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Novel approach to A-ring synthon for Pd-catalyzed synthesis of 1α-hydroxylated vitamin D metabolites☆

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ABSTRACT

A novel approach to an A-ring synthon for Pd-catalyzed synthesis of 1α-hydroxylated vitamin D metabolites is described. Key step is an asymmetric glyoxylate ene reaction to access a highly diastereomerically pure α-hydroxy ester. Subsequent stereospecific transformation to an *anti*-1,3-diol and appropriate chemical modifications at both ends of the acyclic precursor leads to a diastereomerically and enantiomerically pure silylated *anti*-1,3-diol enyne, serving as a versatile A-ring synthon for its use in vitamin D synthesis.

1. Introduction

Since vitamin D is a pleiotropic hormone that is involved in the activation of more than 300 genes, vitamin D deficiency presumably causes a wide variety of human disorders beyond its known role in bone health [1]. As a prerequisite for appropriate diagnosis and therapy of vitamin D related diseases, clinically relevant vitamin D_3 (and D_2) metabolites have to be assayed most accurately and with high specificity. Of particular interest are their 1α-hydroxylated derivatives, such as 3a–d (Scheme 1), among them calcitriol (3a) as the most active vitamin D metabolite known. Particularly, liquid-chromatography tandem mass spectrometry (LC-MS/MS) has been established as a gold standard for a differentiated vitamin D diagnosis [2]. However, to apply this method, the vitamin D metabolites of interest have to be synthesized for their use as calibration and reference standards, preferentially in their isotopically labeled (D,^{13}C) form. An enormous effort has been undertaken in recent decades in the field of vitamin D synthesis [3]. A distinguished methodology, that has initially been developed by B. Trost, and that has in the meanwhile widely been applied, uses a Pd(0) catalyzed reaction of 1,3-diol enynes as an A-ring precursor, such as 1, with CD-ring vinyl bromides 2, in turn obtained by Peterson olefination from the corresponding C8-ketone, derived from Inhoffen-Lythgoe diol [4]. The final vitamin D skeleton is formed by concomitant closure of the acyclic A-ring synthon 1 and its connection with the corresponding CD-ring moiety 2 in a one pot reaction, to access calcitriol 3a as a representative example [5]. Other vitamin D metabolites and analogs can be synthesized by this method simply by appropriate selection of the accordingly substituted enyne 1 and side chain of 2 [6]. A major drawback of this method is the fact that synthesis of acyclic or cyclic 1α-hydroxy-enynes involves numerous synthesis steps, and frequently separation of stereoisomeric mixtures is also necessary to obtain enantiomerically and diastereomerically pure product. However, the suitable starting material can usually be obtained from the natural chiral pool (i.e., terpenes, such as carvone [7], malic acid [8], quinic acid [9] or carbon hydrates, such as D-glucose [10] or D-xylose [11]), and is thus readily available. Here a novel versatile asymmetric synthesis of enyne 1 by application of an ene reaction employing a chiral glyoxylate is described.

2. Methods

The key step is an asymmetric ene reaction of a chiral glyoxylate 4, developed by Whitesell [12]. 4 could be obtained from commercially available *trans-2*-phenylcyclohexanol, in turn available in an industrial scale in both enantiomeric forms, derived from 1-phenyl cyclohexene [13], by reaction with acryloyl chloride and subsequent ozonolysis. Ene reaction of 4 with benzylated alkene 5 leads to α-hydroxyester 6, containing an exo methylene group. After ozonolysis, the resulting ketone could stereospecifically be reduced to obtain the desired *anti*-1,3-diol moiety. Both ends of the molecule are derivatized accordingly to finally obtain enyne 1 (Scheme 2).

☆ In memory of Milan R. Uskokovic

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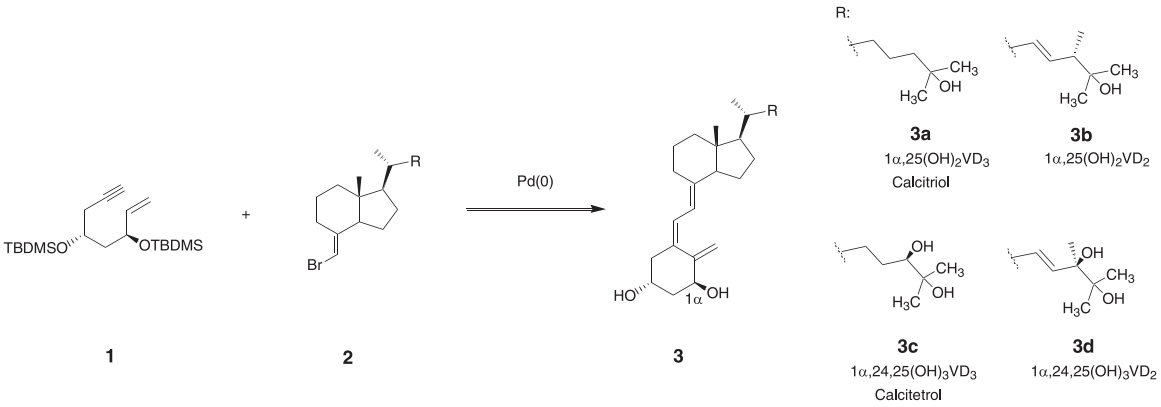
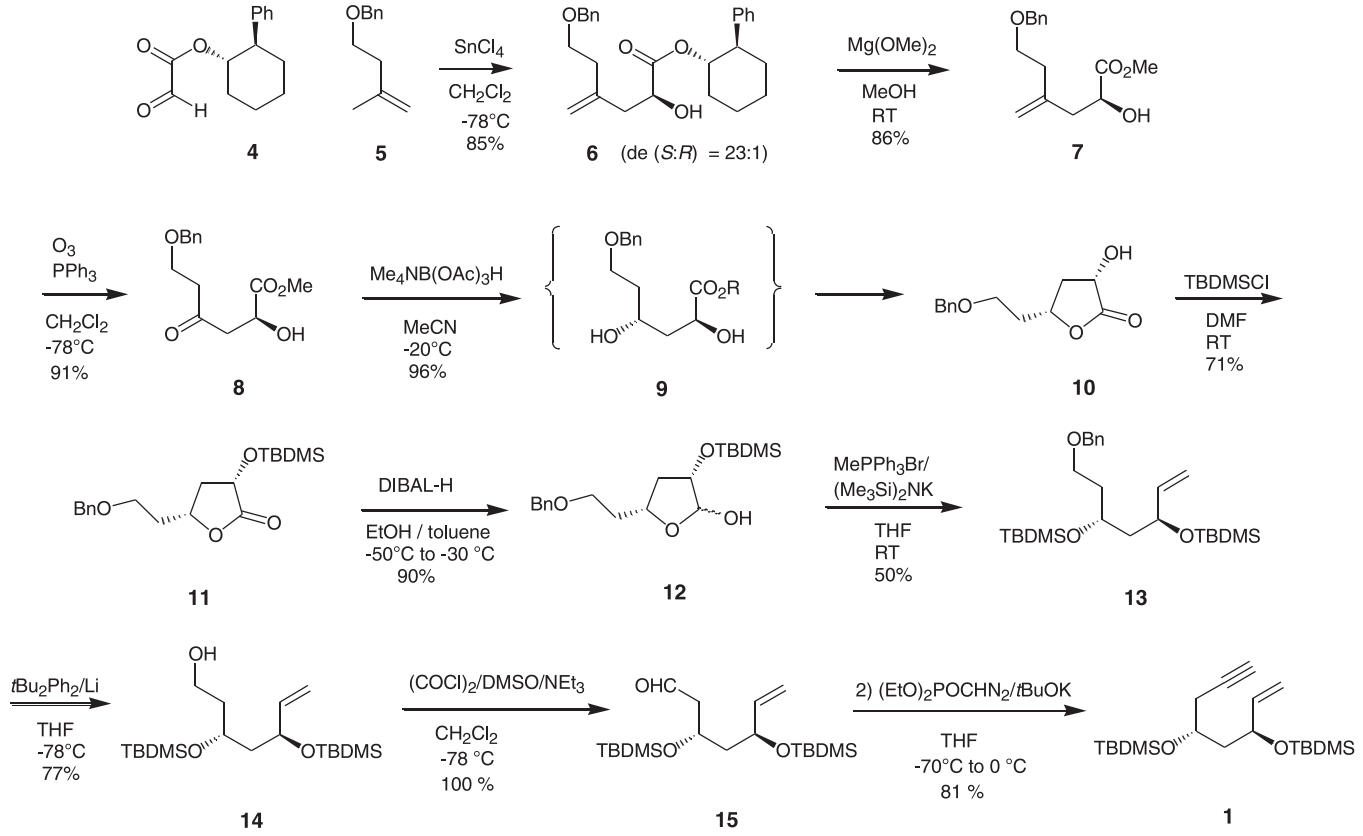


Scheme 1. Pd(0) catalyzed reaction of 1,3-diol enynes with CD-ring vinyl bromides to access 1α-hydroxylated vitamin D metabolites.



Scheme 2. Synthesis of silylated 1,3-diol enyne **1**.

3. Results and discussion

The stereoselective ene reaction of a chiral glyoxylate 4, with a benzylated alkene 5 gave hydroxyl ester 6 in a diastereomeric ratio of 6 (*S*):6(*R*) = 23:1. Although, this high diastereoselectivity was achieved in an 80 g scale (based on 4) and could not be reproduced on lower scale. Several initial and following batches showed a moderate diastereoselectivity of 10:1–8:1. However, the diastereoisomers could be separated by HPLC. The chiral auxiliary was cleaved by transesterification with magnesium methanolate to give the corresponding methyl ester 7 in 86% yield. For a new preparation of the chiral auxiliary (1 *S*,2 *R*)-cyclohexanol could be recovered. Ozonolysis of the exo methylene moiety of 7 and treatment of the resulting α-hydroxyester ketone 8 with [$HB(OAc)_3NMe_4$], first described by Evans [14], gave as expected exclusively *anti*-1,3-diol 9, that surprisingly underwent a spontaneous lactonisation to 10. The hydroxyl group of 10 was protected as a *t*-butyl-dimethylsilyl ether, leading to 11, that was reduced by DIBAL-H to obtain lactol 12. A subsequent methylene Wittig reaction gave the corresponding vinyl compound 13. Cleavage of the benzyl ether with tBu_2Ph_2Li gave alcohol 14, and its oxidation under Swern conditions quantitatively aldehyde 15, that was treated with diazomethyl-phosphonic acid diethylester to give finally the desired enyne 1.

The structure of reaction product 6 was assigned by $^{1}H/^{13}C$ NMR, IR and HRMS [15]. The structures of intermediate 14 [16] and final enyne 1 [17] were assigned by correlation of their analytical data with those already known from literature.

4. Conclusion

The described methodology allows for a rapid, cost effective and highly stereoselective synthesis of both enantiomers of silylated *anti*-1,3-diol enynes in large scale, in turn to be employed in a wide variety of 1α-hydroxylated vitamin D metabolites and related compounds.

Authors' Statement

The author Lars Kattner has conducted the research, performed the experiments, prepared the presentation of the published work, specifically its visualization (drawing of schemes) and text, and has written the initial and revised manuscript.

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[15] ^{1}H NMR (250 MHz, CDCl3) δ 7.33–7.06 (10H, m, Har), 4.95 (1H, td, *J*1 = 10.6, *J*2 = 4.4, H-1), 4.69 (1H, =CH), 4.56 (1H, =CH), 4.42 (2H, s, H-7), 3.98 (1H, ddd, *J*1 = 9.4, *J*2 = 6.0, *J*3 = 3.2, H-2), 3.39 (2H, t, *J* = 6.8, H-6), 2.65–2.53 (2H, m), 2.13 (2H, t, *J* = 6.7), 1.86–1.69 (4H, m), 1.50–1.27 (5H, m). ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.1 (C-1), 142.7 (Car), 141.9 (Car), 138.2 (C-4), 128.4 (4xCHar), 127.6 (2xCHar), 127.6 (CHar), 127.5 (2xCHar), 126.6 (Har), 113.8 (=CH2,), 77.8 (CH-1), 72.9 (CH2–7), 69.0 (CH-2), 68.6 (CH2–6), 49.9 (CH-2), 40.8 (CH2), 35.6 (CH2), 33.8 (CH2), 32.1 (CH2), 25.6 (CH2), 24.6 (CH2). IR (film, cm^{-1}): 3463 (υOH), 3028 (υ=C-H), 2931(υ=C-H), 1727 (υCO). HRMS (ESI-TOF$^+$): *m/z*: calc for $[C_{26}H_{32}O_4Na]^+$: 431.2192; $[M+Na]^+$: found 431.2192.

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