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SYNTHESIS OF 25-HYDROXYVITAMIN D_3-26,23-LACTONE

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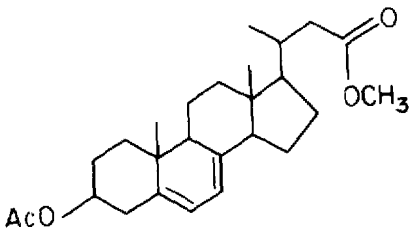
SUMMARY. All four possible C-23 and C-25 stereoisomers of the title compound have been synthesized. One of these isomers is identical to the natural product.

Recently 25-hydroxyvitamin D_3-26,23-lactone has been isolated and identified from chick plasma.[1] We wish to report the synthesis of this compound and confirmation of its structure.

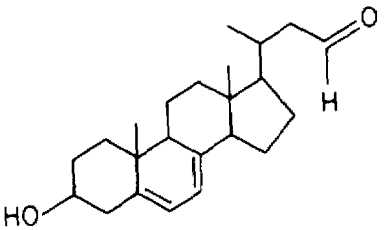
The five step synthesis employed the norcholadienoic acid ester I available as described previously[2] as starting material. This compound was reduced to the aldehyde II, which was condensed with acetone to yield the β-hydroxy ketone III. Cyanohydrin formation[3] and subsequent hydrolysis afforded all four (C-23,25) isomers of the 5,7-diene-lactone IV. Photolysis and thermal isomerization of IV yielded the four isomers of vitamin lactone V. One of these isomers is identical to the natural product as revealed by high performance liquid chromatography (HPLC), UV, NMR, IR and high resolution mass spectrometry.

To 269 mg of I in 12 ml toluene at -78°C was added 0.72 ml of 25% diisobutyl aluminum hydride in toluene. After 30 min, the reaction was worked up in normal fashion and 127 mg of aldehyde II was recovered after silica gel column chromatography. UV (EtOH): 282, 272, 292 (shoulder); MS: m/e 342.2545 (calcd. 342.2558) 100%, M^+; 309, 65%, $M^+-H_2O-CH_3$; 283, 40%, M^+-2CH_3-CHO; 143, 50%, $C_{11}H_{11}^+$; NMR ($CDCl_3$): δ 9.77, s, 1H, C-23; 5.56, m, 1H, C-6; 5-40, m, 1H, C-7; 3.66, m, 1H, C-3; 1.05, d, J = 6.2, 3H, C-21; 0.95, s, 3H, C-19; 0.67, s, 3H, C-18.

A solution of 1.5 ml acetone and 30 µl of 1.0 M KOH in methanol was allowed to react for 15 min at 0°C at which time 122 mg of II in 0.5 ml acetone was added. After 1.5 hr, the reaction is worked up and products are isolated by HPLC on a silica gel column eluted with 2.25% isopropanol in CH_2Cl_2; 37.5 mg of II was recovered, and, in order of elution, 39.5 mg of IIIA and 37.3 mg of IIIB, the two expected C-23-epimers of the hydroxyketone. IIIA: MS: m/e 400.2983 (calcd. 400.2978), 100%, M^+. NMR: ($CDCl_3$), δ, 4.17, m, 1H, C-23; 2.17, s, 3H, C-26; IIIB: MS: m/e 400.2983 (calcd. 400.2978), 100%, M^+. NMR: ($CDCl_3$), δ, 4.14, m, 1H, C-23; 2.19, s, 3H, C-26.



I



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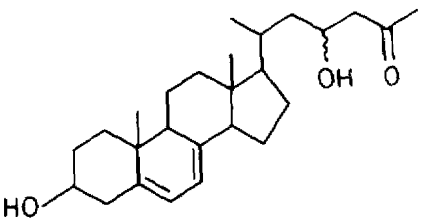

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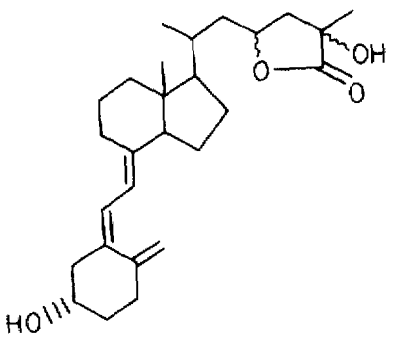

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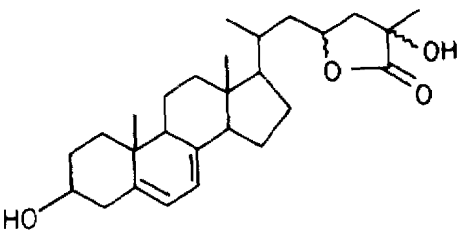

IV

A cyanide slurry was prepared (340 mg NaCN and 540 mg $CaCl_2 \cdot 2H_2O$ ground to homogeniety and slurrying 45 mg of the mixture in 1 ml H_2O) and added in 0.1 ml aliquots at 0, 5, 10, 60, 180, and 270 min to 34 mg of IIIA, and 29 mg of IIIB, each dissolved in 8 ml of EtOH at 50°C. After acidification, products were extracted with CH_2Cl_2 and heated at 45°C for 1 hr in 5:1 EtOH:1 N HCl. The crude lactone products were subjected to HPLC on silica gel eluted with 6% isopropanol in hexane yielding in elution order, 4.3 mg of IVB and 4.0 mg of IVD from IIIA and 2.9 mg of IVA and 2.4 mg of IVC from IIIB. MS: IVA; m/e 428.2931 (calcd. 428.2926) 100%, M^+; NMR ($CDCl_3$), δ, 4.72, m, 1H, C-23; 1.51, s, 3H, C-27; IVB: MS: m/e 428.2935 (calcd. 428.2926), 100%, M^+; NMR ($CDCl_3$), δ, 4.75, m, 1H, C-23; 1.52, s, 3H, C-27. IVC: MS: m/e 428.2917 (calcd. 428.2927), 100%, M^+; NMR ($CDCl_3$), δ, 4.44, m, 1H, C-23; 1.49, s, 3H, C-27. IVD: MS: m/e 428.2927 (calcd. 428.2926), 100%, M^+; NMR ($CDCl_3$), δ, 4.47, m, 1H, C-23; 1.50, s, 3H, C-27.

Solutions of 1 mg of each of IVA, B, C and D in 20% benzene in Et_2O were separately irradiated for 15 min in a quartz immersion well equipped with Hanovia 608A36 lamp and Corex filter. Previtamins were obtained in pure form after HPLC and isomerized to vitamins V in 1 ml EtOH at 70°C for 2 hr. Each vitamin lactone isomer (VA, B, C, and D) was cochromatographed on HPLC with the natural product and only isomer VC was shown to co-migrate. All isomers showed UV (EtOH) λ_{max} 265, λ_{min} 228. VA: MS: m/e 428.2923 (calcd. 428.2926), 24%, M^+; 410, 3%, M^+-H_2O; 395, 11%, $M^+-H_2O-CH_3$; 271, 2%, M^+-side chain; 253, 9%, M^+-side chain-H_2O; 136, 100%, A ring + C_6 + C_7^+; 118, 82%, A ring + C_6 + $C_7^+-H_2O$; NMR ($CDCl_3$): δ 6.28, d, J = 11.8, 1H, C-6; 6.03, d, J = 11.0, 1H, C-7; 5.05, m, 1H, C-19(E); 4.82, m, 1H, C-19(Z); 4.72, m, 1H, C-23; 3.96, m, 1H, C3; 1.51, s, 3H, C-27; 1.03, d, J = 5.5, 3H, C-21; 0.56, s, 3H, C-18; FT-IR (CCl_4): 1780 cm^{-1}. VB: MS: m/e 428.2927 (calcd. 428.2926), 27%, M^+; 410, 2%, M^+-H_2O; 395, 11%, $M^+-H_2O-CH_3$; 271, 2%, M^+-side chain; 253, 7%, M^+-side chain-H_2O; 136, 100%, A ring + C_6 + C_7^+; 118, 92%, A ring + C_6 + $C_7^+-H_2O$; NMR ($CDCl_3$): δ 6.28, d, J = 11.7, 1H, C-6; 6.03, d, J = 11.1, 1H, C-7; 5.05, m, 1H, C-19(E); 4.82, m, 1H, C-19(Z); 4.75, m, 1H, C-23; 3.96, m, 1H, C-3; 1.52, s, 3H, C-27; 1.03, d, J = 5.6, 3H, C-21; 0.56, s, 3H, C-18; FT-IR(CCl_4): 1781 cm^{-1}. VC: MS: m/e 428.2919 (calcd. 428.2926); 26%, M^+; 410, 2%, M^+-H_2O; 395, 9%, $M^+-H_2O-CH_3$; 271, 1%, M^+-side chain; 253, 8%, M^+-side chain-H_2O; 136, 100%, A ring + C_6 + C_7^+; 118, 83%, A ring + C_6 + $C_7^+-H_2O$; NMR ($CDCl_3$): δ 6.28, d, J = 11.8, 1H, C-6; 6.03, d, J = 10.7, 1H, C-7; 5.05, m, 1H, C-19(E); 4.82, m, 1H, C-19(Z); 4.44, m, 1H, C-23; 3.96, m, 1H, C-3; 1.49, s, 3H, C-27; 1.03, d, J = 5.2, 3H, C-21; 0.56, s, 3H, C-18; FT-IR (CCl_4): 1784 cm^{-1}; VD: MS: m/e 428.2927 (calcd. 428.2926), 26%, M^+; 410, 1%, M^+-H_2O; 395, 11%, $M^+-H_2O-CH_3$; 271, 2%, M^+-side chain; 253, 7%, M^+-side chain-H_2O; 136, 100%, A ring + C_6 + C_7^+; 118, 86%, A ring + C_6 + $C_7^+-H_2O$; NMR ($CDCl_3$): δ 6.28, d, J = 11.8, 1H, C-6; 6.03, d, J = 11.0, 1H, C-7; 5.05, m, 1H, C-19(E); 4.82, m, C-19(Z); 4.47, m, 1H, C-23; 3.96, m, 1H, C-3; 1.50, s, 3H, C-27; 1.03, d, J = 5.5, 3H, C-21; 0.56, s, 3H, C-18; FT-IR (CCl_4): 1784 cm^{-1}.

References

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