4.48–4.60 (t, 1 H), 7.00–7.52 (m, 8 H); chemical ionization mass spectrum of LiI complex **18d**, m/z (relative intensity) 441 ($M^+ + 1 - 24$), 306 (42), 266 (80), 257 (85), 266 (100), 201 (63), 173 (47), 142 (92).

Anal. Calcd for $C_{26}H_{36}N_2O_4LiI$: C, 54.36; H, 6.31; N, 4.85; Li, 1.20; I, 22.19. Found: C, 53.96; H, 6.20; N, 4.85; Li, 1.16; I, 22.54. Crystals suitable for X-ray analysis were obtained from methylene chloride and THF by the isothermal distillation technique.

Acknowledgment. We thank the National Institutes of Health for financial support through Grant GM26568 and the National Science Foundation and RPI for funds to purchase the Nicolet R3m X-ray diffractometer. We thank Dr. H. Schwartz for assistance with the NMR measurements. Address correspondence concerning X-ray diffraction analyses of **2c**, **17a**, and **18d** to Dr. Rudolph K. Kullnig.

Registry No. **1a**, 111904-31-5; **1b**, 111904-32-6; **1c**, 111904-33-7; **1d**, 111904-34-8; **1e**, 111904-35-9; **1f**, 111904-36-0; **2a**, 111904-37-1; **2b**, 111904-38-2; **2c**, 111904-39-3; **2d**, 111904-40-6; **2e**, 111904-41-7; **2f**, 111904-42-8; **3a**, 703-51-5; **3b**, 111904-43-9; **3c**, 111904-44-0; **3d**, 111904-45-1; **3e**, 111904-46-2; **3f**, 111904-47-3; **4a**, 111904-48-4; **4b**, 111904-49-5; **4c**, 111904-50-8; **5a**, 111904-51-9; **5b**, 111904-52-0; **6a**, 111904-53-1; **6b**, 111957-22-3; **7a**, 708-05-4; **7b**, 111904-54-2; **8a**, 111904-55-3; **8b**, 111904-56-4; **9**, 94225-47-5; **10**, 111904-57-5; **12**, 111904-58-6; **14**, 111957-23-4; **15**, 111904-59-7; **16**, 111904-60-0; **17a**, 96740-35-1; **17a**·2HCl, 111904-63-3; **17b**, 111904-64-4; **17c**, 111904-65-5; **17d**, 111904-66-6; **17e**, 111904-67-7; **18a**, 111904-68-8; **18b**, 111904-69-9; **18c**, 111904-70-2; **18d**, 111933-51-8; $H_2NCH(Me)CH_2OH$, 78-91-1; $H_2N(CH_2)_2OH$, 141-43-5; 2-FC_6H_4COCl, 393-52-2; (±)-$H_2NCH(CHMe_2)CH_2OH$, 16369-05-4; (±)-$H_2NCH(CH_2CHMe_2)CH_2OH$, 16369-17-8; (±)-$H_2NCH(CH_2SCH_2Ph)CH_2OH$, 65309-78-6; (±)-$MeS(CH_2)_2CH(NH_2)CH_2OH$, 16720-80-2; $MeNH(CH_2)_2OH$, 109-83-1; 2-BrC_6H_4COCl, 7154-66-7; (1*R*,2*R*)-$H_2NCH(Me)CH(Ph)OH$, 37577-07-4; $H_2N(CH_2)_3OH$, 156-87-6; $H_2N(CH_2)_4OH$, 13325-10-5; L-prolinol, 23356-96-9; D-ephedrine, 299-42-3; 1,2-bis(2-iodoethoxy)ethane, 36839-55-1.

Supplementary Material Available: Additional projections, tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **2c**, **17a**, and **18d** (23 pages). Ordering information is given on any current masthead page.

Enantioselective Total Synthesis of (+)-Perhydro-219A from an Anthranilic Acid Derivative

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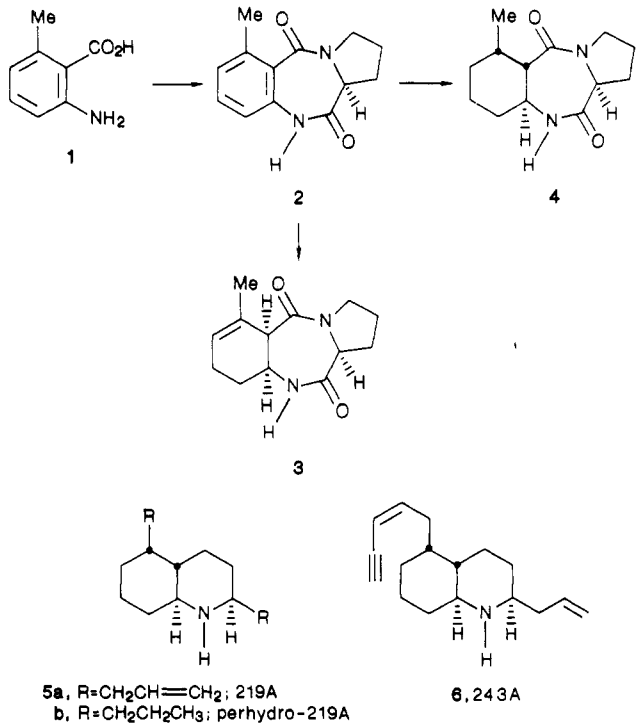
The first total synthesis of a *trans*-decahydroquinoline alkaloid derivative, (+)-perhydro-219A, is described. Key steps of the synthesis include the directed metalation–ethylation of 6-methylpyrrolobenzodiazepine-5,11-dione **2** to give the C(6)-*n*-propyl derivative **7**, the stereoselective Birch reduction of **7** to give the perhydrobenzodiazepinedione **8**, and the stereoselective hydrogenation of the $\Delta^{1,2}$ imine **15** to give (+)-perhydro-219A (**5b**). An enantioselective synthesis of *cis*-decahydroquinoline **18** also is described.

Pyrrolobenzodiazepine-5,11-dione **2**, readily available from 6-methylanthranilic acid (**1**) and the chiral auxiliary L-proline, undergoes Birch reduction with potassium (4.4 equiv) to give the cis-fused tetrahydrobenzene derivative **3**. Removal of the auxiliary from **3** and analogues provides chiral cyclohexanes for use in organic synthesis. A detailed study of the Birch reduction and reductive alkylation of several anthranilic derivatives, together with an enantioselective total synthesis of (+)-pumiliotoxin C from **3**, has been reported.[1] Also described are optimized conditions for the complimentary reduction of **2** to the trans-fused hexahydrobenzene derivative **4** (91% isolated yield).

We were particularly interested in the development of a reliable conversion of **2** into **4**, because of a recent report by Daly and co-workers[2] of a new class of *trans*-decahydroquinoline alkaloids obtained from skin extracts of poison frogs of Colombia. Two alkaloids, 219A (**5a**) and 243A (**6**), have been isolated as major constituents from one population of *Dendrobates histrionicus* and shown to be 2,5-disubstituted *trans*-decahydroquinolines by NMR spectral analysis and an X-ray diffraction study of the hydrochloride salt of 219A. Catalytic hydrogenation of the hydrobromide salt of 219A provided perhydro-219A (**5b**).

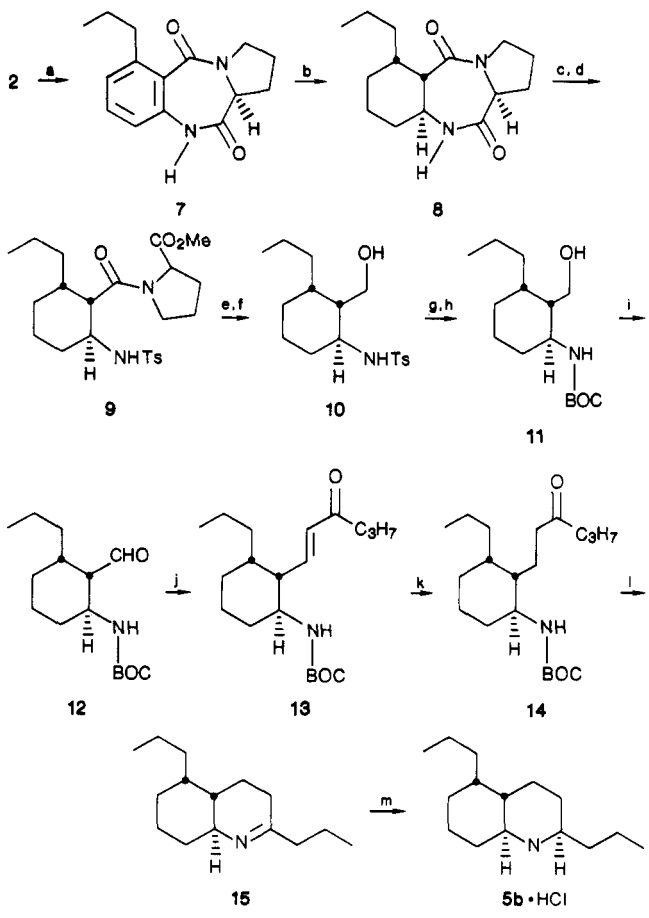


These and other *trans*-decahydroquinoline alkaloids may possess interesting pharmacological properties as has

(1) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.
(2) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453.

0022-3263/88/1953-1380$01.50/0

Scheme I[a]



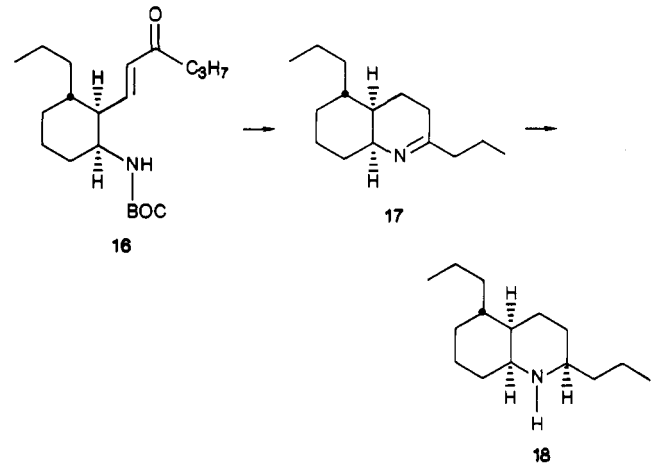
[a] (a) *n*-BuLi, EtI; (b) $K/NH_3/t$-BuOH; (c) H_2SO_4 (cat.)/MeOH; (d) $TsCl/Et_3N$; (e) 6 N H_2SO_4/EtOH; (f) $LiAlH_4$/THF; (g) Na/NH_3; (h) $O[CO_2C(CH_3)_3]_2$/2 N NaOH; (i) $(COCl)_2$, DMSO/CH_2Cl_2; (j) LiCl, $EtN(i\text{-}Pr)_2$, $(MeO)_2POCH_2COC_3H_7/CH_3CN$; (k) H_2 (1 atm) 5% Pd/C/EtOAc; (l) CF_3CO_2H/Et_2O; (m) H_2 (1 atm), Pd/C/MeOH.

been the case for other poison-frog alkaloids,[3] but difficulties in obtaining adequate amounts of the natural compounds have restricted progress in this area.[4] In this paper, we report the first total synthesis of (+)-perhydro-219A (**5b**) in quantities suitable for extensive pharmacological evaluation by a method that holds promise for the preparation of more highly functionalized members of the *trans*-decahydroquinoline alkaloids.

Results and Discussion

A preparation of C(6)-substituted pyrrolobenzodiazepine-5,11-diones that would be compatible with the varied functionality at C(5) of the *trans*-decahydroquinoline alkaloids was desired. Furthermore, although 6-*n*-propylanthranilic acid has been reported,[5] the method of synthesis requires seven steps and the overall yield is less than 5%. Consequently, a route to the 6-*n*-propylpyrrolobenzodiazepine-5,11-dione **7** was developed that involves selective alkylation of the 6-methyl derivative **2** (Scheme I).

Scheme II



Treatment of 6-methylpyrrolobenzodiazepine-5,11-dione **2** with *n*-BuLi (2.5 equiv) at −78 °C generates a blood-red dianion.[6] Alkylation with ethyl iodide, followed by addition of solid ammonium chloride at −78 °C (to prevent N-ethylation), provides **7** in 74% yield after flash column chromatography. The remainder of the reaction mixture consists of recovered starting material and a product of *n*-BuLi addition to the tertiary amide carbonyl group of **2**.

Birch reduction of **7** with potassium (~8 equiv) and 5 equiv of *tert*-butyl alcohol gave perhydrobenzodiazepinedione **8** isolated as a single diastereoisomer (mp 165–166 °C) in 83% yield. Relative configuration at C(5a), C(6), and C(9a) in **8** was assigned on the basis of ^1H NMR decoupling studies. Coupling constants, $J_{5a,9a}$ = 12 Hz and $J_{5a,6}$ = 4.0 Hz, suggestive of dihedral angles of 180° and 60°, respectively, can only be satisfied by the configurational assignment depicted in structure **8**.

The chiral auxiliary was removed by sequential amide bond cleavages. Methanolysis of the secondary amide group occurred in refluxing methanol solution with a catalytic amount of sulfuric acid. Treatment of the resulting amino ester with toluenesulfonyl chloride in triethylamine gave the sulfonamide **9** in 80% yield from **8**. Hydrolysis of the tertiary amide group in **9** occurred in 6 N sulfuric acid–ethanol at 100 °C to give a mixture of carboxylic acid and ethyl ester.[7] Reduction of this mixture with $LiAlH_4$ in THF provided the alcohol **10** in ~80% yield from **9**

Effective cleavage of the sulfonamide protecting group was found to be difficult at subsequent stages of the synthesis; consequently, the sulfonamide group in **10** was reduced with sodium in ammonia, and the resulting amine was reprotected as the BOC derivative **11** by reaction with di-*tert*-butyl dicarbonate. Swern oxidation[8] of **11** provided aldehyde **12** (66% overall yield from **10**).

Condensation of **12** with the sodium salt of dimethyl (2-oxopentyl)phosphonate[9] produced a mixture of enone **13** and the C(5a) epimer **16** in an unfavorable ratio of ~1:5. The distribution of epimeric enones **13** and **16** proved to be relatively insensitive to variation in reaction tempera-

(3) (a) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565. (b) Souccar, C.; Varanda, W. A.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1984**, *25*, 384.

(4) Extracts from 640 frog skins provided 107 mg of 219A and 20 mg of 243A; see ref 2.

(5) Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1946**, *17*, 164.

(6) For related benzylic substitutions directed by a tertiary aromatic amide, see: (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Bindal, R. D.; Katzenellenbogen, J. A. *J. Org. Chem.* **1987**, *52*, 3181.

(7) For a discussion of the factors that may influence the rates of hydrolysis of **9** and related tertiary amides, see: McCloskey, P. J. Ph.D. Thesis, Rensselaer Polytechnic Institute, 1987.

(8) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(9) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.

tures. Relative configuration of the major epimer, **16**, was confirmed by conversion to the *cis*-decahydroquinoline **18**, originally prepared in racemic form by Overman and coworkers (Scheme II).[9]

The sensitivity of aldehyde **12** to basic reaction conditions was demonstrated by treatment with 1 equiv of diazabicyclononene (DBN) in chloroform solution, from which a 1:1 mixture of **12** and a substance presumably epimeric at the carbon atom adjacent to the aldehyde group was obtained. The 1:5 ratio of enones **13** and **16** when compared to the 1:1 ratio of aldehydes (**12** and the epimer) suggests that equilibration of **13** and **16** under basic reaction conditions also is possible.

Fortunately, the problem of epimerization was circumvented by utilization of the Horner–Wadsworth–Emmons reaction modification described by Masamune, Roush, and co-workers.[10] Generation of the conjugate base of dimethyl (2-oxopentyl)phosphonate using diisopropylethylamine in the presence of lithium chloride and reaction with aldehyde **12** gave the desired enone **13** in 88% isolated yield, free of the epimer **16**.

Hydrogenation of enone **13** over 5% palladium on carbon in ethyl acetate gave ketone **14** in quantitative yield, and treatment of **14** with trifluoroacetic acid in ether at 0 °C with warming to room temperature provided the $\Delta^{1,2}$ imine **15**. A highly stereoselective hydrogenation[11] of **15** over palladium on carbon in methanol, followed by crystallization of the hydrochloride salt from 2-propanol–ethyl acetate solution, gave perhydro-219A·HCl in 64% yield from **14**; mp 280 °C (dec). The ^{1}H NMR, ^{13}C NMR, and mass spectral data obtained for synthetic **5b**·HCl were consistent with the assigned structure. Furthermore, the ^{1}H and ^{13}C NMR spectral data obtained from the free base, **5b**, corresponded to the spectral data provided by Tokuyama.[12] The yield of enantiomercially pure **5b** from the starting pyrrolobenzodiazepine-5,11-dione **2** is ~15%.[13] The preparation of more highly functionalized *trans*-perhydroquinoline alkaloids by adaptation of the synthesis of (+)-perhydro-219A is in progress.

Experimental Section

^{1}H NMR spectra were recorded on Varian T-60 (60 MHz), Varian XL-200 (200 MHz), and Hitachi Perkin-Elmer R-600 (600 MHz) NMR spectrometers (tetramethylsilane was used as an internal standard). ^{13}C NMR spectra were obtained on Varian XL-200 and IBM WP-100SY spectrometers. Infrared spectra were recorded on Perkin-Elmer 137b and 298 spectrometers, and optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a Hewlett-Packard 5987A GC-MS system (methane, chemical-ionization gas). Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All solvents were freshly distilled under nitrogen as follows: tetrahydrofuran (THF) from sodium–benzophenone; methanol from $Mg(OMe)_2$; methylene chloride from P_2O_5; *tert*-butyl alcohol from CaH_2; dimethylformamide (DMF) from CaH_2.

6-*n*-Propyl-1,2,3,10,11,11a(*S*)-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (7). To a solution of **2** (1.0 g, 4.35 mmol) in 10 mL of dry THF cooled to −78 °C under nitrogen was added *n*-BuLi (6.80 mL of 1.6 M, 10.9 mmol) over several minutes. The resulting blood-red mixture was stirred for an additional 5 min at −78 °C. Addition of excess ethyl iodide (~2 equiv) resulted in immediate discharge of the red coloration. After 5 min, the reaction mixture was quenched (−78 °C) with solid ammonium chloride and allowed to warm to room temperature. The mixture was diluted with ether and then washed with 10% sodium thiosulfate. The organic layer was dried over magnesium sulfate, concentrated, and chromatographed on silica gel (EtOAc–CH_2Cl_2, 3:1) to give **7** as a colorless solid (830 mg, 3.22 mmol, 74% yield). Crystallization from carbon tetrachloride–hexanes (1:1) provided **7** as colorless crystals: mp 152–153 °C; IR (KBr) 3.80, 3.38, 5.95, 6.16 μm; ^{1}H NMR δ 0.92 (t, 3 H, J = 6.5 Hz), 1.50–1.86 (m, 2 H), 2.04 (m, 3 H), 2.72 (m, 2 H), 3.10 (dq, 1 H), 3.56 (m, 1 H), 3.91 (m, 1 H), 4.09 (d, 1 H), 6.12 (d, 1 H, J = 8 Hz), 7.14 (d, 1 H, J = 8 Hz), 7.36 (t, 1 H, J = 8 Hz), 7.76 (br, s, 1 H); $[\alpha]^{22}_D$ +409° (*c* 1.44, $CHCl_3$); chemical-ionization mass spectrum, m/z (relative intensity) M + 1 (100).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02. Found: C, 69.70; H, 7.03.

(5a*S*,6*S*,9a*S*,11a*S*)-Perhydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (8). Birch reduction of **7** using 5 equiv of *tert*-butyl alcohol and ~8 equiv of potassium by techniques previously described[1] provided an 83% yield of **8** after flash chromatography on silica gel (EtOAc–MeOH, 93:7). Crystallization from carbon tetrachloride–hexanes (1:1) gave colorless needles: mp 165–166 °C; IR (KBr) 3.12, 3.42, 5.93, 6.15 μm; ^{1}H NMR δ 0.76 (t, 3 H, J = 7 Hz), 0.86–2.01 (m, 13 H), 2.27 (dd, 1 H, J = 12, 4 Hz), 2.50 (m, 2 H), 3.46 (m, 1 H), 3.52–3.80 (m, 2 H), 4.57 (dd, 1 H, J = 7.5, 4.6 Hz), 6.66 (br d, 1 H); $[\alpha]^{22}_D$ +101° (*c* 0.74, $CHCl_3$); chemical-ionization mass spectrum, m/z (relative intensity) M + 1 (100).

Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.14. Found: C, 68.29; H, 9.14.

(1*S*,2*S*,6*S*)-2-(*N*-Tosylamino)-6-*n*-propyl-1-[[2(*S*)-(methoxycarbonyl)pyrrolidin-1-yl]carbonyl]cyclohexane (9) was prepared from **8** in 80% yield by techniques previously described.[1] Chromatography on silica gel (EtOAc–hexanes, 1:1) gave **9** as a colorless gum: IR (KBr) 3.05, 3.38, 5.73, 6.13 μm; ^{1}H NMR δ 0.82 (t, 3 H, J = 7 Hz), 0.98–1.58 (m, 9 H), 1.62–2.22 (m, 8 H), 2.42 (s, 3 H), 2.84 (t, 1 H, J = 4 Hz), 3.50 (m, 1 H), 3.71 (m, 1 H, 3.70 overlapping singlet, 3 H), 4.46 (m, 1 H), 5.00 (br d, 1 H), 7.30 (d, 2 H, J = 8 Hz), 7.69 (d, 2 H, J = 8 Hz); $[\alpha]^{23}_D$ −42.8° (*c* 1.72, $CHCl_3$); chemical-ionization mass spectrum, m/z (relative intensity) M + 1 (100).

Anal. Calcd for $C_{23}H_{35}N_2O_5S$: C, 61.32; H, 7.60. Found: C, 60.97; H, 7.58.

(1*S*,2*S*,6*S*)-2-(*N*-Tosylamino)-6-*n*-propylcyclohexanecarboxylic Acid and the Corresponding Ethyl Ester. Subjecting **9** (1.35 g, 2.89 mmol) to 6 mL of a 6 N H_2SO_4–ethanol mixture (3:1) for 40 h at 100 °C, followed by cooling, then extraction with chloroform (3 × 15 mL), drying over $MgSO_4$, and concentration, gave 900 mg (~90%) of a colorless foam. The crude ^{1}H NMR spectrum showed that the product was a ~1:1 mixture of the desired acid and its corresponding ethyl ester. This material was carried on to the next step. A derivative suitable for characterization was prepared from a portion of the mixture. Thus, hydrolysis in methanol–H_2SO_4 gave a mixture of the acid and its methyl ester, which was treated with excess diazomethane in ether. An analytical sample of the methyl ester was prepared by chromatography on silica gel (EtOAc–hexanes, 3:7) to give a colorless gum: IR (film) 3.05, 3.40, 5.78 μm; ^{1}H NMR δ 0.87 (t, 3 H, J = 7 Hz), 0.98–1.60 (m, 9 H), 1.74–2.04 (m, 2 H), 2.44 (s, 3 H), 2.51 (dd, 1 H, J = 7.0, 4.4 Hz), 3.59 (m, 1 H, 3.58 overlapping singlet, 3 H), 4.78 (d, 1 H), 7.32 (d, 2 H, J = 8 Hz), 7.78 (d, 2 H, J = 8 Hz); $[\alpha]^{31}_D$ + 3.4° (*c* 5.92, $CHCl_3$); chemical-ionization mass

(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(11) For related hydrogenations, see: (a) Booth, H.; Griffiths, D. V.; Jozefowicz, M. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 751. (b) Lenz, G. R. *Heterocycles* **1987**, *26*, 721.

(12) Dr. Tokuyama has informed us of an error in the ^{13}C NMR data for perhydro-219A reported in ref 2. The chemical shift for C(2) should be corrected to δ 55.5 (JEOL Model FX100, $CDCl_3$, ~25 °C). We thank Dr. Tokuyama for sending this information to us.

(13) An optical rotation of naturally derived **5b** has not been reported; however, the enantiomeric purity of synthetic **5b** is estimated to be 100%. The estimate is based on the absence of epimerization at the proline chiral center C(11a) during Birch reduction–alkylation of a substrate closely related to **7**; see ref 1. The absence of racemization of **2** during the conversion to **7** was demonstrated by the following experiments. The dianion generated from deprotonation of **7** with *n*-BuLi was quenched at −78 °C with NH_4Cl. Recovered **2**, isolated by flash chromatography of the reaction mixture on silica gel, was found to have, within experimental error, an optical rotation identical with that of starting material. Another sample of the dianion was treated with D_2O. The ^{1}H NMR spectrum of recovered **2** showed that while one deuterium atom had been incorporated in the methyl substituent at C(6), there was no incorporation of deuterium at C(11a).

spectrum, m/z (relative intensity) M + 1 (46), 322 (100), 198 (36).

Anal. Calcd for $C_{18}H_{27}NO_4$: C, 61.18; H, 7.69. Found: C, 60.95; H, 7.67.

(1*S*,2*S*,3*S*)-2-(Hydroxymethyl)-3-*n*-propyl-*N*-tosylcyclohexylamine (10). To a slurry of lithium aluminum hydride (468 mg, 12.3 mmol) in 10 mL of THF was added the mixture of acid and ester from the previous experiment (2.70 g, 7.69 mmol) in 5 mL of THF over 5 min. The mixture was stirred at room temperature for 24 h and then quenched with 20% aqueous KOH (until a colorless solution and suspension of aluminum salts resulted). Filtration and concentration gave **10** as a colorless solid (2.08 g, 83%). Chromatography on silica gel (EtOAc) gave a colorless solid, which was recrystallized from ether–hexanes (1:1) to give colorless needles: mp 90–91 °C; IR (film) 2.80, 3.05, 3.41, 6.90, 7.65 μm; ^{1}H NMR δ 0.80 (t, 3 H, J = 6.7 Hz), 0.90–1.48 (m, 8 H), 1.50–1.88 (m, 5 H), 2.38 (s, 3 H), 3.30–3.56 (m, 2 H), 4.66 (dt, 1 H, J = 11 Hz), 5.10 (m, 1 H), 7.32 (d, 2 H, J = 6.4 Hz), 8.00 (d, 2 H, J = 6.4 Hz); $[\alpha]^{22}_{365}$ −22.9° (*c* 1.53 $CHCl_3$); chemical-ionization mass spectrum, m/z (relative intensity) M + 1 (100), 172 (85), 137 (70).

Anal. Calcd for $C_{17}H_{27}NO_4S$: C, 62.75; H, 8.35. Found: C, 62.73; H, 8.53.

(1*S*,2*S*,3*S*)-2-(Hydroxymethyl)-3-*n*-propyl-*N*-(benzyloxycarbonyl)cyclohexylamine (11) was prepared from **10** by the procedure described for preparation of **43c** in ref 1. Flash chromatography on silica gel (EtOAc–hexanes, 3:7) provided **11** as a colorless oil (76%): IR (film) 2.98, 3.42, 5.98 μm; ^{1}H NMR δ 0.91 (t, 3 H, J = 7 Hz), 1.05–1.72 (m, 9 H, 1.44 overlapping singlet, 9 H), 1.76–2.10 (m, 3 H), 2.51 (m, 1 H), 4.61–4.88 (m, 3 H), 4.64 (br d, 1 H); $[\alpha]^{21}_D$ +20.0° (*c* 1.80, $CHCl_3$).

Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.39; H, 10.76. Found: C, 66.47; H, 10.89.

(1*S*,2*S*,3*S*)-2-Formyl-3-*n*-propyl-*N*-(*tert*-butyloxycarbonyl)cyclohexylamine (12). Oxidation of **11** using the method of Swern[8] and flash chromatograpy on silica gel (EtOAc–hexanes, 3:7) gave **12** as a colorless solid (87%). Recrystallization from ether–hexanes (1:4) gave **12** as colorless needles: mp 85–86 °C; IR (KBr) 2.98, 3.41, 5.80, 5.95 μm; ^{1}H NMR δ 0.90 (t, 3 H, J = 7 Hz), 1.10–1.68 (m, 9 H, 1.45 overlapping singlet, 9 H), 1.80–2.10 (m, 2 H), 2.43 (ddd, 1 H, J = 7.0, 4.4, 2.3 Hz), 4.16 (m, 1 H), 4.52 (br d, 1 H), 9.85 (d, 1 H, J = 2.3 Hz); $[\alpha]^{24}_D$ +20.9° (*c* 1.90, $CHCl_3$); chemical-ionization mass spectrum, m/z (relative intensity) M + 1 (3), 214 (82), 170 (100), 153 (71).

Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.89; H, 10.09. Found: C, 66.92; H, 10.12.

(1*S*,2*R*,3*S*)-2-(3-Oxo-*trans*-hex-1-enyl)-3-*n*-propyl-*N*-(*tert*-butyloxycarbonyl)cyclohexylamine (16) was obtained as the major product from reaction of **12** with the sodium salt of dimethyl (2-oxopentyl)phosphonate by the procedure described by Overman and co-workers.[9] Flash chromatography on silica gel (EtOAc–hexanes, 3:7) provided a colorless oil (93%) containing **13** and **16** in a ratio of 1:5, respectively: ^{1}H NMR **16** δ 0.82 (t, 3 H, J = 7.2 Hz), 0.95 (t, 3 H, J = 7.3 Hz), 0.95–1.90 (m, 9 H, 1.41 overlapping singlet, 9 H, 1.61 overlapping quartet, 2 H), 2.17 (br t, 1 H), 2.53 (t, 2 H, J = 7.2 Hz), 3.51 (t, 2 H), 3.90 (br m, 1 H), 4.66 (br d, 1 H), 6.10 (d, 1 H, J = 16 Hz), 6.74 (dd, 1 H, J = 16, 10 Hz).

Anal. Calcd for $C_{20}H_{35}NO_3$ (mixture of **13** and **16**): C, 71.18; H, 10.44. Found: C, 71.09; H, 10.58.

(1*S*,2*S*,3*S*)-2-(3-Oxo-*trans*-hex-1-enyl)-3-*n*-propyl-*N*-(*tert*-butyloxycarbonyl)cyclohexylamine (13). To a solution of anhydrous lithium chloride (134 mg, 3.30 mmol), dimethyl (2-oxopentyl)phosphonate (349 mg, 1.79 mmol), and diisopropylethylamine (420 g, 3.30 mmol) in dry acetonitrile (15 mL) was added the aldehyde **12** (400 mg, 1.49 mmol).[10] The mixture was stirred at room temperature under nitrogen for 30 h. Concentration to one-half volume under vacuum was followed by the addition of 5 mL of water to the mixture. Extraction with ether (3 × 15 mL), drying of the combined organic layers over magnesium sulfate, concentration, and flash chromatography on silica gel (EtOAc–hexanes, 3:7) gave **13** as a colorless oil (441 mg, 88%): IR (film) 2.99, 3.41, 5.92 (broad), 6.15 μm; ^{1}H NMR δ 0.84 (t, 3 H, J = 6.6 Hz), 0.91 (t, 3 H, J = 7.3 Hz), 1.06–1.98 (complex multiplet, 11 H: overlapping singlet at 1.40, 9 H, quartet at 1.62, 2 H), 2.36 (m, 1 H), 2.50 (t, 2 H, J = 7.1 Hz), 3.72 (m, 1 H), 4.60 (br d, 1 H), 6.15 (d, 1 H, J = 16 Hz), 6.90 (dd, 1 H, J = 16, 10 Hz); $[\alpha]^{22}_D$ +17° (*c* 2.8, $CHCl_3$).

(2*R*,4a*R*,5*S*,8a*S*)-2,5-Di-*n*-propyldecahydroquinoline (18). A solution of **16** (315 mg, 0.93 mmol contaminated with ~15% of **13**) in 5 mL of ethyl acetate was hydrogenated (1 atm) over 5% palladium on carbon (30 mg) until the theoretical amount of hydrogen was absorbed (~1.5 h). Removal of the catalyst by filtration through Celite, followed by concentration, gave an oil in ~quantitative yield. Treatment of a solution of the crude reaction product in 3 mL of ether cooled to 0 °C with trifluoroacetic acid (TFA) at room temperature for 1 h, followed by removal of excess TFA under reduced pressure, provided a yellow gum. This material was neutralized with saturated potassium carbonate and extracted with ether. Drying over anhydrous potassium carbonate and concentration provided **17**, contaminated with **15**: ^{1}H NMR (major diastereomer) δ 0.87 (t, 3 H, J = 6 Hz), 0.96 (t, 3 H, J = 8 Hz), 1.02–2.10 (complex multiplet, 16 H), 2.44 (br t, 2 H, 2.52 overlapping multiplet, 2 H), 3.84 (br m, 1 H). Hydrogenation (1 atm) of the mixture over palladium on carbon (30 mg) in methanol for 6 h, removal of the catalyst by filtration through Celite, and concentration gave a mixture of **18** and **5b** as a colorless oil (198 mg, 96%): ^{1}H NMR (major diastereomer, $CDCl_3$) δ 0.84 (t, 3 H, J = 6 Hz, overlapping triplet, 3 H, J = 6 Hz), 0.96–1.90 (complex multiplet, 20 H), 1.98 (br d, 1 H, J = 12 Hz), 2.50–2.70 (br m, 1 H), 2.92 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 57.99, 56.50, 40.80, 39.78, 35.83, 33.53, 32.51, 31.94, 27.56, 27.04, 21.32, 19.42, 19.13, 14.57, 14.22. The hydrochloride salt of **18** was prepared by addition of concentrated HCl (several drops) to an ethanol solution of **18**. Concentration gave the hydrochloride as an amorphous colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, 0.90 overlapping triplet, 3 H, J = 7 Hz), 0.92–2.28 (complex multiplet, 18 h), 2.40 (br t, 2 H), 2.70–2.86 (br m, 1 H), 3.33 (br d, 1 H, J = 10 Hz), 8.36 (br m, 1 H, NH), 9.44 (br m, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 60.22, 58.56, 39.16, 35.32, 34.64, 31.45, 31.37, 29.15, 25.18, 23.51, 20.54, 19.19, 18.90, 14.40, 13.67. These spectral data compared favorably with those reported for the racemic material prepared by Overman and co-workers.[9]

(2*R*,4a*S*,5*S*,8a*S*)-2,5-Di-*n*-propyldecahydroquinoline (Perhydro-219A, 5b). A solution of **13** (339 mg, 1 mmol) in 8 mL of ethyl acetate was hydrogenated (1 atm) over 5% palladium on carbon (65 mg) until the theoretical amount of hydrogen was absorbed. Removal of the catalyst by filtration through Celite gave **14** as a low-melting solid in ~quantitative yield: IR (film) 2.98, 3.46, 5.88 μm; ^{1}H NMR δ 0.89 (t, 3 H), 0.91 (t, 3 H, J = 7.3 Hz), 1.08–1.86 (m, 16 H, 1.45 overlapping singlet, 9 H), 2.40 (t, 2 H, J = 7.4 H), 2.43 (t, 2 H, J = 7 H), 3.56 (br m, 1 H), 4.64 (br d, 1 H); electron-impact mass spectrum, m/z (relative intensity) 339 (M^+, 0.5), 239 (19), 238 (100). Conversion to the perhydroquinoline was effected as described for preparation of **18**. Recrystallization of the hydrochloride from 2-propanol–ethyl acetate (5:1) gave colorless crystals: mp 280 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.6 Hz, 0.92 overlapping triplet, 3 H, J = 7.2 Hz), 0.96–2.10 (complex multiplet, 19 H), 2.41 (br d, 1 H), 2.74–3.04 (br m, 2 H), 9.00 (br m, 1 H, NH), 9.44 (br m, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 58.36, 57.53, 42.14, 37.46, 35.10, 30.26, 28.40, 28.26, 27.98, 27.31, 21.17, 19.11, 18.85, 14.05, 13.64; electron-impact mass spectrum, m/z (relative intensity) 223 (M^+, 29), 208 (20), 180 (100); $[\alpha]^{23}_D$ +24° (*c* 1.06, $CHCl_3$); ^{13}C NMR (free amine, $CDCl_3$) δ 56.61, 55.64, 46.50, 39.65, 37.92, 34.56, 33.62, 29.81, 29.13, 28.83, 21.61, 19.75, 19.14, 14.18, 14.11.

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