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STEREOSPECIFIC SYNTHESIS OF DINOSTEROL

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Abstract: Using a Claisen ortho-ester rearrangement, the biogenetically important marine sterol dinosterol and its C-24 epimer were synthesized stereospecifically by a sequence which is also attractive for selective isotope labelling in the side chain.

Dinosterol was first isolated from the toxic dinoflagellate, Gonyaulax tamarensis, by Shimizu et al[1] and its stereostructure 12 was established unequivocally by X-ray crystallography.[2] Dinosterol (12) and/or its naturally occurring[3] Δ^5-3β-hydroxy analog 14 have been proposed[1,2,4,5] as possible key precursors in the biosynthesis of the important marine sterol gorgosterol (15).[4] In order to verify such proposals, radioactively labelled dinosterol would have to be synthesized. We now report the first synthesis of dinosterol (12) which is equally applicable to the synthesis of 14; most importantly, it lends itself readily to the selective incorporation of isotopic tracers in the side chain.

The starting alcohol 1 (mp 193-194°C, $[\alpha]_D^{20}$ +26.6 ($CHCl_3$)), obtained by ozonolysis of the tert-butyldimethylsilyl ether of 4α-methyl-5α-dihydrostigmasterol[6] and subsequent $NaBH_4$ reduction, was oxidized with pyridinium dichromate[7] to the corresponding aldehyde which was immediately condensed at -78°C with the vinyl lithium reagent prepared from n-BuLi and (E)-2-iodo-2-butene at -60°C.[8] The vinyl iodide in turn was synthesized by the addition of catecholborane to 2-butyne at 70°C, followed by hydrolysis and treatment of the boranediol with NaOH and I_2.[9] The condensation gave two allylic alcohols easily separable on silica gel: the less polar 22R alcohol 2 (73% yield, mp 171-178°C, $[\alpha]_D^{20}$ +11.9 ($CHCl_3$), m/z 516.4354), and the more polar 22S epimer 3 (9% yield, mp 167-170°C, $[\alpha]_D^{20}$ +30.5 ($CHCl_3$), m/z 516.4306). The configurational assignment was based upon further conversions (vide infra) of each epimer to the final sterols through the well-known Claisen rearrangement which transferred the chirality from C-22 to C-24 with concomitant formation of the trans-Δ^{22} double bond.[10] The stereochemical assignment is also consistent with the fact that condensation of a similar vinyl lithium reagent and aldehyde yielded[11] as the major product a 22-alcohol with the same absolute configuration as 2.

Claisen rearrangement of 2 with triethyl orthopropionate[12] and subsequent deprotection of the silyl ether with $LiBF_4$[13] gave a mixture of C-25 epimeric esters, which were separated by reverse phase HPLC (column: Whatman Partisil M9 10/50 ODS-2; eluent: absolute MeOH): 4a (44% yield from 2, mp 159-160°C, $[\alpha]_D^{20}$ +4.6 ($CHCl_3$), m/z 486.4111), and 4b (22% yield, mp 211-214°C, $[\alpha]_D^{20}$ -7.1 ($CHCl_3$), m/z 486.4060). Similar transformation of 3 and HPLC separation provided 5a (50%

yield, mp 163-164°C, $[\alpha]_D^{20}$ +11.9 ($CHCl_3$), m/z 486.4056); the other C-25 epimer, 5b, could not be obtained in pure form.

Table I. Physical properties of synthetic products 6a-13

Compound	mp°C	$[\alpha]_D^{20}$ ($CHCl_3$)	m/z	Compound	mp°C	$[\alpha]_D^{20}$ ($CHCl_3$)	m/z
6a	145-146	+12.3	600.4891	8a	178-181	+9.7	558.4820
6b	187-189	+3.7	600.4934	8b	202-206	+12.7	558.4910
7a	122-124	+22.4	600.4961	9a	215-220	+28.5	558.4828
10	193-196	+9.6	542.4935	12[a]	211-214	-2.2	428.4018
11	210-212	+29.0	542.4829	13	218-221	+23.3	428.4015

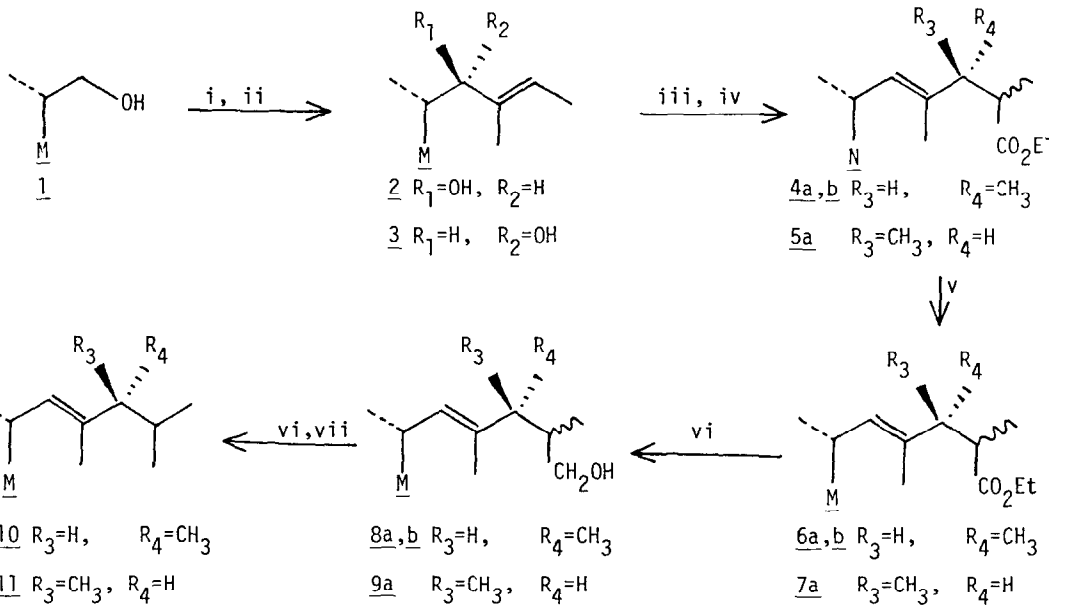
[a] Ref. 1 reports mp 220-222°C ($CHCl_3$-MeOH), $[\alpha]_D$ ±5 ($CHCl_3$) for the natural product. A sample of dinosterol isolated in our laboratory from the cultured zooxanthellae of the gorgonian Briareum asbestinum and purified by HPLC exhibited mp 212-215°C (hot MeOH), $[\alpha]_D^{20}$ -1 ($CHCl_3$).

Each of the isomeric hydroxy ester (4a,4b,5a) was then subjected to a three-step transformation sequence: protection of the 3β-hydroxy group with tert-butyldimethylsilyl chloride[14] (90% yield of 6a,6b,7a), lithium aluminum hydride reduction of the C-26 ester function (85% yield of 8a,8b,9a), mesylation[15] and subsequent reduction with lithium aluminum hydride (93% yield of 10 and 11). With the resulting destruction of the C-25 epimeric center, the products (10) from 8a and 8b were identical by NMR comparison. Finally deprotection of the silyl ethers gave the free sterols (94% yield) 12 and 13. Both exhibited the same GC mobility (3% OV-17, 260°C) as that of natural dinosterol[1] but were separable by reverse phase HPLC (retention times: 12, 1.48; 13, 1.39; cholesterol, 1.00). The physical constants are listed in Table I; unambiguous differentation could be accomplished by 360 MHz NMR comparison (cf. Table II).

Table II. ^1H Chemical Shifts of dinosterol (12) and its C-24 epimer 13 (360 MHz, $CDCl_3$/TMS, coupling constants J in Hz)

Isomer	C-18(s)	C-19(s)	C-21(d)[a]	C-22H(d)
12(nat.)	0.678	0.826	0.917(J=6.5)	4.872(J=9.7)
12(synth.)	0.680	0.827	0.919(J=6.5)	4.873(J=9.7)
13	0.683	0.827	0.910(J=6.8)	4.875(J=9.7)
	C-26(d) or C-27(d)[b]	C-28(d)	C-29(d)	C-30(d)
12(nat.)	0.777(J=6.8)/0.835(J=6.5)	0.927(J=6.5)	1.495(J=1.1)	0.945(J=6.5)
12(synth.)	0.778(J=6.8)/0.837(J=6.5)	0.928(J=6.5)	1.495(J=0.7)	0.946(J=6.1)
13	0.772(J=6.8)/0.848(J=6.5)	0.938(J=6.8)	1.484(J=1.1)	0.945(J=6.5)

[a] C-21 was determined by a decoupling experiment involving irradiation of the allylic proton around 2.3 ppm in both isomers.
[b] C-26 and C-27 were determined by their simultaneous collapse when irradiation occurred around 1.5 ppm.



1

2 R_1=OH, R_2=H

3 R_1=H, R_2=OH

4a,b R_3=H, R_4=CH_3

5a R_3=CH_3, R_4=H

6a,b R_3=H, R_4=CH_3

7a R_3=CH_3, R_4=H

8a,b R_3=H, R_4=CH_3

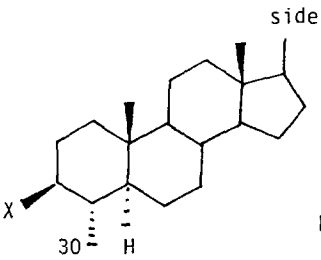
9a R_3=CH_3, R_4=H

10 R_3=H, R_4=CH_3

11 R_3=CH_3, R_4=H

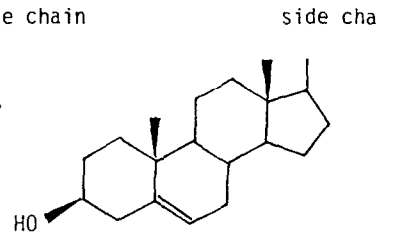
12 R_3=H, R_4=CH_3

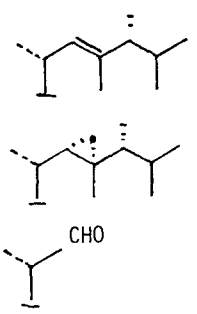
13 R_3=CH_3, R_4=H



M X=$OSi(Me_2)t$-Bu (TBS)

N X=OH





14

15

16

i: Pyr. Dichr., CH_2Cl_2, RT

ii: $LiCH_3C{=}CHCH_3$, -78°C

iii: $EtC(OEt_3)$, EtCOOH cat, 110°C, 3h

iv: $LiBF_4$, CH_2Cl_2, CH_3CN, 65°C, 12h

v: TBSCl, imidazole, DMF, CH_2Cl_2, 50°C, 12h

vi: LAH, Et_2O, RT

vii: MsCl, Et_3N, CH_2Cl_2, 0°C, 15 min

By replacing lithium aluminum hydride with the corresponding tritium or deuterium analog in one or both of the terminal reduction steps (6,7 → 8,9 → 10,11), appropriate tritium or deuterium labelling can be effected. Furthermore, by applying the identical reaction sequence to the well-known[16] i-methyl ether of the aldehyde 16, the naturally occurring[3] 23,24-dimethyl-22-dehydrocholesterol (14) and its 24-epimer were also synthesized in our laboratory.

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