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STEREOCONTROLLED SYNTHESIS AND DETERMINATION OF THE C-24 AND 25 STEREOCHEMISTRY OF GLAUCASTEROL

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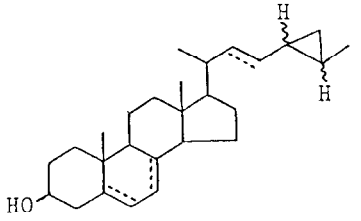
Abstract: (24S,25S)- and (24R,25R)-24,26-Cyclocholesta-5,22E-dien-3β-ols (1a and 1b) were synthesized stereoselectively. Their ^{1}H NMR comparison with natural glaucasterol (1) allowed to conclude that 1 possesses 24S,25S stereochemistry.

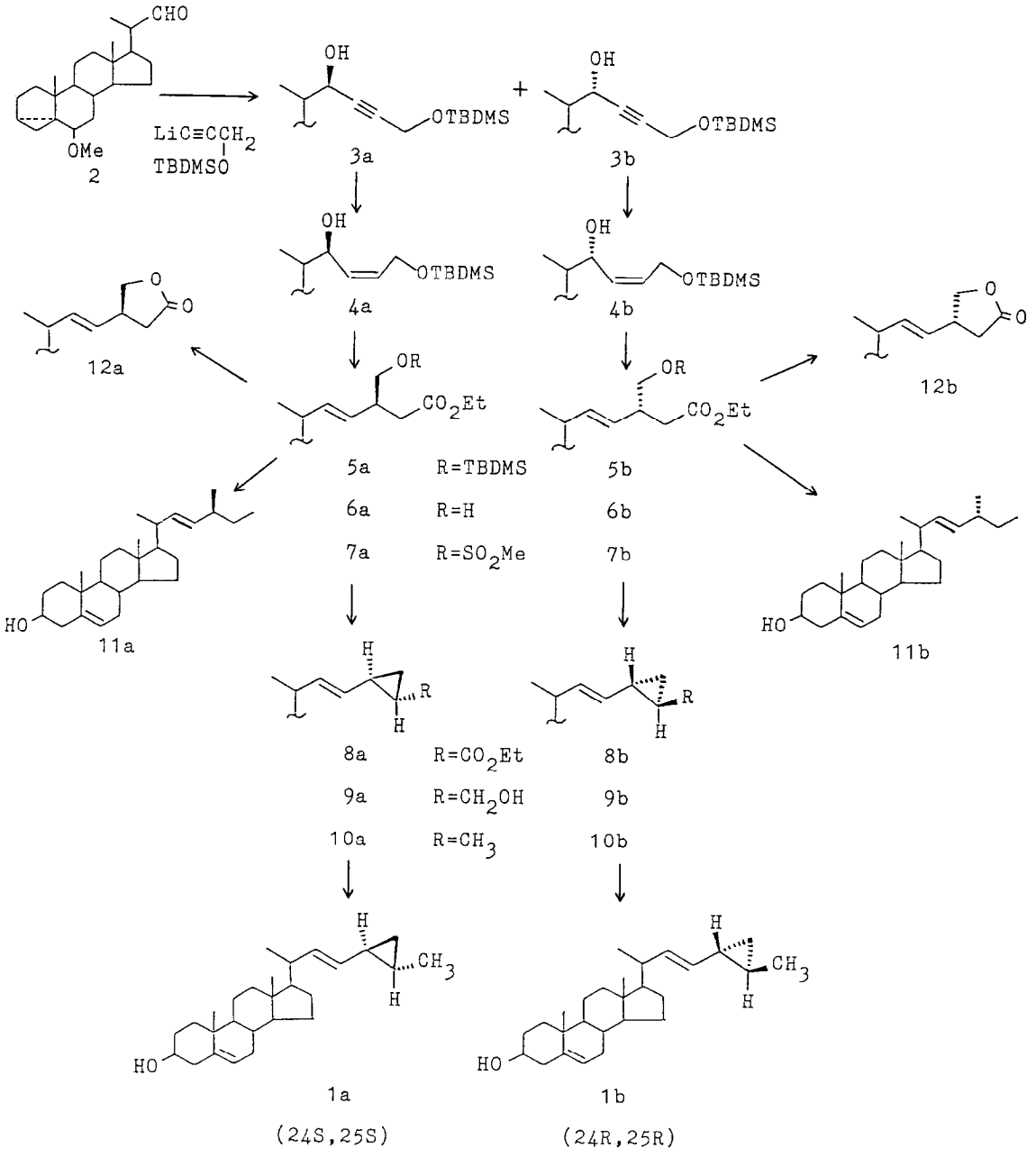
One of the most unique features of marine sterols is the occurrence of cyclopropane ring in the side chain as represented by gorgosterol.[1] Our interest in stereocontrolled synthesis of these cyclopropane-containing sterols has resulted in the successful completion of the synthesis of demethylgorgosterol[2] and gorgosterol.[3] Recently, glaucasterol (1) has been isolated from the soft coral, Sarcophyton glaucum[4] and unidentified deep sea gorgonians.[5] More recently isolation of 22,23-dihydro-,[6] 5,6-dihydro-,[7] 7-dehydro-[5] derivatives of 1 has been reported. However, the absolute configuration of these sterols at positions 24 and 25 remained to be determined. In the present paper, we report the stereoselective synthesis of (24S,25S)- and (24R,25R)-isomers of 1 (1a and 1b) and determination of the absolute stereochemistry of natural glaucasterol as (24S, 25S) by their ^{1}H NMR comparison.



$\Delta^{5,22}$: glaucasterol (1)
Δ^{5} : 22,23-dihydroglaucasterol
Δ^{22} : 5,6-dihydroglaucasterol
$\Delta^{5,7,22}$: 7-dehydroglaucasterol

The synthetic route, as shown in scheme, involves an intramolecular alkylative cyclopropanation in which trans-substituted product on the cyclopropane ring would be formed exclusively.[8] The requisite (24R)- and (24S)-compounds such as 5ab would be obtained by 1,3-chirality transfer using orthoester Claisen rearrangement[9] of a Δ^{23}-22-ol precursor such as 4ab which in turn would be prepared from the known C-22-aldehyde 2.[10]

Coupling of 2 with the t-butyldimethylsilyl (TBDMS) protected propargyl


CHO
OMe
2
LiC≡CCH2
TBDMSO
OH
OTBDMS
3a
3b
4a
4b
OR
CO2Et
5a R=TBDMS
6a R=H
7a R=SO2Me
5b
6b
7b
12a
12b
11a
11b
HO
H
R
8a R=CO2Et
9a R=CH2OH
10a R=CH3
8b
9b
10b
CH3
1a
(24S,25S)
1b
(24R,25R)

Scheme

alcohol (as a lithium salt) afforded a 3:2 mixture of chromatographically separable epimeric alcohols (3a and 3b). The major less polar (22R)-alcohol 3a[11] was hydrogenated over Lindlar catalyst in the presence of quinoline to give the cis-allylic alcohol 4a[11] (90%), which was submitted to orthoester Claisen rearrangement. Refluxing of 4a with ethyl orthoacetate and catalytic amount of propionic acid in toluene afforded the (24S)-ester 5a (65%). The more polar (22S)-alcohol 3b[11] was similarly converted into the (24R)-ester 5b through the cis-allylic alcohol 4b[11] (81% two steps). The esters 5a and 5b were separable on TLC and cross contamination was not detected. Thus, the C-22 chirality was completely transferred to the C-24 position in this rearrangement. The stereochemistry of 5a and 5b was unequivocally established after the transformation of 5a and 5b into the natural occelasterol (11a) and its 24-epimer (11b), respectively.[12]

The silyloxy group should be converted into a leaving group for cyclopropane formation. The attempted deprotection of the ester 5a by the standard procedure using Bu_4NF[13] resulted in the formation of the lactone 12a (12b in the case of 5b) in good yield. However, this undesired reaction was completely suppressed by addition of an acid. Thus 5a (2.6 mM) was converted into the alcohol 6a (70%) by stirring in a mixture of benzoic acid (3.2 mM), 1M Bu_4NF-THF (8.6 mL) and THF (20 mL) at room temperature for 8 hr. Similarly the ester 5b afforded 6b (62%). Alkylative cyclopropane formation of the mesylate 7a and 7b (obtained with MsCl/pyridine from 6a and 6b) was effected by treatment with $KOBu^t$ in THF-benzene, affording the trans-ester 8a (mp 92-93°C) and 8b (mp 117-118°C), respectively, in 76% yield.[14]

The subsequent transformations were straightforward. The compounds 8a and 8b were successively treated with $LiAlH_4$, $MsCl/Et_3N$,[15] $LiAlH_4$, and p-TsOH/H_2O-dioxane to furnish the crystalline (24S,25S)- and (24R,25R)-cyclopropanesterols 1a (mp 112-113°C) and 1b (mp 138-140°C), respectively (50% yield).

Although TLC, GLC and HPLC failed to differentiate the two stereoisomers, ^1H NMR (400 MHz) [1a: ($CDCl_3$) δ 5.284 (dd, J = 15.1 and 8.3 Hz, 22-H), 0.993 (d, J = 6.8 Hz, 20-Me); 1b: δ 5.269 (dd, J = 15.2 and 8.3 Hz, 22-H), 0.998 (d, J = 7 Hz, 20-Me)] was of a diagnostic value as noted by Bonini et al.[5] The ^1H NMR (400 MHz) of glaucasterol provided by Professor Mitsuhashi was essentially identical with that of the synthetic (24S,25S)-isomer 1a, establishing that glaucasterol (also major component of papakusterol[5]) has the 24S,25S configurations. In the course of our work, Catalan and Djerassi have obtained the identical conclusion.[16]

The synthetic route described above would be also applied for the stereoselective synthesis of the other related cyclopropanesterols shown in the first figure. This report is the first, to our knowledge, to demonstrate that orthoester Claisen rearrangement of an allylic alcohol such as 4ab having a oxygen-functionality is an excellent method for synthesis of a various

sterols functionalized at both C-24-alkyl and C-26-terminals.

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References and Notes

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11) The stereochemical assignment of 3ab and 4ab was based on their chromatographic (TLC and GLC) behavior and ^{1}H NMR data [4a: ($CDCl_3$) δ 4.5 (1H, broad d, J = ca. 6 Hz, 22-H); 4b: δ 4.5 (1H, dd, J = 4, 7.5 Hz, 22-H)] (cf. ref. 9) as well as further conversion (vide infra) of each epimers to 5ab through orthoester Claisen rearrangement whose stereochemical course has been well established.

12) The following sequence of reactions was employed for the transformation of 5ab into 11ab: i) $LiAlH_4$; ii) $MsCl/Et_3N$; iii) $LiAlH_4$ and iv) H^+. Somewhat strangely step i afforded the diol together with a small amount of the expected mono-ol. The comparison was carried out by reversed phase HPLC (Zorbax ODS, MeOH eluted) in which 11a eluted faster than 11b (cf. ref. 9c).

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