Stereospecific Synthesis of (22*R*)-22-Hydroxycholesterol and (22*R*)-Cholesta-5,24-diene-3β,22-diol

By **J. Philip Poyser** and **Guy Ourisson,*** Laboratoire de Chimie Organique des Substances Naturelles Associé au C.N.R.S., Institut de Chimie, Université Louis Pasteur, I, Rue Blaise Pascal, 67008–Strasbourg, France

A stereospecific method previously developed in the triterpene series for the synthesis of inotodiol (I) is shown to be equally valid in the steroid series. Addition of the appropriate Grignard reagent to (22ξ)-22,23-epoxy-6β-methoxy-3α,5α-cyclo-24-norcholane (VI) and (VII) [derived from the bromohydrins (Va—c)] furnished, after regeneration of the 5-en-3β-ol system, the title compounds in good yields, almost stereospecifically. It follows that electrophilic addition to the double bond occurs as previously defined for 24,25,26,27-tetranorlanosta-8,22-dien-3β-yl acetate, the (22*S*)-23-bromo-22-hydroxy- and (22*R*)-22-bromo-23-hydroxy-isomers being the major bromohydrins formed.

ADDITION of alkyl- or alkenyl-magnesium halides to isolated steroidal or triterpenoid 22-aldehydes is known to lead predominantly to the 22α-alcohol.[1,†] This epimer is also the major product (though less markedly) from the hydride reduction of the corresponding 22-ketones.[1,2] Since (22*R*)-22-hydroxycholesterol and the related 23,24-didehydro-compound (IIIa) were required for tumour-inhibitory assays, the stereospecific procedure recently developed in these laboratories for the synthesis of inotodiol (I) was adopted for their preparation.

Conversion of the known 22-aldehyde (IVa) (obtained from stigmasterol in three steps[3]) into the 24-norchol-22-ene derivative (IVb) was smoothly carried out by a Wittig reaction with methylenetriphenylphosphorane in 65% yield. Treatment with *N*-bromosuccinimide in aqueous tetrahydrofuran gave a mixture of three bromohydrins, analogous to those isolated in the triterpene series.[4,5] Only the major, least polar isomer (Va) was fully characterised, though correlations were effected by basic hydrolysis of each one. Cyclisation of the bromohydrin mixture gave, as before,[4,5] predominantly the (22*S*)-22,23-epoxide (VI), containing *ca.* 5% of the (22*R*)-epimer (VII) only, provided that the mixture was first partially freed from the bromohydrin of intermediate polarity (Vb). In contrast to the previous case, the (22*S*)-epimer (VI) was the more polar epoxide. Peroxyacid oxidation of the olefin (IVb) in ether[6] gave the less polar epoxide (VII) as the major product (*ca.* 2 : 1 estimated by t.l.c.) as expected. Separation could be achieved by t.l.c. (five elutions in toluene). The n.m.r. spectra of the two epimers exhibited characteristic peaks for the oxiran protons, as observed in the tetranorlanost-8-ene series,[5] and thus, despite the complicating factor of the hydrogen α to the 6β-methoxy-group, confirmed the potential use of n.m.r. for distinguishing between such epimeric pairs of epoxides.

The preparation of the epoxides was also carried out *via* iodoacetoxylation[1] of the olefin (IVb), since the formation of the iodonium ion was expected to be even more stereoselective than that of the bromonium ion. However, there was no noticeable improvement in the ratio of the resulting epoxides, although there was an increase in the regiospecificity of the opening of the intermediate iodonium ion. On a small scale, the iodoacetate (Vd) was predominant over the isomer (Ve) by 3 : 1, and in one large scale experiment, (Vd) was formed almost completely regiospecifically.

† Where α refers to the configuration derived using the Fischer Convention.

[1] D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 1584; D. H. R. Barton, J. P. Poyser, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 53, and references cited therein.

[2] E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 103.

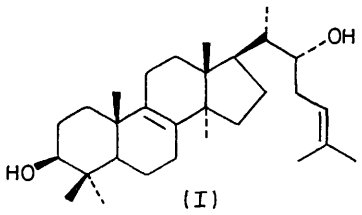
[3] R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, 1970, **15**, 113.

[4] J. P. Poyser, F. de Reinach Hirtzbach, and G. Ourisson, *Tetrahedron*, 1974, in the press.

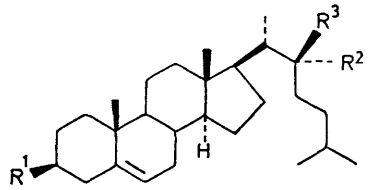
[5] J. P. Poyser, F. de Reinach Hirtzbach, and G. Ourisson, *J.C.S. Perkin I*, 1974, 378.

[6] G. Ponsinet and G. Ourisson, *Bull. Soc. chim. France*, 1967, **12**, 4452.

The crystalline mixture of epoxides (derived from the bromohydrins or iodoacetates) gave one major oily



(I)



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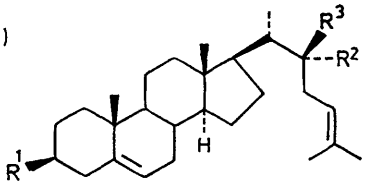
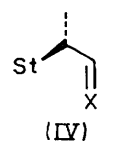


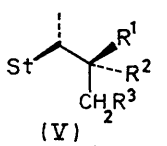
(III)

	R^1	R^2	R^3
a;	OH	OH	H
b;	OAc	OH	H
c;	OAc	OAc	H
d;	OH	H	OH
e;	OAc	H	OH
f;	OAc	H	OAc

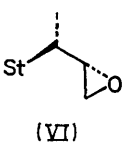


(IV)

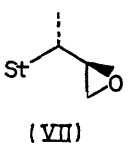
a; X = O
b; X = CH_2



(V)

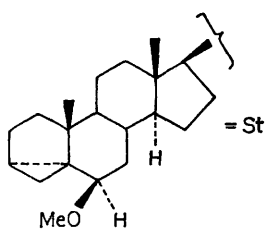


(VI)



(VII)

	R^1	R^2	R^3
a;	H	OH	Br
b;	OH	H	Br
c;	Br	H	OH
d;	H	OAc	I
e;	I	H	OAc



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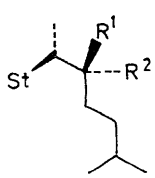
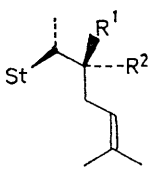


(VIII)



(X)

	R^1	R^2
a;	H	OH
b;	OH	H
c;	O	

product (VIIIa) (70% yield) with isobutylmagnesium bromide in tetrahydrofuran. This was also isolated as a minor product (12%) of the reaction of the aldehyde (IVa) with isopentylmagnesium bromide, the less polar, major product being the epimeric (VIIIb) (72% yield). That these compounds were the C-22 epimers was shown by Jones oxidation [7] to the known ketone (VIIIc),[8] followed by lithium aluminium hydride reduction. The resulting mixture of alcohols contained (VIIIb) and (VIIIa) in the ratio 3 : 1. It is interesting to note the large difference in polarity (R_F 0·33 and 0·22 respectively in ethyl acetate–hexane, 3 : 17). The (22*S*)-alcohol is also the less polar epimer, which (as for the epoxides) represents an inversion with respect to the usual polarities of such pairs of 22-alcohols. This inversion seems to be related to the presence of the methyl ether linkage, since, with the exception of the 3-methyl ethers of (IIa) and (IId),[2] all other examples reported show the less polar epimer to be the (22*R*)-alcohol (*e.g.* refs. 2, 4, and 5).

The *i*-alcohol (VIIIa) was readily converted by the standard procedure [9] into the 5-en-3β-yl acetate (IIb) and the known corresponding diacetate (IIc), and thence by basic hydrolysis into the first title compound (IIa) [8·6% overall yield from the aldehyde (IVa), compared to 4·3% *via* the direct Grignard reaction]. Although the natural product [10] was not available, (IIa) was identical with an authentic sample of synthetic (IIa), prepared by Caspi and his colleagues.[2]

In the same way, (VIIIb) afforded (IIe, f, and d) [55% overall yield from (IVa) by the direct method].

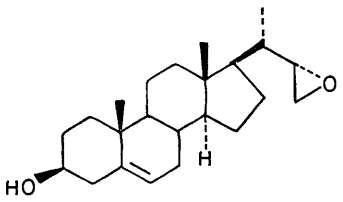
Treatment of the crystalline epoxides with isobutenylmagnesium bromide in tetrahydrofuran gave the (22*R*)-*i*-alcohol (Xa), readily separated from a small amount of (Xb). Regeneration of the 5-en-3β-ol system as above gave the 3β-acetate (IIIb) and the diacetate (IIIc) [the latter requiring purification by conversion into the diol (IIIa), chromatography, and reacetylation]. The Δ^{25}-isomer of (Xa) was present in low yield in (Xa), as in the inotodiol synthesis,[4] but was eliminated chromatographically after the ring-opening as the isomer of (IIIa) of significantly lower R_F value. Basic hydrolysis of (IIIb) or (IIIc) gave the second title compound (IIIa) in overall 20% yield from (IVa). The same sequence of reactions carried out on an impure sample of (Xa) gave in addition a less polar component, (22*S*)-22,23-epoxy-24-norchol-5-en-3β-ol (IX). This presumably arose from the bromohydrins (Va) and (Vc) formed during the Grignard reaction.[5] The n.m.r. spectrum of (IX) clearly showed the low field signals due to the epoxide protons again validating the use of n.m.r. spectroscopy for distinguishing such epimeric epoxides.

The impure (22*S*)-*i*-alcohol (Xb) was also treated as above to give a small sample of (22*S*)-cholesta-5,24-diene-3β,22-diol (IIId).

For the epimeric pairs of alcohols (IIa and d), (IIb

[7] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. L. C. Weedon, *J. Chem. Soc.*, 1946, 39.
[8] F. S. Prout and Z. F. Chmielewicz, *J. Org. Chem.*, 1959, **24**, 308.
[9] J. A. Steele and E. Mosettig, *J. Org. Chem.*, 1963, **28**, 571.
[10] A. Stabursvik, *Acta Chem. Scand.*, 1953, **7**, 1220.

and e), (VIIIa and b), and (IIIa and d), the (22*R*)-epimers had the expected, more positive molecular rotations, as observed in all previously reported cases.[5]



(IX)

The characteristic mass spectral fragmentation noted in the case of inotodiol and related compounds [4] (*m/e* 99 for 24-en-22-ols, and 109 for 24-en-22-yl esters) were again observed for the 22-acetate (IIIc), and for the 22-alcohols (IIIa), (IIIb), and (Xa), though perhaps significantly not for the (22*S*)-alcohol (IIId).

It is clear from the present syntheses that electrophilic addition to the double bond of 6β-methoxy-3α,5α-cyclo-24-norchol-22-ene (IVb) occurs in an analogous manner to that defined completely for the tetranorlanosta-8,22-diene system.[5] In the absence of neighbouring polar groups therefore, the present method is general for both the steroid and the triterpene series.

EXPERIMENTAL

For technical details, see ref. 4. '... chromatography (*x* g)(*y* : *z*) ...' refers to columns of silica gel (*x* g) eluted with hexane–ethyl acetate (*y* : *z*). I.r. spectra were recorded on a Perkin-Elmer 177 spectrophotometer.

6β-*Methoxy*-3α,5α-*cyclo*-24-*norchol*-22-*ene* (IVb).—n-Butyl-lithium (14·8 ml of a 2·25M solution in hexane) was added to a stirred suspension of methyltriphenylphosphonium bromide [11] (13·09 g, 36·6 mmol) in sodium-dried ether (150 ml) under argon at room temperature. After 2 h, the aldehyde [3] (IVa) (11·47 g, 33·3 mmol) in dry tetrahydrofuran (75 ml) was introduced, and the mixture refluxed for 17 h, filtered, and evaporated. The crude product (26·5 g) was chromatographed (300 g) [hexane–benzene (1 : 1)] to yield the *olefin* (IVb) (7·24 g, 63·5%), m.p. (microneedles) 47—49°, $[\alpha]_D^{20}$ +34° (*c* 13·2), $\nu_{max.}$ 1638, 1102, and 908 cm^{-1}, τ 4·3 (1H, m, 22-H), 5·07 (1H, dd, *J* 8·5 and 2·5 Hz, 23-H), 5·28 (1H, d, *J* 2·5 Hz, 23-H), 6·70 (3H, s), 7·26 (1H, t, *J* 3 Hz, 6α-H), 8·98 (3H, d, *J* 6 Hz), 8·98 (3H, s), 9·26 (3H, s), and 9·36—9·69 (cyclopropyl protons), *m/e* 342 (M^+), 327, 310 (M^+ — MeOH), 287 (100%, M^+ — side-chain from C-17), 255, 107, 105, 95, 93, and 55 ($MeCHCH{=}CH_2^+$) (Found: C, 84·1; H, 11·3. $C_{24}H_{38}O$ requires C, 84·15; H, 11·2%).

Epoxidation of the Olefin (IVb).—(a) *Using* N-*bromosuccinimide in aqueous tetrahydrofuran.* As described for a similar transformation,[1] the olefin (IVb) (2·28 g, 6·7 mmol) was converted into a mixture of three bromohydrins (Va—c) (6 : 1 : 4 in increasing order of polarity) analogous to that obtained in the tetranorlanostane series.[5] Chromatography (95 g) (9 : 1) gave first (22S)-23-*bromo*-6β-*methoxy*-3α,5α-*cyclo*-24-*norcholan*-22-*ol* (Va) (1·14 g, 39%), m.p. (chloroform–methanol, chunks) 117—121°, $[\alpha]_D^{20}$ +30·5° (*c* 2·4), $\nu_{max.}$ 3405 and 1073 cm^{-1}, τ 6·09br (1H, m, 22-H), 6·51 (2H, d, *J* 3 Hz), 6·69 (3H, s), 7·23 (1H, t, *J* 3 Hz), 7·58br (1H), 8·98, 9·12, and 9·26 (methyls), and 9·36—9·68 (cyclopropyl protons), *m/e* 440/438 (M^+), 425/423, 408/406, 385/383 (100%), and 303 (Found: C, 65·55; H, 8·8; Br, 18·2. $C_{24}H_{39}BrO_2$ requires C, 65·6; H, 8·9; Br, 18·2%). Treatment of (Va) with methanolic sodium hydroxide gave only the (22*S*)-22,23-epoxide (VI), described below. Next eluted was a partially separated bromohydrin (Vb) (168 mg; <6%) as in the tetranorlanostane series. After repurification by column chromatography, the oil showed $\nu_{max.}$ 3425, 1098, 1040, 1017, and 756 cm^{-1}, τ 5·66br (1H, m, 22-H), 6·25 (2H, m), 6·69 (3H, s), 7·23 (1H, t, *J* 3 Hz, 6α-H), 8·82, 8·94, 8·98, and 9·27 (methyls), and 9·36—9·68 (cyclopropyl protons), *m/e* as described for (Va) (Found: M^+, 438·2132. $C_{24}H_{39}BrO_2$ requires *M*, 438·2134) The epoxide (VII) was the major product of basic hydrolysis. Further elution afforded the (22R)-22-*bromo*-23-*hydroxy-epimer* (Vc) (705 mg, 24%) as a gum or foam (even after further chromatography), $\nu_{max.}$ 3420 and 1090 cm^{-1}, τ 5·74 (1H, 4 lines, apparent *J* 6 Hz, 22-H), 6·15br (2H, d, *J* 6 Hz), 6·66 (3H, s), 7·21 (1H, t, *J* 3 Hz), 7·63br, 8·97, 9·07, and 9·23 (methyls), and 9·35—9·68 (cyclopropyl protons), *m/e* identical with that of (Va) (Found: M^+, 438·2123. $C_{24}H_{39}BrO_2$ requires *M*, 438·2134). The epoxide (VI) was the sole product on treatment with methanolic sodium hydroxide.

Combination of all fractions containing (Va) and (Vc), followed by cyclisation with methanolic sodium hydroxide [4] gave after chromatography (39 : 1) a crystalline mixture of the (22*S*)-22,23-epoxide (VI) containing *ca.* 5% of the less polar (22*R*)-epimer (total yield with respect to the bromohydrins, 86%). This mixture was used for the Grignard reactions. It could, however, be separated by t.l.c. (6 elutions in toluene), to give (22*S*)-22,23-*epoxy*-6β-*methoxy*-3α,5α-*cyclo*-24-*norcholane* (VI), m.p. (chloroform–methanol, needles) 100—104°, $[\alpha]_D^{20}$ +40° (*c* 1·6), $\nu_{max.}$ 1102, 1014, and 838 cm^{-1}, τ 6·69 (3H, s), 7·24 [3H, m, 6α-H (t) and 2 oxiran-H], 7·61 (1H, dd, *J* 3 and 5 Hz, oxiran-H), 8·98, 9·00, and 9·28 (methyls), and 9·37—9·70 (cyclopropyl protons), *m/e* 358 (M^+), 343, 326, and 303 (100%) (Found: C, 80·4; H, 10·8. $C_{24}H_{38}O_2$ requires C, 80·4; H, 10·7%).

(b) via *Iodoacetoxylation.* The olefin (IVb) (342 mg, 1 mmol) on iodoacetoxylation according to the method described previously [1] for 45 min gave a crude product (525 mg) as a foam, part of which (103 mg) was converted into the epoxides (39 mg, 56%) in the usual way, the ratio of (VI) to (VII) being as for the bromohydrins. The remaining material was chromatographed (16 g) (19 : 1) to give first (22S)-22-*acetoxy*-23-*iodo*-6β-*methoxy*-3α,5α-*cyclo*-24-*norcholane* (Vd) (209 mg, 49%) as an oil, $\nu_{max.}$ 1745, 1240, 1025, and 972 cm^{-1}, τ 4·86 (1H, m, 22-H), 6·66 (3H, s), 6·76 (2H, d, *J* 12 Hz), 7·23 (1H, t, *J* 2·5 Hz, 6α-H), 7·91 (3H, s), 8·98, 9·02, 9·13, and 9·29 (methyls), and 9·36—9·69 (cyclopropyl protons), *m/e* 528 (M^+), 513, 496, 473 (100%), 470, 437, 309 (M^+ — MeOH — I — AcOH), 121, 107, 105, and 43 (Found: M^+, 528·2100. $C_{26}H_{41}IO_3$ requires *M*, 528·2102). Further elution gave (22R)-23-*acetoxy*-22-*iodo*-6β-*methoxy*-3α,5α-*cyclo*-24-*norcholane* (Ve) (78 mg, 18%) as an oil, $\nu_{max.}$ 1740, 1238, 1090, 1022, and 970 cm^{-1}, τ 5·63 (3H, m, 22-H and 23-H_2), 6·67 (3H, s), 7·23 (1H, t, *J* 3 Hz, 6α-H), 7·93 (3H, s), 8·97, 9·09, and 9·21 (methyls), and 9·27—9·68 (cyclopropyl protons), *m/e* 528

[11] N. A. Milas and C. P. Priasing, *J. Amer. Chem. Soc.*, 1957, **79**, 6295; C. S. Marvel and E. J. Gall, *J. Org. Chem.*, 1959, **24**, 1494.

(M^+), 513, 496 (M^+ − MeOH, 100%), 473, 470, 418, 401, 386, 369, 309, 139, 128, and 43 (Found: M^+, 528·2100. $C_{26}H_{41}IO_3$ requires M, 528·2102).

Using the olefin (IVb) (3·42 g, 10 mmol) and stirring for 5 h, only (Vd) was present in a significant amount in the product, though the yield (1·3 g, 25%) was considerably lower than in other more typical experiments.

(c) *By peroxyacid oxidation.* The olefin (IVb) (171 mg, 0·5 mmol) in sodium-dried ether [6] (25 ml) was stirred at 0° during the addition of *p*-nitroperoxybenzoic acid (0·55 mmol), and then stirred at room temperature for 24 h. Evaporation and t.l.c. (5 elutions in toluene) allowed the separation of the epimeric epoxides. The more polar, minor component (38·5 mg, 21·5%) was identical with the (22*S*)-epimer (VI) described above. The less polar component was pure (22R)-22,23-*epoxy*-6β-*methoxy*-3α,5α-*cyclo*-24-*norcholane* (VII) (77·5 mg, 43·3%), m.p. (chloroform–methanol, needles) 124—127°, $[\alpha]_D^{20}$ +30·5° (*c* 1·5), $\nu_{max.}$ 1193, 911, and 823 cm^{-1}, τ 6·67 (3H, s), 7·32 (4H, m, 6α-H and 3 oxiran-H), 8·88, 8·96, and 9·28 (methyls), and 9·35—9·68 (cyclopropyl protons), *m/e* as for (VI) (Found: C, 80·45; H, 10·6. $C_{24}H_{38}O_2$ requires C, 80·4; H, 10·7%).

(22R)-6β-*Methoxy*-3α,5α-*cyclocholestan*-22-*ol* (VIIIa).—Using the method described previously,[4] the epoxide mixture [*ca.* 95% of (VI)] (1·042 g) was added to isobutylmagnesium bromide. After 50 h, the same work-up and chromatography (43 g) (19 : 1 and 9 : 1) afforded the (22R)-22-*alcohol* as an oil (847 mg, 70%), $[\alpha]_D^{20}$ +47° (*c* 0·4), $\nu_{max.}$ 3610, 3440, 1095, 1075, and 1018 cm^{-1}, τ 6·32br (1H, 22-H), 6·68 (3H, s), 7·24 (1H, t, *J* 3 Hz, 6α-H), 8·98, 9·04, 9·08—9·15, and 9·26 (methyls), and 9·37—9·63 (cyclopropyl protons), *m/e* 416 (M^+), 401, 384, 361 (100%), and 284 (Found: M^+, 416·3652. $C_{28}H_{48}O_2$ requires M, 416·3654).

No trace of the (22*S*)-22-alcohol (see below) was detected.

(22R)-22-*Hydroxycholest*-5-*en*-3β-*yl Acetate* (IIb) *and* (22R)-*Cholest*-5-*ene*-3β,22-*diyl Diacetate* (IIc).—The *i*-alcohol (VIIIa) (732 mg) in glacial acetic acid (90 ml) containing zinc acetate [9] (9 g; freshly fused and ground) was heated under reflux under argon for 1 h. No change in R_F value was observed for most of the material. The mixture was diluted with chloroform, washed with water until neutral, dried, filtered, and evaporated. Chromatography (34 g) (97 : 3 and 19 : 1) furnished first the known diacetate (IIc) (108 mg, 13%), m.p. (methanol, platelets) 95—97°, $[\alpha]_D^{20}$ −30° (*c* 2·0) (lit.,[2] m.p. 102°, $[\alpha]_D^{20}$ −37·5°), $\nu_{max.}$ 1738, 1237, 1034, and 1020 cm^{-1}, τ 4·63br (1H, m, 6α-H), 5·17br (1H, m, 22-H), 5·47br (1H, 3α-H), 7·98 (6H, s), and 8·98, 9·03, 9·08, 9·14, 9·18, and 9·33 (methyls), *m/e* 426 (M^+ − AcOH, 100%), 411, 366, 351, and 43 (Found: C, 76·4; H, 10·5. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·35%). Further elution gave the 3β-*monoacetate* (IIb) (366 mg, 43%), m.p. (chloroform–methanol, needles) 142—143·5°, $[\alpha]_D^{20}$ −41° (*c* 2·3), $\nu_{max.}$ 3540, 3310, 1738, 1719 (H-bonded acetate carbonyl), 1256, and 1035 cm^{-1}, τ 4·63br (1H, d, *J* 4 Hz), 5·4br (1H, m, 3α-H), 6·37br (1H, m, 22-H), 6·52 (0·2H, s, MeOH of crystallisation), 7·98 (3H, s), and 8·98, 9·03, 9·06, 9·15, and 9·31 (methyls), *m/e* 384 (M^+ − AcOH, 100%), 369, 366, 351, 145, 55, and 43 (Found: C, 78·2; (H, 10·9. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). The yield of potential diol precursors was 56%.

(22R)-*Cholest*-5-*ene*-3β,22-*diol* (IIa).—The monoacetate diol (IIb) (290 mg) in sodium-dried ether (200 ml) at 0° was treated with lithium aluminium hydride (190 mg), and stirred at room temperature for 4 h. The usual work-up and chromatography (12 g) (4 : 1) provided the diol (168 mg, 64%), m.p. (ethyl acetate, needles) 183—185°, $[\alpha]_D^{20}$ −33° (*c* 1·4) (lit.,[10] m.p. 186°, $[\alpha]_D$ −39°, lit.,[2] m.p. 182°, $[\alpha]_D$ −38°), $\nu_{max.}$ 3340, 1052, and 1024 cm^{-1} (identical with that reported by Caspi and his co-workers [4] in the region 1100—700 cm^{-1}), τ 4·65br (1H, m), 6·4br (2H, m), and 8·99, 9·03, 9·06, 9·14, and 9·30 (methyls), *m/e* 402 (M^+), 384, 369, 351, 302 (100%), 213, 191, 145, 107, and 105 (Found: C, 80·3; H, 11·5. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%). The overall yield from the aldehyde (IVa) is 8·6%. Admixture of (IIa) and an authentic synthetic sample [2] did not depress the m.p. Their mass spectra were identical.

(22S)- *and* (22R)-6β-*Methoxy*-3α,5α-*cyclocholestan*-22-*ol* (VIIIb) *and* (VIIIa).—The aldehyde (IVa) (6·88 g, 20 mmol) in tetrahydrofuran (75 ml) was added at 0° under argon with stirring to isopentylmagnesium bromide (0·1 mol) in tetrahydrofuran (30 ml). Stirring was continued for 15 min at room temperature, and the reaction terminated in the normal way. The crude product was chromatographed (236 g) (19 : 1 and 9 : 1) to give first the (22S)-*alcohol* (VIIIb) (6·0 g; 72%) as an oil, $[\alpha]_D^{20}$ +33° (*c* 2·5), $\nu_{max.}$ 3400, 1096, 1080, and 755 cm^{-1}, τ 6·37br (1H, 22-H), 6·69 (3H, s), 7·3br (1H, t, *J* 3 Hz), 8·98, 9·07, 9·16, and 9·28 (methyls), and 9·36—9·67 (cyclopropyl protons), *m/e* identical with that of (VIIIa) (Found: M^+, 416·3652. $C_{28}H_{48}O_2$ requires M, 416·3654). Further elution afforded the (22*R*)-epimer (VIIIa) (990 mg, 12%), identical with the material isolated by the stereospecific route described above. This direct method represents a conversion of the aldehyde (IVa) into the (22*R*)-3β,22-diol (IIa) in 4·3% overall yield.

Oxidation of the i-*Alcohols* (IIa) *and* (IIb).—The epimeric relationship of the alcohols was confirmed by Jones oxidation [7] of either (502 mg) to the known 6β-methoxy-3α,5α-cyclocholestan-22-one (VIIIc) [8] obtained after chromatography (15 g) (97 : 3) as an oil (348 mg; 70%), $[\alpha]_D^{20}$ +18° (*c* 7·0) (lit.,[8] $[\alpha]_D^{21}$ +26—30°), $\nu_{max.}$ 1711, 1097, 1016, and 756 cm^{-1}, τ 6·68 (3H, s), 7·25br (1H, t, *J* 3 Hz), 7·59 (3H, m), 8·86, 8·97, 9·07, 9·16, and 9·26 (methyls), and 9·36—9·7 (cyclopropyl protons), *m/e* 414 (M^+), 399, 382, 359 (100%), 283 (382 − side-chain from C-20), and 71 (Found: M^+, 414·3476. $C_{28}H_{46}O_2$ requires M, 414·3498).

Lithium aluminium hydride reduction at 0° in sodium-dried ether converted the *i*-ketone (VIIIc) into a mixture of the epimeric alcohols (VIIIa and b) in which the less polar (22*S*)-epimer (VIIIb) predominated by *ca.* 3 : 1 (as estimated by t.l.c.).

(22S)-22-*Hydroxycholest*-5-*en*-3β-*yl Acetate* (IIa) *and* (22S)-*Cholest*-5-*ene*-3β,22-*diyl Diacetate* (IIf).—The (22*S*)-*i*-alcohol (VIIIb) (3·35 g) was refluxed under argon for 1 h with freshly fused and powdered zinc acetate (14·2 g) in glacial acetic acid (250 ml).[9] T.l.c. showed the disappearance of (VIIIb), the major product being much more polar than (VIIIb) and more polar than (IIb). The reaction was worked up as described above, and the product chromatographed (107 g) (39 : 1, 19 : 1, and 9 : 1) to yield first the known diacetate (IIf) (426 mg, 11%), m.p. (methanol, plates) 143—145°, $[\alpha]_D^{20}$ −57° (*c* 1·0) (lit.,[4] m.p. 146°, $[\alpha]_D^{20}$ −59°), $\nu_{max.}$ 1736, 1733, 1251, 1238, 1032, and 1015 cm^{-1}, τ 4·58br (1H, m, 6α-H), 5·09 (1H, m, 22-H), 5·38br (1H, 3α-H), 7·96 (6H, s), and 8·97, 9·07, 9·16, and 9·31 (methyls), *m/e* as for (IIc) (Found: C, 76·7; H, 10·3. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·35%). Continued elution afforded the 3β-*monoacetate* (IIe) (2·762 g, 77%), m.p. (chloroform–methanol, needles) 162—164°, $[\alpha]_D^{20}$

−54° (*c* 1·5), $\nu_{max.}$ 3450—3470, 1727, 1711 (H-bonded acetate carbonyl), 1265, and 1034 cm^{-1}, τ 4·59br (1H, m, 6-H), 5·39br (1H, m, 3α-H), 6·35br (1H, m, 22-H), 7·98 (3H, s), and 8·96, 9·05, 9·14, and 9·30 (methyls), *m/e* as for (IIb) (Found: C, 78·5; H, 11·0. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). The yield of potential (22*S*)-3β,22-diol precursors was 88%.

(22S)-*Cholest*-5-*ene*-3β,22-*diol* (IId).—The monoacetate (IIe) (505 mg) was treated by the procedure already described to give after chromatography (15 g) (7 : 3) the (22*S*)-3β,22-diol (IId) (395 mg, 86%), m.p. (methanol, needles) 182—183°, $[\alpha]_D^{20}$ −54° (*c* 1·0) (lit.,[4] m.p. 180°, $[\alpha]_D$ −54°), $\nu_{max.}$ 3320 cm^{-1}, identical with that reported by Caspi and his co-workers [4] in the region 1100—700 cm^{-1}, τ 4·65br (1H, m, 6-H), 6·41br (2H, m, 3α- and 22-H), and 9·00, 9·07, 9·16, and 9·31 (methyls), *m/e* 402 (M^+, 100%), and fragmentation as for (IIa) (Found: C, 80·8; H, 11·4. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%). The overall yield of (IId) from the aldehyde (IVa) was 54·7%.

(22R)-6β-*Methoxy*-3α,5α-*cyclocholesta*-5,24-*dien*-22-*ol* (Xa).—According to the procedure described for the synthesis of inotodiol,[4] the epoxide mixture [*ca.* 95% (VI); 1·115 g] was reacted with isobutenylmagnesium bromide in tetrahydrofuran under argon at room temperature for 63 h. Work-up as before and chromatography (37 g) (19 : 1 and 37 : 3) gave first an impure sample of the (22*S*)-22-alcohol (123 mg), not characterised, but converted into (22*S*)-3β,22-diol (IId) (see below). The major product was the more polar (22*R*)-22-*i*-alcohol (Xa) (1·129 g; 87·5%) as an oil or foam, containing a trace of a slightly less polar component. This gave (22*S*)-22,23-epoxy-24-norchol-5-en-3β-ol (IX) after ring-opening and basic hydrolysis (see below). It was therefore almost certainly a 9 : 1 mixture of the bromohydrins (Va) and (Vc), analogous to that reported in the triterpene series.[5] The sample of (Xa) also contained a little of a more polar compound, which was not investigated further, but which was probably the Δ^{25}-isomer,[5] as deduced from n.m.r. evidence. The dienol (Xa) was further purified to give an *oil* or *foam* (1·035 g, 81%), $\nu_{max.}$ 3450, 3059w, 1097, 1015, 865, and 755 cm^{-1}, τ 4·8br (1H, t, *J* 7·5 Hz, 24-H), 6·35 (1H, dt, 22-H), 6·68 (3H, s), 7·24 (1H, t, *J* 3 Hz, 6α-H), and 8·26br (3H, s), 8·35br (3H, s), 8·97, 9·09, and 9·25 (methyls), and 9·36—9·69 (cyclopropyl protons), *m/e* 414 (M^+), 399, 382, 359 (M^+ − side-chain from C-23), 344 (M^+ − side-chain from C-22), 329, 313, 295, 99, and 70 (100%) (Found: M^+, 414·3491. $C_{28}H_{46}O_2$ requires *M*, 414·3498).

(22R)-22-*Hydroxycholesta*-5,24-*dien*-3β-*yl Acetate* (IIIb) *and* (22R)-*Cholesta*-5,24-*diene*-3β,22-*diyl Diacetate* (IIIc).—Treatment of the pure *i*-alcohol (Xa) (616 mg) with zinc acetate [9] (6 g) in refluxing glacial acetic acid (60 ml) for 1 h, followed by the usual work-up and chromatography (19 g) (97 : 3 and 24 : 1) gave first the impure diacetate (IIIc) (144 mg). Basic hydrolysis to the diol, purification by careful column chromatography, reacetylation, the usual work-up, and chromatography (10 g) (39 : 1) gave the pure *diacetate* (IIIc) (115 mg, 16%), m.p. (ethyl acetate–methanol, platelets) 91—93·5°, $[\alpha]_D^{20}$ −46° (*c* 1·4), $\nu_{max.}$ 1735, 1239, 1035, and 1020 cm^{-1}, τ 4·62br (1H, d, *J* 4 Hz, 6-H), 4·8—5·6br (2H, m, 24-, 22-, and 3α-H), 7·99 (6H, s), and 8·32br (3H, s), 8·38br (3H, s), 8·98, 9·09, and 9·32 (methyls), *m/e* 424 (M^+ − AcOH), 364, 313, 282 (424 − side-chain from C-20, 100%), 253, 109, 69, and 43 (Found: C, 76·9; H, 10·3. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

Further elution furnished the *monoacetate* (IIIb) (361 mg, 55%), m.p. (methanol, plates) 137·5—139·5°, $[\alpha]_D^{20}$ −40° (*c* 1·6), $\nu_{max.}$ 3544, 3300, 1726, 1250, and 1035 cm^{-1}, τ 4·62br (1H, d, *J* 4 Hz, 6-H), overlapping with 4·82br (1H, t, *J* 7 Hz, 24-H), 5·41br (1H, 3α-H), 6·28 (1H, m, 22-H), 6·46 (0·25H, MeOH of crystallisation), 7·99 (3H, s), and 8·26br (3H, s), 8·35br (3H, s), 8·97, 9·09, and 9·29 (methyls), *m/e* 382 (M^+ − AcOH), 364, 312 (M^+ − AcOH − side-chain from C-22, 100%), 297, 295, 99, and 70 (Found: C, 78·5; H, 10·5. $C_{29}H_{46}O_3$ requires C, 78·7; H, 10·5%). The total yield of diol precursors was 71%.

(22R)-*Cholesta*-5,24-*diene*-3β,22-*diol* (IIIa).—The acetate (IIIb) (172 mg) in methanol (50 ml) containing water (5 ml) and potassium carbonate (222 mg) was refluxed for 3 h.[4] The usual work-up and chromatography (8 g) (9 : 1) yielded the *diol* (IIIa) (139 mg, 89%), m.p. (methanol, needles) 182—184°, $[\alpha]_D^{20}$ −37° (*c* 2·0), $\nu_{max.}$ 3330, 1665—1600br,w, 1050, and 1020 cm^{-1}, τ 4·67br (1H, d, *J* 4 Hz, 6-H), 4·85br (1H, t, *J* 7 Hz, 24-H), 6·47br (2H, m, 3α- and 22-H), and 8·27br (3H, s), 8·36br (3H, s), 8·99, 9·10, and 9·30 (methyls), *m/e* 400 (M^+), 382, 330 (M^+ − side-chain from C-22, 100%), 312, 99, and 70 (Found: C, 80·8; H, 11·15. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%). The overall yield of diol (IIIa) from the aldehyde (IVa) was 20%.

(22S)-22,23-*Epoxy*-24-*norchol*-5-*en*-3β-*ol* (IX).—Conversion of the impure (22*R*)-*i*-alcohol (447 mg; containing the less polar component) by the usual procedure [9] into the monoacetate (IIIb), afforded a sample (264 mg, 55%), m.p. (methanol) 128—132°, homogeneous by t.l.c., but containing the (22*S*)-23-bromo-22-hydroxy- and (22*R*)-22-bromo-23-hydroxy-precursors of (IX), as deduced from minor peaks in the n.m.r. spectrum and the fragment ions at *m/e* 408, 406 (M^+ − AcOH), and 326 (M^+ − AcOH − HBr) in the mass spectrum, and by analogy with products obtained previously.[5] Basic hydrolysis of this sample (182 mg), followed by the normal work-up and chromatography (10 g) (9 : 1), gave first a less polar product (IX), and then the diol (IIIa) [89 mg, 54% based on pure (IIIb)], identical with that isolated as above. Recrystallisation of the less polar product furnished pure (IX) (22 mg, 16% based on pure bromohydrins), m.p. (methanol, *plates*) 143—145°, $[\alpha]_D^{20}$ −59° (*c* 0·8), $\nu_{max.}$ 3390, 1645, 1060, 1022, and 841 cm^{-1}, τ 4·64br (1H, m, 6-H), 6·5br (1H, 3α-H), 7·33 (2H, m, 2 oxiran-H), *ca.* 7·6 (1H, m, oxiran-H, partially obscured by other peaks), and 8·99 and 9·32 (methyls), *m/e* 344 (M^+, base peak), 329, 326, 311, 259, 213, 161, 145, 107, 105, 95, 93, 91, and 67 (Found: C, 77·6; H, 10·7%; M^+, 344·2716. $C_{23}H_{36}O_2$,0·67MeOH requires C, 77·7; H, 10·65%; $C_{23}H_{36}O_2$ requires *M*, 344·2715).

(22S)-*Cholesta*-5,24-*diene*-3β,22-*diol* (IIId).—The impure sample of the (22*S*)-*i*-alcohol (Xb) (123 mg) was treated with zinc acetate in acetic acid,[9] and the crude product was submitted to basic hydrolysis as described earlier for (Xa) and (IIIb). Chromatography (7 g) (9 : 1), followed by t.l.c. [4 elutions in hexane–ethyl acetate (4 : 1)], gave the (22S)-3β,22-*diol* (IIId) (12 mg, 10%), m.p. (methanol, needles) 173—176°, $[\alpha]_D^{20}$ −51·3° (*c* 0·3), $\nu_{max.}$ 3320, 1058, 1023, and 983 cm^{-1}, τ 4·67 (1H, m, 6-H), 6·4br (2H, m, 3α- and 22-H), and 8·26br (s), 8·37br (s), 8·76 (s), 9·01, and 9·32 (methyls), *m/e* 400 (M^+), 385, 382, 330 (M^+ − side-chain from C-22), and 70 (100%) (Found: C, 79·9; H, 11·3%; M^+, 400·3337. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%; *M*, 400·3341; $C_{27}H_{44}O_2$,0·33MeOH requires C, 79·8; H, 11·1%).

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