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Synthesis of trifluoromethylated analogues of β-L-fucofuranose and β-L-4,6-dideoxyxylohexopyranose

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Abstract

Efficient strategy to trifluoromethylated *trans*-disubstituted alkene **3** was developed starting from commercially available 4,4,4-trifluoro-3-oxo-butyric acid ethyl ester **12**. 6-Deoxy-6,6,6-trifluorosugars **21** and **30** were synthesized from **3** in high stereoselectivity and in a straightforward fashion. The key steps were Sharpless AD reaction, regioselective ring opening of trifluoromethylated cyclic sulfate, Horner–Wadsworth–Emmons reaction and TEMPO oxidation. It was noteworthy that the oxidation of alcohols **20** and **29** followed by deprotection and acetylation gave the single isomer target molecules **21** and **30**, respectively.
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Keywords: Trifluoromethylated compounds; Sugars; Stereoselectivity

1. Introduction

The incorporation of fluorine atom(s) or fluoroalkyl groups into organic compounds can have profound effects on the material characteristics or biological activity of compounds by changing their physico-chemical and/or pharmacological properties [1]. However, fluorine has been identified only in a relatively small number of tropical and subtropical plants, microorganisms and actinomycetes [2]. Up to date, growing interests in organofluorinated compounds have led to a lot of syntheses of them. Among many fluorine-containing compounds, ''Fluoro Sugars'' have recently attracted more and more attentions from organic chemists and pharmaceutists [3]. Besides of modifying the chemical properties and biological activity, lipophilicity is also an important consideration in the design and synthesis of ''Fluoro Sugars'' since it often controls absorption, transport, or receptor binding [4]. Notable in the lipophilicity category is that fluorine atom(s) and fluoroalkyl groups, especially trifluoromethyl group could influence the lipophilicity of organic compounds [5]. In addition, it is well known that trifluoromethyl groups might be suitable sensors in studies of transport, metabolism and enzymology of fluorinated sugars [6]. Furthermore, what should be also regarded is that Toyokuni group has proposed that replacement of the methyl group in the fucose reside with the more hydrophobic trifluoromethyl group might provide an artificial inhibitor for Le^x–Le^x interaction [7]. After that, several groups [8] also reported the independent synthesis of some other trifluoromethyl analogues of 6-deoxysugars. In spite of these pioneering syntheses, however, many of their methodologies suffered from low stereoselectivity and low yield. 6-Deoxysugars [9] are an interesting class of compounds, which are broadly found in nature as the constituent sugars of various antibiotics. For some of these groups of antibiotics the saccharides have been implicated in the delivery and binding of the biologically active agent to a target site [10]. Modification of these carbohydrate units could be of interest as a mean of changing the biological activity of the parent antibiotics. For example, Kondo group described that the replacement of the six-membered fucose ring with five-membered fucose ring of sialyl Lewis (sLe^X) analogue could also bind to a calcium ion on the E-selectin [11]. In addition, Thiem and co-workers reported the synthesis of GDP-L-xylohexose and analogues for transferase enzymatic studies [12]. In view of the above facts, we herein report an efficient and highly stereoselective synthesis of trifluoromethylated

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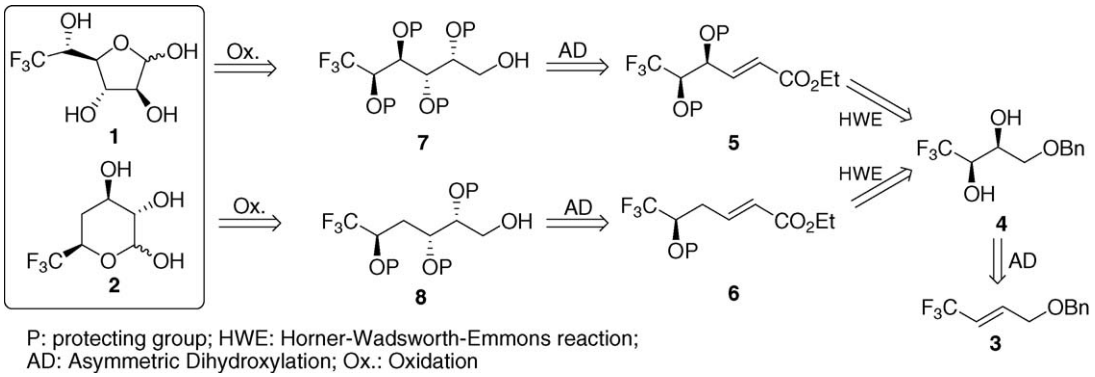


Scheme 1.

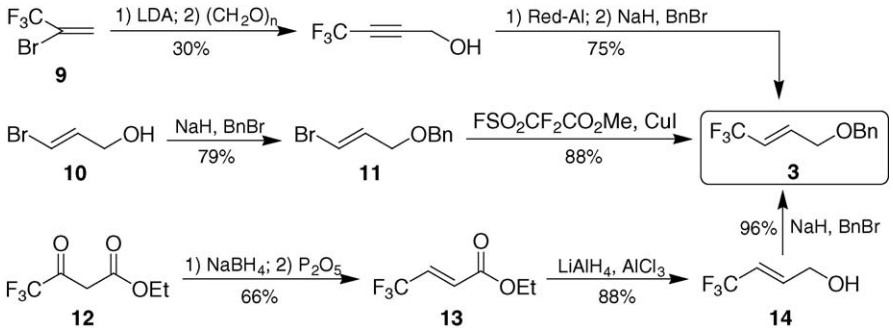
analogues of β-L-fucofuranose and β-L-4,6-dideoxyxylohexopyranose.

2. Results and discussion

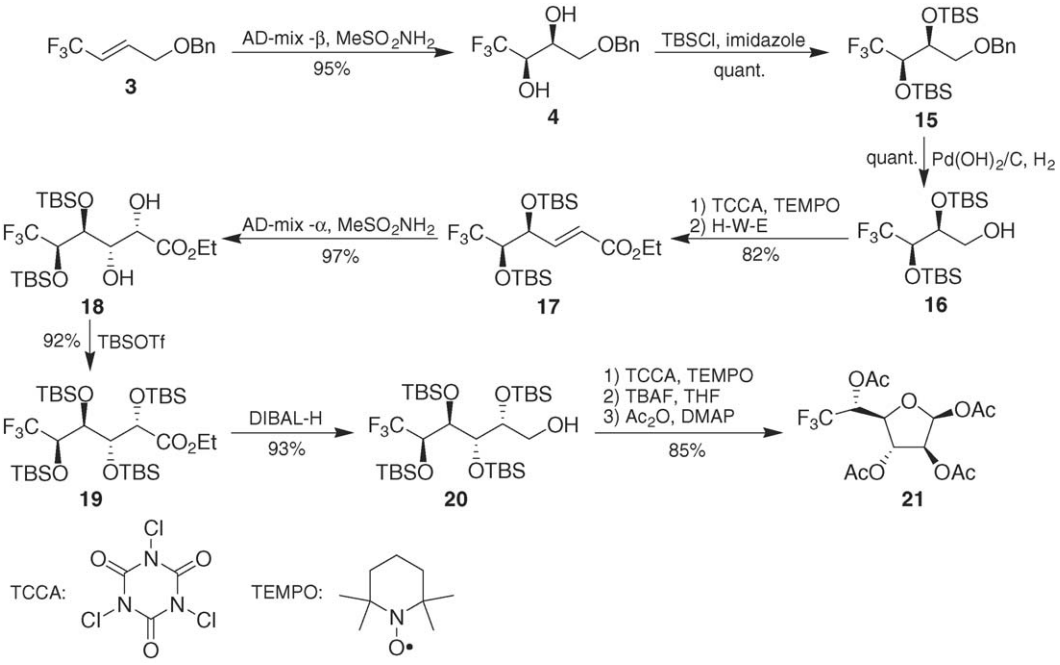
The retrosynthetic analysis showed that fluoro sugars **1** and **2** could be reached from enantiopure diol **4** (Scheme 1). Our group had developed procedures for preparation of compound **4** from *trans*-1-benzyloxy-4,4,4-trifluoro-2-butene **3** in high yield and enantioselectivity [13]. Fluoro sugars **1** and **2** could result from alcohols **7** and **8** via oxidation followed by intramolecular cyclization. Asymmetric dihydroxylation of α, β-unsaturated esters **5** and **6** would reach alcohols **7** and **8**. Lengthening of terminal carbon chain via HWE reaction of the key intermediate **4** might realize the syntheses of compounds **5** and **6**.

Previously, two synthetic strategies were developed to prepare the trifluoromethylated *trans*-disubstituted alkene **3** [13], starting from 2-bromo-3,3,3-trifluoropropene **9** and *trans*-3-bromo-allylic alcohol **10**, respectively (Scheme 2). However, the two strategies both suffered from some drawbacks. The route starting from compound **9** gave the alkene **3** in very low yield. Although the other route from alcohol **10** could produce the desired compound **3** in high yield, it should be pointed that alkene **3** was difficult to separate to give pure form by silica gel chromatography because compound **11** could not always be completely converted and the polarities of substrate **11** and product **3** were very close to each other. Herein, a convenient and efficient route to **3** was developed starting from commercially available 4,4,4-trifluoro-3-oxo-butyric acid ethyl ester **12**. Compound **12** was first converted to (*E*)-α-trifluoromethyl-α, β-unsaturated ester **13** by treatment with sodium borohydride [14] and followed by dehydration with phosphorus pentoxide [15]. Then, reduction of ester **13** with $LiAlH_4/AlCl_3$ produced the allylic alcohol **14** in 88% yield [16], which was treated with NaH/BnBr to smoothly afford the desired trifluoromethylated *trans*-disubstituted alkene **3** in 96% yield.

With trifluoromethylated *trans*-disubstituted alkene **3** in hand, the Sharpless AD reaction was then carried out on **3** to afford the chiral building block **4** [13]. In view of the conveniences of following protecting group removal, the two hydroxyl groups in the diol **4** were protected to the *tert*-butyldimethylsilyl ether form and desired compound **15** was furnished in almost quantitative yield (Scheme 3). Hydrogenation of compound **15** under the catalysis of palladium hydroxide on carbon afforded the expected alcohol **16** in very high yield [17]. Using the recently reported methodology of Giacomelli's group [18], treatment of alcohol **16** with trichloroisocyanuric acid (TCCA)/2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) [19] (0.01 eq.) in CH_2Cl_2 successfully produced the corresponding aldehyde, followed by Wittig–Horner–Emmons condensation with triethyl phosphonoacetate to give the desired (*E*)-conjugated ester **17** in 82% yield over two steps. Under the Sharpless AD reaction condition with AD-mix-α as chiral catalyst, diol **18** was successfully obtained in 97% yield and 98% de determined by ^{19}F NMR from the ester **17**. Silylation of hydroxyl groups of compound **18** with



Scheme 2.

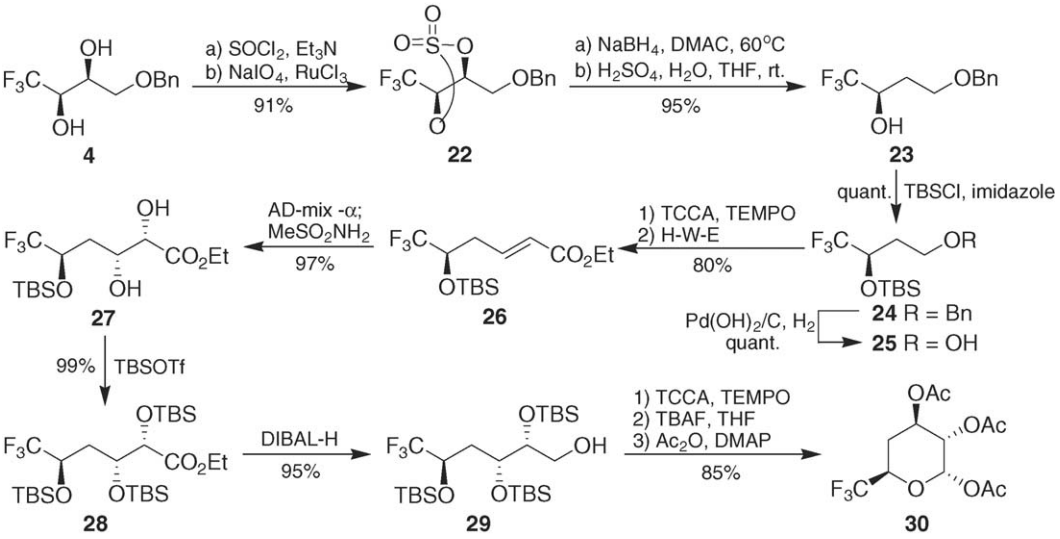


Scheme 3.

tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) gave the tetra-TBS ester **19**, which was then treated with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 at −78 °C to produce the alcohol **20** in 93% yield. Considering the anomeric effect, the hydroxyl groups of compound **1** were acetylated to give its *O*-acetyl form, which would facilitate purification and prevent the conversion of sugar between furanose and pyranose. Finally, oxidation of alcohol **20** with TCCA/TEMPO followed by deprotection and acetylation gave our desired trifluoromethylated sugar **21** in 85% yield for three steps. It was noteworthy that the acetylation of carbohydrates usually gave pyranoid sugars, whereas the acetylation of the tifluoromethylated carbohydrate produced furanoid **21** exclusively.

The stereochemistry of products **21** has been established by ^{1}H NMR and 2D NMR NOESY experiments (Fig. 1). The small coupling constant (J = 4.5 Hz) of the anomeric proton (H-1) indicated the H-1eq-H-2ax relationship. It showed that the configuration of C-1 was *S* configuration and fluoro sugar **21** was the β-anomeric isomer. The strong NOE correlation between H-1 and H-4 of compound **21** showed that the sugar **21** was furanose. In addition, the NOE correlations between H-2 and H-4 along with between H-3 and H-5 further confirmed the configuration of asymmetric dihydroxylation of ester **17**.

We also wanted to extend this strategy to the synthesis of L-xylo-4,6-dideoxy-hexose **2** (Scheme 4). Diol **4** was first converted to the 2,3-cyclicsulfite upon treatment with $SOCl_2$, which was further oxidized to the cyclic sulfate **22** with RuO_4



Scheme 4.

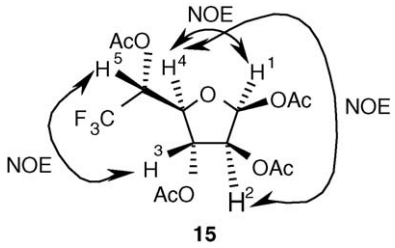


Fig. 1. NOE correlation from NOESY spectra of **21**.

(generated in situ from $NaIO_4$/catalylic $RuCl_3$) in 91% yield for two steps [20]. Nucleophilic ring opening of cyclicsulfate **22** with $NaBH_4$ in *N*,*N*-dimethylacetamide (DMAC) occurred exclusively at C2 position and the resultant compound was directly treated with aqueous H_2SO_4 to give the desired alcohol **23** in almost quantitative yield [20]. Finally, applying the similar route and reaction condition for synthesis of compound **21** from alcohol **4**, trifluoromethylated sugar **30** was successfully prepared from alcohol **23**. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR of compound **30** indicated doubtlessly that it was also single isomer.

In summary, we developed an efficient strategy to synthesis of key intermediate trifluoromethylated *trans*-disubstituted alkene **3** starting from commercially available 4,4,4-trifluoro-3-oxobutyric acid ethyl ester **12**. Then, 6-deoxy-6,6,6-trifluorosugars **21** and **30** were designed and synthesized in highly stereoselectivity. In our opinion, our methodology of synthesizing fluoro sugars **21** and **30** could be applied to prepare the other fluoro sugar isomers by altering ligands of Sharpless AD reaction.

3. Experimental

3.1. Ethyl 4,4,4-trifluorocrotonate (*13*)

To a solution of **12** (55.2 g, 0.300 mol) in Et_2O (600 mL) was added $NaBH_4$ (12.4 g, 0.315 mol) in several portions over 30 min at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature overnight. Then, a solution of aqueous HCl (10%, 300 mL) was carefully added to the reaction mixture and the resultant solid was removed by filtration. The aqueous layer was extracted with Et_2O (2 × 150 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated to give a clear oil (45.7 g). Then, phosphorus pentoxide (16.9 g, 0.12 mol) was added to the above resultant oil and the mixture was stirred at 100 °C for 1 h. After cooled to room temperature, the mixture was distillated to yield **13** [21] (33.3 g, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83–6.73 (m, 1H), 6.50 (d, J = 15.9 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.94 (d, J = 7.9 Hz).

3.2. (E)-4,4,4-Trifluoro-2-buten-1-ol (*14*)

A solution of **13** (31.6 g, 0.188 mol) in Et_2O (90 mL) was added to a suspension of $LiAlH_4$ (15.7 g, 0.414 mol) and $AlCl_3$ (25.1 g, 0.188 mol) in Et_2O (320 mL) at 0 °C for 1 h. After the mixture was stirred overnight at room temperature, 10% aqueous HCl (180 mL) was carefully added to decompose excess $LiAlH_4$. The aqueous layer was extracted with Et_2O (2 × 150 mL), and the combination was dried over Na_2SO_4, filtered and evaporated to give **14** [22] (20.2 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54–6.46 (m, 1H), 6.00–5.91 (m, 1H), 4.33–4.30 (m, 2H), 1.88 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.47 (d, J = 9.0 Hz).

3.3. (E)-1-Benzyloxy-4,4,4-trifluoro-2-butene (*3*)

To a suspension of NaH (7.68 g, 0.19 mol) in THF (100 mL) at 0 °C was added a solution of alcohol **14** (20.17 g, 0.16 mol) in THF (80 mL). After the mixture was stirred about 1 h, Bu_4NI (0.59 g, 1.60 mmol) and BnBr (32.83 g, 0.19 mol) were added. After being stirred at room temperature for 5 h, the reaction mixture was diluted with Et_2O (150 mL), washed with H_2O (200 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent provided the compound **3** [13] (33.18 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 6.49–6.41 (m, 1H), 6.04–5.94 (m, 1H), 4.58 (s, 2H) 4.16–4.11 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.54 (d, J = 8.2 Hz).

3.4. (2S,3R)-1-Benzyloxy-4,4,4-trifluoro-2,3-butanediol (*4*)

$MeSO_2NH_2$ (0.96 g, 10 mmol) was added to a stirring mixture of *t*-BuOH (25 mL), water (25 mL) and AD-mix-β (14.00 g). Then, the mixture was cooled to 0 °C and compound **3** (2.16 g, 10 mmol) was added. After the heterogeneous slurry was stirred vigorously at room temperature for 4 days, Na_2SO_3 was added to quench the reaction. The resultant mixture was stirred for 30 min and then extracted with ethyl acetate. The combined organic layer was washed with 2N KOH and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the resultant residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4** [13] (2.40 g, 95% yield, 94% ee) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 4.59 (s, 2H), 4.18–4.13 (m, 1H), 4.00–3.93 (m, 1H), 3.62 (*d*, J = 6.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.45 (*d*, J = 7.1 Hz).

3.5. (2S,3R)-1-Benzyloxy-2,3-bis-[(tert-butyldimethylsilyl)oxy]-4,4,4-trifluoro-butane (*15*)

To a solution of **4** (280 mg, 1.12 mmol) and DMAP (68 mg, 0.56 mmol) in DMF (2.2 mL) at 0 °C was added imidazole (458 mg, 5.6 mmol), followed by TBDMSCl (844 mg, 5.6 mmol). Then, the mixture was warmed to room temperature and stirred for 30 h. EtOAc (40 mL) was added and the resulting mixture was washed with brine (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (petroleum ether) to afford **15** (536 mg, 100%) as a clear oil: $[\alpha]_D^{21}$ = +8.7 (*c* 1.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.52 (s, 2H), 4.10–4.02 (m, 2H), 3.63 (dd, J = 6.0 Hz, 9.0 Hz, 1H),

3.43–3.38 (m, 1H), 0.91, 0.88 (2s, 18H), 0.10, 0.09, 0.05, 0.04 (4s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.70 (d, J = 6.2 Hz); IR (thin film) 2932, 1474, 1464, 1257, 1170, 1149, 1122, 839, 779 cm^{-1}; MS (ESI) m/z 479.3 ($M + H^+$), 496.3 ($M + NH_4^+$); Anal. Calcd. for $C_{23}H_{41}O_3F_3Si_2$: C, 58.70; H, 8.63. Found: C, 58.45; H, 8.68.

3.6. (2S,3R)-1-Benzyloxy-2,3-bis-[(tert-butyldimethylsilyl)oxy]-4,4,4-trifluorobutan-1-ol (16)

A suspension of 20% $Pd(OH)_2$/C (145 mg) and **15** (536 mg, 0.86 mmol) in THF was stirred under a hydrogen atmosphere for 5 h. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give **16** [17] (432 mg, 100%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94–3.90 (m, 1H), 3.79–3.77 (m, 1H), 3.66–3.62 (m, 1H), 3.54–3.51 (m, 1H), 1.65 (s, 1H), 0.82, 0.79 (2s, 18H), 0.05, 0.03, 0.02, 0.01 (4s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.08 (d, J = 7.3 Hz).

3.7. (E)-(4S,5R)-Ethyl-4,5-bis-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-2-hexenoate (17)

2,2,6,6-Tetramethyl-1-piperidinyloxy (2.6 mg, 0.017 mmol) was added at 0 °C to a solution of **16** (644 mg, 1.66 mmol) and trichloroisocyanuric acid (405 mg, 1.74 mmol) in methylene chloride (5 mL). Then, the mixture was warmed to room temperature and stirred for 15 min. After filtration on silica gel, the filtrate was concentrated in vacuo. The residue was used in next reaction without further purification. To a suspension of sodium hydride (60 mg, 2.49 mmol) in THF (8 mL) at 0 °C was added triethyl phosphonoacetate (558 mg, 2.49 mmol). After the mixture was stirred for 1 h at 0 °C, the above crude product in THF (3 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature over a period of 4 h and then diluted with Et_2O (20 mL). The resultant mixture was washed with H_2O (20 mL) and brine (30 mL), and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the resultant residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 100:1) to give ester **17** (614 mg, 82%) as a clear oil: $[\alpha]_D^{22}$ = +33.7 (c 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (dd, J = 15.6, 3.9 Hz, 1H), 6.06 (dd, J = 15.6, 1.5 Hz, 1H), 4.45 (s, 1H), 4.26–4.16 (m, 2H), 4.01–3.93 (m, 1H), 1.30 (q, J = 7.2 Hz, 3H), 0.92, 0.91 (2s, 18H), 0.11, 0.09, 0.08, 0.05 (4s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.34 (d, J = 5.4 Hz); IR (thin film) 2933, 2862, 1726, 1474, 1261, 1176, 1151, 839, 780 cm^{-1}; MS (ESI) m/z 457.4 ($M + H^+$), 474.4 ($M + NH_4^+$); Anal. Calcd. for $C_{23}H_{41}O_3F_3Si_2$: C, 52.60; H, 8.61. Found: C, 52.92; H, 8.75.

3.8. (2S,3R,4S,5R)-Ethyl-2,3-bis-hydroxy-4,5-bis-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-hexenoate (18)

$MeSO_2NH_2$ (58 mg, 0.61 mmol) was added to a stirring mixture of t-BuOH (4 mL), water (4 mL) and AD-mix-α (854 mg). The mixture was cooled to 0 °C and compound **17** (280 mg, 0.61 mmol) was added. After the heterogeneous slurry was stirred vigorously at room temperature for 36 h, Na_2SO_3 was added to quench the reaction. The resultant mixture was stirred for 30 min and then extracted with ethyl acetate. The combined organic layer was washed with 2N KOH and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to give **18** (290 mg, 97% yield, 98% de) as a clear oil: $[\alpha]_D^{21}$ = +19.7 (c 1.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.23 (m, 4H), 4.08 (d, J = 9 Hz, 1H), 3.95 (d, J = 9.6 Hz, 1H), 3.05 (br, 1H), 2.82 (br, 1H), 1.32 (t, J = 6.9 Hz, 3H), 0.92, 0.90 (2s, 18H), 0.16, 0.14, 0.13, 0.11 (4s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.81 (d, J = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.8, 124.7 (q, J = 284.8 Hz), 72.8, 72.4 (q, J = 28.9 Hz), 69.6, 69.5, 62.1, 25.7, 25.5, 18.1, 14.2, 1.04, −4.6, −4.8, −5.2, −5.3; IR (thin film) 3531, 3461, 2933, 2860, 1730, 1475, 1391, 1261, 1169, 1147, 898, 780 cm^{-1}; MS (ESI) m/z 491.2 ($M + H^+$), 508.4 ($M + NH_4^+$), 529.2 ($M + K^+$); HRMS (ESI) Calcd. for $C_{20}H_{41}O_6F_3Si_2Na$ 513.2286, found 513.2289.

3.9. (2S,3R,4S,5R)-Ethyl-2,3,4,5-tetra-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-hexenoate (19)

TBSOTf (0.29 mL, 1.25 mmol) was added dropwise at 0 °C to a solution of diol **18** (278 mg, 0.57 mmol) and 2,6-lutidine (183 mg, 1.71 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was warmed up to room temperature and stirred for 1 h. The mixture was then diluted with ether (7 mL) and the organic layer was washed with 10% HCl (2 mL), saturated $NaHCO_3$ (2 mL), H_2O (2 mL) and brine (2 mL), and dried over Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 200:1) to give ester **19** (370 mg, 92%) as a clear oil: $[\alpha]_D^{26}$ = +7.9 (c 4.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (d, J = 1.5 Hz, 1H), 4.50 (dd, J = 6.3, 1.8 Hz, 1H), 4.24–4.13 (m, 3H), 3.94 (dd, J = 6, 1.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.93, 0.90, 0.89, 0.87 (4s, 36H), 0.20, 0.16, 0.14, 0.10, 0.09, 0.06, 0.02, 0.01 (8s, 24H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.13 (d, J = 6.8 Hz); IR (thin film) 2932, 2860, 1752, 1473, 1258, 1176, 881, 841, 778 cm^{-1}; MS (ESI) m/z 719.5 ($M + H^+$), 741.5 ($M + Na^+$); Anal. Calcd. for $C_{32}H_{69}O_6F_3Si_4$: C, 53.44; H, 9.67. Found: C, 53.76; H, 9.65.

3.10. (2S,3R,4S,5R)-2,3,4,5-Tetra-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-1-hexanol (20)

DIBAL-H (0.57 mL, 1.0 M in toluene, 0.57 mmol) was added dropwise at −78 °C to a solution of ester **19** (135 mg, 0.19 mmol) in CH_2Cl_2 (1 mL). After stirring for 1.5 h, the reaction was quenched with saturated Rochelle's salt (2 mL) at −78 °C. The mixture was stirred at room temperature for 1 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic layers were dried over Na_2SO_4. After

filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 40:1) to provide ester **20** (120 mg, 93%) as a clear oil: $[\alpha]_D^{22}$ = +2.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95–4.86 (m, 1H), 4.07 (dd, *J* = 5.1, 2.7 Hz, 1H), 3.94–3.88 (m, 2H), 3.80–3.76 (m, 1H), 3.63 (dd, *J* = 8.1, 4.2 Hz), 3.38 (br, 1H), 0.95, 0.91 (2s, 36H), 0.18, 0.16, 0.14, 0.12, 0.11, 0.10, (6s, 24H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.67 (s); IR (thin film) 3455, 2933, 2861, 1474, 1391, 1259, 1120, 838, 779 cm^{-1}; MS (ESI) *m/z* 694.5 ($M + NH_4^+$); Anal. Calcd. for $C_{30}H_{67}O_5F_3Si_4$: C, 53.21; H, 9.97. Found: C, 52.81; H, 9.90.

*3.11. 1,2,3,5-Tetra-O-acetyl-6,6,6-trifluoro-β-L-fucofuranose (**21**)*

2,2,6,6-Tetramethyl-1-piperidinyloxy (0.4 mg, 0.025 mmol) was added at 0 °C to a solution of compound **20** (70 mg, 0.1 mmol) and trichloroisocyanuric acid (29 mg, 0.12 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 15 min at room temperature. Filtration of the mixture and removal of the solvent in vacuo gave a residue, which was used without further purification. To a solution of the above residue in THF (0.4 mL) was added TBAF (0.48 mL, 1.0 M in THF, 0.48 mmol). After stirring for 7 h, Ac_2O (75 μL, 0.8 mmol) and DMAP (1.2 mg, 0.01 mmol) were added. The reaction mixture was stirred for 8 h. The reaction was quenched with saturated $NaHCO_3$. The aqueous phase was extracted with Et_2O (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give compound **21** (32 mg, 85%) as a clear oil: $[\alpha]_D^{22}$ = −1.3 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, *J* = 4.5 Hz, 1H), 5.62 (t, *J* = 6.3 Hz, 1H), 5.54 (dd, *J* = 6.3, 6.9 Hz, 1H), 5.35 (dd, *J* = 2.4, 4.8 Hz, 1H), 4.35 (dd, *J* = 1.5, 4.8 Hz, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H) 2.09 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.39 (d, *J* = 7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.8, 169.7, 169.1, 168.6, 122.0 (q, *J* = 251.3 Hz), 93.4, 75.4, 74.0, 73.9, 69.4 (q, *J* = 31.1 Hz), 20.9, 20.5, 20.4, 20.3. IR (thin film) 1757, 1216 cm^{-1}; MS (ESI) *m/z* 404.0 ($M + NH_4^+$), 409.0 ($M + Na^+$), 425.0 ($M + K^+$); HRMS (ESI) Calcd. for $C_{14}H_{17}O_9F_3Na$ 409.0717, found 409.0720.

*3.12. (3R,4S)-3-Benzyloxymethyl-4-trifluoromethyl-2,2-dioxo-1,3,2-dioxathiolane (**22**)*

To a solution of **4** (617 mg, 2.47 mmol) in methylene chloride (7 mL) was added dropwise thionyl chloride (588 mg, 4.94 mmol) at 0° C during 10 min. The reaction mixture was stirred for another 10 min at 0 °C and then diluted with cold ether. The aqueous phase was extracted with ether. The combined organic phases were washed with brine and concentrated in vacuo. The residue was purified by a short silica gel column to give crude cyclic sulfite. $NaIO_4$ (634 mg, 2.96 mmol) and $RuCl_3{\cdot}3H_2O$ (1.0 mg) were added to the mixture of the crude cyclic sulfite, water (4.5 mL), CH_3CN (3 mL) and CCl_4 (3 mL). Then, the reaction mixture was vigorously stirred for 1 h at room temperature. After that, the mixture was diluted with ether and the resultant organic layer was filtered through a pad of Celite. The filtrate was washed with water, saturated aqueous sodium bicarbonate and brine, dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford compound **22** [13] (701 mg, 91%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H), 5.18 (dq, *J* = 5.9, 6.0 Hz, 1H), 5.03 (dt, *J* = 6.3, 3.6 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 3.92 (dd, *J* = 3.6, 12.0 Hz, 1H), 3.78 (dd, *J* = 3.6, 12.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.30 (d, *J* = 6.2 Hz).

*3.13. (3R)-4-Benzyloxy-1,1,1-trifluorobutan-2-ol (**23**)*

A solution of cyclic sulfate **22** (116 mg, 0.37 mmol) and sodium borohydride (28 mg, 0.74 mmol) in DMF (2 mL) was stirred for 4 h at 80 °C. Then, the solvent was carefully removed under reduced pressure to give a residue. To this residue was added THF (2 mL), water (5 μL) and sulfuric acid (15 μL) and the resulting suspension was stirred for 20 min. After that, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a residue, which was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to afford **23** [20] (87 mg, 95%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 4.54 (s, 2H), 4.21–4.15 (m, 1H), 3.83–3.78 (m, 1H), 3.76–3.66 (m, 1H), 2.03–1.92 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.80 (d, *J* = 6.8 Hz).

*3.14. (3R)-1-Benzyloxy-3-(tert-butyldimethylsilyl)oxy-4,4,4-trifluoro-butane (**24**)*

To a 0 °C solution of **23** (154 mg, 0.66 mmol) and DMAP (8 mg, 0.07 mmol) in DMF (0.25 mL) was added imidazole (68 mg, 1.0 mmol), followed by TBDMSCl (200 mg, 1.32 mmol). Then, the mixture was warmed to room temperature and stirred for 20 h. EtOAc (40 mL) was added and the resulting mixture was washed with brine (3 × 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate = 60:1) to afford **24** (228 mg, 100%) as a clear oil: $[\alpha]_D^{21}$ = −18.5 (*c* 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 4.50 (dd, *J* = 12, 6.9 Hz, 2H), 4.24–4.14 (m, 1H), 3.65–3.53 (m, 2H), 2.09–1.98 (m, 1H), 1.84–1.55 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.87 (d, *J* = 6.2 Hz); IR (thin film) 2933, 2861, 1474, 1363, 1283, 1169, 840, 781 cm^{-1}; MS (EI) *m/z* 348 (M^+, 3), 91 (100), 77 (13), 43 (26). Anal. Calcd. for $C_{17}H_{27}O_2F_3Si$: C, 58.59; H, 7.81; found: C, 58.58; H, 7.84.

*3.15. (3R)-3-(Tert-butyldimethylsilyl)oxy-4,4,4-trifluorobutan-1-ol (**25**)*

Compound **25** (221 mg, 100%) was prepared from compound **24** (300 mg, 0.86 mmol) using the same conditions

as described for compound **16**. $[\alpha]_D^{21} = -18.1$ (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.23–4.17 (m, 1H), 3.82–3.78 (m, 2H), 1.97–1.89 (m, 1H), 1.87–1.77 (m, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.62 (d, $J = 7.3$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.2 (q, $J = 282.4$ Hz), 68.2 (q, $J = 31.3$ Hz), 57.7, 33.4, 25.5, 18.0, −5.2, −5.3; IR (thin film) 3356, 2935, 2862, 1474, 1282, 1169, 841, 781 cm^{-1}; MS (ESI) *m/z* 259.2 ($M + H^+$); HRMS (ESI) Calcd. for $C_{10}H_{21}O_2F_3SiNa$ 281.1155, found 281.1159.

*3.16. (E)-(5R)-Ethyl-5-(tert-butyldimethylsilyl)oxy-6,6,6–trifluoro-2-hexenoate (**26**)*

Compound **26** (107 mg, 80%) was prepared from compound **25** (107 mg, 0.41 mmol) using the same conditions as described for compound **17**. $[\alpha]_D^{19} = -11.4$ (*c* 0.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.95–6.85 (m, 1H), 5.93 (d, $J = 15.6$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.08–4.00 (m, 1H), 2.60–2.49 (m, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.80 (d, $J = 4.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.8, 142.4, 125.0, 124.6 (q, $J = 283.0$ Hz), 70.4 (q, $J = 31.4$ Hz), 60.3, 34.1, 25.5, 18.0, 14.2, −4.9, −5.1; IR (thin film) 2934, 2862, 1726, 1663, 1270, 1169, 841, 781 cm^{-1}; MS (ESI) *m/z* 327.2 ($M + H^+$), 344.2 ($M + NH_4^+$), 349.2 ($M + Na^+$); HRMS (ESI) Calcd. for $C_{14}H_{25}O_3F_3SiNa$ 349.1417, found 349.1420.

*3.17. (2S,3R,5R)-Ethyl-2,3-bis-hydroxy-5-(tert-butyldimethylsilyl)oxy-6,6,6–trifluoro-hexenoate (**27**)*

Compound **27** (290 mg, 97% yield, 96% de) was prepared from compound **26** (280 mg, 0.61 mmol) using the same conditions as described for compound **18**. $[\alpha]_D^{20} = -19.8$ (*c* 2.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.38–4.14 (m, 4H), 4.06 (d, $J = 2.1$ Hz, 1H), 2.01–1.92 (m, 1H), 1.81–1.72 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 0.92 (s, 9H), 0.14 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.84 (d, $J = 7.3$ Hz); IR (thin film) 3502, 2936, 2863, 1730, 1475, 1262, 1170, 1074, 840, 782 cm^{-1}; MS (ESI) *m/z* 361.2 ($M + H^+$), 378.1 ($M + NH_4^+$), 383.1 ($M + Na^+$); Anal. Calcd. for $C_{14}H_{27}O_5F_3Si$: C, 46.65; H, 7.55; found: C, 46.63; H, 7.25.

*3.18. (2S,3R,5R)-Ethyl-2,3,5-tri-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-hexenoate (**28**)*

Compound **28** (310 mg, 99%) was prepared from compound **27** (193 mg, 0.54 mmol) using the same conditions as described for compound **19**. $[\alpha]_D^{26} = -15.5$ (*c* 2.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.21–4.08 (m, 5H), 2.03–1.94 (m, 1H), 1.84–1.76 (m, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.91, 0.90, 0.88 (3s, 27H), 0.14, 0.13, 0.10, 0.09, 0.07, 0.06 (6s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.45 (d, $J = 4.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 129.0 (q, $J = 283.1$ Hz), 75.4, 70.9, 68.7 (q, $J = 31.3$ Hz), 60.6, 35.6, 25.7, 25.6, 18.3, 18.2, 18.1, 14.2, 1.0, −3.8, −4.1, −4.6, −5.0, −5.3; IR (thin film) 2933, 2860, 1753, 1474, 1176, 881, 778 cm^{-1}; MS (ESI) *m/z* 589.2 ($M + H^+$), 606.2 ($M + NH_4^+$), 611.2 ($M + Na^+$); HRMS (ESI) Calcd. for $C_{26}H_{55}O_5F_3Si_3Na$ 611.3202, found 611.3203.

*3.19. (2S,3R,5R)-2,3,5-Tri-[(tert-butyldimethylsilyl)oxy]-6,6,6–trifluoro-1-hexanol (**29**)*

Compound **29** (210 mg, 95%) was prepared from compound **28** (250 mg, 0.43 mmol) using the same conditions as described for compound **20**. $[\alpha]_D^{25} = -19.7$ (*c* 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.15–4.09 (m, 1H), 3.90–3.60 (m, 4H), 2.02–1.93 (m, 1H), 1.78–1.70 (m, 1H), 0.90 (s, 27H), 0.12, 0.10 (2s, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.38 (d, $J = 7.1$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.3 (q, $J = 281.8$ Hz), 73.8, 71.0, 68.5 (q, $J = 30.6$ Hz), 62.5, 34.0, 25.8, 25.7, 18.2, 18.0, 17.9, 1.0, −3.7, −4.1, −4.4, −4.6, −4.7, −4.9, −5.0; IR (thin film) 3487, 2954, 2860, 1473, 1167, 1029, 839, 778 cm^{-1}; MS (ESI) *m/z* 547.2 ($M + H^+$); HRMS (ESI) Calcd. for $C_{24}H_{53}O_4F_3Si_3Na$ 569.3096, found 569.3095.

*3.20. 1,2,3-Tri-O-acetyl-4,6-dideoxy-6,6,6-trifluoro-β-L-xylo-hexopyranose (**30**)*

Compound **30** (10 mg, 85%) was prepared from compound **29** (20 mg, 0.03 mmol) using the same conditions as described for compound **21**. $[\alpha]_D^{25} = +50.1$ (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, $J = 3.3$ Hz, 1H), 5.30 (dt, $J = 5.2$, 10.3 Hz, 1H), 5.07 (dd, $J = 3.3$, 10.3 Hz, 1H), 4.40–4.29 (m, 1H), 2.43 (ddd, $J = 12.8$, 2.5, 5.2, 1H), 2.17 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.85 (q, $J = 12.8$ Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.74 (d, $J = 6.5$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.1, 169.7, 168.4, 121.9 (q, $J = 216.4$ Hz), 89.7, 69.6, 68.2 (q, $J = 33.6$ Hz), 66.0, 29.1, 20.8, 20.7, 20.4. IR (thin film) 2921, 2851, 1751, 1375, 1222, 1153, 1067 cm^{-1}; MS (ESI) *m/z* 346.0 ($M + NH_4^+$); HRMS (ESI) Calcd. for $C_{12}H_{15}O_7F_3Na$ 351.0662, found 351.0663.

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