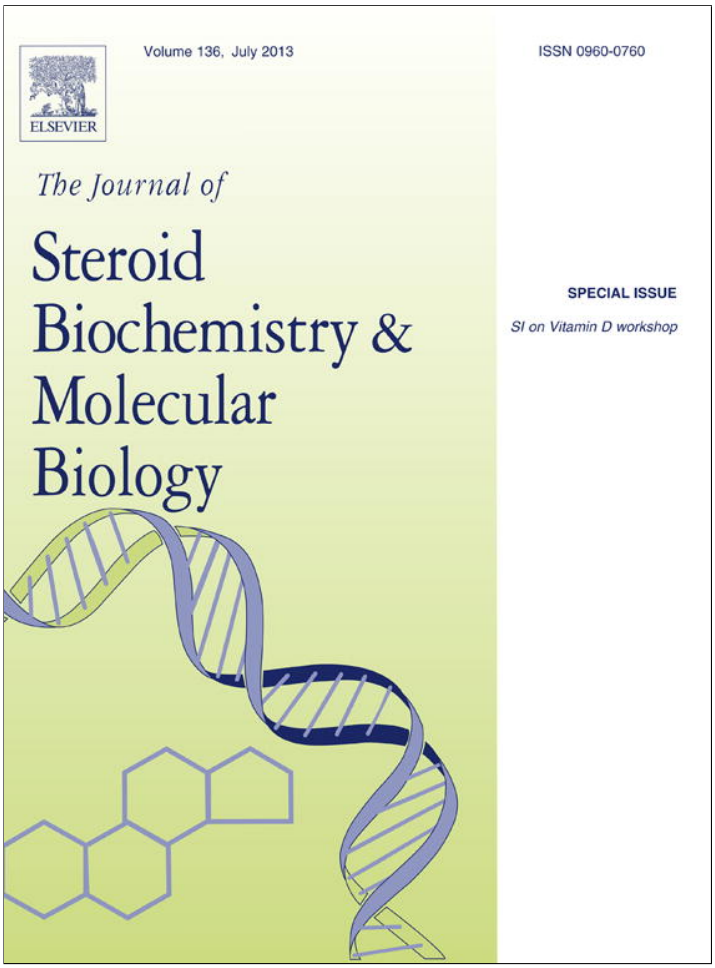

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Review

An efficient synthesis of 1α,25-dihydroxy-20-*epi*-vitamin D_3

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ABSTRACT

The synthesis of 1α,25-dihydroxy-20-*epi*-vitamin D_3 (**1**) by Pd(0)-catalyzed coupling between the boronate ester (**2**) and the enol triflate (**3**) is described.

This article is part of a Special Issue entitled 'Vitamin D Workshop'.

Contents

1. Introduction

Vitamin D_3 is not a real vitamin because it can be produced in the skin by sunlight irradiation of 7-dehydrocholesterol. Vitamin D_3, before eliciting its biological activity, must be hydroxylated to 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], the hormonally active form of vitamin D_3, that interacts with the vitamin D nuclear receptor (VDR) to control important biological functions such as mineral homeostasis, cell differentiation, cell proliferation, cell grow, apoptosis and the immune system [1]. The fact that VDR has been found in more than 30 target tissues and cell tumors has led to the consideration that 1α,25$(OH)_2D_3$is involved in a wider array of biological functions including cancer prevention [1–4]. During the past few years, a new class of analogues of 1α,25$(OH)_2D_3$characterized by a C20-*epi*-methyl group has been identified as potent inhibitors of cell proliferation and inducers of cell differentiation. Among these analogues, 1α,25-dihydroxy-20-*epi*-vitamin D_3 [**1**, 1α,25$(OH)_2$-20-*epi*-D_3], also known as MC1288, is several orders of magnitude more potent than the natural hormone in inhibiting cell growth and inducing cell differentiation with relative low calcemic effects [5,6]. Crystal structure analysis of the VDR in complex with 1α,25$(OH)_2$-20-*epi*-D_3 (**1**) suggests that ligand-VDR complex exhibits higher stability and longer half-life contributing to prolonged biological activity [7]. It has been found that 1α,25$(OH)_2$-20-*epi*-D_3 (**1**) induces the expression of retinoic acid receptor-β and $p21^{Cip1}$ and down-regulates the expression of cyclin D1 resulting in decreased phosphorylation of retinoblastoma protein (pRB) [7] (Fig. 1).

A few syntheses of 1α,25$(OH)_2$-20-*epi*-D_3 (**1**) have been carried out in the past following the biomimetic classical route or using triene-containing precursors and mainly they were published in patents [8]. Also in 2000 Takayama et al. described a convergent synthesis using Trost's method (palladium-catalyzed coupling of the A-ring enyne synthon with the CD-ring portion) [9].

We disclose here a short and practical synthesis of 1α,25$(OH)_2$-20-*epi*-D_3 (**1**) that involves the construction of the triene system by palladium(0)-catalyzed coupling between the boronate ester **2** and the enol triflate **3** (Fig. 2) following the convergent strategy recently developed in our laboratory [10].

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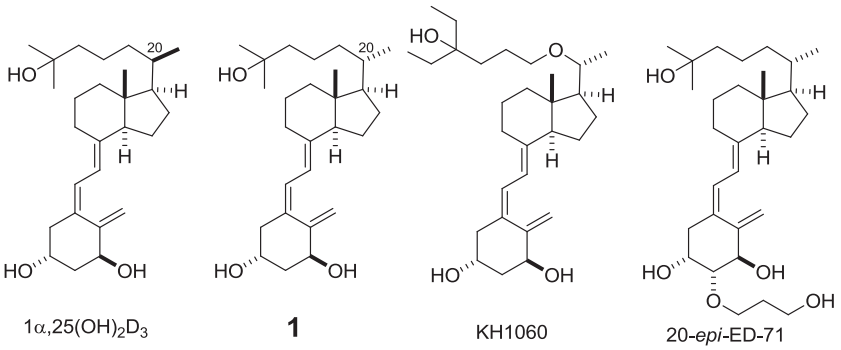

Fig. 1. Chemical structures of hormone 1α,25(OH)$_2$D$_3$ (calcitriol) and C20 analogues: 1α,25(OH)$_2$-20-*epi*-D$_3$ (**1**), KH1060 and 20-*epi*-ED-71.

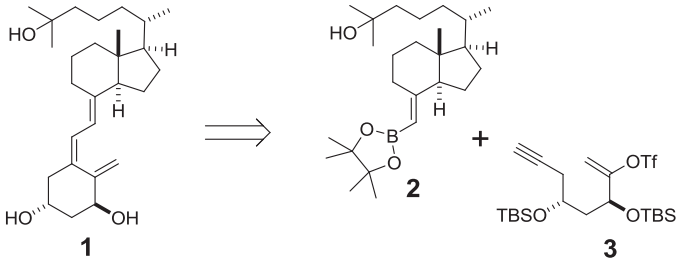

Fig. 2. Retrosynthetic analysis.

2. Results and discussion

The synthesis of the target 1α,25(OH)$_2$-20-*epi*-D$_3$ (**1**) starts with Inhoffen-Lythgoe diol **4** (Fig. 3), which can be prepared in 85% yield from vitamin D$_2$ [11a]. Alcohol **4** was converted to 20-*epi*-alcohol **5** by the sequence: silylation, selective desilylation, oxidation to the aldehyde, base-epimerization of C20 and reduction to alcohol **5** [9,11]. Alcohol **5** was converted to iodide **6** in 95% yield [12]. Sonication of a mixture of iodide **6** and methyl acrylate in the presence of $NiCl_2{\cdot}6H_2O$ and Zn in pyridine provided ester **7** in 88% yield [13]. Methylation of ester **7** with methylmagnesium bromide followed by deprotection with aqueous hydrofluoric acid gave diol **9**, which was oxidized with pyridinium dichromate to produce ketone **10** in 85%. Wittig reaction of **9** with the ylide $Ph_3P{=}CHBr$ afforded the alkenyl bromide **11** (80%), which was treated with bis(pinacolato)diboron in the presence of (dppf)$PdCl_2{\cdot}CH_2Cl_2$ complex as catalyst and tricyclohexylphosphine as ligand to give alkenyl boronate **12** in 80% yield. Aqueous K_3PO_4 (2 M) and $(Ph_3P)_2PdCl_2$ (5 mmol%) were successively added to a solution of boronate **12** (1 equiv) and enol triflate **3** (1.2 equiv) to give, after deprotection with aqueous hydrogen fluoride, the 1α,25-dihydroxy-20-*epi*-vitamin D$_3$ (**1**), in 75% yield (14% overall yield from Inhoffen-Lythgoe diol) [14].

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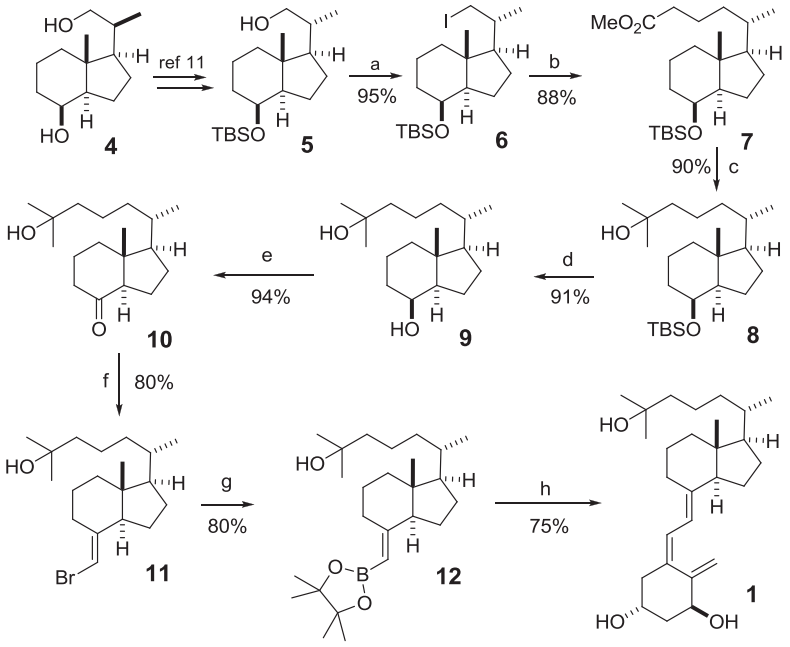

Fig. 3. Synthesis of 1α,25(OH)$_2$-20-*epi*-D$_3$. (a) I$_2$, Ph$_3$P, Im, THF; (b) $NiCl_2{\cdot}6H_2O$, Zn, Py, methyl acrylate, rt, 3 h; (c) MeMgBr, THF, 0 °C; (d) HF (48%), CH_3CN; (e) PDC, CH_2Cl_2; (f) Ph_3PCH_2Br, KO^{t}Bu, toluene, −5 °C → rt; (g) B_2Pin_2 (2 equiv), (dppf)$PdCl_2{\cdot}CH_2Cl_2$ (3 mol%), Cy_3P (3 mol%), KOAc (3 equiv), DMSO, 80 °C; (h) **3**, $(Ph_3P)_2PdCl_2$ (5 mol%), K_3PO_4 (2 M aq), THF, rt, 1 h; then HF (48%), CH_3CN.

References

[1] R. Bouillon, A.W. Norman, J.R. Pasqualini (Eds.), Proceedings of the 14th Workshop on Vitamin D, Journal of Steroid Biochemistry and Molecular Biology 121 (2010) 1–478, and the previous 13 volumes in this series.

[2] D. Feldman, J.W. Pike, J.S. Adams (Eds.), Vitamin D, 3rd ed., Academic Press, New York, 2011.

[3] R. Vieth, The mechanism of vitamin D toxicity, Bone 11 (1990) 267–272.

[4] A.J. Brown, A. Dusso, E. Slatopolsky, Selective vitamin D analogs and their therapeutic applications, Seminars in Nephrology 14 (1994) 156–174.

[5] L. Binderup, S. Latini, E. Binderup, C. Bretting, M. Calverley, K. Hansen, 20-*epi*-Vitamin D_3 analogues: a potent class of potent regulators of cell growth and immune response, Biochemical Pharmacology 42 (1991) 1569–1575.

[6] F.J. Dilworth, M. Calverley, H.L. Makin, G. Jones, Increased biological activity of 20-*epi*-1α,25-dihydroxyvitamin D_3 is due to reduced catabolism and altered protein binding, Biochemical Pharmacology 47 (1994) 987–993.

[7] K. Gumireddy, N. Ikegaki, P.C. Phillips, L.N. Sutton, C.D. Reddy, Effect of 20-*epi*-1α,25-dihydroxyvitamin D_3 on proliferation of human neuroblastoma: role of the cell cycle regulators and the Myc-ID2 pathway, Biochemical Pharmacology 65 (2003) 1943–1955.

[8] (a) M. Calverley, E. Binderup, Preparation of vitamin D analogs, PCT Int. Appl., WO9100271A1 (1991).;
(b) H. DeLuca, J. Wicha, Method of treating hypoparathyroidism with (20S)-vitamin D_3 compounds, US 5552392 A (1996).;
(c) T. Takahashi, I. Tsuchiguro, Preparation of vitamin D derivatives, Jpn. Kokai Tokkyo Koho, JP 2001329066 A (2001).;
(d) H. Kashiwagi, Y. Ono, Process for the synthesis of vitamin D compounds and intermediates for the synthesis of the compounds, PCT Int. Appl., WO 2005074389 A2 (2005).;
(e) A. Bridges, Efficient process for preparing steroids and vitamin D derivatives with the unnatural configuration at C20 (20 alpha-methyl) from pregnenolone, U.S. Pat. Appl. Publ., US 20080171728 A1 (2008).

[9] T. Fujishima, K. Konno, K. Nakagawa, M. Kurobe, T. Okano, H. Takayama, Efficient synthesis and biological evaluation of all A-ring diastereomers of 1α,25-dihydroxyvitamin D_3 and its C-20 epimer, Bioorganic and Medicinal Chemistry 8 (2000) 123–134.

[10] P. Gongoi, R. Sigüeiro, S. Eduardo, A. Mouriño, An expeditious route to 1α,25-dihydroxyvitamin D_3 and its analogues by an aqueous tandem palladium-catalyzed A-ring closure and Suzuki coupling to the C/D unit, Chemistry: A European Journal 16 (2010) 1432–1435.

[11] (a) F.J. Sardina, A. Mouriño, L. Castedo, Studies on the synthesis of side-chain metabolites of vitamin D. 2. Stereospecific synthesis of 25-hydroxyvitamin D_2, Journal of Organic Chemistry 51 (1986) 1264–1268;
(b) Y. Fall, C. Barreiro, C. Fernández, A. Mouriño, Vitamin D heterocyclic analogues. Part 1: A stereoselectiveroute to CD systems with pyrazole rings in their side chains, Tetrahedron Letters 43 (2002) 1433–1436;
(c) S. Hatakeyama, M. Yoshino, K. Eto, K. Takahashi, J. Ishihara, Y. Ono, H. Saito, N. Kubodera, Synthesis and preliminary biological evaluation of 20-*epi*-eldecalcitol [20-*epi*-1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3: 20-*epi*-ED-71], Journal of Steroid Biochemistry and Molecular Biology 121 (2010) 25–28.

[12] P.J. Garegg, B. Samuelson, Novel reagent system for converting a hydroxy-group into a iodo-group in carbohydrates with inversión de configuration, Journal of the Chemical Society, Chemical Communications (1979) 978–980.

[13] S. Sinishtaj, H.B. Jeon, P. Dolan, T.W. Kensker, G.H. Posner, Highly antiproliferative, low-calcemic, side-chain amide and hydroxymate analogs of the hormone 1α,25-dihydroxyvitamin D_3, Bioorganic and Medicinal Chemistry 14 (2006) 6341–6348.

[14] ^{1}H NMR (250 MHz, ppm): δ 6.35 and 6.01 (2H, AB system, d, *J* = 11.2 Hz, H-6 and H-7), 5.31 (1H, s, H-19), 4.98 (1H, s, H-19), 4.40 (1H, dd, *J* = 7.2, 4.3 Hz, H-1), 4.20 (m, 1H, H-3), 2.81 (1H, dd, J = 11.7, 3 Hz), 2.54 (1H, dd, *J* = 13.4, 3 Hz), 2.29 (1H, dd, *J* = 13.3, 6.4 Hz), 1.20 (6H, s, H-27 and H-26), 0.83 (3H, d, *J* = 6.3 Hz, H-21), 0.53 (3H, s, H18). ^{13}C NMR (62.9 MHz, ppm): δ 147.5 (C, C-10), 142.9 (C, C-8), 133.1 (C, C-5) 124.4 (CH, C-6), 117 (CH, C-7), 111.7 (CH_2, C-19), 71.1 (C, C-25), 70.6 (CH, C-1), 66.5 (CH, C-3), 56.3 (CH, C-17), 56.1 (CH, C-14), 45.8 (C, C-13), 45.1 (CH_2), 44.2 (CH_2), 42.7 (CH_2), 40.3 (CH_2), 35.9 (CH_2), 35.4 (CH, C-20), 29.1 (CH_3, C-26 and C-27), 29 (CH_2, C-9), 27.3 (CH_2), 23.5 (CH_2), 22.1 (CH_2), 20.8 (CH_2), 18.5 (CH_3, C-21), 12.2(CH_3, C-18). HR-EIMS: Calc for $C_{27}H_{44}O_3$ (M+), 416.3285; found 416.3295.