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Stereoselective convergent synthesis of 24-substituted metabolites and analogues of vitamin D☆

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Abstract

The synthesis of vitamin D_3 active metabolites [24*R*,25-$(OH)_2$-D_3, 24*S*,25-$(OH)_2$-D_3 and 1α,24*R*,25-$(OH)_3$-D_3] and the first 24-aminovitamin D_3 derivatives [24*S*-benzoylamino-25-OH-D_3 and 24*S*-benzoylamino-1α,25-$(OH)_2$-D_3] are reported. The stereogenic center at C-24 was generated through ultrasonically induced aqueous conjugate addition of iodide **8** to dioxolanone **6** or oxazolidinone **7**. The vitamin D triene system was constructed using the Lythgoe approach. The synthetic route, which is both short (6 or 7 steps from iodide **8**) and efficient (32–45% overall yield), constitutes a practical method for the preparation of 24-functionalized metabolites and analogues of vitamin D_3. The ultrasonically induced conjugate addition in the key step provides a novel example of a highly stereoselective reaction promoted by the zinc–copper couple in aqueous media.

Keywords: Stereoselective synthesis; Conjugate addition; Aqueous media; Zinc–copper couple; 24-Hydroxyvitamin D; 24-Aminovitamin D

1. Introduction

Vitamin D_3 (**1a**) produces biological responses after transformation by successive stereospecific enzymatic hydroxylations into the major active metabolites 1α,25-$(OH)_2$-D_3 (**1b**, calcitriol, Fig. 1) and 24*R*,25-$(OH)_2$-D_3 (**1c**, secalciferol) [1]. These metabolites interact with specific protein vitamin D receptors (VDRs) in the cell nucleus (VDR_{nuc}) or in the membrane (VDR_{mem}) and give rise to the biological responses via genomic or nongenomic pathways [2,3]. Calcitriol and secalciferol are involved in a wide range of biological functions such as calcium homeostasis, cellular differentiation and proliferation processes, as well as other functions related to the immune system. However, the utility of these compounds as drugs in the treatment of tumors and skin diseases is limited since effective doses provoke undesirable calcemic side effects [1]. For this reason, the search for vitamin D_3 analogues with selective biological function, i.e. a low calcemic effect and high activity as a cellular differentiation agent, has been extensively pursued in the last two decades [4,5].

Bearing in mind the influence of the hydroxyl groups at C-24 or C-25 on both the binding to the vitamin D receptor and the associated biological responses [6,7], we considered that replacement of one of these groups by another polar unit, particularly an amino group or derivative thereof, could give rise to novel analogues with a modified affinity for the VDR and hence different biological activity. The development of effective routes for the synthesis of these metabolites and analogues was envisaged as a worthwhile goal.

As part of our long-term programme devoted to the synthesis of vitamin D analogues and metabolites, as well as to the rational understanding of related biological functions, we focused our attention on the development of an efficient and stereoselective approach to 24-substituted vitamin D_3 metabolites and analogues. Several years ago we reported an efficient synthesis of the calcitriol side chain by means of an ultrasonically induced zinc–copper conjugate addition to α,β-unsaturated systems in aqueous media [8–11]—reaction conditions developed by Luche in the eighties [12,13]. The method was employed for the synthesis of calcitriol and 25-dialkyl analogues. Herein we report the use of this methodology for the stereoselective synthesis of 24,25-dihydroxyvitamin D metabolites and 24-amino-25-hydroxyvitamin D analogues.

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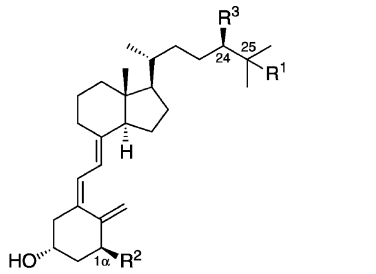


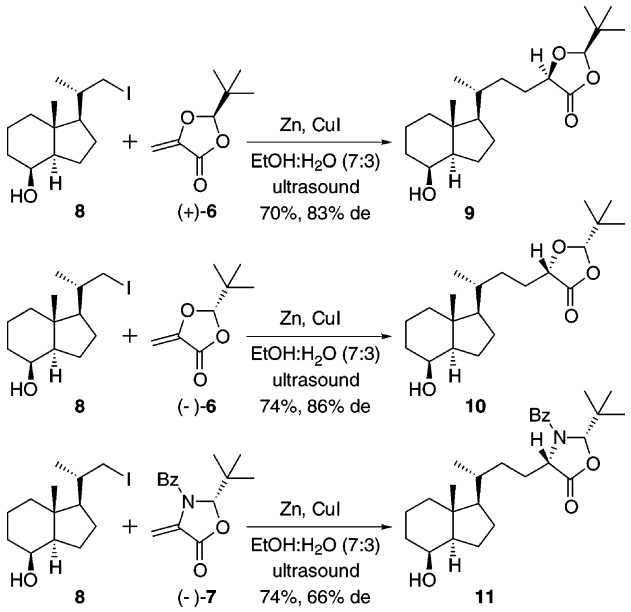
1a, $R^1 = R^2 = R^3 = H$; vitamin D_3
1b, $R^1 = R^2 = OH$, $R^3 = H$; 1α,25-$(OH)_2$-D_3
1c, $R^1 = R^3 = OH$, $R^2 = H$; 24*R*,25-$(OH)_2$-D_3

Fig. 1. Vitamin D_3 (**1a**), calcitriol (**1b**) and secalciferol (**1c**).

2. Results and discussion

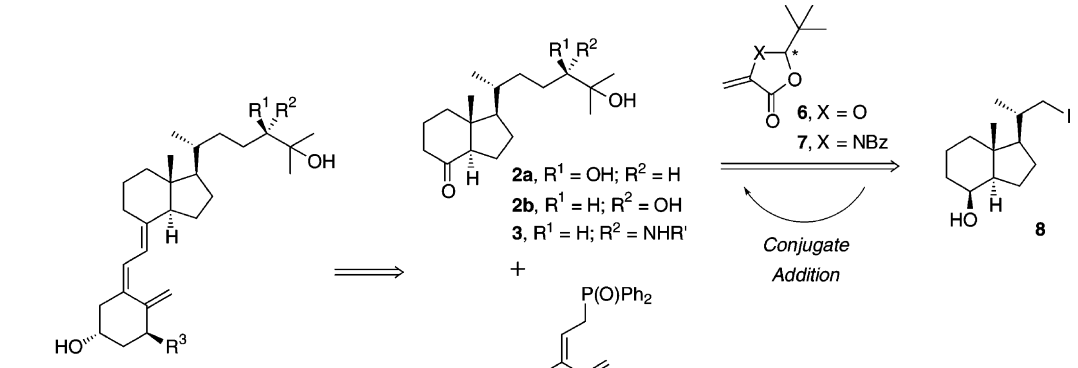
For the stereoselective synthesis of 24,25-dihydroxyvitamin D_3 metabolites (**1c**–**e**), we considered the retrosynthetic analysis depicted in Scheme 1. The conjugated vitamin D triene system would be constructed following the Lythgoe approach [14] from 24-functionalized ketones **2** or **3** and the known phosphine oxides **4** or **5**. The 24-functionalized ketones **2** and **3** would be prepared by stereoselective conjugate addition between the known iodide **8** and Seebach's dioxolanone **6** (for the synthesis of 24,25-dihydroxy metabolites) or oxazolidinone **7** (for the synthesis of 24-amino-25-hydroxy derivatives).

The synthesis starts with iodide **8**, which contains the CD-rings of the vitamin D structure, and Seebach's dioxolanone **6**, which was prepared as both enantiomers [(+)-**6** and (−)-**6**] from enantiomerically pure lactic acid [15–17], or Seebach's oxazolidinone **7**, which was prepared from natural (*S*)-alanine [18]. Our retrosynthetic analysis was tested by performing the sonochemically induced aqueous zinc–copper conjugate addition of iodide **8** to the dioxolanone enantiomer (+)-**6**. Remarkably, the 1,4-



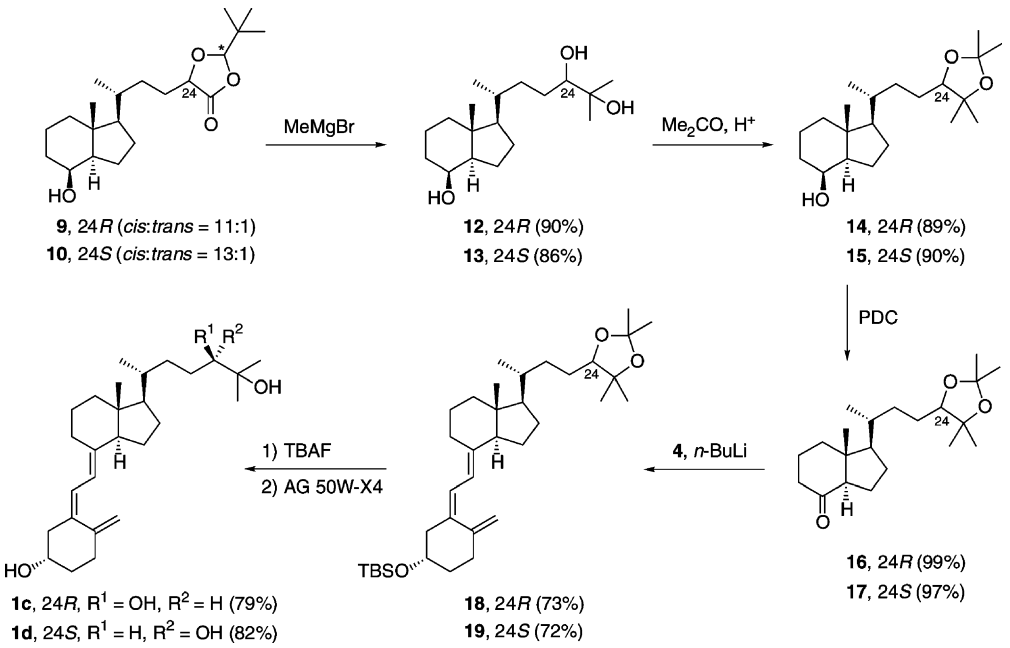
Scheme 2. Diastereoselective conjugate addition.

conjugate addition product **9** was obtained as a *cis*:*trans* mixture of diastereomers in an 11:1 ratio [83% de, major diastereomer: (24*R*)] and 70% yield (Scheme 2). The stereochemistry of the major diastereomer was assigned *cis* (24*R*) on the basis of the NMR assignments described by Axon and Beckwith [19]. When the reaction was performed with the dioxolanone enantiomer (−)-**6**, under the same experimental conditions, the conjugate addition product **10** was obtained in similar yield (74%) and stereoselectivity [*cis*:*trans* ratio of 13:1, 86% de, major diastereomer: (24*S*)]. This result proves that the stereoselectivity of the reaction is independent of the chirality of the iodide and that a remarkable, highly diastereoselective protonation of the enolate in aqueous media occurs [20,21]. On the other hand, ultrasonically induced conjugate addition of iodide **8** to methyleneoxazolidinone (−)-**7**, promoted by a zinc–copper



1c, $R^1 = OH$, $R^2 = R^3 = H$; 24*R*, 25-$(OH)_2$-D_3
1d, $R^1 = R^3 = H$; $R^2 = OH$; 24*S*, 25-$(OH)_2$-D_3
1e, $R^1 = R^3 = OH$; $R^2 = H$; 1α,24*R*, 25-$(OH)_3$-D_3
1f, $R^1 = R^3 = H$; R^2 = NRR"; 24*S*-amino analogues

Scheme 1. Retrosynthetic analysis.



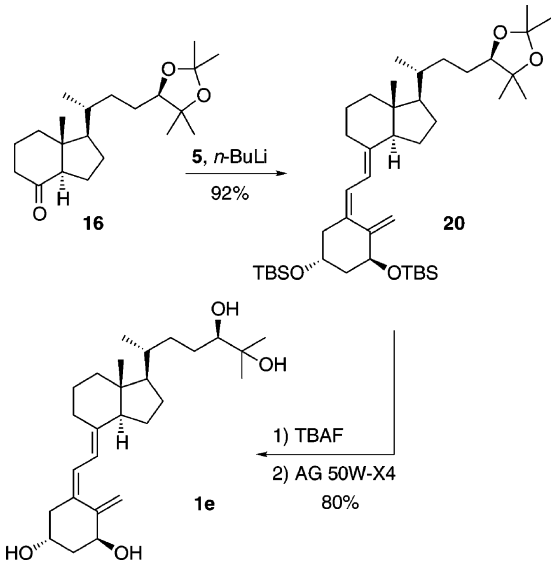
Scheme 3. Synthesis of 24*R*,25-$(OH)_2$-D_3 (**1c**) and 24*S*,25-$(OH)_2$-D_3 (**1d**).

couple in aqueous ethanol, afforded oxazolidinone **11** as a *cis*:*trans* mixture of diastereomers in a 4.9:1 ratio [66% de, major diastereomer: (24*S*)] and 74% yield. This result proves the efficiency of dioxolanones and oxazolidinoes as chiral building blocks in the aqueous zinc–copper sonochemical conjugate addition and allows, in this case, the stereoselective introduction of a heteroatom at the C-24 position of the vitamin D structure.

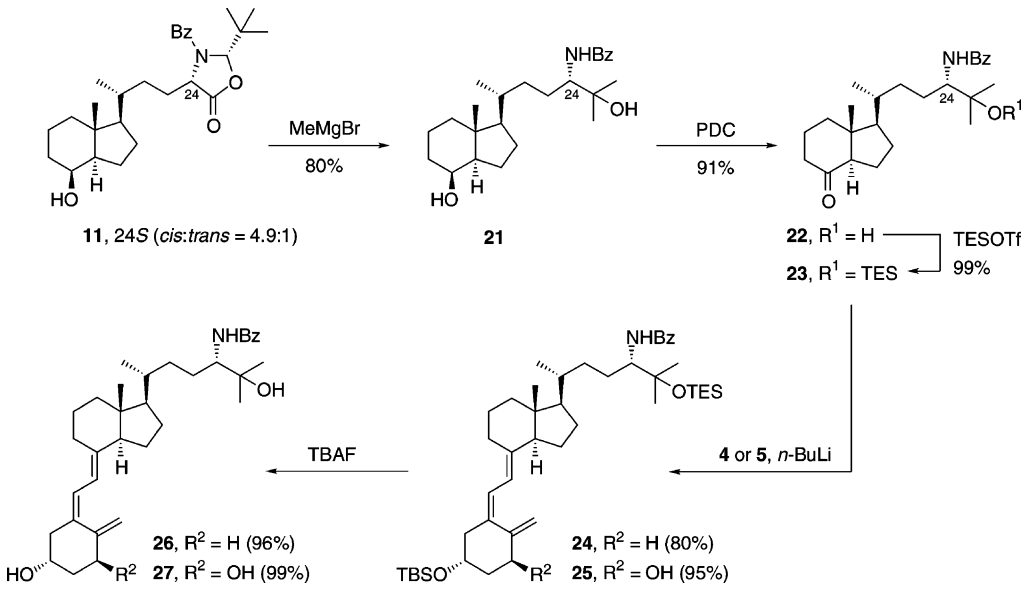
The synthesis of the 24*R*,25-$(OH)_2$-vitamin D_3 metabolite (**1c**, secalciferol) and its 24*S* epimer (**1d**) involved initial cleavage of the protected α-hydroxyacid in **9** and **10**. The C-26 and C-27 methyl groups of the vitamin D side chain were introduced by reaction with MeMgBr and separation of the major stereoisomer (24*R* or 24*S*, respectively) by crystallization or chromatography (Scheme 3). Protection of the 24,25-diol unit as a ketal with acetone and subsequent oxidation of the hydroxyl group at the C-8 position afforded the ketones **16** or **17**. A Wittig–Horner reaction between ketones **16**–**17** and the anion of the phosphine oxide of **4**, which contained the vitamin D ring A, generated by treatment with *n*-BuLi at low temperature, followed by treatment with TBAF and the cationic resin AG® 50W-X4 afforded, in 7 steps from iodide **8**, the 24*R*,25-$(OH)_2$-D_3 (**1c**, secalciferol) in 32% overall yield, and 24*S*,25-$(OH)_2$-D_3 (**1d**) in 38% overall yield [20].

To further exploit the synthetic utility of this approach, we also synthesized the vitamin D_3 metabolite 1α,24*R*,25-$(OH)_3$-D_3 (**1e**, Scheme 4). This is an active metabolite that is generated in vivo from calcitriol, in vitro from secalciferol and has preferential biological action in the transport of calcium in the intestine [22]. A Wittig–Horner reaction between ketone **16** and the anion of the 1α-hydroxylated phosphine oxide **5** [23], generated at low temperature with *n*-BuLi, followed by deprotection with TBAF and treatment with the resin AG® 50W-X4 yielded the desired metabolite 1α,24*R*,25-$(OH)_3$-D_3 (**1e**) in 40% overall yield from **8** [20].

The synthesis of 24-amino-25-hydroxy analogues of vitamin D_3 was accomplished starting form the conjugate addition product **11** (Scheme 5). The first step in the transformation of oxazolidinone **11** into the desired 24-aminovitamin D_3 derivatives involved cleavage of the oxazolidinone ring and introduction of the C-26 and C-27 vitamin D_3 methyl groups. Both objectives were achieved



Scheme 4. Synthesis of 1α,24*R*,25-$(OH)_3$-D_3 (**1e**).



Scheme 5. Synthesis of 24*S*-benzoylamino-25-OH-D_3 (**26**) and 24*S*-benzoylamino-1α,25-$(OH)_2$-D_3 (**27**).

in a single step by reaction of **11** with methylmagnesium bromide to afford the 24*S*-benzoylamino derivative **21** in optically pure form after crystallization (80% yield). Oxidation of alcohol **21** with PDC (91%) followed by protection of the 25-hydroxyl group with TESOTf gave ketone **23** in 99% yield. A stereoselective Wittig–Horner reaction between ketone **23** and the anion of phosphine oxide **4**, generated by treatment with *n*-BuLi at low temperature, afforded the protected vitamin D analogue **24** (80%). Deprotection with TBAF gave the first amino derivative of vitamin D_3, 24*S*-benzoylamino-25-hydroxyvitamin D_3 (**26**), in 96% yield (6 steps from iodide **8**, 36% overall yield) [21].

A similar route was used to prepare the 1α-hydroxylated analogue of **26** from ketone **23** (Scheme 5). Wittig–Horner reaction of ketone **23** with the anion of 1α-hydroxylated phosphine oxide **5** gave the protected vitamin **25** in 95% yield. Deprotection with TBAF gave the desired vitamin analogue, 24*S*-benzoylamino-1α,25-dihydroxyvitamin D_3 (**27**), in 6 steps and 45% overall yield from iodide **8** [21].

In summary, we describe here the first stereoselective convergent synthesis of the 24,25-dihydroxyvitamin D_3 metabolites 24*R*,25-$(OH)_2$-D_3 (**1c**), 24*S*,25-$(OH)_2$-D_3 (**1d**) and 1α,24*R*,25-$(OH)_3$-D_3 (**1e**), and the first synthetic approach to 24-aminovitamin D_3 derivatives (**26** and **27**). The synthetic approach is both short and efficient—six or seven steps from known iodide **8** and 32–45% overall yield—and is a practical method for the synthesis of these natural metabolites and other 24-functionalized analogues. The key step in the synthesis is a novel diastereoselective conjugate addition promoted by the zinc–copper couple in aqueous media. Efforts to explore the scope of this reaction are in progress, as is the synthesis of other 24-aminovitamin D_3 derivatives and related analogues from other chiral α,β-unsaturated systems.

Acknowledgements

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