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Review

Synthesis of novel 19-norvitamin D_3 analogs with unnatural triene system

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ABSTRACT

9-Alkylidene analogs of 19-nor-1α,25-$(OH)_2D_3$ were synthesized, possessing a 'reversed' triene system compared to the natural hormone. The conjugated triene moiety of the novel analogs was constructed by coupling an enyne anion, representing an A-ring synthon, with a 9α-substituted Grundmann ketone derivative. Regioselective dehydration followed by semihydrogenation under Lindlar conditions, provided the desired 9-alkylated 19-norprevitamins which were thermally isomerized to the corresponding 9-methylene and 9-ethylidene analogs of 19-norcalcitriol. It was established that only the former compound had significant binding affinity to the full-length recombinant rat vitamin D receptor. The remaining *in vitro* studies show very low activity of both analogs.

This article is part of a Special Issue entitled 'Vitamin D Workshop'.

Contents

1. Introduction

Among the steroid hormones, only 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**, Fig. 1) is characterized by a presence of conjugated double bond system, derived from the photochemical cleavage of the C(9)–C(10) bond in the ring B of its steroidal 5,7-diene precursor [1]. Calcitriol, the most potent metabolite of vitamin D_3, beyond its classical role in regulation of calcium–phosphorous homeostasis, exerts control over many biological processes such as, for example, induction of cell differentiation and inhibition of cell proliferation. Broad spectrum of activities makes low-calcemic analogs of calcitriol potentially useful in various biomedical applications [2–4].

The majority of calcitriol analogs synthesized to date contain modifications in the side chain or in the ring A [5]. Significantly smaller number of vitamin D compounds is known with an altered triene system, for instance analogs with different configurations of the intercyclic diene moiety (5*E*-, 7*Z*- or 5*E*,7*Z*-geometrical isomers) were reported in the literature [6–8]. It was also established that removal of an exocyclic 10-methylene group reduces the calcemic effect of 19-norcalcitriol compared to the natural hormone while this does not decrease the cell-differentiating activity of such an analog [9]. Therefore, our attention has been focused on analogs of 1α,25-dihydroxyvitamin D_3 possessing a 'reversed' π-system, namely, 19-norvitamin D compounds with an alkylidene

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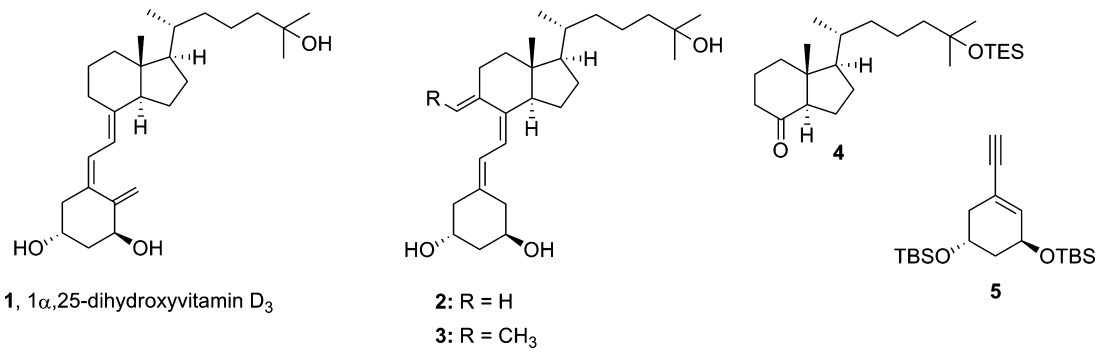
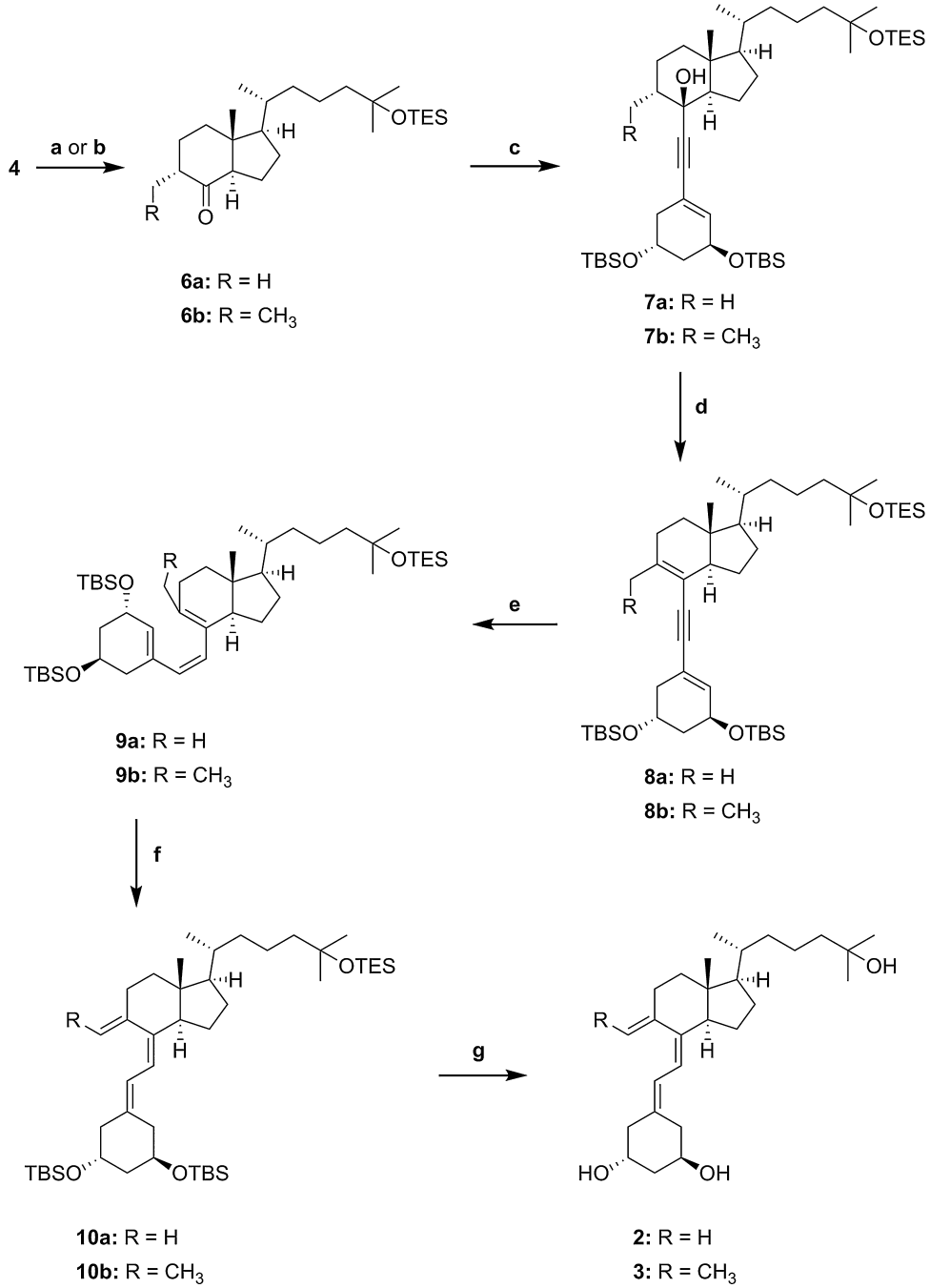


1, 1α,25-dihydroxyvitamin D_3

2: R = H

3: R = CH_3

Fig. 1. Chemical structures of 1α,25-$(OH)_2D_3$ (calcitriol, **1**), the synthesized analogs and their precursors.



6a: R = H

6b: R = CH_3

7a: R = H

7b: R = CH_3

8a: R = H

8b: R = CH_3

9a: R = H

9b: R = CH_3

10a: R = H

10b: R = CH_3

2: R = H

3: R = CH_3

Scheme 1. (a) LDA, CH_3I, DMPU, THF (96%); (b) LDA, CH_3CH_2I, DMPU, THF (66%); (c) *n*-BuLi, $CeCl_3$, **5**, THF (60% for **7a** and 68% for **7b**); (d) Burgess reagent, toluene (95% for **8a** and 96% for **8b**); (e) H_2, Lindlar catalyst, quinoline, hexane (89% for **9a** and 78% for **9b**); (f) isooctane, 100 °C (100%); (g) TBAF, THF (88% for **2** and 90% for **3**).