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SYNTHESIS OF 1α-HYDROXY-PROVITAMIN D$_3$

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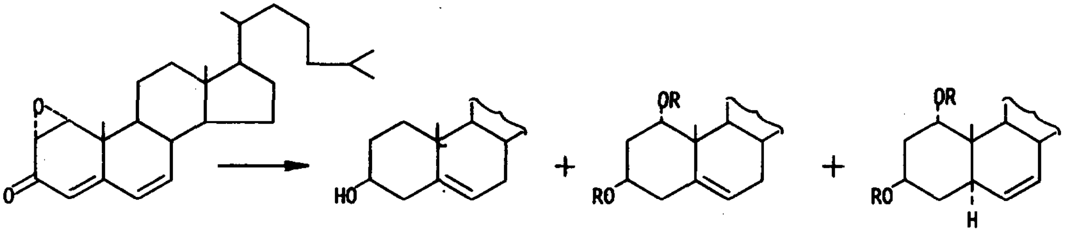
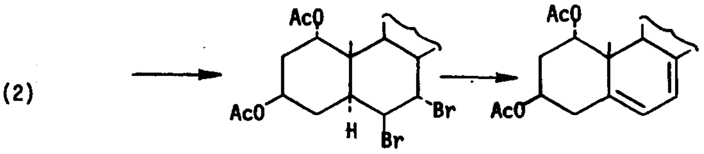
We report on the conversion of cholesterol to $\Delta^{5,7}$-cholestadien-1α,3β-diol diacetate (6) the photoprecursor of the physiologically active 1α-hydroxyvitamin D$_3$,[1] via Δ^6-cholesten-1α,3β-diol (2a). The latter compound was synthesized by modification of a recently published procedure of Li/liquid NH$_3$ reduction of the epoxydienone (1)[2] which is obtained in ca. 35% in two steps from cholesterol.

This reduction was performed as follows: a solution of (1) (4 g) in tetrahydrofuran (350 ml) and liquid ammonia (500 ml) was treated at -30° with NH$_4$Cl (4.3 g) and then with small pieces of Li metal (0.5 g). After the blue colour faded the addition was repeated six times, the quantities of Li being the same and those of NH$_4$Cl reduced to 3.5 g. After the mixture was kept blue for 2 hrs by addition of more Li, the colour was discharged with NH$_4$Cl. Isolation and separation in a dry silica column resulted in 15% cholesterol (4) (0.6 g), 45% of Δ^6-olefin (2a) m.p. 143-145° (1.8 g) and 20% of Δ^5-olefin (3a) m.p. 156-157° (0.8 g).



(1) (4) (3) (2)



(5) (6)

a, R=H
b, R=OAc

Δ^5-olefin (3a) was identified by comparison with a compound prepared from 1α,5α-oxidocholestan-3β-ol acetate.[3] The position of the double bond in (2a) was indicated by its nmr spectrum (2 vinylic protons at 5.21 and 5.33 ppm, AB quartet, J=11.4Hz, and 3 C^{19}-methyl protons at 0.74 ppm), by its comperatively high negative optical rotation value ($[\alpha]_D$-65^o), and by the dichroic ratio d_o, in stretched polyethylene film (the ratio of optical densities of light polarized parallel and perpendicular to the stretching direction)[6] of the absorption band at 180-190 nm[6]. This latter property defines the double bond position in the molecule by relating the direction of C=C bond axis to that of the molecular long axis.[7] Thus the dichroic ratio of the Δ^6-olefin (2b) d_o=1.72, at 185 nm (obtained from the linear dichroic spectrum shown in fig 1) led by calculation[7] to an angle of ca 30^o between the direction of the double bond and that of the molecular long axis which is in accord with the double bond being at Δ^6, since the calculated angle from the molecular models has the value of ca 25^o.

The dichroic ratio of the Δ^5-olefin (3b) d_o=0.87 at 185 nm (fig 2) is similar to that found previously for a Δ^5-cholestene[7] and is thus also indicative of the double bond position in this compound.

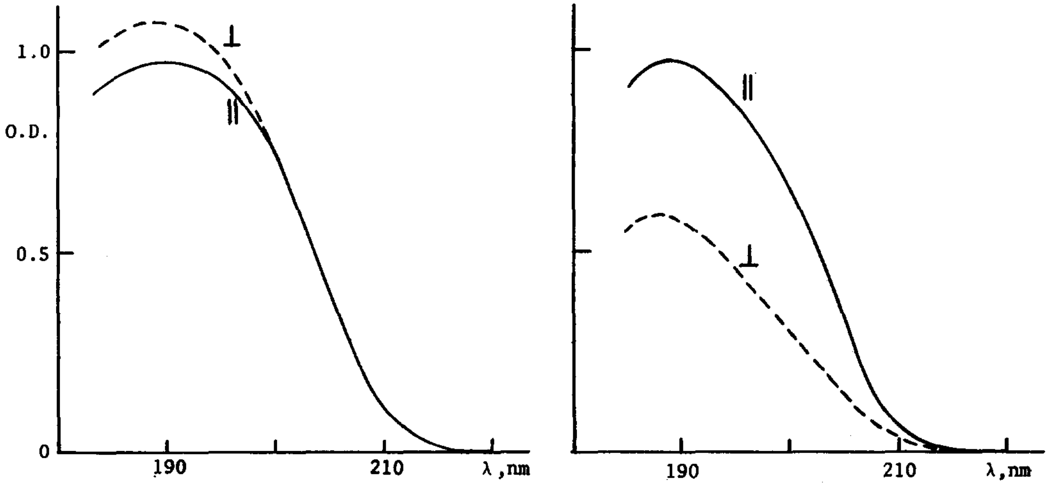


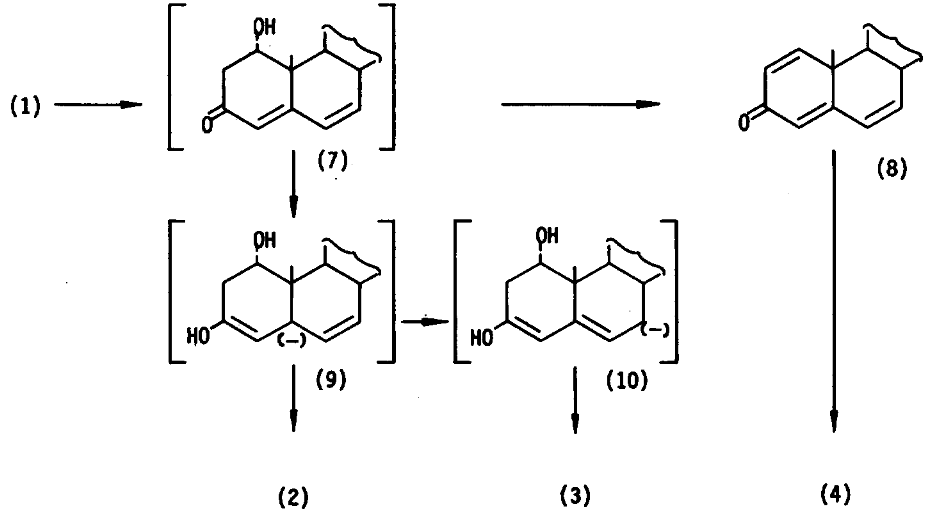
Fig 1 Fig 2

UV linear dichroic spectra (polarization spectra) of (2b), fig 1, and (3b), fig 2, incorporated in stretched polyethylene film measured with polarized light parallel (full line) and perpendicular (broken line) to the direction of stretching.[7]

The position of the two hydroxyl functions in (2a) was confirmed by hydrogenation of the Δ^6-olefin's diacetate (2b) m.p. 116-117°, $[\alpha]_D$-74°, to the 5α-cholestane-1α,3β-diol diacetate, which is identical with that prepared by hydrogenation of the Δ^5-olefin's diacetate (3b).[2]

A plausible reaction path to explain the formation of the three reduction products implies the intermediacy of the 1α-hydroxy-dienone (7).[2] This compound may first dehydrate to $\Delta^{1,4,6}$-cholestatrienone (8), which then undergoes raduction at C_1, C_7 and finally at C_3 resulting in cholesterol. To substantiate this proposal, we have treated the trienone (8) with Li/liq. NH_3 and NH_4Cl under the above mentioned conditions and isolated cholesterol in ca. 50%.

The formation of the Δ^6-olefin proceeds by electron addition to the 1α-hydroxy-dienone (7) at C_5, followed by protonation at the same C atom. Isomerization of the C_5-allylic carbanion (9) prior to the protonation will lead to the more stable C_7-allylic carbanion (10) the precurser of the Δ^5-olefin (3).[8] The presence of hydroxyl at C_1 appears to favour protonation at C_5, since the previously mentioned Li/liq. NH_3 treatment of the trienone (8) as well as of $\Delta^{4,6}$-cholestadienone led to cholesterol and not to the Δ^6-cholestenol.



Bromination of the Δ^6-olefin (2b) led to the diaxial dibromide (5) (m.p. 155-156°, $[\alpha]_D$-25°, 2 CHBr protons centered at 4.55 ppm, having a narrow multiplet of $w_{\frac{1}{2}}$ 10 Hz) which was dehydrobrominated by heating at 130° in hexamethylphosphoramid containing ca. 10% of triethyl methylammonium dimethylphosphate for 4 hrs[9] to give an almost quantitative yield of a 1.3 : 1 mixture of a $\Delta^{5,7}$-diene (λ_{max}262, 271, 282, 294 nm) and of a $\Delta^{4,6}$-diene (λ_{max}232, 240, 249 nm). This mixture was separated on a dry silica column impregnated with silver nitrate, resulting in 40% of the $\Delta^{5,7}$-diene diacetate (6) (m.p. 113-114°, $[\alpha]_D$-30°)[2,10,11], which on irradiation followed by warming was converted to 1α-hydroxy-vitamin D_3.

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