(ddd, 1 H, J = 3, 5, 9 Hz), 5.11 (t, 1 H, J = 3 Hz), 5.42 (dd, 1 H, J = 2, 3Hz); mass spectrum, m/z (relative intensity, %) 303 (M^+, 1), 272 (6), 243 (11), 200 (43), 43 (100).

Benzyl Isoxazolidines 25 and 26. Nitrone **11** (0.11 g, 0.44 mmol) and excess vinylene carbonate (2.0 mL) were heated to 95 °C for 72 h. Flash chromatography (5:1 hexane/EtOAc) to remove excess vinylene carbonate, followed by PLC (2.0-mm plate, 3:1 hexane/EtOAc, two elutions), gave a 9:1 ratio of trans isomers **25** and **26** (0.12 g, 80%). High R_f isomer **25**: IR (CCl_4) 3030 (w), 2980 (m), 1830 (vs), 1140 (s), 1050 (s); NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.27 (s, 3 H), 1.36 (s, 3 H), 3.39 (dd, 1 H, J = 7, 8 Hz), 3.47 (dq, 1 H, J = 6, 7 Hz), 3.54 (d, 1 H, J = 8 Hz), 4.02 (d, 1 H, J = 12 Hz), 4.42 (d, 1 H, J = 12 Hz), 5.55 (d, 1 H, J = 5 Hz), 6.24 (d, 1H, J = 5 Hz), 7.35 (m, 5 H); mass spectrum, m/z (relative intensity, %) 335 (M^+, 1), 320 (2), 115 (11), 90 (100), 59 (13). Low R_f isomer **26**: IR (CCl_4) 3020 (w), 2980 (m), 1830 (vs), 1370 (m), 1140 (vs), 1050 (vs); NMR ($CDCl_3$) δ 0.85 (d, 3 H, J = 6 Hz), 1.34 (s, 3 H), 1.37 (s, 3 H), 3.48 (dq, 1 H, J = 3, 8 Hz), 3.61 (d, 1 H, J = 3 Hz), 3.87 (dq, 1 H, J = 6, 8 Hz), 3.96 (d, 1 H, J = 12 Hz), 4.53 (d, 1 H, J =12 Hz), 5.48 (d, 1 H, J = 5 Hz), 6.22 (d, 1 H, J = 5 Hz); mass spectrum, m/z (relative intensity, %) 335 (M^+, 1), 320 (3), 220 (2), 115 (10), 91 (100), 59 (13).

***N*-Benzyl Nitrone 27.** To a cooled mixture (0 °C) of benzylhydroxylamine (4.5 g, 28 mmol) and $CaCl_2$ (2.0 g) was added aldehyde **19** (4.0 g, 28 mmol) in ether (100 mL). The reaction mixture was stirred at 0 °C for 2 h, filtered and concentrated in vacuo. Column chromatography (85:15 EtOAc/MeOH) afforded the Z nitrone **27** (6.4 g, 93%). IR (neat) 3050 (w), 2920 (s), 1590 (m); NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.41 (s, 3 H), 1.48 (d, 3 H, J = 6 Hz), 4.04 (dq, 1 H, J = 6, 7 Hz), 4.38 (dd, 1 H, J = 6, 7 Hz), 4.89 (s, 2 H), 6.78 (d, 1 H, J = 6 Hz), 7.41 (s, 5 H); mass spectrum, m/z (relative intensity, %) 250 (M^+, 1), 205 (48), 91 (100).

Benzyl Isoxazolidines 28 and 29. Nitrone **27** (0.10 g, 0.43 mmol) and excess vinylene carbonate (2.0 mL) were heated at 90 °C for 72 h. Flash chromatography (3:1 hexane/EtOAc) yielded isoxazolidines **28** and **29** (0.11 g, 81%) as a 2:1 mixture of trans isomers which could be separated by HPLC (cyano column, 9:1 hexane/EtOAc). High R_f isomer **29**: IR (CCl_4) 3030 (w) 2960 (m), 1835 (vs), 1250 (s), 1100 (vs); NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.47 (s, 3 H), 3.40 (d, 1 H, J = 5 Hz), 3.89 (m, 2 H), 4.20 (m, 3 H), 5.30 (d, 1 H, J = 5 Hz), 6.11 (d, 1 H, J = 5 Hz), 7.35 (m, 5 H); mass spectrum, m/z (relative intensity, %) 321 (M^+, 1), 220 (15), 101 (23), 91 (100). Low R_f isomer **28**. IR (CCl_4) 3030 (w), 2960 (m), 1835 (vs), 1250 (s), 1100 (vs); NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.44 (s, 3 H), 3.42 (d, 1 H, J = 9 Hz), 3.79 (dd, 1 H, J = 6, 9 Hz), 4.01 (d, 1 H, J = 14 Hz), 4.22 (d, 1 H, J = 14 Hz), 4.27 (m, 2 H), 5.54 (d, 1 H, J = 5 Hz), 6.18 (d, 1 H, J = 5 Hz), 7.40 (m, 5 H); mass spectrum, m/z (relative intensity, %) 321 (M^+, 1) 220 (10), 101 (25), 91 (100).

Acknowledgment. We thank the National Institutes of Health GM/CA 30743-01) and the Pennsylvania State University Applied Research Laboratory/Navy Sea Systems Command for generous financial support. Alan Freyer, Greg Hancock, and Dr. Robert Minard were invaluable in helping to obtain spectral data. We acknowledge informative discussions with Drs. S. M. Weinreb (PSU), L. M. Jackman (PSU), J. Tufariello (SUNY-Buffalo), R. Friary (Schering Corp.), K. Houk (Pittsburgh), and R. Franck (CUNY, Hunter College). Partial support for the purchase of a Bruker WP-200 NMR spectrometer from the National Science Foundation is also acknowledged.

Registry No. 10, 84894-21-3; **11**, 84851-96-7; **12**, 84851-97-8; **14**, 84894-22-4; **17**, 91237-24-0; **18**, 91190-34-0; **19**, 15186-48-8; **20**, 91237-25-1; **21**, 91190-35-1; **22**, 91237-26-2; **23**, 91190-36-2; **24**, 91190-40-8; **25**, 91190-37-3; **26**, 91237-27-3; **27**, 91190-38-4; **28**, 91237-28-4; **29**, 91190-39-5; methylhydroxylamine, 593-77-1; 2,2,5-trimethyl-4-carboxaldehyl-1,3-dioxole, 91237-23-9; benzylhydroxylamine, 622-30-0; ethyl vinyl ether, 109-92-2; vinyl acetate, 108-05-4; vinylene carbonate, 872-36-6.

Supplementary Material Available: Experimental details, table of bond angles and lengths, and an ORTEP drawing of **21** (5 pages). Ordering information is given on any current masthead page.

Stereochemical Effects in Cyclopropane Ring Openings: Biomimetic Ring Openings of All Isomers of 22,23-Methylenecholesterol Acetate

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Abstract: By using the unique stereochemistry of the side chain in cholesterol, the dynamic influence of proximate chiral centers on the acid-promoted isomerizations of cyclopropanes is defined. Unexpectedly, when the cyclopropane is placed in the 22,23 position, either a backbone rearrangement is induced or a priori unanticipated side-chain olefins arise, each dependent on the stereochemistry of the cyclopropane starting material. The synthesis and sterochemical assignments of the four possible 22,23-methylenecholesterol acetates [22*R*,23*R* (**22**), 22*S*,23*S* (**23**), 22*S*,23*R* (**24**), 22*R*,23*S* (**25**)] are reported as well as the effect of stereochemistry on the acid-promoted isomerization of these compounds. Isomers **22** and **23** under the conditions of ring opening yield unexpected backbone rearrangement products of the 3β-acetoxy-(17*S*)-17,23-dimethyl-18-normethylcholest-5,13(**14**)-diene type (**32-35**), which can also be obtained from rearrangement of the $\Delta^{5,20(22)}$- and $\Delta^{5,17(20)}$-23-methylcholestadien-3β-ol acetates (**42**, **44**, **53**, **54**). The stereochemical criteria governing the course of these isomerizations are discussed.

The recent isolation[1] of 22(*R*),23(*R*)-methylenecholesterol (**1**) offers indirect support for the hypothesis that naturally occurring 23-methyl[2-4] and 22-methylene[5] substituted cholesterols may arise by enzymic isomerization of the corresponding 22,23-cyclopropane analogues. The involvement of an enzyme in the conversion of cycloeucalenol (**2**) to obtusifoliol (**3**) has been described.[6] Several

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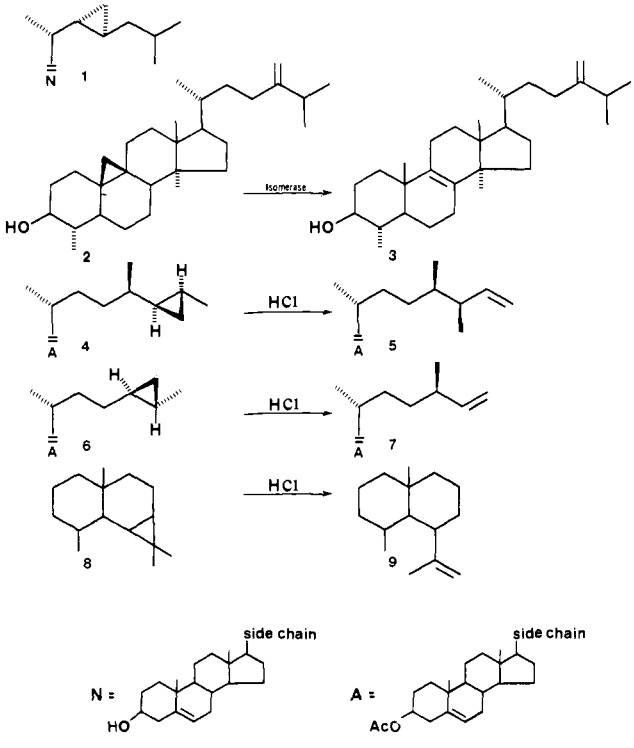
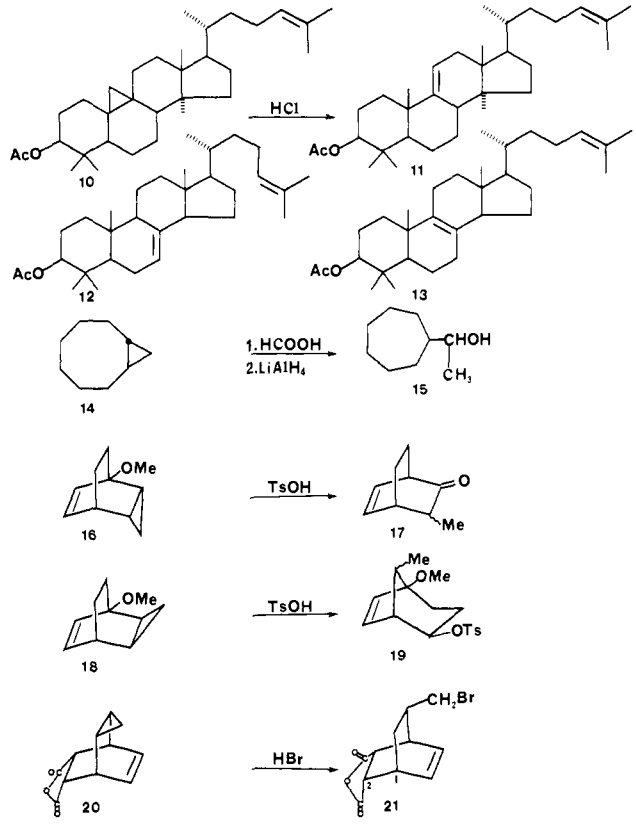
sterols containing cyclopropanes in their side chains (a feature unique to marine sterols) have been isolated, both in this laboratory,[1,7] and in others.[8] We have proposed[9] that a similar enzyme may act on this cyclopropyl substituent and have already demonstrated possible biomimetic counterparts to such a reaction in the acid-catalyzed cyclopropyl ring opening of petrosterol (**4**) to the naturally occurring 26-dehydro-25-*epi*-aplysterol (**5**)[10] and of 24,25-cyclocholesterol acetate (**6**) to (24*R*)-24-methyl-27-norcholesta-5,25-dien-3β-ol acetate (**7**),[11] thus providing a biomimetic route to the 27-norergostene-type marine sterols. We are particularly interested in the broader mechanistic aspects of this reaction, since cyclopropyl side-chain sterols offer a unique opportunity to examine the possible effect of subtle stereochemical alterations around the cyclopropane ring on its acid-catalyzed ring opening. The literature on this topic is relatively sparse.



In the classic approach, the acid-promoted ring cleavage of a cyclopropane is related to that of its olefinic counterpart, and ring cleavage is explained by a modified version of Markownikoff's rule which states that invariably the ring opens between the carbons bearing the largest and the smallest number of alkyl substituents.[12,13] Early structure elucidations of several natural products employed acid-promoted ring cleavage of a cyclopropane and the major product generally fits this rule.

Büchi unequivocally assigned structure **8** to maaliane based on the acid-promoted Markownikoff isomerization product **9**.[14] Spring applied this strategy to the more complex cycloartenol (**10**) and successfully deduced its structure from that of the major product **11**[15] of a mixture in which the minor products **12** and **13** have only recently been detected.[16] Several other cases have been noted[13] in which cyclopropyl steroids and terpenes give mixtures whose composition is not completely explained by this simple rule.

Inevitable complications arise in endeavors to decipher the stereochemical effects in the acid-promoted ring opening of a cyclopropane placed in the defined sterochemistry of a ring system. The effect of ring strain complicates the problem. For example, relief of the cis fusion in the B–C junction presumably plays a role in the isomerization of cycloartenol (**10**) because only the products in which this strain is eliminated occur, although others are possible (e.g., proton elimination from ring A). Also, the relief of medium ring strain may have played a role in the isomerization of the eight-membered ring cyclopropane **14** to the seven-membered ring isomerization product **15**.[18] Finally, an ultimate



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definition of stereochemistry occurs when the cyclopropane is placed in the rigid bicyclic systems **16**, **18**, and **20**. Here the ability of a σ bond to migrate antiperiplanar to the breaking cyclopropane bond plays a significant role in product formation.[19] The anhydride group in **20** retards migration of the C1–C2 bond and a totally different "anti-Markownikoff" product **21** results, whose origin is not completely understood.[19] These complications, compounded with the usual side reactions—nucleophilic addition of the solvent and product isomerization—have kept the broad mechanistic aspects of this reaction hidden.

In this paper and in the one that follows,[20] we avoid the complications of ring systems by defining the sterochemical environment of the cyclopropane by its placement in the proximity to a large chiral group, the steroid nucleus. Here we report synthetic work, stereochemical assignments, and results of ring opening of the four possible 22,23-methylenecholesterol acetates: 22*R*,23*R* (**22**), 22*S*,23*S* (**23**), 22*S*,23*R* (**24**), and 22*R*,23*S* (**25**).

Preparation of 22,23-Methylenecholesterol Acetates and Assignment of Side-Chain Cyclopropane Stereochemistry. The 22,23-methylenecholesterols were generated (Scheme I) in a manner previously established in this laboratory[21] with a few modifications that provided for the unambiguous assignment of stereochemistry. In general, a 6β-methoxy-3α,5-cyclo-5α-cholest-22-ene (*Z* isomer **23**, *E* isomer **27**) undergoes dichlorocarbene addition to produce two 22,23-dichloromethylenes (**28**, **29**, or **30**, **31**) which are then separated by reverse-phase high-performance liquid chromatography (HPLC), reduced by a dissolving metal reduction (Li/NH_3), hydrolyzed (*p*-toluenesulfonic acid, wet dioxane), and finally acylated (acetic anhydride, pyridine) to give the 22,23-methylene systems **22–25**.

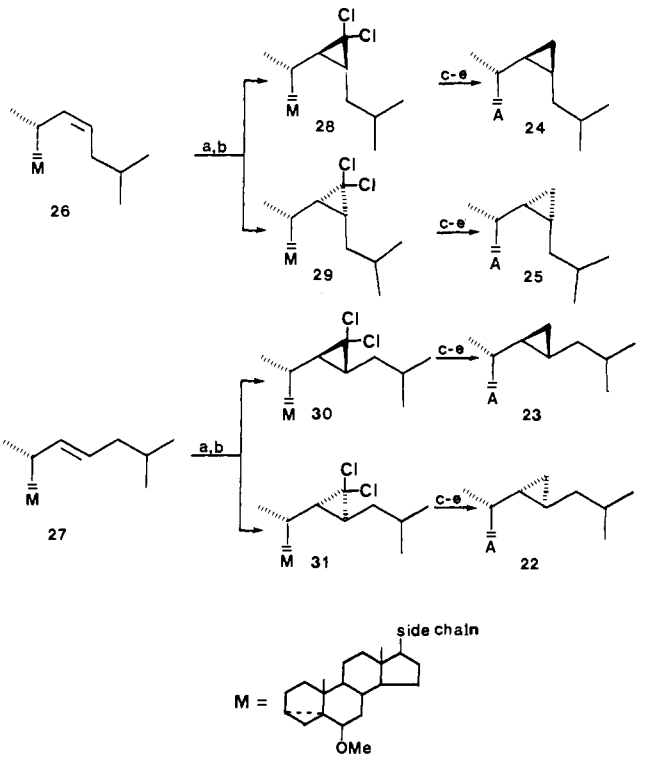
The starting olefin **26**[21] in crude form contains about 10% of the *E* isomer **27**. In the original procedure[21] this crude mixture was used directly in the sequential carbene cyclopropanation to produce four cyclopropanes (**28–31**) of which three were reported (**28**, **29**, **31**).[22] The elusive isomer **30** was not detected, owing to any of several possibilities: (a) the isomer's instability in base under long reaction times (6–9 days), (b) the relatively small amount of material being produced, or (c) the failure of separation from the predominant isomers. A modified synthesis was clearly needed in which cyclopropanation of the *E* isomer **27** could be conducted separately.

The cyclopropanation of the purified (HPLC) cis olefin **26** produced, as expected, only two isomers: the major dichlorocyclopropane **28** was assigned the stereochemistry 22*R*,23*S* and the minor, **29**, 22*S*,23*R*, based on the X-ray structure determinations of the cyclopropyl steroidal acetate **24** and the dichlorocyclopropane **29**. (Routine X-ray data, including ORTEP structures, are found in the supplementary section of this article.)

The side-chain conformations of the two structures **24** and **29** are defined by the torsions angles given in Table I. In each structure the cyclopropyl ring forces the C20–C22 and C23–C24 bonds to be cis coplanar. Although the structures **24** and **29** are isomeric at C22 and C23, the presence of the chlorine atoms in **29** causes both to have the same chiral designation of 22*R*,23*R*. The isomeric relationship between **24** and **29** results in very different orientations of the side chains. These conformations differ significantly from the conformational patterns found in a survey of 96 X-ray crystal structure determinations of cholestanes.[23]

For the generation of the "trans" systems (**22** and **23**), a pure source of (22*E*)-6β-methoxy-3α,5-cyclo-5α-cholest-22-ene (**27**) was required. The expedient source was the inversion of the *Z* olefin **26** using the method of Vedejs and Fuchs.[24] The pure cis olefin **26** was epoxidized (MCPBA) and the resulting 22,23-epoxides deoxygenated (forced rotation of C22–C23) with lithium diphenylphosphide followed by treatment with methyl iodide. Although the yield of **27** was only a modest 58%, the product was pure. Sequential cyclopropanation (86%) produced the dichlorocyclopropanes **30** and **31** in a ratio of 2:3. These two isomers were conveniently separated (HPLC), reduced, and hydrolyzed in the usual manner to **23** and **22** in high yield. The assignment of the relative stereochemistry (22*S*,23*S* for **23** and 22*R*,23*R* for **22**) is based on X-ray data in a previous synthesis of these compounds from our laboratory.[1,25]

Scheme I. Synthesis of Four Isomers of 22,23-Methylenecholesterol Acetate



(a) :CCl_2, (b) HPLC separation, (c) Li/NH_3, (d) PTSA/wet dioxane, (e) acetic anhydride, pyridine.

Table I. Torsion Angles (deg) Defining the Side-Chain Conformation

angles	bonds	24	31
ω_1	C(13)–C(17)–C(20)–C(22)	−174.7	176.9
ω_2	C(17)–C(20)–C(22)–C(23)	−94.1	−170.3
ω_3	C(20)–C(22)–C(23)–C(24)	−1.2	3.4
ω_4	C(22)–C(23)–C(24)–C(25)	−151.4	163.7
ω_5	C(23)–C(24)–C(25)–C(26)	−60.2	−37.8
ω_6	C(23)–C(24)–C(25)–C(27)	177.5	180.0

Course of Cyclopropane Ring Opening. Early studies in this[26] and other[27] laboratories employed HCl gas in acetic acid to promote the cyclopropane ring opening. These conditions led to extensive losses of primary reaction products due to HCl addition to both the side chain and the Δ^5 double bond. This problem was even more pronounced in our efforts to open a cyclopropane in the 22,23 position owing to the longer reaction times required. Table II contains preliminary results of the HCl-promoted ring cleavage of the 22*S*,23*R* (**24**) and the 22*R*,23*S* (**25**) cyclopropanes.

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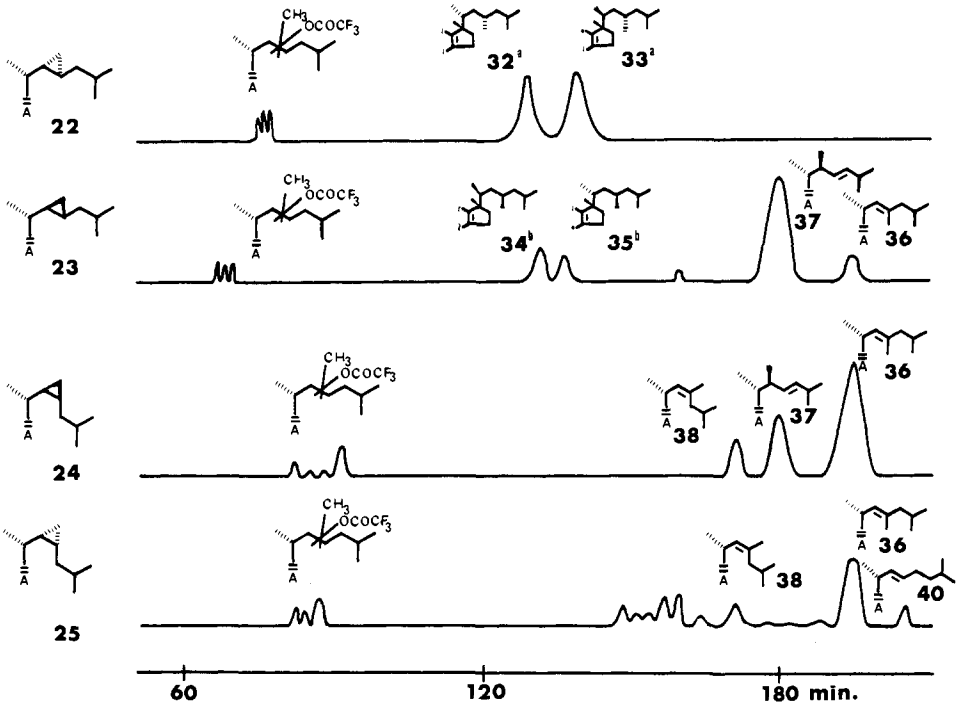


Figure 1. Reverse-phase HPLC separation of the products from TFA-promoted ring cleavages of 22,23-methylenecholesterol acetates. (Assignments labeled a and b may be reversed.)

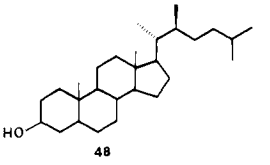
Table II. Course of HCl-Promoted Ring Opening

From (22S,23R)-(24) Reaction time: Four hours		From (22R,23S)-(25) Reaction time: Six hours	
[24]	26%	[25]	27%
[36]	6%	[36]	3%
[38]	3%	[45]	2%
[37]	16%	[40]	2%
Chlorinated or undetermined	49%	Chlorinated or undetermined	66%

Under these conditions, unreacted substrate, nucleophilic addition, and olefin isomerization competed to such a large extent that mechanistic evaluations were fruitless.

To minimize the side and secondary reactions, we chose trifluoroacetic acid (TFA), known for its low nucleophilicity.[28] In a model experiment, cholesterol acetate was recovered in 97% yield after 1 week exposure to 5% TFA in benzene. The steroidal cyclopropanes **22–25** were isomerized in 5% TFA for 72 h. By then, three of steroidal cyclopropanes had been isomerized to a large extent (73–41%) to separable (HPLC) products. Under these conditions the steroidal cyclopropane **25** underwent the lowest conversion (25%) and led to the most complex mixture of products. The record of the product separation is reproduced in Figure 1. The products (Figure 1 and Table III) could be grouped by their chromatographic retention times into two sets: nucleophilic addition products with relatively short retention times (<100 min), and isomerization products with longer retention times (>100 min). The former, addition products of TFA, were complex mixtures that were not investigated. The latter isomerization products were easily characterized from data on compounds previously synthesized in this laboratory.[29] The spectral data were available not only for the observed side-chain olefin products (Table IV) [23-methyl-Δ^{22}-*E*-(**36**),[29] 23-methyl-Δ^{22}-*Z*-(**37**),[29] and the homodehydro- (**40**)[10] sterols] but also for all but one of the possible olefins derived directly from a carbonium ion at position 22 or 23 (Table V). The synthesis of the missing 22-methyl-Δ^{23} isomer (**37**) is described below. Direct comparisons were accomplished by NMR, MS, and chromatographic properties.

Compound **37** (Figure 1 and Table III) was an unknown sterol but was assigned the structure 22(*S*)-methylcholesta-5,23(*E*)-dien-3β-ol acetate by the NMR and mass spectra of the corresponding free sterol: the NMR spectra (Table IV) showed the presence of four methyl groups and a trans double bond in the side chain. Structure **37** was confirmed by the high-resolution mass spectrum where the most intense peak is consistent with the fission of the allylic C20–C22 bond. Hydrogenation of **37** led to 22(*S*)-methylcholesterol (**48**), previously synthesized by a stereospecific Claisen rearrangement from 24(*S*)-hydroxycholesta-5,22-dien-3β-ol.[30]



48

The 22-epimer of **37**, 22(*R*)-methyl-Δ^{23} olefin (**39**), was a theoretically expected product from the 22*R* cyclopropanes **22** and **25**. Its presence could be ruled out totally in the reaction of the natural trans cyclopropane **22** by the chromatographic simplicity of the reaction mixture. This was not the case with the isomerization of the cis cyclopropane **25**. Here the rate of cyclopropane isomerization was abnormally slow, and the side reactions (olefin isomerizations and nucleophilic additions) made the analysis more complex. Some of these by-products were shown to result from the isomerization of the major product **36**, a tri-

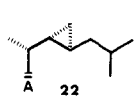
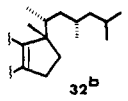
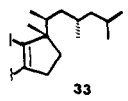
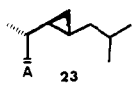
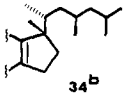
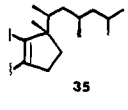
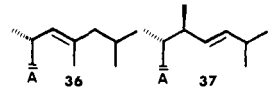
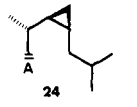
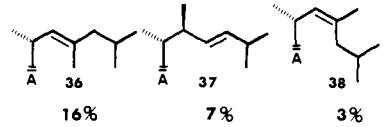
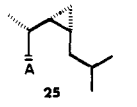
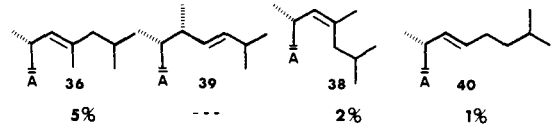
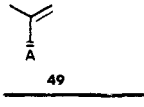
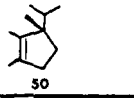
(28) Peterson, P. E.; Thompson, G. *J. Org. Chem.* **1968**, *33*, 968–972.

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

(30) Zielinski, J.; Li, H.-T.; Djerassi, C. *J. Org. Chem.* **1982**, *47*, 620–625.

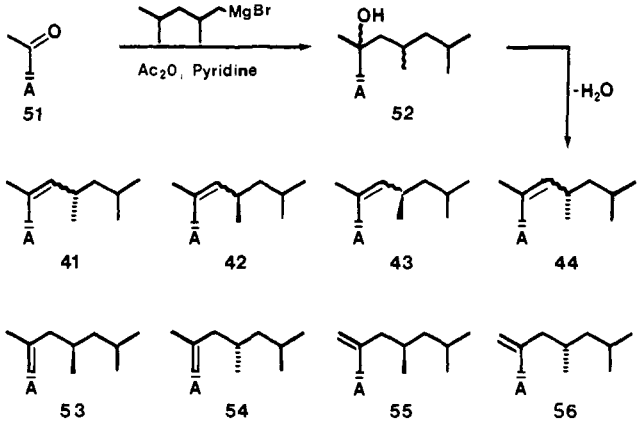
(31) Kohen, F.; Mallory, R. A.; Scheer, I. *J. Org. Chem.* **1971**, *36*, 716–718.

Table III. Isomerization Products[a]

starting materials	backbone rearrangement	simple ring openings	starting material recovered	unidentified
 22	 32[b] 14%  33 26%		27%	5%
 23	 34[b] 6%  35 9%	 36 9% 37 17%	38%	9%
 24		 36 16% 37 7% 38 3%	24%	4%
 25		 36 5% 39 --- 38 2% 40 1%	75%	8%
 49	 50			

[a] The difference between 100% and the sum of these per cents is the yield of side-chain acetates. [b] The assignment of stereochemistry for the methyl group at C-20 is arbitrary.

Scheme II



substituted olefin, but our analysis did not encompass all minor products (>1%), so that the presence of a 22(*R*)-methyl-Δ^{23} olefin (**39**) cannot be ruled out unequivocally.

A potentially important stereochemical effect was suggested by the conspicuous absence of the 23-methylcholesta-5,20-diene-3β-ol acetates (**41–44**, Table V) under the reaction conditions of our steroidal cyclopropane openings. Since none formed (Figure 1), we expected them to be unstable under these conditions. Therefore, we synthesized (Scheme II) eight stereoisomers:[32] 23-methyl-$\Delta^{17(20)}$, -$\Delta^{20(22)}$, and -$\Delta^{20(21)}$ olefins (**41–44**, **53–56**). Grignard condensation of 2,4-dimethyl-1-bromopentane with

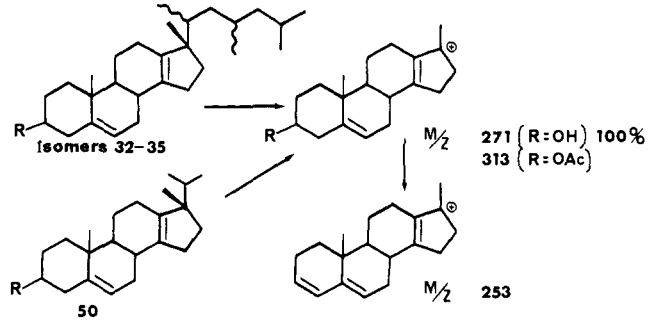


Figure 2. Mass spectral fragmentation of isomers **32–35**.

pregnenolone acetate (**51**) followed by dehydration[33] of the alcohol **52** gave the eight olefin isomers (**41–44**, **53–56**). The NMR spectra of the $\Delta^{20(22)}$ isomers **41–44** of this set are described in Table V.[34] For our purposes, the most important generalization from these collected NMR data is that the $\Delta^{20(22)}$ bond can be characterized by a singlet methyl absorption (C18) at ca. 0.5 ppm. This observation appears to be general for a series of alkyl side chains.[35] Since none of our isolated isomerization products possessed an absorption more upfield than 0.6 ppm, the presence of a $\Delta^{20(22)}$ olefin (**41–44**) was definitely excluded.

Most interesting was the appearance (Figure 1) of the *saturated* side-chain products **32**, **33**, **34**, and **35** which were transformed to the free sterols for mass spectral analysis. The spectra of all four compounds were identical-- the most important peaks corresponding to loss of a saturated side chain with formation of a highly stabilized tertiary allylic carbonium ion (*m/z* 271) and *m/z* 253 due to subsequent loss of water, a type of fragmentation characteristic of Δ^{13} sterols (Figure 2).[31] This assignment was

(32) Actually, there are 10 isomers possible. Two were not detected, presumably because they occurred in such low yield. Those missing are the *Z* isomers of the $\Delta^{17(20)}$ olefins **53** and **54**. For a related reaction see: Ness, W. R.; Varkey, T. E.; Crump, D. R.; Gut, M. *J. Org. Chem.* **1976**, *21*, 3429. These workers report the C21-methyl signal at 1.68 for the *E* isomer and 1.55 for the *Z* isomer. Since our $\Delta^{17(20)}$ isomers exhibited C21-methyl absorption at 1.661, both have been assigned the *E* stereochemistry. Ness et al. further report that the chromatographic mobility of the $\Delta^{17(20)}$ *Z* isomer is grossly different from that of its *E* isomer and that it is more polar than either the $\Delta^{17(20)}$ *E* or the $\Delta^{20(22)}$ isomers. We are therefore confident that, under our conditions of HPLC separation, the $\Delta^{17(20)}$ *Z* and *E* isomers must separate (see Experimental Section).

(33) Roller, P.; Tursch, B.; Djerassi, C. *J. Org. Chem.* **1970**, *35*, 2585–2593.

(34) In the HPLC fractionation of the reaction mixture, three of the $\Delta^{20(22)}$ isomers (**43**, **44**, **45**) were obtained in reasonable (>90%) purity. The spectrum for **42** was obtained from a HPCL fraction that contained 60% **43**, but since the spectrum of pure **43** was available, that of **42** could be generated by subtraction.

(35) Schmit, J. P. *J. Org. Chem.* **1975**, *40*, 1586–1588.

Table IV. Spectral Data of Isomerization Products from 22,23-Methylenecholesterol Acetates

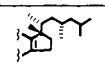
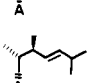
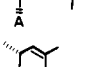
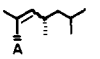
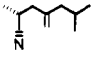
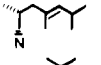
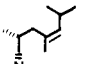
	chemical shift						
	C-18	C-19	C-21	C-28	C-26,27	side-chain olefinic	C-17 methyl
 **32**	none	0.996	0.868 (6.54)	0.818 (6.36)	0.813/0.813	none	0.985
 **33**	none	0.994	0.783 (6.45)	0.680 (6.70)	0.854/0.851 (6.63)/(6.53)	none	0.979
 **34**	none	0.996	0.801 (6.69)	0.754 (6.47)	0.841/0.848 (6.60)/(6.60)	none	0.987
 **35**	none	0.996	0.848 (6.72)	0.690 (6.78)	0.883/0.823 (6.64)/(6.60)	none	0.987
 **36**	0.712	1.021	0.940 (6.51)	1.557	0.811/0.835 (6.21)/(6.27)	4.877 (9.61)	
 **37**	0.691	1.017	0.753 (6.70)	0.790 (6.82)	0.965/0.965 (6.61)/(6.61)	5.320 dd (12.04, 5.3)	
 **38**	0.702	1.021	0.923 (6.59)	1.608 (0.08)	0.889/0.840 (6.35)/(6.47)	4.945 (9.78)	
 **40**	0.685	1.018	0.998 (6.80)	none	0.865/0.862 (6.62)/(6.80)	5.252	

Table V. Spectral Data of Theoretically Possible Products of the Ring-Opening Reaction

	chemical shift[a]						
compd	C-18	C-19	C-21	C-28	C-26,27	olefinic	ref
 **41**[b]	0.585[b]	1.022	1.638 (0.8)	0.880 (6.47)	0.857/0.766 (6.47)/(6.00)	4.913 (9.52)	
 **42**	0.538	1.018	1.638 (0.8)	0.888 (6.66)	0.858/0.837 (6.54)/(6.37)	4.912 (8.80)	
 **43**[b]	0.584[b]	1.021	1.638 (0.8)	0.879 (6.67)	0.857/0.764 (6.52)/(5.87)	4.818 (8.31)	
 **44**	0.543	1.017	1.626 (0.8)	0.880 (6.71)	0.858/0.836 (6.35)/(6.31)	4.815 (9.29)	
 **45**	0.709	1.012	0.904 (6.04)		0.833/0.857 (5.99)/(5.71)	4.694 4.709	29
 **46**	0.701	1.010	0.803 (6.04)	1.546	0.926/0.926 (6.70)/(6.70)	4.904 (8.97)	29
 **47**	0.703	1.013	0.827 (6.51)	1.602	0.891/0.909 (6.59)/(6.59)	4.993 (9.64)	29

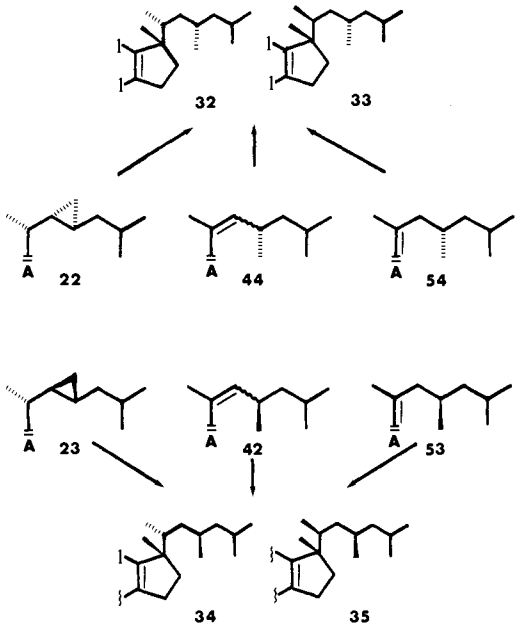
[a] 360-MHz ^{1}H NMR data: shifts are given in parts per million and the J values in parentheses are given in hertz. [b] These assignments may be interchanged. Free sterols (N) and the corresponding acetates (A) have comparable shifts.

further supported by the isomerization of the model 17β-isopropenyl-Δ^5-androsten-3β-ol acetate (**49** in Table III) to the methyl migrated product **50** (Figure 2), which displayed the same diagnostic mass spectral peaks as the four isomeric sterols **32**, **33**, **34**, and **35**, with longer side chains.

The 18-normethyl structures **32–35** arising from methyl migrations were further supported by the NMR data (Table IV). Each of the four NMR spectra contained two methyl singlets within the normal shift range (0.98–0.99 ppm) of a Δ^5-3β-hydroxy steroid. The proposed structures **32–35** possess two methyl groups which are both tertiary and allylic to a double bond (C19-methyl and rearranged C18-methyl now attached at C17). The NMR methyl region also supports two secondary methyl groups in addition to those at C26,27. These methyl shifts vary (cf. Table IV), suggesting epimeric relationships at C21 and C23.

Under the reaction conditions (5% TFA in benzene) of steroidal cyclopropane ring openings, all eight synthetic 23-methyldehydrocholesterol acetates (**41–44** and **53–56**) isomerized to 18-normethyl rearrangement products, i.e., the same products that had arisen (cf. Figure 1 and Table III) from the trans cyclopropanes **22** and **23**. Specifically, we found that the $\Delta^{20(22)}$ olefin **42**, the (22*S*,23*S*)-steroidal cyclopropane **23**, and the $\Delta^{17(20)}$ olefin **53** all gave the same two rearrangement products **34** and **35** (Scheme III). On the other hand, the $\Delta^{20(22)}$ olefin **44**, the (22*R*,23*R*)-steroidal cyclopropane **22**, and the $\Delta^{17(20)}$ olefin **54** yielded the other set of rearrangement products **32** and **33** (Scheme III). In the $\Delta^{20(22)}$ olefins (**41–44**), and even more assuredly in the $\Delta^{17(20)}$ olefins (**53**, **54**), the 23-methyl group is not affected by this reaction, and this functionality, therefore, must also be present in the rearrangement products (**32–35**) with the same C23 stereochemistry as that of the respective starting materials. Since the stereochemistry of the 23 position in the cyclopropane starting materials (**22** and **23**) was known, we were able to assign the stereochemistry to the 23-methyl olefins (**42** and **53** as 23*R*; **44**

Scheme III

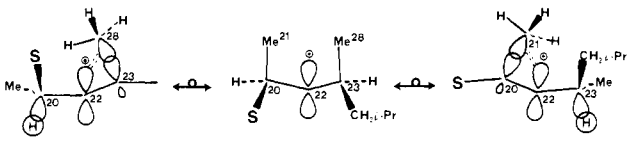


and **54** as 23*S*) by the isomerization products generated.

That a $\Delta^{17(20)}$, $\Delta^{20(22)}$ olefin or a 22,23-cyclopropane all rearrange in acid to only two 18-normethyl isomers has mechanistic significance. We also note in the isomerization of the model system **49** (Table III), as have others[36] in related systems, that the migration of a C18-methyl to C17 is stereospecific—only isomer **50** being formed. Thus, only the 21 position is left stereochemically undefined in Scheme III, an observation which is consistent with a carbonium ion mechanism of the type discussed below.

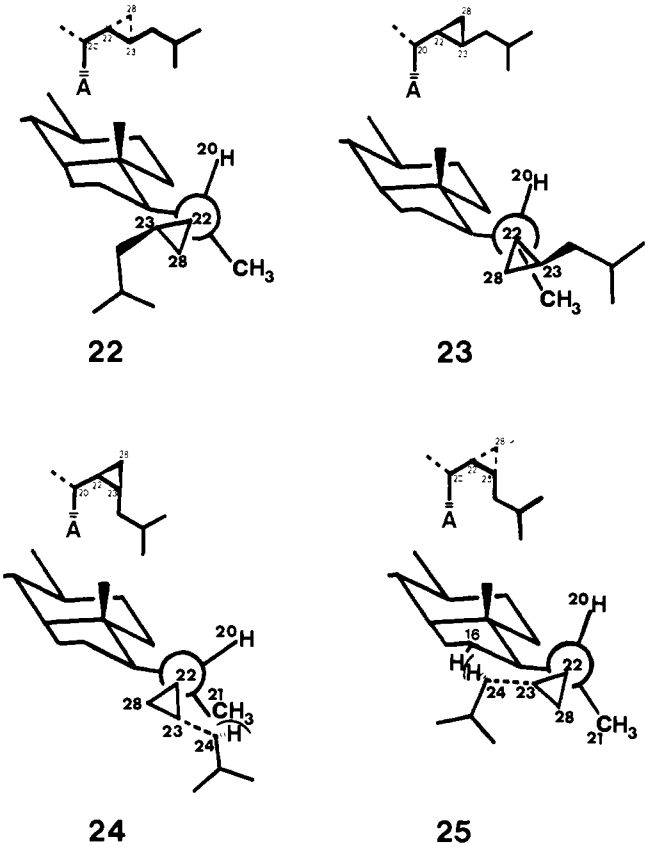
Stereochemical and Mechanistic Aspects of Cyclopropane Ring Opening. Aside from the above-mentioned observation that 23-methylcholesta-5,20-diene-3-ol acetates (**41–44**) are absent in the acid-catalyzed isomerization of all four 22,23-methylenecholesterol acetates (**22–25**), a second mechanistically significant fact (cf. Table III and Figure 1) is that not all 22,23-methylenecholesterol isomers form 18-normethyl rearrangement products. Does this mean that the ability of two (**22** and **23**) of the steroidal cyclopropanes to form 18-normethyl rearrangement products (**32** and **33** or **34** and **35**) is related to the ability to initially produce $\Delta^{20(22)}$ olefins (**41–44**)?

Mechanistic considerations might begin by considering the fate of a totally planar carbonium ion generated at C22 by a totally nonconcerted cleavage of the C22–C28 bond: Energetically, such



a carbonium ion can seek two forms of stabilization—solvation or neighboring group participation. Solvation will obviously be affected by the conformation of the side chain and the ability of the gegenion to approach. This effect probably determines the relative reactivities of the steroidal cyclopropanes **22–25**. More important to this mechanistic argument is the stabilization through neighboring group participation from the adjacent methyl groups attached to C20 and C23. To the planar carbonium ion **57**, these methyl groups are equivalent in their ability to stabilize the carbonium ion, which would make proton loss from C20 (i.e., **57a**) as likely as proton loss from C23 (i.e., **57b**).

Scheme IV



However, we know from the observed product composition (Table III and Figure 1) that this is not true. The trans cyclopropanes (**22** and **23**) favor reaction through proton loss from C20 (via **57a**), whereas the cis cyclopropanes (**24** and **25**) completely bypass this route. The alternative reaction pathways—proton loss from C23 (via **57b**) or loss from C24 with cleavage of the C23–C28 cyclopropane bond—account for the predominant primary side-chain olefinic products (**36** and **37**). Thus the methyl groups at C20 and C23 are not equivalent in their stabilizing abilities and the observed difference must be associated with the stereochemistry of the reacting centers.

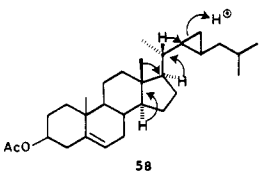
Timing along the reaction coordinate during the acid-promoted ring cleavage differentiates the two methyl groups. During the breaking of the C22–C28 bond, the methyl group at C23 (as in **57a**) has already adopted the conformation needed to stabilize the developing carbonium ion at C22. Therefore this conformation has priority in determining the nature of the reaction, and the reaction form approaches that of a concerted elimination of a proton with simultaneous cleavage of the cyclopropane.

Multiple side-chain conformations are available to the steroid cyclopropanes (**22–25**) but the subset that distinguishes them in reactivity is the set of rotations about the C20–C22 bond. More specifically, the optimum geometry for the formation of a $\Delta^{20(22)}$ double bond is the one in which the C20–H bond forms a trans antiperiplanar relationships with the breaking C22–C28 bond. This alignment allows for maximum overlap of the developing p orbitals on C20 and C22. Scheme IV portrays the Newman projections of the four steroidal cyclopropanes (**22–25**). Each representation is focused along the C20–C22 bond and the C20–H bond is antiperiplanar to the C22–C28 bond. For the trans-derived systems (**22** and **23**), this alignment is easy, but in the cis cyclopropanes (**24** and **25**) severe steric interactions occur between C24–H and C21–H or between C16–H and C24–H. This accounts for the product selectivity between the cis and trans steroidal cyclopropanes.

Somewhere along the reaction coordinate to C20 olefin generation, the criteria for a sequential (or synchronous)[36] reaction

(36) This 1,2 shift of the C18 methyl group (the Kägi–Miescher rearrangement) followed by deprotonation to give the 13,14-tetrasubstituted double bond has been observed in other systems: (a) VanTamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937–5938. Marx, M. *Ibid.* **1969**, *91*, 2371.

are met. Adjacent to C20 are three tertiary and quaternary centers, each with a migrating group with the correct stereochemistry for a sequential migration: The rigid stereochemical



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requirements for these migrations in the nucleus have been well documented,[36,37] and methyl migrations arising from carbonium ion generation at C20 have been noted.[31] However, some question remains as to how concerted this reaction is in the side chain. Partial epimerization at C20 (the only chiral center in the side chain) forces the assignment of sp^2 character at this center. Final support for this partially nonconcerted path is the observation that the rearrangement products (**32–35**) can be obtained both from a $\Delta^{17(20)}$ olefin (such as **53** or **54**) or a $\Delta^{20(22)}$ olefin (**42** or **44**). The fact that the most favored reaction occurs via loss of a tertiary proton (from C20) suggests that olefins (such as **42**, **43**, **53**, **54**, Scheme III) may even be intermediates.

Conclusion

The product distribution (Figure 1 and Table III) from the isomerization of the four possible 22,23-methylenecholesterol acetates (**22–25**) indicates that in the absence of ring constraints, proximate chiral centers influence the acid-promoted isomerizations of cyclopropanes. In the reactions studied in this paper, the most favored mode of reaction was the loss of a tertiary proton trans antiperiplanar to the breaking (or broken) cyclopropane bond. For 22,23-methylenecholesterols, this proton was at C20 and a backbone rearrangement was initiated that culminated in the migration of the C18 methyl group to C17 and double bond formation at C13(14). When this reaction pathway was precluded by steric interactions, tertiary proton elimination (at C23) through carbonium ion intermediates (forming **36**) competes with elimination of secondary protons (at C24) which have available trans antiperiplanar relationships to a breaking (or broken) cyclopropane bond (to form **37**).

Most discussions on the origin of sterols stop at the cyclization of squalene-type precursors and the appropriate 1,2-migrations to adjust the functionality of the nucleus. Our results show that the same chemistry may be extended to the side chain where subtle conformational effects determine the path of reaction.

Experimental Section

General Procedures. Low-resolution 70-eV mass spectra were obtained with a Finnigan MAT-44 spectrometer with a source temperature of 160 °C. High-resolution mass spectra were recorded on a Finnigan MAT-711 double-focusing spectrometer with a direct-inlet system for sample introduction and a PDP-11/45 computer for data acquisition and reduction.

Nuclear magnetic resonance spectra (NMR) were recorded on a Nicolet 300-MHz nuclear magnetic resonance spectrometer, a Bruker HXS-360 spectrometer equipped with a Nicolet TT 1010-A computer (^{1}H NMR), and a Varian FT 80 A spectrometer (^{13}C NMR). All NMR spectra were taken in $CDCl_3$ solution unless otherwise indicated. ^{13}C NMR spectra were recorded by Dr. J. N. Shoolery (Varian Associates).

Melting points are uncorrected and were determined on a Thomas-Hoover "Unimelt" capillary melting point apparatus. Analytical gas–liquid chromatography (GLC) was performed 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 a 3% SP 2250 on GCQ (100–120 mesh). The oven temperature was 260 °C with helium as the carrier gas at a flow rate of 100 mL/min. Retension times (rrt) are recorded relative to that of cholesterol.

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} precoated (0.2 mm) aluminum sheets (E. Merck). The TLC sheets were developed in hexane/ethyl acetate 10:1 and visualized by spraying with a ceric sulfate solution (25 g in 1 L of 25% sulfuric acid) followed by heating. Column chromatography was carried out on E. Merck silica gel 60 (70–230 mesh ASTM) with hexane/ethyl acetate 9:1 as the eluent.

High-performance liquid chromatography (HPLC) was used for preparative-scale separation of diastereoisomeric sterol mixtures as well as for monitoring of product purification and was performed by using a Waters Associates HPLC unit (M 6000 pump, UK 6 injector, R 403 differential refractometer) and two different reversed-phase columns: Whatman Partisil M9 10/50 ODS-2 (9 mm i.d. × 50 cm), with absolute methanol as the mobile phase; Altex Ultraspere ODS 5-μm (10 mm i.d. × 25 cm), with methanol/water 97:3 as the mobile phase. The flow rate was 3 mL/min.

The progress of all reactions and of column chromatography was monitored by TLC and/or GLC. All solvents were purified as necessary before use according to standard procedures. Abbreviations are as follows: t_R = retention time, RV = rotary evaporator.

Synthesis of 22,23-Methylenecholesterol Acetates. 6β-Methoxy-3α,5-cyclo-5α-cholest-22-enes (26 and 27). (20*S*)-6β-Methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde was prepared in the manner of Salmond.[40] To a suspension of isoamyltriphenylphosphonium bromide (2.4 g) in ether (25 mL) was added *n*-butyllithium (2.4 N, 2 mL), and the resulting orange solution was stirred at room temperature for 1 h and then the aldehyde (1.0 g, 3 mmol) was added. When a TLC monitor showed the reaction to be complete, the mixture was poured into water (100 mL) and extracted with hexane (3 × 100 mL). The combined organic fraction was washed with water (3 × 70 mL) and brine (50 mL) and dried over sodium sulfate. Evaporation under reduced pressure gave 1.02 g of a white solid. Purification first by column chromatography (40 g of silica gel, hexane/ethyl acetate 10:1) and then by reversed-phase HPLC (Altex, methanol) to give about 56% yield of Δ^{22} olefins. Reversed-phase HPLC (Altex, methanol) separated this mixture into two fractions containing pure *Z* and *E* olefins.

***Z* Olefin 26** (88%): HPLC (methanol) t_R 69 min; ^{1}H NMR (360 MHz) δ 5.18 (m, 2 H, C22 and C23), 3.321 (s, 3 H, OCH_3), 2.77 (m, 1 H, C6), 1.025 (s, 3 H, C19), 0.949 (d, *J* = 6.6 Hz, 3 H, C21), 0.906, 0.888 (2d, *J* = 6.34, 5.50 Hz, C26,27), 0.754 (s, 3 H, C18); IR 1110 (OCH_3), 1385 cm^{-1} (*gem*-dimethyl); low-resolution mass spectrum *m/z* (rel intensity) 398 (weak), 255 (06), 69 (100).

***E* Olefin 27** (12%): HPLC (methanol) t_R 72 min; ^{1}H NMR (360 MHz) δ 5.35–5.15 (m, 2 H, C22 and C23), 3.32 (s, 3 H, OCH_3), 2.77 (m, 1 H, C_6), 1.019 (s, 3 H, C19), 0.999 (d, *J* = 6.62 Hz, C21), 0.859, 0.855 (2d, *J* = 6.62, 6.62 Hz, 6 H, C26,27), 0.725 (s, 3 H, C18); IR 1100 (OCH_3) 950 cm^{-1}; low-resolution mass spectrum *m/z* (rel intensity) 398 (<5), 343 (04), 255 (10), 69 (90), 55 (100).

Isomerization of the Cis Olefin 26 to the Trans Olefin 27. The Δ^{22} cis i-methyl ether **26** (268 mg, 0.67 mmol) and MCPBA (176 mg, 1 mmol) in 10 mL of methylene chloride was stirred at room temperature for 7 h. At this time TLC (hexane/ethyl acetate 10:1) showed the total loss of the olefin (R_f 0.43) and the appearance of two epoxide products (R_f 0.33, 0.30). The reaction mixture was then diluted with brine and extracted (2 × 3 mL) with methylene chloride. The combined organic layers were washed (2 × 3 mL) with saturated sodium bicarbonate, dried (Na_2SO_4), and concentrated to give 0.263 mg of a yellow oil. Short-path column chromatography (4 g of silica gel, hexane/ethyl acetate 10:1) gave 250 mg (90%) of a clean epoxide fraction consisting of two epoxides separated by reversed-phase HPLC (Altex, methanol): the major fraction (90%) had HPLC t_R 62 min; ^{1}H NMR (360 MHz) δ 3.328 (s, 3 H, OCH_3), 3.03 (m, 1 H, C23), 2.78 (m, 1 H, C5), 2.6 (dd, 1 H, C22), 1.107 (d, *J* = 6.45 Hz, 3 H, C21), 1.027 (s, 3 H, C19), 1.004, 1.003 (2d, *J* = 6.24 Hz, 6.8, 6 H, C26,27), 0.721 (s, 3 H, C18); low-resolution mass spectrum *m/z* (rel intensity) 414 (<5%), 399 (<5), 372 (<5), 359 (<5), 55 (100); the minor fraction (10%) had HPLC t_R 67 min; ^{1}H NMR (360 MHz) δ 3.322 (s, 3 H, OCH_3), 2.88 (m, 1 H, C23), 2.78 (m, 1 H, C5), 2.62 (m, 1 H, C22), 1.025 (s, 3 H, C19), 0.998 (d, *J* = 6.62 Hz, 3 H), 0.988 (d, *J* = 6.41 Hz, 3 H), 0.971 (d, *J* = 6.07 Hz, 3 H), 0.726 (s, 3 H, C18).

Lithium diphenylphosphide (30-fold excess, 0.12 mmol/mL in THF) was added (under argon) portionwise to the crude epoxide of **26** (155.6 mg, 0.38 mmol) in 10 mL of THF (dry) at a rate that maintained the orange color of the reagent for 12 h. An excess of methyl iodide (1 mL) was added and after 30 min, TLC (hexane/ethyl acetate 10:1) showed most of the starting material (R_f 0.42) had been converted to the trans olefin **27** (R_f 0.50). The reaction mixture was then poured into water

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(20 mL) and the resulting mixture was extracted with ether (3 × 15 mL); the combined extracts were dried (Na_2SO_4) and concentrated. Short-path column chromatography (4 g of silica gel, hexane/ethyl acetate 10:1) followed by reversed-phase HPLC (ODS-2, methanol) gave 61 mg (58% based on lost starting material) of pure trans olefin **27** and 40 mg of recovered epoxides (spectra as before).

Dichlorocarbene Addition to 26. Aqueous sodium hydroxide (50%, 0.5 mL) was added to a cooled solution, (0 °C) of the *i*-methyl ether **26** (62 mg, 0.16 mmol) and benzyltriethylammonium chloride (BTEAC, 25 mg, 0.11 mmol) in 5 mL of chloroform. After 3 days, the reaction mixture was diluted with an equal volume of water and extracted with chloroform (3 × 1 mL). The combined organic fraction was washed with brine (2 × 1 mL) and concentrated under reduced pressure. After purification of this crude material by column chromatography (silica gel (6.0 g), hexane/ethyl acetate 10:1), the products were separated by reversed-phase (Altex, methanol/water 97:3) to give fractions A–C, in a ratio 85:11:04. In a similar reaction where the reaction time was 6 days, the ratio was 10:60:18 (A:B:C).

Fraction A: HPLC t_R 160 min. This fraction was previously shown to be the starting material.[21]

Fraction B: HPLC t_R 180 min. (22*R*,23*S*)-22,23-(Dichloromethylene)-6β-methoxy-3α,5-cyclo-5α-cholestane (28): ^{1}H NMR (360 MHz) δ 3.324 (s, 3 H, OCH_3), 1.211 (d, *J* = 5.39 Hz), 1.023 (s, 3 H, C19), 1.008, 0.997 (2d, *J* = 6.62, 6.65 Hz, C26,27), 0.705 (s, 3 H, C18). Previously, this fraction was incorrectly assigned the 22*S*,23*R* stereochemistry.[21]

Fraction C: HPLC t_R 194 min. (22*S*,23*R*)-22,23-(Dichloromethylene)-6β-methoxy-3α,5-cyclo-5α-cholestane (29): ^{1}H NMR (360 MHz) δ 3.33 (s, 3 H, OCH_3), 1.027 (s, 3 H, C19)8 0.994 (d, *J* = 6.66 Hz, 6 H, C26,27), 0.983 (d, *J* = 6.66, 3 H, C21), 0.740 (s, 3 H, C18). This spectrum agrees peak for peak with that of the X-ray sample and was previously incorrectly assigned the 22*R*,23*S* stereochemistry.[21]

Dichlorocarbene Addition to 27. Aqueous sodium hydroxide (50%, 0.5 mL) was added to a cooled solution (0 °C) of 9.9 mg (0.025 mmol) of the i-methyl ether **27** and BTEAC (4.0 mg, 0.02 mmol) in 1 mL of chloroform. The reaction vessel was sealed and allowed to stir for 3 days, by which time TLC (silica gel, hexane/ethyl acetate 9:1) showed products (R_f 0.51) and no starting material (R_f 0.56). The reaction mixture was then diluted to twice its volume and extracted with chloroform (3 × 1 mL). The combined organic fraction was washed with brine (2 × 1 mL) and concentrated under reduced pressure. Purification of the crude material gave a quantitative yield of the product fraction. Separation of the products by reversed-phase HPLC (Altex, ethanol/water 97:3) gave only two large fractions (six minor); the sum of the two major fractions constituted a reaction yield of 86%.

Fraction I: HPLC t_R 139 min. (22*R*,23*R*)-22,23-(Dichloromethylene)-6β-methoxy-3α,5-cyclo-5α-cholestane (30): ^{1}H NMR (360 MHz) δ 3.30 (s, 3 H, OCH_3), 1.18 (d, *J* = 6 Hz, 3 H, C21), 1.022 (s, 3 H, C19), 0.979 (d, *J* = 6.63 Hz, 6 H, C26,27), 0.705 (s, 3 H, C18); mass spectrum *m/z* (rel intensity) 482 (<5), 465 (<5), 450 (<5), 448 (<5), 427 (<5), 426 (<5), 328 (<5), 253 (15), 55 (100).

Fraction II: HPLC t_R 151 min. (22*S*,23*S*)-22,23-(Dichloromethylene)-6β-methoxy-3α,5-cyclo-5α-cholestane (31): ^{1}H NMR (360 MHz) δ 3.33 (s, 3 H, OCH_3), 1.011 (d, *J* = 6.62 Hz, 3 H, C21), 0.977, 0.971 (2d, *J* = 6.6, 6.6 Hz, C26,27), 0.737 (s, 3 H, C18); mass spectrum *m/z* (rel intensity) 482 (<5), 480 (<5), 367 (<5), 365 (<5), 253 (09), 55 (100).

(22*R*,23*S*)-22,23-Methylenecholesterol Acetate (25). Dehalogenation of the *i*-methyl ether **29** was accomplished by using lithium in liquid ammonia according to the literature procedure[26] except that 6 h was required to obtain a complete removal of the halogens to yield **(22*R*,23*S*)-22,23-methylene-6β-methoxy-3α,5-cyclo-5α-cholestane**: ^{1}H NMR (300 MHz) δ 3.325 (s, 3 H, OCH_3), 1.020 (s, 3 H, C19), 1.017 (d, *J* = 6 Hz, 3 H, C21) 0.927 (*J* = 6.38 Hz), 0.919 (d, *J* = 6.33, 3 H, C-26,27), 0.691 (s, 3 H, C18). This cyclopropyl *i*-methyl ether (7.9 mg) was refluxed in dioxane (0.7 mL) and water (0.7 mL) containing *p*-toluenesulfonic acid (PTSA, 0.2 mg). After 1 h a GLC monitor showed the total loss of starting material (t_R 0.7) and a very high yield of the sterol (t_R 1.38). The reaction mixture was then diluted to three times its volume with water and extracted with methylene chloride (5 × 2 mL). The combined organic fraction was dried (Na_2SO_4), passed through a plug of silica gel, and concentrated to give a quantitative yield of **(22*R*,23*S*)-22,23-methylenecholesterol.**

Conversion to the Acetate 25. Acetic anhydride (0.5 mL) and dry pyridine (0.5 mL) were added to the 22*R*,23*S* cyclopropyl sterol. The reaction vessel was sealed and the mixture was allowed to stand overnight. The reagents were then removed under reduced pressure and the resulting residue was purified by passing it through a plug of silica gel to yield pure (99% by GLC) **(22*R*,23*S*)-22,23-methylenecholesterol acetate (25)**: ^{1}H NMR (300 MHz) δ 2.035 (s, 3 H, $COCH_3$), 1.026 (d, *J* = 6 Hz, C21), 1.019 (s, C19) 0.929 (d, *J* = 6.42 Hz, 3 H), 0.921 (d, *J* = 6.34 Hz, 3 H, C26,27), 0.654 (s, 3 H, C18); mass spectrum *m/z* (rel intensity) 380 (22, M^+ - 60), 296 (22), 253 (10), 59 (100), 55 (68).

Table VI. NMR Methyl Signals of 22,23-Methylenecholesterols[a]

sterol	C19	C21	C26	C27	C18
	1.002	0.992 (6.06)	0.910 (6.76)	0.888 (6.77)	0.618
	1.003	0.952 (6.56)	0.891 (6.54)	0.891 (6.54)	0.623
	1.012	1.023 (6.0)	0.932 (6.56)	0.928 (6.46)	0.649
	I.008	1.022	0.929 (6.40)	0.920 (6.33)	0.655

[a] The 300-MHz NMR values are in ppm.

Steroidal cyclopropanes 22a, 23a, and 24a were made in a manner analogous to that of **25**.[21] The time for the dissolving metal reductions was extended to 4–5 h to ensure complete reaction. (Longer times led to cleavage of the *i*-methyl ether.) Hydrolysis of the *i*-methyl ether was monitored by GLC: the *i*-methyl ethers appeared with a t_R of about 0.7; the free sterols, about 1.3. Purifications of the resulting sterols was by reversed-phase HPLC. The purity of each sterol was shown both in its GLC and 300-MHz NMR. The methyl NMR data, summarized in Table VI, contains revisions of assignments published earlier.[21]

Procedure for the Isomerization of Steroidal Cyclopropanes 24 and 25 with HCl. The procedure was the same as reported earlier.[10] The product mixture was separated by HPLC (97% aqueous methanol as the mobile phase). The components and their compositions are summarized in Table II.

General Procedure for the Isomerization of Steroidal Cyclopropanes with TFA. The steroidal cyclopropane (3.3 mg 7.5 × 10^{-3} mmol) and 1 mL of 5% trifluoroacetic acid–benzene were sealed in a 5-cm vial equipped with a polyethylene cap and a stir bar. The cyclopropane starting materials **1–4** were allowed to react 72 h at which time the percent conversions to products (computed by paper weight of the GLC chromatograms) were 74, 63, 41, and 25%, respectively. The solvent and acid were than removed under reduced pressure. The crude material was run through a plug of silica gel (ether), and the products were separated by reversed-phase HPLC using methanol/water (97:3) as the mobile phase.

The reaction components are reported as they appear in Figure 1 and are characterized in the following form: chromatographic data (HPLC, GLC); (% yield); spectral data. The NMR data for the primary products are given in Table IV.

From (22*R*,23*R*)-22,23-Methylenecholest-5-en-3β-ol Acetate (22). Unidentified Diacetates: HPLC t_R 74–81 min. This was shown both by GLC and HPLC of the corresponding diol mixture to be a complex mixture containing no less than six components. Reported are the data of the major component: HPLC t_R 81 min; (15%); ^{1}H NMR (300 MHz) δ 1.016 (s, 3 H, C19) 0.933 (d, *J* = 6.49 Hz, 3 H), 0.896 (d, *J* = 6.51 Hz, 3 H), 0.860 (d, *J* = 6.44 Hz, 3 H) 0.691 (s, 3 H, C18); low-resolution mass spectrum *m/z* 494 (M^+ - 60).

(17*S*,23*S*)-17,23-Dimethyl-18-normethylcholesta-5,13(14)-dien-3β-ol Acetate (32): HPLC t_R 119 min; GLC rrt: 0.71 (14%); NMR (Table IV) low-resolution mass spectrum *m/z* (rel intensity) 440 (<5), 313 (100), 253 (59), 156 (18), 156 (56). Reaction with excess lithium aluminum hydride gave the **free sterol** with the following properties: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.420 (m, 1 H, C6-H), 3.56 (m, 1 H, C3-H), 0.989 (s, 6 H, C19,C17 methyl), 0.867 (d, *J* = 6.59 Hz, C21), 0.812 (d, *J* = 6.48 Hz, 9 H, C23,26,27); low-resolution mass spectrum *m/z* (assignment: rel intensity 398(M^+, weak), 383 (M^+ - CH_3), 380 (M^+ - H_2O), 271 (M^+ - side chain; see Figure 2), and 253 (M^+ - side chain - H_2O; see Figure 2); high-resolution mass spectrum (M^+ was found to be absent) 271.20649 ($C_{19}H_{27}O$, M^+ - side chain; 100), 253.19270 ($C_{19}H_{25}$, M^+ - side chain - H_2O; 17).

(17*S*,23*S*)-17,23-Dimethyl-18-normethylcholesta-5,13(14)-dien-3β-ol Acetate (33): HPLC t_R 142 min; GLC rrt: 0.94 min (26%); mass spectrum (MAT 711) *m/z* (rel intensity) 380 (06), 314 (72), 313 (100), 312 (21), 254 (51), 253 (10), 159 (26). **Free sterol**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.423 (m, 1 H, C6-H), 3.54 (m, 1 H, C3-H), 0.986 (s, 3 H, C19), 0.982 (s, 3 H, C17 methyl), 0.782 (d, *J* = 6.46 Hz, C21), 0.675 (d, *J* = 6.70 Hz, C22), 0.854, 0.850 (d, *J* = 6.53 Hz, d, *J* = 6.57 Hz, C26,27); ^{13}C NMR (20 MHz) 141.39, 140.39, 136.23, 121.91 (olefinic carbons), 71.92 (C(3)), 52.70 (s), 37.0 (s) (28 signals present); high-resolution mass spectrum (398.35511 M^+, $C_{28}H_{46}O$, 1%; calcd 398.3548), 271.20470 ($C_{19}H_{27}O$, M^+ - side chain; 100), 253.19616

Table VII. Methyl NMR and Chromatographic Data for Backbone Rearrangement Products **32–35** Derived from Side-Chain Olefins **42**, **44**, **53**, **55**

starting material	product	NMR methyl signals						GLC
		C19,18		C21,23		C26,27		
42	**34**	0.995	0.981	0.848	0.690	0.882	0.824	0.91
53	**34**	0.996	0.982	0.849	0.691	0.882	0.823	0.92
42	**35**	0.998	0.989	0.803	0.756	0.842	0.850	0.78
53	**35**	0.997	0.988	0.802	0.756	0.842	0.850	0.77
44	**32**	0.997	0.986	0.868	0.819	0.815	0.815	0.70
54	**32**	0.996	0.986	0.868	0.818	0.814	0.814	0.70
44	**33**	0.996	0.981	0.784	0.682	0.856	0.851	0.93
54	**33**	0.996	0.982	0.785	0.683	0.850	0.854	0.92

($C_{19}H_{25}$, M^+ – side chain – H_2O; 49).

From (22*S*,23*S*)-22,23-Methylenecholest-5-en-3β-ol Acetate (23). Unidentified Diacetates: HPLC t_R 70–93 min (12%). No attempt was made to analyze this complex mixture containing no less than five major components.

(17*S*,23*R*)-17,23-Dimethyl-18-normethylcholesta-5,13(14)-dien-3β-ol Acetate (34): HPLC t_R 135 min; GLC rrt: 0.78 (6%). **Free sterol**: mass spectrum, *m/z* (rel intensity) 398 (weak, parent) 272 (22), 271 (100), 253 (14); high-resolution mass spectrum, *m/z* (rel intensity) 398.3551 (5) 271.2056 (100)8 269.1895 (9.36), 254.1990 (7.85), 253.1953 (43.41).

(17*S*,23*R*)-17,23-Dimethyl-18-normethylcholesta-5,13(14)-dien-3β-ol Acetate (35): HPLC t_R 141 min; GLC rrt: 0.92; (9%); low-resolution mass spectrum *m/z* (rel, intensity) 380 (weak, $M^+ - 60$), 313 (100), 253 (68). **Free sterol**: mass spectrum *m/z* (rel intensity) 398 (<5, parent), 272 (22), 271 (100), 253 (15); high-resolution mass spectrum *m/z* (rel intensity) 398.3537 (0.19), 271.2063 (100.00) 269.1903 (14.88), 253.1942 (39.03).

Unidentified Product Fraction: HPLC t_R 156 min; GLC rrt: 0.86, 1.07, 1.24, 1.35 (four peaks in GLC): (12%); ^{1}H NMR (300 MHz, $CDCl_3$) C19 methyl region: δ 1.027, 1.018, C18 methyl region: 0.562, 0.672; $COCH_3$ region: 2.039, 2.033, no less than three olefinic signals between 4.8 and 5.3 (excluding C6).

(22*R*)-22-Methylcholesta-5,23(*E*)-dien-3β-ol Acetate (37): HPLC t_R 180 min; GLC rrt: 1.53; mp 170–172 °C (MeOH) (17%); ^{1}H NMR ($CDCl_3$) 1.017 (s, 3 H, C 19), 0.691 (s, 3 H, C18), 0.691 (s, 3 H, C18), 0.753 (d, *J* = 6.70 Hz, 3 H, C21), 0.790 (d, *J* = 6.82 Hz, 3 H, C28), 0.965 (d, *J* = 6.61 Hz, 6 H, C26,27). **The sterol** by hydrolysis (5% KOH–methanol, reflux, 1 h): ^{1}H NMR (360 MHz) δ 1.009 (s, 3 H, C19), 0.691 (s, 3 H), 0.753 (d, *J* = 6.71 Hz, 3 H, C21), 0.791 (d, *J* = 6.91, 3 H), 5.320 (dd, *J* = 12.38 Hz, 5.52); high-resolution mass spectrum *m/z* (assignment, rel intensity) 398.35181 ($C_{28}H_{46}O$, 11.14) 301.25129 (53.83) 283.24318 (100).

23-Methylcholesta-5,22(*E*)-dien-3β-ol Acetate (36): lit.[29] HPLC t_R 196 min; GLC rrt: 1.37 (9%). Conversion to the free sterol:GLC rrt: 1.09; mass spectrum *m/z* (rel intensity) 398 (31), 380 (6), 300 (26), 272 (9), 271 (9), 255 (10), 125 (34), 69 (100).

From (22*S*,23*R*)-22,23-Methylenecholest-5-en-3β-ol Acetate (24). Unidentified Diacetates: HPLC t_R 88–102 min (11%); low-resolution mass spectrum of major product *m/z* 494 ($M^+ - 80$).

23-Methylcholesta-5,22(*Z*)-dien-3β-ol Acetate (38): HPLC t_R 165 min; GLC rrt: 1.35 (03%). Conversion to sterol: GLC rrt: 0.98 (lit.[29] 0.99); low-resolution mass spectrum *m/z* (rel intensity) 398 (14), 300 (14), 272 (4), 271 (6), 255 (14).

(22*R*)-22-Methylcholesta-5,23(*E*)-dien-3β-ol Acetate (37) (7%): data reported above.

23-Methylcholesta-5,22(*E*)-dien-3β-ol Acetate (36) (16%): data reported above.

From (22*R*,23*S*)-22,23-Methylenecholest-5-en-3β-ol Acetate (25). Unidentified Diacetates: HPLC t_R 83–93 min (30%). No attempt was made to identify this exceedingly complex mixture.

Unidentified Product Fraction: HPLC t_R 159–185 min (30%). This fraction is partially the isomerization secondary products of the major component **36** (shown by GLC analysis of the mixture obtained from the resubmission of **36** to the reaction conditions). It is a very complex mixture with no component greater than 5% yield. The primary reason for these multiple low-yield products is presumably the slow rate of reaction of the starting material **25**.

23-Methylcholesta-5,22(*Z*)-dien-3β-ol Acetate (38) (2%): reported above.

23-Methylcholesta-5,22(*E*)-dien-3β-ol Acetate (36) (5%): reported above.

23-Homocholesta-5,22(*E*)-dien-3β-ol Acetate (40): HPLC t_R 217 min; GLC rrt: 1.18 (this material showed one peak on coinjection with a sample previously reported[10]); ^{1}H NMR (300 MHz) δ 5.25 (m, HC22 and HC23), 2.031 (s, OCH_3), 1.018 (s, C19), 0.998 (d, *J* = 6.8 Hz, C21), 0.865, 0.862 (2d, *J* = 6.8 Hz, C26,27).

Hydrogenation of 37 was effected with 5% platinum on carbon in methanol. After 16 h at room temperature the catalyst was removed by filtration and the solvent evaporated to give only 22(*S*)-methylcholestanol (**48**) which agreed in its NMR properties with the hydrogenation product of synthetic 22(*S*)-methylcholesterol:[30] ^{1}H NMR (360 MHz) δ 0.865 (d, *J* = 6.57 Hz, C26,27), 0.803 (s, C19), 0.740 (d, *J* = 6.64), 0.677 (d, *J* = 6.72 Hz, C28), 0.656 (s, C18); high-resolution mass spectrum *m/z* (rel intensity) 402.38616 (100, $C_{28}H_{50}O$).

20-Hydroxy-23-methylcholest-5-en-3β-ol. Freshly prepared 2,4-dimethylbromopropane (618 mg, 3.5 mmol) in 1 mL of ether was added to 60 mg of magnesium under argon, and the ensuing Grignard reagent was stirred 1.5 h. Pregnenolone acetate (100 mg, 0.28 mmol) in 5 mL of anhydrous benzene was added dropwise; the reaction mixture was stirred for 1 h and then refluxed for 16 h. The reaction was then cooled to room temperature, hydrolyzed with 10 mL of saturated aqueous ammonium chloride, and extracted with ether (3 × 20 mL). The combined organic fractions were washed with brine (2 × 3 mL), dried ($MgSO_4$), and concentrated to give 213 mg of a white solid. TLC (silica gel, hexane/ethyl acetate 8:2) showed the presence of two major fractions, namely, 20-hydroxy compounds (R_f 0.053) and olefinic fractions (R_f 0.24). This mixture gave satisfactory results when used in crude form in the sequential reaction.

Conversion of 20-Hydroxy-23-methylcholest-5-en-3β-ol to 3β-Acetates (52). Acetic anhydride (1 mL) was added to the above reaction mixture, and after 24 h TLC (hexane/ethyl acetate 8:2) showed one broad spot (R_f 0.26). The reagents were removed under reduced pressure and the mixture was purified: first by column chromatography (hexane/ethyl acetate 8:2), then by reversed-phase HPLC (ODS-2, methanol) to give the major product **52**, 61.4 mg (48%): ^{1}H NMR (300 MHz) δ 5.34 (m, 1 H, HC6), 4.60 (m, 1 H, HC3), 2.029 (s, 3 H, CO_2CH_3), 1.305 (s, 3 H, C21), 1.015 (s, 3 H, C18), 0.868, 0.857, 0.852 (3d, *J* = 6 Hz, 9 H), mass spectrum *m/z* (rel intensity) 443 (4, $M^+ - CH_3$), 399 (18), 398 (53), 382 (6) 381 (32), 380 (100), 359 (24), 303 (15), 300 (29), 299 (100), 298 (35), 282 (24), 281 (59), 257 (47), 256 (100), 255 (47), 254 (21).

Dehydration of 20-hydroxy-23-methylcholest-5-en-3β-ol acetate (52) was effected in the manner of Roller.[33] The acetate **52** (29.4 mg, 0.06 mmol) in pyridine (6.7 mL) under argon was treated with phosphorus oxychloride (1.1 mL), and the resulting light brown solution was stirred 24 h. At this time TLC (hexane/ethyl acetate 10:1) showed total loss of starting material (R_f 0.13) and product formation (R_f 0.33). After preliminary purification through a short column (silica gel, 4 g; hexane/ethyl acetate 10:1), the olefin isomers were separated by reversed-phase HPLC to give the following fractions.

Fraction A: HPLC t_R 71 and 75 min. This fraction contains presumably the unreported $\Delta^{17(20)}$ *Z* isomers (2%).[32]

Fraction B: HPLC t_R 80 min. **$\Delta^{20(21)}$ isomer 56**: ^{1}H NMR δ 5.48 (m, C5), 4.815 (s, C21), 4.827 (s, C21), 2.033 (s, 3 H, OCH_3), 1.020 (s, 3 H, C19), 0.869 (d, *J* = 6.67 Hz, 3 H, C28), 0.837 (d, *J* = 6.39 Hz, 3 H, C26), 0.824 (d, *J* = 6.45 Hz, 3 H, C27), 0.586 (s, 3 H, C18); low-resolution mass spectrum *m/z* (rel intensity) 380 (100, M^+ – HOAc), 365 (10), 296 (17, allylic cleavage C22–C23), 253 (19) (10%).

Fraction C: HPLC t_R 82 min. This fraction was found to contain four components. This peak was rechromatographed with a fraction taken every 30 s to give fractions C_1 through C_4 (49%).

Fraction C_1. $\Delta^{20(22)}$ Isomer 41 (40%) and 43 (60%): ^{1}H NMR δ 5.48 (m, C5), 4.91 (d, *J* = 9 Hz, C22), 4.82 (d, *J* = 8.8 Hz, C22), 2.033 (s, OCH_3), 1.638 (d, *J* = 0.8 Hz, C21), 1.022 (s, C19), 1.018 (s, C19), 0.888 (d, *J* = 6.66 Hz, C28), 0.880 (d, *J* = 6.47 Hz), 0.858 (d, *J* = 6.54 Hz, C26), 0.857 (d, *J* = 6.47 Hz, C26), 0.837 (d, *J* = 6.37 Hz, C27), 0.766 (d, *J* = 6.00 Hz, C27), 0.585 (s, C18), 0.538 (s, C18).

Fraction C_2. Isomer 42 (pure): ^{1}H NMR δ 5.38 (m, 1 H, C5), 2.033 (s, 3 H, OCH_3), 1.638 (d, *J* = 0.8 Hz, C21), 1.018 (s, 3 H, C19), 0.888 (d, *J* = 6.66 Hz, C28), 0.880 (d, *J* = 6.47 Hz), 0.858 (d, *J* = 6.54 Hz,

3 H, C26), 0.857 (d, J = 6.47 Hz, C26), 0.837 (d, J = 6.37 Hz, C27), 0.766 (d, J = 6.00 Hz, C27), 0.538 (s, 3 H, C18).

Fraction C_3. $\Delta^{20(21)}$ Isomer 55 (50%) and $\Delta^{20(22)}$ Isomer 42 (50%): ^{1}H NMR δ 5.38 (m, C5), 2.033 (s, OCH_3), 4.912 (d, J = 8.8 Hz, C22), 4.816 (s, C21), 4.831 (s, C21), 1.638 (d, J = 0.8 Hz, C21), 1.023 (s, C19), 1.018 (s, C19), 0.888 (d, J = 6.66 Hz, C28), 0.872 (d, J = 6.57 Hz, C28), 0.858 (d, J = 6.54 Hz, C26), 0.837 (d, J = 6.37 Hz, C27), 0.838 (d, J = 6.45 Hz, C26), 0.827 (d, J = 6.42 Hz, C27), 0.590 (s, C18), 0.538 (s, C18).

Fraction C_4. $\Delta^{20(22)}$ Isomer 43: ^{1}H NMR δ 5.38 (m, C5), 4.818 (d, J = 8.31 Hz, C22), 2.033 (s, OCH_3), 1.638 (d, J = 0.8 Hz, C21), 1.021 (s, C19), 0.879 (d, J = 6.67 Hz, C28), 0.857 (d, J = 6.52 Hz, C26), 0.764 (d, J = 5.87 Hz, C27).

Fraction D: HPLC t_R 85 min. **$\Delta^{20(22)}$ Isomer 44:** ^{1}H NMR δ 5.38 (m, C5), 4.815 (d, J = 9.26 Hz, C22), 1.626 (d, J = 0.8 Hz, C21), 1.017 (s, C19), 0.880 (d, J = 6.71 Hz, C28), 0.858 (d, J = 6.35 Hz, C26), 0.836 (d, J = 6.31 Hz, C27), 0.543 (s, C18) (26%).

Fraction E: HPLC t_R 88 min. **$\Delta^{17(20)}$ Isomer 54:** ^{1}H NMR δ 5.38 (m, C5), 2.033 (s, OCH_3), 1.661 (s, C21), 1.027 (s, C19), 0.869 (s, C18), 0.782 (d, J = 6.19 Hz, C28), 0.831 (d, J = 6.55 Hz, C26), 0.867 (d, J = 6.44, C27) (6%); low-resolution mass spectrum on free sterol, m/z (rel intensity) 398 (9), 315 (2), 300 (7), 299 (26), 281 (6), 271 (11), 230 (20), 95 (100) (6%).

Fraction F: HPLC t_R 88 min. **$\Delta^{17(20)}$ Isomer 53:** ^{1}H NMR δ 5.38 (m, C5), 2.032 (s, OCH_3), 1.661 (C21), 1.027 (s, C19), 0.870 (s, C18), 0.794 (d, J = 5.99 Hz, C28), 0.830 (d, J = 6.53 Hz, C26), 0.868 (d, J = 6.53 Hz, C27); low-resolution mass spectrum m/z (rel intensity) 380 (40, M^+ − HOAc), 365 (10), 281 (70, α-cleavage)[42] (6%).

Isomerization of olefins 42, 44, 53, and 54 with TFA was carried out in the manner previously described for the steroidal cyclopropanes except that a reaction time of 4 h was sufficient for the total conversion of starting material. (Longer reaction times—53 h for reaction of **43**—seemingly did not affect the product compositions.) Shown in Table VII are the actual chromatographic and NMR (300 MHz) data for the reaction products.

The Model System: 17β-Isopropenyl-Δ^5androsten-3β-ol Acetate (49). Pregnenolone acetate (200 mg, 0.56 mmol) in 5 mL of benzene was added to excess methylmagnesium iodide (1 mL methyl iodide, 20 mg magnesium) in 5 mL of ether. After 1 h reaction, the mixture was refluxed overnight. Workup in the usual way using ammonium chloride gave the diol adduct which was acylated with 2 mL of acetic anhydride/pyridine (1:1). After 24 h, an equal volume of water was added and the mixture filtered to yield an intermediate alcohol, 208 mg (94%), mp 146–8°C): ^{1}H NMR (300 MHz) δ 5.38 (m, C5), 4.6 (m, C3), 2.031 (s, 3H, OCH_3), 1.311 (s, 3 H, C21), 1.205 (s, 3 H, C22), 1.020 (s, 3 H, C19), 0.841 (s, 3 H, C18). **Dehydration to 49** was effected in the manner described for 20-hydroxy-23-methylcholest-5-en-3β-ol acetate (**52**). The above alcohol (194 mg, 0.52 mmol) in 40 mL pyridine was added to phosphorus oxychloride (6.6 mL); the reaction mixture was stirred under argon 24 h, then poured slowly (exothermic) into ice water (100 mL), and extracted with methylene chloride (3 × 20 mL). The combined organic fraction was washed with aqueous HCl (10%, 10 mL), saturated sodium bicarbonate (10 mL), and brine (2 × 20 mL), then dried (Na_2SO_4), and concentrated to give the model system **50** as an oil, 183 mg (99%). Purification by reversed-phase HPLC (methanol) gave a white solid, mp 104–9 °C; HPLC t_R 40 min (methanol): GLC rrt 0.44; ^{1}H NMR δ 5.38 (m, C5), 4.855 (s, 1 H, C22), 4.708 (s, 1 H, C22), 2.033 (s, 3 H, OCH_3), 1.552 (s, 3 H, C21), 1.023 (s, 3 H, C19), 0.854, 0.584 (2s, 3 H, C18).

18-(Nor-17β-methyl-17α-isopropylandrosta-5,13(14)-dien-3β-ol Acetate (51). A solution of the 17β-isopropenyl acetate **50** (7.6 mg, 0.02 mmol) in 3 mL of 5% TFA was sealed and allowed to stir 2.5 h. Evaporation of the solvent and reagent under reduced pressure gave a single product, whose spectra are identical with those reported:[16] GLC rt: 0.31; HPLC t_R (methanol) 34 min; ^{1}H NMR (300 MHz) δ 0.995 (s, 3 H, C19), 0.984 (s, 3 H, C17), 0.843 (d, J = 6.77 Hz, 3 H, C21), 0.720 (d, J = 7.0 Hz, C22); low-resolution mass spectrum m/z (rel intensity) 356 (M^+ <5), 313 (70), 253 (58), 59 (100), 55 (98).

Acknowledgment. The Stanford authors wish to acknowledge financial support provided by NIH Grants GM-06840 and GM-28352. We wish to thank Annemarie Wegmann and staff for mass spectral measurements, Dr. Lois Durham and colleagues for the 360-MHz ^{1}H NMR spectra (which were obtained at the Stanford NMR facility funded by NIH Grant RR-0711 and NSF Grant Gp-23633). Use of the 300-MHz NMR spectrometer at Stanford was made possible by NSF Grant CHE 81-09064. We thank the University of California at Berkeley for high-resolution mass spectral determinations and finally Dr. A. A. Leslie Gunatilaka for preliminary experiments in the isomerization of 22(R),23(R)-methylenecholesterol. The Buffalo authors acknowledge financial support from the National Institutes of Health (AM-26546) and the Wendt Foundation, and thank Miss F. Elaine DeJarnette and Miss Phyllis Strong for technical assistance.

Registry No. 22, 91157-06-1; **23**, 91199-77-8; **24**, 91199-78-9; **25**, 91199-79-0; **25**-ol, 80227-02-7; **26**, 25819-78-7; **26** (22R,23S-epoxide), 91157-07-2; **26** (22S,23R-epoxide), 91157-08-3; **27**, 25819-80-1; **28**, 80227-06-1; **29**, 80186-24-9; **29** (didechloro derivative), 80186-25-0; **30**, 91237-13-7; **31**, 80227-07-2; **32**, 91157-09-4; **32**-ol, 91200-55-4; **33**, 91199-80-3; **33**-ol, 91157-10-7; **34**, 91157-11-8; **34**-ol, 91199-81-4; **35**, 91199-82-5; **35**-ol, 91157-12-9; **36**, 91157-13-0; **36**-ol, 71932-06-4; **37**, 91178-17-5; **37**-ol, 91178-18-6; **38**, 91157-14-1; **38**-ol, 82903-20-6; **40**, 91157-15-2; (20E,23S)-**41**, 91199-83-6; (20Z,23R)-**42**, 91199-84-7; (20E,23R)-**43**, 91199-85-8; (20Z,23S)-**44**, 91199-86-9; **45**, 91157-16-3; **48**, 91157-17-4; **49**, 38388-16-8; **50**, 91157-18-5; **51**, 1778-02-5; **52**, 91199-87-0; **52** (diol), 91157-19-6; **53**, 91157-20-9; **54**, 91178-19-7; **55**, 91157-21-0; **56**, 91157-22-1; (20S)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde, 25819-77-6; isoamyltriphenylphosphonium bromide, 28322-40-9; 2,4-dimethyl-1-bromopentane, 6570-91-8.

Supplementary Material Available: Routine X-ray data, including ORTEP structures, for **24**, **29**, and **31** (4 pages). Ordering information is given on any current masthead page.

(41) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1974; Vol. 4, p 303.

(42) Ness et al. (cited in ref 32) show that the cleavage of C20–C21 is important in $\Delta^{17(20)}$ isomers relative to $\Delta^{20(22)}$.