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# Stereocontrolled Synthesis of Petrosterol

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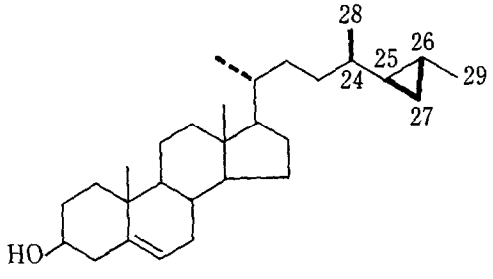
Abstract: Petrosterol (1), a cyclopropane-containing $C_{29}$ marine sterol, has been synthesized in a stereocontrolled manner which involves [2,3]-Wittig rearrangement of the propargyl ether (3) yielding the acetylene alcohol (4) with the required C-24, 25 stereochemistry.

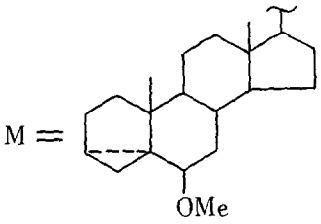
Petrosterol was isolated by Italian group as the major sterol in the marine sponge Petrosia ficiformis[1] and its structure was determined as 26,27-cyclo-aplysterol (1) with 24R,25R,26R configuration by X-ray analysis of the p-bromo-benzoate derivative,[2] although the initially proposed structure (23,28-cyclo-stigmast-5-en-3β-ol) was erroneously assigned. The same sterol was subsequently found from a Pacific sponge Halichondria sp.[3] In the course of our studies on the introduction of functionalities and chiral centers onto sterol side chain, we have selected petrosterol as a synthetic target since a stereocontrolled introduction of the three chiral centers (C-24, 25 and 26 positions) remote from steroid nuclei is an interesting problem. In this paper we describe the stereoselective synthesis of petrosterol (1) in which the C-22 chirality was effectively transferred to the C-24 and 25 positions by use of [2,3]-Wittig rearrangement of propargyl ether.[4] Proudfood and Djerassi have very recently reported on a non-stereoselective synthesis of petrosterol isomers in conjunction with the study of their acid-catalyzed isomerization.[5]

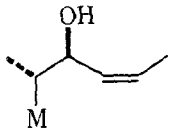
In our retrosynthesis, a (24R,25R)-hydroxy ester such as (8) was assumed as a key intermediate since an intramolecular alkylative cyclization of the corresponding mesylate was expected to afford an trans-substituted cyclopropane derivative from our previous experience.[6] The key intermediate could be obtained from an acetylene alcohol such as (4) in a straightforward manner. According to the study of [2,3]-Wittig rearrangement of propargyl ether by Nakai's group,[4] the (22S,23Z)-propargyl ether (3) should be a precursor requisite for the (24R,25S)-acetylene alcohol (4).

The known (22S,23Z)-allylic alcohol (2)[7] which was obtained from C-22 aldehyde in two steps, was converted into the propargyl ether (3), mp 122-123.5°C in 35% yield (95% corrected for the recovered starting material) by reacting (2) with propargyl bromide in 50% NaOH and tetrahydrofuran containing




1

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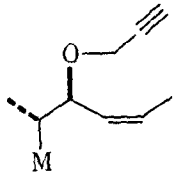


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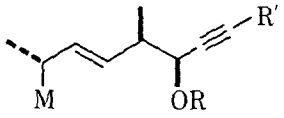
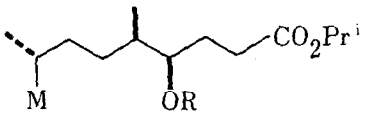
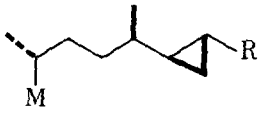



4 R=R'=H
5 R=TBDMS, R'=H
6 R=TBDMS, R'=$CO_2Pr^i$
7 R=H, R'=$CO_2Pr^i$

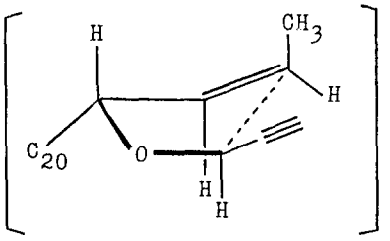



8 R=H
9 R=$SO_2Me$




10 R=$CO_2Pr^i$
11 R=$CH_2OH$
12 R=$CH_2OSO_2Me$
13 R=$CH_3$

$n\text{-}Bu_4NHSO_4$. Treatment of (3) (in THF solution) with 3 eq. of n-BuLi (1.6 M hexane solution) at -78°C→room temperature over a period of 2 hr afforded the rearranged product (4), mp 111-113°C, in 50% yield (38% recovery of starting material). The (24R,25S)-stereochemistry of (4) was assigned on the assumption that the reaction proceeds via the least sterically constrained transition-state model (depicted in the formula) as proposed by Nakai et al.[4] This stereochemical assignment was confirmed by the eventual conversion of (4) into petrosterol. Detailed analysis of 25-MTPA ((+)-α-methoxy-α-trifluoromethylphenylacetic acid) ester derived from (4) in addition to those of the other three possible stereoisomers at C-24 and 25 position,[8] on reversed phase HPLC indicated that the stereochemical purity of (4) is more than 95%.




The following four step sequences led the compound (4) into the hydroxy ester (8). The silyl ether (5) which was obtained quantitatively from (4) by t-butyldimethylsilylchloride/imidazole treatment, was treated with n-BuLi (1.5 eq.) in THF at -78°C and then with chloro isopropylformate[9] (2 eq.) at -78°C→ -10°C to give the acetylene ester (6) in 66% yield. Deprotection of (6) with $n\text{-}Bu_4NF$/THF (1 eq.) afforded the compound (7) in 84% yield, which was hydrogenated over 10% Pd/C in ethyl acetate to give the hydroxy ester (8) in 74% yield.

The following transformation was performed in the same manner as described previously.[6] Thus, the mesylate (9) prepared from (8) by treatment with MsCl/$Et_3N$ in $CH_2Cl_2$ was reacted with 1.0 eq. of $KO^tBu$ in THF/benzene at 0°C to give the trans-substituted cyclopropane (10) in 69% yield (two steps). The reduction of the ester group into the methyl group and regeneration of $\Delta^5$-3β-ol system was undertaken without purification of the intermediate in a standard four-step sequence ($LiAlH_4$, MsCl/$Et_3N$, $LiAlH_4$, and p-TsOH/aqueous dioxane) via the intermediates 11, 12, and 13 (over all yield 49%).

The synthetic petrosterol was fully characterized by mp 156-157°C (methanol) (lit.[5] 157-159°C), $^1$H-NMR ($CDCl_3$, 360 MHz), and mass spectra, which are identical to those of natural petrosterol.

Since (22R)-acetylene alcohol, a precursor of the (22S,23Z)-allylic alcohol, is now available stereoselectively by asymmetric reduction of the corresponding acetylene ketone,[10] it can be said that the present synthesis of petrosterol is highly stereoselective in all aspects.

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## References and Notes

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7. Y. Hirano and C. Djerassi, J. Org , Chem., 47, 2420 (1982).
8. The (24S,25R)-isomer was prepared in the parellel rearrangement of the (22R)-propargyl ether, an epimer of (3),followed by MTPA ester formation, and the (24R,25R)- and (24S,25S)-isomers were obtained by Mitsunobu inversion of (4) and the (24S,25R)-acetylene alcohol mentioned above using MTPA acid, respectively.
9. This bulky ester was used in order to minimize a possible lactonization at the stage of compound (8) and ester exchange during the cyclopropane formation reaction (unpublished results).
10. M. M. Midland and Y. C. Kwon, Tetrahedron Lett., 25, 5981 (1984). See also F. J. Sardina, A. Mourino, and L. Castedo, ibid., 24, 4477 (1983).

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