plexes of 1,4-diaryltetraazadiene. Also, gas-phase mass spectroscopic studies of the reaction of phenyl nitrene anion radical with phenyl azide[39] suggest the formation of the anion radical of 1,4-diphenyltetraazadiene. Experimental evidence for formation of a cyclic triaza species is derived from the photochemical cyclization of an azimine to a triaziridine[40] and from the reaction of ^{15}N-enriched hydrazine with nitrous acid, which may have formed a cyclic azide intermediate.[41] Nanosecond transient absorption spectral studies of PhN_3[42] provide evidence of the intermediacy of phenyl nitrene. Other species were not observed on a time scale as short as 15 ns.

Reaction 4, or the set of reactions 5 and 6 or 7 and 8, may result in the formation of *two* phenyl nitrene intermediates from bimolecular reaction of one phenyl nitrene and one phenyl azide molecule. The net reaction of any set is not only a chain reaction but also specifically a branching chain reaction, known as an autocatalytic or spontaneously explosive reaction.[43] Such reactions occur in the vapor phase and theoretical descriptions have been developed based upon thermal initiation of the chain reaction;[43,44] however, they are not useful to our solution studies. Explosions of metallic azide crystals have been reported;[45-48] however, branching chain reactions (or explosions) were not reported to occur in solution. Nevertheless, the relationship between ϕ-PhN_3 and n with $[PhN_3]$ provides experimental evidence for occurrence of a *branching chain reaction in solution.*

The photochemical initiation of chain reactions is well documented.[49] The photochemical initiation of the branching chain reaction of phenyl azide that we have just examined occurs with an efficiency of 0.5 (Table I). The chain length, n, is therefore calculated by using this experimental value and *assuming* that reaction 4, and/or reactions 5 and 6 and 7 and 8, occurs with unit efficiency. Were the reaction of phenyl nitrene and phenyl azide to be less than unit efficient, then the calculated values of n presented in Table I are necessarily underestimated.

Conclusion

A chain decomposition reaction of phenyl azide can be initiated photochemically. Upon irradiation of phenyl azide in solution, molecular nitrogen is evolved and phenyl nitrene is formed. In dilute solutions of $[PhN_3] \sim 10^{-5}$ M, ϕ-$PhN_3 = 0.5$. Dimerization of two phenyl nitrenes[14] then leads to (*E*)-azobenzene formation. At higher concentrations of phenyl azide, phenyl nitrene can react with a phenyl azide molecule to net *two* phenyl nitrene intermediates. This reaction is repeated, affording *four* phenyl nitrenes, and is manifested as ϕ-PhN_3 values that greatly exceed unit efficiency. ϕ-PhN_3 depends exponentially upon the concentration of phenyl azide, a result indicative of a branching chain or autocatalytic reaction. The results provide experimental data for the occurrence of a molecular explosion in solution.

Acknowledgment. We are indebted to the National Science Foundation for support of this research via a grant to the Center for the Joining of Materials (DMR 76-81561).

Registry No. Phenyl azide, 622-37-7.

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Synthesis of (±)-11-Ketoprogesterone, a Precursor to the Corticosteroids. An Improved Method for the Introduction of the Carbon 19 Methyl Group into A-Ring Aromatic Steroids†

Frederick E. Ziegler* and Tein-Fu Wang

Contribution from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511. *Received July 20, 1983*

Abstract: A new approach to corticosteroids is presented that realizes 11-ketoprogesterone. The C_8-C_{14} stereochemistry of the steroid is established by a Cope rearrangement that allows for the stereocontrolled formation of the C and D rings by acid-catalyzed cyclizations. The formation of an 11β-hydroxyl group permits the stereocontrolled introduction of the C_{19}-methyl group under Simmons-Smith-Sawada conditions having the C_3 ketone protected as a ketal.

We have previously described a formal total synthesis of estrone employing the (trimethylsilyl)cyanohydrin Cope rearrangement.[1] We report in this paper mechanistic aspects of the acid-mediated ring-forming reaction, the applicability of a methyl acetylene terminator to these cyclizations, and an improved method for introduction of the C_{19}-methyl substituent into A-ring aromatic steroids. These studies have culminated in a synthesis of (±)-

† Dedicated to Professor William S. Johnson on the occasion of his seventieth birthday.

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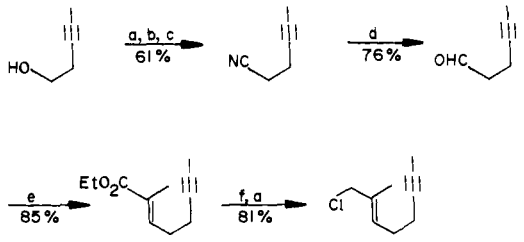
0002-7863/84/1506-0718$01.50/0

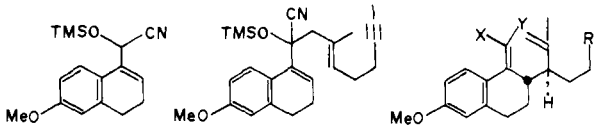
Scheme I

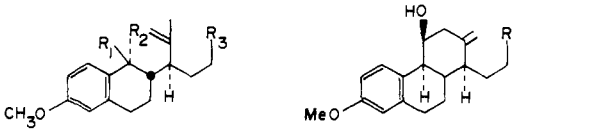


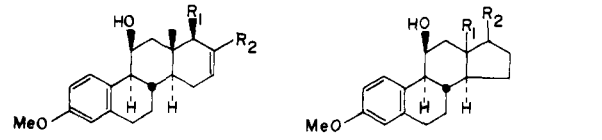
a) MsCl, Et_3N, CH_2Cl_2; b) LiBr, acetone, Δ; c) NaCN, aq. EtOH, Δ; d) DIBAL; e) $(EtO)_2POCMeNaCO_2Et$, THF; f) $LiAlH_4$, Et_2O, inverse.

11-ketoprogesterone, a precursor in the synthesis of corticosteroids.[2]

The lithium anion of (trimethylsilyl)cyanohydrin **1**[1] was treated







(−78 → 25 °C, 6 h at 25 °C) with 1-chloro-2-methyl-2(*E*)-octen-6-yne (prepared as outlined in Scheme I) to afford the alkylation product **2** as an oil in 75% yield. When the (trimethylsilyl)cyanohydrin **2** was heated (160–170 °C, 50 h, neat, N_2), a mixture of *p*-methoxycinnamonitriles **3a** and **3b** (2.5/1) was obtained. The C_1–H of the major *E* isomer was shifted downfield (δ 7.69, d, J = 8.8 Hz) by the cyano group relative to that of the *Z* isomer (δ 7.56, d, J = 8.8 Hz). The mixture was transformed (KF, CH_3OH, reflux) into a 55/45 mixture (cis/trans, **4b**/**4a**) of methyl esters in 80% yield from **2**.[4,5]

Reduction ($LiAlH_4$, ether) of the epimeric esters **4a** and **4b** followed by Swern oxidation[6] [$(COCl)_2$, Me_2SO, CH_2Cl_2, Et_3N, −60 → 25 °C] and subsequent equilibration (NaOMe, MeOH) afforded aldehyde **4c** in 70% overall yield.[7]

Cyclization[8] [$SnCl_4$, $(CH_2O)_2CO$, CH_2Cl_2, 0 °C, 3 min] of aldehyde **4c** gave rise to crystalline tricyclic alcohol **5a** in 68% yield. Examination (NMR) of the mother liquors of the reaction mixture revealed negligible amounts of other olefin isomers. The presence of an axial hydroxyl group at C_{11} (C_{12}–H_a, δ 2.54, dd, J = 16, 3 Hz; C_{12}–H_b, δ 2.58, dd, J = 16, 3 Hz) and an exocyclic olefin (δ 4.85 and 4.95, 2 × 1 H, s) argued for ring formation via a Lewis acid catalyzed ene reaction.[9] Prolonged treatment (3 h) of aldehyde **4c** under the same conditions provided a complex mixture of chlorides.[10] However, 3 min was found to be sufficient time for the formation of both the C and D ring of tetracycle **6a** from aldehyde **4d** bearing the isopropenyl terminator.[1] Stannic chloride mediated cyclization of *trans*-aldehyde **4d** for 20 s at −30 °C provided a 4/1 mixture of tetracycle **6a** and tricycle **5b**. The latter compound underwent facile cyclization at 0 °C in 3 min to provide the tetracycle **6a**.

Two tertiary carbenium ions can be generated by protonation of the double bonds in diene **5b**. Protonation of the exocyclic olefin leads to favorable cyclization through a chairlike transition state to afford the observed product **6a**. Protonation of the isopropenyl group requires a boatlike transition state for cyclization.

Exposure of acetylene **5a** to 95% trifluoroacetic acid (2 h, 25 °C) followed by treatment with potassium carbonate in methanol gave rise to three tetracyclic compounds, **7a** (51%), **7b** (9%), and **6b** (9%).[11] While the infrared and NMR spectra of these compounds were in accord with these structural assignments, single-crystal X-ray analysis confirmed the stereochemical assignment of the isomers of **7**.[12]

The realization of ketoalcohol **7a**[13] set the stage for introduction of the angular C_{19}–β-CH_3 group under the control of the C_{11}–β-OH group. This transformation has been reported to be successful with 17β-acetoxy-11β-hydroxyestr-5(10)-en-3-one employing the Simmons–Smith (Zn/Cu, CH_2I_2) reagent.[14,15]

Reduction of keto alcohol **7a** (Li/NH_3, EtOH, THF) followed by hydrolysis (aqueous THF, oxalic acid, 25 °C) provided a separable mixture of C_{20} epimeric β,γ-unsaturated ketones in 82% yield. Attempted introduction of the C_{19}-methyl group with Zn/Cu couple or under Sawada's conditions (EtZnI)[16] proved to

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(5) All compounds provided correct spectroscopic data and/or combustion analyses.

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(7) Stereochemistry was inferred at this point based upon previous work (ref 1).

(8) Optimal yields were obtained in the presence of ethylene carbonate although there was no sign of trapping of the incipient vinyl cation with this reagent. cf. McCarry, B. E.; Markezich, R. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4416.

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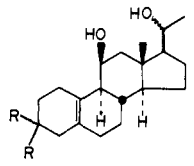
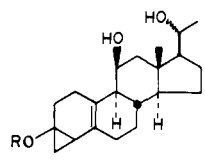
(16) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669.

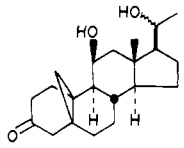
be unsuccessful. However, when the more polar (TLC) dimethoxy ketal **8b** (or the C_{20} epimeric mixture), prepared (MeOH, THF, anhydrous, oxalic acid) from the intermediate enol ether of Birch reduction, was exposed to $EtZnI/CH_2I_2$ followed by mild acid hydrolysis (4/1 THF/3 N HCl, 25 °C, 0.5 h), an 85/15 ratio of products was obtained. The major component was tentatively assigned structure **9a**, whose NMR spectrum revealed a singlet for a methyl ether (δ 3.30, 3 H), high-field signals (δ 0.77, 1 H, m; δ 0.38, 1 H, t, J = 5.3 Hz) for the cyclopropane hydrogens, and the absence of vinylic hydrogens. The minor component was the desired cyclopropyl ketone **10**. The major component ostensibly arises via Lewis acid promoted elimination of the elements of methanol from **8b** followed by cyclopropanation of the resultant dienol ether. This effect could be repressed by rendering the ketal a poorer Lewis base. Accordingly, the diethoxy ketal **8c** provided a 50/50 mixture while the diisobutoxy ketal **8d** provided a 15/85 mixture of **9c** and **10**, respectively. A 70% isolated yield could be realized by the latter cyclopropanation procedure.



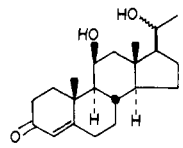
8a, R = O
b, R = OMe
c, R = OEt
d, R = Me_2CHCH_2O



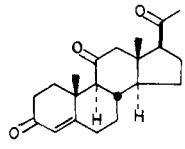
9a, R = Me
b, R = Et
c, R = Me_2CHCH_2



10



11



12

Ring opening was achieved under alkaline conditions (KO-*t*-Bu, Me_2SO, 52%)[15b] to afford enone **11**, which was subsequently oxidized (PDC, CH_2Cl_2, 95%)[17] to provide (±)-11-ketoprogesterone, mp 173–74 °C (lit.[18] mp 175–176 °C), whose NMR spectrum (500 MHz) was found to be indistinguishable from that of an optically active sample prepared from natural sources.[19]

This series of synthetic operations nicely complement one another. The Cope rearrangement controls the initial C_8–C_{14} stereochemistry while the aromatic ring ensures the equilibrium position and the low temperature for rearrangement. The α-[(trimethylsilyl)oxy]cinnamonitrile gives way to an aldehyde function that initiates formation of rings C and D and provides the handle for angular methylation.

Experimental Section

General. Reagents were used as received. Dichloromethane was distilled over calcium hydride before use. Ether was dried over sodium benzophenone ketyl.

Gas chromatography (GC) was carried out on a Perkin-Elmer 3920 FID or a Varian Aerograph 1400 thermal conductivity unit. A 6 ft × $^1/_8$ in. column was used with the flow rate of carrier gas maintained between 50 and 60 mL/min. Analytical thin-layer chromatography (TLC) was carried out using E. Merck silica gel 60 F-254 glass plates (0.25 mm).

Flash chromatography[20] was carried out using E. Merck silica gel 60 (230–400 mesh). Analytical high-performance liquid chromatography (HPLC) was accomplished using a Waters Associates M-45 solvent delivery system, RCM-100 column chamber, R 401 differential refractometer, Model 440 absorbance detector, and Radial-pak B cartridge at a 3 mL/min flow rate.

Melting points (mp) were recorded on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 710B spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on a Bruker HX-500 (or HX270) or a JEOL FX-90Q. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a JEOL FX-90Q. Mass spectra (MS) were recorded on a Hewlett-Packard 5985 GC/MS system containing a 2% OV-101 column (3 ft × $^1/_4$ in. × 2 mm) on Chromosorb WHP 100/120.

Microanalyses were performed by Atlantic Nicrolaboratories, Inc., Atlanta, GA. High-resolution mass spectra were performed by Pfizer Inc., Groton, CT. Single-crystal X-ray crystallography was carried out on an Enraf-Nonius CAD-4F diffractometer (see paragraph at end of paper regarding supplementary material).

Tricyclic 5a. A stirred solution of *trans*-aldehyde **4a** (730 mg, 2.35 mmol) and ethylene carbonate (220 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) was cooled in an ice–water bath to 0 °C. To this mixture was added a solution of $SnCl_4/CH_2Cl_2$ (0.1 M, 25 mL, 2.5 mmol) over a period of 20 s. The resulting brown solution was allowed to stir at 0 °C for 3 min, followed by the addition of saturated $NaHCO_3$ solution (10 mL). After the mixture was stirred vigorously for another 10 min, the resulting yellow mixture was diluted with CH_2Cl_2 (300 mL). The organic layer was washed with water and dried over anhydrous $MgSO_4$ to give a yellow oil after filtration and concentration.

The crude oil was purified by flash chromatography (20% EtOAc/hexane) to give 500 mg (68%) of tricyclic **5a** as a yellow oil, which was crystallized from ether (5 mL), providing 425 mg (58%) of white crystals: mp 102–103 °C; GC R_t = 24 min (5% OV-1, 200 °C); TLC R_f = 0.15 (20% EtOAc/hexane); HPLC R_v = 7.2 (10% EtOAc/heptane); GC/MS (70 eV) *m/e* (rel intensity) 310 (M^+, 20), 292 (3.5), 160 (100); IR ($CHCl_3$) 3560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.27 (1 H, d, J = 8.8 Hz), 6.76 (1 H, dd, J = 8.8, 2.9 Hz), 6.64 (1 H, d, J = 2.9 Hz), 4.95 (1 H, s), 4.85 (1 H, s), 4.68 (1 H, m, C_{11}–H), 3.78 (3 H, s), 2.83–2.78 (2 H, m), 2.71 (1 H, dd, $J_{8,9}$ = 11 Hz, $J_{9,11}$ = 3 Hz, C_9–H), 2.54 (1 H, *A*B, dd, J = 16, 3 Hz, C_{12}–H), 2.58 (1 H, A*B*, dd, J = 16,3 Hz, C_{12}–H), 2.34–2.06 (3 H, m), 2.01–1.88 (2 H, m), 1.82–1.68 (1 H, m), 1.79 (3 H, t, J = 2.5 Hz), 1.62 (1 H, q, J = 11 Hz, C_8–H), 1.47–1.35 (1 H, m), 1.43 (1 H, d, J = 4.7 Hz, –OH); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 157.5, 145.5, 139.3, 128.2, 126.4, 113.9, 112.1, 109.7, 79.2, 75.4, 67.7, 54.9, 47.5, 46.6, 42.5, 38.8, 30.2, 27.9, 26.9, 16.3, 3.3. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.15; H, 8.44.

Cyclization of Tricyclic 5a: 11β-Hydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (7a); (13α,17α)-11β-Hydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (7b); 11β-Hydroxy-3-methoxy-17aβ-methyl-D-homoestra-1,3,5(10)-trien-17-one (6b). A solution of tricyclic **5a** (1.00 g, 3.2 mmol) in trifluoroacetic acid/H_2O (4 mL, 20/1) was stirred at room temperature under nitrogen for 2 h. The resulting deep purple solution was concentrated under reduced pressure. The residue was treated with K_2CO_3 (ca. 1 g) in methanol (20 mL) at room temperature for 1 h. The solvent was removed in vacuo, and the products were taken up in CH_2Cl_2, washed with water, dried over anhydrous sodium sulfate, and concentrated to give a yellow foam. HPLC (20% EtOAc/heptane) showed a mixture of tetracyclic compounds in a ratio of 13/13/73 (**7b**/**6b**/**7a**). The mixture was separated by flash chromatography (20% EtOAc/hexane) to give a total of 750 mg (70%) of three tetracyclic compounds. First fraction: C/D cis compound **7b**; 100 mg; white crystal; mp 146–147 °C (ether); TLC R_f = 0.42 (50% EtOAc/hexane); HPLC R_v = 5.1 (20% EtOAc/heptane); GC/MS (70 eV) *m/e* (rel intensity) 328 (M^+, 100), 310 (12); IR ($CHCl_3$) 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (1 H, d, J = 8.5 Hz), 6.76 (1 H, dd, J = 8.5, 2.7 Hz), 6.66 (1 H, d, J = 2.7 Hz), 4.72 (1 H, br s, C_{11}–H), 3.78 (3 H, s), 3.76 (1 H, t, J = 9.5 Hz, C_{17}–H), 2.85–2.82 (2 H, m), 2.52 (1 H, d, J = 11.3 Hz, C_9–H), 2.45 (1 H, dd, J = 15.2, 3 Hz), 2.21 (3 H, s, C_{21}–H), 2.18–2.06 (2 H, m), 2.01–1.94 (1 H, m), 1.80–1.73 (1 H, m), 1.71–1.59 (4 H, m), 1.41–1.38 (1 H, m), 1.30–1.21 (1 H, m), 0.88 (3 H, s, C_{18}–H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 211.7, 157.7, 140.1, 128.1, 126.0, 114.3, 112.3, 67.4, 56.3, 55.0, 54.3, 46.8, 44.0, 39.4, 34.4, 31.7, 30.5, 27.5, 25.4, 25.0, 23.9. Second fraction: D-homo compound **6b**; 100 mg; white crystal; mp 179–180 °C (ether); TLC R_f = 0.39 (50% EtOAc/hexane); HPLC R_v = 6.2 (20% EtOAc/heptane); GC/MS (70

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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, A*B*, 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, A*B*, 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, A*B*, 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, A*B*, 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.

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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.

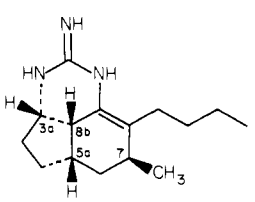
Total Synthesis of (-)-Ptilocaulin

William R. Roush*[1a] and Alan E. Walts[1b]

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



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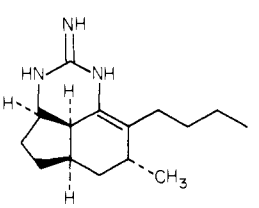

2

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

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