Stereocontrolled Synthesis of Gorgosterol

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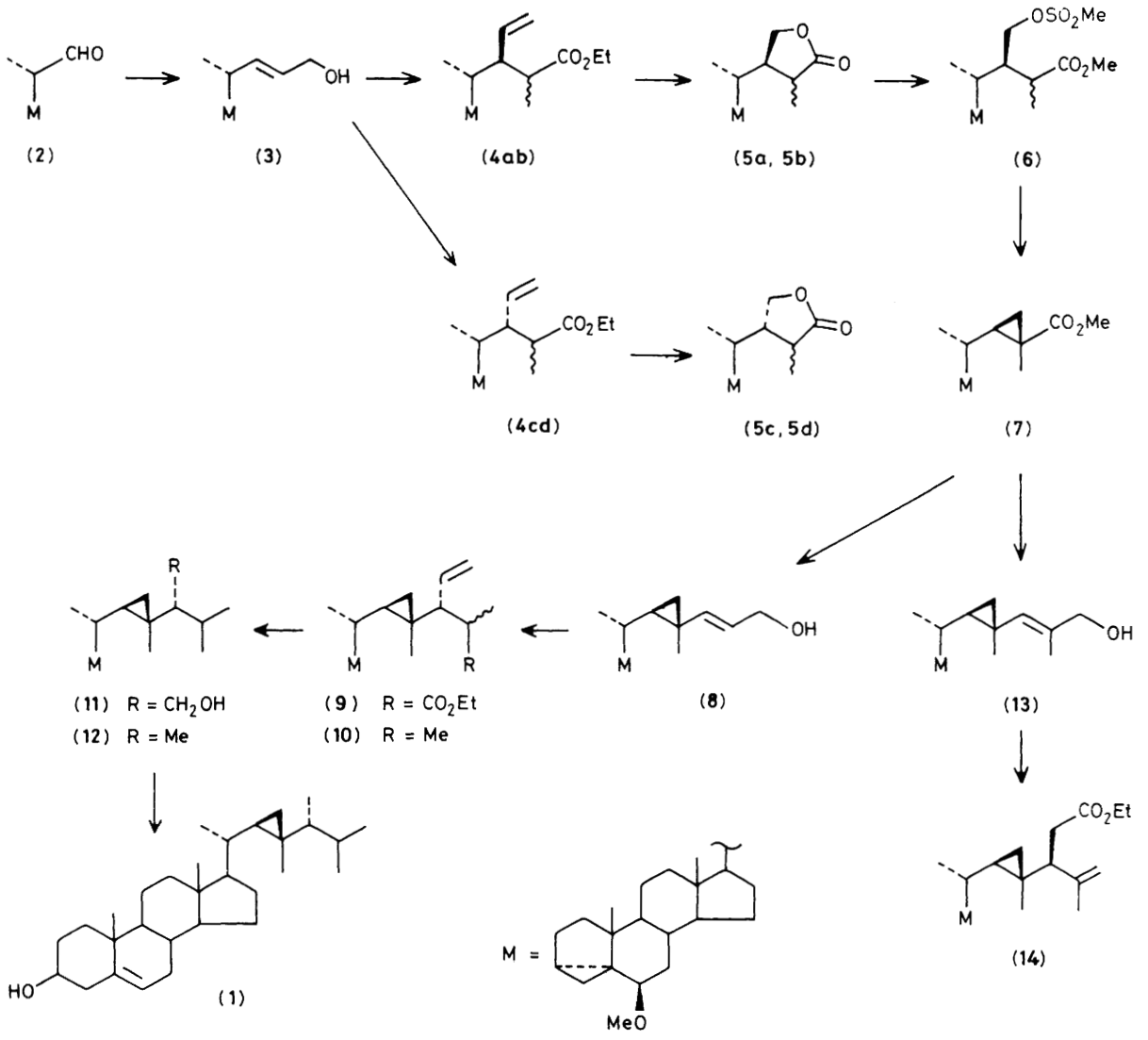
Gorgosterol (**1**), a C_{30} marine sterol containing cyclopropane in the side chain, has been stereoselectively synthesized utilizing orthoester Claisen rearrangement and intramolecular alkylative cyclopropanation.

Gorgosterol[1] (**1**), isolated from the gorgonian, *Plexaura flexuosa* and the zoanthid, *Palythoa tuberculosa*, was the first example of an unprecedented series of sterols with characteristic side chains. Since its isolation, structurally related sterols such as acanthasterol,[2] 5α-gorgostanol,[3] 9-oxo-9,11-seco-gorgost-5-ene-3β,11-diol,[4] and gorgost-5-ene-3β,7α,11α,12β-tetraol 12-monoacetate[5] have been characterized from marine sources. A common structural feature of these sterols is the presence of a cyclopropane ring in the side chain, having 22*R*,23*R*,24*R* stereochemistry, and the quaternary nature of the C-23 carbon. The biosynthesis and possible physiological role of these unique marine sterols have attracted increasing interest.[6] Although the synthesis of demethylgorgosterol,[7] a naturally occurring C-23 demethyl analogue of (**1**), has been



Scheme 1

completed,[8,9] the synthesis of (**1**) has not been reported until now. The three side-chain chiral centres were constructed by highly stereoselective orthoester Claisen rearrangement and the cyclopropane ring was formed by intramolecular alkylation.

The synthesis was achieved as outlined in Scheme 1. The C-22 aldehyde (**2**),[10] readily available from stigmasterol in three steps, was converted into the amorphous (22*E*)-alcohol (**3**) (85%) by Wittig reaction with (ethoxycarbonylmethylene)-triphenylphosphorane followed by di-isobutylaluminium hydride (DIBAH) reduction. Claisen rearrangement of (**3**) with triethyl orthopropionate in the presence of propionic acid (xylene reflux) afforded the more polar (22*R*)-ester (**4ab**) (56%) as an epimeric mixture at C-23 (10:1) and the less polar (22*S*)-ester (**4cd**) (12%) also as an epimeric mixture at C-23 (1:1). The observed stereoselectivity could be explained satisfactorily by the stereochemical consideration discussed in our previous paper.[8b] The C-22 stereochemistry of (**4**) was established by correlating the lactones (**5**) (*vide infra*) with reference samples of unambiguous stereochemistry[11] and confirmed by the eventual conversion of (**5a**) into (**1**). Ozonolysis of (**4ab**) followed by reductive ($NaBH_4$) work up gave chromatographically separable lactones (**5a**) (44%, R_f 0.67 on a silica gel plate with hexane–ethyl acetate 2:1 as a developing solvent, m.p. 198.0—199.5 °C) and (**5b**) (11%, R_f 0.56, m.p. 180.5—182.0 °C). Similarly (**4cd**) afforded (**5c**) (26%, R_f 0.66, m.p. 142.0—144.0 °C) and amorphous (**5d**) (24%, R_f 0.61). Basic hydrolysis (KOH) of (**5a**) followed by *in situ* methylation (buffered with KH_2PO_4) with ethereal diazomethane and methanesulphonation, afforded (**6**) (90%, corrected for the recovered starting material).

Among several conditions examined for the alkylative cyclization of (**6**), the use of Bu^tOK in tetrahydrofuran–benzene was found to give a satisfactory yield of the cyclopropane ester (**7**) (80%) together with a very small amount of the C-23 isomer (>20:1), while treatment with lithium diisopropylamide with or without hexamethylphosphoric triamide resulted in the formation of the lactone (**5ab**) together with (**7**). Transformation of (**7**) to the allylic alcohol (**8**) (72%) or (**13**) (89%) was accomplished by a straightforward four step sequence: $LiAlH_4$ reduction, pyridinium chlorochromate oxidation, Wittig reaction with (ethoxycarbonylmethylene)-triphenylphosphorane or 2-ethoxycarbonylethylidenetriphenylphosphorane, and finally DIBAH reduction.

Claisen rearrangement of the allylic alcohol (**13**) using triethyl orthoacetate yielded the compound (**14**) and the C-24

epimer (40%, 3.5:1). The stereochemistry of (**14**) was established after conversion into the C-24 epimer of (**1**). We therefore reasoned that (**1**) would be obtained with good stereoselectivity on Claisen rearrangement of the other allylic alcohol (**8**) with triethyl orthopropionate. In fact, an 8:1 mixture (45%) of the ester (**9**) and its C-24 epimer was obtained on rearrangement, the ratio being determined by g.l.c. analysis after conversion into (**1**). The crude ester (**9**) was successively treated with $LiAlH_4$, methanesulphonyl chloride–pyridine, and $LiAlH_4$ to afford the olefin (**10**) (79%). The double bond in (**10**) was cleaved by ozonolysis ($NaBH_4$ work up) (55%) and the resulting alcohol was deoxygenated *via* the methanesulphonate affording the compound (**12**) (83%). Regeneration of a Δ^5-3β-ol function (*p*-$MeC_6H_4SO_3H$–aqueous dioxane) (92%) followed by recrystallization completed the synthesis of gorgosterol (**1**), m.p. 182.0—183.5 °C, identical to natural (**1**) in all respects (m.p., mixed m.p., 360 MHz ^1H n.m.r., capillary g.l.c. on OV-101).

It should be noted that the C-24 chiral centre, which was introduced as a 1:1 mixture in the synthesis of demethylgorgosterol[8,9] was successfully controlled in the present work, although the exact nature of the controlling factor remains to be elucidated. The strategy described above combined with asymmetric synthesis in the steroid side chain[12] will be useful in synthesis of other types of cyclopropane sterols such as petrosterol.[13]

We are grateful to Prof. P. J. Scheuer, University of Hawaii, for providing a sample of natural gorgosterol and to Dr. T. Iwashita, Suntory Institute for Bioorganic Research, for recording 360 MHz ^1H n.m.r. spectra.

Received, 28th June 1983; Com. 863

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