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THE SYNTHESIS OF DEMETHYLGORGOSTEROL

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Demethylgorgosterol (I) is one of a growing number of novel cyclopropane-containing sterols which have been isolated from marine organisms.[2] A possible biological role of such sterols has been discussed recently.[3] Chemical and biosynthetic studies of this unusual molecule necessitate the need for a viable synthesis of it, and efforts to accomplish this have led to several approaches. Direct methylenation of brassicasterol (II)[4] and of the activated Δ^{22} double bond of the trans 22-ene-24-one III[5] have resulted in the syntheses of the 22S,23S,24R (IV) and 22S, 23S,24S (V) isomers of demethylgorgosterol. By choosing to form the cyclopropyl moiety by an intramolecular nucleophilic displacement, we have achieved our goal of synthesizing the natural 22R,23R,24R (I) as well as the remaining 22R,23R,24S (VI) isomers.

When the crude aldehyde VII[5] was treated with vinyl magnesium bromide[6] in THF followed by workup and chromatography, the diastereomeric alcohols VIII were obtained as crystalline compounds in a 58% yield[7] (2.5:1 ratio of a less polar:more polar mixture: less polar: m.p. 107-108°, $[\alpha]_D^{20}$ = +18.7°; more polar: m.p. 124-125.5°, $[\alpha]_D^{20}$ = +63.5°; NMR: 5.08-5.93 ppm (3H, ABC splitting pattern, vinyl protons), 4.20 ppm (1H, m, 22-H)). Oxidation of VIII (CrO_3-pyr, CH_2Cl_2, 10 min.)[8] gave the crude vinyl ketone IX ($[\alpha]_D^{20}$ = +20.0°; $[\theta]_m$ = -2509 (295 nm); NMR: 5.70-6.35 ppm (3H, ABC splitting pattern, vinyl protons)) which, upon hydrocyanation (KCN in 98:2 $CH_3CN:H_2O$, 18-crown-6 (cat.) at 15°C. overnight) and chromatography on Si gel, yielded the cyano ketone X (m.p. 117-119°C; $[\alpha]_D^{20}$ = +29.7°; $[\theta]_m$ = -2564 (287 nm); NMR: 2.66 ppm, (6H, m, 20-H, 23-H_2, 24-H_2, 6-H), 1.13 ppm (3H, d, J = 7 Hz, C_{21} methyl); IR: 1715 cm^{-1} (s, CO), 2250 cm^{-1} (w, CN)) in a 55% yield from VIII (plus 27% recovered VIII). Reduction with $NaBH_4$ (MeOH, overnight) gave a quantitative yield of the 22S (XIa) and 22R (XIIa) cyano alcohols in a 5:3 (XIa:XIIa) ratio. These were separated by liquid chromatography on a Waters Prep LC 500 instrument (5% acetone in CH_2Cl_2). The less polar alcohol ($[\alpha]_D^{20}$ = +19.3°; NMR (d_6-DMSO): 4.41 ppm (1H, d, J = 6 Hz, OH), 3.78 ppm (1H, m, 22-H), 2.35 ppm (2H, d of d, J = 5.0 Hz, J' = 8.0 Hz, 24-H_2); IR: 3470 cm^{-1} (br, OH), 2240 cm^{-1} (m, CN)) was identified as the 22S isomer XIa because the CD spectrum of its p-bromobenzoate derivative (XIb) exhibited a positive Cotton effect.[9] The more polar alcohol ($[\alpha]_D^{20}$ = +46.2°; NMR (d_6-DMSO): 4.58 ppm (1H, d, J = 6 Hz, OH), 3.78 ppm (1H, m, 22-H), 2.32 ppm (2H, d of d, J = 5.0 Hz, J' = 8.0 Hz, 24-H_2)) was identified as the 22R isomer (XIIa) in like manner, the CD spectrum of its p-bromobenzoate derivative (XIIb) exhibiting an

obvious negative Cotton effect. Further support for these stereochemical assignments comes from the cyclization/alkylation reactions of the methanesulfonate esters[10] of these alcohols with excess isopropyllithium in THF (0° C., 20 min.). As anticipated, the 22R mesylate (XIIc) yielded, after workup and preparative tlc (10% EtOAc in hexane) the ketone XIII which was identical in all respects to the known 22S,23S product.[5,11] The 22S mesylate (XIc), however, yielded (29% from the alcohol XIa) a chromatographically distinct ketone XIV (m.p. 106-106.5° C., $[\alpha]_D^{20}$ = +116.7°; $[\theta]_m$ = +5372 (280 nm) (= the mirror image of the CD spectrum of XIII); IR: 1690 cm^{-1} (s, CO); NMR: 2.750 ppm (2H, m, 25-H and 6-H), 1.134 ppm (3H, d J = 7 Hz, C_{25}-methyl), 1.164 ppm (3H, d, J = 7 Hz, C_{25}-methyl)). *Treatment with* $Ph_3P{=}CH_2$ *(THF reflux, overnight) gave* (44% after chromatography) the 24-methylene compound XV ($[\alpha]_D^{20}$ = +68.4°; $[\theta]_m$ = +1094 (209 nm); NMR: 4.58 ppm (1H, m, 28-H), 4.44 ppm (1H, m, 28-H), 1.048 ppm (6H, d, C_{25}-methyls), 2.250 ppm (1H, m, 25-H)). Hydroboration[5] and chromatography (preparative tlc, double development in 10% acetone in CH_2Cl_2) yielded the more polar (43%; $[\alpha]_D^{20}$ = +41.0°; NMR: 3.50 ppm (2H, d, J = 6 Hz, C_{28}-H_2), 1.23 ppm (6H, d, J = 5 Hz, C_{25}-methyls), 0.715 ppm (3H, s, C_{18} methyl)) and the less polar (43%; $[\alpha]_D^{20}$ = +31.1°; NMR: 3.58ppm (2H, d, J = 6 Hz, C_{28}-H_2), 1.23 ppm (6H, d, J = 5 Hz, C_{25}-methyls), 0.683 ppm (3H, s, C_{18} methyl)) 24-hydroxymethyl products (XVIIa and XVIIIa, respectively). Treatment of the mesylate XVIIIb from the less polar alcohol with $LiAlH_4$[5] yielded the 24-methyl product XVIIIc which was then converted to the Δ^5-3β-ol (I) (dioxane reflux, 30 minutes, TsOH catalyst). The 360 MHz NMR spectrum of the purified sterol (38% overall yield from XVIIIa; high resolution mass spectrum: m/z 412.3635 (calc. 412.3705)) showed a remarkable correspondence with the spectrum of natural demethylgorgosterol, and we base the structural assignment of I to the less polar alcohol-derived product upon this evidence. The sterol obtained when the more polar alcohol (XVIIa) was subjected to the same reaction sequence (XVIIa → XVIIb → XVIIc → Δ^5-3β-ol; *high resolution mass spectrum:* m/z 412.3680 (calc. 412.3705)) *exhibited a 360 MHz NMR* spectrum markedly different from that of natural demethylgorgosterol and therefore we conclude that it is 22R,23R,24S-demethylgorgosterol (VI). The chemical shifts of the side chain methyl groups of natural demethylgorgosterol and the two synthetic isomers are compared in the table below.[12] In addition, the assigned 24R synthetic isomer (I) exhibited cyclopropyl proton signals (0.53 ppm (m), 0.30 ppm (m) and 0.12 ppm (d of d)) identical to those of the natural sterol, whereas the assigned 24S synthetic isomer (VI) exhibited cyclopropyl protons at 0.58 ppm (m), 0.42 ppm (m), and at 0.07 ppm (d of d). Both of these compounds exhibited identical mass spectral and gas chromatographic properties. However, Ikekawa and co-workers[13] found during their independent synthesis of demethylgorgosterol that a separation of all of the isomers could be achieved using open capillary gas chromatography.

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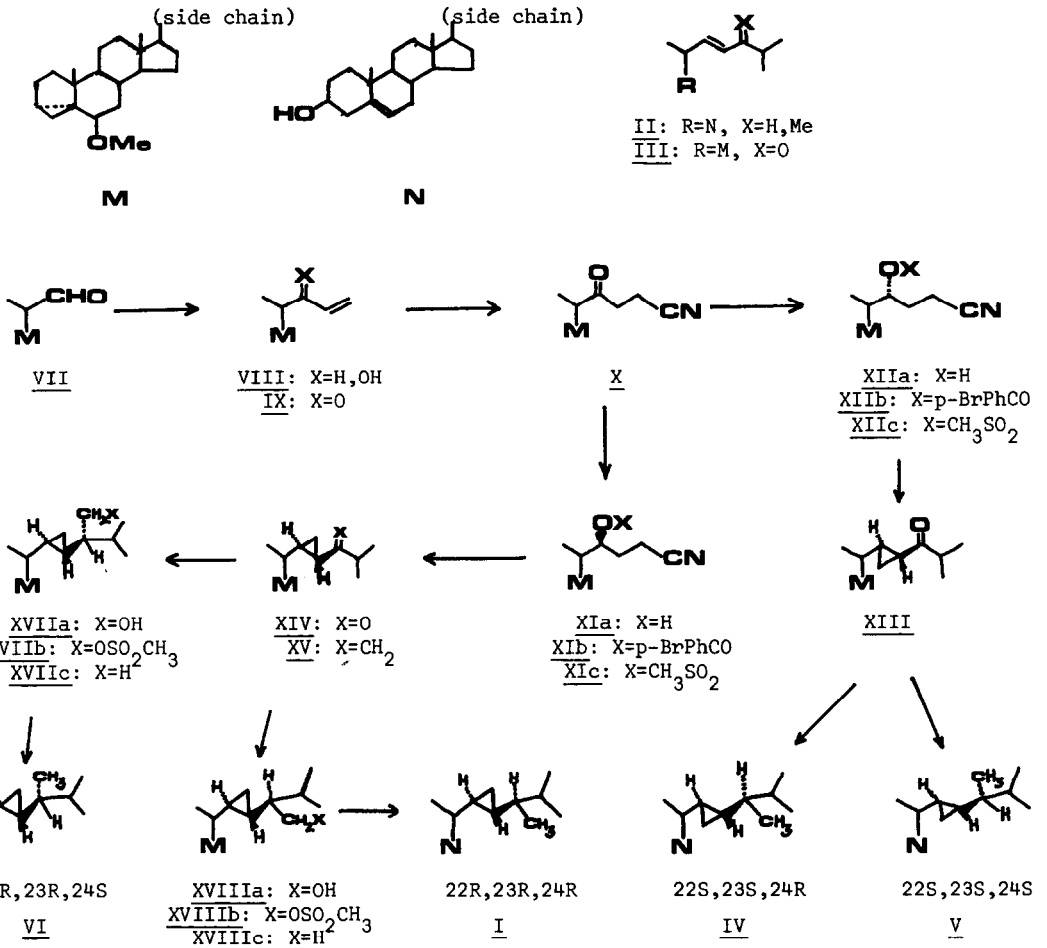

Table of ^{1}H-NMR Chemical Shifts of the Side Chain Methyl Groups of Natural (I) and Synthetic (22R,23R,24R (I) and 22R,23R,24S (VI)) Isomers of Demethylgorgosterol[a]

	C_{19}	C_{18}[b]	C_{21}	C_{26}	C_{27}	C_{28}
Demethylgorgosterol	1.005	.640	.920 (6.1)	.913 (6.3)	.889 (6.9)	.858 (6.8)
22R,23R,24R (I)	1.005	.640	.920 (6.2)	.913 (6.4)	.889 (6.9)	.858 (6.9)
22R,23R,24S (VI)	1.006	.650	.888 (7.1)	.868 (7.1)	.868 (7.1)	.854 (6.5)

a) in ppm; coupling constants of doublets, in cps, in parentheses.
b) The other two synthetic isomers (ref. 5), (22S,23S,24R (IV) and 22S,23S,24S (V)) exhibit C_{18} methyl signals at .621 ppm and at .622 ppm.

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