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Design and Synthesis of a 1α,25-Dihydroxyvitamin D_3 Dimer as a Potential Chemical Inducer of Vitamin D Receptor Dimerization

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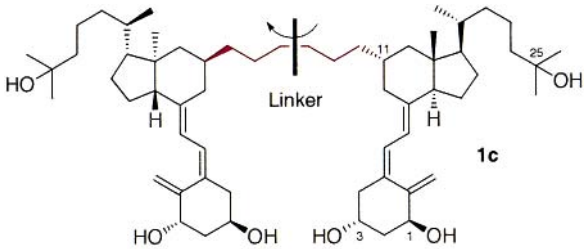
ABSTRACT



Dimeric1α,25-$(OH)_2$-vitamin D_3 (**2**)

A dimer comprising two 1α,25-dihydroxyvitamin D_3 units linked by an alkyl side chain at C-11 was synthesized with a view to the simultaneous binding of two vitamin D receptor (VDR) molecules and the consequent induction of VDR dimerization. The short, convergent synthesis uses a stereoselective cuprate addition to introduce the linking side chain and a key ruthenium olefin metathesis as the dimerization step.

1α,25-Dihydroxyvitamin D_3 (calcitriol, **1c**) (Figure 1), the hormonally active form of vitamin D_3 (**1a**),[1] besides regulating the metabolism of calcium and phosphorus, promotes cell differentiation, inhibits the proliferation of tumor cells, and induces some biological functions related to the immune system.[2] Calcitriol acts in the cell nucleus by binding to the vitamin D receptor (VDR), a member of the nuclear receptor superfamily that can interact with DNA as a homodimer (VDR−VDR) or a heterodimer with the retinoid X receptor (VDR−RXR).[3] The role of dimeric VDR structures in activation of gene transcription is not clear.

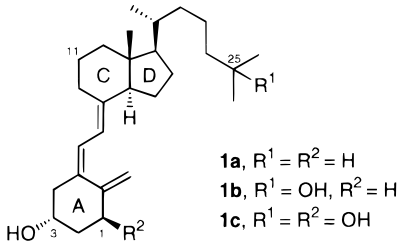


Figure 1. Vitamin D_3, 25-(OH)-D_3, and 1α,25-$(OH)_2$-D_3.

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(1) Vitamin D_3 is transformed to 1α,25-$(OH)_2$-D_3 (**1c**) through 25-(OH)-D_3 (**1b**) by two specific enzymatic hydroxylations.

(2) For a general review of vitamin D chemistry and biology, see: (a) *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds; Vitamin D Workshop, Inc.: Riverside, CA, 1997. (b) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

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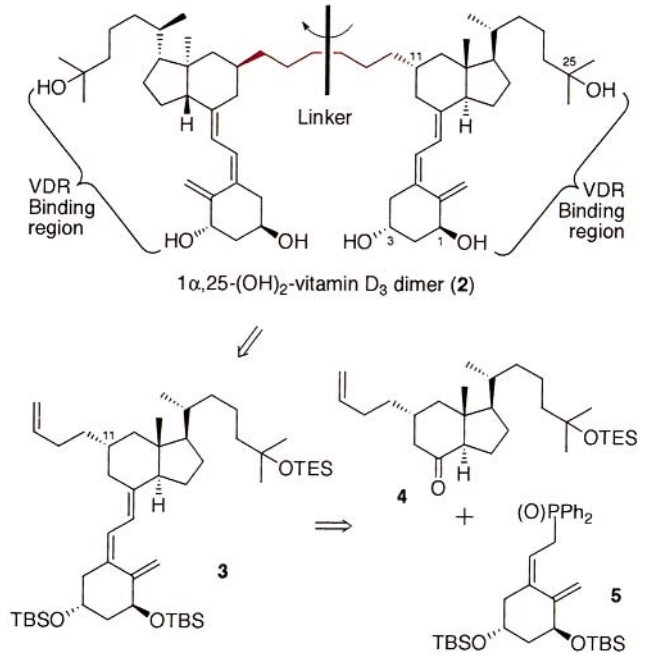
Recently, it has been found possible to influence many cell processes involving proteinic receptors by means of dimeric molecules with two protein-binding regions, which can act by facilitating the dimerization of the ligand receptor and have become known as chemical inducers of dimerization (CIDs).[4] This effect is based on the importance that proximity and orientation have in the protein function during the information transfer process. The few CIDs that have been synthesized to date include the dimers of the immunosuppressive agents FK506 (FK1012) and cyclosporin A [$(CyA)_2$].[5] In this Letter we describe the synthesis of the first calcitriol dimer, which we designed to bind two molecules of VDR and hence, hopefully, facilitate the formation of VDR−VDR dimers with a view to the exploration and possible exploitation of their role in transcription control.

The design of the calcitriol dimer took into account the fact that the triene system and the hydroxyl groups at positions 1α and 25 are crucial for the biological activity of calcitriol[6] and that the incorporation of new functional groups alters its biological activity dramatically.[3,7] These considerations, and the absence of other functional groups in the vitamin D structure, ruled out direct dimerization, and we therefore decided to construct a molecule consisting of two calcitriol moieties linked by an alkyl chain attached to each calcitriol at ring C, which is probably the least active part of the vitamin D structure (Scheme 1). Specifically, we aimed

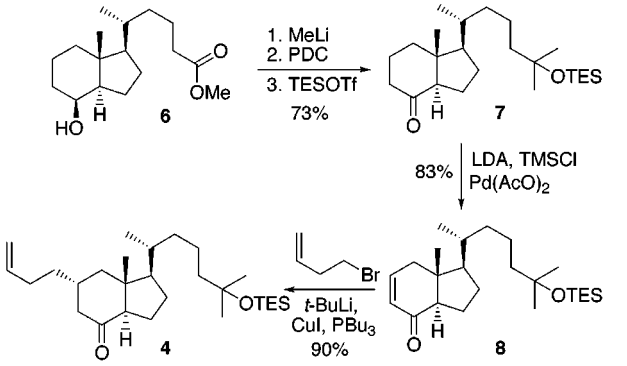
Scheme 1. Retrosynthetic Analysis



to obtain dimer **2** by dimerization of the alkenylic vitamin D analogue **3** using an olefin metathesis reaction.[8] The retrosynthetic analysis includes the formation of **3** from ketone **4** and phosphine oxide **5** using the Wittig−Horner approach[9] and the introduction of the olefinic side chain by cuprate chemistry.[10]

The synthesis of **3** starts with known ester **6**.[11] Addition of MeLi (3 equiv), followed by oxidation with PDC and protection with TESOTf at −78 °C, afforded ketone **7** (73%, three steps) (Scheme 2). Treatment of **7** under Saegusa

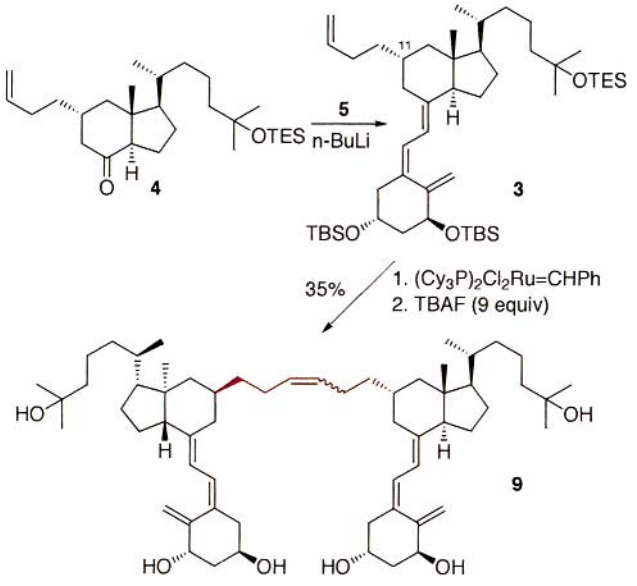
Scheme 2. Synthesis of Ketone **4**



reaction conditions,[12] followed by reaction of the resulting enone **8** with the cuprate derived from 4-bromobutene, gave **4** in 90% yield as the only diastereoisomer detected by ^1H NMR spectroscopy.

Formation of the vitamin D triene system was achieved in 87% yield by the reaction between ketone **4** and the ylide derived from phosphonium oxide **5** containing ring A,[13] to give the protected vitamin D analogue **3** (Scheme 3). Olefin

Scheme 3. Synthesis of Vitamin **3** and Dimerization



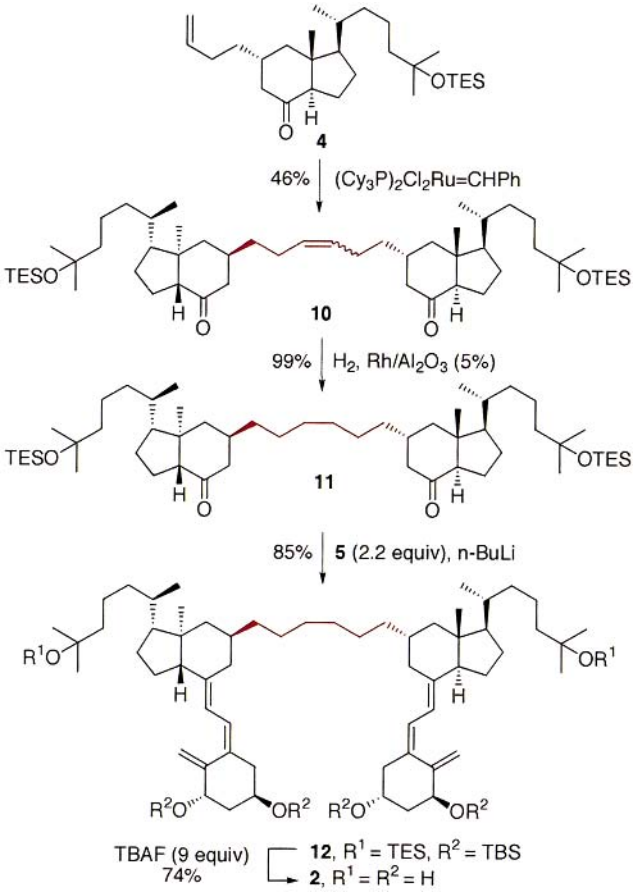
metathesis of **3** with Grubbs's catalyst[14] (10 mol %) in CH_2Cl_2 at room temperature afforded, after 4 h, an inseparable mixture of **3** and its dimer with loss of ethylene.

(3) Freedman, L. P.; Lemon, B. D. In *Vitamin D*; Feldman, D., Glorieux, F. H., Pike, J. W., Eds.; Academic Press: San Diego, 1997; Chapter 9, pp 127−148.

Treatment of the mixture with TBAF in THF allowed the isolation of dimer **9** as a 5:1 mixture of alkene isomers (35%) and deprotected vitamin **3** (52%). Remarkably, the olefin metathesis does not affect the triene system. Unfortunately, attempts to obtain calcitriol dimer **2** by chemoselective hydrogenation of the nonconjugated double bond led to the fully saturated dimer.

To circumvent this problem we decided to carry out the olefin metathesis reaction and hydrogenation before construction of the triene system. Treatment of olefinic ketone **4** with catalytic amounts of $(Cy_3P)_2Cl_2Ru{=}CHPh$[14] (10 mol %) provided dimeric ketone **10** as a mixture of alkene isomers (6:1) in 46% yield together with recovered starting ketone (50%) (Scheme 4). Catalytic hydrogenation of the olefinic mixture **10** for 12 h at atmospheric pressure using a rhodium catalyst gave dimeric ketone **11** in quantitative yield. Treatment of **11** with the ylide derived from phosphonium oxide **5** (2.2 equiv) led to stereoselective formation of protected calcitriol dimer **2a** in excellent yield (85%). Removal of the six silyl groups with TBAF in THF (rt, 24 h) afforded the desired calcitriol dimer **2** in 74% yield.

Scheme 4. Synthesis of Calcitriol Dimer **2**



In conclusion, we have prepared the first dimer containing two calcitriol moieties, in each of which the VDR-binding region is unobstructed. The synthesis is short and convergent and should allow the preparation of an entire family of dimeric vitamin D structures. The length of the linker could be modulated to optimize binding with the receptor and the biological response associated with the binding of two VDR molecules. Biological evaluation of dimer **2** in terms of its VDR binding, dimerization induction capacities, and influence on signal transduction mechanisms are currently underway.

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Supporting Information Available: Complete characterization data (^{1}H NMR and ^{13}C NMR and mass spectral data) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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