Convenient Synthesis of 1α,25-Dihydroxyvitamin D_3 from Vitamin D_2[1,2]

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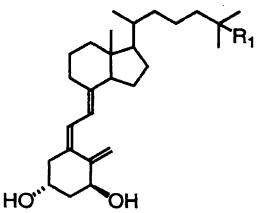
(1*S*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (**7**) was synthesized from vitamin D_2 by five steps. The new compound **7** was ozonized regioselectively and subsequently reduced, leading to (7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclo-9,10-seco-23,24-dinor-7,10(19)-choladien-22-ol (**11**). The alcohol **11** obtained as a key intermediate was tosylated, iodinated, and coupled with 2-methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)butane to give (1*S*,6*R*)-1-hydroxy-6-(1,3-benzodithiol-2-yloxy)-23-phenylsulfonyl-25-tetrahydropyranyloxy-3,5-cyclovitamin D_3 (**16**). By desulfonylation and hydrolysis of the compound **16** 1α,25-dihydoxyvitamin D_3 was obtained selectively.

1α,25-Dihydroxyvitamin D_3 (**1a**) has been widely used as a medicine of bone disease resulting from some metabolic disorder of vitamin D. Therefore **1a** is an important compound, and a more convenient synthetic method has been desired (Chart 1). Since a total synthesis of **1a** was reported by Semmler et al.,[3] many reports[4—10] about improved synthetic methods of **1a** have been published; such synthetic studies have continued. On the other hand, Abe et al.[11] reported that mouse myeloid leukemia cells could be induced to differentiate into macrophages by **1a**. Since then a number of vitamin D derivatives have been synthesized,[12] for example aiming at the development of anticancer drugs.[13] So it is significant to find a practical synthesis of **1a**, which will also be useful for synthesizing other vitamin D derivatives.

In the various synthetic methods of **1a**, it is attractive to employ vitamin D_2 as a starting material. Andrews et al.[14] prepared **1a** via regioselective ozonolysis of vitamin D_2-sulfur dioxide adducts[15] (Scheme 1). In this method, since 5,6-*trans* vitamin D derivatives were obtained by thermal desulfonylation of the adducts, it was indispensable that the derivatives must be photoisomerized to convert to 5,6-*cis* vitamin D derivatives. Such information prompted us to study other methods via vitamin D_2.

In the previous work,[2] we reported a practical method for synthesis of 1α-hydroxyvitamin D_3 (**1b**) via 3,5-cyclovitamin D_3 derivatives bearing a 1,3-benzodithiol-2-yl (BDT) group from vitamin D_3. By the application of the method, a new cyclovitamin D_2 compound was prepared. We discovered that the compound was subject to regioselective ozonolysis at the side-chain double bond. The key intermediate obtained was combined with a new side-chain moiety and cycloreversed, giving the target compound (**1a**) selectively. In our method, the process is not only short (11 steps), as is the Andrews' method described above, but it is easy to scale up, because **1a** is readily obtained in high purity; in addition, the use of harmful sulfur dioxide and the procedure of photoisomerization are unnecessary.

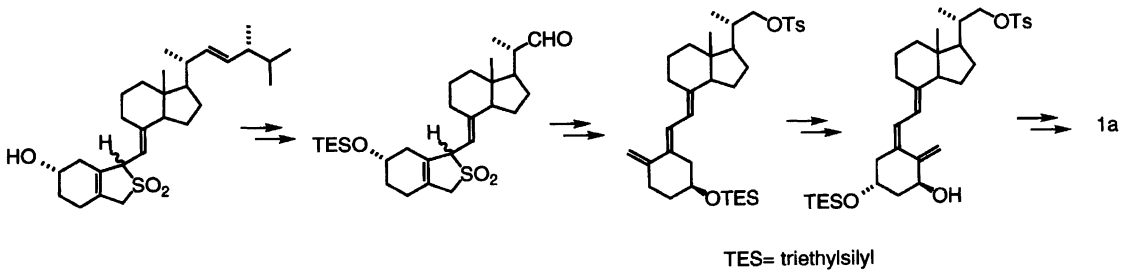


1a : R_1=OH
1b : R_1=H
Chart 1.

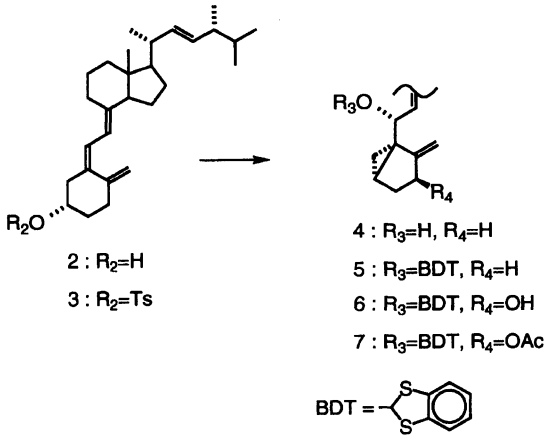
On the other hand, a side-chain fragment was prepared in high yield by a modification of Tachibana's method.[16] In this paper, further details are described.

Vitamin D_2 (**2**) reacted with *p*-toluenesulfonyl chloride in dry pyridine to give vitamin D_2 tosylate (**3**) in 99% yield.[17] The tosylate **3** was converted to (6*R*)-6-hydroxy-3,5-cyclovitamin D_2 (**4**) in 62% yield by hydrolyzing in aqueous acetone buffered with $KHCO_3$.[17] (6*R*)-6-(1,3-Benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (**5**) was prepared from **4** and 1,3-benzodithiolylium tetrafluoroborate (BDTF)[18] in pyridine–CH_2Cl_2 (60% yield). The cyclovitamin **5** was oxidized with SeO_2/*t*-butyl hydroperoxide (TBHP) to give (1*S*,6*R*)-1-hydroxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (**6**)[19] and (6*R*)-1-oxo-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 in 59 and 11% yields, respectively. Compound **6** reacted with acetic anhydride in dry pyridine to give (1*S*,6*R*)-1-acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (**7**) in 97% yield (Scheme 2).

In the synthesis of 1α,25-dihydroxyvitamin D_3 (**1a**) from vitamin D_2 (**2**), regioselective double bond cleavage at its side chain part can be considered a key step. For that purpose, it is necessary to protect the conjugated triene system of vitamin D. There are protection methods leading vitamin D to cyclovitamin D[7,20] and to sulfur dioxide adducts or other Diels–Alder adducts.[14] In the former method, however, we feared that the regioselectivity in the ozonolysis of cyclovitamin D derivatives would be lowered owing to the presence of an *exo*-methylene group, which is liable to be oxidized at the A-ring part. In practice, (1*S*,6*R*)-1-acetoxy-6-methoxy-3,5-cyclovitamin D_2 (**8**)[21] was treated with ozone, followed by addition of dimethyl sulfide to



Scheme 1.



Scheme 2.

give the aldehyde **9a** and the aldehyde **10a** in 24 and 42% yields, respectively. However, when compound **7** underwent ozonolysis in the same manner, the regioselectivity of the reaction was reversed to give the aldehyde **9b** and the aldehyde **10b** in 59 and 15% yields, respectively (Scheme 3).

We presume that the regioselectivity of the reaction is influenced by the differences in stable conformation between **7** and **8**. With (6*R*)-6-methoxy-3,5-cyclovitamin D_3, Sheves and Mazur[20] reported that the methoxyl group is situated at one side of the *exo*-methylene group in its low energy conformation. In view of this, the oxidation of the *exo*-methylene group of **7**, which has the much more bulky BDT group, (compared to the methoxyl group), can be assumed to be depressed.

The aldehyde **9b** was reduced with $NaBH_4$ to give the alcohol **11** in 88% yield. The latter was also obtained in 59% yield by the reductive decomposition of the ozonide of **7** with $NaBH_4$ in situ (Scheme 3). These **9b** and **11** compounds are useful as the intermediates of various vitamin D derivatives.

The alcohol **11** was tosylated in the manner described above to give the tosylate **12** in quantitative yield. The tosylate **12** reacted with NaI in refluxing acetone to afford the iodide **13** in quantitative yield (Scheme 3).

The preparation of 2-methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)butane (**15**)[16,22] as a side-chain fragment is shown in Scheme 4. Lithiation of methyl phenyl sulfone with butyllithium in THF, followed by the addition of 2,2-dimethyloxirane, gave 2-methyl-4-phenylsulfonyl-2-butanol (**14**). The hydroxyl group of **14** was protected as a tetrahydropyranyl (THP) group in the usual manner to afford **15** in 87% yield from methyl phenyl sulfone.

Lithiation of **15** with butyllithium in the presence of hexamethylphosphoric triamide (HMPA) in THF, followed by the addition of the iodide **13**, gave 23-phenylsulfonyl derivative **16** simultaneously deacetylated. The reductive desulfonylation of **16** with sodium amalgam in methanol buffered with Na_2HPO_4 provided cyclovitamin D_3 derivative **17** in 47% yield from **13**. The compound **17** was hydrolyzed with 12-phosphomolybdic acid catalyst in aqueous dioxane and simultaneously subjected to the deprotection of the THP group, giving 1α,25-dihydroxyvitamin D_3 (**1a**) in 30% yield (Scheme 5). In the ^1H NMR (400 MHz) spectra of **1a**, the signals attributed to the 5,6-*trans* isomer were not detected.

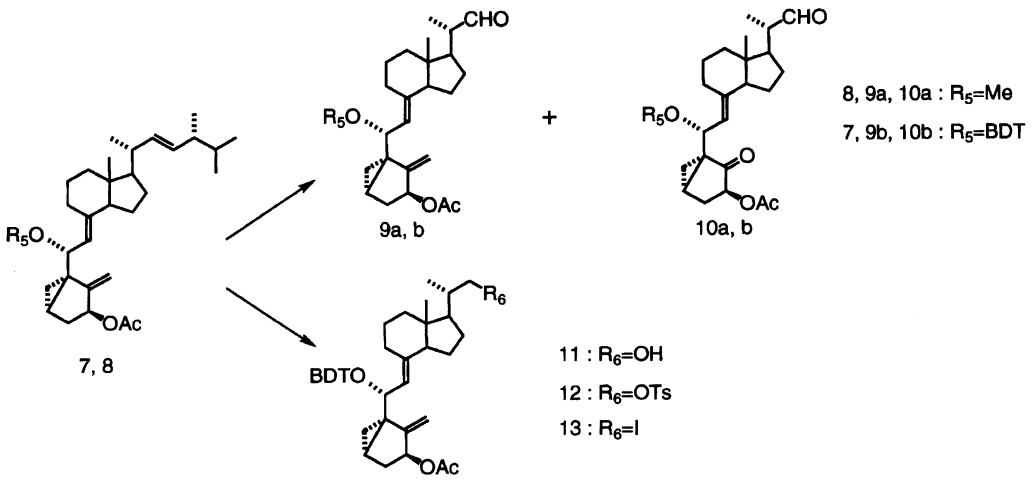
Experimental

^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were measured on a Perkin–Elmer 1720X spectrometer. Mass spectra were obtained at 20 eV on a Hitachi M-80 spectrometer. Fuji Silysia Chemical BW-820H (70—200 mesh) was used for SiO_2 column chromatography. Melting points are uncorrected.

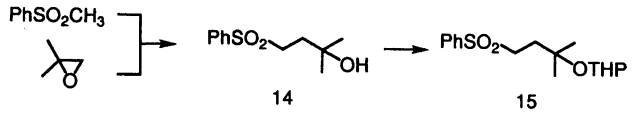
Vitamin D_2 Tosylate (3). Compound **3** was synthesized according to the literature:[17] Mp 89.5—90 °C (decomp); ^1H NMR δ=0.54 (3H, s, 18-H_3), 0.82 and 0.84 (each 3H, d, J=6.5 Hz, 26-H_3 and 27-H_3), 0.91 (3H, d, J=6.8 Hz, 28-H_3), 1.01 (3H, d, J=6.6 Hz, 21-H_3), 2.45 (3H, s, CH_3(tosyl)), 4.70 (1H, m, 3-H), 4.81 (1H, m(sharp), 19-H), 5.02 (1H, m(sharp), 19-H), 5.19 (2H, m, 22-H and 23-H), 5.96 (1H, d, J=11.2 Hz, 7-H), 6.09 (1H, d, J=11.2 Hz, 6-H), 7.33 (2H, m, Ar-H_2), and 7.80 (2H, m, Ar-H_2).

(6*R*)-6-Hydroxy-3,5-cyclovitamin D_2 (4). Compound **4** was synthesized according to the literature:[17] IR (neat) 3392, 1650, 1457, 1372, 1052, 1024, 999, 973, and 869 cm^{-1}; ^1H NMR δ=0.55 (3H, s, 18-H_3), 0.66 (1H, m, 4-H), 0.82 and 0.84 (each 3H, d, J=6.5 Hz, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.8 Hz, 28-H_3), 0.90—0.94 (1H, m, 4-H, overlapped with 28-H_3), 1.02 (3H, d, J=6.6 Hz, 21-H_3), 4.93 (3H, m, 6-H, 7-H, and 19-H), 4.99 (1H, m(sharp), 19-H), and 5.19 (2H, m, 22-H and 23-H).

(6*R*)-6-(1,3-Benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (5). To a solution of **4** (1.25 g, 3.15 mmol) in dry CH_2Cl_2 (28 ml) was added dry pyridine (2.5 ml).



Scheme 3.



Scheme 4.

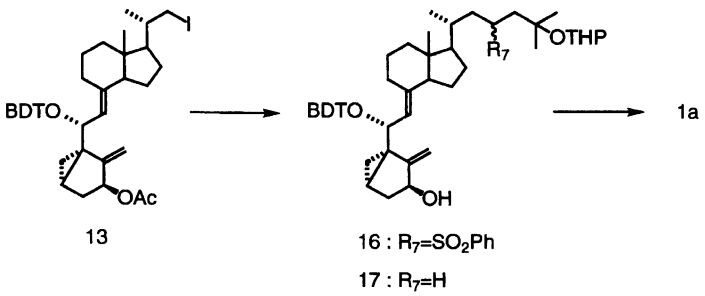
The solution was cooled at −10 °C and BDTF (1.54 g, 6.43 mmol) was added. After stirring for 8 h at −5—0 °C, triethylamine (9 ml) was added. The solution was stirred overnight at room temperature and concentrated in vacuo. The residue was extracted with hexane, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was washed with acetone to give **5** (1.04 g, 60%): Mp 126.5—127 °C (from acetone); IR (KBr) 3060, 3025, 1669, 1646, 1461, 1446, 1371, 1037, 1020, 970, 947, 884, and 740 cm^{-1}; ^1H NMR δ=0.52 (3H, s, 18-H_3), 0.79 (1H, m, 4-H), 0.82 and 0.84 (each 3H, d, J=6.5 Hz, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.8 Hz, 28-H_3), 0.93 (1H, m, 4-H), 1.01 (3H, d, J=6.6 Hz, 21-H_3), 4.59 (1H, d, J=9.5 Hz, 6-H), 4.83 (1H, m(sharp), 19-H), 5.09 (1H, m(sharp), 19-H), 5.15 (1H, d, J=9.5 Hz, 7-H), 5.19 (2H, m, 22-H and 23-H), 6.55 (1H, s, SCHS), 7.06 (2H, m, Ar-H_2), and 7.30 (2H, m, Ar-H_2). Found: m/z 548.3126. Calcd for $C_{35}H_{48}OS_2$: M, 548.3144.

(1*S*,6*R*)-1-Hydroxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (6). A mixture of 70% TBHP–H_2O (0.536 g, 4.16 mmol) and CH_2Cl_2 (6 ml) was dried ($MgSO_4$). The drying agent was filtered off and washed with CH_2Cl_2 (6 ml). To the combined CH_2Cl_2 solutions was added SeO_2 (0.115 g, 1.04 mmol), and after stirring for 15 min, a solution of **5** (1.15 g, 2.10 mmol) in dry CH_2Cl_2 (12 ml) was added to the mixture at 20 °C. The mixture was stirred for ca. 15 min at 20—25 °C and 5% aqueous NaOH (10 ml) was added. After vigorous stirring for 10 min, the CH_2Cl_2 phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (31 g), eluting with hexane–EtOAc (30:1—10:1) to give **6** (0.70 g, 59%): Mp 142—143 °C; IR (KBr) 3540, 1656, 1445, 1370, 1078, 1035, 752, and 718 cm^{-1}; ^1H NMR δ=0.53 (3H, s, 18-H_3), 0.64 (1H, m, 4-H), 0.82 and 0.84 (each 3H, d, J=6.5 Hz, 26-H_3 and 27-H_3), 0.92 (4H, d (J=6.8 Hz) and m, 28-H_3 and 4-H), 1.02 (3H, d, J=6.6 Hz, 21-H_3), 4.16 (1H, m, 1-H), 4.66 (1H, d, J=9.6 Hz, 6-H), 5.05 (1H, d, J=9.6 Hz, 7-H), 5.11 (1H, d, J=2 Hz, 19-H), 5.20 (2H, m, 22-H and 23-H), 5.27 (1H, d, J=2 Hz, 19-H), 6.50 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), and 7.31 (2H, m, Ar-H_2). Found: m/z 564.3106. Calcd for $C_{35}H_{48}O_2S_2$: M, 564.3093.

At this time 0.13 g (11%) of (6*R*)-1-oxo-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 was given as a less polar by-product: ^1H NMR δ=0.48 (3H, s, 18-H_3), 0.53 (1H, m, 4-H), 0.82 and 0.83 (each 3H, d, J=6.6 Hz, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.8 Hz, 28-H_3), 1.01 (3H, d, J=6.6 Hz, 21-H_3), 4.64 (1H, d, J=9.6 Hz, 6-H), 5.04 (1H, d, J=9.6 Hz, 7-H), 5.19 (2H, m, 22-H and 23-H), 5.59 (1H, m(sharp), 19-H), 5.97 (1H, m(sharp), 19-H), 6.48 (1H, s, SCHS), 7.09 (2H, m, Ar-H_2), 7.30 (1H, m, Ar-H), and 7.34 (1H, m, Ar-H). Found: m/z 562.2931. Calcd for $C_{35}H_{46}O_2S_2$: M, 562.2936.

(1*S*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (7). To a solution of **6** (3.78 g, 6.69 mmol) in dry pyridine (38 ml) was added acetic anhydride (3.42 g, 33.5 mmol), and the mixture was stirred overnight at room temperature. Crushed ice was added, and after stirring for 1 h, the mixture was extracted with ether. The ether solution was washed with aqueous $CuSO_4$, H_2O, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (120 g), eluting with hexane–EtOAc (30:1) to give **7** (3.95 g, 97%): ^1H NMR δ=0.53 (3H, s, 18-H_3), 0.71 (1H, m, 4-H), 0.82 and 0.84 (each 3H, d, J=6.5 Hz, 26-H_3 and 27-H_3), 0.92 (3H, d, J=6.8 Hz, 28-H_3), 0.97 (1H, m, 4-H), 1.02 (3H, d, J=6.6 Hz, 21-H_3), 2.07 (3H, s, $OCOCH_3$), 4.65 (1H, d, J=9.8 Hz, 6-H), 4.93 (1H, d, J=2 Hz, 19-H), 5.08 (1H, d, J=9.8 Hz, 7-H), 5.20 (2H, m, 22-H and 23-H), 5.28 (1H, d, J=2 Hz, 19-H), 6.51 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), and 7.31 (2H, m, Ar-H_2). Found: m/z 606.3195. Calcd for $C_{37}H_{50}O_3S_2$: M, 606.3197.

Ozonolysis of (1*S*,6*R*)-1-Acetoxy-6-methoxy-3,5-cyclovitamin D_2 (8). Compound **8** was prepared according to the procedure of Ref. 21.[23] Ozone was bubbled into a mixture of **8** (0.28 g, 0.60 mmol), dry pyridine (0.1 ml), and dry CH_2Cl_2 (32 ml) at −70 °C. The reaction was monitored by TLC (hexane–EtOAc, 5:1). After purging the system with N_2, dimethyl sulfide (0.5 ml) was added. The solution was warmed to room temperature, washed with aqueous $CuSO_4$ and brine, dried ($MgSO_4$), and concentrated



Scheme 5.

in vacuo. The residue was chromatographed on SiO_2 (27 g), eluting with hexane–EtOAc (7 : 1—5 : 1) to give 57 mg (24%) of (7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-acetoxy-6-methoxy-3,5-cyclo-9,10-seco-23,24-dinor-7,10(19)-choladien-22-al (**9a**) as the less polar component and 100 mg (42%) of (7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-acetoxy-6-methoxy-3,5-cyclo-10-oxo-9,10-seco-19,23,24-trinorchol-7-en-22-al (**10a**) as the more polar component.

Aldehyde **9a**: ^{1}H NMR δ=0.59 (3H, s, 18-H_3), 0.70 (1H, m, 4-H), 0.97 (1H, m, 4-H), 1.14 (3H, d, J=6.9 Hz, 21-H_3), 2.09 (3H, s, $OCOCH_3$), 3.26 (3H, s, OCH_3), 4.16 (1H, d, J=9.2 Hz, 6-H), 4.98 (1H, d, J=1.6 Hz, 19-H), 5.03 (1H, d, J=9.2 Hz, 7-H), 5.22 (1H, m, 1-H), 5.24 (1H, d, J=1.6 Hz, 19-H, overlapped with 1-H), and 9.60 (1H, d, J=3.2 Hz, CHO). Found: m/z 400.2615. Calcd for $C_{25}H_{36}O_4$: M, 400.2611.

Aldehyde **10a**: ^{1}H NMR δ=0.57 (3H, s, 18-H_3), 1.14 (3H, d, J=6.9 Hz, 21-H_3), 1.16 (1H, m, 4-H, overlapped with 21-H_3), 2.13 (3H, s, $OCOCH_3$), 3.19 (3H, s, OCH_3), 4.63 and 4.67 (2H, ABq, J=9.5 Hz, 6-H and 7-H), 5.18 (1H, m, 1-H), and 9.59 (1H, d, J=3.2 Hz, CHO). Found: m/z 402.2422. Calcd for $C_{24}H_{34}O_5$: M, 402.2404.

Ozonolysis of (1*S*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclovitamin D_2 (7). Compound **7** (0.24 g, 0.40 mmol) was treated with ozone as described above to give 126 mg (59%) of (7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclo-9,10-seco-23,24-dinor-7,10(19)-choladien-22-al (**9b**) and 31 mg (15%) of (7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclo-10-oxo-9,10-seco-19,23,24-trinorchol-7-en-22-al (**10b**).

Aldehyde **9b**: ^{1}H NMR δ=0.56 (3H, s, 18-H_3), 0.72 (1H, m, 4-H), 0.97 (1H, m, 4-H), 1.14 (3H, d, J=6.9 Hz, 21-H_3), 2.07 (3H, s, $OCOCH_3$), 4.64 (1H, d, J=9.5 Hz, 6-H), 4.94 (1H, d, J=2 Hz, 19-H), 5.13 (1H, d, J=9.5 Hz, 7-H), 5.17 (1H, m, 1-H), 5.27 (1H, d, J=2 Hz, 19-H), 6.52 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), 7.31 (2H, m, Ar-H_2), and 9.59 (1H, d, J=3.1 Hz, CHO). Found: m/z 538.2203. Calcd for $C_{31}H_{38}O_4S_2$: M, 538.2208.

Aldehyde **10b**: ^{1}H NMR δ=0.56 (3H, s, 18-H_3), 1.13 (3H, d, J=6.9 Hz, 21-H_3), 1.17 (1H, m, 4-H), 2.11 (3H, s, $OCOCH_3$), 4.78 and 5.09 (2H, ABq, J=9.6 Hz, 6-H and 7-H), 5.14 (1H, m, 1-H), 6.42 (1H, s, SCHS), 7.09 (2H, m, Ar-H_2), 7.30 (2H, m, Ar-H_2), and 9.59 (1H, d, J=3.2 Hz, CHO). Found: C, 66.44; H, 6.84; S, 11.38%. Calcd for $C_{30}H_{36}O_5S_2$: C, 66.64; H, 6.71; S, 11.86%.

(7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclo-9,10-seco-23,24-dinor-7,10(19)-choladien-22-ol (11). Method A: To a solution of **9b** (100 mg, 0.19 mmol) in CH_2Cl_2–EtOH (1 : 1, 5 ml) was added $NaBH_4$ (21 mg, 0.56 mmol). The mixture was stirred for 1 h at room temperature and concentrated in vacuo. Ether and cold 1 mol dm^{-3} HCl was successively added to the residue, and the mixture was stirred for 20 min. The ether solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (9.5 g), eluting hexane–EtOAc (7 : 3) to give **11** (88 mg, 88%): Mp 159—160 °C; IR (KBr) 3535, 3054, 3027, 1719, 1665, 1445, 1370, 1256, 1045, 1026, 997, 968, and 759 cm^{-1}; ^{1}H NMR δ=0.54 (3H, s, 18-H_3), 0.71 (1H, m, 4-H), 0.97 (1H, m, 4-H), 1.06 (3H, d, J=6.6 Hz, 21-H_3), 2.07 (3H, s, $OCOCH_3$), 3.40 and 3.65 (2H, each m, 22-H_2), 4.66 (1H, d, J=9.6 Hz, 6-H), 4.94 (1H, d, J=2 Hz, 19-H), 5.09 (1H, d, J=9.6 Hz, 7-H), 5.17 (1H, m, 1-H), 5.27 (1H, d, J=2 Hz, 19-H), 6.51 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), and 7.31 (2H, m, Ar-H_2). Found: C, 68.64; H, 7.64; S, 12.08%. Calcd for $C_{31}H_{40}O_4S_2$: C, 68.85; H, 7.46; S, 11.86%.

Method B: Compound **7** (1.00 g, 1.65 mmol) in 1% pyridine–CH_2Cl_2 (30 ml) was treated with ozone at −70 °C, followed by bubbling of N_2 and addition of $NaBH_4$ (200 mg, 5.29 mmol) in EtOH (7.5 ml). The solution was warmed to room temperature and poured into cold 1 mol dm^{-3} HCl. After stirring for 30 min, the CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (50 g), eluting with hexane–EtOAc (7 : 2) to give **11** (0.53 g, 59%). The spectral data were consistent with those obtained by method A.

(7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-3,5-cyclo-9,10-seco-23,24-dinor-7,10(19)-choladien-22-yl Tosylate (12). To a solution of **11** (0.26 g, 0.48 mmol) in dry pyridine (5 ml) was added *p*-TsCl (0.45 g, 2.4 mmol) at 5 °C, and the mixture was stirred overnight at 0—5 °C. Crushed ice was added, and after stirring for 1 h, the mixture was extracted with ether. The ether extract was washed with aqueous $CuSO_4$ and brine, bried ($MgSO_4$), and concentrated in vacuo to give **12** (0.33 g, quant): ^{1}H NMR δ=0.48 (3H, s, 18-H_3), 0.70 (1H, m, 4-H), 0.95 (1H, m, 4-H), 1.00 (3H, d, J=6.6 Hz, 21-H_3), 2.06 (3H, s, $OCOCH_3$), 2.45 (3H, s, CH_3 (tosyl)), 3.81 and 3.98 (2H, each m, 22-H_2), 4.63 (1H, d, J=9.5 Hz, 6-H), 4.93 (1H, d, J=2 Hz, 19-H), 5.08 (1H, d, J=9.5 Hz, 7-H), 5.16 (1H, m, 1-H), 5.25 (1H, d, J=2 Hz, 19-H), 6.50 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), 7.30 (2H, m, Ar-H_2), 7.35 (2H, m, Ar-H_2(tosyl)), and 7.79 (2H, m, Ar-H_2(tosyl)). Found: C, 65.61; H, 6.71; S, 13.67%. Calcd for $C_{38}H_{46}O_6S_3$: C, 65.68; H, 6.67; S, 13.84%.

(7*E*)-(1*S*,3*S*,5*R*,6*R*)-1-Acetoxy-6-(1,3-benzodithiol-2-yloxy)-22-iodo-3,5-cyclo-9,10-seco-23,24-dinor-

7,10(19)-choladiene (13). A solution of **12** (0.30 g, 0.43 mmol) and NaI (0.32 g, 2.1 mmol) in dry acetone (9 ml) was refluxed with stirring for 5 h. After being cooled, the solution was concentrated in vacuo and the residue was extracted with ether. The ether extract was washed with aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give **13** (0.28 g, quant): ^{1}H NMR δ=0.56 (3H, s, 18-H_3), 0.71 (1H, m, 4-H), 0.97 (1H, m, 4-H), 1.04 (3H, d, J=6.3 Hz, 21-H_3), 2.07 (3H, s, $OCOCH_3$), 3.18 and 3.33 (2H, each m, 22-H_2), 4.64 (1H, d, J=9.5 Hz, 6-H), 4.94 (1H, d, J=2 Hz, 19-H), 5.10 (1H, d, J=9.5 Hz, 7-H), 5.17 (1H, m, 1-H), 5.27 (1H, d, J=2 Hz, 19-H), 6.51 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), and 7.31 (2H, m, Ar-H_2). Found: m/z 650.1368. Calcd for $C_{31}H_{39}O_3IS_2$: M, 650.1383.

2-Methyl-4-phenylsulfonyl-2-(tetrahydropyranyloxy)butane (15). To a solution of methyl phenyl sulfone (1.00 g, 6.40 mmol) in dry THF (20 ml) was added 1.6 mol dm^{-3} butyllithium–hexane (6.0 ml, 9.6 mmol) at −25—−20 °C under N_2. After stirring for 20 min, 2,2-dimethyloxirane (1.16 g, 16.1 mmol) was added at −20 °C, and the mixture was stirred for 2 h at 2 °C and quenched by addition of a sat. NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was crude **14**, which was used without further purification. An analytical sample was purified by SiO_2 column chromatography ($CHCl_3$–EtOAc, 10:1), and the spectral data were identical with those reported.[22] According to the literature[16] the crude **14** (1.51 g) was converted to **15** (1.74 g) in 87% yield from methyl phenyl sulfone: Mp 85—86 °C (lit,[22] mp 84—85 °C).

(1*S*,6*R*)-1-Hydroxy-6-(1,3-benzodithiol-2-yloxy)-23-phenylsulfonyl-25-tetrahydropyranyloxy-3,5-cyclovitamin D_3 (16). 1.6 mol dm^{-3} Butyllithium–hexane (3.4 ml, 5.4 mmol) was added to a mixture of **15** (1.73 g, 5.54 mmol), dry HMPA (0.4 ml), and dry THF (8.6 ml) at −50 °C under N_2. After stirring for 20 min at −25—−20 °C, a solution of **13** (0.74 g, 1.14 mmol) in dry THF (3.6 ml) was added, while the temperature was held constant, and the mixture was stirred for 2 h at −20 °C and quenched by addition of a sat. NH_4Cl solution. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (87 g), eluting with hexane–EtOAc (5:2) to give crude **16** (0.78 g) as a foam, which was used without further purification. The ^{1}H NMR spectra indicated that the foam was contaminated with small amounts of impurities: ^{1}H NMR δ=0.46, 0.47, 0.48, and 0.50 (12H, each s, (18−H_3)×4), 4.16 (4H, m, (1−H)×4), 4.68 (8H, m, (6-H, and CH(THP))×4), 5.08 (8H, m, (7-H and 19-H)×4), 5.26 (4H, m(sharp), (19−H)×4), 6.48 (4H, s, (SCHS)×4), 7.07 (8H, m, (Ar−H_2)×4), 7.31 (8H, m, (Ar−H_2)×4), 7.55 (8H, m, (Ar-H_2(SO_2Ph))×4), 7.62 (4H, m, (Ar-H(SO_2Ph))×4), and 7.89 (8H, m, (Ar-H_2(SO_2Ph))×4).

(1*S*,6*R*)-1-Hydroxy-6-(1,3-benzodithiol-2-yloxy)-25-tetrahydropyranyloxy-3,5-cyclovitamin D_3 (17). To a solution of crude **16** (0.78 g) in THF–MeOH (0.8 ml, 27 ml respectively) was successively added Na_2HPO_4 (1.40 g, 9.86 mmol) and 5% Na–Hg (4.52 g, 9.83 mmol), and the mixture was stirred for 3 h at room temperature. The supernatant was concentrated in vacuo and extracted with ether. The ether solution was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (28 g), eluting with hexane–EtOAc (5:1) to afford **17** (0.35 g, 47% from **13**): ^{1}H NMR δ=0.54 (3H, s, 18-H_3), 0.64 (1H, m, 4-H), 0.92 (3H, d, J=6.3 Hz, 21-H_3), 0.90—0.95 (1H, m, 4-H, overlapped with 21-H_3), 1.19 and 1.21 (6H, each s, 26-H_3 and 27-H_3), 3.44 and 3.95 (2H, each m, CH_2(THP)), 4.16 (1H, m, 1-H), 4.67 (1H, d, J=9.6 Hz, 6-H), 4.72 (1H, m, CH(THP)), 5.06 (1H, d, J=9.6 Hz, 7-H), 5.11 (1H, d, J=2 Hz, 19-H), 5.27 (1H, d, J=2 Hz, 19-H), 6.50 (1H, s, SCHS), 7.08 (2H, m, Ar-H_2), and 7.31 (2H, m, Ar-H_2). Found: C, 71.75; H, 8.91; S, 9.75%. Calcd for $C_{39}H_{56}O_4S_2$: C, 71.74; H, 8.64; S, 9.82%.

1α,25-Dihydroxyvitamin D_3 (1a). To a solution of **17** (0.55 g, 0.84 mmol) in 5% H_2O–dioxane (16.5 ml) was added phosphomolybdic acid (53.6 mg, 0.028 mmol as a $H_3PMo_{12}O_{40}\cdot 5H_2O$), and the mixture was stirred for 3 h at 30 °C. After being cooled to 15 °C, the mixture was poured into a sat. $NaHCO_3$ solution and extracted with EtOAc. The EtOAc solution was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2, eluting $CHCl_3$–MeOH (30:1) to give **1a** (104 mg, 30%). The ^{1}H NMR spectra were in accord with those reported:[24] ^{1}H NMR δ=0.55 (3H, s), 0.94 (3H, d, J=6.4 Hz), 1.21 (6H, s), 2.31 (1H, dd, J=13.4 and 6.5 Hz), 2.60 (1H, dd, J=13.4 and 3.2 Hz), 2.82 (1H, dd, J=12.0 and 3.7 Hz), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m(sharp)), 5.33 (1H, m(sharp)), 6.02 (1H, d, J=11.2 Hz), and 6.38 (1H, d, J=11.2 Hz); mp 115—117 °C (from HCO_2Me) (lit,[25] mp 117—118 °C (from HCO_2Me)); $[\alpha]_D^{20}$ +45.0° (c 0.5, EtOH) (lit,[8] $[\alpha]_D^{25}$ +47.9° (c 0.5, EtOH)).

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19) Compound **6** (163 mg) was hydrolyzed similarly to compound **17** and purified by preparative layer chromatography ($CHCl_3$–MeOH, 15 : 1), giving 1α-hydroxyvitamin D_2 (53 mg, 45%). The ^1H NMR spectra were in accord with that reported:[7] ^1H NMR δ=0.56 (3H, s), 0.82 and 0.84 (each 3H, d, J=6.5 Hz), 0.92 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.6 Hz), 4.23 (1H, m), 4.43 (1H, m), 5.00 (1H, m (sharp)), 5.20 (2H, m), 5.32 (1H, m (sharp)), 6.01 (1H, d, J=11.3 Hz), and 6.38 (1H, d, J=11.3 Hz); mp 141.5—142.5 °C (from acetone) (mp 141—143 °C, see: D. R. Andrews, D. H. R. Barton, K. P. Cheng, J.-P. Finet, R. H. Hesse, G. Johnson, and M. M. Pechet, *J. Org. Chem.*, **51**, 1635 (1986)).
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