Facile Stereoselective Synthesis of (23S,25R)-1α,25-Dihydroxyvitamin D_3 26,23-Lactone, a Major Metabolite of 1α,25-Dihydroxyvitamin D_3

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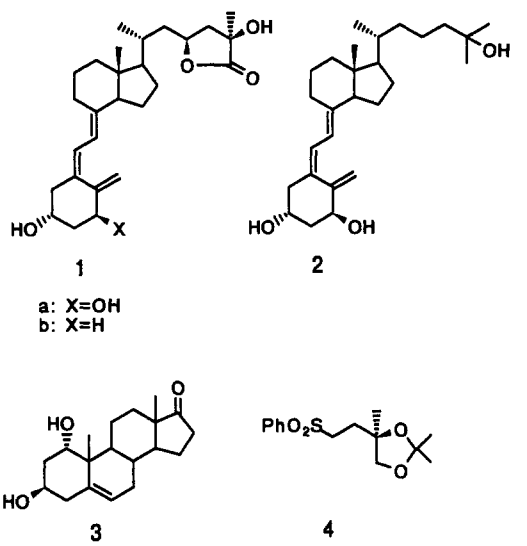
(23S,25R)-1α,25-Dihydroxyvitamin D_3 26,23-lactone (**1a**), a major metabolite of 1α,25-dihydroxyvitamin D_3 **2**, was synthesized efficiently and stereoselectively from 1α-hydroxydehydroepiandrosterone (**3**). The 17-oxosteroid **3** was first converted to C(22)-steroid aldehyde **9** with the natural stereochemistry at C(17) and C(20) using a stereoselective ene reaction as the key step. Then it was combined with the chiral C_5 sulfone **4** having the correct stereochemistry for the lactone in **1a**. Sulfone **4** was readily obtained from commercially available (*R*)-citramalic acid. The side-chain lactone with the natural stereochemistry at C(23) was constructed with high stereoselectivity (84%) by iodo lactonization of the Δ^{22}-26-carboxylic acid **16b** under kinetically controlled conditions in the presence of γ-collidine. The stereoselectivity of the iodo lactonization of steroidal Δ^{22}-25-hydroxy-26-carboxylic acids **16b**, **24**, and **25** was studied in detail, and a mechanism is proposed in which the configuration at C(25) and an added pyridine base play an important role.

1α,25-Dihydroxyvitamin D_3 26,23-lactone (**1a**)[1] is a major metabolite of the active vitamin D_3, 1α,25-dihydroxyvitamin D_3 (**2**). Lactone **1a** has received special attention among the vitamin D metabolites because of its unique biological properties: its serum concentration under physiological conditions is about three times higher than that of the active vitamin D metabolite (**2**);[2] its half-life in serum is considerably longer than that of **2**;[3] it inhibits bone resorption induced by **2**;[4] and it stimulates bone formation.[5] However the biological role of **1a** is still unclear, mainly because it is not readily available for research. There have been many attempts to construct the lactone side chain in connection with the synthesis of the non-1α-hydroxylated metabolite **1b**.[6] However, only two groups have succeeded in synthesizing the 1α-hydroxylated lactone **1a**. The Roche group[7a] synthesized the four possible side-chain diastereomers of the lactone by a convergent method in which an A-ring synthon and a CD-ring plus side-chain synthon were combined in the last stage of the synthesis. Teijin's group[7b] also synthesized the four diastereomers starting with a steroid precursor. The stereochemistry of the side chain of **1a** was determined to be 23S,25R, the same as the non-1α-hydroxylated metabolite **1b**.[6b,8] Although both methods are effective for synthesis of the four side-chain diastereomers of **1a**, they are not appropriate for synthesizing the lactone with the natural stereochemistry, since the stereoselectivities for construction of the asymmetric centers at the 23- and 25-positions are poor (~50% and 50%, respectively, for the former synthesis; 40% and 50%, respectively, for the latter).

Chart I



1 2 3 4

We report here a facile stereoselective synthesis of the natural lactone **1a**. The synthesis was achieved in 15 steps from 1α-hydroxydehydroepiandrosterone (**3**) and 10 steps from the C(22) steroid precursor **9**;[9] each step except for the final photochemical conversion was quite efficient

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(9) Recently C(22)-steroid synthons having 1α-hydroxyl group as well as provitamin D structure are manufactured as a synthetic intermediate of the active vitamin D analogues by chemical industries. So if such a C(22) steroid can be used as a starting material, the synthesis of **1a** become much easier, e.g.: Tsuji, J.; Takahashi, T.; Tsuji, M.; Nakagawa, N.; Takigawa, T. *Eur. Pat. Appl.* **1989**, 245.

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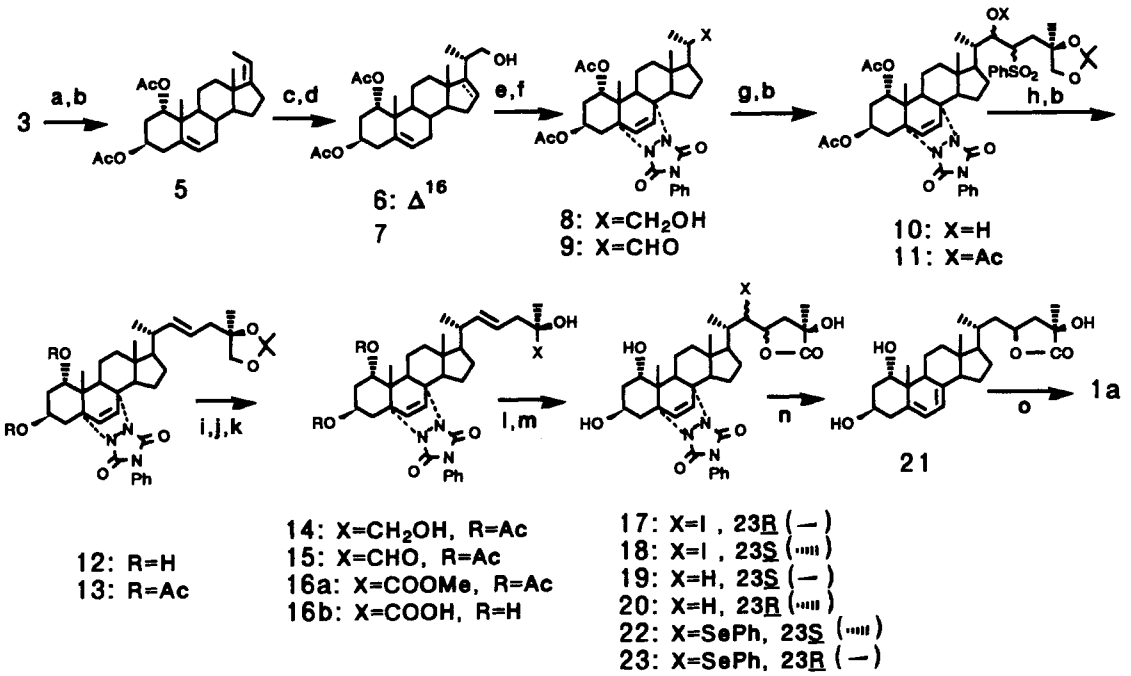
Scheme I[a]



[a] Reagents and conditions: (a) Ph_3EtPBr, *t*-BuOK; (b) Ac_2O, DMAP, pyridine; (c) $(CH_2O)_n$, BF_3–Et_2O; (d) H_2, 5% Pt/C; (e) NBS; *n*-Bu_4NBr, then *n*-Bu_4NF; PTAD; (f) $(COCl)_2$, DMSO, then Et_3N; (g) **4**, LDA, −78 °C; (h) 10% Na–Hg, Na_2HPO_4; (i) PPTS, 95% EtOH; (j) DMSO, pyridine–SO_3, Et_3N; (k) KOH, I_2, MeOH, then 5% KOH in MeOH–H_2O (2:1); (l) I_2, γ-collidine, MeCN; or PhSeCl, pyridine, CH_2Cl_2; (m) *n*-Bu_3SnH; (*n*) DMSO, K_2CO_3, 140 °C; (*o*) *hν*, then heating.

(overall yield of the provitamin D **21** from **9** was 57%); the stereoselectivities for the construction of C(23) and C(25) were excellent, 84% and 100% respectively. Thus, we believe this is the most practical method available to supply **1a** for biological studies.

Results and Discussion

There are two major problems in synthesizing 1α,25-dihydroxy lactone **1a** starting with a steroid precursor. One is the introduction of the 1α-hydroxyl group and the other is the construction of the lactone side chain with the correct stereochemistry. We used **3**, which is obtained in a single step by microbiological oxidation of commercially available dehydroepiandrosterone.[10] The stereochemistry at C(17) and C(20) was introduced by a stereoselective ene reaction followed by regio- and stereoselective hydrogenation.[11] The strategy for constructing the side-chain lactone, including the stereochemistry at C(23) and C(25), is based on our previous synthesis of 25-hydroxy lactone **1b**.[6a,b] The stereochemistry at C(25) was introduced using commercially available (*R*)-citramalic acid, and the stereochemistry at C(23) was created with high selectivity by iodo lactonization under kinetic conditions using a pyridine base.

The (*Z*)-17-ethylidene steroid diacetate **5**, obtained from the 17-oxo steroid **3** by Wittig reaction followed by acetylation, was subjected to a stereoselective ene reaction[11] with paraformaldehyde in the presence of boron trifluoride etherate to give the $\Delta^{5,16}$ alcohol **6** as a single product. The alcohol **6** was hydrogenated (H_2, Pt/C) to give the desired Δ^5-C(22) alcohol **7** with the correct natural stereochemistry at the 17- and 20-positions in 78% overall yield from **5**. The Δ^5-C(22) alcohol **7** was converted to the corresponding 5,7-diene by the usual allylic bromination followed by dehydrobromination under Rappoldt's conditions.[12] The diene was protected with phenyltriazolinedione (PTAD) to give **8** (59% yield from **7**). Alcohol **8** was oxidized (Swern's method) to the aldehyde **9** (90%). Thus, the synthesis of the desired C(22) provitamin D synthon **9** having 1α-hydroxyl group was achieved in 34% overall yield from the C(17) steroid **3**.[9]

The steroid synthon **9** was combined with the side-chain synthon **4** (LDA, THF, −78 °C), which was obtained in six steps (67% overall yield) from commercially available (*R*)-citramalic acid.[6a,b] This gave hydroxy sulfone **10** (83%) as a mixture of the four diastereomers at C(22) and C(23). In this reaction the acetyl group at the 3-position was partly removed but that causes no problem as the deprotected compound was reacetylated in the next step. Elimination of sulfonic acid from β-hydroxy sulfone **10** (10% Na–Hg, Na_2HPO_4, MeOH) was achieved in good yield (98%) via its acetate **11** to give selectively the *E* olefin **12**. After reprotection of the 1- and 3-hydroxyl groups, the acetonide group was removed (95% EtOH, PPTS, reflux) and the resulting C(26) primary alcohol **14** was oxidized in a stepwise manner to the carboxylic acid **16b**. The alcohol **14** was oxidized quantitatively to the aldehyde **15** by Parikh's method[13] (Py–SO_3, DMSO, Et_3N). Oxidation of the α-hydroxy aldehyde having olefinic as well as protected secondary hydroxyl groups was difficult. Oxidation with heavy metallic oxidants did not give satisfactory results. Halogen compounds known as mild oxidants such as hypochlorites,[14] chlorites,[15] and NBS[16] are not appro-

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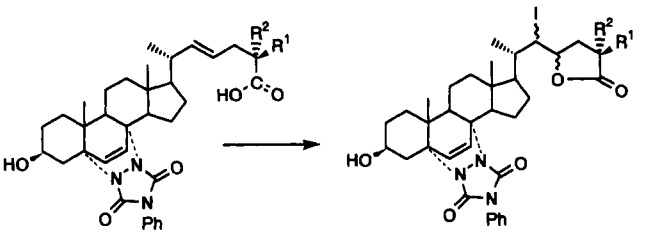
Table I. Stereoselectivity in the Iodo Lactonization of (25R)-Δ²²-26-Carboxylic Acid 16b[a]

entry	solvent	amine (mol equiv)	product ratio 17:18	yield[b]
1	CH_3CN		37:63	18
2	CH_2Cl_2	pyridine (7)	81:19	54
3	CH_2Cl_2	3,5-dimethylpyridine (7)	84:16	30
4	CH_2Cl_2	2,4,6-trimethylpyridine (7)	90:10	46
5	CH_2Cl_2	2,4,6-trimethylpyridine (3)	89:11	29
6	CH_3CN	pyridine (7)	72:28	87
7	CH_3CN	2,4,6-trimethylpyridine (4)	84:16	91
8	CH_3CN	2,6-di-*tert*-butyl-4-methylpyridine (4)	40:60	92
9	$CHCl_3$	2,4,6-trimethylpyridine (4)	73:27	51
10	CH_3CN	triethylamine (4)	70:30	8.5
11	CH_2Cl_2	DBU (7)	60:40	2

[a] Iodine (3 equiv) was added to a solution of the carboxylic acid **16b** and the indicated base in the indicated solvent, and the mixture was stirred at room temperature for 1–4.5 h. After workup the reaction mixture was analyzed on HPLC (LiChrospher Si 60, 5% $MeOH/CH_2Cl_2$) to determine the product ratio as well as the yield. [b] In addition to the iodo lactones unchanged starting carboxylic acid was obtained (entries 2–11). In the case of entry 1, some unknown byproducts were detected.

priate because of the presence of isolated olefinic bonds in the substrate **15**. Alkaline iodine solution was found to be the best oxidant. This classical oxidation method[17] used in carbohydrate chemistry has rarely been used in general organic synthesis, and the mechanism is not well understood. We found useful conditions for alkaline–iodine oxidation of aldehydes to the corresponding carboxylic acids via the ester. Thus, the aldehyde **15** was treated with iodine in methanolic KOH. This gave the methyl ester **16a** of the desired carboxylic acid which was hydrolyzed in situ to the carboxylic acid **16b** in high yield (94%). In the oxidation the olefinic bonds and the triazolidine ring remained intact but the 3β-acetoxy group was partly hydrolyzed. This method for oxidizing aldehydes to carboxylic acids and esters is mild, efficient, and inexpensive and found to be generally applicable to a variety of aldehydes. The scope and limitation of the reaction will be reported elsewhere. The carboxylic acid **16b** was subjected to iodo lactonization. Iodo lactonization under normal conditions (I_2, CH_3CN) gave predominantly (63% selectivity) the undesired (23S)-iodo lactone **18** but addition of a pyridine base changed the selectivity in favor of the desired (23R)-iodo lactone **17** (see below). Carboxylic acid **16b** in CH_3CN was treated with iodine in the presence of collidine to give the (23R)-iodo lactone **17** in 84% selectivity (HPLC) (80% isolated yield). The major (23R)-iodo lactone **17** was isolated by just one crystallization. Isomers **17** and **18** can also be separated by column chromatography (silica gel). The stereochemistry at the 23-position of the iodo lactones **17** and **18** was determined, after conversion to the lactones **19** and **20**, by comparing their ^1H NMR spectra with those of the 1α-H analogues.[6] The signal of H(23) situated trans to the 25-hydroxyl group appears at a higher field (δ 4.43) than that situated cis (δ 4.75). Seleno lactonization of **16b** gave the undesired (23S)-seleno lactone **22** as the major product (80%) together with a minor (23R)-seleno lactone **23** (11%). Deprotection of the triazoline group of **19** (K_2CO_3, DMSO, 140 °C) yielded the provitamin D **21** (90%). The provitamin D **21** was converted to the lactone **1a** by photochemical reaction followed by thermal isomerization. The spectral data (^1H NMR, mass, UV, and IR) of **1a** thus synthesized were in good agreement with those of the natural lactone.[1,7]

Table II. Stereoselectivity of the Iodo Lactonization of (25R)- and (25S)-Δ²²-26-Carboxylic Acids 24 and 25[a]



24: R^1=OH, R^2=Me (25R)

25: R^1=Me, R^2=OH (25S)

26: (22S,23R,25R)
27: (22R,23S,25R)
28: (22S,23R,25S)
29: (22R,23S,25S)

entry	carboxylic acid	solvent	amine	product ratio 26:27
1	**24**	CH_2Cl_2		31:69
2	**24**	CH_3CN		43:57
3	**24**	CH_2Cl_2	pyridine	80:20
4	**24**	CH_3CN	pyridine	73:27
				28:29
5	**25**	CH_2Cl_2		34:66
6	**25**	CH_3CN		10:90
7	**25**	CH_2Cl_2	pyridine	45:55
8	**25**	CH_3CN	pyridine	43:57

[a] Carboxylic acid **24** or **25** was treated with iodine (3 equiv) in the indicated solvent with or without added pyridine at 0 °C for 5 h. The products were analyzed on HPLC (μ-Porasil, ethyl acetate/hexane (7:3) for entries 1–4, 2-propanol/hexane (15:85) for entries 5–8).

Stereoselectivity in the Iodo Lactonization of Δ²²-26-Carboxylic Acids. In the stereoselectivity of the iodo lactonization of Δ²²-26-carboxylic acid **16b**, an added pyridine base played an important role. To clarify the role of the amine, we discuss here in more detail the stereoselectivity of the iodo lactonization of the steroidal Δ²²-26-carboxylic acids with asymmetric center at C(25). Table I lists the results of the iodo lactonization of **16b** under a variety of conditions, and Table II shows the results of non-1α-hydroxylated carboxylic acids **24** and **25**. Under the conditions without added base, the 25R carboxylic acid **16b** gave predominantly the (23S)-iodo lactone **18** (Table I, entry 1). However, the selectivity was dramatically changed by adding pyridine to afford the (23R)-iodo lactone **17** predominantly (entries 2 and 6). The selectivity was improved by increasing the bulkiness of the added base to 3,5-dimethylpyridine (entry 3) and 2,4,6-trimethylpyridine (γ-collidine) (entries 4, 5, and 7). It should be noted that the most bulky 2,6-di-*tert*-butyl-4-methylpyridine had little effect on the selectivity (entry 8). Aliphatic amines, triethylamine, and DBU retarded the lactonization (entries 10 and 11) (most of the starting carboxylic acid was recovered unchanged), since they make a complex with iodine.[18] Similar stereoselectivity was observed in the iodo lactonization of non-1α-hydroxylated 25R carboxylic acid **24** (Table II, entry 1–4).[19] In the case

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Scheme II

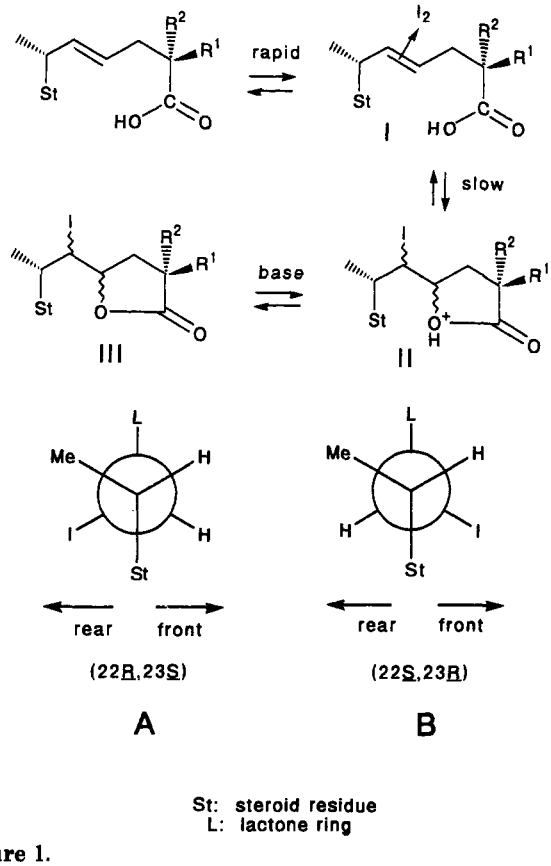

Figure 1.

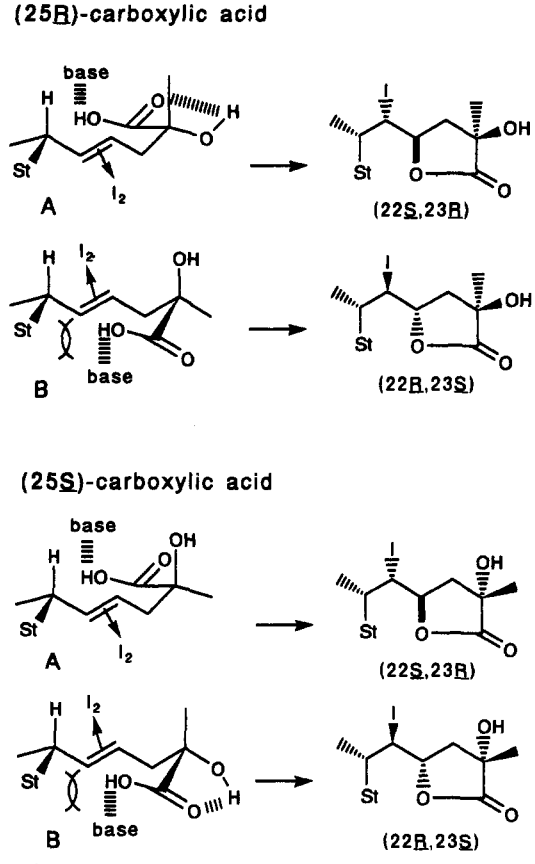

Figure 2.

of 25*S* carboxylic acid **25**, the (23*S*)-iodo lactone **29** was preferably formed regardless of the conditions, though added pyridine increased the proportion of the (23*R*)-iodo lactone **28**.[19]

Following is a mechanism postulated on the basis of the generally accepted mechanism of iodo lactonization[20] and iodo etherification[21] (Scheme II). The reaction starts with the rapid and fully reversible attack of iodine on one of the faces of the olefin to form a π-complex I. This is followed by rate-determining cyclization with concomitant rupture of the I–I bond and formation of the C–I bond to yield the protonated iodo lactone II. Deprotonation of II yields the iodo lactones III. Since all steps are reversible under the conditions without the added base, the reaction usually gives thermodynamically most stable products. But with a base present, the proton is abstracted from II to render the cyclization step irreversible, thus trapping the kinetic product. Under kinetic conditions, the ratio of the products can be determined by the relative energy of the diastereomeric transition structures for the rate-determining cyclization step. In view of this mechanism, the (23*S*)-iodo lactones (**18**, **27**, and **29**) favored in the absence of the base are considered to be thermodynamically more stable products. This can be understood by inspecting the conformations around the C(20)–C(22) bond in the (23*S*)- and (23*R*)-iodo lactones (Figure 1). The (23*S*)-iodo lactone can take the most stable conformation A where the steroid residue is situated anti with respect to the lactone ring and the iodine occupies the less congested gauche rear side. But in the 23*R* isomer, the bulky iodine is directed to the congested front side when the steroid residue and the lactone are placed in the anti position (conformation B). The result of seleno lactonization of **16b**, in which the (23*S*)-seleno lactone **22** was obtained in high selectivity, supports the proposed mechanism, since seleno lactonization has been known to give the thermodynamically more stable product.[22]

The results under kinetic conditions in the presence of pyridines can be explained as follows (Figure 2). The two transition-state conformations, A and B, which lead, respectively, to the (23*R*)- and (23*S*)-iodo lactones, can be assumed for the reaction of each of the epimeric Δ^{22}-26-carboxylic acids **16b**, **24**, and **25**. In conformation A, the carboxyl group is oriented to the rear (the side of the 21-methyl group) of the 22-double bond. In B, it is directed to the front (the steroid-ring side). Two major factors, steric hindrance and hydrogen bonding, may contribute to the transition-state energy. In the presence of pyridine, the carboxyl group complexes with the amine and the congestion between the D ring and the carboxyl group becomes significant, rendering conformation B unstable.[23] This was supported by the fact that increasing bulkiness of the added amine increases the proportion of the (23*R*)-iodo lactone **17**. However, 2,6-di-*tert*-butyl-4-methylpyridine caused no steric effect because the ring nitrogen is so hindered that it cannot complex with the carboxylic acid.[24] The hydrogen bond between the car-

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(23) In analogous intermolecular electrophilic addition reactions of Δ^{22}-steroids, where the formation of a halonium ion is considered to be the rate-limiting step,[20c] the steric interaction between the D ring and the approaching halogen molecule appears to be the major factor determining the stereoselectivity: Barton, D. H. R.; Poyser, J. P.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 53.

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boxyl and the adjacent hydroxyl groups would stabilize the transition structures. This can be expected in conformer A of the (25R)-carboxylic acids **16b** and **24** and in conformer B of the 25S isomer **25**. Thus, with the (25R)-carboxylic acids **16b** and **24**, the two factors work synergistically in favor of conformer A. In the (25S)-carboxylic acid **25**, the two factors would cancel each other to give the two isomeric iodo lactones **28** and **29** in comparable yields.

In summary, we synthesized the major metabolite **1a** of the active vitamin D_3 in a short, stereoselective, and efficient way. We also showed that in the iodo lactonization of α-hydroxy-γ,δ-unsaturated carboxylic acids **16b**, **24**, and **25** the configuration of the carbon bearing the carboxyl group and an added pyridine base play an important role in the stereoselectivity of the reaction. A mechanism to explain the stereoselectivity is suggested.

Experimental Section

General Procedures. Melting points were determined on a micro melting point apparatus and are uncorrected. All mass spectra were measured at 70 eV. Relative intensities are given in parentheses. ^1H NMR spectra were recorded at 270 MHz. Coupling constants are reported in Hz. All air-sensitive reactions were run under Ar, and reagents were added through septa using oven-dried syringes. The phrase "dried and evaporated" indicates drying with Na_2SO_4, followed by evaporation of the solvents under house vacuum.

(17Z)-5,17-Pregnadiene-1α,3β-diol Diacetate (5). Potassium *tert*-butoxide (22.1 g, 197 mmol) was added at rt to a solution of ethyltriphenylphosphonium bromide (73.2 g, 197 mmol) in THF (500 mL). Then the mixture was stirred at 40 °C for 2 h and cooled to rt. To the resulting orange solution of ethylidenetriphenylphosphorane was added the 17-oxosteroid **3** (20.0 g, 65.7 mmol), and the mixture was stirred at rt for 33 h. Most of the solvent was evaporated, then the mixture was poured into ice-water, extracted with $CHCl_3$, dried, and evaporated. The residue was dissolved in pyridine (100 mL), and then acetic anhydride (50 mL) and 4-(dimethylamino)pyridine (1.01 g, 9 mmol) were added and the mixture was stirred for 45 min at rt. Most of the solvent was removed, ice–water was added to the residue, and the whole was stirred at rt for 30 min. The mixture was extracted with ethyl acetate, the extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (850 g) with 10% ethyl acetate/hexane to give diacetate **5** (21.6 g, 82%) as a glass: MS *m/z* 340 (1.5, M^+ – AcOH), 280 (100), 278 (52), 265 (23), 263 (23), 251 (50), 249 (70), 247 (68); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s, H-18), 1.10 (3 H, s, H-19), 1.64 (3 H, d, t *J* = 7.3, 2.0, H-21), 2.03 and 2.05 (each 3 H, s, Ac), 4.92 (1 H, m, H-3), 5.08 (1 H, m, H-1), 5.13 (1 H, m, H-20), 5.54 (1 H, m, H-6); IR (KBr) 2948, 1742 cm^{-1}. Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.95; H, 9.07. Found C, 74.63; H, 8.94.

23,24-Dinor-5,16-choladiene-1α,3β,22-triol 1,3-Diacetate (6). Freshly distilled BF_3–Et_2O (919 μL, 7.5 mmol) was added to a solution of **5** (14.64 g, 36.55 mmol) and 80% paraformaldehyde (1.65 g, 44 mmol) in CH_2Cl_2 (180 mL). The mixture was stirred at rt for 1 h then poured into ice-cold 5% $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel (500 g) with ethyl acetate/hexane (3:17–1:4) to give alcohol **6** (12.6 g, 80%): mp 70–74 °C (colorless needles from ethyl acetate/hexane); MS *m/z* 412 (3, $M^+ - H_2O$), 310 (100), 292 (70), 280 (18), 277 (26), 251 (22), 192 (46), 133 (28); ^1H NMR ($CDCl_3$) δ 0.81 (3 H, s, H-18), 1.03 (3 H, d, *J* = 6.9, H-21), 1.13 (3 H, s, H-19), 2.03 and 2.06 (each 3 H, s, Ac), 3.57 (2 H, m, H-22), 4.92 (1 H, m, H-3), 5.06 (1 H, m, H-1), 5.44 (1 H, m, H-16), 5.56 (1 H, m, H-6); IR (KBr) 1740 cm^{-1}. Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.53; H, 8.90. Found: C, 72.20; H, 8.84.

23,24-Dinor-5-cholene-1α,3β,22-triol 1,3-Diacetate (7). A solution of the alcohol **6** (4.07 g, 9.46 mmol) in ethanol (100 mL) was stirred in the presence of 5% Pt/C (407 mg) under an atmosphere of H_2 at rt until the theoretical amount of H_2 (212 mL) was absorbed. The catalyst was filtered, the filtrate was evaporated, and the residue was chromatographed on silica gel (200 g) with ethyl acetate/hexane (1:4) to give alcohol **7** (4.0 g, 98%): mp 137–138 °C (colorless needles from CH_2Cl_2/hexane); MS *m/z* 312 (44, $M^+ - 2 \times$ AcOH), 118 (100); ^1H NMR ($CDCl_3$) δ 0.69 (3 H, s, H-18), 1.03 (3 H, d, *J* = 6.6, H-21), 1.09 (3 H, s, H-19), 2.02 and 2.05 (each 3 H, s, Ac), 3.36 (1 H, dd, *J* = 10.6, 6.6, H-22), 3.63 (1 H, dd, *J* = 10.6, 3.5, H-22), 4.92 (1 H, m, H-3), 5.06 (1 H, m, H-1), 5.53 (1 H, m, H-6); IR (KBr) 1742 cm^{-1}. Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.17; H, 9.33. Found: C, 72.28; H, 9.19.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 23,24-Dinor-5,7-choladiene-1α,3β,22-triol 1,3-Diacetate (8). *N*-Bromosuccinimide (50 mg, 0.28 mmol) was added to a solution of **7** (100 mg, 0.23 mmol) in CCl_4 (6 mL) under Ar, and the mixture was refluxed for 15 min. After the mixture cooled with ice-water, crystals were precipitated. They were filtered out, and the filtrate was evaporated. The residue was dissolved in THF (6 mL), n-Bu_4NBr (16 mg, 0.05 mmol) was added, and the mixture was stirred at rt for 1 h. A 1.0 M hexane solution of n-Bu_4NF (1.15 mL, 1.15 mmol) was added, and the mixture was stirred at rt for 45 min. Water was added, and the mixture was extracted with ethyl acetate; the extracts were washed with brine, dried, and filtered. PTAD was added portionwise to the filtrate until the red color of the added PTAD was no longer bleached. The solvent was evaporated, and the residue was chromatographed on silica gel (30 g) with ethyl acetate/hexane (1:1) to give adduct **8** (82 mg, 59%): mp 201–203 °C (colorless needles from benzene); MS *m/z* 370 (3.7, M^+ – PTAD – AcOH), 352 (8), 310 (47), 292 (48), 290 (46), 249 (100), 247 (71), 245 (40); ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s, H-18), 1.06 (3 H, d, *J* = 6.3, H-21), 1.07 (3 H, s, H-19), 2.02 and 2.03 (each 3 H, s, Ac), 3.35 (1 H, dd, *J* = 10.6, 7.1, H-22), 3.65 (1, H, dd, *J* = 10.6, 3.3, H-22), 5.11 (1 H, m, H-1), 5.89 (1 H, m, H-3), 6.34 and 6.45 (each 1 H, d, *J* = 8.4, H-6 and 7), 7.26–7.52 (5 H, m, Ar); IR (KBr) 2968, 1742, 1694 cm^{-1}. Anal. Calcd for $C_{34}H_{43}N_3O_7$: C, 67.40; H, 7.16; N, 6.94. Found: C, 67.62; H, 7.12; N, 6.57.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 23,24-Dinor-1α,3β-dihydroxy-5,7-choladien-22-al Diacetate (9). DMSO (273 μL, 3.8 mmol) in CH_2Cl_2 (1 mL) was added to a solution of oxalyl chloride (224 mg, 1.8 mmol) in CH_2Cl_2 (3 mL) at –78 °C, and after 10 min, a solution of the alcohol **8** (0.97 g, 1.6 mmol) in CH_2Cl_2 (1 mL) was added to the mixture. The reaction mixture was stirred at –78 °C for 15 min, triethylamine (810 mg, 8 mmol) was added, and the mixture was allowed to warm to rt for 50 min. Ice–water was added, and the mixture was extracted with CH_2Cl_2, washed with water, dried, and evaporated. The residue was chromatographed on silica gel (30 g) with 50% ethyl acetate/hexane to give aldehyde **9** (0.87 g, 90%): mp 198–201 °C (colorless prisms from ethyl acetate); MS *m/z* 368 (8, M^+ – PTAD – AcOH), 308 (100), 293 (12), 251 (16), 235 (30), 141 (77); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s, H-18), 1.07 (3 H, s, H-19), 1.14 (3 H, d, *J* = 6.6, H-21), 2.02 and 2.04 (each 3 H, s, Ac), 5.12 (1 H, m, H-1), 5.88 (1, H, m, H-3), 6.36 and 6.44 (each 1 H, d, *J* = 8.3, H-6 and 7), 7.26–7.51 (5 H, m, Ar), 9.55 (1 H, d, *J* = 3.3); IR (KBr) 2968, 1742, 1698 cm^{-1}. Anal. Calcd for $C_{34}H_{41}O_7N_3$: C, 67.64; H, 6.85; N, 6.96. Found: C, 67.28; H, 6.89; N, 6.89.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25R)-23-(Phenylsulfonyl)-5,7-cholestadiene-1α,3β,22,25,26-pentol 1,3-Diacetate 25,26-Acetonide (10). Diisopropylamine (132 mg, 1.3 mmol) and a 1.93 M hexane solution of n-BuLi (446 μL, 0.86 mmol) were added to a solution of sulfone **4** (245 mg, 0.86 mmol) in THF (5 mL) at –40 °C in this order. After 15 min, the solution was added with stirring to a solution of the aldehyde **9** (520 mg, 0.86 mmol) in THF (2.5 mL) at –78 °C. The mixture was stirred for 40 min at that temperature, and then saturated NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (50 g) with ethyl acetate/benzene (2:8–6:4) to give the recovered starting material **9** (79 mg, 15%), β-hydroxy sulfone **10** (548 mg, 72%) as a mixture of four diastereomers at the 22- and 23-positions, and partially hydrolyzed (3β-hydroxy) compound **10′** (80 mg, 11%). **10** (colorless glass): MS *m/z* 592 (1, M^+ – PTAD – 2 × AcOH), 516 (3), 479 (5), 465 (4), 368 (12), 308 (100), 269 (69); ^1H NMR ($CDCl_3$) δ 5.10 (1 H, m, H-1), 5.87 (1 H, m, H-3), 6.34 and 6.43 (each 1 H, m H-6 and -7), 7.28–7.95 (10 H, m, Ar); IR (KBr) 2984, 1748, 1698 cm^{-1}; HRMS *m/z* calcd for $C_{38}H_{52}O_7S$ (M^+ – PTAD – AcOH) 652.3430, found 652.3419. **10′** (colorless glass): MS *m/z* 516 (3),

479 (6), 465 (5), 386 (3), 368 (3), 269 (65), 115 (100); ^{1}H NMR ($CDCl_3$) δ 4.85 (1 H, m, H-3), 5.10 (1 H, m, H-1), 6.34 and 6.42 (each 1 H, m, H-6 and -7), 7.28–7.95 (10 H, m, Ar); IR (KBr) 2978, 1744, 1694 cm^{-1}; HRMS m/z calcd for $C_{38}H_{54}O_8S$ (M^+ – PTAD) 670.3536, found 670.3565.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25*R*)-5,7,22-Cholestatriene-1α,3β,25,26-tetrol 25,26-Acetonide (12). The hydroxy sulfone **10** (416 mg, 0.47 mmol) was dissolved in acetic anhydride (300 μL) and pyridine (600 μL), 4-(dimethylamino)pyridine (4 mg, 33 μmol) was added to the mixture, and the whole was stirred at rt for 4 h. The mixture was evaporated to dryness in vacuo, and the residue was chromatographed on silica gel (30 g) with ethyl acetate/benzene (3:7) to give triacetate **11** (430 mg, 99%). To an ice-cooled solution of **11** (430 mg, 0.46 mmol) in methanol (18 mL) were added Na_2HPO_4 (657 mg, 4.6 mmol) and freshly prepared 10% Na–Hg (1.06 g, 4.6 mmol), and the mixture was stirred at rt for 30 min. The reaction was quenched by adding ice, the methanol was removed, and the residue was extracted with ethyl acetate. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (20 g) with ethyl acetate/hexane (8:2) to give **12** (292 mg, 98%): mp 216–219 °C (colorless needles from ethyl acetate/hexane); MS m/z 470 (9, M^+ – PTAD), 452 (5), 412 (2), 394 (7), 376 (10), 251 (21), 177 (75), 115 (100); ^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, s, H-18), 0.93 (1 H, s, H-19), 1.04 (3 H, d, J = 6.6), 1.24 (3 H, s, H-27), 1.39 (6 H, s, acetonide), 3.64 and 3.80 (each 1 H, d, J = 8.2, H-26), 3.86 (1 H, m, H-1), 4.88 (1 H, m, H-3), 5.33 (2 H, m, H-22 and -23), 6.25 and 6.41 (each 1 H, d, J = 8.2), 7.28–7.43 (5 H, m); IR (KBr) 3452, 2932, 1746, 1690, 1412 cm^{-1}. Anal. Calcd for $C_{38}H_{51}O_6N_3$: C, 70.67; H, 7.96; N, 6.51. Found: C, 70.31; H, 7.98; N, 6.36.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25*R*)-5,7,22-Cholestatriene-1α,3β,25,26-tetrol 1,3-Diacetate 25,26-Acetonide (13). Acetic anhydride (300 μL) and 4-(dimethylamino)pyridine (10 mg, 82 μmol) were added to a solution of **12** (530 mg, 0.82 mmol) in pyridine (600 μL), and the mixture was stirred at rt for 3 h. The mixture was evaporated to dryness, and the residue was chromatographed on silica gel (6 g) with ethyl acetate/benzene (4:6) to give acetate **13** as a glass (595 mg, 99.3%): MS m/z 539 (0.6, M^+ – PTAD – Me), 494 (2), 434 (6), 376 (39), 251 (28), 115 (100); ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, s, H-18), 1.02 (3 H, d, J = 6.6, H-21), 1.07 (3 H, s, H-19), 1.23 (3 H, s, H-27), 1.38 (6 H, s, acetonide), 2.01 and 2.03 (each 3 H, s, Ac), 3.64 and 3.80 (each 1 H, d, J = 8.5, H-26), 5.11 (1 H, m, H-1), 5.32 (2 H, m, H-22 and -23), 5.88 (1 H, m, H-3), 6.33 and 6.44 (each 1 H, d, J = 8.2, H-6 and -7), 7.28–7.51 (5 H, m, Ar); IR (KBr) 2978, 1746, 1698, 1400, 1243 cm^{-1}; HRMS m/z calcd for $C_{33}H_{47}O_6$ (M^+ – PTAD – CH_3) 539.3370, found 539.3374.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25*R*)-5,7,22-Cholestatriene-1α,3β,25,26-tetrol 1,3-Diacetate (14). The acetonide **13** (560 mg, 0.77 mmol) was dissolved in 95% ethanol (14 mL), and PPTS (195 mg, 0.77 mmol) was added. The mixture was refluxed for 1 h, and the solvent was evaporated. The residue was chromatographed on silica gel (20 g) with ethyl acetate/benzene (6:4–1:0) to give **14** as a colorless glass (485 mg, 92%): MS m/z 514 (0.2, M^+ – PTAD), 454 (4), 436 (10), 394 (21), 376 (100), 251 (65), 177 (74); ^{1}H NMR ($CDCl_3$) δ 0.84 (3, H, s, H-18), 1.04 (1 H, d, J = 6.3, H-21), 1.06 (3 H, s, H-19), 1.12 (3 H, s, H-27), 2.02 and 2.03 (each 3 H, s, Ac), 3.38 and 3.42 (each 1 H, d, J = 11, H-26), 5.11 (1 H, m, H-1), 5.36 (2 H, m, H-22 and -23), 5.88 (1 H, m, H-3), 6.33 and 6.44 (each 1 H, d, J = 8.2, H-6 and -7), 7.28–7.50 (5 H, m, Ar); IR (KBr) 2972, 1746, 1696 cm^{-1}; HRMS m/z calcd for $C_{31}H_{46}O_6$ (M^+ – PTAD) 514.3291, found 514.3280.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25*R*)-1α,3β,25-Trihydroxy-5,7,22-cholestatrien-26-al 1,3-Diacetate (15). Triethylamine (732 mg, 7.19 mmol) and a solution of pyridine–SO_3 complex (411 mg, 2.58 mmol) in DMSO (1 mL) were added to a solution of **14** (357 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) at rt, and the mixture was stirred for 1 h. The reaction mixture was poured into ice–water, extracted with ethyl acetate, washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (15 g) with ethyl acetate/benzene (2:8–8:2) to give aldehyde **15** as a colorless glass (352 mg, 99%): MS m/z 512 (0.8, M^+ – PTAD), 452 (12), 392 (100), 374 (14), 251 (53), 177 (67); ^{1}H NMR ($CDCl_3$) δ 0.82 (3 H, s, H-18), 1.02 (3 H, d, J = 6.6, H-21), 1.06 (3 H, s, H-19), 1.28 (3 H, s, H-27), 2.01 and 2.03 (each 3 H, s, Ac), 5.11 (1 H, m, H-1), 5.33 (2 H, m, H-22 and -23), 5.88 (1 H, m, H-3), 6.33 and 6.44 (each 1 H, d, J = 8.3), 9.49 (1 H, s, H-26); IR (KBr) 3438, 2972, 1744, 1696, 1402, 1245, 1031 cm^{-1}; HRMS m/z calcd for $C_{31}H_{44}O_6$ (M^+ – PTAD) 512.3135, found 512.3121.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25*R*)-1α,3β,25-Trihydroxy-5,7,22-cholestatrien-26-oic Acid (16b). KOH (106 mg, 1.89 mmol) then I_2 (240 mg, 0.95 mmol) were added to a solution of the aldehyde **15** (500 mg, 0.73 mmol) in methanol (25 mL) at 0 °C. The mixture was stirred at that temperature for 30 min. The mixture was diluted with $CHCl_3$ and washed with aqueous $Na_2S_2O_3$ and brine. The organic layer was dried and evaporated. The residue was dissolved in 5% KOH in MeOH–H_2O (2:1) (30 mL) and stirred at rt for 30 min. The mixture was neutralized by adding a calculated amount of hydrochloric acid under ice cooling and then extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated to give crytalline residue. The residue was recrystallized from MeOH–$CHCl_3$ to give carboxylic acid **16b** (230 mg, 51%) as colorless needles. The filtrate was evaporated and chromatographed on silica gel (10 g) with $CHCl_3$/MeOH/AcOH (95:5:0.1) to give the carboxylic acid **16b** (198 mg, 43%): mp 217–220 °C; ^{1}H NMR (6% CD_3OD/$CDCl_3$) δ 0.83 (3 H, s, H-18), 0.94 (3 H, s, H-19), 1.01 (3 H, d, J = 6, H-21), 1.41 (3 H, s, H-27), 3.88 (1 H, m, H-1), 4.81 (1 H, m, H-3), 5.35 (2 H, m, H-22 and 23), 6.33 and 6.41 (each 1 H, d, J = 8.3, H-6 and -7), 7.3–7.5 (5 H, m, Ar); IR (KBr) 3410, 2964, 1744, 1686, 1421 cm^{-1}.

4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (22*S*,23*R*,25*R*)- and (22*R*,23*S*,25*R*)-1α,3β,25-Trihydroxy-22-iodo-5,7-cholestadiene 26,23-Lactones (17 and 18). A suspension of the carboxylic acid **16b** (237 mg, 0.38 mmol) and 2,4,6-collidine (186 mg, 1.5 mmol) in CH_3CN (27 mL) was stirred at rt for 30 min, it was cooled to 0 °C, and then I_2 (291 mg, 1.15 mmol) was added. After 1 h, the mixture was diluted with $CHCl_3$, washed with aqueous $Na_2S_2O_3$ and brine, dried, and evaporated to give a crystalline residue. The residue was recrystallized from MeOH–$CHCl_3$ to give (23*R*)-iodo lactone **17** (178 mg, 62%). The filtrate was evaporated and chromatographed on silica gel (25 g) with 3% MeOH/CH_2Cl_2 to give (23*S*)-iodo lactone **18** (44 mg, 15%) and **17** (51 mg, 18%) in this order. **17**: mp 194–197 °C (colorless needles, MeOH/$CHCl_3$); MS m/z 570 (M^+ – PTAD, 1.5), 552 (3), 532 (5), 406 (22), 254 (54), 177 (77), 128 (78), 119 (100); ^{1}H NMR (CD_3OD) δ 0.90 (3 H, s, H-18), 0.97 (3 H, s, H-19), 1.20 (3 H, d, J = 6.6, H-21), 1.43 (3 H, s, H-27), 3.86 (1 H, m, H-1), 4.48 (1 H, m, H-23) 4.64 (1 H, m, H-22), 4.88 (H-3 hidden in the peak of the solvent), 6.42 and 6.50 (each 1 H, d, J = 8.5, H-6 and -7), 7.3–7.5 (5 H, m, Ar); IR (KBr) 3406, 2942, 1783, 1738, 1678, 1421 cm^{-1}; HRMS m/z calcd for $C_{27}H_{39}O_5I$ (M^+ – PTAD) 570.1840, found 570.1864. **18**: MS m/z 570 (M^+ – PTAD, 1), 532 (3), 406 (25), 254 (48), 177 (40), 128 (100), 119 (61); ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, s, H-18), 0.91 (3 H, s, H-19), 0.99 (3 H, d, J = 5.9, H-21), 1.50 (3 H, s, H-27), 3.81 (1 H, m, H-1), 3.99 (1 H, m, H-22), 4.80–5.00 (2 H, m, H-3 and -23), 6.28 and 6.40 (each 1 H, d, J = 8.2, H-6 and -7), 7.30–7.46 (5 H, m, Ar); IR (KBr) 3434, 2970, 1777, 1744, 1684, 1415 cm^{-1}; HRMS m/z calcd for $C_{27}H_{39}O_5I$ (M^+ – PTAD) 570.1840, found 570.1856.

4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (23*S*,25*R*)- and (23*R*,25*R*)-1α,3β,25-Trihydroxy-5,7-cholestadiene 26,23-Lactones (19 and 20). Tributyltin hydride (129 mg, 0.44 mmol) was added to a solution of the iodo lactone **17** (100 mg, 0.13 mmol) in DME (5 mL), and the mixture was stirred at 60 °C for 30 min. The solvent was evaporated, and the residue was dissolved in CH_3CN (50 mL) and washed with hexane to remove tin compounds. The CH_3CN was evaporated, and the residue was chromatographed on silica gel (5 g) with 3% MeOH/CH_2Cl_2 to give lactone **19** as a white solid (82 mg, 99%). **19**: mp 191.5–194 °C (colorless needles, MeOH/$CHCl_3$); MS m/z 444 (M^+ – PTAD, 8), 426 (4), 424 (6), 408 (9), 251 (15), 177 (63), 119 (100); ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, s, H-18), 0.95 (3 H, s, H-19), 1.04 (3 H, d, J = 6, H-21), 1.48 (3 H, s, H-27), 3.19 (1 H, dd, J = 14, 4.5, H-4), 3.91 (1 H, m, H-1), 4.43 (1 H, m, H-23), 4.93 (1 H, m, H-3), 6.28 and 6.41 (each 1 H, d, J = 8.4, H-6 and -7), 7.3–7.45 (5 H, m, Ar); IR (KBr) 3424, 2930, 1777, 1744, 1686, 1412 cm^{-1}; HRMS m/z calcd for $C_{27}H_{40}O_5$ (M^+ – PTAD) 444.2873, found 444.2869.

The (23*S*)-iodo lactone **18** was reduced similarly to give **20** as a white solid: mp 183–184.5 °C (colorless needles, CH_2Cl_2); MS

m/z 444 (M^+ - PTAD, 13), 426 (8), 408 (17), 251 (19), 197 (30), 177 (58), 119 (100); ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, H-18), 0.89 (3 H, s, H-19), 1.03 (3 H, d, J = 6.4, H-21), 1.47 (3 H, s, H-27), 3.10 (1 H, dd, J = 14, 4.5, H-4), 3.80 (1 H, m, H-1), 4.75 (1 H, m, H-23), 4.86 (1 H, m, H-3), 6.26 and 6.39 (each 1 H, d, J = 8.4, H-6 and -7), 7.3–7.5 (5 H, m, Ar); IR (KBr) 3424, 2924, 1777, 1744, 1686, 1421 cm^{-1}; HRMS m/z calcd for $C_{27}H_{40}O_5$ (M^+ - PTAD) 444.2873, found 444.2876.

Seleno Lactonization of 4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of (25R)-1α,3β,25-Trihydroxy-5,7,22-cholestatrien-26-oic Acid (16b). Pyridine (10 μL) was added to a stirred suspension of the carboxylic acid **16b** (25 mg, 40 μ mol) in CH_2Cl_2 (1 mL), and the mixture was stirred at rt for 30 min. The mixture was cooled to −78 °C, and phenylselenenyl chloride (12 mg, 63 μmol) was added. After 1 h, the reaction was allowed to warm to 15 °C during 5 h. The mixture was diluted with $CHCl_3$, washed with 2% HCl and water, dried, and evaporated. The reaction mixture was analyzed on HPLC (LiChrospher Si 60, 5% $MeOH/CH_2Cl_2$), and the two seleno lactones, the less polar **22** and the more polar **23**, were detected in a ratio of 85:15. The residue was chromatographed on silica gel (7 g) with MeOH/$CHCl_3$ (1:49–1:19) to give the major seleno lactone **22** (25 mg, 80%) and then the minor one **23** (3.5 mg, 11%). **22**: MS m/z 598 (M^+ - PTAD - 2 H, 3), 580 (13), 578 (10), 554 (15), 552 (9), 444 (16), 443 (11), 267 (21), 265 (21), 251 (25), 239 (36), 157 (69), 155 (65), 119 (100), 69 (95), 55 (83); ^1H NMR ($CDCl_3$–CD_3OD (14:1)) δ 0.92 and 0.95 (each 3 H, s, H-18 and -19), 1.05 (3 H, d, J = 5.9, H-21), 1.28 (3 H, s, H-27), 3.02 (1 H, dd, J = 14.4, 5.4, H-4), 3.17 (1 H, d, J = 10.4, H-22), 3.87 (1 H, m, H-1), 4.82 (1 H, m, H-3), 4.99 (1 H, m, H-23), 6.35 and 6.44 (each 1 H, d, J = 8.4, H-6 and -7), 7.2–7.6 (10 H, m, Ar); IR (KBr) 3416, 2958, 1773, 1744, 1682, 1504, 1412, 745 cm^{-1}; HRMS m/z calcd for $C_{33}H_{42}O_5Se$ (M^+ - PTAD - 2 H) 598.2195, found 598.2192. **23**: MS m/z 598 (M^+ - PTAD - 2 H, 5), 580 (28), 578 (16), 554 (15), 552 (9), 444 (13), 443 (13), 267 (28), 265 (40), 239 (48), 157 (80), 155 (83), 119 (72), 69 (100), 55 (99); ^1H NMR ($CDCl_3$) δ 0.75 (3 H, s, H-18), 0.91 (3 H, s, H-19), 1.17 (3 H, d, J = 6.4, H-21), 1.47 (3 H, s, H-27), 3.14 (1 H, dd, J = 14.8, 4.9, H-4), 3.46 (1 H, m, H-22), 3.81 (1 H, m, H-1), 4.59 (1 H, m, H-23), 4.91 (1 H, m, H-3), 6.26 and 6.36 (each 1 H, d, J = 8.4, H-6 and -7), 7.2–7.65 (10 H, m, Ar); IR (KBr) 3410, 2936, 1775, 1744, 1684, 1504, 1460, 1412, 745 cm^{-1}; HRMS m/z calcd for $C_{33}H_{42}O_5Se$ (M^+ - PTAD - 2 H) 598.2195, found 598.2170.

Reductive Removal of the Phenylseleno Group of 4-Phenyl-1,2,4-triazoline-3,5-dione Adducts of (22R,23S,25R)- and (22S,23R,25R)-1α,3β,25-Trihydroxy-22-(phenylseleno)-5,7-cholestadiene 26,23-Lactones (22 and 23). Tributyltin hydride (23 mg, 79 μmol) and AIBN (1 mg, 6 μmol) were added to a solution of the seleno lactone **22** (20 mg, 26 μmol) in dry toluene (700 μL), and the mixture was refluxed for 10 min. The solvent was evaporated, and the residue was chromatographed on silica gel (7 g) with EtOH/$CHCl_3$ (1:19) to give 23R lactone **20** (14 mg, 88%). The minor seleno lactone **23** (2.5 mg, 3.2 μmol) was reduced similarly to give 23S lactone **19**.

(23S,25R)-1α,3β,25-Trihydroxy-5,7-cholestadiene 26,23-Lactone (21). K_2CO_3 (380 mg, 2.8 mmol) was added to a solution of the adduct **19** (186 mg, 0.3 mmol) in DMSO (10 mL), and the mixture was heated at 140 °C under Ar for 1 h. After being cooled, the mixture was diluted with ethyl acetate and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel (10 g) with 3% MeOH/$CHCl_3$ to give provitamin D **21** (120 mg, 90%): mp 208–212 °C (colorless needles from $CHCl_3$); MS m/z 444 (M^+, 19), 426 (23), 408 (31), 251 (37), 197 (52), 157 (79), 55 (100); ^1H NMR ($CDCl_3$) δ 0.64 (3 H, s, H-18), 0.95 (1 H, s, H-19), 1.05 (1 H, d, J = 6.5, H-21), 1.49 (3 H, s, H-27), 3.78 (1 H, m, H-1), 4.08 (1 H, m, H-3), 4.43 (1 H, m, H-23), 5.39 and 5.74 (each 1 H, m, H-6 and -7); IR (KBr) 3420, 2940, 1769, 1460, 1379, 1212, 1052, 756 cm^{-1}; UV (95% EtOH) λ_{max} 294, 282, 272 nm, λ_{min} 290, 277, 230 nm; HRMS m/z calcd for $C_{27}H_{40}O_5$ (M^+) 444.2873, found 444.2868.

(23S,25R)-1α,25-Dihydroxyvitamin D_3 26,23-Lactone (1a). A solution of the provitamin D **21** (80 mg, 0.18 mmol) in benzene–EtOH (220:10, 230 mL) was flushed with Ar for 10 min and then irradiated at 0 °C under Ar with a 400-W high-pressure mercury lamp (Shigemi Standard, Tokyo), which was kept turned on for 5 min before the irradiation to stabilize the spectral energy of the light source, through a Vycor filter until most of the provitamin D was consumed (previtamin D, 49% HPLC yield). The solvent was evaporated, and the residue was chromatographed on Sephadex LH-20 (20 g) with $CHCl_3$/hexane/MeOH (75:23:2.5) to give the previtamin D (35 mg). The previtamin D was dissolved in 95% ethanol (40 mL), refluxed for 45 min, then stored in the dark at 5 °C under Ar for 10 days. The solvent was evaporated and the residue was chromatographed on Sephadex LH-20 (10 g) with the same solvent system as above to give **1a** (31 mg, 39%) as a colorless glass. By HPLC analysis (YMC-Pack AM-302 S-5 120A ODS, 4.6 × 150 mm, 20% H_2O/MeOH) of **1a**, the only contaminant detected was the corresponding previtamin D (<3%): MS m/z 444 (M^+, 6), 426 (13), 408 (14), 269 (7), 251 (16), 134 (100); ^1H NMR ($CDCl_3$) δ 0.55 (3 H, s, H-18), 1.03 (3 H, d, J = 5.9, H-21), 1.48 (3 H, s, H-27), 4.22 (1 H, m, H-3), 4.44 (2 H, m, H-1 and -23), 5.00 and 5.33 (each 1 H, m, H-19), 6.02 and 6.38 (each 1 H, d, J = 11, H-7 and -6, respectively); ^1H NMR (CD_3OD) δ 0.59 (3 H, s, H-18), 1.05 (3 H, d, J = 6.4, H-21), 1.44 (3 H, s, H-27), 4.14 (1 H, m, H-3), 4.36 (1 H, m, H-1), 4.49 (1 H, m, H-23), 4.91 and 5.29 (each 1 H, m, H-19), 6.09 and 6.33 (each 1 H, d, J = 11, H-7 and -6, respectively); IR (KBr) 3416, 2940, 1771, 1212, 1054 cm^{-1}; UV (95% EtOH) λ_{max} 264 nm, λ_{min} 228 nm; HRMS m/z calcd for $C_{27}H_{40}O_5$ (M^+) 444.2873, found 444.2871; $[\alpha]^{25}_D$ +21.3° (EtOH, c 0.47) (lit.[7a] $[\alpha]_D$ +24.66° EtOH).

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Supplementary Material Available: ^1H NMR spectra of compounds **1a**, **10**, **10′**, and **13–23** (15 pages). Ordering information is given on any current masthead page.