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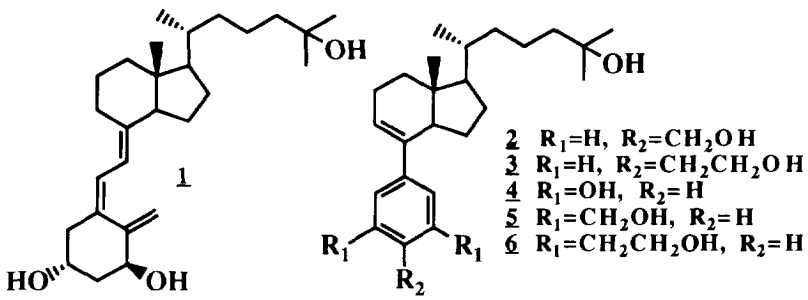
A Novel Class of Vitamin D Analogs Synthesis and Preliminary Biological Evaluation

Silvia Kanzler[a], Sebastian Halkes[b], Jan Paul van de Velde[b], Wolfgang Reischl[a]*

[a] Department of Organic Chemistry, University of Vienna, A-1090 Vienna, Austria
fax: +431313672280, e-mail: a8401dam@helios.edvz.univie.ac.at
[b] Solvay Duphar BV, 1380 DA Weesp, The Netherlands

Abstract: The vitamin D analogs **2**-**6** in which the triene system and the A-ring are replaced by an aromatic ring have been synthesized and their biological properties investigated. Copyright © 1996 Elsevier Science Ltd

The steroid hormone 1α, 25-dihydroxy vitamin D_3 (calcitriol, **1**) plays a central role in the triggering of the calcium homeostasis through specific action with a nuclear receptor [1]. Moreover it has been shown that 1α, 25 $(OH)_2$ vitamin D_3 is a potent inducer of the differentiation of human leucemia cells [2], epidermal keratinocytes [3] and several types of cancer cells [4] as well as a factor influencing the immune response of lymphocites [5]. These findings make this steroid hormone and its analogs potential candidates for the treatment of various diseases like cancer, psoriasis and immune disorders. Due to the high calcemic activity of 1α, 25$(OH)_2$ vitamin D_3, many analogs have been designed with a view to keep the molecule differentiating properties and have no or little bone calcemic activity. Promising results in this respect have been achieved through structural variations in the side chain [6]. With only one exception (19-nor-1α, 25 $(OH)_3$ vitamin D_3 [7]) up to now, analogs possessing a modification in the triene part of the molecule have shown no promising potential biological properties.

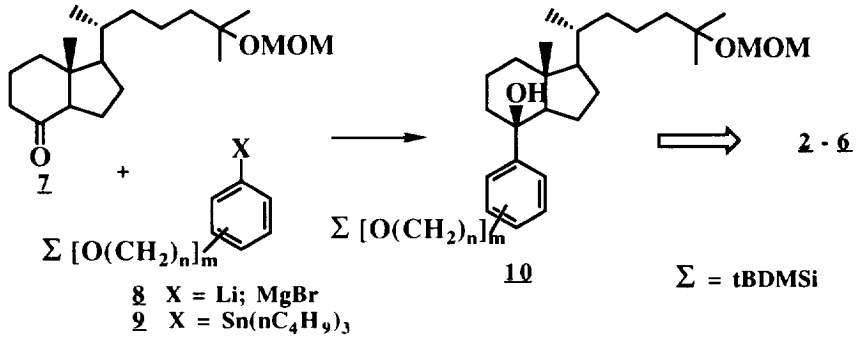


2 R_1=H, R_2=CH_2OH
3 R_1=H, R_2=CH_2CH_2OH
4 R_1=OH, R_2=H
5 R_1=CH_2OH, R_2=H
6 R_1=CH_2CH_2OH, R_2=H

Very recently a publication by Posner et al. [8] appeared in which the synthesis and biological results of a new class of vitamin D analogs is described. This publication urges us to disclose the results of our

research in a very related field of compounds. In this class the triene system and the A-ring are replaced by an aromatic ring system. Replacing the highly flexible seco triene moiety with a rigid benzene ring freezes the conformational mobility, but still keeps a certain π-electron density in this part of the molecule, which may be necessary in the stabilisation of the ligand-receptor interaction through π – π - or CH - π interactions [9]. Hydroxyl bearing sidechains are attached to the aromatic nucleus to simulate the positions of the 1 α- and 3β-hydroxyl groups in **1**, but in such a way to keep a local c2 symmetry in that part of the analogs.

The original strategy was to couple protected 25 hydroxy Grundmann's ketone **7** with organometallic reagents of type **8** to give the carbinols **10** which upon subsequent dehydration should give the target compounds **2** - **6**. Fragment **7** can be easily synthesized by the following well established literature procedures.

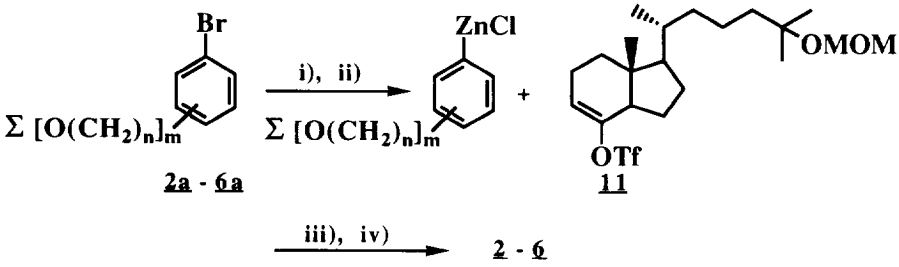


Starting from Grundmann's alcohol, generated via a three step degradation sequence [10] from vitamin D_3, the 25 hydroxy group has been introduced by $RuCl_3/NaIO_4$ oxidation [11]. Protecting the 25-hydroxy with MOM-chloride makes **7** readily available. The aromatic fragments were either commercially available or were synthesized from commercially available bromo-toluenes or bromo-xylenes through side chain bromination and subsequent hydrolysis to the bromo-benzylic alcohols [12]. Sidechain extensions were achieved in a conventional way (nucleophilic displacement of the benzylic bromides with NaCN, conversion to the ethylester (EtOH, H_2SO_4, reflux) and subsequent LAH reduction to the corresponding alcohols [13]). All lower part fragments were used as their tBDMSi-protected derivatives.

To our surprise addition of the lower part reagents (by a Li-reaction as well as by a Grignard-reaction) to **7** was sluggish and the carbinols **10** were produced only in very low yields . Therefore this approach was abandoned.

As an alternative route we turned our attention toward combining the two fragments by standard Stille techniques [14] using enoltriflate **11** [15] and the corresponding organostannanes **9** of the aromatic fragments. Unfortunately this methodology and its variants [16] produced the desired compounds only in very low yields (5 - 12%). Therefore we developed a new protocol for the coupling of an aromatic moiety with an enol triflate. After transmetallation of the aromatic lithium compounds with $ZnCl_2$ and adding Ph_3As as a co-ligand to the Pd_2dba_3 catalyst the coupling proceeded smoothly in yields between 75 -94 % depending on the substitution pattern of the lower part fragment. For a typical procedure see [17]. The

vitamin D analogs **2**-**6** were readily obtained by using this technique followed by deprotection (Dowex-50W/MeOH).



i) 2 eq. t.BuLi, THF, -78°C; ii) $ZnCl_2$; iii) 9 in DMF, $Pd_2(dba)_3$, Ph_3As; iv) Dowex-50W, MeOH

From the compounds tested for the affinity towards the highly selective calf thymus vitamin D receptor (VDR) [18] compounds **2** and **5** showed an affinity respectively 3 and 6 times higher than that of calcitriol itself. Also the compounds **3** and **6** demonstrated a high affinity towards the VDR, although somewhat lower than calcitriol. In the vitamin D binding protein assay (DBP) [19] compounds **2**, **3** and **5** proved also to be relatively good binders; binding is a factor 2 - 10 times less than calcitriol itself. This indicates that these compounds might have systemic activity.

A full account of this work including detailed biological data will be published elsewhere.

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17. representative procedure and spectroscopic data:
The TBDMSi-protected lower part fragment 2-(p-bromophenyl)-ethanol is dissolved in dry THF, cooled to -78°C and treated with 2 equiv. of tert.-BuLi. After 0.5h a dry THF solution of 1 equiv. $ZnCl_2$ is introduced and stirring is continued for another 15 minutes. By double ended needle technique a solution of **11** (1.1 equiv.), Pd_2dba_3 (5 mol%) and Ph_3As (10 mol%) in dry DMF is introduced. The progress of the reaction is monitored by TLC. After work up and flash-chromatography protected **3** is isolated in 88% yield. Complete deprotection is done in dry methanol with DOWEX-50W at RT.
Spectral data of **3**:
^{1}H-NMR (400 MHz): δ= 7.08 (d, J=8.4 Hz, 2H, arom.H), 7.05 (d, J=8.4 Hz, 2H, arom.H), 5.55 (dd, J= 3.4 Hz, 6.4 Hz, 1H, 9-H), 3.78 (t, J=6.4 Hz, 2H), 2.78 (t, J=6.4 Hz, 2H), 2.51 (m, 1H), 2.20 (m, 2H), 1.99 (m, 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.15 (s, 6H, 26-H_3, 27-H_3), 0.93 (d, J=6.4 Hz, 3H, 21-H_3), 0.69 8s, 3H, 18-H_3). - ^{13}C-NMR (400MHz): δ = 141.28 (C-8), 140.12 (arom.C), 138.08 (arom.C), 128.42 (arom.C), 127.09 (arom.C), 124.83 (C-9), 71.09 (C-25), 63.65 (CH_2OH), 54.43 (C-14), 49.97 (C-17), 44.40 (C-24), 42.67 (C-13), 38.85 (CH_2), 36.42 (C-22), 3 6.17 (C-20), 36.02 (C-12), 29.35 (C-26); 29.18 (C-27), 28.35 (C-16), 25.03 (C-11), 24.47 (C-15), 20.83 (C-23), 18.81 (C-21), 11.27 (C-18).- IR (neat): ν= 3350 cm^{-1}, 2960, 1649, 1511, 1468, 1378, 1261, 1150, 1045, 908, 821. - MS (70 eV; 120°C): m/z(%) = 384 (M^+, 97), 366 (21), 351 (17), 255 (10), 253 (20), 237 (24), 211 (41), 183 (53), 168 (15), 143 (26), 107 (15), 105 (16), 91 (15.6), 81 (21), 59 (28), 43. (100). - $C_{26}H_{40}O_2$ calc.: 384.3028 found: 384.3026 ± 0.003
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