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Modified Julia Olefination on Sugar-Derived Lactones: Synthesis of Difluoro-*exo*-glycals

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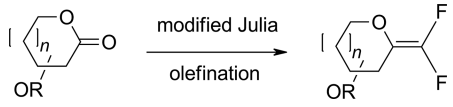
We report the preparation of difluoro-*exo*-glycals by *gem*-difluoroolefination of benzylated sugar-derived lactones using a modified Julia reaction. The addition is highly stereoselective, and the Smiles-rearrangement–elimination sequence can be carried out under microwave irradiation.

Introduction

C-Glycosylidenes or *exo*-glycals are *C*-glycosyl compounds having a carbon–carbon double bond at the anomeric center.[1] Over the last decade, we have been involved in the synthesis of diversely functionalized *exo*-glycals by the modified Julia olefination of sugar-derived lactones.[2] We now report the synthesis of difluoro-*exo*-glycals using difluoromethyl-2-pyridyl sulfone (Scheme 1).[3]



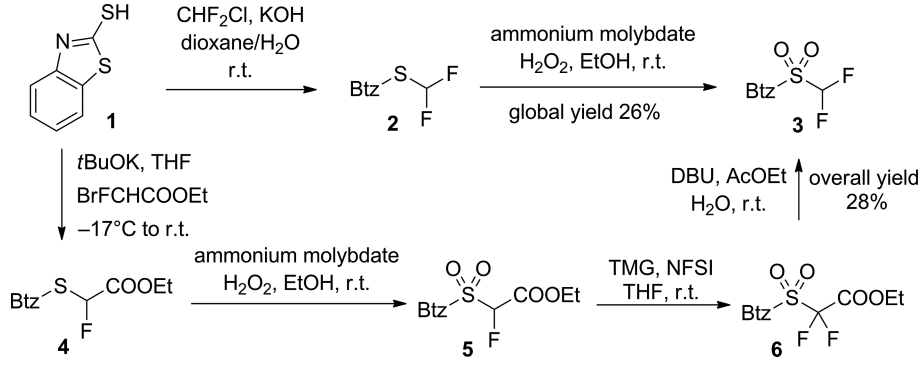
Scheme 1. Julia olefination of sugar-derived lactones.

The synthesis of difluoro-*exo*-glycals was first reported in 1989 by Motherwell[4] using dibromodifluoromethane and HMPA (hexamethylphosphoramide), and it was improved in 1993 by the same group.[5] An indirect method involving an addition–elimination sequence was described in 2006 by Bonnet-Delpon.[6] These compounds are useful synthetic intermediates, and they have been used by Sinaÿ for the preparation of fluorinated analogs of UDP-*C*-D-galactofuranose,[7] and for the synthesis of 5a-*gem*-difluorocarba-α-D-glucopyranose.[8]

Results and Discussion

We started with difluoromethyl-2-benzothiazolyl sulfone and 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone as typical substrates. The sulfone was prepared by two different methods developed by Hu[9] and Lequeux,[10] which gave similar yields (Scheme 2).

The results of this initial study are given in Table 1. Under our standard, two-step reaction conditions (Table 1, entry 1),[2] the difluorinated *exo*-glycal was obtained in low yield (15%). We therefore investigated the nature of the base [LiHMDS (lithium hexamethyldisilazide) or *t*BuOK] and the Lewis acid (BF_3 or $TiCl_4$), and the sulfone/lactone ratio. Changing the nature of the base and/or the Lewis acid



Scheme 2. Synthesis of difluorinated benzothiazolyl sulfone; Btz = benzothiazolyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine, NFSI = *N*-fluorobenzenesulfonimide.

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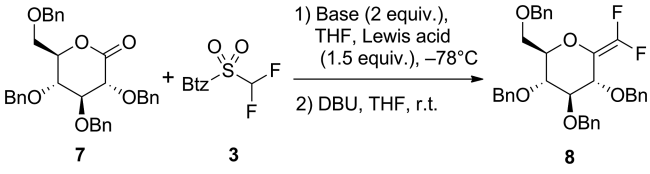
did not improve the yield significantly (Table 1, entries 1–4). When we used an excess (1.5 equiv.) of the sulfone, the yield increased to 25%. The best results were obtained when the reaction was carried out with a slight excess (1.2 equiv.) of the lactone (32% yield). Further increasing the amount of lactone to 1.5 equiv. did not improve the yield (21%).

Table 1. Julia olefination of a sugar-derived lactone.



7 3 8

Entry	Sulfone (equiv.)	Lactone (equiv.)	Base	Lewis acid	Yield [%]
1	1.2	1	LiHMDS	$BF_3{\cdot}Et_2O$	15
2	1.2	1	*t*BuOK	$BF_3{\cdot}Et_2O$	14
3	1.2	1	LiHMDS	$TiCl_4$	18
4	1.2	1	*t*BuOK	$TiCl_4$	15
5	1.5	1	LiHMDS	$BF_3{\cdot}Et_2O$	25
6	1	1.2	LiHMDS	$BF_3{\cdot}Et_2O$	32
7	1	1.5	LiHMDS	$BF_3{\cdot}Et_2O$	21

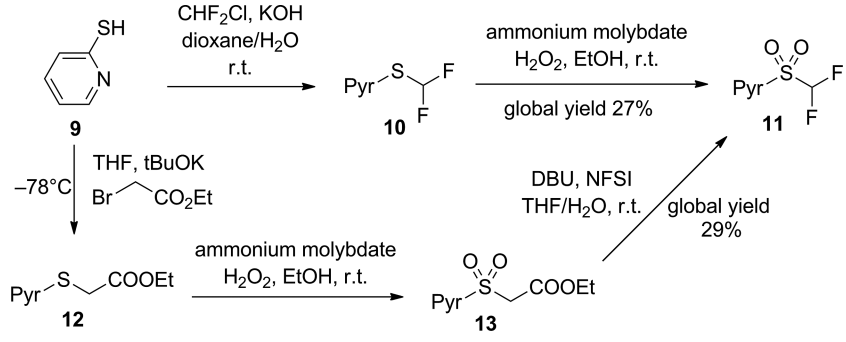
Inspired by the work of Hu[9] using difluoromethyl-2-pyridyl sulfone in a modified Julia olefination with aldehydes and ketones,[11] we decided to modify the nature of the heterocyclic moiety. Thus, the pyridyl sulfone was prepared following a similar approach to that used for the benzothiazolyl sulfone (Scheme 3).

Under our standard conditions using DBU in the second step, we were surprised to observe that the reaction produced mainly the hemiketal intermediate in good yield (62%; Scheme 4). This result showed that the pyridyl sulfone was suitable for the nucleophilic addition of the lithiated sulfone onto the sugar-derived lactone, and that the resulting intermediate was unreactive, since the Smiles rearrangement did not occur in the presence of DBU at room temperature.

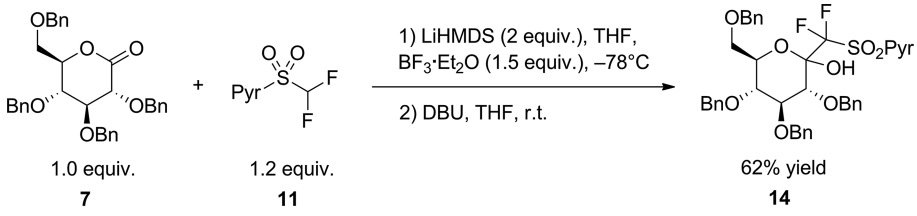
After a brief optimization of the addition step, the intermediate was obtained in 69% yield by using 1.0 equiv. of difluoromethyl-2-pyridyl sulfone **11**, 2.0 equiv. of lactone, 2.0 equiv. of LiHMDS, and 2.0 equiv. of boron trifluoride–diethyl ether in THF at low temperature (Scheme 5). As described by Shen et al.,[3] we observed that the addition was highly stereoselective, and that the compound with the hydroxy group in the axial position was formed exclusively.

We then turned our attention to the elimination step, starting from the intermediate. We decided to investigate this transformation under basic, acidic, and thermal conditions.

Under base-catalyzed conditions, we observed that the Smiles rearrangement did not occur in the presence of NaHMDS. The use of sodium hydride in THF provided the difluoro-*exo*-glycal in poor yield (27%). The use of sodium hydride in other solvents or the use of cesium carbonate led to retroaddition. We then explored the possibility of carrying out the Smiles rearrangement under acidic conditions.[9b] We found that triflic acid in dichloromethane at room temperature was not effective for this transformation, and led instead to decomposition. We ran the reaction using trifluoroacetic acid (TFA) in dichloromethane at 50 °C, and obtained the desired compound in moderate yield (64%). With the same acid, the use of toluene at 70 °C allowed us to increase the yield to 85%. Finally, we decided to investigate the reaction under thermal conditions (toluene at reflux), and we observed that by heating in refluxing toluene for 4 h, the transformation occurred in a satisfactory yield (81%). In order to reduce the reaction time, the reaction was carried out in a microwave oven at 140 °C for 1 h in toluene, and the desired compound was obtained in 93%

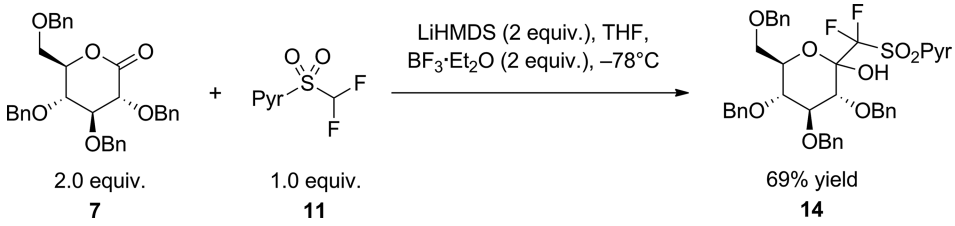


Scheme 3. Synthesis of difluorinated pyridyl sulfone.



1.0 equiv. 7 1.2 equiv. 11 62% yield 14

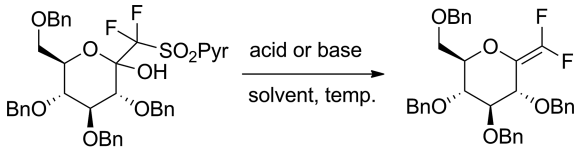
Scheme 4. Use of difluorinated pyridyl sulfone.



Scheme 5. Optimization of the addition step.

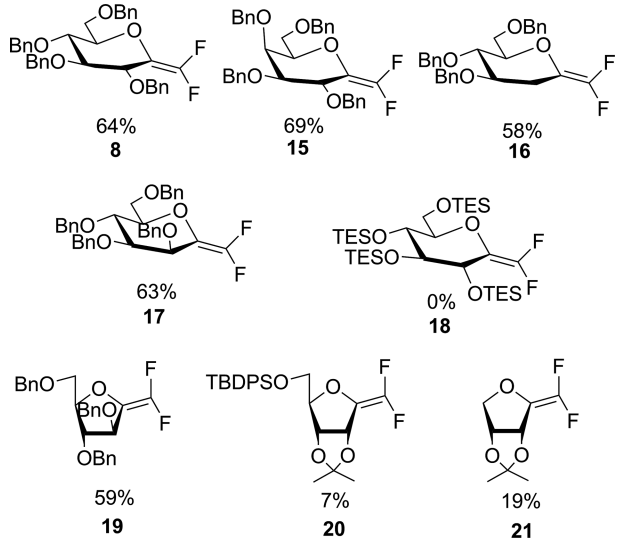
yield (Table 2). We also showed that, similarly to our previous work, we could perform the sequence under our optimized conditions without purification of the hemiketal intermediate without loss of yield.

Table 2. Optimization of the elimination step.



Entry	Acid	Base	Solvent	*T* [°C]	Yield [%]
1	–	NaHMDS	THF	room temp.	no reaction
2	–	NaH	THF	room temp.	27
3	–	NaH	DMF	room temp.	retroaddition
4	–	NaH	toluene	room temp.	retroaddition
5	–	$CsCO_3$	THF	room temp.	retroaddition
6	TfOH	–	CH_2Cl_2	room temp.	degradation
7	TFA	–	CH_2Cl_2	50	64
8	TFA	–	toluene	70	85
9	–	–	toluene	110	81
9	–	–	toluene	140 (microwave)	93

To evaluate the scope and limitations of this method, we carried out the modified Julia olefination with a variety of sugar-derived lactones under the optimized reaction conditions for the two-step process (Scheme 6).



Scheme 6. Synthesis of difluoromethylene-*exo*-glycals in various sugar series. TES = triethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.

The reaction gave the difluoromethylene-*exo*-glycals in good yields (58–69%) with benzyl-protected sugar-derived lactones. The reaction was shown to proceed efficiently in both pyranose (D-*gluco*, D-*galacto*, D-*manno*, 2-deoxy-D-*gluco*) and furanose (D-*arabino*) sugar series. However, the reaction did not provide the desired product with silyl-protected sugar lactones. This could be due to the presence of boron trifluoride in the first step. In addition, the presence of a 2,3-diisopropylidene protecting group in furanose-derived lactones significantly decreased the overall yield of the sequence (to 7 and 19%).

Conclusions

In summary, we have demonstrated that the *gem*-difluoroolefination of benzylated sugar-derived lactones by a modified Julia olefination can be achieved in good yields. This reaction is competitive in term of yield and number of steps compared to the Motherwell[4] and Bonnet-Delpon[5] methods, respectively. This transformation extends the field of applications of modified Julia olefinations of lactones.[2]

Experimental Section

General Methods: All reactions were carried out under an argon atmosphere. Solvents were distilled and dried by standard methods. NMR spectra were recorded at 293 K, unless otherwise stated, using a 300, 400, or 500 MHz spectrometer. Chemical shifts are referenced relative to residual solvent peaks. The following abbreviations are used to explain the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; td, triplet of doublets; m, multiplet; br. s, broad singlet. ^{13}C NMR multiplicities were assigned on the basis of DEPT experiments. Low- and high-resolution mass spectra were recorded with a Bruker MicrOTOF-Q II XL spectrometer. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} (Merck). TLC plates were inspected using UV light (λ = 254 nm), and developed by treatment with H_2SO_4 (10% solution in EtOH/H_2O, 1:1, v/v) followed by heating. Silica gel column chromatography was carried out with silica gel Si 60 (40–63 μm).

Ethyl 2-(Pyridin-2-ylsulfonyl)acetate (13): Ethyl 2-(pyridin-2-ylthio)acetate (2.566 g, 12.96 mmol, 1.0 equiv.) was dissolved in ethanol (43 mL) in a round-bottomed flask (100 mL) under argon. This solution was cooled to 0 °C, and ammonium molybdate (801 mg, 0.05 equiv.) and hydrogen peroxide solution (35% aq.; 10 mL, 8.0 equiv.) were added. The reaction mixture was stirred at room temperature overnight, then it was quenched by the addition of water, and the mixture was extracted twice with ethyl acetate.

The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$, and with brine, dried with sodium sulfate, and the solvents were evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 6:4) to give compound **13** (2.715 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, J = 4.8 Hz, 1 H), 8.07 (d, J = 7.8 Hz, 1 H), 7.97 (td, J = 7.8, 1.8 Hz, 1 H), 7.57 (ddd, J = 7.5, 4.5, 1.2 Hz, 1 H), 4.45 (s, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 1.11 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 162.8, 157.0, 150.6, 138.6, 128.1, 122.8, 62.7, 56.5, 14.2 ppm. HRMS (ESI$^+$): calcd. for $[M + Na]^+$ 252.0301; found 252.0304.

2-[(Difluoromethyl)sulfonyl]pyridine (11): Ethyl 2-(pyridin-2-ylsulfonyl)acetate (53 mg, 0.23 mmol, 1.0 equiv.) and NFSI (167 mg, 2.2 equiv.) were dissolved in THF (500 µL) in a round-bottomed flask (10 mL) under argon at room temperature. DBU (90 µL, 3 equiv.) and water (2 drops, approximately 100 µL) were added, and the reaction mixture was stirred overnight at 50 °C. The reaction was quenched by the addition of water, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried with sodium sulfate, and the solvents were evaporated. The mixture was purified by flash chromatography (petroleum ether/EtOAc, 6:4) to give compound **11** (14 mg, 30%). Data were identical to those described in the literature.[9]

Typical Experimental Procedure for the Synthesis of Difluorinated *exo*-Glycals: Tetra-*O*-benzyl-D-gluconolactone **7** (402 mg, 0.878 mmol, 2.0 equiv.), 2-difluoromethylsulfonylpyridine (85 mg, 1.0 equiv.), and boron trifluoride–diethyl ether (108 µL, 2.0 equiv.) were dissolved in freshly distilled THF (1.7 mL) in a round-bottomed flask (10 mL) at –78 °C under argon. LiHMDS (1 M solution in THF; 880 µL, 2.0 equiv.) was added dropwise over 10 min. The mixture was stirred for a further 30 min, and then the reaction was quenched by the addition of water. The mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried with sodium sulfate, and the solvents were evaporated.

The residue was dissolved in dry toluene (3 mL), and the solution was heated to 140 °C in a microwave oven for 1 h. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give compound **8** (161 mg, 64%).

1-*C*-(Pyridine-2-yl-sulfonyldifluoromethyl)-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (14): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.82 (ddd, J = 4.7, 1.6, 0.7 Hz, 1 H), 8.20 (d, J = 7.9 Hz, 1 H), 7.90 (td, J = 7.8, 1.7 Hz, 1 H), 7.57 (ddd, J = 7.7, 4.7, 1.0 Hz, 1 H), 7.41–7.24 (m, 18 H), 7.24–7.20 (m, 2 H), 4.93–4.88 (m, 2 H), 4.86–4.83 (m, 2 H), 4.76 (d, J = 10.3 Hz, 1 H), 4.65 (d, J = 10.9 Hz, 1 H), 4.61 (d, J = 12.1 Hz, 1 H), 4.53 (d, J = 12.1 Hz, 1 H), 4.09–4.01 (m, 3 H), 3.79–3.73 (m, 2 H), 3.62 (dd, J = 11.6, 1.6 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0 (C^{IV}), 150.6 (CH), 138.5 (C^{IV}), 138.4 (C^{IV}), 138.3 (CH), 138.05 (C^{IV}), 137.4 (C^{IV}), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.2 (CH), 119.5 (dd, J = 303.0, 301.0 Hz, C^{IV}), 97.8 (dd, J = 25.2, 23.8 Hz, C^{IV}), 83.2 (CH), 78.9 (CH), 77.3 (CH), 76.0 (CH_2), 75.5 (CH_2), 75.2 (CH_2), 73.6 (CH_2), 73.1 (CH), 68.1 (CH_2) ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –107.55 (dd, J = 331.7, 237.8 Hz) ppm. HRMS (ESI$^+$): calcd. for $[M + H]^+$ 732.2437; found 732.2463.

2,6-Anhydro-1,3-dideoxy-1,1-difluoro-4,5,7-tri-*O*-benzyl-D-*gluco*-hept-1-enitol (8): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.01 (m, 20 H), 4.65–4.54 (m, 3 H), 4.54–4.40 (m, 4 H), 4.35 (d, J = 11.7 Hz, 1 H), 4.17 (t, J = 3.8 Hz, 1 H), 3.99 (ddd, J = 9.4, 6.4, 2.9 Hz, 1 H), 3.79 (ddd, J = 6.2, 4.1, 1.1 Hz, 1 H), 3.71–3.61 (m, 3 H) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 153.7 (dd, J = 290.3, 278.4 Hz, C^{IV}), 138.2 (C^{IV}), 138.1 (C^{IV}), 137.8 (C^{IV}), 137.5 (C^{IV}), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.1 (CH), 128.02 (CH), 127.9 (CH), 127.7 (CH), 112.4 (dd, J = 38.5, 13.2 Hz, C^{IV}), 82.4 (CH), 77.3 (CH), 76.9 (CH), 73.8 (CH_2), 73.6 (CH_2), 73.1 (t, J = 2 Hz, CH), 73.0 (CH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –99.76 (d, J = 74.3 Hz), –116.71 (dd, J = 74.2, 3.3 Hz) ppm. HRMS (ESI$^+$): calcd. for $[M + Na]^+$ 595.2267; found 595.2252.

2,6-Anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-benzyl-D-*galacto*-hept-1-enitol (15): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 20 H), 4.69–4.50 (m, 8 H), 4.36 (d, J = 11.7 Hz, 1 H), 4.21 (dd, J = 5.7, 3.0 Hz, 1 H), 4.00–3.93 (m, 2 H), 3.85 (dd, J = 12.0, 2.4 Hz, 3 H) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 155.5 (dd, J = 290.3, 278.4 Hz, C^{IV}), 138.4 (C^{IV}), 138.1 (C^{IV}), 138.0 (C^{IV}), 137.5 (C^{IV}), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 108.7 (dd, J = 53.1, 17.6 Hz, C^{IV}), 78.5 (CH), 75.6 (CH), 73.4 (CH), 73.2 (CH_2), 73.1 (CH_2), 71.1 (t, J = 4.2 Hz, CH), 70.5 (CH), 67.4 (CH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –97.48 (d, J = 63.7 Hz), –112.03 (dd, J = 63.7, 2.8 Hz) ppm. HRMS (ESI$^+$): calcd. for $[M + Na]^+$ 595.2267; found 595.2248.

2,6-Anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-benzyl-D-*manno*-hept-1-enitol (16): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 13 H), 7.24–7.18 (m, 2 H), 4.89 (d, J = 10.9 Hz, 1 H), 4.72 (d, J = 11.6 Hz, 1 H), 4.69–4.62 (m, 2 H), 4.58 (d, J = 10.9 Hz, 1 H), 4.54 (d, J = 12.1 Hz, 1 H), 3.84–3.76 (m, 2 H), 3.75 (d, J = 8.9 Hz, 1 H), 3.67 (m, 1 H), 3.58 (dt, J = 9.1, 2.9 Hz, 1 H), 2.83 (dt, J = 13.8, 3.7 Hz, 1 H), 2.24–2.11 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.1 (dd, J = 287.2, 276.7 Hz, C^{IV}), 138.4 (C^{IV}), 138.3 (C^{IV}), 138.2 (C^{IV}), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 127.9 (CH), 112.5 (dd, J = 43.9, 15.7 Hz, C^{IV}), 81.0 (CH), 79.2 (dd, J = 3.0, 1.8 Hz, CH), 77.4 (CH), 75.2 (CH_2), 73.8 (CH_2), 72.0 (CH_2), 68.7 (CH_2), 27.6 (d, J = 2.3 Hz, CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.20 (dd, J = 74.8, 6.4 Hz), –117.41 (dt, J = 74.7, 3.7 Hz) ppm. HRMS (ESI$^+$): calcd. for $[M + Na]^+$ 489.1848; found 489.1838.

2,6-Anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetra-*O*-benzyl-D-*manno*-hept-1-enitol (17): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 18 H), 7.14 (dd, J = 7.2, 1.9 Hz, 2 H), 4.91 (d, J = 10.8 Hz, 1 H), 4.69 (d, J = 12.4 Hz, 1 H), 4.63 (d, J = 12.0 Hz, 1 H), 4.57–4.44 (m, 4 H), 4.35–4.29 (m, 2 H), 4.17 (t, J = 9.6 Hz, 1 H), 3.78 (d, J = 3.1 Hz, 2 H), 3.56 (dd, J = 9.5, 3.5 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.2 (dd, J = 294.7, 281.2 Hz, C^{IV}), 138.5 (C^{IV}), 138.4 (C^{IV}), 138.1 (C^{IV}), 137.7 (C^{IV}), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 112.5 (dd, J = 41.0, 12.2 Hz, C^{IV}), 82.0 (CH), 81.7 (dd, J = 3.1, 1.3 Hz, CH), 75.7 (CH_2), 74.1 (CH), 73.7 (CH_2), 71.6 (CH_2), 70.2 (CH_2), 69.1 (CH_2), 67.9 (t, J = 3.0 Hz, CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –98.09 (dd, J = 63.7, 2.7 Hz), –113.60 (dd, J = 63.7, 3.0 Hz) ppm. HRMS (ESI$^+$): calcd. for $[M + Na]^+$ 595.2267; found 595.2252.

2,5-Anhydro-1-deoxy-1,1-difluoro-3,4,6-tri-*O*-benzyl-D-*arabino*-hept-1-enitol (19): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 15 H), 4.62 (d, J = 3.3 Hz, 1 H), 4.53 (m, 6 H, 5 H), 4.38 (d, J = 11.7 Hz, 1 H), 4.11 (br. s, 1 H), 3.64 (ddd, J = 27.4, 10.0, 6.7 Hz, 2 H) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 151.4 (dd, J = 282.7, 264.0 Hz, C^{IV}), 138.1 (C^{IV}), 137.5 (C^{IV}), 137.3 (C^{IV}), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 119.1 (dd, J = 49.3, 13.1 Hz), 85.9 (CH), 83.4 (CH), 79.1 (t, J = 4.0 Hz, CH), 73.6 (CH_2), 71.9 (CH_2), 71.2 (CH_2),

69.5 (CH_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –103.40 (dd, J = 89.4, 2.0 Hz), –118.13 (dd, J = 89.4, 2.1 Hz) ppm. HRMS (ESI^+): calcd. for $[M + Na]^+$ 475.1691; found 475.1691.

2,5-Anhydro-1-deoxy-1,1-difluoro-3,4-diisopropylidene-6-*O*-*tert*-butyldimethylsilyl-D-*ribo*-hept-1-enitol (20): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 4 H), 7.38–7.30 (m, 6 H), 5.34 (dd, J = 6.0, 3.0 Hz, 1 H), 4.82 (br. d, J = 5.4 Hz, 1 H), 4.40 (br. s, 1 H), 3.75 (dd, J = 11.4, 3.0 Hz, 1 H), 3.64 (dd, J = 11.4, 2.7 Hz, 1 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 0.96 (s, 9 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –105.01 (d, J = 92.2 Hz), –120.82 (d, J = 92.2 Hz) ppm. HRMS (ESI^+): calcd. for $[M + Na]^+$ 483.1774; found 483.1765.

2,5-Anhydro-1-deoxy-1,1-difluoro-3,4-diisopropylidene-D-*erythro*-hept-1-enitol (21): ^1H NMR (300 MHz, $CDCl_3$): δ = 5.26 (dd, J = 6.0, 3.0 Hz, 1 H), 4.82 (m, 1 H), 4.23 (br. d, J = 10.5 Hz, 1 H), 3.89 (dd, J = 10.2, 4.2 Hz, 1 H), 1.43 (s, 3 H), 1.32 (s, 3 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –102.66 (d, J = 85.4, 2.3 Hz), –117.91 (dd, J = 85.2, 2.3 Hz) ppm. HRMS (ESI^+): calcd. for $[M + Na]^+$ 215.0490; found 215.0497.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H, ^{13}C, and ^{19}F NMR spectra of products.

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Difluorinated Enol Ethers

We report the preparation of difluoro-*exo*-glycals by olefination of sugar-derived lactones using a modified Julia reaction.

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