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SYNTHESIS OF FICISTEROL - THE FIRST NATURAL STEROL WITH 23-ETHYL SUBSTITUTION

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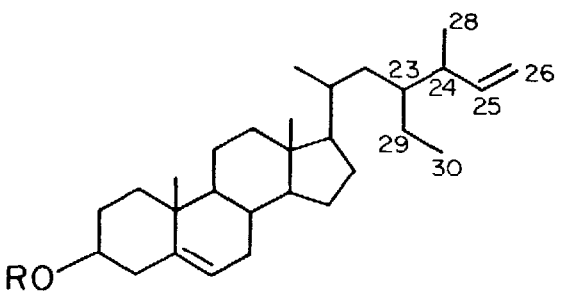
Abstract Using a Claisen ortho-ester rearrangement, all four possible C-23,C-24-stereoisomers of the novel marine sterol ficisterol (23-ethyl-24-methyl-27-norcholesta-5,25-dien-3β-ol, 1) were synthesized and the C-24 configuration of the natural product established

Recently[1] we described the isolation and structural elucidation of ficisterol (23-ethyl-24-methyl-27-norcholesta-5,25-dien-3β-ol, 1), a trace sterol from the marine sponge Petrosia ficiformis Ficisterol (1) is the first example of a sterol - from either terrestrial or marine sources - with an ethyl substituent at position 23, thus representing a new variant of the bioalkylation pattern of sterol side chains The synthesis of 1 was undertaken in order to confirm these unusual structural features deduced solely from the ^{1}H NMR and mass spectral data, and with a view to gaining some insight into the stereochemical relationship of the new side chain

1, R = H
2, R = Ac



For comparison purposes the synthesis of all four possible C-23,C-24-stereoisomers (12a-d) was required, since neither absolute nor relative configurations at these chiral centers of the side chain are known Therefore a preparative route was selected in which both the 23-ethyl and the 24-methyl substituents were introduced by a Claisen ortho-ester rearrangement (6 → 7) 3α,5-Cyclo-6β-methoxy-23-hydroxynorcholane (3), prepared[2] by degradation of methyl 3β-acetoxychol-5-enate, was oxidized with Collins reagent[3] to the aldehyde 4 which without isolation was subjected to Wittig condensation with carbomethoxymethylenetriphenylphosphorane[4] to yield (66% from 3) the trans methyl ester 5 (mp 110-111°C) [5] Nearly quantitative reduction of 5 with sodium bis(2-methoxyethoxy)aluminum hydride in benzene solution[6] to the allylic alcohol 6 (mp 140-141°C) and subsequent Claisen rearrangement of 6 with triethyl orthopropionate[7] led to an oily mixture of

diastereoisomers of the γ,δ-unsaturated esters 7 (77% yield) After catalytic hydrogenation to 8 (97% yield) and lithium aluminum hydride reduction, a mixture of the alcohols 9a-d (97% yield) was obtained At this stage the separation of the stereoisomers (present in approximately equal amounts) was accomplished by preparative high pressure liquid chromatography on silica gel (column Whatman Partisil M9 10/50, eluent hexane/ethyl acetate = 9/1) Each of the alcohols 9a-d (Table I) was then subjected to a three-step reaction sequence performed without isolation of the intermediates Collins oxidation[3] to 10 and Wittig condensation[8] to 11 followed by cleavage of the methoxy-1-ether protecting group to the Δ^5-acetates 12 (HOAc, $Zn(OAc)_2$ cat, reflux 20 min, 24-44% yield from 9) Inspection of the 360 MHz proton NMR spectra of the four diastereomeric acetates 12a-d (Table II) clearly shows that isomer 12a is identical with the acetate of ficisterol (2) GC mobility is a useless criterion since all four isomers (a-d) of 13 behaved identically on co-injection with the natural sterol

TABLE I

^1H Chemical Shifts of the C-23,C-24-Diastereoisomers of 3α,5-Cyclo-6β-methoxy-23-ethyl-24-methyl-26,27-bisnorcholestan-25-ol (9a-d) (360 MHz, $CDCl_3$, coupling constants J in Hz)

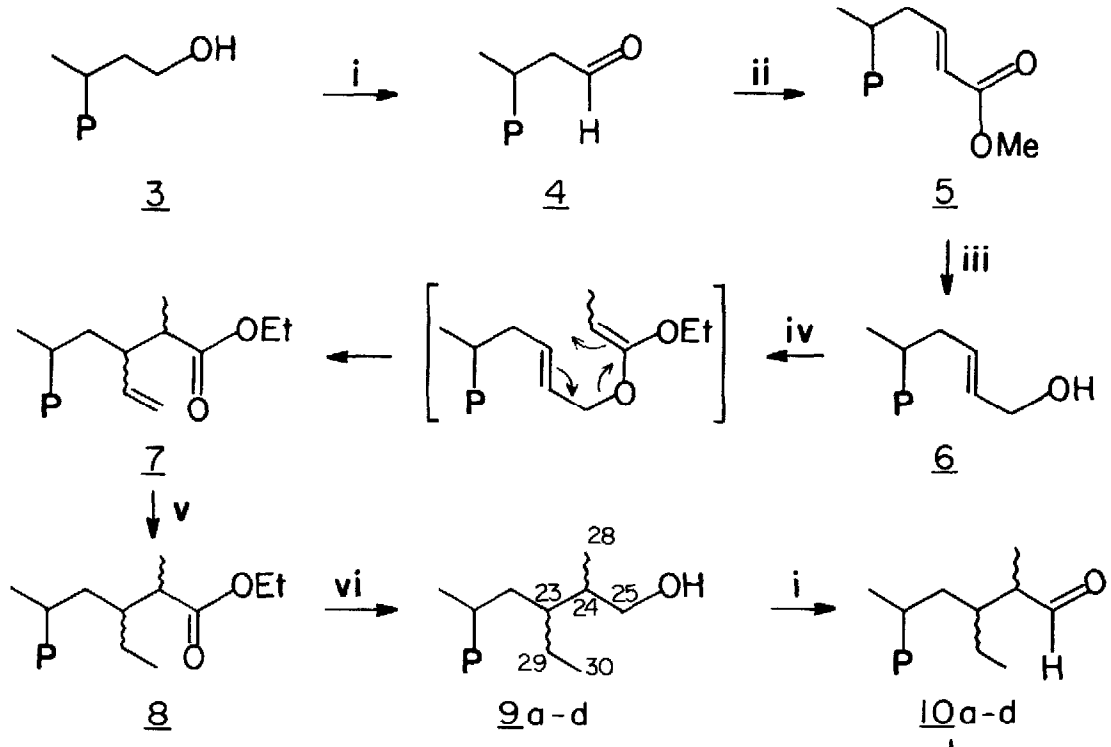
Isomer	Retention Time (HPLC)	C-18	C-19	C-21(d) or C-28(d)	C-30(t)
9a	32 min	0 729	1 022	0 782 /0 885 (J = 6 9)/(J = 6 3)	0 870 (J = 7 5)
9b	40 min	0 726	1 022	0 893 /0 925 (J = 6 5)/(J = 6 9)	0 872 (J = 7 3)
9c	46 min	0 727	1 023	0 775 /0 896 (J = 6 9)/(J = 6 7)	0 866 (J = 6 4)
9d	70 min	0 725	1 023	0 905 /0 922 (J = 6 2)/(J = 6 0)	0 868 (J = 7 3)

TABLE II

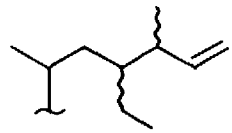
^1H Chemical Shifts of Ficisterol Acetate (2), Synthetic Ficisterol Acetate (12a), and its C-23,C-24-Stereoisomers 12b, 12c, and 12d (360 MHz, $CDCl_3$, coupling constants J in Hz)

Compound	mp (°C)	C-18(s)	C-19(s)	C-21(d)	C-25(m)	C-26(m)	C-28(d)*	C-30(t)
2	99-100	0 687	1 017	0 868 (J = 6 1)	5 77	4 95	0 879 (J = 6 6)	0 850 (J = 7 3)
12a	102-103	0 688	1 018	0 866 (J = 6 1)	5 77	4 95	0 877 (J = 6 6)	0 850 (J = 7 3)
12b	105-106	0 665	0 996	0 856 (J = 6 4)	5 64	4 91	0 949 (J = 6 8)	0 826 (J = 7 1)
12c	116-117	0 670	1 000	0 887 (J = 6 3)	5 81	4 94	0 850 (J = 7 1)	0 816 (J = 7 1)
12d	123-124	0 690	1 021	0 892 (J = 6 4)	5 73	4 96	0 993 (J = 6 9)	0 855 (J = 6 3)

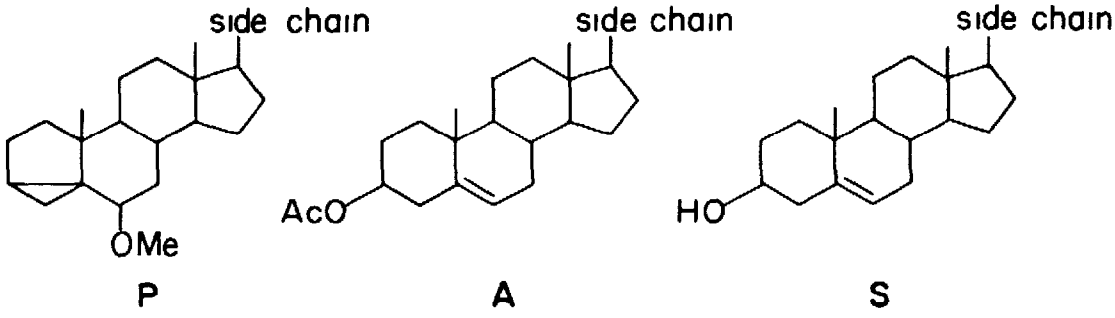
*C-28 was distinguished from C-21 by decoupling experiments involving irradiation of the allylic C-24 proton in the range of δ 2 2-2 3 ppm



i · CrO_3, Py, CH_2Cl_2
ii : $Ph_3P{=}CHCOOMe$, CH_2Cl_2, reflux, 14 hrs
iii $NaAlH_2(OC_2H_4OMe)_2$, C_6H_6, RT
iv · $EtC(OEt)_3$, EtCOOH cat, 140°, 90 min
v H_2, Pd on $BaCO_3$, EtOAc, RT, 3 hrs
vi $LiAlH_4$, Et_2O, RT
vii NaH, DMSO, Ph_3PCH_3I, RT, 30 min



P: 11 a-d
A: 12 a-d
S: 13 a-d



The following tentative assignment can be made about the absolute configuration at C-24 of ficisterol (1) In a series of $\Delta^{25,26}$-sterols it has been shown earlier[9] that the chemical shift position of the C-28 methyl group can be used as an indicator for the absolute configuration at C-24 if both C-24 isomers are available [10] Absorptions for C-24α compounds are found at higher fields compared with their C-24β analogs The chemical shift positions of the C-28 methyl groups in the four isomers 12a-d clearly show a significant upfield shift for the pair 12a (=2) and 12c (δ 0 877 and 0 850) compared to 12b and 12d (δ 0 949 and 0 993) On this basis we suggest that ficisterol (1) belongs to the C-24α series together with its epimer 12c - both having the 24S configuration Establishment of the absolute configuration at C-23 would require x-ray analysis Except for this stereochemical feature, the present synthesis unambiguously confirms that ficisterol (1) is the first naturally occurring 23-ethylated sterol

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