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Creative synthesis of novel vitamin D analogs for health and disease

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Abstract

We report new analogs of 1α,25-dihydroxyvitamin D_3 (**1**) in three categories. First, design and synthesis of ligands for a mutant vitamin D receptor (VDR)(Arg274Leu), which possess proper functional groups at both C1α and C2α positions of **1** to study the biological activity of the mutant VDR. Among our synthetic analogs, 1α-methyl-2α-(3-hydroxypropyl)-25-hydroxyvitamin D_3 (**8**) showed 7.3-fold greater transcriptional activity for the VDR(Arg274Leu) than that of **1**. Next, we examined the antiproliferative activity of 2-substituted 19-norvitamin D_3 analogs on an immortalized normal prostate cell line, PZ-HPV-7, and we found MART 10 (**14**) showed the activity even at very low concentration of 10^{-10} to 10^{-11} M. We also synthesized 25-hydroxy-19-norvitamin D_3 (**13**) using Julia-type olefination to connect between the C5 and C6 positions, effectively, to test it as a prohormone type agent for antiprostate diseases. Synthesized compound **13** showed potent antiproliferative activity in PZ-HPV-7, which has high 1α-hydroxylase activity. Finally, we describe design and synthesis of a new TEI-9647 analog, 2α-(3-hydroxypropoxy)-24-propyl-25-dehydro-1α-hydroxyvitamin D_3-26,23-lactone (**17**), which showed the strongest VDR antagonism. Its IC_{50} value is 7.4 pM to inhibit differentiation of HL-60 cells induced by 10 nM of **1**.
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Keywords: Vitamin D analogs; Chemical synthesis; Structure–activity relationships; Vitamin D receptor; Antagonist

1. Introduction

1α,25-Dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$, **1**), the physiologically active hormonal form of vitamin D_3, regulates cellular proliferation and differentiation in addition to its classical role in calcium and phosphorus homeostasis and bone mineralization [1–4]. The cellular and physiological actions of 1α,25$(OH)_2D_3$ are mediated primarily through the specific receptor, vitamin D receptor (VDR), which belongs to the nuclear receptor superfamily acting as a ligand-dependant transcription factor [5,6]. The VDR–[1α,25$(OH)_2D_3$] signaling works to stimulate intestinal calcium and phosphate absorption to prevent rickets, enhance of bone remodeling, differentiation of skin cells, potential anticancer actions, and so on. Therefore, 1α,25$(OH)_2D_3$ (**1**) and some synthetic analogs of **1** are clinically used in the treatment of bone diseases, secondary hyperparathyroidism, and psoriasis [1].

In order to investigate the structure–activity relationships of the natural hormone, we systematically synthesized the A-ring modified analogs, such as 2α-alkyl-, and 2α-(ω-hydroxyalkyl)-1α,25$(OH)_2D_3$ (Fig. 1) [7–11]. Elongation of the 2α-alkyl chain as in **2b–d**, however, decreased the binding affinity and agonistic activity for the VDR [9]. On the other hand, in regard to modification with the 2α-(ω-hydroxyalkyl) group, it was found that **3c** with the 2α-(3-hydroxypropyl) group on **1** had a three-fold higher binding activity for the VDR than **1** [9,10]. We also synthesized 2α-(ω-hydroxyalkoxy)-1α,25$(OH)_2D_3$ (**4a–c**), and **4b** showed 1.8-fold stronger binding affinity for the VDR than **1** [11–13]. Posner and Johnson also synthesized ED-71 [14] related analogs starting with the [4 + 2] cycloaddition of pyrone derivatives [15]. We report here the design and synthesis of the new analogs of **1** based on our accumulated knowledge of the 2α-functional group in three categories: for

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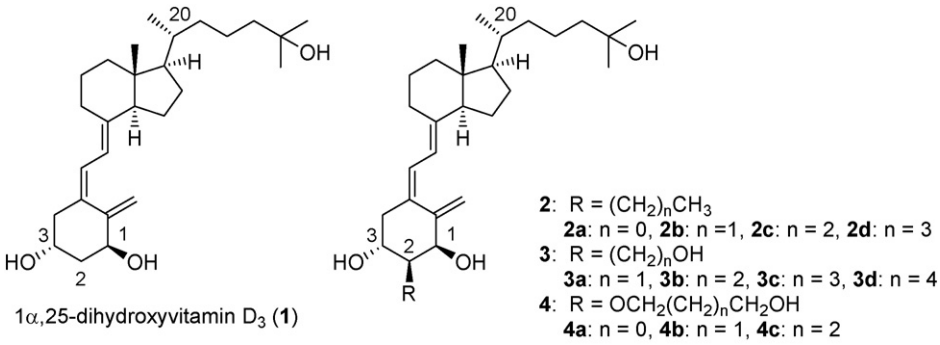


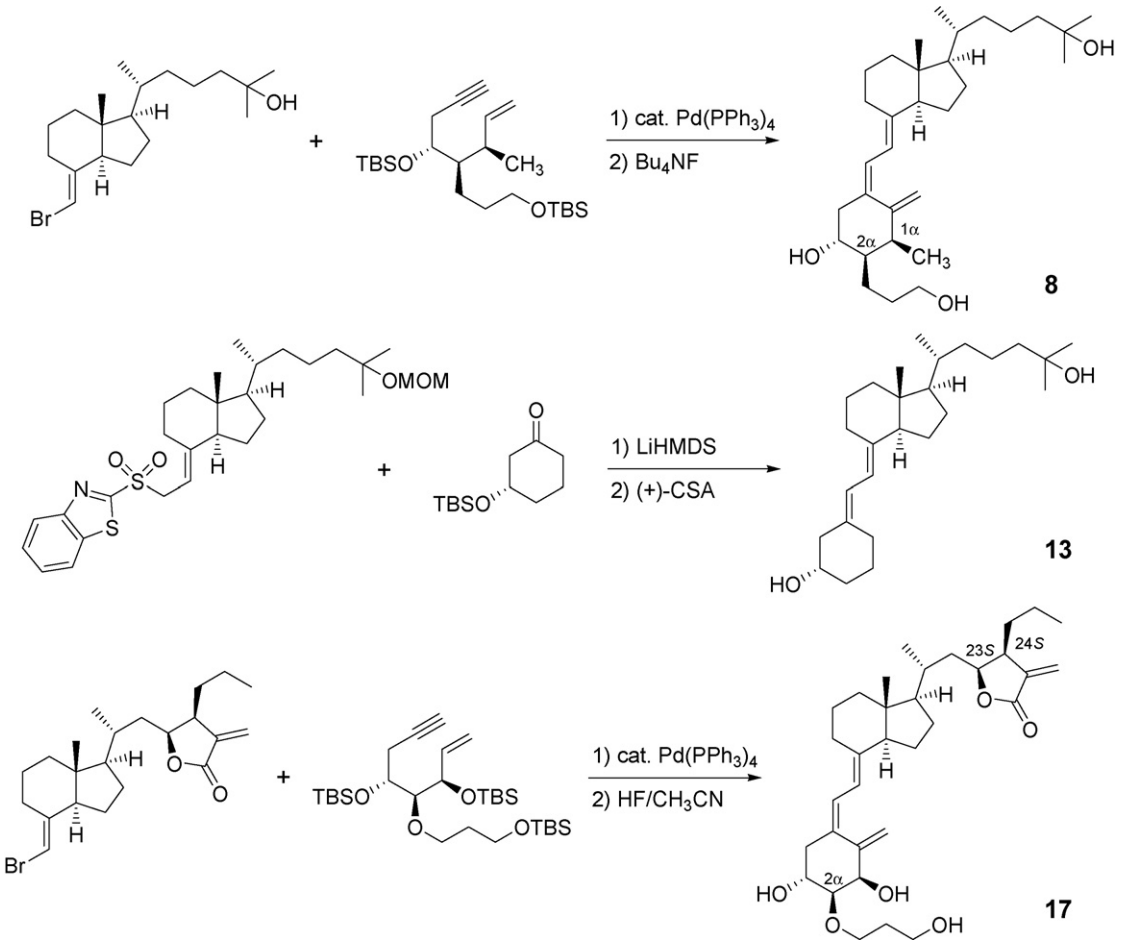
Fig. 1. Structures of 1α,25-dihydroxyvitamin D_3 (**1**) and its 2α-substituted analogs **2**–**4** [7–13].

hereditary vitamin D-resistant rickets (HVDRR), for prostate cancer, and for Paget's disease.

2. Material and methods

2.1. Preparation of vitamin D analogs

All vitamin D analogs in this report were synthesized at the Faculty of Pharmaceutical Sciences, Teikyo University according to the representative synthetic route presented in Scheme 1. Construction of the vitamin D_3 triene skeleton, for example, compounds **8** and **17**, was accomplished by Pd-catalyzed alkenylative cyclization of enyne as the A-ring precursor with the CD-ring bromoolefin [16]. To connect the C5–C6 double bond of 19-norvitamin D_3 analogs, for example, compound **13**, Julia-type olefination was utilized. Full synthetic details and physiological data of the synthetic compounds will be reported elsewhere.



Scheme 1. Synthesis of 1α-alkyl vitamin D_3 analog **8**, 19-norvitamin D_3 analog **13**, and TEI-9647 analog **17**.

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