1.6, 7.3), 3.10 (br s, 1), 3.30–3.50 (br s, 1), 3.51 (dd, 1, J = 1.6, 9.1), 4.01 (s, 1). ^{13}C NMR (75 MHz, C_6D_6): δ 9.7, 18.9, 19.5, 26.3, 30.7, 36.0, 45.7, 75.4, 82.3, 220.0.

(1*R*,2*R*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (20d). ^{1}H NMR (300 MHz): δ 0.94 (s, 9), 1.09 (d, 3, J = 7.2), 3.14–3.25 (br m, 2), 3.25–3.38 (br s, 1), 3.93 (s, 1), 5.11 (d, 1, J = 3.8), 7.25–7.40 (m, 5). ^{13}C NMR (75 MHz): δ 11.2, 26.2, 36.0, 50.8, 72.5, 82.4, 126.1, 127.6, 128.2, 141.2, 218.6.

(3*S*,5*S*,6*S*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (21b). ^{1}H NMR (400 MHz): δ 0.88 (d, 3, J = 6.8), 0.93 (d, 3, J = 6.8), 0.95 (s, 9), 0.97 (d, 3, J = 6.9), 1.82 (double septet, 1, J = 6.9, 2.1), 2.93–2.94 (m, 1), 3.29–3.36 (m, 1), 3.49–3.53 (m, 1), 3.67 (d, 1, J = 2.3), 4.49 (br s, 1). ^{13}C NMR (100 MHz): δ 12.46, 14.47, 19.78, 26.38, 29.95, 35.89, 47.26, 80.34, 85.58, 218.1.

(1*S*,2*R*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (21d). ^{1}H NMR (250 MHz): δ 0.76 (d, 3, J = 6.9), 0.96 (s, 9), 3.38 (d, 1, J = 2.8), 3.42–3.52 (m, 1), 3.72 (d, 1, J = 2.6), 4.53 (d, 1, J = 2.7), 4.55 (d, 1, J = 2.7), 7.35–7.36 (m, 5). ^{13}C NMR (75 MHz): δ 13.37, 26.15, 35.27, 48.31, 78.62, 84.70, 126.86, 128.36, 128.54, 141.75, 217.70.

(3*S*,5*S*,6*S*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (22b). ^{1}H NMR (400 MHz): δ 0.88 (d, 3, J = 6.7), 0.96 (d, 3, J = 6.9), 0.99 (s, 9), 1.01 (d, 3, J = 6.8), 1.77 (dq, 1, J = 3.5, 6.9), 2.28–2.30 (m, 1), 3.04 (d pent, 1, J = 1.7, 6.8), 3.41 (d, 1, J = 7.1), 3.43–3.47 (m, 1), 4.04 (dd, 1, J = 1.2, 7.1). ^{13}C NMR (100 MHz): δ 12.50, 14.53, 19.77, 26.39, 29.99, 35.91, 47.19, 80.41, 85.61.

(1*R*,2*S*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (22d). ^{1}H NMR (300 MHz): δ 0.87 (d, 3, J = 6.7), 0.99 (s, 9), 2.62 (br s, 1), 3.17 (dq, 1, J = 8.8, 6.7), 3.19 (d, 1, J = 2.0), 4.06 (s, 1), 4.59 (d, 1, J = 8.8), 7.30–7.35 (m, 5). ^{13}C NMR (75 MHz): δ 12.78, 26.38, 35.89, 51.40, 79.27, 85.80, 126.57, 128.32, 128.57, 142.09, 218.2.

(−)-(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic Acid (23b). $[\alpha]_D$: −9.5° (c = 0.4, H_2Cl22). Th ^{1}H NMR spectrum of this material was identical to that reported.[26] ^{13}C NMR (50 MHz): δ 14.59, 16.09, 19.75, 30.67, 42.65, 78.04, 180.96.

(−)-(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (23d). $[\alpha]_D$: −29.3° (c = 0.8, $CHCl_3$). [lit. $[\alpha]_D$ −29.5° (c = 2.03, $CHCl_3$)].[27] ^{1}H NMR (400 MHz): δ 1.16 (d, 3, J = 7.2), 2.85 (dq, 1, J = 3.9, 7.2), 5.19 (d, 1, J = 3.9), 7.27–7.37 (m, 5). ^{13}C NMR (100 MHz): δ 10.27, 46.16, 73.37, 125.93, 127.66, 128.35, 141.01, 180.85.

(+)-(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoic Acid (24b). $[\alpha]_D$ +9.1° (c = 2.2, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of this material were identical with those obtained for its enantiomer, **23b**.

(+)-(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (24d). $[\alpha]_D$: +28.5° (c = 1.2, $CHCl_3$). [lit. $[\alpha]_D$ +29.5° (c = 1.27, $CHCl_3$)].[26] The ^{1}H and ^{13}C NMR spectra were identical with those of its enantiomer, **23d**.

(−)-(2*R*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic Acid (25b). $[\alpha]_D$: −14.3° (c = 1.0, $CHCl_3$). The ^{1}H NMR spectrum of this material was identical with that reported.[18] ^{13}C NMR (50 MHz): δ 9.69, 18.72, 19.02, 30.62, 41.77, 76.93, 181.27.

(−)-(2*R*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (25d). $[\alpha]_D$: −17.5° (c = 2.3, $CHCl_3$). ^{1}H NMR (400 MHz): δ 1.00 (d, 3, J = 7.2), 2.84 (dq, 1, J = 7.2, 9.0), 4.75 (d, 1, J = 9.0), 5.70–6.10 (br s, 1), 7.29–7.39 (m, 5). ^{13}C NMR (100 MHz): δ 14.40, 47.20, 76.60, 126.84, 128.40, 128.80, 141.16, 180.72. Compound **25d** was identified by comparison of its ^{1}H NMR spectrum with that reported.[28]

(+)-(2*S*,3*S*)-3-Hydroxy-2,4-dimethylpentanoic Acid (26b). $[\alpha]_D$: +14.1° (c = 1.1, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of this material were identical with those obtained for the enantiomer, **25b**.

(+)-(2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (26d). $[\alpha]_D$: +17.8° (c = 2.0, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were identical with those of the enantiomer, **25d**.

Acknowledgment. This work was supported by a research grant from the U.S. Public Health Service (AI 15027). The Glaxo Corporation is thanked for providing support in the form of supplies.

Supplementary Material Available: Figures 2 and 3 (ORTEP drawings of keto diols **19** and **21**) and ^{1}H and ^{13}C NMR spectra of keto diols **19b**, **19d**, **20b**, **20d**, **21b**, **21d**, **22b**, and **22d** (17 pages). Ordering information is given on any current masthead page.

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Stereocontrolled Preparation of *cis*- and *trans*-2,6-Dialkylpiperidines via 1-Acyldihydropyridine Intermediates. Synthesis of (±)-Solenopsin A and (±)-Dihydropinidine

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Received September 18, 1990

The stereoselective reduction of 1-(*tert*-butoxycarbonyl)-4-chloro-2,6-dialkyl-1,2-dihydropyridines **6** and **22** was studied. Reduction of **6** with Et_3SiH/TFA gave the *cis*-2,6-dialkyl-1,2,5,6-tetrahydropyridine **7** as the major product. The stereoselectivity was reversed by reducing **6** with $NaBH_3CN$/TFA, which gave predominantly the *trans*-2,6-dialkyltetrahydropyridine **10**. Catalytic hydrogenation of **7** and **10** gave the corresponding *N*-Boc-*cis*(or *trans*)-2,6-dialkylpiperidines. Regioselective hydrogenation of **6** gave the 1,2,3,4-tetrahydropyridine **18**, which on treatment with $NaBH_3CN$/TFA provided a 90:10 mixture of *trans*- and *cis*-piperidines **15** and **16**. More vigorous hydrogenation of **6** afforded the *cis*-piperidine **15** with 96% stereoselectivity. Similar stereoselective reductions of dihydropyridine **22** were carried out. Stereoselective reductions of dihydropyridines **6** and **22** were utilized in the synthesis of (±)-solenopsin A and (±)-dihydropinidine from 4-chloropyridine in six and five steps, respectively.

Alkaloids containing a 2,6-disubstituted piperidine ring are abundant in nature and many exhibit significant biological activity.[2] Numerous cis-2,6-disubstituted piperidines can be stereoselectively prepared by simple reduction

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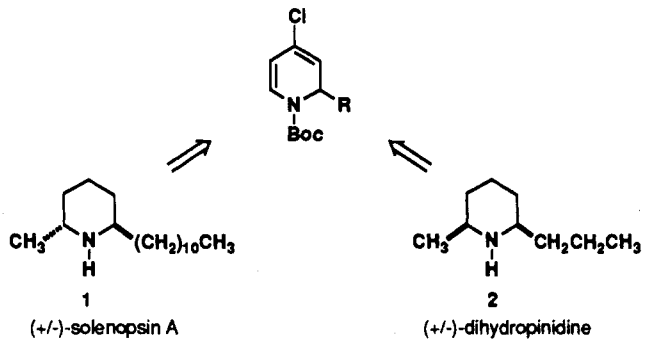
of substituted pyridine derivatives or by various intramolecular cyclizations, although frequently mixtures of cis and trans isomers result.[2] Stereoselective syntheses of trans-2,6-disubstituted piperidines are generally more difficult and include the hydride reduction of cyclic imines,[3] alkene nitrone cycloadditions,[4] alkylation and reduction of cyanopiperidines[5] or bicyclic carbamates,[6] the imine–epoxide rearrangement,[7] and the alkylation of α-lithiated piperidine derivatives.[8] As part of a program directed at developing the utility of 1-acyldihydropyridines as synthetic intermediates,[9] we investigated a strategy for the selective preparation of cis- and trans-2,6-disubstituted piperidines from a common 1-acyl-2-alkyl-1,2-dihydropyridine intermediate.[10] We chose the well-characterized alkaloids (±)-solenopsin A (**1**)[2] and (±)-dihydropinidine (**2**)[2] as targets for this study. In this paper we report the development of methodology that allows the stereoselective preparation of cis- or trans-2,6-disubstituted piperidines from readily prepared 1-acyl-1,2-dihydropyridine intermediates.



1 (+/-)-solenopsin A **2** (+/-)-dihydropinidine

Results and Discussion

Our approach to the *trans*-2,6-dialkylpiperidine (±)-solenopsin A utilized 4-chloropyridine as starting material (Scheme I). Recent work from our laboratories has shown that the addition of Grignard reagents to the 1-phenoxycarbonyl salt of 4-chloropyridine gives 1-acyl-1,2-dihydropyridines in good to excellent yield.[11] A mixture of 4-chloropyridine (**3**) and undecylmagnesium bromide in tetrahydrofuran (THF) at −78 °C was treated with phenyl chloroformate to give the 1,2-dihydropyridine **4**. Crude **4** was converted to the *N*-Boc derivative **5** with potassium *tert*-butoxide in THF in 86% overall yield from **3**. A methyl group was introduced at C6, using directed-lithiation methodology.[11a] Treatment of **5** with *n*-butyllithium

Scheme I

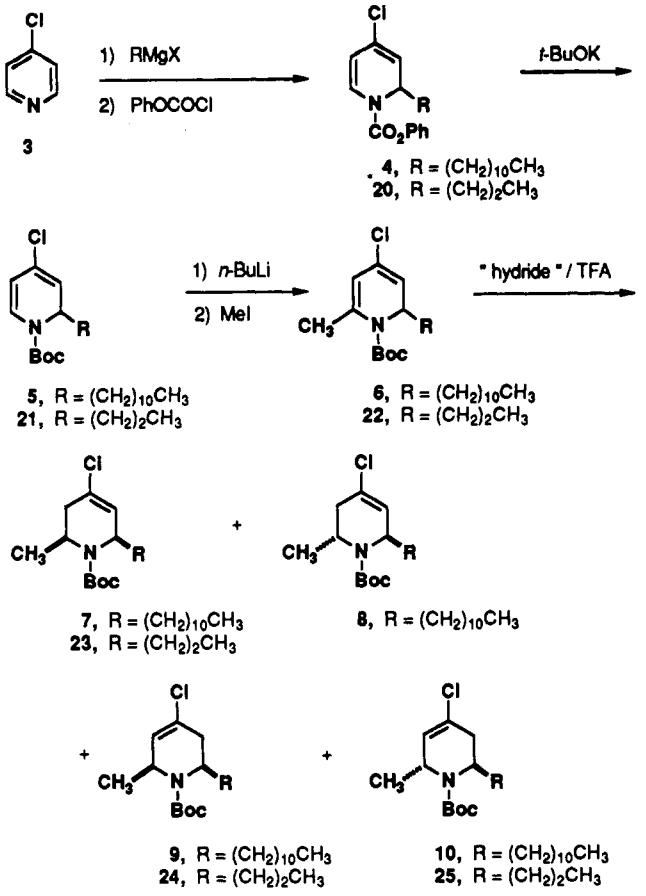


Table I. Stereoselective Reduction of Dihydropyridine 6

entry[a]	reducing agent[b]	conditions	yield,[c] %	ratio[d] 7:8:9:10
a	Et_3SiH	10.0 TFA, −42 °C CH_2Cl_2, 4 h	79	75:0:10:15
b	n-Pr_3SiH	10.0 TFA, −42 °C CH_2Cl_2, 4 h	95[e]	78:0:9:13
c	$NaBH_3CN$	10.0 TFA, −42 °C CH_2Cl_2, 4 h	55	12:4:7:77

[a] Reactions were generally performed on a 0.2–1.0-mmol scale. [b] Six equiv. of reducing agent were used. [c] Yield of isolated products **7**, **8**, **9**, and **10** obtained from MPLC. [d] Ratio determined by GC. [e] Yield of crude reaction product.

and methyl iodide gave an 83% yield of dihydropyridine **6**. At this point the synthetic strategy called for stereoselective reduction of the C5–C6 double bond in **6**. Reaction of **6** with trialkylsilane/trifluoroacetic acid (TFA)[11a] or $NaBH_3CN$/TFA gave a crude product mixture that was analyzed (GC) for compounds **7**–**10**. As is shown in Table I, the major product from the triethylsilane reduction was the *cis*-tetrahydropyridine **7**. Interestingly, minor products (**9** and **10**) derived from double-bond migration were present as well. Use of the slightly larger tri-*n*-propylsilane effected a minor increase in the cis product **7**. *Remarkably, the analogous reduction using sodium cyanoborohydride*

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(10) Yamaguchi and co-workers have carried out a similar strategy preparing both *cis*- and *trans*-2-methyl-6-octylpiperidine selectively from a common 2,6-disubstituted 1,2-dihydropyridine. Nakazono, Y.; Yamaguchi, R.; Kawanisi, M. *Chem. Lett.* **1984**, 1129. Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawansi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215.

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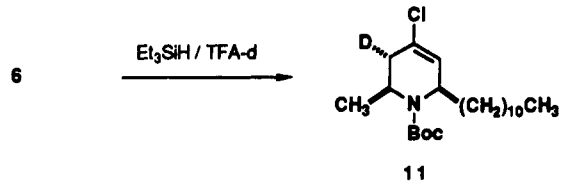
as the reducing agent gave a reversal in stereoselectivity with double-bond migration, producing the trans-tetrahydropyridine 10 as the major product.

The reduction of **6** with triethylsilane and deuterated TFA (TFA-*d*) gave C5-deuterated tetrahydropyridine **11** as the major product, indicating that *N*-acyliminium ion **12** is the reactive intermediate in the formation of **7** from **6** and triethylsilane/TFA. The analogous reaction using



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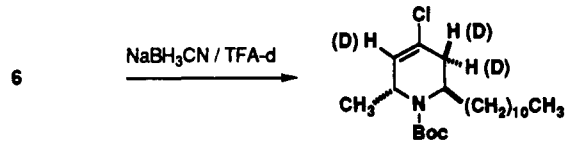

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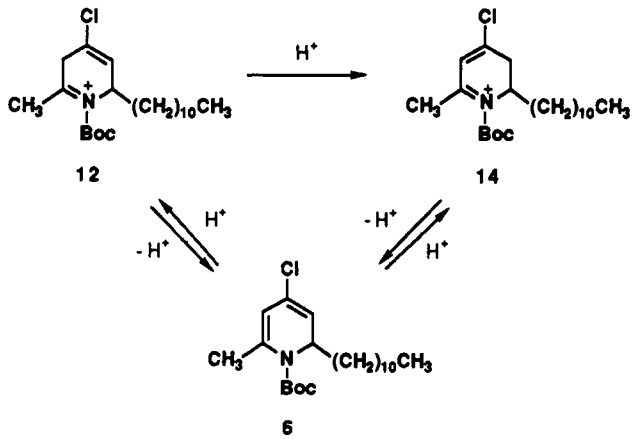
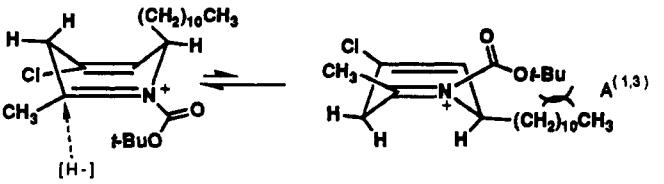
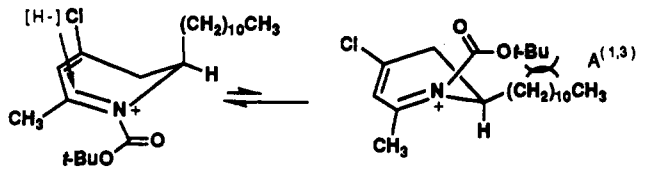
$NaBH_3CN$ and deuterated TFA gave **13** as the major product, which had partial deuterium incorporation at C3 and C5. This result suggests that *N*-acyliminium ion **14** is the reactive species in this reduction *and ion 12 is not readily reduced by $NaBH_3CN$.* *N*-Acyliminium ion **12** is undoubtedly present in situ, but in the presence of $NaBH_3CN$ it may revert back to dihydropyridine **6** at a faster rate than reduction, or a rapid acid-catalyzed double-bond migration[12] may occur to give **14** directly from **12**.

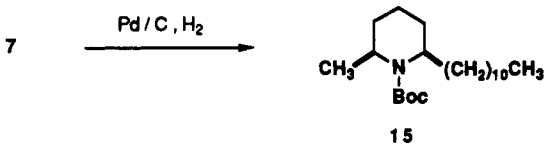


The stereochemical outcome of these reductions can be explained in the following manner. *N*-Acyliminium ion **12** must exist in a boat conformation. Of the two possible boats **12a** and **12b**, **12a** is of much lower energy due to the additional $A^{(1,3)}$ strain[13] present in conformation **12b**. "Bottom side" attack of hydride on acyliminium ion **12a** leads to the observed *cis*-tetrahydropyridine **7**. The *N*-acyliminium ion **14** exists as a flat chair with the 2-substituent in the axial orientation due to $A^{(1,3)}$ strain. Stereoelectronically preferred[14] axial attack of hydride at C6 of **14a** leads to the observed *trans*-tetrahydropyridine **10** as the major product.[15]





The tetrahydropyridine **7** was reduced by catalytic hydrogenation to give carbamate **15**. The cis product **15** could be prepared more conveniently by catalytic reduction of dihydropyridine **6**, which gave a 98:2 mixture of cis and trans isomers **15** and **16**.[16] Removal of the Boc protecting



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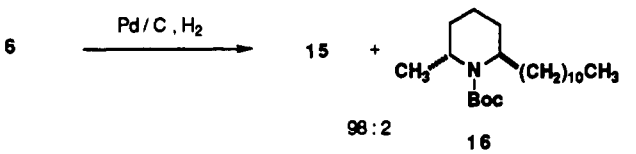

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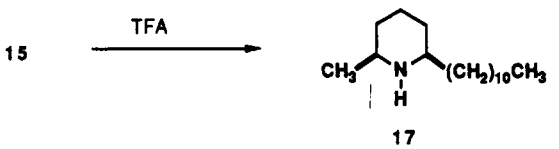
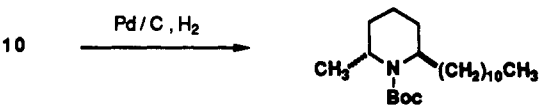


17

group with TFA gave the *cis*-2,6-dialkylpiperidine **17** in good yield. Likewise, the *trans*-tetrahydropyridine **10** was reduced to give the *trans*-*N*-Boc-piperidine **16**, which was treated with TFA to afford (±)-solenopsin A (**1**).



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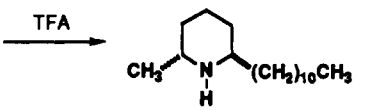

1
(+/-)-solenopsin A

An alternative synthesis of **1** was devised that proved to be more convenient and gave a higher overall yield of

(12) A similar acid-catalyzed rearrangement of an analogous *N*-alkyliminium ion has been proposed. Fry, E. M. *J. Org. Chem.* **1964**, *29*, 1647.

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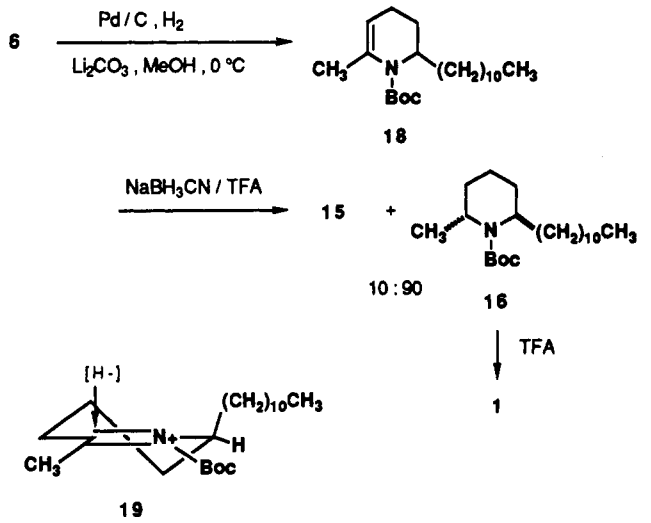
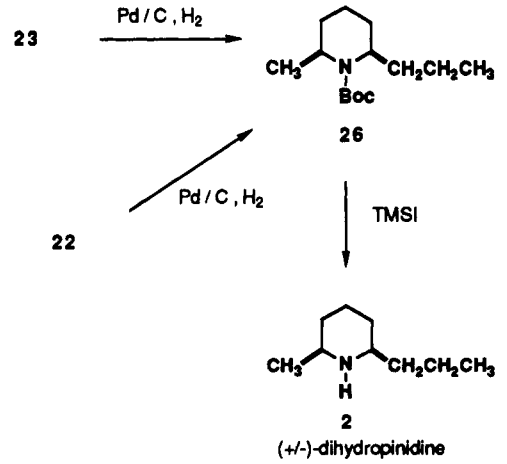
(16) Yamaguchi and co-workers have reduced an *N*-(methoxycarbonyl)-6-methyl-2-alkynyl-1,2-dihydropyridine to a *cis*-*N*-(methoxycarbonyl)-2,6-dialkylpiperidine in two steps using catalytic hydrogenation. See ref 10.

the target compound. Dihydropyridine **6** was partially reduced to tetrahydropyridine **18** in 76% yield. When **18** was subjected to $NaBH_3CN$/TFA reduction, a 90:10 mixture of trans to cis products (**16** and **15**) resulted. The trans stereochemistry results from stereoelectronically preferred[14] axial attack of hydride on the chair iminium ion **19**, which contains the undecyl group in the axial orientation due to $A^{(1,3)}$ strain.[13,15] With use of this route, (±)-solenopsin A (**1**) was prepared in six steps from 4-chloropyridine with an overall yield of 35%.



The *cis*-2,6-dialkylpiperidine (±)-dihydropinidine (**2**) was prepared in a similar manner to the preparation of **17**. A mixture of 4-chloropyridine (**3**) and *n*-propylmagnesium chloride in THF at −78 °C was treated with phenyl chloroformate to give the 1,2-dihydropyridine **20**. Crude **20** was converted to the *N*-Boc derivative **21** with potassium *tert*-butoxide in 93% overall yield from **3**. A methyl group was introduced at C6 in 84% yield via directed lithiation to give **22**. Reduction of **22** with tri-*n*-propylsilane/TFA gave tetrahydropyridines **23**, **24**, and **25** in a ratio of 80/8/12.[17] The *cis*-tetrahydropyridine **23** was isolated from this mixture by chromatography in 72% yield. Catalytic hydrogenation of **23** gave carbamate **26**, which on treatment with TMSI afforded (±)-dihydropinidine (**2**) in 58% yield for the two steps. Alternatively, dihydropyridine **22** could be hydrogenated with 96% stereoselectivity to give *cis*-piperidine derivative **26** in 69% yield.



In summary, the combination of directed lithiation/alkylation of 2-alkyl-*N*-Boc-4-chloro-1,2-dihydropyridines and subsequent reduction with tri-*n*-propylsilane/TFA, $NaBH_3CN$/TFA, or H_2, Pd/C is effective for the preparation of *cis*- or *trans*-2,6-dialkylpiperidine derivatives. The versatility of this strategy was demonstrated by the synthesis of (±)-solenopsin A[18] and (±)-dihydropinidine[19] from 4-chloropyridine in six and five steps, respectively.

Experimental Section

Reactions were performed in oven-dried glassware under an atmosphere of dry argon and were magnetically stirred. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl under nitrogen immediately prior to use. Other solvents were dried over 3-Å or 4-Å molecular sieves prior to use. Radial preparative-layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2, or 4 mm thicknesses of Kieselgel 60 PF_{254} containing gypsum.

4-Chloro-1-(phenoxycarbonyl)-2-*n*-undecyl-1,2-dihydropyridine (4). To a stirred mixture of magnesium turnings (292 mg, 12.0 mmol) in 20 mL of anhydrous diethyl ether was added 1-bromoundecane (2.68 mL, 12.0 mmol). After an initial self-sustained reflux period of 10 min, the solution was refluxed an additional 45 min and then allowed to cool to room temperature. The newly formed Grignard reagent was transferred dropwise via a double-tipped needle into a stirred solution of 4-chloropyridine (0.946 mL, 10.0 mmol) in 80 mL of THF at −78 °C. After 20 min, phenyl chloroformate (1.26 mL, 10.0 mmol) was added dropwise. Stirring was continued for 30 min at −78 °C. The cooling bath was removed and the reaction mixture was allowed to stir for 30 min longer while being slowly warmed to room temperature. Aqueous 20% NH_4Cl (30 mL) and ether (40 mL) were added, the layers were separated, and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic extracts were washed successively with 25-mL portions of saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to give 4.053 g (quantitative) of the crude 1,2-dihydropyridine **4** as a clear yellow oil (This crude material was used directly in the next step to make the *N*-Boc derivative.): ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.10 (m, 5 H), 6.95–6.85 (pair of d due to rotamers, 1 H, J = 7.8 Hz), 5.68 (d, 1 H, J = 6.3 Hz), 5.40–5.28 (pair of dd due to rotamers, 1 H, J = 7.8 Hz and J = 2.0 Hz), 5.00–4.85 (pair of m due to rotamers, 1 H), 1.80–1.40 (m, 2 H), 1.25 (br s, 18 H), 0.88 (t, 3 H, J = 6.8 Hz); FT-IR (neat) 2954, 2923, 2852, 1735, 1635, 1592, 1495, 1471, 1332, 1202, 1050 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-4-chloro-2-*n*-undecyl-1,2-dihydropyridine (5). To a stirred solution of crude dihydropyridine **4** (4.053 g, 10.39 mmol) in 120 mL of THF at −42 °C was added dropwise over 15 min a solution of potassium *tert*-butoxide (4.60 g, 41.0 mmol) in 50 mL of THF. The resulting orange solution was stirred for 1 h at −42 °C (complete reaction verified by TLC). The cooling bath was removed and the reaction mixture was allowed to stir for 20 min while being slowly warmed to room temperature. Water (30 mL) and ether (60 mL) were added, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic extracts were washed with cold 1 N NaOH (2 × 25 mL), water (2 × 25 mL), and brine. The organic phase was dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to give the crude product. Purification by radial PLC (silica gel, 5% EtOAc/hexanes) gave 3.20 g (86%) of **5** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.90–6.60 (pair of br d due to rotamers, 1 H, J = 7.5 Hz), 5.55 (br s, 1 H), 5.25–5.10 (pair of br d due to rotamers, 1 H, J = 7.5 Hz), 4.85–4.60 (pair of br m due

(17) The analogous reduction using triethylsilane/TFA gave **23**, **24**, and **25** in a ratio of 77/9/14.

(18) For previous syntheses of solenopsin A, see: (a) Mundy, B. P.; Bjorklund, M. *Tetrahedron Lett.* **1985**, 3899. (b) Wasserman, H. H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977. (c) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491. (d) Nagasaka, T.; Hagashi, H.; Kumakawa, M.; Sakamoto, M. *Heterocycles* **1989**, *29*, 2157 and references therein.

(19) For previous syntheses of dihydropinidine, see: (a) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569 and references therein. (b) Astier, A.; Plat, M. M. *Tetrahedron Lett.* **1978**, 2051. (c) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369. Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

to rotamers, 1 H), 1.50 (s, 9 H), 1.25 (br s, 20 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 and 151.8 (due to rotamers), 127.7 and 127.5 (due to rotamers), 127.5 and 126.7 (due to rotamers), 117.8 and 117.4 (due to rotamers), 106.6 and 106.2 (due to rotamers), 81.7, 54.1 and 53.2 (due to rotamers), 34.3 and 33.8 (due to rotamers), 31.9, 29.69, 29.62, 29.57, 29.54, 29.50, 29.32, 28.1, 24.3, 22.7, 14.1; FT-IR (neat) 2955, 2926, 2854, 1718, 1633, 1369, 1388, 1171, 1127 1052 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-4-chloro-6-methyl-2-*n*-undecyl-1,2-dihydropyridine (6). To a stirred solution of dihydropyridine **5** (3.20 g, 8.64 mmol) in 120 mL of THF at −42 °C was added 3.91 mL (10.33 mmol, 2.65 M solution in hexane) of *n*-butyllithium dropwise via syringe. After the mixture had stirred at −42 °C for 1 h, iodomethane (1.61 mL, 25.92 mmol) was added and stirring was continued at −42 °C for 1 h and then at room temperature for 1 h. Water (30 mL) and ether (60 mL) were added, the layers were separated, the aqueous phase was extracted with ether (2 × 10 mL), and the combined organic extracts were washed with brine. The organic phase was dried over K_2CO_3, filtered through silica gel/Celite, and concentrated in vacuo to give the crude product. Purification by radial PLC (silica gel, 5% EtOAc/hexanes) gave 2.74 g (83%) of **6** as a clear, light orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dd, 1 H, J = 6.6 Hz and J = 1.5 Hz), 5.32 (m, 1 H, J = 1.5 Hz), 4.76 (dt, 1 H, J = 7.3 Hz and J = 6.6 Hz), 2.14 (s, 3 H), 1.50 (s, 9 H), 1.48–1.40 (m, 2 H), 1.26 (br s, 18 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 137.0, 126.6, 119.4, 112.3, 81.4, 54.2, 31.9, 31.8, 29.69, 29.63, 29.55, 29.44, 29.36, 29.33, 28.2, 24.6, 22.7, 22.0, 14.1; FT-IR (neat) 2954, 2923, 2852, 1709, 1637, 1471, 1393, 1368, 1342, 1169, 1131 cm^{-1}. Anal. Calcd for $C_{22}H_{38}ClNO_2$: C, 68.81; H, 9.98; N, 3.65. Found: C, 69.09; H, 10.16; N, 3.27.

1-(*tert*-Butoxycarbonyl)-4-chloro-*cis*-6-methyl-2-*n*-undecyl-1,2,5,6-tetrahydropyridine (7). To a stirred solution of dihydropyridine **6** (100.6 mg, 0.262 mmol) in CH_2Cl_2 (10 mL) at −42 °C was added dropwise 0.25 mL (1.57 mmol) of triethylsilane followed by 0.202 mL (2.62 mmol) of trifluoroacetic acid. After stirring for 4 h at −42 °C, the cold bath was removed, and the reaction was immediately quenched with 10 mL of a saturated aqueous $NaHCO_3$/THF mixture (50:50). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were washed with water (10 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product as a mixture of 75% cis isomer **7**, 15% trans isomer **10**, and 10% cis isomer **9** as determined by capillary GC and GC/MS analysis. Purification by radial PLC (silica gel, 5% EtOAc/hexanes) gave 79.5 mg (79%) of a colorless oil consisting of the three isomers in approximately the same ratio as found in the crude product. Isomer **7** had the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1 H), 4.67 (m, 1 H), 4.28 (m, 1 H), 2.80–2.65 (dm, 1 H, J = 16.9 Hz), 2.05 (d, 1 H, J = 16.9 Hz), 1.60–1.45 (m, 2 H), 1.47 (s, 9 H), 1.26 (br s, 18 H), 1.21 (d, 3 H, J = 6.6 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 127.5, 123.2, 79.7, 53.0, 44.4, 37.9, 36.3, 31.9, 29.6, 29.5, 29.3, 28.4, 26.9, 22.7, 21.0, 14.1; FT-IR (neat) 2927, 2855, 1697, 1458, 1406, 1392, 1366, 1343, 1177, 1104, 1070 cm^{-1}. Anal. Calcd for $C_{22}H_{40}ClNO_2$: C, 68.45; H, 10.44; N, 3.63. Found: C, 68.23; H, 10.22; N, 3.58.

1-(*tert*-Butoxycarbonyl)-4-chloro-*trans*-2-methyl-6-*n*-undecyl-1,2,5,6-tetrahydropyridine (10). To a stirred solution of dihydropyridine **6** (402 mg, 1.047 mmol) in CH_2Cl_2 (50 mL) was added 395 mg (6.282 mmol) of sodium cyanoborohydride. After being stirred for 15 min at room temperature, the heterogeneous solution was cooled to −42 °C, and trifluoroacetic acid (0.81 mL, 10.47 mmol) was added dropwise. After stirring for 4 h at −42 °C, the cold bath was removed, and the reaction mixture was immediately quenched with 40 mL of a saturated aqueous $NaHCO_3$/THF mixture (50:50). The aqueous phase was exatracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were washed with water (20 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product as a mixture of 77% trans isomer **10**, 12% cis isomer **7**, 7% cis isomer **9**, and 4% trans isomer **8** as determined by capillary GC and GC/MS analysis. Purification by MPLC (silica gel, 2% EtOAc/hexanes) gave 170.5 mg (combined mass) of isomers **10**, **9**, **8** (not completely separated), and 53 mg of **7** (223.5 mg total mass, 55%). Isomer **10** had the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dd, 1 H, J = 5.1 Hz and J = 2.2 Hz), 4.24 (m, 1 H), 4.01 (br m, 1 H), 2.75–2.60 (dm, 1 H, J = 16.9 Hz), 2.29 (dd, 1 H, J = 16.9 Hz and J = 2.9 Hz), 1.60–1.45 (m, 2 H), 1.47 (s, 9 H) 1.31 (d, 3 H, J = 6.6 Hz), 1.26 (br s, 18 H), 0.88 (t, 3 H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 128.0, 127.1, 79.7, 52.9, 49.4, 35.5, 33.2, 31.9, 29.6, 29.4, 29.3, 28.4, 27.0, 22.6, 21.3, 14.1; IR (neat) 2920, 2845, 1695, 1460, 1365, 1315, 1250, 1165, 1125, 1085, 1050 cm^{-1}; HRMS calcd for $C_{22}H_{40}ClNO_2$ 385.2748, found 385.2746.

1-(*tert*-Butoxycarbonyl)-*cis*-2-methyl-6-*n*-undecylpiperidine (15) from 1,2,5,6-Tetrahydropyridine 7. Into an oven-dried, argon-flushed, 500-mL Parr bottle was placed an absolute ethanol solution (20 mL) of 1,2,5,6-tetrahydropyridine **7** (119.1 mg, 0.309 mmol). To the solution was added 120 mg of lithium carbonate and 120 mg of 5% Pd/C. The mixture was placed on a Parr hydrogenation apparatus and shaken for 12 h under 40 psi of hydrogen gas. The mixture was filtered through Celite and concentrated on a rotary evaporator. The residue was dissolved in ether (20 mL), water (10 mL) was added, the aqueous phase was extracted with ether (2 × 5 mL), and the combined ether extracts were washed with 1 N NaOH (2 × 10 mL) and brine. The organic phase was dried over $MgSO_4$, filtered through silica gel/Celite, and concentrated in vacuo to give the crude product. Kugelrohr distillation (0.25 mmHg, 170–185 °C) gave 91 mg (83%) of **15** as a colorless oil.

Preparation of 15 from 1,2-Dihydropyridine 6. Into an oven-dried, argon-flushed, 100-mL round-bottom flask was placed an absolute ethanol solution (20 mL) of 1,2-dihydropyridine **6** (264.5 mg, 0.687 mmol). To the solution was added 250 mg of lithium carbonate and 250 mg of 5% Pd/C. The mixture was placed under a positive pressure of hydrogen gas from a balloon and stirred for 12 h at room temperature. The mixture was filtered through Celite and concentrated on a rotary evaporator. The residue was dissolved in ether (20 mL), water (10 mL) was added, the aqueous phase was extracted with ether (2 × 5 mL), and the combined ether extracts were washed with 1 N NaOH (2 × 10 mL) and brine. The organic phase was dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to give the crude product as a mixture of 98% cis isomer **15** and 2% trans isomer **16** as determined by capillary GC analysis. Purification by MPLC (silica gel, 5% EtOAc/hexanes) gave 201 mg (83%) of **15** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.22 (m, 1 H), 4.08–3.98 (m, 1 H), 1.70–1.30 (m, 8 H), 1.46 (s, 9 H), 1.26 (br s, 18 H), 1.15 (d, 3 H, J = 6.9 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 78.7, 50.3, 45.5, 35.1, 31.9, 30.3, 29.70, 29.66, 29.62, 29.60, 29.56, 29.3, 28.5, 27.6, 27.5, 22.6, 20.3, 14.1; FT-IR (neat) 2927, 2855, 1690, 1467, 1403, 1365, 1179, 1100, 1081 cm^{-1}. Anal. Calcd for $C_{22}H_{43}NO_2$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.99, H, 12.14; N, 3.82.

(±)-*epi*-Solenopsin A. *cis*-2-Methyl-6-*n*-undecylpiperidine (17). To a stirred solution of 192.5 mg (0.544 mmol) of Boc-piperidine **15** in 20 mL of CH_2Cl_2 at 0 °C was added dropwise 5 mL (excess) of trifluoroacetic acid. The cooling bath was removed, and stirring was continued for 1 h at room temperature. After concentrating the resulting solution on a rotary evaporator, the remaining liquid was dissolved in ether (20 mL), water (10 mL) was added, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product. Purification by MPLC (silica gel, Et_2O/1% i-$PrNH_2$) gave 111.5 mg (81%) of **17** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.56 (m, 1 H), 2.53–2.42 (m, 1 H), 1.81–0.94 (m, 9 H), 1.25 (br s, 18 H), 1.06 (d, 3 H, J = 6.3 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.0, 52.4, 37.4, 34.4, 32.2, 31.8, 29.76, 29.61, 29.57, 29.54, 29.52, 29.3, 25.9, 24.8, 23.0, 22.6, 14.0; FT-IR (neat) 3273 (weak), 2955, 2925, 2854, 2799, 2711, 1466, 1441, 1377, 1322, 1129 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-6-methyl-2-*n*-undecyl-1,2,3,4-tetrahydropyridine (18). To a stirred solution of 740 mg (1.93 mmol) of 1,2-dihydropyridine **6** in 40 mL of MeOH at 0 °C was added 143 mg (1.93 mmol) of lithium carbonate followed by 148 mg (20 wt %) of 5% Pd/C. The mixture was placed under a positive pressure of hydrogen gas from a balloon, and the reaction progress was monitored by removing aliquots (0.10 mL) with a syringe, concentrating the aliquot in vacuo, and examining its ^{1}H

NMR spectrum. (Under these conditions the reaction was complete in approximately 60 min.) Upon completion, the mixture was filtered through Celite and concentrated on a rotary evaporator. The residue was dissolved in ether (20 mL), water (10 mL) was added, the aqueous phase was extracted with ether (2 × 5 mL), and the combined ether extracts were washed with 1 N NaOH (2 × 10 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product. Purification by radial PLC (silica gel, 5% EtOAc/hexanes/1% TEA) gave 515 mg (76%) of **18** as a clear, light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (br s, 1 H), 4.39–4.31 (m, 1 H), 2.02 (m, 3 H), 1.99 (m, 2 H), 1.70 (m, 2 H), 1.48 (s, 9 H), 1.25 (br s, 20 H), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 132.6, 111.0, 80.0, 51.9, 31.9, 29.65, 29.62, 29.59, 29.57, 29.52, 29.33, 28.4, 26.4, 25.8, 23.1, 22.7, 19.5, 14.1; ^{1}H NMR (300 MHz, C_6D_6) δ 4.73 (br s, 1 H), 4.62 (m, 1 H), 2.21 (s, 3 H), 1.90–1.60 (m, 4 H), 1.45 (s, 9 H), 1.30 (br s, 20 H), 0.92 (t, 3 H, J = 6.5 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 153.7, 133.4, 110.3, 79.6, 52.1, 32.3, 30.1, 30.0, 29.8, 28.4, 26.9, 26.2, 23.7, 23.1, 19.8, 14.4; FT-IR (neat) 2927, 2855, 1697, 1660, 1456, 1367, 1351, 1170, 1127, 1096, 1073 cm^{-1}. Anal. Calcd for $C_{22}H_{41}NO_2$: C, 75.16; H, 11.76; N, 3.98. Found: C, 74.90; H, 11.88; N, 3.71.

1-(*tert*-Butoxycarbonyl)-*trans*-2-methyl-6-*n*-undecylpiperidine (16) from 1,2,5,6-Tetrahydropyridine 10. Into an oven-dried, argon-flushed, 50-mL round-bottomed flask was placed an absolute ethanol solution (5 mL) of 1,2,5,6-tetrahydropyridine **10** (41.5 mg, 0.188 mmol). To this solution was added 42 mg of lithium carbonate and 42 mg of 5% Pd/C. The mixture was placed under a positive pressure of hydrogen gas from a balloon and stirred for 12 h at room temperature. The mixture was filtered through Celite and concentrated on a rotary evaporator. The residue was dissolved in ether (10 mL), water (5 mL) was added, the aqueous phase was extracted with ether (2 × 5 mL), and the combined ether extracts were washed with 1 N NaOH (2 × 5 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product. Pipet purification (silica gel, 5% EtOAc/hexanes) gave 30.1 mg (80%) of **16** as a colorless oil.

Preparation of 16 from 1,2,3,4-Tetrahydropyridine 18. To a stirred solution of 205 mg (0.584 mmol) of 1,2,3,4-tetrahydropyridine **18** in 40 mL of CH_2Cl_2 was added 220 mg (3.504 mmol) of sodium cyanoborohydride. After being stirred for 15 min at room temperature, the heterogeneous solution was cooled to −42 °C and trifluoroacetic acid (0.45 mL, 5.84 mmol) was added slowly dropwise. After stirring for 4 h at −42 °C, the cold bath was removed and the reaction mixture was immediately quenched with 30 mL of a saturated aqueous $NaHCO_3$/THF mixture (50:50). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were washed with water (10 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give 190 mg (92%) of the crude product as a mixture of 90% trans isomer **16** and 10% cis isomer **15** as determined by capillary GC analysis. This crude material was used directly in the next step (Purification by MPLC (silica gel, 5% EtOAc/hexanes) of the material from a separate reaction provided a sample for elemental analysis.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97–3.86 (m, 1 H), 3.83–3.72 (m, 1 H), 1.90–1.30 (m, 8 H), 1.46 (s, 9 H), 1.26 (br s, 18 H), 1.23 (d, 3 H, J = 6.6 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 78.7, 51.6, 46.9, 34.3, 31.8, 29.57, 29.54, 29.51, 29.25, 28.5, 27.1, 26.8, 23.1, 22.6, 20.7, 14.0, 13.6; FT-IR (neat) 2926, 2855, 1690, 1467, 1393, 1366, 1178, 1090 cm^{-1}. Anal. Calcd for $C_{22}H_{43}NO_2$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.65; H, 12.16; N, 3.96.

(±)-Solenopsin A. *trans*-2-Methyl-6-*n*-undecylpiperidine (1). To a stirred solution of 190 mg (0.537 mmol) of crude piperidine **16** (containing approximately 10% of cis isomer **15**) in 20 mL of CH_2Cl_2 at 0 °C was added dropwise 5 mL (excess) of trifluoroacetic acid. The cooling bath was removed, and stirring was continued for 1 h at room temperature. After concentrating the resulting solution on a rotary evaporator, the remaining liquid was dissolved in ether (20 mL) and 10 mL of water was added. The aqueous phase was extracted with ether (2 × 5 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine. The organic phase was dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to give the crude product as a mixture of 90% (±)-solenopsin A (**1**) and 10% (±)-*epi*-solenopsin A (**17**) as determined by capillary GC analysis. Separation and purification by MPLC (silica gel, Et_2O/1% *i*-$PrNH_2$) gave 94 mg (64% from compound **18**) of pure **1** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12–3.00 (m, 1 H), 2.92–2.82 (m, 1 H), 1.70–1.15 (m, 9 H), 1.26 (br s, 18 H), 1.07 (d, 3 H, J = 6.3 Hz), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.8, 45.8, 34.0, 32.9, 31.9, 30.7, 29.7, 29.59, 29.57, 29.3, 26.4, 22.6, 21.2, 19.5, 14.0; FT-IR (neat) 3292 (weak), 2931, 2853, 1465, 1376, 1141, 1067 cm^{-1}; (±)-solenopsin A·HCl mp 121–122 °C (CH_2Cl_2–Et_2O) (lit.[18d] mp 114 °C). (±)-Solenopsin A·HCl. Anal. Calcd for $C_{17}H_{36}ClN$: C, 70.43; H, 12.52; N, 4.83. Found: C, 70.21; H, 12.39; N, 4.78.

4-Chloro-1-(phenoxycarbonyl)-2-*n*-propyl-1,2-dihydropyridine (20). To a stirred solution of 4-chloropyridine (1.17 g, 10.30 mmol) in 75 mL of THF at −78 °C was added *n*-propylmagnesium chloride (5.15 mL, 10.30 mmol, 2.0 M solution in diethyl ether) followed, after 20 min, by the dropwise addition of phenyl chloroformate (1.29 mL, 10.30 mmol). Stirring was continued for 30 min at −78 °C; then the cooling bath was removed and the reaction mixture was allowed to stir for 30 min longer while being slowly warmed to room temperature. Aqueous 20% NH_4Cl (30 mL) and ether (40 mL) were added, the layers were separated, and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic extracts were washed successively with 25-mL portions of saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to give 3.08 g (quantitative) of crude product **20** as a clear, light yellow oil (This crude material was used directly in the next step to make the *N*-Boc derivative.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.10 (m, 5 H), 6.95–6.85 (pair of d due to rotamers, 1 H, J = 8.1 Hz), 5.68 (dd, 1 H, J = 6.2 Hz and J = 2.2 Hz), 5.40–5.28 (pair of dd due to rotamers, 1 H, J = 8.1 Hz and J = 2.2 Hz), 5.05–4.85 (pair of m due to rotamers, 1 H, J = 6.2 Hz), 1.85–1.30 (m, 4 H), 0.94 (m, 3 H); FT-IR (neat) 3102, 3072, 3045, 2960, 2933, 2873, 1730, 1636, 1593, 1495, 1420, 1358, 1333, 1202, 1043 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-4-chloro-2-*n*-propyl-1,2-dihydropyridine (21). By use of a procedure similar with that described for the preparation of **5**, 3.08 g (10.30 mmol) of **20** was treated with 5.0 g (44.0 mmol) of potassium *tert*-butoxide. Purification by radial PLC (silica gel, 5% EtOAc/hexanes) gave 2.47 g (93%) of **21** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90–6.60 (pair of br d due to rotamers, 1 H, J = 7.3 Hz), 5.55 (br s, 1 H), 5.25–5.05 (pair of br d due to rotamers, 1 H, J = 7.3 Hz), 4.90–4.60 (pair of br m due to rotamers, 1 H), 1.70–1.25 (m, 4 H), 1.50 (s, 9 H), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 and 151.7 (due to rotamers), 127.7 and 127.5 (due to rotamers), 127.4 and 126.7 (due to rotamers), 117.7 and 117.3 (due to rotamers), 106.6 and 106.1 (due to rotamers), 81.7, 53.7 and 52.9 (due to rotamerrs), 36.3 35.8 (due to rotamers), 28.1, 17.4, 13.9; FT-IR (neat) 2961, 2934, 2874, 1715, 1633, 1370, 1338, 1311, 1253, 1172, 1127, 1051 cm^{-1}.

1-(*tert*-Butoxycarbonyl)-4-chloro-6-methyl-2-*n*-propyl-1,2-dihydropyridine (22) was prepared by a procedure similar to that described for the preparation of **6**. To 2.06 g (8.0 mmol) of **21** was added 3.95 mL (9.60 mmol, 2.43 M solution in hexane) of *n*-butyllithium followed after 1 h by 1.50 mL (24.0 mmol) of iodomethane. Purification by radial PLC (silica gel, 10% EtOAc/hexanes) gave 1.83 g (84%) of **22** as a clear, light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dd, 1 H, J = 6.6 Hz and J = 1.5 Hz), 5.33 (m, 1 H, J = 1.5 Hz), 4.80 (dt, 1 H, J = 7.3 Hz and J = 6.6 Hz), 2.14 (s, 3 H), 1.52–1.24 (m, 4 H), 1.50 (s, 9 H), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 137.0, 126.6, 119.3, 112.2, 81.3, 53.9, 33.9, 28.1, 21.9, 17.8, 13.9; FT-IR (neat) 2962, 2932, 2874, 1708, 1637, 1393, 1369, 1343, 1328, 1173, 1132, 1086 cm^{-1}. Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.66; H, 8.16; N, 5.26.

1-(*tert*-Butoxycarbonyl)-4-chloro-*cis*-6-methyl-2-*n*-propyl-1,2,5,6-tetrahydropyridine (23). By use of a procedure similar with that described for the preparation of **7**, 1.0 g (3.68 mmol) of **22** was treated with 4.61 mL (22.08 mmol) of tri-*n*-propylsilane and 2.84 mL (36.80 mmol) of trifluoroacetic acid. The crude product consisted of a mixture of 80% of cis isomer **23**, 12% of trans isomer **25**, and 8% of cis isomer **24** as determined by capillary GC analysis. Purification by MPLC (silica gel, 5%

EtOAc/hexanes) gave 722 mg (72%) of pure **23** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, 1 H, J = 3.75 Hz and J = 2.85 Hz), 4.68 (m, 1 H), 4.31 (m, 1 H), 2.72 (dm, 1 H, J = 16.8 Hz), 2.06 (d, 1 H, J = 16.8 Hz), 1.70–1.30 (m, 4 H), 1.47 (s, 9 H), 1.21 (d, 3 H, J = 7.2 Hz), 0.94 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 127.5, 123.1, 79.8, 52.7, 44.5, 38.4, 37.9, 28.4, 20.9, 20.0, 13.9; FT-IR (neat) 2966, 2934, 2874, 1695, 1479, 1457, 1407, 1367, 1343, 1318, 1177, 1116, 1100, 1070 cm^{-1}. Anal. Calcd for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.84; N, 5.12. Found: C, 61.50; H, 9.07; N, 5.17.

1-(*tert*-Butoxycarbonyl)-*cis*-2-methyl-6-*n*-propylpiperidine (26) from 1,2,5,6-Tetrahydropyridine 23. By use of a procedure similar with that described for the preparation of **15**, a mixture of 587 mg of tetrahydropyridine **23** (2.14 mmol), 590 mg of lithium carbonate, and 590 mg of 10% Pd/C in 30 mL of ethyl acetate was hydrogenated for 2 days. Purification of the crude product by MPLC (silica gel, 10% EtOAc/hexanes) gave 428 mg (83%) of **26** as a colorless oil.

Preparation of 26 from 1,2-Dihydropyridine 22. By use of a procedure similar with that described for the preparation of **15**, a mixture of 304 mg of dihydropyridine **22** (1.12 mmol), 300 mg of lithium carbonate, and 300 mg of 5% Pd/C in 20 mL of ethyl acetate was hydrogenated for 2 days. (Note: Shorter reaction times gave the incomplete reduction product 1,2,3,4-tetrahydropyridine as a significant contaminant.) The crude product consisted of a mixture of 98% cis isomer **26** and 2% of the trans isomer as determined by capillary GC analysis. Purification by MPLC (silica gel, 10% EtOAc/hexanes) gave 187 mg (69%) of **26** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.22 (m, 1 H), 4.10–4.00 (m, 1 H), 1.70–1.20 (m, 10 H), 1.46 (s, 9 H), 1.16 (d, 3 H, J = 7.2 Hz), 0.92 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 78.7, 50.0, 45.5, 37.2, 30.2, 28.4, 27.3, 20.6, 20.3, 14.1, 14.0; FT-IR (neat) 2960, 2936, 2872, 1690, 1458, 1404, 1391, 1365, 1348, 1180, 1103, 1083 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.64; H, 11.27; N, 5.80.

(±)-Dihydropinidine. *cis*-2-Methyl-6-*n*-propylpiperidine (2). To a stirred solution of 226 mg (0.936 mmol) of Boc-piperidine **26** in 15 mL of acetonitrile was added sodium iodide (562 mg, 3.744 mmol) followed by chlorotrimethylsilane (0.48 mL, 3.744 mmol). After stirring for 12 h at room temperature, saturated aqueous K_2CO_3 (5 mL) was added and stirring was continued for 1 h. The layers were separated, the aqueous phase was extracted with ether (3 × 5 mL), and the combined organic extracts were dried over K_2CO_3. Filtration through Celite and concentration on a rotary evaporator with the water bath at 0 °C gave the crude product. Kugelrohr distillation (60–100 °C, 20 mmHg (water aspirator), receiver bulb at −78 °C) gave 93 mg (70%) of **2** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.56 (m, 1 H), 2.55–2.45 (m, 1 H), 1.76 (m, 1 H), 1.60 (m, 2 H), 1.55–0.80 (m, 8 H), 1.06 (d, 3 H, J = 6.6 Hz), 0.91 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8, 52.5, 39.7, 34.4, 32.2, 24.9, 23.1, 19.1, 14.3; ^{1}H NMR (300 MHz, C_6D_6) δ 2.52–2.42 (m, 1 H), 2.40–2.32 (m, 1 H), 1.69 (m, 1 H), 1.48 (m, 2 H), 1.35–0.80 (m, 8 H), 0.99 (d, 3 H, J = 6.3 Hz), 0.88 (t, 3 H, J = 6.3 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 57.1, 52.7, 40.1, 34.8, 32.5, 25.4, 23.2, 19.3, 14.6; FT-IR (neat) 3276 (weak), 2957, 2928, 2857, 2798, 2713, 1463, 1441, 1377, 1321, 1129 cm^{-1}; (±)-dihydropinidine·HCl mp 212–213 °C (2:1 EtOAc–EtOH) (lit.[19a] mp 210–213 °C).

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research.

Registry No. (±)-**1**, 28720-60-7; (±)-**1**·HCl, 63950-17-4; (±)-**2**, 65337-42-0; (±)-**2**·HCl, 121963-72-2; **3**, 626-61-9; (±)-**4**, 132410-08-3; (±)-**5**, 132410-09-4; (±)-**6**, 132438-34-7; (±)-**7**, 132410-10-7; (±)-**8**, 132410-11-8; (±)-**9**, 132410-12-9; (±)-**10**, 132410-13-0; (±)-**15**, 132410-14-1; (±)-**16**, 132410-15-2; (±)-**17**, 63950-16-3; (±)-**18**, 132410-16-3; (±)-**20**, 132410-17-4; (±)-**21**, 132410-18-5; (±)-**22**, 132410-19-6; (±)-**23**, 132410-20-9; (±)-**24**, 132410-21-0; (±)-**25**, 132410-22-1; (±)-**26**, 132410-23-2; $Br(CH_2)_{10}CH_3$, 693-67-4.

Thermal and Lewis Acid Induced Cycloaddition of Thioaldehyde *S*-Oxides (Monosubstituted Sulfines) to Dienes. 3[1,2]

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Received April 25, 1990

The stereochemical course of the 1,4-cycloaddition of thioaldehyde *S*-oxides (monosubstituted sulfines) to 2,3-dimethylbuta-1,3-diene, buta-1,3-diene, and *cis*- and *trans*-penta-1,3-diene was investigated. Unexpectedly, the reactions of buta-1,3-diene and 2,3-dimethylbuta-1,3-diene with *Z*-monoaryl sulfines afforded cis/trans mixtures of the corresponding dihydrothiopyran *S*-oxides, in which the relative amounts of the two isomers depended upon the initial diene/sulfine ratio. A *Z* to *E* isomerization of the dienophiles during the cycloaddition was responsible. On the other hand, *Z*/*E* mixtures of aliphatic *tert*-butyl sulfine gave, with 2,3-dimethylbuta-1,3-diene, only the corresponding trans cycloadduct. Catalysis of the reaction by Lewis acids, heretofore largely unexplored, was also investigated.

Introduction

Considerable attention has been payed to the chemistry of disubstituted sulfines, the literature of which has been recently reviewed.[3] In particular, the stereochemical course of the cycloaddition of unsymmetrically disubstituted sulfines to dienes has been investigated in detail,

† Deceased on March 11, 1989.

(1) Part 2: Barbaro, G.; Battaglia, A.; Giorgianni, P.; Bonini, B. F.; Maccagnani, G.; Zani, P. *J. Org. Chem.* **1990**, *55*, 3744.

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0022-3263/91/1956-2512$02.50/0