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FACILE AND STEREOSELECTIVE SYNTHESIS OF 25-HYDROXYVITAMIN D_2

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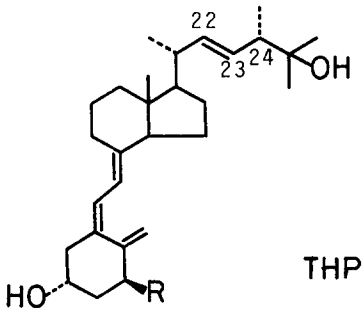
Summary: 25-Hydroxyvitamin D_2 was synthesized conveniently and stereoselectively for the first time by utilizing Sharpless' chiral epoxidation and the subsequent regio- and stereoselective methylation with lithium dimethylcuprate to introduce the desired chirality at C(24) and the reductive elimination of the vicinal hydroxy sulfone to introduce stereoselectively the E double bond at C(22) of the target molecule.

Similarly to the natural vitamin D_3,[1] vitamin D_2 (ergocalciferol) must be hydroxylated at the 25-position in the liver[2,3] and then at the 1α-position in the kidney[3,4] before expressing its biological activity. It has been known that the biological activity of 25-hydroxyvitamin D_2 (1a)[5] and 1α,25-dihydroxyvitamin D_2 (1b)[6] is similar to the corresponding vitamin D_3 derivatives in mammals but the formers are 1/5 to 1/10 less active than the latters in birds. The biological importance of these metabolites, however, has remained uncertain because the synthesis of neither 25-hydroxyvitamin D_2 nor 1α,25-dihydroxyvitamin D_2 has been established and enough material of these compounds has not been available for biological studies. Compared with vitamin D_3 derivatives, vitamin D_2 derivatives have an additional chiral center at C(24) and an E double bond at C(22), making their synthesis more complicated. As a part of our studies[7] on the stereoselective synthesis of vitamin D metabolites possessing chiral center on the side chain, we have developed a facile and stereoselective method for constructing the side chain structure common to 25-hydroxyvitamin D_2 (1a) and 1α,25-dihydroxyvitamin D_2 (1b). We report now the first and stereoselective synthesis of 25-hydroxyvitamin D_2 (1a).[8]

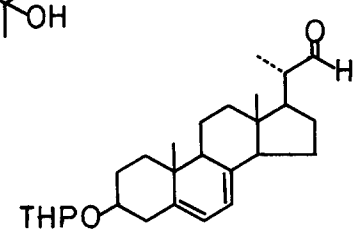
The gross structure of the target compound was constructed from the two segments, C_{22}-steroid synthon 2 and C_6-chiral synthon 3b, in a similar manner as described in our previous reports in this series. The chiral synthon 3b to constitute the C(23)-C(28) side chain part was synthesized starting with prenol (4) and the desired chirality for the 24-position of the target molecule 1a was introduced by utilizing Sharpless' chiral epoxidation[9] followed by

regio- and stereoselective methylation with lithium dimethylcuprate ($LiCuMe_2$).[10] The 22(23) trans-double bond was introduced selectively by reductive desulfonylation[11] of β-hydroxysulfone 7 which in turn was obtained by the coupling of the aldehyde 2 and the sulfone 3b.

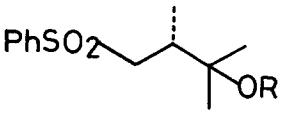
Prenol (4) was treated with tert-butylhydroperoxide (1.1 equiv) and titanium isopropoxide (1 equiv) in the presence of D-(-)-dibutyl tartrate (1 equiv) (CH_2Cl_2, -20 °C) to give chiral epoxide 5a ($[\alpha]^{22}_D$ +17.12°, 1% $CHCl_3$) (25%), which by benzylation ($PhCH_2Cl$, NaH, DMSO, r.t.) gave 5b (92%). The reaction of the epoxide 5b with $LiCuMe_2$ (Et_2O, -20 °C) proceeded with exclusive regio- and stereoselectivity to give alcohol 6a (93%) as the sole product. The optical purity of the alcohol 6a exceeds 90% as determined by its ^1H NMR spectrum in the presence of chiral shift reagent, 3-(heptafluoropropylhydroxymethylene)-d-camphorate. The configuration of the alcohol 6a was assigned S on the basis of the well established stereochemical consequence of the epoxidation[9] and alkylation of epoxides with organo cupper reagent.[10] Diol 6b ($[\alpha]^{22}_D$ -2.5°, 0.18% $CHCl_3$) obtained by deprotection of 6a was converted to the phenylsulfone 3b (71%, overall) by the standard method; tosylation (TsCl, pyridine, 90%), reaction with thiophenol (t-BuOK, DMF, 91%), oxidation (Na_2WO_4, H_2O_2, 70 °C, 99%),[12] and protection of the hydroxyl group (DHP, PPTS, CH_2Cl_2, 95%). The reaction of the sulfone 3b with C(22)-aldehyde 2 (LDA, THF, -78 °C), obtained from ergosterol,[7,13] gave β-hydroxysulfone 7 in good yield (65%). Reductive desulfonylation[9] (5% Na-Hg, Na_2HPO_4, 0 °C) of 7 proceeded stereoselectively affording E olefin 8a (52%) as the sole product which by deprotection (PPTS, 95% EtOH, 40 °C) gave the desired provitamin D (8b) (95%) [^1H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.06 (3 H, d, J = 6 Hz), 1.14 (3H, s), 1.17 (3H, s), 5.3 - 5.6 (4 H, m)]. The E stereochemistry of the newly introduced 22(23) double bond in 8b was supported by the ^1H NMR spectrum, where the coupling pattern of the olefinic protons at the side chain was in good agreement with that of ergosterol. The provitamin D 8b was transformed into 25-hydroxyvitamin D_2 (1a) (31%) by UV irradiation followed by thermal isomerization. The all spectral properties of the vitamin D 1a [MS m/e 412 (M^+), 394, 271, 253, 136, 118; UV (95% EtOH) 265 nm; ^1H NMR ($CDCl_3$) δ 0.56 (3 H, s), 0.99 (3 H, d, J = 7.5 Hz), 1.03 (3 H, d, J = 6.5 Hz), 1.13 (3 H, s), 1.16 (3 H, s), 3.95 (1 H, m), 4.81 (1 H, d, J = 2 Hz), 5.03 (1 H, m), 5.33 (2 H, m), 6.01 (1 H, d, J = 11 Hz), 6.23 (1 H, d, J = 11 Hz)] thus synthesized support the structure and are in good agreement with those of the natural metabolite.[2]



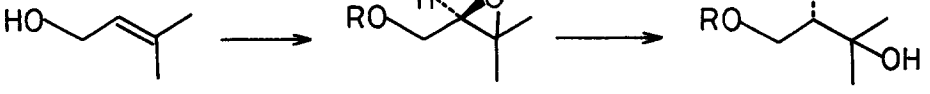
1a : R = H
1b : R = OH



2



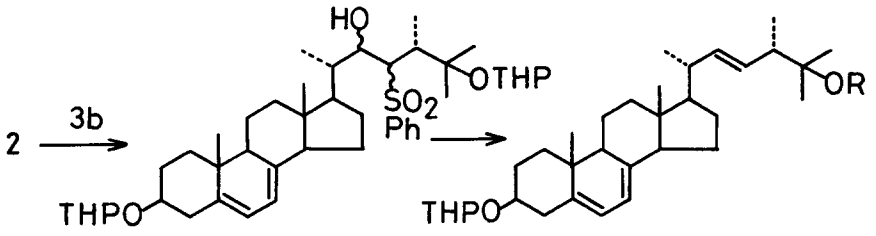
3a : R = H
3b : R = THP



4

5a : R = H
5b : R = CH_2Ph

6a : R = CH_2Ph
6b : R = H



7

8a : R = THP
8b : R = H

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12. $[\alpha]^{22}_{D}$ -22.4° (0.6% $CHCl_3$) for 3a.
13. C(22)-Aldehyde 2 was prepared from the corresponding C(22)-alcohol[7] by oxidation (oxalyl chloride, DMSO, Et_3N).

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