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AN ALLYLIC NUCLEOPHILIC SUBSTITUTION REACTION OF 1α-HYDROXYVITAMIN D DERIVATIVES

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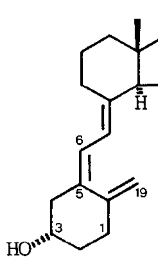
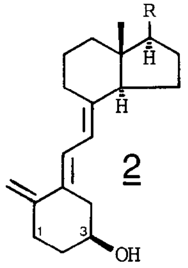
Abstract: The first transformation of the 5,6-trans-vitamin D conjugated triene system into that of isovitamin D occurring under nucleophilic conditions is observed in the reaction of 5 with n-butyl-lithium to give 6.

There is considerable chemical and biological interest[1] in the transformations of (i) vitamin D (1) (5Z) into 5,6-trans-vitamin D (2) (5E) and (ii) 1 and 2 into isovitamin D (3) (5E). These reactions all involve either carbocations[2] or radicals[3] as intermediates, and the reactions of 1 are associated with stereomutation of the 5,6-double bond. I now report on a related transformation (5 → 6) which involves a carbanionic intermediate produced by n-butyl-lithium. The process may be considered as a novel S_N2' reaction in which a trialkylsilyloxide anion is substituted by 1-butyl anion.



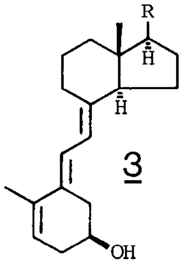
1

VITAMIN D



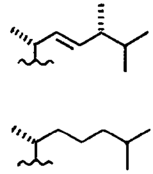
2

5,6-trans-VITAMIN D



3

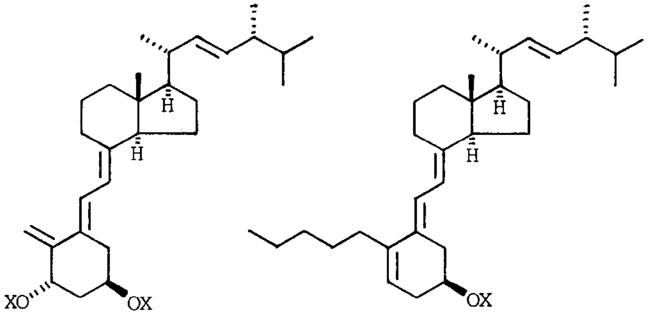
ISOVITAMIN D



D_2 series, R=

D_3 series, R=

Although the synthesis of the important 1α-hydroxylated metabolites of vitamin D has received much attention,[1] very little chemistry relating to further manipulation of the 1α-hydroxy group in this type of compound has been described. Reaction under nitrogen of the bis-tert-butyldimethylsilyl (TBDMS) ether (5)[4] (m.p. 112-113 °C)[5] of 1α-hydroxy-5,6-trans-vitamin D_2 (4)[6] with 1.2 molar equiv. n-butyl-lithium in tetrahydrofuran (THF) (-60° → 20°C during 30 min) gave the oily product (6) (yield 75%),[7] which was converted to the alcohol (7) (m.p. 107-109 °C) by desilylation (Bu_4NF/THF). The molecular formulae of 6 ($C_{38}H_{66}OSi$) and 7 ($C_{32}H_{52}O$) demonstrated the substitution of one tert-butyldimethylsilyloxy group by a butyl group in the transformation 5 → 6, and the regiochemistry clearly followed from mechanistic considerations and the changes which are observed in the UV- and NMR-spectra.[8] This reaction thus constitutes the first example of the conversion of the 5,6-trans-vitamin D triene system into that of the isovitamin under nucleophilic conditions and probably involves addition of butyl anion at C-19 to give a pentadienyl carbanion, followed by expulsion of the silyloxide.[9] Methyl-lithium reacts similarly, and an exploration of the scope of the reaction as regards other types of nucleophiles (including "hydride") is underway.[10]

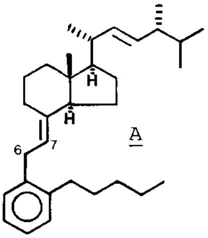


4 X = H
5 X = SiMe$_2$Bu^t

6 X = SiMe$_2$Bu^t
7 X = H

REFERENCES AND NOTES

1. For a review, see P.A. Bell, in "Vitamin D", ed. D.E.M. Lawson, Academic Press, London, 1978, ch. 1.
2. For example, T. Kobayashi and A. Adachi, J. Nutr. Sci. Vitaminol., 1973, 19, 311.
3. For example, A.G.M. Barrett, D.H.R. Barton, G. Johnson and S. Nagubandi, Synthesis, 1978, 741.
4. All new compounds gave satisfactory microanalytical and UV-, IR-, NMR- and mass spectroscopic data.
5. The corresponding derivative in the D$_3$ series has m.p. 96-97.5 °C and reacts analogously in the transformations described here.
6. (a) H.E. Paaren, H.F. DeLuca and H.K. Schnoes, J. Org. Chem., 1980, 45, 3253.
   (b) R.H. Hesse, U.K. P. Appl. 2 108 506A / 1982.
7. In addition, a 10% yield of an oily hydrocarbon was isolated. The NMR-spectrum shows a phenylene group, a new non-conjugated olefinic proton, and other features entirely consistent with the assignment of structure A. [δ *inter alia* 3.43 (2H,d,J 7 Hz,6-H$_2$), 5.04 (1H,t,J 7 Hz,7-H) and 7.14 (4H,s,ArH).] The intermediacy of 6 in the formation of A was demonstrated in a separate experiment in which isolated 6 was treated with n-butyl-lithium.



A

8. Cf. spectra of e.g. 7 with those recorded for 4 (Ref. 6(a)) and isovitamin D$_3$ itself (W. Reischl and E. Zbiral, Helv. Chim. Acta, 1979, 62, 1763): 7; λ_{max} (EtOH) 301, 288 and 278 nm (ϵ 32200, 44100 and 35200); δ (100 MHz, CDCl$_3$) 0.57 (3H,s,18-H$_3$), 0.75-1.05, [15H,m, including 1.02 (d,J 6.6 Hz,21-H$_3$), remaining Me-groups], 3.97 (1H, br m,3-H), 5.2 (2H,m,22-H,23-H), 5.49 (1H,m,1-H), 5.94 and 6.50 (each 1H,d,J 11 Hz,ABq,7-H and 6-H).
9. In principle, the reaction of the 5Z isomer of 5 with n-butyl-lithium should give rise to the 5,6-cis-isovitamin D$_2$ (5Z) derivative corresponding to 6. However, a preliminary experiment with 1α-hydroxyvitamin D$_2$ bis-TBDMS ether (8) failed to give a clean reaction, and indeed when a 1:1 mixture of 8 and 5 (as an internal control) was treated with butyl-lithium, most of the cis-vitamin derivative (8) was recovered scavenged of 5, and the product was 6 contaminated with only a minor amount of its 5Z isomer.
10. I am grateful to Prof. W.D. Ollis for his assistance during the preparation of this manuscript.

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