Stereochemical Effects in Cyclopropane Ring Openings: Synthesis and Isomerization of Petrosterol and All Three of Its Trans Cyclopropane Diastereomers

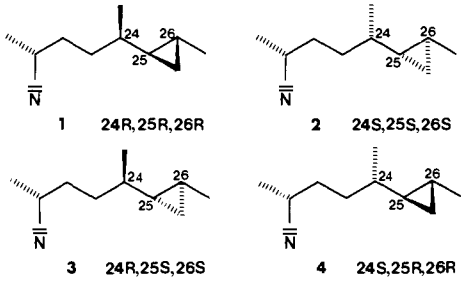
John R. Proudfoot and Carl Djerassi*

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received November 21, 1983. Revised Manuscript Received April 19, 1984*

Abstract: All four trans isomers of the marine sterol petrosterol, with a side chain terminating in a cyclopropane ring, have been synthesized. The absolute stereochemistry of the diastereomers was determined by correlation with compounds of known absolute stereochemistry. The product distribution resulting from the acid-catalyzed isomerization of these four diastereomers shows a marked dependence on the relative stereochemistry between the cyclopropane ring and the adjacent chiral center at C24. A careful examination of the conformations available to the side chain leads to a rational explanation of this dependence, and sheds light on hitherto unrecognized subtle stereochemical features operating among aliphatic cyclopropanes. In addition we report the synthesis and acid-catalyzed ring opening of (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol and the confirmation by this labeling study that one of the products of the isomerization reaction arises via a 1,5-hydride-shift mechanism.

Introduction

The presence in the marine environment of sterols incorporating a cyclopropane ring in the side chain[1] has led to speculation[2] that these compounds are intermediates in biomethylation sequences. Although this postulate has yet to be proven by suitable labeling experiments, the recently reported[3] in vitro isomerization of petrosterol (**1**) to 25-*epi*-26-dehydroaplysterol (**35**), which co-occurs[4] with petrosterol in the sponge *Petrosia ficiformis*, lends it some credence. Unexpectedly, this isomerization also yielded 25-*epi*-22-dehydroaplysterol (**36**) which is formally the product of a 1,5 hydride shift.[3] In order to examine further the stereochemical requirements of this isomerization reaction, we completed a synthesis of petrosterol (**1**) and its 24*S*,25*S*,26*S* (**2**), 24*R*,25*S*,26*S* (**3**), and 24*S*,25*R*,26*R* (**4**) diastereomers. The availability of all



four possible trans cyclopropane diastereomers **1**, **2**, **3**, and **4** provided a rare opportunity to investigate the effect of subtle stereochemical changes around the cyclopropane ring upon the acid-catalyzed ring opening—a study which is of intrinsic mechanistic interest quite beyond the steroid field.

Acid-catalyzed cyclopropane ring openings have received much attention with respect to intermediate chemical species,[5,6] the stereochemistry of electrophilic and nucleophilic attack,[7] and Markownikoff vs. anti-Markownikoff ring cleavage.[8] However, the effect of changes in relative stereochemistry around the cyclopropane ring on the isomerization reaction has been practically neglected.[9]

The labeled derivative (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol (**25**) has also been synthesized and its acid-catalyzed ring opening sheds further light on the processes operating in this reaction.

Synthesis and Stereochemical Assignments

The synthesis of petrosterol (**1**), of its diastereomers **2**, **3**, and **4**, and of (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol (**25**) proceeded as shown in Scheme I. The stabilized phosphorane **10** was synthesized by the reaction[10] of *trans*-2-methylcyclopropanecarbonyl chloride[11] with methylenetriphenylphosphorane. Condensation of this phosphorane **10** with the known[12] aldehyde **8** gave the enone **11** as a mixture of diastereomeric cyclopropanes, which was not resolvable by HPLC. Conjugate reduction of **11** was conveniently achieved using $NaBH_4$ in pyridine. Previous reports[13] on the use of this reagent indicated that reduction to the saturated alcohol was to be expected. However, on quenching the reaction after 1–2 h only the saturated ketone **13** was obtained. A Wittig reaction with methylenetriphenylphosphorane gave the vinylcyclopropane **15** as a 1:1 mixture of compounds diastereomeric with respect to the cyclopropane ring. Again, no fractionation could be achieved by HPLC, and moreover none of the above mixtures showed any doubling of signals in their 300-MHz ^1H NMR spectra. Hydroboration of **15** followed by an oxidative workup gave a separable (HPLC over SiO_2) mixture of the four hydroxymethyl compounds **17–20**, whose absolute stereochemistry at this stage was not known. They were converted to the sterols **1–4** by tosylation, $LiAlH_4$ reduction, and hydrolysis of the *i*-methyl ether protecting group, a sequence which had proved useful in

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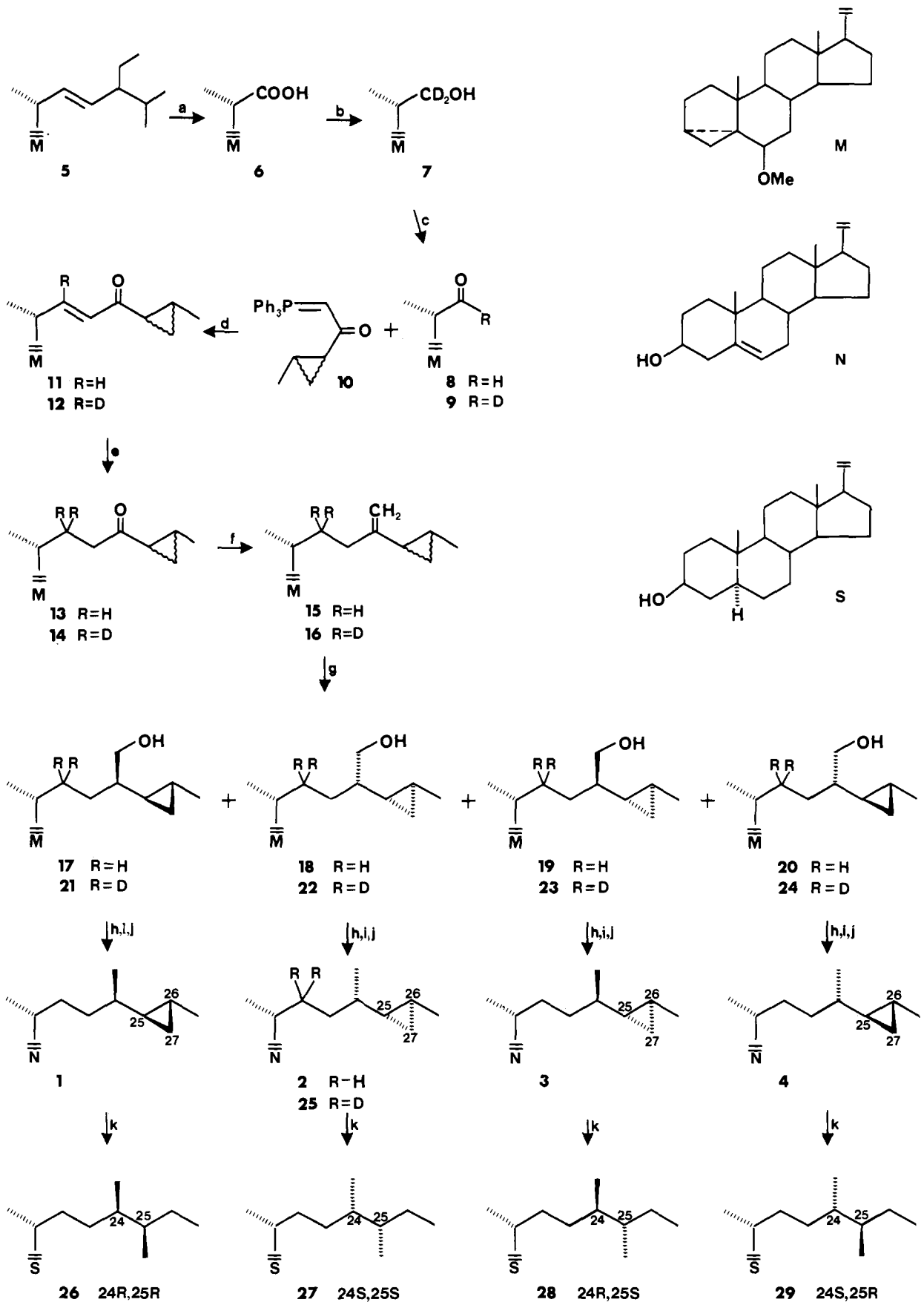
Scheme I[a]

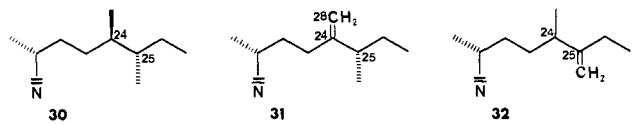


[a] (a) O_3, CH_2Cl_2, −78 °C, H_2O, 33%; (b) $LiAlD_4$, Et_2O, 90%; (c) PCC, CH_2Cl_2, 83%; (d) C_6H_6, reflux, 74%; (e) $NaBH_4$, pyridine, 80%; (f) $Ph_3P{=}CH_2$, THF, 0 °C, 90%; (g) $BH_3{\cdot}THF$, 0 °C, NaOH, H_2O_2, 90%; (h) *p*-toluenesulfonyl chloride, pyridine; (i) $LiAlH_4$, Et_2O; (j) *p*-toluenesulfonic acid, dioxane/water, overall yield h–i 65–80%; (k) Pt/H_2, EtOAc/CH_3COOH, 80–90%.

earlier work dealing with the synthesis of demethylgorgosterol.[12a,14]

For convenience in the following arguments leading to full assignment of the absolute stereochemistry of the side chains, the petrosterol isomers are labeled A, B, C, and D. Inspection shows that only a limited amount of information concerning the side-chain stereochemistry of the isomers is available from the NMR data. For instance, the spectra of isomers A and B are so similar to that of natural petrosterol (**1**) that it is not possible to say with certainty which is the natural product. The problem of assigning the side-chain stereochemistry of each isomer had to be solved by correlation with compounds of known absolute stereochemistry.

Cyclopropane rings are known[15] to be susceptible to reductive cleavage. Specifically, we found that the C26–C27 bond of the petrosterol isomers A–D could be selectively hydrogenolyzed to give the corresponding 5α-5,6-dihydroaplysterol isomers A′–D′. The naturally occurring sponge sterol, aplysterol (**30**), of known 24*R*,25*S* stereochemistry was reduced to (24*R*,25*S*)-5α-5,6-dihydroaplysterol (**28**) whose NMR data were found to be identical with those of C′. Therefore C′ possesses the 24*R*,25*S* stereochemistry, and its progenitor cyclopropane, C, must be (24*R*,25*S*,26*S*)-petrosterol (**3**). Because we are dealing only with



30 **31** **32**

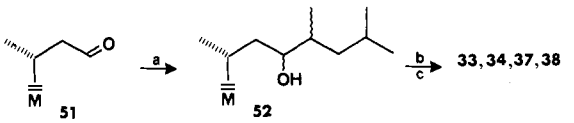
trans cyclopropanes, assignment of the C25 stereochemistry also allows unambiguous assignment of the absolute stereochemistry at C26.

We also had available (25*S*)-24,28-dehydroaplysterol (**31**),[17] and this was converted on hydrogenation to a mixture of (24*R*,25*S*)-5α-5,6-dihydroaplysterol (**28**) and (24*S*,25*S*)-5α-5,6-dihydroaplysterol (**27**). Although these were not separable by HPLC, inspection of the ^{1}H NMR data of the mixture clearly revealed which signals were due to the 24*S*,25*S* epimer **27**. These corresponded to those of the hydrogenolyzed cyclopropane derivative B′. Thus B′ has the 24*S*,25*S* stereochemistry and cyclopropane B must be (24*S*,25*S*,26*S*)-petrosterol (**2**).

Since, from their NMR data, the only candidates for the natural product **1** were A and B and since B is the 24*S*,25*S*,26*S* isomer, this means that A corresponds to natural petrosterol (**1**) of 24*R*,25*R*,26*R* stereochemistry. By elimination, isomer D must possess the 24*S*,25*R*,26*R* stereochemistry **4**.

The synthesis of (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol (**25**) is also outlined in Scheme I. Ozonolysis of stigmasterol *i*-methyl ether (**5**) followed by an aqueous[18] workup gave the acid **6** in modest yield. Reduction of **6** with $LiAlD_4$ gave the dideuterio alcohol **7** which on oxidation with pyridinium chlorochromate gave the deuterio aldehyde **9**. No trace of nondeuterated aldehyde was visible in the NMR spectrum. The synthetic pathway then

Scheme II



(a) 4-Methyl-2-bromopentane, Mg, Et_2O, 90%; (b) $POCl_3$, pyridine, 5–13% of each isomer.

proceeded as described above for the nondeuterated compounds, with the second deuterium atom at C22 being introduced by the use of $NaBD_4$ in the conjugate reduction step.

Of the four deuterated hydroxymethyl isomers **21–24**, only the 24*S*,25*S*,26*S* isomer **22** was carried on to the corresponding petrosterol isomer **25**.

Stereochemical Course of Cyclopropane Ring Opening

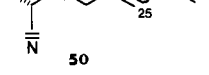
In view of the low yield of isomerization (i.e., olefin) compared to addition (i.e., chloride and acetate) products obtained with the HCl/acetic acid reaction medium,[3] we employed milder conditions, specifically 5% trifluoroacetic acid in benzene, which proved useful also in the isomerization of the 22,23-methylenecholesterol series.[19]

The isomerization was carried out on the sterol acetates, and the product mixture was reconverted to the free sterols by reaction with $LiAlH_4$ for the purpose of separation and characterization. After 48 h a 30–40% yield of isomerization products was realized. The remainder of the reaction mixture, resulting from addition of trifluoroacetic acid to the cyclopropane ring, and yielding (after treatment with $LiAlH_4$) products containing an hydroxylated side chain, was not investigated. Fractionation of the reaction mixtures was accomplished by reversed-phase HPLC.

The results of the isomerization reactions are summarized in Table I. In the case of petrosterol (**1**) five isomerization products were isolated and identified. Two of these have been previously reported,[3] the terminal olefin **35**, and **36**, the product of an unusual 1,5-hydride shift. Both arise by fission of the C26–C27 cyclopropane bond.

By contrast, the three new isomerization products **33**, **34**, and **37** were found to result from cleavage of the C25–C27 cyclopropane bond, thus providing sterols with "unnatural" elongated side chains. The mass spectra of **33** and **34** were identical and their ^{1}H NMR spectra possessed strong similarities; i.e., both displayed a broad triplet (one proton) in the olefinic region, a vinylic methyl group, and three secondary methyl groups. These data indicated that the compounds were *E* and *Z* isomers of the same olefin. The stereochemistry of each was deduced from the chemical shift of the vinylic methyl group. From the examples in Table II,[20] the vinylic methyl group of the *E* olefin consistently appears upfield of that of the *Z* olefin.

That these were the Δ^{23} olefins **33** and **34** and not the a priori expected *E* and *Z* isomers of the $\Delta^{24,25}$ olefin **50** was clear from



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the olefinic absorption in the NMR spectra: a broad triplet as mentioned above and not a broad doublet as would be expected for the *E* or *Z* isomers of **50**. The assigned structures were confirmed by synthesis (dehydration of alcohol **52**) as shown in Scheme II.

The remaining product of this isomerization of petrosterol (**1**) was assigned structure **37**. Its mass spectrum was identical with that of the aplysterol derivative **36**, thus indicating unsaturation at C22–C23. This, along with the presence of four secondary methyl groups and two olefinic protons, apparent from the 300-MHz ^{1}H NMR spectrum, can only be accomodated in the side chains **37** and **53**. That the former was correct was shown by the

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(17) The compound originally reported by the Italian group[16] as 24,28-dehydroaplysterol (**21**) is, in fact, 25,26-dehydroaplysterol (**32**): Catalan, C. A. N.; Thompson, J. E.; Kokke, W. C. M. C.; Djerassi, C. *Tetrahedron*, in press. However, 24,28-dehydroaplysterol (**21**) has been isolated in this laboratory from *Jaspis Stelifera* Theobald, N.; Wells, R. J.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 7677–7684 although the assigned stereochemistry 25*S* (based on the original incorrect report[16]) is without foundation. Fortunately, it is possible to unequivocably assign the stereochemistry of **21** at C25 on the basis of its 300-MHz ^{1}H NMR data. The C28 and C29 methyl absorptions of A′, B′, C′, and D′ (all four possible diastereomers of the aplysterol side chain) are distinctive for each isomer. Hydrogenation of 24,28-dehydroaplysterol (**21**) gave a mixture of C24 epimers whose NMR contained signals (among others) assignable to the C28 and C29 methyl groups of (24*R*,25*S*)-5α-5,6-dihydroaplysterol (**18**). Since the stereochemistry at C25 is not affected by the hydrogenation, 24,28-dehydroaplysterol (**21**) possesses the 25*S* stereochemistry. The original assumed stereochemistry is therefore fortuitously correct.

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(20) Li, H. T.; Djerassi, C. *J. Org. Chem.* **1982**, *47*, 4298–4303.

Table I. Product Distribution Following the Isomerization of Petrosterol (1), 2, 3, 4, and 25[a]

Bond Cleaved	C25-C27	C25-C27	C26-C27	C26-C27	C25-C27	C25-C27
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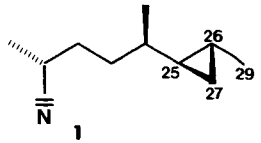
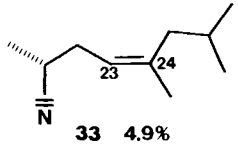
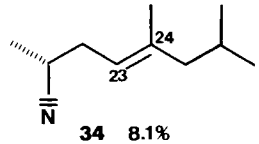
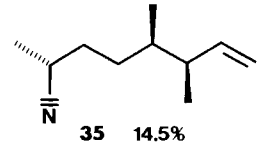
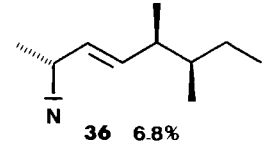
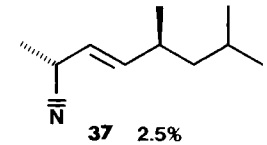
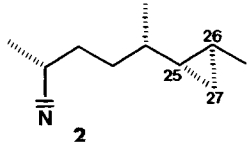
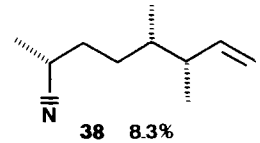
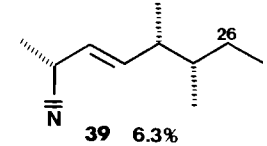
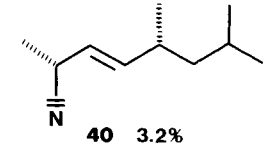
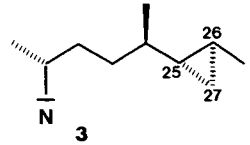
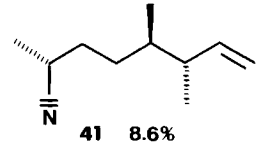
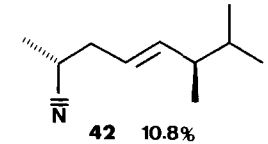
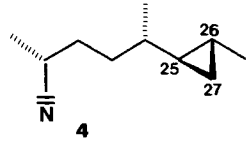
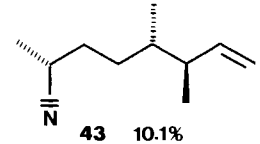
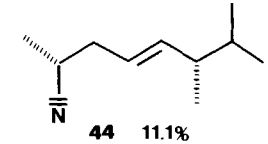
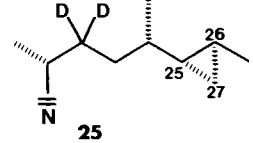
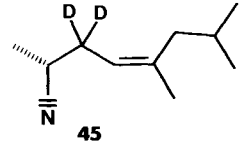
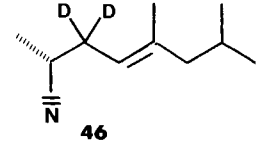
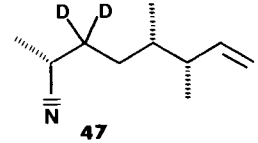
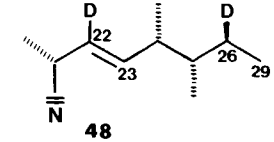
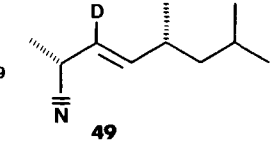
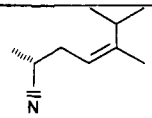
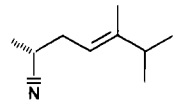
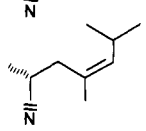
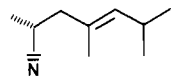
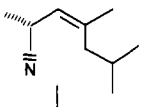
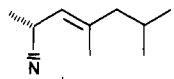
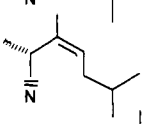
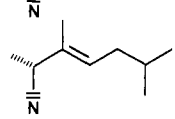
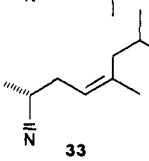
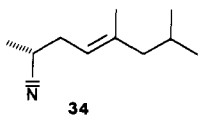
 1	 33 4.9%	 34 8.1%	 35 14.5%	 36 6.8%	 37 2.5%	—
 2	33 4.2%	34 6.9%	 38 8.3%	 39 6.3%	 40 3.2%	—
 3	33 5.2%	34 11.1%	 41 8.6%	—	—	 42 10.8%
 4	33 5.5%	34 8.9%	 43 10.1%	—	—	 44 11.1%
 25	 45	 46	 47	 48	 49	—

[a] Recovered starting material 3.5–7%; unidentified isomerization products 3–7%; the remainder of the reaction mixture consisted of hydroxy sterols which were not investigated (see text).

Table II. The Correlation between Side-Chain Olefin Stereochemistry and Chemical Shift

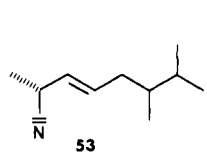
Z-Olefins	δ (vinylic methyl)	E-Olefins	δ (vinylic methyl)
	1.602		1.543
	1.602		1.546
	1.610		1.558
	1.579		1.470
 33	1.669	 34	1.547

fact that dehydration of **52** (Scheme II) also produced a compound identical with this isomerization product **37**. The *E* stereochemistry of the double bond is clear from the coupling constants in the olefinic region of the NMR spectrum (~15 Hz).

The isomerization of (24*S*,25*S*,26*S*)-petrosterol (**2**) yielded essentially the same results (cf. Table I) as the acid-catalyzed isomerization of petrosterol (**1**). Sterols **33**, **34**, **38**, **39**, and **40** were characterized by the identity of their mass spectra and the similarity or identity of their ^1H NMR spectra with those of the corresponding petrosterol isomerization products. For subsequent mechanistic considerations it should be noted at this point that only olefin **37** or **40**, but not both, was isolated from each isomerization, and we consider that these products arise via a 1,3-hydride-shift mechanism (Figure 1).

The isomerization (cf. Table I) of the remaining two petrosterol diastereomers 24*R*,25*S*,26*S* (**3**) and 24*S*,25*R*,26*R* (**4**), while in each case yielding the *E* and *Z* olefins **33** and **34** and the relevant terminal olefin **41** or **43**, respectively, gave no products corresponding to a 1,5- (cf. **36**, **39**) or a 1,3- (cf. **37**, **40**) hydride shift. Instead there was isolated in each case **42** or **44**, respectively, products of a *methyl migration*.

The structures **42** and **44** were proven, over the alternative possibilities **54–56**, by the synthesis outlined in Scheme III. The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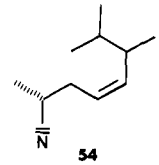
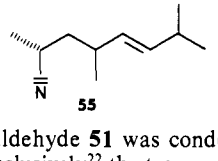

54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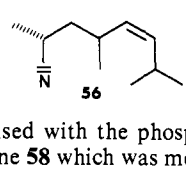

56

known[21] aldehyde **51** was condensed with the phosphorane **57** yielding exclusively[22] the trans enone **58** which was methylenated to give diene **59**. A regioselective hydroboration[23] employing excess

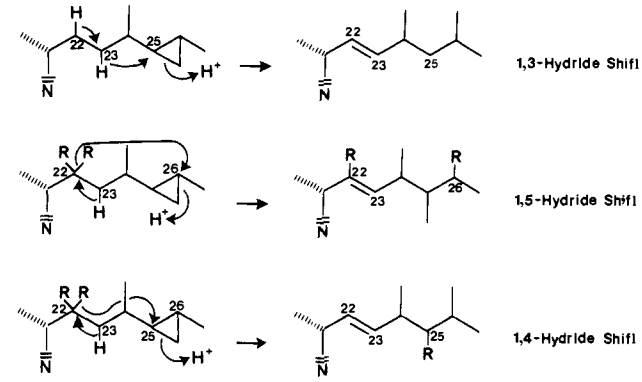
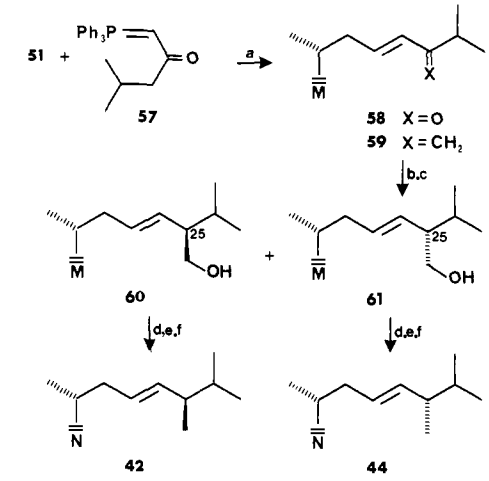


Figure 1.

Scheme III[a]



[a] (a) C_6H_6, reflux, 78%; (b) $Ph_3P{=}CH_2$, THI, 90%; (c) 9-borabicyclo[3.3.1]nonane, THF, NaOH, H_2O_2, 32% of each isomer; (d) *p*-toluenesulfonyl chloride, pyridine; (e) $LiAlH_4$, Et_2O; (f) *p*-toluenesulfonic acid, dioxane/water, reflux.

9-borabicyclo[3.3.1]nonane and a short reaction time gave, after oxidative workup, a 1:1 mixture of 25-hydroxymethyl epimers **60** and **61** which were easily separated by HPLC over SiO_2. Tosylation, $LiAlH_4$ reduction, and deprotection gave the free sterols identical with **42** and **44** isolated from the isomerization reactions.

The isomerization of (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol (**25**) was carried out as described above. The mass spectral data of compound **48**, the product of a presumed 1,5-hydride shift, showed a molecular ion at *m/z* 414 showing that both deuterium atoms of the starting material **25** (*m/z* 414) had been retained. The 300-MHz ^1H NMR spectrum showed that one deuterium remained at the original C22 position. This is clear from comparison of the olefinic region absorptions of the labeled product **48** and the unlabeled **39**. The labeled compound shows only a broad doublet due to the proton at C23. The C22 proton absorption is absent as is the C22-H, C23-H coupling. The position of the second deuterium atom can be deduced from the appearance of the methyl absorption region. The absorption of the C29 methyl group in the unlabeled isomerization product **39** appears as a triplet. In the labeled material **48** it is seen as a broad (due to D–H coupling) doublet. This change in multiplicity can only be due to the replacement of the C26–H_2 group of **39** with a C26–HD group in **48**.

Thus, the second deuterium atom has migrated from C22 to C26, exactly as predicted by a 1,5-hydride-shift mechanism (Figure 1). Although it cannot be shown by NMR, we expect that from the mechanism of the reaction, the stereochemistry at C26 is as shown in Table I.

The product **49**, ascribed to a 1,3-hydride shift, showed the expected loss of one deuterium atom of the starting material, apparent from the mass spectrum (M^+ 413 as opposed to 414 for

(21) (a) Theobald, N.; Wells, R. J.; Djerassi, C. *J. Org. Chem.* **1982**, *47*, 620–625. (b) Li, H. T.; Massey, I. J.; Swenson, D. C.; Duax, W. L.; Djerassi, C. *Ibid.* **1983**, *48*, 48–54.

(22) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278–4281.

(23) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.* **1978**, *43*, 1058–1063.

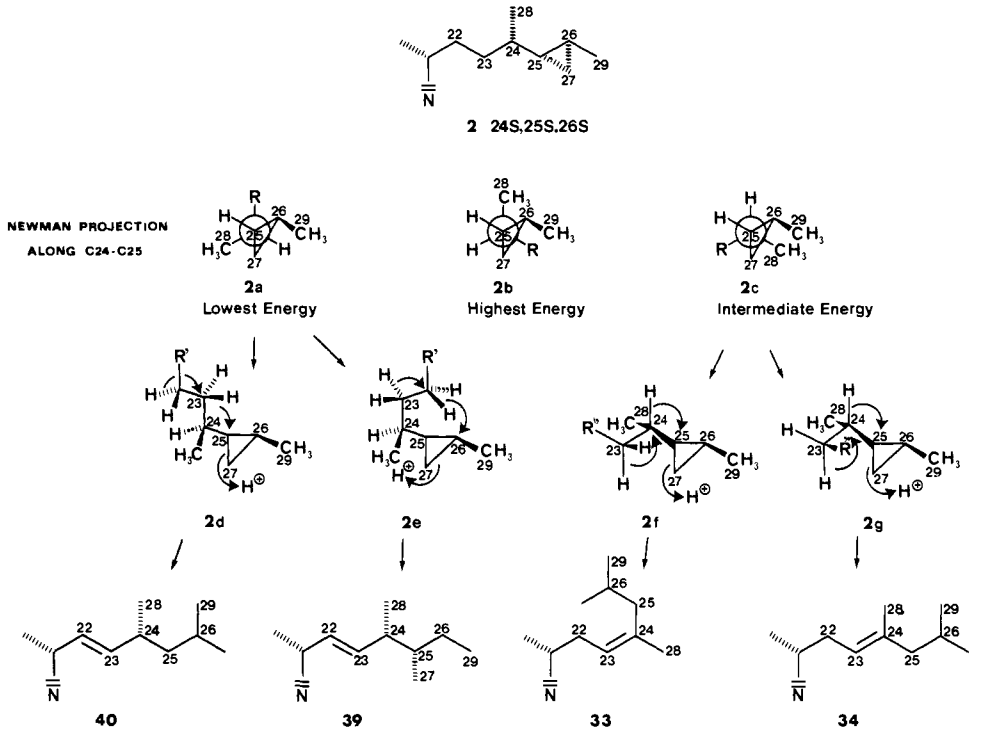


Figure 2.

25). The operation of a 1,4-hydride shift is ruled out by this study since both deuterium atoms would be retained, the second migrating to C25 (Figure 1).

The remaining products of this ring-opening reaction retained both deuterium atoms at C22 as expected. Interestingly, this study confirmed the structures assigned above to olefins **33** and **34**. The position of the double bond at C23 is proven by the fact that the olefinic absorption (broad triplet) of **33** and **34** collapses to a broad singlet in **45** and **46** which is consistent with the Δ^{23} but not the Δ^{24} olefins.

Rationalization of the Stereochemical Dependence in the Isomerization Reactions

From the data presented in Table I it is apparent that there is a correlation between the relative stereochemistries of the cyclopropane ring and C24 and the course of the ring-opening reactions. The results can best be interpreted in terms of the conformations available to the side chains in the vicinity of the cyclopropane ring.

In the following discussion, the effects of the steroid nucleus on the course of the isomerization reactions are assumed to be minimal and its inherent chirality is ignored. Thus petrosterol (**1**) of 24*R*,25*R*,26*R* stereochemistry and (24*S*,25*S*,26*S*)-petrosterol (**2**) are treated as enantiomers as are (24*R*,25*S*,26*S*)-petrosterol (**3**) and (24*S*,25*R*,26*R*)-petrosterol (**4**). The justification for this approach lies in the fact that, in each case, the two isomers with the enantiomeric relationship as regards the side chain give the same distribution of products (Table I). Since the conformations available to enantiomers are identical, we need only consider one isomer from each pair.

In Figure 3 are shown the conformations around the cyclopropane ring available to (24*R*,25*S*,26*S*)-petrosterol (**3**) and in Figure 2, those available to (24*S*,25*S*,26*S*)-petrosterol (**2**). They are qualitatively described as lowest, intermediate, and highest energy conformations on the basis of steric interactions.[24] The distribution of products can be rationalized by examination of these conformations. The points which need clarification are: (a) why a methyl migration is observed for the 24*R*,25*S*,26*S* isomer **3** and not for the 24*S*,25*S*,26*S* isomer **2**; (b) why 1,3- and 1,5-hydride shifts are seen in the isomerization of the 24*S*,25*S*,26*S* isomer **2** but not in the isomerization of the 24*R*,25*S*,26*S* isomers **3**; and (c) why both isomers give a similar distribution of the *E* and *Z* isomers **33** and **34**.

The formation of the terminal olefin product **35**, **38**, **41**, or **43** has no particular conformational requirements, being simply the result of the C26–C27 bond cleavage and proton elimination from the terminal methyl group (C29).[3]

From Figure 3 the lowest energy conformer **3a** of (24*R*,25*S*,26*S*)-petrosterol (**3**), and hence the most populated at ambient temperature, is that in which the C28 methyl group is antiperiplanar to the C25–C27 cyclopropane bond and is ideally situated for methyl migration after ring opening yielding **42**. If we extend the projection back to the C23–C24 bond (Figure 3, **3d** and **3e**), we can even explain the formation of the *E* olefin **42** to the exclusion of its *Z* isomer **54**. The conformer **3e** required for the formation of the *Z* isomer **54** has substantially more severe gauche interactions than conformer **3d** which gives rise to the *E* olefin **42**.

Why, however, is methyl migration to C25 not observed in the isomerization of (24*S*,25*S*,26*S*)-petrosterol (**2**)? From Figure 2, the conformer **2b** of (24*S*,25*S*,26*S*)-petrosterol (**2**), in which the stereochemical requirements for methyl migration are met (antiperiplanar arrangement of the C28 methyl group and the C25–C27 cyclopropane bond), is the highest energy conformer of the three (24*S*,25*S*,26*S*)-petrosterol conformers **2a**, **2b**, and **2c**. It is not surprising, therefore, that no products of methyl migration are seen since the highest energy conformer is the least populated at ambient temperature.

The lowest energy conformer of (24*S*,25*S*,26*S*)-petrosterol (**2**) is represented in **2a**. The alkyl side chain occupies a position antiperiplanar to the C25–C27 bond. This is the conformer from which **39**, the product of a 1,5-hydride shift arises (see **2e**). We consider that **40** also arises from this lowest energy conformer **2a** via a 1,3-hydride shift (see **2d**). The fact that the 1,3- and 1,5-hydride-shift products always co-occur (cf. Table II) favors this supposition. Also the retention of stereochemical integrity at C24, (i.e., the fact that only **40** and not a mixture of **37** and **40** is found) argues against a mechanism involving a carbonium ion at C24. Finally, although **40** could arise from conformer **2c**, which gives rise to the olefins **33** and **34**, via consecutive 1,2-hydride shifts, this is unlikely since **40**, or its epimer **37**, should then be seen in all four isomerization reactions (arising from

(24) (a) Eliel, E. L.; Allinger, L. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965, pp 5–35. (b) Norgradi, M. "Stereochemistry, Basic Concepts and Applications"; Pergamon Press: New York, 1981; pp 201–210.

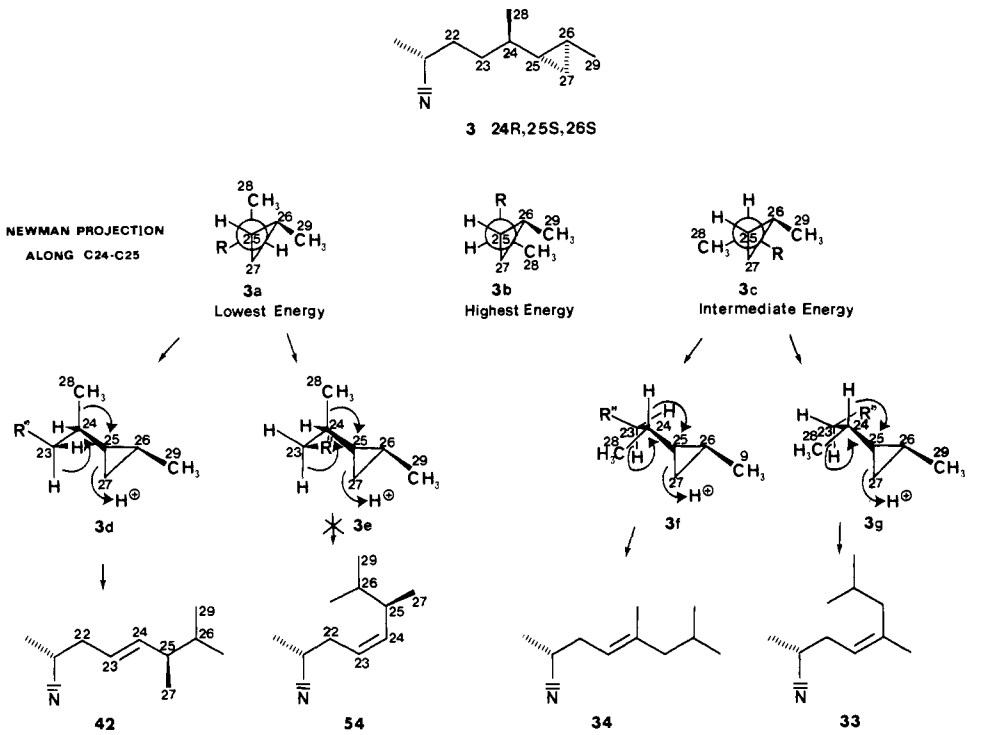


Figure 3.

conformer **3c** (Figure 3) in the case of (24*R*,25*S*,26*S*)-petrosterol (**3**)). In further support, literature reports indicate that 1,3-hydride shifts are favored over consecutive 1,2-hydride shifts for straight-chain systems.[25] In confirmation of this analysis is the observation that the corresponding conformer **3b** (Figure 3) of (24*R*,25*S*,26*S*)-petrosterol (**3**) is this compound's highest energy conformer, and, hence, no products of 1,3- or 1,5-hydride shifts are seen (cf. Table II).

The conformer of intermediate energy in each case (Figure 3, **3c**; Figure 2, **2c**) gives rise to the $\Delta^{23,24}$ olefins via a 1,2-hydride shift and proton elimination. From **2c** and **3c** we can see that the C24 hydrogen is ideally placed for a 1,2-migration. If we examine the projections **2f,g** (Figure 2) and **3f,g** (Figure 3) along the C23–C24 bond of conformers **2c** and **3c**, respectively, we can see that these conformations, which give rise to the *E* and *Z* olefins **33** and **34**, do not differ greatly in energy, both possessing one gauche interaction. Production of the *E* isomer **34** is slightly favored in each case.

Such conformational analysis also differs an explanation of why none of the $\Delta^{24,25}$ olefins, *E*- or *Z*-**50**, was found. The conformer which would give rise to these olefins is presumably that corresponding to **2f,g** (Figure 2) or **3f,g** (Figure 3) in which neither hydrogen on C23 is in a position favorable for elimination. In this case the R′ group must be antiperiplanar to the C24-H. These conformations possess two strong gauche interactions and must be relatively unpopulated. Formation of the Δ^{23} olefins **33** and **34** is thus favored over formation of the $\Delta^{24,25}$ isomers *E*- or *Z*-**50**.

Summary

The synthesis of the four cyclopropyl sterols **1–4**, along with the unambiguous assignment of their absolute stereochemistry, has allowed us to examine in unprecedented detail the influence of relative stereochemistry around the cyclopropane ring on the acid-catalyzed ring-opening reaction. Because of the remoteness of the cyclopropane ring from the steroid ring system, these compounds behave like simple aliphatic systems in terms of their cyclopropane chemistry. Products of 1,2-, 1,3-, and 1,5-hydride shifts and of a 1,2-methyl migration were seen to result from the acid-catalyzed isomerization reaction, and a correlation was noted between some of the reaction types, i.e., 1,3- and 1,5-hydride shifts vs. 1,2-methyl migration, and the relative stereochemistry around the cyclopropane ring. This stereochemical dependence of reaction type is adequately explained by a conformational analysis in which the products arise from the lowest and intermediate energy conformations available.

Experimental Section

General Methods. Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Specific rotations were recorded in chloroform on a Perkin-Elmer 141 polarimeter. Gas chromatography was performed at 260 °C on a U-shaped glass column (1.8 m × 2 mm i.d.) packed with 3% OV-17. The column was mounted in a Hewlett-Packard 402 high-efficiency gas chromatograph equipped with a flame ionization detector. Low-resolution mass spectra were recorded on a Finnigan MAT-44 GLC/MS system at 70 eV and using a 3% OV-17 column. High-resolution mass spectra were recorded on an MS-50 instrument (University of California, Berkeley). ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 with the solvent peak ($CHCl_3$ or C_6H_6, respectively) as an internal standard. HPLC was performed on a Waters Associates HPLC system (M6000 pump, R403 differential refractometer). For reverse-phase chromatography Altex Ultrasphere ODS 5 μm (25 cm × 10 mm i.d., two columns in series) with methanol/water 95:5 as the mobile phase was used. For normal-phase HPLC two Waters Associates semipreparative Microporasil columns were used in series with hexane/ethyl acetate 93:7 as the mobile phase.

(20*S*)-6β-Methoxy-3α,5-cyclo-5α-pregnane-20-carboxylic Acid (6). A solution of stigmasterol *i*-methyl ether (**5**)[26] (960 mg) in CH_2Cl_2 (20 mL) containing pyridine (0.5 mL) was treated with ozone at −78 °C until the blue color persisted. After the mixture was warmed to room temperature, 10 mL of water was added and the mixture was stirred for 5 h. The organic layer was washed, dried, and evaporated. Fractionation of the crude product over SiO_2 (eluent ethyl acetate/hexane gradient 1:10–1:4) gave the acid **6** (271 mg, 33%): ^{1}H NMR (300 MHz) δ 3.322 (3 H, s, OCH_3), 1.237 (3 H, d, J = 6.94 Hz, C-21), 1.023 (3 H, s, C-19), 0.744 (3 H, s, C-18); mass spectrum *m/z* (rel intensity) 360 (M^+ 22), 345 (35), 328 (55), 305 (75), 302 (17), 255 (15), 239 (10), 223 (13), 213 (15), 55 (100).

(20*S*)-6β-Methoxy-3α,5-cyclo-5α-pregnane-20,20-dideuteriomethanol (7). To the acid **6** (400 mg, 1.1 mmol) in dry Et_2O (10 mL) was added $LiAlD_4$ (140 mg, 3.3 mmol). The reaction mixture was stirred overnight at room temperature. The excess $LiAlD_4$ was destroyed by the addition of ethyl acetate and water. Filtration and evaporation gave the crude product which was purified by chromatography over SiO_2 (eluent ethyl

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(26) Steele, J. A.; Mosettig, E. *J. Org. Chem.* **1963**, *28*, 571–572.

acetate/hexane 1:10) to give the alcohol **7** (350 mg, 91%): ^{1}H NMR (300 MHz) δ 3.310 (3 H, s, OCH_3), 1.028 (3 H, d, J = 6.65 Hz, C-21), 1.010 (3 H, s, C-19), 0.724 (3 H, s, C-18); mass spectrum m/z (rel intensity) 348 (M^+ 25), 333 (40), 316 (40), 293 (70), 255 (12), 213 (10), 55 (100).

(20*S*)-6β-Methoxy-3α,5-cyclo-5α-pregnane-20-deuteriocarboxaldehyde (9). To a solution of dideuterio alcohol **7** (422 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added pyridinium chlorochromate (438 mg, 2 mmol). The reaction mixture was stirred for 4 h. Filtration, evaporation, and chromatography over SiO_2 (eluent ethyl acetate/hexane 7:100) gave the deuterioaldehyde **9** (350 mg, 83%): ^{1}H NMR (300 MHz) δ 3.325 (3 H, s, OCH_3), 1.122 (3 H, d, J = 6.83 Hz, C-21), 1.029 (3 H, s, C-19), 0.768 (3 H, s, C-18); mass spectrum m/z (rel intensity) 345 (M^+ 4), 330 (6), 313 (12), 290 (15), 231 (9), 91 (100).

Triphenylphosphoranilidenemethyl (2′-Methyl)cyclopropyl Ketone (10). To a stirred suspension of methyltriphenylphosphonium bromide (10.5 g, 0.03 mol) in dry THF at 0 °C was added dropwise *n*-butyllithium (2.4 M) until a clear orange solution resulted. *trans*-2-Methylcyclopropanecarbonyl chloride[11] (1.67 g, 0.015 mol) in dry THF was added dropwise with vigorous stirring. After the addition, water and ethyl acetate were added; the organic layer was separated, washed, and dried. Evaporation gave an oil which on trituration gave the stabilized phosphorane (**10**) (2.9 g), mp 148–150 °C: ^{1}H NMR (300 MHz) δ 7.667–7.408 (15 H, aromatic), 3.724 (1 H, d, J = 25 Hz, C-1), 1.501, 1.251, 1.049, 0.408 (4 H, m, cyclopropyl H), 1.085 (3 H, d, J = 5.95 Hz); mass spectrum m/z (rel intensity) 358.1479 (M^+ 8; calcd for $C_{24}H_{23}OP$, 358.1486), 357.1396 ($C_{24}H_{22}OP$, 8), 303.0939 ($C_{20}H_{16}OP$, 31), 277.0786 ($C_{18}H_{14}OP$, 18), 262.0908 ($C_{18}H_{15}P$, 32), 57.0709 (C_4H_9, 100).

(25*RS*,26*RS*)-26-Methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholest-22-en-24-one (11). A solution of the aldehyde **8**[12] (0.74 g, 2.15 mmol) and phosphorane **10** (0.75 g, 2.15 mmol) in benzene was heated under reflux for 10 h. The reaction mixture was cooled and evaporated. Chromatography over Florisil (eluent CH_2Cl_2/hexane 1:1) gave **11** (0.71 g, 77%) as an inseparable mixture of diastereomers: ^{1}H NMR (300 MHz) δ 6.717 (1 H, ddd, J = 0.8, 8.8, 15.6 Hz, C-22), 6.126 (1 H, d, J = 15.6 Hz, C-23), 3.323 (3 H, s, OCH_3), 1.134 (3 H, d, J = 5.98 Hz, C-28), 1.108 (3 H, d, J = 6.7 Hz, C-21), 1.025 (3 H, s, C-19), 0.762 (3 H, s, C-18); high-resolution mass spectrum m/z (rel intensity) 424.3328 (M^+ 15; calcd for $C_{29}H_{44}O_2$, 424.3341), 409.3096 ($C_{28}H_{41}O_2$, 43), 392.3067 ($C_{28}H_{40}O$, 68), 377.2838 ($C_{27}H_{37}O$, 11), 369.2779 ($C_{25}H_{37}O_2$, 68), 366.2907 ($C_{26}H_{38}O$, 10), 255.2107 ($C_{19}H_{27}$, 24), 138.1051 ($C_{19}H_{14}O$, 100).

(25*RS*,26*RS*)-22-Deuterio-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholest-22-en-24-one (12) was prepared similary from aldehyde **9**: ^{1}H NMR (300 MHz) δ 6.13 (1 H, br s, C-23), 3.32 (3 H, s, OCH_3), 1.133 (3 H, d, J = 6.04 Hz, C-28), 1.106 (3 H, d, J = 6.65 Hz, C-21), 1.025 (3 H, s, C-19), 0.762 (3 H, s, C-18).

(25*RS*,26*RS*)-26-Methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestan-24-one (13). To 0.249 g (0.58 mmol) of **11** was added 5.6 mL of a 0.55 M solution of $NaBH_4$ in pyridine. After 4 h the reaction mixture was diluted with water (50 mL) and extracted with three portions of Et_2O. The combined organic layers were washed with 5% $CuSO_4$ until no pyridine remained and then dried. Evaporation of the solvent and chromatography over SiO_2 (eluent ethyl acetate/hexane 2:100) gave **13** (0.20 g, 80%) as an inseparable mixture of isomers: ^{1}H NMR (300 MHz) δ 3.316 (3 H, s, OCH_3), 1.104 (3 H, d, J = 5.95 Hz, C-21), 1.015 (3 H, s, C-19), 0.919 (3 H, d, J = 6.55 Hz, C-28), 0.710 (3 H, s, C-18); high-resolution mass spectrum m/z (rel intensity) 426.3490 (M^+ 24; calcd for $C_{29}H_{46}O_2$, 426.3498), 411.3276 ($C_{28}H_{43}O_2$, 33), 394.3240 ($C_{28}H_{42}O$, 36), 379.2999 ($C_{27}H_{39}O$, 11), 371.2941 ($C_{25}H_{39}O_2$, 50), 368.3080 ($C_{26}H_{40}O$, 8), 297.2851 ($C_{22}H_{33}$, 30), 296.2507 ($C_{22}H_{32}$, 27), 57.0710 (C_4H_9, 100).

(25*RS*,26*RS*)-22,22-Dideuterio-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestan-24-one (14) was prepared as described above from enone **12**: ^{1}H NMR (300 MHz) δ 3.318 (3 H, s, OCH_3), 1.105 (3 H, d, J = 5.95 Hz, C-21), 1.016 (3 H, s, C-19), 0.917 (3 H, d, J = 6.60 Hz, C-28), 0.711 (3 H, s, C-18); mass spectrum m/z (rel intensity) 428 (M^+ 100), 413 (35), 396 (55), 373 (60), 299 (50), 285 (20), 255 (10), 253 (8), 213 (20).

(25*RS*,26*RS*)-24-Methylene-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (15). To a stirred suspension of methyltriphenylphosphonium bromide (1.25 g, 3.5 mmol) in dry THF at 0 °C was added *n*-butyllithium (2.4 M) dropwise until a clear solution was obtained. A solution of ketone **13** (0.438 g, 1.03 mmol) in dry THF was added and the reaction mixture was stirred for 4 h. The reaction was quenched with water, ethyl acetate was added, and the organic layer was separated, washed, and dried. Evaporation of the solvent and purification of the residue over SiO_2 (eluent hexane/CH_2Cl_2 10:1) gave 0.415 g (94%) of **15**: ^{1}H NMR (300 MHz) δ 4.552 (1 H, br s, C-28), 4.498 (1 H, br s, C-28), 3.322 (3 H, s, OCH_3), 1.078 (3 H, d, J = 5.84 Hz, C-21), 1.021 (3 H, s, C-19), 0.938 (3 H, d, J = 6.5 Hz, C-29), 0.719 (3 H, s, C-18); high-resolution mass spectrum m/z (rel intensity), 424.3702 (M^+ 1; calcd for $C_{30}H_{48}O$, 424.3705), 409.3480 ($C_{29}H_{45}O$, 2), 392.3445 ($C_{29}H_{44}$, 5), 377.3208 ($C_{28}H_{41}$, 4), 369.3145 ($C_{26}H_{41}O$, 4), 296.2491 ($C_{22}H_{32}$, 22), 253.1495 ($C_{19}H_{25}$, 45), 96.0939 (C_7H_{12}, 100).

(25*RS*,26*RS*)-22,22-Dideuterio-26-methyl-24-methylene-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (16) was prepared as described above, from 14: ^{1}H NMR (300 MHz) δ 4.553 (1 H, br s, C-28), 4.503 (1 H, br s, C-28), 3.324 (3 H, s, OCH_3), 1.080 (3 H, d, J = 5.84 Hz, C-29), 1.024 (3 H, s, C-19), 0.937 (3 H, d, J = 6.58 Hz, C-21), 0.721 (3 H, s, C-18); mass spectrum m/z (rel intensity) 426 (M^+ 1), 411 (1), 394 (2), 379 (1), 371 (2), 330 (3), 315 (3), 286 (10), 253 (20), 96 (100).

Hydroboration of 15. To **15** (240 mg, 0.56 mmol) in dry THF (10 mL) at 0 °C under N_2 was added 1.5 mL of 1 M borane in THF. After 2 h a solution of dilute NaOH was added, followed by 30% H_2O_2. The organic layer was washed, dried, and evaporated. Fractionation of the residue by HPLC over SiO_2 (eluent ethyl acetate/hexane 7:100) gave four compounds described below in order of elution, in a total yield of 80% (20% of each isomer).

Fraction 1. (24*R*,25*S*,26*S*)-24-Hydroxymethyl-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (19): ^{1}H NMR (300 MHz) δ 3.6 (2 H, m, C-28), 3.322 (3 H, s, OCH_3), 1.041 (3 H, d, J = 5.99 Hz, C-29), 1.020 (3 H, s, C-19), 0.914 (3 H, d, J = 6.49 Hz, C-21), 0.711 (3 H, s, C-18); mass spectrum, m/z (rel intensity), 442 (M^+ 1), 427 (1), 410 (2), 395 (1), 387 (3), 255 (3), 253 (6), 229 (2), 213 (4), 201 (3), 45 (100).

Fraction 2. (24*S*,25*R*,26*R*)-24-Hydroxymethyl-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (20): ^{1}H NMR (300 MHz) δ 3.6 (2 H, m, C-28), 3.321 (3 H, s, OCH_3), 1.035 (3 H, d, J = 6.04 Hz, C-29), 1.019 (3 H, s, C-19), 0.917 (3 H, d, J = 6.48 Hz, C-21), 0.709 (3 H, s, C-18); mass spectrum m/z (rel intensity), 442 (M^+ 12), 427 (10), 410 (16), 387 (15), 285 (12), 255 (10), 253 (25), 229 (6), 213 (10), 201 (9), 45 (100).

Fraction 3. (24*R*,25*R*,26*R*)-24-Hydroxymethyl-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (17): ^{1}H NMR (300 MHz) δ 3.6 (2 H, m, C-28), 3.323 (3 H, s, OCH_3), 1.049 (3 H, d, J = 5.92 Hz, C-29), 1.022 (3 H, s, C-19), 0.932 (3 H, d, J = 6.52 Hz, C-21), 0.720 (3 H, s, C-18); high-resolution mass spectrum m/z (rel intensity) 442.3804 (M^+ 3; calcd for $C_{30}H_{50}O_2$, 442.3810), 427.3590 ($C_{29}H_{47}O_2$, 4), 410.3550 ($C_{29}H_{46}O$, 4), 387.3263 ($C_{26}H_{43}O_2$, 8), 255.2115 ($C_{19}H_{27}$, 7), 229.1954 ($C_{17}H_{25}$, 3), 213.1648 ($C_{16}H_{21}$, 5), 201.1664 ($C_{15}H_{21}$, 3), 57.0710 (C_4H_9, 100).

Fraction 4. (24*S*,25*S*,26*S*)-24-Hydroxymethyl-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (18): ^{1}H NMR (300 MHz) δ 3.568 (2 H, m, C-28), 3.323 (3 H, s, OCH_3), 1.046 (3 H, d, J = 5.95 Hz, C-29), 1.021 (3 H, s, C-19), 0.931 (3 H, d, J = 6.48 Hz, C-21), 0.716 (3 H, s, C-18); mass spectrum m/z (rel intensity) 442 (M^+ 8), 427 (5), 410 (11), 387 (11), 285 (5), 255 (10), 253 (9), 229 (5), 213 (10), 201 (6), 45 (100).

(24*S*,25*S*,26*S*)-22,22-Dideuterio-24-hydroxymethyl-26-methyl-6β-methoxy-3α,5:25,27-dicyclo-5α-cholestane (22) was prepared as described above from olefin **16**: ^{1}H NMR (300 MHz) δ 3.564 (2 H, m, C-28), 3.320 (3 H, s, OCH_3), 1.044 (3 H, d, J = 5.93 Hz, C-29), 1.019 (3 H, s, C-19), 0.926 (3 H, d, J = 6.39 Hz, C-21), 0.714 (3 H, s, C-18); mass spectrum m/z (rel intensity) 444 (M^+ 11), 429 (7), 412 (15), 389 (15), 255 (10), 253 (11), 213 (7), 55 (100).

Petrosterol Isomers 1, 2, 3, and 4 and Labeled Isomer 25. Each individual 24-hydroxymethyl compound **17–20**, **22** (20 mg, 0.05 mmol), was dissolved in dry pyridine (1 mL), and *p*-toluenesulfonyl chloride (100 mg) was added. After 24 h the reaction mixture was diluted with ethyl acetate, washed with 5% $CuSO_4$ until no pyridine remained, dried, and evaporated. The crude tosylate was dissolved in dry Et_2O, and $LiAlH_4$ (50 mg) was added. After 12 h the excess $LiAlH_4$ was destroyed with ethyl acetate and the minimum amount of water, and the precipitate removed by filtration. The filtrate was evaporated to give the crude sterol *i*-methyl ether. This was dissolved in dioxane/water (1:1, 5 mL), containing a crystal of *p*-toluenesulfonic acid and heated under reflux for 1 h. Evaporation of the solvents under reduced pressure followed by purification of the residue over SiO_2 (eluent ethyl acetate/hexane 7:100) gave 14 mg of the corresponding petrosterol isomer (70% overall yield). From **19** was obtained **(24*R*,25*S*,26*S*)-24,26-dimethyl-25,27-cyclocholest-5-en-3β-ol (3)**, mp 135–137 °C, $[\alpha]^{20}_D$ −17.3°: mass spectrum m/z (rel intensity) 412 (M^+ 15), 397 (1), 394 (1), 379 (1), 327 (2), 314 (4), 301 (2), 300 (3), 299 (3), 271 (30), 258 (5), 255 (8), 253 (5), 231 (9), 229 (9), 213 (4), 55 (100).

From **20** was obtained **(24*S*,25*R*,26*R*)-24,26-dimethyl-25,27-cyclocholest-5-en-3β-ol (4)**, mp 124–126 °C, $[\alpha]^{20}_D$ −43.3°: mass spectrum m/z (rel intensity) 412 (M^+ 13), 397 (1), 394 (8), 379 (5), 327 (2), 314 (7), 301 (3), 300 (4), 299 (4), 271 (36), 258 (5), 255 (7), 253 (4), 231 (7), 229 (9), 213 (16), 81 (100).

From **17** was obtained (**24*R*,25*R*,26*R*)-24,26-dimethyl-25,27-cyclocholest-5-en-3β-ol** (**1**) (petrosterol), mp 157–159 °C (lit.[1b] 120–121 °C),[27] $[\alpha]^{20}_D$ −36.4° (lit.[28] −40.3°): mass spectrum *m/z* (rel intensity), 412 (M^+ 15), 397 (1), 394 (1), 379 (1), 327 (3), 314 (5), 301 (3), 300 (2), 299 (3), 271 (25), 258 (3), 255 (6), 253 (3), 231 (8), 229 (9), 213 (14), 55 (100).

From **18** was obtained (**24*S*,25*S*,26*S*)-24,26-dimethyl-25,27-cyclocholest-5-en-3β-ol** (**2**), mp 111–113 °C, $[\alpha]^{20}_D$ −24.3°: mass spectrum *m/z* (rel intensity) 412 (M^+ 13), 397 (1), 394 (1), 379 (1), 327 (2), 314 (4), 301 (3), 300 (2), 299 (3), 271 (26), 258 (4), 255 (5), 253 (2), 231 (7), 229 (5), 213 (13), 55 (100).

From **22** was obtained (**24*S*,25*S*,26*S*)-22,22-dideuterio-24,26-dimethyl-25,27-cyclocholest-5-en-3β-ol** (**25**): ^{1}H NMR (300 MHz) 1.007 (3 H, s, C-19), 1.003 (3 H, d, *J* = 5.88 Hz, C-21), 0.918 (3 H, d, *J* = 6.5 Hz, C-29), 0.890 (3 H, d, *J* = 6.67 Hz, C-28), 0.677 (3 H, s, C-18); mass spectrum *m/z* (rel intensity) 414 (M^+ 14), 399 (1), 396 (2), 381 (1), 329 (3), 316 (5), 303 (2), 301 (1), 300 (2), 271 (30), 258 (3), 255 (5), 253 (3), 231 (10), 229 (7), 213 (15), 55 (100).

General Procedure for the Hydrogenation of the Four Petrosterol Isomers 1, 2, 3, 4, Aplysterol (30), and 24,28-Dehydroaplysterol (31) to the Corresponding 5α-5,6-Dihydro Analogues. Platinum oxide (10 mg) was stirred vigorously under H_2 for 1 h in ethyl acetate/acetic acid (1:1, 2 mL). The sterol (0.5–2 mg) in the minimum amount of ethyl acetate was added and hydrogenated for 12 h. Filtration and evaporation of the solvents gave the crude product which was purified by HPLC (eluent methanol), yield 80–90% based on the HPLC traces.

From (24*R*,25*R*,26*R*)-petrosterol (**1**) was obtained (**24*R*,25*R*)-5,6-dihydro-5α-aplysterol** (**26**): high-resolution mass spectrum *m/z* (rel intensity) 416.4032 (M^+ 20; calcd for $C_{29}H_{52}O$, 416.4018), 401.3769 ($C_{28}H_{49}O$, 15), 383.3665 ($C_{28}H_{47}$, 6), 316.3153 ($C_{23}H_{40}$, 1), 290.2967 ($C_{21}H_{38}$, 8), 275.2738 ($C_{20}H_{35}$, 1), 267.3015 ($C_{18}H_{39}$, 1), 248.2127 ($C_{17}H_{28}O$, 3), 233.1904 ($C_{16}H_{25}O$, 43), 215.1802 ($C_{16}H_{23}$, 46), 57.0714 (C_4H_9, 100).

From (24*S*,25*S*,26*S*)-petrosterol (**2**) was obtained (**24*S*,25*S*)-5,6-dihydro-5α-aplysterol** (**27**): mass spectrum *m/z* (rel intensity) 416 (M^+ 13), 401 (2), 383 (1), 316 (1), 290 (3), 275 (2), 248 (3), 233 (35), 215 (40), 57 (100).

From (24*R*,25*S*,26*S*)-petrosterol (**3**) was obtained (**24*R*,25*S*)-5,6-dihydro-5α-aplysterol** (**28**): mass spectrum *m/z* (rel intensity) 416 (M^+ 14), 401 (3), 383 (1), 316 (1), 290 (3), 275 (2), 248 (3), 233 (32), 215 (34), 57 (100).

From (24*S*,25*R*,26*R*)-petrosterol (**4**) was obtained (**24*S*,25*R*)-5,6-dihydro-5α-aplysterol** (**29**): mass spectrum *m/z* (rel intensity) 416 (M^+, 14), 401 (2), 383 (1), 316 (1), 290 (3), 275 (2), 248 (4), 233 (30), 215 (33), 57 (100).

From (24*R*,25*S*)-aplysterol (**30**) was obtained (**24*R*,25*S*)-5,6-dihydro-5α-aplysterol** (**28**): mass spectrum *m/z* (rel intensity) 416 (M^+ 15), 401 (3), 383 (1), 316 (1), 290 (3), 275 (1), 248 (3), 233 (33), 215 (37), 57 (100).

From (25*S*)-24,28-dehydroaplysterol (**31**) was obtained a 1:1 mixture of **(24*R*,25*S*)-5,6-dihydro-5α-aplysterol (28) and (24*S*,25*S*)-5,6-dihydro-5α-aplysterol** (**27**): mass spectrum *m/z* (rel intensity) 416 (M^+ 12), 401 (3), 383 (1), 316 (1), 290 (3), 275 (2), 248 (4), 233 (28), 215 (30), 55 (100).

Acetylation of the Petrosterol Isomers. The petrosterol isomer (10–20 mg) was dissolved in pyridine (0.5 mL), and acetic anhydride (0.5 mL) was added. After 24 h the reaction mixture was diluted with ethyl acetate, washed with 5% copper sulfate solution, and dried. Evaporation of the solvent gave the acetate which was used in the isomerization reaction without further purification.

(24*R*,25*R*,26*R*)-Petrosterol Acetate: ^{1}H NMR (300 MHz) δ 5.4 (1 H, m, C-6), 4.6 (1 H, m, C-3), 2.032 (3 H, s, CH_3COO–), 1.016 (3 H, s, C-19), 1.005 (3 H, d, *J* = 6.65 Hz, C-21), 0.918 (3 H, d, *J* = 6.56 Hz, C-28), 0.888 (3 H, d, *J* = 6.71 Hz, C-29), 0.678 (3 H, s, C-18).

(24*S*,25*S*,26*S*)-Petrosterol Acetate: ^{1}H NMR (300 MHz) δ 5.4 (1 H, m, C-6), 4.6 (1 H, m, C-3), 2.031 (3 H, s, CH_3COO–), 1.020 (3 H, s, C-19), 1.008 (3 H, d, *J* = 7.01 Hz, C-21), 0.924 (3 H, d, *J* = 6.51 Hz, C-28), 0.893 (3 H, d, *J* = 6.73 Hz, C-29), 0.680 (3 H, s, C-18).

(24*R*,25*S*,26*S*)-Petrosterol Acetate: ^{1}H NMR (300 MHz) δ 5.4 (1 H, m, C-6), 4.6 (1 H, m, C-3), 2.031 (3 H, s, CH_3COO–), 1.014 (3 H, s, C-19), 1.003 (3 H, d, *J* = 7.09 Hz, C-21), 0.911 (3 H, d, *J* = 6.65 Hz, C-29), 0.902 (3 H, d, *J* = 6.43 Hz, C-28), 0.669 (3 H, s, C-18).

(24*S*,25*R*,26*R*)-Petrosterol Acetate: ^{1}H NMR (300 MHz) δ 5.4 (1 H, m, C-6), 4.6 (1 H, m, C-3), 2.031 (3 H, s, CH_3COO–), 1.015 (3 H, s, C-19), 1.001 (3 H, d, *J* = 6.18 Hz, C-21), 0.914 (3 H, d, *J* = 6.44 Hz, C-28), 0.914 (3 H, d, *J* = 6.44 Hz, C-29), 0.670 (3 H, s, C-18).

(24*S*,25*S*,26*S*)-22,22-Dideuteriopetrosterol Acetate: ^{1}H NMR (300 MHz) δ 2.031 (3 H, s, CH_3COO–), 1.017 (3 H, s, C-19), 1.005 (3 H, d, *J* = 7.61 Hz, C-21), 0.923 (3 H, d, *J* = 6.69 Hz, C-28), 0.893 (3 H, d, *J* = 6.76 Hz, C-29), 0.677 (3 H, s, C-18); mass spectrum *m/z* (rel intensity) 396 (M^+ − 60, 100), 381 (20), 273 (10), 255 (20), 253 (10), 240 (11), 213 (12).

Petrosterol Isomerization Reactions: General Procedure. The sterol acetate was dissolved in a 5% TFA/benzene solution at a concentration of 1.5 mg/mL and left undisturbed for 48 h. Toluene (1 vol) was then added and the solvents were evaporated at reduced pressure. The residue was dissolved in dry THF, and $LiAlH_4$ (50 mg) was added. After 12 h the excess $LiAlH_4$ was destroyed with ethyl acetate and the minimum amount of water. Filtration and evaporation of the solvents gave the crude reaction mixture. Fractionation was accomplished by HPLC with methanol/water 95:5 as the mobile phase.

The isomerization of (24*R*,25*R*,26*R*)-petrosterol (**1**) gave the following fractions in order of elution.

Fraction 1. (24*S*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,22-dien-3β-ol (**37**): high-resolution mass spectrum *m/z* (rel intensity) 412.3717 (M^+ 39; calcd for $C_{29}H_{48}O$, 412.3705), 397.3495 ($C_{28}H_{45}O$, 6), 394.3610 ($C_{29}H_{46}$, 5), 379.3385 ($C_{28}H_{43}$, 8), 300.2467 ($C_{21}H_{32}O$, 28), 283.2398 (C_{21}, H_{31}, 11), 271.2060 ($C_{19}H_{27}O$, 38), 255.2130 ($C_{19}H_{27}$, 51), 213.1646 ($C_{16}H_{21}$, 17), 83.0867 (C_6H_{11}, 100).

Fraction 2. (*Z*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**33**): high-resolution mass spectrum *m/z* (rel intensity) 412.3707 (M^+ 3; calcd for $C_{29}H_{48}O$, 412.3705), 394.3571 ($C_{29}H_{46}$, 13), 379.3385 ($C_{28}H_{43}$, 6), 299.2377 ($C_{21}H_{31}O$, 19), 283.2441 ($C_{21}H_{31}$, 55), 271.2070 ($C_{19}H_{27}O$, 69), 253.1965 ($C_{19}H_{25}$, 37), 215.1792 ($C_{16}H_{23}$, 23), 213.1642 ($C_{16}H_{21}$, 18), 55.0551 (C_4H_7, 100).

Fraction 3. (24*R*,25*R*)-24-Methyl-26-methylenecholest-5-en-3β-ol (**35**): high-resolution mass spectrum *m/z* (rel intensity) 412.3715 (M^+ 20; calcd for $C_{29}H_{48}O$, 412.3705), 397.3470 ($C_{28}H_{45}O$, 6), 394.3495 ($C_{29}H_{46}$, 23), 379.3347 ($C_{28}H_{43}$, 14), 327.3016 ($C_{23}H_{38}$, 14), 301.2903 ($C_{22}H_{37}$, 7), 255.2100 ($C_{19}H_{27}$, 15), 213.1646 ($C_{16}H_{21}$, 23), 55.0554 (C_4H_7, 100).

Fraction 4. (*E*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**34**): high-resolution mass spectrum *m/z* (rel intensity) 412.3717 (M^+ 9; calcd for $C_{29}H_{48}O$, 412.3705), 394.3566 ($C_{29}H_{46}$, 13), 379.3362 ($C_{28}H_{43}$, 5), 314.2592 ($C_{22}H_{34}O$, 6), 299.2356 ($C_{21}H_{31}O$, 15), 283.2436 ($C_{21}H_{31}$, 52), 271.2055 ($C_{19}H_{27}O$, 73), 253.1948 ($C_{19}H_{25}$, 29), 227.1803 ($C_{17}H_{23}$, 13), 215.1803 ($C_{16}H_{23}$, 23), 201.1645 ($C_{15}H_{21}$, 12), 55.0555 (C_4H_7, 100).

Fraction 5. (24*S*,25*R*)-24,26-Dimethylcholesta-5,22-dien-3β-ol (**36**): high-resolution mass spectrum *m/z* (rel intensity) 412.3708 (M^+ 15; calcd for $C_{29}H_{48}O$, 412.3705), 394.3599 ($C_{29}H_{46}$, 15), 379.3358 ($C_{28}H_{43}$, 7), 300.2463 ($C_{21}H_{32}O$, 12), 283.2427 ($C_{21}H_{31}$, 21), 271.2053 ($C_{19}H_{27}O$, 44), 255.2109 ($C_{19}H_{27}$, 25), 253.1973 ($C_{19}H_{25}$, 22), 213.1641 ($C_{16}H_{21}$, 20), 55.0553 (C_4H_7, 100).

The isomerization of (24*S*,25*S*,26*S*)-petrosterol (**2**) gave the following fractions in order of elution.

Fraction 1. (*Z*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**33**). For spectral data, see above.

Fraction 2. (24*R*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,22-dien-3β-ol (**40**): mass spectrum *m/z* (rel intensity) 412 (M^+ 4), 397 (1), 394 (1), 379 (1), 327 (1), 314 (1), 300 (4), 271 (7), 255 (5), 213 (3), 55 (100).

Fraction 3. (24*S*,25*S*)-24-Methyl-26-methylenecholest-5-en-3β-ol (**38**): mass spectrum *m/z* (rel intensity) 412 (M^+ 6), 397 (1), 394 (1), 379 (1), 327 (3), 314 (1), 300 (2), 271 (3), 255 (3), 231 (3), 213 (5).

Fraction 4. (*E*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**34**). For spectral data, see above.

Fraction 5. (24*R*,25*S*)-24,26-Dimethylcholesta-5,22-dien-3β-ol (**39**): mass spectrum *m/z* (rel intensity), 412 (M^+ 7), 397 (1), 394 (1), 379 (1), 355 (1), 337 (2), 314 (2), 300 (7), 271 (10), 255 (9), 213 (5), 55 (100).

From (24*S*,25*R*,26*R*)-petrosterol (**4**) the following fractions were obtained in order of elution.

Fraction 1. (*Z*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**33**). For spectral data, see above.

Fraction 2. (24*S*,25*R*)-24-Methyl-26-methylenecholest-5-en-3β-ol (**43**): mass spectrum *m/z* (rel intensity) 412 (M^+ 17), 397 (3), 394 (5), 379 (3), 317 (7), 301 (6), 271 (6), 255 (7), 231 (7), 213 (12), 55 (100).

Fraction 3. (*E*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (**34**). For spectral data, see above.

Fraction 4. (25*S*)-26,26-Dimethylcholesta-5,23-dien-3β-ol (**44**): high-resolution mass spectrum *m/z* (rel intensity) 412.3704 (M^+ 2; calcd

(27) A sample of petrosterol (from *Petrosia ficiformis*) was subjected to exhaustive purification by HPLC using methanol and acetonitrile/methanol/ethyl acetate 3:3:1 as mobile phases. This highly purified sample of the natural sterol was found to have mp 157–159 °C.

(28) Lane, C. F.; Brown, H. C. *J. Organomet. Chem.* **1971**, 26 (2), C51–54.

for $C_{29}H_{48}O$, 412.3705), 394.3596 ($C_{29}H_{46}$, 3), 379.3346 ($C_{28}H_{43}$, 3), 283.2440 ($C_{21}H_{31}$, 10), 271.2063 ($C_{19}H_{27}O$, 40), 253.1949 ($C_{19}H_{25}$, 21), 213.1635 ($C_{16}H_{21}$, 6), 57.0710 (C_4H_9, 100).

From (24*R*,25*S*,26*S*)-petrosterol (**3**) the following fractions were obtained in order of elution.

Fraction 1. (*Z*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (33). For spectral data, see above.

Fraction 2. (24*R*,25*S*)-24-Methyl-26-methylenecholest-5-en-3β-ol (41): mass spectrum *m/z* (rel intensity) 412 (M^+ 9), 397 (2), 394 (3), 379 (2), 327 (4), 301 (4), 273 (5), 255 (4), 231 (5), 213 (9), 55 (100).

Fraction 3. (*E*)-24-Methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (34). For spectral data, see above.

Fraction 4. (25*R*)-26,26-Dimethylcholesta-5,23-dien-3β-ol (42): mass spectrum *m/z* (rel intensity) 412 (M^+ 7), 397 (3), 394 (2), 379 (1), 351 (1), 327 (2), 314 (1), 300 (12), 283 (13), 271 (20), 253 (2), 215 (6), 55 (100).

From (24*S*,25*S*,26*S*)-22,22-dideuteriopetrosterol (**25**) the following fractions were obtained, in order of elution.

Fraction 1. (*Z*)-22,22-Dideuterio-24-methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (45): mass spectrum *m/z* (rel intensity) 414 (M^+ 7), 399 (3), 396 (2), 381 (1), 316 (5), 300 (10), 283 (15), 251 (22), 215 (4), 55 (100).

Fraction 2. (24*R*)-22-Deuterio-24-methyl-26,26-dimethyl-27-norcholesta-5,22-dien-3β-ol (49): mass spectrum *m/z* (rel intensity) 413 (M^+ 15), 398 (6), 395 (4), 380 (4), 328 (3), 315 (5), 300 (28), 271 (45), 255 (25), 213 (12), 57 (100).

Fraction 3. (24*S*,25*S*)-22,22-Dideuterio-24-methyl-26-methylenecholest-5-en-3β-ol (47): mass spectrum *m/z* (rel intensity) 414 (M^+ 14), 399 (1), 396 (1), 329 (1), 316 (1), 271 (3), 255 (2), 231 (2), 213 (4), 55 (100).

Fraction 4. (*E*)-22,22-Dideuterio-24-methyl-26,26-dimethyl-27-norcholesta-5,23-dien-3β-ol (46): mass spectrum *m/z* (rel intensity) 414 (M^+ 15), 399 (5), 381 (1), 316 (9), 300 (15), 283 (35), 271 (80), 253 (10), 241 (5), 215 (18), 213 (13), 55 (100).

Fraction 5. (24*R*,25*S*)-22,26-Dideuterio-24,26-dimethylcholesta-5,22-dien-3β-ol (48): mass spectrum *m/z* (rel intensity) 414 (M^+ 8), 399 (1), 396 (1), 381 (1), 356 (1), 338 (2), 329 (1), 315 (2), 300 (7), 271 (15), 255 (10), 213 (6), 55 (100).

(23ξ,24ξ)-23-Hydroxy-24-methyl-26,26-dimethyl-27-nor-6β-methoxy-3α,5-cyclo-5α-cholestane (52). To 2-bromo-4-methylpentane[28] (0.5 mL, 5 mmol) in dry ether under N_2 was added magnesium (240 mg, 10 mmol). After formation of the Grignard reagent, the aldehyde **51**[21] (200 mg, 0.56 mmol) was added. The reaction was quenched after 1 h with water, the solid matter removed by filtration, and the filtrate evaporated to dryness. Purification of the residue by chromatography over SiO_2 (eluent ethyl acetate/hexane 7:100) gave **52** as a mixture of four diastereomers (195 mg): high-resolution mass spectrum *m/z* (rel intensity) 444.3965 (M^+ 4; calcd for $C_{30}H_{52}O_2$, 444.3967), 429.3736 ($C_{29}H_{49}O_2$, 7), 412.3717 ($C_{29}H_{48}O$, 7), 389.3433 ($C_{26}H_{45}O_2$, 11), 327.2682 ($C_{23}H_{35}O$, 2), 255.2119 ($C_{19}H_{27}$, 5), 253.1973 ($C_{19}H_{25}$, 4), 213.1648 ($C_{16}H_{21}$, 6), 57.0707 (C_4H_9, 100).

Dehydration of 52. To a solution of **52** (27 mg) in pyridine (2 mL) at 0 °C was added phosphorus oxychloride (0.5 mL). After 24 h the reaction was quenched by the careful addition of methanol. The mixture was taken up in EtOAc, washed, dried, and evaporated. The crude product was deprotected by reflux in dioxane/water containing a crystal of *p*-toluenesulfonic acid. Chromatography over SiO_2 gave a mixture of sterols (11 mg), which was fractionated by HPLC (mobile phase MeOH/H_2O 95:5) to give **37**, **49**, **33**, and **34** in 5, 4, 13, and 13% overall yields, respectively.

26,26-Dimethyl-25-oxo-27-nor-6β-methoxy-3α,5-cyclo-5α-cholest-23-ene (58). A solution of aldehyde **51**[28] (50 mg) and phosphorane **57** (100 mg) in benzene (3 mL) was heated under reflux for 15 h. The reaction mixture was directly fractionated by chromatography over SiO_2 (eluent hexane/ethyl acetate 100:7) to give **58** (47 mg): ^1H NMR (300 MHz) δ 6.856 (1 H, ddd, *J* = 6.38, 8.59, 15.35 Hz, C-23), 6.140 (1 H, d, *J* = 15.35 Hz, C-24), 3.313 (3 H, s, OCH_3), 1.105 (3 H, d, *J* = 6.89 Hz, C-28), 1.105 (3 H, d, *J* = 6.89 Hz, C-27), 1.012 (3 H, s, C-19), 0.938 (3 H, d, *J* = 6.60 Hz, C-21), 0.724 (3 H, s, C-18); high-resolution mass spectrum *m/z* (rel intensity) 426.3495 (M^+ 13; calcd for $C_{29}H_{46}O$, 426.3498), 411.3261 ($C_{28}H_{43}O_2$, 15), 394.3259 ($C_{28}H_{42}O$, 20), 371.2980 ($C_{25}H_{39}O_2$, 25), 297.2562 ($C_{22}H_{33}$, 15), 296.2502 ($C_{22}H_{32}$, 16), 255.2105 ($C_{19}H_{37}$, 12), 253.1931 ($C_{19}H_{25}$, 7), 227.1791 ($C_{17}H_{23}$, 5), 213.1636 ($C_{16}H_{21}$, 10), 201.1628 ($C_{15}H_{21}$, 5), 57.0706 (C_4H_9, 100).

26,26-Dimethyl-6β-Methoxy-3α,5-cyclo-5α-cholesta-23,25-diene (59). To a suspension of methyltriphenylphosphonium bromide (0.5 g) in dry THF at 0 °C under N_2 was added dropwise *n*-butyllithium (2.4 M) until a clear orange solution was obtained. This phosphorane solution was added via a syringe, dropwise, to a solution of **58** (40 mg, 0.094 mmol) in dry THF at 0 °C until the orange color persisted. After 0.5 h at room temperature the reaction was quenched with methanol, diluted with ethyl acetate, washed, dried, and evaporated. Chromatography of the residue over SiO_2 (eluent ethyl acetate/hexane 7:100) gave **59**: ^1H NMR (300 MHz) δ 5.991 (1 H, d, *J* = 16.80 Hz, C-24), 5.723 (1 H, ddd, *J* = 6.37, 9.15, 16.80 Hz, C-23), 4.863 (1 H, br s, C-27), 4.828 (1 H, br s, C-27), 3.322 (3 H, s, OCH_3), 1.087 (3 H, d, *J* = 6.82 Hz, C-28), 1.087 (3 H, d, *J* = 6.87 Hz, C-29), 1.021 (3 H, s, C-19), 0.931 (3 H, d, *J* = 6.60 Hz, C-21), 0.730 (3 H, s, C-18); mass spectrum *m/z* (rel intensity) 424 (M^+ 6), 409 (32), 392 (22), 359 (59), 356 (12), 341 (19), 327 (19), 324 (16), 310 (15), 301 (21), 285 (80), 253 (85), 222 (30), 215 (20), 213 (20), 201 (25), 55 (100).

Hydroboration of 59. To a solution of **59** (71 mg, 0.17 mmol) in dry THF was added 9-borabicyclo[3.3.1]nonane (0.5 M, 3.0 mL, 10 equiv). After 0.5 h at room temperature, dilute NaOH, followed by H_2O_2 (30%), was added. The organic layer was separated, diluted with ethyl acetate, washed, dried, and evaporated. The crude product mixture was purified by chromatography over SiO_2 (eluent hexane/ethyl acetate 100:14) and then fractionated by HPLC over SiO_2 (eluent hexane/ethyl acetate 100:7) to give **60** (23 mg) and **61** (23 mg).

(25*R*)-26,26-Dimethyl-27-hydroxy-6β-methoxy-3α,5-cyclo-5α-cholest-23-ene (60): ^1H NMR (300 MHz) δ 5.519 (1 H, m, C-23), 5.175 (1 H, dd, *J* = 9.29, 15.25 Hz, C-24), 3.65 (1 H, m, C-27), 3.38 (1 H, m, C-27), 3.323 (3 H, s, OCH_3), 1.018 (3 H, s, C-19), 0.926 (3 H, d, *J* = 6.75 Hz, C-21), 0.903 (3 H, d, *J* = 6.85 Hz, C-28), 0.860 (3 H, d, *J* = 6.80 Hz, C-29), 0.723 (3 H, s, C-18); high-resolution mass spectrum *m/z* (rel intensity) 442.3818 (M^+ 2; calcd for $C_{30}H_{50}O_2$, 442.3811), 427.3518 ($C_{29}H_{47}O_2$, 3), 410.3578 ($C_{29}H_{46}O$, 4), 387.3254 ($C_{26}H_{43}O_2$, 4), 283.2409 ($C_{21}H_{31}$, 8), 253.1949 ($C_{19}H_{25}$, 7), 57.0706 (C_4H_9, 100).

(25*S*)-26,26-Dimethyl-27-hydroxy-6β-methoxy-3α,5-cyclo-5α-cholest-23-ene (61): ^1H NMR (300 MHz) 5.502 (1 H, ddd, *J* = 5.74, 8.61, 15.27 Hz, C-23), 5.167 (1 H, dd, *J* = 9.40, 15.27 Hz, C-24), 3.65 (1 H, m, C-27), 3.37 (1 H, m, C-27), 3.322 (3 H, s, OCH_3), 1.018 (3 H, s, C-19), 0.928 (3 H, d, *J* = 6.28 Hz, C-21), 0.906 (3 H, d, *J* = 6.58 Hz, C-28), 0.865 (3 H, d, *J* = 6.79 Hz, C-29), 0.723 (3 H, s, C-16); mass spectrum *m/z* (rel intensity) 442 (M^+ 4), 437 (3), 400 (5), 387 (6), 304 (3), 285 (12), 283 (12), 253 (16), 55 (100).

The procedure for the conversion of the 26,26-dimethyl-27-hydroxy-6β-methoxy-3α,5-cyclo-5α-cholest-23-enes **42** and **43** to the corresponding 26,26-dimethyl-cholesta-5,23-diene-3β-ols **29** and **31** is described above.

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Registry No. 1, 67314-15-2; **1** (acetate), 83187-97-7; **2**, 91279-13-9; **2** (acetate), 91279-16-2; **3**, 91279-14-0; **3** (acetate), 91279-17-3; **4**, 91279-15-1; **4** (acetate), 91279-18-4; **5**, 53603-94-4; **6**, 91228-89-6; **7**, 91228-90-9; **8**, 25819-77-6; **9**, 91228-91-0; (±)-**10**, 91228-92-1; (25*S*,26*S*)-**11**, 91228-93-2; (25*R*,26*R*)-**11**, 91279-19-5; (25*S*,26*S*)-**12**, 91228-94-3; (25*R*,26*R*)-**12**, 91279-20-8; (25*S*,26*S*)-**13**, 91228-95-4; (25*R*,26*R*)-**13**, 91279-21-9; (25*S*,26*S*)-**14**, 91228-96-5; (25*R*,26*R*)-**14**, 91279-22-0; (25*S*,26*S*)-**15**, 91228-97-6; (25*R*,26*R*)-**15**, 91279-23-1; (25*S*,26*S*)-**16**, 91228-98-7; (25*R*,26*R*)-**16**, 91279-24-2; **17**, 91228-99-8; **17** (tosylate), 91229-00-4; **18**, 91279-25-3; **18** (tosylate), 91279-28-6; **19**, 91279-26-4; **19** (tosylate), 91279-29-7; **20**, 91279-27-5; **20** (tosylate), 91279-89-9; **21**, 91229-01-5; **22**, 91279-30-0; **22** (tosylate), 91229-02-6; **23**, 91279-31-1; **24**, 91279-32-2; **25**, 91229-03-7; **26**, 91279-33-3; **27**, 91279-34-4; **28**, 91279-35-5; **29**, 91279-36-6; **30**, 38636-49-6; **31**, 38636-50-9; **33**, 91229-04-8; **34**, 91229-05-9; **35**, 91279-37-7; **36**, 91229-06-0; **37**, 91229-07-1; **38**, 91279-38-8; **39**, 91279-39-9; **40**, 91229-08-2; **41**, 91326-41-9; **42**, 91229-09-3; **43**, 91279-40-2; **44**, 91229-10-6; **45**, 91229-11-7; **46**, 91229-12-8; **47**, 91229-13-9; **48**, 91229-14-0; **49**, 91229-15-1; **51**, 73583-09-2; (23*R*,24*R*)-**52**, 91229-16-2; (23*R*,24*S*)-**52**, 91279-41-3; (23*S*,24*S*)-**52**, 91229-23-1; (23*S*,24*R*)-**52**, 91229-24-2; **57**, 27653-95-8; **58**, 91229-17-3; **59**, 91229-18-4; **60**, 91229-19-5; **60** (tosylate), 91229-21-9; **61**, 91229-20-8; **61** (tosylate), 91229-25-3; (γ)-2-bromo-4-methylpentane, 91229-22-0.

Supplementary Material Available: Selected 300-MHz ^1H NMR data of compounds **1–4**, **25–29**, and **33–49** are available (2 pages). Ordering information is given on any current masthead page.