Tetrahedron Letters,Vol.28,No.12,pp 1337-1340,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

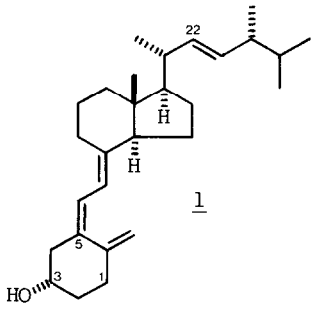
REDUCTIVE ALKYLATION OF A SELENOACETAL IN THE ELABORATION OF STEROID SIDE CHAINS: STEREOCHEMISTRY AND APPLICATION IN A SYNTHESIS OF 1α-HYDROXYVITAMIN D_3[1]

Martin J. Calverley

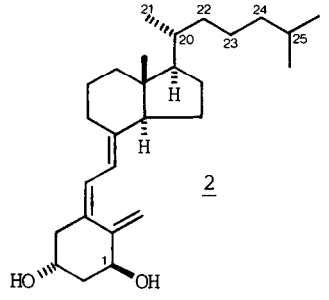
Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark

Summary: A versatile selenoacetal intermediate (8) was prepared by functional group modification of the side chain in 1α-hydroxyvitamin D_2 derivatives. Alkylation with isoamyl bromide gave two diastereoisomers whose configurations were deduced by ^{13}C n.m.r. spectoscopy A photo-induced deselenation reaction was adopted in order to generate the D_3 side chain en route to the title compound.

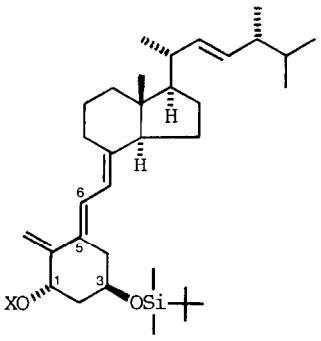
The availability of steroidal aldehydes by cleavage of the side chain double bond in Δ^{22}-steroids (ergosterol, stigmasterol) has made them attractive intermediates for the partial synthesis of compounds having modified side chains via coupling with nucleophilic reagents.[2] The complementary Umpolung alkylation of the aldehyde function in this type of compound has not been described. Prompted by the current interest in the synthesis of vitamin D metabolites and analogues, including the hormonally active 1α-hydroxyl-containing compounds,[3] we have explored the application of this concept in the seco-steroid series. We report here the conversion of vitamin D_2 (1) (ergosterol side chain) to 1α-hydroxyvitamin D_3 (2) (cholesterol side chain), thereby exemplifying an efficient and versatile synthetic route to new analogues.



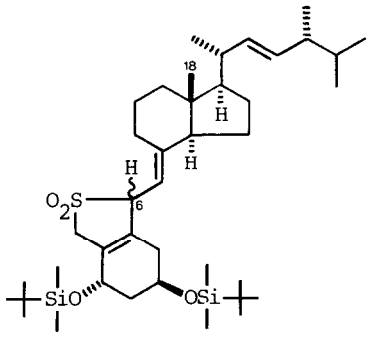
1



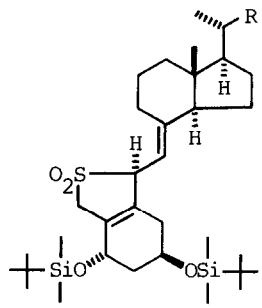
2



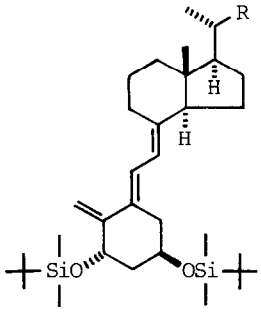
3 X = H
4 X = $SiMe_2Bu^t$

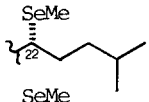
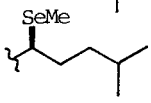
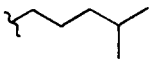


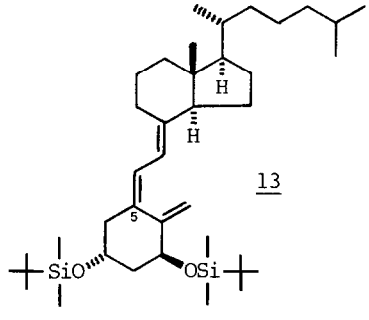
5a 6S
5b 6R



6 R = CHO
7 R = $CH(SeMe)_2$



8 R = $CH(SeMe)_2$
9 R = CH_2SeMe
10 R = 
11 R = 
12 R = 



13

REACTION SEQUENCE
(All reactions except ozonolysis performed under N_2)

1 → 3 → 4 ; i. Ref. 4 (1→3); ii. t-$BuMe_2SiCl$, ImH (DMF, 20 °C): 35%.

4 → 5a + 5b ; SO_2 (l, reflux): 100%.

5a → 6 ; i. O_3; ii. PPh_3 (CH_2Cl_2 - MeOH, -70 °C to 0 °C): 81%.

6 → 7 ; $B(SeMe)_3$, CF_3CO_2H (CH_2Cl_2, 5 °C): 75%.

7 → 8 ; $NaHCO_3$ (EtOH, reflux): 98%.

8 → 9 ; i. n-BuLi (1 mol. equiv., 10 min.); ii. H_2O (THF, -70 °C to 0 °C): 76%.

8 → 10 + 11 ; i. n-BuLi (1 mol. equiv., 10 min.); ii. iso-$C_5H_{11}Br$ (1.5 mol. equiv.) (THF, -70 °C to 20 °C, 1.5 h.): 59%.

10 + 11 → 12 ; i. SO_2 (l, reflux); ii. n-Bu_3SnH (2.2 mol. equiv.) - hν [irradiation through Pyrex filter (reaction flask) with high pressure Hg lamp (type: Hanau TQ 150Z2)] (toluene, 20 °C, 1 h.); iii. $NaHCO_3$ (EtOH, reflux): 80%.

12 → 13 → 2 ; i. anthracene - hν (details as above) (toluene, 20 °C, 1 h.); ii. n-BuLi (0.3 mol. equiv.) (THF, -70 °C to 0 °C, 10 min.);[12] iii. n-Bu_4NF (THF, 55 °C): 70%.

The 1α-hydroxy-5E-vitamin D_2 derivative 4[4] (m.p. 113-114 °C)[5] was converted[6] to a crystalline ca. 3:1 mixture of SO_2-adducts (5), which can be used directly in the subsequent steps. For ease of characterisation, the major (less polar) isomer (5a) (m.p. 107-109 °C dec.) was separated by chromatography. Ozonolysis of 5a gave the aldehyde 6, which was converted to the selenoacetal 7 (m.p. 135-137 °C dec.) using Clive's procedure.[7] Thermal chelotropic extrusion of SO_2 in the presence of $NaHCO_3$[6] then gave the key intermediate (8) (m.p. 115-116 °C), the same product obtained after a parallel sequence of reactions from 5b (combined overall yield from 4; 60%).

Lithio-demethylselenation of 8 followed by quenching with water gave the monomethylseleno compound 9 (m.p. 99-100 °C). This product was also detected as a minor by-product in the alkylation reactions of 8 on the mmol scale. Reaction of the lithio-derivative with isoamyl bromide gave a ca. 2:1 mixture of diastereoisomeric 22-alkylated compounds which was separable by preparative t.l.c. (major, less polar, isomer, 10,[8] m.p. 131-133 °C; minor isomer, 11, m.p. 111-113 °C).

n-Bu_3SnH mediated reductive cleavage[9] of the methylseleno substituent of the side chain presented an unexpected problem. The epimeric mixture of 10 and 11 was not deselenated under the typical radical conditions (n-Bu_3SnH, AIBN, toluene, 100 °C). It was deduced that the conjugated triene system in the molecule inhibits the reaction,[10] so it was necessary once again to mask this function. Vitamin D - SO_2 adducts exemplified by compounds 5 are incompatible with a thermally-initiated reaction because SO_2 is readily extruded. However, a solution to the problem was forthcoming following the observation that the radical deselenation reaction could be effected very efficiently by u.v. illumination without heating. Using this modification, the unseparated mixture of SO_2-adducts formed from the mixture of 10 and 11 was converted to a single 5E-vitamin D_3 derivative 12 (m.p. 96-97 °C) after a subsequent thermal SO_2 extrusion step under basic conditions. Triplet-sensitised photoisomerisation[11] of 12 to the oily 5Z-vitamin derivative 13[12] followed by removal of the alcohol protecting groups completed a synthesis of 1α-hydroxyvitamin D_3 (2) (m.p. 141-142 °C), identical with an authentic sample kindly furnished by Mr. E. Binderup of these laboratories.

The application of the methodology developed here to the synthesis of biologically active analogues of 2, including the side chain hydroxylated vitamin D metabolites, will form the subject of subsequent communications.

REFERENCES AND NOTES

1. 1α-Hydroxyvitamin D_3 is a therapeutically important prodrug for the hormonally active natural vitamin D metabolite, 1α,25-dihydroxyvitamin D_3.
2. For recent reviews, see: (a) J. Redpath and F.J. Zeelen, Chem. Soc. Rev., 1983, 12, 75. (b) R. Pardo and M. Santelli, Bull. Soc. Chim. Fr., 1985, 98.

3. "Vitamin D: Chemical, Biochemical and Clinical Update," eds. A.W. Norman, K. Schaefer, H.-G. Grigoleit and D.v. Herrath, Walter de Gruyter, Berlin, 1985, and previous volumes in this series.

4. The four-step synthesis of the intermediate 3 in the conversion of 1 to 4 is described in: D.R. Andrews, D.H.R. Barton, K.P. Cheng, J.-P. Finet, R.H. Hesse, G. Johnson and M.M. Pechet, J. Org. Chem., 1986, 51, 1635.

5. All new compounds described gave n.m.r., mass, and u.v. spectra fully consistent with the assigned structures and, with the exception of the oily 13, satisfactory combustion analyses.

6. S. Yamada, T. Suzuki, H. Takayama, K. Miyamoto, I. Mitsunaga and Y. Nawata, J. Org. Chem., 1983, 48, 3483, and refs. cited therein. The characteristic differences noted by those authors in the ^{1}H n.m.r. spectra of the 6S and 6R isomers of vitamin D - SO_2 adducts of known configuration were also observed in the present work and allow the assignments shown for 5a and 5b (cf. the positions of the 18-H_3 singlet: 5a, δ 0.66; 5b, δ 0.57). Protection as the SO_2-adducts allows selective ozonolysis at Δ^{22} in vitamin D_2: D.R. Andrews, D.H.R. Barton, R.H. Hesse and M.M. Pechet, J. Org. Chem., 1986, 51, 4819.

7. D.L.J. Clive and S.M. Menchen, J. Org. Chem., 1979, 44, 4279.

8. A comparison of the ^{13}C n.m.r. spectra of 10, 11 and 12 shows that the magnitudes of the β and δ effects of the 22-substituent in 10 and 11 correlate very well with those reported for epimeric pairs of 22-hydroxy- and 22-amino- (Y. Letourneaux, Q. Khung-Huu and M. Lukacs, J. Org. Chem., 1975, 40, 1674) and 22-methyl- (J. Zielinski, H.-t. Li and C. Djerassi, J. Org. Chem., 1982, 47, 620) cholesterol derivatives of known configuration. This observation allows the assignment of the configurations indicated for 10 and 11. [δ_C ($CDCl_3$, 25 MHz) C-20: 10, 41.4; 11, 40.6; 12, 36.0. C-23: 10, 27.0; 11, 33.5; 12, 23.8. C-24: 10, 38.5; 11, 37.7; 12, 39.4. Particularly convincing is the characteristic dramatic difference of the β effect of the 22R and 22S substituent on C-23.]

9. Reviews: (a) K.C. Nikolaou and N.A. Petasis, "Selenium in Natural Product Synthesis," CIS,Inc., Philadelphia, 1984, ch. 5. (b) C. Paulmier, "Selenium Reagents and Intermediates in Organic Synthesis," Pergamon Press, Oxford, 1986, p. 107.

10. The vitamin D conjugated triene system is known to interact with radicals; see: A.G.M. Barrett, D.H.R. Barton, G. Johnson and S. Nagubandi, Synthesis, 1978, 741.

11. J.W.J. Gielen, R.B. Koostra, H.J.C. Jacob and E. Havinga, Recl. Trav. Chim. Pays-Bas, 1980, 99, 306.

12. A small amount of (chromatographically inseparable) residual 5E vitamin derivative 12 was removed by its selective conversion to an isovitamin D derivative by treatment of the reaction product with n-BuLi briefly (M.J. Calverley, Abstracts of Posters Presented at the Belgian Organic Synthesis Symposium, Namur, 1986. Cf. M.J. Calverley, Tetrahedron Letters, 1986, 27, 4903).

(Received in UK 6 January 1987)