(10*Z*)- and (10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3: An Improved Synthesis *via* 19-Nor-10-oxo-vitamin D

Masato SHIMIZU,* Akiko OHNO, and Sachiko YAMADA*

Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2–3–10 Surugadai, Kanda, Chiyoda-ku, Tokyo 101–0062, Japan. Received November 15, 2000; accepted January 4, 2001

An efficient synthetic route to (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3 was developed. The key feature of this pathway is the introduction of a 19-fluoromethylene group to a (5*E*)-19-nor-10-oxo-vitamin D derivative. The 10-oxo-compound was obtained *via* a 1,3-dipolar cycloaddition reaction of (5*E*)-1α,25-dihydroxyvitamin D with *in situ* generated nitrile oxide followed by ring cleavage of the formed isoxazoline moiety with molybdenum hexacarbonyl. Conversion of the keto group of (5*E*)-19-nor-10-oxo-vitamin D to the *E* and *Z* fluoromethylene group was achieved through a two-step sequence involving a reaction of lithiofluoromethyl phenyl sulfone followed by the reductive desulfonylation of the α-fluoro-β-hydroxy sulfone. The dye-sensitized photoisomerization of the (5*E*)-19-fluorovitamin D afforded the desired (5*Z*)-19-fluorovitamin D derivatives, (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3.

Key words fluorovitamin D; 19-nor-10-oxo-vitamin D; synthesis; fluorination; photoisomerization

As a physiologically active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2D_3$; **1**] regulates calcium and phosphate homeostasis and is also involved in controlling cellular growth, differentiation and apoptosis.[1] The vitamin D receptor (VDR) is a member of the nuclear receptor superfamily that regulates gene expression in response to binding of their specific ligands. Ligand binding stabilizes the transcriptionally active conformation of the ligand binding domain of the receptors,[2] enabling the recruitment of coactivators and results in either gene transactivation or repression depending on the target gene.

It is critical for better understanding the molecular mechanism of gene expression by **1** to clarify the 3-dimensional structure of **1** bound to VDR. 1α,25-$(OH)_2D_3$ **1** is a highly flexible molecule and can adopt a number of conformations around the A-ring, seco-B-ring, and side chain. In a series of systematic studies on conformation-function relationship of vitamin D, we have proposed a concept of the active side chain space region of vitamin D using systematic conformational analysis and conformationally-restricted analogs as tools.[3—6] Our research interests have also been directed to the A-ring and the conjugated triene part of **1**. The A-ring conformation of vitamin D is thought to be essential for the recognition of the active site of the VDR ligand binding cavity. In solution, vitamin D exists as an approximate equimolar mixture of rapidly equilibrating A-ring chair conformers, designated as α- and β-forms, according to ^{1}H-NMR analysis (Chart 1).[7] Worldwide controversy concerning which conformation is responsible for VDR binding has continued for a long time. The crystal structures of ligand-binding domains (LBD) of numerous nuclear receptors including a retinoic acid receptor,[2,8] thyroid hormone receptor[9] and estrogen receptor[10] have recently been solved. However, the crystal structure of the wild type VDR–LBD has not been solved. Recently, we proposed a three-dimensional model of a liganded VDR-LBD constructed by the homology modeling technique in conjunction with mutation studies to substantiate the model.[11] The crystal structure of a deletion mutant (Δ 165—215) of VDR–LBD complexed with 1α,25-$(OH)_2D_3$ was also reported recently by Moras *et al.*[12] Our model closely resembles the X-ray structure except for some details. In the crystal structure the A-ring of **1** adopts the β-conformation, while in our model we assumed the α-form.

In our studies to investigate dynamics of the conformation of vitamin D in VDR/vitamin D complex, in particular the A-ring and the triene moieties, by ^{19}F-NMR spectroscopy, we have reported syntheses of 19-fluoro-1α,25-dihydroxyvitamin D_3 (**2** and **3**) and 4,4-difluoro-1α,25-dihydroxyvitamin D_3 as probe compounds (Charts 1 and 2).[13—15] In the synthesis of **2** and **3**, an electrophilic fluorination of a vitamin D–SO_2 adduct (**II**) was used as a key step. The difficulties in this synthesis are 1) electrophilic fluorination of the SO_2 adduct (**II**) is not satisfactory and 2) desulfonylation of 19-fluorovitamin D–SO_2 adduct (**III**) was not effective. To solve these problems, we developed a new method in which a 19-fluoromethylene group was introduced to 19-nor-10-oxo-vitamin D **14**. This paper describes the new efficient route to 19-fluorovitamin D **2** and **3**.

Results and Discussions

Our improved synthesis of 19-fluorovitamin D **2** and **3** is based on the phenylsulfonylfluoromethylation of 19-nor-10-oxo-vitamin D derivative **14** followed by the reductive desulfonylation of **16** as a key step (Chart 4). The synthesis of **14** was accomplished starting from (5*E*)-vitamin D derivative **4** (Charts 3 and 4). First the 1α-hydroxyl group was introduced by Hesse's method[16] (SeO_2–NMO, 66% based on recovered **4**) and the hydroxyl group was protected to give **6** (80%). Then the side chain part was constructed. After protecting the conjugated triene part of **6** with SO_2, the side chain was cleaved by ozonolysis (O_3 then $NaBH_4$) to give C(22)-alcohol **7** (85%). Treatment of **7** with I_2 and Ph_3P afforded C(22)-iodide **8** (96%). After extrusion of SO_2 from **8** by heating, the formed (5*E*)-22-iodo-vitamin D derivative was treated with the five carbon synthon **9** to afford 23-phenylsulfone **10** (83%) as a mixture of two epimers. This phenylsulfone **10** was desulfonylated with 10% sodium amalgam (Na–Hg) to yield **11** (65%).

Finally the 10(19)-methylene was exchanged. Conversion of **11** to the 10-oxo compound **14** was accomplished by em-

* To whom correspondence should be addressed. e-mail: shimizu@i-mde.tmd.ac.jp

ploying Reischl's approach with a minor modification.[17,18] Compound **11** was treated with nitrile oxide generated *in situ* from PhNCO and nitroethane, affording the 3′,5′-disubstituted 2′-isoxazoline **12** (94%) as an epimeric mixture at C(10) in approximately a 1 : 1 ratio. Reischl reported that the isoxazolines derived from vitamin D_3 3-acetate and its (5*E*)-isomer were treated with molybdenum hexacarbonyl [$Mo(CO)_6$] in refluxing anhydrous CH_3CN to afford the corresponding 10-oxo-vitamin D derivatives in good yield (70—80%). In our model experiments with the isoxazolines **13a** and **13b**, the reaction did not proceed under the same conditions as described by Reischl. In addition, nothing happened to the isoxazoline ring when a standard procedure of catalytic hydrogenolysis was applied. Steinmeyer's modification[19] that includes water in the medium gave a satisfactory result. Reaction of both isomeric isoxazolines **12a** and **12b** with $Mo(CO)_6$ in refluxing wet CH_3CN gave the desired 10-oxo compound **14** (69 and 56%, respectively) together with the corresponding isomeric β-hydroxyketones **15a** and **15b** (26 and 39%, respectively). The β-hydroxyketone **15** was readily and quantitatively converted to **14** on treatment with LDA (−78 °C, 1 h).

McCarthy *et al*. have reported a convenient two-step synthesis of vinyl fluorides by the Wittig-Horner reaction of ketones and aldehydes with diethyl fluoro(phenylsulfonyl)-

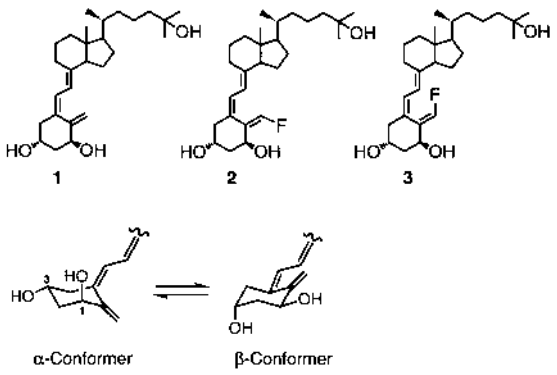


Chart 1

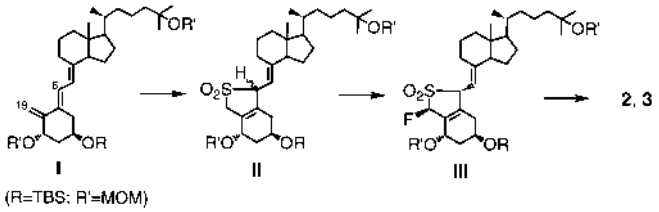


Chart 2

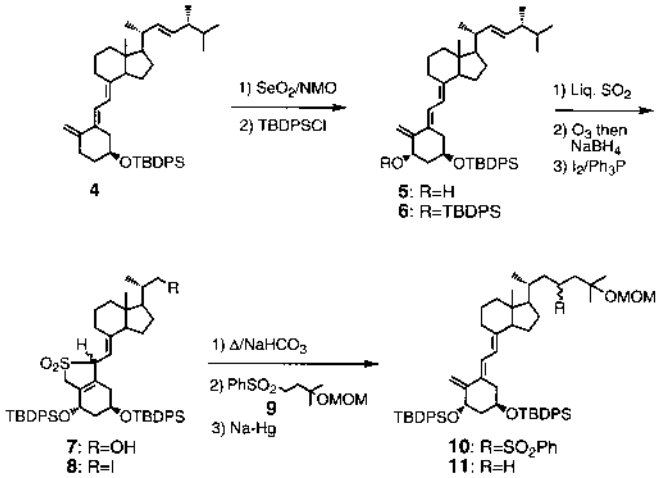
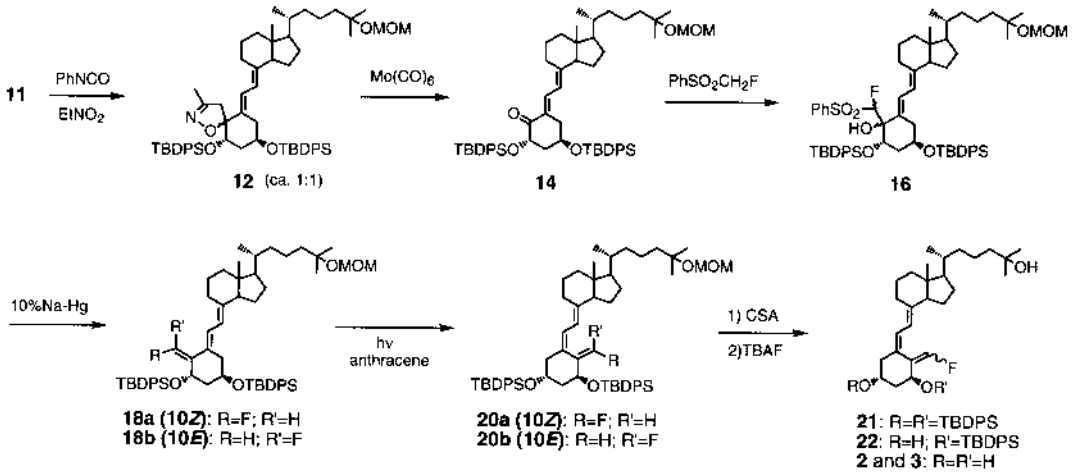


Chart 3



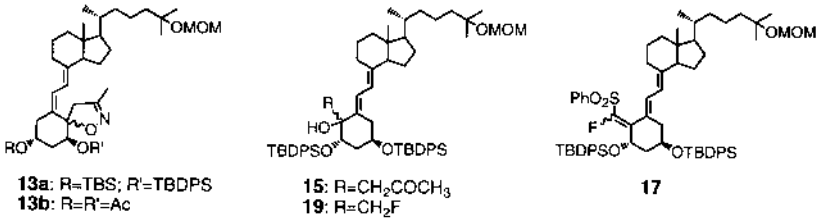


Chart 4

methanephosphonate [prepared from fluoromethylphenylsulfone ($PhSO_2CH_2F$)/diethyl chlorophosphate/2 eq of LDA] followed by the reductive removal of the phenylsulfonyl group of the resulting α-fluoro-α,β-unsaturated sulfones.[20,21] We applied this approach in the synthesis of 19-fluorovitamin D derivatives **2** and **3** from the 10-oxo compound **14**. Under the Wittig–Horner conditions described by McCarthy *et al*., β-hydroxy-α-fluorophenylsulfones **16** were produced in a moderate yield in place of the desired α-fluoro-α,β-unsaturated sulfone **17**. Treatment of **14** with $PhSO_2CH_2F$ alone gave **16** as a mixture of four diastereoisomers in 86% yield, which were difficult to completely separate. In the ^{19}F- NMR spectra of the products, the four diastereomers **16a**, **b**, **c** and **d** were observed as well-separated four set of doublets at -177.0, -180.9, -182.4 and -184.0 ppm in approximately a 37 : 41 : 7 : 15 ratio. Neither the direct dehydration of **16** to **17** nor a mesylation-elimination sequence was successful. A mixture of the β-hydroxy-α-fluorophenylsulfone **16a** and **16d** (approx. 9 : 1) was treated with 10% Na–Hg to afford (10*Z*)-19-fluorovitamin D derivatives **18a** and its (10*E*)-isomer **18b** in about a 1 : 5 ratio in 32% yield along with epimeric fluoro-alcohols **19a** and **19b** (stereochemistry not known) in approximately a 6 : 1 ratio (56%). Under the same conditions, a mixture of **16b**, **16c** and **16d** (approx. 7 : 1 : 2) afforded **18a** and **18b** in approximately a 1 : 2 ratio (24%) as well as epimeric alcohols **19a** and **19b** in approximately a 5 : 2 ratio as major products. Several attempts were made in improving the yield of the desired compound **18**, but satisfactory results have not been obtained yet. The major fluoroalcohol **19a** was produced from the two major diastereomers **16a** and **16b**, indicating that both compounds have the same configuration at C(10).

Two geometrical isomers, **18a** and **18b**, were separated by HPLC [Inertsil Ph 5 μm, 150 mm×4.6 mm i.d.; H_2O : CH_3CN=1 : 9; 1.5 ml/min; ambient temperature], then photoisomerized into the corresponding (5*Z*)-isomers **20** in the presence of anthracene as a sensitizer.[22] First (10*Z*)-isomer **18a** was irradiated at a concentration of about 3 μM of substrate in EtOH–benzene and the progress of reaction was monitored by HPLC. After 1 h of irradiating, the starting material disappeared to give an equilibrium mixture of (10*Z*)-isomer **20a** and (10*E*)-isomer **20b** in about a 4 : 1 ratio. After 4 h, a photostationary state was reached to give an approximately 2 : 3 mixture of **20a** and **20b**. Under the same conditions using (10*E*)-isomer **18b**, similar results (after 1 h and 4 h of irradiating) were also obtained. For practical synthesis at higher substrate concentration, irradiation of isomeric mixture **18** (10*Z* : 10*E*=1 : 5) was stopped after 6 h to yield **20a** and **20b** in approximately a 1 : 1 ratio (95% yield). We have reported that triplet sensitized photoisomerization of (5*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3 (bearing three hydroxyl groups) afforded a mixture of **2** and **3** in about a 6 : 1 ratio at a photostationary state.[13] Interestingly, photoisomerization of isomeric mixture **18** yielded (10*E*)-isomer **20b** as a major product. Detailed studies of the photoisomerization of these compounds will be reported elsewhere.

Geometrical isomers **20** (10*Z* : 10*E*=approx. 1 : 1) were hydrolyzed with camphor sulfonic acid (CSA) to afford the isomeric 25-hydroxy-compounds **21a** and **21b** (48%, approx. 1 : 1) along with the isomeric mixture of 1-silyl ether **22a** and **22b** (53%, approx. 1 : 1). The silyl protecting groups of both **21** and **22** were cleaved by treatment with *n*-Bu_4NF to give the target 19-fluorovitamin D analogs **2** and **3**. Overall yield from **11** through **2** and **3** increased about 6 times with the present method compared with our previous method *via* electrophilic flurorination of vitamin D–SO_2 adducts. In addition, the present method provided a useful way for synthesizing (10*E*)-isomer **3** in a reasonable yield, although it was difficult to obtain **3** by the previous synthetic method.[13]

In conclusion, we have described an efficient pathway for synthesizing the isomeric 19-fluorovitamin D_3 analogs **2** and **3** from a 19-nor-10-oxo-vitamin D derivative. Our current research efforts are aimed at investigating direct interaction of the fluorovitamin D analog **3** with the VDR-ligand binding domain by ^{19}F-NMR. These studies are in progress.

Experimental

The NMR spectra were recorded on a Bruker ARX-400 MHz spectrometer, operating at 400 MHz for ^{1}H and 376 MHz for ^{19}F. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane as an internal standard (δ 0 ppm) for ^{1}H-NMR and trifluorotoluene as an external standard (δ -63 ppm) for ^{19}F-NMR. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained with electronic ionization (EI) on a JEOL JMS-AX505HA spectrometer run at 70 eV for EI; *m*/*z* values are given with relative intensities in parentheses. UV spectra were obtained on a Hitachi U-3200 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel C-200), unless otherwise indicated. All reactions, unless specifically mentioned, were conducted under a atmosphere of argon gas. Yields are not optimized.

Vitamin D_2 3-*tert*-Butyldiphenylsilyl Ether–SO_2 Adducts Vitamin D_2 (20 g, 0.05 mol) was gently refluxed in liquid SO_2 (approx. 50 ml) for 2 h. Excess liquid SO_2 was removed under reduced pressure. To this crude SO_2 adducts in dry DMF (100 ml) was added imidazole (8.63 g, 0.127 mol) and *tert*-butyldiphenylsilyl chloride (17.4 g, 0.06 mol). The mixture was stirred for 2 h at room temperature, poured into ice water, and extracted with 50% AcOEt–hexane. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was subjected to chromatography on silica gel (300 g) with 10% AcOEt–hexane to give (6*S*)- and (6*R*)-SO_2-adducts (33.8 g, 96%) in a 1 : 1 ratio.

(6*S*)-SO_2-Adduct: ^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s, 18-H), 0.82, 0.84 (each 3H, d, *J*=6.4 Hz, 26, 27-H), 0.93 (3H, d, *J*=6.8 Hz, 28-H), 1.03 (3H, d, *J*=6.6 Hz, 21-H), 1.05 (9H, s, Si–*tert*-Bu), 3.61 (2H, m, 19-H), 4.06 (1H, m, 3-H), 4.59 (1H, m, 1-H), 4.44, 4.69 (each 1H, d, *J*=9.4 Hz, 6, 7-H), 5.21 (2H, m, 22, 23-H), 7.3—7.7 (10H, m, arom. H).

(6*R*)-SO_2-Adduct: ^{1}H-NMR ($CDCl_3$) δ: 0.43 (3H, s, 18-H), 0.82, 0.84 (each 3H, d, *J*=6.4 Hz, 26, 27-H), 0.92 (3H, d, *J*=6.8 Hz, 28-H), 1.02 (3H, d, *J*=6.6 Hz, 21-H), 1.07 (9H, s, Si–*tert*-Bu), 3.63, 3.71 (each 1H, d, *J*=15.9 Hz, 19-H), 4.06 (1H, m, 3-H), 4.51, 4.64 (each 1H, d, *J*=10.0 Hz, 6, 7-H), 5.21 (2H, m, 22, 23-H), 7.3—7.7 (10H, m, arom. H).

(6*S*)- and (6*R*)-Adducts: EI-MS *m*/*z* (%): 634 (M^+-SO_2, 73), 577 (46), 509 (4), 378 (18), 317 (43), 253 (19), 199 (100).

(5*E*)-Vitamin D_2 3-*tert*-Butyldiphenylsilyl Ether (4) A mixture of vitamin D_2 3-*tert*-butyldiphenylsilyl ether–SO_2 adducts (33.8 g, 0.048 mol) obtained above, $NaHCO_3$ (90 g, 0.97 mol) and EtOH (700 ml) was refluxed for 1.5 h and cooled to room temperature. The mixture was filtered and the filtrate was concentrated to a small volume. The residue was diluted with water and extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on silica gel (400 g) with 2% AcOEt–hexane to afford **4** (30.0 g, 98%).

4: ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s, 18-H), 0.84, 0.86 (each 3H, d, *J*=6.5 Hz, 26, 27-H), 0.94 (3H, d, *J*=6.8 Hz, 28-H), 1.02 (3H, d, *J*=6.6 Hz, 21-H), 1.06 (9H, s, Si–*tert*-Bu), 3.94 (1H, m, 3-H), 4.62 (1H, s, 19-H), 4.91 (1H, d, *J*=1.8 Hz, 19-H), 5.22 (2H, m, 22, 23-H), 5.71, 6.47 (each 1H, d, *J*=11.5 Hz, 6, 7-H), 7.3—7.7 (10H, m, arom. H). EI-MS *m*/*z* (%): 634 (M^+, 62), 577 (35), 509 (2), 378 (9), 317 (27), 253 (12), 199 (100).

(5*E*)-1α-Hydroxyvitamin D_2 3-*tert*-Butyldiphenylsilyl Ether (5) A mixture of *N*-methylmorpholine oxide (NMO, 5.5 g, 4.43 mmol), anhydrous $MgSO_4$ (3 g) and dry CH_2Cl_2 (30 ml) was stirred for 30 min at room temperature and this NMO solution was filtered directly into a solution of **4** (6.0 g, 9.45 mmol) in dry CH_2Cl_2 (45 ml), and the mixture was refluxed for 5 min. To this solution was added a mixture of selenium oxide (1.05 g, 9.46 mmol)

which was stirred in MeOH (30 ml) for 45 min at room temperature. The whole mixture was refluxed for 2 h and cooled to room temperature, and then poured into ice water. The mixture was extracted with AcOEt and the organic extract was washed with 5% $NaHCO_3$, then brine, and dried ($MgSO_4$). The solvent was removed by reduced pressure and the residue was purified by chromatography on silica gel (200 g). The column was eluted with 4—10% AcOEt–hexane to yield the unreacted starting material (1.7 g, 28%), **5** (2.90 g, 47%) and its isomer with 1β-hydroxyl group (0.6 g, 10%).

5: ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, s, 18-H), 0.84, 0.86 (each 3H, d, J=6.5 Hz, 26, 27-H), 0.95 (3H, d, J=6.8 Hz, 28-H), 1.03 (3H, d, J=6.6 Hz, 21-H), 1.05 (9H, s, Si–*tert*-Bu), 2.47 (1H, dd, J=14.0, 5.9 Hz), 2.85 (1H, m), 4.26 (1H, m, 3-H), 4.59 (1H, m, 1-H), 4.95, 5.07 (each 1H, s, 19-H), 5.22 (2H, m, 22, 23-H), 5.70, 6.53 (each 1H, d, J=11.5 Hz, 6, 7-H), 7.3—7.7 (10H, m, arom. H). EI-MS m/z (%): 650 (M^+, 18), 593 (18), 575 (9), 394 (29), 333 (16), 269 (10), 199 (100). HR-EI-MS m/z: 650.4527 (Calcd for $C_{44}H_{62}O_2Si$: 650.4519).

The isomer of **5** (1β-OH): ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s, 18-H), 0.84, 0.86 (each 3H, d, J=6.4 Hz, 26, 27-H), 0.95 (3H, d, J=6.8 Hz, 28-H), 1.03 (3H, d, J=6.7 Hz, 21-H), 1.06 (9H, s, Si–*tert*-Bu), 2.61 (1H, dd, J=14.2, 4.2 Hz), 2.90 (1H, m), 4.23 (2H, m, 1, 3-H), 4.92 (1H, s, 19-H), 5.05 (1H, d, J=1.9 Hz, 19-H), 5.23 (2H, m, 22, 23-H), 5.73, 6.67 (each 1H, d, J=11.3 Hz, 6, 7-H), 7.3—7.8 (10H, m, arom. H).

(5*E*)-1α-Hydroxyvitamin D_2 1,3-Di-*tert*-butyldiphenylsilyl Ether (6) A mixture of **5** (14.0 g, 0.022 mol), imidazole (3.7 g, 0.054 mol), *tert*-butyldiphenylsilyl chloride (7 ml, 0.027 mol) and dry DMF (40 ml) was stirred for 2 h at room temperature and poured into ice water. The mixture was extracted with 50% AcOEt–hexane and the organic extract was washed with brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was subjected to chromatography on silica gel (200 g). The column was eluted with 2% AcOEt–hexane to give **6** (15.2 g, 80%) and the unreacted starting material (1.0 g, 7%).

6: ^{1}H-NMR ($CDCl_3$) δ: 0.52 (3H, s, 18-H), 0.84, 0.86 (each 3H, d, J=6.4 Hz, 26, 27-H), 0.95 (3H, d, J=6.9 Hz, 28-H), 0.97, 0.98 (each 9H, s, Si–*tert*-Bu), 1.03 (3H, d, J=6.6 Hz, 21-H), 2.27 (1H, dd, J=14.0, 6.6 Hz), 2.84 (1H, m), 4.25 (1H, m, 3-H), 4.64 (1H, m, 1-H), 4.73 (1H, s, 19-H), 4.89 (1H, d, J=1.5 Hz, 19-H), 5.23 (2H, m, 22, 23-H), 5.64, 6.39 (each 1H, d, J=11.4 Hz, 6, 7-H), 7.2—7.65 (20H, m, arom. H). EI-MS m/z (%): 888 (M^+, 4), 831 (2), 632 (11), 575 (8), 376 (5), 372 (2), 251 (4), 199 (100). HR-EI-MS m/z: 888.5675 (Calcd for $C_{60}H_{80}O_2Si_2$: 888.5697).

22-Hydroxy-23,24,25,26,27-pentanor-1α-hydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl Ether–SO_2 Adducts (7) The silyl ether **6** (15.8 g, 0.018 mol) was refluxed with liquid SO_2 (*ca*. 40 ml) for 2 h. Liquid SO_2 was evaporated *in vacuo* to give the SO_2 adducts (17.0 g, quantitative yield, 6*S*: 6*R*=3 : 1). This was used in the next reaction without further purification.

To a stirred, cold (−78 °C) solution of the formed SO_2 adducts (8.1 g, 8.50 mmol) in dry CH_2Cl_2 (65 ml) and dry pyridine (6.5 ml) was passed a steam of ozone. After theoretical amounts of ozone gas were passed in a period of 50 min, the ozone flow was stopped. The mixture was poured into ice water, acidified with 2 N HCl, and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and then evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml) and to this solution was added a solution of $NaBH_4$ (643 mg, 0.017 mol) in EtOH (30 ml) at −78 °C. The whole mixture was stirred for 30 min at 0 °C, diluted with ice water, and extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (100 g) using 2% AcOEt–hexane to give the unreacted starting material (775 mg, 9%) and using 15% AcOEt–hexane to afford **7** (6.4 g, 85%, 6*S*: 6*R*=approx. 3 : 2) as a mixture of two isomers.

(6*S*)-SO_2 Adduct of **6**: ^{1}H-NMR ($CDCl_3$) δ: 0.61 (3H, s, 18-H), 0.82, 0.84 (each 3H, d, J=6.4 Hz, 26, 27-H), 0.93, 1.00 (each 9H, s, Si–*tert*-Bu, overlapped with 21, 28-H), 3.29, 3.84 (each 1H, d, J=16.0 Hz, 19-H), 4.19 (1H, m, 3-H), 4.51, 4.61 (each 1H, d, J=9.7 Hz, 6 or 7-H), 4.56 (1H, m, 1-H), 5.19 (2H, m, 22, 23-H), 7.2—7.7 (20H, m, arom. H).

(6*R*)-SO_2 Adduct of **6**: ^{1}H-NMR ($CDCl_3$) δ: 0.37 (3H, s, 18-H), 0.82, 0.84 (each 3H, d, J=6.4 Hz, 26, 27-H), 0.93, 1.00 (each 9H, s, Si–*tert*-Bu, overlapped with 21, 28-H), 3.29, 3.84 (each 1H, d, J=16.0 Hz, 19-H), 4.19 (1H, m, 3-H), 4.39, 4.67 (1H, d, J=10.2 Hz, 6 or 7-H), 4.56 (1H, m, 1-H), 5.19 (2H, m, 22, 23-H), 7.2—7.7 (20H, m, arom. H).

(6*S*)- and (6*R*)-SO_2 adducts of **6**: EI-MS m/z (%): 888 (M^+-SO_2, 9), 831 (3), 632 (15), 575 (9), 507 (1), 376 (5), 372 (6), 251 (3), 199 (100).

(6*S*)-**7**: ^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s, 18-H), 0.93, 1.00 (each 9H, s, Si–*tert*-Bu), 1.06 (3H, d, J=6.6 Hz, 21-H), 2.49 (1H, br d, J=9.6 Hz), 3.29, 3.85 (each 1H, d, J=15.6 Hz, 19-H), 3.40 (1H, dd, J=10.5, 6.6 Hz, 22-H), 3.65 (1H, dd, J=10.5, 2.9 Hz, 22-H), 4.20 (1H, m, 3-H), 4.51 (1H, d, J=9.6 Hz, 6 or 7-H), 4.58 (1H, m, 1-H), 4.62 (1H, d, J=9.6 Hz, 6 or 7-H), 7.2—7.6 (20H, m, arom. H).

(6*R*)-**7**: ^{1}H-NMR ($CDCl_3$) δ: 0.39 (3H, s, 18-H), 0.92, 1.01 (each 9H, s, Si–*tert*-Bu), 1.05 (3H, d, J=6.6 Hz, 21-H), 2.49 (1H, br d, J=9.6 Hz), 3.29, 3.85 (each 1H, d, J=15.6 Hz, 19-H), 3.40 (1H, dd, J=10.5, 6.6 Hz, 22-H), 3.65 (1H, dd, J=10.5, 2.9 Hz, 22-H), 4.20 (1H, m, 3-H), 4.39 (1H, d, J=10.2 Hz, 6 or 7-H), 4.58 (1H, m, 1-H), 4.68 (1H, d, J=10.2 Hz, 6 or 7-H), 7.2—7.6 (20H, m, arom. H).

(6*S*)- and (6*R*)-**7**: EI-MS m/z (%): 822 (M^+-SO_2, 5), 765 (3), 566 (8), 509 (6), 507 (1), 372 (3), 310 (3), 199 (100). HR-EI-MS m/z: 886.4498 (Calcd for $C_{54}H_{70}O_5SSi_2$: 886.4482).

22-Iodo-23,24,25,26,27-pentanor-1α-hydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl Ether–SO_2 Adducts (8) To a stirred, cold (−20 °C) solution of **7** (5.49 g, 6.19 mmol), Ph_3P (2.03 g, 7.75 mmol), imidazole (1.27 g, 18.6 mmol) in dry THF (100 ml) was added I_2 (1.73 g, 6.82 mmol) and the mixture was stirred for 4 h. After 5% $NaHCO_3$ was added, the mixture was extracted with ether. The organic phase was washed with 2 N $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and then evaporated *in vacuo*. The residue was purified by chromatography on silica gel (100 g) using 20% AcOEt–hexane to afford **8** (5.95 g, 96%, 6*S*: 6*R*=approx. 3 : 2) as a mixture of two isomers.

(6*S*)-**8**: ^{1}H-NMR ($CDCl_3$) δ: 0.64 (3H, s, 18-H), 0.93, 1.00 (each 9H, s, Si–*tert*-Bu, overlapped with 21-H), 2.49 (1H, br d, J=8.4 Hz), 3.21 (1H, dd, J=9.6, 5.1 Hz, 22-H), 3.29, 3.85 (each 1H, d, J=15.9 Hz, 19-H, overlapped with 22-H), 4.20 (1H, m, 3-H), 4.51 (1H, d, J=9.7 Hz, 6 or 7-H), 4.58 (1H, m, 1-H), 4.61 (1H, d, J=9.7 Hz, 6 or 7-H), 7.3—7.7 (20H, m, arom. H).

(6*R*)-**8**: ^{1}H-NMR ($CDCl_3$) δ: 0.40 (3H, s, 18-H), 0.92, 1.02 (each 9H, s, Si–*tert*-Bu, overlapped with 21-H), 2.49 (1H, br d, J=9.6 Hz), 3.16 (1H, dd, J=9.6, 5.8 Hz, 22-H), 3.29, 3.85 (each 1H, d, J=15.9 Hz, 19-H, overlapped with 22-H), 4.20 (1H, m, 3-H), 4.38 (1H, d, J=9.8 Hz, 6 or 7-H), 4.58 (1H, m, 1-H), 4.69 (1H, d, J=9.8 Hz, 6 or 7-H), 7.3—7.7 (20H, m, arom. H).

(6*S*)- and (6*R*)-**8**: EI-MS m/z (%): 932 (M^+-SO_2, 3), 875 (1), 676 (5), 420 (4), 372 (3), 199 (100). HR-EI-MS m/z: 996.3472 (Calcd for $C_{54}H_{69}IO_4SSi$: 996.3500).

(5*E*)-23-Phenylsulfonyl-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (10) A mixture of **8** (12.3 g, 12.3 mmol), $NaHCO_3$ (20.7 g, 0.246 mol) and EtOH (270 ml) was refluxed for 3 h and cooled to room temperature, and then was filtered. The filtrate was concentrated to a small volume, and diluted with water. The mixture was extracted with AcOEt. The AcOEt extract was washed with brine, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by chromatography on silica gel (100 g) using 20% AcOEt–hexane to yield (5*E*)-22-iodo-pentanorvitamin D (10.6 g, 92%).

To a stirred, cold (−20 °C) solution of diisopropylamine (3.2 ml, 23.2 mmol) and *n*-BuLi (1.6 M solution in THF, 23.2 mmol) in dry THF (25 ml) was added a solution of **9** (6.32 g, 23.2 mmol) in dry THF (25 ml) and the mixture was stirred for 20 min. To this solution was added a solution of (5*E*)-22-iodo-pentanorvitamin D (10.8 g, 11.6 mmol) in HMPA (8.07 ml, 46.4 mmol) and dry THF (50 ml) and the whole mixture was stirred for 2 h at −20 °C. The reaction was quenched with sat. NH_4Cl and extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (200 g) using 2—5% AcOEt–hexane to afford the unreacted starting material (1.74 g, 16%) and **10** (10.4 g, 83%, 23*S*: 23*R*=approx. 1 : 1).

10: ^{1}H-NMR ($CDCl_3$) δ: 0.40, 0.47 (1 : 1) (3H, s, 18-H), 0.73, 0.93 (1 : 1) (3H, d, J=6.3 Hz, 21-H), 0.96, 0.97 (9H, s, Si–*tert*-Bu), 0.98 (9H, s, Si–*tert*-Bu), 3.26, 3.30 (1 : 1) (3H, s, OMe), 4.27 (1H, m, 3-H), 4.45—4.70 (4H, m, 1, 22-H, OCH_2O), 4.70, 4.75 (1 : 1) (1H, s, 19-H), 4.87, 4.89 (1 : 1) (1H, d, J=1.6 Hz, 19-H), 5.62, 5.64 (1 : 1) (1H, d, J=11.2 Hz, 6 or 7-H), 6.35, 6.38 (1 : 1) (1H, d, J=11.2 Hz, 6 or 7-H), 7.2—7.9 (20H, m, arom. H). EI-MS m/z (%): 1076 (M^+, 1), 820 (2), 564 (3), 502 (1), 199 (100).

(5*E*)-1α,25-Dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (11) To a stirred, cold (0 °C) solution of **10** (10.4 g, 9.65 mmol) in dry THF (25 ml) and dry MeOH (50 ml) was added 10% Na-Hg (freshly prepared, 22.2 g, 96.7 mmol) and the mixture was filtered through a filter paper. The filtrate was concentrated to a small volume and diluted with a mixture of water and AcOEt. The organic layer was separated and the aqueous phase was extracted with AcOEt. The combined organic extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by chromatography on silica gel (100 g) using 10% AcOEt–hexane to give **11** (5.86 g, 65%) and the unreacted starting material **10** (1.3 g, 13%).

11: ^{1}H-NMR ($CDCl_3$) δ: 0.51 (3H, s, 18-H), 0.94 (3H, d, J=6.7 Hz, 21-H), 0.96, 0.98 (each 9H, s, Si–*tert*-Bu), 1.23 (6H, s, 26, 27-H), 2.27 (1H, dd, J=14.1, 6.1 Hz), 2.36 (1H, m), 2.84 (1H, m), 3,38 (3H, s, OMe), 4.27 (1H,

m, 3-H), 4.65 (1H, m, 1-H), 4.72 (2H, s, OCH_2O), 4.74, 4.89 (each 1H, br s, 19-H), 5.63, 6.39 (each 1H, d, J=11.4 Hz, 6, 7-H), 7.2—7.6 (20H, m, arom. H). EI-MS m/z (%): 936 (M^+, 1), 874 (2), 561 (5), 362 (4), 251 (2), 199 (100). HR-EI-MS m/z: 936.5931 (Calcd for $C_{61}H_{84}O_4Si_2$: 936.5908).

Isoxazoline Derivatives (12a and b) Phenyl isocyanate (3.39 ml, 31.1 mmol) was slowly added to a solution of **11** (6.48 g, 6.91 mmol) in dry toluene (40 ml) and to this solution was added a mixture of nitroethane (1.56 ml, 20.8 mmol) and several drops of triethylamine in dry toluene (10 ml). The mixture was stirred for 16 h at room temperature and was filtered. The filtrate was evaporated *in vacuo* and the residue was subjected to chromatography on silica gel (200 g) using 5% AcOEt–hexane to yield **12a** and **12b** (6.43 g, 94%) in about a 1 : 1 ratio.

The Less Polar Isoxazoline **12a**: ^{1}H-NMR ($CDCl_3$) δ: 0.44 (3H, s, 18-H), 0.84, 1.02 (each 9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=6.3 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 1.93 (3H, s, Me), 2.48 (1H, d, J=16.5 Hz, 19-H), 2.66 (1H, br d, J=14.5 Hz), 2.95 (1H, m), 3.37 (3H, s, OMe), 3.40 (1H, d, J=16.5 Hz, 19-H), 3.91 (1H, m, 3-H), 4.53 (1H, dd, J=11.1, 4.7 Hz, 1-H), 4.71 (2H, s, OCH_2O), 5.65, 6.80 (each 1H, d, J=11.3 Hz, 6, 7-H), 7.2—7.8 (20H, m, arom. H). UV λ_{max} (95% EtOH): 246, 254, 263 nm. EI-MS m/z (%): 993 (M^+, 5), 936 (4), 874 (5), 737 (5), 680 (3), 618 (5), 199 (100). HR-EI-MS m/z: 993.6113 (Calcd for $C_{63}H_{87}NO_5Si_2$: 993.6123).

The More Polar Isoxazoline **12b**: ^{1}H-NMR ($CDCl_3$) δ: 0.49 (3H, s, 18-H), 0.90, 0.97 (each 9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.3 Hz, 21-H), 1.23 (6H, s, 26, 27-H), 1.87 (3H, s, Me), 2.78, 2.92 (each 1H, d, J=17.1 Hz, 19-H), 3.38 (3H, s, OMe), 3.99 (1H, m, 3-H), 4.15 (1H, m, 1-H), 4.72 (2H, s, OCH_2O), 5.64, 6.55 (each 1H, d, J=11.0 Hz, 6, 7-H), 7.2—7.7 (20H, m, arom. H). UV λ_{max} (95% EtOH): 246, 254, 262 nm. EI-MS m/z (%): 993 (M^+, 4), 936 (10), 874 (4), 737 (3), 680 (3), 618 (5), 199 (100). HR-EI-MS m/z: 993.6123 (Calcd for $C_{63}H_{87}NO_5Si_2$: 993.6123).

10-Oxo-19-nor-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (14) and the β-Hydroxyketones (15a and b) A mixture of **12a** (2.73 g, 2.74 mmol), $Mo(CO)_6$ (363 mg, 1.38 mmol, freshly sublimed), CH_3CN (80 ml) and H_2O (8 ml) was refluxed for 17 h and cooled to room temperature. The mixture was filtered through a Celite pad and washed with 50% AcOEt–hexane. The combined filtrate was evaporated to dryness. The residue was separated by chromatography on silica gel (100 g) using 10—20% AcOEt–hexane to give **14** (1.78 g, 69%) and **15a** (661 mg, 26%).

Treatment of the more polar isoxazoline **12b** (3.70 g, 3.73 mmol) with $Mo(CO)_6$ in refluxing wet CH_3CN as described above and the same work-up gave **14** (1.95 g, 56%) and **15b** (1.43 g, 39%).

14: ^{1}H-NMR ($CDCl_3$) δ: 0.51 (3H, s, 18-H), 0.86 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.3 Hz, 21-H), 1.11 (9H, s, Si–*tert*-Bu), 1.22 (6H, s, 26, 27-H), 2.57 (1H, m), 2.97(1H, m), 3.37 (3H, s, OMe), 4.21 (1H, m, 3-H), 4.71 (2H, s, OCH_2O), 4.75 (1H, dd, J=11.2, 6.0 Hz, 1-H), 5.56 (1H, d, J=12.1 Hz, 7-H), 7.2—7.8 (21H, m, arom. H, overlapped with 6-H). EI-MS m/z (%): 938 (M^+, 3), 881 (11), 819 (26), 682 (4), 620 (8), 563 (13), 199 (100). HR-EI-MS m/z: 938.5715 (Calcd for $C_{60}H_{82}O_5Si_2$: 938.5701).

15a: ^{1}H-NMR ($CDCl_3$) δ: 0.43 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.2 Hz, 21-H), 1.03 (9H, s, Si–*tert*-Bu), 1.22 (6H, s, 26, 27-H), 2.06 (3H, s, Me), 2.62 (1H, br d, J=14.5 Hz), 2.73, 2.87 (each 1H, d, J=14.7 Hz, 19-H), 2.83 (1H, m), 3.37 (3H, s, OMe), 3.95 (1H, s, OH), 4.00 (1H, m, 3-H), 4.25 (1H, dd, J=10.3, 4.3 Hz, 1-H), 4.71 (2H, s, OCH_2O), 5.64, 6.60 (each 1H, d, J=11.0 Hz, 6, 7-H), 7.2—7.7 (20H, m, arom. H).

15b: ^{1}H-NMR ($CDCl_3$) δ: 0.50 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.3 Hz, 21-H), 1.00 (9H, s, Si–*tert*-Bu), 1.23 (6H, s, 26, 27-H), 2.04 (3H, s, Me), 2.69 (2H, br s, 19-H), 2.79 (1H, m), 2.89 (1H, m), 2.83 (1H, m), 3.38 (3H, s, OMe), 3.93 (1H, m, 1-H), 4.11 (1H, m, 3-H), 4.72 (2H, s, OCH_2O), 5.64, 6.45 (each 1H, d, J=10.9 Hz, 6, 7-H), 7.2—7.7 (20H, m, arom. H).

Diastereomers (16a, b, c and d) To a cold (−78 °C), stirred solution of LDA (8.15 mmol, prepared from 1.59 M *n*-BuLi in hexane and diisopropylamine) in dry THF (2 ml) was added a solution of fluoromethyl phenyl sulfone (1.14 g, 6.52 mmol) in dry THF (3 ml), and the mixture was further stirred for 1 h. To this solution was added a cold (−78 °C) solution of **14** (3.06 g, 3.26 mmol) in dry THF (10 ml). After being stirred for 2 h at the same temperature, the reaction mixture was quenched with sat. NH_4Cl and extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (150 g) with benzene–2% AcOEt–benzene to give the four diastereoisomers **16**: the less polar fraction contains two isomers **16a** and **16d** in about a 9 : 1 ratio (1.27 g, 35%), while the more polar fraction includes three isomers **16b**, **16c** and **16d** in about a ratio 7 : 1 : 2 (1.80 g, 50%).

16a: ^{1}H-NMR ($CDCl_3$) δ: 0.38 (3H, s, 18-H), 0.78 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.2 Hz, 21-H), 1.06 (9H, s, Si–*tert*-Bu), 1.22 (6H, s, 26, 27-H), 2.32 (1H, m), 2.95 (1H, m), 3.37 (3H, s, OMe), 3.88 (1H, m, 3-H), 4.05 (1H, s, OH), 4.37 (1H, m, 1-H), 4.71 (2H, s, OCH_2O), 5.52 (1H, d, J=11.8 Hz, 6 or 7-H), 5.97 (1H, d, J=44.5 Hz, 19-H), 6.80 (1H, d, J=11.8 Hz, 6 or 7-H), 7.1—7.9 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −170.0 (d, J=44.5 Hz).

16b: ^{1}H-NMR ($CDCl_3$) δ: 0.40 (3H, s, 18-H), 0.84 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.2 Hz, 21-H), 0.96 (9H, s, Si–*tert*-Bu), 1.22 (6H, s, 26, 27-H), 2.72 (1H, m), 2.83 (1H, m), 3.37 (3H, s, OMe), 4.06 (1H, m, 3-H), 4.35 (1H, dd, J=11.0, 4.2 Hz, 1-H), 4.71 (2H, s, OCH_2O), 5.56 (1H, d, J=45.2 Hz, 19-H), 5.72, 6.65 (1H, d, J=11.0 Hz, 6 or 7-H), 7.1—7.9 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −180.9 (d, J=45.2 Hz).

16c: ^{19}F-NMR ($CDCl_3$) δ: −182.4 (d, J=44.3 Hz).

16d: ^{19}F-NMR ($CDCl_3$) δ: −184.0 (d, J=45.6 Hz).

(5*E*,10*Z*)- and (5*E*,10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (18a and b), and (5*E*)-10-Hydroxy-10-fluoromethyl-19-nor-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (19a and b) A mixture of the less polar fraction **16a** and **16d** (2.13 g, 1.91 mmol, approx. 9 : 1), sodiumhydrogenphosphate (2.71 g, 19.1 mmol) in dry THF–MeOH (1 : 2, 15 ml) was stirred for 10 min at 0 °C, and the 10% Na–Hg (4.38 g, 19.1 mmol, freshly prepared) was then added. After being stirred for 3 h at room temperature, the reaction mixture was filtered, and the filtrate was diluted with ice-water, and was extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on silica gel (150 g) using 2% AcOEt–hexane to afford a mixture of **18a** and **18b** (585 mg, 32%, approx. 1 : 5) and using 8% AcOEt–hexane to yield **19a** and **19b** (1.04 g, 56%, approx. 6 : 1) as a mixture of two epimers.

18a: ^{1}H-NMR ($CDCl_3$) δ: 0.52 (3H, s, 18-H), 0.85 (9H, s, Si–*tert*-Bu), 0.95 (3H, d, J=6.1 Hz, 21-H), 1.07 (9H, s, Si–*tert*-Bu), 1.23 (6H, s, 26, 27-H), 2.75 (1H, m), 2.97 (1H, m), 3.38 (3H, s, OMe), 4.45 (1H, m, 3-H), 4.72 (2H, s, OCH_2O), 4.87 (1H, m, 1-H), 5.60, 6.07 (each 1H, d, J=11.2 Hz, 6 or 7-H), 6.20 (1H, d, J=86.1 Hz, 19-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −132.3 (d, J=86.1 Hz). UV λ_{max} (95% EtOH): 266, 270 (sh) nm. EI-MS m/z (%): 954 (M^+, 3), 897 (2), 892 (4), 835 (5), 698 (3), 636 (4), 579 (4), 199 (100).

18b: ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, s, 18-H), 0.91 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.2 Hz, 21-H), 1.02 (9H, s, Si–*tert*-Bu), 1.23 (6H, s, 26, 27-H), 2.68 (1H, dd, J=14.0, 3.8 Hz), 2.76 (1H, m), 3.38 (3H, s, OMe), 4.32 (2H, m, 1, 3-H), 4.72 (2H, s, OCH_2O), 5.71 (1H, d, J=11.4 Hz, 6 or 7-H), 6.01 (1H, d, J=84.9 Hz, 19-H), 6.42 (1H, d, J=11.3 Hz, 6 or 7-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −136.9 (d, J=84.9 Hz). UV λ_{max} (95% EtOH): 270 (sh), 271 nm. EI-MS m/z (%): 954 (M^+, 5), 897 (3), 892 (10), 835 (10), 698 (5), 636 (10), 579 (9), 199 (100). HR-EI-MS m/z: 954.5801 (Calcd for $C_{63}H_{87}NO_5Si_2$: 954.5814).

19a and **b**: ^{1}H-NMR ($CDCl_3$) δ: 0.45, 0.47 (6 : 1) (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=5.7 Hz, 21-H), 1.01 (9H, s, Si–*tert*-Bu), 1.21, 1.22 (6 : 1) (6H, s, 26, 27-H), 2.43 (1H, s, OH), 2.63 (1H, m), 2.87 (1H, m), 3.37, 3.38 (6 : 1) (3H, s, OMe), 4.03 (1H, m, 3-H), 4.34 (1H, m, 1-H), 4.53, 4.71 (each 1H, dd, J=47.8, 9.2 Hz, 19-H), 4.71, 4.72 (6 : 1) (2H, s, OCH_2O), 5.67, 5.71 (1 : 6) (1H, d, J=11.5 Hz, 6 or 7-H), 6.65, 6.68 (1 : 6) 6.42 (1H, d, J=11.5 Hz, 6 or 7-H), 7.2—7.8 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −233.9, −225.9 (6 : 1) (t, J=47.8 Hz).

(10*Z*)- and (10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl-25-methoxymethyl Ether (20a and b) A solution of **18** (140 mg, 0.15 mmol, 10*Z* : 10*E*=1 : 5), anthracene (131 mg, 0.74 mmol) in benzene–EtOH (1 : 9, 250 ml) was purged with Ar, and was irradiated at 0 °C for 6 h using a halogen-lamp (200 W). After evaporation of the solvent, the residue was purified by chromatography on silica gel (10 g) using benzene to afford a mixture of **20a** and **20b** (133.1 mg, 95%) in about a 1 : 1 ratio.

20a: ^{1}H-NMR ($CDCl_3$) δ: 0.40 (3H, s, 18-H), 0.86, 1.04 (each 9H, s, Si–*tert*-Bu, overlapped with 21-H), 1.21 (6H, s, 26, 27-H), 2.56 (1H, m), 2.77 (1H, m), 3.36 (3H, s, OMe), 4.42 (1H, m, 3-H), 4.70 (2H, s, OCH_2O), 4.90 (1H, m, 1-H), 5.91, 6.22 (each 1H, d, J=11.2 Hz, 6 or 7-H), 6.22 (1H, d, J=86.3 Hz, 19-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −129.7 (d, J=86.3 Hz).

20b: ^{1}H-NMR ($CDCl_3$) δ: 0.47 (3H, s, 18-H), 0.92, 0.99 (each 9H, s, Si–*tert*-Bu, overlapped with 21-H), 1.22 (6H, s, 26, 27-H), 2.44 (1H, m), 2.77 (1H, m), 3.37 (3H, s, OMe), 4.33 (2H, m, 1, 3-H), 4.71 (2H, s, OCH_2O), 5.58 (1H, dd, J=11.0, 5.0 Hz, 7-H), 5.98 (1H, d, J=85.0 Hz, 19-H), 6.25 (1H, d, J=11.0 Hz, 6-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −129.6 (broad signal).

20a and **b**: EI-MS *m*/*z* (%): 954 (M^+, 3), 892 (5), 835 (5), 698 (3), 636 (4), 199 (100).

(10*Z*)- and (10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3 1,3-Di-*tert*-butyldiphenylsilyl Ether (21a and b) and (10*Z*)- and (10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3 1-*tert*-Butyldiphenylsilyl Ether (22a and b) A mixture of **20** (127.9 mg, 0.13 mmol, 10*Z*:10*E*=1:1), *d*,*l*-comphor-10-sulfonic acid (77.8 mg, 0.34 mmol) in dry THF–dry MeOH (1:3, 2 ml) was stirred for 3 h at room temperature and quenched with 5% $NaHCO_3$. The mixture was extracted with AcOEt and the AcOEt extract was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was separated by chromatography on silica gel (10 g) using CH_2Cl_2 to afford **21a** and **21b** (58.9 mg, 48%, approx. 1:1) and **22a** and **b** (48 mg, 52%, approx. 1:1).

A mixture of **21** (58.8 mg, 0.065 mmol, 10*Z*:10*E*=1:1), *n*-Bu_4NF (1 M solution in THF, 0.16 mmol) and dry THF (0.5 ml) was heated at 50 °C for 8 h and quenched with 5% $NaHCO_3$. The mixture was extracted with AcOEt and the organic extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatographed on silica gel (20 g) using 50% AcOEt–hexane to give the unreacted **21a** (14.8 mg) and **2** (4.1 mg, 15%), and then using 10% MeOH–AcOEt to give **3** (11.7 mg, 41%).

A mixture of **22** (30.6 mg, 0.046 mmol, 10*Z*:10*E*=1:1), *n*-Bu_4NF (1 M solution in THF, 0.12 mmol) and dry THF (0.5 ml) was heated at 50 °C for 23 h and quenched with 5% $NaHCO_3$. The mixture was extracted with AcOEt and the organic extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatographed on silica gel (20 g) using 50% AcOEt–hexane to give the unreacted **22a** (12.0 mg) and **2** (3.6 mg, 18%), and then using 10% MeOH–AcOEt to give **3** (8.2 mg, 42%).

21a: ^{1}H-NMR ($CDCl_3$) δ: 0.40 (3H, s, 18-H), 0.86, 1.03 (each 9H, s, Si–*tert*-Bu), 1.21 (6H, s, 26, 27-H), 2.55 (1H, m), 2.77 (1H, m), 4.42 (1H, m, 3-H), 4.90 (1H, m, 1-H), 5.91 (1H, d, *J*=11.4 Hz, 7-H), 6.21 (1H, d, *J*=11.4 Hz, 6-H), 6.22 (1H, d, *J*=86.3 Hz, 19-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −129.5 (d, *J*=86.3 Hz).

21b: ^{1}H-NMR ($CDCl_3$) δ: 0.46 (3H, s, 18-H), 0.92, 0.99 (each 9H, s, Si–*tert*-Bu), 1.22 (6H, s, 26, 27-H), 2.44 (1H, m), 2.77 (1H, m), 4.32 (2H, m, 1, 3-H), 5.58 (1H, dd, *J*=11.0, 5.0 Hz, 7-H), 5.98 (1H, d, *J*=84.0 Hz, 19-H), 6.52 (1H, d, *J*=11.0 Hz, 6-H), 7.2—7.7 (20H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −129.6 (broad signal).

21a and **b**: EI-MS *m*/*z* (%): 910 (M^+, 5), 892 (4), 835 (3), 579 (3), 390 (10), 199 (100).

22a: ^{1}H-NMR ($CDCl_3$) δ: 0.46 (3H, s, 18-H), 0.92 (3H, d, *J*=5.4 Hz, 21-H), 1.21 (6H, s, 26, 27-H), 4.30 (1H, m, 3-H), 5.04 (1H, m, 1-H), 6.02 (1H, d, *J*=11.0 Hz, 7-H), 6.33 (1H, d, *J*=86.3 Hz, 19-H), 6.46 (1H, d, *J*=11.0 Hz, 6-H), 7.2—7.7 (10H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −129.5 (d, *J*=86.3 Hz). EI-MS *m*/*z* (%): 672 (M^+, 4), 654 (6), 597 (6), 579 (4), 577 (7), 408 (20), 378 (13), 351 (12), 333(3), 199 (100).

22b: ^{1}H-NMR ($CDCl_3$) δ: 0.49 (3H, s, 18-H), 0.94 (3H, d, *J*=5.9 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 4.30 (2H, m, 1, 3-H), 5.66 (1H, dd, *J*=11.0, 4.7 Hz, 7-H), 6.11 (1H, d, *J*=84.3 Hz, 19-H), 6.49 (1H, d, *J*=11.0 Hz, 6-H), 7.3—7.7 (10H, m, arom. H). ^{19}F-NMR ($CDCl_3$) δ: −128.8 (broad signal). EI-MS *m*/*z* (%): 672 (M^+, 13), 654 (8), 597 (9), 579 (5), 408 (20), 378 (5), 351 (19), 333(2), 199 (100).

^{1}H-NMR, ^{19}F-NMR, MS, and UV spectra of **2** and **3** were in agreement with those of the known specimens prepared earlier in our laboratory.[15)]

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