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Synthetic approach to 4-deoxy-4,4-difluoropyranosides via cycloaddition of 2,4-dialkoxy-1,1-difluoro-1,3-dienes with aldehydes

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ABSTRACT

Preparation of the 2,4-dialkoxy-1,1-difluoro-1,3-diene and its Lewis acid-catalyzed cycloaddition with aldehydes leading to 3,3-difluoro-2,3-dihydro-6*H*-pyrans (**3**) are described. Compound **3** and the derived 4-deoxy-4,4-difluoroglycal were found potentially useful as glycosyl donors.

INTRODUCTION

Fluorinated sugars are of interest because of significant alterations in biological responses as compared with the parent molecules, particularly in the field of medicinal chemistry and biochemistry[1,2]. For these purposes, synthetic methods for preparing fluorinated sugars have been developed[3,4]. Most such methods involve fluorination of sugar derivatives with fluorinating reagents for the displacement of a hydroxyl group, ring opening of epoxides or aziridines and electrophilic addition reactions to afford monofluorinated sugars[3,4]. For the preparation of gem-difluorinated sugars, conversion of the carbonyl group by aminosulfur trifluoride may not always be effective because of undesirable side-reactions[5]. Aldol reactions of mono- and di-fluoroacetate derivatives are an alternative means for the preparation of fluorinated sugars, although these have some limitations because of the low diastereoselectivity with chiral carbonyl compounds and the requirement of multiple steps to the final compounds[6,7]. It was expected that the Diels–Alder type of reaction of oxygenated 1,3-dienes containing fluorine(s) with aldehydes would provide useful building blocks for various fluorinated sugars, based on the well documented methodology in the nonfluorinated counterparts brilliantly developed by Danishefsky[8]. However, to our knowledge, such a fluorinated 1,3-diene has never been reported. In this paper, we report the first synthesis of a 2,4-dialkoxy-

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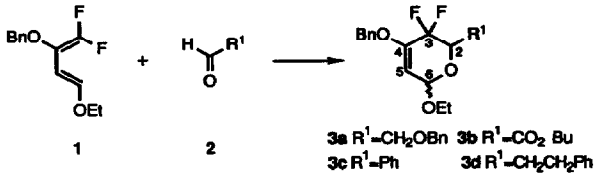


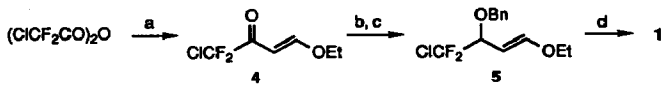
Scheme 1.

1,1-difluoro-1,3-diene (**1**), its cycloaddition reaction with aldehydes, and some reactions of the adducts (**3**) with a view to the preparation of 4-deoxy-4,4-difluoropyranosides[9] (see Scheme 1).

RESULTS AND DISCUSSION

The 1,3-diene (**1**) was prepared from the readily obtainable chlorodifluoromethyl ketone[10] **4** as outlined in Scheme 2. The 1,3-diene (**1**) was obtained in 90–95% yield, as determined by ^{1}H NMR following an extractive work-up of a reaction mixture from dehydrochlorination of the benzyl ether (**5**) with KO*t*-Bu. As **1** was so unstable that it could not be purified by chromatography or distillation, it was used without further purification. It should be noted that a 2-silyloxy derivative of **1** could not be obtained by reaction of the ketone **4** with Zn dust in the presence of trialkylchlorosilane[11]; instead a complex mixture was produced.

The 1,3-diene (**1**) was treated with aldehyde **2** in the presence of a Lewis acid as catalyst to give the desired adduct **3**. The results are shown in Table I. With the aldehyde activated by an α-alkoxy or ester group, $ZnCl_2$ was found suitable for obtaining the adducts **3a** and **3b** in good yields. With benzaldehyde or 3-phenylpropanal, the adduct **3c** or **3d** could be obtained in moderate yield on using $BF_3 \cdot Et_2O$ as catalyst. In all cases, the reactions proceeded with low facial selectivity. The relative stereochemistries of the adducts (**3**) were determined by NOE experiments. For example, the *cis* isomer of **3a** showed a significant NOE (7.5%) between two axial protons (H-2 and H-6) while none was observed for the *trans* isomer. Owing to the presence of geminal fluorines at the allylic position (C-3 in **3**) with consequent lowering of the electron density of the double bond, the enol ether group in the adducts (**3**) was much more stable under acidic conditions than similar, nonfluorinated compounds[8,12]. Thus, the alcoholysis of **3a** (a 1:1 mixture of *trans*:*cis* isomers) with a primary alcohol in the presence of TsOH proceeded



a) CH_2=CHOEt, pyridine b) $LiAlH_4$,Et_2O c) BnBr, NaH, THF-DMF d) *t*-BuOK, THF

Scheme 2.

TABLE I

Lewis acid-catalyzed condensation of **1** with an aldehyde [a]

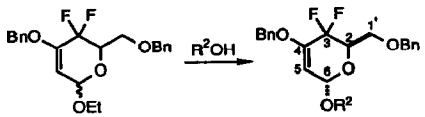
Entry	2 R^1	Lewis acid	temp. (°C) /time (h)	3 Yield [b]	*trans*:*cis*
1	$BnOCH_2$	$ZnCl_2$	−50–r.t/12	**3a** 79%	1.2:1 [c]
2	$CO_2{}^nBu$	$ZnCl_2$	−40/1	**3b** 54%	1:1.6
3	Ph	$BF_3 \cdot Et_2O$	−50/0.5	**3c** 41%	1:3.5 [c]
4	$PhCH_2CH_2$	$BF_3 \cdot Et_2O$	−50/1	**3d** 20%	1:1.6

[a] Solvent: CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{19}F NMR.

smoothly to give a good yield of the 6-alkoxy-2,3-dihydro-6*H*-pyran derivative (**6**) in a highly *trans*-selective manner (**6a**, 84% yield, *trans*:*cis* = 8.2; **6b**, 83% yield, *trans*:*cis* = 9.5) and the benzyl enol ether moiety remained unchanged (Scheme 3). However, similar reaction of **3a** with a secondary alcohol gave rise to a complex mixture. An efficient glycosidation may be achieved by using the glucal derivative **8b** as described next (Scheme 4).

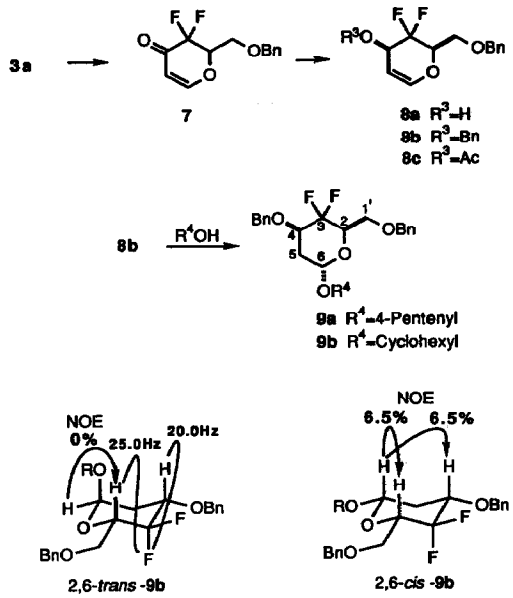
Compound **3a** was converted into the enone **7** in 81% yield by treating **3a** with TsOH in CH_2Cl_2 for 2 h at room temperature. Stereoselective reduction of the carbonyl group of **7** was effected by $NaBH_4$–$CeCl_3 \cdot 7H_2O$ (ref. 13) to give the alcohol (**8a**, *cis*:*trans* = 15), which was then converted into the benzyl ether **8b** or acetate **8c**. Each stereoisomer could be separated by column chromatography. Reaction of *cis*-**8b** with 1.5 equiv of 4-penten-1-ol in the presence of TsOH in CH_2Cl_2 for 24 h at room temperature afforded the corresponding (4-pentenyl)pyranoside **9a** in 96% yield, favoring the 2,6-*trans* isomer (*trans*:*cis* = 5.5)[14]. In a similar manner, with a secondary alcohol (cyclohexanol), *cis*-**8b** provided the cyclohexyl pyranoside **9b** in 84% yield with high *trans*-selectivity (*trans*:*cis* = 13). The stereochemistries of **9** were determined based on their ^1H and ^{19}F NMR spectra and by NOE experiments. Thus, for the cyclohexyl derivative **9c**, typical diaxial coupling constants between the axial fluorine and both H-2 and H-4 (*J* 25.0 and 20.0 Hz, respectively) and no NOE between H-2 and H-6 were observed for the major isomer (2,6-*trans*-**9c**). Clear NOEs between H-6 and both H-2 and H-4 (6.5% for each) were observed for the minor isomer (2,6-*cis*-**9c**).

Although the 2,4-dideoxy-4,4-difluoropyranosides in the present study were racemates, the foregoing results would indicate optically active forms of **8b** and **9a** to be potentially useful as glycosyl donors for preparing di- and oligo-saccharides



3a **6a** R^2=Me **6b** R^2=4-Pentenyl

Scheme 3.



Scheme 4.

containing 2,4-dideoxy-4,4-difluorogalactose[15]. Further investigation along this line is ongoing.

EXPERIMENTAL

Methods.—^{1}H NMR spectra were recorded with a Bruker AM400 or a Varian Gemini-300 spectrometer in $CDCl_3$. ^{19}F NMR spectra were recorded with a Bruker AM400 spectrometer in $CDCl_3$ and chemical shifts are reported as ppm relative to benzotrifluoride as the internal standard. Infrared (IR) spectra were recorded with a Perkin–Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained with a Hitachi M-80 or a VG Auto spec instrument. Column chromatography was performed on silica gel (Wakogel C-200, 75–150 μm) and alumina (ICN Alumina B). Preparative TLC was performed on precoated plates (1-mm thickness, 20 × 20 cm, Merck Silica Gel 60F-254). Medium-pressure liquid chromatography (MPLC) was performed on a 30 × 4 cm (i.d.) prepacked column (silica gel, 50 μm) with a UV detector.

1-Chloro-1,1-difluoro-4-ethoxy-3-buten-2-one (**4**).—To a solution of ethyl vinyl ether (7.7 mL, 80 mmol) and pyridine (2.2 mL, 26.7 mmol) in CH_2Cl_2 (35 mL) was added chlorodifluoroacetic anhydride (20 mL, 115 mmol), and the mixture was stirred for 12 h at room temperature. The mixture was poured into ice–water (100 mL) and extracted with ether. The organic layer was successively washed with aq $NaHCO_3$ and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was distilled under diminished pressure to give **4** as a colorless oil (8.87 g,

60%); bp 66°C/8 mmHg; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3 H, J 7.0 Hz), 4.10 (q, 2 H, J 7.0 Hz), 5.87 (d, 1 H, J 12.3 Hz, H-3), 7.89 (d, 1 H, J 12.3 Hz, H-4); ^{19}F NMR ($CDCl_3$): δ −4.59 (s). High-resolution MS m/z: Calcd for $C_6H_7ClF_2O_2$: 184.0130. Found: 184.0126.

2-Benzyloxy-1-chloro-1,1-difluoro-4-ethoxy-3-butene (**5**).—To a solution of $LiAlH_4$ (475 mg, 12.5 mmol) in ether (50 mL) cooled in a Dry Ice–acetone bath was added a solution of **4** (4.5 g, 24.4 mmol) in ether (20 mL) and then the mixture was stirred for 15 min at the same temperature. To this was added 1 : 1 THF–water (20 mL) and the cooling bath was removed. After being dried over $MgSO_4$, the mixture was concentrated under diminished pressure to leave the crude alcohol (4.46 g, 98%). To a mixture of the crude alcohol and benzyl bromide (4.44 g, 23.8 mmol) in 1 : 1 THF–DMF (50 mL) was added NaH (1.05 g, 26.3 mmol, 60% in mineral oil) in three portions at 0°C (ice–water bath). After being stirred for 1 h, the mixture was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, then concentrated under diminished pressure to leave a residue that was purified by column chromatography on alumina (0.5% AcOEt–hexane) to give **5** as a colorless oil (4.15 g, 64%); ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3 H, J 7.1 Hz), 3.83 (q, 2 H, J 7.1 Hz), 4.03 (dt, 1 H, $J_{2,3}$ 9.1, $J_{2,F}$ 7.4 Hz, H-2), 4.56 (d, 1 H, J 12.1 Hz), 4.72 (dd, 1 H, $J_{3,4}$ 12.9, $J_{2,3}$ 9.1 Hz, H-3), 4.74 (d, 1 H, J 12.1 Hz), 6.52 (d, 1 H, $J_{3,4}$ 12.9 Hz, H-4), 7.30–7.39 (m, 5 H, Ar); ^{19}F NMR ($CDCl_3$): δ −0.18 (dd, 1 F, $J_{F,F}$ 146.0, $J_{2,F}$ 7.4 Hz), 1.05 (dd, 1 F, $J_{F,F}$ 146.0, $J_{2,F}$ 7.4 Hz). High-resolution MS m/z: Calcd for $C_{13}H_{15}ClF_2O_2$: 276.0729. Found: 276.0736.

2-Benzyloxy-4-ethoxy-1,1-difluoro-1,3-butadiene (**1**).—To a suspension of KO*t*-Bu (284 mg, 2.5 mmol) in THF (4 mL) cooled in a Dry Ice–acetone bath at −50°C, was added a solution of **5** (276 mg, 1 mmol) in THF (4 mL). After being stirred for 20 min at the same temperature, the mixture was diluted with water (5 mL) and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$ and K_2CO_3, and then concentrated under diminished pressure to give **1** as a slightly yellowish oil in 95–90% yield: IR (neat) cm^{-1}: 3034, 2982, 1732, 1647, 1632, 1202; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3 H, J 7.0 Hz), 3.81 (q, 2 H, J 7.0 Hz), 4.79 (s, 2 H), 5.25 (ddd, 1 H, J 12.6, 3.3 and 0.9 Hz, H-3), 6.68 (d, 1 H, J 12.6 Hz, H-4), 7.34-7.40 (m, 5 H); ^{19}F NMR ($CDCl_3$): δ −51.24 (dd, 1 F, $J_{F,F}$ 66.0, $J_{3,F}$ 3.3 Hz), −39.44 (brd, 1 F, $J_{F,F}$ 66.0 Hz); MS m/z: 240 (M^+), 220, 162.

General procedure for Lewis acid-catalyzed cycloaddition of **1** *with aldehydes*.—To a cooled solution of 1 mol equiv of aldehyde and Lewis acid (0.1 mol equiv of $BF_3 \cdot Et_2O$ or 0.25 mol equiv of $ZnCl_2$) in CH_2Cl_2 was added **1** freshly prepared from 1.3–1.4 mol equiv of **5**. After being stirred (time and temperature are indicated in Table I), the mixture was diluted with 5% aq $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under diminished pressure. The residue was chromatographed on a silica gel column to give the adduct **3**. The spectral data for each compound are as follows.

trans- *and* cis-*4-Benzyloxy-2-benzyloxymethy-6-ethoxy-3,3-difluoro-2,3-dihydro-6H-pyran* (**3a**).—Compound **3a** was prepared from benzyloxyacetaldehyde (983 mg, 6.6 mmol); *trans*-**3a**: colorless needles (hexane); mp 61.5–62.5°C; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3 H, J 7.1 Hz), 3.59 (dq, 1 H, J 9.6 and 7.1 Hz), 3.76 (dd, 1 H, J_{gem} 11.3, $J_{2,1'}$ 8.0 Hz, H-1'), 3.88 (dq, 1 H, J 9.6 and 7.1 Hz), 3.95 (dd, 1 H, J_{gem} 11.3, $J_{2,1'}$ 3.0 Hz, H-1'), 4.45 (dddd, 1 H, $J_{2,F}$, 22.5, $J_{2,1'}$ 8.0, $J_{2,1'}$ 3.0, $J_{2,F}$ 3.0 Hz, H-2), 4.60 (d, 1 H, J 12.0 Hz), 4.66 (d, 1 H, J 12.0 Hz), 4.81 (d, 1 H, J 11.7 Hz), 4.91 (d, 1 H, J 11.7 Hz), 5.13 (dm, 1 H, $J_{5,6}$ 3.5 Hz, H-5), 5.26 (dd, 1 H, $J_{5,6}$ 3.5, J 2.2 Hz, H-6), 7.28–7.38 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −62.23 (br d, 1 F, $J_{F,F}$ 275.0 Hz), −55.55 (dd, 1 F, $J_{F,F}$ 275.0, $J_{2,F}$ 22.5 Hz). Anal. Calcd for $C_{22}H_{24}F_2O_4$: C, 67.68; H, 6.20. Found: C, 67.75; H, 6.04.

cis-**3a**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3 H, J 7.1 Hz), 3.61 (dq, 1 H, J 9.5 and 7.1 Hz), 3.79 (dd, 1 H, J_{gem} 11.3, $J_{2,1'}$ 8.0 Hz, H-1'), 3.93 (dq, 1 H, J 9.5 and 7.1 Hz), 3.96 (d, 1 H, J_{gem} 11.3 Hz, H-1'), 3.99 (dm, 1 H, $J_{2,F}$ 19.0 Hz, H-2), 4.59 (d, 1 H, J 12.0 Hz), 4.66 (d, 1 H, J 12.0 Hz), 4.84 (d, 1 H, J 11.8 Hz), 4.91 (d, 1 H, J 11.8 Hz), 5.12 (br s, 1 H, H-5), 5.29 (br d, 1 H, J 5.2 Hz, H-6), 7.28–7.41 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −55.34 (br d, 1 F, $J_{F,F}$ 273.5 Hz), −53.49 (ddd, 1 F, $J_{F,F}$ 273.5, $J_{2,F}$ 19.0, J 5.2 Hz). High-resolution MS m/z: Calcd for $C_{22}H_{24}F_2O_4$: 390.1649. Found: 390.1643.

trans- *and* cis-*2-Butoxycarbonyl-4-benzyloxy-6-ethoxy-3,3-difluoro-2,3-dihydro-6H-pyran* (**3b**).—*trans*-**3b**: Colorless needles (hexane); mp 54.5–56.5°C; ^{1}H NMR ($CDCl_3$): δ 0.94 (t, 3 H, J 7.4 Hz), 1.23 (t, 3 H, J 7.1 Hz), 1.42 (m, 2 H), 1.69 (m, 2 H), 3.61 (dq, 1 H, J 9.7 and 7.1 Hz), 3.82 (dq, 1 H, J 9.7 and 7.1 Hz), 4.23 (dt, 1 H, J_{gem} 10.8 J_{vic} 6.7 Hz, OCHPr), 4.37 (dt, 1 H, J_{gem} 10.8, J_{vic} 6.7 Hz, OCHPr), 4.90 (dd, 1 H, $J_{2,F}$ 23.1, $J_{2,F}$ 3.4 Hz, H-2), 5.13 (m, 1 H, H-5), 5.36 (m, 1 H, H-6), 7.32–7.38 (m, 5 H); ^{19}F NMR ($CDCl_3$): δ −58.12 (ddd, 1 F, $J_{F,F}$ 275.4, $J_{2,F}$ 3.4, J 3.4 Hz), −50.31 (ddd, 1 F, $J_{F,F}$ 275.4, $J_{2,F}$ 23.1, J 1.6 Hz). Anal. Calcd for $C_{19}H_{24}F_2O_5$: C, 61.60; H, 6.53. Found: C, 61.70; H, 6.45.

cis-**3b**: Colorless needles (hexane); mp 38.5–39.5°C; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3 H, J 7.4 Hz), 1.24 (t, 3 H, J 7.1 Hz), 1.41 (m, 2 H), 1.67 (m, 2 H), 3.61 (dq, 1 H, J 9.5 and 7.1 Hz), 3.94 (dq, 1 H, J 9.5 and 7.1 Hz), 4.21 (dt, 1 H, J_{gem} 10.8, J_{vic} 6.5 Hz, OCHPr), 4.33 (dt, 1 H, J_{gem} 10.8 J_{vic} 6.7 Hz, OCHPr), 4.38 (dd, 1 H, $J_{2,F}$ 17.6, $J_{2,F}$ 6.3 Hz, H-2), 4.85 (d, 1 H, J 11.8 Hz), 4.94 (d, 1 H, J 11.8 Hz), 5.12 (m, 1 H, H-5), 5.29 (br s, 1 H, H-6), 7.32–7.39 (m, 5 H); ^{19}F NMR ($CDCl_3$): δ −50.86 (dm, 1 F, $J_{F,F}$ 274.3 Hz), −49.50 (dddd, 1 F, $J_{F,F}$ 274.3, $J_{2,F}$ 17.6, J 5.1 and 1.0 Hz). Anal. Calcd for $C_{19}H_{24}F_2O_5$: C, 61.60; H, 6.53. Found: C, 61.37; H, 6.43.

trans- *and* cis-*4-Benzyloxy-6-ethoxy-3,3-difluoro-2-phenyl-2,3-dihydro-6H-pyran* (**3c**).—Compound **3c**, which was an unseparable stereoisomeric mixture, was obtained as a colorless oil; high-resolution MS m/z: Calcd for $C_{20}H_{19}F_2O_3$: 345.1302. Found: 345.1300.

trans-**3c**: ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 3 H, J7.1 Hz), 3.57 (dq, 1 H, J 9.6 and 7.1 Hz), 3.78 (dq, 1 H, J 9.6 and 7.1 Hz), 4.87 (d, 1 H, J 11.8 Hz), 4.96 (d, 1 H, J 11.8 Hz), 5.16 (m, 1 H, H-5), 5.31 (dd, 1 H, $J_{2,F}$ 21.2, J 3.8 Hz, H-2), 5.38 (m, 1 H, H-6),

7.31–7.53 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −61.56 (br d, 1 F, $J_{F,F}$ 274.8 Hz), −52.25 (dd, 1 F, $J_{F,F}$ 274.8, $J_{2,F}$ 21.2 Hz).

cis-**3c**: ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3 H, *J* 7.1 Hz), 3.64 (dq, 1 H, *J* 9.5 and 7.1 Hz), 3.93 (dq, 1 H, *J* 9.5 and 7.1 Hz), 4.76 (dd, 1 H, $J_{2,F}$ 19.0, *J* 3.3 Hz, H-2), 4.89 (d, 1 H, *J* 11.9 Hz), 4.96 (d, 1 H, *J* 11.9 Hz), 5.17 (d, 1 H, *J* 3.3 Hz, H-5), 5.43 (d, 1 H, $J_{6,F}$ 6.6 Hz, H-6), 7.31–7.53 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −55.66 (br d, 1 F, $J_{F,F}$ 272.7 Hz), −48.44 (ddd, 1 F, $J_{F,F}$ 272.7, $J_{2,F}$ 19.0, $J_{6,F}$ 6.6 Hz).

trans- *and* cis-*4-Benzyloxy-6-ethoxy-3,3-difluoro-2-(2-phenylethyl)-2,3-dihydro-6H-pyran* (**3d**).—*trans*-**3d**: Colorless needles (hexane); mp 68.5–70.0°C; ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3 H, *J* 7.1 Hz), 2.02 (m, 1 H), 2.14 (m, 1 H), 2.70 (ddd, 1 H, *J* 13.9, 9.7, and 7.0 Hz), 2.94 (ddd, 1 H, *J* 13.9, 10.0 and 5.2 Hz), 3.57 (dq, 1 H, *J* 9.5 and 7.1 Hz), 3.83 (dq, 1 H, *J* 9.5 and 7.1 Hz), 4.23 (dddd, 1 H, $J_{2,F}$ 21.0, $J_{2,1'}$ 10.0, $J_{2,F}$ 3.3, *J* 3.3 Hz, H-2), 4.81 (d, 1 H, *J* 11.7 Hz), 4.89 (d, 1 H, *J* 11.7 Hz), 5.08 (m, 1 H, H-5), 5.22 (m, 1 H, H-6), 7.18–7.38 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −63.46 (br d, 1 F, $J_{F,F}$ 273.3 Hz), −56.07 (dd, 1 F, $J_{F,F}$ 273.3, $J_{2,F}$ 21.0 Hz). Anal. Calcd for $C_{22}H_{24}F_2O_3$: C, 70.57; H, 6.46. Found: C, 70.54; H, 6.39.

cis-**3d**: Colorless needles (hexane); mp 57.0–58.0°C; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3 H, *J* 7.1 Hz), 2.12 (m, 2 H), 2.75 (dt, 1 H, *J* 13.8 and 8.4 Hz), 2.94 (ddd, 1 H, *J* 13.8, 8.3 and 5.5 Hz), 3.58 (m, 1 H, H-2), 3.61 (dq, 1 H, *J* 9.4 and 7.1 Hz), 3.92 (dq, 1 H, *J* 9.4 and 7.1 Hz), 4.82 (d, 1 H, *J* 11.9 Hz), 4.90 (d, 1 H, *J* 11.9 Hz), 5.07 (br s, 1 H, H-5), 5.17 (m, 1 H, H-6), 7.19–7.39 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −56.05 (br d, 1 F, $J_{F,F}$ 215.4 Hz), −52.90 (ddd, 1 F, $J_{F,F}$ 215.4, *J* 14.6 and 4.9 Hz). Anal. Calcd for $C_{22}H_{24}F_2O_3$: C, 70.57; H, 6.46. Found: C, 70.47; H, 6.48.

4-Benzyloxy-2-benzyloxymethyl-3,3-difluoro-6-(4-pentenyloxy)-2,3-dihydro-6H-pyran (**6b**).—A mixture of **3a** (1 : 1 mixture of *trans* : *cis* isomers, 81 mg), 4-penten-1-ol (0.32 mL), 4A molecular sieves (50 mg), and TsOH monohydrate (200 mg) in ether (5 mL) was stirred for 5 h at room temperature. The mixture was diluted with ether and successively washed with aq $NaHCO_3$ and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by preparative TLC (5 : 1 hexane–EtOAc) to give a stereoisomeric mixture of **6b** (66 mg, 74%) as a colorless oil. Each isomer was obtained individually by separation with MPLC.

trans-**6b**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.73 (m, 2 H), 2.12 (m, 2 H), 3.52 (dt, 1 H, *J* 9.6 and 6.6 Hz, $OCHC_4H_7$), 3.76 (dd, 1 H, *J* 11 and 8.0 Hz, CHOBn), 3.83 (dt, 1 H, *J* 9.6 and 6.6 Hz, $OCHC_4H_7$), 3.95 (dd, 1 H, *J* 11 and 2.6 Hz, CHOBn), 4.52 (ddm, 1 H, $J_{2,F}$ 22.7, *J* 8.0 Hz, H-2), 4.60 (d, 1 H, *J* 12 Hz), 4.65 (d, 1 H, *J* 12 Hz), 4.81 (d, 1 H, *J* 11.7 Hz), 4.91 (d, 1 H, *J* 11.7 Hz), 4.95 (d, 1 H, *J* 10.3 Hz, $CH{=}CH_2$), 5.02 (d, 1 H, *J* 17 Hz, $CH{=}CH_2$), 5.12 (dd, 1 H, *J* 3.3 and 3.3 Hz, H-5), 5.23 (m, 1 H, H-6), 5.80 (ddt, 1 H, *J* 17, 10.3 and 6.6 Hz, $CH{=}CH_2$), 7.29–7.38 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −62.26 (br d, 1 F, $J_{F,F}$ 275 Hz), −55.67 (dd, 1 F, $J_{F,F}$ 275, $J_{2,F}$ 22.7 Hz). High-resolution MS *m/z*: Calcd for $C_{25}H_{28}F_2O_4$: 430.1956. Found: 430.1970.

cis-**6b**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.71 (m, 2 H), 2.12 (m, 2 H), 3.54 (dt, 1 H, *J* 9.5 and 6.8 Hz, $OCHC_4H_7$), 3.76 (dd, 1 H, *J* 10.8 and 7.2 Hz), 3.85 (dt, 1 H,

J 9.5 and 6.6 Hz), 3.95 (dd, 1 H, *J* 10.8 and 3.0 Hz), 3.99 (dm, 1 H, $J_{2,F}$ 19 Hz, H-2), 4.84 (d, 1 H, *J* 11.8 Hz), 4.90 (d, 1 H, *J* 11.8 Hz), 4.97 (d, 1 H, *J* 10.2 Hz, $CH{=}CH_2$), 5.03 (d, 1 H, *J* 17 Hz, $CH{=}CH_2$), 5.10 (br s, 1 H, H-5), 5.27 (dm, 1 H, *J* 5.2 Hz, H-6), 5.81 (ddt, 1 H, *J* 17, 10.2 and 6.7 Hz, $CH{=}CH_2$), 7.29–7.38 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −55.80 (br d, 1 F, $J_{F,F}$ 275 Hz), −53.48 (ddd, 1 F, $J_{F,F}$ 275, $J_{2,F}$ 19, *J* 6.0 Hz). High-resolution MS *m/z*: Found 430.1957.

*2-Benzyloxymethy-3,3-difluoro-3,4-dihydro-2*H*-pyran-4-one* (**7**).—A mixture of **3a** (300 mg, 0.77 mmol) and TsOH monohydrate (60 mg) in CH_2Cl_2 (15 mL) was stirred for 2 h at room temperature. After removal of the solvent, the residue was chromatographed on a column of silica gel (5 : 1 hexane–EtOAc) to give **7** (160 mg, 82%) as a pale-yellow oil; IR (neat) ν cm^{-1}; 1780, 1707, 1150; ^{1}H NMR ($CDCl_3$): δ 3.97 (m, 2 H), 4.62 (s, 2 H), 4.65 (m, 1 H, H-2), 5.59 (dt, 1 H, $J_{5,6}$ 6.4, $J_{5,F}$ 3.0 Hz, H-5), 7.29–7.40 (m, 5 H), 7.45 (br d, 1 H, $J_{5,6}$ 6.4 Hz, H-6); ^{19}F NMR ($CDCl_3$): δ −60.47 (ddd, 1 F, $J_{F,F}$ 282.8, $J_{2,F}$ 18.6, *J* 2.0 Hz), −59.61 (ddd, 1 F, $J_{F,F}$ 282.8, $J_{2,F}$ 9.8, *J* 3.0 Hz). High-resolution MS *m/z*: Calcd for $C_{13}H_{12}F_2O_3$: 254.0755. Found: 254.0728.

*4-Benzyloxy-2-benzyloxymethyl-3,3-difluoro-3,4-dihydro-2*H*-pyran* (**8b**).—To a mixture of **7** (296 mg, 1.17 mmol) and $CeCl_3 \cdot 7H_2O$ (652 mg, 1.75 mmol) in 1 : 1 CH_2Cl_2–EtOH (14 mL) cooled in a Dry Ice–acetone bath was added $NaBH_4$ (100 mg, 2.6 mmol), and the mixture was stirred for 16 h, during which time the temperature rose to room temperature. The mixture was extracted with ether after addition of satd aq NH_4Cl and the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give the alcohol **8a** (282 mg, 94%) as a stereoisomeric mixture (*cis* : *trans* = 15 : 1 by ^{1}H and ^{19}F NMR). To a solution of **8a** (270 mg, 1.05 mmol) and benzyl bromide (0.13 mL, 1.05 mmol) in 1 : 1 THF–DMF (5 mL) at 0°C was added NaH (55 mg, 60% in mineral oil) and the mixture was stirred for 1 h. The mixture was diluted with ether, and then washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (20 : 1 hexane–EtOAc) to give **8b** (336 mg, 92%), which was further submitted to MPLC to separate the steroisomers.

cis-**8b**: Colorless needles (hexane); mp 31.5–32.5°C; ^{1}H NMR ($CDCl_3$): δ 3.93 (d, 2 H, *J* 5.4 Hz), 4.20 (tm, 1 H, $J_{4,F}$ 10.0 Hz), 4.30 (dm, 1 H, $J_{2,F}$ 16.3 Hz, H-2), 4.58 (d, 1 H, *J* 12.0 Hz), 4.66 (d, 1 H, *J* 12.0 Hz), 4.67 (d, 1 H, *J* 12.0 Hz), 4.82 (d, 1 H, *J* 12.0 Hz), 4.85 (m, 1 H, H-5), 6.43 (br d, 1 H, *J* 6.1 Hz, H-6), 7.29–7.40 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −65.68 (ddd, 1 F, $J_{F,F}$ 253.3, $J_{2,F}$ 16.3, $J_{4,F}$ 10.0 Hz), −46.07 (dm, 1 F, $J_{F,F}$ 253.3 Hz). Anal. Calcd for $C_{20}H_{20}F_2O_3$: C, 69.35; H, 5.82. Found. C, 69.48; H, 5.82.

trans-**8b**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 3.81 (dd, 1 H, *J* 11.0 and 7.7 Hz), 3.85 (ddd, 1 H, $J_{4,F}$ 8.0, $J_{4,5}$ 5.6, *J* 3.5 Hz, H-4), 3.95 (dt, 1 H, *J* 11.0 and 2.2 Hz), 4.41 (ddd, 1 H, $J_{2,F}$ 27.3, $J_{2,1'}$ 7.7, $J_{2,1'}$ 2.2 Hz, H-2), 4.61 (d, 1 H, *J* 12.1 Hz), 4.67 (d, 1 H, *J* 12.1 Hz), 4.67 (d, 1 H, *J* 11.8 Hz), 4.80 (d, 1 H, *J* 11.8 Hz), 4.94 (ddd, 1 H, $J_{4,5}$ 5.6, $J_{5,6}$ 5.6, $J_{5,F}$ 5.6 Hz, H-5), 6.52 (dd, 1 H, $J_{5,6}$ 5.6, *J* 1.8 Hz, H-6),

7.29–7.39 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −61.20 (br d, 1 F, $J_{F,F}$ 256.3 Hz), −57.51 (ddd, 1 F, $J_{F,F}$ 256.3, $J_{2,F}$ 27.3, $J_{4,F}$ 8.0 Hz). Anal. Found: C, 69.36; H, 5.85.

4-Benzyloxy-4-benzyloxymethyl-3,3-difluoro-6-(4-pentenyloxy)tetrahydropyran (**9a**). —A mixture of *cis*-**8b** (151 mg, 0.44 mmol), 4-penten-1-ol (70 μL), and TsOH monohydrate (120 mg) in CH_2Cl_2 (1 mL) was stirred for 24 h at room temperature. The mixture was diluted with CH_2Cl_2 and successively washed with aq $NaHCO_3$ and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was submitted to MPLC (5 : 1 hexane–EtOAc) to give (2*R**,4*R**,6*S**)-**9a** (153 mg, 81%) and (2*R**,4*R**,6*R**)-**9a** (28 mg, 15%).

(2*R**,4*R**,6*S**)-**9a**: Colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 2 H), 1.97 (dt, 1 H, *J* 12.5 and 3.4 Hz), 2.08–2.19 (m, 3 H), 3.43 (dt, 1 H, *J* 9.8 and 6.5 Hz, $OCHC_4H_7$), 3.71 (dt, 1 H, *J* 9.8 and 6.5 Hz, $OCHC_4H_7$), 3.73 (dm, 1 H, *J* 10.8 Hz, H-1′), 3.90 (dm, 1 H, *J* 10.8 Hz, H-1′), 3.98–4.09 (m, 2 H, 4.56 (d, 1 H, *J* 12.0 Hz), 4.64 (d, 1 H, *J* 12.0 Hz), 4.67 (d, 1 H, *J* 11.7 Hz), 4.83 (d, 1 H, *J* 11.7 Hz), 4.95 (m, 1 H, H-6), 4.96 (d, 1 H, *J* 10.3 Hz, $CH{=}CH_2$), 5.20 (d, 1 H, *J* 16.9 Hz, $CH{=}CH_2$), 5.80 (ddt, 1 H, *J* 16.9, 10.3, and 6.7 Hz, $CH{=}CH_2$), 7.27–7.39 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −74.35 (ddd, 1 F, $J_{F,F}$ 244, *J* 24.9 and 20.0 Hz), −53.93 (br d, 1 F, $J_{F,F}$ 244 Hz). Anal. Calcd for $C_{25}H_{30}F_2O_4$: C, 69.42; H, 6.99. Found: C, 69.58; H, 7.00.

(2*R**,4*R**,6*R**)-**9a**: Colorless needles (hexane); mp 51.5–52.5°C; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 2 H), 1.92 (ddd, 1 H, *J* 13.0, 12.9, and 9.8 Hz), 2.12 (m, 2 H), 2.20 (d, 1 H, *J* 12.9 Hz), 3.48 (dt, 1 H, *J* 9.5 and 6.7 Hz, $OCHC_4H_7$), 3.62–3.77 (m, 3 H), 3.91 (dt, 1 H, *J* 9.5 and 6.7 Hz, $OCHC_4H_7$), 3.98 (dm, 1 H, *J* 10.9 Hz, H-1′), 4.52 (dm, 1 H, *J* 9.8 Hz, H-6), 4.57 (d, 1 H, *J* 12.0 Hz), 4.64 (d, 1 H, *J* 12.0 Hz), 4.68 (d, 1 H, *J* 12.2 Hz), 4.82 (d, 1 H, *J* 12.2 Hz), 4.96 (dm, 1 H, *J* 10.3 Hz, $CH{=}CH_2$), 5.02 (d, 1 H, *J* 17.1 Hz, $CH{=}CH_2$), 5.81 (ddt, 1 H, *J* 17.1, 10.3, and 6.7 Hz, $CH{=}CH_2$), 7.27–7.38 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −72.59 (ddd, 1 F, $J_{F,F}$ 245, *J* 22.7 and 19.7 Hz), −57.51 (br d, 1 F, $J_{F,F}$ 245 Hz). Anal. Found: C, 69.43; H, 7.01.

4-Benzyloxy-2-benzyloxymethyl-6-cyclohexyloxy-3,3-difluorotetrahydropyran (**9b**). —Similarly to the preparation of **9a**, the cyclohexyl derivative (**9b**) was obtained from **8b** and 1.5 mol equiv of cyclohexanol.

(2*R**,4*R**,6*S**)-**9b**: 79% Yield; colorless needles (hexane); mp 78.5–80°C; ^{1}H NMR ($CDCl_3$): δ 1.18–1.54 (m, 6 H), 1.72 (br s, 2 H), 1.90 (m, 2 H), 1.99 (ddd, 1 H, J_{gem} 13.0, $J_{4,5}$ 13.0, $J_{5,6}$ 3.4 Hz, H-5), 2.14 (dm, 1 H, J_{gem} 13.0 Hz), 3.62 [m, 1 H, $OCH(CH_2)_5$], 3.74 (dd, 1 H, J_{gem} 10.9, $J_{2,1'}$ 7.6 Hz, H-1′), 3.96 (br d, 1 H, J_{gem} 10.9 Hz, H-1′), 4.07 (ddt, 1 H, $J_{4,F}$ 20.0, $J_{4,5}$ 13.0, *J* 5.4 Hz, H-4), 4.16 (ddd, 1 H, $J_{2,F}$ 25.0, $J_{2,1'}$ 7.6, *J* 2.4 Hz, H-2), 4.57 (d, 1 H, *J* 12.0 Hz), 4.64 (d, 1 H, *J* 12.0 Hz), 4.67 (d, 1 H, *J* 11.7 Hz), 4.84 (d, 1 H, *J* 11.7 Hz), 5.13 (br s, 1 H, H-6), 7.27–7.41 (m, 10 H); ^{19}F NMR $CDCl_3$): δ −74.43 (ddd, 1 F, $J_{F,F}$ 243.6, $J_{2,F}$ 25.0, $J_{4,F}$ 20.0 Hz), −53.93 (br d, 1 F, $J_{F,F}$ 243.6 Hz). Anal. Calcd for $C_{26}H_{32}F_2O_4$: C, 69.93; H, 7.22. Found: C, 69.82; H, 7.24.

(2*R**,4*R**,6*R**)-**9b**: 6% Yield; colorless needles (hexane); mp 71.5–72.5°C; ^{1}H NMR ($CDCl_3$): δ 1.14–1.53 (m, 6 H), 1.72–.99 (m, 5 H), 2.16 (d, 1 H, *J* 12.9 Hz, H-5), 3.62–3.77 (m, 4 H), 3.98 (dm, 1 H, *J* 10.8 Hz, H-1′), 4.57 (d, 1 H, *J* 11.9 Hz), 4.63 (d, 1 H, *J* 11.9 Hz), 4.65 (m, 1 H, H-6), 4.68 (d, 1 H, *J* 12.2 Hz), 4.81 (d, 1 H, *J* 12.2 Hz), 7.27–7.40 (m, 10 H); ^{19}F NMR ($CDCl_3$): δ −72.50 (ddd, 1 F, $J_{F,F}$ 245, 23.0, and 19.5 Hz), −57.60 (br d, 1 F, $J_{F,F}$ 245 Hz). High-resolution MS *m/z*: Calcd for $C_{26}H_{32}F_2O_4$: 446.2269. Found: 446.2268.

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