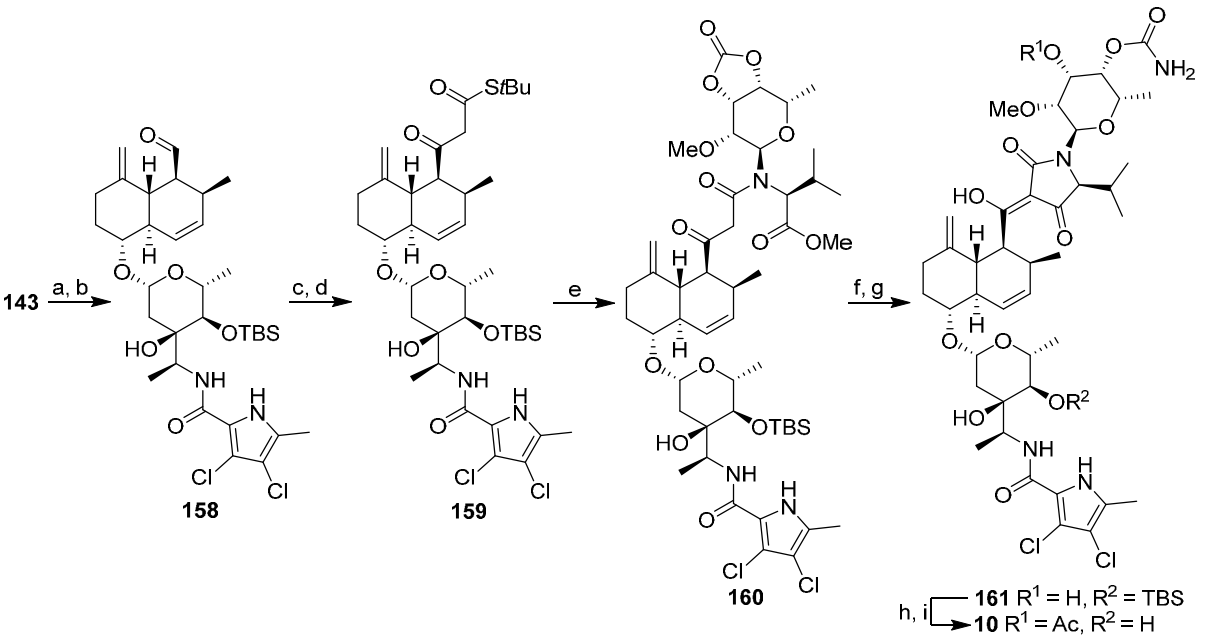
Meguro *et al.* überarbeiteten die Synthese der *N*-acylierten Amycolose **143** von 2019, indem sie an dem bekannten Allylalkohol **107** zunächst eine TBS-Schützung durchführten und die weitere Stereoinformation durch asymmetrische Sharpless-Dihydroxylierung anstatt Sharpless-Epoxidierung einführten (→ **156**, SCHEMA 27).[124,126] Dadurch wurde der ausbeutearme Epoxidierungsschritt umgangen. Die beiden Hydroxy-Gruppen wurden durch regioselektive Tosylierung mit anschließender DMP-Oxidation diskriminiert. S_N2-Reaktion des Tosylats **157** mit NaN_3 führte zum bekannten Azid **110**, aus welchem in vier Stufen das Amycolose-Derivat **143** synthetisiert werden konnte.



SCHEMA 27. Überarbeitete Synthesesequenz für die TBS-geschützte *N*-acylierte Amycolose **143**.[126]
Reagenzien und Bedingungen: a) TBSCl, DMAP, Imidazol, CH_2Cl_2, 0 °C → RT, 14 h, 95%; b) AD-Mix β, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C, 48 h, 94%; c) TsCl, NEt_3, NMe_3·HCl, CH_2Cl_2, 0 °C, 40 min, dann DMP, 0 °C, 1 h, 81%; d) NaN_3, DMF, RT, 30 min, 98%.

Während der darauffolgenden Kupplung des Amycolose-Derivats **143** mit dem Decalin-Fragment **142** sollte zur Aktivierung des Zuckers ein Trichloracetimidat verwendet werden (SCHEMA 28).[126] Ungewöhnlicherweise bildete sich im ersten Schritt aus dem Amid-*NH* der α-Aminoethyl-Verbrückung mit der anomeren Position *in situ* ein *N*,*O*-Acetal, welches aber in einem zweiten Schritt mit dem Alkohol **142** unter TfOH-Katalyse selektiv zur Verbindung **158** geöffnet werden konnte. Die weitere, eher lineare Sequenz nutzte eine Aldol-Reaktion mit

darauffolgender Oxidation zur Darstellung des β-Ketothioesters **159**. Damit wurde in einer Ley-Acylierung des Aminoglykosids **141** ausschließlich das α-Anomer **160** gebildet. Ebendieses wurde einer Lacey-Dieckmann-Cyclisierung unterzogen und *onepot* zu einem Carbamat geöffnet, welches im nächsten Schritt oxidativ zur Carbaminsäure **161** entschützt wurde. Die letzten beiden Stufen beschränkten sich auf die Acetylierung der 3-Position der Amykitanose sowie der TBS-Entschützung der Amycolose (→ **10**).

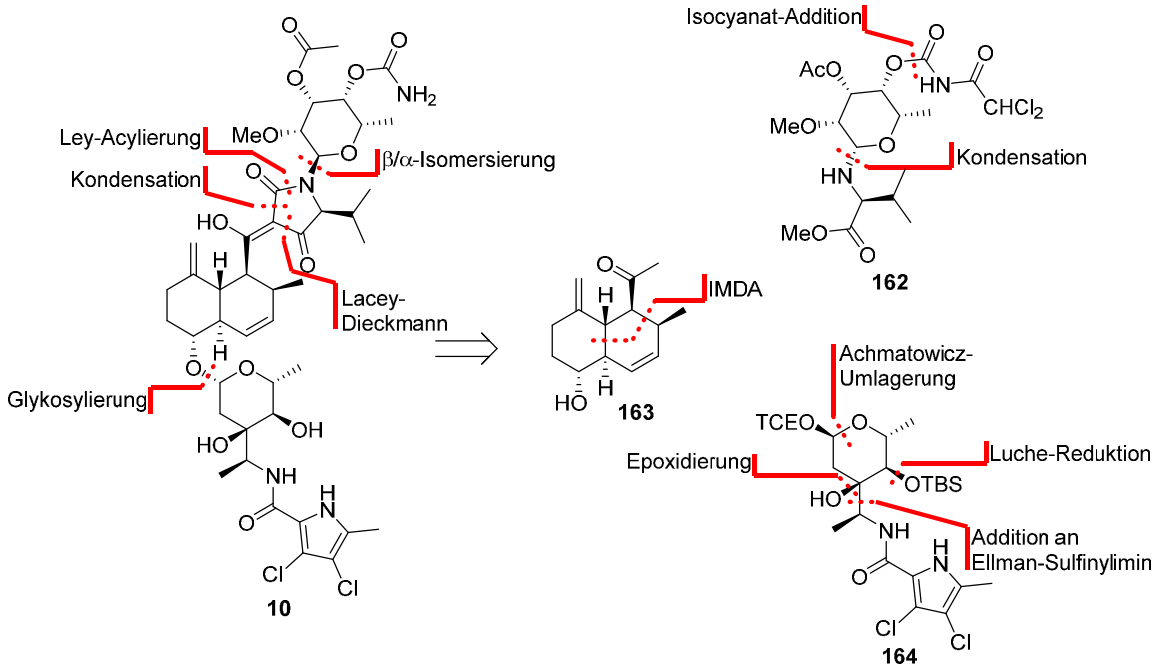


SCHEMA 28. Letzte Schritte zur Synthese von Kibdelomycin (**10**) nach Meguro *et al.*[126]
Reagenzien und Bedingungen: a) Cl_3CCN, DBU, CH_2Cl_2, 0 °C → RT, 1 d, 86%; b) **142**, TfOH, 4 Å MS, CH_2Cl_2, −20 °C → 0 C, 1.5 h, TfOH, 0 °C → −20 °C → 0 C, 12 h, 67%; c) *t*BuSAc, LiHMDS, THF, −78 °C, 30 min, dann **141**, 8 h; d) DMP, CH_2Cl_2, RT, 1 h, 95% (2 Stufen); e) CF_3COOAg, 2,6-Di-*tert*-Butylpyridin, 5 Å MS, THF, 0 °C, 45 min, 72%; f) KO*t*Bu, THF, 0 °C, 1.5 h, dann Pyridin·HCl, CH_2Cl_2, 30 min, dann 2,4-Dimethoxybenzylamin, RT, 3 d, 61%; g) DDQ, 2,6-Di-*tert*-Butylpyridin, CH_2Cl_2, H_2O, 0 °C → RT, 4 h; h) Ac_2O, Li_2CO_3, Pyridin, RT, 24 h, 56% (2 Stufen); i) TASF, THF, DMF, RT, 4 h, 90%.

1.4.3.4 Totalsynthese von Kibdelomycin (10) nach He *et al.*

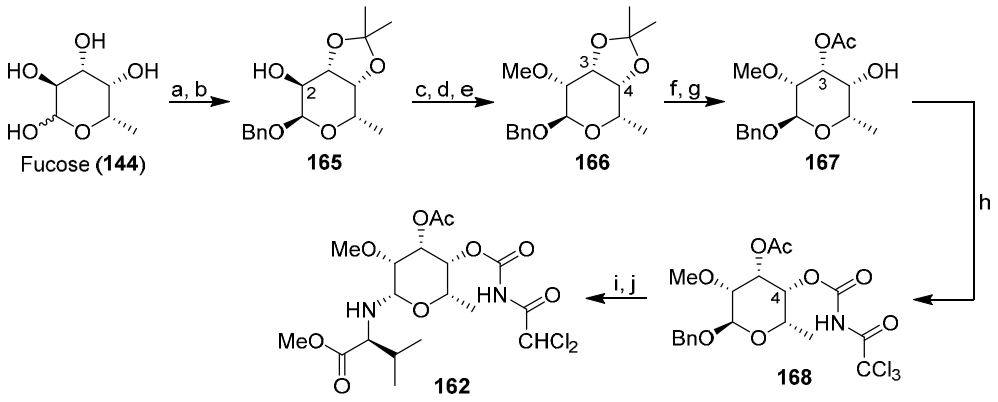
Die neueste Kibdelomycin-Totalsynthese erschien Mitte 2022.[128] Darin sind einige wichtige Schlüsselschritte aus den beiden zuvor publizierten Synthesen vorzufinden. Beim Zusammenfügen der drei Fragmente **162**, **163** und **164** zum Kibdelomycin (**10**) ähneln sowohl die TfOH-vermittelte *O*-Glykosylierung des Decalins **163** als auch die Darstellung der Tetramsäure mittels Ley-Acylierung und Lacey-Dieckmann-Cyclisierung der Synthese von Meguro *et al.* (SCHEMA 29). Ein großer Nachteil der Synthese war die selektive Darstellung des falschen β-Anomers in der Amykitanose-Einheit, was eine β/α-Isomerisierung an dieser Position zur Darstellung des natürlichen Kibdelomycins (**10**) notwendig machte. Das vollständig funktio-

nalisierte Amykitanose-Derivat **162** wurde mittels Kondensation mit dem entsprechenden α-Aminoester äquivalent zu Meguro *et al.* aufgebaut. Während die Bildung des IMDA-Präkursors unterschiedlich zu Meguro *et al.* war, hatte das Decalin-Produkt **163** nur eine weitere Methylgruppe im Vergleich zum äquivalenten Fragment **142** vorzuweisen. Der Aufbau der Hexose **164** enthält die von Yang *et al.* verwendete Achmatowicz-Umlagerung, alle anderen Stereozentren werden aber im Wesentlichen anders synthetisiert.



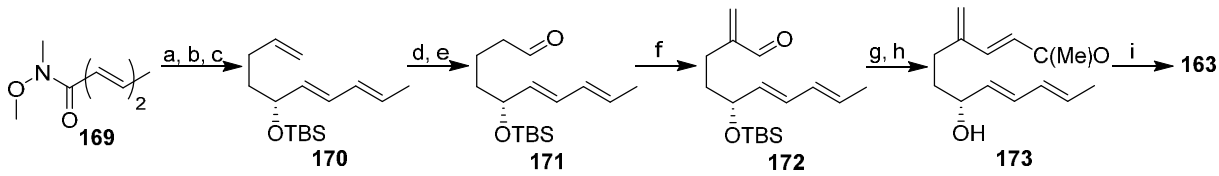
SCHEMA 29. Retrosynthese der Kibdelomycin-Synthese nach He *et al.*[128]

Die Synthese der geschützten Amykitanose **162** startete mit einer Sequenz ausgehend von L-Fucose (**144**, SCHEMA 30).[128] Hierbei wird mit den ersten sechs Stufen maßgeblich den in SCHEMA 25 nicht gezeigten Stufen von Meguro *et al.* bzw. Sawa *et al.*/Takagi *et al.* gefolgt, jedoch mit anderen Schutzgruppen und moderneren Reagenzien.[111,126,127] Es wurde damit begonnen, die anomere Position mit einer Benzyl-Gruppe und den *syn*-Diol mit einem Acetonid zu schützen (→ **165**). Die Inversion der 2-Position wurde durch eine DMP-Oxidations- und DIBAL-Reduktions-Sequenz bewerkstelligt. Die freie Hydroxy-Gruppe wurde Methyl-verethert (→ **166**). Durch Abspaltung der Acetonid-Schutzgruppe konnte die 3-Position regioselektiv acetyliert werden (→ **167**) und der freie Alkohol an 4-Position in das Carbamat **168** überführt werden. Die hydrogenolytische Abspaltung der anomeren Benzyl-Gruppe hatte ebenfalls zur Folge, dass ein Chlor-Substituent im Carbamat-Rest gegen Wasserstoff substituiert wurde, was auf den weiteren Reaktionsverlauf keinen Einfluss hatte. Als letzter Schritt wurde der freie Zucker mit dem Valin-Metyhlester kondensiert (→ **162**).



SCHEMA 30. Synthese der geschützten Amykitanose **162** nach He *et al.*[128]
Reagenzien und Bedingungen: a) BnOH, *p*TsOH, 80 °C, ü.N.; b) 2,2-Dimethoxypropan, *p*TsOH, DMF, RT, ü.N., 50% (2 Stufen); c) DMP, CH_2Cl_2, RT, 2 h; d) DIBAL, THF, −78 °C → RT, ü.N., 87% (2 Stufen); e) MeI, Ag_2O, MeCN, 75 °C, ü.N., 83%; f) aq. AcOH, 80 °C, 1 h; g) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, ü.N., 80% (2 Stufen); h) Trichloracetylisocyanat, CH_2Cl_2, 0°C → RT, 1 h, 95%; i) H_2, Pd/C, EtOAc, RT, 3 h; j) L-Val-OMe, PPTS, RT, 6 h, 84% (2 Stufen).

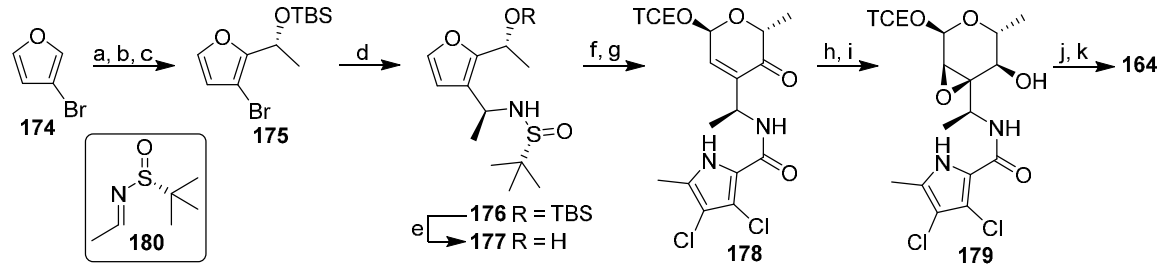
In einer Weinreb-Keton-Synthese wurde das Dien **169** mit But-3-enylmagnesiumbromid umgesetzt (SCHEMA 31).[128] Das korrespondierende Keton wurde stereoselektiv mit dem CBS-Katalysator reduziert und silyliert (→ **170**). In zwei Schritten mittels selektiver Hydroborierung der terminalen Doppelbindung mit oxidativer Aufarbeitung und DMP-Oxidation wurde das Aldehyd **171** hergestellt. Eine Mannich-Reaktion baute das Enal **172** auf, welches in einer Wittig-Reaktion ins Keton **173** überführt wurde. Analog zu Meguro *et al.* wurde in einer Lewis-Säure-katalysierten IMDA **173** zum Decalin **163** cyclisiert.



SCHEMA 31. Synthese des Decalin-Fragments **163** nach He *et al.*[128]
Reagenzien und Bedingungen: a) Homoallylmagnesiumbromid, THF, 0 °C, 4 h, 93%; b) (*S*)-Me-CBS-Kat., BH_3·THF, THF, −78 °C, 5 h, 88% (99% *ee*); c) TBSCl, Imidazol, DMF, 50 °C, ü.N., 93%; d) 9-BBN, THF, 0 °C → RT, 5h, dann $NaBO_3$·$4H_2O$, H_2O, 0 °C → RT, ü.N., 96%; e) DMP, CH_2Cl_2, RT, 2.5 h, 78%; f) L-Prolin, Bn_2NCH_2OMe, DMF, 0 °C → RT, 2 h, dann SiO_2, CH_2Cl_2, RT, 5 h, 85%; g) $Ph_3PCHC(O)Me$, CH_2Cl_2, 45 °C, 1 d, 97%; h) TBAF·$3H_2O$, THF, 0 °C → RT, 2 h, 99%; i) Me_2AlCl, CH_2Cl_2, −20 °C → RT, 18 h, 51%.

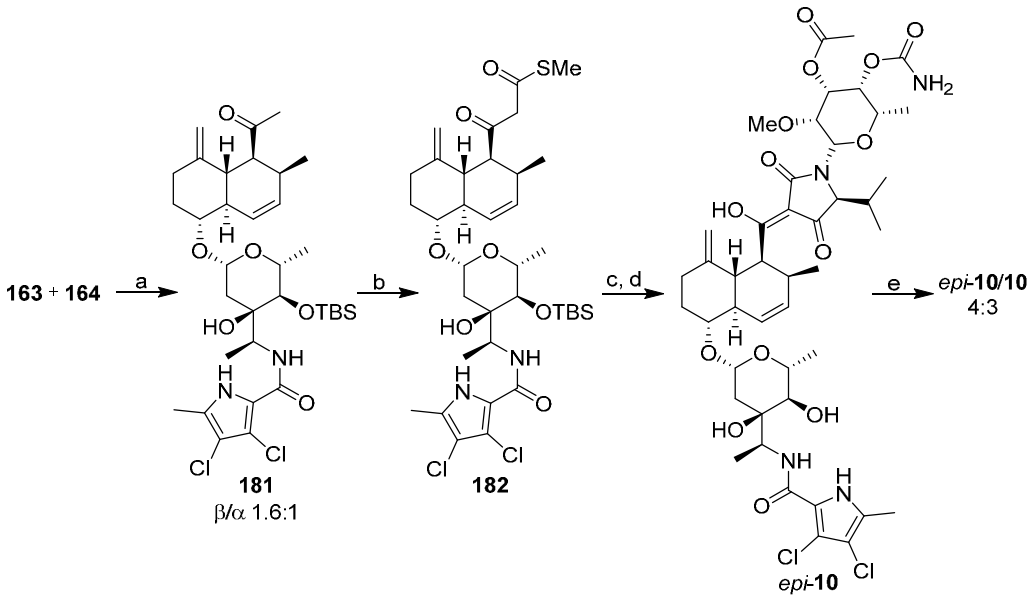
Das letzte Fragment wurde ausgehend von 3-Bromfuran (**174**) synthetisiert (SCHEMA 32).[128] In drei Stufen wurde angefangen mit einer Friedel-Crafts-Acylierung, über eine Noyori-Reduktion, hin zu einer TBS-Schützung der Silyl-Ether **175** dargestellt. Lithiierung des Furans **175** und Angriff an das Ellman-Sulfinylimin **180** resultierte im Sulfinamid **176**, welches TBS-entschützt wurde. Zum Aufbau der Pyranose wurde das Furan **177** ähnlich zu Yang *et al.* in

einer Achmatowicz-Umlagerung umgesetzt. Die weiteren Stufen waren die Installation eines Trichlorethanol-Rests in anomerer Position sowie Abnahme des Auxiliars am Amin und Amidierung mit der Pyrrolcarbonsäure **114** in einem Schritt ohne weitere Aufarbeitung oder Aufreinigung. Die Keto-Gruppe wurde diastereoselektiv reduziert und der daraus entstandene Allylalkohol epoxidiert (→ **179**). Das Epoxid wurde hydridisch geöffnet und der sekundäre Alkohol TBS-geschützt (→ **164**).



SCHEMA 32. Synthese des Amycolose-Derivats **164** nach He *et al.*[128]
Reagenzien und Bedingungen: a) AcCl, $AlCl_3$, CH_2Cl_2, 0 °C → RT, 30 min, 93%; b) RuCl[(*R*,*R*)-TsDPEN](*p*-cymol), Natriumformat, THF, H_2O, 40 °C, 2 d, 92%; c) TBSCl, Imidazol, DMF, RT, ü.N., 95%; d) *n*BuLi, Et_2O, −40 °C, 1 h, dann **180**, −78 °C→RT, 1.5 h, 66%; e) TBAF·$3H_2O$, THF, RT, 0.5 h, 98%; f) Methylenblau, O_2, *hv*, CH_2Cl_2, −78 °C, 2.5 h, dann Me_2S, −78 °C → RT, 2 h, 92%; g) *p*TsOH, TCEOH, RT, 1.5 h, dann HCl, RT, 1.5 h, dann **114**, HATU, DIPEA, DMF, RT, 8 h, 44%, *d.r.* 6:1; h) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 0 °C, 20 min, 88%; i) CF_3CO_3H, CH_2Cl_2, −15 °C → RT, 2 h, 43%; j) $LiBH_4$, PhMe, 60 °C, 3 h, 53%; k) TBSOTf, NEt_3, DCE, RT → 40 °C, 7 h, 56%.

Die letzten Stufen der He-Synthese offenbarten einige Schwächen (SCHEMA 33).[128] Bereits zu Beginn im Zuge der *O*-Glykosylierung des Decalins **163** wurde nur ein schwaches β/α-Verhältnis von 1.6:1 erhalten. Die beiden Diastereomere konnten getrennt und das α-Anomer recycelt werden. Ausgehend vom Keton **181** wurde der β-Ketothioester **182** dargestellt, welcher in einer Ley-Acylierung mit dem Amykitanose-Fragment **162** verknüpft wurde. In einer Stufe wurde daraufhin die Carbaminsäure entschützt und zur Tetramsäure *epi*-**10** ringgeschlossen. Es stellte sich als problematisch heraus, dass lediglich die epimere Form des Kibdelomycins erhalten wurde. Durch Zugabe von Säure konnte ein Epimerenverhältnis von 4:3 zwischen *epi*-Kibdelomycins (*epi*-**10**) und natürlicher Form erhalten werden.

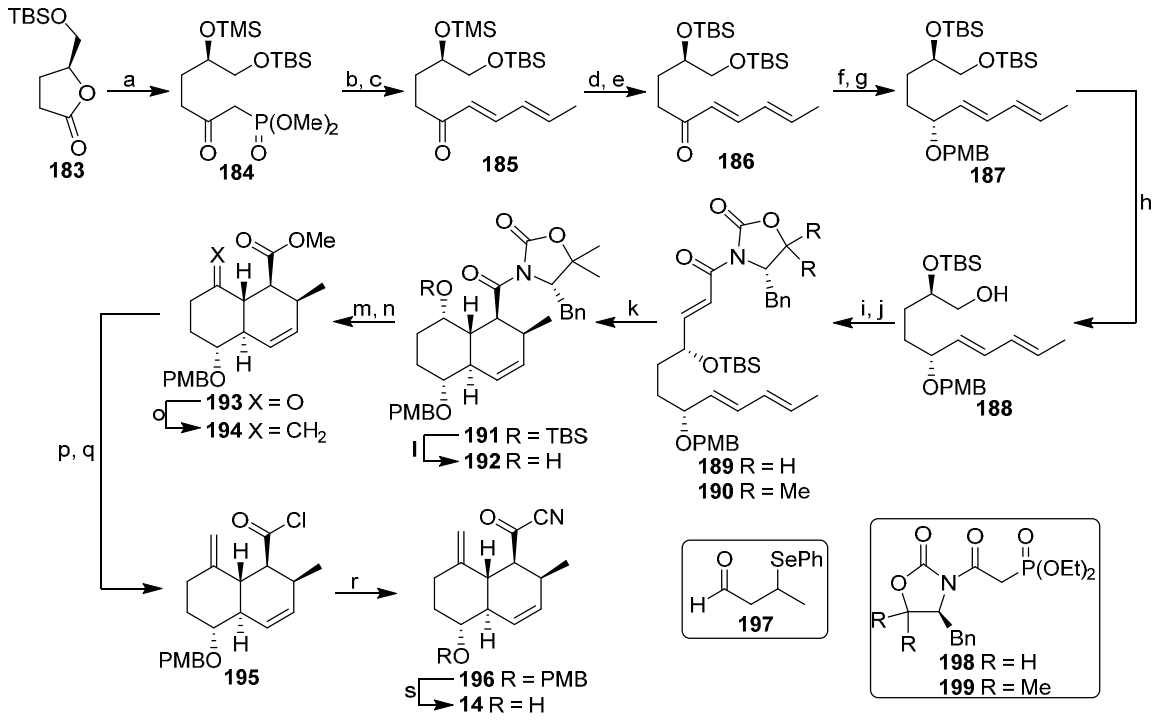


SCHEMA 33. Letzte Schritte zur Synthese von Kibdelomycin (**10**)/*epi*- Kibdelomycin (*epi*-**10**) nach He *et al.*[128] *Reagenzien und Bedingungen*: a) TfOH, 4 Å MS, CH_2Cl_2, RT, 2.5 h, 40% α, 25% β (1:1.6); b) LiHMDS, THF, −78 °C, 30 min, $(SMe)_2CO$, −78 °C → 30 °C, 6 h, 78%; c) **162**, CF_3COOAg, 4 Å MS, THF, RT, 2 h; d) NEt_3, MeOH, RT, 10 min, dann TBAF, THF, RT, 0.5 h, 41% (2 Stufen); e) HCOOH, MeCN, H_2O, RT, 24 h, 46% *epi*-**10**, 32% **10**.

1.4.3.5 Synthese des Decalin-Bausteins 14 nach Frossard *et al.*

Zusätzlich zu den vorher behandelten Totalsynthesen veröffentlichten Frossard *et al.* Mitte 2022 eine 19-stufige (ausgehend von **183**) Synthese des Decalin-Fragments **14** von Yang *et al.* (SCHEMA 34).[129] Gestartet wurde ausgehend vom TBS-geschützten γ-Lacton **183** (Zugang aus L-Glutaminsäure: 3 Stufen, 47%), welches zum Phosphonat **184** geöffnet und die freie Hydroxy-Gruppe TMS-geschützt wurde. HWE-Reaktion mit dem β-Seleno-Aldehyd **197** und Selenoxid-Eliminierung führten zum Dien **185**. Es folgten die Umschützung der TMS- zu einer TBS-Gruppe (→ **186**) sowie die CBS-Reduktion und die Schützung des korrespondierenden Alkohols (→ **187**). Die primäre OTBS-Gruppe wurde selektiv entschützt, zum Aldehyd oxidiert und mit den Phosphonaten **198** oder **199** in einer HWE-Reaktion umgesetzt (→ **189** bzw. **190**). Es stellte sich heraus, dass die Abnahme des Standard-Evans-Auxilars aus **189** nicht möglich war, weswegen auf das sterisch anspruchsvollere SuperQuat-System von Davies umgestiegen wurde. Trien **190** wurde unter Lewis-Säure-Katalyse einer IMDA unterzogen (→ **191**), die OTBS-Gruppe Silyl-entschützt (→ **192**) und mittels DMP oxidiert (→ **193**). Es wurde die terminale Doppelbindung mittels Wittig-Reaktion eingeführt und der Ester **194** in das Säurechlorid **195** überführt. Die Herstellung des Decalin-Bausteins **14** endete mit der Installation des Acylcyanids (→ **196**) und PMB-Entschützung. Als kritisch bei dieser Synthese

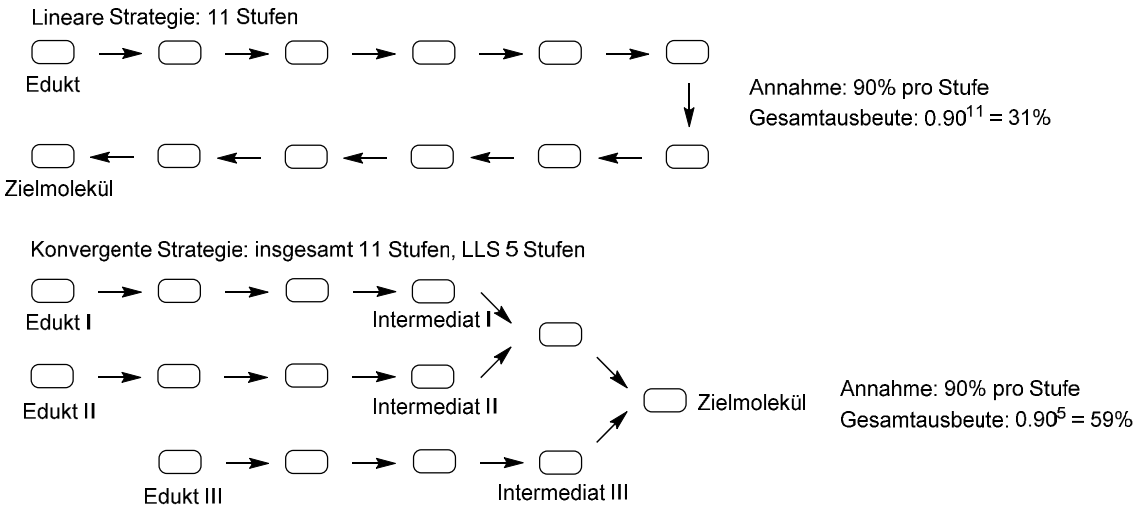
muss die Länge der Sequenz (19 bzw. 22) und die daraus resultierende niedrige Ausbeute gesehen werden.



SCHEMA 34. Synthese des Decalin-Fragments **14** nach Frossard *et al.*[129]
Reagenzien und Bedingungen: a) $MeP(O)(OMe)_2$, *n*BuLi, THF, −78 °C, 2 h, dann LDA, −78 °C → −20 °C, 30 min, dann TMSCl, −20 °C → 0 °C, ü.N., 89%; b) **197**, NaH, THF, 0 °C, 1 h; c) H_2O_2, CH_2Cl_2, 0 °C, 20 min, 89% (2 Stufen); d) NaOH, MeOH, RT, 20 min; e) TBSCl, Imidazol, DMAP, DMF, RT, 5 h, 92% (2 Stufen); f) (*S*)-Me-CBS-Kat., $BH_3{\cdot}SMe_2$, THF, −45 °C, 7 h, 96%, *d.r.* 8:1; g) PMBBr, NaH, TBAI, THF, Δ, 15 h, 92%; h) HF·Pyridin, THF, 0 °C, 39 h, 68%; i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT, 2.5 h – 5 h; j) **198**/**199**, LiCl, DIPEA, MeCN, 0 °C→RT, 17.5 h – 20 h, 64%/66% (2 Stufen); k) Me_2AlCl, CH_2Cl_2, −78 °C → 0 °C, 16 h, 34%, *d.r.* 12:1; l) HF·Pyridin, Pyridin, THF, RT, 25 h, 76%; m) NaOMe, CH_2Cl_2, 0 °C, 2 h, 97%; n) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT, 2 h; o) $MePPh_3Br$, KO*t*Bu, THF, 0 °C → RT, 2 h, 87% (2 Stufen); p) PhSeH, NaH, 18-Krone-6, THF, 80 °C, 5 h, 92%; q) $(COCl)_2$, DMF, CH_2Cl_2, RT, 4 h; r) CuCN, NaI, 4 Å MS, MeCN, 90 °C, 30 min, 64% (2 Stufen); s) DDQ, CH_2Cl_2, Puffer pH=7, 0 °C → RT, 2 h, 83%.

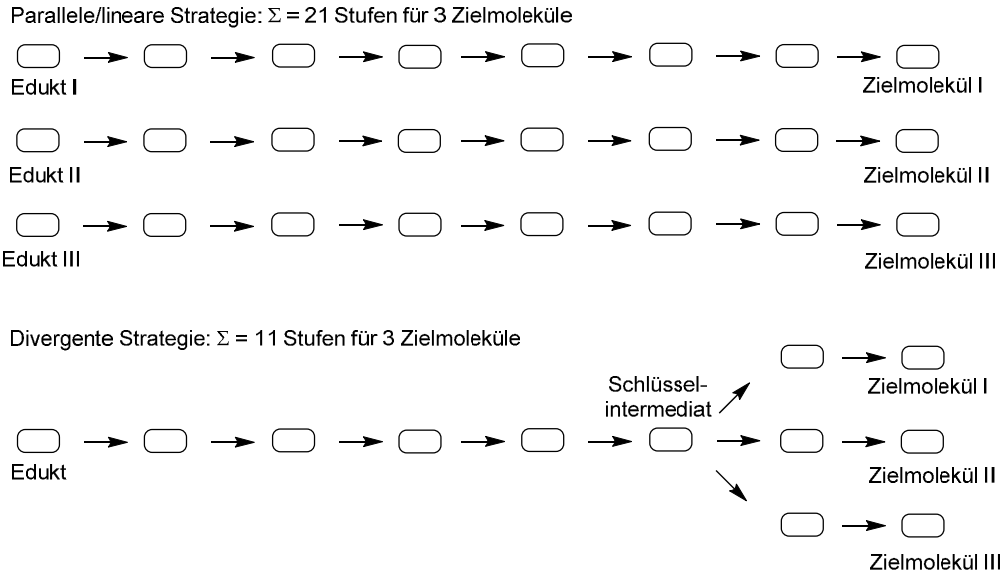
1.5 Synthesestrategien in der organischen Synthese

Die Komplexität organischer Verbindungen zu definieren bzw. indizieren, nahm sich 1980 Bertz an.[130] Hierbei und bei weiteren Arbeiten zu diesem Thema spielten im Wesentlichen Faktoren wie Dichte und Anzahl der funktionellen Gruppen, Anzahl der Stereozentren oder Größe des Moleküls eine Rolle.[131] Außer Acht gelassen wurde häufig die synthetische Zugänglichkeit der Verbindungen bzw. Verbindungsklassen, welche sich zum einen über die Zeit aufgrund innovativer Reaktionen vereinfachte, sich zum anderen aber auch zwischen ähnlich komplexen Molekülen (z.B. bei gleicher Anzahl an Stereozentren) aufgrund deren strukturellen Gegebenheiten deutlich unterscheiden kann. Aus dieser Problemstellung entwickelten sich die in drei Kategorien klassifizierbaren Synthesestrategien: (1) linear, (2) konvergent und (3) divergent.[132] Es ist der Versuch jedes dieser Konzepte, durch die Synthese Komplexität aus dem Molekül bzw. der Molekülklasse herauszunehmen, aber dennoch im Ganzen eine hohe Effizienz aufzuweisen. Innerhalb der drei genannten Synthesestrategien muss zwischen den ersten beiden und der letzten unterschieden werden. Während es bei einer linearen und konvergenten Strategie immer nur um das Herstellen eines einzelnen Zielmoleküls geht, werden bei einer divergenten Strategie eine Vielzahl von (häufig eng verwandten) Zielmolekülen synthetisiert. SCHEMA 35 zeigt, welche Vorteile bei einer konvergenten Methode (SCHEMA 35, unten) gegenüber einer linearen (oben) möglich sind. Durch das Zusammenfügen mehrerer etwa gleich großer Moleküle gegen Ende der Synthese verkleinert sich die längste lineare Sequenz (LLS), wodurch die Gesamtausbeute bzw. Effizienz der Synthese meist höher ist. Darüber hinaus können durch das Verwenden verschiedener kleinerer Intermediate bzw. Fragmente Synthesemethoden angewendet werden, welche mit anderen Molekülteilen nicht vereinbar wären (vgl. Intermediat/Fragment I enthält DB: darin keine Hydrierungen möglich, Intermediate II/III enthalten keine DB: Hydrierung möglich). Andererseits ist es in konvergenten Synthesen auch möglich, eine weniger komplexe Schutzgruppenstrategie zu wählen. Konvergente Strategien werden dann angewendet, wenn sehr große (z.B. Polypeptide) oder sehr komplexe Zielmoleküle (z.B. hoch oxidierte Naturstoffe) synthetisiert werden sollen.[133] Die Schwierigkeit liegt immer im Aufteilen des Zielmoleküls in die sinnvollsten Fragmente.



SCHEMA 35. Schematische Darstellung einer linearen und konvergenten Synthesestrategie.

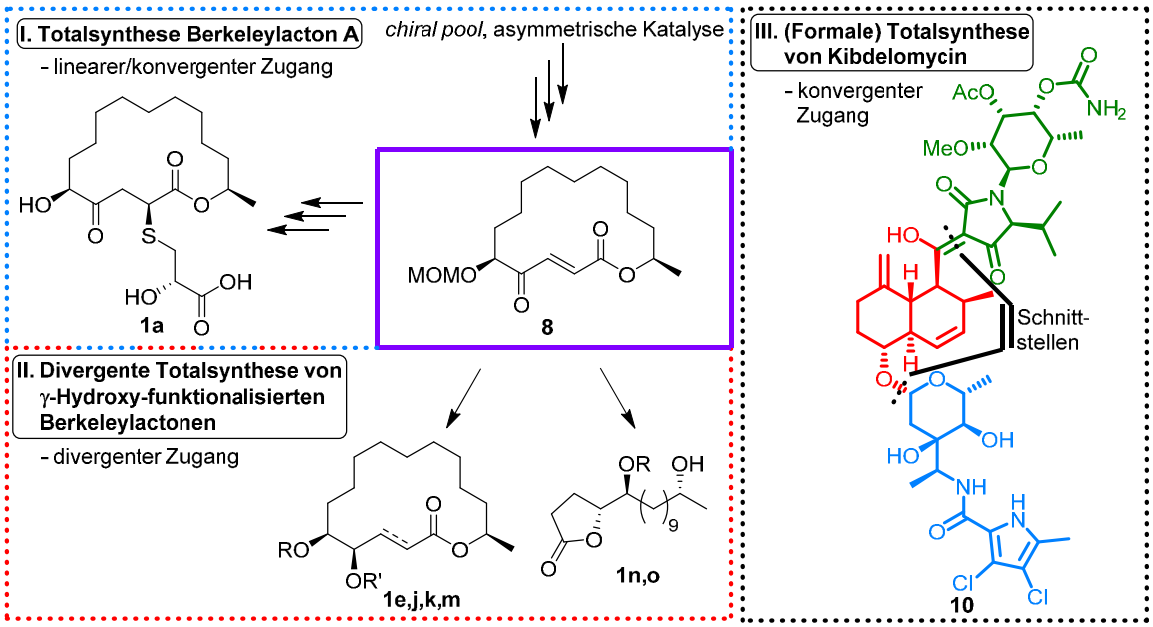
Bei divergenten Synthesen, deren Ziel die Diversifizierung eines Schlüsselintermediats ist, wurden bis heute vor allem strukturähnliche, meist auch aus der gleichen biosynthetischen Familie stammende Verbindungen synthetisiert.[132] Der Großteil bekannter, divergenter Totalsynthesen von Naturstoffen stammt bis heute aus den Klassen der Alkaloide und Terpene. Der Vorteil divergent geführter Synthesen ist die Verringerung paralleler, linearer Sequenzen und damit die Reduzierung der Gesamtstufenanzahl bei mehreren Zielmolekülen (vgl. SCHEMA 36 unten/oben, 21 Stufen/11 Stufen). Schwierigkeiten bestehen vor allem im Finden eines Schlüsselintermediats, welches für sämtliche nachträgliche Diversifikationen geeignet ist.



SCHEMA 36. Schematische Darstellung einer parallelen/linearen und divergenten Synthesestrategie zu mehreren Zielmolekülen.

2 Zielsetzung

Ziel der Arbeit war es, einen totalsynthetischen Zugang zu den in SCHEMA 37 gezeigten und bei Projektbeginn noch nicht synthetisierten antibiotischen Lacton-/Lactam-Naturstoffen zu entwickeln. Der Nutzen davon wäre sowohl die Möglichkeit einer Derivatisierung der Strukturen und damit unter Umständen Steigerung der Aktivität oder Aufschlüsse über Struktur-Wirk-Beziehungen als auch der Gewinn neuer Methoden bzw. Konzepte in der präparativen organischen Synthese. Das erste Teilprojekt mit der Totalsynthese von Berkeleylacton A (**1a**) sollte aufgrund der moderaten Größe und günstig angeordneten funktionellen Gruppen mittels eines linearen bzw. linear/konvergenten Zugangs gelöst werden. Das in dieser Synthese vorkommende Intermediat **8** diente als Ausgangspunkt für das zweite Teilprojekt. Da bis heute kaum divergente Synthesen für Macrolid-Naturstoffe bekannt sind und weil es den Zugang zu vielen strukturähnlichen Berkeleylactonen erleichtert, sollte hierbei eine divergente Strategie angewendet werden. Zuletzt sollte das nahezu 15 Jahre synthetisch nicht erreichte Antibiotikum Kibdelomycin (**10**) dargestellt werden. Wegen der schieren Größe und hohen Anzahl an Stereozentren sollten an zwei Stellen im Molekül retrosynthetische Schnitte gesetzt werden. Die beiden daraus erhaltenen ungewöhnlichen Glykoside (grün, blau) sollten unter der Verwendung natürlicher Zucker synthetisiert werden, die Decalin-Einheit durch eine Diels-Alder-Reaktion.



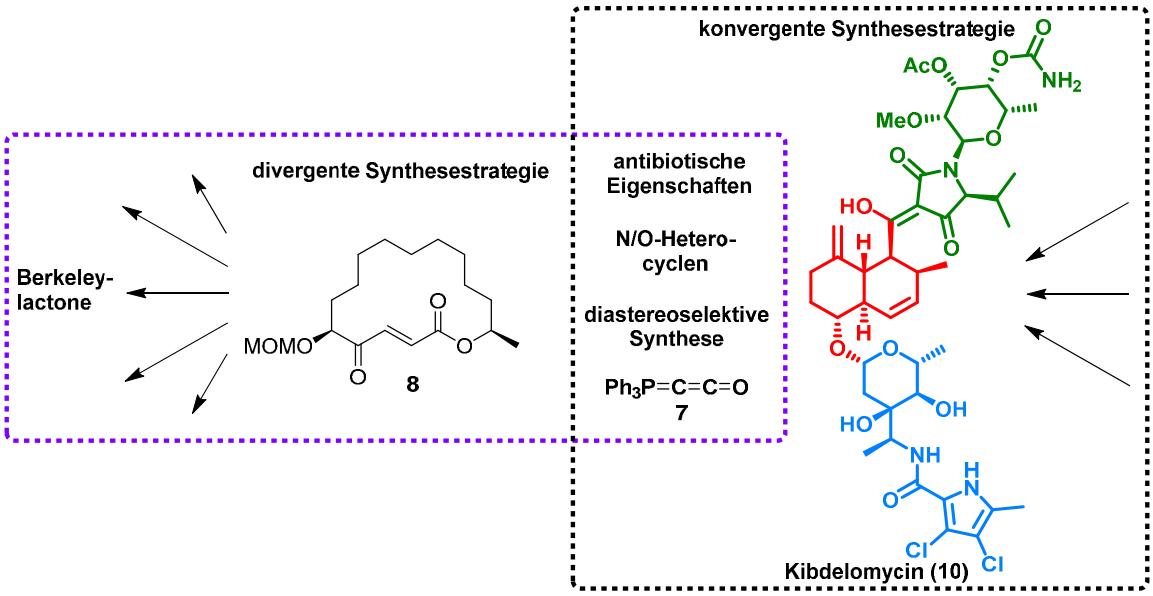
SCHEMA 37. Die drei im Zuge der Doktorarbeit bearbeiteten Projekte.

3 Synopsis

3.1 Übersicht und Zusammenhang der Teilprojekte

Mit Hinblick auf das immer größer werdende Problem der Antibiotikaresistenz-Krise, sind innovative Lösungen gefragt. Bezogen auf die präparative organische Chemie bietet sich die Möglichkeit der Synthese neuer bzw. Derivatisierung alter Wirkstoffe. Aus diesem Grund sollten diverse bioaktive Naturstoffe aus der Berkeleylacton-Klasse sowie Kibdelomycin (**10**) totalsynthetisiert werden (SCHEMA 38). Vor allem Berkeleylacton A (**1a**) und Kibdelomycin (**10**) zeigten eine starke antibiotische Wirkung primär gegen Gram-positive Bakterien. Insbesondere aber die Aktivität gegenüber resistenten Keimen stellt die besondere Motivation für deren Synthese dar. Ein weiterer Aspekt, der im Rahmen der Studien untersucht wurde, ist die Biofilm-Inhibition bzw. -Dispersion durch solche Verbindungen. Biofilme sind ein nur schwach erforschtes Gebiet. Es ist aber bekannt, dass ein Großteil der (chronischen) Infektionen ihren Ursprung in Biofilmen hat.[134] Um z.B. deren Pathogenität, aber auch um deren Resistenzmechanismen zu klären, braucht es die Synthese von Anti-Biofilm-Wirkstoffen.

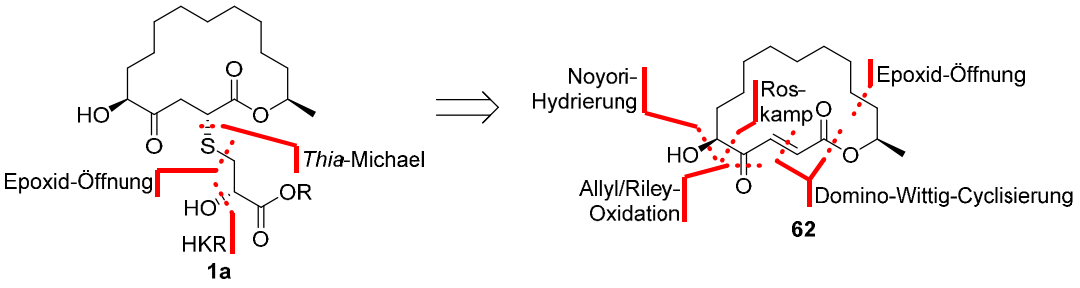
Neben biochemischen/pharmazeutischen Beweggründen spielt bei der durchzuführenden Naturstoffsynthese auch immer die Suche nach neuen Synthesestrategien für einzelne Verbindungen bzw. Verbindungsklassen eine Rolle. So wurden im Zuge der Totalsynthesen Methoden gefunden, welche auch auf andere Problemstellungen angewendet werden können. Es wurde im Speziellen auf die Verwendung solider diastereoselektiver Synthesen sowie den Einsatz des lehrstuhlbekannten Ketenylidentriphenylphosphorans (**7**) geachtet.



SCHEMA 38. Unterschiede und Verknüpfungspunkte der verschiedenen Arbeiten.

3.2 Synthese des Pilz-Macrolids Berkeleylacton A und dessen Inhibition mikrobieller Biofilmbildung

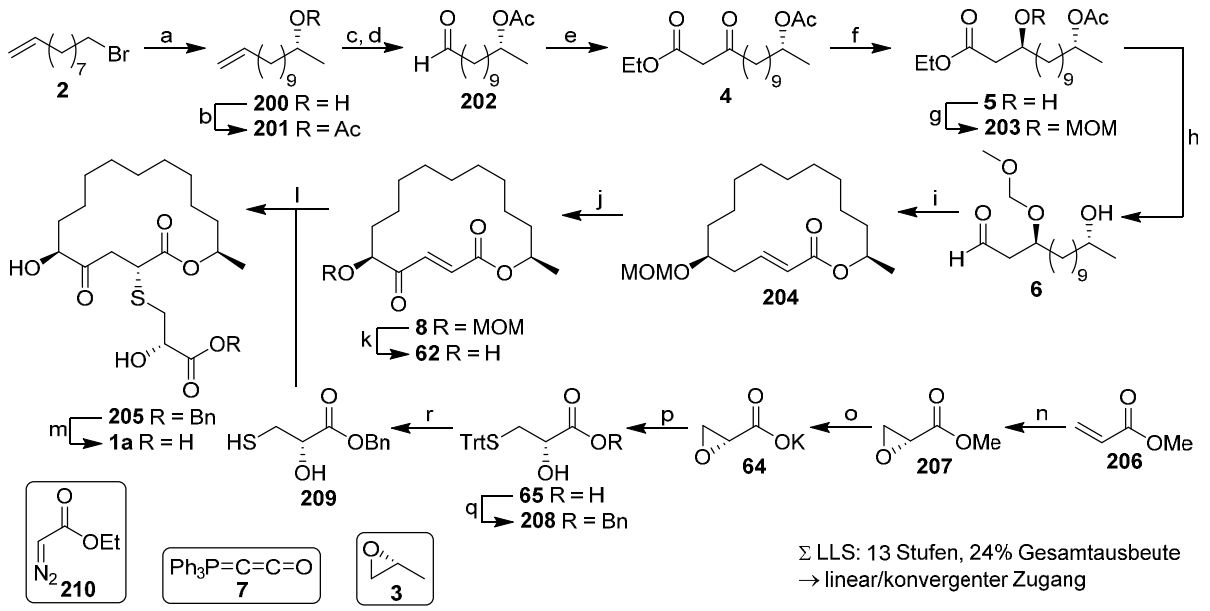
In der ersten Arbeit wurde ein totalsynthetischer Zugang für das 2017 isolierten Berkeleylacton A (**1a**) entwickelt und in Kooperation mit dem Helmholtz-Zentrum für Infektionsforschung die antibiotische und Anti-Biofilm-Wirkung des Naturstoffs evaluiert.[46] In Anbetracht der bis heute schlechten Erforschung von mikrobiellen Biofilmen und der damit verbundenen schwierigen Behandelbarkeit durch Antibiotika sind Biofilm-inhibierende oder -zersetzende Wirkstoffe interessant. Durch die besondere Morphologie von Biofilmen mit mehreren übereinander liegenden Zellschichten sind die inneren Teile eines Biofilms nur schlecht durch Antibiotika adressierbar und neigen zur Resistenzbildung, was einen Bedarf an Biofilm-zersetzenden Stoffen erzeugt. Neben den neuen pharmazeutischen Eigenschaften des Berkeleylactons A (**1a**) war dessen Totalsynthese des zu Projektbeginn (Masterarbeit) noch nicht synthetisierten Naturstoffs interessant.[135] Hierbei wurde eine bis dahin noch nicht bekannte stereoselektive Strategie zum Aufbau des Kernbausteins **62** bzw. des δ-Hydroxy-γ-oxo-α,β-ungesättigten Ester-Motivs erarbeitet, welche aus etlichen A26771B-Darstellungen bekannt sind. Retrosynthetisch betrachtet wurde das Thio-Seitenkettenfragment mittels *Thia*-Michael-Reaktion addiert und zuvor durch hydrolytisch kinetische Racematspaltung sowie Öffnung eines Epoxids gebildet (SCHEMA 39, links). Der Schlüsselschritt für die Synthese des Macrolid-Gerüsts war die Domino-Wittig-Cyclisierung (SCHEMA 39, rechts). Zum Aufbau der beiden Hydroxy-Funktionalitäten wurden einerseits eine asymmetrische Noyori-Hydrierung, andererseits die Öffnung eines enantiomerenreinen Epoxids genutzt. Darüber hinaus war für die Darstellung der γ-Oxo-α,β-ungesättigten Ester-Funktionalität die Roskamp-Reaktion wie auch die Riley-Oxidation zentral.



SCHEMA 39. Retrosynthetische Schnitte für den Seitenketten- (links) und Macrolid-Part (rechts).

Begonnen mit der CuCN-katalysierten Grignard-Ringöffnung von (*R*)-PPO (**3**) wurde der sekundäre Alkohol **200** erhalten, welcher im Anschluss Acetyl-geschützt wurde (SCHEMA 40). Das terminale Olefin **201** wurde in zwei Stufen durch Upjohn-Dihydroxylierung und Diol-

Spaltung mit dem heterogenen und leicht abtrennbaren $NaIO_4 \cdot SiO_2$-Reagenz in das Aldehyd **202** überführt. Die $SnCl_2$-katalysierte Roskamp-Reaktion erzeugte aus **202** unter Einsatz von EDA (**210**) mit dem β-Ketoester **4** das Substrat für die asymmetrische Noyori-Hydrierung (>99% *de*). Vorteil dieser katalytischen Methode ([Ru], BINAP) war die maximale Atomökonomie sowie der Einsatz kleinster Katalysatorbeladungen (<0.5 Mol-%). Der neue sekundäre Alkohol **5** wurde unter Vermeidung des kanzerogenen MOMCl MOM-geschützt. Zu Beginn der Synthese wurde explizit die Acetyl-Schutzgruppe ausgewählt, sodass sie an diesem Punkt gleichzeitig mit der Reduktion des Esters zum Aldehyd abgenommen werden konnte. Das so erhaltene bifunktionale Hydroxyaldehyd **6** war das Edukt für die Domino-Wittig-Makrolactonisierung mit dem kumulierten Ylid **7**. Nach diesem Schlüsselschritt wurde die γ-Position von **204** in einer Allyl-Oxidation zum Keton **8** funktionalisiert. Beste Ergebnisse lieferte die Riley-Oxidation mit SeO_2, aber mit modifizierten Reaktionsbedingungen. Die saure MOM-Entschützung machte das entstehende Macrolid **62** reaktiv genug für die nun folgende *Thia*-Michael-Addition. Der dafür notwendige Thiol **209** wurde ausgehend von Methylacrylat (**206**) synthetisiert. In zwei literaturbekannten Stufen, Epoxidierung und hydrolytisch kinetische Racematspaltung, wurde stereoselektiv das Methylglycidat (**207**) nach Jacobsen aufgebaut.[136] Nach Verseifung des Esters wurde das Epoxid **64** mit dem sterisch anspruchsvollen Tritylthiol selektiv an der terminalen Position angegriffen und geöffnet. Installation einer Benzyl-Gruppe an der freien Carbonsäure mittels Cs_2CO_3/BnBr (→ **208**) gefolgt von saurer *S*-Trityl-Entschützung führte zum Thiol **209**. Dieser wurde unter Basen-Katalyse diastereoselektiv an das Michael-System addiert (→ **205**). Es zeigte sich, dass NEt_3 die besten Ergebnisse bezüglich Diastereoselektivität und Ausbeute lieferte. Nach hydrogenolytischer Abspaltung der Benzyl-Schutzgruppe wurde Berkeleylacton A (**1a**) erhalten. Hervorzuheben ist die effiziente, atomökonomische Reaktionsführung mit in der Regel Ausbeuten >85%. Ausreißer nach unten waren lediglich die Makrolactonisierung wie auch die Allyl-Oxidation. Dennoch konnte der Naturstoff am Ende in 24% Gesamtausbeute über 13 Stufen dargestellt werden. Diese Synthese übertrifft die Ausbeuten der bereits bestehenden von Ferko *et al.* deutlich, sowohl in Bezug auf das Macrolid-Gerüst als auch auf die Thiol-Seitenkette.[75]



SCHEMA 40. Synthese des Naturstoffs Berkeleylacton A (**1a**) mit antibiotischer und Anti-Biofilm-Wirkung. *Reagenzien und Bedingungen*: a) Mg, THF, Δ, 3.5 h, dann CuCN, (*R*)-PPO (**3**), −40 °C → −35 °C, 20 h, dann 0 °C, 93%; b) Ac_2O, Pyridin, DMAP, CH_2Cl_2, RT, 19 h, 98%; c) $K_2OsO_4{\cdot}2H_2O$, NMO, AcMe, H_2O, 0 °C → RT, 28.5 h, 95%; d) $NaIO_4{\cdot}SiO_2$, CH_2Cl_2, RT, 1.75 h, quant.; e) EDA (**210**), $SnCl_2$, CH_2Cl_2, 0 °C → RT, 3 h, 95%; f) H_2, Noyori-Kat. 1.Gen., MeOH, 60 °C, 65 h, 87%; g) DMM, P_2O_5, RT, 2 h, 95%; h) DIBAL, PhMe, −78 °C, 1.5 h, 92%; i) **7**, PhMe, 55 °C, 20 h, 62%; j) SeO_2, 1,4-Dioxan, 155 °C, 55 min, 77%; k) TFA, CH_2Cl_2, −10 °C, 9.5 h, 88%; l) NEt_3, CH_2Cl_2, RT, 3 h, 98%; m) H_2, Pd/C, MeOH, RT, 1.75 h, 89%; n) Ref.[136]; o) KOH, MeOH, 0 °C → RT, 16 h, 79%; p) TrtSH, NaH, THF, 0 °C, dann **64**, 0 °C → RT, 19 h; q) BnBr, Cs_2CO_3, DMF, RT, 16 h, 61% (2 Stufen); r) TFA, *i*PrSiH, CH_2Cl_2, 0 °C, 3.5 h, RT, 45 min, 91%.

In den darauffolgenden Biotests mit dem synthetischen Material wurden die antibiotischen Aktivitäten gegenüber den Gram-positiven Vertretern *B. subtilis* und *S. aureus* (auch Methicillin-resistent) bestätigt. Gram-negative Bakterien sowie Pilze oder Hefen wurden nicht oder nur schwach im Wachstum inhibiert. Ebenso wurde kaum cytotoxische Aktivität festgestellt. Dem gegenüber standen die vielversprechenden Ergebnisse der Biofilm-Inhibition und -Dispersion. Das Wachstum der Biofilme von *S. aureus* wurde im Bereich von 0.3 – 2 µg/mL zwischen 20% und 53% inhibiert. Zur Auflösung vorgeformter Biofilme waren deutlich höhere Konzentrationen (125 – 250 µg/mL) notwendig. Überraschend war der Effekt der Dispersion vorgeformter Biofilme von *C. albicans*. Hier wurde eine Wirkung noch im sub-µg/mL-Bereich (0.17 µg/mL) festgestellt, was im Vergleich zu anderen bekannten Wirkstoffen überdurchschnittlich ist.[137] Demnach ist Berkeleylacton A (**1a**) ein interessanter Wirkstoff, insbesondere im Hinblick auf die häufig letalen Infektionen durch die auf Implantaten wachsenden *C. albicans*-Biofilme.[138]

Weitere Details in: Manuel G. Schriefer, Hedda Schrey, Haoxuan Zeng, Marc Stadler, Rainer Schobert

Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation

Org. Biomol. Chem. **2021**, *19* (21), 4743 – 4751.

3.3 Divergente Synthese sechs aktueller Berkeleylactone

Bei der zweiten Veröffentlichung handelt es sich primär um eine synthetische Arbeit. Hierin wurde eine divergente Totalsynthese von sechs (erst kürzlich entdeckten) Berkeleylactonen sowie eine formale Totalsynthese von A26771B (**53**) entwickelt (ABB. 16).[47] Interesse an diesen Verbindungen besteht insbesondere wegen der außergewöhnlichen Anti-Biofilm-Eigenschaften des strukturverwandten Berkeleylacton A (**1a**). Darüber hinaus wurde ein Überblick über die 22 existierenden A26771B-Totalsynthesen gegeben. Die Synthese der neuen Berkeleylactone konnte aufgrund des schon bestehenden, gut erreichbaren Ketons **8** bereits innerhalb eines Jahres nach deren Entdeckung abgeschlossen werden.

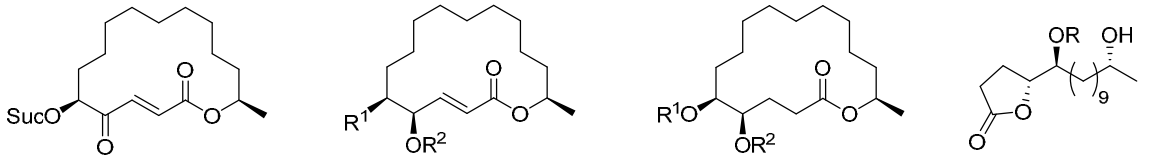
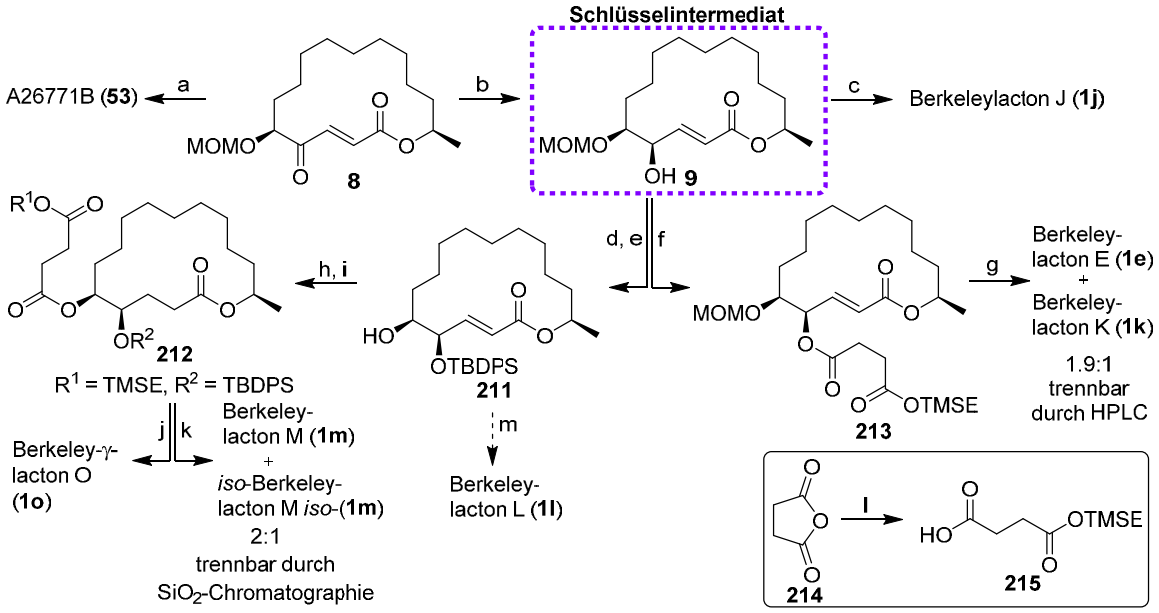


ABBILDUNG 16. Die im zweiten Projekt behandelten (und totalsynthetisierten) Lacton-Naturstoffe.

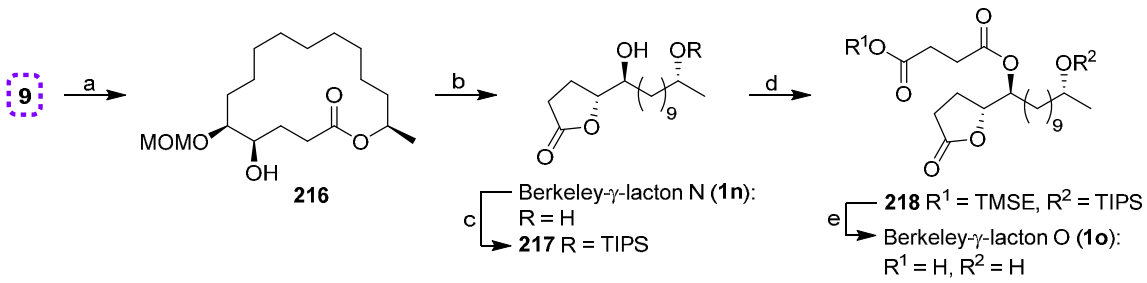
Zunächst wurde die formale Totalsynthese von A26771B (**53**) beschrieben (SCHEMA 41). Erreichbar wäre der Naturstoff **53** durch saure MOM-Entschützung sowie Veresterung mit Bernsteinsäure. Diese Schritte waren zum einen durch die eigens durchgeführte Berkeleylacton A-Synthese sowie durch Blechert literaturbekannt.[68,139] Der eigentliche Schlüsselschritt zum Erschließen der γ-Hydroxy-Ester-Berkeleylactone war die diastereoselektive Reduktion des Ketons **8**. Der Aufbau eines Cram-Chelats mit $Zn(BH_4)_2$ und die darauf folgende Reduktion der Carbonyl-Gruppe erzeugte selektiv den Alkohol **9**. Dieser war das zentrale Schlüsselintermediat für alle weiteren Transformationen zu den einzelnen Naturstoffen. Der kürzeste Weg mittels saurer Abspaltung der MOM-Gruppe war hin zu Berkeleylacton J (**1j**). Mit dem Einsatz von Salzsäure konnte die Nebenreaktion der Bildung eines sehr stabilen Methylenacetals unterdrückt werden. Als nächstes sollte Berkeleylacton K (**1k**) synthetisiert werden. Aus Gründen des niedrigen Umsatzes und sehr langer Reaktionsdauern wurde für die Veresterung des Alkohols **9** nicht Bernsteinsäureanhydrid (**214**) verwendet, sondern die in einer Stufe aus Bernsteinsäureanhydrid (**214**) hergestellte Carbonsäure **215**. In einer Steglich-Hassner-artigen Veresterung wurde das Macrolid **213** erhalten. Saure Entschützung der MOM- und TMSE-Gruppe lieferte allerdings nicht selektiv Berkeleylacton K (**1k**), sondern dieses in Verbindung mit Berkeleylacton E (**1e**). Das Gemisch ließ sich mittels HPLC trennen. Es ist allerdings

literaturbekannt, dass sich diese zwei Naturstoffe durch spontanen Acyl-*shift* ineinander umwandeln lassen und wahrscheinlich nur einen biosynthetischen Ursprung besitzen.[48] Mit der Bestätigung dieser Umwandlung wurde nicht weiter nach einer selektiven Synthese von Berkeleylacton E und K (**1e**/**k**) gesucht. Allerdings rückte Berkeleylacton M (**1m**) in den Fokus, da untersucht werden sollte, ob aufgrund der fehlenden Doppelbindung ein solcher konformeller und elektronischer Unterschied aufträte, sodass dieses ohne Acyl-Migration isoliert werden könnte. Dafür wurde die γ-Hydroxy-Gruppe TBDPS geschützt und die MOM-Gruppe mittels TMSBr entschützt (→ **211**). Der nun in δ-Position sitzende freie Alkohol **211** wurde wiederum gemäß Steglich-Hassner mit der Carbonsäure **215** verestert und die Doppelbindung mittels katalytischer Hydrierung entfernt (→ **212**). Nach der gepufferten globalen Entschützung wurde Berkeleylacton M (**1m**) erhalten. Es wurde jedoch auch ein gewisser Teil *iso*-Berkeleylacton M *iso*-(**1m**) während der Säulenchromatographie abgetrennt. Im Zuge des Screenings der globalen TBAF-Entschützung des Macrolids **212** wurde bei höheren Temperaturen die alleinige Bildung des γ-Lactons **1o** (Berkeley-γ-lacton O) beobachtet. Geplant, aber nicht realisiert, wurde die Synthese von Berkeleylacton L (**1l**), für welches ausgehend vom δ-Alkohol **211** noch eine Deoxygenierung und Silyl-Entschützung durchzuführen wären.



SCHEMA 41 Synthese der makrocyclischen Naturstoffe **1e**, **1j**, **1k** und **1m** sowie des Fünfrings Berkeley-γ-lacton O (**1o**).
Reagenzien und Bedingungen: a) Ref.[68,139]; b) $Zn(BH_4)_2$, Et_2O, −78 °C, 3.75 h, 96%; c) HCl aq., THF, 1 d, 95%; d) TBDPSCl, Imidazol, DMF, 100 °C, 40 h; e) TMSBr, CH_2Cl_2, 0 °C, 1.5 h, 74% (2 Stufen); f) **215**, EDC·HCl, DMAP, CH_2Cl_2, RT, 17.5 h, quant.; g) TFA, CH_2Cl_2, 0 °C, 1 h, RT, 3 h, 59% **1e**, 31% **1k**; h) **215**, EDC·HCl, DMAP, CH_2Cl_2, RT, 19 h; i) H_2, Pd/C, EtOH, RT, 3 d, 98% (2 Stufen); j) TBAF, AcOH, THF, 55 °C, 6 d, 57%; k) TBAF, AcOH, THF, RT → 40 °C, 8 d, 66% **1m**, 31% *iso*-**1m**; l) TMSEOH, DMAP, PhMe, Δ, 17 h. 89%; m) δ-Deoxygenierung und Silyl-Entschützung.

Die Synthese der Fünfring-Lactone startete ein weiteres Mal unter Verwendung des zentralen Schlüsselintermediats **9**, welches zunächst zum gesättigten Macrolid **216** mittels katalytischer Hydrierung umgesetzt wurde (SCHEMA 42). Unter Säurekatalyse (*p*TsOH) in MeOH wurde neben der MOM-Entschützung die selektive Bildung des kinetisch bevorzugten Berkeley-γ-lactons N (**1n**) erzielt. Für die Darstellung des zweiten γ-Lacton-Naturstoffs **1o** wurde die endständige Hydroxy-Gruppe chemoselektiv TIPS-geschützt. Die beiden Alkohole konnten aufgrund der unterschiedlichen sterischen Umgebung diskriminiert werden. Die Veresterung mit der bekannten Säure **215** und globale TBAF-Entschützung führten zu Berkeley-γ-lacton O (**1o**).



SCHEMA 42. Synthese der γ-Lactone **1n** und **1o**.
Reagenzien und Bedingungen: a) H_2, Pd/C, EtOH, RT, 2.75 h, 90%; b) *p*TsOH·H_2O, MeOH, 50 °C, 6 h, 90%; c) TIPSOTf, 2,6-Lutidin, CH_2Cl_2, −80 °C, 4.25 h, 74%; d) **215**, EDC·HCl, DMAP, CH_2Cl_2, RT, 19.5 h, quant.; e) TBAF, AcOH, THF, RT → 55 °C, 44 h, 83%.

Durch die in dieser Arbeit entwickelte divergente Synthesestrategie ließen sich sechs neue Berkeleylactone in kurzen Sequenzen und guten Ausbeuten ausgehend von einem Schlüsselintermediat darstellen. Ein interessanter Anknüpfungspunkt an diese rein synthetische Arbeit wäre die biologische Testung hinsichtlich der Anti-Biofilm-Aktivität.

Weitere Details in: Manuel G. Schriefer, Rainer Schobert

Divergent Synthesis of Six Recent Berkeleylactones

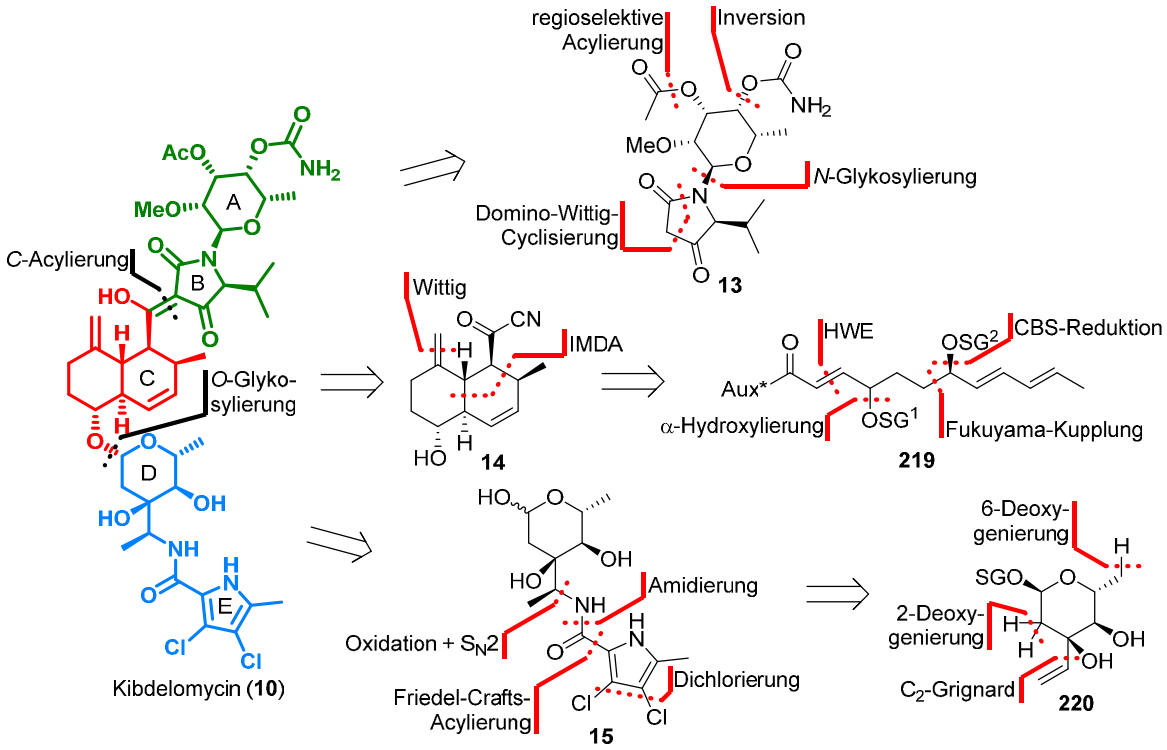
J. Nat. Prod. **2023**, *86* (2), 423 – 428.

3.4 Formale Totalsynthese von Kibdelomycin und die Derivatisierung Amycolose-abgeleiteter Zucker

Das letzte der drei Teilprojekte war die formale Totalsynthese von Kibdelomycin (**10**), einem seit 2008, auch unter dem Namen Amycolamicin bekannten, sehr wirkungsvollen Antibiotikum.[107,110] Bemerkenswert dabei ist der völlig neue antibiotische Wirkmechanismus und das Fehlen von Resistenzen, was Kibdelomycin (**10**) als Zielmolekül im Hinblick auf mögliche Derivatisierung oder Vereinfachung interessant macht. Darüber hinaus ist bekannt, dass auch Fragmente von Wirkstoffen interessante biologische Eigenschaften besitzen können, weswegen eine flexible Synthesestrategie für 3-(α-Aminoalkyl)-verbrückte Zucker (vgl. Amycolose) etabliert wurde. Die Tatsache, dass über zehn Jahre keine synthetischen Arbeiten zu Kibdelomycin (**10**) bekannt wurden, bestätigt die Komplexität der Struktur. Etwa ein Jahr nach Projektbeginn wurden drei verschiedene Totalsynthesen publiziert, was aufgrund ähnlich geplanter Schritte am Ende dazu führte, eine formale Totalsynthese anzustreben. Allein aufgrund der Molekülgröße musste Kibdelomycin (**10**) in Fragmente unterteilt werden, da eine lineare Strategie nicht denkbar gewesen wäre (SCHEMA 43). Verknüpfungspunkte waren zwischen den fünf (Hetero-)Cyclen (A, B, C, D, E) zu suchen. Um ähnlich lange Synthesesequenzen zu erhalten, wurde entschieden, als Fragmente Amykitanose (A) verknüpft mit der Tetramsäure **13** (B, grün), das Decalingerüst **14** (C, rot) sowie die mit einer Pyrrolcarbonsäure (E) acylierte Amycolose **15** (D, blau) einzeln zu synthetisieren und im Nachgang zusammenzufügen. Dieser Plan deckte sich im Wesentlichen mit dem der Totalsynthese von Yang *et al.*, weswegen für die formale Totalsynthese deren finale Schritte als Vorbild galten.[125]

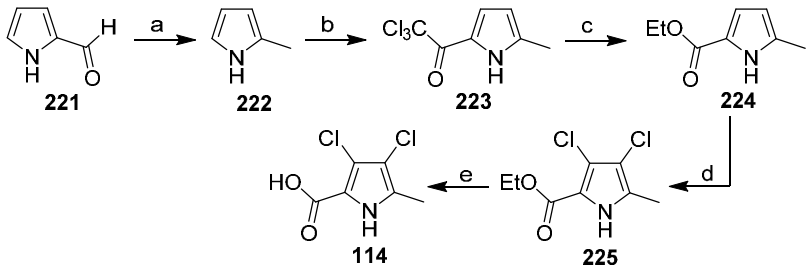
SCHEMA 43 präsentiert den Retrosyntheseplan für Kibdelomycin (**10**). Am Ende sollten die Fragmente **13**, **14** und **15** durch eine (1) *O*-Glykosylierung des Decalin-Bausteins und (2) *C*-Acylierung an der Tetramsäure verknüpft werden. Die beiden partiell deoxygenierten Hexosen wurden aus natürlichen Zuckern aufgebaut. Für die Synthese des Amykitanose-Bausteins **13** (grün) waren die *N*-Glykosylierung und die Tetramsäure-Darstellung Schlüsselschritte. Die Funktionalisierungen am Glykosid wurden in Anlehnung an Protokolle aus dem Bereich der Zuckerchemie durchgeführt. Der Aufbau des Decalins **14** (rot) wurde durch eine IMDA bewerkstelligt. Das dafür benötigte Trien **219** wurde nach einer HWE-Olefinierung und Fukuyama-Kupplung erhalten. Die darin enthaltenen Hydroxy-Gruppen wurden durch CBS-Reduktion und α-Hydroxylierung synthetisiert. Der untere Zucker, die *N*-acylierte Amycolose **15** (blau), wurde wiederum in zwei Fragmente unterteilt. Zum einen in den Pyrrolcarbonsäure-Rest, welcher durch Friedel-Crafts-Acylierung und Dichlorierung gebildet und mit der in der Ethyl-Verbrückung installierten Amino-Gruppe verknüpft wurde. Das Ziel des Aufbaus des

Hexose-Grundgerüsts **220** wurde andererseits durch Deoxygenierungen an 2- und 6-Position sowie mittels diastereoselektiver Addition eines C_2-Nucleophils an 3-Position erreicht.



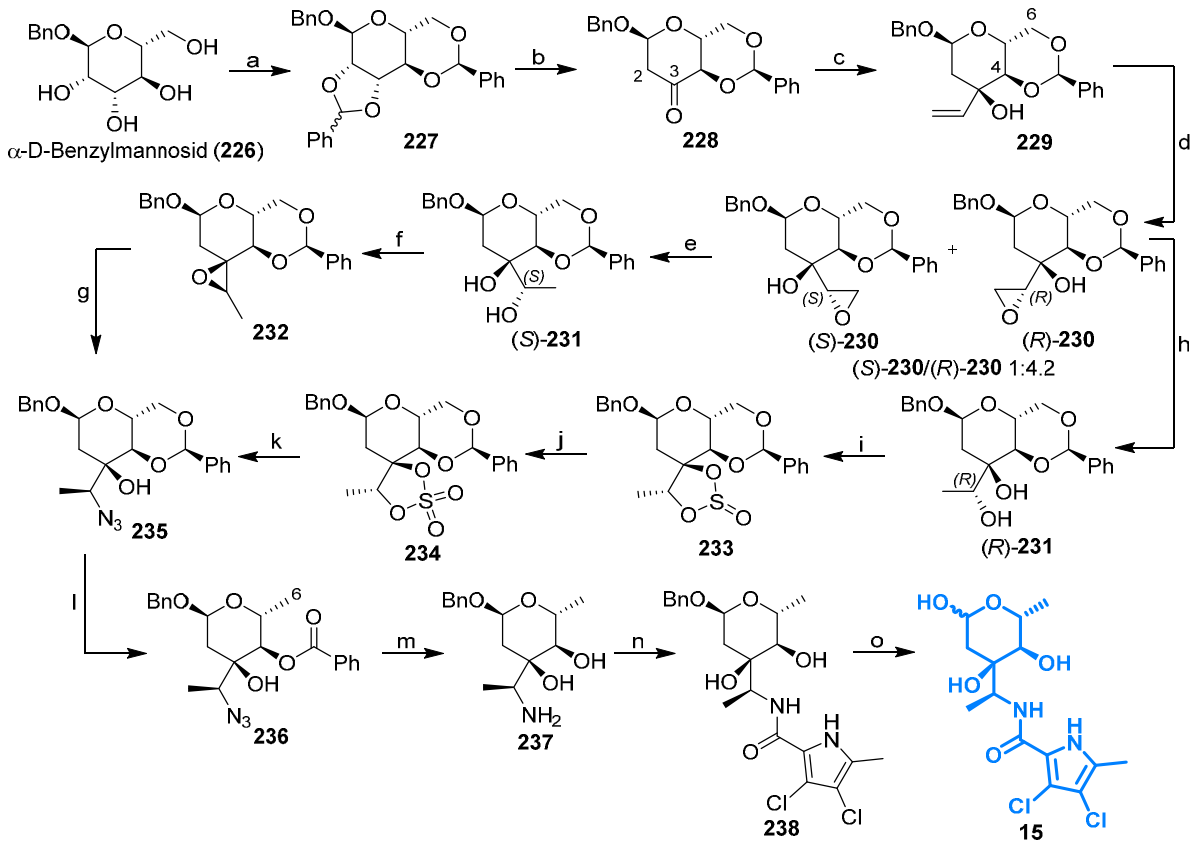
SCHEMA 43. Retrosynthese der verschiedenen Fragmente von Kibdelomycin (**10**).

Zunächst wird kurz die Synthese der Pyrrolcarbonsäure **114** vorgestellt (SCHEMA 44). Beginnend vom Pyrrolcarbaldehyd (**221**) wurde in einer Wolff-Kishner-Reduktion die Carbonyl-Gruppe entfernt. Ester **224** wurde durch Friedel-Crafts-Acylierung von **222** und Ethanolyse des Trichlormethylketons **223** gewonnen. Nach Dichlorierung mit SO_2Cl_2 wurde noch der Ester **225** zur Carbonsäure **114** verseift.



SCHEMA 44. Darstellung der Pyrrolcarbonsäure **114**.
Reagenzien und Bedingungen: a) NaOH, Ethylenglykol, $N_2H_4 \cdot xH_2O$, 210 °C, 2.5 h, 88%; b) Trichloracetylchlorid, THF, 0 °C → RT, 16 h, 96%; c) Na, EtOH, RT, dann **223**, 35 min, 81%; d) SO_2Cl_2, CH_2Cl_2, 0 °C, 3.5 h, 25%; e) NaOH, H_2O, MeOH, RT, 22 h, 95%.

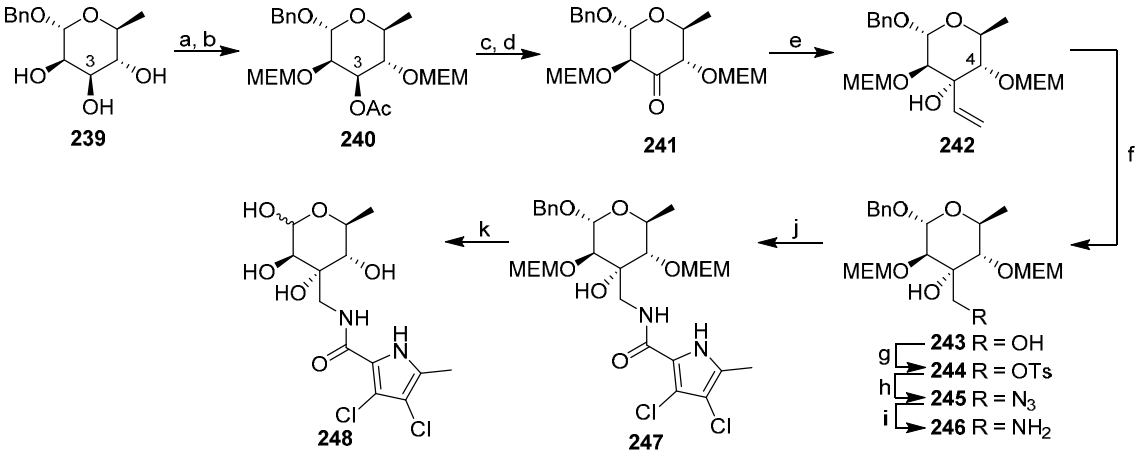
Die Pyrrolcarbonsäure **114** wurde in der Synthese der *N*-acylierten Amycolose **15** verwendet (SCHEMA 45). Startend von Benzylmannosid (**226**) wurde zunächst das Bisbenzylidenacetal **227** generiert, welches in einer Klemer-Rodemeyer-Fragmentierung zum Keton **228** umgesetzt wurde. Diese spezielle Reaktion hatte den Vorteil, gleichzeitig das 2-deoxygenierte sowie an 3-Position Keto-funktionalisierte Glykosid **228** zu erzeugen. Durch den sterischen Anspruch des übrigbleibenden 4,6-Benzylidenacetals verlief die darauffolgende Grignard-Addition mit Vinylmagnesiumbromid hochgradig diastereoselektiv (rückseitiger Angriff, → **229**). Der Allylalkohol **229** sollte stereoselektiv epoxidiert werden. Sharpless-Epoxidierung oder eine Epoxidierung mit $VO(acac)_2$/TBHP, welche zwingend einen Allylalkohol voraussetzen, verliefen erfolglos. Eine Prilezahev-Reaktion mit MCPBA dagegen lieferte die beiden trennbaren Epoxide (*S*)-**230** und (*R*)-**230** mit einem akzeptablen *d.r.* von 4.2:1. Es ist nicht geklärt, ob für diese Stereoselektivität vor allem die Sterik oder die mögliche Vorkoordination der Persäure durch die freie Hydroxy-Gruppe ausschlaggebend ist. Ein großer Vorteil der Synthese war, dass beide Diastereomere in getrennten Sequenzen weiterverwendet werden konnten und nicht verworfen werden mussten. Ausgehend vom Epoxid (*S*)-**230** wurde dieses zunächst hydridisch geöffnet und danach in einer Stufe zum dreifach substituierten Epoxid **232** umgesetzt. Die andere Sequenz, startend von Epoxid (*R*)-**230**, führte über eine hydridische Öffnung [→ (*R*)-**231**], Sulfitbildung (→ **233**) und eine Oxidation zum Sulfat **234**. Sowohl das Epoxid **232** als auch das Sulfat **234** konnten in einer S_N2-Reaktion mit NaN_3 in das Glykosid **235** überführt werden. Für die Öffnung des cyclischen Sulfats **234** wurde zudem eine neuartige Möglichkeit gefunden, auch säurelabile Substrate (hier: Benzylidenacetal) verwenden zu können. Dieses Benzylidenacetal **235** konnte in nur einer Stufe in den 6-deoxygenierten Zucker **236** umgewandelt werden. Der in dieser Reaktion ebenfalls generierte Benzoesäureester konnte gemeinsam mit dem Azid durch $LiAlH_4$ reduziert werden. Das nun freie Amin **237** wurde mit der Pyrrolcarbonsäure **114** verknüpft und die anomere Benzyl-Schutzgruppe abgespalten. Insgesamt wurde die *N*-acylierte Amycolose **15** in 9.8% Ausbeute über elf bzw. zwölf Stufen erhalten.



SCHEMA 45. Darstellung der *N*-acylierten Amycolose **15**.
Reagenzien und Bedingungen: a) BDMA, CSA, $CHCl_3$, Δ, 6.5 h; b) *n*BuLi, THF, −78 °C → −35 °C, 3.75 h, 78% (2 Stufen); c) VinylMgBr, THF, −78 °C, 3 h, 83%; d) *m*CPBA, CH_2Cl_2, RT, 22 h, 17% (*S*)-**230**, 71% (*R*)-**230**; e) $LiAlH_4$, THF, 0 °C → RT, 1.75 h, 97%; f) Tf_2O, Pyridin, CH_2Cl_2, −78 °C → 0 °C, 1.25 h; g) NaN_3, NH_4Cl, MeOH, 80 °C, 12 h, 81% (2 Stufen); h) $LiAlH_4$, THF, 0 °C → RT, 2.5 h; i) $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C, 3 h; j) $NaIO_4$, $RuCl_3 \cdot xH_2O$, MeCN, RT, 7 h; k) NaN_3, DMF, 65 °C, 6.75 h, dann Zitronensäurepuffer, EtOAc, 45 °C, 15 h, dann Zitronensäure, 3.5 h, 61% (4 Stufen); l) TIPST, DTBP, *n*-Octan, 140 °C, 6.75 h, 50%; m) $LiAlH_4$, THF, 0 °C → RT, 24 h, 79%; n) **114**, HOBt, EDC·HCl, NEt_3, CH_2Cl_2, 0 °C → RT, 16 h, 83%; o) BCl_3, CH_2Cl_2, −80 °C, 40 min, 81%.

Nachdem die acylierte Amycolose **15** in der Literatur als mögliches Anti-Krebs-Medikament beschrieben wurde und eine Derivatisierung davon sinnvoll erschien, sollte die zuvor entwickelte Methode zur Darstellung 3-(α-Aminoalkyl)-verbrückter Glykoside auf einen weiteren Zucker angewendet werden.[140] Hierfür wurde die benzylierte L-Rhamnose **239** gewählt. Sie wurde zunächst selektiv in 3-Position acetyliert, danach die restlichen Hydroxy-Gruppen MEM-geschützt (→ **240**, SCHEMA 46). Nach Abspaltung der Acetyl-Gruppe und Oxidation zum Keton **241** wurde wiederum eine Grignardierung mit Vinylmagnesiumbromid durchgeführt (→ **242**). Mittels eines NOESY-NMR-Experiments konnte festgestellt werden, dass der Angriff *anti* zur OMEM-Gruppe an 4-Position verlief. Dies bedeutete mit Hinblick auf die in SCHEMA 45 dargestellte Synthese, dass insbesondere die Stereokonfiguration an C-4 für die Diastereoselektivität der Grignard-Addition ausschlaggebend ist. In vier Stufen (Ozonolyse,

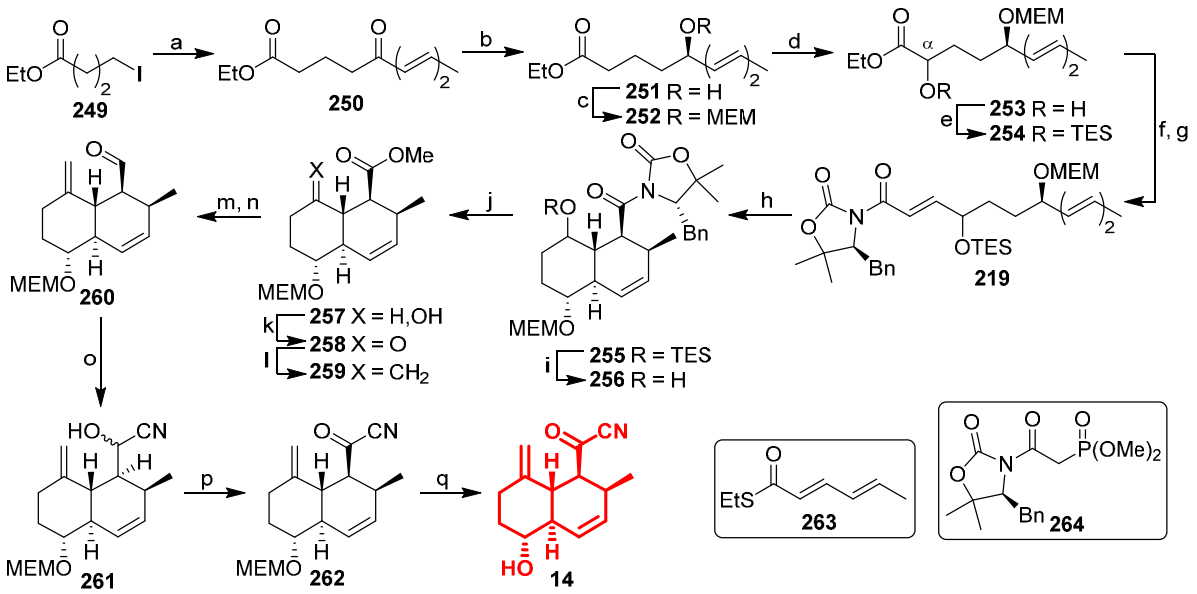
Tosylierung, S_N2-Reaktion, Staudinger-Reaktion) wurde das Amin **246** hergestellt. Dieses wurde analog zu **238** amidiert und danach in einer Stufe mittels BCl_3 global entschützt [→ **248**, Σ 17.5%, 11 Stufen (LLS)]. Neben der Installation einer α-Aminoalkyl-Einheit bietet die Vinyl-Gruppe auch noch andere Möglichkeiten der Modifikation an, wie (Grubbs-)Metathese, Hydroborierung, Wacker-Oxidation, Dihydroxylierungen und weitere. Dies ermöglicht eine flexible Funktionalisierbarkeit des Glykosids.



SCHEMA 46. Synthese des Amycolose-abgeleiteten Derivats **248**.
Reagenzien und Bedingungen: a) AcCl, $MoO_2(acac)_2$, 2,4,6-Collidin, 1,4-Dioxan, RT, 3 h, 95%; b) MEMCl, DIPEA, CH_2Cl_2, 0 °C → 40 °C, 1 d, 80%; c) DIBAL, PhMe, 0 °C, 3 h, 82%; d) DMP, CH_2Cl_2, 0 °C → RT, 5 h, 84%; e) VinylMgBr, THF, −78 °C, 5 h, 79%; f) O_3, CH_2Cl_2, MeOH, −78 °C, 10 min, dann $NaBH_4$, RT, 24 h, 90%; g) *p*TsCl, DMAP, NEt_3, CH_2Cl_2, RT, 21 h, 77%; h) NaN_3, DMF, 65 °C, 17 h, 94%; i) PPh_3, THF, RT, 2 d; dann H_2O, RT, 3 d, 86%; j) **114**, EDC·HCl, HOBt, DMAP, CH_2Cl_2, 0 °C → RT, ü.N., 81%; k) BCl_3, CH_2Cl_2, −78 °C, 3.5 h, 93%.

Die Synthese des mittels Diels-Alder-Reaktion aufzubauenden Decalins **14** wurde mit einer Pd-katalysierten Fukuyama-Kupplung begonnen (SCHEMA 47). Das aus dem Iodid **249** erzeugte Zink-Organyl wurde im Anschluss mit dem Sorbinsäurethioester **263** verknüpft. Der stereoselektive Aufbau des sekundären Alkohols **251** aus dem Keton **250** erfolgte durch die im Labormaßstab besser durchführbare CBS-Reduktion, verglichen mit der ursprünglich geplanten Noyori-Reduktion. Nach MEM-Schützung des freien Alkohols **251** wurde der Ester **252** α-hydroxyliert und diese Gruppe wiederum TES-geschützt (→ **254**). Die Einführung der zweiten Hydroxy-Gruppe war notwendig, um später an dieser Stelle eine Wittig-Reaktion zur Installation der Methylen-Einheit durchführen zu können. Versuche, die Hydroxy- oder eine Methylen-Gruppe aus dem Edukt mitzubringen, schlugen fehl. Durch DIBAL-Reduktion von **254** und HWE-Olefinierung des gebildeten Aldehyds mit dem Phosphonat **264** wurde das SuperQuat-Auxiliar angeheftet (→ **219**). Damit konnte die diastereoselektive IMDA ablaufen. Die besten Ergebnisse wurden mit einer Wärme-induzierten Diels-Alder-Reaktion im

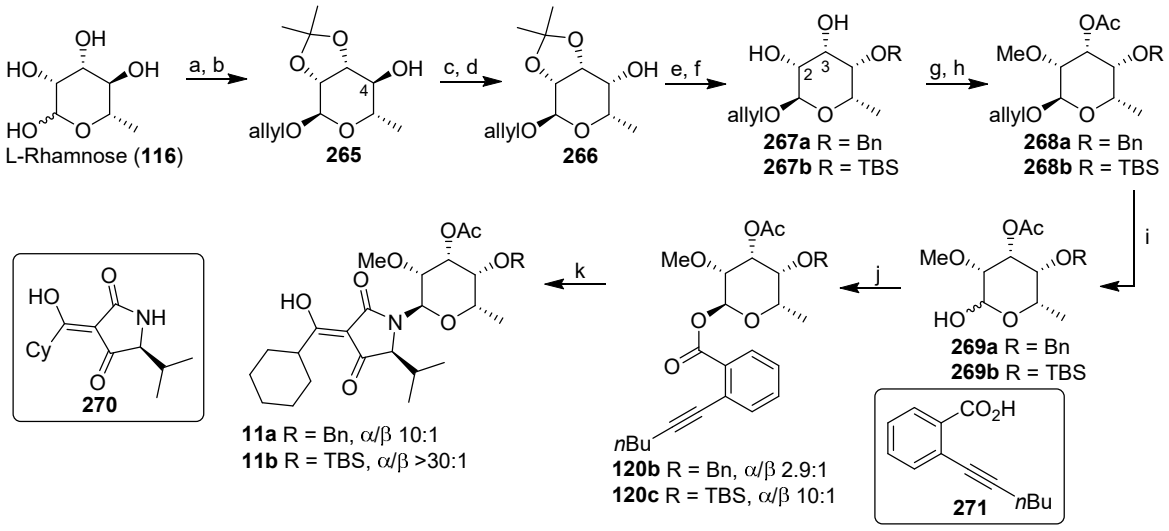
Vergleich zu einer Lewis-Säure-katalysierten DA erzielt. Für die schwierige Abnahme des Auxiliars musste zunächst die TES-Gruppe mittels HF·Pyridin-Komplex entfernt werden (→ **256**), woraufhin die Methanolyse des Imids **256** realisiert werden konnte. Alkohol **257** wurde durch DMP-Oxidation und Wittig-Olefinierung in das terminale Alken **259** überführt, die Ester-Gruppe darin in zwei Schritten zum Aldehyd **260** umgesetzt. Mit TMSCN wurde **260** in das Cyanohydrin **261** überführt, welches mittels DMP zum Acylcyanid **262** oxidiert wurde. Lewis-saure MEM-Entschützung führte zum Fragment **14** [rot, Σ 10.0%, 17 Stufen (LLS)].



SCHEMA 47. Synthese des Decalin-Fragments **14**.
Reagenzien und Bedingungen: a) **249**, Zn, THF, Δ, 3.5 h, dann **263**, $Pd(PPh_3)_4$, PhMe, RT, 23 h, 91%; b) (*S*)-Me-CBS-Kat., BH_3·THF, THF, RT, 1 h, dann **250**, −35 °C, 3.5 h, 90%; c) MEMCl, DIPEA, CH_2Cl_2, 40 °C, 23 h, 79%; d) KHMDS, THF, −78 °C, 30 min, dann MoOPH, −78 °C, 4 h, 89% (*d.r.* 1.9:1); e) TESCl, Imidazol, DMAP, CH_2Cl_2, 0 °C → 40 °C, 4.5 h, quant.; f) DIBAL, PhMe, −78 °C, 5 h; g) **264**, LiHMDS, THF, 0 °C, 1 h, dann Aldehyd, 0 °C → RT, 17 h, 70% (2 Stufen); h) PhMe, 80 °C, 3 d, 43%; i) HF·Pyridin, THF, 0 °C, 15 h, quant.; j) NaOMe, CH_2Cl_2, 0 °C, 3 h, 90%; k) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C → RT, 3 h, 96%; l) $MePPh_3Br$, KO*t*Bu, THF, 0 °C, 45 min, dann **258**, THF, 0 °C → RT, 3 h, 90%; m) DIBAL, CH_2Cl_2, 0 °C, 5 h, quant.; n) DMP, CH_2Cl_2, 0 °C → RT, 3 h, 91%; o) TMSCN, NEt_3, CH_2Cl_2, 0 °C, 20 min, RT, 4 h, dann NH_4F, EtOH, 0 °C, 2 h; p) DMP, CH_2Cl_2, 0 °C, 1.5 h, 82% (2 Stufen); q) $LiBF_4$, MeCN, H_2O, 55 °C, 4.5 h, 99%.

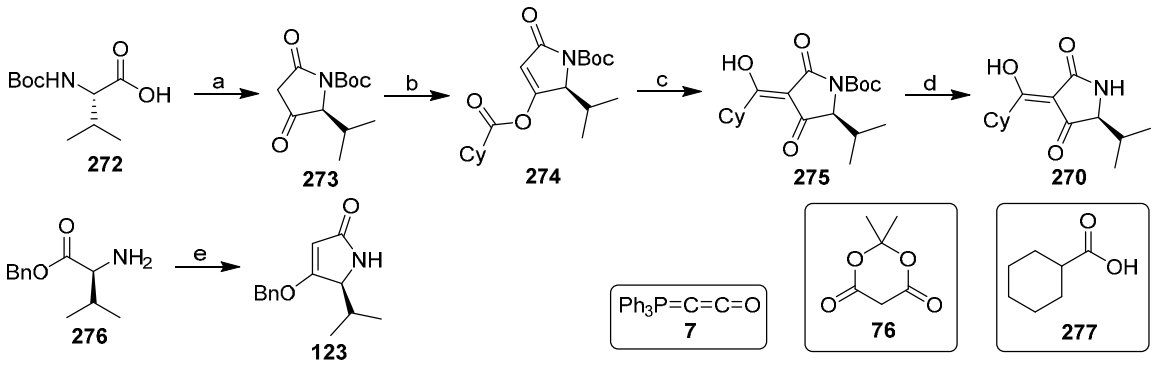
Das Amykitanose-Fragment **13** (SCHEMA 50) wie auch das Amykitanose-Derivate **11a**/**11b** wurden aus L-Rhamnose (**116**) dargestellt (SCHEMA 48). Es wurde mit der Allyl-Schützung der anomeren Position sowie der Acetonid-Schützung des *syn*-Diols gestartet (→ **265**). Das Stereozentrum an 4-Position wurde in einer Oxidation-Reduktions-Sequenz invertiert und die daraus resultierende Hydroxy-Gruppe Benzyl- oder TBS-geschützt. Für die nun folgenden Schritte wurden die Synthesen je nach Schutzgruppe leicht abgeändert und optimiert. Nach Abnahme der Isopropyliden-Gruppe (→ **267a**/**267b**) wurde die Hydroxy-Gruppe an 3-Position

regioselektiv acetyliert sowie die restliche Hydroxy-Gruppe methyliert (→ **268a**/**268b**). Durch die Entschützung der anomeren Position konnte der aktivierte Benzoesäureester installiert werden (→ **120b**/**120c**). Die damit durchführbare Au-katalysierte *N*-Glykosylierung (→ **11a**/**11b**) der Modelltetramsäure **270** war die einzige Möglichkeit der Verknüpfung zwischen Tetramsäure- und Amykitanose-Fragment. Es zeigte sich, dass die Verwendung einer Silyl-Schutzgruppe einen erheblichen Effekt auf das α/β-Verhältnis hatte. Es konnte selektiv das α-Anomer trotz fehlenden Nachbargruppeneffekts erhalten werden. Mit der Synthese der 3-Acyl-Tetramsäuren **11a**/**11b** wurde das erste Mal die Möglichkeit einer direkten *N*-Glykosylierung von 3-Acyl-Tetramsäuren aufgezeigt.



SCHEMA 48. Synthese der *N*-glykosylierten 3-Acyl-Tetramsäuren **11a**/**11b**.
Reagenzien und Bedingungen: a) AcCl, C_3H_5OH, 0 °C → 55 °C, 24 h, 93%; b) $CuSO_4$, AcMe, RT, 17 h, 95%; c) $(COCl)_2$, DMSO, −78 °C, 40 min, dann **265**, 50 min, dann DIPEA, −78 °C → RT, 16 h, 92%; d) $NaBH_4$, 0 °C, EtOH, 1.5 h, 96%; e) **267a**: NaH, Imidazol, DMF, 0 °C, 35 min, dann BnBr, TBAI, RT, 17 h, 99%; **267b**: TBSOTf, Pyridin, CH_2Cl_2, 0 °C, 5 h, quant.; f) **267a**: AcOH, H_2O, Δ, 1.5 h, 94%; **267b**: HCOOH, EtOH, RT, 2.5 h, 42%; g) **268a**: Bu_2SnO, PhMe, Δ, 4 h, dann AcCl, 0 °C, 30 min, 79%; **268b**: Bu_2SnO, PhMe, Δ, 3 h, dann AcCl, RT, 1 h, 93%; h) **268a**: $TMSCHN_2$, HBF_4, CH_2Cl_2, 0 °C, 5 h, 90%; **268b**: Me_3OBF_4, Protonenschwamm, CH_2Cl_2, 0 °C → 40 °C, 21 h, 96%; i) **269a**: $Pd(PPh_3)_4$, AcOH, RT, 17 h, 94%; **269b**: DABCO, $RhCl(PPh_3)_3$, EtOH, Δ, 15 h, dann I_2, Phosphatpuffer pH=7, H_2O, EtOAc, RT, 10 min, 84%; j) **120b**: **271**, DCC, DMAP, CH_2Cl_2, RT, 3 h, 93%; **120c**: **271**, DCC, DMAP, CH_2Cl_2, RT, 3.5 h, 72%; k) **11a**: **270**, PPh_3AuNTf_2, RT → 40 °C, 17 h, 58%; **11b**: **270**, PPh_3AuNTf_2, RT → 40 °C, 20 h, 50%.

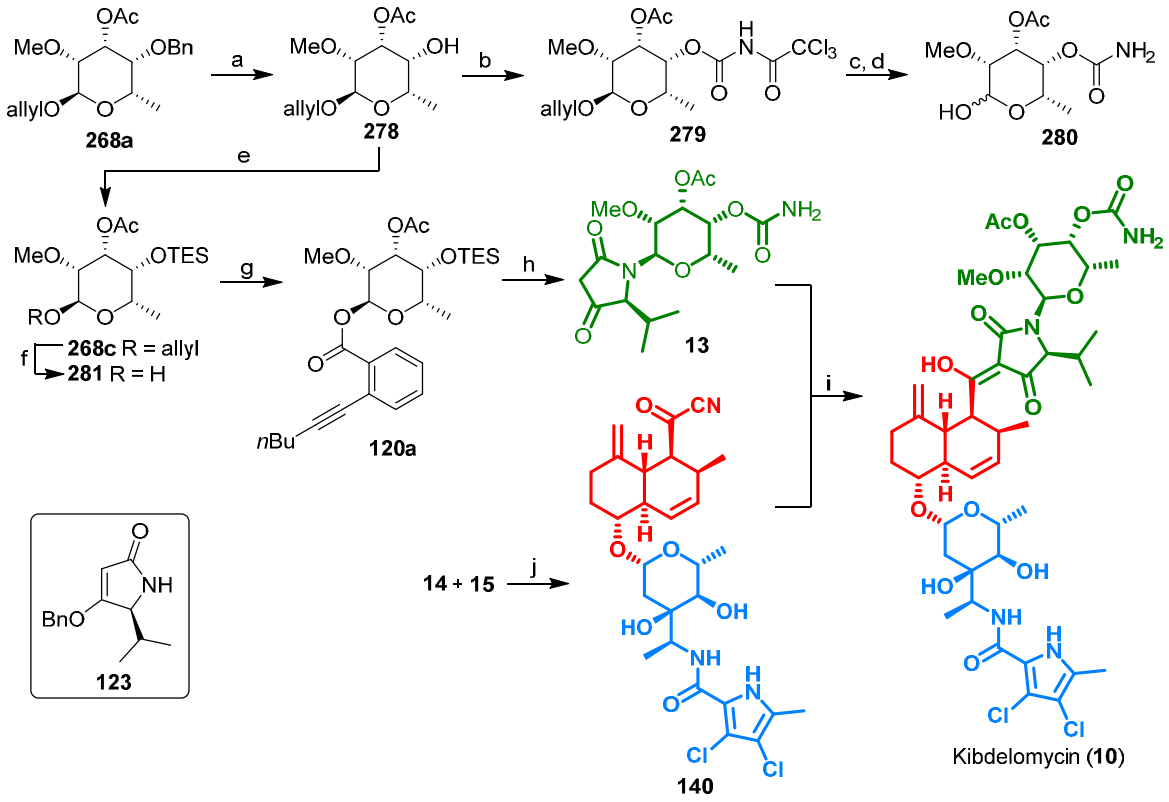
Für die Synthesen der *N*-glykosylierten Tetramsäuren **11a**/**11b** sowie für die formale Totalsynthese von Kibdelomycin (**10**) waren die Tetramsäure **270** sowie das Tetramat **123** notwendig. Die entsprechenden Reaktionssequenzen dazu sind in SCHEMA 49 abgebildet. Die 3-Acyl-Tetramsäure **270** wurde ausgehend von Boc-Val-OH (**272**) unter Verwendung von Meldrumsäure (**76**) und einer Umlagerung nach Yoshii synthetisiert. Das Benzyltetramat **123** wurde nach dem Protokoll von Schobert mit Ph_3PCCO (**7**) hergestellt.



SCHEMA 49. Synthesen der Tetramsäure **270** und des Benzyltetramats **123**.
Reagenzien und Bedingungen: a) Meldrumsäure (**76**), DMAP, EDC·HCl, CH_2Cl_2, RT, 3 h, dann EtOAc, Δ, 2 h; b) **277**, EDC·HCl, DMAP, CH_2Cl_2, 0 °C, 50 min, dann **273**, RT, 2.5 h; c) NEt_3, DMAP, CH_2Cl_2, RT, 2 d, 50% (3 Stufen); d) TFA, CH_2Cl_2, RT, 20 min, 75%; e) Ph_3PCCO (**7**), PhCOOH, THF, 60 °C, 22 h, 63%.

Zuletzt wurden noch die finalen, notwendigen Schritte für die formale Totalsynthese durchgeführt (vgl. 1.4.3.2) sowie die natürliche Amykitanose (**280**) dargestellt (SCHEMA 50). Das bekannte Glykosid **268a** wurde mittels Et_3SiH/I_2 zunächst Benzyl-entschützt (→ **278**). Der Alkohol **278** konnte nun in das Carbamat **279** überführt und zur Amykitanose (**280**) entschützt werden. Die Ausbeute dieser Sequenz war gering, da keinerlei Optimierung vorgenommen wurde. Außerdem wurde der Alkohol **278** TES-geschützt (→ **268c**) und Allyl-entschützt, um das Glykosid **281** zu erhalten. Dieses wurde zum bekannten aktivierten Ester **120a** umgesetzt [Σ 17.1%, 12 Stufen (LLS)]. Ab hier waren die Schritte nach Yang *et al.* literaturbekannt.[125] Es fehlte für die vollständige Synthese noch das Zusammenfügen der drei Fragmente **13**, **14** und **15**.

Insgesamt konnte in dieser Arbeit durch eine effiziente Synthese dreier Bausteine ein alternativer Zugang zum Antibiotikum Kibdelomycin (**10**) geschaffen werden. Durch die flexible, konvergente Synthesestrategie wurde es ermöglicht, einzelne Fragmente zu derivatisieren, was für eine Leitstruktur-Optimierung von Kibdelomycin (**10**) interessant ist. Zusätzlich wurden zwei gänzlich neue Methoden zum Aufbau *N*-glykosylierter 3-Acyl-Tetramsäuren sowie 3-(α-Aminoalkyl)-Glykoside entwickelt.



SCHEMA 50. Letzte Syntheseschritte zur formalen Totalsynthese von Kibdelomycin (**10**).
Reagenzien und Bedingungen: a) I_2, CH_2Cl_2, −65 °C, 35 min, dann Et_3SiH, −65 °C → −20 °C, 2 h, 64%; b) Trichloracetylisocyanat, CH_2Cl_2, 0 °C, 13 min, 91%; c) SiO_2, THF, MeOH, 40 °C, quant.; d) $Pd(PPh_3)_4$, AcOH, RT, 16 h, 17%; e) TESOTf, Pyridin, CH_2Cl_2, 0 °C, 2 h, quant.; f) DABCO, $RhCl(PPh_3)_3$, EtOH, Δ, 5 h, dann I_2, Phosphatpuffer, H_2O, EtOAc, RT, 25 min, 73%; g) **271**, DCC, DMAP, CH_2Cl_2, RT, 3 h, 71%; h) **123**, Ref.[125]; i)/j) Ref.[125].

Weitere Details in:

Manuel G. Schriefer, Laura Treiber, Rainer Schobert

Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides

Chem. Sci. **2023**, *14* (13), 3562 – 3568.

4 Literaturverzeichnis

(1) Ventola, C. L. The antibiotic resistance crisis: part 1: causes and threats. *Pharm. Ther.* **2015**, *40* (4), 277–283.

(2) Goossens, H. Antibiotic consumption and link to resistance. *Clin. Microbiol. Infect.* **2009**, *15 Suppl 3*, 12–15. DOI: 10.1111/j.1469-0691.2009.02725.x

(3) Pulingam, T.; Parumasivam, T.; Gazzali, A. M.; Sulaiman, A. M.; Chee, J. Y.; Lakshmanan, M.; Chin, C. F.; Sudesh, K. Antimicrobial resistance: Prevalence, economic burden, mechanisms of resistance and strategies to overcome. *Eur. J. Pharm. Sci.* **2022**, *170*, 106103. DOI: 10.1016/j.ejps.2021.106103

(4) Ventola, C. L. The antibiotic resistance crisis: part 2: management strategies and new agents. *Pharm. Ther.* **2015**, *40* (5), 344–352.

(5) Giordanetto, F.; Kihlberg, J. Macrocyclic drugs and clinical candidates: what can medicinal chemists learn from their properties? *J. Med. Chem.* **2014**, *57* (2), 278–295. DOI: 10.1021/jm400887j

(6) Marsault, E.; Peterson, M. L. Macrocycles are great cycles: applications, opportunities, and challenges of synthetic macrocycles in drug discovery. *J. Med. Chem.* **2011**, *54* (7), 1961–2004. DOI: 10.1021/jm1012374

(7) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45* (12), 2615–2623. DOI: 10.1021/jm020017n

(8) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23* (1-3), 3–25. DOI: 10.1016/S0169-409X(96)00423-1

(9) Huang, Y.; Strobel, E. D.; Ho, C. Y.; Reynolds, C. H.; Conway, K. A.; Piesvaux, J. A.; Brenneman, D. E.; Yohrling, G. J.; Moore Arnold, H.; Rosenthal, D.; Alexander, R. S.; Tounge, B. A.; Mercken, M.; Vandermeeren, M.; Parker, M. H.; Reitz, A. B.; Baxter, E. W. Macrocyclic BACE inhibitors: Optimization of a micromolar hit to nanomolar leads. *Bioorg. Med. Chem. Lett.* **2010**, *20* (10), 3158–3160. DOI: 10.1016/j.bmcl.2010.03.097

(10) Ermert, P.; Moehle, K.; Obrecht, D. Chapter 8. Macrocyclic Inhibitors of GPCR's, Integrins and Protein–Protein Interactions. In *Macrocycles in Drug Discovery*; Levin, J., Ed.; Drug Discovery; Royal Society of Chemistry, 2014; pp 283–338. DOI: 10.1039/9781782623113-00283

(11) a) Marsault, E.; Benakli, K.; Beaubien, S.; Saint-Louis, C.; Déziel, R.; Fraser, G. Potent macrocyclic antagonists to the motilin receptor presenting novel unnatural amino acids. *Bioorg. Med. Chem. Lett.* **2007**, *17* (15), 4187–4190. DOI: 10.1016/j.bmcl.2007.05.043#; b) Marsault, E.; Hoveyda, H. R.; Peterson, M. L.; Saint-Louis, C.; Landry, A.; Vézina, M.; Ouellet, L.; Wang, Z.; Ramaseshan, M.; Beaubien, S.; Benakli, K.; Beauchemin, S.; Déziel, R.; Peeters, T.; Fraser, G. L. Discovery of a new class of macrocyclic antagonists to the human motilin receptor. *J. Med. Chem.* **2006**, *49* (24), 7190–7197. DOI: 10.1021/jm0606600#;

(12) Mas-Moruno, C.; Rechenmacher, F.; Kessler, H. Cilengitide: the first anti-angiogenic small molecule drug candidate design, synthesis and clinical evaluation. *Anti-Cancer Agents Med. Chem.* **2010**, *10* (10), 753–768. DOI: 10.2174/187152010794728639

(13) a) Kurozumi, K.; Ichikawa, T.; Onishi, M.; Fujii, K.; Date, I. Cilengitide treatment for malignant glioma: current status and future direction. *Neurol. Med. Chir. (Tokyo)* **2012**, *52* (8), 539–547. DOI: 10.2176/nmc.52.539#; b) Stupp, R.; Hegi, M. E.; Gorlia, T.; Erridge, S. C.; Perry, J.; Hong, Y.-K.; Aldape, K. D.; Lhermitte, B.; Pietsch, T.; Grujicic, D.; Steinbach, J. P.; Wick, W.; Tarnawski, R.; Nam, D.-H.; Hau, P.; Weyerbrock, A.; Taphoorn, M. J. B.; Shen, C.-C.; Rao, N.; Thurzo, L.; Herrlinger, U.; Gupta, T.; Kortmann, R.-D.; Adamska, K.; McBain, C.; Brandes, A. A.; Tonn, J. C.; Schnell, O.; Wiegel, T.; Kim, C.-Y.; Nabors, L. B.; Reardon, D. A.; van den Bent, M. J.; Hicking, C.; Markivskyy, A.; Picard, M.; Weller, M. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with

methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **2014**, *15* (10), 1100–1108. DOI: 10.1016/S1470-2045(14)70379-1#;

(14) Johnson, V. A.; Singh, E. K.; Nazarova, L. A.; Alexander, L. D.; McAlpine, S. R. Macrocyclic inhibitors of hsp90. *Curr. Top. Med. Chem.* **2010**, *10* (14), 1380–1402. DOI: 10.2174/156802610792232088

(15) Jhaveri, K.; Modi, S. HSP90 inhibitors for cancer therapy and overcoming drug resistance. *Adv. Pharmacol.* **2012**, *65*, 471–517. DOI: 10.1016/B978-0-12-397927-8.00015-4

(16) a) Rapisarda, A.; Melillo, G. Role of the VEGF/VEGFR axis in cancer biology and therapy. *Adv. Cancer Res.* **2012**, *114*, 237–267. DOI: 10.1016/B978-0-12-386503-8.00006-5#; b) Masoud, G. N.; Li, W. HIF-1α pathway: role, regulation and intervention for cancer therapy. *Acta Pharm. Sin. B* **2015**, *5* (5), 378–389. DOI: 10.1016/j.apsb.2015.05.007#;

(17) Schlünzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. *Nature* **2001**, *413* (6858), 814–821. DOI: 10.1038/35101544

(18) Jelić, D.; Antolović, R. From Erythromycin to Azithromycin and New Potential Ribosome-Binding Antimicrobials. *Antibiotics* **2016**, *5* (3). DOI: 10.3390/antibiotics5030029

(19) Wu, J.; Zhang, Q.; Deng, W.; Qian, J.; Zhang, S.; Liu, W. Toward improvement of erythromycin A production in an industrial Saccharopolyspora erythraea strain via facilitation of genetic manipulation with an artificial attB site for specific recombination. *Appl. Environ. Microbiol.* **2011**, *77* (21), 7508–7516. DOI: 10.1128/AEM.06034-11

(20) Scientific Opinion on the use of natamycin (E 235) as a food additive. *EFSA Journal* **2009**, *7* (12), 1412. DOI: 10.2903/j.efsa.2009.1412

(21) Mesa-Arango, A. C.; Scorzoni, L.; Zaragoza, O. It only takes one to do many jobs: Amphotericin B as antifungal and immunomodulatory drug. *Front. Microbiol.* **2012**, *3*, 286. DOI: 10.3389/fmicb.2012.00286

(22) Huang, W.; Zhang, Z.; Han, X.; Tang, J.; Wang, J.; Dong, S.; Wang, E. Ion channel behavior of amphotericin B in sterol-free and cholesterol- or ergosterol-containing supported phosphatidylcholine bilayer model membranes investigated by electrochemistry and spectroscopy. *Biophys. J.* **2002**, *83* (6), 3245–3255. DOI: 10.1016/S0006-3495(02)75326-5

(23) Zumbuehl, A.; Jeannerat, D.; Martin, S. E.; Sohrmann, M.; Stano, P.; Vigassy, T.; Clark, D. D.; Hussey, S. L.; Peter, M.; Peterson, B. R.; Pretsch, E.; Walde, P.; Carreira, E. M. An amphotericin B-fluorescein conjugate as a powerful probe for biochemical studies of the membrane. *Angew. Chem. Int. Ed.* **2004**, *43* (39), 5181–5185. DOI: 10.1002/anie.200460489

(24) Prota, A. E.; Bargsten, K.; Zurwerra, D.; Field, J. J.; Díaz, J. F.; Altmann, K.-H.; Steinmetz, M. O. Molecular mechanism of action of microtubule-stabilizing anticancer agents. *Science* **2013**, *339* (6119), 587–590. DOI: 10.1126/science.1230582

(25) Stephens, T. C.; Unsworth, W. P. Consecutive Ring-Expansion Reactions for the Iterative Assembly of Medium-Sized Rings and Macrocycles. *Synlett* **2020**, *31* (02), 133–146. DOI: 10.1055/s-0037-1611500

(26) Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Gayatri, G.; Sastry, G. N.; Yadav, J. S. Protecting-Group Directed Stereoselective Intramolecular Nozaki-Hiyama-Kishi Reaction: A Concise and Efficient Total Synthesis of Amphidinolactone A. *Eur. J. Org. Chem.* **2010**, *2010* (25), 4775–4784. DOI: 10.1002/ejoc.201000565

(27) Gil, A.; Albericio, F.; Álvarez, M. Role of the Nozaki-Hiyama-Takai-Kishi Reaction in the Synthesis of Natural Products. *Chem. Rev.* **2017**, *117* (12), 8420–8446. DOI: 10.1021/acs.chemrev.7b00144

(28) Mohapatra, D. K.; Pattanayak, M. R.; Das, P. P.; Pradhan, T. R.; Yadav, J. S. Ring-closing metathesis (RCM) based synthesis of the macrolactone core of amphidinolactone A. *Org. Biomol. Chem.* **2011**, *9* (16), 5630–5632. DOI: 10.1039/C1OB05335C

(29) Monfette, S.; Fogg, D. E. Equilibrium ring-closing metathesis. *Chem. Rev.* **2009**, *109* (8), 3783–3816. DOI: 10.1021/cr800541y

(30) Liu, P.; Xu, X.; Dong, X.; Keitz, B. K.; Herbert, M. B.; Grubbs, R. H.; Houk, K. N. Z-Selectivity in olefin metathesis with chelated Ru catalysts: computational studies of mechanism and selectivity. *J. Am. Chem. Soc.* **2012**, *134* (3), 1464–1467. DOI: 10.1021/ja2108728

(31) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. Ring Closing Alkyne Metathesis. Comparative Investigation of Two Different Catalyst Systems and Application to the Stereoselective Synthesis of Olfactory Lactones, Azamacrolides, and the Macrocyclic Perimeter of the Marine Alkaloid Nakadomarin A. *J. Am. Chem. Soc.* **1999**, *121* (48), 11108–11113. DOI: 10.1021/ja992074k

(32) a) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. Ring-closing alkyne metathesis. Application to the total synthesis of sophorolipid lactone. *J. Org. Chem.* **2000**, *65* (25), 8758–8762. DOI: 10.1021/jo0012952#; b) Fürstner, A.; Davies, P. W. Alkyne metathesis. *Chem. Commun.* **2005**, (18), 2307–2320. DOI: 10.1039/B419143A#;

(33) a) Ronson, T. O.; Taylor, R. J.; Fairlamb, I. J. Palladium-catalysed macrocyclisations in the total synthesis of natural products. *Tetrahedron* **2015**, *71* (7), 989–1009. DOI: 10.1016/j.tet.2014.11.009#; b) White, J. D.; Jackson, R. W.; Hanselmann, R. Total synthesis of rutamycin B via Suzuki macrocyclization. *Chem. Commun.* **1998**, (1), 79–80. DOI: 10.1039/A707251A#;

(34) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. Total synthesis of amphoteronolide B and amphotericin B. 2. Total synthesis of amphoteronolide B. *J. Am. Chem. Soc.* **1988**, *110* (14), 4685–4696. DOI: 10.1021/ja00222a029

(35) a) Bestmann, H. J.; Schobert, R. A Novel Synthesis of Macrocyclic Lactones. *Angew. Chem. Int. Ed.* **1983**, *22* (10), 780–782. DOI: 10.1002/anie.198307801#; b) Schmidt, R.; Ostermeier, M.; Schobert, R. Wittig Cyclization of ω-Hydroxy Hemiacetals: Synthesis of (+)-Aspicilin. *J. Org. Chem.* **2017**, *82* (17), 9126–9132. DOI: 10.1021/acs.joc.7b01702#;

(36) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. Update 1 of: macrolactonizations in the total synthesis of natural products. *Chem. Rev.* **2013**, *113* (1), PR1-40. DOI: 10.1021/cr300129n

(37) a) Mukaiyama, T.; Usui, M.; Saigo, K. The facile synthesis of lactones. *Chem. Lett.* **1976**, *5* (1), 49–50. DOI: 10.1246/cl.1976.49#; b) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. Scandium Trifluoromethanesulfonate as an Extremely Active Lewis Acid Catalyst in Acylation of Alcohols with Acid Anhydrides and Mixed Anhydrides. *J. Org. Chem.* **1996**, *61* (14), 4560–4567. DOI: 10.1021/jo952237x#; c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52* (7), 1989–1993. DOI: 10.1246/bcsj.52.1989#; d) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. Synthesis of erythronolide a via a very efficient macrolactonization under usual acylation conditions with the Yamaguchi reagent. *Tetrahedron Lett.* **1990**, *31* (44), 6367–6370. DOI: 10.1016/S0040-4039(00)97066-7#;

(38) Corey, E. J.; Nicolaou, K. C. Efficient and mild lactonization method for the synthesis of macrolides. *J. Am. Chem. Soc.* **1974**, *96* (17), 5614–5616. DOI: 10.1021/ja00824a073

(39) a) Boden, E. P.; Keck, G. E. Proton-transfer steps in Steglich esterification: a very practical new method for macrolactonization. *J. Org. Chem.* **1985**, *50* (13), 2394–2395. DOI: 10.1021/jo00213a044#; b) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. Synthesis of lactones and cycloalkanes. Cyclization of ω-hydroxy acids and ethyl α-cyano-ω-hydroxycarboxylates. *Tetrahedron Lett.* **1976**, *17* (28), 2455–2458. DOI: 10.1016/0040-4039(76)90018-6#; c) Justus, K.; Steglich, W. First synthesis of a strained 14-membered biaryl ether lactone by macrolactonization. *Tetrahedron Lett.* **1991**, *32* (41), 5781–5784. DOI: 10.1016/S0040-4039(00)93554-8#;

(40) a) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M. Structural and synthetic studies of the spore germination autoinhibitor, gloeosporone. *J. Am. Chem. Soc.* **1988**, *110* (18), 6210–6218. DOI: 10.1021/ja00226a041#; b) Keck, G. E.; Boden, E. P.; Wiley, M. R. Total synthesis of (+)-colletodiol: new methodology for the synthesis of macrolactones. *J. Org. Chem.* **1989**, *54* (4), 896–906. DOI: 10.1021/jo00265a033#; c) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. Multi-step application of immobilized reagents and scavengers: a total synthesis of epothilone C. *Chem. Eur. J.* **2004**, *10* (10), 2529–2547. DOI: 10.1002/chem.200305669#;

(41) Bechtler, C.; Lamers, C. Macrocyclization strategies for cyclic peptides and peptidomimetics. *RSC Med. Chem.* **2021**, *12* (8), 1325–1351. DOI: 10.1039/D1MD00083G

(42) Shen, L.; Simmons, C. J.; Sun, D. Microwave-assisted synthesis of macrocycles via intramolecular and/or bimolecular Ullmann coupling. *Tetrahedron Lett.* **2012**, *53* (32), 4173–4178. DOI: 10.1016/j.tetlet.2012.05.142

(43) Haase, R. G.; Schobert, R. Synthesis of the Bioherbicidal Fungus Metabolite Macrocidin A. *Org. Lett.* **2016**, *18* (24), 6352–6355. DOI: 10.1021/acs.orglett.6b03240

(44) Michel, K. H.; Demarco, P. V.; Nagarjan, R. The isolation and structure elucidation of macrocyclic lactone antibiotic, A26771B. *J. Antibiot.* **1977**, *30* (7), 571–575. DOI: 10.7164/antibiotics.30.571

(45) Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. Stereospecific total synthesis and absolute configuration of a macrocyclic lactone antibiotic, A26771B. *Tetrahedron Lett.* **1980**, *21* (15), 1479–1482. DOI: 10.1016/S0040-4039(00)92751-5

(46) Stierle, A. A.; Stierle, D. B.; Decato, D.; Priestley, N. D.; Alverson, J. B.; Hoody, J.; McGrath, K.; Klepacki, D. The Berkeleylactones, Antibiotic Macrolides from Fungal Coculture. *J. Nat. Prod.* **2017**, *80* (4), 1150–1160. DOI: 10.1021/acs.jnatprod.7b00133

(47) Stierle, A. A.; Stierle, D. B.; Alverson, J.; Gibson, N. Berkeleylactones and a Citreohybriddione Analogue from Penicillium turbatum. *J. Nat. Prod.* **2021**, *84* (12), 3064–3070. DOI: 10.1021/acs.jnatprod.1c00791

(48) Zhang, Y.; Bai, J.; Le Zhang; Zhang, C.; Liu, B.; Hu, Y. Self-Resistance in the Biosynthesis of Fungal Macrolides Involving Cycles of Extracellular Oxidative Activation and Intracellular Reductive Inactivation. *Angew. Chem. Int. Ed.* **2021**, *60* (12), 6639–6645. DOI: 10.1002/anie.202015442

(49) Cowled, M. S.; Li, H.; Gilchrist, C. L. M.; Lacey, E.; Chooi, Y.-H.; Piggott, A. M. Stereodivergent Hydroxylation of Berkeleylactones by Penicillium turbatum. *J. Nat. Prod.* **2023**, 86 (3), 541–549. DOI: 10.1021/acs.jnatprod.2c00946

(50) Malatinský, T.; Valachová, D.; Pinčeková, L.; Scherhaufer, D.; Olejníková, P.; Májeková, M.; Vargová, J.; Gaálová-Radochová, B.; Bujdáková, H.; Nováčiková, J.; Farley, A. J. M.; Berkeš, D.; Jakubec, P.; Kolarovič, A.; Caletková, O. Synthesis and structure-activity relationship of berkeleylactone A-derived antibiotics. *Org. Biomol. Chem.* **2022**, *20* (39), 7821–7832. DOI: 10.1039/D2OB01452A

(51) Arai, K.; Rawlings, B. J.; Yoshizawa, Y.; Vederas, J. C. Biosyntheses of antibiotic A26771B by Penicillium turbatum and dehydrocurvularin by Alternaria cinerariae: comparison of stereochemistry of polyketide and fatty acid enoyl thiol ester reductases. *J. Am. Chem. Soc.* **1989**, *111* (9), 3391–3399. DOI: 10.1021/ja00191a042

(52) Hase, T. A.; Nylund, E.-L. Synthesis of the macrolide antibiotic A26771B methyl ester. *Tetrahedron Lett.* **1979**, *20* (28), 2633–2636. DOI: 10.1016/S0040-4039(01)86370-X

(53) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. Total Synthesis of a Macrocyclic Lactone Antibiotic A26771B and Its Isomers Using Carbohydrates. *Bull. Chem. Soc. Jpn.* **1982**, *55* (10), 3248–3253. DOI: 10.1246/bcsj.55.3248

(54) Asaoka, M.; Yanagida, N.; Takei, H. Total synthesis of the macrolide antibiotic (±)-A26771B. *Tetrahedron Lett.* **1980**, *21* (48), 4611–4614. DOI: 10.1016/0040-4039(80)80087-6

(55) Asaoka, M.; Abe, M.; Mukuta, T.; Takei, H. Synthesis of macrocyclic lactones applying intramolecular 1,3-dipolar cycloaddition: Synthesis of (±)-A26771B. *Chem. Lett.* **1982**, *11* (2), 215–218. DOI: 10.1246/cl.1982.215

(56) Fujisawa, T.; Okada, N.; Takeuchi, M.; Sato, T. A short-step synthesis of antibiotic A26771B utilizing the ring-opening reaction of β-ethynyl-β-propiolactone. *Chem. Lett.* **1983**, *12* (8), 1271–1272. DOI: 10.1246/cl.1983.1271

(57) Trost, B. M.; Brickner, S. J. Palladium-assisted macrocyclization approach to cytochalasins: a synthesis of antibiotic A26771B. *J. Am. Chem. Soc.* **1983**, *105* (3), 568–575. DOI: 10.1021/ja00341a043

(58) Bestmann, H. J.; Schobert, R. Oxidation of α,β-Unsaturated Esters and Lactones with Selenium Dioxide to γ-Oxo or γ-Hydroxy Derivatives; Synthesis of (±)-A 26771 B and Norpyrenophorin. *Angew. Chem. Int. Ed.* **1985**, *24* (9), 791–792. DOI: 10.1002/anie.198507911

(59) Bienz, S.; Hesse, M. Synthese makrocyclischer, α,β-ungesättigter γ-Oxolactone durch Ringerweiterungsreaktionen; ein neuer Weg zum makrocyclischen Lacton-Antibiotikum A 26771 B. *Helv. Chim. Acta* **1987**, *70* (5), 1333–1340. DOI: 10.1002/hlca.19870700515

(60) Ichimoto, I.; Sato, M.; Tsuji, H.; Kirihata, M.; Ueda, H. Stereoselective synthesis of a macrolide antibiotic A26771B. *Chem. Express* **1988**, *3*.

(61) Ichimoto, I.; Sato, M.; Tsuji, H.; Kirihata, M.; Ueda, H. ChemInform Abstract: Stereoselective Synthesis of a Macrolide Antibiotic A26771B. *ChemInform* **1988**, *19* (48). DOI: 10.1002/chin.198848323

(62) Quinkert, G.; Küber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Dürner, G.; Zimmermann, G.; Bats, J. W.; Egert, E. Synthese des Makrolid-Antibiotikums (−)-A26771B mit Photolactonisierung als Schlüsselreaktion und Computersimulation als effektive Optimierungshilfe. *Helv. Chim. Acta* **1991**, *74* (8), 1853–1923. DOI: 10.1002/hlca.19910740828

(63) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. Intramolecular palladium-catalysed cross coupling; a direct route to γ-Oxo-α,β-unsaturated macrocycles. *Tetrahedron* **1992**, *48* (14), 2957–2976. DOI: 10.1016/S0040-4020(01)90977-9

(64) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. A general approach to enantiomerically pure methylcarbinols. Asymmetric synthesis of antibiotic (-)-A26771B and the WCR sex pheromone. *J. Org. Chem.* **1993**, *58* (27), 7789–7796. DOI: 10.1021/jo00079a024

(65) Nagarajan, M. Boc_2O mediated macrolactonisation: Formal chemoenzymatic synthesis of macrolide antibiotic (−) A26771B. *Tetrahedron Lett.* **1999**, *40* (6), 1207–1210. DOI: 10.1016/S0040-4039(98)02567-2

(66) Kobayashi, Y.; Okui, H. An efficient synthesis of antibiotic (-)-A26771B. *J. Org. Chem.* **2000**, *65* (2), 612–615. DOI: 10.1021/jo991282s

(67) Lee, W.-W.; Shin, H. J.; Chang, S. A rapid formal synthesis of the macrolide (−)-A26771B. *Tetrahedron Asymmetry* **2001**, *12* (1), 29–31. DOI: 10.1016/S0957-4166(01)00004-0

(68) Gebauer, J.; Blechert, S. Synthesis of gamma,delta-unsaturated-beta-keto lactones via sequential cross metathesis-lactonization: a facile entry to macrolide antibiotic (-)-A26771B. *J. Org. Chem.* **2006**, *71* (5), 2021–2025. DOI: 10.1021/jo052421a

(69) Raji Reddy, C.; Suman, D.; Narsimha Rao, N. Alkyne-Assisted Approach to the Formal Synthesis of Antibiotic Macrolide (-)-A26771B. *Synlett* **2012**, *2012* (02), 272–274. DOI: 10.1055/s-0031-1290130

(70) Persich, P.; Llaveria, J.; Lhermet, R.; Haro, T. de; Stade, R.; Kondoh, A.; Fürstner, A. Increasing the structural span of alkyne metathesis. *Chem. Eur. J.* **2013**, *19* (39), 13047–13058. DOI: 10.1002/chem.201302320

(71) Chatterjee, S.; Sharma, A.; Chattopadhyay, S. Chemoenzymatic synthesis of the macrolide antibiotic (−)-A26771B. *RSC Adv.* **2014**, *4* (80), 42697–42705. DOI: 10.1039/C4RA05399K

(72) Saidhareddy, P.; Shaw, A. K. Glycal approach to the synthesis of macrolide (−)-A26771B. *RSC Adv.* **2015**, *5* (37), 29114–29120. DOI: 10.1039/C4RA17084A

(73) Chatterjee, S.; Subramanian, M.; Sharma, A.; Chattopadhyay, S. A Concise Asymmetric Synthesis of the Macrolide Antibiotic (-)-A26771B and Evaluation of its Antibacterial Activity and Some of its Precursors. *Nat. Prod. Commun.* **2018**, *13* (11), 1934578X1801301. DOI: 10.1177/1934578X1801301131

(74) Subba, S.; Saha, S. Diyne mediated formal synthesis of (−)-A26771B. *Synth. Commun.* **2022**, *52* (5), 704–711. DOI: 10.1080/00397911.2022.2047729

(75) Ferko, B.; Zeman, M.; Formica, M.; Veselý, S.; Doháňošová, J.; Moncol, J.; Olejníková, P.; Berkeš, D.; Jakubec, P.; Dixon, D. J.; Caletková, O. Total Synthesis of Berkeleylactone A. *J. Org. Chem.* **2019**, *84* (11), 7159–7165. DOI: 10.1021/acs.joc.9b00850

(76) Anschütz, R. Ueber die Benzotetronsäuregruppe. *Liebigs Ann.* **1909**, *367* (1-2), 169–218. DOI: 10.1002/jlac.19093670108

(77) Anschütz, R.; Böcker, R. Ueber die Tetronsäuregruppe. Ueber die Einwirkung von Acetylmandelsäurechlorid auf Natriummalonsäureester und auf Natriumcyanessigester. *Liebigs Ann.* **1909**, *368* (1-2), 53–75. DOI: 10.1002/jlac.19093680104

(78) Mulholland, T. P. C.; Foster, R.; Haydock, D. B. Synthesis of pyrrolidine-2,4-diones(tetramic acids) and some derivatives. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2121. DOI: 10.1039/P19720002121

(79) Jiang, M.; Chen, S.; Li, J.; Liu, L. The Biological and Chemical Diversity of Tetramic Acid Compounds from Marine-Derived Microorganisms. *Mar. drugs* **2020**, *18* (2). DOI: 10.3390/md18020114

(80) Schobert, R.; Schlenk, A. Tetramic and tetronic acids: an update on new derivatives and biological aspects. *Bioorg. Med. Chem.* **2008**, *16* (8), 4203–4221. DOI: 10.1016/j.bmc.2008.02.069

(81) Royles, B. J. L. Naturally Occurring Tetramic Acids: Structure, Isolation, and Synthesis. *Chem. Rev.* **1995**, *95* (6), 1981–2001. DOI: 10.1021/cr00038a009

(82) Henning, H.-G.; Gelbin, A. Advances in Tetramic Acid Chemistry. *Adv. Heterocycl. Chem.* **1993**, *57*, 139–185. DOI: 10.1016/S0065-2725(08)60888-0

(83) Steyn, P. S.; Wessels, P. L. Tautomerism in tetramic acids: ^{13}C nmr determination of the structures and ratios of the tautomers in 3-acetyl-5-isopropylpyrrolidine-2,4-dione. *Tetrahedron Lett.* **1978**, *19* (47), 4707–4710. DOI: 10.1016/S0040-4039(01)85711-7

(84) Nolte, M. J.; Steyn, P. S.; Wessels, P. L. Structural investigations of 3-acylpyrrolidine-2,4-diones by nuclear magnetic resonance spectroscopy and X-ray crystallography. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1057. DOI: 10.1039/P19800001057

(85) a) Steyn, P. S.; Rabie, C. J. Characterization of magnesium and calcium tenuazonate from Phoma sorghina. *Phytochemistry* **1976**, *15* (12), 1977–1979. DOI: 10.1016/S0031-9422(00)88860-3#; b) Rosett, T.; Sankhala, R. H.; Stickings, C. E.; Taylor, M. E.; Thomas, R. Studies in the biochemistry of micro-organisms. 103. Metabolites of Alternaria tenuis auct; culture filtrate products. *Biochem. J.* **1957**, *67* (3), 390–400. DOI: 10.1042/bj0670390#; c) Stickings, C. E. Studies in the biochemistry of micro-organisms. 106. Metabolites of Alternaria tenuis auct.: the structure of tenuazonic acid. *Biochem. J.* **1959**, *72* (2), 332–340. DOI: 10.1042/bj0720332#;

(86) Hubbard, M.; Taylor, W. G.; Bailey, K. L.; Hynes, R. K. The dominant modes of action of macrocidins, bioherbicidal metabolites of Phoma macrostoma , differ between susceptible plant species. *Environ. Exp. Bot.* **2016**, *132*, 80–91. DOI: 10.1016/j.envexpbot.2016.08.009

(87) Kawada, M.; Yoshimoto, Y.; Kumagai, H.; Someno, T.; Momose, I.; Kawamura, N.; Isshiki, K.; Ikeda, D. PP2A inhibitors, harzianic acid and related compounds produced by fungus strain F-1531. *J. Antibiot.* **2004**, *57* (3), 235–237. DOI: 10.7164/antibiotics.57.235

(88) a) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. Synthesis of a tetronic acid library focused on inhibitors of tyrosine and dual-specificity protein phosphatases and its evaluation regarding VHR and cdc25B inhibition. *J. Med. Chem.* **2001**, *44* (20), 3216–3222. DOI: 10.1021/jm0100741#; b) Maarisit, W.; Yamazaki, H.; Kanno, S.-I.; Tomizawa, A.; Rotinsulu, H.; Wewengkang, D. S.; Sumilat, D. A.; Ukai, K.; Kapojos, M. M.; Namikoshi, M. A tetramic acid derivative with protein tyrosine phosphatase 1B inhibitory activity and a new nortriterpene glycoside from the Indonesian marine sponge Petrosia sp. *Bioorg. Med. Chem. Lett.* **2017**, *27* (4), 999–1002. DOI: 10.1016/j.bmcl.2016.12.077#;

(89) Mo, X.; Gulder, T. A. M. Biosynthetic strategies for tetramic acid formation. *Nat. Prod. Rep.* **2021**, *38* (9), 1555–1566. DOI: 10.1039/D0NP00099J

(90) a) Kakule, T. B.; Zhang, S.; Zhan, J.; Schmidt, E. W. Biosynthesis of the tetramic acids Sch210971 and Sch210972. *Org. Lett.* **2015**, *17* (10), 2295–2297. DOI: 10.1021/acs.orglett.5b00715#; b) Kato, N.; Nogawa, T.; Hirota, H.; Jang, J.-H.; Takahashi, S.; Ahn, J. S.; Osada, H. A new enzyme involved in the control of the stereochemistry in the decalin formation during equisetin biosynthesis. *Biochem. Biophys. Res. Commun.* **2015**, *460* (2), 210–215. DOI: 10.1016/j.bbrc.2015.03.011#;

(91) Lacey, R. N. Derivatives of acetoacetic acid. Part VII. α-Acetyltetramic acids. *J. Chem. Soc.* **1954**, *0* (0), 850–854. DOI: 10.1039/jr9540000850

(92) Jouin, P.; Castro, B.; Nisato, D. Stereospecific synthesis of N-protected statine and its analogues via chiral tetramic acid. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. DOI: 10.1039/P19870001177

(93) Jiang, J.; Li, W.-R.; Przeslawski, R. M.; Joullié, M. M. Comparative study of selected reagents for carboxyl activation. *Tetrahedron Lett.* **1993**, *34* (42), 6705–6708. DOI: 10.1016/S0040-4039(00)61680-5

(94) Ma, D.; Ma, J.; Ding, W.; Dai, L. An improved procedure to homochiral cyclic statines. *Tetrahedron Asymmetry* **1996**, *7* (8), 2365–2370. DOI: 10.1016/0957-4166(96)00291-1

(95) Hosseini, M.; Kringelum, H.; Murray, A.; Tønder, J. E. Dipeptide analogues containing 4-ethoxy-3-pyrrolin-2-ones. *Org. Lett.* **2006**, *8* (10), 2103–2106. DOI: 10.1021/ol060500i

(96) Löffler, J.; Schobert, R. Domino syntheses of five-, six- and seven-membered O-, N- and S-heterocycles from α-, β- and γ-substituted carboxylic esters. *J. Chem. Soc., Perkin Trans. 1* **1996**, (23), 2799–2802. DOI: 10.1039/P19960002799

(97) Schobert, R.; Jagusch, C.; Melanophy, C.; Mullen, G. Synthesis and reactions of polymer-bound $Ph_3P{=}C{=}C{=}O$: a quick route to tenuazonic acid and other optically pure 5-substituted tetramates. *Org. Biomol. Chem.* **2004**, *2* (23), 3524–3529. DOI: 10.1039/b412779j

(98) Schobert, R.; Jagusch, C. An expedient synthesis of 3-acyltetramic acids of the melophlin family from α-aminoesters and immobilized Ph_3PCCO. *Tetrahedron* **2005**, *61* (9), 2301–2307. DOI: 10.1016/j.tet.2005.01.036

(99) Ley, S. V.; Smith, S. C.; Woodward, P. R. Further reactions of t-butyl 3-oxobutanthioate and t-butyl 4-diethyl-phosphono-3-oxobutanthioate : Carbonyl coupling reactions, amination, use in the preparation of 3-acyltetramic acids and application to the total synthesis of fuligorubin A. *Tetrahedron* **1992**, *48* (6), 1145–1174. DOI: 10.1016/s0040-4020(01)88210-7

(100) Jones, R. C. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S. Acylation of pyrrolidine-2,4-diones: a synthesis of 3-acyltetramic acids. X-Ray molecular structure of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methyl-pyrrolidine-2,4-dione. *J. Chem. Soc., Perkin Trans. 1* **1990**, (7), 1959. DOI: 10.1039/p19900001959

(101) Hori, K.; Arai, M.; Nomura, K.; Yoshii, E. An efficient 3(C)-acylation of tetramic acids involving acyl migration of 4(O)-acylates. *Chem. Pharm. Bull.* **1987**, *35* (10), 4368–4371. DOI: 10.1248/cpb.35.4368

(102) Sengoku, T.; Wierzejska, J.; Takahashi, M.; Yoda, H. First Stereoselective Synthesis of Penicillenol A1 via Novel O- to C-Acyl Rearrangement of O-Acyltetramic Acid. *Synlett* **2010**, *2010* (19), 2944–2946. DOI: 10.1055/s-0030-1259045

(103) Jeong, Y.-C.; Moloney, M. G. Synthesis of and tautomerism in 3-acyltetramic acids. *J. Org. Chem.* **2011**, *76* (5), 1342–1354. DOI: 10.1021/jo102304y

(104) Abe, M.; Imai, T.; Ishii, N.; Usui, M. Synthesis of quinolactacide via an acyl migration reaction and dehydrogenation with manganese dioxide, and its insecticidal activities. *Biosci. Biotechnol. Biochem.* **2006**, *70* (1), 303–306. DOI: 10.1271/bbb.70.303

(105) van der Baan, J. L.; Barnick, J.; Bickelhaupt, F. The total synthesis of the antibiotic malonomicin (k16). *Tetrahedron* **1978**, *34* (2), 223–231. DOI: 10.1016/S0040-4020(01)93609-9

(106) Schlenk, A.; Diestel, R.; Sasse, F.; Schobert, R. A selective 3-acylation of tetramic acids and the first synthesis of ravenic acid. *Chem. Eur. J.* **2010**, *16* (8), 2599–2604. DOI: 10.1002/chem.200902544

(107) Igarashi, M.; Sawa, R.; Honma, T. New compound amycolamicin, method for producing the same, and use of the same. JP2009203195A, **2009**.

(108) Tohyama, S.; Takahashi, Y.; Akamatsu, Y. Biosynthesis of amycolamicin: the biosynthetic origin of a branched alpha-aminoethyl moiety in the unusual sugar amycolose. *J. Antibiot.* **2010**, *63* (3), 147–149. DOI: 10.1038/ja.2010.1

(109) Zink, D. L.; Goetz, M.; Genilloud, O.; Vicente, F.; Singh, S.; Polishook, J. D. Antibacterial agents. ES2368236A1, **2011**.

(110) Phillips, J. W.; Goetz, M. A.; Smith, S. K.; Zink, D. L.; Polishook, J.; Onishi, R.; Salowe, S.; Wiltsie, J.; Allocco, J.; Sigmund, J.; Dorso, K.; Lee, S.; Skwish, S.; La Cruz, M. de; Martín, J.; Vicente, F.; Genilloud, O.; Lu, J.; Painter, R. E.; Young, K.; Overbye, K.; Donald, R. G. K.; Singh, S. B. Discovery of kibdelomycin, a potent new class of bacterial type II topoisomerase inhibitor by chemical-genetic profiling in Staphylococcus aureus. *Chem. Biol.* **2011**, *18* (8), 955–965. DOI: 10.1016/j.chembiol.2011.06.011

(111) Sawa, R.; Takahashi, Y.; Hashizume, H.; Sasaki, K.; Ishizaki, Y.; Umekita, M.; Hatano, M.; Abe, H.; Watanabe, T.; Kinoshita, N.; Homma, Y.; Hayashi, C.; Inoue, K.; Ohba, S.; Masuda, T.; Arakawa, M.; Kobayashi, Y.; Hamada, M.; Igarashi, M.; Adachi, H.; Nishimura, Y.; Akamatsu, Y. Amycolamicin: a novel broad-spectrum antibiotic inhibiting bacterial topoisomerase. *Chem. Eur. J.* **2012**, *18* (49), 15772–15781. DOI: 10.1002/chem.201202645

(112) Lu, J.; Patel, S.; Sharma, N.; Soisson, S. M.; Kishii, R.; Takei, M.; Fukuda, Y.; Lumb, K. J.; Singh, S. B. Structures of kibdelomycin bound to Staphylococcus aureus GyrB and ParE showed a novel U-shaped binding mode. *ACS Chem. Biol.* **2014**, *9* (9), 2023–2031. DOI: 10.1021/cb5001197

(113) Singh, S. B.; Goetz, M. A.; Smith, S. K.; Zink, D. L.; Polishook, J.; Onishi, R.; Salowe, S.; Wiltsie, J.; Allocco, J.; Sigmund, J.; Dorso, K.; La Cruz, M. de; Martín, J.; Vicente, F.; Genilloud, O.; Donald, R. G. K.; Phillips, J. W. Kibdelomycin A, a congener of kibdelomycin, derivatives and their antibacterial activities. *Bioorg. Med. Chem. Lett.* **2012**, *22* (23), 7127–7130. DOI: 10.1016/j.bmcl.2012.09.071

(114) a) Singh, S. B.; Dayananth, P.; Balibar, C. J.; Garlisi, C. G.; Lu, J.; Kishii, R.; Takei, M.; Fukuda, Y.; Ha, S.; Young, K. Kibdelomycin is a bactericidal broad-spectrum aerobic antibacterial agent. *Antimicrob. Agents Chemother.* **2015**, *59* (6), 3474–3481. DOI: 10.1128/AAC.00382-15#; b) Singh, S. B. Discovery and development of kibdelomycin, a new class of broad-spectrum antibiotics targeting the clinically proven bacterial type II topoisomerase. *Bioorg. Med. Chem.* **2016**, *24* (24), 6291–6297. DOI: 10.1016/j.bmc.2016.04.043#;

(115) a) Drlica, K.; Zhao, X. DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiol. Mol. Biol. Rev.* **1997**, *61* (3), 377–392. DOI: 10.1128/mmbr.61.3.377-392.1997#; b) Maxwell, A.; Lawson, D. M. The ATP-binding site of type II topoisomerases as a target for antibacterial drugs. *Curr. Top. Med. Chem.* **2003**, *3* (3), 283–303. DOI: 10.2174/1568026033452500#;

(116) Wimley, W. C.; White, S. H. Experimentally determined hydrophobicity scale for proteins at membrane interfaces. *Nat. Struct. Mol. Biol.* **1996**, *3* (10), 842–848. DOI: 10.1038/nsb1096-842

(117) Lu, J.; Patel, S.; Sharma, N.; Soisson, S.; Kishii, R.; Takei, M.; Fukuda, Y.; Lumb, K. J.; Singh, S. B. *Crystal Structure of Staph GyraseB 24kDa in complex with Novobiocin*, 2014. DOI: 10.2210/pdb4URO/pdb

(118) Lu, J.; Patel, S.; Sharma, N.; Soisson, S.; Kishii, R.; Takei, M.; Fukuda, Y.; Lumb, K. J.; Singh, S. B. *Crystal Structure of Staph GyraseB 24kDa in complex with Kibdelomycin*, 2014. DOI: 10.2210/pdb4URM/pdb

(119) a) Matsunaga, S.; Fusetani, N.; Kato, Y.; Hirota, H. Aurantosides A and B: cytotoxic tetramic acid glycosides from the marine sponge Theonella sp. *J. Am. Chem. Soc.* **1991**, *113* (25), 9690–9692. DOI: 10.1021/ja00025a054#; b) Sata, N. U.; Matsunaga, S.; Fusetani, N.; van Soest, R. W. Aurantosides D, E, and F: new antifungal tetramic acid glycosides from the marine sponge Siliquariaspongia japonica. *J. Nat. Prod.* **1999**, *62* (7), 969–971. DOI: 10.1021/np9900021#; c) Ratnayake, A. S.; Davis, R. A.; Harper, M. K.; Veltri, C. A.; Andjelic, C. D.; Barrows, L. R.; Ireland, C. M. Aurantosides G, H, and I: three new tetramic acid glycosides from a Papua New Guinea Theonella swinhoei. *J. Nat. Prod.* **2005**, *68* (1), 104–107. DOI: 10.1021/np049721s#; d) Sata, N. U.; Wada, S.; Matsunaga, S.; Watabe, S.; van Soest, R. W. M.; Fusetani, N. Rubrosides A−H, New Bioactive Tetramic Acid Glycosides from the Marine Sponge Siliquariaspongiajaponica1. *J. Org. Chem.* **1999**, *64* (7), 2331–2339. DOI: 10.1021/jo981995v#; e) Rinehart, K. L.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. Streptolydigin. III. Chromophore and Structure. *J. Am. Chem. Soc.* **1963**, *85* (24), 4038–4039. DOI: 10.1021/ja00907a034#; f) Angawi, R. F.; Bavestrello, G.; Calcinai, B.; Dien, H. A.; Donnarumma, G.; Tufano, M. A.; Paoletti, I.; Grimaldi, E.; Chianese, G.; Fattorusso, E.; Taglialatela-Scafati, O. Aurantoside J: a new tetramic acid glycoside from Theonella swinhoei. Insights into the antifungal potential of aurantosides. *Mar. drugs* **2011**, *9* (12), 2809–2817. DOI: 10.3390/md9122809#;

(120) Pronin, S. V.; Kozmin, S. A. Synthesis of streptolydigin, a potent bacterial RNA polymerase inhibitor. *J. Am. Chem. Soc.* **2010**, *132* (41), 14394–14396. DOI: 10.1021/ja107190w

(121) Petermichl, M.; Loscher, S.; Schobert, R. Total Synthesis of Aurantoside G, an N-β-Glycosylated 3-Oligoenoyltetramic Acid from Theonella swinhoei. *Angew. Chem. Int. Ed.* **2016**, *55* (34), 10122–10125. DOI: 10.1002/anie.201604912

(122) Kauhl, U.; Andernach, L.; Weck, S.; Sandjo, L. P.; Jacob, S.; Thines, E.; Opatz, T. Total Synthesis of (-)-Hymenosetin. *J. Org. Chem.* **2016**, *81* (1), 215–228. DOI: 10.1021/acs.joc.5b02526

(123) Kempf, K.; Kempf, O.; Orozco, M.; Bilitewski, U.; Schobert, R. Synthesis and Structural Revision of the Fungal Tetramic Acid Metabolite Spiroscytalin. *J. Org. Chem.* **2017**, *82* (15), 7791–7795. DOI: 10.1021/acs.joc.7b00727

(124) Meguro, Y.; Ogura, Y.; Enomoto, M.; Kuwahara, S. Synthesis of the N-Acyl Amycolose Moiety of Amycolamicin and Its Methyl Glycosides. *J. Org. Chem.* **2019**, *84* (11), 7474–7479. DOI: 10.1021/acs.joc.9b00650

(125) Yang, S.; Chen, C.; Chen, J.; Li, C. Total Synthesis of the Potent and Broad-Spectrum Antibiotics Amycolamicin and Kibdelomycin. *J. Am. Chem. Soc.* **2021**, *143* (50), 21258–21263. DOI: 10.1021/jacs.1c11477

(126) Meguro, Y.; Ito, J.; Nakagawa, K.; Kuwahara, S. Total Synthesis of the Broad-Spectrum Antibiotic Amycolamicin. *J. Am. Chem. Soc.* **2022**, *144* (12), 5253–5257. DOI: 10.1021/jacs.2c00647

(127) Takagi, Y.; Kobayashi, N.; Tsuchiya, T.; Umezawa, S.; Takeuchi, T.; Komuro, K.; Nosaka, C. Syntheses and antitumor activities of 7-O-(6-deoxy-2-O-methyl-alpha-L-talopyranosyl)-daunomycinone and -adriamycinone. *J. Antibiot.* **1989**, *42* (8), 1318–1320. DOI: 10.7164/antibiotics.42.1318

(128) He, C.; Wang, Y.; Bi, C.; Peters, D. S.; Gallagher, T. J.; Teske, J.; Chen, J. S.; Corsetti, R.; D'Onofrio, A.; Lewis, K.; Baran, P. S. Total Synthesis of Kibdelomycin. *Angew. Chem. Int. Ed.* **2022**, *61* (32), e202206183. DOI: 10.1002/anie.202206183

(129) Frossard, T. M.; Trapp, N.; Altmann, K.-H. Studies towards the Total Synthesis of Amycolamicin: A Chiral Auxiliary-Based Diels-Alder Approach towards the Decalin Core. *Eur. J. Org. Chem.* **2022**, *2022* (30). DOI: 10.1002/ejoc.202200761

(130) Bertz, S. H. The first general index of molecular complexity. *J. Am. Chem. Soc.* **1981**, *103* (12), 3599–3601. DOI: 10.1021/ja00402a071

(131) a) Li, J.; Eastgate, M. D. Current complexity: a tool for assessing the complexity of organic molecules. *Org. Biomol. Chem.* **2015**, *13* (26), 7164–7176. DOI: 10.1039/C5OB00709G#; b) Urabe, D.; Asaba, T.; Inoue, M. Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem. Rev.* **2015**, *115* (17), 9207–9231. DOI: 10.1021/cr500716f#;

(132) Li, L.; Chen, Z.; Zhang, X.; Jia, Y. Divergent Strategy in Natural Product Total Synthesis. *Chem. Rev.* **2018**, *118* (7), 3752–3832. DOI: 10.1021/acs.chemrev.7b00653

(133) a) Casi, G.; Hilvert, D. Convergent protein synthesis. *Curr. Opin. Struct. Biol.* **2003**, *13* (5), 589–594. DOI: 10.1016/j.sbi.2003.09.008#; b) Inoue, M. Evolution of Radical-Based Convergent Strategies for Total Syntheses of Densely Oxygenated Natural Products. *Acc. Chem. Res.* **2017**, *50* (3), 460–464. DOI: 10.1021/acs.accounts.6b00475#;

(134) a) Dostert, M.; Trimble, M. J.; Hancock, R. E. W. Antibiofilm peptides: overcoming biofilm-related treatment failure. *RSC Adv.* **2021**, *11* (5), 2718–2728. DOI: 10.1039/D0RA09739J#; b) Sharma, D.; Misba, L.; Khan, A. U. Antibiotics versus biofilm: an emerging battleground in microbial communities. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 76. DOI: 10.1186/s13756-019-0533-3#; c) Davies, D. Understanding biofilm resistance to antibacterial agents. *Nat. Rev. Drug Discov.* **2003**, *2* (2), 114–122. DOI: 10.1038/nrd1008#;

(135) Manuel Georg Schriefer. Totalsynthese der 16-gliedrigen Makrolide Berkeleylacton A, Berkeleylacton B und A26771B. Masterarbeit, Universität Bayreuth, Bayreuth, 2019.

(136) Stevenson, C. P.; Nielsen, L. P. C.; Jacobsen, E. N. Preparation of (S)-Methyl glycidate via hydrolytic kinetic resolution. *Org. Synth.* **2006**, *83*, 162. DOI: 10.15227/orgsyn.083.0162

(137) Mishra, R.; Panda, A. K.; Mandal, S. de; Shakeel, M.; Bisht, S. S.; Khan, J. Natural Anti-biofilm Agents: Strategies to Control Biofilm-Forming Pathogens. *Front. Microbiol.* **2020**, *11*, 566325. DOI: 10.3389/fmicb.2020.566325

(138) Finkel, J. S.; Mitchell, A. P. Genetic control of Candida albicans biofilm development. *Nat. Rev. Microbiol.* **2011**, *9* (2), 109–118. DOI: 10.1038/nrmicro2475

(139) Schriefer, M. G.; Schrey, H.; Zeng, H.; Stadler, M.; Schobert, R. Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation. *Org. Biomol. Chem.* **2021**, *19* (21), 4743–4751. DOI: 10.1039/D1OB00717C

(140) Tohyama, S. Novel compound amycolose derivative, and production process and use of same. JP2011046622A, **2011**.

5 Darstellung der Eigenanteile und Publikationen

5.1 Eigenanteile

Die in dieser Arbeit dargestellten Publikationen wurden in Zusammenarbeit mit weiteren Wissenschaftlern der Universität Bayreuth sowie in Kooperation mit einem Lehrstuhl des *Helmholtz Centre for Infection Research* in Braunschweig unter der Leitung von Prof. Dr. Marc Stadler erarbeitet.

Im Folgenden werden die Eigenanteile der Co-Autoren detailliert aufgelistet.

5.1.1 Eigenanteil Publikation I

Diese Arbeit wurde publiziert in *Org. Biomol. Chem.* **2021**, *19* (21), 4743 – 4751. DOI: 10.1039/D1OB00717C unter dem Titel

Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation

von Manuel G. Schriefer, Hedda Schrey, Haoxuan Zeng, Marc Stadler und Rainer Schobert.

Eigenanteil:	- Syntheseplanung - Versuchsdurchführung und Aufreinigung der Produkte - Charakterisierung der Produkte - Auswertung und Interpretation der Versuchsergebnisse - Mitwirken am Manuskript
Hedda Schrey:	- Durchführung der biologischen Tests und deren Auswertung
Haoxuan Zeng:	- Durchführung der biologischen Tests und deren Auswertung
Marc Stadler:	- Projektüberwachung biologischer Part
Rainer Schobert:	- Projektüberwachung chemischer Part - Verfassen des Manuskripts - Diskussion der Ergebnisse

5.1.2 Eigenanteil Publikation II

Diese Arbeit wurde publiziert in *J. Nat. Prod.* **2023**, *86* (2), 423 – 428. DOI: 10.1021/acs.jnatprod.3c00053 unter dem Titel

Divergent Synthesis of Six Recent Berkeleylactones

von Manuel G. Schriefer und Rainer Schobert.

Eigenanteil:
- Syntheseplanung
- Versuchsdurchführung und Aufreinigung der Produkte
- Charakterisierung der Produkte
- Auswertung und Interpretation der Versuchsergebnisse
- Verfassen des Manuskripts

Rainer Schobert:
- Projektüberwachung
- Verfassen des Manuskripts
- Akquirieren von Geldern

5.1.3 Eigenanteil Publikation III

Diese Arbeit wurde publiziert in *Chem. Sci.* **2023**, *14* (13), 3562 – 3568. DOI: 10.1039/D3SC00595J unter dem Titel

Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides

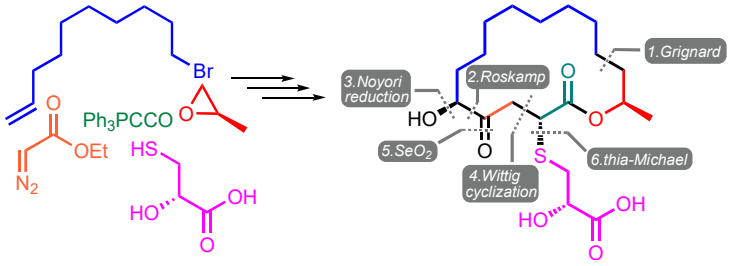
von Manuel G. Schriefer, Laura Treiber und Rainer Schobert.

Eigenanteil:
- Projekt- und Syntheseplanung
- Syntheseplanung und -durchführung im Bereich des Decalin-Fragments, der *N*-acylierten Amycolose und dessen Derivats.
- Charakterisierung ebendieser
- Auswertung und Interpretation der gesamten Versuchsergebnisse
- Verfassen des Manuskripts

Laura Treiber:
- Projekt-/Syntheseplanung und -durchführung im Bereich des Decalin-Fragments, der Amykitanose und des Amycolose-Derivats.
- Charakterisierung ebendieser
- Auswertung und Interpretation der gesamten Versuchsergebnisse
- Verfassen des Manuskripts

Rainer Schobert:
- Projektüberwachung
- Verfassen des Manuskripts
- Akquirieren von Geldern

5.2 Publikation I



Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation

Manuel G. Schriefer, Hedda Schrey, Haoxuan Zeng, Marc Stadler, Rainer Schobert

Org. Biomol. Chem. **2021**, *19* (21), 4743 – 4751.

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: Org. Biomol. Chem., 2021, 19, 4743

Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation†

Manuel G. Schriefer,[a] Hedda Schrey,[b] Haoxuan Zeng,[b] Marc Stadler [b] and Rainer Schobert *[a]

Received 13th April 2021,
Accepted 30th April 2021

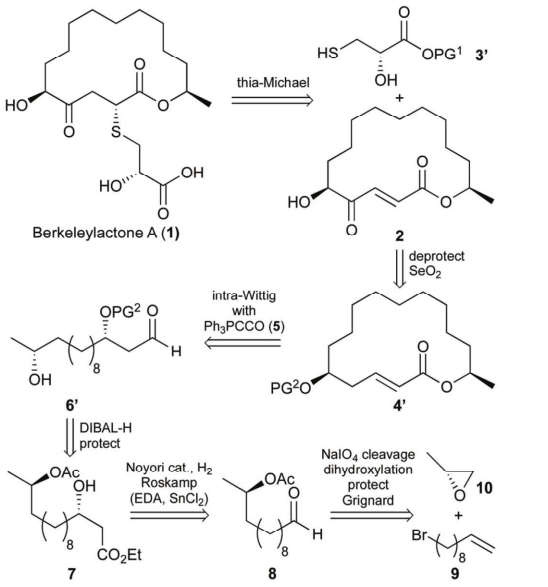
DOI: 10.1039/d1ob00717c

rsc.li/obc

The fungal macrolide berkeleylactone A was synthesised in 13 steps and 24% yield using (*R*)-propylene oxide and an asymmetric Noyori hydrogenation of a β-ketoester to install the stereogenic centres. A domino addition–Wittig olefination of a 13-hydroxytetradecanal intermediate with the cumulated ylide Ph_3PCCO closed the macrocyle by establishing the α,β-unsaturated ester group, necessary for the attachment of the sidechain thiol *via* a thia-Michael reaction. The synthetic berkeleylactone A inhibited the formation of *Staphylococcus aureus* biofilms and showed significant dispersive effects on preformed biofilms of *Candida albicans* by at least 45% relative to untreated controls at concentrations as low as 1.3 μg mL^{-1}.

Introduction

The 16-membered macrolide berkeleylactone A (**1**, Scheme 1) was isolated in 2017 by Stierle *et al.* from a coculture fermentation of *Penicillium fuscum* and *P. camembertii*/*clavigerum*, aside of seven closely related berkeleylactones B–H sharing the same γ-oxopentadecanolide scaffold.[1] They also assigned the structure of macrolide **1**, including its absolute configuration, by ^{1}H NMR, ^{13}C NMR and HMBC spectra, as well as by a single-crystal X-ray diffraction analysis. Berkeleylactone A (**1**) was shown by this group to be the most and highly active congener of this series when tested in a broad screen against bacteria including various MRSA strains, and to operate by a novel mechanism of action not involving the bacterial ribosome. In 2019, Dixon, Caletková *et al.*[2] reported the first synthesis of berkeleylactone A, based upon a convergent approach to macrolide intermediate **2**, which had been employed previously by Chang *et al.*[3] for their formal synthesis of the related macrolide A26771B *via* a ring-closing metathesis (RCM). The product synthesised by Dixon, Caletková *et al.* matched the NMR and even X-ray diffraction analytical data published by Stierle *et al.*, yet differed conspicuously in the specific optical rotations, being $[\alpha]_D^{25}$ +0.5° (*c* 0.170, $CHCl_3$)[1] and $[\alpha]_D^{25}$ +101.0° (*c* 0.105, $CHCl_3$).[2] As a strategic alternative, we now developed a higher-yielding linear route to the target compound **1**. Its key step was a Wittig macrocyclisation of a 13-hydroxtetradecanal intermediate with the cumulated ylide Ph_3PCCO which proceeded in >60% yield and afforded, after allylic oxidation, the Michael system necessary for the attachment of the sidechain thiol. A similar approach had been previously applied by us for the syntheses of the macrolides



Scheme 1 Retrosynthesis of berkeleylactone A (**1**).

[a]*Department of Chemistry, University Bayreuth, Universitaetsstr. 30, D-95440 Bayreuth, Germany. E-mail: Rainer.Schobert@uni-bayreuth.de*
[b]*Department of Microbial Drugs, Helmholtz Centre for Infection Research GmbH, Inhoffenstrasse 7, 38124 Braunschweig, Germany*

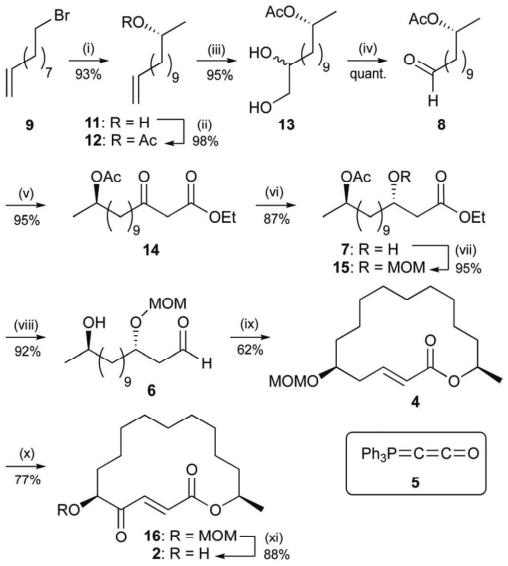
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of **1–4**, **6–9**, **11–16**, *rac*-**18**, (*R*)-**18**, **19–22**; HPLC chromatogrammes of **7**/*epi*-**7** and **1**; antimicrobial, antibiofilm, and cytotoxicity assays. Cell culture conditions and MTT-assay ^{1}H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/d1ob00717c

chloriolide (12-membered ring) and aspicillin (18-membered ring).[4]

Results and discussion

Our retrosynthetic approach is outlined in Scheme 1. The final steps of the synthesis of a suitably protected thiol sidechain **3′** and its attachment to the β-keto-2-enolide **2** by a thia-Michael addition were to follow Dixon's route with slight variations concerning the protecting group strategy. The enolide **2**, however, should be built up quite differently from the Chang/Dixon route. From our synthesis of the related macrolide A26771B,[5] we knew that 2-enoates can be easily oxidised with SeO_2 to the corresponding γ-keto-2-enoates, such as compound **4′** which should have its δ-hydroxy group protected to be on the safe side. Macrolide **4′** was to be obtained by a ring-closing domino addition–Wittig olefination of the secondary hydroxyaldehyde **6′**, carrying both stereogenic centres, with the cumulated phosphorus ylide Ph_3PCCO (**5**),[6] a reaction we had previously utilised to prepare macrolides of ring sizes ranging from 12 to 18.[7] Hydroxyaldehyde **6′** should be prepared by DIBAL-H reduction of a derivative of ester **7** having its second alcohol protected in a way to withstand these conditions. β-Hydroxyester **7** could be obtained by a Roskamp reaction[8] of aldehyde **8** with ethyl diazoacetate (EDA) and a stereoselective Noyori hydrogenation[9] of the resulting β-ketoester (not shown). Aldehyde **8** in turn should be accessible by copper(I) cyanide-catalysed ring opening[10] of epoxide **10** with the Grignard reagent prepared from commercial bromide **9**, followed by protection of the hydroxy group, dihydroxylation of the double bond, and periodate cleavage of the resulting diol.

Most of the planned reactions proceeded with good to excellent yields. 10-Bromodec-1-ene (**9**), which is commercially available or readily accessible by nearly quantitative bromination of the respective alcohol with Ph_3P/Br_2/imidazole,[11] was converted to the Grignard reagent and then treated with (*R*)-propylene oxide ((*R*)-PPO, **10**) and catalytic copper(I) cyanide to afford the secondary alcohol **11** in 93% yield (Scheme 2). Its acetate **12** was dihydroxylated with $NMO/K_2OsO_4{\cdot}2H_2O$ (cat.) leaving diol **13** in 95% yield. It was cleaved with $NaIO_4/SiO_2$ [12] to give (*R*)-11-acetoxydodecanal (**8**) in quantitative yield. For the introduction of the second stereogenic centre, aldehyde **8** was converted to β-ketoester **14** *via* a high-yielding Roskamp extension reaction with EDA/tin(II) chloride. An enantioselective hydrogenation of the keto group of **14** with 1st generation Noyori catalyst and 40 bar H_2 afforded β-hydroxyester **7** in 87% yield and with >99% de. MOM-protection with P_2O_5/dimethoxymethane of the β-hydroxy group gave ester **15** (95%), which was reduced by DIBAL-H with concomitant acetyl deprotection of the 13-hydroxy group to afford hydroxyaldehyde **6** (92%), the immediate precursor for the macrocyclisation reaction with cumulated ylide Ph_3PCCO (**5**). Slow addition of **6** to a diluted solution of ylide **5** in toluene at 55 °C furnished macrolide **4** in 62% yield. Its oxidation with selenium dioxide in dry 1,4-dioxane at 155 °C left γ-keto-enoate **16** in 77% yield.

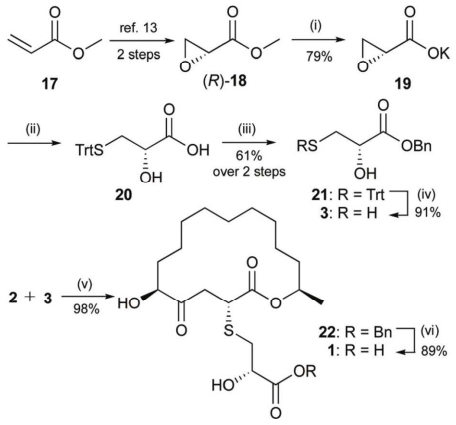


Scheme 2 Synthesis of δ-hydroxy-γ-keto-enolide **2**. Reagents and conditions: (i) Mg^0, THF, reflux, 3.5 h, then cat. CuCN, (*R*)-PPO (**10**), −40 °C (2 h) to −35 °C (18 h) to 0 °C; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 19 h; (iii) $K_2OsO_4{\cdot}2H_2O$ (3 mol%), NMO, acetone/H_2O, 0 °C to rt, 28.5 h; (iv) $NaIO_4/SiO_2$, CH_2Cl_2, rt, 1.75 h; (v) EDA, $SnCl_2$ (12 mol%), CH_2Cl_2, 0 °C, rt, 3 h; (vi) 1st gen. Noyori catalyst (0.29 mol%) prepared from $[RuCl_2(benzene)]_2$ and (*S*)-BINAP, H_2 (40 bar), MeOH, 60 °C, 65 h; (vii) dimethoxymethane, P_2O_5, rt, 2 h; (viii) DIBAL-H, toluene, −78 °C, 90 min; (ix) Ph_3PCCO (**5**, 5 mM in toluene), 55 °C, 20 h; (x) SeO_2, 1,4-dioxane, 155 °C, 55 min; (xi) TFA, CH_2Cl_2, −10 °C, 9.5 h; MOM = methoxymethyl.

Deprotection with TFA gave δ-hydroxy-γ-keto-enolide **2** in 88% yield.

The sidechain was introduced as the (*S*)-benzyl 2-hydroxy-3-mercaptopropanoate (**3**, Scheme 3). It was synthesised from (*R*)-methyl glycidate *R*-(**18**) which is readily accessible in two steps from methyl acrylate (**17**) according to a protocol by Jacobsen.[13] Its saponification left the potassium salt **19**, whose ring was, as in the synthesis of berkeleylactone A by Dixon *et al.*, opened with sodium tritylthiolate to afford hydroxyacid **20**. Esterification with benzyl bromide/cesium carbonate and trityl deprotection gave thiol **3** which was reacted with δ-hydroxy-γ-keto-enolide **2** in the presence of triethylamine (cat.) to furnish **22**, the product of a thia-Michael addition, in 98% yield. The benzyl protecting group was removed by hydrogenolysis with Pd/C (cat.) which afforded berkeleylactone A (**1**) with a dr of 49 : 1 in 23.6% overall yield (longest linear sequence from bromide **9**). The specific optical rotation of our synthetic product was in agreement with that of Dixon's product, yet deviated considerably from that reported for the natural isolate.

The synthetic berkeleylactone A (**1**) was tested against selected bacteria, fungi, and cell lines for antimicrobial (including anti-biofilm) and cytotoxic effects. The minimum inhibitory concentrations (MIC) were assessed as described in



Scheme 3 Synthesis and attachment of sidechain **3**. Reagents and conditions: (i) KOH, MeOH, 0 °C to rt, 16 h; (ii) TrtSH, NaH, THF, then **19**, 0 °C to rt, 19 h; (iii) Cs_2CO_3, BnBr, DMF, rt, 16 h; (iv) TFA, iPr_3SiH, CH_2Cl_2, 0 °C (3.5 h) to rt (45 min); (v) NEt_3 (20 mol%), CH_2Cl_2, rt, 3 h; (vi) Pd/C (10 mol%), H_2, MeOH, rt, 1.75 h; Trt = Ph_3C (trityl).

the ESI† and are listed in Table 1. Compound **1** exhibited weak activities with MICs between 66.6 and 16.6 μg mL^{-1} against several filamentous fungi and yeasts. For the pathogenic yeast *Candida albicans*, weak effects with a MIC of 66.6 μg mL^{-1} were observed. In line with the results of the comprehensive biological studies by Stierle *et al.* and Dixon, Caletková *et al.*, compound **1** exhibited strong antibacterial effects against *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and *Bacillus subtilis* (4.2 μg mL^{-1}). In contrast, no growth inhibition was observed of the Gram-negative bacteria *Acinetobacter baumannii*, *Chromobacterium violaceum*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

Table 1 Antimicrobial activity of synthetic berkeleylactone A (**1**)

		MIC [μg mL^{-1}]	
Tested organisms	Strain no.	**1**	Reference
Bacteria			
Bacillus subtilis	DSM 10	4.2	16.6[a]
Staphylococcus aureus	DSM 346	4.2	0.2[a]
MRSA	DSM 11822	4.2	2.1[b]
Mycobacterium smegmatis	ATCC 700084	66.6	1.7[c]
Acinetobacter baumannii	DSM 30008	—	0.5[d]
Chromobacterium violaceum	DSM 30191	—	0.4[a]
Escherichia coli	DSM 1116	—	3.3[a]
Pseudomonas aeruginosa	PA14	—	0.8[e]
Fungi			
Mucor hiemalis	DSM 2656	16.6	4.2[f]
Pichia anomala	DSM 6766	—	4.2[f]
Rhodoturula glutinis	DSM 10134	33.3	2.1[f]
Candida albicans	DSM 1665	66.6	8.3[f]
Schizosaccharomyces pombe	DSM 70572	66.6	4.2[f]

References: [a] oxytetracycline, [b] vancomycin, [c] kanamycin, [d] ciprobay, [e] gentamicin, [f] nystatin.

Table 2 Inhibition of biofilm formation of *S. aureus* and dispersion of preformed biofilms of *S. aureus* and *C. albicans* by berkeleylactone A (**1**) at various concentrations

		Biofilm inhibition [% ± SD]	Biofilm dispersion [% ± SD]
Tested organisms	Strain no.	**1**	
Staphylococcus aureus	DSM 1104	53 ± 10 (2 μg mL^{-1})[a]	55 ± 8 (250 μg mL^{-1})[b]
		20 ± 8 (0.3 μg mL^{-1})[a]	29 ± 7 (125 μg mL^{-1})[b]
Candida albicans	DSM 11225	—	79 ± 1 (31.3 μg mL^{-1})[c]
			45 ± 6 (1.3 μg mL^{-1})[c]
			17 ± 8 (0.17 μg mL^{-1})[c]

References [%]: [a] microporenic acid A (MAA): 83 (250 μg mL^{-1}), 77 (7.8 μg mL^{-1}), 40 (3.9 μg mL^{-1}); [b] MAA: 68 (250 μg mL^{-1}), 50 (62.5 μg mL^{-1}), 58 (31.3 μg mL^{-1}); [c] MAA: 33 (250 μg mL^{-1}); SD: standard deviation; – not tested.

Table 3 Cytotoxic activities of berkeleylactone A (**1**)

		IC_{50} [μM]	
Cell lines	Strain no.	**1**	Reference
L929	ACC 2	11.1	0.0006[a]
KB3.1	ACC 158	17.1	0.00006[a]

Reference: [a] epothilone B.

After establishing the MICs for *S. aureus*, *C. albicans* und *P. aeruginosa*, the effects of subtoxic concentrations of berkeleylactone Λ (**1**) on biofilms of these organisms were evaluated. More precisely, its inhibitory effects on the formation of biofilms of *S. aureus* and *P. aeruginosa*, and its dispersive effects on preformed biofilms of *S. aureus* and *C. albicans* were established (Table 2; *cf.* ESI† for details). Lactone **1** inhibited the formation of *S. aureus* biofilms by *ca.* 53% relative to untreated controls when applied at a concentration of 2 μg mL^{-1}, and by *ca.* 20% at a concentration of 0.3 μg mL^{-1}. No inhibitory effects were observed against *P. aeruginosa*. Moreover, lactone **1** exhibited significant dipersive effects on preformed biofilms of *C. albicans*, leading to a reduction of *ca.* 17% when applied at a concentration of 0.17 μg mL^{-1}, and of *ca.* 45% at a concentration of 1.3 μg mL^{-1}. Its dispersive effects on preformed biofilms of *S. aureus* were less pronounced. A reduction of the biofilm of *ca.* 55% required a dose of 250 μg mL^{-1}. When applied at 125 μg mL^{-1} it reduced the preformed biofilm by *ca.* 29%. In sum, synthetic berkeleylactone A (**1**) showed distinct effects on preformed biofilms of *C. albicans* at sub-MIC concentrations, a bioactivity that went unnoticed by Stierle *et al.* and Dixon, Caletková *et al.*

Synthetic berkeleylactone Λ (**1**) was also tested for cytotoxicity on mouse fibroblast cells (L929) and human cervix carcinoma cells (KB3.1) as described in the ESI.† Merely moderate cytotoxic activities were observed with half-maximum inhibitory concentrations (IC_{50}) of 11.1 μM (4.5 μg mL^{-1}) and 17.1 μM (6.9 μg mL^{-1}), respectively (Table 3).

Conclusions

Macrolide **1**, which was identified by Stierle *et al.* in a natural isolate and dubbed berkeleylactone A, was synthesised for the first time by Dixon, Caletková *et al.* in 10% yield, and now by us in 24% yield. Our synthesis has a linear rather than convergent character and uses a domino addition–Wittig olefination rather than an RCM reaction to close the macrocyclic ring. As to the identity of the natural product, there remains a shred of doubt, despite of matching single-crystal X-ray diffraction analyses of the isolated compound and the synthetic product of Dixon, Caletková *et al.* The NMR data of both synthetic products and of the isolated compound were consistent, apart from the acidic H-atoms not showing up in the ^{1}H NMR spectrum of the isolate, probably due to the sample preparation employing MeOD. However, the specific optical rotation of the natural isolate differed conspicuously from the similar values of the two synthetic samples. These findings point to a possible inhomogeneity of the natural isolate.

Our comprehensive biological characterisation of the synthetic berkeleylactone A (**1**) by antimicrobial, antibiofilm, and cytotoxicity assays confirmed its known strong antibiotic efficacy against *S. aureus* and MRSA, yet also revealed a distinct and hitherto unknown dispersive effect on preformed biofilms of *C. albicans* and an inhibitory effect on the formation of *S. aureus* biofilms, both at subtoxic concentrations. According to the National Institute of Health, biofilms cause more than 80% of microbial infections.[14,15] Pathogens, which are embedded in biofilms, are difficult to treat with antibiotics due to limits in drug penetration and increasing drug tolerance.[15,16] Strategies employing new agents that disperse preformed biofilms or combination regimens of biofilm inhibitors and established or new antibiotics have recently been recognised as promising and are being introduced in antibacterial drug discovery.[15]

Experimental section

General information

Melting points were determined with a Büchi M-565 melting point apparatus and are uncorrected. IR spectra were recorded with a PerkinElmer Spectrum 100 FT-IR spectrophotometer with ATR sampling unit. Optical rotations were measured at 589 nm (Na-D line) on a PerkinElmer 241 Polarimeter using solutions in chloroform, methanol or water. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance III HD 500 spectrometer. Chemical shifts are given in parts per million using the residual solvent peak as an internal standard, *i.e.* 7.26 ppm (proton) and 77.16 (carbon) for $CDCl_3$, 3.31 ppm (proton) and 49.00 ppm (carbon) for CD_3OD, and 4.80 ppm for D_2O. Coupling constants (*J*) are quoted in Hz. Multiplicity abbreviations used: s singlet, d doublet, t triplet, qu quartet, qn quintet, sex sextet, m multiplet. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. The diastereomeric excess was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak AD-H), by RP-HPLC analysis (Shimadzu Nexera XR, SPD-M20A detector) on a C-18 column (Eurosphere II 100-3 C18 150 × 4 mm) or from ^{1}H NMR spectra.

Chemicals. All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran, 1,4-dioxane and toluene which were freshly distilled over sodium/benzophenone, dichloromethane (CH_2Cl_2) which was freshly distilled over CaH_2, dimethylformamide (DMF) which was dried over molecular sieves (3 Å), and methanol (MeOH) which was freshly distilled over Mg. Moisture or air sensitive reactions were routinely carried out in oven-dried glassware under an argon atmosphere using standard Schlenk technique.

Chromatography. Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} pre-coated aluminum-backed plates. The compounds were visualized with UV light (254 nm) and/or ceric ammonium molybdate (CAM). Column chromatography was performed at medium pressure using wet-packed Macherey–Nagel silica gel 60, pore size 40–63 μm with the eluent specified.

Cell lines. The mouse fibroblasts L929 (DSMZ no. ACC 2) and the human cervix carcinoma cells KB3.1 (DSMZ no. ACC 158) were obtained from the German Collection of Microorganisms and Cell Cultures GmbH (DSMZ), Braunschweig, Germany.

*(R)-Tridec-12-en-2-ol (**11**).*[10] A mixture of magnesium turnings (1.74 g, 71.5 mmol) and a catalytic amount of I_2 in dry THF (72 mL) under argon atmosphere was treated with 10-bromodec-1-ene (**9**, 13.1 mL, 65.0 mmol) while cooling with an ice bath. The resulting suspension was heated under reflux for 3.5 h. The supernatant solution of the Grignard reagent was added over 40 min to a solution of CuCN (537 mg, 6.00 mmol, 12 mol%) and (*R*)-PPO (*R*-**10**, 4.20 mL, 50.0 mmol) in dry THF (88 mL) at −40 °C. The solution was stirred at −40 °C for 2 h, then at −35 °C for 18 h. It was warmed to 0 °C and quenched with aqueous ammonia (50 mL) and sat. aqueous NH_4Cl-solution (100 mL). The aqueous solution was extracted with Et_2O (4 × 150 mL) and the combined organic phases were dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography on silica gel (hexanes/EtOAc 9 : 1) to give alcohol **11** (9.22 g, 93%; loc. cit.:[14]: 85%) as a colourless oil. R_f = 0.33 (hexanes/EtOAc 4 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 6.8, 10.1, 17.0 Hz, 1 H), 4.99 (dd, *J* = 1.6, 17.0 Hz, 1 H), 4.93 (m, 1 H), 3.79 (m, 1 H), 2.04 (m, 2 H), 1.51–1.22 (m, 17 H), 1.18 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 114.2, 68.3, 39.5, 34.0, 29.8, 29.74, 29.68, 29.6, 29.3, 29.1, 25.9, 23.6 ppm.

*(R)-Tridec-12-en-2-yl acetate (**12**).* A solution of alcohol **11** (7.99 g, 40.3 mmol), pyridine (11.2 mL, 137 mmol) and DMAP (98.5 mg, 806 μmol) in CH_2Cl_2 (20 mL) was treated with Ac_2O (11.4 mL, 121 mmol) at room temperature and stirred at room temperature for a further 19 h. It was poured into a mixture of

Et_2O (100 mL) and sat. aqueous NH_4Cl-solution (100 mL). The organic phase was separated and washed with sat. aqueous NH_4Cl-solution (100 mL). The combined aqueous phases were extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with sat. aqueous $CuSO_4$-solution (100 mL) and brine (2 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated, and the crude product was purified by filtration over a plug of silica with hexanes/EtOAc 4 : 1 (500 mL). After removal of the solvent, the ester **12** (9.51 g, 98%) was obtained as a colourless oil. R_f = 0.65 (hexanes/EtOAc 9 : 1); $[\alpha]_D^{23}$ −1.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 6.7, 10.2, 17.0 Hz, 1 H), 4.99 (m, 1 H), 4.93 (m, 1 H), 4.88 (sex, *J* = 6.3 Hz, 1 H), 2.04 (m, 5 H), 1.57 (m, 1 H), 1.45 (m, 1 H), 1.41–1.22 (m, 14 H), 1.19 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 139.4, 114.2, 71.2, 36.1, 34.0, 29.7 (2 C atoms), 29.60, 29.55, 29.3, 29.1, 25.5, 21.6, 20.1 ppm; IR ν_{max} 3080, 2979, 2927, 2855, 1739, 1640, 1464, 1372, 1243, 1128, 1020, 952, 909 cm^{-1}; HRMS (+ESI) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{29}O_2^+$ 241.21621, found 241.21602.

*(2R)-12,13-Dihydroxytridecan-2-yl acetate (**13**).* Ester **12** (4.81 g, 20.0 mmol) was dissolved in acetone (40 mL) and cooled to 0 °C. A solution of $K_2OsO_4 \cdot 2H_2O$ (221 mg, 600 µmol, 3 mol%) in H_2O (20 mL) and NMO (4.8 M in H_2O, 6.88 mL, 33.0 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 28.5 h. Na_2SO_3 (17.6 g, 140 mmol) was added and stirring was continued for a further 1.5 h. The solids were removed by filtration and the filter cake was washed wit EtOAc (150 mL). The volatile parts of the emulsion were removed by evaporation and the aqueous residue was extracted with EtOAc (4 × 200 mL). The combined organic phases were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexanes/EtOAc 1 : 6) to give diol **13** (5.20 g, 95%) as a colourless solid with a mp of 30–32 °C. R_f = 0.34 (hexanes/EtOAc 1 : 6); $[\alpha]_D^{20}$ −1.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (sex, *J* = 6.3 Hz, 1 H), 3.67 (m, 2 H), 3.43 (m, 1 H), 2.12 (s, 1 H), 2.01 (m, 4 H), 1.56 (m, 1 H), 1.43 (m, 4 H), 1.51–1.22 (m, 13 H), 1.20 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 72.4, 71.2, 67.0, 36.0, 33.3, 29.7, 29.6, 29.55, 29.51, 25.6, 25.5, 21.6, 20.1 ppm; IR ν_{max} 3400, 2979, 2926, 2854, 1736, 1463, 1372, 1242, 1125, 1022, 953, 868, 723 cm^{-1}; HRMS (+ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_4Na^+$ 297.20636, found 297.20319.

*(R)-12-Oxododecan-2-yl acetate (**8**).* A solution of diol **13** (5.00 g, 18.2 mmol) in CH_2Cl_2 (182 mL) at room temperature was treated portionwise with $NaIO_4$-coated SiO_2 (approx. 0.7 mmol $NaIO_4$ per g reagent, 41.6 g, 29.1 mmol). The resulting suspension was vigorously stirred for 1.75 h and filtered. The filtrate was evaporated and the unstable aldehyde **8** (4.42 g, quant.) was obtained as a colourless oil. It was immediately used for the next step without further purification. R_f = 0.55 (hexanes/EtOAc 4 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1 H), 4.88 (sex, *J* = 6.3 Hz, 1 H), 2.42 (dt, *J* = 1.8, 7.3 Hz, 2 H), 2.02 (s, 3 H), 1.59 (m, 3 H), 1.45 (m, 1 H), 1.36–1.22 (m, 12 H), 1.20 (d, *J* = 6.3 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 171.0, 71.2, 44.1, 36.0, 29.6, 29.54, 29.46, 29.3, 25.5, 22.2, 21.6, 20.1 ppm.

*Ethyl (R)-13-acetoxy-3-oxotetradecanoate (**14**).* A solution of aldehyde **8** (8.29 g, 34.2 mmol) and EDA (solution with 16 wt% CH_2Cl_2, 5.57 mL, 44.5 mmol) in dry CH_2Cl_2 (188 mL) under argon atmosphere was cooled to 0 °C and treated with dry $SnCl_2$ (777 mg, 4.10 mmol, 12 mol%). The mixture was stirred for 2.25 h at 0 °C, warmed to room temperature and stirred for a further 45 min. Brine (150 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with sat. aqueous $NaHCO_3$-solution (100 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc 10 : 1 to 5 : 1). After removal of the solvent under reduced pressure, the remainder was redissolved in EtOAc (60 mL) and washed with 2 M aqueous HCl (50 mL) and sat. aqueous $NaHCO_3$-solution (50 mL). The organic phase was dried over Na_2SO_4 and removal of the solvent gave the β-ketoester **14** (11.0 g, 98%) as a colourless oil. R_f = 0.38 (hexanes/EtOAc 4 : 1); $[\alpha]_D^{20}$ −2.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *keto-form*: δ 4.88 (sex, *J* = 6.2 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.42 (s, 2 H), 2.52 (t, *J* = 7.4 Hz, 2 H), 2.02 (s, 3 H), 1.57 (m, 3 H), 1.46 (m, 1 H), 1.36–1.22 (m, 15 H), 1.19 (d, *J* = 6.2 Hz, 3 H) ppm; *enol-form*: δ 12.1 (s), 4.97 (s), 4.26 (dq, *J* = 4.4, 7.2 Hz), 3.16 (q, *J* = 5.5 Hz), 2.18 (t, *J* = 7.2 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2, 171.0, 167.4, 71.2, 61.5, 49.5, 43.2, 36.0, 29.58, 29.55, 29.50 (2 C atoms), 29.1, 25.5, 23.6, 21.6, 20.1, 14.3 ppm; *enol-form* δ 89.1, 60.1, 35.2 ppm; IR ν_{max} 2979, 2929, 2856, 1735, 1644, 1464, 1371, 1312, 1245, 1028, 951; HRMS (+ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{32}O_5Na^+$ 351.21420, found 351.21313.

*Ethyl (3S,13R)-13-acetoxy-3-hydroxytetradecanoate (**7**).* The Noyori catalyst was synthesized as described.[9] $[RuCl_2(benzene)]_2$ (75.0 mg, 150 µmol) and (*S*)-BINAP (196 mg, 315 µmol) were dissolved in degassed dry DMF (5.25 mL) under an argon atmosphere. The solution was heated at 100 °C for 10 min, cooled down to 50 °C and the solvent was removed in high vacuum.

In a glove box the degassed β-ketoester **14** (10.3 g, 31.4 mmol) was dissolved in degassed dry MeOH (28 mL). Freshly prepared Noyori catalyst (85 mg, 90.7 µmol, 0.29 mol%) was added and the mixture was stirred until complete solution. It was transferred into a high-pressure autoclave which was purged five times with H_2 and filled with 40 bar H_2. The solution was stirred at 60 °C for 65 h. The pressure was released, and the solvent was evaporated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc 7 : 1 to 4 : 1). Alcohol **7** (9.02 g, 87%) was obtained as a colourless oil with a de >99% (as to chiral HPLC). R_f = 0.23 (hexanes/EtOAc 4 : 1); $[\alpha]_D^{20}$ +13.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (sex, *J* ~ 6.2 Hz, 1 H), 4.17 (q, *J* ~ 7.2 Hz, 2 H), 3.99 (m, 1 H), 2.94 (d, *J* = 4.0 Hz, 1 H), 2.50 (dd, *J* = 3.0, 16.4 Hz, 1 H), 2.39 (dd, *J* = 9.2, 16.4 Hz, 1 H), 2.02 (s, 3 H), 1.61–1.23 (m, 21 H), 1.19 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 171.0, 71.2, 68.1, 60.8, 41.4, 36.6, 36.0, 29.7, 29.62, 29.60, 29.57, 25.6, 25.5, 21.6, 20.1, 14.3 ppm;

IR ν_{max} 3471, 2980, 2927, 2855, 1733, 1464, 1371, 1242, 1023, 951; HRMS (+ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{33}O_5^+$ 331.24790, found 331.24756.

*Ethyl (3S,13R)-13-acetoxy-3-(methoxymethoxy)tetradecanoate (**15**).* A solution of alcohol **7** (330 mg, 1.00 mmol) in dimethoxymethane (5 mL) under argon atmosphere was treated with P_2O_5 (355 mg, 2.50 mmol) at room temperature. The resulting suspension was stirred for 2 h and sat. aqueous $NaHCO_3$-solution (20 mL) was added. The solution was extracted with EtOAc (3 × 50 mL), the combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. Silica gel column chromatography (hexanes/EtOAc 8 : 1) gave MOM-ether **15** (354 mg, 95%) as a colourless oil. R_f = 0.58 (hexanes/EtOAc 3 : 1); $[\alpha]_D^{20}$ +2.4° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (sex, *J* = 6.2 Hz, 1 H), 4.66 (dd, *J* = 7.0, 16.4 Hz, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.98 (qn, *J* = 6.4 Hz, 1 H), 3.35 (s, 3 H), 2.55 (dd, *J* = 7.4, 15.2 Hz, 1 H), 2.45 (dd, *J* = 5.3, 15.2 Hz, 1 H), 2.02 (s, 3 H), 1.63–1.22 (m, 21H), 1.20 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.0, 96.1, 74.9, 71.2, 60.5, 55.7, 40.5, 36.1, 35.0, 29.72, 29.67, 29.64, 29.62, 29.58, 25.5, 25.3, 21.6, 20.1, 14.4 ppm; IR ν_{max} 2979, 2928, 2856, 1733, 1465, 1372, 1242, 1148, 1101, 1033, 918 cm^{-1}; HRMS (+ESI) *m/z* $[M + Na]^+$ calcd for $C_{20}H_{38}O_6Na^+$ 397.25606, found 397.25546.

*(3S,13R)-13-Hydroxy-3-(methoxymethoxy)tetradecanal (**6**).* A solution of MOM-ether **15** (5.71 g, 15.2 mmol) in dry toluene (100 mL) under an argon atmosphere was cooled down to −78 °C and treated with DIBAL (1 M in hexanes, 33.5 mL, 33.5 mmol) while stirring over a period of 15 min. Stirring was continued for a further 75 min at −78 °C. Acetone (500 µL) was added and the solution was stirred for 15 min. The mixture was poured into sat. aqueous Na-K-tartrate solution (300 mL) and stirred for 1.5 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and evaporated. After silica gel column chromatography (petrol ether/EtOAc 2 : 1 to 1 : 1) hydroxyaldehyde **6** (4.03 g, 92%) was obtained as a colourless resin. R_f = 0.50 (hexanes/EtOAc 1 : 1); $[\alpha]_D^{20}$ +9.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (dd, *J* = 1.8, 2.8 Hz, 1 H), 4.66 (dd, *J* = 7.0, 16.1 Hz, 2 H), 4.07 (qn, *J* = 6.5 Hz, 1 H), 3.79 (sex, *J* = 5.9 Hz, 1 H), 3.35 (s, 3 H), 2.64 (ddd, *J* = 2.8, 7.1, 16.3 Hz, 1 H), 2.56 (ddd, *J* = 1.8, 4.7, 16.3 Hz, 1 H), 1.61 (m, 1 H), 1.53 (m, 1 H), 1.47–1.24 (m, 17 H), 1.20 (d, *J* = 6.2 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 95.9, 73.3, 68.3, 55.8, 48.9, 39.5, 35.1, 29.74, 29.69, 29.68, 29.64, 29.60, 25.9, 25.3, 23.7 ppm; IR ν_{max} 3404, 2925, 2854, 1725, 1465, 1373, 1149, 1101, 1031, 918 cm^{-1}; HRMS (+ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{32}O_4Na^+$ 311.21928, found 311.21878.

*(6S,16R,E)-6-(Methoxymethoxy)-16-methyloxacyclohexadec-3-en-2-one (**4**).* A solution of Ph_3PCCO (**5**, 199 mg, 659 µmol) in dry toluene (55 mL) under an argon atmosphere was warmed to 55 °C and treated dropwise with a solution of hydroxyaldehyde **6** (95 mg, 329 µmol) in dry toluene (10 mL) over a period of 15 h. The resulting solution was stirred for a further 5 h before the solvent was removed under reduced pressure. Silica gel column chromatography (hexanes 100% to hexanes/EtOAc 5 : 1) afforded macrolide **4** (64 mg, 62%) as a colourless oil. R_f = 0.60 (hexanes/EtOAc 4 : 1); $[\alpha]_D^{20}$ −43.7° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 7.5, 15.6 Hz, 1 H), 5.87 (d, *J* = 15.6 Hz, 1 H), 5.01 (ddq, *J* = 2.7, 6.3, 9.1 Hz, 1 H), 4.70 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 7.0 Hz, 1 H), 3.68 (m, 1 H), 3.38 (s, 3 H), 2.58 (m, 1 H), 2.38 (m, 1 H), 1.59 (m, 2 H), 1.53 (m, 1 H), 1.63–1.16 (m, 18 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 144.2, 124.8, 95.3, 75.9, 71.1, 55.6, 36.8, 35.3, 31.8, 28.0, 27.7, 27.4, 26.5, 26.4, 23.8, 22.0, 20.5 ppm; IR ν_{max} 2927, 2857, 1715, 1656, 1457, 1355, 1318, 1264, 1147, 1098, 1033, 917 cm^{-1}; HRMS (+ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{33}O_4^+$ 313.23734, found 313.23682.

*(6S,16R,E)-6-(Methoxymethoxy)-16-methyloxacyclohexadec-3-ene-2,5-dione (**16**).* Macrolide **4** (40 mg, 128 µmol) and SeO_2 (42.6 mg, 384 µmol) were suspended in dry 1,4-dioxane (2 mL) in a sealed vessel under argon atmosphere and heated at 155 °C for 55 min. The mixture was filtered over a plug of Celite® and the filtrate was evaporated. After silica gel column chromatography (hexanes/EtOAc 8 : 1) ketone **16** (32 mg, 77%) was obtained as yellowish solid of mp 44–47 °C. R_f = 0.63 (hexanes/EtOAc 4 : 1); $[\alpha]_D^{20}$ −56° (*c* 1.00, $CHCl_3$), lit[17] $[\alpha]_D^{27}$ −49° (*c* 0.282, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 15.8 Hz, 1 H), 6.77 (d, *J* = 15.8 Hz, 1 H), 5.09 (ddq, *J* = 2.9, 6.3, 9.1 Hz, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.65 (d, *J* = 6.8 Hz, 1 H), 4.23 (dd, *J* = 5.1, 7.2 Hz, 1 H), 3.35 (s, 3 H), 1.80 (m, 2 H), 1.59 (m, 2 H), 1.44–1.12 (m, 17 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 165.1, 135.0, 132.1, 96.3, 82.0, 72.7, 56.2, 34.9, 30.6, 27.82, 27.76, 27.7, 26.8, 26.6, 23.7, 22.0, 20.3 ppm; IR ν_{max} 2929, 2857, 1721, 1704, 1623, 1460, 1267, 1031, 951, 919 cm^{-1}; HRMS (+ESI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{30}O_5Na^+$ 349.19855, found 349.19806.

*(6S,16R,E)-6-Hydroxy-16-methyloxacyclohexadec-3-ene-2,5-dione (**2**).* A solution of ketone **16** (50 mg, 153 µmol) in dry CH_2Cl_2 (2 mL) was kept under argon atmosphere at −10 °C and treated with TFA (1 mL). The mixture was stirred for 9.5 h at −10 °C, then treated with sat. aqueous $NaHCO_3$-solution (40 mL), and the aqueous phase was finally extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After silica gel column chromatography (hexanes/EtOAc 8 : 1 to 6 : 1) alcohol **2** (38 mg, 88%) was obtained as a colourless crystalline solid of mp 83–85 °C, lit[10] 84–85 °C. R_f = 0.38 (hexanes/EtOAc 4 : 1); $[\alpha]_D^{20}$ +35.8° (*c* 1.00, $CHCl_3$), lit[10] $[\alpha]_D^{20}$ +22.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 15.9 Hz, 1 H), 6.80 (d, *J* = 15.9 Hz, 1 H), 5.18 (m, 1 H), 4.55 (q, *J* = 4.5 Hz, 1 H), 3.45 (d, *J* = 4.5 Hz, 1 H), 1.85 (m, 2 H), 1.73 (m, 1 H), 1.50 (m, 2 H), 1.46–1.01 (m, 15 H), 0.96 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 165.2, 135.0, 132.7, 76.6, 72.8, 34.3, 31.2, 28.22, 28.17, 27.4, 27.2, 26.9, 23.5, 20.7, 19.8 ppm; IR ν_{max} 3456, 3066, 2923, 2854, 1714, 1696, 1644, 1459, 1353, 1286, 1190, 1057, 984 cm^{-1}; HRMS (+ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{26}O_4Na^+$ 305.17233, found 305.17117.

*Methyl oxirane-2-carboxylate rac-(**18**).* According to the protocol of Jacobsen[13] aqueous NaOCl (6 wt%, 588 mL, 480 mmol) was cooled to 0 °C and methyl acrylate (**17**, 31.6 mL,

348 mmol) was added. The emulsion was stirred for 30 min at 0 °C and the ice bath was removed. The aqueous solution was stirred for another 1.5 h, cooled again by an ice bath, and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at 30 °C (100 mbar). The remaining solution was distilled (85 mbar, 85 °C) which gave *rac*-methyl glycidate (*rac*-**18**, 11.4 g, 32%) as a colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 3.45 (dd, J = 2.5, 4.1 Hz, 1 H), 2.97 (dd, J = 2.5, 6.5 Hz, 1 H), 2.94 (dd, J = 4.1, 6.5 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 52.6, 47.3, 46.4 ppm.

*Methyl (R)-oxirane-2-carboxylate R-(**18**).* (*S*,*S*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (408 mg, 675 µmol, 0.75 mol%) and *p*TsOH (136 mg, 716 µmol, 0.795 mol%) were dissolved in CH_2Cl_2 (9 mL) and stirred, open to air, for 1 h. The solvent was removed under reduced pressure. *rac*-Methyl glycidate (*rac*-**18**, 7.88 mL, 90.0 mmol) and H_2O (1.14 mL, 63.0 mmol) were added and the solution was stirred at room temperature for 21 h and then at 85 °C for 2 h. The precipitate was filtered off and washed with H_2O (3 × 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was removed by rotary evaporation (30 °C, 100 mbar) and the remainder distilled under vacuum (80 °C, 70 mbar). *R*-Methyl glycidate (*R*-**18**, 2.99 g, 33%) was obtained as a colourless liquid. $[\alpha]_D^{25}$ +8.9° (*c* 5.34, MeOH), lit[13] $[\alpha]_D^{26}$ −10.3° (*c* 5.34, MeOH) for the *S*-enantiomer; ^{1}H NMR (500 MHz, $CDCl_3$) 3.79 (s, 3 H), 3.45 (dd, J = 2.5, 4.1 Hz, 1 H), 2.97 (dd, J = 2.5, 6.5 Hz, 1 H), 2.94 (dd, J = 4.1, 6.5 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 52.7, 47.4, 46.5 ppm.

*Potassium (R)-oxirane-2-carboxylate (**19**).* KOH (524 mg, 9.33 mmol) was dissolved in MeOH (18 mL) at 0 °C and (*R*)-methyl glycidate (*R*-**18**, 1.00 g, 9.80 mmol) was added. The solution was warmed to room temperature and stirred for 16 h. The solvent was evaporated, and the crude product recrystallized from MeOH/Et_2O. (*R*)-Potassium glycidate (**19**, 930 mg, 79%) was obtained as a colourless solid which showed decomposition at 141 °C. $[\alpha]_D^{26}$ +31.1° (*c* 1.05, H_2O), lit[18] $[\alpha]_D^{20}$ +31.8° (*c* 1.05, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.35 (m, 1 H), 2.93 (m, 1 H), 2.79 (m, 1 H) ppm; ^{1}H NMR (500 MHz, CD_3OD) δ 3.23 (dd, J = 2.6, 4.4 Hz, 1 H), 2.81 (dd, J = 4.6, 6.4 Hz, 1 H), 2.72 (m, J = 2.6, 6.4 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ 176.8, 50.4, 46.3 ppm.

*(S)-2-Hydroxy-3-(tritylthio)propanoic acid (**20**).* A solution of triphenylmethanethiol (1.32 g, 4.76 mmol) in dry THF (30 mL) was kept under an argon atmosphere at 0 °C and treated portionwise with NaH (60 wt% in mineral oil, 89 mg, 2.22 mmol). The resulting mixture was treated with (*R*)-potassium glycidate (**19**, 400 mg, 3.17 mmol), then warmed to room temperature, stirred for 19 h, and finally poured into H_2O (100 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL), adjusted to pH = 4 and extracted with Et_2O (3 × 70 mL) and EtOAc (70 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The crude carboxylic acid **20** (1.00 g) was used for the next step without further purification. R_f = 0.69 (CH_2Cl_2/MeOH 9 : 1 + 1% HCOOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.6 Hz, 6 H), 7.29 (t, J = 7.6 Hz, 6 H), 7.23 (t, J = 7.6 Hz, 3 H), 3.82 (dd, J = 4.2, 7.2 Hz, 1 H), 2.77 (dd, J = 4.2, 13.2 Hz, 1 H), 2.67 (dd, J = 7.2, 13.2 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 144.4, 129.6, 128.2, 127.1, 69.0, 67.2, 36.2 ppm; IR ν_{max} 3348, 3054, 3031, 2930, 1733, 2605, 1717, 1594, 1488, 1444, 1240, 1183, 1083, 1033, 741, 696 cm^{-1}; HRMS (−ESI) m/z $[M - H]^-$ calcd for $C_{22}H_{19}O_3S^-$ 363.10494, found 363.10468.

*Benzyl (S)-2-hydroxy-3-(tritylthio)propanoate (**21**).* To a solution of crude carboxylic acid **20** (450 mg, 1.23 mmol) in DMF (10 mL) was added Cs_2CO_3 (483 mg, 1.48 mmol). After 30 min of stirring at room temperature, benzyl bromide (584 µL, 4.92 mmol) was added and the suspension was stirred for a further 16 h. The mixture was poured into sat. aqueous NH_4Cl-solution (100 mL) and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (2 × 100 mL), dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (petrol ether/EtOAc 5 : 1 to 1 : 1) gave benzyl ester **21** (276 mg, 61% over two steps) as a colourless resin. R_f = 0.66 (hexanes/EtOAc 2 : 1); $[\alpha]_D^{20}$ −48.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.15 (m, 20 H), 5.15 (q, J = 12.2 Hz, 2 H), 4.04 (q, J = 5.6 Hz, 1 H), 2.82 (d, J = 6.0 Hz, 1 H), 2.58 (d, J = 5.6 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 144.5, 135.1, 129.7, 128.72, 128.66, 128.4, 128.1, 126.9, 69.6, 67.6, 66.8, 36.6 ppm; IR ν_{max} 3472, 3057, 3032, 2930, 1733, 1594, 1489, 1444, 1173, 1082, 741, 695 cm^{-1}; HRMS (+ESI) m/z $[M + Na]^+$ calcd for $C_{29}H_{26}O_3SNa^+$ 477.14949, found 477.14865.

*Benzyl (S)-2-hydroxy-3-mercaptopropanoate (**3**).* A solution of benzyl ester **21** (190 mg, 418 µmol,) and *i*Pr$_3$SiH (103 µL, 502 µmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with TFA (200 µL) and stirred for 3.5 h at 0 °C and for a further 45 min at room temperature. Toluene (2 × 10 mL) was added and the volatiles were removed by rotary evaporation. After silica gel column chromatography (petrol ether/EtOAc 5 : 1 to 3 : 1) thiol **3** (80 mg, 91%) was obtained as a colourless resin. R_f = 0.67 (hexanes/EtOAc 1 : 1); $[\alpha]_D^{20}$ +43.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 5 H), 5.25 (q, J = 12.1 Hz, 2 H), 4.47 (m, 1 H), 3.17 (d, J = 5.8 Hz, 1 H), 2.96 (ddd, J = 3.8, 8.0, 14.0 Hz, 1 H), 2.87 (ddd, J = 4.4, 9.5, 14.0 Hz, 1 H), 1.56 (dd, J = 8.0, 9.5 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 135.0, 128.90, 128.86, 128.7, 70.9, 68.0, 29.0 ppm; IR ν_{max} 3471, 3069, 3035, 2946, 2574, 1733, 1498, 1455, 1256, 1187, 1095 cm^{-1}; HRMS (+ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{13}O_3S$ 213.05799, found 213.05783.

*Benzyl (S)-2-hydroxy-3-(((3R,6S,16R)-6-hydroxy-16-methyl-2,5-dioxooxacyclohexadecan-3-yl)thio)propanoate (**22**).* Macrolide **2** (59 mg, 209 µmol) and thiol **3** (51 mg, 240 µmol) were dissolved at room temperature in CH_2Cl_2 (2 mL) and NEt_3 (4.23 µL, 4.8 µmol, 20 mol%) was added. The solution was stirred for 3 h and the solvent was removed by rotary evaporation. Silica gel column chromatography (CH_2Cl_2/EtOAc 10 : 1 to 4 : 1) afforded thioether **22** (101 mg, 98%) as a colourless oil with a diastereomeric ratio of 15 : 1. R_f = 0.47 (hexanes/EtOAc 1 : 1); $[\alpha]_D^{20}$ +99.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.22 (s, 2 H), 4.94 (m, 1 H), 4.53 (m, 1 H), 4.33

(m, 1 H), 4.02 (dd, J = 6.1, 8.3 Hz, 1 H), 3.52 (s, 1 H), 3.33 (d, J = 4.5 Hz, 1 H), 3.24 (dd, J = 3.7, 14.5 Hz, 1 H), 3.22 (dd, J = 8.3, 18.4 Hz, 1 H), 2.98 (dd, J = 5.7, 14.4 Hz, 1 H), 2.69 (dd, J = 6.1, 18.4 Hz, 1 H), 1.83 (m, 2 H), 1.55 (m, 1 H), 1.47–1.34 (m, 17 H), 0.96 (m, 1 H) ppm; *epimer* δ 3.80 (t, J = 6.9 Hz), 3.10 (m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 172.7, 172.0, 135.0, 128.8, 128.6, 76.2, 72.7, 70.7, 67.9, 41.2, 41.0, 35.8, 34.6, 32.6, 26.9, 26.8, 26.7, 26.1, 25.4, 23.1, 20.9, 19.9 ppm; *epimer* δ 76.6, 73.5, 71.3, 67.7, 43.6, 40.7, 37.3, 35.1, 27.3, 26.4, 26.3, 25.9, 23.3, 21.9, 19.5 ppm; IR ν_{max} 3472, 2929, 2858, 1717, 1456, 1263, 1172, 1092, 1005, 734, 697 cm^{-1}; HRMS (+ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{39}O_7S^+$ 495.24110, found 495.24069.

*Berkeleylactone A (**1**).* To a solution of thioether **22** (22 mg, 44.4 µmol) in MeOH (6 mL) under argon atmosphere was added Pd/C (10 wt%, 4.8 mg, 4.44 µmol, 10 mol%). The reaction flask and the suspension were purged with H_2. The mixture was stirred for 1.75 h at room temperature under an atmosphere of H_2 (1 atm), filtered over a plug of Celite®, and washed with MeOH (30 mL). Rotary evaporation of the filtrate gave the crude product which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH + 0.5% HCOOH 30 : 1 to 25 : 1) to afford berkeleylactone A (**1**, 16 mg, 89%) as a colourless crystalline solid of mp 110–113 °C, lit[2] 119–121 °C. R_f = 0.38 (CH_2Cl_2/MeOH 10 : 1 + 1% HCOOH); $[\alpha]_D^{20}$ +94.5° (c 1.00, $CHCl_3$), lit[1] $[\alpha]_D^{25}$ +0.5° (c 0.17, $CHCl_3$), lit[2] $[\alpha]_D^{25}$ +101.0° (c 0.105, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14–4.83 (m, 4 H), 4.55 (m, 1 H), 4.40 (m, 1 H), 4.03 (t, J = 7.0 Hz, 1 H), 3.28 (m, 1 H), 3.22 (dd, J = 7.7, 18.5 Hz, 1 H), 3.00 (dd, J = 5.5, 14.5 Hz, 1 H), 2.80 (dd, J = 6.3, 18.5 Hz, 1 H), 1.85 (m, 2 H), 1.56 (m, 1 H), 1.51–1.13 (m, 17 H), 0.98 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 175.2, 172.4, 76.3, 73.3, 70.5, 41.4, 41.0, 35.8, 34.6, 32.4, 26.8, 26.75, 26.7, 26.1, 25.3, 23.0, 20.8, 19.9 ppm; IR ν_{max} 3433, 2929, 2858, 1716, 1458, 1261, 1170, 1092, 908, 729 cm^{-1}; HRMS (+ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{33}O_7S^+$ 405.19415, found 405.19345.

Author contributions

MGS planned the chemical synthesis, carried out all chemical reactions, and isolated, purified and analysed all reaction products, and wrote the experimental part of the manuscript. HS and HZ conducted and evaluated all biological assays. MS supervised the biological studies, RS supervised the chemical part and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

H. Z. is grateful for a personal PhD stipend from the "Drug Discovery and Cheminformatics for New Anti-Infectives (iCA)" and is financially supported by the Ministry for Science & Culture of the German State of Lower Saxony (MWK no. 21—78904-63-5/19).

Notes and references

1 A. A. Stierle, D. B. Stierle, D. Decato, N. D. Priestley, J. B. Alverson, J. Hoody, K. McGrath and D. Klepacki, The berkeleylactones, antibiotic macrolides from fungal coculture, *J. Nat. Prod.*, 2017, **80**, 1150–1160.

2 B. Ferko, M. Zeman, M. Formica, S. Vesely, J. Dohonosova, J. Moncol, P. Olejnikova, D. Berkes, P. Jacubec, D. J. Dixon and O. Caletková, Total synthesis of berkeleylactone A, *J. Org. Chem.*, 2019, **84**, 7159–7165.

3 W.-W. Lee, H. J. Shin and S. Chang, A rapid formal synthesis of the macrolide (−)-A26771B, *Tetrahedron: Asymmetry*, 2001, **12**, 29–31.

4 (*a*) M. Ostermeier and R. Schobert, Total synthesis of (+)-chloriolide, *J. Org. Chem.*, 2014, **79**, 4038–4042; (*b*) R. Schmidt, M. Ostermeier and R. Schobert, Wittig cyclization of ω-hydroxy hemiacetals: synthesis of (+)-aspicilin, *J. Org. Chem.*, 2017, **82**, 9126–9132.

5 H.-J. Bestmann and R. Schobert, Oxidation of α,β–unsaturated esters and lactones with selenium dioxide to γ–oxo or γ–hydroxy derivatives; synthesis of (±)–A 26771 B and norpyrenophorin, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 791–792.

6 (*a*) H.-J. Bestmann and D. Sandmeier, Simple synthesis of ketenylidenetriphenylphosphorane and its thioanalogs, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 634; (*b*) R. Schobert, R. K. Boeckman, Jr. and J. E. Pero, Preparation of (triphenylphosphoranylidene)ketene from (methoxycarbonylmethylene)triphenylphosphorane, *Org. Synth.*, 2005, **82**, 140–143.

7 (*a*) H.-J. Bestmann and R. Schobert, A novel synthesis of macrocyclic lactones, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 780–782; (*b*) H.-J. Bestmann and R. Schobert, Totalsynthese des Macrodiolids (*R,R*)-(−)-Grahamimycin A_1, *Tetrahedron Lett.*, 1987, **28**, 6587–6590.

8 C. R. Holmquist and E. J. Roskamp, A selective method for the direct conversion of aldehydes into β-keto esters with ethyl diazoacetate catalyzed by tin(II) chloride, *J. Org. Chem.*, 1989, **54**, 3258–3260.

9 M. Kitamura, M. Tokunaga, T. Ohkuma and R. Noyori, Asymmetric hydrogenation of 3−oxo carboxylates using BINAP–ruthenium complexes: (*R*)–(−)–methyl 3−-hydroxybutanoate, *Org. Synth.*, 1993, **71**, 1.

10 J. Gebauer and S. Blechert, Synthesis of γ,δ-unsaturated-β-keto lactones via sequential cross metathesis−-lactonization: A facile entry to macrolide antibiotic (−)-A26771B, *J. Org. Chem.*, 2006, **71**, 2021–2025.

11 L. Horner, H. Oediger and H. Hoffmann, Reaktionen mit Triphenylphosphin–dihalogeniden, *Liebigs Ann.*, 1959, **626**, 26–34.

12 M. Daumas, Y. Vo-Quang, L. Vo-Quang and F. Le Goffic, New and efficient heterogeneous system for the oxidative

cleavage of 1,2-diols and the oxidation of hydroquinones, *Synthesis*, 1989, 64–65.

13 C. P. Stevenson, L. P. C. Nielsen and E. N. Jacobsen, Preparation of (*S*)-methyl glycidate via hydrolytic kinetic resolution, *Org. Synth.*, 2006, **83**, 162–169.

14 D. Davis, Understanding biofilm resistance to antibacterial agents, *Nat. Rev. Drug Discovery*, 2003, **2**, 114–112.

15 K. Van Dyck, R. M. Pinto, D. Pully and P. Van Dyk, Microbial interkingdom biofilm and the quest for novel therapeutic strategies, *Microorganisms*, 2021, **9**, 412.

16 M. P. de Carvalho, G. Gulotta, M. W. do Amaral, H. Lünsdorf, F. Sasse and W.-R. Abraham, Coprinuslactone protects the edible mushroom *Coprinus comatus* against biofilm infection by blocking quorum-sensing and MurA, *Environ. Microbiol.*, 2016, **18**, 4254–4264.

17 Y. Kobayashi and H. Okui, An efficient synthesis of antibiotic (−)-A26771B, *J. Org. Chem.*, 2000, **65**, 612–615.

18 J. B. Stenlake, N. C. Dhar, J. Haddow, I. M. McDonald, R. B. Maehr and W. B. Wastila, Neuromuscular blocking agents. Some approaches to short acting compounds, *Eur. J. Med. Chem.*, 1992, **27**, 463–477.

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation

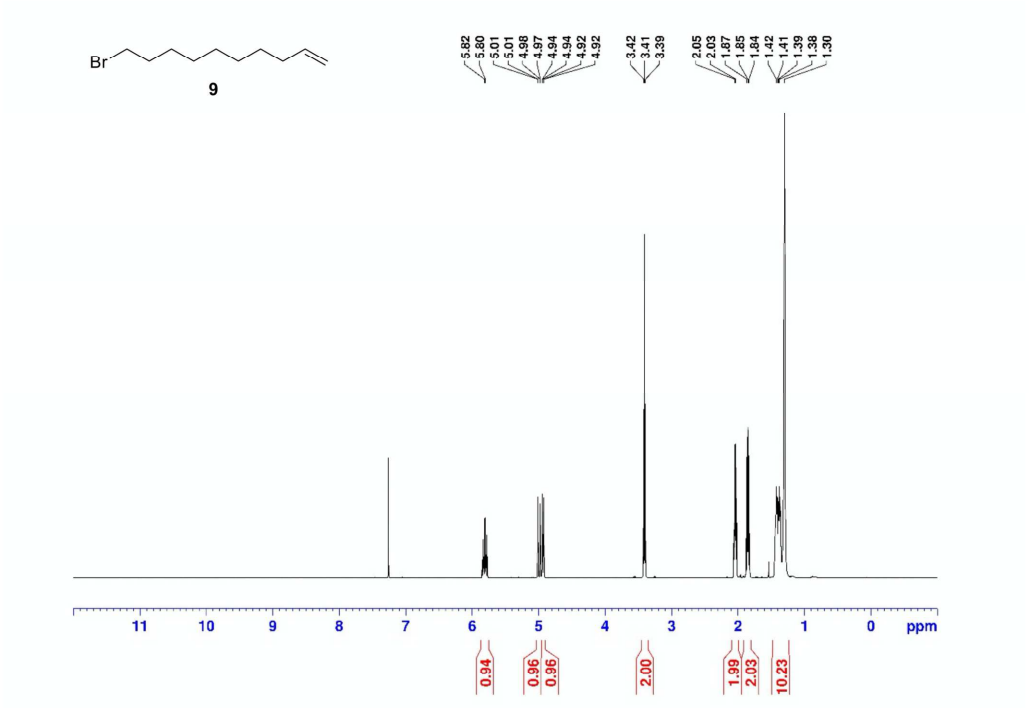
Manuel G. Schriefer,[a] Hedda Schrey,[b] Haoxuan Zeng[b], Marc Stadler[b] and Rainer Schobert [a,*]

[a]Department of Chemistry, University Bayreuth, Universitaetsstrasse 30, 95440 Bayreuth, Germany

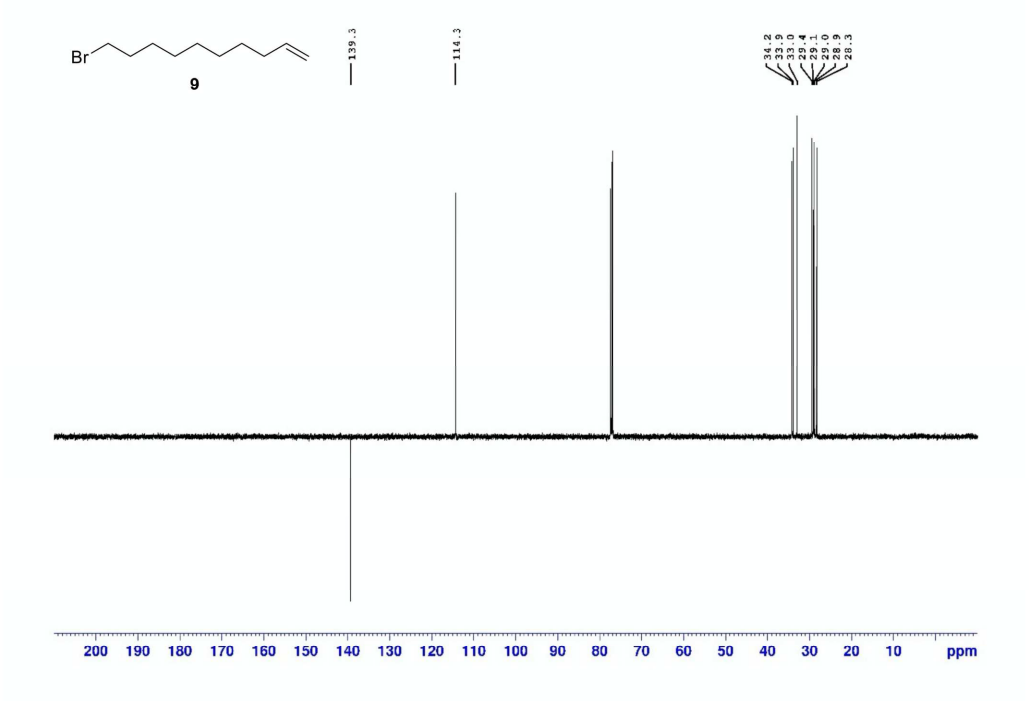
[b]Department of Microbial Drugs, Helmholtz Centre for Infection Research GmbH, Inhoffenstrasse 7, 38124 Braunschweig, Germany

e-mail: Rainer.Schobert@uni-bayreuth.de

Table of contents **page**

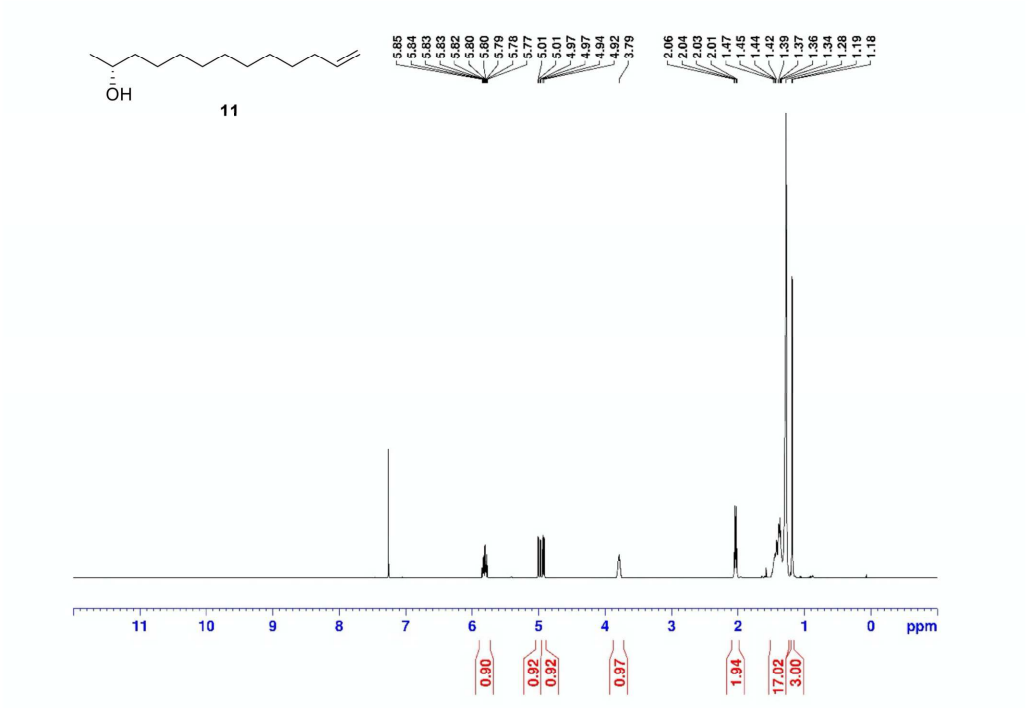


^{1}H-NMR spectrum of compound **9** in $CDCl_3$.

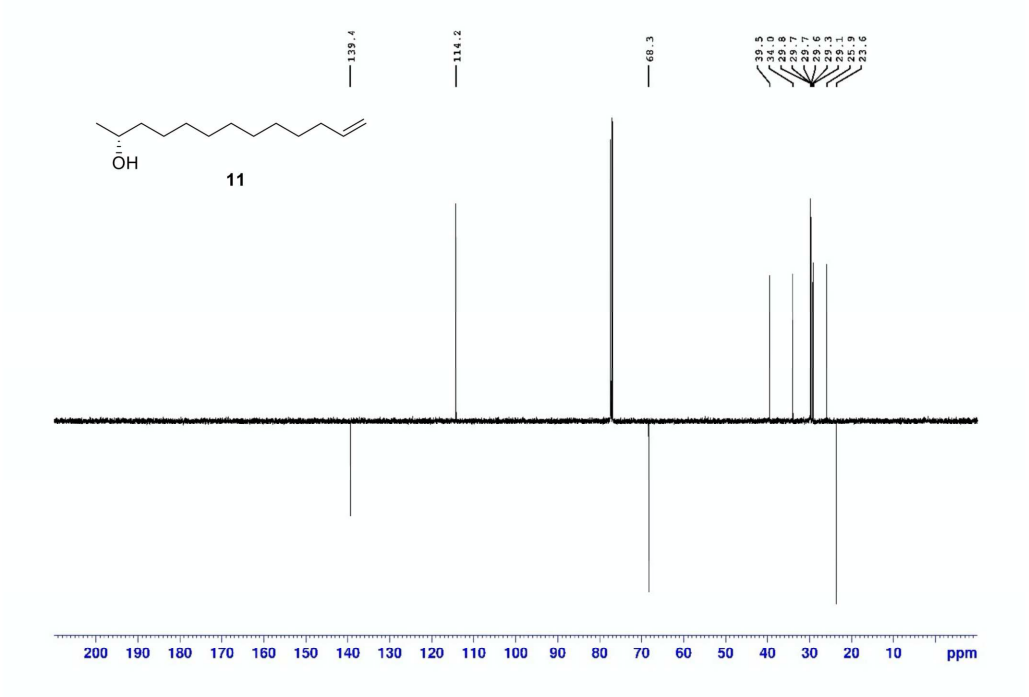


^{13}C-NMR spectrum of compound **9** in $CDCl_3$.

S1

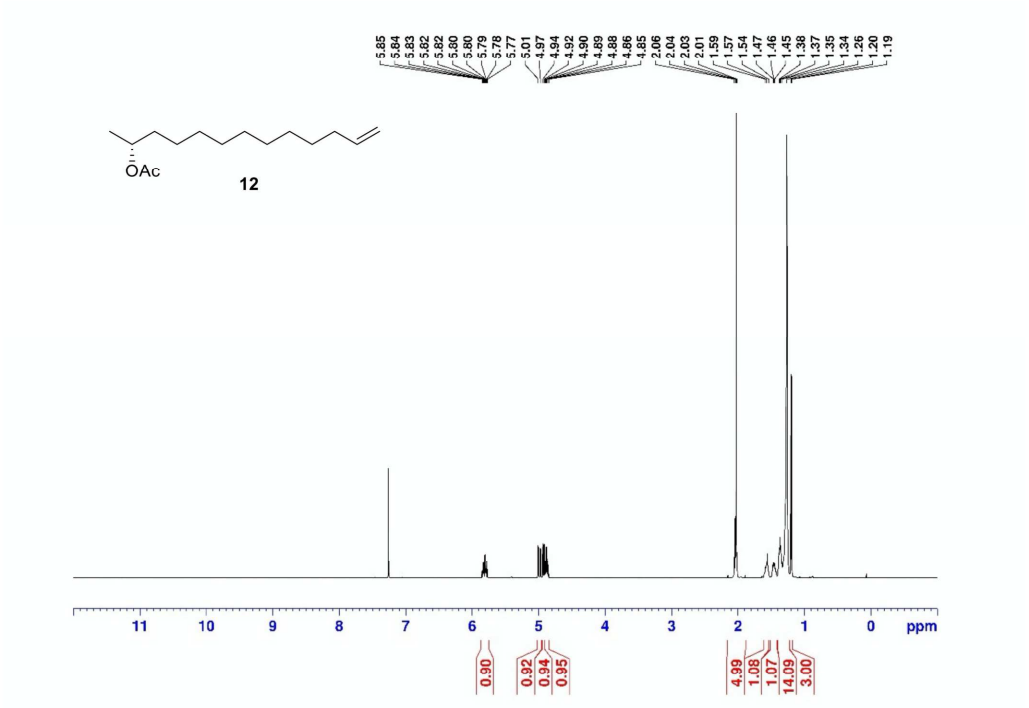


^{1}H-NMR spectrum of compound **11** in $CDCl_3$.

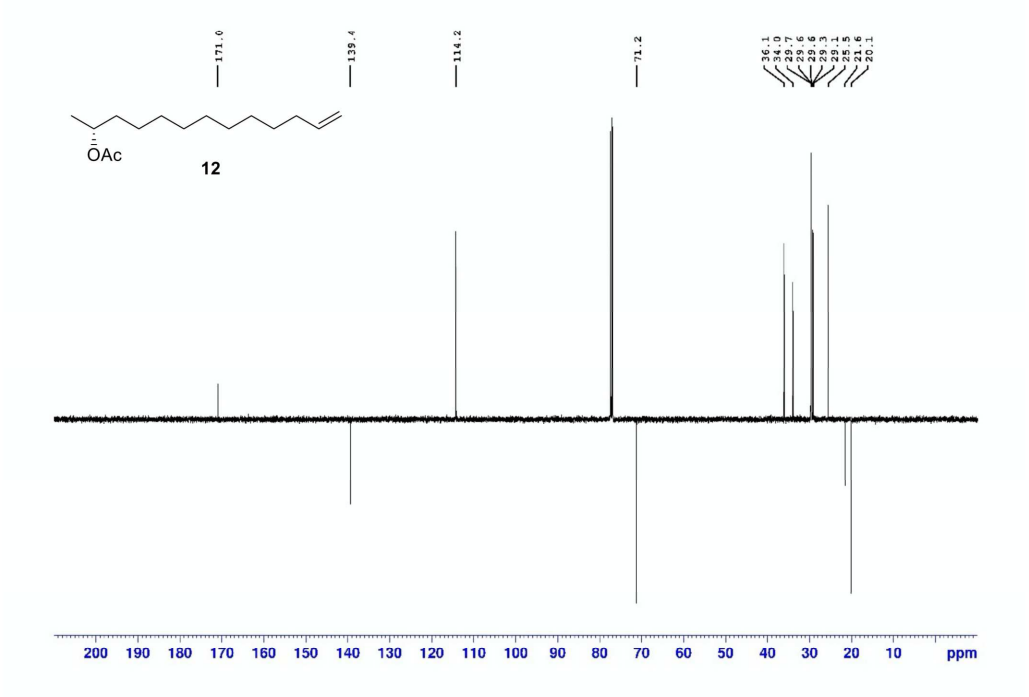


^{13}C-NMR spectrum of compound **11** in $CDCl_3$.

S2

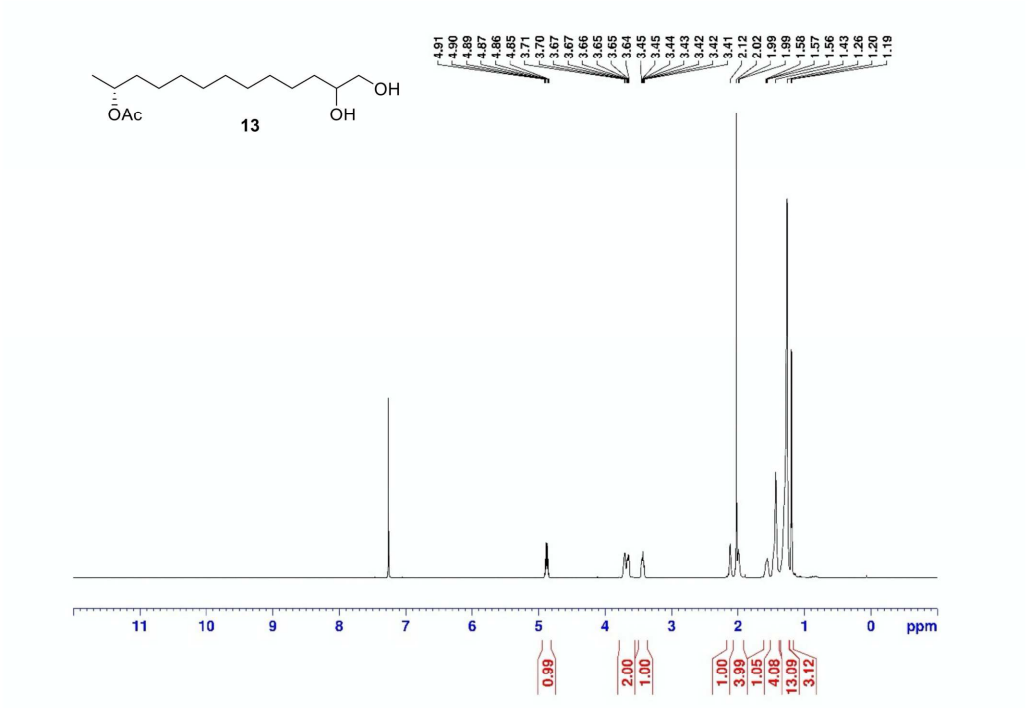


^{1}H-NMR spectrum of compound **12** in $CDCl_3$.

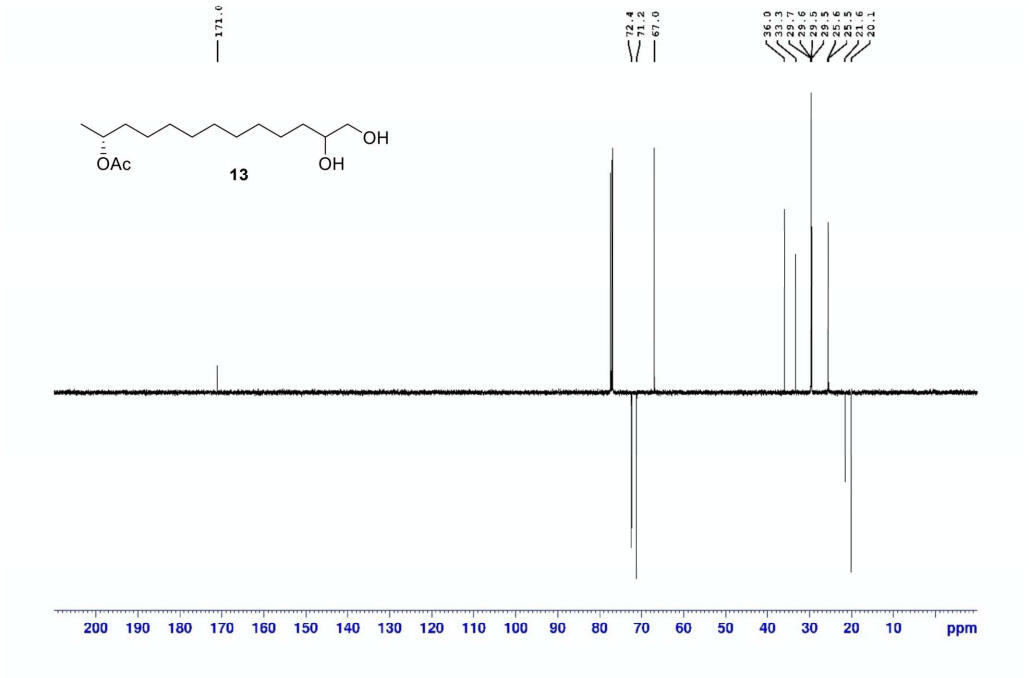


^{13}C-NMR spectrum of compound **12** in $CDCl_3$.

S3

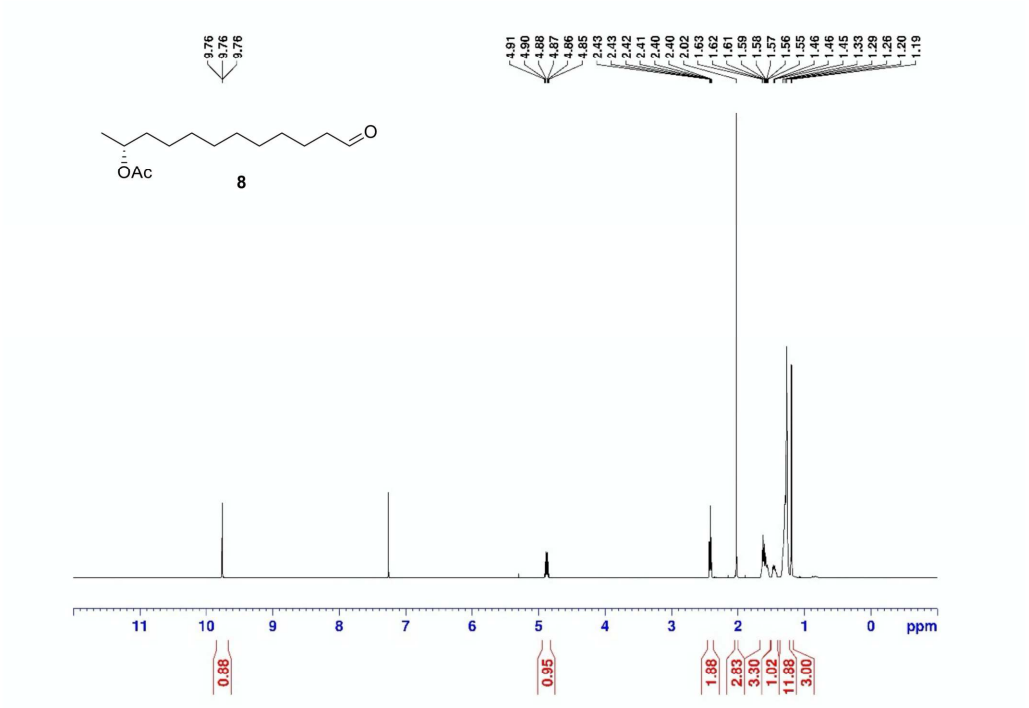


^{1}H-NMR spectrum of compound **13** in $CDCl_3$.

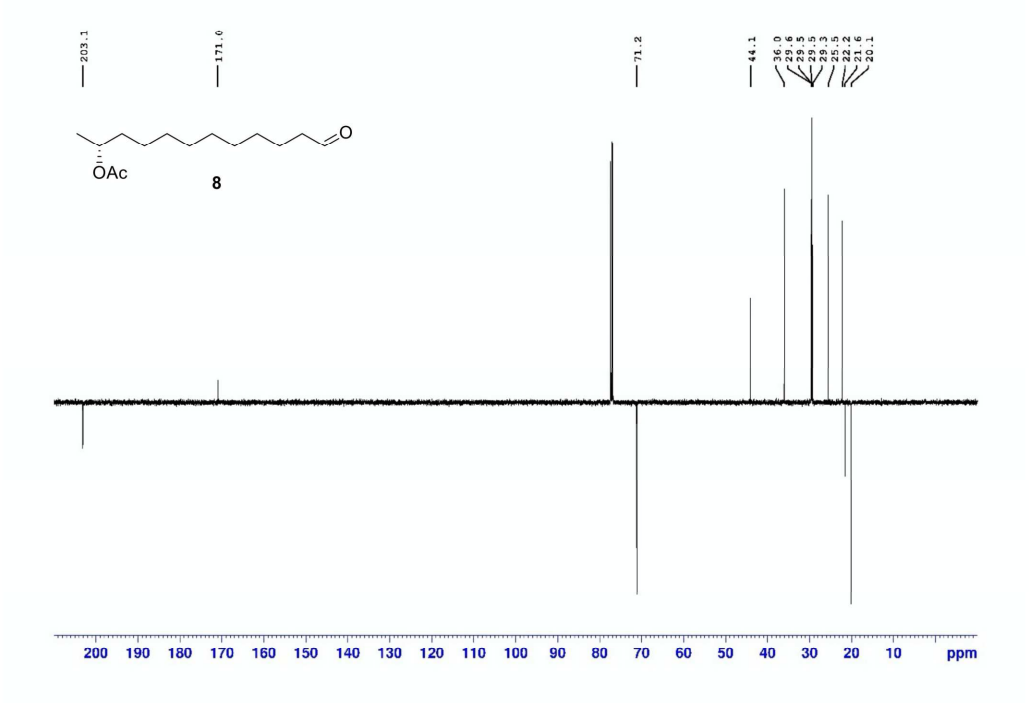


^{13}C-NMR spectrum of compound **13** in $CDCl_3$.

S4

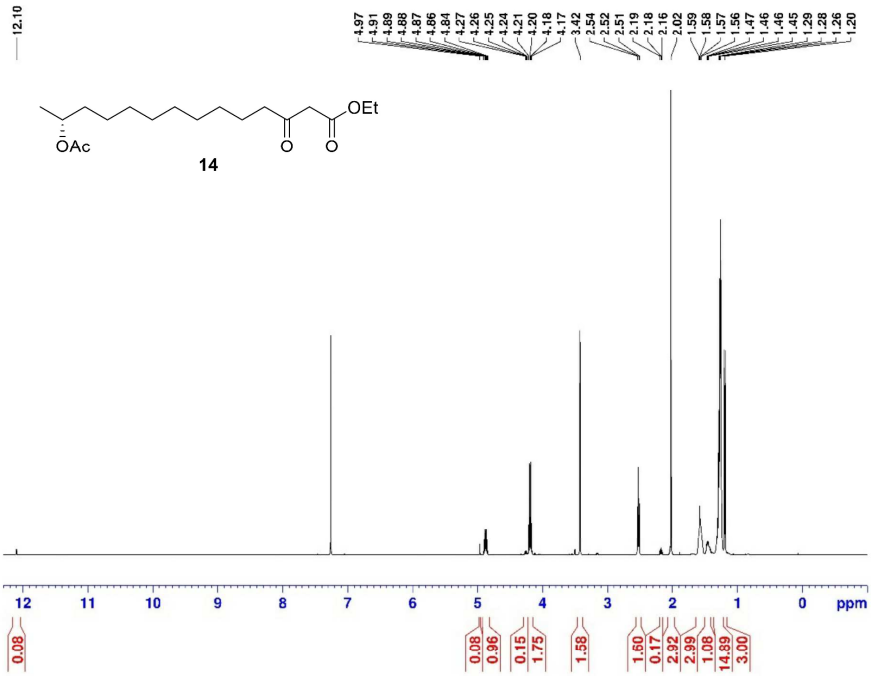


^{1}H-NMR spectrum of compound **8** in $CDCl_3$.

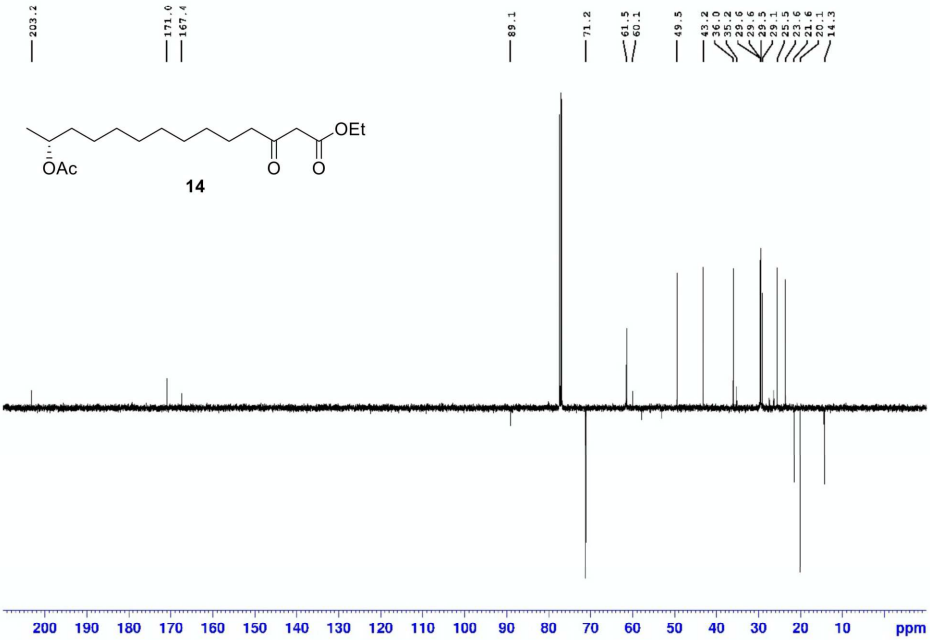


^{13}C-NMR spectrum of compound **8** in $CDCl_3$.

S5

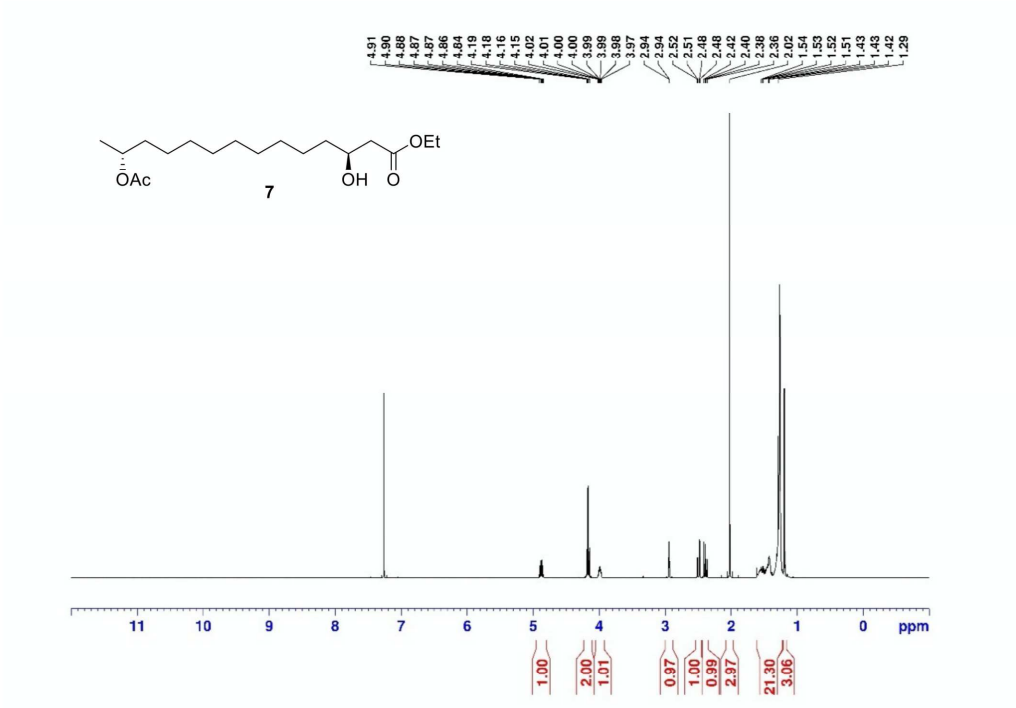


^{1}H-NMR spectrum of compound **14** in $CDCl_3$.



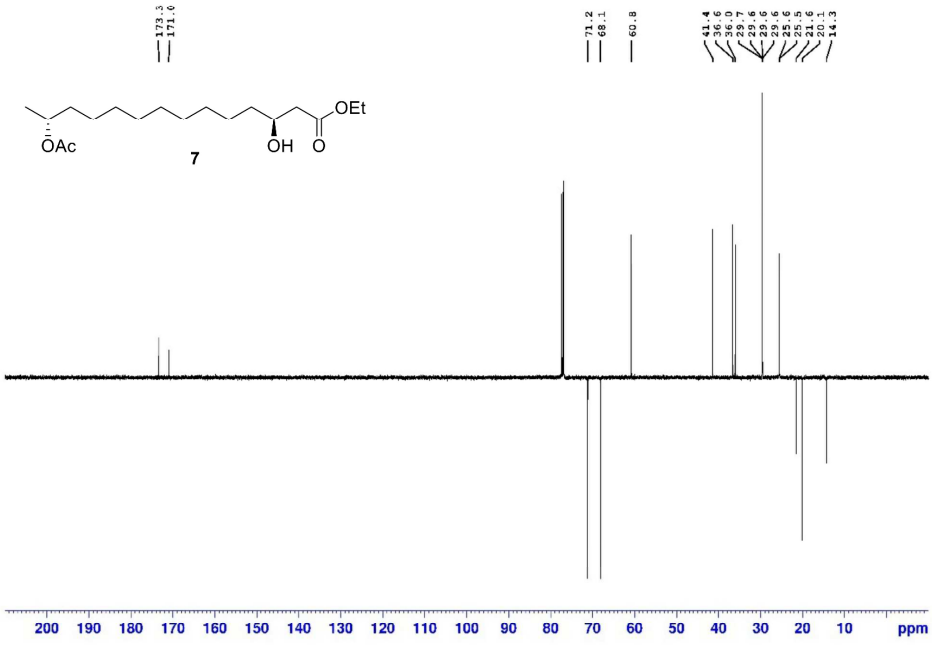
^{13}C-NMR spectrum of compound **14** in $CDCl_3$.

S6

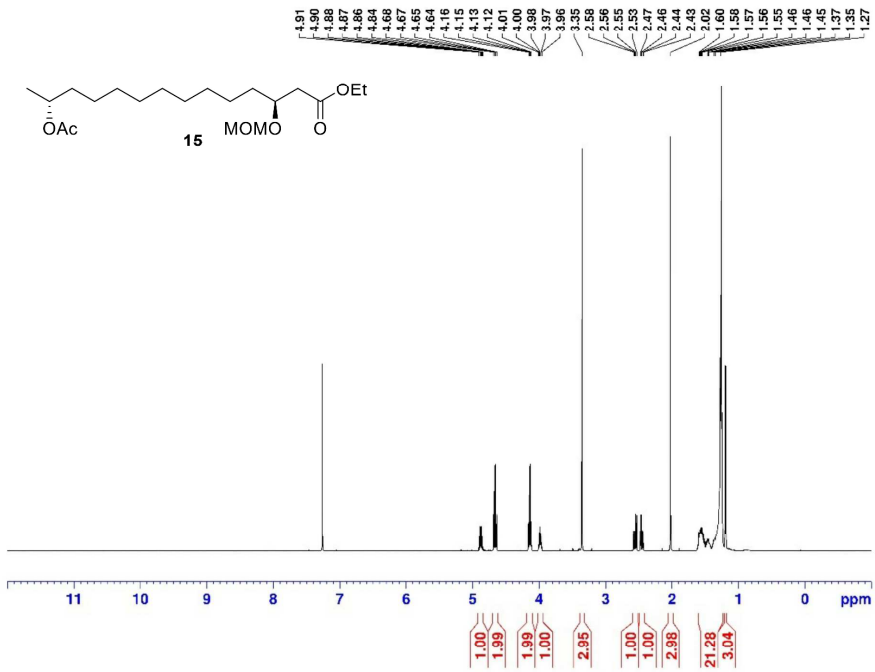


.

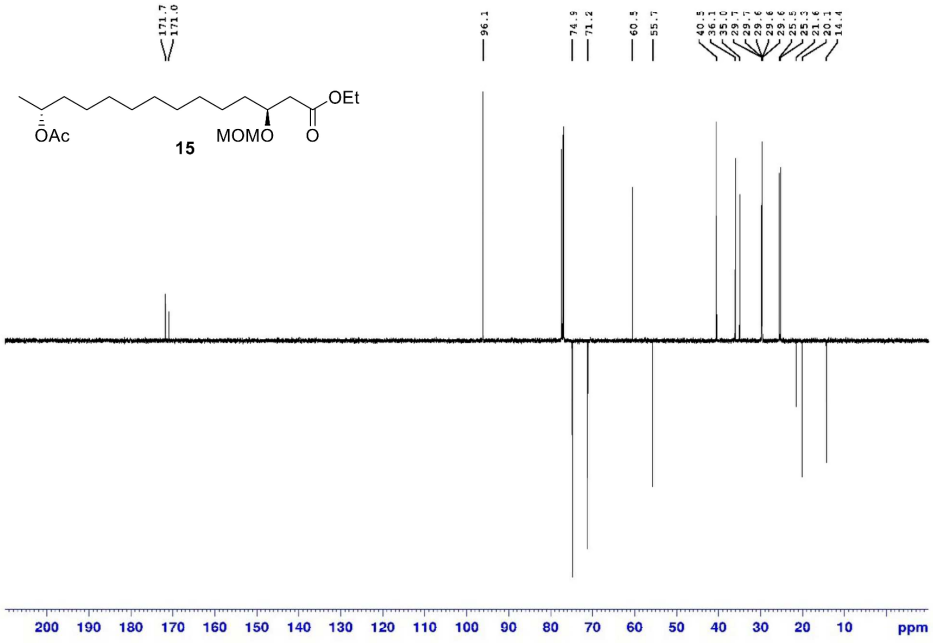
^{1}H-NMR spectrum of compound **7** in $CDCl_3$.



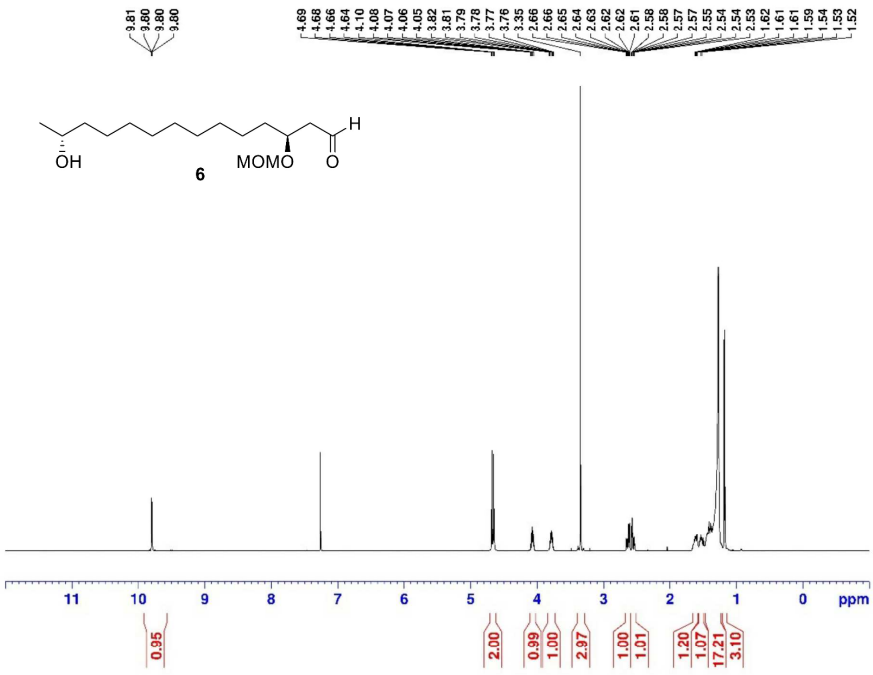
^{13}C-NMR spectrum of compound **7** in $CDCl_3$.



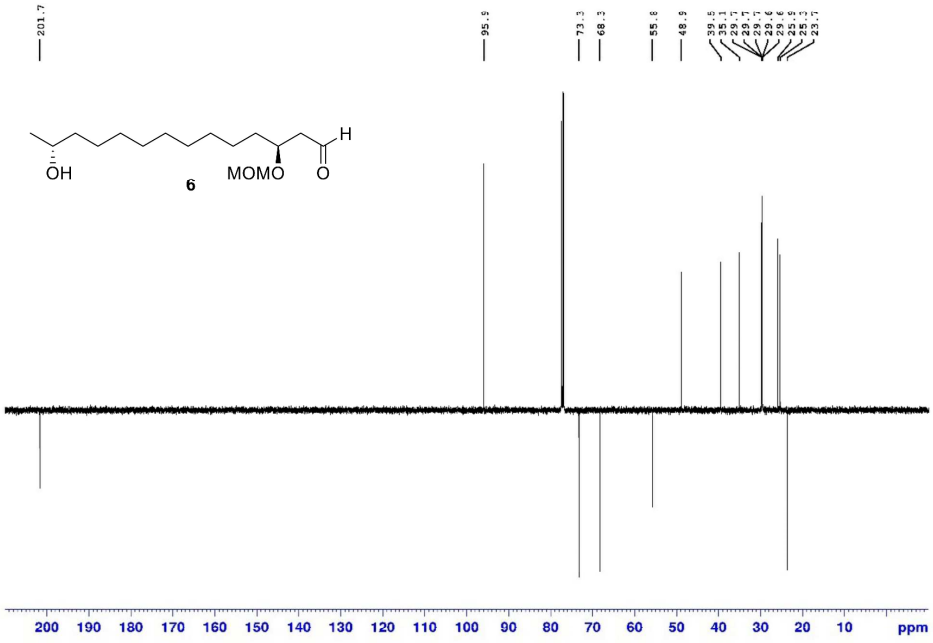
^{1}H-NMR spectrum of compound **15** in $CDCl_3$.



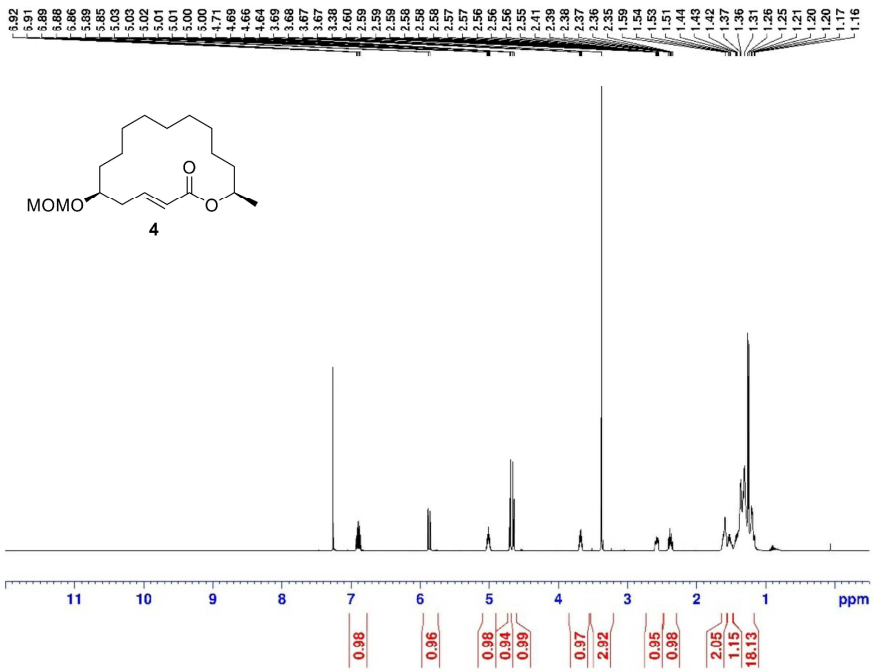
^{13}C-NMR spectrum of compound **15** in $CDCl_3$.



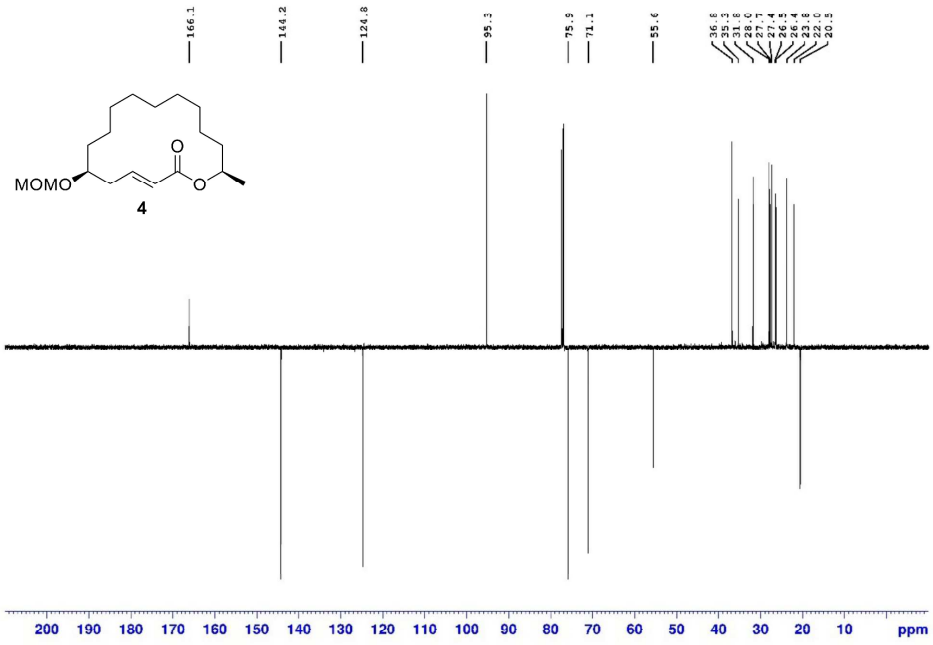
^{1}H-NMR spectrum of compound **6** in $CDCl_3$.



^{13}C-NMR spectrum of compound **6** in $CDCl_3$.

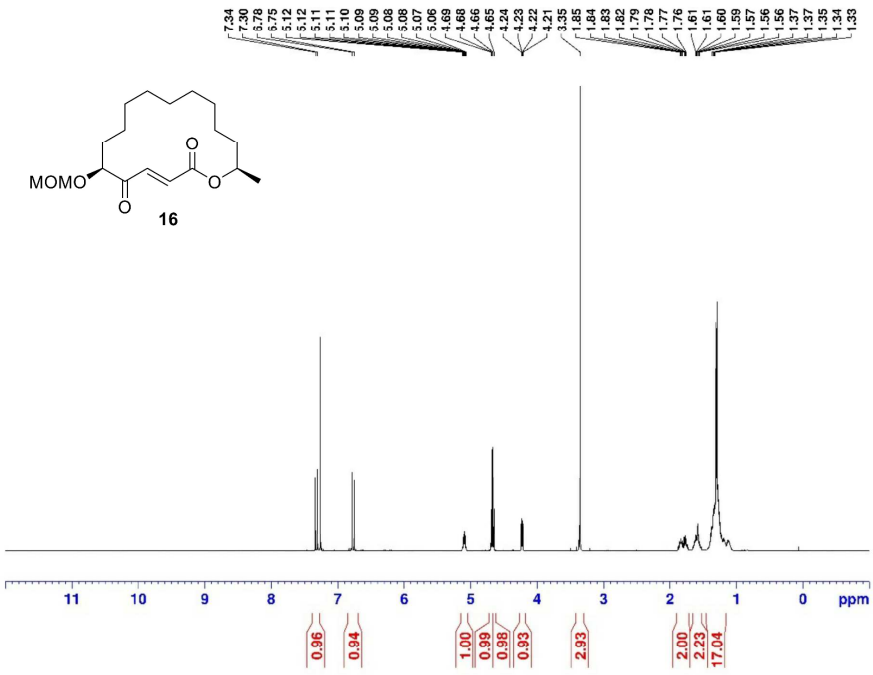


^{1}H-NMR spectrum of compound **4** in $CDCl_3$.

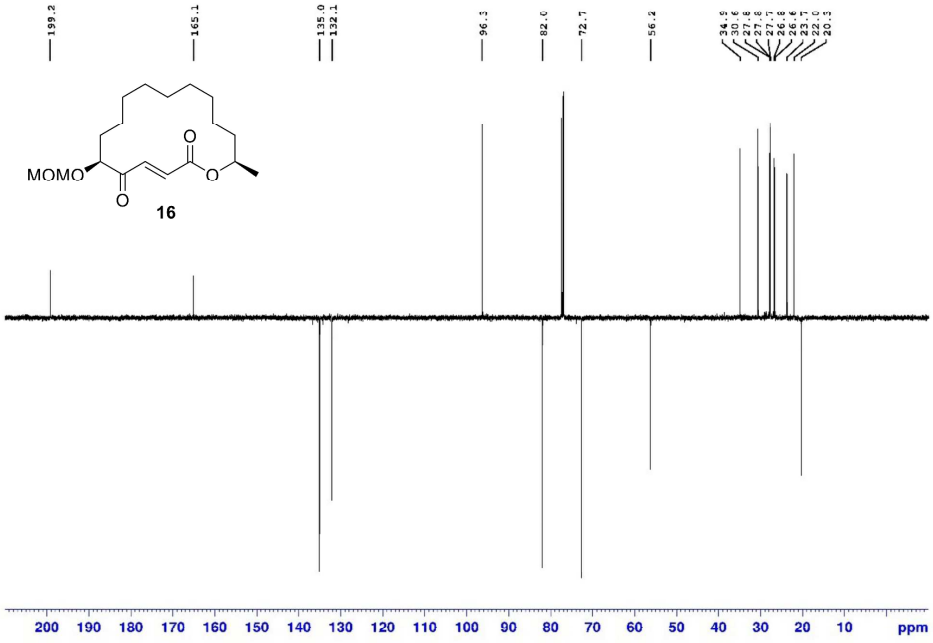


^{13}C-NMR spectrum of compound **4** in $CDCl_3$.

S10

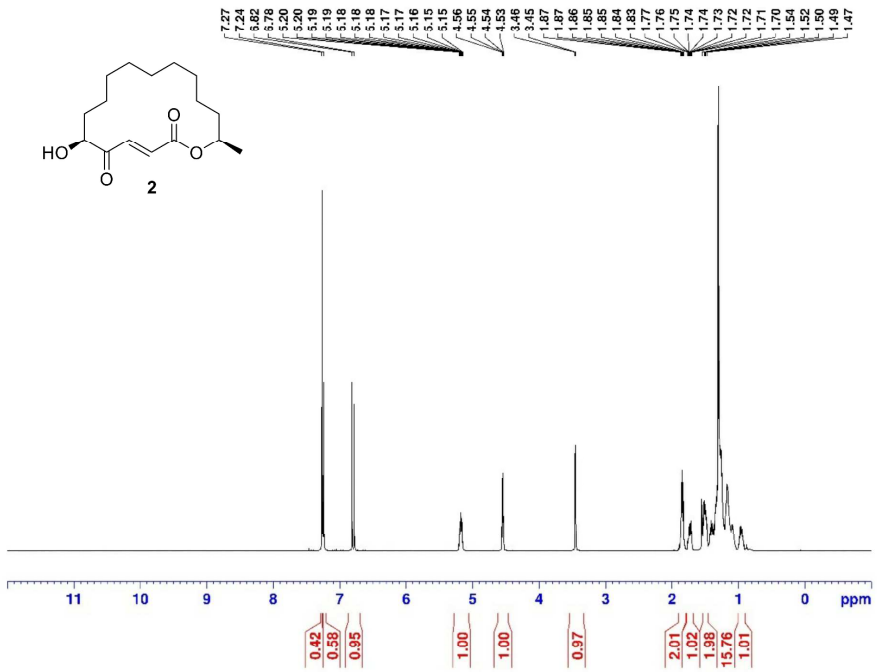


^{1}H-NMR spectrum of compound **16** in $CDCl_3$.

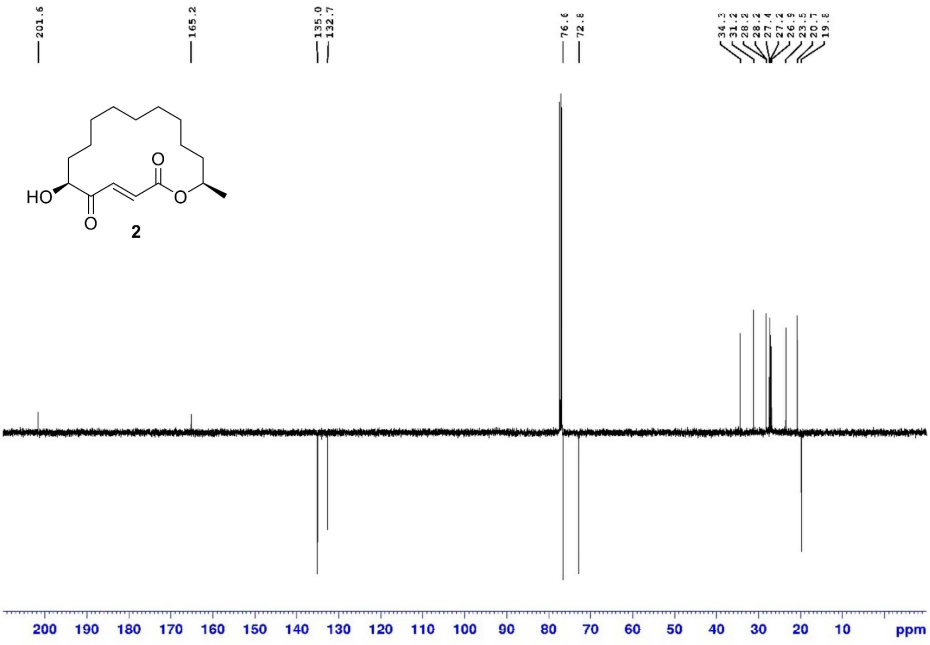


^{13}C-NMR spectrum of compound **16** in $CDCl_3$.

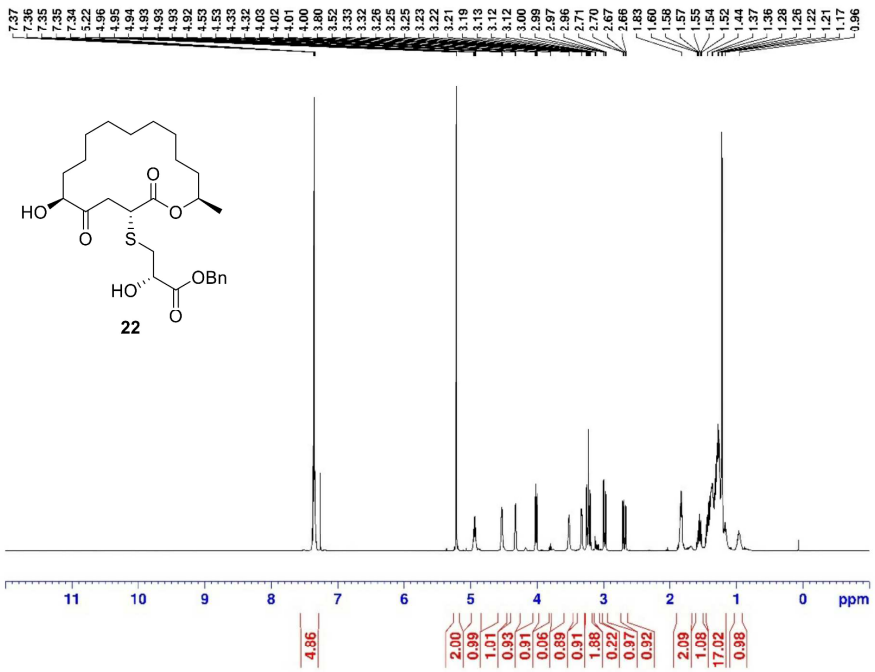
S11



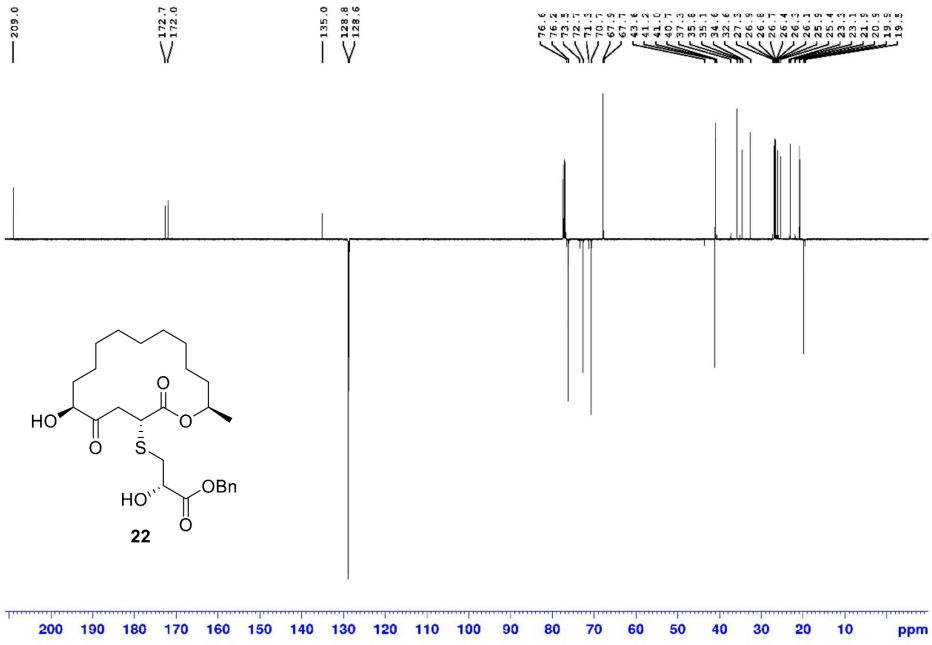
^{1}H-NMR spectrum of compound **2** in $CDCl_3$.



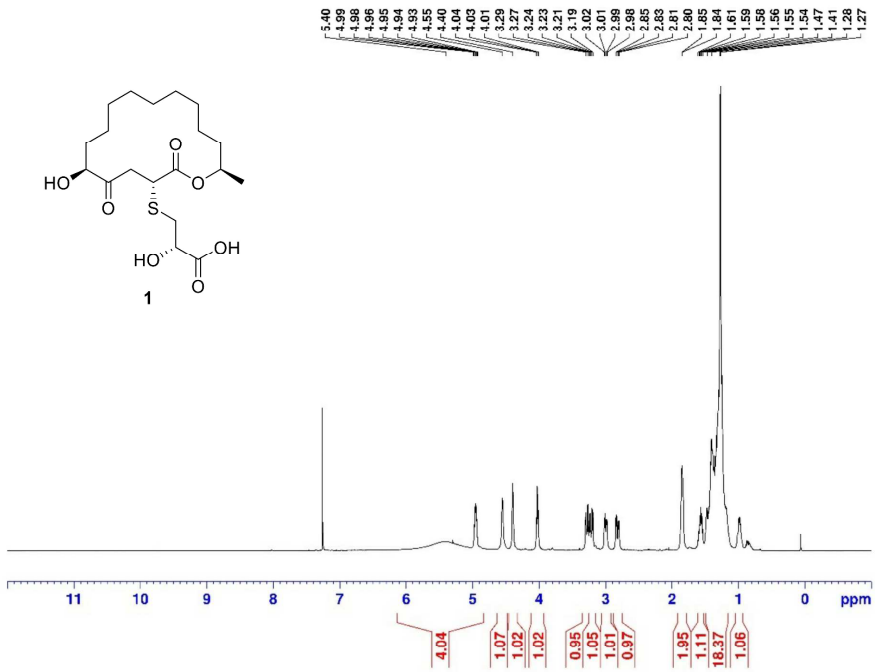
^{13}C-NMR spectrum of compound **2** in $CDCl_3$.



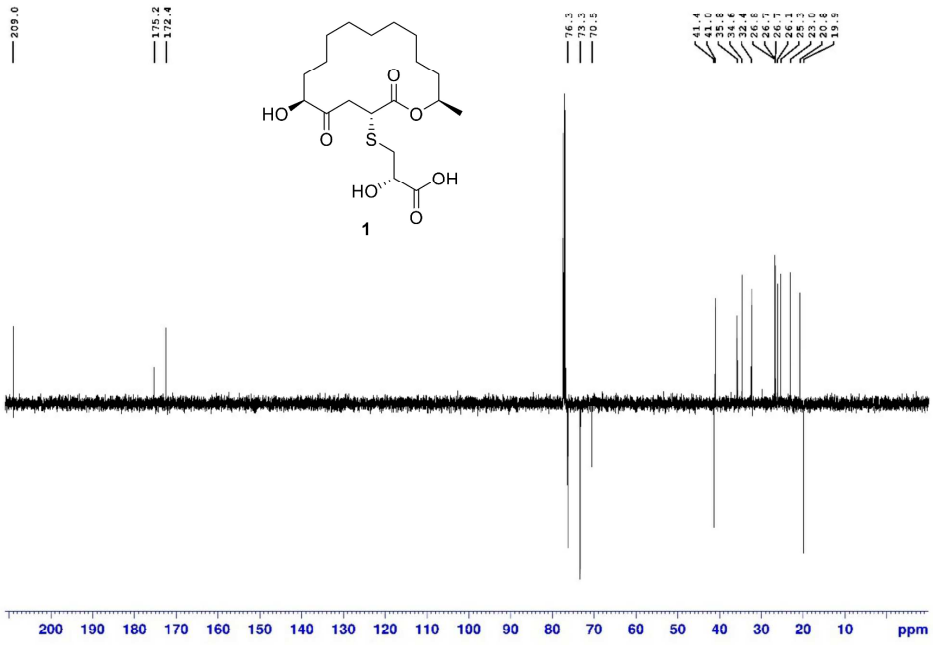
^{1}H-NMR spectrum of compound **22** in $CDCl_3$.



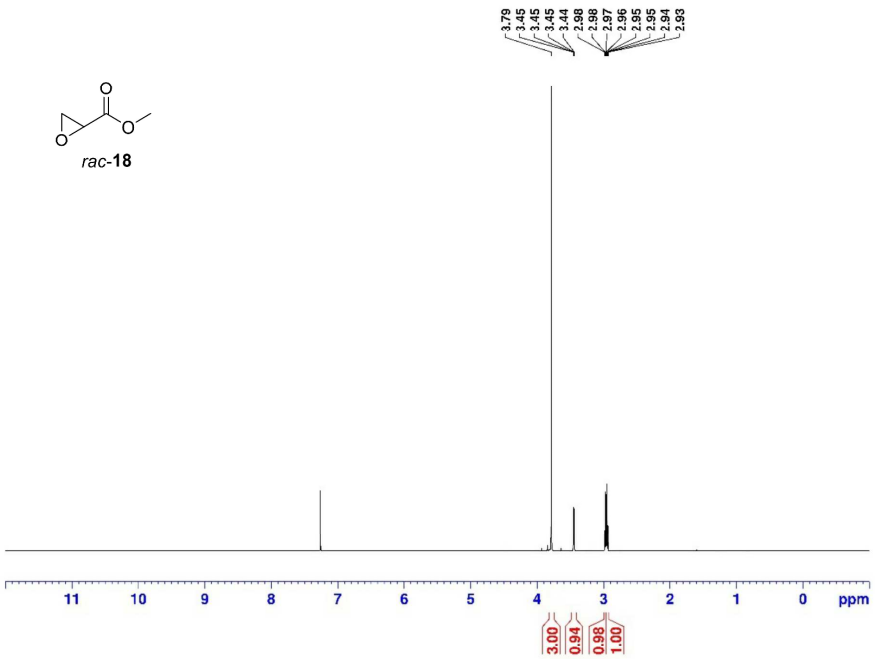
^{13}C-NMR spectrum of compound **22** in $CDCl_3$.



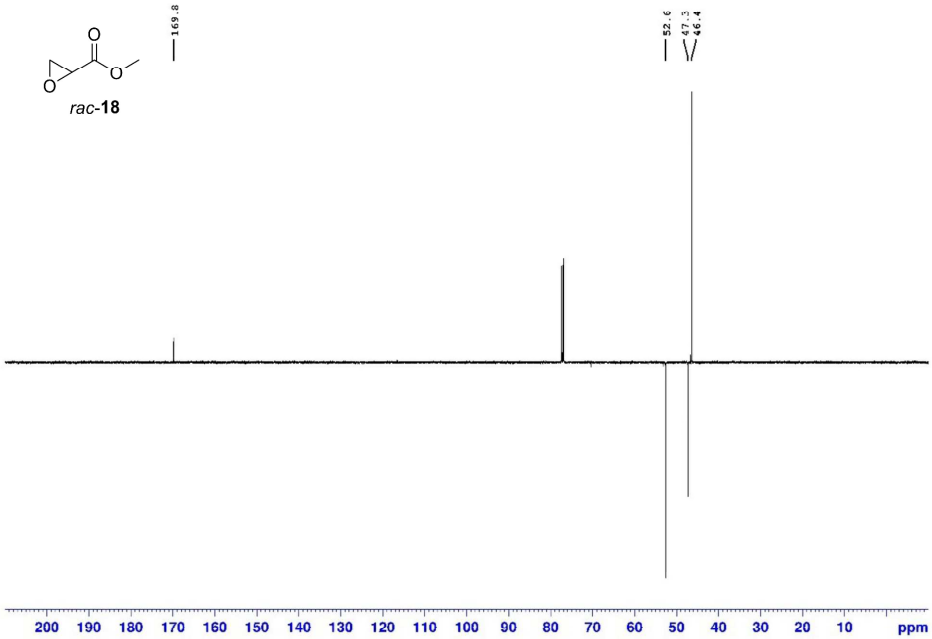
^{1}H-NMR spectrum of compound **1** in $CDCl_3$.



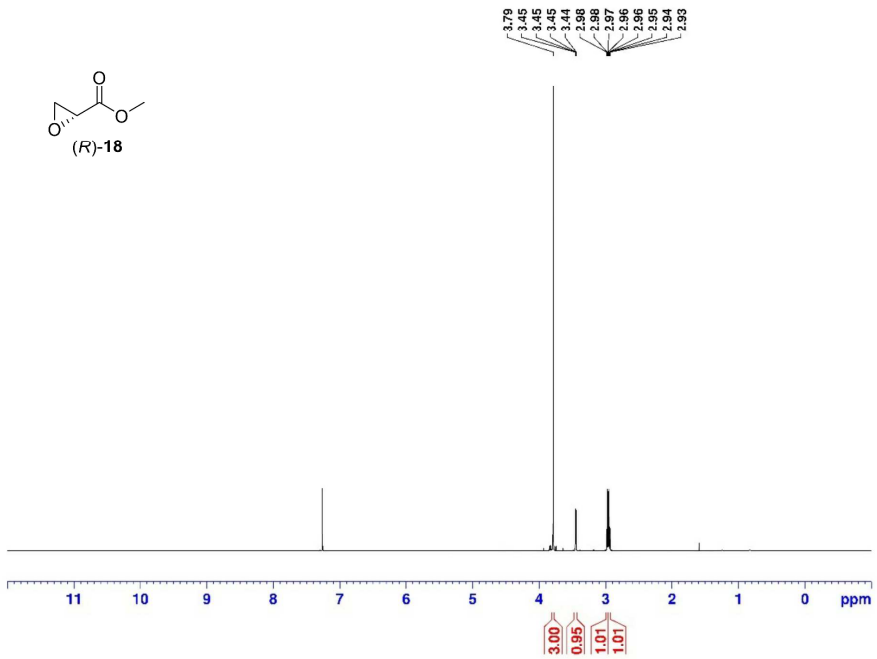
^{13}C-NMR spectrum of compound **1** in $CDCl_3$.



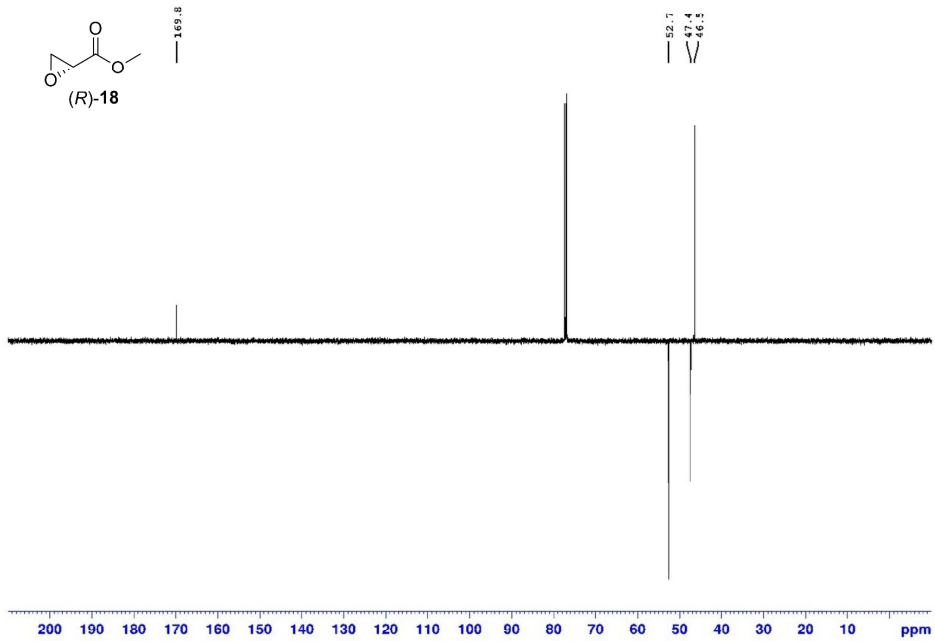
^{1}H-NMR spectrum of compound *rac*-**18** in $CDCl_3$.



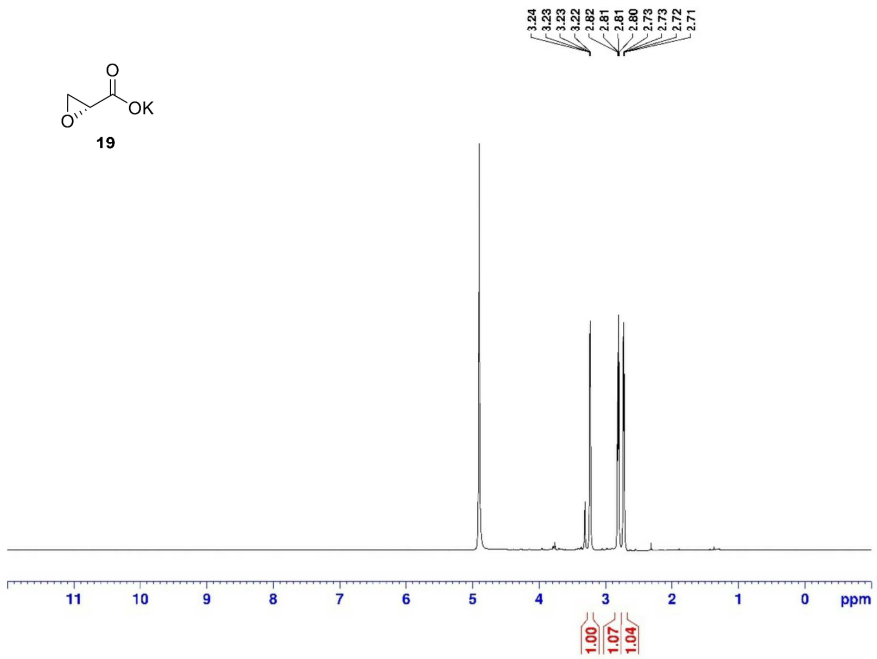
^{13}C-NMR spectrum of compound *rac*-**18** in $CDCl_3$.



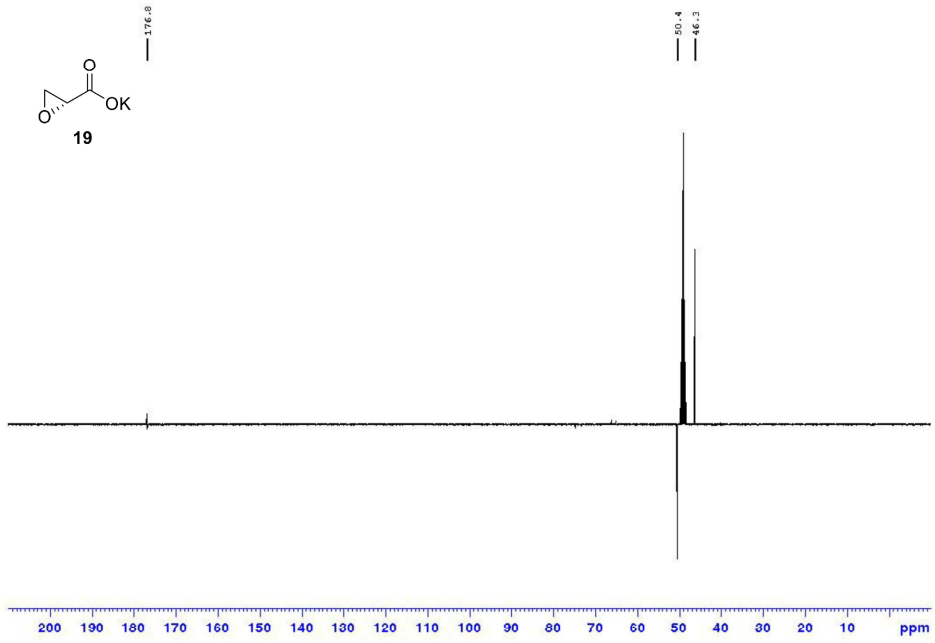
^{1}H-NMR spectrum of compound (*R*)-**18** in $CDCl_3$.



^{13}C-NMR spectrum of compound (*R*)-**18** in $CDCl_3$.

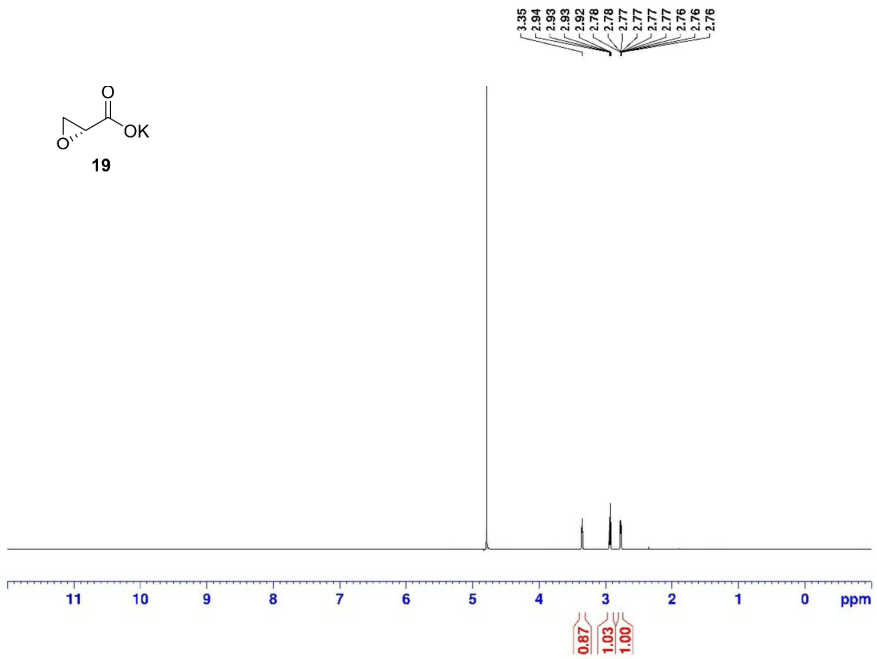


^{1}H-NMR spectrum of compound **19** in CD_3OD.



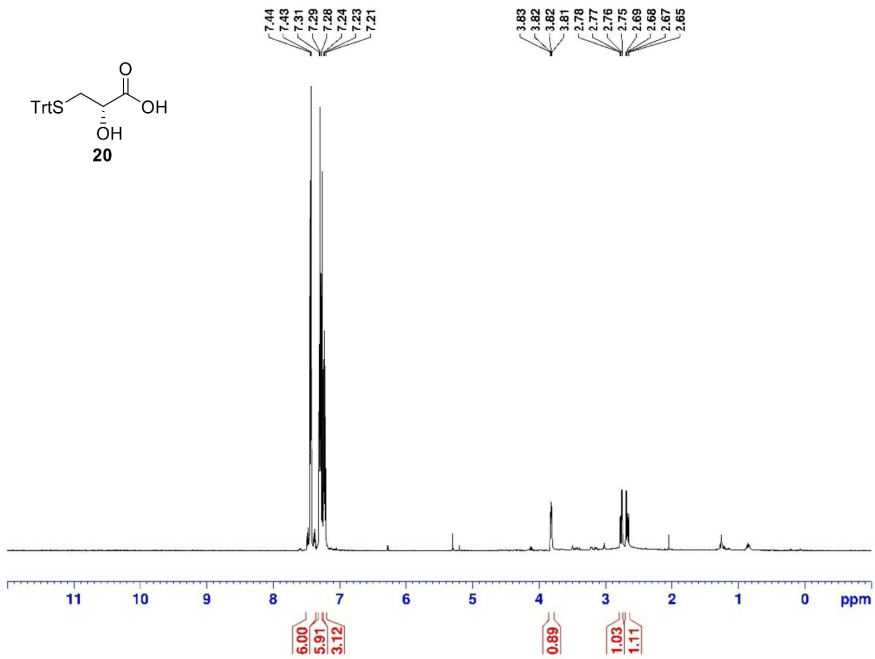
^{13}C-NMR spectrum of compound **19** in CD_3OD.

S17

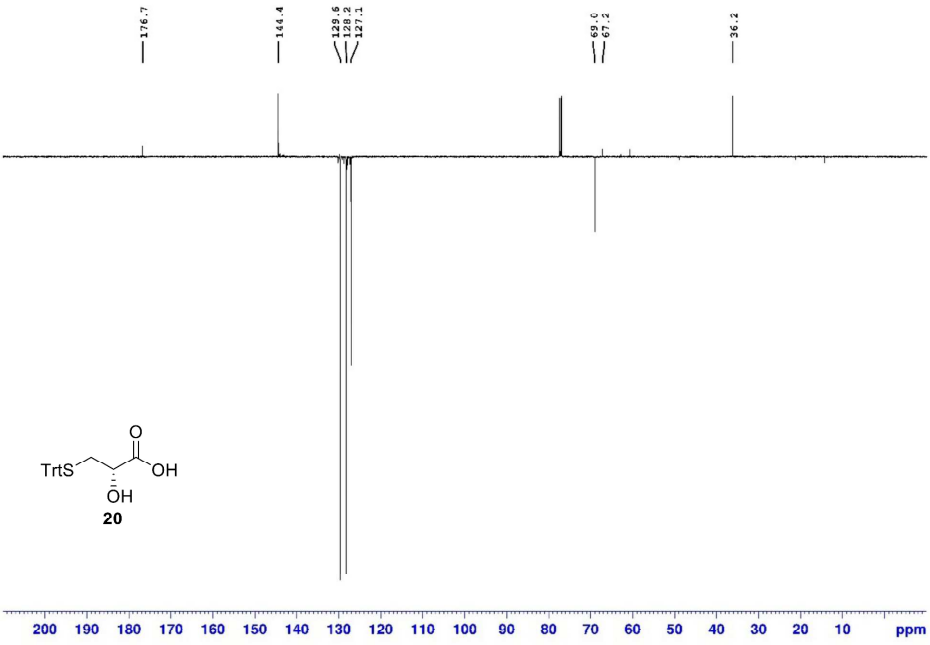


^{1}H-NMR spectrum of compound **19** in D_2O.

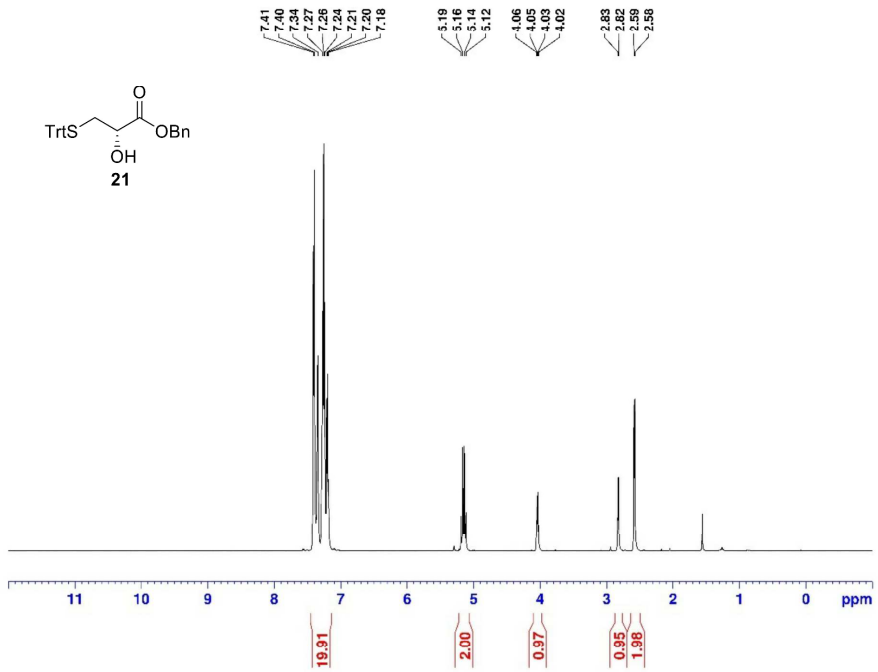
S18



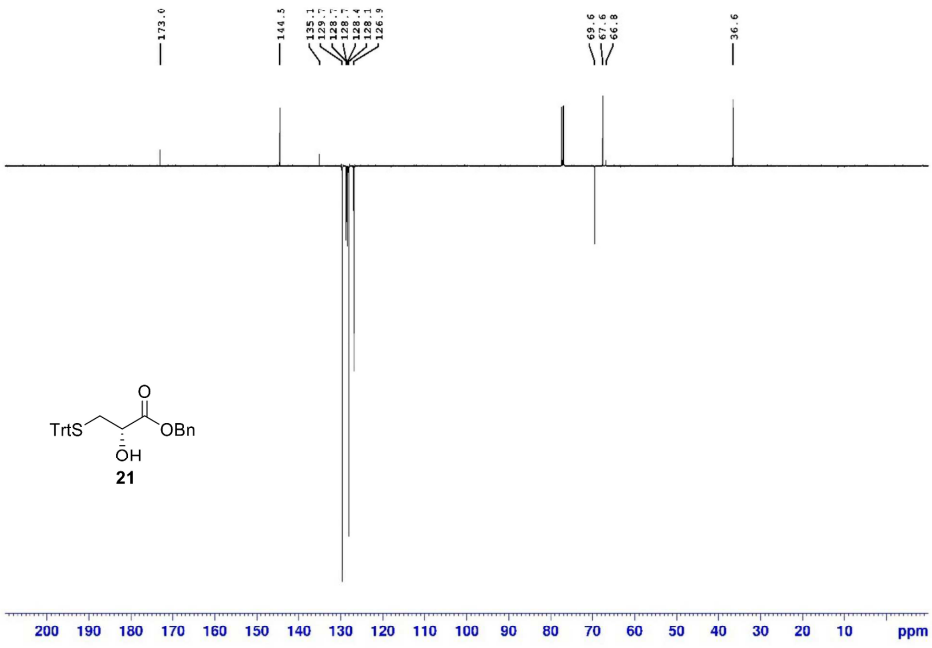
^{1}H-NMR spectrum of compound **20** in $CDCl_3$.



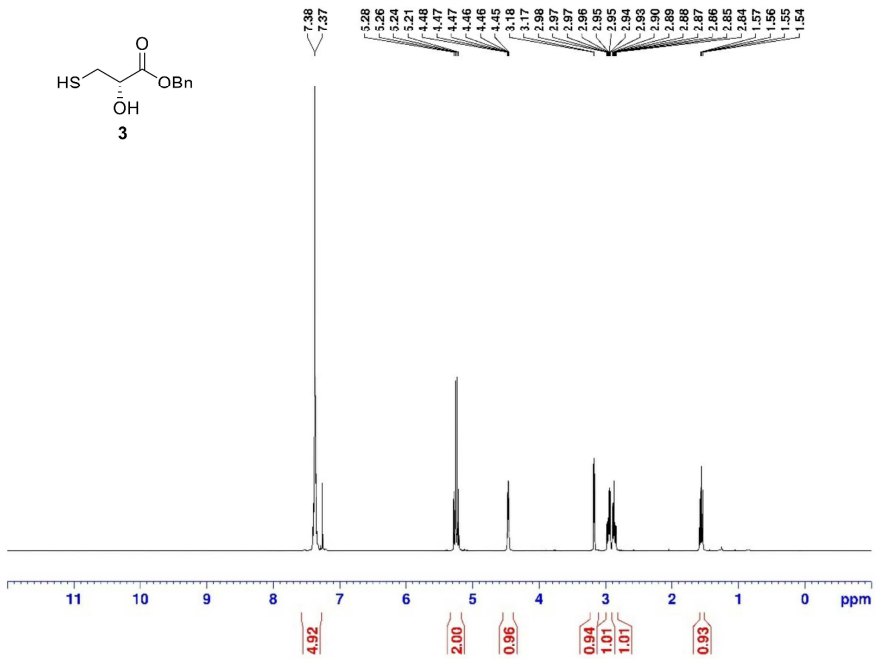
^{13}C-NMR spectrum of compound **20** in $CDCl_3$.



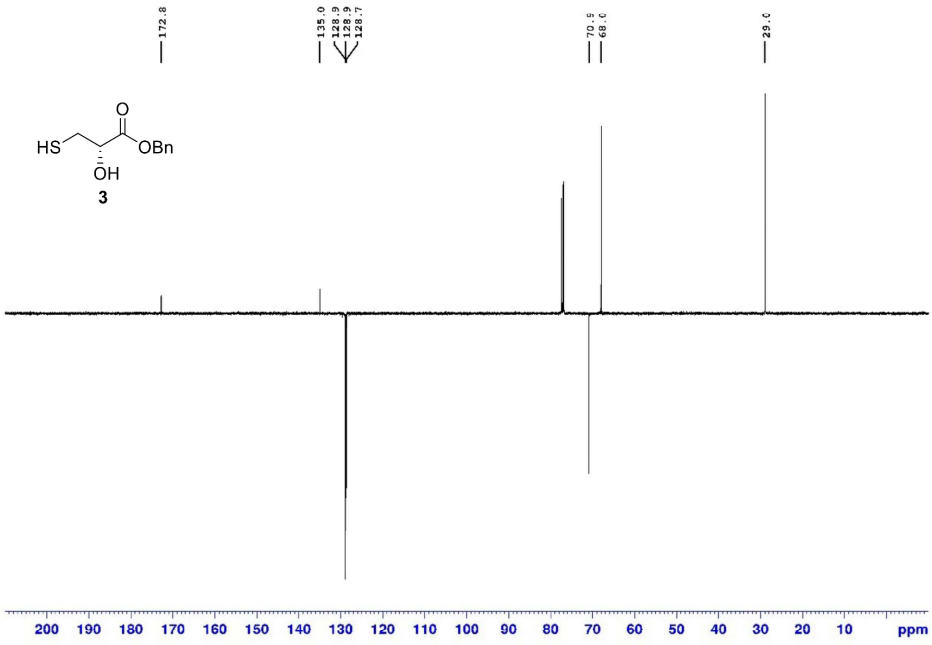
^{1}H-NMR spectrum of compound **21** in $CDCl_3$.



^{13}C-NMR spectrum of compound **21** in $CDCl_3$.

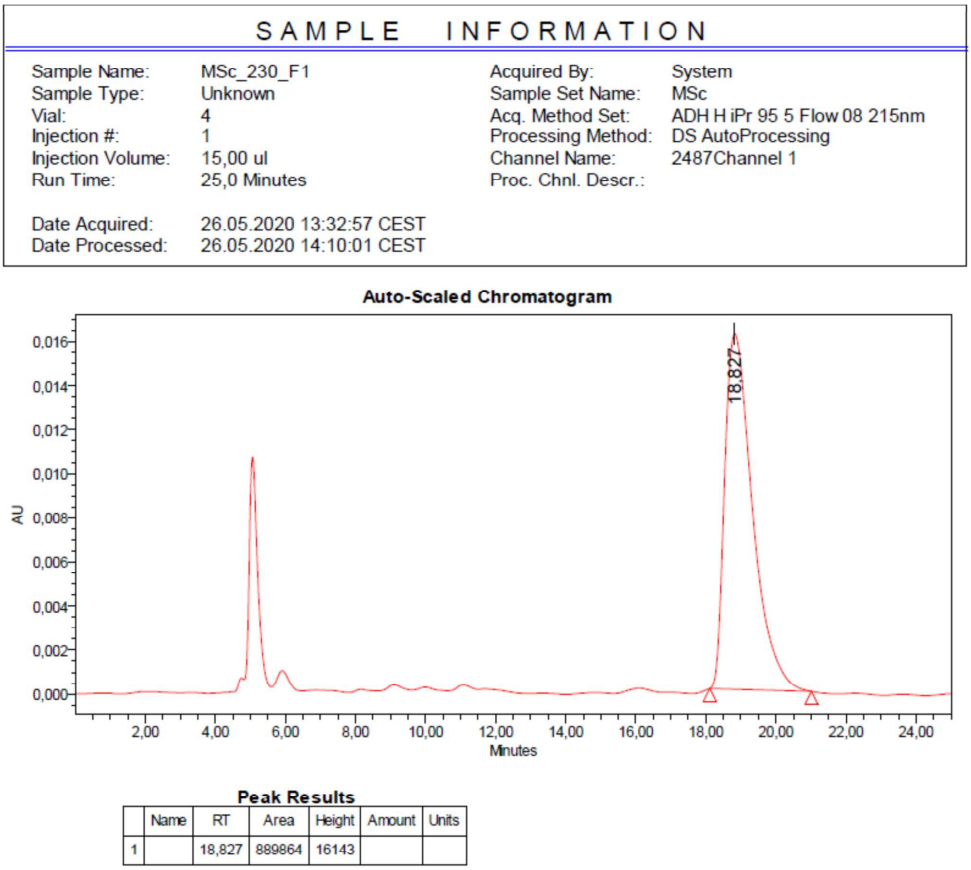


^{1}H-NMR spectrum of compound **3** in $CDCl_3$.



^{13}C-NMR spectrum of compound **3** in $CDCl_3$.

S21

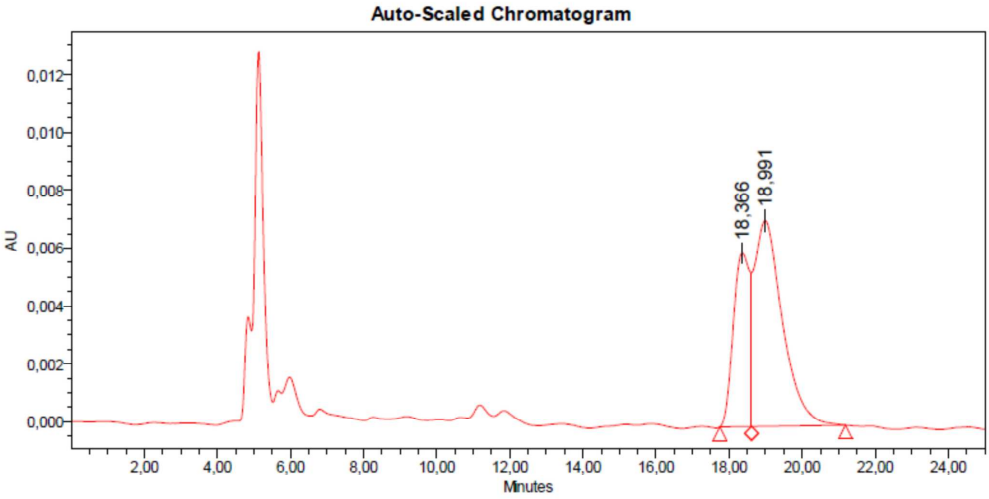


Chromatogram of compound **7** at chiral HPLC.

S22

SAMPLE INFORMATION

Sample Name:	MSc_238_F1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	MSc
Vial:	3	Acq. Method Set:	ADH H iPr 95 5 Flow 08 215nm
Injection #:	1	Processing Method:	DS AutoProcessing
Injection Volume:	15,00 ul	Channel Name:	2487Channel 1
Run Time:	25,0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	26.05.2020 12:56:46 CEST		
Date Processed:	26.05.2020 14:09:25 CEST		



Peak Results

	Name	RT	Area	Height	Amount	Units
1		18,366	187023	5991		
2		18,991	378849	7112		

Chromatogram of a mixture of compounds **7**/*epi*-**7** at chiral HPLC.

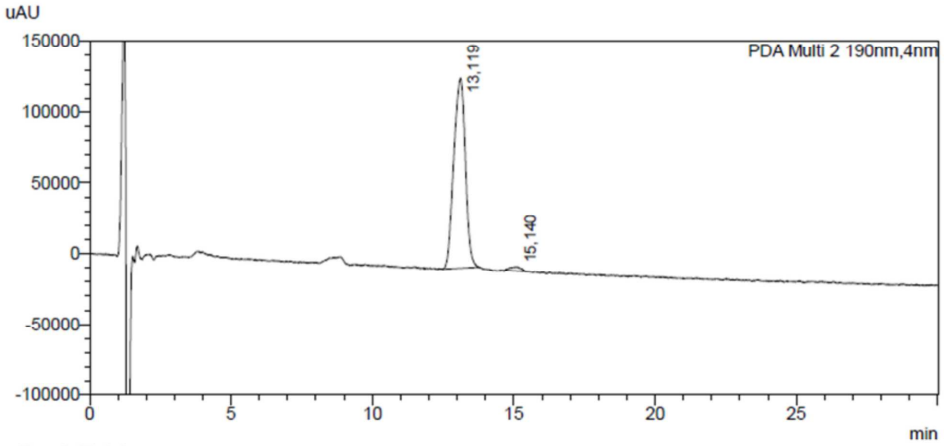
S23

HPLC-Chromatogram of compound **1** at RP-HPLC

<Sample Information>

Sample Name	: MSc304_F1_40isokrat		
Sample ID	:		
Data Filename	: MSc304_F1_40isokrat_05.11.2020_40_isokrat_30min_001.lcd		
Method Filename	: 40_isokrat_30min.lcm		
Batch Filename	: November2020.lcb		
Vial #	: 1-31	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 05.11.2020 13:41:55	Acquired by	: System Administrator
Date Processed	: 14.12.2020 10:16:56	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

PDA Ch2 190nm

Peak#	Ret. Time	Area	Height	Area%
1	13,119	3819024	134249	98,007
2	15,140	77650	3040	1,993
Total		3896674	137289	100,000

S24

Minimum inhibitory concentration (MIC) assay. Compound **1** was tested against several bacterial and fungal strains by using a 96-well serial in Mueller-Hinton broth (MHB) media for bacteria and YMG media for filamentous fungi and yeasts as previously described.[1] The selected organisms represent a broad spectrum of pathogens of clinical interest, as well as sensitive indicator strains (Gram-positive bacteria: *Bacillus subtilis*, *Staphylococcus aureus, methicillin-resistant Stapylococcus aureus* [MRSA], *Mycolicibacterium smegmatis*; Gram-negative bacteria: *Acinetobacter baumannii, Chromobacterium violaceum*, *Escherichia coli*, *Pseudomonas aeruginosa*; filamentous fungi: *Mucor hiemalis*; yeasts: *Candida albicans*, *Pichia anomala, Rhodotorula glutinis, Schizosaccharomyces pombe*). Berkeleylactone A (**1**) was dissolved in MeOH (1 mg/mL), diluted to a final range of 66.6 to 0.52 µg/mL and incubated with the test organisms overnight. MeOH was used as negative control. Kanamycin (1.0 mg/mL; 2 µL [*M. smegmatis*]), vancomycin (10 mg/ml; 2 µL [MRSA]), gentamycin (1.0 mg/mL; 2 µL [*P. aeruginosa*]), ciprobay (2.54 mg/ml; 2 µL [*A. baumannii*]), nystatin (1.0 mg/mL; 20 µL [*S. pombe, P. anomala, M. hiemalis, C. albicans, R. glutinis*), and oxytetracycline (1.0 mg/mL; 2 µL [*C. violaceum*, *E. coli*, *S. aureus*] and 20 µL [*B. subtilis*]) were used as positive controls. The lowest inhibitory concentration of compound **1** (where no growth of the test organism was observed) was visually evaluated the next day.

Biofilm inhibition assay. *Staphylococcus aureus* DSM 1104 was taken from −20 °C stock and precultured in 25 mL CASO (casein-peptone soymeal-peptone) medium in a 250 mL flask at 37 °C at 100 rpm for 20 h. The culture solution was adjusted to match the turbidity of a 0.001 McFarland standard OD_{600} and was incubated in 96-well tissue microtiter plates (TPP tissue culture ref.no 92196m Switzerland) in CASO with 4% glucose broth together with the serially diluted compound **1** (10–0.3 µg/mL) and incubated for 18 h at 37 °C. The biofilm inhibition activity of the test compounds was evaluated by crystal violet (CV) staining (Thermo Fisher, Waltham, USA), following previously established protocols.[2,3] In brief, the supernatant was discarded, the biofilm stained with crystal violet for 15 min, washed three times with PBS (phosphate-buffered saline) buffer, the dye in the biofilm was dissolved in 150 µL ethanol (95%), and the absorbance of this extract was finally quantified using a plate reader (Synergy 2, BioTek, Santa Clara, USA) at 530 nm. Standard deviations (SD) of two repeats with duplicate each were 10% or less. Methanol (2.5%) and microporenic acid A (250–2 µg/mL) were used as a negative control and a positive control, respectively.

P. aeruginosa (PA 14) was taken from −20 °C stock and cultured in 25 mL LB medium (Luria-Bertani Broth) in a 250 mL flask at 37 °C at 100 rpm for 18 h. The OD_{600} of the culture solution was measured and adjusted to 0.025 McFarland standard in LB medium. Compound **1** was diluted into 100 µL bacterial solution at the respective concentration (250–2 µg/mL), then the mixture solution was added in 96-well plates in an MBEC Innovatech incubator (MBEC Assay®, Canada). The plates were incubated at 37 °C at 150 rpm for 24 h. The biofilms were established on the pegs under growth conditions. The pegs and plates were rinsed once with PBS buffer, the biofilms on pegs were stained by 150 µL 0.1% CV at room temperature for 15 min and then rinsed twice with PBS buffer. The pegs were transferred into a new plate with 150 µL ethanol (95%) and the absorbance was quantified using a plate reader (Synergy 2, BioTek, Santa Clara, USA) at 550 nm. SD of two repeats with duplicates each were 10% or less. Myxovalargin A and methanol (2.5 %) were used as the positive and negative controls.

Preformed biofilm dispersion assay. *S. aureus* DSM 1104 and *C. albicans* DSM 11225 were taken from −20 °C stock and precultered in 25 mL CASO medium at 37 °C and YPED (Yeast extract Peptone Dextrose) at 30 °C, respectively, at 100 rpm in 250 mL flasks. *S. aureus* was precultured for 20 h, *C. albicans* was cultured for 18 h. The precultured suspensions of *S. aureus* and *C. albicans* were adjusted so that their OD_{600} matched the turbidity of a 0.001 McFarland standard and 0.05 Mc Farland standard, respectively. *S. aureus* was incubated in 96-well tissue plates for 18 h at 150 rpm in 150 mL CASO medium with 4% glucose broth. For *C. albicans*, the 150 µL fungal solution was added to 96-well non-tissue microtiter plates (Falcon non-tissue plate ref.no 351172) for 90 min at 37 °C at 150 rpm. The supernatant was removed from the wells and 150 µL of the respective media (fresh) was added to the wells, together with the serially diluted compound **1** (*S. aureus*: 250–2 µg/mL; *C. albicans*: 250–2 µg/mL). Due to strong activities in the *C. albicans* assay, a repetition with compound **1** at a higher dilution was carried out (*C. albicans*: 10-0.3 µl/ml). The plates were incubated for a further 24 h at 37 °C. Staining of the preformed biofilm, and the control runs were carried out as described above. SD of two repeats with duplicates each were 10% or less. Methanol (2.5%) and microporenic acid A (250–2 µg/mL) were used as negative and a positive controls.

Cytotoxicity assay. The evaluation of *in vitro* cytotoxicity (IC_{50}) was performed with mouse fibroblast cell line L929 and mammalian HeLa KB3.1 cancer cells for compound **1** as previously described.[1] The compound was dissolved in MeOH (1 mg/mL), MeOH itself was

used as negative control, and epothilone B (1 mg/mL) was used as a positive control. After incubating the cell lines with the serially diluted test compound **1** (37–0.6 x 10^{-3} µg/mL) for five days, the cells were dyed using 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), which is only converted to its purple formazan derivative by living cells. The absorption at 595 nm was measured using a microplate reader, and the percentage of cell viability was calculated. The half maximum inhibitory concentration was calculated and expressed as IC_{50} (µM).

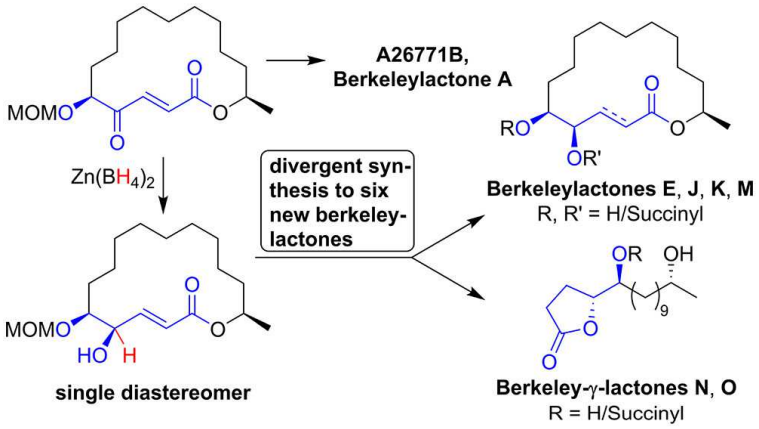
Literature

[1] K. Becker, A. C. Wessel, J. Luangsaard, M. Stadler. Viridistratins A−C, antimicrobial and cytotoxic benzo[*j*]fluoranthenes from stromata of *Annulohypoxylon viridistratum* (Hypoxylaceae, Ascomycota). *Biomolecules*, 2020, **10**, 805.

[2] C. Chepkirui, K. T. Yuyama, L. W. Wanga, C. Decock, J. C. Matasyoh, W. R. Abraham, M. Stadler. Microporenic acids A–G, biofilm inhibitors and antimicrobial agents from the basidiomycete *Microporus* species. *J. Nat. Prod*., 2018, **81**, 778−784.

[3] K. T. Yuyama, C. Chepkirui, L. Wendt, D. Fortkamp, M. Stadler, W. R. Abraham. Bioactive compounds produced by *Hypoxylon fragiforme* against *Staphylococcus aureus* biofilms. *Microorganisms*, 2017, **5**, 80.

5.3 Publikation II



Divergent Synthesis of Six Recent Berkeleylactones

Manuel G. Schriefer, Rainer Schobert

J. Nat. Prod. **2023**, *86* (2), 423 – 428.

JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp Article

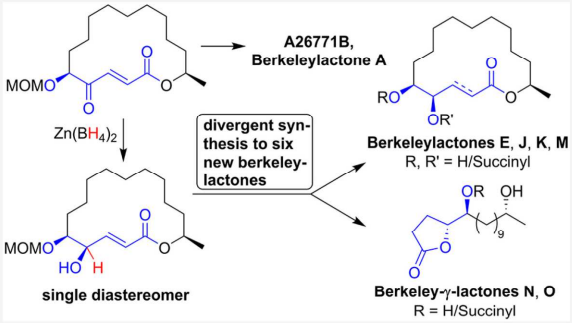
Divergent Synthesis of Six Recent Berkeleylactones

Manuel G. Schriefer and Rainer Schobert*

Cite This: J. Nat. Prod. 2023, 86, 423−428 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The six recently isolated berkeleylactones E, J, K, M, N, and O were synthesized for the first time by a divergent strategy starting from a common intermediate in our synthesis of berkeleylactone A. Key features were the stereoselective formation of the γ,δ-dihydroxy-α,β-unsaturated ester moiety and the development of a general protection group strategy. Along the way we also established a short high-yielding formal synthesis of the often-synthesized antibiotic A26771B.



In 2021 Stierle et al. isolated seven new berkeleylactones (I−O), five of which feature a 16-membered macrolide ring like the long-known A26771B (**1**), and two are γ-lactones (Figure 1).[1] With the berkeleylactones A−H, isolated in 2017, there are now 15 natural berkeleylactones identified so far.[2] Some of them were shown to have distinct antibiotic and antibiofilm activities.[2,3] Studies of the biosynthesis of A26771B (**1**), produced by *Penicillium egyptiacum*, identified berkeleylactones J, E, K, and L (**2**−**5**) as important intermediates, not pinpointed until 2021.[4] The structural resemblance of the lactones **1**−**9**, which share a γ,δ-dihydroxyester or γ-oxo-δ-hydroxyester motif, points to a divergent synthesis of the whole family. Divergent syntheses of natural products have an edge over parallel syntheses by harnessing late-stage modifications of a common intermediate rather than different lengthy approaches to the individual target compounds.[5] The primary issue of divergent syntheses is to identify a suitable common key intermediate. Most divergent syntheses were utilized in the total synthesis of alkaloids, e.g., those of bisquinolizidine alkaloids by Breuning et al.[6] or of terpenes, e.g., those of leucosceptroids by Magauer et al.[7] In comparison, divergent syntheses of natural macrolides are few and far between in the literature. Fürstner et al. used a divergent synthetic approach for establishing the configuration of the macrocyclic leiodermatolide, yet synthesized but a single compound in this way.[8] In 2021 we published a synthesis of berkeleylactone A (**6**) with 24% yield over 13 steps from inexpensive and commercially available starting materials **10** and **11** (Scheme 1).[3] We recognized that the structurally related A26771B (**1**) would be accessible in only two more steps from intermediate **12**, accessible itself in 30% yield over 10 steps.[3] The missing two steps were already performed, in a different context, by us[3] and another group.[9]

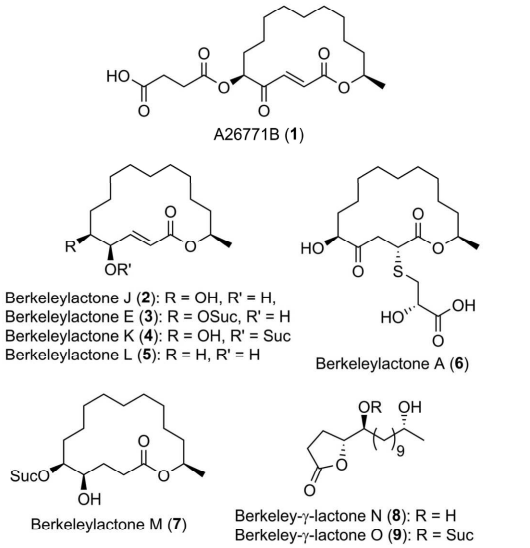
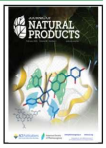


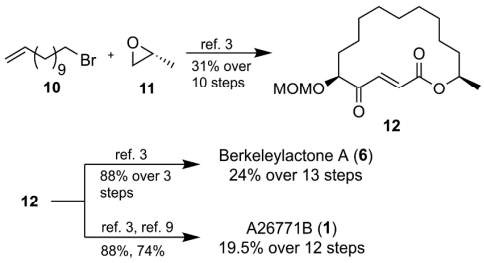
Figure 1. Structures of A26771B (**1**) and Berkeleylactones **2**−**9**. Suc = succinyl.

Received: January 20, 2023
Published: February 13, 2023



https://doi.org/10.1021/acs.jnatprod.3c00053
J. Nat. Prod. 2023, 86, 423−428

Scheme 1. Synthesis of Berkeleylactone A (6) Published in 2021 and a Formal Synthesis of A26771B (1)



MOM-deprotection and esterification of macrolide **12** led to A26771B (**1**) in 19.5% overall yield (12 steps). The brevity and efficiency of this synthesis manifest when compared with those of the 22 alternative (partly formal) syntheses of **1** published until 2022, six of which afforded racemic and 15 enantiopure products.[10−33] Table 1 demonstrates the improvement of the yields with the development of new organic reactions over the years. The number of steps, though, stagnated at ca. 10−13.

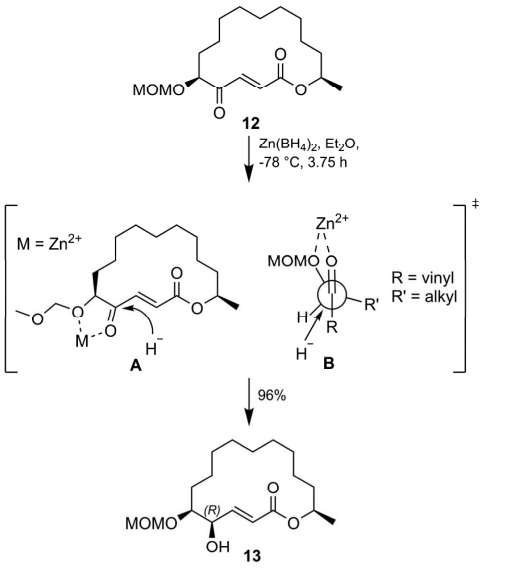
Table 1. (Formal) Total Syntheses of A26771B (1) in Chronological Order

author	year	steps	yield
Hase[a,b]	1979[10]		
Tatsuta	1980,[11] 1982[12]	21	4.4%
Asaoka[a]	1980,[13] 1982[14]		
Fujisawa[a]	1983[15]		
Trost[a]	1983[16]		
Schobert/Bestmann[a]	1985[17]		
Hesse[a]	1987[18]		
Ichimoto	1988[19,20]	16	1.6%[c]
Quinkert	1991[21]	21	2.9%
Baldwin[a]	1992[22]		
Keinan	1993[23]	11	4.1%
		12	6.6%
Nagarajan	1999[24]	12	1.9%
Kobayashi	2000[25]	11	6.2%
Chang	2001[26]	10	2.9%
Blechert	2006[27]	11	17.3%
Reddy	2012[28]	10	14.3%[c]
Fürstner	2013[29]	8	25%
Chattopadhyay	2014[30]	18	9.1%
Shaw	2015[31]	13	13.7%
Chatterjee	2018[32]	10	16.6%
Saha	2022[33]	18	1.3%[d]
Schobert/Schriefer	2022	12	19.5%

[a]No enantioselective total synthesis. [b]Methyl ester of A26771B (**1**). [c]No commercially available starting products used. [d]No formal total synthesis by definition.

Our main interest, however, was the development of a divergent synthesis of the new, not yet synthesized berkeleylactones J, E, K, L, M, N, and O (**2**−**5**, **7**−**9**) in a few steps from a common intermediate. Berkeleylactone E (**3**), isolated in 2017 and featuring a then new γ,δ-dihydroxy-α,β-unsaturated ester moiety, should be accessible from ketone **12** by a diastereoselective reduction involving anti-Felkin product **13**. Scheme 2 shows the assumed transition state A/B. We

Scheme 2. Supposed Transition States (A, B) of the Diastereoselective Reduction of Ketone 12

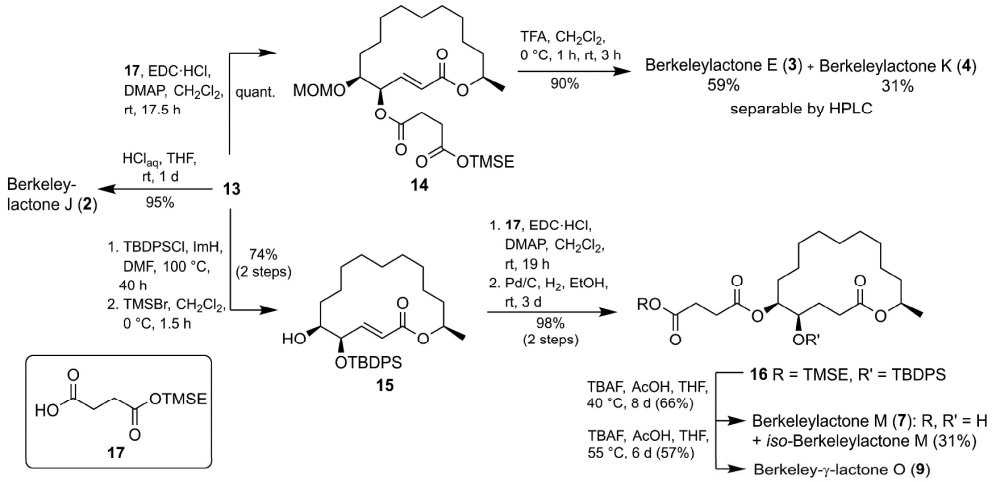


took advantage of the neighboring MOM group, which built up a Cram-chelate with Zn^{2+} when using $Zn(BH_4)_2/2NaCl$ as the reductant.[34] It is worth mentioning that no alkene reduction was observed, as is typical of reductions with $NaBH_4$. The key intermediate **13** was obtained in 96% yield with excellent diastereoselectivity (dr > 99:1, determined by ^1H NMR, cf. Supporting Information). A stereochemical influence in this reaction by the macrocyclic framework might also be possible.

The following diversity-oriented approach toward berkeleylactones **2**−**5** and **7**−**9** used alcohol **13** as a global key intermediate (Scheme 3). Cleavage of the MOM group with aqueous HCl led to berkeleylactone J (**2**) in quantitative yield, whereas other deprotection methods (e.g., TFA) partly afforded the extremely stable internal cyclic methylene acetal. Next, berkeleylactone K (**4**) was to be synthesized in two steps via esterification and deprotection. We did not use succinic anhydride as many before due to its low reaction rate, but mono TMSE-ester **17** (TMSE: trimethylsilylethyl, cf. Supporting Information). It was quite convenient also for the synthesis of other target compounds because the TMSE group is amenable to global deprotections concomitantly with other protection groups. The use of monoester **17** also allowed Steglich−Hassner-type esterifications with easily removable EDC·HCl in quantitative yield. The following concomitant deprotection of TMSE and MOM in macrolide **14** by TFA left us with a 1.9:1 mixture of berkeleylactone E (**3**) and berkeleylactone K (**4**), which could easily be separated by HPLC (cf. Supporting Information). Migrations of the succinyl residues, as those between berkeleylactone E (**3**) and K (**4**), are known in the literature and may occur even without solvents at room temperature.[4] Given this spontaneous interconversion of **3** and **4** we did not search for a selective synthesis of berkeleylactone E (**3**) but concentrated on δ-acylated berkeleylactone M (**7**) and δ-deoxygenated berkeleylactone L (**5**). By consideration of the 3D-model of berkeleylactone M (**7**) we harbored the hope that there is so

https://doi.org/10.1021/acs.jnatprod.3c00053
J. Nat. Prod. 2023, 86, 423−428

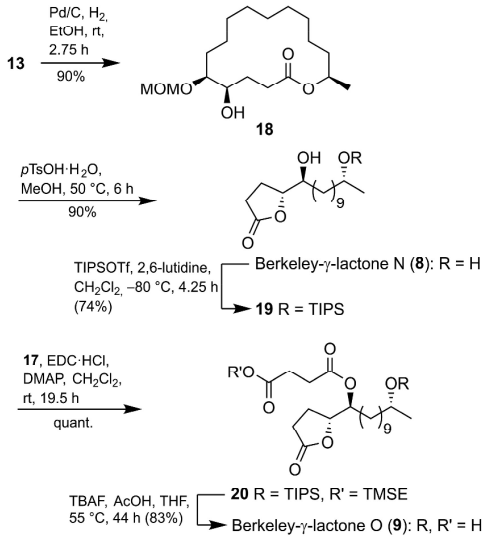
Scheme 3. Synthesis of Berkeleylactones E, J, K, M, and O (2–4, 7, 9) from Key Intermediate 13



great a change in geometry and even electronics by saturation of the α,β-position that no migration of the succinyl residue should happen. Thus, we developed a route to γ-hydroxy-protected macrolides. TBDPS turned out to be the most suitable protection group, which withstands MOM deprotection and which is qualified for a global deprotection of TMSE/TBDPS by TBAF. TBDPS-ether **15** was obtained in two steps by protection of **13** with TBDPSCl/imidazole and subsequent MOM deprotection with TMSBr in 74% overall yield. The following Steglich esterification with carboxylic acid **17** and a subsequent hydrogenation with catalytic Pd/C gave macrolide **16**, which was then globally deprotected by TBAF/AcOH. However, berkeleylactone M (**7**) was obtained with some *iso*-berkeleylactone M due to migration of the succinic acid ester to the γ-hydroxy group. The specific rotation of synthetic lactone **7**, purified by RP column chromatography under acidic conditions ($[\alpha]^{25}_{D}$ −1.5), deviated distinctly from the value reported for the isolate ($[\alpha]^{25}_{D}$ +15.7), which was purified under neutral conditions to presumably give the sodium salt, as apparent from the different high-resolution mass spectra. In contrast, when run at a higher temperature, the TBAF deprotection of macrolide **16** gave solely berkeley-γ-lactone O (**9**) without so much as traces of a δ-lactone. This shows that hydrogenation of the double bond increases the stability of the ester at the δ-hydroxy group compared to unsaturated berkeleylactones **3** and **4**, or else the ring contraction only takes place with δ-acylated macrolide **9**. TBAF-mediated five-ring formation during silyl deprotection is known of acyclic γ-hydroxyesters[35] whereas macrocyclic esters usually show a higher stability toward ring-opening cleavage. Although not yet realized by us, macrolide **15** should be readily converted to berkeleylactone L (**5**) via deoxygenation at the δ-position and cleavage of the TBDPS group.

Finally and adhering to the concept of divergence, we addressed the synthesis of both γ-lactones **8** and **9** from key intermediate **13**. When its saturated derivative **18** was treated with catalytic *p*TsOH in MeOH at 50 °C, it simultaneously underwent a cleavage of the MOM protection group and a transesterification to afford the kinetically favored berkeley-γ-lactone N (**8**) in 90% yield (Scheme 4). For the synthesis of monoacylated berkeley-γ-lactone O (**9**) we had to discriminate the two secondary hydroxy groups of **8** by their steric

Scheme 4. Synthesis of γ-Lactones 8 and 9



encumbrance. Treating diol **8** with TIPSOTf at −80 °C and stopping the reaction after ca. 4 h and 80% conversion afforded mono-TIPS-protected γ-lactone **19** in 74% yield. Steglich–Hassner esterification of the latter with carboxylic acid **17** gave compound **20**, both silyl protecting groups of which were removed at once with TBAF/AcOH to leave berkeley-γ-lactone **9** in 83% yield.

In conclusion, we synthesized six new berkeleylactones and developed a high-yielding formal synthesis of A26771B (**1**, 12 steps, 19.5% yield) in a divergent way, which is rare in the synthesis of macrocyclic natural products. Starting from ketone **12** we built up berkeleylactone E (**3**) in three steps (54% overall yield), berkeleylactone J (**2**) in two steps (91% overall yield), berkeleylactone K (**4**) in three steps (33% overall yield), berkeleylactone M (**7**) in six steps (46% overall yield), berkeley-γ-lactone N (**8**) in three steps (78% overall yield), and berkeley-γ-lactone O (**9**) via two alternative six-step sequences (in 48% yield as in Scheme 4 and 40% yield as in Scheme 3). We also opened access to berkeleylactone L (**5**)

https://doi.org/10.1021/acs.jnatprod.3c00053
J. Nat. Prod. 2023, 86, 423−428

and to differently functionalized γ,δ-dihydroxy-(α,β-unsaturated) (macro)lactones by means of a unique protection group strategy.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were taken with a Büchi melting point H-565 apparatus and are uncorrected. Optical rotations were recorded on a PerkinElmer 241 polarimeter at 589 nm (Na-D line) using solutions in $CHCl_3$ p.a. and MeOH p.a. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz, with a cryoprobe). Chemical shifts are calibrated on the trace proton signals of the used deuterated solvents for ^1H NMR spectra and the ^{13}C signals of the solvents for ^{13}C spectra. For ^1H NMR, $\delta(CDCl_3) = 7.26$, $\delta(CD_3OD) = 3.31$; for ^{13}C NMR, $\delta(CDCl_3) = 77.16$, $\delta(CD_3OD) = 49.00$. The chemical shifts of quaternary carbon atoms with low intensity were determined by 2D spectra (HSQC and HMBC experiments). The data are reported as follows: chemical shift (spin multiplicity, coupling constant (Hz), integration). High-resolution mass spectra (HRMS) were recorded with a ThermoFisher UPLC/Orbitrap MS system in ESI mode. The samples were dissolved in MeCN prior to the measurement. Thin-layer chromatography (TLC) was performed on aluminum plates precoated with silica gel 60 F_{254} by Merck. Detection was done with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate. Column chromatography was performed for purification on normal phase columns (MN silica gel 60 (40−60 μm) from Macherey-Nagel). Analytical high-performance liquid chromatography (HPLC) was carried out on a Shimadzu Nexera XR with autosampler SIL-20A and diode array detector SPD-M20A using a Eurosphere II 100-3 C18 (150 × 4 mm) column from Knauer. All experiments were routinely carried out under a normal atmosphere unless stated otherwise. Reactions under an argon atmosphere were carried out in heat-dried glassware. All reactions that required heating were set up in an oil bath. All reagents were purchased from commercial sources and used without further purification. All solvents were of purity level p.a. (*per analysis*) or were distilled prior to use.

(5*R*,6*S*,16*R*,*E*)-5-Hydroxy-6-(methoxymethoxy)-16-methyloxacyclohexadec-3-en-2-one (13). A suspension of $NaBH_4$ (200 mg, 5.3 mmol) in Et_2O (16 mL) under an argon atmosphere was treated with $ZnCl_2$ (1 M Et_2O, 2.73 mL, 2.7 mmol) and stirred at rt for 2 d. The resulting $Zn(BH_4)_2$/NaCl mixture was cooled down to −78 °C, and a solution of ketone **12** (260 mg, 800 μmol) in Et_2O (10 mL) was slowly added over 14 min. The suspension was stirred at −78 °C for 3.75 h, and brine (100 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by silica gel chromatography (pentane/EtOAc, 9:1 to 4:1) to afford alcohol **13** as a colorless crystalline solid (250 mg, 96%) with a dr > 99:1 (determined by NMR). R_f = 0.50 (hexanes/EtOAc, 1:1, CAM); mp 65.2 °C; $[\alpha]^{25}_D$ +3.2 (*c* 1.0, $CHCl_3$); IR $\tilde{\nu}$ 3471, 2930, 2857, 1716, 1274, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.92 (dd, *J* = 15.7, 4.8 Hz, 1H), 6.11 (dd, *J* = 15.7, 1.9 Hz, 1H), 5.01 (ddq, *J* = 9.3, 6.3, 3.0 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.54 (m, 1H), 3.63 (dt, *J* = 6.1, 2.7 Hz, 1H), 3.41 (s, 3H), 2.90 (m, 1H), 1.67−1.09 (m, 21H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 166.1, 145.5, 122.7, 96.2, 81.3, 72.3, 71.3, 56.0, 35.6, 28.0, 27.9, 27.8, 27.3, 26.2, 26.1, 23.8, 23.4, 20.6; HRESIMS *m*/*z* 267.19557 $[M - OMOM]^+$ (calcd for $C_{16}H_{27}O_3$, 267.19547).

Berkeleylactone J (2). A solution of MOM ether **13** (33 mg, 100 μmol) in THF (2 mL) at 0 °C was treated with 10% aqueous HCl (1 mL) and stirred at rt until TLC showed full conversion (1 d). The solution was neutralized with saturated aqueous $NaHCO_3$ (15 mL), and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (10 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo. Berkeleylactone J (**2**) was obtained by purification of the remainder by silica gel chromatography (pentane/EtOAc, 3:1) as a colorless crystalline solid (27 mg, 95%). R_f = 0.29 (hexanes/EtOAc, 1:1, CAM); mp 98.5 °C; $[\alpha]^{25}_D$ −6.9 (*c* 1.1, MeOH) [lit.[1] $[\alpha]^{25}_D$ − 6.1 (*c* 0.9, MeOH)]; IR $\tilde{\nu}$ 3426, 2929, 2857, 1717, 1659, 1458, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.91 (dd, *J* = 15.8, 5.3 Hz, 1H), 6.09 (dd, *J* = 15.8, 1.7 Hz, 1H), 5.03 (ddq, *J* = 9.1, 6.3, 2.8 Hz, 1H), 4.50 (m, 1H), 3.73 (m, 1H), 2.36 (d, *J* = 3.9 Hz, 1H), 1.99 (d, *J* = 5.6 Hz, 1H), 1.66−1.10 (m, 22H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 166.1, 145.3, 123.0, 74.2, 74.1, 71.4, 35.7, 29.8, 27.9, 27.7, 27.3, 26.1, 26.1, 23.9, 23.3, 20.6; HRESIMS *m*/*z* 285.20574 $[M + H]^+$ (calcd for $C_{16}H_{28}O_4$, 285.2060).

Berkeleylactones E (3) and K (4). Ester **14** (20 mg, 27.8 μmol) was solvated in CH_2Cl_2 (2 mL) at 0 °C, and TFA (1 mL) was slowly added. The solution was stirred at 0 °C for 1 h and a further 3 h at rt. The mixture was co-evaporated with toluene (2 × 5 mL), and the residue was chromatographed (SiO_2, CH_2Cl_2/MeOH + 0.1% HCOOH, 50:1). An isomeric mixture (13 mg, mixture of two regioisomers, 90%) of berkeleylactones E (**3**, 59%) and K (**4**, 31%) was obtained as a colorless resin, which was separable by HPLC. R_f = 0.37 (9:1 CH_2Cl_2/MeOH + 0.1% HCOOH, CAM); IR $\tilde{\nu}$ 3445, 2929, 2857, 1713, 1660, 1266, 1161 cm^{-1}. **3**: ^1H NMR (500 MHz, $CDCl_3$) 6.89 (dd, *J* = 15.7, 4.9 Hz, 1H), 6.13 (dd, *J* = 15.7, 1.7 Hz, 1H), 5.03 (m, 1H), 4.87 (ddd, *J* = 7.6, 5.2, 2.3 Hz, 1H), 4.64 (dt, *J* = 4.8, 2.1 Hz, 1H), 2.80−2.57 (m, 4H), 1.76−1.09 (m, 21H); ^1H NMR (500 MHz, CD_3OD) 6.93 (dd, *J* = 15.7, 4.9 Hz, 1H), 6.10 (dd, *J* = 15.7, 1.9 Hz, 1H), 5.04 (m, 1H), 4.83 (ddd, *J* = 7.8, 5.0, 2.1 Hz, 1H), 4.56 (dt, *J* = 4.8, 2.0 Hz, 1H), 2.74−2.59 (m, 4H), 1.76−1.12 (m, 21H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 177.3, 172.0, 166.2, 144.8, 123.0, 76.9, 71.9, 71.4, 35.7, 29.4, 29.2, 28.0, 27.4, 27.2, 26.3, 26.2, 26.2, 24.0, 23.4, 20.6; $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) 176.1, 174.0, 167.7, 148.2, 123.1, 77.6, 72.8, 72.4, 36.7, 30.3, 29.8, 29.1, 28.4, 28.2, 27.4, 27.3, 27.1, 25.1, 24.6, 20.8; HRMS *m*/*z* 383.20767 $[M - H]^-$ (calcd for $C_{20}H_{31}O_7$, 383.20643). **4**: ^1H NMR (500 MHz, $CDCl_3$) 6.83 (dd, *J* = 15.8, 5.6 Hz, 1H), 5.99 (dd, *J* = 15.8, 1.5 Hz, 1H), 5.63 (ddd, *J* = 5.5, 2.5, 1.7 Hz, 1H), 5.03 (m, 1H), 3.80 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1H), 2.80−2.57 (m, 4H), 1.76−1.09 (m, 21H); ^1H NMR (500 MHz, CD_3OD) 6.85 (dd, *J* = 15.9, 5.6 Hz, 1H), 5.99 (dd, *J* = 15.9, 1.7 Hz, 1H), 5.56 (dt, *J* = 5.3, 2.1 Hz, 1H), 5.03 (m, 1H), 3.72 (m, 1H), 2.74−2.59 (m, 4H), 1.76−1.12 (m, 21H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 177.0, 171.9, 165.5, 141.3, 124.0, 76.5, 73.1, 71.8, 35.7, 29.7, 29.3, 29.2, 28.0, 27.5, 27.3, 26.1, 26.0, 24.0, 23.1, 20.6; $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) 176.1, 173.6, 167.2, 144.4, 123.1, 77.9, 73.3, 72.6, 36.7, 30.3, 30.1, 30.1, 29.7, 29.2, 28.4, 28.3, 27.2, 25.2, 24.5, 20.8; HRESIMS *m*/*z* 383.20755 $[M - H]^-$ (calcd for $C_{20}H_{31}O_7$, 383.20643).

Berkeleylactone M (7). A solution of silylether **16** (25 mg, 34.5 μmol) in THF (1 mL) under an argon atmosphere was treated with TBAF (1 M THF, 103 μL, 103 μmol) and stirred at rt for 3 h. Further TBAF (1 M THF, 138 μmol, 138 μL) and AcOH (15.8 μL, 276 μmol) were added, and the solution was stirred at 40 °C for a further 6 d. More TBAF (1 M THF, 34.5 μmol, 34.5 μL) and AcOH (2.9 μL, 34.5 μmol) were added, and the solution was stirred for two more days at 40 °C and treated with 1 M HCl (5 mL). The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and evaporated to dryness. The crude mixture was separated by silica column chromatography (SiO_2, CH_2Cl_2/MeOH + 0.05% HCOOH, 100:1 to 60:1). Berkeleylactone M (**7**, 8.8 mg, 66%) was obtained as a colorless resin. R_f = 0.49 (9:1 CH_2Cl_2/MeOH + 0.1% HCOOH, CAM); $[\alpha]^{25}_D$ −1.5 (*c* 0.1, MeOH) [lit.[1] $[\alpha]^{25}_D$ +15.7 (*c* 0.1, MeOH)]; IR $\tilde{\nu}$ 3463, 2929, 2858, 1729, 1261, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4.95 (dt, *J* = 6.4, 2.5 Hz, 1H), 4.91 (m, 1H), 3.84 (m, 1H), 3.64−1.76 (brs, OH, COOH), 2.79−2.55 (m, 5H), 2.38 (dt, *J* = 14.6, 8.0 Hz, 1H), 1.85 (d, *J* = 7.6 Hz, 1H), 1.82 (d, *J* = 7.7 Hz, 1H), 1.65 (m, 1H), 1.54 (m, 3H), 1.45−1.21 (m, 20H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 175.8, 173.1, 172.3, 77.7, 71.6, 71.0, 35.9, 32.0, 29.5, 29.3, 28.0, 27.5, 27.3, 26.9, 26.0, 25.8, 24.0, 23.1, 20.5; HRESIMS *m*/*z* 385.22338 $[M - H]^-$ (calcd for $C_{20}H_{32}O_7$, 385.22208).

Berkeley-γ-lactone N (8). *p*TsOH·H_2O (1 mg, 5.45 μmol) was added to a solution of macrolide **18** (18 mg, 54.5 μmol) in MeOH (1 mL). The solution was stirred at 50 °C for 6 h until full conversion

https://doi.org/10.1021/acs.jnatprod.3c00053
J. Nat. Prod. 2023, 86, 423−428

(TLC). The solvent was evaporated, and the remainder purified by silica gel chromatography (pentane/EtOAc, 3:2 to 1:1). Berkeley-γ-lactone N (**8**) was obtained as a colorless crystalline solid (14 mg, 90%). R_f = 0.33 (hexanes/EtOAc, 1:2, CAM); mp 89.2 °C; $[\alpha]^{25}_D$ −16.5 (*c* 1.0, MeOH) [lit.[1] $[\alpha]^{25}_D$ −11.6 (*c* 0.43, MeOH)]; IR $\tilde{\nu}$ 3401, 3279, 2915, 2849, 1777, 1749, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4.44 (dt, *J* = 7.4, 3.3 Hz, 1H), 3.93 (m, 1H), 3.79 (m, 1H), 2.60 (ddd, *J* = 17.8, 10.0, 5.0 Hz, 1H), 2.52 (ddd, *J* = 17.8, 9.8, 8.8 Hz, 1H), 2.26 (m, 1H), 2.14 (dddd, *J* = 12.6, 9.9, 7.4, 5.1 Hz, 1H), 1.86 (m, 1H), 1.55−1.24 (m, 19H), 1.19 (d, *J* 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 177.7, 83.0, 71.4, 68.3, 39.4, 32.0, 29.7, 29.6, 29.6, 29.6, 29.5, 28.9, 25.8, 25.7, 25.6, 23.6, 21.2; HRESIMS *m/z* 269.21092 $[M - OH]^+$ (calcd for $C_{16}H_{29}O_3$, 269.21112).

Berkeley-γ-lactone O (9). A solution of ester **20** (20 mg, 31.1 μmol, 1.00 equiv) in THF (1.5 mL) under an argon atmosphere was treated with TBAF (1 M THF, 77.8 μL, 77.8 μmol, 2.50 equiv) at rt. The solution was stirred for 7 h at rt, and TBAF (1 M THF, 31.1 μL, 31.1 μmol, 1.00 equiv) and AcOH (6.23 μL, 109 μmol, 3.50 equiv) were added. After 11.5 h the mixture was heated to 50 °C, and after a further 7.5 h additional TBAF (187 μL, 187 μmol, 6.00 equiv) and AcOH (10.6 μL, 187 μmol, 6.00 equiv) were added. After 18 h of stirring at 50 °C the solution was cooled to rt and treated with 0.5 M HCl (1 mL) for 30 min. The suspension was poured into 0.5 M HCl (10 mL) and extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with 1 M HCl (2 × 10 mL), dried over Na_2SO_4, and evaporated to dryness. Berkeley-γ-lactone O (**9**) was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH + 0.1% HCOOH, 60:1 to 20:1). R_f = 0.33 (9:1 CH_2Cl_2/MeOH + 0.1% HCOOH, CAM); $[\alpha]^{25}_D$ −10.6 (*c* 0.70, MeOH) [lit.[1] $[\alpha]^{25}_D$ −16.3 (*c* 0.48, MeOH)]; IR $\tilde{\nu}$ 3421, 2926, 2855, 2608, 1778, 1734, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.97−4.65 (brs, 2H), 5.13 (dt, *J* = 8.4, 4.7 Hz, 1H), 4.52 (dt, *J* = 7.2, 4.6 Hz, 1H), 3.82 (m, 1H), 2.75−2.46 (m, 6H), 2.26 (dddd, *J* = 13.2 9.7, 7.6, 5.7 Hz, 1H), 2.13 (dddd, *J* = 13.1, 9.9, 8.2, 7.0 Hz, 1H), 1.59 (m, 2H), 1.50−1.23 (m, 18H), 1.18 (d, *J* = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 177.0, 176.3, 171.8, 80.3, 74.0, 68.5, 39.2, 30.2, 29.4, 29.3 (2 signals), 29.1, 29.1, 28.8, 28.2 (2 C), 25.6, 25.1, 23.5, 23.0; HRESIMS *m/z* 387.23745 $[M + H]^+$ (calcd for $C_{20}H_{35}O_7$, 387.23773).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.3c00053.

Experimental details of all chemical syntheses; characterization of all new compounds; NMR spectra and HPLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Rainer Schobert − *Organic Chemistry Laboratory, University of Bayreuth, 95440 Bayreuth, Germany;* orcid.org/0000-0002-8413-4342; Phone: +49 (0)921 552679; Email: rainer.schobert@uni-bayreuth.de; Fax: +49 (0)921 552671

Author

Manuel G. Schriefer − *Organic Chemistry Laboratory, University of Bayreuth, 95440 Bayreuth, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jnatprod.3c00053

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank E. M. Statelov (University of Bayreuth) for synthesizing a large amount of key intermediate **13** as part of his BSc project.

■ REFERENCES

(1) Stierle, A. A.; Stierle, D. B.; Alverson, J.; Gibson, N. *J. Nat. Prod.* **2021**, *84* (12), 3064−3070.
(2) Stierle, A. A.; Stierle, D. B.; Decato, D.; Priestley, N. D.; Alverson, J. B.; Hoody, J.; McGrath, K.; Klepacki, D. *J. Nat. Prod.* **2017**, *80* (4), 1150−1160.
(3) Schriefer, M. G.; Schrey, H.; Zeng, H.; Stadler, M.; Schobert, R. *Org. Biomol. Chem.* **2021**, *19* (21), 4743−4751.
(4) Zhang, Y.; Bai, J.; Le Zhang; Zhang, C.; Liu, B.; Hu, Y. *Angew. Chem., Int. Ed.* **2021**, *60* (12), 6639−6645.
(5) Li, L.; Chen, Z.; Zhang, X.; Jia, Y. *Chem. Rev.* **2018**, *118* (7), 3752−3832.
(6) Scharnagel, D.; Goller, J.; Deibl, N.; Milius, W.; Breuning, M. *Angew. Chem., Int. Ed.* **2018**, *57* (9), 2432−2435.
(7) Hugelshofer, C. L.; Magauer, T. *J. Am. Chem. Soc.* **2015**, *137* (11), 3807−3810.
(8) Willwacher, J.; Kausch-Busies, N.; Fürstner, A. *Angew. Chem., Int. Ed.* **2012**, *51* (48), 12041−12046.
(9) Gebauer, J.; Blechert, S. *Org. Chem.* **2006**, *71* (5), 2021−2025.
(10) Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, *20* (28), 2633−2636.
(11) Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21* (15), 1479−1482.
(12) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *BCSJ.* **1982**, *55* (10), 3248−3253.
(13) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21* (48), 4611−4614.
(14) Asaoka, M.; Abe, M.; Mukuta, T.; Takei, H. *Chem. Lett.* **1982**, *11* (2), 215−218.
(15) Fujisawa, T.; Okada, N.; Takeuchi, M.; Sato, T. *Chem. Lett.* **1983**, *12* (8), 1271−1272.
(16) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105* (3), 568−575.
(17) Bestmann, H. J.; Schobert, R. *Angew. Chem., Int. Ed.* **1985**, *24* (9), 791−792.
(18) Bienz, S.; Hesse, M. *Helv. Chim. Acta* **1987**, *70* (5), 1333−1340.
(19) Ichimoto, I.; Sato, M.; Tsuji, H.; Kirihata, M.; Ueda, H. *ChemInform* **1988**, *19* (48), 323. Also see ref 20.
(20) Ichimoto, I.; Sato, M.; Tsuji, H.; Kirihata, M.; Ueda, H. *Chem. Express* **1988**, *3* (8), 499−502.
(21) Quinkert, G.; Küber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Dürner, G.; Zimmermann, G.; Bats, J. W.; Egert, E. *Helv. Chim. Acta* **1991**, *74* (8), 1853−1923.
(22) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48* (14), 2957−2976.
(23) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58* (27), 7789−7796.
(24) Nagarajan, M. *Tetrahedron Lett.* **1999**, *40* (6), 1207−1210.
(25) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65* (2), 612−615.
(26) Lee, W.-W.; Shin, H. J.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12* (1), 29−31.
(27) Gebauer, J.; Blechert, S. *J. Org. Chem.* **2006**, *71* (5), 2021−2025.
(28) Raji Reddy, C.; Suman, D.; Narsimha Rao, N. *Synlett* **2012**, *2012*, 272−274.
(29) Persich, P.; Llaveria, J.; Lhermet, R.; Haro, T. de; Stade, R.; Kondoh, A.; Fürstner, A. *Chem.—Eur. J.* **2013**, *19* (39), 13047−13058.
(30) Chatterjee, S.; Sharma, A.; Chattopadhyay, S. *RSC Adv.* **2014**, *4* (80), 42697−42705.
(31) Saidhareddy, P.; Shaw, A. K. *RSC Adv.* **2015**, *5* (37), 29114−29120.

(32) Chatterjee, S.; Subramanian, M.; Sharma, A.; Chattopadhyay, S. *Nat. Prod. Commun.* **2018**, *13* (11), 1934578 × 1801301.
(33) Subba, S.; Saha, S. *Synth. Commun.* **2022**, *52* (5), 704−711.
(34) Setamdideh, D.; Khaledi, L. *S. Afr. J. Chem.* **2013**, *66*, 150−157.
(35) Hanessian, S.; Guindon, Y.; Lavallée, P.; Dextraze, P. *Carbohydr. Res.* **1985**, *141* (2), 221−238.

https://doi.org/10.1021/acs.jnatprod.3c00053
J. Nat. Prod. 2023, 86, 423−428

Supporting Information

Divergent synthesis of six recent berkeleylactones

Manuel Georg Schriefer[†] and Rainer Schobert[†,*]

[†]*Organic Chemistry Laboratory, University Bayreuth, 95440 Bayreuth, Germany*

Rainer.Schobert@uni-bayreuth.de

Table of Contents

1 General

Infrared Spectroscopy: IR spectra were recorded using a Spectrum One FT-IR spectrometer from PerkinElmer with an ATR unit.

Nuclear Magnetic Resonance (NMR) Spectroscopy: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz, with cryoprobe). Chemical shifts are given in parts per million (δ) and calibrated on the trace proton signals of the used deuterated solvents for ^{1}H NMR spectra and the ^{13}C signals of the solvents for ^{13}C spectra. For ^{1}H NMR: δ ($CDCl_3$) = 7.26 ppm, δ ([D_4]MeOD) = 3.31 ppm and for ^{13}C NMR: δ ($CDCl_3$) = 77.16 ppm, δ ([D_4]MeOD) = 49.00 ppm. The signal multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sex), multiplet (m) and broad (br). Coupling constants (*J*) are given in Hertz (Hz). The chemical shifts of quaternary carbon atoms with low intensity were determined by 2D spectra (HSQC and HMBC experiments). The data are reported as follows: chemical shift (spin multiplicity, coupling constant (Hz), integration).

Mass Spectrometry: High resolution mass spectra (HRMS) were recorded with a ThermoFisher UPLC/Orbitrap MS system in ESI mode. The samples were dissolved in MeCN prior to the measurement.

Specific Optical Rotations were recorded on a PerkinElmer 241 Polarimeter at 589 nm (Na-D line) using solutions in chloroform p.a. and MeOH p.a. Specific rotations ($[\alpha]_D$) are reported in units of 10^{-1} deg cm^2 g^{-1}.

Melting Points: All melting points were measured with a Büchi Melting Point H-565 apparatus and have not been corrected.

Thin Layer Chromatography (TLC): To monitor the progress of reactions analytical thin-layer chromatography was performed on aluminum plates pre-coated with silica gel 60 F_{254} by Merck. The compounds were detected with UV light (254 nm and/or 360 nm) and/or ceric ammonium molybdate (CAM) and/or potassium permanganate.

Column Chromatography: Purification was performed using normal phase column chromatography. Normal phase chromatography was performed using MN silica gel 60 (40-60 µm) of the company Macherey-Nagel as stationary phase. The composition of the eluent is given in volume parts.

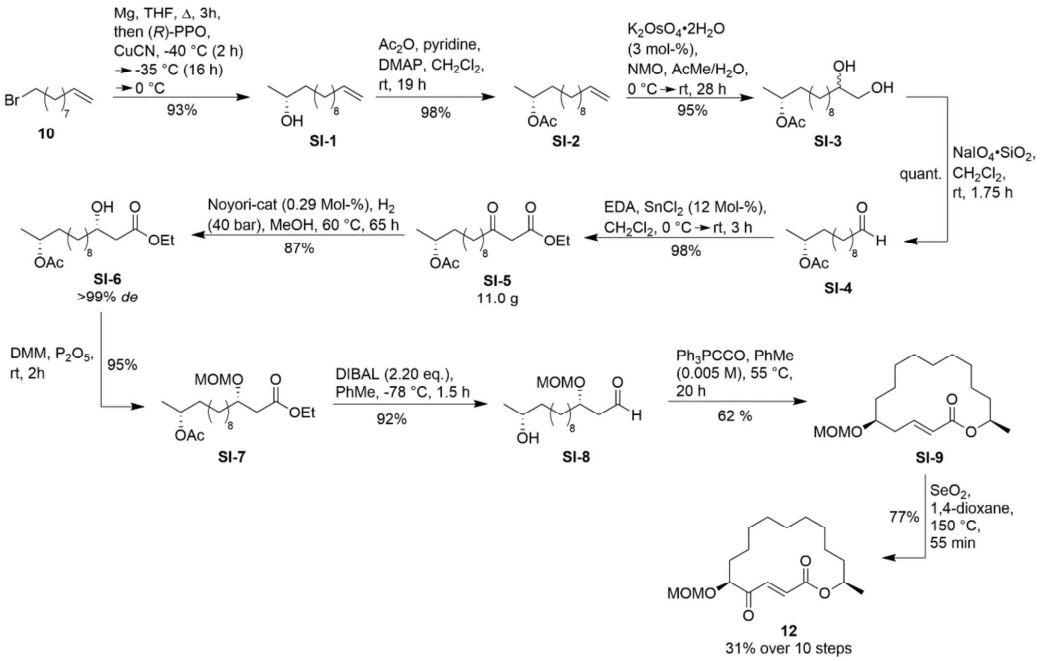
High-Performance Liquid Chromatography (HPLC): Analytical HPLC measurements were carried out on a Shimadzu Nexera XR with autosampler SIL-20A and a diode array detector SPD-M20A using the column Eurosphere II 100-3 C18 (150 × 4 mm) from Knauer.

Chemicals and Procedures: All experiments were routinely carried out under normal atmosphere unless stated otherwise. Reactions under argon atmosphere were carried out in heat-dried glassware. All reactions that required heating were set up in an oil bath. All reagents were purchased from commercial sources and used without further purification unless stated otherwise. All solvents used featured the purity level 'p.a.' or were distilled prior to use. Solvents used for the HPLC system featured the purity level 'HPLC grade'. Absolute solvents were stored over molecular sieves (3 Å or 4 Å) under argon atmosphere. Dry dichloromethane (CH_2Cl_2) was obtained by heating under reflux over CaH_2 and subsequent distillation. Dry tetrahydrofuran (THF), dry toluene (PhMe), dry diethyl ether (Et_2O) and dry 1,4-dioxane were obtained by heating over sodium/benzophenone and subsequent distillation.

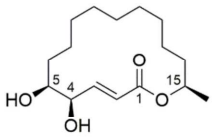
2 Synthesis of Macrolide 12

Ketone **12** was synthesized as shown below.

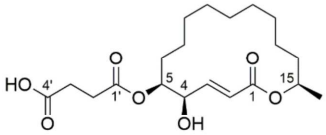
Manuel G. Schriefer; Hedda Schrey; Haoxuan Zeng; Marc Stadler; Rainer Schobert. Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation. *Org. Biomol. Chem.* **2021**, *19* (21), 4743–4751. DOI: 10.1039/D1OB00717C



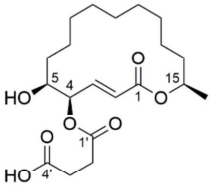
3 Comparison of ^{1}H and ^{13}C NMR Data with the Literature[1,2]



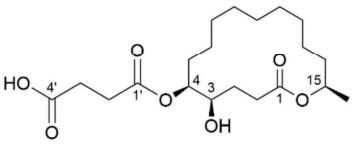
Berkeleylactone J (**2**)



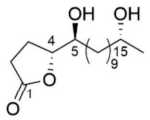
Berkeleylactone E (**3**)



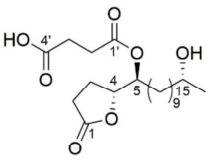
Berkeleylactone K (**4**)



Berkeleylactone M (**7**)



Berkeley-γ-lactone N (**8**)



Berkeley-γ-lactone O (**9**)

The difference in the NMR spectra is due to slightly different calibration values of the residual H-peak of $CDCl_3$. Stierle et al. used $CDCl_3$ = 7.24 ppm, while we used $CDCl_3$ = 7.26 ppm.

Table SI-1: ^{1}H NMR data [δ (ppm); multipl., *J* (Hz)] for compounds 2-4 and comparison with lit.[1,2]

Atom No./ Compound	**2**[1]	**Synthetic 2**	**3**[2] (MeOD)	**Synthetic 3** (MeOD)	**4**[1]	**Synthetic 4**
1	-	-	-	-	-	-
2	6.05, d (15.7)	6.09, dd (15.8, 1.7)	6.10, dd (15.7, 1.8)	6.10, dd (15.7, 1.9)	5.98, dd (15.8, 1.6)	5.99, dd (15.8, 1.5)
3	6.82, dd (15.7, 5.1) SI: 6.88	6.91, dd (15.8, 5.3)	6.93, dd (15.7, 4.9)	6.93, dd (15.7, 4.9)	6.82, dd (15.8, 5.6)	6.83, dd (15.8, 5.6)
4	4.46, bd (5.1)	4.50, m	4.55, m	4.56, dt (4.8, 2.0)	5.61 (5.6, 2.0)	5.63, ddd (5.5, 2.5, 1.7)
5	3.69, m	3.73, m	4.83, m	4.83, ddd (7.8, 5.0, 2.1)	3.78, m	3.80, ddd (7.5, 5.0, 2.5)
6	1.59, bs	1.61, m	1.64, m 1.55, m	1.64, m 1.55, m	1.59, bs 1.40, m	1.60, m 1.40, m
7	1.44, bs	1.46, m	1.33, m	1.47-1.12, m	1.44, bs	1.44, m
8	1.30, bs	1.42-1.10, m	1.69, m 1.51, m	1.70, m 1.51, m	1.30, bs	1.65-1.08, m
9	1.30, bs	1.42-1.10, m	1.33, m	1.47-1.12, m	1.30, bs	1.65-1.08, m
10	1.30, bs	1.42-1.10, m	1.33, m	1.47-1.12, m	1.30, bs	1.65-1.08, m
11	1.30, bs	1.42-1.10, m	1.33, m	1.47-1.12, m	1.30, bs	1.65-1.08, m
12	1.30, bs	1.42-1.10, m	1.33, m	1.47-1.12, m	1.30, bs	1.65-1.08, m
13	1.30, bs	1.42-1.10, m	1.33, m	1.47-1.12, m	1.30, bs	1.65-1.08, m
14	1.55, bs	1.55, m	1.33, m	1.47-1.12, m	1.54, bs	1.65-1.08, m
15	5.00, m	5.03, ddq (9.1, 6.3, 2.8)	5.05, m	5.04, m	5.00, m	5.03, m
16	1.24, d (6.3)	1.27, d (6.3)	1.26, d (6.3)	1.26, d (6.3)	1.24, d (6.3)	1.26, d (6.3)
1'	-	-	-	-	-	-
2'	-	-	2.72, m	2.72, m	2.71, m	2.80-2.57, m
3'	-	-	2.65, m	2.65, m	2.69, m	2.80-2.57, m
4'	-	-	-	-	-	-

Table SI-2: ^{1}H NMR data [δ (ppm); multipl., *J* (Hz)] for compounds 7-9 and comparison with lit.[1,2]

	7[1]	**Synthetic 7**	**8[1]**	**Synthetic 8**	**9[1]**	**Synthetic 9**
1	-	-	-	-	-	-
2	2.56, bs 2.37, bs	2.59, m 2.38, dt (14.6, 8.0)	2.54, m	2.60, ddd (17.8, 10.0, 5.0) 2.52, ddd (17.8, 9.8, 8.8)	2.54, m	2.52, m 2.58, m
3	1.81, bs	1.85, d (7.6) 1.82, d (7.7)	2.24, m 2.11, m	2.26, m 2.14, dddd (12.6, 9.9, 7.4, 5.1)	2.23, m 2.11, m	2.26, m 2.13, m
4	3.82, bs	3.84, m	4.41, m	4.44, dt (7.4. 3.3)	4.51, m	4.52, dt (7.2, 4.6)
5	4.92, bs	4.95, dt (6.4, 2.5)	3.90, m	3.93, m	5.11, m	5.13, dt (8.4, 4.7)
6	1.61, bs	1.65, m	1.40, m	1.55-1.24, m	1.61, m	1.59, m
7	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
8	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
9	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
10	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
11	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
12	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
13	1.30, bs	1.60-1.21, m	1.30, bs	1.55-1.24, m	1.30, bs	1.41-1.23, m
14	1.54, bs	1.54, m	1.40, bs	1.55-1.24, m	1.40, m	1.43, m
15	4.90, bs	4.91, m	3.76, m	3.79, m	3.78, m	3.82, m
16	1.21, d (6.3)	1.23, d (6.3)	1.16, d (6.1)	1.19, (6.2)	1.16, d (6.1)	1.18, d (6.2)
1’	-	-	-	-	-	-
2’	2.62, bs	2.64, m	-	-	2.56, m	2.76-2.55, m
3’	2.68, bs	2.71, m	-	-	2.65, m	2.76-2.55, m
4’	-	-	-	-	-	-

Table SI-3: $^{13}C\{^1H\}$ NMR data [δ (ppm)] for compounds 2-4 and comparison with lit.[1,2]

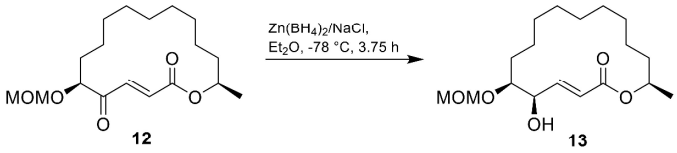
	2[1]	**Synthetic 2**	**3[2]** (MeOD)	**Synthetic 3** (MeOD)	**4[1]**	**Synthetic 4**
1	166.1, C	166.1, C	167.8, C	167.7, C	165.3, C	165.5, C
2	122.5, CH	123.0, CH	123.3, CH	123.1, CH	124.0, CH	124.0, CH
3	145.6, CH	145.3, CH	148.3, CH	148.2, CH	141.1, CH	141.3, CH
4	74.0, CH	74.2, CH	73.0, CH	72.8, CH	76.5, CH	76.5, CH
5	74.1, CH	74.1, CH	77.8, CH	77.6, CH	72.9, CH	73.1, CH
6	29.5, CH_2	29.8, CH_2	30.4, CH_2	30.3, CH_2	29.7, CH_2	29.7, CH_2
7	23.2, CH_2	23.3, CH_2	24.8, CH_2	24.6, CH_2	23.0, CH_2	23.1, CH_2
8	27.8, CH_2	27.9, CH_2	27.3, CH_2	27.1, CH_2	27.4, CH_2	27.5, CH_2
9	27.6, CH_2	27.7, CH_2	28.6, CH_2	28.4, CH_2	27.2, CH_2	27.3, CH_2
10	27.1, CH_2	27.3, CH_2	27.5, CH_2	27.3, CH_2	27.9, CH_2	28.0, CH_2
11	26.0, CH_2	26.1, CH_2	28.4, CH_2	28.2, CH_2	26.1, CH_2	26.1, CH_2
12	26.0, CH_2	26.1, CH_2	27.6, CH_2	27.4, CH_2	25.9, CH_2	26.0, CH_2
13	23.7, CH_2	23.9, CH_2	25.3, CH_2	25.1, CH_2	23.8, CH_2	24.0, CH_2
14	35.5, CH_2	35.7, CH_2	36.8, CH_2	36.7, CH_2	35.6, CH_2	35.7, CH_2
15	71.3, CH	71.4, CH	72.5, CH	72.4, CH	71.6, CH	71.8; CH
16	20.4, CH_3	20.6, CH_3	20.9, CH_3	20.8, CH_3	20.4, CH_3	20.6, CH_3
1’	-	-	174.2, C	174.0, C	171.6, C	171.9, C
2’	-	-	29.3, CH_2	29.1, CH_2	29.2, CH_2	29.3, CH_2
3’	-	-	29.9, CH_2	29.8, CH_2	28.9, CH_2	29.2, CH_2
4’	-	-	176.2, C	176.1, C	176.3, C	177.0, C

Table SI-4: $^{13}C\{^1H\}$ NMR data [δ (ppm)] for compounds 7-9 and comparison with lit.[1,2]

	7[1]	**Synthetic 7**	**8[1]**	**Synthetic 8**	**9[1]**	**Synthetic 9**
1	173.0, C	173.1, C	177.5, C	177.7, C	176.8, C	177.0, C
2	31.9, CH_2	32.0, CH_2	28.7, CH_2	28.9, CH_2	28.1, CH_2	28.2, CH_2
3	27.4, CH_2	27.5, CH_2	21.1, CH_2	21.2, CH_2	22.9, CH_2	23.0, CH_2
4	70.9, CH	71.0, CH	82.8, CH	83.0, CH	80.1, CH	80.3, CH
5	77.6, CH	77.7, CH	71.3, CH	71.4, CH	73.8, CH	74.0, CH
6	27.8, CH_2	28.0, CH_2	31.8, CH_2	32.0, CH_2	29.3, CH_2	29.3, CH_2
7	23.0, CH_2	23.1, CH_2	25.7, CH_2	25.8, CH_2	24.9, CH_2	25.1, CH_2
8	27.4, CH_2	27.3, CH_2	29.4, CH_2	29.5, CH_2	28.2, CH_2	28.2, CH_2
9	27.1, CH_2	26.9, CH_2	29.4, CH_2	29.6, CH_2	29.0, CH_2	29.1, CH_2
10	26.7, CH_2	26.9, CH_2	29.5, CH_2	29.6, CH_2	29.2, CH_2	29.3, CH_2
11	25.7, CH_2	25.8, CH_2	29.4, CH_2	29.6, CH_2	28.7, CH_2	28.8, CH_2
12	25.8, CH_2	26.0, CH_2	29.5, CH_2	29.7, CH_2	29.0, CH_2	29.1, CH_2
13	23.9, CH_2	24.0, CH_2	25.6, CH_2	25.7, CH_2	25.4, CH_2	25.6, CH_2
14	35.7, CH_2	35.9, CH_2	39.3, CH_2	39.4, CH_2	39.1, CH_2	39.2, CH_2
15	71.5, CH	71.6, CH	68.2, CH	68.3, CH	68.3, CH	68.5, CH
16	20.3, CH_3	20.5, CH_3	23.4, CH_3	23.6, CH_3	23.4, CH_3	23.5, CH_3
1’	172.1, C	172.3, C	-	-	171.6, C	171.8, C
2’	29.3, CH_2	29.5, CH_2	-	-	30.1, CH_2	30.2, CH_2
3’	28.9, CH_2	29.3, CH_2	-	-	29.3, CH_2	29.4, CH_2
4’	176.2, C	175.8, C	-	-	175.7, C	176.3, C

4 Experimental Section

4.1 Synthesis of Key Intermediate 13, (5*R*,6*S*,16*R*,*E*)-5-hydroxy-6-(methoxy-methoxy)-16-methyloxacyclohexadec-3-en-2-one (13)

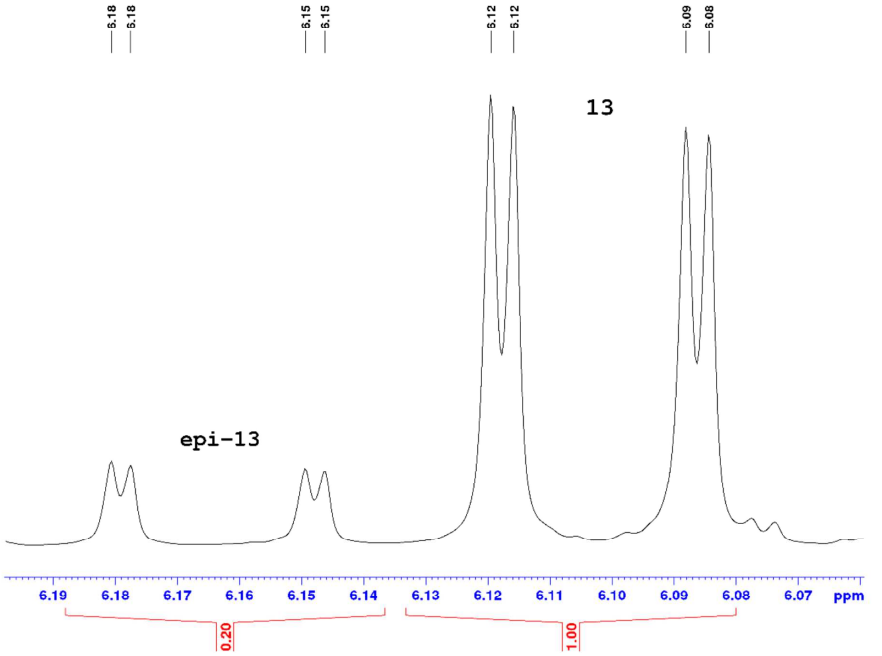


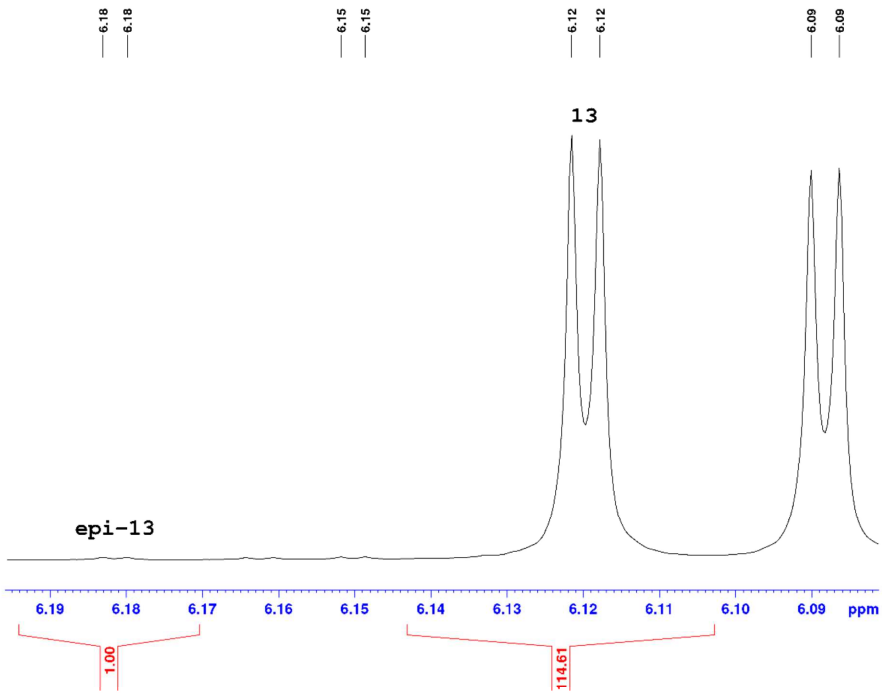
To a suspension of $NaBH_4$ (200 mg, 5.3 mmol, 6.7 equiv.) in dry Et_2O (46 mL) under argon atmosphere was added $ZnCl_2$ (1M Et_2O, 2.73 mL, 2.7 mmol, 3.4 equiv.) and stirred for 2 d at room temperature. The resulting $Zn(BH_4)_2$/NaCl-mixture was cooled down to −78 °C and ketone **12** (260 mg, 800 µmol, 1.0 equiv.) solved in dry Et_2O (10 mL) was slowly added over 14 min. The suspension was stirred at −78 °C for 3.75 h and brine (100 mL) was added. The aqueous phase was separated and extracted with EtOAc (3×60 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (pentane/EtOAc 9:1 to 4:1) and alcohol **13** was obtained as colorless solid with a d.r. >99:1.

Yield: 250 mg (761 µmol, 96%)

R_f = 0.50 (hexanes/ethyl acetate 1:1, CAM); **$[\alpha]_D^{25}$** +3.2 (*c* 1.0, $CHCl_3$); **mp** 65.2 °C; **IR** (cm^{-1}) $\tilde{\nu}$ 3471, 2930, 2857, 1716, 1274, 1033; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.92 (dd, *J*= 15.7, 4.8 Hz, 1H), 6.11 (dd, *J*= 15.7, 1.9 Hz, 1H), 5.01 (ddq, *J*= 9.3, 6.3, 3.0 Hz, 1H), 4.75 (d, *J*= 7.0 Hz, 1H), 4.68 (d, *J*= 7.0 Hz, 1H), 4.54 (m, 1H), 3.63 (dt, *J*= 6.1, 2.7 Hz, 1H), 3.41 (s, 3H), 2.90 (m, 1H), 1.67-1.09 (m, 21H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 166.1, 145.5, 122.7, 96.2, 81.3, 72.3, 71.3, 56.0, 35.6, 28.0, 27.9, 27.8, 27.3, 26.2, 26.1, 23.8, 23.4, 20.6; **IIRMS** (ESI) *m/z* [M − OMOM]$^+$ calculated for $C_{16}H_{27}O_3$ 267.19547; found 267.19557.

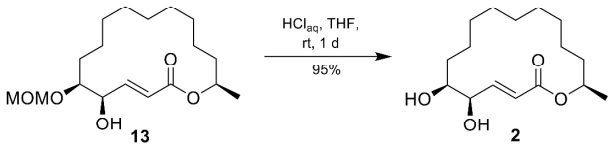
The diastereomeric ratio was determined as shown below. In a small amount of purified sample of *epi*-**13** we detected the chemical shift difference of the alkene-proton in α-position of the minor diastereomer. Integration of both regions led to d.r. >99:1 after purification.


6.18
6.18
6.15
6.15
6.12
6.12
5.09
5.08
13
epi-13
6.19
6.18
6.17
6.16
6.15
6.14
6.13
6.12
6.11
6.10
6.09
6.08
6.07
ppm
0.20
1.00


6.18
6.18
6.15
6.15
6.12
6.12
6.09
6.09
13
epi-13
6.19
6.18
6.17
6.16
6.15
6.14
6.13
6.12
6.11
6.10
6.09
ppm
1.00
114.61

S9

4.2 Synthesis of Berkeleylactone J (2)

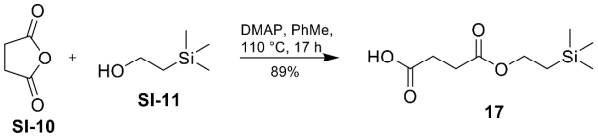


A solution of MOM-Ether **13** (33 mg, 100 µmol, 1.00 equiv.) in THF (2 mL) at 0 °C was treated with 10% aq. HCl (1 mL) and stirred at room temperature until TLC showed full conversion (1 d). The solution was neutralized with sat. aq. $NaHCO_3$ (15 mL) and the aqueous phase was extracted with EtOAc (4×15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was removed in vacuo. Berkeleylactone J (**2**) was obtained by purification of the remainder by silica gel chromatography (pentane/EtOAc 3:1) as a colorless solid.

Yield: 27 mg (94.9 µmol, 95%)

R_f = 0.29 (hexanes/ethyl acetate 1:1, CAM); **$[\alpha]_D^{25}$** −6.9 (*c* 1.1, MeOH); Lit.[1] **$[\alpha]_D^{25}$** −6.1 (*c* 0.9, MeOH); **mp** 98.5 °C; **IR** (cm^{-1}) $\tilde{\nu}$ 3426, 2929, 2857, 1717, 1659, 1458, 1272; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.91 (dd, *J* = 15.8, 5.3 Hz, 1H), 6.09 (dd, *J* = 15.8, 1.7 Hz, 1H), 5.03 (ddq, *J* = 9.1, 6.3, 2.8 Hz, 1H), 4.50 (m, 1H), 3.73 (m, 1H), 2.36 (d, *J* = 3.9 Hz, 1H), 1.99 (d, *J* = 5.6 Hz, 1H), 1.66-1.10 (m, 22H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 166.1, 145.3, 123.0, 74.2, 74.1, 71.4, 35.7, 29.8, 27.9, 27.7, 27.3, 26.1, 26.1, 23.9, 23.3, 20.6; **HRMS** (ESI) *m/z* $[M+H]^+$ calculated for $C_{16}H_{28}O_4$ 285.2060; found 285.20574.

4.3 Synthesis of Succinic Ester 17



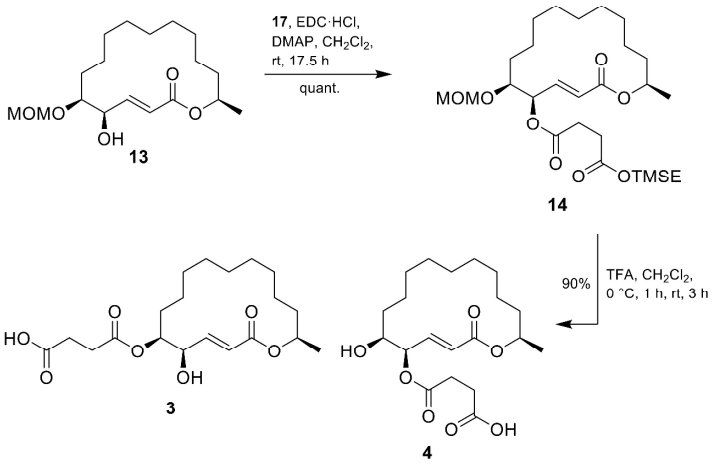
Succinic anhydride (**SI-10**, 2.00 g, 20.0 mmol, 1.89 equiv.) solved in PhMe (20 mL) was treated with DMAP (130 mg, 1.06 mmol, 0.10 equiv.) and TMSEOH (**SI-11**, 1.51 mL, 10.6 mmol, 1.00 equiv.). The solution was stirred under reflux for 17 h, cooled down, and washed with 1M HCl (3×100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and evaporated to dryness. The succinic ester **17** was used without further purification and was protected from light.

Yield: 2.05 g (9.39 mmol, 89%)

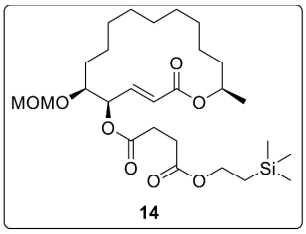
^{1}H NMR (500 MHz, $CDCl_3$): δ 11.45 (brs, 1H), 4.19 (m, 2H), 2.67 (m, 2H), 2.60 (m, 2H), 0.99 (m, 2H), 0.03 (m, 9H).

^{1}H NMR is in accordance with the literature.[3]

4.4 Synthesis of Berkeleylactones E and K (3, 4)



(5*R*,6*S*,16*R*,*E*)-6-(methoxymethoxy)-16-methyl-2-oxooxacyclohexadec-3-en-5-yl (2-(trimethylsilyl)ethyl) succinate (14)

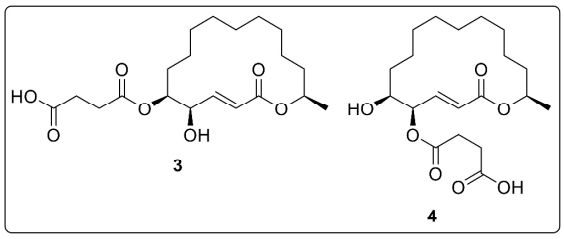


Carboxylic acid **17** (41.7 mg, 191 µmol, 1.25 equiv.) was added to a solution of alcohol **13** (50 mg, 152 µmol, 1.00 equiv.), DMAP (25.2 mg, 206 µmol, 1.35 equiv.) and EDC·HCl (39.5 mg, 206 µmol, 1.35 equiv.) in dry CH_2Cl_2 (2 mL) under argon atmosphere at room temperature. The solution was stirred for 17.5 h, poured into 0.25M HCl (15 mL) and extracted with EtOAc (3×15 mL). The combined organic phases were washed with 0.25M HCl (2×15 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated. The remainder was chromatographed (pentane/EtOAc 10:1) and ester **14** was obtained as colorless resin.

Yield: 80 mg (151 µmol, quant.)

R_f = 0.71 (hexanes/ethyl acetate 2:1, CAM); **$[\alpha]_D^{25}$** −22.3 (*c* 1.0, $CHCl_3$); **IR** (cm^{-1}) $\tilde{\nu}$ 2929, 2858, 1719, 1250, 1152, 1028; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.81 (dd, *J* = 15.9, 5.4 Hz, 1H), 5.98 (dd, *J* = 15.9, 1.6 Hz, 1H), 5.77 (dt, *J* = 5.4, 2.0 Hz, 1H), 5.03 (ddq, *J* = 9.0, 6.4, 2.8 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.59 (d, *J* – 7.2 Hz, 1H), 4.18 (m, 2H), 3.65 (m, 1H), 3.37 (s, 3H), 2.74 (m, 2H), 2.64 (m, 2H), 1.69-1.10 (m, 21H), 0.98 (m, 2H), 0.03 (m, 9H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 172.3, 171.6, 165.4, 142.2, 123.6, 95.6, 77.5, 73.6, 71.5, 63.2, 55.9, 35.9, 29.3, 29.3, 28.2, 27.7, 27.4, 27.3, 26.2, 26.0, 24.3, 23.5, 20.8, 17.4, −1.4; **HRMS** (ESI) *m/z* $[M+Na]^+$ calculated for $C_{27}H_{48}O_8SiNa$ 551.30107; found 551.30094.

Berkeleylactone E (3) and K (4)



Ester **14** (20 mg, 27.8 µmol, 1.00 equiv.) was solved in CH_2Cl_2 (2 mL) at 0 °C and TFA (1 mL) was slowly added. The solution was stirred for 1 h at 0 °C and further 3 h at room temperature. The mixture was coevaporated with PhMe (2×5 mL) and the residue chromatographed (SiO_2, CH_2Cl_2/MeOH+0.1% HCOOH 50:1). An isomeric mixture of Berkeleylactone E (**2**, 59%) and K (**3**, 31%) was obtained as colorless resin which was separable by HPLC.

Yield: 13 mg (mixture of two regioisomers, 33.8 µmol, 90%)

$\mathbf{R_f}$ = 0.37 (CH_2Cl_2/MeOH 9:1 + 0.1% HCOOH, CAM)

IR (cm^{-1}) $\tilde{\nu}$ 3445, 2929, 2857, 1713, 1660, 1266, 1161

3: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.89 (dd, *J* = 15.7, 4.9 Hz, 1H), 6.13 (dd, *J* = 15.7, 1.7 Hz, 1H), 5.03 (m, 1H), 4.87 (ddd, *J* = 7.6, 5.2, 2.3 Hz, 1H), 4.64 (dt, *J* = 4.8, 2.1 Hz, 1H), 2.80-2.57 (m, 4H), 1.76-1.09 (m, 21H); **^{1}H NMR** (500 MHz, [D_4]MeOD): δ 6.93 (dd, *J* = 15.7, 4.9 Hz, 1H), 6.10 (dd, *J* = 15.7, 1.9 Hz, 1H), 5.04 (m, 1H), 4.83 (ddd, *J* = 7.8, 5.0, 2.1 Hz, 1H), 4.56 (dt, *J* = 4.8, 2.0 Hz, 1H), 2.74-2.59 (m, 4H), 1.76-1.12 (m, 21H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 177.3, 172.0, 166.2, 144.8, 123.0, 76.9, 71.9, 71.4, 35.7, 29.4, 29.2, 28.0, 27.4, 27.2, 26.3, 26.2, 26.2, 24.0, 23.4, 20.6; **^{13}C{^{1}H} NMR** (125 MHz, [D_4]MeOD): δ 176.1, 174.0, 167.7, 148.2, 123.1, 77.6, 72.8, 72.4, 36.7, 30.3, 29.8, 29.1, 28.4, 28.2, 27.4, 27.3, 27.1, 25.1, 24.6, 20.8; **HRMS** (ESI) *m/z* $[M-H]^-$ calculated for $C_{20}H_{31}O_7$ 383.20643; found 383.20767.

4: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.83 (dd, *J* = 15.8, 5.6 Hz, 1H), 5.99 (dd, *J* = 15.8, 1.5 Hz, 1H), 5.63 (ddd, *J* = 5.5, 2.5, 1.7 Hz, 1H), 5.03 (m, 1H), 3.80 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1H), 2.80-2.57 (m, 4H), 1.76-1.09 (m, 21H); **^{1}H NMR** (500 MHz, [D_4]MeOD): δ 6.85 (dd, *J* = 15.9, 5.6 Hz, 1H), 5.99 (dd, *J* = 15.9, 1.7 Hz, 1H), 5.56 (dt, *J* = 5.3, 2.1 Hz, 1H), 5.03 (m, 1H), 3.72 (m, 1H), 2.74-2.59 (m, 4H), 1.76-1.12 (m, 21H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 177.0, 171.9, 165.5, 141.3, 124.0, 76.5, 73.1, 71.8, 35.7, 29.7, 29.3, 29.2, 28.0, 27.5, 27.3, 26.1, 26.0, 24.0, 23.1, 20.6; **^{13}C{^{1}H} NMR** (125 MHz, [D_4]MeOD): δ 176.1, 173.6, 167.2, 144.4, 123.1, 77.9, 73.3, 72.6, 36.7, 30.3, 30.1, 30.1, 29.7, 29.2, 28.4, 28.3, 27.2, 25.2, 24.5, 20.8; **HRMS** (ESI) *m/z* $[M-H]^-$ calculated for $C_{20}H_{31}O_7$ 383.20643; found 383.20755.

Column/method: Eurosphere II 100-3 C18 (150 x 4 mm), 45% MeCN, 1.5 mL/min, oven: 60 °C

Sample Information

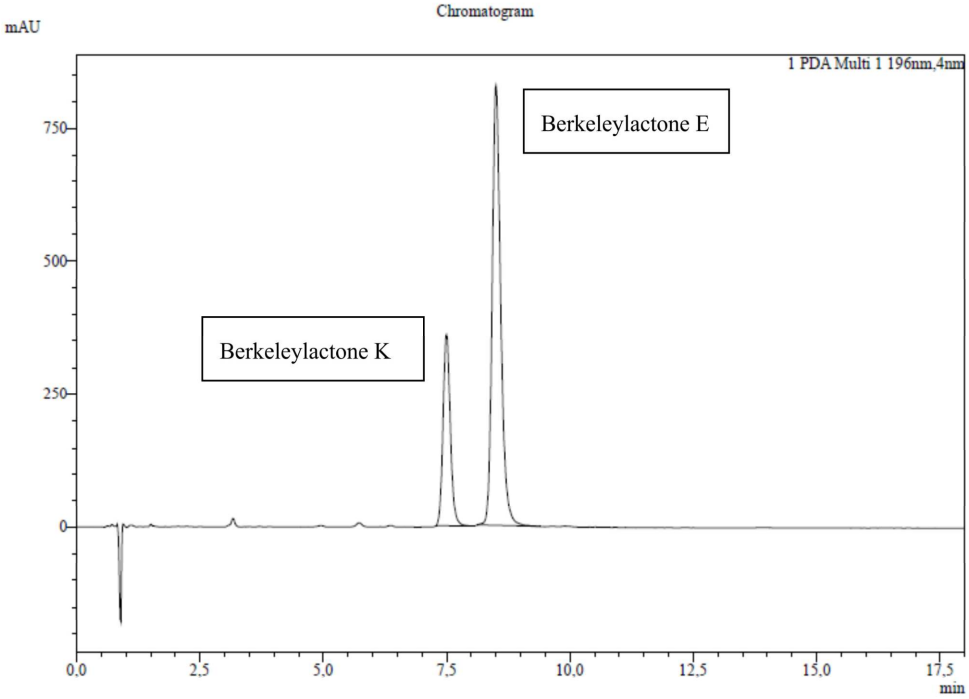
Sample Name	: MSc339_S2_F1
Injection Volume	: 15
Data File	: MSc339_S2_F1_06.10.2022_45_isokrat_60_15_15_001.lcd
Method File	: 45_isokrat_60_15_15.lcm
Batch File	: Oktober_2022.lcb
Month-Day Acquired	: 06.10.2022

Peak Table

PDA Ch1 196nm

Peak#	Ret. Time	Area	Height	Conc	Unit	Mark	Name
1	7.496	3714137	361172	0.000		M	
2	8.499	10008620	827914	0.000		M	
Total		13722756	1189086				

Chromatogram



Method

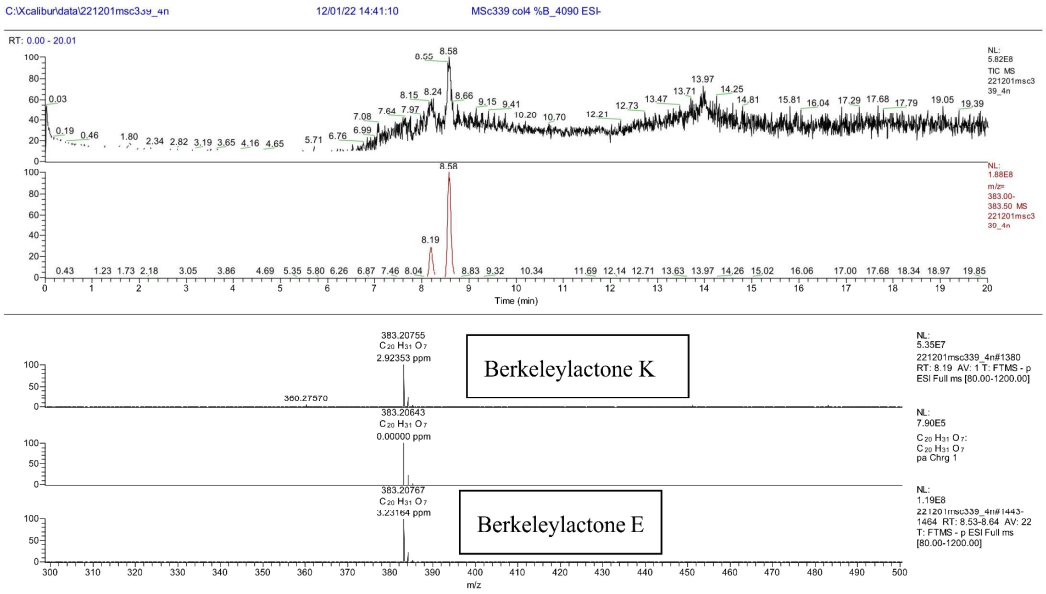
<<Pump>>

Mode	: Binary gradient
Pump A	: LC-20ADXR
Pump B	: LC-20ADXR
Total Flow	: 1,5000 mL/min
B Conc.	: 45,0 %
B Curve	: 0
PressMax	: 350 bar
PressMin	: 10 bar
Compressibility Setting	: Off

<<Oven>>

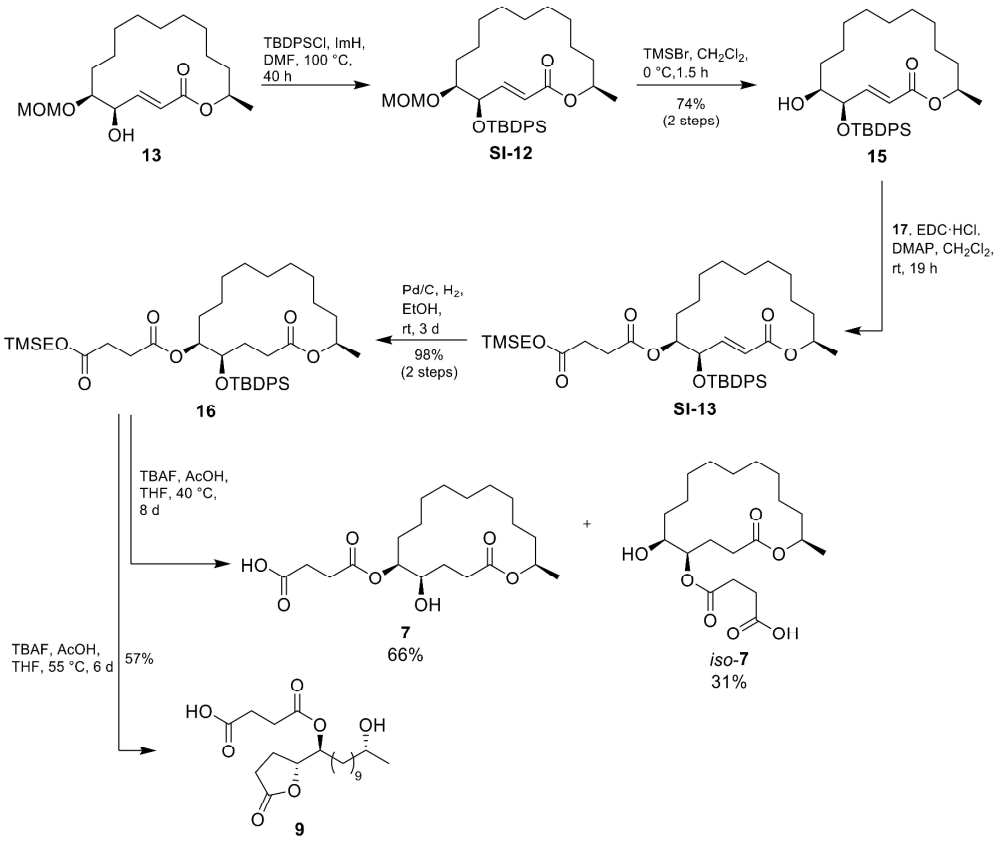
Oven Model	: CTO-20A
Oven Temperature	: 60 C

S13

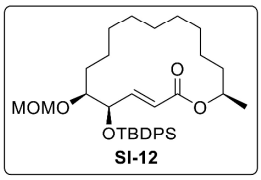

C:\Xcalibur\data\221201msc339_4n
12/01/22 14:41:10
MSc339 col4 %B_4090 ESI-
RT: 0.00 - 20.01
NL: 5.82E8 TIC MS 221201msc339_4n
NL: 1.88E8 m/z= 383.00-383.50 MS 221201msc339_4n
Time (min)

383.20755
C20 H31 O7
2.92353 ppm
Berkeleylactone K
383.20643
C20 H31 O7
0.00000 ppm
383.20767
C20 H31 O7
3.23164 ppm
Berkeleylactone E
NL: 5.35E7
221201msc339_4n#1380 RT: 8.19 AV: 1 T: FTMS - p ESI Full ms [80.00-1200.00]
NL: 7.90E5
C20 H31 O7:
C20 H31 O7
pa Chrg 1
NL: 1.19E8
221201msc339_4n#1443-1464 RT: 8.53-8.64 AV: 22 T: FTMS - p ESI Full ms [80.00-1200.00]
m/z

4.5 Synthesis of Berkeleylactone M (7)

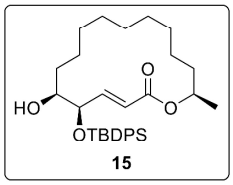


(5*R*,6*S*,16*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-6-hydroxy-16-methyloxacyclohexadec-3-en-2-one (15)



To a solution of alcohol **13** (200 mg, 609 µmol, 1.00 equiv.) and imidazole (187 mg, 2.74 mml, 4.50 equiv.) in dry DMF (6 mL) under argon atmosphere was added TBDPSCl (316 µL, 1.22 mmol, 2.00 equiv.). The solution was heated to 100 °C and after 15 h and 21 h was added further TBDPSCl (1. 31.6 µL, 122 µmol, 0.20 equiv., 2. 158 µL, 609 µmol, 1.00 equiv.). After additional stirring at 100 °C for 18.5 h the solvent was distilled off in vacuo. H_2O (20 ml) and EtOAc (20 mL) were added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic phases were washed with H_2O (2×20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated. The remainder was purified by silica gel chromatography (pentane/EtOAc 18:1 to 15:1). The silyl-ether **SI-12** was obtained as a mixture with TBDPSOH and used for the next step without further purification.

R_f = 0.64 (hexanes/ethyl acetate 5:1, CAM); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.74-7.31 (m, ArH), 6.76 (dd, *J* = 15.8, 6.2 Hz, 1H), 5.71 (m, 1H), 4.95 (ddq, *J* = 9.2, 6.4, 3.0 Hz, 1H), 4.53 (m, 1H), 4.38 (d, *J* = 7.1 Hz, 1H), 4.27 (d, *J* = 7.1 Hz, 1H), 3.39 (ddd, *J* = 8.2, 3.8, 1.8 Hz, 1H), 3.22 (s, 3H), 1.74-1.14 (m, 21H), 1.11 (s, 9H)



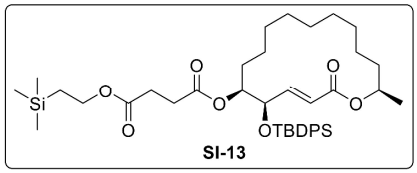
15

The crude silylether **SI-12** (609 µmol, 1.00 equiv.) was solved in dry CH_2Cl_2 (6 mL) at 0 °C under an argon atmosphere and treated with TMSBr (402 µL, 3.05 mmol, 5.00 equiv.). The solution was stirred at 0 °C for 1.5 h and sat. aq. $NaHCO_3$ (25 mL) was added. The mixture was extracted with EtOAc (3×40 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and evaporated. Silica gel chromatography (pentane/EtOAc 15:1 to 12:1) yielded pure alcohol **15** as colorless resin.

Yield: 236 mg (451 µmol, 74% over two steps)

R_f = 0.41 (hexanes/ethyl acetate 5:1, CAM); **$[\alpha]_D^{25}$** −65.6 (*c* 1.1, $CHCl_3$); **IR** (cm^{-1}) $\tilde{\nu}$ 3498, 2930, 2858, 1715, 1270, 1111; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.63 (m, 2H), 7.48-7.33 (m, 6H), 6.79 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.69 (dd, *J* = 15.8, 1.2 Hz, 1H), 4.93 (ddq, *J* = 9.5, 6.4, 3.2 Hz, 1H), 4.43 (ddd, *J* = 6.7, 2.7, 1.2 Hz, 1H), 3.46 (m, 1H), 2.07 (d, *J* = 6.2 Hz, 1H), 1.61-1.44 (m, 3H), 1.41-1.07 (m, 27H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 165.6, 145.2, 136.0, 135.9, 133.3, 133.0, 130.3, 130.2, 128.0, 127.8, 123.3, 76.2, 74.6, 71.4, 35.7, 29.6, 27.9, 27.5, 27.2, 25.9, 25.8, 23.7, 22.6, 20.5, 19.5; **HRMS** (ESI) *m/z* $[M-C_6H_5]^+$ calculated for $C_{26}H_{41}O_4Si$ 445.27686; found 445.27670.

(5*R*,6*S*,16*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-16-methyl-2-oxooxacyclohexadecan-6-yl (2-(trimethylsilyl)ethyl) succinate (16)

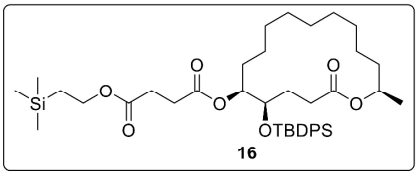


SI-13

To a solution of alcohol **15** (70 mg, 134 µmol, 1.00 equiv.), DMAP (32.7 mg, 268 µmol, 2.00 equiv.) and carboxylic acid **17** (58.5 mg, 268 µmol, 2.00 equiv.) in dry CH_2Cl_2 (1.5 mL) under argon atmosphere was added EDC·HCl (51.4 mg, 268 µmol, 2.00 equiv.). It was stirred at room temperature for 19 h and saturated NH_4Cl-solution (15mL) and H_2O (20mL) was added. The aqueous phase was extracted with EtOAc (4×15 mL) and the combined organic phases were washed wit 1M HCl (3×15 mL), $NaHCO_3$-solution (15 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated. The resinous ester (**SI-13**, quant.) was used without further purification.

R_f = 0.54 (hexanes/ethyl acetate 5:1, CAM); **IR** (cm^{-1}) $\tilde{\nu}$ 3421, 2929, 2858, 1725, 1257, 1099, 1036; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.1 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.47-7.30 (m, 6H), 6.75

(dd, *J* = 15.8,6.1 Hz, 1H), 5.78 (d, *J* = 15.8 Hz, 1H), 4.96 (m, 1H), 4.68 (m, 1H), 4.57 (d, *J* = 6.1 Hz, 1H), 4.16 (m, 2H), 2.56-2.35 (m, 3H), 2.27 (m, 1H), 1.76 (m, 1H), 1.66 (m, 1H), 1.55 (m, 2H), 1.38-1.18 (m, 15H), 1.10 (s, 9H), 0.98 (m, 2H), 0.04 (s, 9H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 172.4, 172.1, 165.6, 145.9, 136.1, 136.1, 133.5, 133.3, 130.0, 130.0, 127.7, 123.1, 76.8, 74.4, 71.3, 63.1, 35.9, 29.3, 29.1, 28.0, 27.3, 27.2, 27.1, 26.2, 26.0, 25.8, 24.2, 23.4, 20.8, 19.7, 17.4, 1.2, −1.4;



16

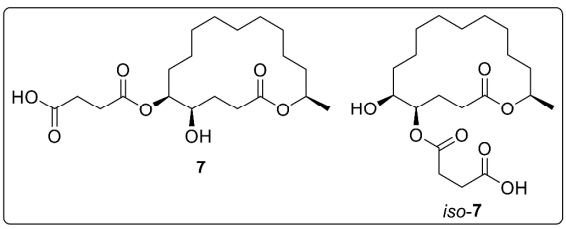
The crude ester **SI-13** (134 µmol, 1.00 equiv.) under argon atmosphere solved in EtOH (5 mL) was treated with Pd/C (10 wt%, 10.6 mg, 7.5 mol%). H_2 was bubbled through the suspension for 6 min and it was kept under a H_2-atmosphere (1 atm) for 3 d. The suspension was filtered through a pad of celite® and washed with MeOH (10 mL) and EtOAc (10 mL). The solvent was removed by rotary evaporation and the residue chromatographed (SiO_2, pentane/EtOAc 15:1). Alcohol **16** was obtained as colorless resin.

Yield: 95 mg (131 µmol, 98% over two steps)

R_f = 0.52 (hexanes/ethyl acetate 5:1, CAM); **[α]$_D^{25}$** −13.5 (*c* 1.0, $CHCl_3$); **IR** (cm^{-1}) $\tilde{\nu}$ 2931, 2858, 1734, 1250, 1157, 1111; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.45-7.33 (m, 6H), 4.81 (m, 1H), 4.74 (m, 1H), 4.18 (m, 2H), 3.81 (ddd, *J* = 6.9, 5.0, 1.9 Hz, 1H), 2.62-2.32 (m, 5H), 2.04 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H), 1.63 (m, 2H), 1.51 (m, 2H), 1.40-1.13 (m, 17H), 1.07 (s, 9H), 0.99 (m, 2H), 0.04 (s, 9H); 332 **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 172.8, 172.5, 172.0, 136.2, 136.0, 134.0, 133.3, 129.9, 129.9, 127.7, 127.7, 77.1, 73.3, 71.4, 63.0, 35.8, 32.0, 29.4, 27.4, 27.4, 27.1, 27.1, 26.1, 25.9, 23.8, 23.1, 20.5, 19.6, 17.4, 1.1, −1.4; **HRMS** (ESI) *m/z* $[M+Na]^+$ calculated for $C_{41}H_{64}O_7Si_2$ 747.40828; found 747.40751.

Berkeleylactone M (7) and *iso*-Berkeleylactone M (*iso*-7)

To a solution of silylether **16** (25 mg, 34.5 µmol, 1.00 eq) in dry THF (1 mL) under an argon atmosphere was added TBAF (1M THF, 103 µL, 103 µmol, 3.00 equiv.). The solution was stirred at room temperature for 3 h. Further TBAF (1M THF, 138 µmol, 138 µL, 4.00 eq.) and AcOH (15.8 µL, 276 µmol, 8.00 equiv.) were added and the solution stirred at 40 °C for 6 d. More TBAF (1M THF, 34.5 µmol, 34.5 µL, 1.00 equiv.) and AcOH (2.9 µL, 34.5 µmol, 1.00 eq.) is added, the solution stirred for two more days at 40 °C and treated with 1M HCl (5 mL). The



7 *iso*-**7**

aqueous phase was extracted with EtOAc (4×10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and evaporated to dryness. The crude mixture was separated by silica column chromatography (SiO_2, CH_2Cl_2/MeOH+0.05% HCOOH 100:1 to 60:1).

Yield: **7** 8.8 mg (22.8 µmol, 66%)

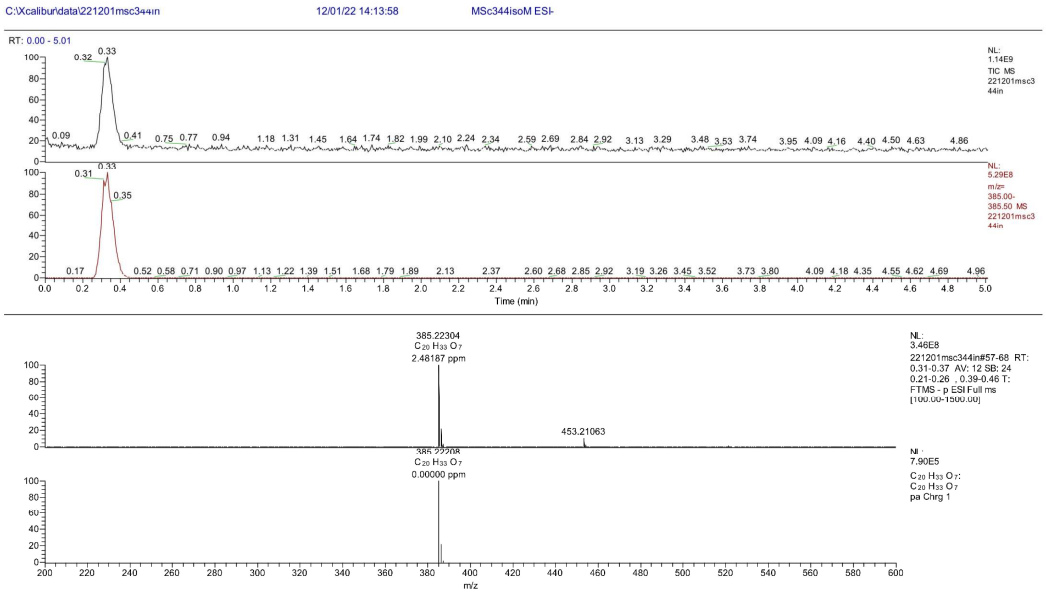
iso-**7** 4.1 mg (10.6 µmol, 31%)

7: $\mathbf{R_f}$ = 0.49 (CH_2Cl_2/MeOH 9:1+0.1% HCOOH, CAM); $\mathbf{[\alpha]_D^{25}}$ −1.5 (*c* 0.1, MeOH); Lit.[1] $\mathbf{[\alpha]_D^{25}}$ +15.7 (*c* 0.1, MeOH); **IR** (cm^{-1}) $\tilde{\nu}$ 3463, 2929, 2858, 1729, 1261, 1164; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.95 (dt, *J* = 6.4, 2.5 Hz, 1H), 4.91 (m, 1H), 3.84 (m, 1H), 3.64-1.76 (brs, O*H*, COO*H*), 2.79-2.55 (m, 5H), 2.38 (dt, *J* = 14.6, 8.0 Hz, 1H), 1.85 (d, *J* = 7.6 Hz, 1H), 1.82 (d, *J* = 7.7 Hz, 1H), 1.65 (m, 1H), 1.54 (m, 3H), 1.45-1.21 (m, 20H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 175.8, 173.1, 172.3, 77.7, 71.6, 71.0, 35.9, 32.0, 29.5, 29.3, 28.0, 27.5, 27.3, 26.9, 26.0, 25.8, 24.0, 23.1, 20.5; **HRMS** (ESI) *m/z* $[M-H]^-$ calculated for $C_{20}H_{32}O_7$ 385.22208; found 385.22338.

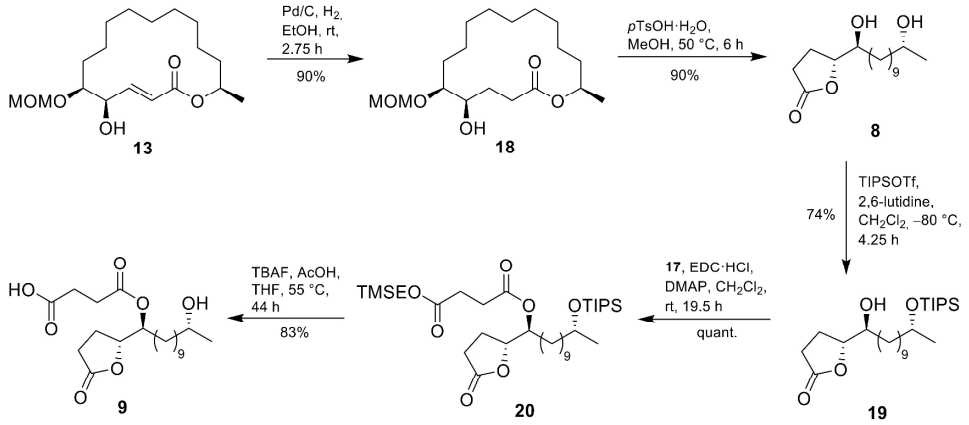
The specific rotations of the isolated and synthetic berkeleylactone M (**7**) differed slightly, with the negative one of our synthetic sample better matching those of the other known, structurally related berkeleylactones and A26771B. The other analytical data is in full accordance with the literature (*cf.* tables SI-2, SI-4).

Iso-**7**: $\mathbf{R_f}$ = 0.56 (CH_2Cl_2/MeOH 9:1+0.1% HCOOH, CAM); $\mathbf{[\alpha]_D^{25}}$ −3.8 (*c* 0.1, MeOH); **IR** (cm^{-1}) $\tilde{\nu}$ 3456, 2928, 2856, 1732, 1261, 1164; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.93 (m, 2H), 3.76 (m, 1H), 3.66-2.79 (brs, 2H), 2.72 (m, 2H), 2.64 (m, 2H), 2.51 (dt, *J* = 16.0, 7.0 Hz, 1H), 2.30 (dt, *J* = 16.0, 7.3 Hz, 1H), 2.14 (m, 1H), 1.91 (ddt, *J* = 14.8, 7.4, 3.7 Hz, 1H), 1.61-1.19 (m, 24H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 175.9, 173.3, 171.9, 76.1, 71.7, 70.7, 35.7, 31.2, 30.5, 29.9, 29.5, 29.1, 27.2, 27.2, 27.0, 26.3, 26.0, 24.1, 23.2, 23.0, 20.5; **HRMS** (ESI) *m/z* $[M-H]^-$ calculated for $C_{20}H_{32}O_7$ 385.22208; found 385.22304.

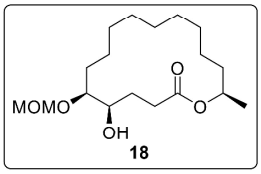
Iso-Berkeleylactone M (**7**): negative ESI mode



4.6 Synthesis of Berkeley-γ-lactones N and O (8, 9)



(5*R*,6*S*,16*R*)-5-hydroxy-6-(methoxymethoxy)-16-methyloxacyclohexadecan-2-one (18)



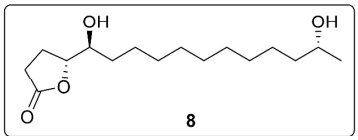
To a solution of vinyl alcohol **13** (150 mg, 457 µmol, 1.00 equiv.) in EtOH (9 mL) under argon atmosphere was added Pd/C (10%, 24.3 mg, 22.8 µmol, 0.05 equiv.). H_2 was bubbled through the suspension for 7 min and it was stirred under H_2-atmosphere (balloon, 1 atm) for 2.75 h. EtOAc (15 mL) was added and the suspension was filtered through a pad of celite®. The solvent was removed by rotary

evaporation and the residue chromatographed (SiO_2, pentane/EtOAc 5:1 to 2:1). Alcohol **18** was obtained as a colorless solid.

Yield: 135 mg (409 µmol, 90%)

R_f = 0.38 (hexanes/ethyl acetate 2:1, CAM); **$[\alpha]_D^{25}$** +20.7 (*c* 1.0, $CHCl_3$); **mp** 63.7 °C, **IR** (cm^{-1}) $\tilde{\nu}$ 3425, 2930, 2858, 1724, 1260, 1101, 1039; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.88 (m, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 3.68 (m, 1H), 3.57 (dt, *J* = 6.3, 2.6 Hz, 1H), 3.39 (s, 3H), 2.81 (d, *J* = 7.0 Hz, 1H), 2.58 (dt, *J* = 14.5, 7.1 Hz, 1H), 2.37 (dt, *J* = 14.6, 8.2 Hz, 1H), 1.77 (m, 2H), 1.62-1.14 (m, 21H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 173.2, 96.9, 82.9, 71.3, 71.2, 55.8, 35.8, 32.2, 29.5, 27.4, 27.4, 27.2, 27.1, 25.9, 25.7, 23.9, 23.3, 20.4; **HRMS** (ESI) *m/z* $[M+Na]^+$ calculated for $C_{18}H_{34}O_5Na$ 353.22985; found 353.22944.

Berkeley-γ-lactone N (8)

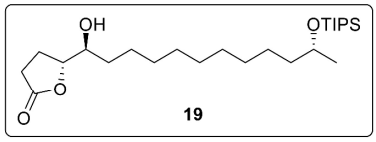


*p*TsOH·H_2O (1 mg, 5.45 µmol, 0.10 equiv.) was added to a solution of macrolide **18** (18 mg, 54.5 µmol, 1.00 equiv.) in MeOH (1 mL). The solution was stirred at 50 °C for 6 h until full conversion (TLC). The solvent was evaporated, and the remainder purified by silica gel chromatography (pentane/EtOAc 3:2 to 1:1). Berkeley-γ-lactone N (**8**) was obtained as a colorless solid.

Yield: 14 mg (409 µmol, 90%)

R_f – 0.33 (hexanes/ethyl acetate 1:2, CAM); **$[\alpha]_D^{25}$** −16.5 (*c* 1.0, MeOH); Lit.[1] **$[\alpha]_D^{25}$** −11.6 (*c* 0.43, MeOH); **mp** 89.2 °C; **IR** (cm^{-1}) $\tilde{\nu}$ 3401, 3279, 2915, 2849, 1777, 1749, 1210; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.44 (dt, *J* = 7.4, 3.3 Hz, 1H), 3.93 (m, 1H), 3.79 (m, 1H), 2.60 (ddd, *J* = 17.8, 10.0, 5.0 Hz, 1H), 2.52 (ddd, *J* = 17.8, 9.8, 8.8 Hz, 1H), 2.26 (m, 1H), 2.14 (dddd, *J* = 12.6, 9.9, 7.4, 5.1 Hz, 1H), 1.86 (m, 1H), 1.55-1.24 (m, 19H), 1.19 (d, *J* 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 177.7, 83.0, 71.4, 68.3, 39.4, 32.0, 29.7, 29.6, 29.6, 29.6, 29.5, 28.9, 25.8, 25.7, 25.6, 23.6, 21.2; **HRMS** (ESI) *m/z* $[M-OH]^+$ calculated for $C_{16}H_{29}O_3$ 269.21112; found 269.21092.

(*R*)-5-((1*S*,11*R*)-1-hydroxy-11-((triisopropylsilyl)oxy)dodecyl)dihydrofuran-2(3*H*)-one (19)



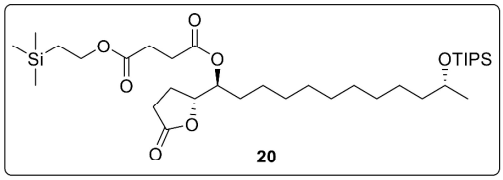
19

To a solution of diol **8** (50 mg, 175 µmol, 1.00 equiv.) in dry CH_2Cl_2 (4 mL) at −80 °C under argon atmosphere were added 2,6-lutidin (93.1 µL, 800 µmol, 4.57 equiv.) and TIPSOTf (80.6 µL, 300 µL, 1.71 equiv.). The solution was stirred at −80 °C for 4.25 h (80% conversion) and sat. aq. NH_4Cl (40 mL) was added. The mixture was extracted with EtOAc (3×20 mL) and the combined organic phases were washed with sat. aq. $CuSO_4$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated to dryness. After silica gel chromatography (pentane/EtOAc 3:1) the mono-TIPS-protected diol **19** was obtained as a colorless resin.

Yield: 57 mg (129 µmol, 74%)

R_f = 0.76 (hexanes/ethyl acetate 1:1, CAM); **$[\alpha]_D^{25}$** −6.5 (*c* 1.0, $CHCl_3$); **IR** (cm^{-1}) $\tilde{\nu}$ 3448, 2926, 2864, 1773, 1463, 1057, 1013; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.44 (dt, *J* = 7.4, 3.3 Hz, 1H), 3.93 (m, 1H), 3.90 (m, 1H), 2.60 (ddd, *J* = 17.8, 10.0, 5.0 Hz, 1H), 2.52 (ddd, *J* = 17.8, 9.9, 8.7 Hz, 1H), 2.27 (m, 1H), 2.14 (dddd, *J* = 12.6, 9.9, 7.4, 5.1 Hz, 1H), 1.95 (m, 1H), 1.58-1.21 (m, 19H), 1.14 (d, *J* 6.1 Hz, 3H), 1.05 (s, 21H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 177.6, 82.9, 71.5, 68.7, 40.1, 32.0, 30.0, 29.7, 29.7, 29.6, 28.9, 25.8, 25.5, 23.6, 21.2, 18.3, 18.3, 12.6; **HRMS** (ESI) *m/z* $[M+H]^+$ calculated for $C_{25}H_{51}O_4Si$ 443.35511; found 443.35469.

(1*S*,11*R*)-1-((*R*)-5-oxotetrahydrofuran-2-yl)-11-((triisopropylsilyl)oxy)dodecyl (2-(trimethylsilyl)ethyl) succinate (20)



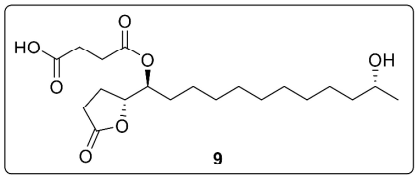
20

Carboxylic acid **17** (39.5 mg, 181 µmol, 2.00 equiv.) was added to a solution of alcohol **19** (40 mg, 90.3 µmol, 1.00 equiv.), DMAP (23.2 mg, 190 µmol, 2.10 equiv.) and EDC·HCl (36.4 mg, 190 µmol, 2.10 equiv.) in dry CH_2Cl_2 (2 mL) under argon atmosphere at room temperature. The solution was stirred for 19.5 h and sat. aq. NH_4Cl (5 mL) was added. The emulsion was poured into 1M aqueous citric acid (20 mL) and extracted with EtOAc (3×15 mL). The combined organic phases were washed with 1M citric acid (10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated. The remainder was chromatographed (pentane/EtOAc 5:1 to 2:1) and ester **20** was obtained as a colorless resin.

Yield: 58 mg (90.2 µmol, quant.)

R_f = 0.37 (hexanes/ethyl acetate 3:1, CAM); **$[\alpha]_D^{25}$** −14.2 (*c* 1.1, $CHCl_3$); **IR** (cm ^{1}) $\tilde{\nu}$ 2927, 2865, 1785, 1736, 1251, 1154, 1060; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.09 (dt, *J* = 7.9, 5.0 Hz, 1H), 4.52 (dt, *J* = 7.1, 4.9 Hz, 1H), 4.17 (m, 2H), 3.90 (sex, *J* = 6.0 Hz, 1H), 2.68-2.46 (m, 6H), 2.26 (dddd, *J* = 13.2 9.7, 7.5, 5.8 Hz, 1H), 2.12 (dddd, *J* = 13.1, 9.9, 8.1, 6.9 Hz, 1H), 1.60 (m, 2H), 1.49 (m, 1H), 1.43-1.21 (m, 16H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 21H), 0.98 (m, 2H), 0.00 (s, 12H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 176.7, 172.4, 171.9, 80.1, 74.1, 68.7, 63.2, 40.1, 30.3, 30.0, 29.8, 29.8, 29.6, 29.6, 29.3, 29.3, 28.2, 25.5, 25.2, 23.6, 23.2, 18.3, 18.3, 17.4, 12.6, −1.4; **HRMS** (ESI) *m/z* $[M+Na]^+$ calculated for $C_{34}H_{66}O_7Si_2Na$ 665.42393; found 665.42369.

Berkeley-γ-lactone O (9)



9

A solution of ester **20** (20 mg, 31.1 µmol, 1.00 equiv.) in dry THF (1.5 mL) under argon atmosphere was treated with TBAF (1M THF, 77.8 µL, 77.8 µmol, 2.50 equiv.) at room temperature. The solution was stirred for 7 h at room temperature and TBAF (1M THF, 31.1 µL, 31.1 µmol, 1.00 equiv.) and AcOH (6.23 µL, 109 µmol, 3.50 equiv.) were added. After 11.5 h the mixture was heated to 50 °C and after a further 7.5 h additional TBAF (187 µL, 187 µmol, 6.00 equiv.) and AcOH (10.6 µL, 187 µmol, 6.00 equiv.) were added. After 18 h stirring at 50 °C the solution was cooled to room temperature and treated with 0.5M HCl (1 mL) for 30 min. The suspension was poured into 0.5M HCl (10 mL) and extracted with EtOAc (4×15 mL). The combined organic phases were washed with 1M HCl (2×10 mL), dried over Na_2SO_4 and evaporated to dryness. Berkeley-γ-lactone O (**9**) was obtained as a colorless oil after silica gel chromatography (CH_2Cl_2/MeOH+0.1% HCOOH 60:1 to 20:1).

Yield: 10 mg (25.9 µmol, 83%)

R_f = 0.33 (CH_2Cl_2/MeOH 9:1 + 0.1% HCOOH, CAM); **$[\alpha]_D^{25}$** −10.6 (*c* 0.7, MeOH); Lit.[1] **$[\alpha]_D^{25}$** −16.3 (*c* 0.48, MeOH); **IR** (cm^{-1}) $\tilde{\nu}$ 3421, 2926, 2855, 2608, 1778, 1734, 1156; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.97-4.65 (brs, 2H), 5.13 (dt, *J* = 8.4, 4.7 Hz, 1H), 4.52 (dt, *J* = 7.2, 4.6 Hz, 1H), 3.82 (m, 1H), 2.75-2.46 (m, 6H), 2.26 (dddd, *J* = 13.2 9.7, 7.6, 5.7 Hz, 1H), 2.13 (dddd, *J* = 13.1, 9.9, 8.2, 7.0 Hz, 1H), 1.59 (m, 2H), 1.50-1.23 (m, 18H), 1.18 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ 177.0, 176.3, 171.8, 80.3, 74.0, 68.5, 39.2, 30.2, 29.4, 29.3 (2 signals), 29.1, 29.1, 28.8, 28.2 (2 signals), 25.6, 25.1, 23.5, 23.0; **HRMS** (ESI) *m/z* $[M+H]^+$ calculated for $C_{20}H_{35}O_7$ 387.23773; found 387.23745.

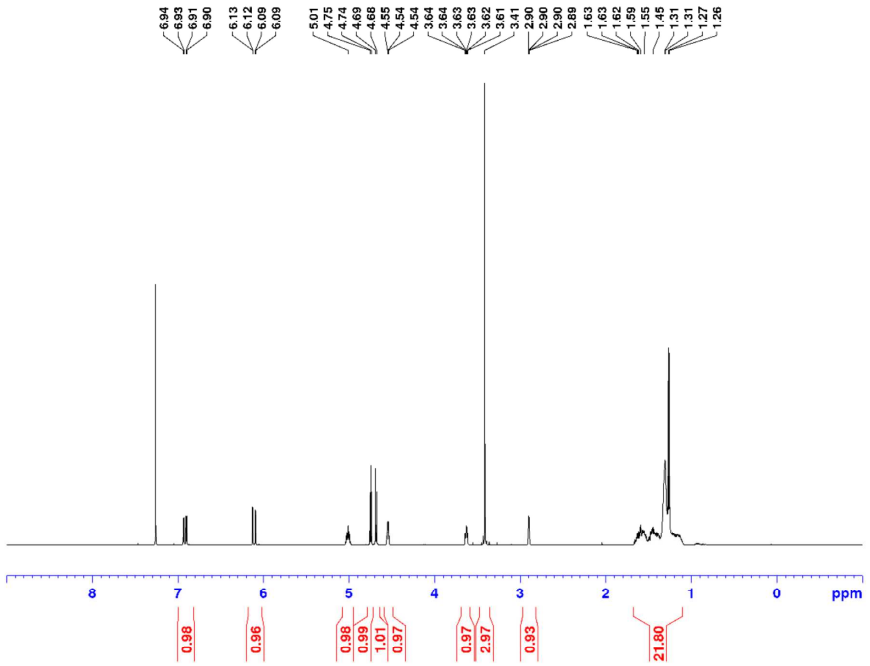
5 References

(1) Stierle, A. A.; Stierle, D. B.; Alverson, J.; Gibson, N. Berkeleylactones and a Citreohybriddione Analogue from Penicillium turbatum. *J. Nat. Prod.* **2021**, *84* (12), 3064–3070. DOI: 10.1021/acs.jnatprod.1c00791

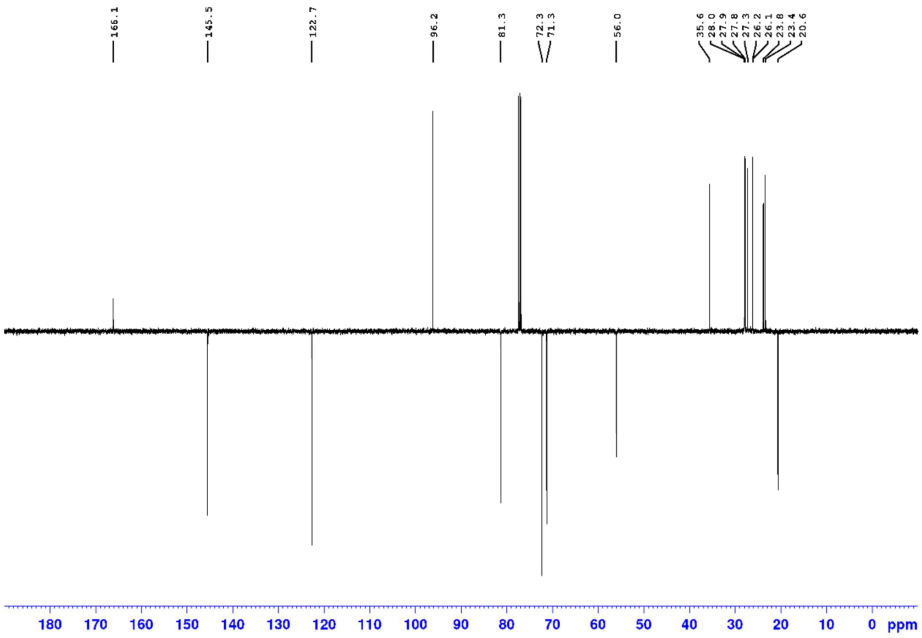
(2) Stierle, A. A.; Stierle, D. B.; Decato, D.; Priestley, N. D.; Alverson, J. B.; Hoody, J.; McGrath, K.; Klepacki, D. The Berkeleylactones, Antibiotic Macrolides from Fungal Coculture. *J. Nat. Prod.* **2017**, *80* (4), 1150–1160. DOI: 10.1021/acs.jnatprod.7b00133

(3) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. Total Synthesis of the Epidermal Growth Factor Inhibitor (−)-Reveromycin B. *J. Org. Chem.* **2001**, *66* (7), 2382–2393. DOI: 10.1021/jo001646c

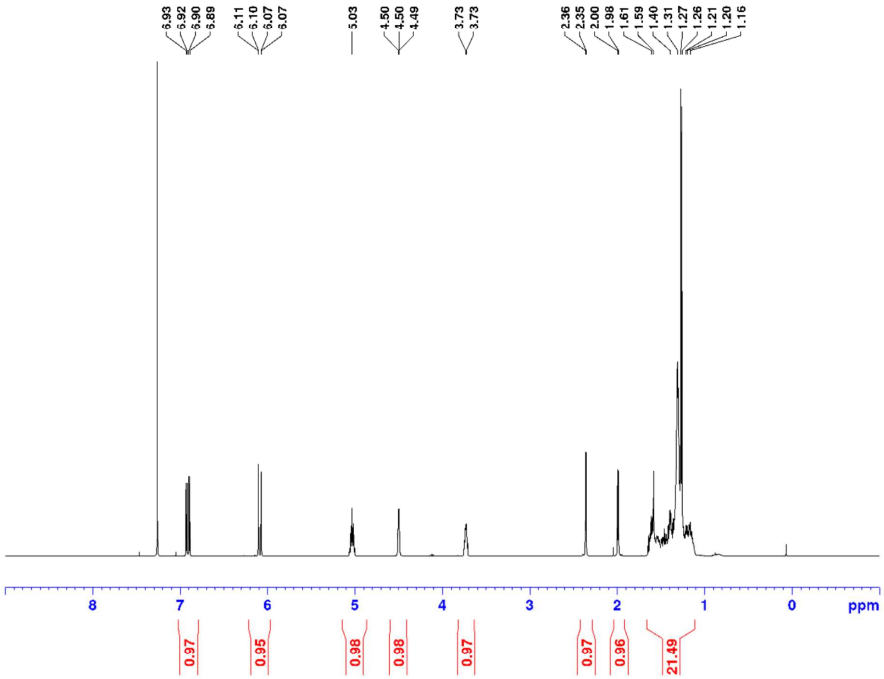
6 NMR-spectra



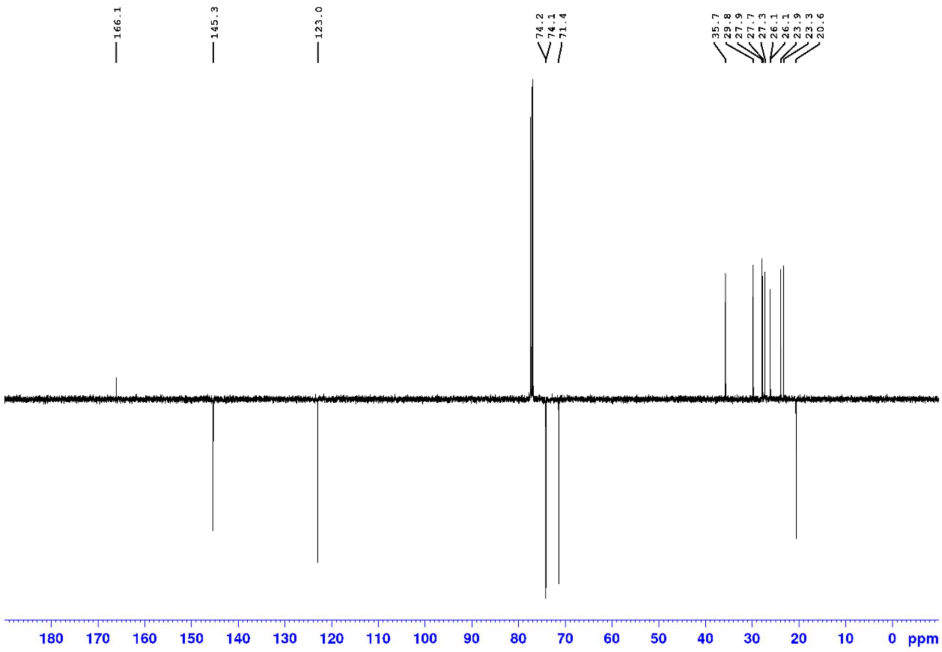
^{1}H NMR spectrum of compound **13** in $CDCl_3$.



^{13}C NMR spectrum of compound **13** in $CDCl_3$.

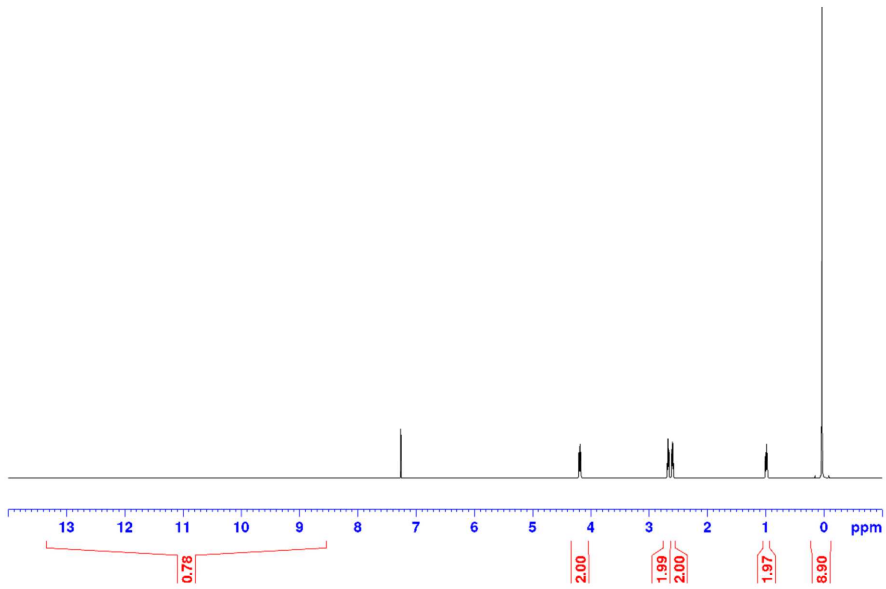


^{1}H NMR spectrum of compound **2** in $CDCl_3$.

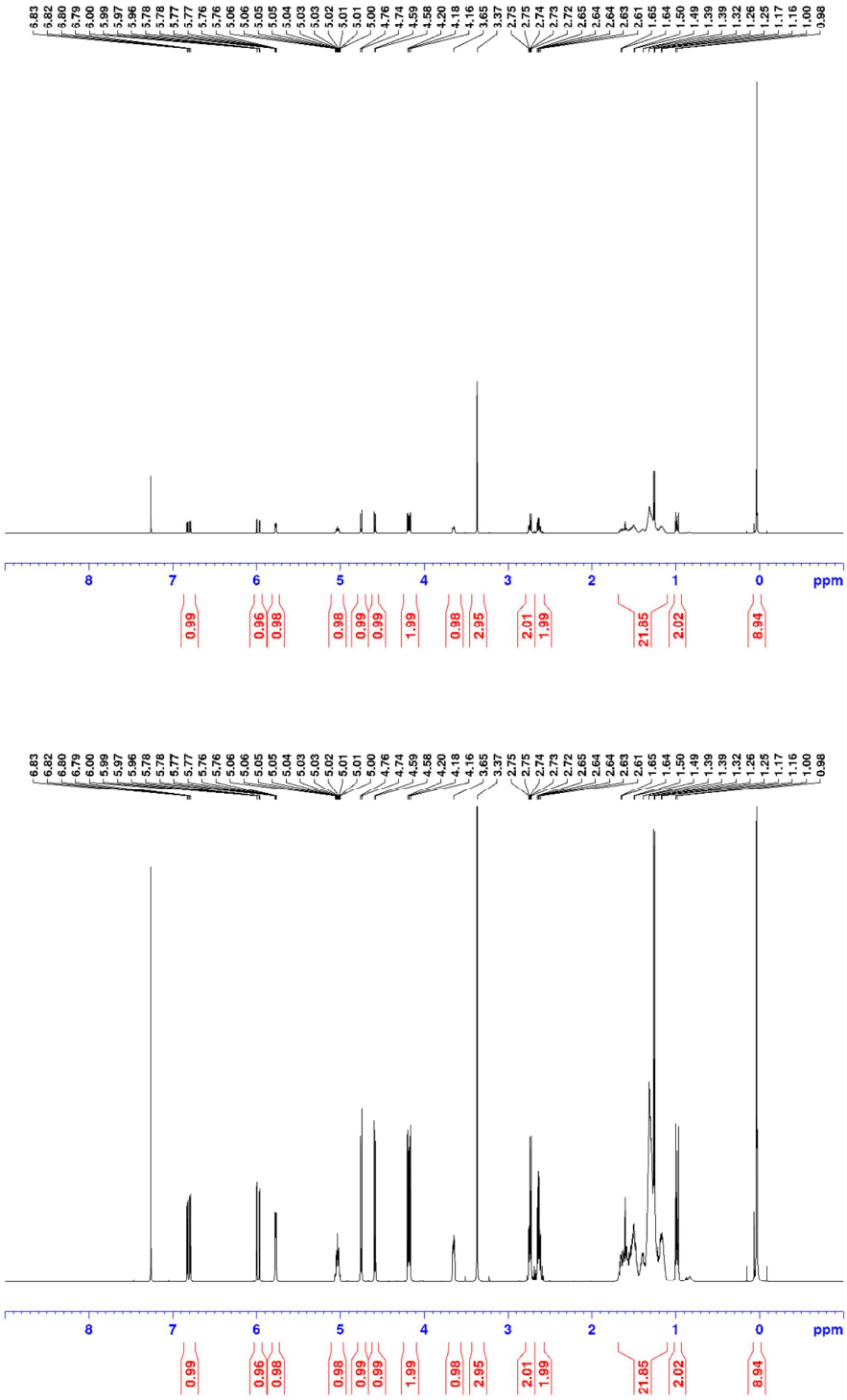


^{13}C NMR spectrum of compound **2** in $CDCl_3$.

S25

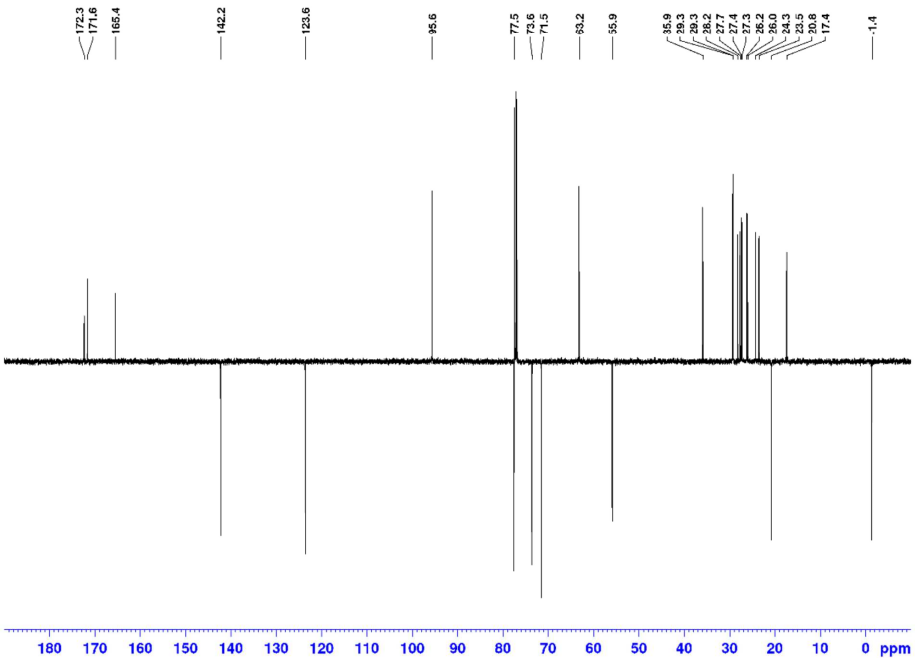


^{1}H NMR spectrum of compound **17** in $CDCl_3$.

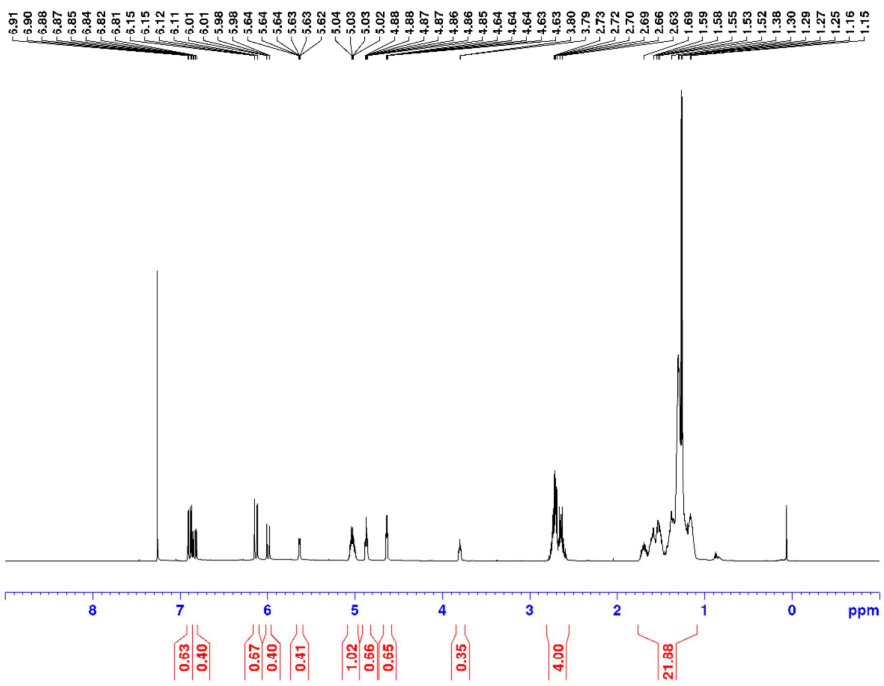


[1]H NMR spectra of compound **14** in $CDCl_3$.

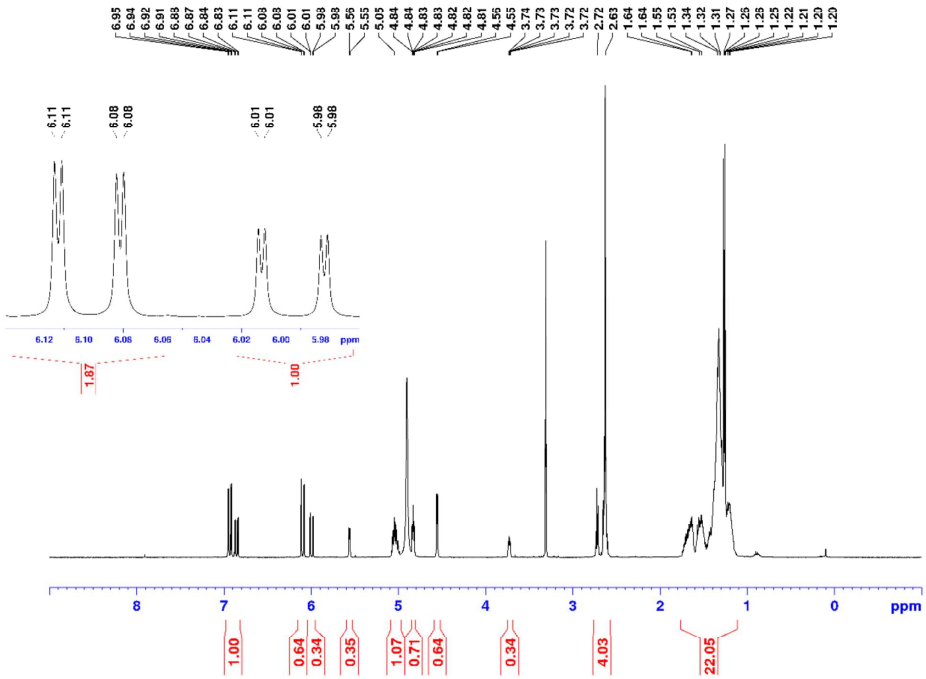
S27



^{13}C NMR spectrum of compound **14** in $CDCl_3$.

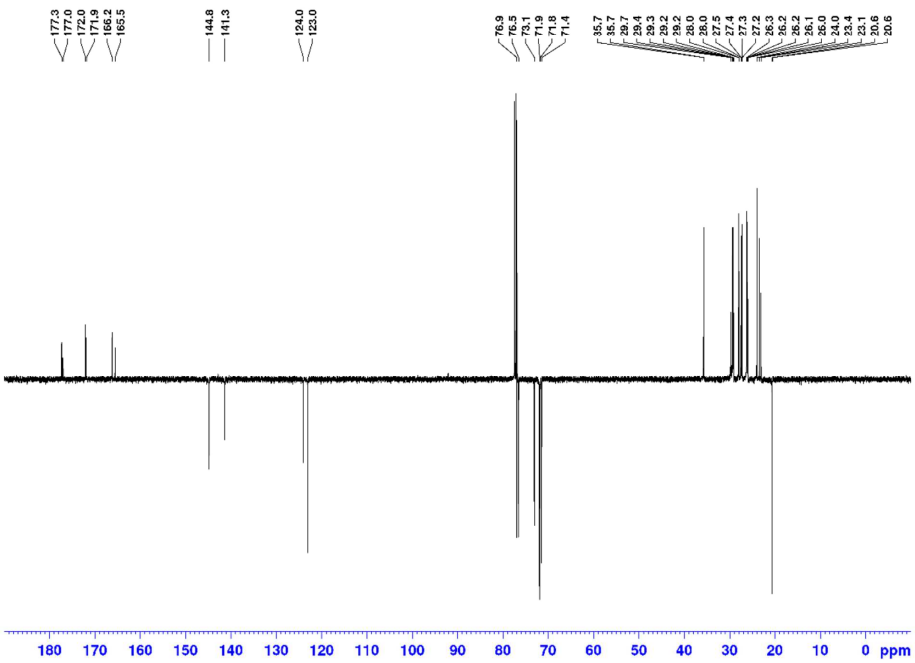


^{1}H NMR spectrum of compound **3/4** in $CDCl_3$.

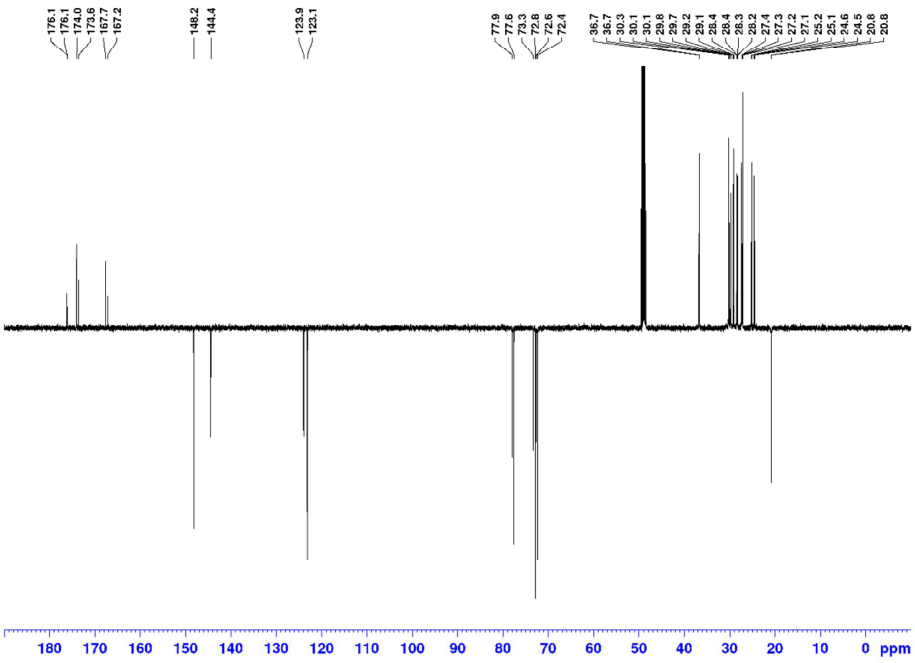


^{1}H NMR spectrum of compound **3/4** in MeOD.

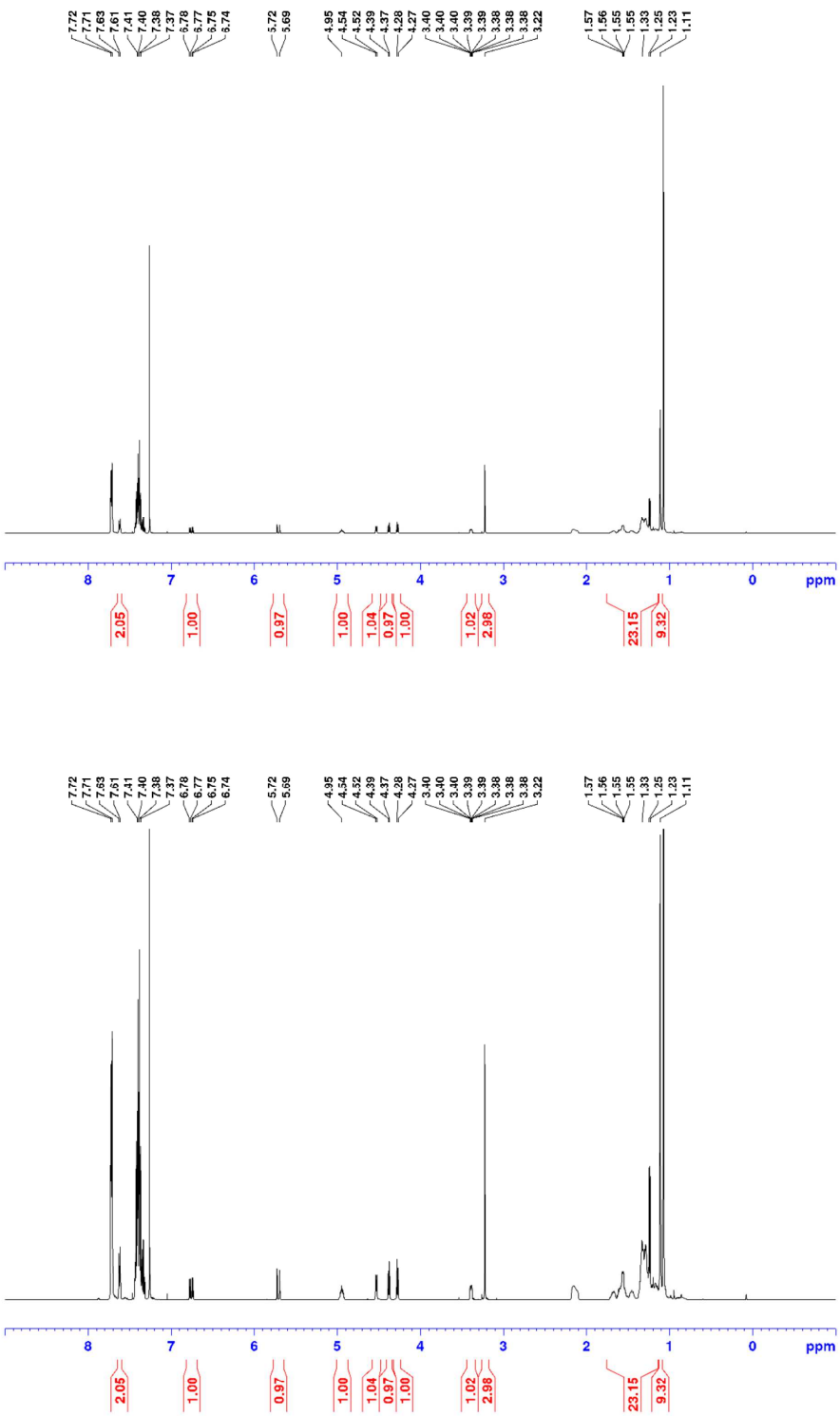
S29



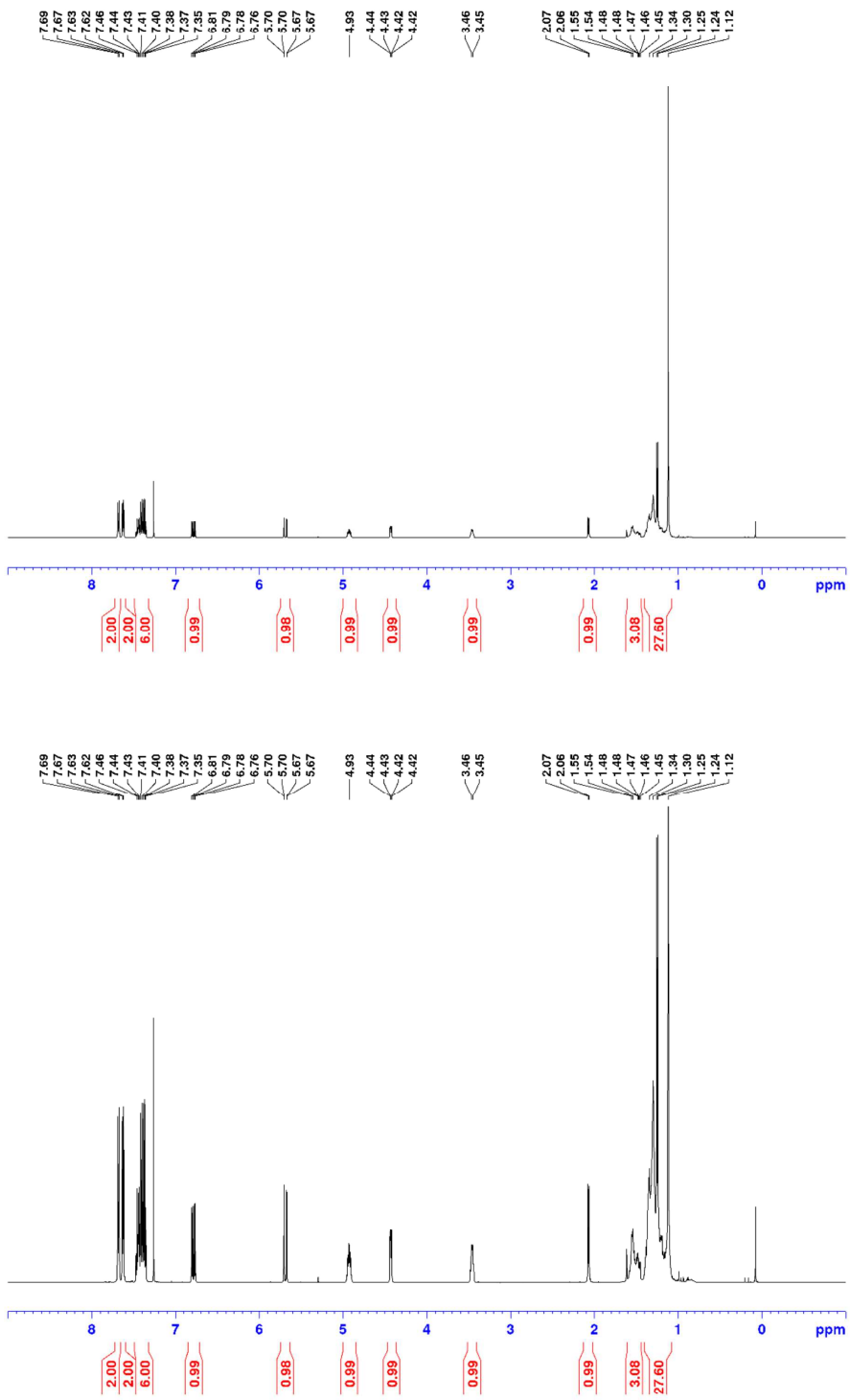
^{13}C NMR spectrum of compound **3/4** in $CDCl_3$.



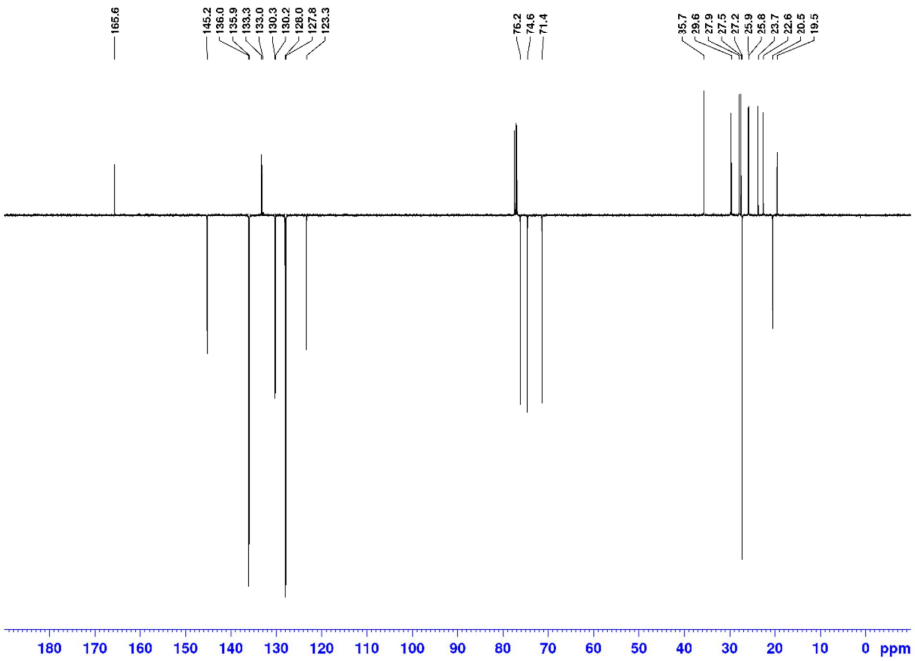
^{13}C NMR spectrum of compound **3/4** in MeOD.



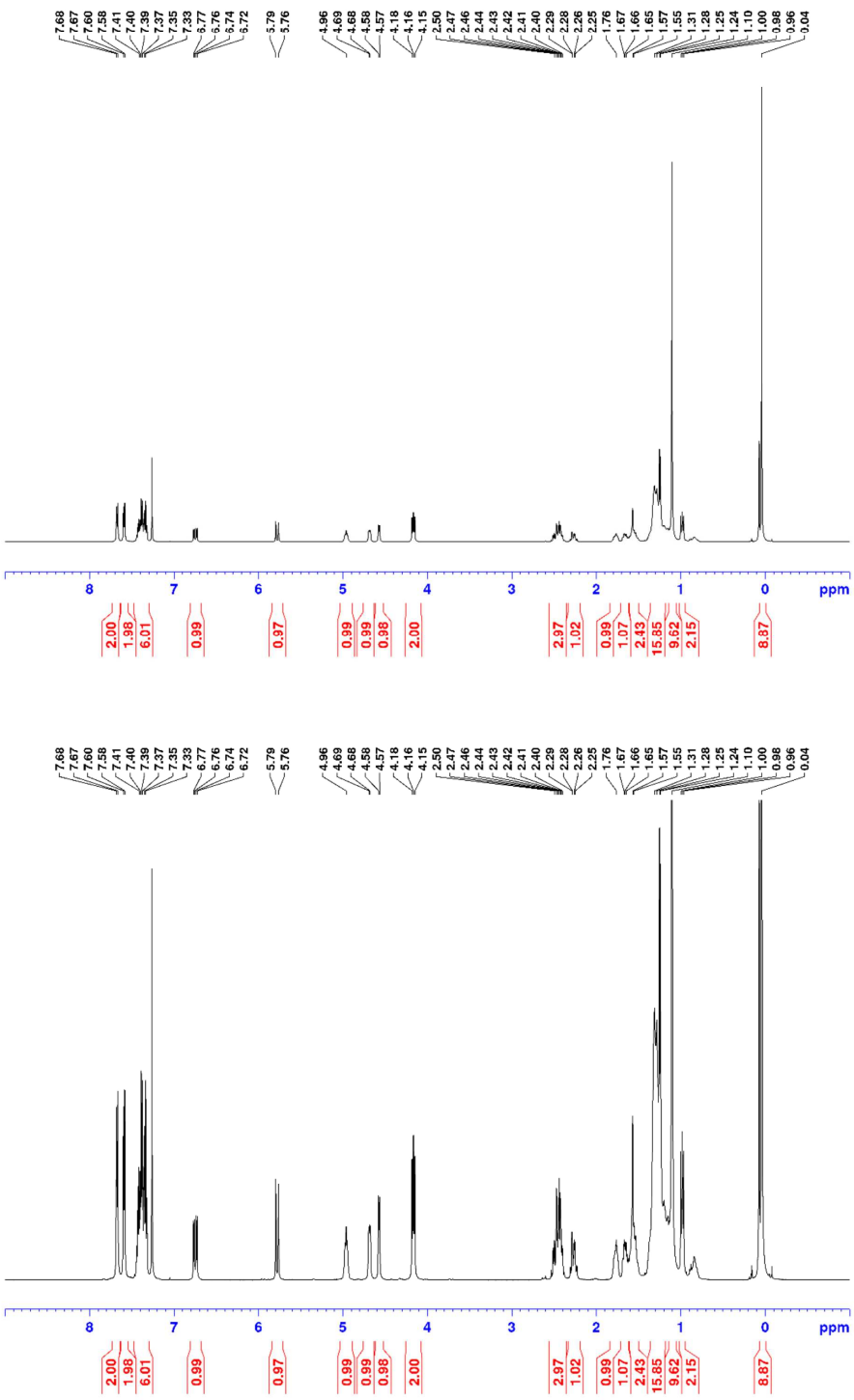
^{1}H NMR spectra of compound **SI-12** in $CDCl_3$.



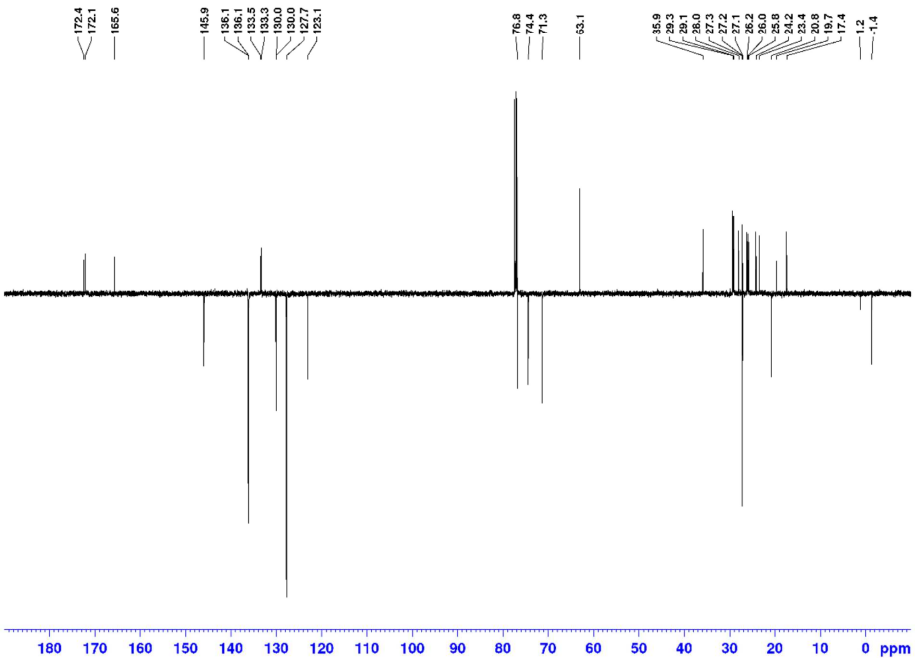
^{1}H NMR spectra of compound **15** in $CDCl_3$.



^{13}C NMR spectrum of compound **15** in $CDCl_3$.

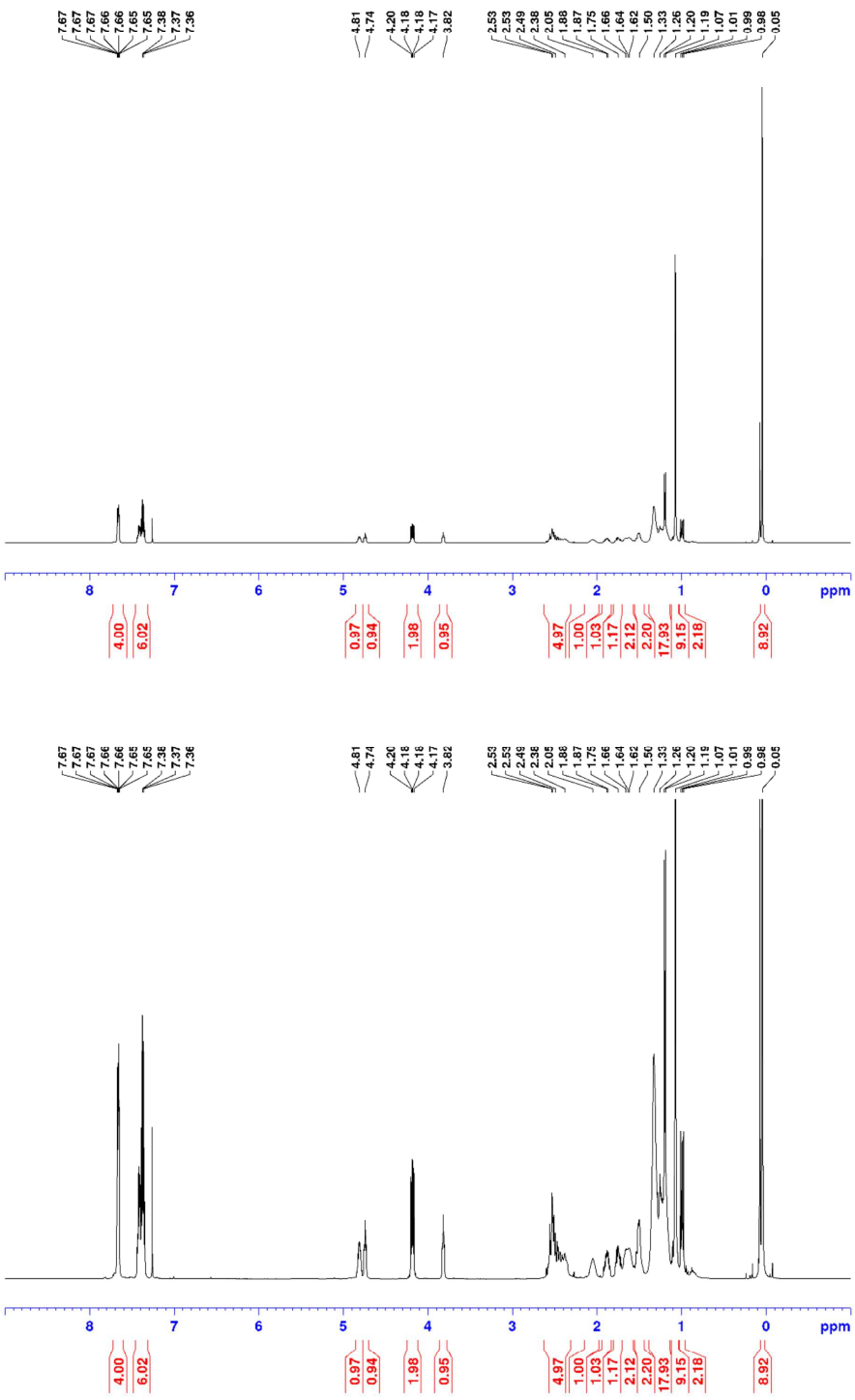


^{1}H NMR spectra of compound **SI-13** in $CDCl_3$.



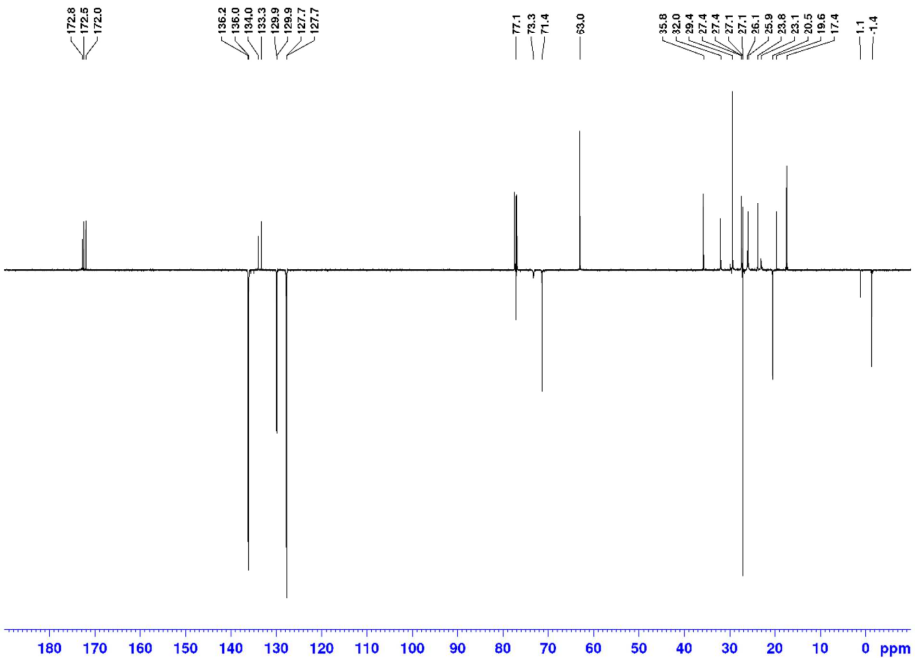
^{13}C NMR spectrum of compound **SI-13** in $CDCl_3$.

S35

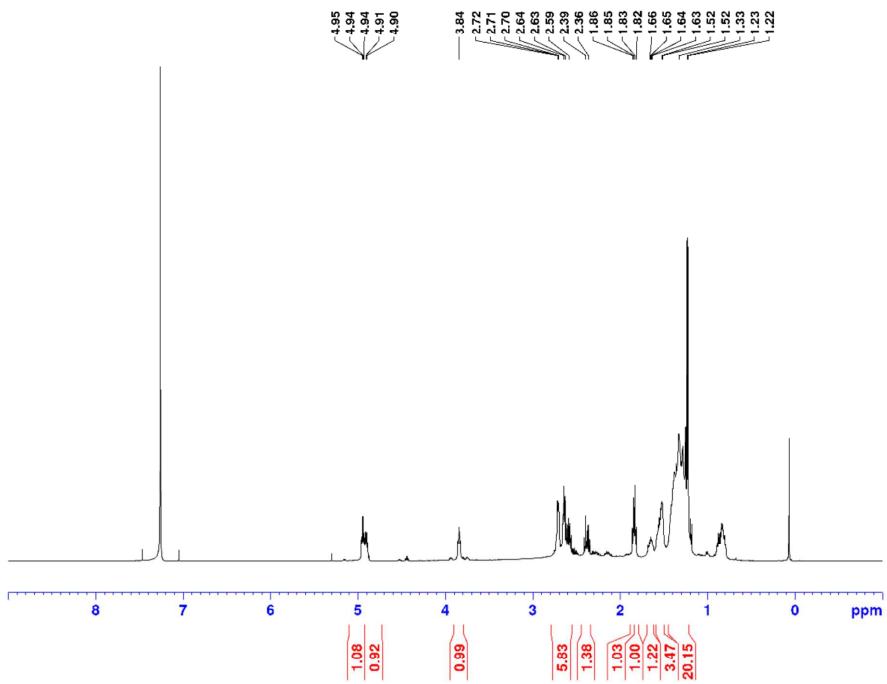


[1]H NMR spectra of compound **16** in $CDCl_3$.

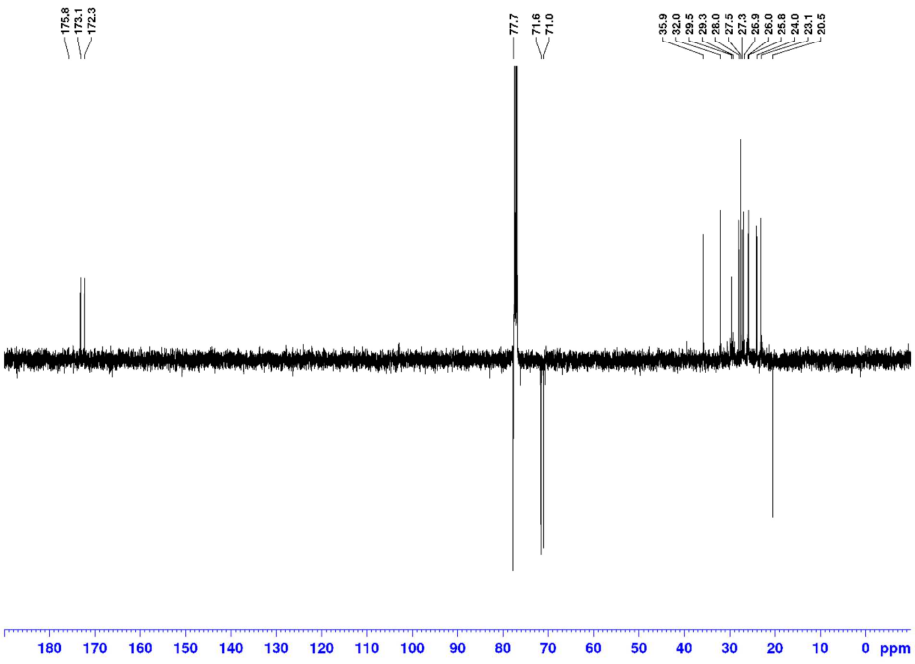
S36



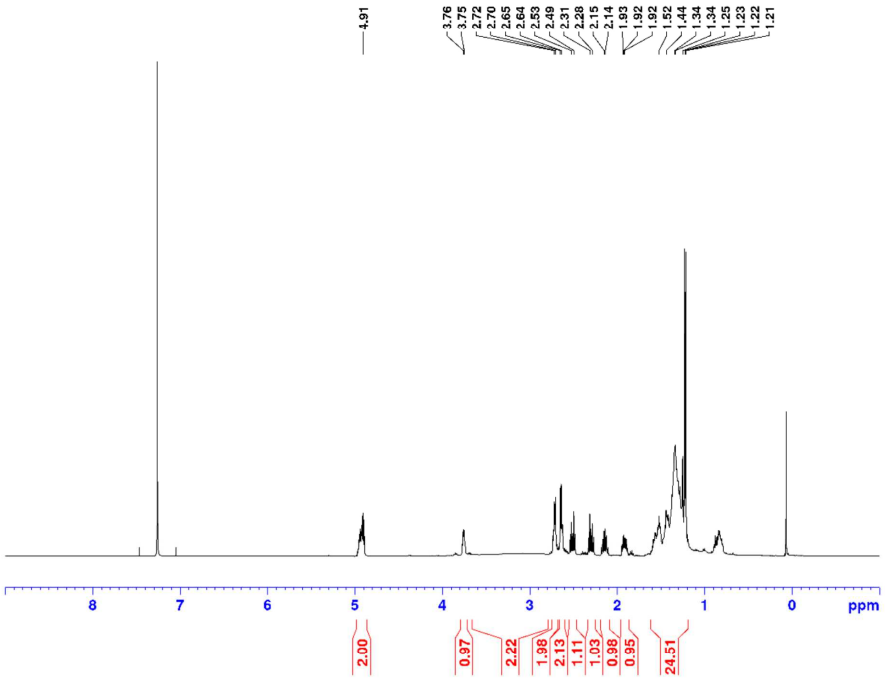
^{13}C NMR spectrum of compound **16** in $CDCl_3$.



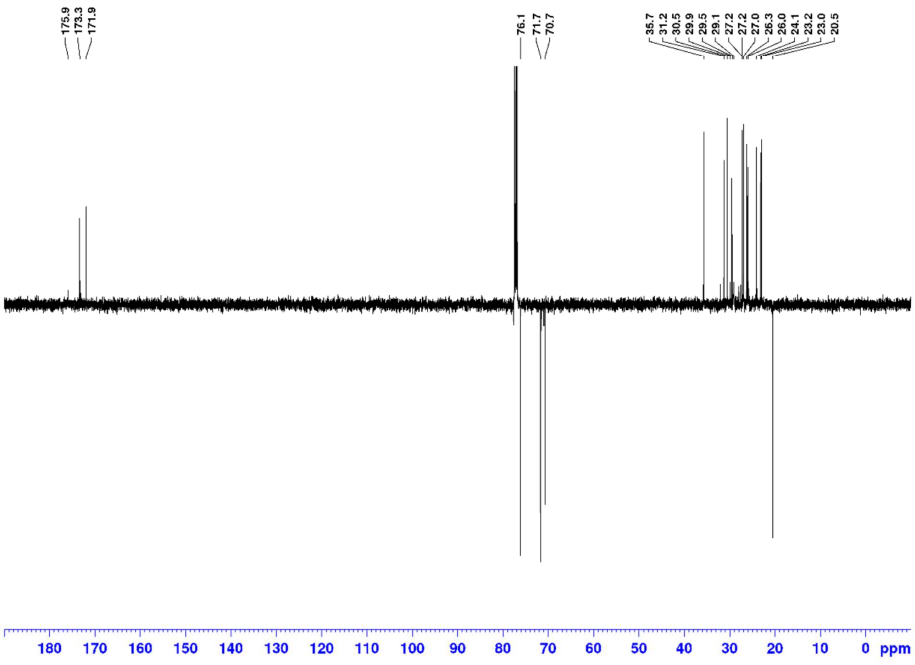
^{1}H NMR spectrum of compound **7** in $CDCl_3$.



^{13}C NMR spectrum of compound **7** in $CDCl_3$.

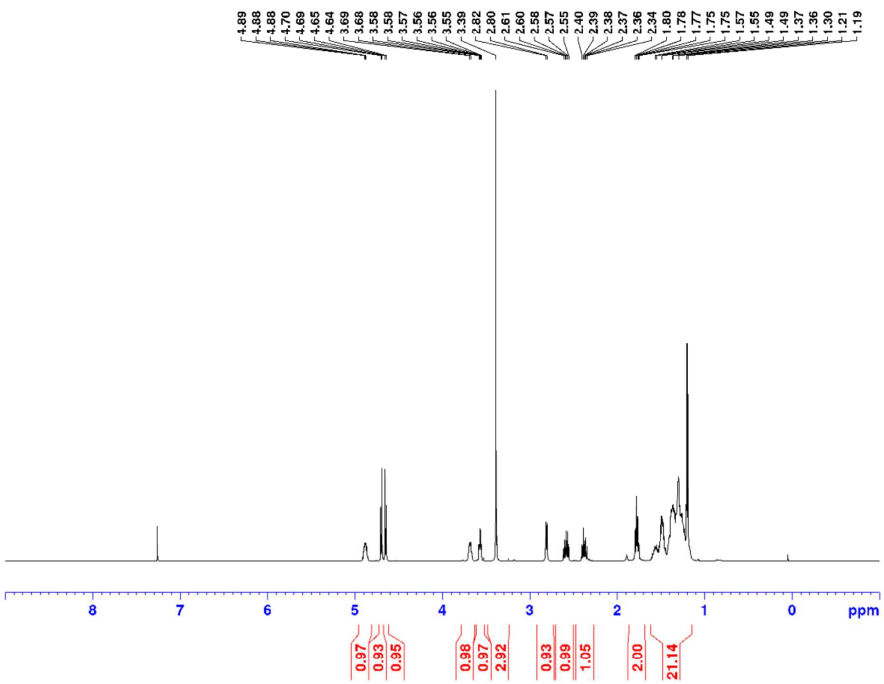


^{1}H NMR spectrum of compound *iso*-**7** in $CDCl_3$.

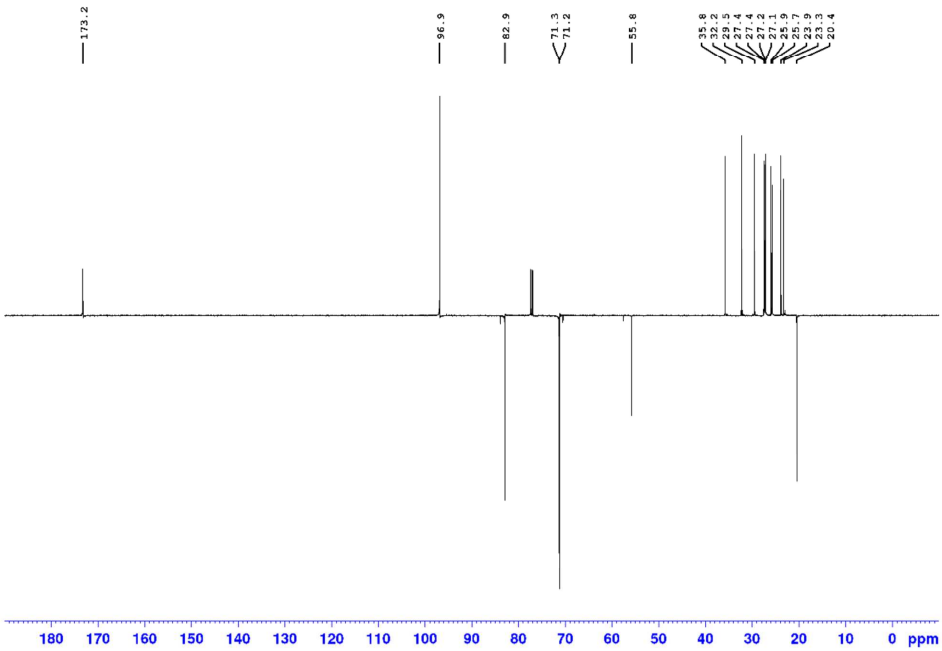


^{13}C NMR spectrum of compound *iso*-**7** in $CDCl_3$.

S39

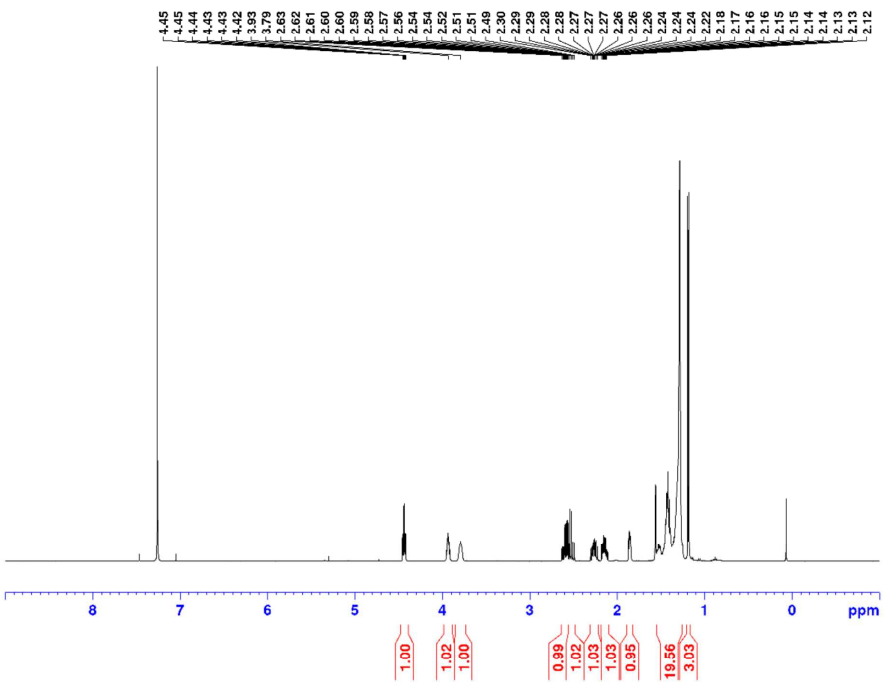


^{1}H NMR spectrum of compound **18** in $CDCl_3$.

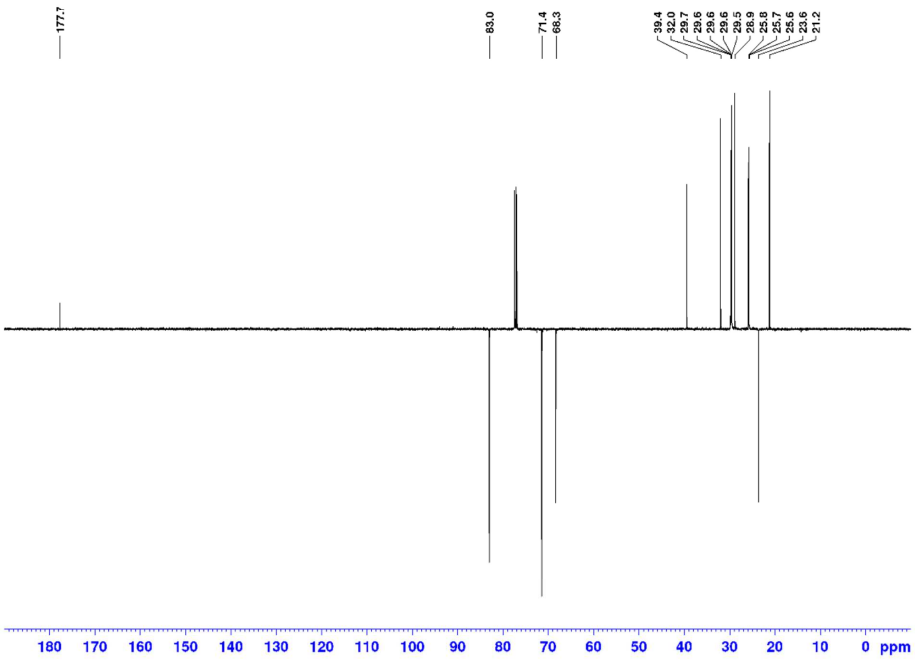


^{13}C NMR spectrum of compound **18** in $CDCl_3$.

S40

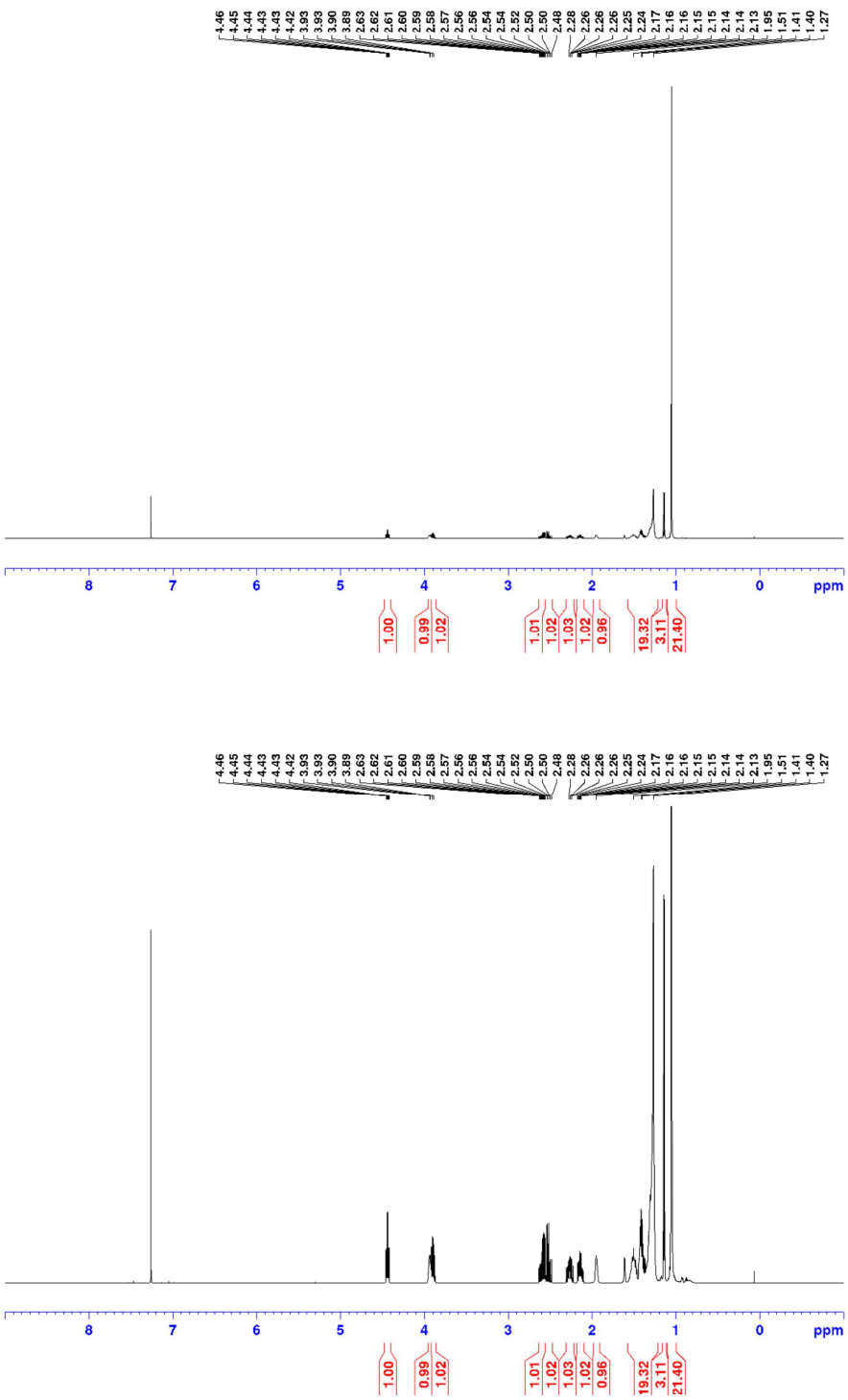


^{1}H NMR spectrum of compound **8** in $CDCl_3$.

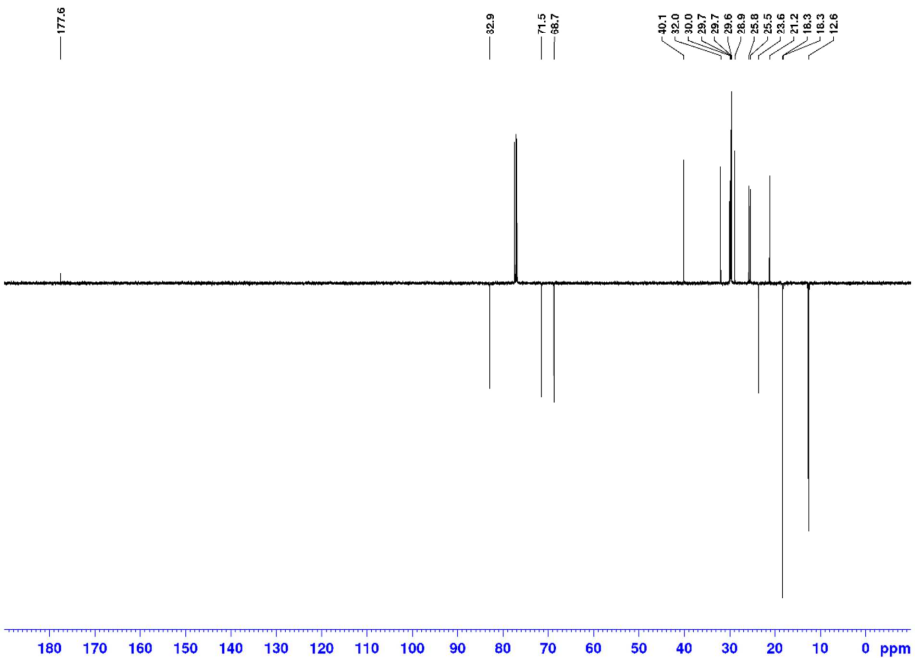


^{13}C NMR spectrum of compound **8** in $CDCl_3$.

S41

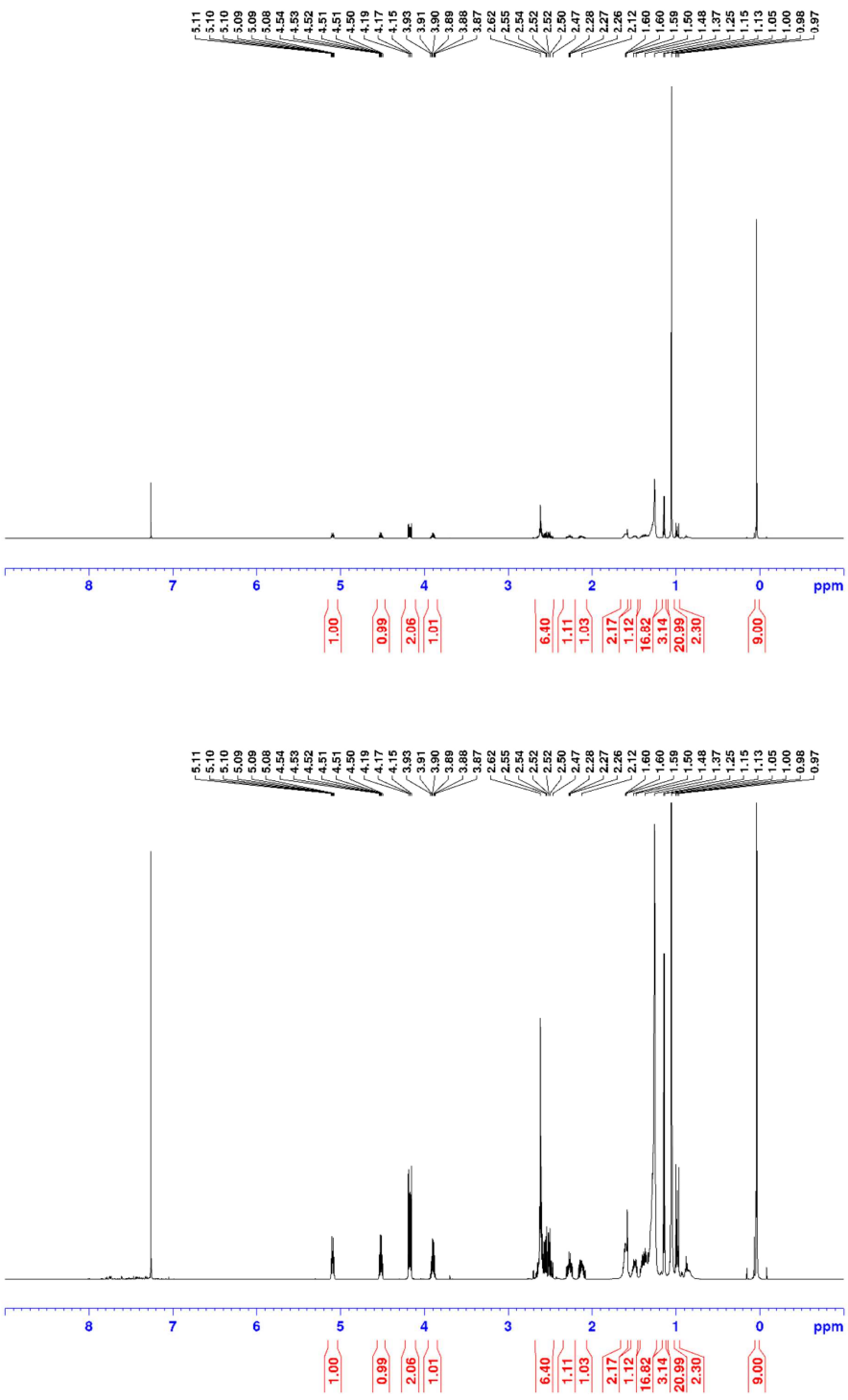


[1]H NMR spectra of compound **19** in $CDCl_3$.



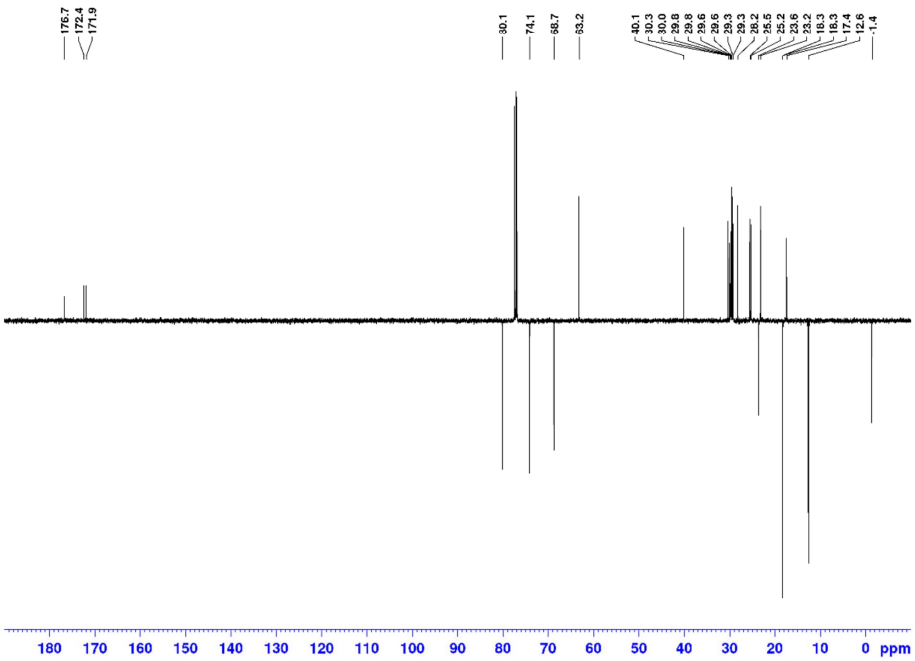
^{13}C NMR spectrum of compound **19** in $CDCl_3$.

S43



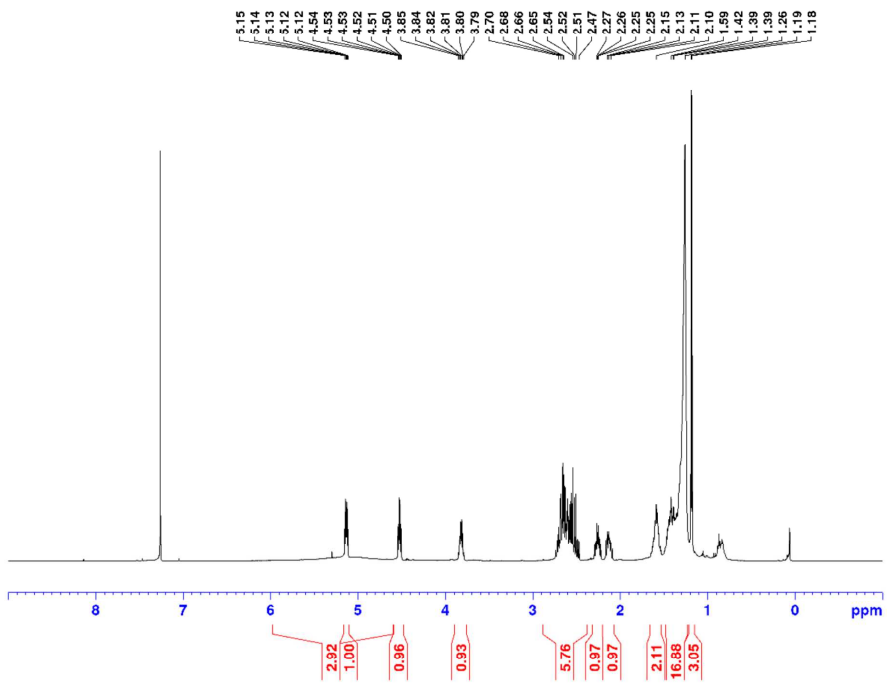
^{1}H NMR spectra of compound **20** in $CDCl_3$.

S44

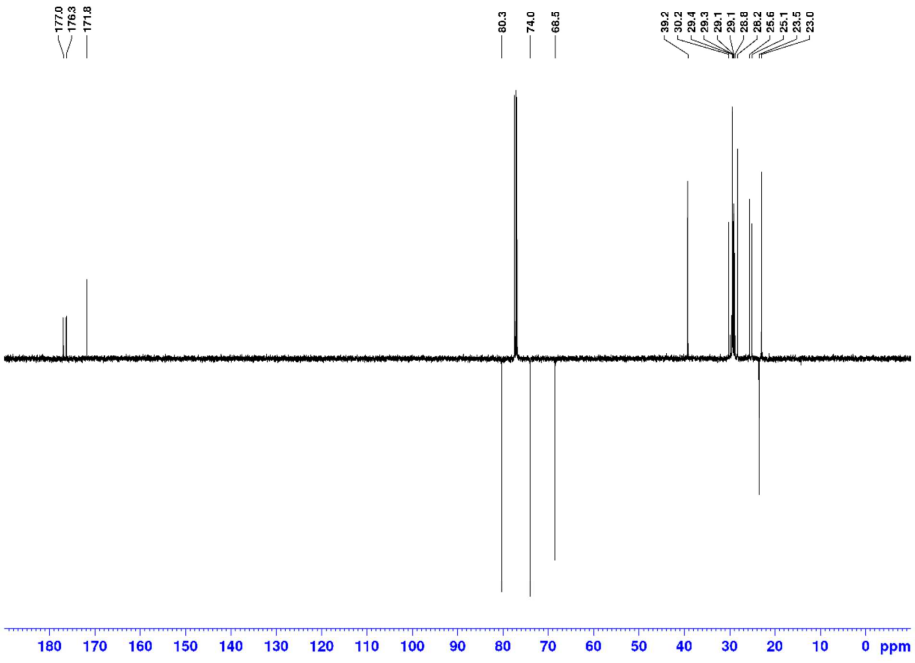


^{13}C NMR spectrum of compound **20** in $CDCl_3$.

S45

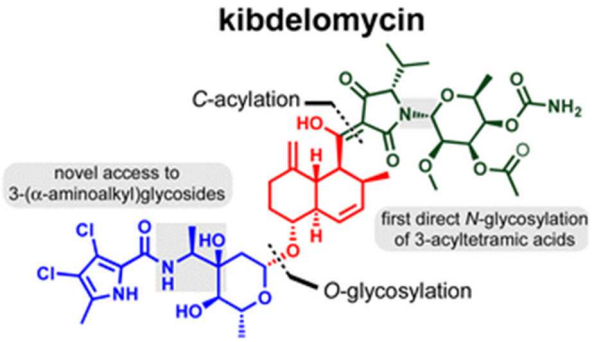


^{1}H NMR spectrum of compound **9** in $CDCl_3$.



^{13}C NMR spectrum of compound **9** in $CDCl_3$.

5.4 Publikation III



Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides

Manuel G. Schriefer, Laura Treiber, Rainer Schobert

Chem. Sci. **2023**, *14* (13), 3562 – 3568.

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2023, **14**, 3562

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd February 2023
Accepted 2nd March 2023

DOI: 10.1039/d3sc00595j

rsc.li/chemical-science

Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides†

Manuel G. Schriefer,‡ Laura Treiber‡ and Rainer Schobert *

A convergent total synthesis of bacterial gyrase B/topoisomerase IV inhibitor kibdelomycin (a.k.a. amycolamicin) (**1**) was devised starting from inexpensive D-mannose and L-rhamnose, which were converted in new efficient ways to an *N*-acylated amycolose and an amykitanose derivative as late building blocks. For the former, we developed an expeditious, general method for the introduction of an α-aminoalkyl linkage into sugars *via* 3-Grignardation. The decalin core was built up in seven steps *via* an intramolecular Diels–Alder reaction. These building blocks could be assembled as published previously, making for a formal total synthesis of **1** in 2.8% overall yield. An alternative order of connecting the essential fragments was also made possible by the first protocol for the direct *N*-glycosylation of a 3-acyltetramic acid.

Introduction

Amycolamicin (**1**) (Scheme 1) was first mentioned in 2008/2009 in patents by Igarashi *et al.* who had isolated it from the bacterium *Amycolatopsis* sp. MK575-fF5.[1] In 2010, proposals for its structure and for the biosynthesis of its *N*-acylated amycolose constituent **4**, featuring an unusual α-aminoethyl branched sugar, were put forward.[2] In 2011 Singh and coworkers isolated a compound from *Kibdelsporangium* sp. MA 7385 which they dubbed kibdelomycin and which they assumed to comprise a largely inverted amykitanose moiety when compared to the purported structure of amycolamicin.[3] They recognised its extraordinary efficacy mainly against Gram-positive bacteria, including multidrug resistant pathogens from the ESKAPE panel. In 2012, a Japanese group disclosed a first crystal structure of the β-methyl anomer of amycolose and a revised structure of amycolamicin differing from the earlier one in the configuration of a stereogenic centre in the amykitanose.[4] In 2014, Singh *et al.* settled the dispute over structure and stereochemistry with an X-ray diffraction analysis of crystals of kibdelomycin (**1**) bound to gyrase B/topoisomerase IV.[5] They revised their original structure proposal and so proved that kibdelomycin and amycolamicin are one and the same.

Singh *et al.* also undertook extensive studies of structure activity relationships.[5] Their crystal structure revealed a horseshoe-like conformation in which the dichlorinated pyrrole of amycolose amide **4** penetrates the ATP-binding pocket of gyrase B/topoisomerase IV which is the usual target of known topoisomerase IV inhibitory antibiotics. In contrast to gyrase-inhibiting antibiotics like novobiocin, the decalin, the tetramic acid and the amykitanose fragments of kibdelomycin protrude from the usual binding pocket, a possible explanation for it not showing cross resistance with established gyrase inhibitors.

Regarding its synthesis, kibdelomycin (**1**) can be dissected in three main parts, which are interesting synthetic targets in their own right. There is a decalinoyltetramic acid, a compound class known for its diverse biological activities.[6] The decalin is *O*-glycosidically bound to a 3-α-aminoethyl-3,6-dideoxyhexopyranose. A 6-deoxygenated talose, carrying a methyl ether, an acetate and a carbamic acid, is attached to the tetramic acid by an *N*-glycosidic bond. The first synthetic foray towards kibdelomycin was the preparation of *N*-acyl amycolose **4** by Kuwahara *et al.* in 2019.[7] Then, in quick succession, the groups of Li, Kuwahara and Baran published total syntheses of kibdelomycin within less than one year from December 2021 until 2022.[8,9]

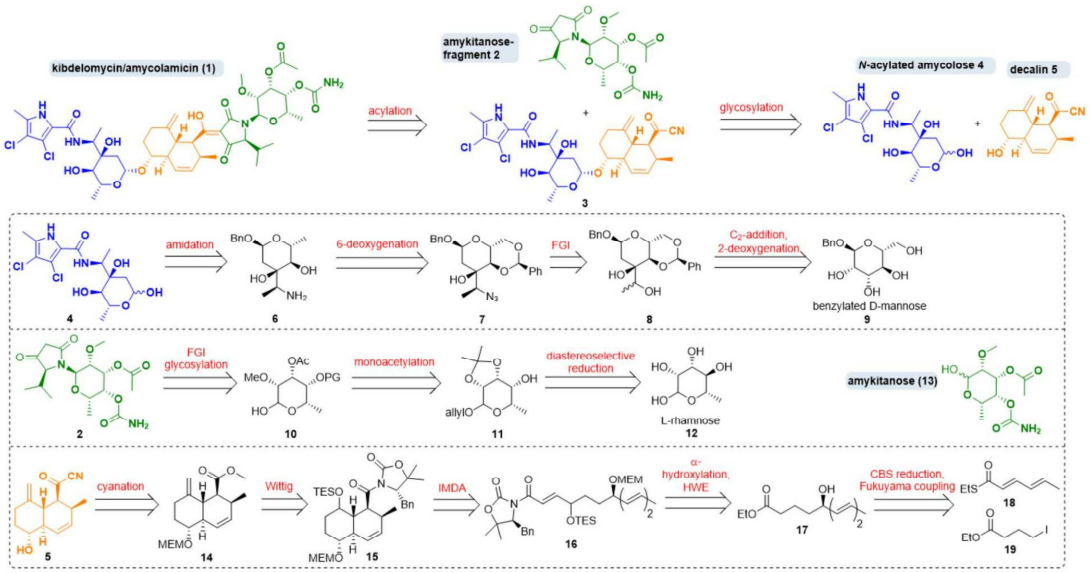
Results and discussion

Our retrosynthetic strategy for kibdelomycin (**1**) took advantage of a convergent route (Scheme 1). Disconnections were set (i) between *N*-acyl amycolose **4** and decalin fragment **5**, requiring a challenging glycosylation of a 2-deoxy sugar in the forward direction, (ii) between decalin fragment **5** and *N*-amykitanosyltetramic acid **2**, to be linked *via* a 3-acylation of the latter, and (iii) between amykitanose (**13**) and 5-isopropyltetramic acid as present in fragment **2**. This strategy would harness our experience with decalinoyl- and *N*-glycosylated tetramic acids.[10] While working on this project the three mentioned total syntheses were released, so that we decided not to frantically avoid a few of

Organic chemistry laboratory, University of Bayreuth, Universitaetsstr. 30, 95447 Bayreuth, Germany. E-mail: Rainer.Schobert@uni-bayreuth.de

† Electronic supplementary information (ESI) available: Syntheses, characterization and NMR spectra of all new compounds. See DOI: https://doi.org/10.1039/d3sc00595j

‡ These authors contributed equally.

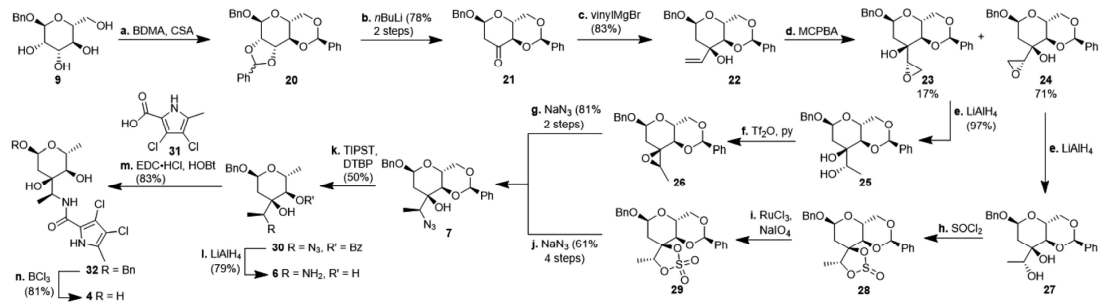


Scheme 1 Retrosynthesis of kibdelomycin (**1**) and key fragments. FGI: functional group interconversion; IMDA: intramolecular Diels–Alder, HWE: Horner–Wadsworth–Emmons; CBS: Corey–Bakshi–Shibata.

their obvious reaction steps but to concentrate on employing new and more efficient functional group interconversions for the sugar chemistry and to develop an expeditious formal total synthesis of **1**.

The first synthesis by Yang *et al.* resembles ours most because of its convergence and the similarity of some retrosynthetic fragments.[9] However, we chose distinctly different routes to decalin **5**, *N*-acylated amycolose **4** and amykitanose **13**. For the latter two we used a glycal approach with the advantage of not having to build up every single stereogenic centre by means of expensive catalysts and starting materials. For amycolose derivative **4** we decided to start from inexpensive benzylated D-mannose **9**, which first had to be deoxygenated at 2-position, and in which it was necessary to instal an oxidised ethyl group at 3-position. After a second deoxygenation at 6-position and formation of the 3-(α-aminoethyl)sugar **6** the amidation with a dichlorinated pyrrole carboxylic acid should afford **4**. For the synthesis of amykitanose fragment **2** we wanted to start from affordable L-rhamnose (**12**) instead of expensive L-fucose or L-talose. Key steps were the inversion at 4-position, the regioselective monoacetylation at 3-position, the *N*-glycosylation of 5-isopropyltetramic acid, and carbamate formation at C-4. For the synthesis of decalin fragment **5** any reaction other than an intramolecular Diels–Alder (IMDA) cycloaddition was out of the question. In a few steps, starting from thioester **18** and iodide **19**, triene **16** should be accessible *via* Fukuyama coupling, stereoselective reduction of the resulting δ-ketoester to give hydroxyester **17**, α-hydroxylation of the latter, and a chain-lengthening HWE-olefination. The following IMDA should afford mainly the *trans*-decalin scaffold, which had to be olefinated once more and converted to acyl cyanide **5**. Due to the complexity of kibdelomycin (**1**) we had to pursue different synthetic routes to these key fragments. Foundered and abandoned attempts are detailed in the ESI.†

For the synthesis of *N*-acylated amycolose **4**, benzyl protected D-mannose **9** was reacted with benzaldehyde dimethyl acetal (BDMA) and camphorsulfonic acid (CSA) to give bisbenzylidene acetal **20**. This was treated, without prior purification, with *n*BuLi at −78 °C to undergo a Klemer–Rodemeyer fragmentation upon warming to −35 °C, affording ketone **21** in 78% yield over two steps (Scheme 2).[11] It is worthy of note that a *p*-methoxyphenyl (PMP) instead of a methyl, benzyl or propargyl protecting group at the anomeric position was cleaved under these conditions with release of PMPOH. The subsequent Grignard addition of vinyl magnesium bromide occurred exclusively from the side opposite to the neighbouring 4,6-benzylidene acetal. For the introduction of the amino group we intended an initial stereoselective formation of a secondary alcohol at the ethylene group, accessible *via* epoxidation and ensuing ring opening by a metal hydride, and its S_N2-type substitution with sodium azide. The enantio- and diastereoselective Sharpless and $VO(acac)_2$/TBHP epoxidations failed, whereas the Prilezhaev epoxidation gave the epoxides **24** and **23** in 88% yield as a separable 4 : 1 mixture of diastereomers which could both be used for the synthesis of **4**. Epoxide opening by $LiAlH_4$ afforded diols **25** (from **23**) and **27** (from **24**) quantitatively. Applying the Mosher ester method, alcohol **27** was found to be (*S*)-configured (Fig. 1, top).[12] For the retention of its terminal stereogenic centre, diol **25** was submitted to two consecutive S_N2-like reactions. Epoxide formation between the secondary and tertiary alcohol with Tf_2O/pyridine afforded compound **26** which was treated immediately with NaN_3 to furnish azide **7** in 81% over two steps. For the inversion of the terminal stereogenic centre of diol **27**, it was first converted to



Scheme 2 Synthesis of amycolose derivative **4**. BDMA: benzaldehyde dimethyl acetal; CSA: camphorsulfonic acid; MCPBA: 3-chloroperbenzoic acid; Tf_2O: triflic anhydride; TIPST: triisopropylsilanethiol; DTBP: di-*tert*-butylperoxide; EDC: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; HOBt: 1-hydroxybenzotriazole.

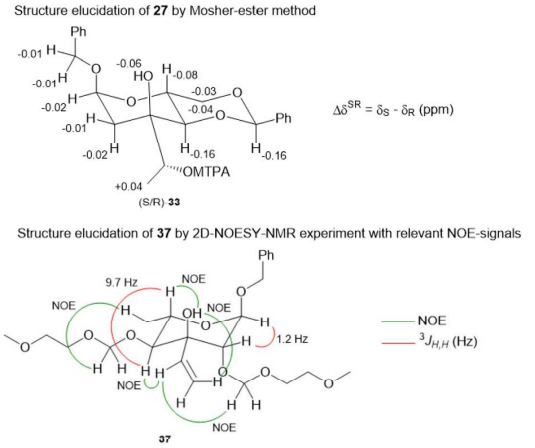
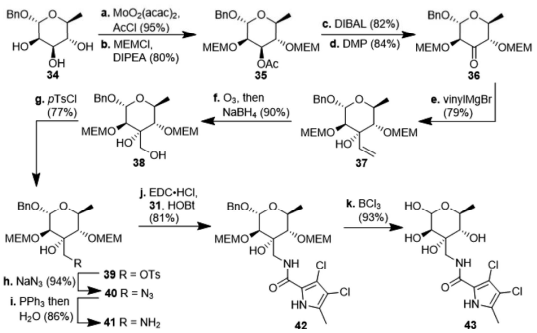


Fig. 1 Structure elucidation of **27** *via* Mosher ester method (top) and significant NOE-signals for the elucidation of the stereoconfiguration of **37** (bottom).

the sulfite **28**. This was oxidised with $RuCl_3/NaIO_4$ to sulfate **29** which was reactive enough to render azide 7 (61% over 4 steps) upon treatment with NaN_3 and subsequent acidic hydrolysis of the intermediate sodium sulfate ester (*cf.* ESI† for details). While on small scale this hydrolysis was possible using aqueous H_2SO_4 (70% yield), at a larger scale aqueous H_2SO_4 led to cleavage of the benzylidene acetal and had to be replaced by a pH 4 citric acid buffer. For the 6-deoxygenation of **7** we followed the protocol of Dang *et al.* and employed a system of DTBP/TIPST for its radical-chain redox rearrangement to give benzoate **30**.[13] After an extensive optimisation this step proceeded with at least 50% yield, which spared us the use of the alternative Hanessian–Hullar reaction with subsequent dehalogenation.[14] Treatment of benzoate **30** with $LiAlH_4$ led to concomitant azide and benzoate reduction with 79% yield. The resulting amine **6** was selectively acylated with carboxylic acid **31** and EDC·HCl/HOBt to give amide **32** in 83% yield. Other amidation reagents such as BOP or HATU were less effective. Because of the potential hydrogenative dechlorination of the pyrrole we used BCl_3 rather than Pd/C and H_2 for the final debenzylation step. We obtained a mixture of α- and β-anomers of **4**, the ratio of which was strongly dependent on the solvent and purification. Next, we checked the applicability of this synthesis to other sugars (Scheme 3). We chose L-rhamnose to test the introduction of an α-aminoalkyl residue. Benzylated L-rhamnose **34** was regioselectively 3-acetylated using a molybdenum catalyst.[15] The hydroxyl groups at 2- and 4-position were MEM-protected (→ **35**, 80%), because the downstream Grignard reaction would not work with bulky (TBS, Bn) or no protecting groups. After removal of the acetyl group by DIBAL (82%) and DMP-oxidation, ketone **36** was obtained with good yield. Its reaction with vinyl magnesium bromide gave the tertiary allyl alcohol **37** in 79% yield and *dr* > 30 : 1. A 2D-NOESY-experiment proved that the Grignard reagent had attacked from the site opposite to the C4-OMEM group (Fig. 1, bottom). This finding also shows that the group at C4, directing diastereoselective additions, need not be a large 4,6-benzylidene acetal. Next, alkene **37** was converted to primary alcohol **38** by ozonolysis which was tosylated to give **39** that was converted to azide **40**. After Staudinger reaction, the resulting amine **41** was acylated with pyrrole carboxylic acid **31** to give amide **42** in 81% yield. Finally, the benzyl group at the anomeric position as well as both MEM protecting groups of **42** were removed by BCl_3 in

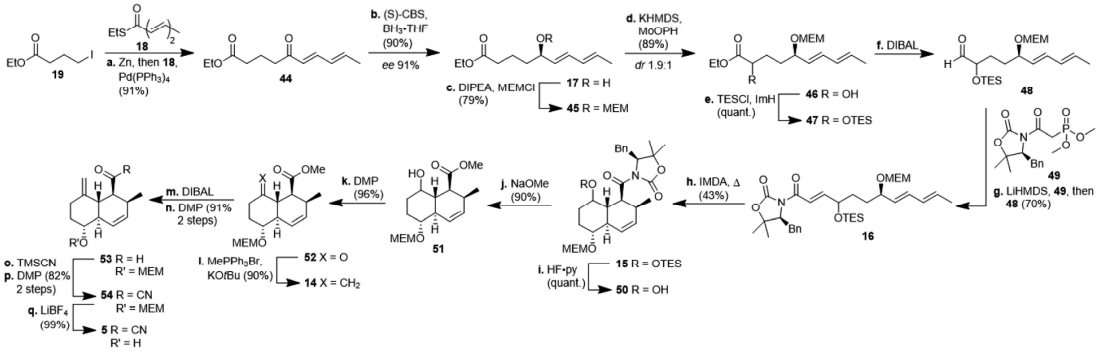


Scheme 3 Synthesis of 3-aminomethyl-6-deoxyhexopyranose derivative **43** starting from benzylated L-rhamnose **34**. MEM: methoxyethoxymethyl; DIPEA: diisopropylethylamine; DMP: Dess–Martin periodinane; Ts: tosyl.

a single step to give the rhamnose derivative **43** in excellent 17% yield over 11 steps. With the synthesis of amycolose and a rhamnose derivative, we demonstrated that this method may be used in general to introduce an α-aminoalkyl linkage in sugars. Moreover, the vinyl group is amenable to a good many other functionalisations (*cf.* ESI†). This aspect might facilitate diversity-oriented syntheses of highly functionalised sugars, including even amycolose, given its known cell growth suppression and possible application as an anticancer medication.[16]

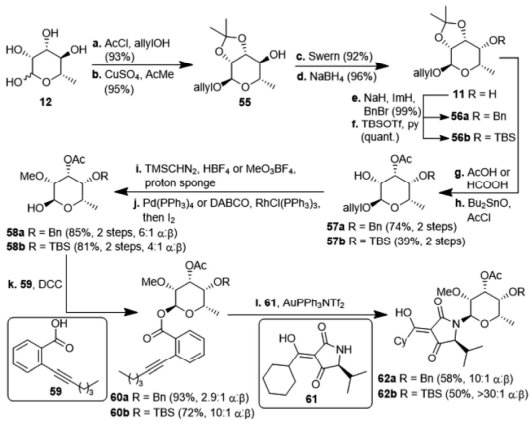
The synthesis of decalin fragment **5** started with a Fukuyama coupling between ethyl 4-iodobutyrate **19** and ethyl (2*E*,4*E*)-hexa-2,4-dienethioate **18** to give δ-ketoester **44** in 91% yield (Scheme 4).[17] The ketone was reduced with BH_3 in the presence of (*S*)-CBS-catalyst affording alcohol **17** with 90% yield and an ee of 91%. This protocol is easier to use on a laboratory scale than a recently published asymmetric Noyori-type hydrogenation of α,β,γ,δ-unsaturated ketones.[18] Unlike other groups who applied a more than quantitative amount of CBS-catalyst, we realised that the reduction proceeded with higher ee when using a merely catalytic amount of CBS-catalyst. After MEM-protection of the alcohol to give ether **45** with 79% yield, a non-trivial α-hydroxylation had to be done at this post-Fukuyama stage, since α-hydroxylated esters from the chiral pool failed to undergo the Fukuyama coupling due to not forming the respective zinc organyl (*cf.* ESI†). After quite a few failed attempts with sulfonyloxaziridines, we identified MoOPH/KHMDS as a viable α-hydroxylating agent affording α-hydroxyester **46** with 89% yield and 1.9 : 1 *dr*. The TES-protected ester **47** was reduced with DIBAL to aldehyde **48** and the latter was submitted to a HWE-olefination with phosphonate **49** to give the triene **16** comprising the SuperQuat auxiliary (70%, two steps). Because HWE-reactions with Evans/Davies auxiliary bearing phosphonates only worked with α-hydroxylated aldehydes but not so with α-methylene substituted aldehydes (*cf.* ESI†) we had to postpone the introduction of the methylene group until after the decalin formation. We opted for Davies' SuperQuat auxiliary for the following Diels–Alder reaction, after many attempts to remove an Evans auxiliary had failed after successful Diels–Alder reaction and in accordance with the results of Frossard *et al.*[19] Unlike most who use $AlMeCl_2$ as a catalyst for the IMDA, we had better results when heating triene **16** in toluene at 80 °C over 3 d which afforded octalin **15** with 43% yield besides some separable undesired *cis*-octalin. Quantitative removal of the TES-protecting group with HF pyridine complex left the alcohol **50** which had its auxiliary cleaved off with sodium methoxide to give hydroxyester **51** with 90% yield. The introduction of the methylene unit was achieved by oxidising alcohol **51** with DMP (96%) and treating the resulting ketone **52** with methylenetriphenylphosphorane. The resulting ester **14** (90%) was reduced to aldehyde **53** in two steps, *i.e.* reduction to the corresponding alcohol with DIBAL and subsequent oxidation with DMP, because of overreduction issues. Reaction of aldehyde **53** with TMSCN led to a cyanohydrin, which was right away oxidised with DMP to acyl cyanide **54**. Cleavage of the MEM-group, liberating decalin **5**, proceeded best using $LiBF_4$ compared to $TiCl_4$ or TFA. This synthesis of the central decalin building block has an edge over those of the previous kibdelomycin syntheses due to its high yielding, simple steps and inexpensive starting materials. Most reactions were performed on a gram scale without yields decreasing.

The second, amykitanose-related sugar fragment was synthesised starting from L-rhamnose (**12**) (Scheme 5). It was allylated at the anomeric position in 93% yield and its *syn*-diol was protected as an isopropylidene acetal using anhydrous $CuSO_4$ (95%). The allyl protecting group was chosen since the cleavage of the comparable methyl acetal later on in the synthesis had failed in the presence of other necessary functional groups, *e.g.* because of the instability of the acetyl group. The configuration at the 4-position of the resulting compound **55** was inverted by a sequence of Swern oxidation and ensuing reduction with $NaBH_4$ to give a single diastereomer of **11** in 88% over two steps. Benzylation of the hydroxyl group led to fully protected sugar **56a**. After deprotection of the *syn*-diol, the hydroxyl group at 3-position was acetylated selectively under optimised conditions to afford sugar **57a** in 74% yield over two steps.[20] Methylation at 2-positon was difficult due to the acetyl group getting easily removed under basic conditions, but was eventually achieved

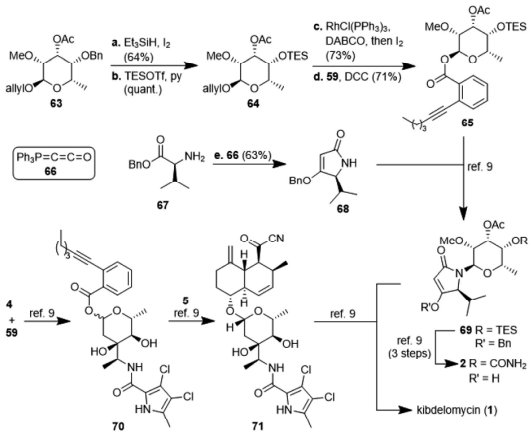


Scheme 4 Synthesis of decalin fragment **5** starting from ethyl 4-iodobutyrate **19**. CBS: Corey–Bakshi–Shibata catalyst; KHMDS: potassium hexamethyldisilazide; MoOPH: oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide); TES: triethylsilyl; ImH: imidazole; LiHMDS: lithium hexamethyldisilazide; TMSCN: trimethylsilyl cyanide.

View Article Online
Chemical Science Edge Article



Scheme 5 Synthesis of *N*-glycosylated 3-cyclohexanoylltetramic acids **62a/b**. TBS: *tert*butyldimethylsilyl; Tf: triflyl; DABCO: 1,4-diazabicyclo[2.2.2]octane; DCC: dicyclohexylcarbodiimide.



Scheme 6 Synthesis of glycoside **65** and tetramate **68** as well as a formal synthesis of kibdelomycin (**1**) according to ref. 9.

using $TMSCHN_2$ and HBF_4. Deprotection of the anomeric position in acidic milieu under Pd-catalysis gave sugar **58a**. All attempts at coupling it with any kind of tetramic acid *via* different customary methods in order to establish analogues of amykitanose fragment **2**, as well as Dieckmann cyclisation based sequences failed (*cf.* ESI†).[21] As a last resort and based on the first total synthesis of kibdelomycin by Li *et al.*,[9] sugar **58a** was esterified with carboxylic acid **59** and the resulting ester **60a** was coupled with 3-cyclohexanoyl-tetramic acid **61** *via* Au-catalysis affording *N*-glycoside **62a** in a decent 58% yield.[22] The cyclohexyl residue was to mimic the octalin moiety. As far as we know, this is the first example of a direct *N*-glycosylation of a 3-acyltetramic acid. The anomeric ratio of 10 : 1 was inferior to the 20 : 1 ratio reported by Li *et al.*[9] for the *N*-glycosylation of 3*H*-5-isopropylpyrrolidin-2,4-dione. The divergent results could only be attributed to the different protecting groups at 4-position of the sugar (Bn *vs.* TES). To verify this assumption, we introduced a silyl protection group as in compound **58b**. The following steps were identical to those for the 4-OBn analogues, albeit with slightly different reaction conditions because of the instability of the TBS-group in an acidic milieu. Even the esterification of **58b** with carboxylic acid **59** showed the influence of the protecting group, since the anomeric ratio of the resulting sugar **60b** increased to 10 : 1 α : β. After coupling with the 3-acyl tetramic acid **61**, the *N*-glycoside **62b** was isolated with an α : β-ratio of >30 : 1. For a strict formal total synthesis, the TES-protected sugar **65** was required (Scheme 6). So, we removed the benzyl group of compound **63**, obtained from methylation of glycoside **57a**, with *in situ* generated HI, and replaced it with a triethylsilyl group to afford compound **64**. Deallylation of the latter and glycosylation with acid **59** gave ester **65** in excellent 15% yield over 12 steps, comparable with the corresponding sequence of the first total synthesis by Li *et al.*[9] Glycoside **65** can then be coupled with 4-*O*-benzyl 5-isopropyltetramate **68** as shown in the first total synthesis of kibdelomycin.[9] Tetramate **68** is readily accessible in one step and 63% yield from reaction of ketenylidenetriphenylphosphorane (**66**) with L-valine benzyl ester (**67**).[23] Removal of the benzyl group in glycoside **63** also opened the door for the synthesis of amykitanose (**13**) in three more steps (*cf.* ESI† for a not yet optimised protocol). The formal synthesis of kibdelomycin (**1**) can be completed by esterification of amycolose derivative **4** with acid **59** to give **70** and subsequent use of the latter for glycosylation of decalin fragment **5** to give compound **71**. Glycoside **65** can be converted to tetramic acid fragment **2** in four steps. Acylation of tetramic acid **2** with ketonitrile **71** using 1-hydroxy-7-azabenzotriazole (HOAt) and triethylamine finally affords kibdelomycin (**1**). For the completion of an alternative total synthesis exploiting the novel *N*-glycosylation of 3-acyltetramic acids *cf.* the ESI.†

Conclusion

In summary we developed an expeditious formal synthesis of kibdelomycin (**1**) starting from inexpensive compounds and employing simple and high-yielding standard protocols, even on a large scale. The stereochemical information stems from the chiral pool or from highly diastereoselective reactions. The longest linear sequence of the factual synthesis of the fragments amounts to a competitive 19 steps. With all fragments in hand, a formal synthesis following the protocol of Yang *et al.* leads to kibdelomycin (**1**, 2.8% overall yield).[9] During our research, we developed a method for introduction of an α-aminoalkyl linkage into sugars *via* Grignard addition to C3 which also opens access to a range of other functionalities. It could be used to synthesise different derivatives of kibdelomycin (**1**) for structure–activity relationship studies or for an optimisation of its applicability and efficacy. As a side benefit, we also report the first *N*-glycosylation of a 3-acyltetramic acid.

Data availability

The datasets and spectra supporting this article have been uploaded as part of the ESI† material.

View Article Online
Edge Article Chemical Science

Author contributions

M. G. S. planned and carried out all reactions concerning amycolose, planned the synthesis of derivatives of amycolose, and wrote parts of the manuscript. L. T. planned and carried out all syntheses concerning amykitanose and rhamnose derivatives and wrote parts of the manuscript. L. T. and M. G. S. planned and realised the synthesis of decalin fragment **5**. R. S. supervised the syntheses and assisted with manuscript preparation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Alessandro Burger, Lina-Marie Beck, Gopal Gupta and Ines Bauer for their practical, synthetic contributions as part of their BSc projects.

References

1 M. Igarashi, R. Sawa and T. Honma, *New compound amycolamicin, method for producing the same, and use of the same*, JP Pat., JP2009203195A, 2009.
2 S. Tohyama, Y. Takahashi and Y. Akamatsu, Biosynthesis of amycolamicin: the biosynthetic origin of a branched alpha-aminoethyl moiety in the unusual sugar amycolose, *J. Antibiot.*, 2010, **63**, 147–149.
3 (*a*) D. L. Zink, M. Goetz, O. Genniloud, F. Vicente, S. Singh and J. D. Polishook, *Antibacterial agents*, Pat., ES 2368236A1, 2011; (*b*) J. W. Phillips, M. A. Goetz, S. K. Smith, D. L. Zink, J. Polishook, R. Onishi, S. Salowe, J. Wiltsie, J. Allocco, J. Sigmund, K. Dorso, S. Lee, S. Skwish, M. de La Cruz, J. Martín, F. Vicente, O. Genilloud, J. Lu, R. E. Painter, K. Young, K. Overbye, R. G. K. Donald and S. B. Singh, Discovery of kibdelomycin, a potent new class of bacterial type II topoisomerase inhibitor by chemical-genetic profiling in *Staphylococcus aureus*, *Chem. Biol.*, 2011, **18**, 955–965.
4 R. Sawa, Y. Takahashi, H. Hashizume, K. Sasaki, Y. Ishizaki, M. Umekita, M. Hatano, H. Abe, T. Watanabe, N. Kinoshita, Y. Homma, C. Hayashi, K. Inoue, S. Ohba, T. Masuda, M. Arakawa, Y. Kobayashi, M. Hamada, M. Igarashi, H. Adachi, Y. Nishimura and Y. Akamatsu, Amycolamicin: a novel broad-spectrum antibiotic inhibiting bacterial topoisomerase, *Chem.–Eur. J.*, 2012, **18**, 15772–15781.
5 J. Lu, S. Patel, N. Sharma, S. M. Soisson, R. Kishii, M. Takei, Y. Fukuda, K. J. Lumb and S. B. Singh, Structures of kibdelomycin bound to *Staphylococcus aureus* GyrB and ParE showed a novel U-shaped binding mode, *ACS Chem. Biol.*, 2014, **9**, 2023–2031.
6 (*a*) R. Schobert and A. Schlenk, Tetramic and tetronic acids: an update on new derivatives and biological aspects, *Bioorg. Med. Chem.*, 2008, **16**, 4203–4221; (*b*) G. Li, S. Kusari and M. Spiteller, Natural products containing 'decalin' motif in microorganisms, *Nat. Prod. Rep.*, 2014, **31**, 1175–1201.
7 Y. Meguro, Y. Ogura, M. Enomoto and S. Kuwahara, Synthesis of the N-acyl amycolose moiety of amycolamicin and Its methyl glycosides, *J. Org. Chem.*, 2019, **84**, 7474–7479.
8 (*a*) C. He, Y. Wang, C. Bi, D. S. Peters, T. J. Gallagher, J. Teske, J. S. Chen, R. Corsetti, A. D'Onofrio, K. Lewis and P. S. Baran, Total synthesis of kibdelomycin, *Angew. Chem., Int. Ed.*, 2022, **61**, e202206183; (*b*) Y. Meguro, J. Ito, K. Nakagawa and S. Kuwahara, Total synthesis of the broad-spectrum antibiotic amycolamicin, *J. Am. Chem. Soc.*, 2022, **144**, 5253–5257.
9 S. Yang, C. Chen, J. Chen and C. Li, Total synthesis of the potent and broad-spectrum antibiotics amycolamicin and kibdelomycin, *J. Am. Chem. Soc.*, 2021, **143**, 21258–21263.
10 (*a*) M. Winterer, K. Kempf and R. Schobert, Synthesis of an isomer of the decalinoyltetramic acid methiosetin by a stereocontrolled IMDA reaction of a metal-chelated 3-trienoyltetramate, *J. Org. Chem.*, 2016, **81**, 7336–7341; (*b*) M. Petermichl, S. Loscher and R. Schobert, Total synthesis of aurantoside G, an N-β-glycosylated 3-oligoenoyltetramic acid from *Theonella swinhoei*, *Angew. Chem., Int. Ed.*, 2016, **55**, 10122–10125.
11 A. Klemer, G. Rodemeyer and F.-J. Linnenbaum, Reaktionen von O-Isopropylidenzuckern mit lithiumorganischen Verbindungen zu ungesättigten Zuckern. Synthese von 4-Desoxy-4-eno-β-D-threo-pentose- und 5-Desoxy-5-eno-β-D-threo-hexulose-Derivaten, *Chem. Ber.*, 1976, **109**, 2849–2861.
12 J. A. Dale and H. S. Mosher, Nuclear magnetic resonance enantiomer reagents. Configurational correlations *via* nuclear magnetic resonance chemical shifts of diastereomeric mandelate, *O*-methylmandelate, and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters, *J. Am. Chem. Soc.*, 1973, **95**, 512–519.
13 H.-S. Dang, B. P. Roberts, J. Sekhon and T. M. Smits, Deoxygenation of carbohydrates by thiol-catalysed radical-chain redox rearrangement of the derived benzylidene acetals, *Org. Biomol. Chem.*, 2003, **1**, 1330–1341.
14 (*a*) D. L. Failla, T. L. Hullar and S. B. Siskin, Selective transformation of *O*-benzylidene acetals into ω-bromo-substituted benzoate esters, *Chem. Commun.*, 1966, 716–717; (*b*) S. Hanessian, The reaction of *O*-benzylidene sugars with *N*-bromosuccinimide, *Carbohydr. Res.*, 1966, **2**, 86–88.
15 E. V. Evtushenko, Regioselective benzoylation of glycopyranosides by benzoyl chloride in the presence of $MoO_2(acac)_2$, *J. Carbohydr. Chem.*, 2010, **29**, 369–378.
16 S. Tohyama, *Amycolose derivative, and production process and use of same*, EP Pat., EP2471788A1, 2012.
17 H. Tokuyama, S. Yokoshima, T. Yamashita and T. Fukuyama, A novel ketone synthesis by a palladium-catalyzed reaction of thiol esters and organozinc reagents, *Tetrahedron Lett.*, 1998, **39**, 3189–3192.
18 C. Li, W. Lu, B. Lu, W. Li, X. Xie and Z. Zhang, Ru-catalyzed chemo- and enantioselective hydrogenation of 2,4-pentadien-1-ones: synthesis of chiral 2,4-pentadien-1-ols, *J. Org. Chem.*, 2019, **84**, 16086–16094.

19 (*a*) S. G. Davies, I. A. Hunter, R. L. Nicholson, P. Roberts, E. D. Savory and A. D. Smith, N-α-Benzyloxyacetyl derivatives of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one for the asymmetric synthesis of differentially protected α,β-dihydroxyaldehydes, *Tetrahedron*, 2004, **60**, 7553–7577; (*b*) T. M. Frossard, N. Trapp and K.-H. Altmann, Studies towards the total synthesis of amycolamicin: a chiral auxiliary-based Diels-Alder approach towards the decalin core, *Eur. J. Org. Chem.*, 2022, **2022**, e202200761.

20 M. A. Nashed and L. Anderson, Organotin derivatives and the selective acylation and alkylation of the equatorial hydroxy group in a vicinal, equatorial-axial pair, *Tetrahedron Lett.*, 1976, **17**, 3503–3506.

21 R. N. Lacey, Derivatives of acetoacetic acid. Part VII. α-Acetyltetramic acids, *J. Chem. Soc.*, 1954, 850–854.

22 For the first use of an *ortho*-alkynylbenzoate/Au-catalytic system see(*a*) Y. Li, Y. Yang and B. Yu, An efficient glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors under the catalysis of $Ph_3PAuOTf$, *Tetrahedron Lett.*, 2008, **49**, 3604–3608, for the use in *N*-glycosylations see; (*b*) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang and B. Yu, Gold(I)-catalyzed glycosylation with glycosyl *ortho*-alkynylbenzoates as donors: general scope and application in the synthesis of a cyclic triterpene saponin, *Chem.–Eur. J.*, 2010, **16**, 1871–1882; (*c*) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, An efficient approach to the synthesis of nucleosides: gold(I)-catalyzed N-glycosylation of pyrimidines and purines with glycosyl *ortho*-alkynyl benzoates, *Angew. Chem., Int. Ed.*, 2011, **50**, 4933–4936.

23 J. Löffler and R. Schobert, Domino syntheses of five-, six- and seven-membered O-, N- and S-heterocycles from α-, β- and γ-substituted carboxylic esters, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2799–2802.

Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides

Manuel Georg Schriefer [a], *Laura Treiber* [a], *Rainer Schobert* [a,*]

[a] *Organic chemistry laboratory, University of Bayreuth, Universitaetsstr. 30, 95447 Bayreuth, Germany.*

Supporting Information

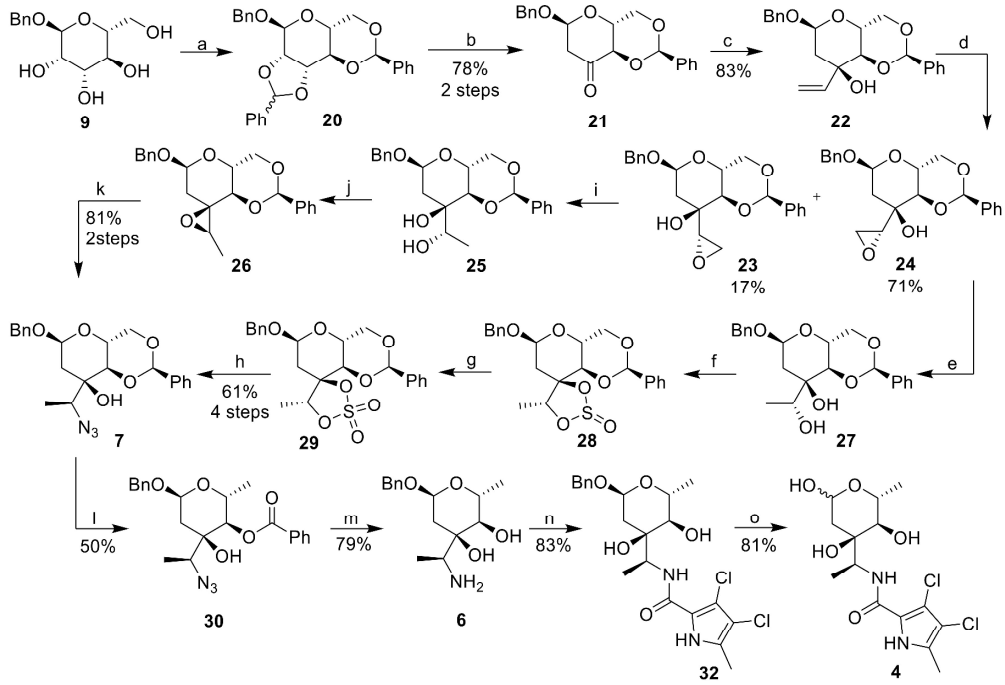
Table of contents

1. General information

Melting points were determined with a Büchi M-565 melting point apparatus and are uncorrected. IR spectra were recorded with a PerkinElmer Spectrum 100 FT-IR spectrophotometer (PerkinElmer, Rodgau, Germany) with ATR sampling unit. Optical rotations were measured at 589 nm (Na-D line) on a PerkinElmer 241 polarimeter (PerkinElmer, Rodgau, Germany); $[\alpha]_D^{20}$ (c g/100mL, solvent) values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode (ThermoFisher Scientific, Bremen, Germany). NMR spectra were recorded with a Bruker Avance III HD 500 spectrometer (^{1}H NMR: 500 MHz and ^{13}C NMR: 125 MHz) (Bruker, Karlsruhe, Germany). Chemical shifts are given in parts per million, relative to the residual solvent peak as an internal standard and coupling constants (*J*) are quoted in Hz. Most tetramic acids were measured in $CDCl_3$ and in CD_3OD. In the latter they usually exist as a single (enol) tautomer. Quaternary C-atoms of tetramic acids were sometimes difficult to spot in JMOD or ^{13}C NMR spectra. For these, more signals cropped up in HMBC and/or HSQC correlation spectra and were considered for peak assignment. In $CDCl_3$ solution, signals of virtually all C-atoms of tetramic acids were visible yet split up in multiple, difficult to assign sets for individual tautomers both in ^{1}H and JMOD/^{13}C NMR spectra. In line with literature, we assume the tautomers with exocyclic C–C double bond as drawn for the 3-acyltetramic acids in scheme S10, to be the major tautomer.[1] For the purification of synthetic products, chromatography silica gel 60 (40–63 µm) or silica gel RP18 (40–63 µm) were used. Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60 F254 pre-coated aluminum-backed plates. Analytical HPLC was performed on a Shimadzu Nexera XR (Shimadzu GmbH, Duisburg, Germany) using a Knauer Eurospher II C18-column (150 × 4 mm) (Knauer GmbH, Berlin, Germany). Enantiomeric excess was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak OD3). All reagents were purchased from commercial sources and were used without further purification. All anhydrous solvents were used as supplied, except tetrahydrofuran, 1,4-dioxane and toluene which were freshly distilled over sodium/benzophenone, dichloromethane (CH_2Cl_2) which was freshly distilled over CaH_2, dimethylformamide (DMF) which was dried over molecular sieves (3 Å), and methanol (MeOH) which was freshly distilled over Mg. Moisture or air sensitive reactions were routinely carried out in oven-dried glassware under an argon atmosphere using standard Schlenk technique.

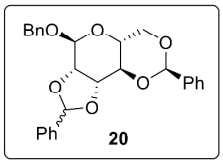
2. Experimental procedure

2.1 Synthesis of amycolose fragment **4**



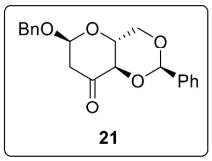
Scheme S1. Synthesis of amycolose derivate **4** starting from benzylated D-mannose **9**.
a) BDMA, CSA, $CHCl_3$, 80 °C, 6.5 h; b) *n*BuLi, THF, −78 °C→−35 °C, 3.75 h; c) VinylMgBr, THF, −78 °C, 3 h; d) *m*CPBA, CH_2Cl_2, rt, 22 h; e) $LiAlH_4$, THF, 0 °C→rt, 2.5 h; f) $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C, 3 h, g) $NaIO_4$, $RuCl_3 \cdot xH_2O$, MeCN, rt, 7 h; h) 1. NaN_3, DMF, 65 °C, 6.75 h, 2. Citric acid buffer, EtOAc, 45 °C, 15 h, 3. Citric acid, 3.5 h; i) $LiAlH_4$, THF, 0 °C→rt, 1.75 h; j) Tf_2O, pyridine, CH_2Cl_2, −78 °C→0 °C, 1.25 h; k) NaN_3, NH_4Cl, MeOH, 80 °C, 12 h; l) TIPST, DTBP, *n*-octane, 140 °C, 6.75 h; m) $LiAlH_4$, THF, 0 °C ›rt, 24 h; n) **31**, HOBt, EDC·HCl, NEt_3, CH_2Cl_2, 0 °C ›rt, 16 h; o) BCl_3, CH_2Cl_2, −80 °C, 40 min.

(2*R*,4a*R*,6*S*,8a*R*)-6-(Benzyloxy)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-8(4*H*)-one (21)



Benzylated mannose (**9**, 5.50 g, 20.3 mmol, 1.00 eq.) was solved in $CHCl_3$ (100 mL) and BDMA (7.02 mL, 46.8 mmol, 2.30 eq.) and CSA (709 mg, 3.05 mmol, 0.15 eq.) was added. The solution was heated at 80 °C and the vapor condensed in another flask. The reaction flask was refilled every hour with $CHCl_3$ (ca. 50 mL) and stirred at 80 °C for 6.5 h. The solution was poured into sat. aq. $NaHCO_3$ solution (200 mL) and extracted with CH_2Cl_2 (3×200 mL). The

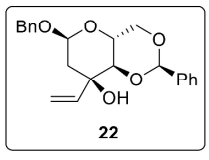
combined organic phases were washed with sat. aq. $NaHCO_3$ solution (3×150 mL) and brine (150 mL), dried over Na_2SO_4 and evaporated. The bis-acetal **20** (7.97 g, quant.) was immediately used without further purification for the next step. It was isolated as a diastereomeric mixture. $\mathbf{R_f}$ = 0.38 (hexanes/EtOAc 6:1); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.56-7.29 (m, 15H), 6.29 (s, 0.60H), 5.96 (s, 0.31H), 5.65 (s, 0.61H), 5.53 (s, 0.32H), 5.28 (s, 0.31H), 5.22 (s, 0.60H), 4.78-4.49 (m, 3H), 4.38-4.19 (m, 2H), 3.94-3.72 (m, 3H) ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{27}H_{27}O_6$ 447.18022, found 447.17924.



21

The raw bis-acetal **20** (7.97 g, 20.3 mmol, 1.00 eq) solved in dry THF (190 mL) at −78 °C under argon atmosphere and was treated with *n*BuLi (2.5M hexanes, 24.4 mL, 2.60 eq.) over 15 minutes. The solution was stirred at −78 °C for 3 h and at −35 °C for 30 min. Sat. aq. NH_4Cl-solution (100 mL) was added and the organic phase was removed by rotary evaporation. The resulting yellow solid was collected by filtration, washed with water (50 mL), crushed, and washed with *n*-pentane (50 mL). The pale yellow solid ketone **21** (5.48 g, 78% over two steps) was dried at the rotary evaporator and was pure enough for the next step. $\mathbf{R_f}$ = 0.47 (hexanes/EtOAc 3:2); **mp** 122 °C (decomposition); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +81.8° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3069 (w), 3032 (w), 2932 (w), 2869 (w), 1733 (w), 1454 (m), 1379 (m), 1267 (m), 1214 (m), 1129 (s), 1093 (s), 1018 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.39-7.30 (m, 8H), 5.59 (s, 1H), 5.33 (d, 1H, J = 4.8 Hz), 4.72 (d, 1H, J = 12.2 Hz), 4.55 (d, 1H, J = 12.2 Hz), 4.32 (m, 2H), 4.22 (dt, 1H, J = 4.8, 10.0 Hz), 3.91 (t, 1H, J = 10.1 Hz), 2.86 (ddd, 1H, J = 1.2, 4.9, 14.7 Hz), 2.72 (dd, 1H, J = 0.9, 14.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 197.7, 136.8, 136.6, 129.5, 128.7, 128.5, 128.2, 128.1, 126.6, 102.3, 98.8, 83.3, 69.6, 69.5, 65.5, 46.5 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{20}O_5Na$ 363.12029, found 363.11918.

(2*R*,4a*R*,6*S*,8*R*,8a*R*)-6-(Benzyloxy)-2-phenyl-8-vinylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol (22)

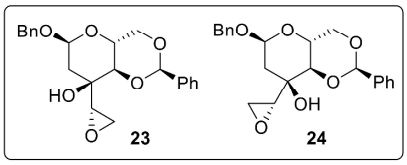


22

Ketone **21** (213 mg, 626 µmol, 1.00 eq.) was solved in dry THF (6.3 mL) under argon atmosphere at −78 °C. VinylMgBr (1M THF, 1.88 mL, 1.88 mmol, 3.00 eq.) was slowly dropped into the solution which was stirred for 3 h at −78 °C. Sat. aq. NH_4Cl solution (30 mL) and H_2O (30 mL) were added, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The crude allyl alcohol **22** was

purified by column chromatography (SiO_2, pentane/EtOAc 4:1). The alcohol **22** (192 mg, 83%) was obtained as colourless solid. $\mathbf{R_f}$ = 0.82 (hexanes/EtOAc 3:2); **mp** 109.6 °C; $[\alpha]_D^{20}$ +139.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3518 (br. w), 3067 (w), 3033 (w), 2968 (w), 2933 (w), 2863 (w), 1455 (m), 1387 (m), 1116 (s), 1089 (s), 1017 (s), 905 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.40-7.28 (m, 8H), 5.89 (dd, 1H, *J* = 10.8, 17.2 Hz), 5.59 (s, 1H), 5.45 (dd, 1H, *J* = 1.3, 17.2 Hz), 5.21 (dd, 1H, *J* = 1.3, 10.8 Hz), 5.00 (dd, 1H, *J* = 1.2, 3.7 Hz), 4.79 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.28 (m, 2H), 4.22 (dt, 1H, *J* = 4.8, 10.0 Hz), 3.78 (m, 1H), 3.59 (d, 1H, *J* = 9.3 Hz), 3.56 (s, 1H), 2.05 (dd, 1H, *J* = 1.3, 14.8 Hz), 2.01 (dd, 1H, *J* = 3.8, 14.8 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 140.5, 137.5, 137.0, 129.0, 128.7, 128.3, 128.2, 128.2, 126.3, 115.3, 102.0, 96.4, 82.3, 71.0, 69.7, 69.4, 60.0, 40.4 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{22}H_{24}O_5Na$ 391.15160, found 391.15074.

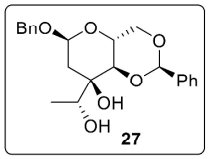
(2*R*,4a*R*,6*S*,8*R*,8a*R*)-6-(Benzyloxy)-8-((*S*)-oxiran-2-yl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol (23) and (2*R*,4a*R*,6*S*,8*R*,8a*R*)-6-(benzyloxy)-8-((*R*)-oxiran-2-yl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol (24)



To a solution of allylalcohol **22** (50 mg, 136 µmol, 1.00 eq.) in CH_2Cl_2 at room temperature was added MCPBA (58.5 mg, 339 µmol, 2.50 eq.). The solution was stirred for 22 h and sat. aq. $Na_2S_2O_3$ solution (2 mL) and sat. aq. $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with EtOAc (3×15 mL), the combined organic phases were washed with 10% K_2CO_3 solution (15 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated. The diastereomeric mixture was separated by SiO_2 column chromatography (pentane/EtOAc 5:1 to 2:1). The optical pure epoxides **24** (37 mg, 71%) and **23** (9 mg, 17%) were isolated as colourless crystalline solids. **24**: $\mathbf{R_f}$ = 0.39 (hexanes/EtOAc 2:1); **mp** 113.9 °C; $[\alpha]_D^{20}$ +99.0° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3507 (br. w), 3067 (w), 3035 (w), 2934 (w), 2864 (w), 1455 (m), 1388 (m), 1099 (s), 1018 (s), 905 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.39-7.28 (m, 8H), 5.65 (s, 1H), 5.06 (d, 1H, *J* = 3.5 Hz), 4.76 (d, 1H, *J* = 11.9 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 4.33 (dd, 1H, *J* = 5.1, 10.2 Hz), 4.23 (dt, 1H, *J* = 5.1, 10.0 Hz), 3.82 (t, 1H, *J* = 10.0 Hz), 3.69 (d, 1H, *J* = 9.6 Hz), 3.63 (s, 1H), 3.16 (dd, 1H, *J* = 2.7, 4.1 Hz), 2.90 (dd, 1H, *J* = 2.7, 5.0 Hz), 2.78 (dd, 1H, *J* = 4.1, 5.0 Hz), 1.99 (dd, 1H, *J* = 1.3, 14.7 Hz), 1.91 (dd, 1H, *J* = 4.0, 14.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.4, 136.7, 129.1, 128.7, 128.3, 128.3, 128.2, 126.3, 102.0, 96.6, 80.6, 69.8, 69.4, 68.9, 59.6, 54.3, 43.8, 35.8 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{22}H_{24}O_6Na$ 407.14651,

found 407.14562. **23**: $\mathbf{R_f}$ = 0.32 (hexanes/EtOAc 2:1); **mp** 120.6 °C; $[\boldsymbol{\alpha}]_D^{20}$ +58.7° (c 0.6 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3506 (br. w), 3067 (w), 3035 (w), 2975 (w), 2931 (w), 2864 (w), 1455 (m), 1386 (w), 1119 (s), 1096 (s), 1025 (s) 911 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.40-7.16 (m, 8H), 5.63 (s, 1H), 4.99 (d, 1H, *J* = 4.4 Hz), 4.77 (d, 1H, *J* = 12.2 Hz), 4.58 (d, 1H, *J* = 12.2 Hz), 4.28 (m, 2H), 3.77 (m, 1H), 3.62 (m, 1H), 3.23 (s, 1H), 3.02 (dd, 1H, *J* = 2.7, 4.1 Hz), 2.90 (dd, 1H, *J* = 2.7, 5.2 Hz), 2.69 (dd, 1H, *J* = 4.1, 5.2 Hz), 2.04 (dd, 1H, *J* = 1.1, 14.9 Hz), 1.97 (dd, 1H, *J* = 0.8, 14.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.3, 137.2, 129.1, 128.7, 128.4, 128.3, 128.1, 126.2, 101.7, 95.8, 80.5, 69.6, 69.3, 68.5, 59.2, 55.9, 43.7, 37.2 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{24}O_6Na$ 407.14651, found 407.14557.

(2*R*,4a*R*,6*S*,8*R*,8a*R*)-8-((*S*)-1-Azidoethyl)-6-(benzyloxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol (7)



27

$LiAlH_4$ (128 mg, 3.38 mmol, 2.00 eq.) was suspended in dry THF (14 mL) at 0 °C under argon atmosphere and epoxide **24** (649 mg, 1.69 mmol, 1.00 eq) in dry THF (20 mL) was added dropwise. The solution was stirred at 0 °C for 30 min and at room temperature for 2 h. AcMe (1.7 mL) was added, the solution stirred for 5 min, poured into a mixture of EtOAc (20 mL) and sat. aq. Na,K-tartrate solution (300 mL) and stirred for 2 h. The aqueous phase was separated and extracted with EtOAc (3×100 mL). The organic phases were washed with brine (100 mL), dried over Na_2SO_4 and the solvent removed in vacuo. Alcohol **27** (669 mg, quant.) was obtained as colourless resin and used without further purification in the next step. $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{20}$ +81.5° (c 0.9 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3500 (br. w), 3067 (w), 3032 (w), 2971 (w), 2934 (w), 2873 (w), 1455 (m), 1397 (m), 1095 (s), 1078 (s), 1014 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.40-7.12 (m, 8H), 5.62 (s, 1H), 5.06 (t, 1H, *J* = 2.7 Hz), 4.77 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.31 (dd, 1H, *J* = 5.1, 10.0 Hz), 4.24 (dt, 1H, *J* = 5.1, 9.8 Hz), 3.94 (qn, 1H, *J* = 6.4 Hz), 3.87 (d, 1H, *J* = 9.6 Hz), 3.79 (t, 1H, *J* = 10.1 Hz), 3.64 (s, 1H), 1.98 (m, 2H), 1.78 (m, 1H), 1.25 (d, 3H, *J* = 6.5 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.5, 137.0, 129.2, 128.7, 128.4, 128.3, 128.2, 126.3, 101.9, 97.0, 79.0, 72.3, 69.7, 69.5, 69.0, 59.6, 34.1, 17.5 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{26}O_6Na$ 409.16216, found 409.16121.

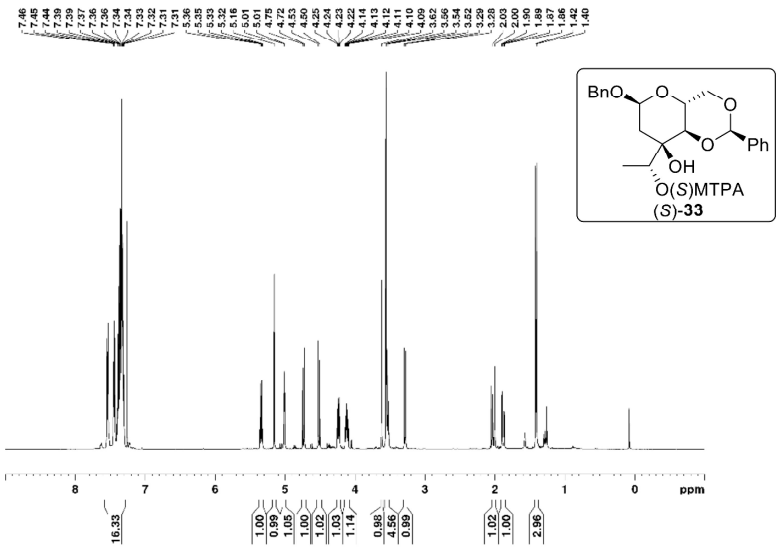


Fig. S1. ^{1}H-NMR-spectrum of (*S*)-**33**. (*S*)-Mosher ester of **27**.

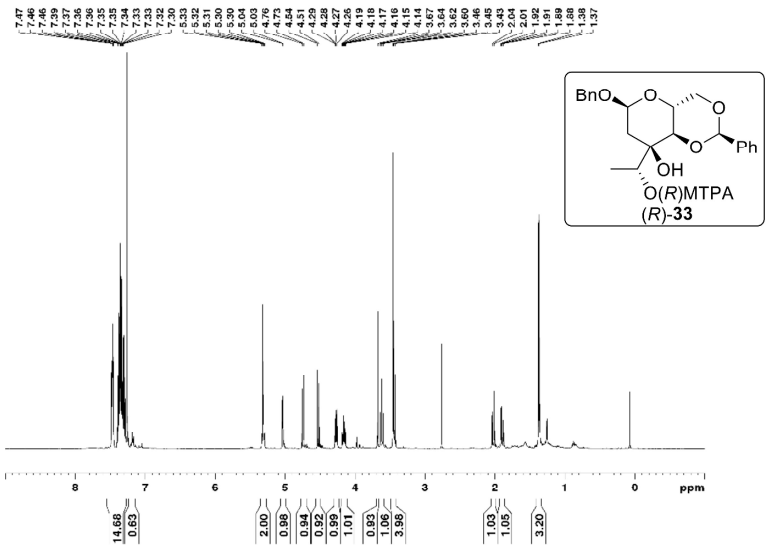
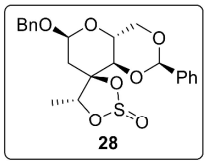


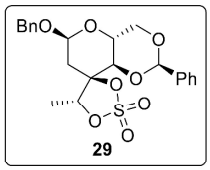
Fig. S2. ^{1}H-NMR-spectrum of (*R*)-**33**. (*R*)-Mosher ester of **27**.

The stereogenic centre of the secondary alcohol in **27** was determined by Mosher ester method. Comparison of the ^{1}H-NMR-spectra of (*S*)-**33** (fig. S1) and (*R*)-**33** (fig. S1) indicated the secondary alcohol to be (*R*)-configurated. Exact $\Delta\delta^{SR} = \delta^{S} - \delta^{R}$–values are shown in Figure 1 (main manuscript). The stereogenic determination was made by standard procedure.



28

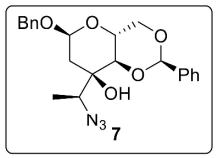
To a solution of diol **27** (654 mg, 1.69 mmol, 1.00 eq.) and dest. dry NEt_3 (1.06 mL, 7.61 mmol, 4.50 eq.) in dry CH_2Cl_2 (16.9 mL) under argon atmosphere was added $SOCl_2$ (307 µL, 4.23 mmol, 2.50 eq.) at 0 °C. The solution was stirred at 0 °C for 3 h and sat aq. NH_4Cl solution (25 mL) was mixed by. The aqueous phase was extracted with EtOAc (4×25 mL) and the combined organic phases were washed with sat. aq. NH_4Cl solution (2×20 mL), sat. aq. $NaHCO_3$ solution (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, evaporated and the raw sulfite **28** (774 mg, quant.) used without purification. $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −10.8° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3065 (w), 3030 (w), 2980 (w), 2932 (w), 2870 (w), 1455 (m), 1386 (m), 1207 (s) 1101 (s), 1026 (s), 911 (s), 878 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.65-7.27 (m, 10H), 5.64 (s, 0.28H), 5.58 (s, 0.72H), 4.98 (m, 1H), 4.78 (m, 1H), 4.69 (q, 0.75H, J = 6.5 Hz) 4.56 (m, 1H), 4.37-4.27 (m, 1.30H), 4.23 (m, 1H), 3.80-3.66 (m, 1.58H), 3.58 (d, 0.73H, J = 9.4 Hz), 2.29 (d, 0.73H, J = 14.8 Hz), 2.10 (m, 1H), 1.95 (dd, 0.29H, J = 4.7, 14.8 Hz), 1.61 (d, 0.81H, J = 6.6 Hz), 1.55 (d, 2.13H, J = 6.5 Hz) ppm; major diastereomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.5, 137.0, 129.3, 128.6, 128.4, 127.8, 127.8, 126.1, 101.1, 94.8, 87.5, 80.9, 77.0, 69.4, 69.2, 58.7, 37.3, 13.7 ppm; minor diastereomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.4, 137.1, 129.1, 128.6, 128.4, 128.0, 128.0, 126.7, 101.9, 94.9, 85.0, 85.0, 77.1, 69.5, 69.3, 59.6, 39.4, 16.1 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{22}H_{24}O_7SNa$ 455.11349, found 455.11272.



29

The sulfite **28** (724 mg, 1.58 mmol, 1.00 eq.) was solved in MeCN (9 mL)/H_2O (4.5 mL) at room temperature and $NaIO_4$ (355 mg, 1.66 mmol, 1.05 eq.) and $RuCl_3 \cdot xH_2O$ (16 mg, 79.0 µmol, 5 mol%) were added. The mixture was stirred at room temperature for 7 h, sat. aq. $Na_2S_2O_3$ solution (40 mL) was added and extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The crude sulfate **29** (678 mg, 96%) was pure enough for the next step without purification. $\mathbf{R_f}$ = 0.34 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ +74.1° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3069 (w), 3033 (w), 2926 (w), 2871 (w), 1455 (m), 1380 (s), 1208 (s), 1130 (m), 1105 (s), 1026 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.41-7.27 (m, 8H), 5.62 (s, 1H), 4.97 (d, 1H, J = 4.7 Hz), 4.75 (d, 1H, J = 12.4 Hz), 4.71 (q, 1H, J = 6.5 Hz), 4.54 (d, 1H, J = 12.4 Hz), 4.30 (dt, 1H, J = 5.2, 9.9 Hz), 4.23 (dd, 1H, J = 5.2, 10.4 Hz), 3.74 (t, 1H, J = 10.4 Hz), 3.71 (d, 1H, J = 9.9 Hz), 2.33 (d, 1H, J = 15.1 Hz), 1.98 (dd, 1H, J = 4.7, 15.1 Hz), 1.25 (d, 3H, J = 6.5 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.2, 136.7, 129.4, 128.6, 128.5, 128.0, 127.9, 126.4, 101.7, 94.5, 88.6, 83.7,

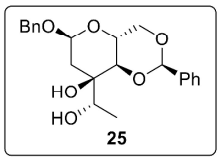
77.0, 69.5, 69.4, 69.1, 58.8, 37.5, 13.6 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{22}H_{25}O_8S$ 449.12646, found 449.12551.



7

A solution of sulfate **29** (640 mg, 1.43 mmol, 1.00 eq.) in dry DMF (7.1 mL) under argon atmosphere was treated with NaN_3 (464 mg, 7.14 mmol, 5.00 eq.) and stirred at 65 °C for 6.75 h. The resulting sodium sulfate was hydrolyzed by adding pH 4.5 citrate-buffer (50 mL) and EtOAc (20 mL) and stirring at 45 °C for 15 h. Further citric acid (5 g) was added and stirring at 45 °C was continued for 3.5 h. The mixture was extracted with EtOAc (4×50 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ solution (50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated. Column chromatography (SiO_2, pentane/EtOAc 6:1) led to azide **7** (370 mg, 63%; 61% over 4 steps) as colourless solid. $\mathbf{R_f}$ = 0.38 (hexanes/EtOAc 4:1); **mp** 86.3 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ +106.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3504 (br. m), 3069 (w), 3037 (w), 2980 (w), 2934 (w), 2872 (w), 2092 (br. s), 1455 (m), 1402 (m), 1264 (m), 1117 (s), 1096 (s), 1019 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.41-7.18 (m, 8H), 5.59 (s, 1H), 5.09 (d, 1H, J = 3.8 Hz), 4.78 (d, 1H, J = 11.9 Hz), 4.56 (d, 1H, J = 11.9 Hz), 4.34 (dd, 1H, J = 5.1, 10.2 Hz), 4.22 (dt, 1H, J = 5.1, 9.8 Hz), 4.08 (s, 1H), 3.84 (q, 1H, J = 6.9 Hz), 3.80 (t, 1H, J = 10.2 Hz), 3.64 (d, 1H, J = 9.5 Hz), 2.06 (d, 1H, J = 14.8 Hz), 1.94 (dd, 1H, J = 4.0, 14.8 Hz), 1.27 (d, 3H, J = 6.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.3, 136.6, 129.2, 128.8, 128.4 (2 signals), 128.3, 126.3, 101.9, 97.0, 79.9, 73.8, 69.9, 69.4, 62.4, 59.7, 35.0, 15.0 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{25}O_5N_3Na$ 434.16864, found 434.16775.

(2*R*,4a*R*,6*S*,8*R*,8a*R*)-6-(Benzyloxy)-8-((*S*)-1-hydroxyethyl)-2-phenylhexahydropyrano-[3,2-*d*][1,3]dioxin-8-ol (25)

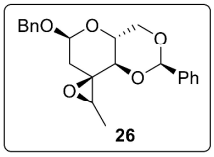


25

Epoxide **23** (475 mg, 1.24 mmol, 1.00 eq.) in dry THF (5 mL) was added to a suspension of $LiAlH_4$ (93.7 mg, 2.47 mmol, 2.00 eq.) in dry THF (20 mL) under argon atmosphere at 0 °C. The solution was stirred at 0 °C for 5 min and at room temperature for 1.75 h. EtOAc (15 mL) was added, the mixture stirred for 5 min and poured into Na,K-tartrate solution (150 mL). After stirring for 40 min the mixture was extracted with EtOAc (3×75 mL). The combined organic phases were washed with brine (75 mL), dried over Na_2SO_4 and evaporated. After column chromatography (SiO_2, pentane/EtOAc 4:1) the diol **25** (462 mg, 97%) was obtained as colourless resin. $\mathbf{R_f}$ =

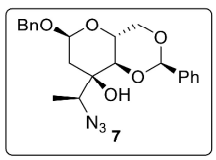
0.46 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ +121.8° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3499 (br. m), 3033 (w), 2975 (w), 2934 (w), 2871 (w), 1455 (m), 1397 (m), 1101 (s), 1018 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.39-7.16 (m, 8H), 5.59 (s, 1H), 5.07 (d, 1H, J = 3.8 Hz), 4.78 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 12.0 Hz), 4.31 (dd, 1H, J = 5.1, 10.2 Hz), 4.24 (dt, 1H, J = 5.1, 9.8 Hz), 4.06 (q, 1H, J = 6.5 Hz), 3.92 (s, 1H), 3.78 (t, 1H, J = 10.1 Hz), 3.64 (d, 1H, J = 9.4 Hz), 2.74 (s, 1H), 2.08 (dd, 1H, J = 1.0, 14.7 Hz), 1.82 (dd, 1H, J = 4.2, 14.7 Hz), 1.25 (d, 3H, J = 6.5 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.2, 136.8, 129.3, 128.7, 128.4, 128.3 (2 signals), 126.3, 102.0, 96.9, 81.3, 72.9, 70.2, 69.8, 69.5, 59.6, 34.0, 16.0 ppm; **HRMS** ESI m/z [M + Na$^+$] calcd. for $C_{22}H_{26}O_6Na$ 409.16216, found 409.16120.

(2R,2'R,3R,4a'R,6'S,8a'R)-6'-(Benzyloxy)-3-methyl-2'-phenyltetrahydro-4'H-spiro-[oxirane-2,8'-pyrano[3,2-d][1,3]dioxine] (26)



26

To a solution of diol **25** (100 mg, 259 µmol, 1.00 eq.) in dry CH_2Cl_2 (2 mL) and pyridine (200 µL) under argon atmosphere at –78 °C was added Tf_2O (87.1 µL, 518 µmol, 2.00 eq.). The solution was stirred at 0 °C for 1.25 h. Sat. aq. $NaHCO_3$ solution(20 mL) and $NaHCO_3$ (solid, 1 g) was mixed by and stirred for 30 min at room temperature. The emulsion was extracted with CH_2Cl_2 (3×20 mL). After washing the combined organic phases with H_2O (20 mL) and brine (20 mL), they were dried over Na_2SO_4 and solvent was removed in vacuo. The pinkish white solid (105 mg, quant.) was used without further purification. $\mathbf{R_f}$ = 0.85 (hexanes/EtOAc 1:1); **mp** 142 °C; $[\alpha]_D^{20}$ +96.0° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3067 (w), 3032 (w), 2968 (w), 2927 (w), 2864 (w), 1454 (m), 1384 (m), 1126 (s), 1095 (s), 1022 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.47-7.26 (m, 10H), 5.58 (s, 1H), 4.98 (d, 1H, J = 4.2 Hz), 4.78 (d, 1H, J = 12.3 Hz), 4.57 (d, 1H, J = 12.3 Hz), 4.30 (dt, 1H, J = 5.0, 9.9 Hz), 4.24 (d, 1H, J = 5.0, 10.3 Hz), 4.05 (d, 1H, J = 9.5 Hz), 3.77 (t, 1H, J = 10.3 Hz), 2.86 (q, 1H, J = 5.7 Hz), 2.37 (dd, 1H, J = 4.2, 14.8 Hz), 1.60 (dd, 1H, J = 0.7, 14.8 Hz), 1.54 (d, 3H, J = 5.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.6, 137.4, 129.0, 128.5, 128.3, 128.1, 127.8, 126.3, 101.7, 96.0, 69.8, 69.2, 61.8, 58.8, 58.3, 38.7, 14.1 ppm; **HRMS** ESI m/z [M + K$^+$] calcd. for $C_{22}H_{24}O_5K$ 407.12553, found 407.12479.

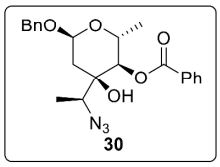


7

Half of the crude epoxide **26** (52.5 mg, 129 µmol, 1.00 eq.) was suspended in MeOH (1.2 mL)/H_2O (300 µL) and treated with NaN_3 (33.5 mg, 516 µmol, 4.00 eq.) and NH_4Cl (13.8 mg, 258 µmol, 2.00 eq.). The mixture was heated at 80 °C for 12 h. The volatile components were

removed by rotary evaporation and the remainder dissolved in EtOAc (15 mL)/H_2O (15 mL). The aqueous phase was separated and extracted with EtOAc (2×10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and evaporated. The crude azide **7** was chromatographed (SiO_2, pentane/EtOAc 3:1) and the pure compound (43 mg, 81%) was obtained as colourless solid. For analytical data see prior performed synthesis of azide **7**.

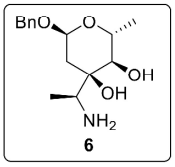
(2*R*,3*R*,4*R*,6*S*)-4-((*S*)-1-Azidoethyl)-6-(benzyloxy)-4-hydroxy-2-methyltetrahydro-2*H*-pyran-3-yl benzoate (30)



30

Azide **7** (360 mg, 875 µmol, 1.00 eq.) was placed in a sealed vessel with TIPST (187 µL, 875 µmol, 1.00 eq), DTBP (81.1 µL, 438 µmol, 0.50 eq.) and degassed *n*-octane (18 mL) under argon atmosphere. The solution was heated at 140 °C for 6.75 h, the solvent was removed in vacuo and the remainder was chromatographed (SiO_2, pentane/EtOAc 15:1 to 12:1). The ester **30** (179 mg, 50%) was obtained as colourless solid. $\mathbf{R_f}$ – 0.59 (hexanes/EtOAc 4:1); **mp** 90.1 °C; $[\boldsymbol{\alpha}]_D^{20}$ +111.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3492 (br. m), 2981 (w), 2937 (w), 2912 (w), 2093 (s), 1721 (s), 1453 (m), 1267 (s), 1113 (s), 1027 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.11 (m, 2H), 7.60 (tt, 1H, J = 1.3, 7.4 Hz), 7.47 (m, 2H), 7.42-7.30 (m, 5H), 5.13 (d, 1H, J = 3.8 Hz), 5.01 (d, 1H, J = 9.7 Hz), 4.78 (d, 1H, J = 11.9 Hz), 4.57 (d, 1H, J = 11.9 Hz), 4.40 (s, 1H), 4.24 (dq, 1H, J = 6.4, 9.7 Hz), 3.60 (q, 1H, J = 6.9 Hz), 2.16 (dd, 1H, J = 1.0, 14.6 Hz), 1.87 (dd, 1H, J = 4.0, 14.6 Hz), 1.22 (d, 3H, J = 6.3 Hz), 1.15 (d, 3H, J = 6.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 166.1, 136.7, 133.7, 130.1, 129.5, 128.8, 128.7, 128.4, 128.3, 96.7, 75.7, 74.4, 69.9, 63.5, 62.1, 34.0, 17.5, 15.0 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{22}H_{25}O_6N_3Na$ 434.16864, found 434.16795.

(2*R*,3*R*,4*R*,6*S*)-4-((*S*)-1-Aminoethyl)-6-(benzyloxy)-2-methyltetrahydro-2*H*-pyran-3,4-diol (6)

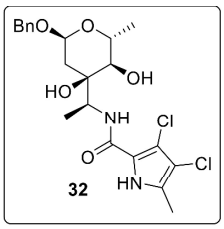


6

To a suspension of $LiAlH_4$ (22 mg, 583 µmol, 3.00 eq.) in dry THF (4 mL) under argon atmosphere at 0 °C was added dropwise ester **30** (80 mg, 194 µmol, 1.00 eq.). The solution was stirred at 0 °C for 7 h and further 17 h at room temperature. EtOAc (1 mL) was mixed by, stirred for 5 min and poured into sat. aq. Na,K-tartrate solution (10 mL). The suspension was stirred further 2 h and extracted with EtOAc (3×40 mL). The combined organic phases were washed with brine, dried

over Na_2SO_4, and evaporated. After column chromatography (SiO_2, CH_2Cl_2/MeOH+0.5% NEt_3 30:1 to 4:1) amine **6** (43 mg, 79%) was obtained as colourless resin. $\mathbf{R_f}$ = 0.11 (CH_2Cl_2/MeOH 4:1); $[\boldsymbol{\alpha}]_D^{20}$ +108.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3500-2500 (m), 3031 (m), 2970 (m), 2931 (m), 1735 (w), 1586 (m), 1455 (m), 1379 (m), 1258 (m), 1126 (s), 1064 (s), 1019 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.97 (d, 1H, J = 3.8 Hz), 4.71 (d, 1H, J = 11.8 Hz), 4.46 (d, 1H, J = 11.9 Hz), 4.09 (br. s, 4H), 3.85 (dq, 1H, J = 6.2, 9.4 Hz), 3.32 (d, 1H, J = 9.5 Hz), 3.05 (q, 1H, J = 6.5 Hz), 1.96 (dd, 1H, J = 0.8, 14.5 Hz), 1.57 (dd, 1H, J = 4.0, 14.5 Hz), 1.31 (d, 3H, J = 6.2 Hz), 1.12 (d, 3H, J = 6.5 Hz) ppm; **^{1}H-NMR** (500 MHz, CD_3OD) δ 7.42-7.26 (m, 5H), 5.03 (d, 1H, J = 3.8 Hz), 4.71 (d, 1H, J = 11.8 Hz), 4.51 (d, 1H, J = 11.9 Hz), 3.88 (dq, 1H, J = 6.3, 9.5 Hz), 3.23 (d, 1H, J = 9.5 Hz), 3.18 (q, 1H, J = 6.7 Hz), 1.93 (dd, 1H, J = 1.1, 14.5 Hz), 1.70 (dd, 1H, J = 4.0, 14.5 Hz), 1.27 (d, 3H, J = 6.3 Hz), 1.08 (d, 3H, J = 6.8 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.0, 128.6, 128.2, 128.1, 96.4, 77.6, 71.7, 69.3, 65.0, 54.3, 36.0, 18.3, 17.8 ppm; **^{13}C-NMR** (125 MHz, CD_3OD) δ 138.7, 129.5, 129.2, 129.0, 98.0, 75.9, 74.5, 70.4, 66.1, 52.6, 34.4, 18.2, 16.4 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{15}H_{24}O_4N$ 282.16998, found 282.16969.

_N_-((_S_)-1-((2_R_,3_R_,4_R_,6_S_)-6-(Benzyloxy)-3,4-dihydroxy-2-methyltetrahydro-2_H_-pyran-4-yl)ethyl)-3,4-dichloro-5-methyl-1_H_-pyrrole-2-carboxamide (32)



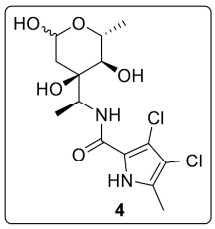
32

A solution of amine **6** (45 mg, 160 µmol, 1.00 eq.), carboxylic acid **31** (38.8 mg, 200 µmol, 1.25 eq.), HOBt (30.6 mg, 200 µmol, 1.25 eq.) and dry NEt_3 (55.8 µL, 400 µmol, 2.50 eq.) in dry CH_2Cl_2 (2 mL) was treated with EDC·HCl (61.3 mg, 320 µmol, 2.00 eq.) at 0 °C under argon atmosphere. The solution was slowly warmed to room temperature over 3 h and stirred further 13 h at room temperature. The reaction was quenched with 1M HCl (2 mL) and poured into a mixture of EtOAc (40 mL) and 1M HCl (40 mL). The organic phase was separated, and the aqueous phase extracted with EtOAc (2×40 mL). The combined organic phases were washed with 1M HCl (40 mL), sat. aq. $NaHCO_3$ solution (2×40 mL) and brine (40 mL). After drying over Na_2SO_4, the organic phase was evaporated and chromatographed (SiO_2, CH_2Cl_2/MeOH 100:1 to 40:1). The amide **32** (61 mg, 83%) was obtained as a reddish solid foam. $\mathbf{R_f}$ = 0.74 (CH_2Cl_2/MeOH 9:1); **mp** 68.6 °C; $[\boldsymbol{\alpha}]_D^{20}$ +90.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3412 (br. m), 3208 (br. m), 2976 (w), 2933 (m), 1629 (s), 1532 (s), 1455 (m), 1413 (m), 1272 (m), 1126 (m), 1047 (s), 1023 (m), 759 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 11.00, (s, 1H), 7.40-7.28 (m, 5H), 6.93 (d, 1H, J = 8.8 Hz), 5.04 (d, 1H, J = 3.4 Hz), 4.72 (d, 1H, J =

11.8 Hz), 4.50 (d, 1H, *J* = 11.9 Hz), 4.46 (m, 1H), 4.16 (s, 1H), 3.76 (dq, 1H, *J* = 6.2, 9.4 Hz), 3.27 (d, 1H, *J* = 9.3 Hz), 2.47 (br. s, 1H), 2.25 (s, 3H), 2.02 (d, 1H, *J* = 14.4 Hz), 1.86 (dd, 1H, *J* = 3.9, 14.4 Hz), 1.34 (d, 3H, *J* = 6.2 Hz), 1.26 (d, 3H, *J* = 6.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 159.6, 136.7, 128.7, 128.5, 128.3, 128.2, 118.5, 111.0, 110.1, 96.3, 74.3, 73.5, 69.6, 65.7, 50.5, 35.2, 18.0, 16.4, 11.2 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{21}H_{26}O_5N_2Cl_2Na$ 479.11110, found 479.11029.

3,4-Dichloro-5-methyl-*N*-((1*S*)-1-((2*R*,3*R*,4*R*)-3,4,6-trihydroxy-2-methyltetrahydro-2*H*-pyran-4-yl)ethyl)-1*H*-pyrrole-2-carboxamide (4)

To a solution of amide **32** (20 mg, 43.7 µmol, 1.00 eq.) in dry CH_2Cl_2 (2 mL) under argon atmosphere was added BCl_3 (1M CH_2Cl_2, 219 µL, 219 µmol, 5.00 eq.) at −80 °C. The solution was stirred at −80 °C for 40 min and a few drops of H_2O were added. The emulsion was evaporated to dryness and chromatographed (SiO_2, CH_2Cl_2/MeOH 40:1 to 15:1). The anomeric mixture of amycolose derivative **4** (13 mg, 81%) was obtained as colourless resin. **R_f** = 0.35, 0.42 (CH_2Cl_2/MeOH 9:1); **IR** ν_{max}/cm^{-1} 3668-3028 (br. m), 2976 (w), 2932 (m), 1758 (w), 1706 (m), 1627 (s), 1536 (s), 1416 (m), 1377 (m), 1269 (m), 1067 (s), 1001 (m), 803 (w), 764 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) *δ* 9.62 (s, 0.83H), 9.56 (s, 0.19H), 6.65 (d, 1H, *J* = 6.5 Hz), 6.21 (br. s, 0.72H), 5.64 (br. s, 0.64H), 5.23 (d, 0.81H, *J* = 3.5 Hz), 5.15 (dd, 0.19H, *J* = 2.1, 9.3 Hz), 4.41 (qn, 1H, *J* = 6.8 Hz), 4.00 (dq, 0.82H, *J* = 6.2, 9.3 Hz), 3.69 (dq, 0.19H, *J* = 6.3, 9.2 Hz), 3.19 (d, 0.74H, *J* = 9.3 Hz), 3.17 (d, 0.26H, *J* = 9.1 Hz), 2.94-1.53 (m, 6.78H), 2.29 (s, 2.23H), 2.28 (s, 0.78H), 1.99 (dd, 0.24H, *J* = 2.3, 13.3 Hz), 1.95 (d, 0.95H, *J* = 1.0, 13.9 Hz), 1.70 (dd, 0.87H, *J* = 3.9, 13.9 Hz), 1.46 (dd, 0.26H, *J* = 9.3, 13.0 Hz), 1.34 (d, 3H, *J* = 6.2 Hz), 1.31 (d, 3H, *J* = 7.0 Hz) ppm; **^{1}H-NMR** (500 MHz, CD_3OD) *δ* 5.21 (m, 0.75H), 5.05 (d, 0.31H, *J* = 2.1, 9.5 Hz), 4.37 (m, 1H), 4.05 (dq, 0.68H, *J* = 6.2, 9.4 Hz), 3.73 (dq, 0.30H, *J* = 6.2, 9.2 Hz), 3.21 (d, 0.73H, *J* = 9.4 Hz), 3.17 (d, 0.33H, *J* = 9.3 Hz), 2.23 (s, 3H), 1.90 (dd, 0.73H, *J* = 1.4, 14.1 Hz), 1.88 (dd, 0.27H, *J* = 2.1, 13.3 Hz), 1.80 (dd, 0.73H, *J* = 3.9, 14.1 Hz), 1.53 (dd, 0.31H, *J* = 9.5, 13.3 Hz), 1.26 (m, 6H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 161.7, 161.5, 129.3, 129.1, 117.4, 117.3, 112.6, 112.4, 111.2, 111.1, 92.9, 92.2, 77.2, 76.3, 74.1, 74.0, 70.8, 64.7, 52.6, 52.5, 37.5, 33.6, 18.2, 18.1, 16.3, 11.5, 11.5 ppm; **^{13}C-NMR** (125 MHz, CD_3OD) *δ* 161.7, 161.6, 129.4, 129.4, 120.0, 120.0, 112.3, 112.2, 110.6, 110.6, 93.5, 92.9, 76.3, 76.1, 75.0, 74.7, 71.6, 65.8, 52.3, 52.0, 39.2, 35.5, 18.6, 18.5, 16.2, 10.8 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{20}O_5N_2Cl_2Na$ 389.06415, found 389.06320.



4

S13

α-/β-Anomeric ratio and signal form of O*H*-groups in ^{1}H-NMR-spectra depends on the purification method as well as solvent and pH.

Spectroscopic data corresponded to those reported in the literature.[2]

Trace impurities in the NMR-spectra of the compounds in the amycolose-sequence can result from the formation of different α-/β-anomers best observed in the ^{1}H-NMR at the anomeric and benzylic position as shown below (fig. S3). The amount of the wrong anomer in the synthesis sequence depends on the purity of the benzyl α-D-mannopyranoside (**9**) as starting material but has no influence on the (diastereoselective) reactions.

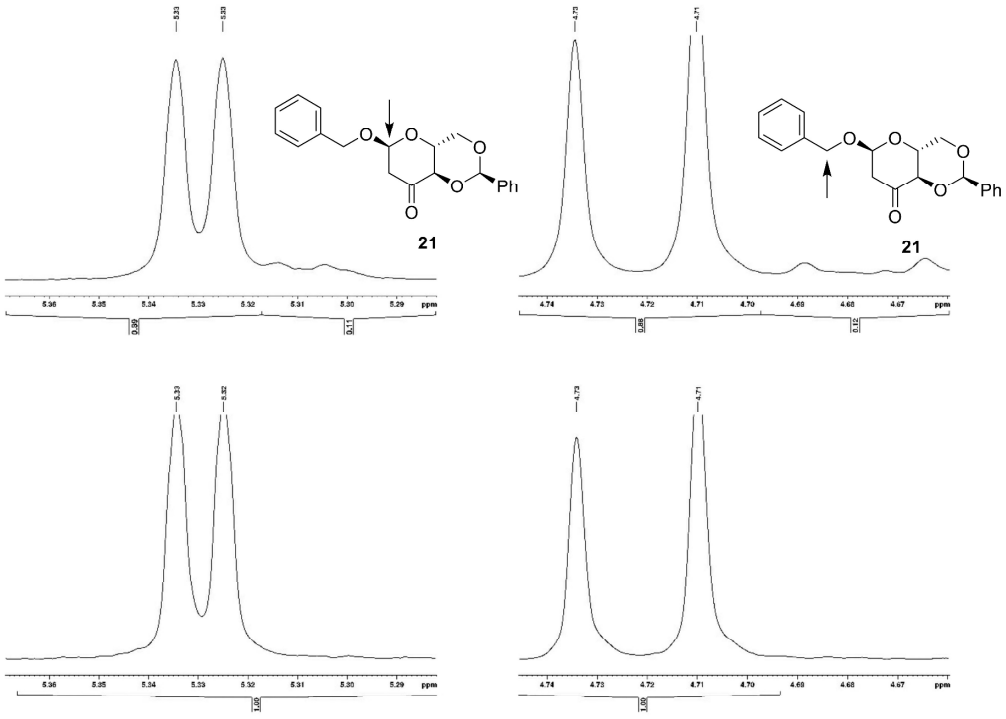
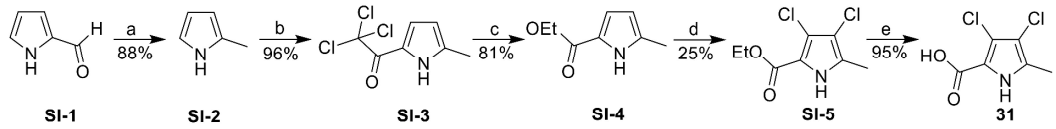


Fig. S3. Comparison of the anomeric (left) and benzylic (right) position of ketone **21** in the ^{1}H-NMR-spectra with different pure starting materials. The upper spectra show a α/β-ratio of ca. 9:1, while the others show 100% α.

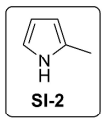
2.2 Synthesis of pyrrole carboxylic acid **31**



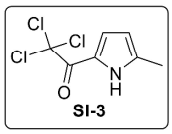
Scheme S2. Synthesis of pyrrole carbonic acid **31**.
Reagents and conditions: a) NaOH, ethylene glycol, $N_2H_4 \cdot xH_2O$, 210 °C, 2.5 h; b) trichloroacetyl chloride, THF, 0 °C, 16 h; c) Na, EtOH, rt, 35 min; d) SO_2Cl_2, CH_2Cl_2, 0 °C, 3.5 h; e) NaOH, H_2O/MeOH, rt, 22 h.

The route is also possible with a methyl ester (Methyl esterification by K_2CO_3/MeOH, 79%).

2,2,2-Trichloro-1-(5-methyl-1*H*-pyrrol-2-yl)ethan-1-one (SI-3)



Pyrrole-2-carbaldehyde (**SI-1**, 5.71 g, 60.0 mmol, 1.00 eq.) and NaOH (12.5 g, 312 mmol, 5.20 eq.) were solved in ethylene glycol (80 mL) under argon atmosphere and hydrazine hydrate (18.1 mL, 372 mmol, 6.20 eq.) was added. The flask was equipped with a Dean-Stark apparatus and heated at 210 °C for 2.5 h. An azeotrope of glycol and 2-methyl pyrrole (**SI-2**) was condensed at the reflux condenser and collected in the Dean-Stark trap as biphasic mixture which was added to Et_2O (200 mL). The organic phase was washed with H_2O (100 mL, 2×50 mL), dried over Na_2SO_4 and evaporated. The raw methyl pyrrole (**SI-2**, 4.28 g, 88%) was used without further purification. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.88 (br. s, 1H), 6.67 (q, 1H, J = 2.2 Hz), 6.15 (q, 1H, J = 2.8 Hz), 5.93 (m, 1H), 2.30 (s, 3H) ppm.
Spectroscopic data corresponded to those reported in the literature.[3]

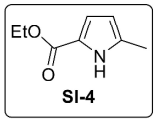


To a solution of trichloro acetylchloride (2.47 mL, 22.0 mmol, 1.10 eq.) in dry THF (10 mL) was slowly added 2-methyl pyrrole (**SI-2**, 1.72 mL, 20.0 mmol, 1.00 eq.) under argon atmosphere at 0 °C. The red solution was stirred at room temperature for 16 h and sat. aq. $NaHCO_3$ solution (100 mL) and 10% aq. K_2CO_3 solution (50 mL) were added. The mixture was extracted with EtOAc (4×50 mL) and the combined organic phases were washed with 10% aq. K_2CO_3 solution (50 mL) as well as brine (50 mL), dried over $NaSO_4$ and evaporated. The pyrrole **SI-3** (4.35 g, 96%) was obtained as

shiny black solid and was pure enough for the next step. **R_f** = 0.85 (hexanes/EtOAc 1:1); **IR** ν_{max}/cm^{-1}3315 (s), 3141 (w), 3102 (w), 2957 (w), 2920 (w), 1764 (w), 1636 (s), 1493 (m), 1399 (m), 1365 (s), 1262 (s), 1218 (s), 1054 (s), 842 (s), 808 (s), 784 (s), 743 (s), 726 (s), 681 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.47 (br. s, 1H), 7.32 (dd, 1H, J = 2.6, 3.7 Hz), 6.11 (t, 1H, J = 3.7 Hz), 2.40 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 172.7, 139.5, 122.8, 122.0, 111.3, 68.7, 13.6 ppm.

Spectroscopic data corresponded to those reported in the literature.[4]

Ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (SI-4)

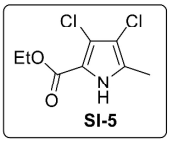


SI-4

Sodium (924 mg, 40.2 mmol, 1.30 eq.) was added to absolute EtOH (33 mL) and stirred until full dilution. Trichloro acetate **SI-3** (7.00 g, 30.9 mmol, 1.00 eq.) was added at room temperature and the solution was stirred for 35 min. It was concentrated at the rotary evaporator and 3M HCl (25 mL) was added. The solution was extracted with Et_2O (3×50 mL) and the organic phases were washed with sat. aq. $NaHCO_3$ solution (50 mL) and brine (50 mL). After drying over Na_2SO_4, the solvent was removed by rotary evaporation. The pale brown pyrrole **SI-4** (3.81 g, 81%) was used without purification. **mp** 97.2 °C, **R_f** = 0.87 (hexanes/EtOAc 2:1); **IR** ν_{max}/cm^{-1} 3288 (s), 3143 (w), 2987 (w), 2913 (w), 1667 (s), 1494 (m), 1321 (s), 1220 (s), 1152 (s), 1025 (s), 801 (s), 774 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 6.81 (m, 1H), 5.95 (m, 1H), 4.30 (q, 2H, J = 7.1 Hz), 2.31 (s, 3H), 1.34 (t, 3H, J – 7.1 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 161.3, 133.7, 121.6, 116.1, 109.0, 60.2, 14.6, 13.3 ppm; **HRMS** ESI m/z $[M + H]^+$ calcd. for $C_8H_{12}NO_2$ 154.08626 found 154.08601.

Spectroscopic data corresponded to those reported in the literature.[4]

Ethyl 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylate (SI-5)

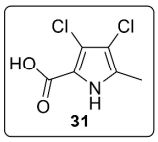


SI-5

Ester **SI-4** (2.06 g, 13.4 mmol, 1.00 eq.) was solved in CH_2Cl_2 (67 mL) at 0 °C and SO_2Cl_2 (2.17 mL, 26.9 mmol, 2.00 eq.) was slowly added. The solution was stirred for 3.5 h at 0 °C and sat. aq. $Na_2S_2O_3$ solution (80 mL) and sat. aq. $NaHCO_3$ solution (100 mL) were added. The mixture was extracted with EtOAc (2×100 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and evaporated. The crude product was chromatographed (SiO_2, pentane/EtOAc 7:1 to 5:1). Pyrrole **SI-5** (741 mg, 25%) was obtained as colourless needles. **R_f** = 0.59

(hexanes/EtOAc 2:1); **IR** ν_{max}/cm^{-1} 3315 (s), 3141 (w), 3102 (w), 2957 (w), 2920 (w), 1764 (m), 1636 (s), 1558 (m), 1493 (m), 1399 (m), 1365 (s), 1262 (s), 1218 (s), 1054 (s), 943 (w), 880 (w), 842 (s), 808 (s), 784 (s), 743 (s), 726 (s), 681 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 4.35 (q, 2H, J = 7.1 Hz), 2.29 (s, 3H), 1.38 (t, 3H, J = 7.1 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 160.0, 129.1, 117.6, 116.2, 111.9, 61.1, 14.5, 11.7 ppm (quaternary C-atoms indicated by HMBC-correlations); **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_8H_{10}Cl_2NO_2$ 222.00831, found 222.00833.

3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (31)

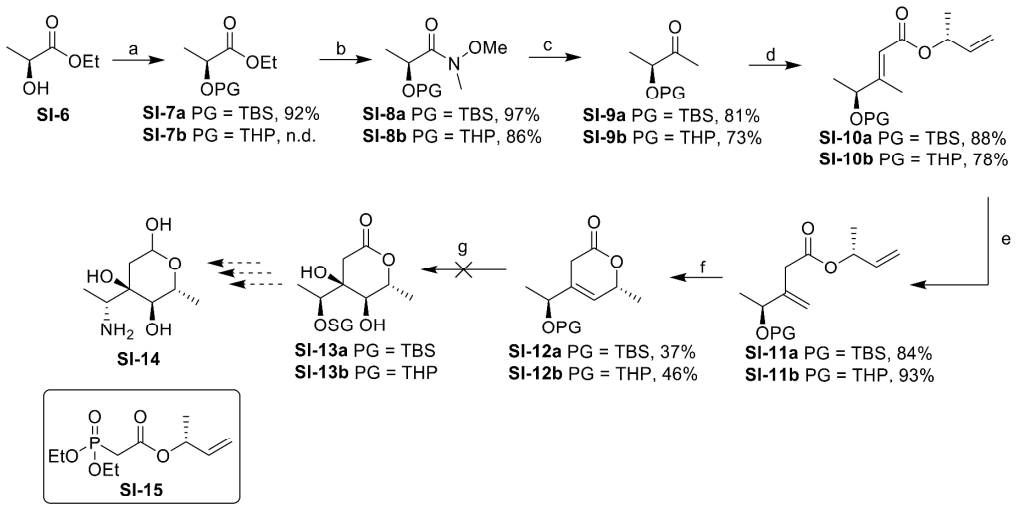


31

Ester **SI-5** (732 mg, 3.30 mmol, 1.00 eq.) was suspended in MeOH (33 mL) and H_2O (8.8 mL) at room temperature and 3M NaOH (4.40 mL, 13.2 mmol, 4.00 eq.) was added. The mixture was stirred for 22 h and further 3M NaOH (20 mL) was added. The mixture was extracted once with EtOAc (20 mL) and the aqueous phase was acidified to pH 1-2 with 1M HCl. The aqueous phase was extracted with EtOAc (3×50 mL). These organic phases were dried over Na_2SO_4 and evaporated. The carboxylic acid **31** (608 mg, 95%) was obtained as red solid. **mp** 102 °C (decomposition).**R_f** = 0.49 (hexanes/EtOAc 2:1); **IR** ν_{max}/cm^{-1} 3113 (s), 2924 (s), 2590 (m), 2325 (s),1646 (s), 1544 (m), 1572 (m), 1498 (s), 1466 (m), 1360 (m), 1326 (m), 1283 (m), 1249 (m), 1102 (m), 1036 (m), 763 (m), 711 (m); **^{1}H-NMR** (500 MHz, CD_3OD) δ 2.23 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, CD_3OD) δ 162.2, 130.6, 117.9, 117.2, 111.6, 10.9 ppm; **HRMS** ESI *m/z* $[M - H]^-$ calcd. for $C_6H_4Cl_2NO_2$ 191.96246, found 191.96179.

2.3 Failed routes amycolose derivative **4**

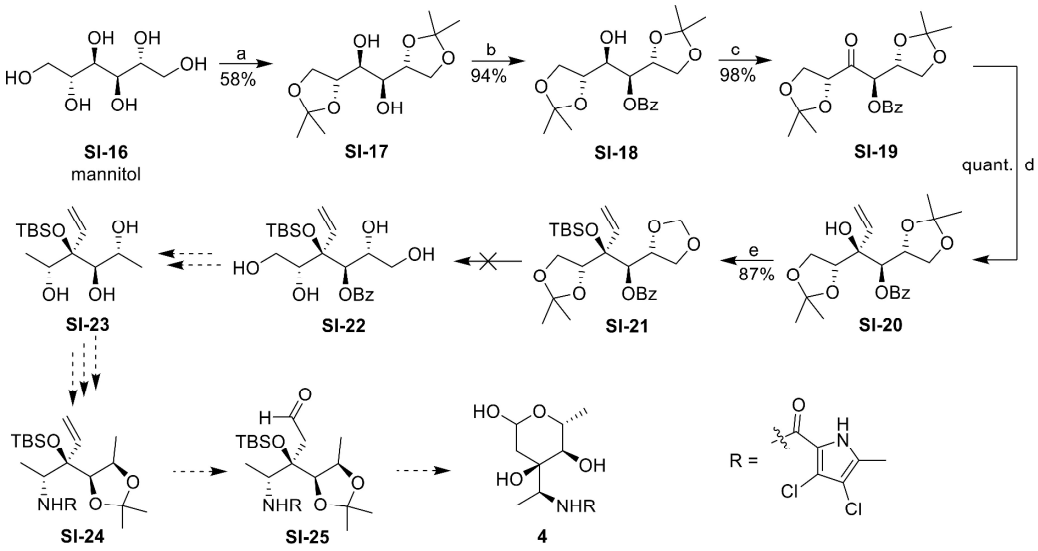
Our first try to build up amycolose derivative **4** was starting from lactic acid ester **SI-6** and perform a *de novo* synthesis of the sugar scaffold. Formation of ketones **SI-9a/b** was accomplished using Weinreb amide method. α,β-unsaturated esters **SI-10a/b** were synthesised in a HWE-olefination of ketones **SI-9a/b** with phosphonate **SI-15** which was itself synthesised by semihydrogenation under Lindlar-conditions of the corresponding alkyne. A base mediated deconjugation formed terminal dienes **SI-11a/b** which led to only low yields in the following Grubbs metathesis reaction. The Sharpless dihydroxylation to diols **SI-13a/b** was not observed. The following steps towards amycolose derived carbohydrate **4** should have been introduction of an amine and reduction of the lactone.



Scheme S3. Attempts to synthesise amycolose derivative **4** starting from lactic acid ester **SI-6**. Reagents and conditions: a) **SI-7a**: TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 19 h; **SI-7b**: DHP, PPTS, CH_2Cl_2, rt; b) MeONHMe·HCl, *i*PrMgCl, LiCl/BuLi, THF, 0 °C, 19 h; c) MeMgBr/MeLi, THF; d) BuLi, LiHMDS, **SI-15**, THF; e) LDA/LiHMDS, HMPT, THF, −78 °C, then AcOH, Et_2O; f) Grubbs catalyst 2nd generation, Ti(O*i*Pr)$_4$, CH_2Cl_2, reflux, 21 h; g) AD-mix.

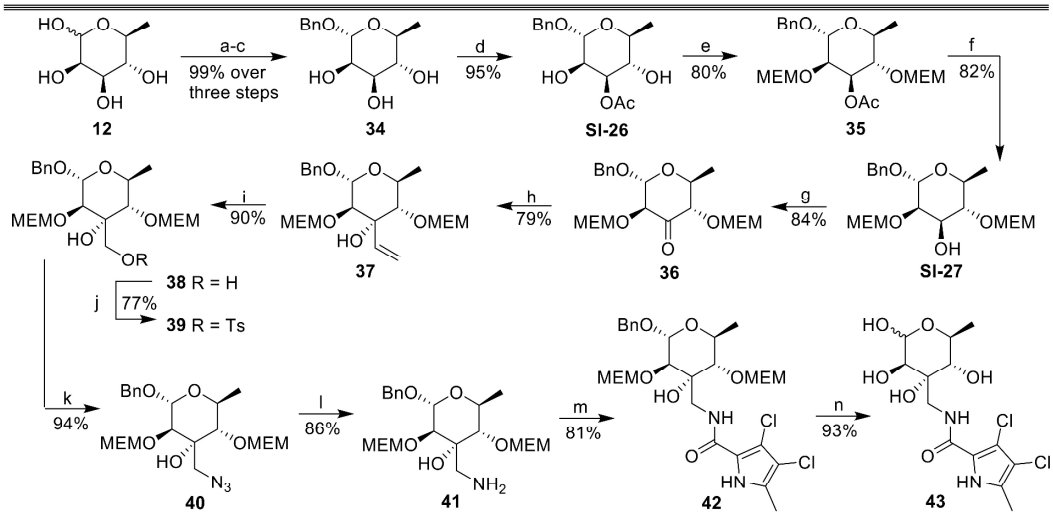
Another idea synthesising amycolose derivative **4** was starting from sugar based mannitol (**SI-16**) using a fully diastereoselective approach. After acetonide protection of both terminal diols a monobenzoylation was carried out (→**SI-18**). The free hydroxyl group was oxidised and ketone **SI-19** was treated with vinylMgBr. After protection of alcohol **SI-20**, the following acetonide deprotection was not possible. The next steps should have been the deoxygenation of

the primary position, protection of the vicinal hydroxy groups as well as amine and aldehyde formation and ultimate deprotection to carbohydrate **4**.



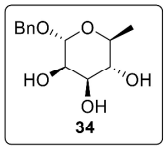
Scheme S4. Attempts to synthesise amycolose starting from mannitol (**SI-16**).
Reagents and conditions: a) $ZnCl_2$, acetone, rt, 15 h; b) Cu(bipy), DIPEA, BzCl, $CH_2Cl_2/CHCl_3$, 0 °C→rt, 5 h; c) DMP, $NaHCO_3$, CH_2Cl_2, rt, 3 h; d) vinylMgBr, THF, −78 °C, 40 min; e) 1. KH, THF, 0 °C, 10 min, 2. TBSCl, rt, 2 h.

2.4 Synthesis of sugar **43** – derivatization of amycolose



Scheme S5. Synthesis of amycolose derived carbohydrate **43**.
Reagents and conditions: a) Ac_2O, pyridine, rt, 22 h; b) BnOH, $BF_3{\cdot}OEt$, 4 Å MS, CH_2Cl_2, 0 °C→rt, on; c) NaOMe, MeOH, rt, 4 d; d) $MoO_2(acac)_2$, collidine, AcCl, 1,4-dioxane, RT, 3 h; e) MEMCl, DIPEA, CH_2Cl_2, 0 °C→40 °C, 1 d; f) DIBAL, toluene, 0 °C, 3 h; g) DMP, CH_2Cl_2, 0 °C→rt, 5 h; h) vinylMgBr, THF, −78 °C, 5 h; i) 1. O_3, CH_2Cl_2/MeOH, −78 °C, 10 min; 2. $NaBH_4$, rt, 24 h; j) *p*TsCl, DMAP, NEt_3, CH_2Cl_2, rt, 21 h; k) NaN_3, DMF, 65 °C, 17 h; l) 1. PPh_3, THF, rt, 2 d; 2. H_2O, rt, 3 d; m) **31**, EDC·HCl, HOBt, DMAP, CH_2Cl_2, 0 °C→rt, on; n) BCl_3, CH_2Cl_2, −78 °C, 3.5 h.

(3*R*,4*R*,5*R*,6*S*)-2-(Benzyloxy)-6-methyltetrahydro-2*H*-pyran-3,4,5-triol (34)



L-Rhamnose (**12**, 10.0 g, 54.9 mmol, 1.00 eq.) was dissolved in Ac_2O (57.0 mL) and pyridine (57.0 mL) at room temperature. The solution was stirred for 22 h and the volatiles were removed under reduced pressure. The crude product was diluted with CH_2Cl_2 and a sat. aq. Cu_2SO_4 solution. The aqueous phase was extracted thrice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. After purification by column chromatography (SiO_2, pentane/EtOAc 5:1→3:1→2:1) the product (18.2 g, 54.9 mmol) was isolated in quantitative yield.

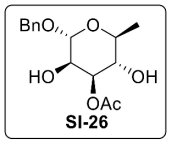
The peracetylated rhamnose (18.0 g, 54.3 mmol, 1.00 eq.) in dry CH_2Cl_2 (147 mL) was treated with BnOH (28.2 mL, 271 mmol, 5.00 eq.) and 4 Å molecular sieve (12 g) at room temperature. After stirring for 30 min $BF_3{\cdot}OEt_2$ (55.0 mL, 434 mmol, 8.00 eq.) was added at 0 °C over a period of 45 min. The mixture was allowed to warm to room temperature overnight. After TLC showed complete conversion of the starting material, the reaction was quenched by slow

addition of H_2O. The mixture was diluted with CH_2Cl_2. The aqueous phase was extracted four times with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was used without further purification.

Fully protected rhamnose (20.7 g, 54.3 mmol, 1.00 eq.) was dissolved in dry MeOH (180 mL) and treated with NaOMe (25wt%, 3.72 mL, 16.3 mmol, 0.30 eq.) at room temperature. After 18 h of stirring, another portion of NaOMe (25wt%, 3.72 mL, 16.3 mmol, 0.30 eq.) was added. Stirring was continued for 3 d. The mixture was neutralised by addition of DOWEX. The solid was filtered off over celite® and the solvents were removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 1:1→0:1) gave the product **34** (13.7 g, 99%, α:β >10:1) as a light yellow resin, minor impurities occurred due to β-anomer. $\mathbf{R_f}$ = 0.40 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −8.52° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3392 (m), 2991 (w), 2906 (w), 1455 (w), 1276 (m), 1261 (m), 1131 (m), 1049 (m), 980 (m), 911 (w), 810 (w), 764 (s), 750 (s), 698 (m); **^{1}H-NMR** (500 MHz, CD_3OD) δ 7.37-7.22 (m, 5H), 4.75 (d, 1H, J – 1.6 Hz), 4.69 (d, 1H, J = 11.9 Hz), 4.51 (d, 1H, J = 11.9 Hz), 3.82 (dd, 1H, J = 1.6, 3.4 Hz), 3.68 (dd, 1H, J = 3.4, 9.5 Hz), 3.62 (dq, 1H, J = 6.2, 9.5 Hz), 3.39 (t, 1H, J = 9.5 Hz), 1.27 (d, 3H, J = 6.2 Hz) ppm; **^{13}C-NMR** (125 MHz, CD_3OD) δ 139.1, 129.4, 129.1, 128.8, 100.8, 74.0, 72.4, 72.3, 70.01, 70.00, 18.0 ppm.

Spectroscopic data corresponded to those reported in the literature.[5]

(3*R*,4*R*,5*S*,6*S*)-2-(Benzyloxy)-3,5-dihydroxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (SI-26)

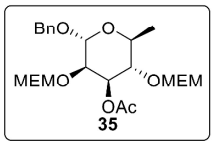


SI-26

Benzylated rhamnose **34** (900 mg, 3.54 mmol, 1.00 eq.) in dry 1,4-dioxane (29 mL) was treated with $MoO_2(acac)_2$ (57.7 mg, 177 µmol, 0.05 eq.), collidine (937 µL, 7.08 mmol, 2.00 eq.) and AcCl (379 µL, 5.31 mmol, 1.50 eq.) at room temperature. The mixture was stirred for 3 h and diluted with H_2O and CH_2Cl_2. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4. The volatiles were removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 2:1→1:1) afforded the product **SI-26** (994 mg, 95%) as a colourless resin. The product was isolated as major isomer of a mixture of different regiosiomers (100:10:7). $\mathbf{R_f}$ = 0.64 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −74.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3439 (m), 2980 (w), 2933 (w), 1717 (m), 1497 (w), 1455 (w), 1372

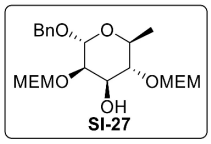
(m), 1275 (m), 1260 (s), 1128 (m), 1049 (s), 983 (m), 886 (w), 842 (w), 805 (w), 764 (s), 750 (s), 699 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.08 (dd, 1H, J = 3.3, 9.8 Hz), 4.83 (d, 1H, J = 1.7 Hz), 4.72 (d, 1H, J = 12.0 Hz), 4.52 (d, 1H, J = 12.0 Hz), 4.05 (dd, 1H, J = 1.7, 3.3 Hz), 3.78 (dq, 1H, J = 6.2, 9.5 Hz), 3.64 (t, 1H, J = 9.8 Hz), 2.45 (br. s, 2H), 2.14 (s, 3H), 1.35 (d, 3H, J = 6.2 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 171.9, 137.0, 128.6, 128.2, 128.1, 98.5, 75.1, 71.7, 70.0, 69.3, 68.9, 21.3, 17.7 ppm; HRMS ESI *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{20}O_6Na$ 315.11521 found 315.11417.

(3*R*,4*R*,5*S*,6*S*)-2-(Benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-2*H*-pyran-4-yl acetate (35)



Carbohydrate **SI-26** (11.4 g, 38.3 mmol, 1.00 eq.) in dry CH_2Cl_2 (58 mL) was treated with DIPEA (20.0 mL, 115 mmol, 3.00 eq.) and MEMCl (13.1 mL, 115 mmol, 3.00 eq.) at 0 °C. After 30 min at 0 °C, the solution was allowed to warm to room temperature. DIPEA (6.67 mL, 38.3 mmol, 1.00 eq.) and MEMCl (4.37 mL, 38.3 mmol, 1.00 eq.) were added after 7 h at 0 °C. The solution was stirred at room temperature overnight and for 6 h at 40 °C. As soon as TLC showed complete conversion, the mixture was allowed to come to room temperature and EtOAc as well as sat. aq. K_2CO_3 solution were added. The organic phase was separated and washed with 1M HCl. The combined aqueous phases were extracted thrice with EtOAc. All organic phases were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the crude product by column chromatography (SiO_2, pentane/EtOAc 4:1→3:1→2:1→1:1) gave the product **35** (14.4 g, 80%) as a colourless resin and as a mixture of regioisomers. $\mathbf{R_f}$ = 0.38 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −79.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2935 (m), 2888 (m), 2816 (w), 1743 (m), 1456 (m), 1367 (m), 1237 (s), 1111 (m), 1035 (s), 750 (m) 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.23 (dd, 1II, J = 3.3, 9.5 IIz), 4.86 (d, 1II, J = 6.7 IIz), 4.85 (d, 1II, J = 2.0 IIz), 4.73 (d, 1II, J = 6.7 Hz), 4.73 (d, 1H, J = 6.7 Hz), 4.72 (d, 1H, J = 6.7 Hz), 4.70 (d, 1H, J = 12.0 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.05 (dd, 1H, J = 2.0, 3.2 Hz), 3.80-3.63 (m, 6H), 3.53 (m, 2H), 3.45 (m, 2H), 3.38 (s, 3H), 3.35 (s, 3H), 2.08 (s, 3H), 1.31 (d, 3H, J = 6.2 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.2, 137.3, 128.5, 128.0, 127.9, 97.7, 96.9, 95.8, 77.7, 75.0, 73.2, 71.8, 71.6, 69.2, 68.0, 67.8, 67.2, 59.22, 59.17, 21.3, 18.1 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{23}H_{36}O_{10}$ 495.21925 found 495.22007.

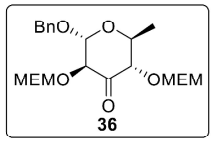
(3*R*,4*R*,5*R*,6*S*)-2-(Benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-2*H*-pyran-4-ol (SI-27)



SI-27

The fully protected sugar **35** (859 mg, 1.82 mmol, 1.00 eq.) in dry toluene (25.0 mL) was treated with DIBAL (3.49 mL, 3.49 mmol, 1.90 eq.) at 0 °C. After stirring for 3 h at this temperature, sat. aq. Na,K-tartrate solution, Na,K-tartrate and acetone were added. The mixture was stirred for 40 min at room temperature. The organic phase was separated, and the aqueous phase was extracted thrice with CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the solvents and purification by column chromatography (SiO_2, pentane/EtOAc 2:1→1:1→0:1) afforded product **SI-27** (640 mg, 82%) as a colourless oil and as a mixture of regioisomers. $\mathbf{R_f}$ = 0.71 (CH_2Cl_2/MeOH 95:5); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ −61.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3463 (m), 2980 (m), 2924 (m), 2889 (m), 2826 (w), 1455 (m), 1366 (w), 1276 (m), 1261 (m), 1112 (m), 1024 (s), 984 (m), 845 (m), 800 (w), 764 (s), 750 (s), 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.93 (d, 1H, J = 6.8 Hz), 4.91 (d, 1H, J = 1.5 Hz), 4.91 (d, 1H, J = 6.8 Hz), 4.80 (d, 1H, J = 7.1 Hz), 4.78 (d, 1H, J = 7.1 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.48 (d, 1H, J = 11.9 Hz), 3.96 (m, 1H), 3.89 (m, 2H), 3.78 (m, 2H), 3.70 (m, 3H), 3.56 (m, 2H), 3.50 (m, 2H), 3.41 (t, 1H, J = 8.5 Hz), 3.38 (s, 3H), 3.36 (s, 3H), 1.29 (d, 3H, J = 6.3 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.6, 128.6, 127.90, 127.89, 98.1, 97.1, 96.6, 83.0, 77.9, 71.8, 71.7, 70.2, 69.2, 67.8, 67.4, 67.3, 59.2, 59.1, 17.9 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{21}H_{34}O_9Na$ 453.20890 found 453.20950.

(3*S*,5*S*,6*S*)-2-(Benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-4*H*-pyran-4-one (36)



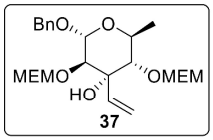
36

Partially protected rhamnose **SI-27** (5.53 g, 12.8 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 *p.a.* (51.0 mL) and DMP (6.53 g, 15.4 mmol, 1.20 eq.) was added at 0 °C. The suspension was allowed to warm to room temperature after 30 min. The reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution after 5 h. The aqueous phase was extracted thrice with EtOAc, combined organic phases were washed with sat. aq. $Na_2S_2O_3$ solution, sat. aq. $NaHCO_3$ solution, brine and dried over Na_2SO_4. Solvents were removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 2:1) to give a mixture of product and residues of DMP. It was diluted in EtOAc and washed

twice with sat. aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution alternately. The product **36** (4.58 g, 84%) was obtained as a colourless oil and as a mixture of regioisomers. $\mathbf{R_f}$ = 0.67 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −143.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2938 (m), 2896 (m), 2826 (w), 1745 (m), 1137 (s), 1123 (s), 1052 (s), 997 (m), 751 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 5.06 (d, 1H, *J* = 1.6 Hz), 4.82 (d, 1H, *J* = 7.1 Hz), 4.76 (d, 1H, *J* = 7.1 Hz), 4.74 (s, 2H), 4.68 (d, 1H, *J* = 12.2 Hz), 4.51 (d, 1H, *J* = 12.2 Hz), 4.40 (d, 1H, *J* = 9.4 Hz), 4.02 (d, 1H, *J* = 1.6 Hz), 3.98 (dq, 1H, *J* = 6.1, 9.4 Hz), 3.76 (m, 2H), 3.71-3.61 (m, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 3.36 (s, 3H), 3.32 (s, 3H), 1.40 (d, 3H, *J* = 6.2 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 202.2, 136.6, 128.5, 128.0, 127.9, 99.7, 95.5, 95.2, 81.2, 80.0, 71.7, 71.6, 70.5, 69.1, 67.8, 67.6, 59.1, 59.0, 18.7 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{21}H_{32}O_9Na$ 451.19321 found 451.19385.

(3*R*,5*S*,6*S*)-2-(Benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyl-4-vinyltetrahydro-2*H*-pyran-4-ol (37)

Ketone **36** (4.45 g, 10.4 mmol, 1.00 eq.) in dry THF (100 mL) was treated slowly with vinylMgBr solution (1M in THF, 30.1 mL, 30.1 mmol, 3.00 eq., 1.00 mL per minute) at −78 °C. After 5 h at this temperature, the reaction was quenched by addition of sat. aq. NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted thrice with EtOAc, combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the solvent under vacuum and purification by column chromatography (SiO_2, pentane/EtOAc 3:1→2:1→1:1) gave the product **37** (3.73 g, 79%, dr >30:1 determined by NMR) as a colourless oil and as a mixture of regioisomers. $\mathbf{R_f}$ = 0.52 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −90.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3498 (m), 2942 (m), 2891 (m), 1455 (w), 1362 (w), 1200 (w), 1173 (m), 1135 (m), 1112 (m), 1024 (s), 958 (m), 847 (w), 739 (w), 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.30-7.07 (m, 5H), 6.07 (ddd, 1H, *J* = 1.2, 10.7, 17.2 Hz), 5.61 (dd, 1H *J* = 2.0, 17.2 Hz), 5.22 (dd, 1H, *J* = 2.0, 10.7 Hz), 4.91 (d, 1H, *J* = 0.9 Hz), 4.77 (d, 1H, *J* = 11.7 Hz), 4.74 (s, 2H), 4.70 (s, 2H), 4.55 (d, 1H, *J* = 11.7 Hz), 4.09 (d, 1H, *J* = 1.2 Hz), 4.00 (dq, 1H, *J* = 6.3, 9.7 Hz), 3.72 (m, 2H), 3.66 (m, 1H), 3.60 (m, 2H), 3.53 (d, 1H, *J* = 9.7 Hz), 3.51 (m, 2H), 3.48-3.39 (m, 2H), 3.38 (s, 3H), 3.35 (s, 3H), 1.33 (d, 3H, *J* = 6.3 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 139.5, 136.7, 128.7, 128.32, 128.27, 116.3, 98.0, 97.1, 96.1, 79.71, 79.69, 74.4, 71.8, 71.6, 69.8, 67.9, 67.5, 64.4, 59.21, 59.15, 18.1 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{23}H_{36}O_9Na$ 479.22483 found 479.22515.



37

S24

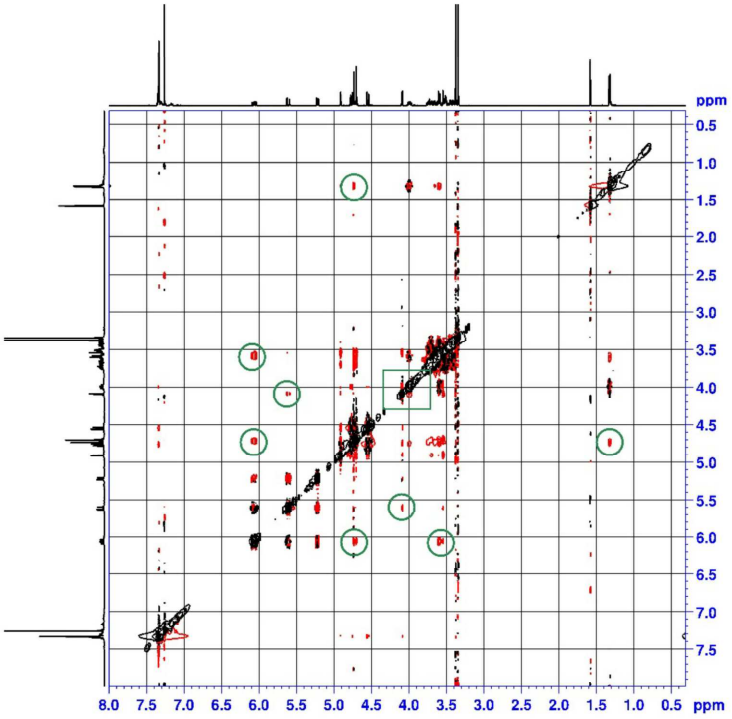


Fig. S4. Relevant NOE-signals for elucidation of stereoconfiguration of glycoside **37.**

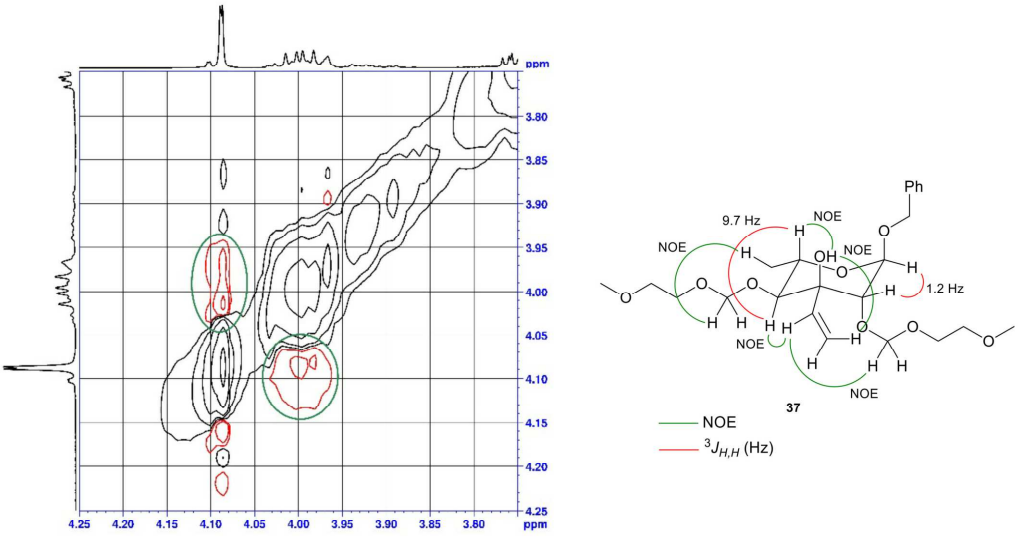
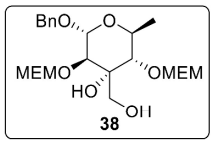


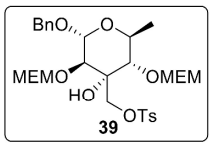
Fig. S5. Relevant NOE-signals for elucidation of stereoconfiguration of glycoside **37.**

(3*R*,5*S*,6*S*)-2-(Benzyloxy)-4-(hydroxymethyl)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-2*H*-pyran-4-ol (38)



Carbohydrate **37** (3.61 g, 7.90 mmol, 1.00 eq.) was dissolved in MeOH *p.a.* (120 mL) and CH_2Cl_2 *p.a.* (120 mL) and cooled to −78 °C. O_3/O_2 was bubbled through the solution until it turned blue. This was followed by passing oxygen through the solution up to the blue colour disappeared. $NaBH_4$ (724 mg, 19.1 mmol, 2.40 eq.) was added and the solution was slowly allowed to come to room temperature. After stirring for 24 h, the residues were filtered off over celite® and the volatiles were removed under reduced pressure. Purification of the crude product by column chromatography (SiO_2, CH_2Cl_2/MeOH 19:1) gave the product **38** (3.28 g, 90%) as a colourless oil and as a mixture of regioisomers. $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ −52.4° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3486 (m), 2977 (m), 2935 (m), 2886 (m), 2819 (w), 1456 (m), 1363 (w), 1276 (m), 1261 (m), 1112 (m), 1024 (s), 847 (w), 764 (s), 750 (s), 701 (w); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.99 (s, 1H), 4.84 (d, 1H, J = 7.0 Hz), 4.80 (d, 1H, J = 7.0 Hz), 4.76 (d, 1H, J = 7.0 Hz), 4.75 (d, 1H, J = 11.5 Hz), 4.73 (d, 1H, J = 7.0 Hz), 4.54 (d, 1H, J = 11.5 Hz), 4.11 (d, 1H, J = 1.2 Hz), 3.98 (dq, 1H, J = 6.3, 9.7 Hz), 3.86 (d, 1H, J = 1.0 Hz), 3.79 (ddd, 1H, J = 3.8, 5.3, 9.1 Hz), 3.76-3.63 (m, 5H), 3.56-3.42 (m, 5H), 3.38 (s, 3H), 3.36 (s, 3H), 2.47 (dd, 1H, J = 3.8, 9.8 Hz), 1.31 (d, 3H, J = 6.3 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 136.5, 128.7, 128.32, 128.26, 98.1, 97.8, 96.0, 78.8, 75.11, 75.06, 71.7, 71.6, 69.9, 68.4, 67.6, 64.1, 63.9, 59.2, 59.1, 18.0 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{36}O_{10}Na$ 483.21957 found 483.22007.

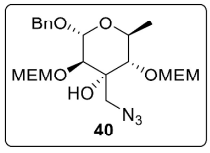
((3*R*,5*S*,6*S*)-2-(Benzyloxy)-4-hydroxy-3,5-bis((2-methoxyethoxy)methoxy)-6-methyl-tetrahydro-2*H*-pyran-4-yl)methyl-4-methylbenzenesulfonate (39)



Carbohydrate **38** (36.0 mg, 78.2 µmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (550 µL) and treated with *p*TsCl (22.4 mg, 117 µmol, 1.50 eq.), dry NEt_3 (16.3 µL, 117 µmol, 1.50 eq.) and DMAP (478 µg, 3.91 µmol, 0.05 eq.) at room temperature. The solution was stirred for 21 h and H_2O was added. The organic phase was separated, and the aqueous phase was extracted thrice with EtOAc. The combined organic phases were washed with 1M HCl, H_2O as well as brine and dried over Na_2SO_4. The solvents were removed under vacuum and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 2:1). The tosylated sugar **39**

(37.1 mg, 77%) was isolated as a colourless oil. It was pure enough for next step. $\mathbf{R_f}$ = 0.41 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −58.8° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3482 (m), 2931 (m), 2890 (m), 1600 (w), 1456 (m), 1362 (m), 1177 (s), 1114 (m), 1033 (s), 972 (m), 841 (m), 752 (w), 700 (m), 663 (w); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.3 Hz), 7.36-7.26 (m, 7H), 5.06 (s, 1H), 4.80 (d, 1H, J = 7.3 Hz), 4.73 (d, 1H, J = 7.2 Hz), 4.71 (d, 1H, J = 11.5 Hz), 4.69 (d, 1H, J = 7.2 Hz), 4.69 (d, 1H, J = 7.3 Hz), 4.51 (d, 1H, J = 11.5 Hz), 4.27 (dd, 1H, J = 2.2, 9.8 Hz), 4.10 (d, 1H, J = 9.8 Hz), 3.93 (dq, 1H, J = 6.1, 9.6 Hz), 3.78 (d, 1H, J = 1.2 Hz), 3.76 (ddd, 1H, J = 2.8, 6.3, 9.3 Hz), 3.69 (m, 1H), 3.61-3.47 (m, 5H), 3.44-3.39 (m, 2H), 3.40 (s, 3H), 3.36 (s, 3H), 2.41 (s, 3H), 1.31 (d, 3H, J = 6.1 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 144.8, 136.4, 133.1, 129.9, 128.7, 128.6, 128.4, 128.33, 128.27, 128.1, 98.0, 97.6, 96.8, 78.9, 75.2, 74.2, 71.6, 70.1, 68.6, 67.6, 63.8, 59.3, 59.1, 21.8, 17.7 ppm; **HRMS** ESI m/z $[M + Na]^+$ calcd. for $C_{29}H_{42}O_{12}SNa$ 637.22820 found 637.22892.

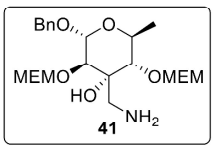
(3*R*,5*S*,6*S*)-4-(Azidomethyl)-2-(benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyl-tetra-hydro-2*H*-pyran-4-ol (40)



Tosylated sugar **39** (2.40 g, 3.90 mmol, 1.00 eq.) in dry DMF (15 mL) was treated with NaN_3 (760 mg, 11.7 mmol, 3.00 eq.) at room temperature. The mixture was stirred at 65 °C for 17 h and NaN_3 (760 mg, 11.7 mmol, 3.00 eq.) was added again. After stirring for a further 35 h at 70 °C, it was allowed to come to room temperature and H_2O was added. The aqueous phase was extracted thrice with EtOAc and the combined organic phases were washed with H_2O, brine and dried over Na_2SO_4. After removal of the solvents under vacuum, the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 2:1→1.5:1) to give azide **40** (1.78 g, 94%) as a colourless oil, minor impurities occur due to regioisomers. $\mathbf{R_f}$ = 0.53 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −41.1° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3484 (m), 2928 (m), 2880 (m), 2826 (w), 2099 (s), 1455 (m), 1364 (w), 1276 (m), 1261 (m), 1200 (w), 1134 (m), 1111 (s), 1022 (s), 977 (m), 919 (m), 847 (m), 764 (m), 750 (s), 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 5.05 (d, 1H, J = 0.9 Hz), 4.85 (d, 1H, J = 7.1 Hz), 4.80 (d, 1H, J = 7.1 Hz), 4.77 (d, 1H, J = 7.1 Hz), 4.75 (d, 1H, J = 11.5 Hz), 4.73 (d, 1H, J = 7.1 Hz), 4.55 (d, 1H, J = 11.5 Hz), 4.18 (d, 1H, J = 2.2 Hz), 3.95 (dq, 1H, J = 6.5, 9.9 Hz), 3.86 (d, 1H, J = 1.4 Hz), 3.85 (ddd, 1H, J = 4.1, 4.9, 10.8 Hz), 3.75 (ddd, 1H, J = 2.9, 6.2, 10.8 Hz), 3.69 (ddd, 1H, J = 4.1, 4.9, 10.8 Hz), 3.65 (d, 1H, J = 12.6 Hz), 3.59 (ddd, 1H, J = 2.9, 6.4, 10.8 Hz), 3.55 (m, 2H), 3.49 (ddd, 1H, J = 2.9, 6.2, 10.8 Hz), 3.42 (ddd, 1H, J = 2.9, 6.4, 10.8 Hz), 3.39 (s, 3H), 3.36

(s, 3H), 3.37 (m, 1H), 3.23 (dd, 1H, *J* = 2.4, 12.5 Hz), 1.29 (d, 3H, *J* = 6.5 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 136.4, 128.8, 128.4 (2 signals), 98.2, 97.9, 96.4, 80.0, 75.9, 75.3, 71.8, 71.6, 70.1, 68.6, 67.6, 64.1, 59.22, 59.16, 54.5, 17.9 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{35}N_3O_9Na$ 508.22636 found 508.22655.

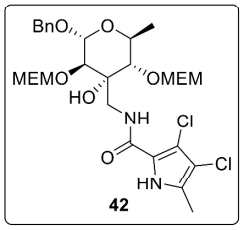
(2*R*,3*R*,4*S*,5*S*,6*S*)-4-(Aminomethyl)-2-(benzyloxy)-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-2*H*-pyran-4-ol (41)



Azide **40** (952 mg, 1.96 mmol, 1.00 eq.) in dry THF (20 mL) was treated with PPh_3 (1.29 g, 4.90 mmol, 2.50 eq.) and stirred until TLC showed full consumption of starting material. H_2O (384 µL, 19.6 mmol, 10.0 eq.) was added and stirring was continued for 3 days. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 15% MeOH in CH_2Cl_2 + 0.5% NEt_3→10 % MeOH in CH_2Cl_2+0.5% NEt_3). Amin **41** (772 mg, 86%) was isolated as a colourless oil, minor impurities occur due to regioisomers. $\mathbf{R_f}$ = 0.24 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ −59.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3495 (m), 2926 (m), 2882 (m), 1456 (m), 1363 (w), 1276 (m), 1261 (m), 1201 (w), 1111 (m), 1021 (s), 846 (m), 765 (s), 750 (s), 846 (m), 765 (s), 750 (s), 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 4.97 (d, 1H, *J* = 0.9 Hz), 4.82 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 7.0 Hz), 4.78 (d, 1H, *J* = 6.9 Hz), 4.76 (d, 1H, *J* = 11.8 Hz), 4.73 (d, 1H, *J* = 7.0 Hz), 4.55 (d, 1H, *J* = 11.8 Hz), 3.98 (dq, 1H, *J* = 6.4, 9.8 Hz), 3.82 (d, 1H, *J* = 1.4 Hz), 3.80 (ddd, 1H, *J* = 3.4, 5.6, 10.9 Hz), 3.76-3.69 (m, 3H), 3.59-3.46 (m, 4H), 3.41 (d, 1H, *J* = 9.8 Hz), 3.39 (s, 3H), 3.37 (s, 3H), 2.97 (d, 1H, *J* = 13.3 Hz), 2.82 (d, 1H, *J* = 13.3 Hz), 1.89 (br. s, 3H), 1.31 (d, 3H, *J* = 6.4 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 136.5, 128.8, 128.4, 128.3, 98.0, 97.9, 95.8, 80.3, 75.0, 74.6, 71.8, 71.7, 69.9, 68.5, 68.0, 64.3, 59.24, 59.21, 44.9, 18.1 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{22}H_{38}NO_9$ 460.25411 found 460.25302.

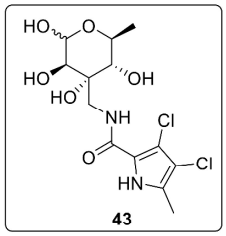
***N*-(((2*R*,3*R*,4*S*,5*S*,6*S*)-2-(Benzyloxy)-4-hydroxy-3,5-bis((2-methoxyethoxy)methoxy)-6-methyltetrahydro-2*H*-pyran-4-yl)methyl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide (42)**

To a solution of amin **41** (42.0 mg, 91.4 µmol, 1.00 eq.) and carbonic acid **31** (21.3 mg, 110 µmol, 1.20 eq.) in dry CH_2Cl_2 (1 mL) was added dry NEt_3 (31.8 µL, 228 µmol, 2.50 eq.), EDC·HCl (26.3 mg, 137 µmol, 1.50 eq.) and HOBt (16.8 mg, 110 µmol, 1.20 eq.) at 0 °C. The



mixture was allowed to warm to room temperature overnight. Reaction was quenched by addition of sat. aq. $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc thrice and combined organic phases were dried over Na_2SO_4. Removal of solvents under reduced pressure and purification by column chromatography (SiO_2, pentane/EtOAc 1:1→CH_2Cl_2/MeOH 50:1) gave amide **42** (47.2 mg, 81%) as a light red oil. Minor impurities occur due to regioisomers. $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −42.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3407 (m), 3208 (m), 2924 (m), 2882 (m), 1629 (m), 1533 (m), 1455 (m), 1417 (w), 1379 (w), 1276 (m), 1262 (m), 1113 (m), 1024 (s9, 847 (m), 764 (s), 750 (s), 700 (m); major regioisomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.41 (m, 1H), 7.38-7.27 (5H, m), 7.23 (m, 1H), 5.02 (d, 1H, J = 1.3 Hz), 4.83 (d, 1H, J = 7.0 Hz), 4.78 (d, 1H, J = 7.0 Hz), 4.75 (d, 1H, J = 11.8 Hz), 4.71 (d, 1H, J = 7.3 Hz), 4.64 (d, 1H, J = 7.3 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.34 (d, 1H, J = 1.6 Hz), 4.00 (m, 2H), 3.75 (t, 2H, J = 4.7 Hz), 3.71 (ddd, 1H, J = 2.9, 5.8, 10.9 Hz), 3.68 (m, 1H), 3.55 (m, 3H), 3.47 (d, 1H, J – 9.5 Hz), 3.46-3.36 (m, 2H), 3.34 (s, 3H), 3.32 (m, 1H), 3.29 (s, 3H), 2.29 (s, 3H), 1.58 (m, 1H), 1.33 (d, 3H, J = 6.3 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 159.8, 136.5, 128.7, 128.31, 128.27, 128.2, 118.6, 111.3, 110.2, 109.2, 98.4, 98.0, 96.8, 79.8, 76.3, 74.4, 71.7, 71.5, 70.0, 68.5, 67.4, 64.4, 59.2, 59.0, 41.9, 29.8, 18.1, 11.3 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{28}H_{41}Cl_2N_2O_{10}$ 635.21328 found 635.21334.

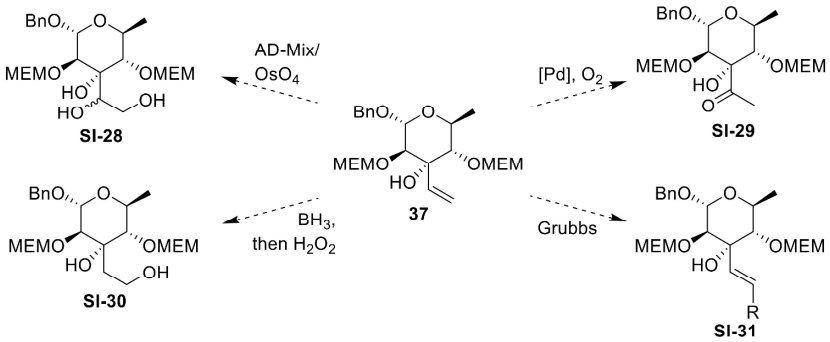
3,4-Dichloro-5-methyl-*N*-(((2*R*,3*R*,4*S*,5*S*,6*S*)-2,3,4,5-tetrahydroxy-6-methyltetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-pyrrole-2-carboxamide (43)



Carbohydrate **42** (24.3 mg, 37.8 µmol, 1.00 eq.) in dry CH_2Cl_2 (1 mL) was treated dropwise with BCl_3 (1M CH_2Cl_2, 453 µL, 12.0 eq.) at −78 °C. The solution was stirred at this temperature for 2 h, before BCl_3 (113 µL, 4.00 eq.) was added again. Stirring was continued for 1.5 h and H_2O was added to stop the reaction. All volatiles were removed at the rotary evaporator and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2 19:1→10:1 MeOH in CH_2Cl_2). This yielded the product **43** (13.3 mg, 93%, α:β 1.7:1) as a colourless foam. $\mathbf{R_f}$ = 0.37 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$+7.17° (c 1.0 in $CHCl_3$); IR ν_{max}/cm^{-1} 3310 (s), 2925 (s), 2530 (m), 1606 (s), 1499 (s), 1450 (s), 1323 (m), 1272 (m), 1164 (m), 1071 (s), 761 (m); major regioisomer, α-anomer **^{1}H-NMR** (500 MHz, CD_3OD) δ 5.06 (d, 1H, J = 1.2 Hz), 3.87 (m, 1H), 3.71 (dq, 1H, J = 6.2, 9.5 Hz), 3.52 (m, 1H), 3.46 (d, 1H, J = 1.0 Hz),

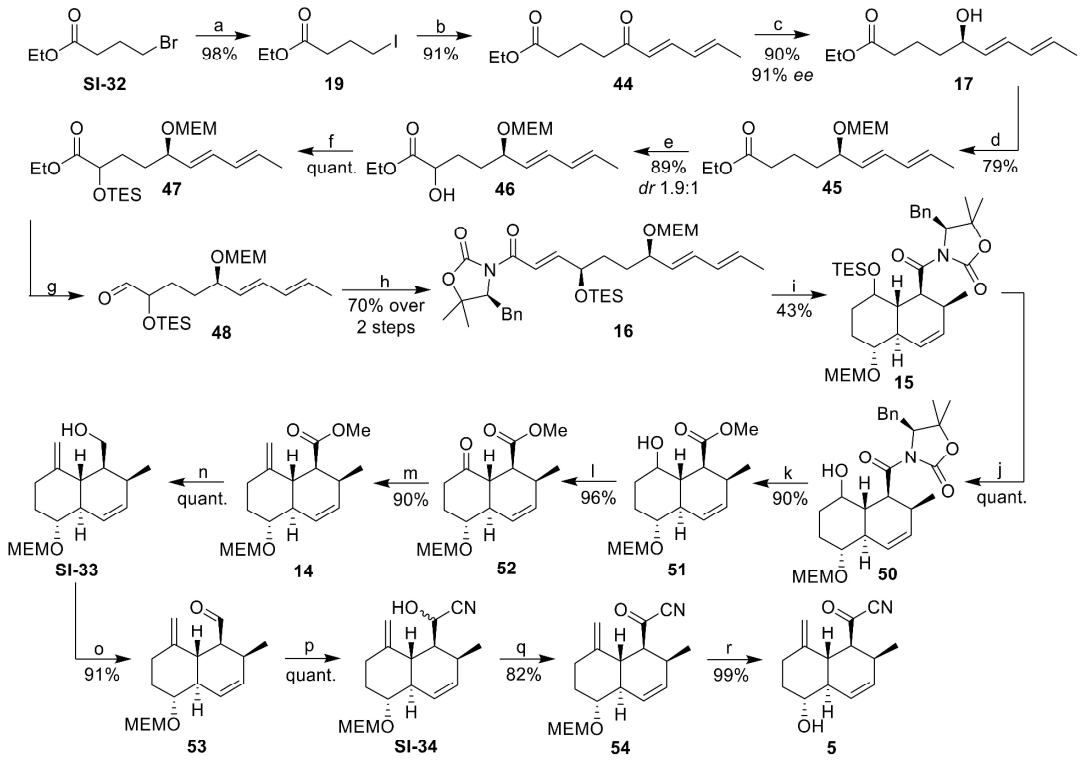
3.34 (d, 1H, *J* = 9.5 Hz), 2.23 (s, 3H), 1.27 (d, 3H, *J* = 6.2 Hz) ppm; major regioisomer, β-anomer **^{1}H-NMR** (500 MHz, CD_3OD) δ 4.96 (d, 1H, *J* = 1.2 Hz), 4.02 (dq, 1H, *J* = 6.2, 9.7 Hz), 3.89 (m, 1H), 3.57 (d, *J* = 1.5 Hz), 3.55 (m, 1H), 3.40 (d, 1H, *J* = 9.7 Hz), 2.23 (s, 3H), 1.29 (d, 3H, *J* = 6.2 Hz) ppm; major regioisomer **^{13}C-NMR** (125 MHz, CD_3OD) δ 162.3, 129.7, 119.6, 112.4, 96.3, 75.7, 72.5, 70.6, 65.6, 44.4, 18.2, 10.8 ppm; minor regioisomer **^{13}C-NMR** (125 MHz, CD_3OD) δ 162.4, 129.6, 119.6, 110.7, 93.6, 75.5, 73.2, 72.6, 71.3, 45.2, 18.3, 14.5 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{13}H_{19}Cl_2N_2O_6$ 369.06147 found 369.06091.

The vinyl group in **37** is amenable to a good many other functionalisations, e.g., dihydroxylations affording vicinal diols such as **SI-28**, Wacker-type oxidations leading to methyl ketones such as **SI-29**, hydroborations to give primary alcohols like **SI-30**, or Grubbs-catalysed metathesis to non-terminal alkenes like **SI-31** (Scheme S6).



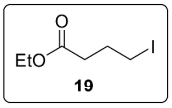
Scheme S6. Possible transformations of olefin **37** as a common intermediate

2.5 Synthesis of decalin fragment **5**



Scheme S7. Synthesis of decalin core **5**.
Reagents and conditions: a) NaI, acetone, reflux, 21 h; b) 1. **19**, Zn, THF, reflux, 3.5 h, 2. Thioester **18**, $Pd(PPh_3)_4$, toluene, rt, 23 h; c) 1. (*S*)-CBS-catalyst, BH_3·THF, rt, 1 h, 2. **44**, −35 °C, 3.5 h; d) MEMCl, DIPEA, CH_2Cl_2, 40 °C, 23 h; e) 1. KHMDS, THF, −78 °C, 30 min, 2. MoOPH, −78 °C, 4 h; f) TESCl, imidazole, DMAP, CH_2Cl_2, 0 °C→40 °C, 4.5 h; g) DIBAL, toluene, −78 °C, 5 h; h) 1. LiHMDS, phosphonate **49**, THF, 0 °C, 1 h, 2. **48**, 0 °C→rt, 17 h; i) toluene, 80 °C, 3 d; j) HF·py, THF, 0 °C, 15 h; k) NaOMe, CH_2Cl_2, 0 °C, 3 h; l) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→rt, 3 h; m) 1. $MePPh_3Br$, KO*t*Bu, THF, 0 °C, 45 min, 2. **52**, THF, 0 °C→rt, 3 h; n) DIBAL, CH_2Cl_2, 0 °C, 5 h; o) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→rt, 3 h; p) 1. TMSCN, NEt_3, CH_2Cl_2, 0 °C→rt, 4 h 20 min, 2. NH_4F, EtOH, 0 °C, 2 h; q) DMP, CH_2Cl_2, 0 °C, 1.5 h; r) $LiBF_4$, MeCN/H_2O, rt→55 °C, 4.5 h.

Ethyl 4-iodobutanoate (19)

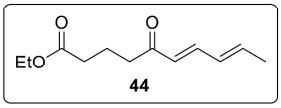


Bromo-butyric acid ester **SI-32** (20.0 mL, 133 mmol, 1.00 eq.) dissolved in acetone *p.a.* (1.3 L) was treated with NaI (100 g, 667 mmol, 5.00 eq.) at room temperature. The mixture was stirred under reflux for 21 h. The suspension was filtered off over celite® and washed with Et_2O. The filtrate was washed with H_2O. The aqueous phase was reextracted with Et_2O thrice and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (SiO_2, pentane→pentane/EtOAc 30:1) furnished

iodide **19** (31.6 g, 98%) as a yellow liquid. $\mathbf{R_f}$ = 0.61 (hexanes/EtOAc 98:2); **IR** ν_{max}/cm^{-1} 2981 (m), 2936 (w), 2908 (w), 1732 (s), 1444 (m), 1374 (m), 1352 (w), 1308 (w), 1226 (m), 1192 (s), 1163 (m), 1121 (m), 1097 (w), 1032 (m), 857 (w), 769 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 4.13 (q, 2H, J = 7.1 Hz), 3.24 (t, 2H, J = 6.7 Hz), 2.44 (t, 2H, J = 7.1 Hz), 2.13 (qn, 2H, J = 7.0 Hz), 1.26 (t, 3H, J = 7.1 Hz) ppm.

Spectroscopic data corresponded to those reported in the literature.[6]

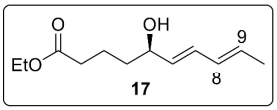
Ethyl (6*E*,8*E*)-5-oxodeca-6,8-dienoate (44)



44

A solution of iodide **19** (26.7 g, 109 mmol, 3.00 eq.) in dry THF (120 mL) was treated with Zn (14.1 g, 215 mmol, 5.90 eq.) and stirred under reflux for 3.5 h. This mixture was added to a solution of thioester **18** (5.99 g, 36.3 mmol, 1.00 eq.) in dry. toluene (125 mL) at room temperature. The mixture was treated with $Pd(PPh_3)_4$ (2.10 g, 1.82 mmol, 0.05 eq.) and stirred for 23 h at room temperature. The solids were filtered off over celite® and the organic phases were washed with 1M HCl, sat. aq. $NaHCO_3$ solution as well as brine and dried over Na_2SO_4. The solvents were removed under vacuum and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 9:1→8:1) to give product **44** (6.93 g, 91%) as a light-yellow oil. $\mathbf{R_f}$ = 0.68 (hexanes/EtOAc 8:1); IR ν_{max}/cm^{-1} 2979 (m), 2940 (m), 1732 (s), 1687 (m), 1664 (m), 1639 (m), 1596 (m), 1447 (w), 1418 (w), 1376 (m), 1323 (w), 1197 (m), 1100 (m), 1028 (m), 1000 (m), 949 (w), 858 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.13 (m, 1H), 6.19 (m, 2H), 6.05 (d, 1H, J = 15.4 Hz), 4.12 (q, 2H, J = 7.2 Hz), 2.62 (t, 2H, J = 7.2 Hz), 2.35 (t, 2H, J = 7.2 Hz), 1.94 (qn, 2H, J = 7.3 Hz), 1.86 (d, 3H, J = 4.9 Hz), 1.25 (t, 3H, J = 7.3 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 200.1, 173.4, 143.2, 140.6, 130.4, 127.7, 60.5, 39.4, 33.6, 19.6, 19.0, 14.4 ppm; **HRMS** ESI m/z $[M + H]^+$ calcd. for $C_{12}H_{19}O_3$ 211.13287 found 211.13260.

Ethyl (*R*,6*E*,8*E*)-5-hydroxydeca-6,8-dienoate (17)



17

A solution of (*S*)-CBS-catalyst (3.95 g, 14.3 mmol, 1.50 eq.) in dry THF (90 mL) was treated with BH_3·THF (10.5 mL, 10.5 mmol, 1.10 eq.) at room temperature. After stirring for 1 h, ketone **44** (2.00 g, 9.51 mmol, 1.00 eq.) was added dissolved in dry THF (22 mL) at -35 °C over 1.5 h. The reaction was stirred for a further 2h and quenched with sat. aq. NH_4Cl solution. The phases

were separated, and the organic phase was washed with sat. aq. NH_4Cl solution again. The combined aqueous phases were reextracted with Et_2O twice, the combined organic phases were washed with brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure. Column chromatography (SiO_2, pentane/EtOAc 8:1→6:1→5:1→4:1→3:1) gave product **17** (1.82 g, 90%, 91% *ee*, E/Z 11:1) as a light-yellow liquid. E/Z isomerization occurred at double bond between position 8 and 9. $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$ −6.97° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3439 (m), 2985 (m), 2935 (m), 2875 (w), 1732 (s), 1448 (m), 1374 (m), 1276 (s), 1261 (s), 1163 (m), 1099 (m), 1030 (m), 990 (m), 860 (w), 765 (s), 750 (s); *E,E*-isomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.18 (dd, 1H, J = 10.5, 15.2 Hz), 6.03 (ddq, 1H, J = 1.4, 10.5, 15.0 Hz), 5.71 (dq, 1H, J = 6.7, 15.0 Hz), 5.55 (dd, 1H, J = 7.1, 15.2 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.12 (m, 1H), 2.33 (t, 2H, J = 7.3 Hz), 1.75 (dd, 3H, J = 1.4, 6.7 Hz), 1.74-1.52 (m, 4H), 1.25 (t, 3H, J = 7.1 Hz) ppm; significant signals *E,Z*-isomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.53 (ddt, 1H, J = 0.9, 11.1, 15.2 Hz), 6.00 (m, 1H), 5.66 (m, 1H), 5.52 (m, 1H), 4.19 (m, 1H), 1.25 (t, 3H, J – 7.1 Hz) ppm; *E,E*-isomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 173.7, 132.9, 131.2, 130.7, 130.2, 72.4, 60.3, 36.6, 34.1, 20.9, 18.1, 14.3 ppm; significant signals *E,Z*-isomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 135.2, 128.5, 127.2, 125.9, 72.5 ppm; **HRMS** ESI *m/z* [M − OH]$^+$ calcd. for $C_{12}H_{19}O_2$ 195.13796 found 195.13789.

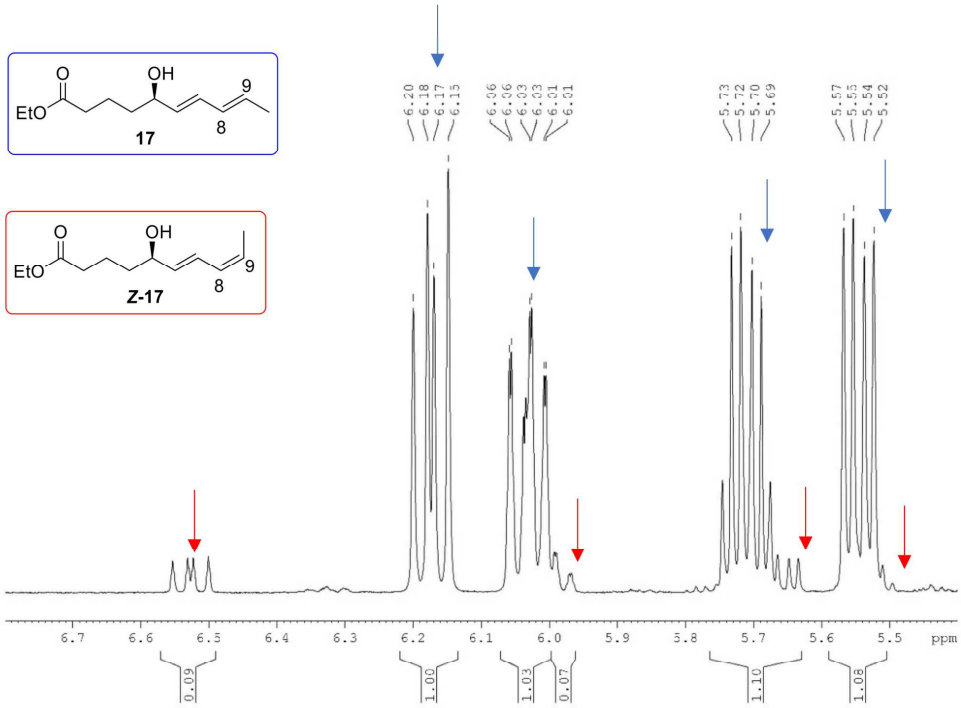
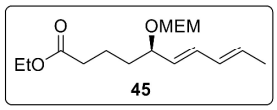


Fig. S6. Differentiation of **17** and *Z*-**17** in ^{1}H-NMR-spectrum.

S33

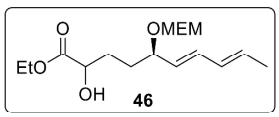
Ethyl (*R*,6*E*,8*E*)-5-((2-methoxyethoxy)methoxy)deca-6,8-dienoate (45)



45

Alcohol **17** (2.28 g, 10.7 mmol, 1.00 eq.) in dry CH_2Cl_2 (100 mL) was treated with MEMCl (2.46 mL, 21.5 mmol, 2.00 eq.) and DIPEA (5.48 mL, 32.2 mmol, 3.00 eq.) at room temperature. The solution was stirred for 23 h at 40 °C. 0.5M HCl was added, and the aqueous phase was extracted with EtOAc thrice. The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the solvent under vacuum and purification by column chromatography (SiO_2, pentane/EtOAc 7:1→5:1) gave MEM-protected alcohol **45** (2.55 g, 79%) as a colourless liquid in 79% yield. $\mathbf{R_f}$ = 0.43 (hexanes/EtOAc 4:1); $[\boldsymbol{\alpha}]_D^{20}$ −96.0° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2977 (m), 2931 (m), 2879 (m), 1733 (s), 1451 (m), 1372 (m), 1276 (m), 1260 (m), 1178 (m), 1135 (m), 1089 (m), 1023 (s), 990 (s), 931 (w), 852 (m), 765 (s), 750 (s); *E,E*-isomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.15 (dd, 1H, *J* = 10.5, 15.3 Hz), 6.02 (ddq, 1H, *J* = 1.3, 10.5, 15.1 Hz), 5.70 (dq, 1H, *J* = 6.8, 15.1 Hz), 5.33 (dd, 1H, *J* = 8.2, 15.3 Hz), 4.76 (d, 1H, *J* = 7.1 Hz), 4.61 (d, 1H, *J* = 7.1 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 4.04 (m, 1H), 3.79 (ddd, 1H, *J* = 2.9, 4.9, 10.3 Hz), 3.60 (m, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 2.30 (t, 2H, *J* = 7.4 Hz), 1.74 (dd, 3H, *J* = 1.3, 6.8 Hz), 1.73-1.48 (m, 4H), 1.24 (t, 3H, *J* = 7.1 Hz) ppm; significant signals *E,Z*-isomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.49 (ddt, 1H, *J* = 0.9, 11.1, 15.3 Hz), 5.98 (m, 1H), 5.51 (dqu, 1H, *J* = 7.0, 10.7 Hz), 5.33 (dd, 1H, *J* = 8.0, 15.3 Hz), 4.79 (d, 1H, *J* = 7.1 Hz), 4.63 (d, 1H, *J* = 7.1 Hz), 4.12 (q, 1H, 7.1 Hz), 4.11 (m, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.57 (m, 2H), 3.39 (s, 3H), 2.31 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz) ppm; *E,E*-isomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 173.7, 133.7, 130.8, 130.5, 130.0, 92.6, 76.2, 71.9, 67.0, 60.4, 59.2, 35.2, 34.3, 21.1, 18.3, 14.4 ppm; significant signals *E,Z*-isomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 132.4, 128.6, 128.4, 127.4, 92.7, 76.4, 67.1 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{28}O_5Na$ 323.18290 found 323.18275.

Ethyl (5*R*,6*E*,8*E*)-2-hydroxy-5-((2-methoxyethoxy)methoxy)deca-6,8-dienoate (46)



46

Ester **45** (2.50 g, 8.32 mmol, 1.00 eq.) was dissolved in dry THF (83 mL) and treated with KHMDS (12.5 mL, 12.5 mmol, 1.50 eq.) at −78 °C. The solution was stirred for 30 min, before MoOPH (4.04 g, 12.5 mmol, 1.50 eq.) was added. Another portion of MoOPH (1.35 g, 4.16 mmol, 0.5 eq.) was added after 2.5 h of stirring at −78 °C. Stirring was continued for 1.5 h and the reaction was quenched with sat. aq. NH_4Cl solution and sat. aq. $Na_2S_2O_3$ solution. The aqueous

phase was extracted thrice with EtOAc, organic phases were washed with H_2O, brine and dried over Na_2SO_4. Crude product was purified by column chromatography (SiO_2, pentane/EtOAc 4:1→3:1) to yield α-hydroxylated ester **46** (2.34 g, 89%, *dr* 1.6:1) as a colourless liquid. $\mathbf{R_f}$ = 0.24 (hexanes/EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ −93.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3462 (w), 2980 (m), 2933 (m), 2884 (m), 1735 (m), 1449 (w), 1368 (w), 1261 (m), 1276 (m), 1199 (m), 1103 (m), 1024 (m), 991 (m), 853 (w), 764 (s), 750 (s); *E,E*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.16 (dd, 1H, *J* = 10.5, 15.2 Hz), 6.02 (dd, 1H, *J* = 10.4, 15.0 Hz), 5.72 (dq, 1H, *J* = 6.8, 15.0 Hz), 5.34 (m, 1H), 4.76 (d, 1H, *J* = 6.9 Hz), 4.62 (d, 1H, *J* = 6.9 Hz), 4.23 (m, 2H), 4.18 (m, 1H), 4.09 (m, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 2.93 (m, 1H), 1.88 (m, 1H), 1.75 (d, 3H, *J* = 6.8 Hz), 1.78-1.58 (m, 3H), 1.29 (t, 3H, *J* = 7.1 Hz) ppm; significant signals *E,E*-isomer minor diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 4.62 (d, 1H, *J* = 7.0 Hz), 3.39 (s, 3H), 2.89 (m, 1H), 1.29 (t, 3H, *J* = 7.1 Hz) ppm; significant signals *E,Z*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.49 (dd, 1H, *J* = 11.0, 15.2 Hz), 5.98 (m, 1H), 5.52 (dq, 1H, *J* – 7.1, 10.6 Hz), 5.34 (m, 1H), 4.78 (d, 1H, *J* – 7.1 Hz), 4.64 (d, 1H, *J* = 7.1 Hz), 3.40 (s, 3H) ppm; *E,E*-isomer major diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 175.1, 133.6, 130.6, 130.4, 129.6, 92.5, 76.2, 71.8, 70.4, 67.0, 61.6, 59.1, 31.1, 30.4, 18.1, 14.2 ppm; significant signals *E,E*-isomer minor diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 175.1, 133.6, 130.6, 130.4, 129.6, 92.5, 76.0, 71.8, 70.1, 67.0, 61.7, 59.1, 30.7, 30.2 ppm; significant signals *E,Z*-isomer major diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 133.1, 128.5, 128.3, 127.3, 92.6, 76.4 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{28}O_6Na$ 339.17781 found 339.17700.

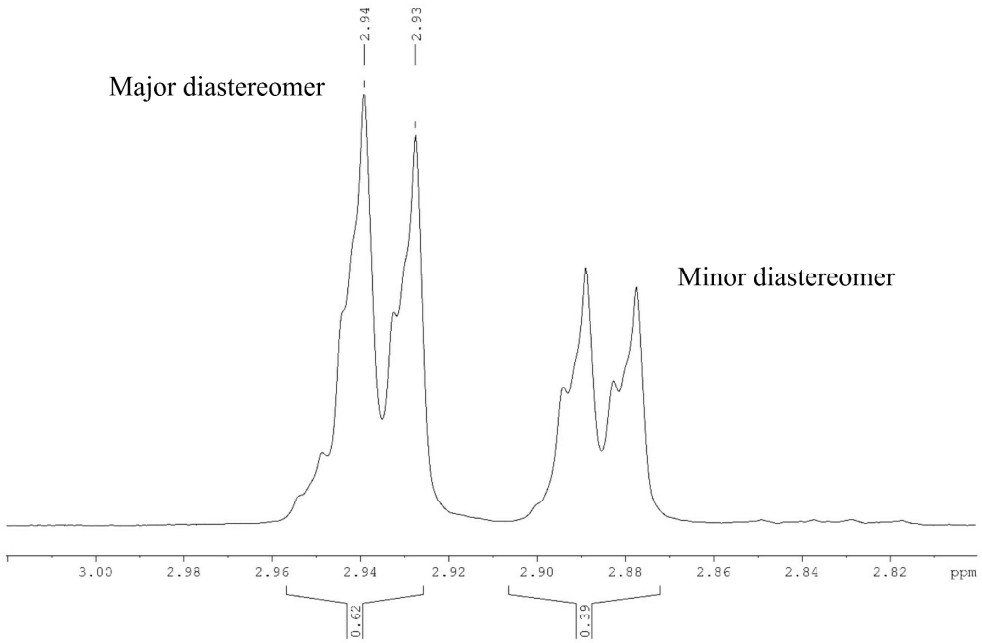
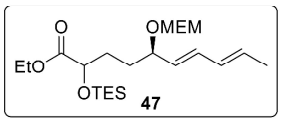


Fig. S7. Significant signals in ^{1}H-NMR-spectrum of ester **46**.

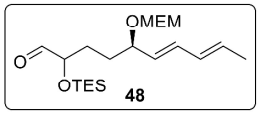
Ethyl (5*R*,6*E*,8*E*)-5-((2-methoxyethoxy)methoxy)-2-((triethylsilyl)oxy)deca-6,8-dienoate (47)



To a solution of α-hydroxylated ester **46** (2.29 g, 7.22 mmol, 1.00 eq.) in dry CH_2Cl_2 (72 mL) TESCl (2.42 mL, 14.4 mmol, 2.00 eq.), imidazole (1.47 g, 21.7 mmol, 3.00 eq.) and DMAP (88.2 mg, 722 µmol, 0.10 eq.) were added at 0 °C. The suspension was stirred at 40 °C for 4.5 h. Sat. aq. NH_4Cl solution was added. The aqueous phase was extracted with CH_2Cl_2 thrice and organic phases were dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 8:1) to give TES-protected α-hydroxylated ester **47** (3.27 g, quant.) as a colourless liquid. $\mathbf{R_f}$ = 0.24 (hexanes/EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ −61.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2956 (m), 2914 (m), 2878 (m), 1752 (m), 1726 (m), 1458 (m), 1276 (m), 1261 (m), 1134 (m), 1023 (m), 990 (m), 764 (s), 750 (s); *E,E*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.14 (dd, 1H, J = 10.5, 15.2 Hz), 6.02 (ddq, 1H, J = 1.4, 10.4, 15.0 Hz), 5.69 (dq, 1H, J = 6.8, 15.0 Hz), 5.33 (dd, 1H, J = 8.2, 15.2 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.61 (d, 1H, J = 6.9 Hz), 4.17 (m, 3H), 4.04 (m, 1H), 3.77 (m, 1H), 3.59 (m, 1H), 3.55

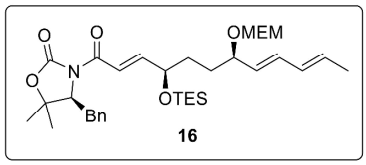
(m, 2H), 3.38 (s, 3H), 1.89-1.76 (m, 1H), 1.75 (d, 3H, *J* = 6.5 Hz), 1.73-1.58 (m, 3H), 1.27 (t, 3H, *J* = 7.1 Hz), 0.95 (t, 9H, *J* = 8.0 Hz), 0.61 (q, 6H, *J* = 8.0 Hz) ppm; significant signals *E,E*-isomer minor diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 4.76 (d, 1H, *J* = 6.9 Hz), 3.39 (s, 3H), 1.75 (d, 3H, *J* = 6.7 Hz), 1.27 (t, 3H, *J* = 7.1 Hz) ppm; significant signals *E,Z*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.48 (dd, 1H, *J* = 11.0, 15.3 Hz), 5.98 (m, 1H), 5.51 (dq, 1H, *J* = 7.2, 10.8 Hz), 5.44 (dd, 1H, *J* = 8.2, 15.2), 4.77 (d, 1H, *J* = 7.1 Hz), 4.63 (d, 1H, *J* = 7.1 Hz), 4.10 (m, 1H), 3.39 (s, 3H) ppm; *E,E*-isomer major diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 173.8, 133.7, 130.8, 130.4, 129.9, 92.6, 76.6, 72.2, 71.9, 67.0, 60.9, 59.2, 31.5, 31.4, 18.3, 14.4, 6.86, 4.71 ppm; significant signals *E,E*-isomer minor diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 130.8, 130.4, 129.9, 92.5, 76.1, 71.8, 31.2, 31.1 ppm; significant signals *E,Z*-isomer major diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 132.34, 132.29, 128.7, 128.4 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{42}O_6SiNa$ 453.26429 found 453.26346.

(S)-4-Benzyl-3-((2*E*,4*R*,7*R*,8*E*,10*E*)-7-((2-methoxyethoxy)methoxy)-4-((triethylsilyl)oxy)-dodeca-2,8,10-trienoyl)-5,5-dimethyloxazolidin-2-one (16)



48

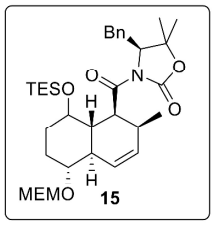
Ester **47** (1.20 g, 2.79 mmol, 1.00 eq.) in dry toluene (28 mL) was treated dropwise with DIBAL (4.18 mL, 4.18 mmol, 1.50 eq.) at −78 °C. The reaction was stirred at this temperature for 5 h, before it was stopped by addition of acetone (1 mL) and sat. aq. Na,K-tartrate solution. The two-phase mixture was stirred vigorously at room temperature for 2 h. The organic phase was separated, and the aqueous phase was extracted with EtOAc four times. The combined organic phases were washed with H_2O and dried over Na_2SO_4. Aldehyde **48** was used without further purification. **R_f** = 0.24 (hexanes/EtOAc 4:1); **IR** ν_{max}/cm^{-1} 3435 (w), 2954 (m), 2933 (m), 2908 (m), 2877 (m), 1731 (m), 1696 (w), 1457 (m), 1414 (m), 1367 (m), 1240 (m), 1199 (w), 1104 (s), 1042 (s), 1018 (s), 975 (s), 849 (m), 809 (m), 741 (s); *E,E*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.58 (t, 1H, *J* = 1.6 Hz), 6.14 (dd, 1H, *J* = 10.4, 15.8 Hz), 6.02 (ddq, 1H, *J* = 1.4, 10.5, 15.0 Hz), 5.70 (dq, 1H, *J* = 6.8, 15.0 Hz), 5.32 (dd, 1H, *J* = 8.1, 15.2 Hz), 4.76 (d, 1H, *J* = 7.0 Hz), 4.61 (d, 1H, *J* = 7.0 Hz), 4.03 (m, 1H), 3.97 (m, 1H), 3.77 (m, 1H), 3.59 (m, 1H), 3.55 (m, 2H), 3.38 (s, 3H), 1.80-1.57 (m, 4H), 1.75 (d, 3H, *J* = 6.5 Hz), 0.95 (t, 9H, *J* = 7.9 Hz), 0.61 (q, 6H, *J* = 7.9 Hz) ppm; significant signals *E,Z*-isomer major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.59 (t, 1H, *J* = 1.4 Hz), 6.48 (dd, 1H, *J* = 11.2, 15.2 Hz), 5.99 (m, 1H), 5.52 (dq, 1H, *J* = 7.1, 10.8 Hz), 5.44 (dd, 1H, *J* = 8.2, 15.2 Hz), 4.10 (m, 1H), 3.40 (s, 3H) ppm.



16

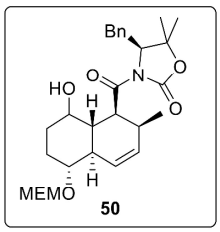
A solution of phosphonate **49** (1.24 g, 3.49 mmol, 1.25 eq.) in dry THF (7 mL) was treated with LiHMDS (3.35 mL, 3.35 mmol, 1.20 eq.) at 0 °C. After stirring for 1 h, crude aldehyde **48** (1.08 g, 2.79 mmol, 1.00 eq.) dissolved in dry THF (3 mL) was added dropwise. The mixture was allowed to warm to room temperature overnight. Sat. aq. NH_4Cl solution stopped the reaction after 17 h of stirring. The aqueous phase was extracted with EtOAc thrice, combined organic phases were washed with H_2O, brine and dried over Na_2SO_4. Removal of the solvent under vacuum and purification by column chromatography (SiO_2, pentane/EtOAc 8:1→6:1→4:1→2:1) furnished trien **16** (1.18 g, 70% over two steps) as a colourless oil. $\mathbf{R_f}$ = 0.38 (hexanes/EtOAc 4:1); $[\boldsymbol{\alpha}]_D^{20}$+27.4° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2952 (m), 2936 (m), 2877 (m), 1778 (s), 1687 (m), 1640 (w), 1497 (w), 1456 (w), 1354 (m), 1329 (w), 1274 (w), 1242 (w), 1207 (w), 1180 (w), 1159 (w), 1100 (s), 1040 (s), 821 (w), 729 (m), 702 (w); *E,E*-isomer major diastereomer ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ 7.39 (dt, 1H, *J* – 1.3, 15.3 Hz), 7.32-7.20 (m, 5H), 7.04 (ddd, 1H, *J* – 2.3, 5.2, 15.3 Hz), 6.14 (dd, 1H, *J* = 10.6, 15.2 Hz), 6.03 (dd, 1H, *J* = 10.6, 14.8 Hz), 5.69 (dq, 1H, *J* = 6.8, 14.8 Hz), 5.32 (dd, 1H, *J* = 8.3, 15.2 Hz), 4.76 (d, 1H, *J* = 7.0 Hz), 4.61 (d, 1H, *J* = 7.0 Hz), 4.55 (dt, 1H, *J* = 3.6, 9.6 Hz), 4.38 (m, 1H), 4.02 (m, 1H), 3.79 (m, 1H), 3.60 (m, 1H), 3.55 (m, 2H), 3.38 (s, 3H), 3.21 (m, 1H), 2.89 (tt, 1H, *J* = 6.0, 9.7 Hz), 1.75 (d, 3H, *J* = 6,7 Hz), 1.71-1.53 (m, 4H), 1.38 (s, 3H), 1.35 (s, 3H), 0.95 (t, 9H, *J* = 8.0 Hz), 0.61 (q, 6H, *J* = 8.0 Hz) ppm; significant signals *E,E*-isomer minor diastereomer ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ 4.76 (d, 1H, *J* = 6.9 Hz), 3.39 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.96 (t, 3H, *J* = 7.9 Hz) ppm; significant signals *E,Z*-isomer major diastereomer ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ 7.40 (dt, 1H, *J* = 1.5, 15.3 Hz), 6.48 (dd, 1H, *J* = 10.7, 15.3 Hz), 5.98 (m, 1H), 5.51 (dq, 1H, *J* = 7.1, 10.4 Hz), 5.44 (dd, 1H, *J* = 8.3, 15.3 Hz), 4.09 (m, 1H), 3.39 (s, 3H) ppm; *E,E*-isomer major diastereomer ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ 165.4, 152.8, 152.6, 137.2, 133.7, 130.8, 130.4, 130.0, 129.2, 128.8, 126.9, 119.6, 92.5, 82.2, 76.7, 72.0, 71.9, 67.0, 63.9, 59.2, 35.4, 33.5, 31.2, 28.8, 22.5, 18.3, 6.99, 4.95 ppm; significant signals *E,E*-isomer minor diastereomer ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ 165.3, 152.7, 137.3, 130.4, 130.0, 119.5, 82.2, 76.4, 71.8, 63.9, 33.4, 31.0, 28.7, 22.5 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{34}H_{53}NO_7SiNa$ 638.34835 found 638.34784.

(4*S*)-4-Benzyl-3-((1*S*,2*S*,4a*R*,5*R*,8a*S*)-5-((2-methoxyethoxy)methoxy)-2-methyl-8-((triethylsilyl)oxy)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyl-oxazolidin-2-one (15)



Trien **16** (513 mg, 833 µmol, 1.00 eq.) was dissolved in dry toluene (28 mL) and heated at 80 °C for 2 days. Temperature was raised to 100°C and stirring was continued for 1 d. The solvent was removed at the rotary evaporator. Crude product was purified by column chromatography (SiO_2, pentane/EtOAc 6:1→8:1) to give Diels-Alder-product **15** (219 mg, 43%, *de* >96%) as a colourless resin. $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$+63.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3030 (w), 2934 (m), 2876 (m), 1776 (s), 1690 (m), 1497 (w), 1456 (m), 1393 (w), 1374 (m), 1352 (m), 1301 (w), 1273 (m), 1242 (m), 1207 (w), 1221 (w), 1180 (w); 1159 (w), 1129 (w), 1101 (s), 1086 (s), 1039 (s), 1005 (s), 984 (m), 919 (m), 882 (w), 839 (w), 821 (m), 805 (w), 764 (w), 727 (s), 702 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.32 (d, 4H, *J* = 4.4 Hz), 7.24 (sex, 1H, *J* = 4.4 Hz), 5.88 (d, 1H, *J* = 10.0 Hz), 5.61 (ddd, 1H, *J* = 2.6, 4.8, 10.0 Hz), 4.89 (d, 1H, *J* = 7.1 Hz), 4.75 (d, 1H, *J* = 7.1 Hz), 4.57 (dd, 1H, *J* = 2.3, 11.0 Hz), 4.30 (s, 1H), 4.05 (dd, 1H, *J* = 5.9, 11.2 Hz), 3.78 (dt, 1H, *J* = 4.6, 11.1 Hz), 3.73 (dt, 1H, *J* = 4.6, 11.1 Hz), 3.58 (t, 2H, *J* = 4.6 Hz), 3.39 (s, 3H), 3.33 (dd, 1H, *J* = 2.1, 14.3 Hz), 3.24 (dt, 1H, *J* = 4.4, 10.7 Hz), 2.84 (m, 1H), 2.79 (dd, 1H, *J* = 11.2, 14.3 Hz), 2.53 (tq, 1H, *J* = 2.0, 10.7 Hz), 1.93 (m, 1H), 1.81 (dq, 1H, *J* = 3.2, 14.0 Hz), 1.77-1.67 (m, 2H), 1.55 (m, 1H), 1.33 (d, 6H, *J* = 6.9 Hz), 0.93 (t, 9H, *J* = 7.9 Hz), 0.85 (d, 3H, *J* = 7.1 Hz), 0.60-0.46 (m, 6H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 174.6, 151.8, 137.3, 131.1, 129.0, 128.9, 126.9, 126.2, 94.8, 81.5, 79.6, 71.9, 67.2, 66.0, 64.0, 59.2, 43.7, 39.0, 38.8, 35.2, 31.9, 31.0, 29.3, 27.0, 23.2, 17.7, 7.16, 5.43 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{34}H_{53}NO_7SiNa$ 638.34835 found 638.34778.

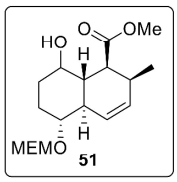
(4*S*)-4-Benzyl-3-((1*S*,2*S*,4a*R*,5*R*,8a*S*)-8-hydroxy-5-((2-methoxyethoxy)methoxy)-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (50)



Diels-Alder product **15** (198 mg, 321 µmol, 1.00 eq.) was dissolved in THF *p.a.* (3.2 mL) and treated with HF·pyridine (459 µL, 17.7 mmol, 55.0 eq.) at 0 °C. The solution was stirred 15 h at this temperature and quenched with sat. aq. $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc four times, combined organic phases were washed

with brine and dried over Na_2SO_4. The deprotected alcohol **50** (161 mg, quant.) was used without further purification. $\mathbf{R_f}$ = 0.42 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$+69.5° (c 1.0 in MeOH); **IR** ν_{max}/cm^{-1} 3485 (w), 2927 (m), 2880 (m), 1775 (s), 1692 (m), 1497 (w), 1455 (m), 1394 (m), 1373 (m), 1353 (m), 1297 (m), 1276 (m), 1230 (m), 1207 (m), 1176 (m), 1159 (m), 1101 (s), 1087 (s), 1036 (s), 956 (m), 921 (w), 844 (w), 822 (w), 766 (w), 730 (s), 700 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 7.23 (m, 1H), 5.88 (d, 1H, J = 10.0 Hz), 5.63 (ddd, 1H, J = 2.6, 4.6, 10.0 Hz), 4.88 (d, 1H, J = 7.1 Hz), 4.74 (d, 1H, J = 7.1 Hz), 4.56 (dd, 1H, J = 4.0, 9.7 Hz), 4.10 (m, 1H), 4.07 (dd, 1H, J = 5.8, 11.2 Hz), 3.77 (dt, 1H, J = 4.6, 11.1 Hz), 3.71 (dt, 1H, J = 4.6, 11.1 Hz), 3.56 (t, 2H, J = 4.6 Hz), 3.39 (s, 3H), 3.24 (m, 1H), 3.14 (dd, 1H, J = 4.0, 14.3 Hz), 2.88 (dd, 1H, J = 9.7, 14.3 Hz), 2.78 (m, 1H), 2.31 (tq, 1H, J = 2.6, 11.2 Hz), 1.98 (m, 1H), 1.84 (m, 1H), 1.74 (dt, 1H, J = 2.2, 11.2 Hz), 1.55 (m, 2H), 1.35 (d, 6H, J = 7.7 Hz), 1.27 (d, 1H, J = 5.3 Hz), 0.80 (d, 3H, J = 7.1 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 174.0, 152.7, 137.0, 131.8, 129.2, 128.8, 127.0, 125.8, 94.7, 82.5, 79.0, 71.9, 67.2, 65.3, 63.8, 59.2, 43.9, 39.9, 38.4, 35.6, 31.4, 31.3, 28.3, 26.7, 22.3, 17.4 ppm; **HRMS** ESI m/z $[M + Na]^+$ calcd. for $C_{28}H_{39}NO_7Na$ 524.26187 found 524.26081.

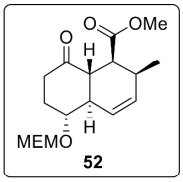
Methyl(1*S*,2*S*,4a*R*,5*R*,8a*S*)-8-hydroxy-5-((2-methoxyethoxy)methoxy)-2-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (51)



Alcohol **50** (554 mg, 1.10 mmol, 1.00 eq.) in dry CH_2Cl_2 (11 mL) was treated with NaOMe (50 wt%, 505 µL, 2.21 mmol, 2.00 eq.) at 0 °C. After stirring for 3 h, sat. aq. NH_4Cl solution was added, and the aqueous phase was extracted wit EtOAc four times. The combined organic phases were washed with sat. aq. $NaHCO_3$ solution as well as brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification by column chromatography (SiO_2, pentane/EtOAc 3:1→2:1→2:3→1:2) gave methylester **51** (325 mg, 90%) in 90% yield as a colourless oil. $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$+82.8° (c 1.0 in MeOH); **IR** ν_{max}/cm^{-1} 3484 (w), 3024 (w), 2932 (m), 2877 (m), 1732 (s), 1453 (w), 1436 (w), 1366 (w), 1296 (w), 1243 (w), 1199 (m), 1172 (m), 1127 (s), 1107 (s), 1032 (s), 1019 (s), 956 (m), 937 (m), 871 (m), 849 (w), 775 (w), 750 (m), 730 (m), 676 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.89 (d, 1H, J = 10.0 Hz), 5.61 (ddd, 1H, J = 2.6, 4.4, 10.0 Hz), 4.88 (d, 1H, J = 7.1 Hz), 4.74 (d, 1H, J = 7.1 Hz), 4.21 (s, 1H), 3.77 (dt, 1H, J = 4.6, 11.1 Hz), 3.71 (dt, 1H, J = 4.6, 11.1 Hz), 3.69 (s, 3H), 3.56 (t, 2H, J = 4.6 Hz), 3.39 (s, 3H), 3.23 (dt, 1H, J = 3.9, 10.6 Hz), 2.90 (dd, 1H, J = 6.0, 11.6 Hz), 2.59 (m, 1H), 2.34 (tq, 1H, J = 2.6, 10.6 Hz), 1.99 (m, 1H), 1.84 (m, 1H), 1.72-1.56

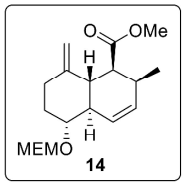
(m, 3H), 1.28 (m, 1H), 0.90 (d, 3H, *J* = 7.1 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 174.2, 131.5, 126.2, 94.7, 79.2, 71.9, 67.2, 65.4, 59.2, 51.5, 45.1, 39.6, 38.1, 32.2, 31.5, 26.7, 17.6 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{17}H_{28}NO_6Na$ 351.17781 found 351.17722.

Methyl(1*S*,2*S*,4a*R*,5*R*,8a*S*)-5-((2-methoxyethoxy)methoxy)-2-methyl-8-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (14)



52

To a solution of alcohol **51** (305 mg, 928 µmol, 1.00 eq.) in CH_2Cl_2 *p.a.* (9.3 mL) was added DMP (590 mg, 1.39 mmol, 1.50 eq.) and $NaHCO_3$ (390 mg, 4.64 mmol, 5.00 eq.) at 0 °C. The suspension was allowed to warm to room temperature and stirred for 3 h. After addition of sat. aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution, the aqueous phase was extracted with EtOAc four times. The combined organic phases were washed with sat. aq. $NaHCO_3$ solution, sat. aq. $Na_2S_2O_3$ solution as well as brine and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 3:1→3:2→1:1) to give ketone **52** (290 mg, 96%) as a colourless resin in 96% yield. The product wasn´t further purified, but directly used in the next reaction. $\mathbf{R_f}$ = 0.53 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{20}$+111.1° (c 1.0 in MeOH); **IR** ν_{max}/cm^{-1} 3035 (w), 2958 (m), 2928 (m), 2877 (m), 1737 (s), 1720 (s), 1455 (m), 1436 (m), 1375 (w), 1326 (w), 1255 (m), 1197 (m), 1174 (m), 1145 (m), 1097 (s), 1034 (s), 927 (w), 854 (w), 814 (w), 742 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.84 (d, 1H, *J* = 10.0 Hz), 5.70 (ddd, 1H, *J* = 2.6, 4.4, 10.0 Hz), 4.89 (d, 1H, *J* = 7.1 Hz), 4.79 (d, 1H, *J* = 7.1 Hz), 3.77 (dt, 1H, *J* = 4.7, 10.9 Hz), 3.71 (m, 1H), 3.69 (s, 3H), 3.57 (t, 2H, *J* = 4.6 Hz), 3.40 (s, 3H), 2.84 (dd, 1H, *J* = 6.4, 11.5 Hz), 2.71 (t, 1H, *J* = 12.0 Hz), 2.66-2.47 (m, 4H), 2.39 (m, 1H), 2.17 (m, 1H), 1.71 (dq, 1H, *J* = 5.7, 13.4 Hz), 0.86 (d, 3H, *J* = 7.2 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 209.6, 174.2, 132.7, 124.7, 95.2, 77.7, 71.8, 67.5, 59.2, 51.7, 46.8, 45.1, 42.6, 38.8, 32.9, 31.0, 17.8 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{17}H_{26}O_6Na$ 349.16216 found 349.16156.

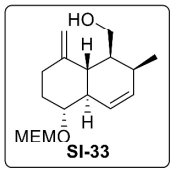


14

Methylphosphoniumbromide (2.14 g, 6.00 mmol, 1.20 eq.) in dry THF (10 mL) was treated with KO*t*Bu (561 mg, 5.00 mmol, 1.00 eq.) at 0 °C. The suspension was stirred for 45 min. A solution of ketone **52** (268 mg, 821 µmol, 1.00 eq.) in dry THF (4.3 mL) was treated with the suspension of ylide (0.5M, 3.28 mL, 1.64 mmol, 2.00 eq.) at 0 °C and stirred for 3 h at room temperature. Sat. aq. NH_4Cl solution was added, and the aqueous phase was extracted with EtOAc four times. The combined organic phases were dried over Na_2SO_4 and the solvents were removed *in vacuo*. Purification of the crude product by column chromatography (SiO_2, pentane/EtOAc 5:1)

delivered decalin **14** (240 mg, 90%) as a colourless liquid in 90% yield. $\mathbf{R_f}$ = 0.74 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$+101.6° (c 1.0 in MeOH); **IR** ν_{max}/cm^{-1} 2934 (m), 2877 (m), 1742 (s), 1653 (w), 1455 (m), 1436 (m), 1365 (w), 1325 (m), 1300 (w), 1256 (m), 1192 (m), 1132 (s), 1109 (s), 1058 (m), 1032 (s), 931 (m), 892 (m), 852 (m), 818 (w), 775 (w), 745 (m), 730 (m), 670 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.84 (dt, 1H, J = 1.4, 10.0 Hz), 5.68 (ddd, 1H, J = 2.6, 4.6, 10.0 Hz), 4.87 (d, 1H, J = 7.1 Hz), 4.75 (d, 1H, J = 7.1 Hz), 4.73 (s, 1H), 4.39 (s, 1H), 3.76 (dt, 1H, J = 4.7, 11.0 Hz), 3.70 (dt, 1H, J = 4.7, 11.0 Hz), 3.67 (s, 3H), 3.57 (t, 2H, J = 4.6 Hz), 3.40 (dt, 1H, J = 4.6, 10.8 Hz), 3.40 (s, 3H), 2.92 (dd, 1H, J = 6.3, 11.9 Hz), 2.62 (m, 1H), 2.38-2.28 (m, 2H), 2.23-2.13 (m, 2H), 1.87 (tq, 1H, J = 2.2, 10.8 Hz), 1.46-1.35 (m, 1H), 0.89 (d, 3H, J = 7.2 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 174.7, 150.3, 131.7, 125.4, 104.7, 95.0, 79.5, 71.9, 67.2, 59.2, 51.5, 48.5, 45.4, 38.5, 34.9, 34.7, 31.7, 18.3 ppm; **HRMS** ESI m/z $[M + H]^+$ calcd. for $C_{18}H_{29}O_5$ 325.20095 found 325.19994.

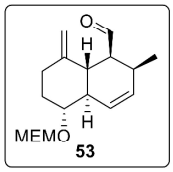
(1*S*,2*S*,4a*R*,5*R*,8a*S*)-5-((2-Methoxyethoxy)methoxy)-2-methyl-8-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (53)



SI-33

Ester **14** (220 mg, 678 µmol, 1.00 eq.) dissolved in dry CH_2Cl_2 (6.8 mL) was treated with DIBAL (2.03 mL, 2.03 mmol, 3.00 eq.) at 0 °C. After stirring at this temperature for 4 h another portion of DIBAL (339 µL, 339 µmol, 0.50 eq.) was added. As soon as TLC showed complete conversion of the starting material, sat. aq. Na,K-tartrate solution was added and the two-phase mixture was stirred vigorously at room temperature for 45 min. The aqueous phase was extracted with EtOAc thrice, combined organic phases were washed with brine and dried over Na_2SO_4. Solvents were removed at the rotary evaporator. Crude product **SI-33** (211 mg, quant.) was used without further purification. $\mathbf{R_f}$ = 0.53 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$+76.5° (c 0.9 in MeOH); **IR** ν_{max}/cm^{-1} 3424 (w), 3027 (w), 2930 (m), 2875 (m), 1649 (m), 1454 (m), 1394 (w), 1366 (m), 1296 (w), 1242 (w), 1200 (w), 1178 (w), 1155 (w), 1109 (m), 1086 (m), 1052 (s), 1037 (s), 1014 (s), 982 (m), 923 (m), 896 (m), 849 (w), 830 (w), 749 (m), 739 (m), 720 (w), 677 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.80 (d, 1H, J = 10.1 Hz), 5.76 (ddd, 1H, J = 1.9, 4.4, 10.1 Hz), 4.88 (s, 1H), 4.85 (d, 1H, J = 7.1 Hz), 4.76 (s, 1H), 4.74 (d, 1H, J = 7.1 Hz), 4.15 (dt, 1H, J = 4.4, 11.3 Hz), 3.76 (dt, 1H, J = 4.7, 10.9 Hz), 3.70 (dt, 1H, J = 4.7, 10.9 Hz), 3.56 (t, 2H, J = 4.7 Hz), 3.55 (m, 1H), 3.40 (s, 3H), 3.37 (dt, 1H, J = 4.5, 10.7 Hz), 2.50 (m, 1H), 2.31 (m, 2H), 2.21 (m, 1H), 2.05 (dt, 1H, J = 4.6, 13.0 Hz), 1.93 (tq, 1H, J = 1.9, 10.7 Hz), 1.75 (t, 1H, J = 10.7 Hz), 1.43 (m, 1H), 1.20 (t, 1H, J = 5.3 Hz), 0.99 (d, 3H, J = 7.1 Hz) ppm; **^{13}C-NMR**

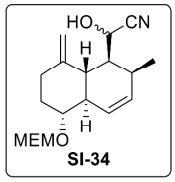
(125 MHz, $CDCl_3$) δ 150.3, 133.4, 125.2, 106.3, 95.0, 80.1, 71.9, 67.2, 62.1, 59.2, 50.6, 39.2, 38.5, 35.8, 35.6, 30.5, 16.4 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{17}H_{29}O_4$ 297.20604 found 297.20509.



53

A solution of alcohol **SI-33** (180 mg, 607 µmol, 1.00 eq.) in CH_2Cl_2 *p.a.* (6 mL) was treated with $NaHCO_3$ (255 mg, 3.04 mmol, 5.00 eq.) and DMP (386 mg, 911 µmol, 1.50 eq.) at 0 °C. The suspension was stirred at this temperature for 1 h and at room temperature for 2 h. Sat. aq. $NaHCO_3$ solution and sat. aq. $Na_2S_2O_3$ solution were added. The aqueous phase was extracted with EtOAc thrice, the combined organic phases were washed with sat. aq. $NaHCO_3$ solution, sat. $Na_2S_2O_3$ aq. solution as well as brine and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 6:1→5:1) to give aldehyde **53** (163 mg, 91%) as a colourless liquid. $\mathbf{R_f}$ = 0.71 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$+43.0° (c 0.4 in MeOH); **IR** ν_{max}/cm^{-1} 2929 (m), 2878 (m), 1720 (m), 1652 (w), 1455 (m), 1366 (w), 1261 (m), 1199 (w), 1166 (w), 1102 (s), 1094 (s), 1032 (s), 895 (m), 849 (w), 803 (m), 741 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.64 (d, 1H, *J* = 4.3 Hz), 5.87 (dt, 1H, *J* = 1.5, 10.1 Hz), 5.67 (ddd, 1H, *J* = 2.6, 4.5, 10.1 Hz), 4.88 (d, 1H, *J* = 7.1 Hz), 4.82 (s, 1H), 4.76 (d, 1H, *J* = 7.1 Hz), 4.38 (s, 1H), 3.77 (dt, 1H, *J* = 4.8, 10.8 Hz), 3.71 (dt, 1H, *J* = 4.8, 10.8 Hz), 3.57 (t, 2H, *J* = 4.8 Hz), 3.44 (dt, 1H, *J* = 4.6, 10.7 Hz), 3.40 (s, 3H), 2.74-2.62 (m, 2H), 2.42-2.29 (m, 3H), 2.18 (dt, 1H, *J* = 4.6, 13.5 Hz), 1.92 (tq, 1H, *J* = 2.1, 10.7 Hz), 1.44 (m, 1H), 1.01 (d, 3H, *J* = 6.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 207.5, 148.8, 132.0, 125.8, 107.5, 94.9, 79.3, 71.9, 67.3, 59.2, 50.3, 48.5, 37.4, 34.74, 34.67, 32.4, 16.9 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{17}H_{27}O_4$ 295.19039 found 295.18976.

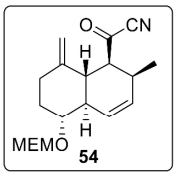
(1*S*,2*S*,4a*R*,5*R*,8a*S*)-5-((2-Methoxyethoxy)methoxy)-2-methyl-8-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl cyanide (54)



SI-34

Aldehyde **53** (86.2 mg, 292 µmol, 1.00 eq.) in dry CH_2Cl_2 (3 mL) was treated with TMSCN (110 µL, 876 µmol, 3.00 eq.) and dry NEt_3 (121 µL, 876 µmol, 3.00 eq.) at 0 °C. The solution was stirred at this temperature for 20 min and at room temperature for 4 h. The volatiles were removed at the rotary evaporator. Crude product was dissolved in EtOH *p.a.* and NH_4F (48.7 mg, 1.31 mmol, 4.50 eq.) was added at 0 °C. After 2 h of stirring TLC showed complete conversion of the starting material. H_2O was added and the aqueous phase was extracted with EtOAc thrice. Combined organic phases were washed with brine and dried over Na_2SO_4. The solvents were

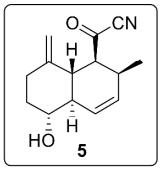
removed under reduced pressure and the oily, colourless product **SI-34** (92.3 mg, quant., *dr* 1.1:1) was used without further purification. $\mathbf{R_f}$ = 0.64 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$+61.1° (c 0.5 in MeOH); **IR** ν_{max}/cm^{-1} 3385 (m), 3076 (w), 3030 (w), 2933 (m), 2881 (m), 1651 (m), 1455 (m), 1395 (w), 1366 (w), 1296 (w), 1244 (w), 1170 (m), 1098 (s), 1036 (s), 894 (m), 848 (m), 754 (m), 737 (w), 677 (w); major diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.83 (d, 1H, *J* = 10.0 Hz), 5.74 (ddd, 1H, *J* = 2.5, 5.1, 10.0 Hz), 5.30 (m, 1H), 4.93 (s, 1H), 4.85 (d, 1H, *J* = 7.1 Hz), 4.74 (d, 1H, *J* = 7.1 Hz), 4.68 (s, 1H), 3.75 (dt, 1H, *J* = 4.7, 10.9 Hz), 3.69 (dt, 1H, *J* = 4.7, 10.9 Hz), 3.56 (t, 2H, *J* = 4.7 Hz), 3.43 (m, 1H), 3.39 (s, 3H), 2.73 (m, 1H), 2.55 (m, 1H), 2.40-2.25 (m, 3H), 2.22-1.95 (m, 3H), 1.44 (m, 1H), 1.19 (d, 3H, *J* = 7.1 Hz) ppm; minor diastereomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.81 (d, 1H, *J* = 10.0 Hz), 5.72 (ddd, 1H, *J* = 2.5, 5.1, 10.0 Hz), 5.30 (m, 1H), 4.94 (s, 1H), 4.85 (d, 1H, *J* = 7.1 Hz), 4.74 (d, 1H, *J* = 7.1 Hz), 4.65 (s, 1H), 3.75 (dt, 1H, *J* = 4.7, 10.9 Hz), 3.69 (dt, 1H, *J* = 4.7, 10.9 Hz), 3.56 (t, 2H, *J* = 4.7 Hz), 3.43 (m, 1H), 3.40 (s, 3H), 2.63 (m, 1H), 2.35 (m, 3H), 2.22-1.95 (m, 4H), 1.44 (m, 1H), 1.21 (d, 3H, *J* = 7.1 Hz) ppm; major diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 150.7, 132.7, 125.4, 119.4, 106.2, 95.0, 79.8, 71.9, 67.2, 61.1, 59.2, 50.5, 40.0, 38.0, 35.8, 35.7, 31.7, 18.2 ppm; minor diastereomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 150.1, 132.7, 125.4, 119.4, 105.7, 95.0, 79.9, 71.9, 67.2, 60.9, 59.2, 50.7, 40.0, 39.5, 35.65, 35.61, 29.3, 17.1 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{18}H_{28}NO_4$ 322.20128 found 322.20044.



54

A solution of cyanohydrin **SI-34** (87.0 mg, 271 µmol, 1.00 eq.) in dry CH_2Cl_2 (2.7 mL) was treated with DMP (138 mg, 325 µmol, 1.20 eq.) at 0 °C. The suspension was stirred for 1.5 h at this temperature, before it was filtered off over celite®. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 5:1) to give the acylcyanide **54** (71.3 mg, 82%) as a colourless liquid. $\mathbf{R_f}$ = 0.77 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$+111.3° (c 1.0 in MeOH); **IR** ν_{max}/cm^{-1} 2934 (m), 2879 (m), 2217 (w), 1708 (m), 1653 (w), 1455 (w), 1177 (m), 1096 (s), 1054 (s), 1026 (s), 897 (m), 744 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.91 (dt, 1H, *J* = 1.5, 10.1 Hz), 5.70 (ddd, 1H, *J* = 2.6, 4.6, 10.1 Hz), 4.87 (s, 1H), 4.87 (d, 1H, *J* = 7.1 Hz), 4.75 (d, 1H, *J* = 7.1 Hz), 4.29 (s, 1H), 3.76 (dt, 1H, *J* = 4.8, 10.9 Hz), 3.70 (dt, 1H, *J* = 4.8, 10.9 Hz), 3.56 (t, 2H, *J* = 4.8 Hz), 3.45 (dt, 1H, *J* = 4.6, 10.7 Hz), 3.39 (s, 3H), 3.18 (dd, 1H, *J* = 6.3, 12.1 Hz), 2.82 (m, 1H), 2.45-2.33 (m, 3H), 2.22 (dt, 1H, *J* = 4.7, 13.5), 1.94 (tq, 1H, *J* = 2.1, 10.7 Hz), 1.43 (m, 1H), 1.04 (d, 3H, *J* = 7.1 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 180.6, 148.8, 130.8, 125.9, 113.6, 107.2, 94.9, 79.0, 71.8, 67.4, 59.2, 52.7, 48.4, 37.8, 34.7, 34.3, 32.0, 17.4 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{18}H_{25}NO_4Na$ 342.16758 found 342.16726.

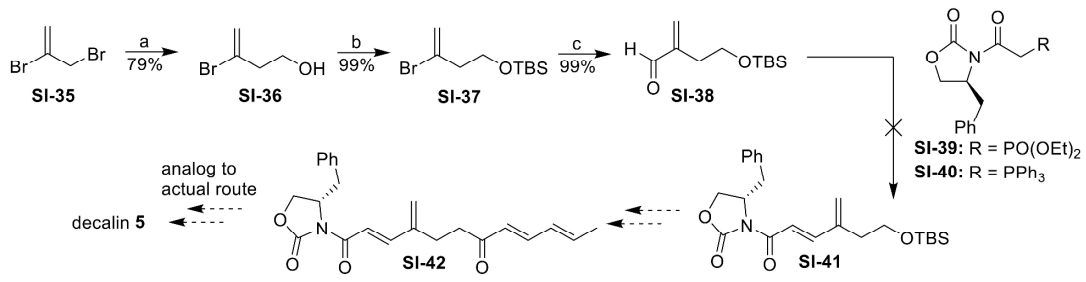
(1*S*,2*S*,4a*R*,5*R*,8a*S*)-5-Hydroxy-2-methyl-8-methylene-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbonyl cyanide (5)



MEM-ether **54** (25.1 mg, 78.3 µmol, 1.00 eq.) in MeCN *p.a.* (1.5 mL) and H_2O (0.1 mL) was treated with $LiBF_4$ (183 mg, 1.96 mmol, 25.0 eq.) at room temperature. The mixture was stirred at 55 °C for 4.5 h. H_2O was added at 0 °C and the aqueous phase was extracted with EtOAc thrice. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification of the crude product by column chromatography (SiO_2, pentane/EtOAc 4:1→3:1) gave product **5** (18.2 mg, 99%) as a colourless resin. $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$+157.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3375 (m), 3081 (w), 3032 (w), 2965 (w), 2939 (m), 2877 (m), 2217 (m), 1708 (s), 1652 (m), 1454 (m), 1377 (w), 1328 (w), 1260 (w), 1163 (m), 1062 (s), 1029 (s), 999 (w), 896 (m), 868 (w), 838 (w), 741 (s), 674 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.00 (dt, 1H, J = 1.4, 10.1 Hz), 5.73 (ddd, 1H, J = 2.6, 4.6, 10.1 Hz), 4.89 (s, 1H), 4.30 (s, 1H), 3.52 (dt, 1H, J = 4.6, 10.5 Hz), 3.18 (dd, 1H, J = 6.3, 12.2 Hz), 2.83 (m, 1H), 2.43 (m, 1H), 2.36 (t, 1H, J = 11.6 Hz), 2.30-2.22 (m, 2H), 1.84 (tq, 1H, J = 2.2, 10.6 Hz), 1.65 (br. s, 1H), 1.52-1.43 (m, 1H), 1.05 (d, 3H, J = 7.2 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 180.7, 148.8, 130.9, 125.8, 113.6, 107.4, 73.3, 52.6, 49.9, 37.8, 37.5, 34.5, 32.1, 17.4 ppm.

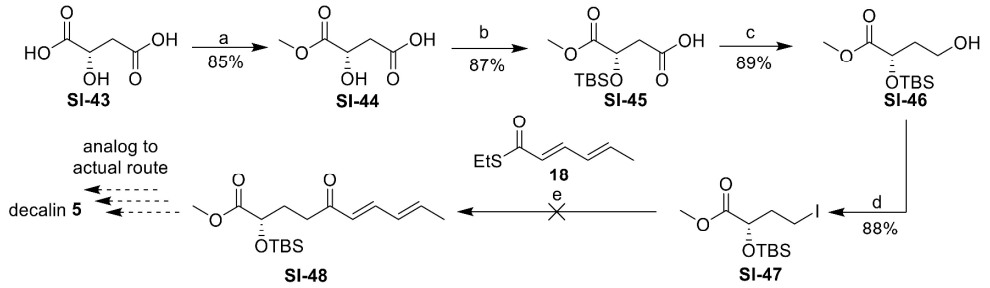
2.6 Failed routes to the decalin

One promising and short route started from dibromide **SI-35** which was elongated by a tin mediated reaction to alcohol **SI-36**. After TBS-protection and formylation an HWE- or Wittig olefination with an auxiliary based phosphonate **SI-39** or ylide **SI-40** was not possible. The following steps should have been performed analogously to the actual route.



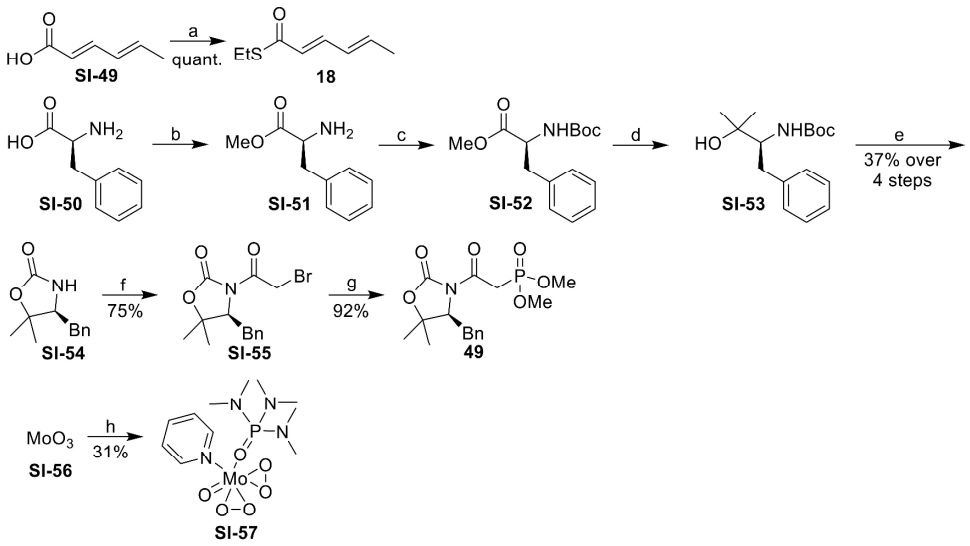
Scheme S8. Attempt to synthesise triene **SI-42** starting from vinylbromide **SI-35**.
Reagents and conditions: a) Sn, CH_2O, cat. HBr, Et_2O/H_2O, rt, 19 h; b) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 21 h, c) 1. *t*BuLi, Et_2O, −78 °C, 30 min, 2. DMF, 3.5 h.

After failure of the olefination of an α,β-unsaturated aldehyde we had the plan to introduce the terminal alkene after the olefination reaction. Starting with malic acid (**SI-43**) it was first chemoselectively esterified and TBS-protected (→ **SI-45**). The carboxyl group was reduced to alcohol **SI-46** which was iodinated in an Appel-reaction (→**SI-47**). The following Fukuyama coupling was not successful due to low formation of the zinc organyl.



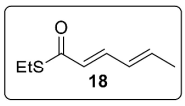
Scheme S9. Tested route to α-hydroxylated ester **SI-48**.
Reagents and conditions: a) 1. $(TFA)_2$, rt, 3 h, 2. MeOH, rt, 22.5 h, b) 1. TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 23 h, 2. K_2CO_3, H_2O, MeOH, rt, 2.5 h, c) 1. EtOCOCl, NMM, THF, −10 °C, 1.2 h, 2. $NaBH_4$, H_2O, 1 h; d) PPh_3, imidazole, I_2, THF, 0 °C, 1 h.

2.7 Synthesis of reagents for the decalin fragment



Scheme S10. Synthesis of thioester **18**, phosphonate **49** and molybdenum reagent **SI-57** needed for formation of decalin **5**.
Reagents and conditions: a) DCC, DMAP, EtSH, CH_2Cl_2, 0 °C→rt, 21 h; b) $SOCl_2$, MeOH, 0 °C→reflux, 20 h; c) Boc_2O, NEt_3, imidazole, CH_2Cl_2, 17 h; d) MeMgBr, THF, 0 °C→rt, 2 d; e) KO*t*Bu, THF, 0 °C, 30 min; f) 1. *n*BuLi, THF, −80 °C, 10 min, 2. Bromoacetylbromide, −80 °C→rt, 13.5 h; g) $P(OMe)_3$, 20.5 h, rt→60 °C; h) 1. H_2O_2, 40 °C, 4.25 h, 2. HMPA, rt, 5 min, 3. Pyridine, THF, rt, 15 min.

(*S*)-Ethyl (2*E*,4*E*)-hexa-2,4-dienethioate (18)



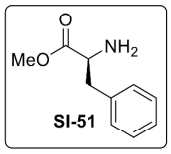
Sorbic acid (**SI-49**) (5.00 g, 44.6mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (203 mL). DCC (9.66 g, 46.8 mmol, 1.05 eq.), DMAP (545 mg, 4.46 mmol, 0.10 eq.) were added at room temperature. At 0 °C EtSH (4.29 mL, 58.0 mmol, 1.30 eq.) was dripped to the mixture and it was stirred for 21 h at room temperature. The reaction mixture was filtered off over celite® and the solvents were partially removed. The organic phase was washed with sat. aq. $NaHCO_3$ solution and H_2O. The combined aqueous phases were reextracted with CH_2Cl_2 once and the organic phases were washed with brine. It was dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 30:1→20:1) to give thioester **18** (6.97 g, quant.) as a light-yellow liquid. $\mathbf{R_f}$ = 0.92 (CH_2Cl_2/MeOH 25:1); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.17 (dd, 1H, J = 10.2, 15.2 Hz), 6.25-6.11 (m, 2H), 6.06 (d, 1H, J =

15.2 Hz), 2.95 (q, 2H, *J* = 7.4 Hz), 1.86 (d, 3H, *J* = 6.1 Hz), 1.28 (t, 3H, *J* = 7.4 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 190.3, 141.0, 140.8, 129.8, 126.3, 23.3, 19.0, 15.0 ppm.

Spectroscopic data corresponded to those reported in the literature.[7]

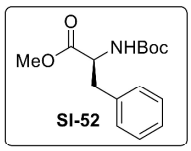
(*S*)-4-Benzyl-5,5-dimethyloxazolidin-2-one (SI-54)

L-Phenylalanin (**SI-50**, 19.8 g, 120 mmol, 1.00 eq.) in MeOH *p.a.* (300 mL) was treated with $SOCl_2$ (26.1 mL, 360 mmol, 3.00 eq.) at 0 °C. The mixture was stirred at reflux for 20 h. The volatiles were removed under reduced pressure. The crude product was dissolved in MeOH *p.a.* and solvents were removed. This procedure was carried out multiple times. Methylesterhydrochlorid **SI-51** (25.7 g, quant.) was isolated as a colourless solid and used without further purification.



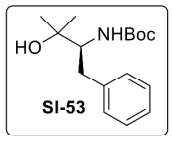
SI-51

Methylester **SI-51** (25.7 g, 119 mmol, 1.00 eq.) in dry CH_2Cl_2 (300 mL) was treated with dry NEt_3 (18.3 mL) and Boc_2O (27.3 g, 125 mmol, 1.05 eq.) in dry CH_2Cl_2 (100 mL) at 0 °C. The suspension was stirred at this temperature for 20 min, dry NEt_3 (4.15 mL, 29.8 mmol, 0.25 eq.) was added again and stirring was continued at room temperature for 16 h. Imidazole (810 mg, 11.9 mmol, 0.10 eq.) was added and stirring was continued for 30 min. The mixture was poured into citric acid solution (1M). Organic phase was separated and washed with citric acid solution (1M) twice, with 1 vol% HCl twice and with brine once. They were dried over Na_2SO_4, and solvents were removed at the rotary evaporator. The Boc-protected phenylalanineester **SI-52** (33.1 g, 92%) was isolated as a clear brownish resin and was used without further purification.



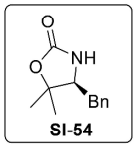
SI-52

Ester **SI-52** (27.9 g, 100 mmol, 1.00 eq.) in dry THF (200 mL) was treated with MeMgBr (3M in Et_2O, 133 mL, 400 mmol) at 0 °C over 45 min. Solution was stirred at room temperature for 2 d. MeOH and H_2O was added, and the suspension was filtered off over celite®. The solvent was removed under reduced pressure and the crude product was suspended in Et_2O, filtered off over celite® and the solvent was again removed at the rotary evaporator. This procedure was repeated once. Alcohol **SI-53** (25.4 g, 91%) was isolated as a pale brown resin.



SI-53

Alcohol **SI-53** (25.4 g, 90.9 mmol, 1.00 eq.) in dry THF (364 mL) was treated with KO*t*Bu (12.2 g, 109 mmol, 1.20 eq.) at 0 °C. After stirring for 30 min, sat. aq. NH_4Cl solution and EtOAc were added, and the aqueous phase was extracted with EtOAc twice. Combined organic phases were washed with brine and dried

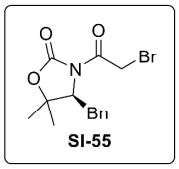


SI-54

over Na_2SO_4. After removal of the volatiles under reduced pressure, the crude product was recrystallised with pentane/Et_2O twice. Oxazolidinone **SI-54** (8.29 g, 44%) was obtained as colourless needles. $\mathbf{R_f}$ = 0.26 (hexanes/EtOAc 2:1); **mp** 66.5 °C; Lit.[8] **mp** 66-67 °C; **IR** ν_{max}/cm^{-1} 3263 (m), 3030 (w), 2980 (m), 2933 (w), 1739 (s), 1604 (w), 1496 (m), 1455 (m), 1374 (m), 1298 (m), 1271 (m), 1241 (w), 1218 (w), 1189 (w), 1143 (w), 1085 (m), 995 (m), 967 (w), 940 (w), 914 (w), 884 (w), 771 (m), 744 (m), 700 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 4.87 (br. s , 1H), 3.69 (ddd, 1H, J = 0.6, 3.7, 10.8 Hz), 2.84 (dd, 1H, J = 3.7, 13.3 Hz), 2.67 (dd, 1H, J = 10.8, 13.3 Hz), 1.48 (s, 3H), 1.46 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 158.0, 137.0, 129.2, 129.0, 127.4, 127.1, 83.3, 63.2, 37.2, 27.7, 22.1 ppm.

Spectroscopic data corresponded to those reported in the literature.[8]

(*S*)-4-Benzyl-3-(2-bromoacetyl)-5,5-dimethyloxazolidin-2-one (SI-55)

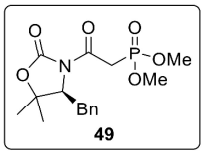


SI-55

A solution of oxazolidinone **SI-54** (6.00 g, 29.2 mmol, 1.00 eq.) in dry THF (73 mL) was treated with *n*BuLi (12.3 mL, 30.7 mmol, 1.05 eq.) at −80 °C. After 10 min, bromoacetylbromide (2.67 mL, 32.7 mmol, 1.12 eq.) was added at −80 °C and stirring was continued for 13.5 h at room temperature. Sat. aq. NH_4Cl solution and EtOAc were added and the aqueous phase was extracted with EtOAc thrice. Combined organic phases were washed with sat. aq. $NaHCO_3$ solution as well as brine and dried over Na_2SO_4. Crude product was purified by column chromatography (SiO_2, pentane/EtOAc 5:1) to yield bromide **SI-55** (7.14 g, 75%) as a light-yellow oil. $\mathbf{R_f}$ = 0.76 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$ −26.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3060 (w), 3028 (w), 2983 (w), 2940 (w), 1773 (s), 1698 (s), 1605 (w), 1497 (w), 1455 (w), 1415 (w), 1393 (m), 1358 (s), 1327 (m), 1276 (s), 1234 (m), 1207 (m), 1184 (m), 1161 (m), 1142 (m), 1094 (s), 1024 (w), 962 (m), 920 (w), 902 (w), 849 (w), 761 (m), 731 (m), 700 (m), 653 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 4.58 (d, 1H, J = 12.4 Hz), 4.51 (dd, 1H, J = 3.8, 9.7 Hz), 4.44 (d, 1H, J = 12.4 Hz), 3.19 (dd, 1H, J = 3.8, 14.6 Hz), 2.90 (dd, 1H, J = 9.7, 14.6 Hz), 1.42 (s, 3H), 1.41 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 166.4, 152.3, 136.6, 129.2, 128.9, 127.1, 83.4, 64.2, 35.1, 28.8, 28.5, 22.4 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{14}H_{17}NO_3Br$ 326.03863 found 326.03800.

Spectroscopic data corresponded to those reported in the literature.[9]

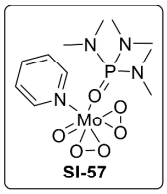
Dimethyl-(*S*)-(2-(4-benzyl-5,5-dimethyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate (49)



49

Bromide **SI-55** (5.17 g, 15.8 mmol, 1.00 eq.) was treated with $P(OMe)_3$ (9.36 mL, 79.2 mmol, 5.00 eq.) at room temperature. The mixture was stirred for 17 h at room temperature and for 3.5 h at 60 °C. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, EtOAc) to give phosphonate **49** (5.15 g, 92%) as a colourless resin. $\mathbf{R_f}$ = 0.59 (EtOAc); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −12.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3011 (w), 2957 (w), 2854 (w), 1771 (s), 1695 (s), 1605 (w), 1498 (w), 1456 (w), 1396 (m), 1357 (s), 1322 (m), 1265 (s), 1211 (m), 1185 (m), 1160 (m), 1094 (m), 1056 (m), 1020 (s), 964 (m), 926 (w), 901 (w), 882 (m), 846 (m), 806 (m), 764 (m), 731 (s), 700 (m), 677 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 4.53 (dd, 1H, J = 3.7, 9.8 Hz), 4.06 (dd, 1H, J = 14.1, 22.0 Hz), 3.82 (d, 3H, J = 4.9 Hz), 3.80 (d, 3H, J = 4.9 Hz), 3.56 (dd, 1H, J = 14.1, 22.2 Hz), 3.18 (dd, 1H, J = 3.7, 14.6 Hz), 2.89 (dd, 1H, J = 9.8, 14.6 Hz), 1.40 (s, 3H), 1.37 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 165.0 (d, J = 7.0 Hz), 152.8, 136.9, 129.2, 128.8, 127.0, 82.8, 64.1, 53.4 (d, J = 5.8 Hz), 53.3 (d, J = 5.8 Hz), 35.3, 34.4, 33.3, 28.5, 22.4 ppm; **HRMS** ESI m/z $[M + H]^+$ calcd. for $C_{17}H_{22}NO_6P$ 356.12575 found 356.12491.

Oxodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (SI-57)

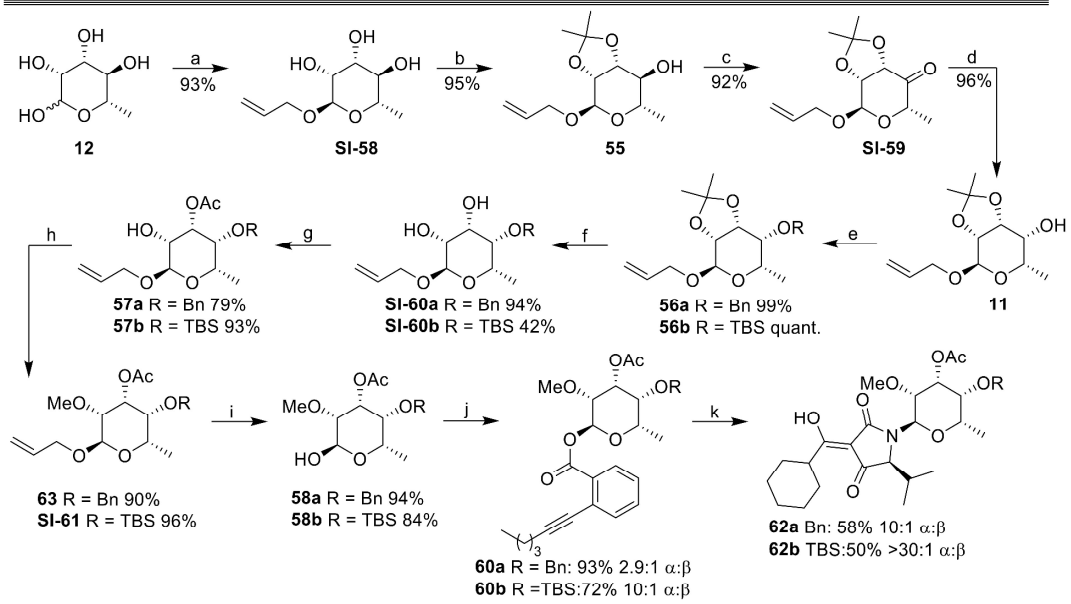


SI-57

MoO_3 (**SI-56**, 30.0 g, 208 mmol, 1.00 eq.) was dissolved in H_2O_2 (30 wt%, 150 mL) and stirred at 40 °C. Temperature was strictly kept at max. 40 °C, while stirring for 4.25 h. The suspension was filtered off over celite® and the mother liquor was treated with HMPA (36.2 mL, 208 mmol, 1.00 eq.) and stirred vigorously for 5 min. It was again filtered off and the solid was recrystallized in MeOH. The solid (27.6 g, 77.4 mmol, 1.00 eq.) was dried in the desiccator and dissolved in dry THF (115 mL). Pyridine (6.26 mL, 77.4 mmol, 1.00 eq.) was added at room temperature and the mixture was stirred for 15 min. The solid was filtered off, washed with dry THF as well as dry Et_2O and dried in a desiccator filled with P_2O_5. The Vedejs-reagent (**SI-57**, 27.8 g, 31%) was isolated as yellow crystals.

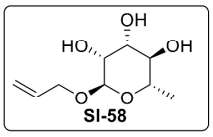
There is no convenient analytical method for characterization of this compound.[10]

2.8 Synthesis of glycosides **62a** and **62b**



Scheme S11. Synthesis of glycosides **62a/b**.
Reagents and conditions: a) AcCl, allylOH, 0 °C→55 °C, 24 h; b) $CuSO_4$, AcMe, rt, 17 h; c) 1. $(ClCO)_2$, DMSO, −78 °C, 40 min, 2. **55**, 50 min, 3. DIPEA, −78 °C→rt, 16 h; d) $NaBH_4$, 0 °C, 1.5 h; e) 1. **56a**: NaH, imidazole, DMF, 0 °C, 35 min, 2. BnBr, TBAI, rt, 17 h; **56b**: TBSOTf, pyridine, CH_2Cl_2, 0 °C, 5 h; f) **SI-60a**: AcOH, H_2O, reflux, 1.5 h; **SI-60b**: HCOOH, EtOH, rt, 2.5 h; g) **57a**: 1. Bu_2SnO, toluene, reflux, 4 h, 2. AcCl, 0 °C, 30 min; **57b**: 1. Bu_2SnO, toluene, reflux, 3 h, 2. AcCl, rt, 1 h; h) **63**: $TMSCHN_2$, HBF_4, CH_2Cl_2, 0 °C, 5 h; **SI-61** MeO_3BF_4, proton sponge, CH_2Cl_2, 0 °C→40 °C, 21 h; i) **58a**: $Pd(PPh_3)_4$, AcOH, rt, 17 h; **58b**: 1. DABCO, Wilkinson´s catalyst, EtOH, Δ, 15 h, 2. I_2, phosphate buffer pH=7/H_2O/EtOAc, rt, 10 min; j) **60a/b**: acid **59**, DCC, DMAP, CH_2Cl_2, rt, 3-3.5 h; k) **62a/b**: tetramic acid **61**, $AuPPh_3NTf_2$, rt→40 °C, 17-20 h.

(3*R*,4*R*,5*R*,6*S*)-2-(Allyloxy)-6-methyltetrahydro-2*H*-pyran-3,4,5-triol (SI-58)

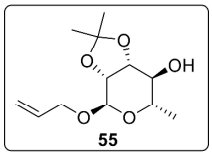


L-Rhamnose (**12**; 10.0 g, 54.9 mmol, 1.00 eq.) was added to a solution of AcCl (10.1 mL, 141 mmol, 1.10 eq.) and allylic alcohol (100 mL) at 0 °C. The mixture was stirred at 55 °C for 24 h. The reaction was quenched with $NaHCO_3$ and the solid was filtered off. The volatiles were removed in vacuo, toluene was added, and the solvent was concentrated under reduced pressure. This procedure was repeated twice. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 10:1→9:1→8:1) to yield the allylated carbohydrate **SI-58** (10.3 g, 93%, α:β 9:1) as a colourless resin. $\mathbf{R_f}$ = 0.74 (CH_2Cl_2/MeOH 4:1); $[\boldsymbol{\alpha}]_D^{20}$ −85.6° (c 1.0, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3376 (s), 2978 (m), 2919 (m), 1451 (w), 1423 (w), 1384 (w), 1265 (w), 1130 (m), 1050 (s), 985 (m), 927 (w), 810 (w); α-anomer: **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.89 (dddd, 1H, *J* – 5.1, 6.0, 10.7, 16.9 Hz), 5.29 (dq, 1H, *J* – 1.5, 16.9 Hz), 5.20 (dq, 1H, *J* – 1.5, 10.7 Hz),

4.83 (d, 1H, *J* = 1.0 Hz), 4.18 (ddt, 1H, *J* = 1.3, 5.1, 13.0 Hz), 3.99 (ddt, 1H, *J* = 1.3, 6.0, 13.0 Hz), 3.96 (m, 1H), 3.79 (m, 1H), 3.69 (m, 1H), 3.49 (d, 1H, *J* = 5.5 Hz), 3.46 (dt, 1H, *J* = 3.5, 9.4 Hz), 3.04-2.86 (br. s, 1H), 2.78-2.56 (br. s, 2H), 1.32 (d, 3H, *J* = 6.3 Hz) ppm; β-anomer: **^{1}H-NMR** (500 MHz, $CDCl_3$) *δ* 5.93 (m, 1H), 5.30 (m, 1H), 5.23 (m, 1H), 4.51 (s, 1H), 4.40 (ddt, 1H, *J* = 1.3, 5.2, 12.8 Hz), 4.13 (ddt, 1H, *J* = 1.3, 6.6, 12.8 Hz), 3.99 (m, 2H), 3.79 (m, 1H), 3.69 (m, 1H), 3.27 (m, 1H), 2.93 (br. s, 1H), 1.64 (br. s, 1H), 1.37 (d, 3H, *J* = 6.2 Hz), 0.99 (m, 1H) ppm. α-anomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 133.8, 117.7, 99.0, 73.1, 71.9, 71.1, 68.3, 68.1, 17.7 ppm; β-anomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 133.6, 118.6, 98.6, 74.2, 72.9, 72.2, 71.2, 70.1, 17.7 ppm.

Spectroscopic data corresponded to those reported in the literature.[11]

(3a*R*,6*S*,7*S*,7a*R*)-4-(Allyloxy)-2,2,6-trimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-ol (55)

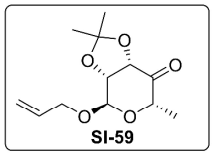


55

A solution of glycoside **SI-58** (7.74 g, 37.9 mmol, 1.00 eq.) in acetone (1.60 L) was treated with $CuSO_4$ (96.8 g, 606 mmol, 16.0 eq.) and stirred for 17 h at room temperature. The solid was removed by filtration over celite®. Removing of the solvent under reduced pressure gave the product **55** (8.68 g, 94%, α:β 16:1) as a colourless resin. $\mathbf{R_f}$ = 0.75 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ −26.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3470 (m), 2985 (m), 2937 (m), 2905 (m), 1456 (w), 1383 (m), 1244 (m), 1220 (m), 1141 (m), 1077 (s), 1053 (s), 1023 (s), 997 (m), 922 (w), 860 (m), 818 (w); α-Anomer: **^{1}H-NMR** (500 MHz, $CDCl_3$) *δ* 5.91 (dddd, 1H, *J* = 5.3, 6.2, 10.3, 17.0 Hz), 5.31 (dq, 1H, *J* = 1.4, 17.0 Hz), 5.22 (dq, 1H, *J* = 1.4, 10.3 Hz), 5.01 (s, 1H), 4.20 (ddt, 1H, *J* = 1.4, 2.8, 5.3 Hz), 4.17 (d, 1H, *J* = 5.8 Hz), 4.10 (dd, 1H, *J* = 5.8, 7.1 Hz), 4.01 (ddt, 1H, *J* = 1.4, 6.2, 12.8 Hz), 3.70 (dq, 1H, *J* = 6.3, 9.1 Hz), 3.42 (ddd, 1H, *J* = 4.6, 7.1, 9.1 Hz), 2.19 (m, 1H), 1.53 (s, 3H), 1.36 (s, 3H), 1.30 (d, 3H, *J* = 6.3 Hz) ppm; β-Anomer: **^{1}H-NMR** (500 MHz, $CDCl_3$) *δ* 5.96 (m, 1H), 5.31 (m, 1H), 5.23 (m, 1H), 4.78 (d, 1H, *J* = 2.2 Hz), 4.43 (ddt, 1H, *J* = 1.5, 4.9, 13.0 Hz), 4.25 (dd, 1H, *J* = 2.2, 5.7 Hz), 4.19 (m, 1H), 4.10 (m, 1H), 3.54 (m, 1H), 3.30 (m, 1H), 2.11 (m, 1H), 1.57 (s, 3H), 1.39 (s, 3H), 1.35 (m, 3H) ppm. α-Anomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 133.7, 118.0, 109.6, 96.4, 78.5, 75.9, 74.6, 68.1, 66.1, 28.1, 26.3, 17.6 ppm; β-Anomer: **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 133.9, 118.5, 111.0, 97.0, 80.3, 75.1, 75.0, 71.1, 70.3, 28.2, 26.4, 17.9 ppm.

Spectroscopic data corresponded to those reported in the literature.[12]

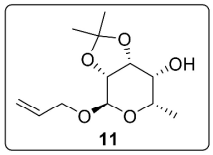
(3a*R*,6*S*,7a*S*)-4-(Allyloxy)-2,2,6-trimethyldihydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7(6*H*)-one (SI-59)



Oxalyl chloride (7.90 mL, 92.1 mmol, 2.00 eq.) was dissolved in dry CH_2Cl_2 (38 mL) and treated with dry DMSO (13.1 mL, 184 mmol, 4.00 eq.) at -78 °C. After stirring for 40 min, glycoside **55** (11.3 g, 46.1 mmol, 1.00 eq.) was added. Stirring was continued for 50 min at −78 °C and DIPEA (31.5 mL, 184 mmol, 4.00 eq.) was dropped into the mixture. The solution was allowed to warm to room temperature and stirred for a further 16 h. Sat. aq. $Na_2S_2O_3$ solution was added, and the aqueous phase was extracted thrice with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 8:1) afforded ketone **SI-59** (9.52 g, 92%, only α) as a colourless oil. $\mathbf{R_f}$ = 0.79 (hexanes/EtOAc 7:3); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −125.1° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2989 (m), 2938 (m), 2922 (m), 2876 (w), 1742 (s), 1456 (w), 1375 (m), 1228 (m), 1162 (m), 1107 (s), 1979 (s), 1012 (s), 932 (m), 857 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.31 (m, 1H), 5.24 (m, 1H), 5.00 (s, 1H), 4.45 (q, 2H, J = 5.7 Hz), 4.28 (q, 1H, J = 6.8 Hz), 4.24 (m, 1H), 4.08 (m, 1H), 1.49 (s, 3H), 1.39 (d, 3H, J = 6.8 Hz), 1.36 (s, 3H), ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 204.8, 133.1, 118.5, 111.5, 96.1, 78.9, 76.1, 70.2, 68.9, 26.9, 25.6, 16.0 ppm.

Spectroscopic data corresponded to those reported in the literature.[13]

(3a*R*,6*S*,7*R*,7a*R*)-4-(Allyloxy)-2,2,6-trimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-ol (11)

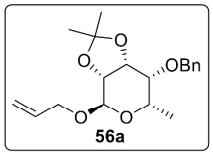


A solution of ketone **SI-59** (9.52 g, 39.3 mmol, 1.00 eq.) in EtOH *p.a.* (157 mL) was treated with $NaBH_4$ (1.64 g, 43.2 mmol, 1.10 eq.) at 0 °C. The suspension was stirred for 1.5h and the solid was filtered off over celite®. The solvent was removed under reduced pressure. Column chromatography (SiO_2, pentane/EtOAc, 7:1→6:1→4:1) gave alcohol **11** (9.19 g, 96%, only α) as a colourless liquid. $\mathbf{R_f}$ = 0.53 (hexanes/EtOAc 3:2); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −38.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3528 (m), 2984 (m), 2936 (m), 1381 (m), 1255 (m), 1215 (m), 1152 (m), 1073 (s), 1019 (m), 991 (s), 852 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.31 (d, 1H, J – 17.0 Hz), 5.22 (d, 1H, J = 10.3 Hz), 5.08 (s, 1H), 4.22 (q, 1H, J = 5.9 Hz), 4.20 (m, 1H), 4.07 (d, 1H, J = 6.2 Hz), 4.03 (dd, 1H, J = 6.2, 12.8 Hz), 3.89 (q, 1H, J = 6.7 Hz), 3.55 (t, 1H, J =

5.9 Hz), 2.18 (d, 1H, *J* = 6.7 Hz), 1.59 (s, 3H), 1.38 (s, 3H), 1.32 (d, 3H, *J* = 6.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 133.8, 118.0, 109.4, 96.8, 73.4, 73.1, 68.4, 67.0, 64.5, 26.0, 25.4, 16.8 ppm.

Spectroscopic data corresponded to those reported in the literature.[13]

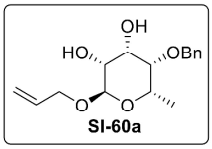
(3a*R*,6*S*,7*R*,7a*R*)-4-(Allyloxy)-7-(benzyloxy)-2,2,6-trimethyltetrahydro-4*H*-[1,3]dioxolo-[4,5-c]pyran (56a)



A solution of alcohol **11** (8.98 g, 36.8 mmol, 1.00 eq.) in dry DMF (142 mL) was treated with NaH (2.82 g, 118 mmol, 3.20 eq.) and imidazole (225 mg, 3.31 mmol, 0.09 eq.) at 0 °C. The solution was stirred for 35 min, BnBr (6.33 mL, 53.3 mmol, 1.45 eq.) and TBAI (1.36 g, 3.68 g, 0.10 eq.) were added and stirring was continued for 17 h at room temperature. H_2O and EtOAc were added, the phases were separated, and the aqueous phase was extracted thrice with EtOAc. The combined organic phases were washed with H_2O and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 7:1) afforded benzylated glycoside **56a** (12.2 g, quant., only α) as a colourless solid. **R_f** = 0.76 (hexanes/EtOAc 3:2); **mp** 27 °C; $[\alpha]_D^{20}$ −12.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2984 (m), 2933 (m), 2910 (m), 1455 (m), 1380 (m), 1369 (m), 1252 (m), 1214 (m), 1161 (m), 1144 (m), 1055 (s), 1025 (s), 924 (w), 858 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.89 (dddd, 1H, *J* = 5.6, 6.2, 10.5, 17.1 Hz), 5.27 (dq, 1H, *J* = 1.6, 17.1 Hz), 5.18 (d, 1H, *J* = 1.6, 10.5 Hz), 4.98 (d, 1H, *J* = 1.5 Hz), 4.85 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.40 (dd, 1H, *J* = 4.6, 6.6 Hz), 4.18 (ddt, 1H, *J* = 1.5, 5.1, 12.7 Hz), 4.07 (dd, 1H, *J* = 1.7, 6.7 Hz), 4.01 (ddt, 1H, *J* = 1.5, 6.3, 12.8 Hz), 3.88 (dq, 1H, *J* = 3.3, 6.7 Hz), 3.59 (dd, 1H, *J* = 3.3, 4.3 Hz), 1.56 (s, 3H), 1.37 (s, 3H), 1.20 (d, 3H, *J* = 6.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 138.1, 134.0, 128.7, 128.4, 127.9, 117.7, 110.1, 97.0, 74.5, 74.3, 73.8, 72.8, 68.6, 65.8, 26.4, 25.6, 16.9 ppm. **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{26}O_5Na$ 357.16685, found 357.16725.

(3*R*,4*S*,5*S*,6*S*)-2-(Allyloxy)-5-(benzyloxy)-6-methyltetrahydro-2*H*-pyran-3,4-diol (SI-60a)

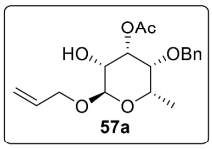
Carbohydrate **56a** (12.2 g, 36.4 mmol, 1.00 eq.) was dissolved in H_2O (7 mL) and AcOH (64 mL). The solution was stirred at 110 °C for 1.5 h. Toluene was added and the volatiles were



SI-60a

removed under reduced pressure. This procedure was repeated twice. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 4:1→2:1) to give deprotected carbohydrate **SI-60a** (9.94 g, 93%, only α) as a colourless oil in 93% yield. $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc 3:2); $[\alpha]_D^{20}$ −103.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3475 (m), 2932 (m), 1736 (w), 1455 (w), 1383 (w), 1360 (w), 1103 (s), 1052 (s), 1008 (s), 928 (w), 813 (m), 737 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 5.89 (m, 1H), 5.28 (dq, 1H, J = 1.4, 17.2 Hz), 5.19 (dq, 1H, J = 1.4, 10.4 Hz), 4.90 (d, 1H, J = 1.1 Hz), 4.78 (d, 1H, J = 11.0 Hz), 4.70 (d, 1H, J = 11.0 Hz), 4.15 (ddt, 1H, J = 1.4, 5.1, 13.0 Hz), 3.99 (ddt, 1H, J = 1.4, 6.0, 13.0 Hz), 3.92 (q, 1H, J = 6.6 Hz), 3.88 (dt, 1H, J = 3.4, 10.3 Hz), 3.69 (m, 1H), 3.64 (m, 1H), 3.39 (m, 1H), 2.79 (m, 1H), 1.27 (d, 3H, J = 6.6 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 137.6, 133.9, 128.7, 128.3, 128.2, 117.4, 100.2, 81.5, 76.8, 70.9, 68.3, 66.9, 66.1, 17.1 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{22}O_5Na$ 317.13568, found 317.13594.

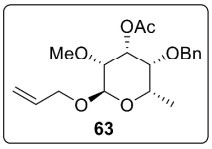
(3*R*,4*S*,5*R*,6*S*)-2-(Allyloxy)-5-(benzyloxy)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (57a)



57a

A solution of diol **SI-60a** (6.12 g, 21.0 mmol, 1.00 eq.) in toluene *p.a.* (1.00 L) was treated with Bu_2SnO (6.27 g, 25.2 mmol, 1.20 eq.) and stirred for 4 h under reflux with a water separator. AcCl (1.60 mL, 22.1 mmol, 1.05 eq.) was added at 0 °C and stirred for a further 30 min. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 5:1) to give product **57a** (5.56 g, 79%) as a colourless oil. $\mathbf{R_f}$ = 0.56 (hexanes/EtOAc 3:2); $[\alpha]_D^{20}$ −128.0° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3487 (m), 2937 (w), 1740 (s), 1432 (w), 1455 (w), 1362 (m), 1229 (s), 1150 (m), 1116 (s), 1045 (s), 1011 (s), 919 (m), 752 (m), 731 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.88 (m, 1H), 5.28 (dq, 1H, J = 1.4, 17.2 Hz), 5.19 (d, 1H, J = 1.4, 10.4 Hz), 5.08 (t, 1H, J = 3.1 Hz), 4.90 (d, 1H, J = 1.5 Hz), 4.77 (d, 1H, J = 11.3 Hz), 4.61 (d, 1H, J = 11.3 Hz), 4.16 (ddt, 1H, J = 1.3, 5.3, 13.0 Hz), 4.11, (d, 1H, J = 11.1 Hz), 4.00 (m, 2H), 3.83 (m, 1H), 3.77 (m, 1H), 2.11 (s, 3H), 1.25 (d, 3H, J = 6.5 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.6, 137.3, 133.9, 128.7, 128.4, 128.4, 117.6, 100.7, 79.0, 76.1, 70.1, 69.3, 68.4, 66.4, 21.3, 16.9 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{18}H_{24}O_6Na$ 359.14651, found 359.14602.

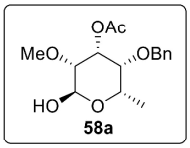
(3*R*,4*R*,5*R*,6*S*)-2-(Allyloxy)-5-(benzyloxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (63)



63

A solution of carbohydrate **57a** (2.75 g, 8.20 mmol, 1.00 eq.) in dry CH_2Cl_2 (33 mL) was treated with $TMSCHN_2$ (1.8-2.4M in hexanes, 20.5 mL, 40.9 mmol, 5.00 eq.) and HBF_4 (50 wt% in H_2O, 2.00 mL, 16.4 mmol, 2.00 eq.) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, $TMSCHN_2$ (1.8-2.4M in hexanes, 20.5 mL, 40.9 mmol, 5.00 eq.) and HBF_4 (50 wt% in H_2O, 2.00 mL, 16.4 mmol, 2.00 eq.) were added again and stirring was continued for 1 h. This was repeated a second time. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution. The aqueous phase was extracted thrice with CH_2Cl_2, the combined organic phases were washed with brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 4:1→2:1) gave product **63** (2.58 g, 90%) as a colourless resin. $\mathbf{R_f}$ = 0.61 (hexanes/EtOAc 3:2); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −79.1° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3004 (w), 2989 (w), 1744 (w), 1276 (m), 1261 (m), 1092 (w), 1051 (w), 764 (s), 750 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.89 (m, 1H), 5.28 (dq, 1H, J = 11.6, 7.2 Hz), 5.18 (d, 1H, J = 1.4, 10.4 Hz), 5.17 (t, 1H, J = 3.5 Hz), 4.95 (d, 1H, J = 2.1 Hz), 4.71 (d, 1H, J = 12.2 Hz), 4.65 (d, 1H, J = 12.2 Hz), 4.17 (ddt, 1H, J = 1.5, 5.1, 13.0 Hz), 4.02-3.94, (m, 2H), 3.61 (m, 1H), 3.51 (s, 3H), 3.43 (m, 1H), 2.03 (s, 3H), 1.24 (d, 3H, J = 6.7 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 138.6, 134.0, 128.4, 128.3, 127.7, 127.6, 117.4, 97.5, 77.5, 76.1, 74.7, 71.3, 68.2, 67.0, 59.9, 21.3, 16.6 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{26}O_6Na$ 373.16216, found 373.16129.

(2*S*,3*R*,4*R*,5*R*)-3-(Benzyloxy)-6-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-4-yl acetate (58a)

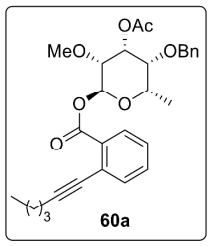


58a

Glycoside **63** (1.00 g, 2.85 mmol, 1.00 eq.) was dissolved in AcOH (29 mL) and $Pd(PPh_3)_4$ (989 mg, 856 µmol, 0.30 eq.) was added at room temperature. The mixture was stirred for 17 h and quenched with sat. aq. $NaHCO_3$ solution as well as solid $NaHCO_3$. The aqueous phase was extracted thrice with EtOAc, the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by column chromatography (SiO_2, pentane/EtOAc 1.5:1→1:1) to afford hemi-acetal **58a** (784 mg, 89%, α:β 6:1) as a light yellow resin. $\mathbf{R_f}$ = 0.52 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ −41.1° (c

1.0 in $CHCl_3$); IR ν_{max}/cm^{-1} 3438 (m), 2977 (w), 2934 (m), 2896 (m), 2837 (w), 1739 (s), 1497 (w), 1455 (m), 1372 (m), 1236 (s), 1157 (m), 1132 (m), 1096 (s), 1044 (s), 968 (m), 913 (m), 817 (w), 750 (s), 699 (m), 677 (m); α-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.31 (t, 2H, J = 3.2 Hz), 4.71 (d, 1H, J = 12.1 Hz), 4.64 (d, 1H, J = 12.1 Hz), 4.22 (dq, 1H, J = 2.6, 6.6 Hz), 3.63 (t, 1H, J = 2.8 Hz), 3.51 (s, 3H), 3.87 (t, 1H, J = 3.2 Hz), 2.70 (d, 1H, J = 3.7 Hz), 2.06 (s, 3H), 1.28 (d, 3H, J = 6.7 Hz) ppm; β-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 4.85 (t, 1H, J = 3.3 Hz), 4.75 (d, 1H, J = 12.3 Hz), 4.68 (dd, 1H, J = 1.8, 12.8 Hz), 4.63 (d, 1H, J = 12.3 Hz), 4.04 (d, 1H, J = 12.8 Hz), 3.67 (s, 3H), 3.56 (m, 2H), 3.53 (m, 1H), 1.99 (s, 3H), 1.30 (m, 3H) ppm; α-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 138.4, 128.4, 128.3, 127.8, 92.7, 77.9, 75.7, 74.2, 70.3, 67.8, 59.7, 21.3, 16.4, ppm; β-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.3, 138.3, 128.8, 128.4, 128.0, 93.8, 77.9, 75.6, 75.4, 74.4, 71.4, 61.6, 21.1, 16.9 ppm; **HRMS** ESI m/z $[M + Na]^+$ calcd. for $C_{16}H_{22}O_6Na$ 333.13033, found 333.213086.

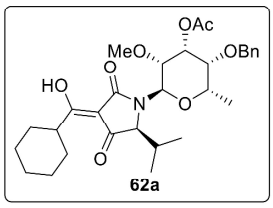
(3*R*,4*R*,5*R*,6*S*)-4-Acetoxy-5-(benzyloxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-2-yl-2-(hex-1-yn-1-yl)benzoate (60a)



A solution of hemi-acetal **58a** (784 mg, 2.53 mmol, 1.00 eq.) in dry CH_2Cl_2 (3.6 mL) was treated with acid **59** (656 mg, 3.03 mmol, 1.20 eq.), DCC (782 mg, 3.79 mmol, 1.50 eq.) and DMAP (463 mg, 3.79 mmol, 1.50 eq.) at room temperature. After stirring for 3 h, the solids were filtered off over celite®. The organic phase was washed with sat. aq. $NaHCO_3$ solution and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, and solvents were removed under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 6:1→4:1→2:1) gave product **60a** (1.16 g, 93% mmol, α:β 2.9:1) as a colourless resin. $\mathbf{R_f}$ = 0.71 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ −9.6° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2934 (w), 2872 (w), 2229 (w), 1737 (s), 1596 (w), 1567 (w), 1484 (w), 1456 (w), 1366 (m), 1275 (m), 1233 (s), 1131 (m), 1069 (s), 1042 (s), 989 (m), 946 (m), 916 (m), 751 (s), 698 (m); α-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.89 (dd, 1H, J = 1.2, 8.0 Hz), 7.53 (dd, 1H, J = 1.2, 8.0 Hz), 7.45 (dq, 1H, J = 2.3, 7.6 Hz), 7.40-7.27 (m, 6H), 6.51 (d, 1H, J = 2.0 Hz), 5.23 (t, 1H, J = 3.5 Hz), 4.75 (d, 1H, J = 12.2 Hz), 4.69 (d, 1H, J = 12.2 Hz), 4.24 (dq, 1H, J = 1.8, 6.5 Hz), 3.73 (m, 1H), 3.60 (s, 3H), 3.59 (s, 1H), 2.47 (m, 2H), 2.06 (s, 3H), 1.61 (m, 2H), 1.48 (m, 2H), 1.28 (d, 3H, J = 6.6 Hz), 0.94 (t, 3H, J = 7.4 Hz) ppm; β-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.09 (dd, 1H, J = 1.2,

8.0 Hz), 7.53 (dd, 1H, *J* = 1.2, 8.0 Hz), 7.45 (dq, 1H, *J* = 2.3, 7.6 Hz), 7.40-7.27 (m, 6H), 6.07 (d, 1H, *J* = 2.2 Hz), 5.24 (t, 1H, *J* = 3.5 Hz), 4.72 (d, 1H, *J* = 12.2 Hz), 4.68 (d, 1H, *J* = 12.2 Hz), 3.89 (dq, 1H, *J* = 2.9, 6.7 Hz), 3.69 (dd, 1H, *J* = 1.8, 3.5 Hz), 3.65 (t, 1H, *J* = 3.5 Hz), 3.57 (s, 3H), 2.45 (m, 2H), 2.09 (s, 3H), 1.61 (m, 2H), 1.48 (m, 2H), 1.37 (d, 3H, *J* = 6.7 Hz), 0.94 (t, 3H, *J* = 7.3 Hz) ppm; α-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 170.5, 164.4, 138.3, 135.0, 132.1, 130.7, 130.6, 128.4, 128.3, 127.8, 125.0, 96.6, 93.2, 79.6, 76.3, 75.5, 74.8, 70.9, 70.0, 60.1, 30.8, 22.2, 21.2, 19.6, 16.8, 13.8 ppm; significant signals β-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 170.5, 164.0, 138.2, 134.6, 130.75, 130.73, 128.34, 128.27, 127.3, 127.0, 125.7, 97.1, 92.2, 79.1, 76.4, 74.2, 73.7, 72.2, 60.7, 30.8, 22.2, 21.1, 19.7, 17.0 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{29}H_{34}O_7Na$ 517.21967, found 517.21924.

(2*S*,3*R*,4*R*,5*R*)-3-(Benzyloxy)-6-((*S*,*Z*)-3-(cyclohexyl(hydroxy)methylene)-5-isopropyl-2,4-dioxopyrrolidin-1-yl)-5-methoxy-2-methyltetrahydro-2*H*-pyran-4-yl acetate (62a)



62a

Ester **60a** (200 mg, 404 µmol, 1.00 eq.) and 3-acyl tetramic acid **61** (152 mg, 607 µmol, 1.50 eq.) were dissolved in dry toluene (1.00 mL). $AuPPh_3NTf_2$ (59.8 mg, 80.9 µmol, 0.20 eq.) was added and the mixture was stirred at 40 °C for 17 h. All volatiles were removed in vacuo. The crude product was purified by column chromatography (SiO_2 C-18, 40% MeCN in H_2O + 0.1% HCO_2H→60% MeCN in H_2O + 0.1% HCO_2H→80% MeCN in H_2O + 0.1% HCO_2H→100% MeCN in H_2O + 0.1% HCO_2H) to give product **62a** as a light-yellow resin (127 mg, 58%, α:β 10:1). Anomers were separated by HPLC. Minor impurities occurred due to third tautomer $\mathbf{R_f}$ = 0.49 (hexanes/EtOAc 1:1); $[\boldsymbol{\alpha}]_D^{20}$ −8.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2932 (m), 2857 (w), 1744 (s), 1796 (s), 1647 (s), 1607 (s), 1453 (m), 1364 (w), 1312 (w), 1232 (s), 1089 (s), 1027 (w), 752 (m), 698 (w); α-anomer **^{1}H-NMR** (500 MHz, CD_3OD) *δ* 7.40-7.26 (m, 5H), 6.00 (t, 1H, *J* = 3.0 Hz), 5.09 (br. s, 1H), 4.67 (d, 1H, *J* = 11.6 Hz), 4.51 (d, 1H, *J* = 11.6 Hz), 4.26 (m, 2H), 3.84 (br. s, 1H), 3.83 (dd, 1H, *J* = 3.2, 6.5 Hz), 3.43 (tt, 1H, *J* = 3.3, 11.5 Hz), 3.32 (s, 3H), 2.24 (m, 1H), 2.13 (s, 3H), 1.86-1.70 (m, 5H), 1.51 (m, 2H), 1.43 (d, 3H, *J* = 7.1 Hz), 1.39 (m, 2H), 1.27 (m, 1H), 1.17 (d, 3H, *J* = 7.1 Hz), 0.89 (d, 3H, *J* = 7.1 Hz) ppm; α-anomer major tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 193.9, 192.6, 175.9, 170.4, 137.8, 128.6, 128.0, 127.7, 101.2, 75.6, 74.2, 73.2, 71.9, 71.0, 66.4, 57.1, 41.0, 30.4, 29.0, 28.5, 25.8, 25.71, 25.70, 25.6, 21.4, 18.1, 16.1, 13.6 ppm; significant signals α-anomer minor tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) *δ* 199.7, 197.6, 170.5, 168.4, 137.8, 128.6, 128.2, 127.7, 104.8, 73.1, 71.7, 70.9, 66.6, 57.0, 41.8, 30.2,

29.1, 28.4, 25.8, 25.5, 21.4, 18.2, 15.7, 13.6 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{30}H_{42}NO_8$ 544.29049, found 544.28949.

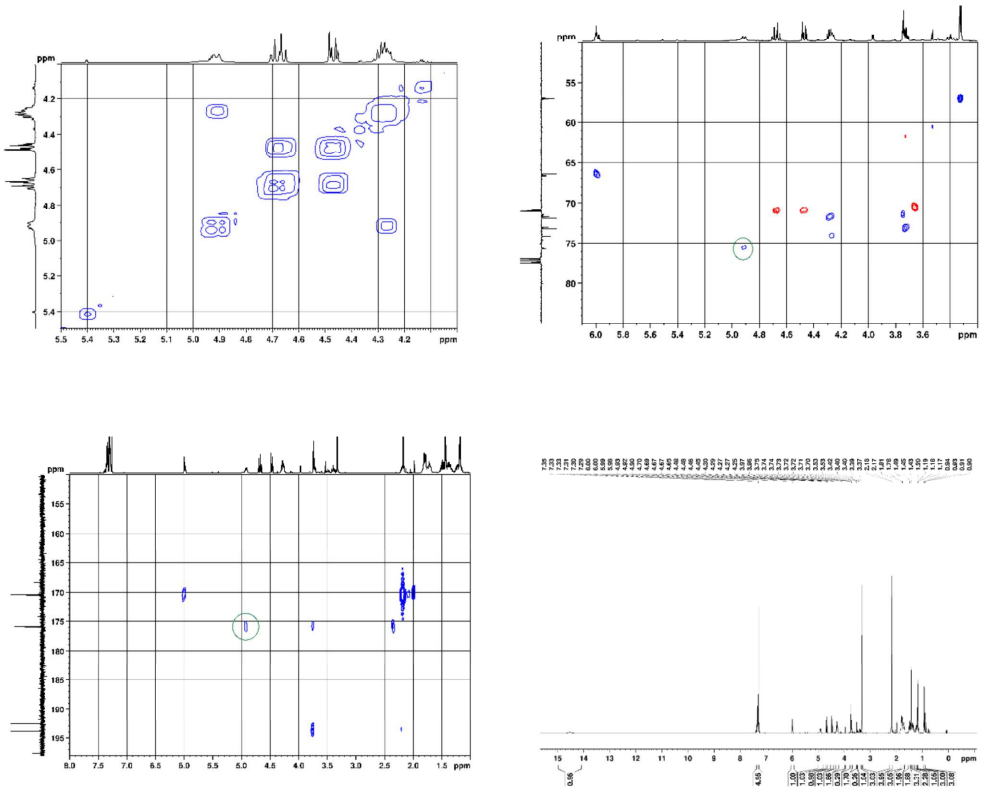


Fig. S8. 2D-NMR-spectra [^{1}H-^{1}H-COSY (top, left), ^{1}H-^{13}C-HSQC (top, right), ^{1}H-^{13}C-HMBC (bottom, left)] of **62a** for elucidation of *N*,*O*-acetal formation. ^{1}H-NMR-spectrum ($CDCl_3$) of **62a** (bottom, right).

2D-NMR-spectra (COSY, HSQC, HMBC) as well as 1D-NMR-spectra (^{1}H and ^{13}C, $CDCl_3$) clearly showed the exclusive formation of an *N*,O-acetal. An *O*-glycosylation with tautomers of 3-acyl-tetramic acids could is conceivable, yet was not observed.[1] Via COSY and HSQC the signal at 4.92 ppm was assigned to the anomeric proton (Fig. S8, top). The chemical shift of the anomeric C-atom (δ = 75.6 ppm) had a distinct high-field shift compared to an *O*,*O*-acetal (δ ≈ 95 ppm). The chemical shifts of the anomeric position are in full accordance with the results of Yang *et al*.[2] As known from the literature the enolization of the amide is highly unfavoured and therefore an *O*-glycosylation with enolized amide is unlikely.[1] HMBC indicated a coupling of the anomeric proton of talose-derivative with amide-C-atom (Fig. S8, bottom left, green circle) confirming the spatial proximity to the amide-C. In the ^{1}H-NMR-spectrum a signal for an enolic

proton was found at 14.5 ppm while no signal for NH was observed. In an additional experiment for *N*-glycosylation of tetramic acid derivatives, the *O*-glycosylation took place (for synthesis see Scheme S19). For proof of *N*-glycosylation the spectra can be compared with those of the accidently formed *O*,*O*-acetal **SI-62**. In the ^{1}H-spectrum of **SI-62** (Fig. S9, top) a signal for an amide proton (no HSQC-correlation, Fig. S9 bottom) instead of enolic proton signal was indicated at 5.84 ppm. The anomeric H-atom (δ = 5.52 ppm) and the anomeric C-atom (δ = 98.3 ppm) of **SI-62** were shifted downfield compared to the *N*,*O*-acetal **62a**.

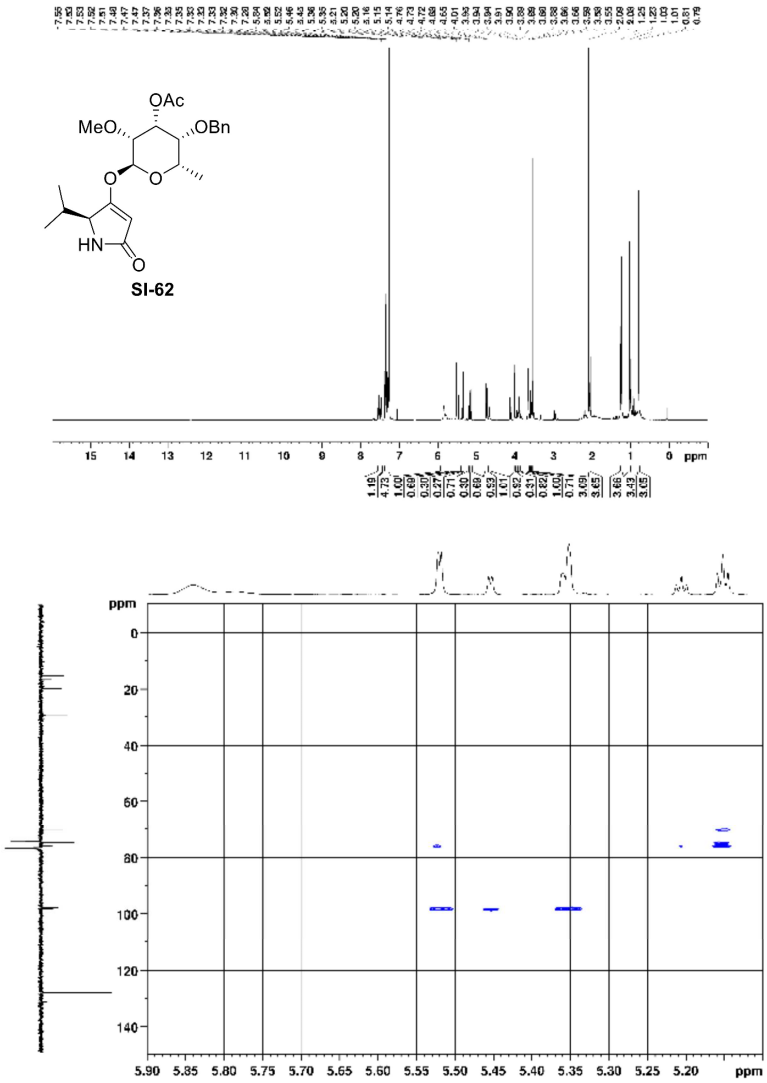
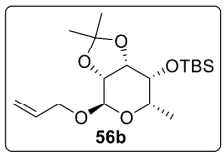


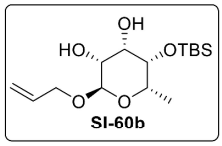
Fig. S9. ^{1}H-NMR-spectrum (top) and ^{1}H-^{13}C-HSQC-spectrum (bottom) of **SI-62** for comparison with spectra of the *N*,*O*-acetal.

(((3a*R*,6*S*,7*R*,7a*S*)-4-(Allyloxy)-2,2,6-trimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-c]pyran-7-yl)oxy)(*tert*-butyl)dimethylsilane (56b)



Alcohol **11** (772 mg, 3.16 mmol, 1.00 eq.) in dry CH_2Cl_2 (55 mL) was treated with pyridine (2.55 mL, 31.6 mmol, 10.0 eq.) and TBSOTf (2.18 mL, 9.48 mmol, 3.00 eq.) at 0 °C. The solution was stirred for 5 h and the reaction was quenched by addition of sat. aq. $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc thrice and the combined organic phases were washed with brine as well as dried over Na_2SO_4. After removal of the solvent *in vacuo* the crude product was purified by column chromatography (SiO_2, pentane/EtOAc 6:1) to give TBS-ether **56b** (1.16 g, quant.) as a colourless liquid. $\mathbf{R_f}$ = 0.88 (hexanes/EtOAc 3:2); $[\alpha]_D^{20}$ −58.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2988 (m), 2933 (m), 2889 (m), 2865 (m), 1473 (w), 1381 (w), 1276 (s), 1260 (s), 1979 (m), 1056 (m), 838 (m), 764 (s), 750 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.92 (dddd, 1H, *J* = 5.2, 6.3, 10.7, 17.2 Hz), 5.30 (dq, 1H, *J* = 1.5, 17.2 Hz), 5.19 (dq, 1H, *J* = 1.5, 10.7 Hz), 4.85 (d, 1H, *J* = 4.1 Hz), 4.29 (dd, 1H, *J* = 3.6, 7.5 Hz), 4.26 (ddt, 1H, *J* = 1.3, 5.2, 12.8 Hz), 4.13 (dd, 1H, *J* = 3.6, 4.1 Hz), 4.08 (ddt, *J* = 1.3, 6.3, n.d. Hz), 4.07 (m, 1H), 3.95 (m, 1H), 1.52 (s, 3H), 1.33 (s, 3H), 1.33 (d, 3H, *J* = 6.5 Hz), 0.92 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 134.2, 117.6, 110.2, 97.2, 76.2, 75.5, 69.8, 69.2, 67.5, 26.7, 26.2, 24.8, 18.5, 17.2, −4.01, −4.58 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{18}H_{34}O_5SiNa$ 381.20677, found 381.20547.

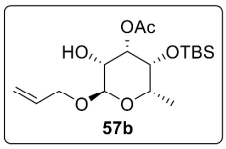
(3*R*,4*S*,5*S*,6*S*)-2-(Allyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-3,4-diol (SI-60b)



Fully protected carbohydrate **56b** (310 mg, 865 µmol, 1.00 eq.) was dissolved in EtOH *p.a.* (1.3 mL) and formic acid (1.3 mL). The solution was stirred at room temperature for 2.5 h. After addition of sat. aq. $NaHCO_3$ solution, the aqueous phase was extracted with EtOAc thrice. The combined organic phases were dried over Na_2SO_4, and the volatiles were removed *in vacuo*. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 9:1) to yield deprotected diol **SI-60b** (116 mg, 42%) as a colourless solid. $\mathbf{R_f}$ = 0.58 (hexanes/EtOAc 3:1); **mp** 69 °C; $[\alpha]_D^{20}$ −91.6° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3405 (m), 3359 (m), 2945 (m), 2929 (m), 2882 (w), 2858 (m), 1471 (w), 1425 (w), 1351 (w), 1276 (m), 1260 (m), 1167 (w), 1143 (w), 1104 (m), 1067 (m), 1044 (w), 1014 (m), 996 (m), 916 (w), 837 (m), 765 (s), 749 (s),

678 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.89 (dddd, 1H, J = 5.2, 6.2, 10.7, 17.0 Hz), 5.28 (dq, 1H, J = 1.6, 17.0 Hz), 5.19 (dq, 1H, J = 1.6, 10.7 Hz), 4.92 (d, 1H, J = 1.3 Hz), 4.16 (ddt, 1H, J = 1.4, 5.2, 13.0 Hz), 4.00 (ddt, J = 1.4, 6.0, 13.0 Hz), 3.89 (q, 1H, J = 6.6 Hz), 3.80 (m, 1H), 3.75 (dt, 1H, J = 3.1, 10.7 Hz), 3.68 (m, 1H), 3.43 (d, 1H, J = 12.0 Hz), 2.61 (d, 1H, J = 10.7 Hz), 1.23 (d, 3H, J = 6.6 Hz), 0.95 (s, 9H), 0.19 (s, 3H), 0.12 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 134.0, 117.5, 100.2, 75.1, 71.4, 68.3, 66.6, 66.4, 26.1, 18.4, 17.6, −3.88, −4.50 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{30}O_5SiNa$ 341.17547, found 341.17505.

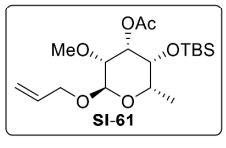
(3*R*,4*S*,5*R*,6*S*)-2-(Allyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (57b)



57b

To a solution of diol **SI-60b** (210 mg, 659 µmol, 1.00 eq.) in dry toluene (33 mL) was added Bu_2SnO (197 mg, 791 µmol, 1.20 eq.). The suspension was stirred under reflux for 3 h. AcCl (49.4 µL, 692 µmol, 1.05 eq.) was added at room temperature and stirring was continued for 1 h. All volatiles were removed under reduced pressure. Purification of the crude product (SiO_2, pentane/EtOAc 9:1) resulted in acetylated carbohydrate **57b** (220 mg, 93%) as a colourless liquid. $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc 5:1); $[\alpha]_D^{20}$ −93.8° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3504 (m), 2956 (m), 2932 (m), 2900 (m), 2860 (m), 1741 (m), 1473 (w), 1432 (w), 1374 (w), 1276 (m), 1260 (s), 1235 (m), 1180 (w), 1118 (m), 1070 (m), 1001 (s), 938 (w), 839 (m), 765 (s), 750 (s), 680 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.89 (dddd, 1H, J = 5.1, 6.2, 10.5, 17.1 Hz), 5.29 (dq, 1H, J = 1.6, 17.1 Hz), 5.19 (dq, 1H, J = 1.6, 10.5 Hz), 5.00 (t, 1H, J = 2.9 Hz), 4.90 (d, 1H, J = 1.5 Hz), 4.17 (ddt, 1H, J = 1.5, 5.1, 13.0 Hz), 4.11 (d, 1H, J = 11.1 Hz), 4.01 (ddt, J = 1.5, 6.2, 13.0 Hz), 3.99 (q, 1H, J = 6.6 Hz), 3.92 (m, 1H), 3.80 (m, 1H), 2.15 (s, 3H), 1.23 (d, 3H, J = 6.6 Hz), 0.96 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.6, 134.0, 117.6, 110.7, 73.2, 69.66, 69.65, 68.4, 66.8, 26.0, 21.5, 18.3, 17.5, −4.24, −4.41 ppm; **IIRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{17}II_{32}O_6SiNa$ 383.18604, found 383.18468.

(3*R*,4*S*,5*R*,6*S*)-2-(Allyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (SI-61)

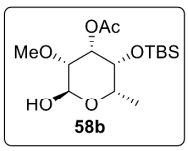


SI-61

Alcohol **57b** (40 mg, 111 µmol, 1.00 eq.) in dry CH_2Cl_2 (1.10 mL) was treated with Me_3OBF_4 (65.6 mg, 444 µmol, 4.00 eq.) and proton sponge (95.1 mg, 444 µmol, 4.00 eq.) at 0 °C and stirred at 40 °C for 21 h. The

reaction was quenched by addition of sat. aq. NH_4Cl solution. The aqueous phase was extracted with EtOAc thrice. Combined organic phases were washed with sat. aq. citric acid solution as well as brine and dried over Na_2SO_4. After removal of the solvent *in vacuo* and purification of the crude product by column chromatography (SiO_2, pentane/EtOAc 9:1) product **SI-61** (40 mg, 96%) was isolated as a colourless liquid. $\mathbf{R_f}$ = 0.63 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$ −30.0° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2930 (m), 2900 (m), 2857 (m), 1745 (s), 1463 (w), 1374 (w), 1237 (s), 1197 (w), 1130 (m), 1091 (m), 1053 (m), 1004 (m), 859 (m), 838 (m), 765 (s), 750 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.91 (dddd, 1H, J = 5.2, 6.1, 10.5, 17.1 Hz), 5.29 (dq, 1H, J = 1.6, 17.1 Hz), 5.18 (dq, 1H, J = 1.6, 10.5 Hz), 5.16 (t, 1H, J = 3.4 Hz), 4.93 (d, 1H, J = 2.9 Hz), 4.18 (ddt, 1H, J = 1.4, 5.1, 13.0 Hz), 4.01 (ddt, J = 1.4, 6.1, 13.0 Hz), 3.96 (dq, 1H, J = 2.6, 6.6 Hz), 3.80 (t, 1H, J = 2.8 Hz), 3.43 (s, 3H), 3.36 (m, 1H), 2.13 (s, 3H), 1.25 (d, 3H, J = 6.6 Hz), 0.93 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 134.1, 117.5, 97.1, 77.5, 71.3, 70.4, 70.1, 68.4, 68.3, 59.6, 26.0, 21.5, 18.5, 16.6, −4.40, −4.48 ppm; **HRMS** ESI m/z $[M + Na]^+$ calcd. for $C_{18}H_{34}O_6SiNa$ 397.20169, found 397.20114.

(2*S*,3*R*,4*S*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-4-yl acetate (58b)

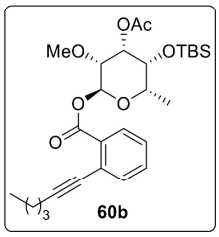


58b

Glycoside **SI-61** (820 mg, 2.19 mmol, 1.00 eq.) dissolved in EtOH *p.a.* (15 mL) was treated with DABCO (128 mg, 1.09 mmol, 0.50 eq.) and Wilkinson catalyst (101 mg, 109 µmol, 0.05 eq.). The reaction mixture was stirred at reflux for 15 h. After cooling down to room temperature, the suspension was filtered off over celite® and solvents were removed under reduced pressure. The crude product was dissolved in EtOAc *p.a.* (226 mL), H_2O (226 mL) and phosphate buffer (22.6 mL). A solution of I_2 (1.67 g, 6.57 mmol, 3.00 eq.) in EtOAc *p.a.* (92 mL) was added dropwise at room temperature. The mixture was stirred vigorously for 10 min. The reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ solution. The aqueous phase was extracted with EtOAc thrice. Combined organic phases were washed with sat. aq. $Na_2S_2O_3$ solution as well as sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvents under reduced pressure, purification of the crude product by column chromatography (SiO_2, pentane/EtOAc 2:1) gave semi-acetal **58b** (618 mg, 84%, α:β 4:1) as a colourless liquid. $\mathbf{R_f}$ = 0.86 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$ −45.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3402 (m), 2949 (m), 2931 (m), 2886 (w), 2858 (m), 1746 (m), 1464 (w), 1373 (m), 1276 (s), 1260 (s), 1198 (m), 1139 (m), 1090 (m), 1047 (m), 962 (w), 858 (m), 837 (m), 765 (s), 750 (s); α-anomer **^{1}H-NMR**

(500 MHz, $CDCl_3$) δ 5.32 (t, 1H, J = 3.3 Hz), 5.25 (t, 1H, J = 4.3 Hz), 4.15 (m, 1H), 3.85 (t, 1H, J = 3.4 Hz), 3.44 (s, 3H), 3.28 (m, 1H), 2.57 (d, 1H, J = 4.1 Hz), 2.12 (s, 3H), 1.30 (d, 3H, J = 6.8 Hz), 0.92 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; β-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 4.84 (t, 1H, J = 3.3 Hz), 4.70 (dd, 1H, J = 1.9, 12.5 Hz), 3.99 (d, 1H, J = 12.5 Hz), 3.72 (dt, 1H, J = 1.3, 3.3 Hz), 3.56 (dd, 1H, J = 1.6, 6.6 Hz), 3.54 (s, 3H), 3.49 (m, 1H), 2.17 (s, 3H), 1.28 (d, 3H, J = 6.6 Hz), 0.96 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H) ppm; α-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.4, 91.7, 78.3, 70.5, 69.9, 69.6, 59.1, 26.0, 21.4, 18.4, 15.9, −4.54, −4.60 ppm; significant signals β-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 93.5, 77.9, 74.1, 71.7, 69.5, 61.5, 26.1, 21.5, 17.5, −4.28 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{30}O_6SiNa$ 357.17039, found 357.17020.

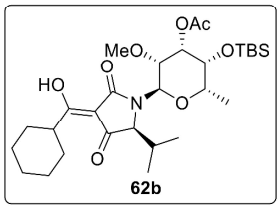
(3*R*,4*S*,5*R*,6*S*)-4-Acetoxy-5-((*tert*-butyldimethylsilyl)oxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-2-yl 2-(2,2-dimethyl-2l6-but-1-yn-1-yl)benzoate (60b)



Semi-acetal **58b** (52.8 mg, 158 µmol, 1.00 eq.) in dry CH_2Cl_2 (1.2 mL) was treated with acid **59** (41.0 mg, 190 µmol, 1.20 eq.), DMAP (28.9 mg, 237 µmol, 1.50 eq.) and DCC (48.9 mg, 237 µmol, 1.50 eq.) at room temperature. The reaction mixture was stirred for 3.5 h and quenched by addition of sat. aq. $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 thrice and combined organic phases were dried over Na_2SO_4. After removal of all volatiles and purification by column chromatography (SiO_2, pentane/EtOAc 11:1) glycoside **60b** (59.1 mg, 72%, α:β 10:1) was isolated as a light-yellow oil. $\mathbf{R_f}$ = 0.80 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$ −60.9° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2931 (m), 2854 (m), 1744 (s), 1276 (s), 1260 (s), 1136 (m), 1081 (m), 838 (m), 762 (s), 750 (s); α-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 1.3, 8.1 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.44 (dt, 1H, J = 1.3, 7.5 Hz), 7.32 (dt, 1H, J = 1.3 Hz, 7.5 Hz), 6.47 (d, 1H, J = 2.7 Hz), 5.23 (t, 1H, J = 3.5 IIz), 4.20 (dq, 1II, J = 2.2, 6.7 IIz), 3.89 (t, 1II, J = 2.7 IIz), 3.54 (t, 1II, J = 3.2 IIz), 3.45 (s, 3H), 2.46 (dt, 2H, J = 3.3, 7.2 Hz), 2.15 (s, 3H), 1.62 (m, 2H), 1.50 (m, 2H), 1.30 (d, 3H, J = 6.7 Hz), 0.95 (s, 9H), 0.95 (t, 3H, J = 7.0 Hz), 0.10 (s, 3H), 0.06 (s, 3H) ppm; β-anomer significant signals **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, 1H, J =7.8 Hz), 7.67 (dt, 1H, J = 1.5, 7.8 Hz), 7.45 (m, 1H), 7.34 (m, 1H), 6.23 (s, 1H), 2.55-2.39 (m, 2H), 1.72-1.37 (m, 4H) ppm ; α-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 164.5, 135.0, 132.1, 130.9, 130.6, 127.3, 125.1, 96.7, 92.9, 79.6, 76.3, 70.9, 70.8, 69.9, 59.7, 30.9, 26.0, 22.2, 21.5, 19.7, 18.6, 16.9, 13.8,

−4.34, −4.48 ppm; **HRMS** ESI *m/z* [M + Na]$^+$ calcd. for $C_{28}H_{42}O_7SiNa$ 541.25868, found 541.25920.

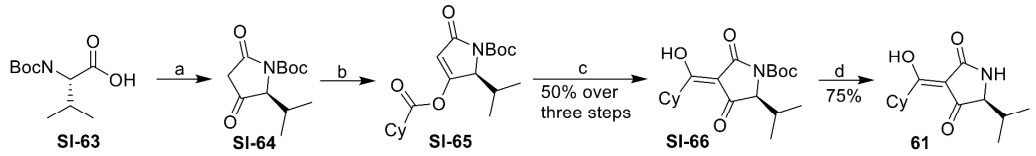
(2*S*,3*R*,4*S*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-((*S*,*Z*)-3-(cyclohexyl(hydroxy)-methylene)-5-isopropyl-2,4-dioxopyrrolidin-1-yl)-5-methoxy-2-methyltetrahydro-2*H*-pyran-4-yl acetate (62b)



62b

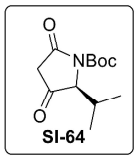
Glycoside **60b** (200 mg, 386 µmol, 1.00 eq.) and tetramic acid **61** (145 mg, 578 µmol, 1.50 eq.) were dissolved in toluene and the solvent was removed on a rotary evaporator. This procedure was repeated twice. The substances were dissolved in dry toluene (1 mL) and treated with $AuPPh_3NTf_2$ (57.0 mg, 77.1 µmol, 0.20 eq.) at room temperature. After stirring for 20 h at 40 °C the volatiles were removed *in vacuo* and crude product was purified by column chromatography (SiO_2 C-18, 40% MeCN in H_2O + 0.1% HCOOH ›60% MeCN in H_2O + 0.1% HCOOH ›80% MeCN in H_2O + 0.1% HCOOH→90% MeCN in H_2O + 0.1% HCOOH). The product **62b** (110 mg, 50%, α:β >30:1) was isolated as a light-yellow solid. $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc 3:1); **mp** 88 °C; $[\alpha]_D^{20}$ −44.6° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2991 (w), 2931 (m), 2858 (m), 1748 (m), 1705 (m), 1652 (m), 1607 (m), 1452 (m), 1361 (w), 1276 (m), 1260 (m), 1231 (m), 1106 (m), 1987 (m), 1007 (w), 963 (m), 863 (m), 838 (m), 764 (s), 751 (s); α-anomer **^{1}H-NMR** (500 MHz, CD_3OD) δ 5.72 (t, 1H, J = 3.3 Hz), 5.06 (br. s, 1H), 4.26 (br. s, 1H), 4.10 (m, 2H), 3.85 (br. s, 1H), 3.45 (m, 1H), 3.30 (s, 3H, under solvent signal), 2.23 (m, 1H), 2.12 (s, 3H), 1.86-1.69 (m, 5H), 1.50 (m, 2H), 1.41 (d, 3H, J = 6.8 Hz), 1.44-1.23 (m, 3H), 1.17 (d, 3H, J = 6.9 Hz), 0.89 (s, 9H), 0.89 (d, 3H, J = 6.9 Hz), 0.13 (s, 3H), 0.11 (s, 3H) ppm; α-anomer major tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 193.9, 192.6, 175.9, 170.2, 104.9, 101.3, 75.4, 74.0, 73.7, 71.5, 69.8, 67.7, 57.1, 41.0, 30.3, 29.0, 28.5, 25.8, 25.7, 25.6, 18.1, 18.0, 16.0, 13.1, −4.89, −4.98 ppm; significant signals α-anomer minor tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 199.7, 197.6, 170.2, 75.9, 73.5, 73.0, 71.3, 70.1, 67.8, 57.0, 41.8, 30.2, 29.1, 28.4, 25.8, 25.7, 21.4, 18.2, 15.7, 13.1, −4.90, −4.98 ppm; **HRMS** ESI *m/z* [M + H]$^+$ calcd. for $C_{29}H_{50}NO_8Si$ 568.33002, found 568.32990.

2.9 Synthesis of 3-acyltetramic acid **61**

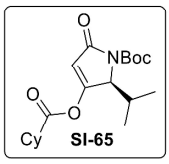


Scheme S12. Synthesis of 3-acyltetramic acid **61**.
Reagents and conditions: a) 1. Meldrum´s acid, DMAP, EDC·HCl, CH_2Cl_2, rt, 3 h, 2. EtOAc, Δ, 2 h; b) 1. cyclohexylcarbonic acid, EDC·HCl, DMAP, CH_2Cl_2, 0 °C, 50 min, 2. tetramic acid **SI-64**, rt, 2.5 h; c) NEt_3, DMAP, CH_2Cl_2, rt, 2 d; d) TFA, CH_2Cl_2, rt, 20 min.

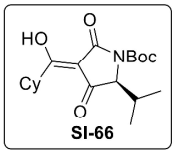
tert-Butyl(*S*,*Z*)-3-(cyclohexyl(hydroxy)methylene)-5-isopropyl-2,4-dioxopyrrolidine-1-carboxylate (SI-66)



Amino acid **SI-63** (5.00 g, 23.0 mmol, 1.00 eq.) in dry CH_2Cl_2 (74 mL) was treated with Meldrum´s acid (3.65 g, 25.3 mmol, 1.10 eq.), DMAP (3.93 g, 32.2 mmol, 1.40 eq.) and EDC·HCl (5.29 g, 27.6 mmol, 1.20 eq.). at room temperature. The reaction mixture was stirred for 3 h. 0.5M H_2SO_4 and EtOAc were added. The organic phase was separated, and the aqueous phase was extracted thrice with EtOAc. Combined organic phases were washed with H_2O and dried over Na_2SO_4. After filtration, organic phase was stirred under reflux for 2 h. The solvent was removed under reduced pressure. The product **SI-64** was used without further purification.



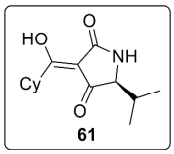
Cyclohexylcarbonic acid (2.58 mL, 20.9 mmol, 1.00 eq.) in dry CH_2Cl_2 (70 mL) was treated with EDC·HCl (4.79 g, 25.0 mmol, 1.20 eq.) and DMAP (511 mg, 4.18 mmol, 0.20 eq.) at 0 °C. After 50 min at room temperature, tetramic acid **SI-64** (5.55 g, 23.0 mmol, 1.10 eq.) in dry CH_2Cl_2 (55 mL) was added. Stirring was continued for 2.5 h. Addition of CH_2Cl_2 and 0.5M H_2SO_4 was followed by separation of organic phase. The aqueous phase was extracted thrice with CH_2Cl_2, combined organic phases were washed with brine, dried over Na_2SO_4 and volatiles were removed under reduced pressure. Purification over a short SiO_2-plug (SiO_2, pentane/EtOAc 20:1 →10:1→7:1→5:1) led to 4-*O*-acyl tetramic acid **SI-65** (6.65 g). It was pure enough for the next step. $\mathbf{R_f}$ = 0.92 (hexanes/EtOAc 3:1); **^{1}H-NMR** (500 MHz, CD_3OD) δ 6.10 (d, 1H, J = 0.7 Hz), 4.49 (dd, 1H, J = 0.7, 2.4 Hz), 2.49 (m, 2H), 1.99 (m, 2H), 1.79 (m, 2H), 1.67 (m, 1H), 1.54 (s, 9H), 1.51 (m, 1H), 1.32 (m, 4H), 1.12 (d, 3H, J = 6.8 Hz), 0.82 (d, 3H, J = 6.8Hz) ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{29}NO_5Na$ 374.19375, found 374.19308.



SI-66

4-*O*-Acyltetramic acid **SI-65** (6.65 g, 18.8 mmol, 1.00 eq.) in dry CH_2Cl_2 (190 mL) was treated with dry NEt_3 (3.20 mL, 22.6 mmol, 1.20 eq.) and DMAP (1.15 g, 9.40 mmol, 0.50 eq.) at room temperature. After stirring for 22 h DMAP (575 mg, 4.70 mmol, 0.25 eq.) was added again and stirring was continued for 24 h. Sat. aq. $NaHCO_3$ solution and CH_2Cl_2 were added. The aqueous phase was extracted thrice with CH_2Cl_2, combined organic phases were washed with brine and dried over Na_2SO_4. Removal of all volatiles under reduced pressure and purification by column chromatography (SiO_2 C-18, 40% McCN in H_2O + 0.1% HCO_2H→60% McCN in H_2O + 0.1% HCO_2H→80% MeCN in H_2O + 0.1% HCO_2H→100% MeCN in H_2O + 0.1% HCO_2H) gave 3-acyl tetramic acid **SI-66** as an orange resin (4.04 g, 50% over three steps). $\mathbf{R_f}$ = 0.72 (CH_2Cl_2/MeOH 9:1); $[\boldsymbol{\alpha}]_D^{20}$ +37.2° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2970 (m), 2933 (m), 2857 (m), 1771 (m), 1744 (m), 1713 (s), 1652 (m), 1599 (s), 1452 (m), 1393 (m), 1228 (m), 1308 (s), 1277 (s), 1259 (s), 1154 (s), 1022 (w), 931 (m), 913 (m), 857 (w), 764 (s), 751 (s); **^{1}H-NMR** (500 MHz, CD_3OD) δ 4.33 (s, 1H), 3.46 (tt, 1H, J – 3.0, 11.5 Hz), 2.45 (dqn, 1H, J – 3.0, 7.1 Hz), 1.84 (m, 4H), 1.75 (m, 1H), 1.55 (s, 9H), 1.48 (dt, 2H, J = 2.9, 12.1 Hz), 1.40 (m, 2H), 1.28 (m, 1H), 1.17 (d, 3H, J = 7.1Hz), 0.82 (d, 3H, J = 7.1 Hz); mixture of three tautomers **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 201.2, 197.7, 195.4, 192.4, 174.5, 165.8, 165.0, 163.3, 149.7, 149.0, 117.3, 104.5, 101.4, 84.0, 83.5, 83.3, 69.1, 65.6, 61.8, 42.7, 41.3, 30.8, 30.3, 29.2, 28.8, 28.6, 28.4, 28.3, 28.1, 26.0, 25.8, 25.7, 25.6, 25.5, 19.0, 18.6, 18.5, 16.2, 15.7, 15.1 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{29}NO_5Na$ 374.19379, found 374.19296.

(*S*,*Z*)-3-(Cyclohexyl(hydroxy)methylene)-5-isopropylpyrrolidine-2,4-dione (61)

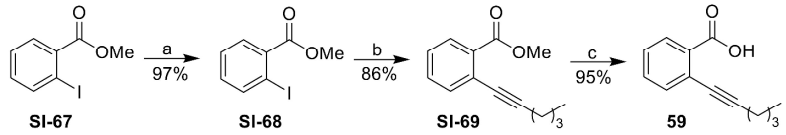


61

Tetramic acid **SI-66** (606 mg, 1.71 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (32 mL) and treated with TFA (3.20 mL, 10 vol% CH_2Cl_2) at room temperature. The solution was stirred for 20 min. All volatiles were removed at the rotary evaporator. The crude product was purified by column chromatography (SiO_2 C-18, 40% MeCN in H_2O + 0.1% HCO_2H→50% MeCN in H_2O + 0.1% HCO_2H→60% MeCN in H_2O + 0.1% HCO_2H→80% MeCN in H_2O + 0.1% HCO_2H→100% MeCN in H_2O + 0.1% HCO_2H) to afford product **61** as a light orange solid (323 mg, 75%). $\mathbf{R_f}$ = 0.68 (CH_2Cl_2/MeOH 9:1); **mp** 109 °C; $[\boldsymbol{\alpha}]_D^{20}$ −109.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3219 (m), 2931 (m), 2856 (m), 1653 (s), 1606 (s), 1448 (m), 1352 (m), 1308 (m), 1276 (m), 1261 (m), 1227 (m), 1137 (w), 1024 (w), 920 (m), 817 (m), 765 (s), 750 (s); **^{1}H-NMR** (500 MHz, CD_3OD) δ 3.75 (br. s, 1H), 3.40 (br. s, 1H), 2.17 (m, 1H), 1.86-1.70 (m, 4H), 1.56-1.20 (m,

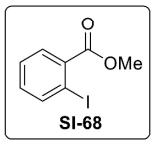
6H), 1.03 (d, 3H, *J* = 7.1 Hz), 0.82 (d, 3H, *J* = 7.1 Hz) ppm; major tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 196.6, 192.6, 176.7, 100.4, 67.3, 41.0, 30.26, 28.9, 28.6, 25.74, 25.67, 25.61, 19.6, 16.0 ppm; minor tautomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 201.5, 194.9, 169.5, 103.8, 64.0, 41.6, 30.30, 28.9, 28.8, 25.8, 25.61, 25.56, 19.3, 16.3 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{14}H_{22}NO_3$ 252.15942, found 252.15883.

2.10 Synthesis of acid **59**



Scheme S13. Synthesis of acid **59**.
Reagents and conditions: a) $SOCl_2$, MeOH, −10 °C→40 °C, 17 h; b) 1. $PdCl_2(PPh_3)_2$, PPh_3, CuI, *i*Pr_2NH, rt, 1 h, 2. 1-hexyne, 0 °C→rt, 18.5 h; c) NaOH, THF, 50 °C, 19 h.

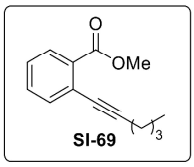
Methyl 2-iodobenzoate (SI-68)



2-Iodobenzoic acid **SI-67** (5.00 g, 20.2 mmol, 1.00 eq.) was dissolved in dry MeOH (35.0 mL) and $SOCl_2$ (2.20 mL, 30.2 mmol, 1.20 eq.) was slowly added at −10 °C. After 15 min the solution was heated to 40 °C and stirred for a further 17 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution and EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc thrice, combined organic phases were washed with H_2O twice and dried over Na_2SO_4. The solvents were removed *in vacuo*. Purification by column chromatography (SiO_2, pentane/EtOAc 6:1) afforded product **SI-68** (5.11 g, 97%) as a colourless liquid. $\mathbf{R_f}$ = 0.70 (hexanes/EtOAc 4:1); **IR** ν_{max}/cm^{-1} 2950 (m), 1727 (s), 1583 (m), 1562 (w), 1465 (m), 1432 (s), 1289 (s), 1251 (s), 1191 (m),1131 (s), 1104 (s), 1043 (m), 1016 (s), 963 (m), 826 (w), 739 (s), 688 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, 1H, *J* = 7.9 Hz), 7.80 (dd, 1H, *J* = 1.5, 7.9 Hz), 7.40 (t, 1H, *J* = 7.7 Hz), 7.15 (t, 1H, *J* = 7.7 Hz), 3.93 (s, 3H) ppm.

Spectroscopic data corresponded to those reported in the literature.[14]

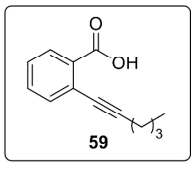
Methyl 2-(hex-1-yn-1-yl)benzoate (SI-69)



Methyl 2-iodobenzoate (**SI-68**, 100 mg, 382 µmol, 1.00 eq.) was dissolved in *i*Pr$_2$NH (1.00 mL) and treated with PdCl$_2$(PPh$_3$)$_2$ (13.4 mg, 19.1 µmol, 5 mol%), PPh$_3$ (10.0 mg, 38.2 µmol, 10 mol%) and CuI (3.63 mg, 19.1 µmol, 5 mol%). The mixture was stirred at room temperature for 1h. At 0 °C, hexyne (65.7 µL, 572 µmol, 1.50 eq.) was added, stirring was continued for a further 18.5 h and the mixture was allowed to warm to room temperature. Addition of sat. aq. NH$_4$Cl solution stopped the reaction. Pentane was added and the organic phase was separated. The aqueous phase was extracted with pentane/EtOAc 100:1 and the combined organic phases were washed with H$_2$O and brine. They were dried over Na$_2$SO$_4$ and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc 30:1→20:1) to give alkyne **SI-69** as a colourless liquid (76.0 mg, 86%). $\mathbf{R_f}$ = 0.79 (hexanes/EtOAc 9:1); **IR** ν_{max}/cm^{-1} 2956 (m), 2934 (m), 2873 (m), 1733 (s), 1718 (s), 1597 (w), 1577 (w), 1485 (m), 1447 (m), 1433 (m), 1294 (s), 1276 (s), 1249 (s), 1190 (w), 1129 (m), 1083 (s), 1043 (w), 966 (w), 757 (s), 702 (m); **^{1}H-NMR** (500 MHz, CDCl$_3$) δ 7.88 (dd, 1H, J = 1.1, 7.9 Hz), 7.51 (dd, 1H, J = 1.1, 7.9 Hz), 7.42 (dt, 1H, J = 1.4, 7.6 Hz), 7.31 (t, 1H, J = 1.4, 7.6 Hz), 3.91 (s, 3H), 2.48 (t, 2H, J = 7.1 Hz), 1.62 (m, 2H), 1.51 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz) ppm.

Spectroscopic data corresponded to those reported in the literature.[15]

2-(Hex-1-yn-1-yl)benzoic acid (59)

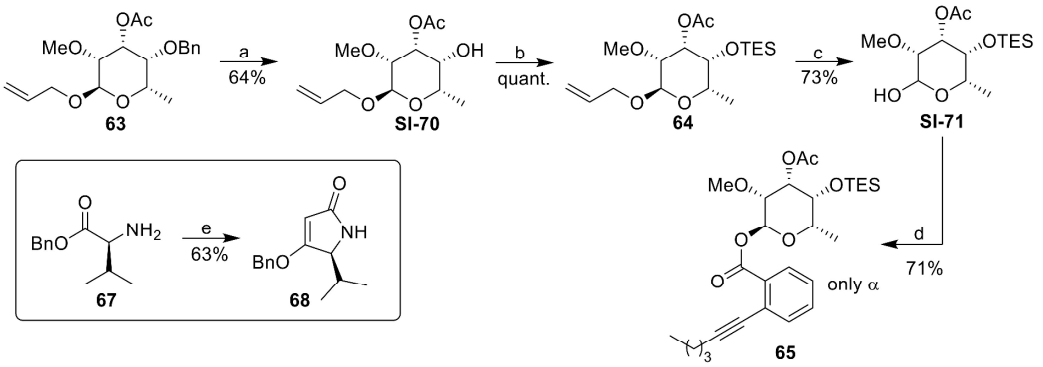


Ester **SI-69** (76.0 mg, 330 µmol, 1.00 eq.) in THF *p.a.* (1.40 mL) and 1M NaOH (1.40 mL) was stirred at 50 °C for 19 h. The solution was treated with conc. HCl until pH value reached 1. The aqueous phase was extracted five times with CH$_2$Cl$_2$. The combined organic phases were dried over Na$_2$SO$_4$, and the volatiles were removed under reduced pressure. Product **59** (68.2 mg, 95%) was isolated as a colourless resin and used without further purification. $\mathbf{R_f}$ = 0.23 (hexanes/EtOAc 9:1); **IR** ν_{max}/cm^{-1} 3077 (m), 2958 (m), 2932 (m), 2873 (m), 2656 (m), 2229 (w), 1693 (s), 1600 (w), 1568 (w), 1487 (w), 1455 (w), 1409 (m), 1379 (w), 1297 (m), 1274 (m), 1141 (w),1086 (w), 922 (w), 756 (m); **^{1}H-NMR** (500 MHz, CDCl$_3$) δ 8.11 (d, 1H, 7.7 Hz), 7.51 (dd, 1H, J = 1.2, 7.7 Hz), 7.42 (dt, 1H, J = 1.2, 7.7 Hz), 7.31 (t, 1H, J = 1.2, 7.7 Hz), 2.48

(t, 2H, *J* = 7.1 Hz), 1.62 (m, 2H), 1.51 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz) ppm. COO*H* not detectable.

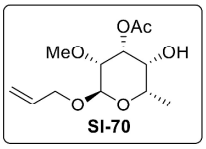
Spectroscopic data corresponded to those reported in the literature.[15]

2.11 Synthesis of glycoside **65** for formal synthesis



Scheme S14. Synthesis of glycoside **65** for formal synthesis.
Reagents and conditions: a) 1. I_2, CH_2Cl_2, −65 °C, 35 min, 2. Et_3SiH, −65 °C→−20 °C, 2 h; b) TESOTf, pyridine, CH_2Cl_2, 0 °C, 2 h; c) 1. DABCO, Wilkinson´s catalyst, EtOH, Δ, 5 h, 2. I_2, phosphate buffer/H_2O/EtOAc, rt, 25 min; d) DCC, DMAP, CH_2Cl_2, rt, 3 h; e) Ph_3PCCO (**66**), benzoic acid, THF, 60 °C, 22 h.

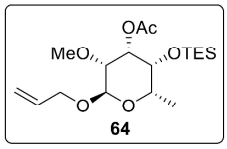
(3*R*,4*R*,5*R*,6*S*)-2-(Allyloxy)-5-hydroxy-3-methoxy-6-methyltetrahydro-2*H*-pyran-4-yl acetate (SI-70)



Glycoside **63** (141 mg, 402 µmol, 1.00 eq.) in dry CH_2Cl_2 (10.9 mL) was treated with I_2 (153 mg, 604 µmol, 1.50 eq.) at −65 °C. The mixture was stirred for 35 min and Et_3SiH (96.4 µL, 604 µmol, 1.50 eq.) was added. After 40 min at −65 °C, the solution was allowed to warm to −20 °C. Stirring was continued for 1 h 30 min. Allylic alcohol (136 µL, 2.01 mmol, 5.00 eq.) and $NaHCO_3$ (169 mg, 2.01 mmol, 5.00 eq.) were added. After stirring for 10 min, the mixture was treated with sat. aq. $Na_2S_2O_3$ solution and CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the volatiles and purification by column chromatography (SiO_2, pentane/EtOAc 3:1) product **SI-70** (67.0 mg, 64%) was obtained as a colourless liquid. $\mathbf{R_f}$ = 0.63 (hexanes/EtOAc 4:1); $[\alpha]_D^{20}$ −110.3° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 3510 (m), 2987 (m), 2938 (m), 1744 (m), 1429 (m), 1375 (m), 127 (m), 1237 (s), 1178 (w), 1114 (s), 1984 (m), 1045 (s), 981 (m), 933 (w), 764 (s), 750 (s),687 (w); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.90 (dddd, 1H, J = 5.2, 6.1, 10.4, 17.3 Hz), 5.30 (dq, 1H, J = 1.5, 17.3 Hz), 5.21 (dq, 1H, J = 1.5, 10.4 Hz), 5.07 (t, 1H, J = 3.3 Hz), 4.97 (d, 1H, J = 0.8 Hz), 4.20 (ddt, 1H, J = 1.4, 5.2, 12.8 Hz), 4.01 (ddt, 1H, J = 1.4, 6.1, 12.8 Hz), 3.94 (d, 1H, J = 6.6 Hz), 3.70 (m, 1H), 3.55

(m, 1H), 3.52 (s, 3H), 3.38 (d, 1H, *J* = 11.0 Hz), 2.13 (s, 3H), 1.29 (d, 3H, *J* = 6.6 Hz) ppm; **^{13}CNMR** (125 MHz, $CDCl_3$) δ 170.5, 133.7, 117.8, 96.7, 78.7, 71.0, 69.9, 68.3, 67.5, 59.8, 21.3, 16.4 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{12}H_{20}O_6Na$ 283.11521, found 283.11435.

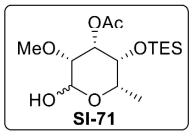
(3*R*,4*S*,5*R*,6*S*)-2-(Allyloxy)-3-methoxy-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-4-yl acetate (64)



64

Carbohydrate **SI-70** (30.0 mg, 115 µmol, 1.00 eq.) in dry CH_2Cl_2 (2.30 mL) was treated with pyridine (576 µL, 231 µL, 5.00 eq.) and TESOTf (52.1 µL, 231 µL, 2.00 eq.) at 0 °C. After stirring at this temperature for 2 h, sat. aq. $NaHCO_3$ solution and CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 thrice and the combined organic phases were dried over Na_2SO_4. After removal of the volatiles under reduced pressure and purification by column chromatography (SiO_2, pentane/EtOAc 4:1) product **64** (43.1 mg, quant.) was isolated as a colourless liquid. $\mathbf{R_f}$ = 0.59 (hexanes/EtOAc 3:1); $[\boldsymbol{\alpha}]_D^{20}$ −77.5° (c 1.0 in $CHCl_3$); **I**R ν_{max}/cm^{-1} 2854 (m), 2878 (m), 1744 (s), 1459 (m), 1413 (w), 1374 (m), 1235 (s), 1197 (m), 1128 (m), 1090 (s), 1052 (s), 1031 (s), 1003 (s), 962 (m), 848 (m), 747 (s), 724 (s), 677 (m); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.90 (dddd, 1H, *J* = 5.3, 6.0, 10.5, 16.9 Hz), 5.29 (dq, 1H, *J* = 1.6, 16.9 Hz), 5.18 (dq, 1H, *J* = 1.6, 10.5 Hz), 5.10 (t, 1H, *J* = 3.5 Hz), 4.94 (d, 1H, *J* = 2.5 Hz), 4.17 (ddt, 1H, *J* = 1.5, 5.3, 12.9 Hz), 4.00 (ddt, *J* = 1.5, 6.0, 12.9 Hz), 3.95 (dq, 1H, *J* = 2.1, 6.6 Hz), 3.80 (m, 1H), 3.42 (s, 3H), 3.39 (m, 1H), 2.14 (s, 3H), 1.26 (d, 3H, *J* = 6.6 Hz), 0.98 (t, 9H, *J* = 7.9 Hz), 0.65 (q, 6H, *J* = 7.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 134.1, 117.4, 97.3, 77.5, 71.2, 70.3, 68.3, 67.9, 59.8, 21.4, 16.5, 7.07, 5.14 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{18}H_{35}O_6Si$ 375.21930, found 375.21974.

(3*R*,4*S*,5*R*,6*S*)-2-Hydroxy-3-methoxy-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-4-yl acetate (SI-71)

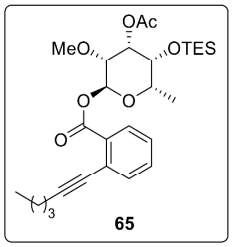


SI-71

Glycoside **64** (168 mg, 449 µmol, 1.00 eq.) was dissolved in EtOH *p.a.* (3.00 mL) and treated with Wilkinson catalyst (4.15 mg, 44.9 µmol, 1 mol%) as well as DABCO (7.55 mg, 67.3 µmol, 15 mol%). The suspension was stirred at 95 °C for 24 h. Rhodium-catalyst (4.15 mg, 44.9 µmol, 1 mol%) and DABCO (7.55 mg, 67.3 µmol, 15 mol%) were added again at room temperature. Stirring was continued for 24 h at 95 °C. A third portion of Wilkinson catalyst (4.15 mg, 44.9 µmol,

1 mol%) and DABCO (7.55 mg, 67.3 µmol, 15 mol%) was added. After stirring for a further 3 days the mixture was filtered off over celite® and the volatiles were removed under reduced pressure. The crude product was dissolved in EtOAc (48 mL) and H_2O (48 mL). A buffer (pH=7, 4.8 mL) was added. The mixture was treated dropwise with a solution of iodine (342 mg, 1.35 mmol, 3.00 eq.) in EtOAc (19 mL). After 25 min, sat. aq. $Na_2S_2O_3$ solution was added. The aqueous phase was extracted with EtOAc thrice, combined organic phases were washed with sat. aq. $NaHCO_3$ solution and dried over Na_2SO_4. Removal of the volatiles *in vacuo* and purification by column chromatography (SiO_2, pentane/EtOAc 2:1→1:1) afforded product **SI-71** (109 mg, 73%) as a colourless resin. $\mathbf{R_f}$ = 0.33 (hexanes/EtOAc 2:1); $[\alpha]_D^{20}$ −64.5° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2930 (m), 2900 (m), 2857 (m), 1745 (s), 1463 (w), 1374 (m), 1238 (s), 1130 (m), 1091 (s), 1053 (s), 1004 (m), 940 (w), 859 (m), 838 (m), 765 (s), 750 (s); α-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 5.27 (t, 1H, J = 2.6 Hz), 5.22 (t, 1H, J = 3.4 Hz), 4.16 (dq, 1H, J = 3.0, 6.7 Hz), 3.82 (t, 1H, J = 3.0 Hz), 3.43 (s, 3H), 3.32 (dt, 1H, J = 0.6, 3.5 Hz), 3.03 (br. s, 1H), 2.13 (s, 3H), 1.69 (br. s, 1H), 1.29 (d, 3H, J – 6.7 Hz), 0.97 (t, 9H, J = 7.9 Hz), 0.66 (q, 6H, J = 7.9 Hz) ppm; β-anomer **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 4.81 (t, 1H, J = 3.2 Hz), 4.67 (dd, 1H, J = 1.6, 12.5 Hz), 4.09 (d, 1H, J = 12.6 Hz), 3.72 (dt, 1H, J = 1.1, 3.2 Hz), 3.55 (s, 3H), 3.55 (dq, 1H, J = 1.4, 6.7 Hz), 3.50 (m, 1H), 2.18 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 0.99 (t, 9H, J = 7.9 Hz), 0.66 (q, 6H, J = 7.9 Hz) ppm; α-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.4, 92.2, 78.1, 70.6, 69.9, 69.1, 59.5, 21.3, 16.0, 7.01, 5.05 ppm; β-anomer **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.3, 93.8, 73.9, 71.9, 69.7, 61.7, 21.3 17.1, 7.12, 5.22 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{30}O_6SiNa$ 357.17039 found 357.16962.

(2*S*,3*R*,4*S*,5*R*,6*S*)-4-Acetoxy-3-methoxy-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl 2-(hex-1-yn-1-yl)benzoate (65)



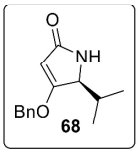
65

Semi-acetal **SI-71** (110 mg, 329 µmol, 1.00 eq.) and acid **59** (85.4 mg, 395 µmol, 1.20 eq.) were dissolved in dry CH_2Cl_2 (1.5 mL) and treated with DCC (102 mg, 493 µmol, 1.50 eq.) as well as DMAP (60.3 mg, 493 µmol, 1.50 eq.) at room temperature. The suspension was stirred for 3 h, before sat. aq. $NaHCO_3$ solution was added. The aqueous phase was extracted with CH_2Cl_2 thrice and the combined organic phases were dried over Na_2SO_4. Removal of the solvent at the rotary evaporator and purification by column chromatography (SiO_2, pentane/EtOAc 6:1→4:1) as well as a second column chromatography (SiO_2, pentane/EtOAc 9:1→8:1) furnished glycoside **65** (122 mg, 71%, single diastereomer) as

a colourless oil. $\mathbf{R_f}$ = 0.80 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}$ −61.7° (c 1.0 in $CHCl_3$); **IR** ν_{max}/cm^{-1} 2956 (m), 2938 (m), 2877 (m), 1744 (m), 1458 (w), 1375 (w), 1276 (s), 1261 (s), 1236 (m), 1136 (m), 1081 (m), 1031 (w), 921 (w), 853 (w), 764 (s), 750 (s); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, 1H, *J* = 1.0, 7.9 Hz), 7.53 (dd, 1H, *J* = 1.0, 7.9 Hz), 7.44 (dt, 1H, 7.8 Hz), 7.32 (dt, 1.2, 7.5 Hz), 6.49 (d, 1H, *J* = 2.3 Hz), 5.18 (t, 1H, *J* = 3.5 Hz), 4.22 (dq, 1H, *J* = 1.7, 6.5 Hz), 3.89 (m, 1H), 3.56 (ddd, 1H, *J* = 0.9, 2.3, 3.5 Hz), 3.50 (s, 3H), 2.46 (dt, 2H, *J* = 3.2, 7.2 Hz), 2.17 (s, 3H), 1.61 (m, 2H), 1.49 (m, 2H), 1.31 (d, 3H, *J* = 6.5 Hz), 1.00 (t, 9H, *J* = 7.9 Hz), 0.95 (t, 3H, *J* = 7.3 Hz), 0.68 (q, 6H, *J* = 7.9 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.5, 164.5, 135.0, 132.1, 130.9, 130.7, 127.3, 125.1, 96.7, 93.1, 79.7, 76.3, 70.7, 70.1, 60.0, 30.9, 22.3, 21.4, 19.7, 16.8, 13.8, 7.05, 5.15 ppm; **HRMS** ESI *m/z* $[M + Na]^+$ calcd. for $C_{28}H_{42}O_7SiNa$ 541.25920, found 541.25885.

Spectroscopic data corresponded to those reported in the literature.[2]

(*S*)-4-(Benzyloxy)-5-isopropyl-1,5-dihydro-2*H*-pyrrol-2-one (68)

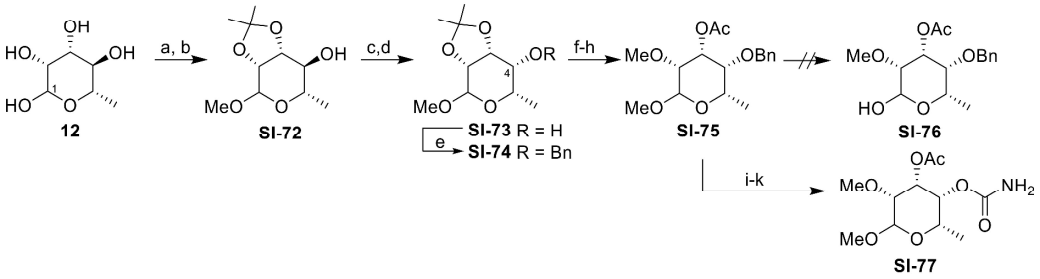


Amino acid **67** (500 mg, 2.41 mmol, 1.00 eq.) in dry THF (8.00 mL) was treated with Ph_3PCCO (**66**, 802 mg, 2.65 mmol, 1.10 eq.) and benzoic acid (58.9 mg, 482 µmol, 0.20 eq.) at room temperature. The mixture was heated to 60 °C and stirred for 22 h. The volatiles were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, acetone/CH_2Cl_2 19:1→6:1→4:1→3:1 →2:1→1.5:1) to furnish 4-*O*-alkyl tetramic acid **68** (351 mg, 1.52 mmol) as a colourless solid. $\mathbf{R_f}$ = 0.59 (CH_2Cl_2/MeOH 9:1); **mp** 129 °C; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.37 (m, 5II), 6.76 (br. s, 1II), 5.10 (d, 1II, *J* = 1.5 IIz), 4.99 (d, 1II, *J* = 11.6 IIz), 4.94 (d, 1H, *J* = 11.6 Hz), 4.04 (d, 1H, *J* = 3.3 Hz), 2.14 (dqn, 1H, *J* = 3.3, 7.0 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 0.80 (d, 3H, *J* = 7.0 Hz) ppm; **^{13}C-NMR** (125 MHz, $CDCl_3$) 176.3, 175.2, 135.0, 128.82, 128.78, 127.9, 95.4, 73.2, 63.0, 29.4, 19.6, 15.2 ppm; **HRMS** ESI *m/z* $[M + H]^+$ calcd. for $C_{14}H_{18}NO_2$ 232.13321, found 232.13260.

Spectroscopic data corresponded to those reported in the literature.[2]

2.12 Failed routes to amykitanose

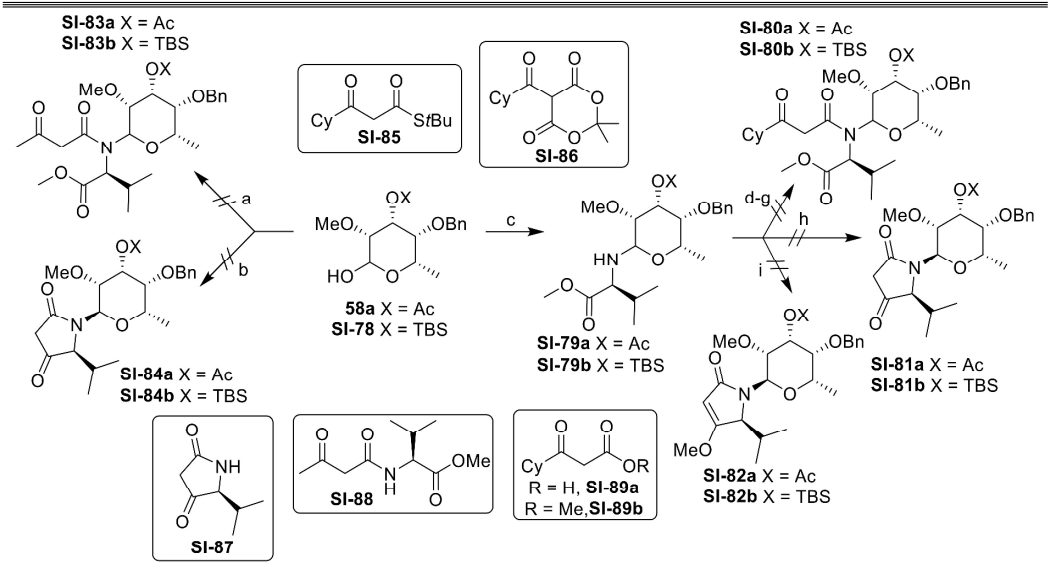
Before the synthesis with an allyl function at the anomeric position was completed, we tried to use a methyl acetal at 1-position. It was introduced with sulfuric acid in MeOH in quantitative yield. Protection of the *syn*-diol furnished carbohydrate **SI-72** in 93% yield. Swern-oxidation in 77% yield and consequent reduction with $NaBH_4$ in 99% yield gave alcohol **SI-73** with inverted stereoconfiguration at 4-position as a single diastereomer. The remaining hydroxyl group was benzylated in 99%. Removal of the acetal with $BiCl_3$ provided a diol, which was regioselectively acetylated at 3-position. This was followed by methylation with $TMSCHN_2$ and HBF_4 (→ **SI-75**). Different acidic conditions were used to cleave the acetal at the anomeric position. However, either the acetyl group was removed too, or no reaction was observed. Therefore, it was switched to the allyl group at the anomeric position. It was also tried, to introduce the carbamate at 4-position. The benzyl group was removed via hydrogenation. The resulting hydroxyl group reacted quickly with trichloroacetylisocyanate to an intermediate, which was converted to carbamate **SI-77** by stirring with SiO_2 in a THF/MeOH mixture.



Scheme S15. Performed steps towards methyl-acetal of L-rhamnose **SI-76**.
Reagents and conditions: a) H_2SO_4, MeOH, RT, on, quant.; b) $CuSO_4$, acetone, rt, 21 h, 93%; c) 1. $(ClOC)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, 2. **SI-72**, 30 min, 3. DIPEA, rt, 18 h, 77%; d) $NaBH_4$, EtOH, 0 C, 21 h, 99%, single diastereomer; e) 1. NaH, imidazole, DMF, 0 °C ›rt, 35 min, 2. BnBr, TBAI, rt, 18 h, 99%; f) $BiCl_3$, MeCN/H_2O, rt, 1 d, 99%; g) 1. Bu_2SnO, toluene, reflux, 2 h, 2. AcCl, rt, 3 h, 85%; h) $TMSCHN_2$, HBF_4, CH_2Cl_2, 0 °C, 5 h, 77%; i) Pd/C, H_2, MeOH, 20 h, quant.; j) trichloroacetylisocyanate, CH_2Cl_2, 0 °C, 10 min; k) SiO_2, THF/MeOH, 40 °C, 16 h, 65% over two steps.

The main problem of the synthesis of the upper part of kibdelomycin was the coupling of the sugar and tetramic acid. Our first concept was to build *N*-glycosides **SI-79a/b** with L-valine, which we achieved in excellent 99% yield and α:β-ratio of 2:1 by simply adding the amino acid in EtOH or MeOH. However, it was not possible to convert the aminoglycosides **SI-79a/b** into the corresponding β-ketoamides **SI-80a/b**, tetramic acids **SI-81a/b** or 4-*O*-alkyl tetramic acids

SI-82a/b. All of them could be converted to 3-acyltetramic acid in well studied reactions and therefore could have been possible intermediates. For building β-ketoamides **SI-80a/b**, we focused on Ley´s acylation with β-ketothioester **SI-85**. This method was successfully used for acylation of a aminoglycoside by our group in 2016.[16] Different equivalents, reaction time, temperature, different silver salts and additional reagents were tested (Table S1). Most of the times the acetyl group or valine was removed, sometimes complete decomposition was observed or educt was reisolated. Also, an attempt to introduce a β-ketoamide by conversion with adduct **SI-86** under reflux only led to removal of the acetyl group. Likewise, the *in situ* formation of the acid chloride of carboxylic acid **SI-89a** and conversion with aminoglycoside **SI-79a** under basic conditions gave decomposition of starting materials. After multiple attempts, the acetyl group turned out to be instable under different conditions. So instead of the acetyl group, a TBS protecting group was introduced to try some of the reactions already carried out again. Each of them also lead to decomposition or removal of acetyl group or no transformation. Further attempts to convert the aminoglycosides **SI-79a/b** into a tetramic acid via Meldrum´s acid method led to elimination of valine. Also, the conversion with ketenylidentriphenylphosphorane to give 4-*O*-alkyltetramic acids **SI-82a/b** wasn´t successful, only decomposition products were isolated. After trials to convert the aminoglycoside, the β-ketoamide or tetramic acid should be introduced directly. Therefore, a Mitsunobu reaction with β-ketoamide **SI-88** was carried out, but only educt was reisolated. Conversion of semi-acetal **58a** with tetramic acid **SI-87** and *p*TsOH led to decomposition. The experiments with TBS-group instead of acetyl group led to similar results.



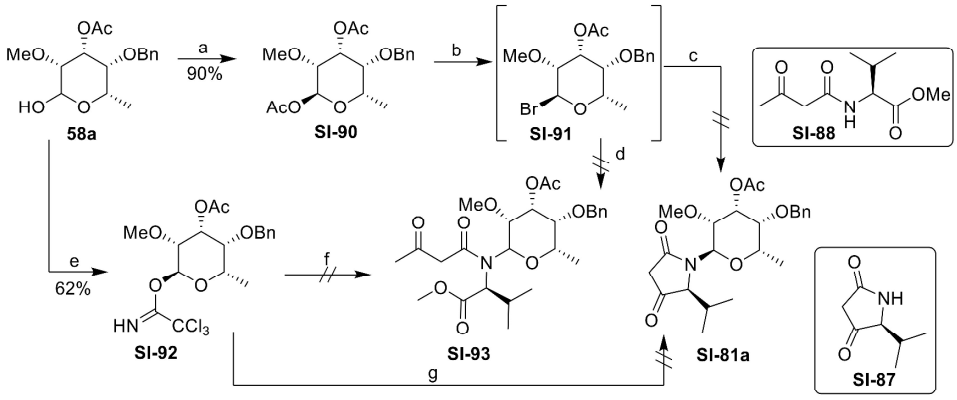
Scheme S16. Failed attempts to attach a tetramic acid or β-ketoamide at the glycoside or aminoglycoside.
Reagents and conditions: a) PPh_3, DIAD, β-ketoamide **SI-88**, THF, −78 °C; b) **SI-87**, *p*TsOH, CH_2Cl_2, reflux, 2 d; c) X = Ac L-valine methyl ester, EtOH/MeOH, rt, 3 d, 99%; X = TBS 86%; d) Table S1 e) X = Ac adduct **SI-86**, toluene, 120 °C, 2 h; f) X = Ac 1. oxalyl chloride, acid **SI-89a**, DMF, 0 °C, 2 h, 2. **SI-79a**, 0 °C, 21 h; g) X = Ac β-ketoester **SI-89b**, toluene, reflux, 22 h; h) X = Ac/TBS 1. Meldrum´s acid, DMAP, EDC·HCl, CH_2Cl_2, rt, 3 h, 2. EtOAc, reflux, 3 h, i) X = Ac/TBS Ph_3PCCO, THF, reflux, 19 h.

Table S1. Reaction conditions for Ley-acylation of aminoglycosides **SI-79a/b**.

Entry	X	Reagents and conditions	Temperature[°C]	Time	Result
1	Ac	Educt (1.00 eq.), **SI-85** (1.25 eq.), AgO_2CCF_3 (1.60 eq.), 4 Å MS, TIIF, aq. Work-up	0	3 h	Removal of Ac
2	Ac	Educt (1.00 eq.), **SI-85** (1.25 eq.), AgO_2CCF_3 (1.60 eq.), 4 Å MS, THF, without aq. work-up	0	3 h	Removal of Ac/valine
3	Ac	Educt (1.20 eq.), **SI-85** (1.00 eq.), AgO_2CCF_3 (1.20 eq.), NEt_3, THF	0	3 h	Removal of valine
4	Ac	Educt (1.00 eq.), **SI-85** (1.20 eq.), AgO_2CCF_3 (1.50 cq.), NEt_3, THF	0	3 h	Removal of Ac/valine

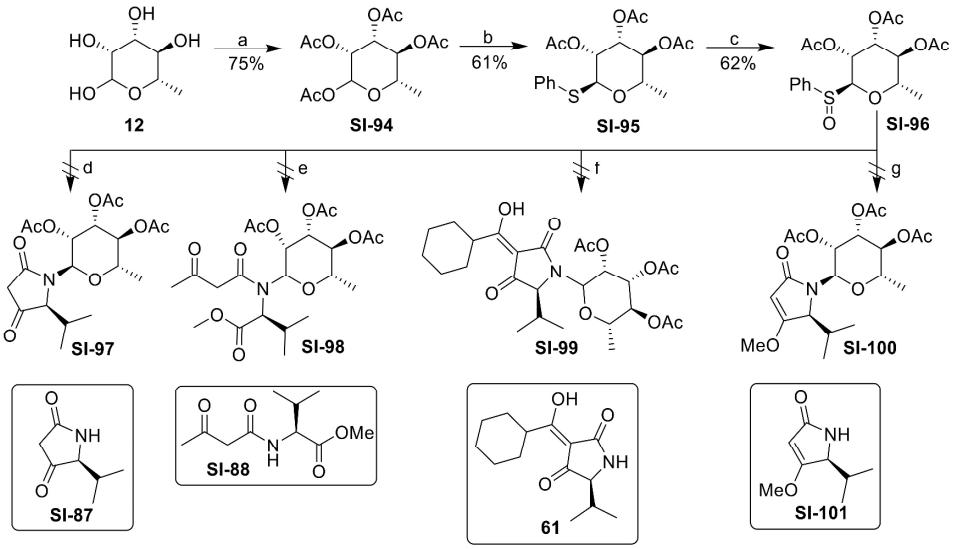
6	Ac	Educt (1.00 eq.), **SI-85** (1.20 eq.), AgO_2CCF_3 (1.25 eq.), Na_2KHPO_4, THF	0	6 h	Removal of valine
7	Ac	Educt (1.00 eq.), **SI-85** (1.25 eq.), AgO_2CCF_3 (1.25 eq.), 4 Å MS, THF	−78	1 h	Removal of Ac
8	Ac	Educt (1.00 eq.), **SI-85** (1.20 eq.), AgO_2CCF_3 (1.25 eq.), Na_2KHPO_4, THF	−78	1.5 h	Removal of Ac
9	Ac	Educt (1.00 eq.), **SI-85** (1.50 eq.), AgO_3SCF_3 (2.00 eq.), NEt_3, THF	0	6 h	educt
10	Ac	Educt (1.00 eq.), **SI-85** (1.25 eq.), AgO_3SCF_3 (1.60 eq.), 4 Å MS, THF	0	22 h	Removal of Ac/valine
11	TBS	Educt (1.00 eq.), **SI-85** (1.25 eq.), AgO_2CCF_3 (1.25 eq.), 4 Å MS, THF	−78	4 h	Decompo-sition
12	TBS	Educt (1.00 eq.), **SI-85** (1.25 eq. + 1.25 eq.), AgO_2CCF_3 (1.25 eq. + 1.25 eq.), Na_2KHPO_4, THF	−78→rt	1 d	Decompo-sition
13	TBS	Educt (1.20 eq.), **SI-85** (1.00 eq.), AgO_2CCF_3 (1.20 eq.), NEt_3, THF	0→rt	2 d	educt

Some reactions were carried out with activated forms of carbohydrate **58a**. Therefore, it was first acetylated at the anomeric position in 90% yield. The bromide **SI-91** was formed by addition of TMSBr and had to be used directly in the next step because of its instability. On the one hand it was reacted with tetramic acid **SI-87** and KO*t*Bu and on the other hand it was converted with β-ketoamide **SI-88** and KO*t*Bu. Both reactions led to decomposition of starting material. The trichloroacetimidate **SI-92** was easily built by conversion of sugar **58a** with trichloroacetonitrile in 62% yield. Though, the attempts to couple it with tetramic acid **SI-87** or β-ketoamide **SI-88** weren´t successful and led to reisolation of starting material and decomposition, respectively.



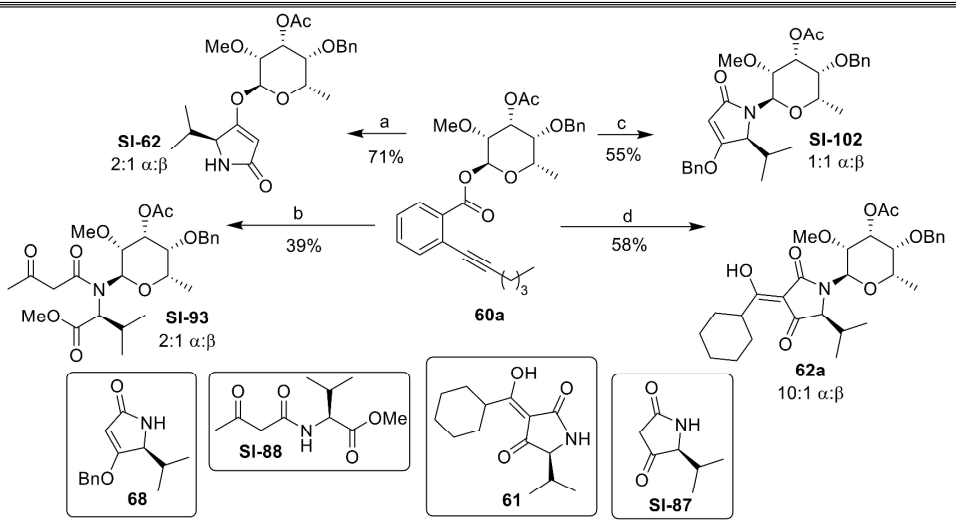
Scheme S17. Failed attempts to attach a tetramic acid or β-ketoamide at activated glycosides **SI-92** and **SI-91**.
Reagents and conditions: a) Ac_2O, pyridine, rt, 2 h; b) TMSBr, CH_2Cl_2, 0 °C, 2 h; c) tetramic acid **SI-87**, KO*t*Bu, THF, 0 °C, 20 h; d) β-ketoamide **SI-88**, KO*t*Bu, THF, 0 °C, 20 h; e) DBU, Cl_3CCN, CH_2Cl_2, 0 °C→rt, 1 d, f) β-ketoamide **SI-88**, TMSOTf, 4 Å MS, CH_3NO_2, rt, 4 d; g) tetramic acid **SI-87**, TMSOTf, 4 Å MS, CH_3NO_2, 0 °C, 1 d.

On the basis of the work of Beretta *et al.*[17] we synthesized the sulfoxide donor **SI-96** in three steps out of L-Rhamnose (**12**) by complete acetylation, *S*-glycosylation and oxidation to the sulfoxide with *m*CPBA. This sugar was used instead of the ready functionalised sugar to try the coupling reactions. Sulfoxide **SI-96** was reacted with tetramic acid **SI-87**, β-ketoamide **SI-88**, 3-acyltetramic acid **61** and 4-*O*-alkyltetramic acid **SI-101**. Before, they were activated by conversion with BSA, which should silylate the nitrogen. Second step is the addition of sugar **SI-96** and a lewis-acid, for which we choose TMSOTf. All the experiments led to decomposition of the starting material.



Scheme S18. Failed attempts to attach a tetramic acid or β-ketoamide to sulfoxide **SI-96**.
Reagents and conditions: a) Ac_2O, pyridine, rt, 22 h; b) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 22 h; c) *m*CBPA, CH_2Cl_2, −78 °C→0 °C, 7 h; d) 1. tetramic acid **SI-87**, BSA, dichloroethane, 90 °C, 2 h, 2. **SI-96**, TMSOTf, rt, 23 h; e) 1. β-ketoamide **SI-88**, BSA, dichloroethane, 90 °C, 2 h, 2. **SI-96**, TMSOTf, rt, 19 h; f) 1. 3-acyl tetramic acid **61**, BSA, dichloroethane, 90 °C, 1 h, 2. **SI-96**, TMSOTf, rt, 22 h; g) 1. 4-*O*-alkyltetramic acid **SI-101**, BSA, dichloroethane, 90 °C, 2 h, 2. **SI-96**, TMSOTf, rt, 20 h.

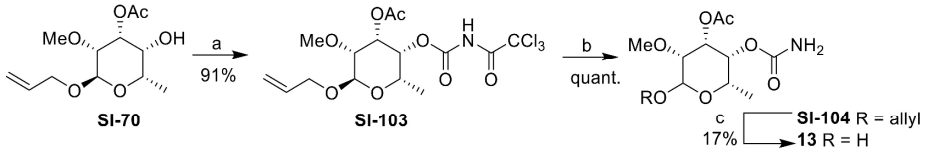
Finally, we decided to use the established method of the first total synthesis.[2] Ester **60a** was treated with gold-catalyst and all of the coupling products used before. Conversion with tetramic acid **SI-87** led to a defined product. 2D-NMR-experiments indicated that tetramic acid is bound to the sugar via a *O*-glycosidic linkage. This is possible because of the tautomeric character of tetramic acid **SI-87**. Reaction with β-ketoamide **SI-88** led to a product mixture. Here *O*-, *C*- or *N*-glycosidic linkages are possible. The different products couldn´t be separated. The glycosylation with 4-*O*-alkyltetramic acid **68** as well as 3-acyltetramic acid **61** gave the desired products but with a α:β ratio of 1:1 and 10:1, respectively.



Scheme S19. Investigations on attaching different forms of tetramic acids to a glycoside via an Au-catalysed reaction.
Reagents and conditions: a) tetramic acid **SI-87**, $AuPPh_3NTf_2$, toluene, 40 °C, 20 h; b) β-ketoamide **SI-88**, $AuPPh_3NTf_2$, toluene, 40 °C, 20 h; c) 4-*O*-alkyltetramic acid **68**, $AuPPh_3NTf_2$, toluene, 40 °C, 20 h; d) 3-acyltetramic acid **61**, $AuPPh_3NTf_2$, toluene, 40 °C, 20 h.

2.13 Synthesis of amykitanose (**13**)

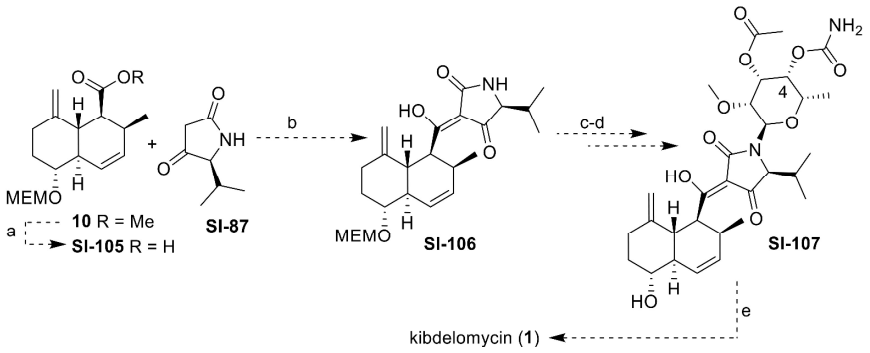
Glycoside **SI-70** was reacted with trichloroacetylisocyanate to give product **SI-103**, which gave the carbamate **SI-104** after stirring with SiO_2 in 91% yield over two steps. Deprotection at the anomeric position in 17% yield gave amykitanose (**13**). The synthesis wasn´t optimised yet but can easily be used to introduce the carbamate function.



Schema S20. Synthesis of amykitanose (**13**).
Reagents and conditions: a) trichloroacetylisocyanate, CH_2Cl_2, 0°C, 13 min; b) SiO_2, THF/MeOH, 40°C; c) $Pd(PPh_3)_4$, AcOH, rt, 16 h.

2.14 Alternative formal synthesis of kibdelomycin (**1**)

For the completion of an alternative total synthesis exploiting the novel *N*-glycosylation of 3-acyltetramic acids, tetramic acid **SI-87** would have to be attached to the decalin fragment **SI-105** via an established Yoshii-Yoda acylation (Scheme S21).[18] The resulting 3-acyltetramic acid **SI-106** would then be *N*-glycosylated with the sugar fragments **60a/b** via the known Au-catalysed reaction and the 4-position be converted into a carbamic acid to give **SI-107** (analogue to the synthesis of amykitanose (**13**) *cf.* Scheme S20). Finally, building block **SI-107** would be *O*-glycosylated with the amycolose derivative **4** to afford kibdelomycin (**1**).



Schema S21. Synthetic plan for an alternative synthesis of kibdelomycin (**1**).
Reagents and conditions: a) LiOH; b) EDC·HCl, DMAP, then NEt_3, DMAP, $CaCl_2$; c) **60a/b**, $AuPPh_3NTf_2$; d) deprotection 4-position, then $Cl_3CCONCO$, then SiO_2, then MEM-deprotection; e) **4**, TfOH.

3. References

1 B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981.

2 S. Yang, C. Chen, J. Chen and C. Li, *J. Am. Chem. Soc.*, 2021, **143**, 21258.

3 R. J. Abraham and M. Reid, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1081.

4 A. M. Molins-Pujol, C. Moranta, C. Arroyo, M. T. Rodríguez, M. C. Meca, M. D. Pujol and J. Bonal, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2277.

5 H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed.*, 2007, **46**, 5206.

6 T. J. Kucharski, N. Ferralis, A. M. Kolpak, J. O. Zheng, D. G. Nocera and J. C. Grossman, *Nat. Chem.*, 2014, **6**, 441.

7 T. den Hartog, D. van Jan Dijken, A. J. Minnaard and B. L. Feringa, *Tetrahedron Asymmmetry*, 2010, **21**, 1574.

8 H. Sakaguchi, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2007, **9**, 1635.

9 S. G. Davies, I. A. Hunter, R. L. Nicholson, P. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2004, **60**, 7553.

10 E. Vedejs, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, Chichester, UK, 2001.

11 J. Willwacher and A. Fürstner, *Angew. Chem. Int. Ed.*, 2014, **53**, 4217.

12 T. Hanaya, H. Baba, H. Toyota and H. Yamamoto, *Tetrahedron*, 2009, **65**, 7989.

13 E. Danieli, D. Proietti, G. Brogioni, M. R. Romano, E. Cappelletti, M. Tontini, F. Berti, L. Lay, P. Costantino and R. Adamo, *Bioorg. Med. Chem.*, 2012, **20**, 6403.

14 B. J. Dahl and B. P. Branchaud, *Tetrahedron Lett.*, 2004, **45**, 9599.

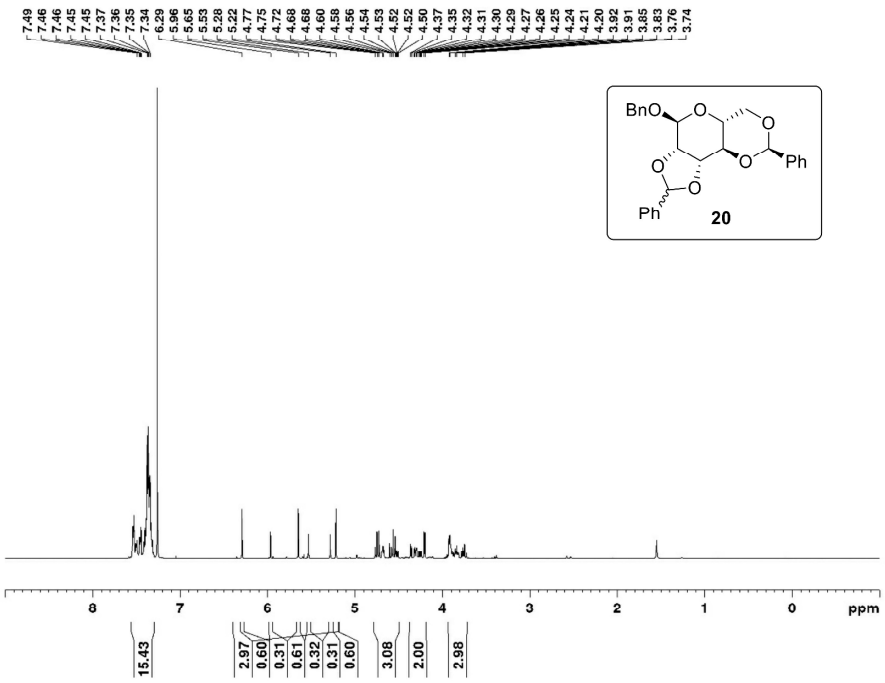
15 A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. de Buck Becker, M. Rudolph, C. Scholz and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 133.

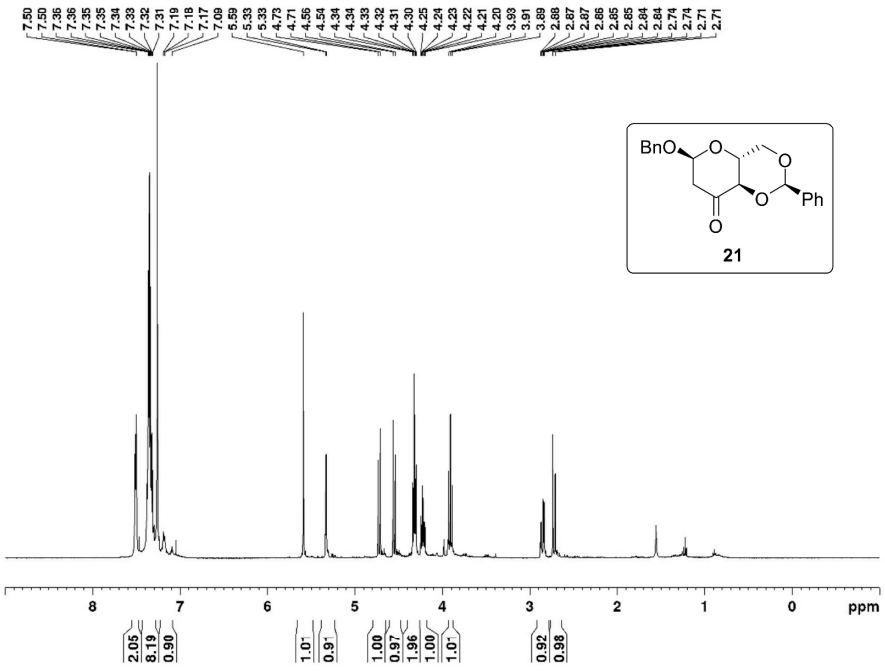
16 M. Petermichl, S. Loscher and R. Schobert, *Angew. Chem. Int. Ed.*, 2016, **55**, 10122.

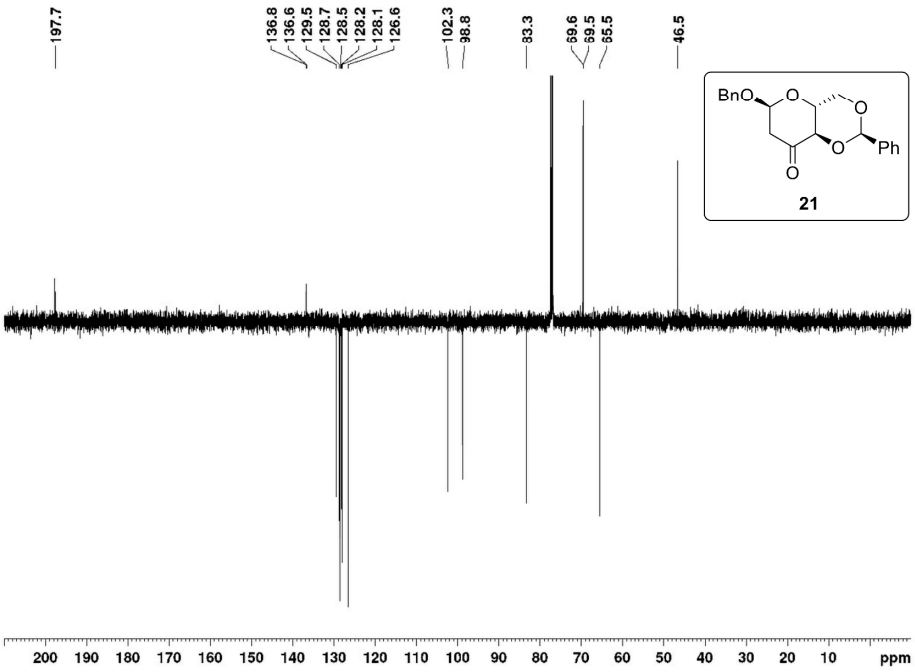
17 M. Beretta, E. Rouchaud, L. Nicolas, J.-P. Vors, T. Dröge, M. Es-Sayed, J.-M. Beau and S. Norsikian, *Org. Biomol. Chem.*, 2021, **19**, 4285.

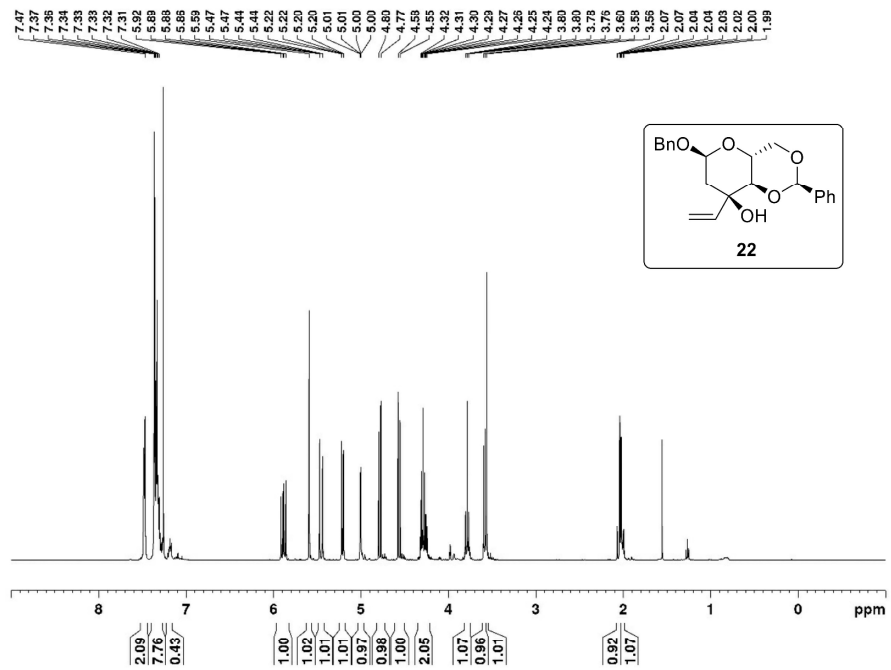
18 a) T. Sengoku, J. Wierzejska, M. Takahashi and H. Yoda, *Synlett*, 2010, **2010**, 2944; b) K. Hori, M. Arai, K. Nomura and E. Yoshii, *Chem. Pharm. Bull.*, 1987, **35**, 4368.

4. NMR-Spectra

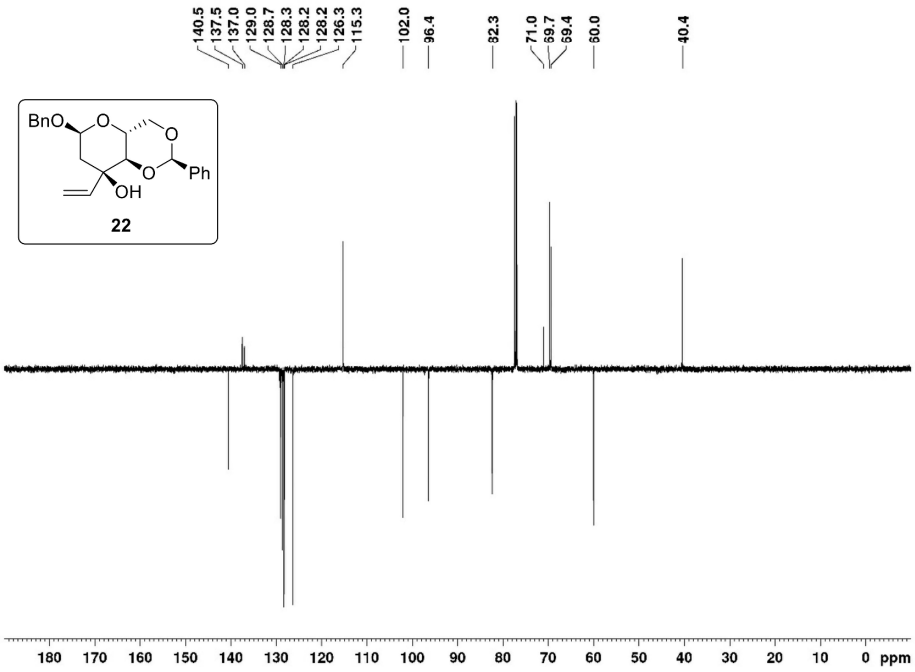


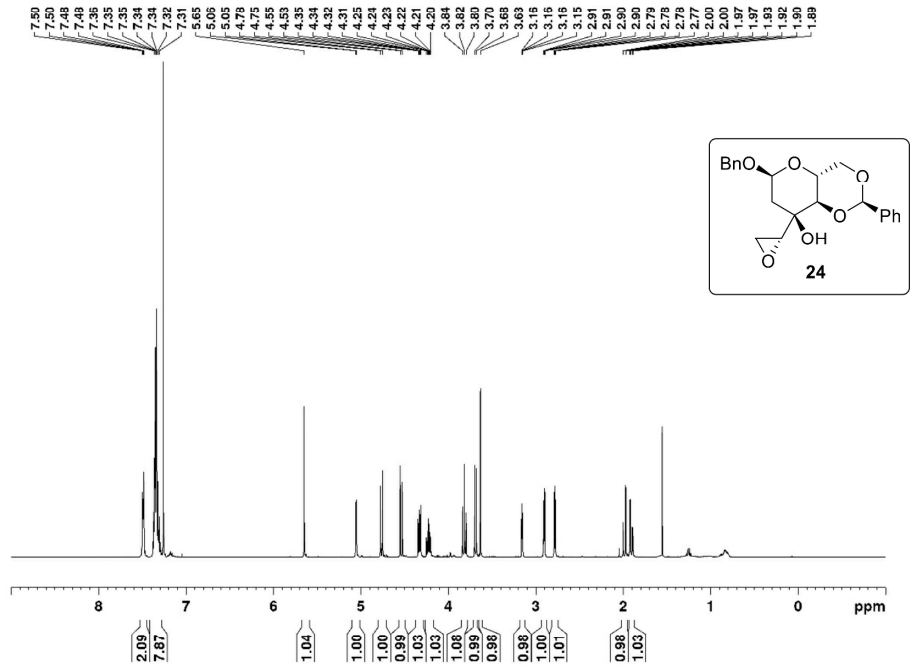


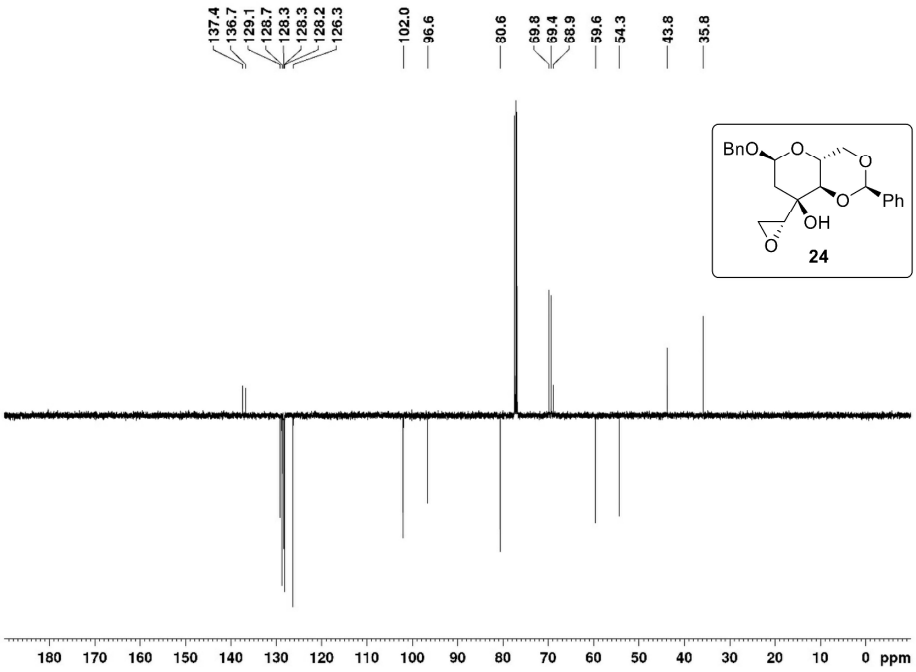

197.7
136.8
136.6
129.5
128.7
128.5
128.2
128.1
126.6
102.3
98.8
83.3
69.6
69.5
65.5
46.5
BnO
O
O
O
Ph
O
21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

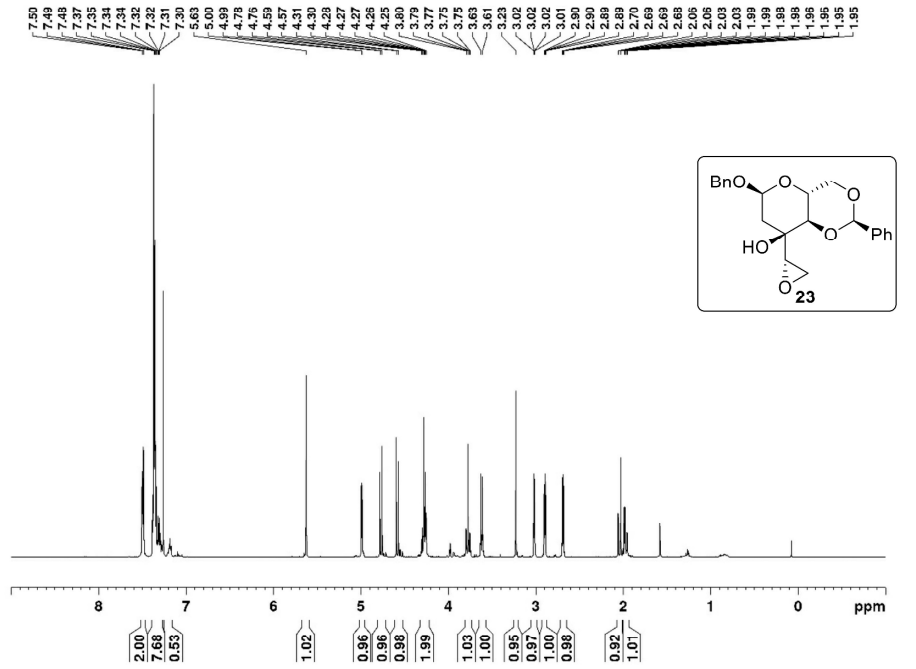

7.47
7.37
7.36
7.34
7.33
7.33
7.32
7.31
5.92
5.88
5.88
5.86
5.59
5.47
5.47
5.44
5.44
5.22
5.22
5.20
5.20
5.01
5.01
5.00
5.00
4.80
4.77
4.59
4.55
4.32
4.31
4.30
4.29
4.27
4.26
4.25
4.24
3.80
3.80
3.78
3.76
3.60
3.58
3.56
2.07
2.07
2.04
2.04
2.03
2.02
2.00
1.99
BnO
O
O
O
Ph
OH
22
8 7 6 5 4 3 2 1 0 ppm
2.09
7.76
0.43
1.00
1.02
1.01
1.01
0.97
0.98
1.00
2.05
1.07
0.96
1.01
0.92
1.07

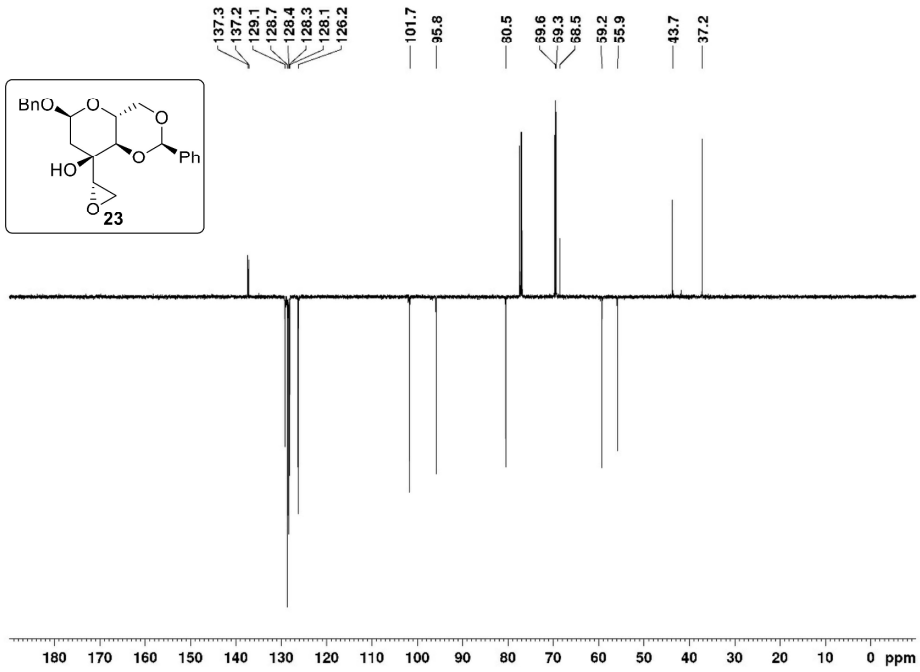
S85

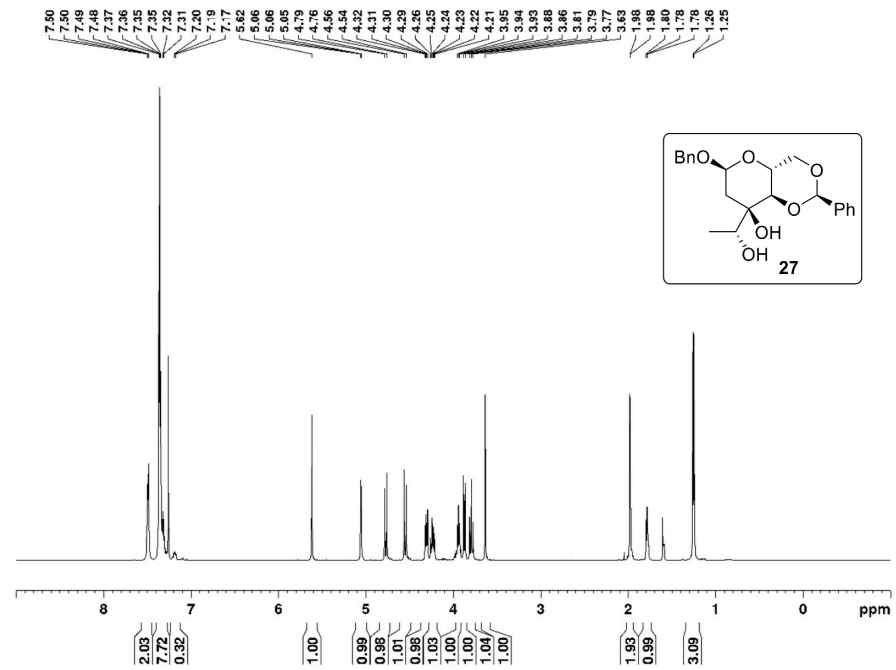

140.5
137.5
137.0
129.0
128.7
128.3
128.2
128.2
126.3
115.3
102.0
96.4
82.3
71.0
69.7
69.4
60.0
40.4
BnO
O
O
O
Ph
OH
22
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

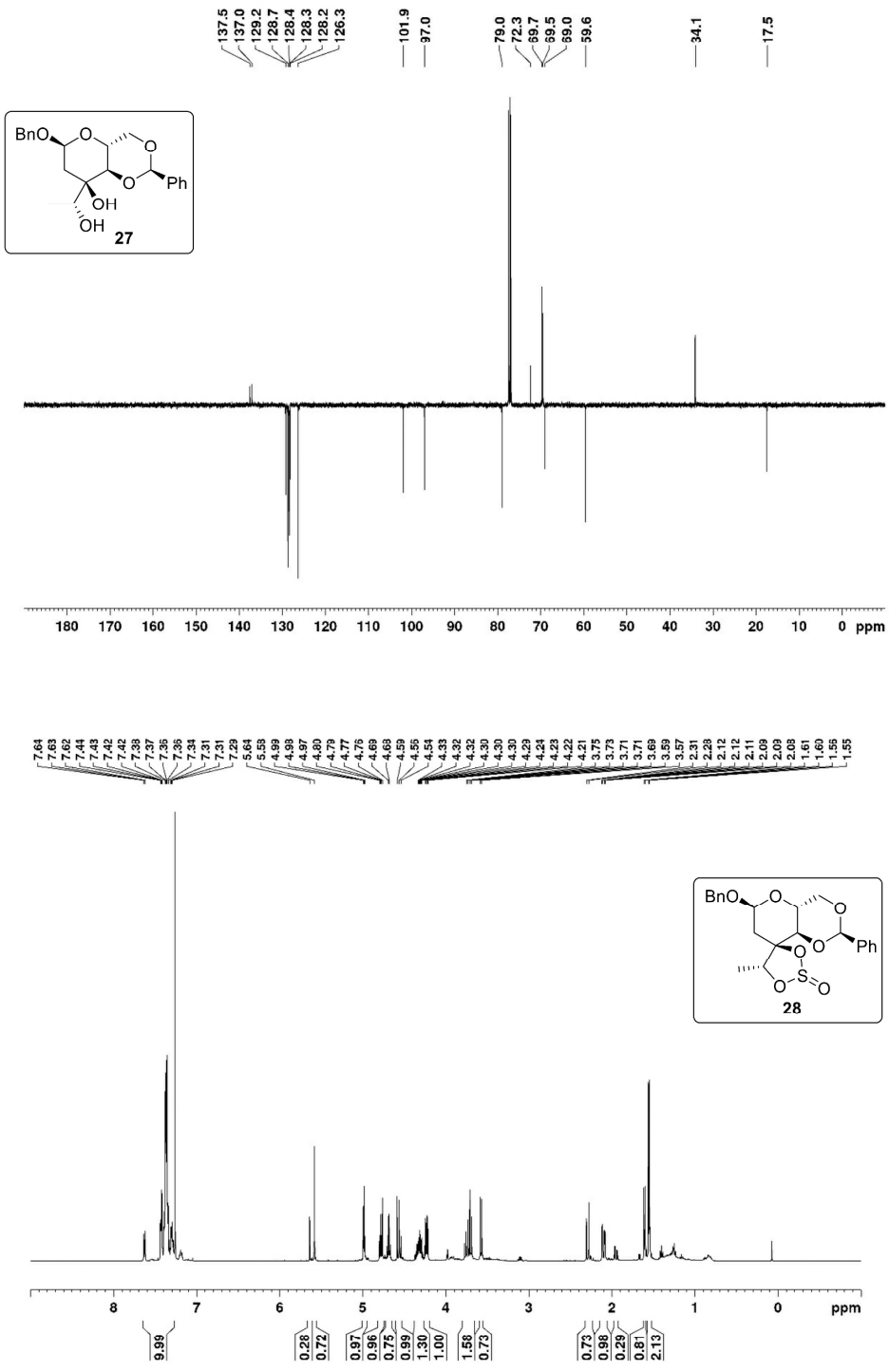

7.50
7.50
7.48
7.48
7.36
7.35
7.35
7.34
7.34
7.32
7.31
5.65
5.05
5.05
4.78
4.75
4.55
4.53
4.35
4.34
4.32
4.31
4.25
4.24
4.23
4.22
4.21
4.20
3.84
3.82
3.80
3.70
3.68
3.63
3.16
3.15
3.16
3.15
2.91
2.91
2.90
2.90
2.79
2.78
2.78
2.77
2.00
2.00
1.97
1.97
1.93
1.92
1.90
1.89
BnO
O
O
O
Ph
OH
O
24
8 7 6 5 4 3 2 1 0 ppm
2.09
7.87
1.04
1.00
1.00
0.99
1.03
1.03
1.08
0.99
0.96
0.98
1.00
1.01
0.98
1.03


137.4
136.7
129.1
128.7
128.3
128.3
128.2
126.3
102.0
96.6
80.6
69.8
69.4
68.9
59.6
54.3
43.8
35.8
BnO
O
O
O
Ph
OH
O
24
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

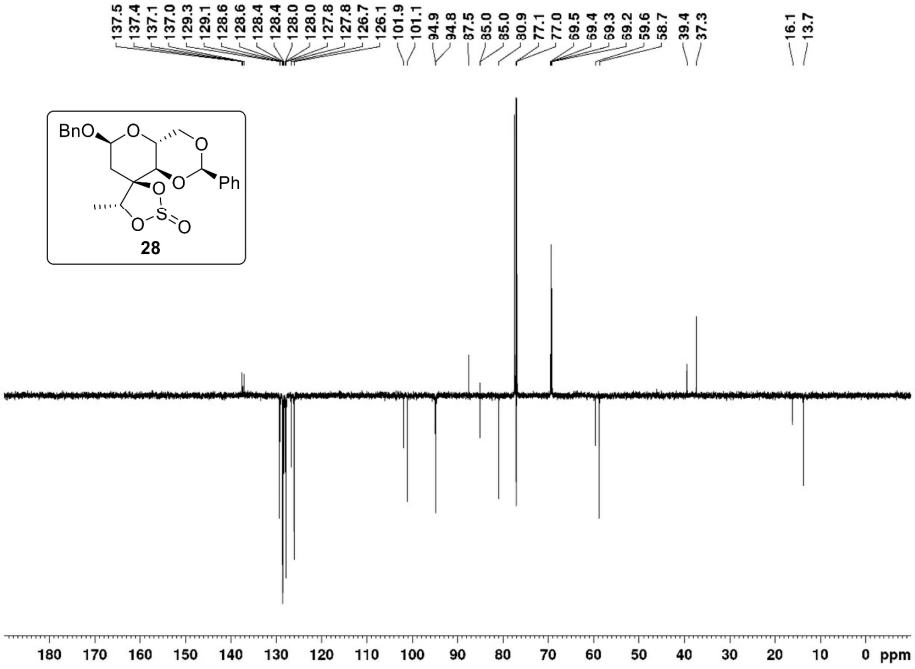

7.50
7.49
7.48
7.37
7.35
7.34
7.34
7.32
7.32
7.31
7.30
5.63
5.00
4.99
4.73
4.75
4.59
4.57
4.31
4.30
4.28
4.27
4.27
4.26
4.25
3.80
3.79
3.77
3.75
3.75
3.63
3.61
3.23
3.02
3.02
3.02
3.01
2.90
2.90
2.89
2.89
2.70
2.69
2.69
2.68
2.05
2.05
2.03
2.03
1.99
1.99
1.98
1.98
1.96
1.95
1.95
1.95
BnO
O
O
O
Ph
HO
O
23
8 7 6 5 4 3 2 1 0 ppm
2.00
7.68
0.53
1.02
0.96
0.96
0.98
1.99
1.03
1.00
0.95
0.97
1.00
0.98
0.92
1.01

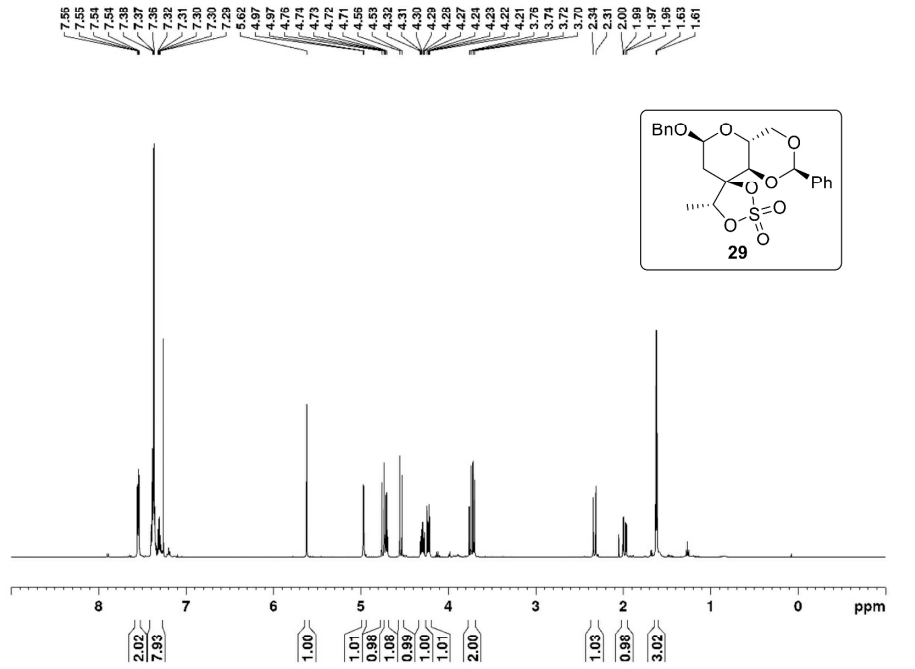

137.3
137.2
129.1
128.7
128.4
128.3
128.1
126.2
101.7
95.8
80.5
69.6
69.3
68.5
59.2
55.9
43.7
37.2
BnO
HO
Ph
23
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

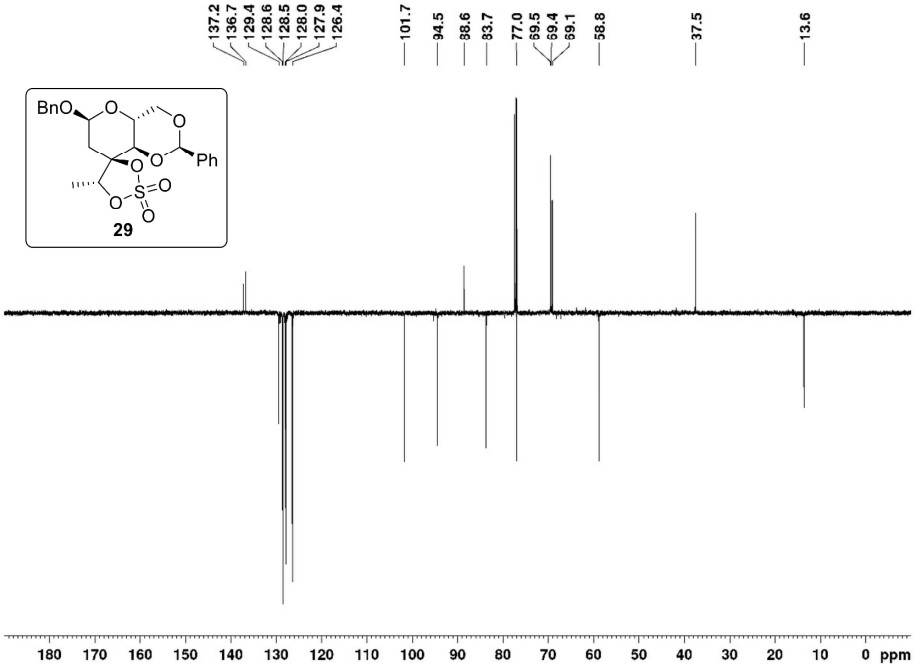

7.50
7.50
7.49
7.48
7.37
7.36
7.35
7.35
7.32
7.31
7.20
7.19
7.17
5.62
5.06
5.06
5.05
4.79
4.76
4.56
4.34
4.32
4.31
4.30
4.29
4.26
4.25
4.24
4.23
4.22
4.21
3.95
3.94
3.93
3.88
3.86
3.81
3.79
3.77
3.63
1.98
1.98
1.80
1.78
1.78
1.26
1.25
BnO
Ph
OH
OH
27
8 7 6 5 4 3 2 1 0 ppm
2.03
7.72
0.32
1.00
0.99
0.98
1.01
0.98
1.03
1.00
1.00
1.04
1.00
1.93
0.99
3.09

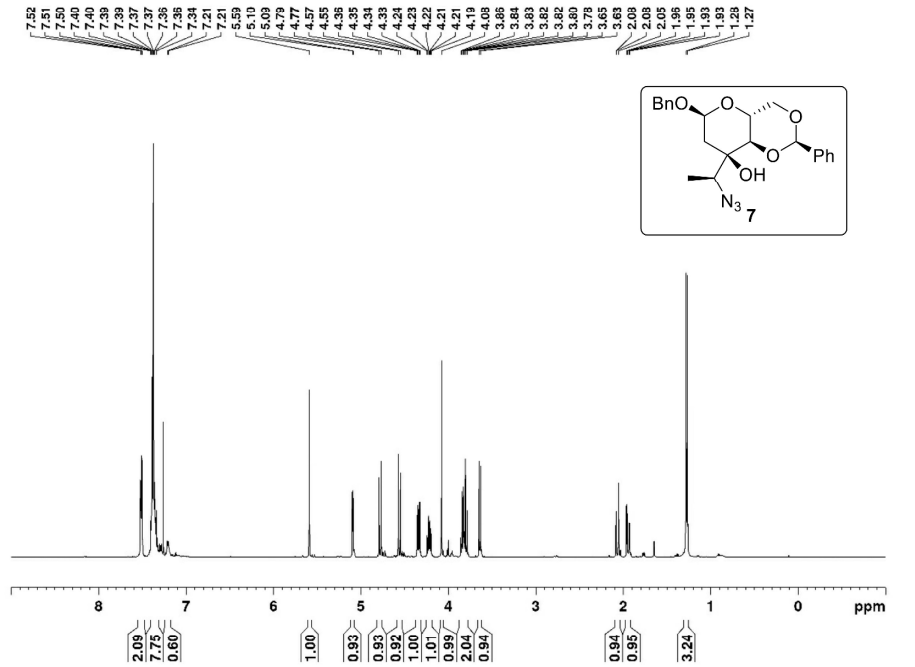

137.5
137.0
129.2
128.7
128.4
128.3
128.2
126.3
101.9
97.0
79.0
72.3
69.7
69.5
69.0
59.6
34.1
17.5
BnO
O
O
O
Ph
OH
OH
27
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
7.64
7.63
7.62
7.44
7.43
7.42
7.42
7.38
7.37
7.36
7.35
7.34
7.31
7.31
7.29
5.64
5.53
4.99
4.98
4.97
4.80
4.79
4.77
4.76
4.69
4.68
4.59
4.55
4.54
4.33
4.32
4.32
4.30
4.30
4.30
4.29
4.24
4.23
4.22
4.21
3.75
3.73
3.71
3.71
3.69
3.59
3.57
2.31
2.28
2.12
2.12
2.11
2.09
2.09
2.08
1.61
1.60
1.55
1.55
BnO
O
O
O
O
Ph
O
S
O
28
8 7 6 5 4 3 2 1 0 ppm
9.99
0.28
0.72
0.97
0.96
0.75
0.99
1.30
1.00
1.58
0.73
0.73
0.98
0.29
0.81
2.13

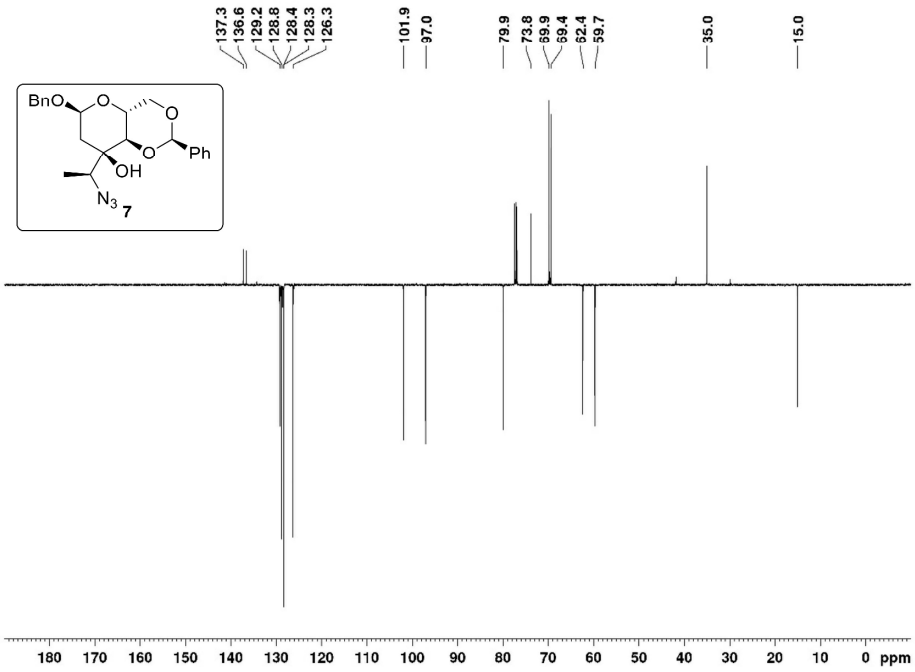
S89

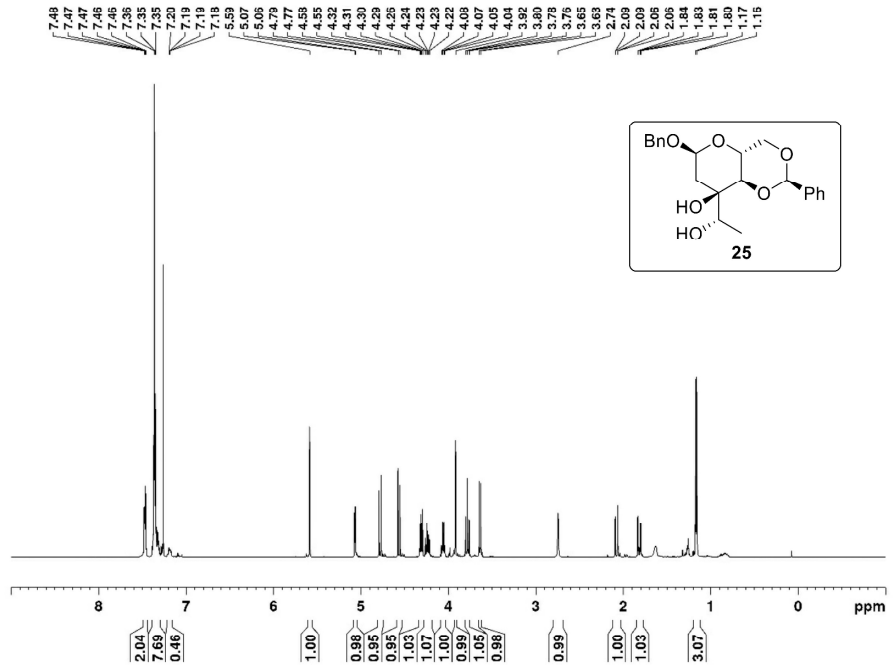

137.5
137.4
137.1
137.0
129.3
129.1
128.6
128.6
128.4
128.4
128.0
128.0
127.8
127.8
126.7
126.1
101.9
101.1
94.9
94.8
87.5
85.0
85.0
80.9
77.1
77.0
69.5
69.4
69.3
69.2
59.6
58.7
39.4
37.3
16.1
13.7
BnO
Ph
28
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

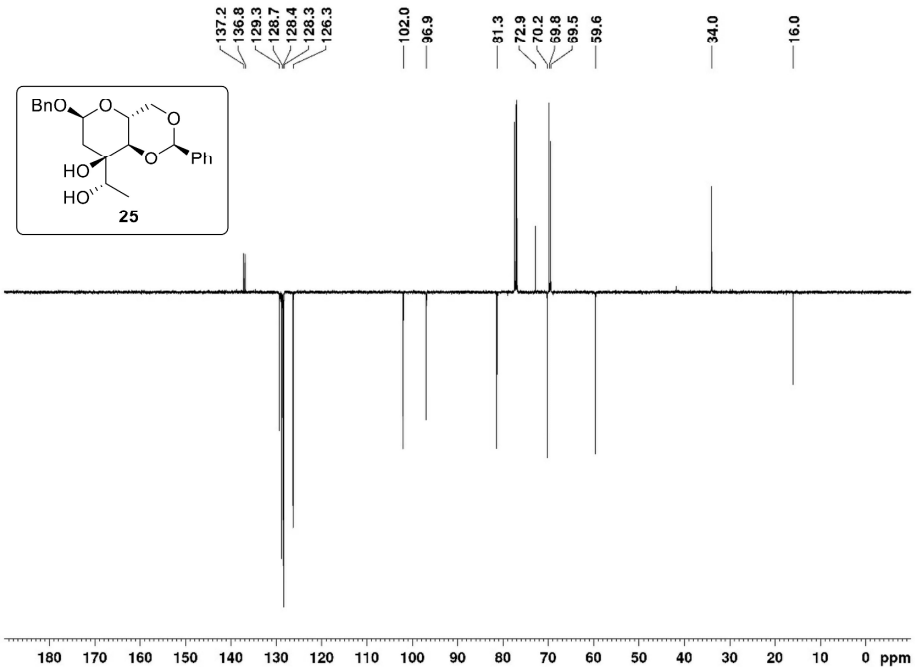

7.55
7.55
7.54
7.54
7.38
7.37
7.36
7.32
7.31
7.30
7.30
7.29
5.62
4.97
4.97
4.76
4.74
4.73
4.72
4.71
4.56
4.53
4.32
4.31
4.30
4.29
4.28
4.27
4.24
4.23
4.22
4.21
3.75
3.74
3.72
3.70
2.34
2.31
2.00
1.99
1.97
1.96
1.63
1.61
BnO
Ph
29
8 7 6 5 4 3 2 1 0 ppm
2.02
7.93
1.00
1.01
0.98
1.08
0.99
1.00
1.01
2.00
1.03
0.98
3.02

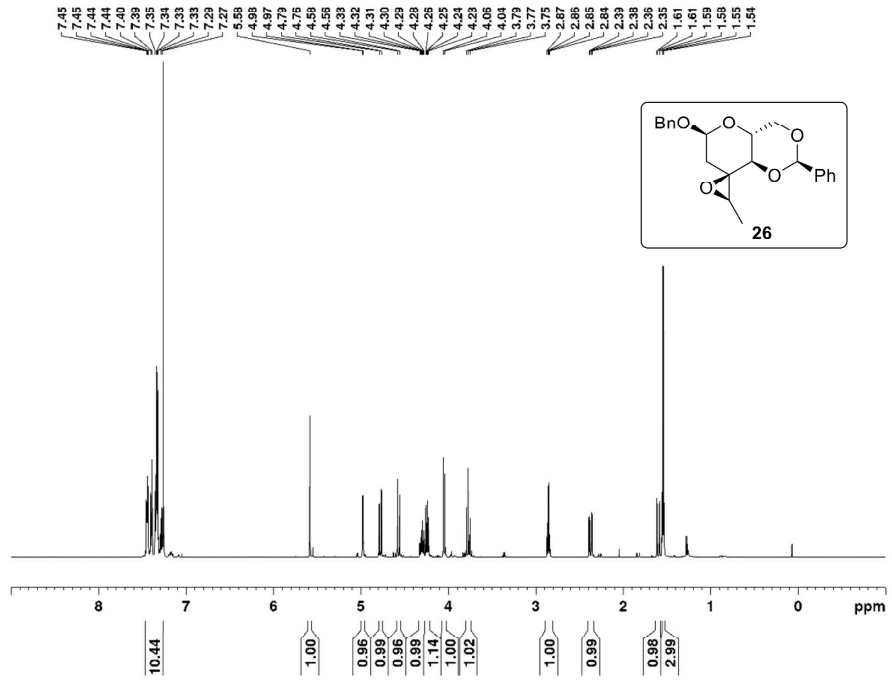

137.2
136.7
129.4
128.6
128.5
128.0
127.9
126.4
101.7
94.5
88.6
83.7
77.0
69.5
69.4
69.1
58.8
37.5
13.6
BnO
O
O
O
Ph
O
S
O
O
O
29
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

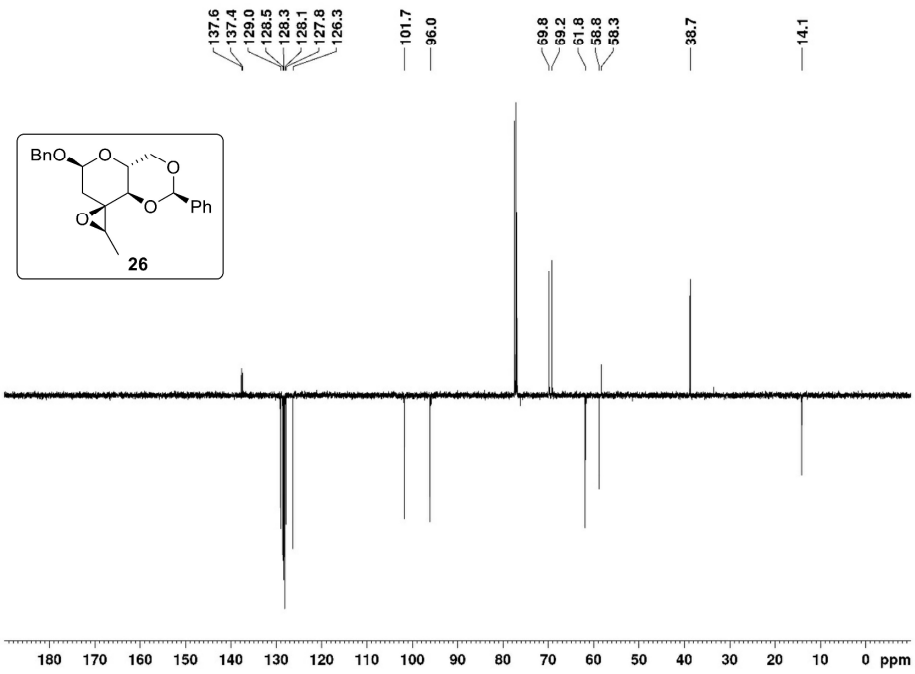

7.52
7.51
7.50
7.40
7.40
7.39
7.39
7.37
7.37
7.36
7.36
7.34
7.21
7.21
5.59
5.10
5.09
4.79
4.77
4.57
4.55
4.36
4.35
4.34
4.33
4.24
4.23
4.22
4.21
4.21
4.19
4.08
3.86
3.84
3.83
3.82
3.82
3.80
3.73
3.65
3.63
2.08
2.08
2.05
1.96
1.95
1.93
1.93
1.28
1.27
BnO
O
O
O
Ph
OH
N3
7
8 7 6 5 4 3 2 1 0 ppm
2.09
7.75
0.60
1.00
0.93
0.93
0.92
1.00
1.01
0.99
2.04
0.94
0.94
0.95
3.24

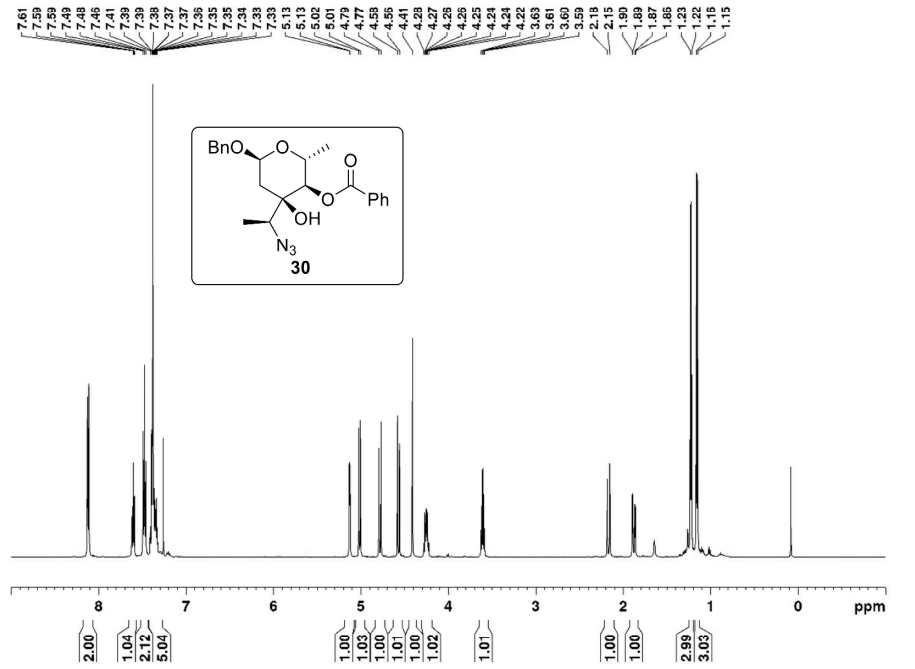

137.3
136.6
129.2
128.8
128.4
128.3
126.3
101.9
97.0
79.9
73.8
69.9
69.4
62.4
59.7
35.0
15.0
BnO
O
O
O
Ph
OH
N3
7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

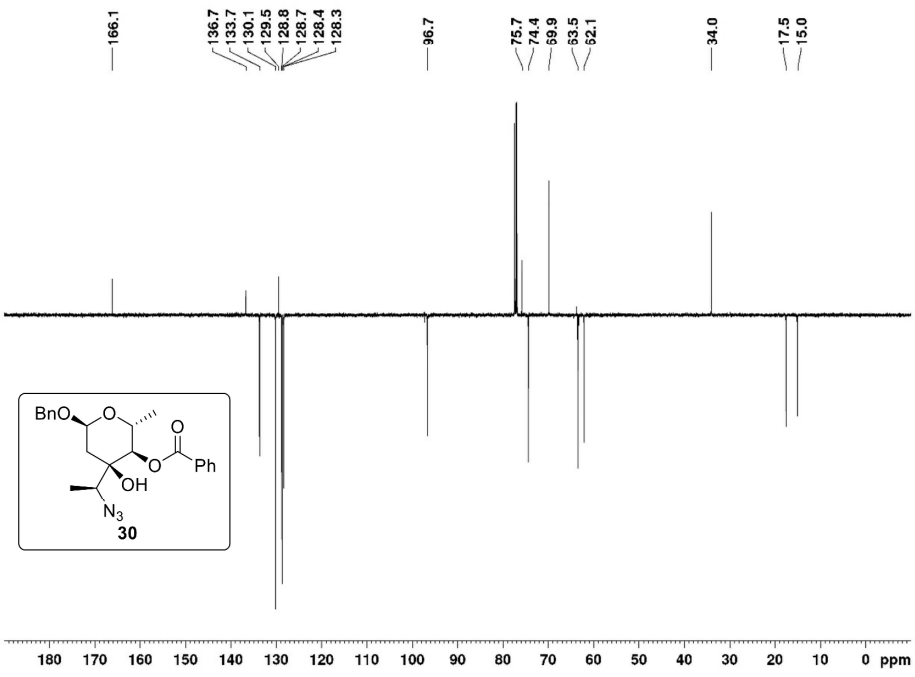

7.48
7.47
7.47
7.46
7.46
7.36
7.35
7.35
7.20
7.19
7.19
7.18
5.59
5.07
5.05
4.79
4.77
4.58
4.55
4.32
4.31
4.30
4.29
4.26
4.24
4.23
4.23
4.22
4.08
4.07
4.05
4.04
3.92
3.80
3.78
3.75
3.65
3.63
2.74
2.09
2.09
2.06
2.06
1.84
1.83
1.81
1.80
1.17
1.15
BnO
O
O
O
Ph
HO
HO
25
8 7 6 5 4 3 2 1 0 ppm
2.04
7.69
0.46
1.00
0.98
0.95
0.95
1.03
1.07
1.00
0.99
1.05
0.98
0.99
1.00
1.03
3.07

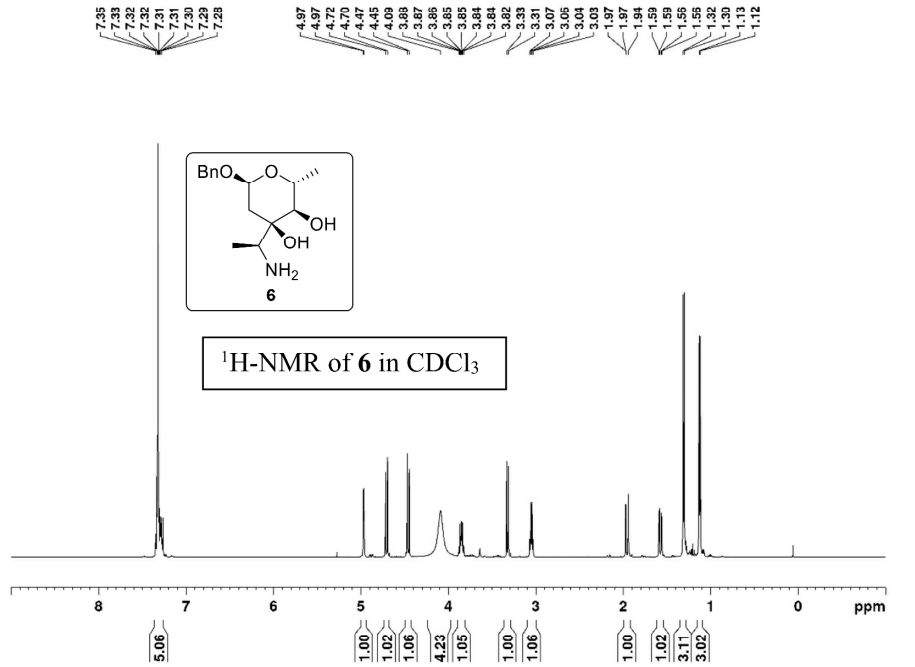

137.2
136.8
129.3
128.7
128.4
128.3
126.3
102.0
96.9
81.3
72.9
70.2
69.8
69.5
59.6
34.0
16.0
BnO
O
O
O
Ph
HO
HO
25
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

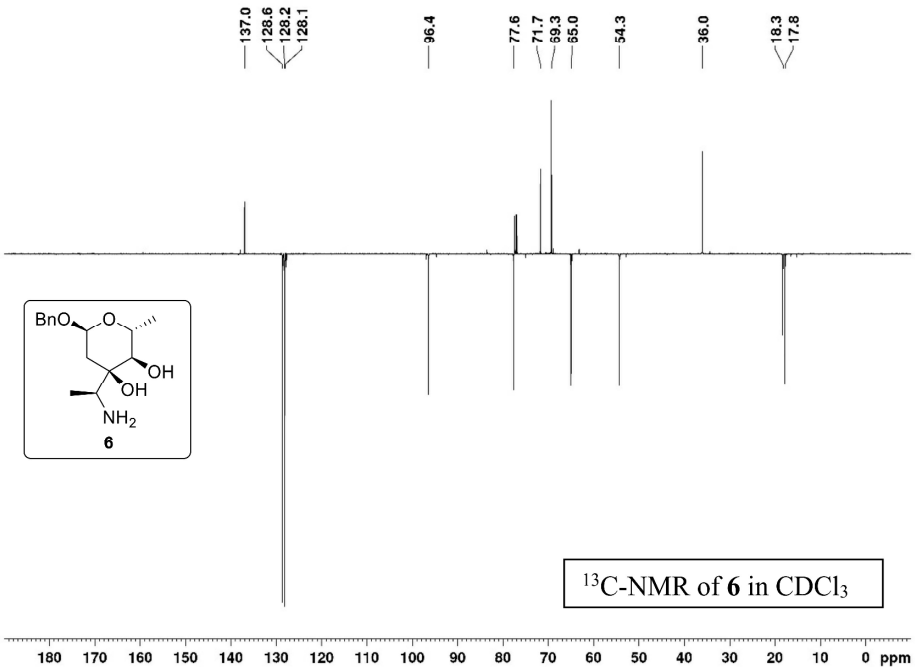

7.45
7.45
7.44
7.44
7.40
7.39
7.35
7.34
7.33
7.33
7.29
7.27
5.58
4.98
4.97
4.79
4.75
4.58
4.55
4.33
4.32
4.31
4.30
4.29
4.28
4.26
4.25
4.24
4.23
4.06
4.04
3.79
3.77
3.75
2.87
2.85
2.84
2.39
2.38
2.36
2.35
1.61
1.61
1.59
1.58
1.55
1.54
BnO
O
O
O
Ph
O
26
8 7 6 5 4 3 2 1 0 ppm
10.44
1.00
0.96
0.99
0.96
0.99
1.14
1.00
1.02
1.00
0.99
0.98
2.99

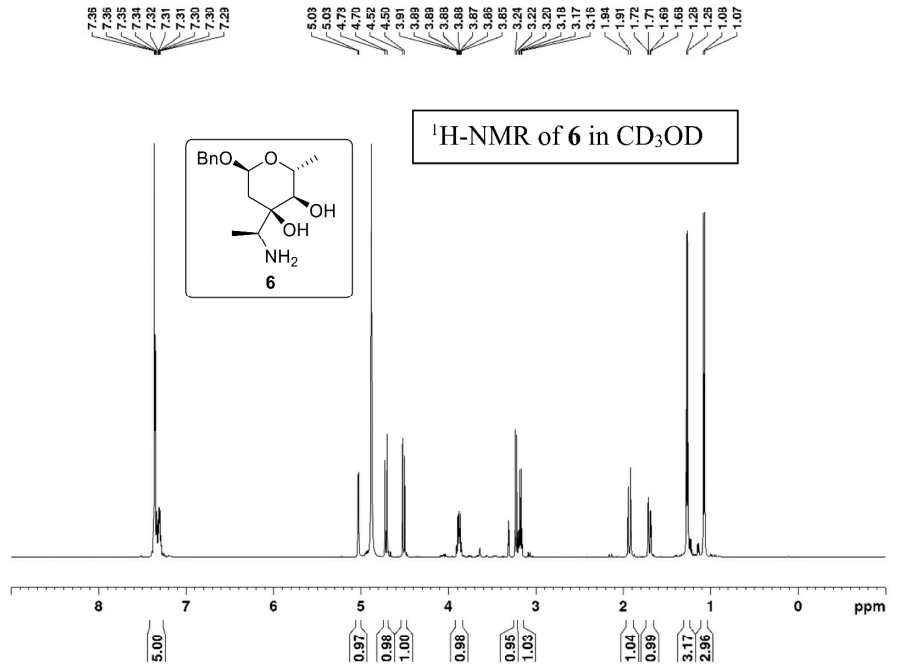

137.6
137.4
129.0
128.5
128.3
128.1
127.8
126.3
101.7
96.0
69.8
59.2
51.8
58.8
58.3
38.7
14.1
BnO
O
O
O
O
Ph
26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

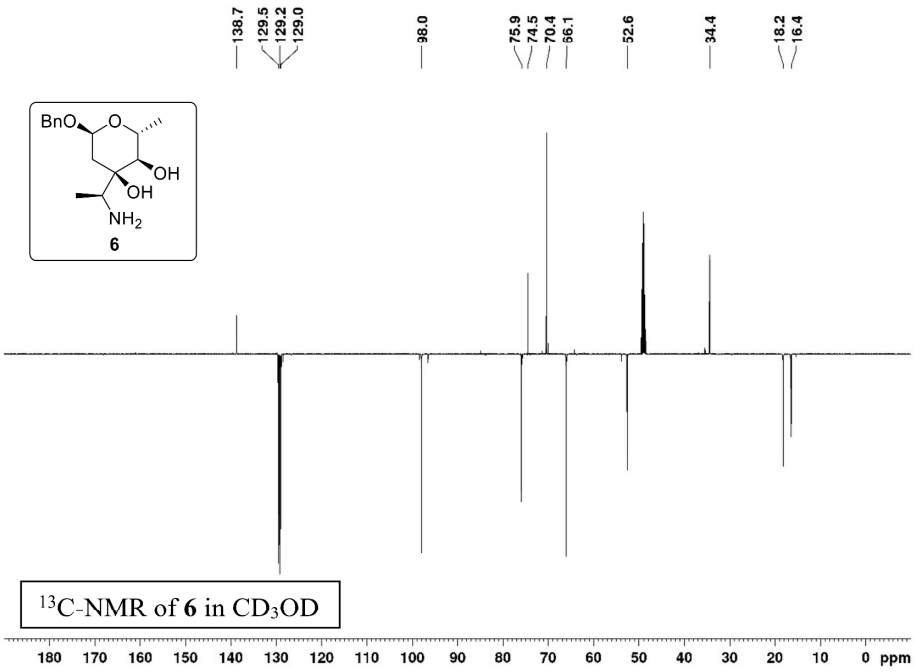

7.61
7.59
7.59
7.49
7.48
7.46
7.41
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.33
5.13
5.13
5.02
5.01
4.79
4.77
4.58
4.55
4.41
4.28
4.27
4.26
4.26
4.25
4.24
4.24
4.22
3.63
3.61
3.60
3.59
2.18
2.15
1.90
1.89
1.87
1.86
1.23
1.22
1.16
1.15
BnO
O
O
O
Ph
OH
N3
30
8 7 6 5 4 3 2 1 0 ppm
2.00
1.04
2.12
5.04
1.00
1.03
1.00
1.01
1.00
1.02
1.01
1.00
1.00
2.99
3.03

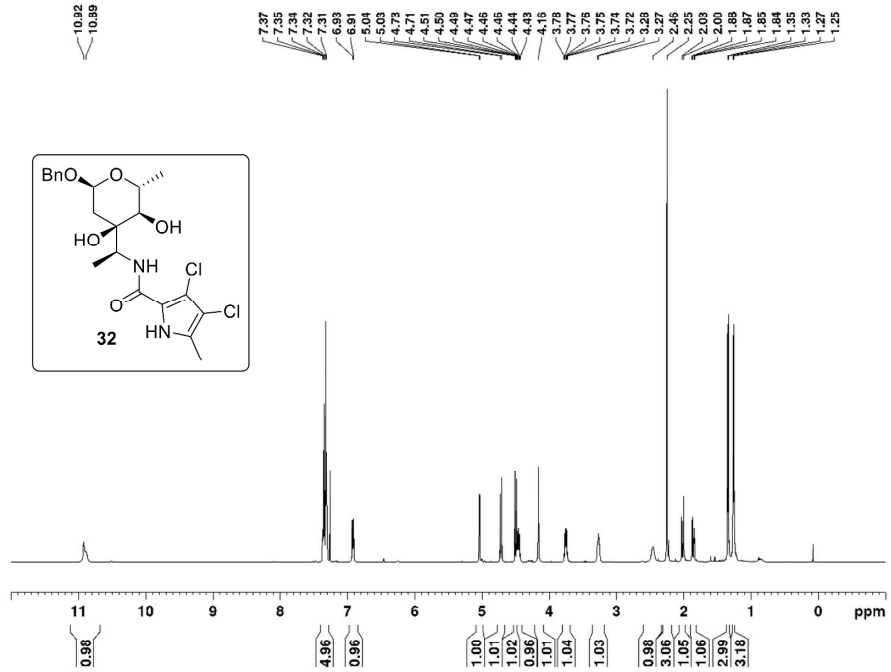

166.1
136.7
133.7
130.1
129.5
128.8
128.7
128.4
128.3
96.7
75.7
74.4
69.9
63.5
62.1
34.0
17.5
15.0
BnO
O
O
Ph
OH
N3
30
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

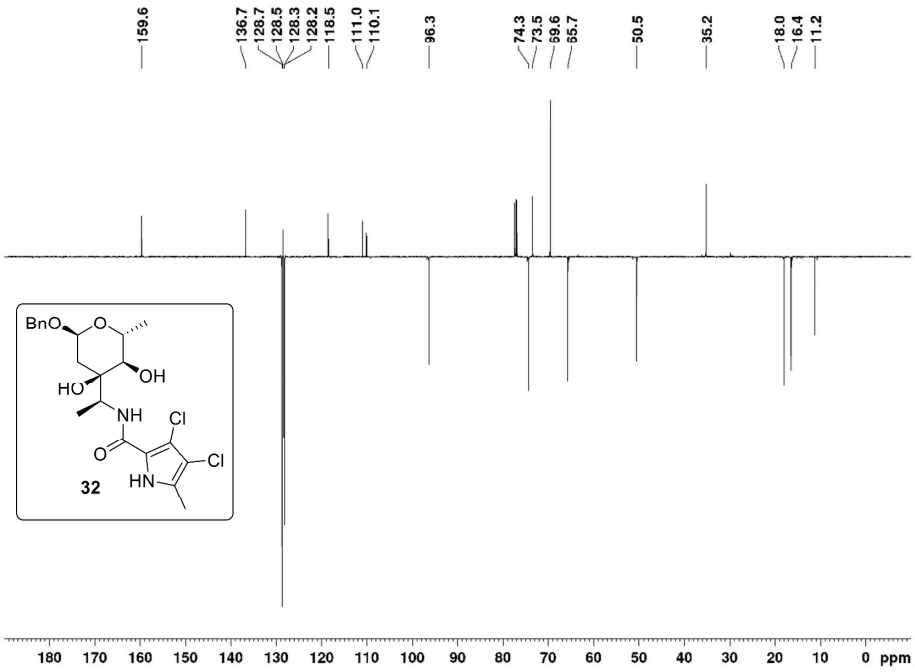

7.35
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.28
4.97
4.97
4.72
4.70
4.47
4.45
4.09
3.88
3.87
3.86
3.85
3.85
3.84
3.84
3.82
3.33
3.31
3.07
3.06
3.04
3.03
1.97
1.97
1.94
1.59
1.59
1.55
1.55
1.32
1.30
1.13
1.12
BnO
O
OH
OH
NH2
6
1H-NMR of 6 in CDCl3
8 7 6 5 4 3 2 1 0 ppm
5.06
1.00
1.02
1.06
4.23
1.05
1.00
1.06
1.00
1.02
3.11
3.02

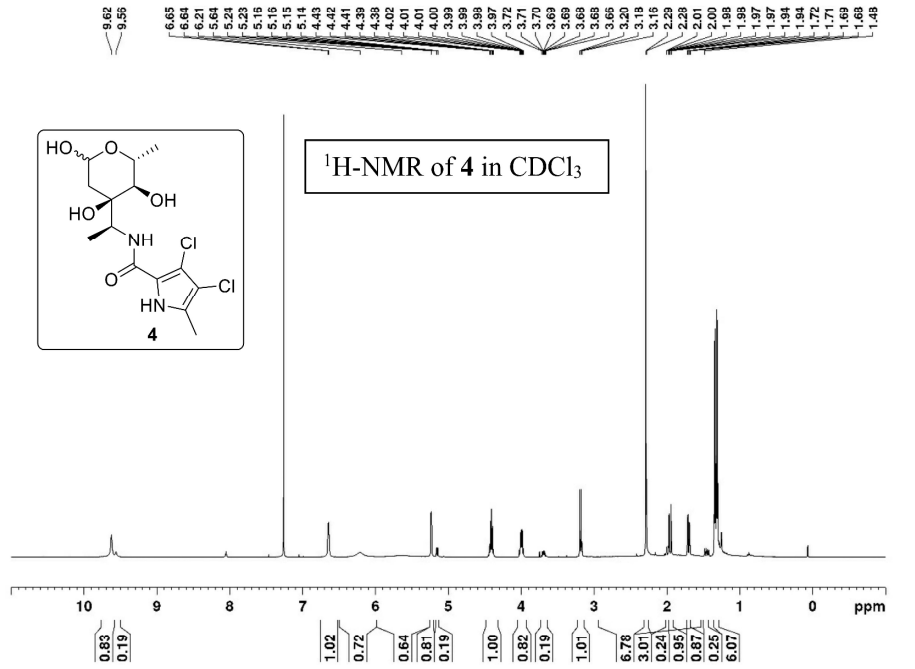

137.0
128.6
128.2
128.1
96.4
77.6
71.7
69.3
65.0
54.3
36.0
18.3
17.8
BnO
O
OH
OH
NH2
6
13C-NMR of 6 in CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

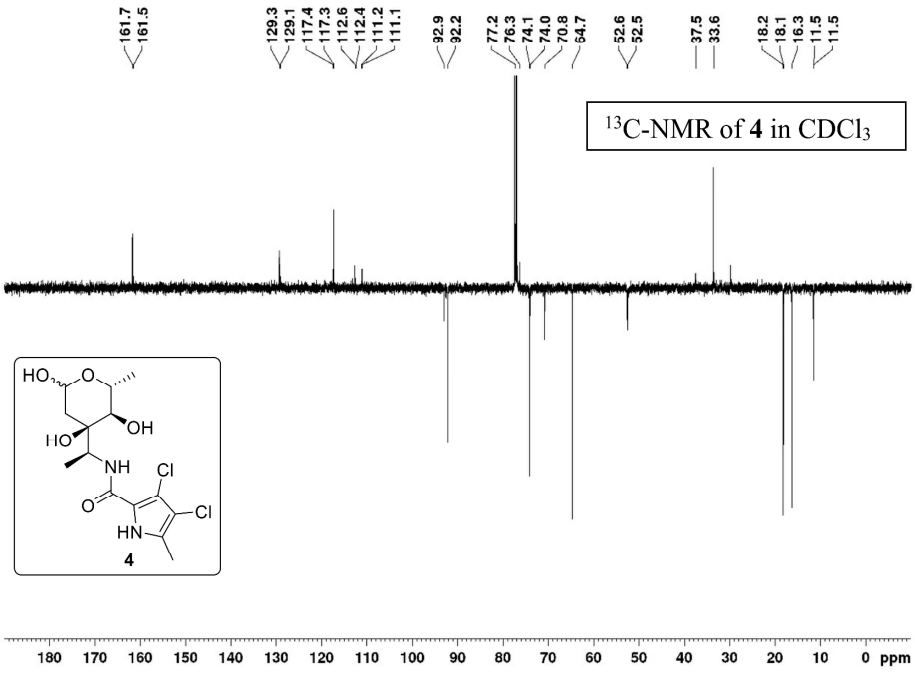

7.36
7.36
7.35
7.34
7.32
7.31
7.31
7.30
7.30
7.29
5.03
5.03
4.73
4.70
4.52
4.50
3.91
3.89
3.89
3.88
3.88
3.87
3.86
3.85
3.24
3.22
3.20
3.18
3.17
3.16
1.94
1.91
1.72
1.71
1.69
1.68
1.28
1.25
1.08
1.07
1H-NMR of 6 in CD3OD
BnO
O
OH
OH
NH2
6
8 7 6 5 4 3 2 1 0 ppm
5.00
0.97
0.98
1.00
0.98
0.95
1.03
1.04
0.89
3.17
2.96

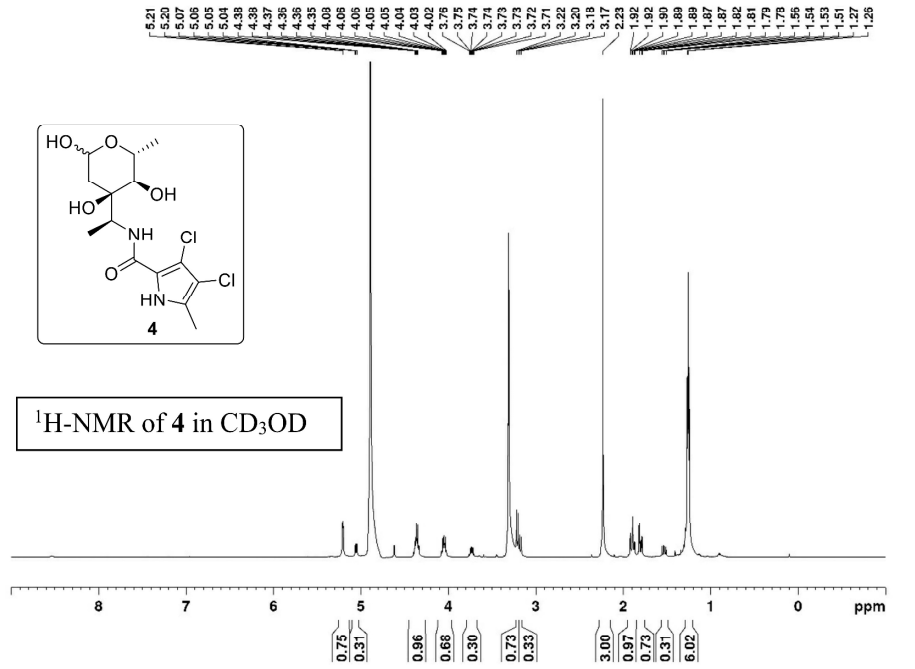

138.7
129.5
129.2
129.0
98.0
75.9
74.5
70.4
66.1
52.6
34.4
18.2
16.4
BnO
O
OH
OH
NH2
6
13C-NMR of 6 in CD3OD
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

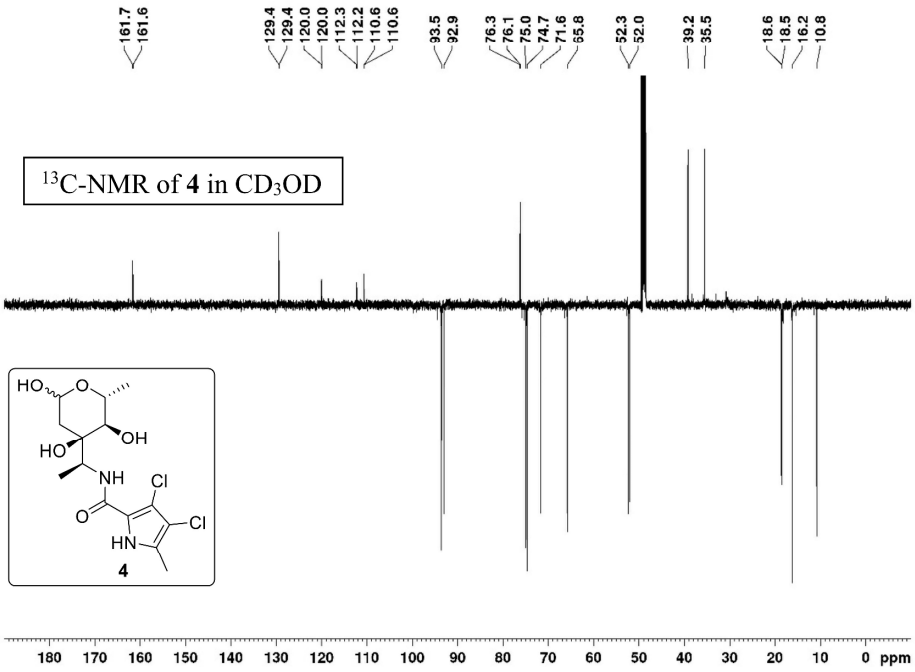

10.92
10.89
7.37
7.35
7.34
7.32
7.31
6.93
6.91
5.04
5.03
4.73
4.71
4.51
4.50
4.49
4.47
4.46
4.45
4.44
4.43
4.16
3.78
3.77
3.76
3.75
3.74
3.72
3.28
3.27
2.46
2.25
2.03
2.00
1.88
1.87
1.85
1.84
1.35
1.33
1.27
1.25
BnO
O
OH
HO
NH
Cl
Cl
O
HN
32
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.98
4.96
0.96
1.00
1.01
1.02
0.96
1.01
1.04
1.03
0.98
3.06
1.05
1.06
2.99
3.18

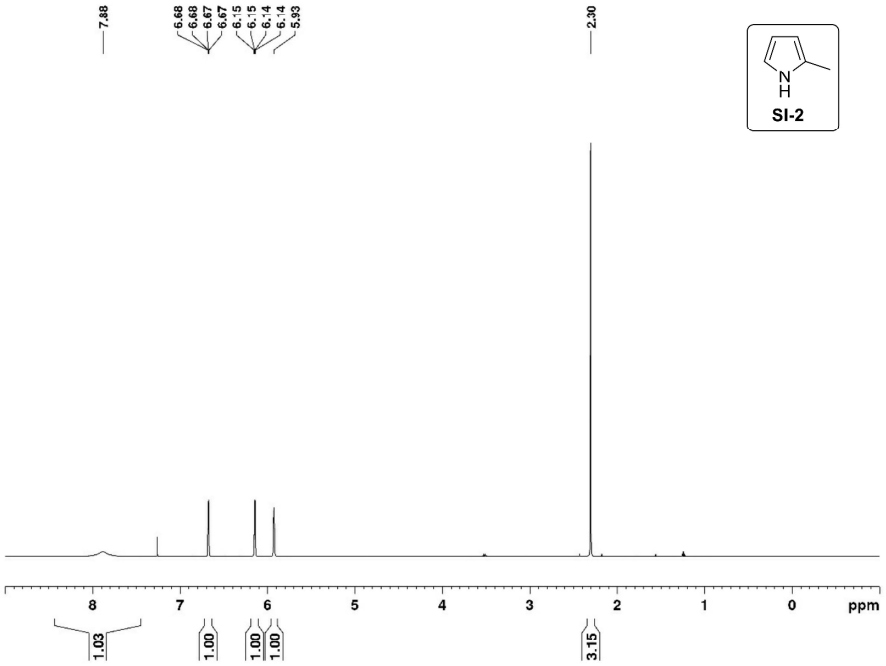

159.6
136.7
128.7
128.5
128.3
128.2
118.5
111.0
110.1
96.3
74.3
73.5
69.6
65.7
50.5
35.2
18.0
16.4
11.2
BnO
HO
OH
NH
Cl
Cl
O
HN
32
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.62
9.56
6.65
6.64
6.21
5.64
5.24
5.23
5.16
5.16
5.15
5.14
4.43
4.42
4.41
4.39
4.38
4.02
4.01
4.01
4.00
3.99
3.99
3.98
3.97
3.72
3.71
3.70
3.69
3.69
3.68
3.68
3.66
3.20
3.18
3.16
2.29
2.28
2.01
2.00
1.98
1.98
1.97
1.97
1.94
1.94
1.72
1.71
1.69
1.68
1.48
HO
OH
HO
NH
Cl
Cl
O
HN
4
^{1}H-NMR of **4** in $CDCl_3$
10 9 8 7 6 5 4 3 2 1 0 ppm
0.83
0.19
1.02
0.72
0.64
0.81
0.19
1.00
0.82
0.19
1.01
6.78
3.01
0.24
0.95
0.87
0.25
6.07

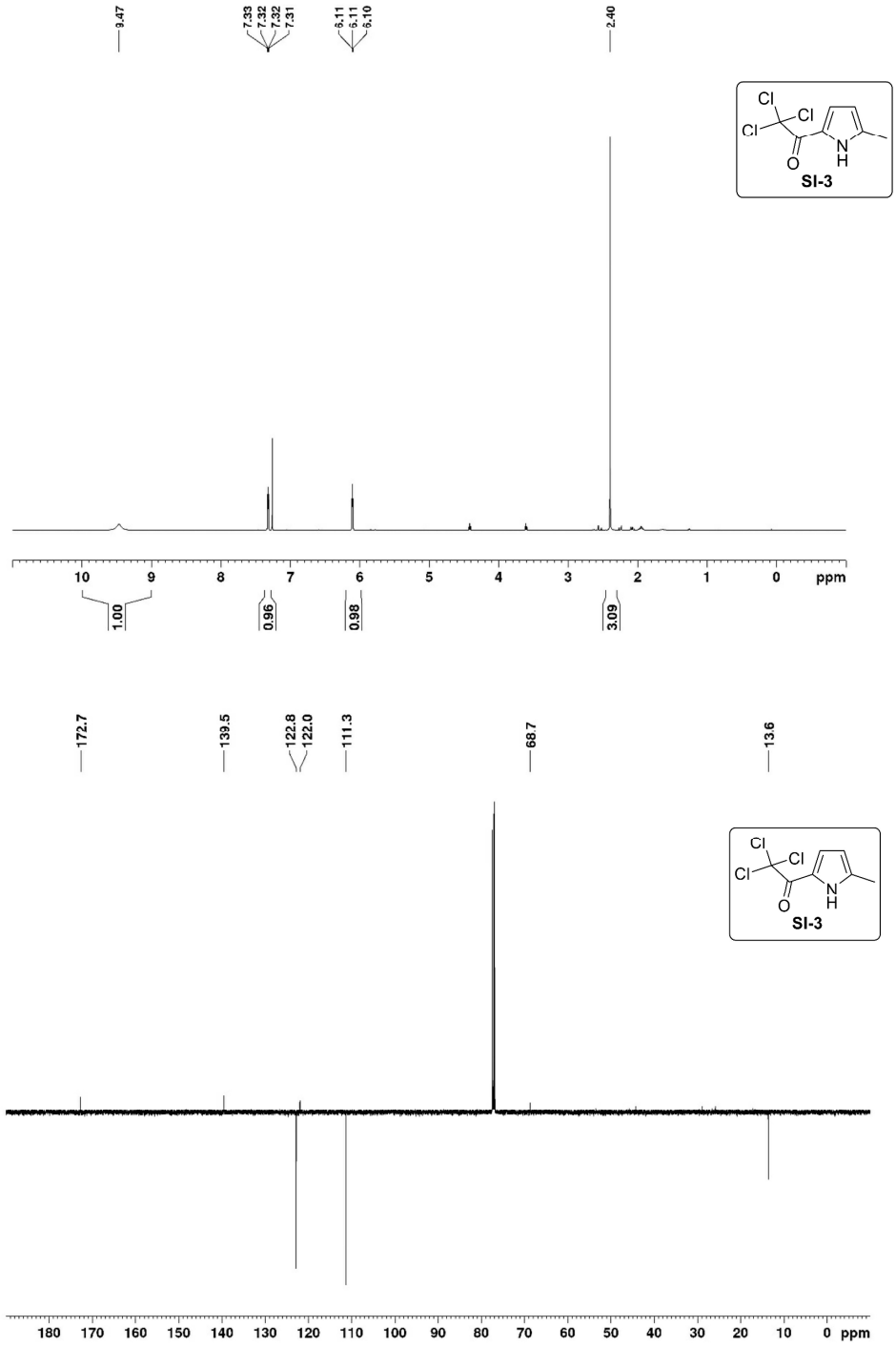

161.7
161.5
129.3
129.1
117.4
117.3
112.6
112.4
111.2
111.1
92.9
92.2
77.2
76.3
74.1
74.0
70.8
64.7
52.6
52.5
37.5
33.6
18.2
18.1
16.3
11.5
11.5
^{13}C-NMR of **4** in $CDCl_3$
HO
O
OH
HO
NH
Cl
Cl
O
HN
4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


5.21
5.20
5.07
5.06
5.05
5.04
4.38
4.37
4.36
4.35
4.08
4.06
4.05
4.04
4.03
4.02
3.76
3.75
3.74
3.73
3.72
3.71
3.22
3.20
3.18
3.17
2.23
1.92
1.92
1.90
1.89
1.89
1.87
1.87
1.82
1.81
1.79
1.78
1.56
1.54
1.53
1.51
1.27
1.25
HO
O
OH
HO
NH
Cl
Cl
O
HN
4
^{1}H-NMR of **4** in CD_3OD
8 7 6 5 4 3 2 1 0 ppm
0.75
0.31
0.96
0.68
0.30
0.73
0.33
3.00
0.97
0.73
0.31
6.02

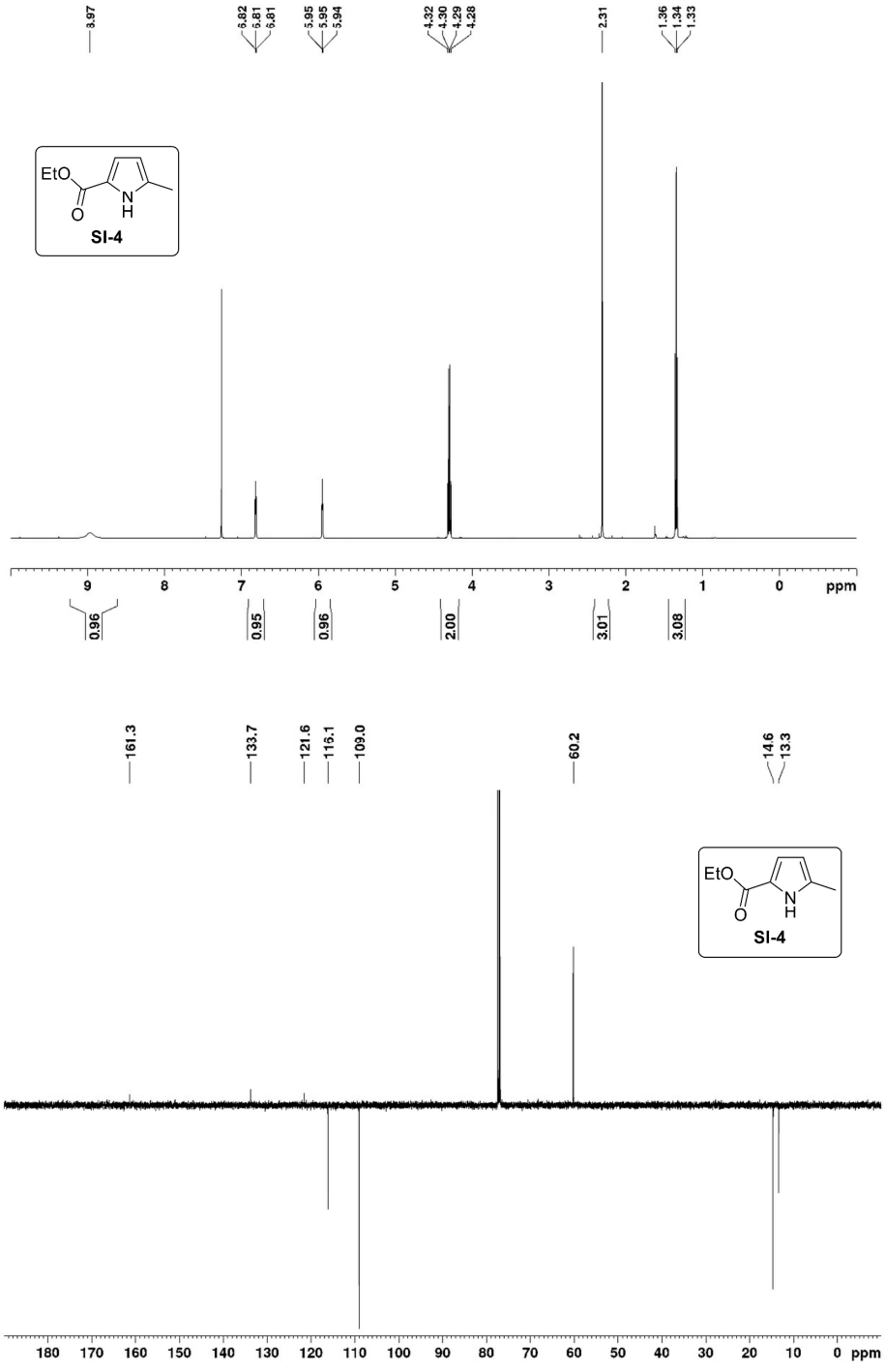

161.7
161.6
129.4
129.4
120.0
120.0
112.3
112.2
110.6
110.6
93.5
92.9
76.3
76.1
75.0
74.7
71.6
65.8
52.3
52.0
39.2
35.5
18.6
18.5
16.2
10.8
^{13}C-NMR of **4** in CD_3OD
HO
O
OH
HO
NH
Cl
O
Cl
HN
4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.88
6.68
6.68
6.67
6.67
6.15
6.15
6.14
6.14
5.93
2.30
N
H
SI-2
8 7 6 5 4 3 2 1 0 ppm
1.03
1.00
1.00
1.00
3.15

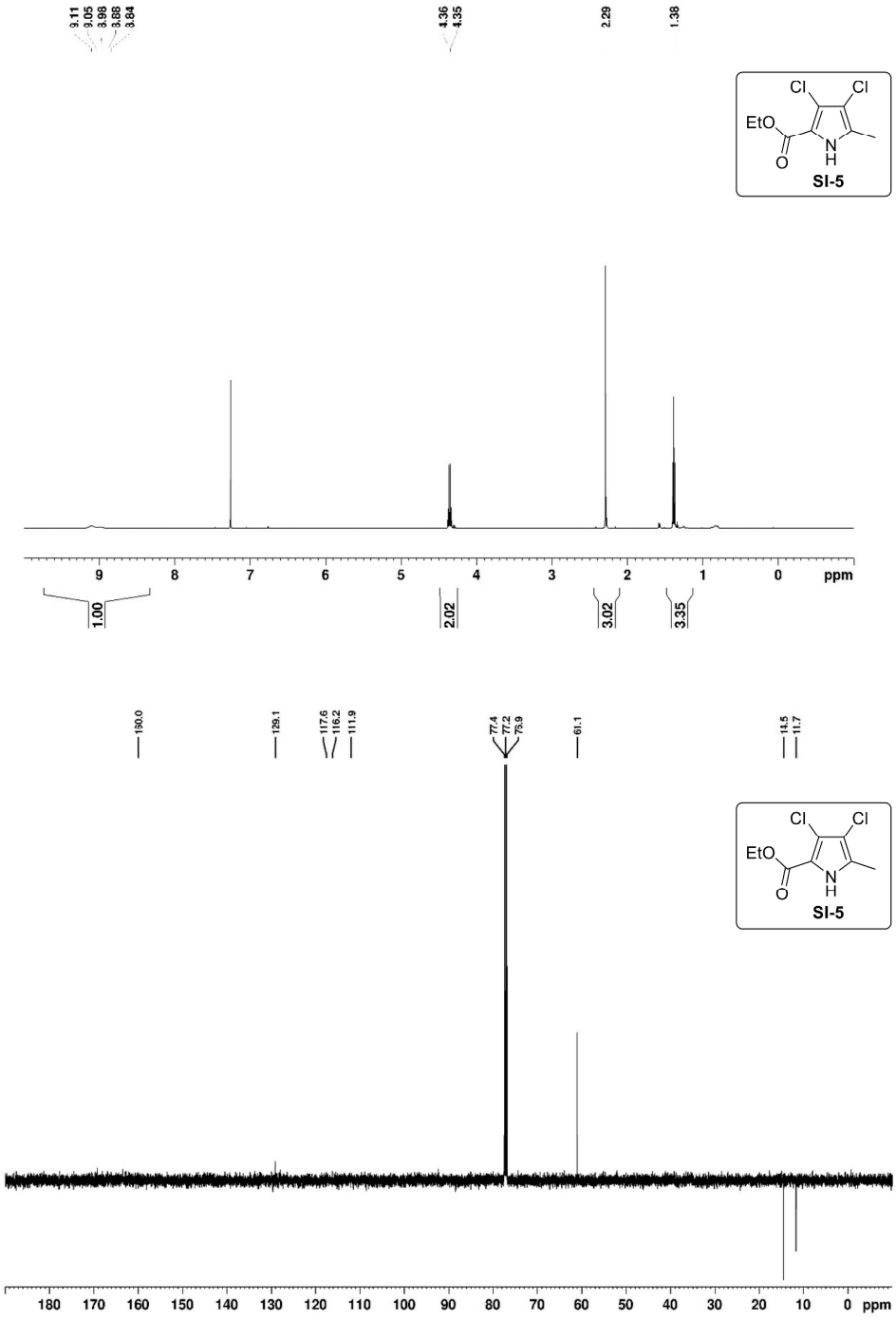
S100

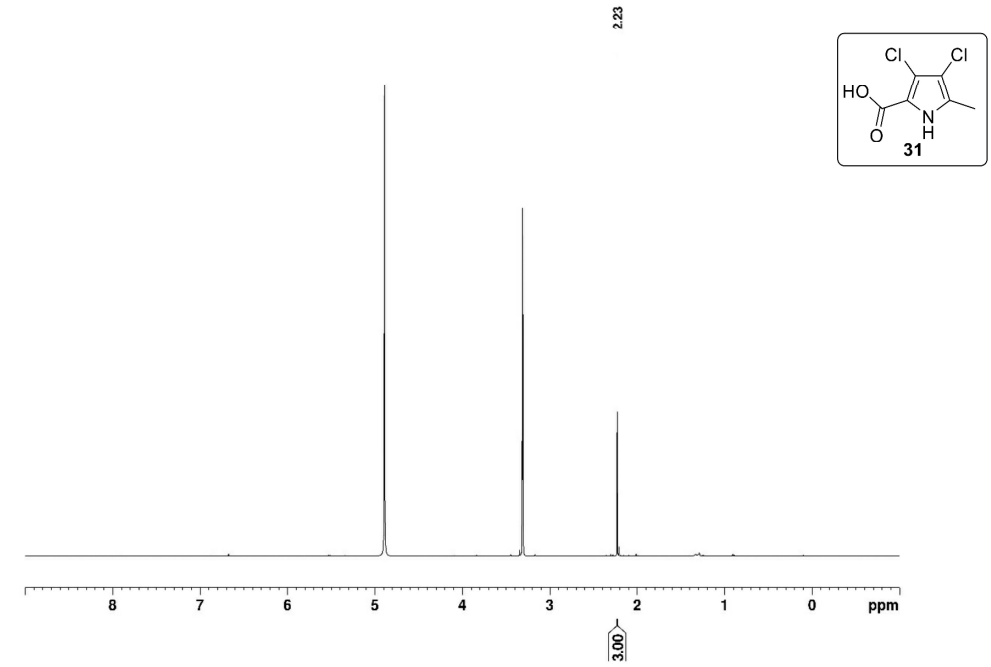

3.47
7.33
7.32
7.32
7.31
6.11
6.11
6.10
2.40
Cl
Cl
Cl
O
N
H
SI-3
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.96
0.98
3.09
172.7
139.5
122.8
122.0
111.3
68.7
13.6
Cl
Cl
Cl
O
N
H
SI-3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

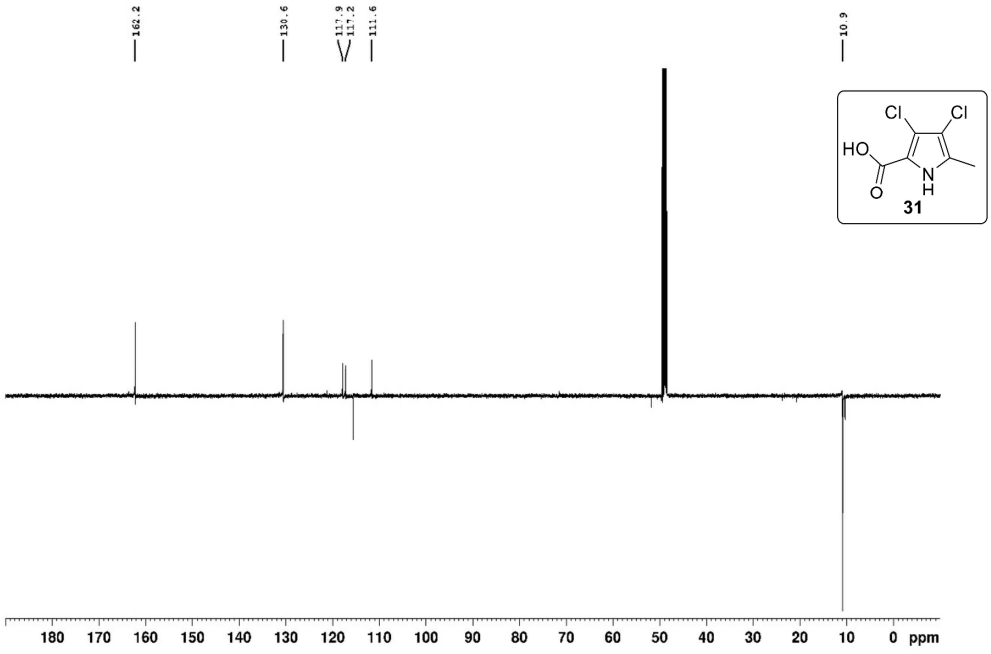
S101

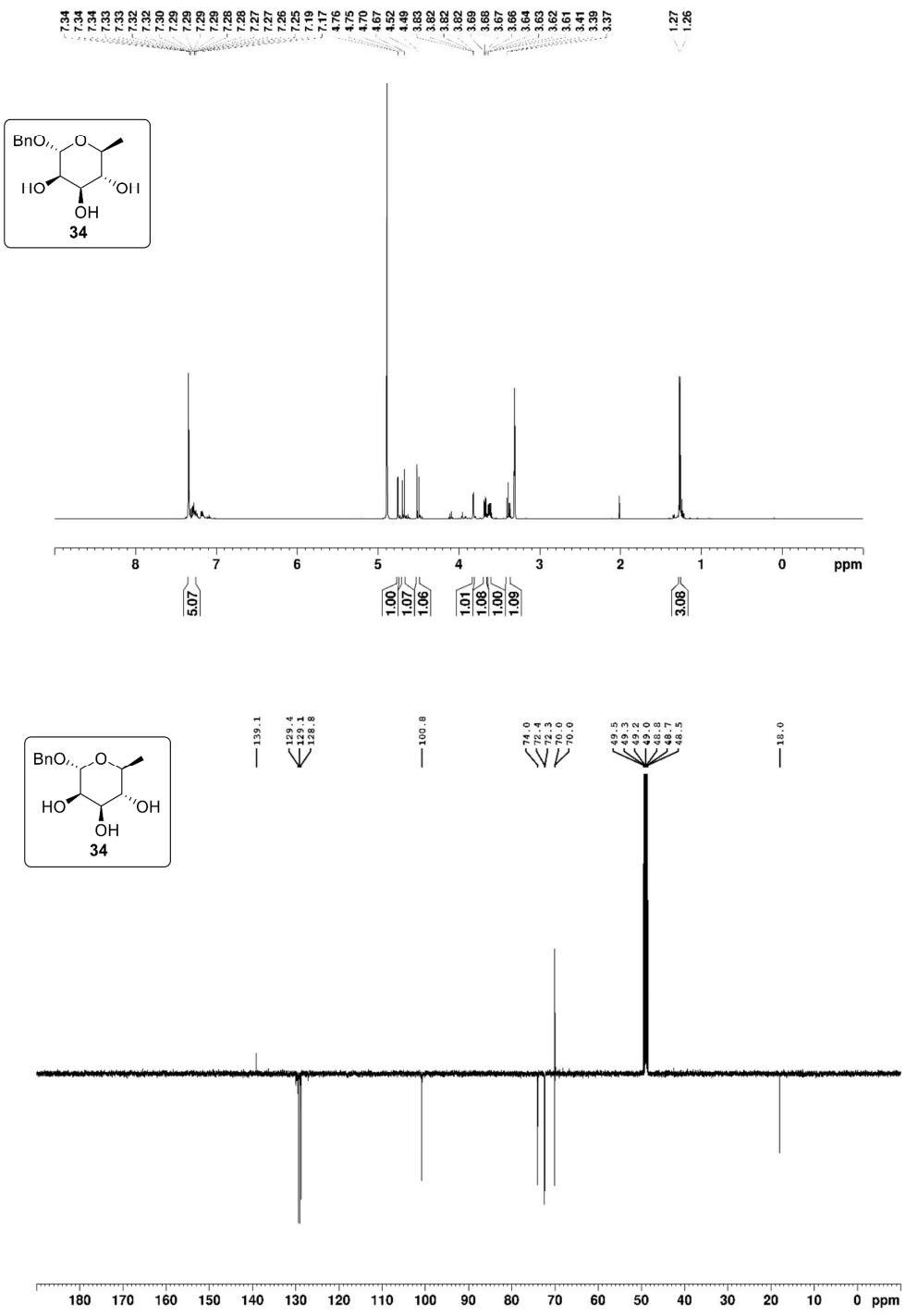

3.97
5.82
5.81
5.81
5.95
5.95
5.94
4.32
4.30
4.29
4.28
2.31
1.36
1.34
1.33
EtO
O
N
H
SI-4
9
8
7
6
5
4
3
2
1
0
ppm
0.96
0.95
0.96
2.00
3.01
3.08
161.3
133.7
121.6
116.1
109.0
60.2
14.6
13.3
EtO
O
N
H
SI-4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

S102

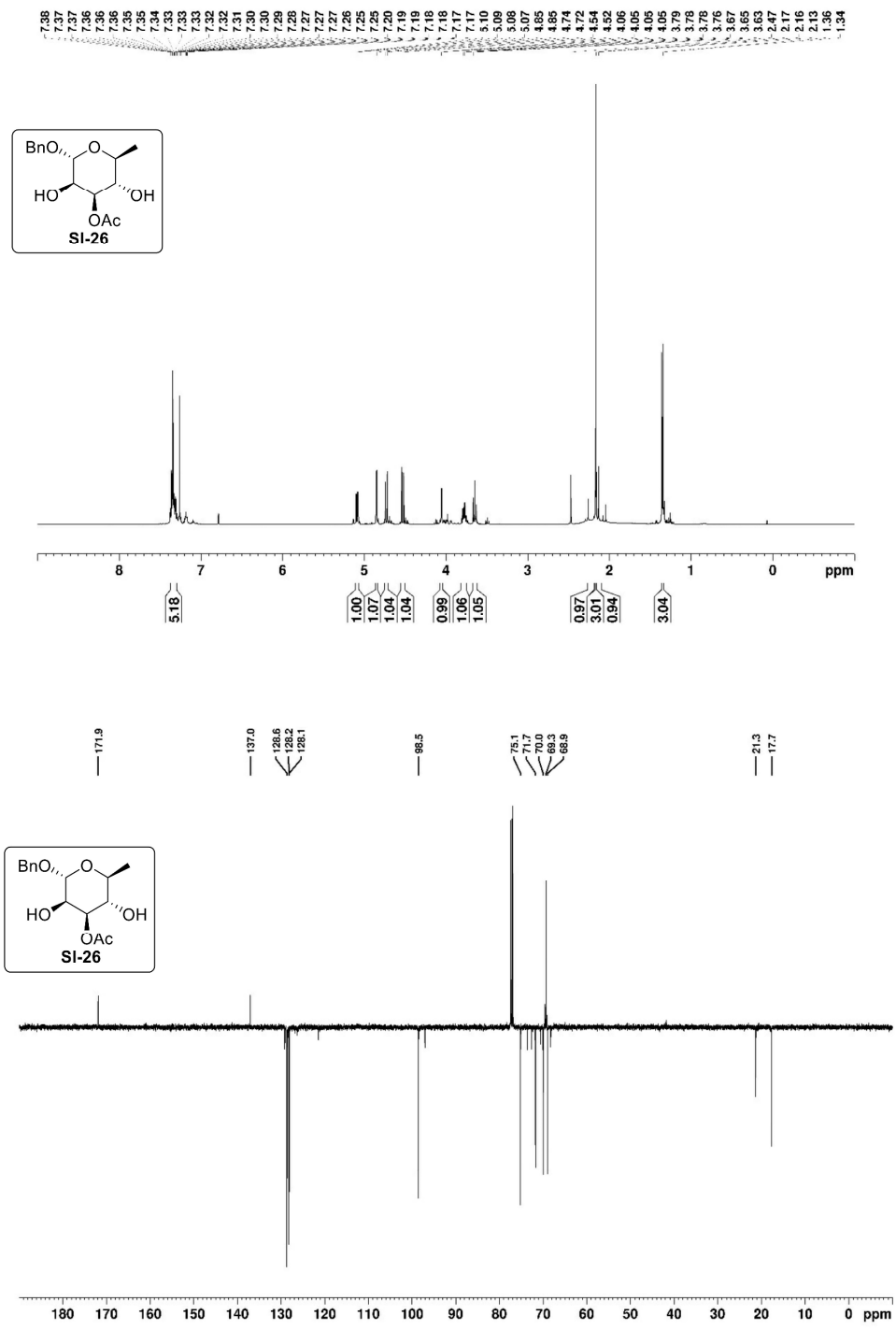

9.11
9.05
8.98
8.88
8.84
4.36
4.35
2.29
1.38
Cl
Cl
EtO
O
N
H
SI-5
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.02
3.02
3.35
160.0
129.1
117.6
116.2
111.9
77.4
77.2
76.9
61.1
14.5
11.7
Cl
Cl
EtO
O
N
H
SI-5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

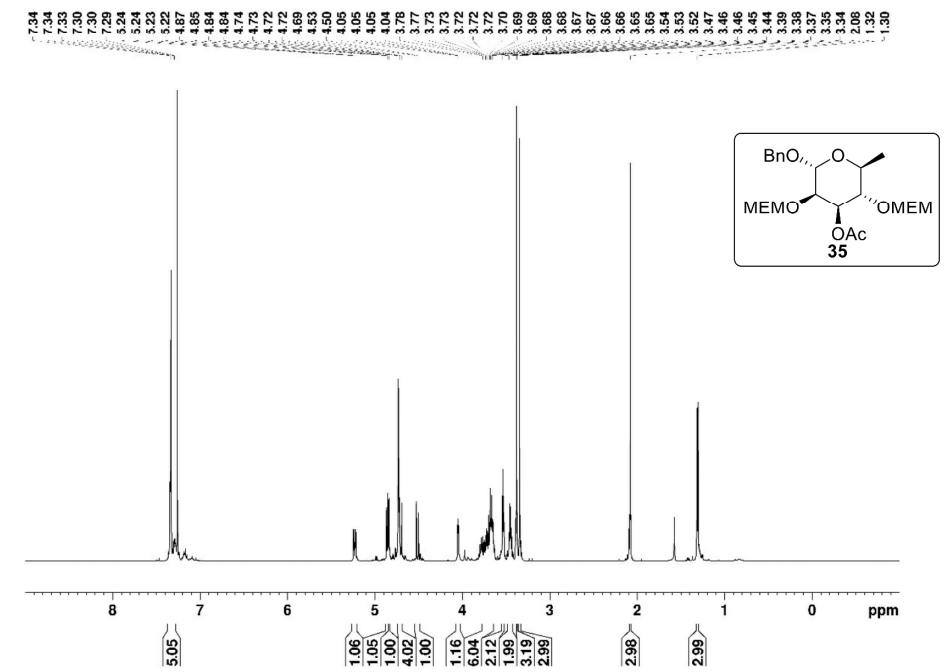

2.23
Cl
Cl
HO
O
N
H
31
8
7
6
5
4
3
2
1
0
ppm
3.00

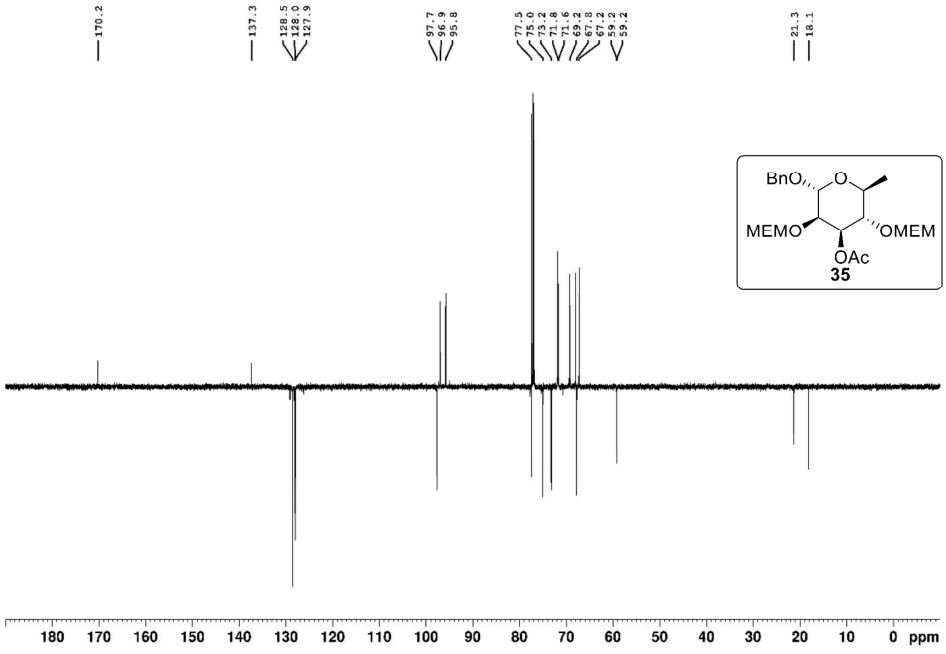

162.2
130.6
117.9
117.2
111.6
10.9
Cl
Cl
HO
O
N
H
31
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

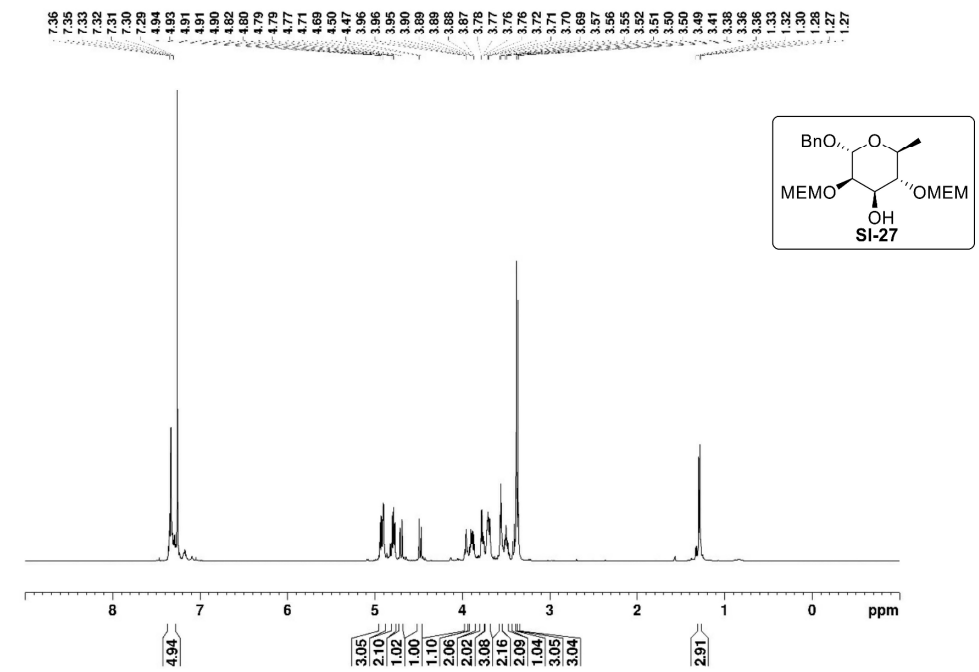

7.34
7.34
7.34
7.33
7.33
7.32
7.32
7.30
7.29
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.25
7.19
7.17
4.76
4.75
4.70
4.67
4.52
4.49
3.83
3.82
3.82
3.82
3.69
3.68
3.67
3.66
3.64
3.63
3.62
3.61
3.41
3.39
3.37
1.27
1.26
BnO
O
HO
OH
OH
34
8
7
6
5
4
3
2
1
0
ppm
5.07
1.00
1.07
1.06
1.01
1.08
1.00
1.09
3.08
139.1
129.4
129.1
128.8
100.8
74.0
72.4
72.3
70.0
70.0
49.5
49.3
49.2
49.0
48.8
48.7
48.5
18.0
BnO
O
HO
OH
OH
34
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

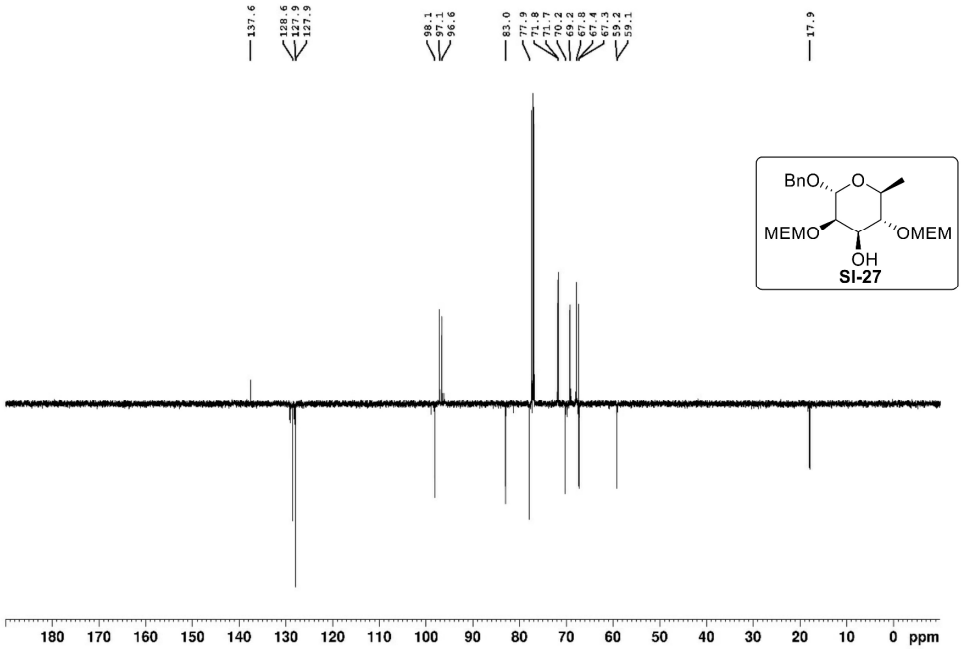
S105

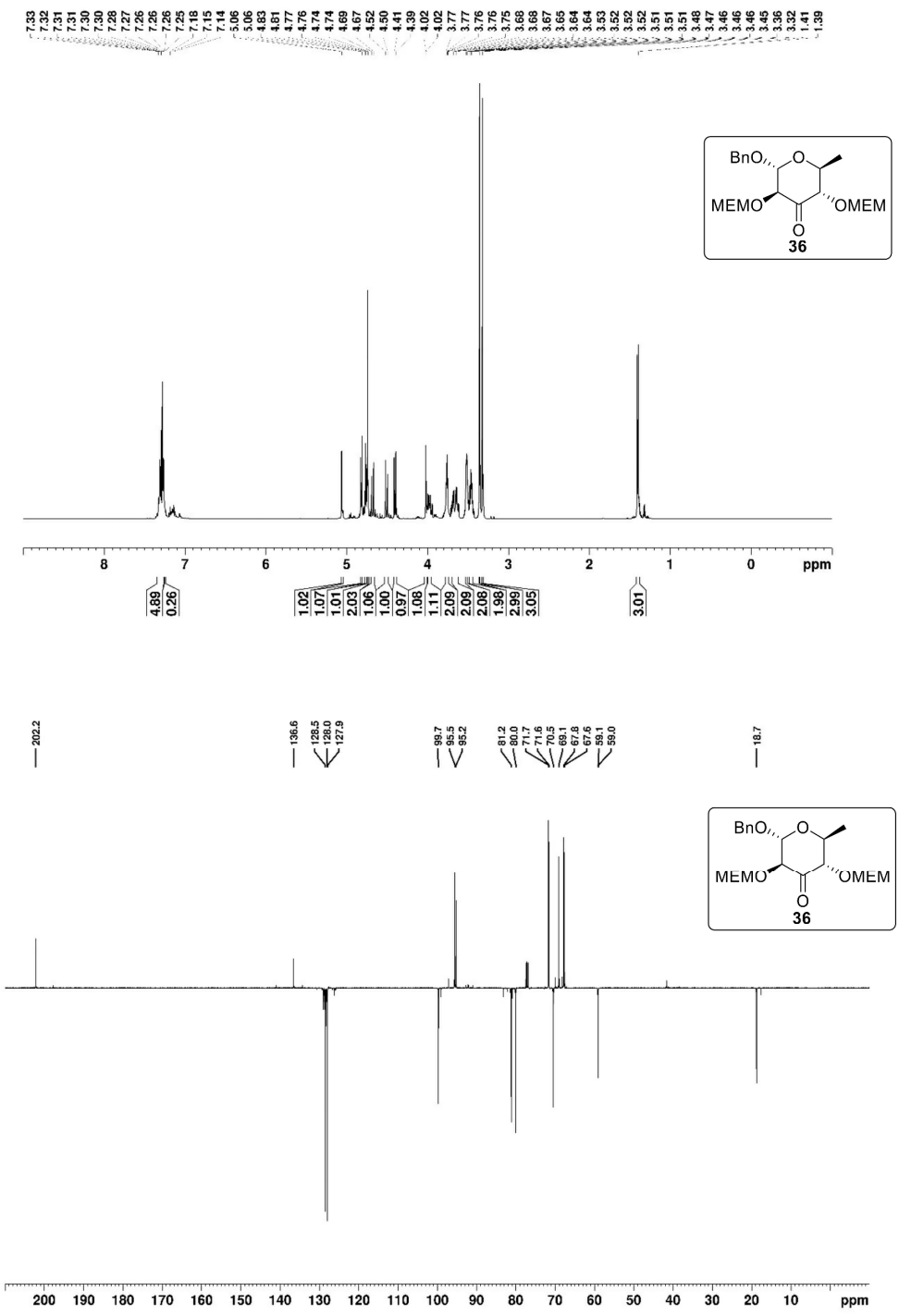

BnO
O
HO
OH
OAc
SI-26
ppm
5.18
1.00
1.07
1.04
1.04
0.99
1.06
1.05
0.97
3.01
0.94
3.04
171.9
137.0
128.6
128.2
128.1
98.5
75.1
71.7
70.0
69.3
68.9
21.3
17.7

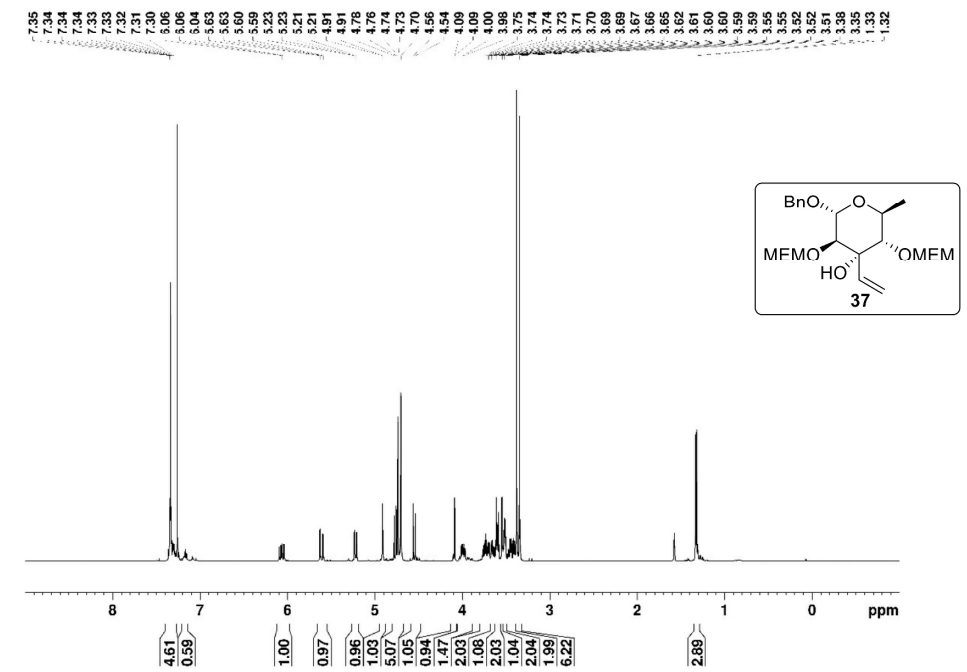

BnO
O
MEMO
OMEM
OAc
35
ppm

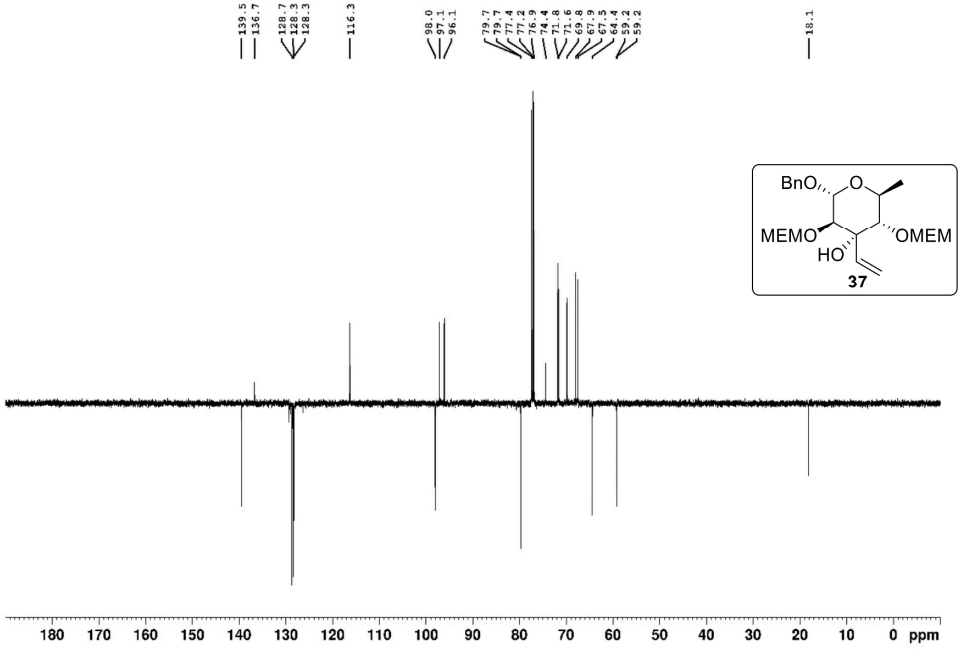

BnO
O
MEMO
OMEM
OAc
35
ppm

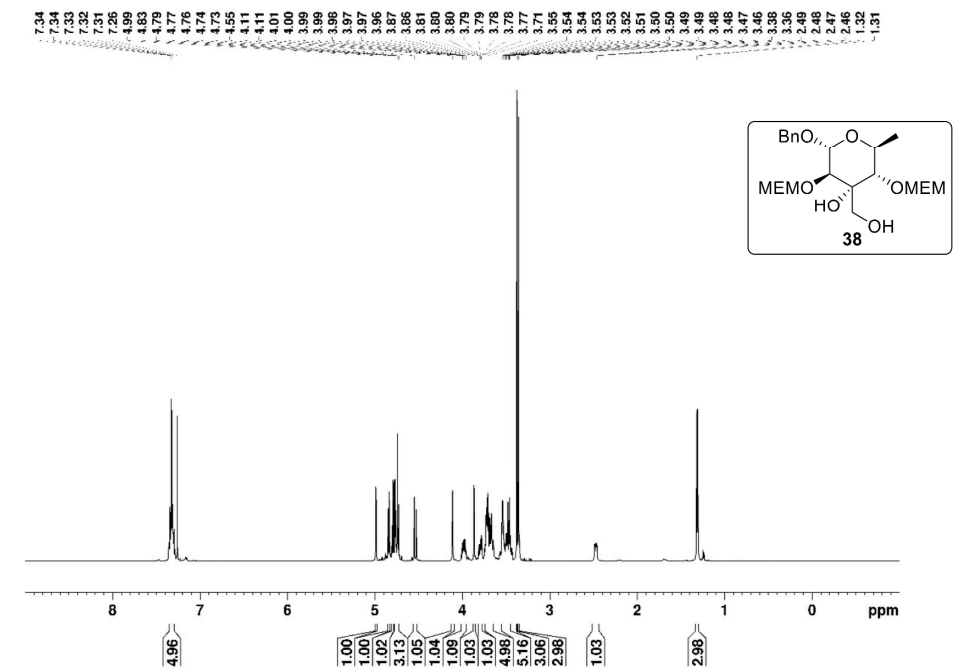

BnO
O
MEMO
OMEM
OH
SI-27
ppm

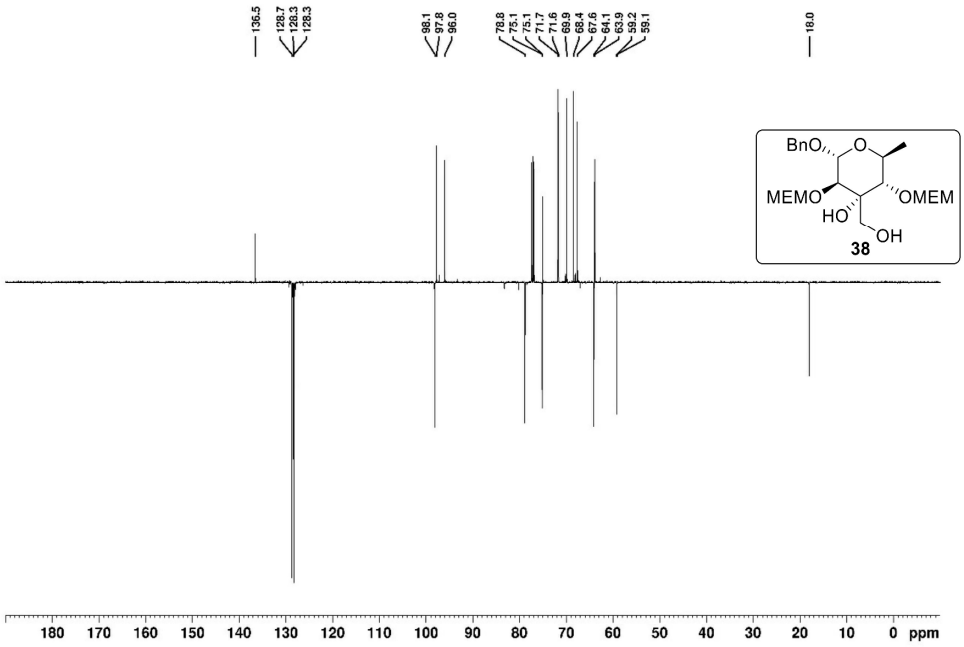

BnO
O
MEMO
OMEM
OH
SI-27
ppm

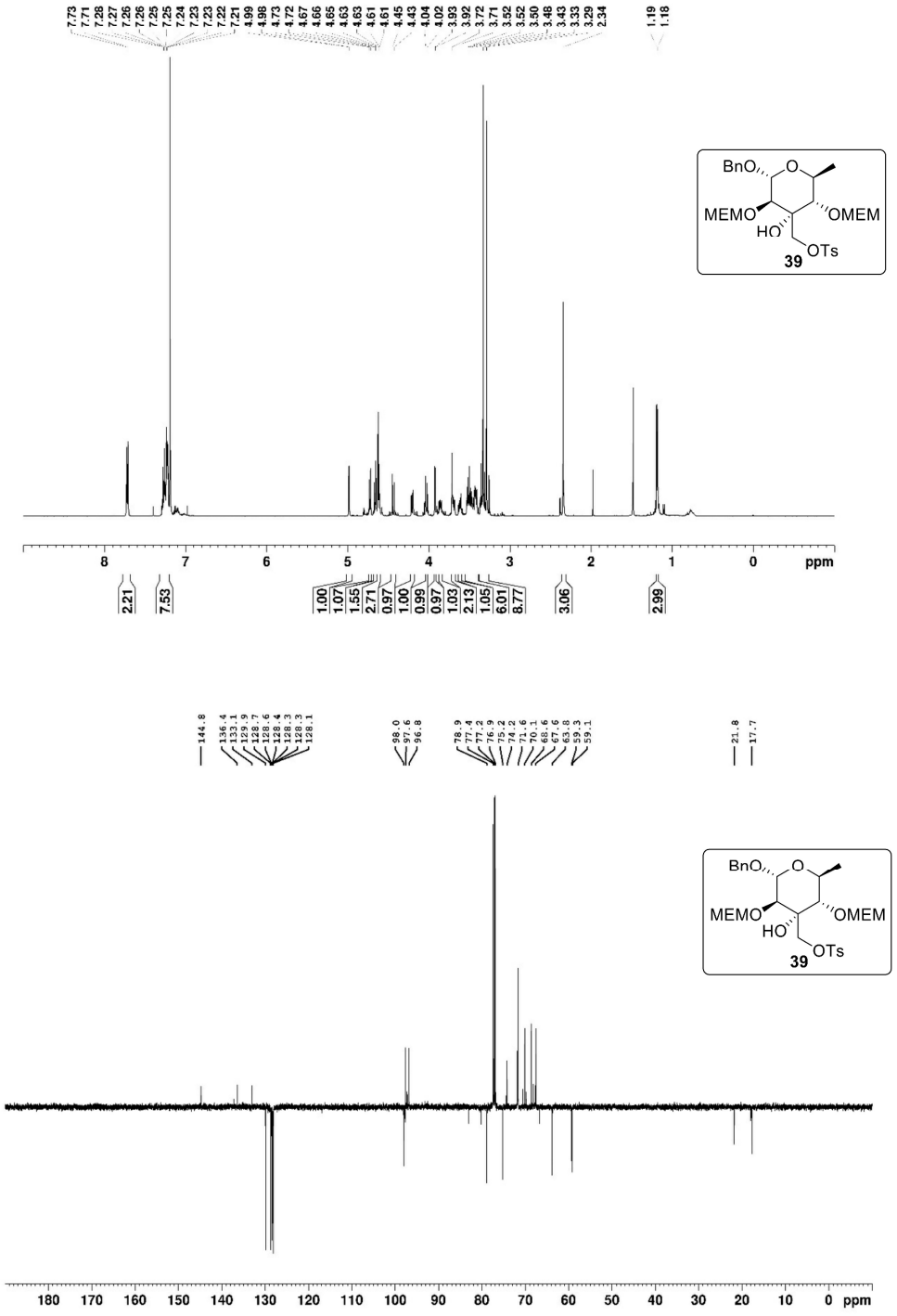

BnO
MEMO
OMEM
O
36
ppm
202.2
136.6
128.5
128.0
127.9
99.7
95.5
95.2
81.2
80.0
71.7
71.6
70.5
69.1
67.8
67.6
59.1
59.0
18.7

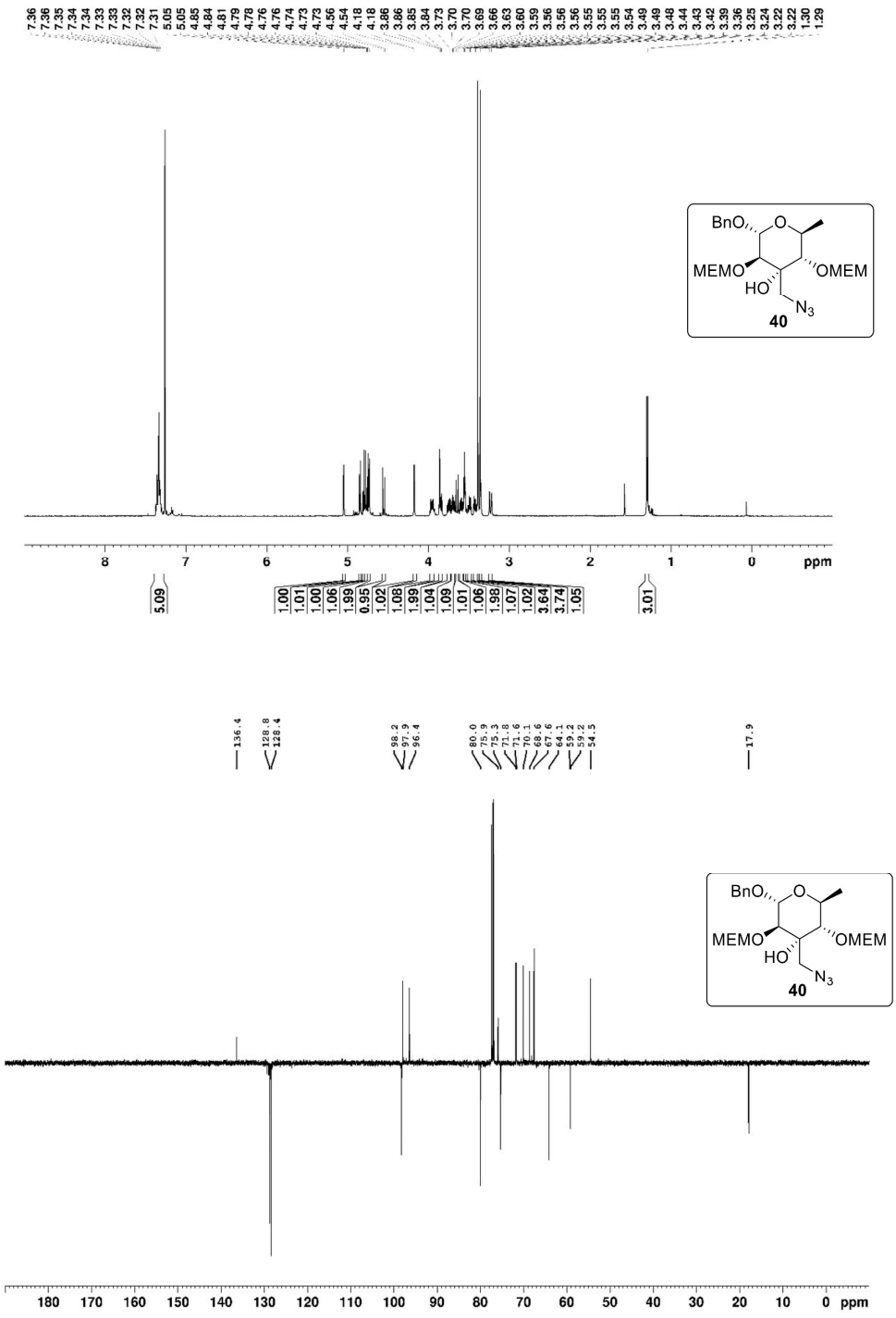

BnO
MEMO
HO
OMEM
37
ppm

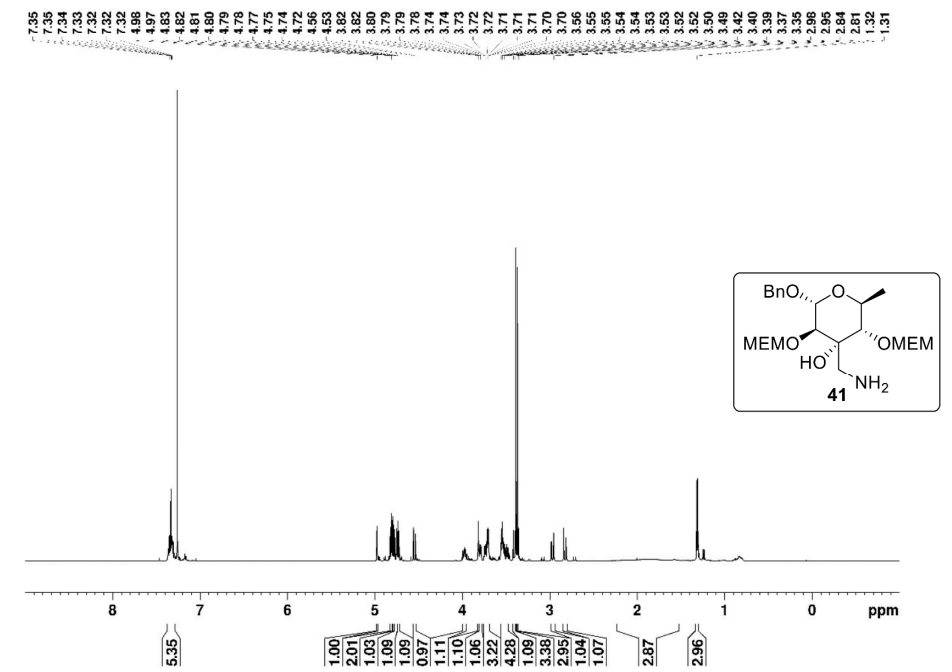

BnO
MEMO
HO
OMEM
37
ppm

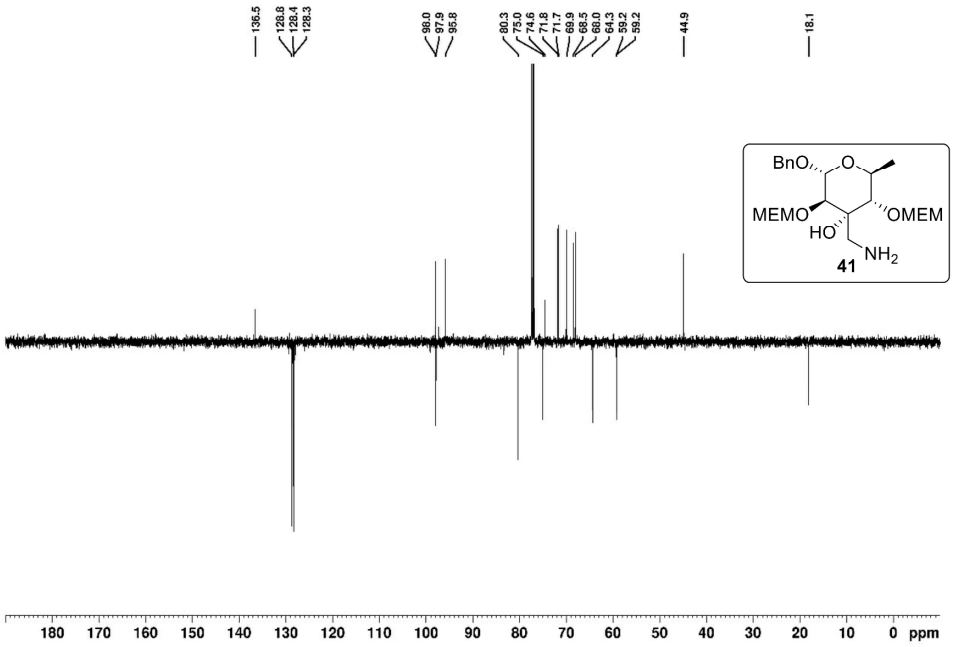

BnO
O
MEMO
OMEM
HO
OH
38
ppm

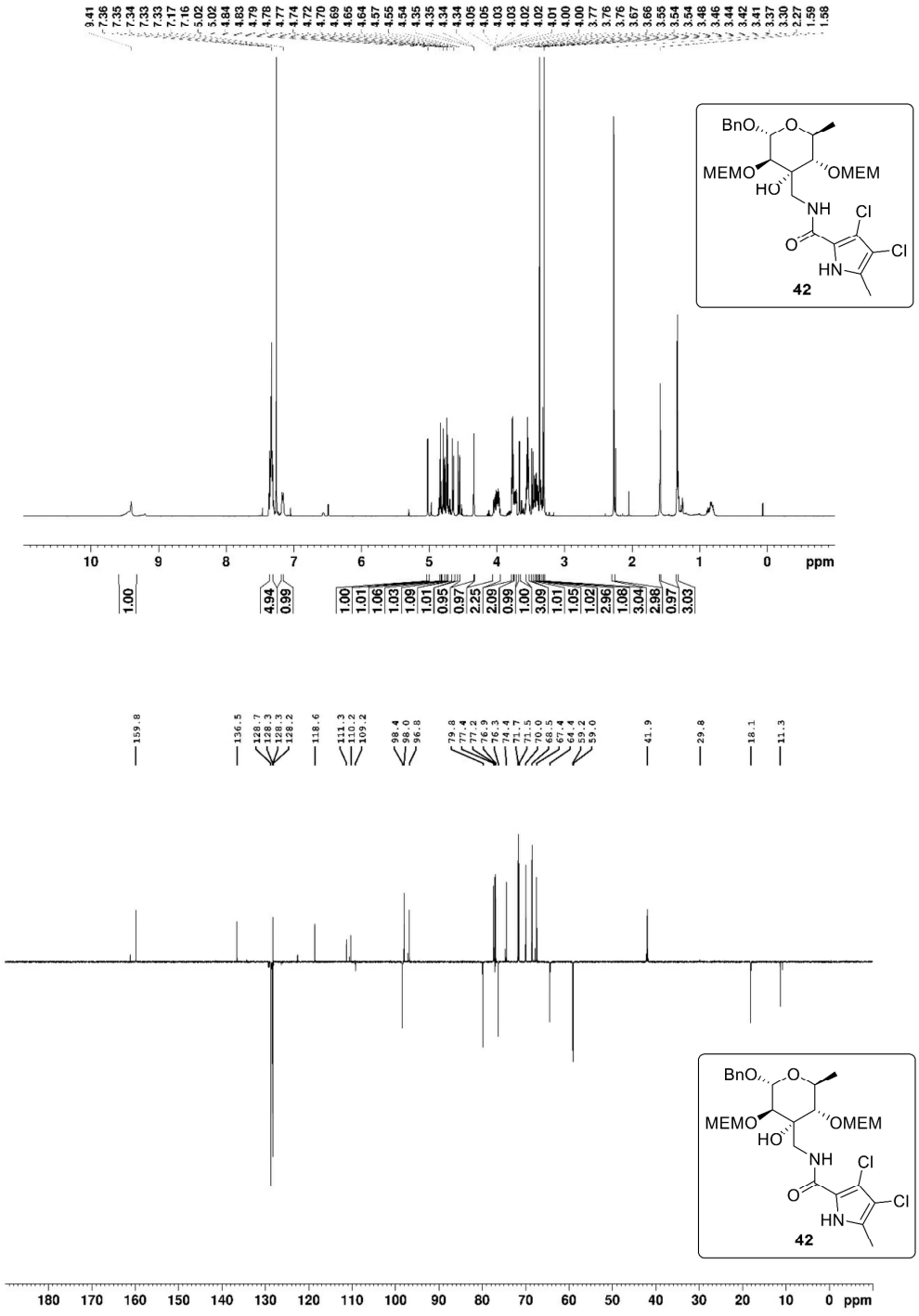

BnO
O
MEMO
OMEM
HO
OH
38
ppm

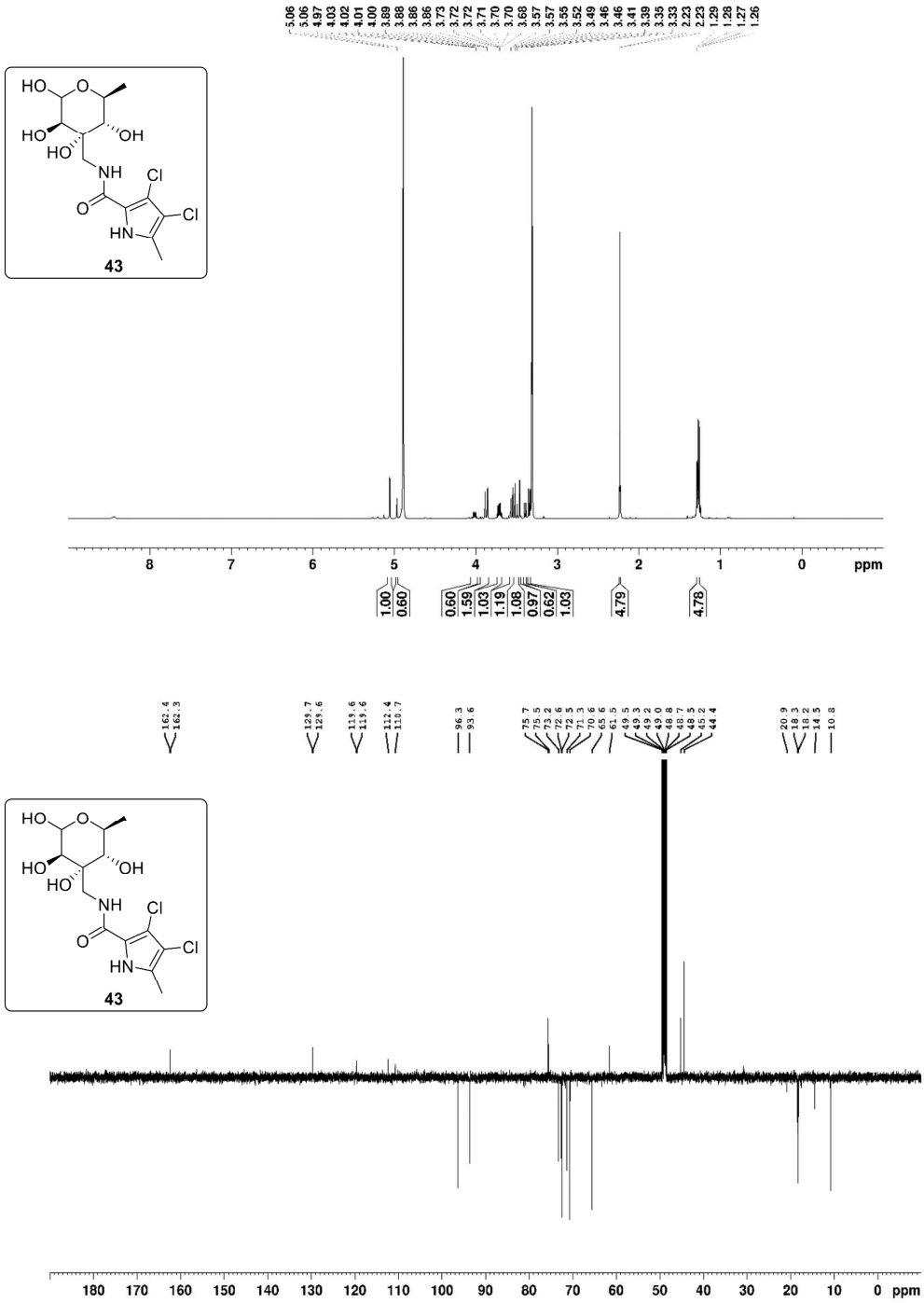

BnO
MEMO
HO
OMEM
OTs
39
ppm

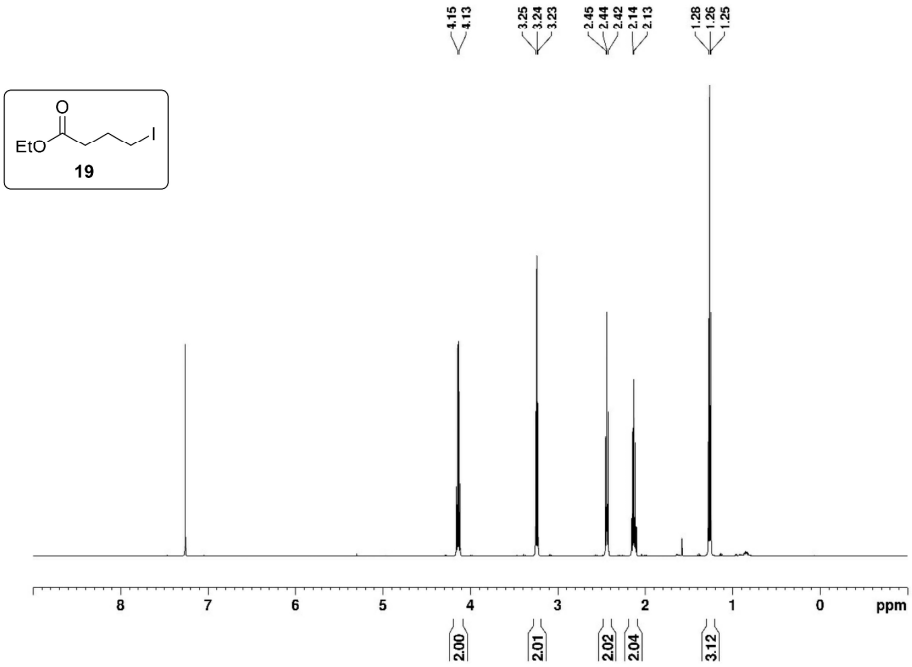

BnO
O
MEMO
OMEM
HO
N3
40
ppm
BnO
O
MEMO
OMEM
HO
N3
40
ppm

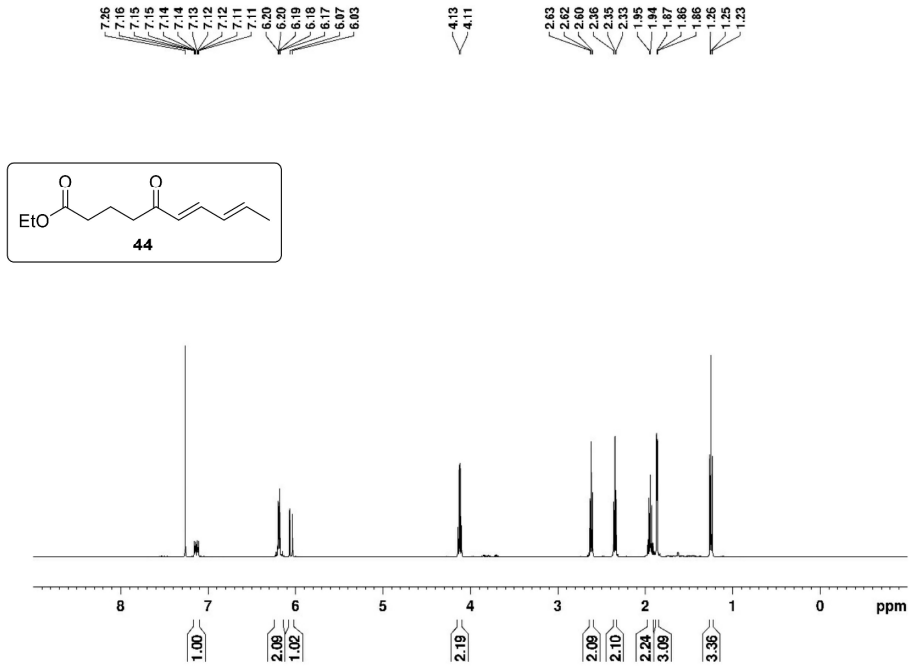

BnO
MEMO
HO
OMEM
NH2
41
ppm

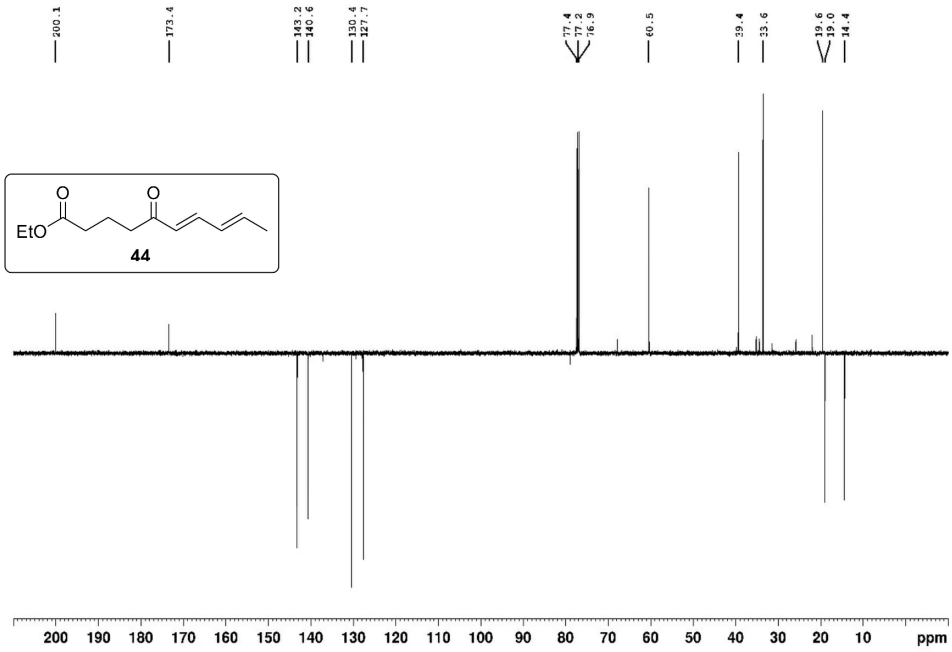

BnO
MEMO
HO
OMEM
NH2
41
ppm

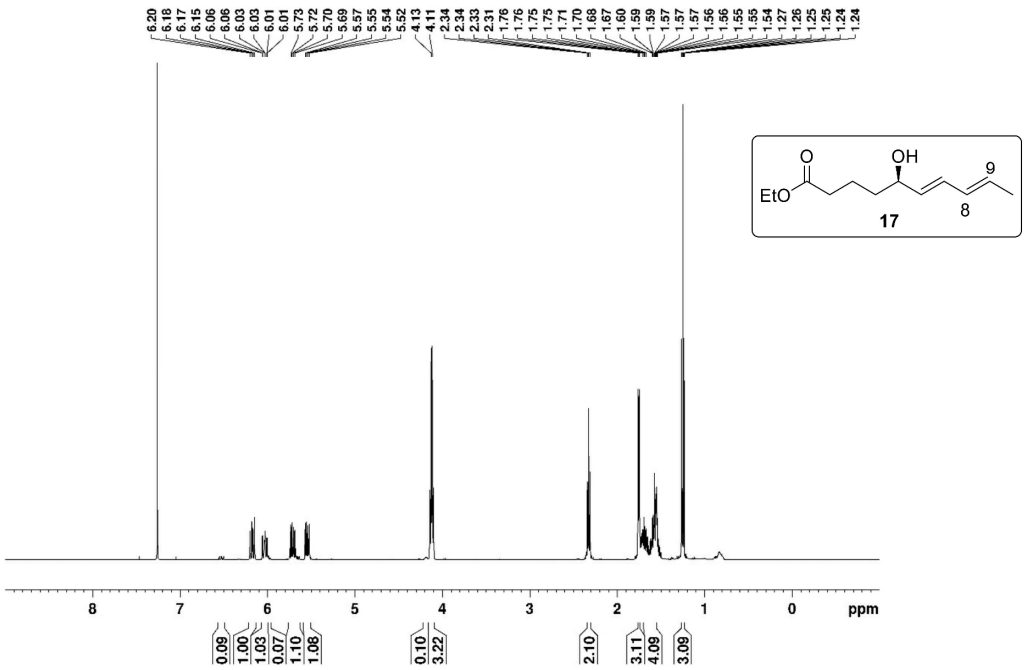

BnO
O
MEMO
OMEM
HO
NH
Cl
O
Cl
HN
42
ppm
BnO
O
MEMO
OMEM
HO
NH
Cl
O
Cl
HN
42
ppm

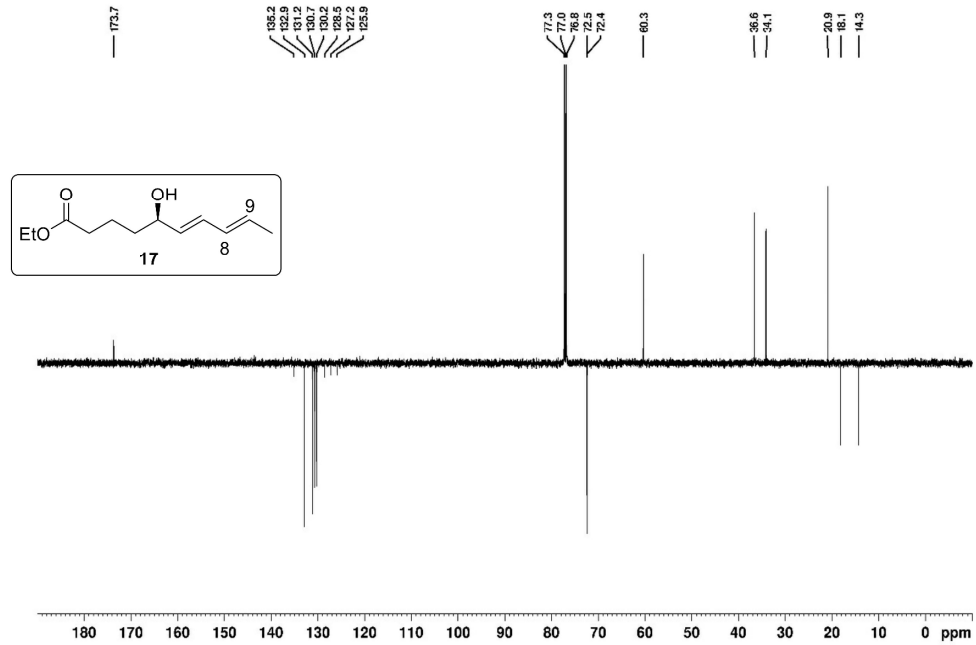

43
ppm
43
ppm

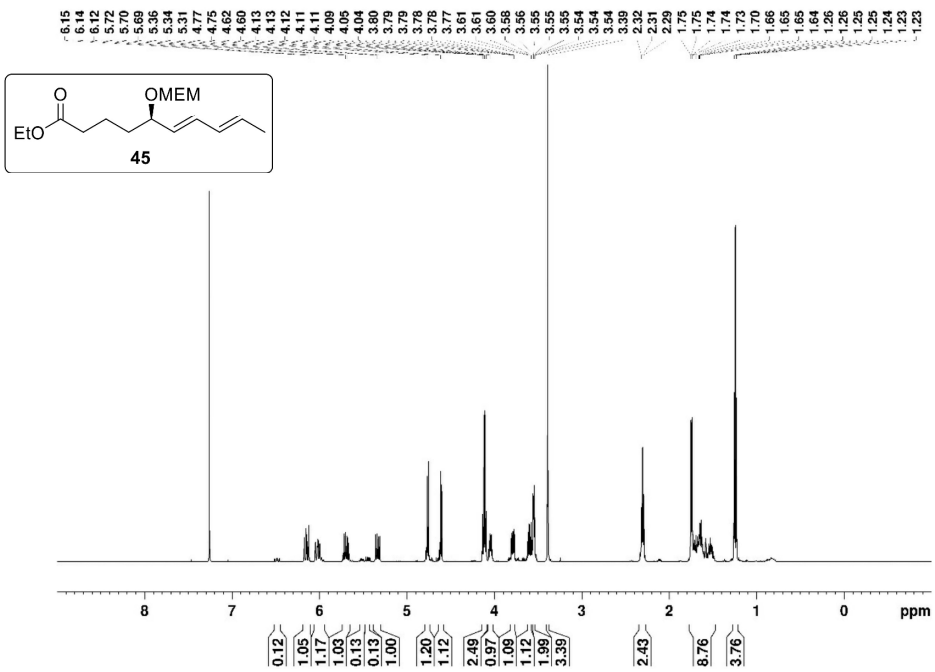

4.15
4.13
3.25
3.24
3.23
2.45
2.44
2.42
2.14
2.13
1.28
1.26
1.25
O
EtO
I
19
8
7
6
5
4
3
2
1
0
ppm
2.00
2.01
2.02
2.04
3.12

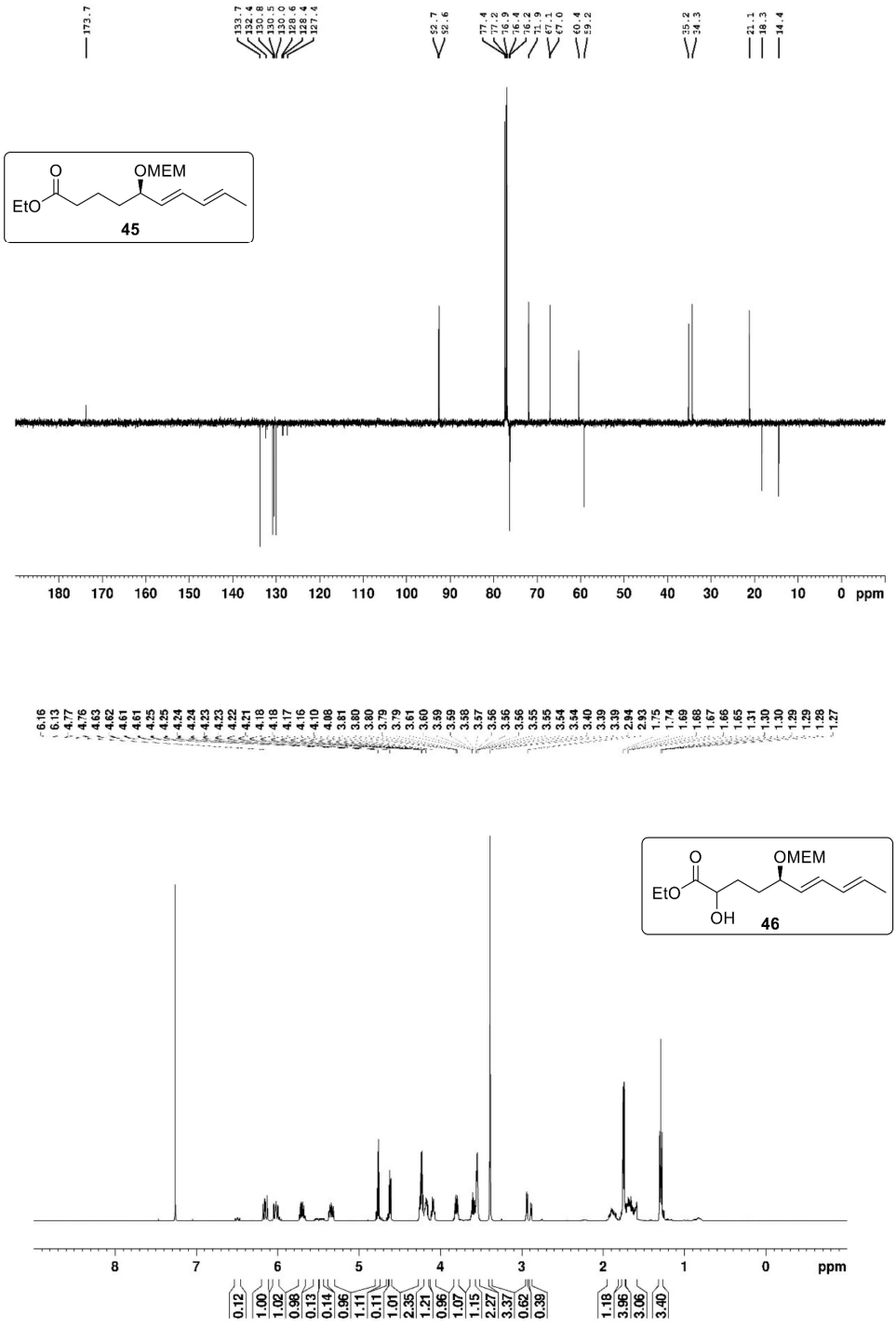

7.26
7.16
7.15
7.15
7.14
7.14
7.13
7.12
7.12
7.11
7.11
6.20
6.20
6.19
6.18
6.17
6.07
6.03
4.13
4.11
2.63
2.62
2.60
2.36
2.35
2.33
1.95
1.94
1.87
1.86
1.86
1.26
1.25
1.23
O
O
EtO
44
8
7
6
5
4
3
2
1
0
ppm
1.00
2.09
1.02
2.19
2.09
2.10
2.24
3.09
3.36


200.1
173.4
143.2
140.6
130.4
127.7
77.4
77.2
76.9
60.5
39.4
33.6
19.6
19.0
14.4
O
O
EtO
44
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

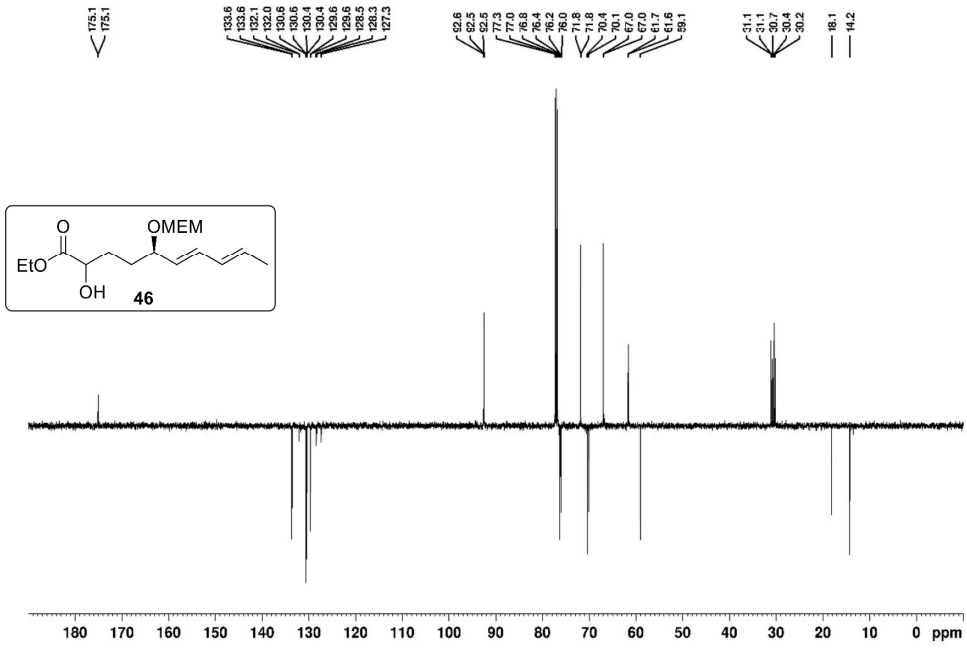

6.20
6.18
6.17
6.15
6.06
6.06
6.03
6.03
6.01
6.01
5.73
5.72
5.70
5.69
5.57
5.55
5.54
5.52
4.13
4.11
2.34
2.34
2.33
2.31
1.76
1.76
1.75
1.75
1.71
1.70
1.68
1.67
1.60
1.59
1.59
1.57
1.57
1.57
1.56
1.56
1.55
1.55
1.54
1.27
1.26
1.25
1.25
1.24
1.24
O
OH
EtO
9
8
17
8 7 6 5 4 3 2 1 0 ppm
0.09
1.00
1.03
0.07
1.10
1.08
0.10
3.22
2.10
3.11
4.09
3.09

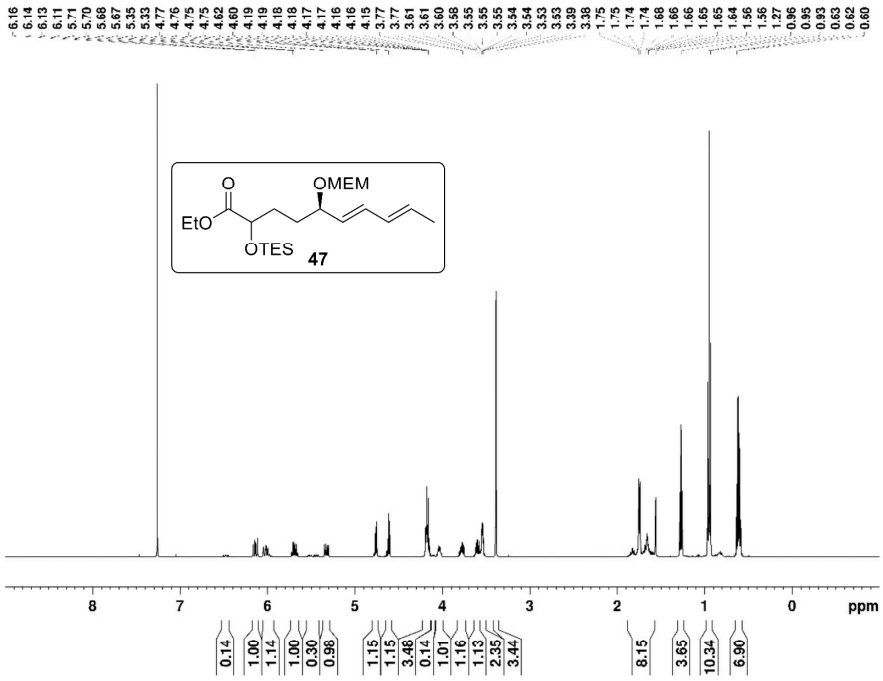

173.7
135.2
132.9
131.2
130.7
130.2
128.5
127.2
125.9
77.3
77.0
76.8
72.5
72.4
60.3
36.6
34.1
20.9
18.1
14.3
O
OH
9
EtO
8
17
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

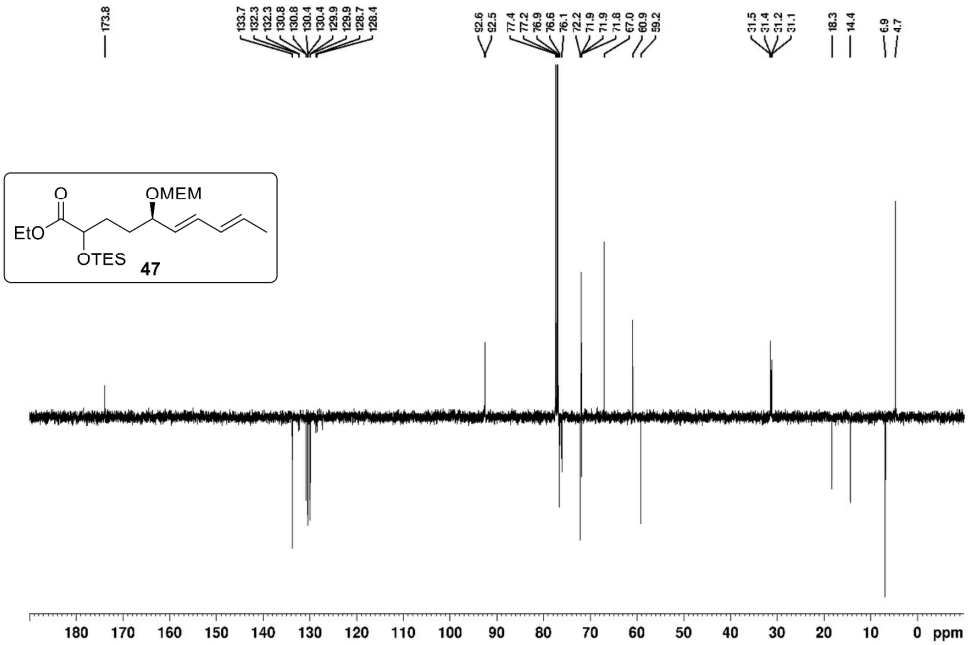

O
OMEM
EtO
45
8 7 6 5 4 3 2 1 0 ppm
0.12
1.05
1.17
1.03
0.13
1.00
1.20
1.12
2.49
0.97
1.09
1.12
1.99
3.39
2.43
8.76
3.76

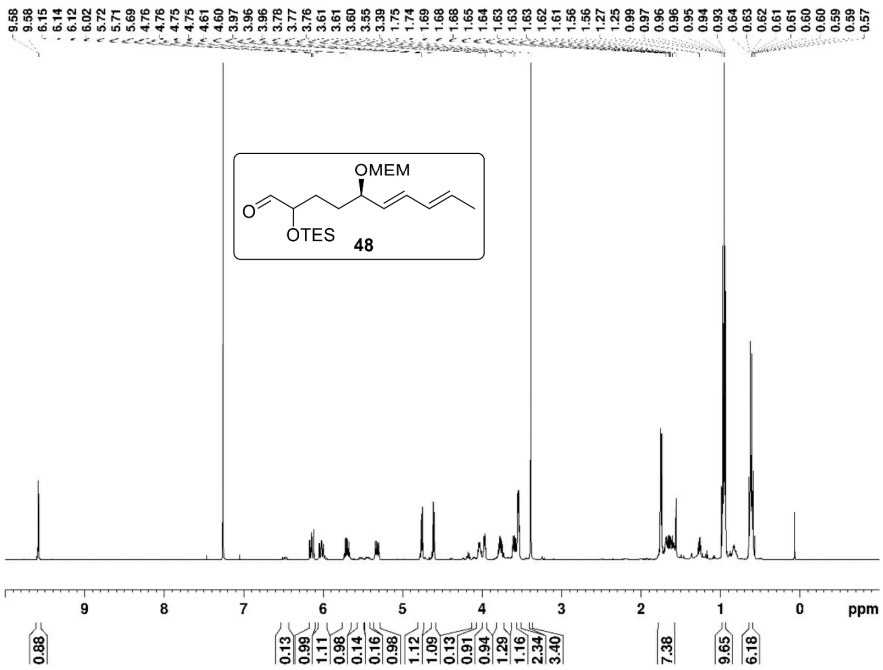

173.7
133.7
132.4
130.8
130.5
130.0
128.6
128.4
127.4
52.7
52.6
77.4
77.2
76.9
16.4
16.2
11.9
67.1
67.0
60.4
59.2
35.2
34.3
21.1
18.3
14.4
O
OMEM
EtO
45
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
6.16
6.13
4.77
4.76
4.63
4.62
4.61
4.61
4.25
4.25
4.24
4.24
4.24
4.23
4.23
4.22
4.21
4.18
4.18
4.17
4.16
4.10
4.08
3.81
3.80
3.80
3.79
3.79
3.61
3.60
3.59
3.59
3.58
3.57
3.56
3.56
3.56
3.55
3.55
3.54
3.40
3.39
3.39
2.94
2.93
1.75
1.74
1.69
1.68
1.67
1.66
1.65
1.31
1.30
1.30
1.29
1.29
1.28
1.27
O
OMEM
EtO
OH
46
8 7 6 5 4 3 2 1 0 ppm
0.12
1.00
1.02
0.98
0.13
0.14
0.96
1.11
0.11
1.01
2.35
1.21
0.96
1.07
1.15
2.27
3.37
0.62
0.38
1.18
3.96
3.06
3.40

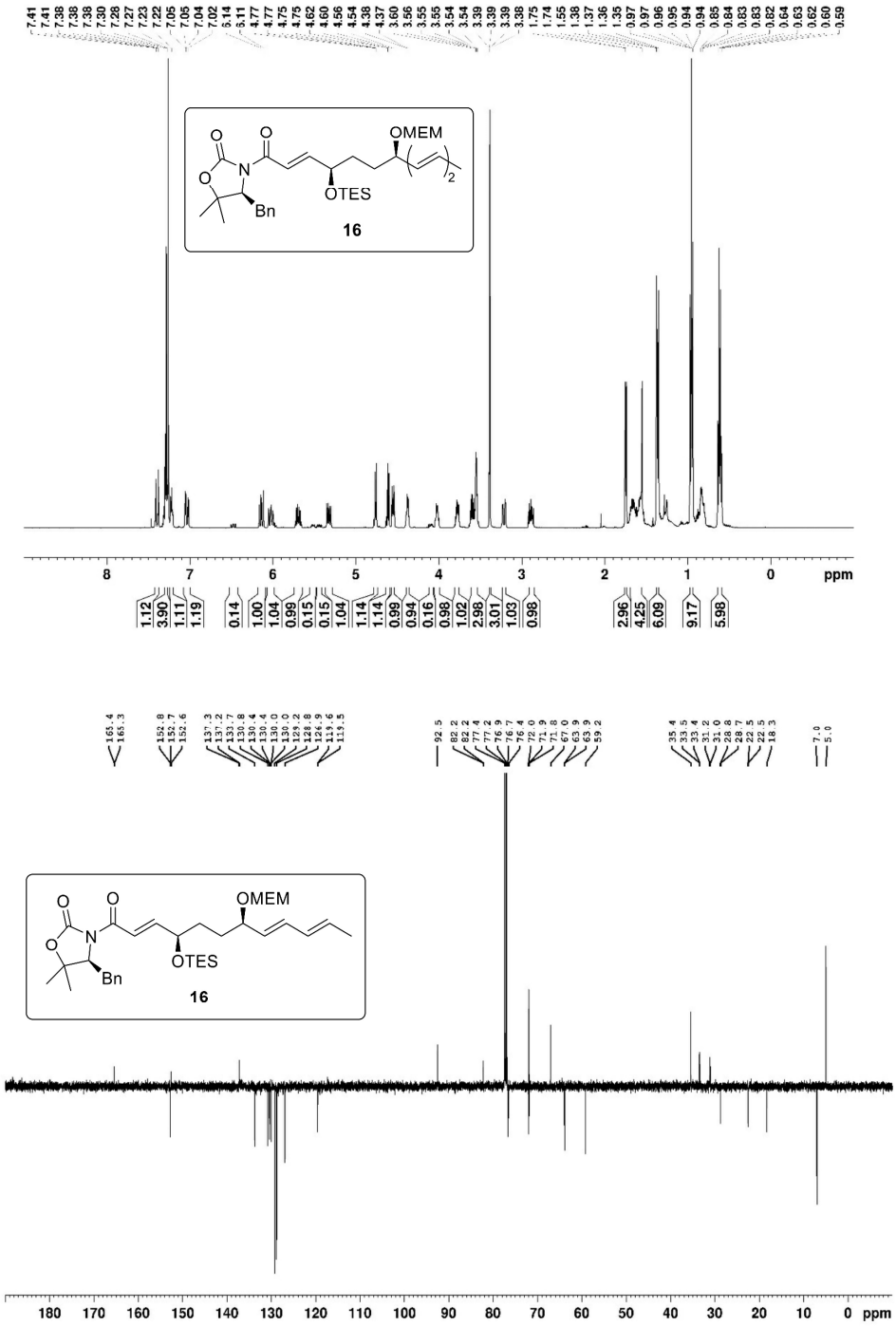
S120

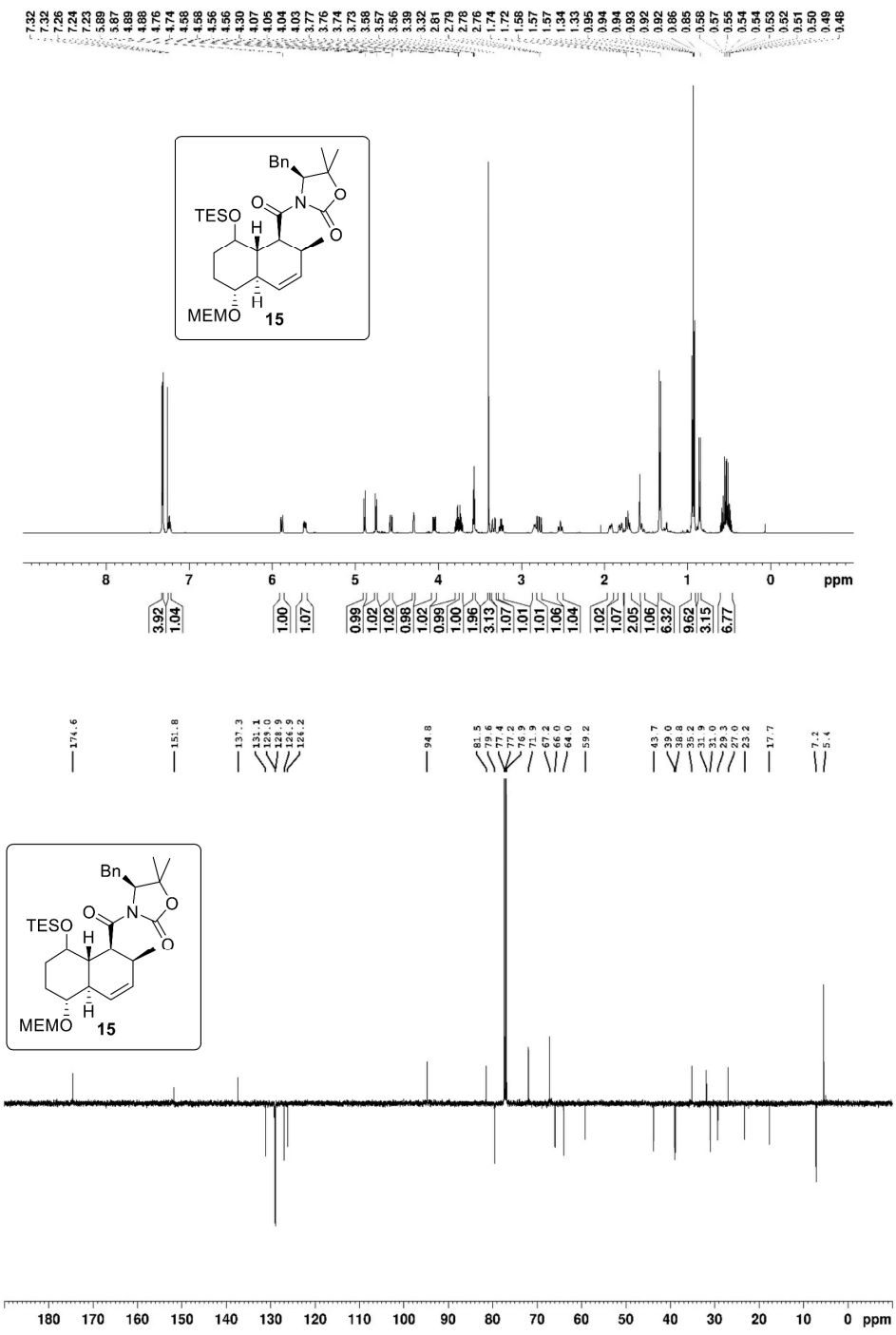

O
OMEM
EtO
OH
46

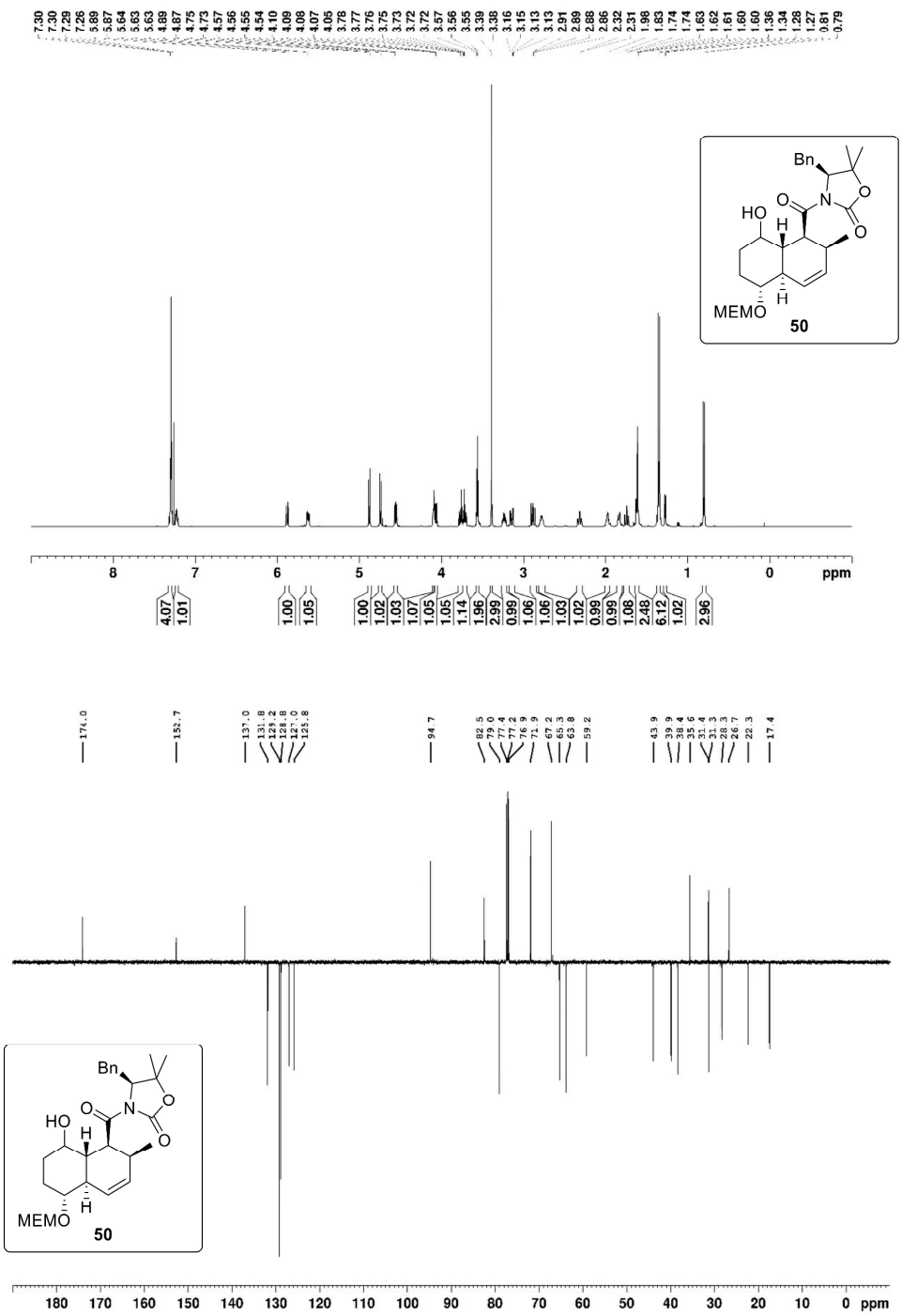

O
OMEM
EtO
OTES
47

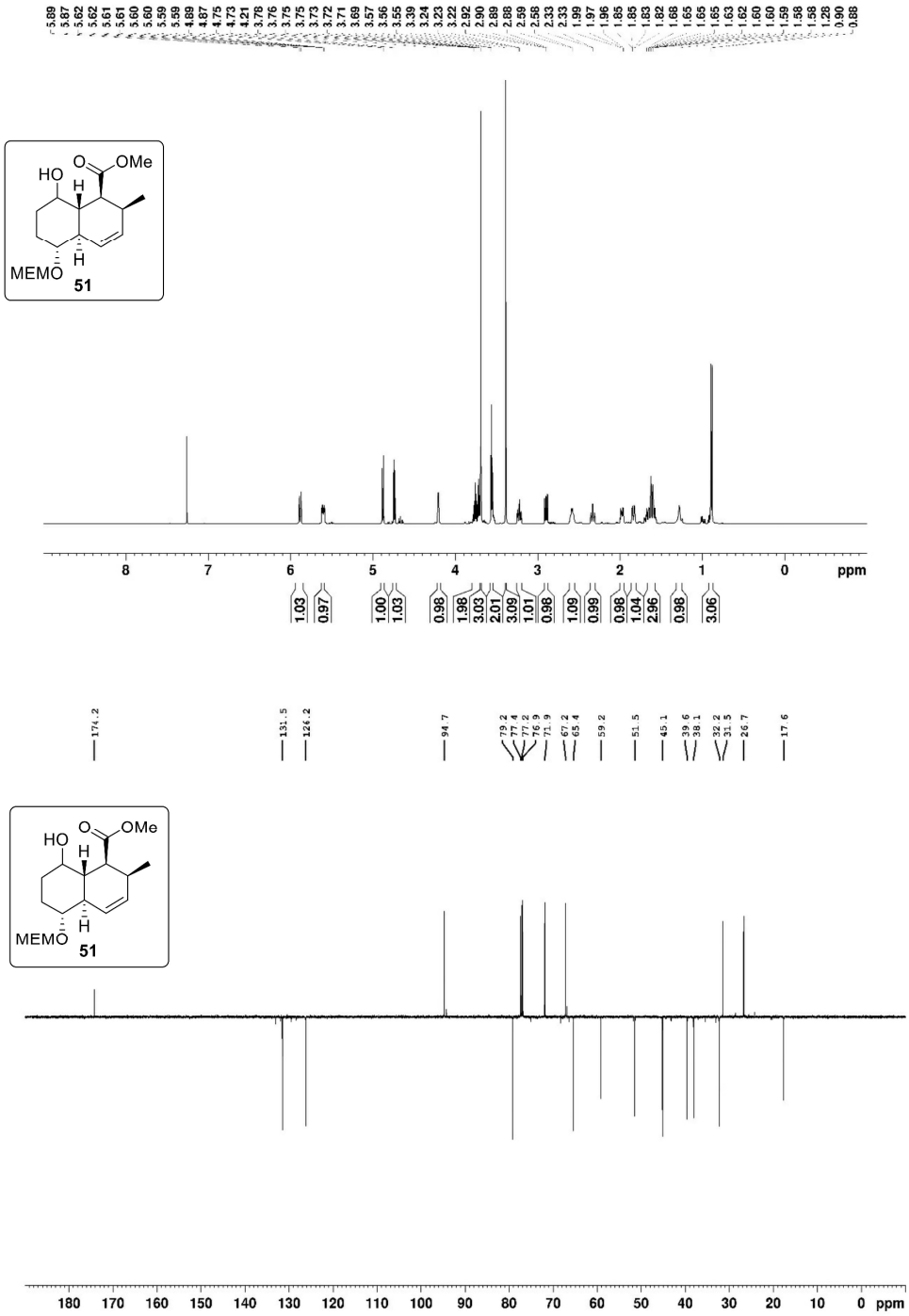

173.8
133.7
132.3
132.3
130.8
130.8
130.4
130.4
129.9
129.9
128.7
128.4
92.6
92.5
77.4
77.2
76.9
76.6
76.1
72.2
71.9
71.9
71.8
67.0
60.9
59.2
31.5
31.4
31.2
31.1
18.3
14.4
6.9
4.7
O
OMEM
EtO
OTES
47
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

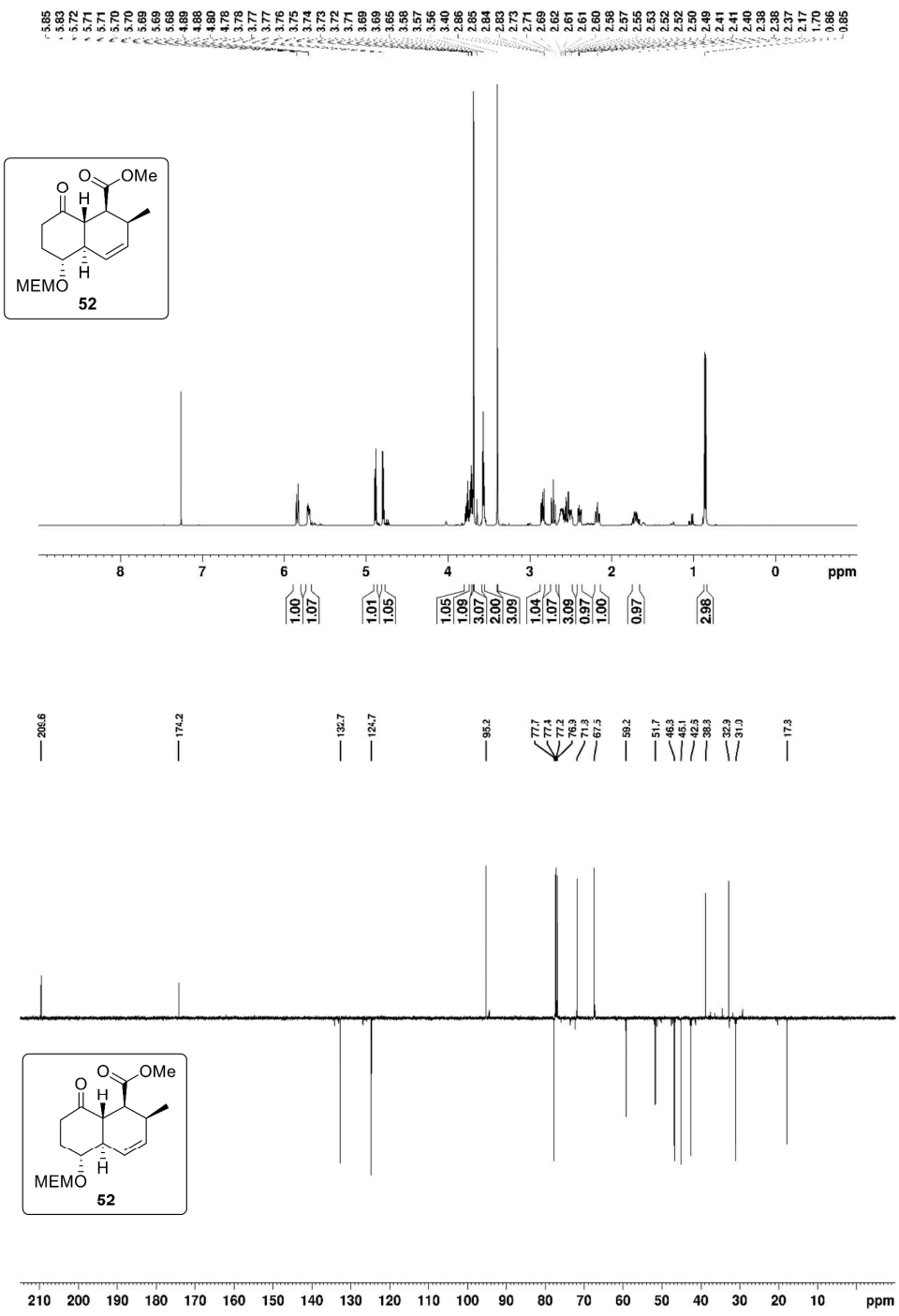

9.58
9.58
6.15
6.14
6.12
6.02
5.72
5.71
5.69
4.76
4.76
4.76
4.75
4.75
4.61
4.60
3.97
3.96
3.96
3.78
3.77
3.76
3.61
3.61
3.60
3.55
3.39
1.75
1.74
1.69
1.68
1.68
1.65
1.64
1.63
1.63
1.63
1.62
1.61
1.56
1.56
1.27
1.25
0.99
0.97
0.96
0.96
0.95
0.94
0.93
0.64
0.63
0.62
0.61
0.61
0.60
0.60
0.59
0.59
0.57
OMEM
O
OTES
48
9 8 7 6 5 4 3 2 1 0 ppm
0.88
0.13
0.99
1.11
0.98
0.14
0.16
0.98
1.12
1.09
0.13
0.91
0.94
1.29
1.16
2.34
3.40
7.38
9.65
6.18

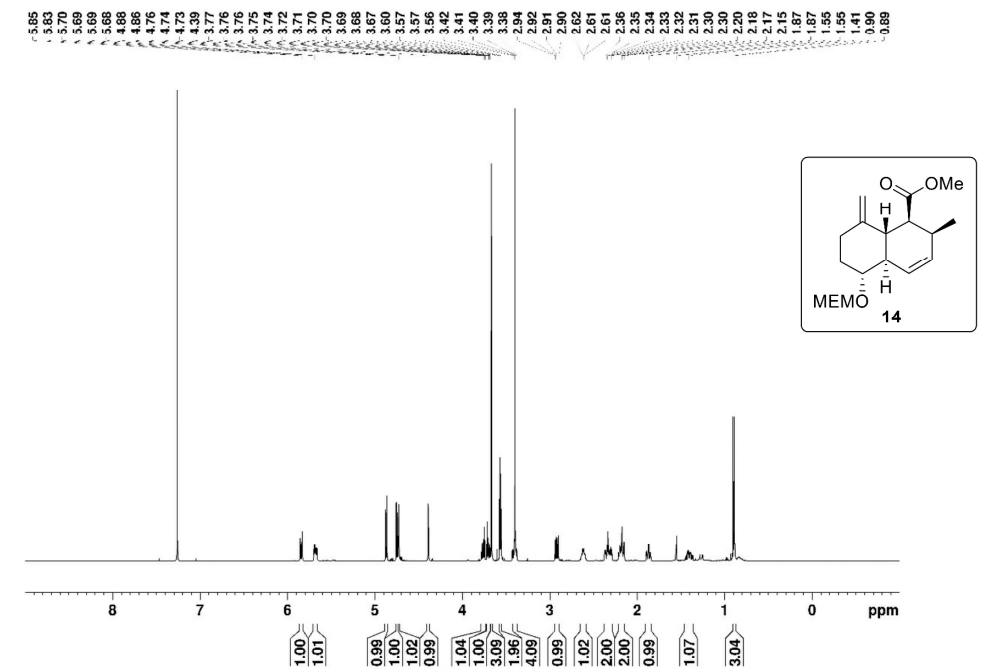

OMEM
OTES
Bn
16
ppm

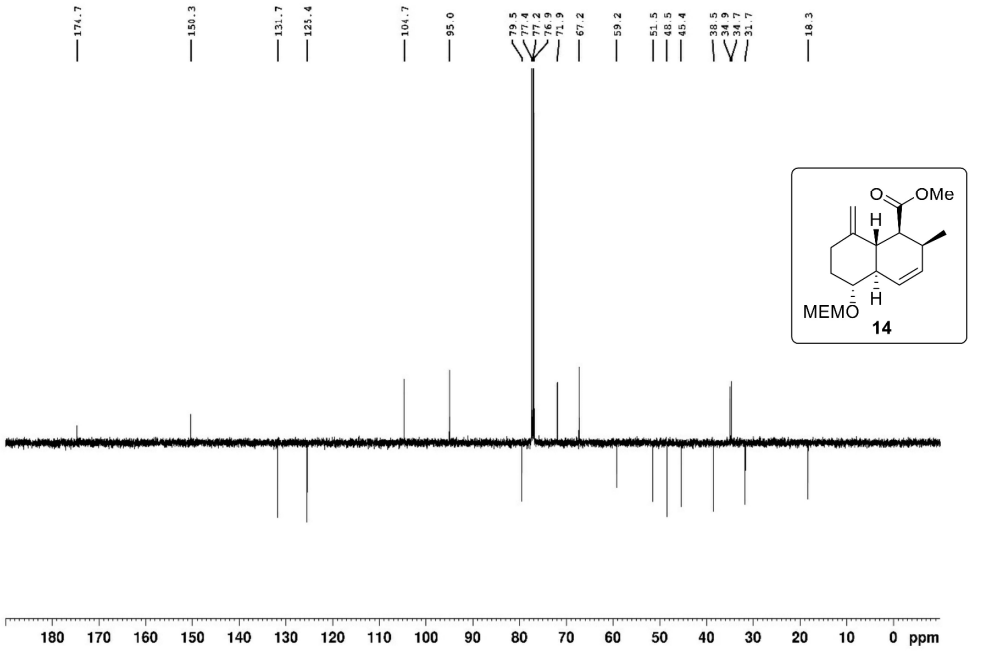

Bn
TESO
MEMO
15
ppm
Bn
TESO
MEMO
15
ppm

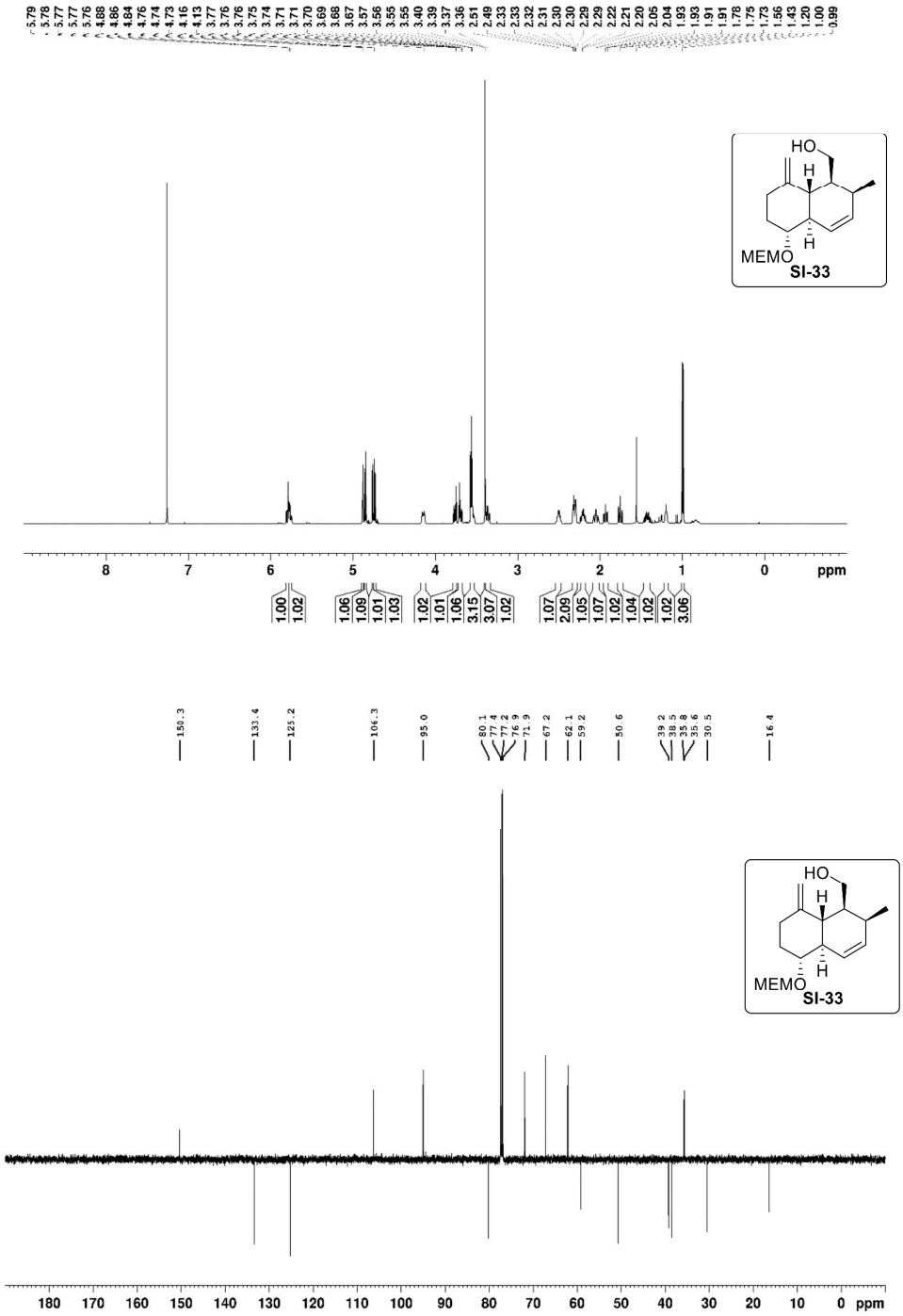

Bn
HO
MEMO
50
ppm
Bn
HO
MEMO
50
ppm

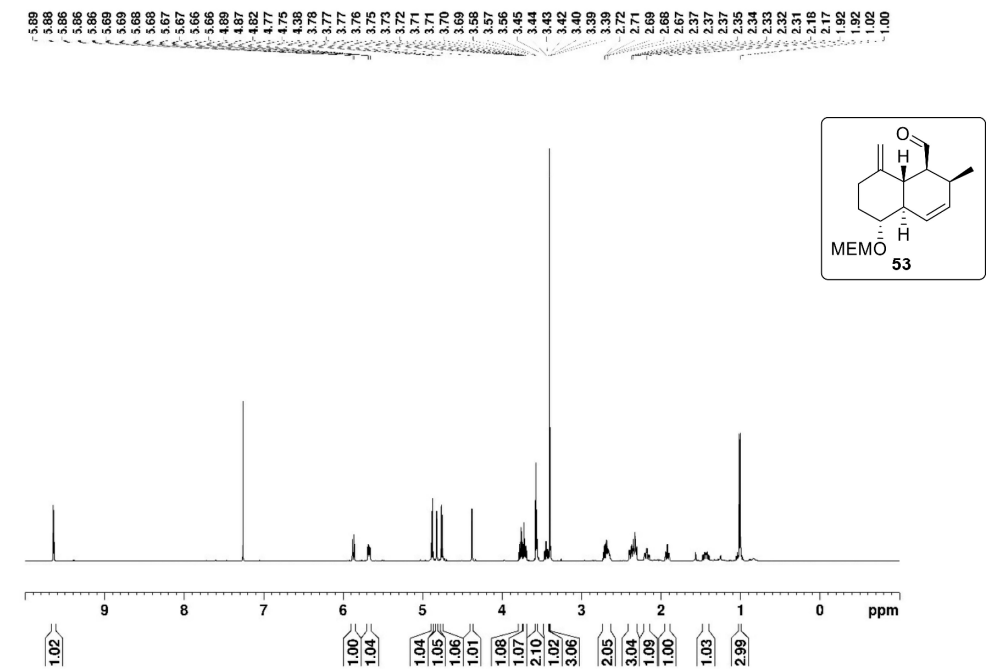

HO
O
OMe
H
MEMO
H
51
ppm
174.2
131.5
126.2
94.7
79.2
77.4
77.2
76.9
71.9
67.2
65.4
59.2
51.5
45.1
39.6
38.1
32.2
31.5
26.7
17.6
ppm

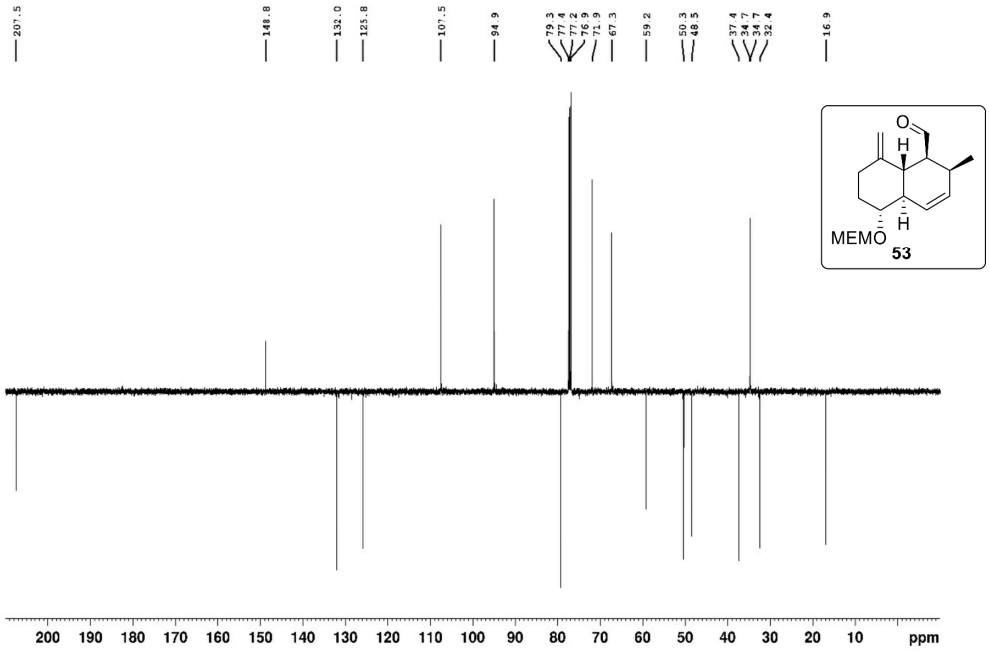

OMe
O
H
MEMO
52
ppm
206.6
174.2
130.7
124.7
95.2
77.7
77.4
77.2
76.9
71.3
67.5
59.2
51.7
46.3
45.1
42.5
38.3
32.9
31.0
17.3

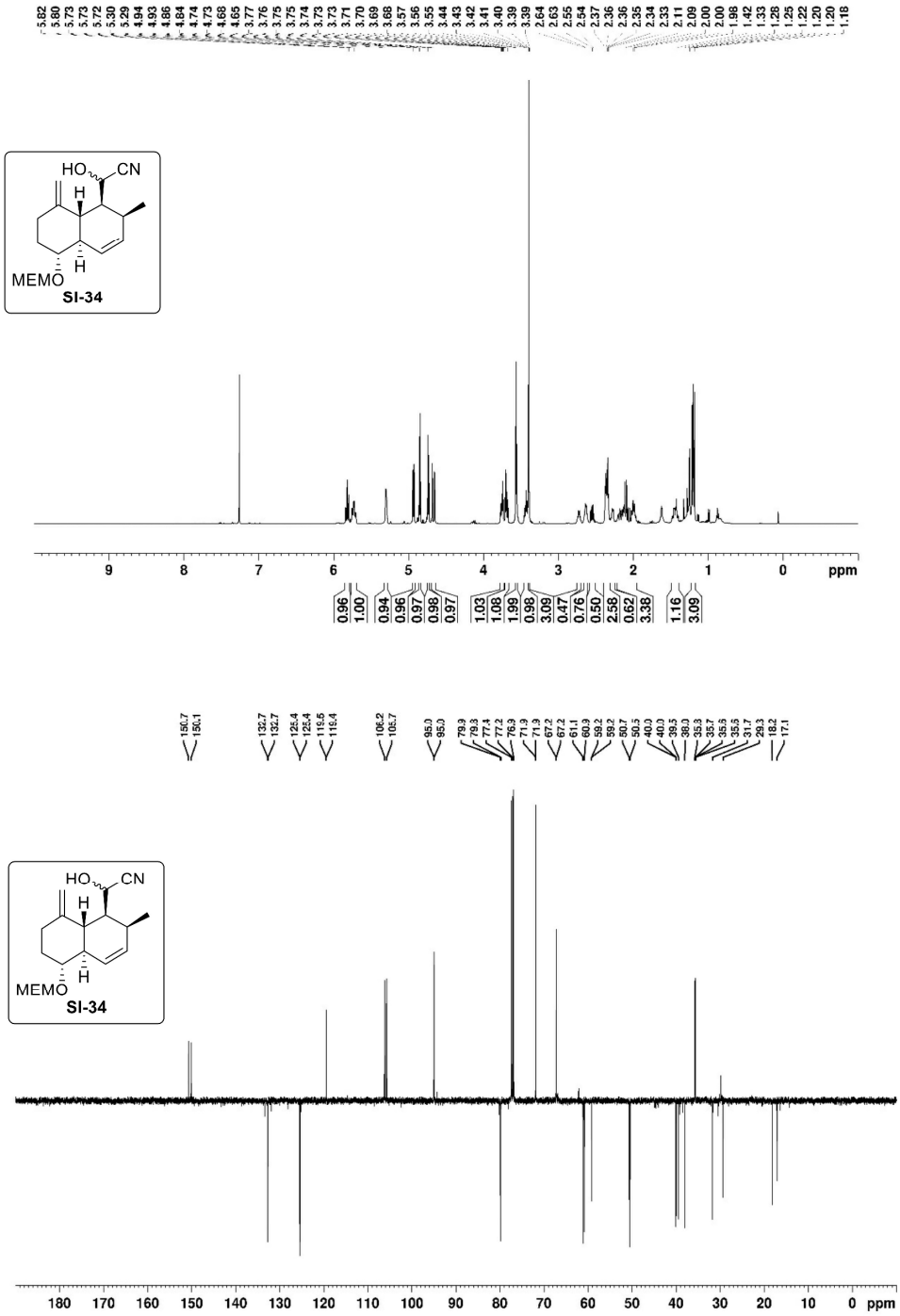

OMe
H
H
MEMO
14
ppm

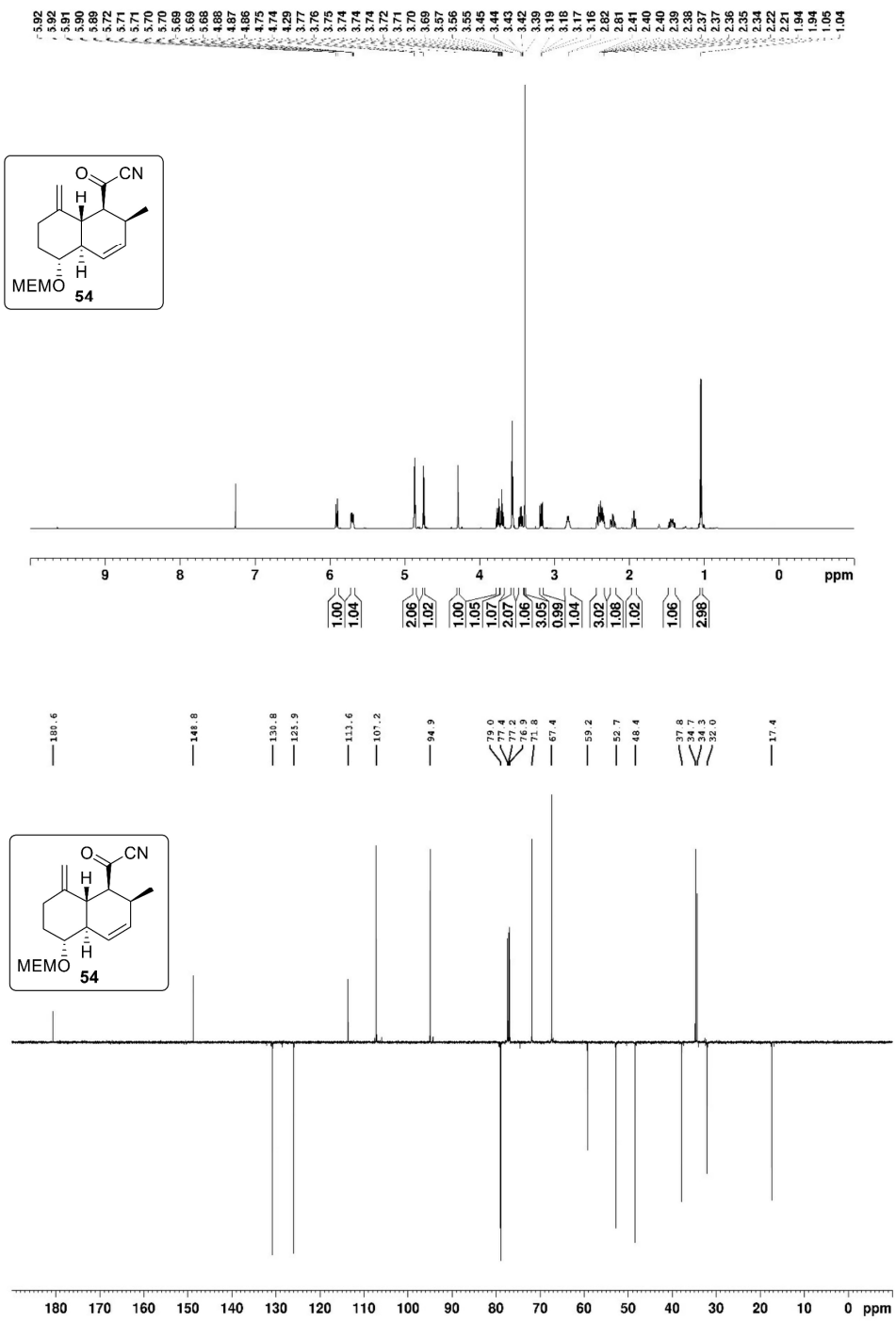

OMe
H
H
MEMO
14
ppm

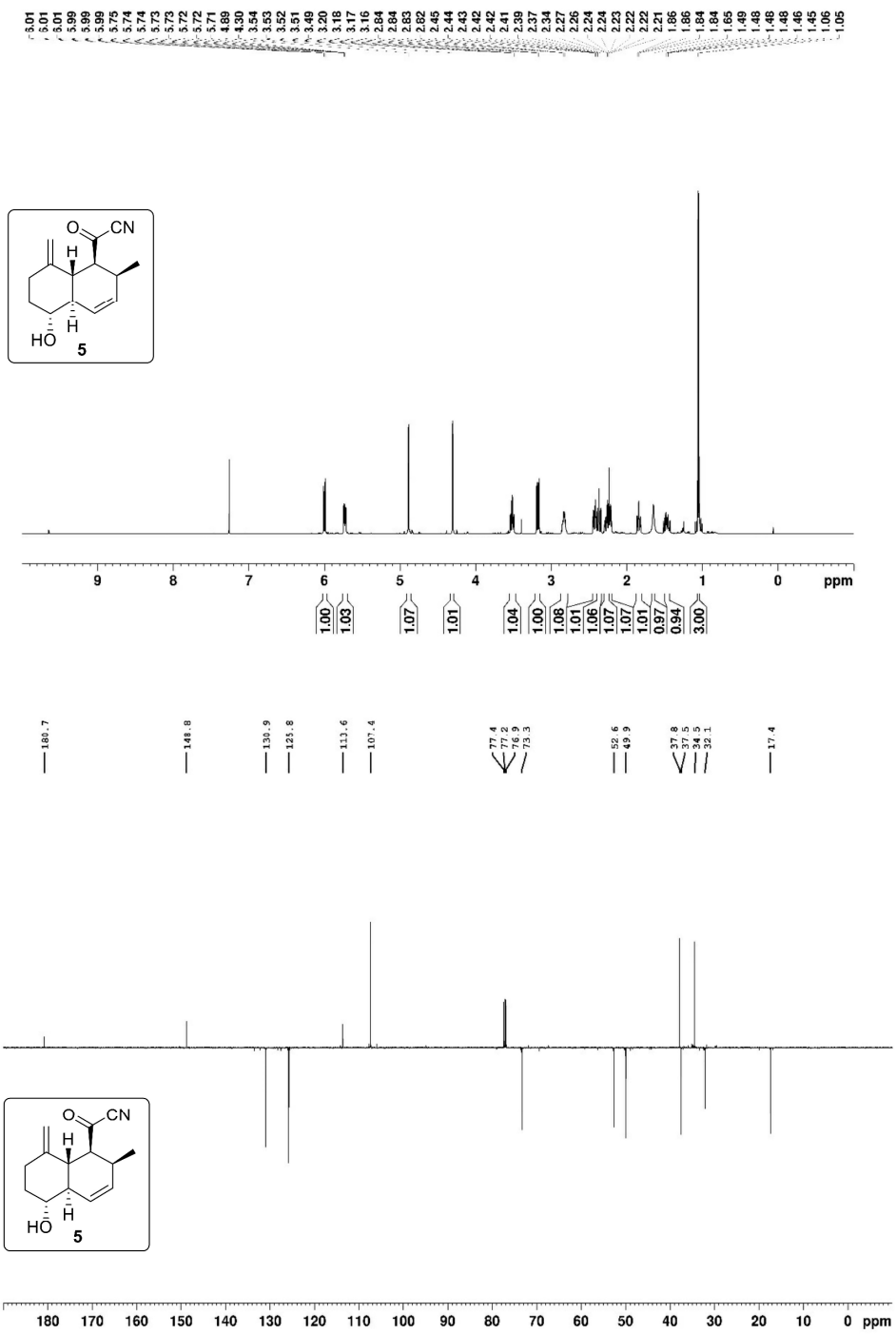

HO
H
H
MEMO
SI-33
ppm
HO
H
H
MEMO
SI-33
ppm

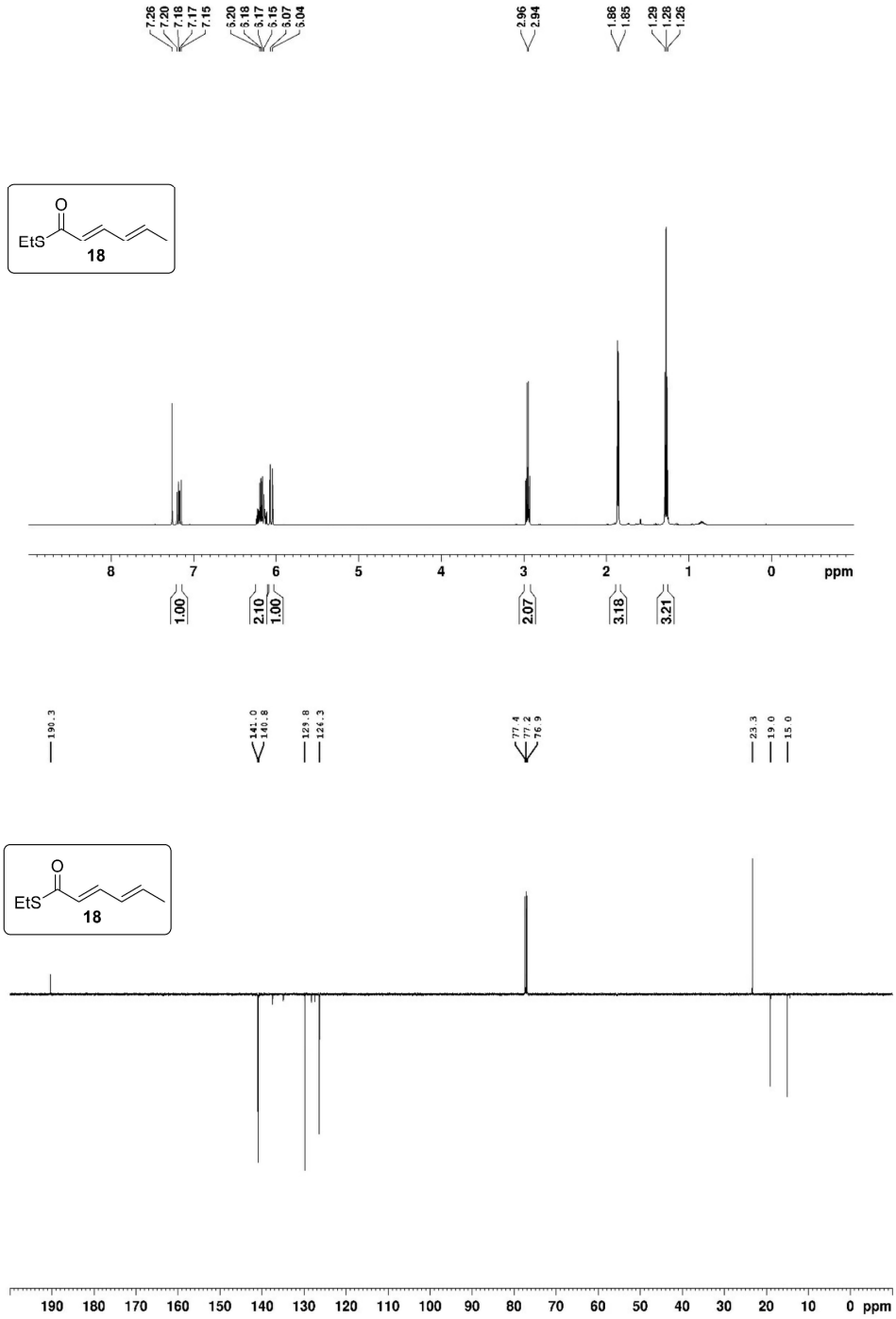

MEMO
53
ppm

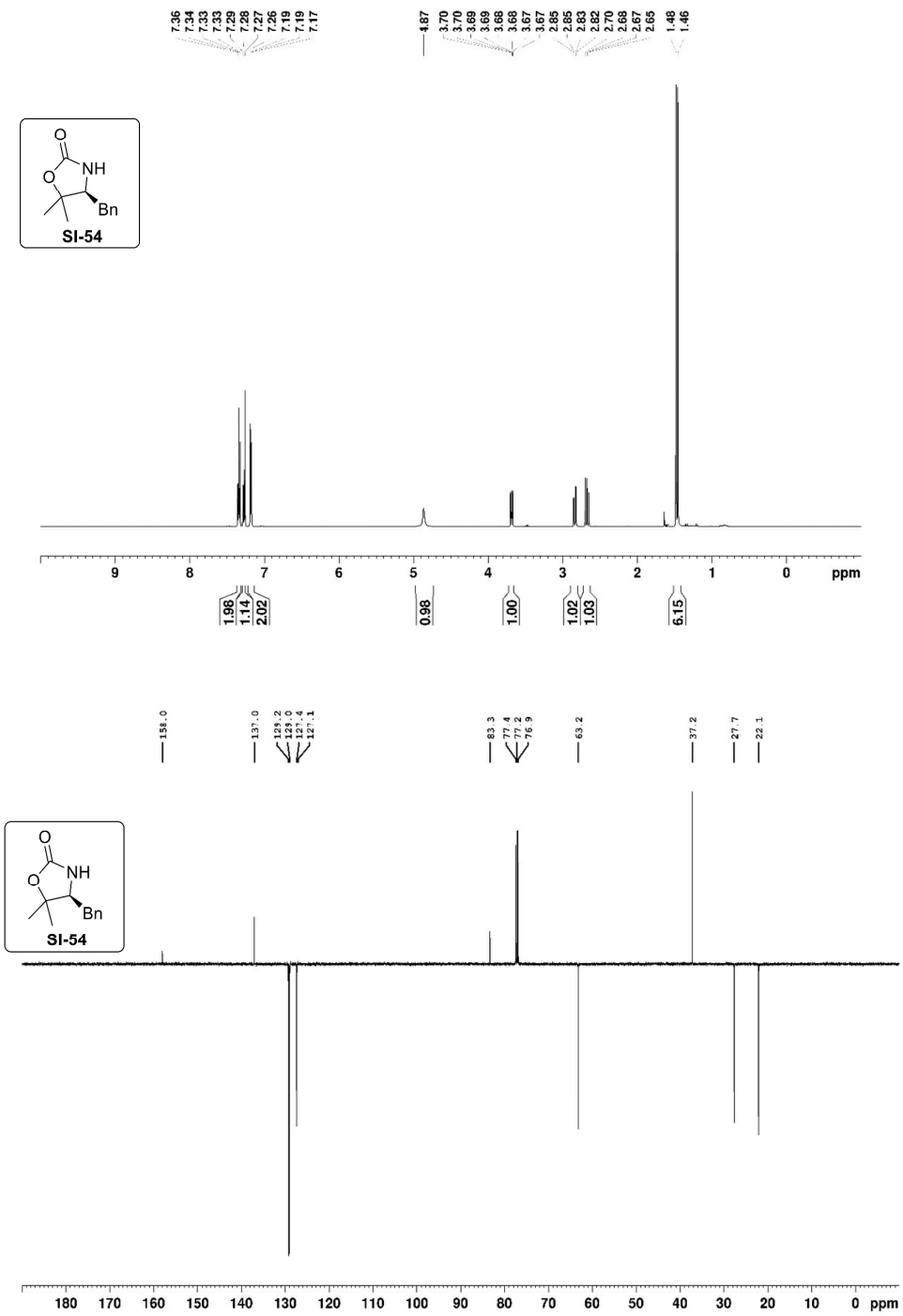

MEMO
53
ppm

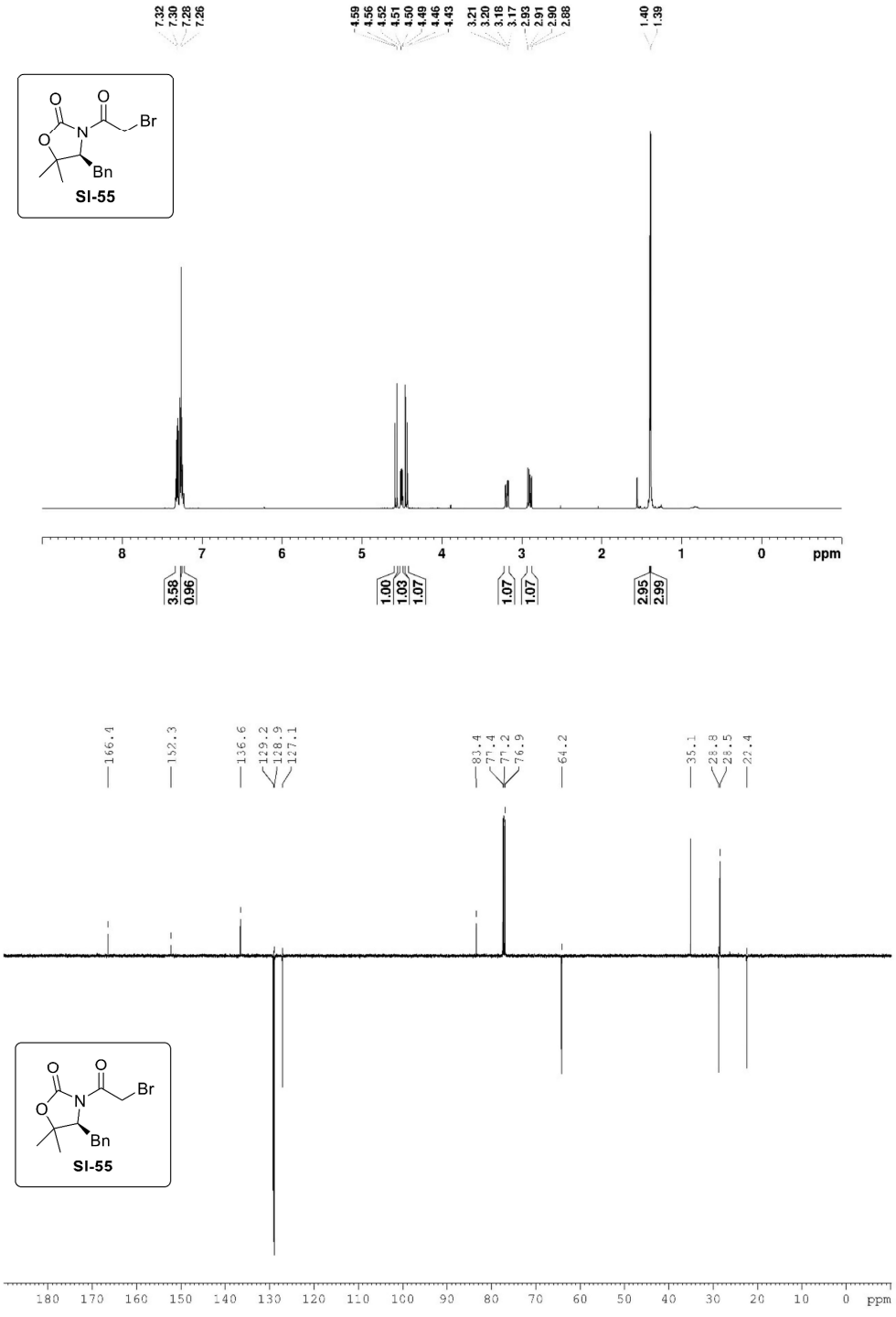

HO
CN
H
H
MEMO
SI-34
ppm
HO
CN
H
H
MEMO
SI-34
ppm

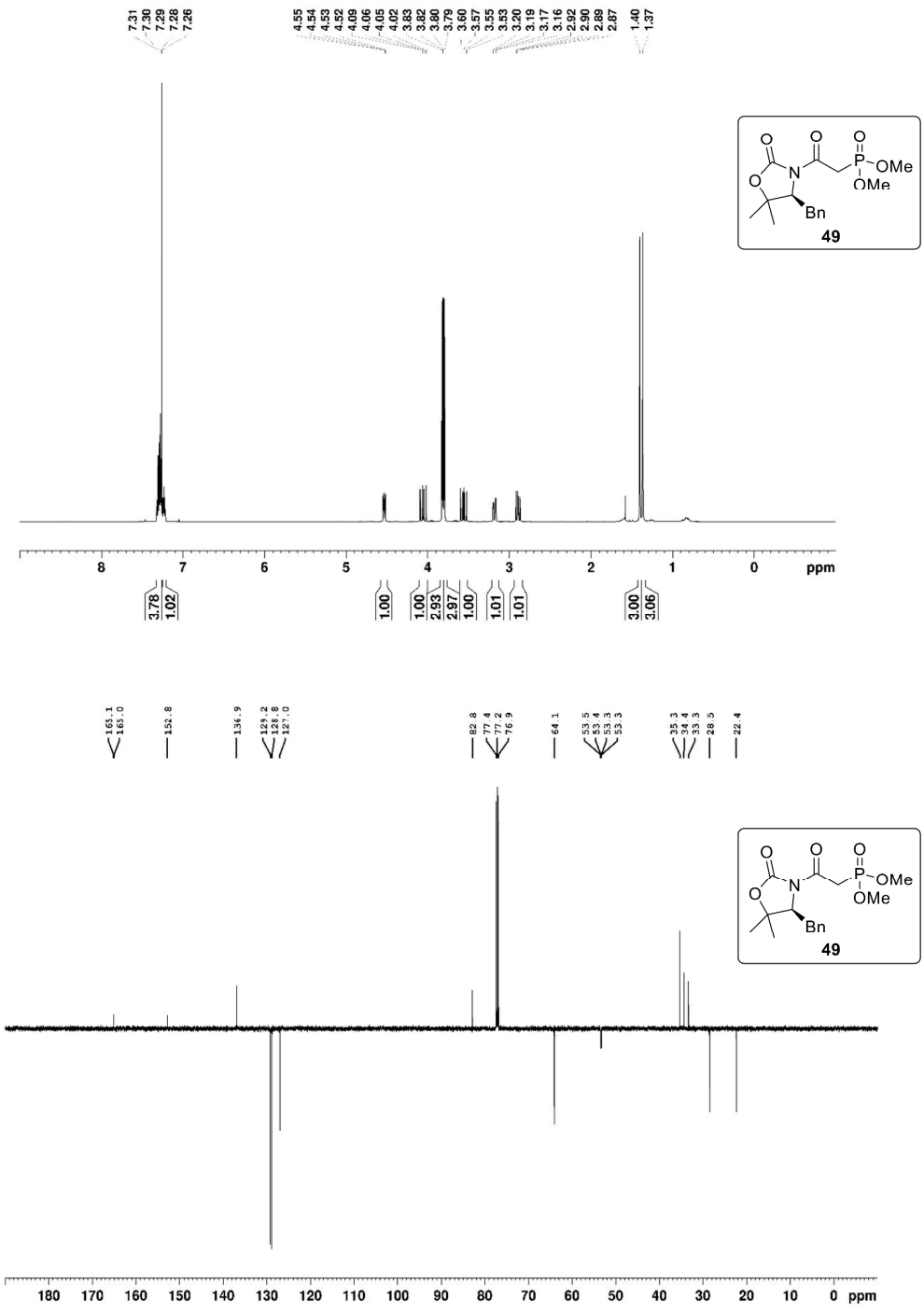

MEMO
54
ppm
MEMO
54
ppm

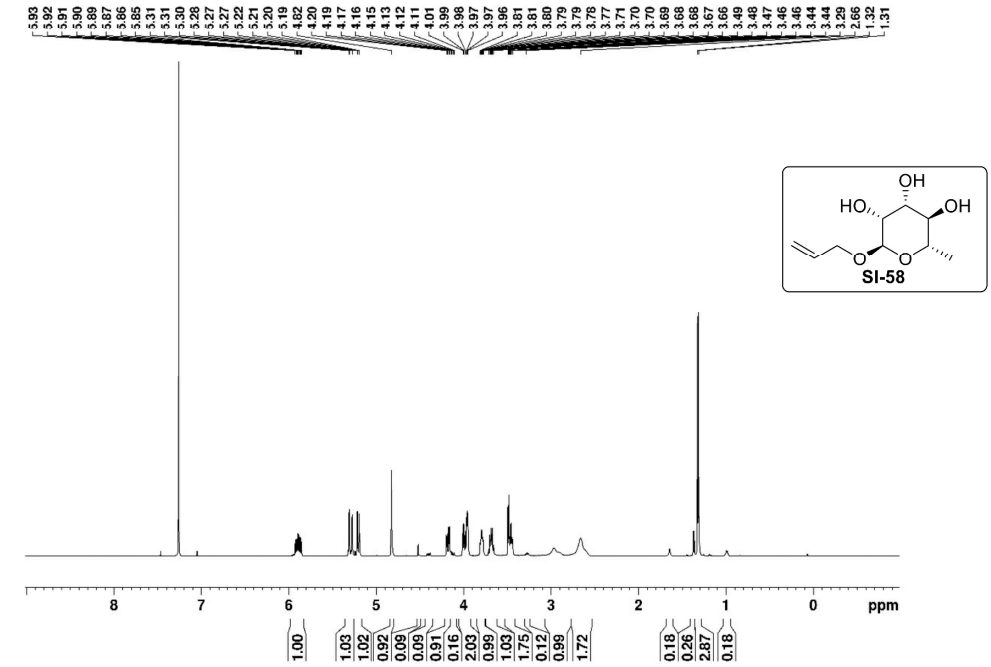

O
CN
H
HO
H
5
ppm
1.00
1.03
1.07
1.01
1.04
1.00
1.08
1.01
1.06
1.07
1.07
1.01
0.97
0.94
3.00
180.7
148.8
130.9
125.8
113.6
107.4
77.4
77.2
76.9
73.3
52.6
49.9
37.8
37.5
34.5
32.1
17.4
ppm

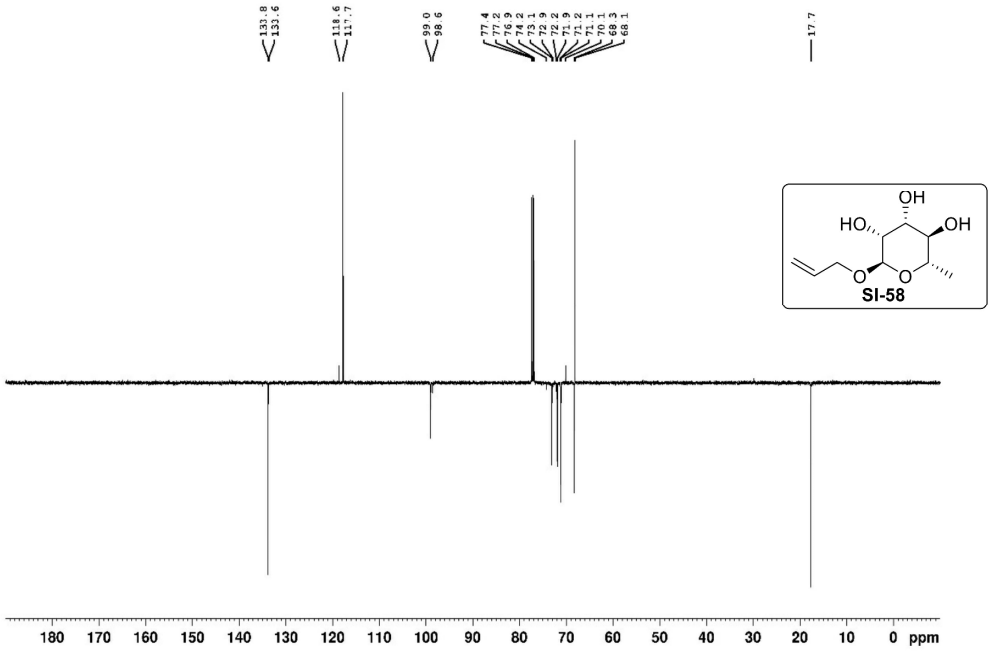

7.26
7.20
7.18
7.17
7.15
5.20
5.18
5.17
5.15
5.07
5.04
2.96
2.94
1.86
1.85
1.29
1.28
1.26
EtS
O
18
8
7
6
5
4
3
2
1
0
ppm
1.00
2.10
1.00
2.07
3.18
3.21
190.3
141.0
140.8
129.8
126.3
77.4
77.2
76.9
23.3
19.0
15.0
EtS
O
18
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

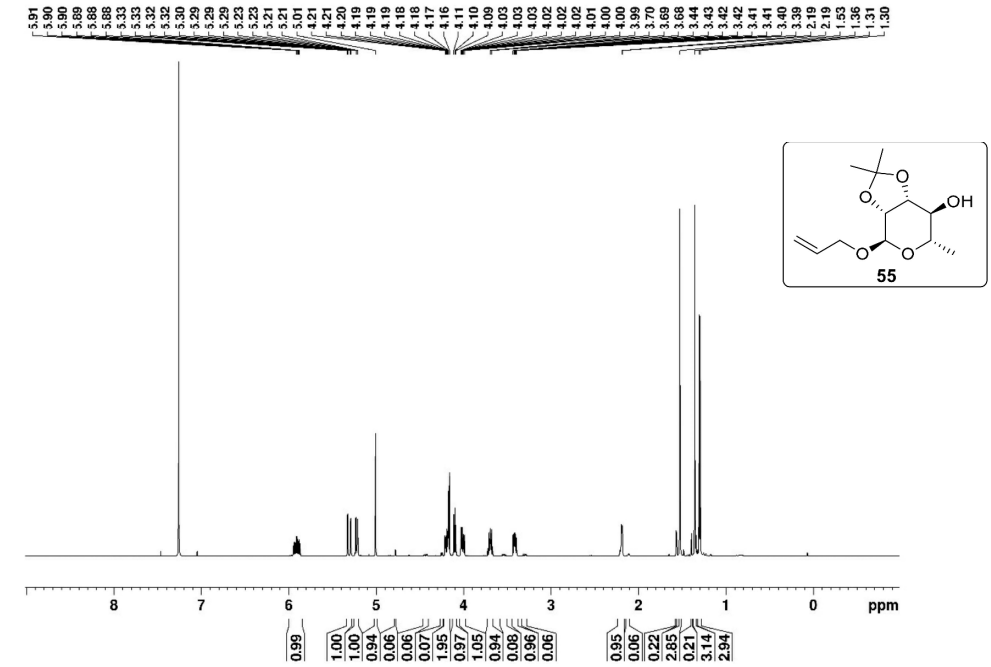

7.36
7.34
7.33
7.33
7.29
7.28
7.27
7.26
7.19
7.19
7.17
4.87
3.70
3.70
3.69
3.69
3.68
3.68
3.67
3.67
2.85
2.85
2.83
2.82
2.70
2.68
2.67
2.65
1.48
1.46
O
NH
O
Bn
SI-54
9
8
7
6
5
4
3
2
1
0
ppm
1.98
1.14
2.02
0.98
1.00
1.02
1.03
6.15
158.0
137.0
129.2
129.0
127.4
127.1
83.3
77.4
77.2
76.9
63.2
37.2
27.7
22.1
O
NH
O
Bn
SI-54
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

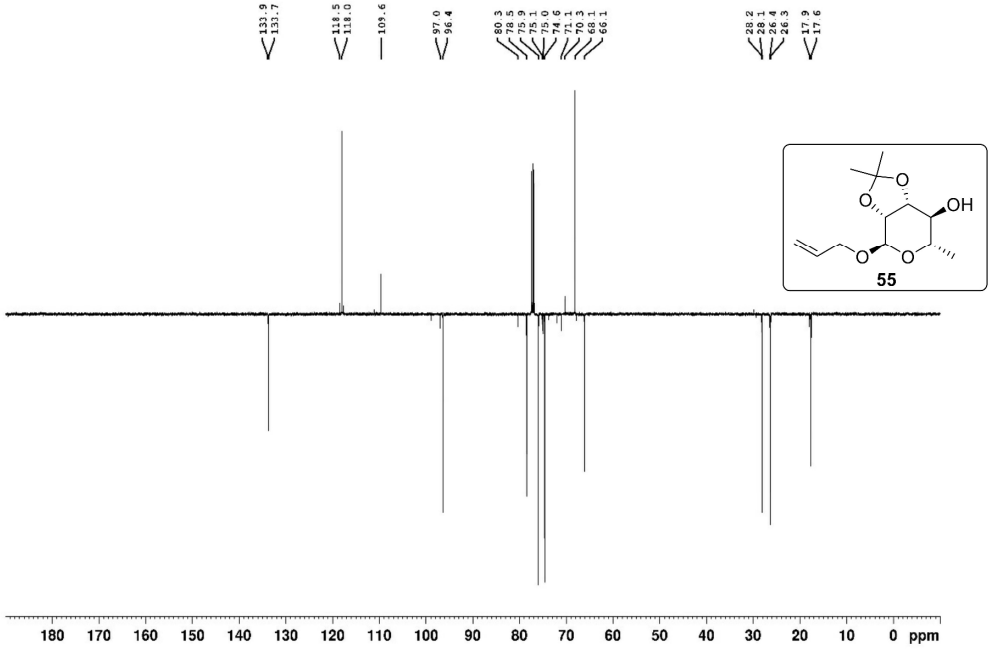

7.32
7.30
7.28
7.26
4.59
4.56
4.52
4.51
4.50
4.49
4.46
4.43
3.21
3.20
3.18
3.17
2.93
2.91
2.90
2.88
1.40
1.39
Br
Bn
SI-55
ppm
3.58
0.96
1.00
1.03
1.07
1.07
1.07
2.95
2.99
166.4
152.3
136.6
129.2
128.9
127.1
83.4
77.4
77.2
76.9
64.2
35.1
28.8
28.5
22.4
Br
Bn
SI-55
ppm

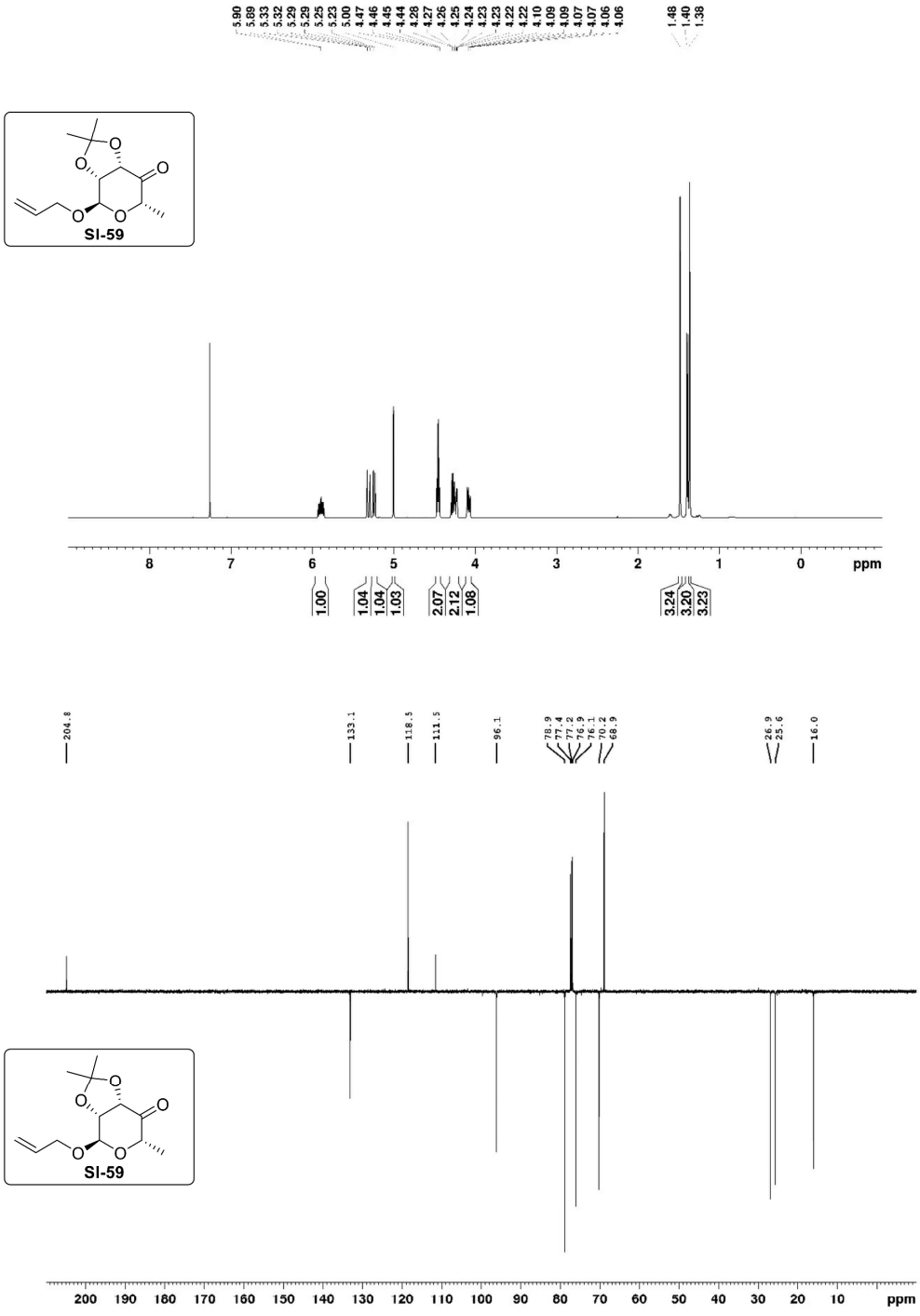

7.31
7.30
7.29
7.28
7.26
4.55
4.54
4.53
4.52
4.08
4.06
4.05
4.02
3.83
3.82
3.80
3.79
3.60
3.57
3.55
3.53
3.20
3.19
3.17
3.16
2.92
2.90
2.89
2.87
1.40
1.37
OMe
OMe
Bn
49
ppm
3.78
1.02
1.00
1.00
2.93
2.97
1.00
1.01
1.01
3.00
3.06
165.1
165.0
152.8
136.9
129.2
128.8
127.0
82.8
77.4
77.2
76.9
64.1
53.5
53.4
53.3
53.3
35.3
34.4
33.3
28.5
22.4
OMe
OMe
Bn
49
ppm

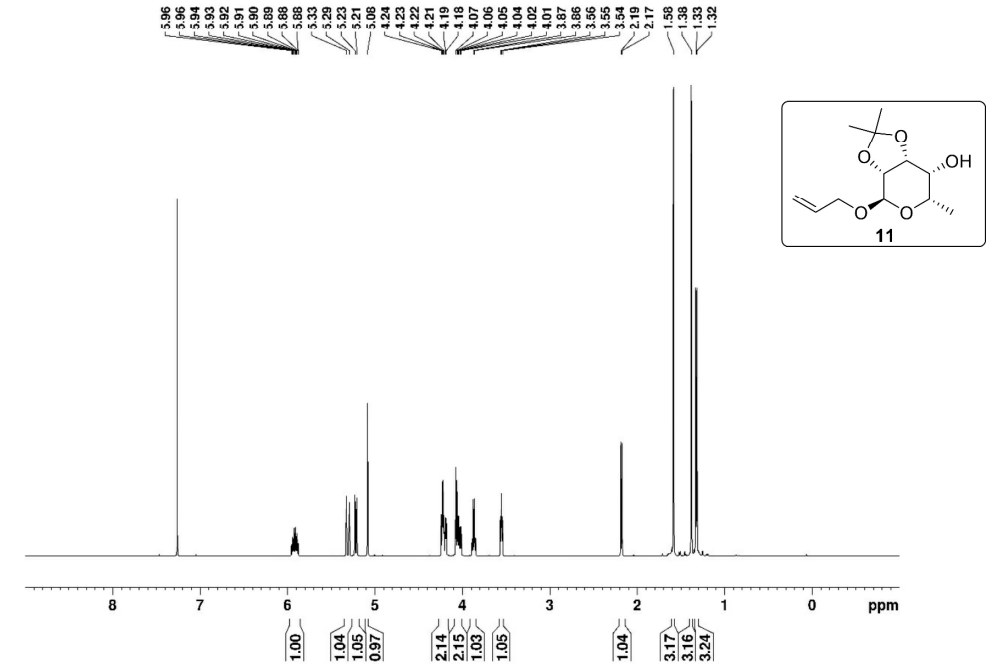

OH
HO
OH
O
O
SI-58
8
7
6
5
4
3
2
1
0
ppm

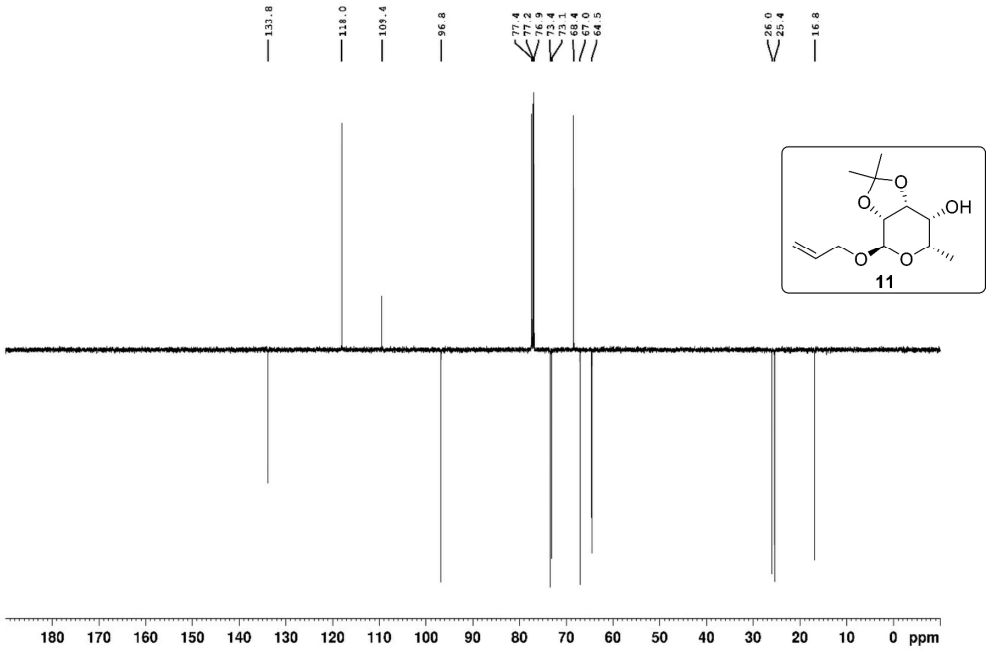

OH
HO
OH
O
O
SI-58
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

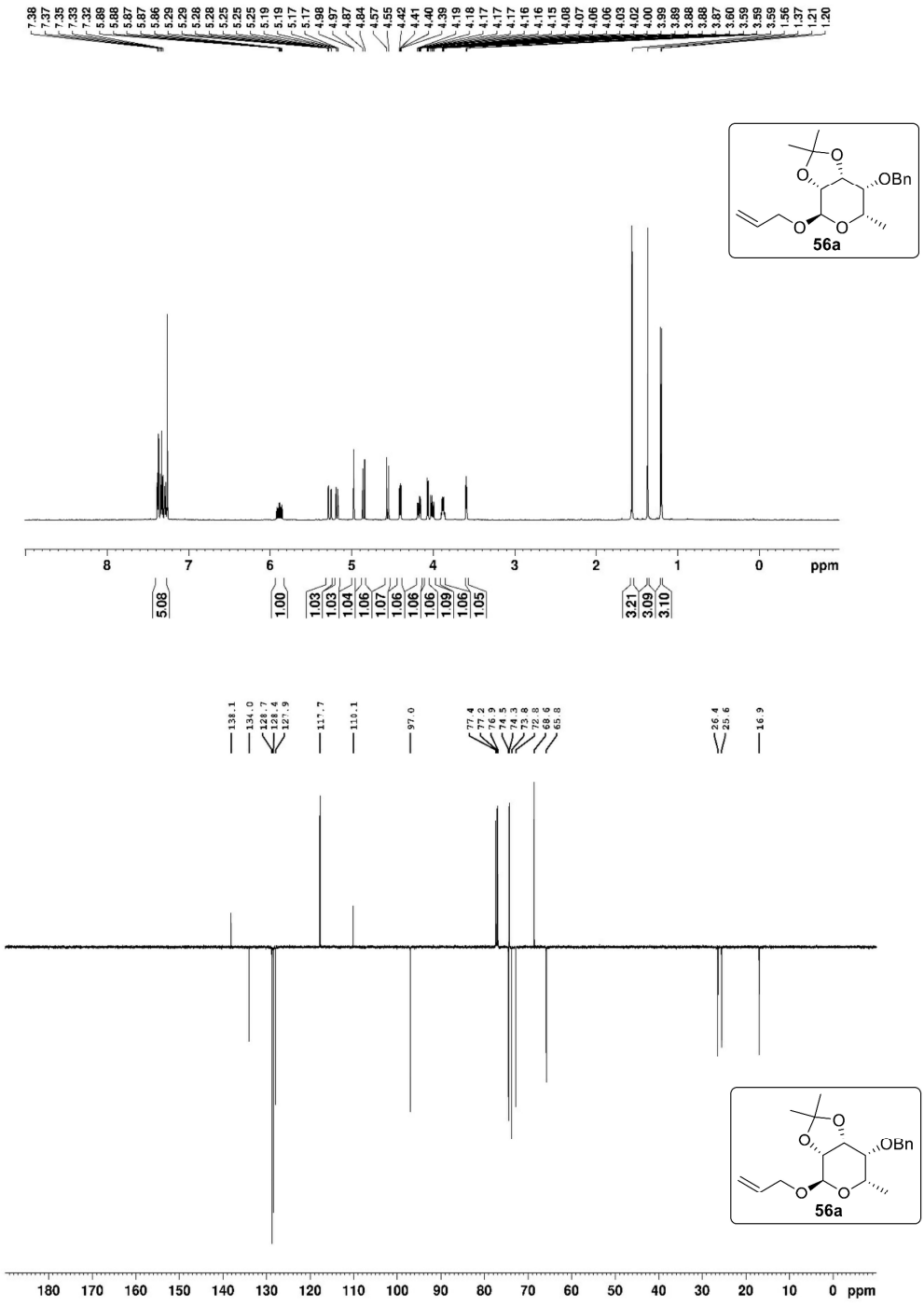

OH
55
ppm

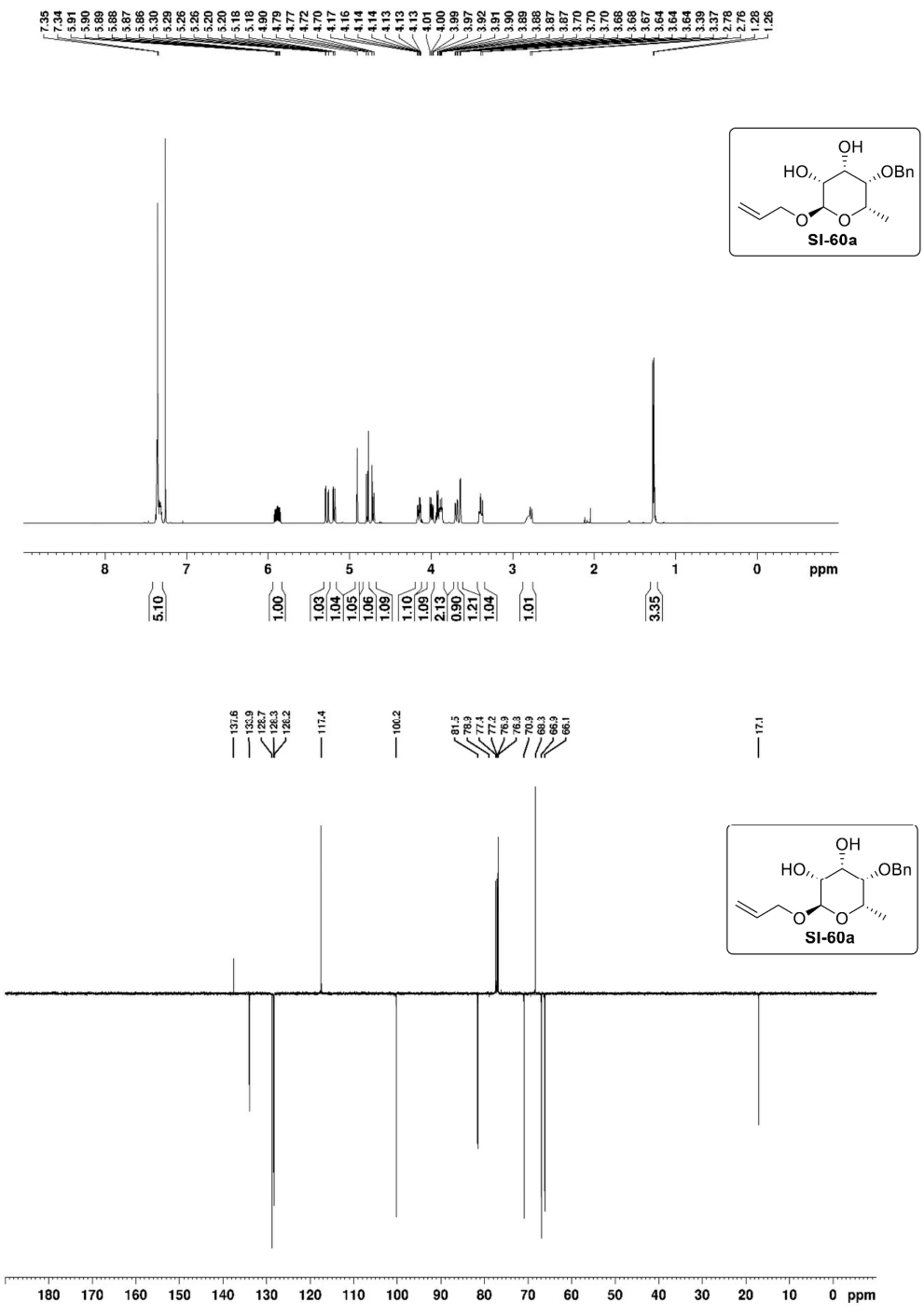

OH
55
ppm

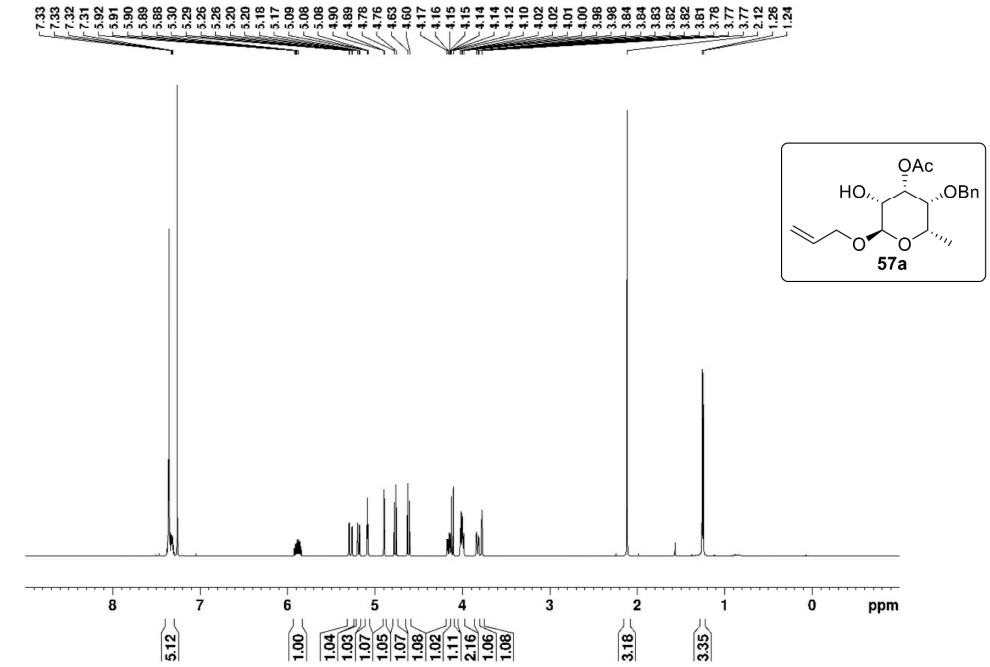

SI-59
ppm
SI-59
ppm

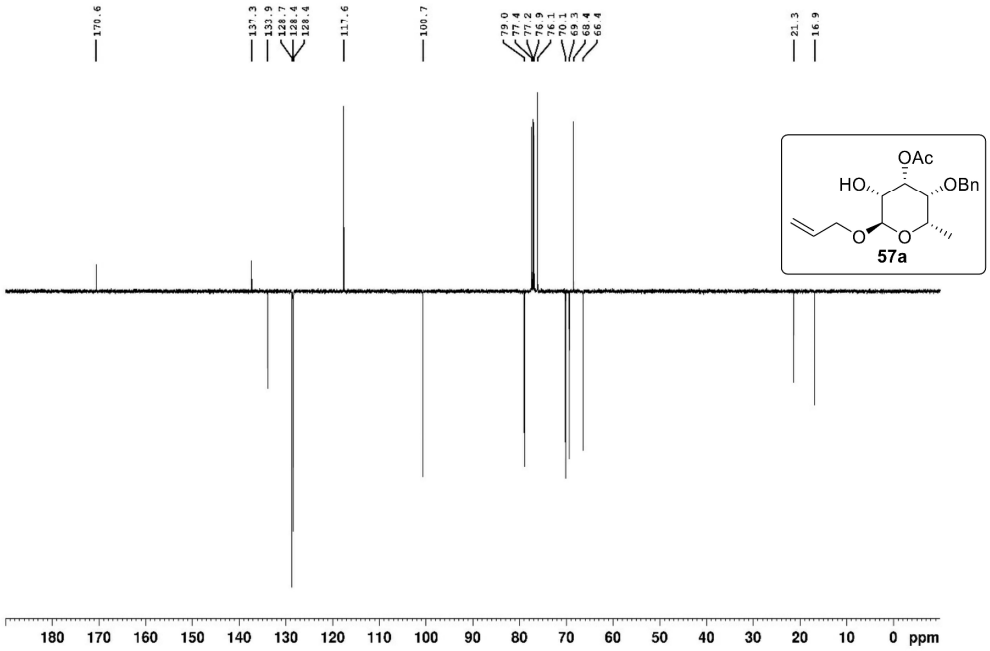

5.96
5.96
5.94
5.93
5.92
5.91
5.90
5.89
5.88
5.88
5.33
5.29
5.23
5.21
5.08
4.24
4.23
4.22
4.21
4.19
4.18
4.07
4.06
4.05
4.04
4.02
4.01
3.87
3.86
3.56
3.55
3.54
2.19
2.17
1.58
1.38
1.33
1.32
OH
O
O
O
O
11
8
7
6
5
4
3
2
1
0
ppm
1.00
1.04
1.05
0.97
2.14
2.15
1.03
1.05
1.04
3.17
3.16
3.24

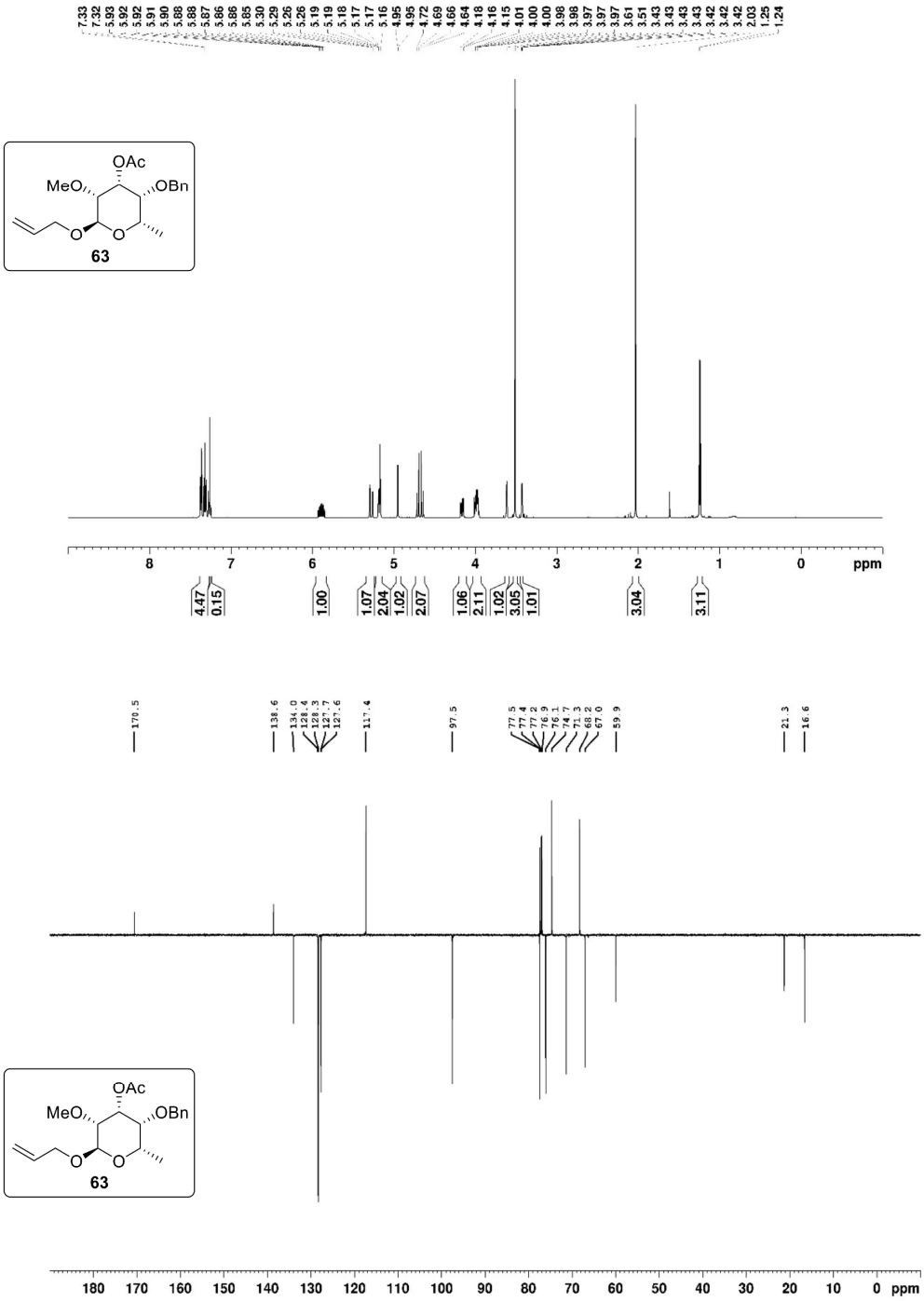

133.8
118.0
105.4
96.8
77.4
77.2
76.9
73.4
73.1
68.4
67.0
64.5
26.0
25.4
16.8
OH
O
O
O
O
11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

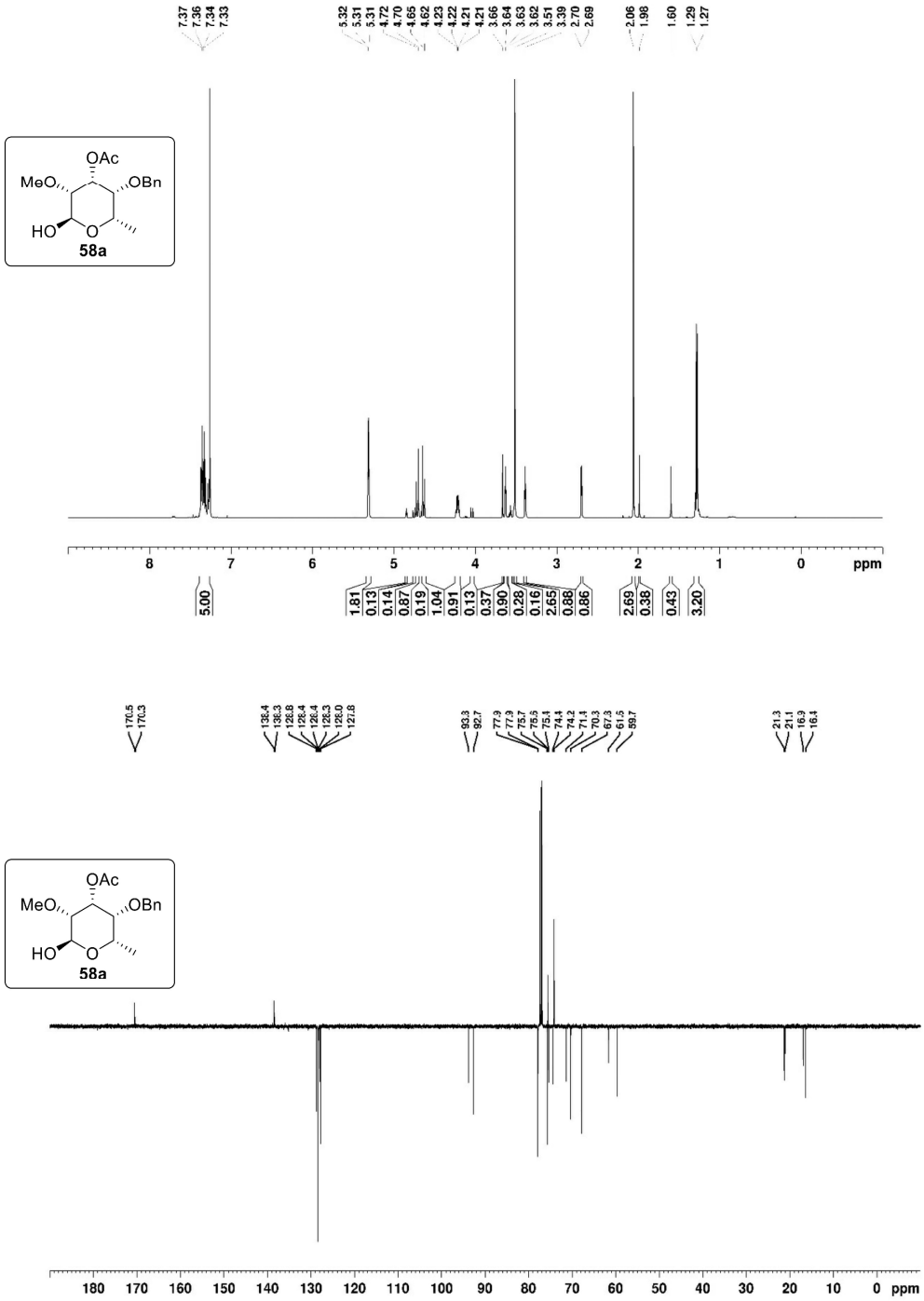

OBn
56a
ppm
OBn
56a
ppm


7.35
7.34
5.91
5.90
5.89
5.88
5.87
5.86
5.30
5.29
5.26
5.26
5.20
5.20
5.18
5.18
4.90
4.79
4.77
4.72
4.70
4.17
4.16
4.14
4.14
4.13
4.13
4.13
4.01
4.00
4.00
3.99
3.97
3.92
3.91
3.90
3.89
3.88
3.87
3.87
3.70
3.70
3.70
3.68
3.68
3.67
3.64
3.64
3.64
3.39
3.37
2.78
2.76
1.28
1.26
OH
HO
OBn
O
O
SI-60a
8
7
6
5
4
3
2
1
0
ppm
5.10
1.00
1.03
1.04
1.05
1.06
1.09
1.10
1.09
2.13
0.90
1.21
1.04
1.01
3.35
137.6
132.9
128.7
128.3
126.2
117.4
100.2
81.5
78.9
77.4
77.2
76.9
76.3
70.9
68.3
66.9
66.1
17.1
OH
HO
OBn
O
O
SI-60a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

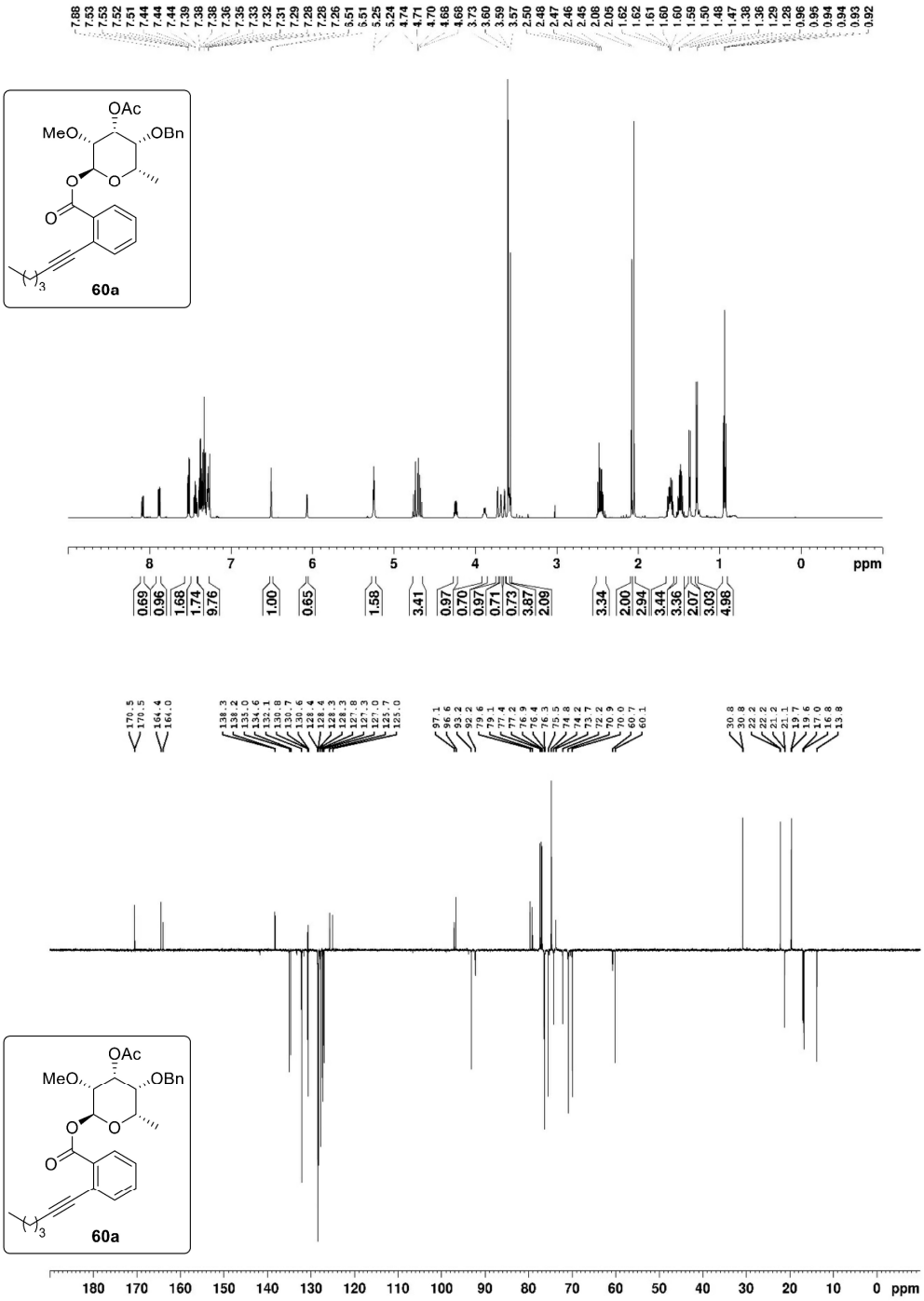

OAc
HO
OBn
O
O
57a
ppm

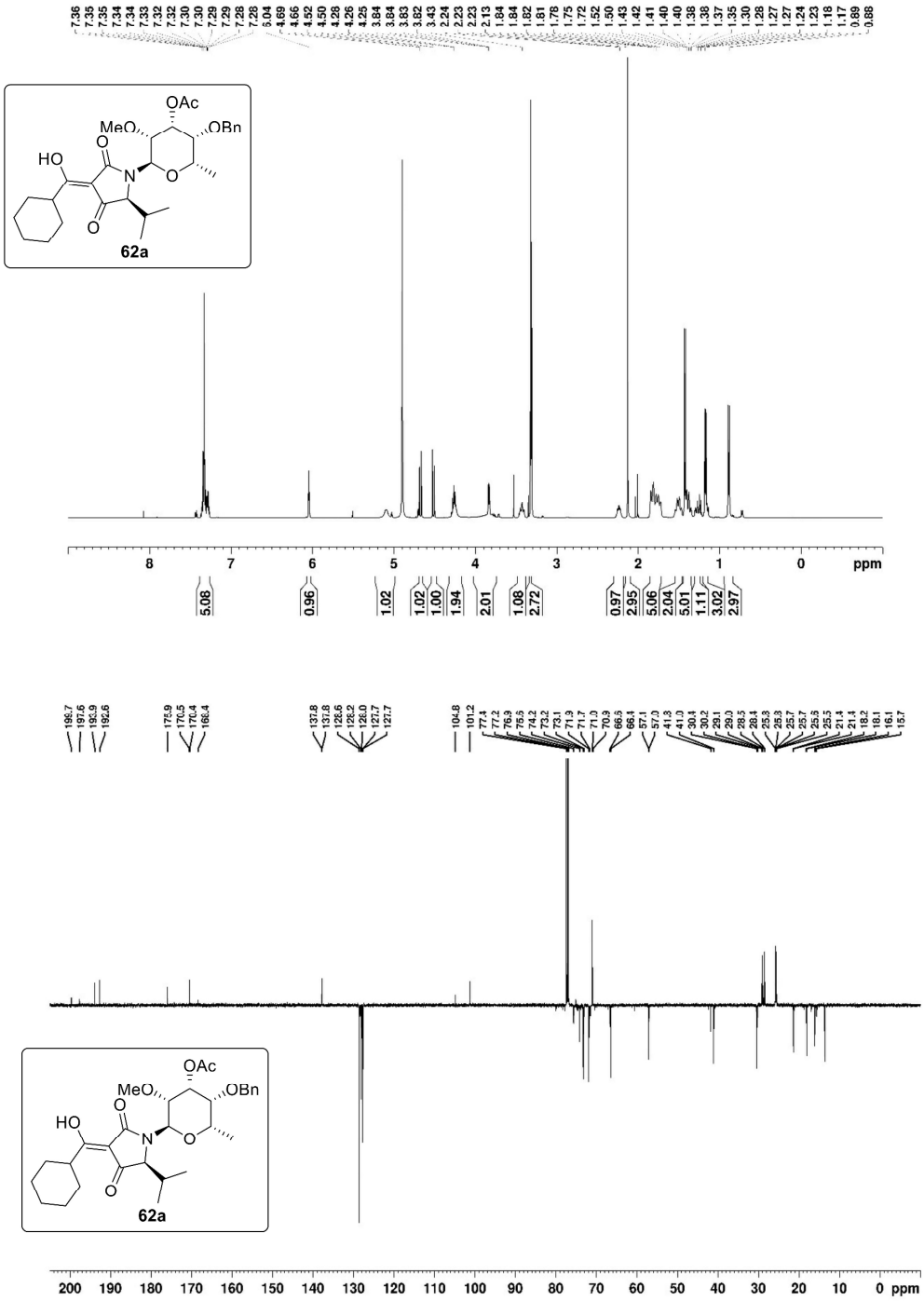

OAc
HO
OBn
O
O
57a
ppm

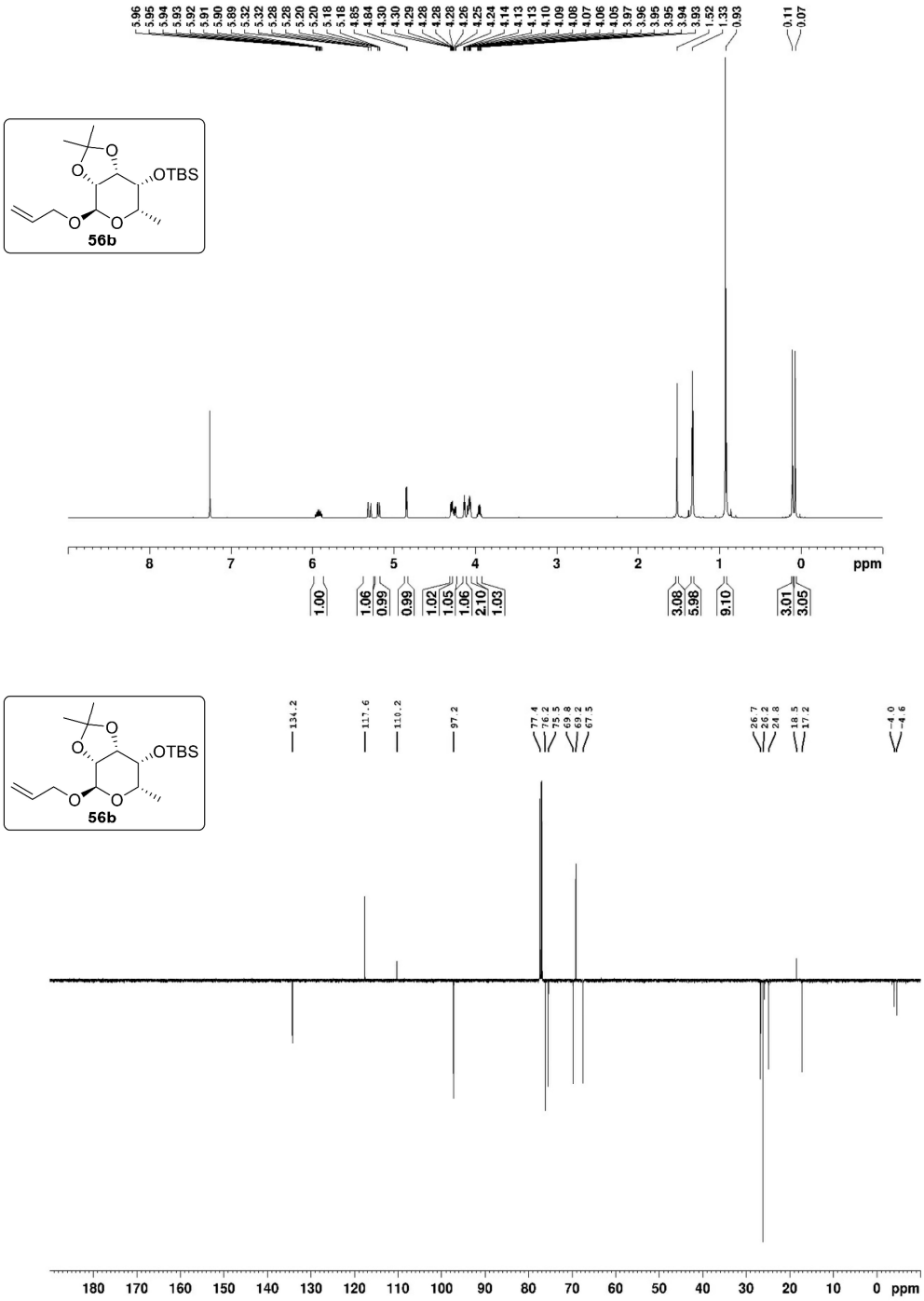

OAc
MeO
OBn
63
ppm
OAc
MeO
OBn
63
ppm

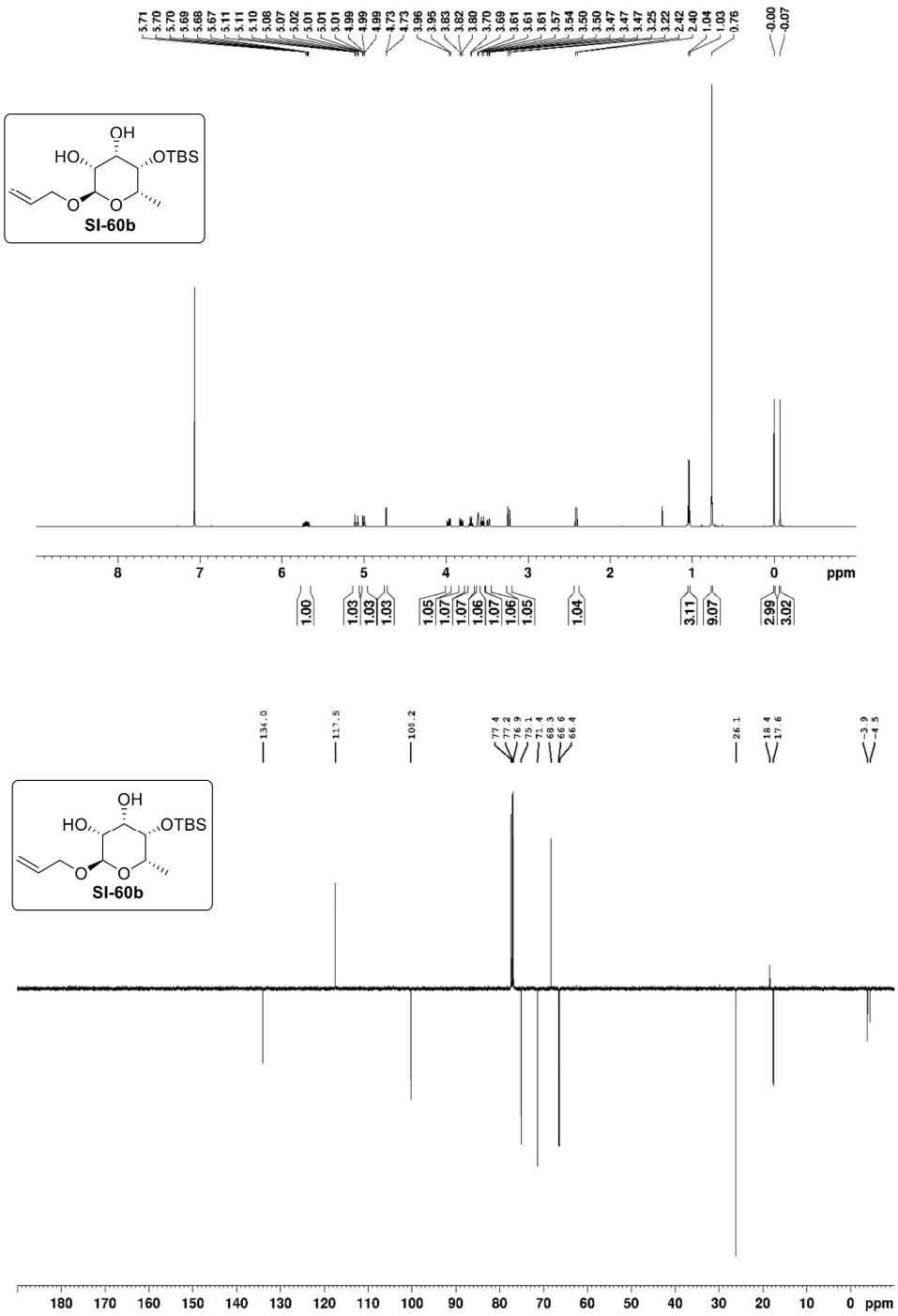

OAc
MeO
OBn
HO
O
58a
7.37
7.36
7.34
7.33
5.32
5.31
5.31
4.72
4.70
4.65
4.62
4.23
4.22
4.21
4.21
3.66
3.64
3.63
3.62
3.51
3.39
2.70
2.69
2.06
1.98
1.60
1.29
1.27
8
7
6
5
4
3
2
1
0
ppm
5.00
1.81
0.13
0.14
0.87
0.19
1.04
0.91
0.13
0.37
0.90
0.28
0.16
2.65
0.86
0.86
2.69
0.38
0.43
3.20
170.5
170.3
136.4
136.3
128.8
128.4
128.4
128.3
128.0
127.8
93.3
92.7
77.9
77.3
75.7
75.5
75.1
74.4
74.2
71.4
70.3
67.3
61.5
59.7
21.3
21.1
15.9
15.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

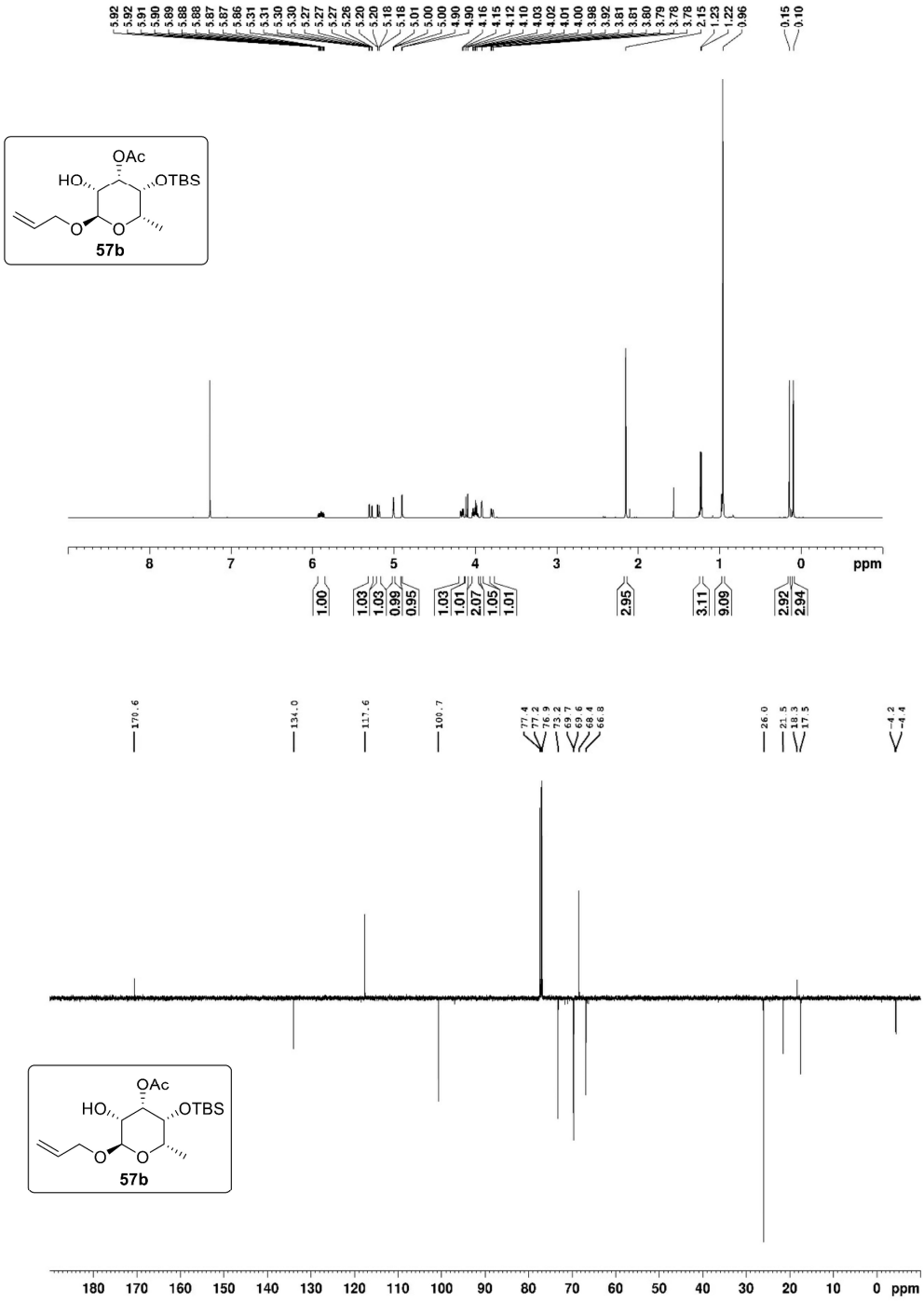
S146

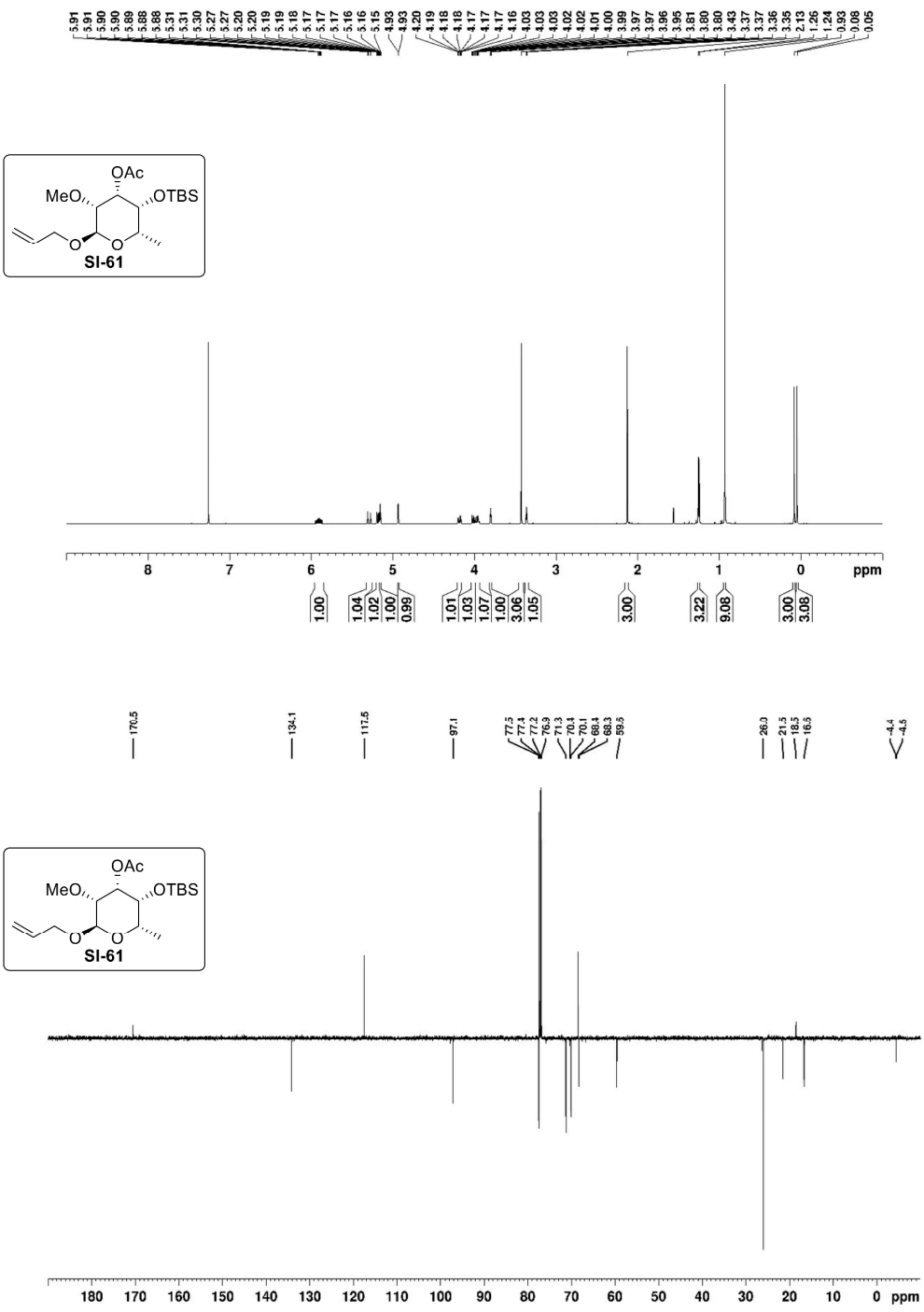

OAc
MeO
OBn
O
O
O
3
60a
ppm
OAc
MeO
OBn
O
O
O
3
60a
ppm

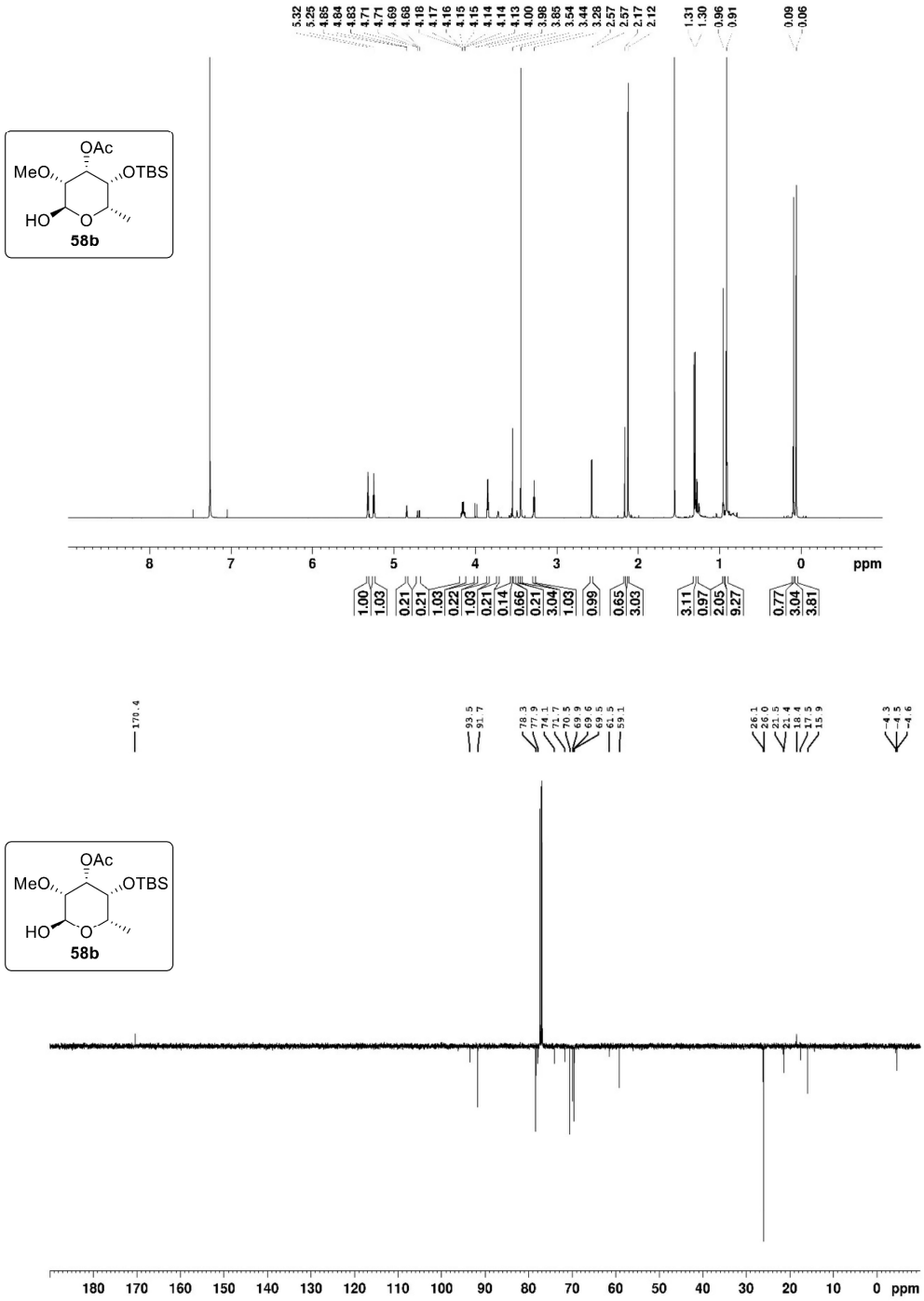

OAc
MeO
OBn
HO
O
N
O
O
62a
ppm
OAc
MeO
OBn
HO
O
N
O
O
62a
ppm

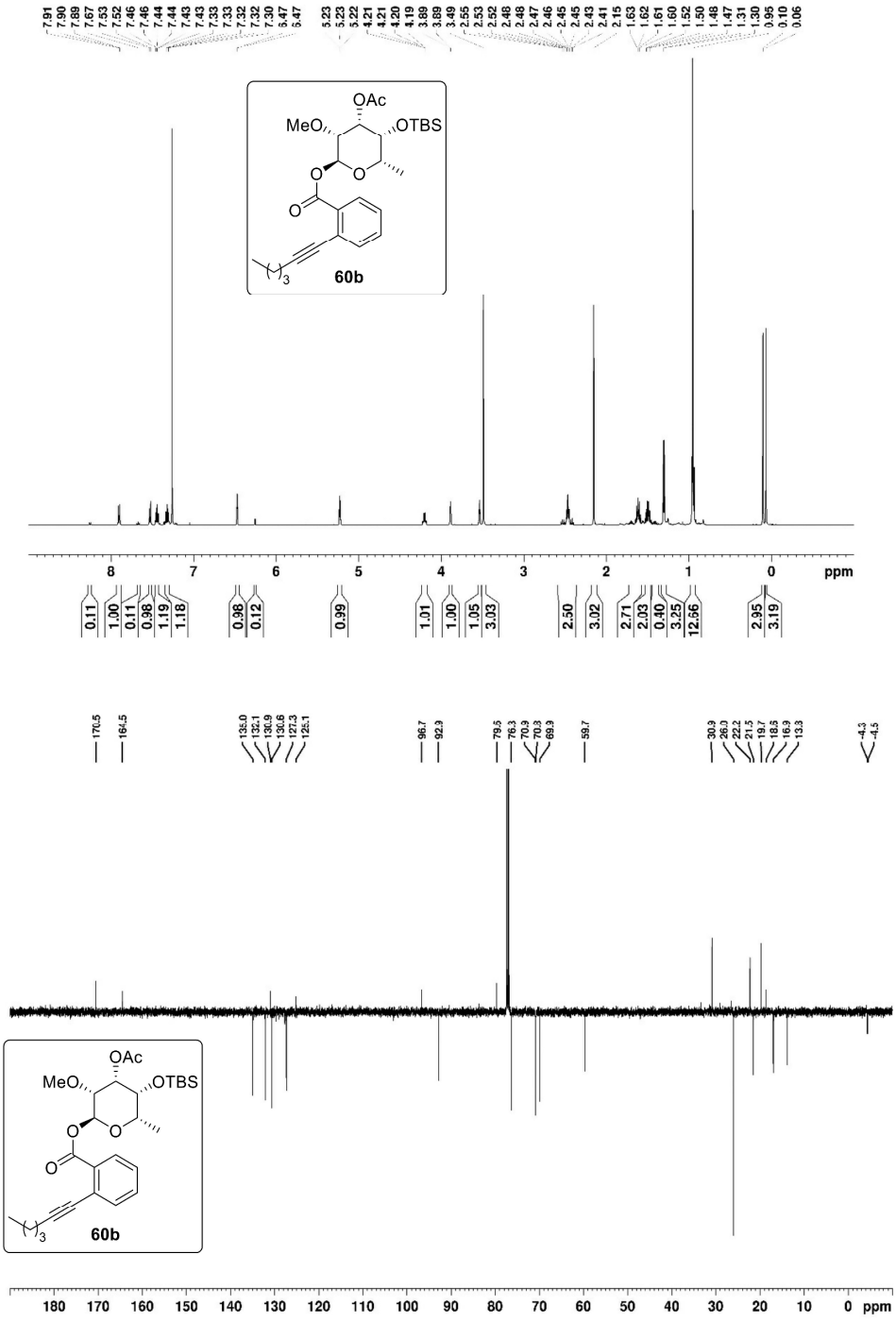

OTBS
56b
ppm
OTBS
56b
ppm

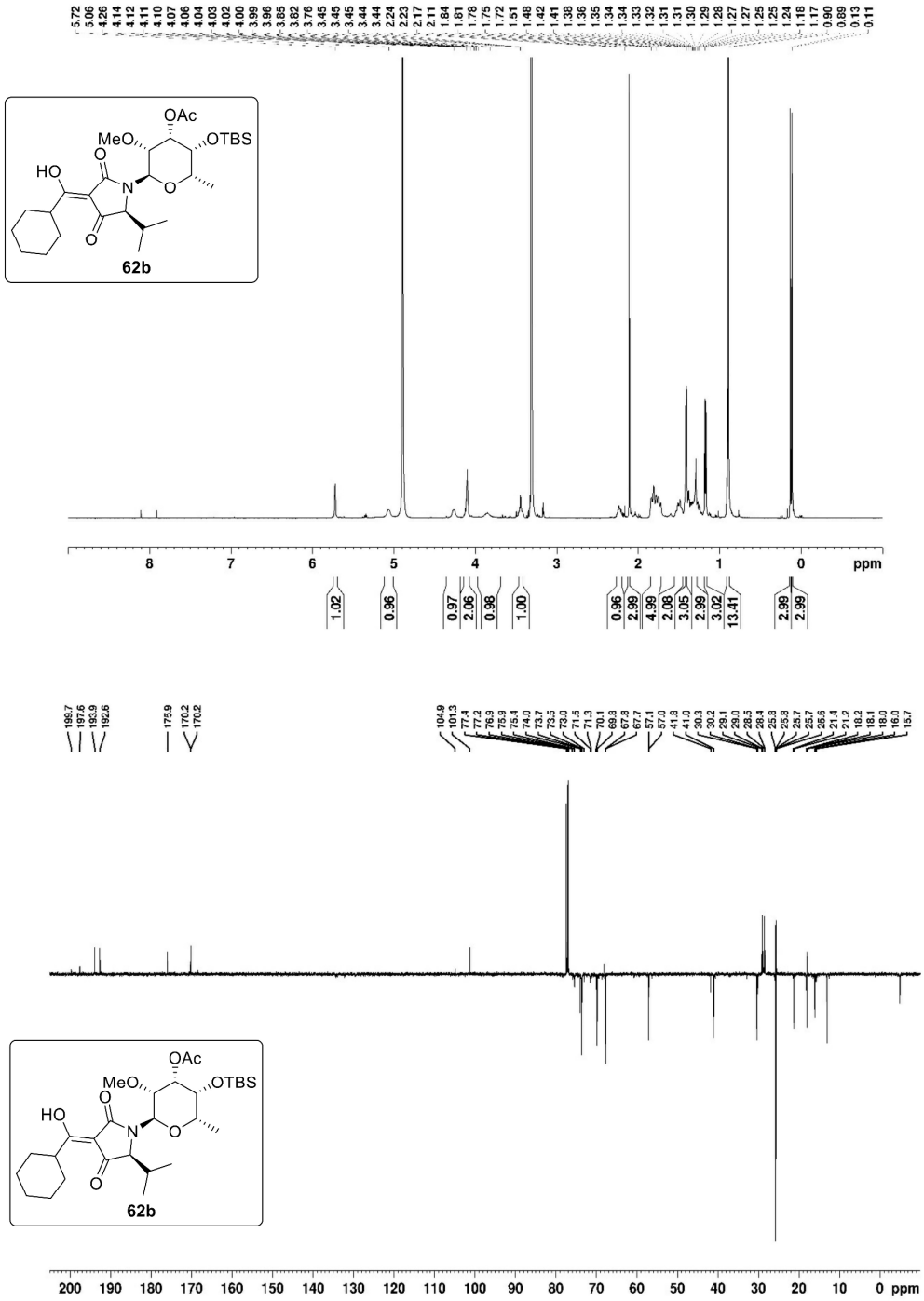

SI-60b
SI-60b
ppm
ppm

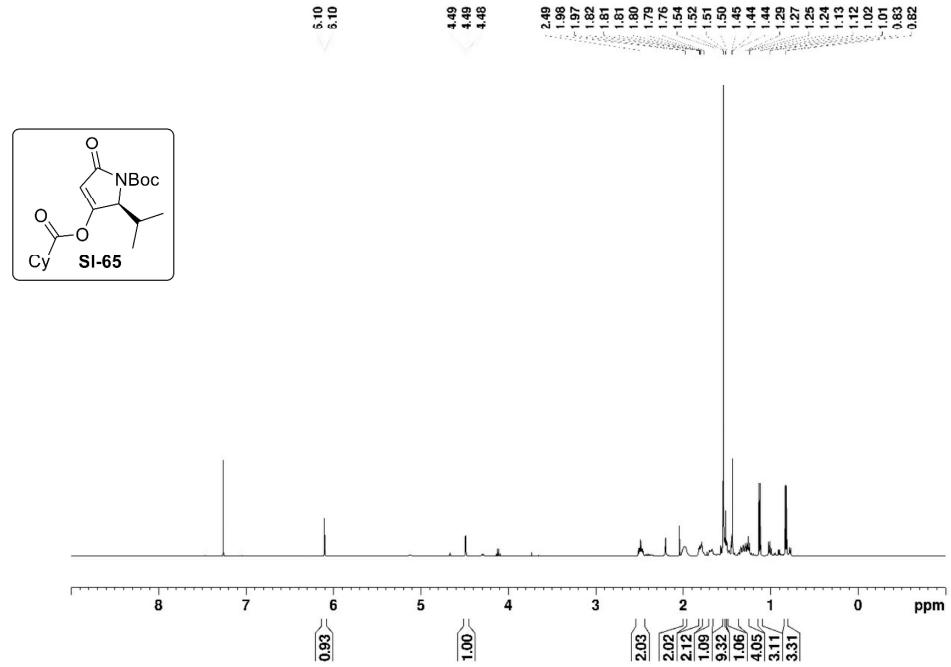

OAc
HO
OTBS
O
O
57b
ppm
OAc
HO
OTBS
O
O
57b
ppm

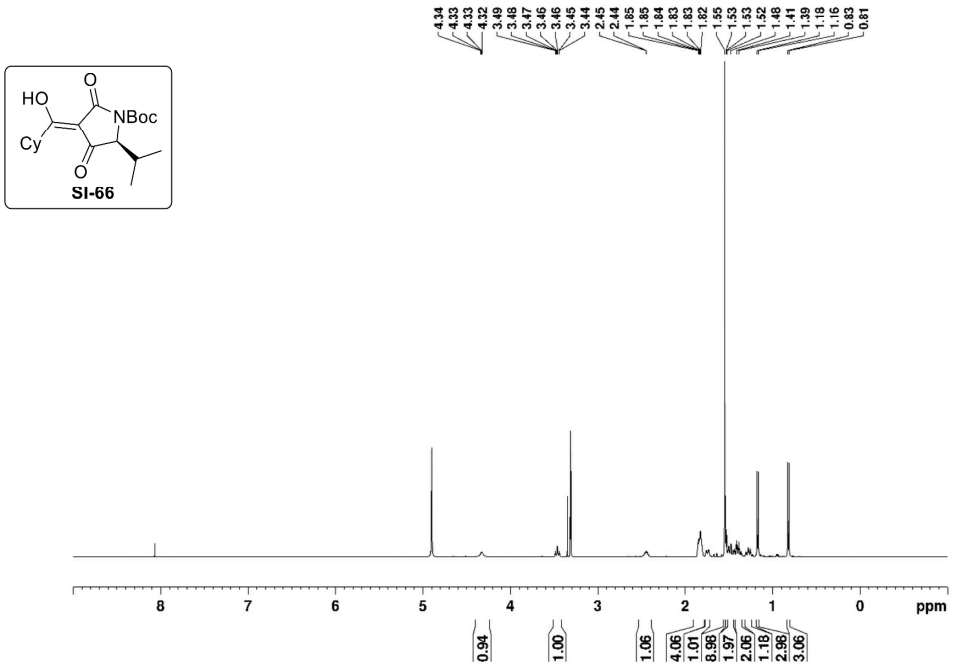

OAc
MeO
OTBS
O
O
SI-61
ppm
OAc
MeO
OTBS
O
O
SI-61
ppm

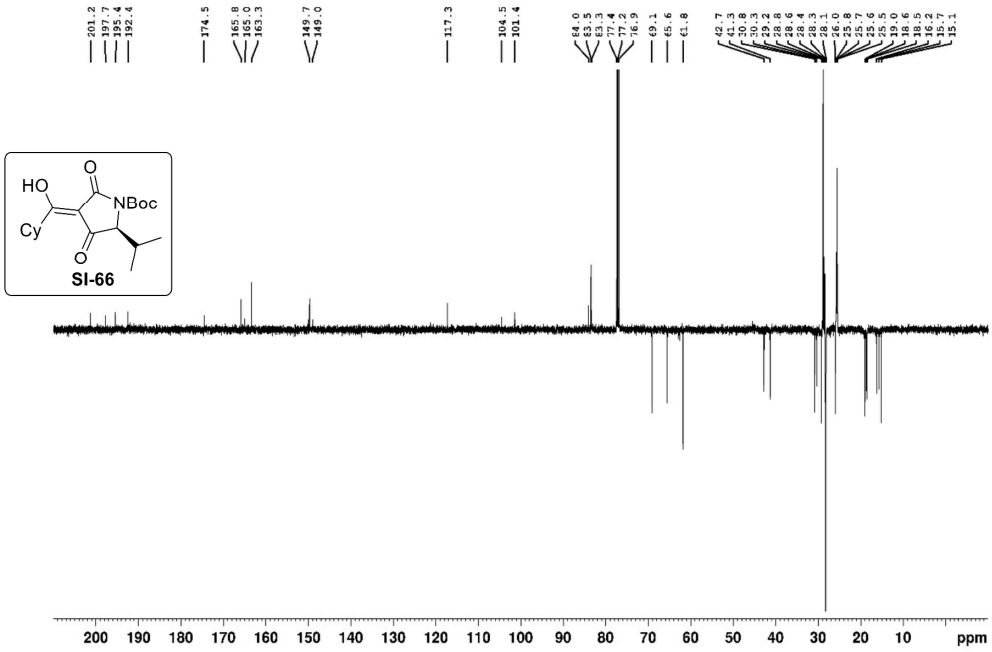

OAc
MeO
OTBS
HO
O
58b
5.32
5.25
4.85
4.84
4.83
4.71
4.71
4.69
4.68
4.18
4.17
4.16
4.15
4.15
4.14
4.14
4.13
4.00
3.98
3.85
3.54
3.44
3.28
2.57
2.57
2.17
2.12
1.31
1.30
0.96
0.91
0.09
0.06
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
0.21
0.21
1.03
0.22
1.03
0.21
0.14
0.66
0.21
3.04
1.03
0.99
0.65
3.03
3.11
0.97
2.05
9.27
0.77
3.04
3.81
170.4
93.5
91.7
78.3
77.9
74.1
71.7
70.5
69.9
69.6
69.5
61.5
59.1
26.1
26.0
21.5
21.4
18.4
17.5
15.9
-4.3
-4.5
-4.6
OAc
MeO
OTBS
HO
O
58b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

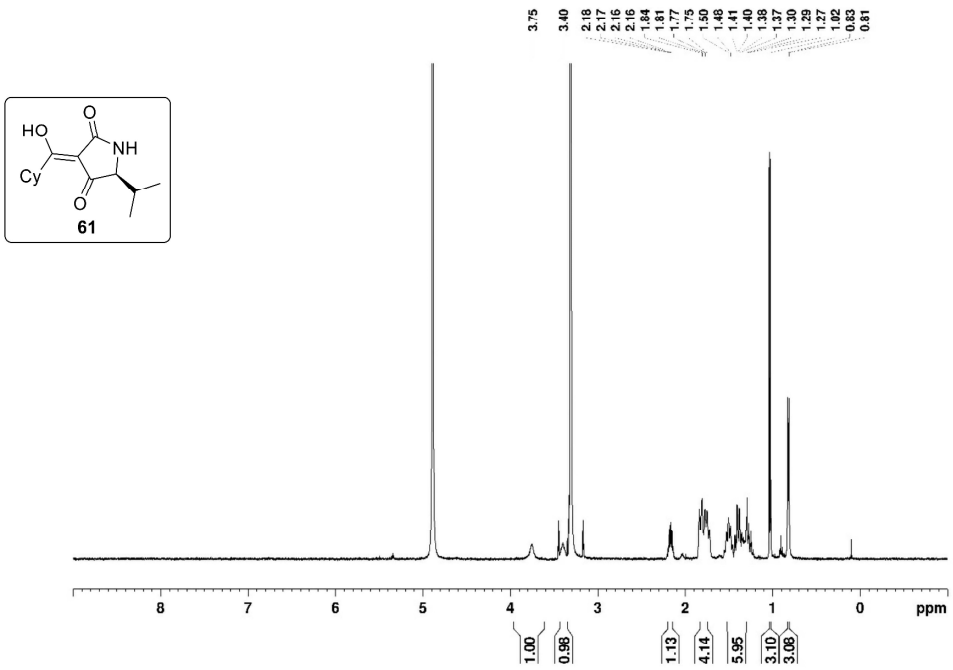

OAc
MeO
OTBS
O
O
O
60b
ppm
OAc
MeO
OTBS
O
O
O
60b
ppm

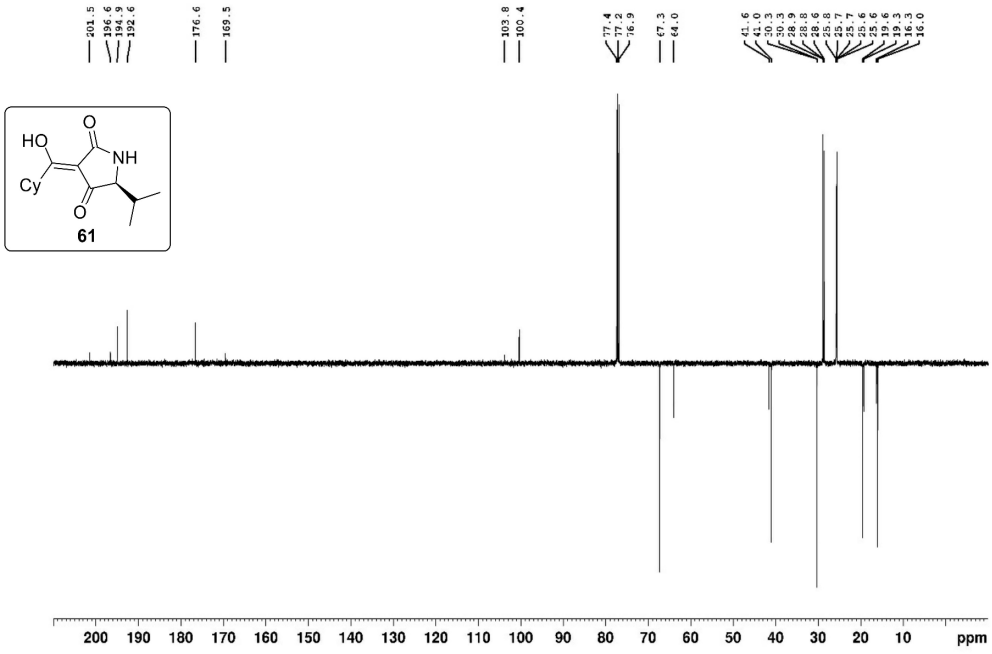

OAc
MeO
OTBS
HO
O
N
O
O
62b
ppm
1.02
0.96
0.97
2.06
0.98
1.00
0.96
2.99
4.99
2.06
3.05
2.99
3.02
13.41
2.99
2.99
OAc
MeO
OTBS
HO
O
N
O
O
62b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

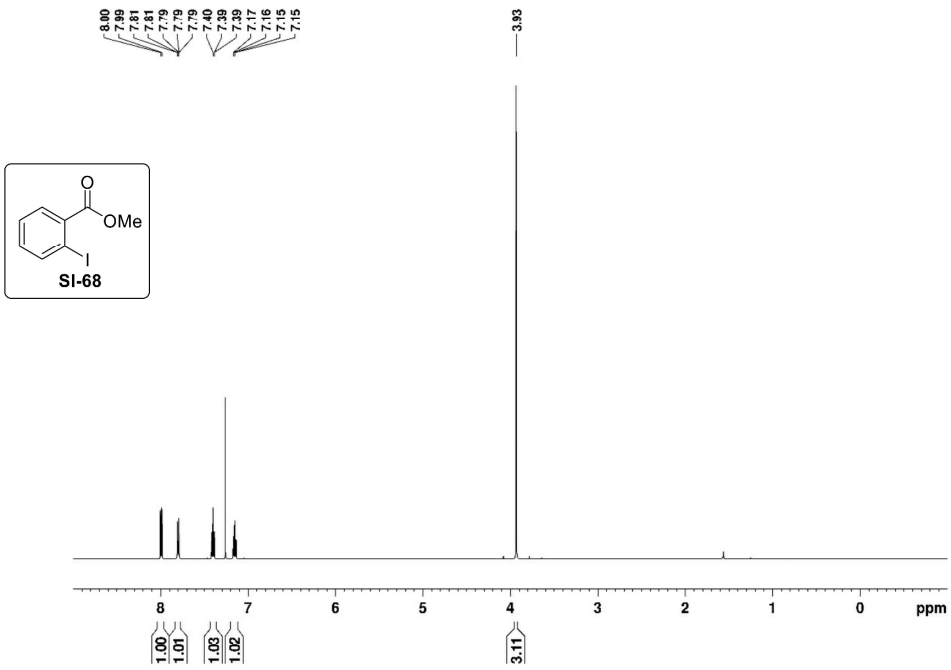

5.10
6.10
4.49
4.49
4.48
2.49
1.98
1.97
1.82
1.81
1.81
1.80
1.79
1.76
1.54
1.52
1.51
1.50
1.45
1.44
1.44
1.29
1.27
1.25
1.24
1.13
1.12
1.02
1.01
0.83
0.82
O
NBoc
O
O
Cy
SI-65
8
7
6
5
4
3
2
1
0
ppm
0.93
1.00
2.03
2.02
2.12
1.09
9.32
1.06
4.05
3.11
3.31

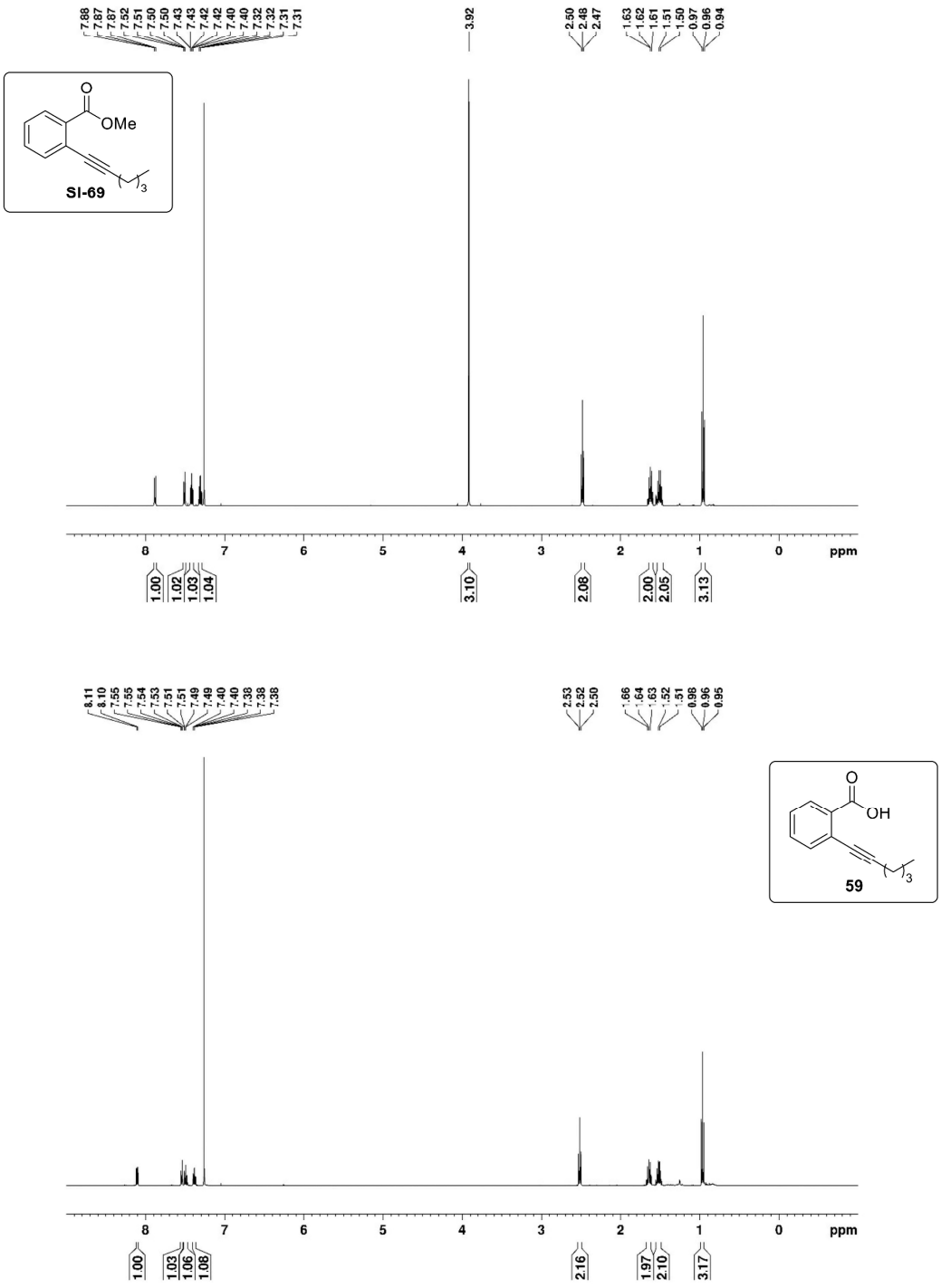

4.34
4.33
4.33
4.32
3.49
3.48
3.47
3.46
3.46
3.45
3.44
2.45
2.44
1.85
1.85
1.84
1.83
1.83
1.82
1.55
1.53
1.53
1.52
1.46
1.41
1.39
1.18
1.16
0.83
0.81
HO
O
NBoc
Cy
O
SI-66
8
7
6
5
4
3
2
1
0
ppm
0.94
1.00
1.06
4.06
1.01
8.98
1.97
2.05
1.18
2.96
3.06


HO
O
NBoc
Cy
O
SI-66
201.2
197.7
195.4
192.4
174.5
165.8
165.0
163.3
149.7
149.0
117.3
104.5
101.4
64.0
63.5
63.3
77.4
77.2
76.9
69.1
65.6
61.8
42.7
41.3
30.8
30.3
29.2
28.8
28.6
28.4
28.3
28.1
26.0
25.8
25.7
25.6
25.5
19.0
18.6
18.5
16.2
15.7
15.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

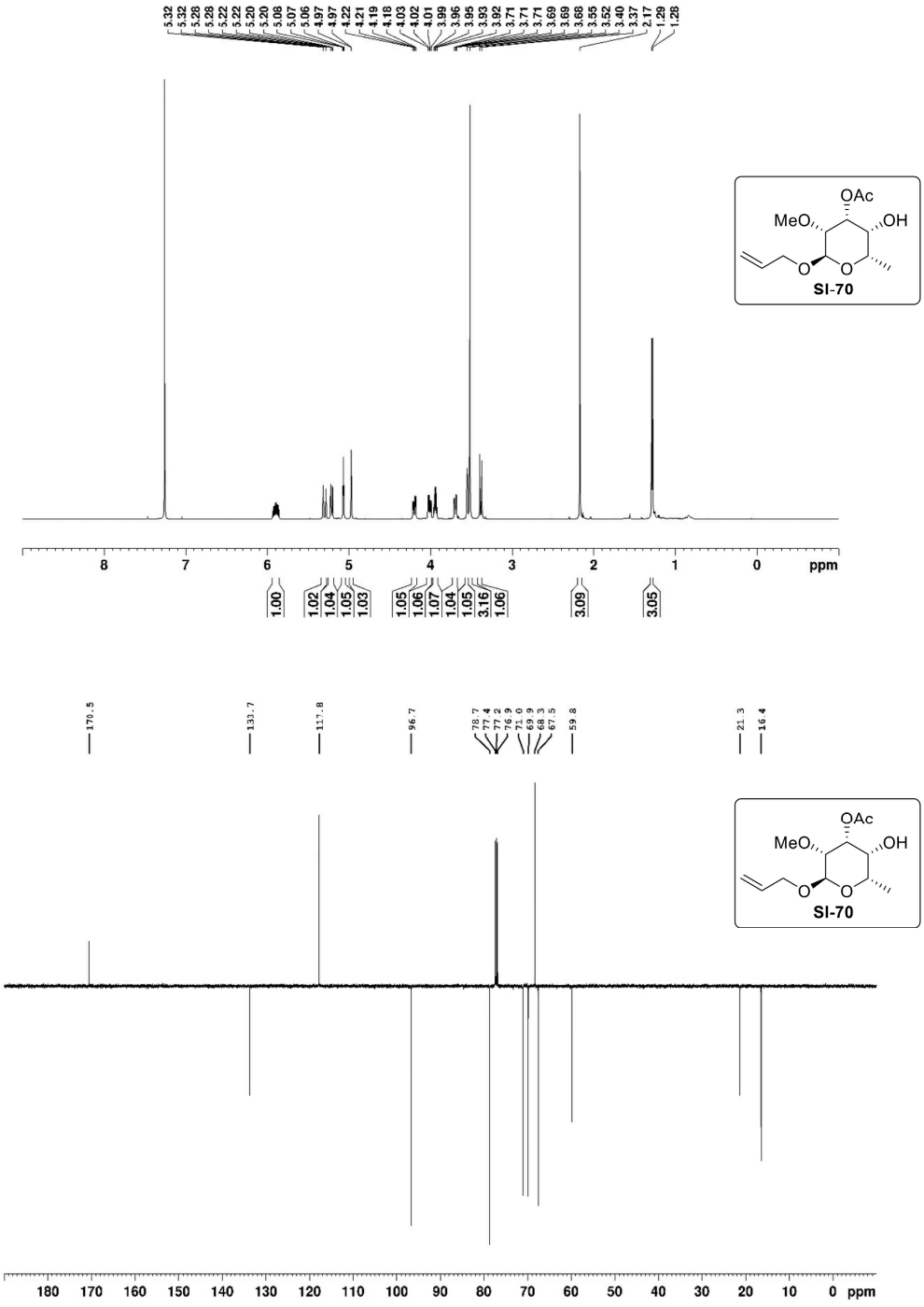

HO
O
NH
Cy
O
61
3.75
3.40
2.18
2.17
2.16
2.16
1.84
1.81
1.77
1.75
1.50
1.48
1.41
1.40
1.38
1.37
1.30
1.29
1.27
1.02
0.83
0.81
8 7 6 5 4 3 2 1 0 ppm
1.00
0.98
1.13
4.14
5.95
3.10
3.08

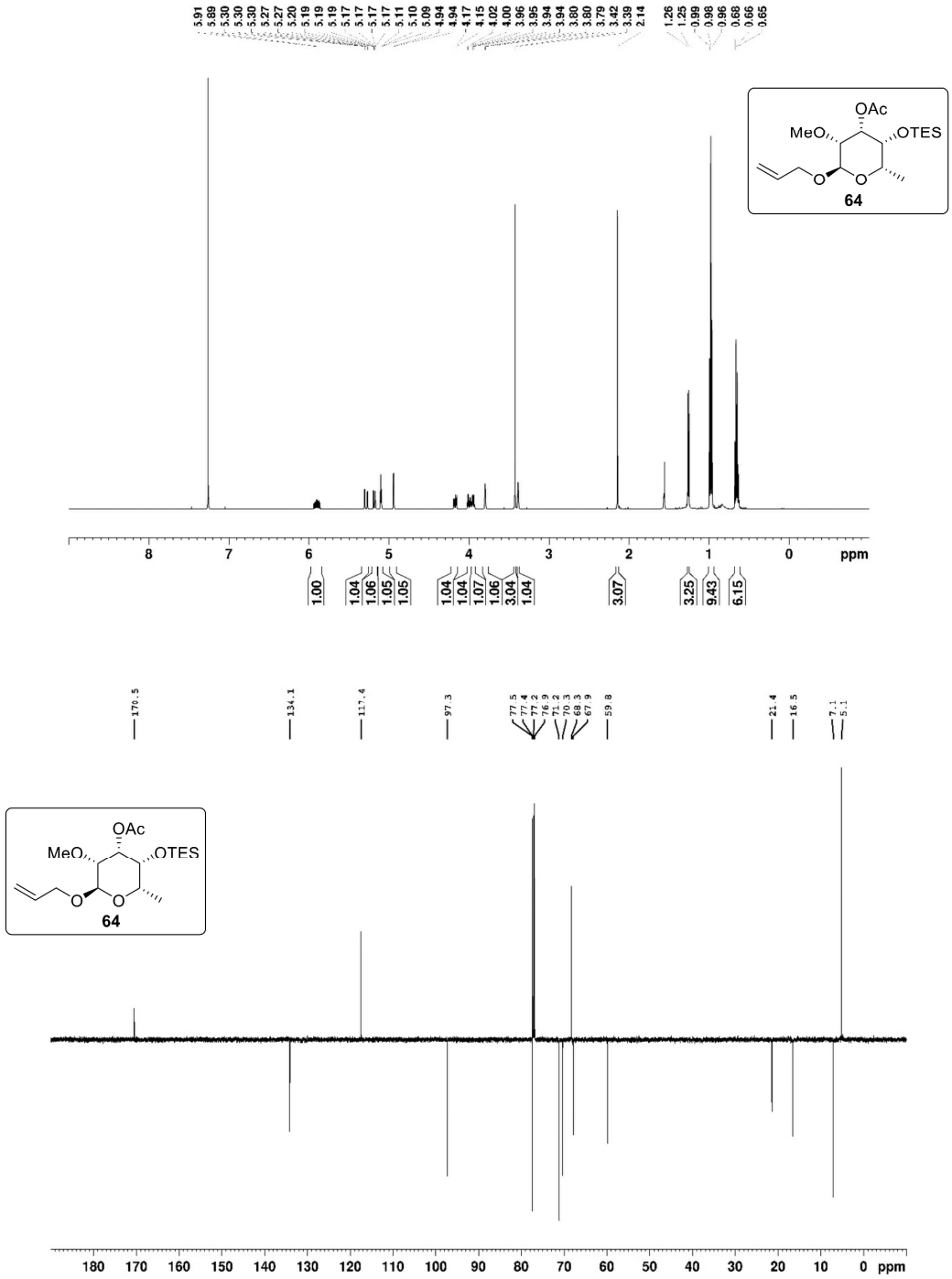

201.5
196.6
194.9
192.6
176.6
169.5
103.8
100.4
77.4
77.2
76.9
67.3
64.0
41.6
41.0
30.3
28.9
28.8
28.6
25.8
25.7
25.7
25.6
25.5
19.6
19.3
16.3
16.0
HO
O
NH
Cy
O
61
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

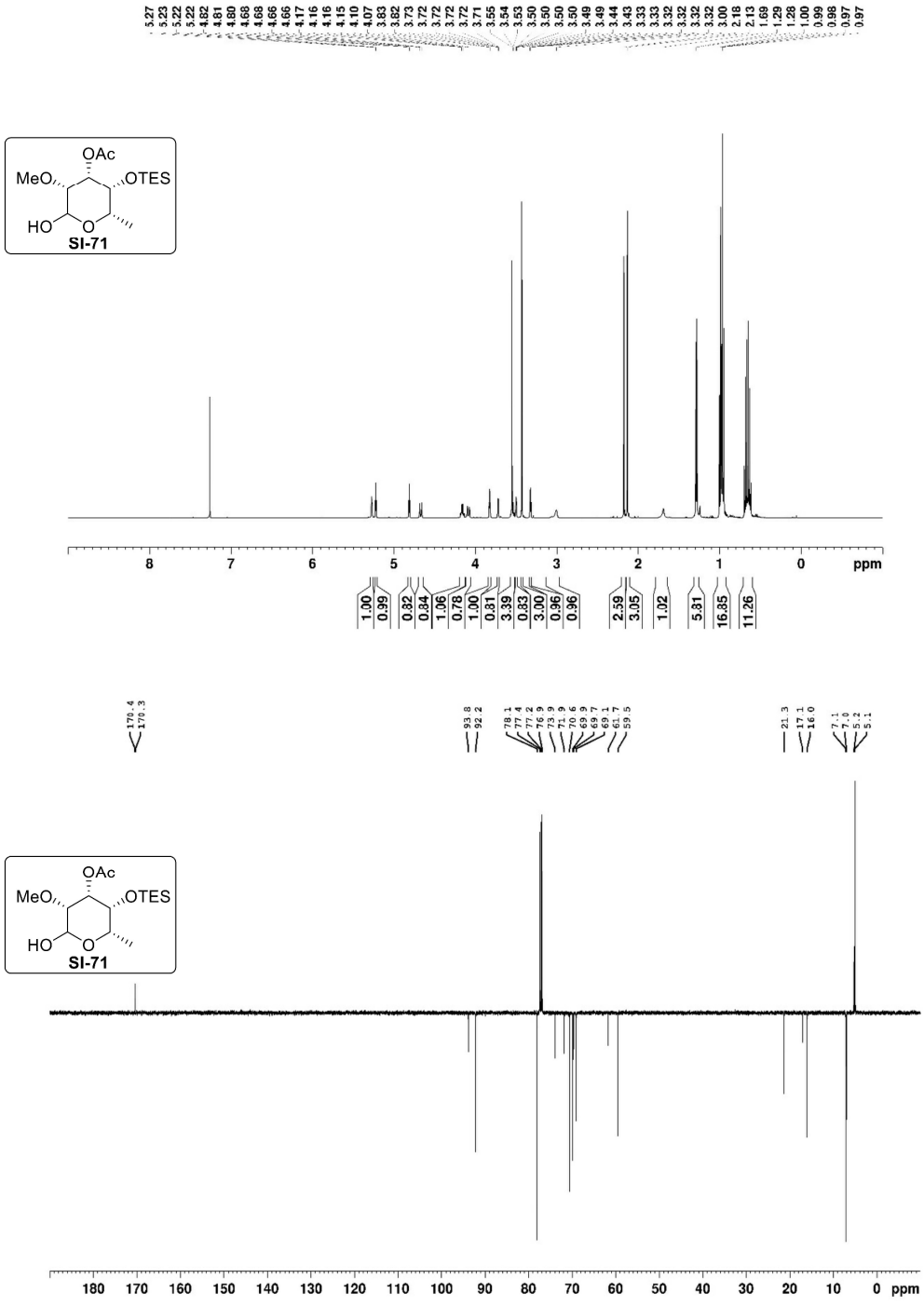

8.00
7.99
7.81
7.81
7.79
7.79
7.79
7.40
7.39
7.39
7.17
7.16
7.15
7.15
7.15
3.93
O
OMe
I
SI-68
8 7 6 5 4 3 2 1 0 ppm
1.00
1.01
1.03
1.02
3.11

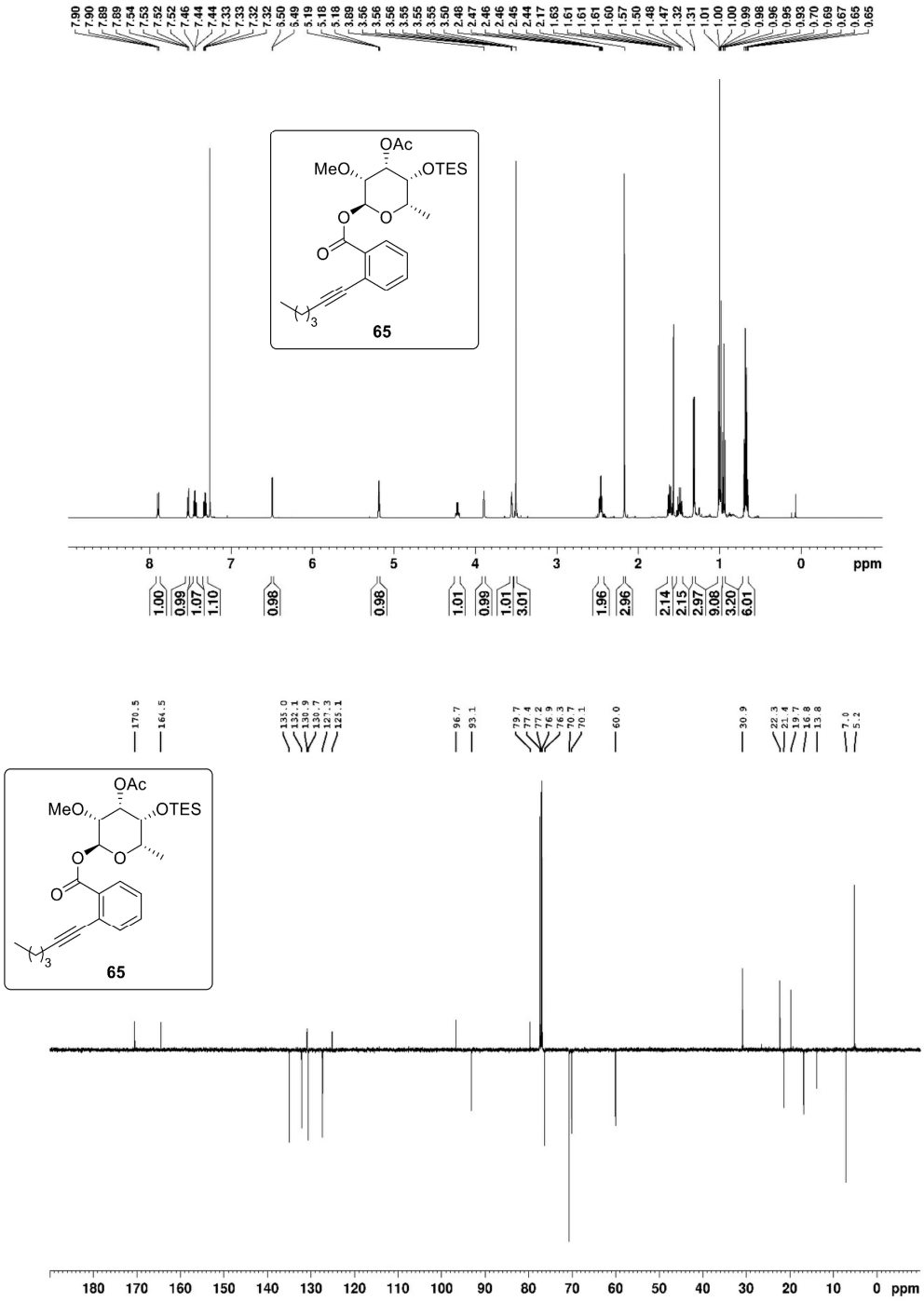

7.88
7.87
7.87
7.52
7.51
7.50
7.50
7.43
7.43
7.42
7.42
7.40
7.40
7.32
7.32
7.31
7.31
3.92
2.50
2.48
2.47
1.63
1.62
1.61
1.61
1.51
1.50
0.97
0.96
0.94
O
OMe
3
SI-69
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
1.03
1.04
3.10
2.08
2.00
2.05
3.13
8.11
8.10
7.55
7.55
7.54
7.53
7.51
7.51
7.49
7.49
7.40
7.40
7.38
7.38
7.38
2.53
2.52
2.50
1.66
1.64
1.63
1.52
1.51
0.98
0.96
0.95
O
OH
3
59
8
7
6
5
4
3
2
1
0
ppm
1.00
1.03
1.06
1.08
2.16
1.97
2.10
3.17

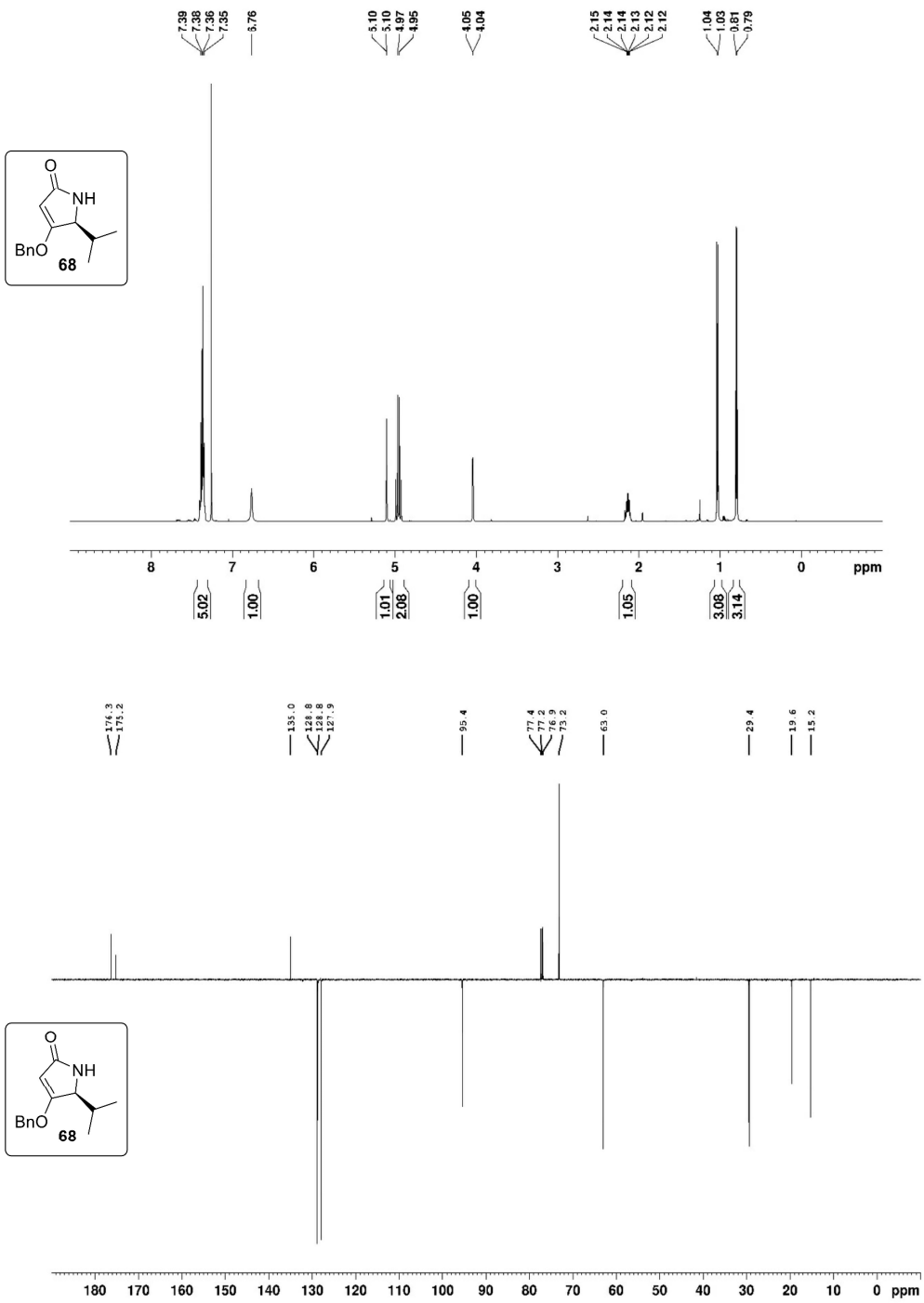
S159


OAc
MeO
OH
O
O
SI-70
ppm
OAc
MeO
OH
O
O
SI-70
ppm


OAc
MeO
OTES
64
ppm
OAc
MeO
OTES
64
ppm


OAc
MeO
OTES
HO
O
SI-71
ppm
OAc
MeO
OTES
HO
O
SI-71
ppm


OAc
MeO
OTES
O
O
O
65
ppm
OAc
MeO
OTES
O
O
O
65
ppm


7.39
7.38
7.36
7.35
5.76
5.10
5.10
4.97
4.95
4.05
4.04
2.15
2.14
2.14
2.13
2.12
2.12
1.04
1.03
0.81
0.79
O
NH
BnO
68
8
7
6
5
4
3
2
1
0
ppm
5.02
1.00
1.01
2.08
1.00
1.05
3.08
3.14
176.3
175.2
135.0
128.8
128.8
127.9
95.4
77.4
77.2
76.9
73.2
63.0
29.4
19.6
15.2
O
NH
BnO
68
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

5.5 Publikationsliste

1. **Synthesis of the fungal macrolide berkeleylactone A and its inhibition of microbial biofilm formation**

   Manuel G. Schriefer, Hedda Schrey, Haoxuan Zeng, Marc Stadler, Rainer Schobert

   Org. Biomol. Chem. **2021**, *19* (21), 4743 – 4751.

2. **Divergent Synthesis of Six Recent Berkeleylactones**

   Manuel G. Schriefer, Rainer Schobert

   J. Nat. Prod. **2023**, *86* (2), 423 – 428.

3. **Formal synthesis of kibdelomycin and derivatisation of amycolose glycosides**

   Manuel G. Schriefer, Laura Treiber, Rainer Schobert

   Chem. Sci. **2023**, *14* (13), 3562 – 3568.

Danksagung

Mein besonderer Dank gilt Herrn Prof. Dr. Rainer Schobert für die Ermöglichung meiner Doktorarbeit sowie die großen Freiheiten bei der Auswahl der Themenstellung und der Bewältigung der Probleme.

Außerdem sei an dieser Stelle meinen Eltern und meiner Familie Dank auszusprechen, die mir meinen Lebensweg und mein Studium ermöglicht haben.

Zudem möchte ich mich bei allen Arbeitskollegen des Lehrstuhls OC I bedanken, die mir bei Problemen behilflich waren.

Darüber hinaus muss ich mich namentlich bei Lina Beck und Evgeni Statelov für deren Mitwirken an einigen Forschungsprojekten im Rahmen ihrer von mir betreuten Bachelor-Arbeit bedanken.

Zuletzt muss ich noch vor allem Laura Treiber danken, ohne deren unermüdlichen Arbeitswillen der Abschluss des Kibdelomycin-Projekts nicht möglich gewesen wäre. Von daher hoffe ich, dass wir auch in Zukunft noch weitere gemeinsame (wissenschaftliche) Projekte realisieren werden.

(Eidesstattliche) Versicherungen und Erklärungen

(§ 8 Satz 2 Nr. 3 PromO Fakultät)

Hiermit versichere ich eidesstattlich, dass ich die Arbeit selbstständig verfasst und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe (vgl. Art. 64 Abs. 1 Satz 6 BayHSchG).

(§ 8 Satz 2 Nr. 3 PromO Fakultät)

Hiermit erkläre ich, dass ich die Dissertation nicht bereits zur Erlangung eines akademischen Grades eingereicht habe und dass ich nicht bereits diese oder eine gleichartige Doktorprüfung endgültig nicht bestanden habe.

(§ 8 Satz 2 Nr. 4 PromO Fakultät)

Hiermit erkläre ich, dass ich Hilfe von gewerblichen Promotionsberatern bzw. –vermittlern oder ähnlichen Dienstleistern weder bisher in Anspruch genommen habe noch künftig in Anspruch nehmen werde.

(§ 8 Satz 2 Nr. 7 PromO Fakultät)

Hiermit erkläre ich mein Einverständnis, dass die elektronische Fassung der Dissertation unter Wahrung meiner Urheberrechte und des Datenschutzes einer gesonderten Überprüfung unterzogen werden kann.

(§ 8 Satz 2 Nr. 8 PromO Fakultät)

Hiermit erkläre ich mein Einverständnis, dass bei Verdacht wissenschaftlichen Fehlverhaltens Ermittlungen durch universitätsinterne Organe der wissenschaftlichen Selbstkontrolle stattfinden können.

Ort, Datum, Unterschrift