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1α-Hydroxy-19-Nor-Vitamin D C-22 Aldehyde. A Valuable Intermediate in the Synthesis of Side Chain Modified 1α,25-Dihydroxy-19-Nor-Vitamin D_3

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Summary. A side chain homologated 1α,25-dihydroxy-19-nor-vitamin D_3 analog was prepared in a double convergent synthesis with 1α-hydroxy-19-nor-vitamin D C-22 aldehyde as a key intermediate.

In recent years many structural analogs of the natural hormone, 1α,25-dihydroxyvitamin D_3 have been prepared and found to exhibit an interesting separation of activities of cell differentiation and calcium mobilization.[1] Elongation of the side chain of the hormone[2] or replacement of the A-ring exocyclic methylene group (C-19) by two hydrogen atoms (19-nor-vitamin D)[3] provided compounds with high potency in inducing differentiation of malignant cells and very low calcium mobilization activity. We wished to examine the biological effect of side chain modifications on 1α,25-dihydroxy-19-nor-vitamin D_3.

Recently we developed a total synthesis of 1α,25-dihydroxy-19-nor-vitamin D_3[4] based on Lythgoe's concept. The crucial step of this approach was a Wittig Horner reaction of the ring-A precursor **8** with the protected 25-hydroxy-Windaus Grundmann ketone.

In this paper we describe an efficient synthesis of the 1α-hydroxy-19-nor-vitamin D-22-aldehyde (**11**), a key intermediate for the synthesis of side chain modified 19-nor-vitamin D analogues. We further used this intermediate to prepare Δ^{22},22E,19-nor-24,24-dihomo-26,27-dihomo-1α,25-dihydroxyvitamin D_3 as an example of its usefulness.

The aldehyde (**11**) was prepared in a convergent synthesis from the A-ring synthon (**8**) obtained from commercially available quinic acid.[4,5] The readily available Inhoffen Lythgoe diol[6] (**5**) served as the basic building block, providing the CD ring. Partial acetylation of **5** gave **6** (Ac_2O, pyr, -20°C, then 0°C) in 87% yield. Controlled acetylation affected mainly the primary alcohol and only traces of the diacetate formed. The acetoxy alcohol **6** was then oxidized with pyridinium chlorochromate in CH_2Cl_2 to give the 22-acetoxy-Grundmann ketone **7** (PCC, CH_2Cl_2, RT, 1 h) in 88% yield. The 22-acetoxy group gave the desired chemoselectivity of the primary hydroxyl, which had to be later converted to the aldehyde.

Condensation of the A-ring synthon **8** with the ketone **7** in a Lythgoe-Horner-Wittig reaction gave diene **9** (n. BuLi, THF, -78°C) in 74-90% yield. The 22-acetoxy group of **9** was now easily

converted to the desired aldehyde by $LiAlH_4$ reduction to the alcohol 10 ($LiAlH_4$, THF, 0°C, 25 min, then RT, 20 min, 88% yield) and subsequent Swern oxidation gave the desired protected 19-nor-vitamin D-22-aldehyde 11 ($(COCl)_2$, DMSO, CH_2Cl_2, -60°C, 30 min, then TEA) in 80% yield.

As a representative example of a side chain homologated 1α,25-dihydroxy-19-nor-vitamin D_3, we chose Δ^{22}-24,24-dihomo-26,27-dihomo analogue (14) because of the favorable biological properties of the corresponding compound in the vitamin D_3 series.[7]

For the synthesis of 14, we applied the methodology developed by us previously in the vitamin D series:[8] Julia olefination of the 19-nor-22-aldehyde with the corresponding protected phenylsulfone side chain fragment.

The protected phenylsulfone derivative 4 was prepared from 5-chlorovaleryl chloride by treatment with ethylmagnesium bromide to give the chloro-alcohol 1 (EtMgBr in ether, THF, -5°C, then RT, 2 h) in 84% yield. The chloro-compound was then treated with potassium thiophenoxide in DMF to give the phenylthioether (not shown) (PhSH, t.BuOK, DMF, RT, 16 h) (92% yield) which in turn was oxidized with 3-chloroperbenzoic acid (mCPBA, CH_2Cl_2, 2 h, RT) to the phenylsulfone 3 in 67% yield. The very hindered tertiary hydroxyl of 3 was protected with triethylsilyl triflate to give the protected phenylsulfone 4 (TES-triflate, CH_2Cl_2, TEA, 0°C, then RT, 1.5 h, 99%).

Lithiation of phenylsulfone derivative 4 (LDA, THF, -78°C, 30 min) followed by the addition of aldehyde 11 (THF, -78°C, 1 h) gave 12 as a mixture of diastereoisomers which were immediately acetylated (Ac_2O, pyr, DMAP, 4°C, 16 h) and then desulfonylated with fresh 5% Na/Hg (THF, MeOH, Na_2HPO_4) to give the protected triol 13. Deprotection with Bu_4NF^- in THF (Bu_4NF^- in THF, RT) gave the final Δ^{22}-1α,25-dihydroxy-19-nor-vitamin D_3 homolgue 14 (25% overall yield from 11).

The homologated Δ^{22}-1α,25-dihydroxy-19-nor-vitamin D_3 14 showed no calcemic activity but high cell differentiation activity, making it a potentially useful analog in the treatment of psoriasis and/or malignancy.

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References and Notes

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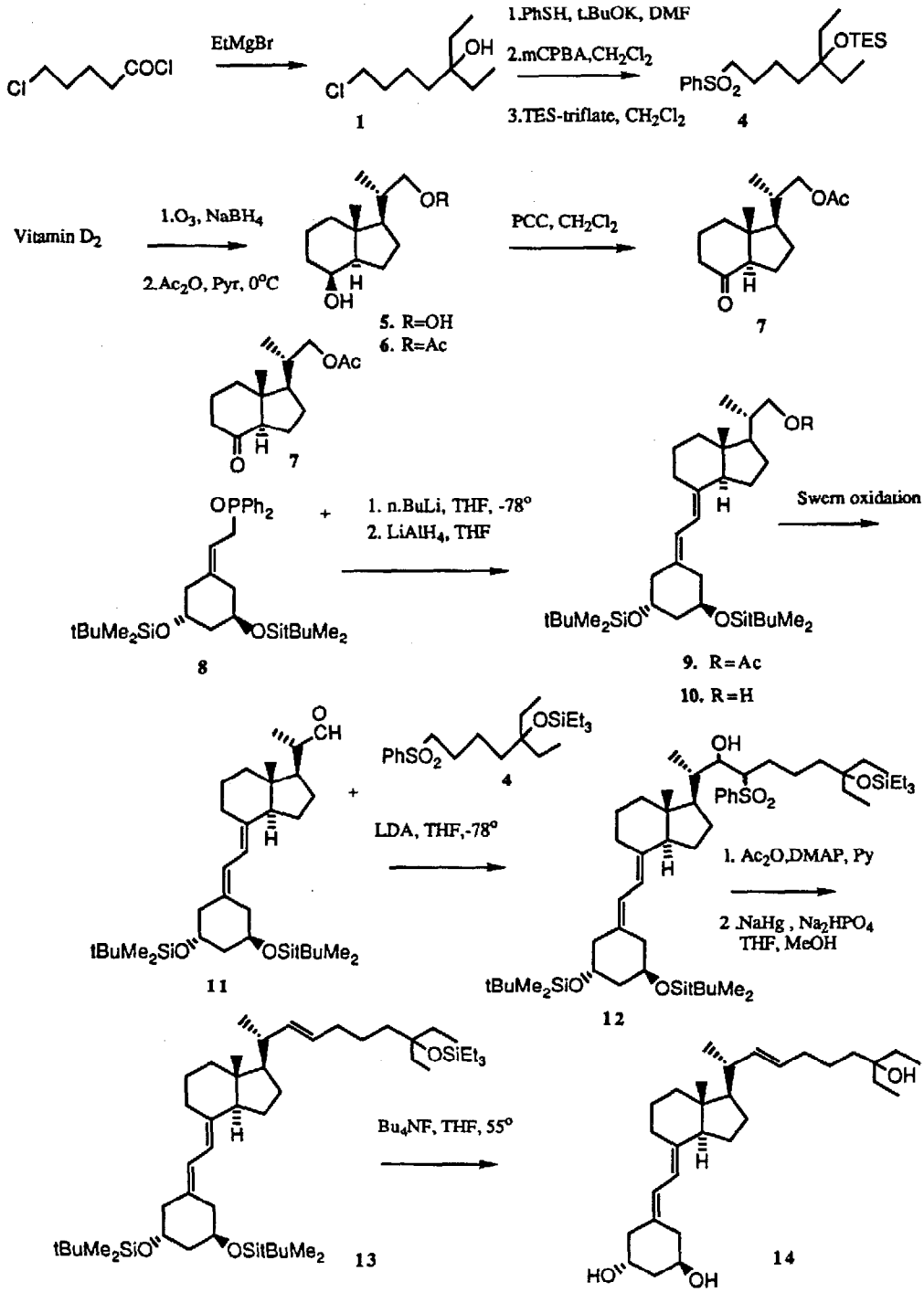
EtMgBr
1.PhSH, t.BuOK, DMF
2.mCPBA,CH2Cl2
3.TES-triflate, CH2Cl2
1
4
Vitamin D2
1.O3, NaBH4
2.Ac2O, Pyr, 0°C
PCC, CH2Cl2
5. R=OH
6. R=Ac
7
1. n.BuLi, THF, -78°
2. LiAlH4, THF
Swern oxidation
8
9. R=Ac
10. R=H
LDA, THF,-78°
11
1. Ac2O,DMAP, Py
2 .NaHg , Na2HPO4
THF, MeOH
12
Bu4NF, THF, 55°
13
14

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5. We found that the synthesis of **8** in ref. 4 worked better if the in situ generated 22-tosylate was used instead of the allylic chloride. The tosylate was generated according to Lythgoe's earlier work: B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, S. Ruston, J. Chem. Soc. Perkin Trans. I, 1976, 2386.
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Analytical Data: All NMR in $CDCl_3$ at 600 or 400 MHz, All MS, EI, 70 ev.

4: Anal. calcd. for $C_{21}H_{38}O_3SSi$, C, 63.26; H, 9.61; S, 8.04; Found: C, 63.41; H, 9.54; S, 8.11.

7: ^1H NMR δ: 0.66 (3H, s, 18-CH_3), 1.05 (3H, d, J=6.6 Hz, 21-CH_3), 2.06 (3H, s, $COCH_3$), 3.82 (1H, dd, J_{gem}=10.7 Mz, J_{vic}=7.1 Hz, one of 22-H), 4.08 (1H, dd, J_{gem}=10.7 Hz, J_{vic}=3.4 Hz). MS, m/z (rel. int.): 252 (M^+, 9), 237 (10), 209 (17), 192 (40), 55 (100).

9: ^1H NMR δ: 0.56 (3H, s, 18-CH_3), 1.02 (3H, d, J=6.6 Hz, 21-CH_3), 2.06 (3H, s, $COCH_3$), 3.77 (1H, dd, J_{gem}=10.7 Hz, J_{vic}=7.6 Hz, one of 22-H), 4.1 (2H, m, 3α-H and one of 22-H), 4.20 (1H, m, 1β-H), 5.82 (1H, d, J=11.0 Hz, 7-H), 6.16 (1H, d, J=11.0 Hz, 6-H). MS, m/z (rel. int.): 604 (M^+, 18), 547 (2), 472 (15), 75 (100). UV (EtOH) λ_{max}: 243, 251.5, 261 nm.

11: ^1H NMR δ: 0.59 (3H, s, 18-CH_3), 1.14 (1H, d, J=7.0 Hz, 21-CH_3), 4.08 (2H, m, 1 & 3 H-s), 5.84 (1H, d, J=11.1 Hz, 7-H), 6.17 (1H, d, J=11.1 Hz, 6-H), 9.60 (1 H, d, J=3.2 Hz, 22-H). MS m/z (rel. int.) 560 (M^+, 4), 545 (1), 503 (2), 428 (18), 73 (199). UV (EtOH) λ_{max}: 243, 251.5, 261 nm.

14: ^1H NMR δ: 0.56 (3H, s, 18-CH_3), 0.98 (3H, d, J=6.6 Hz, 21-CH_3), 4.03 (1H, m, 3α-H), 4.09 (1H, m, 1β-H), 5.29 (2H, m, 22 & 23-Hs), 5.83 (1H, d, J=11.3 Hz, 7-H), 6.29 (1H, d, J=11.3 Hz, 6-H). MS m/z (rel. int.), 458 (M^+, 25), 440 (16), 422 (3), 275 (44), 257 (23), 239 (33), 211 (20), 147 (35), 135 (65), 133 (78), 95 (70), 81 (100). Exact mass calcd. for $C_{30}H_{50}O_3$ 458.3759, found: 458.3755. UV (EtOH) λ_{max}: 243, 251.5, 261 nm.

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