Permanganate Oxidation of Ergosterol

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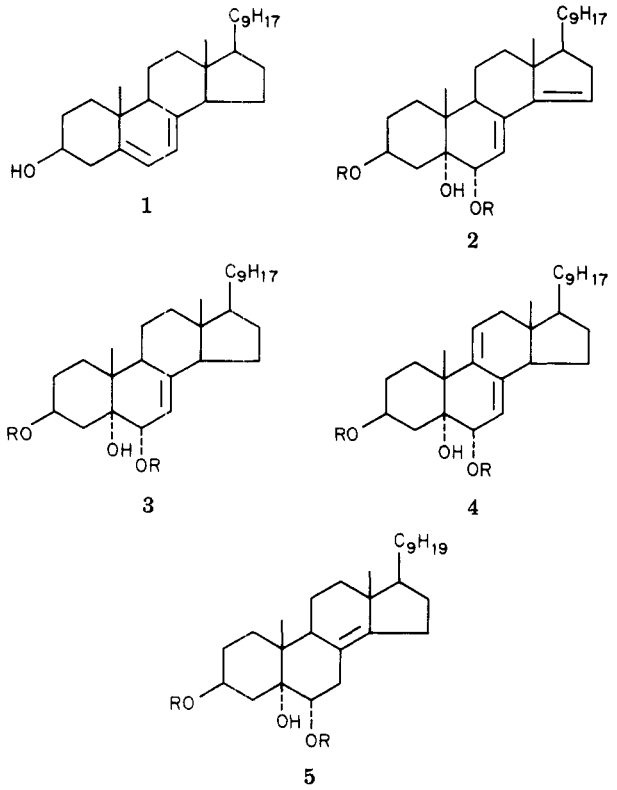
The oxidation of ergosterol in methylcyclohexane with aqueous permanganate affords 3β,5α,6α-trihydroxyergosta-7,22-diene, 7α,8α-epoxy-5α-ergost-22-ene-3β,5,6α-triol (major component), 3β,5α,6α,7α-tetrahydroxyergosta-8(14),22-diene, and 3β,5α,6α,7α-tetrahydroxyergosta-8(9),22-diene. The product obtained by M. Fieser et al. and identified as 3β,5α,6α-trihydroxyergosta-7,14,22-triene has been demonstrated to be constituted mainly of 3β,5α,6α-trihydroxyergosta-7,9(11),22-triene and 3β,5α,6α-trihydroxyergosta-7,22-diene, with 3β,5α,6α-trihydroxyergosta-7,14,22-triene as a minor component. The trienic compounds were formed during the isolation procedure used by the authors.

The oxidation of ergosterol (1) with aqueous potassium permanganate–methylcyclohexane was first attempted by Reindel about 50 years ago.[1] This author obtained an oxidation product, the nature of which was not established. In 1953 the reaction was reinvestigated by Fieser et al.[2,3] who reported that the product was a mixture of 7 parts of an O_3 compound and 3 parts of an O_5 compound. The structure of 3β,5α,6α-trihydroxyergosta-7,14,22-triene (**2a**) was proposed for the main product. The authors found that purification of the triene component was best accomplished through the acetates of the oxidation products.



a, R = H; b, R = CH_3CO

We recently had cause to prepare the 3β,6α-diacetate **2b** as an intermediate in the synthesis of oxygenated steroids. Upon carefully repeating the published procedure,[2] we indeed isolated an acetylated product whose melting point and optical rotation were identical with those reported for the supposed diacetate **2b**, but the UV spectrum showed maxima at 236, 243, and 251 nm, in contrast with the reported single value at 244 nm. The TLC analysis of the product on silica gel G–$AgNO_3$ revealed the presence of three different components in different ratios.

The least-retained compound was identified as the known 3β,6α-diacetoxy-5α-hydroxyergosta-7,22-diene (**3b**)[2] (melting point, mixture melting point, NMR, mass spectrum). It was present in the mixture in about a 20% ratio.

The second retained compound was the main component of the mixture (about 60%) and was identified as 3β,6α-diacetoxy-5α-hydroxyergosta-7,9(11),22-triene (**4b**). The microanalysis and mass spectrum yielded the formula $C_{32}H_{48}O_5$ for the compound. The UV spectrum showed the presence of a 7,9(11)-diene system (absorption maxima at 236, 242, and 250 nm, log ε 4.20, 4.23, and 4.05, respectively).[4] The IR spectrum showed the presence of a free hydroxy group. ^1H NMR spectrum exhibited two signals for acetate methyl groups, four signals in the olefinic resonance region, and the chemical shift for the C-18 and C-19 angular methyl groups all in good agreement with the value calculated for **4b**.[5] Catalytic hydrogenation of **4b** gave the known 3β,6α-diacetoxy-5α-hydroxyergost-8(14)-ene (**5b**), thus confirming position and configuration assignments of the C-5 and C-6 hydroxy groups. Finally, **4b** was obtained by mercuric acetate dehydrogenation of the Δ^7 compound **3b**.[14]

The most retained compound was identified as the triene **2b**. It was present in the mixture in about a 20% ratio. The elemental analysis and mass spectrum were in accord with molecular formula $C_{32}H_{48}O_5$. The position of UV absorption maximum (242 nm),[4] the low extinction coefficient (log ε 3.99), and the strong levorotatory power[6] all point to the presence of a 7,14-diene system in the molecule. The IR spectrum showed the presence of a nonacetylated hydroxy group. Moreover, the ^1H NMR spectrum exhibited two signals for acetate methyl groups, four signals in the olefinic resonance region, and the position of the C-18 and C-19 methyl signals in accordance with the calculated values for **2b**.[5] Formation of a maleic anhydride adduct of **2b** in quantitative yield and isolation of **5b** upon hydrogenation of **2b** afford final evidence in support of the **2b** formulation for the compound.

The acetates **2b**, **3b**, and **4b** were quantitatively recovered after saponification and reacetylation. TLC, NMR, and mass spectral evidence showed that the three triols **2a**, **3a**, and **4a** were the main components of the "O_3 compound" and were accompanied by minor quantities of two more polar UV-transparent compounds, now identified

(1) F. Reindel, *Justus Liebigs Ann. Chem.*, **466**, 131 (1928).
(2) M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4066 (1953).
(3) L. Fieser and M. Fieser "Reagents for Organic Synthesis", Wiley, New York, 1967, p 949.
(4) L. Dorfman, *Chem. Rev.*, **53**, 52 (1953).
(5) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, 1964, p 13.
(6) L. F. Fieser and G. Ourisson, *J. Am. Chem. Soc.*, **75**, 4404 (1953).

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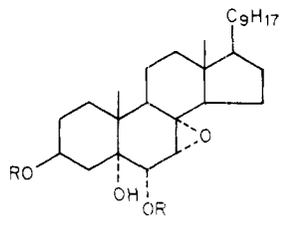
as the tetrols **7a** and **8a**. The presence of these last substances and of **3a** was responsible of the low extinction coefficient observed for the O_3 compound.[2] When the O_3 compound was acetylated and crystallized, these more polar compounds remained in solution.

The presence of the 7,22-diene **3a** in the ergosterol oxidation product is readily rationalized by a cis dihydroxylation of the more reactive Δ^5 double bond by permanganate. Less easily rationalized is the formation of the triene components. They can be formed from parent oxidation products during the isolation procedure, which includes bubbling of SO_2, steam distillation, evaporation, and acetylation. In order to identify the possible precursors of the trienes, the oxidation product was recovered without destroying the MnO_2 formed. The crude mixture did not absorb UV light above 220 nm. It was resolved by LC into two components, both unhomogeneous (NMR evidence). Better separation was achieved by chromatography of the acetylated mixture. Four homogeneous compounds were obtained by this procedure.

The first eluted compound was the main component (75% of the mixture) and gave analytical figures and a mass spectrum corresponding to $C_{30}H_{50}O_6$. It was identified as 7α,8α-epoxy-5α-ergost-22-ene-3β,5,6α-triol 3,6-diacetate (**6b**). Strong supporting evidence for this



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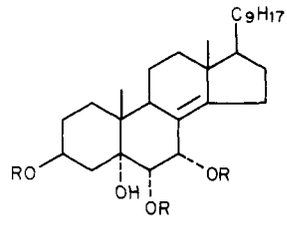

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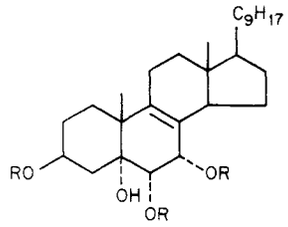

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a, R = H; b, R = CH_3CO

structure is provided by the ^1H NMR spectrum, which exhibits two one-proton signals at δ 5.18 and 3.6 for 6β and 7β protons, respectively. The very small values observed for both coupling constants were in accordance with a dihedral angle of approximately 85° measured between the 6β and the 7β hydrogens in the Dreiding model of **6b**. The treatment of **6b** with aqueous acetic acid at 45 °C gave, after reacetylation, a mixture of the trienes **2b** and **4b** in about a 1:3 ratio, in accord with the behavior of 7α,8α-epoxy-5α-ergost-22-en-3β-ol acetate.[7] As a final confirmation of the foregoing structure assignment, we carried out an unambiguous synthesis of **6b** by the action of *m*-chloroperbenzoic acid on **3b**. It is well-known that steroidal allylic alcohols suffer epoxidation syn to the hydroxy group.[8]

The second eluted compound (15% of the mixture) was identified as the known 7,22-diene **3b**.

The third eluted compound (about 2% of the mixture) was identified as 3β,5α,6α,7α-tetrahydroxyergosta-8(14),22-diene 3,6,7-triacetate (**7b**). Microanalysis and mass spectrometry gave for the compound the formula $C_{34}H_{52}O_7$. The IR spectrum showed the presence of a hydroxy group in addition to the acetate band. The ^1H NMR spectrum showed the characteristic signals due to 22 and 23 vinylic protons superimposed to the 3α-proton signal at δ 5.20 and two one-proton broad doublets (J = 4 Hz for both) at δ 4.9 (6β-proton) and 5.92, respectively. The last signal was assigned to the 7β-proton, which is deshielded by the $\Delta^{8(14)}$ double bond. In fact the 7β proton of 3β,7α-diacetoxy-5α-cholestane absorbs at δ 5.72. The positions of the C-18 and C-19 methyl signals were all within 0.02–0.04 ppm of the values calculated by Zürcher's rules.[4] These latter values were computed from the additive chemical shifts of the appropriate 7α-$OCOCH_3$ and C_9H_{17} side-chain entities with respect to the values observed for the acetate **5a**. Saponification of **7b** gave the parent tetrol **7a**. This compound, when hydrogenated in acetic acid, suffered hydrogenolysis of the allylic 7α-hydroxy group to give **5a**. The treatment of **7a** with aqueous acetic acid at 45 °C and its acetylation yielded the expected triene **2b**, in accordance with the behavior of a $\Delta^{8(14)}$-7α-hydroxy compound in acidic medium.[6]

The last eluted compound (about 8% of the mixture) was identified as 3β,5α,6α,7α-tetrahydroxyergosta-8,22-diene 3,6,7-triacetate (**8b**). It was also obtained by mild-acid cleavage of the 7α,8α-epoxide **6b** and reacetylation, together with minor amounts of **7b**. Microanalysis and mass spectrometry gave for **8b** the formula $C_{34}H_{52}O_7$. The action of hydrogen on **8b** in acetic acid in the presence of PtO_2 yielded the $\Delta^{8(14)}$ compound **5b**, thus indicating that the double bond in **8b** may be in either the 8(9) or the 8(14) position and that one of the acetoxy groups is in the allylic 7 position. The 7α configuration of the allylic acetoxy group of **8b** and consequently the 8(9) position of the double bond can be deduced with a high degree of certainty from the NMR spectrum of **8b**. Two of the C*H*OAc protons absorb as broad doublets at δ 5.54 ($W_{1/2}$ ca. 9 Hz) and 5.32 ($W_{1/2}$ ca. 8 Hz). The former signal was assigned to the C-7 allylic proton and the latter to C-6β proton. Molecular models indicate that it is impossible for the 6β and 7α protons of a hypothetical 7β epimer of either **7b** or **8b** to give rise to signals of half bandwidth as low as 9 and 8 Hz, respectively. This is confirmed by the value of ca. 12 Hz for the 7α proton of 7β,11β-dihydroxy-5α-cholest-8-ene[9] and of ca. 15 Hz for the 6β proton of **5b**. As a result of the skeletal deformations caused by the $\Delta^{8(9)}$ double bond, the observed position of the C-19 angular methyl resonance in the spectrum of **8b** does not agree particularly well with the calculated value.[4,9] In contrast, the C-18 methyl group showed the expected chemical shift. As a final confirmation of the assigned structure, **8b** was saponified to give the parent tetrol **8a** which suffered acid dehydration to yield the triene **4a** and no trace of the triene **2a**, the product of acid dehydration of the $\Delta^{8(14)}$-7α-hydroxy compounds.

Our results demonstrate that the oxidation of ergosterol by potassium permanganate in the heterogeneous phase yields as the main product the epoxytriol **6a**, accompanied by the Δ^7-triol **3a** and minor amounts of tetrols **7a** and **8a**. This is the first example of formation of an epoxide in the neutral (or basic) permanganate oxidation of steroidal dienes. In the few cases of formation of epoxides in the permanganic oxidation of steroidal enes,[10] the reaction conditions were quite different, the reaction medium being

(7) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 1356 (1954).
(8) G. Berti, *Top. Stereochem.*, 7, 130 (1973).
(9) J. Midgley and C. Djerassi, *J. Chem. Soc., Perkin Trans. 1*, 2771 (1972).
(10) J. M. Constantin and L. H. Sarett, *J. Am. Chem. Soc.*, 74, 3908 (1952).

acetic acid. In view of the markedly different manganese oxide anions which predominate in acidic and alkaline media, the last examples can hardly be considered analogous to the present case.[11] A quite pertinent precedent is the oxidation of cyclopentadiene and 1,3-cyclohexadiene in aqueous acetone with neutral or basic permanganate.[12] The *all-cis*-1,2-epoxycyclopentane-3,4-diol and the *all-cis*-1,2-epoxycyclohexane-3,4-diol, respectively, were obtained together with substantial amounts of dihydroxy and tetrahydroxy derivatives. It can be observed that in the present case only the relatively hindered Δ^7 double bond is epoxidized. Tetrols **7a** and **8a** were also present when the formed MnO_2 was not destroyed. Due to the fact that the epoxide **6a** is quantitatively recovered after rechromatography, **7a** and **8a** should not be formed from **6a** on silica. However, the possibility exists that they are formed from **6a** or a related intermediate in the oxidation.

The sequence of events in the experiment of Fieser et al.[2] is thus the formation of the 5α,6α-dihydroxy-7α,8α-epoxide **6a**, acid cleavage to the $\Delta^{8(9)}$-ene tetrol **8a** (with the $\Delta^{8(14)}$-ene tetrol **7a** as a minor product), and conversion to the triene **4a** (and **2a** a minor component). A trace of acid suffices for the cleavage of the oxide ring, and the more drastic acid conditions during the steam distillation of the reaction solvent convert the allylic alcohols into the trienes **4a** and **2a**. In order to prove this assumption, ergosterol was oxidized as reported above and MnO_2 destroyed by bubbling SO_2 through the solution. The reaction mixture contains as main components the tetrols **7a** and **8a**. Subsequent steam distillation of the solvent transforms these compounds into the trienes **2a** and **4a**. However, substantial amounts of **7a** and **8a** survive these acid treatments and constitute the main components of Fieser's "O_5 compound", which also contains small amounts of **2a**, **3a**, and **4a**.

The physicochemical constants of the "O_4 compound" and its acetate, isolated by Reindel,[1] are very similar to those of the epoxide **6a** and its diacetate **6b**. Reindel also isolated a product, corresponding in constants to the triol **5a**, by hydrogenation on PtO_2 in acetic acid of the O_4 compound. Clearly, the acid cleaves the oxide ring with formation of **7a** and **8a**, which are transformed into **5a**,[13] after hydrogenolysis of 7α-hydroxy group.

Experimental Section

All melting points are uncorrected. Infrared spectra were obtained for solutions in chloroform, UV spectra were recorded for solutions in absolute ethanol, NMR spectra were taken on a Varian HA-100 as chloroform-*d* solutions and are reported as δ units relative to Me_4Si, and optical rotations were taken as chloroform solutions when not otherwise indicated. The mass spectra were determined on an LKB 9000 by direct inlet. The progress of all reactions and column chromatographs (silica gel G–Celite 1:1 v/v) was monitored by TLC on silica gel (HF_{254}) microplates. Benzene–ethyl acetate (80:20) and dichloromethane–acetone (100:6) were used as developing solvents, and spots were detected by spraying with 70% sulfuric acid, followed by heating.

Permanganate Oxidation of Ergosterol According to Fieser et al. Ergosterol (4 g) was dissolved in methylcyclohexane (100 mL) at 100 °C, and aqueous potassium permanganate (3.2 g/80 mL), preheated to 100 °C, was added at once to the hot solution of the sterol. The flask was stoppered and shaken vigorously. The permanganate was all consumed in 10 min, the thin suspension of brown manganese dioxide was destroyed after cooling of the mixture at room temperature, with sulfur dioxide (2.9 g), and the resulting suspension of white solid was transferred to a separatory funnel and shaken gently with three successive portions of water to extract inorganic salts. The milky organic layer consisting of a suspension of the sparingly soluble oxidation products was then steam-distilled for separation of the solvent. The distillation was stopped after 1 h, when the foaming became excessive. The mixture was then transferred to a large porcelain dish and evaporated on the steam bath (3 h, internal temperature 90 °C) to a thick gelatinous curd. After drying under high vacuum the crude product was acetylated at room temperature with acetic anhydride and pyridine to yield, after the usual workup, a crystalline material (2.5 g; large prisms): mp 183–184 °C (after three crystallizations from 95% ethanol); $[\alpha]^{23}_D$ +34°; UV λ_{max} 236, 243, 251 nm (log ε 4.09, 4.12, 3.98) [(lit.[2] mp 183–184 °C; $[\alpha]^{23}_D$ +34°; UV λ_{max} 244 nm (log ε 4.12)]. A crystalline product with the same physicochemical characteristics was obtained by first isolating and purifying the crude oxidation product, as reported by Fieser et al.,[2] and then acetylating the resulting crystalline material, mp 223–224 °C (lit.[2] mp 223–224 °C). As pointed out by the authors,[2] the acetylated material can be obtained more readily by acetylation of the crude oxidation mixture. TLC analysis of the acetylated material on silica gel G–$AgNO_3$ revealed the presence of three different components. Chromatography on silica gel G–Celite–$AgNO_3$ (1:1:0.3) (150 g), 20% benzene–hexane eluant, afforded 3β,6α-diacetoxy-5α-hydroxyergosta-7,22-diene (**3b**) (470 mg): mp 181–182 °C (from methanol); $[\alpha]^{23}_D$ +44°; IR 3500, 1730 cm^{-1}; ^1H NMR δ 0.56 (s, 3 H, 18-CH_3; calcd[5] 0.54), 1.04 (s, 3 H, 19-CH_3; calcd[5] 1.01), 2.00, 2.04 (2 s, 6 H, OAc), 4.94 (m, 1 H, 6β-H, $W_{1/2}$ ca. 6 Hz), 5.2–5.3 (overlapping, 3 H, 7-H, 22-H, and 23-H); mass spectrum, *m/e* (rel intensity) 454 (14, M – AcOH). Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.77; H, 9.90. The compound was identical with an authentic sample[2] (melting point, mixture melting point NMR and mass spectra). Saponification of **3b** with 0.2 N methanolic potassium hydroxide gave the triol **3a**: mp 243–244 °C (from ethyl acetate); $[\alpha]^{23}_D$ +30° (py). The compound was identical with an authentic sample[2] and regenerated **3b** when acetylated.

A 30% benzene–hexane mixture eluted 3β,6α-diacetoxy-5α-hydroxyergosta-7,9(11),22-triene (**4b**) (1.3 g): mp 184–185 °C (from methanol); $[\alpha]^{23}_D$ +88°; IR 3460, 1720 cm^{-1}; UV λ_{max} 236, 243, 251 nm (log ε 4.20, 4.23, 4.05); ^1H NMR δ 0.54 (s, 3 H, 18-CH_3; calcd[5] 0.52), 1.12 (s, 3 H, 19-CH_3; calcd[5] 1.11), 2.00, 2.13 (2 s, 6 H, OAc), 5.02 (m, 1 H, 6β-H, $W_{1/2}$ ca. 7 Hz), 5.1 (m, 1 H, 3α-H, $W_{1/2}$ ca. 14 Hz), 5.25 (m, 2 H, 22-H and 23-H), 5.43 (m, 1 H, 7-H, $W_{1/2}$ ca. 7 Hz), 5.7 (m, 1 H, 11-H, $W_{1/2}$ ca. 10 Hz); mass spectrum, *m/e* (rel intensity) 512 (8, M^+), 434 (100, M – AcOH + H_2O). Anal. Calcd for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 74.80; H, 9.50.

Saponification of **4b** with methanolic potassium hydroxide gave the triol **4a**: mp 210–211 °C; $[\alpha]^{23}_D$ +63°; IR 3450, 3330 cm^{-1}; UV λ_{max} 236, 243, 251 nm (log ε 4.20, 4.23, 4.05); ^1H NMR δ 0.53 (s, 3 H, 18-CH_3; calcd[5] 0.53), 1.06 (s, 3 H, 19-CH_3; calcd[5] 1.04), 4.00 (m, 1 H, 3α-H, $W_{1/2}$ ca. 14 Hz), 5.14 (m, 1 H, 7-H, $W_{1/2}$ ca. 6 Hz), 5.23 (m, 2 H, 22-H and 23-H), 5.65 (m, 1 H, 11-H); mass spectrum, *m/e* 410 (M – H_2O). Acetylation of **4a** regenerated **4b**.

A 40% benzene–hexane mixture eluted 3β,6α-diacetoxy-5α-hydroxyergosta-7,14,22-triene (**2b**) (320 mg): mp 179–180 °C (from methanol); $[\alpha]^{23}_D$ −91°; IR 3450, 1725, 1635 cm^{-1}; UV λ_{max} 242 nm (log ε 3.99); ^1H NMR δ 0.86 (s, 3 H, 18-CH_3; calcd[5] 0.82), 1.02 (s, 3 H, 19-CH_3; calcd[5] 1.02), 2.01, 2.12 (2 s, 6 H, OAc), 5.18, 5.20, 5.30 (overlapping, 4 H, 3α-H, 6β-H, 22-H, 23-H), 5.41 (m, 1 H, 7-H, $W_{1/2}$ ca. 7 Hz), 5.60 (m, 1 H, 15-H, $W_{1/2}$ ca. 7 Hz); mass spectrum, *m/e* (rel intensity) 512 (2, M^+), 392 (100, M – 2AcOH). Anal. Calcd for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 74.90; H, 9.55. Saponification of **2b** with methanolic potassium hydroxide gave the triol **2a**: mp 175 °C (from ethyl acetate); $[\alpha]^{23}_D$ −119°; IR 3450, 3330 cm^{-1}; UV λ_{max} 242 nm; ^1H NMR δ 0.79 (s, 3 H, 18-CH_3; calcd[5] 0.77), 0.96 (s, 3 H, 19-CH_3; calcd[5] 0.94). Acetylation of **2a** regenerated **2b**. Treatment of **2b** (100 mg) in dry benzene (5 mL) with maleic anhydride (40 mg, redistilled) for 4 h afforded the adduct (116 mg, from acetone): mp 278–279

(11) J. W. Ladbury and C. F. Lullis, *Chem. Rev.*, **58**, 403 (1958).
(12) H. Z. Sable, K. A. Powell, H. Katchain, C. B. Niewoehner, and S. B. Kadlec, *Tetrahedron*, **26**, 1509 (1970).
(13) We have carried out the reactions described in this paper on both ergosterol and cholesta-5,7-dien-3β-ol. In both instances analogous products were obtained. Under our conditions we never observed the formation of 3β,5α,6α,7α,8β-pentols. During the typing of the manuscript, a short communication was published in which Polish workers report the isolation of 3β-acetoxy-5α,6α,7α,8β-tetrahydroxycholestane by permanganate oxidation of 3β-acetoxycholesta-5,7-diene.[15] However, the oxidation procedure was not described.

°C dec; $[\alpha]^{23}_D$ -29° (lit.[2] mp 280–281 °C dec; $[\alpha]^{23}_D$ -30.3); mass spectrum, *m/e* (rel intensity) 610 (1.5, M^+), 457 (100, M - 2AcOH + H_2O). Anal. Calcd for $C_{36}H_{50}O_8$: C, 70.79; H, 8.25. Found: C, 70.91; H, 8.28.

Oxidation of 3β,6α-Diacetoxy-5α-hydroxyergosta-7,22-diene (3b) by Mercuric Acetate. Mercuric acetate (1 g) was added to a solution of diene **3b** (500 mg) in chloroform (12 mL) and acetic acid (20 mL), and the mixture was stirred vigorously for 24 h at room temperature.[14] The oil obtained after usual workup was chromatographed to give 3β,6α-diacetoxy-5α-hydroxyergosta-7,9(11),22-triene (**4b**) (600 mg), mp 184–185 °C, identical with that described above (NMR and mass spectra).

Permanganate Oxidation of Ergosterol without Destroying the Formed Manganese Dioxide. The oxidation was conducted as described, starting from 4 g of ergosterol dissolved in methylcyclohexane. The thin suspension obtained (due to the presence of brown, powdered manganese dioxide) between the aqueous and hydrocarbon phases was filtered through a pad of Celite. The solid material was resuspended in hot acetone (500–600 mL) and refiltered. The methylcyclohexane was separated and combined with the acetone washings. Solvent evaporation gave a pale yellow crude product (ca. 3.20 g) which was chromatographed. Elution with 5% diethyl ether–hexane yielded 20% of several less polar, unidentified impurities. Elution with 15% diethyl ether–hexane produced first a mixture of **3a** and **6a** (NMR and mass spectra) and then a mixture of **7a** and **8a** (NMR and mass spectra). Better separation was achieved by acetylation of the crude oxidation product and chromatography. A 5% diethyl ether–hexane mixture eluted unidentified impurities (20%); 10% diethyl ether–hexane eluted 7α,8α-epoxy-5α-ergost-22-ene-3β,5,6α-triol 3,6-diacetate (**6b**) (1.8 g): mp 152–154 °C (from benzene–hexane); $[\alpha]^{23}_D$ +8°; IR 3410, 3350, 1720 cm^{-1}; NMR δ 0.78 (s, 3 H, 18-CH_3), 1.11 (s, 3 H, 19-CH_3), 2.00, 2.20 (2 s, 6 H, OAc), 3.58 (m, 1 H, 7β-H, $W_{1/2}$ ca. 3.5 Hz), 4.52 (m, 1 H which disappears after treatment with D_2O), 5.1 (m, 1 H, 3α-H), 5.18 (m, 1 H, 6β-H, $W_{1/2}$ ca. 3.5 Hz), 5.25 (m, 2 H, 22-H, and 23-H); mass spectrum, *m/e* (rel intensity) 530 (2, M^+), 319 (100), 277 (83). Anal. Calcd for $C_{32}H_{50}O_6 \cdot 0.5H_2O$: C, 71.2; H, 9.5. Found: C, 70.9; H, 9.2.

Saponification of **6b** gave the corresponding triol **6a**: mp 199–200 °C (from acetone); $[\alpha]^{23}_D$ -9.7°; IR 3450, 3330 cm^{-1}; ^1H NMR δ 0.78 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 2.95 (m, 1 H, OH, *J* = 10 Hz), 3.58 (br d, 1 H, 7β-H, $W_{1/2}$ ca. 3.5 Hz), 3.78 (dd, 1 H, 6β-H, *J* = 10 Hz, $W_{1/2}$ ca. 3.5 Hz), 3.97 (m, 1 H, 3α-H, $W_{1/2}$ ca. 25 Hz), 4.3 (m, 1 H, OH, $W_{1/2}$ ca. 3 Hz), 5.25 (m, 2 H, 22-H and 23-H). Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.57; H, 10.40. Found: C, 75.29; H, 10.38.

A 10% diethyl ether–hexane mixture eluted, also with some overlapping, 3β,6α-diacetoxy-5α-hydroxyergosta-7,22-diene (**3b**) (375 mg), 181–182 °C, identical with that described above.

A 15% diethyl ether–hexane mixture eluted 3β,5α,6α,7α-tetrahydroxyergosta-8(14),22-diene 3,6,7-triacetate (**7b**) (53 mg): mp 173–174 °C (from methanol); $[\alpha]^{23}_D$ -16.4°; IR 3450 cm^{-1}; ^1H NMR δ 0.86 (s, 3 H, 18-CH_3; calcd[5] 0.85), 0.94 (s, 3 H, 19-CH_3; calcd[5] 0.91), 2.00, 2.04, 2.07 (3 s, 9 H, OAc), 4.92 (br d, 1 H, 7β-H, $J_{6\beta,7\beta}$ = 4 Hz), 5.05 (m, 1 H, 3α-H, $W_{1/2}$ 25 Hz), 5.20 (m, 2 H, 22-H and 23-H), 5.92 (br d, 1 H, 6 β-H, $J_{7\beta,6\beta}$ = 4 Hz); mass spectrum, *m/e* (rel intensity) 452 (1, M - 2AcOH), 392 (100, M - 3AcOH). Anal. Calcd for $C_{34}H_{52}O_7$: C, 71.3; H, 9.1. Found: C, 71.1; H, 9.2.

Saponification of **7b** gave the tetrol **7a** (from which **7b** was regenerated): mp 207–208 °C; $[\alpha]^{23}_D$ - 58.8° (dioxane); IR 3600, 3380 cm^{-1}; ^1H NMR δ 0.80 (s, 3 H, 19-CH_3; calcd[5] 0.82), 0.89 (s, 3 H, 18-CH_3); mass spectrum, *m/e* (rel intensity) 428 (30, M - H_2O), 285 (100, M - $2H_2O$ + side chain). Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.67; H, 10.46.

Finally, 15% diethyl ether–hexane mixture eluted 3β,5α,-6α,7α-tetrahydroxyergosta-8(9),22-diene 3,6,7-triacetate (**8b**) (150 mg): mp 157–158 °C (from methanol); $[\alpha]^{23}_D$ +6°; IR 3600, 3400 cm^{-1}; ^1H NMR δ 0.62 (s, 3 H, 18-CH_3; calcd[5] 0.59), 1.26 (s, 3 H, 19-CH_3; calcd[5] 1.16), 2.00, 2.03, 2.05 (3 s, 9 H, OAc), 5.05 (m, 1 H, 3 α-H), 5.25 (m, 2 H, 22-H and 23-H), 5.32 (br s, 1 H, 7β-H, $W_{1/2}$ ca. 8 Hz), 5.52 (br d, 1 H, 6 β-H; $W_{1/2}$ ca. 9 Hz); mass spectrum, *m/e* (rel intensity) 512 (10, M - AcOH), 392 (100, M - 3AcOH). Anal. Calcd for $C_{34}H_{52}O_7$: C, 71.3; H, 9.1. Found: C, 71.5; H, 9.3.

Saponification of **8b** gave the tetrol **8a** (from which **8b** was regenerated): mp 215–216 °C; $[\alpha]^{23}_D$ -27° (dioxane); IR 3600, 3380 cm^{-1}; ^1H NMR δ 0.55 (s, 3 H, 18-CH_3; calcd[5] 0.59), 0.98 (s, 3 H, 19-CH_3; calcd[5] 1.08); mass spectrum, *m/e* (rel intensity) 446 (16, M^+), 285 (100, M - $2H_2O$ + side chain). Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.10; H, 10.15.

Oxidation of 3β,5α,6α-Trihydroxyergosta-7,22-diene (3a) with *m*-Chloroperbenzoic Acid. An ice-cold dichloromethane solution of *m*-chloroperbenzoic acid (80 mg) was added to an ice-cold solution of the triol **3a** (200 mg) dissolved in dichloromethane (15 mL). The solution was kept at 0–2 °C for 2 h and then washed with aqueous $NaHCO_3$, dried, and evaporated. Purification by preparative TLC on silica afforded the epoxytriol **6a** (100 mg), mp 199–200 °C, identical with that described above.

Synthesis of 3β,6α-Diacetoxy-5α-hydroxyergost-8(14)-ene (5b). Compound **5b** was obtained by action of hydrogen on **2b**, **3b**, **4b**, **6b**, **7b**, and **8b** in acetic acid in the presence of PtO_2 by the following general procedure. The steroid (250 mg), PtO_2 (100 mg), and acetic acid (20 mL) were stirred for 1–4 h at room temperature under a slight positive pressure of hydrogen. After the usual workup, **5b** was recovered (200 mg) by crystallization from methanol: mp 176–177 °C (from methanol); $[\alpha]^{23}_D$ -19° (dioxane); (lit.[2] mp 174.5–177.5 °C; $[\alpha]_D$ -18.5° (dioxane)); IR 3410, 1730 cm^{-1}; NMR δ 0.82 (s, 3 H, 18-CH_3; calcd[5] 0.84), 0.90 (s, 3 H, 19-CH_3; calcd[5] 0.93), 2.00, 2.07 (2 s, 6 H, OAc), 4.7–5.4 (br m, 2 H, 3α-H and 6β-H); mass spectrum, *m/e* (rel intensity) 454 (12, M - AcOH). Anal. Calcd for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.20; H, 10.20).

When the reaction was performed on alcohols **2a**, **3a**, **4a**, **6a**, **7a**, and **8a**, the product obtained was **5a**: mp 234–235 °C; $[\alpha]^{23}_D$ -4° (py) (lit.[2] mp 232–235 °C; $[\alpha]^{23}_D$ -4.6° (py)). Anal. Calcd for $C_{28}H_{48}O_3 \cdot 0.5H_2O$: C, 76.14; H, 11.18. Found: C, 76.08; H, 11.22.

Treatment of 7α,8α-Epoxy-5α-ergost-22-ene-3β,5,6α-triol (6a) with 90% Acetic Acid. Compound **6a** (200 mg) was dissolved in acetic acid (20 mL, 90%) and was kept 2 h at room temperature. After the usual workup an unseparable mixture of tetrols **7a** and **8a** (1:3) was obtained (NMR and mass spectral evidence); the mixture was separated after acetylation and chromatography. Both products were identified by melting pount, mixture melting point, optical rotation, and comparison of their mass spectra with those of compounds described.

Analogous treatment of **6a** at 45 °C for 30 min yielded a mixture of trienes **2a** and **4a** (ca. 1:3). Separation on preparative TLC (silica–$AgNO_3$) gave pure **2a** and **4a** which were identical with those described above.

Treatment of 3β,5α,6α,7α-Tetrahydroxyergosta-8(14),22-diene (7a) and 3β,5α,6α,7α-Tetrahydroxyergosta-8(9),22-diene (8a) with 90% Acetic Acid. Isomeric tetrols **7a** and **8a** (100 mg) were treated, separately, with acetic acid (10 mL, 90%) at 45 °C for 30 min. Usual workup gave **2a** (80 mg) from **7a** and **4a** (85 mg) from **8a**. Both obtained trienes were identical with those described above.

Permanganate Oxidation of Ergosterol and Sulfur Dioxide Reduction of Formed Manganese Dioxide. The same oxidation procedure as that described above was followed starting from 4 g of ergosterol. When the permanganate was all consumed, sulfur dioxide was bubbled through the mixture to reduce the formed MnO_2. The product was extracted with chloroform (3 × 200 mL).

The organic layers were washed with $NaHCO_3$ solution, dried, and evaporated. The crude product (3.2 g) was chromatographed to yield first 3β,5α,6α-triydroxyergosta-7,22-diene (**6a**) (400 mg) accompanied by a small amount of epoxytriol (**6a**) and then a mixture of isomeric tetrols **7a** and **8a** (2.00 g) (NMR and mass spectral evidence). After acetylation of the tetrol mixture, triacetates **7b** (mg 550), mp 173–174 °C, and **8b** (1.3 g), mp 215–216 °C, were obtained and were identical with those described above.

Composition of the Fieser "O_3-Oxidation Product". The oxidation of 4 g of ergosterol was conducted according to Fieser et al.[2] under the same conditions reported above. The crude oxidation product was crystallized from benzene saturated with water and then from methanol. TLC analysis of this material,

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(15) W. J. Rodewald and Z. Bończa-Tomaszewski, *Tetrahedron Lett.*, 169 (1979).

mp 223–224 °C (lit.[2] mp 223–224 °C) (6% methanol–ethyl acetate), showed that **2a**, **3a**, and **4a** (one spot, R_f 0.42) were present, accompanied by minor quantities of the two more polar products **7a** and **8a** (one spot, R_f 0.22). Preparative TLC (on silica) separated (^{1}H NMR and mass spectral evidence) **2a**, **3a**, and **4a** from small amounts of **7a** and **8a**. **2a**, **3a**, and **4a** were then separated on silica–$AgNO_3$. The mixture of **7a** and **8a** could not be separated by preparative TLC. After acetylation the acetates **7b** and **8b** could be separated. Saponification of **7b** and **8b** regenerated **7a** and **8a** which were inseparable on TLC. When O_3-oxidation product was acetylated and crystallized from 95% ethanol, **7b** and **8b** remained in solution.

Composition of the Fieser "O_5-Oxidation Product". The O_5 product was isolated by following the described procedures.[2] TLC analysis (on silica) and development with 6% methanol–ethyl acetate showed the presence of **7a** and **8a** (one spot, R_f 0.22) and of small amounts of **2a**, **3a**, and **4a** (one spot, R_f 0.42). Preparative TLC on silica–$AgNO_3$ separated **2a**, **3a**, and **4a**, which were identical with those described above. **7a** and **8a** were separated as triacetates and were identical with those described above.

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Registry No. 1, 57-87-4; **2a**, 71097-06-8; **2b**, 35691-23-7; **2b** maleic anhydride adduct, 71097-16-0; **3a**, 60497-23-6; **3b**, 33824-22-5; **4a**, 71097-07-9; **4b**, 71097-08-0; **5a**, 71097-09-1; **5b**, 71097-10-4; **6a**, 71097-11-5; **6b**, 71106-22-4; **7a**, 71097-12-6; **7b**, 71097-13-7; **8a**, 71097-14-8; **8b**, 71097-15-9; potassium permanganate, 7722-64-7; mercuric acetate, 1600-27-7; maleic anhydride, 108-31-6.

Short, Simple, Stereocontrolled, Steroid Synthesis: (±)-11-Oxoequilenin Methyl Ether and a New 9,11-Seco-13-ethyl Steroid

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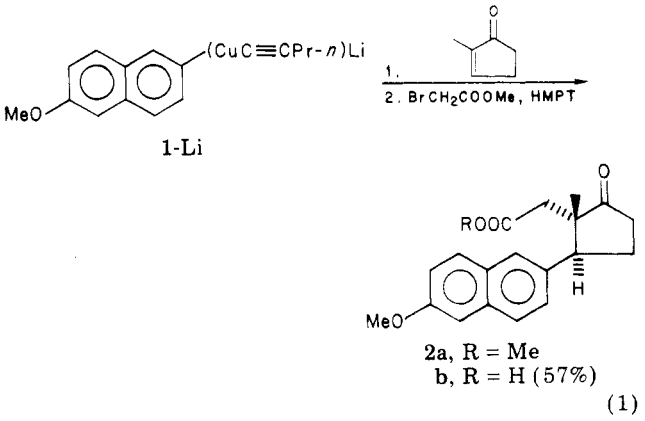
An improved procedure has been developed for efficient preparation of 9,11-seco steroid **2b** from 2-methyl-2-cyclopentenone in 85% yield and >99% stereochemical purity over three steps without chromatography. This high yield, almost double that previously reported by us, is achieved by using a magnesium instead of a lithium cuprate and ethyl iodoacetate instead of methyl bromoacetate. This procedure has been extended to stereocontrolled preparation of a new 9,11-seco-13-*ethyl* steroid (**5**) of potential contraceptive value directly from 2-ethyl-2-cyclopentenone. ^{1}H and ^{13}C NMR data confirm that the incipient C,D-ring stereochemistry of seco steroids **2** and **5** is that of the natural steroids (i.e., trans). A high-yield HF-promoted Friedel–Crafts intramolecular acylation completes an efficient (>50% overall yield) and stereocontrolled total synthesis of (±)-11-oxoequilenin methyl ether.

Two of the most challenging problems in devising new syntheses of steroids are control of stereochemistry[1] and efficiency in construction of the tetracyclic carbon skeleton. We have recently reported a new, convergent, steroid total synthesis based on organocopper β-addition and subsequent α-alkylation of a cyclopentenone in which control of relative stereochemistry is virtually complete and in which a usefully functionalized steroid is produced expeditiously in 31% yield over four steps from readily available starting materials.[2] We now report an improved procedure for stereocontrolled preparation of (±)-11-oxoequilenin methyl ether in >50% yield over four steps without chromatography. This improved procedure further permits stereocontrolled preparation of a new 9,11-seco-13-*ethyl* steroid of potential contraceptive value directly in a "one-pot" reaction from 2-ethyl-2-cyclopentenone.

Results and Discussion

The mixed aryl(alkynyl)copperlithium reagent 1-Li, prepared from the aryllithium and the alkynylcopper species, was allowed to react with 1 equiv of 2-methyl-2-cyclopentenone and then with methyl bromoacetate in hexamethylphosphoric triamide (HMPT) to give tricyclic keto ester **2a** which was isolated and, without purification, was saponified to form keto acid **2b**. One recrystallization gave pure 9,11-seco steroid **2b** in 57% yield (eq 1).[2]



2a, R = Me
b, R = H (57%)

(1)

Various attempts were made to improve the yield of this type of organocopper conjugate addition–α-alkylation process.[3] Variation of the Y group in aryl(Y)CuLi species[4] included Y = aryl, SPh,[5] and CN.[6] Despite the fact that

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