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STEREOSELECTIVITY IN THE ELECTROPHILIC ADDITION REACTIONS OF STIGMAST-22(23)-ENE DERIVATIVES[1]

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Abstract—Oxidation of 5α-stigmast-22-en-3-one (1) with *m*-chloroperbenzoic acid afforded [22R,23R]-epoxide 3 and [22S, 23S]-epoxide 2, in a 5:3 ratio. Reaction of 1 with iodine/silver acetate gave a mixture of iodoacetates 8 and 9, which on treatment with base yielded the single epoxide 2. Those results suggest that electrophiles may preferentially approach the Δ^{22}-bond from the side of the 21-Me group, in accordance with observations with the ergosterol-like side chain.

In continuation of our studies on the conformational analysis of the steroidal side chain, we have now examined some electrophilic addition reactions of stigmast-22(23)-ene derivatives, and in particular the stereochemical aspects of these reactions. In this connection, Barton *et al.* recently reported highly stereo- and regio-selective iodoacetoxylation and related electrophilic additions across the 22(23)-bond of 3α,5α-cycloergosta-7,22-dien-6-one.[2] The double bonds in these compounds are in similar situations in the steroidal side chain, except with respect to one of the adjacent carbons: one has a 24-R-Et group (I) while the other contains a 24-S-Me chain (II).

Comparison of our results with those of Barton *et al.* should therefore prove useful in revealing the factors responsible for the stereoselectivity of these reactions.

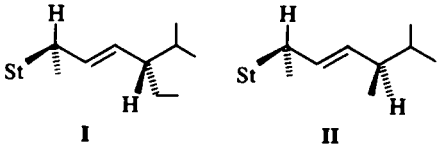

Chart 1.

Reaction at the Δ^{22}-bond of stigmasterol derivatives. Bromination and ozonisation are two well-known electrophilic reactions at the Δ^{22}-bond of stigmasterol derivatives.[3] However, these reactions, including peracid oxidation,[4] have not so far been subject to any stereochemical discussion.

To avoid the complication of the reaction resulting from the Δ^5-bond, 5α-stigmast-22-en-3-one(1)[5] was selected as the common substrate for our present experiments. The olefin 1 was prepared from stigmasterol by an Oppenauer oxidation, followed by reduction with lithium in liquid ammonia. Since oxidation of the olefin 1 with *m*-chloroperbenzoic acid was accompanied by Baeyer Villiger reaction in ring A, the ketone in ring A was first converted to the alcohol by reduction with LAH, and the alcohol was then treated with the peracid. The crude product was immediately oxidized with chromic acid/pyridine to afford the ketoepoxides 2 and 3. Five developments on TLC with hexane-chloroform (1:1) revealed the presence of a mixture of two epimers, whose isolation was achieved by careful column chromatography on silica gel. The less polar epoxide 2, m.p. 180–180·5°, and the more polar epoxide 3, m.p. 129·5–131°, were obtained in a 3:5 ratio.

Treatment of the olefin 1 with iodine and silver acetate in glacial acetic acid yielded a mixture of iodoacetates 8 and 9. NMR analysis of the crude product revealed pairs of signals assignable to 22–H, 23–H, acetyl and 18-methyl, suggesting the presence of epimeric isomers in a 3:1 ratio, although attempts to isolate the two iodoacetates failed.

Hydroboration of the 22(23)-bond of 1 with diborane/diglyme, and oxymercuration with mercuric acetate/THF-water were attempted, but there was no appreciable reaction. In addition to those electrophilic reactions, the double bond also showed marked resistance to photo-sensitized oxygenation with oxygen/heamatoporphyrin/pyridine. The reluctance of the 22(23)-bond of stigmasterol derivatives towards these reactions may reflect the severe steric hindrance by the adjacent tertiary carbons.

Structures of the reaction products. On treatment with 10% NaOH, iodoacetates 8 and 9 afforded the same epoxide, 2, which was identical with the minor epoxide obtained from peracid oxidation of olefin 1. We next undertook an investigation of the structures of epoxides 2 and 3. Contrary to the results obtained with the corresponding epoxide of an ergosterol derivative,[6] epoxides 2 and 3 were completely resistant to reductive ring opening with LAH. However, reaction of epoxides 2 and 3 with dilute hydrobromic acid readily gave the corresponding bromohydrins quantitatively. Thus, from epoxide 2, bromohydrins 4 and 5 were produced in a 9:2 ratio; while epoxide 3 afforded bromohydrins 6 and 7 in a 2:1 ratio.

To determine the position of the OH group in bromohydrins 4–7, they were converted into the corresponding ketones. Jones oxidation of 4 and 6 gave bromoketones 10 and 12 respectively, whose bromine functions were removed by treatment with BF_3-etherate/lithium iodide,[7] yielding the 23-ketone 14.[4] By the same procedure, bromohydrines 5 and 7 were transformed to the 22-ketone 15,[8] *via* bromoketones 11 and 13 respectively. The position of the ketone function in the side chain was also confirmed by the mass spectrum fragmentation pattern (Experimental).

The configuration of OH groups of bromohydrins 4, 6 and 7 was determined by application of Horeau's method to the hydroxyketones, 16, 17 and 18, derived from the

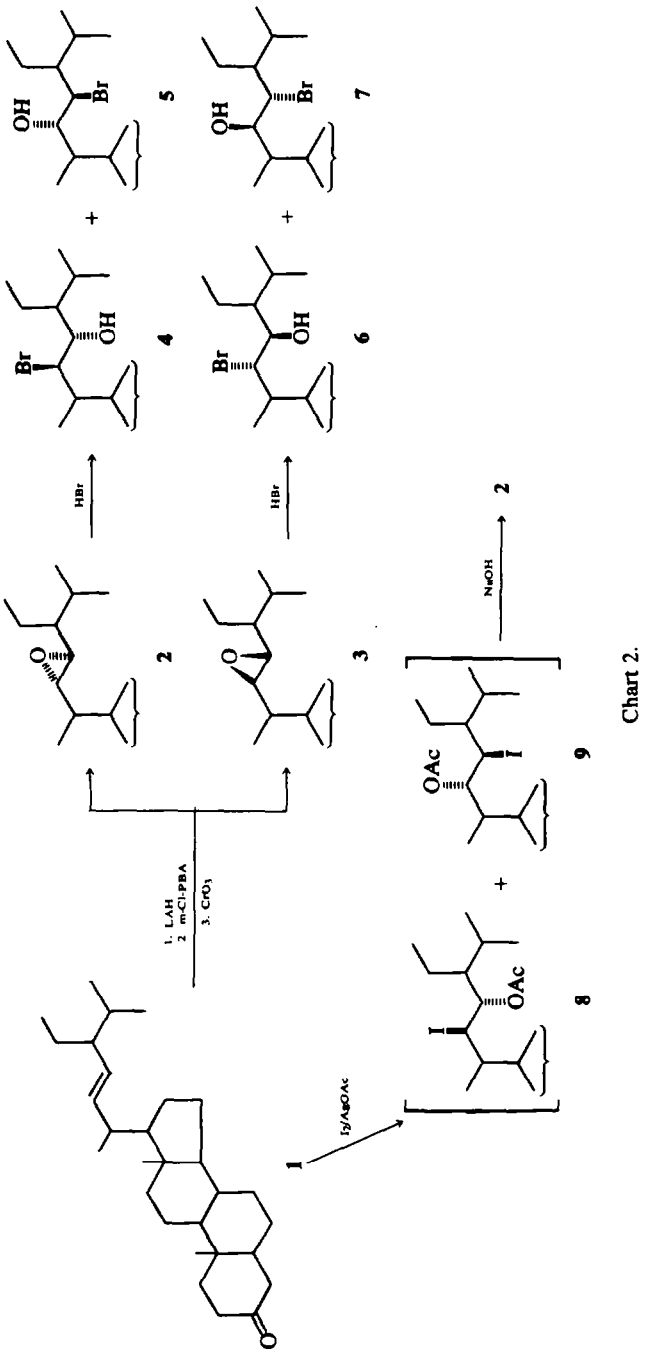

Chart 2.

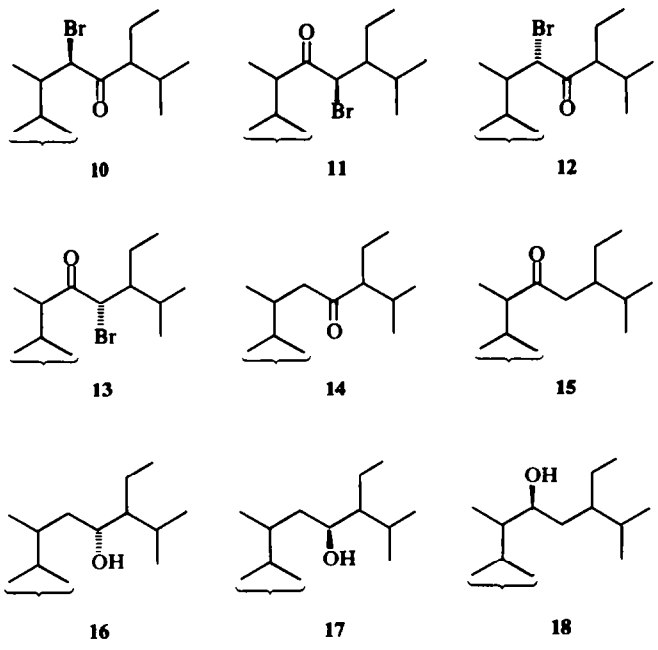

Chart 3.

bromohydrins by the following sequence: (1) acetylation with acetic anhydride/pyridine, (2) reduction with tributyltin hydride to remove the bromine function,[9] (3) methyl ketalization of the 3-ketone group, (4) reduction of the acetate with LAH, and finally (5) acid treatment to remove the ketal function.

According the method of Brooks and Gilbert,[10] the alcohols **16**, **17** and **18** were treated with a little excess of (±)-α-phenylbutyric anhydride, and then with (+)-[R]-α-phenylethylamine, yielding diastereoisomeric amides. The relative proportions of the amides of (−)-[R]- and (+)-[S]-α-phenylbutyric acid were estimated from the heights of their respective peaks on GLC (Table 1). From these data, and using the rule that alcohols of configurational type (III) react preferentially with the [R]-α-phenylbutyryl group, the stereochemistry of alcohols **16**, **17** and **18** was firmly established as shown in Table 1.

Table 1. GLC determination of (+)-α-phenylethylamides representing unreacted anhydride from Horeau reaction

Alcohol	Peak increment (R)-acids[a]	Configuration	M HO—C—H L
16	−11 %	23R	
17	+ 6	23S	
18	+18	22S	

a. The difference of peak heights was divided by the sum of peak heights and the value is corrected by that of cyclohexanol.

†The very high values observed for the molar ellipticity indicate that rotation about the C_{22}–C_{23} bond of **10–13** is quite restricted and that one rotamer predominates in each compound. If the axial haloketone rule is applied to models of **10–13**, the preferred rotamers may be drawn as shown:

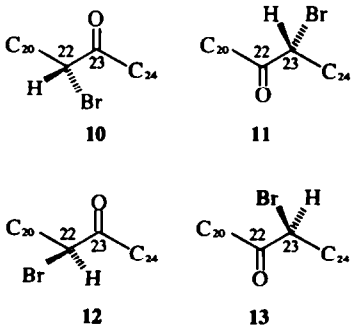

Chart 4.

The negative values (−0·03 to −0·16 ppm) in their NMR solvent shifts (δC_6D_6–$\delta CDCl_3$) due to α-H to bromine, and also the single IR absorption band of CO at around 1710 cm^{-1}, support these conformations.

Since *trans* ring opening of epoxide **2** and **3** by reaction with HBr can be reasonably assumed, the epimeric nature of bromine in **4** vs **6** and **5** vs **7** can be expected. This was corroborated by CD analysis of their corresponding bromoketones **10–13** (Fig. 1). Thus, the curve for **10** was practically the mirror image of that for **12**, likewise with the pair **11** and **13**†.

From these results, the configuration of bromine in the fourth bromohydrin **5** can also be deduced as antipodal to that in bromohydrin **7**.

Thus, the structures of the four bromohydrins were determined as [22R,23S]-22-bromo-23-ol **4**, [22S,23R]-23-bromo-22-ol **5**, [22S,23R]-22-bromo-23-ol **6** and [22R,23S]-23-bromo-22-ol **7**.

From the foregoing arguments, the more polar, major epoxide **3** was assigned as [22R, 23R]; the less polar, minor epoxide **2** consequently being [22S,23S]. On the other hand, as the same epoxide **2** was obtained on alkaline treatment of the iodoacetoxylation products of olefin **1**, they should have the structures [22R,23S]-22-iodo-23-acetate **8** and [22S,23R]-23-iodo-22-acetate **9**.

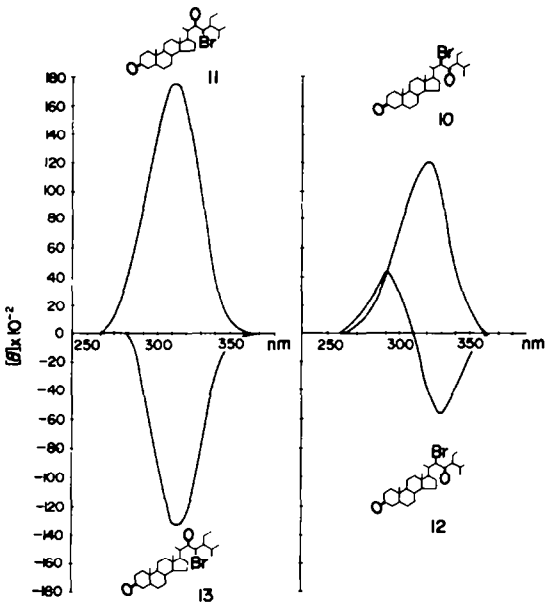

Fig. 1. CD curves of 10, 11, 12 and 13.

DISCUSSIONS

Since the preferred conformation of the starting olefin 1 is probably similar to that of the ergosterol-like side chain,[2] it can be represented as in I†.

The present results suggest that electrophiles preferentially approach the 22(23)-double bond of 1 from the side of the 21-methyl group. This preference is more marked with larger electrophiles; thus, with I^+ (IV) complete stereoselectivity was obtained, in comparison with the 5:3 ratio of products obtained from approach of peracid (V). These findings are in keeping with those for electrophilic addition to the Δ^{22}-bond of 3α,5α-cycloergosta-7,22-dien-6-one.[2] It may be, therefore, that the asymmetry of C-20 is more important than that of C-24 for determining the stereoselectivity of these reactions. Thus, it may be that the side on which the 21-Me group is situated is the less hindered side of the Δ^{22}-bond, and that the major impedance to electrophilic approach from the other side is due to a 1,3-parallel interaction (VI) between the reagent and the C-16(17)-bond of ring D.

It should be also noted that although initial iodonium ion formation occurs stereoselectively in both cases, subsequent attack of acetate ion in the anti-sense is less regioselective in 1 than in the ergosterol derivative.[2] This is probably because the C-23 of the stigmasterol derivative is more hindered than that of ergosterol derivative. This will also be, at least partly, the reason for the resistance of the epoxides 2 and 3 to ring opening in lithium aluminum hydride reduction.

EXPERIMENTAL

M.ps were determined on a hot stage and are uncorrected. IR spectra were obtained with a Perkin–Elmer PE-125 spectrometer. NMR spectra were recorded on a JEOL JNM-4H-100 spectrometer and chemical shifts are expressed in ppm downfield from TMS as internal standard. CD spectra were taken with a JASCO, Model ORD/UV-5 or J-40. Mass spectra were obtained on Hitachi RMU-7L or JEOL JMS-01-SG spectrometers. Column chromatography was carried out using Wakogel C-200 (silica gel). Merck silica gel 60 F_{254} (0·25 mm thick) was used for TLC.

[22S,23S] - 22,23 - *Epoxy* - 5α - *stigmastan* - 3 - *one*(2). Compound 1[5] (600 mg) was reduced with LAH (300 mg) in diethylether (20 ml) at room temp for 10 min to give a mixture of 3β- and 3α-alcohols. To a soln of the crude product in chloroform (25 ml), *m*-chloroperbenzoic acid (400 mg) was added, and the mixture was stirred at room temp for 6 hr. The mixture was washed with 1N NaOH and then with water, dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue (634 mg) was dissolved in methylene chloride (5 ml) and the soln was added to a stirred mixture of chromic acid (1·92 g), pyridine (3·04 g) and methylene chloride (48 ml).[11] After being stirred at room temp for 30 min, the soln was decanted from the tarry deposite. The residue was triturated with ether and the combined organic fraction (200 ml) was washed successively with 1N HCl, 3N NaOH, and

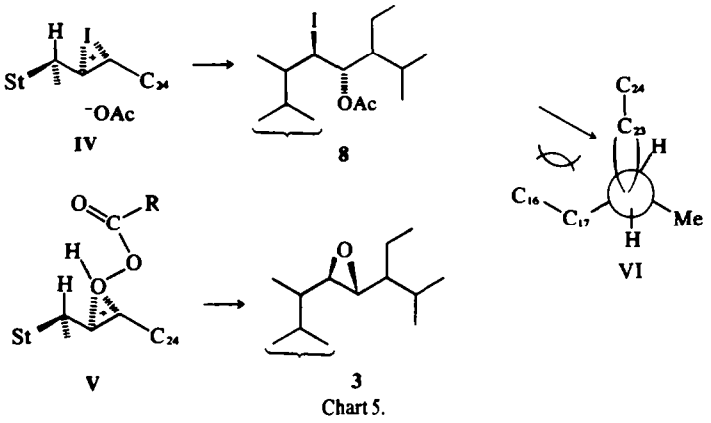

Chart 5.

†Although we have no direct evidence that 1 has the conformation I in solution, at least the restricted rotation around the C(20)–C(22) bond seems to be analogized from CD and/or NMR data (unpublished) of the following compounds, including the acetates of bromohydrins 4–7:

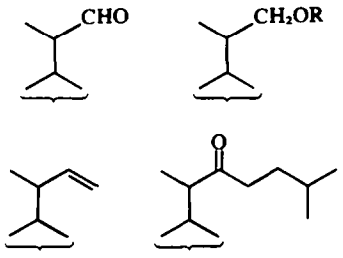

Chart 6.

water. Evaporation of solvent gave white crystals (630 mg), which were chromatographed on a column of silica gel (25 g). From the fraction eluted with *n*-hexane-benzene (5:1), starting compound 1 (53 mg) was recovered. Elution with *n*-hexane-benzene (1:1) afforded epoxide 2 (203 mg), m.p. 180–180·5° (MeOH); NMR ($CDCl_3$), 0·67 (3H, s, 18-Me) and 2·46 (2H, m, 22,23-Hs); M^+, 428·3634 ($C_{29}H_{48}O_2$ requires: 428·3654).

[22R,23R] - 22,23 - *Epoxy* - 5*α* - *stigmastan* - 3 - *one*(3). Further elution with the same solvent mixture gave 3 (330 mg), m.p. 129·5–131° (EtOH): NMR ($CDCl_3$), 0·69 (3H, s, 18-Me), and 2·72 (1H, dd, J = 8 and 2 Hz, 22 or 23-H): M^+, 428·3706 ($C_{29}H_{48}O_2$ requires: 428·3654).

[22R,23S] - 22 - *Bromo* - 23 - *hydroxy* - 5*α* - *stigmastan* - 3 - *one*(4). [22S,23S]-Epoxide 2 (152 mg) was stirred in a mixture of chloroform (15 ml), AcOH (1·5 ml) and 47% HBr (1·5 ml) at room temp for 16 hr. The soln was washed with water and dried over Na_2SO_4. Evaporation of solvent *in vacuo* at below 30° gave white crystals (153 mg), which were chromatographed on silica gel (6 g). From the fraction eluted with *n*-hexane-benzene (1:1), 4, (92 mg) was obtained, m.p. 222–225° (MeOH-ether), NMR ($CDCl_3$), 0·73 (3H, s, 18-Me), 3·92 (1H, dd, J = 2·5 Hz, 9·2 Hz, 22-H), and 4·22 (1H, d, J = 9·2 Hz, 23-H), M^+-HBr, 428·3609 ($C_{29}H_{48}O_2$ requires: 428·3654).

[22S,23R] - 23 - *Bromo* - 22 - *hydroxy* - 5*α* - *stigmastan* - 3 - *one* (5). Further elution with the same solvent afforded 5 (20 mg), m.p. 203–206° (MeOH-chloroform).

[22S,23R] - 22 - *Bromo* - 23 - *hydroxy* - 5*α* - *stigmastan* - 3 - *one* (6). [22R,23R]-Epoxide 3 (152 mg) was treated in exactly the same manner as described for the preparation of 4. From the less polar fraction on the column chromatography 6 (98 mg) was obtained, m.p. 200–202° (MeOH-ether), NMR ($CDCl_3$), 0·65 (3 H, s, 18-Me), 4·03 (1 H, d, J = 10 Hz, 22-H) and 4·21 (1 H, d, J = 10 Hz, 23-H). M^+–HBr, 428·3624 ($C_{29}H_{48}O_2$ requires: 428·3654).

[22R,23S] - 23 - *Bromo* - 22 - *hydroxy* - 5*α* - *stigmastan* - 3 - *one* (7). From the more polar fraction 7 (46 mg) was obtained, m.p. 209–211° (MeOH-ether), NMR ($CDCl_3$), 0·71 (3 H, s, 18-Me), 3·97 (1 H, d, J = 10 Hz, 23-H) and 4·13 (1 H, dd, J = 10 and 2·5 Hz, 22-H).

Iodoacetoxylation of olefin 1. To a stirred mixture of 1 (459 mg), AgOAc (500 mg) and glacial AcOH (12 ml) was added iodine powder (370 mg) dropwise over 15 min. After 3 hr the mixture was diluted with chloroform (100 ml) and precipitated AgI was filtered off. The filtrate was washed successively with water, sat $NaHCO_3$, and water. The soln was dried over Na_2SO_4, then evaporated to give a syrup (695 mg), which was chromatographed on a column of silica gel (28 g). From the fraction eluted with n-hexane–benzene (2:1), a mixture of 8 and 9 (423 mg) was obtained, m.p. 143–144°; NMR ($CDCl_3$), 0·67 and 0·70 (3 H, two s, 18-Me), 1·00 (3 H, s, 19-Me), 2·02 and 2·10 (3 H, two s, acetyl), 4·34 (0·75 H, dd, J = 11 and ~1 Hz, hydrogen *α* to iodide), 4·50 (0·25 H, dd, J = 8·5 and 2·5 Hz, hydrogen *α* to acetate) and 5·43 (0·75 H, dd, J = 11 and 1 Hz, hydrogen *α* to acetate).

Base-treatment of the iodoacetates 8 *and* 9. The iodoacetate (400 mg) was dissolved in 10 ml of 10% NaOH aq (tetrahydrofuran–ethanol–water, 4:4:1) and heated at 40° for 5 hr. After neutralization by addition of 1 N HCl, the mixture was diluted with ether, washed with water and dried over Na_2SO_4. Evaporation of solvent gave the crude product (290 mg), which was purified by column chromatography on silica gel (12 g). From the fraction eluted with *n*-hexane–benzene (1:1), [22S,23S]-epoxide 2 (230 mg) was obtained. This was identified with the less polar epoxide produced by peracid oxidation of olefin 1 by mixed m.p., TLC (5 times development by hexane–chloroform (1:1)), and spectral data.

[22R] - 22 - *Bromo* - 5*α* - *stigmastane* - 3,23 - *dione* (10). Bromohydrin 4 (33 mg) was oxidized with a slight excess of Jones reagent [from chromium trioxide (1·32 g) and conc H_2SO_4 (1·15 ml) made up to 5 ml with water] at room temp for 30 min. The product (30 mg) was crystallized from MeOH to give 10, m.p. 167–170°, IR, $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, NMR ($CDCl_3$), 0·74 (3 H, s, 18-Me), 2·70 (1 H, m, 24-H) and 4·55 (1 H, broad s, W ½ 1·5 Hz, 22-H), NMR (C_6D_6), 0·56 (3 H, s, 18-Me), 1·12 (3 H, d, J = 6·2 Hz, 21-Me), 2·74 (1 H, m, 24-H) and 4·52 (1 H, broad s, W ½ 1·5 Hz, 22-H), CD, $[\theta]_{320\cdot5\,nm}$ + 11880.

[23R] - 23 - *Bromo* - 5*α* - *stigmastane* - 3,22 - *dione* (11). Bromohydrin 5 was oxidized as described above to afford 11, m.p. 178–181° (MeOH), IR, $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}, NMR ($CDCl_3$), 0·71 (3 H, s, 18-Me), 1·22 (3 H, d, J = 6·2 Hz, 21-Me) 2·87 (1 H, m, 20–H) and 4·54 (1 H, d, J = 3·1 Hz, 23-H), NMR (C_6D_6), 0·56 (3 H, s, 18-Me), 1·26 (3 H, d, J = 6·1 Hz, 21-Me), and 2·88 (1 H, m, 20-H). 4·47 (1 H, d, J = 3·1 Hz, 23-H), CD, $[\theta]_{311\cdot5\,nm}$ + 17500.

[22S] - 22 - *Bromo* - 5*α* - *stigmastane* - 3,23 - *dione* (12). Bromohydrin 6 was oxidized as described above to afford 12, m.p. 147° (MeOH); IR, $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}; NMR ($CDCl_3$), 0·69 (3 H, s, 18-Me), 1·23 (3 H, d, J = 6·5 Hz, 21-Me), 2·61 (1 H, m, 24-H), and 4·65 (1 H, d, J = 3·1 Hz, 22-H); NMR (C_6D_6), 0·48 (3 H, s, 18-Me), 1·38 (3 H, d, J = 6·2 Hz, 21-Me), 2·58 (1 H, m, 24-H) and 4·56 (1 H, d, J = 3·1 Hz, 22-H); CD, $[\theta]_{328\,nm}$ − 5610.

[23S] - 23 - *Bromo* - 5*α* - *stigmastane* - 3,23 - *dione* (13). Bromohydrin 7 was oxidized as described above to afford 13, m.p. 159–163° (MeOH); IR $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}; NMR ($CDCl_3$), 0·72 (3 H, s, 18-Me), 1·13 (3 H, d, J = 7·1 Hz, 21-Me), 2·87 (1 H, m, 21-H) and 4·38 (1 H, d, J = 9·6 Hz, 23-H); NMR (C_6D_6), 0·62 (3 H, s, 18-Me), 0·96 (3 H, d, J = 6·1 Hz, 21-Me), 2·78 (1 H, m, 21-H) and 4·42 (1 H, d, J = 9·6 Hz, 23-H); CD, $[\theta]_{315\,nm}$ − 13250.

5*α*-*Stigmastane*-3,23-*dione* (14). To a stirred suspension of LiI (45 mg) in ether (1·0 ml) was added a mixture of 10 (50 mg), BF_3-etherate (15 *μ*l) and ether (1·0 ml) over 10 min under N_2. After stirring at room temp for 4 hr, the reaction was stopped by addition of sat $NaHCO_3$ aq. The mixture was extracted with ether and the extract soln was washed with 10% $Na_2S_2O_3$ and then with water. The dried soln was evaporated to give white crystals (41 mg). Crystallization from acetone–*n*-hexane gave the 3,23-dione 14, m.p. 160·5–162° (ref,[4] m.p. 159–160°); *m/e*, 428(M^+), 343 (cleavage of 23,24-bond) and 330 (cleavage of 20,22 bond with McLafferty rearrangement). Treatment of 12 (20 mg) under similar conditions afforded the same dione 14 (15 mg).

5*α*-*Stigmastane*-3,22-*dione* (15). The bromoketones 11 and 13 were debrominated as described above to afford the 3,22-dione, m.p. 175·5–177·5° (acetone-*n*-hexane) (ref,[8] m.p. 176–177°); *m/e*, 428 (M^+), 344 (cleavage of 23,24-bond with McLafferty rearrangement), 329 (cleavage of 22,23-bond) and 301 (cleavage of 20,22-bond).

[23R] - 23 - *Hydroxy* - 5*α* - *stigmastan* - 3 - *one* (16). Bromohydrin 4 (92 mg) was acetylated with Ac_2O-pyridine at room temp for 2 days to give the bromoacetate, m.p. 149–151° (acetone); NMR ($CDCl_3$), 0·69 (3 H, s, 18-Me), 2·05 (3 H, s, acetyl), 4·25 (1 H, d, J = 10·6 Hz, 22-H) and 5·37 (1 H, dd, J = 10·6 and 1·5 Hz, 23-H). The bromoacetate (100 mg) was stirred under N_2 with a mixture of tri-*n*-butyltin hydride (0·4 g), azobisisobutyronitrile (5 mg) and toluene (10 ml) at 80° for 1 hr. To recover the 3-keto function, the crude product was directly oxidized with a slight excess of Jones reagent. The mixture was extracted with ether and the extract soln was washed with sat $NaHCO_3$ aq and then with water and dried over Na_2SO_4. The evaporated crude product was chromatographed on silica gel (8 g) and [23R]-23-acetoxy-5*α*-stigmastan-3-one (80 mg) was obtained from the fraction eluted with benzene. Crystallization from MeOH gave the corresponding methyl ketal, m.p. 113–114°, NMR ($CDCl_3$) 0·63 (3 H, s, 18-Me), 2·0 (3 H, s, acetyl), 3·11 and 3·17 (6 H, two s, methyl ketal) and 5·1 (1 H, m, 23-H).

The ketoacetate (20 mg) was refluxed with MeOH containing ortho-formic acid trimethyl ether (80 *μ*l) and *p*-toluenesulfonic acid (1 mg) for 2 hr. After addition of sat $NaHCO_3$ (1 ml), most of MeOH was evaporated off. The residue was redissolved in ether, washed with water, and dried over Na_2SO_4. The evaporated product was treated with LAH (7 mg) in ether (2 ml) for 10 min at room temp. To the mixture were added 6 N HCl (3 ml) and MeOH (5 ml), and the soln was stirred for 10 min at room temp. The mixture was diluted with ether, washed with sat $NaHCO_3$ aq and then with water. The dried soln was evaporated to give white crystals (19 mg). Crystallization from acetone-water gave (16) m.p. 144–145°, NMR ($CDCl_3$) 0·71 (3 H, s, 18-Me), 1·00 (3 H, s, 19-Me) and 3·7 (1 H, m, 23-H); M^+–H_2O, 412·3668 ($C_{29}H_{48}O$ requires 412·3705).

[23S] - 23 - *Hydroxy* - 5*α* - *stigmastan* - 3 - *one* (17). Bromohydrin 6 was treated by essentially the same manner as described above to give 17, m.p. 144–146° (acetone), NMR ($CDCl_3$)

0·68 (3 H, s, 18-Me), 0·99 (3 H, s, 19-Me) and 3·9 (1 H, m, 23-H); M^+, 430·3815 ($C_{29}H_{50}O_2$ requires 430·3810).

[22S] - 22 - *Hydroxy* - 5α - *stigmastan* - 3 - *one* (**18**). Bromohydrin **7** was treated by essentially the same manner as described above to give **18**, m.p. 180·5–181·5° (acetone), NMR ($CDCl_3$), 0·68 (3 H, s, 18-Me), 1·09 (3 H, s, 19-Me) and 3·7 (1 H, t, J = 6 Hz, 22-H); M^+, 430·3766 ($C_{29}H_{50}O_2$ requires 430·3810).

Determination of the configuration by Horeau's method. To a soln of **16**, **17** or **18** (2·2 mg) in pyridine was added (10 μl), (±)-α-phenylbutylic anhydride (2·4 μl), and the mixture was allowed to stand at room temp for 12 hr. d-(+)-α-methylbenzylamine (2·4 μl) was then added, and after 30 min the mixture was diluted with EtOAc. In each case a parallel reaction was carried out with cyclohexanol. The resulting diastereoisomeric amides were analyzed by GLC at 260° on a glass-capillary column (20 m × 0·25 mm i.d.) coated with OV-17. The relative proportions of the amides were indicated by the heights of their respective peaks (Table 1).

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