A Stereoselective Synthesis of Two Stereoisomers of Demethylgorgosterol

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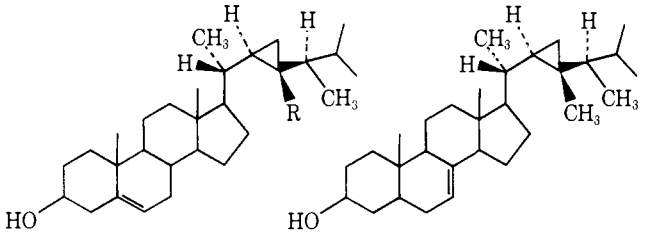
Abstract: A synthesis of the 22*S*,23*S*,24*S* and 22*S*,23*S*,24*R* isomers of the marine sterol demethylgorgosterol from stigmasterol is described. The stereochemistry of the synthetic material was confirmed by an X-ray crystallographic analysis of one of the synthetic intermediates.

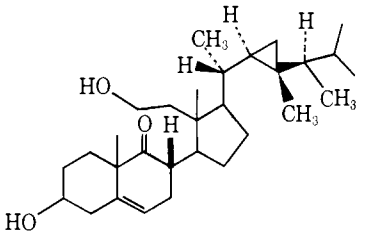
Discussion

In connection with our work on steroids and terpenoids from marine sources and because the very existence of the unusual cyclopropane-containing marine sterols gorgosterol (**1**),[2] demethylgorgosterol (**2**),[3] acanthasterol (**3**),[4] and 9-oxo-9,11-secogorgost-5-ene-3β,11-diol (**4**)[5] raises new questions about the mechanism of biological C-alkylations, we have been engaged in synthetic studies of such sterols for a number of years. Since the X-ray crystallographic analysis[2,5] of **1, 2,** and **4,** had established the presence of a trans cyclopropane ring (carbons 22, 23, and 24, all have *R* stereochemistry), methylenation of a trans Δ^{22} steroidal olefin, after appropriate protection of the Δ^5-3β-hydroxy system, appeared to be an attractive route.



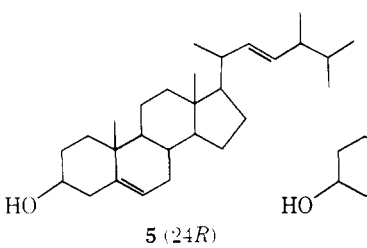
1, R = CH_3 (22*R*,23*R*,24*R*)
2, R = H (22*R*,23*R*,24*R*)

3 (22*R*,23*R*,24*R*)

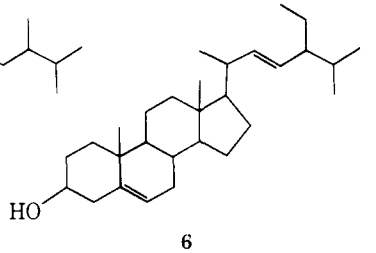


4 (22*R*,23*R*,24*R*)

Attempts to methylenate brassicasterol (**5**) and stigmasterol (**6**) under a variety of Simmons–Smith[6] conditions resulted only in the recovery of starting material. Similarly, dichlorocarbene generated by the pyrolysis of sodium trichloroacetate[7] or by refluxing phenyltrichloromethylmercury in benzene[8] failed to yield cyclopropane products.



5 (24*R*)



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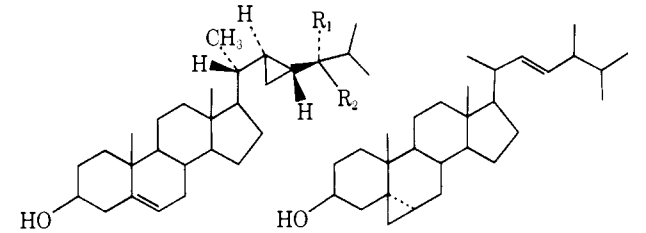
When a more reactive dichlorocarbene source[9] was used with brassicasterol, a complex mixture of cyclopropanoid and noncyclopropanoid products was obtained. Sodium–ammonia reduction of this mixture furnished **7,** the 22*S*,23*S* isomer of demethylgorgosterol in poor yield along with **8, 9, 10,** and recovered **5.**[10]



7, R_1 = H; R_2 = CH_3 (22*S*,23*S*,24*R*)
34, R_1 = CH_3; R_2 = H (22*S*,23*S*,24*S*)

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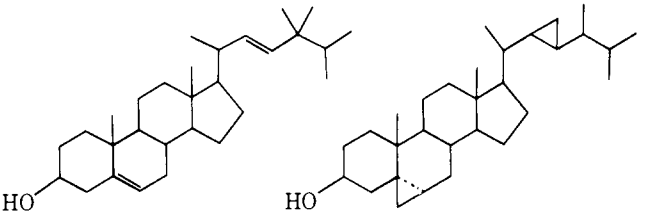
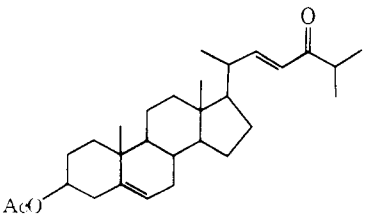


9 **10**

Since carbene or carbenoid addition to an isolated Δ^{22} double bond is not only unsatisfactory, but also leads to the wrong stereochemistry at carbons 22 and 23, it became necessary to resort to the methylenation of an activated Δ^{22} double bond. An investigation of the literature pointed to *trans*-3β-acetoxycholesta-5,22-dien-24-one (**11**), readily accessible[11] in high yield from readily available stigmasterol (**6**), as an attractive candidate for such an activated Δ^{22} double-bond intermediate. In order to avoid complications in the later stages of the synthesis, we decided to protect the Δ^5-3β-hydroxy system as its 3,5-cyclo-6-methyl ether.



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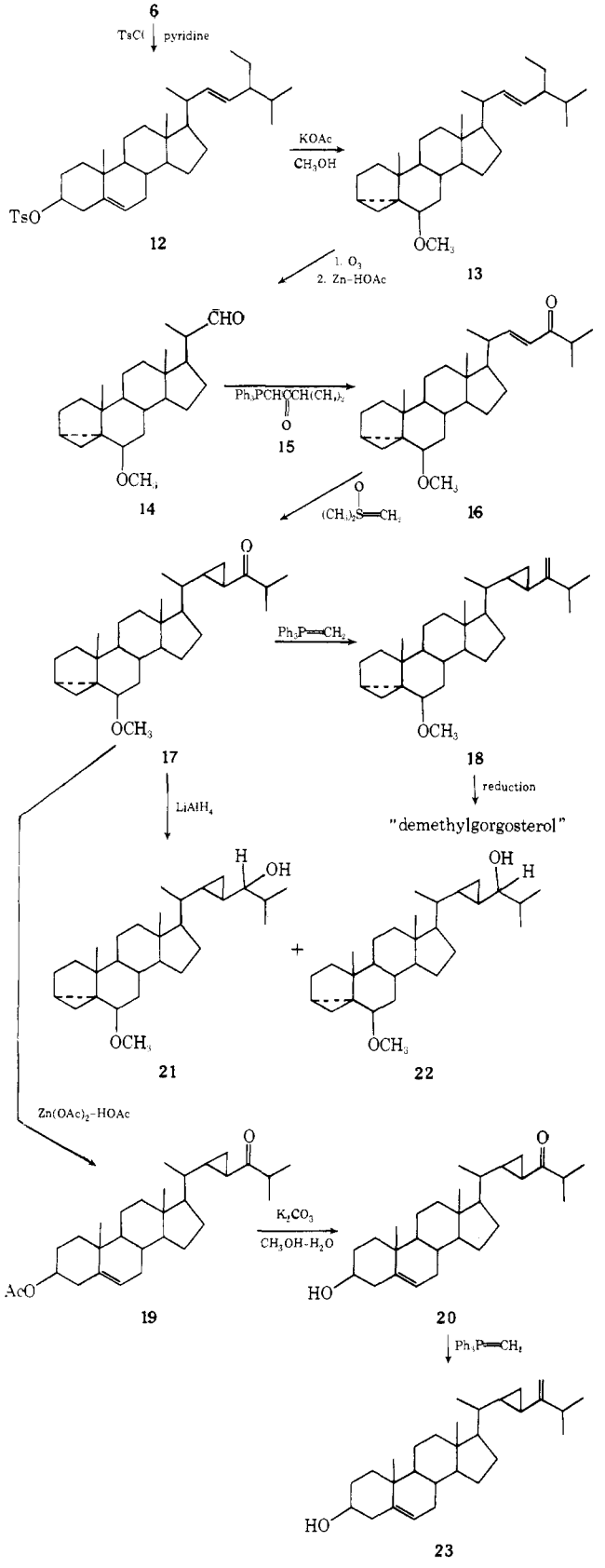
The synthetic route envisioned for demethylgorgosterol (**2**) is shown in Scheme I. Basically, it involves methylenation of the activated double bond in **16** and conversion of the 24-oxo functionality to a methyl group.

Scheme I



Stigmasterol (**6**) was treated with *p*-toluenesulfonyl chloride in pyridine to yield the tosylate[12] (**12**) which was then converted to the cyclo ether (**13**) by methanolysis in the presence of anhydrous potassium acetate.[12] Ozonolysis of **13** in methylene chloride–pyridine at −78° followed by zinc–acetic acid work-up afforded the unstable aldehyde[13] (**14**), which was immediately reacted with the phosphorane[11] **15** in dimethyl sulfoxide to give the desired *trans*-3α,5-cyclo-6β-methoxy-5α-cholesta-22-en-24-one (**16**). The Δ^{22} double bond was shown to be trans by the olefinic region of the nmr: 6.71 ppm (1 H, doublet of doublets, J = 16 and 9 Hz, -CH=C—CO-) and 6.05 ppm (1 H, doublet of doublets, J = 16 and 1 Hz, -C=CHCO-).

Dimethyloxosulfonium methylide[14] can be used for the methylenation of α,β-unsaturated ketones, and it has been shown that when the reaction is performed on an acyclic enone, the trans cyclopropane is the usual product.[15] When **16** was treated with dimethyloxosulfonium methylide in tetrahydrofuran, the trans cyclopropyl ketone **17** was obtained in excellent yield. The product had a strong infrared absorption at 1685 cm^{-1} and exhibited ultraviolet maxima at 202 nm (ϵ 7000) and 276 (50). These values are in good agreement with the spectral data for other cyclopropyl ketones in the literature.[16,17] The nmr spectrum (100 MHz) exhibited signals at 3.31 ppm (3 H, s, $-OCH_3$), 2.75 (2 H, m, $-COCHMe_2$ and -CHOMe), 1.01 (C-19 methyl), 0.67 (C-18 methyl), and 0.3–0.7 (3 H, m, cyclopropyl). The olefinic protons in **16** are no longer present. The three-proton multiplet at 0.3–0.7 ppm is due to the A-ring cyclopropyl group. The presence of the C-24 carbonyl group shifts the side-chain cyclopropyl protons downfield, and they are buried beneath the resonances of the other upfield steroidal protons.

The mass spectrum of **17** is characterized by important ions at *m/e* 426 (M^+), 411 ($M^+ - CH_3$), 394 ($M^+ - CH_3OH$), 371 ($M^+ - C_4H_7$), 286 ($M^+ - C_9H_{16}O$), 285 ($M^+ - C_9H_{17}O$), 253 ($M^+ - C_9H_{17}O + CH_3OH$), 71 ($C_4H_7O^+$), and 43 ($C_3H_7^+$). The peak at *m/e* 371 probably involves ring-A cyclopropyl cleavage,[18] because no analogous peak appears in the mass spectra of Δ^5-3β-hydroxy compounds. The *m/e* 286 ion presumably arises from loss of the side chain with transfer of one hydrogen, while *m/e* 285 and 253 both involve loss of the side chain accompanied by the transfer of two hydrogens.[19] The base peak (*m/e* 71) is the product of α cleavage of the 23,24 bond, and *m/e* 43 comes from α cleavage of the 24,25 bond.

In order to further characterize **17**, the 3,5-cyclo-6-ether protecting group was removed. Solvolysis of **17** with acetic acid in the presence of zinc acetate[12] provided **19** which was saponified with potassium carbonate in aqueous methanol[12] to give **20**. This Δ^5-3β-hydroxy compound exhibited uv maxima at 201 nm (ϵ 7500) and 275 (53) and a strong ir absorption at 1685 cm^{-1}. The 100-MHz nmr of **20** showed peaks at 5.34 ppm (1 H, m, olefinic), 3.46 (1 H, broad, -CHOH), 2.74 (1 H, septet, $-COCHMe_2$), 1.01 (C-19 methyl), and 0.64 (C-18 methyl). Again, the side-chain cyclopropyl protons are buried beneath the other upfield protons.

The mass spectrum of **20** reveals important peaks at *m/e* 412 (M^+), 394 ($M^+ - H_2O$), 379 ($M^+ - CH_3 + H_2O$), 272 ($M^+ - C_9H_{16}O$), 271 ($M^+ - C_9H_{17}O$), 71 ($C_4H_7O^+$), and 43 ($C_3H_7^+$). The peaks at 272 and 271 are analogous to the *m/e* 286 and 285 peaks in the spectrum of **17**, arising from the loss of the side chain with loss of one or two hydrogens,[19] respectively. The *m/e* 71 and 43 (base peak) peaks are again due to α cleavage.

In addition to the removal of the cyclo ether protecting group, **17** was further characterized by reduction with lithium aluminum hydride to a mixture of isomeric alcohols, **21** and **22**. The two compounds were readily separable by thin-layer chromatography and gave very similar spectra. The nmr spectra clearly reveal the signals of the side-chain cyclopropyl protons in the 0.3–0.7 ppm region, although the exact pattern is masked by the A-ring cyclopropyl and C-18 methyl proton signals. The mass spectra exhibit important peaks at *m/e* 428 (M^+), 413 ($M^+ - CH_3$), 396 ($M^+ -$

CH_3OH), 373 ($M^+ - C_4H_7$), 353 ($M^+ - C_3H_7 + CH_3OH$), 328 ($M^+ - C_6H_{12}O$), 296 ($M^+ - C_6H_{12}O + CH_3OH$), 285 ($M^+ - C_9H_{17}O$), 253 ($M^+ - C_9H_{17}O + CH_3OH$), and 71 ($C_4H_7O^+$). The *m/e* 328 and 296 ions are presumably produced by cleavage of the side-chain cyclopropyl ring[18] in the manner previously observed in the mass spectra of gorgosterol[2] and demethylgorgosterol.[3]

It is important to note at this point that only one cyclopropyl ketone was formed while two trans stereoisomers (22*R*, 23*R* and 22*S*, 23*S*) are possible.

The demethylgorgosterol carbon skeleton was completed by converting cyclopropyl ketones **17** and **20** to the corresponding vinylcyclopropanes **18** and **23** *via* the Wittig reaction with methylenetriphenylphosphorane[20] in dimethyl sulfoxide–tetrahydrofuran. The vinyl cyclopropane **18** exhibited a uv maximum at 198 nm (ϵ 9000) in good agreement with literature values of other vinylcyclopropanes.[21] The nmr spectrum (100 MHz) displayed signals at 4.57 and 4.45 ppm (1 H, m and 1 H, m, $-C{=}CH_2$), 3.34 (3 H, s, $-OCH_3$), 2.78 (1 H, m, —CH—OMe), 2.32 (1 H, m, $=CCHMe_2$), 1.04 (C-19 methyl), 0.69 (C-18 methyl), and 0.3–0.7 (3 H, m, A-ring cyclopropyl). Again, the side-chain cyclopropyl proton resonances are shifted downfield and buried. The related vinylcyclopropane **23,** a compound which was not only of interest for purposes of characterization, but which may eventually be encountered in nature since it may be on the biogenetic route to demethylgorgosterol, exhibited a uv maximum at 199 nm (ϵ 9000) and nmr signals (100 MHz) at 5.36 ppm (1 H, m, olefinic), 4.58 and 4.45 (1 H, m and 1 H, m, $-C{=}CH_2$), 1.02 (C-19 methyl), and 0.66 (C-18 methyl) with the side-chain cyclopropyl proton signals being again obscured.

The mass spectra of **18** and **23** both show small molecular ions and similar fragmentation patterns. The important ions in the spectrum of **18** are *m/e* 392 ($M^+ - CH_3OH$), 377 ($M^+ - CH_3 + CH_3OH$), 308 ($M^+ - C_6H_{12} + CH_3OH$), 296 ($M^+ - C_7H_{12} + CH_3OH$), and 253 ($M^+ - C_{10}H_{19} + CH_3OH$). The mass spectrum of **23** shows important ions at *m/e* 395 ($M^+ - CH_3$), 326 ($M^+ - C_6H_{12}$), 314 ($M^+ - C_7H_{12}$), and 271 ($M^+ - C_{10}H_{19}$). The base peak (*m/e* 253) in the spectrum of **18** is analogous to the base peak (*m/e* 271) in the spectrum of **23.** Both result from the loss of the side chain,[19] accompanied by the transfer of two hydrogens. The *m/e* 308 and 296 ions for **18** and the *m/e* 326 and 314 ions for **23** are presumably products of cyclopropane cleavage.[18]

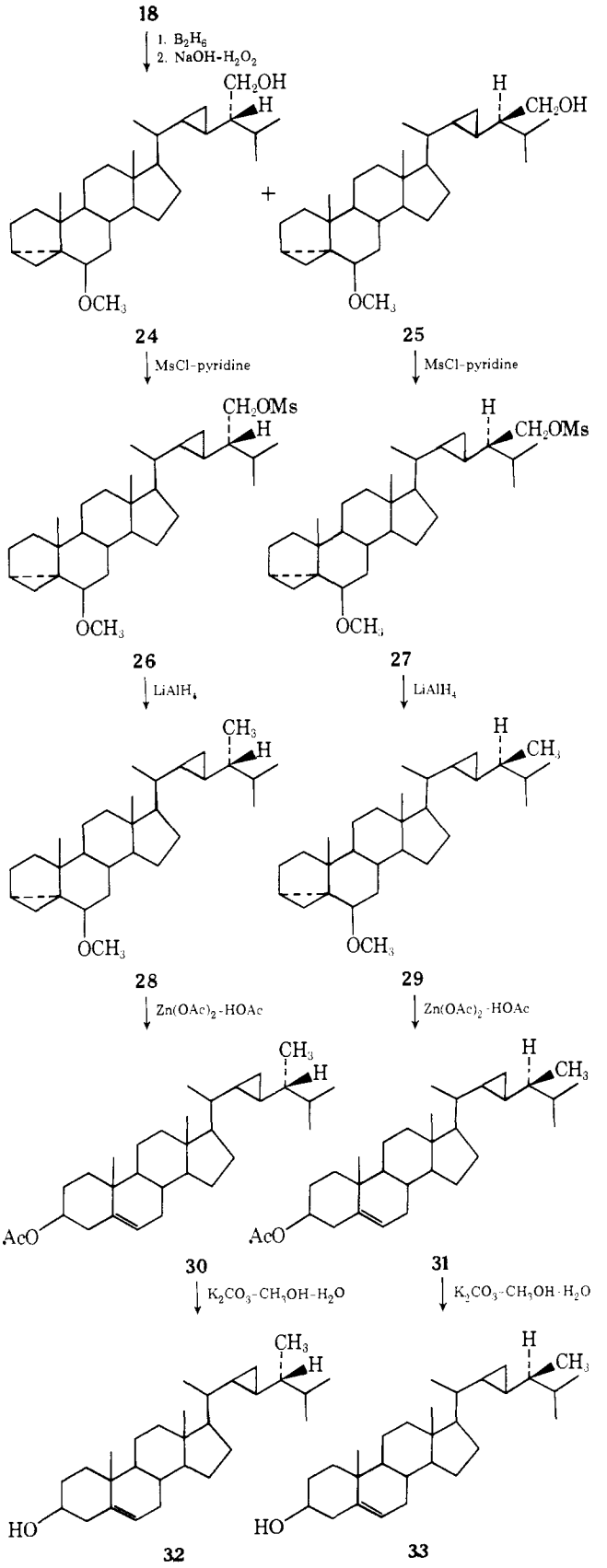
Limited preliminary attempts at catalytic hydrogenation of **18** gave either starting material or ring-opened products. The reduction steps shown in Scheme II were selected since the alcohol isomers **24** and **25** would be more readily separable than the hydrocarbon isomers **28** and **29.**

Hydroboration of **18** with borane in tetrahydrofuran followed by sodium hydroxide–hydrogen peroxide oxidation of the organoborane yielded the two isomeric primary alcohols **24** and **25** in roughly equal quantities. These two isomers were readily separable by thin-layer chromatography and gave very similar spectra.

The mass spectra show important peaks at *m/e* 442 (M^+), 427 ($M^+ - CH_3$), 410 ($M^+ - CH_3OH$), 387 ($M^+ - C_4H_7$), 329 ($M^+ - C_7H_{13}O$), 328 ($M^+ - C_7H_{14}O$), 313 ($M^+ - C_7H_{14}O + CH_3$), 297 ($M^+ - C_7H_{13}O + CH_3OH$), 296 ($M^+ - C_7H_{14}O + CH_3OH$), 285 ($M^+ - C_{10}H_{21}O$), 273 ($M^+ - C_7H_{14}O + C_4H_7$), 254 ($M^+ - C_{10}H_{20}O + CH_3OH$), and 253 ($M^+ - C_{10}H_{21}O + CH_3OH$). The peak at *m/e* 387 probably involves ring-A cyclopropyl cleavage,[18] while the peaks at *m/e* 329, 328, 313, 297, and 296 probably derive from side-chain cyclopropane cleavage.[18] The peaks at *m/e* 285, 254, and 253 presumably arise from the loss of the side chain accompanied by the transfer of one or two hydrogens.[19] The peak at *m/e* 273 presumably involves cleavage of both cyclopropane rings.

Each of the alcohols **24** and **25** was treated with pyridine and methanesulfonyl chloride to give the mesylate which was immediately reduced with lithium aluminum hydride. Removal of the cyclo ether protecting group followed by sa-

Scheme II



ponification[12] gave the free sterols **32** and **33**. The spectra of each of these sterols were very similar to those of natural demethylgorgosterol. The gc retention times were very similar to those of demethylgorgosterol on both OV-25 and OV-17. One was indistinguishable, and the other gave a slightly longer retention time, although the difference was insufficient to allow separation of a mixed injection.

Since only one of the two possible trans cyclopropane isomers was formed, and since the normal physical methods could not unambiguously determine the absolute stereochemistry at carbons 22 and 23, a sample of **23** was subjected to X-ray crystallographic analysis. Structure **23** was solved by routine direct methods and illustrates the final X-ray model. The absolute configuration was not determined during the course of the X-ray study but is deduced from that of the naturally occurring starting material. The gross structure contains, as anticipated, a trans cyclopropane ring. The crucial centers at carbons 22 and 23 are both *S*. There is a double bond between carbons 24 and 28 and hence no C(24) stereochemistry. All bond distances and angles agree well with generally accepted values.

In summary, the results of the X-ray analysis showed that the stereochemistry of the synthetic material is opposite to that of natural demethylgorgosterol at carbons 22 and 23. Thus, one of the synthetic isomers is the 22*S*, 23*S*, 24*R* isomer (**7**) previously reported,[10] and the other is the 22*S*, 23*S*, 24*S* isomer (**34**).

In conclusion, it is important to note that three isomers of demethylgorgosterol, one natural and two synthetic, are now known and that mass spectra, nmr spectra, and gc retention times are insufficient for the identification of these isomers. Consequently, when demethylgorgosterol is isolated from natural sources, it is vital that the rotation be measured to ascertain which isomer is present. Also, it is our hope to eventually conduct feeding experiments using labeled demethylgorgosterol in a study of the biosynthetic origin of gorgosterol. Thus, it is important to be sure that the demethylgorgosterol fed to the organism has the same absolute configuration as that occurring in the organism.

Experimental Section

General. Low-resolution mass spectra were measured on either an AEI MS-9 mass spectrometer, operated by Mr. R. Ross, or on an Atlas CH-4 mass spectrometer, operated by Mr. R. Conover (as indicated in the text). The 60-MHz nuclear magnetic resonance (nmr) spectra were taken on a Varian Associates T-60 nmr spectrometer, and the 100-MHz spectra were run on a Varian Associates HA-100 nmr spectrometer by Dr. M. Bramwell and Dr. L. Durham. All nmr spectra were taken in $CDCl_3$ solution unless otherwise specified. Infrared (ir) spectra were obtained on a Perkin-Elmer 700 infrared spectrophotometer, and ultraviolet spectra (uv) were obtained on a Cary 14 recording spectrophotometer. Melting points were determined on a Thomas-Hoover "Uni-Melt" capillary melting point apparatus. All melting and boiling points reported are uncorrected.

Gas chromatography of all steroids was performed on U-shaped, glass columns, packed with 3% OV-25 on 100–120 mesh Gas-Chrom Q. These columns were mounted in a Hewlett-Packard 402 high efficiency gas chromatograph with a hydrogen flame detector. All injections were made with both the flash heater and the detector temperatures at approximately 300°.

All preparative thin-layer chromatography (tlc) plates were 20 × 20 cm.

Microanalyses were performed in the Microanalytical Laboratory, Department of Chemistry, Stanford University.

Anhydrous ether and anhydrous tetrahydrofuran were prepared by distillation from lithium aluminum hydride. Anhydrous dimethyl sulfoxide was obtained by vacuum distillation from sodium hydride into 4A molecular sieves.

22-*trans*-6β-Methoxy-3α,5-cyclo-5α-cholest-22-en-24-one (16) (Preparation of Intermediate Aldehyde 14). Compound **13**[12] (2.0 g, 4.7 mmol) was dissolved in 150 ml of dry dichloromethane containing 1% pyridine. Then ozone was bubbled slowly into the stirred solution at −70°. The reaction was judged to be complete after 1 hr. The reaction vessel was then removed from the cooling bath, and 2.0 g of zinc dust was added, followed immediately by 5 ml of glacial acetic acid. This mixture was stirred at room temperature for 1 hr. The zinc was then filtered off, and the filtrate was concentrated, diluted with water, and extracted thoroughly with hexane. The combined hexane extracts were washed with saturated sodium bicarbonate and water and then dried over anhydrous magnesium sulfate. The solvent was removed, giving 1.6 g of a yellowish oil: ir ($CHCl_3$) 1720 cm^{-1} (strong) (lit.[11] 1723 cm^{-1}).

This material was immediately treated with 10.0 g (29 mmol) of phosphorane **15**[11] in 125 ml of anhydrous dimethyl sulfoxide and stirred at 95° for 72 hr. Then the reaction mixture was cooled to room temperature, and 75 ml of cold water was added. This mixture was extracted thoroughly with hexane, and the combined hexane extracts were washed with 75:25 methanol–water and pure water and then dried over anhydrous magnesium sulfate. Removal of solvent afforded 1.2 g of crude material, which was purified by column chromatography (activity **II** alumina; 2% ethyl acetate in hexane). This gave 0.89 g (2.2 mmol; 57%) of solid product. The analytical sample was prepared by several recrystallizations from methanol, giving white crystals with mp 115–116°: nmr (100 MHz) 6.71 ppm (1 H, d of d, J = 16 and 9 Hz, -CH=C—CO-), 6.05 (1 H, d of d, J = 16 and 1 Hz, -C=CHCO-) 3.28 (3 H, s, $-OCH_3$), 2.77 (2 H, m, $-COCHMe_2$ and -CHOMe), 1.01 (C-19 methyl), 0.74 (C-18 methyl), 0.3–0.8 (3 H, m, cyclopropyl); ir ($CHCl_3$) 1690, 1660, and 1620 cm^{-1} (all strong); uv (ethanol) λ_{max} 228 nm (ε 15,000); mass spec (MS-9, 70 eV): M^+ at *m/e* 412, base peak at *m/e* 126; $[\alpha]^{19}D$ ($CHCl_3$) +48.1°.

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.56; H, 10.53.

6β-Methoxy-3α,5-cyclo-22,23-methylene-5α-cholestan-24-one (17). A mixture of trimethyloxosulfonium iodide[22] (0.66 g, 3.0 mmol), 57% sodium hydride–mineral oil dispersion (0.13 g, contaning 3.0 mmol of sodium hydride), and 30 ml of anhydrous tetrahydrofuran was stirred at reflux for 2 hr. Then a solution of α,β-unsaturated ketone **16** (0.65 g, 1.6 mmol) in anhydrous tetrahydrofuran was added with stirring to the refluxing reaction mixture, which was then stirred at reflux for 30 min. After cooling and adding 60 ml of water, the mixture was extracted thoroughly with hexane, and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent left about 0.8 g of crude product. This material was purified by column chromatography (activity II alumina; 4% ethyl acetate in hexane) to give 0.575 g (1.35 mmol; 85%) of solid product. The analytical sample was obtained by recrystallization from methanol–water to give a white crystalline solid with mp 113–114°: nmr (100 MHz) 3.31 ppm (3 H, s, $-OCH_3$), 2.75 (2 H, m, $-COCHMe_2$ and -CHOMe), 1.01 (C-19 methyl), 0.67 (C-18 methyl), 0.3–0.7 (3 H, m, cyclopropyl); ir ($CHCl_3$) 1685 cm^{-1} (strong); uv (ethanol) λ_{max} 202 nm (ε 7000), 276 (50); mass spec (MS-9, 70 eV) M^+ at *m/e* 426, base peak at *m/e* 71; $[\alpha]^{20}D$ ($CHCl_3$) −32.5°.

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.79; H, 10.57.

$LiAlH_4$ Reduction of Cyclopropyl Ketone 17 to Alcohols 21 and 22. A solution of 39 mg (0.092 mmol) of ketone **17** and 4.0 mg (0.105 mmol) of lithium aluminum hydride in 10 ml of dry tetrahydrofuran was stirred at reflux for 15 min under anhydrous conditions. Then the reaction mixture was cooled. Following careful addition of ethyl acetate and then water, the resulting mixture was extracted thoroughly with hexane. Evaporation of the solvent left 34 mg of crude oily material, which was purified by preparative tlc (two alumina plates, 0.750 mm thick; 10% ethyl acetate in hexane as eluent). This gave two isomeric alcohols: **21** and **22** (10 mg of each). The former had the greater R_f.

21 had: mp 109–110°; nmr (100 MHz) 3.34 ppm (3 H, s, $-OCH_3$), 2.78 (1 H, m, -CHOMe), 2.59 (1 H, m, -C*H*OH), 0.96 (C-19 methyl), 0.69 (C-18 methyl), 0.3–0.7 (7 H, m, cyclopropyl); mass spec (MS-9, 70 eV) M^+ at *m/e* 428, base peak at *m/e* 71.

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.20; H, 11.06.

22 had: mp 142–143°; nmr (100 MHz) 3.33 ppm (3 H, s, $-OCH_3$), 2.76 (2 H, m, -CHOMe and -C*H*OH), 0.97 (C-19 methyl), 0.68 (C-18 methyl), 0.3–0.7 (7 H, m, cyclopropyl); mass

spec (MS-9, 70 eV) M^+ at *m/e* 428, base peak at *m/e* 253.

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29; mol wt, 428.36541. Found: C, 80.46; H, 11.19; mol wt (high-resolution mass spec), 428.36447.

6β-Methoxy-3α,5-cyclo-22,23-methylene-5α-ergost-24(28)-ene (18). A mixture of 40 mg of 57% sodium hydride–mineral oil dispersion (0.95 mmol of sodium hydride) in 5 ml of anhydrous dimethyl sulfoxide was stirred at 70° under a nitrogen atmosphere for about 45 min. After the mixture was cooled to room temperature, a solution of methyltriphenylphosphonium bromide (340 mg, 0.95 mmol) in 5 ml of anhydrous dimethyl sulfoxide was added to the dark green mixture. The solution turned yellowish immediately. After 10 min, a solution of cyclopropyl ketone **17** (100 mg, 0.23 mmol) in 5 ml of anhydrous tetrahydrofuran was added, and the resulting mixture was stirred at 50° for 2 hr. The reaction was then cooled, and 10 ml of cold water was added. This mixture was extracted thoroughly with hexane, and the combined extracts were washed with 75:25 methanol–water, water, and saturated sodium chloride. After the extracts were dried over anhydrous magnesium sulfate, the solvent was removed to yield about 100 mg of yellowish oil. This material was purified by preparative tlc (three silica gel plates, 0.750 mm thick; 8% ethyl acetate in hexane as eluent), giving 74 mg (0.174 mmol; 74% of oily product, which could be crystallized from methanol–water: mp 57–59°; nmr (100 MHz) 4.57 and 4.45 ppm (1 H, m and 1 H, m, $-C{=}CH_2$), 3.34 (3 H, s, $-OCH_3$), 2.78 (1 H, m, $-CHOMe$), 2.32 (1 H, m, $=C-CHMe_2$), 1.04 (C-19 methyl), 0.69 (C-18 methyl); ir ($CHCl_3$) 1640 cm^{-1} (weak); uv (ethanol) λ_{max} 109 nm (ϵ 9000); mass spec (MS-9, 70 eV) M^+ at *m/e* 424 ($C_{30}H_{48}O$), base peak at *m/e* 253; mol wt (high-resolution mass spec), 424.36875 (calcd for $C_{30}H_{48}O$, 424.37050).

3β-Acetoxy-22,23-methylene-5-cholesten-24-one (19). A mixture of 120 mg (0.28 mmol) of cyclopropyl ketone **17**, 600 mg of freshly fused zinc acetate, and 3.0 ml of glacial acetic acid was stirred at reflux for 2 hr. Then the mixture was cooled, diluted with 5 ml of water, and extracted thoroughly with 50:50 hexane–benzene. The combined organic extracts were then washed with water, 5% sodium bicarbonate, and saturated sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was removed, leaving 102 mg of crude product as a yellow solid: nmr (60 MHz) 5.4 ppm (1 H, m, olefinic), 4.6 (1 H, broad, $-CHOAc$), 2.7 (1 H, septet, $-COCHMe_2$), 2.0 (3 H, s, CH_3CO_2-), 1.0 (C-19 methyl), 0.65 (C-18 methyl).

3β-Hydroxy-22,23-methylene-5-cholesten-24-one (20). A mixture of 100 mg (0.23 mmol) of crude acetate **19**, 140 mg of potassium carbonate, and 10 ml of 9:1 methanol–water was stirred at reflux for 2 hr. The reaction mixture was then neutralized with 5% hydrochloric acid (about 1 ml) and diluted with water. This mixture was extracted thoroughly with benzene, and the combined benzene extracts were washed with water and saturated sodium chloride. After the extracts were dried over anhydrous magnesium sulfate, the solvent was evaporated to give 90 mg of crude solid product. Purification by preparative tlc (three silica gel plates, 1.000 mm thick; 20% ethyl acetate in benzene as eluent), followed by recrystallization from aqueous acetone, gave 75 mg (0.18 mmol; 78%) of white crystals with mp 191–193°: nmr (100 MHz) 5.34 ppm (1 H, m, olefinic), 3.46 (1 H, broad, $-CHOH$), 2.74 (1 H, septet, $-COCHMe_2$), 1.01 (C-19 methyl), 0.64 (C-18 methyl); ir ($CHCl_3$) 1685 cm^{-1} (strong); uv (ethanol) λ_{max} 201 nm (ϵ 7500), 275 (53); mass spec (MS-9, 70 eV) M^+ at *m/e* 412, base peak at *m/e* 43.

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.25; H, 10.71.

22,23-Methylene-5,24(28)-ergostadien-3β-ol (23). A mixture of 36 mg of 57% sodium hydride–mineral oil dispersion (0.86 mmol of sodium hydride) in 3 ml of anhydrous dimethyl sulfoxide was stirred at 70° for 45 min under a nitrogen atmosphere. After cooling to room temperature, a solution of 310 mg (0.86 mmol) of methyltriphenylphosphonium bromide in 3 ml of anhydrous dimethyl sulfoxide was added, and the reaction mixture was stirred for 10 min. Then a solution of 62 mg (0.15 mmol) of cyclopropyl ketone **20** in 4 ml of anhydrous tetrahydrofuran was added, and the mixture was stirred at 60° for 2 hr. At the end of this time, the reaction mixture was cooled, diluted with 15 ml of cold water, and extracted thoroughly with 50:50 hexane–benzene. The combined organic extracts were washed with 75:25 methanol–water, water, and saturated sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed, and the resulting crude product was purified by preparative tlc (three silica gel plates, 0.750 mm thick; 20% ethyl acetate in benzene as eluent) to yield 31 mg (0.076 mmol; 51%) of product. Recrystallization from aqueous acetone gave white crystals with mp 170–171°: nmr (100 MHz) 5.36 (1 H, m, olefinic), 4.58 and 4.45 (1 H, m and 1 H, m, $-C{=}CH_2$), 1.02 (C-19 methyl), 0.66 (C-18 methyl); ir ($CHCl_3$) 1640 cm^{-1} (weak); uv (ethanol) λ_{max} 199 nm (ϵ 9000); mass spec (MS-9, 70 eV) M^+ at *m/e* 410 ($C_{29}H_{46}O$), base peak at *m/e* 271.

Hydroboration of 18. A solution of 200 mg (0.47 mmol) of **18** in 15 ml of tetrahydrofuran was cooled in an ice bath under a nitrogen atmosphere, and 15 ml of an approximately 1 *M* solution of borane in tetrahydrofuran was added with stirring. The mixture was stirred for 1 hr in the ice bath and then overnight at room temperature. The solution was again cooled in an ice bath, and 10 ml of water was added. Then, 10 ml of 3 *N* sodium hydroxide was added followed by the slow addition of 10 ml of 30% hydrogen peroxide. The solution was removed from the ice bath and stirred at room temperature for 2 hr. The mixture was extracted with four 50-ml portions of chloroform. The combined chloroform extracts were washed with 25 ml of water followed by 10 ml of saturated sodium chloride solution and dried over magnesium sulfate. The chloroform was evaporated *in vacuo*, and the gummy residue was purified by preparative tlc (four plates, silica gel HF, 1 mm thick, 10% ethyl acetate in hexane as eluent). This gave the two isomeric alcohols **24** (75 mg) and **25** (78 mg). The former had the greater R_f.

The alcohol 24 was crystallized from methanol–water, mp 109–111°: $[\alpha]^{20}D$ +14.7° (*c* 0.116, (MeOH); nmr (60 MHz) 3.70 ppm (2 H, d, J = 6 Hz, $-CH_2OH$), 3.34 (3 H, s, $-OCH_3$), 2.78 (1 H, m, $-CHOCH_3$), 1.02 (3 H, s, C-19 methyl), 0.67 (3 H, s, C-18 methyl), 0.2–0.7 (7 H, complex, cyclopropyls); mass spec (MS-9, 70 eV), M^+ at *m/e* 442 ($C_{30}H_{50}O_2$), base peak at *m/e* 328.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.64; H, 11.40.

The isomeric alcohol **25** was crystallized from methanol–water, mp 91–92°; $[\alpha]^{20}D$ +10.4° (*c* 0.09, MeOH); nmr (60 MHz) 3.65 ppm (2 H, d, J = 6 Hz, $-CH_2OH$), 3.32 (3 H, s, $-OCH_3$), 2.77 (1 H, m, $-CHOCH_3$), 1.02 (3 H, s, C-19 methyl), 0.67 (3 H, s, C-18 methyl), 0.2–0.7 (7 H, complex, cyclopropyls); mass spec (MS-9, 70 eV), M^+ at *m/e* 442 ($C_{30}H_{50}O_2$), base peak at *m/e* 328.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.40; H, 11.48.

Conversion of 24 to 32. A solution of 35 mg (0.079 mmol) of alcohol **24** in 5 ml of pyridine was cooled in an ice bath, and 1 ml of methanesulfonyl chloride was added dropwise with stirring. The ice bath was removed, and the mixture was stirred for 3 hr at room temperature. The mixture was poured into 50 ml of ice water, and the resulting solution was extracted with four 25-ml portions of chloroform. The combined chloroform extracts were washed with 10 ml of water and then with 10 ml of saturated sodium chloride solution and dried over magnesium sulfate. The chloroform was removed *in vacuo* to give the crude mesylate **26** which was immediately taken up in 50 ml of dry tetrahydrofuran. Excess lithium aluminum hydride was added, and the mixture was stirred at reflux overnight. The excess lithium aluminum hydride was destroyed with water, the mixture was acidified with 6 *N* HCl, and 50 ml of ether was added. The layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 10 ml of water and 10 ml of saturated sodium chloride solution and then dried over magnesium sulfate. The ether was removed *in vacuo*. The resulting gum was purified by preparative tlc (one plate, silica gel HF, 1 mm thick, 10% ethyl acetate in hexane as the eluent) to give the slightly impure **28**. The nmr spectrum (60 MHz) of this intermediate showed peaks at 3.28 ppm (3 H, s, OCH_3), 2.75 (1 H, m, $-CHOCH_3$), 1.00 (3 H, s, C-19 methyl), 0.65 (3 H, s, C-18 methyl), and 0.2–0.7 (7 H, complex, cyclopropyls).

No attempt was made to further purify this intermediate which was taken up in 10 ml of glacial acetic acid. Freshly fused zinc acetate (1 g) was added, and the mixture was refluxed for 2 hr. Water was added, and the resulting solution was extracted with four 50-ml portions of chloroform. The combined chloroform extracts were washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The chloroform was removed *in*

Table I. Final Coordinates for **23**[a]

	$x/a \times 10^3$	$y/b \times 10^3$	$z/c \times 10^3$
C(1)	233(1)	450(3)	166(1)
C(2)	148(1)	475(4)	130(1)
C(3)	102(1)	375(5)	0(1)
C(4)	125(1)	143(5)	−7(2)
C(5)	208(1)	115(4)	33(1)
C(6)	232(1)	2(4)	−44(1)
C(7)	317(1)	−48(3)	−15(1)
C(8)	366(1)	0	122(1)
C(9)	342(1)	227(3)	161(1)
C(10)	258(1)	204(3)	154(1)
C(11)	394(1)	297(3)	289(1)
C(12)	478(1)	296(3)	304(1)
C(13)	499(1)	72(3)	271(1)
C(14)	443(1)	35(3)	132(1)
C(15)	479(1)	−157(3)	94(1)
C(16)	565(1)	−124(3)	162(1)
C(17)	573(1)	75(3)	247(1)
C(18)	497(1)	−98(3)	360(1)
C(19)	255(1)	70(3)	261(1)
C(20)	650(1)	66(3)	371(1)
C(21)	656(1)	264(3)	451(1)
C(22)	710(1)	60(4)	318(1)
C(23)	787(1)	−18(4)	422(1)
C(24)	857(1)	125(5)	431(2)
C(25)	881(2)	296(7)	531(3)
C(26)	938(1)	141(6)	639(2)
C(27)	896(2)	491(10)	501(4)
C(28)	881(1)	117(5)	327(1)
C(29)	747(1)	−131(3)	298(1)
O	25(1)	349(5)	−14(1)

[a] The estimated standard deviation of the least significant figure is given in parentheses.

vacuo to give the crude acetate **30** which was taken up in 10 ml of 9:1 methanol–water. Potassium carbonate (100 mg) was added, and the mixture was refluxed overnight. After addition of 25 ml of water, the solution was extracted with four 50-ml portions of chloroform. The combined chloroform extracts were washed with water and saturated sodium chloride solution and then dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left a colorless gum which readily crystallized from methanol–water to give 10 mg of **32**, mp 164–166°: $[\alpha]^{20}D$ −47.5° (*c* 0.13, MeOH); nmr (60 MHz) 5.40 ppm (1 H, m, -C=CH), 3.49 (1 H, m, -C*H*OH), 1.00 (3 H, s, C-19 methyl), 0.63 (1 H, s, C-18 methyl), and 0.2–0.4 (4 H, complex, cyclopropyl), essentially superimposable on that of natural demethylgorgosterol[3] (isolated from *P. porosa*); mass spec (MS-9, 70 eV) M^+ at *m/e* 412 ($C_{29}H_{48}O$), base peak at *m/e* 314, essentially superimposable on that of natural demethylgorgosterol.

Anal. Calcd for $C_{29}H_{48}O{\cdot}CH_3OH$: C, 81.02; H, 11.79. Found: C, 81.47; H, 11.45.

Conversion of 25 to 33. When 25 mg (0.057 mmol) of alcohol **25** was treated in the manner described above, 8 mg of **33** was obtained. The nmr spectrum (60 MHz) of intermediate **29** showed peaks at 3.30 ppm (3 H, s, $-OCH_3$), 2.78 (1 H, m, $-CHOCH_3$), 1.00 (3 H, s, C-19 methyl), 0.65 (3 H, s, C-18 methyl), and 0.2–0.7 (7 H, complex, cyclopropyls).

33 had: mp 162–165°; $[\alpha]^{20}D$ −67.1° (*c* 0.085, MeOH) [lit.[10] mp 163–165°; $[\alpha]^{21}D$ −64.4° (*c* 0.09)]; nmr (60 MHz) 5.37 ppm (1 H, m -C=CH), 3.50 (1 H, m, -C*H*OH), 1.00 (3 H, s, C-19 methyl), 0.63 (3 H, s, C-18 methyl), and 0.20–0.4 (4 H, complex, cyclopropyl) essentially superimposable on that of natural demethylgorgosterol; mass spec (MS-9, 70 eV) M^+ at *m/e* 412 ($C_{29}H_{48}O$), base peak at *m/e* 314, essentially superimposable on that of natural demethylgorgosterol.

Anal. Calcd for $C_{29}H_{48}O{\cdot}CH_3OH$: C, 81.02; H, 11.79. Found: C, 81.27; H, 11.52.

Crystallographic and X-Ray Data. Large, clear crystals of **23** were grown by slow evaporation of an aqueous acetone solution. Preliminary photographic experiments revealed monoclinic crystal symmetry. Precise lattice constants were determined by a least-squares fit of 12 strong, high-order reflections measured at both $+\theta$ and $-\theta$ to eliminate problems of instrumental zeroing on a Hil-

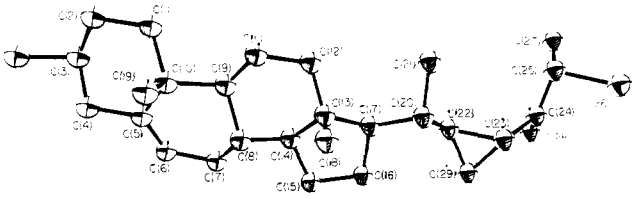


Figure 1. A computer-generated perspective drawing of **23**. Hydrogen atoms are not shown.

ger-Watts four-circle diffractometer using Cu $K\alpha_1$ radiation (1.54056 Å). They are a = 19.61 (2), b = 6.080 (5), c = 11.72 (1) Å and β = 112.65 (4)°. The calculated density for two molecules of formula $C_{29}H_{45}OH$ per unit cell was 1.058 g/cm^{-3} which agreed well with a measured density of 1.0 g/cm^{-3} (flotation).

All unique diffraction maxima with $\theta \leq 60°$ for Ni-filtered Cu $K\alpha$ radiation (1.5418 Å) were recorded using a computer-controlled four-circle diffractometer, a take-off angle of 4°, and a θ–2θ scan technique. All scans were of variable increment to allow for spectral dispersion. A background of one-half the time of the scan was measured at the extremes of the scan. Three standard reflections were measured every 100 reflections throughout data collection. These showed no appreciable decrease in intensity. The intensity data were reduced to a set of relative squared amplitudes, $|F_o|^2$, by application of the standard Lorentz and polarization factors. Data were retained if $|F_o| \geq 3\sigma(F_o)$ where $\sigma(F_o)$ was computed from $\{[I + \sigma(I)]/(Lp)\}^{1/2} - F_o$,[24] and $\sigma(I)$ was computed from [total count + background count + 0.05(total count)^2 + 0.05(background)^2]$^{1/2}$. A total of 1821 of the 2204 recorded reflections was judged observed by this procedure.

Determination and Refinement of Structure. The observed structure factor amplitudes ($|F_o|^2$) were converted to normalized structure factors ($|E|$) by removing the angular dependence of the reflections. These normalized structure factors with magnitude greater than 1.4 (180) were assigned initial phases by the multisolution tangent formula program MULTAN.[23]

One of the solutions with the best figure of merit revealed a plausible 20 atom molecular fragment. An electron density synthesis,[24] with phases computed from the 20 atom fragment, revealed the remaining 10 heavy atoms.

Full-matrix, least-squares refinements[25] reduced the conventional discrepancy index to 9.8% for the observed reflections. A computer-generated drawing of the X-ray model is given in Figure 1.[26] Table I lists fractional coordinates and their errors for the nonhydrogen atoms. There were no abnormally short intermolecular contacts, and bond distances and angles generally agreed well with anticipated values.

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Model Studies for Steroid C/D Ring Synthesis. Stereoselective Hydrindan Formation by Means of Acetylene–Cation Cyclization

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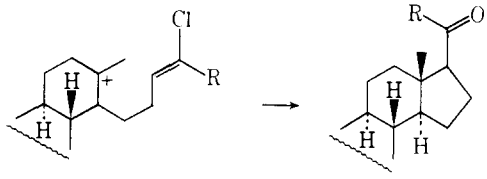
Abstract: Intramolecular attack upon a 1-methylcyclohexyl cation by the triple bond of an adjacent 3-hexynyl side chain provides a synthetic entry into the acylhydrindan system characteristic of many 20-ketosteroids. *trans*-Decalyl substrates bearing an equatorial alkynyl side chain at C_1 and a potential tertiary carbonium ion at C_2 cyclize stereoselectively to yield predominantly *trans*- or *cis*-hydrindan systems, depending on whether carbonium or episulfonium ions are involved.

During studies of chloroalkene–carbonium ion cyclization relating to annelation of cyclopentanes, cyclohexanes, and cycloheptanes,[1] we investigated such reactions for assembling the C/D trans-fused hydrindane portion of 20-keto steroids,[2] *e.g.*



Initially it was observed that monocyclic model compounds such as **1–3** cyclized efficiently during formolysis but with predominating formation of cis-fused hydrindans (the ratio of **4:5** was usually *ca.* 75:25). The product ratios were essentially identical regardless of carbonium ion precursor,[3] thus leading to our assumption that, by means of deprotonation–reprotonation equilibria, the same classical carbonium ion was probably involved in each case. Reasoning that conformationally flexible carbonium ions derived from **1–3** might favor cis-fused product by cyclizing more rapidly from that conformer with an axial side chain ($k_a > k_e$ and/or $k_{e'}$), we subsequently investigated the appropriate *trans*-decalyl system in which a "k_a-like process" (Scheme I) would only come about *via* higher energy "twist-boat" conformers and thus be a less serious complication.[4a] Scheme II shows that during mild solvolysis in 97% formic acid,[5] wherein hydrolysis of the initially produced α-chlorocarbornium ion essentially eliminates retroyclization,[1] the expected change in stereoselectivity occurred: however, the twofold preference for trans-fused hydrindans could not be improved to the higher levels needed for incorporating this approach into steroid synthesis.

From considerations of molecular geometry it appeared likely that an acetylenic cyclization[6] could have a different stereochemical outcome from the corresponding chloroalkene one, since the predominantly linear side chain might have a grossly different steric requirement from the angular vinyl one for axial *vs.* equatorial approach to the cyclization terminus. At the same time, however, solvolysis of **9** could result in six-membered ring formation (→**10**) as well as five (→**4** and **5**) (Scheme III). This expectation was based originally on previously observed product compositions resulting from intramolecular alkynyl participation in solvolysis of secondary substrates[7] as well as rearrangements of cycloalkenyl triflates.[8] If acetylenic cyclization could be directed toward methylenecyclopentanes, an additional useful possibility would be regiospecific electrophilic funtionalization of the initial enol derivative.

The present investigation began about 5 years ago[3] with acid solvolysis of **9**, the acetylene analog of **1**, since information on *tert*-carbonium ion–alkyne combination was then not available. Carbinol **9** was readily prepared by alkylating the cyclohexylimine salt of cyclohexanone with 3-pentynyl tosylate and treating the resultant ketone with methyllithium. Formolyses and trifluoroacetolyses[9] of **9**, followed by saponification of the resultant enol esters, resulted in a ketone mixture containing all of the products expected (*vide supra*). These are shown in Scheme IV, which also summarizes how the decalones were independently prepared[10] and the hydrindans degraded.[2,3] Gas chromatography allowed separation of the acetylhydrindans **4** and **5** from the longer retention time decalones **13** and **14**; in addition, nmr spectral examination of the angular methyl group signals in **4**