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Facile Intramolecular Ene Reactions of Steroidal Unsaturated Acyloins†

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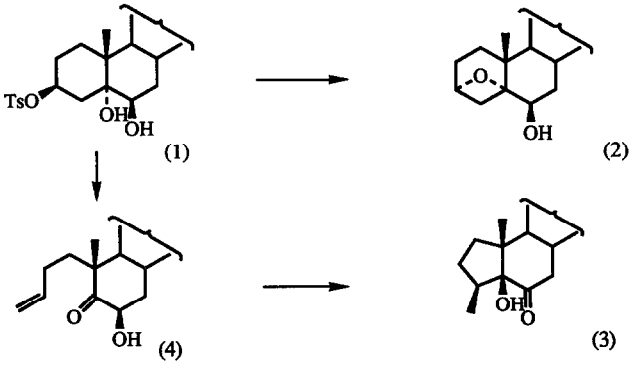
Abstract: The relatively low temperature (200°C) intramolecular ene reaction of 4,5-seco-5β-cholest-3-en-5-ol-6-one followed by *in situ* rearrangement affords 3-methyl-B-nor-5β-cholest-2-en-4-one and 5-hydroxy-5β-cholestan-6-one and supports the view that 3β-methyl-A-nor-5β-cholestan-5-ol-6-one arises from 3β-tosyloxy-5ξ-cholestane-5,6β-diols in the presence of KOBu^t by similar ene reactions.

The ene reaction[1] has gained wider acceptance in recent years as a viable synthetic method largely owed to the development of reactive electron deficient enophiles and the use of Lewis acid catalysts allowing reactions to proceed close to room temperature or below.[2,3,4] Little work has been reported on reactions of electron rich enes although the related metalloene reaction is well known.[5]

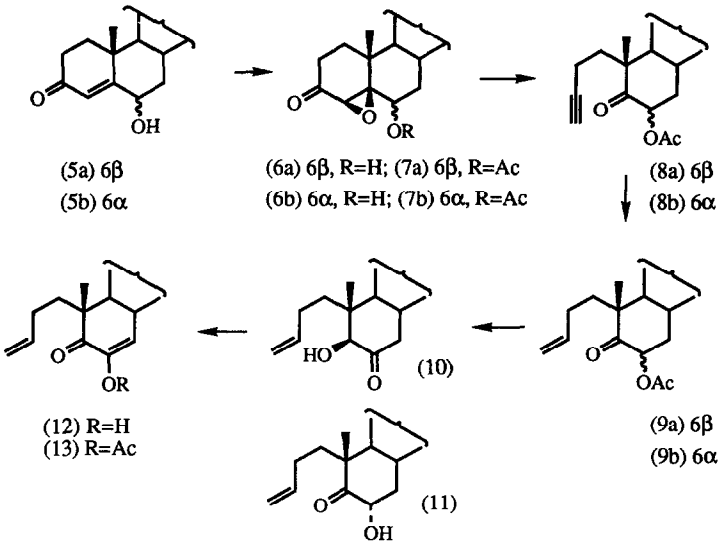
We have observed[6] that preparation of the oxetane (2) by reaction of the tosyloxy diol (1) with KOBu^t/Bu^{t}OH gave 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3) as a by-product (≤25%). This was believed to arise from a novel intramolecular ene reaction of the intermediate unsaturated acyloin (4) (Scheme 1). We report here further exploration of this novel ene reaction[7,8] by a study of the unsaturated acyloin (10) which is the regioisomer of the proposed intermediate (4). A preliminary account of some of this work has been reported.[9]



Scheme 1

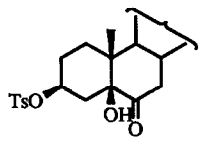
†*Dedicated to the memory of our friend and colleague Barrie C. Uff; 13 Feb 1937 - 19 Oct 1991*

Oxidation of the 6β-hydroxycholestenone (5a)[10] and the 6α-isomer (5b)[11] with alkaline hydrogen peroxide afforded the expected 4β,5β-epoxides (6a) and 6b) respectively after crystallisation which were converted to their acetates (7a) and 7b). Eschenmoser fragmentation[12] of each of these using $TsNHNH_2$ afforded the 4,5-seco alkynes (8a) and (8b) respectively which on partial hydrogenation over a palladium/$BaSO_4$ catalyst, poisoned with quinoline, gave the 4,5-seco alkenes (9a) and (9b). The products of hydrolysis of the 4,5-seco alkenes (9a) and (9b) were dependent on the reaction conditions. Using concentrated HCl in ethanol containing water (10%) the 4,5-seco alkene (9a) gave largely the unsaturated acyloin (10). The i.r. spectrum confirmed the presence of the OH (ν_{max} 3470 cm^{-1}), alkene (ν_{max} 3070, 1640 cm^{-1}) and CO (ν_{max} 1710 cm^{-1}) groups and the ^1H n.m.r. spectrum confirmed the regiochemistry of the acyloin by the presence of a 1 H singlet at δ 4.08. Presumably the unsaturated acyloin (10) is the thermodynamically stable product and may arise from its regioisomers through tautomerisation. The 5β (equatorial)-configuration is assumed. Using dilute HCl in ethanol both (9a) and (9b) gave the unsaturated acyloin (10) and its regioisomer (11). The stereochemistry and regiochemistry of the latter was confirmed by the presence of a 1 H double doublet at δ 4.38 (J 7 and 11 Hz) in the ^1H n.m.r. spectrum. Base-catalysed hydrolysis of (9a) in an atmosphere of argon with thoroughly degassed solutions gave the unsaturated acyloin (10) in good yield but even traces of air led to the isolation of the diosphenol (12) by autoxidation.[13] Acetylation of the diosphenol (12) gave its acetate (13) (Scheme 2).

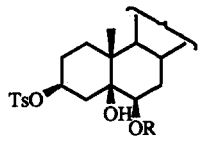


Scheme 2

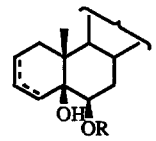
Treatment of the unsaturated acyloin (10) in an atmosphere of argon with $BuOK^t$ in Bu^tOH at 78°C did not give the A-nor-compound (3). A re-investigation of the reaction[6] of the tosyloxy diol (1) with $KOBu^t$ in Bu^tOH confirmed the formation of the A-nor-compound (3) (11%) and it was also possible to isolate a small quantity of the unsaturated acyloin (10) (4%) provided that the experiments were carried out in an inert atmosphere. In the presence of air, however, the A-nor-compound (3) was not detected and only the diosphenol (12) was isolated in addition to the expected oxetane (2). These observations support the intermediacy of the unsaturated acyloin (10) in the formation of the A-nor-compound (3) assuming autoxidation competes with the ene reaction. However, the failure to observe the ene reaction under air-free conditions was unexpected. Interestingly, treatment of the 5β-tosyloxy diol (15) with $KOBu^t$ in Bu^tOH gave a much greater yield of the A-nor-compound (3) (45%) along with some unsaturated acyloin (10) (5%), the diosphenol (12) (3%) and the Δ^2/Δ^3-diols (17) (18%) which were acetylated to give (18). The reactions of (15) were somewhat variable. The unfavourable stereochemistry for 3β,5β-oxetane formation from (15) is presumably important[14] even though the stereochemistry is also not favourable for fragmentation.[15] The 5β-tosyloxy diol (15) was prepared from the 5β-tosyloxy ketone (14)[16] by $NaBH_4$ reduction and it was further characterised as its acetate (16).



(14)



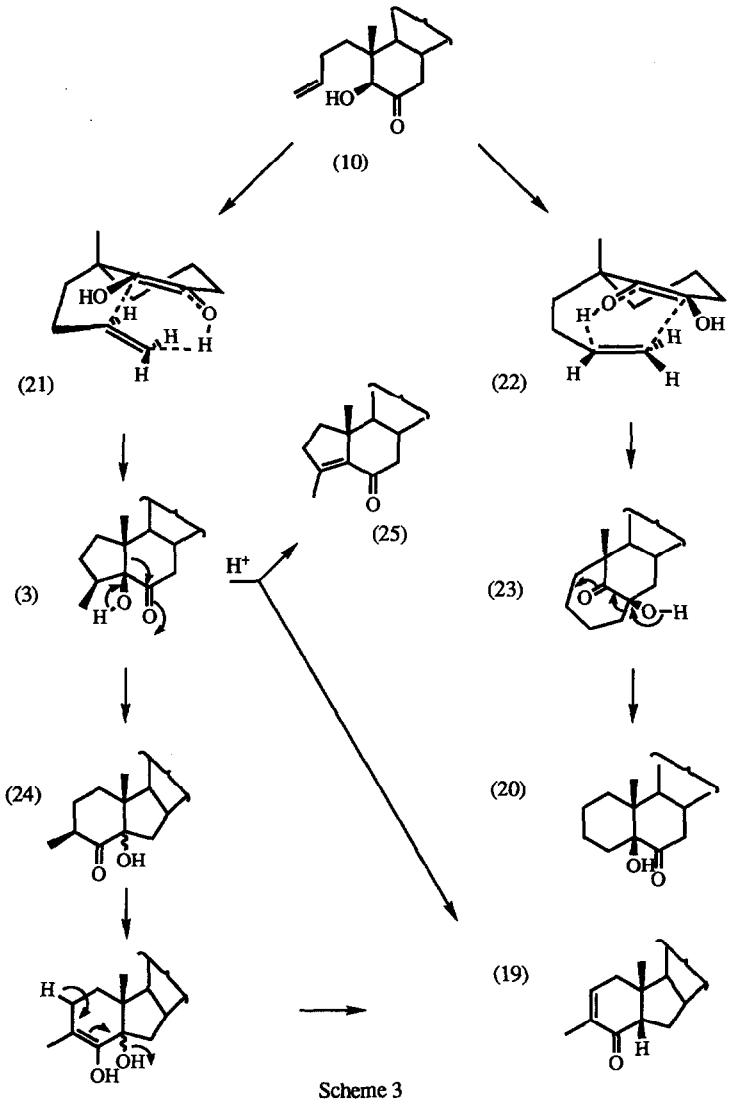
(15) R=H
(16) R=Ac



(17) R=H
(18) R=Ac

Given that intramolecular ene reactions of unsaturated ketones require quite high temperatures, reaction of the unsaturated acyloin in an argon atmosphere in solution in decalin at 200°C (sealed tube) was investigated. Thin layer chromatography of the crude product gave the B-norcholestenone (19) (26%) and the 5β-hydroxy 6-ketone (20) (13%).[17] The i.r. (ν_{max} 1665 cm^{-1}) and u.v. (λ_{max} 240nm, ε,9820) spectra confirmed the presence of the enone in the B-norcholestenone (19) and important signals in the ^1H n.m.r. spectrum were observed at δ 6.50 (1H, m, 2-H) and 1.80 (3H, brs, 3-Me). Double irradiation of the signal at δ1.80 caused the collapse of the multiplet at δ 6.50 to a double doublet (J~2.8 and 5.8 Hz) and key ^{13}C n.m.r. signals at δ 203.1 (C-4), 142.0 (C-2), 134.6 (C-3) and 25.7 (C-19) confirmed the structure. Further support for the structure (19) came from the observation that a maximum of 3-deuterium atoms (C-1 and C-5) were incorporated when the compound was treated with $NaOD/D_2O$) in refluxing dioxane solution. The 5β-configuration is assumed on the basis of thermodynamic stability. It is assumed that this thermal reaction of (10) proceeds *via* the diene diol in conformations (21) and (22) to give respectively the A-nor-compound (3) and the bridged hydroxy ketone (23). Under the reaction conditions, these primary products are further modified to give the B-norcholestenone (19) and the 5β-hydroxy 6-ketone (20) (Scheme 3). It is possible for the latter to arise directly from the diene diol but models suggest that the transition state would be too strained. Support for the suggested pathways comes from the observation that the A-nor-compound (3) is converted partially to the B-norcholestenone (19) on heating under similar conditions in decalin and there are several known examples[18,19] of acyloin rearrangements similar to those proposed here [(3) → (24) and (23) → (20)]. Possibly acid catalysis on the glass surface is important in the modification of the primary products. In fact, treatment of the A-nor-compound (3) with *p*-toluenesulphonic acid in benzene did give the

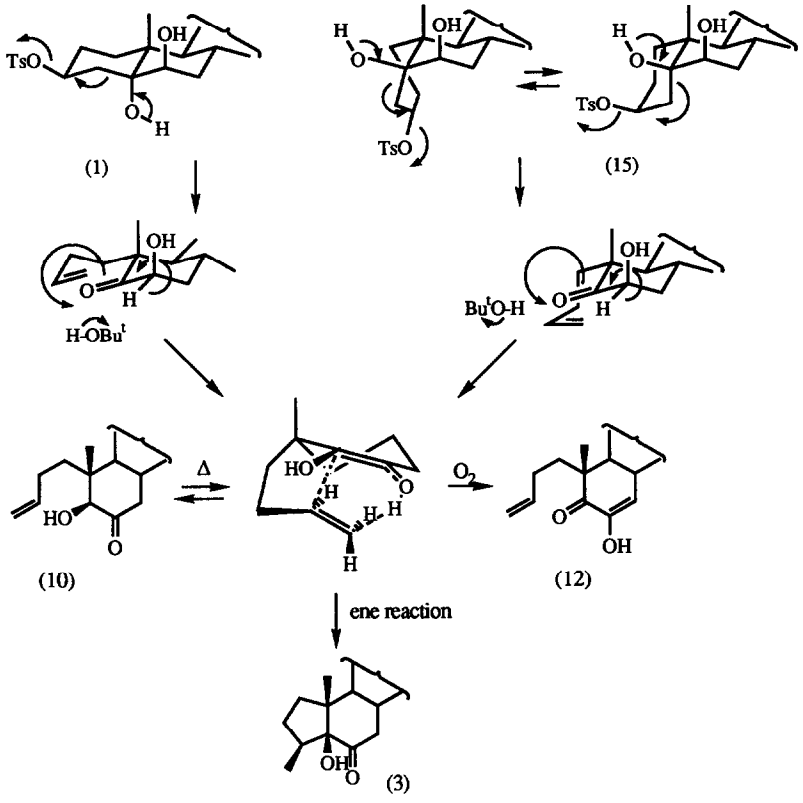
B-norcholestenone (19) and in addition the A-norcholestenone (25) (Scheme 3). The spectroscopic data for (25) [ν_{max} 1680 (CO), 1625 (alkene) cm^{-1},.λ_{max} 260 nm ε 11,500 (enone), δ_H 2.04 (3H, br s, 3-Me) and δ_C 201.3 (C-6), 148.9 (C-3) 141.9(C-5)] were in accordance with the proposed structure.



Scheme 3

The observed ene reaction of the unsaturated acyloin (10) occurs at relatively low temperatures compared to those of unsaturated ketones and suggests that the electron rich diene diol is relatively reactive. It is also unusual in that one of the products (23) is formed by carbon-carbon bond formation to the terminal carbon atom of the olefin. There appears to be circumstantial evidence that the unsaturated acyloin (4) also undergoes the ene reaction when formed *in situ* from the tosyloxy diols (1) and (15). Perhaps the rate of

enolisation of the unsaturated acyloin formed *in situ* in Bu^tOK/Bu^tOH competes with the rate at which the C1-C4 chain unfolds and thereby allows the ene reaction to compete since the acyloin, when first formed, will be in a conformation close to the required reacting conformation. The essential features of the reactions of (1) and (15) are shown in Scheme 4.



Scheme 4

Experimental

Solutions were dried over anhydrous magnesium sulphate and solvents were removed under reduced pressure with a rotary evaporator. Preparative t.l.c. was performed on Kieselgel $60PF_{254}$ and PF_{360}. Flash chromatography was carried out with Merck silica gel (230-240 mesh). I.r. spectra were recorded for nujol mulls (solids) or as thin films with a Perkin-Elmer 177 spectrometer. ^1H spectra were determined for solutions in $CDCl_3$ with tetramethylsilane as internal standard at 60 MHz (Varian EM360) or 90MHz (Perkin-Elmer R32). ^{13}C nmr were similarly determined with a Bruker WP80 spectrometer. Mass spectra were recorded with a Kratos MS80 spectrometer, with a DS55 data system. Melting points were determined with a Kofler hot-stage microscope. Optical rotations were measured for solutions in chloroform with an Automatic digital polarimeter AA-10.

6β-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (6a). A solution of hydrogen peroxide (30%, 1.5 ml) in aqueous sodium hydroxide (2M, 10 ml) was added to 6β-hydroxycholest-4-en-3-one (5a) (1.0g) in methanol (80 ml). The mixture was stirred at room temperature for 3 hours, then diluted with water (200 ml)

and extracted with ether (3 x 50 ml). The combined ether extracts were washed with brine (2 x 50 ml), dried and evaporated *in vacuo* to give *6β-hydroxy-4β,5-epoxy-5β-cholestan-3-one* (6a) (0.67g, 64%), m.p. 174-176°C (methanol), $[\alpha]_D$ + 85°C (c=1.7), ν_{max} 3520 (sharp, OH), 1710 (C=0) cm^{-1}, δ_H 3.48 (br s, 1H, 6α-H, W1/2 6Hz), 3.02 (s, 1H, 4α-H), 1.36 (s, 3H, 10β-Me), 0.74 (s, 3H, 13β-Me). (Found: m/z 416.3268 ($M^{+\cdot}$). C, 77.8; H, 11.0%. $C_{27}H_{44}O_3$ requires M 416.3290. C, 77.8; H, 10.6%).

6α-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (6b). 6α-Hydroxycholest-4-en-3-one (5b) (2.2g) was treated as above with hydrogen peroxide (30%, 4 ml) and sodium hydroxide (4N, 10 ml) in methanol (200 ml) to give 6α-hydroxy-4ξ,5-epoxy-5ξ-cholestan-3-one (1.4g, 61%), an oil, $[\alpha]_D$ + 42° (c=0.98). Recrystallisation from methanol gave the pure 4β,5β-epoxide (6b) m.p. 138°C, $[\alpha]_D$ +58° (c=2.5), ν_{max} 3440 (brd, OH), 1710 (C=O) cm^{-1}, δ_H 4.14 (dd, 1H, 6β-H J= 5 and 11Hz), 3.46 (s, 1H, 4α-H), 1.14 (s, 3H, 10β-Me) and 0.69 (s, 3H, 13β-Me). (Found: m/z 416.3294 ($M^{+\cdot}$). C,.77.5; H, 10.8%. $C_{27}H_{44}O_3$. requires M 416.3290. C, 77.8; H, 10.6%).

6β-Acetoxy-4β,5-epoxy-5β-cholestan-3-one (7a). 6β-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (6a) (0.5g) was dissolved in pyridine (20 ml) and acetic anhydride (5 ml) and allowed to stand at room temperature overnight. The reaction mixture was poured over ice and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (2 x 25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml)dried and evaporated *in vacuo* to give the *acetate* (7a) (0.343g, 78%) m.p. 106-107°C (methanol), $[\alpha]_D$ + 45° (c=1.19), ν_{max} 1740 (C=O, ester), 1720 (shoulder, C=O, ketone) cm^{-1}, δ_H 4.60 (br, s, 1H, 6α-H, W1/2 6Hz), 3.06 (s, 1H, 4α-H), 2.11 (s, 3H, OAc), 1.30 (s, 3H, 10β-Me) and 0.72 (s, 3H, 13β-Me). (Found: m/z 458.3428 ($M^{+\cdot}$) C, 75.8; H, 10.2%. $C_{29}H_{46}O_4$ requires M 458.3396. C, 75.9; H, 10.1%).

6α-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (7b). 6α-Hydroxy-4β,5-epoxy-5β-cholestan-3-one (6b) (0.82g) was acetylated with acetic anhydride in pyridine as above. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave the acetate (7b) (0.57g, 63%), an oil, $[\alpha]_D$ +53° (c=1.55), ν_{max} 1745 (C=O, ester), 1710 (shoulder, C=O, ketone) cm^{-1}, δ_H 5.43 (dd, 1H, 6β-H, J=5 and 11Hz), 3.40 (s, 1H, 4α-H), 2.05 (s, 3H, OAc), 1.22 (s, 3H, 10β-Me) and 0.72 (s, 3H, 13β-Me). (Found: m/z 458.3393 ($M^{+\cdot}$) $C_{29}H_{46}O_4$ requires M 458.3396).

6β-Acetoxy-4,5-secocholest-3-yn-5-one (8a). *p*-Toluenesulphonylhydrazide (0.94g, 1.1 mol equiv.) was added to a solution of 6β-acetoxy-4β,5-epoxy-5β-cholestan-3-one (7a) (2.3g) in absolute ethanol (80 ml). The solution was stirred at 50°C for two and a half hours, then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (25 ml), aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated *in vacuo* to give an orange oil. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:2 (v/v)] gave the pure *acetylene* (8a) (0.89g, 40%), an oil, $[\alpha]_D$ -42° (c=1.2), ν_{max} 3300 (C≡C-H), 2120 (C≡C), 1745 (C=O, acetate) 1728 (C=O, ketone), δ_H 5.39 (br t, 1H, 6α-H, J 9Hz), 2.12 (s, 3H, OAc), 1.08 (s, 3H, 10β-Me), 0.70 (s, 3H, 13β-Me). (Found: m/z 442.3443 ($M^{+\cdot}$). $C_{29}H_{46}O_4$ requires M 442.3447).

6α-Acetoxy-4,5-secocholest-3-yn-5-one (8b). 6α-Acetoxy-4β,5-epoxy-5β-cholestan-3-one (7b) (0.59g) was treated as above with *p*-toluenesulphonylhydrazide (0.25g) in ethanol (40 ml). Preparative thin layer chromatography gave *6α-acetoxy-4,5-secocholest-3-yn-5-one* (8b) (0.241g, 42%), an oil, $[\alpha]_D$ -12° (c=0.97), ν_{max} 3315 (C≡C-H), 2120 (C≡C), 1745 (C=O, ester), 1728 (C=O, ketone) cm^{-1}, δ_H 5.46 (dd, 1H, 6β-H, J=6 and 11 Hz), 2.18 (s, 3H, OAc), 1.20 (s, 3H, 10β-Me) and 0.77 (s, 3H, 13β-Me). (Found: m/z 442.3444 ($M^{+\cdot}$). $C_{29}H_{46}O_3$ requires M 442.3447).

6β–Acetoxy-4,5-secocholest-3-en-5-one (9a). 6β-Acetoxy-4,5-secocholest-3-yn-5-one (8a) (0.73g) in ethyl acetate (20 ml) was added to a pre-hydrogenated suspension of 5% palladium on barium sulphate (~200 mg) in ethyl acetate (20 ml) poisoned with quinoline (4 drops 20% solution). The suspension was stirred vigorously until 1 mole of hydrogen had been consumed. The catalyst was filtered off and the resulting solution washed with dilute hydrochloric acid (10 ml) and water (10 ml) dried and evaporated *in vacuo*. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:2 (v/v)] gave the pure *olefin* (0.571g, 78%), an oil, $[\alpha]_D$ -31° (c=1.08), ν_{max} 3080 (RCH=CH_2), 1745 (C=O, acetate), 1728 (C=O, ketone), 1640 (RCH=CH_2) cm^{-1}, δ_H 5.6-6.0 (m, 1H, RC*H*=CH_2), 5.42 (br t, 1H, 6α-H, J 9Hz), 4.85-5.15 (m, 2H, RCH=CH_2), 2.14 (s, 3H, OAc), 1.08 (s, 3H, 10β-Me), and 0.69 (s, 3H, 13β-Me). (Found: m/z 444.3607 ($M^{+\cdot}$). $C_{29}H_{48}O_3$ requires M 444.3603).

6α–Acetoxy-4,5-secocholest-3-en-5-one (9b). 6α–Acetoxy-4,5-secocholest-3-yn-5-one (0.188g) was hydrogenated as above. Preparative thin layer chromatography [SiO_2, petrol:ether, 3:1 (v/v)] gave the *olefin* (0.106g, 56%), an oil, $[\alpha]_D$ -4.5° (c=1.10), ν_{max} 3075 (RCH=CH_2), 1750 (C=O, ester), 1728 (C=O, ketone), 1640 (RCH=CH_2) cm^{-1}, δ_H 5.6-6.1 (m, 1H, RC*H*=CH_2), 5.48 (dd, 1H, 6β-H, J=6 and 11 Hz), 4.85-5.20 (m, 2H, RCH=CH_2), 2.17 (s, 3H, OAc), 1.19 (s, 3H, 10β-Me) and 0.76 (s, 3H, 13β-Me). (Found: m/z 444.3586 ($M^{+\cdot}$). $C_{29}H_{48}O_3$ requires M 444.3603).

Hydrolysis of 6β-Acetoxy-4,5-secocholest-3-en--5-one (9a). (a) With ethanol and concentrated hydrochloric acid: A solution of 6β-acetoxy-4,5-secocholest-3-en-5-one (9a) (0.52g) in ethanol (50 ml), water (5 ml) and concentrated hydrochloric acid (5 ml) was heated under reflux for one and a half hours. The solution was diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (25 ml) and water (25 ml), dried and evaporated *in vacuo* to give *5β-hydroxy-4,5-secocholest-3-en-6-one* (10) (0.41g, 88%), an oil, $[\alpha]_D$ +12° (c=1.2), ν_{max} 3470 (OH), 3070 (RCH=CH_2), 1710 (C=O), 1640 (RCH=CH_2) cm^{-1}, δ_H 5.55-6.10 (m, 1H, RC*H*=CH_2), 4.9-5.25 (m, 2H, RCH=CH_2), 4.25 (br s, 1H, OH, D_2O exchangeable), 4.08 (s, 1H, 5α-H), 0.69 (s, 6H, 10β-Me and 13β-Me). (Found: m/z 402.3506 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires M 402.3498).

(b) With ethanol and dilute hydrochloric acid: 6β-Acetoxy-4,5-secocholest-3-ene-5-one (9a) (1.3g) was dissolved in ethanol (50 ml) and dilute hydrochloric acid (2M, 10 ml). The solution was heated under reflux for five hours (t.l.c.) then diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with aqueous sodium bicarbonate (25 ml) and water 25 ml), dried and evaporated *in vacuo*. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 5β-hydroxy-4,5-secocholest-3-en-6-one (10) (0.36g, 30%) and *6α-hydroxy-4,5-secocholest-3-en-5-one* (11) (0.294g, 24%), an oil, $[\alpha]_D$ +17° (c=0.93), ν_{max} 3470 (OH), 3070 (RCH=CH_2), 1700 (C=O), 1640 (RCH=CH_2) cm^{-1}, δ_H 5.5-6.2 (m, 1H, RC*H*=CH_2), 4.9-5.2 (m, 2H, RCH=CH_2), 4.38 (dd, 1H, 6β-H, J=7 and 11 Hz), 3.9 (br s, 1H, OH), 1.10 (s, 3H, 10β-Me) and 0.65 (s, 3H, 13β-Me). (Found: m/z 402.3498 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires M 402.3498).A similar result was obtained with (9b): (10) (33%) and (11) (26%).

(c) With ethanolic potassium hydroxide under an inert atmosphere: 6β-Acetoxy-4,5-secocholest-3-en-5-one (9a) (0.385g) was added to a solution of potassium hydroxide in thoroughly deoxygenated ethanol (30%, 30 ml) under argon. The solution was heated under reflux for one hour, then acidified with dilute hydrochloric, diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (50 ml), dried and evaporated *in vacuo* to give 5β-hydroxy-4,5-secocholest-3-en-6-one (10) (0.285g, 90%).

(d) With ethanolic potassium hydroxide in the presence of air: 6β-acetoxy-4,5-secocholest-3-ene-5-one (9a) (0.45g) was added to ethanolic potassium hydroxide (5%, 30 ml) and stirred for one hour at room temperature. The solution was diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (50 ml), dried and evaporated *in vacuo* to give *6-hydroxy-4,5-secocholest-3,5-dien-5-one* (12) (0.36g, 80%), m.p. 125-127°C (methanol), $[\alpha]_D$ -66° (c=1.43), ν_{max} 3430 (sharp, OH), 3080 (RCH=CH_2), 1670 (C=O), 1650 (C=C) cm^{-1}, δ_H 6.09 (s, 1H, OH, D_2O exchangeable), 6.01 (d, 1H, 7-H, J 2Hz), 5.5-6.0 (m, 1H, RC*H*=CH_2), 4.9-5.2 (m, 1H, RCH=CH_2), 1.06 (s, 3H, 10β-Me) and 0.78 (s, 3H, 13β-Me). (Found: m/z 400.3334 ($M^{+\cdot}$). C, 80.7; H, 11.5%. $C_{27}H_{44}O_2$ requires M 400.3341. C, 80.9; H, 11.1%.

The diosphenol (12) was acetylated with acetic anhydride in pyridine at room temperature overnight to give the diosphenol acetate (13), an oil, 3080 (RCH=CH_2), 1765 (C=O, ester), 1690 (C=O), 1640 (RCH=CH_2) cm^{-1}, δ_H 6.47 (d, 1H 7-H, J 2Hz), 5.6-6.2 (m, 1H, RC*H*=CH_2), 4.85-5.2 (m, 2H, RCH=CH_2), 2.22 (s, 3H, OAc), 1.08 (s, 3H, 10β-Me) and 0.79 (s, 3H, 13β-Me). (Found: m/z 442.3451 ($M^{+\cdot}$). $C_{29}H_{44}O_3$ requires M 442.3348).

Reaction of 3β-tosyloxy-5a-cholestane-5,6β-diol (1) with potassium t-butoxide in t-butanol.

(a) Under an inert atmosphere: A deoxygenated solution of potassium *t*-butoxide (0.46g, 2 mol. equiv.) in *t*-butanol was added to a deoxygenated solution of 3β-tosyloxy-5α-cholestane-5,6β-diol (1) (1.2g) in *t*-butanol (90 ml). The mixture was stirred at 50°C for two hours under argon then diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 50 ml), dried and evaporated *in vacuo*. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3) (0.096g, 11%), m.p. 116-118°C,[6] a second fraction 5β-hydroxy-4,5-secocholest-3-en-6-one (10) (0.034g, 4%) and a further polar fraction 6β-hydroxy-5α-cholestan-3α,5-epoxide (2) (0.41g, 49%), m.p. 121-123°C.[20]

(b) In the presence of air: 3β-Tosyloxy-5α-cholestane-4,6β-diol (1) (1.2g) was treated as above in the presence of air. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 6-hydroxy-4,5-secocholesta-3,6-dien-5-one (12) (0.140g, 17%) and 6β-hydroxy-5α-cholestan-3α,5-epoxide (2) (0.449g, 53%).

3β-Tosyloxy-5β-cholestane-5,6β-diol. Sodium borohydride (0.25g, 3 mol. equiv.) was added to a rapidly stirred suspension of 3β-tosyloxy-5β-cholestan-5-ol-6-one (14) (1.0g) in methanol (50 ml)and ether (5 ml). Stirring was continued for thirty minutes, then the solution was diluted with water (200 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with dilute hydrochloric acid (50 ml), aqueous sodium bicarbonate (50 ml) and water (50 ml), dried and evaporated *in vacuo*. Recrystallisation from methanol gave *3β-tosyloxy-5β-cholestane-5,6β-diol* (15) (0.86g, 85%) m.p. 88°C, $[\alpha]_D$ +19° (c=1.1), ν_{max} 3530 (OH), 1600 (C=C aromatic) cm^{-1}, δ_H 7.88 and 7.42 (ABq, 4H, tosyl aromatics), 4.97 (br s, 1H,3α-H, W1/2 7Hz), 3.53 (br s, 1H, 6α-H, W1/2 6Hz), 2.64 (s, 2H, OH), 2.47 (s, 3H, tosyl methyl), 1.11 (s, 3H, 10β-Me) and 0.68 (s, 3H 13β-Me).

The tosyloxy diol was acetylated with acetic anhydride in pyridine overnight at room temperature to give *3β-tosyloxy-6β-acetoxy-5β-cholestan-5-ol* (16), m.p. 119-120°C dec. (methanol), ν_{max} 3620 (OH), 1730 (C=O), 1630 (C=O, ester), 1600 (C=C, aromatic) cm^{-1}, δ_H 7.84 and 7.38 (ABq, 4H, tosyl aromatics), 4.94 (br s, 1H,3β-H), 4.76 (br s, 1H, 6α-H), 2.47 (s, 3H, tosyl methyl), 2.10 (s, 3H, OAc), 1.07 (s, 3H, 10β-Me), and 0.68 (s, 3H, 13β-Me). (Found: C, 69.9; H, 9.4%. $C_{36}H_{56}O_6$ requires C, 70.1; H, 9.1%).

Reaction of 3β-tosyloxy-5β-cholestane-5,6β-diol (15) with potassium t-butoxide in t-butanol. A solution of potassium *t*-butoxide (9.31g, 2 mol. equiv.) in deoxygenated *t*-butanol (30 ml) was added to a solution of 3β-tosyloxy-5β-cholestane-5,6β-diol (15) (0.8g) in deoxygenated *t*-butanol (80 ml). The solution was stirred at 55°C for sixteen hours under argon. Work-up and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3) (0.23g, 45%), 6-hydroxy-4,5-secocholest-3,6-dien-5-one (12) (0.019g, 3%), 5β-hydroxy-4,5-secocholest-3-en-6-one (10) (0.031g, 5%), and a mixture of Δ^2- and Δ^3-5β-cholestene-5,6β-diol (17) (0.099g, 18%), a gum, ν_{max} 3450 (br, OH), 1670 (C=C) cm^{-1}, δ_H 5.2-6.0 (m, olefinic protons), 3.69 (s, 1H, 6α-H), 1.09 (s, 3H, 10β-Me) and 0.68 (s, 3H, 13β-Me). (Found: m/z 402.3484 ($M^{+\cdot}$). $C_{27}H_{46}O_2$ requires M 402.3498).

Acetylation of (17) with acetic anhydride in pyridine gave Δ^2- and Δ^3-6β-acetoxy-5β-cholesten-5-ol (18), a gum, ν_{max} 3450 (br, OH), 1725 (C=O, ester) cm^{-1}, δ_H 5.2-6.0 (m, olefinic protons), 4.87 (s, 3H 6α-H), 2.12 (s, 3H, OAc), 1.05 (s, 3H, 10β-Me) and 0.68 (s, 3H, 13β-Me).

Cyclisation of 5β-hydroxy-4,5-secocholest-3-en-5-one (10). A solution of 5β-hydroxy-4,5-secocholest-3-en-5-one (10) (0.40g) in decalin (5 ml) was heated under argon in a sealed tube for five and a half hours at 200°C. The decalin was removed *in vacuo*. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 5β-cholestan-5-ol-6-one (20) (0.0528g, 13%), m.p. 104-105°C (methanol)[17] and *3-methyl-B-nor-5β-cholest-2-en-4-one* (19) (0.102g, 26%) m.p. 83-84° (methanol),$[\alpha]_D$ + 146° (c=0.63), ν_{max} 1665 (C=O) cm^{-1}, λ_{max} 240 nm (ε 9820), δ_H 6.50 (m, 1H, 2-H, W1/2 10Hz, collapses to dd, J=2.8 and 5.8 Hz on irradiating at δ 1.80 ppm), 1.80 (br s, 3H,3-Me, collapses to dd J=1.2 and 2.4 Hz, on irradiating at δ 6.50: long range coupling to C-1), 0.96 (s, 3H, 10β-Me) and 0.65 (s, 3H, 13β-Me), δ_C 55.7 (C-1), 142.0 (C-2), 134.6 (C-3), 203.1 (C-4), 55.8 (C-5), and 25.7 (C-19). (Found: m/z 384.3363 ($M^{+\cdot}$). C,84.3; H, 11.9%. $C_{27}H_{44}O$ requires M 384.3392. C, 84.3; H, 11.5%).

Deuteriation of 3-methyl-B-nor-5β-cholest-2-en-4-one (19). A solution of 3-methyl-B-nor-5β-cholest-2-en-4-one (19) (0.0364g)in dioxane (2 ml) was added to a solution of sodium (0.07g) in deuterium oxide (3 ml) and dioxane (4 ml). The solution was heated under reflux for twenty seven hours under nitrogen, then diluted with ether (50 ml) and washed with water (15 ml). The ether was dried and evaporated *in vacuo* to give an oil which, on crystallisation from methanol, gave [1α,1β,5β,^{2}H]-3-methyl-B-nor-cholest-2-en-4-one (19) δ_H 6.50 (m, 1H, 2-H, W1/2 5Hz, collapses to s on irradiating at δ 1.80), 1.80 (d, 3H, 3-Me, collapses to s on irradiating at δ 6.50). (Found: m/z 387.3583 ($M^{+\cdot}$). $C_{27}H_{41}D_3O$ requires M 387.3850).

Thermal rearrangement of 3-methyl-A-nor-5β-cholestan-5-ol-6-one (3). A solution of 3-methyl-A-nor-5β-cholestan-5-ol-6-one (3) (0.188g) in decalin (5 ml) was heated in a sealed tube under argon at 200°C for five and a half hours. The decalin was removed in vacuo and preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave unchanged starting material (0.097g, 57%) and 3-methyl-B-nor-5β-cholest-2-en-4-one (19) (0.025g, 15%).

Acid catalysed rearrangement of 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3). p-Toluenesulphonic acid (0.01g) was added to a solution of *3β-methyl-A-nor-5β-cholestan-5-ol-6-one (3)* (0.180g) in benzene (30 ml). The solution was heated at reflux overnight then washed with aqueous sodium bicarbonate (5 ml) and water (5 ml), dried and evaporated *in vacuo*. Preparative thin layer chromatography [SiO_2, petrol:ether, 2:1 (v/v)] gave 3-methyl-A-norcholest-3-en-6-one (25) (0.058g, 32%), m.p. 80-81°C (methanol), $[\alpha]_D$ + 56° (c=0.63), ν_{max} 1680 (C=O), 1625 (C=C) cm^{-1}, λ_{max} 260 nm (ε 11,500), δ_H 2.04 (s, 3H, 3-Me), 0.98 (s,

3H, 10β-Me) and 0.71 (s, 3H, 13β-Me), δC 47.3 (C-1), 148.9 (C-3), 141.9 (C-5), 201.3 (C-6) and 16.0 (C-19). (Found: m/z 384.3390 ($M^{+\cdot}$). C, 84.4; H, 11.5%. $C_{27}H_{44}O$ requires M 384.3391. C, 84.3; H, 11.5%), and 3-methyl-B-nor-5β-cholest-2-en-4-one (19) (0.89g, 49%).

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