Steroid Analogues. Part 4.[1] Synthesis of Δ^9-6,7-Dinor-5,8-seco-steroids *via* β-Lactones †

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The condensation of cycloalkanones with cycloalkanecarboxylic acids has been shown to be a general method for the preparation of cycloalkylidenecycloalkanes bearing different functional groups in the two halves of the molecule.

Condensation of bicyclic hydroxy-ketones representing rings C and D of the steroid nucleus with the dilithium salts of 4-substituted cyclohexanecarboxylic acids (representing ring A) gave β-hydroxy-acids, which were transformed by lactonisation and subsequent pyrolysis into 3-substituted Δ^9-6,7-dinor-5,8-seco-estrenes and -pregnenes. The stereochemistry of these compounds has been elucidated by n.m.r. spectroscopy using a lanthanoid shift reagent, and by reference to conformation theory and the Woodward–Hoffmann rules.

In order to provide model routes to 11-hydroxy-analogues of these compounds, 2-hydroxy-1,1′-bi(cyclohexylidene) (46) was prepared from 1-(cyclohex-1-enyl)cyclohexanecarbonitrile (38) by epoxidation and reduction with lithium–ammonia, and from 1-(cyclohex-1-enyl)cyclohexanecarboxylic acid (40) by epoxidation, chromatography over silica gel, and pyrolysis of the resulting γ-hydroxy-β-lactone. Similar treatment of βγ-unsaturated acids derived from the seco-steroidal β-hydroxy-acids mentioned above gave none of the desired 3-substituted 11α-hydroxy-Δ^9-6,7-dinor-5,8-seco-steroids.

In the preceding paper [1] we described the synthesis of some $\Delta^{4,9}$-6,7-dinor-5,8-seco-steroids and the attempted saturation of the disubstituted double bond in related model compounds. In this and the following paper [2] we report the synthesis of a variety of Δ^9-6,7-dinor-5,8-seco-estrenes and -pregnenes.‡

† Part of the material contained in this and the following paper was presented at the 4th International Symposium on Synthesis in Organic Chemistry, Cambridge, July 1975.

‡ All compounds are racemic; the tricyclic compounds have been named using steroid nomenclature for two reasons: first, a a greater degree of consistency is thereby attained, and secondly, the names are shorter and simpler, partly because the stereochemistry at several centres of asymmetry does not then need to be specified.

The synthesis of tetrasubstituted olefins by the pyrolysis of β-lactones was described by Adam *et al.*,[3] and the extension of this procedure to a general synthesis of unsubstituted unsymmetrical cycloalkylidenecycloalkanes has been reported more recently.[4] We considered that this approach would provide a simple and

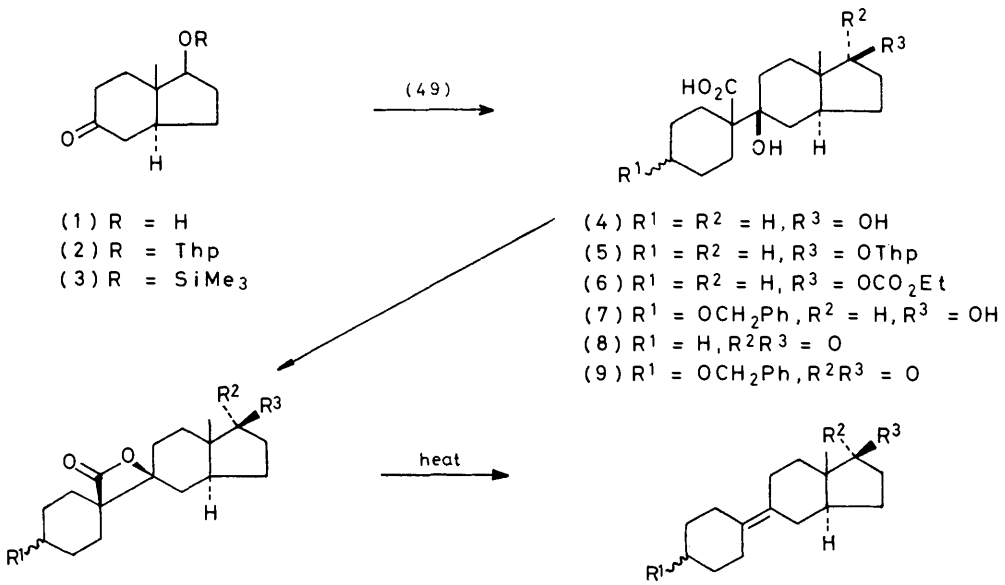
[1] Part 3, D. J. Humphreys, P. M. Lawrence, C. E. Newall, G. H. Phillipps, and P. A. Wall, preceding paper.

[2] D. J. Humphreys, C. E. Newall, G. H. Phillipps, and G. A. Smith, following paper.

[3] W. Adam, J. Baeza, and J. C. Liu, *J. Amer. Chem. Soc.*, 1972, **94**, 2000.

[4] A. P. Krapcho and E. G. E. Jahngen, *J. Org. Chem.*, 1974, **39**, 1650.

efficient route to the tetrasubstituted olefins that were our objective. Thus, the sequence envisaged involved condensation of the dianion of a suitable 4-substituted cyclohexanecarboxylic acid with a functionalised bicyclic ketone incorporating rings C and D of the steroid nucleus,[5] lactonisation of the resulting β-hydroxy-acid, and subsequent pyrolysis to give the desired seco-steroids which could be further modified as necessary.

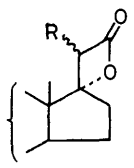


(1) R = H
(2) R = Thp
(3) R = $SiMe_3$

(4) $R^1 = R^2 = H, R^3 = OH$
(5) $R^1 = R^2 = H, R^3 = OThp$
(6) $R^1 = R^2 = H, R^3 = OCO_2Et$
(7) $R^1 = OCH_2Ph, R^2 = H, R^3 = OH$
(8) $R^1 = H, R^2R^3 = O$
(9) $R^1 = OCH_2Ph, R^2R^3 = O$

(10) $R^1 = R^2 = H, R^3 = OH$
(11) $R^1 = R^2 = H, R^3 = OThp$
(12) $R^1 = R^2 = H, R^3 = OCO_2Et$
(13) $R^1 = R^2 = H, R^3 = OAc$
(14) $R^1 = H, R^2R^3 = O$
(15a) $R^1 = \alpha\text{-}OCH_2Ph, R^2R^3 = O$
(15b) $R^1 = \beta\text{-}OCH_2Ph, R^2R^3 = O$
(16a) $R^1 = \alpha\text{-}OH, R^2R^3 = O$
(16b) $R^1 = \beta\text{-}OH, R^2R^3 = O$

(17) $R^1 = R^2 = H, R^3 = OH$
(18) $R^1 = R^2 = H, R^3 = OThp$
(19) $R^1 = R^2 = H, R^3 = OAc$
(20) $R^1 = H, R^2R^3 = O$
(21a) $R^1 = \alpha\text{-}OH, R^2R^3 = O$
(21b) $R^1 = \beta\text{-}OH, R^2R^3 = O$



(22a) R = OAc
(22b) R = OCO_2Et

6,7-Dinor-5,8-secoestr-9-en-17-ones.—Our initial objective was the unsubstituted 17-ketone (20). Treatment of the protected hydroxy-ketone (2) with the dilithium salt of cyclohexanecarboxylic acid and acidification of the reaction mixture to pH 5 afforded a mixture of the β-hydroxy-acids (4) and (5), in which the latter predominated. Cyclisation of (5) to the β-lactone (11) by benzenesulphonyl chloride in pyridine was nearly quantitative. Pyrolysis of (11) at 150 °C in the absence of solvent resulted in partial thermal removal of the tetrahydropyranyl group as well as elimination of carbon dioxide to give a mixture of the olefins (17) and (18); acidic hydrolysis of this mixture yielded the pure alcohol (17). Oxidation of the latter to the ketone (20) was carried out in high yield by the Moffatt procedure; [6] earlier experience had indicated that the double bond system might be sensitive to more vigorous reagents.

The tetrahydropyranyl ether function is less than ideal as a protecting group and its partial premature removal at the hydroxy-acid stage, together with difficulties in freeing the ketone (20) from dicyclohexylurea, prompted us to investigate an alternative route to (20).

[5] D. J. Humphreys, C. E. Newall, H. A. Paskins, and G. H. Phillipps, *J.C.S. Perkin I*, 1978, 15.

[6] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5661, 5670.

Condensation of the dilithium salt of cyclohexanecarboxylic acid with the trimethylsilyl ether (3) led to a 77% yield of the dihydroxy-acid (4). Lactonisation of this compound directly with benzenesulphonyl chloride was precluded by the likelihood of elimination of the 17-hydroxy-group; we therefore sought other lactonising reagents which might effect more readily reversible protection of this function.

Lewbart [7] has reported that treatment of a steroidal 17α,20ξ-dihydroxy-21-oic acid with acetic anhydride in pyridine gave the 20ξ-acetoxy-β-lactone (22a) as the major product; when ethyl chloroformate in pyridine was used, the corresponding 20ξ-ethoxycarbonyloxy-β-lactone (22b) was formed nearly quantitatively. Treatment of the dihydroxy-acid (4) with ethyl chloroformate in pyridine produced a mixture of the desired 17-ethoxycarbonyloxy-β-lactone (12) and the corresponding hydroxy-acid (6) in the ratio 2 : 5. Acetic anhydride in pyridine gave a low yield of the acetoxy-β-lactone (13), while acetyl chloride in pyridine produced a small amount of the acetoxy-olefin (19) as the only identifiable product. In the last case the mixture became hot, resulting in decarboxylation of the intermediate lactone (13).

Since none of these reagents was satisfactory the dihydroxy-acid (4) was oxidised with Jones reagent to the ketone (8) which, on lactonisation with benzenesulphonyl chloride in pyridine and subsequent pyrolysis at 150 °C in the absence of solvent, afforded the olefin (20) in an overall yield of more than 60% [based on the hydroxy-ketone (1)]. The product, however, contained up to 5% of a second ketonic component, from which the ketone (20) could not be separated, and which was possibly formed by thermal migration of the exocyclic double bond during the pyrolysis.

When the lactone (11) was deprotected by heating under reflux in methanol containing dilute sulphuric acid, some elimination of carbon dioxide occurred, and the product was a mixture of the lactone (10) and the olefin (17). It was subsequently shown that the pyrolysis of β-lactones could be carried out in a solvent, provided that this was hydroxylic. When the lactone (14) was heated under reflux for 8 h in benzene or tetrahydrofuran, virtually none of the olefin (20) was produced, whereas in methanol there was a 50% conversion into (20) after this time. In ethanol and in butan-2-ol there was >90% conversion into (20) after 8 h, whereas in 2-methoxyethanol (b.p. 125°) complete reaction occurred within 30 min. The product was much purer than that formed by pyrolysis in the absence of solvent, and all subsequent pyrolyses were therefore carried out in boiling 2-methoxyethanol. The solvent dependence of this reaction implies that the mechanism is not wholly thermal. Lewbart [7] reported similar experiences with the less stable steroidal β-lactones of the type (22).

The 3α- and 3β-hydroxy-17-ketones (21a and b) were prepared in similar fashion by condensation of the silyl ether (3) with 4-benzyloxycyclohexanecarboxylic acid [8] (49a). Oxidation of the resulting dihydroxy-acid (7) with Jones reagent and treatment of the product with benzenesulphonyl chloride in pyridine yielded a mixture of the oxo-lactones (15a and b). The more polar isomer crystallised preferentially from ether–petrol and was assigned the 3β-substituted structure (15b) on spectral evidence (see later); the liquors contained a mixture of the 3α- and 3β-epimers, which was converted by hydrogenation into the alcohols (16a and b) and thence by pyrolysis into the olefins (21a and b), which were separated by preparative t.l.c. A sample of the pure 3β-benzyloxy-lactone (15b) was also carried through this sequence, and gave the more polar isomers of the hydroxy-lactone (16) and the olefin (21), which were accordingly assigned the 3β-configuration.

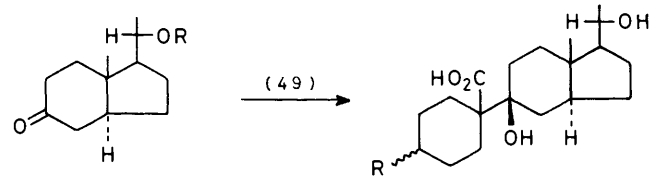
6,7,19-*Trinor*-5,8-*secopregn*-9-*en*-20-*ones*.—The unsubstituted 20-ketone (32) was prepared by the general route outlined above in 44% overall yield from the hydroxy-ketone (23).[5] Condensation of the silyl ether (24) with the dilithium salt of 4-benzyloxycyclohexanecarboxylic acid and reaction of the product successively with Jones reagent and benzenesulphonyl chloride, afforded a mixture of the lactones (28a and b) which was separated by extensive preparative t.l.c.; the major product was the more polar 3β-benzyloxy-isomer (28b). The lactones (28a and b) were converted as described above into the olefins (33a and b), respectively, which were indistinguishable by i.r. and n.m.r. spectroscopy, g.l.c., and t.l.c.

Stereochemistry.—It appears that the condensation between the dianion of a cyclohexanecarboxylic acid and a *trans*-bicyclo[4.3.0]nonan-3-one is stereospecific, presumably involving attack by the dianion from the less hindered (*i.e.* α-) face of the ketone, since there is no evidence for the formation of isomers of the β-hydroxy-acids or β-lactones. The n.m.r. spectra of the 3-benzyloxylactones show either a fairly broad multiplet at τ 6.65 attributable to an axial 3-H, or a somewhat sharper multiplet at τ 6.35 due to an equatorial 3-H. This implies that ring A is held in a rigid conformation, presumably a chair, with respect to the lactone function. If the lactone function be on the β-face of the molecule, only one chair conformation is possible for ring A (*viz.* that in which the lactone carbonyl group is axially oriented) since the alternative must involve massive steric interactions between rings A and C (assuming a chair conformation for ring C). In this conformation a 3β-substituent would lie in an equatorial position, and a 3α-substituent would adopt an axial position. Hence, it is possible to specify the absolute stereochemistry at C-3 if the lactone function can be definitely assigned the β-configuration.

A means of achieving this objective consisted in demonstrating, with the aid of an n.m.r. shift reagent, that, before cyclisation to a lactone, the 9-hydroxy-group and the angular methyl are on the same face of the molecule. A suitable substrate, *viz.* the hydroxy-ester (67), was encountered during an approach to the

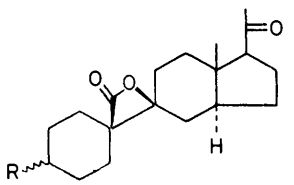
[7] M. L. Lewbart, *J. Org. Chem.*, 1972, **37**, 1224.
[8] S. Parkhi, *J. Indian Chem. Soc.*, 1956, **33**, 313.

synthesis of an 11-hydroxy analogue (see later). Addition of the lanthanoid shift reagent Eu(fod)$_3$ produced a large downfield shift in the 13-methyl resonance of (67)

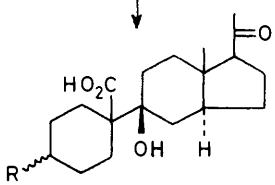


(23) R = H
(24) R = $SiMe_3$

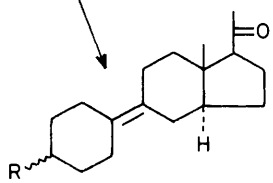
(25) R = H
(26) R = OCH_2Ph



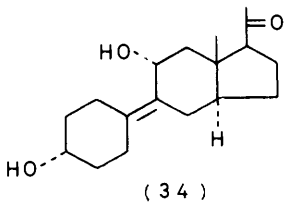
(27) R = H
(28a) R = α-OCH_2Ph
(28b) R = β-OCH_2Ph
(29a) R = α-OH
(29b) R = β-OH



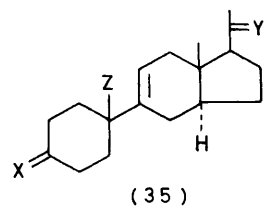
(30) R = H
(31) R = OCH_2Ph



(32) R = H
(33a) R = α-OH
(33b) R = β-OH



(34)



(35)

and a much smaller downfield shift in the 20-methyl resonance (see Experimental section). This provides good evidence that the 9-hydroxy-group and the angular methyl are in close proximity, *i.e.* attached to the same face of the molecule. The 20-methyl resonance is shifted very little as, in its normal conformation, this group is held downwards and away from the 13-methyl group.[9] Had the hydroxy-group been α-oriented, one would expect the shifts in the 13- and 20-methyl resonances to have been of the same order. Thus, the oxygen function at C-9 in β-hydroxy-acids and β-lactones may be assigned the β-configuration. The stereochemistry at C-3 follows from the n.m.r. spectra: in a 3α-substituted lactone the 3-H is equatorially oriented, and in a 3β-substituted lactone the 3-H is axially oriented. The thermal decomposition of β-lactones is known [3,7] to proceed with retention of configuration in the resulting olefin, so that the stereochemistry at C-3 in an olefin derived from a given β-lactone can be specified, *e.g.* pyrolysis of a 3β-substituted lactone will give a 3β-substituted olefin.

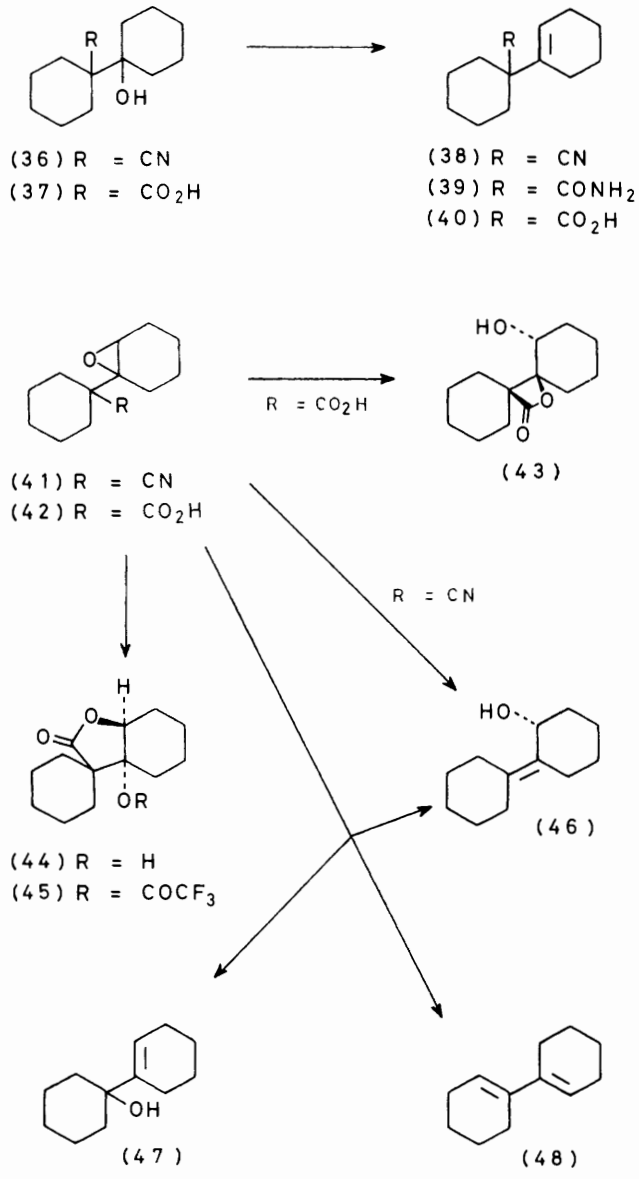
11-Hydroxy-analogues.—For comparison with 11-oxygenated steroids we wished to prepare the 3α,11α-diol (34). There appeared to be two potential methods for the regiospecific and stereospecific production of such an allylic alcohol, these having been used to prepare simple 2-alkylidenecycloalkanols. The first would involve reduction of a βγ-epoxy-nitrile by sodium and ammonia,[10] and the second pyrolysis of a βγ-epoxy-acid.[11] In either case our initial aim was an intermediate of the type (35), where Y is an oxygen function, X is a protected oxygen function, and Z is CN or CO_2H. This compound might be prepared by condensation of the bicyclic ketone (23) with an appropriately substituted α-lithiated cyclohexanecarbonitrile or cyclohexanecarboxylic acid, and dehydration of the resulting tertiary alcohol; the double bond in a *trans*-bicyclo[4.3.0]nonane is more stable in the 3,4- than in the 2,3-position.[12] The potential usefulness of these two reactions in the present work was first evaluated by their application to the synthesis of the known 2-hydroxy-1,1′-bi(cyclohexylidene) (46).[13]

Condensation of cyclohexanone with the lithium derivative of cyclohexanecarbonitrile gave the β-hydroxy-nitrile (36) [14] in 45% yield. Dehydration of the latter by toluene-*p*-sulphonic acid in toluene and treatment of the product (38) with *m*-chloroperoxybenzoic acid yielded the epoxy-nitrile (41), which was reduced by sodium and ammonia [10] in 68% yield to the desired alcohol (46).

Treatment of 1-(cyclohex-1-enyl)cyclohexanecarboxylic acid (40) [15] with *m*-chloroperbenzoic acid afforded not the expected epoxy-acid (42) but the γ-hydroxy-β-lactone (43). This presumably arose by rearrangement of (42) during work-up. Pyrolysis of the lactone (43) in 2-methoxyethanol for 2 h yielded the allylic alcohol (46) in 80% yield. When the crude β-lactone (43) was heated under reflux for 6 h in toluene,[11] the major product was

[9] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965.
[10] J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, 1971, **36**, 877.
[11] W. C. Still, A. J. Lewis, and D. Goldsmith, *Tetrahedron Letters*, 1971, 1421.
[12] L. Velluz, J. Valls, and G. Nomine, *Angew. Chem. Internat. Edn.*, 1965, **4**, 181.
[13] G. Laber, *Annalen*, 1958, **588**, 79.
[14] E. Vedejs and J. E. Telschow, *J. Org. Chem.*, 1976, **41**, 740.
[15] J. Jacques and C. Wiedmann-Hattier, *Bull. Soc. chim. France*, 1958, 1478.

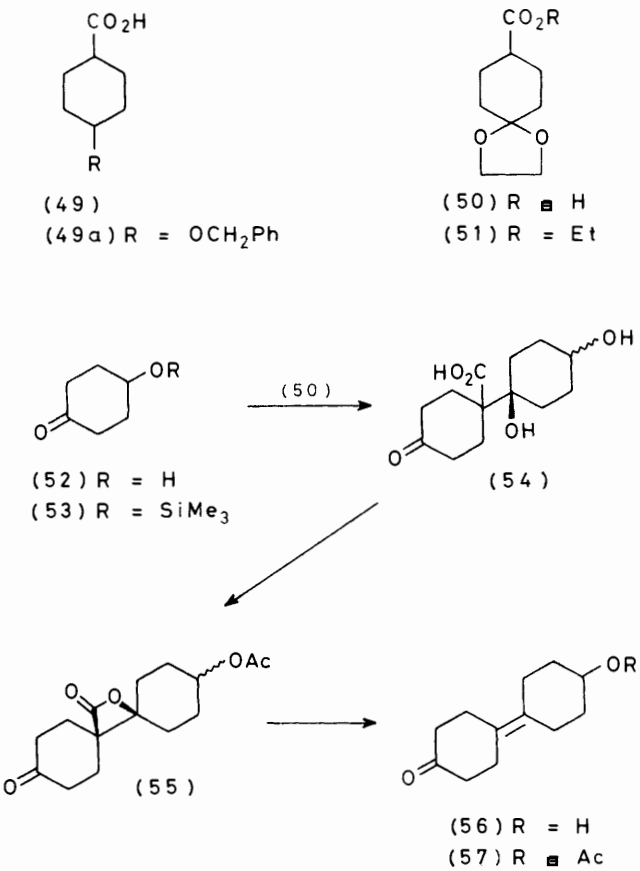
the isomeric allylic alcohol (47); some of the desired alcohol (46) and its dehydration product (48) were also



formed. When the crude epoxidation mixture was treated with trifluoroacetic acid, the product was the trifluoroacetoxy-γ-lactone (45), which was hydrolysed to the corresponding alcohol (44) during chromatography on silica gel. This reaction confirmed the intermediacy of the epoxy-acid (42).

For the synthesis of the tricyclic compound (34) the route *via* an epoxy-acid was chosen as it was potentially the simpler and more efficient of the two alternatives. Our initial aim, therefore, was the intermediate (35; Z = CO_2H, Y = H,OH). The choice of the ring A fragment lay between 4-benzyloxycyclohexanecarboxylic acid [8] (49a) and 4,4-ethylenedioxycyclohexanecarboxylic acid [16] (50). Previous experience indicated that if the former were used the major isomer produced would be the 3β-isomer. We decided, therefore, to use the acetal–acid (50) as the ring A synthon, hoping to accomplish selective reduction of the 3-ketone to a 3α-ol by hexachloroiridic acid (*cf.* ref. 2).

The acid (50) was prepared by standard methods [16] but in increased yield, 84% from 4-ethoxycarbonylcyclohexanol. Its usefulness in this context is illustrated by the synthesis of the olefin (56), which bears different functional groups in each half of the molecule. The dianion of the acid (50) was treated in tetrahydrofuran with the trimethylsilyl ether (53) of 4-hydroxycyclohexanone.[17] Isolation of the resulting dihydroxy-acid (54) was difficult owing to its great water solubility. Treatment of (54) with acetic anhydride in pyridine effected simultaneous protection of the secondary hydroxy-group and cyclisation of the β-hydroxy-acid, to give the acetoxy-β-lactone (55) (*cf.* ref. 7). Pyrolysis of the latter in 2-methoxyethanol proceeded almost quantitatively to give the acetoxy-olefin (57) in an overall yield of 55%. The acetate (57) was hydrolysed to the hydroxy-ketone (56) using potassium hydrogen carbonate.



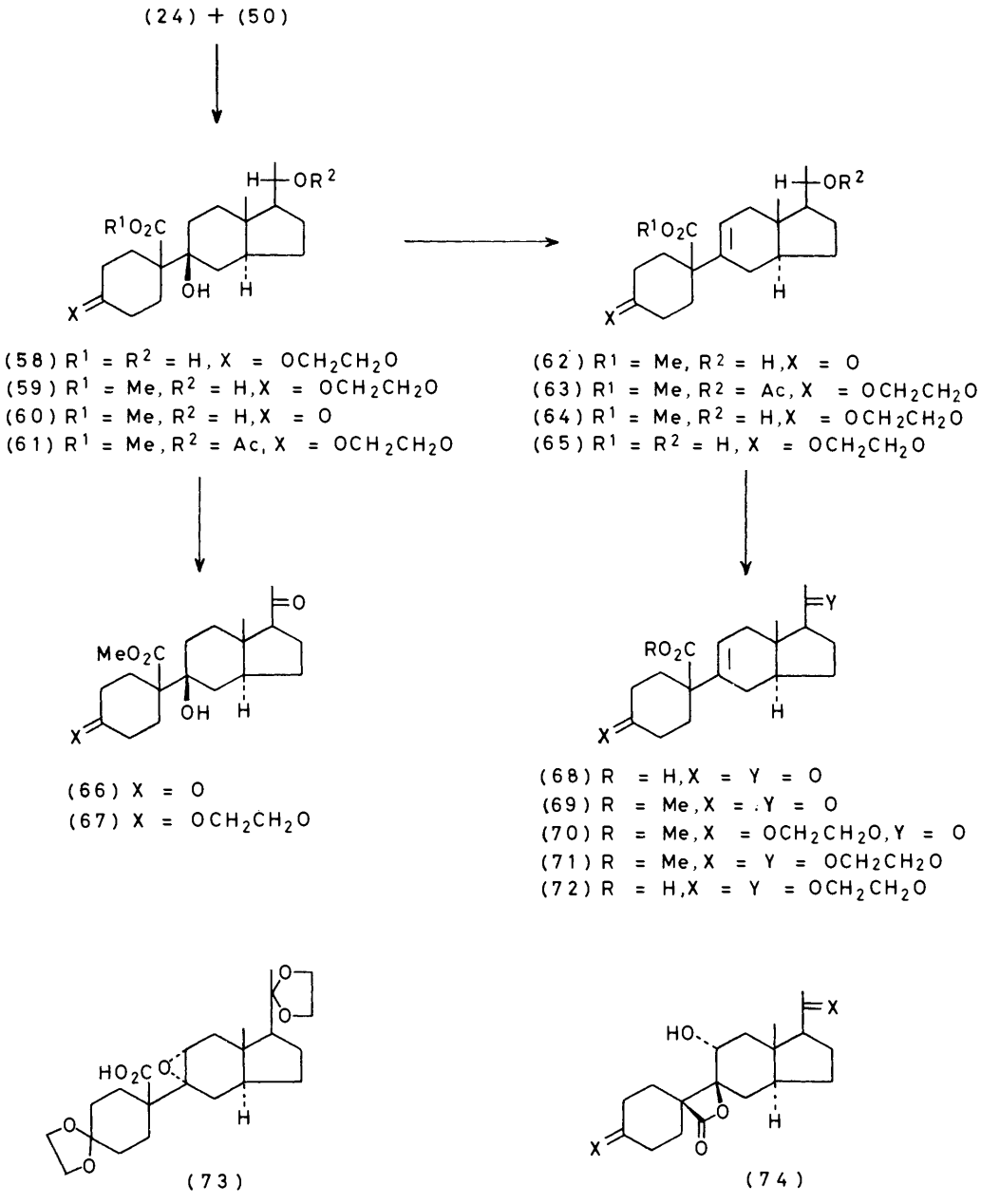
Condensation of the dilithium salt of the acid (50) with the silylated hydroxy-ketone (24) and treatment of the product (58) with diazomethane yielded the β-hydroxy-ester (59). Prolonged heating of the latter

[16] N. Itoh and S. Sugasawa, *Tetrahedron*, 1959, **6**, 16.
[17] E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 1949, 615.

with 90% formic acid gave a mixture of the desired unsaturated ester (62) (37%) and the deacetalised hydroxy-ester (60) (28%). On heating (59) or (60) with 98% formic acid, complex mixtures were obtained, possibly owing to formylation of the 20-hydroxy-group and subsequent elimination and/or rearrangement. It was hoped that modification of the 20-hydroxy-group by oxidation or acylation might avoid such complications.

Jones reagent brought about efficient oxidation of the 20-hydroxy-group in (59), but also effected partial removal of the acetal group, to give a mixture of (66) and (67). Oxidation of (59) by the Moffatt procedure,[6] however, gave the desired ketone (67) in 87% yield. As mentioned earlier, an examination of the effect of a lanthanoid shift reagent on the n.m.r. spectrum of (67) permitted the assignment of stereochemistry at C-9 in this compound and, by analogy, in all other related hydroxy-acids and derived β-lactones.

Treatment of the dihydroxy-ester (59) with acetic anhydride and pyridine gave in 90% yield the 20-acetate (61), which was dehydrated quantitatively by thionyl chloride and pyridine to give (63). Brief treatment of the latter with aqueous methanolic potassium hydroxide cleaved the acetoxy-group to give the hydroxy-ester (64) almost quantitatively. Even after prolonged heating the hindered methyl ester was hydrolysed only to a small extent. However, when the ester (64) was heated with sodium cyanide in boiling dimethylform-



amide,[18] a quantitative yield of the hydroxy-acid (65) was obtained. Oxidation of the latter with Jones reagent, followed by treatment with acid, furnished the desired dione (68) in 98% yield.

m-Chloroperbenzoic acid was very slow to react with the unsaturated acid (68) and mixtures resulted. There was no direct evidence of epoxidation and no β-lactone was detected in the product by i.r. spectroscopy. Those products isolated appeared to be lactones formed by Baeyer–Villiger oxidation of the 3-ketone.

It was therefore necessary to protect the carbonyl groups, and this was most conveniently achieved by acetalisation. The unsaturated hydroxy-ester (64) was oxidised with Jones reagent, the protecting group being lost during the reaction, to give the dione (69) which, with ethylene glycol and toluene-*p*-sulphonic acid, yielded the 3,20-diacetal (71), together with some of the 20-oxo-3-acetal (70). Hydrolysis of the ester (71) was accomplished in 97% yield by use of sodium cyanide in dimethylformamide.[18]

The protected acid (72) reacted more rapidly with *m*-chloroperbenzoic acid than did (68), to give one product (by t.l.c.), presumably the epoxy-acid (73); as expected, this could not be isolated. However, the desired rearrangement to a γ-hydroxy-β-lactone (74) did not take place during the work-up; instead, a mixture was formed which contained no β-lactone (by i.r.).

Owing to a lack of time and materials this route was not explored further. It constitutes the second example of a failure to extend to the ACD tricyclic series a method efficient for the synthesis of AC bicyclic compounds; the coupling of two monocyclic components *via vic*-dinitro-compounds (the Kornblum synthesis [19]) gave excellent yields of bi(cyclohexylidene)s but, when one component was a *trans*-bicyclo[4.3.0]nonane, the yield of tetra-substituted olefin was negligible.[20] It is possible that the more rigid conformation in which the six-membered ring of a bicyclo[4.3.0]nonane is held may have been a factor in these failures.

EXPERIMENTAL

For preamble see Part 1.[5]

Preparation of β-Hydroxy-acids.—In a typical experiment, *N*-isopropylcyclohexylamine (20 mmol) in dry tetrahydrofuran (25 ml) was treated with n-butyl-lithium in hexane (20 mmol), followed by the cyclohexanecarboxylic acid (10 mmol) in tetrahydrofuran (25 ml), and the mixture was stirred overnight at room temperature. Water was added and the aqueous phase was washed with ether and acidified with 6N-hydrochloric acid. The product was either collected or extracted into chloroform.

In some preparations, some of the hydroxy-acid was extracted into the ether phase, from which it was recovered by chromatography. This could be largely prevented by addition of potassium hydroxide after pouring into water.

Cyclisation of β-Hydroxy-acids.—The hydroxy-acid (5 mmol) in dry pyridine (10 ml) was treated with benzenesulphonyl chloride (10 mmol) and the mixture was kept at 0 °C overnight in a stoppered flask, then poured onto ice–water. The product was extracted into dichloromethane and the extract was washed with aqueous 5% sodium hydrogencarbonate, dried, and evaporated with the aid of toluene. The residue was crystallised from a suitable solvent.

Pyrolysis of β-Lactones.—The lactone was heated under reflux in 2-methoxyethanol until the elimination of carbon dioxide was complete, as shown by t.l.c. (15—45 min). The solution was then poured into water and the product was isolated by filtration (if appropriate) or by extraction into dichloromethane.

(±)-9β-*Hydroxy*-17β-*tetrahydropyran*-2-*yloxy*-6,7-*dinor*-5,8-*secoandrostan*-19-*oic Acid* (5).—The hydroxy-ketone (1) (1.80 g, 10.7 mmol) was stirred overnight with freshly distilled dihydropyran (2.9 ml) and toluene-*p*-sulphonic acid (20 mg) in dry ether (25 ml) and dry tetrahydrofuran (10 ml). The mixture was diluted with ether and shaken with 2N-sodium hydroxide and water. The organic phase was dried and evaporated to an oil (3.96 g). Chromatography on alumina [acetone–petrol (1 : 4) as eluant] yielded the tetrahydropyranyl ether (2) (3.17 g), 81% pure by g.l.c.

Condensation of the latter with the dilithium derivative of cyclohexanecarboxylic acid (107 mmol) gave after acidification of the mixture, a gummy solid (868 mg) which gave (from petrol) white crystals (300 mg, 7.5%) of the *hydroxy-acid* (5), m.p. 176°, $\nu_{max.}$ 3 610, 3 500, and 3 400—2 300 (OH), and 1 720 and 1 690 cm^{-1} (CO_2H), τ 9.29 (3 H, s, CH_3), 5.8—6.8br (3 H, m, 17-H and Thp 5-H), and 5.40 (3 H, m, Thp 2-H, OH, and CO_2H) (Found: C, 68.4; H, 9.5. $C_{22}H_{36}O_5$,0.25H_2O requires C, 68.6; H, 9.55%).

The aqueous liquors were extracted with dichloromethane and the extract was combined with the mother liquors from the above crystallisation. Evaporation left a gum (1.37 g) which was treated with 2N-sulphuric acid in methanol for 30 min. The mixture was partitioned between water and chloroform and the organic phase was dried and evaporated to give the dihydroxy-acid (4) (965 mg, 31.5%) as a pale yellow gum.

(±)-17β-*Tetrahydropyran*-2-*yloxy*-6,7-*dinor*-5,8-*secoandrostano*-19,9β-*lactone* (11).—The hydroxy-acid (5) (190 mg, 0.5 mmol) was cyclised using benzenesulphonyl chloride and pyridine to give a brown gum (200 mg) which was boiled in petrol with charcoal; the solution was then filtered and cooled to give crystals of the *lactone* (11) as a mixture of diastereoisomers, m.p. 120—121°, $\nu_{max.}$ 1 803 cm^{-1} (β-lactone), τ 9.21 and 9.22 (3 H, both s, CH_3), 6.0—6.7br (3 H, m, 17-H and Thp 5-H), and 5.42 (1 H, m, Thp 2-H)(Found: C, 72.3; H, 9.2. $C_{22}H_{34}O_4$, 0.25H_2O requires C, 72.0; H, 9.5%).

(±)-6,7-*Dinor*-5,8-*secoestr*-9-*en*-17β-*ol* (17).—The lactone (11) (3.68 g, 10.1 mmol) was heated at 140—160 °C in the absence of solvent until evolution of gas ceased (10 min). T.l.c. showed that the product (3.24 g) was a mixture of the alcohol (17) and the diastereoisomers of the tetrahydropyranyl ether (18). It was dissolved in methanol (50 ml) and treated with 2N-sulphuric acid (2 ml). After 1 h, the mixture was partitioned between water and dichloromethane and the organic phase was dried and evaporated to a brown gum which was boiled with petrol (charcoal). The resulting gum (1.94 g, 75%) crystallised from petrol as

[18] J. E. McMurry and G. B. Wong, *Synth. Comm.*, 1972, **2**, 389.
[19] N. Kornblum, S. D. Boyd, and F. W. Stuchal, *J. Amer. Chem. Soc.*, 1970, **92**, 5783; N. Kornblum, S. D. Boyd, H. W. Pinnick, and R. G. Smith, *ibid.*, 1971, **93**, 4316.
[20] D. J. Humphreys, P. M. Lawrence, and C. E. Newall, *J.C.S. Perkin I*, 1978, 19.

needles of the *alcohol* (17), m.p. 91—93°, $\nu_{max.}$ 3 615 cm^{-1} (OH), τ 9.17 (3 H, s, CH_3) and 6.38 (1 H, m, C*H*OH) (Found: C, 80.6; H, 11.0. $C_{16}H_{26}O,0.25H_2O$ requires C, 80.4; H, 11.2%).

(±)-9β,17β-*Dihydroxy*-6,7-*dinor*-5,8-*secoandrostan*-19-*oic Acid* (4).—The hydroxy-ketone (1) (1.73 g, 10.3 mmol) in dry dichloromethane (15 ml) was treated with dry pyridine (4 ml) and trimethylchlorosilane (2 ml) for 1 h at 5 °C. The mixture was diluted with petrol (50 ml) and filtered through kieselguhr. Evaporation of the filtrate with the aid of benzene gave the trimethylsilyl ether (3) (2.35 g, 96%) as an oil. Condensation of the latter with the dilithium derivative of cyclohexanecarboxylic acid (1.32 g, 10.3 mmol) gave as the crude product a white froth (2.33 g, 75%). This gave, from ether, crystals of the *dihydroxy-acid* (4), m.p. 197—199° (decomp.), $\nu_{max.}$ (Nujol) 3 750—2 100 (OH) and 1 705 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.43 (3 H, s, CH_3) and 6.48 (1 H, m, C*H*OH) (Found: C, 68.6; H, 9.6. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%).

Treatment of the Dihydroxy-acid (4) *with Ethyl Chloroformate.*—The dihydroxy-acid (4) (500 mg, 1.7 mmol) in pyridine (5 ml) was treated with ethyl chloroformate (1 ml); the solution became hot and was quickly cooled to room temperature. After a few minutes pyridine hydrochloride separated and the mixture was kept at room temperature for 16 h. Water (5 ml) was added and after 1 h the product was extracted into ether. The extracts were washed with 5% sodium hydrogen carbonate and water, dried, and evaporated. P.l.c. ($CHCl_3$–MeOH, 19 : 1) of the residual gum (586 mg) afforded (i) (±)-17β-*ethoxycarbonyloxy*-9β-*hydroxy*-6,7-*dinor*-5,8-*secoandrostan*-19-*oic acid* (6) as a white froth (351 mg, 56%), $\nu_{max.}$ 3 600, 3 480, and 3 400—2 200 (OH), 1 738, 1 715, and 1 698 cm^{-1} (CO_2R), τ 9.24 (3 H, s, CH_3), 8.71 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 5.81 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), and 5.45 (1 H, m, 17-H) (Found: C, 64.4; H, 8.6. $C_{20}H_{32}O_6,0.25H_2O$ requires C, 64.4; H, 8.8%); (ii) (±)-17β-*ethoxycarbonyloxy*-6,7-*dinor*-5,8-*seco-androstano*-19,9β-*lactone* (12) as a gum (127 mg, 22%), $\nu_{max.}$ 1 800 (β-lactone) and 1 739 cm^{-1} (OCO_2R), τ 9.19 (3 H, s, CH_3), 8.72 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 5.83 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), and 5.41 (1 H, m, 17-H) (Found: C, 66.7; H, 8.5. $C_{20}H_{30}O_5,0.5H_2O$ requires C, 66.8; H, 8.7%).

Treatment of the Dihydroxy-acid (4) *with Acetic Anhydride.*—The dihydroxy-acid (4) (810 mg) was treated overnight with pyridine (15 ml) and acetic anhydride (3 ml). The solvents were removed *in vacuo* with the aid of toluene to give a yellow oil (800 mg) which, after extensive chromatography, yielded the acetoxy-lactone (13) (44 mg), $\nu_{max.}$ 1 800 (β-lactone) and 1 728 cm^{-1} (ester), τ 9.21 (3 H, s, CH_3), 8.00 (3 H, s, $OCOCH_3$), and 5.31 (1 H, m, C*H*OAc).

Treatment of the Dihydroxy-acid (4) *with Acetyl Chloride.*—The dihydroxy-acid (4) (980 mg) in pyridine (25 ml) was treated with acetyl chloride (5 ml); a violent reaction ensued and the mixture became very hot. Pyridine (25 ml) was added and the mixture was kept at 0 °C overnight, then partitioned between water and dichloromethane. The organic phase was washed with aqueous sodium hydrogen carbonate, dried, and evaporated with the aid of toluene. P.l.c. (CH_2Cl_2) of the residue yielded the acetoxy-olefin [2] (19) (133 mg, 15%) as the major product.

(±)-17β-*Hydroxy*-6,7-*dinor*-5,8-*secoandrostano*-19,9β-*lactone* (10).—The lactone (11) (362 mg, 1 mmol) in methanol (50 ml) was treated with 2N-sulphuric acid (1 ml) at room temperature for 1 h. The mixture was partitioned between water and dichloromethane and the organic phase was dried and evaporated to give a pale yellow gum (300 mg) which solidified. This gave (from ether–petrol) crystals of the *hydroxy-lactone* (10), m.p. 125° (decomp.), $\nu_{max.}$ 3 620 (OH) and 1 800 cm^{-1} (β-lactone), τ 9.24 (3 H, s, CH_3) and 6.24 (1 H, m, C*H*OH) (Found: C, 71.9; H, 9.3. $C_{17}H_{26}O_3,0.25H_2O$ requires C, 72.2; H, 9.4%).

(±)-9β-*Hydroxy*-17-*oxo*-6,7-*dinor*-5,8-*secoandrostan*-19-*oic Acid* (8).—The dihydroxy-acid (4) (3.815 g, 12.9 mmol) in acetone (130 ml) was treated dropwise with Jones reagent until the oxidation was complete. Water (400 ml) was added and the solution was acidified to pH 1 with 6N-hydrochloric acid. The product was extracted into dichloromethane and the extracts were washed with water, dried, and evaporated to a white froth (3.725 g, 97%). This gave (from ether–petrol) crystals of the *hydroxy-oxo-acid* (8), m.p. 162—165°, $\nu_{max.}$ 3 600, 3 490, and 3 500—2 300 (OH), 1 739 (C=O), 1 715, and 1 700 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.31 (3 H, s, CH_3) (Found: C, 69.2; H, 9.1. $C_{17}H_{26}O_4$ requires C, 69.35; H, 8.9%).

(±)-17-*Oxo*-6,7-*dinor*-5,8-*secoandrostano*-19,9β-*lactone* (14).—The hydroxy-acid (8) (295 mg, 1 mmol) was cyclised in the usual manner to give a solid (268 mg, 97%) which crystallised from dichloromethane–petrol as plates of the *lactone* (14), m.p. 144—147° (decomp.), $\nu_{max.}$ 1 805 (β-lactone) and 1 739 cm^{-1} (C=O), τ 9.11 (3 H, s, CH_3) (Found: C, 73.6; H, 8.65. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%).

(±)-6,7-*Dinor*-5,8-*secoestr*-9-*en*-17-*one* (20).—(a) *By oxidation of the alcohol* (17). The alcohol (17) (469 mg, 2 mmol) in dry dimethyl sulphoxide (3 ml) and dry benzene (3 ml) was treated with pyridine (0.16 ml, 2 mmol) and trifluoroacetic acid (0.08 ml, 1 mmol). Dicyclohexylcarbodi-imide (1.24 g, 6 mmol) was added and the mixture was stirred in a stoppered flask overnight. Benzene (50 ml) was added, followed by oxalic acid (540 mg, 6 mmol) in methanol (5 ml), and the mixture was stirred for 1 h. Water was then added and dicyclohexylurea was filtered off and washed with petrol. The organic phase was washed with 5% sodium hydrogencarbonate and water, dried, and evaporated to a gum (608 mg). P.l.c. (CH_2Cl_2) gave material (538 mg) which still contained dicyclohexylurea; trituration with petrol and evaporation of the liquors yielded the *ketone* (20) as a gum (430 mg, 93%), $\nu_{max.}$ 1 740 cm^{-1} (C=O), τ 9.06 (3 H, s, CH_3), g.l.c. purity 96% (Found: C, 81.0; H, 10.4. $C_{16}H_{24}O,0.25H_2O$ requires C, 81.1; H, 10.4%). A portion of this material was converted into the *semicarbazone* which gave (from benzene) crystals, m.p. 213—216° (decomp.) (Found: C, 70.35; H, 9.35; N, 14.6. $C_{17}H_{27}N_3O$ requires C, 70.55; H, 9.4; N, 14.5%).

(b) *By pyrolysis of the lactone* (14) *in the absence of solvent.* The oxo-lactone (14) (2.79 g, 10.1 mmol) was heated under nitrogen at 175 °C with stirring until evolution of nitrogen ceased (10 min). The residue was cooled and triturated with ether. The solution was filtered and evaporated to a light brown oil which was passed in dichloromethane through alumina (50 g) to give the ketone (20) as an oil (2.268 g, 96%), g.l.c. purity 95%. When this product was kept in petrol (20 ml) at −15 °C for 3 days, laths, m.p. 52—53°, g.l.c. purity 98%, were deposited.

(c) *By pyrolysis of the lactone* (14) *in boiling 2-methoxyethanol.* Pyrolysis of the lactone (14) (7.2 g, 26 mmol) in 2-methoxyethanol (125 ml) gave a gum (5.69 g, 94%) which gave (from petrol) crystals of the olefin (20), m.p. 45—48°, g.l.c. purity 98.5%.

(±)-3ξ-*Benzyloxy*-9β,17β-*dihydroxy*-6,7-*dinor*-5,8-*seco*-*androstan*-19-*oic Acid* (7).—The hydroxy-ketone (1) (675 mg, 4.0 mmol) was converted as above into the trimethylsilyl ether (3). Condensation of the latter with the dilithium derivative of 4ξ-benzyloxycyclohexanecarboxylic acid (49a) (936 mg, 4.0 mmol) and crystallisation of the product (943 mg, 59%) from chloroform gave the *dihydroxy-acid* (7) as crystals, m.p. 175—177°, $\nu_{max.}$ (Nujol) 3 462 and 3 650—2 300 (OH), and 1 682 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.48 (3 H, s, CH_3), 5.53 (2 H, m, PhCH_2O), and 2.68 (5 H, s, C_6H_5) (Found: C, 70.1; H, 8.4. $C_{24}H_{34}O_5$,0.5H_2O requires C, 70.0; H, 8.6%).

(±)-3ξ-*Benzyloxy*-9β-*hydroxy*-17-*oxo*-6,7-*dinor*-5,8-*seco*-*androstan*-19-*oic Acid* (9).—The dihydroxy-acid (4) (291 mg, 0.72 mmol) in acetone (25 ml) was oxidised with Jones reagent in the usual way. The mixture was poured into rapidly stirred water (150 ml) to give the *hydroxy-oxo-acid* (9) as a white crystalline solid (226 mg, 78%), m.p. 209°, $\nu_{max.}$ (Nujol) 3 520, 3 480, and 3 400—2 300 (OH), 1 738 (C=O), and 1 698 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.33 (3 H, s, CH_3), 5.48 and 5.54 (2 H, both s, OCH_2Ph), and 2.60 (5 H, s, C_6H_5) (Found: C, 70.6; H, 7.9. $C_{24}H_{32}O_5$,0.5H_2O requires C, 70.4; H, 8.1%).

(±)-3α-(*and* β-)*Benzyloxy*-17-*oxo*-6,7-*dinor*-5,8-*secoandro*-*stano*-19,9β-*lactone* (15a *and* b).—The hydroxy-acid (9) (385 mg, 0.96 mmol) was cyclised in the usual way to give a gum (391 mg). Crystallisation from ether–petrol gave the more polar 3β-*benzyloxy-isomer* (15b) as crystals (95 mg), m.p. 132° (decomp.), $\nu_{max.}$ 1 805 (β-lactone) and 1 730 cm^{-1} (C=O), τ 9.12 (3 H, s, CH_3), 6.58 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, *ax*-3-H), 5.40 (2 H, s, OCH_2Ph), and 2.65 (5 H, s, C_6H_5) (Found: C, 75.2; H, 8.0. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%). The liquors contained a mixture of the 3β-benzyloxy-lactone (15b) and the less polar 3α-benzyloxy-isomer (15a) in which the latter predominated.

(±)-3ξ-*Hydroxy*-17-*oxo*-6,7-*dinor*-5,8-*secoandrostano*-19,9β-*lactone* (16a *and* b).—The benzyl ether (15a and b; liquors from the previous experiment) (298 mg, 0.78 mmol) was hydrogenated in ethyl acetate over 10% palladium–charcoal to give a gum (212 mg, 93%). This gave (from ether–petrol) crystals of the *hydroxy-lactone* (16a and b), m.p. 145° (decomp.), $\nu_{max.}$ 3 598 (OH), 1 802 (β-lactone), and 1 735 cm^{-1} (C=O), τ 9.15 (3 H, s, CH_3), 5.75 (*ca.* 0.4 H, m, $W_{\frac{1}{2}}$ *ca.* 10 Hz, *eq*-3-H), and 6.45 (*ca.* 0.6 H, m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, *ax*-3-H) (Found: C, 69.0; H, 8.3. $C_{17}H_{24}O_4$,0.25H_2O requires C, 68.8; H, 8.3%). The crystals were shown by t.l.c. ($CHCl_3$–MeOH, 19 : 1) to be richer in the more polar (3β-) isomer (16b); the liquors were richer in the less polar (3α-) isomer (16a).

(±)-3α-(*and* β-)*Hydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (21a *and* b).—The hydroxy-lactone (16a and b; liquors from the previous experiment) (162 mg, 0.55 mmol) was pyrolysed in 2-methoxyethanol (5 ml) to give a gum (127 mg, 92%). P.l.c. ($CHCl_3$) afforded (i) the less polar 3α-*alcohol* (21a) (67 mg), $\nu_{max.}$ 3 620 (OH) and 1 722 cm^{-1} (C=O), τ 9.02 (3 H, s, CH_3) and 6.18 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 16 Hz, 3-H) (Found: C, 65.9; H, 9.6. $C_{16}H_{24}O_2$,0.25H_2O requires C, 76.0; H, 9.8%); (ii) the more polar 3β-alcohol (21b) (30 mg), $\nu_{max.}$ 3 620 (OH) and 1 722 cm^{-1} (C=O), τ 9.05 (3 H, s, CH_3) and 6.20 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 16 Hz, 3-H), for which a correct elemental analysis was not obtained.

(±)-3β-*Hydroxy*-17-*oxo*-6,7-*dinor*-5,8-*secoandrostano*-19,9β-*lactone* (16b).—The 3β-benzyloxy-lactone (15b) (30 mg) was hydrogenated in ethyl acetate over 10% palladium–charcoal to give the 3β-hydroxy-lactone (16b) as a white solid (29 mg), $\nu_{max.}$ 3 590 (OH), 1 800 (β-lactone), and 1 730 cm^{-1} (C=O), τ[($CDCl_3$ + few drops $(CD_3)_2SO$] 9.14 (3 H, s, CH_3) and 6.45 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, *ax*-3-H). T.l.c. ($CHCl_3$–MeOH, 19 : 1) showed that the product was identical with the more polar isomer in the mixture of lactones (16a and b) described above.

(±)-3β-*Hydroxy*-6,7-*dinor*-5,8-*secoestr*-9-*en*-17-*one* (21b).—Samples of the 3β-hydroxy-lactone (16b) and of the crystalline mixture of isomers (16a and b) obtained previously were spotted on a t.l.c. plate. The plate was baked on a hotplate, then run in $CHCl_3$ against the two isomers of the hydroxy-ketone (21a and b). This showed that the more polar 3β-hydroxy-lactone (16b) was converted on pyrolysis into the more polar 3β-hydroxy-olefin (21b) and that, conversely, the less polar 3α-hydroxy-lactone (16a) was converted into the less polar 3α-hydroxy-olefin (21a).

(±)-9β,20α-*Dihydroxy*-6,7-*dinor*-5,8-*secopregnan*-19-*oic Acid* (25).—The hydroxy-ketone (23) [5] (4.338 g, 22.1 mmol) in dichloromethane (35 ml) was treated with dry pyridine (4 ml) and chlorotrimethylsilane (4 ml). After 1 h, the mixture was diluted with petrol (75 ml) and filtered through kieselguhr. The residue was washed with petrol and the combined filtrates were evaporated with the aid of toluene to give the trimethylsilyl ether (24) as an oil (6.6 g). The latter was condensed in the usual way with the dilithium derivative of cyclohexanecarboxylic acid (2.83 g, 22.1 mmol). The product (4.35 g, 61%) gave (from chloroform) crystals of the *dihydroxy-acid* (25), m.p. 200—202°, $\nu_{max.}$ (Nujol) 3 440, 3 390, 3 270, and 3 600—2 200 (OH), and 1 682 and 1 665 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.50 (3 H, s, CH_3) and 8.90 (3 H, d, *J* 6 Hz, CHCH_3) (Found: C, 66.6; H, 9.7. $C_{19}H_{32}O_4$,H_2O requires C, 66.6; H, 10.0%).

(±)-9β-*Hydroxy*-20-*oxo*-6,7-*dinor*-5,8-*secopregnan*-19-*oic Acid* (30).—The dihydroxy-acid (25) (3.92 g, 12.1 mmol) in acetone (130 ml) and dimethylformamide (100 ml) was treated dropwise with Jones reagent until all the starting material had been consumed. The mixture was partitioned between water and chloroform and the organic phase was washed with water, dried, and evaporated. The residual oil (containing dimethylformamide) was dissolved in a little acetone and added dropwise to rapidly stirred water (1 l). The resulting white solid was collected and dried, and gave (from ether–dichloromethane) crystals of the *ketone* (30) (3.03 g, 78%), m.p. 175—177°, $\nu_{max.}$ (Nujol) 3 420 and 3 200—2 000 (OH) and 1 680 cm^{-1} (C=O and CO_2H), τ[$(CD_3)_2SO$] 9.56 (3 H, s, CH_3) and 7.91 (3 H, s, $COCH_3$) (Found: C, 70.6; H, 9.3. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%). Extraction of the aqueous liquors yielded the crude ketone (30) as a gum (350 mg, 9%).

(±)-20-*Oxo*-6,7-*dinor*-5,8-*secopregnano*-19,9β-*lactone* (27).—The hydroxy-acid (30) (2.95 g, 9.16 mmol) was cyclised in the usual way and the product (2.588 g, 92%) was crystallised from ether–petrol to give the *lactone* (27) as a white solid, m.p. 121—123°, $\nu_{max.}$ 1 792 (β-lactone) and 1 693 cm^{-1} (C=O), τ 9.35 (3 H, s, CH_3) and 7.86 (3 H, s, $COCH_3$) (Found: C, 74.8; H, 9.1. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%).

(±)-6,7,19-*Trinor*-5,8-*secopregn*-9-*en*-20-*one* (32).—The lactone (27) (1.332 g, 4.38 mmol) was pyrolysed in 2-methoxyethanol (50 ml) to give *compound* (32) as a viscous oil (1.17 g), $\nu_{max.}$ 1 690 cm^{-1} (C=O), τ 9.30 (3 H, s, CH_3) and 7.88 (3 H, s, $COCH_3$) (Found: C, 82.8; H, 11.0. $C_{18}H_{28}O$ requires C, 88.0; H, 10.8%).

(±)-3ξ-*Benzyloxy*-9β,20α-*dihydroxy*-6,7-*dinor*-5,8-*seco*-*pregnan*-19-*oic Acid* (26).—The hydroxy-ketone (23) (1.96 g,

10 mmol) was converted as above into the silyl ether (24), which was condensed in the usual manner with the dilithium derivative of 4ξ-benzyloxycyclohexanecarboxylic acid (49a) (2.34 g, 10 mmol). Chromatography of the product gave the hydroxy-acid (26) as a white solid, m.p. 175° (decomp.), $\nu_{max.}$ 3 635, 3 530, and 3 200—2 300 (OH) and 1 695 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.50 (3 H, s, CH_3), 8.90 (3 H, d, *J* 6 Hz, $CHCH_3$), 5.50 and 5.55 (2 H, both s, OCH_2Ph), and 2.65 (5 H, s, C_6H_5), for which a satisfactory microanalysis was not obtained.

(±)-3ξ-*Benzyloxy*-9β-*hydroxy*-20-*oxo*-6,7-*dinor*-5,8-*seco*-*pregnan*-19-*oic Acid* (31).—The dihydroxy-acid (26) (215 mg, 0.5 mmol) in acetone (25 ml) was oxidised with Jones reagent in the usual manner to give the *acid* (31) as a white solid (196 mg, 91.5%), m.p. 172—179°, $\nu_{max.}$ 3 600, 3 500, and 3 200—2 400 (OH), and 1 700 cm^{-1} (C=O and CO_2H), τ[$(CD_3)_2SO$] 9.56 (3 H, s, CH_3), 7.92 (3 H, s, $COCH_3$), 5.49 (2 H, m, OCH_2Ph), and 2.65 (5 H, s, C_6H_5) (Found: C, 72.2; H, 8.5. $C_{26}H_{36}O_5$,0.25H_2O requires C, 72.1; H, 8.5%).

(±)-3α-(*and* β-)*Benzyloxy*-20-*oxo*-6,7-*dinor*-5,8-*secopregnano*-19,9β-*lactone* (28a *and* b).—The hydroxy-acid (31) (1.046 g, 2.44 mmol) was cyclised in the usual way and the product was subjected to p.l.c. (acetone–petrol, 1 : 4) to give (i) the less polar isomer (210 mg, 21%) which gave (from ether–petrol) crystals of the 3α-*benzyloxy-lactone* (28a), m.p. 116° (decomp.), $\nu_{max.}$ 1 792 (β-lactone) and 1 692 cm^{-1} (C=O), τ 9.37 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), 6.34 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, *eq*-3-H), 5.52 (2 H, m, OCH_2Ph), and 2.67 (5 H, s, C_6H_5) (Found: C, 75.95; H, 8.4. $C_{26}H_{34}O_4$ requires C, 76.1; H, 8.35%); (ii) the more polar isomer (250 mg, 25%), which gave (from ether–petrol) crystals of the 3β-*benzyloxy-lactone* (28b), m.p. 120° (decomp.), $\nu_{max.}$ 1 804 (β-lactone) and 1 698 cm^{-1} (C=O), τ 9.39 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), 6.65 (1 H, m, $W_{\frac{1}{2}}$ 19 Hz, *ax*-3-H), 5.48 (2 H, m, OCH_2Ph), and 2.67 (5 H, s, C_6H_5) (Found: C, 75.2; H, 8.5. $C_{26}H_{34}O_4$,0.25H_2O requires C, 75.2; H, 3.4%).

(±)-3α-*Hydroxy*-20-*oxo*-6,7-*dinor*-5,8-*secopregnano*-19,9β-*lactone* (29a).—The 3α-benzyloxy-lactone (28a) (130 mg, 0.32 mmol) was hydrogenated in ethyl acetate over 10% palladium–charcoal to give a gum (106 mg) which gave (from ether–petrol) crystals of the 3α-*hydroxy-lactone* (29a), m.p. 132° (decomp.), $\nu_{max.}$ 3 580 (OH), 1 795 (β-lactone), and 1 695 cm^{-1} (C=O), τ 9.38 (3 H, s, CH_3), 7.87 (3 H, s, $COCH_3$), and 6.00 (1 H, m, $W_{\frac{1}{2}}$ 14 Hz, *eq*-3-H) (Found: C, 71.1; H, 8.9. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%).

(±)-3β-*Hydroxy*-20-*oxo*-6,7-*dinor*-5,8-*secopregnano*-19,9β-*lactone* (29b).—The 3β-benzyloxy-lactone (28b) (150 mg, 0.37 mmol) was hydrogenated in ethyl acetate over 10% palladium–charcoal to give a gum (138 mg). This gave (from ether–petrol) needles of the 3β-*hydroxy-lactone* (29b), m.p. 144° (decomp.), $\nu_{max.}$ 3 585 (OH), 1 805 (β-lactone), and 1 700 cm^{-1} (C=O), τ 9.38 (3 H, s, CH_3), 7.87 (3 H. s. $COCH_3$), and 6.39 (1 H, m, $W_{\frac{1}{2}}$ 25 Hz, *ax*-3-H) (Found: C, 71.0; H, 8.9. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%).

(±)-3α-*Hydroxy*-6,7,19-*trinor*-5,8-*secopregn*-9-*en*-20-*one* (33a).—The 3α-hydroxy-lactone (29a) (309 mg, 0.96 mmol) was pyrolysed in 2-methoxyethanol (30 ml) to give a gum (283 mg). P.l.c. (acetone–petrol, 1 : 4) afforded *compound* (33a) as a gum (223 mg, 84%), $\nu_{max.}$ 3 630 (OH) and 1 695 cm^{-1} (C=O), τ 9.30 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), and 5.16 (1 H, m, 3-H) (Found: C, 78.1; H, 10.25. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%).

(±)-3β-*Hydroxy*-6,7,19-*trinor*-5,8-*secopregn*-9-*en*-20-*one* (33b).—The 3β-hydroxy-lactone (29b) (499 mg, 1.56 mmol) was pyrolysed in 2-methoxyethanol (50 ml) to give a gum (455 mg). P.l.c. (acetone–petrol, 1 : 4) yielded *compound* (33b) as a gum (310 mg, 72%), $\nu_{max.}$ 3 630 (OH) and 1 695 cm^{-1} (C=O), τ 9.30 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), and 5.16 (1 H, m, 3-H) (Found: C, 77.9; H, 10.3. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%).

1-(1-*Hydroxycyclohexyl*)*cyclohexanecarbonitrile* (36).—Cyclohexanone (1.96 g, 20 mmol) was condensed by the general method outlined above with α-lithiated cyclohexanecarbonitrile (2.18 g, 20 mmol). The product was crystallised from petrol to give crystals (1.85 g, 45%) of the hydroxy-nitrile (36), m.p. 118—119° (lit.,[14] 116—118°), $\nu_{max.}$ 3 600 (OH) and 2 248 cm^{-1} (C≡N) (Found: C, 75.4; H, 10.1; N, 6.6. Calc. for $C_{13}H_{21}NO$: C, 75.3; H, 10.2; N, 6.8%).

1-(*Cyclohex*-1-*enyl*)*cyclohexanecarbonitrile* (38).—The hydroxy-nitrile (36) (430 mg, 2.1 mmol) was heated under reflux in toluene (30 ml) containing toluene-*p*-sulphonic acid (330 mg, 2.1 mmol) for 48 h. The mixture was diluted with dichloromethane, washed with 5% sodium hydrogen carbonate, dried, and evaporated to a light brown gum. P.l.c. (acetone–petrol, 1 : 4) yielded (i) the *olefin* (38) as a mobile oil (110 mg, 28%), $\nu_{max.}$ 2 245 cm^{-1} (C≡N), τ 4.15 (1 H, m, =CH–) (Found: C, 81.5; H, 10.1; N, 7.4. $C_{13}H_{19}N$,0.125H_2O requires C, 81.5; H, 10.1; N, 7.3%); (ii) the starting material (30 mg); (iii) 1-(*cyclohex*-1-*enyl*)-*cyclohexanecarboxamide* (39) (263 mg, 60%) which gave (from ether–petrol) crystals, m.p. 76—78°, $\nu_{max.}$ 3 570 and 3 460 (NH), 1 705 and 1 610 cm^{-1} ($CONH_2$), τ 4.2—4.7 (3 H, m, =CH– and NH_2) (Found: C, 75.3; H, 10.25; N, 6.8. $C_{13}H_{21}NO$ requires C, 75.3; H, 10.2; N, 6.75%).

In a second experiment, the hydroxy-nitrile (36) (1.035 g, 5 mmol) was heated under reflux for 48 h in toluene (50 ml) containing toluene-*p*-sulphonic acid (250 mg, 1.6 mmol). The mixture was adsorbed onto alumina and eluted with dichloromethane to give the olefin (38) (655 mg, 69%).

1-(7-*Oxabicyclo*[4.1.0]*heptan*-1-*yl*)*cyclohexanecarbonitrile* (41).—The olefin (38) (524 mg, 2.77 mmol) in dichloromethane (30 ml) was treated with *m*-chloroperbenzoic acid (85%; 584 mg, 2.9 mmol). The mixture was stirred for 1 h, then shaken with aqueous 5% sodium hydrogen carbonate and water, dried, and evaporated. P.l.c. (CH_2Cl_2) of the residue (647 mg) gave a white solid which was crystallised from petrol to give needles of the *epoxy-nitrile* (41), m.p. 75—76°, $\nu_{max.}$ 2 248 cm^{-1} (C≡N), τ 6.68 (1 H, m, CH–O) (Found: C, 75.9; H, 9.3; N, 6.6. $C_{13}H_{19}NO$ requires C, 76.1; H, 9.3; N, 6.8%).

Reduction of the Epoxy-nitrile (41).—The epoxy-nitrile (41) (410 mg, 2 mmol) in ether (5 ml) was added over 5 min to a stirred solution of sodium (690 mg, 30 mmol) in liquid ammonia (50 ml). After 20 min, ammonium chloride was added to discharge the colour and the ammonia was evaporated off. The residue was partitioned between water and dichloromethane, and the organic phase was washed with water, dried, and evaporated. The residue was chromatographed on alumina (CH_2Cl_2) to give 2-hydroxybi(cyclohexylidene) (46) (246 mg, 68%), which gave (from petrol) crystals, m.p. 102—103° (lit.,[13] 97—99°) (Found: C, 78.2; H, 11.0. Calc. for $C_{12}H_{20}O$,0.25H_2O: C, 78.0; H, 11.2%).

Epoxidation of 1-(*Cyclohex*-1-*enyl*)*cyclohexanecarboxylic Acid.*—(*a*) The unsaturated acid (40) (330 mg, 1.58 mmol) was treated in dichloromethane (25 ml) with *m*-chloroperbenzoic acid (85%; 320 mg, 1.58 mmol). After 3 days the mixture was washed with aqueous 10% sodium sulphite

and water, dried, and evaporated. P.l.c. (CH_2Cl_2) of the residue (346 mg) afforded (7RS,8SR)-8-*hydroxy*-13-*oxadispiro*[5.0.5.2]*tetradecan*-14-*one* (43) (102 mg, 29%), which crystallised from acetone–hexane as prisms, m.p. 116—118°, $\nu_{max.}$ 3 610 (OH) and 1 800 cm^{-1} (β-lactone), τ 5.84 (1 H, m, C*H*OH) (Found: C, 69.3; H, 8.8. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%).

(*b*) The acid (40) (2.08 g, 10 mmol) in dichloromethane (100 ml) was treated as above with *m*-chloroperbenzoic acid (85%; 2.72 g, 8.5 mmol). When the reaction was complete the mixture was divided into three parts.

(i) A small portion was treated with trifluoroacetic acid (12 drops) and left overnight. The solution was washed with water, dried, and evaporated to give a white solid (70 mg), $\nu_{max.}$ 1 760 (γ-lactone) and 1 790 cm^{-1} ($OCOCF_3$). P.l.c. (CH_2Cl_2) yielded a white solid (57 mg) which gave (from petrol) crystals of (1RS,6SR)-1-*hydroxy*-7-*oxabicyclo*-[4.3.0]*nonane*-9-*spirocyclohexan*-8-*one* (44), m.p. 177—178°, $\nu_{max.}$ 3 600 and 3 490 (OH), and 1 760 cm^{-1} (γ-lactone), τ 5.62 (1 H, m, C*H*–OCO–) (Found: C, 69.0; H, 9.0. $C_{13}H_{20}O_4$,0.125H_2O requires C, 68.9; H, 9.0%).

(ii) Half the remaining mixture was shaken successively with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The residue (1.515 g) was heated under reflux in toluene for 6 h. Removal of the solvent left a gummy solid (1.266 g). P.l.c. (CH_2Cl_2) yielded (i) an oil (290 mg) identified as bi(cyclohex-1-enyl) [21] (48); (ii) a white solid (262 mg) which was shown by g.l.c. and spectroscopy to be a mixture of 1,1′-bi(cyclohexyliden)-2-ol [13] (46) and 1-(cyclohex-1-enyl)cyclohexanol [22] (47) in the ratio *ca.* 3 : 7.

(iii) The remainder of the mixture was worked up as in the previous experiment to give the hydroxy-lactone (43).

Pyrolysis of the γ-Hydroxy-β-lactone (43).—The hydroxy-lactone (43) (150 mg, 0.67 mmol) was pyrolysed in 2-methoxyethanol (15 ml) and the product was subjected to p.l.c. (acetone–petrol, 1 : 4) to give the olefin (46) (96 mg, 80%).

4,4-*Ethylenedioxycyclohexanecarboxylic Acid* (50).—Ethyl 4,4-ethylenedioxycyclohexanecarboxylate [23] (51) (28.3 g, 132 mmol) in methanol (100 ml) was treated with a solution of sodium hydroxide (10.5 g, 260 mmol) in water (25 ml) and the solution was heated under reflux for 30 min. After addition of water (150 ml) the methanol was removed *in vacuo* and the residual aqueous solution was stirred with ether (100 ml) and cation-exchange resin AG 50W-X8 (50 g). The resin was filtered off and washed with water and ether. The aqueous phases were separated and extracted with ether. The extracts were combined with the organic phases, washed with water, dried, and evaporated to give the acid [16] (50) (2.32 g, 9%) as an oil which solidified overnight at 1 mmHg; m.p. 50° (Found: C, 57.9; H, 7.55. Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.6%). The aqueous phase was treated with more resin and the acid (50) (15.74 g, 64%) was isolated by extraction with dichloromethane. Finally, the aqueous liquors were evaporated *in vacuo* to give more crude acid (50) (4.57 g, 18.5%; total yield 92%).

1-(1,4-*Dihydroxycyclohexyl*)-4-*oxocyclohexanecarboxylic Acid* (54).—4-Hydroxycyclohexanone (52) (3.42 g, 30 mmol) in dichloromethane (30 ml) was treated with pyridine (5 ml) and chlorotrimethylsilane (5 ml) and the mixture was stirred for 1 h, then diluted with petrol and filtered through kieselguhr. The filtrate was evaporated to low volume, again diluted with petrol, filtered, and finally evaporated to give the silyl ether (53) (5.43 g, 97%) as an oil. The latter was condensed in the usual way with the dilithium derivative of the acid (50) (5.58 g, 30 mmol). The mixture was poured into water and extracted with dichloromethane. The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with dichloromethane to give the acid (50) (1.01 g). The aqueous phase was continuously extracted with ether for 4 h to give a gum (1.35 g) which was a mixture of the acid (50) and the desired product (54). Evaporation of the aqueous phase to low volume resulted in the separation of a solid (1.975 g, 26%) which was recrystallised from ethyl acetate–methanol to give the *hydroxy-acid* (54) as an off-white powder, m.p. 189° (decomp.), $\nu_{max.}$ (Nujol) 3 582, 3 460, 3 355 (OH), and 1 697 cm^{-1} (C=O), τ[$(CD_3)_2SO$] 6.2 (1 H, m, C*H*OH) (Found: C, 60.9; H, 8.05. $C_{13}H_{20}O_5$ requires C, 60.9; H, 7.8%). The residual liquors were continuously extracted with chloroform for several days to give more of the acid (54) as a gum (3.64 g, 47%) which solidified on trituration with ether.

10ξ-*Acetoxy*-13-*oxadispiro*[5.0.5.2]*tetradecane*-3,14-*dione* (55).—The dihydroxy-acid (54) (2.87 g, 11.2 mmol) was kept overnight in pyridine (15 ml) and acetic anhydride (5 ml) and the mixture was poured onto ice, acidified to pH 1 with 6N-hydrochloric acid, and extracted with chloroform. The extracts were washed with water, dried, and evaporated to a gum (3.57 g), which was triturated with ether to give a white solid (1.775 g, 56.5%). Recrystallisation from ether–dichloromethane gave crystals of the *acetoxy-lactone* (55), m.p. 135—137° (decomp.), $\nu_{max.}$ 1 785 (β-lactone) and 1 705 cm^{-1} (C=O and ester), τ 7.95 (3 H, s, $OCOCH_3$) and 5.25 (1 H, m, C*H*OAc) (Found: C, 64.0; H, 7.2. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%).

4′-*Acetoxy*-1,1′-*bi*(*cyclohexyliden*)-4-*one* (57).—The lactone (55) (1.65 g, 5.89 mmol) was pyrolysed in 2-methoxyethanol (35 ml) and the product was recrystallised from petrol to give the *olefin* (57) (1.019 g, 73%) as white crystals, m.p. 97—98°, $\nu_{max.}$ 1 705 cm^{-1} (C=O and ester), τ 7.96 (3 H, s, $OCOCH_3$) and 5.05 (1 H, m, C*H*OAc) (Found; C, 71.2; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.5%). Evaporation of the liquors yielded a pale yellow solid (373 mg, 27%), g.l.c. purity 97.5%.

4′-*Hydroxy*-1,1′-*bi*(*cyclohexyliden*)-4-*one* (56).—The acetate (57) (118 mg, 0.5 mmol) in methanol (25 ml) was treated with a solution of potassium hydrogen carbonate (500 mg) in water (10 ml) and the mixture was heated under reflux for 1 h, then partitioned between water and dichloromethane. The organic phase was dried and evaporated to give a white solid (102 mg) which gave (from petrol–dichloromethane) white crystals of the *hydroxy-ketone* (56), m.p. 119—121°, $\nu_{max.}$ 3 500 (OH) and 1 715 cm^{-1} (C=O), τ 6.10 (1 H, m, C*H*OH) (Found: C, 74.0; H, 9.3. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%).

(±)-3,3-*Ethylenedioxy*-9β,20α-*dihydroxy*-6,7-*dinor*-5,8-*secopregnan*-19-*oic Acid* (58).—The hydroxy-ketone (23) (5.855 g, 30 mmol) was converted as above into the trimethylsilyl ether (24). The latter was condensed in the usual way with the acid (50) (5.1 g, 30 mmol). The product

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was triturated with petrol to remove the acid (50), and yielded the *dihydroxy-acid* (58) as a white solid (7.50 g, 71%), m.p. 85° (decomp.), $\nu_{max.}$ (Nujol) 3 400—2 200 (OH) and 1 683 cm^{-1} (CO_2H), τ[$(CD_3)_2SO$] 9.50 (3 H, s, CH_3), 8.92 [3 H, d, *J* 5 Hz, CH(OH)CH_3], 6.52 [1 H, m, CH·C*H*(OH)-CH_3], and 6.15 (4 H, s, OCH_2CH_2O) (Found: C, 63.4; H, 8.7. $C_{21}H_{34}O_6$,0.875H_2O requires C, 63.3; H, 9.0%).

(±)-*Methyl* 3,3-*Ethylenedioxy*-9β,20α-*dihydroxy*-6,7-*dinor*-5,8-*secopregnan*-19-*oate* (59).—A stirred suspension of the dihydroxy-acid (58) (1.02 g, 2.67 mmol) in ether (100 ml) was treated with an excess of ethereal diazomethane. After 10 min, sufficient acetic acid was added to decolourise the solution, which was then washed with 2N-sodium hydroxide and water, dried, and evaporated to give the *methyl ester* (59) as a white froth (1.07 g, 100%), $\nu_{max.}$ 3 605 (OH) and 1 710 cm^{-1} (ester), τ 9.42 (3 H, s, CH_3), 8.80 [3 H, d, *J* 6 Hz, CH(OH)CH_3], 6.28 (3 H, s, CO_2CH_3), 6.3 [1 H, m, CH·C*H*(OH)CH_3], and 6.10 (4 H, s, OCH_2CH_2O) (Found: C, 66.3; H, 9.1. $C_{22}H_{36}O_6$ requires C, 66.6; H, 9.15%).

(±)-*Methyl* 9β,20α-*Dihydroxy*-3-*oxo*-6,7-*dinor*-5,8-*seco-pregnan*-19-*oate* (60) *and* (±)-*Methyl* 20α-*Hydroxy*-3-*oxo*-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oate* (62).—The hydroxy-ester (59) (777 mg, 1.96 mmol) was heated at 100 °C in 90% formic acid (20 ml) for 45 min. The solvent was removed *in vacuo* with the aid of benzene to give a brown gum (717 mg). P.l.c. (acetone–petrol, 1 : 4) separated this into a less polar (145 mg) and a more polar (320 mg) component.

Further p.l.c. (ether) of the less polar component yielded the *olefin* (62) as a gum (95 mg, 28%), $\nu_{max.}$ 3 600 (OH) and 1 710 cm^{-1} (C=O and ester), τ 9.42 (3 H, s, CH_3), 8.76 [3 H, d, *J* 6 Hz, CH(OH)CH_3], 6.29 (3 H, s, CO_2CH_3), 6.3 [1 H, m, CH·C*H*(OH)CH_3], and 4.37 (1 H, m, =CH–) (Found: C, 70.8; H, 9.0. $C_{20}H_{30}O_4$,0.25H_2O requires C, 70.9; H, 9.1%).

P.l.c. of the more polar component (ether) afforded an off-white froth (256 mg, 37%) which crystallised from ether–petrol–dichloromethane to give the *dihydroxy-ester* (60), m.p. 160—162°, $\nu_{max.}$ 3 600—3 300 (OH) and 1 715 cm^{-1} (ester), τ 9.41 (3 H, s, CH_3), 8.79 [3 H, d, *J* 6 Hz, CH(OH)CH_3], 6.19 (3 H, s, CO_2CH_3), and 6.30 [1 H, m, CH·C*H*(OH)CH_3] (Found: C, 67.4; H, 9.1. $C_{20}H_{32}O_5$,-0.25H_2O requires C, 67.3; H, 9.2%).

Oxidation of the Dihydroxy-ester (59).—(a) *With Jones reagent.* The dihydroxy-ester (59) (100 mg) in acetone (50 ml) was treated with Jones reagent in the usual manner. The product was subjected to p.l.c. (ether) to give (i) the acetal (67) (42 mg, 42%); (ii) *methyl* 9β-*hydroxy*-3,20-*dioxo*-6,7-*dinor*-5,8-*secopregnan*-19-*oate* (66) (41 mg, 46%), m.p. 164—168°, $\nu_{max.}$ 3 580 and 3 540 (OH) and 1 710 cm^{-1} (C=O and ester), τ 9.45 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), and 6.19 (3 H, s, CO_2CH_3) (Found: C, 68.5; H, 8.7 $C_{20}H_{30}O_5$ requires C, 68.5; H, 8.6%).

(b) *With dimethyl sulphoxide—dicyclohexylcarbodi-imide.* A solution of the dihydroxy-ester (59) (100 mg) in dimethyl sulphoxide (0.4 ml) and benzene (0.4 ml) was treated successively with pyridine (0.02 ml), trifluoroacetic acid (0.01 ml), and dicyclohexylcarbodi-imide (150 mg) and the mixture was set aside for 70 h. Benzene (7 ml) was added, followed by a solution of oxalic acid (70 mg) in methanol (1 ml), and the mixture was stirred for 1 h before dilution with water and extraction with dichloromethane. The extracts were washed with 5% sodium hydrogencarbonate, dried, and evaporated. P.l.c. (acetone–petrol, 1 : 4) of the residue gave a white foam (87 mg, 87%) which crystallised from ether–petrol to give the *hydroxy-oxo-ester* (67), m.p. 114—116° (decomp.), $\nu_{max.}$ 3 580 and 3 510 (OH) and 1 695 cm^{-1} (C=O and ester), τ 9.36 (3 H, s, CH_3), 7.89 (3 H, s, $COCH_3$), 6.25 (3 H, s, CO_2CH_3), and 6.07 (4 H, s, OCH_2CH_2O) (Found: C, 66.2; H, 8.6. $C_{22}H_{34}O_6$,0.25H_2O requires C, 66.2; H, 8.7%). Successive addition of 10 mg portions of [$^2H_{27}$]tris(heptafluorodimethyloctanedionato)-europium(III) [Eu(fod)$_3$] to 0.5 ml of a 7% solution of (67) in $CDCl_3$ produced the following downfield shifts in the 18- and 21-H_3 resonances (in p.p.m.):

Eu(fod)$_3$ (mg):	10	20	30	40
Δ (18-H)	−0.30	−0.64	−1.03	−1.35
Δ (21-H)	−0.01	−0.04	−0.12	−0.22

(±)-*Methyl* 20α-*Acetoxy*-3,3-*ethylenedioxy*-9β-*hydroxy*-6,7-*dinor*-5,8-*secopregnan*-19-*oate* (61).—The dihydroxy-ester (59) (6.0 g, 15.3 mmol) was kept overnight in pyridine (25 ml) and acetic anhydride (10 ml). The mixture was partitioned between water and dichloromethane and the organic phase was washed with 5% sodium hydrogencarbonate, dried, and evaporated with the aid of toluene. The residue was chromatographed on silica gel (chloroform as eluant) to give (i) the *acetate* (61) (3.9 g, 58%) which gave (from ether–petrol) crystals, m.p. 118° (softened 108°), $\nu_{max.}$ 3 550 (OH) and 1 710 cm^{-1} (esters), τ 9.40 (3 H, s, CH_3), 8.80 [3 H, d, *J* 6 Hz, CH(OAc)CH_3], 8.01 (3 H, s, $OCOCH_3$), 6.25 (3 H, s, CO_2CH_3), 6.08 (4 H, s, OCH_2CH_2O), and 5.12 [1 H, m, CH·C*H*(OAc)CH_3] (Found: C, 65.7; H, 8.4. $C_{24}H_{38}O_7$ requires C, 65.7; H, 8.7%).

(±)-*Methyl* 20α-*Acetoxy*-3,3-*ethylenedioxy*-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oate* (63).—The hydroxy-ester (61) (100 mg) in pyridine (5 ml) was treated with thionyl chloride (1 ml) and the mixture was left for 70 h, then poured on ice. 5% Sodium hydrogencarbonate was added and the product was extracted into dichloromethane. The extract was washed with water, dried, and evaporated with the aid of toluene. The residue (95 mg, 99%) gave (from ether–petrol) crystals of the *unsaturated ester* (63), m.p. 148.5—150°, $\nu_{max.}$ (CS_2) 1 730 cm^{-1} (esters), τ 9.42 (3 H, s, CH_3), 8.78 [3 H, d, *J* 6 Hz, CH(OAc)CH_3], 8.01 (3 H, s, $OCOCH_3$), 6.34 (3 H, s, CO_2CH_3), 6.08 (4 H, s, OCH_2CH_2O), 5.04 [1 H, m, CH·C*H*(OAc)CH_3], and 4.43 (1 H, m, =CH–) (Found: C, 68.3; H, 8.6. $C_{24}H_{36}O_6$ requires C, 68.5; H, 8.6%).

Hydrolysis of the Acetoxy-ester (63).—(*a*) The diester (63) (420 mg, 1 mmol) in methanol (45 ml) was treated with a solution of potassium hydroxide (1 g) in water (5 ml) and the solution was heated under reflux for 5 h, then left overnight at room temperature. The mixture was partitioned between water and dichloromethane and the organic phase was washed with water, dried, and evaporated to give (±)-*methyl* 3,3-*ethylenedioxy*-20α-*hydroxy*-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oate* (64) as a gum (285 mg, 78%), $\nu_{max.}$ 3 635 (OH) and 1 718 cm^{-1} (ester), τ 9.44 (3 H, s, CH_3), 8.77 [3 H, d, *J* 6 Hz, CH(OH)CH_3], 6.35 [1 H, m, CH·C*H*-(OH)CH_3], 6.24 (3 H, s, CO_2CH_3), 6.08 (4 H, s, OCH_2CH_2O), and 4.40 (1 H, m, =CH–) (Found: C, 70.15; H, 9.1. $C_{22}H_{34}O_5$ requires C, 69.85; H, 9.05%).

The aqueous phase was acidified to pH 5 with 2N-hydrochloric acid and extracted with dichloromethane, and the extracts were washed with water, dried, and evaporated to give (±)-3,3-*ethylenedioxy*-20α-*hydroxy*-6,7-*dinor*-5,8-*seco-pregn*-9(11)-*en*-19-*oic acid* (65) as a white solid (70 mg, 18.5%), m.p. 177.5—181°, $\nu_{max.}$ 3 620 and 3 500—2 200

(OH), and 1 721 and 1 690 cm^{-1} (CO_2H), τ 9.43 (3 H, s, CH_3), 8.78 [3 H, d, *J* 6 Hz, CH(OH)C*H*$_3$], 6.34 [1 H, m, CH·C*H*(OH)CH_3], 6.09 (4 H, s, OCH_2CH_2O), and 4.41 (1 H, m, =CH–) (Found: C, 68.4; H, 8.8. $C_{21}H_{32}O_5$,-0.25H_2O requires C, 68.35; H, 8.9%).

(*b*) The diester (63) (1.905 g, 4.53 mmol) in methanol (50 ml) was treated with a solution of potassium hydroxide (2 g) in water (10 ml). The mixture was heated under reflux for 45 min, then worked up as above to give the hydroxy-ester (64) (1.83 g, 99.5%).

Hydrolysis of the Hydroxy-ester (64).—The ester (64) (190 mg, 0.5 mmol) was heated under reflux for 4 h in dimethylformamide (5 ml) containing sodium cyanide (125 mg). The mixture was partitioned between water and chloroform and the aqueous phase was acidified with 6N-hydrochloric acid and extracted with chloroform. The extracts were washed with water, dried, and evaporated to give the acid (65) as a gum (185 mg, 100%).

(±)-3,20-*Dioxo*-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oic Acid* (68).—The hydroxy-acid (65) (185 mg) in acetone (20 ml) was treated dropwise with Jones reagent until no starting material remained. The mixture was filtered through kieselguhr and the filtrate was treated with 2N-sulphuric acid and set aside overnight. Water was added and the product was extracted into chloroform. The extracts were washed with water, dried, and evaporated to a gum (167 mg). Trituration with ether yielded white crystals of the *dione* (68) (84 mg, 52%), m.p. 153—154°, $\nu_{max.}$ 3 460, 3 050—2 000 (OH), 1 725 [C(17)=O], 1 705 (CO_2H), and 1 700 cm^{-1} [C(3)=O], τ 9.46 (3 H, s, CH_3), 7.87 (3 H, s, $COCH_3$), and 4.27 (1 H, m, =CH–) (Found: C, 71.5; H, 8.1. $C_{19}H_{26}O_4$ requires C, 71.7; H, 8.2%).

(±)-*Methyl* 3,20-*Dioxo*-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oate* (69).—The hydroxy-ester (64) (1.33 g, 3.51 mmol) was treated with Jones reagent, followed by 2N-sulphuric acid, as in the previous experiment. The product was chromatographed on alumina (dichloromethane as eluant) to give the *dioxo-ester* (69) as an oil (811 mg, 69%), $\nu_{max.}$ 1 715 and 1 705 cm^{-1} (C=O and ester), τ 9.45 (3 H, s, CH_3), 7.86 (3 H, s, $COCH_3$), 6.24 (3 H, s, CO_2CH_3), and 4.28 (1 H, m, =CH–) (Found: C, 71.4; H, 8.5. $C_{20}H_{28}O_4$,0.25H_2O requires C, 71.3; H, 8.5%).

Acetalisation of the Dioxo-ester (69).—The ester (69) (745 mg, 2.25 mmol) was heated at 90 °C and 1 mmHg in ethylene glycol (30 ml) containing toluene-*p*-sulphonic acid (200 mg) for 1 h. 5% Sodium hydrogencarbonate was added and the mixture was extracted with dichloromethane. The extracts were washed with water, dried, and evaporated to a pale yellow gum. P.l.c. (acetone–petrol, 1 : 4) gave (i) *methyl* 3,3:20,20-*bis*(*ethylenedioxy*)-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oate* (71) as a gum (707 mg, 75%), $\nu_{max.}$ 1 712 cm^{-1} (ester), τ 9.34 (3 H, s, 18-H_3), 8.69 (3 H, s, 21-H_3), 6.32 (3 H, s, CO_2CH_3), 6.06 (8 H, s, 2 × OCH_2CH_2O), and 4.40 (1 H, m, =CH–) (Found: C, 68.7; H, 8.8. $C_{24}H_{36}O_6$ requires C, 68.5; H, 8.6%); (ii) the 3-monoacetal (70) as a gum (106 mg, 12.5%), $\nu_{max.}$ 1 718 (ester) and 1 700 cm^{-1} (C=O), τ 9.48 (3 H, s, CH_3), 7.87 (3 H, s, $COCH_3$), 6.32 (3 H, s, CO_2CH_3), 6.06 (4 H, s, OCH_2CH_2O), and 4.34 (1 H, m, =C*H*–), for which a correct elemental analysis was not obtained.

3,3:20,20-*Bis*(*ethylenedioxy*)-6,7-*dinor*-5,8-*secopregn*-9(11)-*en*-19-*oic Acid* (72).—The ester (71) (665 mg, 1.6 mmol) was heated under reflux for 6 h in dimethylformamide (25 ml) containing sodium cyanide (400 mg). The mixture was partitioned between water and dichloromethane and the aqueous phase was acidified with 2N-hydrochloric acid and extracted with chloroform. The extract was washed with water, dried, and evaporated to a pale yellow gum (635 mg) which was boiled with petrol. Insoluble material was filtered off, and the filtrate was evaporated to a gum (575 mg, 89%). This gave (from petrol) prisms of the *acid* (72), m.p. 147—148°, $\nu_{max.}$ 3 500 (OH) and 1 732 cm^{-1} (CO_2H), τ 9.32 (3 H, s, 18-H_3), 8.72 (3 H, s, 21-H_3), 6.08 (8 H, s, 2 × OCH_2CH_2O), and 4.32 (1 H, m, =CH–) (Found: C, 67.8; H, 8.6. $C_{23}H_{34}O_6$ requires C, 67.95; H, 8.4%).

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