Enantioselective Access to *Lobelia* Alkaloids

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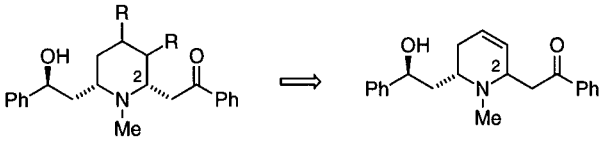
Lobeline **1a**[1,2] is the main active alkaloid constituent of *Lobelia inflata*, a plant sometimes called "Indian tobacco" because it was initially used by Indians of North America as a tobacco substitute. The crude extract is toxic but has been widely recommended for treatment of respiratory illnesses such as asthma, bronchitis, pneumonia, and whooping cough. Lobeline itself mildly mimics the effect of nicotine, and this has prompted people who are trying to quit smoking to use it as a temporary substitute. For further biochemical evaluation of the activity of this alkaloid toward nicotinic receptors, we needed a tritiated analogue of lobeline. For this purpose, we planned the synthesis of a dehydro precursor **2**, treatment of which with tritium would provide in one step $^3H_2$-lobeline **1b**. In this paper, we report the enantioselective synthesis of dehydrolobeline **2** and conditions for the hydrogenation of this precursor to give natural (−)-lobeline **1a**.[3] Evidence showing the phenylacetyl side chain at position 2 in lobeline base **1a** and dehydrolobeline **2** to be in a thermodynamic equilibrium are also presented.

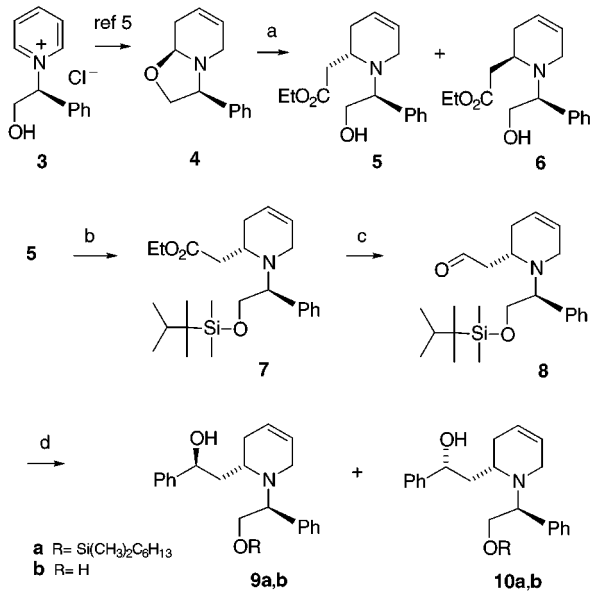


1a, R=H
1b, R= ^{3}H

2

Our synthesis started from chiral pyridinium salt **3**[4] (Scheme 1), which was reduced to oxazolidine **4**, a dihydropyridine equivalent, according to our reported procedure.[5] Treatment of this intermediate with an excess of Reformatsky reagent[6] gave a mixture of two isomers **5** and **6** in a 3:2 ratio, as shown by GC analysis.

Scheme 1[a]



[a] Key: (a) EtO_2CCH_2ZnBr, Et_2O; (b) $C_6H_{13}(CH_3)_2SiCl$, CH_2Cl_2, DMAP; (c) (i) $LiAlH_4$, THF, (ii) Swern oxidation; (d) (i) PhMgCl, Et_2O, (ii) HCl, H_2O, THF.

Albeit the de of the reaction was low, the easy separation of the diastereoisomers by chromatography over silica gel made possible the preparation of the desired derivative **5** in multigram quantities (30% isolated yield from oxazolidine **4**). Protection of this product as silyl derivative **7** allowed its transformation to the unstable aldehyde **8** by a two-step sequence ($LiAlH_4$ reduction, followed by Swern oxidation). This aldehyde was immediately treated with an excess of phenylmagnesium chloride to give diastereoisomeric alcohols **9a** and **10a** in a 3:2 ratio (GC analysis). After separation by chromatography over alumina, the two isomers were deprotected to give each of the desired isomers **9b** (25% overall yield from **5**) and **10b** in a pure state.

The next step of the synthesis was the removal of the phenylethanol auxiliary with concomitant introduction of the methyl group at nitrogen. For this purpose, we used a two-step sequence[7] that is depicted in Scheme 2. The first step, quaternarization of the nitrogen atom in **9b** or **10b**, turned out to be difficult because of steric hindrance, but good yields of salts **12** and **14** were obtained by using the sulfonium salt **11**, a practical and powerful alkylating agent.[8] Treatment of salts **12** and **14** with *t*-BuOK afforded *N*-methyl derivatives **13a** (50% overall yield from **9b**) and **15a** (21% overall yield from **10b**),[9] respectively. Catalytic hydrogenation of isomer **13a** gave (−)-sedamine **13b**,[10] while hydrogenation of

(1) Wieland, H.; Koshara, W.; Dane, E.; Renz, J.; Schwarze, W.; Linde, W. *Justus Liebigs Ann. Chem.* **1939**, *540*, 103.

(2) For a recent X-ray study of (−)-lobeline hydrobromide and hydrochloride, see: Glaser, R.; Hug, P.; Drouin, M.; Michael, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1071.

(3) The synthesis of (−)-lobeline itself has not yet been reported, but in a series of papers, Hootelé et al. have reported the syntheses of related sedum alkaloids. These compounds were obtained as racemates or as pure enantiomers using advanced chiral precursors of natural origin or obtained by resolution. See inter alia: (a) Driessens, F.; Hootelé, C. *Can. J. Chem.* **1991**, *69*, 1. (b) Ibebeke-Bomangwa, W.; Hootelé, C. *Tetrahedron* **1987**, *43*, 935. (c) Halin, F.; Slosse, P.; Hootelé, C. *Tetrahedron* **1985**, *41*, 2891.

(4) Wong, Y.-S.; Marazano, C.; Dino Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729 and references therein.

(5) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39* (2), 811; Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185.

(6) Andres, C.; Gonzalez, A.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895.

(7) Roussi, G.; Zhang, J. *Tetrahedron* **1991**, *47*, 5161.

(8) Julia, M.; Marazano, C. *Tetrahedron* **1985**, *41*, 3717 and references therein.

(9) The yield is lower in these series as a result of a competing ring opening of the nitrogen heterocycle when isomer **14** was treated with *t*-BuOK.

(10) For an enantioselective synthesis and main references, see: Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035.

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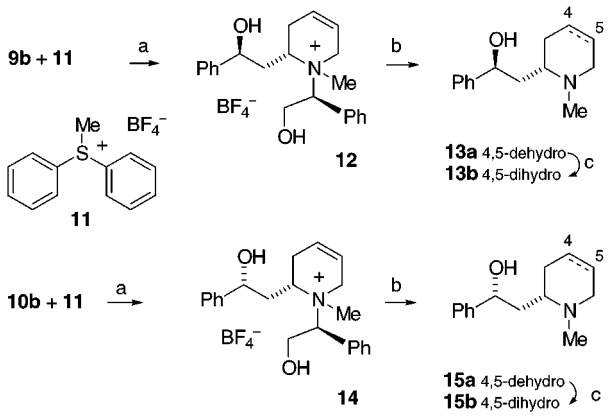
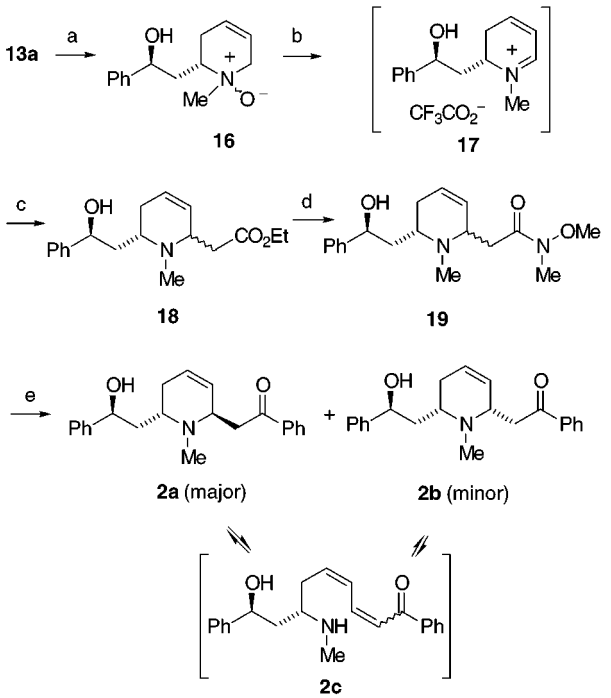
Scheme 2[a]



[a] Key: (a) CH_3CN, reflux; (b) *t*-BuOK, *t*-BuOH; (c) H_2, Pd/C, EtOAc

Scheme 3[a]

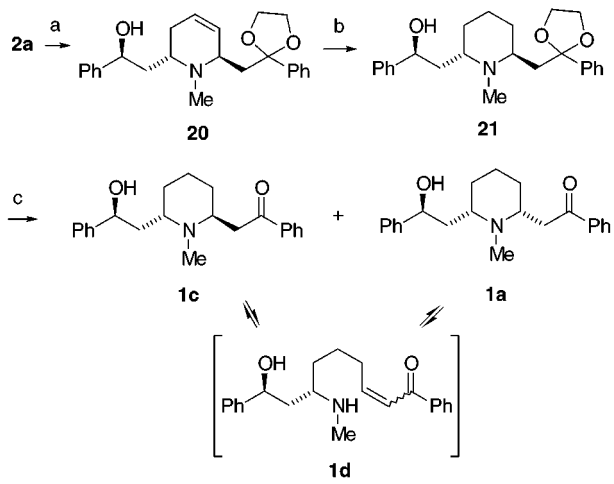


[a] Key: (a) *m*-CPBA, CH_2Cl_2; (b) $(CF_3CO)O$, CH_2Cl_2; (c) EtO_2CCH_2ZnBr, Et_2O; (d) MeO(Me)NAl(Me)Cl, toluene, 80° C; (e) PhLi, THF.

isomer **15a** furnished (−)-allosedamine **15b**.[11] Since (−)-sedamine and (−)-allosedamine are naturally occurring compounds of known absolute configuration, these results established unambiguously the absolute configuration of all of the above synthetic intermediates.

Introduction of the second phenacetyl side chain (Scheme 3) began with the oxidation of derivative **13a** to give the *N*-oxide **16**, which was not characterized but was treated in the conditions of the modified Polonovski reaction[12] to give dihydropyridinium salt **17**. This unstable salt was immediately treated with an excess of the Reformatsky reagent to furnish base **18** as an unseparable 3:2 mixture of diastereoisomers (undefined stereochemistry at C2), which were then transformed to the corresponding Weinreb amides **19**, suitable for final introduction of one phenyl ring.[13] Thus, treatment of amides **19** with an excess of phenyllithium provided the desired dehydrolobeline as a mixture of the two diastereoisomers **2a**,**b** in an 85:15 ratio at equilibrium and 25% overall yield from **13a**. The diastereoisomeric equilibration is very likely due to a transient retro-Michael reaction via intermediate **2c**.[3a,14,15]

Scheme 4[a]



[a] Key: (a) HO-CH_2-CH_2-OH, benzene, reflux; (b) H_2, Pd/C, EtOAc; (c) (i)0.12N HCl (ii) $NaHCO_3$.

The hydrogenation of the 85:15 mixture of isomers **2a**,**b** to give the lobeline skeleton **1** was not successful because it was accompanied, under all conditions, by reduction of the carbonyl group. We therefore used a protected analogue, dioxolane **20** (*trans* isomer >90%), hydrogenation of which gave pure piperidine **21** (Scheme 4). We anticipated that the hydrolysis of the dioxolane group would give lobeline isomer **1c**, which was expected to equilibrate to natural isomer **1a** via intermediate **1d**.

We thus carefully checked by ^1H NMR spectroscopy, in $CDCl_3$, the crude mixture resulting from the hydrolysis of dioxolane **21**. An isomer assigned as the structure **1c** (N-Me at δ 2.56 ppm) was in fact largely predominant at first and, as expected, slowly isomerized to give a product whose characteristics were in complete agreement with the data reported[2] for natural lobeline base (**1a**, N-Me at δ 2.37 ppm). To our surprise, an equilibrium was reached after 48 h, wherein we observed an equal mixture of the two isomers **1a** and **1c**, without further evolution. To our knowledge, this fact was not yet indicated for natural lobeline base itself, which was reported as a single product in $CDCl_3$.[2] Our own investigation of the ^1H NMR, in $CDCl_3$, of natural lobeline base

(11) For an enantioselective synthesis and leading references, see: Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554.

(12) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064−1082. (b) For a review, see: Grierson, D. S. *Org. React.* **1990**, *39*, 85−295.

(13) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Levin, J. I.; Turos, E., Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(14) The crude product of the phenyllithium addition consists of a mixture of **2a** and **2b** in a 3:2 to 2:1 ratio, which reflected approximately the diastereoisomeric ratio observed for adduct **17**. We attributed the 2,6-*trans* stereochemistry to isomer **2a** by comparison with the reported structure of a closely related natural product, (−)-sedacrine: Colau, B.; Hootelé, C. *Can. J. Chem.* **1983**, *61*, 470.

(15) For epimerization of related β-amino-ketone derivatives, see: Durant, A.; Hootelé, C. *Can. J. Chem.* **1992**, *70*, 2722. Colau, B.; Hootelé, C. *Can. J. Chem.* **1983**, *61*, 470. Barringer, D. F.; Berkelhammer, G.; Carter, S. D.; Goldman, L.; Lanzilotti, A. E. *J. Org. Chem.* **1973**, *38*, 1933.

(obtained from the corresponding commercially available hydrochloride) indeed displayed, in the spectrum recorded immediately after extraction, only the isomer **1a** but, after about 48 h, reached the same equilibrium observed for our synthetic product, i.e., an equal mixture of isomers **1a** and **1c**.[16] This new and interesting fact concerning the stereochemistry of lobeline confirmed the identity of our synthetic product with natural lobeline. Finally, these equilibrated mixtures of **1a** and **1c** (50:50, obtained from synthetic product **20** and also from natural lobeline base in $CDCl_3$ solution) were treated with an excess of HCl. In each case only one isomer was obtained and identified as (−)-lobeline hydrochloride (**1a**, HCl) by comparison of the NMR data in $CDCl_3$ with a commercial sample of the natural salt. This result confirms that the salts of (−)-lobeline **1a** exists in solution as a single stereoisomer **1a**[2] and validated our synthesis of this natural product and its desired dehydroprecursor **2**, suitable for the synthesis of a tritiated analogue.

Experimental Section

(3*S*,8a*S*)-(+)-3-Phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo-[3,2-*a*]pyridine (4). Pyridinium salt **3**[4] (10.0 g, 42.5 mmol) in H_2O (50 mL) was added dropwise to a two-phase solution of $NaBH_4$ (5.0 g, 132.0 mmol) in aqueous 5 N NaOH (100 mL) and Et_2O (400 mL) under vigorous stirring at room temperature. After 1 h, the organic phase was decanted and rapidly filtered over alumina (60 g). Removal of solvent gave the unstable oxazolidine **4** (5.97 g, 70% yield) as a yellow oil, which was used immediately or could be stored at −20 °C: $[\alpha]^{20}_D$ +154 (*c* 3.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (m, 1 H), 2.50 (m, 1 H), 2.80 (m, 1 H), 3.30 (m, 1 H), 3.60 (dd, J = 8.0, 8.0 Hz, 1 H), 3.75 (dd, J = 8.0, 8.0 Hz, 1 H), 4.05 (dd, J = 9.0, 4.0 Hz, 1 H), 4.25 (dd, J = 8.0, 8.0 Hz, 1 H), 5.70 (m, 2 H), 7.35 (m, 5 H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 32.3, 49.5, 67.8, 73.4, 91.3, 123.2, 125.3, 127.8, 127.9, 128.7, 138.6; MS (EI) *m*/*z* (rel intensity) 201 (100) $[M]^{\bullet+}$, 170 (13), 148 (13), 117 (64), 106 (46).

(1*S*,2*S*)-(+)-[1-(2-Hydroxy-1-phenylethyl)-1,2,3,6-tetrahydropyridin-2-yl]-acetic Acid Ethyl Ester (5). Zinc powder was activated by treatment with 10% HCl, followed by filtration and rinsing with H_2O and acetone until neutrality. The powder was then dried overnight under reduced pressure. To this activated zinc (20 g, 348 mmol) was added anhydrous Et_2O (170 mL) followed by ethyl bromoacetate (20 mL, 174 mmol). The solution was refluxed for 3 h (the reaction, which started after 30 min, was characterized by an intense green coloration). After decantation, the supernatant liquid was removed to attain an approximate concentration of 1 M. The solution could be stored at room temperature for 1 month under argon atmosphere: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 2.08 (s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H). To the above Reformatsky reagent (474 mL, 474 mmol) was added dropwise, at 0 °C under argon atmosphere, a solution of oxazolidine **4** (23.84 g, 118.61 mmol) in dry Et_2O (180 mL). After addition, the solution was warmed to room temperature and stirred overnight. The resulting mixture was poured into a vigorously stirred ice-cooled saturated solution of NH_4Cl and filtered on a Büchner to eliminate the insoluble precipitates. This solution was then extracted with Et_2O, and the extract was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a mixture of tetrahydropyridines **5** and **6** in a 3:2 ratio (determined by GC). The diastereoisomers were separated over silica gel (690 g) with a gradient of heptane/EtOAc (100:0 to 50:50) as eluent. Major diastereoisomer **5** (10.28 g, 30% yield) was isolated as a yellow-orange oil: $[\alpha]^{22}_D$ +90 (*c* 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.88 (m, 1 H), 2.35 (dd, J = 14.6, 9.3 Hz, 2 H), 2.42 (m, 1 H), 2.94 (broad d, J = 16.7 Hz, 1 H), 3.12 (bd, J = 16.7 Hz, 1 H), 3.68 (m, 2 H), 3.77 (dd, J = 11.1, 4.9 Hz, 1 H), 3.88 (m, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.60 (m, 2 H), 7.34 (m, 5 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 14.3, 30.1, 32.7, 43.6, 51.8, 60.5, 62.6, 68.7, 123.0, 125.0, 127.9, 128.5, 128.7, 139.1, 173.0; IR (film) 3451, 2980, 2938, 1729 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{24}NO_3$ *m*/*z* 290.1756, found 290.1769. Minor diastereoisomer **6** (8.57 g, 25% yield): $[\alpha]^{22}_D$ +4 (*c* 1.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.83 (broad d, J = 16 Hz, 1 H), 2.31 (m, 2 H), 2.41 (m, 1 H), 3.24 (m, 2 H), 3.49 (m, 1 H), 3.72 (dd, J = 5.2, 5.2 Hz, 1 H), 3.85 (m, 2 H), 4.06 (q, J = 7.1 Hz, 2 H), 5.65 (m, 2 H), 7.33 (m, 5 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 14.2, 28.7, 33.2, 44.4, 49.1, 60.4, 63.1, 67.2, 123.3, 125.2, 127.8, 128.3, 128.6, 139.7, 172.9; HRMS (CI) calcd for $C_{17}H_{24}NO_3$ *m*/*z* 290.1756, found 290.1768.

(1*S*,2*S*)-(+)-(1-{2-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxy]-1-phenylethyl}-1,2,3,6-tetrahydropyridin-2-yl)-acetic Acid Ethyl Ester (7). To an ice-cooled solution of compound **5** (8.86 g, 30.65 mmol) in dry CH_2Cl_2 (70 mL) was added under argon thexyldimethylsilyl chloride (9.0 mL, 45.98 mmol) followed by NEt_3 (10.8 mL, 76.64 mmol) and a catalytic amount of DMAP. The resulting solution was warmed to room temperature and stirred overnight. The mixture was poured into a saturated solution of NH_4Cl at 0 °C and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$ and filtered. Evaporation of solvent left the crude product, which was flash chromatographed over alumina (140 g) with heptane/EtOAc (100:0 to 70:30) as eluent. The compound **7** (11.83 g, 90% yield) was isolated as a yellow oil: $[\alpha]^{20}_D$ +24 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6 H), 0.60−0.75 (m, 12 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.42 (heptuplet, J = 6.9 Hz, 1 H), 1.81 (m, 1 H), 2.28 (dd, J = 14.5, 10.0 Hz, 1 H), 2.39 (m, 1 H), 2.50 (dd, J = 14.5, 3.6 Hz, 1 H), 2.65 (m, 1 H), 2.89 (m, 1 H), 3.49 (dd, J = 4.9, 4.9 Hz, 1 H), 3.64 (m, 1 H), 3.68 (dd, J = 10.5, 4.9 Hz, 1 H), 3.78 (dd, J = 10.5, 4.9 Hz, 1 H), 3.98 (q, J = 7.1 Hz, 2 H), 5.48 (m, 2 H), 7.08 to 7.22 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 3.7, 14.3, 18.6, 20.2, 29.4, 31.1, 34.2, 45.9, 49.3, 60.2, 65.7, 68.4, 122.8, 125.9, 127.1, 128.0, 128.5, 142.0, 173.2.

(1*S*,2*S*)-2-(1-{2-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxy]-1-phenylethyl}-1,2,3,6-tetrahydropyridin-2-yl)-ethanal (8). To an ice-cooled solution of compound **7** (11.83 g, 27.45 mmol) in dry THF (90 mL) was added portionwise $LiAlH_4$ (1.56 g, 41.17 mmol). The solution was warmed to room temperature and stirred overnight. After the reaction went to completion, EtOAc was carefully added under vigorous stirring followed by a few drops of H_2O. The resulting mixture was filtered over Celite and rinsed with EtOAc and MeOH. The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude alcohol, which was purified by filtration over a short column of alumina (110 g) with heptane/EtOAc (100:0 to 80:20) as eluent to give the pure alcohol **[(1*S*,2*S*)-(−)-2-(1-{2-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxy]-1-phenylethyl}-1,2,3,6-tetrahydropyridin-2-yl)-ethanol]** (9.49 g, 89% yield) as a pale yellow oil: $[\alpha]^{21}_D$ −11 (*c* 0.65, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.75−0.95 (m, 12 H), 1.13 (ddd, J = 14.6, 6.6, 3.3 Hz, 1 H), 1.45 (m, 1 H), 1.55 (heptuplet, J = 6.9 Hz, 1 H), 2.23 (ddt, J = 15.3, 11.0, 4.5 Hz, 1 H), 2.35 (m, 1 H), 3.00 (m, 1 H), 3.60 (m, 2 H), 3.65−3.90 (m, 5 H), 5.60−5.80 (m, 2 H), 7.25−7.40 (m, 5 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 3.8, 18.6, 20.1, 24.9, 31.9, 34.0, 41.9, 53.3, 63.6, 66.7, 66.8, 123.7, 124.1, 127.3, 128.2, 128.3, 141.6; HRMS (CI) calcd for $C_{23}H_{40}NO_2Si$ *m*/*z* 390.2828, found 390.2803. To a cooled (−78 °C) solution of oxalyl chloride (8.40 mL, 97.56 mmol) in dry CH_2Cl_2 (180 mL) was added DMSO (10.40 mL, 146.34 mmol) in dry CH_2Cl_2 (180 mL) under argon atmosphere. After 10 min at −78 °C, the above alcohol (9.49 g, 24.39 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise, and the resulting solution was stirred at −78 °C for 15 min. NEt_3 (27.5 mL, 195 mmol) was then added, and the mixture was warmed to room temperature. The reaction mixture was washed with H_2O and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude aldehyde **8**: MS (EI) *m*/*z* (rel intensity) 214 (100) $[M^{\bullet+} - {}^{\bullet}CH_2OSiMe_2$-

(16) Intermediates **5**−**8** have also the structural requirements to undergo the same type of equilibration but by contrast proved to be stereochemically stable in our hands. For example, all of our efforts to equilibrate adduct **6** to desired isomer **5** using various basic or acidic conditions failed. Aldehyde **8** was too unstable to allow such studies but gave isomers **9** and **10** without epimerization at C2. We believe that this retro-Michael process depends on various parameters, in particular the nitrogen substituent, as benzylic nitrogen derivatives are much less sensitive.

Thex]. Because of its instability, the aldehyde **8** was not further characterized.

(1*S*,2*S*)-(−)-2-(1-{2-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxy]-1-phenylethyl}-1,2,3,6-tetrahydropyridin-2-yl)-1-phenylethanol (9a). A solution of crude aldehyde **8** (9.44 g, 24.39 mmol) in dry Et_2O (80 mL) was added dropwise to an ice-cooled solution of phenylmagnesium chloride in Et_2O (61 mL, 36.59 mmol) under an argon atmosphere. After the addition was complete, the reaction mixture was warmed to room temperature and stirred overnight. The resulting solution was poured into a saturated solution of NH_4Cl at 0 °C. This solution was then extracted with Et_2O followed by CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and filtered, and the solvents were evaporated under reduced pressure to give a mixture of alcohols **9a** and **10a** in a 3:2 ratio (determined by integration of the ^{1}H NMR spectrum). The diastereoisomers were separated over alumina (360 g) with heptane/EtOAc (100:0 to 80:20) as eluent. Major diastereoisomer **9a** (4.56 g, 40% yield from **8**) was isolated as a gum: $[\alpha]^{20}_D$ −18 (*c* 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.75−0.85 (m, 12 H), 1.30 (ddd, J = 14.7, 2.6, 2.6 Hz, 1 H), 1.40 (m, 1 H), 1.55 (heptuplet, J = 6.9 Hz, 1 H), 2.12 (m, 1 H), 2.38 (m, 1 H), 3.15 (m, 1 H), 3.75 (m, 2 H), 3.80−4.00 (m, 3 H), 4.70 (dd, J = 10.9, 2.1 Hz, 1 H), 5.60−5.80 (m, 2 H), 7.15−7.45 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 3.6, 18.5, 20.2, 24.8, 34.1, 40.2, 41.8, 53.3, 66.9, 67.4, 75.2, 123.7, 125.5, 126.2, 128.6, 141.4, 145.2; MS (CI) *m*/*z* (rel intensity) 466 (100) $[MH]^+$, 344 (42), 292 (15); HRMS (CI) calcd for $C_{29}H_{44}NO_2Si$ *m*/*z* 466.3141, found 466.3152. Minor diastereoisomer **10a** (3.63 g, 32% yield from **8**): $[\alpha]^{20}_D$ +24 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.75−0.85 (m, 12 H), 1.40 (m, 1 H), 1.42−1.55 (m, 2 H), 2.30 (m, 1 H), 2.32−2.45 (ddd, J = 14.8, 10.3, 5.2 Hz, 1 H), 2.90 (m, 1 H), 3.55 (m, 2 H), 3.70 (m, 2 H), 3.85 (dd, J = 11.8, 6.5 Hz, 1 H), 4.93 (dd, J = 5.1, 5.1 Hz, 1 H), 5.60−5.80 (m, 2 H), 7.10−7.42 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 3.6, 18.5, 20.3, 25.7, 34.1, 37.3, 42.8, 48.7, 66.5, 67.0, 72.2, 123.9, 124.7, 125.7, 128.5, 141.4, 145.3; HRMS (CI) calcd for $C_{29}H_{44}NO_2Si$ *m*/*z* 466.3141, found 466.3123.

(1*S*,1*S*,2*S*)-(−)-2-[1-(2-Hydroxy-1-phenylethyl)-1,2,3,6-tetrahydropyridin-2-yl]-1-phenylethanol (9b). Adduct **9a** (4.56 g, 9.81 mmol) was diluted in a mixture of an aqueous solution of 10 N HCl and THF (3:1) at room temperature, and the resulting solution was stirred overnight. The reaction mixture was extracted in the presence of K_2CO_3 with Et_2O followed by CH_2Cl_2, and the extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product, which was chromatographed over alumina (95 g) with heptane/EtOAc (100:0 to 0:100) followed by CH_2Cl_2/MeOH (100:0 to 95:5) as eluent. Diol **9b** (2.38 g, 75% yield) was isolated as a yellow oil: $[\alpha]^{21}_D$ −49 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (ddd, J = 14.5, 5.1, 2.4 Hz, 1 H, H), 1.62 (m, 1 H), 2.07 (ddd, J = 14.5, 10.9, 9.1 Hz, 1 H), 2.40 (m, 1 H), 3.35 (m, 2 H), 3.56 (m, 1 H), 3.80 to 4.00 (m, 3 H), 4.70 (dd, J = 10.9, 2.4 Hz, 1 H), 5.58−5.80 (m, 2 H), 7.20−7.45 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 26.5, 38.9, 42.8, 52.6, 65.4, 67.2, 74.7, 124.0, 125.6, 127.2, 128.9, 140.4, 145.1; HRMS (CI) calcd for $C_{21}H_{26}NO_2$ *m*/*z* 324.1964, found 324.1965.

(1*R*,1*S*,2*S*)-(+)-2-[1-(2-Hydroxy-1-phenylethyl)-1,2,3,6-tetrahydropyridin-2-yl]-1-phenylethanol (10b). Deprotection of derivative **10a** (3.63 g, 7.80 mmol) under the conditions used for the deprotection of **9a** gave diol **10b** (1.79 g, 71% yield): $[\alpha]^{21}_D$ +52 (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−1.70 (m, 2 H), 2.08 (ddd, J = 13.9, 7.4, 5.7 Hz, 1 H), 2.30 (m, 1 H), 3.02 (dd, J = 13.1, 6.5 Hz, 1 H), 3.20 (bd, 1 H) 3.28 (bd, 1 H), 3.60 (dd, J = 9.4, 4.5 Hz, 1 H), 3.68−3.78 (m, 2 H), 4.84 (dd, J = 6.0, 6.0 Hz, 1 H), 5.57−5.72 (m, 2 H), 7.20−7.35 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.9, 37.7, 43.0, 50.1, 63.5, 67.5, 72.5, 124.1, 124.7, 125.8, 128.7, 139.9, 145.0; HRMS (CI) calcd for $C_{21}H_{26}NO_2$ *m*/*z* 324.1963, found 324.1941.

(1*S*,2*S*)-(−)-2-(1-Methyl-1,2,3,6-tetrahydropyridin-2-yl)-1-phenylethanol (13a). To a solution of diol **9b** (4.96 g, 15.3 mmol) in distilled CH_3CN (160 mL) was added diphenylmethyl sulfonium tetrafluoroborate **11** (6.67 g, 21.09 mmol), and the resulting mixture was refluxed for 48 h. After removal of the solvent under reduced pressure, the crude product was chromatographed over alumina (195 g) with CH_2Cl_2/MeOH (100:0 to 50:50) as eluent. Salt **12** (4.53 g, 70% yield) was isolated as a pale beige froth: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3 H); MS (FAB) *m*/*z* (rel intensity) 338 (87) $[M]^+$, 320 (100), 218 (21). To this salt (1.509 g, 3.56 mmol) in distilled *t*-BuOH (40 mL) was added freshly sublimated *t*-BuOK. The reaction mixture was refluxed for 2 h and then cooled to room temperature. This solution was poured into a saturated NH_4Cl solution and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$ and filtered. The procedure was repeated three times under the same conditions. After evaporation of the solvent under reduced pressure, the crude product was chromatographed over alumina (70 g) with CH_2Cl_2/MeOH (100:0 to 94:6) as eluent. Dehydrosedamine **13a** (1.618 g, 70% yield) was isolated as a yellow-orange oil: $[\alpha]^{21}_D$ −100 (*c* 0.9, $CHCl_3$), −71 (*c* 2.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (ddd, J = 14.6, 2.7, 2.7 Hz, 1 H), 1.80−2.00 (m, 2 H), 2.15 (m, 1 H), 2.45 (s, 3 H), 3.20−3.40 (m, 3 H), 4.95 (dd, J = 10.9, 2.7 Hz, 1 H), 5.55−5.80 (m, 2 H), 7.18−7.40 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.0, 37.1, 40.0, 51.0, 58.2, 75.8, 123.9, 124.5, 125.7, 127.1, 128.3, 145.3; MS (EI) *m*/*z* (rel intensity) 217 (7) $[M]^{\bullet+}$, 96 (100); HRMS (EI) calcd for $C_{14}H_{19}NO$ *m*/*z* 217.1467, found 217.1464.

(1*S*,2*S*)-(−)-2-(1-Methylpiperidin-2-yl)-1-phenylethanol [(−)-Sedamine (13b)]. Dehydrosedamine **13a** (53 mg, 0.244 mmol) was dissolved in EtOAc (5 mL), and a catalytic amount of 5% palladium on carbon was added to this solution, which was stirred overnight under a hydrogen atmosphere. After filtration on Celite and washing with EtOAc and MeOH, the solvents were evaporated at reduced pressure. The residue was then filtered over a short column of alumina with heptane/EtOAc (100:0 to 50:50). (−)-Sedamine **13b** (45 mg, 85% yield) was obtained as white crystals, from which an analytical sample was recrystallized in Et_2O/pentane: $[\alpha]^{21}_D$ −95 (*c* 0.9, EtOH), lit.[10] $[\alpha]_D$ −93 (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26−2.81 (m, 7 H), 2.12 (ddd, J = 14.4, 10.6, 9.7 Hz, 1 H), 2.50 (s, 3 H), 2.55 (m, 1 H), 2.87 (m, 1 H), 3.10 (m, 1 H), 4.88 (dd, J = 10.6, 2.8 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 20.55, 22.50, 25.83, 39.88, 40.06, 51.31, 61.06, 74.98, 125.68, 127.133, 128.39, 145.76; MS (EI) *m*/*z* (rel intensity) 219 (57) $[M]^{\bullet+}$, 98 (100) $[M]^{\bullet+}$ − $^{\bullet}CH_2CH(OH)Ph$]; HRMS (EI) calcd for $C_{14}H_{21}NO$ *m*/*z* 219.1623, found 219.1614. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.64; H, 9.60; N, 6.25.

(1*R*,2*S*)-(+)-2-(1-Methyl-1,2,3,6-tetrahydropyridin-2-yl)-1-phenylethanol (15a). Treatment of the dialcohol **10b** (1.631 g, 5.05 mmol) using the procedure described above for the preparation of derivative **12** gave salt **14** (1.506 g, 70% yield) as a pale beige froth. To this salt (1.506 g, 3.54 mmol) in distilled *t*-BuOH (40 mL) was added *t*-BuOK under the conditions described previously for the preparation of derivative **13a**. The desired dehydroderivative **15a** (235 mg, 31% yield) was isolated as a yellow-orange oil: $[\alpha]^{21}_D$ +29.5 (*c* 1.86, $CHCl_3$), −5.5 (*c* 1.8, MeOH), −5 (*c* 1.24, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.60 (ddd, J = 14.5, 4.6, 3.5 Hz, 1 H), 1.92 (m, 2 H), 2.25 (ddd, J = 14.8, 10.1, 4.8 Hz, 1 H), 2.40 (s, 3 H), 2.89 (m, 1 H), 3.23 (m, 2 H), 5.05 (dd, J = 4.7, 4.7 Hz, 1 H), 5.50−5.75 (m, 2 H), 7.20−7.40 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.6, 37.7, 37.9, 51.5, 53.9, 73.0, 123.9, 124.6, 125.7, 126.8, 128.3, 145.6; MS (EI) *m*/*z* (rel intensity) 217 (3) $[M]^{\bullet+}$, 96 (100); HRMS (EI) calcd for $C_{14}H_{19}NO$ *m*/*z* 217.1467, found 217.1466.

(1*R*,2*S*)-(−)-2-(1-Methylpiperidin-2-yl)-1-phenylethanol [(−)-Allosedamine (15b)]. Dehydroallosedamine (**15a**) (68 mg, 0.313 mmol) was hydrogenated under the conditions used for preparation of (−)-sedamine. (−)-Allosedamine (61 mg, 90% yield) was obtained as white crystals, from which an analytical sample was recrystallized in Et_2O/pentane: $[\alpha]^{21}_D$ −25 (*c* 1.95, MeOH)), lit.[11] $[\alpha]_D$ −30 (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (m, 1 H), 1.55−1.75 (m, 4 H), 1.78−1.90 (m, 2 H), 2.05 (m, 1 H), 2.17 (m, 1 H), 2.28 (m, 1 H), 2.43 (s, 3 H), 2.97 (m, 1 H), 5.12 (dd, J = 10.7, 3.6 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 24.4, 25.5, 29.3, 39.5, 43.9, 57.0, 62.7, 72.0, 125.7, 127.0, 128.3, 145.6; MS (EI) *m*/*z* (rel intensity) 219 (6) $[M]^{\bullet+}$, 98 (100). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.54; H, 9.69; N, 6.52.

(2*S*,6*S*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl]-acetic Acid Ethyl Ester (18). To an ice-cooled solution of dehydrosedamine **13a** (218 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (371 mg, 1.5 mmol). After 15 min, the reaction mixture was briefly filtered over a short column of alumina with a gradient of CH_2Cl_2/MeOH (100:0 to 95:5) as eluent. Evaporation of solvents afforded *N*-oxide **16**,

which was directly used for the next reaction step. To the *N*-oxide **16** (232 mg, 1.00 mmol) was slowly added trifluoroacetic anhydride (0.35 mL, 2.5 mmol). The reaction mixture was stirred for 30 min at 0 °C. Evaporation of the solvent and excess reagent at reduced pressure gave unstable dihydropyridinium salt **17**, which was added dropwise, under an argon atmosphere, to an ice-cooled solution of the Reformatsky reagent (5 mL, 5 mmol). After addition, the reaction mixture was warmed to room temperature and stirred overnight. This solution was poured into a saturated NH_4Cl solution at 0 °C and extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$ and filtered. After evaporation of the solvent under reduced pressure, the crude product was filtered over a short column of alumina with heptane/EtOAc (50:50) as eluent. A mixture of inseparable diastereoisomers **18** (182 mg, 60% yield) was obtained in a 3:2 ratio in favor of the *trans* isomer (determined by integration of signals in the ^{1}H NMR spectrum) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (2 t, J = 8.0 Hz, 3 H), 1.55 (m, 1 H), 1.90 (m, 3 H), 2.25 (s, 3 H minor isomer), 2.40 (s, 3 H major isomer), 2.43−2.70 (m, 2 H), 3.30−3.55 (m, 1 H), 4.08 (m, 1 H), 4.18 (2 q, J = 8.0 Hz, 2 H), 4.95 (dd, J = 10.7, 2.8 Hz, 1 H), 5.45 and 5.63 (2 bd, 3:2 ratio, 1 H), 5.80 (m, 1 H), 7.18−7.40 (m, 5 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 14.3, 25.4, 27.6 (major isomer), 34.5 (minor isomer), 38.2, 39.8, 57.8, 60.7, 60.8, 75.7, 125.6, 126.7, 128.2, 126.3, 126.4, 145.0, 171.3; MS (EI) *m*/*z* (rel intensity) 303 (36) $[M]^{\bullet+}$, 258 (14), 216 (100), 182 (64).

(2*S*,6*S*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl]-*N*-methox-*N*-methyl-acetamide (19). To a solution of *N*,*O*-dimethylhydroxylamine chloride (88 mg, 0.90 mmol) in dry toluene (1.8 mL) under argon atmosphere was added dropwise commercially available $AlMe_3$ (2 M, 0.52 mL, 1.04 mmol) in toluene. After addition, the reaction was warmed to room temperature and stirred for 2 h to give the Weinreb reagent, which was immediately added to a solution of the ester (**18**) (91 mg, 0.30 mmol) in dry toluene (3 mL) under an argon atmosphere. The mixture was heated at 80 °C under argon atmosphere for 3 h and then slowly poured into an ice-cooled solution of HCl (0.12 N). The resulting mixture was stirred for 2 min and neutralized by a diluted solution of $NaHCO_3$ at 0 °C. This solution was extracted with Et_2O followed by CH_2Cl_2 (five times), and the combined extracts were dried over $MgSO_4$ and filtered. Evaporation of solvents under reduced pressure afforded hydroxyamide **19** (90 mg), which was used in subsequent experiments without further purification: MS (EI) *m*/*z* (rel intensity) 318 (5) $[M]^{\bullet+}$, 287 (100) $[M^{\bullet+} - {}^{\bullet}OCH_3]$, 216 (85) $[M^{\bullet+} - CH_2C(O)NMeOMe]$; MS (CI) *m*/*z* (rel intensity) 319 (100) $[M + H]^+$, 216 (10) $[M\text{-}CH_2C(O)NMeOMe]^+$.

(2*S*,6*S*,2*S*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethanone [Dehydrolobeline (2)]. A solution of phenyllithium in cyclohexane/Et_2O (0.88 mL, 1.41 mmol) was added dropwise to a solution of hydroxyamides **19** (90 mg, 0.28 mmol) in dry THF (3 mL) at −78 °C. After addition, the reaction was warmed to room temperature and stirred overnight. This solution was poured into a saturated NH_4Cl solution at 0 °C and extracted with Et_2O followed by CH_2Cl_2, and the extract was dried over $MgSO_4$ and filtered. The crude product was directly converted to the corresponding hydrochloride salt and evaporated under reduced pressure. For further purification, the residue was taken up in a minimum amount of MeOH and washed with heptane. The hydrochloride salt was then purified over silica gel with CH_2Cl_2/MeOH (100:0 to 100:2) as eluent to give the pure hydrochloride of dehydrolobeline **2** (42 mg, 40% yield). The corresponding base showed a mixture of two inseparable diastereoisomers in a ratio 85:15 in favor of *trans* isomer **2a** (determined by integration of the ^{1}H NMR spectrum): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (dt, J = 14.6, 2.6 Hz, 1 H), 1.72−2.10 (m, 3 H), 2.30 (s, 3 H, minor isomer), and 2.44 (s, 3 H, major isomer), 3.02 (dd, J = 16.7, 7.4 Hz, 1 H, minor isomer), 3.32 (dd, J = 16.7, 7.4 Hz, 1 H, major isomer), 3.36−3.46 (m, 2 H), 3.80 (m, 1 H), 4.85 (dd, J = 10.7, 2.6 Hz, 1 H, major isomer), 4.95 (dd, J = 10.7, 2.6 Hz, 1 H, minor isomer), 5.50−5.85 (m, 2 H), 7.15−8.00 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.0, 34.8, 39.7, 43.8, 53.7, 57.8, 75.8, 127.1, 127.6, 125.0, 125.8, 128.2, 128.3, 133.2, 137.1, 144.9, 198.1; MS (EI) *m*/*z* (rel intensity) 335 (10) $[M]^{\bullet+}$, 230 (21), 216 (100), 105 (57), 94 (99).

(2*S*,6*S*,2*S*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl]-1-phenylethan-[1,3]-dioxolane (20). In a small flask were added benzene (5 mL), ethylene glycol (1 mL), and *p*-toluenesulfonic acid (27 mg, 0.143 mmol). The resulting mixture was refluxed in a Dean Stark for 10 min to eliminate traces of H_2O. To this solution was added dehydrolobeline base **2** (40 mg, 0.119 mmol) in benzene. After 4 h of reflux, the reaction mixture was poured into an ice-cooled solution of $NaHCO_3$ and extracted with Et_2O and CH_2Cl_2, and the extract was dried over $MgSO_4$ and filtered. Evaporation of solvents under reduced pressure gave crude **20**, which was briefly filtered over alumina with CH_2Cl_2. Ketal **20** (40 mg, 89% yield) was isolated as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (dt, J = 14.6, 2.4 Hz, 1 H), 1.68 (m, 1 H), 1.75−2.05 (m, 2 H), 2.18 (dd, J = 14.4, 6.0 Hz, 1 H), 2.30 (s, 3 H), 2.36 (dd, J = 14.3, 6.1 Hz, 1 H), 3.10 (m, 1 H), 3.36 (m, 1 H), 3.68−3.72 (m, 2 H), 4.05 (m, 2 H), 4.95 (dd, J = 10.8, 2.2 Hz, 1 H), 5.55−5.75 (m, 2 H), 7.20−7.55 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 24.9, 34.3, 40.0, 45.1, 53.4, 57.6, 64.3, 64.6, 76.0, 109.9, 124.4, 127.0, 125.7, 125.9, 128.0, 128.3, 128.3, 129.0, 145.3, 142.4; MS (EI) *m*/*z* (rel intensity) 379 (10) $[M]^{\bullet+}$, 258 (61), 216 (100), 149 (99).

(2*S*,6*S*,2*R*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methylpiperidin-2-yl]-1-phenylethan-[1,3]-dioxolane (21). Derivative **20** (10 mg, 0.026 mmol) was dissolved in EtOAc (5 mL), and a catalytic amount of 5% palladium on carbon was added to this solution, which was stirred for 4 h under a hydrogen atmosphere. After filtration on Celite and washing with EtOAc and MeOH, the solvents were evaporated under reduced pressure. Dioxolane **21** (6 mg, 61% yield) was directly obtained without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.75 (m, 7 H), 1.85−2.30 (m, 3 H), 2.50 (s, 3 H), 3.25 (bs, 2 H), 3.70 (m, 2 H), 4.08 (m, 2 H), 4.90 (dd, J = 10.9, 2.5 Hz, 1 H), 7.20−7.50 (m, 10 H); MS (EI) *m*/*z* (rel intensity) 381 (51) $[M]^{\bullet+}$, 260 (100), 218 (100), 149 (90).

(2*S*,6*S*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methylpiperidin-2-yl]-1-phenylethanone Hydrochloride [(−)-Lobeline (1a, HCl)]. Dioxolane **21** (6 mg, 0.016 mmol was refluxed for 30 min) in 0.12 N HCl (7 mL). The reaction was cooled to room temperature, poured into a $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over $MgSO_4$, and filtered. After evaporation of solvent under reduced pressure, the crude product was purified over alumina with CH_2Cl_2 as eluent. Lobeline base (4 mg, 74% yield) was isolated as a mixture of the two diastereoisomers **1a** and **1c** in a 1:1 ratio, as shown by the ^{1}H NMR data in $CDCl_3$, which were identical to those of natural lobeline base at thermodynamic equilibrium (see below). Physical data for the corresponding hydrochloride (**1a**, HCl) were identical with those reported[2] for natural (−)-lobeline hydrochloride.

(2*S*,6*S*,2*R*)-2-[6-(2-Hydroxy-2-phenylethyl)-1-methylpiperidin-2-yl]-1-phenylethanone [Natural (−)-Lobeline Base)]. Commercial lobeline hydrochloride was dissolved in water. Addition of an excess of $NaHCO_3$ followed by extraction with CH_2Cl_2 afforded, after removal of organic solvent under reduce pressure, the corresponding base. Immediate recording of the ^{1}H or ^{13}C NMR spectrum of this base showed signals corresponding only to *cis* diastereoisomer **1a**.[2] Two epimers **1a** and **1c**, in a 1:1 ratio, were observed after equilibration for 48 h in the NMR tube: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.85 (m, 7 H), 1.95 (m, 1 H), 2.25 (m, 1 H), 2.37 (s, 3 H, *cis* isomer), 2.56 (s, 3 H, *trans* isomer), 3.01 (dd, J = 16.0, 8.4 Hz, 1 H, *cis* isomer), 3.03 (dd, J = 15.3, 9.2 Hz, 1 H, *trans* isomer), 3.19−3.30 (ddm, J = 15.9, 5.0 Hz, 2 H), 3.55 (m, 1 H, *cis* isomer), 3.78 (m, 1 H, *trans* isomer), 4.90 (dd, J = 10.7, 2.6 Hz, 1 H, *trans* isomer), 4.95 (dd, J = 10.6, 3.0 Hz, 1 H, *cis* isomer), 7.18−8.06 (m, 10 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 20.6, 23.0, 23.5, 24.8, 27.5, 35.8, 38.9, 40.6, 43.3, 43.9, 51.6, 59.2, 61.2, 64.6, 75.8, 75.8, 125.6−133.3, 136.8, 137.1, 145.2, 145.6, 198.3, 198.4.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of natural lobeline base **1a** before and after equilibration to a mixture of **1a** and **1c**, dehydrolobeline **2**, and compounds **5**−**7**, **9a**,**b**, **10a**,**b**, **13a**,**b**, **15a**,**b**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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