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VITAMIN D C-22 ALDEHYDES. NEW KEY INTERMEDIATES FOR THE SYNTHESIS OF SIDE CHAIN MODIFIED VITAMIN D ANALOGUES

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Summary: Vitamin D C-22 aldehyde and 1α-hydroxyvitamin D C-22 aldehyde were efficiently synthesized starting from the readily available 22,23-bisnorcholenic acid. The usefulness of the compounds as common intermediates for the synthesis of side chain modified analogues of vitamins D_2 and D_3 has been demonstrated.

Steroid-type aldehydes have long been used in this[2] and other laboratories[3] as intermediates for the synthesis of side chain modified analogues of vitamins D_2 and D_3. In the commonly used methodology the coupling of the steroid aldehyde with the respective side chain fragment was followed by the elaboration of the vitamin D triene system and regio- and stereoselective 1α-hydroxylation[4] of the resulting vitamin. The main disadvantage of this approach is that the multi-step procedure of the generation of the vitamin D triene system and the 1α-hydroxylation process is to be repeated every time when synthesizing any single analogue. Recently, a 1α-hydroxyvitamin D C-22 alcohol[5] was prepared via the SO_2 adduct of the C-22 aldehyde. However, in this method[5], regeneration of the vitamin D (5Z,7E)-triene system required additional photoisomerization.

As a part of our systematic studies on the biological action of side chain modified analogues of vitamin D_2 and D_3, we developed a new synthetic strategy based on the use of the new vitamin D C-22 aldehydes 1 and 2.

In this paper we describe an efficient synthesis of aldehydes 1 and 2 as well as some representative examples demonstrating the usefulness of these compounds as new key intermediates for the synthesis of vitamin D_2 and D_3 analogues of our current interest.

The synthesis of aldehydes 1 and 2 started from the commercially available 3β-acetoxy-22,23-bisnor-5-cholenic acid 3 (Steraloids, Inc., Wilton, NH). Hydrolysis of the acetate group of 3 followed by the protection of both functional groups afforded silyl ester 4. Allylic bromination (dibromantin anh. $NaHCO_3$ in hexane, reflux, 30 min) and dehydrobromination[6] (Bu_4NBr, Bu_4NF, s-collidine, THF, 4 hrs) with simultaneous desilylation gave the 5,7-diene 5 in 48% overall yield. Diene 5 gave after UV irradiation (Hanovia 608A36 lamp, Vycor filter, benzene-ethyl ether 1:4 v/v) the respective previtamin[7]. The previtamin (not shown) and the starting diene 5 were separated by silica gel flash chromatography. The

vitamin D-type ester 6 was obtained by the usual isomerization of the previtamin (36% yield from 5). Ester 6 was then stereoselectively hydroxylated at C-1 by SeO_2 catalyzed t-BuOOH oxidation[4] of the 3,5-cyclovitamin intermediate (not shown) to give 1α-hydroxy ester 7 (19% overall yield). The ester was partially hydrolyzed at C-3 position (0.1N KOH in MeOH, ether) and then both hydroxyls were silylated (TBDMSCl, imidazole, DMF, 55°C, 15 min) to form silyl ester 10 in nearly quantitative yield. Title aldehyde 1 was obtained by $LiAlH_4$ reduction of ester 10 (92%) followed by Swern oxidation (DMSO, oxalyl chloride, CH_2Cl_2, TEA, -61°C, 62%) of alcohol 11. Alternatively, aldehydes 1 and 2[8] were also obtained by DIBAL reduction[9] of the respective esters 6 and 7 (54 and 57%). Alcohols 8 and 9, respectively, were formed as by-products of the reduction (29 and 32%). Alcohol 11 can also serve as intermediate in the synthesis of vitamin D_3 analogues (with a single 22-23 bond).

Our approach to the chiral synthon 14 utilizes the now available methyl R-(-)-3-hydroxy-2-methylpropionate (Aldrich, Milwaukee, WI). The ester was converted to the sulfone 13 ($[\alpha]_D^{22}$ =+27.9° c 1.3 $CHCl_3$) using standard procedure (MeMgBr, Et_2O-THF, 57%; TsCl, Py, 90%; PhSH, t-BuOK, DMF, 95%; m-CPBA, CH_2Cl_2, 74%). The tertiary hydroxyl in 13 was protected with 2,3-dihydrofuran to form 14 (76%). For the synthesis of vitamin D_2 analogue 16 aldehyde 12 was condensed with sulfone 14 (LDA, THF, -75°C, 65%). Dehydroxy-desulfonylation of the condensation product (not shown) with sodium amalgam in buffered methanol provided the vitamin D_2 analogue 15 (55%) with the desired E stereochemistry[10] of the side chain olefin and the retained natural configuration at C-20[11]. Deprotection of the 25-hydroxyl in 15 (PPTS, MeOH, r.t., 20 min, 95%) followed by the cleavage of the silyl ethers ($[Bu_4N]F$, THF, 55°C, 15 min, 80%) afforded (24R)-1,25-dihydroxyvitamin D_2 (16). The vitamin D_2 analogue 16 obtained by the new procedure described here was identical in all respects[12] (HPLC, UV, NMR and MS spectra) with an authentic sample obtained previously in this laboratory[2b]. It was found that the vitamin D triene system of both aldehydes 1 and 2 was not affected under the above conditions of Swern oxidation and the condensation reaction. Thus, the methodology we developed clearly demonstrates that the protection of the vitamin D triene system, commonly used by other authors, is not necessary for the side chain constructions exemplified in this paper.

For the preparation of vitamin D_3 analogues, a series of intermediates described in this paper may be employed, including aldehydes 1, 2, and 12, esters 6 and 7 and alcohols 8 and 9. As a representative example from the D_3 series, the new analog 17 was easily prepared (91% yield) by treating ester 7 with the respective Grignard reagent.

Analogue 17 with the tertiary hydroxyl in the side chain (as in the natural hormone) is being evaluated in this laboratory for its biological activity.

The synthetic scheme outlined in this letter represents, to the best of our knowledge, the most versatile and straightforward synthetic strategy for the preparation of side chain modified analogues of 1α-hydroxyvitamin D_2 and 1α-hydroxyvitamin D_3.

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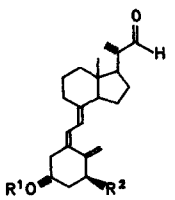
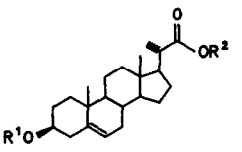


1, R^1, R^2= H

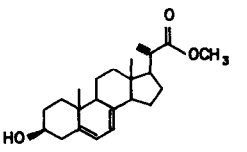
2, R^1= H; R^2= OH

12, R^1 = TBDMS; R^2= OTBDMS



3, R^1= Ac; R^2= H

4, R^1= TBDMS; R^2= CH_3



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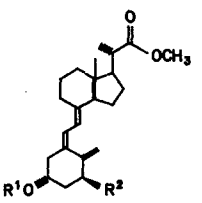
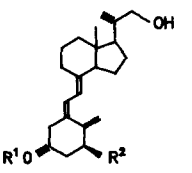


6, R^1, R^2= H

7, R^1= Ac; R^2= OH

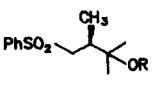
10, TBDMS; R^2= OTBDMS



8, R^1= R^2= H

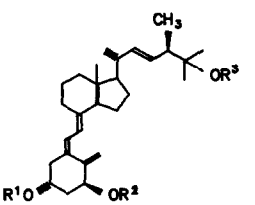
9, R^1= H; R^2= OH

11, R^1 = TBDMS; R^2= OTBDMS



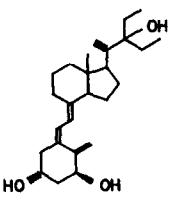
13, R = H

14, R = THF



15, R^1= R^2= TBDMS; R^3= THF

16, R^1 = R^2= R^3= H



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7. H. F. DeLuca, H. K. Schnoes, and S-H. Lee, U. S. Patent 4,512,925, 1985 (C.A., 103:105227c).
8. Analytical data are as follows:
   1 MS: 328 (M^+, 29), 310 (5), 295 (31), 269 (11), 253 (6), 136 (47), 118 (86), 29 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.59 (3H, s, 18-CH_3), 1.14 (3H, d, J=7 Hz, 21-CH_3), 4.0 (1H, m, 3-H), 4.81 (1H, d, J=1.2 Hz, 19E-H), 5.05 (1H, d, J=1.2 Hz, 19Z-H), 6.05 (1H, d, J=11 Hz, 7-H), 6.23 (1H, d, J=11 Hz, 6-H), 9.58 (1H, d, J=3.8 Hz, 22-H).
   2 MS: 344 (M^+, 22), 326 (13), 311 (2), 285 (4), 269 (4), 152 (29), 134 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.59 (3H, s, 18-CH_3), 1.15 (3H, d, J=7 Hz, 21-CH_3), 4.2 (1H, m, 3-H), 4.4 (1H, m, 1-H), 4.99 (1H, d, J=1.2 Hz, 19Z-H), 5.31 (1H, d, J=1.2 Hz, 19E-H), 6.02 (1H, d, J=11 Hz, 7-H), 6.36 (1H, d, J=11 Hz, 6-H), 9.56 (1H, d, J=4 Hz, 22-H).
9. Single isomer of natural C-20 configuration was exclusively formed as determined by ^{1}H-NMR.
10. The reductive elimination of α-hydroxysulfones have been known to generate exclusively trans olefins. P. J. Kocienski, B. Lythgoe and I. Waterhouse, J. Chem. Soc. Perkin I, 1980, 1045 and references cited therein.
11. Epimerization at C-20 has not been observed at the condensation of C-22 steroid aldehydes with various carboanions. S. C. Eyley and D. H. Williams, J. Chem. Soc. Perkin I, 1976, 727 and 731; see also reference 1a.
12. See ref. 2b for HPLC, UV and MS spectra. ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s, 18-CH_3), 0.97 (3H, d, J=6.9 Hz, 28-CH_3), 1.01 (3H, d, J=6.6 Hz, 21-CH_3), 1.10 and 1.15 (3H and 3H, each s, 26-CH_3 and 27-CH_3), 4.21 (1H, m, 3-H), 4.41 (1H, m, 1-H), 4.97 (1H, brs, 19Z-H), 5.29 (2H, m, 22-H and 23-H), 5.31 (1H, brs, 19E-H), 5.99 (1H, d, J=11.2 Hz, 7-H), 6.35 (1H, d, J=11.2 Hz, 6-H).

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