Clemmensen Reduction. Part 5.[1] Chiral γ-Hydroxy-ketones

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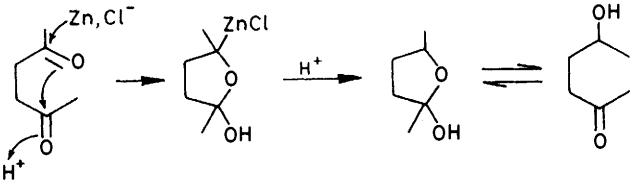
The reduction of some chiral γ-hydroxy-ketones by amalgamated zinc–hydrochloric acid (Clemmensen reduction) has been studied. Reduction of the carbonyl group occurs rapidly with retention of configuration at the carbinol carbon atom. This result invalidates part of an earlier hypothesis.

WORK on the Clemmensen reduction of a variety of 1,4-diketones has shown that alcohols are often the major reduction products;[1,2] we proposed[3] that alcohol formation was favoured when conformational mobility allowed the carbonyl groups to interact in a process analogous to that found in solvolysis reactions.[4] Thus, using the general mechanism for the Clemmensen reduction proposed by Nakabayashi,[5] we suggested that the reduction of hexane-2,5-dione proceeded initially as shown in Scheme 1.

The intermediacy of 5-hydroxyhexan-2-one and the subsequent reduction pathway shown in Scheme 2 were supported by the observation that the reductions of 5-hydroxy-, 5-chloro-, and 5-methoxy-hexan-2-one all gave mixtures of the same alcohol products as the diketone.[6]

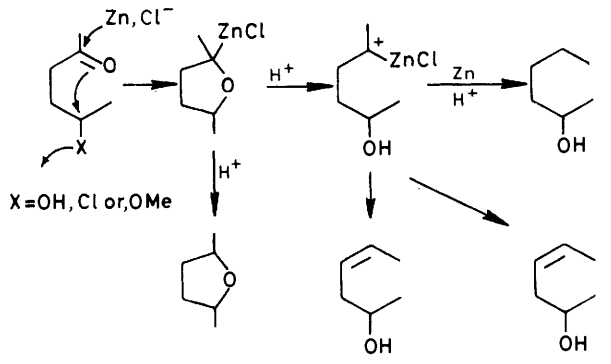


SCHEME 1

In order to verify the latter mechanism, which requires inversion of stereochemistry at the chiral centre, we

[1] J. G. St. C. Buchanan and B. R. Davis, *J. Chem. Soc.* (*C*), 1967, 1340.
[2] J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev.*, 1969, **23**, 522; E. Wenkert and J. E. Yoder, *J. Org. Chem.*, 1970, **35**, 2986; E. Vedejs, *Org. Reactions*, 1975, **22**, 401.
[3] D. R. Crump and B. R. Davis, *Chem. Comm.*, 1970, 768.
[4] D. J. Pasto and M. P. Serve, *J. Amer. Chem. Soc.*, 1965, **87**, 1515; H. R. Ward and P. D. Sherman, *ibid.*, 1968, **90**, 3812.
[5] T. Nakabayashi, *J. Amer. Chem. Soc.*, 1960, **82**, 3900, 3906, 3909.
[6] D. R. Crump and B. R. Davis, unpublished work.

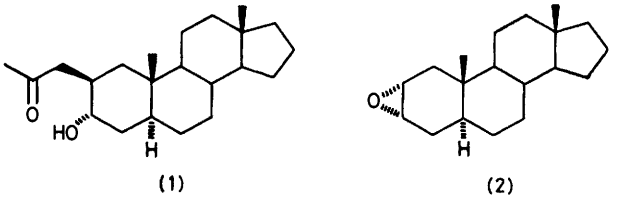
have synthesized two optically active γ-hydroxy-ketones and determined the stereochemistry of the



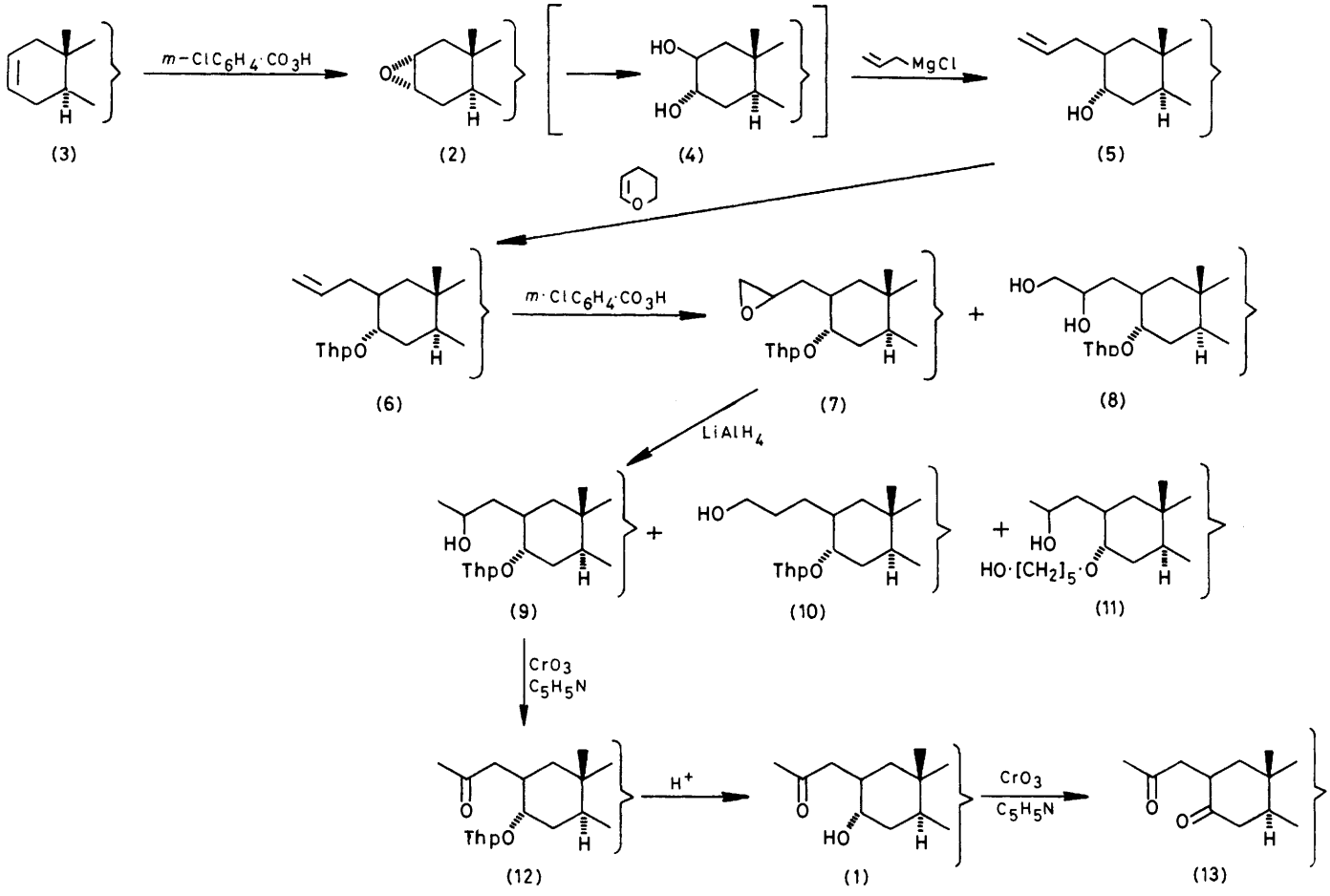
SCHEME 2

alcohols isolated after reduction under Clemmensen conditions. Thus enantiomerically enriched 5-hydroxy-hexan-2-one [71% (5*R*)] was prepared by oxidation

The 2α,3α-epoxide (2) was opened *trans*-diaxially with an excess of allylmagnesium chloride. Cleavage of the epoxide to the diol (4) occurred on exposure to silica gel. Treatment of (5) with 2,3-dihydropyran slowly afforded the axial tetrahydropyranyl (Thp) ether (6) as a mixture



of diastereoisomers, as shown by the ^{13}C n.m.r. spectrum. Epoxidation gave the epoxy-Thp ether (7), which was unstable with respect to the corresponding diol (8), so crude (7) was reduced directly to the secondary alcohol (9), obtained along with smaller amounts of the primary alcohol (10) and the dihydroxy-ether (11), resulting from



SCHEME 3

(silver carbonate–Celite) of partially resolved hexane-2,5-diol;[7] for an alicyclic example, 1-(3α-hydroxy-5α-androstan-2β-yl)propan-2-one (1) was synthesized from the 2α,3α-epoxide (2) as shown in Scheme 3.

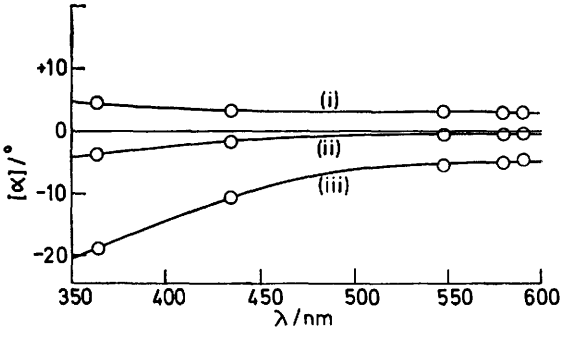
reductive cleavage of the tetrahydropyran ring. Oxidation of (9) yielded the oxo-ether (12), which was readily

[7] R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, 1968, **33**, 3966.

hydrolysed to the required γ-ketol (1); further independent oxidation gave the diketone (13).

The stereochemistry of the C-2 side-chain of (1) and all related compounds was verified by an o.r.d. study of the two ketones (16) and (17), prepared as shown in Scheme 4. The o.r.d. curves of both ketones were as expected,[8] *i.e.* both positive but with smaller amplitude for the equatorial epimer, so the *trans*-diaxial stereochemistry of (1) was confirmed. With two chiral ketols in hand we were in a position to study their Clemmensen reductions, and particularly to examine the chirality of the hydroxy-group in the derived alcohols.

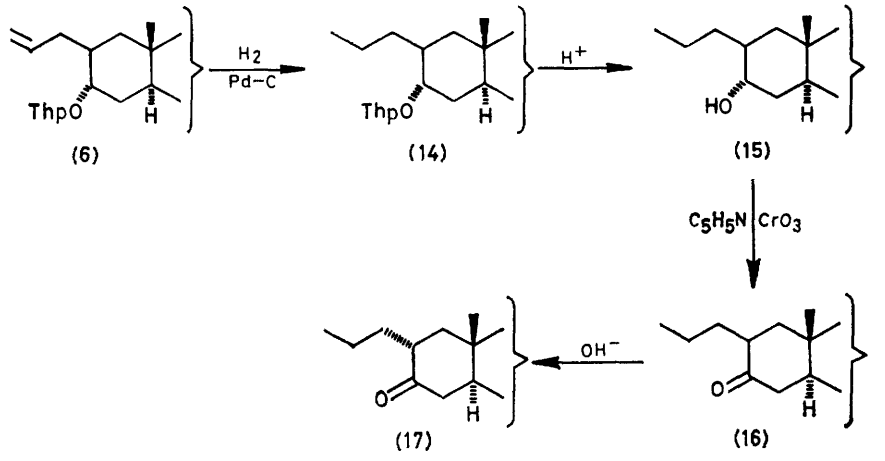
Reduction of (5*R*)-5-hydroxyhexan-2-one under Clemmensen conditions gave an optically active mixture of the expected alcohols (hexan-2-ol, and *cis*- and *trans*-hex-4-en-2-ol), pure samples of which were obtained by preparative g.l.c. The rotations are shown in the Figure.



Optical rotations of alcohols produced by reduction of (5*R*)-5-hydroxyhexan-2-one : (i) *cis*-hex-4-en-2-ol; (ii) *trans*-hex-4-en-2-ol; (iii) hexan-2-ol

The saturated alcohol was shown to be (2*R*)-hexan-2-ol [9,10] with an optical purity of 70%,[11] identical within experimental error with that of the starting ketol (71%). The opposite signs of rotation for the two geometrically isomeric alkenols suggested the possibility of different chiralities; their smaller rotations, as compared with hexan-2-ol, suggested partial racemization. However, pent-4-en-2-ol [9] and 4-methylpent-4-en-2-ol [11] both show smaller rotations than their saturated analogues.[12]

The absolute configuration of each alcohol was determined by formation of the ester with α-methoxy-α-trifluoromethylphenylacetic acid (Mtpa). A mixture of three diastereoisomeric pairs of esters of (—)-(*S*)-MTPA was formed by treating the acid chloride [13] with the alcohol mixture from the Clemmensen reduction of (5*R*)-5-hydroxyhexan-2-one and the three pairs were separated by preparative g.l.c. In all cases the ^{1}H n.m.r. spectra contained a set of overlapping doublets (*J* 6 Hz) characteristic of the carbinyl methyl groups, with the low-field doublet of greater intensity in each case. Application of the configurational rules of Dale and Mosher [13] showed that in all cases the predominant diastereomer contained the alcohol of 2*R*-configuration, with optical purity *ca.* 70%. The coincidence of this figure with the optical purity of the parent ketol argues against any optical fractionation having occurred during g.l.c. separation of the diastereomeric pairs. Hence no racemization or inversion of stereochemistry was occurring in the Clemmensen reduction.

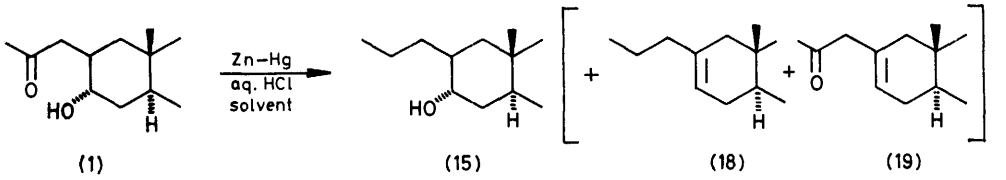


SCHEME 4

Reduction of the steroidal ketol (1) was initially attempted by using a two-phase benzene–aqueous acid system, but elimination of the hydroxy-group was promoted by this method. Either a reduced (18) or an unreduced (19) alkene was isolated from this system depending on the reaction temperature (Scheme 5). However, use of a homogeneous system (1,2-dimethoxyethane–aqueous acid) prevented elimination and allowed

[8] C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Amer. Chem. Soc.*, 1964, **86**, 78; C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, p. 85.
[9] P. A. Levene and A. Rothen, *J. Org. Chem.*, 1936, **1**, 76.
[10] W. Klyne and J. Buckingham, ' Atlas of Stereochemistry,' Chapman and Hall, London, 1974.
[11] J. Kenyon and D. P. Young, *J. Chem. Soc.*, 1938, 1452.
[12] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1911, **99**, 45.
[13] J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, 1973, **95**, 512; J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

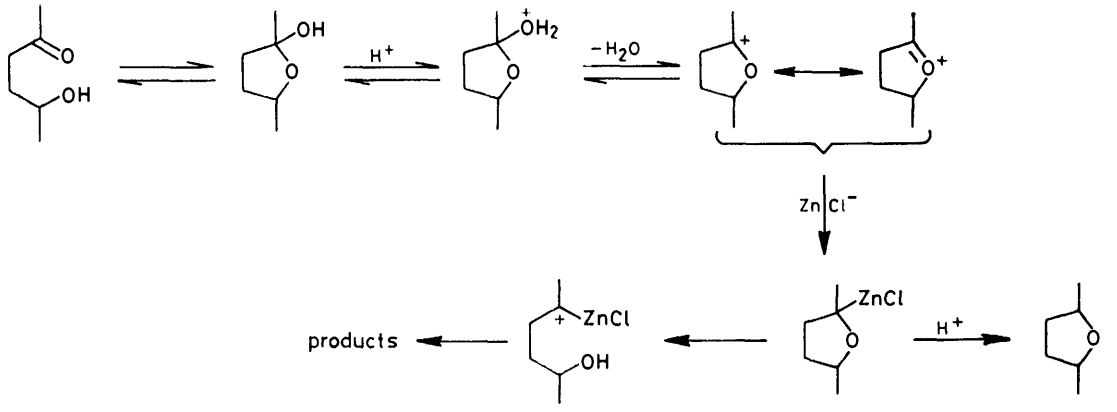
isolation of the saturated alcohol (15). This alcohol was identical with that previously formed (Scheme 4); the ^{1}H n.m.r. spectrum confirmed the stereochemistry of the axial hydroxy-group. Thus the steroidal reduction further confirms the retention of configuration in the reduction of chiral γ-hydroxy-ketones, thereby invalidating Scheme 2.



SCHEME 5

Support for Scheme 2 came from the Clemmensen reductions of 5-chloro- and 5-methoxy-hexan-2-one, which gave the same products as the reduction of 5-hydroxyhexan-2-one.[6] However, we established that solvolysis of the γ-substituent was occurring prior to reduction,[4] treatment of the methoxy-ketone with 6M-hydrochloric acid giving a mixture of chloro- and hydroxy-ketones at a rate at least as great as that found for the analogous reduction.

A resonance-stabilized oxycarbocation can be formed readily from 5-hydroxyhexan-2-one (*via* the hemiacetal), and the rapid reduction of this ketol, with retention of C–O chirality, may be explained by attack of zinc at C-2 (Scheme 6), to produce an organometallic intermediate which can collapse to the observed products without rupture of the C–OH bond. Reduction may be occurring by direct electron and proton transfer without the intermediacy of organozinc species. We propose that any γ-hydroxy-ketone which is conformationally mobile enough to form a hemiacetal and an oxycarbocation as in Scheme 6 should be reduced rapidly to an alcohol.



SCHEME 6

EXPERIMENTAL

M.p.s were determined with a Reichert–Kofler hot-stage apparatus. I.r. spectra were measured with a Perkin-Elmer 237 spectrometer for solutions in carbon tetrachloride. O.r.d. curves were recorded with a JASCO ORD/UV-5 spectrophotometer; optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^{1}H N.m.r. spectra were measured with a Varian T60 spectrometer (solvent $CDCl_3$ or CCl_4) and ^{13}C n.m.r. spectra with a JEOL JNM-FX60 Fourier transform spectrometer. Low resolution mass spectra were obtained with a Varian MAT CH-7 spectrometer; high resolution spectra were determined by Professor R. Hodges, Massey University, New Zealand. Microanalyses were performed by Professor A. D. Campbell, University of Otago, New Zealand. For all the steroidal compounds the carbon atoms of the Thp group are denoted by double primes (″) and those of the propyl side-chain by single primes (′).

(2R,5R)-*Hexane*-2,5-*diol*.—This diol,[14] $[\alpha]_D^{22}$ −14.9° (*c* 2.58 in $CHCl_3$) {lit.,[14] $[\alpha]_D$ −35.6° (*c* 8.29 in $CHCl_3$)}, was resolved by fractional crystallization of the dibrucine salt of its bis(hydrogen phthalate) according to the method of Dodson and Nelson.[7]

(5R)-5-*Hydroxyhexan*-2-*one*.— (2*R*,5*R*)-Hexane-2,5-diol (2.8 g, 2.4 × 10^{-2} mol), dry benzene (150 ml), and finely powdered silver carbonate–Celite [15] (56 g, 4 mol. equiv.) were mixed together and, after any moisture was removed by azeotropic distillation, the mixture was heated under reflux for 30 min, and filtered. Removal of the benzene left a product which was chromatographed on silica to give the ketol (1.25 g, 46%), $[\alpha]_D^{22}$ −5.7° (*c* 1.07 in EtOH), $\nu_{max.}$

[14] K. Serck-Hanssen, S. Ställberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, 1953, **5**, 203.

[15] M. Fétizon, M. Golfier, and J.-M. Louis, *Chem. Comm.*, 1969, 1102; M. Fétizon and M. Golfier, *Compt. rend.*, 1968, **267C**, 900.

3 600 and 3 420 (OH), 1 720 (C=O), 1 440 (CH_2·CO), 1355 (CH_3·CO), and 1 110 cm^{-1} (C–O); ^1H n.m.r. peaks corresponding to a tautomeric mixture of the hydroxy-ketone and its *cis*- and *trans*-hemiacetals were seen. Peaks identified for the hydroxy-ketone were: δ 1.15 (3 H, d, *J* 6 Hz, 6-H_3), 2.10 (3 H, s, 1-H_3), 2.65br (s, exchangeable on deuteriation, OH), and 3.50—3.87 (m, 5-H).

5α-*Androst*-2-*ene* (3).[16]—This was prepared from commercially available 3β-hydroxy-5α-androstan-17-one by Wolff–Kishner reduction of the 17-oxo-group and alumina-catalysed elimination of the 3β-hydroxy-group as its toluene-*p*-sulphonate.

2α,3α-*Epoxy*-5α-*androstane* (2).—A solution of 85% *m*-chloroperbenzoic acid (4.3 g, 2.2 × 10^{-2} mol) in dichloromethane (40 ml) was added to a solution of 5α-androst-2-ene (2) (5 g, 1.94 × 10^{-2} mol) in dichloromethane (20 ml) at room temperature. The mixture was stirred for 12 h and excess of reagent was destroyed with aqueous 10% sodium disulphite. The organic layer was worked up to give an oil (5.14 g, 97%), which was purified by bulb-to-bulb distillation to give 2α,3α-*epoxy*-5α-*androstane* (2), m.p. 39—40°, $[\alpha]_D$ +15.4° (*c* 1.00 in $CHCl_3$) (Found: C, 83.2; H, 11.1. $C_{19}H_{30}O$ requires C, 83.15; H, 11.0%); $\nu_{max.}$ 810 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.78 (3 H, s, 19-H_3), and 3.12 (2 H, m, 2β- and 3β-H); δ_C 13.0 (C-19), 51.0 (C-2), and 52.3 (C-3).

5α-*Androstane*-2β,3α-*diol* (4).—Decomposition of the epoxide (2) on prolonged chromatography on silica gel yielded a diol which was independently synthesized as follows. Aqueous perchloric acid (1.5 mol l^{-1}; 0.5 ml) was added to a solution of 2α,3α-epoxy-5α-androstane (2) in acetone (10 ml) and the mixture was stirred at room temperature for 20 h. Dilution with water and extraction with ether gave the diol (4) [17] (90 mg, 85%), which was purified by bulb-to-bulb distillation; m.p. 201—202°, $[\alpha]_D^{24}$ +12.4° (*c* 0.89 in $CHCl_3$) (Found: C, 78.0; H, 11.1. Calc. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0%); $\nu_{max.}$ 3 590 and 3 360 (OH), and 1 100 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3), 1.74 (2 H, m, exchangeable on deuteriation, OH), and 3.87 (2 H, m, 2α- and 3β-H).

2β-(*Prop*-2-*enyl*)-5α-*androstan*-3α-*ol* (5).—A solution of allyl chloride (20.4 g, 0.27 mol) in dry ether (35 ml) was added dropwise with stirring to a cooled mixture of magnesium (6.80 g, 0.28 mol) and dry ether (35 ml). The suspension was stirred for a further 15 min and a solution of the epoxide (2) (7.4 g, 2.7 × 10^{-2} mol) in dry ether (20 ml) was added dropwise over 15 min. The mixture was stirred for 5 h and quenched with dilute hydrochloric acid. Work-up gave 2β-(*prop*-2-*enyl*)-5α-*androstan*-3α-*ol* (5) (8.21 g, 97.5%), b.p. 185—188° at 0.8 mmHg, $[\alpha]_D$ +15.7° (*c* 3.47 in $CHCl_3$) (Found: C, 83.2; H, 11.3. $C_{22}H_{36}O$ requires C, 83.5; H, 11.5%); $M^{+\cdot}$ 316.2771; $\nu_{max.}$ 3 620 and 3 300 (OH), 3 070 (CH_2=C), 1 635 (C=C), 1 025 (C–O), and 905 cm^{-1} (CH_2=C); δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 1.97br (1 H, s, exchangeable on deuteriation, OH), 3.73 (1 H, m, $W_{1/2}$ 7 Hz, 3β-H), and 4.80 (m), 5.08 (m), and 5.56—6.15 (m) (3 H, characteristic of allyl group); δ_C 15.2 (C-19), 38.2 (C-2), 65.7 (C-1′), 69.7 (C-3), 115.6 (C-3′), and 138.6 (C-2′).

3-[3α-(*Tetrahydropyran*-2-*yloxy*)-5α-*androstan*-2β-*yl*]-*propene* (6). Concentrated hydrochloric acid (6 drops) was added to a solution of the alkene (5) (7.7 g, 2.4 × 10^{-2} mol) in 2,3-dihydropyran (25 ml; freshly distilled from sodium). The mixture was shaken at room temperature for 6 days; work-up with ether gave a product which was chromatographed on alumina to give the *tetrahydropyranyl ether* (6) (8.63 g, 89%) as an oil, b.p. 178° at 1.2 mmHg (Found: C, 81.0; H, 11.0. $C_{27}H_{44}O_2$ requires C, 81.0; H, 11.1%); $M^{+\cdot}$ 400; $\nu_{max.}$ 3 070 (CH_2=C), 1 635 (C=C), 1 025 (C–O), and 905 cm^{-1} (CH_2=C); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 3.25—4.22 (3 H, m, 3β-H and 6″-H_2), 4.70 (1 H, m, $W_{1/2}$ 10 Hz, 2″-H), and 4.80 (m), 5.08 (m), and 5.56—6.15 (m) (3 H, characteristic of allyl group); δ_C 15.2 (C-19), 62.2 and 62.6 (C-6″), 65.7 (C-3′), 71.9 (C-3), 95.8 and 97.5 (C-2″), 115.5 (C-1′), and 138.0 (C-2′).

2β-(2,3-*Epoxypropyl*)-3α-(*tetrahydropyran*-2-*yloxy*)-5α-*androstane* (7).—A solution of 85% *m*-chloroperbenzoic acid (5.6 g, 2.7 × 10^{-2} mol) in dichloromethane (50 ml) was added over 3 min to a stirred solution of compound (6) (7.3 g, 1.82 × 10^{-2} mol) in dichloromethane (25 ml). Dilute aqueous sodium hydrogen carbonate (50 ml) was then added to extract *m*-chlorobenzoic acid as it was formed. The mixture was stirred for 24 h at room temperature, and excess of reagent was destroyed by the addition of aqueous 10% sodium disulphite (20 ml). Work-up gave the product (7.82 g), which was not purified further in bulk. Preparative t.l.c. of a sample gave a trace of starting material (6) and, as oils: (i) 2β-(2,3-*epoxypropyl*)-3α-(*tetrahydropyran*-2-*yloxy*)-5α-*androstane* (7) (Found: $M^{+\cdot}$, 416.3293. $C_{27}H_{44}O_3$ requires *M*, 416.3290); $\nu_{max.}$ 1 210 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 2.35—2.53 (1 H, m, 2′-H), 2.63—3.07 (2 H, m, 3′-H_2), 3.26—4.10 (3 H, m, 3β-H and 6″-H_2), and 4.70 (1 H, m, $W_{1/2}$ 8 Hz, 2″-H); δ_C 15.3 (C-19), 37.1 (C-1′), 37.5 (C-2), 46.3 (C-3′), 50.9 (C-2′), and 72.2 (C-3); and (ii) the product of epoxide opening, 3-[3α-(*tetrahydropyran*-2-*yloxy*)-5α-*androstan*-2β-*yl*]*propane*-1,2-*diol* (8) (Found: C, 74.3; H, 10.9. $C_{27}H_{46}O_4$ requires C, 74.6; H, 10.7%); $M^{+\cdot}$ 434.339; $\nu_{max.}$ 3 619 and 3 350 (OH), and 1 030 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 3.20br (2 H, s, exchangeable on deuteriation, OH), 3.1—4.13 (6 H, m, 1′-H_2, 2′-H, 3β-H, and 6″-H_2), and 4.70 (1 H, m, $W_{1/2}$ 8 Hz, 2″-H).

1-[3α-(*Tetrahydropyran*-2-*yloxy*)-5α-*androstan*-2β-*yl*]-*propan*-2-*ol* (9).—The crude epoxy-ether (7) (7.51 g, 1.73 × 10^{-2} mol) in dry ether was slowly added to a stirred suspension of lithium aluminium hydride (0.342 g, 9.0 × 10^{-3} mol) in dry ether (10 ml) so that gentle reflux was maintained. The mixture was stirred at room temperature for 18 h and further lithium aluminium hydride (0.34 g) was added. After stirring for a further 5 h the mixture was worked up with ether to give an oil (6.57 g). Preparative t.l.c. (hexane–ether, 3 : 7) of a sample (5 g) gave: (i) the allyl derivative (6) (0.26 g, 5.2%); (ii) the epoxy-ether (7) (0.32 g, 6.4%); (iii) 1-[3α-(*tetrahydropyran*-2-*yloxy*)-5α-*androstan*-2β-*yl*]*propan*-2-*ol* (9) (2.10 g, 42%) as an oil (Found: $M^{+\cdot}$, 418.3449. $C_{27}H_{46}O_3$ requires *M*, 418.3446); $\nu_{max.}$ 3 618 and 3 450 (OH) and 1 025 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 1.18 (3 H, d, *J* 6 Hz, 3-H_3), 2.90br (1 H, s, exchangeable on deuteriation, OH), 3.27—4.23 (4 H, m, 2′-H, 3β-H, and 6″-H_2), and 4.70 (1 H, m, $W_{1/2}$ 8 Hz, 2″-H); δ_C 14.9 (C-19), 23.8 (C-3′), 37.5 (C-2), 43.9 and 44.4 (C-1′), 66.1, 66.5, 67.4, and 68.3 (C-2′), and 75.7 (C-3); (iv) a mixture (0.476 g, 9.5%), the major component of which was 3-[3α-(tetrahydropyran-2-yloxy)-5α-androstan-2β-yl]propan-1-ol (10) [Found: *m/e*, 333.2800 ($M^{+\cdot}$ − C_5H_9O, 7.1%). Calc. for $C_{22}H_{37}O_2$: 333.2792.

[16] J. M. Evans, G. D. Meakins, Y. Morisawa, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1968, 2841.

[17] R. C. Cambie, G. J. Potter, P. S. Rutledge, and P. D. Woodgate, *J.C.S. Perkin I*, 1977, 530.

Found: *m/e* 301.2535 ($M^{+\cdot} - C_5H_9O$ — MeOH, 41.4%). Calc. for $C_{21}H_{33}O$: 301.2535]; $\nu_{max.}$ 3 590 and 3 400 (OH), and 1 030 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 2.45br (1 H, s, exchangeable on deuteriation, OH), 3.23—4.10 (5 H, m, 1′-H_2, 3β-H, and 6″-H_2), and 4.70 (1 H, m, $W_{1/2}$ 8 Hz, 2″-H); and (v) a mixture of two compounds (1.10 g, 22%) which were further separated by preparative t.l.c. (ether) to give the dihydroxy-ether (8) (0.65 g) and 1-[3α-(5-hydroxypentyloxy)-5α-androstan-2β-yl]propan-2-ol (11) (0.29 g) [Found: *m/e* 332.2805 ($M^{+\cdot} - C_5H_{11}O$, 59%). Calc. for $C_{22}H_{37}O_2$: 333.2793. Found: *m/e*, 87.0808. Calc. for $C_5H_{11}O$: 87.0809]; $\nu_{max.}$ 3 610 and 3 490 (OH), and 1 080 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 1.18 (3 H, d, *J* 7 Hz, 3′-H_3), 2.35br (2 H, s, exchangeable on deuteriation, OH), and 3.23—4.17 (6 H, m, 3β-H, 2′-H, 1″-H_2, and 5″-H_2). Acetylation with acetic anhydride–pyridine gave the *diacetate* (Found: $M^{+\cdot}$ 504.3808. $C_{31}H_{52}O_5$ requires *M*, 504.3812); $\nu_{max.}$ 1 740 (C=O) and 1 240 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 1.22 (3 H, d, *J* 7 Hz, 3′-H_3), 2.02 (3 H, s, OAc), 2.03 (3 H, s, OAc), 3.13—3.67 (3 H, m, 3β-H and 1″-H_2), 3.93—4.27 (2 H, m, 5″-H_2), and 4.66—5.20 (1 H, m, 2′-H).

1-[3α-(*Tetrahydropyran-2-yloxy*)-5α-*androstan*-2β-*yl*]-*propan*-2-*one* (12).—Dry, finely ground chromium trioxide (2.31 g, 2.31 × 10^{-2} mol) was added to a stirred solution of dry pyridine (3.65 g, 4.62 × 10^{-2} mol) in dichloromethane (5.5 ml) and the red-brown mixture was stirred for 15 min.[18] The hydroxy-ether (9) (1.61 g, 3.85 × 10^{-3} mol) dissolved in dichloromethane (5 ml) was added in one portion; a tarry black deposit separated immediately. The mixture was stirred at room temperature for 3 h, diluted with ether, and filtered, and the filtrate washed with dilute hydrochloric acid. Work-up gave the *ketone* (12) (1.51 g, 94%) as an oil (Found: $M^{+\cdot}$, 416.3288. $C_{27}H_{44}O_3$ requires *M*, 416.3290); $\nu_{max.}$ 1 720 (C=O), 1 440 (CH_2·CO), 1 355 (CH_3·CO), and 1 020 cm^{-1} (C–O), δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 2.12 (3 H, s, 3′-H_3), 2.46br (2 H, apparent s, 1′-H_2), 3.27—4.07 (3 H, m, 3β-H and 6″-H_2), and 4.70 (1 H, m, $W_{1/2}$ 7 Hz, 2″-H); δ_C 15.4 (C-19), 30.4 (C-3′), 48.5 (C-1′), 73.2 (C-3), and 207.6 (C-2′).

1-(3α-*Hydroxy*-5α-*androstan*-2β-*yl*)*propan*-2-*one* (1). Concentrated hydrochloric acid (1.25 ml) in 95% ethanol (50 ml) was added to a solution of the oxo-ether (12) (1.00 g, 2.4 × 10^{-3} mol) in ethanol (25 ml). The mixture was warmed to 50 °C and maintained there for 5 min before cooling. Water was added and the product was extracted with ether to give the *ketone* (1) (0.68 g, 85%), m.p. 146—147° (from pentane–acetone), $[\alpha]_D$ +27.4° (*c* 1.10 in $CHCl_3$), (Found: C, 79.5; H, 10.9. $C_{22}H_{36}O_2$ requires C, 79.5; H, 10.9%); $M^{+\cdot}$ 332.2700; $\nu_{max.}$ 3 615 and 3 400 (OH), 1 718 (C=O), 1 440 (CH_2·CO), 1 355 (CH_3·CO), and 1 025 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 2.07br (1 H, s, exchangeable on deuteriation, OH), 2.12 (3 H, s, 3′-H_3), 2.46br (2 H, apparent s, 1′-H_2), and 3.73 (1 H, m, $W_{1/2}$ 8 Hz, 3β-H); δ_C 15.4 (C-19), 30.3 (C-3′), 48.4 (C-1′), 69.8 (C-3), and 208.1 (C-2′).

2β-(2-*Oxopropyl*)-5α-*androstan*-3-*one* (13).—The ketol (1) (50 mg, 1.5 × 10^{-4} mol) in dichloromethane was oxidized with chromium trioxide–pyridine complex [18] as above to give 2β-(2-*oxopropyl*)-5α-*androstan*-3-*one* (13) (45 mg, 90%), m.p. 135—136° (from hexane–ether), $[\alpha]_D$ −12.9° (*c* 1.47 in $CHCl_3$) (Found: C, 80.0; H, 10.4. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.4%); $M^{+\cdot}$ 330; $\nu_{max.}$ 1 715 (C=O), 1 440 (CH_2·CO), and 1 335 cm^{-1} (CH_3·CO); δ_H 0.70 (3 H, s, 18-H_3), 1.12 (3 H, s, 19-H_3), 2.21 (3 H, s, 3′-H_3), and 2.13—3.23 (5 H, m, 2α-H, 2′-H_2, and 4-H_2).

2β-*Propyl*-3α-(*tetrahydropyran*-2-*yloxy*)-5α-*androstane* (14). The allyl derivative (6) (0.5 g, 1.25 × 10^{-3} mol) in absolute ethanol (15 ml) was hydrogenated over 10% palladium–charcoal (0.05 g) for 4 h to give the *propyl compound* (14) (0.49 g, 97.5%) as an oil, b.p. 160° at 0.25 mmHg (Found: C, 80.55; H, 11.2. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%); $\nu_{max.}$ 1 020 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 3.20—4.10 (3 H, m, 3β-H and 6′-H_2), and 4.70 (1 H, m, $W_{1/2}$ 7 Hz, 2′-H).

2β-*Propyl*-5α-*androstan*-3α-*ol* (15).—The ether (14) (0.45 g, 3.6 × 10^{-3} mol) was hydrolysed with concentrated hydrochloric acid (0.6 ml) in ethanol (25 ml) to give 2β-*propyl*-5α-*androstan*-3α-*ol* (15) (0.35 g, 98.3%) as an oil, b.p. 176° at 0.7 mmHg, $[\alpha]_D$ +13.2° (*c* 0.82 in $CHCl_3$) (Found: C, 83.3; H, 11.6. $C_{22}H_{38}O$ requires C, 83.0; H, 12.0%); $\nu_{max.}$ 3 605 and 3 420 (OH), and 1 025 cm^{-1} (C–O); δ_H 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 2.02br (1 H, s, exchangeable on deuteriation, OH), and 3.82 (1 H, m, $W_{1/2}$ 7 Hz, 3β-H).

2β-*Propyl*-5α-*androstan*-3-*one* (16).—The alcohol (15) (0.1 g, 3.14 × 10^{-4} mol) was oxidized with chromium trioxide–pyridine as above. The product was purified by preparative t.l.c. (hexane–ether, 9 : 1) to give starting material (25 mg) and 2β-*propyl*-5α-*androstan*-3-*one* (16) (60 mg, 60%), b.p. 145° at 0.1 mmHg; o.r.d. (*c* 0.34 in EtOH) $[\phi]_{589}$ +265°, $[\phi]_{436}$ +621°, $[\phi]_{365}$ +1 244°, $[\phi]_{330}$ +2 334°, $[\phi]_{313}$ +4 084° (pk), $[\phi]_{300}$ +2 217° (Found: C, 83.6; H, 11.5. $C_{22}H_{36}O$ requires C, 83.5; H, 11.5%); $\nu_{max.}$ 1 705 cm^{-1} (C=O); δ_H 0.70 (3 H, s, 18-H_3), 0.77 (3 H, s, 19-H_3), and 1.97—2.57 (3 H, m, 2α-H and 4-H_2).

2α-*Propyl*-5α-*androstan*-3-*one* (17).—A solution of the axial propyl ketone (16) (35 mg, 1.1 × 10^{-4} mol) in methanol (7 ml) and aqueous 5% sodium hydroxide (3 ml) was heated under reflux for 4 h, cooled, diluted with water, and extracted with ether to give the product (32 mg) as an oil. Preparative t.l.c. (hexane–ether, 9 : 1) gave a trace (1 mg) of starting material and the equatorial propyl ketone (30 mg), b.p. 148° at 0.1 mmHg; o.r.d. (*c* 0.23 in EtOH) $[\phi]_{589}$ +26.8°, $[\phi]_{436}$ +86°, $[\phi]_{365}$ +268°, $[\phi]_{330}$ +852° $[\phi]_{313}$ +1 428° (pk), $[\phi]_{300}$ +420°; $M^{+\cdot}$ 316; $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ_H 0.70 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), and 1.97—2.56 (3 H, m, 2β-H and 4-H_2).

Clemmensen Reduction of (5R)-5-*Hydroxyhexan*-2-*one*.—A mixture of (5*R*)-5-hydroxyhexan-2-one (0.98 g, 8.4 × 10^{-3} mol), amalgamated zinc wool (2.0 g), water (8 ml), and concentrated hydrochloric acid (4 ml) was heated under reflux for 5 min, cooled, and extracted with ether to give the liquid product (0.52 g). Analytical g.l.c. (OV-17) indicated the presence of: *cis*- and *trans*-2,5-dimethyltetrahydrofuran (3%); hexan-2-ol (44%); *trans*-hex-4-en-2-ol (30%); and *cis*-hex-4-en-2-ol (23%). The three major products were separated by preparative g.l.c. (DEGS); their rotations were: (i) hexan-2-ol (*c* 0.65 in EtOH), $[\alpha]_D^{20}$ −4.8° {lit.,[14] $[\alpha]_D^{18}$ −12.0° (neat)}, $[\alpha]_{578}$ −5.2°, $[\alpha]_{546}$ −6.0°, $[\alpha]_{436}$ −10.6°, $[\alpha]_{365}$ −19.1°; (ii) *trans*-hex-4-en-2-ol (*c* 1.64 in EtOH), $[\alpha]_D^{20}$ −0.4°, $[\alpha]_{578}$ −0.6°, $[\alpha]_{546}$ −0.7°, $[\alpha]_{436}$ −1.7°, $[\alpha]_{365}$ −3.8°; (iii) *cis*-hex-4-en-2-ol (*c* 0.20 in EtOH), $[\alpha]_D^{20}$ +2.9°, $[\alpha]_{578}$ +2.9°, $[\alpha]_{546}$ +2.9°, $[\alpha]_{436}$ +3.4°, $[\alpha]_{365}$ +4.4°.

(−)-(S)-α-*Methoxy*-α-*trifluoromethylphenylacetic Acid* (*MTPA*) *Derivatives*.—(−)-(*S*)-MTPA (1.0 g, 4.3 × 10^{-3}

[18] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.

mol) and thionyl chloride (3 ml) were heated together under gentle reflux for 50 h. The excess of thionyl chloride was removed under vacuum to give the crude (−)-acid chloride,[13] which was used as such. A mixture (0.40 g, 4.0×10^{-3} mol) of the three optically active alcohols (hexan-2-ol, *trans*-hex-4-en-2-ol, and *cis*-hex-4-en-2-ol) prepared as above was added to a solution of the acid chloride, dry pyridine (8 ml), and carbon tetrachloride (8 ml), and left overnight. Work-up with ether yielded a mixture of the diastereoisomeric MTPA esters of the three alcohols (0.78 g, 61% based on alcohol). Preparative g.l.c. (Carbowax 20 M) gave as oils: (i) *MTPA ester of hexan-2-ol*, b.p. 112° at 0.2 mmHg, $[\alpha]_D$ −46.2° (*c* 2.25 in $CHCl_3$) (Found: C, 60.8; H, 6.5; F, 18.0. $C_{16}H_{21}F_3O_3$ requires C, 60.4; H, 6.65; F, 17.9%); $\nu_{max.}$ 3 070 (aromatic C–H), 1 745 (C=O), 1 600 (C=C), and 1 260, 1 170, and 1 110 cm^{-1} (C–F); δ_H 1.23 (d, *J* 6 Hz, 1-H_3), 1.33 (d, *J* 6 Hz, 1′-H_3), 3.57 (3 H, q, OMe), 5.10 (1 H, sext, *J* 6 Hz, 2-H), and 7.36 (5 H, m, aromatic); (ii) *MTPA ester of* trans-*hex-4-en-2-ol*, b.p. 108° at 0.1 mmHg, $[\alpha]_D$ −40.4° (*c* 1.41 in $CHCl_3$) (Found: C, 61.0; H, 6.1; F, 17.8. $C_{16}H_{19}F_3O_3$ requires C, 60.75; H, 6.05; F, 18.0%); $\nu_{max.}$ 3 060 (aromatic C–H), 3 010 (vinyl C–H), 1 745 (C=O), 1 600 (C=C), 1 260, 1 170, and 1 120 (C–F), and 960 cm^{-1} (*trans*-C=C); δ_H 1.23 (d, *J* 6 Hz, 1-H_3), 1.33 (d, *J* 6 Hz, 1′-H_3), 1.62 (3 H, m, 6-H_3), 2.22 (2 H, m, 3-H_2), 3.56 (3 H, q, OMe), 4.80—5.73 (3 H, m, 2-H, 4-H, and 5-H), and 7.36 (5 H, m, aromatic); (iii) *MTPA ester of* cis-*hex-4-en-2-ol*, b.p. 111° at 0.2 mmHg, $[\alpha]_D$ −39.2 (*c* 1.25 in $CHCl_3$) (Found: C, 60.8; H, 6.2; F, 18.0%); $\nu_{max.}$ 3 060 (aromatic C–H), 3 010 (vinyl C–H), 1 745 (C=O), 1 600 (C=C), and 1 260, 1 170, and 1 120 cm^{-1} (C–F); δ_H 1.23 (d, *J* 6 Hz, 1-H_3), 1.33 (d, *J* 6 Hz, 1′-H_3), 1.57 (3 H, m, 6-H_3), 2.28 (2 H, m, 3-H_2), 3.56 (3 H, q, OMe), 4.80—5.75 (3 H, m, 2-H, 4-H, and 5-H), and 7.35 (5 H, m, aromatic).

Clemmensen Reduction of 1-(3α-*Hydroxy*-5α-*androstan*-2β-*yl*)*propan*-2-*one* (1).—The hydroxy-ketone (1) (0.10 g, 3×10^{-4} mol) was added to a mixture of amalgamated zinc (0.25 g), water (0.12 ml), concentrated hydrochloric acid (0.18 ml), and 1,2-dimethoxyethane (0.75 ml). The mixture was heated to 60 °C and stirred for 2 h. Cooling and extraction with ether gave the crude product. Preparative t.l.c. (hexane–ether, 7 : 3) yielded starting material (29 mg) and 2β-propyl-5α-androstan-3α-ol (15) (30 mg), identical i.r. and ^1H n.m.r. spectra with the compound previously formed. When the reduction was attempted in refluxing benzene for 3 h elimination of the hydroxy-group gave as the major product 2-propyl-5α-androst-2-ene (18), $[\alpha]_D$ +36.8° (*c* 0.54 in $CHCl_3$); $M^{+\cdot}$ 300; $\nu_{max.}$ 1 660 cm^{-1} (C=C); δ_H 0.70 (6 H, s, 18- and 19-H_3) and 5.33 (1 H, m, $W_{1/2}$ 8 Hz, 3-H). Repeating this reduction at room temperature for 2 h followed by refluxing for 30 min gave as the major product 2-(2-oxopropyl)-5α-androst-2-ene (19), $M^{+\cdot}$ 314; $\nu_{max.}$ 1 710 (C=O) and 1 640 cm^{-1} (C=C); δ_H 0.70 (3 H, s, 18-H_3), 0.75 (3 H, s, 19-H_3), 2.15 (3 H, s, 3′-H_3), 3.00br (2 H, apparent s, 1′-H_2), and 5.53 (1 H, m, $W_{1/2}$ 8 Hz, 3-H).

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