Tetrahedron Letters, Vol.32, No.52, pp 7663-7666, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

NOVEL SYNTHESIS OF 19-NOR-VITAMIN D COMPOUNDS

Kato L. Perlman, Rolf E. Swenson[1], Herbert E. Paaren[†], Heinrich K. Schnoes and Hector F. DeLuca*.

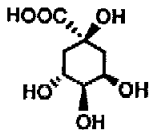
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin, Madison, Wisconsin 53706, and [†]Tetrionics, 565 Science Drive, Madison, WI 53711.

Summary: 1α,25-Dihydroxy-19-nor-vitamin D_3 was prepared efficiently in a convergent synthesis starting with (-)-quinic acid and a ketone of the Windaus-Grundmann type.

The hormone, 1α,25-dihydroxyvitamin D_3, is a highly potent regulator of calcium homeostasis in animals, and more recently, its activity in cellular differentiation has been established.[2] Many structural analogs have been prepared and tested and found to exhibit an interesting separation of activities in cell differentiation and calcium regulation.[3] This difference in activity may be useful in the treatment of malignancy and psoriasis. In our systematic investigation of structure-activity relationships of the vitamin D molecule, we recently prepared the 19-nor compound **13**, in which the ring-A exocyclic methylene group (carbon 19) has been replaced by two hydrogen atoms. Analog **13** showed a selective activity profile, combining high potency in inducing differentiation of malignant cells with very low or no bone calcification activity.

Originally, analog **13** was prepared via oxidative degradation of the 1α-hydroxy-3,5-cyclo-derivative of 25-hydroxyvitamin D_3.[4] We describe here an alternative approach, illustrated by a convergent synthesis of **13**, that is more suitable for the large-scale preparations and, like the original synthesis, can be applied to other 1-hydroxylated-19-nor-vitamin D compounds. The new synthesis entails the independent preparation of a ring-A unit (**10**) and CD-ketone (**11**), and their eventual condensation in a Horner-Wittig reaction, according to the general approach pioneered by Lythgoe,[5] to give, after deprotection, 1α,25-dihydroxy-19-nor-vitamin D_3 (**13**).

We chose as our starting material commercially available (1R,3R,4R,5R)(-)quinic acid (**1**), which can serve as a ring-A building block,[6] since it features the correct hydroxy-stereochemistry (3R,5R) at the centers destined to become C-1 and C-3 in the desired product. Esterification of **1**, followed by hydroxy protection, gave ester **2** (p TsOH, MeOH, RT, 24 h, 92%; TBDMSCl, TEA, DMF, RT, 18 h, 70%). For removal of the 4-hydroxy group, we applied Barton's free radical reduction procedure[7] to



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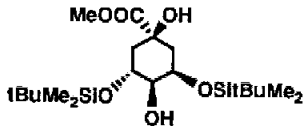

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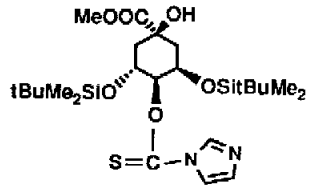

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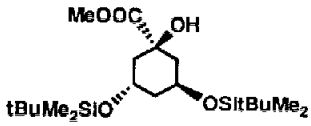

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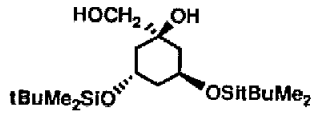

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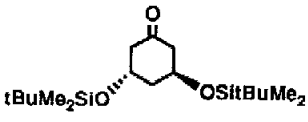

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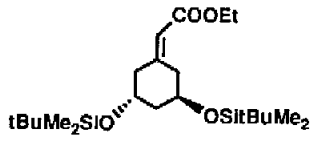

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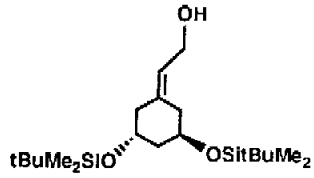

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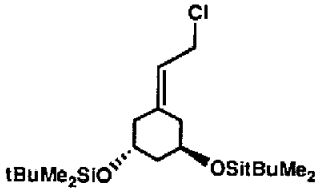

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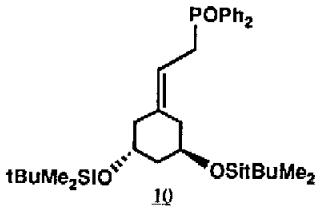

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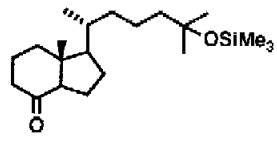

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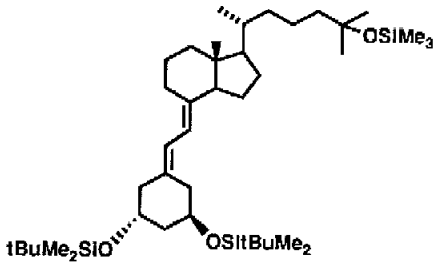

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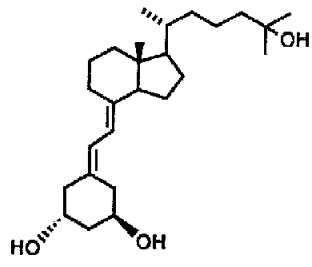

13

the thioimidazolide **3**, prepared from **2** with 1,1'-thiocarbonyl-diimidazole in CH_2Cl_2 (60 h, RT, 91%). Radical deoxygenation with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave the 4-desoxy-ester **4** (Bu_3SnH, AIBN, toluene, 80°C, 2 h, 90%). Reduction of the ester to alcohol **5** (DIBAL-H, toluene, -78°C, 2h, 60%) was followed by oxidation to the cyclohexanone derivative **6** (satd. $NaIO_4$ in H_2O, MeOH, 0°C, 30 min., 78%). Reaction with ethyl (trimethylsilyl)acetate in the presence of LDA in THF[8] (-78°C, 2 h, 86%) gave the cyclohexylidene ester **7**.[9] The latter was reduced to the allylic alcohol **8** (DIBAL-H, toluene, -78°C, 1 h, 78-95%) which, after conversion to the chloride **9** by reaction with the complex made from N-chlorosuccinimide and dimethyl sulfide,[10] ($NCS,(CH_3)_2S$, CH_2Cl_2, -25°C, then 0°C, 80%) was transformed to the desired phosphine oxide **10** on treatment with lithium diphenylphosphide followed by oxidation with hydrogen peroxide (Ph_2PH, nBuLi, 0°C, then -78°C, 30 min., then H_2O_2, $CHCl_3$, 82%).

The synthesis of the CD-ring ketone (**11**) with the appropriate protected side chain is well known.[11] With the required synthons in hand, their condensation to **13** involved the reaction of the phosphinoxy carbanion prepared from **10** with protected **11** to give the 19-nor-vitamin derivative **12** (nBuLi, THF, -78°C, 1 h, 56%) and, after deprotection (THF, Bu_4NF, 1 h, 60%), the desired 1α,25-dihydroxy-19-nor-vitamin D_3 (**13**) (4% overall yield from **1**).[12]

References and Notes

1. Current address: Abbott Laboratories, Dept. 47E; AP10, Abbott Park, IL 60064-3500.
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9. We have also prepared **7** by an alternative route in which formation of the cyclohexylidene ester precedes removal of the C-4-hydroxy group,

i.e. the sequence comprising reduction of ester **2** to the vicinal diol, periodate cleavage to the ketone (the C-4-OH analog of **6**) condensation of the latter with TMS-CH_2COOEt (after temporary C-4-OH-protection as the TMS ether) to obtain the cyclohexylidene ester and then C-4-deoxygenation, by the two-step procedure described in the text, to ester **7** (overall yield, **1**→**7**, 23%).

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12. This work was supported by a program project grant no. DK-14881 from the National Institutes of Health.

Analytical Data: All NMR in $CDCl_3$ at 500 MHz; all MS, EI, 70 eV.

2 ^{1}H NMR, δ: 0.09, 0.11, 0.14, 0.15 (s, 4x3H), 0.89, 0.91 (s, 2x9H), 1.82 (dd, J=10.3, 13.0 Hz 1H), 2.01 (dm, 1H), 2.07 (dd, J=2.5, 14.3 Hz, 1H), 2.18 (dm, 1H), 2.31 (d, J=2.7 Hz, 1H, C-4-OH), 3.42 (dm, 1H), 3.76 (s, 3H), 4.11 (ddd, J=4.5 10, 13.2 Hz, 1H), 4.36 (m, 1H), 4.53 (bs, 1H, C-1-OH). MS m/z (rel. int.) 377 (70), 227 (91).

3 ^{1}H NMR, δ: 0.02, 0.07, 0.09, 0.14 (s, 4x3H), 0.77, 0.91 (s, 2x9H), 2.00 (dd, J=10.4, 13.5 Hz, 1H), 2.09 (dm, 1H), 2.27 (dd, 2.5, 14.7 Hz, 1H), 2.33 (dm, 1H), 3.80 (s, 3H), 4.43 (brs, 1H, C-1-OH), 4.58 (ddd, J=4.9, 10.2, 14.1 Hz, 1H), 4.66 (m, 1H), 5.52 (dd, 1H, J=2.8, 9.1 Hz), 7.06 (sharp m, 1H), 7.64 (t, J=1.4 Hz, 1H), 8.38 (s, 1H).

4 ^{1}H NMR, δ: 0.09, 0.11, 0.14, 0.15 (s, 4x3H), 0.89, 0.91 (s, 2x9H), 1.49 (m, 1H), 1.71 (m, 1H), 1.95 (m, 2H), 2.04 (dm, 1H), 2.20 (dm, 1H), 3.76 (s, 3H), 4.32 (ddd, J=4.4, 10.8, 15.3 Hz, 1H), 4.41 (m, 1H0, 4.75 (s, 1H).

5 ^{1}H NMR, δ: 0.11, 0.12, 0.14, 0.16 (s, 4x3H), 0.90, 0.91 (s, 2x9H), 1.28 (dd, J=11.4, 12.2 Hz, 1H), 1.43 (m, 2H), 1.96 (m, 2H), 2.05 (dm, 1H), 2.12 (dd, J=4.4, 8.3 Hz, 1H), 3.33 (dd, J=8.8, 11.1 Hz, 1H), 3.40 (dd, J=4.2, 11.0 Hz, 1H), 4.33 (m, 1H), 4.37 (m, 1H), 4.54 (s, 1H, C-1-OH).

6 ^{1}H NMR, δ: 0.11, 0.12, 0.14, 0.15 (s, 4x3H), 0.91, 0.90 (s, 2x9H), 1.94 (t, 5.3 Hz, 2H), 2.35 (dd, J=6.9, 14.1 Hz, 2H), 2.54 (dd, J=3.7, 14.5 Hz, 2H), 4.35 (m, 2H).

7 ^{1}H NMR, δ: 0.04 (s, 12H), 0.85, 0.87 (s, 2x9H), 1.26 (t, J=7.3 Hz, 3H), 1.70 (m, 1H), 1.80 (m, 1H), 2.15 (dd, J=7.8, 13.0 Hz, 1H), 2.38 (dd, J=3.2, 13.0 Hz, 1H), 2.78 (dd, J=2.8, 13.5 Hz, 1H), 3.05 (dd, J=6.2, 13.5 Hz, 1H), 4.13 (m, 4H), 5.70 (s, 1H).

8 ^{1}H NMR, δ: 0.06 (br s, 12H), 0.87 (s, 18H), 1.63 (m, 1H), 1.80 (m, 1H), 2.05 (dd, J=4.7, 8.6 Hz, 1H), 2.18 (dm, J=13 Hz, 1H), 2.34 (m, 2H), 4.02 (m, 2H), 4.13 (m, 2H), 5.60 (br t, J=7.1 Hz, 1H). MS, m/z (rel. int.) 237 (85), 211 (83), 171 (100).

9 ^{1}H NMR, δ: 0.06 (s, 12H), 0.89 (s, 18H), 1.73 (br m, 2H), 2.08 (dd, 1H), 2.20 (dd, 1H), 2.32 (m, 2H), 4.04 (m, 2H), 4.11 (m, 2H), 5.51 (br t, 1H). MS, m/z (rel. int.): 237 (93), 215 (52), 189 (79), 105 (100). UV (EtOH): λ_{max}: 258, 265, 272 nm.

10 ^{1}H NMR, δ: 0.01 (m s, 12H), 0.85 (m s, 18H), 1.65 (t, J=5.25 Hz, 2H), 1.90 (m, 1H), 2.01 (m, 2H), 2.22 (brd, J=3.5 Hz, 1H), 3.05 (ddd, J=6.75, 14.9, 14.9 Hz, 1H), 3.14 (ddd, J=8.5, 14.9, 14.9 Hz, 1 H), 3.98 (m, 2H), 5.28 (m, 1H), 7.46 (m, Ar-4H), 7.52 (m, 2H, Ar), 7.73 (m, Ar-4H). MS, m/z (rel. int.): 570 (M+, 1), 513 (100), 381 (46), 306 (20), 202 (55), 75 (20).

13 ^{1}H NMR, δ: 0.52 (3H, s, 18-CH3), 0.92 (3H, d, J=6.9 Hz, 21-CH3), 1.21 (6H, s, 26 & 27-CH3), 4.02 (1H, m, 3-H), 4.06 (1H, m, 1-H), 5.83 (1H, d, J=11.6 Hz, 7-H), 6.29 (1H, d, J=10.7 Hz, 6-H). MS, m/z (rel. int.): 404 (M+, 100), 386 (41), 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 95 (82), 59 (18). UV (EtOH) λ_{max}: 243, 251.5, 261 nm.

(Received in USA 13 August 1991)