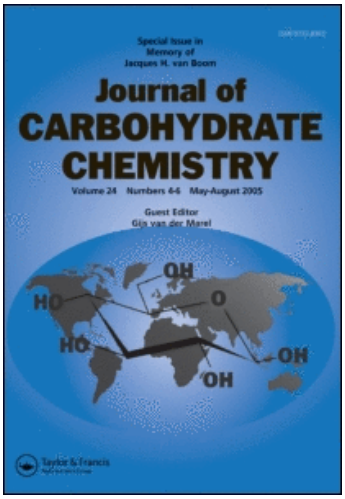

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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Online publication date: 13 December 2010

To cite this Article Esmurziev, Aslan M. , Simic, Nebojsa , Hoff, Bård Helge and Sundby, Eirik(2010) 'Synthesis and Structure Elucidation of Benzoylated Deoxyfluoropyranosides', Journal of Carbohydrate Chemistry, 29: 7, 348 — 367
To link to this Article: DOI: 10.1080/07328303.2010.540055
URL: http://dx.doi.org/10.1080/07328303.2010.540055

Journal of Carbohydrate Chemistry, 29:348–367, 2010

ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328303.2010.540055

Synthesis and Structure Elucidation of Benzoylated Deoxyfluoropyranosides

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Benzoylated deoxyfluoropyranosides have been synthesized, starting with protected, unprotected, or fluorinated precursors. Fluorination of eight derivatives was compared using DAST and Deoxo-Fluor as reagents. Deoxo-Fluor was found to be especially useful in the fluorination of methyl 2,3,4-*O*-tribenzoyl α-*D*-mannopyranoside and β-*D*-glucopyranoside, resulting in better yields and avoiding the 1,6-methoxy migration experienced with DAST for one derivative. The two reagents gave comparable yields in the fluorination of other methyl pyranosides, confirming Deoxo-Fluor as a safer alternative to DAST. Methyl α-*D*-mannopyranoside underwent fluorination to yield the 4,6-difluorotalopyranoside and the corresponding cyclic sulfite. The NMR spectroscopic properties of 11 benzoyl deoxy-fluoropyranosides are reported.

Keywords Deoxyfluorosugars; Diethylaminosulfur trifluoride; Bis-(2-methoxyethyl) aminosulfur trifluoride; DAST; Deoxo-Fluor; Benzoyl pyranosides; ^{19}F NMR

INTRODUCTION

Fluorinated molecules have found widespread applications in the field of medicinal chemistry.[1,2] Also, fluorinated carbohydrates have found their use among others as biocompatible surfactants,[3,4] mechanistic probes,[5–7] positron-emitting radiopharmaceuticals,[8,9] potential anticancer agents,[10–13] and building blocks for other bioactive compounds.[14–16] As compared to their natural derivatives, fluorinated carbohydrates have altered hydrogen bonding

Received February 25, 2010; accepted November 10, 2010.
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abilities and metabolic stability. ^{19}F NMR opens new possibilities for tracking distribution, transport, and metabolism of drug derivatives.

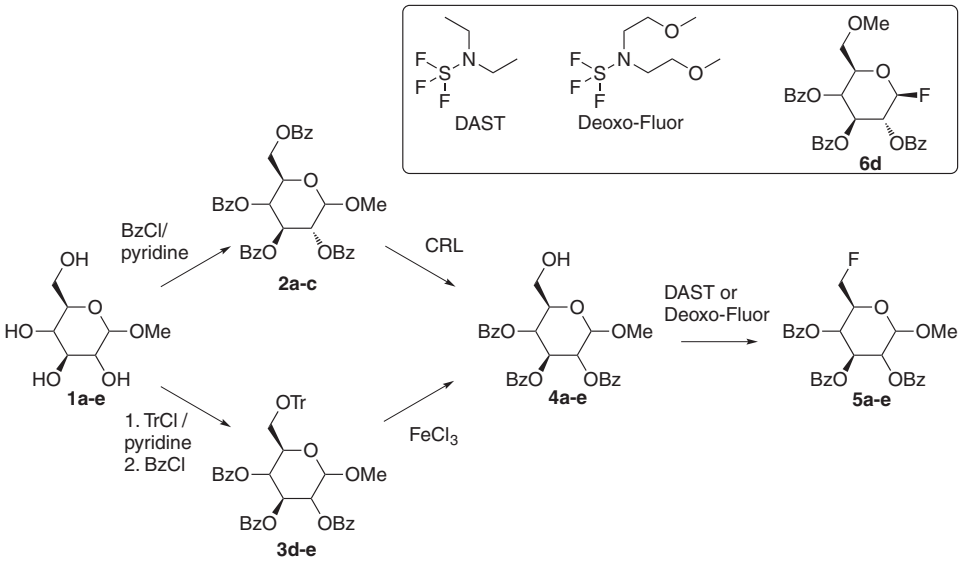
Although some unprotected carbohydrates can be fluorinated in decent yield, most often protection and deprotection schemes are utilized. Having the options of employing different protecting groups is of importance depending on the following chemical steps. Esters are often employed, and in terms of molecular mass and cost, the acetate ester is preferred. On the other hand, using aromatic esters allows for a higher stability, the avoidance/reduction of acyl migration, and the ability to analyze compounds by UV spectroscopic methods. Diethylaminosulfur trifluoride (DAST) is a commonly used reagent for the conversion of hydroxyl groups into fluorinated derivatives.[17,18] Also, partly benzoylated carbohydrates have been fluorinated with this reagent.[6,19–23] However, there are hazards connected to the use of DAST, and a safer alternative, bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), has been developed.[24–26] As part of our effort to prepare building blocks for bioactive compounds, a series of benzoylated deoxy-fluoropyranosides have been synthesized and characterized. The use of DAST and Deoxo-Fluor has also been compared in fluorination of various hexapyranosides.

RESULTS AND DISCUSSION

Synthesis of Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-pyranosides

As monofluorination of unprotected carbohydrates can be problematic, the 6-deoxy-6-fluorohexapyranosides were targeted by fluorination of the methyl 2,3,4-tri-O-benzoylpyranosides (**4a**–**e**). These were obtained by two different routes: compounds **4a**–**c** were synthesized by *Candida rugosa* lipase (CRL)-catalyzed hydrolysis of the corresponding tetrabenzoates, **2a**–**c**, as previously reported,[27] while **4d**–**e** were obtained by a tritylation/benzoylation/detritylation protocol (Sch. 1).

The methyl 2,3,4-tri-*O*-benzoylhexapyranosides **4a–e** were then subjected to fluorination using DAST in dichloromethane, THF and diglyme, and Deoxo-Fluor in THF. The degree of conversion obtained under the various conditions is shown in Table 1. The galacto derivatives **4a**–**b** were fluorinated very slowly, giving a maximum of 14% conversion using DAST in dichloromethane. No improvement was observed using Deoxo-Fluor. In fluorination of structurally related methyl 2,3,4-tribenyl *D*-galactopyranoside, Tashiro et al.[28] also obtained a cyclic 3,6-ether byproduct. This was not seen in reaction of **4a–b**. The low degree of conversion for **4a–b** is most likely due to steric hindrance imposed by the benzoyl groups.



Scheme 1: Route to **5a–e**, α-*D*-galactopyranoside (**a**), β-*D*-galactopyranoside (**b**), α-*D*-glucopyranoside (**c**), β-*D*-glucopyranoside (**d**), α-*D*-mannopyranoside (**e**).

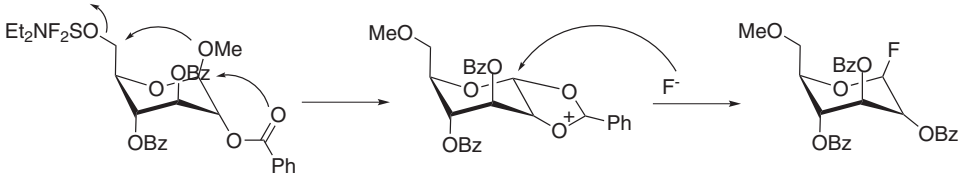
Higher reactivity was observed in fluorination of **4c**. The use of DAST in dichloromethane gave a 54% conversion. This could be increased to 91% by applying a 1-h refluxing period at the end of the reaction. The use of Deoxo-Fluor led to a comparable 88% conversion. In fluorination of **4a–c**, the 6-deoxy-6-fluoroderivatives, **5a–c**, were the only products in each case. However, in line with that reported by Lin et al.,[19] DAST fluorination of methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranoside (**4d**) gave rise to both **5d** and the migration

Table 1: Degree of conversion (%)[a] in fluorination of **4a–e** in various solvents using DAST (4 eq) and Deoxo-Fluor (4 eq)

	DAST					Deoxo-Fluor		
Substrate	CH_2Cl_2	CH_2Cl_2[b]	THF	Di-glyme	Product	THF	THF[b]	Product
4a	14	14	<1	<1	**5a**	13	13	**5a**
4b	12	10	<1	<1	**5b**	7	9	**5b**
4c	54	91	41	<1	**5c**	88	88	**5c**
4d	74[c]	>99[d]	[e]	[e]	**5d** + **6d**	85	>99	**5d**
4e	60	62	[e]	[e]	**5e**	77	78	**5e**

[a]Conv. by HPLC.
[b]Refluxed for 1 h after standard reaction.
[c]Products: **5d**, 41%; **6d**, 33%.
[d]Products: **5d**, 38%; **6d**, 62%.
[e]Not performed.

product **6d**. A refluxing period at the end of the reaction increased the amount of the rearrangement product further to 62%. A mechanistic rationale for this migration has been proposed,[19,29,30] where the glycosidic oxygen acts as a nucleophile on the RO-SF_2NEt_2 intermediate, possibly assisted by the carbonyl oxygen situated at C-2 (Sch. 2).

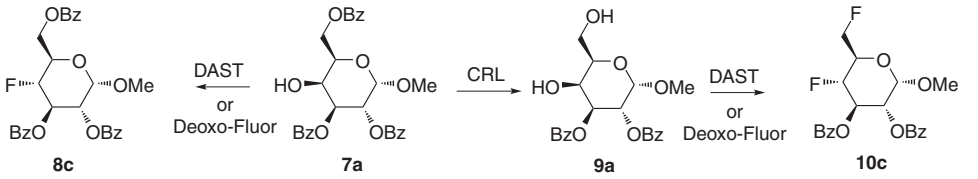


Scheme 2: Possible mechanism for the C-1 to C-6 methoxy migration.

In contrast, the use of Deoxo-Fluor gave **5d** as the only product. Full conversion to **5d** was obtained when applying a refluxing period at the end of the reaction. The reason why Deoxo-Fluor does not cause this migration is not understood. However, DFT calculations have indicated that the increased stability of Deoxo-Fluor as compared to DAST is due to coordination of the ether oxygen with the sulphur atom of the reagent.[24] Possibly, such a coordination could also be present in the RO-$SF_2N(CH_2CH_2OCH_3)_2$ intermediate, both shielding C-6 toward nucleophilic attack from oxygen at C-1 and increasing the strength of the susceptible C-O bond. Deoxo-Fluor also proved to be the best fluorinating agent for the synthesis of **5e** from **4e** (77% conv.). Fluorination of **4e** with DAST in dichloromethane gave 60% conversion.

Synthesis of Other Benzoylated Deoxy-fluoropyranosides

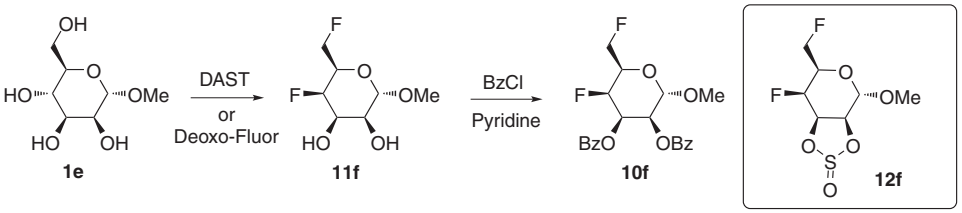
We continued to compare the performance of DAST and Deoxo-Fluor in fluorination of other methyl pyranosides. Methyl 2,3,6-tri-*O*-benzoyl-α-*D*–galactopyranoside (**7a**), obtained by abrupt benzoylation of **1a**, was fluorinated using DAST and Deoxo-Fluor (Sch. 3). The product **8c** has been prepared previously using DAST.[20,21]



Scheme 3: Synthesis of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-*D*-glucopyranoside (**8c**) and methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-glucopyranoside (**10c**) using DAST or Deoxo-Fluor.

Fluorination of **7a** with DAST and Deoxo-Fluor using 2.5 equivalents of fluorinating agent gave a 67% and 65% conversion, respectively. The degree of conversion for both systems could be improved to 90% by addition of a second portion of reagent after 6 h reaction time. The reaction of **7a** with DAST was run in a 23.3 mmol scale, giving 72% isolated yield of **8c**. Further, from **7a**, *Candida rugosa* lipase-catalyzed hydrolysis gave **9a**, which was submitted to DAST and Deoxo-Fluor fluorination (Sch. 3). The difluorinated α-*D*-glucopyranoside **10c** was obtained in 74% and 72% isolated yield, respectively, indicating very similar reactivity for the two reagents. No other fluorinated byproducts were observed.

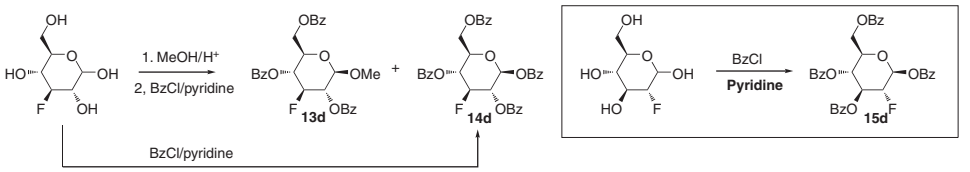
DAST fluorination of methyl α-*D*-mannopyranoside (**1e**) to yield methyl 4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoiside (**11f**) has been reported.[21,31] The preparation of methyl 4,6-dideoxy-4,6-difluoro-2,3-di-*O*-benzoyl-α-*D*–talopyranoside (**10f**) was attempted using both DAST and Deoxo-Fluor followed by benzoylation without isolation of **11f** (Sch. 4). In both cases 9 equivalents of fluorinating agent was used and a similar low 26% isolated yield of **10f** was obtained.



Scheme 4: Synthesis of methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-difluoro-α-*D*–talopyranoside (**10f**) and the structure of the byproduct **12f**.

The reasons for the loss in yield were investigated by isolation of **11f**. However, in addition to **11f**,[31] another difluorinated carbohydrate was isolated. NMR spectroscopy confirmed this to be a methyl 4,6-dideoxy-difluorotallopyranoside, but with higher shift values for H-1, H-2, and H-3 as compared to **11f**. Whereas compound **11f** underwent benzoylation to afford **10f** (77% isolated yield), the unknown compound failed to react under similar conditions. Based on previous reports on fluorination of inositol derivatives using SF_4[32,33] and a characteristic IR band at 1215 cm^{-1}, a cyclic sulfite was the most likely candidate structure. The presence of sulphur was confirmed by ICP-MS, and a reaction of **11f** with thionyl chloride gave a compound with the same chemical and spectroscopic properties, thus confirming the structure **12f**. The mechanism of formation is expected to follow that outlined for SF_4.[33]

We were also interested in obtaining the benzoylated 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-*D*-gluco derivatives as building blocks for bioactive compounds. Methylation and benzoylation of commercially available 3-deoxy-3-fluoro-*D*-glucose was attempted as shown in Scheme 5. To avoid the isolation



Scheme 5: Synthesis of benzoylated 3-deoxy-3-fluoro- and 2-deoxy-2-fluoro-*D*-glucopyranoside.

of the intermediate methyl glucoside, benzoylation was performed on the crude reaction product. This, however, gave a mixture of the β-anomer **13d** (12% isolated yield) and the tetrabenzoate **14d** (3%). Both the low yield and formation of the β-anomer **13d** correspond with results for synthesis of the corresponding acetates.[34]

Attempts to prepare methyl 3,4,6-tri-*O*-benzoyl-2-deoxy-2-fluoro-*D*–glucopyranoside were also made by the two-step route shown in Scheme 5, but were unsuccessful. Due to the low efficiency in forming the methyl glycosides, it was considered more useful to prepare the corresponding tetrabenzoates **14** and **15** by benzoylation (Sch. 5). Crystallization gave 48% and 51% isolated yield of the β-anomers **14d** and **15d**, respectively. We were not able to purify the α-anomers present in the mother liquor.

NMR Spectroscopy

The NMR assignments of the compounds **5a–e**, **8c**, **10c**, **10f**, **13d**, **14d**, and **15d** were based on the data obtained from 1D ^{1}H, ^{13}C, and ^{19}F and various 2D experiments. Spin systems and connectivity in the pyranose ring and in the aromatic systems were identified by DQF-COSY, HMQC, and HSQC-TOCSY experiments. The connectivity between the pyranose ring and benzoyl groups was identified in HMBC spectra from long-range correlations between protons H-2, H-3, H-4, and H-6, the corresponding carbonyl-, and its directly attached aromatic carbon (Fig. 1).

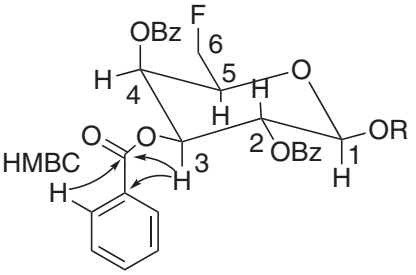


Figure 1: HMBC correlations revealing connectivity between the pyranoside and benzoyl groups.

The ^{1}H and ^{13}C chemical shifts are given in the Experimental section; the resolved ^{1}H-^{1}H and ^{19}F-^{1}H coupling constants and the ^{19}F chemical shifts are given Table 2.

^{1}H NMR data of the pyranose part of **5c** corresponded with that published previously.[35] ^{1}H NMR of **5d** has been reported, but not assigned,[19] while in the case of **8c**, previously reported shifts for protons at C-6, C-1, and C-2 have to be revised.[20,21] The ^{1}H chemical shift of H-1 depended on the anomeric configuration and the configuration at C-2. For the α-anomers **5a**, **5c**, **8c**, and **10c**, the H-1 signal resided at higher ppm values than for their β-anomers. The coupling constants between H-1 and H-2 are also of diagnostic value. In the case of **13d**, both the H-1 shift value and the coupling between H-1 and H-2 enabled assignment of stereochemistry as β-configured.

The $^{2}J_{HF}$ couplings for 6-deoxy-6-fluoroderivatives **5a–e**, **10c**, and **10f** were in the range of 45.6 to 47.5 Hz, while when the fluorine was situated at C-2, C-3, and C-4, slightly higher coupling values were observed (50.3–52.0 Hz).

The ^{13}C NMR data for **5c** corresponded with that reported[35]; data for **8c** has not been found, while in the case of **5d**,[19] assignment has not been provided. The C-1 and the methoxy carbon shifts are strong indicators of anomeric configuration, and the α-anomers had lower shift values than the β-anomers for both signals. The chemical shifts of C-6 in the 6-deoxy-6-fluoropyranosides were only slightly affected by structural variation and appeared from 80.7 to 81.7 ppm. The $^{1}J_{CF}$ coupling constants varied from 169.6 to 193.2 Hz depending on the position of the fluorine and pyranose structure. Among others, the $^{1}J_{CF}$ coupling constants at C-6 depended on the stereochemistry at C-4 and were higher for **5c–e** and **10c** than for **5a–b** and **10f**.

The ^{19}F NMR data of **8c** corresponded well with those reported,[20,21] while reference data for the other compounds have not been published. The shifts for the fluorine at C-6 varied from −230.50 to −236.15 ppm, while the fluorines at C-2, C-3, and C-4 resided from −195.53 to −200.19. The ^{19}F-^{1}H coupling constants were in good agreement with those observed from the ^{1}H 1D spectrum.

CONCLUSION

Eleven deoxy-fluoro benzoyl pyranosides, eight of which are new chemical entities, have been synthesized and characterized by high-field NMR spectroscopy. The use of DAST and Deoxy-Fluor was compared in the fluorination of eight different carbohydrate derivatives and in most cases the reagents gave similar yields. Surprisingly, in reaction of methyl α-D-mannopyranoside, a cyclic sulfite was discovered as the major byproduct using both reagents. The use of Deoxy-Fluor was found to be superior for the fluorination of methyl 2,3,4,-tribenzoyl-β-*D*-glucopyranoside, avoiding a 1,6-migration experienced with DAST. Moreover, with Deoxy-Fluor, as compared to DAST, fluorination

Table 2: The resolved ^{1}H-^{1}H, ^{19}F -^{1}H coupling constants (Hz) and ^{19}F chemical shift (δ, ppm) for **5a-e**, **8c**, **10c**, **10f**, **13d**, **14d** and **15d** in $CDCl_3$ at 298 K using TMS (^{1}H) and hexafluorobenzene (^{19}F) as standards.

	5a	**5b**	**5c**	**5d**	**5e**	**8c**	**10c**	**10f**	**13d**	**14d**	**15d**
$^{3}J_{H1-H2}$	3.6	8.0	NR	7.8	NR	3.5	3.6	NR	7.9	8.2	7.8
$^{3}J_{H2-H3}$	10.4	10.4	NR	9.5	NR	10.2	9.8	NR	9.0	8.9	8.9
$^{3}J_{H3-H4}$	3.5	3.5	9.4	9.5	NR	9.0	9.0	1.2	9.0	8.9	NR
$^{3}J_{H4-H5}$	NR[a)]	1.2	10.4	9.8	NR	9.3	9.9	NR	9.9	NR	9.9
$^{3}J_{H5-H6a}$	6.1	6.7	3.5	4.0	NR	5.0	NR	NR	5.3	4.7	5.0
$^{3}J_{H5-H6b}$	NR	5.0	3.5	4.0	NR	2.1	NR	NR	3.1	2.0	2.9
$^{2}J_{H6a-H6b}$	NR	NR	NR	NR	NR	12.2	NR	NR	12.1	12.3	12.3
^{2}J (^{19}F-^{1}H)	47.3	45.8	47.0	47.3	47.3	50.4	47.3[d)] 50.4[e)]	45.8[d)] 50.4[e)]	51.9	51.9	50.4
^{3}J (^{19}F-^{1}H)	15.3	13.7	23.0	19.8	22.9	13.7[b)] NR[c)]	13.7[b)] 27.5[c)]	30.5[d)] 29.6[c)]	13.7[b, f)]	13.7[b), f)]	13.7[b)] 3.3 [g)]
^{19}F (δ, ppm)	−231.66	−230.50	−232.04	−230.91	−232.10	−197.52	−236.15	−232.19[h)]	−195.53	−196.18	−200.19
^{19}F (δ, ppm)	(td)	(td)	(td)	(td)	(td)	(dd)	(td)[h)] −198.17[i)] (dd)	(td) −217.06[i)] (m)	(dt)	(dt)	(ddd)

[a)]NR = not resolved, [b)] Coupling to H-3, [c)] Coupling to H-5, [d)] Coupling to H-6, [e)] Coupling to H-4, [f)] Coupling to H-2, [g)] Coupling to H-1, [h)] Fluorine at C-6, [i)] Fluorine at C-4.

of carbohydrates can be performed with good conversion in nonchlorinated solvents (THF) with a less hazardous reagent.

EXPERIMENTAL

General

Methyl α-*D*-mannopyranoside (**1e**) was prepared by a known method,[36] while **1a–d**, DAST, and Deoxo-Fluor were purchased from Sigma-Aldrich. Benzoyl chloride and pyridine were from Fluka. 2-Deoxy-2-fluoro-*D*-glucose and 3-deoxy-3-fluoro-*D*-glucose were from Toronto Research Chemicals Inc. The compounds **2a–c**, **4a–c**, and **9a** were prepared as described previously.[27,37] Solvents were from VWR and were used as received, except for CH_2Cl_2, which was dried over $CaCl_2$. Column chromatography was performed using silica gel 60A from Fluka (pore size 40–63 μm). *Candida rugosa* lipase (type VII, $\geq$700 units/mg solid) was from Sigma-Aldrich.

Analysis

The HPLC system consisted of an Agilent 1100 series quaternary pump, Agilent 1100 series variable wavelength UV detector (200–315 nm), and thermostated column compartment. Conversion was analyzed on a Supelcosil C18 column (5-μm particle size, 25 cm) at 254 nm, eluting with a mixture of deionized water containing TFA (0.01%) and MeOH (30:70, vol.-%). Melting points were determined by a Mettler FP 5 melting point apparatus and are uncorrected. Optical rotations were measured using the sodium D line at 589 nm on a Perkin-Elmer 243 B polarimeter.

NMR Spectroscopic Methods

Unless otherwise stated, ^{1}H and ^{13}C NMR data were recorded using a Bruker Avance 600 spectrometer operating at a proton frequency of 600.18 MHz with a 5-mm triple-resonance cryo probe equipped with a z-gradient. The samples containing a solution of 20 mg of substances in $CDCl_3$ were measured at 298 K with TMS as reference standard. The ^{19}F NMR data were recorded with a Bruker Avance 500 spectrometer using hexafluorobenzene as reference standard. Pulse sequences from the Bruker user library were used. The acquisition details for the 1D ^{1}H and ^{13}C NMR, HMQC, HSQC-TOCSY, HMBC, and ^{1}H,^{1}H DQF-COSY were as described previously.[37] 470 MHz ^{19}F 1D: π/2 pulse for ^{19}F 15.0 μs, spectral width 100 kHz, acquisition time 0.35 s, relaxation delay 1.0 s. 470 MHz ^{19}F 1D with proton BB decoupling: π/2 pulse for ^{19}F 15.0 μs, spectral width 94.3 kHz, acquisition time 0.66 s, WALTZ proton decoupling during acquisition, relaxation delay 1.0 s. In order to distinguish

close resonances for some of the compounds, additional experiments were run to obtain higher resolution.

Synthesis

*Methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranoside (**4d**)*[38]

Methyl *β-D*-glucopyranoside (**1d**) (1.00 g, 5.15 mmol) was first converted to methyl 2,3,4-tri-*O*-benzoyl-6-trityl-*β-D*-glucopyranoside (**3d**) by tritylation and benzoylation according to the procedure of Ding et al.[39] This resulted in an oil that crystallized from EtOH giving 1.25 g (1.67 mmol, 32%) of **3d** as a white solid, mp. 115–116°C, $[\alpha]_D^{22} = -12.2^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (m, 2 H, Ar), 7.82 (m, 2 H, Ar), 7.70 (m, 2 H, Ar), 7.51–7.29 (m, 9 H, Ar), 7.16 (m, 8 H, Ar), 7.09 (m, 7 H, Ar), 5.79 (t, $J = 9.6$, 1 H, H-3), 5.63 (t, $J = 9.6$, 1 H, H-4), 5.54 (dd, $J_{2,3} = 9.6$, $J_{2,1} = 8.0$, 1 H, H-2), 4.72 (d, $J_{1,2} = 8.0$, 1 H, H-1), 3.85 (m, 1 H, H-5), 3.62 (s, 3 H, O$\underline{C}H_3$), 3.35 (dd, $J_{5,6a} = 2.5$, $J_{6a,6b} = 10.7$, 1 H, H-6_a), 3.26 (dd, $J_{5,6b} = 5.1$, $J_{6b,6a} = 10.7$, 1H, H-6_b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 165.4, 164.9, 143.9 (3 C), 133.3, 133.25, 133.2, 130.0 (2 C), 129.92 (2 C), 129.8 (2 C), 129.7, 129.5, 129.3, 129.1 (2 C), 128.7 (6 C), 128.4 (2 C), 128.3 (2 C), 127.9 (6 C), 127.0 (3 C), 102.1 (C-1), 86.8 (O-$\underline{C}Ph_3$), 74.0 (C-5), 73.4 (C-3), 72.2 (C-2), 69.6 (C-4), 62.6 (C-6), 56.9 (O-$\underline{C}H_3$).

Compound **3d** (1.00 g, 1.34 mmol) was detritylated using $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 according to the procedure described by Ding et al.[40] This gave a white foam, which was purified by silica gel column chromatography (toluene/EtOAc, 1/1) and then crystallized from pentane/$CHCl_3$ to give 450 mg (0.89 mmol, 66%) of **4d** as white solid, mp. 79–80°C, $[\alpha]_D^{22} = -8.4^\circ$ (c 1.1, $CHCl_3$), *lit.*[38] -6.6° (c 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) corresponded with data reported previously.[27,38]

*Methyl 2,3,4-tri-*O*-benzoyl-α-*D*-mannopyranoside (**4e**)*[41,42]

Methyl *α-D*-mannopyranoside (2.00, 10.30 mmol) was converted to methyl 2,3,4-tri-*O*-benzoyl-6-trityl-*α-D*-mannopyranoside (**3e**)[40,43] as described for **4d**. This gave 2.70 g (3.61 mmol, 35%) of **3e** as a white solid, mp. 113–114°C, *lit.*[43] 110–120°C, $[\alpha]_D^{22} = -90.5^\circ$ (c 1.0, $CHCl_3$), *lit.*[40] -45°(c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (m, 2 H, Ar), 7.83 (m, 2 H, Ar), 7.73 (m, 2 H, Ar), 7.61 (m, 1 H, Ar), 7.51–7.38 (m, 10 H, Ar), 7.30 (m, 3 H, Ar), 7.18–7.06 (m, 10 H, Ar), 6.02 (t, $J = 10.2$, 1H, H-4), 5.77 (dd, $J_{3,2} = 3.3$, $J_{3,4} = 10.2$, 1 H, H-3) 5.68 (m, 1 H, H-2), 5.03 (d, $J = 1.5$, 1 H, H-1), 4.17 (m, 1 H, H-5), 3.55 (s, 3 H, O$\underline{C}H_3$), 3.40 (dd, $J_{5,6a} = 2.5$, $J_{6a,6b} = 10.5$, 1 H, H-6_a), 3.29 (dd, $J_{5,6b} = 4.9$, $J_{6b,6a} = 10.5$, 1 H, H-6_b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8, 165.7, 165.2, 143.9 (3C), 133.6, 133.2, 133.1, 130.1 (2 C), 129.9 (2 C), 129.8 (2 C), 129.7, 129.5, 128.8 (2 C), 128.77 (6 C), 128.4 (2 C), 128.3 (2 C), 127.8 (6 C), 127.0 (3

C), 98.7 (C-1), 86.8 (O-$\underline{C}Ph_3$), 70.9 (C-2), 70.7 (C-3), 70.4 (C-5), 67.2 (C-4), 62.5 (C-6), 55.4 (O-$\underline{C}H_3$).

Detritylation of **3e** (2.50 g, 3.34 mmol) was performed as described for **3d** to give **4e**, 1.31 g (2.59 mmol, 77%) as a white solid, mp. 69–70°C, $[\alpha]_D^{22} = -127.5^\circ$ (c 0.5, $CHCl_3$), *lit.*[27] -126.0° (c 0.5, $CHCl_3$), *lit.*[38] -154° (c 1.1, $CHCl_3$). NMR corresponded with that reported previously.[27]

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-α-*D*-galactopyranoside (**5a**)*

DAST (106 μL, ~129 mg, ~0.80 mmol) was added drop-wise to a solution of **4a** (100 mg, 0.20 mmol) and DMAP (50 mg, 0.40 mmol) in dry CH_2Cl_2 (2 mL) at -25°C under argon. After 12 h the reaction mixture was allowed to slowly warm to rt and stirred overnight. The reaction mixture was then cooled to 0°C and methanol (0.3 mL) was added to quench the reaction. The resulting solution was further diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ (3 × 5 mL) and water (5 mL), and the combined aqueous phase was back-extracted once with CH_2Cl_2 (5 mL). The organic phases were washed once more with water (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (toluene/EtOAc, 9/1) to give 10 mg (0.02 mmol, 10%) of compound **5a** as a colorless foam; $[\alpha]_D^{22} = +78.1^\circ$ (c 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.07 (m, 2 H, Ar), 7.98 (m, 2 H, Ar), 7.79 (m, 2 H, Ar), 7.62 (m, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.48 (m, 2 H, Ar), 7.43 (m, 1 H, Ar), 7.38 (m, 2 H, Ar), 7.24 (m, 2 H, Ar), 5.96 (m, 1 H, H-3), 5.94 (m, 1 H, H-4), 5.67 (dd, 1 H, H-2), 5.32 (d, 1 H, H-1), 4.57 (m, 2 H, H-6_{ab}), 4.52 (m, 1 H, H-5) 3.50 (s, 3 H, OC$\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.08, 165.58, 165.50, 133.63, 133.41, 133.18, 129.92 (2 C), 129.86 (2 C), 129.69 (2 C), 129.14, 129.10, 129.03, 128.66 (2 C), 128.44 (2 C), 128.27 (2 C), 97.57 (C-1), 81.72 (d, J = 171.2, C-6), 69.26 (C-2), 69.02 (d, J = 6.6, C-4), 68.23 (C-3), 67.65 (d, J = 23.0, C-5), 55.79 (O$\underline{C}H_3$). HRMS (ESI): 509.1619 (calcd 509.1606, M+H$^+$).

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-β-*D*-galactopyranoside (**5b**)*

Compound **5b** was synthesized as described for **5a**, starting with **4b** (100 mg, 0.20 mmol) giving 9 mg (0.02 mmol, 9%) of a colorless oil; $[\alpha]_D^{22} = +146.0^\circ$ (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.06 (m, 2 H, Ar), 7.97 (m, 2 H, Ar), 7.78 (m, 2 H, Ar), 7.62 (m, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.48 (m, 2 H, Ar), 7.43 (m, 1 H, Ar), 7.39 (m, 2 H, Ar), 7.24 (m, 2 H, Ar), 5.91 (dd, 1 H, H-4), 5.78 (dd, 1 H, H-2), 5.58 (dd, 1 H, H-3), 4.75 (m, 1 H, H-1), 4.62 (m, 2 H, H-6_{ab}), 4.26 (m, 1 H, H-5), 3.62 (s, 3 H, OC$\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.58, 165.53, 165.32, 133.69, 133.32, 133.29, 130.01 (2 C), 129.80 (2 C), 129.77 (2 C), 129.30, 128.82, 128.68, 128.64 (2 C), 128.39 (2 C), 128.31 (2 C), 102.42 (C-1), 81.17 (d, J = 172.4, C-6), 72.27 (d, J = 23.0, C-5), 71.65 (C-3),

69.61 (C-2), 67.93 (d, $J = 6.6$, C-4), 57.38 (OCH_3). HRMS (ESI): 509.1612 (calcd 509.1606, $M+H^+$).

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-α-*D*-glucopyranoside (**5c**)*[35]

DAST (190 μL, ∼232 mg, ∼1.44 mmol) was added drop-wise to a solution of **4c**[27] (180 mg, 0.36 mmol) and DMAP (100 mg, 0.80 mmol) in dry CH_2Cl_2 (3 mL) at −25°C. After stirring under argon for 12 h, the reaction mixture was allowed to warm to ambient temperature, stirred overnight, and refluxed for 1 h. The mixture was then cooled to 0°C and methanol (0.5 mL) was added to quench the reaction. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (3 × 10 mL) and water (10 mL), and the aqueous phase was back-extracted once with CH_2Cl_2 (10 mL). The combined organic phases were washed once with water (15 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was crystallized twice from MeOH to give 135 mg (26.55 mmol, 75%) as a white solid, mp. 143–144°C, (*lit.*[35] 145–146°C), $[\alpha]_D^{22} = +46.8°$ (c 1.5, $CHCl_3$), *lit.*[35] +52.7° (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.97 (m, 4 H, Ar), 7.87 (m, 2 H, Ar), 7.54 (m, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.43 (m, 1 H, Ar), 7.38 (m, 4 H, Ar), 7.29 (m, 2 H, Ar), 6.19 (t, 1 H, H-3), 5.56 (t, 1H, H-4), 5.28 (m, 1 H, H-2), 5.27 (m, 1 H, H-1), 4.59 (dd, 2 H, H-6_{ab}), 4.27 (ddt, 1 H, H-5), 3.49 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.80, 165.77, 165.29, 133.56, 133.41, 133.16, 129.94 (2 C), 129.88 (2 C), 129.67 (2 C), 129.12, 128.99, 128.74, 128.49 (2 C), 128.44 (2 C), 128.31 (2 C), 97.04 (C-1), 81.50 (d, $J = 175.6$, C-6), 71.92 (C-2), 70.25 (C-3), 68.55 (d, $J = 6.6$, C-4), 68.55 (d, $J = 19.8$, C-5), 55.74 (OCH_3).

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-β-*D*-glucopyranoside (**5d**)*[19]

Deoxo-Fluor in THF (50%, 350 μL, 0.81 mmol) was added drop-wise to a solution of **4d** (100 mg, 0.20 mmol) in THF (1 mL) at −25°C. After stirring under argon for 12 h, the reaction mixture was allowed to warm to ambient temperature, stirred overnight, and refluxed for 1 hour. The reaction mixture was cooled to 0°C and methanol (0.5 mL) was added to quench excess of the reagent. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ (3 × 5 mL) and water (5 mL), and the aqueous phases were back-extracted once with CH_2Cl_2 (5 mL). The combined organic phases were washed once with water (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (toluene/EtOAc, 9/1) to give an oil, which was crystallized twice from MeOH to give 74 mg (0.15 mmol, 74%) of a white solid, mp. 64–65°C, $[\alpha]_D^{22} = -1.6°$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.96 (m, 2 H, Ar), 7.94 (m, 2 H, Ar),7.82 (m, 2 H, Ar), 7.52 (m, 2 H, Ar), 7.42 (m, 1 H, Ar), 7.38 (m, 4 H, Ar), 7.28 (m, 2 H, Ar), 5.91 (t, 1 H, H-3), 5.51 (m, 1 H, H-4), 5.50 (m, 1 H, H-2), 4.76 (d, 1 H, H-1), 4.62 (dd, 2 H, H-6_{ab}), 4.05 (qt, 1 H, H-5), 3.58 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.79, 165.24, 165.10, 133.62, 133.28, 133.25, 129.85 (4

C), 129.75 (2 C), 129.23, 128.72, 128.63, 128.50 (2 C), 128.36 (2 C), 128.31 (2 C), 101.94 (C-1), 81.56 (d, $J = 175.6$, C-6), 73.22 (d, $J = 19.8$, C-5), 72.76 (C-3), 71.66 (C-2), 68.83 (d, $J = 7.7$, C-4), 57.20 ($O\underline{C}H_3$).

*Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-fluoro-α-*D*-mannopyranoside (**5e**)*

Compound **5e** was prepared as described for **5d**, starting with **4e** (100 mg, 0.20 mmol). Purification by silica gel column chromatography (toluene/EtOAc, 9/1), followed by crystallization from MeOH gave 64 mg (0.13 mmol, 64%) of a white solid, mp. 67–68°C, $[\alpha]_D^{22} = -154.3°$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.10 (m, 2 H, Ar), 7.97 (m, 2 H, Ar), 7.83 (m, 2 H, Ar), 7.61 (m, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.49 (m, 2 H, Ar), 7.43 (m, 1 H, Ar), 7.39 (m, 2 H, Ar), 7.26 (m, 2 H, Ar), 5.91 (m, 1 H, H-3), 5.89 (m, 1 H, H-4), 5.68 (m, 1 H, H-2), 5.01 (bs, 1 H, H-1), 4.63 (m, 2 H, H-6_{ab}), 4.27 (m, 1 H, H-5), 3.54 (s, 3 H, $OC\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.53, 165.49, 165.42, 133.56 (2 C), 133.19, 129.93 (2 C), 129.80 (2 C), 129.73 (2 C), 129.24, 129.03, 128.84, 128.63 (2 C), 128.50 (2 C), 128.30 (2 C), 98.66 (C-1), 81.70 (d, $J = 174.5$, C-6), 70.34 (C-2), 69.82 (C-3), 69.58 (d, $J = 19.8$, C-5), 66.24 (d, $J = 6.6$, C-4), 55.62 ($O\underline{C}H_3$). HRMS (ESI): 509.1611 (calcd 509.1606, $M+H^+$).

*2,3,4-Tri-*O*-benzoyl-1-deoxy-1-fluoro-6-methyl-β-*D*-glucopyranoside (**6d**)*[19]

Compound **6d** was obtained according to the procedure described for **5c**, starting with **4d** (50 mg, 0.10 mmol) and DAST (52 μL, ~64 mg, ~0.40 mmol) in dry CH_2Cl_2 (1 mL). Purification by silica gel column chromatography (toluene/EtOAc, 9.5/0.5) gave 19 mg (0.04 mmol, 38%) of **6d**. The structure of compound **6d** was verified by comparing ^{1}H NMR to that reported previously.[19]

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-*D*-glucopyranoside (**8c**)*[20,21] *using DAST*

Compound **8c** was synthesized as described for **5a** starting with **7a** (11.80 g, 23.30 mmol) and DAST (7.5 mL, ~9.2 g, ~56 mmol). After 6 h reaction time a second portion of DAST (7.5 mL, ~9.2 g, ~56 mmol) was added. This resulted in a syrup, which, upon crystallization from EtOH, gave 8.50 g (16.72 mmol, 72%) of a white solid, mp. 140–141°C (*lit.*[21] 139–141°C), $[\alpha]_D^{22} = +101°$ (c 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.10 (m, 2 H, Ar), 8.02 (m, 2 H, Ar), 7.98 (m, 2 H, Ar), 7.60 (m, 1 H, Ar), 7.52 (m, 2 H, Ar), 7.49 (m, 2 H, Ar), 7.39 (m, 2 H, Ar), 7.38 (m, 2 H, Ar), 6.13 (m, 1 H, H-3), 5.20 (dd, 1 H, H-2), 5.17 (m, 1 H, H-1), 4.77 (m, 1 H, H-4), 4.62 (ddd, 1 H, H-6_a), 4.72 (m, 1 H, H-6_b), 4.32 (m, 1 H, H-5), 3.47 (s, 3H, $OC\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.16, 165.85, 165.58,133.51, 133.32, 133.30, 129.96 (2 C), 129.80 (2 C), 129.73 (2 C), 129.65, 129.27, 128.83, 128.52 (2 C), 128.47 (2 C), 128.39 (2 C), 96.88 (C-1),

87.36 (d, $J = 187.7$, C-4), 71.36 (d, $J = 7.7$, C-2), 70.45 (d, $J = 19.8$, C-3), 67.10 (d, $J = 23.0$, C-5), 62.57, 55.69 ($O\underline{C}H_3$).

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-*D*-glucopyranoside (**8c**)*[20,21] *using Deoxo-Fluor*

Compound **8c** was synthesized using Deoxo-Fluor (50% in THF, 415 μL, ~215 mg, ~0.97 mmol) and **7a** (200 mg, 0.39 mmol) at −25°C for 12 h followed by stirring overnight in ambient temperature. Workup was performed as for **5d** and crystallization from EtOH gave 90 mg (0.18 mmol, 45%) of a white solid. Physical and spectroscopic properties were identical to that obtained using DAST.

*Methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-glucopyranoside (**10c**) using DAST*

Compound **10c** was synthesized as described for **5a**, starting with **9a**[27] (100 mg, 0.25 mmol) and DAST (300 μL, ~366 mg ~2.3 mmol) to give 75 mg (0.18 mmol, 74%) of the product as a colorless oil, $[\alpha]_D^{22} = +29.4^\circ$ (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.01 (m, 2 H, Ar), 7.97 (m, 2 H, Ar), 7.52 (m, 2 H, Ar), 7.38 (m, 4 H, Ar), 6.10 (m, 1 H, H-3), 5.18 (d, 1 H, H-1), 5.16 (m, 1 H, H-2), 4.76 (dt, 1 H, H-4), 4.73 (m, 2 H, H-6_{ab}), 4.11 (m, 1 H, H-5), 3.46 (s, 3 H, $O\underline{C}H_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.78, 165.58, 133.48, 133.32, 129.95 (2 C), 129.80 (2 C), 129.26, 128.84, 128.45 (2 C), 128.39 (2 C), 97.04 (C-1), 86.01 (dd, $J = 187.7$, 7.7, C-4), 80.75 (d, $J = 174.5$, C-6), 71.31 (d, $J = 7.7$, C-2), 70.39 (d, $J = 19.8$, C-3), 68.02 (dd, $J = 23.0$, 17.6, C-5), 55.81 ($O\underline{C}H_3$). HRMS (ESI): 429.1136 (calcd 429.1126, $M+Na^+$).

*Methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-glucopyranoside (**10c**) using Deoxo-Fluor*

Compound **10c** was synthesized using Deoxo-Fluor as described for **5d** starting with **9c** (100 mg, 0.25 mmol) and Deoxo-Fluor (50% in THF, 960 μL, ~498 mg ~2.25 mmol). Purification by silica gel column chromatography (toluene/EtOAc, 9/1) gave 73 mg (0.18 mmol, 72%) of **10c** as colorless oil.

*Methyl 2,3-*O*-dibenzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside (**10f**) using DAST*

The fluorination was performed as described for **5a** starting with methyl α-*D*-mannopyranoside (100 mg, 0.51 mmol) and DAST (610 μL, ~740 mg ~4.6 mmol). The reaction mixture was freeze dried to give 108 mg of methyl 4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside (**11f**) as yellowish oil. Crude **11f** was dissolved in dry pyridine (2 mL) and cooled to −10°C. Benzoyl chloride (1.46 g, 10.39 mmol) was added drop-wise and the mixture was allowed to reach rt. After 3 d the reaction mixture was cooled to 0°C, and saturated $NaHCO_3$ (2 mL) was added. The mixture was then extracted with $CHCl_3$ (2 × 10 mL)

and the organic phase was washed with saturated $NaHCO_3$ (3 × 15 mL) and water (15 mL), dried over $MgSO_4$, and concentrated under vacuum to give yellow oil. Purification by silica gel column chromatography (toluene/EtOAc, 9/1), followed by two crystallizations from EtOH, gave 57 mg (0.14 mmol, 27%) of a yellow amorphous solid, which melted when handled, $[\alpha]_D^{22} = -16.4^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.15 (m, 2 H, Ar), 7.93 (m, 2 H, Ar), 7.60 (m, 1 H, Ar), 7.51 (m, 1 H, Ar), 7.48 (m, 2 H, Ar), 7.34 (m, 2 H, Ar), 5.53 (m, 1 H, H-3), 5.52 (m, 1 H, H-2), 5.03 (dd, 1 H, H-4), 5.01(bs, 1 H, H-1), 4.73 (m, 2 H, H-6_{ab}), 4.31 (m, 1 H, H-5), 3.50 (s, 3H, OC$\underline{H}_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 165.91, 165.33, 133.48, 133.41, 130.09 (2 C), 129.90 (2 C), 129.54, 129.04, 128.51 (2 C), 128.43 (2 C), 99.19 (C-1), 84.95 (dd, J = 190.7, 6.3, C-4), 81.26 (dd, J = 169.9, 7.1, C-6), 67.99 (C-2), 67.90 (dd, J = 23.6, 18.5, C-5), 66.69 (d, J = 15.9, C-3), 55.63 (O$\underline{C}$H$_3$). HRMS (ESI): 429.1132 (calcd 429.1126, M+Na^+).

*Methyl 2,3-*O*-dibenzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside (**10f**) using Deoxo-Fluor*

Compound **10f** was synthesized as described for **5d** starting with methyl *α-D*-mannopyranoside (100 mg, 0.51 mmol) and Deoxo-Fluor (50% in THF, 1.95 mL, ~1.02 g ~4.6 mmol). Benzoylation and purification as described above gave 55 mg (0.14 mmol, 26%) of **10f**.

*Methyl 2,3-*O*-dibenzoyl-4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside (**10f**) from **11f***

To a stirred solution of **11f** (50 mg, 0.26 mmol) in pyridine (2 mL) at −10°C was added benzoyl chloride (0.70 g, 4.99 mmol). After addition the mixture was reacted for 3 d at rt. Then the mixture was cooled to 0°C, and saturated $NaHCO_3$ (2 mL) was added. The mixture was extracted with $CHCl_3$ (2 × 10 mL), washed with saturated $NaHCO_3$ (3 × 10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated under vacuum to give yellow oil. Purification by silica gel column chromatography (toluene/EtOAc, 9/1), followed by two crystallizations from EtOH, gave 78 mg (0.19 mmol, 74%) of a yellow amorphous solid **10f**. The spectroscopic properties corresponded with that described above.

*Isolation of methyl 4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside 2,3-cylic sulfite (**12f**) and methyl 4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside (**11f**)[21,31] using DAST*

Compound **12f**: To a stirred solution of methyl *α-D*-mannopyranoside (800 mg, 4.12 mmol) in anhydrous CH_2Cl_2 (25 mL) at −20°C was added DAST (2.5 mL, 20 mmol). After adding of DAST the mixture was stirred for 2 h at rt. Then the mixture was cooled and quenched with MeOH (10 mL). The resulting mixture was concentrated under reduced pressure. Upon addition of MeOH

(5 mL) and water (20 mL) a white solid precipitated, which was separated by filtration. This procedure was repeated twice and the combined solid was recrystallized from MeOH/water to give 270 mg (1.11 mmol, 27%) of **12f** as a white solid, mp. 122.5–123.0°C, $[\alpha]_D^{22} = +3.8^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 5.21 (bs, 1 H, H-1), 5.01 (dt, J = 23.8, 4.5, 1 H, H-3,), 4.76 (bd, J = 4.9, 1-H, H-2), 4.66 (dd, J = 49.5, 4.5, 1 H, H-4), 4.63 (m, 2 H, H-6_{ab}), 4.07 (m, J = 28.9, 13.7, 6.1, 1 H, H-5), 3.48 (s, 3 H, OC$\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 96.50 (C-1), 81.48 (dd, J = 170.8, 6.1, C-4), 80.84 (dd, J = 188.5, 6.1, C-6), 76.10 (d, J = 17.1, C-3), 73.67 (C-2), 65.25 (dd, 24.3, 18.2, C-5), 55.83 (O-C$\underline{H_3}$). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −231.87 (dt, J = 46.0, 13.8), −210.38 (m) HRMS (ESI): 245.0289 (calcd 245.0290, M+H$^+$). Compound **11f**: Concentration of the mother liquor followed by silica gel column chromatography ($CHCl_3$/MeOH, 9/1) yielded 390 mg (1.97 mmol, 48%) of **11f** as colorless crystals, mp. 88–89°C, lit.[21] 90–92°C. $[\alpha]_D^{22} = +96.2^\circ$ (c 1.0, $CHCl_3$), lit.[31] 101.9 (c 1.02 MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 4.88 (bs, 1 H, H-1), 4.80 (m, J = 50.5, 1.4, 1 H, H-4), 4.63 (m, J = 46.8, 2 H, H-$6_{a,b}$), 4.08 (m, 1 H- H-5, J = 31.9, 19.3, 6.1), 3.83 (m, J = 31.6, 3.0, 1 H, H-3), 3.79 (m, 1 H, H-2), 3.43 (s, O-C$\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 150) δ: 101.53 (C-1), 90.05 (dd, J = 178.0, 6.1, C-4), 81.27 (dd, J = 169.7, 7.2, C-6), 69.86 (C-2), 67.40 (dd, 23.8, 18.2, C-5), 65.27 (d, J = 16.6, C-3), 55.55 (O-C$\underline{H_3}$). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −231.71 (dt, J = 46.0, 13.8), −216.73 (m).

*Methyl 4,6-dideoxy-4,6-difluoro-α-*D*-talopyranoside 2,3-cylic sulfite (**12f**) from **11f***

The synthesis was done essentially as described by Lohray et al.[44] To a solution of **11f** (20 mg, 0.1 mmol) in dry CCl_4 (1 mL) was added $SOCl_2$ (20 μL, 0.25 mmol) and triethylamine (35 μL, 0.25 mmol). The mixture was refluxed for 45 min, then cooled to rt, diluted with $CHCl_3$ (3 mL), and washed with $NaHCO_3$ (3 × 5 mL) and water (5 mL). Drying over $MgSO_4$ and concentration in vacuum gave 21 mg of yellow oil. Crystallization from MeOH (0.2 mL) and water (0.5 mL) gave 11 mg (0.04 mmol, 44%) of a white solid with identical NMR spectroscopic properties as for **12f** described above.

*Methyl 2,4,6-tri-*O*-benzoyl-3-deoxy-3-fluoro-β-*D*–glucopyranoside (**13d**)*

3-Deoxy-3-fluoro-*D*-glucose (200 mg, 1.10 mmol) was dissolved in HCl·MeOH (1 mL, 0.5 N) and refluxed for 3 d. Then, the reaction mixture was concentrated and submitted to the same treatment once more to give 237 mg of colorless oil. The crude mixture was then dissolved in dry pyridine (2 mL) and cooled to 0°C, followed by drop-wise addition of benzoyl chloride (1.46 g, 10.4 mmol). The reaction mixture was warmed to rt and stirred for 3 d. The reaction mixture was then cooled to 0°C, treated with saturated $NaHCO_3$ (5 mL), and extracted with $CHCl_3$ (4 × 10 mL). The organic phases were washed

with water (20 mL) and concentrated under vacuum. TLC indicated two products that were separated by silica gel column chromatography (toluene/EtOAc, 9.5/0.5). This gave 22 mg (0.04 mmol, 3%) of **14d**, and after two crystallizations from EtOH 70 mg (0.14 mmol, 13%) of **13d**, white solid, mp. 146–147°C, $[\alpha]_D^{22} = -17.4^\circ$ (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.08 (m, 2 H, Ar), 8.03 (m, 2 H, Ar), 8.01 (m, 2 H, Ar), 7.59 (m, 1 H, Ar), 7.58 (m, 1 H, Ar), 7.54 (m, 1 H, Ar), 7.45 (m, 2 H, Ar), 7.42 (m, 2 H, Ar), 7.39 (m, 2 H, Ar), 5.66 (m, 1 H, H-4), 5.48 (m, 1 H, H-2), 4.96 (dt, 1 H, H-3), 4.66 (m, 1 H, H-6_b), 4.64 (d, 1 H, H-1), 4.47 (dd, 1 H, H-6_a), 4.02 (m, 1 H, H-5), 3.52 (s, 3 H, OC$\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.17, 164.95, 164.92, 133.62, 133.40, 133.20, 129.93 (2 C), 129.92 (2 C), 129.73 (2 C), 129.50, 129.38, 128.91, 128.51 (2 C), 128.44 (2C), 128.39 (2 C), 101.37 (d, J = 10.7, C-1), 91.79 (d, J = 191.3, C-3), 71.99 (d, J = 18.7, C-2), 71.10 (d, J = 7.7, C-5), 69.73 (d, J = 18.7, C-4), 62.96 (d, J = 1.6, C-6), 57.12 (O$\underline{C}H_3$). HRMS (ESI): 509.1611 (calcd 509.1612, M+H$^+$).

1,3,4,6-Tetra-O-*benzoyl-3-deoxy-3-fluoro-β*-D–*glucopyranoside (**14d**)*

3-Deoxy-3-fluoro-*D*-glucose (70 mg, 0.38 mmol) was dissolved in dry pyridine (1 mL) and cooled to −10°C. Benzoyl chloride (220 mg, 1.57 mmol) was added drop-wise and the mixture was stirred at rt. After 3 d the reaction mixture was cooled, diluted with saturated $NaHCO_3$ (0.5 mL), and extracted with $CHCl_3$ (4 × 10 mL). The organic phases were then washed with saturated $NaHCO_3$ (3 × 10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The resulting oil was crystallized twice from MeOH to give 111 mg (0.19 mmol, 49%) of compound **14d** as a white solid, mp. 231–232°C, $[\alpha]_D^{22} = +9.6^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.04 (m, 2 H, Ar), 8.02 (m, 6 H, Ar), 7.58 (m, 1 H, Ar), 7.54 (m, 2 H, Ar), 7.53 (m, 1 H, Ar), 7.43 (m, 2 H, Ar), 7.40 (m, 4 H, Ar), 7.39 (m, 2 H, Ar), 6.18 (d, 1 H, H-1), 5.84 (m, 1 H, H-2), 5.81 (m, 1 H, H-4), 5.11 (dt, 1 H, H-3), 4.66 (dd, 1 H, H-6_b), 4.46 (dd, 1 H, H-6_a), 4.26 (m, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.09, 164.89, 164.84, 164.61, 133.94, 133.72, 133.62, 133.16, 130.21 (2 C), 129.96 (2 C), 129.89 (2 C), 129.82 (2 C), 129.43, 128.82, 128.76, 128.56 (4 C), 128.50 (2 C), 128.36 (2 C), 128.27, 91.95 (d, J = 11.0, C-1), 91.64 (d, J = 193.2, C-3), 72.12 (d, J = 6.6, C-5), 70.87 (d, J = 19.8, C-2), 69.02 (d, J = 19.8, C-4), 62.47 (C-6). HRMS (ESI): 621.1542 (calcd 621.1531, M+Na$^+$).

1,3,4,6-Tetra-O-*benzoyl-2-deoxy-2-fluoro-β*-D–*glucopyranoside (**15d**)*

Compound **15d** was synthesized as described for **14d**, starting with 2-deoxy-2-fluoro-*D*-glucose (70 mg, 0.38 mmol). This gave after crystallization from MeOH 118 mg (0.20 mmol, 52%) of compound **15d** as a white solid, mp. 169–170°C, $[\alpha]_D^{22} = +23.7^\circ$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 8.12 (m, 2 H, Ar), 8.00 (m, 2 H, Ar), 7.99 (m, 2 H, Ar), 7.92 (m, 2 H, Ar), 7.61 (m, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.51 (m, 1 H, Ar), 7.46 (m, 2 H, Ar), 7.38 (m, 2 H, Ar), 7.37 (m, 2 H, Ar), 7.35 (m, 2 H, Ar), 6.28 (dd, 1 H, H-1),

5.97 (m, 1 H, H-3), 5.71 (t, 1 H, H-4), 4.91 (ddd, 1 H, H-2), 4.62 (dd, 1 H, H-6_b), 4.46 (dd, 1 H, H-6_a), 4.34 (m, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.03, 165.47, 165.15, 164.44, 133.97, 133.63, 133.51, 133.11, 130.22 (2 C), 129.88 (4 C), 129.78 (2 C), 129.47, 128.82, 128.56 (2 C), 128.53, 128.50 (2 C), 128.45 (2 C), 128.36, 128.34 (2 C), 91.98 (d, $J = 24.2$, C-1), 88.64 (d, $J = 192.1$, C-2), 73.03 (d, $J = 19.8$, C-3), 72.98 (C-5), 68.62 (d, $J = 6.6$, C-4), 62.58 (C-6). HRMS (ESI): 621.1549 (calcd 621.1531, M+Na^+).

ACKNOWLEDGMENTS

NTNU is acknowledged for use of NMR facilities, Anders Jahres Foundation for financial support, and Anders Brunsvik for HRMS.

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