2,2-Difluoro Enol Silyl Ethers: Convenient Preparation and Application to the Synthesis of a Novel Fluorinated Brassinosteroid

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On treatment with Grignard reagents, trifluoroacetyltriphenylsilane was converted into 2,2-difluoro enol silyl ethers in almost quantitative yields. As a synthetic application of the 2,2-difluoro enol silyl ether, a novel fluorinated brassinosteroid was synthesized.

The growing demand for specifically fluorinated compounds, due to their unique physical and biological properties imparted by the fluorine atom(s), has led to a continuing search for new routes to these compounds.[1] One promising approach is to prepare fluorine-containing intermediates and then utilize them as building blocks for the synthesis of the desired fluorinated molecules.[1c,2] Because of their easy preparation and versatile reactions, enol silyl ethers have been recognized as one of the most important types of intermediates in synthetic organic chemistry.[3] In contrast, fluorine-containing enol silyl ethers appear to be much less exploited in organofluorine chemistry. So far, there exist few reports on the preparation and utilization of these enol silyl ethers.[4] In view of their synthetic potential in the construction of fluorinated molecules of biological interest, it is of great value to develop convenient methods for the generation of these enol silyl ethers and to exploit their utilization.

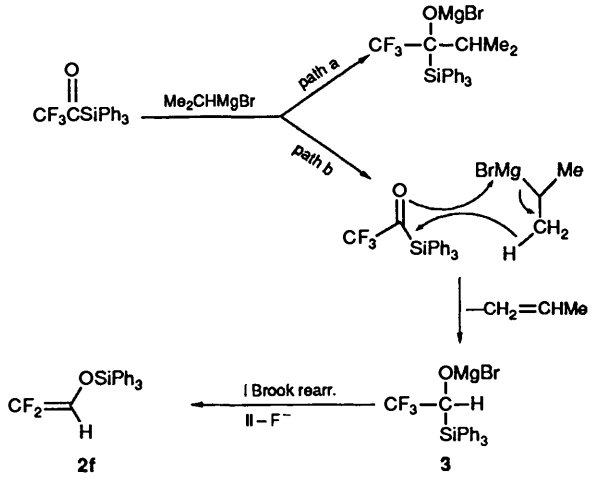
Previously, we have reported that trifluoroacetyltriphenylsilane **1**, on reaction with organolithiums, gave rise to 2,2-difluoro enol silyl ethers **2** in high yields.[5] This procedure provides a novel synthesis of 2,2-difluoro enol silyl ethers. However, there are some disadvantages associated with this procedure, *e.g.* strictly equal equivalents of **1** and an organolithium should be used in order to obtain a high yield of product[6] and organolithiums are not easily available in many cases. To both obviate the above disadvantages and broaden the scope of the procedure, we have examined the reactions by using Grignard reagents in place of organolithiums. Herein, we wish to report our results.

On treatment with Grignard reagents, **1** could also afford the 2,2-difluoro enol silyl ether under very mild conditions in almost quantitative yields, indicating that Grignard reagents are equally effective as organolithiums in this respect. The results are shown in Table 1.

It should be mentioned that use of an excess of a Grignard reagent did not affect the yield of the product, this combined with the easy availability of Grignard reagents ensures a wide applicability of the present procedure.

However, in the case of isopropylmagnesium bromide, we obtained the compound **2f** instead of the expected 1,1-difluoro-2-triphenylsiloxy-3-methylbut-1-ene. Obviously, in this case, isopropylmagnesium bromide was unable to undergo nucleophilic addition with the carbonyl group in **1** (Scheme 1, path a) due to the steric encumbrance exerted by the bulky triphenylsilyl moiety, but acted as a reducing reagent. As a result, compound **1** was first reduced with isopropylmagnesium bromide to the intermediate **3**, then resulting in the formation of **2f** *via* a sequence of Brook rearrangement and β-elimination of fluorine[5] (Scheme 1, path b). Compound **2f** represents a novel synthetic building block and further studies on the utilization of this compound will be reported elsewhere.

Fluorinated analogues have been recognized as useful tools



2f **3**

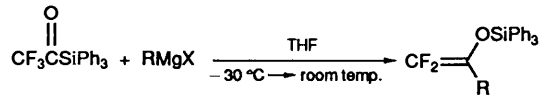
Scheme 1 Formation of **2f**

for pharmaco- and patho- physiological studies in natural products.[1b] Among these are fluorine-modified steroids such as Vitamin D_3.[7] For their unique biological properties, fluorinated steroids have been widely studied. Selective fluorination of steroids has been employed to block hydroxylation or to modify the reactivity of the neighbouring hydroxy group.[8] Brassinosteroids are known to exhibit outstanding plant growth-promoting ability.[9] Both to establish the relationship between structure and biological activity and to find new simple analogues with high activity, various structurally modified brassinosteroids have been synthesized.[10] However, no fluorine-modified brassinosteroid has been reported. In view of the utility of fluorinated derivatives in pharmaco- and patho-physiological studies, we have synthesized a novel fluorinated brassinosteroid in an attempt to find new analogues with high activity and simple structure and to gain more information about structure–activity relationship.

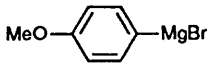
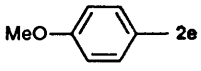
The $TiCl_4$-promoted aldol condensation of 20-carbaldehyde **4** obtained from hydeoxycholic acid by a known procedure[11] with 2,2-difluoro enol silyl ethers was proved to proceed without difficulty to afford steroidal compounds with a 23,23-difluorinated side chain in good yield and with high diastereoselectivity. Thus, difluoro compound **5** was obtained from compounds **4** and **2a** in 71% yield. It should be noted that the reaction of **4** and **2a** yielded (22*R*)-**5** only and no detectable amount of (22*S*)-**5** was formed, suggesting that attack of the enol silyl ether on the $TiCl_4$-activated 20-carbaldehyde **15** was possible from only one side, *e.g.*, side **a**, and that from the other side (side **b**) was greatly disfavoured for steric reasons.

Protection of the hydroxy group in **5** by the methoxymethyl (MOM) group gave **6**, which was then subjected to Wittig reaction. It has been reported that the Wittig reaction of

Table 1 Preparation of 2,2-difluoro enol silyl ethers **2** from silane **1** and Grignard reagents[a]



1 **2**

Entry	RMgX	Products **2**[b] R	Yield[c] (%)
1	MeMgI	Me **2a**	99
2	EtMgBr	Et **2b**	97
3	CH_2=$CHCH_2MgBr$	CH_2=$CHCH_2$ **2c**	94
4	Me_3SiCH_2MgCl	Me_3SiCH_2 **2d**	88
5			100
6	$Me_2CHMgBr$	H **2f**	95

[a] The reaction was conducted by using 1 equiv. of **1** and 1.2 equiv. of a Grignard reagent in THF. [b] All new compounds were fully characterized by ^{19}F NMR, ^1H NMR, IR, MS and C, H, F elemental analyses. [c] Isolated yield based on **1**.

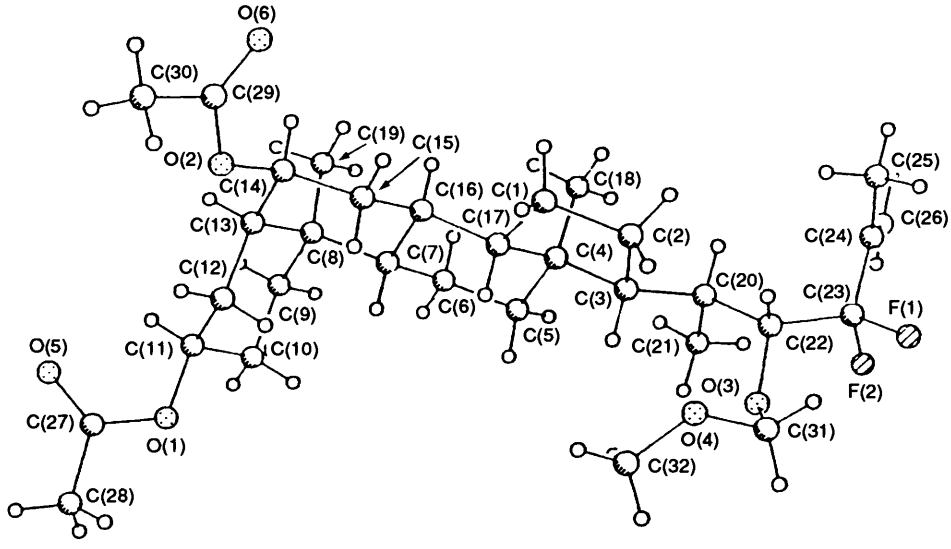
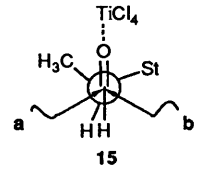


Fig. 1 X-Ray structure of **7**



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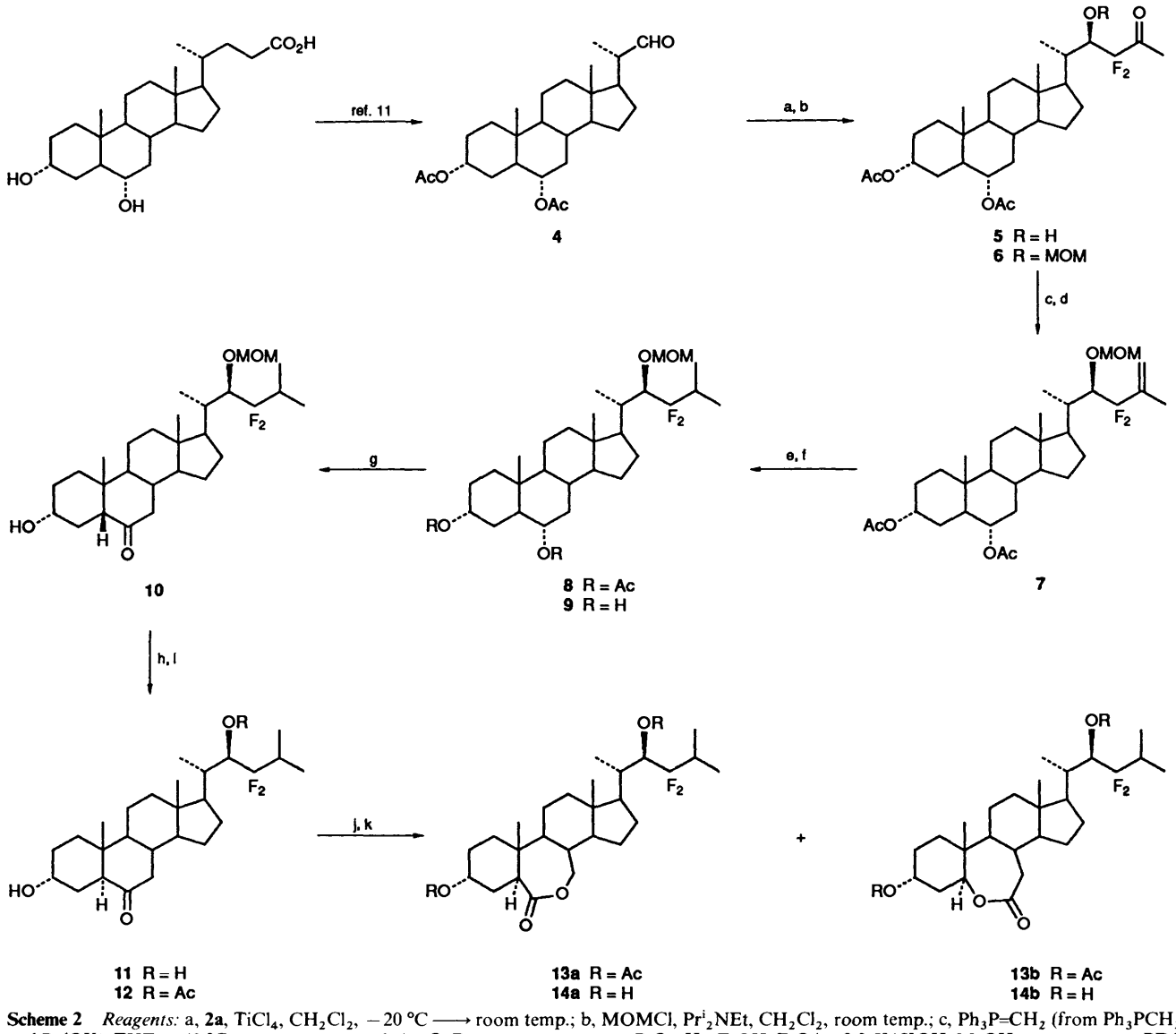
steroidal compounds bearing one or more acetyl groups usually gives unsatisfactory yields,[12] even when a considerable excess of Wittig reagent is used. Initially, we tried the conditions reported in the literature[13] and found the results were disappointing. After several trials, we found that the yield of the desired product could be greatly improved when the Wittig reaction was conducted at low temperature and using THF as the solvent and six-fold excess of the methylenetriphenylphosphorane, which was formed from Ph_3PCH_3I by the action of Bu^{t}OK. This improvement appears mainly due to the partial suppression of deacetylation of the reactant under very mild conditions. Thus, **7** was obtained after re-acetylation in 93% yield. The assignment of *R* configuration to C-22 in **5** was based on the X-ray structure of **7** as illustrated in Fig. 1.

Catalytic hydrogenation of **7** with PtO_2 gave rise to **8** (98%), which was converted into **10** (82%) by successive alkaline hydrolysis and selective oxidation with pyridinium dichromate (PDC). Compound **11** could be obtained from **10** by acidic isomerization and spontaneous deprotection of the methoxymethyl group (83%). After protective acetylation of **11**, **12** was subjected to Baeyer–Villiger oxidation with CF_3CO_3H and finally deprotective hydrolysis with K_2CO_3 in refluxing methanol afforded **14a** in 40% along with **14b** (36%). Thus, we obtained a novel fluorinated brassinosteroid **14a** from 20-carbaldehyde in 10 steps and 16% overall yield (Scheme 2).

Examination of the biological activity of **14a** is in progress.

Experimental

M.p.s were determined on a Kofler heating-stage apparatus and were uncorrected. ^1H NMR spectra were recorded on a Varian EM-360, Varian XL-200 or Bruker AM-300 spectrometer with Me_4Si as an internal standard; and ^{19}F NMR spectra were obtained on a Varian EM-360 or JEOL FX-90 with trifluoroacetic acid (δ, 0.00) as an external standard, downfield shifts were designated as negative. *J* Values are given in Hz. Infrared spectra were taken on a Shimadzu IR-440 spectrometer and mass spectra (MS) and high resolution mass spectra (HRMS) were run respectively on a Finnigan 4021 GC/MS/DC and a Varian MAT 212 instrument with an ionizing voltage of 70 eV. The optical rotation was measured on an autopol III polarimeter. The usual work-up refers to dilution with water, extraction with ethyl acetate, washing to neutrality, drying (Na_2SO_4),



Scheme 2 *Reagents:* a, **2a**, $TiCl_4$, CH_2Cl_2, −20 °C ⟶ room temp.; b, MOMCl, Pr^i_2NEt, CH_2Cl_2, room temp.; c, $Ph_3P{=}CH_2$ (from Ph_3PCH_3I and Bu'OK), THF, −40 °C ⟶ room temp.; d, Ac_2O–Py, room temp.; e, cat. PtO_2, H_2, EtOH–EtOAc; f, 2.5% KOH–MeOH, room temp.; g, PDC, room temp.; h, 2.5% conc. HCl–MeOH; i, Ac_2O–Py, room temp.; j, CF_3CO_3H, CH_2Cl_2, 0 °C ⟶ room temp.; k, K_2CO_3, moist MeOH

removal of the solvent under reduced pressure, and finally chromatography on silica gel [light petroleum (60–90 °C)–acetone].

Trifluoroacetyltriphenylsilane was prepared as described in our previous work.[5]

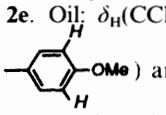
Reaction of Trifluoroacetyltriphenylsilane **1** *with Grignard Reagents.—General procedure.* To a solution of the silane **1** (1 mmol) in dry THF (10 cm^3), cooled with dry ice at −30 °C, was added *via* syringe a Grignard reagent (1.2 mmol) and stirring was continued at −30 °C for 15 min, and then at room temp. for 1 h. Hexane (30 cm^3) was added and the solid portion was filtered off. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using 99:1 mixture of light petroleum (60–90 °C) and ethyl acetate as the eluent to afford product **2a–f**.

1,1-*Difluoro*-2-*triphenylsilyloxypropene* **2a**. M.p. 51–52.5 °C (lit.,[5] 52.5–53.5 °C); $\delta_H(CCl_4)$ 1.6 (t, *J* 4, 3 H, CH_3) and 7.10–7.80 (m, 15 H, ArH); $\delta_F(CCl_4;\ \delta_{TFA})$ +28.5 (dq, *J* 90 and 4, 1 F) and +45.5 (dq, *J* 90 and 4, 1 F); ν_{max}(KBr)/cm^{-1} 1780, 1590, 1480, 1250, 1120, 740 and 700; *m/z* (assignment, relative intensity) 352 (M, 3) and 259 (Ph_3Si, 100).

1,1-*Difluoro*-2-*triphenylsilyloxybut*-1-*ene* **2b**. Oil; $\delta_H(CCl_4)$ 0.85 (t, *J* 7, 3 H, CH_2CH_3), 1.90 (m, 2 H, CH_2CH_3) and 7.1–7.5 (m, 15 H, ArH); $\delta_F(CCl_4;\ \delta_{TFA})$ +26.7 (d, *J* 85, 1 F) and +43.3 (d, *J* 85, 1 F); ν_{max}(film)/cm^{-1} 3050, 1770, 1590, 1430, 1110, 740, 720 and 700; *m/z* (assignment, relative intensity) 366 (M, 11) and 259 (Ph_3Si, 100) (Found: C, 72.05; H, 5.5; F, 10.25. Calc. for $C_{22}H_{20}F_2OSi$: C, 72.10, H, 5.50, F, 10.37%).

1,1-*Difluoro*-2-*triphenylsilyloxypenta*-1,4-*diene* **2c**. Oil; δ_H-($CDCl_3$) 2.73 (m, 2 H, $-CH_2CH{=}CH_2$), 5.07 (d, *J* 17, 1 H, H H / C=C, H), 5.10 (d, *J* 11, 1 H, H H / C=C, H), 5.64 (m, 1 H, $-CH{=}CH_2$) and 7.26–7.65 (m, 15 H, ArH); $\delta_F(CCl_4;\ \delta_{TFA})$ +25.5 (d, *J* 85, 1 F) and +41.0 (d, *J* 85, 1 F); ν_{max}(film)/cm^{-1} 3050, 1770, 1590, 1430, 1120, 740, 720 and 700; *m/z* (assignment, relative intensity) 378 (M, 1) and 259 (Ph_3Si, 100) (Found: C, 73.0; H, 5.35; F, 10.05. Calc. for $C_{23}H_{20}F_2OSi$: C, 72.98; H, 5.23; F, 10.04%).

1,1-*Difluoro*-3-*trimethylsilyl*-2-*triphenylsilyloxypropene* **2d**. Oil; $\delta_H(CCl_4)$ −0.12 [s, 9 H, $Si(CH_3)_3$], 0.73 (s, 2 H, $-CH_2Si$) and 6.80–7.60 (m, 15 H, ArH); $\delta_F(CCl_4;\ \delta_{TFA})$ +30.0 (d, *J* 90, 1 F) and +45.8 (d, *J* 90, 1 F); ν_{max}(film)/cm^{-1} 3050, 1760, 1590, 1430, 1120, 740, 720 and 700; *m/z* (assignment, relative intensity) 424 (M, 10), 259 (Ph_3Si, 100) and 73 (Me_3Si, 53) (Found: C, 67.85; H, 6.20; F, 9.15. Calc for $C_{24}H_{26}F_2OSi_2$: C, 67.88; H, 6.17; F, 8.96%).

1,1-*Difluoro*-2-(4-*methoxyphenyl*)-2-*triphenylsilyloxyethene* **2e**. Oil; $\delta_H(CCl_4)$ 3.5 (s, 3 H, OCH_3), 6.55 (d, *J* 8, 2 H, ) and 6.90–7.60 (m, 17 H, ArH); $\delta_F(CCl_4; \delta_{TFA})$ +22.5 (d, *J* 75, 1 F) and +37.3 (d, *J* 75, 1 F); ν_{max}(film)/cm^{-1} 3050, 1740, 1600, 1510, 1120, 740, 720 and 700; *m*/*z* (assignment, relative intensity) 444 (M, 83) and 259 (Ph_3Si, 100) (Found: C, 72.95; H, 4.95; F, 8.65. Calc. for $C_{27}H_{22}F_2O_2Si$: C, 72.83; H, 4.99; F, 8.55%).

1,1-*Difluoro*-2-*triphenylsilyloxyethene* **2f**. M.p. 96–97 °C; $\delta_H(CDCl_3)$ 5.88 (dd, *J* 16 and 4, 1 H, CF_2=CH–) and 7.30–7.70 (m, 15 H, ArH); $\delta_F(CCl_4; \delta_{TFA})$ +22.7 (dd, *J* 85 and 16, 1 F) and +44.5 (dd, *J* 85 and 4, 1 F); ν_{max}(KCl)/cm^{-1} 1770, 1590, 1470, 1120, 800, 740, 720 and 700; *m*/*z* (assignment, relative intensity) 338 (M, 2) and 259 (Ph_3Si, 100) (Found: C, 71.3; H, 4.8; F, 10.9. Calc. for $C_{20}H_{16}F_2OSi$: C, 70.98; H, 4.77; F, 11.22%).

Aldol Condensation of 20-*Carbaldehyde* **4** *with* 1,1-*Difluoro*-2-*triphenylsilyloxyprop*-1-ene **2a**; **4** ⟶ **5** ⟶ **6**.—To a solution of **4** (430 mg, 1 mmol) and **2a** (530 mg, 1.5 mmol) in dry CH_2Cl_2 (20 cm^3) cooled at −60 °C was added 1 equiv. of $TiCl_4$ and the mixture was stirred at −20 °C for 8 h and then at room temp. for 20 h. Usual work-up provided (22*R*)-23,23-difluoro-22-hydroxy-24-methyl-24-oxo-5α-cholane-3α,6α-diyl diacetate **5** (373 mg, 71%); $\delta_H(CDCl_3)$ 0.69 (s, 3 H, 18-H), 0.98 (s, 3 H, 19-H), 1.05 (d, *J* 6, 3 H, 21-H), 2.01 (s, 3 H, 3-CH_3CO), 2.04 (s, 3 H, 6-CH_3CO), 2.38 (s, 3 H, CH_3COCF_2–), 4.14 (dd, *J* 21 and 6, 1 H, 22-H), 4.70 (m, 1 H, 3β-H) and 5.15 (m, 1 H, 6β-H); $\delta_F(CDCl_3; \delta_{TFA})$ +35.61 (dd, *J* 297 and 6, 1 F), 45.21 (dd, *J* 297 and 21, 1 F); *m*/*z* (assignment, relative intensity) 527 (M + 1, 1) and 406 (M − 2HOAc, 100).

Compound **5** (530 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 cm^3) and diisopropylethylamine (0.26 g, 2 mmol) was added. The mixture was cooled to 0 °C and chloromethyl methyl ether (0.16 g, 2 mmol) was added dropwise in 15 min; stirring was continued at room temp. for 72 h. Usual work-up afforded (22*R*)-23,23-difluoro-22-methoxymethoxy-24-methyl-24-oxo-5α-cholane-3α,6α-diyl diacetate **6** (570 mg, 100%) as an amorphous solid: $[\alpha]_D^{25}$ +16.1 (*c*, 1.34, $CHCl_3$); $\delta_H(CDCl_3)$ 0.68 (s, 3 H, 18-H), 0.98 (s, 3 H, 19-H), 1.03 (d, *J* 6, 3 H, 21-H), 2.01 (s, 3 H, 3-CH_3CO), 2.03 (s, 3 H, 6-CH_3CO), 2.36 (s, 3 H, CH_3COCF_2–), 3.40 (s, 3 H, OCH_3), 4.06 (dd, *J* 18 and 10, 1 H, 22-H), 4.58–4.80 (m, 3 H, 3β-H and –OCH_2O–) and 5.16 (m, 1 H, 6β-H); $\delta_F(CCl_4; \delta_{TFA})$ +33.0 (dd, *J* 280 and 10, 1 F), +43.0 (dd, *J* 280 and 18, 1 F); ν_{max}(KCl)/cm^{-1} 2900, 1740, 1360, 1240 and 1130; *m*/*z* (assignment, relative intensity) 526 (M − MOM + 1, 1), 450 (M − 2AcOH, 39), 45 (MOM, 100) (Found: C, 65.55; H, 8.65; F, 6.9. Calc. for $C_{31}H_{48}F_2O_7$: C, 65.24; H, 8.48; F, 6.66%).

Wittig Reaction of **6**; **6** ⟶ **7**.—A solution of methylenetriphenylphosphorane [obtained from Ph_3PCH_3I (2.4 g, 6 mmol) and Bu^{t}OK (0.67 g, 6 mmol)] in THF (35 cm^3) was cooled to −40 °C and then compound **6** (570 mg, 1 mmol) dissolved in THF (10 cm^3) was added dropwise in 10 min. Stirring was continued at −40 °C for 6 h and then at room temp. for 8 h. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. After evaporation of ethyl acetate, the amorphous solid thus obtained was dissolved in pyridine (10 cm^3); $(CH_3CO)_2O$ (2 cm^3) was added and the mixture was stirred overnight at room temp. Usual work-up provided (22*R*)-23,23-difluoro-22-methoxymethoxy-24-methyl-24-methylene-5α-cholane-3α,6α-diyl diacetate **7** (528 mg, 93%) as a solid: m.p. 167–169 °C; $[\alpha]_D^{25}$ +37.3 (*c*, 0.98, $CHCl_3$); $\delta_H(CDCl_3)$ 0.66 (s, 3 H, 18-H), 0.97 (s, 3 H, 19-H), 1.01 (d, *J* 6, 3 H, 21-H), 1.85 (s, 3 H, ), 2.01 (s, 3 H, 3-CH_3CO), 2.03 (s, 3 H, 6-CH_3CO), 3.45 (s, 3 H, OCH_3), 3.86 (dd, *J* 12 and 12, 1 H, 22-H), 4.60–4.86 (m, 3 H, 3β-H and –OCH_2O–), 5.14 (m, 1 H, 6β-H), 5.20 (s, 1 H, vinyl-H) and 5.36 (s, 1 H, vinyl-H); $\delta_F(CDCl_3; \delta_{TFA})$ +32.5 (dd, *J* 248 and 12, 1 F) and +27.1 (dd, *J* 248 and 12, 1 F); ν_{max}(KCl)/cm^{-1} 2900, 1740, 1440, 1360, 1240, 1110 and 890; *m*/*z* (assignment, relative intensity) 537 (M − OCH_3, 0.5), 417 (M − 2AcOH − OCH_3, 13), 403 (M − 2-AcOH − MOM, 3), 256 (M − 2AcOH-side chain + 1, 49) and 45 (MOM, 100) (Found: C, 67.35; H, 8.9. Calc. for $C_{31}H_{50}F_2O_7$: C, 67.58; H, 8.86%).

Hydrogenation of **7**; **7** ⟶ **8** ⟶ **9**.—To a solution of compound **7** (570 mg, 1 mmol) in ethanol–ethyl acetate (1:1, 40 cm^3) was added platinum dioxide (20 mg). The mixture was hydrogenated at room temperature. After the absorption of H_2 had ceased, the mixture was filtered. Usual work-up gave (22*R*)-23,23-difluoro-22-methoxymethoxy-24,24-dimethyl-5α-cholane-3α,6α-diyl diacetate **8** as a solid (580 mg, 98%): m.p. 115–116 °C; $[\alpha]_D^{25}$ +20.9 (*c*, 0.74, $CHCl_3$); $\delta_H(CDCl_3)$ 0.69 (s, 3 H, 18-H), 0.98 (s, 3 H, 19-H), 2.01 (s, 3 H, 3-CH_3CO), 2.04 (s, 3 H, 6-CH_3CO), 3.46 (s, 3 H, OCH_3), 3.80 (t, *J* 13.5, 1 H, 22-H), 4.64–4.82 (m, 3 H, 3β-H and –OCH_2O–) and 5.16 (m, 1 H, 6β-H); $\delta_F(CDCl_3; \delta_{TFA})$ +38.2 (dd, *J* 19.8 and 13.5); ν_{max}(KCl)/cm^{-1} 2950, 1740, 1240 and 1030; *m*/*z* (assignment, relative intensity) 450 (M − 2AcOH, 25), 313 (M − 2AcOH − MOM − CF_2  + 1, 99), 255 (M − 2AcOH-side chain, 75) and 45 (MOM, 100) (Found: C, 67.45; H, 9.0. Calc. for $C_{32}H_{52}F_2O_6$: C, 67.34; H, 9.18%).

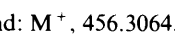
Compound **8** (570 mg, 1 mmol) was dissolved in methanol (50 cm^3) containing KOH (1.25 g). The mixture was stirred overnight at room temp. and then the methanol was evaporated off under reduced pressure. Usual work-up afforded (22*R*)-23,23-difluoro-22-methoxymethoxy-24,24-dimethyl-5α-cholane-3α,6α-diol **9** (486 mg, 100%) as a solid: m.p. 184–185 °C; $[\alpha]_D^{25}$ +10.4 (*c*, 0.25, $CHCl_3$); $\delta_H(CDCl_3)$ 0.68 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 3.46 (s, 3 H, OCH_3), 3.64 (m, 1 H, 3β-H), 3.80 (t, *J* 14, 1 H, 22-H), 4.08 (m, 1 H, 6β-H) and 4.70–4.84 centred at 4.76 (AB, *J* 7, 2 H, OCH_2O); $\delta_F(CDCl_3; \delta_{TFA})$ +38.3 (dd, *J* 17 and 14); ν_{max}(KCl)/cm^{-1} 3400, 2950, 1240 and 1030; *m*/*z* (assignment, relative instensity) 486 (M − H_2O, 2), 405 (M − $2H_2O$ − MOM, 7), 255 (M − $2H_2O$-side chain, 43) and 45 (MOM, 100) (Found: C, 68.9; H, 9.95. Calc. for $C_{28}H_{48}F_2O_4$: C, 69.10; H, 9.94%).

Selective Oxidation of **9**; **9** ⟶ **10**.—To a stirred solution of compound **9** (300 mg, 0.62 mmol) in CH_2Cl_2 (10 cm^3) was added PDC (480 mg) and stirring was continued at room temp. for 2 h. Usual work-up provided (22*R*)-23,23-difluoro-3α-hydroxy-22-methoxymethoxy-24,24-dimethyl-5β-cholan-6-one **10** (240 mg, 82%) as an amorphous solid: $\delta_H(CDCl_3)$ 0.70 (s, 3 H, 18-H), 0.85 (s, 3 H, 19-H), 3.47 (s, 3 H, OCH_3), 3.54 (m, 1 H, 3β-H), 3.80 (t, *J* 13.5, 1 H, 22-H), and 4.70–4.84 centred at 4.76 (AB, *J*, 2 H, OCH_2O); $\delta_F(CDCl_3; \delta_{TFA})$ +40.01 (dd, *J* 19 and 13.5); ν_{max}(KCl)/cm^{-1} 3400, 1730, 1430, 1240 and 1110; *m*/*z* (assignment, relative intensity) 485 (M + 1, 1), 467 (M − OH, 1), 391 (M − CF_2  , 3), 329 (M − MOMOH − CF_2, 48) and 45 (MOM, 100) (Found: C, 69.55; H, 9.4. Calc. for $C_{28}H_{46}F_2O_4$: C, 69.38; H, 9.57%).

Isomerization of **10**; **10** ⟶ **11**.—A solution of compound **10** (200 mg, 0.41 mmol) in methanol (50 cm^3) containing conc. HCl (1.25 cm^3) was refluxed for 30 min and then allowed to stand overnight. The methanol was removed under reduced pressure. Usual work-up provided (22*R*)-23,23-difluoro-3α,22-dihydroxy-24,24-dimethyl-5α-cholan-6-one **11** (150 mg, 83%): m.p. 189–191 °C; $[\alpha]_D^{25}$ −13.13 (*c*, 0.48, $CHCl_3$); $\delta_H(CDCl_3)$ 0.69 (s, 3 H, 18-H), 0.72 (s, 3 H, 19-H), 3.87 (t, *J* 13.5, 1 H, 22-H)

and 4.16 (m, 1 H, 3β-H); $\delta_F(CDCl_3; \delta_{TFA})$ +40.01 (dd, *J* 19.8 and 13.5); $\nu_{max}(KCl)/cm^{-1}$ 3450, 1720, 1430, 1240 and 1110; *m/z* (assignment, relative intensity) 440 (M, 82), 423 (M − OH, 21), 271 (M − H_2O-side chain, 26) and 95 ( + 2, 100) (Found: M^+, 440.3084. $C_{26}H_{42}F_2O_3$ requires *M*, 440.3102).

Lactonization of **11**; **11** ⟶ **14a** + **14b**.—Compound **11** (50 mg, 0.11 mmol) was dissolved in pyridine (2 cm^3) and Ac_2O (0.4 cm^3) was added. The mixture was stirred overnight. Usual work-up afforded an amorphous solid, which was directly dissolved in CH_2Cl_2 (3 cm^3) and cooled at 0 °C; $(CF_3CO)_2O$ (0.24 cm^3) and H_2O_2 (60%, 0.2 cm^3) were added successively. The solution was stirred at 0 °C for 1 h and at room temp. for 3 h. Usual work-up provided (22*R*)-3α,22-diacetoxy-23,23-difluoro-24,24-dimethyl-7-oxa-7a-homo-5α-cholan-6-one **13a** and (22*R*)-3a,22-diacetoxy-23,23-difluoro-24,24-dimethyl-6-oxa-7a-homo-5α-cholan-7-one **13b** both as amorphous solids.

Compound **13a** thus obtained was dissolved in moist methanol (5 cm^3) containing K_2CO_3 (20 mg). The solution was refluxed for 30 min and then the methanol was removed under reduced pressure. Usual work-up gave (22*R*)-23,23-difluoro-3α,22-dihydroxy-24,24-dimethyl-7-oxa-7a-homo-5α-cholan-6-one **14a** (21 mg, 40% from **11**): m.p. 211–212 °C; $[\alpha]_D^{25}$ +39.1 (*c*, 1.6, $CHCl_3$); $\delta_H(CDCl_3)$ 0.77 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 3.2 (m, 1 H, one of 8-H), 3.85 (t, *J* 13.7, 1 H, 22-H) and 4.04–4.20 (m, 2 H, 3β-H and one of 8-H); $\delta_F(CDCl_3; \delta_{TFA})$ +40.50 (dd, *J* 19 and 13.7); $\nu_{max}(KCl)/cm^{-1}$ 3400, 1710, 1430, 1220, 1110 and 1030; *m/z* (assignment, relative intensity) 456 (M, 5), 457 (M + 1, 42), 121 ( − 2, 100) (Found: M^+, 456.3064. Calc. for $C_{26}H_{42}F_2O_4$: *M*, 456.3052).

(22*R*)-23,23-Difluoro-3α,22-dihydroxy-24,24-dimethyl-6-oxa-7a-homo-5α-cholan-7-one **14b** (18 mg, 35% from **11**) was obtained from **13b** as described above for the synthesis of **14a** from **13a**: m.p. 247–249 °C; $[\alpha]_D^{25}$ +8.2 (*c*, 1.5, $CHCl_3$); $\delta_H(CDCl_3)$ 0.73 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 3.86 (t, *J* 13.8, 1 H, 22-H), 4.22 (m, 2 H, 3β-H) and 4.62 (m, 1 H, 5-H); $\delta_F(CDCl_3; \delta_{TFA})$ +40.37 (dd, *J* 19 and 13.8); $\nu_{max}(KCl)/cm^{-1}$ 3400, 1710, 1430, 1220, 1110 and 1030; *m/z* (assignment, relative intensity) 456 (M, 13), 457 (M + 1, 16), 439 (M − OH, 19) and 421 (M + 1 − $2H_2O$, 100). (Found: M^+, 456.3058 Calc. for $C_{26}H_{42}F_2O_4$: *M*, 456.3052).

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