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# Synthesis of 1α-Fluorovitamin $D_3$

ETSUO OHSHIMA,[a] SUGURU TAKATSUTO,[a] NOBUO IKEKAWA,*,[a] and Hector F. DELUCA[b]

*Department of Chemistry, Tokyo Institute of Technology,[a] Ookayama, Meguro-ku, Tokyo 152, Japan and Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin,[b] Madison, Wisconsin 53706, U.S.A.*

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1α-Fluorovitamin $D_3$ has been synthesized from 6β-acetoxy-5α-cholest-1-en-3-one (**2**) *via* 1α-fluorocholesterol (**11**). The key reaction was the *trans* diaxial ring opening of the 1β,2β-epoxide **5** with potassium hydrogen difluoride in ethyleneglycol by heating. The resulting 1α-fluoro-2β,3β-diol was subjected to regeneration of the 5-ene function and reductive removal of the 2β-hydroxyl group by Barton's method to give 1α-fluorocholesterol (**11**). Transformation of **11** into 1α-fluorovitamin $D_3$ led to revision of the previously reported stereochemical assignment of 1α,25-difluorovitamin $D_3$.

**Keywords**——vitamin $D_3$; 1α-fluorovitamin $D_3$; 1α,25-difluorovitamin $D_3$; 1α-fluorocholesterol; hydroxyl group fluorination

It is well known that vitamin $D_3$ undergoes metabolic transformation before eliciting its biological activities. The major circulating form of the vitamin, 25-hydroxyvitamin $D_3$, is further hydroxylated by kidney to yield 1α,25-dihydroxyvitamin $D_3$ or (24*R*)-24,25-dihydroxyvitamin $D_3$. The physiological actions of hormonal 1α,25-dihydroxyvitamin $D_3$ on intestine, skeleton, and a variety of other target tissues are well established,[1,2] while those of (24*R*)-24,25-dihydroxyvitamin $D_3$ are still controversial.[3] Our approach to clarify the problems has been the use of fluorinated vitamin $D_3$ analogues. We synthesized 24,24-difluoro-25-hydroxyvitamin $D_3$[4] and 24,24-difluoro-1α,25-dihydroxyvitamin $D_3$[5] and examined their biological activities.[6] As a result, we concluded that 24-hydroxylation does not play an important role in the known function of vitamin D.

The vitamin $D_3$ analogues blocked for hydroxylation at the 1α-position by fluorine, *i.e.*, 1α-fluoro-25-hydroxyvitamin $D_3$ and (24*R*)-1α-fluoro-24,25-dihydroxyvitamin $D_3$, may also be useful tools to clarify the biological significance of 1α-hydroxylation and 24-hydroxylation. Although 1-fluorovitamin $D_3$[7] and 1,25-difluorovitamin $D_3$[8] have already been prepared from 1α-hydroxyvitamin $D_3$ and 1α,25-dihydroxyvitamin $D_3$, respectively, by direct fluorination with dimethylaminosulphurtrifluoride (DAST), the configuration at the C-1 position remained uncertain. Thus, we have investigated an alternative approach to the 1α-fluorovitamin $D_3$ analogues, which will allow us to determine unambiguously the orientation of fluorine introduced at the C-1 position. In this paper, we describe the regio- and stereoselective introduction of fluorine at the 1α-position of the steroid skeleton and the synthesis of 1α-fluorovitamin $D_3$.

6β-Acetoxy-1β,2β-epoxy-5α-cholestan-3β-ol (**5**), the key compound for fluorination at the C-1 position, was prepared from the known 6β-acetoxy-5α-cholest-1-en-3-one (**2**).[9] Reduction of **2** with one equivalent of lithium aluminium hydride at −10 °C for 15 min gave an epimeric mixture of the allylic alcohol **3**. Hydroxy-directing epoxidation[10] of **3** with *m*-chloroperbenzoic acid gave two separable epoxides, the less polar epoxide **4**, mp 80—81 °C,

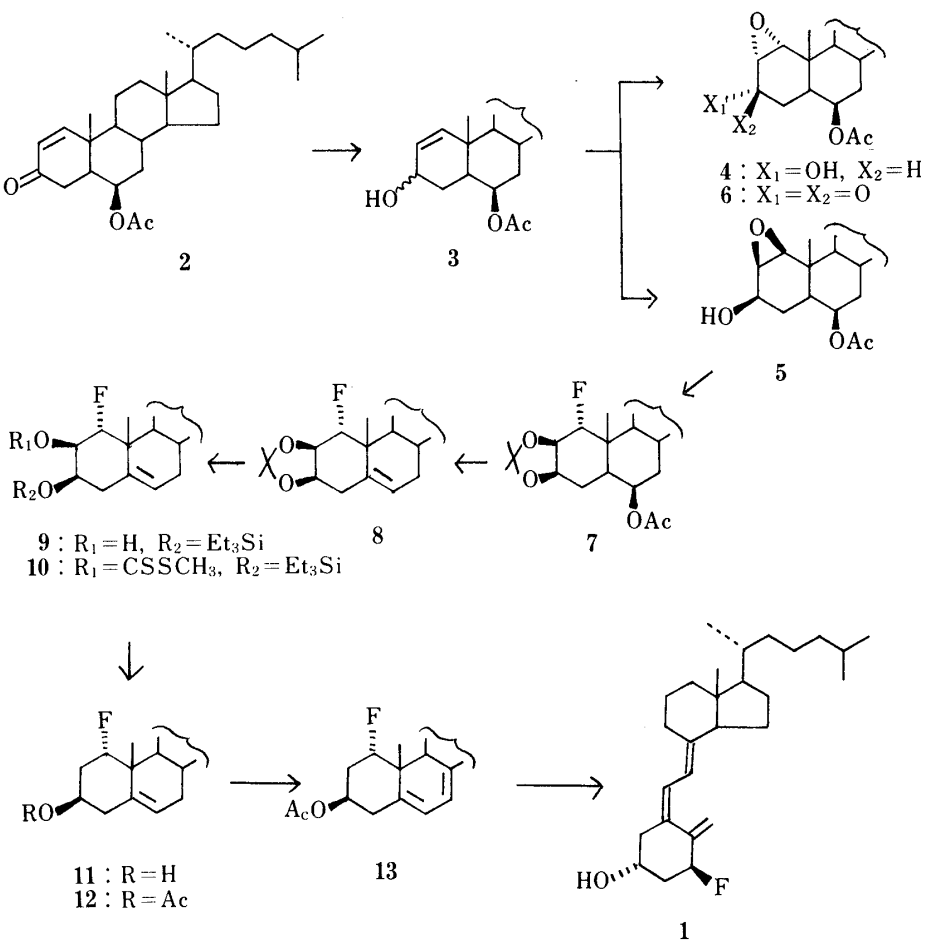


Chart 1

and the more polar epoxide **5**, mp 121—123 °C, in 35 and 43% yields, respectively, from **2**. The stereochemistry of **4** and **5** was determined as follows. Oxidation of the less polar epoxide **4** with Jones reagent gave the known 6$\beta$-acetoxy-1$\alpha$,2$\alpha$-epoxy-5$\alpha$-cholestan-3-one (**6**).[9] Thus, the more polar epoxide **5** was assigned as 6$\beta$-acetoxy-1$\beta$,2$\beta$-epoxy-5$\alpha$-cholestan-3$\beta$-ol, since it is well known that in the steroidal 1-en-3-ol system epoxidation with peracid proceeds according to Henbest's rule.[10]

Introduction of fluorine at the 1$\alpha$-position of the 1$\beta$,2$\beta$-epoxyalcohol **5** was performed regio- and stereoselectively. Treatment of **5** with potassium hydrogen difluoride in ethyleneglycol at 160 °C for 7 h and the subsequent acetonide formation provided the 1$\alpha$-fluoroacetonide **7**; $\delta$ 4.65 (1H, dd, $J$=44 and 3 Hz, 1$\beta$-H), in 45% yield after chromatographic purification. The $\alpha$-orientation of fluorine of **7** was predicted from the *trans* diaxial opening of the epoxide[11] and the facile acetonide formation of the resulting 2$\beta$,3$\beta$-diol. The assignment was supported by proton nuclear magnetic resonance ($^1$H-NMR) analysis of the 5-ene derivative **8** as follows. Compound **7** was saponified with 5% KOH–MeOH under reflux and then dehydrated with $POCl_3$ in pyridine to give, in 90% yield, the 5-ene **8**, mp 140—142 °C. In its $^1$H-NMR spectrum, the fluoroacetonide **8** showed a characteristic signal due to 1$\beta$-H at $\delta$ 4.72 as a double doublet with coupling constants of 44 and 3 Hz. The large coupling constant (44 Hz) was ascribed to the geminal hydrogen–fluorine coupling, and the small one (3 Hz) to the vicinal coupling between 1$\beta$-H and 2$\alpha$-H. From an examination of a Dreiding model, the dihedral angle between 1$\beta$-H and 2$\alpha$-H of **8** was *ca.* 60°, which is in good agreement with that predicted from the observed coupling constant (3 Hz). Another characteristic signal was the one due to 19-H at $\delta$ 1.15 as a doublet with the coupling constant

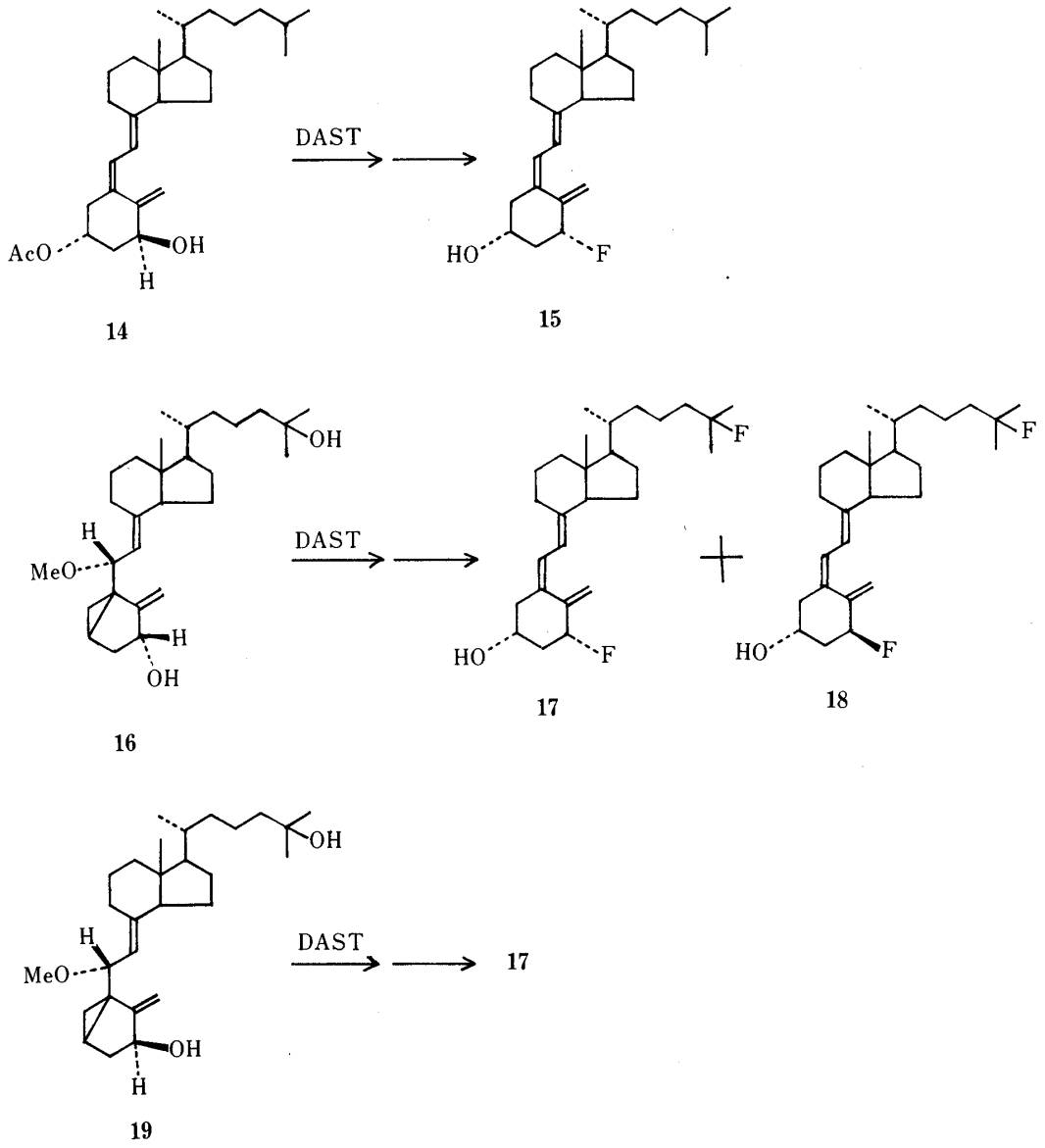


Chart 2

of 3 Hz. This splitting can be ascribed to a long-range W-type coupling between 19-H and 1α-axial fluorine.[12]

Removal of the acetonide protecting group of **8** was followed by selective silylation of the 3β-hydroxyl group with triethylsilyl chloride in pyridine at 0 °C to provide the 3β-monosilyl ether **9** in 89% yield. Reductive removal of the 2β-hydroxyl group was achieved using Barton's method.[13] Xanthate ester formation, reductive cleavage with tributyltinhydride, and deprotection gave 1α-fluorocholesterol (**11**), mp 129—130 °C, in 90% yield. In its $^1$H-NMR spectrum, compound **11** showed the signal due to 3α-H at $\delta$ 3.95, while cholesterol and 1α-hydroxycholesterol showed signals at $\delta$ 3.53 and $\delta$ 3.90, respectively. This downfield shifts of 3α-H can be ascribed to the 1,3-diaxial interaction between 1α-fluorine and 3α-hydrogen and also supports the structure of 1α-fluorocholesterol (**11**).

Transformation of **11** into 1α-fluorovitamin $D_3$ (**1**) was carried out by the standard procedure.[14] Allylic bromination of the acetate **12** with *N*-bromosuccinimide and dehydrobromination with tetrabutylammonium fluoride gave a mixture of the 4,6-diene and the 5,7-diene, from which the desired 5,7-diene **13** was isolated, in 30% yield, by treatment of the mixture in acetone with *p*-toluenesulphonic acid (to transform the 4,6-diene into the less polar 2,4,6-triene) followed by preparative thin layer chromatography (TLC). The 5,7-diene **13** was

irradiated with a medium pressure mercury lamp in a mixture of benzene–ethanol (2 : 1) for 5 min and then refluxed for 1 h to give the vitamin D acetate in 22% yield. Saponification and purification by high performance liquid chromatography afforded 1α-fluorovitamin $D_3$ (**1**); $\lambda_{max}^{EtOH}$: 271 and 243 nm; $\delta$ 4.23 (1H, m, 3α-H), 5.14 (1H, ddd, $J$=49, 5.7, and 2 Hz, 1β-H), 5.11 and 5.39 (2H, a pair of m, 19-$H_2$), 6.03 (1H, d, $J$=11 Hz, 7-H), and 6.41 (1H, d, $J$=11 Hz, 6-H).

It should be noted that our synthetic 1α-fluorovitamin $D_3$ (**1**) obtained in the present work showed the typical $^1$H-NMR resonances of the vitamin D triene system and our transformation procedure of 1α-fluorocholesterol (**11**) into 1α-fluorovitamin $D_3$ (**1**) is apparently devoid of epimerization at the C-1 position. Since the ultraviolet (UV) and $^1$H-NMR spectral data of the fluoro compound **1** are not in agreement with those previously reported for 1-fluorovitamin $D_3$, $\lambda_{max}$: 264 nm; $\delta$ 5.03 ($J_{HF}$=52 Hz), which was prepared by direct fluorination of 1α-hydroxyvitamin $D_3$ 3β-acetate (**14**) with DAST followed by deacetylation, the previously synthesized 1-fluorovitamin $D_3$ should be assigned as 1β-fluorovitamin $D_3$ (**15**). Therefore, the direct fluorination of 1α-hydroxyvitamin $D_3$ 3β-acetate with DAST was proved to proceed with inversion of the configuration of the 1α-hydroxyl group. It is of interest that introduction of fluorine at the 1α-position but not at the 1β-position dramatically affected the UV absorption of the vitamin D triene system, as shown in Fig. 1.

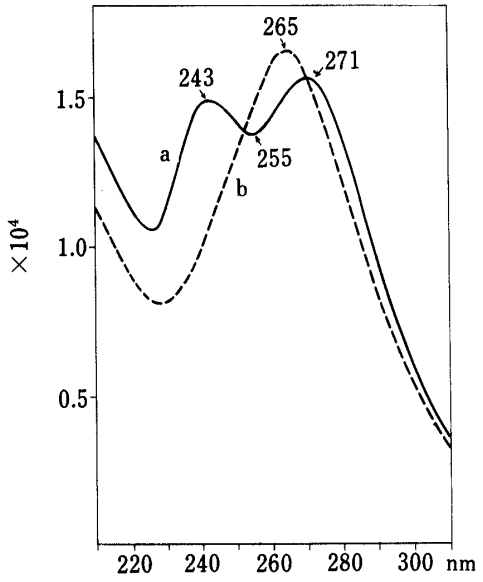


Fig. 1. Ultraviolet Spectra of 1α-Fluorovitamin $D_3$ (a) and 1β-Fluorovitamin $D_3$ (b)

It was reported in our previous paper[8] that fluorination of 1β,25-dihydroxycyclovitamin $D_3$ (**16**) with DAST and further elaboration gave a mixture of 1α,25-difluorovitamin $D_3$ (**17**), $\lambda_{max}$: 264 nm, $\delta$ 5.03 ($J_{HF}$=52 Hz), and 1β,25-difluorovitamin $D_3$ (**18**), $\lambda_{max}$: 274 and 248 nm, $\delta$ 5.14 ($J_{HF}$≒49 Hz), in a ratio of 3 : 2, while the same treatments of 1α,25-dihydroxycyclovitamin $D_3$ (**19**) gave 1α,25-difluorovitamin $D_3$ (**17**) as a sole product. A comparison of the reported spectral data of the two fluorovitamin $D_3$ compounds with those of our 1α-fluorovitamin $D_3$ (**1**) showed that the reported assignment should be revised, and that the reported 1α,25-difluorovitamin $D_3$ is in fact 1β,25-difluorovitamin $D_3$.

## Experimental

Melting points were determined with a hot-stage microscope apparatus and are uncorrected. $^1$H-NMR spectra were taken with a Hitachi R-24A or a JEOL PS-100 spectrometer, unless otherwise noted, in deuteriochloroform solution with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a Shimadzu LKB 9000S or a Hitachi M 80 spectrometer. UV spectra were obtained in ethanol solution with a Shimadzu UV-200 double beam

spectrometer. Column chromatography was performed with silica gel (E. Merck, 70—230 mesh). Preparative thin layer chromatography was carried out on precoated plates of silica gel (E. Merck, 0.25 mm thickness). The usual work-up refers to dilution with water, extraction with the organic solvent indicated in parenthesis, washing of the extract to neutrality, drying ($MgSO_4$), filtration, and removal of the solvent under reduced pressure.

**6β-Acetoxy-3ξ-hydroxy-5α-cholest-1-ene (3)**——Lithium aluminium hydride (58 mg) was added to a solution of 6β-acetoxy-5α-cholest-1-en-3-one (**2**)[9] (1.0 g, 2.26 mmol) in ether (40 ml) at −15 °C with stirring and the mixture was stirred at −15 °C for 15 min. The usual work-up (ethyl acetate) and chromatography on silica gel (70 g) with benzene–ethyl acetate (20 : 1) gave the epimeric allyl alcohols **3** (698 mg, 70%), as an amorphous solid; δ 4.30 (1H, m, 3ξ-H), 5.00 (1H, m, 6β-H), 5.36—5.92 (2H, ABq × 2, $J$ = 10 Hz, 1- and 2-H).

**6β-Acetoxy-1α,2α-epoxy-3α-hydroxy-5α-cholestane (4)**——A solution of *m*-chloroperbenzoic acid (500 mg) in $CH_2Cl_2$ (28 ml) was added dropwise to a solution of the allylic alcohol 3 (648 mg, 1.46 mmol) in $CH_2Cl_2$ (28 ml) at 0 °C. The mixture was stirred at room temperature overnight, then calcium hydroxide (10 g) was added and the whole was stirred at room temperature for 1 h. The insoluble salts were filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (40 g). Elution with benzene–ethyl acetate (15 : 1) gave the α-epoxide **4** (231 mg, 35%), mp 80—81 °C (MeOH–$H_2O$). δ 0.70 (3H, s, 18-$H_3$), 0.85 (6H, d, $J$ = 6 Hz, 26-$H_3$ and 27-$H_3$), 0.91 (3H, d, $J$ = 6 Hz, 21-$H_3$), 1.16 (3H, s, 19-$H_3$), 2.05 (3H, s, acetyl), 3.08 (2H, s, 1β-H and 2β-H), 4.08 (1H, m, $W_{1/2}$ = 18 Hz, 3β-H), and 4.92 (1H, m, 6α-H). High resolution MS, Calcd for $C_{27}H_{44}O_2$ ($M^+ - AcOH$) $m/z$ 400.3357, Found $m/z$ 400.3343.

**6β-Acetoxy-1β,2β-epoxy-3β-hydroxy-5α-cholestane (5)**——Further elution with the same solvent gave the β-epoxide **5** (289 mg, 43%), mp 121—123 °C (hexane). δ 0.75 (3H, s, 18-$H_3$), 0.86 (6H, d, $J$ = 6 Hz, 26-$H_3$ and 27-$H_3$), 0.91 (3H, d, $J$ = 6 Hz, 21-$H_3$), 1.12 (3H, s, 19-$H_3$), 2.02 (3H, s, acetyl), 3.32 (2H, s, 1α-H and 2α-H), 3.99 (1H, m, $W_{1/2}$ = 20 Hz, 3α-H), 4.92 (1H, m, 6α-H). High resolution MS, Calcd for $C_{27}H_{44}O_2$ ($M^+ - AcOH$) $m/z$ 400.3357, Found $m/z$ 400.3349.

**6β-Acetoxy-1α,2α-epoxy-5α-cholestan-3-one (6)**——A solution of the epoxyalcohol **4** (20 mg, 0.043 mmol) in acetone (2 ml) was treated with Jones reagent (1 eq) at room temperature for 15 min. The usual work-up (ether) gave the known epoxyketone **6** (20 mg), mp 141—142 °C (MeOH) (lit.[9] mp 141—142 °C). δ 0.75 (3H, s, 18-$H_3$), 1.04 (3H, s, 19-$H_3$), 2.06 (3H, s, acetyl), 2.24 (2H, br s, 4-$H_2$), 3.24 (1H, d, $J$ = 4 Hz, 1β-H), 3.46 (1H, d, $J$ = 4 Hz, 2β-H).

**6β-Acetoxy-1α-fluoro-2β,3β-isopropylidenedioxy-5α-cholestane (7)**——The β-epoxide **5** (1.4 g, 3.14 mmol) and potassium hydrogen difluoride (5.8 g) in ethyleneglycol (58 ml) were heated at 160 °C for 7 h. The usual work-up (ethyl acetate) gave a crude product, which was treated with acetone (100 ml) containing a catalytic amount of *p*-toluenesulphonic acid at room temperature for 1 h. The usual work-up (ethyl acetate) and chromatography on silica gel (40 g) with benzene gave the fluoroacetonide **7** (1.1 g, 68%), as an amorphous solid. δ 0.68 (3H, s, 18-$H_3$), 0.86 (6H, d, $J$ = 6 Hz, 26-$H_3$ and 27-$H_3$), 0.90 (3H, d, $J$ = 6 Hz, 21-$H_3$), 1.10 (3H, d, $J$ = 2.5 Hz, 19-$H_3$), 1.31 and 1.50 (6H, s × 2, acetonide), 2.04 (3H, s, acetyl), 4.00—4.40 (2H, m, 2α-H and 3α-H), 4.65 (1H, dd, $J$ = 44 and 3 Hz, 1β-H), and 5.05 (1H, m, 6α-H).

**1α-Fluoro-2β,3β-isopropylidenedioxycholest-5-ene (8)**——The acetate **7** (703 mg, 1.35 mmol) was treated with 5% KOH–MeOH (5 ml) and dioxane (20 ml) at 80 °C for 3 h. The usual work-up (ethyl acetate) gave the corresponding 6β-alcohol (628 mg, 97%), which was dissolved in pyridine (9 ml). Phosphorus oxychloride (0.4 ml) was added to the solution at 0 °C, and the mixture was stirred at room temperature for 2 h. The usual work-up (ethyl acetate) and chromatography on silica gel (10 g) with benzene gave the 5-ene **8** (544 mg, 90%), mp 140—142 °C ($CHCl_3$–MeOH), δ 0.69 (3H, s, 18-$H_3$), 0.87 (6H, d, $J$ = 6 Hz, 26-$H_3$ and 27-$H_3$), 0.91 (3H, d, $J$ = 6 Hz, 21-$H_3$), 1.15 (3H, d, $J$ = 3 Hz, 19-$H_3$), 1.34 and 1.55 (6H, s × 2, acetonide), 4.08—4.44 (2H, m, 2α-H and 3α-H), 4.72 (1H, dd, $J$ = 44 and 3 Hz, 1β-H), 5.52 (1H, m, 6-H). High resolution MS, Calcd for $C_{30}H_{49}O_2F$ ($M^+$) $m/z$ 460.3719, Found $m/z$ 460.3743.

**3β-Triethylsilyloxy-1α-fluoro-2β-hydroxycholest-5-ene (9)**——The acetonide **8** (374 mg, 0.813 mmol) was treated with MeOH–THF (1 : 1, 80 ml) containing a catalytic amount of *p*-toluenesulphonic acid at room temperature for 5 h. The usual work-up (ethyl acetate) gave the corresponding 2β,3β-diol (346 mg). A mixture of the diol (346 mg), triethylsilyl chloride (0.2 ml) and pyridine (4.5 ml) was stirred at 0 °C for 15 min. The usual work-up (ethyl acetate) and chromatography on silica gel (10 g) with benzene gave the silyl ether **9** (410 mg, 94% from **8**), mp 174—176 °C (MeOH–$CHCl_3$). δ 0.68 (3H, s, 18-$H_3$), 0.85 (6H, d, $J$ = 6 Hz, 26-$H_3$ and 27-$H_3$), 0.88—0.98 (12H, br s, 21-$H_3$ and $-SiCH_2CH_3$), 1.15 (3H, d, $J$ = 2 Hz, 19-$H_3$), 3.70—4.10 (2H, m, 2α-H and 3α-H), 4.64 (1H, dd, $J$ = 44 and 3 Hz, 1β-H), and 5.48 (1H, m, 6-H).

***O*-[3β-Triethylsilyloxy-1α-fluorocholest-5-en-2β-yl]-*S*-methyl Dithiocarbonate (10)**——A mixture of the silyl ether **9** (410 mg, 0.77 mmol), sodium hydride dispersion (60%, 120 mg), imidazole (2.0 mg), and THF (60 ml) was refluxed for 3 h under argon, then carbon disulphide (1.2 ml) was added and refluxing was continued for another 0.5 h. Then, methyl iodide (1.2 ml) was added to the mixture. The whole was refluxed for 0.5 h. The usual work-up (ethyl acetate) and chromatography on silica gel (10 g) with hexane–ethyl acetate (20 : 1) gave the xanthate ester **10** (384 mg, 80%) as a glass. δ 0.67 (3H, s, 18-$H_3$), 2.60 (3H, s, $-SCH_3$), 4.00 (1H, m, 3-H), 4.76 (1H, dd, $J$ = 44 and 4 Hz, 1β-H), 5.54 (1H, m, 6-H), and 6.00 (1H, m, 2α-H).

**1α-Fluoro-3β-hydroxycholest-5-ene (11)**——A solution of the xanthate ester **10** (135 mg, 0.216 mmol) in xylene (5 ml) was added over 0.5 h to tributyltinhydride (126 mg) with stirring and refluxing under argon. After the mixture

had been refluxed for 2 h, the solvent was evaporated off. The residue was applied to a column of silica gel (5 g). Elution with hexane gave the residual tributyltin hydride. Further elution with ethyl acetate gave the silyl ether **12** (113 mg, 98%), which was treated with tetrabutylammonium fluoride (2 ml, 2 mmol) in THF (10 ml) at room temperature overnight. The usual work-up (ethyl acetate) and chromatography on silica gel with benzene–ethyl acetate (20 : 1) gave the alcohol **11** (83.8 mg, 98%), mp 129—130 °C (MeOH). $\delta$ 0.70 (3H, s, 18-$H_3$), 0.88 (6H, d, $J$= 6 Hz, 26-$H_3$ and 27-$H_3$), 0.92 (3H, d, $J$=6 Hz, 21-$H_3$), 1.00 (3H, d, $J$=2 Hz, 19-$H_3$), 3.95 (1H, m, 3$\alpha$-H), 4.66 (1H, dm, $J$=48 Hz, 1$\beta$-H), and 5.52 (1H, m, 6-H). High resolution MS, Calcd for $C_{27}H_{45}OF$ ($M^+$) $m/z$ 404.3451, Found $m/z$ 404.3475.

**3$\beta$-Acetoxy-1$\alpha$-fluorocholesta-5,7-diene (13)**——The alcohol **11** (45 mg, 0.11 mmol) was treated with acetic anhydride (0.5 ml) and pyridine (2 ml) at room temperature for 4 h. The usual work-up (ethyl acetate) and chromatography on silica gel (4 g) with benzene gave the acetate **12** (48 mg, 98%), mp 119—120 °C (MeOH). *N*-Bromosuccinimide (26 mg) was added to a refluxing solution of the acetate **12** (48 mg, 0.108 mmol) in carbon tetrachloride (2.5 ml) and the mixture was refluxed under argon for 0.5 h. After the reaction mixture had been cooled to room temperature, the precipitate was filtered off. The filtrate was concentrated under reduced pressure below 40 °C to give the crude bromide, which was treated with THF (5 ml) containing a small amount of tetrabutylammonium bromide at room temperature under argon in the dark for 50 min. Next, a solution of tetra-*n*-butylammonium fluoride (0.5 ml, 0.5 mmol) in THF was added to the mixture. The usual work-up (ethyl acetate) gave the crude diene, which was treated with acetone (15 ml) containing a catalytic amount of *p*-toluenesulphonic acid for 15 h under argon in the dark. The usual work-up (ethyl acetate) gave a crude product (45 mg). This was purified with preparative thin layer chromatography (hexane–ethyl acetate (30 : 1), developed three times) to give the 5,7-diene **13** (13.7 mg, 30%), $Rf$=0.48, $\lambda_{max}$: 261, 270, 280, and 292 nm.

**1$\alpha$-Fluorovitamin $D_3$ (1)**——A solution of the 5,7-diene **13** (2.7 mg) in benzene (80 ml) and ethanol (40 ml) was irradiated with a medium pressure mercury lamp through a Vycol filter for 5 min with ice-cooling under argon. The reaction mixture was then refluxed for 1 h under argon. Evaporation of the solvent gave a crude product. This was purified by preparative TLC (hexane–ethyl acetate (30 : 1), developed three times) to give the vitamin $D_3$ acetate (0.567 mg, 21%), $Rf$=0.60, $\lambda_{max}$: 243 and 271 nm, $\lambda_{max}$: 255 nm. The acetate was treated overnight with a mixture of 5% KOH–MeOH (2 ml) and THF (2 ml) at room temperature under argon in the dark. The usual work-up (ethyl acetate) gave a crude product, which was purified by high performance liquid chromatography (Shimadzu LC-3A; column, Zorbax SIL, 4.6 mm i.d. × 15 cm; eluant, hexane–$CH_2Cl_2$ (1 : 2); flow rate, 0.5 ml/min; retention time, 11 min) to give 1$\alpha$-fluorovitamin $D_3$ (**1**) (0.489 mg, 95%), $\lambda_{max}$: 243 and 271 nm, $\lambda_{min}$: 255 nm. $\delta$ (400 MHz) 0.550 (3H, s, 18-$H_3$), 0.865 (6H, d, $J$=6 Hz, 26-$H_3$ and 27-$H_3$), 0.915 (3H, d, $J$=6 Hz, 21-$H_3$), 4.225 (1H, m, 3$\alpha$-H), 5.140 (1H, ddd, $J$=49, 5.7, and 2 Hz, 1-H), 5.11 and 5.39 (2H, br s × 2, 19-$H_2$), 6.03 and 6.41 (2H, ABq, $J$=11 Hz, 6-H and 7-H). MS $m/z$ 402 ($M^+$), 382, and 364.

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