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SYNTHESES OF SQUALENE EPOXIDE AND LANOSTEROL ANALOGUES FOR A BIOSYNTHETIC EXPERIMENT

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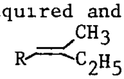
The syntheses of (21-^{14}C)-2,3(RS)-oxido-2,6,10,15,19-pentamethyl-heneicosa-6E-10E, 14E,18Z-tetraene from squalene and of pure 20R and 20S 24,25,26,27-tetranorlanosteryl acetates from lanosteryl acetate are disclosed.

We recently needed, for a project in our sterol biosynthetic work[1], a sample of pure radiolabelled 2,3-oxido-2,6,10,15,19-pentamethyl-heneicosa-*6E,10E,14E,18Z*-tetraene 7 and the two stereoisomers of 24,25,26,27-tetranorlanosteryl acetates 18 possessing respectively the natural (*R*) 18a and unnatural(*S*) 18b configuration at the C-20 carbon atom. This report discloses the synthesis of these derivatives.

I. *Synthesis[2] of (21-^{14}C)-2,3(RS)-oxido-2,6,10,15,19-pentamethyl-heneicosa-6E,10E,14E,18Z-tetraene 7*

2,6,11,15,19-pentamethyl-eicosa-*2Z,6E,10E,14E,18*-pentaene-1-ol 2 was chosen as a good candidate for the desired synthesis since it possesses : 1) the required polyenic system with the right stereochemistry - 2) two terminal double bonds of very different nucleophilicity which should allow the selective oxidation of the Δ^{18} double bond using van Tamelen's procedure[3] - 3) a suitable function at C-1 which would allow at the same time and at the end of the synthesis the introduction of the last carbon atom required and the radioactive label. And last but not least, a similar transformation [RCH=O → ] has been used by Corey[4] for the stereoselective synthesis of Cecropia juvenile hormone.

The allyl alcohol 2 was stereoselectively prepared from readily available aldehyde[5] 1 via β-oxido-ylide reaction[6] [i-ethylidenetriphenylphosphorane, THF; -78°, 0.05 hr — ii-tBuLi 1.2 eq; -78°, 0.1 hr; -25°, 0.5 hr — iii-CH_2O(gas) 10 eq.; -20° to 0°, 0.7 hr; 20°, 0.3 hr - 30% overall yield, tlc SiO_2 ether/pentane : 3/7 R_f 0.26], benzoylated [C_6H_5COCl/pyridine, 90% yield] and selectively transformed to the terminal bromohydrin[3] [NBS (1.14 eq), DME/water : 4/1, 10°, 5 hr; 45% yield; tlc SiO_2 ether/pentane : 3/7 R_f 0.37]. Starting material (18%) is also recovered.

Reaction of the bromohydrin 3 with sodium methylate affords the epoxy-alcohol 4[7] by simultaneous ring closure and cleavage of the benzoate [CH_3ONa (6 eq), CH_3OH/THF : 14/1; 5°, 0.3 hr; 72% yield, tlc, SiO_2, ether/pentane : 4/6 R_f 0.24].

The epoxy-alcohol 4 is oxidized to the epoxyaldehyde 5 (MnO_2[8], 16 eq, hexane, 20°, 2 hr; 98% yield, tlc, SiO_2 ether/pentane : 4/6, R_f 0.5) which is in turn transformed into the radiolabelled epoxydiene 6 ($^{14}CH_2=P\phi_3$[9], THF, 40% yield; 6.4 10^3 dpm/nmole ; tlc SiO_2 ether/pentane :

3/7 R_f 0.57, the starting material 5 is also recovered in 45% yield).

The last step of the synthesis requires the selective reduction of terminal carbon-carbon double bond of the epoxydiene 6 which is achieved by diimide in ethanol[10,11] [hydrazine hydrate (20eq) H_2O_2 (30% aqueous solution, 2leq), ethanol, 0°, 2 hrs; 75% yield; tlc SiO_2 ether/pentane : 3/7, R_f 0.57].

The physicochemical data (IR, ^1H NMR, Mass spectra) agree with the proposed structure for 7. Its ^1H NMR spectrum clearly shows the presence of a vinylic methyl group cis to a hydrogen ($CDCl_3$ δ 1.66 ppm; methyl groups trans to hydrogen : δ 1.60 ppm relative to TMS) but does not ensure its stereochemical purity.

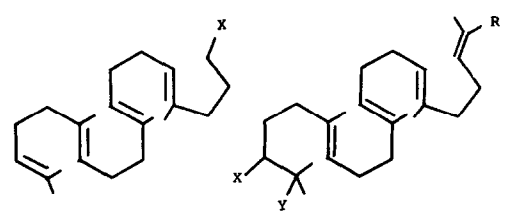
In order to check its stereochemical purity, the radiolabelled epoxide 7 just prepared was transformed into the corresponding polyene[12,13] 10 [i-$HClO_4$(70%)/H_2O/DME : 0.5/35.5/74; 0° → 20°, 5 hrs; 8:75% yield - ii-thiocarbonyldiimidazole, toluene; 110°, 3hrs; 9:81% yield - iii-$P(OCH_3)_3$, 130°, 63hrs; 10:83% yield; tlc SiO_2 hexane R_f 0.55] and analysed by $|GC|^2$ under conditions which allow the separation of the *18E* and *18Z* isomers of 2,6,10,15,19-pentamethyl-heneicosa-*2,6E,10E,14E,18*-tetraene.This mixture was prepared from aldehyde 1 and 2-butylidene triphenylphosphorane [2 eq, -78° → 20°, 0.7 hr, 83% yield, $|GC|^2$ on a 50m x 0.5 mm, glass capillary column statically coated with SE-30, column temp. 200°, carrier gas (He), flow rate : 9 ml/min. Rt 10b (*18Z*): 38 min., 10a (*18E*) : 39.7 min.] . We found that our labelled polyene 10, and consequently the epoxide 7, is a 95/5 mixture of the two *18Z/18E* stereoisomers.

II. Synthesis of pure 20R 18a and 20S 18b 24,25,26,27-tetranorlanosteryl acetates

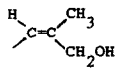
3β-acetoxy-4,4,14α-trimethyl-5α-pregnadiene 12 was chosen as the ideal *key intermediate* for the synthesis of 18a and 18b since the complete tetracyclic system *is retained, the former stereochemistry at C-20 is absent and a functionality (Δ^{20}) is present* for the elaboration of the final structures 18a and 18b. Moreover, 12 is conveniently prepared from lanosteryl acetate 11, without significant Δ^8 migration, according to the modified Brigg procedure[14b] described by Fetizon[14a] (19% overall yield, 3 steps)[14].

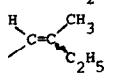
The synthesis of norlanosteryl acetates 18a and 18b was effectively performed as follows. The dienoic acetate[14] 12 is rapidly transformed into the corresponding tetrahydropyranyl derivatives 13 [i:KOH/CH_3OH 10%, +60°, 2 hrs, 98% yield - ii:dihydropyrane (7 eq), TosOH catal., dioxane; 20°, 2.5 hr; 80% yield] which are in turn reduced to a mixture of the two isomeric alcohols[15,17] 14a and 14b by borane-THF reaction[16] followed by *in situ* hydrogen peroxide oxidation of the resulting product [i:BH_3-THF, 25°, 1hr - ii:NaOH 2N, H_2O_2 30%, 20°, 0.2 hr; 64% yield; tlc SiO_2 benzene ethyl acetate : 95/5 R_f[15] 0.12 and 0.19].

The mixture of alcohols[15] 14a+14b is oxidized to the corresponding aldehydes[15] 15a+15b by the Corey Suggs reagent[18] [CrO_3, Pyr, HCl(5eq) CH_3COONa,CH_2Cl_2,+20°,2.5hr; 70% yield -tlc SiO_2; benzene/ethyl acetate : 97/3 R_f[15] 0.51 and 0.58]. Further Wittig reaction using methylenetriphenylphosphorane allows the synthesis of the complete desired carbon framework [84% yield; tlc SiO_2 benzene/ethyl acetate : 98/2 R_f[15] 0.66 and 0.75]. The THP blocking group was removed [CH_3OH/CH_2Cl_2(5/3), TosOH catal., 20°, 3hrs, 100% yield] and replaced by the desired acetyl group [Ac_2O/pyr (1/1.5), 20°, 12 hrs; 91% yield; tlc SiO_2, benzene/ethyl acetate : 92/8, R_f 0.75].



1 X : CHO

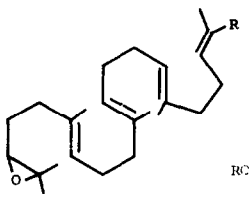
2 X : 

10 X : 

3 X:Br, Y:OH, R:CH_2OH

8 X:Y:OH, R:C_2H_5

9 X Y:O-C(=O)-O, R:C_2H_5

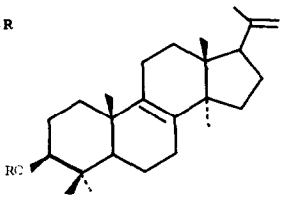


4 R: CH_2OH

5 R: CHO

6 R: $CH=\overset{*}{C}H_2$

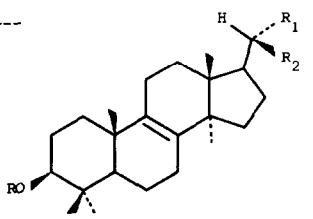
7 R: $CH_2\overset{*}{C}H_3$



12 R: $COCH_3$

13 R: THP

	R	R_1	R_2	R_1	R_2
11	Ac	CH_3	C_6H_{11}		
14	THP	a : CH_3	CH_2OH	b : CH_2OH	CH_3
15	THP	a : CH_3	CHO	b : CHO	CH_3
16	THP	a : CH_3	$CH=CH_2$	b : $CH=CH_2$	CH_3
17	Ac	a : CH_3	$CH=CH_2$	b : $CH=CH_2$	CH_3
18	Ac	a : CH_3	C_2H_5	b : C_2H_5	CH_3
19	Ac	a : CH_3	$(CH_2)_2$-CHO		



Now only two stereoisomers 17a+17b are present, which show different behaviour on |GC|^2 [on a 25m x 0.5 mm glass capillary column coated with SE.30, column temp. 260°, carrier gas :(He), flow rate: 5ml/min., Rt : 17b (*20S*) 8 min., 17a (*20R*) 8.5 min.[19]]and on silver nitrate impregnated tlc plates [SiO_2, Merck, 0.5 mm (dropped in acetonitrile/ethanol : 1/1 solution of $AgNO_3$ (10%) for 20 sec., then dried at 120° for 1 hr) using ether/pentane : 1/4 as eluant, R_f:17b (*20S*) 0.8, 17a(*20R*) 0.65].

Both stereoisomers 17a and 17b are easily and quantitatively separated by the latter technique [17a, 30% yield, mp inst 150°, 17b , 70% yield, mp inst 142°] and each stereoisomer was found tobe homogeneous by silver nitratetlc and |GC|^2 (conditions as just described). 17a and 17b have been fully caracterized by their physicochemical behaviour [IR, ^{1}H NMR, MS]. These are very similar except for the NMR spectra which are substantially different in the "methyl region".

Each stereoisomer 17a and 17b is further reduced to 18a and 18b [H_2/PtO_2/ethyl acetate, 20°, 0.5hr, 96% yield; tlc SiO_2 benzene/ethyl acetate : 97/3 R_f 18a and 18b 0.75] . These two stereoisomers are indistinguishable by tlc SiO_2 and $SiO_2/AgNO_3$ eluted with various solvent systems. Both stereoisomers are homogeneous by |GC|^2 and free from each other[on a 40mx0.25mm glass capillary column coated with SE.52, column temp. 240°, carrier gas (He), flow rate : 4.2ml/min., Rt:18b (*20S*) 27.9 min., 18a (*20R*) 28.7 min.]. Both have very similar physicochemical data : 18a (*20R*) : mp(inst) 148°C;$[\alpha]_D^{CHCl_3}$: +45° (C:0.625) - 18b (*20S*) : mp(inst) 143°C; $[\alpha]_D^{CHCl_3}$:+42° (C:1.660). Their infrared (IR) and mass spectra (MS) are quite identical [even in the fingerprint region for IR and MS (M^+) 414]. Their ^{1}H NMR spectra are very similar in $CDCl_3$ but substantially different in hexadeuterobenzene (C_6H_6, 100 MH_Z^{20a} and 270MH_Z^{20b}).

In order to unambiguously assess the absolute configuration of each isomer 18a and 18b, they have been both compared with a sample of stereochemically pure (100%)norlanosteryl acetate 18a possessing the natural *20R* configuration, unambiguously prepared from natural lanosteryl acetate

using a set of reactions which do not involve the *C20* carbon atom and do not isomerise it. This compound prepared by rhodium promoted decarbonylation[21] of 3β-acetoxy-25,26,27 trisnorlanost-8-en-24al 19a[22] [$ClRh(P\phi_3)_3$ 1eq, benzene, 80°, 7 hrs, 71% yield] is identical in all respect (tlc, IR, NMR, MS, |GC|[2]) to be stereoisomer 18a previously obtained.

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