AN IMPROVED SYNTHESIS OF 24,24-DIFLUORO-1α,25-DIHYDROXY-VITAMIN D_3 FROM VITAMIN D_2

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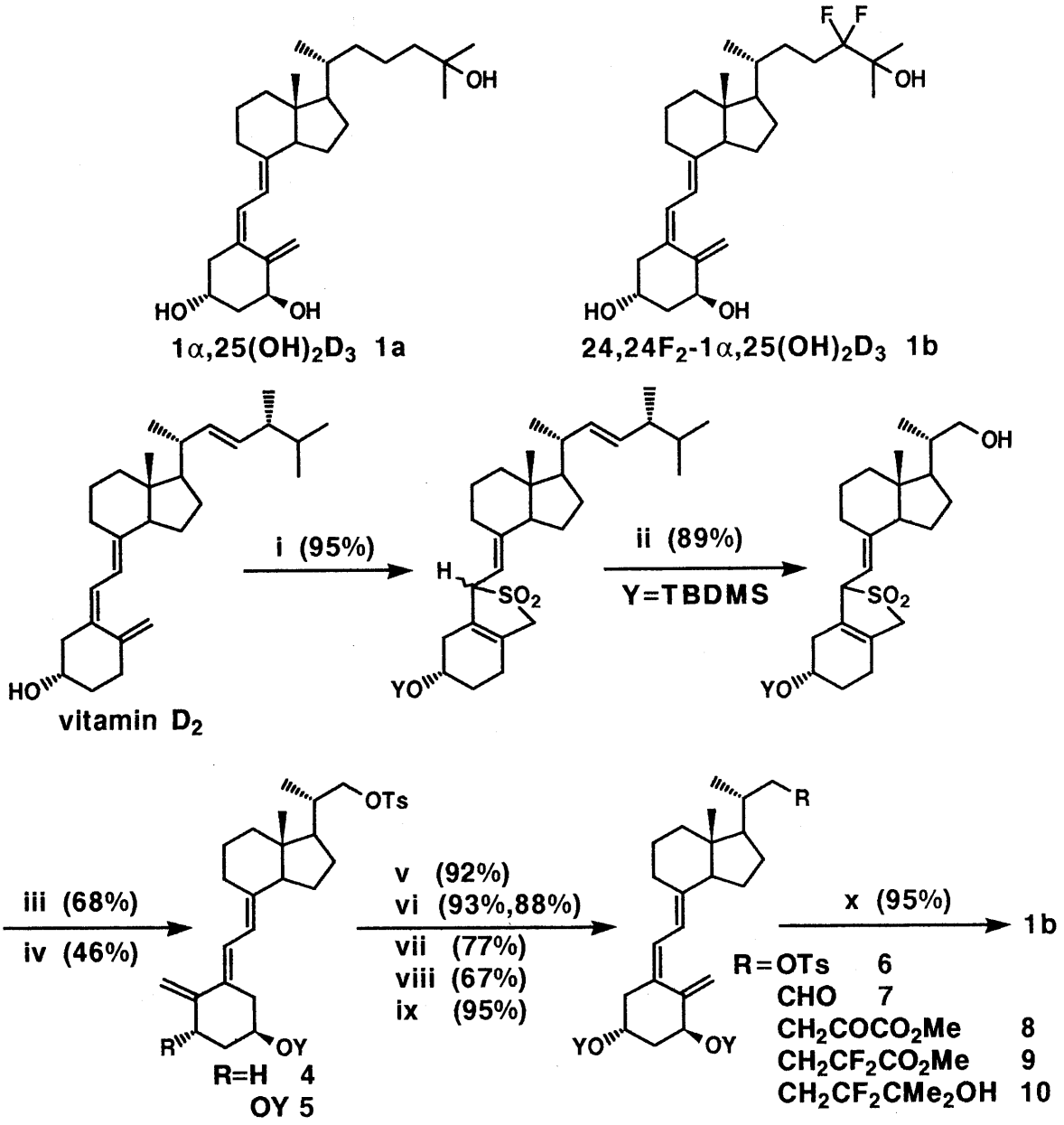
An improved synthesis of a highly potent vitamin D_3 analog, 24,24-difluoro-1α,25-dihydroxyvitamin D_3 has been accomplished. The total yield was 9.3% from inexpensive vitamin D_2 in 11 steps.

KEYWORDS 1α,25-dihydroxyvitamin D_3; vitamin D_2-SO_2 adduct; Horner-Emmons reaction; α-keto ester; fluorination; 24,24-difluoro-1α, 25-dihydroxyvitamin D_3

1α,25-Dihydroxyvitamin D_3 (**1a**), the physiologically active form of vitamin D, acts as one of the most potent regulators of calcium homeostasis and also induces differentiation in myeloid leukemia cells. The recognition of these important biological activities has stimulated a great deal of interest in the synthesis of vitamin D_3 analogs. In the course of our study of the modification of **1a**, we prepared 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**1b**)[1] in which the 24-hydroxylation was blocked with fluorine atoms. The biological tests show that the 24-difluoro compound **1b** is approximately 4-5 times more active than **1a** in the calcium uptake by chick duodonal discs and 4-7 times more potent than **1a** in inducing phagocytosis of HL-60 cells.[2]

Because of the obvious medicinal importance of **1b**, we reinvestigated the general and efficient approach to **1b**. In this report, the improved economic synthesis of **1b** from the readily available vitamin D_2 is described.

First of all, vitamin D_2 was converted to its SO_2-adducts using our procedure,[3] in which vitamin D_2 is dissolved in liquid sulfur dioxide and the solution is refluxed for 30 min. After evaporation of excess sulfur dioxide, the SO_2-adducts were directly silylated to give **2** as a separable 1.2:1 mixture in 95% yield. The major isomer **2a** was separated by silica gel chromatography and treated with ozone at -78°C in dichloromethane-methanol,[4] followed by the addition of $NaBH_4$ in methanol to afford the alcohol **3**[5] in 89% yield. The mixture of SO_2-adducts **2** was found to be convenient for use directly in the subsequent steps at the same efficiency to give alcohols **3** in 89% yield. Tosylation[4] of **3** followed by thermal cheletropic extrusion of SO_2 in refluxing ethanol containing $NaHCO_3$ gave the trans vitamin **4** in 68% yield. The direct 1α-hydroxylation of **4** was performed by Hesse's procedure [SeO_2 (0.7 eq), NMO (4



(i) (a) SO_2, reflux (b) TBDMSCl, imidazole, DMF (ii) (a) O_3, MeOH-CH_2Cl_2, pyridine, -78°C (b) $NaBH_4$, 0°C (iii) (a) TsCl, pyridine, 5°C (b) $NaHCO_3$, EtOH, reflux (iv) (a) SeO_2-NMO, CH_2Cl_2-MeOH, reflux (b)TBDMSCl, imidazole, DMF (v) hν-anthracene, Et_3N, toluene, 0°C (vi) (a) NaCN, DMSO, 90°C (b) DIBAH, CH_2Cl_2, -15°C→0°C (Vii) (a) $(MeO)_2P(O)CH(OEE)CO_2Me$, LDA (b) 0.05N HCl (viii) DAST, CH_2Cl_2, r.t. (ix) MeMgBr, THF, -78°C→0°C→r.t. (x) Bu_4NF, THF, r.t.

eq) in methanol-CH_2Cl_2].[4] Silylation of the crude hydroxylation products and the following purification by silica gel chromatography gave the pure bis-TBDMS ether **5** (46%) along with the unreacted starting material **4** (6%) and 1β-hydroxylated compound (7%). Compound **5** was photoisomerized (a high pressure mercury lamp, Pyrex)[6,4] to the cis isomer **6** in the presence

of anthracene as a triplet sensitizer in 92% yield. Displacement of the tosyl group with cyanide generated the nitrile, which on reduction with diisobutylaluminum hydride (DIBAH) gave aldehyde **7** in high yield. Horner-Emmons reaction of aldehyde **7** with trimethyl 2-ethoxyethyl-oxyphosphonoacetate[7] and subsequent acid hydrolysis gave the α-keto ester **8** in 77% yield. Introduction of fluorine atoms into **8** was performed by treatment with diethylaminosulfur trifluoride (DAST[8]) in dichloromethane at room temperature to provide the difluoro ester **9** in 67% yield. The use of DAST requires vigorous conditions for most ketones and aldehydes. But fluorination of α-keto esters with DAST is an efficient and mild process, as we have shown before.[1a] The difluoro ester **9** was treated with excess methylmagnesium bromide to afford the tertiary alcohol **10**. After deprotection with Bu_4NF in tetrahydrofuran, 24,24-difluoro-1α,25-dihydroxyvitamin D_3 **1b** was obtained as a white amorphous powder. The total yield was 9.3% from inexpensive vitamin D_2 by 11 steps. The compound **1b** thus obtained showed identical spectroscopic data with the compound **1b** from the low-yielding electrocyclic photochemically induced opening of the corresponding provitamin.[1a,b]

The more detailed biological activity of 24,24-difluoro-1α,25-dihydroxyvitamin D_3 (**1b**) is currently being investigated. The results will be reported elsewhere.

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