eV) *m/e* (rel intensity) 328 (M^+, 100), 310 (6.6), 186 (59); IR (CCl_4) 3584 (m), 1715 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.23 (1 H, d, *J* = 8.5 Hz), 6.79 (1 H, dd, *J* = 8.5, 2.6 Hz), 6.68 (1 H, d, *J* = 2.6 Hz), 4.74 (1 H, br s, C_{11}–H), 3.80 (3 H, s), 2.87–2.85 (2 H, m), 2.64 (1 H, d, *J* = 11 Hz, C_9–H), 2.50–2.46 (1 H, m), 2.37–2.16 (5 H, m), 1.91–1.84 (1 H, m), 1.70–1.64 (1 H, m), 1.63–1.57 (2 H, m), 1.42 (1 H, br s), 1.40–1.33 (1 H, m), 1.01 (3 H, d, *J* = 6.6 Hz, C_{17a}–CH_3), 0.94 (3 H, s, C_{13}–CH_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 212.4, 157.8, 139.7, 127.6, 125.9, 114.2, 112.5, 67.4, 56.8, 55.1, 50.1, 48.4, 43.4, 40.9, 40.8, 33.2, 30.2, 25.7, 25.4, 15.6, 7.2. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.87; H, 8.62. Third fraction: C/D trans compound **7a**; 550 mg; white crystal; mp 189–190 °C (ether); TLC R_f = 0.30 (50% EtOAc/hexane); HPLC R_v = 9.3 (20% EtOAc/heptane); GC/MS (70 eV) *m/e* (rel intensity) 328 (M^+, 100), 310 (8); IR ($CHCl_3$) 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21 (1 H, d, *J* = 8.8 Hz), 6.77 (1 H, dd, *J* = 8.8, 2.7 Hz), 6.68 (1 H, d, *J* = 2.7 Hz), 4.77 (1 H, br s, C_{11}–H), 3.79 (3 H, s), 2.94–2.81 (2 H, m), 2.57 (1 H, t, *J* = 9 Hz, C_{17}–H), 2.51 (1 H, dd, *J* = 13.6, 2.3 Hz, C_9–H), 2.30–2.23 (1 H, m), 2.17 (3 H, s), 1.97–1.94 (1 H, m), 1.84–1.78 (2 H, m), 1.73–1.66 (1 H, m), 1.59–1.55 (1 H, m), 1.48–1.36 (4 H, m), 0.89 (3 H, s, C_{18}–H); $^{13}C^{13}C$ NMR ($CDCl_3$, 22.5 MHz) δ 208.8, 157.7, 139.8, 127.5, 125.9, 114.6, 112.3, 67.6, 64.3, 56.2, 55.0, 49.7, 44.5, 43.8, 33.2, 31.0, 29.9, 27.1, 23.7, 22.4, 15.8.

11β,20-Dihydroxy-5,19-cyclopregnan-3-one (10). To a stirred solution of diisobutoxy ketal **8d** (85 mg, 0.19 mmol) in ether (5 mL) at room temperature was added CH_2I_2 (0.16 mL, 2 mmol), followed by EtZnI[16] in ether solution (2 mL, 1 M, 2 mmol). The mixture was allowed to stir at room temperature for 10 h during which time a white precipitate formed. A solution of sodium thiosulfate (1 g of $Na_2S_2O_3$ in 20 mL of H_2O) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried, filtered, and concentrated to give an oil that was treated with 3 N HCl (0.5 mL) in THF (2 mL) at room temperature for 30 min. The mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic layer was dried, filtered, and concentrated to provide crude cyclopropyl ketone as an oil that was purified by flash chromatography (100% EtOAc) to give three fractions.

The first fraction was tentatively assigned as cyclopropane **9c**: white foam, 8 mg, R_f = 0.51 (TLC, 100% EtOAc); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.40–3.22 (m), 0.85–0.38 (cyclopropyl H). The second and third fractions, 44 mg, 0.13 mmol, 70% yield, were diastereomers (C_{20}). Each of them was successively crystallized from ethyl acetate, displaying the following properties. Isomer A: white crystal; mp 197–200 °C; TLC R_f = 0.20 (100% EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.37 (1 H, br s, C_{11}–H), 3.72 (1 H, m, C_{20}–H), 2.61 (1 H, *AB*, *J* = 17.6 Hz, C_4–H), 2.55 (1 H, *AB*, *J* = 17.6 Hz, C_4–H), 2.37–2.30 (1 H, m), 2.24 (1 H, dd, *J* = 14. 2.5 Hz), 2.17–2.09 (2 H, m), 2.05–2.00 (1 H, m), 1.98–1.90 (1 H, m), 1.80 (1 H, br s), 1.78–1.64 (3 H, m), 1.61–1.49 (2 H, m), 1.41–1.31 (3 H, m), 1.29–1.23 (2 H, m), 1.27 (3 H, d, *J* = 6 Hz, C_{21}–H), 1.22–1.17 (1 H, m), 1.16–1.12 (1 H, m), 0.96–0.88 (1 H, m), 0.90 (3 H, s, C_{18}–H), 0.75 (1 H, *AB*, *J* = 6 Hz, cyclopropyl H), 0.74 (1 H, *AB*, *J* = 6 Hz, cyclopropyl H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 211.3, 70.2, 68.0, 59.2, 55.8, 50.2, 47.5, 45.2, 41.4, 35.7, 31.3, 30.2, 27.2, 25.8, 25.6, 23.8, 23.3, 21.8, 18.4, 15.7, 14.9; high-resolution MS exact mass calcd for $C_{21}H_{32}O_3$, 332.2351; found, 332.2395. Isomer B: white crystal; mp 176–178 °C; TLC R_f = 0.10 (100% EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.35 (1 H, br s, C_{11}–H), 3.77–3.74 (1 H, m, C_{20}–H), 2.60 (1 H, *AB*, *J* = 17.6 Hz, C_4–H), 2.55 (1 H, *AB*, *J* = 17.6 Hz, C_4–H), 2.43 (1 H, dd, *J* = 14.2, 2.5 Hz), 2.36–2.31 (1 H, m), 2.19–2.10 (2 H, m), 2.09–2.01 (1 H, m), 1.79–1.62 (4 H, m), 1.60–1.48 (3 H, m), 1.38–1.28 (3 H, m), 1.22–1.12 (3 H, m), 1.15 (3 H, d, *J* = 6.2 Hz, C_{21}–H), 0.99 (3 H, s, C_{18}–H), 0.97–0.88 (1 H, m), 0.76 (1 H, *AB*, *J* = 5.6 Hz, cyclopropyl H), 0.74 (1 H, *AB*, *J* = 5.6 Hz, cyclopropyl H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 211.5, 70.2, 68.2, 59.1, 55.5, 50.3, 47.6, 46.4, 42.2, 35.8, 31.4, 30.6, 27.4, 26.0, 25.2, 24.2, 23.5, 21.9, 18.6, 15.8, 14.9.

Acknowledgment. This research was supported by the National Institute of Child Health and Human Development, National Institutes of Health (HD-14669). High-field NMR spectra were recorded at the National Science Foundation Northeast Regional NMR Facility, Yale University, Department of Chemistry. We are grateful to Dr. Brigette Segmuller for the X-ray structure of **7b** and Dr. Earl B. Whipple (Pfizer) for the high-resolution mass spectra.

Registry No. (±)-**1**, 88212-14-0; **1**·Li, 79066-28-7; (±)-**2**, 88212-15-1; (±)-**3a**, 88212-16-2; (±)-**3b**, 88212-17-3; (±)-**4a**, 88212-18-4; (±)-**4b**, 88212-19-5; (±)-**4c**, 88212-20-8; (±)-**4d**, 79066-20-9; (±)-**5a**, 88212-21-9; (±)-**5b**, 88212-22-0; (±)-**6a**, 79066-16-3; (±)-**6b**, 88212-23-1; (±)-**7a**, 88212-24-2; (±)-**7b**, 88269-19-6; (±)-**8a** (isomer 1), 88212-25-3; (±)-**8a** (isomer 2), 88212-26-4; (±)-**8b** (isomer 1), 88212-27-5; (±)-**8b** (isomer 2), 88212-28-6; (±)-**8c** (isomer 1), 88212-29-7; (±)-**8c** (isomer 2), 88212-30-0; (±)-**8d** (isomer 1), 88212-31-1; (±)-**8d** (isomer 2), 88212-32-2; (±)-**9a** (isomer 1), 88212-33-3; (±)-**9b** (isomer 2), 88212-34-4; (±)-**9c** (isomer 1), 88212-35-5; (±)-**10** (isomer 1), 88212-36-6; (±)-**10** (isomer 2), 88212-37-7; (±)-**11** (isomer 1), 88269-20-9; (±)-**11** (isomer 2), 88269-21-0; (±)-**12** (isomer 1), 81800-93-3; $CH_3C{\equiv}CCH_2CH_2OH$, 10229-10-4; $CH_3C{\equiv}CCH_2CH_2CN$, 18719-29-4; $CH_3C{\equiv}CCH_2CH_2CHO$, 41143-14-0; $(EtO)_2POCMeNaCo_2Et$, 67492-95-9; (*E*)-$CH_3C{\equiv}CCH_2CH_2CH{=}C(CH_3)COOEt$, 88212-38-8; (*E*)-$CH_3C{\equiv}CCH_2CH_2CH{=}C(CH_3)CH_2OH$, 88212-39-9; (*E*)-$CH_3C{\equiv}CCH_2CH_2CH{=}C(CH_3)CH_2Cl$, 58403-77-3.

Supplementary Material Available: Listing of additional spectral data (5 pages). Ordering information is given on any current masthead page.

Total Synthesis of (−)-Ptilocaulin

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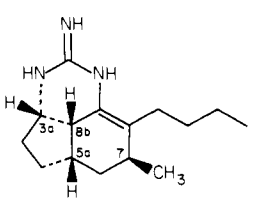
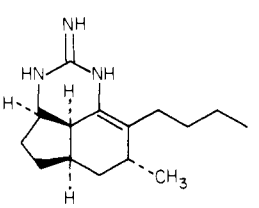
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received June 20, 1983*

Abstract: An efficient 14-step synthesis of (−)-ptilocaulin (**2**) from (*R*)-(+)-3-methylcyclohexanone is described (7.4% overall yield). This work establishes the absolute stereochemistry of the natural product to be that shown for **1**.

Ptilocaulin (**1**) is a novel antitumor antibiotic isolated from the Caribbean sponge *Ptilocaulis aff. P. spiculfer* (Lamarck, 1814).[2] We have developed and report herein an efficient synthesis of (−)-ptilocaulin (**2**),[3] which establishes the absolute stereochemistry



1



2

of the natural product be that shown for **1**. A key feature of our approach is the use of an intramolecular nitrone cyclization[4] to

(1) (a) Roger and Georges Firmenich Assistant Professor of Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–1984. (b) National Cancer Institute Predoctoral Trainee.

(2) Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L, Jr.; Shaw, P. D.; Hughes, R. G., Jr.; Mizsak, S. A.; Coats, J. H.; Zurenko, G. E.; Li, L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5604.

0002-7863/84/1506-0721$01.50/0

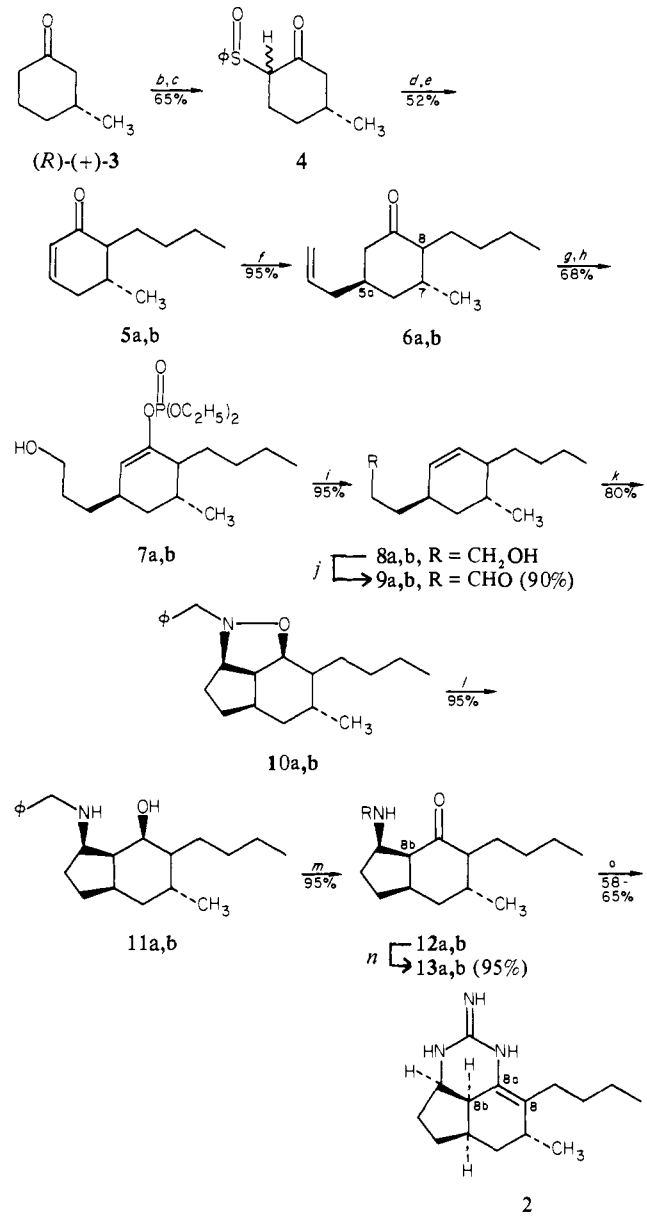
establish the stereochemistry of C-3a and C-8b relative to C-5a. We assumed from the outset that control of these centers would be crucial to the success of the plan. In practice, however, the center at C-8b proved to be of little strategic importance since the natural product possesses the thermodynamically most stable configuration at this center.

Our synthesis of **2** (Scheme I) originates from (*R*)-(+)-**3** ($[\alpha]^{23}_D$ +12.0°),[5] which, in turn, is readily available from (+)-pulegone.[6] Sulfenylation of **3** with diphenyl disulfide followed by oxidation of the resulting sulfide with MCPBA provided the known sulfoxide **4** in 65% yield.[7] Alkylation of **4** with *n*-butyl iodide via the dianion[8] (2.2 equiv of 1 M LDA in THF, 6 equiv of HMPT, −35 °C, 3 h; then 1.2 equiv of *n*-butyl iodide, 2 h, −35 °C) afforded a complex mixture of diastereomeric butylated sulfoxides[9] (80% after chromatography), which, without separation, was heated in CCl_4 in the presence of 0.95 equiv of $CaCO_3$ (24 h), thus affording enone **5** in 52% overall yield from **4**.[10] Treatment of **5** with 1.2 equiv of $TiCl_4$ and 1.5 equiv of allytrimethylsilane[11] at −78 °C in CH_2Cl_2 afforded ketone **6a/6b** in 95% yield, with complete control of the stereochemistry at C-5a relative to C-7.[12] A mixture of isomers, however, was obtained at C-8, the ratio of which varied as a function of the reaction scale.[13] These isomers have been separated and brought independently through the synthesis to **2**. On a routine basis, however, such mixtures were used without separation.[14]

Conversion of **6a/6b** to aldehyde **9a/9b** and thence to isoxazolidine **10a/10b** proceeded in a straightforward fashion. Thus, the kinetic enolate of **6a/6b** (generated by using 1.6 equiv of 0.5 M LDA, THF, −78 °C, 1.5 h) was treated with 2.0 equiv of HMPT (0 °C, 20 min) followed by 2.8 equiv of chlorodiethyl phosphate (23 °C, 4 h). Selective hydroboration of the resulting enol phosphate derivative using 2.0 equiv of 9-BBN (0.35 M in THF, 0 °C, 4 h) provided alcohol **7a/7b** in 68% overall yield. Addition of a THF solution of **7a/7b** (0.35 M, containing 3.75 equiv of *t*-BuOH) to excess lithium (10 equiv) in ethylamine (0.5 mL/mol of Li, containing 2 equiv of *t*-BuOH) provided alcohol **8a/8b**, oxidation of which with 1.5 equiv of pyridinium chlorochromate afforded aldehyde **9a/9b** in 85% yield. Finally, treatment of **9a/9b** with 1.0 equiv of benzylhydroxylamine in benzene (0.05 M, 80 °C, 8 h) effected smooth conversion to isoxazolidine **10a/10b** via the intermediate nitrone[4] in 80% yield (R_f **10a**, 0.5; R_f **10b**, 0.57, silica gel, 1:4 ether–hexane). A single diastereomer (**10a** or **10b**, repsectively) was obtained when isomerically pure **9a** or **9b** was subjected to these conditions.

Final elaboration of **10a/10b** to ptilocaulin required considerably more experimentation than orginally anticipated. The route that proved most efficacious is oulined below. Cleavage of the nitrogen–oxygen bond of **10a/10b** was effected by using excess Zn in 10 M aqueous acetic acid (55 °C, 3.5 h), which provided **11a/11b** in 95% yield. The hydrochloride salt of **11a/11b** was then oxidized with a large excess of Jones reagent in glacial acetic acid (0 °C, 2.5 h) to give **12a/12b** in 95% yield. Under these conditions, however, some epimerization (ca. 5–10%) occurred at C-8b.[15] Whereas this epimerization was initially very trou-

Scheme I[a]



[a] Series "a" designates C-8 α-butyl epimer, "b" designates the β-butyl epimer. [b] LDA, THF, −78 °C; $(PhS)_2$. [c] MCPBA, CH_2Cl_2, −78 °C. [d] 2.2 equiv of 1 M LDA in THF, 6 equiv of HMPT, −35 °C, 3 h; 1.2 equiv of *n*-butyl iodide, 2 h, −35 °C. [e] 0.95 equiv of $CaCO_3$, CCl_4, 65 °C, 24 h. [f] $TiCl_4$, allyltrimethylsilane, −78 °C, 1.5 h. [g] 1.6 equiv of 0.5 M LDA, −78 °C, 1.5 h; 2.8 equiv of chlorodiethyl phosphate, 23 °C, 4 h. [h] 2.0 equiv of 0.35 M 9-BBN in THF, 0 °C, 4 h. [i] 10 equiv of Li, $CH_3CH_2NH_2$, *t*-BuOH, THF. [j] PCC, CH_2Cl_2, 23 °C. [k] 1.0 equiv of $PhCH_2NHOH$, C_6H_6, 80 °, 8 h. [l] Excess Zn, 10 M AcOH, 55 °C, 3.5 h. [m] Excess Jones reagent, AcOH, aqueous HCl, 0 °C. [n] Pd black, 10% HCO_2H/CH_3OH, 23 °C, 1.5 h. [o] 1-Guanyl-3,5-dimethylpyrazole nitrate, 145–155 °C, neat, 6 h.

(3) A synthesis of racemic **1** has been recently reported: Snider, B. B.; Faith, W. C. *Tetrahedron Lett.*, **1983**, 861.

(4) (a) Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205. (b) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. (c) Oppolzer, W. *Ibid.* **1977**, *16*, 10. (d) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396.

(5) Literature $[a]_D^{20}$ +12.5°: Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.* **1955**, *77*, 5172.

(6) (a) Rupe, H. *Liebigs Ann. Chem.* **1927**, *459*, 195. (b) Allinger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316.

(7) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.

(8) Grieco, P. A.; Pogonowski, C. S. *J. Chem. Soc., Chem. Commun.* **1975**, 72.

(9) Structures for all new compound (**a** *and* **b** series) are fully consistent with the spectroscopic data summarized in the supplementary material section.

(10) Compound **5** is a ca. 6:1 mixture of epimers at C.8, with the major epimer tentatively assigned the β configuration. Racemic **5** served as an intermediate in Synder's synthesis (see ref 3).

(11) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

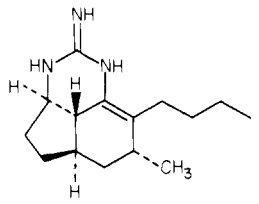
(12) The stereochemistry of the Sakurai reaction with a variety of cycloalkenones was reported while our work was in progress: Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354. See also: Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.

(13) The ratios of **6a/6b** produced from **5** were 1:6 (0.5 mmol scale), 1:2 (3 mmol), and 2:1 (6 mmol). The latter is the equilibrium mixture, as determined by K_2CO_3–MeOH equilibration of either pure **6a** or **6b**. Relevant data for **6a**: ^1H NMR δ 0.77 (d, 3 H, C-7 CH_3); R_f 0.63 (silica gel, 1:4 ether–hexane). **6b**: ^1H NMR δ 0.98 (d, 3H, C-7 CH_3); R_f 0.58 (silica gel 1:4 ether–hexane). **Note Added in Proof**: We have recently observed that this epimerization occurs during reaction workup. Essentially no epimerization occurred, even in large-scale experiments, when the dark red reaction mixture was quenched with H_2O and maintained at −78 °C until the solution turned colorless.

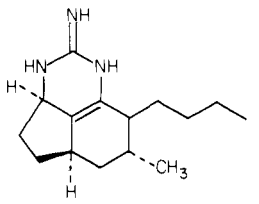
(14) The yields for each step leading from **6a/6b** to **2** were comparable whether pure **a**, pure **b** or **a/b** mixtures were used.

blesome, it proved, ultimately, to be of no major consequence to the successful completion of the syntheis.[16]

Benzylamino ketone **12a/12b** so obtained was smoothly deprotected, albeit again with considerable epimerization, via transfer hydrogenolysis (Pd black, 10% HCO_2H/CH_3OH, 23 °C, 1.5 h) to give the sensitive amino ketone **13a/13b** in 95% yield. Condensation of **13b** with the nitrate salt of 1-guanyl-3,5-dimethylpyrazole (GDMP)[17] (1 equiv, 120 °C, neat, 15 min) provided a ~1:1:2 mixture of three isomers (inseparable) tentatively assigned structures **14**, **15b**, and **2**, respectively, in 48% yield.[18] Under



14



15a,b

the same conditions **13a** afforded a mixture containing predominately **15a** and a small amount of **14**, but with only a trace of **2** present. Either mixture, however, could be equilibrated to **2** (89% after chromatography) by treatment with guanidine in refluxing C_6H_6 (12-24 h). Alternatively, treatment of **13a/13b** with 1.1 equiv of GDMP under equilibrating conditions (145-155 °C, neat, 6 h) afforded (-)-**2** directly in 58-65% yield. The ptilocaulin nitrate (mp 183-184 °C; $[\alpha]^{22}_D$ - 73.9° (*c* 0.31, 99.9% CH_3OH)) so obtained was identical in all respects (with the exception of optical rotation) with an authentic sample of the natural product.[19] The absolute configuration of (+)-ptilocaulin is thus established as that represented by **1**.

Acknowledgment. This research was generously supported by grants from the National Cancer Institute (Training Grant No. T32-CA-09112) and the National Science Foundation (Grant No. 8106987-CHE).

Registry No. 1, 78777-02-3; **2**, 88154-76-1; **2**·HNO_3, 88195-34-0; **3**, 13368-65-5; **4**, 88154-77-2; **4** (butylated), 88057-80-1; **5a**, 88154-78-3; **5b**, 88154-79-4; **6a**, 88154-80-7; **6a**-enol diethylphosphate, 88057-81-2; **6b**, 88155-70-8; **6b**-enol diethylphosphate, 88057-82-3; **7a**, 88057-64-1; **7b**, 88057-65-2; **8a**, 88057-66-3; **8b**, 88057-67-4; **9a**, 88057-68-5; **9b**, 88057-69-6; **10a**, 88057-70-9; **10b**, 88154-81-8; **11a**, 88057-71-0; **11a**·HCl, 88057-73-2; **11b**, 88057-72-1; **11b**·HCl, 88057-74-3; **12a**, 88057-75-4; **12a** (C-8b epimer), 88057-83-4; **12b**, 88057-76-5; **12b** (C-8b epimer), 88057-84-5; **13a**, 88057-77-6; **13a** (C-8b epimer), 88057-85-6; **13b**, 88057-78-7; **13b** (C-8b epimer), 88057-86-7; **14**, 88154-82-9; **15a**, 88057-79-8; **15b**, 88154-83-0; GDMP, 38184-47-3; benzylhydroxylamine, 622-30-0; 4 (butylated), 88057-80-1.

Supplementary Material Available: Spectroscopic data and physical constants for **5a,b, 6a,b, 7a,b, 8a,b, 9b, 10a,b, 11a,b, 12a,b, 13a,b,** and synthetic ptilocaulin (9 pages). Ordering information is given on any current masthead page.

(15) Greater amounts of epimerization occurred when the Jones oxidation of **11a/11b** was performed in aqueous acetone. The use of acetic acid as solvent greatly accelerated the rate of oxidation (this solvent effect has previously been noted: Mueller, R. H.; DiPardo, R. M. *J. Org. Chem.* **1977**, *42*, 3210), which allowed this step to be performed at 0 °C. Although the trans-fused epimers could be removed by chromatography, this separation proved unnecessary on a routine basis (see ref 16).

(16) The successful solution to this synthesis relies on thermodynamic control. Indeed, epimeric mixture of **12a/12b** brought through the sequence afford ptilocaulin by using the high-temperature GDMP step described in the text.

(17) Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541.

(18) All compounds containing the guanidinium moiety were isolated and characterized as nitrate salts.

(19) Natural ptilocaulin nitrate has mp 183-185 °C (ref 2) and $[\alpha]^{23}_D$ +74.4° (99.5% CH_3OH) (Prof. K. L. Rinehart, personal communication). We thank Prof. Rinehart for providing the optical rotation data as well as a sample of natural ptilocaulin nitrate. We are also grateful to Prof. B. B. Snider for providing spectroscopic data and a sample of racemic **1**.

Synthesis of (*R*)-(+)-[10.10]- and -[22.10]Betweenanene and Related *trans*-Cyclododecenes

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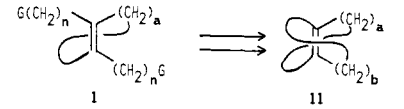
Abstract: A general synthesis of 1,2-disubstituted *trans*-cycloalkenes is described starting from 2-methylenecyclododecanone. Addition of dimethylsulfonium methylide affords the vinyl oxirane **1** which undergoes highly selective S_N2' addition with organocopper reagents derived from alkylmagnesium bromides and copper(I) iodide in THF-Me_2S. The resulting *trans*-cyclododecenylcarbinols **2** are coupled via the diethyl phosphate derivatives **3** to the dialkylcyclododecenes **4**. Sharpless resolution of alcohols **2** leads via the same sequence to optically active cyclododecenes **4** of *R* configuration. A second coupling route entails oxidation of the alcohols **2** to aldehydes **12**, addition of Grignard reagents to give the allylic alcohols **13**, and Birch reduction of the derived acetates **14**. Conversion of the ω-alkenyl-substituted cyclododecenes **4b** and **14** to the dialdehydes **6** and **17** followed by McMurry Ti(0) cyclization and catalytic hydrogenation affords optically active [10.10]- and [22.10]betweenanene of *R* configuration.

The inherent chirality of *trans*-cycloalkenes was noted by Blomquist[1] in 1952 and experimentally confirmed some ten years later by Cope.[2] In a brilliant series of studies, Cope resolved

Scheme I



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trans-cyclooctene[2a] and correlated the (-)-enantiomer with (+)-tartaric acid thus establishing the absolute stereochemistry as (*R*)-(-).[2b,3] He also found that while *trans*-cyclononene could

(1) Blomquist, A. T.; Liu, L. H.; Bohrer, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 3643-7.

(2) (a) Cope, A. C.; Howell, C. F.; Knowles, A. *J. Am. Chem. Soc.* **1962**, *84*, 3190-1. Cope, A. C.; Ganellin, C. R.; Johnson, H. W. *Ibid.* **1962**, *84*, 3191-2. Cope, A. C.; Ganellin, C. R.; Johnson, H. W. Jr.; Van Auken, T. V.; Winkler, H. J. S. *Ibid.* **1963**, *85*, 3276-9. (b) Cope, A. C.; Mehta, A. S. *Ibid.* **1964**, *86*, 5626-30. (c) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *Ibid.* **1965**, *87*, 3644-9. (d) Cope, A. C.; Pawson, B. A. *Ibid.* **1965**, *87*, 3649-51. (e) Binsch, G.; Roberts, J. D. *Ibid.* **1965**, *87*, 5157-62.

(3) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385-415. See pp 400-3.

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