Acetylation of **4b** (Ac_2O, py, room temperature, overnight) gave **4d**: mp 205–208 °C; IR ($CHCl_3$) 3540, 1770, 1735, 1630, 1600, 1240, 1120, 1100, 950, 910 cm^{-1}; ^1H NMR (Table I); ^{13}C NMR (Table II); CIMS m/z 465 ($M^+ + 1$) (Calcd for $C_{23}H_{28}O_{10}$: M^+ m/z at 464).

X-ray Analysis of 4d. Crystals of the title compound were obtained by slow evaporation from acetone–hexane. These crystals are monoclinic. Data were collected by using a single crystal (0.20 × 0.28 × 0.40 mm) mounted on top of a glass fiber. Systematic absences established the space group $P2_1$. Intensities were collected on a Nicolet R3m diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). Lattice constants were determined from the setting angles of 25 machine-centered reflections with $5.0 < 2\theta < 19.1°$: a = 7.222 (2) Å, b = 17.194 (5) Å, c = 9.423 (4) Å, β = 97.63 (3)°, V = 1160 (1) Å^3, $F(000)$ = 492, T = 293 K, D_{calcd} = 1.33 g cm^{-3}, Z = 2, and μ(Mo Kα) = 0.98 cm^{-1}. Reflections in two octants of reciprocal space were measured with an index range of $h \pm 8$, k 0→19, l 0→11, using the $2\theta/\theta$ scan mode, a variable scan speed, a scan width of 1.0 (°θ), and two standard reflections ($\bar{1}1\bar{2}$; $\bar{1}00$) monitored every 50 measurements. The intensities were corrected for Lorentz and polarization effects but no absorption corrections were applied. Of the 2135 reflections within the 2θ range of 3–50° collected, 1798 had values of $|F_o|^2 > 2.5\sigma(I)$ and were used in the final refinement of structural parameters. The data were adjusted to an approximately absolute scale and an overall U value of 0.050 Å^2. The crystal structure was solved by combination of direct methods and partial structure expansion by an iterative E-Fourier procedure using the SHELXTL[17] system of programs. The trial structure was refined by a blocked cascade least-squares procedure with anisotropic temperature factors for the non-H atoms. The H atoms of the CH, CH_2, and CH_3 groups were allowed to ride on bonded C. The H atom attached to the O(1) atom was found on a difference Fourier map at an advanced stage of the anisotropic refinement, and all H atoms had a fixed isotropic temperature factor, U = 0.06 Å^2. The function minimized was $\sum\omega(\Delta F)^2$ with a statistical weight of the form $\omega = \{\sigma^2(F_o) + 0.001(F_o)^2\}^{-1}$, where σ is the standard deviation of the observed amplitudes based on counting statistics. The final conventional R factor was 0.044 and R_ω = 0.047; the isotropic extinction parameter X = 0.0012 and the goodness-of-fit value S = 1.19. Atomic scattering factors for C, O, and H atoms were from the *International Tables for X-ray Crystallography*.[18] The final difference map had a $\Delta\rho$ from −0.18 to 0.19 e Å^{-3}. All computations were performed on a Nova 4S computer, and plots were drawn on a Tektronix plotter with the SHELXTL system of programs.

Acknowledgment. We are very grateful to Messrs. R. Villena, L. Velasco, F. del Río, R. Gaviño, and A. Cuellar for technical assistance.

Supplementary Material Available: Tables of final atomic coordinates for the non-hydrogen atoms, bond distances and angles, final hydrogen coordinates, and thermal parameters for **4d** (4 pages). Ordering information is given on any current masthead page.

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Enantioselective Construction of Heterocycles: Synthesis of (*R*,*R*)-Solenopsin B

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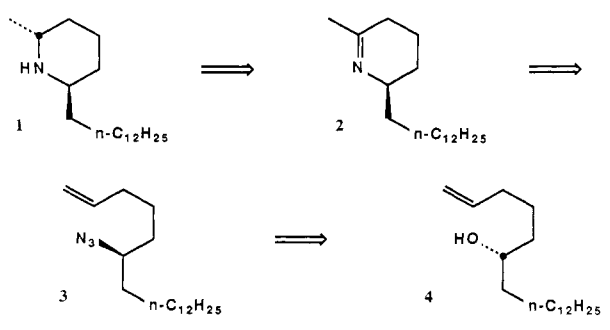
An enantioselective route to solenopsin B (**1**), the major saturated component of the alkaloid mixture isolated from the venom of the fire ant, *Solenopsis invicta*, is reported. The key transformation in this synthesis is the smooth thermolytic cyclization of alkenyl azide **3**. The precursor to **3**, alcohol **4**, is prepared by stereoselective reduction of an enantiomerically pure β-keto ester.

The fire ant, *Solenopsis invicta*, is a ubiquitous pest in the southeastern United States.[1] The 2,6-*trans*-dialkylpiperidine derivative solenopsin B (**1**), the major saturated component of a closely related family of alkaloids isolated from the ant,[2] has been shown to have both vesicant and hemolytic activity and to cause histamine release from mast cells.[3] Other, more complex alkaloids containing this same 2,6-dialkylpiperidine nucleus have been shown to have diverse physiological activity.[4] We have developed

Scheme I



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(2) (a) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1971**, *26*, 1129. (b) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949.

(3) (a) Caro, M. R.; Derbes, V. J.; Jung, R. *Arch. Derm.* **1957**, *75*, 475. (b) Androuny, G. A.; Derbes, V. J.; Jung, R. C. *Science (Washington, D.C.)* **1959**, *130*, 449. (c) Read, G. W.; Lind, N. K.; Oda, C. S. *Toxicon* **1978**, *16*, 361.

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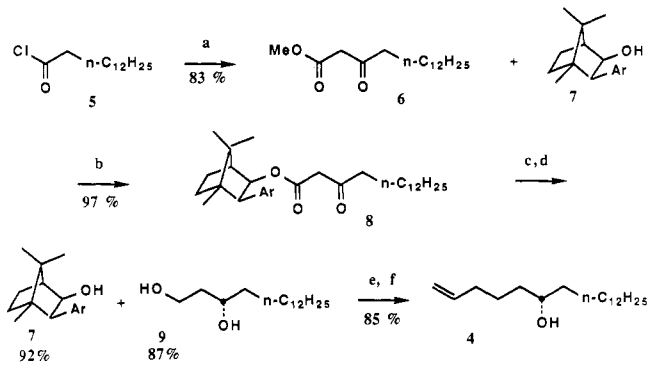
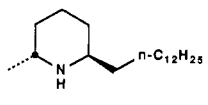
Scheme II[a]



[a] (a) LDA/methyl acetate, THF, −78 °C → room temperature (0.5 h); (b) **6** (3.0 equiv), **7** (1.0 equiv), 4-DMAP, toluene, reflux (40 h); (c) Dibal/BHT (0.66/1), toluene, −65 → 60 °C (1.5 h); (d) $LiAlH_4$ (3.0 equiv), THF, 0 °C; (e) TsCl (1.1 equiv); 4-DMAP, CH_2Cl_2, −30 °C → room temperature; allylmagnesium chloride (5.0 equiv), THF, 0 °C (0.5 h), reflux (3 h).

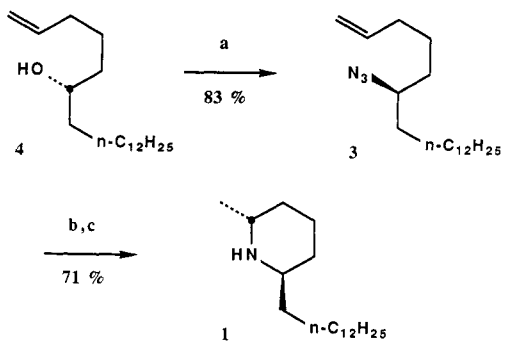
what promises to be a general method for the enantioselective construction of such heterocycles,[5] as exemplified by the synthesis[6,7] of (*R,R*)-solenopsin B (**1**) with control of both relative and absolute stereochemistry.



1

Our retrosynthetic analysis of **1** (Scheme I) was derived from the published observation[7f] that imine **2** could, in the racemic series, be reduced to **1** with excellent relative stereocontrol. We reasoned[8] that imine **2** could be derived from **4**. The problem then devolved to the preparation of secondary alcohol **4** with control of absolute stereochemistry.

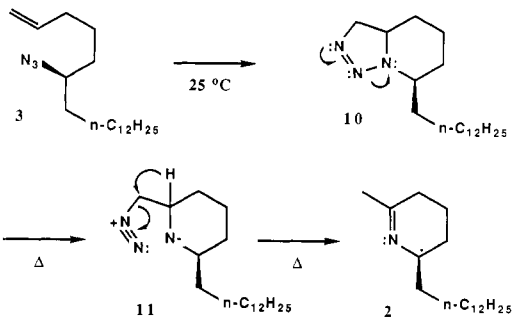
Scheme III[a]



(R,R) - Solenopsin B

[a] (a) Ph_3P, diethyl azodicarboxylate, diphenyl phosphorazidate, THF, room temperature (24 h); (b) 165 °C (2.5 h); (c) $LiAlH_4$ (7.0 equiv), Me_3Al (7.0 equiv), THF, −78 → 0 °C.

Scheme IV



We have recently developed procedures for the reduction of enantiomerically pure β-keto esters with excellent relative stereocontrol.[9a] Application of this method to the preparation of alcohol **4** required β-keto ester **6** (Scheme II). This is prepared by Rathke homologation[10] of commercial myristoyl chloride. Ester exchange[11] with naphthylborneol **7**[12] proceeds to give **8**. Stereocontrolled ketone reduction,[13] followed by ester reduction with $LiAlH_4$, then returns crystalline **7** for recycling, along with diol **9** of high[9b] enantiomeric purity. Exposure to excess allylmagnesium chloride[14] cleanly converts the monotosylate of **9**[15] to the desired secondary alcohol **4**.

(4) For examples, see the following. (a) Pseudocarpaine: Gouindachari, T. R.; Pai, B. R.; Narasimhan, M. S. *J. Chem. Soc.* **1954**, 1847. Gouindachari, T. R.; Nagarajan, K.; Viswanathan, N. *Tetrahedron Lett.* **1965**, 1907. (b) Lythranine and lythranidine: Fujita, E.; Fugi, K.; Bessho, K.; Sumi, A.; Nakamura, S. *Tetrahedron Lett.* **1967**, 4595. (c) Gephyrotoxin: Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128. Souccar, C.; Varanda, W. A.; Aronstam, R. S.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1984**, *25*, 395.

(5) As evidenced by ref 7, a variety of strategies for alkaloid construction with control of relative stereochemistry have been developed. Any of these strategies might be applied toward synthesis of enantiomerically pure material, if a way to control the first stereogenic center were developed. In general, such initial centers have been derived from either amino acids or carbohydrates. More recently, methods for auxiliary-mediated induction of amine-bearing centers have been developed. For leading references, see the following. (a) From amino acids: Shiosaki, H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229. Ho, T.-L.; Gopalan, B.; Nestor, J. J., Jr. *J. Org. Chem.* **1986**, *51*, 2405. Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. (b) From carbohydrates: Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (c) By induction: Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265.

(6) For a previous enantioselective synthesis of solenopsin A, see: Husson, H.-P.; Grierson, D. S.; Royer, J.; Guerrier, L. *J. Org. Chem.* **1986**, *51*, 4475.

(7) For other syntheses of solenopsin A or B, see the following. (a) Reference 2. (b) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569. (c) Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. *Tetrahedron Lett.* **1977**, *10*, 825. (d) Fuji, K.; Ichikawa, K.; Fujita, E. *Chem. Pharm. Bull.* **1979**, *27*, 3183. (e) Husson, H.-P.; Romero, J. R.; Grierson, D. S.; Bonin, M. *Tetrahedron Lett.* **1982**, *23*, 3369. (f) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (g) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597. (h) Yamaguchi, R.; Kawanishi, M.; Nakazono, Y. *Chem. Lett.* **1984**, 1129.

(8) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749.

(9) (a) For the assignment of the absolute stereochemistry of these reduction products, see: Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488. (b) The alcohol methines of the diastereomers of the β-hydroxy ester come, respectively, at 2.74 and 2.98. Using Dibal-BHT in the reduction of **8**, *only* the 2.74 diastereomer was observed. (c) For the direct enantioselective hydrogenation of β-keto esters, see: Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856 and references cited therein.

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(11) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

(12) (a) For the preparation of **7**, see: Taber, D. F.; Raman K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (b) Concurrently with our work, others have investigated chiral induction with modified bornyl esters. For leading references, see: Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665. Somfai, P.; Tanner, D.; Olsson, T. *Tetrahedron* **1985**, *41*, 5973.

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(14) The use of copper catalysis is not necessary with allylmagnesium chloride: (a) Whitesides, G. M.; Fisher, W. F.; Filippo, J. S.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. (b) Kochi, J.; Tamura, M. *Synthesis* **1971**, 303.

(15) (a) Nicolaou, K. C.; Hwang, C. K.; Li, W. S. *Tetrahedron Lett.* **1984**, *25*, 2295. (b) Kabalka, G. W.; Varmu, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386. (c) Poulter, C. D.; Dauisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M. *J. Org. Chem.* **1986**, *51*, 4768.

Alcohol 4 smoothly undergoes Mitsunobu coupling,[16,17] to give the inverted azide 3 (Scheme III). Thermolysis of such alkenyl azides has been reported[8,18] to give the imines (via dipolar cycloaddition followed by fragmentation, Scheme IV) in mediocre yield. We reasoned that the low yields reported might be due to the inherent instability of the product imines. In fact, direct hydride reduction[7f] of the *crude* thermolysis product yields (*R,R*)-solenopsin B (1) in 71% isolated yield from azide 3.

As solenopsin B from *S. invicta*[23] shows only negligible $[\alpha]_D$, we resorted to the preparation and analytical separation of diastereomeric derivatives to assign the absolute configuration of the natural product. To this end, racemic solenopsin B was prepared, beginning with $LiAlH_4$ reduction of β-keto ester 6. The diastereomeric pentaacetylglucosylthiourea derivatives[19] of this racemate were nicely resolved on reverse-phase HPLC. Under the same conditions, the same derivative of naturally derived solenopsin B (1) eluted as a single peak, showing the same retention volume as the pentaacetylglucosylthiourea derivative of synthetic (*R,R*)-1. Thus, the absolute stereochemistry of the naturally derived alkaloid is also *R,R*, as illustrated.

As conditions for reducing the imine 2 to the alternative *cis*-2,6-dialkylpiperidine have also been reported,[7f] the strategy described herein should be a general one for the construction of 2,6-dialkylpiperidine (and, potentially, pyrrolidine) derivatives with control of both relative and absolute stereochemistry. The application of this strategy to the synthesis of more complex alkaloids is currently under investigation.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-250 spectrometer as solutions in $CDCl_3$. ^{13}C multiplicities were determined with the aid of an INEPT[20] sequence, separating methyl and methine = up (u), from methylene and quaternary carbon = down (d). The infrared (IR) spectra were determined as solutions in CCl_4. Mass spectra (MS) were obtained at an ionizing potential of 70 eV. Substances for which C, H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Optical rotations were measured on a Rudolph Autopol III polarimeter. Samples for determination of optical rotation or for C, H analysis were purified by column chromatography, followed by bulb-to-bulb distillation. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF and developed in 10% EtOAc/hexane unless otherwise indicated. Column chromatography was performed with TLC-mesh silica gel, following the procedure we have described.[21] Solvent mixtures are volume/volume mixtures. THF and ether were distilled from sodium/benzophenone under N_2 and used immediately. CH_2Cl_2 was distilled from CaH_2 and stored over K_2CO_3 under an N_2 atmosphere. Diisopropylamine distilled from Na, and toluene distilled from CaH_2 were stored over 4-Å molecular sieves under an N_2 atmosphere. Methyl acetate was passed through a pipette column of activated alumina and used immediately. Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2. Unless otherwise indicated, the solution obtained by extractive workup was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

Methyl 3-Oxohexadecanoate (6). Acylation was performed following the method of Rathke.[10] Thus, methyl acetate (29.0 mL, 365 mmol) was added to lithium diisopropylamide (from diisopropylamine, 56.2 mL, 401 mmol, and *n*-BuLi, 365 mmol) in 250 mL of THF at a rate that allowed the temperature to remain at or below −65 °C. This mixture was stirred at −78 °C for 5 min; then myristoyl chloride (30.00 g, 122 mmol) was introduced in one portion. The −78 °C bath was removed immediately and the reaction was allowed to warm to room temperature. The mixture was diluted with 10% aqueous HCl and extracted with Et_2O to give a viscous crude product (41.35 g). A portion of this crude material (10.3 g) was chromatographed on 100 g of silica gel to give 7.2 g (83%) of 6 as a colorless oil: TLC R_f = 0.56; ^1H NMR δ 0.88 (t, J = 6.4 Hz, 3 H), 1.27 (br s, 20 H), 1.59 (m, 2 H), 2.54 (t, J = 7.4 Hz, 2 H), 3.45 (s, 2 H), 3.73 (s, 3 H); ^{13}C NMR δ 14.0 (u), 22.6 (d), 23.3 (d), 28.9 (d), 29.3 (d), 29.4 (d), 29.5 (d), 29.6 (d), 31.8 (d), 43.0 (d), 48.9 (d), 52.2 (u), 167.6 (d), 202.8 (d); IR 2963, 2913, 2859, 1758, 1728, 1656, 1629, 1449, 1318, 1235; MS (CH_4, CI) 285 ($(M + H)^+$, 100), 284 (M^+, 3), 283 (13), 265 (13), 253 (38), 251 (16), 212 (93), 211 (66), 191 (93), 116 (24). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 72.17; H, 11.27.

4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]hept-2-*exo*-yl 3-Oxohexadecanoate (8). Ester exchange was accomplished by our previously reported[11] method. Thus, a mixture of methyl β-keto ester 6 (4.9 g, 18.2 mmol), 4,7,7-trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-ol (7)[12] (1.7 g, 6.1 mmol), 4-(dimethylamino)pyridine (0.37 g, 3 mmol), and toluene (18 mL) was stirred at reflux for 40 h, allowed to cool to room temperature, and quenched with aqueous NH_4Cl. The resulting solution was extracted with EtOAc and then bulb-to-bulb distilled (bath 155 °C, 0.2 mmHg) to remove excess methyl β-keto ester. The residual oil (3.3 g) was chromatographed on 100 g of silica gel to give 3.1 g (97%) of 8 as a colorless viscous oil: TLC R_f 0.45; ^1H NMR δ 0.88 (t, J = 6.4 Hz, 3 H), 0.98 (s, 3 H), 1.22 (s, 3 H), 1.27 (br s, 23 H), 0.80–2.07 (m, 9 H), 2.61 (s, 2 H), 4.06 (d, J = 8.8 Hz, 1 H), 5.54 (d, J = 8.8 Hz, 1 H), 7.25–7.52 (m, 3 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.80 (br d, J = 8.3 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 14.1 (u), 14.7 (u), 21.5 (u), 22.6 (d), 23.1 (d), 23.7 (u), 23.8 (d), 28.7 (d), 29.3 (d), 29.4 (d), 29.6 (d), 31.9 (d), 42.0 (d), 42.4 (d), 48.3 (d), 48.7 (d), 49.4 (d), 51.1 (u), 55.2 (u), 80.7 (u), 123.5 (u), 124.5 (u), 125.1 (u), 126.1 (u), 126.6 (u), 127.2 (u), 128.8 (u), 133.1 (d), 133.4 (d), 135.2 (d), 166.1 (d), 202.3 (d); IR: 3056, 2959, 2932, 2855, 1741, 1718, 1643, 1465, 1394, 1232.

(+)-(*S*)-Hexadecane-1,3-diol (9). A solution of diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide was prepared by analogy to the method of Yamamoto.[13] Thus, diisobutylaluminum hydride (1 M solution in toluene, 23.5 mmol) was added dropwise via syringe to 2,6-di-*tert*-butyl-4-methylphenol (7.75 g, 35.2 mmol) in dry toluene (30 mL) at 0 °C. After 1 h, the mixture was chilled to −78 °C, and a solution of β-keto ester 8 (1.56 g, 2.9 mmol) in toluene (30 mL) was added dropwise via syringe. After 30 min, the mixture was warmed to −60 °C. After an additional 1.5 h, the reaction mixture was quenched with 10% aqueous HCl (20 mL) and extracted three times with 100 mL of EtOAc. The combined organic phases were washed with brine (2 × 20 mL), dried over $NaSO_4$, and concentrated. The residual oil was chromatographed on 100 g of silica gel to give recovered starting material 8 (0.35 g, 22%) followed by 1.19 g, 76% (98% based on 8 consumed), of the *exo*-borneol-3-hydroxyhexadecanoate as a viscous oil: TLC R_f 0.26; ^1H NMR: δ 0.87 (t, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.22 (br s, 20 H), 1.32 (s, 3 H), 0.75–2.05 (m, 15 H), 2.74 (br s, 1 H), 4.07 (d, J = 8.6 Hz, 1 H), 5.56 (d, J = 8.6 Hz, 1 H), 7.38–7.52 (m, 3 H), 7.65 (d, J = 7.2 Hz, 1 H), 7.70 (d, J = 7.8 Hz, 1 H), 7.81 (d, J = 7.8 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 14.1 (u), 14.7 (u), 20.9 (u), 22.6 (d), 23.8 (d), 23.9 (u),

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(22) "Et_2O-buffer" is the ethyl ether phase of a mixture of 80% ethyl ether, 18% pH 10 aqueous carbonate buffer, and 2% $HNEt_2$.
(23) Natural solenopsin B was prepared from *S. invicta* (= *S. saevissima*) by extraction and catalytic hydrogenation, following ref 2 above. Preparative gas chromatography was carried out on a Varian Model 920, equipped with a 2 m × 5 mm i.d. column packed with 10% SP-1000 on 100/120 Supelcoport. We thank Professor Murray S. Blum for providing the ants.

25.3 (d), 29.2 (d), 29.3 (d), 29.5 (d), 29.6 (d), 31.9 (d), 35.9 (d), 42.0 (d), 42.4 (d), 48.3 (d), 49.3 (d), 51.1 (u), 55.3 (u), 67.5 (u), 79.9 (u), 123.5 (u), 124.6 (u), 125.3 (u), 126.1 (u), 126.7 (u), 127.1 (u), 128.9 (u), 133.0 (d), 133.4 (d), 135.5 (d), 171.1 (d); IR 3588, 3056, 2958, 2930, 2856, 1733, 1724, 1465, 1394, 1175; MS, *m/e* (relative intensity) 534 (M^+, 5), 406 (2), 263 (18), 262 (40), 171 (20), 170 (100), 142 (10), 141 (20), 121 (11); EI exact mass calcd for $C_{36}H_{54}O_3$ 534.4072, obsd 534.4078. This material was a single diastereomer, by ^1H and ^{13}C NMR.

The above alcohol (1.11 g, 2.1 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.237 g, 6.25 mmol) in dry THF (10 mL) at 0 °C. The reaction mixture was allowed to come to room temperature over 1.5 h and then was quenched by sequential addition of H_2O (0.24 mL), 10% NaOH (0.24 mL), and additional H_2O (0.48 mL). The precipitated lithium salts were separated by filtration and washed with ethyl acetate (100 mL). The resulting filtrate was dried over Na_2SO_4 and concentrated. The residual oily solid was chromatographed on 10 g of silica gel to give recovered chiral auxiliary **7** (0.551 g, 94%), and 0.48 g (89%) of diol **9** as a yellow-white "sticky" solid: TLC R_f (60% EtOAc/hexane) = 0.24. Bulb-to-bulb distillation of the chromatographed diol (bath 145 °C, 0.2 mmHg) gave a white wax-like solid: 0.463 g (86% from **8**); $[\alpha]^{22}_D$ +2.53° (*c* 1.7, EtOH); ^1H NMR δ 0.88 (t, *J* = 6.4 Hz, 3 H), 1.27 (br s, 22 H), 1.45 (m, 2 H), 1.68 (m, 2 H), 2.90 (br s, 1 H), 3.04 (br s, 1 H), 3.84 (m, 3 H); ^{13}C NMR δ 14.1 (u), 22.7 (d), 25.5 (d), 29.3 (d), 29.6 (d), 31.9 (d), 37.8 (d), 38.2 (d), 61.7 (d), 72.2 (u); IR 3625, 3428, 2928, 2921, 2857, 1467, 1435, 1379, 1069; MS (CI), *m/e* (relative intensity) 259 (27), 258 (M^+, 13), 242 (30), 241 (100), 211 (18), 139 (14), 125 (24), 111 (41), 109 (19). Anal. Calcd for $C_{16}H_{34}O_2$: C, 74.36; H, 13.26. Found: C, 74.26; H, 13.38.

(−)-(*S*)-Nonadec-1-en-6-ol (4). *p*-Toluenesulfonyl chloride (0.106 g, 0.55 mmol) and 4-(dimethylamino)pyridine (0.081 g, 0.66 mmol) in 1.0 mL of CH_2Cl_2 and diol **9** (0.119 g, 0.46 mmol) in 1.3 mL of CH_2Cl_2 were combined sequentially at −30 °C. The reaction flask was transferred to a 0 °C bath. After 2 h, the bath was removed. After 1 h, the reaction mixture was diluted with hexanes (50 mL). The combined precipitate and supernatant were chromatographed on 5 g of silica gel to give 0.168 g (89%) of the primary monotosylate as a white glass-like solid: TLC R_f (20% EtOAc/hexane) 0.34; ^1H NMR δ 0.87 (t, *J* = 6.4 Hz, 3 H), 1.25 (br s, 22 H), 1.39 (br s, 2 H), 1.65 (m, 1 H), 1.82 (m, 1 H), 1.90 (s, 1 H, dilution dependent), 2.45 (s, 3 H), 3.70 (br s, 1 H), 4.14 (m, 1 H), 4.24 (m, 1 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR δ 14.1 (u), 21.6 (u), 22.7 (d), 25.5 (d), 29.3 (d), 29.6 (d), 31.9 (d), 36.3 (d), 37.5 (d), 67.8 (u), 67.9 (d), 127.9 (u), 129.8 (u), 133.0 (d), 144.8 (d); IR 3629, 3589, 3459, 2957, 2928, 2856, 1371, 1189, 1179, 1099, 970.

Allylmagnesium chloride (2 M) in THF (2.31 mL, 4.61 mmol) (Aldrich) was added dropwise via syringe over 10 min to the monotosylate (0.380 g, 0.921 mmol) in 4.6 mL of THF at 0 °C. After 20 min, the mixture was warmed to reflux for 3 h and then partioned between 10% aqueous HCl and Et_2O. The combined organic phases were washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on 10 g of silica gel to give 0.249 g (96%) of **4** as a white oily solid: TLC R_f 0.38. Bulb-to-bulb distillation of chromatographed **4** (bath 135 °C, 0.2 mmHg) gave a wax-like white amorphous solid: 0.244 g (94% from monotosylate); $[\alpha]^{24}_D$ −1.72° (*c* 0.70, EtOH); ^1H NMR δ 0.89 (t, *J* = 6.4 Hz, 3 H), 1.27 (br s, 22 H), 1.43 (m, 7 H), 2.07 (m, 2 H), 3.59 (m, 1 H), 5.01 (m, 2 H), 5.81 (m, 1 H); ^{13}C NMR δ 14.1 (u), 22.6 (d), 24.9 (d), 25.6 (d), 29.3 (d), 29.6 (d), 29.7 (d), 31.9 (d), 33.7 (d), 36.8 (d), 37.5 (d), 71.8 (u), 114.4 (d), 138.6 (u); IR 3631, 3369, 2951, 2934, 2909, 2859, 1641, 1467, 1459, 1378; MS *m/e* (relative intensity) 282 (M^+, 6), 281 (13), 265 (44), 213 (32), 139 (37), 127 (43), 125 (65), 111 (100). Anal. Calcd for $C_{19}H_{38}O$: C, 80.78; H, 13.56. Found: C, 80.98; H, 13.35.

(*R*)-Nonadec-1-en-6-yl Azide (3). Alcohol **4** (0.231 g, 0.82 mmol) in dry tetrahydrofuran (3.3 mL), triphenylphosphine (0.214 g, 0.82 mmol), and diethyl azodicarboxylate (0.129 mL, 0.82 mmol) were combined sequentially. Diphenyl phosphorazidate[16] (0.176 mL, 0.82 mmol) was added dropwise over a period of 15 min. After 24 h, the mixture was concentrated, and the residue was chromatographed on 10 g of silica gel to give 0.208 g (83%) of **3** as a viscous oil: TLC R_f (20% EtOAc/hexane) 0.82; ^1H NMR δ 0.87 (t, *J* = 6.4 Hz, 3 H), 1.28 (br s, 22 H), 1.50 (m, 6 H), 2.07 (m, 2 H), 3.24 (m, 1 H), 5.01 (m, 2 H), 5.81 (m, 1 H); ^{13}C NMR δ 14.1 (u), 25.3 (d), 26.1 (d), 29.3 (d), 29.4 (d), 29.5 (d), 29.6 (d), 29.7 (d), 31.9 (d), 33.4 (d), 33.8 (d), 34.4 (d), 62.9 (u), 114.8 (d), 138.2 (u); IR 3075, 2952, 2929, 2909, 2852, 2098, 1644, 1480, 1467, 1445; MS, *m/e* (relative intensity) 308 (M^+, 19), 280 (38), 210 (16), 152 (39), 138 (66), 124 (56), 111 (71), 110 (100).

(−)-(*R*,*R*)-*trans*-2-Methyl-6-*n*-tridecylpiperidine (1). Azide **3** (0.548 g, 1.78 mmol) in o-dichlorobenzene solvent (3.6 mL) was magnetically stirred at 165 °C for 2.5 h under an N_2 atmosphere.[8] The reaction mixture was allowed to cool to room temperature before removal of the solvent by bulb-to-bulb distillation (bath 50 °C, 0.5 mmHg). The resulting dark viscous crude concentrate was taken up in 5 mL of THF and added dropwise to a suspension of $LiAlH_4$ (0.473 g, 12.5 mmol) in dry THF (3.5 mL) at −78 °C, followed by dropwise addition of trimethylaluminum (6.24 mL of a 2 M toluene solution, 12.5 mmol). The reaction mixture was maintained at −78 °C for 30 min, at −45 °C for 1 h, at −20 °C for 1 h, and finally at 0 °C for 1 h. While still at 0 °C, the reaction mixture was diluted with Et_2O (20 mL) and treated with solid NaF (2.094 g, 49.9 mmol), followed by the cautious dropwise addition of H_2O (0.67 mL, 37 mmol). After stirring for 15 min, the resulting slurry was filtered through a short pad of Celite that was subsequently washed with Et_2O (100 mL). The combined filtrate and washings were dried (Na_2SO_4), concentrated, and chromatographed on 10 g of silica gel to give 0.357 g (71%) of **1** as a faintly yellow oil: TLC R_f (60% Et_2O-buffer/hexane) 0.27. Bulb-to-bulb distillation of chromatographed **1** (bath 155 °C, 0.2 mmHg) gave a colorless oil: 0.324 g (65% from **3**); $[\alpha]^{23}_D$ −0.51° (*c* 1.97, EtOH); ^1H NMR δ 0.88 (t, *J* = 6.6 Hz, 3 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 1.27 (br s, 22 H), 1.35–1.71 (m, 8 H), 2.05 (br s, 1 H, dilution dependent), 2.88 (m, 1 H), 3.07 (m, 1 H); ^{13}C NMR δ 14.0 (u), 19.4 (d), 21.0 (u), 22.6 (d), 26.3 (d), 29.2 (d), 29.6 (d), 29.7 (d), 30.4 (d), 30.6 (d), 31.8 (d), 32.8 (d), 33.9 (d), 45.7 (u), 50.7 (u); IR: 3301, 2966, 2935, 2861, 2812, 1468, 1443, 1377, 1141; MS(CI), *m/e* (relative intensity) 282 (M + H, 29), 281 (71), 280 (24), 268 (29), 267 (76), 266 (100), 124 (29), 110 (47). Anal. Calcd for $C_{19}H_{39}N$: C, 81.06; H, 13.96. Found: C, 81.35; H, 13.52.

HPLC Analysis of 1. HPLC (at the NIH) was carried out on a Nova-Pak C_{18}, 5 mm × 10 cm column packed with 4-μm particles, eluting with 85:15 CH_3CN/H_2O at 1 mL/min. Detection was by UV at 254 nm. Samples were prepared by mixing 70 μL of a 5 mg/mL solution of tetraacetyl-β-D-glucopyranosyl isothiocyanate (Polysciences)[19] in CH_3CN with 50 μL of 5 mg/mL of the alkaloid in CH_3CN, followed by immediate injection. Under these conditions, racemic **1** gave two peaks, at retention volumes of 18.75 and 19.0 mL, respectively. Both natural[23] solenopsin B (**1**) and the synthetic (*R*,*R*)-**1** gave only the first peak.

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