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SYNTHESIS OF POSTULATED METABOLITES OF 1α,25-DIHYDROXY-22-OXAVITAMIN D_3[1]

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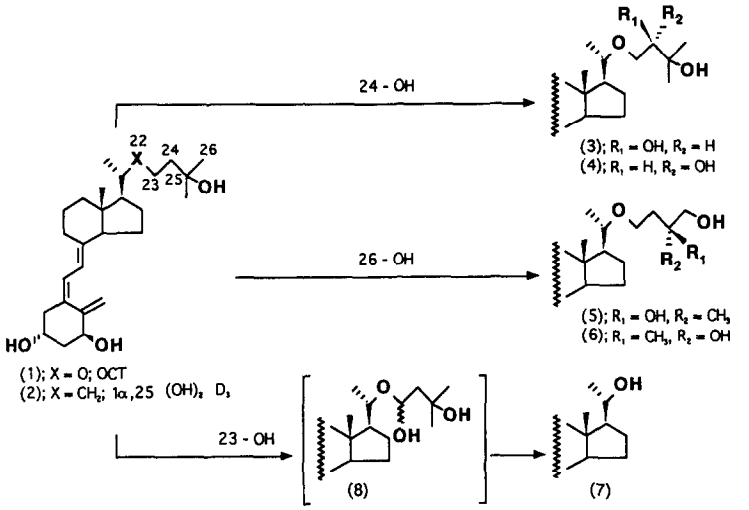
Abstract: As the postulated metabolites of 1α,25-dihydroxy-22-oxavitamin D_3 (OCT) (1), 24-hydroxylated OCT (3 and 4), 26-hydroxylated OCT (5 and 6), and pentanorOCT (7) were synthesized from the 20(S)-alcohol (9).

1α,25-Dihydroxy-22-oxavitamin D_3 (OCT) (1), the 22-oxa analogue of 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3] (2), showed potent in vitro differentiation-inducing activities with low in vivo calcemic liability.[3-5] OCT (1) is being clinically investigated as a candidate for treatment of secondary hyperparathyroidism[6] and psoriasis.[7]

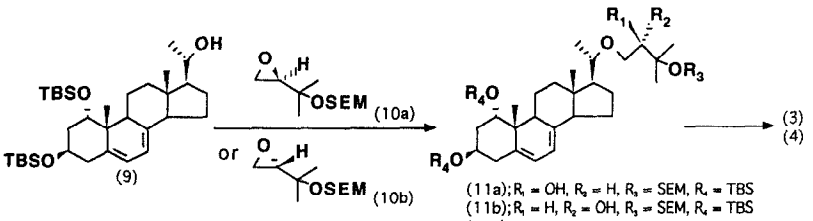
During the course of our development of OCT (1), the synthesis of the possible metabolites of OCT (1) was needed for pharmacokinetic and metabolic studies. It is well known that the active vitamin D_3, 1α,25-$(OH)_2$-D_3 (2), is hydroxylated at C-23, C-24 or C-26 positions as the first step in its metabolism.[8-9] Taking the same hydroxylation of OCT (1) as 1α,25-$(OH)_2$-D_3 (2) into consideration, we undertook the synthesis of hydroxylated OCT at C-23, C-24 or C-26 positions as the postulated metabolites of OCT (1). In this paper we wish to describe the synthesis of 24-hydroxylated OCT (3 and 4) in 24(R) and 24(S) forms, 26-hydroxylated OCT (5 and 6) in 25(S) and 25(R) forms and pentanorOCT (7), possibly derived from the 23-hydroxylated hemiacetal (8).



First, we performed the synthesis of 24-hydroxylated OCT (3 and 4). The 20(S)-alcohol (9)[3] was alkylated with the (R)-epoxide (10a) and the (S)-epoxide (10b), prepared from D-mannitol and L-serine according to the literature,[10] in the presence of dibenzo-18-crown-6 and potassium *tert*-butoxide to give the alcohols (11a or 11b) in 24% and 10% yields, respectively. The alcohols (11a and 11b) were then separately deprotected with tetra-butylammonium fluoride in N,N'-dimethylpropyleneurea at 80°C to give the tetraols (12a and 12b) in 77% and 70% yields. Subsequent irradiation of 12a and 12b in ethanol at 0°C using a high-pressure mercury lamp through a Vycor filter followed by thermal isomerization under reflux in ethanol gave rise to 24(R)-hydroxylated OCT (3)[11] and 24(S)-hydroxylated OCT (4)[12] in 17% and 13% yields, respectively.

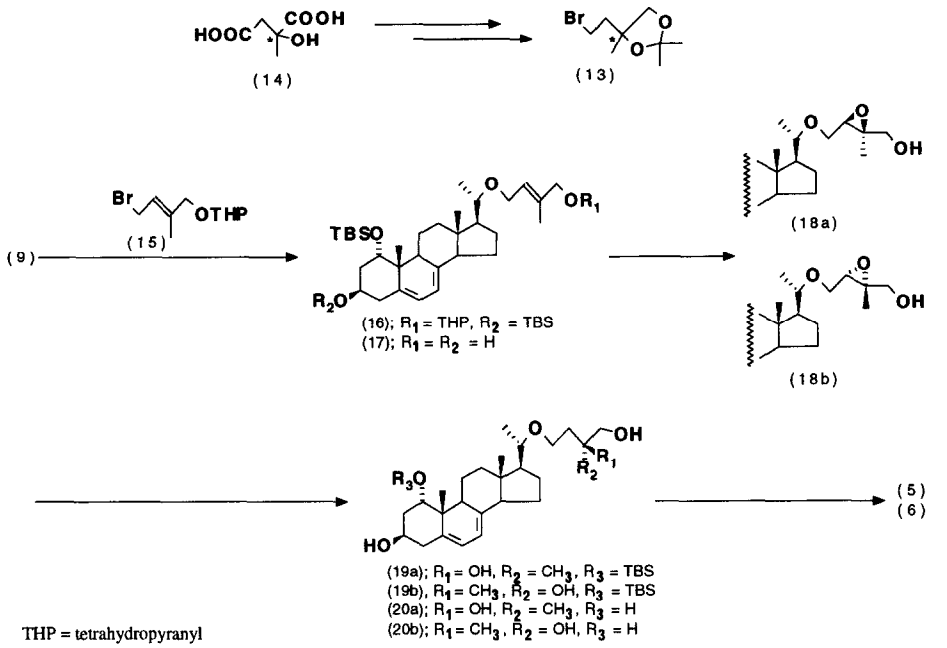
Next, to synthesize 26-hydroxylated OCT (5 and 6), we unsuccessfully attempted the alkylation of the 20(S)-alcohol (9) with the fully functionalized bromide (13), prepared from (R)- or (S)-citramalic acid (14) in both enantiomeric forms.[13] These efforts lead only to the recovery of the 20(S)-alcohol (9) and the decomposition of the bromide (13) under several conditions. The reaction between the 20(S)-alcohol (9) and the bromide (15)[14] in the presence of potassium hydride, however, resulted in the formation of the ether (16) in 94% yield based upon the recovery of 9. Therefore, we turned our attention to a different route using the Katsuki-Sharpless epoxidation.[15] Thus, the THP moiety of 16 was cleaved using pyridinium *p*-toluenesulfonate in methanol forming the allyl alcohol (17) with concomitant desilylation at C-3 position in 82% yield. The subsequent Katsuki-Sharpless epoxidation[15] of 17 with *tert*-butyl hydroperoxide in the presence of (-)- or (+)-diisopropyl tartrate and titanium (IV) tetraisopropoxide provided the epoxides (18a or 18b) in 89% and 86% yields, respectively. Regioselective cleavage of the epoxy-rings in 18a and 18b with diisobutylaluminum hydride was achieved at the less congested C-24 position to give the triols (19a and 19b). Both 19a and 19b were then desilylated to the tetraols (20a and 20b), in 86% and 77% yields from the epoxides (18a and 18b), which were irradiated and thermally isomerized to 26-hydroxylated OCT with 25(S)- and 25(R)-configuration (5[16] and 6[17]), in 18% and 19% yields, respectively.

The last target was pentanorOCT (7), which might be obtained from 23-hydroxylated hemiacetal (8) in the metabolic experiments. Thus, the 20(S)-alcohol (9) was irradiated, thermally isomerized and desilylated to give pentanorOCT(7)[18] in 25% yield.



TBS = tert - butyldimethylsilyl
SEM = (2-trimethylsilyl)ethoxymethyl

(11a); R_1 = OH, R_2 = H, R_3 = SEM, R_4 = TBS
(11b); R_1 = H, R_2 = OH, R_3 = SEM, R_4 = TBS
(12a); R_1 = OH, R_2 = R_3 = R_4 = H
(12b); R_1 = H, R_2 = OH, R_3 = R_4 = H



In the preliminary metabolic studies of OCT (1), the metabolites possessing the same retention time in high-performance liquid chromatography analysis as pentanorOCT (7) and 24(R)-hydroxylated OCT (3) were observed. The detailed metabolism of OCT (1) will be reported elsewhere.

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References and notes

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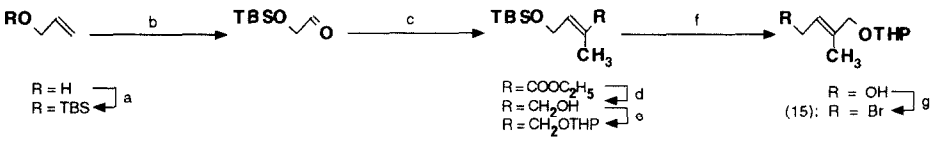
11) **3**: NMR δ 0.53 (3H, s), 1.19 (3H, d, *J*=6.1Hz), 1.22 (3H, s), 1.24 (3H, s), 3.26-3.32 (1H, m), 3.37-3.47 (2H, m), 3.73-3.82 (1H, m), 4.16-4.27 (1H, m), 4.38-4.45 (1H, m), 4.99 (1H, s), 5.33 (1H, s), 6.02 (1H, d, *J*=11.5Hz), 6.37 (1H, d, *J*= 11.5Hz). MS *m/z*: 434 (M^+), 134 (100%). HRMS Calcd for $C_{26}H_{42}O_5$ 434.3032. Found 434 3023. UV λ_{max}nm: 262, λ_{min}nm: 227 $[\alpha]_D^{20}$ 44.00 (c=0.29, EtOH).

12) **4**: NMR δ 0.54 (3H, s), 1.19 (3H, d, *J*=5.8Hz), 1.22 (3H, s), 1.25 (3H, s), 3.22-3.29 (1H, m), 3.34-3.46 (2H, m), 3.76 (1H, brd, *J*=6.3Hz), 4.14-4.25 (1H, m), 4.37-4.44 (1H, m), 4.99 (1H, s), 5 33 (1H, s), 6.02 (1H, d, *J*=11.0Hz), 6.37 (1H, d, *J*=11.0Hz). MS *m/z*: 434 (M^+), 134 (100%). HRMS Calcd for $C_{26}H_{42}O_5$ 434.3032. Found: 434.3039. UV λ_{max}nm: 263, λ_{min}nm: 227. $[\alpha]_D^{20}$ 29.00 (c=0.19, EtOH).

13) Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett* **1981**, *22*, 2591.

14) The bromide (15) was prepared from allyl alcohol as follows:



a; TBSCl, Et_3N, b, i) O_3, ii) Ph_3P, c; $Ph_3PC(CH_3)COOC_2H_5$, d, DIBAH, e, Dihydropyran, f, TBAF, g, Ph_3P, CBr_4

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16) **5**: IR (neat): 3385, 2920, 2865, 1050, 730cm^{-1}. NMR δ: 0.54 (3H, s), 1.19 (3H, d, *J*=5.9Hz), 1.19 (3H, s), 3.21-3.34 (1H, m), 3.42 (2H, s), 3.44-3.61 (1H. m), 3.69-3.81 (1H, m), 4.22 (1H, brs), 4.43 (1H, brs), 5.00 (1H, s), 5.33 (1H, s), 6.02 (1H, d, *J*=11.2Hz), 6.37 (1H, d, *J*=11 2Hz). MS *m/z*: 434 (M^+), 85 (100%). HRMS Calcd for $C_{26}H_{42}O_5$ 434.3032. Found: 434.3048. UV λ_{max}nm. 264, λ_{min}nm: 227. $[\alpha]_D^{20}$ 65 85 (c=0.08, EtOH).

17) **6**: IR (neat): 3375, 2920, 2865, 1050cm^{-1}. NMR δ: 0.53 (3H, s), 1.18 (3H, s), 1.20 (3H, d, *J*=7.3Hz), 3.25-3.50 (3H, m), 3.57 (1H, s), 3.81-3.93 (1H, m), 4.23 (1H, brs), 4.42 (1H, brs), 4.99 (1H, s), 5.33 (1H, s), 6.02 (1H, d, *J*=11.6Hz), 6.37 (1H, d, *J*=11.6Hz). MS *m/z*: 434 (M^+), 85 (100%). HRMS Calcd for $C_{26}H_{42}O_5$ 434.3032. Found: 434.3048 UVλ_{max}nm: 263, λ_{min}nm: 227. $[\alpha]_D^{20}$ 49.35 (c=0.08, EtOH).

18) **7**: NMR δ: 0.55 (3H, s), 1.23 (3H, d, *J*=6.6Hz), 2.33 (1H, dd, *J*=6.0, 13.1Hz), 2.61 (1H, dd, *J*= 2.9, 13.1Hz), 2.85 (1H, dd, *J*=2.9, 10.8Hz), 3.62-3.76 (1H, m), 4.17-4.31 (1H, br), 4.37-4.51 (1H, br), 5.00 (1H, s), 5.33 (1H, s), 6.04 (1H, d, *J*=11.7Hz), 6.37 (1H, d, *J*=11.7Hz). MS *m/z*: 332 (M^+), 134 (100%). HRMS Calcd for $C_{21}H_{32}O_3$ 332.2351. Found: 332.2369 UV λ_{max}nm: 263, λ_{min}nm; 227. $[\alpha]_D^{20}$ 55.10 (c=0.10, EtOH).

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