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STEREOSELECTIVE SYNTHESIS OF DEMETHYLGORGOSTEROL[1]

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Several unique sterols having a cyclopropane ring in the side chain have been isolated from marine sources[2,3,4] and all of these sterols have 22R, 23R and 24R configurations. The synthesis of the isomers of demethylgorgosterol was reported by Djerassi et at.[5], however, no synthesis of any of the naturally occurring compounds has been reported so far.[6] We describe herein a stereoselective synthesis of natural demethylgorgosterol(19).[3]

The starting aldehyde 3,[7] mp 123-125°, $[\alpha]_D$-149.8°, was obtained in 30% overall yield from 1 by Wittig reaction of the intermediate C-22 aldehyde 2 with triphenylmethoxymethylenephosphorane followed by acid hydrolysis of the resulting enol ether. The aldehyde 3 was also obtained by refluxing the known 23-dithioacetal[8] with mercuric chloride in aq. acetonitrile in a yield of 60%. Several attempts to alkylate the enolate anion of the aldehyde 3 directly with alkyl bromides were unsuccessful. However, treatment of the piperidine enamine 4(without isolation) with allyl bromide in benzene under reflux and subsequent hydrolysis with 2N HCl provided a mixture of the 22-alkylated products(95%), which on chromatography over silica gel yielded the more polar major isomer 5, mp 146-148°, NMR δ 9.81(1H, d, J=2Hz,CHO), 6.0-5.5(1H,m,24-H), 5.40(1H,m,6-H), 5.2-4.9(2H,m,25-H_2), 4.6(1H,m,3-H), 2.04(3H,s,AcO), 1.03(3H,s,c-19 Me), 1.03(3H,d,J=7Hz,C-21 Me), 0.71(3H,s,C-18 Me) and the less polar minor isomer 6 mp 113-115°, NMR δ 9.69(1H,s,CHO), 6.1-5.6(1H,m,24-H), 5,38(1H,m,6-H), 5.2-4.9(2H,m,25-H_2), 4.6(1H,m,3-H), 2.03(3H,s,OAc), 1.02(3H,s,C-19 Me), 0.82(3H,d,J=7Hz,C-21 Me), 0.75 3H,s,C-18 Me). ^{13}C-NMR chemical shifts[9] of the $NaBH_4$ reduction products, 7a, mp

156.5-157.5° and 8a, mp 139-140°, suggested 22S and 22R configurations for the major and minor isomer , respectively. This was confirmed by converting the minor isomer 12 to the cyclopropyl ketone 21.

The mesylate 7b, mp 123-124.5°, was oxidized with OsO_4 and then with $NaIO_4$ to give the 24-aldehyde mesylate 9. Treatment of the mesylate 9 with t-BuOK in ether yielded the cyclopropane derivative 11, mp 185-186.5°, NMR δ 8.97(1H,d,J= 5Hz,CHO), 5.4(1H,m,6-H), 4.6(1H,m,3-H), 2.00(3H,s,OAc), 1.00(3H,s,C-19 Me), 0.60 (3H,s,C-18 Me), in 70% yield. An alternative and more simple synthesis of 11 was achieved by Grignard reaction of the 22-aldehyde 2 with 3-butenyl magnesium bromide yielding stereoselectively the 22S-alcohol 13a, mp 169-170.5°. The mesylate 13b, mp 106.5-109.5°, was converted to the 25-aldehyde 14 by oxidation with OsO_4 followed by $NaIO_4$. Treatment of 14 with 1 eq. of t-BuOK or n-BuLi afforded a cyclopropane derivative which was identical with the compound 11. By the same procedure, 6 was converted to the isomeric cyclopropyl aldehyde 12, mp 151.5-152,5°, via the alcohol 8a, the mesylate 8b, and the aldehyde 10.

Grignard reaction of 12 with isopropyl magnesium bromide followed by pyridnium chlorochromate oxidation gave the cyclopropyl ketone 21, which was identical with the 22S,23S-cyclopropane derivative, mp 155-157°, prepared by the methylenation of 3β-acetoxy-cholest-5,22-dien-24-one.[5] Thus, the configuration of the compound 15, mp 142-143.5°, NMR δ 5.4(1H,m,6-H), 4.6(1H,m,3-H), 2.72(1H,m,25-H), 2.00(3H, s,OAc), 1.00(3H,s,C-19 Me), 0.62(3H,s,C-18 Me), led from 5 by the same method, could be assigned as 22R,23R.[10]

The synthesis of natural demethylgorgosterol 19 from 15 was completed by a similar procedure as described by Djerassi et al.[5] Wittig reaction of 15 with triphenylmethylenephosphorane gave the 24-methylenecyclopropane 16a, mp 128-130°. Hydroboration of the 3,5-cyclo-6β-methyl ether 16b afforded a mixture of two isomers, resolved by preparative TLC(benzene-ethyl acetate 10 : 1, developed twice) to yield 17(R_f 0.35) and 18(R_f 0.39). Removal of the hydroxy group of the more polar isomer(17) by mesylation followed by $LiAlH_4$ reduction, and subsequent regeneration of the 3β-hydroxy group with acid afforded 22R,23R,24R-demethyl-gorgosterol(19), mp 161-162°, $[\alpha]_D$-31.9°, which was identical with a sample of natural demethylgorgosterol[12] in all respects including NMR, mass spectrum and

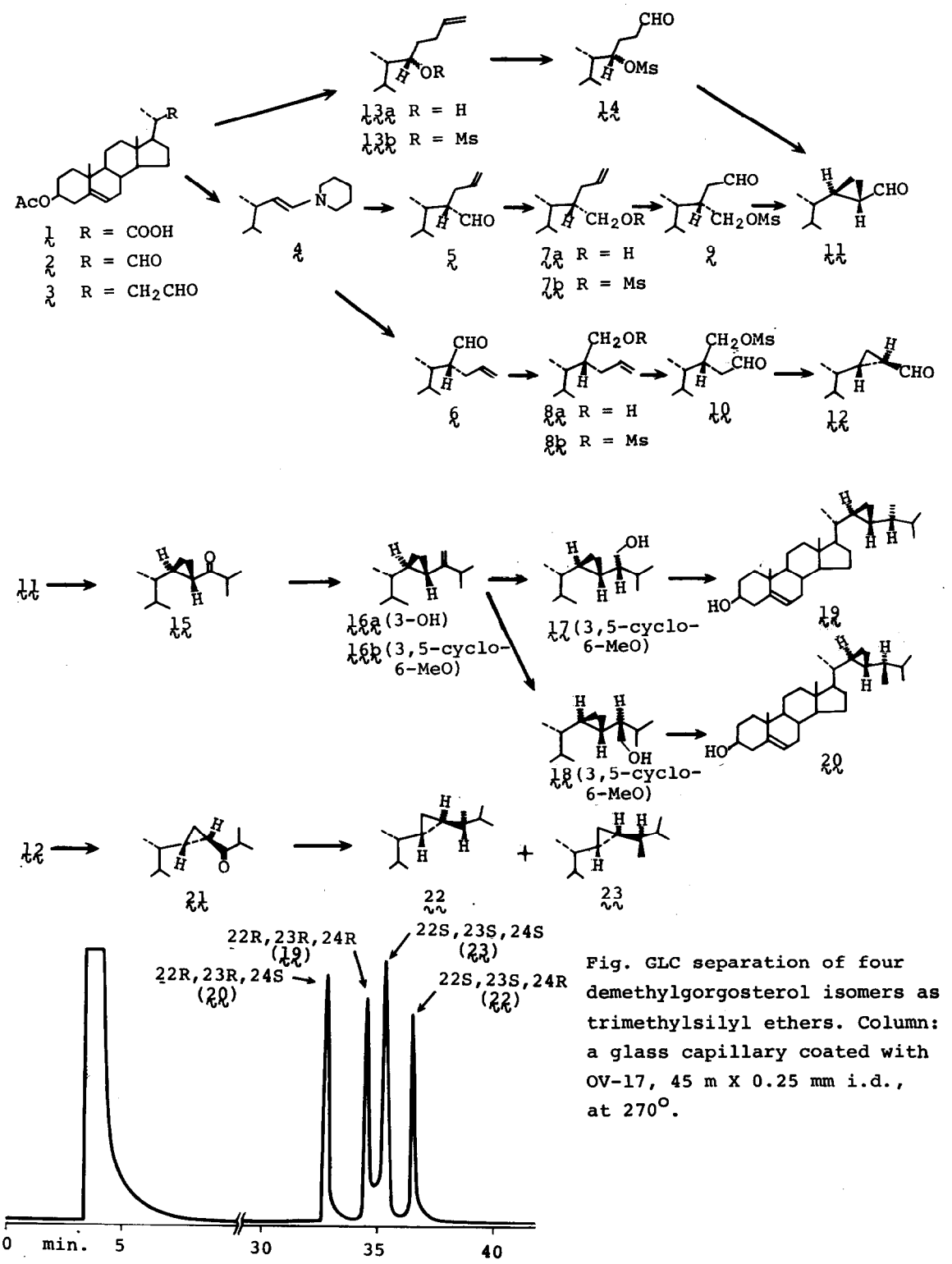

Fig. GLC separation of four demethylgorgosterol isomers as trimethylsilyl ethers. Column: a glass capillary coated with OV-17, 45 m X 0.25 mm i.d., at 270°.

GLC(Fig.).[11] Therefore, the configuration of the isomer 20, mp 139-140°, $[\alpha]_D$ -9.7°, obtained from 18 could be assigned 22R,23R,24S. By the same sequence of reactions, 21 gave the other two isomers, 22S,23S,24R-(22) and 22S,23S,24S-demethylgorgosterol(23), which exhibited identical retention times on GLC(Fig.) [11] with the samples synthesized by another route.[5,12]

REFERENCE AND NOTES

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6. According to the private communication from Prof. C.Djerassi, recently they also completed the synthesis of natural demethylgorgosterol.
7. Analytical and spectral data of all crystalline compounds reported here are consistent with the structures assigned.
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9. ^{13}C-NMR chemical shifts(ppm): 7a, C-23 63.0, C-24 31.9; 8a, C-23 64.5, c-24 30.5. Recorded on PS/PFT-100(JEOL) in $CDCl_3$ with tetramethylsilane as an internal standard. The slight shielding of C-23 in 7a and C-24 in 8a with respect to the other isomer could be explained as due to steric compression; M.Nakane and N.Ikekawa, J. Chem. Soc., Perkin I, 1426(1977).
10. On this type of cyclization, trans substituted cyclopropane may be formed preferentially.[5]
11. The NMR and mass spectra of the four isomers were very close but they could be clearly distinguished by GLC on glass capillary column(Fig.).
12. We thank Professor F.J.Schmitz for providing the sample of natural demethylgorgosterol, and also Professor C.Djerassi for the samples of synthetic 22S, 23S,24S and 22S,23S,24R isomers.

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