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A Short, Flexible Approach to Vitamin D_3 Analogues with Modified Side Chains

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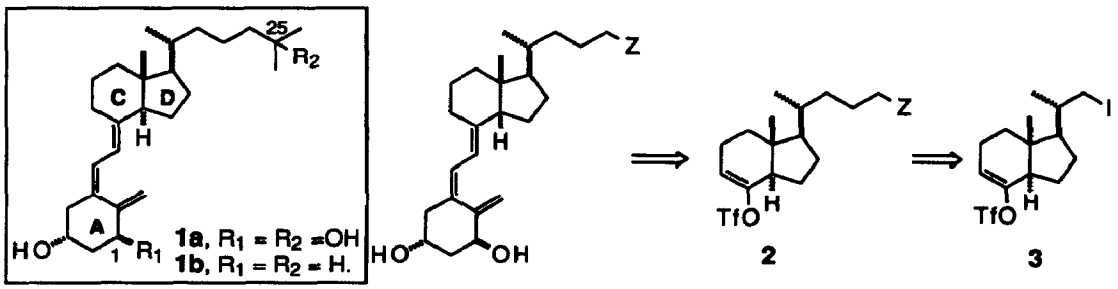
Abstract. An efficient convergent synthesis of the iodide **6a**, which contains the vitamin D triene system, and the ultrasonically induced reactions between **6a** and **6b** and electron-deficient olefins to give several vitamin D_3 analogues with modified side chains are described.

The discovery that 1α,25-dihydroxyvitamin D_3 (**1a**), the hormonally active form of vitamin D_3 (**1b**),[1] is a potent inhibitor of cell proliferation and inducer of cell differentiation[2] has stimulated the search for new vitamin D analogues with strong cell-differentiating and weak calcemic effects as potentially valuable drugs for the treatment of certain cancers and skin disorders.[3] Several analogues of **1a** with modified side chains are of particular interest for the treatment of psoriasis.[4]

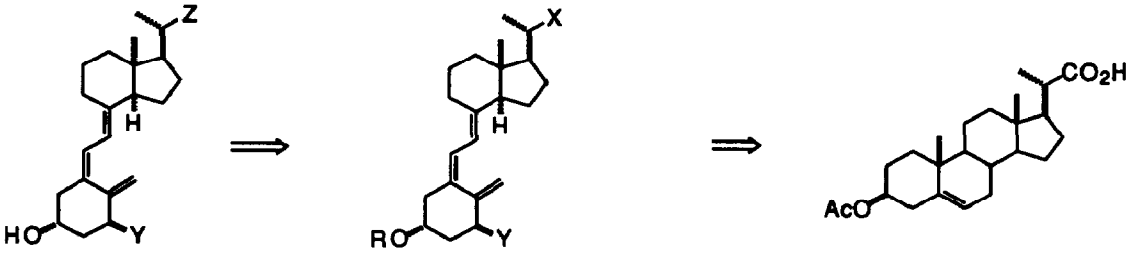
We have recently reported an efficient convergent synthetic method for the preparation of several vitamin D analogues with modified side chains.[5] In this approach the unit containing the CD-side chain fragment **2** (Scheme 1) is constructed by means of ultrasonically induced reaction of iodide **3** with electron-deficient olefins in an aqueous medium. However this strategy and other currently used methods[6] are inconvenient if numerous vitamin D side-chain-modified analogues are to be prepared for biological testing, since they require the construction of the triene unit on the CD fragments after the introduction of each side chain.

Scheme 1



Deluca et al.[7] and Kutner et al.[8] have overcome this problem by preparing the target analogues from the key intermediates **4a** or **4b**, which already contain the labile vitamin D triene system (Scheme 2).

Scheme 2

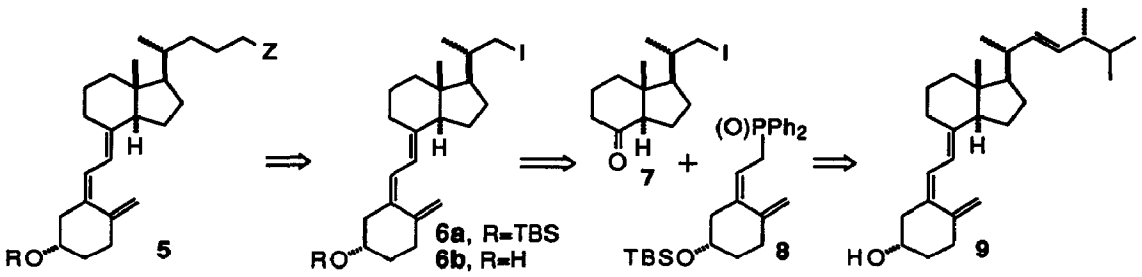


Z = Side chain
Y= H or OH

4a, X= CO_2Me, R=Y=H (8 steps, 17%).
4b, X= CHO, R=TBS, Y=OTBS (16 steps, 3%)

Given that the sonochemical methodology easily allows for the formation of carbon-carbon bonds by means of the conjugate addition of iodides to electron-deficient olefins in an aqueous medium,[5] it was of interest to see if iodides of type **6** (Scheme 3) would also undergo the conjugate addition without disruption of the labile vitamin D triene system. We describe here a short, efficient method for the synthesis of the required iodides **6a** and **6b** and their successful use for the preparation of several vitamin D_3 analogues with modified side chains.

Scheme 3

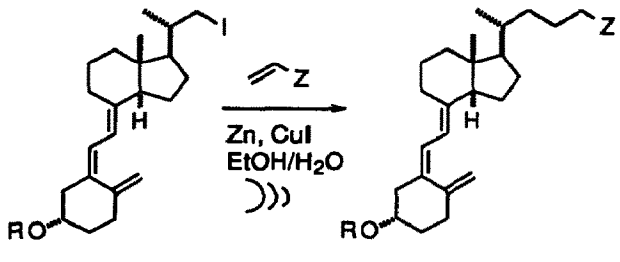


The iodide **7** and phosphine oxide **8** were prepared in 72 % and 68 % yields respectively from commercially available vitamin D_2 (**9**) by means of known procedures.[5,9] The key intermediate **6a** was prepared in the following way. A solution of *n*-BuLi in hexanes (0.86 mL, 2.1 mmol, 2.44 M) was slowly added to a cooled (-78 °C) solution of **8** (1.1 g, 2.43 mmol) in THF (15 mL). The mixture was stirred at -78 °C for 30 min. The resulting red solution of the phosphine oxide anion was cooled to -92 °C, and a solution of iodide **7** (0.6 g, 1.74 mmol) in THF (10 mL) was added at a rate of 10 mL/h. The mixture was stirred at -92 °C until disappearance of the starting iodide. Quenching at -70 °C with water, conventional work-up and flash chromatography afforded the iodide **6a** (95 %, foam).

Preparation of protected vitamin D_3 side-chain-modified analogues (**5a**, R= TBS, Scheme 4). *Typical procedure*. A mixture of CuI (0.1 g, 0.51 mmol), Zn (0.08 g, 1.2 mmol) in deoxygenated EtOH/H_2O (4 mL, 7/3) was sonicated under argon for 5 min.[5] The resulting black suspension was added to a solution of iodide **6a** (0.1 g, 0.18 mmol) and the α,β-unsaturated side chain precursor CH_2=CHZ (20 equiv) in EtOH/H_2O (1 mL, 7/3). The mixture was sonicated until disappearance of the starting iodide. Filtration through celite and washing with EtOAc (3x50 mL) gave an organic solution that was washed with brine, dried, filtered and concentrated in vacuo. The residue was flash chromatographed (1.4x18 cm, 4% Et_2O/hexanes) to afford the desired vitamin D_3 analogue (Table 1).[10,11]

Preparation of vitamin D_3 side-chain-modified analogues (**5b**, R= H, Scheme 4).The efficiency of the ultrasonically induced conjugated addition was improved using the deprotected iodide **6b**, which is more soluble under the reaction conditions. *Typical procedure*. A solution of the protected iodide **6a** (0.44 g, 0.77 mmol) in THF (3 mL) and CH_3CN (15 mL) was treated, in the absence of light, with aqueous HF (6 drops, 48%). The mixture was stirred for 90 min. Work-up (brine, CH_2Cl_2 , Na_2SO_4, concentration in vacuo) gave the iodide **6b** (0.33 g, 97 %), which was immediately used in the next step. A mixture of CuI (0.12 g, 0.66 mmol) and Zn (0.11 g, 1.54 mmol) in deoxygenated EtOH/H_2O (1 mL, 7:3) was sonicated under argon until a black suspension appeared. An additional amount of EtOH/H_2O (3 mL, 7/3), the α,β-unsaturated side chain precursor CH_2=CHZ (2 mmol) and the iodide **6b** (0.1 g, 0.23 mmol) were successively added. The mixture was sonicated until disappearance of the starting iodide. Work-up as above gave a residue which was subjected to HPLC (Zorbax silica 250x10 mm, 2-propanol/hexanes) to separate **5b** from its 5,6-*trans*-isomer (7 % as determined by ^{1}H NMR) (Table 1).[11,12]

Scheme 4



6a, R=TBS
6b, R=H

5a, R=TBS
5b, R= H

Table 1

Z	R	Reaction time (min)	Yield (%)
CO_2Me	TBS	80	50
COMe	TBS	35	70
CN	TBS	70	48
CO_2Me	H	35	62
COMe	H	25	74
CN	H	30	68
SO_2Me	H	40	64

In conclusion, we have devised methodology for the preparation of vitamin D_3 analogues with modified side chains by reaction of an iodide containing the vitamin D triene unit with α,β-unsaturated compounds under aqueous sonochemical conditions. Work is in progress to extend this short, efficient approach (6 steps from vitamin D_2, 30-46 % overall yield) to the synthesis of side-chain-modified analogues of the hormone 1α,25-dihydroxyvitamin D_3.

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10. The use of DMF or THF to improve the solubility of the starting iodide **6a** resulted in lower yields of reaction products.

11. The formation of the 5,6-*trans*-isomer takes place during the deprotection of iodide **6a**. It is known that the vitamin D triene system can be equilibrated into the 5,6-*trans*-derivative in the presence of traces of I_2 (Cota, J.G.; Meilán, M.C.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1988**, *53*, 6094 and ref. cited therein).

12. All new compounds gave satisfactory ^1H and ^{13}C NMR and high resolution mass data.

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