# Total Synthesis of 1α,25-Dihydroxy-18-Norvitamin $D_3$

B. Sas, P. De Clercq and M. Vandewalle*

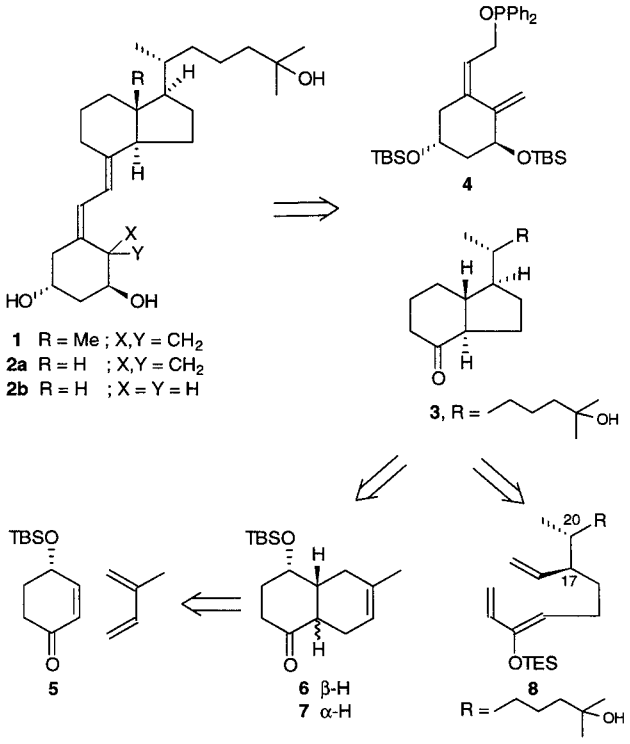
Department of Organic Chemistry, Universitiy of Gent, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

Fax: (32-9) 264.49.98

*Received 25 June 1997*

**Abstract:** 1α,25-Dihydroxy-18-norvitamin $D_3$ **2a** has been synthesized *via* two routes. In the first one, the CD-ring fragment **3** was obtained by an intermolecular Diels-Alder reaction via a decalin intermediate and subsequent ring contraction. The second approach is based on an intramolecular Diels-Alder reaction of a preconstructed nonatriene **8**.

The observation that 1α,25-dihydroxy-vitamin $D_3$ (**1**; calcitriol) is active in the regulation of cell proliferation and differentiation, next to the classical role in calcium-bone homeostasis, has led in recent years to the development of analogues capable of dissociating cell differentiating effects from calcemic effects.[1,2] Among the three fragments of the vitamin D skeleton structural modifications of the side chain and of the A-ring have been especially studied in the past.[3]




**Scheme 1**

Some years ago, we embarked on an extensive study of the structure-function relationship focussing on the least studied part of the module, i.e. the central CD-ring region.[4] In this context we presently want to describe the total synthesis of 18-nor analogues. It can be expected that the absence of the angular methyl group will have an influence on the side chain orientation.[3] It is generally assumed that the relative position in space of the 1α- and 25-hydroxy groups is important for the biological activity and that the side chain occupies a very restricted topology at the binding site of the vitamin D receptor (VDR).[3]

Recently Deluca *et al*[5] reported a partial synthesis of 1α,25-dihydroxy-18-norvitamin $D_3$ **2a** and its 19-nor analogue **2b** starting from Grundmann's ketone.

We have studied two strategies for the total synthesis of the title compound **2a** (Scheme 1). The first one is based on the Diels-Alder reaction of known **5**[6] with isoprene. It has indeed been shown by Danishefsky *et al*[7] that reaction of **5** with butadiene occurs *syn* to the oxy-substituent. Epimerization of **6** to **7** and ring contraction will then provide an entry into a *trans*-hydrindane intermediate of type **3**.

A second approach to these key-intermediates involves an intramolecular Diels-Alder reaction (IMDA) of a nonatriene[8] such as **8**. Final construction of the vitamin D skeleton is based on the Lythgoe coupling[9] of hydrindanone **3** with A-ring precursor **4**.[10]

*Route involving the intermolecular Diels-Alder reaction.*

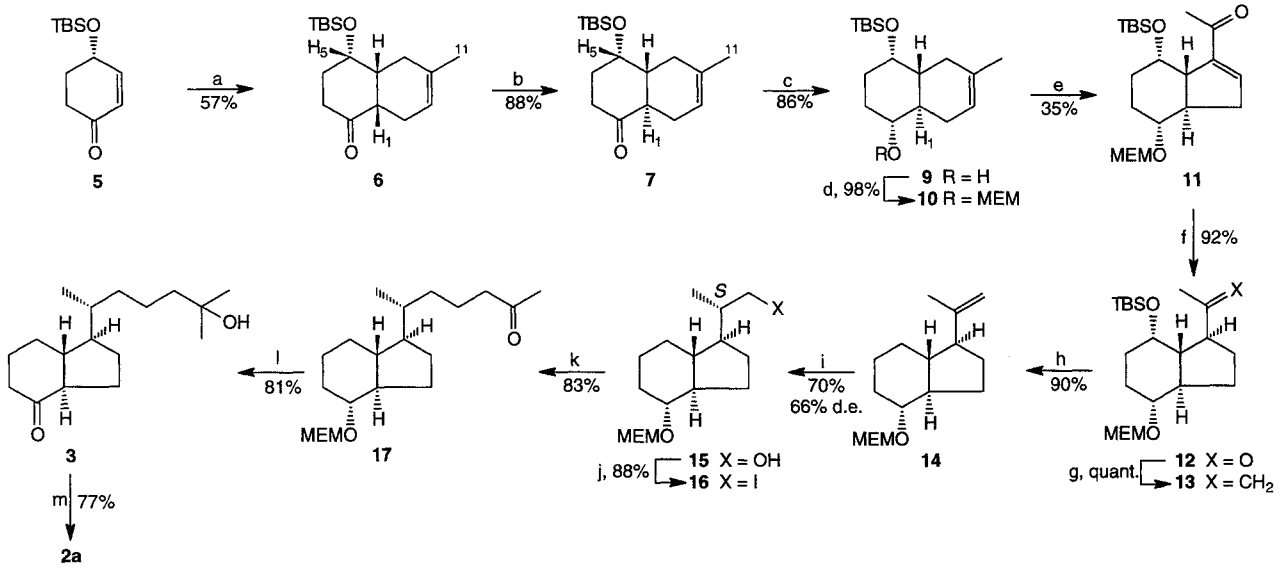
Lewis acid catalyzed reaction of **5** with isoprene led regioselectively to a 3:1 mixture of **6** and the *anti*-adduct (Scheme 2).[11] The *syn*-selectivity is lower than reported for the addition involving butadiene[7] where a 10:1 ratio was found. Base catalyzed equilibration afforded the *trans*-fused decalone **7** (92% d.e.) which was subsequently reduced to **9** as the major isomer (86% d.e.).[12] Structural assignment of **6** and **7** is based on the analogy of the $^1H$ NMR signals (δ and J values)[13] of relevant protons ($H_1$ and $H_5$) with those of the respective 11-nor compounds described by Danishefsky *et al*.[7]

After protection of the hydroxy group in **9**, the hydrindane skeleton was now created in a 3-step sequence, involving dihydroxylation of the double bond (66%), α-diol cleavage (98%) and intramolecular aldol reaction (55%). It is noteworthy that the $OsO_4$-$NaIO_4$ mediated direct cleavage of **10** led to the dicarbonyl intermediate in low yield (16%).

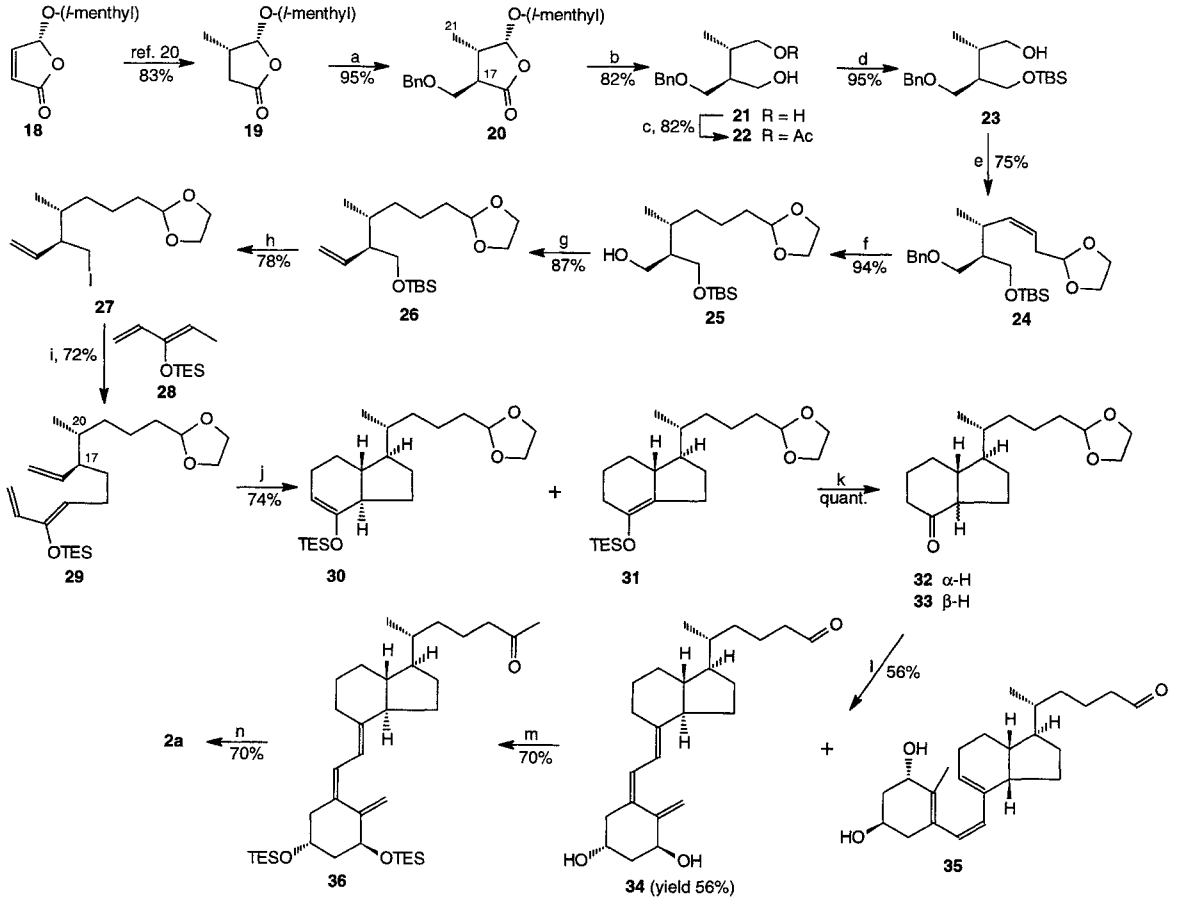
Hydrogenation of the 16,17-double bond in **11** led to an epimeric mixture (8:1) in favour of 17-*epi*-**12**, this in contrast to the analoguous reaction[14] in steroids where the 18-angular methyl substituent exerts stereocontrol affording the equatorially 17-substituted epimer. Subsequent treatment of this mixture with base gave exclusively the thermodynamically more stable ketone **12**. This is in accord with MM2 conformational calculations[15] which show an 99:1 equilibrium for **12** and 17-*epi*-**12**.

Subsequent to a Wittig olefination and desilylation, the 12-oxy function in **13** was removed using the Barton-McCombie procedure.[16] In accord with Midland's observation[17] in steroids we expected that hydroboration of **14** would lead to the steroidal natural configuration at C-20, i.e. the (*S*)-configuration, upon *si*-face attack on the preferred 17,20-rotamer (1,2-allylic strain). However starting from **14** alcohol **15** was obtained with a much lower stereoselectivity (60% d.e.; total yield of 88%). Again this can be attributed to the absence of the 18-angular methyl substituent. As separation of the epimers was not possible (separation was possible only at the stage of the title compound **2a**), the mixture was taken through the subsequent steps. At this stage the 20-(*S*) configuration for the major isomer **15** was assumed and will be proven later (*vide infra*).

Among the methods available for introducing the side chain, the conjugate addition of **16** to methyl vinyl ketone, under sonochemical aqueous conditions[18] gave the best results. Subsequent Grignard reaction on **17** and formation of the C-8 carbonyl function led to **3**, the 18-nor CD ring intermediate needed for the Lythgoe coupling[9] with phosphine oxide **4**.[10] This coupling and subsequent deprotection of the hydroxy functions afforded title compound **2a**.



**Scheme 2.**(a) $CH_2$=CH(Me)-CH=$CH_2$, $AlCl_3$, toluene, -78°C, 6h; (b) MeONa, MeOH, r.t., 1h; (c) $NaBH_4$, MeOH, r.t., 12h; (d) DIPEA, MeMCl, r.t., 3h; (e) (i) $OsO_4$, *N*-methylmorpholine *N*-oxide, $Me_2CO$-$H_2O$ (3:1), r.t., 12h; (ii) $NaIO_4$ $Me_2CO$-$H_2O$ (3:1); (iii) KOH (2%), Δ, 12h; (f) (i) Pd/$CaCO_3$, $H_2$, EtOAc, r.t.; (ii) NaOMe, MeOH, r.t.; (g) $Ph_3P$=$CH_2$, THF-HMPA (1:1), 0°-r.t., 1h; (h) (i) TBAF, THF, r.t., 5d; (ii) NaH, $CS_2$, MeI, THF, r.t., 2h; (iii) n-$Bu_3SnH$, AIBN, toluene, 110°C, 8h; (i) 9-BBN, THF, r.t., 2h, then EtOH, NaOH (6N), $H_2O_2$ (30%), 60°C, 1h; (j) (i) TsCl, DMAP, $Et_3N$, $CH_2Cl_2$, r.t., 12h; (ii) KI, DMSO, 60°C, 4h; (k) MVK, CuI, Zn, ))), $H_2O$-EtOH (3:7), 40°C, 30 min; (l) (i) MeMgBr, THF, r.t., 80 min; (ii) Amberlyst, MeOH, r.t., 5d; (iii) PDC, $CH_2Cl_2$, r.t., 3h; (m) (i) *N*-trimethylsilylimidazole, THF, r.t., 1h then **4**, n-BuLi, THF, -78°C, 30 min; (ii) TBAF, THF, dark, r.t., 12h.



**Scheme 3.**(a) $BnOCH_2Cl$, LDA, THF, -78°C -r.t., 12h; (b) DIBAL, THF, r.t., 12h; (c) SAM II lipase, vinylacetate, r.t.; 12h; (d) (i) TBSCl, imid, $Et_3N$, $CH_2Cl_2$, r.t., 14h; (ii) $K_2CO_3$, MeOH, r.t., 4h; (e) (i) $SO_3$.py, DMSO, $Et_3N$, $CH_2Cl_2$, -5°C, 5h; (ii) $Ph_3PCH_2CH_2CH(OCH_2)_2$.Br, *n*-BuLi, THF, -78°C -r.t., 2.5h; (f) Raney-Ni EtOH, $H_2$, 80°C; (g) (i) tetrapropyl ammoniumperruthenaat, *N*-methylmorpholine *N*-oxide, $CH_2Cl_2$, MeCN, mol. sieves 4Å, r.t., 12h; (ii) $Ph_3P$=$CH_2$, THF, -78°C -r.t., 12h; (h) (i) TBAF, THF, r.t., 4h; (ii) TosCl, $CH_2Cl_2$, $Et_3N$, DMAP, r.t., 12h; (iii) LiI, THF, Δ, 12h; (i) sec-BuLi, -78°C, 0.5h, r.t. 30 min then $Et_3N$; (j) toluene, 140°C, 15h; (k) KF, MeOH, 0°C, 1h; (l) (i) n-BuLi, **4**, THF, -78°C -r.t., 15h; (ii) PTSA, $Me_2CO$, r.t., 12h; (m) (i) TESCl, imid, $CH_2Cl_2$, $Et_3N$, r.t., 4h; (ii) MeMgBr, $Et_2O$, r.t., 2h, (iii) PDC, $CH_2Cl_2$, r.t., 12h; (n) (i) MeMgBr, $Et_2O$, r.t., 2h; (ii) TBAF, THF, r.t., 1h.

*Route via the intramolecular Diels-Alder (IMDA) strategy.*

This strategy involves a precursor such as **8** in which the stereochemistry at C-17 and C-20 is fully established. This route has been well studied for the synthesis of the natural CD ring fragment and up to *circa* 60% d.e. in favour of the *trans*-fused *endo*-adducts was observed; this stereoselectivity largely depends on the C-17 substitution.[8,19] In the present case the nonatriene **30** is lacking the 18-methyl substituent and no prior information is available with respect to the resulting ring fusion of the adducts.

Nonatriene **29** was constructed starting from the known (l-menthyloxy)-butenolide **18**[20] (Scheme 3), which represents carbon atoms 16, 17, 20 and 22 of the vitamin D skeleton. As we planned to introduce first the 21-methyl group, **18** was transformed into the known **19** using a procedure described by Feringa *et al.*[20]

α-Alkylation, introducing C-12, from the less hindered *si*-face led exclusively to **20** which was subsequently reduced to the diol **21**. Differentiation of the hydroxy functions was easily performed *via* enzyme (SAM II lipase)[21] catalyzed chemoselective (96:4) mono-acetylation, affording **22** as the major isomer, which was then transformed into alcohol **23**.

We now turned our attention to the formation of the vitamin D side chain. While approaches involving nucleophilic displacements[19b] at C-22 failed, a viable route was found *via* Wittig olefination of the corresponding aldehyde (only the *Z*-isomer **24** was obtained). Hydrogenation of the double bond in **24**, with concomitant benzyl ether hydrogenolysis, led to alcohol **25** which was transformed *via* oxidation[22] and Wittig reaction into **26**, carrying the dienophilic double bond.

The reason for introducing a truncated side chain in **24** is based on the fact that this will allow us to synthesize also 18-nor analogues with side chain modifications *via* reactions with aldehyde **34**.

The remaining C-atoms of the skeleton were now introduced *via* treatment of iodide **27** with the anion of 3-triethylsilyloxy-1,4-pentadiene[23] **28** affording the α-adduct **29** next to the γ-adduct (ratio 8:2) which could be separated by preparative HPLC. The cycloaddition reaction of **29** was performed in toluene at 140°C, in a sealed tube (pretreated with base) for 15h affording an unseparable mixture (4:6; deduced from the $^1$H NMR) of **30** and **31** in 74% combined yield. The presence of **31** must result from proton catalyzed double-bond isomerization of the normal adduct. This has been observed before.[23,24] Upon standing for longer times the mixture gradually changes to solely **31**. *Trans*-fused **30** is indeed the thermodynamically least stable of the two isomers. Cleavage of the silyl enolether afforded a 2:3 unseparable mixture of the *trans*- and *cis*-fused hydrindanes **32** and **33**. Although the outcome of the intramolecular Diels-Alder reaction is uncertain with regard to the stereochemical outcome, the subsequent observations and the final synthesis of **2a** and the formation of **35** provide conclusive proof for the *trans*-fusion of **30**.

Lythgoe coupling[9] with **4** was carried out on the mixture, with the idea in mind that separation would be easy by the interplay of the well-known vitamin-previtamin equilibrium. The stability of the triene system in the vitamin D form is a consequence of conformational constraints imposed by the *trans*-fused 5-membered D ring on the C-ring.[25] Intrinsically the isomer with 3 *exo*-cyclic double bonds on 6-membered rings is thermodynamically less stable than the triene system of the previtamin form (2 endocyclic bonds). When a *cis*-fused hydrindane is present or when the D-ring is absent the triene system of the previtamin form is largely preferred and will be formed *via* the 1,7-sigmatropic shift.[26] Thus during the deprotection of the hydroxy- and carbonyl functions the coupling product of the *cis*-precursor **33** is transformed into the previtamin D analogue **35**, enabling us to obtain pure **34**. The yield for the two steps (l; 56%) is calculated from the amount of **32** present in the mixture.

Finally title compound **2a** was obtained by fully constructing the side chain *via* **36**, involving hydroxy group protection in **34**, MeMgBr treatment (2x) and an intermediate oxidation step.

Also analogues with a 20-(*S*) side chain could be obtained starting from the known enantiomer of **18.**[20] Evidently, this enantiomeric butenolide now represents carbon atoms 13, 17, 20 and 22, while α alkylation (compare **19** → **20**) provide C-16. This leads to the natural configuration at C-17; in fact the 20-*epimer* of triene **29** is thus obtained.

Full structural assignement is now possible as 1α,25-dihydroxy-18-norvitamin $D_3$ **2a** has been obtained by two routes. The first route ascertains the *trans*-fusion and the relative C-13, C-17 configuration while the C-20 and C-17 configurations are established from the IMDA approach. Furthermore the spectral data[27] of **2a** are in full accord with those described by Deluca *et al.*[5]

**Acknowledgement**. We thank the "FWO", the "Ministerie voor Wetenschapsbeleid" and Théramex S.A. for financial support to the laboratory.

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11. The expected regioselectivity was proven by the COSY spectra of **6** and **7**.
12. Although the C-8 configuration in **9** is of no consequence for the synthesis of **2a**, the equatorial position of the hydroxy group 15 was proven by $^1$H-NMR (500 MHz, $CDCl_3$): H-C-OH (3.24, br dt 4.2, 10.3 Hz). For the minor, axial alcohol: H-C-OH 3.78 (br s).

13. For product **6**: $^1$H-NMR (500 MHz, $CDCl_3$): 5.29 (1H, br s); 4.3 (1H, ddd, *J* = 10.0, 5.0, 5.0 Hz); 2.65 (1H, *app* t, *J* = 5.4 Hz); 2.5 (1H, m); 2.4 (1H, dddd, *J* = 10.0, 5.0, 5.0, 5.0 Hz); 2.29-2.30 (2H, m); 2.0 (2H, m), 1.97 (1H, m); 1.89 (1H, m); 1.73 (1H, *app* t, *J* = 14.9 Hz); 1.6 (3H, s); 0.88 (9H, s); 0.07 (6H, s).
*Anti-adduct:* H-5: 3.9 (*app* dd, *J* = 6.6, 3.4 Hz), 2.67 (td, *J* = 13.1, 6.8 Hz).
**7**: H-5: 3.91 (s), H-1: 2.58 (dt, *J* = 10.2, 6.45 Hz).
11-*nor*-**6**[7]: H-5: 4.31 (ddd, *J* = 10.0, 5.0, 5.0 Hz), H-1: 2.76 (*app* t, *J* = 5.5 Hz).
11-*nor anti-adduct*[7]: H-5: 3.91 (*app* dd, *J* = 6.4, 3.2 Hz), H-1: 2.69 (td, *J* = 13.1, 6.8 Hz).
11-*nor*-**7**[7]: H-5: 3.93 (bs), H-1: 2.68 (dt, *J* = 12.3, 8.2 Hz).
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27. **2a** Rf: 0.32 ($Me_2CO$:hexane 4:6). U.V. ($\lambda_{max}$, EtOH): 261 nm. I.R. (KBr, film): 3355, 2934, 2861, 1441, 1377, 1215, 1143, 1054, 909, 732 $cm^{-1}$. M.S. (m/z): 402 ($m^{+\cdot}$, 2), 384 ($m^{+\cdot}$- $H_2O$,10) 366 ($m^{+\cdot}$-2 x $H_2O$, 4), 348 ($m^{+\cdot}$-3 x $H_2O$, 2), 271 (4), 253 (7), 171 (23), 134 (100), 91 (48), 59 (94). $^1$H-NMR (360 MHz, $CDCl_3$): 6.37 (1H, d, *J* = 11.4 Hz); 6.08 (1H, d, *J* = 11.4 Hz); 5.32 (1H, br s); 5.02 (1H, s); 4.43 (1H, m); 4.21 (1H, m); 2.87 (1H, br d, *J* = 13.6 Hz); 2.61 (1H, dd, *J* = 3.4, 13.2 Hz); 2.30 (1H, dd, *J* = 7.3, 13.2 Hz); 2.01-1.93 (2H, m); 1.21 (6H, s); 0.87 (3H, d, *J* = 6.7 Hz).