1365, 1350, 1299, 1145, 1045, and 835 cm^{-1}; nmr δ 2.23 (s, 3 H), 3.63 (s, 3 H), 4.20 (d, J = 2 Hz, 1 H), 5.05 (d, J = 2 Hz, 1 H); mass spectrum m/e 100.0523 (M$^+$, calcd for $C_5H_8O_2$, 100.0523).

3-Isopropoxy-3-buten-2-one (2c). In the way just described for **2a**, **2c** was prepared in 50% yield from a mixture of **3c** and **4c** (2:3): ir 3000, 1720, 1610, 1355, 1280, 1140, and 1105 cm^{-1}; nmr δ 1.27 (d, J = 6 Hz, 6 H), 2.15 (s, 3 H), 4.15 (d, J = 2 Hz, 1 H), 4.20 (septet, J = 6 Hz, 1 H), 5.06 (d, J = 2 Hz, 1 H); mass spectrum m/e 128.0843 (M$^+$, calcd for $C_7H_{12}O_2$, 128.0837).

3-Propoxy-3-buten-2-one (2d). In the way just described for **2a**, **2d** was prepared from a mixture of **3d** and **4d:** ir 3000, 2970, 1715, 1615, 1370, 1355, 1300, 1150, and 840 cm^{-1}; nmr δ 1.04 (t, J = 6 Hz, 3 H), 1.77 (dt, $J = J_2$ = 6 Hz, 2 H), 2.20 (s, 3 H), 3.68 (t, J = 6 Hz, 2 H), 4.23 (d, J = 2 Hz, 1 H), 5.05 (d, J = 2 Hz, 1 H); mass spectrum m/e 128.0860 (M$^+$, calcd for $C_7H_{12}O_2$, 128.0837).

Hydrolysis of Enol Ethers to Biacetyl. A solution of **2a** (150 mg) in ether (15 ml) was treated with 10% aqueous HCl (0.5 ml) at room temperature for 12 hr. Then 2 g of Na_2CO_3 was added and the ethereal layer was filtered and dried over 4A molecular sieves. Solvent was removed by distillation, and biacetyl was isolated as the only product by vpc on column B. The same results were obtained with **2c**.

Reaction of 2a with Methanol. Treatment of **2a** with methanolic hydrogen chloride following essentially the procedure described above for alcohol interchange gave **3a** as the only isolated product.

endo- **and** *exo-***2-Methoxy-5-norbornen-2-yl Methyl Ketone (6 and 7).** A solution of 500 mg of **2a**, 450 mg of cyclopentadiene, and 10 mg of hydroquinone in 5 ml of benzene was heated in a sealed tube at 120° for 48 hr. Solvent was removed, and bulb-to-bulb distillation of the residue gave 465 mg (56%) of a mixture of **6** and **7** (63:37 by nmr). These were separated and purified on column B. Major isomer **6** showed the following properties: ir 3010, 2960, 1715, 1340, 1240, 1090, 1075, 1060, and 700 cm^{-1}; nmr δ 1.50 (d, J = 13 Hz, 1 H), 1.54 (d, J = 13 Hz, 1 H), 1.78 (m, 2 H), 2.09 (s, 3 H), 2.18 (d, J = 6 Hz, 1 H), 2.86 (d, J = 6 Hz, 1 H), 3.02 (s, 3 H), 5.80 (dd, J_1 = 3, J_2 = 6 Hz, 1 H), 6.08 (dd, J_1 = 3, J_2 = 6 Hz, 1 H); mass spectrum m/e 166.0989 (M$^+$, calcd for $C_{10}H_{14}O_2$, 166.0993). Minor isomer **7** showed the following properties: ir 3010, 1715, 1345, 1120, 1080, 1070, and 705 cm^{-1}; nmr δ 1.07 (dd, J_1 = 4, J_2 = 12 Hz, 1 H), 1.27 (m, 2 H), 1.43 (m, 1 H), 1.95 (dd, J_1 = 4, J_2 = 12 Hz, 1 H), 2.14 (s, 3 H), 2.72 (m, 1 H), 2.98 (s, 3 H), 5.93 (dd, J_1 = 4, J_2 = 5.5 Hz, 1 H), 6.23 (dd, J_1 = 4, J_2 = 5.5 Hz, 1 H); mass spectrum m/e 166.0947 (M$^+$, calcd for $C_{10}H_{14}O_2$, 166.0993).

Registry No.—**2a**, 51933-10-9; **2c**, 51933-11-0; **2d**, 51933-12-1; **3a**, 21983-72-2; **3b**, 51933-13-2; **3c**, 51933-14-3; **3d**, 51933-15-4; **3e**, 51933-16-5; **3f**, 51933-17-6; **4c**, 51933-18-7; **4d**, 51933-19-8; **4e**, 51933-20-1; **4f** isomer A, 51933-21-2; **4f** isomer B, 51933-22-3; **6**, 51933-23-4; **7**, 51933-24-5.

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(7) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Structure and Stereochemistry of Simmondsin

Carl A. Elliger,* A. C. Waiss, Jr., and R. E. Lundin

Western Regional Research Laboratory, Agricultural Research Service, U. S. Department of Agriculture, Berkeley, California 94710

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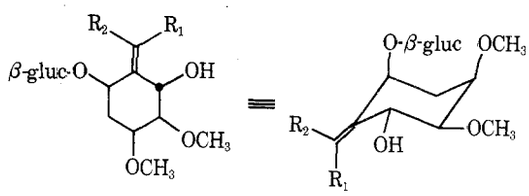
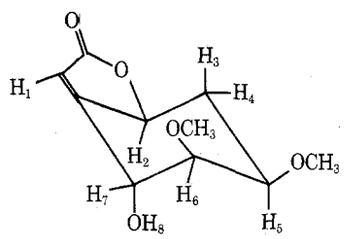
We recently[1] reported the isolation of a naturally occurring toxicant from *Simmondsia californica* and tentatively characterized its structure as **1a**. We now wish to report the definite establishment of structure **1b** in which the configuration of the cyano group is syn to the axial β-glucosyl substituent.



1a, R_1 = CN; R_2 = H
b, R_1 = H; R_2 = CN

Acid hydrolysis of the parent glucoside in boiling 1 *N* HCl for 1.5 hr produces, in addition to the previously reported phenolic derivatives, an α,β-unsaturated lactone, mp 138–140°, whose structure (**2**) is very closely related to



2

the starting glucoside. Satisfactory elemental analysis was obtained, and its infrared absorptions at 1665 and 1755 cm^{-1} are consistent with the proposed structure.[2] The nmr spectrum (Table I) permits unequivocal assignment of

Table I
Nmr Spectrum of 2 [$(CD_3)_2CO$]

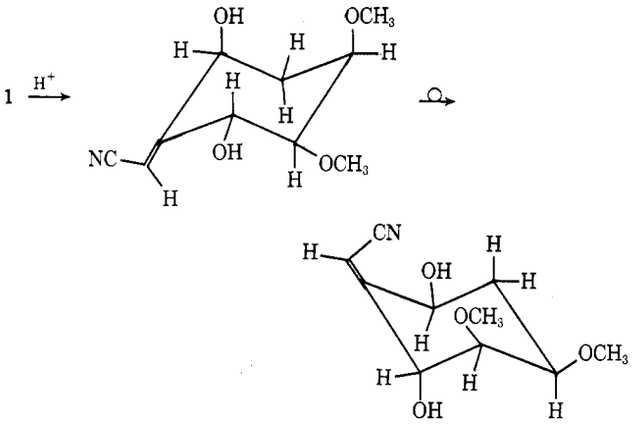
H_1 δ 5.98, d, $J_{1,2}$ = 2 Hz
H_2 δ 5.12, 8 lines, $J_{1,2}$ = 2, $J_{2,3}$ = 11, $J_{2,4}$ = 6.5 Hz
H_3 δ 1.58, q, $J_{2,3} = J_{3,4} = J_{3,5}$ = 11 Hz
H_4 δ 2.52, complex, $J_{3,4}$ = 11, $J_{2,4}$ = 6, $J_{4,5}$ = 4 Hz
H_5 δ 3.90 (d), d, d (upfield half concealed by H_6), $J_{4,5}$ = 4, $J_{5,6}$ = 2 Hz
H_6 δ 3.83, complex (partially obscured by upfield half of H_5), $J_{5,6}$ = 3, $J_{6,7}$ = 3 Hz
H_7 δ 4.90, t, $J_{6,7} = J_{7,8}$ = 3, $J_{1,7}$ = 0 Hz
H_8 δ 5.03, d, $J_{7,8}$ = 3 Hz (31°)
$-OCH_3$'s (6 H) δ 3.40, 3.44

stereochemistry (spin-decoupling techniques were used for proton assignment). Protons H_{2-5} neatly reveal their orientation by the quartet exhibited by H_3 in which coupling of the adjacent axial hydrogens as well as the geminal coupling constant is 11 Hz. The observation that H_1 and H_2 possess a coupling of 2 Hz while that of H_1 and H_7 is zero is consistent with approximate 90° orientation of the C–H_2 bond with respect to the plane of the lactone ring. The orientation of H_7 nearly within the same plane would result in minimal coupling to H_1, as is found.[3] Hydrogens 6 and 7 are equatorially located.

The formation of lactone **2** must occur *via* initial hydrolysis of the glucosyl residue as in Scheme I followed by ring inversion to place the now equatorial hydroxyl group extremely close to the nitrile function. Under acid catalysis ring closure may occur easily to give lactone from the initially formed imino ester.

The proximity of the nitrile function to any adjacently located equatorial substituent no doubt is the cause of the rather unusual stereochemistry in simmondsin (**1b**) itself. To minimize the interaction of the glucosyl portion of the molecule with the cyano group, the glycosidic linkage assumes axial geometry even though this introduces 1,3-diax-

Scheme I



ial strain between the glucose and the methoxyl in this conformation. Such interaction in the vicinity of a double bond has been termed allylic 1,3 strain [$A^{(1,3)}$] by Johnson,[4] and he has pointed out that this can be of higher energy than 1,3-diaxial interaction in a cyclohexane system, even when the groups involved are of moderate size. The observed conformation of simmondsin is consistent with this theory.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer 257 instrument. Nmr spectra were measured on a Varian A-60 instrument or on a HA-100 spectrometer. Spin-decoupled spectra were obtained on the latter machine in the frequency mode. Elemental analyses were performed in this laboratory.

Treatment of Simmondsin with Acid. Simmondsin (4.40 g) dissolved in 1 *N* hydrochloric acid (50 ml) was refluxed for 1.5 hr. After cooling to room temperature, the mixture was concentrated under reduced pressure to a semisolid paste which was triturated with four 25-ml portions of ethyl acetate. Evaporation gave an oil (2.19 g) which was applied in ethyl acetate to a column (25 × 1000 mm) prepared with 190 g of silica gel (Mallinckrodt SilicAR CC-7, special) in chloroform. Elution was carried out at 60 ml/hr in a linear gradient from 100% chloroform to 20% methanol–chloroform (2 l.). Three major fractions were obtained: (i) between 370 and 580 ml (0.16 g), (ii) between 860 and 740 ml (0.33 g), and (iii) between 1040 and 1160 ml (1.31 g). Fraction iii was dissolved in ethyl acetate (40 ml) and extracted with 5% sodium hydrogen carbonate solution (3 × 30 ml). The organic layer was dried over magnesium sulfate and evaporated to give 0.32 g of crude lactone **2**, which was crystallized from benzene to give 0.17 g of material, mp 138–140°. *Anal.* Calcd for $C_{10}H_{14}O_5$: C, 59.34; H, 5.53. Found: C, 59.6; H, 5.57. The infrared spectrum, ν_{max} ($CHCl_3$), showed absorptions at 1665 (conjugated double bond in C-5 ring) and 1755 cm^{-1} (α,β-unsaturated, five-ring lactone). The nmr spectrum in deuterioacetone is shown in Table I.

Acidification of the aqueous extract from iii followed by extraction with ethyl acetate provided 2-hydroxy-5-methoxyphenylacetic acid (0.40 g). Fractions i and ii were shown to be respectively the lactone of the above phenolic acid and the corresponding methyl ester (formed during chromatography).[1]

Acknowledgments. We wish to thank Mrs. Mabry Benson for obtaining the 100-MHz nmr spectra and Miss G. E. Secor for elemental analysis.

Registry No.—**1b**, 51771-52-9; **2**, 52032-66-3.

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Studies on Vitamin D and Its Analogs. I. Synthesis of 1α-Hydroxycholest-5-ene

Manindra N. Mitra,[1a,b] Anthony W. Norman,[1a-c] and William H. Okamura*[1d,e]

Departments of Biochemistry and Chemistry, University of California, Riverside, California 92502

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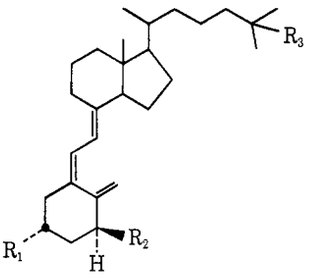
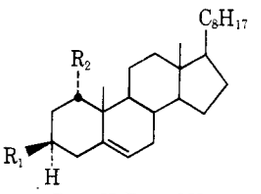
Vitamin D_3 (**1a**),[2] a steroidal hormone intimately associated with calcium transport, must be successively hydroxylated in the liver[3] and then in the kidney to produce the metabolite 1α,25-dihydroxyvitamin D_3 (**1b**)[4] before elic-



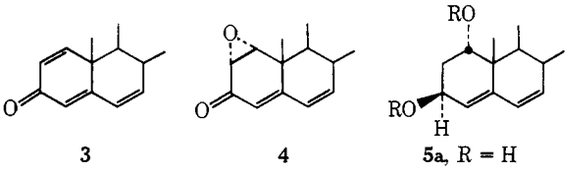
1a, R_1 = OH; R_2 = R_3 = H
b, R_1 = R_2 = R_3 = OH
c, R_2 = OH; R_1 = R_3 = H

iting its physiological action. Recent investigations have led to the suggestion that the 1α-hydroxyl contained in the carbon framework represented by structure 1 may be the critical functionality necessary for vitamin D activity.[5] If this is the case, an attractive substance for study is the analog **1c**, which lacks both the seemingly unnecessary 3β- and 25-hydroxyl groups of the natural system **1b**. Our ongoing studies directed toward synthesizing **1c** and related analogs required the availability of the hitherto unknown cholesterol isomer 1α-hydroxycholest-5-ene (**2a**). It is the purpose of this note to provide the details for its preparation.



2a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H
c, R_1 = H; R_2 = OAc
d, R_1 = R_2 = OH
e, R_1 = OTs; R_2 = OH

The title compound **2a** has been prepared by two different routes. Cholesterol was converted as described previously to the epoxydienone **4** by successive treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] and alkaline hydrogen peroxide.[7] In the first route, **4** was reduced with lithium aluminum hydride yielding **5a** (62%), which upon subsequent reduction with lithium–ammonia pro-



3 **4** **5a**, R = H; **b**, R = Ac