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AN EFFICIENT SYNTHESIS OF 1α,25-DIHYDROXY VITAMIN D_3

L. VANMAELE, P.J. DE CLERCQ and M. VANDEWALLE*

State University of Ghent, Department of Organic Chemistry,
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

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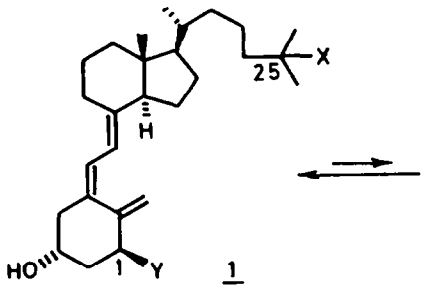
Abstract - An efficient synthesis of the title compound is reported based on C-1 functionalization of the triazoline Diels-Alder adduct of 25-OH previtamin D_3 (2c).

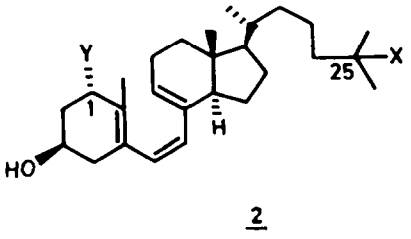
1α,25-Dihydroxy vitamin D_3 (1a) is considered as the most important and active natural metabolite of vitamin D_3[1]. Recently we have described a novel synthesis[2] of the 1α-hydroxy vitamin D_3 analogue (1b), via a route essentially based on the C-1 functionalization of a previtamin D_3 derivative (2b) in which the unstable triene system is protected as a Diels-Alder adduct (cf. 3). We now report the application of this general plan to the synthesis of the title compound[3].
Treatment of crude 25-hydroxy previtamin D_3 (2c) (obtained upon low temperature irradiation of 25-hydroxy-7-dehydrocholesterol with a high-pressure Hg-lamp)[4] with phenyl-1,2,4-triazoline-3,5-dione in CH_2Cl_2 led with complete regio- and stereoselectivity (α attack) to the adduct 3 in 49 % yield.
After selective protection of the 3-hydroxyl function as the tert-butyldimethylsilyl ether (4; 92 % yield), allylic bromination with 1,3-dibromo-5,5-dimethylhydantoin in hexane-CH_2Cl_2 (collidine, AIBN, 20 min reflux) led with high regioselectivity to the diastereoisomeric bromides at C-1 (crude yield > 80 %). Immediate oxidation of the allylic bromides with bis-tetrabutyl-ammoniumdichromate[5] in $CHCl_3$ (reflux, 3 h) led to enone 5 in 56 % overall yield (from 4) after column chromatography on silica gel. This two-step C-1 functionalization is a modification superior to the three-step procedure previously described, for the synthesis of the 1α-hydroxy vitamin D_3 analogue[2] (1b).
After cleavage of the silyl ether in 5 (n-butyric acid, $(n.Bu)_4NF$, THF, 2 h, 20°C; 84 % yield), the reduction of 6 with aluminumhydride in THF at -70°C afforded with high stereoselectivity the triol 7 (yield 87 % after HPLC purification). The stereochemical result is rationalized by an intramolecular hydride transfer after reaction of the reducing agent with the 3-hydroxyl group.
Deprotection of the 6,8-diene system upon refluxing 7 at 85°C in carefully degassed methanol - 15 N KOH under Ar for 70 h afforded after HPLC purification 1(S),25-dihydroxy vitamin D_3 (1a) next to 1(S),25-dihydroxy previtamin D_3 (2a) in a 5.7:1 ratio (61 % yield). The assignment of the 1(S)-configuration in diols 1a, 2a and 7 follows from the analysis of the ^1H NMR spectral data obtained for the previtamin derivative 2a, which showed patterns for H-1 and H-3, i.e., broad

signal at 4.20 ppm (W 1/2 = 9.5 Hz), multiplet at 4.06 ppm (ΣJ = 27.5 Hz), almost identical to those obtained for the trans-diol 2b[6,7], i.e., broad signal at 4.20 (W 1/2 = 9.0 Hz), multiplet at 4.05 (ΣJ = 28.0 Hz); the corresponding cis-diol (1-epi-2b)[6], however, shows resonances at 4.02 (broad signal, W 1/2 = 10.0 Hz) and 4.24 (multiplet, ΣJ = 14.5 Hz).

Heating of 2a for 2 h at 70°C in order to establish equilibration gave 1a which after crystallization from benzene-ethyl acetate (m.p. 95-96°C) showed spectral properties in accord with previous reports (UV, ^{1}H NMR)[3d]. The overall yield of crystalline 1a starting from the adduct 3 is 20 %.

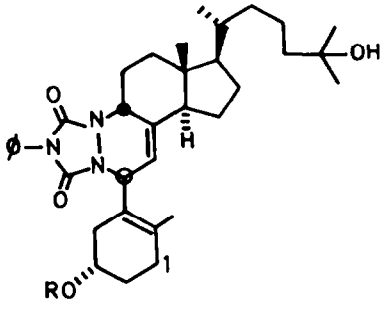


1

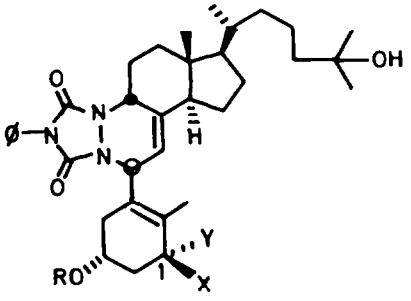


2

a X = OH, Y = OH
b X = H ; Y = OH
c X = OH ; Y = H



3 R = H
4 R = Si(t-Bu)Me$_2$



5 R = Si(t-Bu)Me$_2$; X, Y = O
6 R = H; X, Y = O
7 R = H; X = OH; Y = H

EXPERIMENTAL SECTION

The m.ps. are uncorrected. IR spectra were recorded on a Beckman IR 4230 spectrophotometer, UV spectra on a Unicam SP 1750 ultraviolet spectrophotometer and mass spectra on a AEI MS-50 spectrometer. The ^{1}H NMR spectra were recorded at 360 MHz (WH-Brucker) in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silica gel 60 GF_{254} TLC plates of thickness 0.25 mm. HPLC separations were performed on silica gel, on a Prep LC/System 500 (Waters) apparatus or on a Model 6000 A Solvent Delivery System HPLC (Waters).

The adduct 3

To a soln of crude 2c (19.0 g) obtained upon low temperature irradiation of 25-hydroxy-7-dehydrocholesterol in dry CH_2Cl_2 (300 mL) is added dropwise at 10°C a soln of 4-phenyl-1,2,4-triazoline-3,5-dione (8.6 g; 49.1 mmol) in CH_2Cl_2 (100 mL). After concentration in vacuo the residue is dissolved in acetone (60 mL) and cooled to -20°C. After separation of crystalline 3 (6.9 g), the mother liquor is purified by column chromatography affording another 6.7 g of 3. Total yield 49 %, calculated on consumed 25-hydroxy-7-dehydrocholesterol. Rf (hexane/acetone, 7:3) : 0.16; UV (CH_3OH) : λ_{max} 216 nm; IR (KBr) : 3420, 2960, 2930, 2860, 1760, 1700, 1600, 1500, 1410, 760, 680, 635 cm^{-1}; ^{1}H NMR : 0.78 (s, 3H), 0.94

(d, J = 5.5 Hz, 3H), 1.22 (s, 6H), 1.80 (s, 3H), 3.99 (m, 1H), 4.46 (m, 1H), 5.15 (m, 1H), 5.35 (m, 1H), 7.31-7.49 (m, 5H); MS : m/z 575 ($M^{+\cdot}$, 2), 557 (1.5), 59 (100).

The silyl ether 4

A soln of adduct 3 (1 g; 1.74 mmol), imidazole (295 mg; 4.35 mmol) and tert-butyldimethylsilyl chloride (367 mg; 2.44 mmol) in DMF (20 mL) is stirred under argon at 25°C for 5 h. After addition of an equal volume of hexane stirring is continued for 10 min. After addition of satd NaCl soln (2 mL) and extraction with hexane (4 x 10 mL), the combined organic phases are washed with 5 % HCl soln (5 mL), satd $NaHCO_3$ soln (5 mL) and brine (2 x 5 mL). The oil obtained after drying over $MgSO_4$ and concentration is treated with CH_3CN. Separation of crystalline 4 and purification of the mother liquor by column chromatography (hexane/acetone, 9:1) affords 4 (1.101 g; 92 % yield). M.p. = 153°C (CH_3CN); Rf (hexane/acetone, 4:1) = 0.28; UV (CH_3OH) : λ_{max} = 216 nm; IR (KBr) : 3400, 3020, 2950, 2860, 1770, 1715, 1600, 1540, 1420, 1380, 1220, 860, 840, 690, 670 cm^{-1}; ^1H NMR : 0.05 (2 x s, 6H), 0.79 (s, 3H), 0.88 (s, 9H), 0.94 (d, J = 5.5 Hz, 3H), 1.22 (s, 6H), 1.77 (s, 3H), 3.75 (m, 1H), 4.47 (m, 1H), 5.17 (m, 1H), 5.30 (m, 1H), 7.30-7.51 (m, 5H); MS : m/z 689 ($M^{+\cdot}$, < 1), 671 (5), 75 (100).

The enone 5

To a soln of 4 (0.564 g; 0.819 mmol) in dry hexane (9 mL) and CH_2Cl_2 (1.3 mL) at reflux is added collidine (108 µl, 0.819 mmol), AIBN and dimethyldibromohydantoine (234 mg; 0.819 mmol). After 20 min the cooled suspension is filtered over celite and washed with hexane (20 mL) and $CHCl_3$ (10 mL). The residual oil, obtained after concentration, is dissolved in dry $CHCl_3$ (6 mL) and treated with bis-tetrabutylammoniumdichromate (3.2 g; 4.59 mmol). After reflux for 3 h the cooled suspension is filtered over silica gel (20 g) and eluted with ether (400 mL). Concentration and purification by column chromatography (hexane/acetone, 85:15) affords 5 (320 mg; 56 % yield). Rf (hexane/acetone, 7:3) = 0.39; UV (CH_3OH) : λ_{max} = 222 nm; IR (KBr) : 3500, 2960, 2930, 2860, 1770, 1715, 1670, 1630, 1500, 1410, 1375, 1260, 1100, 870, 840, 760, 640 cm^{-1}; ^1H NMR : 0.04 (2 x s, 6H), 0.79 (s, 3H), 0.88 (s, 9H), 0.95 (d, J = 5 Hz, 3H), 1.22 (s, 6H), 1.91 (s, 3H), 2.49 (dd, J = 12,16 Hz, 1H), 2.72 (dd, J = 4.16 Hz, 1H), 3.98 (m, 1H), 4.54 (m, 1H), 5.15 (m, 1H), 5.37 (m, 1H), 7.31-7.51 (m, 5H); MS : m/z 207 (22), 75 (100).

The enone 6

To a soln of enone 5 (409 mg; 0.582 mmol) and butyric acid (0.266 mL; 2.909 mmol) in dry THF (5 mL) under argon is added dropwise a soln of tetrabutylammonium fluoride (5.818 mL of a 1 M soln) in THF. After stirring for 2 h at 20°C the mixture is treated with ether (40 mL) and washed with 5 % HCl soln (5 mL), satd $NaHCO_3$ soln (2 x 5 mL) and brine (5 mL). After drying ($MgSO_4$) and concentration the residue is purified by column chromatography (hexane/acetone, 3:2) affording 6 (288 mg; 84 % yield). Rf (hexane/acetone, 3:2) = 0.30; UV (CH_3OH) : λ_{max} = 223 nm; IR (KBr) : 3420, 2960, 2930, 2860, 1765, 1705, 1665, 1625, 1600, 1500, 1415, 1380, 1360, 1260, 1230, 1160, 1140, 1105, 1090, 1050, 940, 910, 760, 740, 690, 635 cm^{-1}; ^1H NMR : 0.79 (s, 3H), 0.94 (d, J = 5 Hz, 3H), 1.22 (s, 6H), 1.95 (s, 3H), 4.23 (m, 1H), 4.53 (m, 1H), 5.15 (m, 1H), 5.41 (m, 1H), 7.31-7.49 (m, 5H); MS : m/z 396 (10), 394 (25), 59 (100).

The diol 7

To a suspension of $LiAlH_4$ (132 mg; 3.438 mmol) in dry THF (10 mL) is added dropwise at 25°C a soln of $AlCl_3$ (152 mg; 1.146 mmol) in dry THF (4 ml). After stirring vigorously for 10 min 3.24 mL of the above soln is added cautiously to a cooled (-70°C) soln of enone 6 (125 mg; 0.2122 mmol) in dry THF (1 mL). After stirring for 1 h at -60°C a soln of 5 % HCl/THF (1:1; 5 mL) is added dropwise and the resulting suspension brought to 25°C. After the addition of ether (40 ml) and CH_2Cl_2 (10 mL) the suspension is stirred vigorously for 5 min. The aqueous phase is extracted with ether (3 x 15 mL) and the combined organic phases washed with 5 % HCl (15 mL), satd $NaHCO_3$ (15 mL) and brine (2 x 10 mL). After drying and concentration in vacuo the residue is purified by HPLC (benzene/acetone, 7:3) affording 7 (91 mg; 73 % yield). Rf (benzene/acetone, 7:3) = 0.14; UV (CH_3OH) : λ_{max} = 215 nm; IR (KBr) : 3400, 2960, 2930, 2860, 1770, 1710, 1600, 1500, 1420, 1375, 1270, 1235, 1150, 1110, 1045, 910, 760, 710, 690, 640 cm^{-1}; ^1H NMR : 0.78 (s, 3H), 0.94 (d, J = 5.5 Hz, 3H), 1.22 (s, 6H), 1.93 (s, 3H), 4.09 (m, 1H), 4.27 (m, 1H), 4.47 (m, 1H), 5.19 (m, 1H), 5.29 (m, 1H), 7.31-7.49 (m, 5H).

1(S)-25-dihydroxyvitamin D_3 (1a)

A degassed soln of diol 7 (140 mg; 0.237 mmol) and of KOH in aqueous MeOH (8.4 mL of a soln of 112 g KOH in 84 ml H_2O-MeOH, 1:1) is stirred under argon at 85°C for 70 h. The MeOH is removed in vacuo and the aqueous phase extracted with ether. The combined organic phases are washed with 10 % KOH soln (5 mL), 5 % HCl soln (2 x 10 mL), satd $NaHCO_3$ soln (5 mL) and brine (8 mL). After drying ($MgSO_4$) and concentration the residue is purified by HPLC (hexane/acetone, 7:3) affording 51 mg of 1(S),25-dihydroxy vitamin D_3 (1a) and 9 mg of 1(S),25-dihydroxy previ-

tamin D_3 (2a); total yield 61 %. 1a : m.p. = 95-96°C (benzene/ethyl acetate); Rf (hexane/acetone, 7:3) = 0.13; UV (CH_3OH) = λ_{max} = 266 nm; IR (KBr) : 3350, 2940, 2860, 1690, 1630, 1470, 1375, 1360, 1210, 1145, 1050, 960, 910, 800, 740 cm^{-1}; ^1H NMR : 0.55 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 1.22 (s, 6H), 4.23 (m, 1H, ΣJ = 20.0 Hz), 4.43 (m, 1H, ΣJ = 12.0 Hz), 5.00 (m, 1H), 5.33 (m, 1H), 6.02 (d, J = 11 Hz, 1H), 6.38 (d, J = 11 Hz, 1H). 2a : Rf (hexane/acetone, 7:3) = 0.13; UV (CH_3OH) : λ_{max} = 260 nm; ^1H NMR : 0.71 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), 1.23 (s, 6H), 1.77 (s, 3H), 4.06 (m, 1H), 4.20 (m, 1H), 5.51 (m, 1H), 5.79 (d, J = 12 Hz, 1H), 5.91 (d, J = 12 Hz, 1H).

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7. Absolute proof of the 1(S)-configuration in 1α-hydroxyvitamin D_3 (1b) and hence 2b was obtained by comparison with an authentic sample (see ref. 2).