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# Pd-allylic substitution mediated synthesis of 25-amino vitamin $D_3$ derivatives

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ABSTRACT

Vitamin $D_3$ analogues with a nitrogen atom linked to C-25 have been synthesized. The key step involves an allylic substitution with 2-nitropropane using catalytic species of Pd(0). This optimized procedure gave the desired compound with complete regioselectivity and high yields and was used for the successful preparation of targeted vitamin D derivatives. The chosen strategy for the construction of the triene unit was totally compatible with the new functional groups.

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## Introduction

1α,25-Dihydroxyvitamin $D_3$ (**3**, calcitriol) is the hormonally active metabolite of vitamin $D_3$. The importance of calcitriol resides in its activity in a multitude of biological processes related to calcium and phosphorus homeostasis, cell proliferation, differentiation, and apoptosis.[1]

One current target in organic chemistry is the design and synthesis of new analogues of **3** having a relatively weak systemic effect on calcium metabolism while maintaining potent regulatory effects on cell differentiation and proliferation.

Trying to achieve this goal, many groups were focused in the study of structural modifications of vitamin D. DeLuca and co-workers synthesized and tested 25-azavitamin $D_3$ **4**[2] (Fig. 1). They found that it is a competitor for the biological site of 25 hydroxylation,[3] showing an important effect of nitrogen in this position. Also, previous reports displayed that the hydroxyl group in 25 position of vitamin D is essential due to the affinity for the transporter protein DBP in blood.[4]

Here, we report the synthesis of new analogues of vitamin $D_3$ **1** and **2**, with amine and amide groups linked to $C_{25}$. Our retrosynthetic analysis for **1** and **2** is depicted in Scheme 1. We anticipated that the side chains of analogues **1** and **2** could result from the reduction of nitroderivate **6** which could be prepared from Inhoffen-Lythgoe diol **5** using the allylic substitution catalyzed by Pd (Pd-AS) strategy. The triene system would then be installed using the Wittig–Horner coupling between the A ring synthon (**7**) and the corresponding Grundmann ketone derived from **6**, with the hope that the nitro functional group would be compatible with the coupling conditions (Scheme 1).

## Results and discussion

The synthesis of nitro derivative **6** started from Inhoffen-Lythgoe diol **5**, which was obtained by reductive ozonolysis of commercially available vitamin $D_2$.[5] Treatment of **5** with TESCl and subsequent selective deprotection of the primary silyl ether afforded alcohol **8** in 92% yield. The hydroxyl group was oxidized to the corresponding aldehyde and treated with a Wittig reagent giving the unsaturated ester **9** in 93% yield. The reduction of the ester with Dibal-H and acetylation furnished in high yields the ideal substrate **11** for Pd-allylic substitution.

The homoallylic nitro compound **12** was obtained in high yield by treatment of allylic acetate **11** with 2-nitropropane in the presence of $Pd(PPh_3)_4$ as the catalyst. Catalytic hydrogenation of **12** afforded almost quantitatively nitro-derivative **6**. It is remarkable that the synthesis of this intermediate is easily scalable to gram quantities and with the use of highly efficient catalytic procedures (Scheme 2).

The key step of the first part of the synthesis was the Pd-AS of allylic acetate **11**. The Pd-AS is an outstanding procedure in the synthesis of natural products.[6] This particular case is an example of the Tsuji–Trost reaction.[7] Compound **6** was thus easily obtained in high overall yield (eight steps, 71% from **5**).

Once the nitroderivate **6** was prepared, the synthesis of analogue **1** was performed. The desilylation of compound **6** and posterior oxidation with PDC afforded ketone **14** in excellent yields. The coupling of ketone **14** with phosphine oxide **7**[8] afforded analogue **15** in 96% yield. The conditions for the reduction of the nitro group in **15** should be compatible with the triene system. After much experimentation the optimized reaction conditions were found to be $LiAlH_4$ in $Et_2O$, affording the amine derivative **16** in high yields. This advanced intermediate was transformed into compound **1**[9] by treatment with TBAF in 83% yield (Scheme 3).

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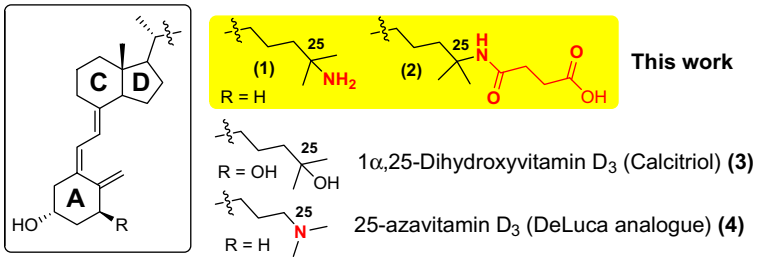
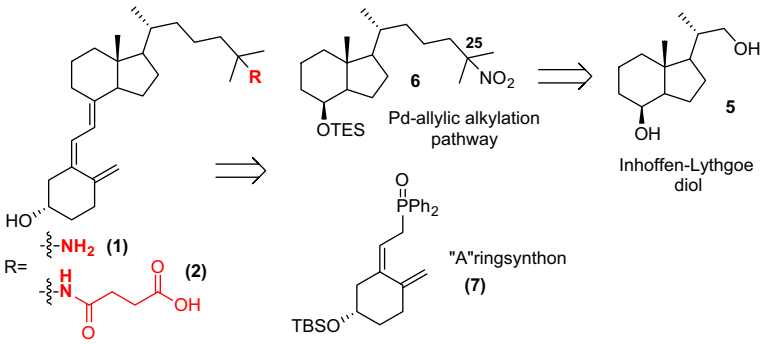
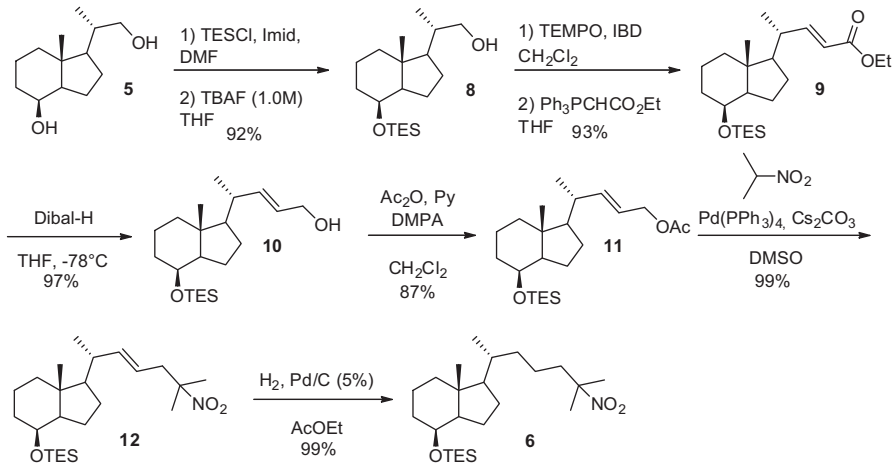


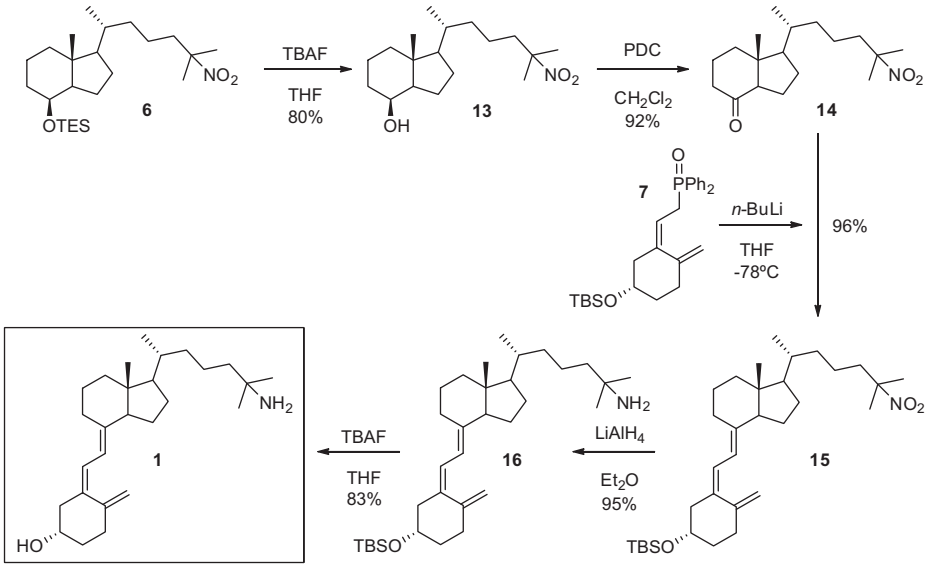

**Figure 1.**



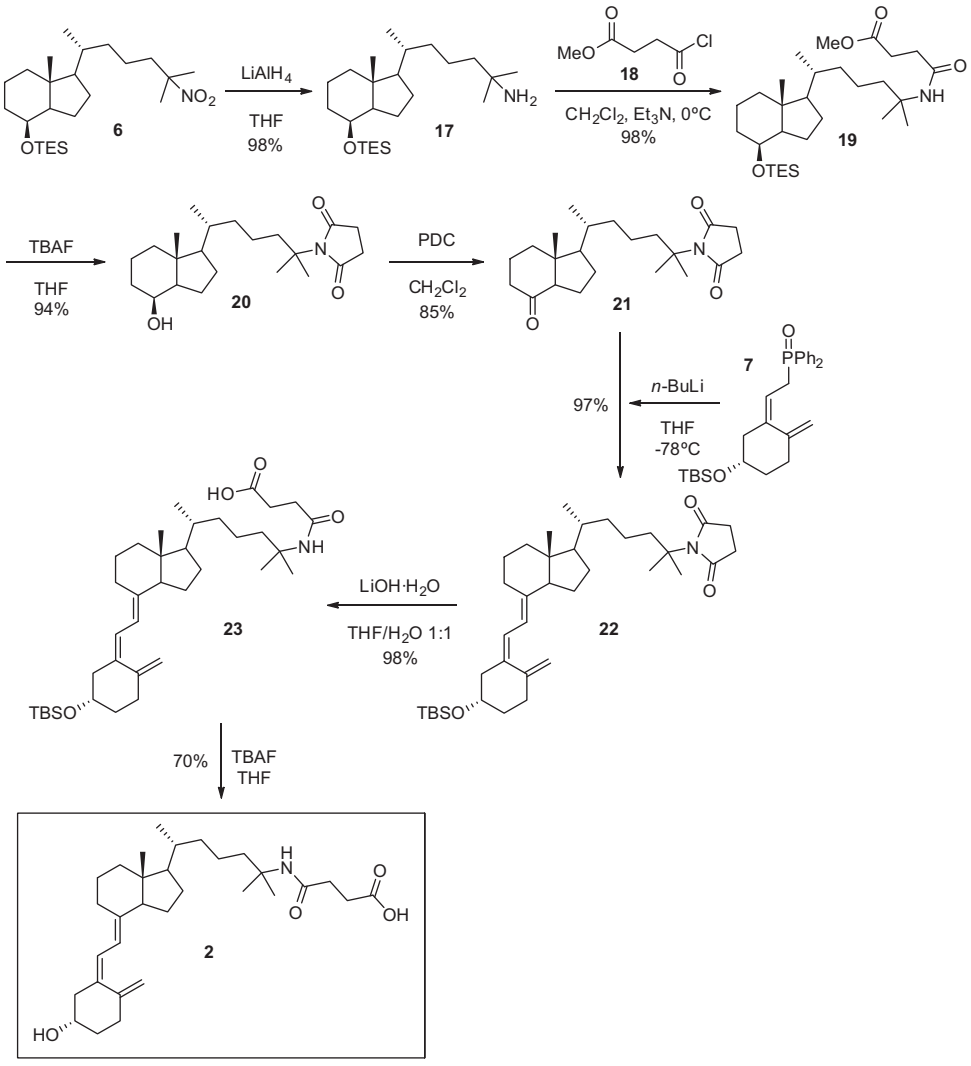

**Scheme 1.** Retrosynthetic scheme.




**Scheme 2.** Synthesis of nitro derivative **6**.




**Scheme 3.** Synthesis of analogue **1**.




**Scheme 4.** Synthesis of analogue **2**.

The synthesis of analogue **2** was carried out as follows (Scheme 4): reaction of nitroderivate **6** with $LiAlH_4$ afforded amine **17** in 97% yield. Amine **17** gave amide **19** on reaction with acyl chloride **18** in almost quantitative yield. Amide **19** reacted with TBAF resulting in the removal of the silyl protecting group and the concomitant formation of a pyrrolidine derivative **20** in 94% yield. Pyrrolidine **20** was successfully oxidized with PDC and the resulting ketone **21** was coupled with phosphine oxide **7**,[8] affording 97% yield of compound **22**. The subsequent pyrrolidine opening with LiOH afforded the desired functionalization of targeted compound **23** in 98% yield. The last step was the deprotection of the silyl ether **23** with TBAF, giving vitamin $D_3$ analogue **2**[9] in 70% yield.

In summary, we have developed a very efficient synthesis of two new 25-amino vitamin $D_3$ analogues, the key step of the synthesis being an allylic substitution catalyzed by Pd (Pd-AS). Work is now in progress for the synthesis of other aza analogues of calcitriol with a view to their biological evaluation.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.019.

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