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1α,25-DIHYDROXY-19-NOR-VITAMIN D_3, A NOVEL VITAMIN D-RELATED COMPOUND WITH POTENTIAL THERAPEUTIC ACTIVITY

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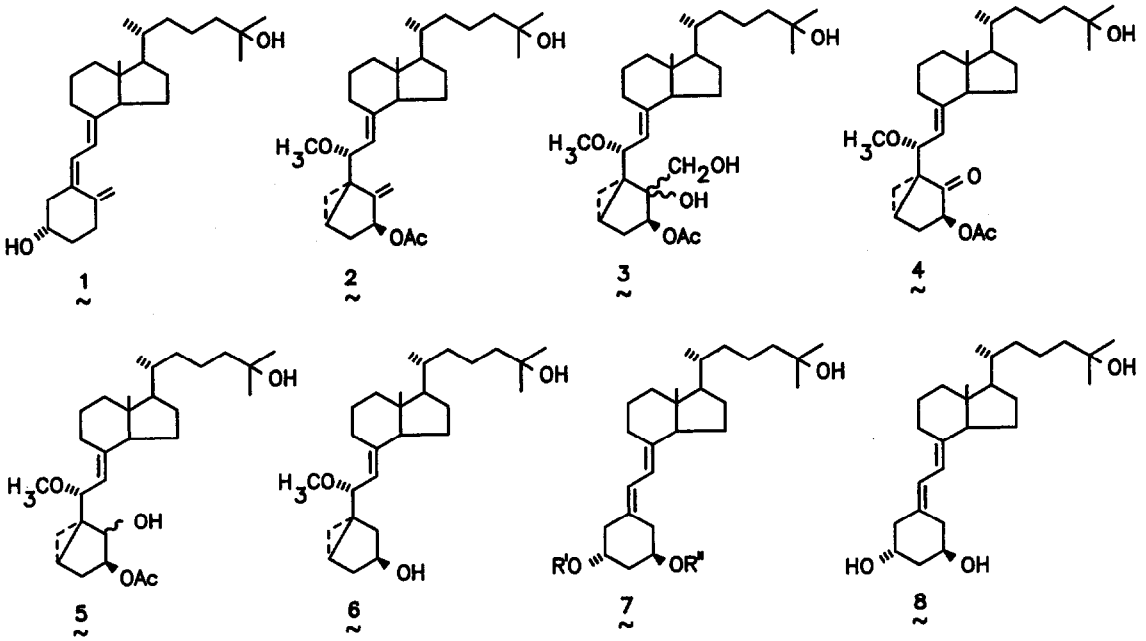
Summary: 1α,25-Dihydroxy-19-nor-vitamin D_3 has been synthesized via oxidative degradation of the 1α-hydroxycylcovitamin intermediate. Preliminary studies indicate that the new analog induces the differentiation of human leukemia HL-60 cells, with little or no calcemic activity.

The hormone, 1α,25-dihydroxyvitamin D_3 (1), is known to be a highly potent regulator of calcium homeostasis in animals and more recently, its activity in cellular differentiation has also been established.[2] Many structural analogs have been prepared and tested and found to exhibit a highly promising dichotomy between cell differentiation and calcium regulation. This difference in activity may be useful in the treatment of some cancers or osteoporosis.[3] In our systematic investigation of structure activity relationship of the vitamin D molecule, we chose to investigate the potency of the 19-nor analogs, i.e. compounds in which the ring A exocyclic methylene group (carbon 19), typical of the vitamin D system, has been removed and replaced by two hydrogen atoms (8).

In this paper we describe the synthesis of 1α,25-dihydroxy-19-nor-vitamin D_3. 25-Hydroxyvitamin D_3 was converted to the 1α-acetoxy-25-hydroxy-3,5-cyclovitamin D_3 (2),[4] as described for the 1α-acetoxy-3,5-cyclovitamin D_3.[5] Only the cyclovitamin is a suitable intermediate for a controlled oxidative degradation of vitamin D derivatives.[6] Cyclovitamin 2 was treated with a slight molar excess of osmium tetroxide in pyridine, according to the procedure of Paaren,[6] to obtain the mixture of diols 3,[7] in 55-60% yield (OsO_4, Pyr, RT, 15 min). 10,19-Dihydroxy compound 3 was subjected to diol cleavage using sodium metaperiodate in methanol at 0° to give the 10-oxo-1α,25-dihydroxycylcovitamin D_3 4[8] in 60% yield (saturated $NaIO_4$ solution in MeOH, 0°, 1 h). The 10-oxo-analog 4 was then reduced with $NaBH_4$ in EtOH to give the epimeric 10-alcohol 5[9] ($NaBH_4$, EtOH, 0°C, 16 h) in 63% yield. Alcohols 5 were mesylated with mesyl chloride in the presence of triethylamine (MsCl, TEA, in CH_2Cl_2, 0°C, 1 h), and after evaporation of the solvents, the crude mesylates were treated with $LiAlH_4$ in THF ($LiAlH_4$, THF, 0°C, 16 h) to give in a nucleophilic displacement reaction the desired 1α,25-dihydroxy-19-nor-cyclovitamin D_3 analog 6. Cycloreversion with acetic acid (AcOH, 55°C, 30 min) gave a mixture of 3-acetoxy-1α,25-dihydroxy-19-nor-vitamin D_3 and 1α-acetoxy-25-hydroxy-19-nor-vitamin D_3 7a and 7b. Overall yields for the 3 steps from the alcohol were 10-12%. KOH-MeOH-ether hydrolysis (0.1 n KOH-MeOH, ether, RT, 2 h) gave the final product of 1α,25-dihydroxy-19-nor-vitamin D_3 8.[10]

The new 19-nor analog 8 shows a selective activity profile, combining high potency in inducing differentiation of malignant cells, with very low or no bone calcification activity. The compound of this novel structural class opens up a new field of vitamin D analogs which could be useful as therapeutic agents for the treatment of malignancies. The detailed biological profile of this compound will be published elsewhere.



7a R'=Ac, R"=H

7b R'=H, R"=Ac

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6. Satisfactory spectral characterization of all intermediates was obtained.
7. 8 MS: 404 (M^+) (100), 386 (41), 371 (20), 275 (53), 245 (51), 180 (43), 135 (72), 95 (82), 59 (18). Exact mass calcd. for $C_{26}H_{44}O_3$ 404.3290, found 404.3272. ^1H NMR ($CDCl_3$) δ: 0.52 (3H, s, 18-CH_3), 0.92 (3H, d, J=6.9 Hz, 21-CH_3), 1.21 (6H, s, 26-CH_3 and 27-CH_3), 4.02 (1H, m, 3-αH), 4.06 (1H, m, 1β-H), 5.83 (1H, d, J=11.6 Hz, 7-H), 6.29 (1H, d, J=10.7 Hz, 6-H). UV (in EtOH) λ_{max} 243 (ε 15,100), 251.5 (ε 17,400), 261 (ε 12,600).

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