Tetrahedron Letters No. 34, pp 2987 - 2990, 1976. Pergamon Press. Printed in Great Britain.

CYCLOVITAMINS D_3: THE PREPARATION OF C_6-KETOCYCLOVITAMIN AND ITS CONVERSION TO A RING B/C SPIROSTEROID

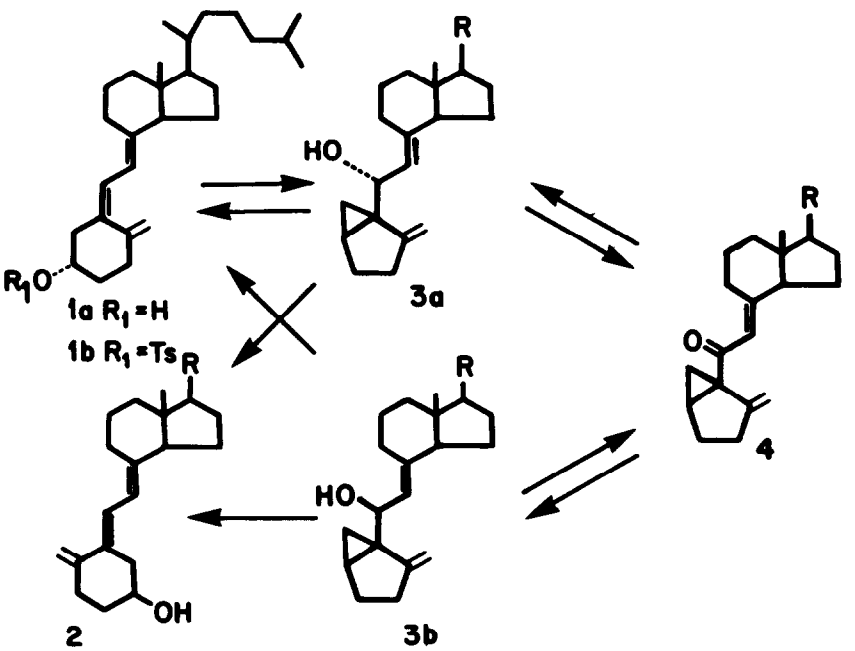
Mordechai Sheves and Yehuda Mazur
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

(Received in UK 9 June 1976; accepted for publication 5 July 1976)

We have recently described[1] the conversion of vitamin D_3 (1a) into the 6R-methylether of 3,5-cyclovitamin D_3 and its reconversion to the starting vitamin. Although the labile conjugated triene system of vitamin D_3 is protected in this methylether its use as an intermediate for vitamin functionalizations proved limited due to its instability. Looking for a compound better suited for this purpose we have found the C_6-keto-derivative (4) which is both comparatively stable and easily reconvertible to the vitamin.

We report here on the preparation of this ketone and its reactions leading to the formation of ring B/C spirosteroids.

Vitamin D_3 tosylate (1b) was solvolysed in aqueous acetone buffered with $KHCO_3$ to give the 6R-alcohol (6α in the s-trans conformation) (3a)[2] as the major product (60% yield). The structure of (3a) was inferred from its solvolysis with p.-toluenesulfonic acid in aqueous dioxane which restored the conjugated triene system, yielding a 2.5:1 ratio of vitamin and trans-vitamin D_3 (2).



The comparatively high ratio of the vitamin in this mixture pointed to the 6R-configuration of the hydroxy group in (3a) which has a geometry favourable for stereoselective formation of the vitamin's triene system. In the ^{1}H-NMR spectrum of (3a) the signals of the three vinylic protons and of the proton α to OH appeared at the same chemical shift. These signals separated on addition of Eu(Fod)$_3$ to give an AB quartet (vicinal protons at C_6 and C_7) and two broad singlets (geminal protons at C_{19} (Table)

Table: ^{1}H-NMR chemical shifts in 3,5-cyclovitamin D$_3$ derivatives[a]

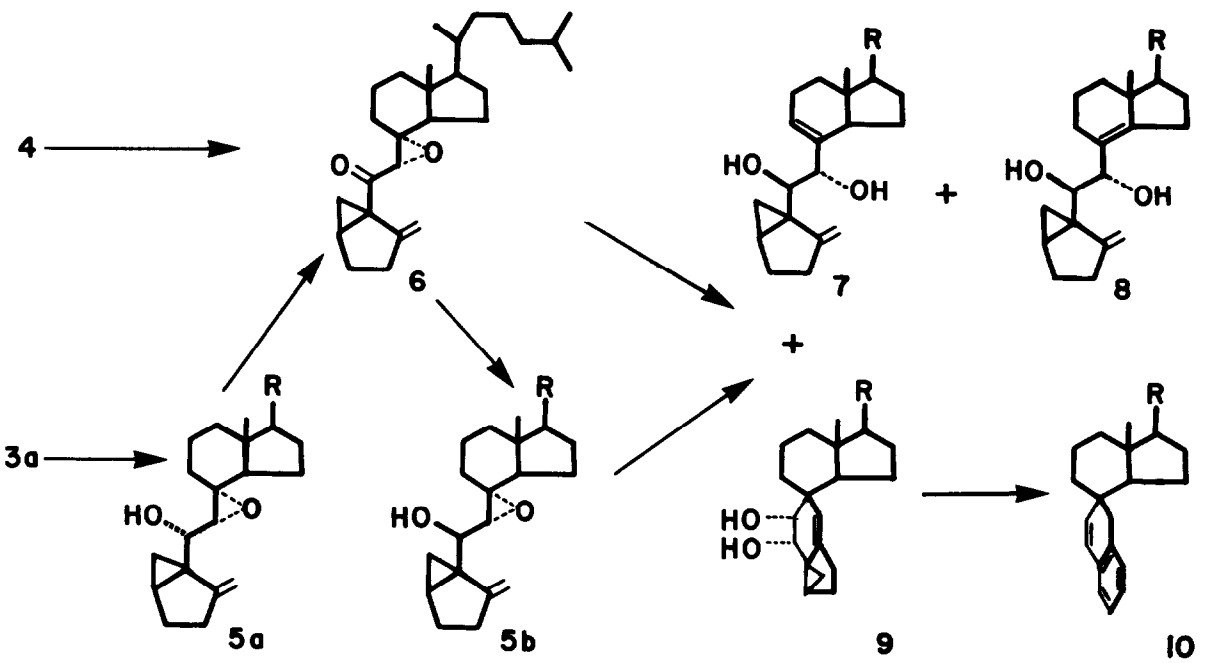
Substance	H at: C_{18}	C_6	C_7	$^3J_{H(6)H(7)}$ Hz	C_{19}-Z	C_{19}-E
3a	0.56	4.98	4.98	9[b]	4.98	4.98
3b	0.57	4.93	4.93	8[b]	5.10	4.93
4	0.58		6.10	-	5.24	5.05
5a	0.71	3.68	3.33	7	5.30	4.97
5b	0.80	3.75	2.93	8	5.01	4.84
6	0.77	-	4.36	-	5.33	5.09
7	0.71	4.05	4.05		4.99	4.92
8	0.90	4.44	3.92	7	5.03	4.92
9	0.75	4.05	3.49	3.5	-	5.37

[a]Taken in $CDCl_3$ solution on a Bruker HFX-90 spectrometer, the values in ppm, the estimated error being ±0.03 ppm. [b]Observed on addition of Eu(Fod)$_3$.

Oxidation of the 6R-alcohol (3a) with freshly prepared MnO_2 gave the C_6-ketone (4)[2], whose structure was assigned from its spectral properties ($\lambda_{max}^{C_6H_{12}}$ 248 nm, ε 14,000) and from the fact that its reduction with diisobutylaluminium hydride led to the C_6-alcohols (3a) and (3b)[2] (formed in a 1:3 ratio). The 6S-alcohol (6β in the s-trans conformation)(3b) had a similar ^{1}H-NMR spectrum as its 6R-epimer (3a), but the four low field protons (at C_6,C_7 and C_{19}) showed two instead of one signal. On addition of Eu(Fod)$_3$ these separated, to give an AB quartet and two broad singlets (Table).

The 6R-alcohol (3b) was converted in the same way as its epimer (3a) to a 1:1 mixture of vitamin D$_3$ (1a) and its trans isomer (2). This non-stereoselective solvolysis of (3b) is analogous to that of its methyl ether[1] and confirms the assignment of the hydroxyl configuration at C_6. The high ratio of the 6R-alcohol (3b) formed on reduction of the ketone (4) assuming hydride attack from the less hindered α-side, suggests this ketone to be in an extended conformation, the carbonyl and the double bond having syn relationship.

Epoxidation of the ketone (4) with NaOH and H_2O_2 gave a single crystalline product, the α-epoxy-ketone (6)(mp 72-73°)[2]. The same ketone was also formed when the 6R-epoxy-alcohol (5a)[2] obtained from the allylic alcohol (3a) and metachloroperbenzoic acid was oxidized with pyridinium chlorochromate. The α-configuration of the epoxy group in both (5a) and (3a) was deduced from the direction of attack, occuring from the sterically more accessible α-side, and which in (3a) might also have been influenced by the directive effect of its OH group. Lithium aluminium hydride reduced stereoselectively the carbonyl group in the epoxy-ketone (6) resulting in the C_6-epimer of (5a), the 6S-epoxy-alcohol (5b)[2].



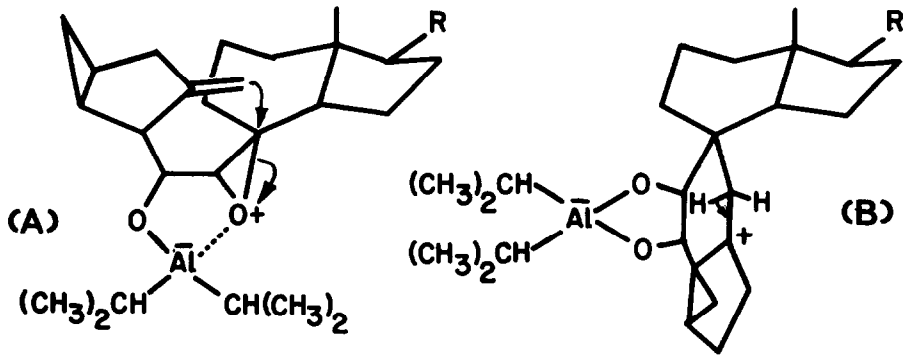
The reaction of diisobutylaluminium hydride with the epoxy-ketone (6) differed from that of lithium aluminium hydride, since it led both to reduction of the carbonyl group and rearrangement of the epoxide linkage, forming three vicinal diols (7), (8) and (9) in 4, 12 and 68% yield respectively. An identical mixture of these diols was also obtained by treating the 6S-epoxy-alcohol (5b) with diisobutylaluminium hydride, suggesting its intermediacy (in the form of aluminate) in the reaction of the epoxy-ketone (6) with the same reagent.

Two of the diols (7)[2] and (8)[2] possessed the same carbon skeleton as the starting material as evidenced by the presence of signals due to the $C{=}CH_2$ group in their ^{13}C and ^{1}H-NMR spectrum (Table). The position of the double bond in (8) was indicated by the relative downfield shift of its C_{18} protons resonance (Table) and that in (7) by the presence of additional vinylic proton (δ 5.62 ppm, H at C_9). The configuration of C_6 and C_7 in (7) and (8) is assumed to be the same as in (5b).

The major reaction product of diisobutylaluminium hydride with (6), the diol (9)(mp 118-119°)[2], had a rearranged carbon skeleton as evidenced by the presence of signals in its ^{13}C spectrum due to one quarternary, one tertiary vinylic carbon and four saturated quaternary carbons and the absence of a signal due to the $=CH_2$ function. In the ^{1}H-spectrum only one vinylic proton was observed appearing as a sharp singlet (Table). These data suggests (9) being a ring B/C-spiro-diol.

We assume that the configuration of the two OH groups in (9) is the same as in the other two diols (7) and (8) while the configuration at the C_8-spiro junction is determined by the mechanism of its formation (see below).

The formation of the spiro-diol (9) may be explained by the primary reduction of the carbonyl group to give the C_6-aluminate which in turn complexes with the epoxy oxygen atom - upon which molecule changes its extended conformation to a folded one (fig. A). The epoxy group is then opened with a concomitant ring cyclization leading to a spiro structure with a positive charge on C_{19} (fig. B). After an assumed intramolecular H^+ abstraction at C_{19}, the spiro-olefin (9) is formed[3].



The formation of the diol (7) may also involve intermediate (fig. A) having a positive charge on C_8, which however instead of cyclizing, loses its C_9 proton to give a C_8-C_9 double bond. The third diol (8) has the double bond in a more stable position, and thus may be the thermodynamically controlled product.

Treatment of the spiro-diol (9) with p- toluenesulfonic acid in aqueous dioxane results in a 1,2-dihydronaphtalene derivative (10)[2] [λ_{max}261, 268, 297 nm, ε 6200, 5900, 820; ^{1}H-NMR (ppm) 4 aromatic (δ 7.06 m) 2 vinylic (δ 5.46, 6.27, AB q J=9.5 Hz) and 2 benzylic (δ 2.84, 2.96 AB q J=16 Hz) protons]. The formation of this compound may be explained by the cyclopropane ring opening to the $\Delta^{5(6)9(10)}$-dien-3,7-diol followed by dehydration and double bond isomerization to give the thermodynamically more stable ring A aromatic derivative.

Acknowledgement.- We are indebted to Dr. Z.V.I. Zaretskii for the mass spectra and to Mr. Elisha Berman for the ^{13}C-NMR spectra[2]. We thank Dr. M.P. Rappoldt from Philips Duphar, Weesp, Netherland and Dr. A. Furst from Hoffman-La Roche, Basel, Switzerland for the gift of vitamin D_3. This research was supported by a grant from United States - Israel Binational Science Foundation (BSF) Jerusalem, Israel.

References

1. M. Sheves and Y. Mazur, J. Amer. Chem. Soc., 97, 6249 (1975); Tetrahedron Letters, in press.
2. The analytical data, the full analysis of the ^{1}H and ^{13}C-NMR spectra as well as the mass spectral data of all the new compounds will be published separately.
3. For analogous mechanism see: W. Kirchhof, Chem. Ber., 93, 2712 (1960).