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SYNTHESIS OF THE PUTATIVE MARINE STEROLS [24R]- AND [24S]-23,24-DIMETHYL-5α-CHOLEST-23(29)-EN-3β-OL.

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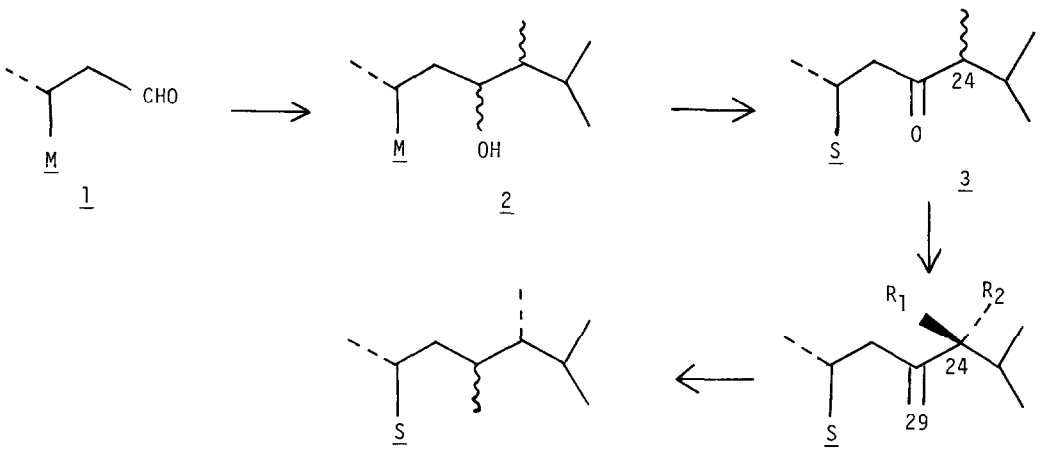
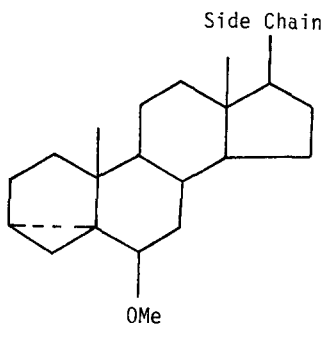
Abstract: The synthesis and stereochemistry of [24R]- and [24S]-23,24-dimethyl-5α-cholest-23(29)-en-3β-ol is reported; both isomers are different from a natural marine sterol to which the structure had been assigned.

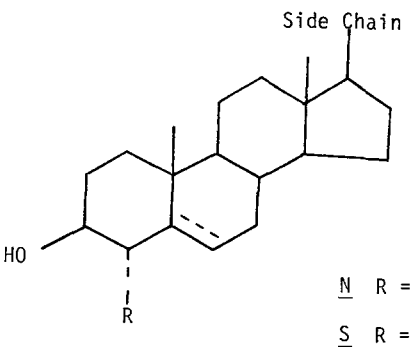
One of the unique features of marine sterols, as compared to those from terrestrial sources, is the presence of side chains with C-23 methyl substituents;[1] in addition, one 23-ethylated sterol, ficisterol (6),[2] has also been encountered. We postulated[3] that a 23-methylene sterol side chain, such as is found in 4, might be a plausible precursor of ficisterol (6). The recent report[4] of the isolation of the first sterol with such a side chain, 23,24-dimethyl-5α-cholest-23(29)-en-3β-ol (4), from the dinoflagellate Gonyaulax monilata, its importance as a likely biosynthetic intermediate for 23-ethylated sterols, and the fact that the C-24 stereochemistry had not been established prompted us to undertake the synthesis of both C-24 stereoisomers of 4.

The earlier described[5] aldehyde 1 was treated with the Grignard reagent from 2-bromo-3-methylbutane[6] to give a mixture of isomeric alcohols 2. Oxidation with Jones reagent, removal of the i-methyl ether protecting group followed by hydrogenation (Pd/C, EtAc) of the Δ^5 double bond gave the ketone 3 (mp 164-165°C, m/z 414.35151, NMR (360 MHz, $CDCl_3$): 0.688 [C-18]; 0.797 [C-19]; 0.979 (J=7.0), 0.971 (J=6.9) [C-28]; and six doublets at 0.833 (J=6.8), 0.845 (J=6.8), 0.874 (J=6.7), 0.891 (J=5.5), 0.893 (J=7.3) and 0.902 (J=6.7) for C-21, C-26 and C-27) as a mixture of C-24 epimers. Wittig condensation (nBuLi, C_6H_6, 24 hrs, reflux) with methyltriphenylphosphonium bromide afforded a mixture of C-24 epimeric olefins 4, which were separated by reverse phase HPLC (column: Altex-Ultrasphere; eluent: absolute MeOH). They displayed the following properties: 4A: RRT 1.09 (cholesterol = 1), mp 171-172°C, m/z 414.38518; 4B: RRT 1.12, mp 159-160°C, m/z 414.38386. Hydrogenation (PtO_2, EtAc) of isomer 4A gave two C-23 isomeric 23,24-dimethyl-5α-cholestanols (5), which were separated by reverse phase HPLC. Their side chain NMR signals (see Table) were identical with those of the two hydrogenation products[7] of dinosterol (7).[8] Since the stereochemistry of

dinosterol (7) at C-24 has been established by X-ray analysis,[9] it follows that both C-23 isomers of 5 have the 24R (β) configuration and that this must therefore apply to its precursor 4A which is [24R]-23,24-dimethyl-5α-cholest-23(29)-en-3β-ol. Isomer 4B therefore has the 24S (α) configuration.







N R = H, Δ5

S R = H, 5α-H

T R = CH3, 5α-H

The mass spectra of both 24R-(4A) and 24S-(4B) isomers of 23,24-dimethyl-5α-cholest-23(29)-en-3β-ol are identical and are characterized by the following diagnostic peaks (relative intensity in parentheses): m/z M^+ 414(2), 302(100), 287(35), 285(20), 274(4), 273(14), 257(4), 233(8), 69(21). The mass spectrum shows major differences [e.g. m/z 371(0) vs. 371(21); 274(4) vs. 274(100); 257(4) vs. 257(78); 69(21) vs. 69(0)] from that reported for the naturally occurring sterol[4] and the NMR spectra (cf. Table) are also quite different. It is clear, therefore, that the sterol isolated[4] from G. monilata cannot have the assigned 23,24-dimethyl-5α-cholest-23(29)-en-3β-ol (4) structure. Through the courtesy of Dr. M. Alam, a crude sample of G. monilata sterol[4] was acquired. After purification, the major component was shown to be identical (chromatographic retention time, mass spectrum and NMR spectrum - see Table) with the recently described[10] 4-demethyldinosterol (8).

Table ^{1}H Chemical Shifts of Selected Signals of [24R]- and [24S]-23,24-Dimethyl-5α-cholest-23(29)-en-3β-ol (4), [23ξ,24R]-23,24-Dimethyl-5α-cholestan-3β-ol (5), 4-Demethyl-dinosterol (8) and Naturally Occurring G. monilata Sterol[4] (360 MHz, $CDCl_3$; J values given in Hz in parentheses).

Compound	C-18(s)	C-19(s)	C-21(d)	C-26(d) or C-27(d)[a]	C-28(d)[a]	C-29(d)	C-23
4A	0.680	0.805	0.846(5.7)	0.781(6.7) 0.887(6.7)	0.929(7.0)		4.724 4.715 (2H)
4B	0.676	0.802	0.886(6.3)	0.848(6.3)	0.949(6.7)		4.745 4.688 (2H)
G.monilata sterol[b]	0.62	1.05(?)	0.91(6.4)	0.86(6.8)	0.93(6.3)		5.233 5.237 (2H)
5A[c]	0.661	0.801	0.698(6.7)	0.721(6.9) 0.811(6.9)	0.878(6.7)	0.871(6.4)	
5B[c]	0.648	0.799	0.758(7.0)	0.789(7.4) 0.871(6.7)	0.886(6.7)	0.917(6.5)	
8[d]	0.681	0.805	0.918(6.6)	0.778(6.6) 0.836(6.6)	0.928(6.6)	1.495(s)	4.875(d, J=9.6, 1H)

a These assignments were based on the course of decoupling experiments involving irradiation at 1.5 ppm (C-21 collapse), 1.64 ppm (simultaneous collapse of C-26 and C-27) and 1.85 ppm (C-28 collapse).

b 100 MHz spectrum - assignments not given[4] except for olefinic protons.

c Except for C-18 and C-19, the assignments are highly tentative.

d These data were taken from Table 4 of ref. 10 where the column headings 4h and 5h were mistakenly interchanged.

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