Tetrahedron Letters No. 13, pp 1107 - 1108, 1977. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF POTENTIAL VITAMIN D ANTAGONISTS

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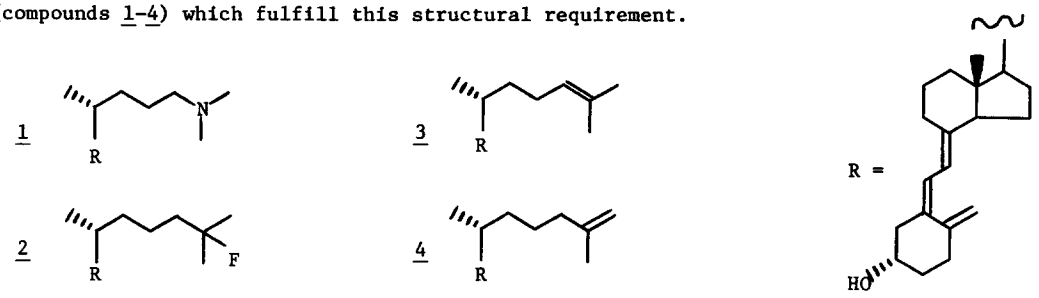
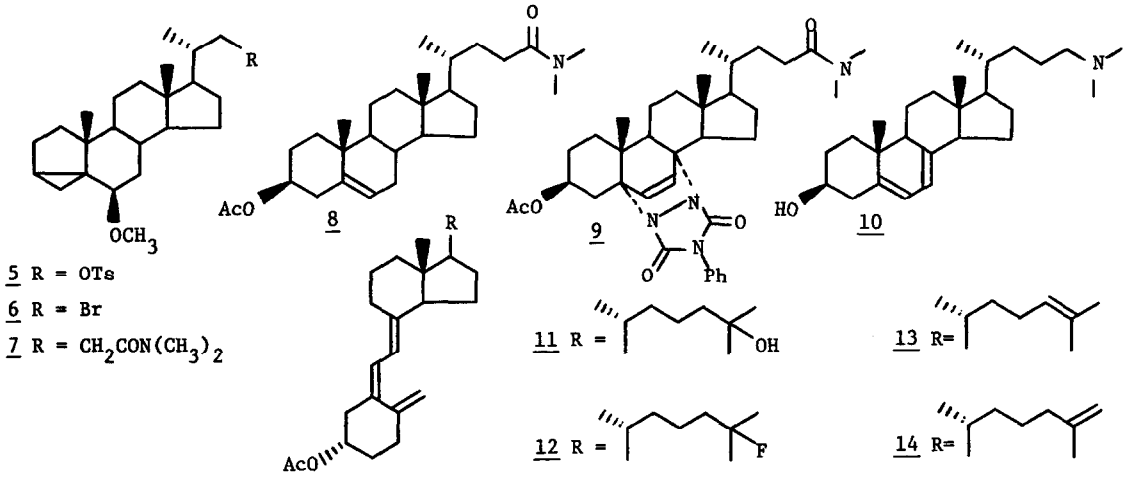
(Received in USA 30 November 1976; received in UK for publication 16 February 1977)

The biological activity of vitamin D_3 results from its metabolic conversion to 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$) in a two-step process involving hydroxylation of vitamin D_3 by the liver to 25-hydroxyvitamin D_3 (25-OH-D_3), and subsequent hydroxylation to 1α,25-$(OH)_2D_3$ by the kidney (1). Vitamin D analogs with altered side-chains that cannot be directly 25-hydroxylated by a mixed-function oxidase, but closely resemble the natural substrate, are thus potential inhibitors of the liver enzyme. We wish to report the synthesis of four new vitamin D analogs (compounds 1-4) which fulfill this structural requirement.



For the synthesis of 25-azavitamin D_3 (1) tosylate 5 served as starting material, in turn obtained in five steps and 61% yield from stigmasterol by the procedure of Partridge et al. (2). Compound 5 (mp 144-145°), treated with LiBr in refluxing acetonitrile (6.5 hr) gave, in 85% yield, the crystalline bromo derivative 6 (mp 63.5-65°). Condensation of 6 with the enolate of dimethyl acetamide (generated by treatment with lithium diisopropyl amide at -78°) yielded the cholanic acid dimethylamide derivative 7 (M^+ 415.3430) in 70% yield (3). Amide 7 heated in acetic acid (70°, 18 hr) gave cholenic acid dimethylamide 8 (93%, mp 192-193.5°). Treatment of 8 with 1,3-dibromo-5,5-dimethylhydantoin in refluxing CCl_4 (20 min, N_2 atmosphere) and subsequent dehydrohalogenation with collidine (in xylene, 140°, 1.5 hr, N_2) gave a mixture of 4,6 and 5,7-dienes from which the desired 5,7-diene was isolated by Diels-Alder adduct formation with 4-phenyl-1,2,4-triazolin-3,5-dione (4) to give product 9 (mp 122-125°) in ca. 20% overall yield. Reduction of adduct 9 with $LiAlH_4$ in boiling THF (7 hr) gave 25-aza-7-dehydrocholesterol (10; 84%; mp 141.5-143°). Irradiation of 10 in ether (6 min, 0°, N_2) followed by purification of the pre-vitamin D derivative and thermal isomerization of the latter at 70° provided the desired analog, 25-azavitamin D_3 [1; 23% yield; uv (EtOH) λ_{max} 265 nm; nmr (270 MHz, $CDCl_3$) δ 6.24 and 6.03 (AB, J = 11 Hz, 2H, C-6,7), 5.05 (m, 1H, C-19), 4.82 (m, 1H, C-19), 3.95 (t of t, J = 7.4 and 3.7 Hz, 1H, C-3), 2.31 (s, 3H, C-26,27), .93 (d, J = 6 Hz, 3H, C-21), .54 (s, 3H, C-18); m/e (rel. intensity) 385 (M^+, 15), 370 (3), 352 (1), 84 (10), 71 (4), 58 (100); M^+, m/e calcd. for $C_{26}H_{43}NO$: 385.3345, found: 385.3340; purity > 99% by tlc and glc].



The other analogs, 25-fluorovitamin D_3 (2), 24-dehydrovitamin D_3 (3) and 25-dehydrovitamin D_3 (4) are derived directly from monoacetate 11, itself obtained by selective acetylation of 25-OH-D_3. For example, reaction of 11 with diethylaminosulfur trifluoride (5) (15 min, -78° in CH_2Cl_2) gave tertiary fluoride 12 [yield 59%; M^+ 444.3385] which after hydrolysis with potassium hydroxide/methanol provided 25-fluorovitamin D_3 [2; 72% yield; uv (EtOH) λ_{max} 265 nm; nmr (270 MHz, $CDCl_3$) δ 6.24 and 6.03 (AB, J = 11 Hz, 2H, C-6,7), 5.05 (m, 1H, C-19), 4.82 (m, 1H, C-19), 3.95 (t of t, J = 7.1 and 3.6 Hz, 1H, C-3), 1.34 (d, $J_{H,F}$ = 21 Hz, 6H, C-26,27), .93 (d, J = 6 Hz, 3H, C-21), .54 (s, 3H, C-18); m/e (rel. intensity) 402 (M^+, 13), 369 (4), 271 (4), 253 (5), 136 (100), 118 (88); M^+, m/e calcd. for $C_{27}H_{43}OF$:402.3298, found: 402.3284; purity > 99% by tlc and glc]. Alternatively, treatment of 11 with phosphorus oxychloride/pyridine (1 hr, 25°) gave a 2:1 mixture of 13 to 14 which after chromatography (silver nitrate/silica gel) afforded intermediate 13 [37% yield] and intermediate 14 [11% yield]. Hydrolysis with potassium hydroxide transformed 13 to 24-dehydrovitamin D_3 [3; 79% yield; uv (EtOH) λ_{max} 265 nm; nmr (270 MHz, $CDCl_3$) δ 6.24 and 6.03 (AB, J = 11 Hz, 2H, C-6,7), 5.09 (t, J = 7 Hz, 1H, C-24), 5.05 (m, 1H, C-19), 4.82 (m, 1H, C-19), 3.95 (t of t, J = 7.4 and 3.7 Hz, 1H, C-3), 1.68 (s, 3H, C-26), 1.60 (s, 3H, C-27), .94 (d, J = 6 Hz, 3H, C-21), .54 (s, 3H, C-18); m/e (rel. intensity) 382 (M^+, 24), 349 (8), 253 (6), 136 (100), 118 (78), 69 (41), 55 (30); M^+, m/e calcd. for $C_{27}H_{42}O$:382.3236, found: 382.3229; purity > 99% by tlc and glc]. Acetate 14 was similarly hydrolyzed to 25-dehydrovitamin D_3 [4; uv (EtOH) λ_{max} 265 nm; nmr ($CDCl_3$) 6.24 and 6.04 (AB, J = 12 Hz, 2H, C-6,7), 5.05 (m, 1H, C-19), 4.82 (m, 1H, C-19), 4.69 (s, 1H, C-26), 4.66 (s, 1H, C-26), 3.95 (m, 1H, C-3), 1.72 (s, 3H, C-27), .93 (d, J = 6 Hz, C-21), .54 (s, 3H, C-18); m/e (rel. intensity) 382 (M^+, 26), 349 (5), 253 (5), 136 (100), 118 (78), 69 (18), 55 (30); M^+, m/e calcd. for $C_{27}H_{42}O$:382.3236, found: 382.3233; purity > 99% by tlc and glc].

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6. Support through grants AM-14881 and GM00236BCH from the NIH is acknowledged.