the equilibrium concentration of CH_2=$CHCH_2SR$ was of about the same magnitude as the estimated uncertainty in measuring the concentrations;[9] furthermore, steric effects should be smaller with SR than with SOR, SO_2R, or OR. In the series n-C_nH_{2n+1} > i-Pr ≈ t-Bu it is again not clear that the observed differences are significant, and it is a series in which steric crowding of the CH_2 group in XCH_2CH=CHY should be less than with OBu-t, SO_2Bu-t, etc. groups. Steric hindrance can decrease resonance interactions with the double bond, as in the first part of the series 2-naphthyl > 1-naphthyl ≈ 9-anthryl, but when there is too much hindrance, this resonance effect is counteracted, presumably by crowding the CH_2 group, as in the last part of the series.

Notes

The Periodination Reaction: Fast One-Step Synthesis of C_6I_6 from C_6H_6

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In an attempt to prepare the unknown compound, periodyl benzene ($PhIO_3$), benzene was added dropwise over a period of around 15 min to a 1.0 M solution of H_5IO_6 in concentrated H_2SO_4 in an open beaker at 0–5 °C, whereupon the colorless solution turns green,[1] then red, and finally light yellow, as a yellow-tan precipitate gradually forms, which, after recrystallization from Me_2SO, is insoluble in all common solvents except Me_2SO and MeCN: mp ~260 °C with decomposition, giving off I_2; elemental analysis, 8.5% C and 91.5% I; $M_r \gtrsim 800$ by freezing point depression of camphor; mass spectrum parent peak at 834 ($C_6I_6^{+\cdot}$) and M − 1 at 707 ($C_6I_5^{+\cdot}$); proton NMR, no resonance absorption; burns with an aromatic sooty flame along with dense purple fumes of I_2, from all of which evidence one would rightly conclude that the compound prepared here is C_6I_6,[2] and, on the basis of the quantity of benzene used, the yield is 48% peridobenzene.

Registry No. H_5IO_6, 10450-60-9; C_6I_6, 608-74-2; $PhIO_3$, 82891-66-5; benzene, 71-43-2.

(1) The green intermediate first formed (presumably $PhIO_3$), and the red one, should be further investigated, as well as the generality of the periodination of aromatics. The authors invite any investigator interested in this unusual reaction, which might be of use in deuterating aromatic compounds, to pursue this research.

(2) The stoichiometric equation used to calculate yield is $2C_6H_6 + 3IO_4^- + 9I^- + 12H_3O^+ \rightarrow 2C_6I_6 + 24H_2O$, the I^- indicating that some of the benzene is oxidized, presumably to CO_2.

Stereoselective Synthesis of (23*S*,25*R*)-23,25,26-Trihydroxyvitamin D_3 and (23*S*,25*R*)-25-Hydroxyvitamin D_3 26,23-Lactol, Presumed Vitamin D_3 Metabolites

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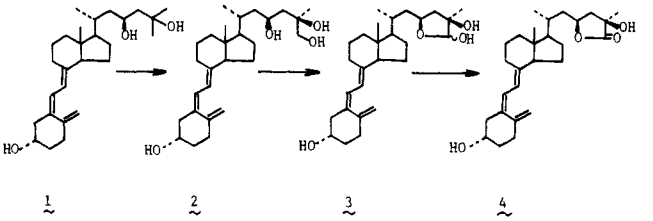
Calcidiol lactone, 25-hydroxyvitamin D_3 26,23-lactone (**4**),[1] is a unique metabolite of vitamin D_3 which exhibits a weak activity in intestinal calcium transport and bone calcium mobilization but shows the most potent activity[2] toward vitamin D binding protein in blood plasma of all known vitamin D metabolites. These characteristics have suggested that the metabolite may have an important role in other aspects of vitamin D action. As one of our projects on the stereoselective synthesis of vitamin D metabolites using chiral templates,[3] we have synthesized (23*R*,25*S*)-[4] and (23*S*,25*R*)-calcidiol lactones[5] stereoselectively and for the first time determined the stereochemistry of the natural metabolite[5] to be *S* at C-23 and *R* at C-25. Recently a new metabolite, (23*S*)-23,25-dihydroxyvitamin D_3 (**1**),[6] has been isolated and has been shown to be a biosynthetic precursor of calcidiol lactone (**4**).[7] It can be assumed that biological transformation of 23,25-dihydroxyvitamin D_3 (**1**) to the lactone (**4**) may proceed via 23,25,26-trihydroxyvitamin D_3 (**2**) through 25-hydroxyvitamin D_3 26,23-lactol (**3**; Scheme I) and that these postulated biosynthetic intermediates have the same stereochemical configuration at C-23 and C-25 as those of calcidiol lactone (**4**). So we planned the stereoselective synthesis of these two presumed vitamin D_3 metabolites.

Scheme I. Presumed Metabolic Pathway of (23*S*)-23,25-Dihydroxyvitamin D_3 (**1**) to Calcidiol Lactone (**4**)



1 **2** **3** **4**

In this paper we report the stereoselective synthesis of (23*S*,25*R*)-23,25,26-trihydroxyvitamin D_3 (**2**) and (23*S*,25*R*)-25-hydroxyvitamin D_3 26,23-lactol (**3**). Both compounds have been demonstrated to be converted to

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(2) (a) Tanaka, Y.; Wichmann, J. K.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6411. (b) Horst, R. L. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 286.

(3) Takayama, H.; Ohmori, M.; Yamada, S. *Tetrahedron Lett.* **1980**, *21*, 5027.

(4) Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett.* **1981**, *22*, 2591.

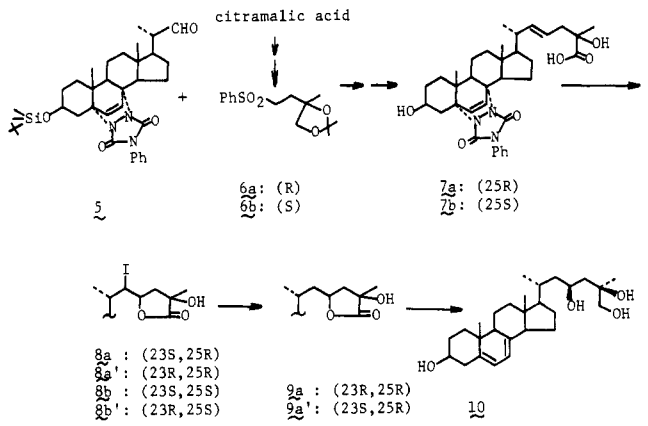
(5) Yamada, S.; Nakayama, K.; Takayama, H. *Chem. Pharm. Bull.* **1981**, *29*, 2393.

(6) Tanaka, Y.; Wichmann, J. K.; Schnoes, H. K.; DeLuca, H. F. *Biochemistry* **1981**, *20*, 3895.

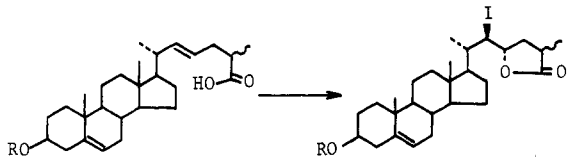
(7) Tanaka, Y.; DeLuca, H. F.; Schnoes, H. K.; Ikekawa, N.; Eguchi, T. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4805.

0022-3263/82/1947-4770$01.25/0

Scheme II



Scheme III



calcidiol lactone (4) by in vitro incubation with chick kidney homogenates, as expected.[8,9]

The strategy for the synthesis of the two compounds (2 and 3) is essentially the same as that for calcidiol lactone;[4,5] an *R* configuration at C-25 is introduced by utilizing the chirality of (*R*)-(−)-citramalic acid, and the *S* configuration at C-23 is induced by the stereoselective iodolactonization of the Δ^{22}-26-carboxylic acid **7a**. The (25*R*)-carboxylic acid **7a**[4,5] was synthesized by starting with C(22)-steroid aldehyde **5** and optically pure (*R*)-sulfone **6a** (Scheme II), which was readily obtained from (*R*)-citramalic acid in eight steps in 67% overall yield.[4,5]

Iodolactonization of the unsaturated carboxylic acid **7** was studied in some detail to induce the desired chirality at C-23. It has been reported by Barton et al.[10] that the iodoacetoxylation of steroids with a 22(23) double bond proceeds in a regio- and stereoselective manner to yield the iodoacetate in which the bulky iodine is introduced at C-22 from the sterically less hindered side of the molecule. In accord with their results, the iodolactonization (I_2, CH_3CN) of Δ^{22}-steroidal carboxylic acid **11** has been reported[11] to yield exclusively the (23*S*)-iodolactone **12** (Scheme III). It was also found, in our stereoselective synthesis of (23*R*,25*S*)-calcidiol lactone,[4] that the iodolactonization (I_2, CH_3CN) of (25*S*)-carboxylic acid **7b** gave the (23*S*)-iodolactone **8b** in 90% stereoselectivity, in accord with the precedents. In the extensive studies on the stereoselective iodolactonization of acyclic γ,δ-unsaturated carboxylic acids,[12] it has been reported that the stereoselectivity of the reaction depends on the reaction conditions, and under acidic conditions (I_2, CH_3CN) the thermodynamically more stable isomers are produced selectively while under basic conditions (I_2, Et_2O–THF, aqueous $NaHCO_3$) thermodynamically less stable isomers, kinetic products, are formed predominantly. We examined the iodolactonization of the two epimeric carboxylic acids **7a** and **7b** under thermodynamic and kinetic conditions. As Table I shows, the stereoselectivity of the reaction depends on both the stereochemistry at C-25 of the carboxylic acid **7** and the reaction conditions. Although the 25*S* isomer **7b** gave the (23*S*)-iodolactone **8b**[13] in high selectivity under acidic conditions as described above, the 25*R* isomer **7a** yielded both (23*S*)- and (23*R*)-iodolactones **8a** and **8a′** in a comparable ratio under the same conditions (entry 1). However, in an attempted iodolactonization of **7a** and **7b** under the kinetic conditions reported by Chamberlin et al.[12b] (entry 2), no appreciable change was observed in the ratio of the products. A remarkable change in the stereoselectivity was observed when pyridine was added to the reaction mixture as the base (entry 3 and 4), and in the case of (25*R*)-carboxylic acid **7a** the selectivity was reversed, giving rise to the desired iodolactone **8a′** in 80% selectivity. It is likely that the function of pyridine in the stereochemical consequence of the reaction may be similar to that of $NaHCO_3$, because it was also found that in a well-studied system,[12] iodolactonization of 3-methyl-4-pentenoic acid, pyridine worked similarly to $NaHCO_3$, yielding the kinetic product predominantly.[14] Although it is not clearly understood why the addition of $NaHCO_3$ was not effective in our system in altering the stereochemical course of the reaction, pyridine is shown to be a useful reagent for the purpose.

Table I. Iodolactonization of Δ^{22}-26-Carboxylic Acid (7a,b)

entry	substrate	conditions	product distribution, % 8a	8a′	8b	8b′
1	7a	I_2, CH_3CN	57	43		
	7b				90	10
2	7a	I_2, Et_2O–THF, aqueous $NaHCO_3$	43	57		
	7b				88	12
3	7a	I_2, CH_3CN, pyridine	27	73		
	7b				57	43
4	7a	I_2, CH_2Cl_2, pyridine	20	80		
	7b				55	45

The mixture of the (23*R*,25*R*)- and (23*S*,25*R*)-iodolactones **8a′** and **8a** from the entry 4 experiment was subjected to reduction with *n*-Bu_3SnH without separation. After purification on a silica gel column, the major (23*S*,25*R*)-lactone **9a′** was obtained in pure form in 56% overall yield (from **7a**). Reduction of the lactone **9a′** with $LiAlH_4$ was accompanied by the deprotection of the 5,7-diene group to afford the desired provitamin D (**10**) in 90% yield. The provitamin D (**10**) was transformed into the corresponding vitamin D (**2**) by UV irradiation followed by thermal isomerization as usual.

The synthesis of (23*S*,25*R*)-25-hydroxyvitamin D_3 26,23-lactol (**3**) was performed in one step from

(8) We have noticed the presence of a new metabolite which migrated to the same retention volume as that of (23*S*,25*R*)-23,25,26-trihydroxyvitamin D_3 in the incubates of chick kidney homogenate with 25-hydroxyvitamin D_3. Detailed studies on the metabolite are currently progressing.

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(13) The stereochemistry of the iodo lactones 8 and lactones 9 at C-23 was determined on the basis of the spectral data and closely related precedents.[4,5] The assignments are in complete agreement with those reported: Morris, D. S.; Williams, D. H.; Norris, A. F. *J. Org. Chem.* **1981**, *46*, 3422.

(14) Nakayama, K.; Yamada, S.; Takayama, H., unpublished results.

(23S,25R)-calcidiol lactone (4)[5] by reduction with diisobutyl alminium hydride (DIBAL) (toluene, -70 °C) in high yield (93%). It is interesting to note that only one anomer at C-26 was obtained as verified by the ^{1}H NMR spectrum ($CDCl_3$): δ 1.34 (3 H, s, H-27) 3.8-4.20 (2 H, m, H-3 and H-23), 4.83 (2 H, br s, H-19 and H-26), 5.07 (1 H, br s, H-19), 6.14 (2 H, AB q, J = 11 Hz, H-6 and H-7).

Experimental Section

The melting point was determined with a Yanaco micro melting point apparatus and was not corrected. ^{1}H NMR spectra were obtained with a Varian XL-100 instrument. Chemical shifts are reported in parts per million relative to tetramethylsilane. Mass spectra were obtained with a JEOL JMS-D300 spectrometer. Infrared spectra were obtained with a JASCO A-302 spectrometer. UV spectra were recorded on a Union Giken SM 401 spectrometer.

Iodolactonization of 4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (25*R*)- and (25*S*)-3β,25-Dihydroxy-5,7,22-cholestatrien-26-oic Acids (7a,b). Method A. Iodine (25 mg, 9.8 × 10^{-2} mmol) was added to a solution of carboxylic acid **7** (20 mg, 3.3 × 10^{-2} mmol) in CH_3CN (1 mL) at 0 °C, and the solution was stirred at that temperature for 5 h. After addition of aqueous $Na_2S_2O_3$, the mixture was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated. The product ratio was analyzed by HPLC [column, μ-Porasil; solvent, 2-propanol-hexane (15:85) for the analysis of the products from **7b** and ethyl acetate-hexane (7:3) for those from **7a**].

Method B. Carboxylic acid **7** (20 mg) was dissolved in Et_2O-THF (1:1 2 mL) and combined with aqueous saturated $NaHCO_3$ (2 mL). The solution was stirred for 30 min at room temperature and cooled to 0 °C, and then iodine (25 mg) was added. After 5 h, the reaction mixture was worked up as above, and the products were analyzed by HPLC.

Method C. A solution of carboxylic acid **7** (20 mg) and pyridine (20 μL, 2.5 × 10^{-1} mmol) in CH_3CN or CH_2Cl_2 (1 mL) was stirred at room temperature for 30 min and cooled to 0 °C, and then iodine (25 mg) was added. The mixture was stirred at that temperature for 5 h and then worked up as above. The products were analyzed by HPLC.

The results of the iodolactonization are shown in Table I.

4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (23*S*,25*R*)- and (23*R*,25*R*)-3β,25-Dihydroxy-22-iodo-5,7-cholestadiene 26,23-Lactone (8a,a′). A solution of **7a** (105 mg, 1.74 × 10^{-1} mmol) and pyridine (105 μL, 1.3 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 30 min and cooled to 0 °C, and then iodine (133 mg, 5.24 × 10^{-1} mmol) was added. After 2.5 h, iodine (133 mg) and pyridine (105 μL) were added, and the resultant solution was stirred for a further 7.5 h at 0 °C. Aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (6 g) by using hexane-ethyl acetate (2:8) as the eluent to give a 1:4 mixture of **8a** and **8a′** (95 mg). The mixture was subjected to the next reaction without separation.

4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (23*R*,25*R*)- and (23*S*,25*R*)-3β,25-Dihydroxy-5,7-cholestadiene 26,23-Lactone (9a,a′). To a solution of the iodolactone (**8a** and **8a′**, 1:4; 100 mg, 1.37 × 10^{-1} mmol) in DME (4 mL) was added n-Bu_3SnH (300 μL, 1.14 mmol), and the mixture was stirred at 60 °C for 1.5 h. After evaporation of the solvent, the residue was dissolved in CH_3CN and washed with hexane to remove organic tin compounds, and the CH_3CN was evaporated. The residue was chromatographed on silica gel (10 g) with hexane-ethyl acetate (2:8) as the eluent to yield **9a** (16 mg) and **9a′** (62 mg) in that order. **9a**: MS, m/e 428 (M^+ - triazoline), 395. **9a′**: MS, m/e 428 (M^+ - triazoline), 395; IR ($CHCl_3$) 1685, 1785, 1770; ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, s, H-18), 0.94 (3 H, s, H-19), 1.44 (3 H, s, H-27), 4.15-4.65 (2 H, m, H-3 and H-23).

(23*S*,25*R*)-5,7-Cholestadiene-3β,23,25,26-tetrol (10). To a suspension of $LiAlH_4$ (10 mg, 0.26 mmol) in THF (1 mL) was added a solution of **9a′** (28 mg, 4.6 × 10^{-2} mmol) in THF (1 mL), and the mixture was refluxed for 50 min. After the excess of the reagent was quenched with aqueous THF, the mixture was filtered and washed with THF and $CHCl_3$-MeOH (2:1), and the combined filtrate and washings were dried over Na_2SO_4 and evaporated. The residue was chromatographed on Sephadex LH-20 (10 g) with hexane-$CHCl_3$-MeOH (25:75:2) as the eluent to yield **10**: 18 mg; mp 225-228 °C; MS, m/e 432 (M^+), 414, 399, 383; ^{1}H NMR (Me_2SO-d_6) δ 0.58 (3 H, s, H-18), 0.86 (3 H, s, H-19), 1.07 (3 H, s, H-27), 3.6-4.0 (2 H, m, H-3 and H-23), 5.37 and 5.52 (2 H, m, H-6 and H-7); UV (95% EtOH) 272, 282, 293 nm.

(23*S*,25*R*)-23,25,26-Trihydroxyvitamin D_3 (2). A solution of **10** (6 mg) in 95% EtOH (200 mL) was irradiated by a high-pressure mercury lamp (200 W) through a Vycor filter for 5 min under an argon atmosphere, the temperature being maintained below 5 °C. The solvent was evaporated, and the residue was chromatographed on Sephadex LH-20 (25 g) and eluted with hexane-$CHCl_3$-MeOH (25:75:2.5) to yield previtamin D: 2.6 mg; UV (95% EtOH) 260 nm. The previtamin D was dissolved in 95% EtOH (2 mL), heated for 7 h at 60-63 °C, and then allowed to stand at room temperature for 8 h. After evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 (25 g) and eluted with hexane-$CHCl_3$-MeOH (25:75:2.5) to give vitamin D **2**: 1.9 mg; high-resolution MS, $C_{27}H_{44}O_4$ requires m/e 432.3239, found m/e 432.3256; ^{1}H NMR ($CDCl_3$) δ 0.56 (3 H, s, H-18), 1.22 (3 H, s, H-27), 3.57 (2 H, AB q, J = 11 Hz, H-26), 3.8-4.2 (2 H, m, H-3 and H-23), 4.82 (1 H, br s, H-19), 5.04 (1 H, br s, H-19), 6.13 (2 H, AB q, J = 11 Hz, H-6 and -7); UV (95% EtOH) 265 nm.

(23*S*,25*R*)-25-Hydroxyvitamin D_3 26,23-Lactol (3). A solution of (23S,25R)-calcidiol lactone (**4**;[5] 1.8 mg, 4.2 × 10^{-3} mmol) in toluene (300 μL) was cooled to -70 °C under argon, diisobutyl aluminium hydride (25% hexane solution, 26.5 μL, 4.7 × 10^{-2} mmol) was added, and the mixture was stirred for 2 h at that temperature. The reaction was quenched with cold ethanol (150 μL) at -70 °C, stirred for 20 min at that temperature, and then allowed to warm to room temperature. The mixture was diluted with $CHCl_3$, washed with 5% HCl and water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on Sephadex LH-20 (10 g) with hexane-$CHCl_3$-MeOH (35:65:2) as the eluent to give lactol **3**: 1.67 mg; MS, m/e 430 (M^+), 412, 394, 379, 356, 342; IR ($CHCl_3$) 3400 cm^{-1}; UV (95% EtOH) 265 nm.

Registry No. **2**, 83198-41-8; **3**, 83136-06-5; **4**, 77714-47-7; **7a**, 81495-58-1; **7b**, 80320-87-2; **8a**, 80320-88-3; **9a**, 78109-10-1; **9a′**, 78183-86-5; **10**, 83136-07-6; (23S,25R)-23,25,26-trihydroxyprevitamin D_3, 83136-08-7.

Reaction between 2-Amino-2-deoxy-D-glucose Derivatives and Sulfite. 2. Synthesis of 2-(D-*arabino*-Tetrahydroxybutyl)-5-(3,4-dihydroxy-2-sulfobutyl)pyrazine

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In continuation of our studies of the reaction of 2-amino-2-deoxy-D-glucose (**1**) derivatives in sodium bisulfite solution we recently reported the condensation of 2-amino-2-deoxy-D-glucose oxime with glyoxal-sodium bisulfite.[1] We now report the condensation of 2 mol of **1** in heated sodium bisulfite solution. The principal product is a pyrazine derivative with two polyhydroxyalkyl side chains one of which is sulfonated. The reaction constitutes a new route to sulfonated polyhydroxyalkylpyrazine derivatives.

The formation of the two pyrazine derivatives "fructosazine" (**2**) and "deoxyfructosazine" (**3**) from **1** has been reported.[2,3] Excessive side reactions of **1** in alkaline media resulted, however, in a low yield of **2**. Ingles[4,5] found

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