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Convenient and Highly Efficient Inversion of 1β-OH Configuration of *trans*-Vitamin D_3

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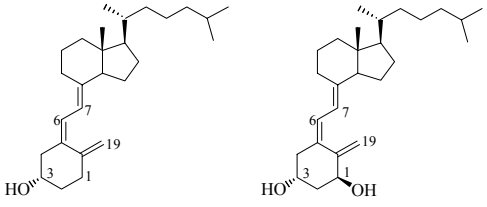
Abstract: A convenient and highly efficient conversion of 1β-OH-*trans*-vitamin D_3, a main byproduct in synthesis of active vitamin D_3, to 1α-OH-*trans*-vitamin D_3 is reported. The conversion could be accomplished in 1 minute with 90% yield.

Keywords: Vitamin D_3, Mitsunobu reaction.

1α-OH-Vitamin D_3 **4**, well known as a hormonally active form of vitamin D_3 **3**, plays an important role in the regulation of mineral metabolism, the promotion of cell differentiation and the inhibition of proliferation of various types of tumor cells. It is also very possible to be used in the treatment of cancer and other hyper-proliferation diseases[1].

Figure 1 Vitamin D_3 **3** and 1α-OH-vitamin D_3 **4**



3 **4**

Some of the major synthetic routes utilized in recent years to synthesize **4** and its analogues have been amply reviewed by Zhu and Okamura[2]. In these strategies, direct modification of vitamin D_3 (**3**) is becoming more attractive in the practice application[3] (**Scheme 1**). Unfortunately, a 1β-byproduct, a stereoisomer of 1α-product **2**, is produced accompanying with the formation of **2**. The ratio of 1β- to 1α-product is about 1/3~1/5 (in our experiments) and usually **1** is thrown away.

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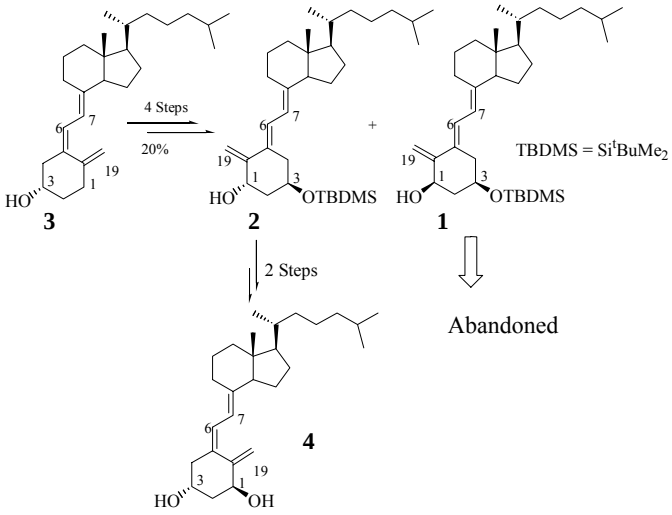
Scheme 1 Preparation of 1α-OH-vitamin D_3 **4**



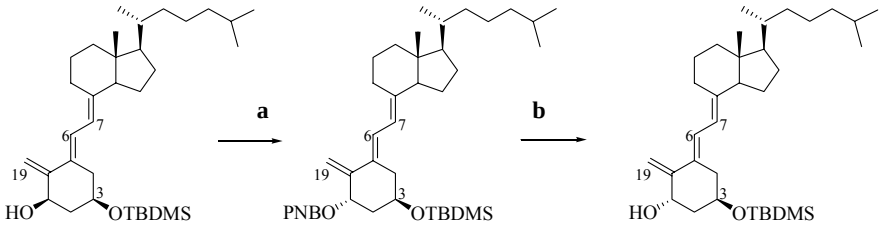
Our aim is to make 1β-OH-*trans*-vitamin D_3 **1** convert to 1α-OH product **2** in a convenient and highly efficient way. The Mitsunobu reaction[4], which can virtually complete the inversion of configuration of the alcoholic hydroxyl group under the mild and neutral conditions, has been applied to the synthesis of A-ring synthons by Gotor and his co-workers[5]. In this paper we give an example of transferring 1β-OH-*trans*-vitamin D_3 **1**, which has a conjugated triene system, to 1α-OH-*trans*-vitamin D_3 **2** by using the Mitsunobu reaction.

Inversion of 1β-OH configuration of compound **1**[6] under Mitsunobu conditions using *p*-nitrobenzoic acid afforded *p*-nitrobenzoate ester **5**[7] immediately with high yield. Subsequently, a selected and quantitative deprotection of ester group in **5** with KOH in THF produced **2**[8] quantitatively (**Scheme 2**). The conjugated triene structure, which is very sensitive to the acid, kept stable during reactions and the total isolated yield from **1** to **2** reached 90%.

We also found that the order of addition of reactants has a significant effect on the reaction. DEAD, Ph_3P and *p*-nitrobenzoic acid must be mixed together in the solvent before **1** was added. Otherwise only a very poor yield or even no desired product could be expected. This can be explained by the mechanism suggested by Brunn and Huisgen[9]. The formation of an intermediate, a protonated quaternary, is a very important step which makes system free of acid and keeps the conjugated triene structure stable during the reaction.

The Mitsunobu reaction has been used in the synthesis and the transformation of various kinds of natural products because of its mild and neutral conditions, stereospecificity, functional selectivity and regioselectivity. We demonstrated here an approach of convenient and efficient configuration conversion of the compound with conjugated triene structure, which increases the total yield in the synthesis of 1α-OH-vitamin D_3 and its analogues. This expands the applications of the Mitsunobu reaction.

Scheme 2 Conversion of **1** to **2**



1 **5** **2**

(a) DEAD, Ph_3P, *p*-nitrobenzoic acid, THF, rt., 1 min (90%);
(b) KOH, THF, H_2O, rt., 1 min (quantitative).

Acknowledgment

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References and Notes

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6. The procedures were indicated in detail in Calverey's paper. ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 6.66 (d, 1H, *J* = 11.5 Hz, H-6), 5.87 (d, 1H, *J* = 11.5 Hz, H-7), 5.06 (s, 1H, H-19 (Z)), 4.92 (s, 1H, H-19 (E)), 4.29 (m, 1H, H-1), 4.26 (m, 1H, H-OH), 4.16 (m, 1H, H-3), 2.89 (t, 2H, *J* = 11.5 Hz, H-2).
7. Preparation of *p*-nitrobenzoate ester **5**: Diethyl azodicarboxylate (DEAD) (0.18 mL, 1.16 mmol), Ph_3P (306 mg, 1.17 mmol) and *p*-nitrobenzoic acid (PNB) (96 mg, 0.57 mmol) were dissolved in dry THF (6 mL). After stirring for 10 min under argon, **1** (151 mg, 0.292 mmol, a solution in 4 mL THF) was added dropwise. After 1 minute at rt. the reaction was quenched by the successive addition of H_2O (20 mL). Then the mixture was extracted with Et_2O (3 × 20 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), dried, filtered and concentrated in vacuo. The residue was purified by a 5 cm flash column chromatography (Et_2O/petroleum ether = 1/50, R_f = 0.3 for **5** and R_f = 0 for others), to give the desired *p*-nitrobenzoate ester **5** (180 mg, 0.264 mmol, 90%). ^{1}H NMR

($CDCl_3$, 300 MHz, δppm): 8.31-8.18 (q, 4H, AB H-Ar), 6.55 (d, 1H, *J* = 11.5 Hz, H-6), 5.88 (d, 1H, *J* = 11.5 Hz, H-7), 5.89 (m, 1H, overlapped signals, H-1) 5.23 (s, 1H, H-19(Z)), 5.03 (s, 1H, H-19(E)), 4.25 (m, 1H, H-3), 2.87 (d, 1H, *J* = 18 Hz, H-9β), 2.56 (d, 1H, *J* = 30 Hz, H-4α), 2.45 (d, 1H, *J* = 30 Hz, H-4β).

8. Preparation of **2**: KOH (100 mg, a solution in 5 mL THF and a few drops of water) was dripped to a solution of 5 (180 mg, 0.264 mmol) in THF (5 mL) at rt. After stirring for 1 more minute, the reaction was quenched by the successive addition of H_2O (20 mL). Then the mixture was extracted with Et_2O (3 × 20 mL) and the combined organic phase was washed with saturated aqueous NaCl (20 mL), dried, filtered and concentrated in *vacuo*. The residue was the desired 1α-OH-*trans*-vitamin D_3 **2** (quantitative). ^1H NMR ($CDCl_3$, 300 MHz, δppm): 6.53 (d, 1H, *J* = 11.5 Hz, H-6), 5.86 (d, 1H, *J* = 11.5 Hz, H-7), 5.08 (s, 1H, H-19 (Z)), 4.96(s, 1H, H-19 (E)), 4.50(m, 1H, H-1), 4.20(m, 1H, H-3), 2.87(d, 1H, *J* = 18 Hz, H-9β), 2.56(d,1H, *J* = 30 Hz, H-4α), 2.45(d, 1H, *J* = 30 Hz, H-4β).
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