Tetrahedron Letters, Vol.30, No.6, pp 677-680, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE SYNTHESIS OF 25-OXO-25-PHOSPHAVITAMIN D_3

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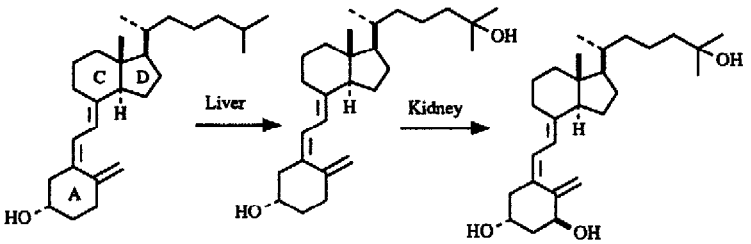
Summary: The synthesis of 25-oxo-25-phosphavitamin D_3, the first phosphorus analog of vitamin D_3 is reported.

The metabolism of vitamin D_3 (1) involves sidechain hydroxylation to 25-hydroxyvitamin D_3 (2) with subsequent A-ring hydroxylation to 1α,25-dihydroxyvitamin D_3 (3).[1,2] Compound 3,

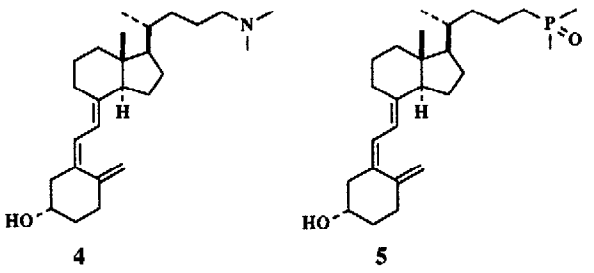


1 2 3

acting as a steroidal hormone, controls calcium and phosphorus homeostasis in higher organisms through intestinal calcium absorption (ICA) and bone calcium mobilization (BCM),[2] induces differentiation of mouse myeloid leukemia cells to microphages,[3] and appears to be effective in the treatment of psoriasis.[4]

In order to test the structural parameters necessary for 25-hydroxylation, many analogs of vitamin D_3 have been prepared and tested for biological activity.[2] DeLuca and coworkers synthesized 25-azavitamin D_3 (4),[5] which was found to inhibit both ICA and BCM of rats by acting as a vitamin D antagonist via inhibition of 25-hydroxylation in the liver.[6] Along these lines, the first phosphorus analog of vitamin D_3, 25-oxo-25-phosphavitamin D_3 (5) has been prepared and the synthesis is reported in this communication. The compound is of interest because it contains a hetero atom in the 25-position as in

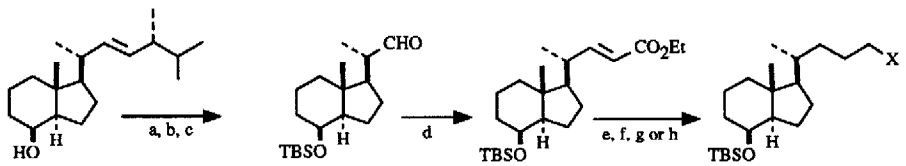
compound 4 and it has an oxygen atom attached to the 25-position as in metabolite 2. The synthesis of this compound involves building a sidechain on a



4 5

suitable protected CD-ring vitamin D fragment, followed by Lythgoe coupling with a suitably functionalized A-ring piece.

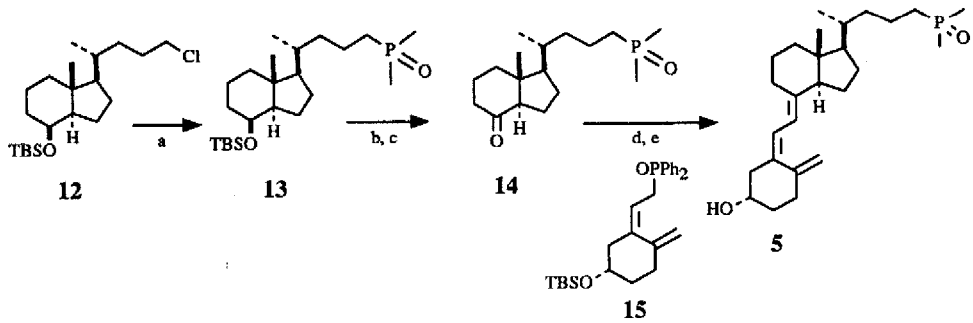
Alcohol 6, prepared using the procedure of Okamura,[7] was protected as the silyl ether and the sidechain was cleaved by ozone in methanol to give a mixture of aldehyde 7 and the corresponding dimethyl acetal. The mixture was hydrolyzed with acid under mild conditions, to yield pure 7.



6 7 8 9 X = OH 10 X = OMs 11 X = I 12 X = Cl

(a) TBDMSCl, imidazole, DMF, 93%; (b) 1) O_3, methanol, methylene chloride, -78° C, 2) dimethylsulfide, -78° C to RT, 82%; (c) oxalic acid, SiO_2, methylene chloride, 95%; (d) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 72%; (e) Li, ammonia, ethanol, 85%; (f) mesyl chloride, TEA, methylene chloride, 99%; (g) NaI, acetone; (h) NaCl, acetone.

A two carbon homologation of 7, using Wadsworth-Emmons conditions,[8] yielded α,ß-unsaturated ester 8 which was reduced by lithium-ammonia in the presence of ethanol to alcohol 9. The alcohol was transformed to mesylate 10, and on to iodide 11 and to chloride 12. A solution of sodium dimethyl phosphide was prepared from the reductive desulfurization of tetramethylbiphosphine disulfide with iron, followed by the reductive cleavage of the resulting biphosphine with sodium metal in ammonia.[9] The ammonia solution was used directly, and attempts to displace the iodide of compound 11 were unsuccessful, giving products resulting from reduction of the halogen. Displacement occurred smoothly with chloride 12 to give, after oxidation with hydrogen peroxide, phosphine oxide 13.[10] The silyl group was removed and the resulting



(a) $(Me)_2P$-Na, THF, -78° C, 92%; (b) tetra-n-butylammonium fluoride, THF, Δ, 99%; (c) oxalyl chloride, DMSO,TEA, methylene chloride, 90%; (d) **15**, butyl lithium, THF, -78° C, 56%; (e) Tetrabutylammonium fluoride, THF, 76%.

alcohol oxidized under Swern conditions to give ketone 14 which was immediately coupled to A-ring moiety[7] 15 yielding the phosphorus vitamin 5, after deprotection.[11]

The biological activity of 5 has been investigated and initial results provide evidence of significant ICA at administered doses of 4000 and 16000 units (1 unit = 65 pmol) and a somewhat weaker response for BCM. These results are reflective of the fact that 5, when administered in vivo to rachitic chicks, is capable of being metabolized to the 1α-hydroxylated form which elicits the biological responses. The ability of 5 to compete for an active site of 2 and their ability to differentiate HL-60 cells is being investigated.

Acknowledgement: This research was supported by PHS Grant DK 00709, National Institute of Diabetes and Digestive and Kidney Diseases. We express our appreciation to Professor Anthony Norman and his research group of the Department of Biochemistry, University of California, Riverside for performing the bioassays. Generous support of this work by BASF AG., Ludwigshafen/Rh, Verband der Chemischen Industrie - Fonds der Chemie -, Frankfurt/M and Deutsche Forschungsgemeinschaft is grateful acknowledged. We also thank BAYER AG, Leverkusen and HOECHST AG, Frankfurt/M-Hoechst for generous gifts of chemicals, as well as ICN BIOMEDICALS GmbH, Eschwege for providing us with generous supplies of silica gel.

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10. The initially formed phosphine was not air stable and was, therefore, converted directly to the phosphine oxide.
11. 25-Oxo-phosphavitamin D_3: mp 97-98° C; $[\alpha]_D$ = +100° (EtOH, c 1.00); ^{1}H NMR (500.135 MHz, CD_2Cl_2) δ 6.20 (1 H, d, J = 11.2 Hz), 6.02 (1 H, d, J = 11.1 Hz), 5.02 (1 H, s), 4.76 (1 H, d, J = 2.2 Hz), 3.80 (1 H, m), 2.82 (1 H, m), 2.82 (1 H, m), 2.52 (1 H, dd), 2.36 (1 H, m), 2.21 (1 H, m), 2.11 (1 H, m), 1.96 - 2.00 (2 H, m), 1.40 (6 H, d, J = 12.5 Hz), 1.14 - 1.39 (10 H, m), 0.94 (3 H, d, J = 6.2 Hz), 0.94 (3 H, s), 0.53 (3 H, s); ^{13}C NMR (125.47 MHz, CD_2Cl_2) δ 145.97, 141.97, 136.38, 122.05, 118.01, 112.21, 69.32, 56.62, 56.57, 46.50, 46.08, 40.83, 37.70 (d, J = 14.3 Hz), 36.23, 35.88, 32.47 (d, J = 69.2 Hz), 32.64, 29.24, 27.97, 23.85, 22.52, 20.67, 18.82, 16.32 (d, J = 67.9 Hz), 16.25 (d, J = 67.9 Hz), 12.03; ^{31}P NMR (201 MHz, 1 % TMP in CD_2Cl_2) δ 42.21; Mass spectrum (high resolution m/e 419.3096, 419.3079 calcd for $C_{20}H_{44}O_2P$).

(Received in Germany 13 October 1988)