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STEREOSELECTIVE SYNTHESIS OF (25S)-25-HYDROXYVITAMIN D_3 26,23-LACTONE

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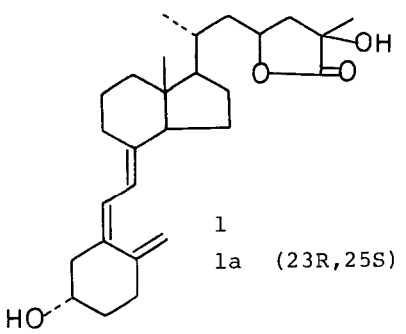
Summary: Stereoselective synthesis of (25S)-25-hydroxyvitamin D_3 26,23-lactone (1a) is described starting from C-22 steroidal aldehyde and (S)-citramalic acid. The spectral properties of the compound are almost identical with those of the natural product.

25-Hydroxyvitamin D_3 26,23-lactone (calcidiol lactone) (1) has been isolated and identified recently[1] as one of the metabolites of vitamin D_3. Although non-stereospecific syntheses of all of the four possible diastereomers at C-23 and C-25 of the compounds (1) have already been reported[2] and one of the isomers synthesized has been demonstrated to be identical with the natural product,[2a] the stereochemistry of the metabolite at C-23 and C-25 has still been remained to be clarified. It was assumed, from inspection of the metabolic pathways of vitamin D_3,[3] that the new metabolite might be derived from (25S)-25,26-dihydroxyvitamin D_3[4] as a result of further metabolic oxidation and, therefore, might have 25S configuration. This speculation was supported by the recent report by Hollis et al. in which they demonstrated the formation of calcidiol lactone from 25,26-dihydroxyvitamin D_3 by in vitro incubation with chick kidney homogenate.[5] In this respect, we carried out the stereoselective synthesis of the calcidiol lactone with 25S configuration using readily available (S)-(+)-citramalic acid[6] as a chiral template for the construction of the side chain.[7]

(S)-Dimethyl citramalate ($[\alpha]_D^{24}$ +27.23°, c = 2.11, $CHCl_3$) (2b) was converted to 1,2-isopropylidene-2-methyl-4-phenylsulphonylbutane-1,2-diol (3d) (mp 67-68°; $[\alpha]_D^{24}$ -8.2°, c = 1.5, $CHCl_3$) in five steps in 62% overall yield. The ester (2b) was reduced ($LiAlH_4$, THF), and the resulting triol (2c) was transformed into the acetonide (3a) (acetone, TsOH, 65% overall yield) without purification. The tosylate (3b) derived from 3a (TsCl, pyridine, 96% yield) was converted to the thioether (3c) (PhSH, t-BuOK, DMF, room temp., quantitative yield), which upon treatment with m-chloroperbenzoic acid afforded the desired sulphone (3d) in quantitative yield. The sulphone (3d) was combined with the aldehyde (4)[8] (LDA, THF, -20°) to give the α-hydroxysulphone (5a)[9] [MS m/e 726 (M^+ - triazoline); ^1H NMR ($CDCl_3$) δ 1.25 (3H, s, H-27), 1.32 (6H, s, isopropylidene), 6.25 (2H, ABq, J = 8 Hz, H-6 and 7)] in 98% yield, as a mixture of the diastereomers at the 22-

and 23-positions. The phenylsulphonyl and the hydroxyl groups of 5a were removed together by reduction with sodium amalgum (MeOH, Na_2HPO_4, 0° - room temp.), directly (69% yield) or via the mesylate (5b) (77% yield), to afford the trans-olefin (6a)[10] [MS m/e 568 (M^+ - triazoline); ^1H NMR ($CDCl_3$) δ 1.24 (3H, s, H-27), 3.70 (2H, ABq, J = 8 Hz, H-26), 5.32 (2H, m, H-22 and 23)]. After exchanging the protecting group of the 3β-hydroxyl function from t-butyldimethylsilyl to acetyl ((i) $TsOH \cdot H_2O$, acetone, room temp., (ii) Ac_2O, pyridine), the vicinal diol group of 6b was deprotected (EtOH, PPTS, reflux) to afford the α-glycol (7a) [MS m/e 396 (M^+ - triazoline - AcOH); ^1H NMR ($CDCl_3$) δ 1.10 (3H, s, H-27), 3.37 (2H, s, H-26), 5.36 (2H, m, H-22 and 23)] in 97% overall yield. Conversion of the glycol (7a) to the α-hydroxycarboxylic acid (7c) [MS m/e 428 (M^+ - triazoline); ^1H NMR ($CDCl_3$) δ 1.37 (3H, s, H-27)] was achieved by the two-steps oxidation via the aldehyde (7b) [MS m/e 394 (M^+ - triazoline - AcOH); ^1H NMR ($CDCl_3$) δ 1.26 (3H, s, H-27), 9.53 (1H, s, H-26)], modified Moffatt oxidation (DMSO, pyridine-SO_3, Et_3N, room temp., 87% yield) followed by oxidation with alkaline iodine solution (I_2, KOH, MeOH-H_2O, room temp., quantitative yield). The γ,δ-unsaturated carboxylic acid (7c) thus obtained was subjected to the successive reactions of iodolactonization (I_2, MeCN, 0°, 72% yield) and reduction (n-Bu_3SnH, THF, 60°, 66% yield) to afford the lactone (8b) [MS m/e 428 (M^+ - triazoline); ^1H NMR ($CDCl_3$) δ 0.82 (3H, s, H-18), 0.97 (3H, s, H-19), 1.48 (3H, s, H-27), 4.10 - 4.75 (2H, m, H-3 and 23); IR ($CHCl_3$) 1685, 1745, 1770 cm^{-1}] along with a small amount of its C-23 epimer. The ratio of 8b and its epimer was ~8.5:1. The configuration at C-23 of the lactone (8b) was assigned as R based on the precedents similar to this case.[11] Removal of the protecting group of the 5,7-diene (K_2CO_3, DMSO, 120°) afforded the desired provitamin D (9) [MS m/e 428 (M^+); ^1H NMR ($CDCl_3$) δ 0.65 (3H, s, H-18), 0.95 (3H, s, H-19), 1.50 (3H, s, H-27), 3.64 (1H, m, H-3), 4.46 (1H, m, H-23); IR ($CHCl_3$) 1770 cm^{-1}] in 55% yield.[12] The provitamin (9) was transformed into the corresponding vitamin D (1a) by the standard method, UV irradiation (Et_2O, Vycor filter, 35% yield) followed by thermal isomerization (EtOH, room temp., 75% yield). The spectral properties of 1a [MS m/e 428 (M^+), 410, 395, 369, 136, 118; ^1H NMR ($CDCl_3$) δ 0.57 (3H, s, H-18), 1.01 (3H, d, J = 6 Hz, H-21), 1.50 (3H, s, H-27), 3.97 (1H, m, H-3), 4.45 (1H, m, H-23), 4.83 (1H, bs, H-19), 5.06 (1H, bs, H-19), 6.13 (2H, ABq, J = 11 Hz, H-6 and 7); UV (95% EtOH) 265 nm; IR ($CHCl_3$) 1772 cm^{-1}] were almost identical with those of the natural calcidiol lactone.[1,2a] This result suggests the possibility that the natural calcidiol lactone has 23R,25S configuration.

Direct comparison of 1a with the natural product and confirmation of the stereochemistry at C-23 of 1a by X-ray analysis are progressing.



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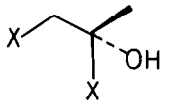
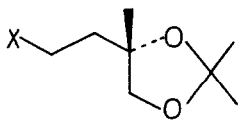
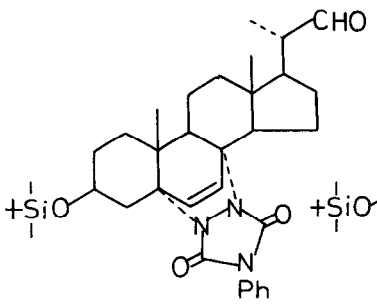
1a (23R,25S)



	X
2a	COOH
b	COOMe
c	CH_2OH



	X
3a	OH
b	OTs
c	SPh
d	SO_2Ph



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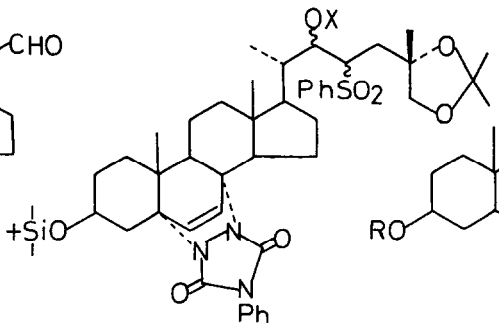
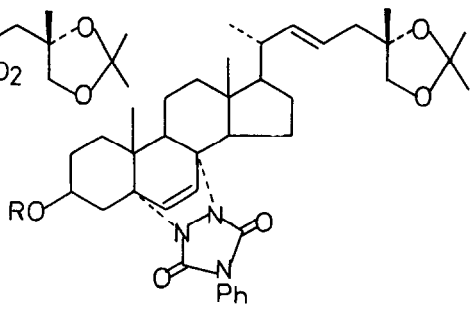
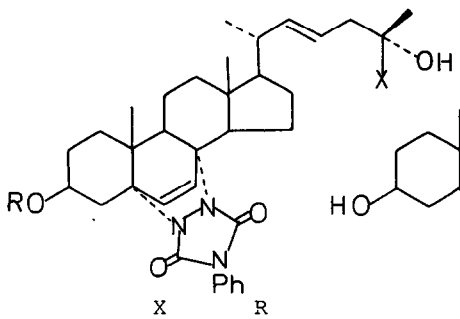


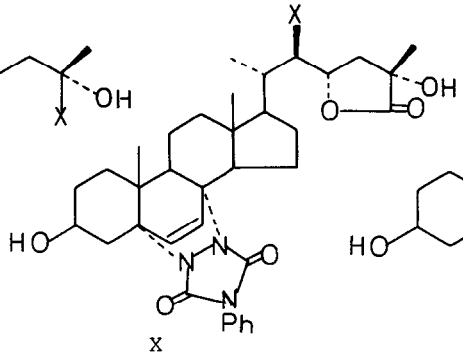
	X
5a	H
b	Ms



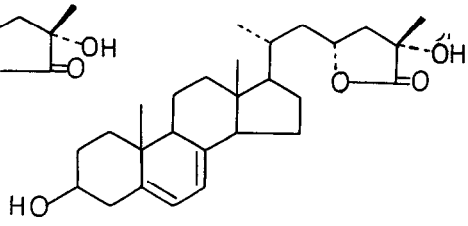
	R
6a	Si
b	Ac



	X	R
7a	CH_2OH	Ac
b	CHO	Ac
c	COOH	H



	X
8a	I
b	H



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12) The spectral data of the provitamin D obtained from the minor 23S epimer: MS m/e 428 (M^+); ^1H NMR ($CDCl_3$) δ 0.64 (3H, s, H-18), 0.95 (3H, s, H-19), 1.51 (3H, s, H-27), 3.65 (1H, m, H-3), 4.73 (1H, m, H-23); IR ($CHCl_3$) 1765 cm^{-1}.

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