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Enantioselective Total Synthesis of (−)-Limaspermidine and Formal Synthesis of (−)-1-Acetylaspidoalbidine

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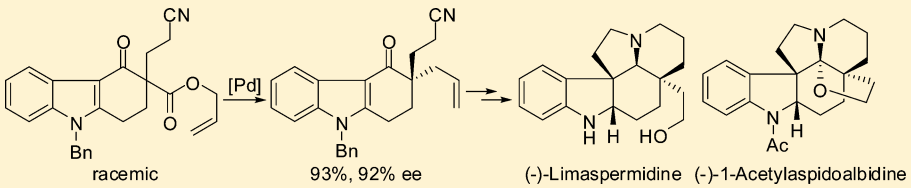
Supporting Information



ABSTRACT: Evolution of the synthetic strategy that culminated in the first asymmetric total synthesis of the *Aspidosperma* alkaloid limaspermidine is described. The successful enantioselective route to (−)-limaspermidine proceeds in 10 steps and with the isolation of only six intermediates using a Pd-catalyzed enantioselective decarboxylative allylation we have recently developed. This first enantioselective synthesis of (−)-limaspermidine establishes unambiguously its absolute configuration and allows the first asymmetric formal total synthesis of the *Aspidoalbine* alkaloid (−)-1-acetylaspidoalbidine.

INTRODUCTION

The natural product limaspermidine is an *Aspidosperma* alkaloid[1] isolated from the trunk bark of the small tree *A. rhombeosignatum* MARKGRAF found growing in the Venezuelan Amazonas (Figure 1).[2] The synthesis of limaspermidine was first completed by Ban et al. in 1976, who obtained limaspermidine as a racemic mixture.[3] Since then, there have been only a few successful total syntheses of this target. In 1991, the Overman group disclosed an elegant total synthesis of limaspermidine, where a signature aza-Cope−Mannich rearrangement was used as the key reaction.[4] During the course of our studies, Banwell and co-workers reported an impressive total synthesis of it wherein the B and D rings were formed in a Raney cobalt-mediated tandem reductive cyclization process,[5] and Canesi et al. described a nice new route to limaspermidine (limaspermidine was not isolated) employing an oxidative shift process in combination with a Fischer indole protocol.[6] In all these reports, however, limaspermidine was prepared in racemic form, and an asymmetric total synthesis of this target has not yet been realized. This background in conjunction with their potential as precursors to a range of alkaloids, including those of the aspidofractinine, kopsine, and vincadifformine series,[7] led us to focus our attention on the asymmetric synthesis of limaspermidine. Herein, we report the development of the first catalytic enantioselective total synthesis of (−)-limaspermidine and the determination of its absolute configuration. The synthesis employs Pd-catalyzed enantioselective decarboxylative allylation[8] of carbazoleones we have recently developed[9] as a central enabling feature. This first enantioselective synthesis of (−)-limaspermidine also allows the first asymmetric formal total synthesis of *Aspidoalbine* alkaloid (−)-1-acetylaspidoalbidine.[10]

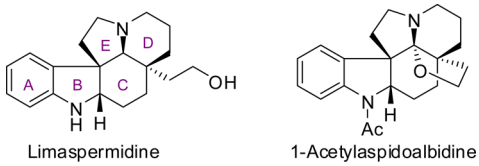


Figure 1. Structures of limaspermidine and 1-acetylaspidoalbidine.

RESULTS AND DISCUSSION

Very recently, we developed a novel palladium-catalyzed decarboxylative allylation, enabling the first enantioselective synthesis of carbazoleones **2** bearing a quaternary carbon center (Figure 2a).[9] We reasoned that enantioenriched carbazoleone **2a** could be used as a starting point for a distinct approach toward the synthesis of limaspermidine (Figure 2b). Crucial to the success of this approach would be chemoselective oxidation of the pentacycle **3** into the aldehyde **4**. If this reaction were successful, the reduction of the resulting aldehyde **4** with $LiAlH_4$ would provide directly the target limaspermidine. While there are several methods available for the oxidation of an allyl group into a $-CH_2CHO$ group, there are no precedents for such chemoselective issues. Thus, we initially decided to utilize *rac*-**3** to explore this chemistry.

The synthesis of *rac*-**3** is shown in Scheme 1. Reduction of the amide group of *rac*-**5** prepared from *rac*-**2**[9] with $LiAlH_4$ in

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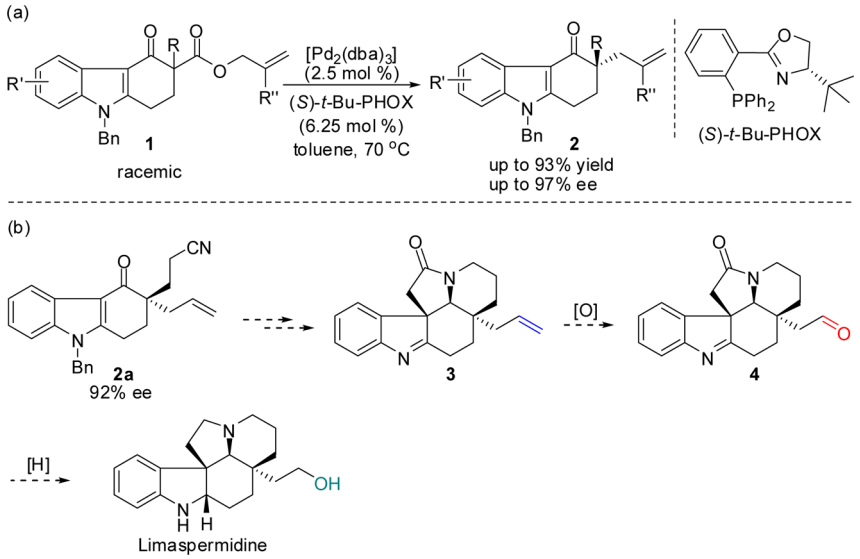
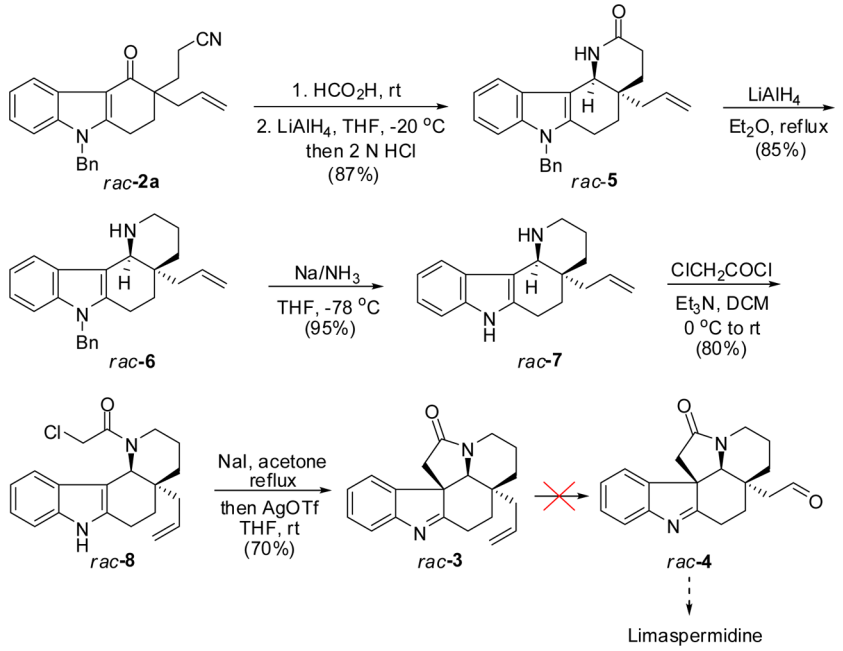


Figure 2. (a) Our Pd-catalyzed decarboxylative allylation. (b) Working hypothesis for the enantioselective synthesis of limaspermidine.

Scheme 1. Attempts To Secure Pentacycle *rac*-3 en Route to Limaspermidine



Et_2O at reflux afforded the amine *rac*-**6** in 85% yield. Interestingly, the LAH reduction reaction performed in THF under reflux conditions resulted in the compound *rac*-**6** in much lower yield (21%) together with inseparable complexes. Then *rac*-**6** was debenzylated by a Birch reduction with Na/NH_3 to provide the free (NH)-indole *rac*-**7** in almost quantitative yield. Treatment of *rac*-**7** with α-chloroacetyl chloride in the presence of triethylamine delivered chloroamide *rac*-**8** in good yield (80%). The resulting acylated compound *rac*-**8** was transformed into an iodide, which subsequently underwent Heathcock annulation[11] to yield *rac*-**3** in 70% yield, setting the stage for the chemoselective oxidation reaction. Unfortunately, all attempts, including ozonization (O_3, CH_2Cl_2. −78 °C then Me_2S) and the osmate−periodate procedure ($K_2OsO_4{\cdot}2H_2O$, NMO, THF/H_2O (1/1) then $NaIO_4$), led to the formation of complex mixtures. Although the strategy of introducing the hydroxyl group of limaspermidine at a later stage failed, these results inspired us to adapt the approach with a prehydroxylated compound, perhaps permitting elaboration to the target limaspermidine.

Selective reduction of aldehyde *rac*-**9**[9] with $NaBH_4$ in MeOH afforded the alcohol *rac*-**10** in 95% yield (Scheme 2). Protection of the hydroxyl group with TBSCl and imidazole produced the compound *rac*-**11** in almost quantitative yield. Although seemingly straightforward, reduction of the amide *rac*-**11** to the prehydroxylated amine *rac*-**12** proved problematic. Treatment of *rac*-**11** with $LiAlH_4$ in Et_2O at reflux yielded a mixture of the desired amine *rac*-**12** and the unexpected deprotected alcohol *rac*-**13** in the ratio of 1.2:1. While the alcohol *rac*-**13** could be converted into silyl-protected *rac*-**12** for recycling by reaction with TBSCl and imidazole, this would require additional tedious steps. Thus, we decided to give up this route (Scheme 2). However, we recognized that the alcohol **13** could serve as a suitable intermediate for the

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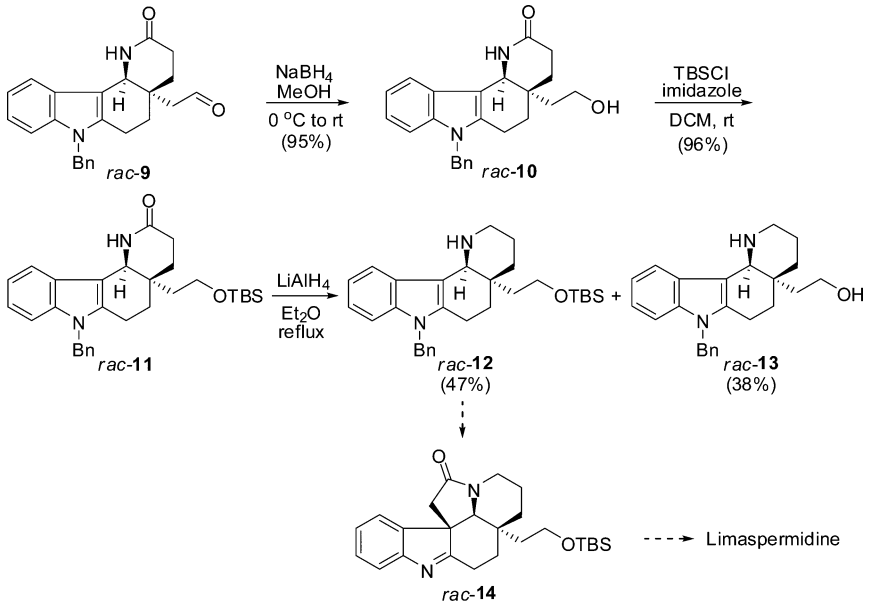
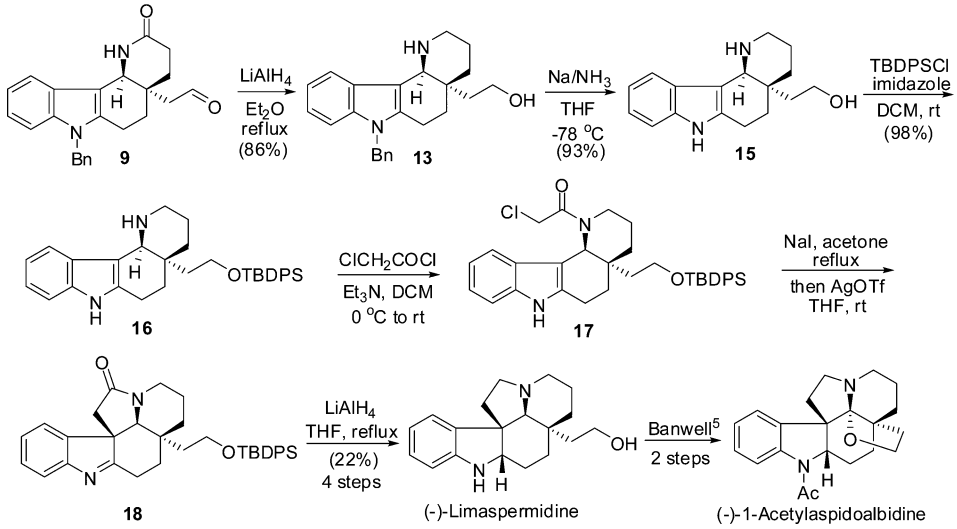
Scheme 2. Attempts To Secure Prehydroxylated *rac*-12 en Route to Limaspermidine



Scheme 3. Completion of Enantioselective Synthesis of (−)-Limaspermidine



synthesis of limaspermidine. We then turned our attention to developing a concise route to prepare **13** directly from enantioenriched **2a**.

As shown in Scheme 3, reduction of the amide and aldehyde groups of the compound **9** prepared from enantioenriched **2a** by a two-step route[9] with $LiAlH_4$ in Et_2O at reflux delivered the enantioenriched amino alcohol **13** in good yield (86%). Then the compound **13** was debenzylated by a Birch reduction with Na/NH_3 to afford the free (NH)-indole **15** in 93% yield. Protection of the hydroxyl group with TBDPSCl and imidazole at room temperature gave the compound **16** in quantitative yield, setting the stage for the E-ring annulation reaction again. Reaction of the amine **16** with α-chloroacetyl chloride in the presence of triethylamine occurred as expected. Unexpectedly, the resulting acylated compound **17** partially decomposed during the purification with silica gel column chromatography. For this reason, chloroamide **17** was used directly in the next step without further purification. Then the chloroamide **17** underwent a Finkelstein reaction with NaI/acetone to provide the corresponding iodoamide, which was treated with AgOTf to produce the desired cyclized product **18**. Interestingly, although the pentacycle *rac*-**3** (Scheme 1) was stable to silica gel column chromatography, this was not the case for the structurally similar pentacycle **18**. The attempt with neutral Al_2O_3 failed to give pure pentacycle **18**. Thus, once the annulation reaction was complete, the resulting crude product **18** was treated with $LiAlH_4$. To our delight, the target alkaloid (−)-limaspermidine ($[\alpha]^{D}_{20}$ = −30.5° (*c* 0.5, $CHCl_3$)) was obtained directly in one operation with reduction of the amide and the imine groups and concomitant removal of the silyl ether protecting group. All spectroscopic data (^{1}H NMR and ^{13}C NMR) of our synthetic (−)-limaspermidine were in accord with those for (±)-limaspermidine reported previously (for a comparison of ^{13}C NMR chemical shifts, see Table 1 in the Supporting Information).[5] Thus, the first asymmetric total synthesis of (−)-limaspermidine has been accomplished, thus confirming unambiguously its absolute configuration.

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The present route also constitutes the first formal asymmetric total synthesis of the complex *Aspidoalbine* alkaloid (−)-1-acetylaspidoalbidine,[10] as this target can be synthesized in two steps from limaspermidine.[5]

CONCLUSION

In summary, we have developed the first enantioselective total synthesis of the *Aspidosperma* alkaloid (−)-limaspermidine, confirming its absolute configuration. Our synthesis features a Pd-catalyzed asymmetric decarboxylative allylic alkylation that we have recently developed. On the other hand, we have accomplished the first asymmetric formal total synthesis of the *Aspidoalbine* alkaloid (−)-1-acetylaspidoalbidine. Our synthetic strategy also opens a pathway for the asymmetric syntheses of other *Aspidosperma* alkaloids containing a functionalized two-carbon unit at C-20.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded with a 300 or 400 MHz spectrophotometer. Chemical shifts (δ) are expressed in ppm, and J values are given in Hz. High-resolution mass spectrometry (HRMS) was recorded on a spectrometer using a time-of-flight (TOF) analyzer. IR spectra were obtained as KBr pellets. Optical rotations were measured on a polarimeter. Flash column chromatography was performed on silica gel (230−400 mesh). All chemicals and solvents were used as received without further purification unless otherwise stated.

Compound *rac*-6. To a solution of the compound *rac*-**5**[9] (450 mg, 1.21 mmol) in Et_2O (20 mL) was added $LiAlH_4$ (276.9 mg, 7.3 mmol). The reaction mixture was stirred under reflux for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with DCM, and the extract was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (silica gel) to give the pure compound *rac*-**6** (367 mg, 85% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (dd, J = 4.5 Hz, 1H), 1.40−1.59 (m, 3H), 1.67−1.83 (m, 2H), 1.92 (brs, 1H), 2.08 (m, 1H), 2.31 (m, 1H), 2.43−2.63 (m, 2H), 2.67 (m, 1H), 2.93 (m, 1H), 3.71 (s, 1H), 4.81 (d, J = 17.1 Hz, 1H), 4.91 (d, J = 9 Hz, 1H), 5.16 (dd, J = 16.8 Hz, 2H), 5.76 (m, 1H), 6.88 (d, J = 6.6 Hz, 2H), 7.01 (m, 2H), 7.15 (m, 4H), 7.56 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 22.8, 24.8, 34.9, 42.0, 46.3, 56.4, 109.2, 111.8, 117.3, 117.7, 119.3, 120.9, 126.1, 127.1, 127.3, 128.8, 134.8, 135.5, 137.1, 137.9. HRMS (EI): calcd for $C_{25}H_{28}N_2$ $[M]^+$ 356.2252, found 356.2254. IR (KBr): v 3391, 2927, 1730, 1600, 1455, 1309, 1193, 1001, 914, 737 cm^{-1}.

Compound *rac*-7. To a solution of NH_3 at −78 °C were slowly added Na (237 mg, 10.3 mmol, 10 equiv) and the compound *rac*-**6** (367 mg, 1.03 mmol) in THF (15 mL). The reaction mixture was stirred at −78 °C for 0.5 h. The reaction was quenched with the addition of MeOH. After NH_3 evaporated at room temperature, the crude product was purified by flash chromatography (silica gel) to give the compound *rac*-**7** (260 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (m, 1H), 1.41−1.57 (m, 3H), 1.71 (m, 1H), 1.78 (m, 1H), 2.11 (m, 1H), 2.25 (m, 1H), 2.57−2.73 (m, 3H), 2.94 (m, 1H), 3.66 (s, 1H), 4.90 (d, J = 16.8 Hz, 1H), 4.96 (d, J = 10 Hz, 1H), 5.78 (m, 1H), 7.00 (m, 2H), 7.16 (m, 1H), 7.49 (m, 1H), 8.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.9, 22.6, 24.9, 34.7, 34.9, 41.8, 46.1, 56.2, 110.6, 111.8, 117.4, 117.6, 119.3, 121.0, 127.3, 134.1, 134.7, 136.2. HRMS (EI): calcd for $C_{18}H_{22}N_2$ $[M]^+$ 266.1783, found 266.1791. IR (KBr): v 3397, 3288, 3058, 2931, 1729, 1631, 1443, 1296, 1104, 1007, 904, 735 cm^{-1}.

Compound *rac*-8. To a solution of the compound *rac*-**7** (260 mg, 0.98 mmol) in DCM (15 mL) was added Et_3N (156 mg, 1.46 mmol, 1.5 equiv). To the resulting solution was added 2-chloroacetyl chloride (73.8 μL, 0.98 mol, 1 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with addition of H_2O (5 mL) and extracted with DCM and the extract dried with Na_2SO_4. The solvent was removed by evaporation to dryness. The crude product was purified by flash chromatography (silica gel) to give the compound *rac*-**8** (269 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22−1.39 (m, 2H), 1.49−1.82 (m, 4H), 1.83−1.93 (m, 0.38H), 1.97−2.20 (m, 1H), 2.25−2.42 (m, 1H), 2.48−2.63 (m, 1H), 2.64−2.73 (m, 1H), 2.76−2.89 (m, 0.72H), 3.54 (d, J = 13.5 Hz, 0.68H), 4.21 (dd, J = 12 Hz, 1.38H), 4.33 (s, 0.61H), 4.46 (m, 0.33H), 4.69 (s, 0.32H), 4.96−5.14 (m, 2H), 5.67 (s, 0.68H), 5.78 (m, 1H), 6.86−6.98 (m, 1H), 6.98−7.09 (m, 1H), 7.09−7.26 (m, 2H), 8.00 (br s, 0.68H), 8.19 (br s, 0.31H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.6, 20.2, 21.6, 24.6, 25.5, 32.1, 36.7, 37.3, 37.8, 40.4, 40.7, 41.7, 41.9, 42.2, 53.1, 59.0, 106.8, 107.6, 110.5, 110.8, 118.1, 118.3, 118.4, 118.8, 119.7, 120.2, 121.3, 121.5, 126.2, 133.4, 133.9, 134.9, 135.0, 136.3, 166.1. HRMS (EI): calcd for $C_{20}H_{23}ClN_2O$ $[M]^+$ 342.1499, found 342.1505. IR (KBr): v 3395, 3265, 2924, 1625, 1455, 1327, 1249, 1102, 996, 914, 743 cm^{-1}.

Compound *rac*-3. To a solution of *rac*-**8** (269 mg, 0.78 mmol) in acetone (15 mL) was added NaI (1.18 g, 7.8 mmol, 10 equiv). The reaction mixture was stirred under reflux for 2 h. EtOAc (50 mL) was added, and the resulting solution was washed with H_2O. The solvent was removed by evaporation to dryness. The crude product was dissolved in THF (15 mL), and AgOTf (400 mg, 1.56 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h. EtOAc (10 mL) was added. The solution was washed with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed by evaporation to dryness, and the resulting crude product was purified by flash chromatography (silica gel) to give the compound *rac*-**3** (167 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44−1.68 (m, 5H), 1.71−1.83 (m, 2H), 2.21 (m, 1H), 2.54 (d, J = 1.2 Hz, 1H), 2.69−2.83 (m, 2H), 2.92−3.03 (m, 2H), 3.65 (s, 1H), 4.33 (m, 1H), 4.80 (d, J = 1.2 Hz, 1H), 4.98 (d, J = 1.8 Hz, 1H), 5.60 (m, 1H), 7.22 (m, 1H), 7.34 (m, 2H), 7.54 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.2, 24.1, 24.3, 34.3, 37.2, 38.7, 40.7, 41.2, 53.8, 69.2, 119.2, 120.5, 120.9, 126.2, 128.5, 131.9, 145.4, 154.5, 170.3, 186.6. HRMS (EI): calcd for $C_{20}H_{22}N_2O$ $[M]^+$ 306.1732, found 306.1734. IR (KBr): v 3297, 2935, 1678, 1456, 1286, 1243, 1047, 923, 748 cm^{-1}.

Compound *rac*-10. To a solution of the compound *rac*-**9**[9] (372.5 mg, 1 mmol) in MeOH (10 mL) was added $NaBH_4$ (45 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl (3 mL). The reaction mixture was extracted with DCM, and the extract was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (silica gel) to give the pure compound *rac*-**10** (356 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47−1.57 (m, 2H), 1.62−1.69 (m, 1H), 1.79−1.87 (m, 2H), 1.96−2.00 (m, 1H), 2.02 (s, 1H), 2.13−2.33 (m, 2H), 2.58−2.62 (m, 2H), 3.65 (t, J = 6.9 Hz, 2H), 4.44 (s, 1H), 5.16 (s, 2H), 5.88 (s, 1H), 6.87 (d, J = 6.3 Hz, 2H), 7.03−7.06 (m, 2H), 7.13−7.19 (m, 4H), 7.40−7.43 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.0, 25.8, 27.8, 28.0, 30.4, 33.7, 38.0, 46.5, 53.6, 58.6, 108.7, 109.7, 117.0, 120.0, 121.7, 126.0, 127.5, 128.9, 135.6, 137.1, 137.3, 171.0. HRMS (EI): calcd for $C_{24}H_{26}N_2O_2$ $[M]^+$ 374.1994, found 374.1993. IR (KBr): v 3448, 2937, 1642, 1460, 1060, 739 cm^{-1}.

Compound *rac*-11. To a solution of the compound *rac*-**10** (75 mg, 0.2 mmol) in DCM (3 mL) was added TBSCl (36 mg, 0.24 mmol, 1.2 equiv) and imidazole (41 mg, 0.6 mmol, 3 equiv). The reaction mixture was stirred at room temperature overnight. Then saturated aqueous NaCl (1 mL) was added, and the resulting mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash column chromatography (silica gel) to give the pure compound *rac*-**11** (94 mg, 96% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.49−1.53 (m, 1H), 1.68−1.79 (m, 2H), 1.96−2.05 (m, 2H), 2.09−2.15 (m, 1H), 2.42−2.49 (m, 2H), 2.71−2.73 (m, 2H), 3.76 (t, J = 6.6 Hz, 2H), 4.58 (s, 1H), 5.28 (s, 2H), 5.89 (s, 1H), 6.96 (d, J = 6.6 Hz, 2H), 7.14−7.16 (m, 2H), 7.24−7.29 (m, 4H), 7.50−7.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4, 18.2, 19.1, 25.8, 25.9, 27.8, 30.5, 33.9, 38.0, 46.5, 53.8, 59.2, 108.8, 109.6, 117.0, 119.9, 121.7, 126.0, 127.5, 128.9, 135.7, 137.1, 137.4, 170.8. HRMS (EI): calcd for

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$C_{30}H_{40}N_2O_2Si$ $[M]^+$ 488.2859, found 488.2866. IR (KBr): v 3447, 3201, 2937, 2858, 1653, 1461, 1417, 1086, 836, 734 cm^{-1}.

Compound *rac*-12. To a solution of the compound *rac*-**11** (98 mg, 0.2 mmol) in Et_2O (15 mL) was added LAH (46 mg, 1.2 mmol, 6 equiv). The reaction mixture was stirred at reflux overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The reaction mixture was extracted with DCM, and the extract was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (silica gel) to give the pure compound *rac*-**12** (45 mg, 47% yield) together with the alcohol *rac*-**13** (27 mg, 38% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.01 (s, 6H), 0.87 (s, 9H), 1.30−1.37 (m, 1H), 1.55−1.64 (m, 3H), 1.72−1.77 (m, 2H), 1.86 (d, J = 11.1 Hz, 1H), 2.46−2.51 (m, 1H), 2.73−2.79 (m, 3H), 2.99−3.03 (m, 1H), 3.73 (t, J = 7.2 Hz, 2H), 3.82 (s, 1H), 5.28 (s, 2H), 7.03 (d, J = 6.6 Hz, 2H), 7.11−7.14 (m, 2H), 7.21−7.30 (m, 4H), 7.67−7.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.4, 18.2, 19.5, 22.4, 25.1, 25.9, 34.2, 34.9, 39.8, 46.1, 46.4, 56.8, 59.3, 109.1, 111.4, 117.8, 119.3, 120.9, 126.1, 127.1, 127.2, 128.8, 135.6, 137.1, 137.9. HRMS (EI): calcd for $C_{30}H_{42}N_2OSi$ $[M]^+$ 474.3066, found 474.3055. IR (KBr): v 3444, 2945, 2851, 1638, 1458, 1401, 1094, 743 cm^{-1}.

Compound 13. To a solution of the compound **9**[9] (187 mg, 0.5 mmol) in Et_2O (20 mL) was added LAH (114 mg, 3 mmol, 6 equiv). The reaction mixture was stirred at reflux for 36 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with DCM, and the extract was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash chromatography (silica gel) to give the pure compound **13** (155 mg, 86% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.42−1.52 (m, 5H), 1.59−1.69 (m, 2H), 2.12 (s, 1H), 2.49−2.70 (m, 4H), 2.77 (s, 1H), 3.56−3.71 (m, 2H), 3.82 (s, 1H), 5.15 (s, 2H), 6.88 (d, J = 6.9 Hz, 2H), 7.00−7.03 (m, 2H), 7.11−7.18 (m, 4H), 7.49−7.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.3, 22.6, 29.7, 33.3, 34.6, 41.6, 44.4, 46.4, 56.4, 58.9, 109.3, 111.1, 117.8, 119.4, 121.0, 126.1, 126.8, 127.3, 128.8, 135.7, 137.2, 137.9. HRMS (EI): calcd for $C_{24}H_{28}N_2O$ $[M]^+$ 360.2202, found 360.2199. $[\alpha]_D^{20}$ = +7.7° (c 0.5, $CHCl_3$). IR (KBr): v 3410, 2927, 2843, 1641, 1609, 1455, 1043, 737 cm^{-1}.

Compound 15. To a solution of NH_3 at −78 °C were slowly added Na (64.4 mg, 2.8 mmol, 10 equiv) and the compound **13** (100 mg, 0.28 mmol) in THF (10 mL). The reaction mixture was stirred −78 °C for 0.5 h. The reaction was quenched with the addition of MeOH (1 mL). After NH_3 evaporated at room temperature, the crude product was purified by flash chromatography (silica gel) to give the compound **15** (69.7 mg, 93% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40−1.42 (m, 3H), 1.44−1.49 (m, 2H), 1.59−1.70 (m, 2H), 2.10 (s, 1H), 2.53−2.59 (m, 2H), 2.66−2.69 (m, 1H), 2.77 (s, 1H), 3.61−3.65 (m, 1H), 3.67−3.69 (m, 1H), 3.71−3.75 (m, 1H), 6.98−7.05 (m, 2H), 7.17−7.18 (m, 1H), 7.43−7.45 (d, J = 7.5 Hz, 1H), 7.97 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.1, 22.7, 28.2, 33.0, 34.7, 41.8, 44.4, 56.3, 59.0, 110.7, 111.5, 117.6, 119.4, 121.1, 127.1, 134.3, 136.3. HRMS (EI): calcd for $C_{17}H_{22}N_2O$ $[M]^+$ 270.1732, found 270.1737. $[\alpha]_D^{20}$ = +8.9° (c 0.5, $CHCl_3$). IR (KBr): v 3399, 3284, 2929, 1629, 1459, 1319, 1047, 894, 745 cm^{-1}.

Compound 16. To a solution of the compound **15** (90 mg, 0.33 mmol) in DCM (10 mL) were added imidazole (34.5 mg, 0.5 mmol, 1.5 equiv), DMAP (8 mg, 0.066 mmol, 0.2 equiv), and TBDPSCl (110 mg, 0.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 1.5 h. Then saturated aqueous NH_4Cl (5 mL) was added, and the resulting mixture was extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified by flash column chromatography (silica gel) to give the pure compound **16** (164.6 mg, 98% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (s, 9H), 1.09−1.14 (m, 1H), 1.31−1.36 (m, 2H), 1.50−1.66 (m, 4H), 1.95−1.97 (m, 1H), 2.37−2.45 (m, 1H), 2.58−2.61 (m, 1H), 2.96−3.02 (m, 2H), 3.44−3.52 (m, 2H), 3.72 (d, J = 10.2 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.19−7.26 (m, 5H), 7.30−7.34 (m, 2H), 7.41−7.46 (m, 4H), 7.58 (d, J = 7.5 Hz, 1H), 9.72−9.76 (m, 1H), 10.69 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.9, 19.0, 19.4, 24.3, 26.8, 33.2, 34.3, 38.0, 44.7, 55.4, 59.6, 102.9, 111.9, 117.9, 119.0, 120.9, 125.4, 127.7, 129.78, 129.84, 133.1, 135.4, 136.3, 138.2. HRMS (EI): calcd for $C_{33}H_{40}N_2Osi$ $[M]^+$ 508.2910, found 508.2914. $[\alpha]_D^{20}$ = −6.5° (c 0.5, $CHCl_3$). IR (KBr): v 3417, 3207, 2936, 2859, 1617, 1460, 1423, 1103, 742, 700 cm^{-1}.

Synthesis of (−)-Limaspermidine. To a solution of the compound **16** (101.6 mg, 0.2 mmol) in DCM (4 mL) was added Et_3N (15 mg, 0.3 mmol, 1.5 equiv). To the resulting solution was added 2-chloroacetyl chloride (15.0 μL, 0.2 mol, 1 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with addition of H_2O (1.5 mL) and extracted with DCM, and the extract was dried with Na_2SO_4. The solvent was removed by evaporation to dryness. The crude product was used without further purification. To a solution of the crude compound obtained above in acetone (5 mL) was added NaI (210 mg, 1.4 mmol). The reaction mixture was stirred under reflux for 2 h. EtOAc (5 mL) was added, and the resulting solution was washed with H_2O. The solvent was removed by evaporation to dryness. The crude product was dissolved in THF (5 mL), and AgOTf (72 mg, 0.28 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h. EtOAc (10 mL) was added. The solution was washed with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed by evaporation to dryness, and the resulting crude product was used without further purification. To a solution of this crude product in THF (5 mL) was added LAH (17.3 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 0.5 h and under reflux overnight. H_2O (35 μL), KOH (35 μL, 15% aqueous), and H_2O (100 μL) were added in sequence. The resulting slurry was filtered and rinsed with THF. The crude product was purified by flash chromatography (silica gel) to give (−)-limaspermidine (13 mg, 22% yield over four steps). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.01 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 3.56 (m, 1H), 3.47 (m, 2H), 3.05 (m, 1H), 2.25 (m, 3H), 1.97 (m, 3H), 1.74−1.62 (m, 5H), 1.46−1.42 (m, 3H), 1.24−1.12 (m, 2H), 1.03 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 24.3, 28.2, 29.8, 35.5, 38.5, 40.5, 52.8, 53.4, 53.7, 58.6, 65.3, 70.6, 110.5, 119.2, 122.7, 127.4, 135.2, 149.5. HRMS (EI): calcd for $C_{19}H_{26}N_2O$ $[M]^+$ 298.2045, found 298.2041. $[\alpha]_D^{20}$ = −30.5° (c 0.5, $CHCl_3$). IR (KBr): v 3444, 2929, 1601, 1544, 1470, 1392, 1037, 898, 755 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H NMR and ^{13}C NMR spectra of the compounds *rac*-**6**, *rac*-**7**, *rac*-**8**, *rac*-**3**, *rac*-**10**, *rac*-**11**, *rac*-**12**, **13**, **15**, **16**, and limaspermidine. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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