Short Enantioselective Total Syntheses of the Piperidine Alkaloids (*S*)-Coniine and (2*R*,6*R*)-*trans*-Solenopsin A via Catalytic Asymmetric Imine Hydrosilylation

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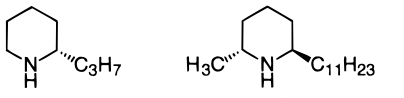
The enantioselective syntheses of (*S*)-coniine and (2*R*,6*R*)-*trans*-solenopsin A are reported. The key step in both syntheses is the catalytic asymmetric hydrosilylation of a cyclic imine.

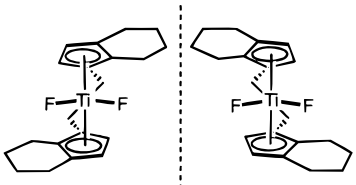
Introduction

We have recently described an efficient and highly enantioselective catalytic method for the hydrosilylation of imines.[1] To demonstrate the utility of our method, we undertook the preparation of (*S*)-coniine (**1**), the poisonous hemlock alkaloid, and (2*R*,6*R*)-*trans*-solenopsin A (**2**), a constituent of fire-ant venom.



(*S*)-Coniine, **1** (2*R*,6*R*)-*trans*-Solenopsin A, **2**

Due to their often potent biological activities, optically active piperidine alkaloids containing a stereogenic carbon atom in the 2-position are an important group of natural products, and they have been the target of numerous synthetic strategies.[2] Prior syntheses of this type of alkaloid (vide infra) have generally involved the use of asymmetry derived from naturally occurring compounds; most often, this requirement directly prohibits the availability of both antipodes of a given product. The key step in our synthesis is the asymmetric reduction of a cyclic imine using a chiral titanocene catalyst. Since both enantiomers of the ethylenebis(η^5-1,2,3,4-tetrahydroindenyl)titanium difluoride precatalyst employed here ((EBTHI)TiF_2, **3**) can be obtained from a single synthetic procedure,[3,4] products of either absolute configuration can be prepared from the same substrate. This is demonstrated in principle here by the opposing sense of asymmetry required for the syntheses of natural coniine (*S*) and solenopsin A (*R*).



(*S*,*S*)-**3** (*R*,*R*)-**3**

Recent asymmetric syntheses of coniine have generally involved the use of auxiliaries derived from the chiral pool.[2,5] An asymmetric aza-Diels−Alder reaction requiring a stoichiometric amount of a chiral Lewis acid promoter has also been described,[6] as well as the use of a chiral borohydride reducing agent that was employed in greater than stoichiometric amounts.[7] A recent approach utilized the Sharpless asymmetric dihydroxylation reaction to catalytically introduce chirality for the synthesis of **1**.[8]

The solenopsin alkaloids were the subject of a recent exhaustive review.[9] In addition to numerous routes to racemic *trans*-solenopsin A, there have also been reports of several asymmetric syntheses, all of which began with optically active amino acids or employed chiral auxiliaries. Our synthesis of *trans*-solenopsin A (vide infra) is the first to take advantage of a catalytic asymmetric transformation.

Results and Discussion

Endocyclic imines of the type required by our synthetic strategy have themselves been the subject of much synthetic effort.[10−13] Our attempt at direct synthesis of these compounds from 5-chlorovaleronitrile and organometallic reagents[10,13,14] did not afford the expected cyclic

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(4) The difluoride precatalyst **3** is available in one step from enantiomerically pure (EBTHI)Ti-2,2′-binaphth-1,1′-diol or (EBTHI)-TiCl_2. See the Experimental Section and ref 1.

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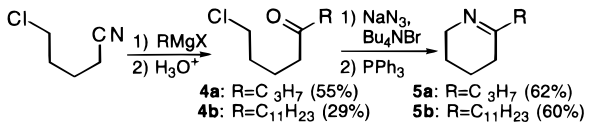
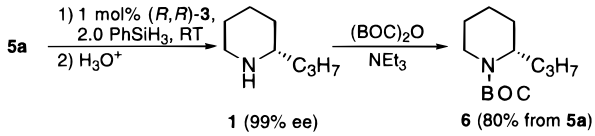
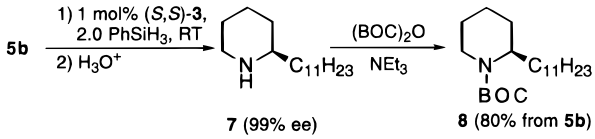
Scheme 1



Scheme 2



Scheme 3

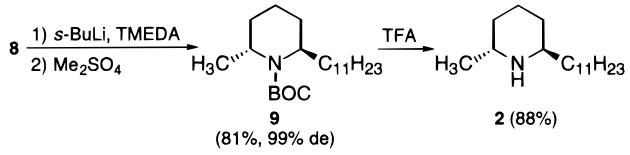


imines; however, ω-chloro ketones **4a** and **4b** which were instead obtained (Scheme 1) served as useful synthetic intermediates.[15] Transient preparation of ω-azido ketones via solid/liquid phase-transfer catalysis[16] followed by aza-Wittig cyclization[12,17,18] afforded the desired imines.

Our stereochemical model for the hydrosilylation of imines[1] (which follows from the related imine hydrogenation)[19] predicts that the precatalyst required for the production of the natural *S* enantiomer of coniine is (*R*,*R*)-**3**. Accordingly, room-temperature reaction of imine **5a** with 2 equiv of phenylsilane in the presence of 1 mol % (*R*,*R*)-**3** (which had been activated by treatment with pyrrolidine and methanol; see Experimental Section), followed by acidic hydrolysis of the initially formed aminosilane, afforded (*S*)-coniine (**1**) with an ee of 99% (Scheme 2). This product was immediately converted in 80% overall yield from **5a** to the *tert*-butoxycarbamate (BOC) derivative **6** to facilitate product isolation, due to the volatility of **1**.

The synthesis of *trans*-solenopsin A required the construction of a new stereogenic center with *R* absolute configuration (in contrast to the case of coniine). Therefore, in a similar sequence, imine **5b** was hydrosilylated using (*S*,*S*)-**3** to give (*R*)-amine **7** with an ee greater than 99%. Amine **7** was directly converted to the BOC derivative **8** (Scheme 3). Optically active carbamate **8** was methylated in the 6-position in a stereocontrolled manner. The resulting carbamate **9** was deprotected to afford (2*R*,6*R*)-*trans*-solenopsin A (**2**) in 88% yield (Scheme 4). This alkylation procedure was previously applied to the synthesis of racemic **2** by Beak and co-workers.[20]

Scheme 4



Conclusion

Asymmetric syntheses of the piperidine alkaloids (*S*)-coniine and (2*R*,6*R*)-*trans*-solenopsin A have been carried out. Our recently published method for highly enantioselective imine hydrosilylation allows for a direct and efficient route to these interesting chiral amines.

Experimental Section

General Methods. All manipulations, unless otherwise specified, were carried out under an argon atmosphere using standard air-free techniques; glassware was oven-dried and cooled under vacuum. All reagents were either commercially available and used as obtained or were prepared according to published methods. Ether and THF were distilled from sodium/benzophenone ketyl under argon. TMEDA (Aldrich) was distilled from calcium hydride prior to use. Yields, unless otherwise stated, refer to isolated yields of compounds greater than 95% pure as assessed by capillary GC and ^{1}H NMR. All compounds were further characterized by IR, and previously unreported compounds gave satisfactory elemental analyses.

(*R*,*R*)-Ethylenebis(η^5-tetrahydroindenyl)titanium Difluoride ((*R*,*R*)-(EBTHI)TiF$_2$), (*R*,*R*)-3. (*R*,*R*,*R*)-(EBTHI)-Ti-2,2′-binaphth-1,1′-diol[3] (1.0 g, 1.68 mmol) was suspended in ether (50 mL). Methyllithium (1.4 M in hexanes, 6.0 mL, 8.40 mmol) was added with stirring over 10 min at room temperature. The deep red mixture turned bright yellow over the next 1.25 h. The ether was removed in vacuo, and hexane (20 mL) was added. The supernatant was removed by cannula filtration, and the solids were rinsed with additional hexane (10 mL). The combined orange filtrates were cooled on an ice bath, and pyridine·HF adduct (0.15 mL, approximately 5 mmol) was added via syringe (**Caution:** this complex will etch glass syringes; use of a plastic syringe is advised). The yellow mixture was stirred for an additional 30 min, and the reaction mixture was quenched with saturated sodium bicarbonate. The layers were separated, and the aqueous portion was extracted (3 × 20 mL CH_2Cl_2). The combined organic layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a bright yellow solid. This was recrystallized in two crops from hot toluene/hexane as air-stable yellow plates, 481 mg, 82%.[21] The ee of this complex was determined to be ≥99%, as demonstrated by using it as a precatalyst for the hydrosilylation of *N*-(1-phenylethylidene)methylamine, which afforded (*R*)-*N*-methyl-1-phenylethylamine with 99% ee:[1] mp 235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 2.9 Hz, 2 H), 5.68 (d, J = 3.0 Hz, 2 H), 3.16 (m, 2 H), 3.13 (m, 2 H), 2.41−2.75 (m, 8 H), 1.88 (m, 4 H), 1.58 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 133.9, 125.5, 123.8, 108.8, 27.9, 23.9, 23.6, 22.0 (2 carbons); IR (KBr pellet, cm^{-1}) 3083, 2930, 2852, 1444, 1290, 832, 810, 566, 551, 499; $[\alpha]^{20}_D$ = +85.2° (*c* 0.81, CH_2Cl_2 (lit.[1] for (*S*,*S*)-**3** $[\alpha]^{20}_D$ = −76.0° (*c* 0.96, $CHCl_3$)).[1] Anal. Calcd for $C_{20}H_{24}F_2Ti$: C, 68.57; H, 6.91. Found: C, 68.73; H, 7.15.

(14) Treatment of 5-bromovaleronitrile with *n*-propylmagnesium chloride provided a mixture that was 52% **5a** by GC analysis (uncorrected for response factors). Reaction of *n*-undecylmagnesium bromide with the same bromonitrile gave a mixture that contained only 5% **5b** by GC analysis.

(15) By employing benzene as a cosolvent during the Grignard reaction and performing the imine hydrolysis at 60 °C instead of room temperature, we have been able to prepare the related 2-ethyl-3,4,5,6-tetrahydropyridine without isolation of the intermediate chloroketone in 67% overall yield after distillation: Yang, B. H.; Buchwald, S. L. Unpublished results. See also ref 10.

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(21) This compound may also be obtained by treating the binaphthol complex with KHF_2: Hansen, M. C.; Buchwald, S. L. Unpublished results.

1-Chloro-5-octanone, 4a.[12] To a solution of *n*-propylmagnesium bromide (1.0 M in ether, 27.0 mL, 27.0 mmol) in a 100 mL Schlenk flask was added 5-chlorovaleronitrile (3.04 mL, 27.0 mmol), dropwise, via syringe. The reaction mixture was stirred for 2 h, at which time analysis by GC showed no remaining nitrile. The reaction vessel was cooled on an ice bath, and ice was added in portions to the reaction mixture. Vigorous bubbling took place. The reaction mixture was acidified (1 M HCl) and extracted (5 × 30 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a yellow oil. This was passed through a plug of silica gel (10:1 hexane/ethyl acetate), concentrated, and vacuum distilled to afford a clear oil: 2.44 g, 55%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (t, 2 H, J = 6.4 Hz), 2.44 (t, 2 H, J = 6.8 Hz) 2.38 (t, 2 H, J = 7.7 Hz), 1.77 (m, 4 H), 1.59 (m, 2 H), 0.94 (t, 3 H, J = 7.3 Hz); IR (neat, cm^{-1}) 1714.

1-Chloro-5-hexadecanone, 4b. A three-necked 100 mL round-bottomed flask was equipped with a stirbar, condenser, and an addition funnel and purged with argon. Magnesium turnings (729 mg, 30 mmol) and a small crystal of iodine were placed in the flask, and 10 mL of ether was added. A solution of undecyl bromide (6.70 mL, 30 mmol) in 10 mL of ether was prepared in the addition funnel, and a few drops of this was added to the magnesium with stirring; the brown suspension immediately became colorless. Additional ether (10 mL) was placed in the addition funnel, and the solution was added dropwise, with stirring, to the magnesium at such a rate to maintain a gentle reflux. The mixture was stirred for an additional 3 h and then transferred via cannula into a 100 mL Schlenk flask. 5-Chlorovaleronitrile (3.38 mL, 30.0 mmol) was added dropwise, via syringe, and the reaction mixture was stirred overnight. The reaction vessel was then cooled on an ice bath, and ice was added in portions to the reaction mixture. Vigorous bubbling took place. The reaction mixture was acidified (1 M HCl) and extracted (5 × 30 mL ether). GC analysis showed approximately 45% desired product, along with undecane and docosane as impurities. The undecane was removed by vacuum distillation, and the remaining material was purified by column chromatography (20:1 hexane/ethyl acetate) to afford a clear oil, 2.41 g, 29%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (t, 2 H, J = 7.0 Hz), 2.41 (m, 4 H), 1.77 (m, 4 H), 1.57 (m, 2 H), 1.29 (br, s, 16 H), 0.88 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 44.9, 43.2, 42.0, 32.4, 32.3, 29.9, 29.8, 29.7, 29.6, 24.2, 23.0, 21.4, 14.4; IR (neat, cm^{-1}) 1715. Anal. Calcd for $C_{16}H_{31}ClO$: C, 69.91; H, 11.37. Found: C, 69.75; H, 11.23.

2-Propyl-3,4,5,6-tetrahydropyridine, 5a.[12] Sodium azide (1.95 g, 30.0 mmol) and tetrabutylammonium bromide (0.48 g, 1.5 mmol) were suspended in benzene (10 mL) in a 100 mL Schlenk flask. **4a** (2.44 g, 15.0 mmol) was added as a solution in benzene, and the flask was equipped with a condenser equipped with an argon balloon. The mixture was heated in an 80 °C oil bath overnight (ca. 12 h). At this point, GC analysis showed no remaining chloroketone, and the reaction mixture was cooled to room temperature. The mixture was filtered, and the solids were rinsed with ether; the filtrate was washed (1 × 20 mL water) and the aqueous layer was extracted (3 × 20 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), and filtered. The volume of solvent was reduced to 20 mL (**Caution:** azides are potential shock and contact explosives),[22] and the resulting solution was placed in a dry 100 mL Schlenk flask and purged with argon. Triphenylphosphine (3.93 g, 15.0 mmol) was added, and the reaction mixture was stirred overnight. The mixture was diluted with pentane and filtered, and the solids were rinsed with additional pentane. The solution was then passed through neutral Activity I alumina. The solution was concentrated in vacuo, and the resulting oil was distilled (short-path, 1 atm Ar, 168 °C) to give a clear, faintly yellow, air-sensitive oil, 1.16 g, 62%. The imine was stored at −20 °C in a nitrogen-filled glovebox: ^{1}H NMR (300 MHz, C_6D_6) δ 3.55 (br, s, 2 H), 2.02 (t, 2 H, J = 3.9 Hz), 1.69 (m, 2 H), 1.61 (m, 2 H), 1.29 (m, 4 H), 0.81 (t, 3 H, J = 7.2 Hz); IR (neat, cm^{-1}) 1662.

2-Undecyl-3,4,5,6-tetrahydropyridine, 5b.[23] Sodium azide (1.07 g, 16.5 mmol) and tetrabutylammonium bromide (8.2 mmol, 0.26 g) were suspended in benzene (5 mL) in a 100 mL Schlenk flask. To the resulting solution was added a benzene solution of **4b** (8.2 mmol, 2.25 g), and then the flask was equipped with a condenser equipped with an argon balloon. The mixture was heated in an 80 °C oil bath overnight (ca. 12 h). GC analysis showed no remaining chloroketone, and the reaction mixture was cooled to room temperature. The mixture was filtered, and the solids were rinsed with ether; the filtrate was washed (1 × 20 mL water), and the aqueous layer was extracted (3 × 20 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), and filtered. The volume of solvent was reduced to 20 mL (see warning above), and the resulting solution was placed in a dry 100 mL Schlenk flask and purged with argon. Triphenylphosphine (3.93 g, 15.0 mmol) was added, and the reaction mixture was stirred overnight. The mixture was diluted with pentane and filtered, and the solids were rinsed with additional pentane. The solution was then passed through neutral Activity I alumina. The solution was concentrated in vacuo, and the resulting oil was distilled (Kugelrohr, 10^{-2} Torr, 90−95 °C) to give a clear, faintly yellow, air-sensitive oil, 1.16 g, 60%. The imine was stored at −20 °C in a nitrogen-filled glovebox: ^{1}H NMR (300 MHz, C_6D_6): δ 3.55 (m, 2 H), 2.10 (m, 4 H), 1.64 (m, 2 H), 1.54 (m, 4 H), 1.29 (br s, 16 H), 0.88 (t, J = 6.3 Hz, 3 H); IR (neat, cm^{-1}) 1664.

(*S*)-(+)-*N*-(*tert*-Butoxycarbonyl)-2-propylpiperidine ((*S*)-(+)-*N*-BOC-coniine), 6.[5g] A resealable Schlenk flask was charged with (*R*,*R*)-**3** (3.5 mg, 10 μmol). THF (0.8 mL) was then added via syringe, followed by phenylsilane (0.25 mL, 2.0 mmol), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol). The mixture was stirred in a 50 °C oil bath for 10 min. During this time, a color change from yellow to emerald green occurred. The flask was then sealed and transferred to a nitrogen-filled glovebox. Imine **5a** was added (125 mg, 1.0 mmol), and the flask was resealed, removed from the glovebox, and stirred at room temperature. When GC analysis showed consumption of the starting material was complete (about 6 h), the reaction mixture was diluted with THF (20 mL) and stirred with 1 M HCl (10 mL) for 0.5 h (**Caution**: vigorous bubbling). The mixture was washed (3 × 20 mL of 1 M HCl), and the combined aqueous layers were made basic with 4 M NaOH and extracted (3 × 20 mL of ether). The combined ether layers were washed (brine), dried ($MgSO_4$), and filtered. To this solution of the free amine was immediately added di-*tert*-butyl dicarbonate (0.218 g, 1.0 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the mixture was stirred for 2−3 h at room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in THF (10 mL). Unreacted di-*tert*-butyl dicarbonate was destroyed by adding 4 M NaOH (5 mL). After 1 h, the reaction mixture was acidified and extracted (5 × 15 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a slightly yellow oil. This was purified by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) to give a clear oil, 183 mg, 80% from **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (br s, 1 H), 3.95 (br, d, 1 H, J = 11.0 Hz), 2.74 (t, 1 H, J = 12.5 Hz), 1.45 (s, 9H), 1.20−1.65 (m, 10 H), 0.92 (t, 3 H, J = 7.2 Hz); IR (neat, cm^{-1}) 1694. Chiral GC analysis of the trifluoroacetamide derivative (prepared after removing the BOC group with TFA in CH_2Cl_2) showed an ee of 99%: $[\alpha]^{20}_D$ = +29.8° (*c* 1.3, $CHCl_3$)[24] (lit.[5g] $[\alpha]^{20}_D$ = +33.5° (*c* 0.43, $CHCl_3$)). The spectral data for this compound matched that reported in the literature.[5g]

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(24) The specific optical rotation for this compound was determined on a sample obtained according to the method described herein that was spectroscopically (^{1}H NMR) identical to previously prepared samples.

(*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-2-undecylpiperidine, 8. A resealable Schlenk flask was charged with (*S*,*S*)-**3**[1] (3.5 mg, 10 μmol). THF (0.8 mL) was then added via syringe, followed by phenylsilane (0.25 mL, 2.0 mmol), pyrrolidine (8 μL, 0.1 mmol), and methanol (4 μL, 0.1 mmol). The mixture was stirred in a 50 °C oil bath for 10 min. During this time, a color change from yellow to emerald green occurred. The flask was then sealed and transferred to a nitrogen-filled glovebox. Imine **5b** was added (237 mg, 1.0 mmol), and the flask was resealed, removed from the glovebox, and stirred at room temperature. When GC analysis showed consumption of the starting material was complete (about 6 h), the reaction mixture was diluted with THF (20 mL) and stirred with 1 M HCl (10 mL) for 0.5 h (**Caution**: vigorous bubbling). The mixture was washed (3 × 20 mL of 1 M HCl), and the combined aqueous layers were made basic with 4 M NaOH and extracted (3 × 20 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), and filtered. To this solution of the free amine were immediately added di-*tert*-butyl dicarbonate (0.218 g, 1.0 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the mixture was stirred for 2−3 h at room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in THF (10 mL). Unreacted di-*tert*-butyl dicarbonate was destroyed by adding 4 M NaOH (5 mL). After 1 h, the reaction mixture was acidified and extracted (5 × 15 mL ether). The combined ether layers were washed (brine), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a faintly yellow oil. This was purified by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) to give a clear oil, 279 mg, 82% from **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (br s, 1 H), 3.96 (br d, 1 H, J = 14.7 Hz), 2.74 (t, 1 H, J = 16.4 Hz), 1.55 (s, 9 H), 1.20−1.65 (m, 26 H), 0.88 (t, 3 H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 78.8, 50.4, 38.7, 31.9, 29.7, 29.6, 29.5, 29.3, 28.5, 26.3, 25.7, 22.6, 19.0, 14.0; IR (neat, cm^{-1}) 1693. Chiral GC analysis of the trifluoroacetamide derivative (prepared after removing the BOC group with TFA in CH_2Cl_2) showed an ee of 99%: $[\alpha]^{20}_D$ = −21.2° (*c* 4.4, CH_2Cl_2). Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17. Found: C, 74.15; H, 11.99.

(2*R*,6*R*)-(−)-*trans*-*N*-(*tert*-Butoxycarbonyl)-2-undecyl-6-methylpiperidine ((2*R*,6*R*)-(−)-*trans*-*N*-BOC-solenopsin A), 9. The title compound was prepared according to the method of Beak.[20] Carbamate **8** (170 mg, 0.5 mmol) was placed in a dry Schlenk tube under argon. Ether (1.7 mL) and TMEDA (0.1 mL) were added, and the solution was cooled to −65 °C. *sec*-Butyllithium (1.4 M in cyclohexane, 0.46 mL, 0.65 mmol) was added dropwise, and the solution was allowed to warm slowly over 1 h to −20 °C and stirred at that temperature for an addition 30 min. The solution was then recooled to −65 °C, and dimethyl sulfate (1.0 mmol, 0.1 mL) was added. The mixture was allowed to warm to room temperature overnight. The reaction mixture was then quenched with water (10 mL), extracted (6 × 10 mL ether), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a clear oil. Purification by column chromatography (15:1 hexane/ethyl acetate, 0.5% triethylamine) gave a clear oil, 154 mg, 87%. ^{1}H NMR indicated the presence of a single diastereomer. The de of this compound was determined to be ≥99% by chiral GC analysis of the trifluoroacetamide derivative (prepared after removing the BOC group with TFA in CH_2Cl_2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (m, 1 H), 3.80 (m, 1 H); 1.46 (s, 9 H), 1.20−1.90 (m, 29 H). 0.88 (t, 3 H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 78.6, 51.7, 47.0, 34.4, 31.9, 29.6, 29.5, 29.3, 28.5, 27.1, 23.5, 22.6, 20.8, 14.0; IR (neat, cm^{-1}) 2923, 2854, 1690, 1392, 1364, 1324, 1178; $[\alpha]^{20}_D$ = −26.3° (*c* 4.7, CH_2Cl_2). Anal. Calcd for $C_{22}H_{43}NO_2$: C, 74.73; H, 12.26. Found: C, 74.46; H, 12.20.

(2*R*,6*R*)-(−)-*trans*-2-Undecyl-6-methylpiperidine ((2*R*,6*R*)-(−)-*trans*-Solenopsin A), 2.[25] The title compound was prepared by stirring carbamate **9** (28.1 mg, 0.08 mmol) with excess TFA (ca. 10 equiv) in CH_2Cl_2 (1 mL) overnight. The reaction mixture was quenched with saturated $NaHCO_3$, and the aqueous layers were extracted (5 × 10 mL ether). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a clear oil, 18.4 mg, 91%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (m, 2 H), 2.85 (m, 2 H), 1.35−1.65 (m, 9 H), 1.25 (br s, 18 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.88 (t, J = 7.2 Hz, 3 H); IR (neat, cm^{-1}) 2935, 2851, 1467, 1382, 1140, 1064. Chiral GC of the trifluoroacetamide derivative showed a de of 99%: $[\alpha]_D$ = −1.2° (*c* = 1.2 in $CHCl_3$[24]) (lit.[25] $[\alpha]_D$ = −1.3° (*c* = 1.3 in $CHCl_3$)).[25] The spectral data for those compound matched that reported in the literature.[25]

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