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Synthesis of New Vitamin D_3 Analogues with a Decalin-type CD-Ring

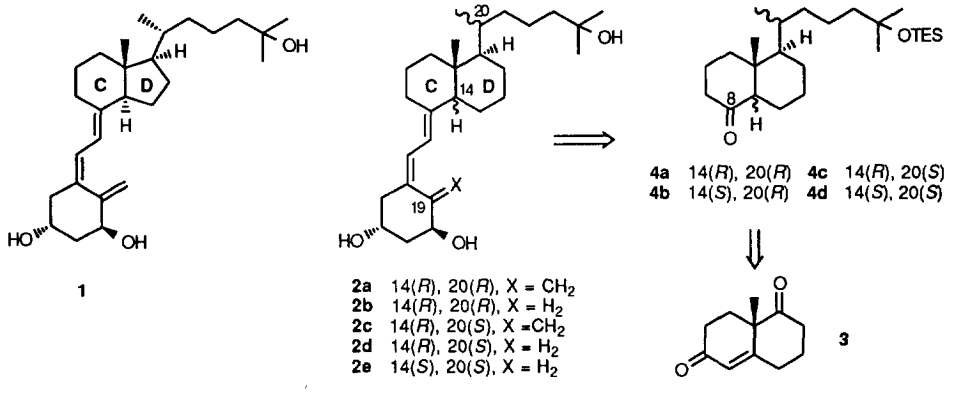
Yong-Jun Chen, Pierre De Clercq and Maurits Vandewalle*

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

Abstract : Vitamin D analogues, characterized by a decalin CD-ring fragment are described.

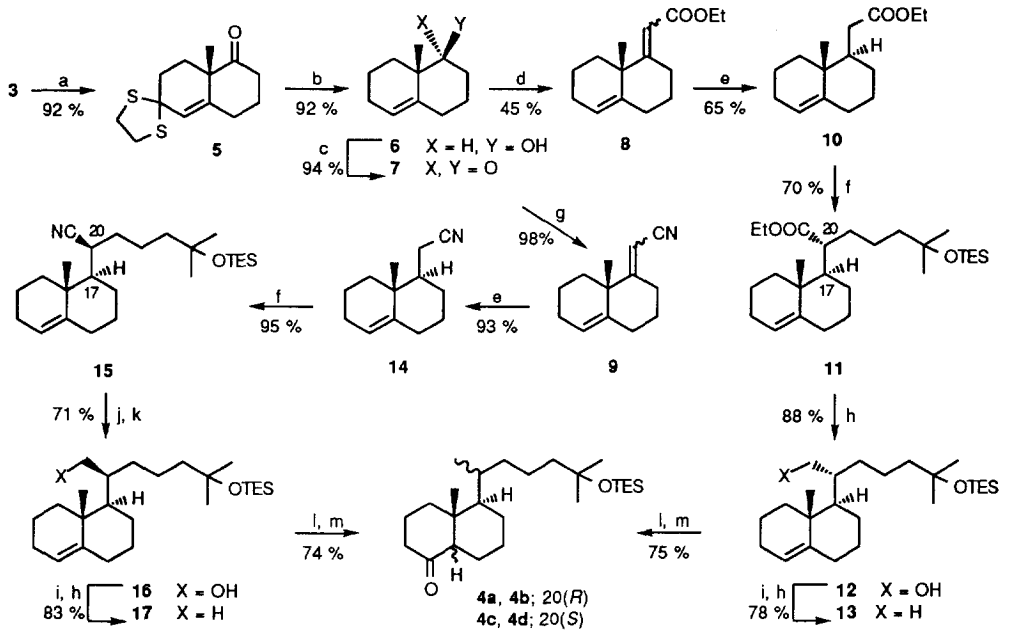
The observation that 1α,25-dihydroxy-vitamin D_3 (**1**; calcitriol) is active in the regulation of cell proliferation and differentiation, together with its classical role in calcium-bone homeostasis, has led in recent years to the development of analogues capable of dissociating cell differentiating 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]

Some years ago, we embarked on an extensive study of the structure-function relationship focussing on the least studied part of the molecule, i.e. the central CD-ring region.[4] In the present paper we want to describe the synthesis of analogues based on a decalin type CD-ring fragment. Next to the fundamental change of the natural hydrindane CD-ring fragment into a decalin system we also had the intention to combine this with other modifications, thus leading to analogues with general formula **2** (vitamine D_3 numbering). Indeed in the natural series, it has been shown that 19-nor analogues[5] as well as 20-*epi* analogues[6] can induce interesting differentiations between calcemic activities and new actions.[6] Furthermore next to *trans*-fused decalin analogues we also envisaged the synthesis of members of the *cis*-fused series for biological evaluation.



Scheme 1

The starting material is the (*S*)-Wieland-Miescher ketone **3** which was obtained in enantiopure form by the modified Hajos-Parrish procedure (scheme 1).[7] Transformation into the 8-oxo-intermediate **4** will involve (i) removal of the keto function, (ii) hydroboration of the double bond, and (iii) elaboration of the side chain. The most efficient sequence is depicted in scheme 2.



(a) 1,2 ethanedithiol (1.1 eq), PTSA, HOAc, r.t., 5 h; (b) Na, *liq*.NH_3, -78°C → 30°C, 4 h; (c) SO_3.py, py, r.t., 12 h; (d) $(EtO)_2POCH_2COOEt$ (6 eq), KHMDS, -78°C, 5 d; (e) Mg, dry MeOH, r.t., 12 h; (f) $Br(CH_2)_3CMe_2OTES$, THF, LDA, -78°C → 0°C, 10 h; (g) $(EtO)_2POCH_2CN$, (4 eq) $NaNH_2$, THF, r.t., 12 h; (h) $LiAlH_4$, Et_2O, r.t.; (i) TsCl, py, 0°C, 14 h; (j) DIBAL, hexane, -78° → 0°C, 12 h then $(COOH)_2$, H_2O_2 (pH = 4) 0°C, 1 h; (k) DIBAL, hexane, -78°C → 0°C, 6 h; (l) BH_3.THF, THF, 0°C → r.t., 14 h, then 3N NaOH, H_2O_2 (30 %); (m) PDC, CH_2Cl_2, r.t., 14 h.

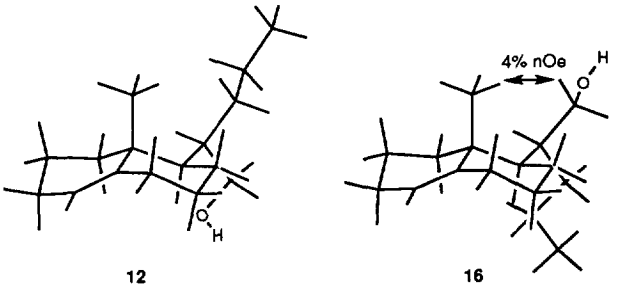
Scheme 2

Selective dithioketalization[8] of **3** gave **5** which was desulfurized to **6** with sodium in *liq.* ammonia. Subsequent oxidation then afforded **7** which upon Horner-Emmons-Watson reaction with ethyl diethylphosphonoacetate led to **8**, albeit in low yield (which is often a common problem with hindered cyclohexanones).[9,10] Alternatively the use of the less steric demanding diethyl cyanomethylphosphonate gave **9** in an excellent yield.[11] Selective reduction[12] of the conjugated double bond in **8** and **9** afforded respectively **10** and **14** (88-86 % de).[13] In the case of **14** flash chromatography allowed purification and the structure was confirmed by n.O.e., (4.2% enhancement was observed between the angular methyl group and one of cyanomethylene protons), while for **11**, purification was possible only after reduction to **12**.

In analogy with Wicha's observation[14] in steroids, stereoselective alkylation of the enolate anion of **10** provided **11** with 88 % d.e.. The structural assignment of **11** was confirmed at the stage of alcohol **12** (*vide infra*). However, when the enolate anion of **14** was alkylated (90 % d.e.), we observed that, after the two-step reduction to the alcohol, the major isomer obtained was not identical to **12** but rather its 20-epimer **16**.

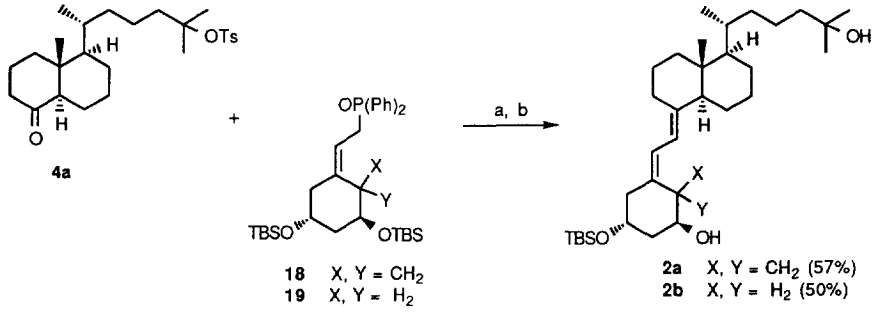
The relative configurations of **12** and **16** were assigned on the basis of Macromodel calculations[15] and n.O.e. experiments. In epimer **16** a 4 % n.O.e. enhancement was observed between one of the 21-hydroxymethyl protons and the angular methyl group while no enhancements were found for **12**. This is consistent with the calculated side chain geometries for both **12** and **16** (scheme 3). This result indicates that the alkylation of the enolate anion of **14** has proceeded with the opposite stereoselectivity to yield **15**. Indeed

epimerization at C-20 of the expected[14] alkylated product 20-*epi*-**15** can be excluded since the epimeric ratio of the intermediate aldehyde and of **16** remained practically identical to the % d.e. of the starting cyanide **15**.



Scheme 3

Reductive removal of the hydroxy group, via the tosylate, in **12** and **16** led respectively to **13** and **17**. Finally *syn*-hydroxylation of the double bond led in both cases to a *circa* 2:1 mixture of *cis* and *trans*-fused decalins, which upon oxidation of the hydroxy group led to separable mixtures of respectively **4a**, **4b** (from **13**) and **4c**, **4d** (from **17**).[16] This gave us access to the thermodynamically less stable *cis*-fused CD precursor for coupling with the A-ring. Base induced equilibration of the 14-epimeric mixtures allowed us to produce the more stable *trans*-fused precursors (ratio 10:1) **4a** and **4c** in good overall yield.



Scheme 4

Construction of the title compounds **2** involves the Lythgoe[17] coupling of intermediates **4** with the A-ring phosphine oxides **18**[18] (natural A-ring) and **19**[5] (19-nor A-ring) (scheme 4). The yields of the coupling of the *trans*-fused intermediates **4a** and **4b** (range 40-68 %) were lower than normally observed when the natural hydrindane CD fragment is involved (*circa* 85-90 %). This could be due to a more severe steric hindrance exerted by the cyclohexane D ring. Finally deprotection gave the analogues **2a,b,c,d**. Reaction of the *cis*-fused decaline precursor **4d** with **19** gave **2e** in an even lower yield (7 %) again indicating the influence of the nature of the C-8 ketone on the Lythgoe coupling.

The synthesis of decalin type vitamin D analogues having non-natural side chains *via* initial methylation of intermediates **10** and **14** and using the ester or cyanide function for elaborating the side chain is in progress. The remarkable difference in alkylation of **10** and **14** is presently evaluated for side chain construction in

steroids (see ref 14). Results of the biological activities will be published elsewhere; several analogues show interesting differentiations between calcemic activities and new actions.

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16. Selected analytical data (^{1}H NMR in $CDCl_3$ at 500 MHz without TES signals) : **4a** (**14*R*,20*R***) d : 2.3 (2H, dd, J = 9.5, 4.6 Hz); 2.13 (1H, dd, J = 12.2, 2.8 Hz); 2.05 (1H, ddd, J = 13, 3.0, 3.0 Hz); 1.98 (1H, m); 1.84 (2H, m); 1.73 (1H, m); 1.6 (1H, m); 1.44 (4H, m); 1.31 (4H, m); 1.17 (6H, s); 1.16 (3H, m); 0.92 (3H, d, J = 7.9 Hz); 0.75 (3H, s) ppm. $[a]_D^{20}$ +4.6 (c 0.89, $CHCl_3$).
4b (**14*R*,20*R***) d : 2.38 (1H, dddd, J = 14.9, 4.48, 2.27, 2.27 Hz); 2.23 (1H, m); 2.07 (3H, m); 1.79 (2H, m); 1.63 (1H, m); 1.57 (1H, m); 1.44 (6H, m); 1.34 (4H, m); 1.22 (1H, m); 1.18 (6H, s); 1.12 (3H, s); 0.87 (3H, d, J = 6.8 Hz) ppm. $[a]_D^{20}$ +39.06 (c 0.43, $CHCl_3$).
4c (**14*R*,20*S***) d : 2.29 (2H, dd, J = 9.2, 4.6 Hz); 2.15 (1H, dd, J = 12.0, 2.89 Hz); 2.02 (1H, ddd, J = 13.8, 3.3, 3.3 Hz); 1.98 (1H, m); 1.85 (2H, m); 1.77 (1H, dd, J = 13.9, 7.1 Hz); 1.61 (1H, m); 1.39 (7H, m); 1.29 (2H, m); 1.2 (6H, s); 1.19 (3H, m); 0.77 (3H, d, J = 6.9 Hz); 0.76 (3H, s) ppm. $[a]_D^{20}$ -10.2 (c 0.96, $CHCl_3$).
4d (**14*S*,20*S***) d : 2.37 (1H, m); 2.23 (1H, m); 2.05 (3H, m); 1.8 (2H, m); 1.68 (1H, dd, J = 13.6, 6.82 Hz); 1.56 (2H, m); 1.42 (8H, m); 1.26 (2H, m); 1.17 (6H, s); 1.15 (1H, m); 1.13 (3H, s); 0.77 (3H, d, J = 6.8 Hz) ppm. $[\alpha]_D^{20}$ +24.3 (c 0.22, $CHCl_3$).
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