ethylammonium bromide (1 g, 5 mmol) were heated at 180 °C for 1 h. The resulting mixture was dissolved in methylene chloride and first extracted repeatedly with 10% NaOH solution until the washings were colorless and then with 10 mL of water. The methylene chloride layer was dried over anhydrous Na_2SO_4 and concentrated to yield the product which was crystallized in petroleum ether (2.5 g, 68% yield; mp 92 °C; lit.[13] mp 86–87.5 °C).

b. *N*-[3-(2-Hydroxyethoxy)phenyl]hydroxylamine, 1. *m*-Nitrophenoxyethanol (1 g, 6 mmol) and ammonium chloride (0.7 g, 13 mmol) were suspended in a mixture of ethanol (10 mL) and water (3 mL). The mixture was stirred and deoxygenated with argon for 15 min. Zinc dust (0.7 g, 11 mmol) was then added over a 3-min period and the mixture was stirred for an additional 7 min.[11] Water (5 mL) was added, the suspension filtered, and the cake washed with methylene chloride. The aqueous layer was extracted with methylene chloride, and the CH_2Cl_2 layers were combined and washed sequentially with water (10 mL) and saturated NaCl solution. The CH_2Cl_2 layer was dried over Na_2SO_4 and then reduced in volume to 5 mL. Chloroform (10 mL) and petroleum ether (10 mL) were added, and the solution was deoxygenated with argon and cooled to 0 °C. Pale yellow crystals formed which were recovered by filtration and recrystallized from petroleum ether to give colorless crystals (0.3 g, 30% yield; mp 73–74 °C).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.50; N, 8.28. Found: C, 56.90; H, 6.82; N, 8.60.

c. *m*-Ethoxynitrobenzene. *m*-Nitrophenol (3 g, 20 mmol), anhydrous potassium carbonate (2 g, 15 mmol), and iodoethane (2.35 g, 15 mmol) were dissolved in 20 mL of dry acetone and the solution was heated at reflux for 2 days. Water (10 mL) was added and the acetone removed by distillation. The aqueous layer remaining was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 10% NaOH until the washings were colorless. The $CHCl_3$ layer was dried over Na_2SO_4, and the $CHCl_3$ layer was removed to yield 2.5 g (75% yield) of yellow crystals (mp 34 °C; lit.[14] mp 34 °C).

d. *N*-(*m*-Ethoxyphenyl)hydroxylamine, 2. *m*-Ethoxynitrobenzene (1 g, 6 mmol) and ammonium chloride (0.8 g, 16 mmol) were added to 10 mL of 95% ethanol and 3 mL of water. After deoxygenating the solution with argon for 15–20 min, zinc dust (0.8 g, 13 mmol) was added.[11] The yellow solution was stirred for 15 min (and become colorless). Water (5 mL) was added, the suspension was filtered, and the resulting filter cake was washed with chloroform (25 mL). The aqueous layer was extracted with $CHCl_3$, and the $CHCl_3$ layers were combined, washed with saturated NaCl solution (10 mL), and dried over Na_2SO_4. The dried $CHCl_3$ layer was evaporated to 5 mL, hexane (20 mL) was added, and the solution was cooled to 0 °C. Colorless crystals (0.26 g, 28% yield; mp 69 °C) were formed, filtered, and washed with hexane. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.75; H, 7.19; N, 9.15. Found: C, 63.05; H, 7.27; N, 9.30.

Kinetic Studies. Reactions were carried out in a 50-mL flask fitted with a thermostatted water jacket and inlet and outlet for argon gassing and provided with a pH electrode. Metal free[15] H_2SO_4 solution [20 mL of 0.01, 0.05, or 0.1 M, μ = 0.5 ($NaClO_4$)] was introduced into the reaction vessel which was then flushed with argon for 30 min; thereafter a positive pressure of Ar was maintained over the contents of the flask. A methanolic solution (1 mL of a solution containing 1 mg of 1 or 2 dissolved in 1 mL of methanol that had been previously deoxygenated with Ar) was added to the H_2SO_4 solution and the reaction monitored by HPLC as a function of time. Components were separated on a Waters (Milford, MA) μ-Bondapak C-18 column (300 × 4.6 mm i.d.) using a mobile phase of phosphate buffer (10 mM; pH 5.8):methanol (90:10). A flow rate of 2 mL/min was maintained and the column effluent monitored spectrophotometrically at 280 nm.

Degradation of 1 produced a single product identified to be 4 by comparison of mass and NMR spectra with an authentic sample of material and from elemental analysis. Anal. Calcd for $C_8H_9NO_2$: C, 63.58;, H, 5.96; N, 9.27. Found: C, 63.40; H, 5.89; N, 8.90. ^1H NMR ($CDCl_3$) δ 6.81 (1 H, br d), 6.25 (1 H, br s), 6.15 (1 H br d), 4.19 (4 H, s), 3.42 (2 H, br s, NH_2).

Degradation of 2 produced a single product identified from melting point (210 °C; lit.[11] mp 210–212 °C), by comparison of mass spectral and ^1H NMR data with authentic material, and from elemental analysis to be 3. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.48, H, 7.18; N, 8.84. ^1H NMR (Me_2SO-d_6) δ 6.85–6.40 (3 H, m), 4.20 (1 H, br s, OH), 3.35 (2 H, br t), 3.12 (2 H, br t), 1.92 (2 H, br s).

Registry No. 1, 91861-92-6; 2, 91861-93-7; 3, 55483-70-0; 4, 22013-33-8; *m*-nitrophenol, 554-84-7; ethylene carbonate, 96-49-1; iodoethane, 75-03-6; *m*-nitrophenoxyethanol, 16365-26-7; *m*-ethoxynitrobenzene, 621-52-3.

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Direct Transformation of Ergosterol to (22*S*,23*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-23-en-22-ol, a Key Intermediate for the Synthesis of Brassinolide

Mario Anastasia, Pietro Allevi, Pierangela Ciuffreda, Alberto Fiecchi,* and Antonio Scala

Chemistry and Biochemistry Department, School of Medicine, University of Milan, I-20133 Milan, Italy

Received March 6, 1984

Brassinolide (**1a**) is a plant growth promoting steroidal lactone, first isolated from rape pollen.[1] Brassinolide contains a lactone group in ring B, and 22*R*,23*R* oxygen functions associated with a 24*S* methyl group in the side chain. Until now, at different laboratories,[2-6] brassinolide (**1a**) and its possible biological precursor castasterone (**2**) have been synthesized starting with a C_{22} steroid. A key intermediate in the first synthesis[2] of **1a** is (22*S*,23*E*)-6β-methoxy-3α,5-cyclo-5α-ergost-23-en-22-ol (**3a**), whose side chain was constructed by lithium alanate alkylation of (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde derived from stigmasterol (**4**). We now describe the first synthesis of **3a** by the direct modification of the side chain of ergosterol (**4**). Up to now only the C-24 epimer of brassinolide was obtained from ergosterol.[7,8]

Ergosterol was reduced,[9,10] with lithum dissolved in ethylamine to a 3:2 mixture of (22*E*)-ergosta-5,22-dien-3β-ol (**5a**) and (22*E*)-5α-ergosta-7,22-dien-3β-ol (**6a**). The mixture of **5a** and **6a** was esterified with *p*-toluenesulfonyl chloride[8] in dry pyridine and the mixture of tosylates **5b** and **6b** was treated with methanol and pyridine[11] to afford

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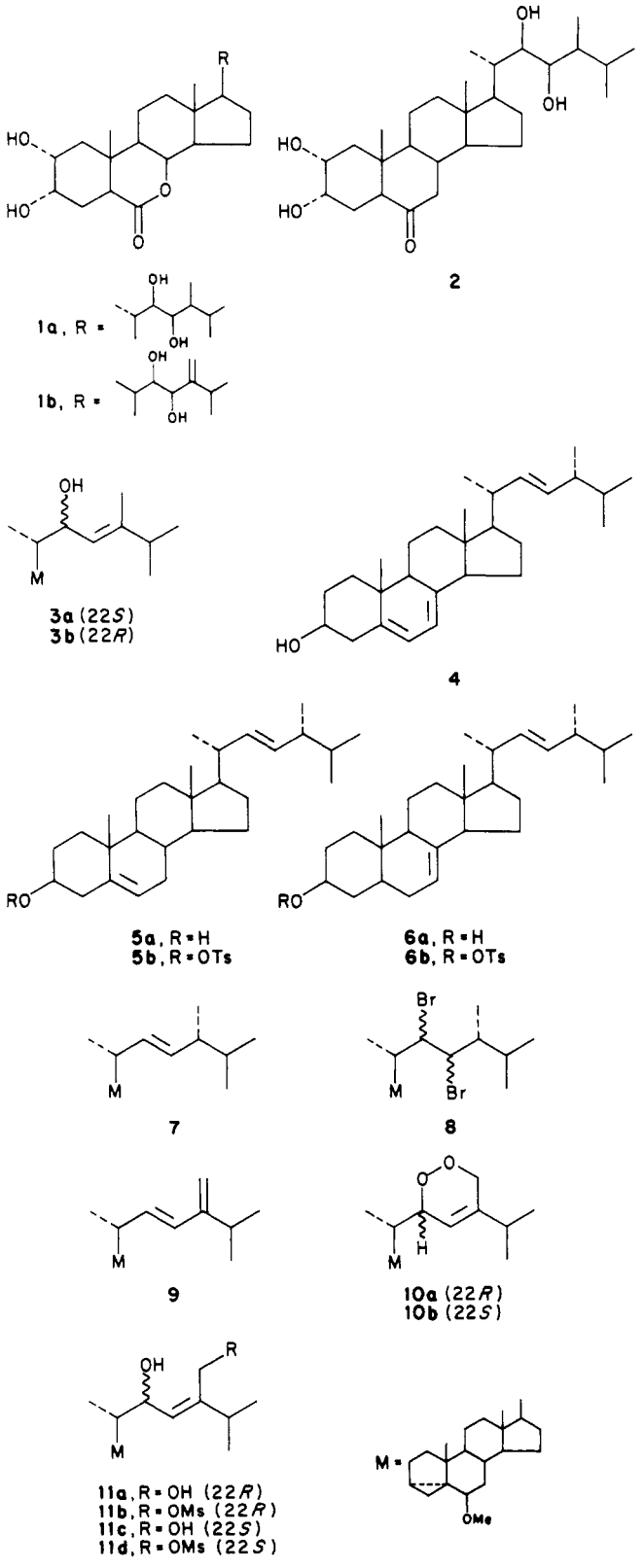

(22*E*)-6β-methoxy-3α,5-cyclo-5α-ergost-22-ene (**7**) and unchanged **6b**. The methyl ether **7** was easily separated from **6b** by chromatography on silica and reacted at 25 °C with bromine dissolved in methylene chloride containing pyridine[12] to afford a diastereomeric mixture of 22,23-dibromosteroid **8**. Dehydrobromination of **8** with boiling tetramethylguanidine[13] for 15 min gave (22*E*)-6β-methoxy-3α,5-cyclo-5α-ergosta-22,24(28)-diene (**9**), identical (^{1}H NMR, mp) with the compound obtained by the condensation of (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde with the ylide from (3-methyl-2-methylenebutyl)triphenylphosphonium bromide.

Treatment of **9** dissolved in pyridine with molecular oxygen under intense lighting in the presence of haematoporphyrin afforded a chromatographically separable (7:3) mixture of two epidioxydes of assigned structure (22*R*)- and (22*S*)-6β-methoxy-22,28-epidioxy-3α,5-cyclo-5α-ergost-23-ene (**10a** and **10b**). Compounds **10a** and **10b** showed correct elemental analyses and mass spectra which differed only in the relative intensities of the peaks. The ^{1}H NMR spectra of the two compounds show distinct differences both in the olefinic proton signal at C-23 and in the C-21 methyl doublet. The olefinic proton of **10a** gave a multiplet at δ 5.38 while that of the epimer **10b** resonates at δ 5.56. The doublet the C-21 methyl is centered at δ 0.88 in the spectrum of **10a** and at δ 0.82 in the spectrum of **10b**. These differences in the ^{1}H NMR spectra do not permit assignment of the appropriate stereochemistry to **10a** and **10b**; however, this was derived by the successive transformation of these compounds into the known compounds[2] **3a** and **3b**.

The less polar (10% ethyl acetate–hexane) 22*R* isomer **10a** was separated by chromatography on silica and reduced with molecular hydrogen over Lindlar catalyst to give (22*R*,23*E*)-6β-methoxy-3α,5-cyclo-5α-ergost-23-ene-22,28-diol (**11a**). Selective esterification of the primary hydroxy group of **11a** with methanesulfonyl chloride followed by lithium aluminum hydride reduction of the crude mesylate[14] **11b** afforded the title compound **3a**, which physicochemical properties are in complete agreement with those reported for the compound affording brassinolide.[2] Similary the more polar epidioxide **10b** was converted, via **11c** and **11d**, into **3b**, a glass,[2] more polar than **3a** and showing a mass spectrum identical with that of **3b**. Since Fung and Siddall[2] were able to transform **3a** into brassinolide, our work represents the first possibility to transform ergosterol into brassinolide without "transplanting" the side chain. In addition the recent paper of Okada and Mori[15] suggests that **3a** could be transformed into dolicholide (**1b**), a lactone belonging to the brassinolide family of phytosterols which have plant growth promoting activity.[16]

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360L or on a Varian XL-200 spectrometer as chloroform-*d* solutions and are reported in δ units relative to Me_4Si. Optical rotations were taken as chloroform solutions. The mass spectra were determined on a Varian MAT 112 S spectrometer by direct inlet methods. The progress of all reactions and column chromatographies (silica, 230–400 mesh) was monitored by TLC on silica gel (HF_{254}) plates. Hexane–ethyl acetate mixtures were used as developing solvents and spots were detected by spraying with 70% sulfuric acid followed by heating.

Synthesis of (22*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-22-ene (7). Ergosterol (**4**, 8 g) dissolved in ethylamine (40 mL) was treated with lithium (1.6 g), and the mixture was stirred at reflux for 30 min longer than required for the initial appearance of a blue color. Workup afforded, after extraction with chloroform, a crude

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mixture (6.4 g) of (22*E*)-ergosta-5,22-dien-3β-ol (**5a**) and (22*E*)-5α-ergosta-7,22-dien-3β-ol (**6a**) in a 3:2 ratio. In one case the two isomers **5a** and **6a** were separated by chromatography on silica gel G–Celite–$AgNO_3$ (1:1:0.3) with 30% ethyl acetate–hexane as eluant to afford (i) **5a** (3.84 g): mp 149–150 °C (from methanol); $[\alpha]^{20}_D$ –60° (*c* 1); ^1H NMR δ 0.69 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 3.60 (m, 1 H, 3α-H), 5.10–5.40 (m, 3 H, 5-H, 22-H, and 23-H); mass spectrum, *m/z* 398 (M^+).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.20; H, 11.50.

(ii) The isomer **6a** (2.56 g): mp 172–173 °C (from ethyl acetate); $[\alpha]^{20}_D$ –20° (*c* 1); ^1H NMR δ 0.55 (s, 3 H, 18-CH_3), 0.88 (s, 3 H, 19-CH_3), 3.60 (m, 1 H, 3α-H), 5.10–5.30 (m, 3 H, 7-H, 22-H, and 23-H); mass spectrum, *m/z* 398 (M^+).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.50; H, 11.60.

All physical and spectroscopic properties of **5a** and **5b** are identical with those reported.[8] Since it was unnecessary to separate the mixture of **5a** and **6a**, they were used in mixture in the following reaction.

A mixture of dried **5a** and **6a** (10 g, 3:2) dissolved in pyridine (80 mL) was treated with *p*-toluenesulfonyl chloride (10 g) dissolved in pyridine (25 mL) at room temperature for 24 h. After usual workup the tosylates **5b** and **6b** (13 g) were dissolved in methanol (130 mL) and pyridine (8 mL) and stirred at 75 °C for 3 h (method of Steele and Mosettig[11]) and cooled, and the solvent was partially removed under reduced pressure, poured into water, and extracted with ethyl acetate. Evaporation of the organic layer afforded a residue (11.5 g) which was chromatographed on silica (eluting with 4% ethyl acetate–hexane) to afford (22*E*)-6β-methoxy-3α,5-cyclo-5α-ergost-22-ene (**7**, 5.8 g): mp 72–74 °C (from methanol); ^1H NMR δ 0.30–0.60 (m, 3 H), 0.72 (s, 3 H), 1.02 (s, 3 H), 2.73 (m, 1 H), 3.30 (s, 3 H), 5.10–5.30 (m, 2 H, 22- and 23-H); mass spectrum, *m/z* 412 (M^+).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.50; H, 11.60.

The tosylate **6b** (5.2 g) was recovered unchanged in the last fractions of the chromatography.[8]

(22*E*)-6β-Methoxy-3α,5-cyclo-5α-ergosta-22,24(28)-diene (9). A. A solution of **7** (2 g) in methylene chloride (100 mL) and pyridine (10 mL) was treated at 25 °C with a solution of bromine (1.20 g) in methylene chloride (20 mL) with stirring. After 24 h the solution was poured into 10% potassium metabisulfite solution (50 mL) and the product isolated to yield 22,23-dibromo-6β-methoxy-3α,5-cyclo-5α-ergostane (**8**, 2.6 g): mp 103–105 °C (tritured with ethanol); ^1H NMR δ 0.30–0.60 (m, 3 H), 2.73 (m, 1 H, 6α-H), 3.30 (m, 3 H, OCH_3), 4.45 (m, 2 H, 22- and 23-H); mass spectrum, *m/z* 572 (M^+).

Anal. Calcd for $C_{29}H_{48}OBr_2$: C, 60.84; H, 8.45; Br, 27.90. Found: C, 60.85; H, 8.50; Br, 27.60.

The 22,23-dibromo compound **8** (2.4 g) was dissolved in tetramethylguanidine (20 mL) and refluxed for 15 min. The cooled mixture was diluted with water and the product isolated with diethyl ether. Crystallization from methanol afforded pure (22*E*)-6β-methoxy-3α,5-cyclo-5α-ergosta-22,24(28)-diene (**9**, 1.6 g): mp 79–81 °C; ^1H NMR δ 0.30–0.60 (m, 3 H), 2.73 (s, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.83 (m, 2 H, 28-H), 5.55 (dd, 1 H, 22-H; *J* = 15.6 and 10.0 Hz), 5.95 (d, 1 H, 23-H; *J* = 15.6 Hz); mass spectrum, *m/z* 410 (M^+). Spectra were superimposable on those of the product obtained by the independent partial synthesis B.

Anal. Calcd for $C_{29}H_{46}O$: C, 84.80; H, 11.29. Found: C, 85.00; H, 11.40.

B. A solution of (3-methyl-2-methylenebutyl)triphenylphosphonium bromide[17] (0.2 g) in tetrahydrofuran (20 mL) was treated with methyllithium (0.5 mL of a 1.6 M solution in diethyl ether) under nitrogen at 0–3 °C. After 1 h at room temperature, (20*S*)-6β-methoxy-3α,5-cyclopregnane-20-carboxaldehyde[2] (250 mg) was added in tetrahydrofuran (5 mL). The solution was stirred overnight and was then refluxed for 1 h. Filtration of the solution and removal of the solvent gave a product which was chromatographed to afford (22*E*)-6β-methoxy-3α,5-cyclo-5α-ergosta-22,24(28)-diene (**9**, 120 mg), mp 79–81 °C (from methanol), having physical and spectroscopic properties identical with those of the compound described above.

(22*R*)- and (22*S*)-6β-Methoxy-22,28-epidioxy-3α,5-cyclo-5′α-ergost-23-ene (10a and 10b). A solution of the diene **9** (500 mg) in pyridine (40 mL) and haematoporphyrin (10 mg) was irradiated with a single photospot flood lamp under a fine stream of oxygen for 3 h at 15 °C. The usual workup followed by chromatography afforded first (22*R*)-6β-methoxy-22,28-epidioxy-3α,5-cyclo-5α-ergosta-23-ene (**10a**, 365 mg): mp 102–104 °C (from moist methanol); ^1H NMR δ 0.30–0.60 (m, 3 H), 0.70 (s, 3 H, 18-CH_3), 0.88 (d, 3 H, 21-CH_3, *J* = 6 Hz), 1.00 (s, 3 H, 19-CH_3), 2.73 (m, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.22 (ddd, 1 H, 28-H, *J* = 16, 1.7 and 1.6 Hz), 4.64 (ddd, 1 H, 28-H, *J* = 16, 3 and 2.4 Hz), 4.74 (m, 1 H, 22 H, $w_{1/2}$ ~7.2 Hz), 5.38 (m, 1 H, 23-H; $w_{1/2}$ ~4 Hz); mass spectrum, *m/z* 442 (M^+).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.50; H, 10.50.

Further elution yielded (22*S*)-6β-methoxy-22,28-epidioxy-3α,5-cyclo-5α-ergosta-23-ene (**10b**, 155 mg): glass; ^1H NMr δ 0.30–0.60 (m, 3 H), 0.76 (s, 3 H, 18-CH_3), 0.82 (d, 3 H, 21-CH_3, *J* = 6 Hz), 1.03 (s, 3 H, 19-CH_3), 2.73 (m, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.24 (ddd, 1 H, 28-H, *J* = 16, 3 and 1.6 Hz), 4.70–4.82 (m, 2 H, overlapping, 22- and 28-H), 5.56 (m, 1H, 23-H; $w_{1/2}$ ~4 Hz); mass spectrum, *m/z* 442 (M^+).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.70; H, 10.45.

(22*R*,23*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-23-ene-22,28-diol (11a). The epidioxide **10a** (500 mg) dissolved in ethyl acetate (distilled on potassium carbonate) (100 mL) was hydrogenated over Lindlar catalyst (80 mg). After 2 h, 1 mol of hydrogen had been absorbed and hydrogen uptake ceased. Concentration of the filtered reaction mixture afforded the 22*R* diol **11a** (500 mg): mp 69–72 °C (from hexane); ^1H NMR δ 0.30–0.60 (m, 3 H), 0.70 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 2.73 (m, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.02 (d, 1 H, 28-H, *J* = 12.4 Hz), 4.24 (d, 1 H, 28-H, *J* = 12.4 Hz), 4.54 (d, 1 H, 22-H, *J* = 6.8 Hz), 5.47 (d, 1 H, 23-H, *J* = 6.8 Hz); mass spectrum, *m/z* 444 (M^+).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.50; H, 10.70.

(22*S*,23*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-23-ene-22,28-diol (11c). The epidioxide **10b** (500 mg) when reduced in the same conditions reported for **10a** afforded the 22*S* diol **11c** (500 mg): mp 121–123 °C (from methanol); ^1H NMR δ 0.30–0.60 (m, 3 H), 0.78 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 2.73 (m, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.00 (d, 1 H, 28-H, *J* = 12 Hz), 4.45 (d, 1 H, 28-H, *J* = 12 Hz), 4.53 (dd, 1 H, 22-H, *J* = 9 and 4 Hz), 5.53 (d, 1 H, 23-H, *J* = 9 Hz); mass spectrum, *m/z* 444 (M^+).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.40; H, 10.85.

(22*S*,23*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-23-en-22-ol (3a). The 22*R*,23*E* diol **11a** (570 mg) in methylene chloride (10 mL) containing triethylamine (0.3 mL) was treated at 0 °C with methanesulfonyl chloride (0.1 mL) over a period of 10 min. The mixture was stirred for 10 min at room temperature and then the solvent was evaporated under nitrogen. Then the residue was dissolved in diethyl ether (20 mL) and treated with lithium aluminum hydride (250 mg). After stirring for 5 h, usual workup and chromatography afforded the alcohol **3a** (400 mg): mp 127–129 °C (from moist methanol); $[\alpha]^{20}_D$ 37° (*c* 0.4) (lit.[2] mp 127–129 °C); ^1H NMR δ 0.30–0.60 (m, 3 H), 0.70 (s, 3 H, 18-CH_3), 1.60 (d, 3 H, 28-CH_3, *J* = 3 Hz), 2.73 (m, 1 H, 6α-H), 3.30 (s, 3 H, OCH_3), 4.48 (d, 1 H, 22-H, *J* = 8 Hz), 5.36 (d, 1 H, 23-H, *J* = 8 Hz); mass spectrum, *m/z* 428 (M^+).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.28. Found: C, 81.30; H, 11.30.

The acetate showed mp 113–115 °C (from moist methanol; lit.[2] mp 113–114 °C).

(22*R*,23*E*)-6β-Methoxy-3α,5-cyclo-5α-ergost-23-en-22-ol (3b). Mesilation of **10b** (570 mg) followed by reduction with lithium aluminum hydride in the same conditions described for **10a** afforded the 22*R* alcohol **3b** (400 mg): a glass; ^1H NMR δ 0.30–0.60 (m, 3 H), 0.70 (s, 3 H, 18-CH_3), 1.58 (d, 3 H, 28-CH_3, *J* = 4 Hz), 2.73 (m, 1 H, 6β-H), 3.30 (s, 3 H, OCH_3), 4.48 (d, 1 H, 22-H, *J* = 6.5 Hz) 5.36 (d, 1 H, 23-H, *J* = 6.5 Hz); mass spectrum, *m/z* 428 (M^+). The mass spectrum was very similar to that of **3a**.

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Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25, H, 11.28. Found: C, 81.40; H, 11.20.

Acknowledgment. This work was supported by the Italian Research Council (Progetto Finalizzato Chimica Fine e Secondaria). We thank Professor G. Galli for mass spectra.

Registry No. **1a**, 72962-43-7; **3a**, 91861-37-9; **3b**, 91879-21-9; **4**, 57-87-4; **5a**, 474-67-9; **5b**, 91926-36-2; **6a**, 2465-11-4; **6b**, 61425-09-0; **7**, 88852-68-0; **8**, 91861-38-0; **9**, 91861-39-1; **10a**, 91861-40-4; **10b**, 91861-41-5; **11a**, 91861-42-6; **11c**, 91861-43-7; (3-methyl-2-methylenebutyl)triphenylphosphonium bromide, 33355-56-5; (20*S*)-6β-methoxy-3α,5-cyclopregnane-20-carboxaldehyde, 25819-77-6.

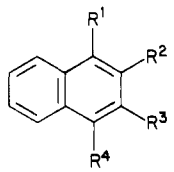
Ozonolysis of 1,2,4-Tri-*tert*-butylnaphthalene

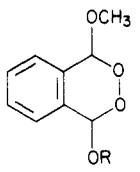
Yoshikatsu Ito,* Akira Matsuura, and Teruo Matsuura

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan

Received April 5, 1984

Naphthalenes **1a–g** are readily attacked by 2 mol of ozone exclusively at 1,2 and 3,4 bonds.[1,2] Final products





A

1a, $R^1=R^3=R^4=H$
1b, $R^1=R^4=H$; $R^2=R^3=CH_3$
1c, $R^1=R^3=R^4=H$; $R^2=CH_3$
1d, $R^1=R^3=R^4=H$; $R^2=OH$
1e, $R^1=R^3=R^4=H$; $R^2=OCH_3$
1f, $R^1=R^3=R^4=H$; $R^2=OEt$
1g, $R^1=CH_3$; $R^2=R^3=R^4=H$
1h, $R^1=R^2=R^4=CH_3$; $R^3=H$
1i, $R^1=R^2=R^4=t\text{-Bu}$; $R^3=H$

were shown to depend on the nature of solvents employed and workup conditions. For example, cyclic peroxides A were obtained from **1a–f** in CH_3OH, a participating solvent, while phthalic acid derivatives were isolated in nonparticipating solvents.[2]

Ozonolysis of naphthalenes having bulky substituents is interesing in view of the effects of the bulky substituents on the reactivity to ozone and on the stability of peroxide intermediates. It is known that the bulky *tert*-butyl group can stabilize certain initial ozone addcuts; the primary ozonide of *trans*-di-*tert*-butylethylene[3] and the transannlar ozonide of 9-*tert*-butyl-10-methylanthracene[4] are typical examples. It is also known that many hindered olefins often produce so-called "partial cleavage" products instead of usual ozonolysis products.[5] We have report that 1,2,4-tri-*tert*-butylnaphthalene (**1i**) reacts, in contrast with the ozonolysis of the unhindered naphthalenes **1a–8**, with only 1 mol of ozone.

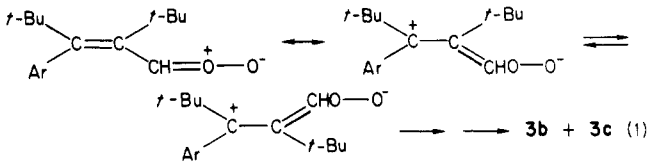
Results and Discussion

Table I summarizes the products obtained from ozonolyses of 1,2,4-tri-*tert*-butylnaphthalene (**1i**) and 1,2,4-trimethylnaphthalene (**1h**). As expected, they were highly dependent on the reaction media. Scheme I describes possible reaction sequences.

o-Dipivaloylbenzene (**5a**) was a sole identified product in CH_3OH–$CHCl_3$ (1:1 v/v) and on SiO_2 (Table I, entries 3 and 7). The other expected product *t*-BuCOCHO was not looked for. SiO_2 is functioning like a participating solvent, probably due to adsorbed water or surface-OH groups.

In nonparticipating solvents (Freon-11 and *n*-hexane) **1i** gave **5a** and two stereoisomeric ketone diperoxides **2a** and **2b** as major products (Table I, entries 1 and 2). The diperoxides **2a** and **2b** were converted by catalytic reduction on Pd–C into a single aldehyde **3a** in 80% and 67% yield, respectively. This reduction reaction indicates that **2a** and **2b** differ as cis–trans isomers about the peroxide ring, not as cis–trans isomers about the C–C double bond. The diperoxides were probably formed via dimerization of an intermediate carbonyl oxide **7** (Scheme I). In general, carbonyl oxides generated in nonparticipating solvents dimerize or polymerize as major modes of reactions.[3a,6]

In acetone, ozonation of **1i** afforded cis and trans isomers of a cinnamic acid derivative **3b** and **3c** in addition to **5a** (Table I, entry 4). A cis–trans isomerization of the C–C double bond of **7** may occur as shown in eq 1, leading



(1)

ultimately to **3b** and **3c** probably via a dioxirane intermediate. However, it is not clear why the cis–trans isomerism about the C–C double bond was observed only in acetone.

Pyridine has been shown to function as a reducing agent of peroxidic intermediates in ozonolysis.[7] In fact, the cinnamaldehyde **3a** was produced as a major product upon ozonolysis of **1i** in the presence of pyridine (Table I, entries 5 and 6).

The ozonolysis of **1i** differs from that of the previously studied unhindered naphthalenes **1a–g** in that most of the products (except in CH_3OH–$CHCl_3$ and on SiO_2) result from addition of only 1 mol of ozone; i.e., **2a**, **2b**, and **3a–c** were formed.[8] These products were found to be entirely inert toward ozone under the reaction conditions mentioned in Table I. Thus, as illustrated in Scheme I, the reaction of **1i** with ozone may be explained by addition of an ozone molecule to the 3,4 bond to form a primary ozonide **6**, which subsequently decomposes into **2** and **3** via the carbonyl oxide **7** or undergoes further ozonolysis to give **5a**. The failure to isolate **2** and **3** upon ozonolysis in the presence of CH_3OH may be ascribed to rapid methanolysis[9] of **6** (or addition of methanol to **7**) leading

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(6) (a) Reference 5b, p 83. (b) Schroder, G. *Chem. Ber.* **1962**, *95*, 733. (c) Criegee, R.; Bath, S. S.; von Bornhanpt, B. *Chem. Ber.* **1960**, *93*, 2891.

(7) Reference 5b, p 133.

(8) It was reported that 2-naphthol reacted with 1 mol of ozone to afford *O*-carboxycinnamic acid: Johnson, C. D.; Bailey, P. S. *J. Org. Chem.* **1964**, *29*, 703. However, this is thought to be a rare example.

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