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Synthesis of Demethylgorgosterol and Its Stereoisomers[1)]

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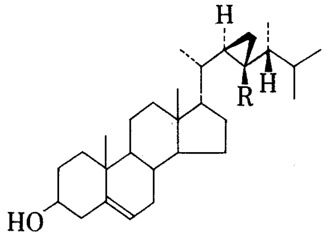
A stereoselective synthesis of demethylgorgosterol (**2**) is described. Alkylation at the C-22 position of the steroidal 23-aldehyde (**5**) was achieved by Claisen rearrangement of the piperidine enamine to give the (22*S*)-22-aldehyde (**10a**) predominantly. Compound **10a** was transformed to the 22-hydroxymethyl-24-aldehyde mesylate (**15a**). When the mesylate was treated with potassium *t*-butoxide, the 22,23-cyclopropyl 24-aldehyde (**19a**) was obtained in high yield. An isopropyl group was introduced at the C-24 position by means of the Grignard reaction and subsequently the hydroxy group was oxidized to provide the 24-ketone (**25a**). Wittig reaction of **25a** followed by hydroboration and then $LiAlH_4$ reduction of the mesylate gave **2**, which was identical with the natural compound in all physical properties. Three other epimers, the (22*R*,23*R*,24*S*)-isomer (**32**), (22*S*,23*S*,24*R*)-isomer (**34**) and (22*S*,23*S*,24*S*)-isomer (**35**), were prepared by the same procedure. These four isomers can be separated by gas–liquid chromatography on a glass capillary column coated with OV-17.

Keywords——demethylgorgosterol; isomers of demethylgorgosterol; sterol with cyclopropane ring; steroidal side chain; C-22 alkylation by Claisen rearrangement; stereoselective synthesis; marine sterol

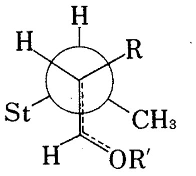
In 1969, Scheuer[3)] reported the isolation of gorgosterol (**1**) from *Palythoa tuberculosa*, and subsequently its structure, with an unusual side chain including a cyclopropane ring was established.[4)] Other 22,23-cyclopropyl sterols, *i.e.*, demethylgorgosterol (**2**),[5)] acanthasterol,[6)] demethylacanthasterol,[7)] acanthastanol,[8)] and 9,11-secogorgosterol,[9)] all of which have 22*R*, 23*R* and 24*R* configurations, have been isolated from marine sources. A stereoselective synthesis of the natural demethylgorgosterol was reported by us[10)] in a preliminary form. The synthesis was also reported by Djerassi[11)] at the same time. This paper describes our synthesis of the compound in detail.

As a part of our investigation on the stereochemistry in the reaction of steroidal side chains, we explored some reactions of the C-22 double bond and aldehyde in order to elucidate their stereochemical course, and we proposed a model to explain the observed stereoselectivity.[12)] According to this model, we can assume that alkylation at the C-22 position of a steroidal 23-aldehyde will proceed *via* conformation I rather than conformation II. This will afford the asymmetric carbon at C-22 in a suitable configuration for the synthesis of demethylgorgosterol (**2**). Thus, the alkylation of C-23 aldehyde was investigated first.

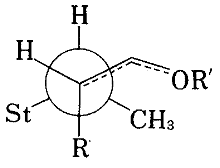
The 23-aldehyde **5** was prepared from the C-22 aldehyde **3** *via* the methoxyolefin **4** and from the 22-iodide (**6**)[13)] *via* the dithiane derivative **7** in 30% and 60% yields, respectively. This aldehyde **5** was converted to the enamine **8** by using piperidine as a secondary amine in benzene. The double bond of the enamine **8** was shown to be *trans* by the signals in the olefinic region of the proton magnetic resonance (PMR) spectrum (δ 3.96 ppm, dd, $J=8$, 12 Hz for C-22-H and 5.96 ppm, d, $J=12$ Hz for C-23-H). Although this enamine **8** could be isolated, it was more convenient to react it with alkyl halides without isolation. Reactions of the enamine **8** with isoamyl bromide, methyl iodide or methyl α-bromoacetate, however, gave no C-alkylation product but afforded immonium salts which precipitated in the reaction medium. This result led us to prepare the immonium salt of the enamine **8** with allylbromide for a subsequent Claisen rearrangement[14)] to give the C-alkylation product. As we expected,



1 : R=CH_3
2 : R=H



I



II

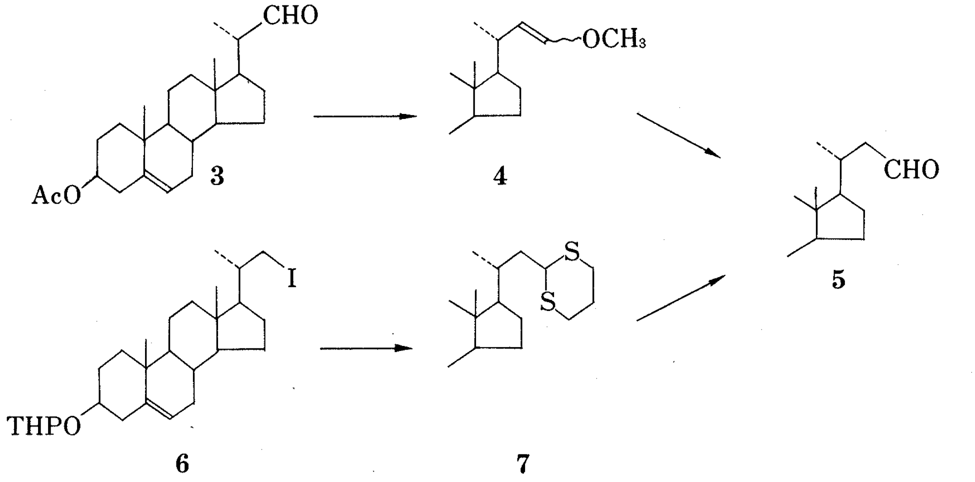


Chart 1

the reaction proceeded smoothly in refluxing benzene to provide an epimeric mixture of aldehydes, **10a** and **10b** thin–layer chromatography ((TLC), *Rf* 0.54 and 0.58, respectively, in benzene–ethyl acetate 30: 1 as a mobile phase), after hydrolysis of the resulting iminium salts. Gas–liquid chromatography (GLC) analysis on OV-101 at 260° revealed the ratio of aldehydes **10a** and **10b** to be 3: 2. Separation of these epimers by silica gel column chromatography provided **10a** and **10b** with the above ratio. The characteristic difference between these epimers in their PMR spectra was in the chemical shift of C-21-H_3, which was 0.82 ppm (d, $J=7$ Hz) for the less polar aldehyde **10b** and 1.02 ppm (d, $J=7$ Hz) for the more polar aldehyde **10a**. Reduction of the epimeric aldehyde **10a** or **10b** with sodium borohydride in ethanol gave the alcohol **11a** or **11b**, respectively, in quantitative yield. For practical preparation, an epimeric mixture of aldehyde **10a** and **10b** was reduced, and the resulting epimeric alcohols **11a** and **11b** were separated by silica gel column chromatography.

The configurations at C-22 of the epimeric alcohols **11a** and **11b** were deduced from their ^{13}C nuclear magnetic resonance (NMR) spectra. It is known that the C-23 carbon of 22*R*-hydroxycholesterol resonates at a higher field (27.5 ppm) than that of 22*S*-hydroxycholesterol (33.3 ppm), as a consequence of steric compression in conformation III and IV.[15] Therefore, we can assume that the chemical shift of the C-23 carbon will be higher in **11a** than in **11b**, and the opposite will be the case for the C-26 carbon. In fact, the major product **11a** showed a higher chemical shift (63.0 ppm) than the minor alcohol **11b** (64.5 ppm) for the C-26 carbon, and the C-23 carbon of the minor product **11b**, showed a higher chemical shift (30.5 ppm) than that of the major one **11a** (31.9 ppm). Thus, it can be concluded that the major alcohol **11a** has the *S* configuration at C-22 position and the minor product **11b** has the *R* configuration. This conclusion was confirmed by the successful conversion of the major epimer **11a** into 23-demethylgorgosterol **2**, as described later in this report. Consequently, the results obtained are consistent with the prediction of our model.

In addition, crotyl bromide reacted with the enamine **8** in refluxing benzene to give only one epimeric aldehyde (**12a**) after hydrolysis of the resulted enamine salt. The chemical shift of C-21-H_3 (1.02 ppm) in the PMR of the aldehyde **12a** and that of the C-26 carbon (62.3 ppm) in the ^{13}C NMR of the alcohol **12b** indicated that the product has *S* configuration at the 22-carbon. As expected from the model (conformations I and II), the γ-alkyl substituent (*i.e.* methyl group) of allyl bromide effectively influenced the stereoselectivity of this alkylation reaction at the C-22 position.

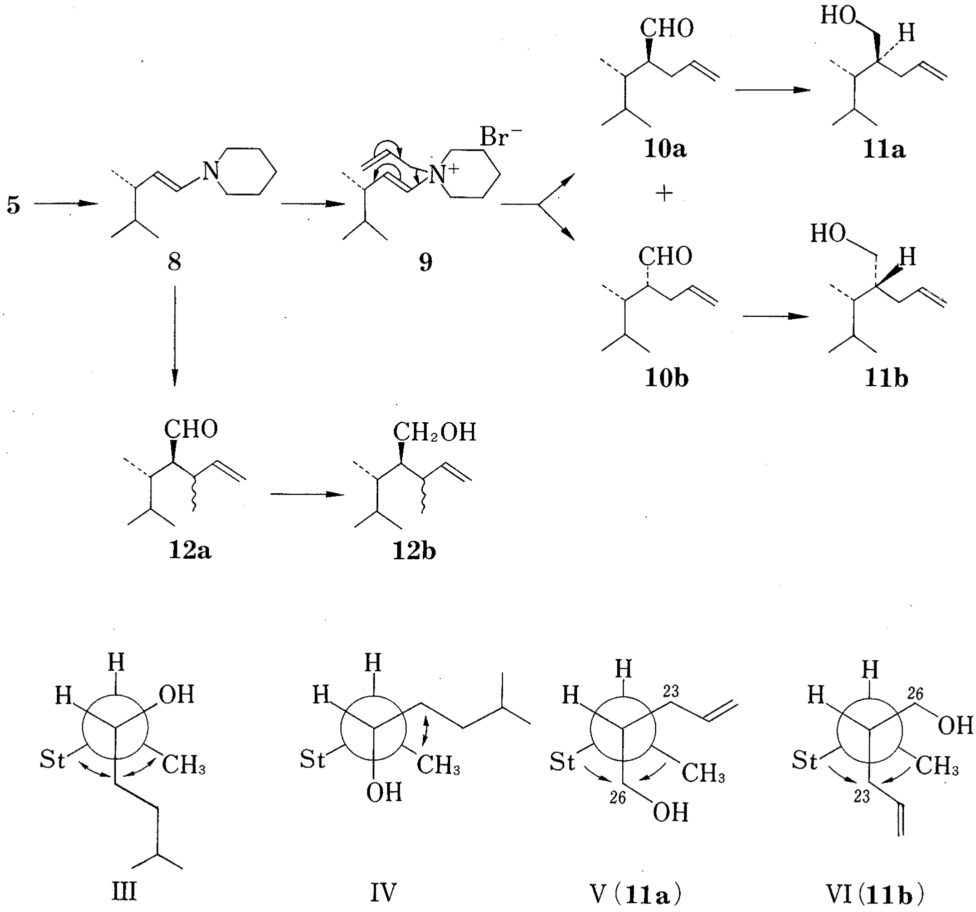


Chart 2

A synthetic approach to demethylgorgosterol (**2**) has already been reported by Djerassi *et al.*[16] They have, however, obtained only diastereomeric **25b** by direct methylenation of the Δ^{22}-24-ketone **26**. Since they reported that the 24-epimers of the 24-hydroxymethyl compounds, **33a** and **33b**, could be separated by chromatography, we anticipated that the 24-hydroxymethyl epimers, **29a** and **29b** could also be separated without difficulty. Therefore, we considered the 24-ketone **25a** to be the key compound. As described above, the major product **11a** from the alkylation of the 23-aldehyde **5** possesses a suitable configuration at C-22 for the synthesis of demethylgorgosterol 2. We attempted to convert this compound into the 24-ketone **25a**.

Treatment of the alcohol **11a** with methanesulfonyl chloride in pyridine gave the mesylate **13a** which was oxidized with N-methylmorpholine oxide in the presence of a catalytic amount of osmium tetroxide. The resulting diol **14a** was then cleaved by sodium metaperiodate in aqueous tetrahydrofuran to give the aldehyde **15a** (80% overall yield). In the same fashion, the minor alcohol **11b** was converted into the aldehyde **15b** in a similar yield. It is interesting to note that when the mesylate **16** of **12b** was treated with a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine oxide, only the cyclic ether **18** was isolated in 95% yield. This phenomenon can be explained in terms of the gem-dialkyl effect.[17] In other words, the extra methyl group at the C-23 position made the side chain of the diol **17** more flexible, and provided a suitable conformation for the formation of the cyclic ether **18**.

Treatment of the aldehydes **15a** and **15b** with 1.2 equivalents of potassium *t*-butoxide in ether at room temperature produced the cyclopropyl aldehydes **19a** and **19b** respectively, with similar reaction rates and in yields of 80%. The geometries of the cyclopropyl aldehydes **19a** and **19b** could be *trans* form.

The aldehyde **19a** was prepared from the 22-aldehyde **3** by an alternative method in a moderate yield (20%). Treatment of the aldehyde **3** with 3-butenyl magnesium bromide afforded the 22*S*-alcohol **20**, the configuration of which could be deduced from Cram's rule.[18] After mesylation of the alcohol **20**, the mesylate **21** was treated with a catalytic amount

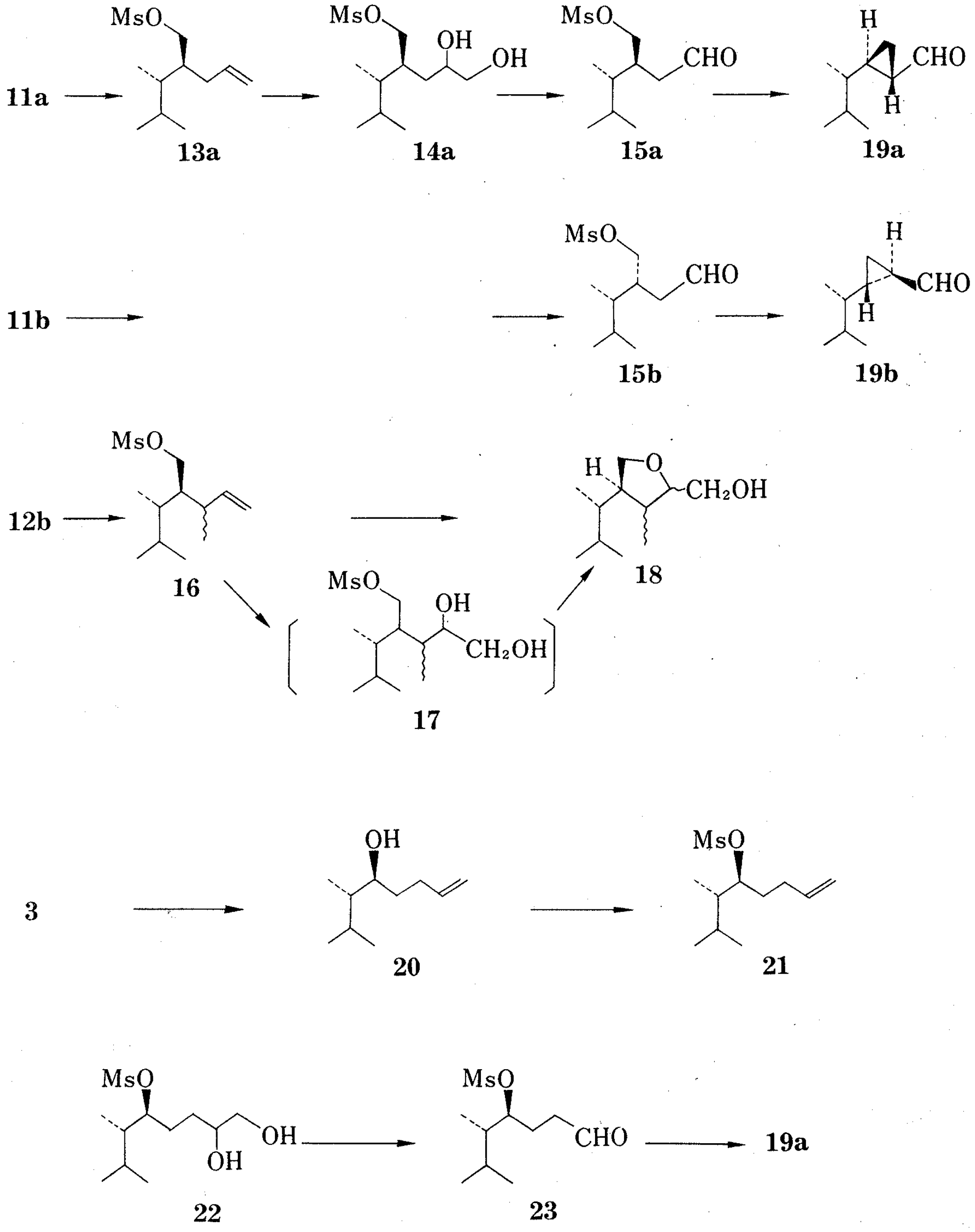


Chart 3

of osmium tetroxide in the presence of N-methylmorpholine oxide to provide the unstable diol **22**, which was converted into the aldehyde **23** by oxidation with sodium metaperiodate. Since this aldehyde **23** was too unstable to isolate, crude **23** was immediately treated with potassium t-butoxide at 0° to give the cyclopropyl aldehyde **19a**.

The aldehyde **19a** reacted with isopropyl magnesium bromide at −18° to afford the 24-alcohol **24a** which was oxidized with pyridinium chlorochromate in methylene chloride to give the desired cyclopropyl ketone **25a**. The isomeric cyclopropyl aldehyde **19b** was also converted into the 24-ketone **25b** in a similar yield.

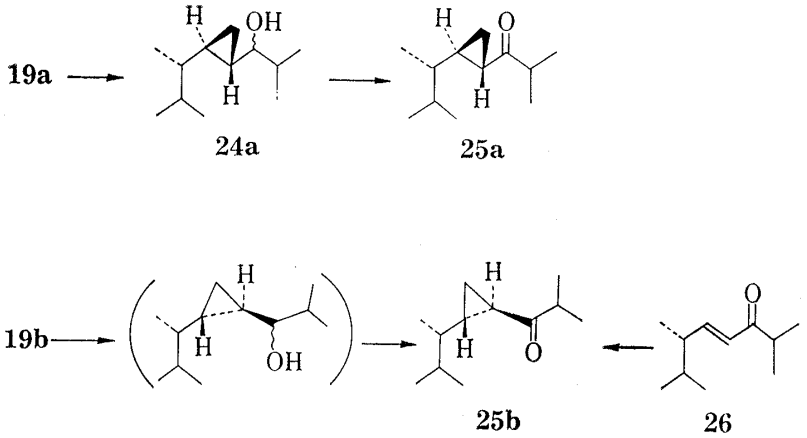


Chart 4

At this stage, we attempted to compare the synthesized samples of these two isomeric cyclopropyl ketones **25**, with a sample of the known 22*S*,23*R*-cyclopropyl ketone **25b**, which had been structurally confirmed by X-ray analysis.[16], Thus we prepared a sample of this ketone **25b** from the enone **26** according to the method reported by Djerassi *et al.*[16] Comparison of their spectra, melting points and chromatographic behavior (TLC) showed that the more polar cyclopropyl ketone **25b** (*Rf* 0.45: five developments with 1% ethyl acetate in benzene as the mobile phase) was identical with the known cyclopropyl ketone **25b** derived from the enone **26**. Accordingly, the less polar ketone **25a** (*Rf*, 0.48) has the desired configuration (22*R*, 23*S*), confirming our assignments of the configurations at C-22 position of the 22-hydroxymethyl derivative **11a** and **11b** from their C-13 NMR spectra.

The cyclopropyl ketone **25a** was converted into demethylgorgosterol **2** and its C_{24}-epimer **32** by the method described by Djerassi *et al.*[16] Treatment of the 24-ketone **25a** with methylene triphenylphosphorane in tetrahydrofuran gave the 24-methylene derivative **27a**. For protection of the 5,6-double bond, this compound **27a** was converted to a 3,5-cyclo-6β-methoxy derivative **28a** by a usual method.[19] Hydroboration of this protected olefin **28a** with excess diborane-THF complex at room temperature and subsequent oxidation with 30% hydrogen peroxide gave an epimeric mixture of 24-hydroxymethyl derivatives **29a** and **29b** in an almost equimolar ratio. These epimers were separated by preparative TLC (developing twice with 1% ethyl acetate in benzene) to give the more polar epimer **29a** (*Rf* 0.35) and the less polar one **29b** (*Rf* 0.39).[20] The hydroxy group of the more polar epimer **29a** was mesylated with methanesulfonyl chloride in pyridine. This mesylate **30** was refluxed with excess lithium aluminum hydride in tetrahydrofuran to yield the 24-methyl compound **31**. Acid treatment (*p*-toluenesulfonic acid in aqueous dioxane) of the 3,5-cyclo-6-methyl ether **31** afforded the desired demethylgorgosterol **2**. This compound was identical with the natural demethylgorgosterol as regards PMR, infrared (IR) and mass spectra (MS), melting point, molecular rotation and chromatographic behavior (TLC and GLC). The less polar hydroxymethyl derivative **29b** was also converted into 24-epidemethylgorgosterol **32**. The other two diastereoisomers **34** and **35**, previously prepared by Djerassi *et al.*,[16] were also obtained from cyclopropyl ketone **25b** in the same fashion.

As described here, we could prepare demethylgorgosterol **2** and its three isomers **32**, **34** and **35**. Separation of these four isomers was previously thought to be impossible by conventional methods (TLC and GLC). However, we found that GLC equipped with a glass capillary column coated with OV-17 could resolve these four diastereomers.[10] This method should be very useful for analysis of synthetic and/or natural sterols which bear epimeric carbons on their side chains. These four epimers can also be distinguished by NMR (360 MHz) as reported by Djerassi.[11]

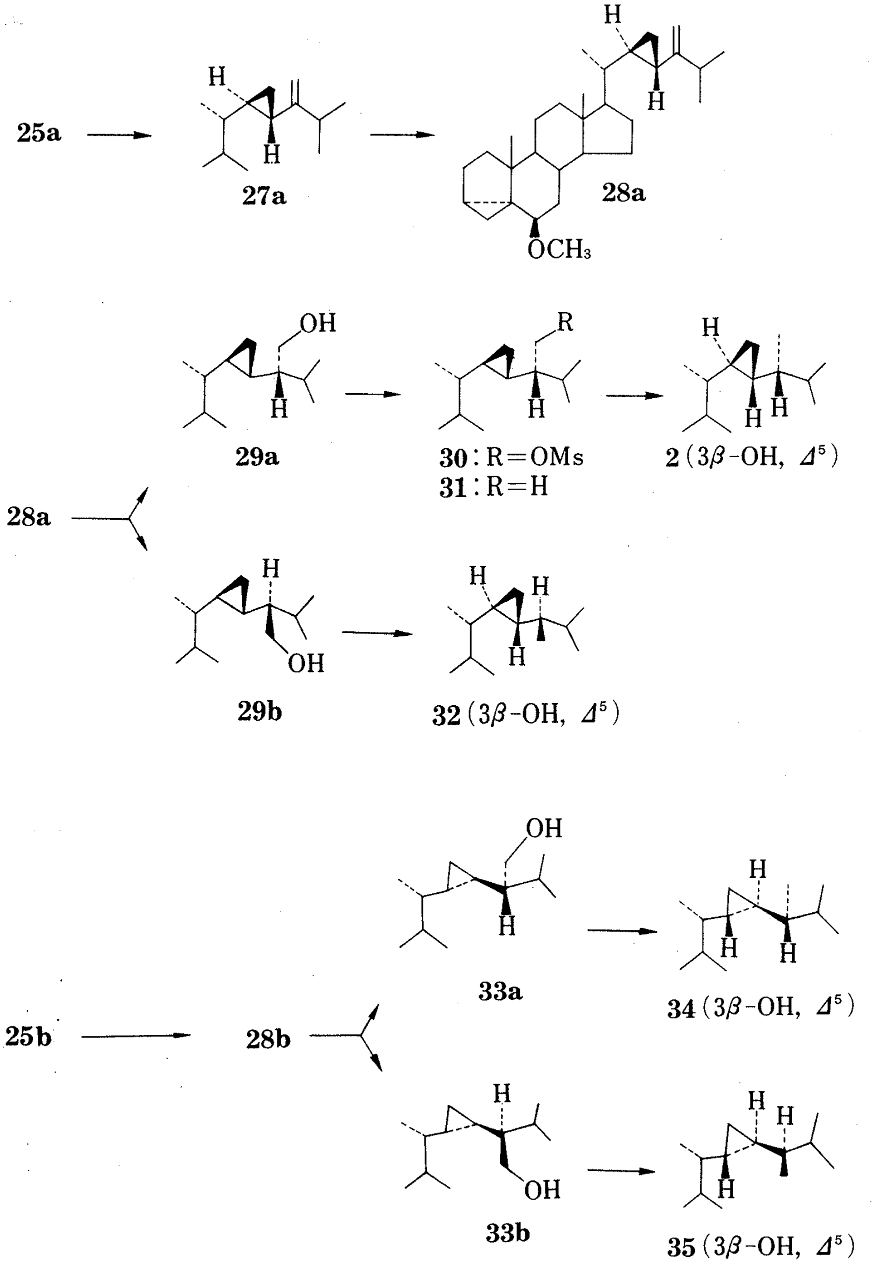


Chart 5

Experimental

Melting points were determined with a hot-stage microscope and are uncorrected. NMR spectra were obtained with a Hitachi R-24A spectrometer and a JEOL PS-100 spectrometer as solutions in $CDCl_3$. Chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane (TMS), and coupling constants (J) are expressed in Hz. MS were run on a Shimadzu-LKB 9000S instrument. Chloroform was used as a solvent for $[\alpha]_D$ measurements. "The usual work-up" refers to extraction with organic solvent, washing to neutrality, drying ($MgSO_4$), filtration, and evaporation to dryness under a vacuum. The following abbreviations are used: THF, tetrahydrofuran; *p*-TsCl, *p*-toluenesulfonyl chloride; THP, tetrahydropyranyl ether; NMO, N-methylmorpholin oxide; MsCl, methanesulfonyl chloride; s, singlet; d, doublet; t, triplet; m, multiplet; AcOEt, ethyl acetate; r.t., room temperature.

3β-Acetoxy-23-nor-chol-5-en-24-al (5)——*n*-Butyl lithium (103 ml; 1.56 M solution in hexane) was added dropwise to a stirred solution of methoxymethyl triphenyl phosphonium chloride (61.5 g) in THF (500 ml) at −10°. The mixture was stirred at r.t. for 5 min, then a solution of **3** (15.6 g) in THF (100 ml) was added. The mixture was stirred at r.t. for 30 min. The usual work-up with AcOEt for extraction gave the product **4** (3-OH). The crude product was dissolved in a mixture of acetic anhydride and pyridine, and the solution was stirred at r.t. for 2 hr. The usual work-up with AcOEt for extraction gave yellow crystals, which were chromatographed on silica gel. The methoxyolefin **4** (14 g) was eluted with benzene/AcOEt (100/1).

4a (*E* form): mp 136—137°, NMR δ: 6.24 (1H, d, $J=12$ Hz, 23-H), 5.37 (1H, m, 6-H), 4.61 (1H, dd, $J=12$ Hz, 8 Hz, 22-H), 4.6 (1H, m, 3-H), 3.48 (3H, s, CH_3O), 2.03 (3H, s, AcO), 1.05 (3H, d, $J=6$ Hz, C-21-H_3), 1.03 (3H, s, C-19-H_3), 0.71 (3H, s, C-18-H_3), *Anal.* Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 78.17; H, 10.09.

4b (*Z* form): mp 148—154°, NMR δ: 5.70 (1H, d, $J=6$ Hz, 23-H), 5.34 (1H, m, 6-H), 4.6 (1H, m, 3-H), 4.15 (1H, dd, $J=6$ Hz, 22-H), 3.57 (3H, s, CH_3O), 2.05 (3H, s, AcO), 1.07 (3H, s, C-19-H_3), 0.99 (3H, d, $J=7$ Hz, C-21-H_3), 0.66 (3H, s, C-18-H_3), *Anal.* Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 77.91; H, 10.09.

A stirred solution of **4** (13 g) in dioxane (200 ml) was treated with 2 N H_2SO_4 (100 ml) at r.t. and the mixture was heated at 70° for 30 min. The usual work-up with ether for extraction gave a crude product, which was chromatographed on silica gel. The 23-aldehyde **5** (6.2 g) was eluted with benzene, mp 123—125°, $[\alpha]_D$: −149.8°, NMR δ: 9.72 (1H, t, $J=2$ Hz, CHO), 5.35 (1H, m, 6-H), 4.58 (1H, m, 3-H), 2.01 (3H, s, AcO), 1.02 (3H, d, $J=6$ Hz, C-21-H_3), 1.02 (3H, s, C-19-H_3), 0.72 (3H, s, C-18-H_3); MS *m/e*: 326 (M^+-AcOH), 315 (C_{17-22} cleavage), 255 (315−AcOH). *Anal.* Calcd for $C_{24}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.68; H, 9.94.

24-Iodo-22,23-bisnorchol-5-en-3β-ol 3-THP (6)——NaI (39.6 g) was added to a solution of the 22-alcohol tosylate (50.2 g) in acetone (1300 ml). The mixture was refluxed for 18 hr. The solvent was evaporated off and the usual work-up with AcOEt for extraction gave a yellow product (36.4 g), which was chromatographed on silica gel. The iodide **6** (27 g) was eluted with benzene. **6**: NMR δ 5.3 (1H, m, 6-H), 4.7 (1H, m), 4.2—3.1 (5H, m, 3-H, THP-6-H_2, CH_2I), 1.00 (3H, s, C-19-H_3), 0.71 (3H, s, C-18-H_3); MS *m/e*: 442 (M^+-DHP), 424 ($M^+-THPOH$), 409 ($424-CH_3$), 357 (C_{17-22} cleavage), 255 (357−THPOH).

3β-Tetrahydropyranyloxy-22,23-bisnorchol-5-en-24-al-24-(1,3-dithiane-2-)acetal (7)——*n*-Butyl lithium (52 ml, 1.56 M solution in hexane) was added to a solution of 1,3-dithiane (9.4 g) in THF (120 ml) at −18° under argon. A solution of the iodide **6** (27 g) in THF (100 ml) was added dropwise to the mixture. The mixture was stirred at −18° for 2 hr, and at r.t. for 24 hr, then 2 N H_2SO_4 was added and the usual work-up, with AcOEt for extraction, gave the dithioacetal **7** (oil, 9.24 g): NMR δ: 5.35 (1H, m, 6-H), 4.7 (1H, m), 4.4—3.1 (4H, m, 3-H, THP-6-H_2, $CH{=}S_2$), 3.2—2.6 (4H, m, 1,3-dithiane 4,6-H_4), 1.01 (3H, s, C-19-H_3), 0.70 (3H, s, C-18-H_3).

3β-Acetoxy-23-norchol-5-en-24-al (5)——$HgCl_2$ (70 g) was added to a solution of acetal **7** (24.0 g) in aqueous CH_3CN (75%, 3000 ml), and the mixture was stirred under reflux for 2 hr. After filtration, the organic solution was washed with aqueous ammonium acetate. The usual work-up, with AcOEt for extraction, gave a yellow oil which was then dissolved in a mixture of pyridine (60 ml) and acetic anhydride (60 ml). This solution was heated at 70° for 3 hr. The usual work-up, with AcOEt for extraction, gave a yellow oil (16 g), which was chromatographed on silica gel. The aldehyde **5** (13 g) was eluted with benzene.

[22*S*] and [22*R*]-22-Formyl-26,27-bisnorcholesta-5,24-dien-3β-ol 3-Acetate (10a and 10b)——Piperidine (10 ml) was added to a solution of the 23-aldehyde **5** (9 g) in benzene (500 ml), and the mixture was refluxed for 1.5 hr, using a Dean–Stark trap. Allyl bromide (14 ml) was added and the mixture was refluxed for 45 hr. Water (100 ml) was then added and the whole was refluxed for 30 min. The usual work-up with ether for extraction gave a yellow oil (a mixture of **10a** and **10b**, 9.3 g), which was chromatographed on silica gel. The less polar aldehyde **10b** (2.74 g) was eluted with benzene/*n*-hexane (1/1). The more polar aldehyde **10a** (3.95 g) was eluted with benzene.

10a: mp 146—148°, NMR δ: 9.81 (1H, d, $J=2$ Hz, CHO), 6.0—5.5 (1H, m, 24-H), 5.4 (1H, m, 6-H), 5.2—4.9 (2H, m, 25-H_2), 4.6 (1H, m, 3-H), 2.04 (3H, s, AcO), 1.03 (3H, s, C-19-H_3), 1.03 (3H, d, $J=7$ Hz, C-21-H_3), 0.71 (3H, s, C-18-H_3); MS *m/e*: 366 (M^+-AcOH), 351 ($366-CH_3$), 255 (C_{17-22} cleavage−AcOH), 253 ($255-H_2$). *Anal.* Calcd for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 78.58; H, 9.86.

10b: mp 113—115°, NMR δ: 9.69 (1H, s, CHO), 6.1—5.6 (1H, m, 24-H), 5.38 (1H, m, 6-H), 5.2—4.9 (2H, m, 25-H_2), 4.6 (1H, m, 3-H), 2.03 (3H, s, AcO), 1.02 (3H, s, C-19-H_3), 0.82 (3H, d, $J=7$ Hz, C-21-H_3), 0.75 (3H, s, C-18-H_3); MS *m/e*: 366 (M^+-AcOH), 351 ($366-CH_3$), 255 (C_{17-22} cleavage−AcOH), 253 ($255-H_2$).

[22*S*] and [22*R*]-22-Hydroxymethyl-26,27-bisnorcholesta-5,24-dien-3β-ol 3-Acetate (11a and 11b)——A solution of the aldehyde **10a** (1.35 g) in THF (50 ml) and EtOH (5 ml) was treated with added $NaBH_4$ (120 mg), and the mixture was stirred at 0° for 1 hr. The usual work up, with AcOEt for extraction, gave white crystals of the alcohol **11a** (1.37 g): mp 156—157.5°, NMR δ: 5.84 (1H, m, 24-H), 5.39 (1H, m, 6-H), 5.08 (2H, m, 25-H_2), 4.60 (1H, m, 3-H), 3.58 (2H, m, CH_2OH), 2.04 (3H, s, AcO), 1.04 (3H, s, C-19-H_3), 0.86 (3H, d, J=6 Hz, C-21-H_3), 0.69 (3H, s, C-18-H_3); MS *m/e* 368 (M^+−AcOH), 353 (368−CH_3), 350 (368−H_2O), 255 (C_{17-22} cleavage−AcOH), 253 (255−H_2), *Anal.* Calcd for $C_{28}H_{44}O_3$: C, 76.38; H, 10.35. Found: C, 76.20; H, 10.41.

11b was prepared by the same procedure. **11b**: mp 139—140°, NMR δ: 5.80 (1H, m, 26-H), 5.37 (1H, m, 6-H), 5.04 (2H, m, 25-H_2), 4.6 (1H, m, 3-H), 3.56 (2H, m, CH_2OH), 2.04 (3H, s, AcO), 1.04 (3H, s, C-19-H_3), 0.85 (3H, d, J=7 Hz, C-21-H_3), 0.73 (3H, s, C-18-H_3).

22-Hydroxymethyl-23-methyl-26,27-bisnorcholesta-5,24-dien-3β-ol 3-Acetate (12b)——By the procedure described for **10a**, the reaction of the 23-aldehyde **5** (1 g) with crotyl bromide (0.5 ml) gave 600 mg of 22-formyl-23-methyl-26,27-bisnorcholesta-5,24-dien-3β-ol 3-acetate (**12a**) as an oil; NMR δ: 9.32 (1H, d, J=5 Hz, CHO), 5.60 (1H, m, 24-H), 5.18 (1H, m, 6-H), 5.0 (2H, m, 25-H), 4.60 (1H, m, 3-H), 2.70 (1H, m, 22-H), 2.03 (3H, s, Ac), 1.05 (3H, d, J=7 Hz, C_{23}–Me), 1.02 (3H, d, J=7 Hz, 21-C–H_3), 1.01 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3).

The aldehyde **12a** (300 mg) was reduced with 30 mg of $NaBH_4$ in a mixture of THF (6 ml) and EtOH (0.6 ml) to afford 280 mg of the crude 22-hydroxymethyl compound **12b**. Recrystallization from hexane gave 150 mg of **12b**: mp 177.5—178°, NMR δ: 5.87 (1H, m, 23-H), 5.37 (1H, m, 6-H), 5.06 (2H, dd, J=7, 14 Hz, 24-H), 4.60 (1H, b, 3-H), 3.62 (2H, m, CH_2OH), 2.03 (3H, s, AcO), 1.02 (3H, s, C-19-H_3), 1.00 (3H, d, J=6 Hz, C_{23}–Me), 0.86 (3H, d, J=6 Hz, C-21-H_3), 0.70 (3H, s, C-18-H_3); ^{13}C NMR 145.2 (C-24), 113.4 (C-25), 62.3 (C-26), 19.2 (C-19), 18.9 (C-21), 14.1 (C-23), 11.7 (C-18).

[22*S*]-22-Methanesulfonyloxymethyl-26,27-bisnorcholesta-5,24-dien-3β-ol 3-Acetate (13a)——A solution of the alcohol **11a** (1.37 g) and MsCl (1.0 ml) in pyridine (10 ml) was stirred at r.t. for 1 hr. Several pieces of ice and 2 N HCl solution were added, and the usual work up, with AcOEt for extraction, gave a foam (1.46 g), which was chromatographed on silica gel. The mesylate **13a** (1.37 g) was eluted with benzene. **13a**: mp 123.5—124.5°, NMR δ: 6.0—5.6 (1H, m, 24-H), 5.40 (1H, m, 6-H), 5.2—4.8 (2H, m, 25-H_2), 4.8—4.4 (1H, m, 3-H), 4.4—3.9 (2H, m, CH_2OMs), 2.99 (3H, s, CH_3SO_3), MS *m/e*: 446 (M^+−AcOH), 431 (446−CH_3), 350 (446−MsOH), 255 (C_{17-22} cleavage−AcOH), 253 (255−H_2), *Anal.* Calcd for $C_{29}H_{46}O_5S$: C, 68.72; H, 9.36. Found: C, 69.10; H, 9.36.

[22*S*]-22-Methanesulfonyloxy-26,27-bisnorcholest-5-ene-3β,24,25-triol 3-Acetate (14a)——To a solution of **13a** (1.01 g) in THF (20 ml), *t*-BuOH/THF/H_2O (10/3/1, 20 ml), NMO (640 mg) and a catalytic amount of osmium tetroxide were added. The mixture was stirred at r.t. for 6 hr. Saturated aq. $NaHSO_3$ solution was added to the mixture, and the whole was stirred at r.t. for 1 hr. The usual work-up, with AcOEt for extraction, gave an oil, which was chromatographed on silica gel. The glycol **14a** (1.13 g) was eluted with benzene/AcOEt (1/1). **14a**: NMR δ: 5.40 (1H, m, 6-H), 4.9—3.3 (6H, m, 3-H, CH_2OMs, 24-H, 25-H_2), 3.01 (3H, s, CH_3SO_3), 2.03 (3H, s, AcO), 1.00 (3H, s, C-19-H_3), 0.68 (3H, s, C-18-H_3).

[22*S*]-3β-Acetoxy-22-methanesulfonyloxymethyl-chol-5-en-24-al (15a)——Sodium metaperiodate (2.67 g) was added to a solution of the glycol **14a** (949 mg) in THF/H_2O (3/1) (36 ml) and the mixture was stirred at r.t. for 25 min. The usual work-up, with AcOEt for extraction, gave the aldehyde **15a** (foam, 921 mg): NMR δ: 9.50 (1H, bs, CHO), 5.4 (1H, m, 6-H), 4.7—3.7 (3H, m, 3-H, –CH_2OMs), 2.90 (3H, s, CH_3SO_3–) 2.00 (3H, s, AcO), 1.00 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3).

[22*R*,23*S*]-3β-Acetoxy-22,23-methanato-chol-5-en-24-al (19a)——A solution of the mesylate **15a** (555 mg) in ether (100 ml) was treated with *t*-BuOK (151 mg) under argon.

This solution was stirred at r.t. for 30 min, then a piece of ice and 2 N HCl solution were added. The usual work-up, with AcOEt for extraction, gave an oil **19a** (667 mg), which was chromatographed on silica gel. The cyclopropyl aldehyde **19a** (351 mg) was eluted with benzene/AcOEt (100/1). **19a**: mp 185—186.5°, NMR δ: 8.97 (1H, d, J=5 Hz, CHO), 5.4 (1H, m, 6-H), 4.6 (1H, m, 3-H), 2.00 (3H, s, AcO), 1.00 (3H, s, C-19-H_3), 0.60 (3H, s, C-18-H_3); MS *m/e*: 352 (M^+−AcOH), 337 (352−CH_3), 255 (C_{17-22} cleavage−AcOH), 253 (255−H_2), *Anal.* Calcd for $C_{27}H_{40}O_3$: C, 78.57; H, 9.77. Found: C, 78.79; H, 9.78.

[22*S*,23*R*]-3β-Acetoxy-22,23-methanato-chol-5-en-24-al (19b)——By the same procedure described for **19a**, **15b** provided the isomeric cyclopropyl aldehyde **19b**: mp 151.5—152.5°, NMR δ: 8.93 (1H, d, J=5 Hz, CHO), 5.4 (1H, m, 6-H), 4.6 (1H, m, 3-H), 2.00 (3H, s, AcO), 1.02 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3), *Anal.* Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.86; H, 10.01.

[22*S*]-26-Norcholesta-5,25-diene-3β,22-diol 3-Acetate (20)——4-Bromo-1-butene (8.2 g) was added dropwise to a mixture of magnesium (1.44 g) and THF (50 ml) at r.t. under argon. The mixture was stirred at −18° for 1 hr. A solution of the 22-aldehyde **3** (1.48 g) in THF (200 ml) was added to the Grignard reagent at −18° and the whole was stirred at −18° for 3 hr. Saturated aq. NH_4Cl solution was added to this reaction mixture at −18° and the usual work-up, with AcOEt for extraction, gave white crystals of **20** (15.9 g), which were recrystallized from methanol to give the pure alcohol **20** (10.9 g): mp 169—170.5°, NMR 6.1—5.6 (1H, m, 25-H), 5.5—5.3 (1H, m, 6-H), 5.2—4.8 (2H, m, 26-H_2), 4.8—4.4 (1H, m, 3-H), 3.8—3.6 (1H, m, 22-H), 2.03 (3H, s, AcO), 1.02 (3H, s, C-19-H_3), 0.90 (3H, d, J=6 Hz, C-21-H_3), 0.68 (3H, s, C-18-H_3). MS *m/e*:

368 (M^+-AcOH), 350 ($368-H_2O$), 335 ($350-CH_3$), 255 (C_{17-22} cleavage$-$AcOH), 253 ($255-H_2$), *Anal.* Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.25; H, 10.74.

[22*S*]-3*β*-Acetoxy-26-norcholesta-5,25-dien-22-ol 22-Methanesulfonate (**21**)——MsCl (5.8 ml) was added to a solution of the 22-alcohol **20** (10.9 g) in pyridine (75 ml) at r.t. and this solution was stirred at r.t. for 1 hr. The usual work-up with ether for extraction gave the mesylate **21** (12.6 g): mp 106.5—109.5°, NMR δ: 6.0—4.0 (5H, m, 25-H, 6-H, 26-H_2, =CHOMs), 2.99 (3H, s, CH_3SO_3), 2.00 (3H, s, AcO), 1.01 (3H, s, C-19-H_3), 0.69 (3H, s, C-18-H_3); MS *m/e* 446 (M^+-AcOH), 350 ($446-MsOH$), 335 ($350-CH_3$), 313 (C_{17-22} cleavage$-H_2$), 253 ($313-AcOH$).

[22*R*,23*S*]-3*β*-Acetoxy-22,23-methanato-chol-5-en-24-al (**19a**)——An alternative method: To a solution of **21** (12.6 g) in THF (90 ml), *t*-BuOH/THF/H_2O (10/3/1) (200 ml), NMO (8.6 g) and a catalytic amount of osmium tetroxide were added. The solution was stirred at r.t. for 2 hr. Saturated aq.$NaHSO_3$ solution was added to the mixture, and the whole was stirred at r.t. for 1 hr. The usual work-up with AcOEt for extraction gave a crude oil **22** (13.3 g).

Sodium metaperiodate (15 g) was added to a solution of a crude sample of the diol **22** (13.3 g) in THF/H_2O (3/1) (200 ml) and the mixture was stirred at r.t. for 30 min. The usual work-up, with AcOEt for extraction, gave the unstable aldehyde **23** (oil, 12.1 g): NMR δ: 9.27 (1H, s, CHO), 5.38 (1H, m, 6-H), 5.0—4.3 (1H, m, 3-H), 4.0—3.3 (1H, m, =CHOMs), 3.02 (3H, s, CH_3SO_3-), 2.00 (3H, s, AcO), 1.01 (3H, s, C-19-H_3), 0.69 (3H, s, C-18-H_3).

A solution of a crude sample of the aldehyde **23** (12.1 g) in THF (100 ml) was treated with *t*-BuOK (2.67 g) at 0° and the mixture was stirred at 0° for 20 min. Next, 2 N HCl solution was added, and the usual work-up with AcOEt for extraction gave a crude oil (11 g) (**19a**), which was chromatographed on silica gel.

Elution with benzene provided pure cyclopropylaldehyde **19a** which was identical with the aldehyde **19a** previously prepared from **15a** in terms of the NMR spectra and chromatographic behavior (TLC and GLC).

[22*R*,23*S*,24*R* and *S*]-22,23-Methanato-cholest-5-en-3*β*,24-diol 3-Acetate (**24a**)——Isopropyl bromide (8.0 ml) was added to a suspension of magnesium (2.15 g) in THF (100 ml) at r.t. under argon. The solution was stirred at r.t. for 1 hr, then a solution of the aldehyde **19a** (2.35 g) in THF (100 ml) was added at -18°. The mixture was stirred at -18° for 2 hr. Saturated aq. NH_4Cl solution was added and the usual work-up, with AcOEt for extraction, gave the 24-alcohol **24a** (oil, 2.72 g): NMR δ: 5.38 (1H, m, 6-H), 5.0—4.3 (1H, m, 3-H), 2.97 (1H, d.d, $J=6$ Hz, 24-H), 2.00 (3H, s, AcO), 1.01 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3).

[22*R*,23*S*]-3*β*-Acetoxy-22,23-methanato-cholest-5-en-24-one (**25a**)——A solution of a crude sample of **24a** (2.72 g) in CH_2Cl_2 (50 ml) was treated with pyridinium chlorochromate (1.6 g) at r.t. The mixture was stirred at r.t. fot 2 hr. Ether (100 ml) was added, and the mixture was filtered through a Florisil column. Concentration of the eluate gave the 24-ketone **25a** (2.50 g): mp 142—143.5°, NMR δ: 5.4 (1H, m, 6-H), 4.6 (1H, m, 3-H), 2.72 (1H, q, $J=7$ Hz, 25-H), 2.00 (3H, s, AcO), 1.00 (3H, s, C-19-H_3), 0.62 (3H, m, C-18-H_3); MS *m/e*: 394 (M^+-AcOH), 379 ($394-CH_3$), 253 (C_{17-22} cleavage$-AcOH-H_2$), *Anal.* Calcd for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.72; H, 10.25.

[22*R*,23*S*]-22,23-Methanato-ergosta-5,24(28)-dien-3*β*-ol (**27a**)——*n*-Butyl lithium (26 ml) was added to a suspension of methyltriphenylphosphonium iodide (11.1 g) in THF (100 ml) at r.t. The mixture was stirred at r.t. for 30 min. A solution of 24-ketone **25a** (2.5 g) in THF (50 ml) was then added to this Wittig reagent at r.t. and the resulting mixture was stirred at r.t. for 18 hr. The usual work-up, with AcOEt for extraction, gave crude **27a** (oil, 3.8 g), which was chromatographed on silica gel. The 24-ketone **27a** (537 mg) was eluted with benzene/AcOEt (100/1). **27a**: mp 128—130°, NMR δ: 5.34 (1H, m, 6-H), 4.48 (2H, d, $J=14$ Hz, =H_2), 3.7—3.3 (1H, m, 3-H), 1.07 (6H, d, $J=7$ Hz, C-26, 27-H_6), 1.02 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3); MS *m/e*: 410 (M^+), 395 ($410-CH_3$), 392 ($410-H_2O$), 377 ($392-CH_3$), 255 (C_{17-22} cleavage$-H_2O$), 253 ($255-H_2$). $C_{29}H_{44}O$ requires MS *m/e*: 410.689. Found: 410.690.

3*α*,5-Cyclo-22,23-methanato-24-methylene-6*β*-methoxy-5*α*-cholestane (**28a**)——By a standard procedure,[19] 500 mg of **27a** was reacted with 13 ml of pyridine and 0.4 g of *p*-toluenesulfonyl chloride to give the 3-tosylate, which was treated with KOAc (0.7 g) in methanol (50 ml) (reflux, 3 hr) to afford 508 mg of compound **28a**.

[22*R*,23*S*,24*R*] and [22*R*,23*S*,24*S*]-3*α*,5-Cyclo-22,23-methanato-6*β*-methoxy-5*α*-ergostan-28-ol (**29a and 29b**)——Diborane–THF complex (1 M solution, 38 ml) was added to a solution of the olefin **28a** (508 mg) in THF (40 ml) at 0° under argon. The solution was stirred at 0° for 1 hr and then at r.t. for 15 hr. The solution was then cooled at 0° and H_2O (30 ml) was added dropwise, followed by 3 N NaOH (30 ml) and 30% H_2O_2 (30 ml). The mixture was stirred at r.t. for 30 min. The usual work-up, with AcOEt for extraction, gave an epimeric mixture of alcohols **29a** and **29b** (oil, 498 mg) which was separated by preparative TLC (developed, two times, benzene/AcOEt: 100/1) to yield the more polar epimer **29a** (*Rf*: 0.35, 49 mg) and the less polar one **29b** (*Rf*: 0.39, 58 mg). **29a**: NMR δ: 3.69 (2H, d, $J=5$ Hz, CH_2OH), 3.31 (3H, s, CH_3O), 2.9—2.7 (1H, m, 6-H), 1.01 (3H, s, C-19-H_3), 0.96 (6-H, d, $J=7$ Hz, C-26, 27-H_6), 0.68 (3H, s, C-18-H_3); MS *m/e*: 442 (M^+), 427 ($442-CH_3$), 410 ($442-MeOH$), 395 ($410-CH_3$), 392 ($410-H_2O$), 255 (C_{17-22} cleavage$-$MeOH), 253 ($255-H_2$). **29b**: NMR δ: 3.61 (2H, d, $J=6$ Hz, CH_2OH), 3.32 (3H, s, MeO), 2.9—2.6 (1H, m, 6-H), 1.03 (3H, s, C-19-H_3), 0.96 (6H, d, $J=7$ Hz, C-26, 27-H_6), 0.71 (3H, s, C-18-H_3).

[22*R*,23*R*,24*R*]-3*α*,5-Cyclo-22,23-methanato-5*α*-ergostan-6*β*-ol 6-Methyl Ether (**31**)——MsCl (1.5 ml) was added to a solution of the more polar alcohol **29a** (49 mg) in pyridine (5 ml) at 0° and the mixture was stirred at r.t. for 2 hr. The usual work-up, with AcOEt for extraction, gave the mesylate **30** (oil, 50 mg). A solution of the mesylate **30** in THF (50 ml) was treated with excess lithium aluminum hydride and the mixture was stirred at r.t. for 1 hr, then refluxed for 2 hr. The solution was cooled to r.t., then ether and 2 N HCl solution were added. The usual work-up, with ether for extraction, gave crude **31**, which was purified by preparative TLC to give the desired product **31** (6 mg): NMR δ: 3.30 (3H, s, CH_3O), 2.9—2.7 (1H, m, 6-H), 1.02 (3H, s, C-19-H_3), 0.67 (3H, s, C-18-H_3); MS *m/e*: 426 (M^+), 411 ($426-CH_3$), 394 ($426-MeOH$), 379 ($394-CH_3$), 255 C_{17-22} cleavage$-$MeOH), 253 ($255-H_2$).

Demethylgorgosterol (**2**)——A solution of the cyclopropyl ether **31** (6 mg) in dioxane/H_2O (4.5 ml/1.5 ml) in the presence of a catalytic amount of *p*-TsOH was refluxed for 2 hr. The usual work-up, with ether for extraction, gave crude demethylgorgosterol **2**, which was chromatographed on silica gel. Elution with benzene/AcOEt (100/1) gave pure demethylgorgosterol **2** (5 mg): mp 161—162°, $[\alpha]_D$: $-31.9°$ (ref; $-34.5°$),$^{5)}$ NMR δ: 5.36 (1H, m, 6-H), 3.8—3.2 (1H, m, 3-H), 1.01 (3H, s, C-19-H_3), 0.65 (3H, s, C-18-H_3); MS *m/e*: 412 (M^+), 397 ($412-CH_3$), 394 ($412-CH_3$), 379 ($394-CH_3$), 255 (C_{17-22} cleavage$-H_2O$), 253 ($255-H_2$).

24-Epidemethylgorgosterol (**32**)——The alcohol **29b** (58 mg) was converted into the mesylate, which was treated with lithium aluminum hydride to afford the 3α,5-cyclo compound (13 mg): NMR δ: 3.30 (3H, s, CH_3O), 2.9—2.7 (1H, m, 6α-H), 1.02 (3H, s, C-19-H_3), 0.68 (3H, s, C-18-H_3).

Treatment of this cyclo compound with a catalytic amount of *p*-TsOH in aqueous dioxane gave crude **32**, which was purified by preparative TLC to give 24-epidemethylgorgosterol **32** (9 mg): mp 139—140°, $[\alpha]_D$ $-9.7°$, NMR δ: 5.36 (1H, m, 6-H), 3.8—3.2 (1H, m, 3-H), 1.03 (3H, s, C-19-H_3), 0.66 (3H, s, C-18-H_3).

Separation of the Four Epimers, 2, 32, 34 and 35, by GLC——A Shimadzu 7A GLC machine equipped with a hydrogen flame ionization detector was used. The trimethylsilyl derivative was analyzed on a glass capillary column, 45 m × 0.25 mm i.d., coated with OV-17 at 270°. Retention times: demethylgorgosterol (22*R*,23*R*,24*R*)(**2**)-TMSi, 34.6 min; (22*R*,22*R*,24*S*)-isomer (**32**)-TMSi, 32.8 min; (22*S*,23*S*,24*R*)-isomer (**34**)-TMSi, 36.6 min; (22*S*,23*S*,24*S*)-isomer (**35**)-TMSi, 35.4 min.

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