4-[(-*p*-fluorophenyl)acetyl]anisole, 59043-87-7; 2,3-dichloro-4-propionylanisole, 41715-70-2; *N,N,N′,N′*-tetramethylmethanediamine, 51-80-9.

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Communications

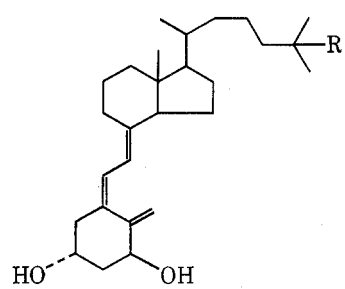
Hydroxylation with Ozone on Silica Gel. The Synthesis of 1α,25-Dihydroxyvitamin D_3

Summary: A convenient synthesis of 1α,25-dihydroxyvitamin D_3, the natural calcium regulating hormone, based on a regioselective C_{25}-hydroxylation of 1α,3β-diacetoxy-6β,7α-dibromocholestane by means of ozone absorbed on silica gel, is reported.

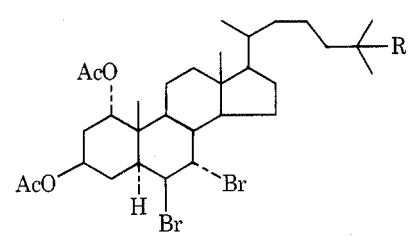
Sir: As a further development of our studies on the functionalization of unactivated carbon atoms,[1] we report on the utilization of the recently published method of dry ozonation[2] for a relatively simple synthesis of the calcium regulating hormone, viz., the 1α,25-dihydroxyvitamin D_3 (**1b**).[3]

The key step in this synthesis is the highly regioselective C_{25}-hydroxylation of a tetrasubstituted cholestane derivative, the dibromide **2a,** which is an intermediate in the preparation of a physiological useful substitute of **1b,** viz., the 1α-hydroxyvitamin D_3[4] (**1a**). We obtained this dibromide intermediate, **2a,** in a five-step synthesis from cholesterol, by the following sequence: cholesterol → **3a** → **4a** → **5a** → **5c** → **2a.**[4]

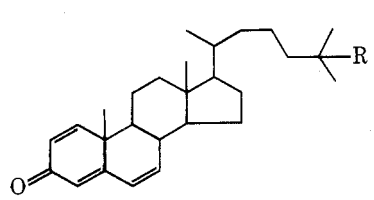
Silica gel for chromatography (Merck-Kieselgel 60, 70–220 mesh) containing 1% by weight of adsorbed **2a** was saturated with ozone (generated from Welsbach ozonizer) at −78 °C and allowed to warm to room temperature. This procedure was repeated altogether five times. Elution and chromatographic separation yielded, in addition to recovered starting material **2a,** the C_{25}-hydroxy derivative, **2b,** mp 174–175 °C, $[\alpha]_D$ −24°, as the only isolated product (11% conversion and 51% yield). The presence of OH at C_{25} in **2b** was indicated by its NMR spectrum which was similar to that of the starting compound **2a**[4] except for the signals due to the methyl protons at C_{25} appearing as a singlet at δ 1.20 ppm instead of a doublet at 0.85 and by its mass spectrum [M^+ at *m/e* 660 (^{79}Br) and 59 of $(CH_3)_2C^+OH$]. The structure of **2b** was proved by comparison of its C_{25} acetate, **2d** [NMR δ 1.41, 1.96 ppm (CH_3 and OAc at C_{25}); mass spectra M^+ at *m/e* 702 (^{79}Br) and 101 of $(CH_3)_2C^+OAc$] with a compound synthesized by us from the previously described C_{25}-hydroxy epoxide **4b.**[5,6] Reduction of the epoxide with Li/NH_3 in the presence of NH_4Cl resulted in 20% Δ^6-triol, **5b**[7] [mp 193–196 °C; $[\alpha]_D$ −62°; NMR ($CDCl_3$) δ 0.70 (s, 3, C_{18} H), 0.80 (s, 3, C_{19} H), 0.91 (d, 3, J = 7 Hz, C_{21}



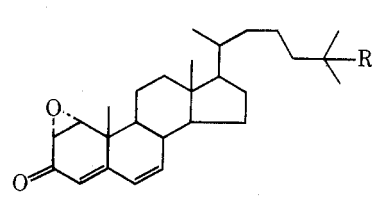
1a, R = H
b, R = OH



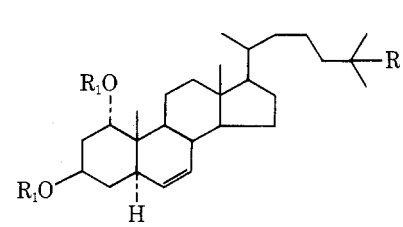
2a, R = H
b, R = OH
c, R = $OCOCF_3$
d, R = OAc



3a, R = H
b, R = OH



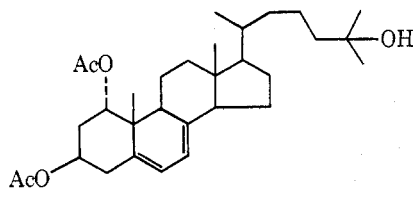
4a, R = H
b, R = OH



5a, R = H; R_1 = H
b, R = OH; R_1 = H
c, R = H; R_1 = Ac
d, R = OAc; R_1 = Ac

H), 1.19 (s, 6, C_{26},C_{27} H), 3.80, 3.93 (m, 2, C_4,C_5 H) 5.33, 5.21 ppm (ABq, J = 11.4 Hz, C_6,C_7 H)] which was acetylated with Ac_2O and pyridine at 80 °C to yield the triacetate **5d** (mp 89–91 °C). Bromination in $CHCl_3$ with $C_6H_5IBr_2$ gave the dibromide **2d** which was found to be identical with the product obtained from **2a.**

The C_{25}-hydroxy dibromide **2b** was treated with $(CF_3CO)_2O$ at room temperature for 4 h, and the C_{25}-trifluoroacetate, **2c,** obtained after evaporation to dryness, was dehydrobrominated by heating at 135 °C for 2 h in hexamethylphosphoramide containing 10% triethylmethylammonium dimethylphosphate[4,8] to give 20% 1α,3β-diacetoxy-25-hydroxycholesta-$\Delta^{5,7}$-diene (**6**)[5,9,10] [uv λ_{max} 262, 271, 282, and 294 nm; NMR ($CDCl_3$) δ 0.61 (s, 3, C_{18} H), 1.14 (s, 3, C_{19} H), 1.18 (s, 6, $C_{26}C_{27}$, H), 1.94, 1.97 (s, 6 OAc), 4.87 (m, 2, C_1,C_3



6

H), 5.29, 5.39 (AB q, J = 10.3 Hz, C_6,C_7 H)], accompanied by the $\Delta^{4,6}$-diene (uv λ_{max} 230, 240, 249 nm). The $\Delta^{5,7}$-diene, **6,** was transformed by irradiation, heating, and hydrolysis, as described elsewhere,[5,10] to the desired 1α,25-dihydroxyvitamin D_3 (**1b**) [uv λ 264 nm (ϵ 18 000); mass spectra M^+ at m/e 416; rapidly stimulating the formation of calcium binding protein and increasing the calcium content in the intestine of rachitic chicks].[3,5,10]

The direct introduction of OH into the side chain of a cholestane derivative at C_{25} significantly simplifies the synthesis of 1α,25-dihydroxyvitamin D_3; its photoprecursor, the $\Delta^{5,7}$-diene, can now be obtained from cholesterol by a seven-step reaction sequence.

Acknowledgment. The mass spectra were done by Dr. Zeev V. Zaretskii and the biological assay by Dr. Arieh Bar of the Volcani Institute, Rehovot, to whom we are greatly indebted.

Supplementary Material Available. The experimental details for preparation of new compounds (3 pages). Ordering information is given on any current masthead page.

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(6) C_{25}-Hydroxy epoxide **4b,** was prepared by us by a different route: lithocholic acid → 3α,25-dihydroxy-5β-cholestane → **3b** (by DDQ oxidation) → **4b.**
(7) This compound was contaminated with ~10% Δ^5 isomer.
(8) J. L. Kraus and G. Sturz, *Bull. Soc. Chim. Fr.*, 2551 (1971).
(9) Hydrolysis of the trifluoroacetate occurs during the isolation. The yield of $\Delta^{5,7}$-diene **6,** when omitting trifluoroacetylation at C_{25}, is ~15%.
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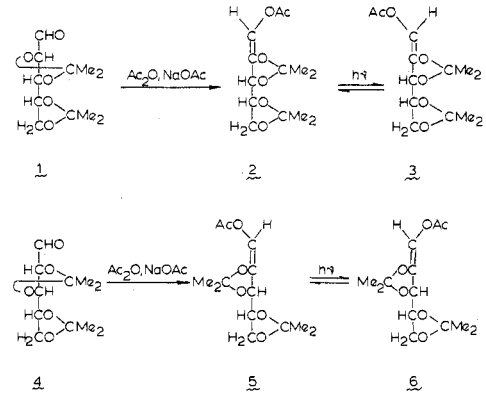
Enol Acetates of Aldehydo Sugar Derivatives. Synthesis and Crystallographic Determination of Double-Bond Geometry[1,2]

Summary: Enol acetates produced by action of acetic anhydride–sodium acetate on 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose and -D-xylose are shown by X-ray crystallography to be the *Z* isomers, and they undergo photoisomerization to the *E* isomers.

Sir: Although aldehydo and keto derivatives of sugars are frequently used in synthesis and their derived enediols often postulated as reaction intermediates,[3] there have been few reports of stable derivatives of such enediols. Enol acetates of keto sugars have been studied in one of our laboratories,[4] and this communication reports the synthesis and characterization of enol acetates derived from some aldehydo sugar derivatives.

Heating 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[5] (**1**) or the D-ribose analogue in an excess of acetic anhydride containing sodium acetate for 30 min at 140 °C gave in 60% yield the *Z* isomer (**2**) of 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-D-*erythro*-pent-1-enitol, mp 100–100.5 °C, $[\alpha]^{23}D$ +1.85° (chloroform), whose general structure, except for the geometry about the double bond, was evident from its NMR and mass spectra. Photoisomerization of **2** in benzene–acetone with uv light gave the *E* isomer **3** as an oil, $[\alpha]^{24}D$ +122° (chloroform). Similarly, acetic anhydride–sodium acetate converted 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-xylose[6] (**4**) into (*Z*)-1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-D-



1 **2** **3**

4 **5** **6**

threo-pent-1-enitol (**5**), mp 61–62 °C, $[\alpha]^{22}D$ +8.4° (chloroform), which gave a first-order NMR spectrum (100 MHz) in acetone-d_6 and which could be photoisomerized to the *E* isomer (**6**), mp 68–70 °C, $[\alpha]^{24}D$ −198° (chloroform).

Assignment of double-bond geometry was achieved by crystallographic analysis of single crystals of **2** grown from ether–pentane and of **5** obtained from absolute ethanol. Intensities were collected on a Philips diffractometer with Cu Kα radiation and structures were solved by use of the Riche phase function.[7] The erythro compound (**2**, $C_{13}H_{20}O_6$) was monoclinic, space group $P2_1$, cell dimensions a = 5.435, b = 14.703, c = 9.332 Å, β = 104.15°, Z = 2, and volume 723 Å^3. The threo compound (**5**) was orthorhombic, space group $P2_12_12_1$, cell dimensions a = 5.543, b = 8.240, c = 32.336 Å, Z = 4, and volume 1477 Å^3. All hydrogen atoms were located on difference Fourier syntheses and their coordinates refined. The final R indices were 0.04 for **2** and 0.05 for **5**. Figure 1 presents a three-dimensional view of each molecule, listing bond distances, and short interatomic contacts, and Figure 2 depicts Newman projections along each carbon–carbon bond to show dihedral bond angles.

The crystallographic structures establish that the stereochemistry about the double bond is *Z* in **2** and **5**. The C-2–C-5 carbon–carbon chain of the erythro isomer (**2**) is approxi-