Short Total Synthesis of (–)-Lupinine and (–)-Epiquinamide by Double Mitsunobu Reaction

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Abstract: Alternative total syntheses of (–)-lupinine (**1**) and (–)-epiquinamide (**2**) have been described via the key intermediate **3** obtained from the addition of 2-trialkylsilyloxyfuran **5** to *N*-acyliminium intermediate derived from **4**. The major *R*,*R*-isomer **8** obtained from the Mannich reaction was converted into its *R*,*S*-isomer through Mitsunobu reaction. Then, a second Mitsunobu reaction of **3** led to cyano **9** and azido **11** derivatives, which were converted into **1** and **2** in 33 and 36% overall yield from **4**, respectively. The synthetic route is amenable for the generation of several quinolizidine alkaloids.

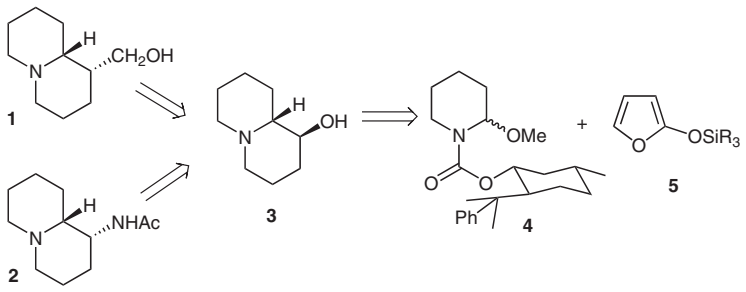
Key words: quinolizidine alkaloids, azido reduction, nickel boride, microwave irradiation, Mitsunobu reaction

The search towards efficient stereoselective methodologies for the construction of organic molecules with enhanced complexity and functions continues to challenge chemists. Over the last few years 2-trialkylsilyloxyfurans[1] have been used as versatile reagents for the preparation of several enantiomerically pure compounds of biological interest.[2] We have investigated the nucleophilic addition of carbon nucleophiles to cyclic *N*-acyliminium ions and found the relevant role played by the *N*-acyliminium ring size in the stereochemical outcome of the reaction.[3] As studies involving the intermolecular nucleophilic addition of 2-trialkylsilyloxyfurans to cyclic *N*-acyliminium ions are so far restricted to five-membered *N*-acyliminium ion rings and mainly to *N*-carbobenzyloxy derivatives,[2] it was decided to explore these studies for the construction of chiral quinolizidines based on 8-phenylmenthyl induction.

As part of our efforts in the field of biologically relevant quinolizidines, attention was turned toward an alternative synthetic route for (–)-lupinine[4] and (1*R*,9a*R*)-epiquinamide,[5] figured out through the addition of siloxyfuran **5** to key iminium intermediate derived from **4**. Recently, we reported enantioselective total syntheses of arborescidine alkaloids,[6a] (–)-quinolactacin B antibiotic,[6b] PDE5 inhibitors,[6c] noscapine, bicuculline, and egenine, as well as capnoidine and corytensine alkaloids.[3e]

Structurally, compounds **1** and **2** comprise a common quinoline core. Our approach to lupinine (**1**) and epiquinamide (**2**) is based on the preparation of azabicyclo compound **3** through the addition of silyloxyfuran **5** to an *N*-acyliminium ion derived from **4**, followed by the introduction of the CH_2OH and NHAc groups based on double stereoselective Mitsunobu reactions (Scheme 1). Although demonstrated as a useful synthetic method, these asymmetric additions remain to be fully explored in the arena of total syntheses of alkaloid natural products.

Our investigation began by examining the addition of different silyloxyfurans **5** (R = Me, Bu, *i*-Pr) to the *N*-acyliminium ion derived from chiral 2-methoxypiperidine carbamate **4**[2g,3c] (Scheme 2). Previously, D'oca and coworkers reported the addition of 2-tributylsilyloxyfuran to **4** achieving a low diastereoselectivity of **6** (2:1, *threo*/*erythro*) in 73% yield.[2g] Furthermore, it was observed that



Scheme 1 Retrosynthetic analysis of (–)-lupinine and (1*R*,9a*R*)-epiquinamide based on the key intermediate **3**

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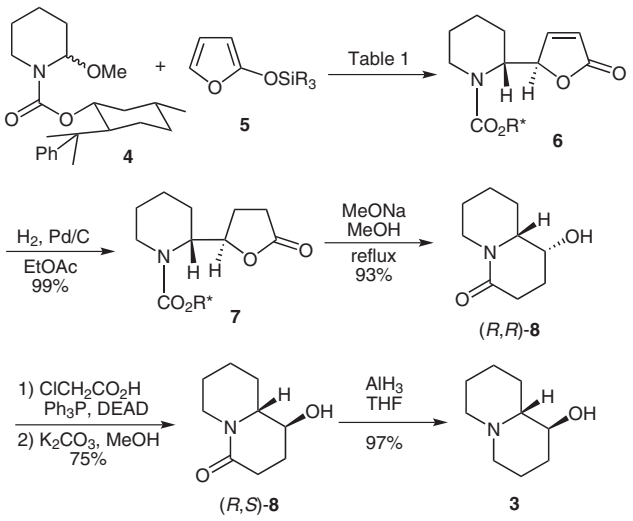
the nature of solvent, Lewis acids, and additives have great influence on selectivities in this kind of reactions.[3] Thus, the scope of the addition of **5** to the *N*-acyliminium ion derived from carbamate **4** was investigated with and without additives in different conditions (Table 1). First, TMSOTf as Lewis acid was used in a mixture of solvent ($THF–CH_2Cl_2$), which proved to improve selectivities for the addition of silyloxyfurans to cyclic *N*-acyliminium ions.[3,6] Table 1 shows the addition of nucleophiles **5a–c** in the absence of additives affording *threo*-**6** isomer in diastereoisomeric ratios ranging from 4.5–8.1:1 (*threo*/*erythro*) when TMSOTf was used as Lewis acid. The reactions proceeded in reaction times of around 7 hours in 75–76% yields (Table 1, entries 1–3). Then, **5c** was selected as nucleophile and $TiCl_4$ and TIPSOTf were used as Lewis acid (Table 1, entries 4, 5). After 7 hours of reaction, neither the diastereoselection was improved favoring the *threo*-isomer nor the yields. Finally, the addition of CsF[3e] (Table 1, entry 6) and butylmethylimidazolinium tetrafluoroborate[3e] ($BMI·BF_4$, Table 1, entry 7) as additive was tested in the reaction of TMSOTf with **5c**. The diastereoselectivity of the reaction was significantly affected by the nature of the additive ($BMI·BF_4$), which improved yields and selectivities. In fact, in the presence of $BMI·BF_4$ the preference for the *threo*-isomer **6** increased to 9.7:1 (Table 1, entry 7) when compared with no additive. The diastereoisomeric ratios of *threo*/*erythro* **6** obtained were determined by capillary GC analysis.



Scheme 2 Synthesis of **3** (R* denotes the 1-(1*R*,2*S*,5*R*)-8-phenylmenthylpiperidine part of the structure; cf. **4**).

Then, compound **6** was converted into quinolizidinone (*R*,*R*)-**8** in 92% overall yield according to previously studied methodologies.[2g,3b,c] Having prepared (*R*,*R*)-**8**, the next step was the inversion of configuration at C-10 in (*R*,*R*)-**8** via Mitsunobu reaction ($ClCH_2CO_2H$, DEAD, Ph_3P) to give the corresponding chloroacetate, which was hydrolyzed with K_2CO_3 in MeOH to afford the diastereomeric alcohol (*R*,*S*)-**8** in 75% yield. Reduction of (*R*,*S*)-**8** with alane (AlH_3) gave after silica gel purification **3** in 97% yield. This route provides enantiomerically pure 1-azabicyclo[4.4.0]decane **3**.[7] These results reveal the exclusive addition of silyloxyfuran **5** to the *Si* face of the *N*-acyliminium ions derived from **4**, as depicted in Figure 1.

Table 1 Asymmetric Addition of **5** to *N*-Acyliminium Precursor from **4**[a]

Entry	**5**, R	Lewis acid	Additive	**6**, *threo*/*erythro*[b]	Yield (%)[c]
1	**5a**, Bu	TMSOTf	–	5:1	75
2	**5b**, Me	TMSOTf	–	4.5:1	76
3	**5c**, *i*-Pr	TMSOTf	–	8:1	75
4	**5c**, *i*-Pr	$TiCl_4$	–	5:1	72
5	**5c**, *i*-Pr	TIPSOTf	–	8:1	74
6	**5c**, *i*-Pr	TMSOTf	CsF	7.5:1	73
7	**5c**, *i*-Pr	TMSOTf	$BMI·BF_4$	9.7:1	80

[a] All reactions were performed in $THF–CH_2Cl_2$ (1:1) as solvent at –78 °C for 7 h.
[b] Diastereomeric ratio (dr) was calculated based on GC analysis.
[c] Isolated yields.

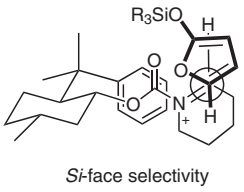
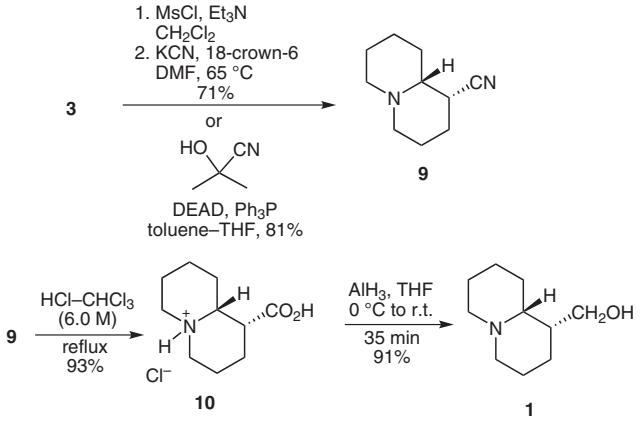


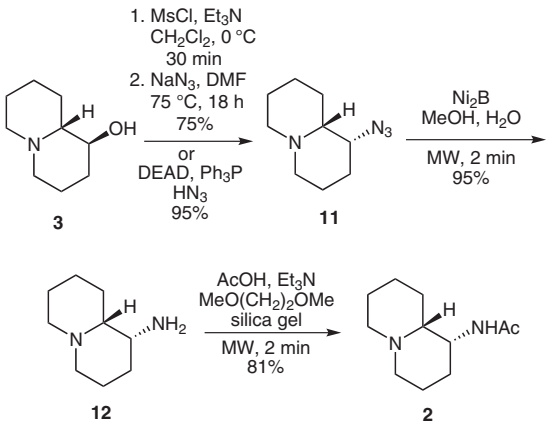
Figure 1 Facial selectivity for the addition of **5** to *N*-acyliminium precursor **4**

Next, efforts were directed to the preparation of cyano compound **9**. The first approach was to convert the alcohol **3** via the mesylate affording **9** in 71% overall yield using 18-crown-6 ether. In the absence of crown ether, the yields of the reaction were lower (15%). Furthermore, it was observed that temperatures higher than 70 °C caused epimerization at C-10 (Scheme 3). Then, it was attempted to carry out this transformation in one-step applying the synthetic versatility of the Mitsunobu reaction. First, KCN, DEAD, and Ph_3P were tested, which afforded **9** in disappointing 31% yield, without epimerization. Then, **3** was subjected to Mitsunobu reaction by using acetone cyanohydrin, DEAD, and Ph_3P in toluene–THF as solvent,[8] which converted the C-10 hydroxy group into the homologated nitrile group in **9** in 81% yield. The reaction proceeded very clean affording **9** with no epimerization as determined by GC analysis (Scheme 3).

The cyano compound **9** was then hydrolyzed to acid **10** using 6 M HCl in refluxing $CHCl_3$ in 93% yield. Interestingly, compound **10** showed differences in chemical shifts and coupling constants in $CDCl_3$, probably due to the acid content of the solvent, for hydrogens on carbons 1, 4, 5 and 10, suggesting an equilibrium among the iminium,



Scheme 3 Synthesis of (–)-lupinine (**1**).



Scheme 4 Synthesis of (–)-equiquinamide (**2**)

zwitterion and hydrochloride salt.[9] Finally, (–)-lupinine (**1**) was obtained in 91% yield by alane reduction of **10**, as depicted in Scheme 3.

For the synthesis of epiquinamide, the alcohol **3** was converted via the mesylate into azido **11** in 75% overall yield.[10] However, Cohen and Overman, in their synthesis of batzelladine F, used the Mitsunobu reaction with hydrazoic acid to install an azide group.[11] Thus, testing Mitsunobu reaction of **3** with DEAD, Ph_3P, and hydrazoic acid afforded **11** in yields of around 90–95%. Then, nickel boride (Ni_2B) reduction of azide **11** afforded **12**[12] in 85% yield after two hours at 65 °C.[13] The nickel boride (amorphous fine black granules) was freshly prepared by mixing $Ni(OAc)_2$ and $NaBH_4$.[14] With the aim of increasing the yields along with shortening the reaction times, we decided to explore microwave irradiation in the reduction of **11**.[15] The same reaction as described above was carried out under microwave-assisted conditions in a sealed vessel. Reaction times were reduced to two minutes for azide **11**, the yields (93–95%) were better than using thermal heating. Further, it was also observed that by applying the described protocol, temperatures of the reaction mixture inside the reaction vessel reached values of 39 °C (2 min) for the microwave-assisted reductions at a power of 70 W. These temperatures were lower than used in the thermal conditions, preventing in this way degradation of reactants and products, and favoring the enhancement of yields. Finally, a mixture of acetic acid, Et_3N and 1,2-dimethoxyethane (DME) in silica gel using microwave irradiation converted crude **12** into (–)-epiquinamide (**2**) in 81% yield after two minutes[5,16] (Scheme 4).

In conclusion, these results reveal an attractive route to enantiomerically pure piperidine derivatives through quinolididinone **8**, which is a potentially useful intermediate for the asymmetric synthesis of quinolizidine alkaloids. Although the Mitsunobu reaction is a classical one, its use continues to be interesting and should not be discarded when asymmetry is required in systems featuring chiral OH groups. An efficient microwave-assisted methodology employing Ni_2B for the preparation of amine **12** is described. Ni_2B reagent is easy to prepare, inexpensive, safe to handle, stable, does not require inert atmosphere, and not pyrophoric. Interestingly, the microwave-assisted irradiation reactions enhanced yields with very short reaction times in contrast to the conventional thermal reactions. The reaction conditions are particularly attractive and are an example of green chemistry approach.

Commercially available chemical reagents were used without further purification. HN_3, DEAD, NaN_3, DME, and acetone cyanohydrin were purchased from Sigma-Aldrich. Ph_3P was purchased from Merck. Anhyd THF, CH_2Cl_2, MeOH, and DMF were prepared by distillation under N_2 over Na/benzophenone, CaH_2, Na/P_2O_5, and CaH_2/molecular sieves, respectively. Solvents for extraction and column chromatography were distilled prior to use. NaN_3 was handled with care by wearing safety glasses, facemask, gloves, and the reactions were performed in a fume hood. All the microwave reactions were performed in CEM Discover LabMate equipment in a closed vessel (built-in infrared sensor) with cooling system. IR spectra were recorded as film on KBr cells and the wave numbers are expressed in cm^{-1}. Melting points were measured with an Eletrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker WH Avance 300, and Varian Unity 400 MHz spectrometers using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Spin multiplicities are described as s (singlet), br s (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in Hertz (Hz). Mass spectra were recorded on a Qtof Micro (Waters-Micromass). Column chromatography was performed using silica gel 100–200 mesh. TLC analyses were performed with silica gel plates using I_2, $KMnO_4$, or UV-lamp for visualization.

1-(1*R*,2*S*,5*R*)-8-Phenylmenthylpiperidine

This compound was prepared following the experimental procedure according to reference 3c; mp 55.3–56.6 °C; $R_f = 0.5$ (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ –40 (*c* 1.07, $CHCl_3$).

FTIR (KBr film): 2927, 2854, 1691, 1599, 1429, 1261, 1232, 1149, 1092, 1026, 764, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.75–0.84 (m, 3 H), 0.85 (d, *J* = 6.7 Hz, 1 H), 0.87–0.93 (m, 1 H), 1.15–1.18 (m, 1 H), 1.21 (s, 3 H), 1.34 (s, 3 H), 1.37–1.67 (m, 9 H), 1.89–2.03 (m, 2 H), 3.03–3.09 (m, 4 H), 4.77 (dt, *J* = 4.5, 11.0 Hz, 1 H), 7.13–7.17 (m, 1 H), 7.21–7.32 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 24.1, 25.3 (2C), 25.9 (2C), 26.4, 26.5, 31.1, 34.3, 39.3, 42.3, 43.9, 50.5, 75.0, 124.7, 125.3 (2C), 127.9 (2C), 151.9, 154.9.

HRMS (EI) *m/z* $[M]^{+\cdot}$ calcd for $C_{22}H_{33}NO_2$: 343.2511; found: 343.2515.

1-(1*R*,2*S*,5*R*)-8-Phenylmenthyl-2-(*R*/*S*)-methoxypiperidine (4)
This compound was prepared following the experimental procedure according to reference 3c.

FTIR (KBr film): 3023, 2917, 2952, 2829, 1702, 1602, 1402, 1180, 1083, 755, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.82–0.87 (m, 1 H), 0.91–1.20 (m, 2 H), 1.20 (s, 3 H), 1.22 (s, 3 H), 1.38 (s, 3 H), 1.39–1.81 (m, 9 H), 1.92–1.96 (m, 1 H), 2.01–2.10 (m, 2 H), 2.39, 2.43, 2.74, 2.80, and 2.94 (5 × m, 1 H), 3.07, 3.19, 3.26, and 3.48 (4 × s, 3 H), 4.70–4.92 (m, 1 H), 3.94, 4.45, 5.33, and 5.40 (4 × m, 1 H), 7.10–7.17 (m, 1 H), 7.22–7.30 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.9, 24.3, 26.0, 27.7, 30.5, 32.1, 35.1, 38.4, 39.4, 40.9, 42.7, 50.8, 54.8, 75.0, 82.0, 125.3, 125.6 (2C), 128.2 (2C), 152.3, 155.0.

HRMS (EI): *m/z* $[M]^{+\cdot}$ calcd for $C_{23}H_{35}NO_3$: 373.2617; found: 373.2601.

Compound 6
To a solution of methoxycarbamate **4** (672 mg, 1.80 mmol) in anhyd CH_2Cl_2–THF (1:1, 10.0 mL) at –78 °C was added BMI·BF_4 (0.020 mL, 1.80 mmol) and the mixture was stirred for 30 min under argon atmosphere, followed by slow addition of 2-triisopropylsilyloxyfuran (460 mg, 1.80 mmol) in CH_2Cl_2–THF (1:1, 1.00 mL). After 7 h, sat. aq NH_4Cl (10.0 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude (9.7:1 diastereoisomeric mixture) was submitted to flash column chromatography purification (hexane–EtOAc, 2:1) affording pure *threo*-**6** (557 mg, 1.31 mmol) in 73% yield and *erythro*-**6** (61 mg, 0.144 mmol) in 8% yield.

***threo*-6**
$[\alpha]_D^{20}$ –22 (*c* 1.05, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.6 Hz, 3 H), 0.75–1.0 (m, 2 H), 1.07–1.65 (m, 10 H), 1.23 (s, 3 H), 1.39 (s, 3 H), 1.93–2.10 (m, 2 H), 2.68 (dt, *J* = 3.4, 12.5 Hz, 1 H), 3.35–3.42 (m, 1 H), 4.28 (q, *J* = 4.1 Hz, 1 H), 4.46 (m, 1 H), 4.96 (dt, *J* = 4.5, 10.1 Hz, 1 H), 5.61 (br d, *J* = 6.6 Hz, 1 H), 6.99 (d, 1 H, *J* = 6.6 Hz, 1 H), 7.00–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 155.6, 155.3, 152.3, 151.7, 127.9, 125.3, 125.0, 121.4, 120.5, 88.2, 81.4, 75.8, 52.5, 51.9, 50.3, 42.1, 39.9, 34.5, 31.2, 27.3, 26.7, 24.7, 24.6, 21.8, 19.5.

HRMS (ESI-MS): *m/z* calcd for $[C_{26}H_{35}NO_4 + H]^+$: 426.2644; found: 426.2601.

Compound 7
To a solution of *threo*-**6** (510 mg, 1.20 mmol) in EtOAc (12.0 mL) was added 10% Pd/C (38 mg) and the mixture was stirred under H_2 (1 atm) for 4 h. The mixture was then filtered through Celite, and the pad was rinsed with EtOAc–MeOH (4:1, 200 mL). The organic layer was concentrated under reduced pressure to furnished pure **7** as a colorless oil; yield: 508 mg (99%, 1.19 mmol); $[\alpha]_D^{20}$ –55 (*c* 1.5, $CHCl_3$).

FTIR (KBr film): 1780, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.79–1.00 (m, 2 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.12–1.29 (m, 3 H), 1.33 (s, 3 H), 1.39–1.81 (m, 12 H), 1.98–2.12 (m, 2 H), 2.22–2.28 (m, 1 H), 2.41–2.46 (m, 1 H), 2.48–2.54 (m, 1 H), 2.57–2.67 (m, 1 H), 2.89, 3.10 and 3.30 (3 × m, 1 H), 4.14, 4.24, and 4.31 (3 × m, 1 H), 4.60–4.67 (m, 1 H), 4.68–4.80 (m, 1 H), 7.10–7.17 (m, 1 H), 7.19–7.33 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 154.7, 154.2, 128.3, 127.6, 127.4, 126.4, 121.2, 80.0, 77.1, 52.2, 50.2, 42.9, 41.1, 39.5, 33.7, 33.0, 32.7, 26.0, 25.8, 24.8, 24.7, 24.1, 21.9 (2 × CH_3), 19.7.

HRMS (ESI-MS): *m/z* calcd for $[C_{26}H_{37}NO_4 + H]^+$: 428.2801; found: 428.2811.

(1*R*,9a*R*)-1-Hydroxyoctahydro-4*H*-quinolizin-4-one [(*R*,*R*)-8]
A solution of NaOMe in MeOH (1.1 mol/L, 5.2 mL) was added to **7** (384 mg, 0.90 mmol) at 0 °C, and the mixture was stirred at r.t. After 2 h, a 2 mol/L HCl–MeOH solution (10.0 mL) was carefully added. The organic layer was concentrated under reduced pressure, providing (*R*,*R*)-**8** in 93% yield as a colorless oil; yield: 142 mg (93%, 0.84 mmol); $[\alpha]_D^{20}$ +17 (*c* 1.5, MeOH).

FTIR (KBr film): 1780, 1680 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.50 (m, 1 H), 1.51–1.58 (m, 1 H), 1.65 (br s, 1 H), 1.65–1.70 (m, 1 H), 1.70–1.77 (m, 1 H), 1.79–1.89 (m, 1 H), 1.89–2.03 (m, 1 H), 2.36 (t, *J* = 5.4 Hz, 1 H), 2.44 (dt, *J* = 11.5, 4.2 Hz, 1 H), 2.60 (ddd, *J* = 17.1, 10.7, 5.6 Hz, 1 H), 3.30 (br dd, *J* = 11.5, 2.5 Hz, 1 H), 4.04 (br s, 1 H), 4.73 (br d, *J* = 17.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 25.3, 26.9, 27.2, 28.0, 42.8, 60.6, 66.4, 168.5.

HRMS (ESI-MS): *m/z* calcd for $[C_9H_{15}NO_2 + H]^+$: 170.1181; found: 170.1175.

(1*R*,9a*S*)-1-Hydroxyoctahydro-4*H*-quinolizin-4-one [(*R*,*S*)-8]
Compound (*R*,*R*)-**8** (135 mg, 0.80 mmol), Ph_3P (378 mg, 1.45 mmol), and $ClCH_2CO_2H$ (137 mg, 1.45 mmol) were dissolved in anhyd CH_2Cl_2 (10 mL). DEAD (0.23 mL, 1.45 mmol) was added dropwise to the solution and the resulting pale yellow solution was stirred at r.t. for 6 h. The reaction mixture was concentrated and the residue was purified by flash chromatography ($CHCl_3$–MeOH, 95:5) to give a mixture of chloroacetate contaminated with trace amounts of Ph_3PO. The chloroacetate was hydrolyzed using K_2CO_3 (331 mg, 2.4 mmol) in MeOH (10 mL). The MeOH was evaporated and CH_2Cl_2 (10 mL) was added to the residue. The mixture was filtered through a column of Celite and the filtrate was concentrated. The crude product was purified by flash chromatography ($CHCl_3$–MeOH–NH_4OH, 95:4.5:0.5; R_f = 0.42) to give (*R*,*S*)-**8**; yield: 102 mg (75%); $[\alpha]_D^{20}$ –10.5 (*c* 1.0, $CHCl_3$).

FTIR (KBr film): 3374, 2934, 2857, 1610, 1445, 1048 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.25 (m, 1 H), 1.31–1.43 (m, 1 H), 1.43–1.55 (m, 1 H), 1.67 (br d, *J* = 13.0 Hz, 1 H), 1.77–2.01 (m, 4 H), 2.31 (ddd, *J* = 17.1, 7.8, 6.0 Hz, 1 H), 2.38 (dt, *J* = 12.8, 2.5 Hz, 1 H), 2.54 (ddd, *J* = 17.1, 7.8, 6.0 Hz, 1 H), 3.15 (ddd, *J* = 12.0, 4.5, 2.5 Hz, 1 H), 3.19 (br s, 1 H), 3.68–3.74 (m, 1 H), 4.68–4.75 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 25.2, 26.9, 28.5, 31.5, 42.9, 63.7, 69.6, 168.4.

HRMS (ESI-MS): *m/z* calcd for $[C_9H_{15}NO_2 + H]^+$: 170.1181; found: 170.1188.

(1*R*,9a*R*)- 1-Hydroxyoctahydro-1*H*-quinolizine (3)
To a solution of (*R*,*S*)-**8** (220 mg, 1.30 mmol) in THF (10.0 mL) was added a solution of AlH_3 (1.55 M, 2.50 mL, 3.90 mmol; previously prepared by mixing 1 equiv of $AlCl_3$ and 3 equiv of $LiAlH_4$ solution in THF) at r.t. After 10 min, the reaction was quenched with sat. aq Na_2SO_4 (3.0 mL) and filtered. The solids were washed with CH_2Cl_2 (200 mL) and acidified with HCl–MeOH (10%) to effect complete conversion into the hydrochloride salt. Evaporation at reduced pressure afforded crude **3**, which was purified by flash chromatography eluting with $CHCl_3$–MeOH–NH_4OH (95:4.5:0.5, R_f = 0.42) to afford pure **3** as an oil; yield: 196 mg (97%). The spectroscopic data

are in accordance with previously described for **3**[7]; $[\alpha]_D^{20}$ –22.7 (*c* 1.05, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.39 (m, 10 H), 2.17–2.38 (m, 5 H), 3.48–3.56 (m, 1 H).

(1*R*,9a*R*)- 1-Cyanooctahydro-1*H*-quinolizine (9)

To a stirred solution of **3** (105 mg, 0.68 mmol), acetone cyanohydrin (1.38 mL, 1.36 mmol) and Ph_3P (232 mg, 0.88 mmol) in THF (5.0 mL) was added a 2.2 M solution of diethyl azodicarboxylate in toluene (0.372 mL, 0.82 mmol) over 1 h at 0 °C, and then the reaction mixture was allowed to warm to r.t. After stirring for 40 min, the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (5.0 mL) and hexane (3.0 mL), and then filtered to remove Ph_3PO. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography to give **9** containing some Ph_3P=O as impurity; yield: 90 mg (81%). Further purification was not done at this stage; $[\alpha]_D^{20}$ –18.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.42 (m, 9 H), 2.15–2.45 (m, 5 H), 2.68–2.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 23.4, 24.5, 27.0, 28.4, 38.3, 54.5, 55.8, 63.0, 122.4.

HRMS (ESI-MS): *m*/*z* calcd for $[C_{10}H_{16}N_2 + H]^+$: 165.1392; found: 165.1398.

(1*R*,9a*R*)-Octahydro-1*H*-quinolizine-1-carboxylic Acid (10)

Compound **9** (90 mg, 0.55 mmol) was dissolved in a 6 M HCl–$CHCl_3$ solution (2.0 mL) and stirred under reflux (60 °C) for 2 h. The mixture was washed with sat. aq $NaHCO_3$ (4.0 mL), and the organic extract separated. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The solvents from the combined organic layers were evaporated under vacuum and the crude product was purified by flash chromatography to afford the amino acid **10** as a white solid; yield: 93 mg (93%); mp 242–244 °C (Lit.[17] mp 255 °C); R_f = 0.3 ($CHCl_3$–MeOH–NH_4OH, 4:1:0.1); $[\alpha]_D^{20}$ +9.0 (*c* 0.5, $CHCl_3$).

FT-IR (KBr film): 3410 (br), 2940, 2868, 1593 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (tq, *J* = 4.1, 12.5 Hz, 1 H), 1.60–1.80 (m, 6 H), 1.86 (d, *J* = 13.8 Hz, 1 H), 2.04 (dd, *J* = 4.7, 13.8 Hz, 1 H), 2.13 (d, *J* = 12.9 Hz, 1 H), 2.30 (dt, *J* = 2.8, 12.5 Hz, 2 H), 2.41 (dt, *J* = 2.3, 12.5 Hz, 1 H), 2.43 (m, 1 H), 2.62 (br s, 1 H), 3.20 (ddd, *J* = 2.0, 4.7, 12.1 Hz, 1 H), 3.30 (dd, *J* = 2.0, 12.1 Hz, 1 H), 8.0 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 63.9, 56.0, 54.7, 46.1, 29.4, 27.3, 24.2, 23.0, 20.9.

HRMS (ESI-MS): *m*/*z* calcd for $[C_{10}H_{17}NO_2 + H]^+$: 184.1338; found: 184.1338.

(–)-Lupinine (1)

To a solution of **10** (24 mg, 0.13 mmol) in THF (2.0 mL) was added a solution of AlH_3 (1.55 M, 0.25 mL, 0.39 mmol, previously prepared by mixing 1 equiv of $AlCl_3$ and 3 equiv of $LiAlH_4$ solution in THF) at r.t. After 20 min, the reaction was quenched with sat. aq Na_2SO_4 (0.70 mL) and filtered. The solids were washed with CH_2Cl_2 and acidified with HCl–MeOH (10%) to effect complete conversion into the hydrochloride salt. Evaporation at reduced pressure afforded the crude **1**, which was purified by flash chromatography eluting with MeOH–NH_4OH (99.5:0.5, R_f = 0.8) to afford pure **1**; yield: 20 mg (91%). The spectroscopic data are in accordance with the data described previously;[18] mp 59–60 °C (Lit.[18] mp 58–59 °C); $[\alpha]_D^{20}$ –21.5 (*c* 1.05, $CHCl_3$) {Lit.[19] $[\alpha]_D^{20}$ –21.0 (*c* 0.25, EtOH)}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.25 (m, 1 H), 1.43–1.91 (m, 10 H), 1.99–2.02 (m, 1 H), 2.13–2.16 (m, 2 H), 2.78–2.83 (m, 2 H), 3.66 (d, *J* = 10.5 Hz, 1 H), 4.14 (ddd, *J* = 10.5, 5.5, 1.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 24.5, 25.7, 29.8, 31.3, 38.3, 57.0, 57.2, 65.0, 65.9.

HRMS (ESI-MS): *m*/*z* calcd for $[C_{10}H_{19}NO + H]^+$: 170.1545; found: 170.1551.

(1*R*,9a*R*)-1-Azidooctahydro-1*H*-quinolizine (11)

Diethyl azodicarboxylate (DEAD, 0.20 mL, 1.25 mmol) was added dropwise to solution of **3** (50 mg, 0.32 mmol), H_3N (0.53 mL, 2.7 M in toluene, 1.45 mmol), Ph_3P (332 mg, 1.27 mmol), and THF (4.0 mL) at 0 °C over 15 min using a syringe pump. After an additional 30 min, hexanes (5.0 mL) were added, and Ph_3PO was filtered off. The residue was purified by flash chromatography to provide **11**; yield: 39.5–41.6 mg (90–95%);[10] $[\alpha]_D^{20}$ –36.1 (*c* 1.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.42 (m, 10 H), 2.10–2.33 (m, 5 H), 3.35–3.39 (m, 1 H).

HRMS (ESI-MS): *m*/*z* calcd for $[C_9H_{16}N_4 – N_3]^+$: 138.1277; found: 138.1274.

(1*R*,9a*R*)-1-Aminooctahydro-1*H*-quinolizine (12)

Compound **11** (13.7 mg, 0.10 mmol) was dissolved in MeOH (2.0 mL), and then Ni_2B (25 mg, 0.30 mmol) and aq 1 M HCl (0.4 mL) were added. The mixture was irradiated at 70 W using CEM Discover LabMate equipment in a closed vessel with the temperature monitored by a built-in infrared sensor for 2 min at 39 °C with cooling. The resulting mixture was filtered, and then the MeOH was evaporated under vacuum. Then, sat. aq $NaHCO_3$ (2.0 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic layers were dried (Na_2SO_4), then evaporated under reduced pressure to afford crude compound **12**; yield: 15 mg (95%).

HRMS (ESI-MS): *m*/*z* calcd for $[C_9H_{18}N_2 + H]^+$: 155.1548; found: 155.1552.

(–)-Epiquinidine (2)

The crude amine **12** (11 mg, 0.07 mmol) was mixed with silica gel (100 mg, 100–200 mesh). To the mixture was added in the following order: DME (0.09 mL, 1.25 equiv), Et_3N (0.50 mL, 51 equiv), and AcOH (0.0135 mL, 0.176 mmol). The reaction mixture was heated by microwave-assisted irradiation at 70 W using a CEM Discover LabMate equipment in a closed vessel with the temperature monitored by a built-in infrared sensor for 2 min at 39 °C with cooling. The resulting mixture was diluted with $CHCl_3$ (4.0 mL) and filtered; then the organic solvent evaporated under vacuum to afford the pure compound **2** as a colorless solid; yield: 11.1 mg (81%). The spectroscopic data were in accordance with the data described previously;[5,16] mp 133–135 °C (Lit.[9] mp 131–133 °C; $[\alpha]_D^{20}$ –22 (*c* 0.5, $CHCl_3$) {Lit.[10] for (+)-**2**: $[\alpha]_D^{22}$ +26.2 (*c* 0.25, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.62 (m, 7 H), 1.73 (br d, *J* = 13.0 Hz, 2 H), 1.85 (br d, *J* = 13.0 Hz, 1 H), 1.91–1.95 (m, 3 H), 2.02 (s, 3 H), 2.74–2.80 (m, 2 H), 3.90–3.95 (br dd, *J* = 9.0, 2.0 Hz, 1 H), 6.25 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 23.4, 24.0, 25.4, 28.8, 29.5, 47.9, 56.6, 56.7, 64.3, 168.9.

HRMS (ESI-MS): *m*/*z* calcd for $[C_{11}H_{20}N_2O + H]^+$: 197.1654; found: 197.1650.

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