

PREPARATION OF (22*S*)- AND (22*R*)-24-HOMO-26,26,26,27,27,27-HEXAFLUORO-1,22,25-TRIHYDROXY-24-YNE-VITAMIN D₃

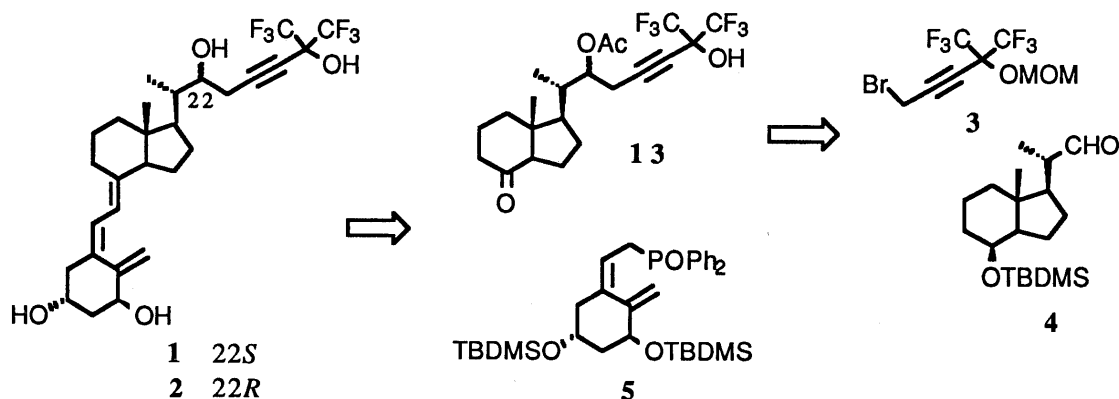
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A convergent synthesis of the titled fluorinated analogs of the 1,25-dihydroxyvitamin D₃, which modulates butyrate-induced differentiation of HT-29 human colonic carcinoma cells with very little effect on bone calcium mobilization, is reported.

KEYWORDS vitamin D₃; vitamin D₃ fluoro analog; calcium-regulating activity; Wittig reaction; cell differentiation

It is well known that 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] is a hormonal metabolite of vitamin D₃, which regulates calcium and phosphorous metabolism.¹⁾ Since its discovery, extensive efforts have been made to synthesize a number of analogs of vitamin D₃ with the aim of increasing and/or separating the biological activities.²⁾ It was demonstrated that 24,24-difluoro-³⁾ and 26,26,26,27,27,27-hexafluoro analogs⁴⁾ of 1,25(OH)₂D₃ are 5~10 times more active than 1,25(OH)₂D₃ in various vitamin D bioassays. It was also reported that the active forms of vitamin D₃, 1,25(OH)₂D₃⁵⁾ as well as the fluoro analogs⁶⁾, show the ability to induce differentiation of malignant cells. Although there is an important possibility that those active forms of vitamin D₃ might be effective in modulating malignant cell growth and differentiation *in vivo*, problems would be encountered by inducing severe hypercalcemia at the concentrations required for cell differentiation. Therefore, analogs having a strong effect on cell differentiation without showing calcium-regulating activity would be desirable for possible therapeutic use.⁷⁻⁹⁾ Among the reported analogs with structural alterations in 1,25(OH)₂D₃ in this line, 24- and 26-homo analogs⁸⁾ and 23-yne analogs⁹⁾ are classes of compounds which show effects on cell differentiation with decreased calcium-regulating activity. It was also reported that 22-hydroxylated vitamin D₃ exerts no calcium-regulating activity.¹⁰⁾

In this paper, we report the preparation of the titled new fluoro analogs (1, 2), which are highly potent in cell differentiation of HT-29 human colonic carcinoma cells with very little effect on bone calcium mobilization. The structural features of the present fluoro analogs as compared with those of hormonal metabolite are an additional hydroxyl at C-22, one carbon longer in side chain and 24-yne structure. For the preparation of the fluoro analogs (1, 2), we employed a convergent methodology using the three fragments 3, 4 and 5. This methodology would provide a general route for a variety of active form of vitamin D₃ and its analogs.



As preliminary results of biological assays, both **1** and **2** showed over 10 times more activity than $1,25(\text{OH})_2\text{D}_3$ in butyrate-induced differentiation of HT-29 human colonic carcinoma cells, whereas these fluoro analogs did not show any activity in bone calcium mobilization in rats. Details will be reported elsewhere soon.

ACKNOWLEDGEMENT The authors are grateful to Prof. N. Ikekawa of Iwaki-Meisei University for helpful discussion, to Dr. Y. Tanaka of Albany Medical College, Albany, NY, to Dr. M. Kawai and Dr. S. Unten of Aichi Medical University for biological assays, and to Dr. M. Shiro of Rigaku Corporation for X-ray crystallographic analysis.

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- 16) **1**: $[\alpha]_D^{20} = +16.7^\circ$ (c 0.54, CH_3OH); $\lambda_{\text{max}}^{\text{EtOH}} 264\text{nm}$ (ϵ 15272). $^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 0.58 (s, 3H), 0.91 (d, $J=5.6\text{Hz}$, 3H), 3.90 (m, 1H), 4.12 (m, 1H), 4.36 (m, 1H), 4.91 (brs, 1H), 5.30 (brs, 1H), 6.10 (d, $J=11\text{Hz}$, 1H), 6.34 (d, $J=11\text{Hz}$, 1H); $^{19}\text{F-NMR}(\text{CD}_3\text{OD}, \text{relative to } \text{CFCl}_3)$ δ : -77.58 (s), -77.60 (s).
- 17) **2**: $^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 0.56 (s, 3H), 0.95 (d, $J=6\text{Hz}$, 3H), 2.59 (dd, $J=11\text{Hz}$ and 3Hz , 1H), 2.85 (dd, $J=11\text{Hz}$ and 3Hz , 1H), 3.94 (m, 1H), 4.23 (m, 1H), 4.43 (m, 1H), 5.00 (brs, 1H), 5.33 (brs, 1H), 6.02 (d, $J=11\text{Hz}$, 1H), 6.37 (d, $J=11\text{Hz}$, 1H).

(Received March 11, 1992)