Synthesis of (23*R*)- and (23*S*)-Methylcholesterol

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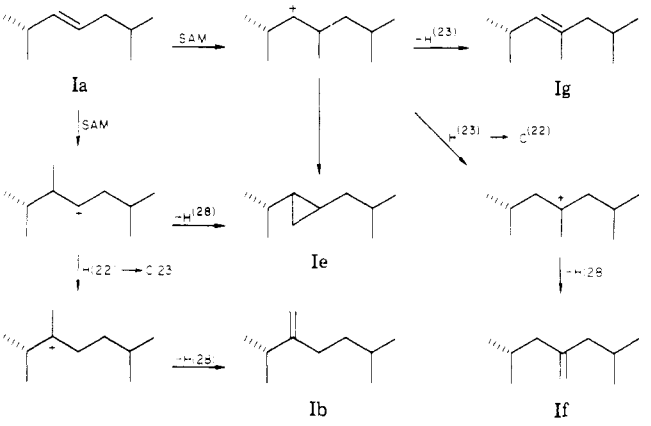
23-Methylcholesterol is likely to exist in nature. In order to facilitate its recognition, (23*R*)- and (23*S*)-methylcholesterol have been synthesized, and the absolute configuration has been established by X-ray analysis. Substantial differences were encountered in comparing the course of catalytic hydrogenation and of double-bond isomerization of 22- and 23-methylenecholesterol.

The existence of (22*R*,23*R*)-methylenecholesterol (Ie,[2] see Chart I) and 22-methylenecholesterol (Ib)[3] in marine organisms demonstrates that direct bioalkylation of 22-dehydrocholesterol (Ia) is possible in nature. Since (24*R*)-methylcholesterol (Ip) and its 24*S* epimer (Iq) coexist with 24-methylenecholesterol (Ik),[4] it is likely that (22*R*)-methylcholesterol (Im) and its 22*S* epimer (Il) may also be naturally occurring. Similarly, the isolation of 23-methyl-22-dehydrocholesterol (Ig)[5,6] and its 4-methyl analogue (IIg)[7] from marine animals suggests that 23-alkylsterols could also exist in nature. As shown in Scheme I, 23-methylenecholesterol (If) is a prime candidate, but the side chain saturated (23*R*)- (In) and (23*S*)-methylcholesterol (Io) may also exist in the marine environment as predicted several years ago.[8]

We now report the synthesis of (23*R*)-methylcholesterol (In), (23*S*)-methylcholesterol (Io), and their possible precursor, 23-methylenecholesterol (If), together with the appropriate physical properties in order to facilitate the search for these compounds. Previously, (22*R*)-methylcholesterol (Im) and its 22*S* epimer (Il) were stereoselectively synthesized by Claisen rearrangement of appropriate precursors of established absolute configuration.[9] Since no such precursor is available for stereoselective introduction of the 23-methyl function into the side chain, we chose a method of reduction of the newly synthesized 23-methylenecholesterol (If) so as to provide both epimers In and Io of 23-methylcholesterol followed by determination of the absolute configuration at C-23 via X-ray analysis.

The synthesis (Scheme II) started with methyl 3β-acetoxychol-5-enate (IVv), which was converted to the *i*-methyl ether of 2-(3β-hydroxybisnorchol-5-enyl)-1,1-diphenylethylene (IIIw) by a known method.[10] Ozonolysis of IIIw gave the aldehyde IIIx, which was subjected to Grignard addition, oxidation and Wittig reaction to form the *i*-methyl ether of 23-methylenecholesterol (IIIf). Hydroboration of the 23-methylene group of IIIf gave a nearly equal mixture of the *i*-methyl ether of (23*R*)-(hydroxy-

Scheme I



methyl)cholesterol (IIIr) and its (23*S*)-epimer (IIIs), which could be separated by HPLC. Each pure alcohol was transformed, via lithium aluminum hydride reduction of its mesylate and removal of the protecting group, to pure (23*R*)-In and (23*S*)-methylcholesterol (Io). In order to establish the absolute configuration, one of the isomers (eventually shown to possess the 23*R* configuration) was transformed to its 3-methyl ether derivative (Vn), which proved to be suitable for X-ray analysis.

In addition to the above described hydroboration, an attempt was also made to saturate the 23-methylene group by catalytic hydrogenation (Table I). When tris(triphenylphosphine)rhodium(I) chloride was used as a homogeneous catalyst to hydrogenate 23-methylenecholesterol (If) or its i methyl ether analogue (IIIf), the ratio of (23*R*)-methylcholesterol (In) and its 23*S* epimer (Io) was 1:1.5. Apparently, rear attack predominated slightly. By contrast, in the hydrogenation of 22-methylenecholesterol (1b), the ratio of (22*R*)-methylcholesterol (Im)[9] to its 22*S* epimer (Il)[9] under the same reaction conditions is 1:3 (see Table II), thus pointing to a steric effect of the 21-methyl group.

Of considerable interest was the heterogeneous catalytic hydrogenation of 23-methylenecholesterol i-methyl ether (IIIf) with palladium in ethyl acetate. After 1.5 h there was obtained 97% of a mixture of isomerization products composed of the 23-methyl-Δ^{22}-cholesterols (Ig, Ih) and their Δ^{23} epimers (Ii, Ij)[11] accompanied by only 2% of the reduction product (23*S*)-methylcholesterol (Io). Under the same hydrogenation conditions 22-methylenecholesterol i-methyl ether (IIIb, Table II) gave only 62% of the isomerization products Ic and Id together with 28% of the saturated 22*S*-methyl sterol Il. These results show that the 23-methylene group is more easily isomerized than the 22-methylene function by means of palladium, which is in full accord with the results obtained with basic isomerization.[11]

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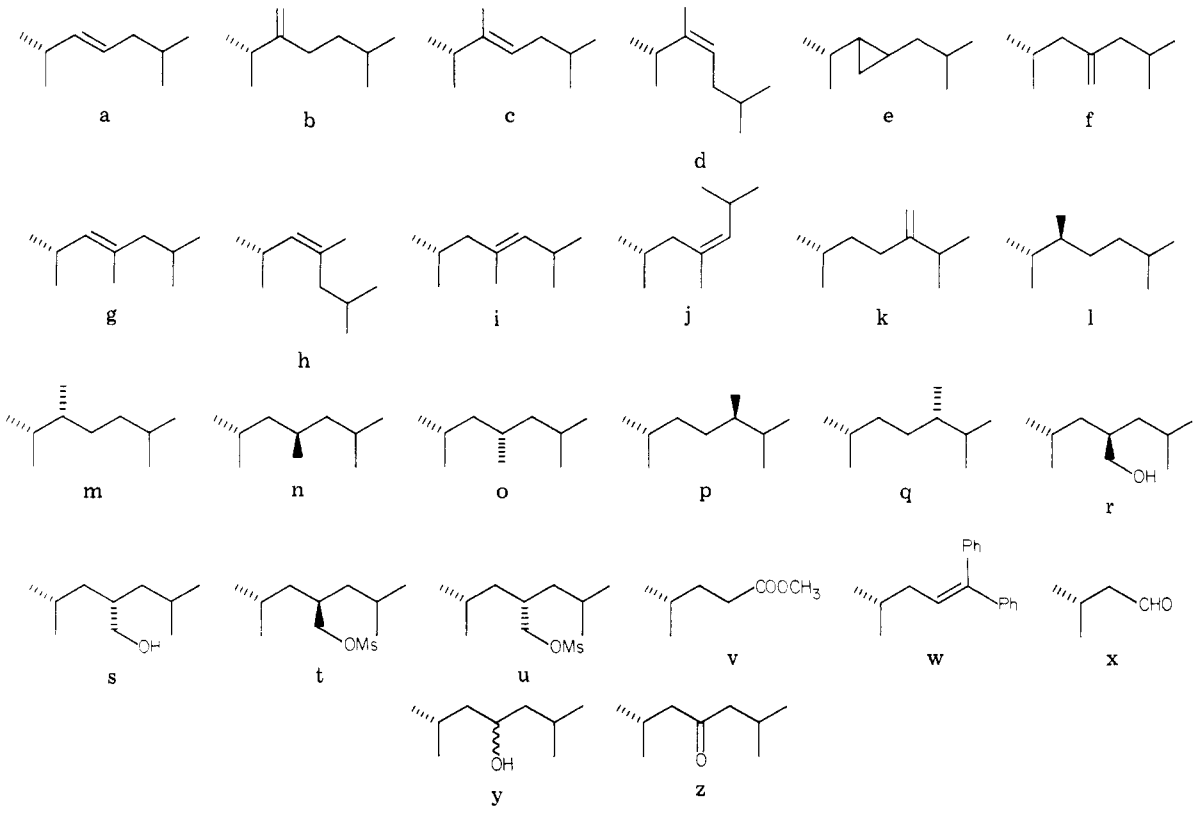
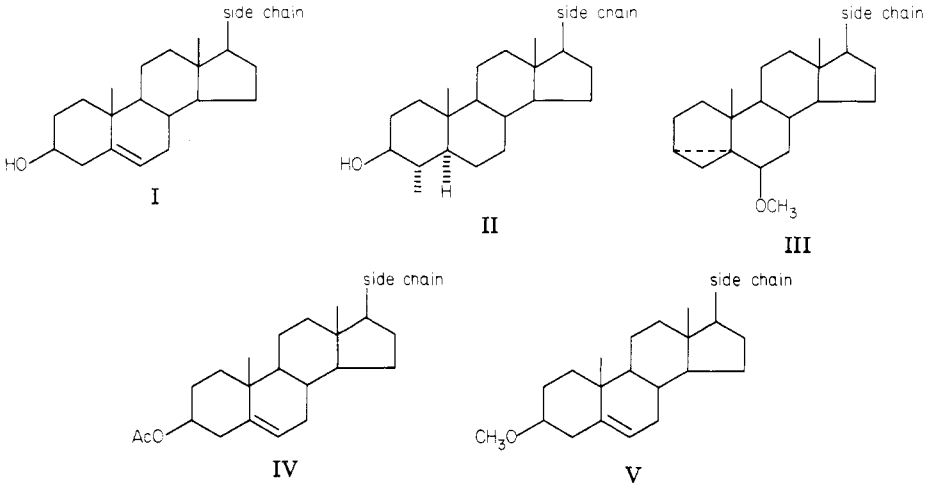
Chart I



Nuclei



Scheme II. Synthetic Route to (23*R*)- and (23*S*)-Methylcholesterol

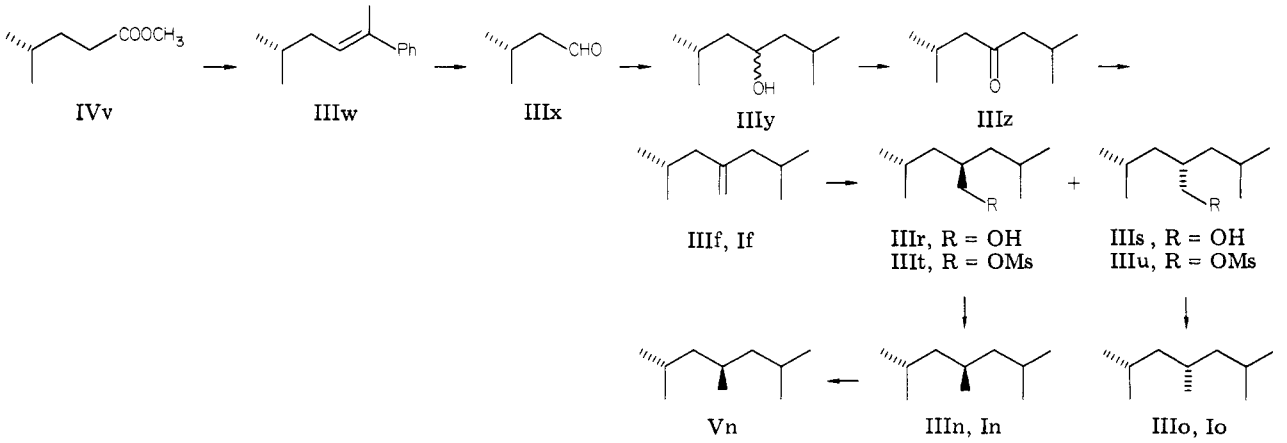
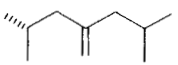
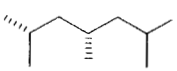
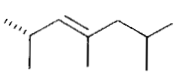
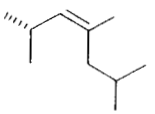
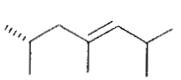
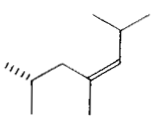
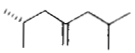
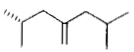
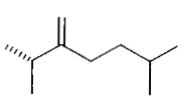
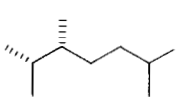
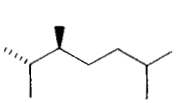
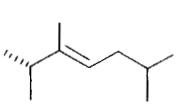
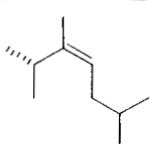
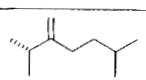
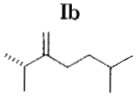


Table I. Catalytic Hydrogenation of the 23-Methylene Group of 23-Methylenecholesterol (If) and Its *i*-Methyl Ether (IIIf)

		reaction products, %						
starting material	reaction condition	 If	 In	 Io	 Ig	 Ih	 Ii	 Ij
 If	*a*	18	33	49				
 IIIf	*a*	38[c]	25[c]	37[c]				
 III	*b*			2	35	6	36	20

[a] $(C_6H_5)_3PRhCl$, benzene, room temperature, 24 h. [b] 5% $Pd/BaSO_4$, ethyl acetate, room temperature, 1.5 h. [c] *i*-Methyl Ether.

Table II. Catalytic Hydrogenation of the 22-Methylene Group of 22-Methylenecholesterol (Ib) and Its *i*-Methyl Ether (IIIb)

		reaction products, %				
starting material	reaction condition	 Ib	 Im	 Il	 Ic	 Id
 Ib	*a*	15	20	63		
 IIIb	*b*			28	59	3

[a, b] See footnotes in Table I.

Table III. ^1H (360 MHz) and ^{13}C NMR Spectral Data[a] ($CDCl_3$) of Isomeric 23-Methylcholesterols In and Io

	(23R)-methylcholesterol (In)		(23S)-methylcholesterol (Io)	
C	^{13}C NMR	^1H NMR	^{13}C NMR	^1H NMR
1	37.31		37.31	
2	31.74		31.73	
3	71.80		71.81	
4	42.47		42.47	
5	140.82		140.82	
6	121.63		121.64	
7	31.91		31.91	
8	31.97		31.98	
9	50.25		50.26	
10	36.55		36.55	
11	21.13		21.12	
12	28.40		28.44	
13	42.38		42.38	
14	57.35		57.25	
15	24.19		24.26	
16	39.90		39.92	
17	56.88		56.92	
18	11.88	0.695	11.90	0.694
19	19.36	1.010	19.36	1.009
20	33.68		33.61	
21	19.01	0.883 (d, J = 6.60 Hz)[b]	19.47[b]	0.886 (d, J = 6.42 Hz)
22	45.33		44.02	
23	25.38		25.16	
24	45.84		48.44	
25	27.76		27.34	
26	21.42	0.824 (d, J = 6.49 Hz)	22.69	0.845 (d, J = 6.78 Hz)
27	21.63	0.828 (d, J = 6.45 Hz)	22.99	0.847 (d, J = 6.70 Hz)
28	24.16	0.890 (d, J = 6.42 Hz)[b]	18.62[b]	0.778 (d, J = 6.46 Hz)

[a] The ^{13}C NMR data are for the carbons indicated, and the ^1H NMR data for the corresponding hydrogens on those carbons. [b] Assignment could be reversed.

In Table III we summarize the ^1H and ^{13}C NMR spectral data of the two 23-methylcholesterol isomers In and Io. Evidently, the 28-methyl group in the 23S-configuration is more shielded than that in the 23R orientation. In connection with another problem, we recently synthesized[12] two 23-ethylcholestanol epimers (A and B) and now record their proton NMR spectra in Table IV. A comparison of the data in Tables III and IV suggests that epimer A of 23-ethylcholestanol may possess the 23S configuration, because the chemical shift of its 29-methyl group occurs at a higher field (0.792 ppm) than that (0.821 ppm) of its other (B) isomer, which should be assigned the 23R configuration. In addition to the diagnostic NMR data, the physical constants collected in Table V demonstrate that the differences in chromatographic mobility definitely distinguish the 23-methylcholesterol isomers (In, Io) from their 22-methyl (Im, Il) and 24-methyl (Ip, Iq) epimers. In fact, the chromatographic mobility differs even between the two 23-methyl epimers. As expected the mass spectra of the two epimers In and Io are identical and furthermore are indistinguishable from those of the 22-methyl (Im, Il) or 24-methyl (Ip, Iq) epimers.

With the availability of these properties of authentic reference compounds, the search for naturally occurring 22- or 23-methylcholesterols in marine organisms should be greatly facilitated.

(12) Li, L. N.; Li, H.-T.; Lang, R. W.; Itoh, T.; Sica, D.; Djerassi, C. *J. Am. Chem. Soc.*, in press.

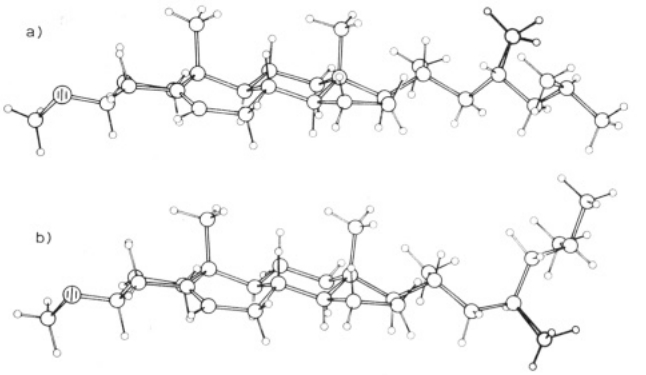


Figure 1. Observed absolute configuration and conformation of the two crystallographically independent molecules of (23R)-methylcholesterol methyl ether.

X-ray diffraction data were collected with a Nicolet P3 automated diffractometer using Cu Kᾱ radiation. Crystal data are given in Table VI. The lattice constants were determined by least-squares analysis of the θ values of 25 diffractometer-centered reflections.

The 5098 independent reflections were reduced to structure factors in the standard manner. The structure was solved with the direct methods computer program MULTAN[13] and refined by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms except the C-26 and C-27 hydrogen atoms were refined with fixed isotropic B values equal to the B_{iso} of the appropriate carbon atom. Due to computer limitations, the final least-squares cycle was performed with the parameters of the two molecules in the asymmetric unit being alternately held fixed. The largest shift estimated standard deviation for the last two cycles were less than 0.10. The data were weighted by $1/\sigma_{F^2}$ during refinement with 403 parameters. Data where $F^2 < \sigma_{F^2}$ were not included in the refinement. The refinement converged to a conventional R of 0.067 for 4386 data and 0.104 for all data. The weighted residual R was 0.063.

The final positional parameters are listed in Table VII. Coordinates for hydrogen atoms, anisotropic thermal parameters, and other crystallographic details are available from the authors upon request.

The observed conformations of the molecules are illustrated in Figure 1. The absolute configuration at the C-23 carbon atom is R for both molecules in the asymmetric unit. The only significant difference between the two molecules is the conformation of the C-17 side chain. The conformation of the side chain can be defined by the torsion angles given in Table VIII. Both of these side chain conformations have been observed in a sample of 96 cholestanes whose X-ray crystal structures have been surveyed.[14] Molecule a in Figure 1 has the most commonly observed fully extended side chain conformation. The 23-methyl substitution appears to enhance the relative stability of a conformation in which this methyl is trans to the C-20–C-22 bond (Figure 2b). Corresponding bond lengths and angles are not significantly different between conformers and are comparable to previous X-ray structure determinations of similar compounds.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and

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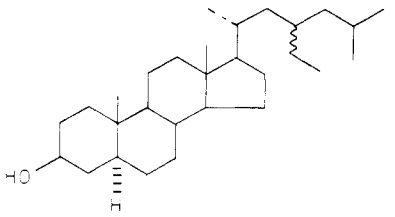
(14) Duax, W. L.; Griffin, J. F.; Rohrer, D. C.; Weeks, C. M. *Lipids* **1980**, *15*, 783.

Table IV. ^1H (360 MHz) Spectral Data of Isomeric 23-Ethylcholestanols



	18-CH_3	19-CH_3	21-CH_3	26-CH_3	27-CH_3	29-CH_3
A	0.660	0.802	0.835 (d, 6.64)	0.863 (d, 6.51)	0.872 (d, 6.39)	0.792 (t, 7.22)
B	0.664	0.804	0.836 (d, 6.80)	0.867 (d, 6.33)	0.875 (d, 6.51)	0.821 (t, 6.40)

Table V. Physical Constants of 22-, 23-, and 24-Methylcholesterols

sterol	mp, °C	$[\alpha]^{20}D$ ($CDCl_3$), deg	GC rel t_r[a] (3% OV-17)	HPLC rel t_r[a] (ODS-2)
22*R*-Im	161-162	−40.5	1.12	0.80
22*S*-Il	160-161	−45.8	1.21	0.93
23*R*-In	178-179	−8	1.02	0.96
23*S*-Io	171-172	−19	1.09	1.13
24*R*-Ip	158-159	−33	1.32	1.08
24*S*-Iq	158-159	−46	1.32	1.08

[a] Cholesterol $t_r = 1.00$.

Table VI. Crystal Data

M_r	$C_{29}H_{50}O$	b, Å	68.743 (9)
mol wt	414.79	c, Å	7.647 (1)
space group	$P2_12_12_1$	V, Å^3	5298.1
Z	8	d_{calcd}, g/cm^3	1.04
a, Å	10.079 (1)	cryst size, mm	0.18 × 0.20 × 0.8
		λ, Å	1.5418

are uncorrected. Specific rotations were recorded on a Perkin-Elmer 141 polarimeter in chloroform. Gas chromatography was performed on an U-shaped column packed with 3% OV-17 at 260 °C. This column was mounted in a Hewlett-Packard 402 high-efficiency gas chromatograph equipped with a flame-ionization detector. HPLC was performed on a Waters Associates HPLC system (M6000 pump, R403 differential refractometer, and a Whatman Partisil M9 10/50 ODS-2 column) with absolute methanol as the mobile phase.

^1H NMR spectra were recorded on a Bruker HXS-360 spectrometer equipped with a Nicolet TT 1010-A computer with $CDCl_3$ as solvent and Me_4Si as an internal standard. ^{13}C spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts are given in parts per million and J values in hertz. High-resolution mass spectral data were obtained on a Finnigan MAT 711 spectrometer.

6β-Methoxy-3α,5-cyclo-5α-cholestan-23-ol (IIIy). Ozone was bubbled at −70 °C through a solution of 3.6 g (7 mmol) of 2-(3β-hydroxybisnorchol-5-enyl)-1,1-diphenylethylene *i*-methyl ether (IIIw) in 100 mL of anhydrous dichloromethane until a light blue appeared. Zinc dust (3 g) and acetic acid (5 mL) were added to the cold solution, and the mixture was stirred for 2 h at room temperature. After removal of zinc dust the solvent was evaporated in vacuo. The residue was then diluted with water and extracted with hexane (4 × 50 mL). The combined organic phases were washed with 5% $NaHCO_3$ and NaCl solution and dried over anhydrous Na_2SO_4 to give the crude aldehyde IIIx. It was dissolved in 20 mL of ether and added to a Grignard solution formed from 2.4 g (0.1 mol) of Mg and 13.7 g (0.1 mol) of isobutyl bromide in 50 mL of ether. The mixture was heated under reflux for 2 h and then treated as usual to give a crude product which was

Table VII. Non-Hydrogen Atomic Coordinates (×10^4) and Isotropic Thermal Parameters (×10) for the Two Crystallographically Independent (23*R*)-Methylcholesterol Methyl Ethers

atom	X/A (σ)	Y/B (σ)	Z/C (σ)	B_{iso} (σ)	atom	X/A (σ)	Y/B (σ)	Z/C (σ)	B_{iso} (σ)
C(1A)	992 (5)	5562 (1)	2316 (4)	52 (1)	C(1B)	7826 (5)	5530 (1)	5095 (5)	66 (2)
C(2A)	1630 (5)	5363 (1)	2120 (5)	57 (1)	C(2B)	8089 (6)	5312 (1)	5066 (6)	71 (2)
C(3A)	1523 (5)	5295 (1)	230 (4)	54 (1)	C(3B)	8474 (6)	5243 (1)	6872 (6)	76 (2)
C(4A)	2240 (5)	5438 (1)	−925 (5)	58 (1)	C(4B)	7397 (6)	5294 (1)	8173 (6)	75 (2)
C(5A)	1696 (4)	5643 (1)	−733 (4)	45 (1)	C(5B)	7048 (5)	5506 (1)	8159 (5)	66 (1)
C(6A)	1305 (4)	5744 (1)	−2102 (4)	50 (1)	C(6B)	7016 (5)	5611 (1)	9627 (5)	71 (2)
C(7A)	788 (4)	5946 (1)	−2056 (4)	47 (1)	C(7B)	6668 (5)	5819 (1)	9800 (5)	67 (2)
C(8A)	1025 (4)	6047 (1)	−292 (4)	39 (1)	C(8B)	6005 (4)	5897 (1)	8108 (4)	56 (1)
C(9A)	723 (4)	5904 (1)	1178 (4)	39 (1)	C(9B)	6776 (4)	5821 (1)	6508 (4)	54 (1)
C(10A)	1611 (4)	5723 (1)	1145 (4)	40 (1)	C(10B)	6738 (5)	5594 (1)	6375 (5)	58 (1)
C(11A)	713 (5)	6005 (1)	2984 (4)	52 (1)	C(11B)	6323 (5)	5922 (1)	4822 (4)	63 (1)
C(12A)	−137 (5)	6189 (1)	3029 (4)	51 (1)	C(12B)	6243 (5)	6144 (1)	4943 (5)	60 (1)
C(13A)	277 (4)	6336 (1)	1623 (4)	42 (1)	C(13B)	5400 (4)	6210 (1)	6471 (4)	54 (1)
C(14A)	160 (4)	6225 (1)	−127 (4)	41 (1)	C(14B)	6012 (5)	6117 (1)	8101 (4)	58 (1)
C(15A)	240 (5)	6385 (1)	−1507 (4)	58 (1)	C(15B)	5340 (5)	6228 (1)	9619 (5)	72 (2)
C(16A)	−433 (5)	6560 (1)	−675 (4)	58 (1)	C(16B)	5122 (6)	6431 (1)	8929 (5)	77 (2)
C(17A)	−720 (4)	6507 (1)	1271 (4)	46 (1)	C(17B)	5457 (5)	6430 (1)	6938 (5)	61 (1)
C(18A)	1662 (5)	6413 (1)	1953 (5)	55 (1)	C(18B)	3964 (5)	6146 (1)	6212 (6)	63 (1)
C(19A)	3036 (5)	5763 (1)	1776 (6)	62 (1)	C(19B)	5403 (6)	5518 (1)	5790 (7)	76 (2)
C(20A)	−727 (4)	6686 (1)	2478 (4)	47 (1)	C(20B)	4598 (5)	6573 (1)	5917 (5)	64 (1)
C(21A)	−942 (6)	6629 (1)	4402 (5)	59 (1)	C(21B)	4896 (7)	6570 (1)	3926 (6)	78 (2)
C(22A)	1790 (5)	6828 (1)	1839 (5)	55 (1)	C(22B)	4770 (6)	6785 (1)	6619 (7)	79 (2)
C(23A)	−2163 (5)	6999 (1)	3045 (6)	61 (1)	C(23B)	3514 (6)	6879 (1)	7289 (7)	75 (2)
C(24A)	−992 (5)	7129 (1)	3414 (7)	69 (2)	C(24B)	3871 (7)	7071 (1)	8183 (7)	91 (2)
C(25A)	−1225 (7)	7287 (1)	4824 (11)	107 (3)	C(25B)	2776 (11)	7168 (1)	9190 (9)	127 (3)
C(26A)	−1553 (9)	7202 (1)	6579 (10)	159 (4)	C(26B)	2380 (11)	7057 (1)	10667 (16)	203 (5)
C(27A)	13 (8)	7413 (1)	4967 (10)	135 (3)	C(27B)	3237 (10)	7365 (1)	9862 (11)	171 (4)
C(28A)	−3320 (6)	7111 (1)	2209 (8)	81 (2)	C(28B)	2548 (11)	6901 (1)	5852 (11)	141 (4)
C(29A)	1354 (6)	4955 (1)	686 (7)	78 (2)	C(29B)	9855 (8)	4971 (1)	6241 (9)	97 (2)
O(3A)	2112 (3)	5109 (1)	−50 (3)	66 (1)	O(3B)	8641 (4)	5036 (1)	6968 (5)	90 (1)

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

	molecule 1	molecule 2
ω_1, C(13)-C(17)-C(20)-C(22)	−180.0	178.4
ω_2, C(17)-C(20)-C(22)-C(23)	168.6	−120.2
ω_3, C(20)-C(22)-C(23)-C(24)	60.4	171.3
ω_4, C(22)-C(23)-C(24)-C(25)	−171.4	−170.0
ω_5, C(23)-C(24)-C(25)-C(26)	61.4	65.9
ω_6, C(23)-C(24)-C(25)-C(27)	−176.4	−174.8

purified by chromatography on 120 g of silica gel with 88:12 hexane/ethyl acetate as eluent to afford in 61% yield a mixture of the (23R)- and (23S)-hydroxy compounds IIIy. These two epimers could be separated by chroamtography on silica gel with 9:1 hexane/ethyl acetate as eluent.

More polar alcohol: ^{1}H NMR (60 MHz) δ 3.76 (1 H, m, 23-CH), 3.32 (3 H, s, 6-OCH_3), 1.02 (3 H, s, 19-CH_3), 0.97 (3 H, d, J = 5 Hz, 21-CH_3), 0.89 (6 H, d, J = 6.4 Hz, 26- and 27-CH_3); mass spectrum, m/z (relative intensity) 416 (46), 401 (65), 384 (60), 361 (100), 358 (23), 255 (15), 145 (22).

Less polar alcohol: ^{1}H NMR (60 MHz) δ 3.76 (1 H, m, 23-CH), 3.32 (3 H, s, 6-OCH_3), 1.03 (3 H, s, 19-CH_3), 0.93 (3 H, d, J = 6 Hz, 21-CH_3), 0.91 (6 H, d, J = 6 Hz, 26- and 27-CH_3). The mass spectrum was indistinguishable from that of the more polar alcohol.

6β-Methoxy-3α,5-cyclo-5α-cholestan-23-one (IIIz). A solution of 1.8 g (4 mmol) of the mixture of (23R)- and (23S)-hydroxy compounds IIIy in 88 mL of acetone was oxidized with Jones reagent at 10 °C. The usual work up followed by purification through chromatography on 50 g of silica gel (97:3 hexane/ethyl acetate as eluent) afforded the 23-ketone IIIz in 58% yield; ^{1}H NMR 0.752 (3 H, s, 18-CH_3), 1.013 (3 H, s, 19-CH_3), 0.893 (3 H, d, J = 6.41 Hz, 21-CH_3), 0.905 (6 H, d, J = 6.54 Hz, 26- and 27-CH_3), 3.315 (3 H, s, 6-OCH_3); mass spectrum, m/z (relative intensity) 414 (52), 399 (54), 383 (21), 367 (11), 359 (100), 356 (17), 282 (57), 267 (18), 256 (20).

6β-Methoxy-3α,5-cyclo-23-methylene-5α-cholestane (IIIf) and 23-Methylenecholesterol (If). Methyltriphenylphosphonium bromide (4.5 g, 12.5 mmol) in dry benzene (105 mL) was treated with n-BuLi (5 mL of a 2.4 N solution in hexane, 12.5 mmol). After 1 h of reflux, a solution IIIz (1.04 g in 20 mL of benzene) was added and the reaction mixture heated under reflux for 20 h. After ether extraction and the usual workup, the 23-methylene compound IIIf was obtained in 86% yield after preparative thin-layer chromatography on silica gel plates with 9:1 hexane/ethyl acetate as eluent; mp 91–92 °C (CH_3OH); $[\alpha]^{20}_D$ 31.4°; ^{1}H NMR 0.745 (3 H, s, 18-CH_3), 1.026 (3 H, s, 19-CH_3), 0.906 (3 H, d, J = 6.08 Hz, 21-CH_3), 0.835 (3 H, d, J = 5.98 Hz, 26-CH_3), 0.851 (3 H, d, J = 5.56 Hz, 27-CH_3), 4.689 and 4.708 (2 H, 2 s, 28-CH_2), 3.330 (3 H, s, 6-OCH_3); high-resolution mass spectrum, m/z (relative intensity, assignment) 412.369 67 (29.3, $C_{29}H_{48}O$, M), 397.343 91 (33.6, $C_{28}H_{45}O$), 380.345 86 (32.5, $C_{28}H_{44}$), 357.315 87 (57, $C_{25}H_{41}O$), 314.262 13 (100, $C_{22}H_{34}O$), 299.238 72 (14, $C_{21}H_{31}O$), 283.240 67 (39.3, $C_{21}H_{31}$), 282.234 36 (56.4, $C_{21}H_{30}$). Hydrolysis of IIIf with p-toluenesulfonic acid in aqueous dioxane gave 23-methylenecholesterol If: HPLC relative t_r 0.82 (cholesterol = 1); GC relative t_r 1.19 (cholesterol = 1); mp 148–149 °C (CH_3OH), $[\alpha]^{20}_D$ −60°; ^{1}H NMR δ 0.709 (3 H, s, 18-CH_3), 1.012 (3 H, s, 19-CH_3), 0.904 (3 H, d, J = 6.04 Hz, 21-CH_3), 0.833 (3 H, d, J = 5.99 Hz, 26-CH_3), 0.857 (3 H, d, J = 5.71 Hz, 27-CH_3), 4.691 and 4.709 (2 H, 2 s, 28-CH_2); high-resolution mass spectrum, m/z (relative intensity, assignment) 398.354 63 (2.4, $C_{28}H_{46}O$, M^+), 383.333 34 (1.7, $C_{27}H_{43}O$), 380.346 32 (5, $C_{28}H_{44}$), 300.246 78 (100, $C_{21}H_{32}O$), 285.222 30 (20.4, $C_{20}H_{29}O$), 283.242 30 (20.3, $C_{21}H_{31}$), 282.234 24 (17.2, $C_{21}H_{30}$), 271.205 41 (17, $C_{19}H_{27}O$), 267.211 13 (24.5, $C_{20}H_{27}$).

Hydroboration of 6β-Methoxy-3α,5-cyclo-23-methylene-5α-cholestane (IIIf). A solution of 160 mg (0.4 mmol) of IIIf in 13 mL of tetrahydrofuran was cooled in an ice bath under nitrogen, and 13 mL of an approximately 1 M solution of diborane in tetrahydrofuran was added with stirring. The mixture was stirred for 1 h in an ice bath and then at room temperature overnight. The mixture was cooled again, and 8.6 mL of water was added dropwise followed by addition of 8.6 mL of 3 N sodium hydroxide and finally by the slow addition of 8.6 mL of 30% hydrogen peroxide. The mixture was stirred at room temperature for 2 h and then extracted with chloroform (4 × 40 mL). The combined extracts were washed with 20 mL of water followed by 10 mL of saturated sodium chloride solution and dried over magnesium sulfate. These two C-23 epimeric isomers could be separated by HPLC (ODS-2 column, absolute methanol as eluent). The combined yield (almost equal ratio) of 6β-methoxy-3α,5-cyclo-(23R)-23-(hydroxymethyl)-5α-cholestane (IIIr) and its (23S)-epimer (IIIs) was 76%.

IIIr: ^{1}H NMR δ 0.739 (3 H, s, 18-CH_3), 1.025 (3 H, s, 19-CH_3), 0.917 (3 H, d, J = 5.93 Hz, 21-CH_3), 0.883 (3 H, d, J = 6.80 Hz, 26-CH_3), 0.902 (3 H, d, J = 6.81 Hz, 27-CH_3).

IIIs: ^{1}H NMR δ 0.727 (3 H, s, 18-CH_3), 1.022 (3 H, s, 19-CH_3), 0.927 (3 H, d, J = 6.43 Hz, 21-CH_3), 0.876 (3 H, d, J = 6.58 Hz, 26-CH_3), 0.900 (3 H, d, J = 6.68 Hz, 27-CH_3); high-resolution mass spectrum, m/z (relative intensity, assignment) 430.380 46 (94.9, $C_{29}H_{50}O_2$, M^+), 415.358 94 (53.4, $C_{28}H_{47}O_2$), 398.358 79 (100, $C_{28}H_{46}O$), 383.332 26 (12.5, $C_{27}H_{43}O$), 375.329 06 (81.9, $C_{25}H_{43}O_2$), 372,341 42 (29.1, $C_{26}H_{44}O$), 255.210 75 (30.9, $C_{19}H_{27}$). The mass spectrum of IIIr was indistinguishable from that of IIIs.

(23R)-Methylcholesterol *i*-Methyl Ether (IIIn). A solution of 65 mg (0.15 mmol) of the (23R)-alcohol IIIr in 1 mL of methylene chloride containing 0.032 mL (0.225 mmol) of triethylamine was cooled in an ice bath, and 0.013 mL (0.165 mmol) of methanesulfonyl chloride was added with stirring.[15] After 30 min the solvent was removed in vacuo to give the crude mesylate (IIIt), which was immediately taken up in 20 mL of dry tetrahydrofuran. Excess lithium aluminum hydride was added, and the mixture was heated to reflux with stirring overnight. Excess lithium aluminum hydride was destroyed with water, the product extracted with ether, and the residue purified by preparative TLC (silica gel HF, 8% ethyl acetate in hexane as the eluent) to give IIIn in 81% yield; ^{1}H NMR 0.731 (3 H, s, 18-CH_3), 1.023 (3 H, s, 19-CH_3), 0.884 (6 H, d, J = 6.50 Hz, 21- and 28-CH_3), 0.823 (3 H, d, J = 6.48 Hz, 26-CH_3), 0.828 (3 H, d, J = 6.54 Hz, 27-CH_3), 3.327 (3 H, s, 6-OCH_3); mass spectrum, m/z (relative intensity) 414 (31, M) 399 (29), 382 (100), 367 (20), 359 (57).

(23S)-Methylcholesterol *i*-Methyl Ether (IIIo). The (23S)-alcohol IIIs was treated as above to give IIIo: ^{1}H NMR 0.730 (3 H, s, 18-CH_3), 1.022 (3 H, s, 19-CH_3), 0.880 (3 H, d, J = 6.47 Hz, 21-CH_3), 0.846 (3 H, d, J = 6.41 Hz, 26-CH_3), 0.848 (3 H, d, J = 6.41 Hz, 27-CH_3), 0.779 (3 H, d, J = 6.45 Hz, 28-CH_3), 3.326 (3 H, s, 6-OCH_3); mass spectrum, m/z (relative intensity) 414 (33, M) 399 (13), 382 (100), 367 (14), 359 (26).

(23R)-Methylcholesterol (In, Tables III and IV). The protecting group of IIIn was removed by hydrolysis with p-toluenesulfonic acid in aqueous dioxane to afford In: high-resolution mass spectrum, m/z (relative intensity, assignment) 400.371 02 (100, $C_{28}H_{48}O$, M), 385.346 55 (14.1, $C_{27}H_{45}O$), 382.359 69 (30.4, $C_{28}H_{46}$), 367.331 53 (15.2, $C_{27}H_{43}$), 315.302 81 (20.8, $C_{23}H_{39}$), 289.289 97 (21.8, $C_{21}H_{37}$), 273.224 16 (16.1, $C_{19}H_{29}O$), 255.212 63 (10, $C_{19}H_{27}$), 213.163 70 (15.2, $C_{16}H_{21}$).

(23S)-Methylcholesterol (Io, Tables III and IV). The isomer IIIo was hydrolyzed as above to give Io: high-resolution mass spectrum, m/z (relative intensity, assignment) 400.371 75 (100, $C_{28}H_{48}O$, M), 385.349 63 (22, $C_{27}H_{45}O$), 382.361 66 (35, $C_{28}H_{46}$), 367.331 55 (14.4, $C_{27}H_{43}$), 315.303 48 (22.6, $C_{23}H_{39}$), 289.288 75 (26.8, $C_{21}H_{37}$), 273.221 60 (14.4, $C_{19}H_{29}O$), 255.210 59 (17.6, $C_{19}H_{27}$), 213.165 20 (23, $C_{16}H_{21}$).

(23R)-Methylcholesterol 3-Methyl Ether (Vn). For X-ray analysis, a sample was purified by HPLC (ODS-2 column) and then allowed to crystallize from benzene/methanol; ^{1}H NMR δ 0.694 (3 H, s, 18-CH_3), 1.002 (3 H, s, 19-CH_3), 0.884 (3 H, d, J = 6.13 Hz), 0.886 (3 H, d, J = 7 Hz, 21- and 28-CH_3), 0.824 (3 H, d, J = 6.72 Hz, 26-CH_3), 0.827 (3 H, d, J = 6.68 Hz, 27-CH_3), 3.357 (3 H, s, 6-OCH_3); mass spectrum (MAT-44), m/z (relative intensity) 414 (11, M), 399 (3), 382 (16), 367 (7), 340 (4), 315 (5), 255 (10), 57 (100).

General Procedure for Homogeneous Catalytic Hydrogenation. A solution of 65 mg of 23-methylenecholesterol *i*-methyl ether (IIIf) in 10 mL of benzene was hydrogenated with 32 mg of tris(triphenylphoshine)rhodium(I) chloride at room temperature

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for 24 h. The catalyst was removed by filtration of the mixture through a neutral Al_2O_3 column, and the residue was then subjected to separation by HPLC on an ODS-2 column. The composition of this mixture is listed in Table I.

General Procedure for Heterogeneous Catalytic Hydrogenation. A solution of 46 mg of 23-methylenecholesterol *i*-methyl ether (IIIf) in 5 mL of ethyl acetate was hydrogenated with 20 mg of 5% Pd-$BaSO_4$ at room temperature for 1.5 h. After removal of the catalyst, the solvent was evaporated under reduced pressure. The residue was then dissolved in 10 mL of aqueous dioxanne (containing 2 mg of *p*-toluenesulfonic acid) and heated under reflux for 1 h. The mixture was treated in the usual way to give the crude product, which was separated by HPLC on an ODS-2 column; for product composition see Table I.

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Oxidation of Alcohols with Dimethyl Selenide–*N*-Chlorosuccinimide Complex

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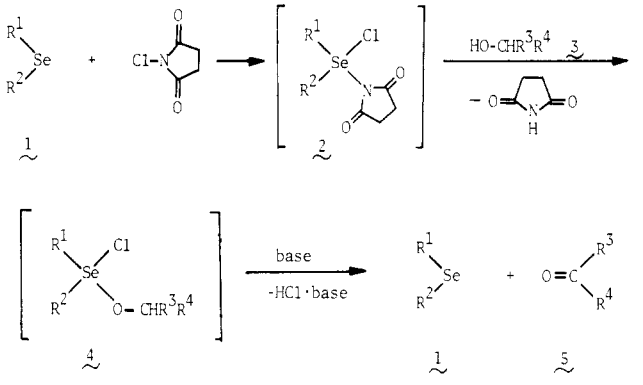
Dimethyl selenide reacts with *N*-chlorosuccinimide (NCS) to give a new complex, with which various alcohols are successfully oxidized to carbonyl compounds. Notably, this method is applicable to allylic alcohols without formation of allylic chlorides and rearranged products. β-Hydroxy selenide **8** is converted to β-oxo selenide **9** by the treatment with NCS. On the other hand, facile deselenization occurs in the case of γ-hydroxy selenide **10** under similar conditions. A plausible mechanism of the reactions is also discussed.

Oxidation of alcohols via oxasulfonium ion intermediates is a useful synthetic method;[1] however, it is one which has serious limitations: (i) it is not applicable to allylic alcohols, as it results in the formation of allylic halides; (ii) alkylthio methyl ethers are formed by Stevens rearrangement in polar solvents.[2] On the other hand, there is currently a significant interest in the development of selenium chemistry,[3] for example, oxidation of alcohols with benzeneseleninic anhydride[4] and selenium-catalyzed chlorination of olefins.[5] Nevertheless, selenium(IV) compounds have been little investigated. In contrast to sulfur analogues, they are relatively stable,[6] and therefore oxaselenium(IV) species are potentially valuable intermediates for oxidation of alcohols, as they are expected to overcome the limitations described above. We report here a new oxidation of alcohols with dimethyl selenide–*N*-chlorosuccinimide complex.

When dimethyl selenide (1) was added to a solution or suspension of NCS, a new white precipitate was formed immediately, which gradually disappeared upon addition of alcohol **3** (Scheme I). GLC analyses showed formation of a small amount of carbonyl compound **5** at this stage. The product was dramatically increased after addition of base, but long reaction times and heating were not as effective. An aqueous workup gave a clean mixture containing the carbonyl compound **5** and the starting alcohol **3**; other products were not detected. Of course, the selenide **1** could be recovered quantitatively, if necessary.

Scheme I



We examined the reactions of benzyl alcohol and *p*-nitrobenzyl alcohol in order to determine the optimum conditions (Table I). As shown in Table I, the following series of decreasing reactivities is observed: selenides, CH_3SeCH_3 > $PhSeCH_3$ > PhSePh; solvents, $C_6H_5CH_3$ >

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