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Diastereodivergent Synthesis of the Quinolizidine-Indolizidine Alkaloids of the Leontidine/Camoensine Family

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In memoriam of Professor Siegfried Hünig.

Leontidine and camoensine, the main representatives of the small quinolizidine-indolizidine alkaloid subgroup, are characterized by an inner bispidine system to which a 2-pyridone and a pyrrolidine are fused on opposite sides. We efficiently synthesized both natural products from the commercially available and abundant alkaloid cytisine, which was converted into the key intermediate, *N*-Boc-11-oxocytisine, by iodine oxidation and protection. Grignard addition, Paal-Knorr type cyclization, and hydrogenation delivered *endo*-pyrrolidine fused leontidine, while the reversed reaction order, *viz.* reduction, Sakurai allylation, and ring closure, afforded *exo*-pyrrolidine annulated camoensine. Hydrogenation and deoxygenation of the pyridone moieties provided four further alkaloids, tetrahydroleontidine, camoensidine, 11-epileontidane and leontidane. In addition, the artificial alkaloid isoleontidine, carrying an *endo*-fused pyrrolidine on the same side as the pyridone, was prepared from C-13 oxidized cytisine.

Introduction

Tri- and tetracyclic (bis)quinolizidine alkaloids (Figure 1) are the most prominent secondary metabolites in the Papilionoideae subfamily of the plant family Fabaceae (Leguminosae).[1,2] These natural products are all structurally characterized by an inner bispidine core (3,7-diazabicyclo[3.3.1]nonane, **6**), to which normally combinations of an *exo*- or *endo*-piperidine, as in sparteine (**1**), lupanine (**2**), anagyrine (**4**), and thermopsine (**5**), or an oxidized version thereof, such as the 2-piperidone in **2** or the 2-pyridone in cytisine (**3**), **4**, and **5**, are attached on opposite sides. This structural feature is a consequence of their biosynthesis from three molecules of L-lysine (C_5N source): two of them form the outer piperidines while the third one completes the central bispidine core (see arrangement **A**, n = 1).[1,3] The initially produced metabolites are sparteine (**1**) and lupanine (**2**), which get further modified, for example by oxidation, degradation, and epimerization, thus setting the basis for the roughly 200 known (bis)quinolizidine alkaloids.

In addition to the 'standard' (bis)quinolizidine alkaloids, a small number of atypical quinolizidine-indolizidine derivatives (**7**–**12**) exists that possess an *exo*- or *endo*-fused pyrrolidine.[4] It is hypothesized that the smaller ring size results from a replacement of one molecule of L-lysine by L-ornithine (C_4N source) during their biosynthesis.[5] The first member of this subclass, leontidine (**7**), was already isolated in 1932 from *Leontice ewersmannii*,[6] camoensine (**10**)[7] and camoensidine (**11**),[8] both first extracted from *Camoensia maxima*, followed in 1975. Tetrahydroleontidine (**8**)[8d] and 11-epileontidane (**12**)[8d] were detected by GC-MS in *Maackia amurensis*, their only natural source so far. The fully reduced derivative in the leontidine row, leontidane (**12**), has not yet been found in nature.

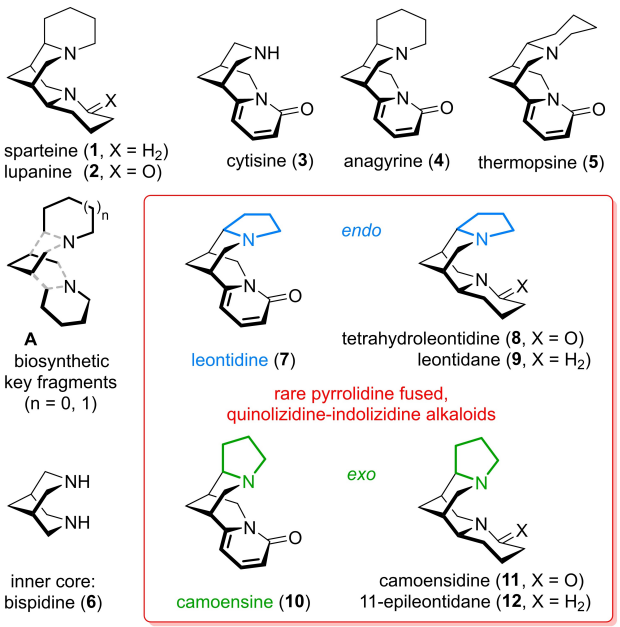

Figure 1. Natural (bis)quinolizidine alkaloids (**1**–**5**), the inner bispidine core **6**, and the rare quinolizidine-indolizidine alkaloids (**7**–**12**).

The first syntheses of these alkaloids were done in the context of their (stereo)structure elucidation. Santamaria and Khuong-Huu prepared camoensidine (**11**) from lupanine (**2**) by

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formal ring contraction (4 steps, 7% yield),[6g] while Yunusov's route from cytisine (**3**) to leontidine (**7**) included an unintended epimerization (4 steps, 0.4% yield).[6e,g] The synthesis of camoensine (**10**) by Ohmiya and coworkers is illustrated in Scheme 1 (bottom).[10] Chlorination of cytisine (**3**) followed by HCl elimination furnished the imine **16** in low 40% yield because of regioselectivity issues.[11] Addition of the Grignard reagent **17** occurred highly diastereoselectively to the less hindered *exo*-face of **16**, but in low 23% yield, thus giving, after acetal hydrolysis and reductive cyclization, the alkaloid **10** in overall 4 steps and meager 8% yield. Furthermore, *exo*-configured camoensine (**10**) and camoensidine (**11**) were transformed into their *endo*-counterparts, leontidine (**7**) and tetrahydroleontidine (**8**), by an oxidation-reduction sequence, but again in low yields (9–11%).[6g] Satisfying yields (>80%) were solely obtained in the hydrogenations of the pyridone derivatives **7** and **10** to the respective piperidones **8** and **11**.[6g]

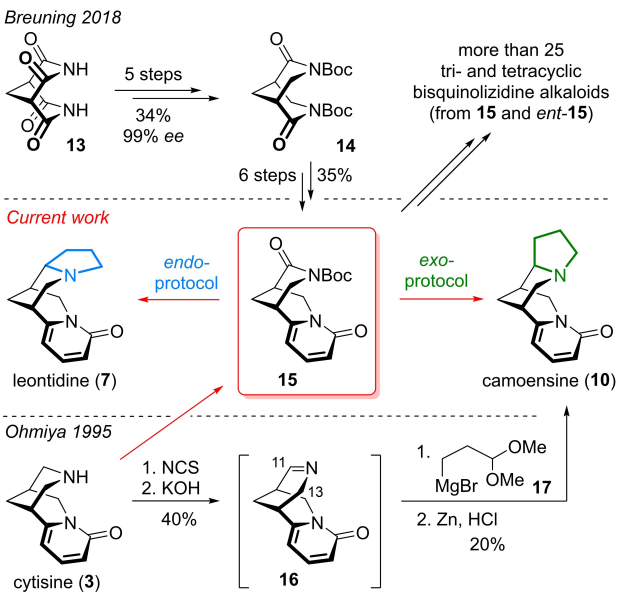
We recently presented an effective inside-out approach to tri- and tetracyclic bisquinolizidine alkaloids that permits access to more than 25 members of this class in both enantiomeric forms (Scheme 1, top).[12–14] Key sequences include the reductive desymmetrization of the bisimide **13** and the transformation of the resulting dioxobispidine **14** into the α,*N*-pyridone annulated tricycle **15**. An important stereochemical feature is that the *N*-Boc activated lactam function in **15** allows an introduction of either an *endo*- or, optionally, an *exo*-fused ring by a simple change of the reaction order. Since all nucleophilic attacks on the carbonyl group in **15** or on related functionalities occur highly selectively from the less hindered, convex *exo*-face, a reduction-organyl addition sequence will install an *exo*-substituent (*exo*-protocol), while the reversed organyl addition-reduction procedure will generate an *endo* one (*endo*-protocol).

Given the ease of stereoselective ring annulation at **15**, we decided to develop the first efficient and diastereodivergent route to the quinolizidine-indolizidine alkaloids **7**–**12** of the leontidine/camoensine family. Although key intermediate **15** can be prepared from **13** by total synthesis,[12] we searched for a straightforward ex-natural-pool approach. The abundant, commercially available alkaloid cytisine (**3**), which can be isolated in good quantities from the seeds of the Golden Rain tree, *Laburnum anagyroides*,[15] seemed to be an ideal source.

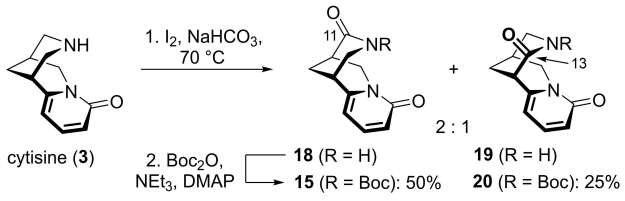
Results and Discussion

Our synthesis commenced with the search for a suitable method that permits an oxidation of the amino function in cytisine (**3**) to an amide. Screening of several reagents (e.g. $K_3Fe(CN)_6$, $PhI(OAc)_2$, $KMnO_4$) and optimization of the reaction conditions revealed iodine as oxidant of choice,[16] which is also advantageous with regard to environmental aspects. Treatment of **3** with an excess of iodine (7.5 equivalents) in THF/sat. $NaHCO_3$ (1:1) at 70 °C delivered a 2:1 mixture of desired 11-oxocytisine (**18**), a natural product by itself,[17] and the unwanted C-13 oxidation product **19** (Scheme 2). Thus, the effect of the fused pyridone on the regioselectivity of the oxidation step is just small,[18] which is in good agreement with the results of earlier NCS oxidations of **3** (see Scheme 1).[11] Since chromatographic separation of the isomers **18** and **19** proved to be tedious, the crude reaction mixture was subjected to *N*-Boc protection, which provided, after column chromatography or, even more conveniently, after MPLC separation, the key intermediate **15** in analytically pure form and overall 50%. The *N*-Boc lactam **20** was obtained in 25% yield.

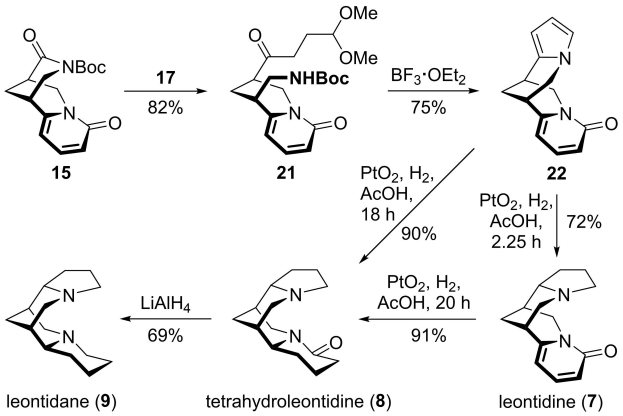
The leontidine-type natural products were accessed from **15** by applying the *endo*-protocol (Scheme 3). Addition of the functionalized Grignard reagent **17** occurred smoothly at the *N*-Boc imide function and delivered, after ring opening of the primarily resulting hemiaminal during work up, the ketone **21** in high 82% yield. The *N*-Boc group was cleaved under Lewis acidic conditions, which triggered a Paal-Knorr type intramolecular pyrrole synthesis that afforded the unnatural pyrrolocytisine **22**[19,20] in a single step and 75% yield. Preferential hydrogenation of the electron-rich pyrrole in the presence of the pyridone was achieved with PtO_2 under acidic conditions and a short reaction time. Other catalysts, such as Pd/C, $Pd(OH)_2$/C, $Pd(OAc)_2$, Ru/C, $RhCl(PPh_3)_3$, or Raney-Ni, afforded mixtures of **7** and **8**. As expected, hydrogenation exclusively occurred from the less concave *exo*-site and solely provided natural, *endo*-pyrrolidine fused leontidine (**7**). Under the same



Scheme 1. Known[10,12,13] and current strategies for the total synthesis of bisquinolizidine and quinolizidine-indolizidine alkaloids.



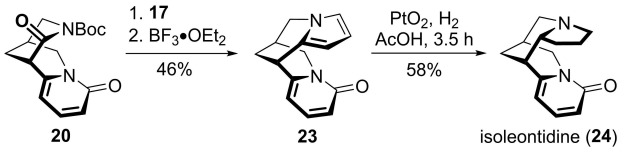
Scheme 2. Preparation of the key intermediate **15** by oxidation of cytisine (**3**) and *N*-Boc protection.



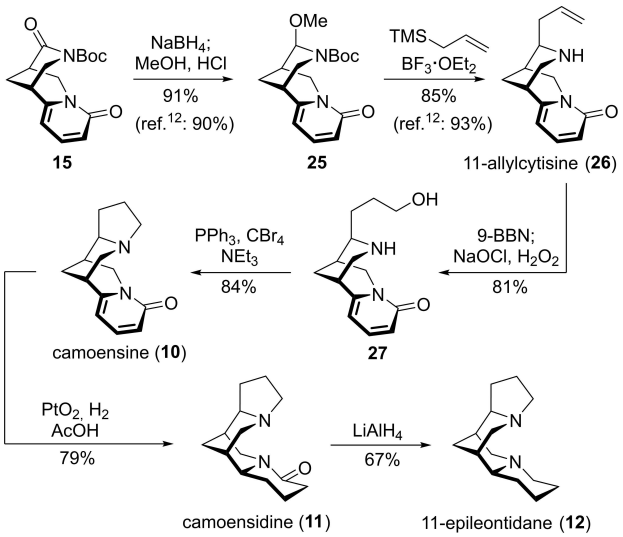
Scheme 3. Synthesis of the *endo*-pyrrolidine fused quinolizidine-indolizidine alkaloids **7**–**9** of the leontidine family.

conditions, but at prolonged reaction times, the pyridone moieties in **22** and **7** were hydrogenated, too, giving the alkaloid tetrahydroleontidine (**8**) as the only product and in high $\geq$90% yield. Final reduction of **8** with $LiAlH_4$ afforded leontidane (**9**), an alkaloid which has not yet been found in nature.

Submission of the C-13 oxidized cytisine derivative **20** to the addition-cyclization sequence described above delivered the tetracyclic pyrrolo alkaloid **23** (Scheme 4).[21] Mild hydrogenation afforded the artificial alkaloid isoleontidine (**24**), a regioisomer of leontidine (**7**) with both fused rings on the same side, in 33% overall yield over three steps.



Scheme 4. Synthesis of the artificial alkaloid isoleontidine (**24**).



Scheme 5. Synthesis of the *exo*-pyrrolidine fused quinolizidine-indolizidine alkaloids **10**–**12** of the camoensine family.

The members of the camoensine family, **10**–**12**, were synthesized by using the *exo*-protocol, which is based on a reduction-addition sequence (Scheme 5). Reduction of the lactam **15** and acetalization, as developed earlier in our group,[12] provided the *N,O*-acetal **25** in high 91% yield. All attempts to introduce functionalized lithium, magnesium, zinc, and copper organyls (e.g. **17**) to **25** or the iminium species derived thereof were met with low success,[22] which parallels the insufficient yields reached by Ohmiya *et al.* in their additions to the imine **16** (see Scheme 1).[10] To circumvent this problem, *N,O*-acetal **25** was converted into the natural alkaloid 11-allylcytisine (**26**),[23,24] following a known Sakurai protocol (85%).[12] The direct hydroamination of **26** to camoensine (**10**) in the presence of a catalytic amount of a Rh^I-phosphine complex[25] failed, and one-pot protocols such as hydrozirconation with the Schwartz reagent cp_2ZrHCl or hydroboration with $BH_3 \cdot SMe$, both followed by a metal/iodine exchange and an intramolecular substitution to close the pyrrolidine, delivered **10** in just low yields (<20%).[26] By far more efficient was a two-step sequence: Hydroboration of **26** with 9-BBN and subsequent oxidation[27] afforded selectively the terminal alcohol **27**, which was subjected to hydroxy/bromide exchange under Appel conditions providing, after *in-situ* ring closure under HBr elimination, the desired natural product camoensine (**10**) in good 68% yield over two steps. Hydrogenation of **10** over PtO_2 under acidic conditions delivered camoensidine (**11**), which was reduced with $LiAlH_4$ to give the third natural alkaloid in this row, 11-epileontidane (**12**).

We finally tested the alkaloids **7**–**12**, **15**, **18**–**22**, and **25**–**27**, on their activity against the cancer lines U87 (glioblastoma), 518A2 (melanoma), and HCT116 (colon cancer), but no noticeable cytotoxicity (MTT assay, IC_{50} (72 h) < 50 μM) was observed.

Conclusion

We successfully developed an efficient route to the quinolizidine-indolizidine alkaloids **7**–**12**. Key intermediate was *N*-Boc activated 11-oxocytisine (**15**), which was accessed in 50% yield by iodine oxidation and protection of the commercially available alkaloid cytisine (**3**). Grignard addition, Paal-Knorr type cyclization, *exo*-hydrogenation, and reduction afforded the three *endo*-pyrrolidine annulated alkaloids leontidine (**7**), tetrahydroleontidine (**8**), and leontidane (**9**) in a row (3–4 steps, 55–38% yield). Their *exo*-pyrrolidine fused counterparts, camoensine (**10**), camoensidine (**11**), and 11-epileontidane (**12**), were prepared from **15** in 4–6 steps and 53–28% yield by reduction, *exo*-selective Sakurai allylation, ring closure, and adjustment of the oxidation state in the original pyridone moiety. In addition, the artificial alkaloid isoleontidine **24**, a regioisomer of **7** that carries an 13,*N*-fused pyrrolidine, was synthesized from the C-13 oxidized cytisine derivative **20**.

Experimental Section

All reactions with moisture-sensitive reagents were carried out under argon atmosphere in anhydrous solvents, prepared using standard procedures.[28] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Merck TLC Silica gel 60 F_{254}). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or Dragendorff's reagent. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography. Melting points were measured on a Thermo Scientific 9300 melting point apparatus. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell) and are given in units of $deg cm^3 g^{-1} dm^{-1}$. NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. All signal assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR spectra (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a ThermoFisher Scientific Q-Exactive (Orbitrap) mass spectrometer using ESI (electrospray ionization). The alkaloid cytisine (**3**), which is also commercially available, was isolated from the seeds of *Laburnum anagyroides* following ref. [15]. For reasons of consistency, all tri- and tetracyclic alkaloids prepared are numbered following the standard alkaloid numbering (for details, see Supporting Information).

Oxidation of cytisine (3): Cytisine (**3**; 2.00 g, 10.5 mmol), dissolved in THF (300 mL) and H_2O (120 mL), was treated with I_2 (20.0 g, 78.8 mmol) and $NaHCO_3$ (8.82 g, 105 mmol). After 5 h at 70 °C, the reaction mixture was cooled to rt, and sat. aq. $Na_2S_2O_3$ (120 mL) and sat. aq. Na_2CO_3 (200 mL) were added. The organic solvent THF was removed under vacuum and the remaining aqueous layer was exhaustively extracted with CH_2Cl_2/MeOH (4:1, 20×100 mL) and, after addition of NH_3 (aq., 25%, 30 mL), with CH_2Cl_2 (15×100 mL) and $CHCl_3$ (5×100 mL). Evaporation of the solvent delivered a 2:1 mixture of crude **18** and **19** (2.14 g). CH_2Cl_2 (100 mL) was added and the slurry was treated with Boc_2O (5.73 g, 26.3 mmol), NEt_3 (4.37 mL, 3.19 g, 31.5 mmol), and DMAP (128 mg, 1.05 mmol) at rt. After 19 h, sat. aq. NH_4Cl (200 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and the residue was purified by MPLC [Grace Reveleris apparatus, SiO_2 cartridge (80 g), CH_2Cl_2/MeOH 100:0→80:20] to give the *N*-Boc imides **15** and **20** in analytically pure form each. Purification and separation of **15** and **20** by column chromatography (SiO_2, CH_2Cl_2/MeOH 100:0→95:5) is also possible, but more tedious. Analytically pure samples of **18** and **19** were obtained from the intermediate mixture of **18** and **19** by repeated column chromatography (SiO_2, CH_2Cl_2/MeOH 100:0→95:5). **11-Oxocytisine (18)**: All characterization data were in full agreement with those reported in ref. [12]. **13-Oxocytisine (19)**: Colorless crystals. R_f=0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); m.p. 255–260 °C (decomp.); $[\alpha]_D^{28}$ = +138.4 (*c* = 1.0, MeOH); ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (m, 1 H, 5-H), 6.63 (s, 1 H, NH), 6.46 (d, *J* = 9.1 Hz, 1 H, 3-H), 6.24 (d, *J* = 6.8 Hz, 1 H, 4-H), 4.10 (d, *J* = 15.9 Hz, 1 H, 10-*H*H), 4.02 (dd, *J* = 15.9 Hz, 6.8 Hz, 1 H, 10-H*H*), 3.67 (dd, *J* = 12.4 Hz, 5.1 Hz, 1 H, 11-*H*H), 3.57 (s, 1 H, 7-H), 3.36 (d, *J* = 12.4 Hz, 1 H, 11-H*H*), 2.78 (s, 1 H, 9-H), 2.22 (dm, *J* = 13.2 Hz, 1 H, 8-*H*H), 2.10 (dm, *J* = 13.2 Hz, 1 H, 8-H*H*) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.6 (C-13), 163.5 (C-2), 143.8 (C-6), 139.2 (C-5), 118.5 (C-3), 106.7 (C-4), 49.8 (C-10), 48.5 (C-11), 42.9 (C-7), 24.7 (C-9), 22.9 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 3237, 2925, 1651, 1567, 1544, 1490, 1362, 1146,782 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}N_2O_2+H^+$: 205.09715 $[M+H]^+$; found: 205.09700. ***N*-Boc-11-oxocytisine (15)**: Colorless crystals; yield: 1.59 g (5.22 mmol, 50%); R_f = 0.35 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). All characterization data were in full agreement with those reported in ref. [12]. ***N*-Boc-13-oxocytisine (20)**: Colorless crystals; yield: 785 mg (2.53 mmol, 25%); R_f = 0.54 (CH_2Cl_2/MeOH 95:5); m.p. 172–175 °C; $[\alpha]_D^{25}$ = −399.4 (*c* = 1.0, MeOH); ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (dd, *J* = 9.0 Hz, 7.0 Hz, 1 H, 4-H), 6.52 (d, *J* = 9.2 Hz, 1 H, 3-H), 6.29 (d, *J* = 6.8 Hz, 1 H, 5-H), 4.22 (d, *J* = 15.7 Hz, 1 H, 10-*H*H), 3.96 (dd, *J* = 15.7 Hz, 6.4 Hz, 1 H, 10-H*H*), 3.86 (dd, *J* = 13.3 Hz, 5.7 Hz, 1 H, 11-*H*H), 3.76 (m, 2 H, 7-H, 11-H*H*), 2.88 (s, 1 H, 9-H), 2.28 (d, *J* = 13.3 Hz, 1 H, 8-*H*H), 2.13 (d, *J* = 13.2 Hz, 1 H, 8-H*H*), 1.49 (s, 9 H, $C(CH_3)_3$) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 167.9 (C-13), 163.5 (C-2), 152.0 (CO_2N), 142.7 (C-6), 139.3 (C-4), 119.0 (C-3), 107.2 (C-5), 84.1 ($C(CH_3)_3$), 52.5 (C-11), 49.6 (C-10), 45.8 (C-7), 28.1 ($C(CH_3)_3$), 25.8 (C-9), 23.1 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 2985, 1719, 1696, 1650, 1576, 1544, 1367, 1273, 1256, 1136, 790 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_4+H^+$: 305.15015 $[M+H]^+$; found: 305.14828.

(7*R*,9*R*)-*N*-Boc-9-(aminomethyl)-7-(4,4-dimethoxybutanoyl)-6,7,8,9-tetrahydro-4*H*-quinolizin-4-one (21): The Grignard reagent **17** was freshly prepared from 3-bromo-1,1-dimethoxypropane (518 μL, 705 mg, 3.85 mmol), which was added to Mg (85.1 mg, 3.50 mmol) and I_2 (catalytic amount) in anhydr. THF (10 mL). The reaction mixture was refluxed for 60 min and then cooled to rt. This Grignard reagent was added dropwise at 0 °C to a solution of the *N*-Boc imide **15** (366 mg, 1.20 mmol) in THF (11 mL). After 2 h, sat. aq. NH_4Cl (50 mL) was added and the reaction mixture was successively extracted with CH_2Cl_2/MeOH (90:10, 2×50 mL) and CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 100:0→95:5) to give ketone **21** as a colorless oil; yield: 402 mg (986 μmol, 82%); R_f = 0.41 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{25}$ = −110.7 (*c* = 0.5, MeOH); ^1H NMR ($CDCl_3$, 500 MHz, 9:1 mixture of rotamers, * = isolated signal of the minor rotamer): δ = 7.27 (dd, *J* = 9.2 Hz, 6.9 Hz, 1 H, 4-H), 6.46 (d, *J* = 9.1 Hz, 1 H, 3-H), 6.10 (d, *J* = 6.8 Hz, 1 H, 5-H), 4.83 (m, 0.9 H, NH), 4.66 (m, 0.1 H, NH*), 4.58 (m, 0.1 H, 10-*H*H*), 4.44 (dd, *J* = 14.4 Hz, 4.8 Hz, 0.9 H, 10-*H*H), 4.34 (t, *J* = 5.4 Hz, 1 H, $CH(OCH_3)_2$), 4.00 (dd, *J* = 14.3 Hz, 8.7 Hz, 0.9 H, 10-H*H*), 3.78 (m, 0.1 H, 10-H*H**), 3.54 (dt, *J* = 14.0 Hz, 6.3 Hz, 1 H, NHC*H*H), 3.31 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 3.28 (m, 1 H, NHCH*H*), 3.08 (m, 0.9 H, 7-H), 3.00 (m, 1.1 H, 9-H, 7-H*), 2.62 (td, *J* = 7.1 Hz, 2.7 Hz, 2 H, $COCH_2$), 2.17 (dt, *J* = 13.7 Hz, 7.2 Hz, 1 H, 8-*H*H), 1.90 (m, 2 H, $COCH_2CH_2$), 1.77 (dt, *J* = 13.7 Hz, 8.8 Hz, 1 H, 8-H*H*), 1.43 (s, 9 H, $C(CH_3)_3$) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 209.0 ($COCH_2$), 163.1 (C-2), 156.0 (CO_2N), 147.6 (C-6), 138.9 (C-4), 117.7 (C-3), 104.3 (C-5), 103.8 ($CH(OCH_3)_2$), 80.0 ($C(CH_3)_3$), 53.7 (OCH_3), 53.4 (OCH_3), 45.4 (C-9), 44.0 ($NHCH_2$), 41.2 (C-10), 38.1 (C-7), 36.1 ($COCH_2$), 28.5 ($C(CH_3)_3$), 26.7 ($COCH_2CH_2$), 25.3 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 2935, 1707, 1653, 1545, 1366, 1271, 1251, 1165, 1127, 1057, 797, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}N_2O_6+Na^+$: 431.21526 $[M+Na]^+$; found: 431.21402.

Pyrrolocytisine 22: A solution of ketone **21** (565 mg, 1.39 mmol) in anhydr. CH_2Cl_2 (20 mL) was slowly treated with $BF_3 \cdot OEt_2$ (878 μL, 984 mg, 6.93 mmol) at 0 °C. After 1 h at 0 °C and 1 h at rt, MeOH/NH_3 (aq., 25%; 9:1, 2 mL) was added and stirring was continued for 10 min. The crude reaction mixture was directly subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 99:0.9:0.1→95:4.5:0.5) to give **22** as colorless crystals; yield: 236 mg (1.04 mmol, 75%); R_f = 0.42 (CH_2Cl_2/MeOH 95:5); m.p. 202–204 °C {ref. [19]: 225–226 °C}[29]; $[\alpha]_D^{25}$ = −120.3 (*c* = 0.5, MeOH) {ref. [19]: $[\alpha]_D$ −113.5 (*c* = 1.5, MeOH)}[29]. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.27 (dd, *J* = 9.0 Hz, 6.9 Hz, 1 H, 4-H), 6.44 (m, 1 H, 12-H), 6.42 (m, 1 H, 5-H), 6.15 (d, *J* = 6.9 Hz, 1 H, 3-H), 6.12 (t, *J* = 3.1 Hz, 1 H, 14-H), 5.97 (m, 1 H, 13-H), 4.33 (dm, *J* = 14.5 Hz, 1 H, 10-*H*H), 4.28 (dd, *J* = 11.9 Hz, 4.2 Hz, 1 H, 16-*H*H), 4.10 (dm, *J* = 11.9 Hz, 1 H, 16-H*H*), 3.75 (dd, *J* = 14.5 Hz, 4.5 Hz, 1 H, 10-H*H*), 3.69 (m, 1 H, 9-H), 3.44 (m, 1 H, 7-H), 2.21 (dm, *J* = 13.0 Hz, 1 H, 8-*H*H), 2.16 (dm, *J* = 13.0 Hz, 1 H, 8-H*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.5 (C-2), 149.1 (C-6), 138.8 (C-4), 130.6 (C-11), 118.9 (C-12), 118.1 (C-5), 109.0 (C-14), 106.2

(C-3), 105.1 (C-13), 53.8 (C-16), 52.6 (C-10), 33.8 (C-7), 27.4 (C-9), 24.5 (C-8); ppm; IR (ATR): $\tilde{\nu}$ = 2939, 1651, 1573, 1544, 1345, 1316, 1139, 800, 709 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}N_2O+H^+$: 227.11789 $[M+H]^+$; found: 227.11717.

General hydrogenation procedure: A mixture of the pyridone (**7**, **10**, **22**, or **23**) and PtO_2 (10 mol%) in AcOH (5 mL/200 μmol pyridone) was hydrogenated at rt and 1 bar H_2 pressure. The reaction mixture was filtered through a pad of celite and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (80:20, 25 mL/200 μmol pyridone). After evaporation of the solvent, the crude product was dissolved in aq. NaOH (20 mL/200 μmol pyridone) and extracted with CH_2Cl_2 (5×5 mL/200 μmol pyridone). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuum. Column chromatography ((deactivated) SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 100:0:0→95:4.5:0.5) afforded the hydrogenated product.

Leontidine (7): Following the general hydrogenation procedure, the pyrrole **22** (98.5 mg, 435 μmol) was hydrogenated for exactly 2.25 h. Work up and chromatography afforded, besides small amounts of **22** (7%) and **8** (9%), the natural alkaloid leontidine (**7**) as colorless crystals; yield: 72.3 mg (314 μmol, 72%); R_f = 0.29 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); m.p. 120–122 °C {ref. [6a, 6b, 6c, 6e]: 116–120 °C; ref. [6g]: 145 °C[29]}; $[\alpha]_D^{30}$ = −170.5 (*c* = 1.22, MeOH)[30] {ref. [6b]: $[\alpha]_D$ = −188.7 (*c* = 1.7, MeOH); ref. [6c]: $[\alpha]_D$ = −192.2 (*c* = 1.7, MeOH); ref. [6e]: $[\alpha]_D$ = −186.5 (*c* = 1.22, MeOH); ref. [6 g]: $[\alpha]_D$ = −180}; ^{1}H NMR ($CDCl_3$, 500 MHz):[31] δ = 7.25 (m, 1 H, 4-H), 6.42 (d, *J* = 9.0 Hz, 1 H, 3-H), 5.96 (d, *J* = 6.8 Hz, 1 H, 5-H), 4.04 (d, *J* = 15.7 Hz, 1 H, 10-*H*H), 3.73 (dd, *J* = 15.7 Hz, 7.0 Hz, 1 H, 10-H*H*), 3.06 (d, *J* = 10.3 Hz, 1 H, 16-*H*H), 2.93 (s, 1 H, 7-H), 2.82 (m, 1 H, 14-*H*H), 2.37 (m, 1 H, 9-H), 2.33 (dm, *J* = 10.3 Hz, 1 H, 16-H*H*), 2.12 (m, 1 H, 11-H), 1.99 (m, 2 H, 14-H*H*, 8-*H*H), 1.81–1.58 (m, 5 H, 8-H*H*, 12-H_2, 13-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.0 (C-2), 152.1 (C-6), 138.7 (C-4), 116.7 (C-3), 104.6 (C-5), 67.9 (C-11), 60.1 (C-16), 53.9 (C-14), 44.3 (C-10), 35.3 (C-7), 29.6 (C-9), 27.5 (C-8), 26.8 (C-12), 20.9 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2935, 2784, 1651, 1570, 1547, 1341, 798 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}N_2O+H^+$: 231.14919 $[M+H]^+$; found: 231.14860.

Tetrahydroleontidine (8) from 7: Following the general hydrogenation procedure, leontidine (**7**; 50.0 mg, 217 μmol) was hydrogenated for 20 h. Work up and chromatography (deactivated SiO_2) delivered the natural alkaloid tetrahydroleontidine (**8**) as a yellowish resin which partially crystallized upon standing; yield: 46.3 mg (198 μmol, 91%); R_f = 0.28 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); m.p. 60–64 °C {ref. [19]: 62.5–64.5 °C; ref. [6g]: 62–67 °C}; $[\alpha]_D^{26}$ = −44.3 (*c* = 1.0, MeOH) {ref. [19]: $[\alpha]_D$ = −45.3 (*c* = 4.4, EtOH); ref. [6 g]: $[\alpha]_D$ = −46}; ^{1}H NMR (MeOD, 500 MHz): δ = 4.74 (dt, *J* = 13.9 Hz, 2.0 Hz, 1 H, 10-*H*H), 3.59 (m, 1 H, 6-H), 3.35 (dt, *J* = 11.4 Hz, 2.0 Hz, 1 H, 16-*H*H), 2.88 (m, 1 H, 14-*H*H), 2.71 (dd, *J* = 13.9 Hz, 3.6 Hz, 1 H, 10-H*H*), 2.32 (m, 1 H, 3-*H*H), 2.23 (m, 1 H, 3-H*H*), 2.12 (dd, *J* = 11.4 Hz, 2.5 Hz, 1 H, 16-H*H*), 2.07 (m, 1 H, 11-H), 1.96 (dm, *J* = 12.5 Hz, 1 H, 8-*H*H), 1.91–1.77 (m, 6 H, 4-*H*H, 5-H_2, 8-H*H*, 9-H, 14-H*H*), 1.73 (m, 1 H, 7-H), 1.70–1.58 (m, 5 H, 4-H*H*, 12-H_2, 13-H_2); ^{13}C NMR (MeOD, 125 MHz): δ = 171.5 (C-2), 68.6 (C-11), 60.6 (C-6), 55.1 (C-14), 53.9 (C-16), 42.3 (C-10), 35.8 (C-8), 35.4 (C-7), 33.7 (C-3), 32.2 (C-9), 28.5 (C-5), 28.0 (C-12), 21.8 (C-13), 20.7 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2932, 2777, 1622, 1547, 1445, 1351, 1256, 1163, 1101 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{22}N_2O+H^+$: 235.18049 $[M+H]^+$; found: 235.18058.

Tetrahydroleontidine (8) from 22: Following the general hydrogenation procedure, pyrrole **22** (53.6 mg, 237 μmol) was hydrogenated for 18 h, giving, after work up and chromatography (deactivated SiO_2), tetrahydroleontidine (**8**) as a colorless resin; yield: 50.0 mg (213 μmol, 90%). All characterization data were identical to those given above.

Leontidane (9): Tetrahydroleontidine (**8**; 30.0 mg, 128 μmol) was dissolved in anhydr. THF (6 mL) and cooled to 0 °C. $LiAlH_4$ (2.4 M in THF, 425 μL, 1.02 mmol) was added and the reaction mixture was refluxed for 19 h. At rt, sat. aq. Na_2SO_4 (15 mL) was added dropwise until gas evolution ceased. The aqueous layer was extracted with Et_2O (5×10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in aq. HCl (4 M, 15 mL) and extracted with hexanes (15 mL) and Et_2O (15 mL). The organic layers were discarded. The aqueous layer was basified (pH = 14) with aq. NaOH (6.0 M, 15 mL) and extracted with Et_2O (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum to give the alkaloid leontidane (**9**) as a colorless oil (note: this compound slowly decomposes upon exposure to air); yield: 19.5 mg (88.5 μmol, 69%); R_f = 0.15 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1); $[\alpha]_D^{25}$ = +17.8 (*c* = 0.1, MeOD) {ref. [6c]: $[\alpha]_D$ = +16.5 (*c* = 6.1, EtOH)}; ^{1}H NMR (MeOD, 500 MHz): δ = 3.23 (d, *J* = 11.3 Hz, 1 H, 16-*H*H), 3.04 (m, 1 H, 14-*H*H), 2.98 (d, *J* = 11.8 Hz, 1 H, 10-*H*H), 2.78 (d, *J* = 10.7 Hz, 1 H, 2-*H*H), 2.20 (d, *J* = 11.9 Hz, 1 H, 10-H*H*), 2.13 (m, 2 H, 11-H, 16-H*H*), 2.05 (d, *J* = 11.3 Hz, 1 H, 6-H), 1.88–1.73 (m, 7 H, 2-*H*H, 3-*H*H, 5-*H*H, 8-*H*H, 9-H, 13-*H*H, 14-*H*H), 1.68–1.49 (m, 7 H, 4-*H*H, 5-H*H*, 7-H, 8-H*H*, 12-H_2, 13-H*H*), 1.43–1.33 (m, 2 H, 3-H*H*, 4-H*H*); ^{13}C NMR (MeOD, 125 MHz): δ = 68.7 (C-11), 68.1 (C-6), 58.9 (C-2), 56.4 (C-10), 55.4 (C-14), 53.7 (C-16), 37.3 (C-8), 36.5 (C-7), 33.2 (C-9), 31.4 (C-4), 27.8 (C-12), 26.1 (C-3), 26.0 (C-5), 21.6 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2928, 2857, 2755, 2719, 1463, 1442, 1332, 1279, 1117, 1102, 1064, 1042, 802, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{24}N_2+H^+$: 221.20123 $[M+H]^+$; found: 221.20081.

Pyrrolocytisine 23: The reaction sequence **20**→**23** was performed in analogy to the sequence **7**→**21**→**22** described above. Treatment of a solution of the *N*-Boc imide **20** (101 mg, 332 μmol) in anhydr. THF (3 mL) with **17** (0.29 M in THF, 3.43 mL, 996 μmol), prepared from 3-bromo-1,1-dimethoxypropane (299 μL, 406 mg, 2.22 mmol) and Mg (49.0 mg, 2.02 mmol) in anhydr. THF (7 mL), afforded, after aqueous work up, the crude addition product (158 mg), which was directly subjected to deprotection and cyclization by treatment with BF_3•OEt_2 (210 μL, 230 mg, 1.66 mmol) in anhydr. CH_2Cl_2 (5 mL). After work up and column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25%) 100:0:0→95:4.5:0.5), the pyrrolocytisine **23** was obtained as a colorless resin; yield: 34.9 mg (154 μmol, 46%); R_f = 0.48 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 97:2.7:0.3); $[\alpha]_D^{25}$ = −192.0 (*c* = 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.24 (dd, *J* = 9.0 Hz, 6.9 Hz, 1 H, 4-H), 6.55 (dd, *J* = 2.4 Hz, 1.7 Hz, 1 H, 13-H), 6.38 (dd, *J* = 9.0 Hz, 1.1 Hz, 1 H, 3-H), 6.10 (m, 2 H, 5-H, 14-H), 5.94 (dd, *J* = 3.4 Hz, 1.6 Hz, 1 H, 15-H), 4.30 (dd, *J* = 16.1 Hz, 8.4 Hz, 1 H, 10-*H*H), 4.21 (dd, *J* = 12.4 Hz, 4.5 Hz, 1 H, 11-*H*H), 4.12 (s, 1 H, 7-H), 4.07 (d, *J* = 12.4 Hz, 1 H, 11-H*H*), 3.95 (d, *J* = 16.1 Hz, 1 H, 10-H*H*), 2.95 (m, 1 H, 9-H), 2.21 (dm, *J* = 12.9 Hz, 1 H, 8-*H*H), 2.14 (dm, *J* = 12.9 Hz, 1 H, 8-H*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.6 (C-2), 149.9 (C-6), 139.4 (C-4), 129.2 (C-16), 120.1 (C-13), 117.2 (C-3), 109.0 (C-14), 105.0 (C-15), 104.0 (C-5), 52.1 (C-11), 48.5 (C-10), 34.1 (C-7), 26.4 (C-9), 24.2 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 2935, 1653, 1572, 1542, 1494, 1280, 1142, 1053, 803, 749, 721 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}N_2O+H^+$: 227.11845 $[M+H]^+$; found: 227.11812.

Isoleontidine (24): Following the general hydrogenation procedure, pyrrole **23** (40.9 mg, 181 μmol) was hydrogenated for 3.5 h. Work up and chromatography afforded the non-natural alkaloid isoleontidine (**24**) as a colorless resin; yield: 24.2 mg (105 μmol, 58%); R_f = 0.31 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{25}$ = −186.6 (*c* = 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.25 (dd, *J* = 8.9 Hz, 7.0 Hz, 1 H, 4-H), 6.44 (d, *J* = 8.3 Hz, 1 H, 3-H), 5.83 (d, *J* = 6.5 Hz, 1 H, 5-H), 3.97 (d, *J* = 15.4 Hz, 1 H, 10-*H*H), 3.88 (dd, *J* = 15.4 Hz, 7.0 Hz, 1 H, 10-H*H*), 3.08 (d, *J* = 10.4 Hz, 1 H, 11-*H*H), 2.87 (m, 2 H, 7-H, 13-*H*H), 2.44 (s, 1 H, 9-H), 2.28 (d, *J* = 10.5 Hz, 1 H, 11-H*H*), 2.09 (m, 1 H, 16-H), 2.00 (m, 2 H, 8-*H*H, 13-H*H*), 1.78 (m, 1 H, 8-H*H*), 1.66 (m, 1 H, 15-*H*H), 1.55 (m, 2 H,

14-H_2), 1.44 (m, 1 H, 15-H*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.1 (C-2), 147.7 (C-6), 137.7 (C-4), 117.0 (C-3), 107.7 (C-5), 67.3 (C-16), 59.4 (C-11), 53.7 (C-13), 50.6 (C-10), 37.6 (C-7), 28.0 (C-9), 27.3 (C-8), 27.0 (C-15), 20.6 (C-14) ppm; IR (ATR): $\tilde{\nu}$ = 2932, 2782, 1651, 1568, 1547, 1367, 1347, 1142, 800 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}N_2O$ + H^+: 231.14919 $[M+H]^+$; found: 231.14881.

***N*-Boc-11-methoxycytisine (25)**: According to ref. [12], a solution of the *N*-Boc imide **15** (307 mg, 1.01 mmol) in anhydr. MeOH (30 mL) was treated with $NaBH_4$ (114 mg, 3.03 mmol) at 0 °C and stirred for 90 min at this temperature. Methanolic HCl (2.0 M; 2.83 mL) was added and the reaction mixture was allowed to reach rt over 4 h. Sat. aq. $NaHCO_3$ (20 mL) was added and the solvent was removed under vacuum. The aqueous layer was extracted with CH_2Cl_2 (5× 25 mL) and the combined organic layers were dried over Na_2SO_4. Column chromatography (SiO_2, CH_2Cl_2/MeOH 100:0→95:5) delivered the *N*,*O*-acetal **25** as a colorless resin; yield: 295 mg (921 μmol, 91 %; ref. [12]: 90 %). All characterization data were in full agreement with those reported in ref. [12].

11-Allylcytisine (26): According to ref. [12], allyltrimethylsilane (390 μL, 281 mg, 2.46 mmol) and $BF_3{\cdot}OEt_2$ (156 μL, 175 mg, 1.23 mmol) were added at 0 °C to a solution of the *N*,*O*-acetal **25** (132 mg, 410 μmol) in anhydr. CH_2Cl_2 (6 mL). After 16 h at rt, the crude mixture was adsorbed to a small amount of silica and subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 100:0:0→90:9.1:0.9) to give 11-allylcytisine (**26**) as a white solid; yield: 80.0 mg (347 μmol, 85 %; ref. [12]: 93 %). All characterization data were in full agreement with those reported in refs. [10, 12, 23a, 23c, 23d].

11-(3-Hydroxypropyl)cytisine (27): 9-BBN (0.5 M in THF, 1.21 mL, 605 μmol) was slowly added at 0 °C to a solution of 11-allylcytisine (**26**; 69.5 mg, 302 μmol) in anhydr. THF (7 mL). The mixture was refluxed for 5 h and cooled to rt. Aq. H_2O_2 (30 wt%, 7 mL, 68.5 mmol) and aq. NaOCl (5 wt% active Cl, 7 mL, 10.0 mmol) were added and stirring was continued for 2 h. Aq. NaOH (6 M, 3.5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (20×9 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 100:0:0→90:9:1), providing the alcohol **27** as a colorless resin; yield: 61.1 mg (246 μmol, 81 %); R_f = 0.14 (CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 95:4.5:0.5); $[\alpha]_D^{25}$ = −74.0 (*c* = 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (dd, *J* = 9.0 Hz, 6.9 Hz, 1 H, 4-H), 6.44 (dd, *J* = 9.0 Hz, 1.0 Hz, 1 H, 3-H), 5.99 (dd, *J* = 6.8 Hz, 0.7 Hz, 1 H, 5-H), 4.14 (d, *J* = 15.8 Hz, 1 H, 10-*H*H), 3.89 (dd, *J* = 15.8 Hz, 6.5 Hz, 1 H, 10-H*H*), 3.68 (ddd, *J* = 11.0 Hz, 5.5 Hz, 4.2 Hz, 1 H, C*H*HOH), 3.54 (ddd, *J* = 11.0 Hz, 8.0 Hz, 3.0 Hz, 1 H, CH*H*OH), 3.32 (br. s, 2 H, NH, OH), 3.26 (dd, *J* = 13.4 Hz, 2.4 Hz, 1 H, 13-*H*H), 2.94 (d, *J* = 10.1 Hz, 1 H, 11-H), 2.86 (s, 1 H, 7-H), 2.75 (dt, *J* = 13.4 Hz, 2.1 Hz, 1 H, 13-H*H*), 2.22 (d, *J* = 2.5 Hz, 1 H, 9-H), 2.15 (d, *J* = 13.3 Hz, 1 H, 8-*H*H), 1.99 (m, 1 H, C*H*H$(CH_2)_2$OH), 1.89–1.74 (m, 2 H, 8-H*H*, C*H*HCH_2OH), 1.69–1.54 (m, 2 H, CH*H*$(CH_2)_2$OH, CH*H*CH_2OH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.7 (C-2), 150.5 (C-6), 139.2 (C-4), 117.1 (C-3), 105.2 (C-5), 62.9 (*C*H_2OH), 59.4 (C-11), 51.1 (C-10), 47.3 (C-13), 35.2 (C-7), 32.0 (C-9), 31.6 (*C*H_2CH_2OH), 29.5 (*C*$H_2(CH_2)_2$OH), 21.3 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 2932, 2236, 1645, 1544, 1356, 1144, 1059, 909, 796, 723 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}N_2O_2$ + H^+: 249.15975 $[M+H]^+$; found: 249.15971.

Camoensine (10): A solution of the alcohol **27** (112 mg, 451 μmol) in anhydr. CH_2Cl_2 (5 mL) was treated at 0 °C with CBr_4 (329 mg, 992 μmol), NEt_3 (81.3 μL, 59.3 mg, 586 μmol), and PPh_3 (213 mg, 812 μmol). After 18 h at rt, the reaction mixture was quenched with aq. HCl (0.5 M, 7 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (7 mL). The organic layers were discarded. The aqueous layer was basified (pH = 14) with aq. NaOH (6.0 M; 3 mL) and extracted with CH_2Cl_2 (5×12 mL). The organic layers were combined and dried over Na_2SO. Removal of the solvent under vacuum and column chromatography (deactivated SiO_2, CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 98:1.8:0.2→90:9.1:0.9) afforded the natural alkaloid camoensine (**10**) as a colorless oil; yield: 87.4 mg (379 μmol, 84 %); R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 95:4.5:0.5); $[\alpha]_D^{24}$ = −113.1 (*c* = 0.5, $CHCl_3$) {ref. [10]: $[\alpha]_D^{20}$ = −112.9 (*c* = 0.5, $CHCl_3$); ref. [4e]: $[\alpha]_D$ = −108 (*c* = 1.0, $CHCl_3$); ref. [6g]: $[\alpha]_D$ = −186}[29]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.27 (dd, *J* = 9.0 Hz, 7.0 Hz, 1 H, 4-H), 6.42 (d, *J* = 9.0 Hz, 1 H, 3-H), 6.00 (d, *J* = 6.6 Hz, 1 H, 5-H), 4.17 (d, *J* = 15.3 Hz, 1 H, 10-*H*H), 3.88 (dd, *J* = 15.3 Hz, 6.2 Hz, 1 H, 10-H*H*), 2.99 (tm, *J* = 8.7 Hz, 1 H, 11-H), 2.92 (s,1 H, 7-H), 2.75–2.63 (m, 4 H, 14-H_2, 16-H_2), 2.48 (s, 1 H, 9-H), 2.00–1.87 (m, 2 H, 8-*H*H, 13-*H*H), 1.83–1.60 (m, 4 H, 8-H*H*, 12-H_2, 13-H*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 163.7 (C-2), 150.9 (C-6), 138.9 (C-4), 116.9 (C-3), 105.0 (C-5), 66.1 (C-11), 55.0 (C-14 or C-16), 54.9 (C-14 or C-16), 51.8 (C-10), 35.0 (C-7), 29.0 (C-9), 25.2 (C-12), 21.3 (C-13), 20.8 (C-8) ppm; IR (ATR): $\tilde{\nu}$ = 2949, 2873, 1648, 1565, 1547, 1163, 1142, 800, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}N_2O$ + H^+: 231.14919 $[M+H]^+$; found: 231.14842. The ^{13}C NMR data are in full agreement with those reported for synthetic **10** in ref. [10]. For a detailed comparison of our NMR data with literature NMR data of isolated **10**,[4e,6g] see Supporting Information.

Camoensidine (11): Following the general hydrogenation procedure, camoensine (**10**, 90.7 mg, 394 μmol) was hydrogenated for 15 h. Work up and chromatography (deactivated SiO_2) delivered the natural alkaloid camoensidine (**11**) as a pale yellow oil; yield: 73.1 mg (312 μmol, 79 %); R_f = 0.27 (CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 90:9:1); $[\alpha]_D^{27}$ = −72.5 (*c* = 1.13, EtOH) {ref. [6g]: $[\alpha]_D$ = −67; ref. [4a]: $[\alpha]_D^{27}$ = −73 (*c* = 1.13, EtOH)}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.57 (d, *J* = 13.1 Hz, 1 H, 10-*H*H), 3.34 (t, *J* = 7.0 Hz, 1 H, 6-H), 2.73 (m, 2 H, 14-*H*H, 16-*H*H), 2.63 (d, *J* = 13.1 Hz, 1 H, 10-H*H*), 2.43–2.20 (m, 5 H, 3-H_2, 11-H, 14-H*H*, 16-H*H*), 2.02 (m, 1 H, 5-*H*H), 1.94 (s, 1 H, 9-H), 1.85–1.68 (m, 6 H, 4-*H*H, 7-H, 8-*H*H, 12-H_2, 13-*H*H), 1.63–1.45 (m, 3 H, 4-H*H*, 8-H*H*, 13-H*H*), 1.35 (d, *J* = 12.5 Hz, 1 H, 5-H*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.4 (C-2), 64.6 (C-11), 60.1 (C-6), 54.5 (C-14), 49.4 (C-16), 47.6 (C-10), 33.2 (C-3), 33.2 (C-7), 31.2 (C-9), 28.9 (C-8), 27.6 (C-12), 27.6 (C-5), 21.1 (C-4), 20.1 (C-13) ppm; IR (ATR): $\tilde{\nu}$ = 2945, 2866, 1619, 1442, 1253, 1163, 1018, 916, 726, 641 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{22}N_2O$ + H^+: 235.18049 $[M+H]^+$; found: 235.18016. For a detailed comparison of our NMR data with literature NMR data of isolated **11**,[4a,e] see Supporting Information.

11-Epileontidane (12): Camoensidine (**11**; 62.7 mg, 268 μmol) was dissolved in anhydr. THF (4 mL) and cooled to 0 °C. $LiAlH_4$ (2.4 M in THF, 893 μL, 2.14 mmol) was added and the reaction mixture was refluxed for 23 h. At rt, sat. aq. Na_2SO_4 (8 mL) was added dropwise until gas evolution ceased. The aqueous layer was extracted with Et_2O (5×8 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in aq. HCl (1 M, 15 mL) and extracted with hexanes (15 mL) and Et_2O (15 mL). The organic layers were discarded. The aqueous layer was basified (pH = 14) with aq. NaOH (6.0 M, 15 mL) and extracted with Et_2O (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum to give the natural alkaloid 11-epileontidane (**12**) as a pale yellow oil (note: this compound slowly decomposes upon exposure to air); yield: 39.4 mg (179 μmol, 67 %); R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25 %) 90:9:1); $[\alpha]_D^{25}$ = +23.2 (*c* = 1.0, MeOH); ^{1}H NMR (MeOD, 500 MHz): δ = 2.87 (m, 1 H, 6-H), 2.84–2.70 (m, 4 H, 2-*H*H, 10-*H*H, 14-*H*H, 16-*H*H), 2.64 (m, 2 H, 2-H*H*, 10-H*H*), 2.24 (dd, *J* = 10.9 Hz, 2.4 Hz, 1 H, 16-H*H*), 1.98–1.86 (m, 5 H, 5-*H*H, 7-H, 11-H, 13-*H*H, 14-H*H*), 1.79 (m, 2 H, 3-*H*H, 4-*H*H), 1.68 (m, 3 H, 3-H*H*, 8-*H*H, 13-H*H*), 1.63–1.51 (m, 3 H, 8-H*H*, 9-H, 12-*H*H), 1.39–1.28 (m, 3 H, 4-H*H*, 5-H*H*, 12-H*H*); ^{13}C NMR (MeOD, 125 MHz): δ = 67.4 (C-11), 65.9 (C-6), 63.5 (C-16), 58.1 (C-14), 55.4 (C-2), 50.6 (C-10), 35.8 (C-9), 33.6 (C-7), 31.1 (C-12), 29.6

(C-3), 29.1 (C-5), 26.4 (C-8), 26.0 (C-13), 22.1 (C-4) ppm; IR (ATR): $\tilde{\nu}$ = 2931, 2758, 1442, 1347, 1265, 1142, 1116, 1072 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{24}N_2 + H^+$: 221.20123 $[M+H]^+$; found: 221.20079.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkaloids · Asymmetric synthesis · Bispidine · Cytisine · Quinolizidine

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[20] According to ref. [19], pyrrolocytisine **22** had been prepared earlier by dehydrogenation of leontidine (**7**) over Pd/asbestos at 270–300 °C. The melting point and optical rotation given, however, significantly differ from ours.

[21] The lower yield in the transformation of **20** to **23**, as compared to the analogous conversion of **15** to **22** (46% *vs.* 62%, see Scheme 3), might be a consequence of an interfering retro-Claisen type fragmentation at the stage of the intermediate hemiaminal. This would be in analogy to a side reaction occurring in the NCS-oxidation of cytisine (**3**), as proposed by Ohmiya *et al.*[11].

[22] For the successful twofold addition of a functionalized zinc organyl into a related bispidine bis-*N*,*O*-acetal under Lewis acid catalysis, see ref. [12].
[23] The tricyclic alkaloid 11-allylcytisine (**26**) was extracted from *Sophora secundiflora* (ref. a), *Clathrotropis brachypetala* (ref. b), *Bolusanthus speciosus* (ref. c), and *Lupinus princei* (ref. d), and detected by GC-MS in more than 15 other species: a) W. J. Keller, M. Hatfield, *Phytochemistry* **1979**, *18*, 2068–2069; b) G. M. Hatfield, W. J. Keller, J. M. Rankin, *J. Nat. Prod.* **1980**, *43*, 164–167; c) K. Asres, J. D. Phillipson, P. Mascagni, *Phytochemistry* **1986**, *25*, 1449–1452; d) K. Asres, *Egypt. J. Pharm. Sci.* **1996**, *37*, 1–10.
[24] For earlier syntheses of 11-allylcytisine (**26**) see ref. [6e,10,12] and: F. Bohlmann, E. Winterfeldt, H. Overwien, H. Pagel, *Chem. Ber.* **1962**, *95*, 944–948.
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[26] Oxymercuration-reduction ($Hg(OAc)_2$; $NaBH_4$) of **26** provided camoensine (**10**), the product of an initial *anti*-Markovnikov addition, in up to 40% yield. Markovnikov products with an internal OH group were not detected, indicating a reversible oxymercuration step. Main side reaction, which caused us to abandon this sequence, was an epimerization at C-11 leading to 11-*endo*-allylcytisine in up to 33%, most likely through a C–N oxidation-reduction sequence (see ref. [6 g]).
[27] 9-BBN was used to ensure excellent terminal regioselectivity. The oxidative cleavage of the C–B bond proceeded sluggishly under standard conditions (NaOH, H_2O_2), but good results were obtained with a $NaOCl/H_2O_2$ mixture.
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[29] This literature value significantly differs from ours (and other literature values).
[30] The optical rotation measured by us is somewhat lower than all other literature values. We re-measured the optical rotation several times with the same result and ensured that our compound was analytically pure.
[31] The ^{1}H NMR data given in ref. [6e] [$\delta = 7.04$ (q), 6.12 (d), 5.75 (d), 4.03 (m) ppm] do not match with ours.

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