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SYNTHESIS OF 23,23-DIFLUORO-25-HYDROXYVITAMIN D_3

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Abstract: 23,23-Difluoro-25-hydroxyvitamin D_3 was synthesized from 6β-methoxy-3α,5-cyclo-23,24-dinor-5α-cholan-22-ol.

It is well known that vitamin D_3 is hydroxylated at C-1 and C-25 before it can carry out the biological functions.[1] The hydroxylation of 25-hydroxyvitamin D_3 at C-24 or C-26 has attracted attention in consideration of the possible physiological significance. To clarify it, the 25-hydroxyvitamin D_3 analogs blocked at C-24 or C-26 by substitution of the hydrogen atoms with fluorine atoms were synthesized[2),3)] and their biological activities were tested.[4),5)] Both fluorinated analogs [24,24-F_2-1,25-$(OH)_2D_3$ and 26,26,26,27,27,27-F_6-1,25-$(OH)_2D_3$] were more active than 1,25-$(OH)_2D_3$, the active form of vitamin D_3 possibly because of the slow metabolism resulting from the presence of fluorine atoms at these positions. In recent studies on the metabolism and function of vitamin D_3 metabolites hydroxylated at C-23 or further oxidized compounds have been isolated and their structures were determined.[6)] However, the physiological significance of 23-hydroxylation still remains to be clarified. Substitution of hydrogen atoms at 23-position with fluorine to block metabolic hydroxylation should provide important information on this point.

In this paper, we wish to report the synthesis of 23,23-difluoro-25-hydroxyvitamin D_3 (1,23,23-F_2-25-OH-D_3), in which 1) the introduction of the geminal fluorines was achieved by the reaction of the α-keto ester (4) and diethylaminosulfur trifluoride (DAST), 2) only the triflate of the difluoro-alcohol (8) was found to react with the pottasium salt of malonic ester to give the alkylated compound in good yield and 3) the monoalkylated malonic ester (10)

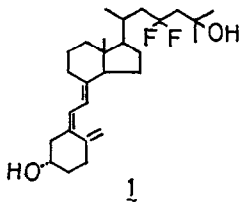
could be converted to the desired 25-hydroxycholesterol (15) via chlorohydrin intermediate (11).

For the synthesis of 23,23-difluoro ester (6), 6β-methoxy-3α,5-cyclo-23,24-dinor-5α-cholan-22-ol[7] was converted to the aldehyde (2)[8] [PCC, CH_2Cl_2, 73%, δ($CDCl_3$) 9.51 (1H, d, J=3.5Hz, -CHO)] followed by the reaction of 2 with the silyloxyphosphonoacetate (4) to afford the α-triethylsilyloxy-α,β-unsaturated ester (3) [81%, oil; ^{1}H-n.m.r. δ($CDCl_3$) 3.30 (3H, s, 6β-OCH_3), 3.73 (3H, s, -$COOCH_3$), 5.26 (1H, d, J=10Hz, 22-H); m/z:530(M^+)].[9] After acid treatment of 3 [CH_3COOH, 80-90°C, 6h then p-TsOH, dioxane-H_2O (1:1), 85-95°C, 7h; 5, 90%],[7] the reaction of the α-ketoester (5) with DAST (10 eq., CH_2Cl_2, r.t., 16h) gave the difluoro ester 6 [74%, mp 132-132.5°C; i.r.(cm^{-1}) 1770, 1730; ^{1}H-n.m.r. ($CDCl_3$) δ 0.70 (3H, s, 18-H_3), 1.01 (3H, s, 19-H_3), 1.10 (3H, d, J=6Hz, 21-H_3), 2.03 (3H, s, acetyl), 3.87 (3H, s, -$COOCH_3$), 4.60 (1H, m, 3-H), 5.38 (1H, m, 6-H); ^{19}F-n.m.r.[10] +40.3; m/z 406 (M^+-CH_3COOH)].[2b] The tetrahydropyranyl ether (7) was converted to the triflate (9) ($LiAlH_4$, ether, 8, 86% then Tf_2O-Py; CH_2Cl_2, r.t., 40 min., 9, quant.) which reacted with diethyl malonate [4 eq. tBuOK, THF-HMPA (3:1), r.t., 26 h) to give the malonate 10 [81%, mp 79-80°C, ^{1}H-n.m.r. ($CDCl_3$) δ 3.62 (1H, t, J=6Hz, 25-H), m/z 538 (M^+-DHP), 520, 505].

An attempt to convert the difluoro ester (10) to the corresponding allyl alcohol by Marchall's method failed.[11] Thus, we tried the synthesis of the 25-hydroxylated cholesterol 15 through the chlorohydrin derivative (12). Chlorination of 10 (NaH, DME then NCS; 11, quant.) and subsequent reduction ($LiAlH_4$, ether) gave the chlorohydrin (12) which was treated with base [NaH, THF-HMPA (10:1), r.t., 8 days] to afford the epoxide (13) [82%; ^{1}H-n.m.r. ($CDCl_3$) δ 2.92 (2H, m, 26-H_2), 3.67-4.16 (3H, m, 3-H and 27-H_2); m/z 434 (M^+-THP-OH), 416, 404]. The desired 25-hydroxycholesterol derivative (15) was obtained from 13 by a two step procedure (MsCl-Et_2N, CH_2Cl_2 then $LiAlH_4$, ether) in 80% yield. Removal of the THP group and acetylation (Ac_2O-Py, r.t.) gave the monoacetate (16) [96%, mp 168-170°C; ^{1}H-n.m.r. ($CDCl_3$) δ 0.82 (3H, s, 18-H_3), 1.02 (3H, s, 19-H_3), 1.07 (3H, d, J=6Hz, 21-H_3), 1.35 (6H, s, 26-H_3 and 27-H_3), 2.03 (3H, s, acetyl), 4.55 (1H, m, 3-H), 5.36 (1H, m, 6-H); m/z Calcd. for $C_{27}H_{42}F_2O$ (M^+-CH_3COOH): 420.3202. Found: 420.3206]. The transformation of 16 to the desired vitamin D_3 (1) was achieved by the standard method. Thus, bromination (NBS, CCl_4), dehydrobromination (s-collidine, xylene, refl., 20 min.) and subsequent saponification (5% KOH-MeOH, r.t., 30 min.) provided the 5,7-diene 17 (21.7%, UV λ_{max}^{EtOH} 294, 282, 272 nm). This was irradiated with a medium pressure mercury lamp through a Vycor filter (benzene-EtOH, 0°C, 2.5 min) and purified by prep. TLC (benzene-ethyl acetate 2:1, developed twice) to give the 23,23-F_2-25-OH D_3 (1) (25.6%). The physical data of 1 support its structure [UV λ_{max}^{EtOH} 265, λ_{min}^{EtOH} 228 nm; ^{1}H-n.m.r. ($CDCl_3$) δ 0.58 (3H, s, 18-H_3), 1.07 (3H, d, J=6.1Hz, 21-H_3), 1.34 (6H, s, 26-H_3 and 27-H_3), 3.95 (1H, m, 3-H), 4.81 (1H, bs, 19-H), 5.04 (1H, bs, 19-H), 6.03 (1H, d, J=10.7Hz, 7-H), 6.23

(1H, J=10.7Hz, 6-H). m/z 436(M^+), 418, 403. Calcd. for $C_{27}H_{42}F_2O_2$: 436.3150. Found: 436.3155].

The biological activity of 1 is currently being investigated by Prof. H. F. DeLuca's group at Wisconsin University.



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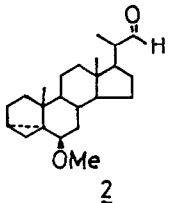

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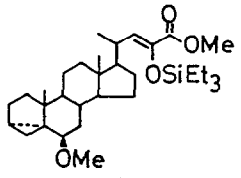

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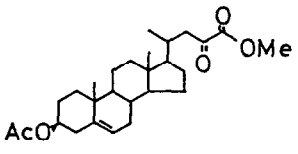

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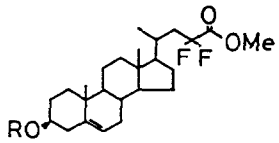

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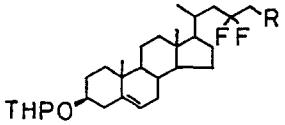
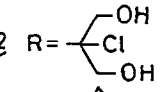
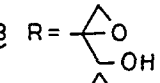
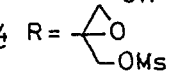
7 R=THP

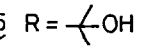


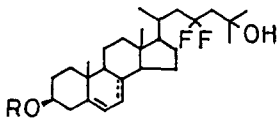
8 R=OH
9 R=OTf
10 R=CH(COOEt)$_2$
11 R=CCl(COOEt)$_2$

12 R= 

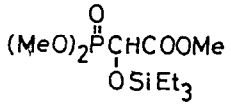
13 R= 

14 R= 

15 R= 



16 R=Ac
17 R=H, 5,7-diene



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