

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

Stefan Wagner,^[a] Susanne Sigl,^[a] Melanie Schenkl,^[a] and Matthias Breuning^{*[a]}

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

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 (C₅N 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 (C₄N source) during their biosynthesis.^[5] The first member of this

[a]	S. Wagner, S. Sigl, M. Schenkl, Prof. Dr. M. Breuning
	Department of Chemistry
	University of Bayreuth
	Universitätsstraße 30, 95440 Bayreuth, Germany
	E-mail: matthias.breuning@uni-bayreuth.de
	http://www.breuning.uni-bayreuth.de/de/index.html
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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.



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

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.

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, exoconfigured 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



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

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. $K_3Fe(CN)_{64}$, PhI(OAc)₂₄, KMnO₄) 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. NaHCO₃ (1:1) at 70°C delivered a 2:1 mixture of desired 11oxocytisine (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 pyrrolocvtisine 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 PtO₂ under acidic conditions and a short reaction time. Other catalysts, such as Pd/C, Pd(OH)₂/C, Pd(OAc)₂, Ru/C, RhCl(PPh₃)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 2. Preparation of the key intermediate **15** by oxidation of cytisine **(3)** and *N*-Boc protection.

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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 LiAlH₄ 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 hydro-



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.

genation 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.

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 11allylcytisine (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 cp₂ZrHCl 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 twostep 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 PtO₂ under acidic conditions delivered camoensidine (11), which was reduced with LiAlH₄ 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 μ M) 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 guality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Merck TLC Silica gel 60 F₂₅₄). Spots were visualized by UV light (254 nm) or by staining with aqueous KMnO₄, 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 degcm³g⁻¹dm⁻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 ¹³C 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 NaHCO₃ (8.82 g, 105 mmol). After 5 h at 70 °C, the reaction mixture was cooled to rt, and sat. aq. Na₂S₂O₃ (120 mL) and sat. aq. Na₂CO₃ (200 mL) were added. The organic solvent THF was removed under vacuum and the remaining aqueous layer was exhaustively extracted with CH₂Cl₂/MeOH (4:1, 20×100 mL) and, after addition of NH₃ (aq., 25%, 30 mL), with CH₂Cl₂ (15×100 mL) and CHCl₃ (5×100 mL). Evaporation of the solvent delivered a 2:1 mixture of crude 18 and 19 (2.14 g). CH₂Cl₂ (100 mL) was added and the slurry was treated with Boc₂O (5.73 g, 26.3 mmol), NEt₃ (4.37 mL, 3.19 g, 31.5 mmol), and DMAP (128 mg, 1.05 mmol) at rt. After 19 h, sat. aq. NH₄Cl (200 mL) was added and the reaction mixture was extracted with CH_2CI_2 (3×200 mL). The combined organic layers were dried over Na₂SO₄, evaporated, and the residue was purified by MPLC [Grace Reveleris apparatus, SiO₂ cartridge (80 g), $CH_2Cl_2/MeOH$ 100:0 \rightarrow 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 (SiO₂, CH₂Cl₂/MeOH 100:0 \rightarrow 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 (SiO₂, CH₂Cl₂/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. $R_f = 0.23$ (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 95:4.5:0.5); m.p. 255–260 °C (decomp.); $[\alpha]_D^{28} = +138.4$ (c = 1.0, MeOH); ¹H NMR (CDCl₃, 500 MHz): $\delta = 7.26$ (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-HH), 4.02 (dd, J=15.9 Hz, 6.8 Hz, 1 H, 10-HH), 3.67 (dd, J=12.4 Hz, 5.1 Hz, 1 H, 11-HH), 3.57 (s, 1 H, 7-H), 3.36 (d, J=12.4 Hz, 1 H, 11-HH), 2.78 (s, 1 H, 9-H), 2.22 (dm, J=13.2 Hz, 1 H, 8-HH), 2.10 (dm, J=13.2 Hz, 1 H, 8-HH) ppm; ¹³C NMR (CDCl₃, 125 MHz): $\delta =$ 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): $\tilde{v} = 3237$, 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%); $R_f = 0.35$ (CH₂Cl₂/ MeOH/NH₃ (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 (CH₂Cl₂/MeOH 95:5); m.p. 172–175°C; $[α]_D^{25}$ =-399.4 (*c*=1.0, MeOH); ¹H NMR (CDCl₃, 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-HH), 3.96 (dd, *J*=15.7 Hz, 6.4 Hz, 1 H, 10-HH), 3.86 (dd, *J*=13.3 Hz, 5.7 Hz, 1 H, 11-HH), 3.76 (m, 2 H, 7-H, 11-HH), 2.88 (s, 1 H, 9-H), 2.28 (d, *J*=13.3 Hz, 1 H, 8-HH), 2.13 (d, *J*=13.2 Hz, 1 H, 8-HH), 1.49 (s, 9 H, C(CH₃)₃) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ =167.9 (C-13), 163.5 (C-2), 152.0 (CO₂N), 142.7 (C-6), 139.3 (C-4), 119.0 (C-3), 107.2 (C-5), 84.1 (C(CH₃)₃), 52.5 (C-11), 49.6 (C-10), 45.8 (C-7), 28.1 (C(CH₃)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 C₁₆H₂₀N₂O₄+H⁺: 305.15015 [M + H]⁺; found: 305.14828.

(7R,9R)-N-Boc-9-(aminomethyl)-7-(4,4-dimethoxybutanoyl)-

6,7,8,9-tetrahydro-4H-quinolizin-4-one (21): The Grignard reagent 17 was freshly prepared from 3-bromo-1,1-dimethoxypropane (518 $\mu\text{L},~705$ 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. NH₄Cl (50 mL) was added and the reaction mixture was successively extracted with $CH_2Cl_2/MeOH$ (90:10, 2×50 mL) and CH_2CI_2 (3×50 mL). The combined organic layers were dried over Na₂SO₄, evaporated, and the residue was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 100:0 \rightarrow 95:5) to give ketone **21** as a colorless oil; yield: 402 mg (986 μ mol, 82%); R_f =0.41 $(CH_2CI_2/MeOH 95:5); [\alpha]_D^{25} = -110.7 (c = 0.5, MeOH); ^{1}H NMR$ (CDCl₃, 500 MHz, 9:1 mixture of rotamers, *=isolated signal of the minor rotamer): $\delta = 7.27$ (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-HH*), 4.44 (dd, J=14.4 Hz, 4.8 Hz, 0.9 H, 10-HH), 4.34 (t, J=5.4 Hz, 1 H, CH(OCH₃)₂), 4.00 (dd, J=14.3 Hz, 8.7 Hz, 0.9 H, 10-HH), 3.78 (m, 0.1 H, 10-HH*), 3.54 (dt, J=14.0 Hz, 6.3 Hz, 1 H, NHCHH), 3.31 (s, 3 H, OCH₃), 3.29 (s, 3 H, OCH3), 3.28 (m, 1 H, NHCHH), 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, COCH₂), 2.17 (dt, J= 13.7 Hz, 7.2 Hz, 1 H, 8-HH), 1.90 (m, 2 H, COCH₂CH₂), 1.77 (dt, J= 13.7 Hz, 8.8 Hz, 1 H, 8-HH), 1.43 (s, 9 H, C(CH₃)₃) ppm; ¹³C NMR (CDCl₃, 125 MHz): $\delta = 209.0$ (COCH₂), 163.1 (C-2), 156.0 (CO₂N), 147.6 (C-6), 138.9 (C-4), 117.7 (C-3), 104.3 (C-5), 103.8 (CH(OCH₃)₂), 80.0 (C(CH₂)₃), 53.7 (OCH₃), 53.4 (OCH₃), 45.4 (C-9), 44.0 (NHCH₂), 41.2 (C-10), 38.1 (C-7), 36.1 (COCH2), 28.5 (C(CH3)3), 26.7 (COCH2CH2), 25.3 (C-8) ppm; IR (ATR): $\tilde{v} = 2935$, 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. CH₂Cl₂ (20 mL) was slowly treated with BF₃·OEt₂ (878 µL, 984 mg, 6.93 mmol) at 0°C. After 1 h at 0°C and 1 h at rt, MeOH/ NH₃ (ag., 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, $CH_2CI_2/MeOH/NH_3$ (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 (CH₂Cl₂/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]. 1}H NMR (CDCl₃, 500 MHz): $\delta\!=\!7.27$ (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-HH), 4.28 (dd, J=11.9 Hz, 4.2 Hz, 1 H, 16-HH), 4.10 (dm, J=11.9 Hz, 1 H, 16-HH), 3.75 (dd, J=14.5 Hz, 4.5 Hz, 1 H, 10-HH), 3.69 (m, 1 H, 9-H), 3.44 (m, 1 H, 7-H), 2.21 (dm, J=13.0 Hz, 1 H, 8-HH), 2.16 (dm, J=13.0 Hz, 1 H, 8-HH); 13 C NMR (CDCl₃, 125 MHz): $\delta = 163.5$ (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 C₁₄H₁₄N₂O + H⁺: 227.11789 [M + H]⁺; found: 227.11717.

General hydrogenation procedure: A mixture of the pyridone (7, **10**, **22**, or **23**) and PtO₂ (10 mol%) in AcOH (5 mL/200 µmol pyridone) was hydrogenated at rt and 1 bar H₂ pressure. The reaction mixture was filtered through a pad of celite and the filter cake was thoroughly washed with CH₂Cl₂/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 CH₂Cl₂ (5×5 mL/200 µmol pyridone). The organic layer was dried over Na₂SO₄ and the solvent was removed in vacuum. Column chromatography ((deactivated) SiO₂, CH₂Cl₂/ MeOH/NH₃ (aq., 25%) 100:0:0 \rightarrow 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 μ mol, 72%); R_f =0.29 (CH₂Cl₂/MeOH/NH₃ (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]: [α]_D = -180}; ^1H NMR (CDCl_3, 500 MHz): $^{[31]}$ $\delta\!=\!7.25$ (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-HH), 3.73 (dd, J=15.7 Hz, 7.0 Hz, 1 H, 10-HH), 3.06 (d, J=10.3 Hz, 1 H, 16-HH), 2.93 (s, 1 H, 7-H), 2.82 (m, 1 H, 14-HH), 2.37 (m, 1 H, 9-H), 2.33 (dm, J=10.3 Hz, 1 H, 16-HH), 2.12 (m, 1 H, 11-H), 1.99 (m, 2 H, 14-HH, 8-HH), 1.81-1.58 (m, 5 H, 8-HH, 12-H₂, 13-H₂); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 164.0$ (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): $\tilde{v} = 2935$, 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 SiO₂) delivered the natural alkaloid tetrahydroleontidine (8) as a yellowish resin which partially crystallized upon standing; yield: 46.3 mg (198 μ mol, 91%); $R_f = 0.28$ (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 95:4.5:0.5); m.p. 60-64 °C {ref. [19¹: 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]: [α]_D=-46}; ¹H NMR (MeOD, 500 MHz): δ =4.74 (dt, J= 13.9 Hz, 2.0 Hz, 1 H, 10-HH), 3.59 (m, 1 H, 6-H), 3.35 (dt, J=11.4 Hz, 2.0 Hz, 1 H, 16-HH), 2.88 (m, 1 H, 14-HH), 2.71 (dd, J=13.9 Hz, 3.6 Hz, 1 H, 10-HH), 2.32 (m, 1 H, 3-HH), 2.23 (m, 1 H, 3-HH), 2.12 (dd, J=11.4 Hz, 2.5 Hz, 1 H, 16-HH), 2.07 (m, 1 H, 11-H), 1.96 (dm, J=12.5 Hz, 1 H, 8-HH), 1.91–1.77 (m, 6 H, 4-HH, 5-H₂, 8-HH, 9-H, 14-HH), 1.73 (m, 1 H, 7-H), 1.70–1.58 (m, 5 H, 4-HH, 12-H₂, 13-H₂); ¹³C NMR (MeOD, 125 MHz): $\delta = 171.5$ (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): $\tilde{v} =$ 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 μ mol) was hydrogenated for 18 h, giving, after work up and chromatography (deactivated SiO₂), tetrahydroleontidine (**8**) as a colorless resin; yield: 50.0 mg (213 μ mol, 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. LiAlH₄ (2.4 M in THF, 425 uL, 1.02 mmol) was added and the reaction mixture was refluxed for 19 h. At rt, sat. ag. Na₂SO₄ (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 Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in aq. HCl (4 M, 15 mL) and extracted with hexanes (15 mL) and Et₂O (15 mL). The organic layers were discarded. The agueous layer was basified (pH = 14) with ag. NaOH (6.0 M, 15 mL) and extracted with Et_2O (3×15 mL). The combined organic layers were dried over Na₂SO₄ 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 μ mol, 69%); $R_f = 0.15$ (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 90:9:1); $[\alpha]_{D}^{25} = +17.8$ (c=0.1, MeOD) {ref. [6c]: $[\alpha]_{D} = +16.5$ (c= 6.1, EtOH)}; ¹H NMR (MeOD, 500 MHz): $\delta = 3.23$ (d, J = 11.3 Hz, 1 H, 16-HH), 3.04 (m, 1 H, 14-HH), 2.98 (d, J=11.8 Hz, 1 H, 10-HH), 2.78 (d, J=10.7 Hz, 1 H, 2-HH), 2.20 (d, J=11.9 Hz, 1 H, 10-HH), 2.13 (m, 2 H, 11-H, 16-HH), 2.05 (d, J=11.3 Hz, 1 H, 6-H), 1.88-1.73 (m, 7 H, 2-HH, 3-HH, 5-HH, 8-HH, 9-H, 13-HH, 14-HH), 1.68-1.49 (m, 7 H, 4-HH, 5-HH, 7-H, 8-HH, 12-H₂, 13-HH), 1.43–1.33 (m, 2 H, 3-HH, 4-HH); ^{13}C NMR (MeOD, 125 MHz): $\delta\!=\!68.7$ (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): $\tilde{v} = 2928$, 2857, 2755, 2719, 1463, 1442, 1332, 1279, 1117, 1102, 1064, 1042, 802, 734 cm⁻¹; HRMS (ESI): *m/z* calcd for C₁₄H₂₄N₂ +H⁺: 221.20123 [M+H]⁺; found: 221.20081.

Pyrrolocytisine 23: The reaction sequence 20→23 was performed in analogy to the sequence $7 \rightarrow 21 \rightarrow 22$ 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 BF₃•OEt₂ (210 µL, 230 mg, 1.66 mmol) in anhydr. CH₂Cl₂ (5 mL). After work up and column chromatography (SiO₂, CH₂Cl₂/MeOH/ NH_3 (aq., 25%) 100:0:0 \rightarrow 95:4.5:0.5), the pyrrolocytisine 23 was obtained as a colorless resin; yield: 34.9 mg (154 μ mol, 46%); R_f = 0.48 (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 97:2.7:0.3); $[\alpha]_D^{25} = -192.0$ (c = 0.5, MeOH); ¹H NMR (CDCl₃, 500 MHz): $\delta = 7.24$ (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-HH), 4.21 (dd, J=12.4 Hz, 4.5 Hz, 1 H, 11-HH), 4.12 (s, 1 H, 7-H), 4.07 (d, J=12.4 Hz, 1 H, 11-HH), 3.95 (d, J=16.1 Hz, 1 H, 10-HH), 2.95 (m, 1 H, 9-H), 2.21 (dm, J=12.9 Hz, 1 H, 8-HH), 2.14 (dm, J=12.9 Hz, 1 H, 8-HH); ¹³C NMR (CDCl₃, 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{v} = 2935, 1653, 1572, 1542, 1494, 1280, 1142, 1053, 803, 749, 721 cm⁻¹; HRMS (ESI): m/z calcd for C₁₄H₁₄N₂O + 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 (CH₂Cl₂/MeOH 95:5); $[\alpha]_D^{25}$ = -186.6 (c=0.5, MeOH); ¹H NMR (CDCl₃, 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-HH), 3.88 (dd, J=15.4 Hz, 7.0 Hz, 1 H, 10-HH), 3.08 (d, J= 10.4 Hz, 1 H, 11-HH), 2.87 (m, 2 H, 7-H, 13-HH), 2.44 (s, 1 H, 9-H), 2.28 (d, J=10.5 Hz, 1 H, 11-HH), 2.09 (m, 1 H, 16-H), 2.00 (m, 2 H, 8-HH, 13-HH), 1.78 (m, 1 H, 8-HH), 1.66 (m, 1 H, 15-HH), 1.55 (m, 2 H,



14-H₂), 1.44 (m, 1 H, 15-H*H*); ¹³C NMR (CDCl₃, 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 C₁₄H₁₈N₂O + 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 NaBH₄ (114 mg, 3.03 mmol) at 0 °C and stirred for 90 min at this temperature. Methanolic HCI (2.0 M; 2.83 mL) was added and the reaction mixture was allowed to reach rt over 4 h. Sat. aq. NaHCO₃ (20 mL) was added and the solvent was removed under vacuum. The aqueous layer was extracted with CH₂Cl₂ (5 × 25 mL) and the combined organic layers were dried over Na₂SO₄. Column chromatography (SiO₂, CH₂Cl₂/MeOH 100:0 \rightarrow 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 μ L, 281 mg, 2.46 mmol) and BF₃·OEt₂ (156 μ L, 175 mg, 1.23 mmol) were added at 0 °C to a solution of the *N*,*O*-acetal **25** (132 mg, 410 μ mol) in anhydr. CH₂Cl₂ (6 mL). After 16 h at rt, the crude mixture was adsorbed to a small amount of silica and subjected to column chromatography (SiO₂, CH₂Cl₂/MeOH/NH₃ (aq., 25%) 100:0:0 \rightarrow 90:9.1:0.9) to give 11-allylcytisine (**26**) as a white solid; yield: 80.0 mg (347 μ mol, 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 μ mol) in anhydr. THF (7 mL). The mixture was refluxed for 5 h and cooled to rt. Aq. H₂O₂ (30 wt%, 7 mL, 68.5 mmol) and aq. NaOCI (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_2CI_2 (20×9 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH/NH₃ (aq., 25%) 100:0:0 \rightarrow 90:9:1), providing the alcohol **27** as a colorless resin; yield: 61.1 mg (246 µmol, 81%); R_f=0.14 (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 95:4.5:0.5); $[\alpha]_D^{25} = -74.0$ (c = 1.0, MeOH); ¹H NMR (CDCl₃, 500 MHz): $\delta =$ 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-HH), 3.89 (dd, J=15.8 Hz, 6.5 Hz, 1 H, 10-HH), 3.68 (ddd, J=11.0 Hz, 5.5 Hz, 4.2 Hz, 1 H, CHHOH), 3.54 (ddd, J= 11.0 Hz, 8.0 Hz, 3.0 Hz, 1 H, CHHOH), 3.32 (br. s, 2 H, NH, OH), 3.26 (dd, J=13.4 Hz, 2.4 Hz, 1 H, 13-HH), 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-HH), 2.22 (d, J=2.5 Hz, 1 H, 9-H), 2.15 (d, J=13.3 Hz, 1 H, 8-HH), 1.99 (m, 1 H, CHH(CH₂)₂OH), 1.89–1.74 (m, 2 H, 8-HH, CHHCH₂OH), 1.69–1.54 (m, 2 H, CHH(CH₂)₂OH, CHHCH₂OH); 13 C NMR (CDCl₃, 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 (CH₂OH), 59.4 (C-11), 51.1 (C-10), 47.3 (C-13), 35.2 (C-7), 32.0 (C-9), 31.6 (CH₂CH₂OH), 29.5 (CH₂(CH₂)₂OH), 21.3 (C-8) ppm; IR (ATR): $\tilde{v} = 2932$, 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_2CI_2 (5 mL) was treated at 0 °C with CBr_4 (329 mg, 992 µmol), NEt₃ (81.3 µL, 59.3 mg, 586 µmol), and PPh₃ (213 mg, 812 µmol). After 18 h at rt, the reaction mixture was quenched with aq. HCI (0.5 M, 7 mL). The organic layer was separated and the aqueous layer was extracted with CH_2CI_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_2CI_2 (5×12 mL). The organic layers were combined and dried over Na2SO. Removal of the solvent under vacuum and column chromatography (deactivated SiO₂, CH₂Cl₂/MeOH/NH₃ (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 (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 95:4.5:0.5); $[\alpha]_D^{24} = -113.1$ (c=0.5, CHCl₃) {ref. [10]: $[\alpha]_D^{20} = -112.9$ $(c = 0.5, \text{CHCl}_3)$; ref. [4e]: $[\alpha]_D = -108 (c = 1.0, \text{CHCl}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: $[\alpha]_D = -108 (c = 1.0, \text{CHC}_3)$; ref. [6g]: [6g]: −186}^[29]; ¹H NMR (CDCl₃, 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-HH), 3.88 (dd, J=15.3 Hz, 6.2 Hz, 1 H, 10-HH), 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-H₂, 16-H₂), 2.48 (s, 1 H, 9-H), 2.00-1.87 (m, 2 H, 8-HH, 13-HH), 1.83–1.60 (m, 4 H, 8-HH, 12-H₂, 13-HH); ¹³C NMR (CDCl₃, 125 MHz): $\delta = 163.7$ (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): $\tilde{v} = 2949$, 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 ¹³C 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 SiO₂) delivered the natural alkaloid camoensidine (11) as a pale yellow oil; yield: 73.1 mg (312 μ mol, 79%); R_f =0.27 (CH₂Cl₂/MeOH/NH₃ (ag., 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)}; ¹H NMR (CDCl₃, 500 MHz): $\delta = 4.57$ (d, J=13.1 Hz, 1 H, 10-HH), 3.34 (t, J=7.0 Hz, 1 H, 6-H), 2.73 (m, 2 H, 14-HH, 16-HH), 2.63 (d, J=13.1 Hz, 1 H, 10-HH), 2.43-2.20 (m, 5 H, 3-H₂, 11-H, 14-HH, 16-HH), 2.02 (m, 1 H, 5-HH), 1.94 (s, 1 H, 9-H), 1.85-1.68 (m, 6 H, 4-HH, 7-H, 8-HH, 12-H₂, 13-HH), 1.63-1.45 (m, 3 H, 4-HH, 8-HH, 13-HH), 1.35 (d, J = 12.5 Hz, 1 H, 5-HH); ¹³C NMR (CDCl₃, 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): v = 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 μ mol) was dissolved in anhydr. THF (4 mL) and cooled to 0 °C. LiAlH₄ (2.4 M in THF, 893 μ L, 2.14 mmol) was added and the reaction mixture was refluxed for 23 h. At rt, sat. aq. Na₂SO₄ (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 Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in aq. HCl (1 M, 15 mL) and extracted with hexanes (15 mL) and Et₂O (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 Na2SO4 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 μ mol, 67%); $R_f = 0.23$ (CH₂Cl₂/MeOH/NH₃ (aq., 25%) 90:9:1); $[\alpha]_{D}^{25} = +23.2$ (c = 1.0, MeOH); ¹H NMR (MeOD, 500 MHz): δ = 2.87 (m, 1 H, 6-H), 2.84–2.70 (m, 4 H, 2-HH, 10-HH, 14-HH, 16-HH), 2.64 (m, 2 H, 2-HH, 10-HH), 2.24 (dd, J=10.9 Hz, 2.4 Hz, 1 H, 16-HH), 1.98–1.86 (m, 5 H, 5-HH, 7-H, 11-H, 13-HH, 14-HH), 1.79 (m, 2 H, 3-HH, 4-HH), 1.68 (m, 3 H, 3-HH, 8-HH, 13-HH), 1.63-1.51 (m, 3 H, 8-HH, 9-H, 12-HH), 1.39-1.28 (m, 3 H, 4-HH, 5-HH, 12-HH); ¹³C NMR (MeOD, 125 MHz): $\delta = 67.4$ (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 C₁₄H₂₄N₂ + 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

- a) G. Boschin, D. Resta, in: Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes (Eds.: K. G. Ramawat, J.-M. Merillon), Springer-Verlag, Berlin, Heidelberg, 2013, pp. 381–403; b) S. Ohmiya, K. Saito, I. Murakoshi, in: The Alkaloids: Chemistry and Physiology, Vol. 47 (Ed.: G. A. Cordell), Academic Press: New York, 1995, pp. 1–114; c) K. Saito, I. Murakoshi, in: Studies in Natural Product Chemistry (Ed.: Atta-ur-Rahman), Elsevier, 1995, pp. 519–549.
- [2] a) M. Lourenço, P. Máximo, L. M. Ferreira, M. M. A. Pereira, in: Studies in Natural Products Chemistry: Bioactive Natural Products, Part H (Ed.: Attaur-Rahman), Elsevier, Amsterdam, New York, 2002, pp. 233–298; b) K. A. Aslanov, Y. K. Kushmuradov, A. S. Sadykov, in: The Alkaloids: Chemistry and Physiology, Vol. 31 (Ed.: A. Brossi), Academic Press, 1987, pp. 117–192; c) A. D. Kinghorn, M. F. Balandrin, in: Alkaloids: Chemical and Biological Perspectives, Vol. 2 (Ed.: S. W. Pelletier), John Wiley & Sons, New York, 1984, pp. 105–141; d) T. Robinson in Molecular Biology, Biochemistry and Biophysics Molekularbiologie, Biochemie und Biophysik, Springer-Verlag, Berlin, Heidelberg, 1981, pp. 67–75; e) F. Bohlmann, D. Schumann, in: The Alkaloids: Chemistry and Physiology (Ed.: R. H. F. Manske), Academic Press, New York, 1967, pp. 1175–221; f) N.J. Leonhard, in: The Alkaloids: Chemistry and Physiology, Vol. 3 (Ed.: R. H. F. Manske, H. L. Holmes), Academic Press: New York, 1953, pp. 119–199.
- [3] a) K. M. Frick, L. G. Kamphuis, K. H. M. Siddique, K. B. Singh, R. C. Foley, Front. Plant Sci. 2017, 8, 87; b) S. Bunsupa, M. Yamazaki, K. Saito, Front. Plant Sci. 2012, 3, 239; c) M. Wink, Planta Med. 1987, 53, 509–514.
- [4] At least six further natural quinolizidine-indolizidine derivatives are known or proposed, the camoensidine-11-*N*-oxide (ref. a), guianodendrine (10-oxo-2,3-dehydroleontidine, ref. b, c), an isomer of camoensidine (ref. e), 12α-hydroxy-camoensine (ref. e), 12α-hydroxycamoensidine (ref. e, and 12-hydroxy-16-methoxy-11:12,13:14-tetradehydrocamoensine (ref. e): a) S. Ohmiya, H. Kubo, Y. Nakaaze, K. Saito, I. Murakoshi, H. Otomasu, *Chem. Pharm. Bull.* **1991**, *39*, 1123–1125; b) G. C. Kite, *Biochem. Syst. Ecol.* **2017**, *73*, 47–49; c) G. C. Kite, D. Cardoso, N. C. Veitch, G. P. Lewis, S. Afr. J. Bot. **2013**, *89*, 176–180; d) A. El-Shazly, T. Sarg, A. Ateya, E. Abdel Aziz, L. Witte, M. Wink, *Pharmazie* **1996**, *51*, 768–772; e) P. G. Waterman, D. F. Faulkner, *Phytochemistry* **1982**, *21*, 215–218.
- [5] Currently, it cannot be fully excluded that the quinolizidine-indolizidine alkaloids are biosynthetically derived from the corresponding bisquinolizidine alkaloids by contraction of the fused piperidine to a pyrrolidine. The genus *Maackia*, however, one source of these alkaloids, is known to produce both, quinolizidine and indolizidine natural products in parallel, which supports, at least for this genus, a mixed biosynthesis from L-lysine and L-ornithine, see ref. [8b, 8c] and: J. P. Michael, *Nat. Prod. Rep.* 2001, *18*, 520–542.
- [6] Leontidine (7) was isolated from Leontice ewersmannii (ref. a-d), L. albertii (ref. e), L. smirnowii (ref. f), and Camoensia maxima (ref. g): a) A. Oryekhov, R. Konovalova, Arch. Pharm. Ber. Dtsch. Pharm. Ges. 1932, 270, 329–334; b) S. Yunusov, L. G. Sorokina, J. Gen. Chem. USSR 1949, 19, A427–A435; Zh. Obshch. Khim. 1949, 19, 1955–1963; c) T. F. Platonova,

A. D. Kuzovkov, P. S. Massagetov, J. Gen. Chem. USSR **1953**, 23, 921–926; Zh. Obshch. Khim. **1953**, 23, 880–886; d) G. Gresser, P. Bachmann, L. Witte, F. C. Czygan, Biochem. Syst. Ecol. **1993**, 21, 679–685; e) S. Iskandarov, R. A. Shaimardanov, S. Y. Yunusov, Chem. Nat. Compd. **1971**, 7, 611–614; Khim. Prir. Soedin. **1971**, 631–636; f) E. G. Tkeshelashvili, K. S. Mudzhiri, Chem. Nat. Compd. **1975**, 11, 823; Khim. Prir. Soedin. **1975**, 11, 807; g) J. Santamaria, F. Khuong-Huu, Phytochemistry **1975**, 14, 2501– 2504.

- [7] Camoensine (10) was isolated from Camoensia maxima,^[6g] C. brevica-lyx,^[4e] and Daphniphyllum oldhami (ref. a), and detected by GC-MS in Leontice ewersmanni,^[6d] L. leontopetalum,^[6d] Orphanodendron bernalii,^[4b] O. grandiflorum,^[4b] and diverse Melolobium species (ref. b): a) S.-Z. Mu, J.-S. Wang, X.-S. Yang, H.-P. He, C.-S. Li, Y.-T. Di, Y. Wang, Y. Zhang, X. Fang, L.-J. Huang, X.-J. Hao, J. Nat. Prod. 2008, 71, 564–569; b) B. E. van Wyk, G. H. Verdoorn, L. Burger, R. Greinwald, S. Afr. J. Bot. 1988, 54, 386–388.
- [8] Camoensidine (11) was isolated from Camoensia maxima,^[6g] C. brevicalyx,^[4e] Maackia amurensis (ref. a–d), and M. tashiroi,^[4a] and detected by GC-MS in Orphanodendron bernalii,^[4b] O. grandiflorum,^[4b] Sakoanala villosa (ref. e), Poecilanthe parviflora (ref. f), P. subcordata (ref. f), P. itapuana (ref. f), Lupinus latifolius (ref. g), and L. sericeus (ref. g): a) K. Saito, S. Tsai, S. Ohmiya, H. Kubo, H. Otomasu, I. Murakoshi, Chem. Pharm. Bull. 1986, 34, 3982–3985; b) K. Saito, T. Yoshino, T. Sekine, S. Ohmiya, H. Kubo, H. Otomasu, I. Murakoshi, Phytochemistry 1989, 28, 2533–2534; c) Y.-H. Wang, J.-S. Li, Z.-R. Jiang, H. Kubo, K. Higashiyama, S. Ohmiya, Chem. Pharm. Bull. 2000, 48, 641–645; d) A. D. Kinghorn, M. F. Balandrin, L. J. Lin, Phytochemistry 1982, 21, 2269–2275; e) B. E. van Wyk, R. Greinwald, L. Witte, Biochem. Syst. Ecol. 1993, 21, 711–714; f) R. Greinwald, P. Bachmann, G. Lewis, L. Witte, F.-C. Czygan, Biochem. Syst. Ecol. 1995, 38, 139–153.
- [9] The intermediate of this synthesis, 11-allylcytisine (26), was treated with HI at 230 °C. With leontidine (7) being formed, epimerization at C-11 must have occurred under the harsh conditions, see ref. [10].
- [10] H. Kubo, S. Ohmiya, I. Murakoshi, Can. J. Chem. 1994, 72, 214–217.
- [11] Y.-H. Wang, K. Higashiyama, H. Kubo, J.-S. Li, S. Ohmiya, *Heterocycles* 2000, *53*, 545–548.
- [12] D. Scharnagel, J. Goller, N. Deibl, W. Milius, M. Breuning, Angew. Chem. 2018, 130, 2456–2460; Angew. Chem. Int. Ed. 2018, 57, 2432–2435.
- [13] J. Goller, C. B. Hübschle, M. Breuning, *Eur. J. Org. Chem.* **2019**, *2019*, 895–899.
- [14] For the synthesis of artificial bispidines and 9-oxabispidines by our group see: a) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, Chem. Eur. J. 2015, 21, 12488–12500; b) M. Breuning, D. Hein, Eur. J. Org. Chem. 2013, 7575–7582; c) M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, Chem. Eur. J. 2009, 15, 12764–12769; d) M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, J. Org. Chem. 2009, 74, 1407–1410; e) M. Breuning, M. Steiner, Tetrahedron: Asymmetry 2008, 19, 1978–1983; f) M. Breuning, A. Paasche, M. Steiner, S. Dilsky, V. H. Gessner, C. Strohmann, B. Engels, J. Mol. Struct. 2011, 1005, 178–185.
- [15] A. J. Dixon, M. J. McGrath, P. O'Brien, Org. Synth. 2006, 83, 141-154.
- [16] For the oxidation of cyclic amines to lactams with iodine, see: R. J. Griffiths, G. A. Burley, E. P. A. Talbot, Org. Lett. 2017, 19, 870–873.
- [17] I. Murakoshi, H. Kubo, M. Ikram, M. Israr, N. Shafi, S. Ohmiya, H. Otomasu, *Phytochemistry* 1986, 25, 2000–2002.
- [18] We also tested the oxidation of *N*-Boc protected cytisine, speculating that the attached pyridone might induce a preferred orientation of the *N*-Boc group, which, in turn, might favor a regioselective oxidation. All oxidants tested (I₂, K₃Fe(CN)₆, PIDA, KMnO₄, RuO₂·H₂O/NalO₄), however, failed to produce any oxidation products.
- [19] J.-S. Hsu, A. D. Kuzovkov, J. Gen. Chem. USSR 1963, 33, 2012–2015; Zh. Obshch. Khim. 1963, 33, 2067–2070.
- [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.
- [25] Z. Liu, J. F. Hartwig, J. Am. Chem. Soc. 2008, 130, 1570–1571.
- [26] Oxymercuration-reduction (Hg(OAc)₂; NaBH₄) 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.
- [28] Purification of Laboratory Chemicals, Eds.: W. L. F. Armarego, D. D. Perrin, 4th ed., Butterworth-Heinemann, Oxford, **2000**.
- [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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