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REACTIONS OF EPOXIDES—XXIII[*]

ELIMINATION–REARRANGEMENT REACTIONS OF 3-*p*-TOLYLSULPHONYLOXY-4,5-EPOXYCHOLESTANES

J. M. Coxon, R. P. Garland, M. P. Hartshorn and G. A. Lane

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

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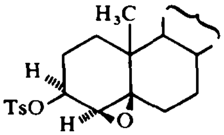
Abstract—Reaction of 3-*p*-tolylsulphonyloxy-4,5-epoxy-cholestanes with collidine gives 1-methyl- and 4-methyl-19-nor-cholesta-1,3,5(10)-trienes, 4a-oxa-cholesta-3,5-diene and Δ^2-4,5-epoxycholestenes. Reaction of the epoxy-tosylates with Li_2CO_3-N,N-dimethylformamide gives 4a-oxa-cholesta-3,5-diene and Δ^2-4,5-epoxy-cholestenes and C-3 substitution products.

During studies directed towards the synthesis of 4,5-epoxycholest-2-enes we investigated the elimination reactions of each of the 3-*p*-tolylsulphonyloxy-4,5-epoxycholestanes. The four isomeric 4,5-epoxy-3-tosylates were prepared from the corresponding epoxy-alcohols by reaction with toluene-*p*-sulphonyl chloride in pyridine solution.

Reaction of the 4β,5β-epoxy-3β-tosylate (**1**) with Li_2CO_3-dimethylformamide



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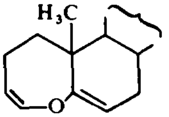

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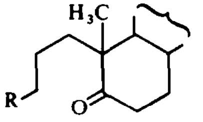
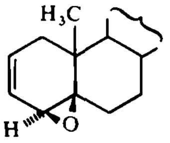


3a- R, CHO
b: R, CO_2H



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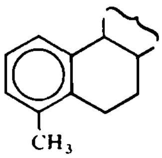

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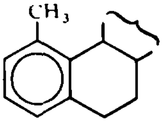

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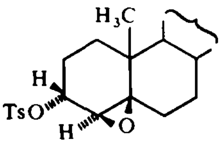

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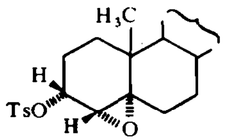

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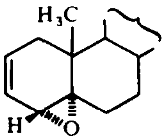

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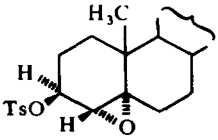

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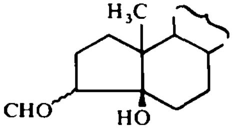

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[*] Pt. XXII. B. N. Blackett, J. M. Coxon, M. P. Hartshorn and K. E. Richards, *Tetrahedron Letters* 1737 (1969).

(DMF) gave a mixture separable into 3 major fractions. The least polar product was identified as the diene-ether[1] (**2**) on the basis of the following evidence. The NMR spectrum of the diene-ether (**2**) revealed signals due to vinylic protons at 4·48 ppm (C^3—$\underline{H}$) coupled with the 4-, 2α- and 2β- protons, 6·18 ppm (C^4-$\underline{H}$) coupled with the 3- and 2α-protons, and 5·17 ppm (C6—$\underline{H}$) coupled with the 7α- and 7β-protons; these assignments were confirmed[1] by double irradiation experiments. Hydrolysis of the diene-ether (2) gave the keto-aldehyde (**3a**), identical with an authentic sample (cf. ref. 2) obtained by periodate cleavage of 4β,5-dihydroxy-5β-cholestane. Similarly CrO_3-acetic acid reaction of the diene-ether (**2**) gave the keto-acid (**3b**), also obtained by oxidation of 4β,5-dihydroxy-5β-cholestane.

The second product was the Δ^2-4β,5β-epoxide (**4**) identified as follows. The NMR spectrum revealed signals at 5·83 ppm ($W_{h/2}$ 6 c/s; C^2—$\underline{H}$, C^3—$\underline{H}$) and at 2·98 ppm (C^4—$\underline{H}$). The coupling of the C^4—$\underline{H}$ with the C^2—$\underline{H}$ and C^3—$\underline{H}$ ($J^{app.}_{4,3}$ 3·5 c/s, $J^{app.}_{4,2}$ 2·5 c/s) was confirmed by double irradiation (−173 c/s).

The third fraction was a mixture (ca. 2:1) of 3β- and 3α-hydroxy-4β,-5-epoxy-5β-cholestanes.

Reaction of the epoxy-tosylate (**1**) in collidine gave, in addition to the Δ^2-4β,5β-epoxide (**4**) and the diene-ether (**2**), a mixture (ca. 9:1) of 4-methyl-(**5**) and 1-methyl-(**6**) 19-norcholesta-1,3,5(10)-trienes and unidentified polar material. The trienes (**5** and **6**) were identified by their physical constants and NMR spectra.[3]

Comparison of the relative yields of the products from the Li_2CO_3-DMF and collidine reactions (Table 1) might seem at first sight to suggest that under the latter conditions the diene-ether (**2**) was being converted into the triene mixture (**5** and **6**). However, while the diene-ether (**2**) was recovered from treatment with collidine or collidine containing toluene-p-sulphonic acid (TsOH), the Δ^2-4β,5β-epoxide (**4**) was largely converted into the triene mixture (5:6) under the latter conditions.

Reaction of 4β,5β-epoxy-3α-tosylate (7) in collidine gave mainly unidentified polar material with only minor conversion into diene-ether (**2**), Δ^2-4β,5β-epoxide (**4**) and the triene mixture (5:6, ca. 9:1). On treatment with Li_2CO_3-DMF the epoxy-tosylate (7) was converted (TLC evidence only) into a mixture of the diene-ether (**2**), Δ^2-4β,5β-epoxide (**4**) and two polar compounds, probably the epimeric 3-hydroxy-4β,5β-epoxides

TABLE 1. PRODUCT ANALYSIS FOR 4,5-EPOXY-3-TOSYLATE REACTIONS

Epoxytosylate	Reaction conditions	Trienes (**5**, **6**)	Diene-ether (**2**)	Δ^2-epoxide	Others
1	collidine, 45 min	35	9	27	22[a]
1	Li_2CO_3-DMF	—	57	24	13[b]
7	collidine, 30 min	10	6	7	70[a]
7	Li_2CO_3-DMF	—	2	1	[b]
8	collidine, 15 min	2	2	74	13[a]
8	Li_2CO_3-DMF	—	31	44	10[b]
10	collidine, 15 min	2	7	—	35+[a]
10	Li_2CO_3-DMF	—	32	2	21[b]

[a] Unidentified compounds containing a steroid nucleus, a collidine and a toluene-*p*-sulphonate unit.
[b] 3-hydroxy-4,5-epoxycholestanes.

The major product from reaction of the 4α,5α-epoxy-3α-tosylate (**8**) with collidine was the Δ^2-4α,5α-epoxide (**9**) with only minor amounts of diene-ether (**2**), triene mixture (**5**:**6**, ca. 9:1) and polar material. The Δ^2-4α,5α-epoxide (**9**) was identified from a consideration of its NMR spectrum, which exhibited signals at 5·86 ppm ($W_{h/2}$ 5·5 c/s; C^2—$\underline{\mathrm{H}}$, C^3—$\underline{\mathrm{H}}$) and at 3·01 ppm (C^4-$\underline{\mathrm{H}}$); double irradiation (–171·5 c/s) confirmed the coupling of the C^4—$\underline{\mathrm{H}}$ with C^3—$\underline{\mathrm{H}}$ and C^2—$\underline{\mathrm{H}}$ ($J^{\mathrm{app.}}_{4,3}$ 2 c/s, $J^{\mathrm{app.}}_{4,2}$ 1·5 c/s). The lower conversion of the Δ^2-4α,5α-epoxide (**9**) into trienes (**5** and **6**) is due to the lower reactivity of the epoxide (**9**) in collidine-TsOH solution; in control experiments the Δ^2-4β,5β-epoxide (**4**) was completely converted into trienes (**5** and **6**) under conditions which resulted in poor and incomplete conversion of the Δ^2-4α,5α-epoxide (**9**) into triene (**5** and **6**).

With Li_2CO_3-DMF the 4α,5α-epoxy-3α-tosylate (**8**) gave the diene-ether (**2**), the Δ^2-4α,5α-epoxide (**9**) and 4α,5-epoxy-5α-cholestan-3β-ol.

Reaction of the 4α,5α-epoxy-3β-tosylate (**10**), both with collidine and Li_2CO_3-DMF, gave low recoveries of identifiable products. Product yields are given in Table 1.

DISCUSSION

In the reactions of the 4,5-epoxy-3-tosylates with Li_2CO_3-DMF and with collidine two elimination processes, to form diene-ether (**2**) and Δ^2-4,5-epoxides, are in competition. The relative yields of these products are shown in Table 2; allowance is made in the recorded yield of Δ^2-4,5-epoxides for the trienes (**5** and **6**) which have been shown to arise from these compounds. For the reactions of the 4,5-epoxy-3-tosylates there is a markedly greater tendency towards C^6—$\underline{\mathrm{H}}$ loss in the elimination reactions in the Li_2CO_3-DMF system compared with the collidine solution reactions.

Recent studies[4] of the reaction of 2-deuterated-4,4-dimethyl-3-tosylates in collidine have revealed that elimination to form the corresponding Δ^2-olefin from the equatorial 3β-tosylate was 75% *syn* and from the axial 3α-tosylate 46% *syn*. This *syn*-elimination has been envisaged as involving abstraction of the C^2-proton by the departing tosylate anion. It thus appears likely that a considerable proportion of the Δ^2-4,5-epoxide produced in the reaction of the 4,5-epoxy-3-tosylates in collidine are formed by such a *syn*-elimination with the tosylate anion as the internal base. In contrast the elimi-

TABLE 2. RELATIVE YIELDS OF DIENE-ETHER (2) AND Δ^2-4,5-EPOXIDES

Epoxy-tosylate	Reaction conditions	Diene-ether (2)	Δ^2-4,5-Epoxides[a]
1	collidine	13	27
1	Li_2CO_3-DMF	70	30
7	collidine	26	74
7	Li_2CO_3-DMF	ca. 67[b]	33[b]
8	collidine	3	97
8	Li_2CO_3-DMF	41	59
10	collidine	78[c]	22[c]
10	Li_2CO_3-DMF	94[c]	2[c]

[a] This column includes the trienes (5 and 6) which arise from the Δ^2-4,5-epoxides.

[b] Estimated by TLC and NMR.

[c] These ratios are derived from low percentage yields of the two products in poor recovery experiments.

nation of a C^6-proton to form the diene-ether (**2**) must involve attack by an external base. The greater tendency for C^2-proton abstraction in collidine and for C^6-proton abstraction in Li_2CO_3-DMF may therefore represent a decrease in the significance of *syn*-elimination from an ion-pair in a solvent of higher dielectric constant.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solns at 20°. IR spectra were recorded on a Perkin–Elmer 337 spectrometer. UV spectra were recorded for cyclohexane solns. Alumina used for chromatography was P. Spence Grade H; "deactivated alumina" refers to Grade H treated with 5% of 10% AcOH. Silica gel used for chromatography was Crosfield Sorbsil Grade 60–120. Light petroleum refers to the fraction of b.p. 50–70°. NMR spectra were determined at 60 Mc for 10% w/v $CDCl_3$ solns with $CHCl_3$ and $(CH_3)_4Si$ as internal standards.

4β,5β-*Epoxy*-3β-*tosylate* (**1**). To a soln of 3β-hydroxy-4β,5-epoxy-5β-cholestane (5 g) in pyridine (10 ml) was added a soln of toluene-*p*-sulphonyl chloride (4·5 g) in pyridine (10 ml) and the resulting soln kept at 20° for 24 hr. The crude product, isolated by means of ether, was adsorbed onto deactivated alumina (200 g). Elution with light petroleum–benzene (1:1) and crystallization from acetone gave the *epoxy-tosylate* (**1**; 6·3 g) as needles, m.p. 106–107°, $[\alpha]_D$ −10° (*c* 1·01), ν_{max}(KBr) 1187, 1167 cm^{-1}, NMR δ7·66, 7·32 ppm (aromatic-$\underline{H}$); 4·96 ppm ($W_{h/2}$ 8 c/s; C^3—$\underline{H}$); 3·02 ppm ($J_{4\alpha,3\alpha}$ 3 c/s; C^4—$\underline{H}$); 2·43 ppm ($C\underline{H}_3$—C_6H_4—); 1·01 ppm ($C^{19}H_3$); 0·66 ppm ($C^{18}H_3$); 0·91, 0·81 ppm (side-chain CH_3). (Found: C, 73·2; H, 9·3; S, 6·5. $C_{34}H_{52}O_4S$ requires: C, 73·3; H, 9·4; S, 5·8%).

4β,5β-*Epoxy*-3α-*tosylate* (**7**). Reaction of 3α-hydroxy-4β,5-epoxy-5β-cholestane (1·2 g) as above gave **7** (740 mg) as needles (ether–pentane), m.p. 130–131°, $[\alpha]_D$ +32° (*c* 1·10), ν_{max} (KBr) 1192, 1180 cm^{-1}, NMR δ7·83, 7·35 ppm (aromatic-$\underline{H}$); 4·60 ppm (*J* 7·5, *J'* 8·5 c/s; C^3-$\underline{H}$); 2·87 ppm ($W_{h/2}$ 1·5 c/s; C^4-$\underline{H}$); 2·45 ppm ($C\underline{H}_3$—C_6H_4—); 0·96 ppm ($C^{19}H_3$); 0·66 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 73·05; H, 9·4; S, 5·8. $C_{34}H_{52}O_4S$ requires: C, 73·3; H, 9·4; S, 5·8%).

4α,5α-*Epoxy*-3β-*tosylate* (**10**). Reaction of 3β-hydroxy-4α,5-epoxy-5α-cholestane (1·2 g) as above gave **10** (823 mg) as prisms (ether), m.p. 108–109°, $[\alpha]_D$ +25° (*c* 1·00), ν_{max}(KBr) 1185, 1179 cm^{-1}, NMR δ7·81, 7·33 ppm (aromatic $\underline{H}$); 4·62 ppm (*J* 8·5, J' 8·5 c/s; C^3-$\underline{H}$); 2·91 ppm ($W_{h/2}$ 1·75 c/s; C^4-$\underline{H}$); 2·44 ppm ($C\underline{H}_3$—C_6H_4—); 1·08 ppm ($C^{19}H_3$); 0·68 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 73·55; H, 9·4; S, 5·75. $C_{34}H_{52}O_4S$ requires: C, 73·3; H, 9·4; S, 5·8%).

4α,5α-*Epoxy*-3α-*tosylate* (**8**). Reaction of 3α-hydroxy-4α,5-epoxy-5α-cholestane (2 g) as above gave **8** (1·7 g) as needles (acetone), m.p. 107–108° (dec), $[\alpha]_D$ +84° (*c* 0·985), ν_{max}(KBr) 1182, 1165 cm^{-1}, NMR δ7·84, 7·33 ppm (aromatic-$\underline{H}$); 5·00 ppm ($W_{h/2}$ 10 c/s; C^3-$\underline{H}$); 3·02 ppm ($J_{4\beta,3\beta}$ 4 c/s, decoupled −120 c/s; C^4-$\underline{H}$); 2·47 ppm (CH_3—C_6H_4—); 0·98 ppm ($C^{19}H_3$); 0·68 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 73·3; H, 9·4. $C_{34}H_{52}O_4S$ requires: C, 73·3; H, 9·4%).

Reactions of 4,5-*epoxy*-3-*tosylates with* 2,4,6-*collidine*

(a) 4β,5β-*Epoxy*-3β-*tosylate* (**1**). A soln of **1** (5·3 g) in dry collidine (500 ml) was heated under reflux under N_2 for 45 min. The solvent was removed at 0·1 mm, the residue dissolved in CH_2Cl_2, and this soln washed with $NaHCO_3$ aq, dried and the solvent removed. The residue was extracted with pentane to separate soluble material (3·6 g) from the remainder (1·46 g). The pentane-soluble fraction was adsorbed onto deactivated alumina (150 g).

Elution with light petroleum gave a mixture (1·54 g), separable by chromatography on alumina into a mixture of trienes (**5** and **6**, 9:1; 1·21 g) identified by NMR spectra[3], and 4a-*oxacholesta*-3,5-*diene* (**2**; 315 mg) as needles (MeOH), m.p. 81–82·5°, $[\alpha]$ −2·5° (*c* 1·02), NMR δ6·33 ppm ($J_{4,3}$ 6·5 c/s, $J_{4,2\alpha}$ 2 c/s; C^4—$\underline{H}$); 5·32 ppm ($J_{6,7\alpha}$ 2 c/s, $J_{6,7\beta}$ 6 c/s; C^6—$\underline{H}$); 4·61 ppm ($J_{3,4}$ 6·5 c/s, $J_{3,2\beta}$ 2 c/s, $J_{3,2\alpha}$ 6 c/s; C^3—$\underline{H}$); 1·06 ppm ($C^{19}H_3$); 0·69 ppm ($C^{18}H_3$); 0·91, 0·81 ppm (side-chain CH_3). (Found: C, 84·3; H, 11·4. $C_{27}H_{44}O$ requires: C, 84·3; H, 11·5%).

Further elution with light petroleum gave 4β,5-*epoxy*-5β-*cholest*-2-*ene* (**4**; 991 mg) as needles (acetone), m.p. 90–91°, $[\alpha]_D$ +11·5° (*c* 1·23), NMR δ5·83 ppm ($W_{h/2}$ 6 c/s; C^2—$\underline{H}$, C^3—$\underline{H}$); 2·98 ppm ($J_{4,3}$ 3·5 c/s, $J_{4,2}$ 2·5 c/s, decoupled ~173 c/s; C^4-$\underline{H}$); 1·09 ppm ($C^{19}H_3$); 0·68 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 84·4; H, 11·8. $C_{27}H_{44}O$ requires: C, 84·3; H, 11·5%).

(b) 4β,5β-*Epoxy*-3α-*tosylate* (**7**). Reaction of **7** (600 mg) as above but with reaction time 30 min gave pentane insoluble material (473 mg), containing two compounds (TLC) and identical with the material from (a). The pentane soluble material (176 mg) on chromatography gave trienes (5:6, 9:1; 40 mg), 4α-oxa-cholesta-3,5-diene (24 mg), and 4β,5-epoxy-5β-cholest-2-ene (29 mg).

(c) 4α,5α-*Epoxy*-3α-*tosylate* (**8**). Reaction of **8** (1 g) as above but with reaction time 15 min gave pentane insoluble material (153 mg). The pentane-soluble material (800 mg) on crystallization from acetone gave 4α,5-*epoxy*-5α-*cholest*-2-*ene* (**9**; 297 mg) as plates, m.p. 87–88°, $[\alpha]_D$ +81° (*c* 1·04), NMR δ5·86 ppm ($W_{h/2}$ 5·5 c/s; C^2—$\underline{H}$, C^3—$\underline{H}$); 3·01 ppm ($J_{4,3}$ 2 c/s, $J_{4,2}$ 1·5 c/s; C^4—$\underline{H}$); 0·93 ppm ($C^{19}H_3$); 0·70 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 84·5; H, 11·85. $C_{27}H_{44}O$ requires C, 84·3; H, 11·5%).

Chromatography of the mother liquor residue from the above crystallization gave trienes (5:6, 9:1; 17 mg); **2** (15 mg), and further **9** (212 mg).

(d) 4α,5α-*Epoxy*-3β-*tosylate* (**10**). Reaction of **10** (900 mg) as above but with reaction time 15 min, isolation by means of ether and chromatography on deactivated alumina gave trienes (5:6, 9:1; 10 mg), **2** (35 mg), starting material **10** (180 mg) and polar products (300 mg).

Reactions of 4,5-*epoxy*-3-*tosylates with* Li_2CO_3-N,N-*dimethyl formamide*

(a) 4β,5β-*Epoxy*-3β-*tosylate* (**1**). A soln of **1** (5 g) in N,N-dimethylformamide (80 ml) containing Li_2CO_3 (anhydrous; 5 g) was heated at 153° for 2 hr under N_2. The steroidal material (3·68 g), isolated by means of ether, was adsorbed onto deactivated alumina (200 g). Elution with light petroleum gave **2** (1·97 g) followed by **4** (838 mg). Elution with light petroleum to light petroleum–benzene (1:1) gave mixtures (240 mg). Finally elution with ether gave a mixture (ca. 1:2) of 3α- and 3β-hydroxy-4β,5-epoxy-5β-cholestanes (474 mg), identified by TLC.

(b) 4β,5β-*Epoxy*-3α-*tosylate* (**7**). Reaction of **7** (20 mg) as above gave a crude product which consisted (TLC) of **2** and **4** (*ca.* 2:1) and two polar compounds.

(c) 4α,5α-*Epoxy*-3α-*tosylate* (**8**). Reaction of **8** (200 mg) as above gave **2** (43 mg), **9** (61 mg) and 4α,5-epoxy-5α-cholestan-3β-ol (15 mg).

(d) 4α,5α-*Epoxy*-3β-*tosylate* (**10**). Reaction of **10** (600 mg) as above gave **2** (132 mg), **9** (6 mg), unidentified mixtures (130 mg) and a mixture of 3α-hydroxy- and 3β-hydroxy-4α,5-epoxy-5α-cholestanes (96 mg).

Reactions of 4β,5β- *and* 4α,5α-*epoxycholest*-2-*enes with toluene*-p-*sulphonic acid in collidine*

(a) 4β,5-*Epoxy*-5β-*cholest*-2-*ene* (**4**). A soln of **4** (100 mg) and toluene-*p*-sulphonic acid (75 mg) in collidine (2·5 ml) was treated under reflux for 15 min. The steroidal material, isolated by means of ether, was identified as a mixture of trienes (5:6, 9:1; 60 mg).

(b) 4α,5-*Epoxy*-5α-*cholest*-2-*ene* (**9**). The epoxide **9** (60 mg) reacted as above gave recovered **9** (21 mg) and a mixture of trienes (5:6, 9:1; 8 mg).

Reactions of 4a-*oxa*-*cholesta*-3,5-*diene* (**2**)

(a) *Hydrolysis.* To a soln of **2** (200 mg) in dioxan (12 ml) was added $HClO_4$aq (0·66 ml; 3M) and the resulting soln kept at 20° for 10 hr. The steroidal material, isolated by means of ether, was adsorbed on silica gel (10 g). Elution with light petroleum gave **2** (16 mg). Elution with light petroleum–benzene (3:2) gave **3a** (86 mg) as an oil, $[\alpha]_D$ +46° (*c* 0·95), ν_{max} 2710, 1730, 1703 cm^{-1}, NMR δ9·92 ppm (*J*, *J'* 1·5 c/s; —C$\underline{H}$O); 1·07 ppm ($C^{19}H_3$); 0·73 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3).

Elution with light petroleum–benzene (1:1) gave the *hydroxy-aldehyde* (**11**; 51 mg), m.p. 114–116°, $[\alpha]_D$ +36° (*c* 1·35), ν_{max} 3590, 3518, 1703 cm^{-1}, NMR δ 9·98 (*J* 2 c/s, decoupled +398 c/s; —C$\underline{H}$O); 3·10 ppm ($W_{h/2}$ 20 c/s; —C$\underline{H}$—CHO); 0·92 ppm ($C^{19}H_3$); 0·67 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 79·9; H, 11·9. $C_{27}H_{46}O_2$ requires: C, 80·5; H, 11·5 %).

(b) *Oxidative hydrolysis.* To a soln of **2** (18 mg) in AcOH (2·5 ml) and water 0·5 ml) was added Jones reagent, and the soln heated to 60° for 1 hr. The product, isolated by means of ether, was the keto-acid (**3b**; 10 mg), identical (TLC, NMR, IR) with an authentic sample.

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