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Stereoselective synthesis of C24-hydroxylated vitamin D_3 analogs: A practical and expeditius route to calcipotriol☆

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ABSTRACT

The synthesis of the clinically important drug calcipotriol (**2**, MC903) is described as an example of a new and efficient approach to C24-hydroxylated analogs and metabolites of vitamin D_3 (**1**). The key step of the process is the generation of the C24 stereocenter by DAIB [(−)-3-*exo*-(dimethylamino)isoborneol]-catalyzed addition of the alkenylzinc derivative of alkyne **3** to cyclopropylcarboxaldehyde.

1. Introduction

Before bringing about its biological effects, the natural vitamin D_3 (**1**) undergoes successive hydroxylations to produce the major circulating metabolites 25-hydroxyvitamin D_3 (25-OH-D_3), 24*R*,25-dihydroxyvitamin D_3 [24*R*,25-$(OH)_2$-D_3] and 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3] [1] (Fig. 1). Both 25-OH-D_3 and 1α,25-$(OH)_2$-D_3 are used clinically to treat numerous diseases. The latter (also known as calcitriol) is considered to be the hormonally active form of vitamin D_3, playing important physiological roles in the regulation of mineral metabolism and of the proliferation and differentiation of both normal and malignant cells [1,2]. Due to lack of synthetic material, the precise biological roles of 24*R*,25-$(OH)_2$-D_3 and other 24-hydroxylated metabolites of vitamin D_3 have not been clearly established [1,3].

Interestingly, however, the only members of the vitamin D_3 family apart from the natural hormone 1α,25-$(OH)_2$-D_3 that are being successfully used to treat psoriasis are 1α,24*R*-dihydroxyvitamin D_3 (tacalcitol) and the similarly C24-hydroxylated analog calcipotriol (**2**) [1,2a,3]. Most of the many approaches to the synthesis of 24-hydroxylated metabolites and analogs of vitamin D_3 have involved linear routes and chromatographic separation of complex mixtures of diastereoisomers [4]. Only recently have convergent and stereoselective approaches been developed [5,6]. We describe here an efficient synthesis of calcipotriol (**2**) [7] that illustrates a new approach to C24-hydroxylated vitamin D side chains. The synthetic plan for the preparation of the target compound **2** involves the stereoselective introduction of the C24 hydroxyl group via alkyne **3**, which is obtained by the convergent Lythgoe's Wittig–Horner approach (Scheme 1).

2. Results and discussion

Alkyne **3** was prepared in 95% yield by coupling the anion of phosphine oxide **4** to ketone **5**, which was straightforwardly prepared in 68% yield from the Inhoffen-Lythgoe diol (**6**) [8] (Scheme 2).

To introduce the requisite stereocenter at C24 we chose the method developed by Oppolzer and Radinov [9] for enantioselective synthesis of (*E*)-allylic alcohols by reaction of alkenylzinc reagents derived from alkenylboranes with aldehydes in the presence of catalytic (−)-3-*exo*-(dimethylamino)isoborneol [(−)-DAIB, 7] or (+)-DAIB.

Preliminary experiments to study the reliability of this reaction were undertaken using the protected alkyne **5a**. Addition of dicyclohexylborane to **5a** and transmetalation of the resulting alkenylborane with diethylzinc furnished the corresponding organozinc derivative, treatment of which with cyclohexycarboxaldehyde in the presence of (+)-DAIB [10] provided a chromatographically separable mixture of allylic alcohols **8** and **9**

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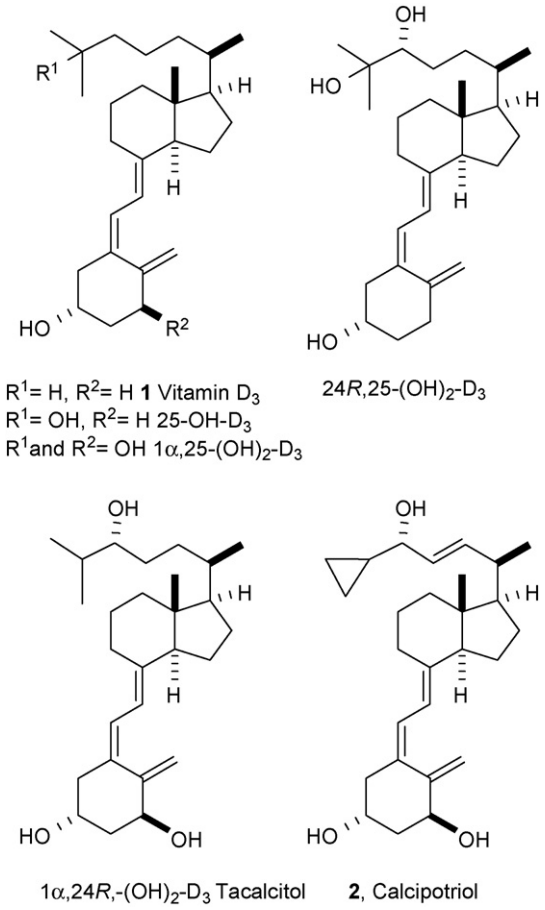
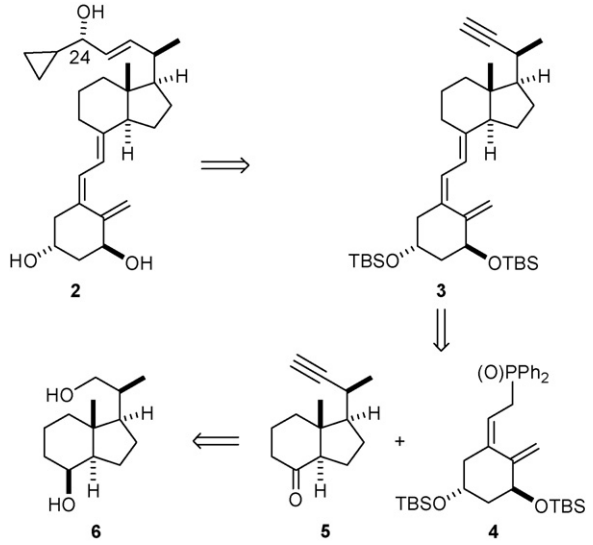
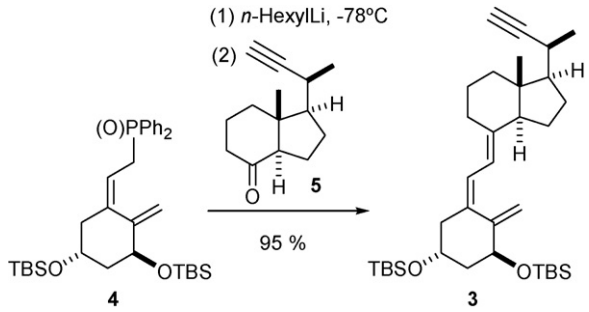


Fig. 1. Biosynthesis and metabolism of vitamin D_3.

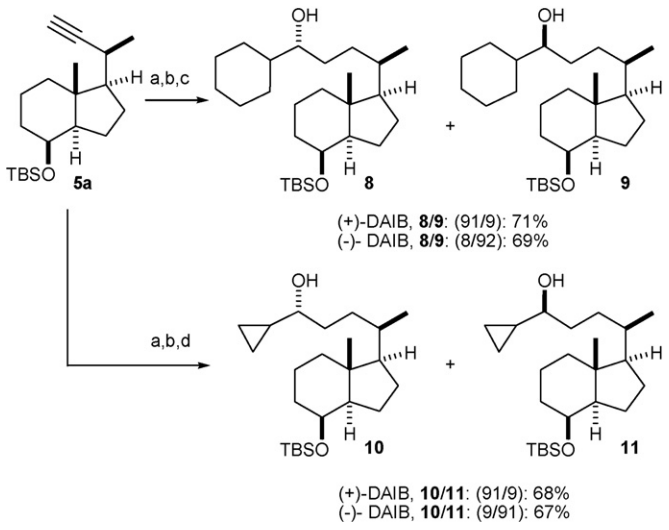
in 71% yield and 91:9 ratio. Although the stereochemistry of the reaction is established by the mechanism [11], we checked the stereochemistry of each isolated alcohol by ^{1}H RMN analysis of respective mandelate derivatives [12]. The result was consistent with the proposal mechanism [11b]. The use of (−)-DAIB instead of (+)-DAIB reversed the diastereomeric ratio (Scheme 3). Thus DAIB catalysts successfully controlled the asymmetric addition of the



Scheme 1. Synthetic strategy (Wittig–Horner approach).



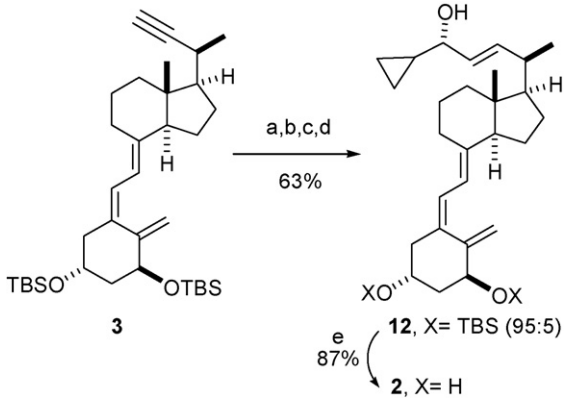
Scheme 2. Construction of the vitamin D triene system.



Scheme 3. Asymmetric introduction of 24-hydroxy side chains on alkyne **5a**. Reagents and conditions. (a) Cyclohexene, $BH_3{\cdot}SMe_2$, hexane, 0 °C, 3 h; addition of alkyne **5a**, −20 °C. (b) Et_2Zn and (+)- or (−)-DAIB. (c) Cyclohexycarboxaldehyde, 0 °C. (d) Cyclopropylcarboxaldehyde, 0 °C.

organozinc intermediates to the aldehydes with negligible interference from the alkyne framework. With cyclopropylaldehyde instead of cyclohexylcarboxaldehyde as substrate, **10** and **11** were formed in similar ratios and overall yields to **8** and **9** above.

In accordance with the results achieved in the preliminary experiments, the 24 stereocenter of **2** was successfully introduced on alkyne **3** by reaction of the latter with dicyclohexylborane, followed by transmetalation of the resulting alkenylborane to the



Scheme 4. Synthesis of calcipotriol from alkyne **3**. Reagents and conditions. (a) Dicyclohexylborane, hexane, 0 °C, 3 h. (b) Alkyne **3**, −20 °C. (c) Et_2Zn and (+)-DAIB. (d) Cyclopropylaldehyde, 0 °C. (e) TBAF (3 equiv.), THF, rt.

organozinc derivative and its subsequent addition of the latter to cyclopropylaldehyde in the presence of (+)-DAIB. After desilylation, this procedure afforded the desired compound calcipotriol (**2**) in 55% overall yield from **3** (Scheme 4).

In conclusion, we have developed a short and efficient synthesis of the clinically important drug calcipotriol from the Lythgoe-Inhoffen diol. A key feature of this synthesis is the generation of the C24 stereocenter by (+)-DAIB-catalyzed addition of alkenylzinc to aldehyde, which works despite the presence of the labile vitamin D triene system. Application of this strategy to the synthesis of other vitamin D metabolites and analogs will be reported in due course.

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