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The Stereochemical Course of the Previtamin-Vitamin Conversion with C_{19}-Substituted 7-Dehydrocholesteryl Derivatives

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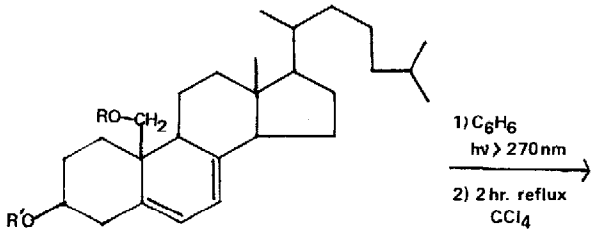
Abstract

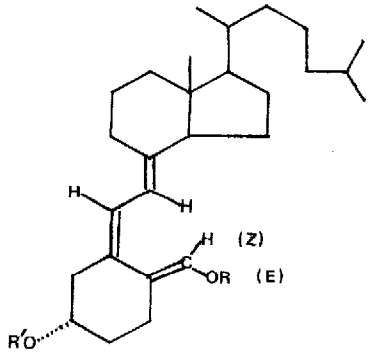
The stereochemistry of intramolecular hydrogen transfer was determined for the title process using [19-pro-S-^{2}H]-cholesta-5,7-dien-3β,19-diol diacetate.

Conversion of 7-dehydrocholesterol into vitamin D_3 involves photochemical opening of the B-ring diene to the cisoid zCz triene previtamin followed by an intramolecular[1], 1,7-antarafacial[2] hydrogen shift to yield the vitamin. The C_{19}-acetoxyl and methoxyl derivatives, cholesta-5,7-dien-3β,19-diol diacetate (1) and cholesta-5,7-dien-3β,19-diol-3-acetate-19-methyl ether (1a), analogously yield vitamin D_3 derivatives, 2 and 2a, respectively.[3] Interestingly, in each case, only one of the two possible stereoisomers of the C_{19} carbon atom is formed, namely, the C_{19}-E-isomer[4]



1, R=Ac; R'=Ac

1a, R=CH_3; R'=Ac

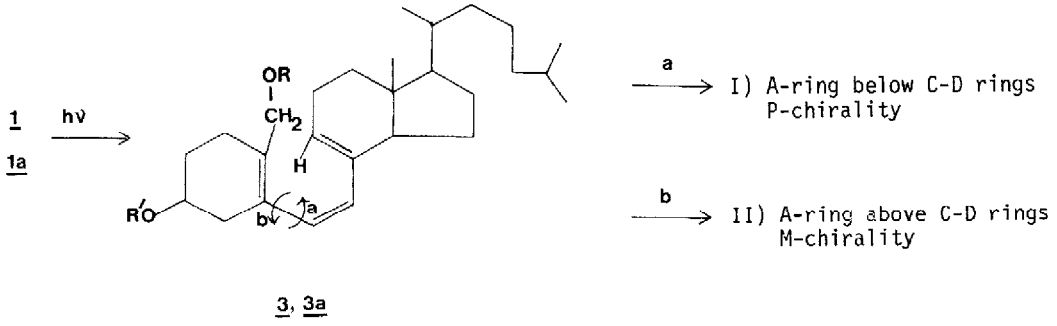


2, R=Ac; R'=Ac

2a, R=CH_3; R'=Ac

Akhtar and Gibbons have shown that the 1,7 hydrogen shift in the vitamin D_3 series is non-stereospecific.[5] Accordingly, one might expect both the C_{19} E and Z isomers to form in 1 → 2; 1a → 2a, contrary to what is actually observed.

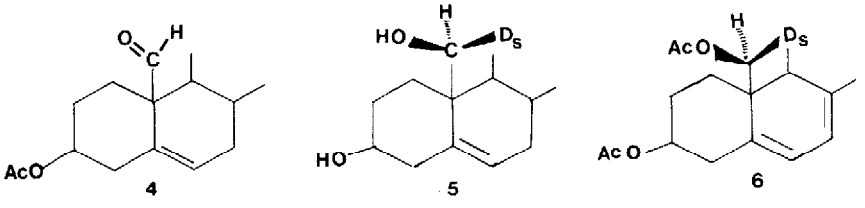
The observed stereospecific result could come about in two stereochemically distinct ways. First ring-opening could yield the previtamin (3 or 3a) and one of the diastereotopic protons at C_{19} could be preferentially transferred to the C_9 position in a transition state involving one of the two possible twist senses of the cisoid-triene, I or II,



3, 3a

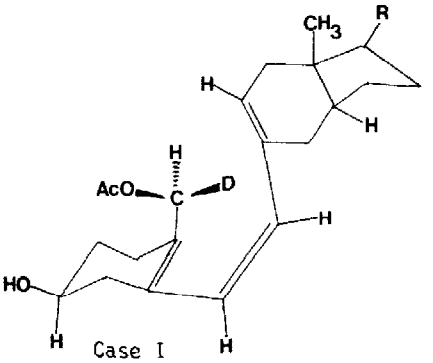
The formation of the observed E-isomer from I requires transfer of the pro-S C_{19}-hydrogen to the C_9-α position. Likewise, formation of the observed E-isomer from II requires transfer of the pro-R C_{19}-hydrogen to the C_9-β position.

In order to probe this point the stereospecifically labeled C_{19}-pro S-^2H compound 5 was synthesized by Li Al $^2H_4$ reduction of 4:[6]

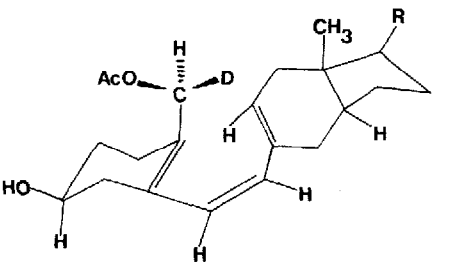


The incorporation of deuterium was 78% and the pro-S stereochemistry has been established by work of Arigoni et al.[7] Subsequent conversion of 5 to 6 did not alter the stereochemical homogeneity of the compound.

If 1,7 hydrogen transfer involved the right-handed twist sense of the cisoid-triene (Case I) then selective transfer of a deuterium atom should occur and this would be detected by formation of C_{19}-vinylic group with ∿78%H. If a left-handed cisoid-triene (Case II) intervened then a protium atom would be transferred and the C_{19}-vinylic group should contain ∿22%H.



Case I



Case II

Irradiation of 6 (C_6H_6, ca. 280 nm) followed by heating at 80° for 18 hr. led to the vitamin analog 9,19-^{2}H-2 with 26.4% hydrogen in the C_{19}-Z position.[8] This result is close to the predicted 22% value for the left-handed A-ring above the C-D rings, 9β-transfer of the pro R hydrogen.

This stereochemistry is opposite to the conclusion of Mazur et al.[9] for the present system; i.e., the vitamin D_3-previtamin D_3 isomerization was proposed to prefer the right-handed conformation of the cZc triene system. Results in the two systems may not be strictly comparable since in the present case two opposing factors are present. In the left-handed conformation a destabilizing steric interaction exists between C_{18}-C_{19}. In the right-handed conformation, formation of [^{2}H]-2 requires transfer of a deuterium atom and a large deuterium isotope effect may operate in this process kH/kD ∿45.[9]

The remarkable stereospecific formation 2 is apparently due to stereospecificity in the conformation of triene 3 for intramolecular hydrogen transfer.

References

1. J. L. M. A. Schlatmann, J. Pot and E. Havinga, Rec. Trav. Chim., 83, 1173 (1964).
2. R. B. Woodward and R. Hoffman, J. Am. Chem. Soc., 87, 2511 (1965).
3. R. M. Moriarty and H. E. Paaren, J. Chem. Soc. Chem. Comm., 927 (1974).
4. Product analysis was by HPLC using a Dupont Zorbax-Sil, 6.2 mm X 25 cm column with 0.25% isopropyl alcohol-hexane as a solvent. NMR spectra were determined using a Bruker WR-270 instrument operating in the Fourier transform mode. Chemical shifts were measured using $CHCl_3$ as internal standard and are in ppm from TMS.

   The E configuration of 2a is based upon the fact that both the E and Z isomers are known in the related 3β alcohol series (J. Bland and B. Craney, Tetrahedron Letters, 4041 (1974)). The Z-C_{19}-OCH_3 in this compound was assigned in the nmr spectrum ($CDCl_3$) δ=3.43 ppm and the E-C_{19}-OCH_3 appeared at δ=3.51 ppm. In the present case the C_{19}-OCH_3 resonance in 2a appears at δ=3.63 ppm which accords with the expected relatively deshielded E position. In the case of 2 only one isomer is known. We base the E-C_{19}-OAc configuration on the chemical shift of the Z-C_{19}-proton at 6.89 ppm (C_6D_6) and 6.96 ppm (CD_2Cl_2). The analogous proton in vinyl acetate occurs at δ∿7.25 ppm. The Z-C_{19}-proton of 2 should experience relative shielding due to its position with respect to the adjacent diene system.
5. M. Akhtar and G. J. Gibbons, J. Chem. Soc., 5964 (1963).
6. The nmr spectrum of 5 showed the pro-R-H at 4.59 ppm and the pro-S-H at 3.89 ppm. The integrated relative intensities indicated 78% incorporation.
7. D. Arigoni, R. Battaglia, M. Akhtar and T. Smith, J. Chem. Soc. Chem. Comm., 185 (1975).
8. These rather strenuous conditions, 80°, 18 hrs, were necessary for complete equilibration. The chemical shift of the C_{19}-Z proton in 9, 19-^{2}H-2 occurred at 6.89 ppm in C_6D_6. Its intensity was compared with that of the 3α-proton at 4.74 ppm.
9. M. Sheves, E. Berman, Y. Mazur and Z. V. I. Zaritskii, J. Am. Chem. Soc., 101, 1882 (1979)

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