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A CONVENIENT SYNTHESIS OF 1α, 25-DIHYDROXY-28-NORVITAMIN D_2

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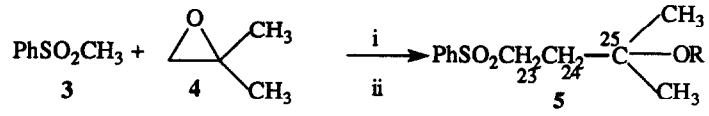
Abstract: The title compound was synthesized *via* the Julia olefination using ring B-diene protected 3β-hydroxy-23,24-bisnorchola-5,7-diene-22-al acetate and the side-chain synthon 2-methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)butane. Ring B-deprotection, photolysis, Paaren-DeLuca hydroxylation and separation of the 5,6 E and Z stereoisomers completed the synthesis in overall 3% yield.

1α,25-Dihydroxyvitamin D_3 (**1**), (1,25-$(OH)_2D_3$) is the hormonally active metabolite of vitamin D_3.[1] This compound is highly efficacious in bone calcium mobilization,[2] but therapeutic use in bone disease (osteoporosis, osteomalacia) is limited by its toxicity.[3] Thus a basis exists for synthetic structural modification aimed at a favorable balance between efficacy and toxicity.

1α, 25-Dihydroxy-28-norvitamin D_2 (**2**) (9,10-secocholesta-5,7,10(19),22(E) tetraene, 1α,3β, 25-triol) was reported by DeLuca and Schnoes to be highly active in promoting a rise in serum calcium levels in vitamin D deficient rats and determined to possess equivalent biological potency compared to 1,25$(OH)_2D_3$ (**1**).[4a,b] This result is supported by data of Holick, Uskokovic and Persons who report that **2** (designated as Ro-23-6710) is 33% more effective than 1,25-$(OH)_2D_3$ (**1**) in bone calcium mobilization and shows a 22% higher binding affinity for the 1,25-$(OH)_2D_3$ (**1**) rat intestine receptor.[5] From a structural viewpoint **2** may be formally considered a side-chain hybrid between the vitamin D_2 series which possesses a $C_{22\text{-}23}$ *trans* double bond with the C_{28} methyl group having the R-configuration at C_{24} (as in ergosteryl acetate **6**), and vitamin D_3 in which the side chain is saturated and does not have a C_{28} methyl group (as in **1**). Noting that toxicity is determinative in restricting the therapeutic use of 1,25$(OH)_2D_3$ (**1**),[3] the recent report of DeLuca et al, that 1α-hydroxy D_2 is 5 to 15 less toxic than 1α-hydroxy D_3 in the rat, but with equal potency in bone calcium mobilization[6] suggests the potential value of side-chain modification in which elements of the vitamin D_2 side-chain are introduced into the vitamin D_3 counterpart. 1α-25-Dihydroxy -28-norvitamin D_2 (**2**) embodies this concept. Finally, **2** has been obtained by deLuca and Schnoes *via* enzymatic hydroxylation at C_{25} of 1α-hydroxy-28-norvitamin D_2.[4a] The present synthesis affords research samples of **2**. The side-chain constituting carbon atoms C_{23}-C_{27} was obtained as the tetrahydropyranyl ether using a known route involving condensation of 2,2-dimethyloxirane **4** and the sodium hydride generated anion of methyl phenylsulfone followed by THP protection[7a,b] (**3**→**4**→**5**).



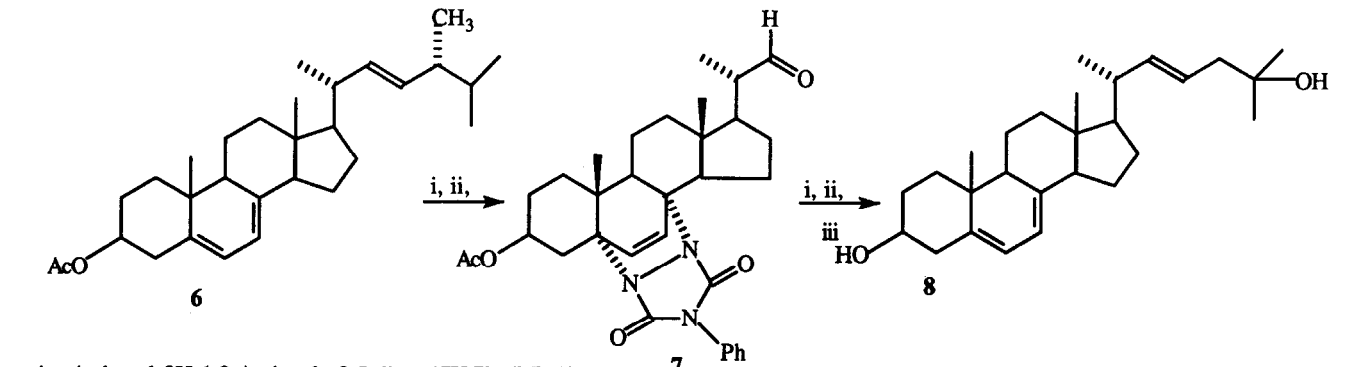
i = NaH/DMSO, 3 hr, 0° (3+4→5a)
ii = DHF/CH_2Cl_2/PPTS, 4hr, RT (5a→5b)

5a = R = H
5b = R = THP

Ergosteryl acetate (**6**) as converted into the known C-22 aldehyde (**7**) *via* preliminary protection of the 5,7-diene with 4-phenyl-3H-1,2,4-triazole-3,5-dione and ozonolysis according to the procedure described by Barton et al.[8] Julia olefination was employed to attach the side-chain with the desired trans C_{22}-C_{23} stereochemistry, specifically *via* addition of aldehyde **7** to the carbanion generated from sulfone **5b**, followed by sodium amalgam reductive elimination from the thus formed hydroxysulfone.[9] Ring B-diene regeneration with concomitant removal of the C_3-acetoxy group was effected by $LiAlH_4$ reduction. Final deprotection at C_{25} of the THP group using PPTS/EtOH yielded diol **8** which was prepared earlier by a Russian group using a Wittig reaction [$(Ph_3P^+CH_2CH_2COOH)Br^-$, then CH_2N_2, then CH_3MgI) to attach the side-chain using aldehyde (**7**).[10] Our product m.p. 184-87°, lit.[10] 186-88° was essentially identical to theirs and was obtained in 17% yield from **7**.

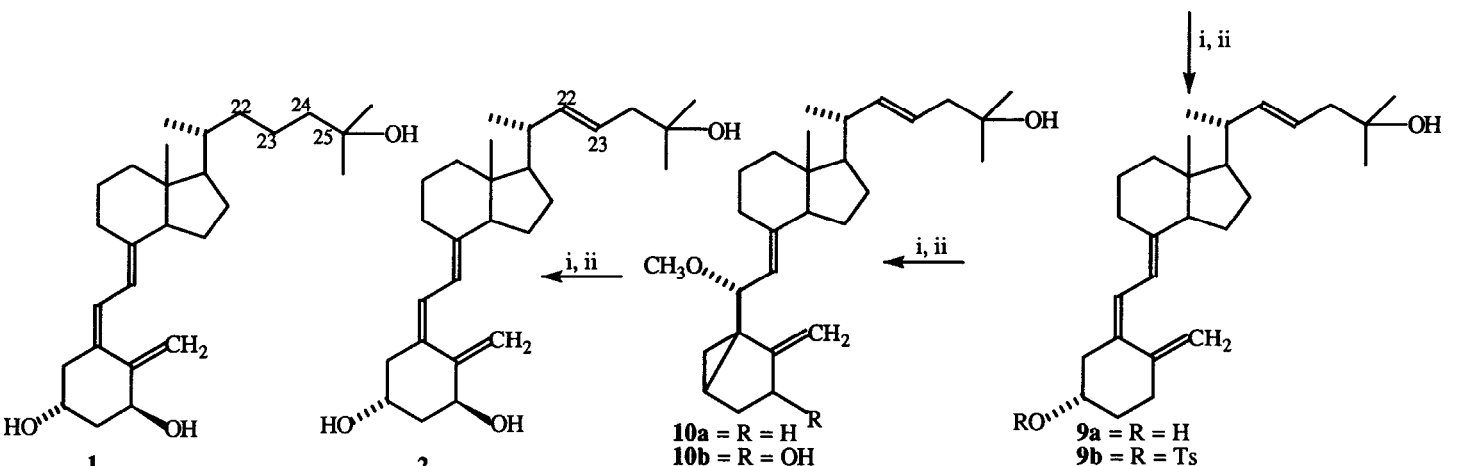
Irradiation of the diol (**8**) with a high-pressure mercury lamp followed by thermal-isomerization gave the known 25-hydroxy-28-norvitamin D_2 (**9a**).[10] Hydroxylation at the C_1 position of **9a** was carried out using the DeLuca-Paaren procedure *via* 3β-tosylate derivative (**9b**) which was directly solvolyzed to obtain the 3,5-cyclovitamin D_2 intermediate (**10a**).[11] Treatment of **10a** with selenium dioxide and *tert*-butyl hydroperoxide yielded after chromatographic purification the corresponding 1α-hydroxylated product (**10b**); (^{1}H NMR (400 MHz, $CDCl_3$)δ 0.55 (3H, s, 18-CH_3), 1.0 (3H, d, 21-CH_3, J=8.2 Hz), 1.13 (3H, s, 27-CH_3), 1.17 (3H, s, 26-CH_3), 3.26 (3H, s, OCH_3), 4.2 (2H, m, 1H and 6H), 4.96 (1H, d, 7-H, J=10.3 Hz), 5.18 (1H, d, (19Z)-H, J=1.7 Hz), 5.24 (1H, d, (19E)-H, J=1.7 Hz), 5.34 (2H, m, 22-H and 23-H)). Heating of this 1α-hydroxylated product (**10b**) in glacial acetic acid/DMSO at 55°C provided 5,6-*cis* and 5,6-*trans* 1α, 25-dihydroxy-28-norvitamin D_2 which was separated by maleic anhydride adduction and column chromatography (EtOAc: Hex=1:1, flash silica gel) to give 1α, 25-dihydroxy-28-norvitamin D_2 (**2**) in 3% yield from (**6**). Product (**2**) was further purified by HPLC (Zorbax CN column, 4.6 mm x 250 mm, 7% isopropanol in hexane),mp 82-84°. The mass spectrum and UV spectral data of (**2**) were in accord with those reported earlier[4a] (UV absorption (MeOH): λ max 266 nm (ε 17,300), λ min, 228 nm, mass spectrum: (CI) m/z 415 (6.8%) (M^++1), 397 (100%) (M^++1-H_2O), 379 (38%) (M^++1-2 x H_2O), 287 (6.4%) (M^+-side chain), 269 (7.2%), 251 (2.0%), 152 (2.4%), 134 (2.0%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (3H, s 18-CH_3), 1.05 (3H, d, J=6.6Hz, 21-CH_3), 1.20 (6H, s, 26-CH_3 and 27-CH_3). 4.23 (1H, m, 3-H), 4.45 (1H, m 1-H), 5.02 (1H, m (sharp), 19Z-H), 5.35 (1H, m (sharp), 19E-H), 5.42 (2H, m, 22-H and 23-H), 6.04 (1H, d, Z=11.3Hz, 7-H), 6.39 (1H, d, J=11.3Hz, 6-H), optical rotation ($[\alpha]_D^{20}$ + 57.2° C=0.14, EtOH)).

Finally the more extensively hydroxylated analog of **2** 1α,25S-26-trihydroxy-28-norvitamin D_2, has been reported to be a potent inducer of cell differentiation,[12] and an indication for the use of **2** and hydroxylated side-chain analogs in the treatment of hyperparathyroidism has appeared.[13]



i = 4-phenyl-3H-1,2,4-triazole-3,5-dione/$CHCl_3$, RT, 1hr
ii = O_3/CH_2Cl_2, -78°, 2.5hr then Me_2S

i: **5b**, n-BuLi/THF, -70°, 30 min
ii: Na-Hg(5%)/Na_2HPO_4/MeOH, 0°, 15 hr
iii: $LiAlH_4$/THF, reflux, 3 hr



i: AcOH/DMSO, 55°C, 1 hr
ii: Maleic anhydride/ EtOAc, 35°C, 24 hr

i: $NaHCO_3$/MeOH, reflux, 24 hr
ii: SeO_2/tBuOOH/CH_2Cl_2, RT, 3hr

i: hυ/Benzene-ether, RT, 2.5 hr
ii: TsCl/pyridine, 5°, 24 hr, Δ/EtOH, 8 hr

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