Stereoselective Synthesis via Claisen Rearrangements of the Marine Sterols Occelasterol, Patinosterol, and 22,23-Dihydrooccelasterol

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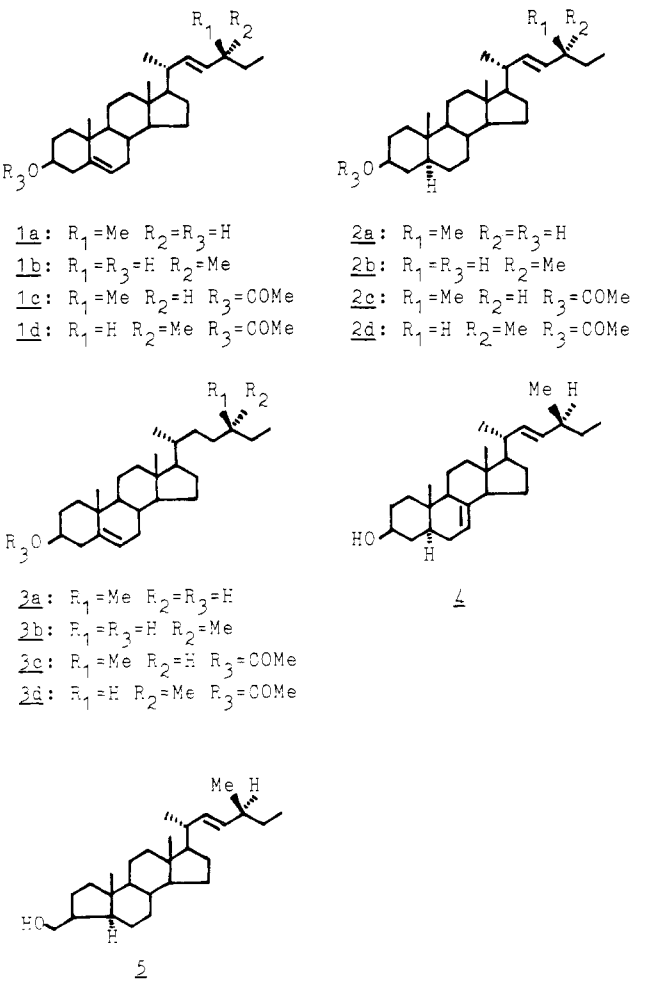
Occelasterol (**1a**), patinosterol (**2a**), 22,23-dihydrooccelasterol (**3a**), and their 24-stereoisomers (**1b**, **2b**, and **3b**) were stereoselectively synthesized. The i-methyl ether **6**, derived from stigmasterol, was coupled with propynylmagnesium bromide to afford an easily separable 1:1 epimeric mixture of 26,27-dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-yn-22-ols (**7a,b**). The stereochemistry at C-22 was determined unequivocally by direct comparison of the corresponding 26,27-dinorcholestene-3β,22-diols **9a** and **9b** and their diacetates **9c** and **9d** with the Grignard reaction product of **6** with propylmagnesium bromide. The acetylenic alcohols **7a** and **7b** were then reduced stereoselectively to give the epimeric (23*Z*)- or (23*E*)-26,27-dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-en-22-ols **10a,b** and **11a,b**, respectively, depending upon the choice of the reducing agent. Claisen rearrangement of the appropriate allylic alcohols led stereoselectively to (22*E*,24*S*)- or (22*E*,24*R*)-27-nor-3α,5-cyclo-6β-methoxy-5α-cholest-22-en-26-oic acid ethyl esters **12a** and **12b**, which in turn were converted to **1a,b**, **2a,b**, and **3a,b**, respectively. With these reference compounds of established stereochemistry, it is now possible to use high-field ^1H NMR spectroscopy to assign the absolute configuration at C-24 of naturally occurring sterols with the 27-norergostene side chain.

The unique feature of the marine sterols occelasterol (**1a**), patinosterol (**2a**), and 22,23-dihydrooccelasterol (**3a**) is their 27-norergostane-type side chain (Chart I). The first isolation of sterols with such a hitherto unknown side chain (e.g., amuresterol (**4**), isolated from the asteroid *Asterias amurensis*) was reported by Kobayashi and Mitsuhashi[2] in 1974. Occelasterol (**1a**) was isolated first from the annelid *Pseudopotamilla ocelata*,[3] and patinosterol (**2a**) was found in the scallop *Patinopecten yessoensis*.[4] More recently, 3-(hydroxymethyl)-*A*-norpatinosterol (**5**) has been encountered[5] in a sponge (*Teichaxinella morchella*), which effected enzymatically the contraction of ring A from externally ingested patinosterol. 22,23-Dihydrooccelasterol (**3a**) has not yet been found in nature, but it seems very likely that it will be found eventually in marine organisms as a biosynthetic metabolite. The importance of these 27-norergostane C_{27} sterols resides in the fact that they are probably the biosynthetic precursors of the unique C_{26} sterols (e.g., 24-norcholesta-5,22-dien-3β-ol and 24-norcholest-22-en-3β-ol) of planktonic origins.[6] The structure of the C_{27} sterols was confirmed by synthesis via a Wittig reaction of the appropriate C-22 aldehydes with (2*S*)-1-bromo-2-methylbutane and the configuration at C-24 was tentatively assigned as 24*S* based on spectral identity and biogenetic analogy.[2,3,7] However, the differences in physical properties, chromatographic behavior, and spectral data of epimeric C-24 alkylsterols are generally so small that direct comparison of both stereoisomers is necessary for unequivocal determination of the stereochemistry.

In this report we describe a stereoselective synthesis of occelasterol (**1a**), patinosterol (**2a**), 22,23-dihydrooccelasterol (**3a**), and their 24-stereoisomers **1b–3b** via a Claisen rearrangement reaction[8] which affords stereoselectively either the 22*E*,24*R* or the 22*E*,24*S* stereoisomer and thus provides for the first time reference standards of established absolute configuration.

Chart I



The 22-aldehyde **6**, (Chart II) derived from stigmasterol by established procedures,[9] was coupled with propynylmagnesium bromide[10] to give a 1:1 mixture of the yne

(1) To whom correspondence should be addressed.
(2) Kobayashi, M.; Mitsuhashi, H. *Tetrahedron* **1974**, *30*, 2147.
(3) Kobayashi, M.; Mitsuhashi, H. *Steroids* **1974**, *24*, 399.
(4) Kobayashi, M.; Mitsuhashi, H. *Steroids* **1975**, *26*, 605.
(5) Bohlin, L.; Sjöstrand, U.; Djerassi, C.; Sullivan, B. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1023.
(6) Djerassi, C.; Theobald, N.; Kokke, W. C. M. C.; Pak, C. S.; Carlson, R. M. K. *Pure Appl. Chem.* **1979**, *51*, 1851 and references cited therein.
(7) Kobayashi, M.; Minazawa, T.; Mitsuhashi, H. *Steroids* **1977**, *29*, 823.
(8) (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
(9) (a) Hutchins, R. F. N.; Thompson, J. J.; Svoboda, J. A. *Steroids* **1970**, *15*, 113. (b) Salmond, W. G.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1695.

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Chart II

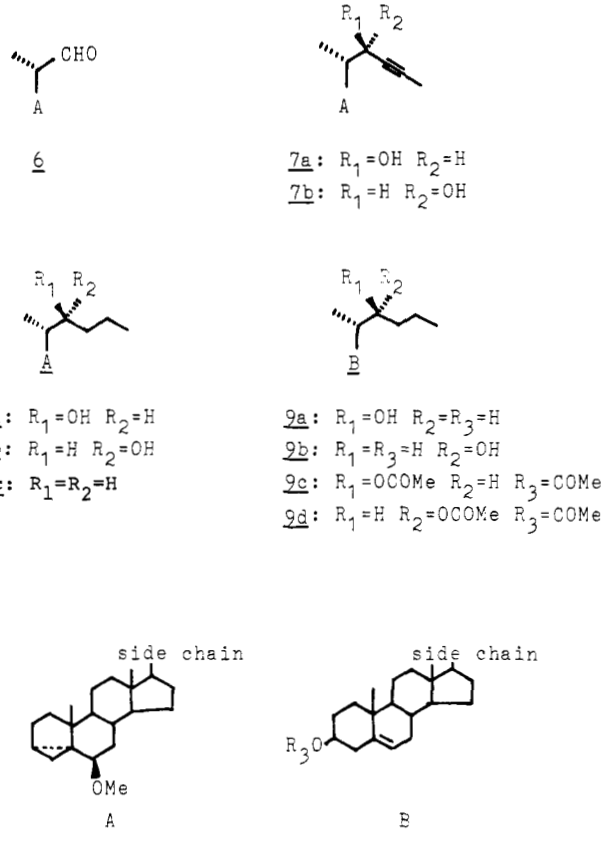
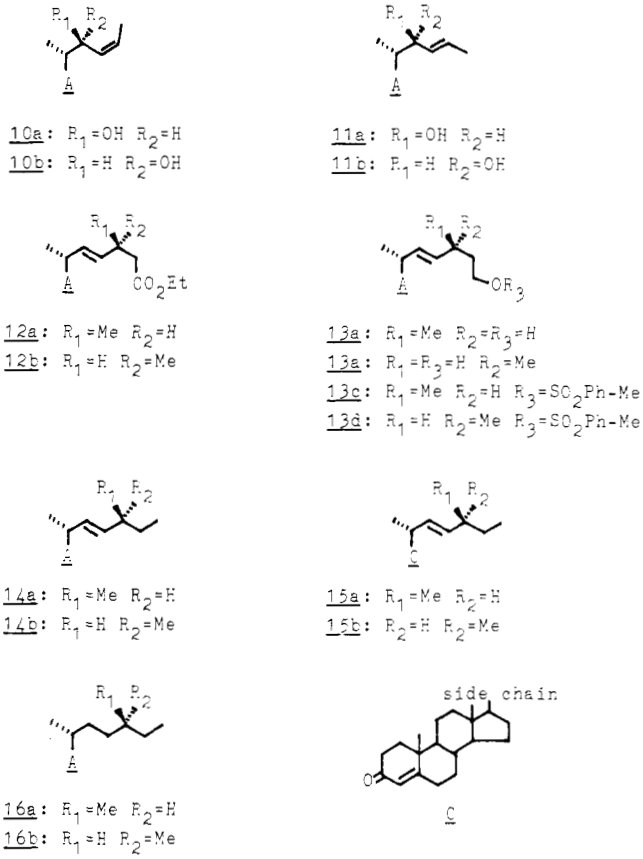


Chart III



alcohols **7a** and **7b** which were separated by column chromatography on silica gel. In order to determine the stereochemistry at C-22, we converted both stereoisomers to the corresponding side-chain-saturated 3,22-diols **9a** and **9b** and their diacetates **9c** and **9d**, respectively, by catalytic hydrogenation with Pd/C followed by regeneration of the 3β-hydroxy 5-ene system and acetylation. Earlier work[11] has shown that the Grignard reaction of the 22-aldehyde **6** with a "saturated" alkyl halide affords predominantly the corresponding 22S/α alcohol. Therefore, the 22-aldehyde **6** was treated with propylmagnesium bromide to give the 22*S*-alcohol **8a** which was then converted to the corresponding 3β,22*S*-diol **9a** and its diacetate **9c**. The physical, chromatographic, and spectral data were identical with those of the products derived from the less polar yne alcohol **7a**. Accordingly, the configuration at C-22 of the less polar yne alcohol **7a** is assigned as *R*, while the more polar yne alcohol **7b** has the 22*S* configuration.[12]

The 22*R* yne alcohol **7a** was partially hydrogenated with Lindlar catalyst in hexane in the presence of quinoline to give the 22*S*,23*Z* allylic alcohol **10a** (Chart II), while the 22*S*,23*E* isomer **11a** was obtained by reduction with lithium aluminum hydride in refluxing THF. When the more polar 22*S* yne alcohol **7b** was treated with lithium aluminum hydride under the same conditions, a considerable amount (30%) of hydrogenolysis product[13] was generated together with the desired product **11b**. However, on substitution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[14] in refluxing THF in the reduction of **7b**, the 22*R*,23*E* allylic alcohol **11b** could be obtained in good yield. The required 22*R*,23*Z* allylic alcohol **10b** was synthesized from the 22*S* yne alcohol **7b** by partial hydrogenation under the same conditions as employed with **7a**.

The resulting four stereoisomers **10a,b** and **11a,b** were then subjected to a Claisen rearrangement reaction which is known[15] to generate exclusively either the (22*E*,24*R*)- or the (22*E*,24*S*)-24-alkyl 26-oate moiety from the appropriate C-22 allylic alcohols of the sterol side-chain system. Thus, treatment of the 22*S*,23*Z* and 22*R*,23*E* allylic alcohols **10a** and **11b** with triethyl orthoacetate in xylene in the presence of a catalytic amount of propionic acid at 130 °C afforded exclusively the (22*E*,24*S*)-26-oate **12a**, while the (22*E*,24*R*)-26-oate **12b** was obtained in good yield from the 22*S*,23*E* and 22*R*,23*Z* allylic alcohols **11a** and **10b**. The configurational assignment at C-24 of the rearranged products **12a** and **12b** follows from literature precedents for this type of reaction,[15] which require that the 24*S* isomer **12a** should be produced from the 22*S*,23*Z* or 22*R*,23*E* allylic alcohols **10a** and **11b**, while the 24*R* isomer **12b** should be obtained from the 22*S*,23*E* or 22*R*,23*Z* allylic alcohols **11a** and **10b**, respectively.

The (24*S*)-26-oate **12a** was converted to occelasterol (**1a**) by a standard four-step sequence (LAH–ether; TsCl–pyridine; LAH–THF; TsOH–aqueous dioxane). The naturally occurring[4] 5,6-dihydro analogue with 5α stereochemistry, patinosterol (**2a**), was obtained from occelasterol (**1a**) by Oppenauer oxidation followed by Birch reduction. Finally, hydrogenation of the olefin **14a** followed by usual

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(11) Poyser, J. P.; Ourisson, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2061.
(12) It should be noted that the *R,S* convention changes in going from **7a** to **8a** and from **7b** to **8b** because of the change in priority upon saturation of the triple bond.
(13) Fujimoto, Y.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin I Trans. 1* **1975**, 2302.
(14) Chan, K.-K.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1978**, *43*, 3435.
(15) (a) Wiersig, J. R.; Waespe-Sarcevic, N.; Djerassi, C. *J. Org. Chem.* **1979**, *44*, 3374 and references cited therein. (b) Anastasia, M.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Chem. Commun.* **1979**, 858. (c) Preuss, M. W.; McMorris, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 3066.

Table I. Physical Properties of 27-Nor-24-methyl Sterols

sterol	mp, °C obsd	mp, °C reported	$[\alpha]^{20}_D$, deg obsd	$[\alpha]^{20}_D$, deg reported
occelasterol (1a)	137.5	128-129[3]	−37.9	−44[3]
24-epioccelasterol (1b)	137		−61.0	
occelasterol acetate (1c)	148.5	142-144[3]	−41.7	−47[3]
24-epioccelasterol acetate (1d)	148		−68.5	
patinosterol (2a)	147	139-141[7]	+23.0	+13.5[7]
24-epipatinosterol (2b)	140		−8.7	
patinosterol acetate (2c)	137-137.5	133[7]	+8.9	+8[7]
24-epipatinosterol acetate (2d)	134-135		−9.8	
22,23-dihydrooccelasterol (3a)	147-149		−34.0	
24-epi-22,23-dihydrooccelasterol (3b)	153-154		−38.5	
22,23-dihydrooccelasterol acetate (3c)	138		−35.5	
24-epi-22,23-dihydrooccelasterol acetate (3d)	137-138		−34.6	

Table II. Chromatographic Mobility of 27-Nor-24-methyl Sterols

sterol	RRT GLC		RRT HPLC	
occelasterol (1a)	0.90[a]	0.88[b]	0.70[c]	
24-epioccelasterol (1b)	0.90	0.88	0.74	
patinosterol (2a)	0.90	0.90	0.79	
24-epipatinosterol (2b)	0.90	0.90	0.83	
22,23-dihydrooccelasterol (3a)	1.00	1.02	0.98	0.98[d]
24-epi-22,23-dihydrooccelasterol (3b)	1.00	1.02	0.98	0.98

[a] 3% OV-17, column temperature = 260 °C, cholesterol = 1.00 (t_R = 20 min). [b] SE-54 capillary column, column temperature = 260 °C, cholesterol = 1.00 (t_R = 10 min). [c] ODS-2, eluent = absolute methanol, cholesterol = 1.00 (t_R = 80 min). [d] Altex ultrasphere ODS, eluent = methanol-water (96:4), cholesterol = 1.00 (t_R = 210 min).

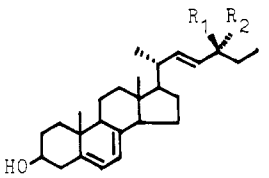
deprotection of the i-methyl ether group yielded the hitherto unknown 22,23-dihydrooccelasterol (**3a**). Application of the same procedures to the (24*R*)-26-oate **12b** led to the corresponding 24*R* isomers **1b–3b**.

The physical properties, chromatographic behavior, and NMR spectral data are summarized in Tables I–IV. As far as physical constants (Table I) are concerned, specific rotations can be used to good advantage for assignment of the C-24 stereochemistry, provided there is also present a Δ^{22} double bond. No secure differentiation is possible in the saturated series (**3a** vs. **3b**; **3c** vs. **3d**) by using either specific rotation or chromatographic behavior under the conditions listed in Table II. The epimeric sterols possessing Δ^{22} double bonds are separable by HPLC using a reverse-phase column.

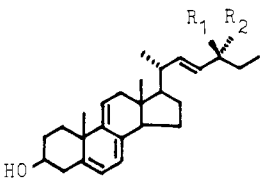
Recently it has been shown that differentiation of epimeric C-24 alkyl sterols with conventional side chains can be achieved by capillary GLC,[16] high-magnetic-field ^{1}H NMR,[17] and ^{13}C NMR.[18] In the case of the presently described sterols having a 27-norergostane-type side chain, diagnostic differences can be noted (Table III) in the chemical shift of the C-21 methyl signal in the ^{1}H NMR spectra.[19] The same tendency has been seen earlier in the ^{1}H NMR spectra of epimeric C-24 alkyl sterols with a conventional side chain.[15,17]

^{13}C NMR spectroscopy (Table IV) is useless in differentiating between such C-24 isomers and so is mass spectrometry. Since the isolation of such C-27 sterols usually yields quantities of material which are insufficient for accurate measurement of specific rotation, ^{1}H NMR measurements at high magnetic field[19] are the most reliable means of making stereochemical assignments.

The utility of the above-summarized conclusions was recently documented in our laboratory[20] by enabling us to make stereochemical assignments at C-24 in the isomeric 27-norergosta-5,7,22-trien-3β-ols (**17a,b**) and 27-norergosta-5,7,9(11),22-tetraen-3β-ols (**18a,b**) which were found to co-occur in the sponge *Axinella cannabina*.



17a: R_1=Me R_2=H
17b: R_1=H R_2=Me



18a: R_1=Me R_2=H
18b: R_1=H R_2=Me

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were taken in chloroform solution (c = 1.0) on a Rudolph Research Autopol III automatic polarimeter equipped with a thermostated 1.00-dm microcell. The 100-MHz ^{1}H NMR spectra were recorded on a Varian XL-100 spectrometer, and 360-MHz ^{1}H-NMR spectra were obtained with a Bruker HX-360 spectrometer in deuteriochloroform solution with tetramethylsilane as an internal reference. ^{13}C NMR spectra were recorded with a Varian FT-80A spectrometer in deuteriochloroform as the solvent and internal reference. Gas–liquid chromatography (GLC) was performed on a Hewlett-Packard 402A chromatograph equipped with a flame-ionization detector and a 1.80 m × 4 mm i.d. U-shaped glass column containing 3% OV-17 on 100/200 Gas-Chrom Q (Applied Scientific, Inc.) and helium as the carrier gas. Capillary GLC was carried out with a Carlo Erba Series 4160 Fractovap chromatograph equipped with a 30 m × 0.32 mm fused silica column coated with SE-54 (J & W Scientific, Inc.) and a flame-ionization detector (hydrogen as the carrier gas). High-performance liquid chromatography (HPLC) was performed with a Waters Associates pump and dual cell refractometer detector and a Whatman Partisil M9 10/50 ODS-2 reverse-phase column or with an Altex ultrasphere ODS 5μ reverse-phase column (10 mm i.d. × 25 cm).

(16) (a) Maxwell, J. R.; Mackenzie, A. S.; Volkman, J. K., *Nature (London)* **1980**, *286*, 694. (b) Itoh, T.; Fukushima, K.; Tamura, T.; Matsumoto, T. *Yukagaku* **1981**, *30*, 586. (c) Thompson, R. H., Jr.; Patterson, G.; Thompson, M. J.; Slover, H. T. *Lipids* **1981**, *16*, 694.

(17) (a) Rubinstein, I.; Goad, L. J.; Clague, A. D. H.; Mulheirn, L. *Phytochemistry* **1976**, *15*, 195. (b) Khalil, M. W.; Idler, D. R.; Patterson, G. W. *Lipids* **1980**, *15*, 69. (c) Iida, T.; Tamura, T.; Matsumoto, T. *J. Lipid Res.* **1980**, *21*, 326.

(18) (a) Wright, J. L. C.; McInnes, A. G.; Shimizu, S.; Smith, D. G.; Walter, J. A.; Idler, D.; Khalil, W. *Can. J. Chem.* **1978**, *56*, 1898. (b) Koizumi, N.; Fujimoto, Y.; Takeshita, T.; Ikekawa, N. *Chem. Pharm. Bull.* **1979**, *27*, 38.

(19) Caution should be exercised in the assignment of the configuration at C-24 position when a sterol has a nucleus different from those described in this report because the diagnostic (cf. Table III) chemical shift of the C-21 methyl group could be affected by certain changes in the nucleus.

(20) Itoh, T.; Sica, D.; Djerassi, C., to be submitted for publication.

Table III. 360-MHz ^{1}H NMR Chemical Shifts ($CDCl_3$) of 27-Nor-24-methyl Sterols

sterol	C-24 config	chemical shift,[d] (J[e]) C-18[a]	C-19[a]	C-21[b]	C-26[c]	C-28[b]
occelasterol (1a)	S/α	0.691[d]	1.009	1.001 (6.0)[e]	0.831 (7.4)	0.927 (6.8)
24-epioccelasterol (1b)	R/β	0.691	1.010	1.009 (6.3)	0.829 (7.4)	0.929 (6.7)
patinosterol (2a)	S/α	0.659	0.802	0.985 (6.7)	0.828 (7.4)	0.923 (6.7)
24-epipatinosterol (2b)	R/β	0.659	0.802	0.991 (6.6)	0.825 (7.4)	0.925 (6.7)
22,23-dihydrooccelasterol (3a)	S/α	0.677	1.008	0.908 (6.5)	0.849 (9.5)	0.846 (7.4)
24-epi-22,23-dihydrooccelasterol (3b)	R/β	0.676	1.008	0.912 (6.5)	0.849 (7.3)	0.840 (6.5)

[a] Singlet. [b] Doublet. [c] Triplet. [d] All values given in parts per million. [e] All values in parentheses are given in Hz.

Table IV. ^{13}C NMR Chemical Shifts of 27-Nor-24-methyl Sterols

atom	chemical shift, ppm 1a	1b	2a	2b	3a	3b
C-1	37.1	37.1	36.9	36.9	37.1	37.1
C-2	31.5	31.5	31.4	31.4	31.5	31.5
C-3	71.6	71.6	71.2	71.2	71.6	71.6
C-4	42.1	42.1	38.1	38.1	42.1	42.1
C-5	140.6	140.5	44.8	44.7	140.6	140.5
C-6	121.5	121.5	29.8	29.7	121.5	121.5
C-7	31.7	31.7	31.9	31.9	31.7	31.7
C-8	31.8	31.7	35.4	35.4	31.7	31.7
C-9	50.0	50.0	54.3	54.3	50.0	50.0
C-10	36.3	36.3	35.3	35.3	36.3	36.3
C-11	20.9	20.9	21.1	21.1	20.9	20.9
C-12	28.4	28.2	28.6	28.6	28.0	28.0
C-13	42.1	42.1	42.4	42.4	42.1	42.1
C-14	56.7	56.6	56.5	56.4	56.6	56.6
C-15	24.1	24.0	24.1	24.0	24.1	24.1
C-16	39.5	39.5	39.8	39.8	39.6	39.6
C-17	55.8	55.8	55.9	56.0	55.9	55.8
C-18	11.9	11.9	12.1	12.1	11.7	11.6
C-19	19.2	19.2	12.1	12.1	18.9	19.3
C-20	38.3	38.0	38.3	38.1	34.6	34.6
C-21	20.8	20.7	20.6	20.4	18.5	18.6
C-22	133.3	133.2	135.2	135.0	32.6	32.6
C-23	135.1	134.9	133.3	133.2	33.0	33.0
C-24	39.9	39.8	40.0	39.9	35.7	35.9
C-25	29.8	29.7	28.5	28.3	29.7	28.9
C-26	20.5	20.3	20.8	20.7	19.2	19.2
C-28	11.7	11.5	11.7	11.5	11.3	11.1

Low-resolution mass spectra were obtained with a Varian MAT-44 spectrometer, and high-resolution mass spectra were recorded on a Varian MAT-711 double-focusing spectrometer equipped with a PDP-11/45 computer for data acquisition and reduction and with a direct-inlet system.

"The usual workup" refers to dilution with water, extraction with ether, washing to neutrality, drying over $MgSO_4$, filtration, and evaporation under vacuum. The following abbreviations were used: ether = diethyl ether, THF = tetrahydrofuran, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(22*R*)- and (22*S*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-yn-22-ol (7a,b). To a suspension of magnesium (6.42 g) in ether (80 mL) was added ethyl bromide (15 mL) over 1 h and the mixture stirred at room temperature for 1 h under argon. The resulting ethylmagnesium bromide solution (44 mL) was added to a solution of propyne (25.2 mL) in THF (64 mL) at −78 °C, and the mixture stirred at −15 °C for 30 min and then at room temperature for 1 h. Benzene (64 mL) was added followed by a solution of the aldehyde 6[9] (6.542 g) in THF (80 mL) at 0 °C. The mixture was stirred at room temperature for 1 h under argon. Saturated ammonium chloride solution was added to quench the reaction. The usual workup gave a crude product which was chromatographed on silica gel. Elution with hexane–ethyl acetate (25:1) gave an oily unknown product (1.025 g). Elution with hexane–ethyl acetate (20:1) afforded a less polar product (**7a**, 2.834 g). Further elution with hexane–ethyl acetate (10:1) gave a 1:1 mixture of less polar and more polar products (0.944 g). Further elution with the same solvent system afforded a more polar product **7b**, 2.233 g (total yield 79.2%).

Less polar product **7a** (22*R* isomer): mp 129–130 °C (ethyl acetate); $[\alpha]^{20}_D$ +52.9°; NMR (100 MHz) δ 0.728 (3 H, s, 18-Me), 1.022 (3 H, s, 19-Me), 1.100 (3 H, d, J = 6.0 Hz, 21-Me), 1.850 (3 H, d, J = 2.1 Hz, C≡CMe), 2.77 (1 H, m, 6-H), 3.318 (3 H, s, OMe), 4.44 (1 H, br, 22-H); MS calcd for $C_{26}H_{40}O_2$ (M^+) m/z 384.3028, found 384.3042.

More polar product **7b** (22*S* isomer): mp 133–134.5 °C (hexane); $[\alpha]^{20}_D$ +56.9°; NMR (100 MHz) δ 0.742 (3 H, s, 18-Me), 1.024 (3 H, s, 19-Me), 1.034 (3 H, d, J = 6.3 Hz, 21-Me), 1.851 (3 H, d, J = 2.2 Hz, C≡CMe), 2.77 (1 H, m, 6-H), 3.320 (3 H, s, OMe), 4.41 (1 H, br, 22-H); MS calcd for $C_{26}H_{40}O_2$ (M^+) m/z 384.3028, found 384.3031.

(22*S*)- and (22*R*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholestan-22-ol (8a,b). A mixture of the 22*R* yne alcohol **7a** (120 mg) and 5% Pd/C (30 mg) in ethyl acetate (10 mL) was stirred at room temperature for 2 h under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated to give a product which was purified by chromatography on silica gel. Elution with hexane gave hydrogenolysis product **8c** (37 mg) as an oil: NMR (100 MHz) δ 0.714 (3 H, s, 18-Me), 0.904 (3 H, d, J = 5.7 Hz, 21-Me), 1.021 (3 H, s, 19-Me), 2.77 (1 H, m, 6-H), 3.320 (3 H, s, OMe); MS m/z 372 ($C_{26}H_{44}O$, M^+), 357, 340, 325, 317, 255.

Elution with hexane–ethyl acetate (100:1) afforded the 22*S*-alcohol **8a** (74 mg) as an oil: NMR (100 MHz) δ 0.728 (3 H, s, 18-Me), 0.975 (3 H, d, J = 6.8 Hz, 21-Me), 1.024 (3 H, s, 19-Me), 2.78 (1 H, m, 6-H), 3.323 (3 H, s, OMe), 3.70 (1 H, m, 22-H); MS m/z 388 ($C_{26}H_{44}O_2$, M^+), 373, 356, 341, 333, 315, 283.

The 22*S* yne alcohol **7b** (120 mg) was similarly hydrogenated to give the hydrogenolysis product **8c** (27 mg) and the (22*R*)-alcohol **8b** (63 mg) as oils: NMR (100 MHz) δ 0.793 (3 H, s, 18-Me), 0.911 (3 H, d, J = 6.6 Hz, 21-Me), 1.023 (3 H, s, 19-Me), 2.77 (1 H, m, 6-H), 3.320 (3 H, s, OMe), 3.68 (1 H, m, 22-H). The mass spectrum of **8b** was identical with that of **8a**.

(22*S*)- and (22*R*)-26,27-Dinorcholest-5-ene-3β,22-diol (9a,b). A solution of the i-methyl ether **8a** (60 mg) and a catalytic amount of *p*-toluenesulfonic acid in 10% aqueous dioxane (5 mL) was heated at reflux for 1 h. The usual workup gave a product which was chromatographed on silica gel. Elution with hexane–ethyl acetate (5:1) afforded the (22*S*)-diol **9a**: 45 mg; mp 209 °C (dichloromethane–methanol); $[\alpha]^{20}_D$ −54.3°; NMR (100 MHz) δ 0.692 (3 H, s, 18-Me), 1.011 (3 H, s, 19-Me), 3.30–3.80 (2 H, m, 3,22-H_2), 5.36 (1 H, m, 6-H); MS m/z 374 ($C_{25}H_{42}O_2$, M^+), 359, 356, 341, 338, 331, 323, 302.

The (22*R*)-alcohol **8b** (50 mg) yielded the (22*R*)-diol **9b**: 46 mg; mp 181–183 °C dec (dichloromethane–methanol); $[\alpha]^{20}_D$ −35.0°; NMR (100 MHz) δ 0.703 (3 H, s, 18-Me), 1.011 (3 H, s, 19-Me), 3.30–3.80 (2 H, m, 3-, 22-H), 5.36 (1 H, m, 6-H). The mass spectrum of **9b** was identical with that of **9a**.

(22*S*)- and (22*R*)-26,27-Dinorcholest-5-ene-3β,22-diol Diacetate (9c,d). The (22*S*)-diol **9a** (25 mg) was acetylated with acetic anhydride (0.5 mL) and pyridine (0.5 mL) to yield the (22*S*)-diacetate **9c**: 27 mg; mp 132 °C (acetone–methanol); $[\alpha]^{20}_D$ −58.7°; NMR (100 MHz) δ 0.679 (3 H, s, 18-Me), 1.015 (3 H, s, 19-Me), 2.028 and 2.033 (6 H, 2 s, 3-, 22-OCOMe), 4.58 (1 H, m, 3-H), 4.99 (1 H, m, 22-H), 5.37 (1 H, m, 6-H); MS m/z 398 (M^+ − CH_3COOH), 383, 356, 338, 323, 309, 295, 281, 253.

The (22*R*)-diol **9b** (33 mg) was acetylated to give the (22*R*)-diacetate **9d**: 34 mg; mp 100–101 °C (acetone–methanol); $[\alpha]^{20}_D$ −22.8°; NMR (100 MHz) δ 0.679 (3 H, s, 18-Me), 1.014 (3 H, s, 19-Me), 2.028 (6 H, s, 3-, 22-OCOMe), 4.60 (1 H, m, 3-H), 4.90 (1 H, m, 6-H), 5.38 (1 H, m, 6-H). The mass spectrum of **9d** was identical with that of **9c**.

Grignard Reaction of the 22-Aldehyde 6 with 1-Bromopropane. 1-Bromopropane (2.63 mL) was added dropwise to a

suspension of magnesium (775 mg) in dry THF (20 mL) at room temperature under argon. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of the 22-aldehyde **6** (450 mg) in dry THF (50 mL) was added to the Grignard reagent at 0 °C, and the whole was stirred at room temperature for 1 h under argon. The reaction was quenched by the addition of saturated ammonium chloride solution, and the usual workup afforded a crude product. Chromatography on silica gel with hexane–ethyl acetate (50:1) as the eluent gave the 22-alcohol **8a**: 452 mg; NMR (100 MHz) δ 0.728 (3 H, s, 18-Me), 1.025 (3 H, s, 19-Me), 2.78 (1 H, m, 6-H), 3.323 (3 H, s, OMe), 3.70 (1 H, br, 22-H). Without further purification, a 240-mg sample of **8a** was converted to the 3β-alcohol **9a**: mp 209.5 °C (dichloromethane–methanol); $[\alpha]^{20}_D$ −48.0°; NMR (100 MHz) δ 0.692 (3 H, s, 18-Me), 1.011 (3 H, s, 19-Me), 3.30–3.80 (2 H, m, 3-, 22-H), 5.36 (1 H, m, 6-H).

The 3,22-diol **9a** (45 mg) was acetylated to give the 3,22-diacetate **9c**: 47 mg; mp 131 °C (acetone–methanol); $[\alpha]^{20}_D$ −55.3°; NMR (100 MHz) δ 0.680 (3 H, s, 18-Me), 1.015 (3 H, s, 19-Me), 2.028 and 2.033 (6 H, 2 s, 3-, 22-OCOMe), 4.58 (1 H, m, 3-H), 4.99 (1 H, m, 22-H), 5.36 (1 H, m, 6-H). The physical, chromatographic, and spectral data are in good agreement with those of **9a** and **9c** obtained by the alternate route via **7a**.

(22*S*,23*Z*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-en-22-ol (10a). A mixture of the 22*R* acetylenic alcohol **7a** (1.2 g), Lindlar catalyst (120 mg), and quinoline (1 mL) in hexane (60 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h. The catalyst was removed and washed with hexane. The usual workup gave a crude product which was crystallized from acetone–methanol to afford the 22*S*,23*Z* allylic alcohol **10a**: 0.969 g; mp 85–87 °C; $[\alpha]^{20}_D$ +43.0°; NMR (100 MHz) δ 0.730 (3 H, s, 18-Me), 0.956 (3 H, d, J = 5.8 Hz, 21-Me), 1.025 (3 H, s, 19-Me), 1.661 (3 H, d, J = 5.2 Hz, C=CMe), 2.78 (1 H, m, 6-H), 3.326 (3 H, s, OMe), 4.509 (1 H, br d, J = 6.0 Hz, 22-H), 5.510 (2 H, m, 23-, 24-H); MS calcd for $C_{26}H_{42}O_2$ (M^+) m/z 386.3185, found 386.3201.

(22*S*,23*E*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-en-22-ol (11a). A suspension of the 22*R* acetylenic alcohol **7a** (350 mg) and lithium aluminum hydride (104 mg) in THF (8 mL) was stirred at reflux for 16 h under nitrogen. Moist ether and then water were carefully added to decompose excess hydrides. The usual workup gave a crude product (413 mg). Chromatography on silica gel with hexane–ethyl acetate (20:1) as the eluent afforded the 22*S*,23*E* allylic alcohol **11a**: 299 mg; mp 103–104 °C (hexane); $[\alpha]^{20}_D$ +26.2°; NMR (100 MHz) δ 0.726 (3 H, s, 18-Me), 0.899 (3 H, d, J = 5.8 Hz, 21-Me), 1.022 (3 H, s, 19-Me), 1.699 (3 H, d, J = 4.9 Hz, C=CMe), 2.578 (1 H, m, 6-H), 3.321 (3 H, s, OMe), 4.18 (1 H, br, 22-H), 5.518 (2 H, m, 23-, 24-H); MS calcd for $C_{26}H_{42}O_2$ (M^+) m/z 386.3185, found 386.3151.

(22*R*,23*Z*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-en-22-ol (10b). The 22*S* acetylenic alcohol **7b** (350 mg) was hydrogenated under the same conditions as for **7a** to afford the 22*R*,23*Z* allylic alcohol **10b** (339 mg) as an amorphous solid: $[\alpha]^{20}_D$ +26.4°; NMR (100 MHz) δ 0.753 (3 H, s, 18-Me), 1.005 (3 H, d, J = 6.6 Hz, 21-Me), 1.019 (3 H, s, 19-Me), 1.727 (3 H, d, J = 5.2 Hz, C=CMe), 2.770 (1 H, m, 6-H), 3.318 (3 H, s, OMe), 4.51 (1 H, dd, J = 8.2, 3.6 Hz, 22-H), 5.60 (2 H, m, 23-, 24-H); MS calcd for $C_{26}H_{42}O_2$ (M^+) m/z 386.3185, found 386.3185.

(22*R*,23*E*)-26,27-Dinor-3α,5-cyclo-6β-methoxy-5α-cholest-23-en-22-ol (11b). To a solution of the 22*S* acetylenic alcohol **7b** (1.2 g) in ether (30 mL) was added dropwise a solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al; 70% in toluene, 2 mL) in ether (5 mL) at room temperature under argon. The mixture was stirred at reflux for 2 days. After the mixture cooled to room temperature, 10% sulfuric acid solution (25 mL) was added and the mixture extracted with ether. After the usual workup the crude product (1.324 g) was purified by chromatography on silica gel. Elution with hexane–ethyl acetate (20:1) gave the 22*R*,23*E* allylic alochol **11b**: 885 mg; mp 129–130 °C (hexane); $[\alpha]^{20}_D$ +52.1°; NMR (100 MHz) δ 0.745 (3 H, s, 18-Me), 0.946 (3 H, d, J = 6.7 Hz, 21-Me), 1.020 (3 H, s, 19-Me), 1.717 (3 H, d, J = 5.1 Hz, C=CMe), 2.76 (1 H, m, 6-H), 3.318 (3 H, s, OMe), 4.12 (1 H, br dd, J = 6.8, 3.6 Hz, 22-H), 5.58 (2 H, m, 23-, 24-H); MS calcd for $C_{26}H_{42}O_2$ (M^+) m/z 386.3185, found 386.3176.

Ethyl (22*E*,24*S*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholest-22-en-26-oate (12a). (A) From the (22*S*,23*Z*)-Alcohol 10a. A solution of the (22*S*,23*Z*)-alcohol **10a** (430 mg), triethyl orthoacetate (0.52 mL), and 2 drops of propionic acid in xylene (12 mL) was heated at 130 °C for 2 h under argon. The solvent was evaporated under vacuum, and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (100:1) yielded the (24*S*)-26-oate **12a**: 481 mg; oil; $[\alpha]^{20}_D$ +42.5°; NMR (360 MHz) δ 0.713 (3 H, s, 18-Me), 0.985 (3 H, d, J = 7.7 Hz, 28-Me), 1.006 (3 H, d, J = 7.2 Hz, 21-Me), 1.019 (3 H, s, 19-Me), 1.246 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 2.77 (1 H, m, 6-H), 3.321 (2 H, s, OMe), 4.105 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 5.23 (2 H, m, 22-, 23-H); MS calcd for $C_{30}H_{48}O_3$ (M^+) m/z 456.3603, found 456.3600.

(B) From the (22*R*,23*E*)-Alcohol 11b. The (22*R*,23*E*)-alcohol **11b** (688 mg) was converted to the (22*E*,24*S*)-26-oate **12a** (774 mg) in the same way as described in part A. All physical and spectral data of this product were identical with those of the product derived from the (22*S*,23*Z*)-alcohol **10a**.

Ethyl (22*E*,24*R*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholest-22-en-26-oate (12b). (A) From the (22*R*,23*Z*)-Alcohol 10b. Claisen rearrangement of the 22*R*,23*Z* allylic alcohol **10b** (300 mg) under the same conditions as for **12a** yielded the (24*R*)-26-oate **12b**: 262 mg; oil; $[\alpha]^{20}_D$ +21.0°; NMR (360 MHz) δ 0.716 (3 H, s, 18-Me), 0.976 (3 H, d, J = 6.6 Hz, 28-Me), 1.010 (3 H, d, J = 7.1 Hz, 21-Me), 1.019 (3 H, s, 19-Me), 1.250 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 2.77 (1 H, m, 6-H), 3.232 (3 H, s, OMe), 4.107 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 5.23 (2 H, m, 22-, 23-H); MS calcd for $C_{30}H_{48}O_3$ (M^+) m/z 456.3603, found 456.3616.

(B) From the (22*S*,23*E*)-Alcohol 11a. Claisen rearrangement of the (22*S*,23*E*)-alcohol **11a** (690 mg) afforded the (24*R*)-26-oate **12b** (680 mg). All physical and spectral data were identical with those of the product derived from the (22*R*,23*Z*)-alcohol **12b**.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholest-22-en-26-ol (13a,b). To a suspension of lithium aluminum hydride (480 mg) in dry ether (30 mL) was added dropwise a solution of the ester **12a** (580 mg) in dry ether (10 mL) at 0 °C, and the mixture was stirred at reflux for 1 h. The usual workup gave the 26-alcohol **13a**: 503 mg; amorphous solid; $[\alpha]^{20}_D$ +46.7°; NMR (360 MHz) δ 0.725 (3 H, s, 18-Me), 0.980 (3 H, d, J = 6.8 Hz, 28-Me), 0.998 (3 H, d, J = 6.7 Hz, 21-Me), 1.022 (3 H, s, 19-Me), 2.77 (1 H, m, 6-H), 3.324 (3 H, s, OMe), 3.65 (2 H, m, 26-H_2), 5.164 and 5.247 (2 H, 2 dd, J = 13.4, 6.8 Hz, 22-, 23-H); MS calcd for $C_{28}H_{46}O_2$ (M^+) m/z 414.3498, found 414.3490.

The ester **12b** (660 mg) was reduced in the same way to give the 26-alcohol **13b**: 587 mg; oil; $[\alpha]^{20}_D$ +18.6°; NMR (360 MHz) δ 0.725 (3 H, s, 18-Me), 0.983 (3 H, d, J = 6.9 Hz, 28-Me), 1.002 (3 H, d, J = 6.8 Hz, 21-Me), 1.022 (3 H, s, 19-Me), 2.78 (1 H, m, 6-H), 3.324 (3 H, s, OMe), 3.65 (2 H, m, 26-H_2), 5.186 and 5.265 (2 H, 2 dd, J = 14.4, 6.8 Hz, 22-, 23-H); MS calcd for $C_{28}H_{46}O_2$ (M^+) m/z 414.3498, found 414.3512.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholest-22-en-26-ol *p*-Toluenesulfonate (13c,d). A solution of the 26-alcohol **13a** (560 mg) and *p*-toluenesulfonyl chloride (387 mg) in pyridine (10 mL) was stirred at room temperature overnight. The usual workup and chromatography on silica gel afforded the 26-tosylate **13c**: 521 mg; NMR (100 MHz) δ 0.697 (3 H, s, 18-Me), 0.914 (3 H, d, J = 6.7 Hz, 28-Me), 0.939 (3 H, d, J = 6.6 Hz, 21-Me), 1.026 (3 H, s, 19-Me), 2.453 (3 H, s, OSO_2PhMe), 2.78 (1 H, m, 6-H), 3.330 (3 H, s, OMe), 4.02 (2 H, m, CH_2OTs), 5.02 (2 H, m, 22-, 23-H), 7.35 and 7.79 (4 H, 2 d, J = 8.5 Hz, OSO_2PhMe).

The 26-alcohol **13b** (580 mg) was converted to the 26-tosylate **13d** (650 mg) in the same way: NMR (100 MHz) δ 0.702 (3 H, s, 18-Me), 0.915 (6 H, d, J = 6.6 Hz, 21-, 28-Me), 1.024 (3 H, s, 19-Me), 2.448 (3 H, s, OSO_2PhMe), 2.78 (1 H, m, 6-H), 3.324 (3 H, s, OMe), 4.00 (2 H, m, CH_2OTs), 5.05 (2 H, m, 22-, 23-H), 7.36 and 7.80 (4 H, 2 d, J = 8.5 Hz, OSO_2PhMe).

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholest-22-ene (14a,b). To a suspension of lithium aluminum hydride (282 mg) in THF (16 mL) was added dropwise a solution of the 26-tosylate **13c** (421 mg) in THF (4 mL) at 0 °C, and the mixture was stirred at reflux for 1 h. The usual workup afforded the i-methyl ether **14a**: 290 mg; oil; $[\alpha]^{20}_D$ +44.2°;

NMR (360 MHz) δ 0.727 (3 H, s, 18-Me), 0.833 (3 H, t, J = 7.4 Hz, 26-Me), 0.928 (3 H, d, J = 6.7 Hz, 28-Me), 0.996 (3 H, d, J = 6.6 Hz, 21-Me), 1.023 (3 H, s, 19-Me), 2.78 (1 H, m, 6-H), 3.323 (3 H, s, OMe), 5.144 (2 H, m, 22-, 23-H); MS calcd for $C_{28}H_{46}O$ (M^+) m/z 398.3549, found 398.3554.

The 26-tosylate **13d** (520 mg) was reduced in the same way to yield the i-methyl ether **14b**: 350 mg; oil; $[\alpha]^{20}_D$ +25.2°; NMR (360 MHz) δ 0.727 (3 H, s, 18-Me), 0.829 (3 H, t, J = 7.4 Hz, 26-Me), 0.930 (3 H, d, J = 6.7 Hz, 28-Me), 1.003 (3 H, d, J = 6.6 Hz, 21-Me), 1.024 (3 H, s, 19-Me), 2.77 (1 H, m, 6-H), 3.324 (3 H, s, OMe), 5.16 (2 H, m, 22-, 23-H); MS calcd for $C_{28}H_{46}O$ (M^+) m/z 398.3549, found 398.3542.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-24-methylcholesta-5,22-dien-3β-ol (1a,b). A solution of the i-methyl ether **14a** (290 mg) and a catalytic amount of *p*-toluenesulfonic acid in 10% aqueous dioxane (20 mL) was stirred at reflux for 1 h. The usual workup and chromatography on silica gel with hexane–ethyl acetate (10:1) as the eluent gave the 3β-alcohol **1a**: 216 mg; mp 137.5 °C (methanol); $[\alpha]^{20}_D$ −37.9°; NMR (360 MHz) δ 0.691 (3 H, s, 18-Me), 0.831 (3 H, t, J = 7.4 Hz, 26-Me), 0.927 (3 H, d, J = 6.8 Hz, 28-Me), 1.001 (3 H, d, J = 6.0 Hz, 21-Me), 1.009 (3 H, s, 19-Me), 3.53 (1 H, m, 3-H), 5.164 (2 H, m, 22-, 23-H), 5.36 (1 H, m, 6-H); MS calcd for $C_{27}H_{44}O$ (M^+) m/z 384.3392, found 384.3372.

The i-methyl ether **14b** (358 mg) was similarly converted to the 3β-alcohol **1b**: 342 mg; mp 137 °C (methanol); $[\alpha]^{20}_D$ −61.0°; NMR (360 MHz) δ 0.691 (3 H, s, 18-Me), 0.829 (3 H, t, J = 7.4 Hz, 26-Me), 0.929 (3 H, d, J = 6.7 Hz, 28-Me), 1.009 (3 H, d, J = 6.3 Hz, 21-Me), 1.010 (3 H, s, 19-Me), 3.52 (1 H, m, 3-H), 5.161 (2 H, m, 22-, 23-H), 5.36 (1 H, m, 6-H); MS calcd for $C_{27}H_{44}O$ (M^+) m/z 384.3392, found 384.3382.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-24-methylcholesta-5,22-dien-3β-ol Acetate (1c,d). A solution of the 3β-alcohol **1a** (40 mg) was acetylated with acetic anhydride (0.5 mL) and pyridine (0.5 mL) to give the acetate **1c**: 42 mg; mp 148.5 °C (acetone–methanol); $[\alpha]^{20}_D$ −41.7°; NMR (360 MHz) δ 0.689 (3 H, s, 18-Me), 0.831 (3 H, t, J = 7.4 Hz, 26-Me), 0.927 (3 H, d, J = 6.7 Hz, 28-Me), 1.002 (3 H, d, J = 6.7 Hz, 21-Me), 1.019 (3 H, s, 19-Me), 2.033 (3 H, s, OCOMe), 4.61 (1 H, m, 3-H), 5.16 (1 H, m, 6-H); MS calcd for $C_{27}H_{42}$ ($M^+ - CH_3COOH$) m/z 366.3287, found 366.3266.

The 3β-alcohol **1b** (40 mg) was acetylated to give the acetate **1c**: 43 mg; mp 148 °C (acetone–methanol); $[\alpha]^{20}_D$ −68.5°; NMR (360 MHz) δ 0.688 (3 H, s, 18-Me), 0.829 (3 H, t, J = 7.4 Hz, 26-Me), 0.929 (3 H, d, J = 6.7 Hz, 28-Me), 1.009 (3 H, d, J = 7.1 Hz, 21-Me), 1.019 (3 H, s, 19-Me), 2.033 (3 H, s, OCOMe), 4.61 (1 H, m, 3-H), 5.17 (2 H, m, 22-, 23-H), 5.37 (1 H, m, 6-H); MS calcd for $C_{27}H_{42}$ ($M^+ - CH_3COOH$) m/z 366.3287, found 366.3297.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-24-methylcholesta-4,22-dien-3-one (15a,b). To a solution of the 3β-alcohol **1a** (105 mg) in dry acetone (2 mL) and dry benzene (2 mL) was added in one portion a solution of aluminum isopropoxide (84 mg) in refluxing dry benzene (2 mL). The mixture was stirred at 75–80 °C for 16 h under nitrogen. After the mixture cooled to room temperature, water (1 mL) and then 10% sulfuric acid solution (2 mL) were added, and the mixture was stirred vigorously. The organic layer was separated, and the aqueous layer was extracted with benzene. The usual workup gave a crude product which was chromatoraphed on silica gel. Elution with hexane–ethyl acetate (50:1) yielded the enone **15a**: 56 mg; mp 106–118 °C (acetone–methanol); $[\alpha]^{20}_D$ +64.8°; NMR (360 MHz) δ 0.722 (3 H, s, 18-Me), 0.833 (3 H, t, J = 7.4 Hz, 26-Me), 0.929 (3 H, d, J = 6.6 Hz, 28-Me), 0.999 (3 H, d, J = 6.5 Hz, 21-Me), 1.182 (3 H, s, 19-Me), 5.15 (2 H, m, 22-, 23-H), 5.722 (1 H, s, 4-H); MS calcd for $C_{27}H_{42}O$ (M^+) m/z 382.3236, found 382.3228.

The 3β-alcohol **1b** (100 mg) was converted to the enone **15b** (59 mg) in the same way: mp 103.5–104.5 °C (acetone–methanol); $[\alpha]^{20}_D$ +38.6°; NMR (360 MHz) δ 0.721 (3 H, s, 18-Me), 0.829 (3 H, t, J = 7.4 Hz, 26-Me), 0.930 (3 H, d, J = 6.7 Hz, 28-Me), 1.005 (3 H, d, J = 6.6 Hz, 21-Me), 1.181 (3 H, s, 19-Me), 5.16 (2 H, m, 22-, 23-H), 5.722 (1 H, s, 4-H); MS calcd for $C_{27}H_{42}O$ (M^+) m/z 382.3236, found 382.3251.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-24-methyl-5α-cholest-22-en-3β-ol (2a,b). To a solution of lithium (60 mg) in ammonia (20 mL) and absolute ethanol (8 mL) at −78 °C was added a solution of the enone **15a** (30 mg) in dry ether (5 mL). The mixture was stirred at the same temperature for 1.5 h. Ammonium chloride (500 mg) was carefully added, and the ammonia was then allowed to evaporate. The usual workup gave a crude product which was chromatographed on silica gel. Elution with hexane–ethyl acetate (10:1) gave the 3β-alcohol **2a**: 27 mg; mp 147 °C (methanol) $[\alpha]^{20}_D$ +23.0°; NMR (360 MHz) δ 0.659 (3 H, s, 18-Me), 0.802 (3 H, s, 19-Me), 0.828 (3 H, t, J = 7.4 Hz, 26-Me), 0.923 (3 H, d, J = 6.7 Hz, 28-Me), 0.985 (3 H, d, J = 6.7 Hz, 21-Me), 3.59 (1 H, m, 3-H), 5.134 (2 H, m, 22-, 23-H); MS calcd for $C_{27}H_{46}O$ (M^+) m/z 386.3549, found 386.3554.

By the same procedure the enone **15b** (40 mg) was converted to the 3β-alcohol **2b**: 34 mg; mp 140 °C (methanol); $[\alpha]^{20}_D$ −8.7°; NMR (360 MHz) δ 0.659 (3 H, s, 18-Me), 0.802 (3 H, s, 19-Me), 0.825 (3 H, t, J = 7.4 Hz, 26-Me), 0.925 (3 H, d, J = 6.7 Hz, 28-Me), 0.991 (3 H, d, J = 6.6 Hz, 21-Me), 3.59 (1 H, m, 3-H), 5.150 (2 H, m, 22-, 23-H); MS calcd for $C_{27}H_{46}O$ (M^+) m/z 386.3549, found 386.3561.

(22*E*,24*S*)- and (22*E*,24*R*)-27-Nor-24-methyl-5α-cholest-22-en-3β-ol Acetate (2c,d). The 3β-alcohol **2a** (15 mg) was acetylated to give the acetate **2c**: 16 mg; mp 137–137.5 °C (acetone–methanol); $[\alpha]^{20}_D$ +8.9°; NMR (360 MHz) δ 0.657 (3 H, s, 18-Me), 0.816 (3 H, s, 19-Me), 0.828 (3 H, t, J = 7.2 Hz, 26-Me), 0.923 (3 H, d, J = 6.7 Hz, 28-Me), 0.984 (3 H, d, J = 6.6 Hz, 21-Me), 2.020 (3 H, s, OCOMe), 4.68 (1 H, m, 3-H), 5.134 (2 H, m, 22-, 23-H); MS calcd for $C_{29}H_{48}O$ (M^+) m/z 428.3654, found 428.3633.

The 3β-alcohol **2b** (15 mg) was acetylated to give the acetate **2d**: 16 mg; mp 134–135 °C (acetone–methanol); $[\alpha]^{20}_D$ −9.8°; NMR (360 MHz) δ 0.657 (3 H, s, 18-Me), 0.817 (3 H, s, 19-Me), 0.826 (3 H, t, J = 7.4 Hz, 26-Me), 0.925 (3 H, d, J = 6.7 Hz, 28-Me), 0.992 (3 H, d, J = 6.7 Hz, 21-Me), 2.020 (3 H, s, OCOMe), 4.68 (1 H, m, 3-H), 5.151 (2 H, m, 22-, 23-H); MS calcd for $C_{29}H_{48}O$ (M^+) m/z 428.3654, found 428.3648.

(24*S*)- and (24*R*)-27-Nor-3α,5-cyclo-6β-methoxy-24-methyl-5α-cholestane (16a,b). A mixture of the olefin **14a** (44 mg) and 5% Pd/C (5 mg) in ethyl acetate (10 mL) was stirred under a hydrogen atmosphere for 2 h. The catalyst was filtered and washed with ethyl acetate. The filtrate was concentrated to give the i-methyl ether **16a**: 41 mg; oil; $[\alpha]^{20}_D$ +49.1°; NMR (360 MHz) δ 0.714 (3 H, s, 18-Me), 0.836 (3 H, t, J = 6.1 Hz, 26-Me), 0.867 (3 H, d, J = 7.4 Hz, 28-Me), 0.902 (3 H, d, J = 6.6 Hz, 21-Me), 1.021 (3 H, s, 19-Me), 2.77 (1 H, m, 6-H), 3.322 (3 H, s, OMe); MS m/z 400 (M^+), 385, 368, 359, 353, 345, 342, 313, 255.

The olefin **14b** (45 mg) was hydrogenated to give the i-methyl ether **16b**: 45 mg; oil; $[\alpha]^{20}_D$ +42.2°; NMR (360 MHz) δ 0.713 (3 H, s, 18-Me), 0.850 (3 H, t, J = 6.5 Hz, 26-Me), 0.844 (3 H, d, J = 8.8 Hz, 28-Me), 0.907 (3 H, d, J = 6.4 Hz, 21-Me), 1.021 (3 H, s, 19-Me) 2.77 (1 H, m, 6-H), 3.322 (3 H, s, OMe). The mass spectrum of **16b** was identical with that of **16a**.

(24*S*)- and (24*R*)-27-Nor-24-methylcholest-5-en-3β-ol (3a,b). The i-methyl ether **16a** (32 mg) was converted by the same method as for **1a** to the 3β-alcohol **3a**: 28 mg; mp 147–149 °C (methanol); $[\alpha]^{20}_D$ +34.0°; NMR (360 MHz) δ 0.677 (3 H, s, 18-Me), 0.846 (3 H, d, J = 7.4 Hz, 28-Me), 0.849 (3 H, t, J = 9.5 Hz, 26-Me), 0.908 (3 H, d, J = 6.5 Hz, 21-Me), 1.008 (3 H, s, 19-Me), 3.53 (1 H, m, 3-H), 5.356 (1 H, m, 6-H); MS calcd for $C_{27}H_{46}O$ (M^+) m/z 386.3559, found 386.3513.

The i-methyl ether **16b** (32 mg) was converted to the 3β-alcohol **3b**: 29 mg; mp 153–154 °C (methanol); $[\alpha]^{20}_D$ −38.5°; NMR (360 MHz) δ 0.676 (3 H, s, 18-Me), 0.840 (3 H, d, J = 6.5 Hz, 28-Me), 0.849 (3 H, t, J = 7.3 Hz, 26-Me), 0.912 (3 H, d, J = 6.5 Hz, 21-Me), 1.008 (3 H, s, 19-Me), 3.54 (1 H, m, 3-H), 5.353 (1 H, m, 6-H); MS calcd for $C_{27}H_{46}O$ (M^+) m/z 386.3559, found 386.3539.

(24*S*)- and (24*R*)-27-Nor-24-methylcholest-5-en-3β-ol (3c,d). The 3β-alcohol **3a** (30 mg) was acetylated to give the acetate **3c**: 32 mg; mp 138 °C (acetone–methanol); $[\alpha]^{20}_D$ −35.5°; NMR (360 MHz) δ 0.674 (3 H, s, 18-Me), 0.845 (3 H, d, J = 7.2 Hz, 28-Me), 0.849 (3 H, t, J = 6.4 Hz, 26-Me), 0.907 (3 H, d, J = 6.4 Hz, 21-Me), 1.017 (3 H, s, 19-Me), 2.033 (3 H, s, OCOMe), 4.52 (1 H, m, 3-H), 5.378 (1 H, m, 6-H); MS, calcd for $C_{27}H_{44}$ ($M^+ - CH_3COOH$) m/z 368.3443, found 368.3426.

The 3β-alcohol **3b** (28 mg) was acetylated to afford the acetate **3d**: 30 mg; mp 137–138 °C (acetone–methanol); $[\alpha]^{20}_D$ −34.6°; NMR (360 MHz) δ 0.674 (3 H, s, 18-Me), 0.840 (3 H, d, J = 6.5 Hz, 28-Me), 0.849 (3 H, t, J = 7.8 Hz, 26-Me), 0.912 (3 H, d, J = 6.5 Hz, 21-Me), 1.018 (3 H, s, 19-Me), 2.033 (3 H, s, OCOMe), 4.61 (1 H, m, 3-H), 5.376 (1 H, br m, 6-H); MS calcd for $C_{27}H_{44}$

($M^+ - CH_3COOH$) m/z 368.3443, found 368.3427.

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Stereoselectivities in Methylcyclopropanations of Cycloalken-3-ols with Ethylidene Iodide Using Zinc Dust–Cuprous Chloride or Diethylzinc Reagents

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A study of stereoselectivity differences in methylcyclopropanations of cycloalken-3-ols with ethylidene iodide using zinc dust–cuprous chloride or diethylzinc reagents has been carried out for the entire cyclopenten-3-ol to cycloocten-3-ol series. For each of the systems, both reagents afforded the same products and in very similar ratios. Also, with either reagent the stereoselectivities for endo/exo alcohol formation with ethylidene iodide paralleled those observed on using a zinc–copper couple with methylene iodide. The [3.1.0] and [4.1.0] alcohol products were exclusively endo, the [5.1.0] products were predominantly endo, and the [6.1.0] products were exclusively exo. Furthermore, endo alcohol formation was associated with preferential *anti*-methyl stereochemistry, and exo alcohol formation with preferential *syn*-methyl stereochemistry.

We recently reported[1] our discovery that methylcyclopropanations of allylic alcohols with ethylidene iodide do not require use of diethylzinc[2] or ethylzinc iodide[3] reagents as previously believed. Instead, they may be accomplished readily and in high yields by using the more convenient zinc dust–cuprous chloride reagent.[4] In a continuation of our investigations into this procedural variation, the yields and stereoselectivity differences in the reactions of ethylidene iodide with the entire cyclopenten-3-ol to cycloocten-3-ol series using either the zinc dust–cuprous chloride or the diethylzinc reagent were examined. The results of this study are described below.

Results and Discussion

Stereoselectivities in Reactions of Cycloalken-3-ols with Ethylidene Iodide. In earlier work we[1] had determined the zinc dust–cuprous chloride promoted methylcyclopropanation products of cyclopenten-3-ol and cycloocten-3-ol with ethylidene iodide, and Kawabata and co-workers[5] had determined the diethylzinc-promoted methylcyclopropanation products of cyclohexen-3-ol, cycloheptenol-3-ol, and cycloocten-3-ol with ethylidene iodide. Thus, for completion of the series, only the zinc dust–cuprous chloride promoted reactions of cyclohexen-3-ol and cycloheptenol-3-ol and the diethylzinc-promoted reaction of cyclopenten-3-ol with ethylidene iodide needed to be carried out. However, as initial studies revealed conflicting results in the zinc dust–cuprous chloride and in the literature[5] diethylzinc-promoted reactions of ethylidene iodide with cycloheptenol-3-ol, a diethylzinc-promoted reaction of cycloheptenol-3-ol with ethylidene iodide was also run. The results are summarized in Table I.

The methylcyclopropanation stereoselectivities for both the zinc dust–cuprous chloride and diethylzinc-promoted reactions of cycloalken-3-ols with ethylidene iodide were found with all of the systems to be almost identical. This indicates that in these reactions either the same reactive intermediates are involved with both zinc reagents or that it is unimportant to the reaction stereochemistries whether an ethyl group or an iodo group is present on zinc.

Comparison of the results summarized in Table I with published data[6,7] reveals that with a given cycloalken-3-ol, the endo/exo alcohol product stereochemistries are the same for cyclopropanations with either ethylidene iodide or with methylene iodide. Thus, both reagents give exclusively endo alcohol products in the [3.1.0] and [4.1.0] systems, a mixture predominating in endo of endo and exo alcohol products in the [5.1.0] system, and exclusively exo alcohol products in the [6.1.0] system.

The results in Table I also indicate that for the [3.1.0] and [4.1.0] systems where endo alcohol stereochemistry predominates, *anti*-methyl stereochemistry predominates. On the other hand, exo alcohol stereochemistry in the [6.1.0] system is associated with predominant *syn*-methyl stereochemistry. The product mixture in the 8-methyl-2-bicyclo[5.1.0]octanol system is rather complex. However, predominance of the endo,anti over the endo,syn and the exo,syn over the exo,anti products appears to follow the

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