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Studies on Steroids. LI.[1] Stereoselective Introduction of 22- and 24-Hydroxyl Function in the Steroidal Side Chain[2]

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Osmium tetroxide oxidation of the 22-olefin (**4**) and reaction of sodium dimethylsulfonium methylide with the 22-aldehyde (**3a**) afforded stereoselectively the 22*S*- and 22*R*-epoxides (**7a** and **7b**), respectively. Those epoxide can be led to the 22*R*- and 22*S*-hydroxy steroides by Grignard reaction. Inversion of the configuration of hydroxyl group on C-22 and C-24 positions was achieved in high yield by means of superoxide displacement reaction.

Keywords——stereoselective introduction of hydroxyl group; 22-hydroxysteroid; 24-hydroxysteroid; steroidal side chain; inversion of hydroxyl by superoxide

Stereoselective introduction of hydroxyl group at steroidal side chain is crucial for synthesis of biologically active steroids, such as ecdysones (22*R*-hydroxyl group),[4] withanolides (22*R*-lactone),[5] vitamin D_3 metabolites (24*R*-hydroxyl group),[6] *etc.* We have already reported on a stereoselective synthesis of 22,23-epoxide starting from commercially available 22,23-bisnorcholenic acid.[7] Recent paper on the synthesis of ecdysone side chain by Trost *et al.*[8] prompted us to publish our further work on the stereoselective introduction of 22- and 24-hydroxyl groups in the steroidal side chain.

Bisnorcholenic acid (**1**) was converted to mixed anhydride, which was reduced to the alcohol (**2**) by treatment with sodium borohydride. Perchlorochromate oxidation or Collins oxidation of the alcohol (**2**) afforded the aldehyde (**3a**) in a good yield. The aldehyde (**3a**) was treated with triphenylmethylene phosphorane to give the 22-olefin (**4**) in 80% yield. Osmium tetroxide oxidation of the 22-olefin (**4**) gave the 22,23-glycol (**5a** and **5b**) as an epimeric mixture at C-22 without oxidation of 5,6-double bond.[9] Selective tosylation of a mixture of glycol (**5a** and **5b**) using 1.1 equivalent of tosyl chloride afforded the 23-monotosylate (**6a** and **6b**) which showed two spots on the thin-layer chromatography (TLC) as less polar tosylate (**6a**) being the major one. Separation by silica gel column chromatography or high pressure liquid chromatography revealed the ratio of epimeric mixture as 6:1. Treatment of each tosylate (**6a** and **6b**) with anhydrous potassium carbonate in refluxing methanol provided the 22,23-epoxides (**7a** and **7b**), respectively. Comparison of these proton nuclear magnetic resonance (PMR) spectra[10] with those of the 5,6-dihydroepoxides[7] indicated

1) Part L: N. Koizumi, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, **1978**, 2899.
2) Presented at the 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1977. Abstracts II, p. 207.
3) Location: *Nagatsuta, Midori-ku, Yokohama, 227, Japan.*
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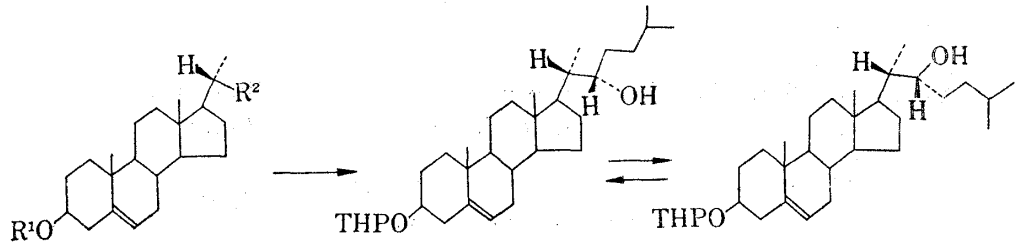
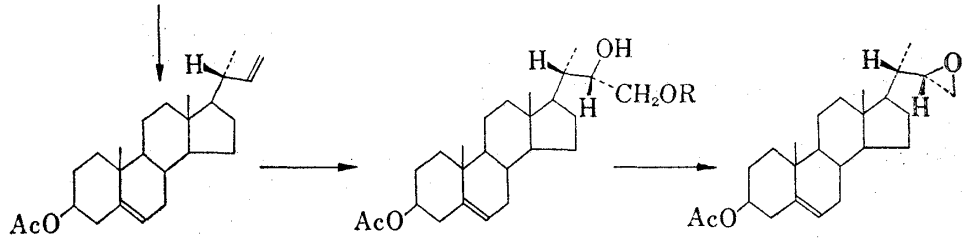
9) When the bromohydrination or iodoacetoxylation followed by base treatment is employed for the 22*S*-epoxide formation, C-5 double bond should be protected as 6β-methoxy-3,5-cyclo compound. See ref. 8) and 12).
10) The C-22 and C-23 proton signals of [22*R*]-epoxide appeared at δ 2.53—2.86 (3H, m) and of [22*S*]-epoxide, 2.33—2.46 (1H, dd) and 2.52—2.87 (2H, m).

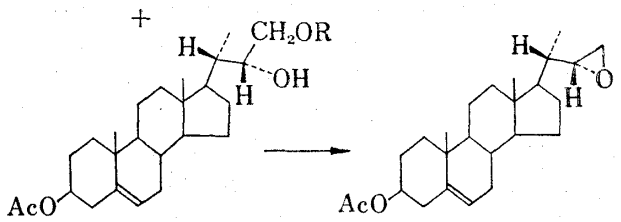


1 : R_1=Ac, R_2=COOH
2 : R_1=Ac, R_2=CH_2OH
3a : R_1=Ac, R_2=CHO
3b : R_1=THP, R_2=CHO

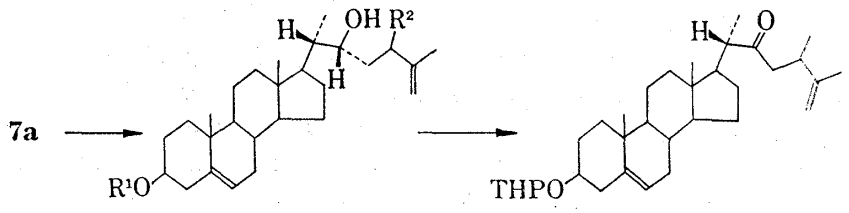
12b **12a**



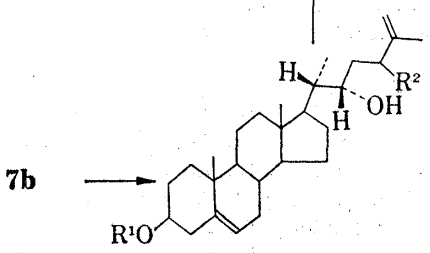
4 **5a** : R=H **7a**
6a : R=Ts



5b : R=H **7b**
6b : R=Ts



8a : R^1=H, R^2=H
9a : R^1=H, R^2=Me
10a : R^1=THP, R^2=Me



8b : R^1=H, R^2=H
9b : R^1=H, R^2=Me
10b : R^1=THP, R^2=Me

Chart 1

the major epoxide (**7a**) has 22*S*-configuration, which is desired for synthesis of 22*R*-hydroxy steroids such as ecdysones.

For other method of preparation of 22,23-epoxide, it was found that treatment of the aldehyde (**3a**) with sodium dimethylsulfonium methylide[11] gave exclusively 22*R*-epoxide (**7b**), configuration of which was deduced by comparison of its PMR spectrum.

Coupling reaction of the epoxides (**7a** and **7b**), with β-methally magnesium chloride gave [22*R*]- and [22*S*]-22-hydroxycholesta-5,25-dien-3β-ol (**8a** and **8b**), respectively.[12] By the similar procedure using β,γ-dimethylallyl magnesium chloride, [22*R*]- and [22*S*]-22-hydroxy 24-methylcholesta-5,25-dienes (**9a** and **9b**) were obtained in quantitative yield. The position of the hydroxyl group was confirmed by the mass spectrum (MS) of the 22-oxo compound (**11**) which was derived as follows. After conversion of the 3β-acetyl group of **7a** to THP group, Grignard reaction and subsequent Collins oxidation afforded the compound (**11**), whose mass spectrum showed *m/e* 329 ($M^+-84-83$) and 301 ($M^+-84-111$) characteristic peaks for the 22-ketone. Thus, [22*R*]-22-hydroxy steroids (**8a** and **9a**) which could be used as the synthetic precursors of ecdysones or withanolides[13] were effectively prepared from the 22-aldehyde (**3a**).

As an alternative synthesis of 22*R*-hydroxy steroids, we have next tried to invert the configuration at C-22 in 22*S*-hydroxy steroids, which are easily prepared from the 22-aldehyde by Grignard reaction.[14] For this purpose, the Corey's procedure using potassium superoxide[15] appeared to be suitable. The mesylate of [22*S*]-22-hydroxycholesterol (**12b**) was treated with potassium superoxide to give [22*R*]-22-hydroxycholesterol (**12a**) in 90% yield. By the same procedure, 22*S*-isomer (**8b** or **9b**) gave 22*R*-epimer (**8a** or **9a**) in almost quantitative yield. Thus Corey's method of the inversion of the configuration of hydroxyl group can be effectively applied to the stereoselective introduction of 22*R*-hydroxyl group in steroidal side chain.

Now we have extended this method of configurational inversion to the 24-hydroxylated steroides. Recently several metabolites of vitamin D_3 were isolated and their functional importance have also been established.[6] Among those metabolites we have focussed our attention on the 24-hydroxylated analogs and the 24*R* and 24*S* stereoisomers of 24-hydroxy,[16] 24,25-[17] and 1,24-dihydroxy-[18] and 1,24,25-trihydroxy-vitamin D_3[19] were synthesized. Since the 24*R* compounds were found to exhibit higher biological activity than the 24*S* counterparts,[20] it would be worthwhile to transform the [24*S*]-24-hydroxycholesterol derivatives into the 24*R* isomers, the synthetic precursors of the more desirable vitamin D_3 analogs. The 24-hydroxylated cholesterol analogs were usually prepared by hydride reduction of the 24-oxo

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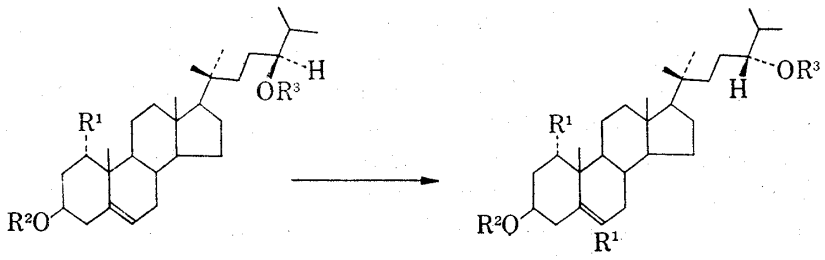
derivative to yield a 1:1 epimeric mixture at C-24. This mixture, in the form of appropriate derivative, can be resolved chromatographically or by fractional crystallization. The superoxide displacement method was found to be also useful for the inversion of the configuration at C-24 position, as shown in the case of 24-hydroxy- and 1α,24-dihydroxy-cholesterols.



	R¹	R²	R³
13a :	H	H	Bz
13b :	H	THP	H
13c :	H	THP	Ms
13d :	THPO	THP	Bz
13e :	THPO	THP	H
13f :	THPO	THP	Ms

	R¹	R²	R³
14a :	H	THP	H
14b :	H	Bz	Bz
14c :	THPO	THP	H
14d :	OH	Bz	Bz

Chart 2

The [24*S*]-24-hydroxy 3-THP ether (**13b**) was prepared by the following procedure. Partial hydrolysis of the 3,24-dibenzoate of [24*S*]-24-hydroxycholesterol[16] to the 24-monobenzoate (**13a**) was achieved with 5% KOH–methanol at room temperature in a 90% yield. After protection with THP ether at 3-position, the 24-benzoate group was removed by 5% KOH–methanol at reflux condition. The 24-mesylate 3-THP ether (**13c**) was converted to the [24*R*]-hydroxy compound (**14a**) by treatment with potassium superoxide in almost theoretical yield. Partial hydrolysis of [24*S*]-1α,24-dihydroxycholesterol 1-acetate 3,24-dibenzoate[18] was also carried out with 5% KOH–methanol at room temperature for 12 hr. After THP ether formation to **13d**, the 24-benzoate was hydrolyzed to **13e**. The mesylate (**13f**) was led to the [24*R*]-hydroxy compound (**14c**) by the same procedure as for **13c**.

Those stereoselective introduction methods of [22*R*]-hydroxyl and the configurational inversion at C-22 and C-24 using superoxide displacement reaction would be applicable to synthesis of biological active steroids having hydroxyl function in the side chain.

Experimental

Melting points were determined on a hot stage microscope and uncorrected. Optical rotation were taken for chloroform solution on a JASCO-DIP-S polarimeter. NMR spectra were run on a JEOL JNM-4H-100 spectrometer with $CDCl_3$ as solvent and with tetramethylsilane as internal reference. Mass spectra were taken on a Shimadzu-LKB-9000 mass spectrometer. Column chromatography was normally effected with Wako silica gel C-200. "The usual work-up" refers to dilution with water, extraction with organic solvent which is indicated in the parenthesis, washing to neutrality, drying, filtration and evaporation under vacuum. Ether refers diethyl ether, THF to tetrahydrofuran and THP to tetrahydropyranyl ether.

23,24-Bisnorchol-5-ene-3β,22-diol 3-Acetate (2)——To a solution of **1** (7.8 g) in 100 ml of THF, 2.6 g of chloromethyl formate and 2.4 g of triethylamine were added at 0°. After stirring for 20 min, a solution of 7.6 g of sodium borohydride in 40 ml of water was added and the mixture was stirred for 1 hr. The usual work up (ether) gave 6.4 g of **2**, mp 153—154° (from methanol). $[\alpha]_D^{20}$ −53.8° (c=4.5). NMR δ: 0.69 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.05 (3H, d, J=6 Hz, 20-Me), 3.34 (1H, dd, J=7.5 and 10 Hz, 22-H), 3.65 (1H, dd, J=2.5 and 10 Hz, 22-H), 4.60 (1H, m, 3α-H), 5.35 (1H, m, 6-H). *Anal.* Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.17; H, 10.28.

3β-Acetoxy-23,24-bisnorchol-5-en-24-al (3)——To a solution of **2** (6 g) in CH_2Cl_2 (34 ml) was added pyridinium chlorochromate (6 g) in CH_2Cl_2 (34 ml). After stirring for 1.5 hr at 0°, the reaction mixture was extracted with ether. The crude product was chromatographed on florisil column to give **3** (5.1 g), mp 111.5—112.5°. $[\alpha]_D^{20}$ −5.34° (c=4.2).

24-Norchola-5,22-dien-3β-ol Acetate (4)——*n*-Butyl lithium (10.3 ml of 15% solution in *n*-hexane) was added to a suspension of methyl triphenyl phosphonium bromide (6.3 g) in ether. After stirring for 1 hr, 3 (2 g) in THF (40 ml) was added, and the mixture was further stirred for 1 hr and refluxed for 17 hr. After the usual work up (ether), the crude product was acetylated with acetic anhydride and pyridine. The acetate was purified on silica gel column. Elution with benzene gave 1.63 g of **4**, mp 122—124° (from methanol). $[\alpha]_D^{20}$ −66.7° (c=5.5). IR ν_{max}^{KBr}: 1730, 1635, 1255 cm^{-1}. NMR δ: 0.69 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.04 (3H, d, J=6 Hz, 20-Me), 2.01 (3H, s, Ac), 4.60 (1H, m, 3α-H), 4.78 (1H, dd, J=9.8 Hz, 5 Hz, 23-H), 4.86 (1H, dd, J=17.5 Hz, 5 Hz, 23-H), 5.65 (1H, m, J=9.8 Hz, 17.5 Hz, 8 Hz, 22-H). *Anal.* Calcd. for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.06; H, 10.26.

24-Norchol-5-ene-3β,22,23-triol 3-Acetate (5a and 5b)——The olefin (**4**) (140 mg, 0.55 mM) in dry ether (10 ml) was stirred with osmium tetroxide (140 ml, 0.55 mM) at room temperature for 19 hr. After evaporation of ether, the residue was treated with sodium bisulfite (520 mg) in aqueous pyridine (5 ml) at room temp. for 3 hr. The usual work-up (ether) afforded the 22,23-glycol (a mixture of **5a** and **5b**), mp 219—222° (from acetone). $[\alpha]_D^{20}$ −49.7° (c=3.0). IR ν_{max}^{KBr}: 3330, 1735, 1255 cm^{-1}. NMR δ: 0.69 (3H, s, 13-Me), 0.97 (3H, d, J=6 Hz, 20-Me), 1.02 (3H, s, 10-Me), 2.02 (3H, s, Ac), 3.5—3.9 (3H, m, 22-H, 23-H_2), 4.6 (1H, m, 3α-H), 3.37 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.21; H, 9.91.

[22*S*]-3β-Acetoxy-24-norchol-5-ene-22,23-diol 23-*p*-Toluenesulfonate (6a) and [22*R*]-3β-Acetoxy-24-norchol-5-ene-22,23-diol 23-*p*-Toluenesulfonate (6b)——The 22,23-glycol (a mixture of **5a** and **5b**) (3.3 g, 8.18 mM) in pyridine (43 ml) was stirred with *p*-toluenesulfonyl chloride (1.87 g, 9.87 mM) at room temp. for 24 hr. The usual work-up (ether) gave the crude tosylate (4.8 g), which was chromatographed on silica gel (300 g). Benzene fraction gave the pure 22*S*-tosylate (2.78 g), mp 104—106° (from hexane–acetone). $[\alpha]_D^{20}$ −14.2° (c=10.0). NMR δ: 0.66 (3H, s, 13-Me), 0.92 (3H, d, J=6 Hz, 20-Me), 1.01 (3H, s, 10-Me), 2.03 (3H, s, Ac), 2.46 (3H, s, CH_3-Ph), 3.90—4.20 (3H, m, 22-H, 23-H_2), 4.60 (1H, m, 3α-H), 5.37 (1H, m, 6-H). *Anal.* Calcd. for $C_{32}H_{46}O_6S$: C, 68.78; H, 8.30; S, 5.74. Found: C, 68.68; H, 8.38; S, 5.68. Benzene–ether (50: 1) fraction gave the 22*R*-tosylate (0.78 g), mp 98—101° (from methanol). $[\alpha]_D^{20}$ −15.8° (c=3.0). NMR δ: 0.65 (3H, s, 13-Me), 0.84 (3H, d, J=6 Hz, 20-Me), 1.01 (3H, s, 10-Me), 2.03 (3H, s, Ac), 2.44 (3H, s, CH_3-Ph), 3.97 (3H, bs, 22-H, 23-H_2), 4.60 (1H, m, 3α-H), 5.37 (1H, m, 6-H), 7.34 (2H, d, J=8 Hz, Ph), 7.78 (2H, d, J=8 Hz, Ph). *Anal.* Calcd. for $C_{32}H_{46}O_6S$: C, 68.78; H, 8.30; S, 5.74. Found: C, 68.42; H, 8.27; S, 5.74.

[22*S*]-22,23-Epoxy-24-norchol-5-en-3β-ol Acetate (7a)——The 22*S*-monotosylate (**6a**) (249 mg, 0.45 mM) in methanol (9.5 ml) was refluxed with anhydrous potassium carbonate (48 mg) for 10 min. The usual work-up (ether) afforded the crystalline epoxide (**7a**), mp 139—141° (from methanol). $[\alpha]_D^{20}$ −59.9° (c=5.0). NMR δ: 0.68 (3H, s, 13-Me), 0.96 (d, J=6 Hz, 20-Me), 1.02 (3H, s, 10-Me), 2.02 (3H, s, Ac), 2.40 (1H, q, 23-H), 2.70 (2H, m, 22-H, 23-H), 4.60 (1H, m, 3α-H), 5.37 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{38}O_3$: C, 77.61; H, 9.91. Found: C, 77.71; H, 9.92.

[22*R*]-22,23-Epoxy-24-norchol-5-en-3β-ol Acetate (7b)——By the same procedure described in **7a**, the 22*R*-monotosylate (93 mg, 0.17 mM) gave the 22*R*-epoxide (**7b**) (61 mg), mp 128—130° (from methanol) $[\alpha]_D^{20}$ −64.62° (c=1.0). NMR δ: 0.68 (3H, s, 13-Me), 0.96 (3H, d, J=6 Hz, 20-Me), 1.02 (3H, s, 10-Me), 2.02 (3H, s, Ac), 2.70 (3H, m, 22-H, 23-H_2), 4.60 (1H, m, 3α-H), 5.70 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{38}O_3$: C, 77.61; H, 9.91. Found: C, 77.43; H, 9.84.

[22*R*]-22,23-Epoxy-24-norchol-5-en-3β-ol Acetate (7b)——To a stirred solution of sodium dimethylsulfonium methylide in DMSO prepared by the Corey's method[11] from 612 mg of trimethylsulfonium iodide was added a solution of the 22-aldehyde (**3a**) (200 mg) in THF (2 ml) at 0°. After 1 hr, ice was added and extracted with chloroform. The crude product was chromatographed on silica gel column with benzene to afford 100 mg of the 22*R*-epoxide 3-acetate (**7b**) and 99 mg of the 22*R*-epoxide 3β-ol (**7b**, 3-OH).

[22*R*]-Cholesta-5,25-diene-3β,22-diol (8a)——Methally chloride (1 ml) was added to a mixture of magnesium (240 mg) and THF (1.5 ml) in a portion of 0.2 ml every 15 min at 0°. After stirring for 1 hr at 0°, the 22*S*-epoxide (**7a**) (144 mg) was added to the solution and the stirring was continued for further 1 hr at 0°. After addition of 2 N HCl, the product was extracted with ethyl acetate. The usual work-up (ethyl acetate) afforded the 22*R*-hydroxy compound (**8a**) (183 mg), mp 174—175° (from hexane-acetone). NMR δ (C_5D_5N): 0.67 (3H, s, 13-Me), 1.70 (3H, bs, 25-Me), 3.70 (2H, m, 3α-H, 22-H), 4.66 (2H, bs, 26-H_2), 5.35 (1H, m, 6-H). *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.85; H, 10.97.

[22*S*]-Cholesta-5,25-diene-3β,22-diol (8b)——By the same procedure for **8a**, **7b** (25 mg) afforded the 22*S*-hydroxy compound (**8b**) (21 mg) (amorphous). NMR δ (C_5D_5N); 0.75 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.70 (3H, bs, 25-Me), 3.80 (2H, m, 3α-H, 22-H), 4.70 (2H, bs, 26-H_2), 5.30 (1H, m, 6-H).

[22*R*]-24ξ-Methylcholesta-5,25-diene-3β,22-diol (9a)——β,γ-Dimethylallyl chloride (1.05 ml) was added to a stirring mixture of magnesium (750 mg) and THF (1.5 ml) in a portion of 0.1 ml every 10 min at 0—10°, and the mixture was stirred for 1 hr. To this solution, the 22*S*-epoxide 3-THP ether (**7a**, 3-THP) (450 mg) in THF (5 ml) was added and the mixture was stirred for 1 hr at 0°. Addition of 2 N HCl and extraction with ethyl acetate gave 500 mg of the 22*R*-hydroxyl 3-THP ether (**10a**) (amorphous). NMR δ: 0.66 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.65 (3H, bs, 25-Me), 3.2—4.0 (4H, m), 4.65 (3H, m, 26-H_2, 2′H of THP), 5.30 (1H, m, 6-H).

The 3-THP ether (**10a**) was hydrolyzed with 3 N HCl in methanol at room temp. for 1 hr to give the 3-ol (**9a**) (amorphous). NMR δ: 0.65 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.67 (3H, bs, 25-Me), 3.60 (2H, m, 3α-H, 22-H), 4.70 (2H, m, 26-H_2), 5.35 (1H, m, 6-H).

24ξ-Methyl-3β-tetrahydropyranyloxy-cholesta-5,25-dien-22-one (**11**)——The 22-ol 3-THP ether (**10a**) (55 mg) in dichloromethane (1 ml) was added to a mixture of chromic trioxide (90 mg), pyridine (0.3 ml) and dichloromethane (2 ml), and the reaction mixture was stirred for 1.5 hr. The crude product (54 mg) was extracted and chromatographed on silica gel affording 22 mg of the 22-one (**11**), mp 139.5—141°. MS *m/e*: 412, 394, 301, 283. *Anal.* Calcd. for $C_{33}H_{52}O_3$: C, 79.78; H, 10.55. Found: C, 79.73; H, 10.53.

[22*S*]-**24ξ-Methylcholesta-5,25-diene-3β,22-diol** (**9b**)——By the similar procedure as for **9a**, the 22*R*-epoxide (**7b**) (190 mg) gave the 22*S*-ol (**9b**) (180 mg), mp 176—178°. NMR δ: 0.70 (3H, s, 13-Me), 1.02 (3H, s, 10-Me), 1.67 (3H, bs, 25-Me), 3.65 (2H, m, 3α-H, 22-H), 4.80 (2H, m, 26-H_2), 5.35 (1H, m, 6-H).

[22*S*]-**22-Hydroxycholesterol 3-THP Ether** (**12b**)——A solution of isoamyl bromide (1.36 g) in THF (7 ml) was added to magnesium (243 mg) and the mixture was stirred for 1 hr at room temp. To this Grignard solution, the 22-aldehyde 3-THP ether (**3b**) (1.24 g) in THF (20 ml) was added dropwise at 0°. After stirring for 2 hr, ammonium chloride solution was added and the mixture was extracted with ether. The usual work-up gave 1.21 g of crude product. Recrystallization from acetone gave 840 mg of **12b**.

[22*R*]-**22-Hydroxycholesterol 3-THP Ether** (**12a**)——A solution of **12b** (292 mg) in pyridine (4 ml) and methanesulfonyl chloride (1 ml) was stirred for 4 hr at room temp. Ice-water was added to the solution and the mixture was extracted with ether. The usual work-up gave 321 mg of the crude product. NMR δ: 0.70 (3H, s, 13-Me), 0.90 (6H, d, 25-Me_2), 1.01 (3H, s, 10-Me), 2.99 (3H, s, mesylate), 4.75 (1H, 2'H of THP).

The crude mesylate (208 mg) was dissolved in dimethylsulfoxide (7 ml)–dimethylformamide (7 ml), and dicyclohexyl-18-crown-6 (560 mg) and potassium superoxide (107 mg) were added. After stirring for 1 hr at room temp., the solution was extracted with ether. The usual work-up gave 180 mg of crude product, which was dissolved in methanol (20 ml). Then 3 drops of 2 N HCl was added. After stirring for 2 hr, the mixture was extracted with ether. The usual work-up afforded the [22*R*]-22-hydroxycholesterol (155 mg) (**12a**, 3-OH), mp 180—182°.[21]

[22*S*]-**22-Hydroxycholesterol** (**12b, 3-OH**)——By the same procedure for [22*R*]-22-hydroxycholesterol, 22*R*-hydroxy 3-THP ether (**12a**) (200 mg) gave [22*S*]-22-hydroxycholesterol (**12b**, 3-OH) (170 mg), mp 179°.[21]

[22*R*]-**24ξ-Methylcholesta-5,25-diene-3β,22-diol** (**9a**) **from** [22*S*]-**24ξ-Methylcholesta-5,25-diene-3β,22-diol 3-THP Ether** (**10b**)——22*R*-Epoxide 3-acetate (**7b**) (470 mg) was treated with 3% NaOH in methanol–ether (3: 1) for 1 hr at room temp. The usual work-up (ether) gave the crude 3-ol, which was treated with dihydropyran (450 mg) in methylene chloride (20 ml) containing catalytic amount of *p*-toluenesulfonic acid for 1 hr at room temp. The usual work-up (CH_2Cl_2) afforded the 3-THP ether (**7b**, 3-THP). The Grignard reaction was carried out by the same method for **9a**, and the 3-THP ether (**10b**) was treated with methanesulfonyl chloride followed by potassium superoxide as the same procedure described for **12a** yielding 350 mg of **9a**.

[24*S*]-**Cholest-5-ene-3β,24-diol 3-THP Ether** (**13b**)——A solution of [24*S*]-cholest-5-ene-3β,24-diol dibenzoate[16] (200 mg) in THF (20 ml) and methanol (5 ml), was added to 5% KOH–methanol (0.37 ml), and the mixture was stirred for 12 hr. The usual work-up (ethyl acetate) gave 183 mg of crude product. The product in benzene (10 ml) was stirred with dihydropyran (0.2 ml) and *p*-toluenesulfonic acid (20 mg) for 30 min at room temp. After the usual work-up (ethyl acetate), the product was chromatographed on silica gel column. Fraction of hexane–benzene (1: 1) gave 120 mg of the 3-THP 24-benzoate, which was hydrolyzed in THF (3 ml) with 5% KOH–methanol (7 ml) for 2.5 hr at reflux. The usual work-up (ethyl acetate) gave 100 mg of **13b** (amorphous). NMR δ: 0.68 (3H, s, 13-Me), 3.2—3.4 (4H, m), 1.00 (3H, s, 10-Me), 4.7 (1H, m, 2'H of THP), 5.4 (1H, m, 6-H).

[24*R*]-**Cholest-5-ene-3β,24-diol 3-THP Ether** (**14a**)——A mixture of **13b** (68 mg), pyridine (1.1 ml) and methanesulfonyl chloride (0.3 ml) was stirred for 20 min at room temp. The usual work-up (ethyl acetate) gave 82 mg of the mesylate. The mesylate was dissolved in DMF (4 ml) and DMSO (4 ml), and potassium superoxide (41 mg) and dicyclohexyl-18-crown-6 (207 mg) were added. The mixture was stirred for 1 hr at 0°, and then for 12 hr at room temp. The usual work-up (ether) and silica gel chromatography gave 49 mg of **14a**. After hydrolysis of THP ether, the diol was led to dibenzoate, mp 143.5—145.5°, which was identical with that of the authentic sample.[16]

[24*S*]-**Cholest-5-ene-1α,3β-24-triol 1,3-DiTHP Ether** (**13e**)——A solution of [24*S*]-cholest-5-ene-1α,3β,24-triol 1-acetate 3,24-dibenzoate[18] (150 mg) in THF (10 ml), MeOH (10 ml) and 5% KOH–MeOH (2.7 ml), was stirred for 12 hr at room temp. The usual work-up gave 123 mg of crude product of the 1α,3β,24-triol 24-benzoate (foam). NMR δ: 0.64 (3H, s, 13-Me), 3.7—4.1 (2H, m, 1β-H, 3α-H), 4.8—5.2 (1H, m, 24-H), 5.5—5.7 (1H, m, 6-H), 7.4—8.2 (5H, m, Ph).

To a solution of the 24-benzoate (165 mg), was added dihydropyran (0.4 ml) and *p*-toluenesulfonic acid (20 mg), and the mixture was stirred for 30 min. The usual work-up (ethyl acetate) and silica gel chromatography provided the 1,3-di-THP 24-benzoate (**13d**) (amorphous). NMR δ: 0.66 (3H, s, 13-Me), 1.02 (3H, s,

21) E.P. Burrows, G.M. Hornby, and E. Caspi, *J. Org. Chem.*, 34, 103 (1969).

10-Me), 3.2—4.2 (6H, m), 4.7—5.1 (3H, m, 2'H of THP, 24-H), 5.5 (1H, m, 6-H), 7.4—8.2 (5H, m, Ph).

The 24-benzoate 1,3-di-THP ether (**13d**) was dissolved in THF (6 ml) and 5% KOH–MeOH (15 ml), and refluxed for 2.5 hr. The usual work-up (ethyl acetate) and silica gel chromatography gave 93 mg of the 1,3-di-THP ether 24-ol (**13e**). NMR δ: 0.69 (3H, s, 13-Me), 1.00 (3H, s, 10-Me), 3.2—4.2 (7H, m), 4.7 (2H, m, 2'H of THP), 5.5 (1H, m, 6-H).

[24*R*]-Cholest-5-ene-1α,3β,24-triol 1,3-DiTHP Ether (14c)——To a solution of **13e** (92 mg) in pyridine (1.5 ml) was added methanesulfonyl chloride (0.4 ml), and stirred for 15 min at room temp. The usual work-up (ether) gave 97 mg of the crude mesylate (**13f**). The mesylate was dissolved in DMSO (4 ml) and DMF (4 ml), and potassium superoxide (40 mg) and dicyclohexyl-18-crown-6 (200 mg) were added. The mixture was stirred for 1 hr at 0° and for 12 hr at room temp. The usual work-up (ethyl acetate) and silica gel chromatography of the crude product provided 89 mg of [24*R*]-cholest-5-ene-1α,3β,24-triol 1,3-di-THP ether (**14c**). As the usual procedure the compound (**14c**) was led to [24*R*]-cholest-5-ene-1α,3β,24-triol 3,24-dibenzoate (**14d**), mp 168.5—169.6°, which was identical with that of the authentic sample.[18]

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