Synthesis and Stereochemistry of Ficisterol and Norficisterol: Biosynthetic Implications

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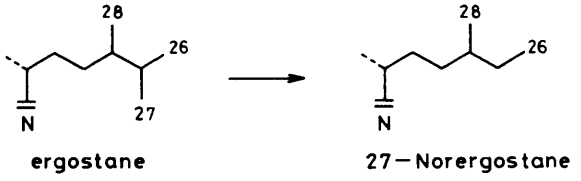
All four possible C-23 and C-24 stereoisomers of ficisterol and norficisterol were synthesized *via* Ireland's ester enolate Claisen rearrangement. The stereochemistry of each isomer was determined by a combination of stereochemical deductions derived from the Claisen mechanism, and chemical correlations with known standards. The resulting stereostructures (**1a**) and (**2a**) are consistent with the hypothesis that dihydrocalysterol (**3**) and (23*R*,24*R*)-methylenecholesterol (**42**) are the respective biosynthetic precursors of ficisterol and norficisterol, thus supporting a novel mechanism for 27-norergostane biosynthesis. In the course of the stereochemically significant synthesis, 23,24-dimethyl-22-dehydrocholesterol (**37**)—the presumed biosynthetic precursor of gorgosterol (**41**)—was prepared by a route that lends itself readily to the synthesis of isotopically labelled analogues.

Ficisterol (**1**) is structurally and biosynthetically one of the most interesting marine sterols. In one sense, it belongs to the rare 27-norergostane class,[1] which is peculiar to certain marine organisms. In addition, it is the only sterol (from any source) which contains a 23-ethyl substituent. Nothing concrete is known about the biosynthesis of 27-norergostanes, although suggestions[1,2] have been made that they arise from dealkylation of the terminal 27-methyl group from precursors possessing the ergostane side-chain (Scheme 1). In an earlier paper,[2] a suggestion was made that a 23-methylene-ergostane might be a key intermediate in the generation of the 23-ethyl substituent of ficisterol. Subsequently, a sterol with such a side-chain was claimed to have been isolated,[3] but synthetic work in our laboratory[4] showed this to be incorrect.

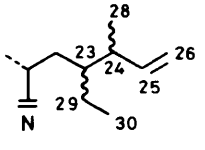


Scheme 1.

Our recent proposal[5] that dihydrocalysterol (**3**),[6] which co-occurs in the same sponge with ficisterol and its lower homologue norficisterol (**2**), may be the common biosynthetic intermediate to a variety of marine sterols including ficisterol (**1**) carries with it an important stereochemical implication. If ficisterol indeed arises from dihydrocalysterol (**3**), whose absolute configuration has recently been established by synthesis,[5] then ficisterol must have the absolute configuration shown in structure (**1a**). No such stereochemical assignment had been made in the earlier structural elucidation work,[7] nor did the earlier non-stereospecific synthesis[8] of all four possible stereoisomers of ficisterol shed any light on the actual stereochemistry of this intriguing sterol. We now describe a stereo-rational synthesis of ficisterol (**1**) and its lower homologue norficisterol (**2**) which, combined with correlations to reference standards of known absolute configuration, settles the absolute configuration of these two unique marine sterols. As will be shown in the sequel, the observed configuration is exactly the one predicted if dihydrocalysterol (**3**) were the biosynthetic precursor of ficisterol (**1a**).

Results and Discussion

Synthesis of Ficisterol and Norficisterol.—All eight stereoisomers of ficisterol (**1a—d**) were synthesized (Schemes 2—4) from the common intermediates (**10a—d**), prepared *via* Ireland's ester enolate rearrangement.[9] The 3β-hydroxy group of methyl 3β-hydroxychol-5-en-24-oate (**4**), was first protected as the dimethyl-t-butylsilyl ether (**5**),[10] which underwent base-



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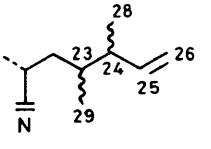

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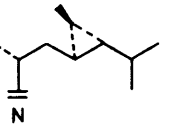

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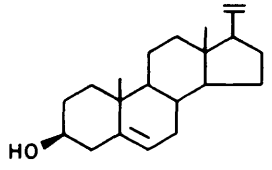

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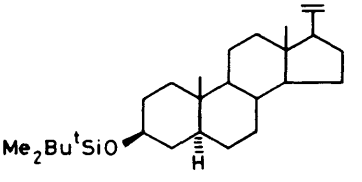

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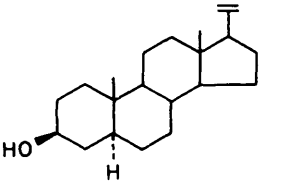

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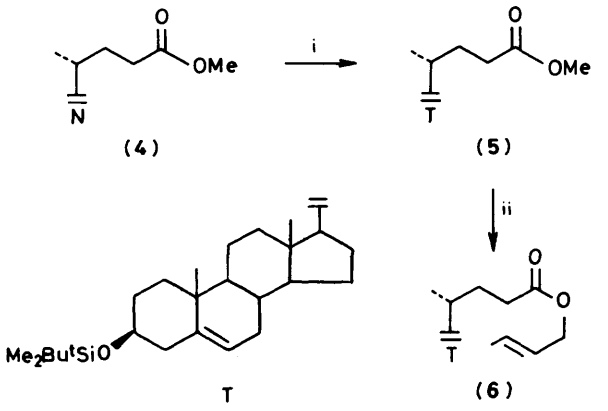


Scheme 2. i, TBDMSCI, imidazole, CH_2Cl_2–DMF; ii, Na, *trans*-crotyl alcohol, benzene

catalyzed alcohol exchange with *trans* crotyl alcohol to furnish the crotyl ester (**6**) (Scheme 2). The ester enolate Claisen rearrangement was subsequently performed on this *trans* crotyl ester (**6**) according to Ireland's procedure:[9] treatment with LDA base under HMPA–THF and THF conditions generated the *Z*-(**7a**) and *E*-(**7b**) ester enolates respectively,[9,11] which were trapped as their trimethylsilyl (TMS) ketene acetals by addition of TMSCI. Upon heating, the TMS ester enolates rearranged to the trimethylsilyloxycarbonyl adducts, which, during subsequent methanolic work-up, decomposed to the corresponding free acids (**9a**—**d**).

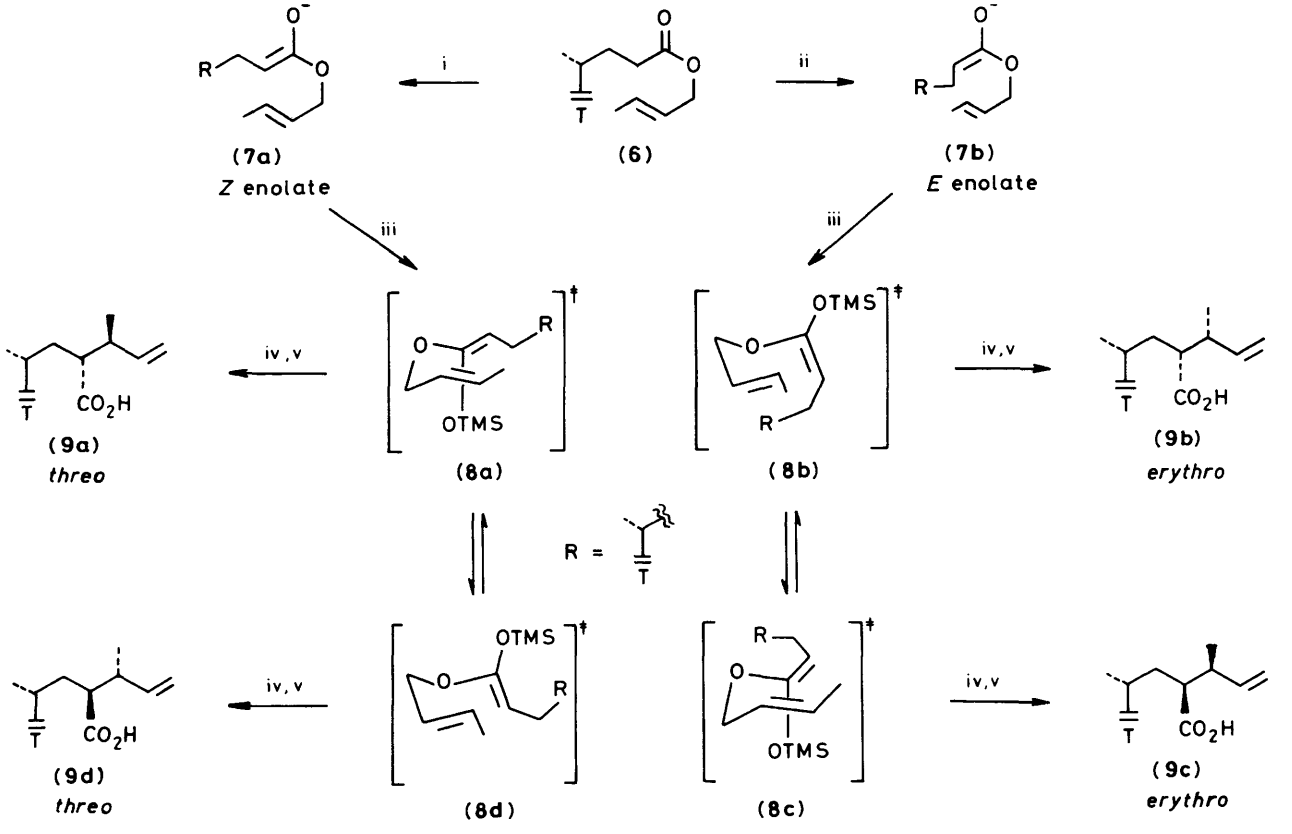
The aliphatic Claisen rearrangement is believed to proceed *via* a six-centred transition state, in which chair conformers are energetically favoured.[12] The *Z*-enolate (**7a**), after being trapped as its TMS ester enolate derivative, would give rise to two equally populated chair-like transition states (**8a**) and (**8d**) which would then rearrange and decompose to provide the *threo** isomers (**9a**) and (**9d**),† respectively, of the free acids with the depicted stereochemistry at C-23 and C-24. Analogously, the *E* enolate (**7b**) would go through the transition states (**8b**) and (**8c**) to form the corresponding *erythro** isomers (**9b**) and (**9c**) with the C-23 and C-24 stereochemistry as shown in Scheme 3. The sterol moiety in the free acids (**9a**—**d**) served as the inherent chiral resolving agent: the *threo* and *erythro* isomers, which would have been enantiomeric had the sterol nucleus been removed, were now diastereomeric. Hence, no external chiral resolving reagents were necessary for their separations or those of their derivatives.

The stereoselective formation based on ester enolate configurations following Ireland's Claisen methodology[9] not only facilitated product isolation by reducing the number of isomers generated, but even more importantly, provided crucial stereochemical information. When the two *threo* isomers (**9a**) and (**9d**)‡ were prepared experimentally [the same applied to the *erythro* pair (**9b**) and (**9c**)]‡, their actual stereostructures could not be distinguished and had to be solved by correlation

* The original nomenclature of the *threo* and *erythro* notation devised by Ireland *et al.* is used here; see ref. 9.

† If the *cis*- rather than the *trans*-crotyl alcohol were used, the *erythro* and *threo* isomers would be generated under HMPA–THF and THF conditions respectively.

‡ The Nes notation (see W. R. Nes and M. L. McKean, 'Biochemistry of Steroids and Other Isopentenoids,' University Park Press, Baltimore, Maryland, 1977, p. 54) for side-chain substituents is more appropriate here, due to the change of multiple functional groups at the same positions. From the Claisen mechanism, the *threo* isomers in the 'a' and 'd' series would have the 23β,24α- and 23α,24β-configurations, respectively; whereas the *erythro* isomers in the 'b' and 'c' series would have the 23β,24β- and 23α,24α-configurations, respectively.



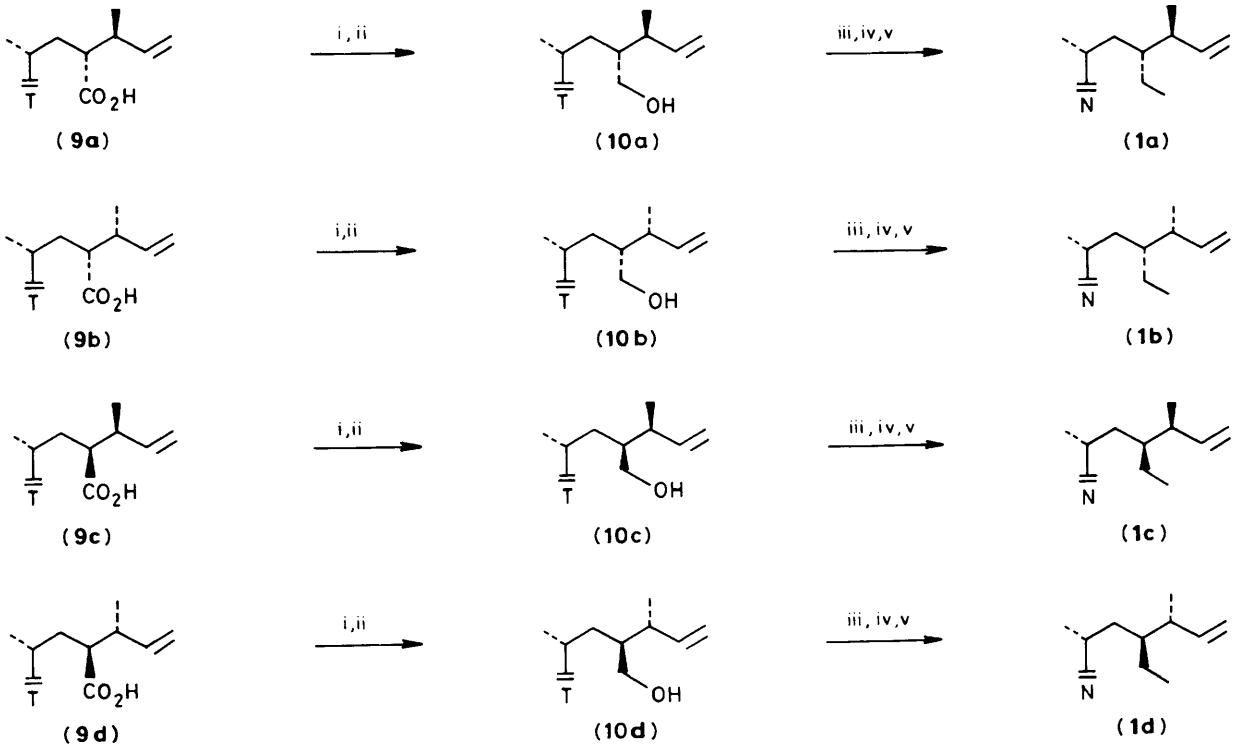
Scheme 3. i, LDA, HMPA/THF, −78 °C; ii, LDA, THF, −78 °C; iii, TMSCI, −78 °C; iv, 70 °C; v, MeOH

with known standards. However, by means of the *threo* (*erythro*) relationship derived from the Claisen mechanism, determination of the absolute configuration of one member of the pair would automatically lead to deduction of the other's absolute stereochemistry. Thus, only two isomers, one from each of the *threo* and *erythro* pairs, required stereochemical correlation experiments.

The free acids (**9a**—**d**) were not isolated. Instead, they were converted by treatment with diazomethane[13] into their methyl esters, which were reduced with lithium aluminium hydride (LAH) to the alcohols (**10a**—**d**). The actual stereochemistry of these alcohols as well as all sterols derived from them were indeed those depicted in Schemes 3, 4, and 5. However, this was only established after all the stereochemical correlations had been completed (*vide infra*). Under HMPA/THF conditions, the *threo*-alcohols (**10a**) and (**10d**) were obtained in 57% yield from the crotyl ester (**6**) before h.p.l.c. purification. Under THF conditions, the *erythro*-alcohols (**10b**) and (**10c**) were secured similarly in 62% yield. Normal-phase h.p.l.c. separation * of the HMPA–THF mixture gave the alcohols (in order of elution) (**10a**), (**10b**), (**10c**), and (**10d**) in an 8:1:1:8 ratio,† respectively. The same h.p.l.c. elution of the THF mixture provided the alcohols (**10a**), (**10b**), (**10c**), and (**10d**) in the ratio of 1:7:7:1.†

dimethyl-t-butylsilyl ether protecting group to the free sterol with lithium tetrafluoroborate ($LiBF_4$).[16] The ficisterol isomers (**1a**), (**1b**), (**1c**), and (**1d**) were thus synthesized from the alcohols (**10a**), (**10b**), (**10c**), and (**10d**). Table 1 summarizes their ^1H n.m.r. spectra, which show that the C-28 and C-30 signals serve as diagnostic means for differentiation. The chemical shift values of natural ficisterol were identical with those of the synthetic isomer (**1a**), confirming the absolute sterochemistry of (**1**) predicted from biosynthetic insights.[5] Structure (**1a**) also verified the previous speculation, based solely on ^1H n.m.r. arguments, that natural ficisterol had the 24α(24*S*)-configuration.[8]

The second set of conversions (Scheme 5) generated the norficisterol series: (1) mesylation;[17] (2) LAH displacement of the mesylate;[18] (3) deprotection of the dimethyl-t-butylsilyloxy group to the free sterol with $LiBF_4$.[16] The alcohols (**10a**), (**10b**), (**10c**), and (**10d**) furnished the norficisterol isomers (**2a**), (**2b**), (**2c**), and (**2d**), respectively, whose ^1H n.m.r. spectra are shown in Table 2. Although the chemical shift values of the isomers (**2a**) and (**2b**) were very similar, the difference in their C-28 signals was large enough to distinguish them. The spectrum of natural norficisterol (**2**) was identical with that of the synthetic isomer (**2a**).



Scheme 4. i, CH_2N_2; ii, LAH, ether; iii, TsCl, pyridine; iv, Li_2CuCl_4, MeMgI; v, $LiBF_4$, CH_2Cl_2–MeCN, reflux

Each of the alcohols (**10a**—**d**), purified by h.p.l.c., was then subjected to two sets of transformations.

The ficisterol series was generated by a sequence (Scheme 4) which included: (1) tosylation; (2) coupling of the tosylate with methylmagnesium iodide in the presence of dilithium tetrachlorocuprate as the catalyst;[15] (3) removal of the

The norficisterol isomers (**2a**—**d**) were hydrogenated in the presence of Adam's catalyst in HOAc–hexane (1:4). Previously, very little epimerization at C-24 had been observed under the same conditions in the reduction of dinosterol (**12**) and the Δ^5 analogue of its C-24 epimer (**13**).[19] Indeed, each norficisterol isomer gave one product. The four hydrogenated isomers (**11a**—

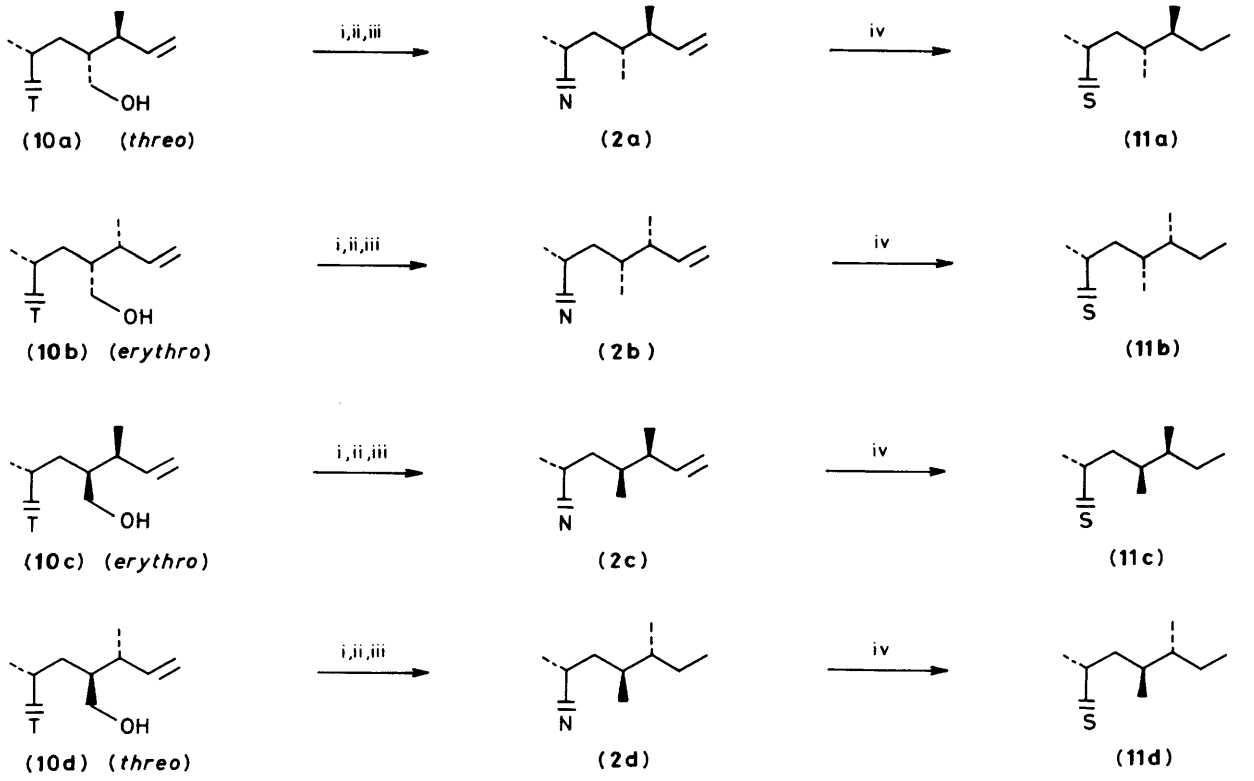
* Normal-phase silica-gel chromatography was employed previously on numerous occasions to separate sterols with diastereoisomeric side chain hydroxymethyl substituents.[14]

† Since the *trans* crotyl ester (**5**) was homogeneous (see Experimental section), the observed ratios reflected the proportion of the *Z* and *E* ester enolates generated under the corresponding reaction conditions.

Table 1. ^{1}H N.m.r. chemical shifts of ficisterol isomers (300 MHz, $CDCl_3$, coupling constants, J in Hz)

	Natural (1)[a]	(1a) (23*R*,24*S*)	(1b) (23*R*,24*R*)	(1c) (23*S*,24*S*)	(1d) (23*S*,24*R*)
C-18 (s)	0.688	0.684	0.683	0.689	0.687
C-19 (s)	1.007	1.008	1.002	1.006	1.006
C-21 (d)	0.866	0.862	0.872	0.903	0.888
	(*J* 6.3)	(*J* 6.0)	(*J* 6.0)	(*J* 6.6)	(*J* 6.6)
C-25H (m)	5.70—5.85	5.71—5.82	5.60—5.71	5.77—5.88	5.66—5.75
C-26H's (m)	4.90—5.00	4.91—4.98	4.90—4.95	4.92—4.99	4.92—4.98
C-28 (d)[b]	0.876	0.872	0.966	0.867	0.989
	(*J* 6.9)	(*J* 6.6)	(*J* 6.9)	(*J* 6.9)	(*J* 7.2)
C-30 (t)	0.850	0.846	0.842	0.831	0.848
	(*J* 7.0)	(*J* 7.2)	(*J* 6.0)	(*J* 6.9)	(*J* 5.1)

[a] Isolated from the sponge *Petrosia ficiformis*. Except for the C-18 and C-19 methyl doublets, all the signals matched the reported acetate derivative (ref. 8). [b] The C-28 signals were distinguished from the C-21 signals by decoupling experiments involving simultaneous irradiations of the C-25 vinyl protons and the allylic protons at 2.3 p.p.m.



Scheme 5. i, MsCl, Et_3N, CH_2Cl_2; ii, LAH, ether; iii, $LiBF_4$, CH_2Cl_2–MeCN, reflux; iv, PtO_2, H_2, HOAc–hexane

d) were distinguishable by their ^{1}H n.m.r. spectra as indicated in Table 3. This was important, because as will be shown below, they served as relays for stereochemical correlation with *X*-ray standards.

Stereochemical Correlations.—An orthoester Claisen rearrangement[20] of the 22*R*(22α-hydroxy)allylic alcohol (**14**)* with trimethyl orthoacetate led (Scheme 6) to the 24*R*(24β) ester (**15**),† which was hydrogenated‡ in the presence of Pd/C in ethyl acetate with the expection that all four diastereoisomers at positions 23 and 24 would be formed as was observed earlier in a similar hydrogenation of dinosterol (**12**).[19] Subsequent $LiBF_4$ deprotection of the 3β-silyloxy group of the hydrogenated mixture§ and separation on reverse-phase h.p.l.c. (ODS-2, MeOH, 3 ml min^{-1}) gave only two isolable isomers (**16b**) and (**16d**) in a 2:1 ratio. Hydrogenation of the free sterol ester (**17**), secured from the desilylation of the Claisen product (**15**), with Adam's catalyst in HOAc–hexane (1:4) resulted almost

* This 22*R*-allylic alcohol was previously prepared during the synthesis of dinosterol (see A. Y. L. Shu and C. Djerassi, *Tetrahedron Lett.*, 1981, 4627).

† The 24*R* configuration could be assigned to the 27-nor ester (**15**) based on the mechanism of the Claisen rearrangement and the known stereochemistry of the precursor (**14**).

‡ The silyl ether was hydrogenated because the free sterol could give rise to the 3-ketone under Pd/C conditions; see ref. 19.

§ The silyl ethers were not very soluble in MeOH and gave extremely long retention times in reverse-phase h.p.l.c. with MeOH as the eluant. Thus the free sterols were separated instead.

Table 2. ^{1}H N.m.r. chemical shifts of norficisterol isomers (300 MHz, $CDCl_3$, coupling constants *J* in Hz)

	Natural (2)[a]	(2a) (23*R*,24*S*)	(2b) (23*R*,24*R*)	(2c) (23*S*,24*S*)	(2d) (23*S*,24*R*)
C-18 (s)	0.688	0.687	0.688	0.686	0.682
C-19 (s)	1.006	1.004	1.005	1.005	1.005
C-21 (d)[b]	0.872	0.872	0.874	0.917	0.901
	(*J* 6.3)	(*J* 6.3)	(*J* 6.3)	(*J* 6.6)	(*J* 6.6)
C-25H (m)	5.66—5.80	5.67—5.78	5.65—5.77	5.75—5.86	5.66—5.78
C-26's (m)	4.89—4.94	4.90—4.95	4.89—4.95	4.92—4.98	4.93—5.00
C-28 (d)[c]	0.951	0.950	0.940	0.852	0.986
	(*J* 6.9)	(*J* 6.6)	(*J* 6.9)	(*J* 6.9)	(*J* 7.2)
C-29 (d)[b]	0.783	0.783	0.784	0.747	0.773
	(*J* 6.9)	(*J* 6.9)	(*J* 6.6)	(*J* 6.6)	(*J* 6.6)

[a] Isolated from the sponge *Petrosia ficiformis*. [b] The signals for C-21 and C-29 were distinguished by specifically labelling C-29 with two deuterium atoms, which was accomplished by using lithium aluminium deuteride in the reduction of the Claisen esters to the alcohols (**9a—d**). The deuteriated alcohols were purified by h.p.l.c. and transformed exactly as their unlabelled counterparts to the C-29 labelled free sterols. The signals for C-29 were recognized by their decreased peak heights in the deuteriated samples when the ^{1}H n.m.r. spectra of both labelled and unlabelled sterols were compared. [c] The C-28 assignments were made by decoupling experiments involving simultaneous irradiations of the 25-H's and the allylic protons at 2.3 p.p.m.

Table 3. ^{1}H N.m.r. chemical shifts of hydrogenated norficisterol isomers (300 MHz, $CDCl_3$, coupling constants *J* in Hz)

	(11a) (23*R*,24*S*)	(11b) (23*R*,24*R*)	(11c) (23*S*,24*S*)	(11d) (23*S*,24*R*)
C-18 (s)	0.657	0.657	0.655	0.647
C-19 (s)	0.798	0.798	0.798	0.799
C-26 (t)	0.851	0.852	0.871	0.872
	(*J* 7.2)	(*J* 7.2)	(*J* 7.2)	(*J* 6.9)
Unassigned methyl doublets	0.777	0.707	0.682	0.756
	(*J* 6.6)	(*J* 6.6)	(*J* 6.6)	(*J* 6.6)
	0.777	0.756	0.687	0.838
	(*J* 6.6)	(*J* 6.6)	(*J* 6.9)	(*J* 6.9)
	0.855	0.864	0.870	0.871
	(*J* 6.3)	(*J* 6.9)	(*J* 6.3)	(*J* 6.0)

exclusively in the formation of the major component (**16b**).* On the basis of the previous hydrogenation of dinosterol (**12**) under either conditions,[19] the major isomer (**16b**) was predicted to have the 23*R*,24*R*(23β,24β) stereochemistry as was indeed proven (*vide infra*).

The 3β-hydroxy group of the 27-nor ester (**16b**) was reprotected as the silyl ether to provide the ester (**18b**), which was methylated with an excess of methyl iodide.[21] Only monomethylated esters (**19b**) (epimeric at C-25) were observed. The esters (**19b**) were reduced with LAH to the alcohols, which were then subjected to the conventional three-step reaction sequence (mesylation, removal of the mesylate with LAH to the alkane, and desilylation with $LiBF_4$) to yield the free sterol (**20b**), which proved to be identical (see Table 4) with dinostanol, characterized unequivocally by *X*-ray crystallography to have the 23*R*,24*R*(23β,24β) configuration.[22] It follows that the precursor 27-nor ester (**18b**) must have the same stereochemistry at C-23 and C-24.

In a second transformation sequence (Scheme 6), the 27-nor ester (**18b**) was reduced to the alcohol (**21b**). Removal of the side-chain hydroxy group and subsequent cleavage of the 3β-dimethyl-t-butylsilyl ether afforded the free 27-nor sterol (**22b**),† whose ^{1}H n.m.r. spectrum (Table 4) matched that of the hydrogenated norficisterol isomer (**11b**) (Table 3).‡ Based upon the elucidated 23*R*,24*R*(23β,24β) configuration[19,22] of dinostanol (**20b**) and the configuration of key intermediates, such as the 27-nor ester (**18b**) and the saturated norficisterol isomer (**11b**), all the structures in the '*b*' series must have the identical stereochemistry at C-23 and C-24. Since the *erythro* relationships for series '*b*' and '*c*' had already been established through the mechanism derived from the Claisen rearrangement (see Scheme 3), all the structures in the '*c*' series had exactly the opposite stereochemistry at C-23 and C-24 from the '*b*' series, *i.e.* the 23α,24α configuration.

The minor 27-nor sterol ester isomer (**16d**) was treated analogously to its major component (**16b**) and led *via* intermediates (**18d**) and (**19d**) to the free sterol (**20d**). The ^{1}H n.m.r. spectrum of (**20d**) (Table 4) was identical with that of the minor Pd/C hydrogenation product of dinosterol, which had previously been assigned the 23*S*,24*R*(23α,24β) configuration.[19] But this assignment was based upon the assumption that the Pd/C hydrogenation was non-stereoselective and took place from both sides of the Δ^{22} double bond of dinosterol (**12**). Given that allylic epimerization could occur during heterogeneous hydrogenations,[24] the minor hydrogenation component could also be the 24-epimer of (**20d**).§ The stereochemical information obtained from the presently described ester enolate Claisen rearrangement can clarify this ambiguity. If the original

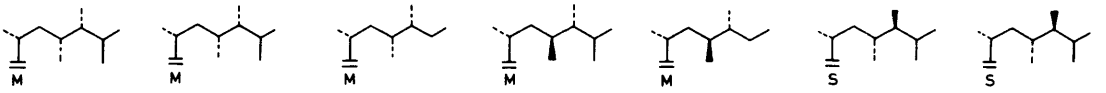
* The ratio was shown by h.p.l.c. (ODS-2, MeOH, 3 ml min^{-1}) to be 20:1 for (**16b**) : (**16d**).

† This sterol was identical with a natural sterol (T. B. Tam Ha, *et al.*; unpublished results from this laboratory) isolated from the zooxanthellae of *Orbulina universa* (see ref. 19).

‡ Sterols with the same side-chain but different nuclei can be correlated because they have virtually identical ^{1}H n.m.r. chemical shift values of their side-chain methyl groups.[23]

§ The other alternative with the 23β,24α- configuration was ruled out because this would have been correlated with the known sterol (**29a**); see ref. 19.

Table 4. ^{1}H N.m.r. chemical shifts of saturated 27-nor and normal sterols used for correlations (300 MHz, $CDCl_3$, coupling constant J in Hz)



Methyl group	(**20b**) (23*R*,24*R*)	Dinostanol[a] (23*R*,24*R*)	(**22b**) (23*R*,24*R*)	(**20d**) (23*S*,24*R*)	(**22d**) (23*S*,24*R*)	(**29a**) (23*R*,24*S*)	(**29a**)[a] (23*R*,24*S*)
C-18 (s)	0.658	0.661	0.655	0.648	0.650	0.659	0.660
C-19 (s)	0.820	0.823	0.819	0.822	0.824	0.798	0.800
C-26 (t)	—	—	0.852 (*J* 6.6)	—	0.877 (*J* 6.3)	—	—
4α-Me (d)	0.943 (*J* 6.3)	0.946 (*J* 6.3)	0.942 (*J* 6.3)	0.946 (*J* 6.3)	0.946 (*J* 6.3)	—	—
Unassigned methyl doublets	0.697 (*J* 6.9)	0.700 (*J* 6.7)	0.707 (*J* 6.6)	0.759 (*J* 7.0)	0.762 (*J* 6.6)	0.721 (*J* 6.9)	0.721 (*J* 6.8)
	0.720 (*J* 7.2)	0.724 (*J* 6.9)	0.756 (*J* 6.3)	0.789 (*J* 6.8)	0.840 (*J* 7.2)	0.804 (*J* 6.6)	0.808 (*J* 5.8)
	0.809 (*J* 6.6)	0.813 (*J* 7.0)	0.863 (*J* 6.6)	0.872 (*J* 6.7)	0.875 (*J* 6.6)	0.805 (*J* 6.6)	0.808 (*J* 5.8)
	0.869 (*J* 6.3)	0.872 (*J* 6.0)	—	0.887 (*J* 6.8)	—	0.862 (*J* 6.6)	0.863 (*J* 6.1)
	0.876 (*J* 6.6)	0.880 (*J* 6.8)	—	0.918 (*J* 6.6)	—	0.873 (*J* 6.6)	0.874 (*J* 6.5)

[a] See reference 19.

assignment is correct, then the free 27-nor sterol (**22d**), derived from the minor isomer (**18d**) *via* reduction and deprotection, would correlate with one of the two saturated *threo* norficisterol isomers (**11a**) or (**11d**),* which turned out to be the case. The ^{1}H n.m.r. spectrum of the 27-nor sterol (**22d**) (Table 4) matched that of the hydrogenated norficisterol isomer (**11d**) (Table 3), which came from one of the *threo* pairs (**10a**) or (**10d**). Thus, all sterols in the '*d*' series must have the 23α,24β configuration. Again, by means of the *threo* relationship, the structures in the '*a*' series must have the opposite configuration, *i.e.* 23β,24α.

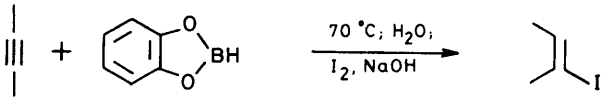
The stereochemistry of the '*a*' series was further confirmed by correlation (Scheme 7) with the known sterol (**29a**), which had been prepared earlier by hydrogenation[19] of the Δ^5 analogue of 24-epidinosterol (**13**) with Adam's catalyst; its stereochemistry had been established by *X*-ray analysis of its 3β-bromo benzoate derivative.[19] Orthoester Claisen rearrangement of the 22*S*(22β-hydroxy) allylic alcohol (**23**) with trimethyl orthoacetate gave the 24*S*(24α) ester (**24**), which was immediately converted into its 3β-hydroxy-Δ^5-analogue (**25**). The C-24 stereochemistry of the adduct (**24**) could be deduced from the well-accepted 1,3 chiralty transfer mechanism of the aliphatic Claisen reaction[12] provided that the Δ^{23} configuration and the C-22 stereochemistry of the starting allylic alcohol (**23**) were established, which was done (*vide supra*). Hydrogenation of the ester (**25**) with Adam's catalyst in HOAc–hexane (1:4) gave exclusively the 3β-hydroxy derivative (**26a**). Once more, two sets of reaction sequences were repeated on the 3β-hydroxy silyl ether (**27a**). First, monomethylation to the epimeric esters (**28a**), followed by reduction and desilylation, led to the expected free sterol (**29a**). Second, reduction of the ester functionality of (**27a**) to the alkane and subsequent desilylation afforded the desired hydrogenated norficisterol isomer (**11a**), which further verified that the '*a*' series had the 23β,24α configuration.

The 22*S*,23*E* allylic alcohol (**23**) was obtained as the minor component during the addition of the vinyl-lithium reagent (**31**) to the aldehyde that was freshly prepared from the pyridinium dichromate oxidation[25] of the known 22-alcohol (**30**)[26] (derived from stigmasterol). The (*E*)-vinyl-lithium (**31**), in turn, was generated from the exchange between the (*E*)-vinyl iodide (**32**)‡ with BuLi at −60 °C.[28] After chromatography, a 10% overall yield of the 22*S*-alcohol (**23**) and 70% of the 22*R*-epimer (**33**) were obtained. Assignment of the Δ^{23} double bonds of both allylic alcohols was based upon the observation that the exchange reaction between a vinyl halide and an alkyl-lithium proceeds with retention of configuration.[28] The configuration at C-22 in (**33**) and (**23**), which are crucial to the subsequent stereochemical arguments, were established as follows: (1) the isomer (**23**) was produced as the minor adduct;* (2) the major isomer (**33**) is chromatographically (silica gel) the less polar component;† (3) conversion of the Claisen substrates (**33**) and (**23**) into the known 4-demethyl-5-dehydrodinosterol (**37**) and its 24-epimer (**13**) respectively (Scheme 8).

Claisen rearrangement of the major 22*R*,23*E*-allylic alcohol (**33**) with triethyl orthopropionate resulted in a mixture of 24*R*(24β) esters (**34**), epimeric at C-25. Standard LAH reduction led to the alcoholic mixture (**35**), which was directly mesylated. Removal of the mesylates with LAH afforded the

* If not, the 27-nor sterol derived from the reduction and deprotection would correlate with the hydrogenated norficisterol isomer (**11c**).

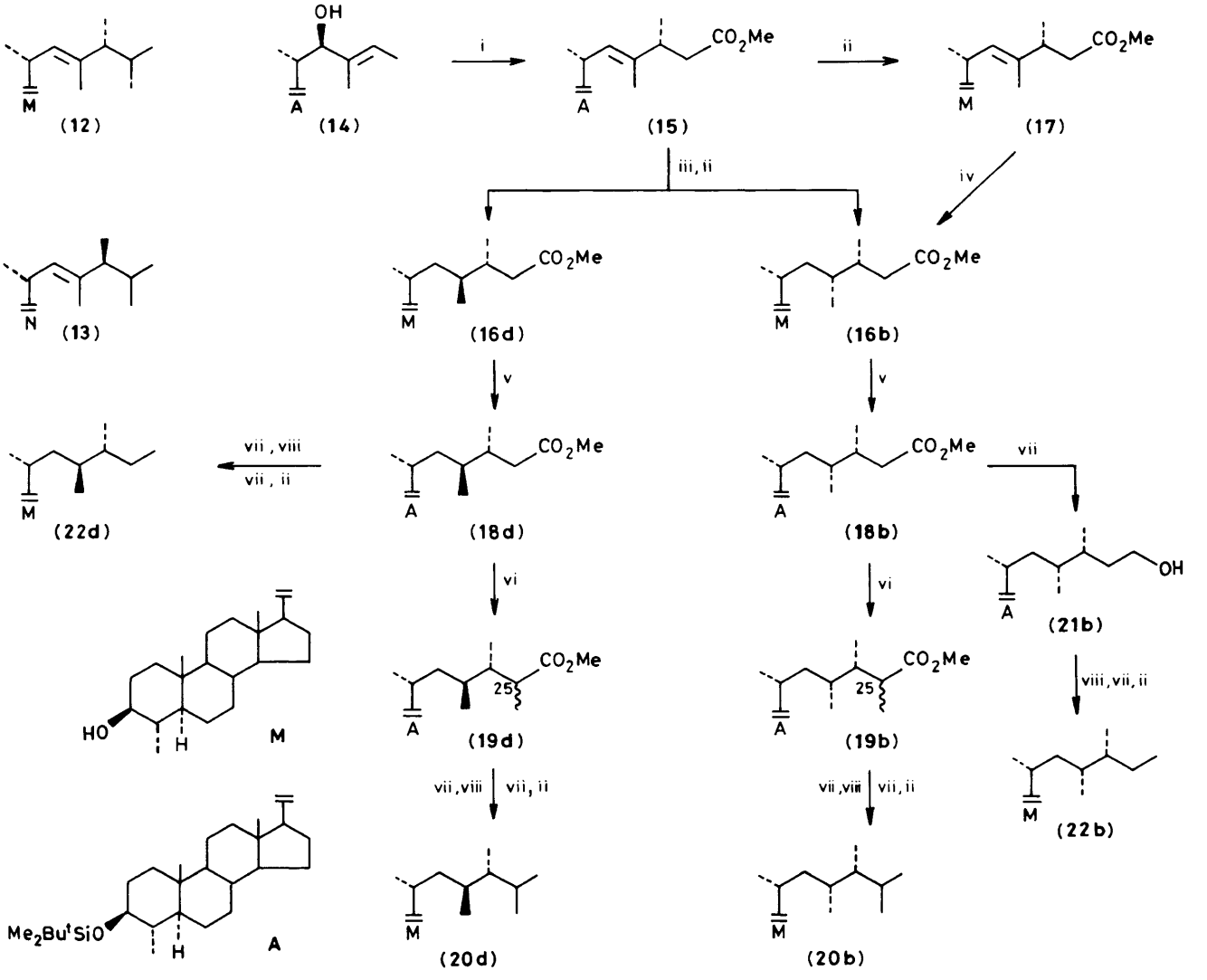
‡ The vinyl iodide (**32**) was synthesized by hydroboration of but-2-yne (**43**) with the borane (**44**) according to a literature procedure.[27]



(**43**) (**44**) (**32**)

* Nucleophilic additions of organometallic reagents to 22-aldehydes resulted predominantly in the 22α-hydroxy isomers, which in our case is the (22*R*)-allylic alcohol (**33**).[29]

† The 22α-hydroxy isomers with an iso-methyl ether nucleus usually are the less-polar epimers in normal-phase silica-gel column chromatography; see footnote 25 in ref. 20*c*.



Scheme 6. i, $MeC(OMe)_3$, xylenes, 120 °C; ii, $LiBF_4$, CH_2Cl_2–MeCN, reflux; iii, Pd/C, H_2 EtOAc; iv, PtO_2, H_2, HOAc–hexane; v, TBDMSCl, imidazole, CH_2Cl_2–DMF; vi, LDA, MeI, HMPA, 70 °C; vii, LAH, ether; viii, MsCl, Et_3N, CH_2Cl_2

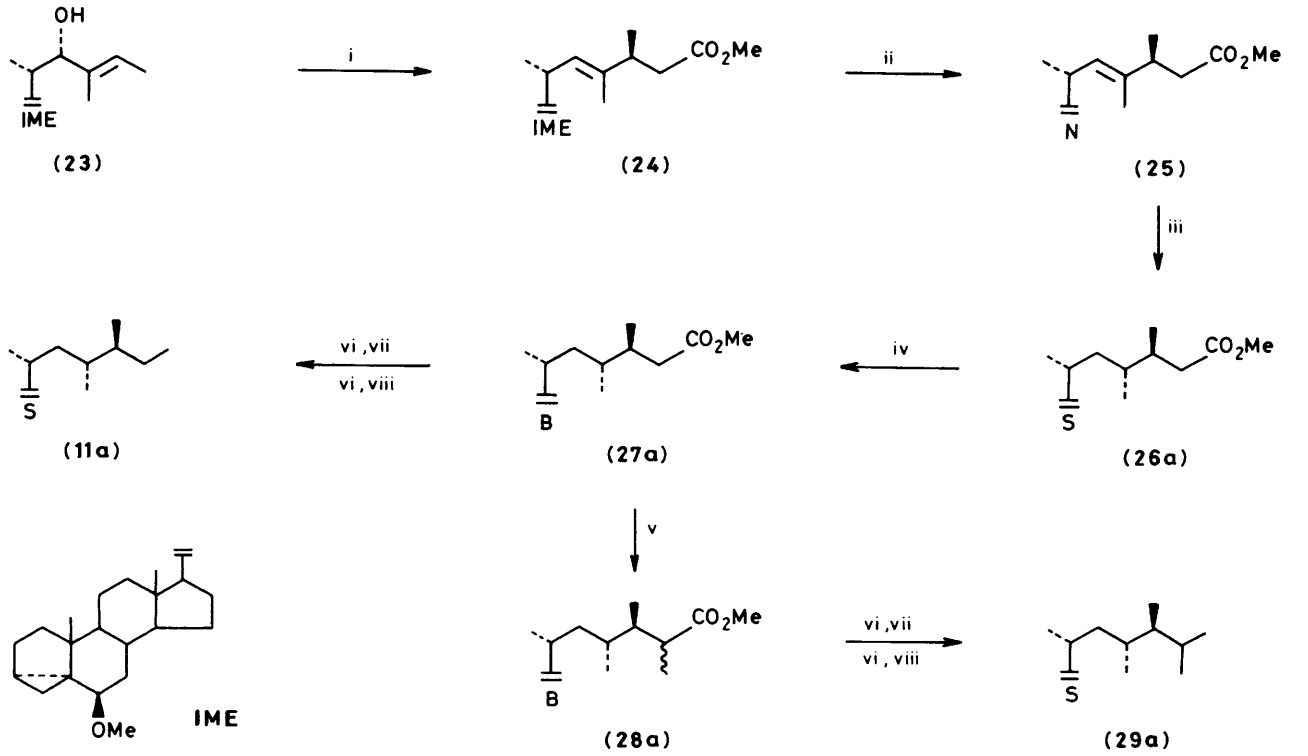
Table 5. ^{1}H N.m.r. chemical shifts of 4-demethyl-5-dehydrodinosterol (**37**) and its 24-epimer (**13**) (360 MHz, $CDCl_3$, coupling constants *J* in Hz)

	Natural (**37**)[a]	(**37**)	(**13**)
C-18 (s)	0.712	0.709	0.715
C-19 (s)	1.012	1.010	1.012
C-21 (d)[b]	0.934	0.931	0.926
	(*J* 6.5)	(*J* 6.5)	(*J* 6.5)
C-22 (d)	4.884	4.880	4.884
	(*J* 9.5)	(*J* 9.4)	(*J* 9.7)
C-26 (d)[c]	0.780	0.778	0.773
	(*J* 6.5)	(*J* 6.5)	(*J* 6.5)
C-27 (d)[c]	0.838	0.836	0.850
	(*J* 6.6)	(*J* 6.5)	(*J* 6.5)
C-28 (d)	0.934	0.931	0.940
	(*J* 6.5)	(*J* 6.5)	(*J* 6.5)
C-29 (s)	1.501	1.500	1.490

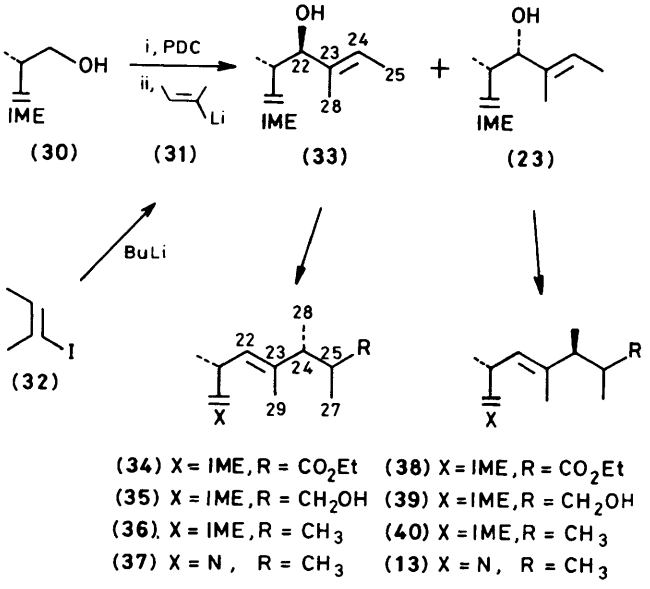
[a] See ref. 30. [b] C-21 Was determined by a decoupling experiment involving simultaneous irradiation of the 22-vinyl proton and the allylic proton around 2.3 p.p.m. in both isomers. [c] C-26 and C-27 Were determined by their simultaneous collapse when irradiation occurred around 1.5 p.p.m.

iso-methyl ether (**36**). Regeneration of the 3β-hydroxy-Δ^5 skeleton gave (**37**), which was identical (Table 4) with natural 4-demethyl-5-dehydrodinosterol.[30] Exactly the same sequence was applied to the minor 22*S*,23*E*-allylic alcohol (**23**) to provide the 24-epimer (**13**). The above transformations not only verified the stereochemistry at C-22 of the allylic alcohol (**23**), but also constituted a stereoselective synthesis of 4-demethyl-5-dehydrodinosterol (**37**), which was postulated[2,31] to be the penultimate biosynthetic precursor of gorgosterol (**41**), one of the most important cyclopropane-containing sterols. By replacing LAH with the corresponding tritium or deuterium counterparts in one or both of the terminal reduction steps (**34**) - - → (**35**) - - → (**36**), appropriate tritium or deuterium labelled analogue of 4-demethyl-5-dehydrodinosterol (**37**) (23,24-dimethyl-22-dehydrocholesterol; 23-methylbrassicasterol) were synthesized, which we are currently using in biochemical incorporation studies.

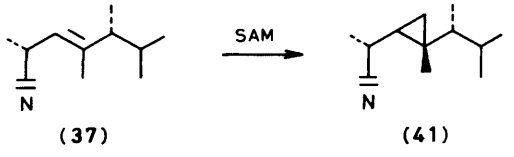
In conclusion, the side-chain stereochemistry of ficisterol and norficisterol is now firmly settled. The observed configuration of ficisterol is that predicted recently,[5] which is consistent with the view that dihydrocalysterol (**3**) is the immediate biosynthetic precursor of ficisterol. Analogously, the determined stereo-



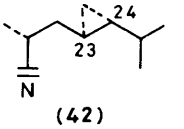
Scheme 7. i, $CH_3C(OMe)_3$, xylenes, 120 °C; ii, *p*-TsOH, *p*-dioxane–H_2O; iii, PtO_2, H_2, HOAc–hexane; iv, TBDMSCl, imidazole, CH_2Cl_2–DMF; v, LDA, MeI, HMPA, 70 °C; vi, LAH, ether; vii, MsCl, Et_3N, CH_2Cl_2; viii, $LiBF_4$, CH_2Cl_2–MeCN, reflux



Scheme 8.



chemistry of norficisterol also fits into the same scheme, which means that the recently discovered (23*R*,24*R*)-methylene-cholesterol (**42**)[32] should be its progenitor. Biosynthetic experiments devised to verify these unexpected functions of such cyclopropanes are underway in our laboratory.



Experimental

General Procedures.—All organic solvents were purified according to literature procedures,[33] and distilled prior to use. 'The usual work-up' refers to dilution with water, extraction with the stated organic solvent, washing to neutrality, drying ($MgSO_4$), filtration, and evaporation of the organic solvent under reduced pressure. M.p.s were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Optical rotations were taken in chloroform ($CHCl_3$) at 20 °C on a Rudolph Research Autopol III polarimeter equipped with a thermostatted 1.00 dm microcell. I.r. spectra were recorded in $CHCl_3$ solution in a 1 mm NaCl cell in a Beckman Acculab 3 i.r. spectrometer.

Routine g.c. analysis on sterols was carried out on a Hewlett-Packard Model 402A chromatograph equipped with a flame-ionization detector and a U-shaped glass column (4 mm i.d. × 1.8 m) packed with 3% OV-17 on 100/200 Gas-chrom Q (Applied Scientific, Inc.). The oven temperature, unless otherwise stated, was 260 °C with helium as the carrier gas. G.c. values were reported as relative retention times (rel.-R_t) with respect to cholesterol. Volatile compounds were processed on a Varian Aerograph Series 2700 gas chromatograph using a 10 ft × 318 in aluminium column packed with 20% Carbowax

20M on 80/100 Chromosorb W at a column temperature of 120 °C and helium as the carrier gas.

High resolution mass spectra were taken on a Varian Mat-711 double-focusing spectrometer equipped with a PDP-11/45 computer for data acquisition and reduction. Sterols with dimethyl-t-butylsilyloxyl protecting groups only showed $M^+ - C_4H_9$ as the most intense peaks and so their molecular ions were not reported. Low-resolution mass spectra were obtained either with a gas chromatograph/mass spectrometer Hewlett-Packard HP 5995 or a Varian MAT-44 instrument.

The 100 MHz ^{1}H n.m.r. spectra of vinyl iodides were recorded on a Varian XL-100 spectrometer; 300 MHz ^{1}H n.m.r. spectra were recorded on a Nicolet NT 300WB instrument; and 360 MHz ^{1}H n.m.r. spectra were obtained with a Bruker HX-360 spectrometer. The solvents used were $CDCl_3$ or C_6D_6 with the solvent peaks ($CHCl_3$ at 7.60 p.p.m. and C_6H_6 at 7.15 p.p.m.) as the internal standards. The chemical shift values were reported as δ in p.p.m. The coupling constant (J) values are recorded as Hz. Whenever appropriate, the homoallylic methyl groups were distinguished from the other methyl doublets by decoupling experiments involving irradiation at allylic proton regions (2.3 p.p.m.). ^{13}C N.m.r. spectra were recorded on a Varian FT-80A spectrometer with $CDCl_3$ as the solvent and internal standard.

High performance liquid chromatography (h.p.l.c.) was performed on a Waters Associates unit (M6000 pump, UK 6 injector, R403 differential refractometer). For reverse-phase h.p.l.c., two different columns were employed: Whatman Partisil M9 10/50 ODS-2 (9 mm i.d. × 50 cm) with absolute methanol (MeOH) as the eluant; and two Altex Ultrasphere ODS 5 μm columns (10 mm i.d. × 25 cm) connected in series with MeOH as the mobile phase. The flow rate, unless otherwise stated, was 3 ml/min. Cholesterol was used as the standard for rel-R_t. The normal-phase h.p.l.c. was performed on a Whatman Partisil M9 10/50 silica gel column with 7% ethyl acetate in hexane as the mobile phase, and the flow rate was 3 ml/min. The retention times (R_t) were recorded in min.

All reactions were conducted in either argon or nitrogen atmosphere, and monitored by analytical t.l.c. or g.c. Analytical t.l.c. was performed on silica gel 60 F_{24} pre-coated (0.2 mm) aluminium sheets (E. Merck), developed in a hexane–ethyl acetate mixture (5:1) unless otherwise stated, and visualized by spraying with a ceric sulphate solution in sulphuric acid, followed by heating. Column chromatography was carried out on E. Merck silica gel 60 (70—230 mesh ASTM) eluting with gradient solvents (hexane–ethyl acetate or hexane–ether mixtures) in increasing polarity.

Most reagents were used in excess to ensure high yields of the desired sterol products. The protection of the 3β-hydroxy group with dimethyl-t-butylsilyl chloride (TBDMSCl) was carried out in a refluxing solution of dichloromethane (CH_2Cl_2)–dimethylformamide (DMF) (1:1) in the presence of imidazole.[10] The deprotection of TBDMS ether was performed by its treatment with an excess of lithium tetrafluoroborate ($LiBF_4$) in a refluxing mixture of CH_2Cl_2–acetonitrile (MeCN) (1:1).[16] Mesylation of alcohols was executed by dissolving the alcohols in dry CH_2Cl_2 and triethylamine (Et_3N) at 0 °C.[17] Then methanesulphonyl chloride (MsCl) was added dropwise *via* a syringe. The reaction mixture was stirred at ambient temperature for 30 min and the solvents were removed under reduced pressure. Lithium di-isopropylamide (LDA) base in tetrahydrofuran (THF) was prepared by adding an appropriate molar amount of MeLi to a solution of a slight excess of di-isopropylamine in THF at 0 °C, followed by stirring at the same temperature for 15 min, and was used immediately. Ester enolates were prepared by the addition of the corresponding esters to the LDA solution at −78 °C. Ester methylations were carried out by adding an excess of methyl iodide (MeI) in hexamethylphosphoramide (HMPA) into the ester enolates at −78 °C followed by refluxing the reaction at 70 °C for 30 min.[21] In all instances, only the desired monomethylation was observed. However, no methylation occurred if neither HMPA nor heating was employed.

The coupling of tosylates with methylmagnesium iodide, freshly prepared from MeI and magnesium turnings in ether, was performed according to Schlosser's procedure.[15] Twenty percent molar amount (with respect to the tosylate) of lithium chloride (LiCl) and cupric chloride ($CuCl_2$) were pre-mixed in THF to give a red solution at room temperature.[34] This dilithium tetrachlorocuprate (Li_2CuCl_4) catalyst was added to the tosylate at −78 °C followed by the slow addition of MeMgI. The reaction was warmed up to 0 °C for 2 h and stirred at room temperature for 4 h.

Hydrogenations were performed under a positive atmospheric pressure of hydrogen in a balloon. Platinum(IV) oxide (Adam's catalyst, from Aldrich) or palladium on charcoal (10% Pd/C, from Aldrich) in the appropriate solvents were first degassed and then saturated with hydrogen. To these solutions were added olefinic sterols. The work-up involved filtration through Celite to get rid of the catalysts and evaporation of the solvents.

The work-up of lithium aluminium hydride (LAH) reductions was performed according to a literature procedure[35] by adding, in sequence, an equivalent portion of water, an equivalent portion of 15% aqueous sodium hydroxide, three portions of water, followed by filtration. Regeneration of the 3β-hydroxy-Δ^5 system from the iso-methyl ether skeleton was accomplished by refluxing at 100 °C for 1 h the iso-methyl ether compound in a *p*-dioxane–water (4:1) solution with a small crystal of toluene-*p*-sulphonic acid.[26]

Methyl 3β-*Dimethyl-t-butylsilyloxychol*-5-*en*-24-*oate* (**5**).—Methyl 3β-hydroxychol-5-en-24-oate (**4**) (3.2 g, 8.25 mmol), obtained from methyl 3β-acetoxychol-5-en-24-oate by means of a known procedure,[36] was refluxed with TBDMSCl (2 g) and imidazole (1 g) in CH_2Cl_2–DMF (1:1; 40 ml) overnight. The usual work-up with CH_2Cl_2, followed by vacuum distillation to remove solvents, and column chromatography gave (**5**) (3.5 g, 88%), m.p. 141—142 °C (ether–MeOH); $[\alpha]_D^{20}$ −31.5° (*c* 2.16); δ (300 MHz; $CDCl_3$) 0.051 (6 H, s, 2 × SiMe), 0.672 (3 H, s, 18-Me), 0.885 (9 H, s, $SiCMe_3$), 0.923 (3 H, d, *J* 6.3 Hz, 21-Me), 0.994 (3 H, s, 19-Me), and 3.660 (3 H, s, CO_2CH_3) (Found: $M^+ - C_4H_9$, 445.3184. $C_{27}H_{45}O_3Si$ requires 445.3138).

(E)-*But*-2-*enyl* 3β-*Dimethyl-t-butylsilyloxychol*-5-*en*-24-*oate* (**6**).—A small piece of freshly cut sodium metal was added to a stirred mixture of benzene (6 ml) and *trans*-crotyl alcohol (4 ml; from Aldrich) until the sodium dissolved completely. The methyl ester (**5**) (0.96 g, 1.91 mmol) was then added to this mixture after which it was stirred for 6 h. The usual work-up with ether and purification on a silica gel column gave (**6**) (0.90 g, 87%: m.p. 92—93 °C (ether–MeOH); $[\alpha]_D^{20}$ −28.2° (*c* 1.24); δ (300 MHz, $CDCl_3$) 0.051 (6 H, s, 2 × SiMe), 0.664 (3 H, s, 18-Me), 0.882 (9 H, s, $SiCMe_3$), 0.915 (3 H, d, *J* 6.6 Hz, 21-Me), 0.989 (3 H, s, 19-Me), 1.719 (3 H, dd, *J* 1.2 Hz, *J* 6.5 Hz, $CO_2CH_2CH{=}CHCH_3$), 4.491 (2 H, d, *J* 6.3 Hz, $CO_2CH_2CH{=}CHCH_3$), 5.582 (1 H, dtd, J_d 15.3 Hz, J_t 6.2 Hz, J_d 1.5 Hz, $CO_2CH_2CH{=}CHCH_3$), 5.787 (1 H, dq, J_d 15.3 Hz, J_q 6.3 Hz, $CO_2CH_2CH{=}CHCH_3$) (Found: $M^+ - C_4H_9$, 485.3427. $C_{30}H_{49}O_3Si$ requires 485.3451).

(23R,24S)- *and* (23S,24R)-3β-*Dimethyl-t-butylsilyloxy*-23-*hydroxymethyl*-27-*norcholesta*-5,25-*diene* (**10a**) *and* (**10d**).—To an equimolar solution of LDA in THF (4 ml) at −78 °C was added dropwise the ester (**6**) (500 mg, 0.92 mmol) in THF (4 ml) *via* a syringe, followed by HMPA (2 ml). After 15 min, trimethylsilyl chloride (TMSCl; 0.3 ml) was added. The mixture

was warmed to room temperature and refluxed at 70 °C (oil-bath temp.) for 30 min. Upon cooling to room temperature, MeOH (2 ml) was added and the mixture was stirred for an additional 30 min. The usual work-up with ether gave the acids, which were filtered through a short silica-gel column to remove nonpolar impurities and subsequently esterified with diazomethane (from Diazald, Aldrich). The methyl esters were reduced with LAH (0.5 g) in ether to give 280 mg (57%) of the alcoholic mixture after silica gel column chromatography. Normal-phase h.p.l.c. of the alcoholic mixture gave (in order of elution) (**10a**), (**10b**), (**10c**), and (**10d**) in an 8:1:1:8 ratio, respectively. The alcohol (**10a**) was the 23*R*,24*S*-isomer, m.p. 161—163 °C (ether–MeOH); $[\alpha]_D^{20}$ −21.6° (*c* 1.15). H.p.l.c. (Whatman Partilsil M9 10/50 silica gel column, 7% ethyl acetate in hexane), R_t 49 min; δ (300 MHz, $CDCl_3$) 0.052 (6 H, s, 2 × SiMe), 0.677 (3 H, s, 18-Me), 0.883 (9 H, s, Si-CMe_3), 0.905 (3 H, d, *J* 6.6 Hz, 21-Me), 0.973 (3 H, d, *J* 6.9 Hz, 28-Me), 0.991 (3 H, s, 19-Me), 4.98—5.07 (2 H, m, 26-H's), 5.78—5.90 (1 H, m, 25-H) (Found: $M^+ - C_4H_9$, 471.3674. $C_{30}H_{51}O_2Si$ 471.3658). The 23*S*,24*R*-isomer (**10d**) had m.p. 169—170 °C (hexane); $[\alpha]_D^{20}$ −9.3° (*c* 0.95); h.p.l.c. [see (**10a**)] R_t 68 min; δ (300 MHz, $CDCl_3$) 0.053 (6 H, s, 2 × SiMe), 0.684 (3 H, s, 18-Me), 0.884 (9 H, s, $SiCMe_3$), 0.926 (3 H, d, *J* 6.6 Hz, 21-Me), 0.995 (3 H, s, 19-Me), 1.065 (3 H, d, *J* 6.9 Hz, 28-Me), 4.98—5.05 (2 H, m, 26-H's), 5.74—5.86 (1 H, m, 25-H); it had the same mass spectrum as (**10a**).

(23R,24R)- *and* (23S,24S)-3β-*Dimethyl-t-butylsilyloxy*-23-*hydroxymethyl*-27-*norcholesta*-5,25-*diene* (**10b**) *and* (**10c**).—The same procedure to prepare the alcohols (**10a**) and (**10d**) was employed here with the exception that HMPA was not added. The ester (**6**) (420 mg, 0.77 mmol) in THF (5 ml) was added to an equal molar solution of LDA in THF (4 ml) at −78 °C, followed by TMSCl (0.3 ml). The reaction was heated at 70 °C (oil-bath temp.) for 30 min after which it was cooled to room temperature and MeOH (2 ml) was added. The usual work-up gave the free acids which were esterfied with diazomethane and reduced with LAH, followed by silica-gel column chromatography, to give the alcohols (252 mg, 62%). Normal-phase h.p.l.c. [see conditions for (**10a**)] separation gave (in order of elution) (**10a**), (**10b**), (**10c**), and (**10d**) in the ratio of 1:7:7:1, respectively. The 23*R*,24*R*-isomer was (**10b**), m.p. 159—160 °C (MeOH); $[\alpha]_D^{20}$ −9.3° (*c* 1.16); h.p.l.c. [see (**10a**)] R_t 52 min; δ (300 MHz, $CDCl_3$) 0.053 (6 H, s, 2 × SiMe), 0.674 (3 H, s, 18-Me), 0.884 (9 H, s, $SiCMe_3$), 0.991 (3 H, d, *J* 6.6 Hz, 21-Me), 0.991 (3 H, s, 19-Me), 1.031 (3 H, d, *J* 6.9 Hz, 28-Me), 4.97—5.05 (2 H, m, 26-H's), and 5.68—5.80 (1 H, m, 25-H); it has the same mass spectrum as that of (**10a**). The 23*S*,24*S*-isomer was (**10c**), m.p. 172—173 °C (hexanes); $[\alpha]_D^{20}$ −27.4° (*c* 1.52); h.p.l.c. [see (**10a**) for conditions] R_t 60 min; δ (300 MHz, $CDCl_3$) 0.052 (6 H, s, 2 × SiMe), 0.686 (3 H, s, 18-Me), 0.885 (9 H, s, SiCMe), 0.939 (3 H, d, *J* 6.6 Hz, 21-Me), 0.967 (3 H, d, *J* 7.2 Hz, 28-Me), 0.996 (3 H, s, 19-Me), 5.00—5.07 (2 H, m, 26-H's), and 5.86—5.98 (1 H, m, 25-H); it had the same mass spectrum as that of (**10a**).

(23R,24S)-23-*Ethyl*-24-*methyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**1a**): *Synthetic Ficisterol*.—The alcohol (**10a**) (48 mg) was tosylated and coupled with MeMgI in the presence of Li_2CuCl_4 as described in the general procedures. Removal of the TBDMS ether group with $LiBF_4$ (100 mg) in refluxing CH_2Cl_2–MeCN (1:1; 15 ml) overnight, and the usual work-up with CH_2Cl_2 gave (**1a**) (30 mg, 80%), m.p. 143—145 °C (MeOH); $[\alpha]_D^{20}$ −10.6° (*c* 0.85); g.c. (3% OV-17) rel.-R_t 1.53; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.96; for ^{1}H n.m.r. see Table 1; *m/z* (assignment, relative intensity) 412.3675 (M^+, $C_{29}H_{48}O$, 100%, calc. 412.3705), 397.3525 ($C_{28}H_{45}O$, 17), 394.3607 ($C_{29}H_{46}$, 31), 357.3166 ($C_{25}H_{41}O$, 19), 314.2621 ($C_{22}H_{34}O$, 42), 274.2268 ($C_{19}H_{30}O$, 42), 271.2056 ($C_{19}H_{27}O$, 49), 231.1725 ($C_{16}H_{23}O$, 23), and 213.1601 ($C_{16}H_{21}$, 24).

(23R,24R)-23-*Ethyl*-24-*methyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**1b**).—The same methods that were employed to synthesize (**1a**) were utilized to convert the alcohol (**10b**) into (**1b**): the latter had m.p. 129—130 °C (MeOH); $[\alpha]_D^{20}$ −20.0° (*c* 0.77); g.c. (3% OV-17) rel.-R_t 1.53; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.92; for ^{1}H n.m.r. see Table 1; its mass spectrum was identical with that of (**1a**).

(23S,24S)-23-*Ethyl*-24-*methyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**1c**).—This compound (**1c**) was prepared from the alcohol (**10c**) analogously to the synthesis of (**1a**): it had m.p. 144—146 °C (MeOH); $[\alpha]_D^{20}$ +33.6° (*c* 1.42); g.c. (3% OV-17) rel.-R_t 1.53; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.99; for ^{1}H n.m.r. see Table 1; its mass spectrum was identical with that of (**1a**).

(23S,24S)-23-*Ethyl*-24-*methyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**1d**).—This compound was prepared from the alcohol (**10d**) in the same manner as (**1a**): it had m.p. 143—145 °C (MeOH); $[\alpha]_D^{20}$ −10.6° (*c* 0.85); g.c. (3% OV-17) rel.-R_t 1.53; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.94; for ^{1}H n.m.r. see Table 1; its mass spectrum was identical with that of (**1a**).

(23R,24S)-23,24-*Dimethyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**2a**): *Synthetic Norficisterol*. The alcohol (**10a**) (35 mg) was mesylated according to the method described in general procedures, and reduced by LAH in ether. The TBDMS ether protecting group was removed with $LiBF_4$ (100 mg) in refluxing CH_2Cl_2–MeCn (1:1; 15 ml) for 10 h. The usual work-up with CH_2Cl_2 and purification on a silica-gel column gave (**2a**) (23 mg, 87% overall): it had m.p. 158—161 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ −30.7° (*c* 3.20); g.c. (3% OV-17) rel.-R_t 1.26; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.85; for ^{1}H n.m.r. see Table 2; δ (300 MHz, C_6D_6) δ 0.685 (3 H, s, 18-Me), 0.854 (3 H, d, *J* 6.6 Hz, 21-Me or 29-Me), 0.943 (3 H, s, 19-Me), 0.956 (3 H, d, *J* 7.5 Hz, 29-Me or 21-Me), 1.003 (3 H, d, *J* 6.9 Hz, 28-Me), 4.99—5.01 (2 H, m, 26-H's), and 5.70—5.85 (1 H, m, 25-H); *m/z* (assignment, relative intensity) 398.3544 (M^+, $C_{28}H_{46}O$, 100%, calc. 398.3549), 383.3381 ($C_{27}H_{43}O$, 19), 380.3485 ($C_{28}H_{44}$, 24), 313.2907 ($C_{23}H_{37}$, 17), and 271.2008 ($C_{19}H_{27}O$, 21).

(23R,24R)-23,24-*Dimethyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**2b**).—The same procedure for preparing (**2a**) was employed to convert the alcohol (**10b**) into (**2b**): the latter had m.p. 157—158 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ −17.2° (*c* 1.24); g.c. (3% OV-17) rel.-R_t 1.26; h.p.l.c. (Altex Ultrasphere ODA column, MeOH) rel.-R_t 0.85; for ^{1}H n.m.r. see Table 2; δ (300 MHz; C_6D_6) 0.683 (3 H, s, 18-Me), 0.858 (3 H, d, *J* 6.6 Hz, 21-Me or 29-Me), 0.942 (3 H, s, 19-Me), 0.953 (3 H, d, *J* 6.3 Hz, 29-Me or 21-Me), 0.995 (3 H, d, *J* 6.6 Hz, 28-Me), 4.99—5.15 (2 H, m, 26-H's), and 5.70—5.85 (1 H, m, 25-H); its mass spectrum was identical with that of (**2a**).

(23S,24S)-23,24-*Dimethyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**2c**).—The same procedures to prepare (**2a**) were used to transform the alcohol (**10c**) into the sterol (**2c**): the latter had m.p. 147—150 °C (MeOH); $[\alpha]_D^{20}$ −22.3° (*c* 0.60); g.c. (3% OV-17) rel.-R_t 1.25; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.88; for ^{1}H n.m.r. see Table 2; its mass spectrum was identical with that of (**2a**).

(23S,24R)-23,24-*Dimethyl*-27-*norcholesta*-5,25-*dien*-3β-*ol* (**2d**).—This sterol (**2d**) was prepared from the alcohol (**10d**) analogously to the synthesis of its isomer (**2a**); it had m.p. 154—

155 °C (MeOH); $[\alpha]_D^{20}$ −23.8° (*c* 1.36); g.c. (3% OV-17) rel.-R_t 1.24; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 0.87; for ^{1}H n.m.r. see Table 2; its mass spectrum was identical with that of (**2a**).

(23R,24S)-23,24-*Dimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**11a**).—Norficisterol (**2a**) (10 mg) was hydrogenated under a slight pressure in acetic acid-hexane (1:4; 8 ml) for 8 h with (10 mg Adam's catalyst). Filtration through Celite and removal of solvent gave (**11a**) (8 mg, 80%). The same compound was obtained when the 27-nor ester (**27a**) (18 mg; *vide infra*) was reduced by LAH to the corresponding alcohol, which was mesylated. Reduction of the mesylate with LAH and removal of the TBDMS ether protecting group with $LiBF_4$ gave (**11a**) (10 mg, 77%), m.p. 159—161 °C (MeOH); $[\alpha]_D^{20}$ +35.4° (*c* 1.27); g.c. (3% OV-17) rel.-R_t 1.24; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.22; for ^{1}H see Table 3; *m/z* (assignment, relative intensity) 402.3785 (M^+, $C_{28}H_{50}O$, 100%, calc. 402.3862), 387.3674 ($C_{27}H_{47}O$, 15) 317.2843 ($C_{22}H_{37}O$, 17), 248.2134 ($C_{17}H_{28}O$, 8), 234.1980 ($C_{16}H_{26}O$, 31), 215.1764 ($C_{16}H_{23}$, 20), and 165.1332 ($C_{11}H_{17}O$, 12).

(23R,24R)-23,24-*Dimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**11b**).—This had m.p. 164—166 °C (MeOH); $[\alpha]_D^{20}$ +37.8° (*c* 1.17); g.c. (3% OV-17) rel.-R_t 1.24; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.15; for ^{1}H n.m.r. see Table 3; for mass spectrum see (**11a**).

(23S,24S)-23,24-*Dimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**11c**).—This had m.p. 177—180 °C (MeOH); $[\alpha]_D^{20}$ +26.3° (*c* 0.57); g.c. (3% OV-17) rel.-R_t 1.24; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.10; for ^{1}H n.m.r. see Table 3; for mass spectrum see (**11a**).

(23S,24R)-23,24-*Dimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**11d**).—This had m.p. 157—158 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +11.0° (*c* 0.76); g.c. (3% OV-17) rel.-R_t 1.24; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.14; for ^{1}H n.m.r. see Table 3; for mass spectrum see (**11a**).

(22E,24R)-*Methyl* 3β-*Dimethyl-t-butylsilyloxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholest*-22-*en*-26-*oate* (**15**).—The 22*R*-allylic alcohol (**14**) (500 mg, 0.97 mmol) in mixed xylenes (10 ml), trimethyl orthoacetate (0.5 ml), and propionic acid (40 μl) was heated at 140 °C for 2 h. Evaporation of solvents and separation on silica gel gave the ester (**15**) [292 mg, 65% yield based on 24% recovery of the starting allylic alcohol (**14**)], m.p. 146—147 °C (ether–MeOH); $[\alpha]_D^{20}$ +16.7° (*c* 1.87); g.c. (3% OV-17) rel.-R_t 6.23; δ (300 MHz, $CDCl_3$) 0.036, 0.041 (3 H each, s, 2 × SiMe), 0.657 (3 H, s, 18-Me), 0.814 (3 H, s, 19-Me), 0.861 (3 H, d, *J* 7.2 Hz, 4α-Me), 0.884 (3 H, d, *J* 6.3 Hz, 21-Me), 0.886 (9 H, s, $SiCMe_3$), 1.009 (3 H, d, *J* 6.9 Hz, 28-Me), 1.557 (3 H, d, *J* 1.2 Hz, 29-Me), 3.624 (3 H, s, CO_2CH_3), 4.951 (1 H, d, *J* 9.3 Hz, 22-H) (Found: $M^+ - C_4H_9$, 515.3947. $C_{32}H_{55}O_3Si$ requires *m/z* 515.3921).

(22E,24R)-*Methyl* 3β-*Hydroxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholestan*-26-*oate* (**17**).—The silyloxy ester (**15**) (110 mg, 0.18 mmol) was deprotected with $LiBF_4$ (100 mg) in CH_2Cl_2–MeCN (1:1; 20 ml) at reflux for 12 h. The usual work-up with CH_2Cl_2 and separation on a silica gel column gave (**17**) (80 mg, 91%), m.p. 181—182 °C (ether–MeOH); $[\alpha]_D^{20}$ +7.8° (*c* 1.10); g.c. (3% OV-17) rel.-R_t 3.47; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.64; δ (300 MHz, $CDCl_3$) 0.662 (3 H, s, 18-Me), 0.819 (3 H, s, 19-Me), 0.885 (3 H, d, *J* 6.6 Hz, 21-Me), 0.940 (3 H, d, *J* 6.6 Hz, 4α-Me), 1.008 (3 H, d, *J* 6.9 Hz, 28-Me), 1.559 (3 H, d, *J* 1.2 Hz, 29-Me), 3.623 (3 H, s, CO_2CH_3), and 4.951 (1 H, d, *J* 9.6 Hz, 22-H); *m/z* (assignment, relative intensity) 458.3789 (M^+, $C_{30}H_{50}O_3$, 27%, calc. 458.3760), 316.2797 ($C_{22}H_{36}O$, 23), 287.2437 ($C_{20}H_{31}O$, 23), 196.1444 ($C_{12}H_{20}O_2$, 21), and 169.1265 ($C_{10}H_{17}O_2$, 37).

(23R,24R)-*Methyl and* (23S,24R)-*Methyl* 3β-*Hydroxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholestan*-26-*oates* (**16b**) *and* (**16d**).—The silyloxy ester (**15**) (120 mg, 0.21 mmol) in ethyl acetate (25 ml) and 10% Pd/C (120 mg) were stirred under hydrogen for 24 h. Filtration through Celite and deprotection with $LiBF_4$ gave a mixture of two esters in a 2:1 ratio. The esters were subjected to reverse-phase h.p.l.c. separation (ODS-2, MeOH). The isomer with the longer retention time was (**16b**) (50 mg, 52% overall yield), m.p. 169—172 °C (CH_2Cl_2–hexane); $[\alpha]_D^{20}$ +35.3° (*c* 0.92); g.c. (3% OV-17) rel.-R_t 4.18; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.86; δ (300 MHz, $CDCl_3$) 0.650 (3 H, s, 18-Me), 0.759 (3 H, d, *J* 6.6 Hz, one of 21-, 28-, and 29-Me's), 0.817 (3 H, s, 19-Me), 0.839 (3 H, d, *J* 6.6 Hz), 0.858 (3 H, d, *J* 4.8 Hz) two of 21-, 28-, and 29-Me's, 0.941 (3 H, d, *J* 6.3 Hz, 4α-Me), 3.659 (3 H, s, CO_2CH_3); *m/z* (assignment, relative intensity (460.3993 (M^+, $C_{30}H_{52}O_3$, 88%, calc. 460.3917), 442.3805 ($C_{30}H_{50}O_2$, 100), 427.3414 ($C_{32}H_{43}$, 27), 263.2284 ($C_{18}H_{31}O$, 13), 247.2121 ($C_{17}H_{27}O$, 55), 229.1949 ($C_{17}H_{25}$, 53), and 179.1424 ($C_{12}H_{19}O$, 40). The isomer with the shorter retention time was (**16d**) (25 mg, 26%), m.p. 141—143 °C (H_2O–MeOH); $[\alpha]_D^{20}$ +18.5° (*c* 1.69); g.c. (3% OV-17) rel.-R_t 3.80; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.70; δ (300 MHz, $CDCl_3$) 0.652 (3 H, s, 18-Me), 0.773 (3H, d, *J* 6.9 Hz, one of 21-, 28-, and 29-Me's), 0.817 (3 H, s, 19-Me), 0.890 (3 H, d, *J* 6.3 Hz), 0.911 (3 H, d, *J* 6.6 Hz, two of the 21-, 28-, and 29-Me's), 0.940 (3 H, d, *J* 6.6 Hz, 4α-Me), and 3.660 (3 H, s, CO_2CH_3); its mass spectrum was identical with that of (**16b**).

Methyl (23R,24R)-3β-*Dimethyl-t-butylsilyloxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholestan*-26-*oate* (**18b**).—The hydroxy ester (**16b**) (60 mg, 0.13 mmol) was protected with TBDMSCl according to the described general procedures to provide the protected TBDMS ether (**18b**) (69 mg, 92%), m.p. 174—176 °C (ether–MeOH), $[\alpha]_D^{20}$ +38.6° (*c* 1.23); g.c. (3% OV-17) rel.-R_t 6.20; δ (300 MHz, $CDCl_3$) 0.035, 0.040 (3 H each, s, 2 × SiMe), 0.645 (3 H, s, 18-Me), 0.759 (3 H, d, *J* 6.6 Hz, one of 21-, 28-, and 29-Me's), 0.812 (3 H, s, 19-Me), 0.840 (3 H, d, *J* 6.3 Hz, one of the 21-, 28-, and 29-Me's), 0.860 (6 H, d, *J* 6.0 Hz, 4α-Me and one of the 21-, 28-, and 29-Me's), 0.885 (9 H, s, $SiCMe_3$), 3.660 (3 H, s, CO_2CH_3) (Found: $M^+ - C_4H_9$, 517.4052. $C_{32}H_{57}O_3Si$ requires 517.4077).

(23R,24R)-4α,23,24-*Trimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**22b**).—The silyloxy ester (**18b**) (26 mg) was reduced with LAH (100 mg) in anhydrous ether (20 ml) to afford (23R,24R)-3β-*dimethyl-t-butylsilyloxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholestan*-26-*ol* (**21b**); δ (300 MHz, $CDCl_3$) 0.035, 0.040 (3 H each, s, 2 × SiMe), 0.649 (3 H, s, 18-Me), 0.747 (3 H, d, *J* 6.3 Hz), 0.804 (3 H, d, *J* 5.7 Hz) two of 21-, 28-, and 29-Me's, 0.813 (3 H, s, 19-Me), 0.861 (6 H, d, *J* 6.3 Hz, 4α-Me and one of the 21-, 28-, and 29-Me's), and 0.885 (9 H, s, $SiCMe_3$) (Found: $M^+ - C_4H_9$, 489.4126. $C_{31}H_{57}O_2Si$ requires 489.4128). The alcohol was then mesylated with methanesulphonyl chloride (20 μl), triethylamine (0.1 ml) in dry CH_2Cl_2 (5 ml) for 30 min. After evaporation of the solvent, the mesylate was reduced with LAH (200 mg) in ether (20 ml) to give the silyl ether of the saturated 27-nor side-chain, which was deprotected with $LiBF_4$ according to the described general procedures to give (**22b**) (12 mg, 65% overall yield), m.p. 196—198 °C (MeOH); g.c. (3% OV-17) rel.-R_t 1.47; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.60; for ^{1}H n.m.r. see Table 4; δ (300 MHz, C_6D_6) 0.704 (3 H, s), 0.745 (3 H, s), 0.821 (3 H, d, *J* 6.6 Hz), 0.859 (3 H, d, *J* 6.6 Hz), 0.916 (3 H, t, *J* 7.5 Hz, 26-Me), and 1.001 (6 H, d, *J* 6.6 Hz); *m/z* (assignment, relative intensity) 416.3894 (M^+, $C_{29}H_{52}O$, 91%, calc. 416.4018), 401.3696 ($C_{28}H_{49}O$, 24), 398.3834 ($C_{29}H_{50}$, 23),

331.3083 ($C_{23}H_{39}O$, 23), 299.2759 ($C_{22}H_{35}$, 18), 262.2253 ($C_{18}H_{30}$, 23), 248.2181 ($C_{17}H_{28}O$, 64), and 229.2020 ($C_{17}H_{25}$, 84).

(23R,24R)-4α,23,24-*Trimethyl*-5α-*cholestan*-3β-*ol* (**20b**).—The silyloxy 27-nor ester (**18b**) (20 mg) in THF (1 ml) was added dropwise to a solution of LDA at −78 °C, prepared by addition of MeLi (1.55M in ether; 0.1 ml) to di-isopropylamine (0.2 ml) in THF (2 ml) at 0 °C. MeI (0.2 ml) in HMPA (0.5 ml) was added in one portion to the ester enolate, followed by refluxing at 70 °C (oil-bath temp.) for 30 min. The usual work-up and purification on silica gel gave the epimeric esters. The major isomer (23R,24S,25ξ)-*methyl* 3β-*dimethyl-t-butylsilyloxy*-4α-23,24-*trimethyl*-5α-*cholestan*-26-*oate* (**19b**) displayed the following properties: δ (300 MHz; $CDCl_3$) 0.035, 0.040 (3 H each, s, 2 × SiMe), 0.643 (3 H, s, 18-Me), 0.744 (3 H, d, *J* 7.2 Hz), 0.768 (3 H, d, *J* 7.2 Hz), 0.812 (3 H, s, 19-Me), 0.838 (3 H, d, *J* 6.6 Hz), 0.860 (3 H, d, *J* 6.6 Hz, 4α-Me), 0.886 (9 H, s, $SiCMe_3$), 1.070 (3 H, d, *J* 6.9 Hz, 27-Me), and 3.657 (3 H, s, CO_2CH_3). A small amount of the methylated silyloxy esters, prepared in a separate run, were deprotected with $LiBF_4$ to give the 3β-hydroxy esters for further identification purposes. The major 3β-hydroxy isomer was (23R,24S,25ξ)-*methyl* 3β-*hydroxy*-4α,23,24-*trimethyl*-5α-*cholestan*-26-*oate*: g.c. (3% OV-17) rel.-R_t 4.65; δ (300 MHz, $CDCl_3$) 0.649 (3 H, s, 18-Me), 0.745 (3 H, d, *J* 6.9 Hz), 0.768 (3 H, d, *J* 7.2 Hz), 0.818 (3 H, s, 19-Me), 0.839 (3 H, d, *J* 6.6 Hz), 0.942 (3 H, d, *J* 6.3 Hz, 4α-Me), 1.070 (3 H, d, *J* 6.9 Hz, 27-Me), and 3.657 (3 H, s, CO_2CH_3) (Found: M^+, 474.4114. $C_{31}H_{54}O_3$ requires M^+, 474.4073). The 25-epimeric silyl ether methylated esters were reduced to the alcohols. Mesylation, reduction, and desilylation gave (**20b**) (11 mg, 73% overall), m.p. 195—197 °C (MeOH) [lit.,[19] m.p. 196—199 °C (MeOH)]; $[\alpha]_D^{20}$ +35.6° (*c* 1.00); g.c. (3% OV-17) rel.-R_t 1.85; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.77; for ^1H n.m.r. see Table 4; *m/z* (assignment, relative intensity) 430.4175 (M^+, $C_{30}H_{54}O$, 83%, calc. 430.4175), 415.3887 ($C_{29}H_{51}O$, 14), 248.2155 ($C_{17}H_{28}O$, 31), 229.1919 ($C_{17}H_{25}$, 36), 179.1449 ($C_{12}H_{19}O$, 26), and 161.1324 ($C_{12}H_{17}$, 15).

(23S,24R)-*Methyl* 3β-*Dimethyl-t-butylsilyloxy*-4α,23,24-*trimethyl*-27-*nor*-5α-*cholestan*-26-*oate* (**18d**).—The minor hydrogenated 3β-hydroxy ester (**16d**) (38 mg) was protected as previously mentioned to provide (**18d**) (35 mg, 74%), 135—138 °C (benzene–MeOH); $[\alpha]_D^{20}$ +24.9° (*c* 1.75); δ (300 MHz, $CDCl_3$) 0.035, 0.040 (3 H each, s, 2 × SiMe), 0.647 (3 H, s, 18-Me), 0.775 (3 H, d, *J* 6.9 Hz, one of 21-, 28-, and 29-Me's), 0.813 (3 H, s, 19-Me), 0.860 (3 H, d, *J* 6.3 Hz, 4α-Me), 0.885 (9 H, s, $SiCMe_3$), 0.893 (3 H, d, *J* 4.8 Hz), 0.912 (3 H, d, *J* 6.6 Hz, two of the 21-, 28-, and 29-Me's), and 3.663 (3 H, s, CO_2CH_3); its mass spectrum was identical with that of (**18b**).

(23S,24R)-4α,23,24-*Trimethyl*-27-*nor*-5α-*cholestan*-3β-*ol* (**22d**).—The silyloxy ester (**18d**) (20 mg) was treated analogously to its isomer (**18b**) to furnish the free sterol (**22d**) (12 mg, 83%), m.p. 186—189 °C (MeOH); $[\alpha]_D^{20}$ +12.6° (*c* 0.50); g.c. (3% OV-17) rel.-R_t 1.47; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.45; for ^1H n.m.r. see Table 4; its mass spectrum was identical with that of (**22b**).

(23S,24R)-4α,23,24-*Trimethyl*-5α-*cholestan*-3β-*ol* (**20d**).—The 27-nor ester (**18d**) (15 mg) was methylated in the same manner as its 23-epimer (**18b**). The major isomer (23S,24S,25ξ)-*methyl* 3β-*dimethyl-t-butylsilyloxy*-4α,23,24-*trimethyl*-5α-*cholestan*-26-*oate* (**19d**) exhibited the following spectral properties: δ (300 MHz, $CDCl_3$) 0.037, 0.042 (3 H each, s, 2 × SiMe), 0.645 (3 H, s, 18-Me), 0.811 (3 H, d, *J* 6.6 Hz), 0.816 (3 H, s, 19-Me), 0.864 (3 H, d, *J* 6.6 Hz, 4α-Me), 0.888 (3 H, d, *J* 5.7 Hz), 0.889 (9 H, s, $SiCMe_3$), 0.900 (3 H, d, *J* 6.6 Hz), 1.059 (3 H, d, *J* 7.2 Hz, 27-Me), and 3.650 (3 H, s, CO_2CH_3). The methylated esters were reduced to their alcohols, which were mesylated, reduced, and desilylated to provide (**20d**) (8 mg, 71%), m.p. 183—187 °C (MeOH); $[\alpha]_D^{20}$ +8.3° (*c* 0.78); g.c. (3% OV-17) rel.-R_t 1.85; h.p.l.c. (Altex Ultrasphere ODS column, MeOH) rel.-R_t 1.66; for ^1H n.m.r. see Table 4; its mass spectrum was identical with that of its 23-epimer (**20b**).

(E)-2-*Iodobut*-2-*ene* (**32**).—But-2-yne (**43**) (25 ml, 0.32 mol; from K&K, ICN Pharmaceuticals) and hydridopyrocatecholatoboron (**44**) (95%; 42 g, 0.34 mol, from Aldrich) were sealed in a glass tube under argon at the temperature of solid CO_2 and then heated to 70 °C for 2 h. After cooling to room temperature, the tube was broken and the content was poured into water (250 ml), which was stirred at ambient temperature for 3 h. Attempts to purify the boronic acid derivative for characterization failed owing to its high volatility and great solubility in water. Thus a cold solution of aqueous NaOH (100 ml, 20 g, 0.5 mol) was slowly poured into the hydrolysed mixture at 0 °C, followed by a cold solution of elemental iodine (80 g, 0.31 mol) in ether (200 ml). After being stirred at 0 °C for 30 min, the mixture was extracted with ether (200 ml × 5). The combined organic layer was washed with saturated aqueous sodium thiosulphate, water, and brine and then dried (anhydrous $MgSO_4$). The ether was distilled off at atmospheric pressure and g.c. analysis (20% Carbowax, 120 °C) indicated a mixture of two components in a ratio of 1:6. Each sample was purified by preparative g.c. The minor compound (shorter retention time) was the (Z)-2-*iodobut*-2-*ene*: δ (100 MHz, $CDCl_3$) 1.71 (3 H, dq, J_d 6.3 Hz, J_q 1.6 Hz, 1-Me), 2.49 (3 H, q, J_q 1.6 Hz, 4-Me), 5.48 (1 H, qq, J_q 6.3 Hz, J_q 1.6 Hz, 3-H).* The major component (longer retention time) was the desired (E)-2-*iodobut*-2-*ene* (**32**): δ (100 MHz, $CDCl_3$) 1.61 (3 H, dq, J_d 7.0 Hz, J_q 1.2 Hz, 2-Me), 2.36 (3 H, q, J_q 1.2 Hz, 4-Me), 6.20 (1 H, qq, J_q 7.0 Hz, J_q 1.5 Hz, 3-H).* Short-path (glass beaded) distillation at reduced pressure (50 mmHg) was fractionated. The later fractions (b.p. 51—53 °C) were combined and gave (**32**) (6.2 g, 10% yield from but-2-yne) which was enriched to 95% pure by g.c.

(22R,23E)- *and* (22S,23E)-6β-*Methoxy*-23-*methyl*-3α,5-*cyclo*-26,27-*nor*-5α-*cholest*-23-*en*-22-*ol* (**33**) *and* (**23**).—The iso-methyl ether alcohol (**30**) (2.59 g, 7.4 mmol) was stirred at room temperature with pyridinium dichromate (5 g) in anhydrous CH_2Cl_2 (50 ml) overnight. Filtration through Florisil and removal of solvent under reduced pressure gave the aldehyde that was used immediately. The vinyl-lithium reagent was prepared by the addition of butyl-lithium in hexane (2.4M; 6 ml, 14.4 mmol) to a stirred solution of (*E*)-2-iodobut-2-ene (**32**) (3.17 g, 17.4 mmol) and anhydrous ether (20 ml) at −78 °C. The mixture was stirred at −60 °C for 20 min and then cooled to −78 °C. The aldehyde in anhydrous ether (20 ml) was added dropwise very slowly to the stirring vinyl-lithium solution such that the reaction temperature was kept close to −78 °C. After completion of addition, the reaction was stirred at −78 °C for 30 min, and then allowed to warm to −20 °C, and hydrolysed by careful addition of saturated aqueous NH_4Cl. The usual work-up with ether and chromatography on a silica gel column using ether–hexane (1:9) gave (**33**) (2.1 g, 70%), m.p. 120—

* The ^1H n.m.r. spectra of both isomers were identical to those of the reported (*Z*)- and (*E*)- vinyl iodides (*cf.* A. Pross and S. Steinhall, *Aust. J. Chem.*, 1970, **23**, 989). Notwithstanding that the configurations of the reported iodides were only assumed, the observation that the δ value of the vinyl proton of the *E* isomer occurred at lower field, which correlated with the known bromo analogue (*cf.* J. H. Richards and W. F. Beach, *J. Org. Chem.*, 1961, **26**, 623), confirmed that the assignment was correct.

121 °C (MeOH–H_2O); $[\alpha]_D^{20}$ +23.9° (*c* 1.06); R_F 0.37; g.c. (3% OV-17, 240 °C) rel.-R_t 0.92; $\nu_{max.}$($CHCl_3$) 3 440 and 960 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.737 (3 H, s, 18-Me), 0.766 (3 H, d, *J* 6.5 Hz, 21-Me), 1.026 (3 H, s, 19-Me), 1.527 (3 H, s, 28-Me), 1.645 (3 H, d, *J* 6.8 Hz, 25-Me), 3.331 (3 H, s, OMe), 4.064 (1 H, br, 22-H), and 5.477 (1 H, q, *J* 6.5 Hz, 24-H); *m/z* (assignment, relative intensity) 400.3352 (M^+, $C_{27}H_{44}O_2$, 9%, calc. 400.3392); 345.2781 ($C_{23}H_{37}O_2$, 6), 316.2761 ($C_{22}H_{36}O$, 37), 284.2494 ($C_{21}H_{32}$, 100), 269.2277 ($C_{20}H_{29}$, 41), 261.2223 ($C_{18}H_{29}O$, 11), 253.1968 ($C_{19}H_{25}$, 11), 227.1814 ($C_{17}H_{23}$, 8), and 213.1660 ($C_{16}H_{21}$, 19). Further elution with ether–hexane (1:4) gave a noncrystalline glass (**23**) (310 mg, 10%); $[\alpha]_D^{20}$ +49.2° (*c* 1.21); R_F 0.26; g.c. (3% OV-17), rel.-R_t 0.92; $\nu_{max.}$($CHCl_3$) 3 440, 960 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.756 (3 H, s, 18-Me), 0.923 (3 H, d, *J* 6.8 Hz, 21-Me), 1.017 (3 H, s, 19-Me), 1.612 (3 H, d, *J* 4.0 Hz, 25-Me), 1.617 (3 H, s, 28-Me), 3.320 (3 H, s, OMe), 4.025 (1 H, br, 22-H), and 5.443 (1 H, q, *J* 6.5 Hz, 24-H); its mass spectrum was identical with that of (**33**).

(23E,24S)-*Methyl* 3β-*Hydroxy*-23,24-*dimethyl*-27-*nor*-*cholesta*-5,22-*dien*-26-*oate* (**25**).—The allylic alcohol (**23**) (177 mg, 0.44 mmol) was refluxed with trimethyl orthoacetate (0.5 ml), mixed xylenes (3 ml), and propionic acid (20 μl) at 120 °C for 90 min. Removal of solvent, chromatography on silica gel and reverse-phase h.p.l.c. (ODS-2, MeOH) purification gave the iso-methyl ether ester (**24**) (175 mg) which was refluxed with toluene-*p*-sulphonic (10 mg) acid in *p*-dioxane–water (4:1; 15 ml). The usual work-up with ether gave (**25**) (130 mg, 66% overall), m.p. 113—114 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ −29.6° (*c* 3.02); g.c. (3% OV-17) rel.-R_t 3.19; δ (300 MHz, $CDCl_3$) 0.694 (3 H, s, 18-Me), 0.910 (3 H, d, *J* 6.3 Hz, 21-Me), 1.004 (3 H, s, 19-Me), 1.014 (3 H, d, *J* 5.7 Hz, 28-Me), 1.560 (3 H, d, *J* 1.2 Hz, 29-Me), 3.626 (3 H, s, CO_2Me), and 4.971 (1 H, d, *J* 9.6 Hz, 22-H); *m/z* (assignment, relative intensity) 442.3413 (M^+, $C_{29}H_{46}O_3$, 57%, calc. 442.3447), 427.3257 ($C_{28}H_{43}O_3$, 16), 424.3355 ($C_{29}H_{44}O_2$, 23), 368.3052 ($C_{26}H_{40}O$), 300.2384 ($C_{21}H_{32}O$, 55), 285.2271 ($C_{20}H_{29}O$, 20), 283.2404 ($C_{21}H_{31}$, 29), 271.2061 ($C_{19}H_{27}O$, 48), and 255.2103 ($C_{19}H_{27}$, 54).

(23R,24S)-*Methyl* 3β-*Hydroxy*-23,24-*dimethyl*-27-*nor*-5α-*cholestan*-26-*oate* (**26a**).—The 3β-hydroxy ester (**25**) (128 mg, 0.29 mmol) was hydrogenated under slight excess atmospheric pressure in acetic acid–hexane (1:4; 17 ml) with Adam's catalyst (70 mg) for 1 day at ambient temperature. Filtration through Celite, removal of solvents, and reverse-phase h.p.l.c. (ODS-2, MeOH) purification gave (**26a**) (90 mg, 70%), m.p. 152—154 °C (MeOH); $[\alpha]_D^{20}$ +37.3° (*c* 1.96); g.c. (3% OV-17) rel.-R_t 3.90; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.60; δ (300 MHz, $CDCl_3$) 0.651 (3 H, s, 18-Me), 0.795 (3 H, s, 19-Me), 0.797 (3 H, d, *J* 6.9 Hz), 0.847 (3 H, d, *J* 6.3 Hz), 0.860 (3 H, d, *J* 6.6 Hz) (21-, 28-, and 29-Me's), 3.655 (3 H, s, CO_2CH_3); *m/z* (assignment, relative intensity) 446.3763 (M^+, $C_{29}H_{50}O_3$, 95%, calc. 446.3760), 428.3680 ($C_{29}H_{48}O_2$, 100), 413.3493 ($C_{28}H_{45}O_2$, 17), 302.2637 ($C_{21}H_{34}O$, 14), 248.2093 ($C_{17}H_{28}O$, 23), 233.1896 ($C_{16}H_{25}O$, 45), and 215.1817 ($C_{16}H_{23}$, 47).

(23R,24S)-*Methyl* 3β-*Dimethyl*-*t*-*butylsilyloxy*-23,24-*dimethyl*-27-*nor*-5α-*cholestan*-26-*oate* (**27a**).—The 3β-hydroxy ester (**26a**) (80 mg, 0.18 mmol) was refluxed with TBDMSCl (150 mg) and imidazole (50 mg) in CH_2Cl_2–DMF (1:1; 20 ml) until there was no starting material left. The usual work-up with CH_2Cl_2 gave (**27a**) (90 mg, 89%), m.p. 148—149 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +33.2° (*c* 2.06); δ ($CDCl_3$) 0.043 (6 H, s, 2 × SiMe), 0.646 (3 H, s, 18-Me), 0.786 (3 H, s, 19-Me), 0.797 (3 H, d, *J* 6.6 Hz), 0.847 (3 H, d, *J* 6.3 Hz), 0.859 (3 H, d, *J* 5.1 Hz) (21-, 28-, and 29-Me's, 0.876 (9 H, s, $SiCMe_3$), and 3.657 (3 H, s, CO_2CH_3) (Found: $M^+ - C_4H_9$, 503.3922. $C_{31}H_{55}O_3Si$ requires 503.3921).

(23R,24S)-23,24-*Dimethyl*-5α-*cholestan*-3β-*ol* (**29a**).—The 27-nor ester (**27a**) (17 mg) in THF (1 ml) was added to a solution of LDA in THF at −78 °C, which was prepared by adding MeLi (1.5M) in ether (0.1 ml) to di-isopropylamine (0.3 ml) in THF (2 ml) at 0 °C, and stirred for 15 min to generate the ester enolate. After remaining at −78 °C for an additional 15 min, MeI (0.2 ml) and HMPA (0.5 ml) were added to the ester enolate solution, which was subsequently warmed to room temperature and heated at 70 °C (oil-bath temp.) for 30 min. The usual work-up with ether gave the methylated esters (15 mg). The major epimer (23R,24R,25ξ)-*methyl* 3β-*dimethyl*-*t*-*butylsilyloxy*-23,24,25-*trimethyl*-5α-*cholestan*-26-*oate* (**28a**) showed δ (300 MHz; $CDCl_3$) 0.042 (6 H, s, 2 × SiMe), 0.644 (3 H, s, 18-Me), 0.767 (3 H, d, *J* 6.9 Hz), 0.789 (3 H, s, 19-Me), 0.815 (3 H, d, *J* 5.7 Hz), 0.835 (3 H, d, *J* 6.3 Hz), 0.876 (9 H, s, $SiCMe_3$), 1.070 (3 H, d, *J* 7.2 Hz, 27-Me), and 3.648 (3 H, s, CO_2CH_3). The 25-epimeric esters were reduced with LAH to the alcohols, which were then mesylated. Reduction of the mesylates and desilylation with $LiBF_4$ gave (**29a**) (10.5 mg, 83%), m.p. 162—164 C (MeOH); $[\alpha]_D^{20}$ +34.1° (*c* 1.15); g.c. (3% OV-17) rel.-R_t 1.67; h.p.l.c. (ODS-2, MeOH) rel.-R_t 1.55; for ^1H n.m.r. see Table 4; *m/z* (assignment, relative intensity) 416.4014 (M^+, $C_{29}H_{52}O$, 73%, calc. 416.4018), 401.3797 ($C_{28}H_{49}O$, 28), 383.3693 ($C_{28}H_{47}$, 11), 317.2865 ($C_{22}H_{37}O$, 16), 290.2974 ($C_{21}H_{38}$, 11), 287.2402 ($C_{20}H_{31}O$, 12), 248.2133 ($C_{17}H_{28}O$, 13), and 233.1910 ($C_{16}H_{25}O$, 74).

(22E,24R,25ξ)-*Ethyl* 6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*en*-26-*oates* (**34**).—The 22*R*-alcohol (**33**) (720 mg, 1.8 mmol) in xylenes (20 ml), triethyl orthopropionate (4 ml), and propionic acid (60 μl) was refluxed at 140 °C for 140 min under nitrogen. The reaction was monitored by g.c. (3% OV-17) until all the starting alcohol disappeared. Removal of solvents under reduced pressure and chromatography on silica gel gave an oil (649 mg, 75% which was a 2:1 mixture of ethyl esters according to g.c. and ^1H n.m.r. Reverse-phase h.p.l.c. (ODS-2, MeOH) did not give a baseline separation. Analytical samples were obtained by cutting peaks. The major isomer: R_F 0.48, g.c. (3% OV-17) rel.-R_t 1.78, h.p.l.c. (ODS-2, MeOH), R_t 32 min; $\nu_{max.}$($CHCl_3$) 1 730 and 980 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.735 (3 H, s, 18-Me), 0.893 and 0.961 (3 H each, d, *J* 6.8 Hz, 21- and 28-Me), 1.023 (3 H, s, 19-Me), 1.069 (3 H, d, *J* 6.8 Hz, 27-Me), 1.227 (3 H, t, *J* 7.2 Hz, OCH_2CH_3), 1.576 (3 H, s, 29-Me), 3.323 (3 H, s, O-Me), 4.047 (2 H, dq, J_d 2.5 Hz, J_q 7.2 Hz, OCH_2CH_3), and 4.932 (1 H, d, *J* 9.7 Hz, 22-H); *m/z* (assignment, relative intensity) 484.3904 (M^+, $C_{32}H_{52}O_3$, 23%, calc. 484.3916), 452.3640 ($C_{31}H_{48}O_2$, 67), 429.3341 ($C_{29}H_{45}O_3$, 12), 314.2587 ($C_{22}H_{34}O$, 15), 285.2231 ($C_{20}H_{29}O$, 13), 283.2425 ($C_{21}H_{31}$, 30), 253.1956 ($C_{19}H_{25}$, 72), 224.1774 ($C_{14}H_{24}O_2$, 16), and 213.1637 ($C_{16}H_{21}$, 14). The minor isomer: R_F 0.48; g.c. (3% OV-17) rel.-R_t 1.95; h.p.l.c. (ODS-2, MeOH), R_t 34 min; δ (360 MHz, $CDCl_3$) 0.747 (3 H, s, 18-Me), 0.941 (3 H, d, *J* 6.1 Hz, 21-Me or 28-Me), 0.958 (3 H, d, *J* 6.1 Hz, 27-Me), 0.999 (3 H, d, *J* 6.8 Hz, 28-Me or 21-Me), 1.026 (3 H, s, 19-Me), 1.265 (3 H, t, *J* 7.2 Hz, OCH_2CH_3), 1.493 (3 H, s, 29-Me), 3.326 (3 H, s, O-Me), 4.136 (2 H, q, *J* 7.2 Hz, OCH_2CH_3), and 5.031 (1 H, d, *J* 9.7 Hz, 22-H); its mass spectrum was identical with that of its major isomer.

(22E,24R,25ξ)-*Ethyl* 6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*en*-26-*ols* (**35**).—The mixture of ethyl esters (**34**) (503 mg, 1.04 mmol) in anhydrous ether (10 ml) was added to a suspension of LAH (500 mg) in anhydrous ether (20 ml). The usual work-up gave an oil (427 mg, 93%). An analytical sample of each alcohol was obtained by similar reduction of the corresponding pure ester mentioned above. The major isomer: R_F 0.23; g.c. (3% OV-17) rel.-R_t 1.68; $\nu_{max.}$($CHCl_3$) 3 440 and 980 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.750 (3 H, s, 18-Me), 0.896 (3 H, d, *J* 6.5 Hz, 27-Me), 0.943 (3 H, d, *J* 7.9 Hz, 21-Me), 0.964 (3 H, d, *J*

7.2 Hz, 28-Me), 1.027 (3 H, s, 19-Me), 1.569 (3 H, s, 29-Me), 3.327 (3 H, s, OMe), and 4.997 (1 H, d, *J* 9.4 Hz, 22-H); *m/z* (assignment, relative intensity) 442.3837 (M^+, $C_{30}H_{50}O_2$, 22%, calc. 442.3811), 410.3507 ($C_{29}H_{46}O$, 30), 387.3269 ($C_{26}H_{43}O_2$, 19), 323.2756 ($C_{24}H_{35}$, 18), 314.2627 ($C_{22}H_{34}O$, 31), 285.2217 ($C_{20}H_{29}O$, 14), 282.2353 ($C_{21}H_{30}$, 21), 253.1957 ($C_{19}H_{25}$, 100), 227.1785 ($C_{17}H_{23}$, 17), and 213.1660 ($C_{16}H_{21}$, 13). The minor isomer: R_F 0.20; g.c. (3% OV-17) rel.-R_t 1.95; δ (360 MHz, $CDCl_3$) 0.750 (3 H, s, 18-Me), 0.869 (3 H, d, *J* 6.8 Hz, 28-Me or 27-Me), 0.939 (3 H, d, *J* 6.5 Hz, 21-Me), 0.997 (3 H, d, *J* 6.8 Hz, 27-Me or 28-Me), 1.026 (3 H, s, 19-Me), 1.541 (3 H, s, 29-Me), 3.325 (3 H, s, O-Me), and 4.953 (1 H, d, *J* 9.7 Hz, 22-H); its mass spectrum was identical with that of its major isomer.

(22E,24R)-6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*ene* (**36**).—Methanesulphonyl chloride (300 μl) was added dropwise at 0 °C to a stirred solution of the epimeric alcohols (**35**) (645 mg, 1.46 mmol accumulated from several runs), anhydrous dichloromethane (20 ml), and triethylamine (600 μl). The mixture was stirred at 0 °C for 15 min and at room temperature for 30 min. After removal of solvents under reduced pressure, anhydrous ether (50 ml) was added to the mesylate, followed by LAH (900 mg), the mixture was then stirred at room temperature overnight. After the usual work-up and chromatography on silica gel, pure (**36**) (550 mg, 88%) was obtained: m.p. 94—95 °C (MeOH); $[\alpha]_D^{20}$ +25.0° (*c* 2.90); R_F 0.63; g.c. (3% OV-17) rel.-R_t 0.60; $\nu_{max.}$($CHCl_3$) 980 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.747 (3 H, s, 18-Me), 0.780 and 0.839 (3 H each, d, *J* 6.5 Hz, 26-Me and 27-Me), 0.930 (6 H, d, *J* 6.5, 21-Me and 28-Me), 1.025 (3 H, s, 19-Me), 1.504 (3 H, s, 29-Me), 3.326 (3 H, s, O-Me), and 4.883 (1 H, d, *J* 9.7 Hz, 22-H); *m/z* (assignment, relative intensity) 426.3852 (M^+, $C_{30}H_{50}O$, 23%, calc. 426.3862), 394.3628 ($C_{29}H_{46}$, 17), 371.3315 ($C_{26}H_{43}O$, 11), 314.2607 ($C_{22}H_{34}O$, 15), 282.2363 ($C_{21}H_{30}$, 12), 253.0817 ($C_{19}H_{25}$, 24), and 227.1800 ($C_{17}H_{23}$, 5).

(22E,24R)-23,24-*Dimethylcholesta*-5,22-*dien*-3β-*ol* (**37**).—The iso-methyl ether (**36**) (35 mg), in *p*-dioxane–water (4:1) with one crystal of toluene-*p*-sulphonic acid was refluxed at 100 °C for 1 h. The usual work-up with ether and chromatography on silica gel gave the free sterol (**37**) (21 mg, 87%), m.p. 170—172 °C (ether–MeOH); $[\alpha]_D^{20}$ −53.4° (*c* 1.97); R_F 0.18; g.c. (3% OV-17) rel.-R_t 1.39; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.98; $\nu_{max.}$($CHCl_3$) 3 440 and 965 cm^{-1}; for ^1H n.m.r. see Table 5; δ_C ($CDCl_3$) 37.3 (C-1), 31.7 (C-2), 71.8 (C-3), 42.2 (C-4), 140.8 (C-5), 121.7 (C-6), 31.7 (C-7), 31.9 (C-8), 50.2 (C-9), 36.5 (C-10), 21.1 (C-11), 27.9 (C-12), 42.3 (C-13), 56.8 (C-14), 24.3 (C-15), 39.7 (C-16), 56.8 (C-17), 12.2 (C-18), 19.4 (C-19), 34.5 (C-20), 20.1 (C-21), 131.7 (C-22), 135.2 (C-23), 50.2 (C-24), 30.9 (C-25), 20.7 (C-26), 21.7 (C-27), 13.2 (C-28), and 16.9 (C-29); *m/z* (assignment, relative intensity) 412.3712 (M^+, $C_{29}H_{48}O$, 22%, calc. 412.3705), 369.3195 ($C_{26}H_{41}O$, 4), 300.2440 ($C_{21}H_{32}O$, 22), 271.2069 ($C_{19}H_{27}O$, 35), and 255.2116 ($C_{19}H_{27}$, 14).

(22E,24S,25ξ)-*Ethyl* 6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*en*-26-*oates* (**38**).—The 22*S*-alcohol (**23**) (290 mg, 0.73 mmol), accumulated from other runs, in a mixture of triethyl orthoacetate (1.5 ml), xylenes (10 ml), and propionic acid (30 μl) was heated at 130 °C under nitrogen. The reaction was monitored by both g.c. (3% OV-17) and t.l.c. until all the allylic alcohol disappeared (1 h). Removal of solvents under reduced pressure and purification on silica gel gave a 2.6:1 mixture of ethyl esters. Analytical samples were obtained by cutting peaks from h.p.l.c. The major isomer: R_F 0.49; g.c. (3% OV-17) rel.-R_t 1.78; h.p.l.c. (ODS-2, MeOH), R_t 33 min; $\nu_{max.}$($CHCl_3$) 1 725 and 980 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.736 (3 H, s, 18-Me), 0.903 (3 H, d, *J* 6.5 Hz), 0.961 (3 H, d, *J* 6.8 Hz) 21-Me and 28-Me, 1.023 (3 H, s, 19-Me), 1.068 (3 H, d, *J* 6.8 Hz, 27-Me), 1.226 (3 H, t, *J* 7.2 Hz, OCH_2CH_3), 1.585 (3 H, s, 29-Me), 3.322 (3 H, s, O-Me), 4.060 (2 H, q, *J* 7.2 Hz, OCH_2CH_3), and 4.959 (1 H, d, *J* 9.7 Hz, 22-H). The minor isomer: R_F 0.49; g.c. (3% OV-17) rel.-R_t 1.95; h.p.l.c. (ODS-2, MeOH), R_t 36 min; $\nu_{max.}$($CHCl_3$) 1 725 and 980 cm^{-1}; δ (360 MHz, $CDCl_3$) 0.750 (3 H, s, 18-Me), 0.930 (3 H, d, *J* 6.8 Hz, 21-Me or 28-Me), 0.959 (3 H, d, *J* 6.8 Hz, 27-Me), 1.002 (3 H, d, *J* 6.8 Hz, 28-Me or 21-Me), 1.026 (3 H, s, 19-Me), 1.246 (3 H, t, *J* 7.2 Hz, OCH_2CH_3), 1.484 (3 H, s, 29-Me), 3.326 (3 H, s, O-Me), 4.137 (2 H, q, *J* 7.2 Hz, OCH_2CH_3), 5.025 (1 H, d, *J* 9.4 Hz, 22-H); both isomers had mass spectra identical with that of the major isomer of (**34**).

(22E,24S,25ξ)-6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*en*-26-*ols* (**39**).—A mixture of ethyl esters (**38**) (98 mg, 0.20 mmol) in anhydrous ether was added to a solution of LAH (300 mg) in anhydrous ether (20 ml). The usual work-up gave an oil (81 mg, 90%). An analytical sample of each alcohol was obtained by similar reduction of the corresponding pure ethyl ester obtained from h.p.l.c. The major alcohol: R_F 0.23; g.c. (3% OV-17) rel.-R_t 1.68; $\nu_{max.}$($CHCl_3$) 3 440 and 980 cm^{-1}; δ (360 MHz; $CDCl_3$) 0.754 (3 H, s, 18-Me), 0.922 (3 H, d, *J* 6.5 Hz, 27-Me or 28-Me), 0.929 (3 H, d, *J* 6.5 Hz, 21-Me), 0.973 (3 H, d, *J* 6.8 Hz, 28-Me or 27-Me), 1.026 (3 H, s, 19-Me), 1.553 (3 H, s, 29-Me), 3.326 (3 H, s, O-Me), and 4.983 (1 H, d, *J* 9.4 Hz, 22-H). The minor isomer: R_F 0.20, g.c. (3% OV-17), rel.-R_t 1.79, δ (360 MHz, $CDCl_3$) 0.755 (3 H, s, 18-Me), 0.865 (3 H, d, *J* 6.8 Hz, 27-Me or 28-Me), 0.929 (3 H, d, *J* 6.5 Hz, 21-Me), 1.004 (3 H, d, *J* 6.8 Hz, 28-Me or 27-Me), 1.028 (3 H, s, 19-Me), 1.533 (3 H, s, 29-Me), 3.28 (3 H, s, OMe), and 4.952 (1 H, d, *J* 9.4 Hz, 22-H); both isomers had mass spectra identical with the spectrum of the major isomer of (**35**).

(22E,24S)-6β-*Methoxy*-23,24-*dimethyl*-3α,5-*cyclo*-5α-*cholest*-22-*ene* (**40**).—Methanesulphonyl chloride (250 μl) was added dropwise at 0 °C to a stirred solution of the alcohols (**39**) (510 mg, 1.15 mmol accumulated from several runs), dichloromethane (10 ml), and Et_3N (0.5 ml) at 0 °C. The same procedure for preparing (**36**) was employed here. After LAH reduction and purification on silica gel, the 24*S*-iso-methyl ether (**40**) (424 mg, 86%) was obtained: m.p. 107—108 °C (MeOH); $[\alpha]_D^{20}$ +49.0° (*c* 1.93); R_F 0.63; g.c. (3% OV-17), rel.-R_t 0.60; δ (360 MHz, $CDCl_3$) 0.751 (3 H, s, 18-Me), 0.776 (3 H, d, *J* 6.5 Hz), 0.852 (3 H, d, *J* 6.5 Hz) (26-Me and 27-Me), 0.922 (3 H, d, *J* 6.8 Hz, 21(Me), 0.941 (3 H, d, *J* 7.2 Hz, 28-Me), 1.026 (3 H, s, 19-Me), 1.491 (3 H, s, 29-Me), 3.326 (3 H, s, OMe), and 4.884 (1 H, d, *J* 9.7 Hz, 22-H); its mass spectrum was identical with that of (**36**).

(22E,24S)-23,24-*Dimethylcholesta*-5,22-*dien*-3β-*ol* (**13**).—The iso-methyl ether (**40**) (198 mg, 0.46 mmol) in glacial acetic acid (10 ml) and fused zinc(II) acetate (1 g) were refluxed for 3 h. Work-up with CH_2Cl_2 and isolation on a silica-gel column gave the acetate (185 mg, 88%), m.p. 184—187 °C (MeOH); $[\alpha]_D^{20}$ −37.80° (*c* 1.89); R_F 0.53; g.c. (3% OV-17) rel.-R_t 1.92. This acetate (160 mg, 0.35 mmol) was then refluxed in 5% methanolic KOH (10 ml) for 1 h. After the usual work-up with CH_2Cl_2 and purification on silica gel column, the free sterol (**13**) was obtained (143 mg, 98%), m.p. 181—184 °C (ether–MeOH); $[\alpha]_D^{20}$ −25.4° (*c* 1.27); R_F 0.18; g.c. (3% OV-17) rel.-R_t 1.39; h.p.l.c. (ODS-2, MeOH) rel.-R_t 0.91; $\nu_{max.}$($CHCl_3$) 3 440 and 975 cm^{-1}; for ^1H n.m.r. see Table 5; δ_C ($CDCl_3$) 37.1 (C-1), 31.5 (C-2), 71.6 (C-3), 42.0 (C-4), 140.6 (C-5), 121.5 (C-6), 31.7 (C-7), 30.7 (C-8), 50.1 (C-9), 36.4 (C-10), 20.9 (C-11), 28.2 (C-12), 42.2 (C-13), 56.7 (C-14), 24.2 (C-15), 39.6 (C-16), 56.7 (C-17), 12.0 (C-18), 19.3 (C-19), 34.5 (C-20), 20.1 (C-21), 131.8 (C-22), 135.3 (C-23), 50.3 (C-24), 30.7 (C-25), 20.5 (C-26), 21.9 (C-27), 12.7 (C-28), and 17.1 (C-29); its mass spectrum was identical with that of (**37**).

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