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Synthesis of 20-Fluorovitamin D Analogues

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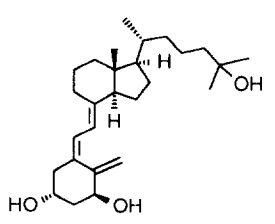
Key Words: calcitriol analogues, 20-fluoro substitution, electrophilic fluorination, calcipotriol derivatives

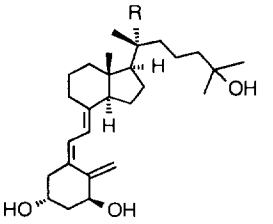
Abstract: A synthetic approach to novel 20-fluorovitamin D analogues is described. Introduction of fluorine has been performed by electrophilic fluorination followed by elaboration of biologically interesting side chain substructures.

The discovery of 1α,25-dihydroxyvitamin D_3 **1** (calcitriol) as the biologically active metabolite of vitamin D_3,[1, 2] and a deeper insight into its spectrum of functions has revitalized research in this traditional field. Besides the classical regulation of calcium and phosphorous homeostasis, calcitriol was found to inhibit proliferation and to induce differentiation of various cell types such as keratinocytes, tumor cells or lymphocytes.[3] However, the therapeutic usefulness of the natural hormone is rather limited by the inherent risk of hypercalcemia. As a consequence, considerable efforts have been made to detect synthetic analogues more or less devoid of calcium mobilizing potential but with conserved antiproliferative activity.[4, 5, 6, 7] Such compounds could eventually be useful new drugs both for treatment of hyperproliferative skin diseases (psoriasis) and for certain types of malignant tumors.

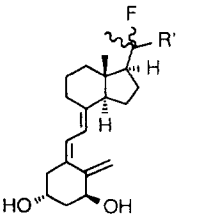
The vitamin D side chain known to be the primary site of metabolic degradation[8] has been a preferred target of synthetic efforts. As a result of this work, several assumptions on structure activity relations had to be revised. The recently published syntheses and pharmacological evaluation of 20-epi-analogues[9] (**2**) and 20-methyl derivatives[10] (**3**) (Figure 1) clearly question the notion that a natural configuration at carbon 20 is an essential prerequisite for biological activity. Stimulated by these findings we envisaged the synthesis of 20-fluoro substituted calcitriol analogues (**4**) which could be expected to display an interesting spectrum of pharmacological activities.



calcitriol **1**



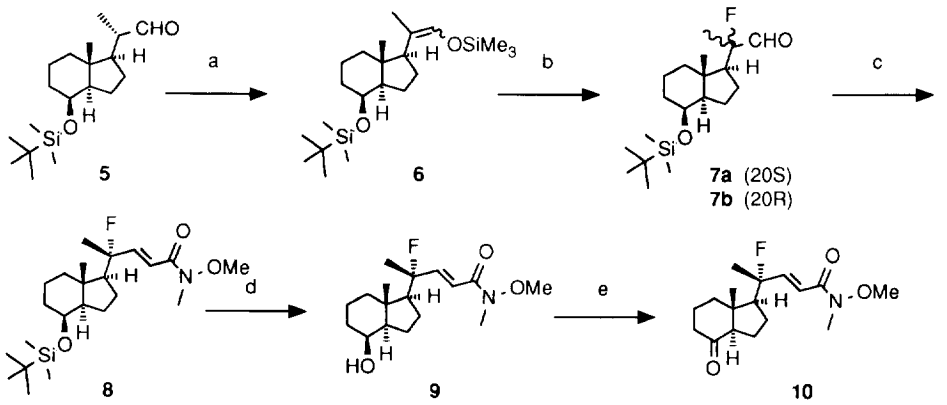
R=H, 20-epi-calcitriol **2**
R=CH_3, 20-methylcalcitriol **3**



4, R'=vitamin D side chain

Figure 1

The known steroid CD fragment **5**[11] was used for our first attempts to introduce a C-20-fluoro substituent (Scheme 1). The aldehyde **5** was transformed to silylenol ether **6** (*E*/*Z*-mixture) by action of trimethylsilyl trifluoromethanesulfonate in the presence of N,N-diisopropylethylamine (Hünig base). The reagent of choice for the electrophilic introduction of fluorine proved to be *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide[12] which gave a mixture of diastereomeric fluoro aldehydes **7a** and **7b** separable by chromatography. Although the ^{1}H NMR spectra showed distinct differences between both diastereomers, the assignment of the absolute configuration turned out to be impossible at this stage (Scheme 1).



reaction conditions: a: Me_3SiOTf, $(iPr)_2NEt$, CH_2Cl_2; b: $FN(SO_2Ph)_2$, CH_2Cl_2; c: $Ph_3PCHCON(OCH_3)CH_3$, toluene; d: HF, CH_3CN; e: PCC, CH_2Cl_2.

Scheme 1

In order to obtain a crystalline derivative the less polar diastereomer **7a** was converted to Weinreb amide **8** upon reaction with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide.[13] Silyl ether cleavage and subsequent PCC oxidation resulted in nicely crystalline ketone **10** which was subjected to X-ray crystallographic analysis.[14] Thus, the 20*R*-configuration of compund **10** was unequivocally confirmed (Figure 2).

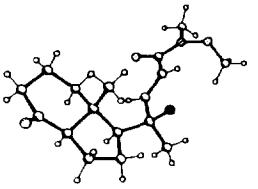
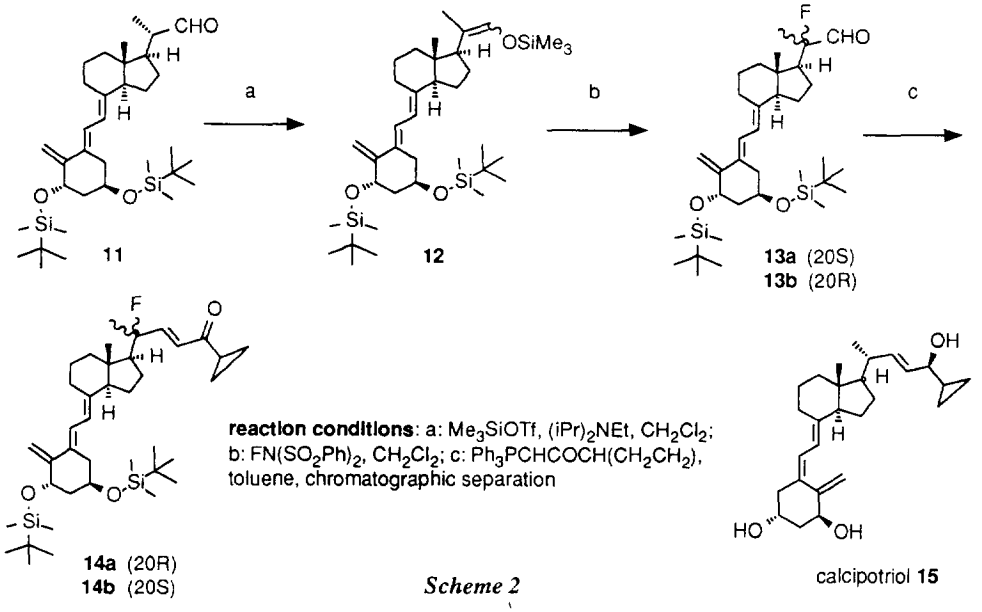


Figure 2

Although, in principle, ketone **10** could have served to complete the synthesis of 20-fluorocalcitriols by following the established routes of convergent total synthesis,[15] we terminated the approach at this stage and turned our attention to the intact vitamin D system.

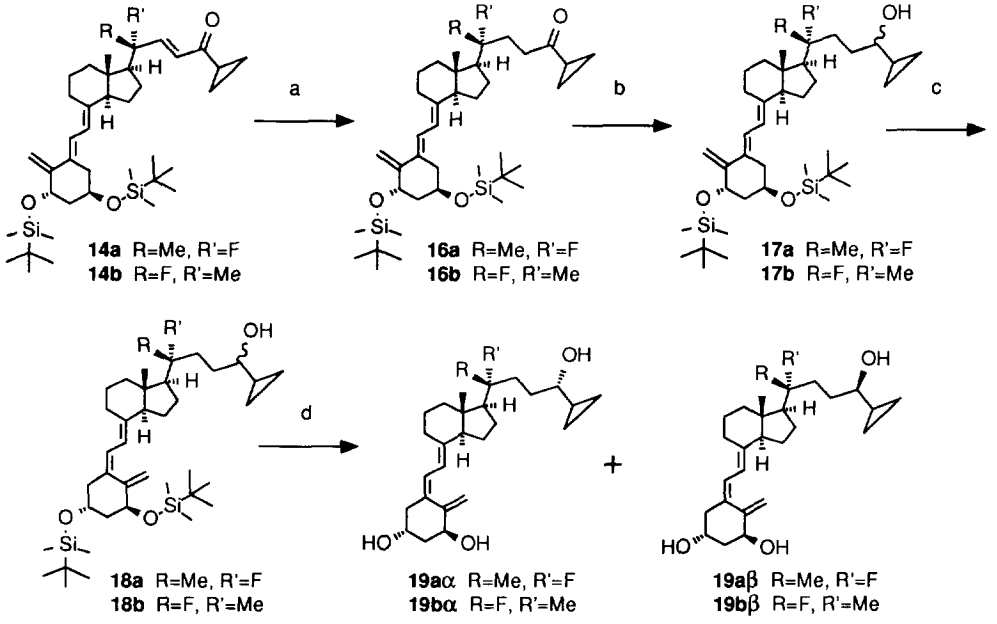
Vitamin D aldehyde **11** easily accessible from vitamin D_2 by a seven step sequence[16] is a convenient starting material for a wide range of side chain variations. The methology described above proved to be applicable to aldehyde **11**. Silylenol ether formation followed by reaction with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide[12] gave the expected mixture of diastereomeric fluoro aldehydes **13a** and **13b** (Scheme 2). Chromatographic separation at this stage is not advisable due to the chemical instability of mixture **13a** and **13b**. After Wittig reaction with 1-cyclopropyl-2-(triphenylphosphoranylidene)ethanone,[16] the resultant ketones **14a** and **14b** could be separated without difficulty. The stereochemical assignment could easily be made by comparing the NMR data of **14a** and **14b** with the corresponding signals obtained for CD fragment **10**.



Scheme 2

Originally, ketones **14a** and **14b** were meant to serve as precursors for the synthesis of 20-fluoro analogues of calcipotriol **15** which is the first synthetic calcitriol derivative available for the treatment of psoriasis.[17] Unfortunately, the 20-fluorocalcipotriol situation turned out to be rather susceptible to hydrogen

fluoride elimination. The problem of insufficient chemical stability could be overcome by removing the 22,23-double bond. The 22,23-dihydro analogue **16a** was obtained by reduction of enone **14a** with sodium borohydride in pyridine (Scheme 3). Subsequent reduction of the carbonyl with sodium borohydride in ethanol gave alcohol **17a** as epimeric mixture at C-24 which was exposed to the usual photochemical isomerization of the triene system affording 5*Z*-isomer **18a**. Finally, deprotection with tetrabutylammonium fluoride followed by chromatographic separation gave 20*R*-fluoro-22,23-dihydrocalcipotriol **19aβ** and its 24*S*-diastereomer **19aα**. By applying the identical sequence, 20*S*-fluoro derivative **14b** was converted to 20*S*-fluoro- 22,23-dihydrocalcipotriol **19bβ** and the corresponding 24*S*-analogue **19bα**.



reaction conditions: a: $NaBH_4$, pyridine; b: $NaBH_4$, EtOH; c: hv, anthracene, NEt_3, toluene; d: TBAF, THF, chromatography

Scheme 3

Preliminary biological investigations (binding affinity to pig intestine vitamin D receptor, induction of differentiation of human leukemia cells)[6] revealed activities for all diastereomers similar to those of calcitriol and calcipotriol. Calcemic activity (acute administration to rats),[6] however, appeared to be considerably reduced with regard to both reference substances. In marked contrast to the known examples,[18] no major differences were found between the activities os 24*S* and 24*R* epimers. The 20-fluoro substitution seems to compensate for the decrease of potency normally observed after epimerisation at carbon 24. A more detailed description of the respective pharmacological profiles will be published elsewhere.

In conclusion, a new method for introducing fluorine into position 20 of the vitamin D system has been developed. For the first time calcitriol analogues exhibiting this novel structural feature have been synthesized and tested biologically. Furthermore, aldehydes **13a** and **13b** could serve as a valuable intermediates for the generation of a broad range of 20-fluorocalcitriols.

EXPERIMENTAL

NMR: General Electric QE 300 and Bruker AC 300 spectrometers; δ in ppm rel. to TMS as internal standard. IR: Perkin Elmer PE 621 spectrometer. MS: Finnigan TSQ 700 spectrometer. Combustion analyses were carried out by Schering analytical department. TLC analyses were performed on Merck 60 F_{254} silica gel plates. Melting points were uncorrected.

Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone prior to use. All other solvents were purchased as p.a. (pro analysi) quality and dried over molecular sieves. All reactions were run under positive argon pressure.

Unless noted otherwise, usual work-up means quenching of the reaction mixture with sodium chloride solution, extraction with ethyl acetate, washing of the organic layer with either sodium bicarbonate solution or dilute hydrochloric acid and sodium chloride solution, drying over sodium sulfate, and evaporation of the solvent. Purification of crude materials was performed by chromatography on silica gel (Merck silica gel 60, 70-230 mesh) using ethyl acetate/hexane as eluents. For assignments of spectroscopical data the usual steroid numbering is applied.

[1*R*-(1α,3aβ,4α,7aα)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7a-methyl-1-[1-methyl-2-[(trimethylsilyl)oxy]-1-ethenyl]octahydro-1*H*-indene (**6**): A solution of 9.0 g (28 mmol) [1*R*-[1α(*R**),3aβ,4α,7aα)]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-α,7a-dimethyloctahydro-1*H*-inden-1-acetaldehyde **5**[13] in 600 ml dichloromethane was added at 5°C to a mixture of 37.7 g (170 mmol) trimethylsilyl trifluoromethanesulfonate and 21.9 g (170 mmol) N,N-diisopropylethylamine and was stirred for 1 h at 25°C. After evaporation of the solvent the residue was dissolved in hexane, filtered and evaporated again yielding 11 g (100%) **6** as colourless oil (*E*/*Z*-mixture 3:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02/6.18 ppm m (1H each, H-22), 4.02 m (1H, H-8), 1.50/1.57 brs (3H each, H-21), 0.88 s (9H, *tert.*-butylsilyl), 0.78 s (3H, H-18), 0.13 s (9H, methylsilyl), 0.00 s (6H, methylsilyl).

[1*S*-[1α(*R),3aβ,4α,7aα)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-fluoro-α,7a-dimethyloctahydro-1*H*-inden-1-acetaldehyde** (**7a**) and **[1*S*-[1α(*S**),3aβ,4α,7aα)]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-α-fluoro-α,7a-dimethyloctahydro-1*H*-inden-1-acetaldehyde** (**7b**): To a solution of 15.0 g (38 mmol) **6** in 300 ml dichloromethane was slowly added 26.0 g (82 mmol) *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide in 250 ml dichloromethane at 5°C. After stirring overnight at 25°C the usual work-up procedure was carried out. Subsequent chromatography gave 3.85 g (30%) **7a** and 2.08 g (17%) **7b** as colourless oils. **7a**: **IR** (KBr, cm^{-1}): 3420, 2940, 1745. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 9.75 ppm d (J=7 Hz, 1H, H-22), 4.01 m (1H, H-8), 1.42 d (J=20 Hz, 3H, H-21), 1.02 d (J=2 Hz, 3H, H-18), 0.88 m (9H, *tert.*-butylsilyl), 0.01 and 0.00 s (3H each, methylsilyl). **MS** (CI, NH_3) m/z: 360 ($M+NH_4^+$, 7%), 343 (8%), 328 (57%), 211 (90%), 179 (88%), 35 (100%). **$C_{19}H_{35}FO_2Si$** calcd. C 66.62; H 10.30, found C 66.67; H 10.33 %. **7b**: **IR** (KBr, cm^{-1}): 3420, 2940, 1730. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 9.87 ppm d (J=6 Hz, 1H, H-22), 4.01 m (1H, H-8), 1.46 d (J=21 Hz, 3H, H-21), 1.08 d (J=4.5 Hz, 3H, H-18), 0.88 m (9H, *tert.*-butylsilyl), 0.01 s (3H, methylsilyl). **$C_{19}H_{35}FO_2Si$** calcd. C 66.62; H 10.30, found C 66.71; H 10.34 %.

[1*S*-[1α[*S-(*E*)],3aβ,4α,7aα)]-4-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7a-methyloctahydro-1*H*-inden-1-yl]-4-fluoro-*N*-methoxy-*N*-methyl-2-pentenamide** (**8**): A solution of 342 mg (1 mmol) **7a** in 30 ml toluene was stirred with 2.50 g (7 mmol) *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)-acetamide[13] at 80°C for 48 hours. The cooled mixture was evaporated and purified chromatographically yielding 380 mg (89%) **8** as colourless oil. **IR** (KBr, cm^{-1}): 3440, 2940, 1670, 1640. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.93 ppm dd (J=20, 15.5 Hz, 1H, H-22), 6.55 d (J= 15.5 Hz, 1H, H-23), 4.01 m (1H, H-8), 3.70 s (3H, N-OMe), 3.27 s (3H, N-Me), 1.50 d (J=20 Hz, 3H, H-21), 1.05 d (J=2 Hz, 3H, H-18), 0.88 m (9H, *tert.*-butylsilyl), 0.01 and 0.00 s (3H each, methylsilyl). **MS** (EI) m/z: 412 ($M-Me^+$, 3%), 370 (100%), 350 (3%), 75 (67%). **$C_{23}H_{42}FNO_3Si$** calcd. C 64.59; H 9.90; N 3.28, found C 64.65; H 9.97; N 3.29 %.

[1*S*-[1α[*S-(*E*)],3aβ,4α,7aα)]-4-Fluoro-4-(4-hydroxy-7a-methyloctahydro-1*H*-inden-1-yl)-*N*-methoxy-*N*-methyl-2-pentenamide** (**9**): A solution of 100 mg (0.23 mmol) **8** in acetonitrile was stirred with 1.4 ml aqueous hydrogen fluoride (40%) for 90 minutes at 25°C. The usual work-up was performed giving after purification via chromatography 53 mg (74%) **9** as colourless oil. **IR** (KBr, cm^{-1}): 3460, 2940, 1670, 1630. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.89 ppm dd (J=20, 15.5 Hz, 1H, H-22), 6.54 d (J= 15.5 Hz, 1H, H-23), 4.07 m (1H, H-8), 3.68 s (3H, N-OMe), 3.25 s (3H, N-Me), 1.50 d (J=20 Hz, 3H, H-21), 1.08 d (J=2 Hz, 3H, H-18). **MS** (EI) m/z: 314 ($M+1^+$, 67%), 296 (15%), 253 (100%), 253 (22%), 215 (20%), 187 (88%), 135 (60%). **$C_{17}H_{28}FNO_3$** calcd. C 65.15; H 9.00; N 4.47, found C 64.99; H 8.96; N 4.31 %.

[1*S*-[1α[*S-(*E*)],3aβ,7aα)]-4-Fluoro-*N*-methoxy-*N*-methyl-4-(7a-methyl-4-oxooctahydro-1*H*-inden-1-yl)-2-pentenamide (10)**: A mixture of 427 mg (1.36 mmol) **9** and 63 mg (0.76 mmol) sodium acetate in 12 ml dichloromethane was treated with 414 mg (1.92 mmol) pyridinium chlorochromate at 0°C. After stirring for 3 hours at 25°C the mixture was diluted with 50 ml diethyl ether and filtered. The filtrate was evaporated and purified by chromatography giving 357 mg (85%) **10**. After dissolving the compund in ethyl acetate at 60°C, the solvent was allowed to evaporate slowly at 25°C yielding crystals suitable for X-ray analysis. **Melting point** 115°C. **IR** (KBr, cm^{-1}): 3440, 2950, 1705, 1670, 1640. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.93 ppm dd (J=20, 15.5 Hz, 1H, H-22), 6.56 d (J= 15.5 Hz, 1H, H-23), 3.72 s (3H, N-OMe), 3.26 s (3H, N-Me), 2.46 dd (J=10.5, 7.5 Hz, 1H, H-14), 1.53 d (J=20 Hz, 3H, H-21), 0.77 d (J=2 Hz, 3H, H-18). **MS** (EI) m/z: 311 (M^+, 5%), 251 (100%), 231 (9%), 213 (10%), 185 (12%), 133 (47%), 55 (56%). **$C_{17}H_{26}FNO_3$** calcd. C 65.57; H 8.42; N 4.50, found C 65.63; H 8.50; N 4.61 %. **Crystal data**:[14] colourless, needle-shaped crystals, monoclinic, space-group P 2_1, a=7.214 (8) Å, b=8.173 (9) Å, c=14.409 (8) Å, β=94.79 (7)°, V=845 (1) $Å^3$, Z=2, D_c=1.224 g/cm^3, μ=0.9 cm^{-1}, F(000)=336, graphite monochromated MoKα radiation from a fine focus sealed tube (λ=0.71073 Å), 2θ-θ scan mode, ω scan width=1.6°, scan time 1.91-29.3°/min in ω, temperature 21°C. 3051 intensity data (1611 unique reflections, R_{int}=5.8%, $3.0 \le 2\theta \le 50.0°$, $-8 \le h \le 6$, $-9 \le k \le 0$, $-17 \le l \le 17$) of which 1222 unique reflections were observed ($F>4\sigma(F)$) were measured on a Siemens P4 four circle diffractometer. The data were corrected for Lorentz- and polarization effects. The structure determination by direct methods and all subsequent calculations were carried out using version 4.0 of the SHELXTL+ program package (SHELXTL PLUS™, Siemens Analytical X-Ray Instruments, Inc.). Hydrogen atoms were included in calculated positions. Refinement by full-matrix least-square method with anisotropic parameters for all non-hydrogen atoms converged at R=0.047, R_w=0.048. Relative to the known configuration of C-13, the *R*-configuration could unambiguously be assigned for C-20.

(5*E*,7*E*)-(1*S*,3*R*,20ξ)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-20-methyl-9,10-secopregna-5,7,10(19)-trien-21-al (13a and 13b): A solution of 5.73 g (10 mmol) (5*E*,7*E*)-(1*S*,3*R*,20*S*)-1,3-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-methyl-9,10-secopregna-5,7,10(19)-trien-21-al **11** in 220 ml dichloromethane was added at 5°C to a mixture of 13.3 g (60 mmol) trimethylsilyl trifluoromethanesulfonate and 7.7 g (60 mmol) N,N-diisopropylethylamine and was stirred for 1 hour at 25°C. After evaporation of the solvent the residue was dissolved in hexane, filtered and evaporated again. The crude product **12** was dissolved in 100 ml dichloromethane and treated with 9.45 g (30 mmol) *N*-fluoro-*N*-(phenylsulfonyl)-benzenesulfonamide in 150 ml dichloromethane. After stirring for 45 minutes at 25°C the mixture was evaporated and purified by flash chromatography yielding 1.96 g (33%) **13** as diastereomeric mixture. **IR** (KBr, cm^{-1}): 3450, 2930, 1730. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 9.75 ppm d (J=5.5 Hz, 1H, H-21)/9.87 d (J=6 Hz, 1H, H-21), 5.81 and 6.45 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.95 and 4.99 2x s (1H each, H-19), 4.53 m (1H, H-1), 4.21 m (1H, H-3), 1.46 d (J=20 Hz, 3H, H-21), 0.87 and 0.89 2x s (9H each, *tert.*-butylsilyl), 0.65 d (J=2.5 Hz, 3H, H-18)/0.68 d (J=4 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 590 (M^+, 17%), 533 (10%), 458 (50%), 248 (100%). **$C_{34}H_{59}FO_3Si_2$** calcd. C 69.10; H 10.06, found C 68.98; H 9.99 %.

(5*E*,7*E*,22*E*)-(1*S*,3*R*,20*R*)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one (14a) and **(5*E*,7*E*,22*E*)-(1*S*,3*R*,20*S*)-1,3-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one (14b)**: A mixture of 5.07 g (8.6 mmol) **13** and 7.82 g (21.5 mmol) 1-cyclopropyl-2-(triphenylphosphoranylidene)ethanone[16] in 120 ml toluene was stirred for 4 hours at 85°C. The mixture was cooled, evaporated and purified chromatographically yielding 4.4 g (78%) **14a** and **14b** as a mixture. Repeated chromatography gave 973 mg (17%) **14a**, 1.71 g (31%) **14b** and 370 mg of a mixture of **14a**:**14b** as colourless foams. **14a**: **IR** (KBr, cm^{-1}): 3400, 2920, 1690, 1630. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.89 ppm dd (J=24, 15 Hz, 1H, H-22), 6.48 d (J=15 Hz, 1H, H-23), 5.82 and 6.43 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.95 and 4.98 2x s (1H each, H-19), 4.53 m (1H, H-1), 4.21 m (1H, H-3), 1.42 d (J=20 Hz, 3H, H-21), 0.87 and 0.89 2x s (9H each, *tert.*-butylsilyl), 0.60 d (J=3 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 656 (M^+, 8%), 524 (42%), 467 (7%), 355 (10%), 341 (35%), 149 (28), 75 (100%). **$C_{39}H_{65}FO_3Si_2$** calcd. C 71.29; H 9.97, found C 71.35; H 10.04 %. **14b**: **IR** (KBr, cm^{-1}): 3400, 2930, 1690, 1630. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.82 ppm dd (J=21, 15 Hz, 1H, H-22), 6.39 d (J=15 Hz, 1H, H-23), 5.80 and 6.42 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.94 and 4.98 2x s (1H each, H-19), 4.52 m (1H, H-1), 4.21 m (1H, H-3), 1.50 d (J=21 Hz, 3H, H-21), 0.85 and 0.88 2x s (9H each, *tert.*-butylsilyl), 0.64 d (J=3 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 656 (M^+, 17%), 599 (8%), 524 (60%), 467 88%), 379 (10%), 248 (100%). **$C_{39}H_{65}FO_3Si_2$** calcd. C 71.29; H 9.97, found C 71.33; H 10.06 %.

(5*E*,7*E*)-(1*S*,3*R*,20*R*)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one (16a): A solution of 200 mg (0.3 mmol) **14a** in 8 ml pyridine was treated with 114 mg (3 mmol) sodium borohydride at 25°C. After stirring for 90 minutes at this temperature the mixture was poured into 0.5 n hydrochloric acid and the usual work-up procedure was carried out giving after chromatography 150 mg (75%) **16a** as colourless foam. **IR** (KBr, cm^{-1}): 3420, 2940, 1705. **^{1}H NMR**

(300 MHz, $CDCl_3$) δ= 5.82 and 6.47 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.95 and 4.99 2x s (1H each, H-19), 4.54 m (1H, H-1), 4.22 m (1H, H-3), 1.29 d (J=20 Hz, 3H, H-21), 0.87 and 0.89 2x s (9H each, *tert.*-butylsilyl), 0.70 d (J=3 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (CI, NH_3) m/z: 676 ($M+NH_4^+$), 416 (30%), 324 (60%), 275 (100%). $C_{39}H_{67}FO_3Si_2$ calcd. C 71.07; H 10.25, found C 70.98; H 10.16 %.

(5*E*,7*E*)-(1*S*,3*R*,20*R*,24ξ)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-ol (17a): To a solution of 235 mg (0.35 mmol) **16a** in 10 ml tetrahydrofuran and 10 ml methanol were added 130 mg (0.35 mmol) cerium trichloride (hydrate) and 26 mg (0.7 mmol) sodium borohydride at 5°C. After stirring for 30 minutes at this temperature the mixture was worked up as usual giving after chromatography 230 mg (100%) **17a** as colourless foam (mixture of diastereomers). **IR** (KBr, cm^{-1}): 3380, 2920. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 5.82 and 6.47 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.94 and 4.99 2x s (1H each, H-19), 4.55 m (1H, H-1), 4.22 m (1H, H-3), 2.90 m (1H, H-24), 1.32 d (J=20 Hz, 3H, H-21), 0.87 and 0.89 2x s (9H each, *tert.*-butylsilyl), 0.70 d (J=3 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 660 (M^+, 8%), 640 (15%), 528 (30%), 508 (40%), 355 (5%), 248 (100%). $C_{39}H_{69}FO_3Si_2$ calcd. C 70.85; H 10.52, found C 70.91; H 10.54 %.

(5*Z*,7*E*)-(1*S*,3*R*,20*R*,24ξ)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-ol (18a): A solution of 220 mg (0.33 mmol) **17a**, 50 mg (0.3 mmol) anthracene and 2 drops of triethylamine in 140 ml degassed toluene in a pyrex apparatus was irradiated with light from a high pressure mercury lamp for 10 minutes at 25°C. After evaporation the mixture was purified by chromatography giving 190 mg (86%) **18a** as colourless foam (mixture of diastereomers). **IR** (KBr, cm^{-1}): 3400, 2910. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.23 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.88 and 5.20 2x s (1H each, H-19), 4.38 m (1H, H-1), 4.20 m (1H, H-3), 2.88 m (1H, H-24), 1.32 d (J=20 Hz, 3H, H-21), 0.90 s (18H, *tert.*-butylsilyl), 0.70 d (J=3 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 660 (M^+, 5%), 640 (10%), 528 (30%), 508 (33%), 379 (5%), 248 (100%). $C_{39}H_{69}FO_3Si_2$ calcd. C 70.85; H 10.52, found C 70.92; H 10.53 %.

(5*Z*,7*E*)-(1*S*,3*R*,20*R*,24*S*)-20-Fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3,24-triol (19aα) and **(5*Z*,7*E*)-(1*S*,3*R*,20*R*,24*R*)-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3,24-triol (19aβ)**: A mixture of 190 mg (0.28 mmol) **18a** and 730 mg (2.8 mmol) tetrabutylammonium fluoride (hydrate) in 24 ml tetrahydrofuran was stirred at 25°C overnight. The usual work-up was carried out and the residue was purified by chromatography yielding 75 mg (60%) **19a** as mixture of diastereomers which was separated by HPLC giving 17 mg **19aα** and 24 mg **19aβ** as colourless foams. **19aα**: **IR** (KBr, cm^{-1}): 3400, 2900. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.39 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 5.01 and 5.34 2x s (1H each, H-19), 4.43 m (1H, H-1), 4.22 m (1H, H-3), 2.85 m (1H, H-24), 1.30 d (J=20 Hz, 3H, H-21), 0.90 m (1H, H-25), 0.70 d (J=3 Hz, 3H, H-18), 0.53 and 0.27 2x m (2H each, H-26 and H-27). **MS** (EI) m/z: 432 (M^+, 8%), 414 (13%), 394 (14%), 376 (8%), 358 (3%), 134 (100%). $C_{27}H_{41}FO_3$ calcd. C 74.96; H 9.55, found C 75.03; H 9.60 %. **19aβ**: **IR** (KBr, cm^{-1}): 3400, 2900. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.39 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 5.00 and 5.34 2x s (1H each, H-19), 4.43 m (1H, H-1), 4.22 m (1H, H-3), 2.88 m (1H, H-24), 1.30 d (J=20 Hz, 3H, H-21), 0.90 m (1H, H-25), 0.70 d (J=3 Hz, 3H, H-18), 0.54 and 0.28 2x m (2H each, H-26 and H-27). **MS** (EI) m/z: 432 (M^+, 9%), 414 (10%), 394 (10%), 376 (7%), 358 (3%), 134 (100%). $C_{27}H_{41}FO_3$ calcd. C 74.96; H 9.55, found C 74.93; H 9.48 %.

(5*E*,7*E*)-(1*S*,3*R*,20*S*)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one (16b) and **(5*E*,7*E*)-(1*S*,3*R*,20*S*,24ξ)-1,3-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-ol (17b)**: A solution of 100 mg (0.15 mmol) **14b** in 3 ml pyridine was treated with 12 mg (0.30 mmol) sodium borohydride. After 30 minutes at 25°C another 37 mg (1 mmol) of sodium borohydride were added and the mixture was again stirred for 30 minutes and then poured into 0.5 n aqueous hydrochloric acid. Extraction with dichloromethane was carried out followed by drying of the solution with sodium sulfate. Evaporation of the solvent and chromatographic purification gave 51 mg (50%) **16b** and 30 mg (30%) **17b** as colourless foams. A solution of 51 mg (0.08 mmol) **16b** in 2 ml tetrahydrofuran and 2 ml methanol was treated with 29 mg (0.08 mmol) cerium trichloride (hydrate) and 5 mg (0.13 mmol) sodium borohydride at 5°C. After 15 minutes of stirring at this temperature the mixture was worked up as usual yielding after chromatography 29 mg (58%) **17b** (mixture of diastereomers). **16b**: **IR** (KBr, cm^{-1}): 3420, 2940, 1700. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 5.82 and 6.48 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.95 and 4.99 2x s (1H each, H-19), 4.55 m (1H, H-1), 4.22 m (1H, H-3), 1.40 d (J=21 Hz, 3H, H-21), 0.87 and 0.90 2x s (9H each, *tert.*-butylsilyl), 0.70 d (J= 4 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 658 (M^+, 7%), 638 (6%), 526 (17%), 506 (20%), 248 (100%). $C_{39}H_{67}FO_3Si_2$ calcd. C 71.07; H 10.25, found C 71.16; H 10.33 %. **17b**: **IR** (KBr, cm^{-1}): 3420, 2940. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 5.82 and 6.48 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.95 and 4.99 2x s (1H each, H-19), 4.53 m (1H, H-1), 4.22 m (1H, H-3), 2.89 m (1H, H-24), 1.40 d (J=21 Hz, 3H, H-21), 0.87 and 0.90 2x s (9H each, *tert.*-butylsilyl), 0.70 d (J= 4 Hz, 3H, H-18), 0.07 s (12H,

methylsilyl). **MS** (EI) m/z: 660 (M^+, 17%), 640 (24%), 528 (63%), 508 (70%), 248 (100%). **$C_{39}H_{69}FO_3Si_2$** calcd. C 70.85; H 10.52, found C 70.72; H 10.41 %.

(5*Z*,7*E*)-(1*S*,3*R*,20*S*,24ξ)-1,3-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-ol (18b): A solution of 250 mg (0.37 mmol) **17b**, 53 mg (0.32 mmol) anthracene and 2 drops of triethylamine in 140 ml degassed toluene in a pyrex apparatus was irradiated with light from a high pressure mercury lamp for 8 minutes at 25°C. After evaporation the mixture was purified by chromatography giving 227 mg (90%) **18b** as colourless foam (mixture of diastereomers). **IR** (KBr, cm^{-1}): 3420, 2940. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.23 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 4.88 and 5.19 2x s (1H each, H-19), 4.38 m (1H, H-1), 4.20 m (1H, H-3), 2.87 m (1H, H-24), 1.42 d (J=21 Hz, 3H, H-21), 0.90 s (18H, *tert.*-butylsilyl), 0.70 d (J=4 Hz, 3H, H-18), 0.07 s (12H, methylsilyl). **MS** (EI) m/z: 660 (M^+, 8%), 640 (9%), 528 (30%), 508 (22%), 248 (100%). **$C_{39}H_{69}FO_3Si_2$** calcd. C 70.85; H 10.52, found C 70.92; H 10.53 %.

(5*Z*,7*E*)-(1*S*,3*R*,20*S*,24*S*)-20-Fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3,24-triol (19bα) and **(5*Z*,7*E*)-(1*S*,3*R*,20*S*,24*R*)-20-fluoro-26,27-cyclo-9,10-secocholesta-5,7,10(19)-triene-1,3,24-triol (19bβ)**: A mixture of 200 mg (0.30 mmol) **18b** and 783 mg (3 mmol) tetrabutylammonium fluoride (hydrate) in 24 ml tetrahydrofuran was stirred at 25°C overnight. The usual work-up procedure followed by chromatographic purification was performed yielding 95 mg (73%) **19b** as diastereomeric mixture. An amount of 80 mg of this mixture was separated by HPLC giving 32 mg **19bα** and 29 mg **19bβ** as colourless foams. **19bα**: **IR** (KBr, cm^{-1}): 3400, 2920. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.39 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 5.00 and 5.33 2x s (1H each, H-19), 4.43 m (1H, H-1), 4.22 m (1H, H-3), 2.85 m (1H, H-24), 1.41 d (J=21 Hz, 3H, H-21), 0.70 d (J=4 Hz, 3H, H-18). **MS** (EI) m/z: 432 (M^+, 8%), 414 (13%), 394 (12%), 376 (9%), 152 (33%), 134 (100%). **$C_{27}H_{41}FO_3$** calcd. C 74.96; H 9.55, found C 75.02; H 9.61 %. **19bβ**: **IR** (KBr, cm^{-1}): 3400, 2930. **^{1}H NMR** (300 MHz, $CDCl_3$) δ= 6.02 and 6.39 ppm 2x d (J=11 Hz, 1H each, H-6 and H-7), 5.00 and 5.33 2x s (1H each, H-19), 4.43 m (1H, H-1), 4.22 m (1H, H-3), 2.85 m (1H, H-24), 1.41 d (J=21 Hz, 3H, H-21), 0.70 d (J=4 Hz, 3H, H-18). **MS** (EI) m/z: 432 (M^+, 7%), 414 (10%), 394 (8%), 376 (7%), 152 (34%), 134 (100%). **$C_{27}H_{41}FO_3$** calcd. C 74.96; H 9.55, found C 74.99; H 9.63 %.

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This paper is dedicated to Professor Helmut Vorbrüggen on occasion of his 65th birthday.

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