Synthesis of (10*Z*)- and (10*E*)-19-Fluoro-1α,25-dihydroxyvitamin D_3: Compounds to Probe Vitamin D Conformation in Receptor Complex by ^{19}F-NMR

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To study the interaction of vitamin D with its receptor by ^{19}F-NMR, (5*Z*,10*Z*)- and (5*Z*,10*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3 were synthesized starting from vitamin D_2 *via* electrophilic fluorination of vitamin D–SO_2 adducts as the key step. Regio- and stereoselective electrophilic fluorination at C(19) of vitamin D–SO_2 adducts was achieved under the conditions using $(PhSO_2)_2NF$ and bulky bases. The stereochemistry of the addition and elimination of SO_2 of various vitamin D derivatives was studied in detail. SO_2 causes *Z–E* isomerization of the 5,6-double bond of vitamin D and adds to the resulting (5*E*)-isomer from the sterically less hindered side opposite to the substituent at C(1). Elimination of SO_2 from 19-substituted vitamin D–SO_2 adducts proceeded exclusively in a suprafacial manner with respect to the diene part under either thermal or reductive conditions. Dye-sensitized photochemical isomerization of 19-fluorovitamin D derivatives was studied in detail. The rapid isomerization at the 5,6-double bond was followed by the slow isomerization at the 10,19-double bond to yield the (5*E*,10*Z*)-isomer (by nomenclature of the 1-OH derivatives) as the major product. (10*Z*)- and (10*E*)-19-Fluorovitamin Ds were also interconverted thermally probably *via* the corresponding previtamin D by 1,7-sigmatropic isomerization.

Key words fluorovitamin D; vitamin D–sulfur dioxide adduct; electrophilic fluorination; synthesis; sigmatropic reaction; cheletropic reaction; photochemical isomerization

1α,25-Dihydroxyvitamin D [1,25-$(OH)_2D_3$] **1a** exhibits various activities including classical actions in calcium metabolism and basic functions of regulating the proliferation and differentiation of cells and the immune response by regulating the transcription of vitamin D target genes.[1] The vitamin D receptor (VDR) is a member of the nuclear receptor (NR) superfamily which includes steroid and thyroid hormone receptors, retinoic acid receptors and numerous orphan receptors for which currently no natural ligand has been defined.[2] Thus, natural and synthetic ligands of NRs have been known as biologically as well as clinically important compounds, and still many efforts have been devoted to finding better and novel drug candidates from NR potential ligands.

Binding of small lipophilic ligands of NRs can induce crucial conformational changes in the cognate receptors whose molecular weights are nearly 100 times those of the ligands.[3] The crystal structures of a number of NR members have been solved in the past five years, and this provides us with indispensable information on the transactivation function of NR-ligand binding domains on structural basis.[4—8] We learned that, upon ligand binding, drastic conformational changes in the C-terminal region called transactivation function 2 (AF-2) are induced to generate the transcriptionally active form to which coactivators can be recruited.

In the course of continuing research on the conformation and activity relationship of vitamin D,[9—12] we turned our attention to the conformation of the A-ring plus the conjugated triene part of vitamin D in the VDR complex. To specifically observe the ligand counterpart in the ligand–VDR complex, we have planned to use the signal of ^{19}F incorporated in the vitamin D molecule by ^{19}F-NMR spectroscopy.[13] Because of the wide chemical-shift range of organic fluorine atoms, we expected to be able to discriminate the fluorine in different ligand conformations. For this purpose, we have synthesized 4,4-difluoro-1,25-dihydroxyvitamin D_3,[14,15] and now we report another probe in this study, the geometrical isomers of 19-fluoro-1,25-dihydroxyvitamin D_3 (**2** and **3**). Whether the reduced electron density on the triene of vitamin D affects the biological property is also interesting.

The synthesis of 6-fluorovitamin D_3 **4** has been reported by Dauben *et al.*, and this compound was shown to have some antagonistic activity *in vivo*.[16,17] An attempted synthesis of 19,19-difluorovitamin D_3 by Mazur's group *via* a general photochemical approach through the corresponding provitamin D was unsuccessful,[18] because the thermal [1,7]-sigmatropic rearrangement of the difluoroprevitamin D to the corresponding vitamin D was prohibited by the strong electronic effect of the two fluorine atoms on C(19) (Chart 2). Therefore, we adopted a novel way of synthesizing 19-fluorovitamin D analogs *via* regioselective electrophilic fluorination of vitamin D–SO_2 adducts **6** or **7** as a key step (Chart 3). In this paper, we describe the first synthesis of (5*Z*,10*Z*)- and (5*Z*,10*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3 [19-F-1α,25-$(OH)_2D_3$] **2a** and **3a** and their related compounds **2b**, **2c**, **3b**, and **3c** (Chart 1).[19] We also describe the stereochemistry of the cheletropic reaction of vitamin D with SO_2 and the photochemical isomerization of 19-fluorovitamin D geometrical isomers.

Results and Discussions

Synthetic Strategy Both geometrical isomers of 19-F-1α,25-$(OH)_2D_3$ **2a** and **3a** were synthesized from vitamin D_2 *via* the route outlined in Chart 3. Vitamin D compounds **1** and **5** possessing the necessary hydroxyl groups at C(1) and C(25) were prepared by known methods.[10,20,21] Briefly, the 1α-hydroxyl was introduced *via* (5*E*)-vitamin D by allylic oxidation using SeO_2.[22] The side chain with the 25-hydroxyl group was readily constructed by exchanging C(23) to C(27)

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Dedicated to the memory of Dr. Kyosuke Tsuda.

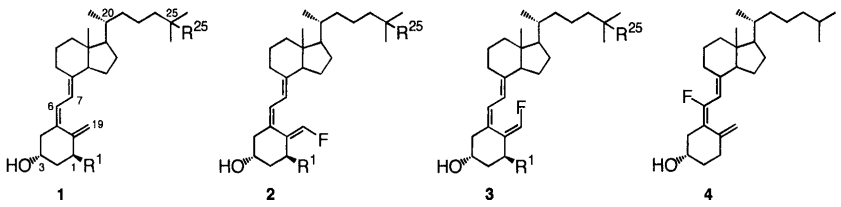


Chart 1

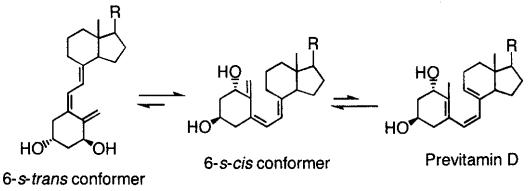


Chart 2. The Dynamic Changes Occurring within the Seco-B, Conjugated Triene Part of Vitamin D Molecule

part *via* the C(22)-aldehyde, which is obtained by the ozonolysis of the vitamin D$_2$–SO$_2$ adduct. Treatment of **1** and **5** with liquid SO$_2$ would afford the SO$_2$ adduct as a mixture of the two epimers **6** and **7** at C(6).[23,24] The 6 and 19-positions activated by the adjacent SO$_2$ group can be readily substituted with electrophilic reagents under basic conditions.[25—30] By choosing the proper combination of a base and an electrophilic fluorination reagent, regioselective 19-fluorination to afford **8**—**11** can be achieved in moderate yields.[19] Cheletropic desulfonylation followed by dye-sensitized photoisomerization would afford the desired 19-fluorovitamin D **2** and **3**.

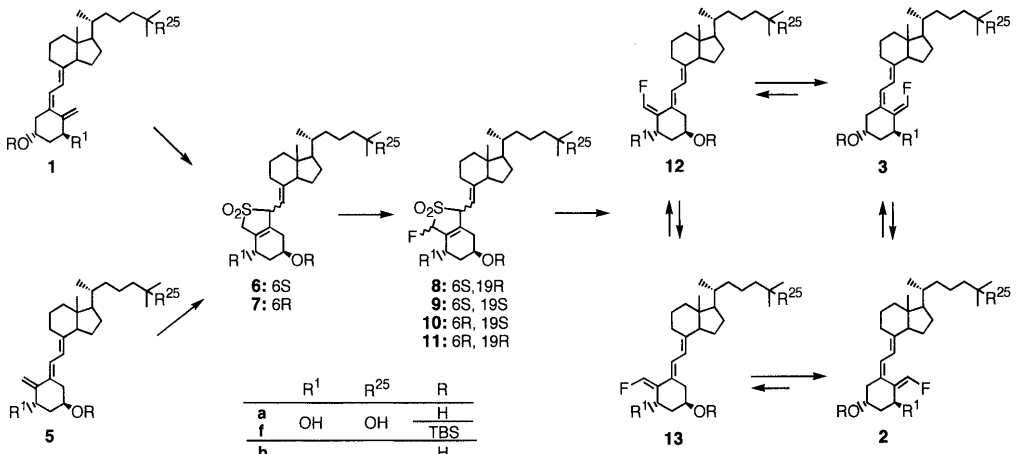
Stereochemistry of the Reaction of (5*Z*)- and (5*E*)-Vitamin D with Liquid SO$_2$ The s-*cis*-diene part of vitamin D (**1** and **5**) reacts quantitatively with SO$_2$ to afford the sulfolenes **6** and **7** (Chart 4). The reversible addition–elimination reaction of SO$_2$ on dienes is a typical cheletropic reaction. The stereochemistry of the extrusion of SO$_2$ from sulfolenes has been extensively studied and shown to proceed in suprafacial manner with respect to the diene part.[31,32] However, the stereochemistry of the SO$_2$ addition reactions has not been clearly understood. In the syntheses of vitamin D derivatives, SO$_2$ adducts (**6** and **7**) have been used for three major purposes:[23,24] (i) to protect the conjugated triene structure under acidic and oxidative conditions;[25] (ii) to introduce electrophiles to the 6- and 19-positions; and (iii) to selectively transform vitamin D (**1**) to (5*E*)-vitamin D (**5**).[22,29,30] Nevertheless, not much attention has been paid to the stereochemistry of the addition of SO$_2$.

We investigated the effects of the substituents at C(1) and the solvent on the face selectivity of the SO$_2$ addition, and the results are summarized in Table 1. In the reaction of (5*Z*)-vitamin D **1h** without the 1-OH group, the isomeric adducts (6*S*)-**6h** and (6*R*)-**7h** were produced in about a 1 : 1 ratio regardless of the conditions used (entries 1—3). The face selectivity of vitamin D with a 1α-OH group (**1g**) and its 5*E*-isomer (**5g**) depends on the conditions (entries 4—8). The proportion of the upper-face adduct (6*S*-**6g**) was increased with increasing polarity of the solvents. In the reactions of vitamin D **1i** and **5i** with the bulkier 1α-OMOM group, SO$_2$ is added preferentially from the upper-face regardless of the conditions (entries 9—13). However, it should be noted that the reactivity of the 5*Z*-isomer (**1i**) was considerably decreased, and the addition did not even proceed with SO$_2$ in CH$_2$Cl$_2$ solution (entry 9). The 5*E*-vitamin D with 1β-OH **14** yielded predominantly the lower-face adduct (6*R*)-**16** (entries 14—16).

Thus, in the case of 5*E*-vitamin D, it is likely that SO$_2$ adds to the s-*cis*-diene part from the side opposite to the C(1) substituent. The polar solvent MeOH may form a hydrogen bond with the 1α-OH group thereby increasing the steric bulkiness of the C(1) substituent and, in turn, causing the addition of SO$_2$ from the face opposite to the C(1) substituent. We have observed that vitamin D undergoes reversible *Z*–*E* isomerization at the 5,6-double bond in the presence of SO$_2$, the 5*E*-isomer being far more predominant. It was also found that the 5*E*-isomer is about 8 times more reactive than the 5*Z*-isomer in the SO$_2$-adduct formation (unpublished results). Therefore, it is likely that 5*Z*-vitamin D (**1**) reacts with SO$_2$ after being isomerized to the 5*E*-isomer (**5**). The vitamin D **1i** with a 1α-OMOM group reacts very sluggishly with SO$_2$ probably because it hardly undergoes *Z* to *E* isomerization (unpublished results). Details of the mechanism of the reaction of SO$_2$ with the diene in vitamin D will be reported elsewhere.

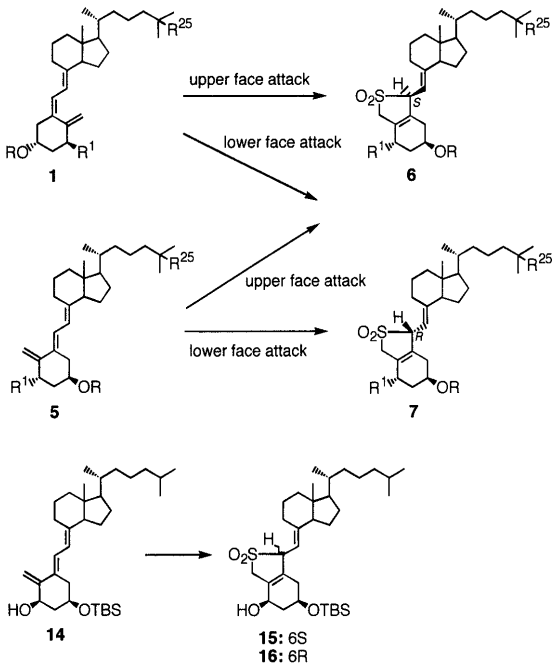
Electrophilic Fluorination of Vitamin D-SO$_2$ Adducts In the electrophilic substitution of the 6- and 19-positions of vitamin D–SO$_2$ adducts, the regioselectivity of the reaction can be controlled by selecting the base: for example, the selective electrophilic substitution at C(6) occurs under the conditions using a smaller and weaker base such as NaH, while the selective substitution at C(19) proceeds under conditions using a stronger and bulkier base such as LiHMDS.[25] By forming the SO$_2$ adducts, vitamin D is activated for the electrophilic substitution at the 6- and 19-positions under basic conditions. On the other hand, vitamin D–SO$_2$ adducts are unstable under the basic conditions: irreversible double bond isomerization and sulfolene ring opening with SO_2^- as a leaving group occur readily as side reactions under these conditions.[29,33] Therefore, the fluorination reactions described in this study were terminated, while a large amount of the starting material remained.

We investigated the electrophilic fluorination at C(19) of vitamin D–SO$_2$ adducts (Chart 5) under various conditions, and the results are summarized in Table 2. Upon treatment with (PhSO$_2$)$_2$NF in the presence of the bulky base LiHMDS, the (6*S*)-isomer (**6h**) without 1α-OH group afforded the epimeric (*R*)- and (*S*)-19-fluoro-compounds **8h** and **9h** (3 : 1 ratio) in 51% total yield based on the recovered starting material (entry 1). The (6*R*)-isomer **7h** gave the (19*S*)-**10h** and



	R^1	R^{25}	R
a	OH	OH	H
f			TBS
b	OH	H	H
g			TBS
c	H	H	H
h			TBS
d	OMOM	H	H
i			TBS
e	OMOM	OMOM	H
j			TBS

Chart 3



	R^1	R^{25}	R
a	OH	OH	H
f			TBS
b	OH	H	H
g			TBS
c	H	H	H
h			TBS
d	OMOM	H	H
i			TBS
e	OMOM	OMOM	H
j			TBS
k	OTMS	H	TBS

Chart 4. Reaction of Vitamin D with SO_2

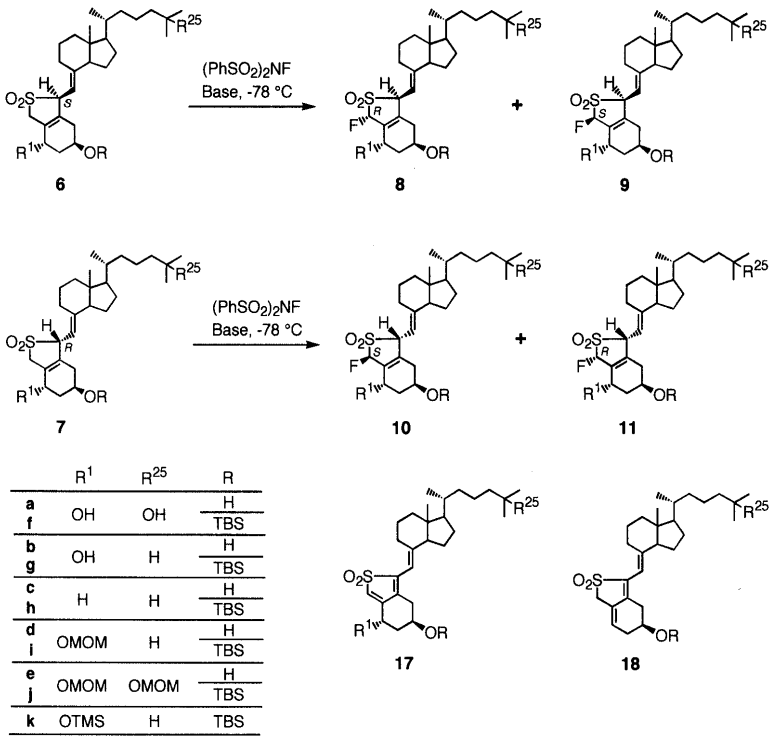
Table 1. Faceselectivity of the Reaction of SO_2 with Vitamin D[a)]

Entry	Compound	Substituents C(1)	Substituents C(3)	Conditions	Adducts 6*S*:6*R*
1	**1h**	—	β-OTBS	SO_2/CH_2Cl_2 (1:2)	1:1
2	**1h**	—	β-OTBS	SO_2	1:1
3	**1h**	—	β-OTBS	SO_2/MeOH (1:2)	1:1
4	**1g**	α-OH	β-OTBS	SO_2/CH_2Cl_2 (1:2)	2:3
5	**1g**	α-OH	β-OTBS	SO_2	3:2
6	**5g**	α-OH	β-OTBS	SO_2/CH_2Cl_2 (1:2)	2:3
7	**5g**	α-OH	β-OTBS	SO_2	3:2
8	**5g**	α-OH	β-OTBS	SO_2/MeOH (1:2)	4:1
9	**1i**	α-OMOM	β-OTBS	SO_2/CH_2Cl_2 (1:2)	NR[b)]
10	**1i**	α-OMOM	β-OTBS	SO_2[c)]	3.7:1
11	**5i**	α-OMOM	β-OTBS	SO_2/CH_2Cl_2 (1:2)	4:1
12	**5i**	α-OMOM	β-OTBS	SO_2	4:1
13	**5i**	α-OMOM	β-OTBS	SO_2/MeOH (1:2)	4:1
14	**14**	β-OH	β-OTBS	SO_2/CH_2Cl_2 (1:2)	1:5
15	**14**	β-OH	β-OTBS	SO_2	1:6
16	**14**	β-OH	β-OTBS	SO_2/MeOH (1:2)	1:4

a) The reaction was conducted at the refluxing temperature of SO_2 (−10 °C) for 30 min. *b*) NR: no SO_2-adduct was produced within 4 h. *c*) The reaction was continued for 4 h.

(19*R*)-**11h** compounds (3:1 ratio) in 51% yield (entry 2). In both cases, the fluorination occurred predominantly at the site *trans* to the substituent at C(6), and no epimerization at C(6) was observed in either the fluorinated products or the starting materials. Under the same conditions, no 19-fluorination product was obtained from the (6*S*)-SO_2-adducts (**6g**, **6i** and **6k**) bearing 1α-OH or its protected ones. Instead, a conjugated triene compound **17** or **18** was produced (entries 3, 9 and 10). The by-products (**17i**) are probably formed by the elimination of hydrogen fluoride from the 19-fluorinated adducts (**8i** and/or **9i**). Therefore, the yield of the by-product **17** is higher from sterically congested 1α-substituted adducts. The MOM ether **6i** gave 19-fluoro compounds (**8i** and **9i**) in low yield when a less bulky base was used (entries 4 and 5). The (6*R*)-isomer **7i** afforded solely (19*R*)-fluorinated compound **10i** (entry 6) when LiHMDS was used. The yield (55%) of the fluorination product **10i** was improved with a less bulky base LDA, but the by-product **17i** was also produced (30%) (entry 7).

In summary, the 19-fluorination of vitamin D–SO_2 adducts occurs preferentially *trans* to the C(6) substituent. Fluorination using other electrophilic fluorinating reagents such as *N*-



	R^1	R^{25}	R
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b	OH	H	H
g			TBS
c	H	H	H
h			TBS
d	OMOM	H	H
i			TBS
e	OMOM	OMOM	H
j			TBS
k	OTMS	H	TBS

Chart 5. Electrophilic Fluorination of Vitamin D–SO_2 Adducts

Table 2. Electrophilic Fluorination of Vitamin D–SO_2 Adducts

Entry	Substr.	Base	Products (%)[a]					Recov. (%)
			8	**9**	**10**	**11**	Others	
1	**6h**	LiHMDS	38	13	—	—	**17** (18)	21
2	**7h**	LiHMDS	—	—	39	12	**17** (24)	30
3	**6i**	LiHMDS	—	—	—	—	**17** (65)	48
4	**6i**	LDA	23	36	—	—	**17** (20)	70
5	**6i**	*n*-BuLi	6	8	—	—	**17** (31)	49
6	**7i**	LiHMDS	—	—	47	—	**17** (43)	24
7	**7i**	LDA	—	—	55	—	**17** (30)	40
8	**7i**	*n*-BuLi	—	—	45	—	—	78
9	**6g**	LiHMDS	—	—	—	—	**18** (50)	50
10	**6k**	LiHMDS	—	—	—	—	**18** (69)	46
11	**7j**	LiHMDS	—	—	42	—	**17** (46)	50

a) Yields based on the recovered starting material.

fluoro-pyridinium triflate was unsuccessful. It should be noted that, under the fluorination conditions described above, no epimerization at the C(6) position occurred.

The stereochemistry of the 19-fluorinated compounds was assigned on the basis of the ^{1}H-NMR: The C(6) proton *cis* to the 19-fluorine appears at about 0.2 ppm lower field than the C(6) proton *trans* to the 19-fluorine. The stereochemistry of the cheletropic desulfonylation of the fluorinated adducts **8**, **9**, **10**, and **11** described below provided supporting evidence for the stereochemistry.

Desulfonylation of 19-Fluorinated SO_2-Adducts On thermal desulfonylation ($NaHCO_3$/refluxing EtOH) (Chart 6), both 6,19-*trans*-adducts **8h** and **10h** gave (5*E*,10*Z*)-**12h** and (5*Z*,10*E*)-**2h** in a 5—8 : 1 ratio in high yields (*ca.* 70%), whereas the two 6,19-*cis*-isomers **9h** and **11h** yielded (5*E*)-**13h** as a sole product (60—80%). These results indicate that the desulfonylation proceeded selectively in a suprafacial manner with respect to the diene part and that no *cis–trans* isomerization on the sulfolene ring occurred during the reaction. These results are in contrast with the precedents: the desulfonylation of *trans*-2,5-disubstituted sulfolenes under similar conditions gave predominantly 1,4-disubstituted (*E*,*E*)-dienes, contrary to the selection rule of the cheletropic reaction.[26,27] This stereoselectivity was explained by the *trans–cis* isomerization of the starting sulfolenes occurring under the basic desulfonylation conditions. In the present cases, 6,19-*trans* adducts (**8h** and **10h**) underwent the suprafacial desulfonylation following the selection rule of the cheletropic reaction. Thus no *trans–cis* isomerization occurred with these *trans*-substituted sulfolenes (**8h** and **10h**) probably because the terminal substituent fluorine is smaller than an alkyl group and the pathways to the (*Z*,*E*,*E*)- and (*E*,*Z*,*E*)-trienes (**12h** and **2h**) might not be sterically unfavorable.

The hydroxyl protecting groups of the fluorinated SO_2-adducts (**8i**, **9i**, **10i** and **8j**, **9j**, **10j**) were deprotected under mild conditions (TMSBr in CH_2Cl_2 at −20 °C, 52—63%), and the resulting sulfolenes (**8a**, **b**, **9a**, **b**, and **10a**, **b**) were subjected to desulfonylation. The hydroxyl protecting groups of **8i**, **9i**, **10i** and **8j**, **9j**, **10j** were removed prior to the desulfonylation reaction, because the vitamin D triene part decomposes under the deprotection conditions. However, thermal desulfonylation of 1α-hydroxylated SO_2-adducts (**8b**, **9b**, and **10b**) in the presence of $NaHCO_3$ yielded no desired 19-fluorovitamin D derivatives but gave only the hydrogen-fluoride elimination product **19**. Reductive desulfonylation ($LiAlH_4$ in ether, room temperature) gave the desired 19-fluorovitamin D as a mixture of (5*Z*,10*Z*)-isomers (**2b**) and (5*E*,10*E*)-(**12b**) in a 2 : 3 ratio (30% yield). The 6,19-*cis*-isomer (**9b**) was desulfonylated under the same conditions, yielding (5*E*,10*Z*)-**13b** (31%) as a single isomer. The above results indicated that the desulfonylation proceeded in the suprafacial manner under both thermal and reductive condi-

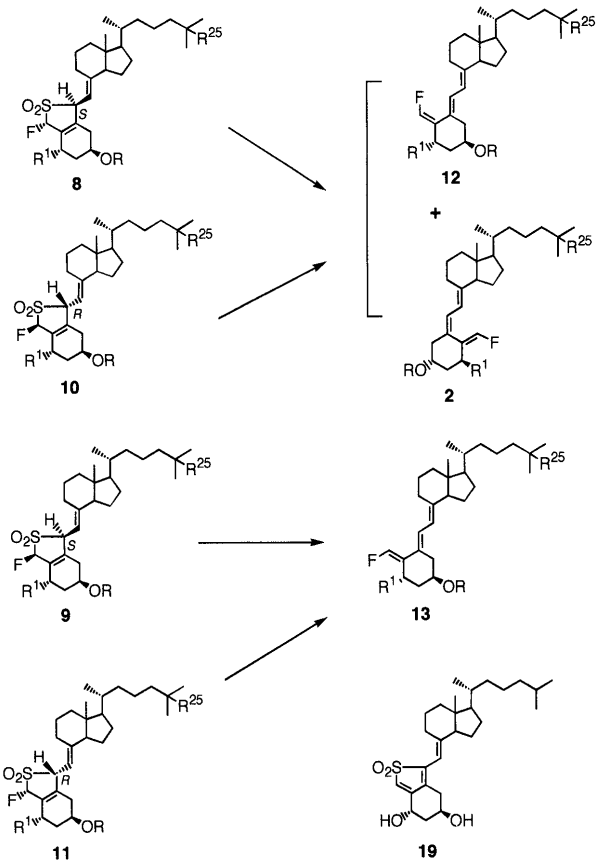
tions.

To prepare 19-fluoro-1α-hydroxylated vitamin D derivatives more efficiently, we examined the introduction of the 1α-OH group into (5*E*)-19-fluorinated vitamin D **12c** and **13c**. Allylic oxidation with SeO_2–NMO is a convenient and the most widely used method for introducing a 1α-hydroxyl group into (5*E*)-vitamin D.[22] However, oxidation of **12h** with SeO_2 causes mostly decomposition of the starting material, and the only product detected (less than 5% yield) was a 9-hydroxylated compound. An alternative method using $Hg(OCOCF_3)_2$[34] caused only the geometrical isomerization at C(10) yielding a mixture of isomers **12h** and **13h** in *ca.* 25 : 75 ratio. Thus direct 1α-hydroxylation of the 19-fluorovitamin D was unsuccessful.

Photochemical and Thermal Isomerization of 19-Fluorovitamin D The (5*E*)-19-fluorovitamin D derivatives (**12** and **13**) were converted to the corresponding vitamin D derivatives (**2** and **3**) by photochemical isomerization.[35] (5*E*)-Vitamin D can be readily and selectively converted to the (5*Z*)-vitamin D by dye-sensitized photochemical double bond isomerization. (5*E*)-Vitamin D **12c** and **13c** were irradiated (halogen lamp) in benzene/ethanol in the presence of anthracene as a sensitizer until the starting materials disappeared (10—15 min), both yielding 19-fluorovitamin D_3 **2c** as the sole product (*ca.* 75%). Upon prolonged irradiation, slow isomerization of the 10,19-double bond occurred: thus, **2c** was irradiated until a photostationary state was reached (5 h under the same conditions) to yield a 65 : 35 mixture of **2c** and **3c** without any appreciable decomposition of the substrates. Irradiation of (5*E*,10*E*)-**12b** bearing the 1α-OH group afforded a mixture of three isomers (5*Z*,10*Z*)-**2b**, (5*Z*,10*E*)-isomer **3b** and (5*E*,10*Z*)-**13b** in a 85 : 10 : 5 ratio (70% yield) at a photostationary state (60 min).

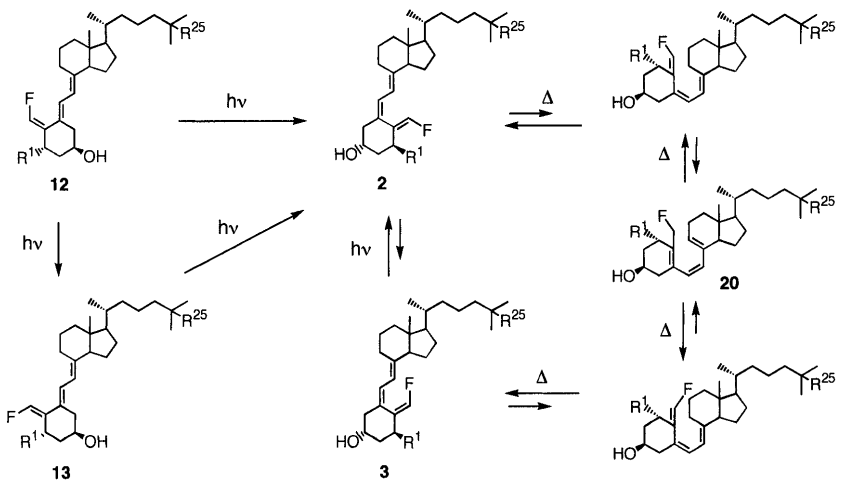
19-Fluorovitamin D **2** also undergoes thermal isomerization to give **3**. When heated in octane at 120 °C in a sealed tube for 4 h, **2c** (or **2b**) was isomerized to afford a 85 : 15 mixture of **2c** and **3c** (or **2b** and **3b**). This isomerization probably occurred *via* the 19-fluoroprevitamin D_3 **20**, though it was not detected in the reaction mixture. This result is in contrast to the results in which 19,19-difluoroprevitamin D did not undergo the thermal 1,7-sigmatropic rearrangement to the corresponding vitamin D (Chart 2).[18] Mono-fluorine substitution would not have much electronic effect on the 1,7-sigmatropic rearrangement.

(10*Z*)- and (10*E*)-19-Fluorovitamins **2b** and **2c** absorb UV at shorter wavelength (262 and 260 nm, respectively) than the parent vitamin D_3 (265 nm) does, while the (10*E*)-isomers **3b**



	R^1	R^{25}	R
a	OH	OH	H
f			TBS
b	OH	H	H
g			TBS
c	H	H	H
h			TBS
d	OMOM	H	H
i			TBS
e	OMOM	OMOM	H
j			TBS

Chart 6. Thermal Desulfonylation of 19-Fluorovitamin D–SO_2 Adducts



	R^1	R^{25}
a	OH	OH
b	OH	H
c	H	H

Chart 7. Photochemical and Thermal Isomerization of 19-Fluorovitamin D

and **3c** absorb in the normal range of 264 nm.

The stereochemistries of the fluorinated vitamin D_3 analogs **2**, **3**, **12** and **13** at C(5) and C(19) were unambiguously determined by their phase-sensitive 2D NOESY spectra. In **2b** and **2c**, a correlation cross peak was observed between H-7 and H-19, but not between H-1 and H-19. An NOE was observed between H-1 and H-19 in **3b** and **3c**. A cross peak was observed between H-1 and H-19 in **12b** and **12c**, while in **13b** and **13c** a cross peak between H-6 and H-19 was detected.

Synthesis and Biological Activity of (10*Z*)- and (10*E*)-19-Fluoro-1α,25-Dihydroxyvitamin D_3 Having examined the chemical and stereochemical details, the syntheses of (10*Z*)- and (10*E*)-19-fluoro-1,25-dihydroxyvitamin D_3, **2a** and **3a**, were achieved as shown in Chart 3. (5*E*)-1,25-Dihydroxyvitamin D_3 3-*tert*-butyldimethylsilyl ether **5f**, which was synthesized from vitamin D_2,[14,20,21] was converted to the corresponding SO_2 adducts **6f** and **7f** (6*S*:6*R*=2:3, 60%). After protecting hydroxyl groups at C(1) and C(25) as MOM ethers, the major (6*R*)-SO_2 adduct **7j** was fluorinated by $(PhSO_2)_2NF$ to yield only the expected (6*R*,19*S*)-isomer **10j** (41% based on the recovered starting material). Deprotection with TMSBr (55%), followed by reductive desulfonylation, afforded (5*E*,10*Z*)-**12a** (15%) and **2a** (4%). To prepare an isomeric (5*E*,10*Z*)-**13a**, the same sequence of synthetic procedure using the (6*S*)-SO_2 adduct-1,25-MOM ether **6j** was used to give **13a**, together with **12a**. Each (5*E*)-19-fluorovitamin D **12a** and **13a** was converted to **2a** and **3a** by photochemical isomerization.

The binding affinity of **2a** and **2b** for the bovine thymus vitamin D receptor (VDR) was evaluated. The affinity of compounds **2a** and **2b** was about 1/10 as effective as that of the natural ligand **1a**.

In conclusion, we have established a facile method for converting vitamin D to 19-fluorinated vitamin D derivatives *via* regioselective electrophilic fluorination of vitamin D–SO_2 adducts as a key reaction. Using this method, syntheses of (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxyvitamin D_3 (**2a** and **3a**) were accomplished starting from vitamin D_2. We are now pursuing a ^{19}F-NMR study of the molecular recognition between VDR and these fluorovitamin D analogs.

Experimental

The NMR spectra were recorded on a Bruker ARX-400 MHz spectrometer, operating at 400 MHz for ^{1}H, 376 MHz for ^{19}F and 101 MHz for ^{13}C. 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. IR spectra were recorded on a Jasco Janssen Microsampling FT IR spectrometer. 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.

(6*S*) and (6*R*)-SO_2-Adduct of (5*Z*,7*E*)-3-(*tert*-Butyldimethylsilyloxy)-9,10-seco-5,7,10(19)-cholestatriene (6h and 7h) Vitamin D_3–SO_2 adducts **6c** and **7c** were prepared following the reference methods.[23,24] Vitamin D_3 **1c** (4.10 g, 10.65 mmol) was refluxed in liquid SO_2 (approximately 20 ml) for 30 min and then excess of liquid SO_2 was removed by flashing with the aid of N_2 gas, and the residue was dried *in vacuo* to afford a mixture of (6*S*)- and (6*R*)-SO_2-adducts **6c** and **7c**.

To a stirred solution of crude SO_2-adducts **6c** and **7c** in dry DMF (10 ml) was added imidazole (2.9 g, 42.6 mmol) and TBDMSCl (3.21 g, 21.3 mmol) and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O and extracted with hexane, then ether. The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (150 g) using 10% AcOEt–hexane to give **6h** (2.98 g) and **7h** (2.67 g) in a 94.6% total yield.

6h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.06 (each 3H, s, 2×Si–Me), 0.65 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, *J*=6.5 Hz, 21-H), 2.60 (1H, m), 3.65 (2H, m, 19-H), 4.01 (1H, m, 3-H), 4.52 (1H, d, *J*=9.5 Hz, 7-H), 4.71 (1H, d, *J*=9.5 Hz, 6-H).

7h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.06 (each 3H, s, 2×Si–Me), 0.57 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, *J*=6.3 Hz, 26, 27-H), 0.88 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, *J*=6.1 Hz, 21-H), 2.57 (1H, m), 3.64, 3.68 (each 1H, d, *J*=16.0 Hz, 19-H), 3.97 (1H, m, 3-H), 4.63 (1H, d, *J*=10.2 Hz, 7-H), 4.78 (1H, d, *J*=10.2 Hz, 6-H).

(6*S*)- and (6*R*)-SO_2-Adduct of (5*Z*,7*E*)-3-(*tert*-Butyldimethylsilyloxy)-9,10-seco-5,7,10(19)-cholestatriene-1-ol (6g and 7g) (5*E*)-1α-Hydroxyvitamin D_3 3-*tert*-butyldimethylsilyl ether **5g** was synthesized by the published procedure.[20,21] To a stirred, cold (−10 °C) solution of **5g** (90.1 mg, 0.18 mmol) in dry CH_2Cl_2 or CCl_4 (3 ml) was added liquid SO_2 (*ca.* 1.5 ml) and the mixture was refluxed for 30 min. Excess of liquid SO_2 and the solvent were evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (7 g) with 20% AcOEt–hexane to afford **6g** and **7g** (79.0 mg, 6*S*:6*R*=2:3, 78.0%).

6g: ^{1}H-NMR ($CDCl_3$) δ: 0.061 (6H, s, Si–Me), 0.65 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.92 (3H, d, *J*=6.3 Hz, 21-H), 2.60 (1H, m), 3.73 (1H, m, 19-H), 4.02 (1H, m, 19-H), 4.19 (1H, m, 3-H), 4.34 (1H, m, 1-H), 4.62 (1H, d, *J*=9.5 Hz, 7-H), 4.70 (1H, d, *J*=9.5 Hz, 6-H).

7g: ^{1}H-NMR ($CDCl_3$) δ: 0.057 (6H, s, Si–Me), 0.56 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.93 (3H, d, *J*=6.0 Hz, 21-H), 2.56 (2H, m), 3.73 (1H, m, 19-H), 4.02 (1H, m, 19-H), 4.16 (1H, m, 3-H), 4.34 (1H, m, 1-H), 4.65 (1H, d, *J*=10.2 Hz, 7-H), 4.80 (1H, d, *J*=10.2 Hz, 6-H).

6g and **7g** Mixture: EI-MS *m/z* (%): 514 (M^+-SO_2, 70), 496 (26), 457 (44), 455 (35), 439 (8), 382 (57), 364 (22), 247 (26), 209 (21), 134 (100). HR-EI-MS *m/z*: 514.4243 (M^+-SO_2; Calcd for $C_{33}H_{58}O_2Si$: 514.4206).

(6*S*)- and (6*R*)-SO_2-Adduct of (5*Z*,7*E*)-1-(Methoxymethyloxy)-3-(*tert*-butyldimethylsilyloxy)-9,10-seco-5,7,10(19)-cholestatriene (6i and 7i) A mixture of **6g** and **7g** (170.9 mg, 0.30 mmol), *N*,*N*-diisopropylethyl amine (0.51 ml, 2.95 mmol), chloromethyl methyl ether (0.11 ml, 1.47 mmol) in dry CH_2Cl_2 (5 ml) was stirred at 0 °C. After 5 h, additional *N*,*N*-diisopropylethyl amine (0.51 ml, 2.95 mmol) and chloromethyl methyl ether (0.11 ml, 1.47 mmol) were added and the mixture was stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with 1% HCl, 5% $NaHCO_3$, followed by brine, and dried ($MgSO_4$), and then evaporated *in vacuo*. The residue was purified by chromatography on silica gel (22 g) using 20—40% AcOEt–hexane to yield (6*S*)-**6i** (52.6 mg) and (6*R*)-**7i** (97.7 mg) in a total yield of 81.7%.

6i: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, Si–Me), 0.66 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.92 (3H, d, *J*=6.3 Hz, 21-H), 2.19 (1H, m), 2.61 (1H, m), 3.38 (3H, s, OMe), 3.66, 3.98 (each 1H, d, *J*=15.7 Hz, 19-H), 4.16 (1H, m, 3-H), 4.22 (1H, m, 1-H), 4.59, 4.72 (each 1H, d, *J*=7.0 Hz, OCH_2O), 4.65 (1H, d, *J*=9.6 Hz, 7-H), 4.72 (1H, d, *J*=9.6 Hz, 6-H). EI-MS *m/z* (%): 558 (M^+-SO_2, 25), 528 (47), 513 (17), 498 (100), 496 (22), 441 (26), 439 (17), 426 (15), 381 (40), 364 (12), 178 (74). HR-EI-MS *m/z*: 558.4447 (M^+-SO_2; Calcd for $C_{35}H_{62}O_3Si$: 558.4468.

7i: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, Si–Me), 0.56 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.93 (3H, d, *J*=6.1 Hz, 21-H), 2.35 (1H, m), 2.55 (1H, m), 3.39 (3H, s, OMe), 3.68 (1H, dd, *J*=16.1, 2.9 Hz, 19-H), 3.96 (1H, d, *J*=16.1 Hz, 19-H), 4.12 (1H, m, 3-H), 4.22 (1H, m, 1-H), 4.60, 4.73 (each 1H, d, *J*=7.0 Hz, OCH_2O), 4.62 (1H, d, *J*=10.2 Hz, 7-H), 4.80 (1H, d, *J*=10.2 Hz, 6-H). EI-MS *m/z* (%): 558 (M^+-SO_2, 29), 528 (39), 513 (15), 498 (100), 496 (30), 441 (22), 439 (16), 426 (14), 381 (31), 364 (14), 178 (62). HR-EI-MS *m/z*: 558.4483 (M^+-SO_2; Calcd for $C_{35}H_{62}O_3Si$: 558.4468).

(6*S*,19*R*)- and (6*S*,19*S*)-SO_2-Adduct of (5*Z*,7*E*)-3-(*tert*-Butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (8h and 9h) (6*S*)-SO_2-adduct **6h** (225 mg, 0.40 mmol), HMPA (139 μl, 0.80 mmol) and *N*-fluorodibenzenesulfonamide (151.4 mg, 0.48 mmol) were dissolved in dry THF (3 ml) and the solution was cooled to −78 °C. To this solution was added LiHMDS (1 M solution in THF, 480 μl, 0.48 mmol) and the whole mixture was stirred for 10 min and then quenched with sat. NH_4Cl. The mixture was

taken up in ether and the organic layer was washed with brine, dried ($MgSO_4$), and then evaporated to dryness. The residues was separated by chromatography on silica gel (50 g) using 3% AcOEt–hexane to give **8h** (less polar, 69.7 mg, 30.0%), **9h** (more polar, 23.5 mg, 10.1%), **17h** (32.6 mg, 14.0%) and the unreacted starting material (47.9 mg, recovery 21.3%).

8h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, 2×Si–Me), 0.65 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=6.4 Hz, 21-H), 2.32 (2H, m), 2.60 (1H, m), 4.04 (1H, m, 3-H), 4.66 (2H, m, 6, 7-H), 5.42 (1H, d, J=56.9 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −165.2 (d, J=56.9 Hz). EI-MS m/z (%): 516 (M^+-SO_2, 100), 496 (11), 459 (13), 439 (7), 431 (4), 403 (10), 384 (19), 364 (47), 271 (19), 259 (30), 251 (45), 211 (61), 136 (37), 117 (47). HR-EI-MS m/z: 516.4178 (M^+-SO_2; Calcd for $C_{33}H_{57}OFSi$: 516.4163).

9h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, 2×Si–Me), 0.66 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=7.0 Hz, 21-H), 4.04 (1H, m, 3-H), 4.43, 4.65 (each 1H, d, J=9.6 Hz, 6, 7-H), 5.35 (1H, d, J=56.3 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −161.0 (d, J=56.3 Hz). EI-MS m/z (%): 516 (M^+-SO_2, 40), 496 (3), 459 (5), 439 (3), 431 (1), 402 (43), 403 (16), 384 (16), 364 (11), 271 (17), 259 (23), 251 (16), 211 (37), 136 (84), 135 (100), 117 (40). HR-EI-MS m/z: 516.4135 (M^+-SO_2; Calcd for $C_{33}H_{57}OFSi$: 516.4163).

17h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, 2×Si–Me), 0.62 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=6.1 Hz, 21-H), 2.38 (1H, dd, J=17.9, 5.8 Hz), 2.51 (2H, m), 2.85 (1H, m), 4.06 (1H, m, 3-H), 5.41 (1H, s, 7-H), 6.24 (1H, s, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −165.2 (d, J=56.9 Hz). EI-MS m/z (%): 560 (M^+, 100), 545 (7), 503 (15), 476 (9), 447 (48), 398 (10), 364 (8), 315 (5), 295 (7), 247 (14), 195 (17), 133 (13). HR-EI-MS m/z: 560.3719 (Calcd for $C_{33}H_{56}O_3FSiS$: 560.3719).

(6*R*,19*S*)- and (6*R*,19*R*)-SO_2-Adduct of (5*Z*,7*E*)-3-(*tert*-Butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (10h and 11h) (6*R*)-SO_2-adduct **7h** (2.64 g, 4.69 mmol) was fluorinated as described for the preparation of **8h** and **9h** to give **10h** (less polar, 744.3 mg, 27.4%), **11h** (more polar, 233.3 mg, 8.6%), **17h** (451.9 mg, 17.2%) and the recovered starting material (796.7 mg, 30.2%).

10h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.06 (each 3H, s, 2×Si–Me), 0.56 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=5.9 Hz, 21-H), 2.33 (1H, m), 2.48 (1H, m), 2.55 (1H, m), 3.99 (1H, m, 3-H), 4.74 (2H, s, 6, 7-H), 5.37 (1H, d, J=56.7 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −164.7 (d, J=56.7 Hz). EI-MS m/z (%): 516 (M^+-SO_2, 100), 496 (9), 459 (8), 439 (5), 431 (4), 403 (11), 384 (11), 364 (13), 271 (17), 259 (33), 251 (16), 211 (39), 136 (31), 117 (37). HR-EI-MS m/z: 516.4184 (M^+-SO_2; Calcd for $C_{33}H_{57}OFSi$: 516.4163).

11h: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.06 (each 3H, s, 2×Si–Me), 0.55 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.93 (3H, d, J=6.0 Hz, 21-H), 2.35 (2H, m), 2.57 (1H, m), 4.01 (1H, m, 3-H), 4.50, 4.69 (each 1H, d, J=10.1 Hz, 6, 7-H), 5.40 (1H, d, J=54.6 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −161.6 (d, J=54.6 Hz). EI-MS m/z (%): 516 (M^+-SO_2, 100), 496 (4), 459 (8), 439 (4), 431 (3), 403 (9), 384 (10), 364 (29), 271 (14), 259 (27), 251 (32), 211 (30), 136 (19), 117 (27). HR-EI-MS m/z: 516.4181 (M^+-SO_2; Calcd for $C_{33}H_{57}OFSi$: 516.4163).

(6*S*,19*R*)- and (6*S*,19*S*)-SO_2-Adduct of (5*Z*,7*E*)-1-(Methoxymethyloxy)-3-(*tert*-butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (8i and 9i) To a stirred, cold (−78 °C) solution of (6*S*)-**6i** (85 mg, 0.14 mmol), *N*-fluorodibenzenesulfonamide (52 mg, 0.16 mmol), HMPA (60 μl) in THF (3 ml) was added LDA (2 M solution in THF, 82 μl, 0.16 mmol) and the mixture was stirred for 10 min. The reaction mixture was quenched with sat. NH_4Cl and extracted with ether. The extracts were rinsed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was separated by chromatography on silica gel (10 g) with 20% AcOEt–hexane to give **8i** and **9i** (21 mg) as two isomeric fluoro-adducts, **17i** (5.2 mg, 6.1%) and the unreacted starting material **6i** (60 mg, 70%). The epimeric 19-fluoro-adducts were re-purified by chromatography on silica gel with 35% $CHCl_3$-benzene to yield the less polar **9i** (9.4 mg, 10.8%) and the more polar **8i** (6.0 mg, 6.9%).

8i: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.08 (each 3H, s, Si–Me), 0.63 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.93 (3H, d, J=6.3 Hz, 21-H), 2.25 (1H, m, 4-H), 2.62 (1H, m, 9-H), 3.42 (3H, s, OMe), 4.20 (1H, m, 3-H), 4.46 (1H, m, 1-H), 4.64, 4.77 (each 1H, d, J=7.1 Hz, OCH_2O), 4.72 (1H, d, J=10.1 Hz, 7-H), 4.84 (1H, dd, J=10.1, 4.3 Hz, 6-H), 5.51 (1H, d, J=56.4 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −157.5 (d, J=56.4 Hz). EI-MS m/z (%): 576 (M^+-SO_2, 14), 546 (35), 512 (15), 494 (3), 399 (4), 362 (29), 135 (21), 75 (100). HR-EI-MS m/z: 576.4354 (M^+-SO_2; Calcd for $C_{35}H_{61}O_3FSi$: 576.4374).

9i: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.08 (each 3H, s, Si–Me), 0.66 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.92 (3H, d, J=6.4 Hz, 21-H), 2.11 (1H, m, 4-H), 2.28 (1H, m, 4-H), 2.58 (1H, m, 9-H), 3.40 (3H, s, OMe), 4.20 (1H, m, 3-H), 4.46 (1H, m, 1-H), 4.54 (1H, dd, J=9.6, 6.7 Hz, 6-H), 4.65 (1H, d, J=9.6 Hz, 7-H), 4.67, 4.75 (each 1H, d, J=6.9 Hz, OCH_2O), 5.70 (1H, d, J=56.1 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −163.3 (d, J=56.1 Hz). EI-MS m/z (%): 576 (M^+-SO_2, 4), 546 (100), 531 (4), 494 (5), 489 (5), 457 (4), 381 (7), 362 (9), 241 (19), 135 (37). HR-EI-MS m/z: 546.4299 (M^+-SO_2; Calcd for $C_{34}H_{59}O_2FSi$: 546.4268).

17i: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.09 (each 3H, s, Si–Me), 0.61 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.93 (3H, d, J=6.1 Hz, 21-H), 2.04 (1H, m), 2.12 (1H, m), 2.20 (1H, m, 2-H), 2.46 (1H, m, 4-H), 2.54 (1H, m, 4-H), 3.41 (3H, s, OMe), 4.31 (1H, m, 3-H), 4.71, 4.75 (each 1H, d, J=6.9 Hz, OCH_2O), 4.80 (1H, br s, 1-H), 5.41 (1H, s, 7-H), 6.54 (1H, d, J=2.0 Hz, 19-H). MS m/z (%): 620 (M^+, 5), 558 (4), 445 (3), 309 (36), 252 (44), 235 (19), 135 (19), 64 (100).

(6*R*,19*S*)-SO_2-Adduct of (5*Z*,7*E*)-1-(Methoxymethyloxy)-3-(tert-butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (10i) (6*R*)-SO_2-adduct **7i** (97.7 mg, 0.16 mmol) was fluorinated as described for the preparation of **8i** and **9i**, but using LiHMDS as a base to give **10i** (36.0 mg, 35.8%), **17i** (31.6 mg, 32.4%) and the unreacted starting material (23.7 mg, 24.3%).

10i: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, Si–Me), 0.57 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.86—0.88 (6H, 26, 27-H, overlapped with Si–*tert*-Bu), 0.93 (3H, d, J=5.9 Hz, 21-H), 2.42 (1H, m), 2.54 (1H, m), 3.40 (3H, s, OMe), 4.16 (1H, m, 3-H), 4.44 (1H, br s, 1-H), 4.67, 4.76 (each 1H, d, J=7.0 Hz, OCH_2O), 4.78 (2H, br s, 6, 7-H), 5.70 (1H, d, J=56.9 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −166.3 (d, J=56.9 Hz). EI-MS m/z (%): 576 (M^+-SO_2, 33), 546 (100), 531 (8), 514 (8), 489 (5), 465 (6), 457 (6), 381 (10), 363 (7), 259 (28), 207 (29), 135 (83). HR-EI-MS m/z: 576.4412 (M^+-SO_2; Calcd for $C_{35}H_{61}O_3FSi$: 576.4374).

(6*S*,19*S*)-SO_2-Adduct of (5*Z*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3-diol (9b) and (6*R*,19*S*)-SO_2-Adduct of (5*Z*,7*E*,10*Z*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3-diol (10b) To a stirred, cold (−40 °C) solution of (6*R*)-**10i** (21.9 mg, 0.03 mmol) in dry CH_2Cl_2 (1 ml) was added bromotrimethylsilane (18 μl, 0.14 mmol) and the mixture was stirred for 4 h and then an additional trimethylbromosilane (9 μl) was added. After being stirred for 2 h, the reaction was quenched with 5% $NaHCO_3$ and the mixture was extracted with AcOEt. The organic extract was rinsed with H_2O, brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel (5 g) using 50% AcOEt–hexane to yield **10b** (10.2 mg, 62.6%).

The same procedure and work-up as mentioned above except employing (6*S*)-**9i** (8.7 mg, 0.014 mmol) gave **9b** (3.6 mg, 54.0%).

9b: ^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, 21-H), 2.40 (1H, m), 2.58 (1H, m, 9-H), 4.28 (1H, m, 3-H), 4.58 (1H, dd, J=9.8, 6.5 Hz, 6-H), 4.66 (1H, m, 1-H), 4.69 (1H, d, J=9.8 Hz, 7-H), 5.77 (1H, d, J=56.0 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −163.4 (d, J=56.0 Hz). EI-MS m/z (%): 418 (M^+-SO_2, 20), 398 (29), 380 (17), 362 (25), 305 (10), 285 (16), 267 (18), 249 (30), 135 (100). HR-EI-MS m/z: 418.3217 (M^+-SO_2; Calcd for $C_{27}H_{43}O_2F$: 418.3247).

10b: ^{1}H-NMR ($CDCl_3$) δ: 0.57 (3H, s, 18-H), 0.867, 0.873 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.93 (3H, d, J=6.0 Hz, 21-H), 2.45—2.60 (2H, m), 4.28 (1H, m, 3-H), 4.66 (1H, m, 1-H), 4.75 (1H, d, J=10.0 Hz, 6-H), 4.85 (1H, d, J=10.0 Hz, 7-H), 5.78 (1H, d, J=56.5 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −165.9 (d, J=56.5 Hz). IR: 3354, 1325 cm^{-1}. EI-MS m/z (%): 418 (M^+-SO_2, 33), 398 (100), 380 (15), 362 (10), 305 (14), 285 (48), 267 (31), 249 (24), 135 (77). HR-EI-MS m/z: 418.3248 (M^+-SO_2; Calcd for $C_{27}H_{43}O_2F$: 418.3247).

(5*E*,7*E*,10*Z*)- and (5*Z*,7*E*,10*E*)-3-(*tert*-Butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (12h and 2h) A solution of (6*S*,19*R*)-**8h** (842.5 mg, 1.45 mmol) and $NaHCO_3$ (609.2 mg, 7.25 mmol) in EtOH (20 ml) was heated at 80 °C for 1.5 h in a sealed tube. The mixture was cooled to room temperature and filtered. The filtrate was partitioned between water and AcOEt and the aqueous layer was extracted with AcOEt. The combined organic phase was washed with H_2O, dried ($MgSO_4$), then evaporated to dryness. The crude product was chromatographed on silica gel (80 g), using 2% AcOEt–hexane to yield (5*E*)-**12h** (447.2 mg, 59.7%), (5*Z*)-**2h** (94.0 mg, 12.5%) and the unreacted starting material (193.0 mg, 22.9%).

(6*R*,19*S*)-Isomer **10h** (103.6 mg, 0.18 mmol) was thermal-desulfonylated as mentioned above to yield **12h** (60.3 mg, 65.5%), **2h** (7.5 mg, 8.2%) and the unreacted starting material (8.9 mg, 8.6%).

12h: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, 2×Si–Me), 0.56 (3H, s, 18-H), 0.868, 0.873 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.88 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.4 Hz, 21-H), 2.26 (2H, m), 2.64 (1H, m), 2.81 (1H, m), 3.84 (1H, m, 3-H), 5.92, 6.57 (each 1H, d, J=11.5 Hz, 7-, 6-H), 6.48 (1H, d, J=85.7 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −135.9 (d, J=85.7 Hz). EI-MS *m/z* (%): 516 (M^+, 100), 496 (5), 459 (7), 439 (4), 431 (4), 403 (9), 384 (8), 365 (37), 364 (4), 271 (15), 259 (29), 251 (10), 211 (28), 136 (22), 117 (29). HR-EI-MS *m/z*: 516.4193 (Calcd for $C_{33}H_{57}OFSi$: 516.4163). UV λ_{max} (hexane): 204, 269 nm.

2h: ^{1}H-NMR ($CDCl_3$) δ: 0.069, 0.073 (each 3H, s, 2×Si–Me), 0.55 (3H, s, 18-H), 0.869, 0.874 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.89 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.4 Hz, 21-H), 2.20, 2.45 (each 1H, m, 4-H), 2.72 (1H, m, 1-H), 2.80 (1H, m), 3.81 (1H, m, 3-H), 5.92, 6.21 (each 1H, d, J=11.0 Hz, 6, 7-H), 6.49 (1H, d, J=87.6 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −133.0 (d, J=87.6 Hz). EI-MS *m/z* (%): 516 (M^+, 44), 496 (7), 459 (18), 439 (10), 431 (2), 403 (6), 384 (23), 365 (21), 364 (20), 271 (13), 259 (9), 251 (17), 211 (100), 136 (81), 117 (83). HR-EI-MS *m/z*: 516.4141 (Calcd for $C_{33}H_{57}OFSi$: 516.4163). UV λ_{max} (hexane): 262 nm.

(5*E*,7*E*,10*E*)-3-(*tert*-Butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (13h) (6*S*,19*S*)-Isomer **9h** (206.7 mg, 0.36 mmol) or (6*R*,19*R*)-isomer **11h** (49.7 mg, 0.09 mmol) was thermal-desulfonylated as described for the preparation of **2h** and **12h** to yield **13h** (111.5 mg, 60.6% from **9h**; 35.2 mg, 79.6% from **11h**).

13h: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, 2×Si–Me), 0.55 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.89 (9H, s, Si–*tert*-Bu), 0.92 (3H, d, J=6.3 Hz, 21-H), 2.25 (1H, m), 2.61 (2H, m), 2.81 (1H, m), 3.85 (1H, m, 3-H), 5.81, 6.29 (each 1H, d, J=11.4 Hz, 6, 7-H), 6.66 (1H, d, J=87.1 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −137.2 (d, J=87.1 Hz). EI-MS *m/z* (%): 516 (M^+, 100), 496 (5), 459 (10), 439 (6), 431 (3), 403 (7), 384 (14), 365 (13), 364 (6), 271 (18), 259 (21), 251 (12), 211 (94), 136 (74), 117 (84). HR-EI-MS *m/z*: 516.4133 (Calcd for $C_{33}H_{57}OFSi$: 516.4163).

(5*E*,7*E*,10*Z*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-3-ol (12c) and (5*E*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-3-ol (13c) To a stirred solution of **12h** (27.6 mg, 0.05 mmol) in dry THF (2 ml) was added *n*-Bu_4NF (1 M solution in THF, 0.16 mmol). The mixture was stirred for 1 h at room temperature and diluted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (5 g) with 3% AcOEt–hexane to afford **12c** (20.1 mg, 93.6%).

The same procedure and work-up as described in the preceding experiment, but using **13h** (100.0 mg, 0.19 mmol) gave **13c** (68.2 mg, 87.5%).

12c: ^{1}H-NMR ($CDCl_3$) δ: 0.56 (3H, s, 18-H), 0.867, 0.871 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, J=6.4 Hz, 21-H), 2.83 (2H, m), 3.86 (1H, m, 3-H), 5.93, 6.63 (each 1H, d, J=11.5 Hz, 6, 7-H), 6.51 (1H, d, J=86.6 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −134.8 (d, J=86.6 Hz). EI-MS *m/z* (%): 402 (M^+, 100), 384 (7), 382 (4), 364 (4), 317 (20), 289 (42), 271 (18), 269 (7), 259 (47), 194 (12), 176 (16), 154 (20), 136 (39), 135 (67). HR-EI-MS *m/z*: 402.3320 (Calcd for $C_{27}H_{43}OF$: 402.3298). UV λ_{max} (95% EtOH): 270 nm (ε 22000).

13c: ^{1}H-NMR ($CDCl_3$) δ: 0.55 (3H, s, 18-H), 0.868, 0.873 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, J=6.7 Hz, 21-H), 2.67 (1H, m), 2.82 (2H, m), 3.88 (1H, m, 3-H), 5.83, 6.35 (each 1H, d, J=11.5 Hz, 6, 7-H), 6.69 (1H, d, J=86.7 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −135.4 (d, J=86.7 Hz). EI-MS *m/z* (%): 402 (M^+, 84), 384 (7), 382 (3), 364 (4), 317 (11), 289 (25), 271 (13), 269 (7), 259 (21), 194 (6), 176 (13), 154 (50), 136 (89), 135 (100). HR-EI-MS *m/z*: 402.3268 (Calcd for $C_{27}H_{43}OF$: 402.3298). UV λ_{max} (95% EtOH): 269 nm.

Thermal Desulfonylation of **10b**: A solution of (6*R*,19*S*)-**10b** (10.0 mg, 0.02 mmol) in 95% EtOH was heated at 80 °C for 1 h in the presence of $NaHCO_3$ (35 mg, 0.42 mmol). The mixture was cooled to room temperature and filtered. The filtrate was partitioned between water and AcOEt and the aqueous layer was extracted with AcOEt. The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on silica gel (4 g) with 80% AcOEt–hexane to give **19** (8.0 mg, 83.0%).

19: ^{1}H-NMR ($CDCl_3$) δ: 0.63 (3H, s, 18-H), 0.87, 0.88 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.93 (3H, d, J=6.1 Hz, 21-H), 2.12 (1H, m), 2.27 (1H, m, 2-H), 2.48, 2.57 (each 1H, m, 4-H), 4.43 (1H, m, 3-H), 4.94 (1H, m, 1-H), 5.43 (1H, s, 7-H), 6.61 (1H, d, J=2.0 Hz, 19-H).

(5*Z*,7*E*,10*Z*)-, (5*E*,7*E*,10*E*)- and (5*E*,7*E*,10*Z*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatri-ene-1,3-diol (2b, 12b and 13b) To a stirred solution of **10b** (8.6 mg, 0.02 mmol) in dry ether (1 ml) was added $LiAlH_4$ (5.4 mg, 0.14 mmol) and the mixture was stirred at room temperature for 30 min and then quenched with sat. sodium potassium tartarate. The resulting slurry was filtered and washed with ether. The ether layer was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (3 g) using 40—50% AcOEt–hexane to afford **2b** (0.9 mg, 12.1%), **12b** (1.3 mg, 17.4%) and the unreacted starting material (0.9 mg, 10.2%).

The same procedure and work-up as described in the preceding experiment, but using **9b** (1.2 mg, 0.0025 mmol) gave **13b** (0.32 mg, 30.6%) and the unreacted starting material (0.8 mg, 66.7%).

2b: ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, s, 18-H), 0.863, 0.867 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.91 (3H, d, J=6.3 Hz, 21-H), 2.19 (1H, m), 2.32 (1H, m), 2.68 (1H, m), 2.80 (1H, m, 9-H), 4.16 (1H, m, 3-H), 5.09 (1H, br s, 1-H), 5.90 (1H, d, J=11.1 Hz, 7-H), 6.46 (1H, d, J=11.1 Hz, 6-H), 6.50 (1H, d, J=86.0 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −129.8 (d, J=86.0 Hz). EI-MS *m/z* (%): 418 (M^+, 6), 400 (5), 398 (5), 380 (10), 362 (52), 347 (8), 305 (5), 287 (5), 285 (5), 267 (8), 249 (34), 195 (35), 135 (100). HR-EI-MS *m/z*: 418.3224 (Calcd for $C_{27}H_{43}O_2F$: 418.3247). IR: 3290 cm^{-1}. UV λ_{max} (95% EtOH): 262 nm.

12b: ^{1}H-NMR ($CDCl_3$) δ: 0.57 (3H, s, 18-H), 0.87, 0.88 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.93 (3H, d, J=6.3 Hz, 21-H), 2.19 (1H, m), 2.32 (1H, m), 2.68 (1H, m), 2.80 (1H, m, 9-H), 3.07 (1H, dd, 4-H), 4.19 (1H, m, 3-H), 4.34 (1H, br s, 1-H), 5.97 (1H, d, J=11.6 Hz, 7-H), 6.68 (1H, d, J=11.6 Hz, 6-H), 6.74 (1H, d, J=83.4 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −132.8 (d, J=83.4 Hz). EI-MS *m/z* (%): 418 (M^+, 100), 398 (61), 380 (23), 362 (54), 347 (14), 305 (30), 287 (19), 285 (36), 267 (30), 249 (53), 195 (40), 135 (88). HR-EI-MS *m/z*: 418.3234 (Calcd for $C_{27}H_{43}O_2F$: 418.3247). UV λ_{max} (95% EtOH): 272 nm.

13b: ^{1}H-NMR ($CDCl_3$) δ: 0.55 (3H, s, 18-H), 0.868, 0.872 (each 3H, d, J=6.5 Hz, 26, 27-H), 0.93 (3H, d, J=6.2 Hz, 21-H), 2.31 (1H, m), 2.81 (1H, m, 9-H), 3.15 (1H, m, 4-H), 4.15 (1H, m, 3-H), 5.05 (1H, d, J=3.2 Hz, 1-H), 5.87 (1H, d, J=11.4 Hz, 7-H), 6.38 (1H, d, J=11.4 Hz, 6-H), 6.69 (1H, d, J=85.6 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −133.2 (d, J=85.6 Hz). EI-MS *m/z* (%): 418 (M^+, 12), 398 (26), 380 (31), 362 (51), 347 (13), 305 (7), 287 (7), 285 (15), 267 (26), 249 (44), 195 (41), 135 (100). HR-EI-MS *m/z*: 418.3232 (Calcd for $C_{27}H_{43}O_2F$: 418.3247). UV λ_{max} (95% EtOH): 269 nm.

(5*Z*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-3-ol (2c) A solution of **12c** (20.0 mg, 0.05 mmol) in benzene–EtOH (5 : 95, v/v, 200 ml) was cooled to 0 °C and with Ar passed through it the mixture was irradiated using halogen lamp (200 W) in the presence of anthracene (44.0 mg, 0.25 mmol). After being stirred for 15 min, solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (5 g) using 4% AcOEt–hexane to yield **2c** (15.4 mg, 76.8%).

A solution of **13c** (4.1 mg, 0.01 mmol) and anthracene (9 mg, 0.05 mmol) dissolved in benzene–EtOH (5 : 95, 100 ml) was photo-irradiated for 10 min and the same work-up and purification as described above gave **2c** (2.7 mg, 65.9%).

2c: ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, J=6.4 Hz, 21-H), 2.56 (2H, m), 2.78 (1H, m), 3.93 (1H, m, 3-H), 5.93, 6.28 (each 1H, d, J=11.1 Hz, 6, 7-H), 6.51 (1H, d, J=87.4 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −132.5 (d, J=87.4 Hz). EI-MS *m/z* (%): 402 (M^+, 36), 384 (21), 382 (8), 364 (16), 317 (5), 289 (13), 271 (19), 269 (6), 259 (11), 154 (45), 136 (70), 135 (100). HR-EI-MS *m/z*: 402.3301 (Calcd for $C_{27}H_{43}OF$: 402.3298). UV λ_{max} (95% EtOH): 260 nm (ε 20900).

(5*Z*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3-diol (3b) A stirred, cold (0 °C) solution of **12b** (7.5 mg, 0.02 mmol), anthracene (15.9 mg, 0.090 mmol) in benzene–EtOH (5 : 95; v/v; 150 ml) was purged with Ar and irradiated at 0 °C for 60 min (halogen lamp; 200 W). The solvent was evaporated to dryness and the residue was chromatographed on silica gel (3 g). A mixture of **2b** and **13b** (6.1 mg) was eluted with 30% AcOEt–hexane and **3b** (549 mg, 7.3%) was eluted with 70% AcOEt–hexane. The mixture of **2b** and **13b** was further purified by HPLC [YMC pack ODS-AM SH-342-5AM 120A; 150 mm×20 mm; 8% H_2O–MeOH; 8 ml/min.; room temperature] to afford **2b** (4.45 mg, 59.3%) and **13b** (227 mg, 3.0%).

3b: ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, J=6.3 Hz, 21-H), 2.14 (1H, m), 2.28 (1H, dd, J=13.0, 8.6 Hz, 4-H), 2.66 (1H, dd, J=13.0, 3.9 Hz, 4-H), 2.82 (1H, m, 9-H), 4.20 (1H, m, 3-H), 4.44 (1H, dd, J=9.2, 4.7 Hz, 1-H), 5.62 (1H, dd, J=11.3, 5.4 Hz, 7-H), 6.52 (1H, d, J=11.3 Hz, 6-H), 6.70 (1H, d, J=84.0 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −127.8 (broad s). EI-MS *m/z* (%): 418 (M^+, 55), 400 (7), 398 (12), 380 (22), 362 (100), 347 (21), 305 (16), 287 (9), 285 (10), 267 (16), 249 (68), 195 (52), 135 (43). HR-EI-MS *m/z*: 418.3221 (Calcd for $C_{27}H_{43}O_2F$: 418.3247). UV λ_{max} (95% EtOH): 264 nm.

Thermal Isomerization of 2c and 2b: (5*Z*,7*E*,10*Z*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-3-ol (3c) A solution of **2c** (10 mg, 0.025

mmol) in deoxygenated, dry octane (10 ml) was heated at 120 °C for 4 h in a sealed tube and evaporated to dryness to give a mixture of **2c** : **3c** (approximately 85 : 15 by HPLC analysis). The residue was purified by HPLC (LiChrosorb Si60, 250 mm×10 mm, 1% 2-PrOH–hexane, 6 ml/min, room temperature) to give **2c** (6.98 mg) and its isomer **3c** (1.4 mg).

A solution of **2b** (1.23 mg, 0.003 mmol) in dry octane (2 ml) was heated at 120 °C for 2.5 h in a sealed tube and evaporated *in vacuo*. The residue (**2b** : **3b**=approximately 85 : 15 by HPLC analysis) was purified by HPLC (the same conditions as described above except using 10% 2-PrOH–hexane as a mobile phase) to afford **2b** (0.902 mg) and its isomer **3b** (0.145 mg).

3c: ^{1}H-NMR ($CDCl_3$) δ: 0.55 (3H, s, 18-H), 0.86, 0.87 (each 3H, d, J=6.6 Hz, 26, 27-H), 0.92 (3H, d, J=6.2 Hz, 21-H), 2.60 (1H, dd, J=13.2, 3.5 Hz, 4-H), 2.81 (1H, m, 9-H), 3.95 (1H, tt, J=7.3, 3.6 Hz, 3-H), 5.63 (1H, d, J=11.3, 5.3 Hz, 7-H), 6.37 (1H, d, J=11.3 Hz, 6-H), 6.47 (1H, d, J=85.5 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −127.5 (d, J=85.5 Hz). UV λ_{max} (95% EtOH): 264 nm.

(6*S*)- and (6*R*)-SO_2-Adduct of (5*Z*,7*E*)-1,25-Bis-(methoxymethyloxy)-3-(*tert*-butyldimethylsilyloxy)-9,10-seco-5,7,10(19)-cholestatriene (6j and 7j) (5*E*)-1α,25-Dihydroxyvitamin D_3 3-*tert*-butyldimethylsilyl ether **5f** (190 mg, 0.003 mmol) was synthesized by the published procedure[14,20,21] and was converted to the corresponding (6*S*)- and (6*R*)-SO_2-adducts **6f** and **7f** (127 mg, 60.2%, 6*S* : 6*R*=2 : 3) as described for the preparation of **6g** and **7g**.

A mixture of **6f** and **7f** (320 mg, 0.54 mmol), *N*,*N*-diisopropylethylamine (1.39 g, 10.8 mmol) and chloromethyl methyl ether (434 mg, 5.4 mmol) in dry CH_2Cl_2 (10 ml) was stirred for 2 h at 0 °C and for 7 h at room temperature. The mixture was acidified with 1% HCl and extracted with CH_2Cl_2. The organic phase was washed with 5% $NaHCO_3$, brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (30 g) with 10% AcOEt–hexane to give (6*S*)-**6j** (105 mg) and (6*R*)-**7j** (145 mg) (total 68%, *ca.* 6*S* : 6*R*=2 : 3).

6f: ^{1}H-NMR ($CDCl_3$) δ: 0.057, 0.07 (each 3H, s, Si–Me), 0.65 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.4 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.23 (1H, m), 2.60 (1H, m, 9-H), 3.70, 4.01 (each 1H, br d, J=15.9 Hz, 19-H), 4.18 (1H, m, 3-H), 4.38 (1H, m, 1-H), 4.61 (1H, d, J=9.5 Hz, 6-H), 4.70 (1H, d, J=9.5 Hz, 7-H).

7f: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, Si–Me), 0.56 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.95 (3H, d, J=6.3 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.34 (1H, m), 2.57 (1H, m, 9-H), 3.70, 4.01 (each 1H, br d, J=15.9 Hz, 19-H), 4.18 (1H, m, 3-H), 4.38 (1H, m, 1-H), 4.65 (1H, d, J=10.1 Hz, 6-H), 4.80 (1H, d, J=10.1 Hz, 7-H).

6j: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.07 (each 3H, s, Si–Me), 0.65 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.4 Hz, 21-H), 1.21 (6H, s, 26, 27-H), 2.19 (1H, m), 2.62 (1H, m, 9-H), 3.37, 3.38 (each 3H, s, OMe), 3.66 (1H, br d, J=15.8 Hz, 19-H), 3.98 (1H, dm, J=15.8 Hz, 19-H), 4.16 (1H, m, 3-H), 4.21 (1H, m, 1-H), 4.59 (1H, d, J=7.0 Hz, OCH_2O), 4.65 (1H, d, J=9.5 Hz, 6-H), 4.71 (2H, s, OCH_2O), 4.72 (1H, d, J=9.5 Hz, 7-H). EI-MS *m*/*z* (%): 618 (M^+-SO_2, 13), 588 (16), 558 (44), 496 (63), 455 (12), 437 (17), 424 (14), 379 (24), 362 (28), 265 (20), 251 (36), 178 (98), 133 (77), 75 (100). HR-EI-MS *m*/*z*: 618.4698 (M^+-SO_2; Calcd for $C_{37}H_{66}O_5Si$: 618.4680).

7j: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, Si–Me), 0.56 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.2 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.35 (1H, m), 2.56 (1H, m, 9-H), 3.37, 3.69 (each 3H, s, OMe), 3.67 (1H, br d, J=16.0 Hz, 19-H), 3.96 (1H, br d, J=16.0 Hz, 19-H), 4.13 (1H, m, 3-H), 4.22 (1H, m, 1-H), 4.60, 4.73 (each 1H, d, J=7.0 Hz, OCH_2O), 4.62 (1H, d, J=10.0 Hz, 6-H), 4.71 (2H, s, OCH_2O), 4.80 (1H, d, J=10.0 Hz, 7-H). EI-MS *m*/*z* (%): 618 (M^+-SO_2, 22), 588 (26), 558 (72), 496 (62), 455 (10), 437 (15), 424 (16), 379 (23), 362 (21), 265 (20), 251 (29), 178 (100), 133 (69), 75 (75). HR-EI-MS *m*/*z*: 618.4655 (M^+-SO_2; Calcd for $C_{37}H_{66}O_5Si$: 618.4680).

(6*R*,19*S*)-SO_2-Adduct of (5*Z*,7*E*,10*Z*)-1,25-Bis-(methoxymethyloxy)-3-(*tert*-butyldimethylsilyloxy)-19-fluoro-9,10-seco-5,7,10(19)-cholestatriene (10j) To a stirred, cold (−78 °C) solution of (6*R*)-**7j** (35.0 mg, 0.05 mmol), *N*-fluorobenzenesulfonimide (19.4 mg, 0.06 mmol), HMPA (22.3 ml, 0.06 mmol) and dry THF (2 ml) was added LiHMDS (1 M solution in THF, 62 μl, 0.06 mmol). The mixture was stirred for 10 min, quenched with sat. NH_4Cl and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on silica gel (5 g) using 0.5% AcOEt–hexane to afford **10j** (7.7 mg, 21%), **17j** (9.7 mg, 23.0%) and the unreacted starting material (17.7 mg, 50%).

10j: ^{1}H-NMR ($CDCl_3$) δ: 0.05, 0.07 (each 3H, s, Si–Me), 0.56 (3H, s, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.94 (3H, d, J=6.0 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.54 (1H, m, 9-H), 3.37, 3.40 (each 3H, s, OMe), 4.31 (1H, m, 3-H), 4.44 (1H, m, 1-H), 4.65—4.80 (6H, m, OCH_2O, 6, 7-H), 5.70 (1H, d, J=56.8 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −166.4 (d, J=56.8 Hz). EI-MS *m*/*z* (%): 636 (M^+-SO_2, 40), 606 (73), 574 (53), 544 (98), 512 (23), 135 (73), 73 (100). HR-EI-MS *m*/*z*: 636.4615 (M^+-SO_2; Calcd for $C_{37}H_{65}O_5FSi$: 636.4585).

17j: ^{1}H-NMR ($CDCl_3$) δ: 0.06, 0.09 (each 3H, s, Si–Me), 0.61 (3H, s, 18-H), 0.87 (9H, s, Si–*tert*-Bu), 0.95 (3H, d, J=6.0 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 3.37, 3.40 (each 3H, s, OMe), 4.32 (1H, m, 3-H), 4.44 (1H, m, 1-H), 4.60—4.80 (7H, m, 2×OCH_2O, 1, 6, 7-H), 5.41 (1H, s, 7-H), 6.54 (1H, d, J=2.1 Hz, 19-H).

(6*R*,19*S*)-SO_2-Adduct of (5*Z*,7*E*,10*Z*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3,25-triol (10a) A mixture of **10j** (34.7 mg, 0.05 mmol), bromotrimethylsilane (31.5 μl, 0.29 mmol) and dry CH_2Cl_2 (1.5 ml) was stirred at −40 °C for 6 h. The mixture was poured into cold 5% $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (1 g) with 50% $CHCl_3$–benzene to give **10a** (13.3 mg, 55%).

10a: ^{1}H-NMR ($CDCl_3$) δ: 0.57 (3H, s, 18-H), 0.95 (3H, d, J=6.0 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 4.27 (1H, m, 3-H), 4.65 (1H, m, 1-H), 4.75 (1H, d, J=10.3 Hz, 7-H), 4.85 (1H, br d, J=10.3 Hz, 6-H), 5.77 (1H, d, J=56.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: −165.6 (d, J=56.5 Hz). EI-MS *m*/*z* (%): 434 (M^+-SO_2, 40), 416 (24), 396 (52), 378 (45), 360 (66), 305 (17), 287 (18), 285 (25), 267 (31), 265 (36), 249 (57), 133 (100). HR-EI-MS *m*/*z*: 434.3224 (M^+-SO_2; Calcd for $C_{27}H_{43}O_3F$: 434.3196).

(5*Z*,7*E*,10*Z*)- and (5*E*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3,25-triol (2a and 12a) To a stirred suspension of $LiAlH_4$ (8.1 mg, 0.21 mmol) in dry Et_2O (0.25 ml) was added a solution of **10a** (13.3 mg, 0.03 mmol) in dry Et_2O (0.25 ml) and the slurry was stirred for 30 min at room temperature. Excess of $LiAlH_4$ was decomposed with sat. sodium potassium tartarate. The resulting gray salt was filtered and washed with excess of Et_2O. The filtrate was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on silica gel (1 g) with 10% AcOEt–hexane to give **12a** (1.8 mg, 15%) and **2a** (0.45 mg, 4%).

12a: ^{1}H-NMR ($CDCl_3$) δ: 0.58 (3H, s, 18-H), 0.95 (3H, d, J=6.4 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.25 (1H, m), 2.68 (1H, m), 2.81 (1H, m, 9-H), 3.07 (1H, dd, J=13.7, 3.7 Hz, 4-H), 4.19 (1H, tt, J=10.0, 4.4 Hz, 3-H), 4.34 (1H, t, J=3.6 Hz, 1-H), 5.97 (1H, d, J=11.5 Hz, 7-H), 6.68 (1H, d, J=11.5 Hz, 6-H), 6.75 (1H, d, J=83.4 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −132.6 (d, J=83.4 Hz). ^{13}C-NMR (CD_2Cl_2–CD_3OD=2 : 1) δ: 12.3, 19.1, 21.5, 22.9, 24.2, 28.2, 29.0, 29.1, 29.6, 36.8, 37.1, 37.2, 41.2, 42.5, 44.9, 46.5, 57.2, 57.3, 65.6, 67.7 (d, J=9.0 Hz), 71.3, 116.5, 116.5, 125.7 (d, J=6.1 Hz), 127.7 (d, J=5.7 Hz), 145.6, 145.8 (d, J=264.4 Hz). EI-MS *m*/*z* (%): 434 (M^+ 59), 416 (35), 398 (19), 396 (33), 378 (21), 360 (52), 305 (31), 287 (32), 285 (31), 269 (30), 267 (36), 249 (66), 135 (100). HR-EI-MS *m*/*z*: 434.3169 (Calcd for $C_{27}H_{43}O_3F$: 434.3196). UV λ_{max} (95% EtOH): 269 nm.

2a: ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, s, 18-H), 0.93 (3H, d, J=6.4 Hz, 21-H), 1.21 (6H, s, 26, 27-H), 2.18 (1H, t, J=11.6 Hz, 4-H), 2.31 (1H, m, 2-H), 2.67 (1H, dm, J=11.6 Hz, 4-H), 2.80 (1H, m, 9-H), 4.17 (1H, tt, J=10.9, 4.4 Hz, 3-H), 5.08 (1H, t, J=3.1 Hz, 1-H), 5.90 (1H, d, J=11.1 Hz, 7-H), 6.46 (1H, d, J=11.1 Hz, 6-H), 6.50 (1H, d, J=86.1 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −129.6 (d, J=86.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.3, 19.0, 21.0, 22.5, 23.6, 27.9, 29.4, 29.6, 29.9, 36.3, 36.6, 40.7, 42.0, 44.6, 46.2, 46.3, 56.5, 56.7, 63.1 (d, J=6.2 Hz), 66.5, 71.4, 116.6, 121.4 (d, J=4.1 Hz), 126.1, 126.7 (d, J=6.1 Hz), 144.5, 146.5 (d, J=267.9 Hz). EI-MS *m*/*z* (%): 434 (M^+, 13), 416 (17), 398 (13), 396 (18), 378 (25), 360 (52), 305 (8), 287 (16), 285 (11), 269 (9), 267 (13), 249 (32), 135 (100). HR-EI-MS *m*/*z*: 434.3204 (Calcd for $C_{27}H_{43}O_3F$: 434.3196). UV λ_{max} (95% EtOH): 261 nm.

(5*E*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3,25-triol (12a) (6*S*)-SO_2-adduct **6j** (34.4 mg, 0.05 mmol) was fluorinated as described for the preparation of **10j** to give **8j** and **9j** (an approximately 1 : 1 ratio, 3.1 mg, 9%).

The epimeric compounds **8j** and **9j** (28.1 mg, 0.04 mmol) were treated with bromotrimethylsilane as described for the preparation of **10a** affording **8a** and **9a** (10.4 mg, 52%).

The triols **8a** and **9a** (7.2 mg, 0.014 mmol) were reduced with $LiAlH_4$ as described above to give **12a** (0.23 mg, 4%) and **13a** (0.25 mg, 4%).

8j and **9j**: ^{1}H-NMR ($CDCl_3$) δ: 0.07, 0.08 (each 3H, s, Si–Me), 0.63, 0.66 (3H, s, *ca.* 1 : 1, 18-H), 0.88 (9H, s, Si–*tert*-Bu), 0.95 (3H, d, J=6.0 Hz, 21-H), 1.21 (6H, s, 26, 27-H), 2.54 (1H, m, 9-H), 3.37, 3.40 (3H, s, *ca.* 1 : 1, OMe), 3.38, 3.42 (3H, s, *ca.* 1 : 1, OMe), 4.21 (1H, m, 3-H), 4.46 (1H, m, 1-H), 4.6—4.8 (6H, m, OCH_2O, 6, 7-H), 5.50, 5.70 (1H, d, J=56.0 Hz, *ca.*

1 : 1, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −163.1, −157.2 (each d, J=56.0 Hz, *ca.* 1 : 1). **8a** and **9a**: ^{1}H-NMR ($CDCl_3$) δ: 0.65, 0.66 (3H, s, *ca.* 1 : 1, 18-H), 0.94 (3H, d, J=6.0 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 4.27 (1H, m, 3-H), 4.55—4.90 (3H, m, 1, 6, 7-H), 5.60, 5.76 (1H, d, J=56.0 Hz, *ca.* 1 : 1, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −163.5, −156.9 (each d, J=56.0 Hz, *ca.* 1 : 1).

13a: ^{1}H-NMR ($CDCl_3$) δ: 0.56 (3H, s, 18-H), 0.95 (3H, d, J=6.4 Hz, 21-H), 1.22 (6H, s, 26, 27-H), 2.31 (1H, m), 2.81 (1H, m, 9-H), 3.15 (1H, dm, J=13.2 Hz, 4-H), 4.16 (1H, tt, J=11.0, 4.3 Hz, 3-H), 5.05 (1H, br s, 1-H), 5.87 (1H, d, J=11.5 Hz, 7-H), 6.38 (1H, d, J=11.5 Hz, 6-H), 6.69 (1H, d, J=86.5 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −133.2 (d, J=86.5 Hz). ^{13}C-NMR (CD_2Cl_2–CD_3OD=2 : 1) δ: 12.3, 19.1, 21.5, 22.8, 24.1, 28.2, 29.0, 29.1, 29.6, 36.8, 37.1, 37.9, 41.1, 42.0, 44.8, 46.5, 57.1, 57.3, 62.5 (d, J=5.9 Hz), 65.4, 71.3, 116.3, 122.8, 127.6 (d, J=6.2 Hz), 128.4 (d, J=6.2 Hz), 144.1 (d, J=266.1 Hz), 145.6. EI-MS *m/z* (%): 434 (M^+, 25), 416 (18), 398 (10), 396 (19), 378 (15), 360 (61), 305 (13), 287 (18), 285 (21), 269 (15), 267 (21), 249 (53), 135 (100). HR-EI-MS *m/z*: 434.3198 (Calcd for $C_{27}H_{43}O_3F$: 434.3196). UV λ_{max} (95% EtOH): 269 nm.

(5*Z*,7*E*,10*E*)-19-Fluoro-9,10-seco-5,7,10(19)-cholestatriene-1,3,25-triol (3a) A stirred, cold (0 °C) solution of **12a** (0.93 mg, 0.002 mmol), anthracene (8 mg, 0.02 mmol) in benzene–EtOH (1 : 9; 100 ml) was purged with Ar and irradiated at 0 °C for 20 min (halogen lamp, 200 W). The solvent was evaporated to dryness. The residue was purified by HPLC [LiChrosorb Si 60 (250 mm×10 mm); 10% iso-PrOH–hexane; 7 ml/min; room temperature] to give **2a** (0.96 mg, 52%) and **3a** (0.16 mg, 9%).

3a: ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, s, 18-H), 0.93 (3H, d, J=6.4 Hz, 21-H), 1.21 (6H, s, 26, 27-H), 2.13 (1H, m, 2-H), 2.27 (1H, dd, J=13.0, 8.5 Hz, 4-H), 2.66 (1H, dd, J=13.0, 3.8 Hz, 4-H), 2.82 (1H, m, 9-H), 4.20 (1H, tt, J=8.5, 3.8 Hz, 3-H), 4.43 (1H, dd, J=5.5, 3.8 Hz, 1-H), 5.63 (1H, d, J=11.3, 5.4 Hz, 7-H), 6.51 (1H, d, J=11.3 Hz, 6-H), 6.70 (1H, d, J=83.8 Hz, 19-H). ^{19}F-NMR ($CDCl_3$) δ: −128.0 (br signal). ^{13}C-NMR ($CDCl_3$) δ: 12.2, 19.0, 21.0, 22.4, 23.8, 27.6, 29.36, 29.39, 29.5, 36.3, 36.6, 40.7, 43.2, 44.6, 45.1, 46.1, 56.5, 56.8, 66.8, 67.7 (d, J=9.5 Hz), 71.4, 117.9 (d, J=3.0 Hz), 122.0 (d, J=4.8 Hz), 124.9, 126.7, 143.4 (d, J=265.2 Hz), 144.4. EI-MS *m/z* (%): 434 (M^+, 28), 416 (31), 398 (13), 396 (11), 378 (20), 360 (100), 305 (16), 287 (14), 285 (10), 269 (14), 267 (15), 249 (69), 135 (42). HR-EI-MS *m/z*: 434.3180 (Calcd for $C_{27}H_{43}O_3F$: 434.3196). UV λ_{max} (95% EtOH): 264 nm.

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