Glycosyl fluorides from *n*-pentenyl-related glycosyl donors — Application to glycosylation strategies

Bert Fraser-Reid, J. Cristobal Lopez, Paloma Bernal-Albert, Ana M. Gomez, Clara Uriel, and Juan Ventura

Abstract: *n*-Pentenyl glycosides (NPGs) and *n*-pentenyl orthoesters (NPOEs) have been transformed into glycosyl fluorides by a variety of methods. In the case of NPGs, Barluenga's reagent, bis(pyridinium)iodonium(I)tetrafluoroborate (IPy_2BF_4), gives good yields of glycosyl fluorides when HF–pyridine complex is used as an additional fluoride source. NPOEs can be activated either by a combination of electrophilic iodonium (Barluenga's reagent) and HBF_4 or by the action of HF–pyridine complex. The ensuing glycosyl fluorides form a semiorthogonal pair of glycosyl donors when confronted with NPGs.

Key words: pentenyl glycosides, glycosyl fluorides, pentenyl orthoesters, glycosylation, orthogonal.

Résumé : Les glycosides de *n*-penténylе (GNP) et les orthoesters de *n*-penténylе (OENP) peuvent être transformés en fluorures de glycosyles par diverses méthodes. Dans les cas des GNP, le réactif de Barluenga, le tétrafluoroborate de bis(pyridinium)iodonium(I) (IPy_2BF_4) permet d'obtenir de bons rendements de fluorures de glycosyles si on utilise le complexe de HF–pyridine comme source additionnelle de l'ion fluorure. Les OENP peuvent être activés soit par une combinaison d'iodonium électrophile (tel le réactif de Barluenga) et de l'acide HBF_4 ou par l'action du complexe HF–pyridine. Les fluorures de glycosyles qui en résultent conduisent à la formation d'une paire semi-orthogonale de donneurs glycosyles lorsqu'ils sont confrontés à des glycosides de penténylе, GNP.

Mots-clés : glycosides de penténylе, fluorures de glycosyle, orthoesters de penténylе, glycosylation, orthogonal.

[Traduit par la Rédaction]

Introduction

Biologically active oligosaccharides are rarely simple uniform linear structures such as those found in other biopolymers.[1] Branched motifs are frequently encountered, and these substructures convey biological information and therefore cannot be ignored in view of their biological significance. These complex oligosaccharides present multiple challenges to laboratory synthesis because issues of regioselectivity, chemoselectivity, and stereoselectivity must be addressed.[2] Frush and Isbell's[3] discovery of neighboring group participation 71 years ago showed how the last of these three selectivities, 1,2-trans stereoselectivity, could be optimized in donor–acceptor coupling.

Regio- and chemo-selectivities are principles of interest to our groups in view of their potential for reducing the time-consuming, and frequently frustrating, demands of protect–deprotect synthetic strategies. Regioselectivity requires that a donor be induced to display a preference for one of several available hydroxyls of an acceptor, thereby reducing the need to protect all hydroxyls except the targeted one. Chemoselectivity is required when two (or more?) donors are prone to the same activation process, but one must be preferably triggered. The 20-year-old armed–disarmed strategy is a case in point.[4]

Prior to these developments, the concept of orthogonal glycosylation had been introduced by Ogawa and co-workers[5] in 1994. The strategy involves the coupling of two *potential* donors with *different* leaving groups, one of which can be activated without disturbing the other, which can then become an acceptor. Glycosyl fluorides were one of the donors featured in the original experiments and, since their emergence in 1981,[6] have proven to be valuable in glycosylation strategies.[7] The interest in these glycosyl donors, because of their enhanced stability compared with other glycosyl halides, has continued to flourish over the last two decades,[8] and a variety of methods are now available for their activation.[9]

Results and discussion

Glycosyl fluorides from *n*-pentenyl glycosides

In view of these properties, the preparation of glycosyl fluorides continues to be a topic of interest. *n*-Pentenyl glycosyl donors are ready precursors of other donors, e.g., glycosyl bromides[10] and trichloroacetimidates,[11] hence, we were interested in adding glycosyl fluorides to this list. *n*-Pentenyl donors are usually triggered by halonium ions[4d] and (or) acids.[12] In view of the latter, the Barluenga reagent, bis(pyridinium) iodonium(I)tetrafluoroborate (IPy_2BF_4), was of interest as a possible electrophilic agent.[13,14] In this connection, it should

Received 24 July 2012. Accepted 28 August 2012. Published at www.nrcresearchpress.com/cjc on 2 January 2013.

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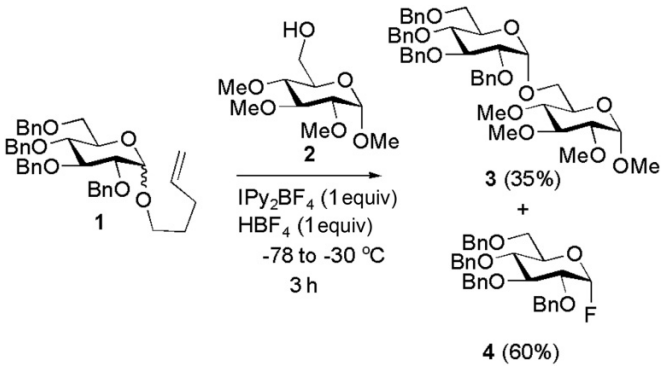
Scheme 1. Attempted activation–glycosylation of **2** with NPG **1**.



be noted that Clausen and Madsen[15] previously converted *n*-pentenyl glycosides (NPGs) to glycosyl fluorides.

This interest was sparked by attempts to glycosylate acceptor **2** with donor **1** using the Barluenga reagent, along with an equimolar amount of HBF_4 to neutralize nucleophilic pyridine that is released during the reaction. As shown in Scheme 1, the hoped-for disaccharide (**3**) was obtained in a 35% yield; however, the formation of twice as much glycosyl fluoride (**4**) indicated that fluoride ion was competing strongly for the donor (**1**).

The 2:1 formation of products **4** and **3** indicated the potential of the process as a route to glycosyl fluorides.[16] The chances of improving glycosyl fluoride formation should be enhanced by removing the acceptor **2** and increasing fluoride ion supply.

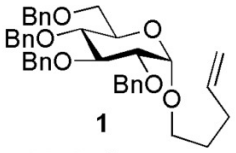
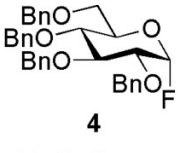
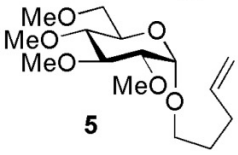
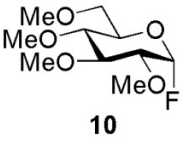
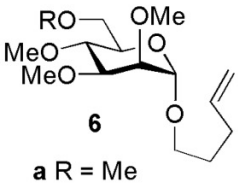
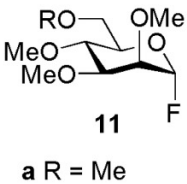
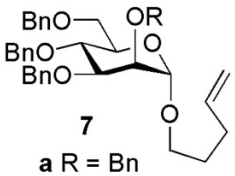
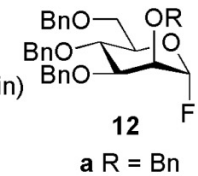
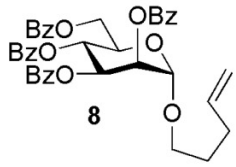
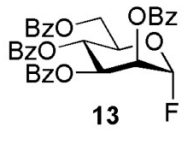
Accordingly, a collection of NPGs, Table 1 (**1**, **5**–**8**), armed and disarmed, with diverse protecting groups, was treated at −40 °C with 1 equiv of IPy_2BF_4 and a slight excess of HBF_4. Entries *i*–*v* of Table 1 showed that the formation of fluorides **4** and **10**–**13**, respectively, was usually complete in 10–40 min (TLC), with very good to excellent results. Notably, silyl protecting groups were compatible with the reaction conditions, as is clear from the conversion of NPG **6b** to glycosyl fluoride **11b** (Table 1, entry *iii*).

The reaction of the NPG tetrabenzoate **8** (Table 1, entry *v*) requires special comment. Under the indicated conditions of Table 1, but with a temperature of –78 °C, the starting material (**8**) disappeared after 30 min to give a stable substance. Exposing the latter to $BF_3{\cdot}OEt_2$ for 20 min led to the tetrabenzoyl glycosyl fluoride **13**. The intermediacy of the orthoacyl fluoride **9** was indicated, with this possibility being supported by the prior work of Griffith and Hindsgaul.[17]

Our interest in the use of partially protected NPG donors for regioselective glycosylations prompted us to examine the synthesis of comparable glycosyl fluoride donors (Table 2). Accordingly, the partially protected NPG mannoside **14** was treated with 2 equiv of an IPy_2BF_4/HBF_4 mixture at –55 °C for 10 min. As seen from entry *i* (Table 2), the desired fluoride (**16**) was obtained in a 42% yield, but was accompanied by 15% of disaccharide **17**. The gluco analog **15** gave an equal distribution of products, **18** and **19** (40% and 15%, respectively). Obviously the concentration of nucleophilic fluoride was not enough to preclude self-coupled formation of the disaccharides.

The HF–pyridine complex (or Olah's reagent) has been used as a source of nucleophilic fluoride,[18,19] so it was a logical choice as a partner for the Barluenga reagent in our efforts to enhance the formation of glycosyl fluorides.[20] Accordingly, NPGs **14** and **15** were exposed to IPy_2BF_4 in the presence of an excess of Olah's reagent at low temperature. Indeed, the use of a 2:10 ratio of IPy_2BF_4/HF (Table 2, entry *iii*) on mannoside **14** gave a considerable increase in the yield of the desired fluoride, **16**. However, this was accompanied by a substantial amount of compound **20**, resulting from iodofluorination of the olefinic residue of the precursor. Lowering the ratio of the fluoride source by 50% to 2:5 (Table 2, entry *iv*) had the desired effect in that the yield of fluoride **16**

Table 1. IPy_2BF_4/HBF_4 mediated transformation of *n*-pentenyl glycosides to glycosyl fluorides in CH_2Cl_2.

Entry	Substrate	Temp. (°C) (time)	Product	Yield (%)
i	 **1**	-40 (30 min)	 **4**	83
ii	 **5**	-40 (15 min)	 **10**	99
iii	 **6**	-40 (15 min)	 **11**	
	a R = Me		**a** R = Me	94
	b R = TBDPS		**b** R = TBDPS	75
iv	 **7**	-40 (15-30 min)	 **12**	
	a R = Bn		**a** R = Bn	94
	b R = Bz		**b** R = Bz	90
v	 **8**		 **13**	75

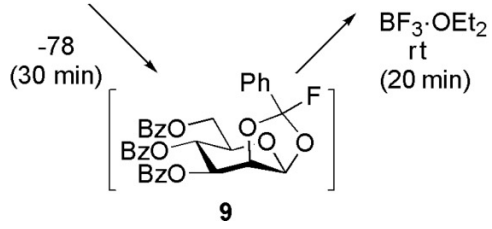
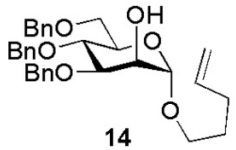
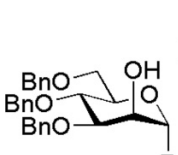
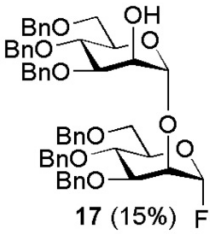
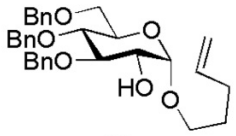
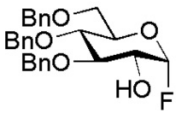
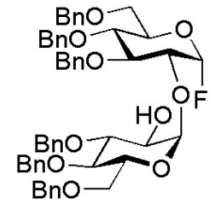
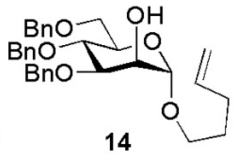
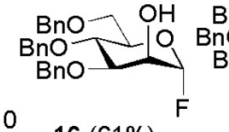
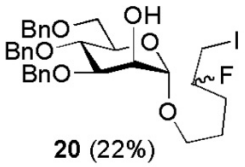
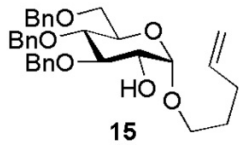
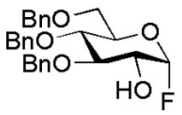


Table 2. IPy_2BF_4/HBF_4 and IPy_2BF_4/HF–pyridine mediated transformation of partially unprotected *n*-pentenyl glycosides to glycosyl fluorides.

Entry	Substrate	IPy_2BF_4(equiv)/HBF_4 or HF (equiv) Temp., time	Product (Yield)
i	 **14**	2 / (HBF_4) 2 -55 °C, 10 min	 **16** (42%)  **17** (15%)
ii	 **15**	2 / (HBF_4) 2 -55 °C, 1 h	 **18** (40%)  **19** (15%)
iii	 **14**	2 / (HF) 10 -55 °C, 10 min	 **16** (61%)  **20** (22%)
iv	**14**	2 / (HF) 5 -55 °C, 10 min	**16** (85%) **20** (10%)
v	 **15**	2 / (HF) 10 -40 °C, 1h	 **18** (94%)

had increased to 85%. Unfortunately, the iodofluorination product **20** was still produced in a substantial amount.

With the gluco NPG **15** (Table 2, entry *v*), the desired fluoride **18** was obtained in a 94% yield with no evidence of the corresponding iodofluorination product. Notably, this result was obtained even though the ratio of reagents (IPy_2BF_4/HF, 2:10) was very favorable for iodofluorination (Table 2, entries *iii* and *iv*).

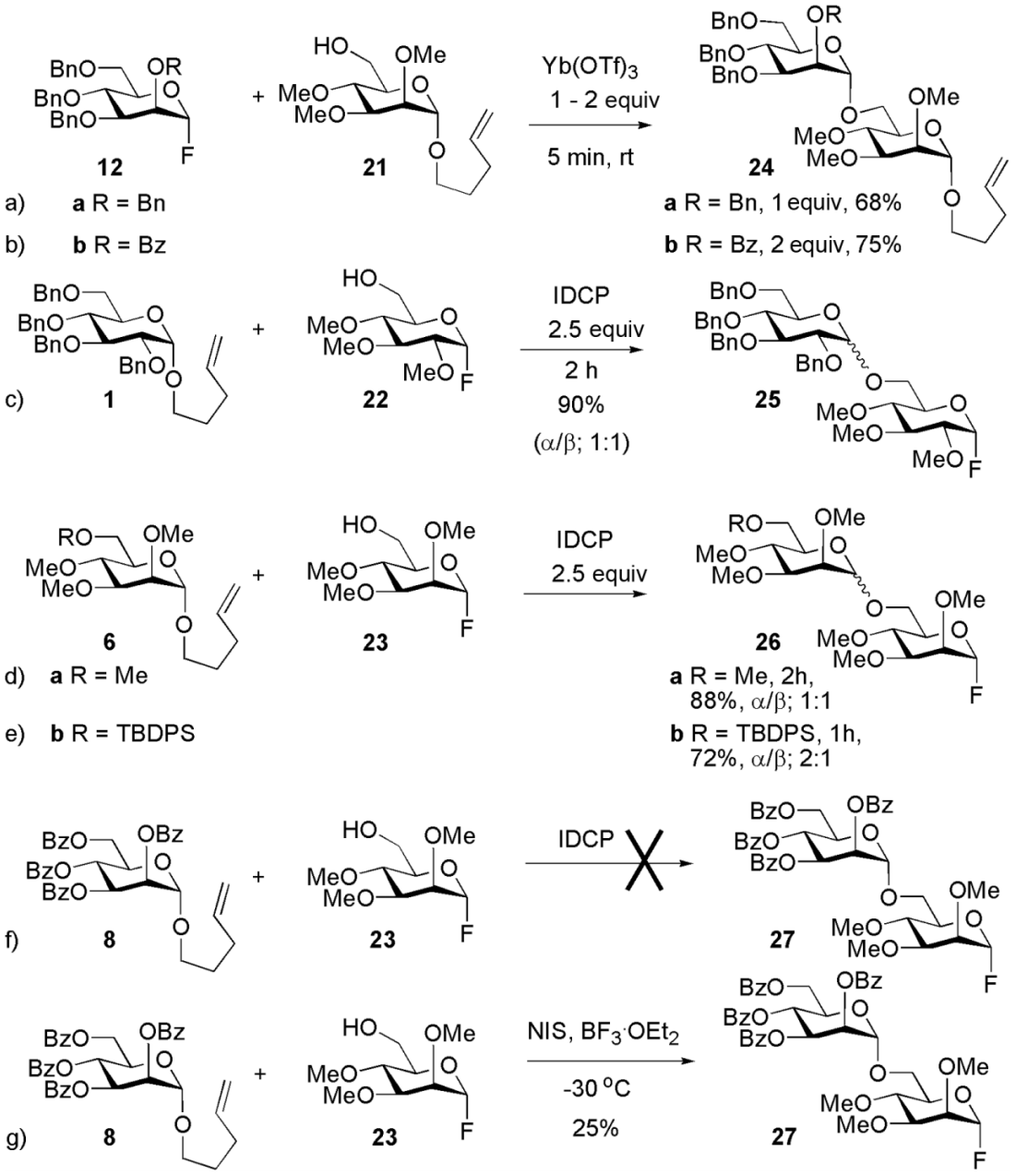
Glycosyl fluorides and *n*-pentenyl glycosides as semiorthogonal glycosyl donors

With the availability of glycosyl fluorides and NPGs, the possibility of orthogonal coupling between both was now explored (Scheme 2). To activate the glycosyl fluoride as a donor, ytterbium triflate ($Yb(OTf)_3$) was chosen as the fluorophilic agent. Schemes 2*a* and 2*b* record the results of coupling armed and disarmed donors **12a** and **12b**, respectively, with the NPG **21** as acceptor. Disaccharides **24a** and **24b** were obtained in encouraging yields of 68% and 75%, respectively.

Reversing the roles of orthogonal donor and acceptor required a source of iodonium ions for activating the NPG donor. Iodonium dicollidine perchlorate (IDCP),[21] which has served us well in the past,[22] was chosen for coupling glycosyl fluoride acceptors **22** and **23** with armed gluco (**1**, Scheme 2*c*) and manno (**6a** and **6b**, Scheme 2*d* and 2*e*, respectively) donors. Products **25**, **26a**, and **26b** were obtained in excellent yields of 90%, 88%, and 72%, respectively, albeit as α/β mixtures. The result in Scheme 2*e* is noteworthy because of the survival of the silyl protecting group under the reaction conditions.

The donors in Scheme 2*c*–2*e*, were armed; however, the disarmed counterpart, **8**, (Scheme 2*f*) failed to give **27** with IDCP as the electrophile. The use of *N*-iodosuccinimide (NIS) with $BF_3{\cdot}OEt_2$ proved better, although product **27** was obtained in only in a 25% yield. Because of these facts, the glycosyl fluoride – NPG couple could be best described as a semiorthogonal donors pair of donors.[23]

Scheme 2. *n*-Pentenyl glycosides (NPGs) and glycosyl fluorides as a pair of semiorthogonal donors.



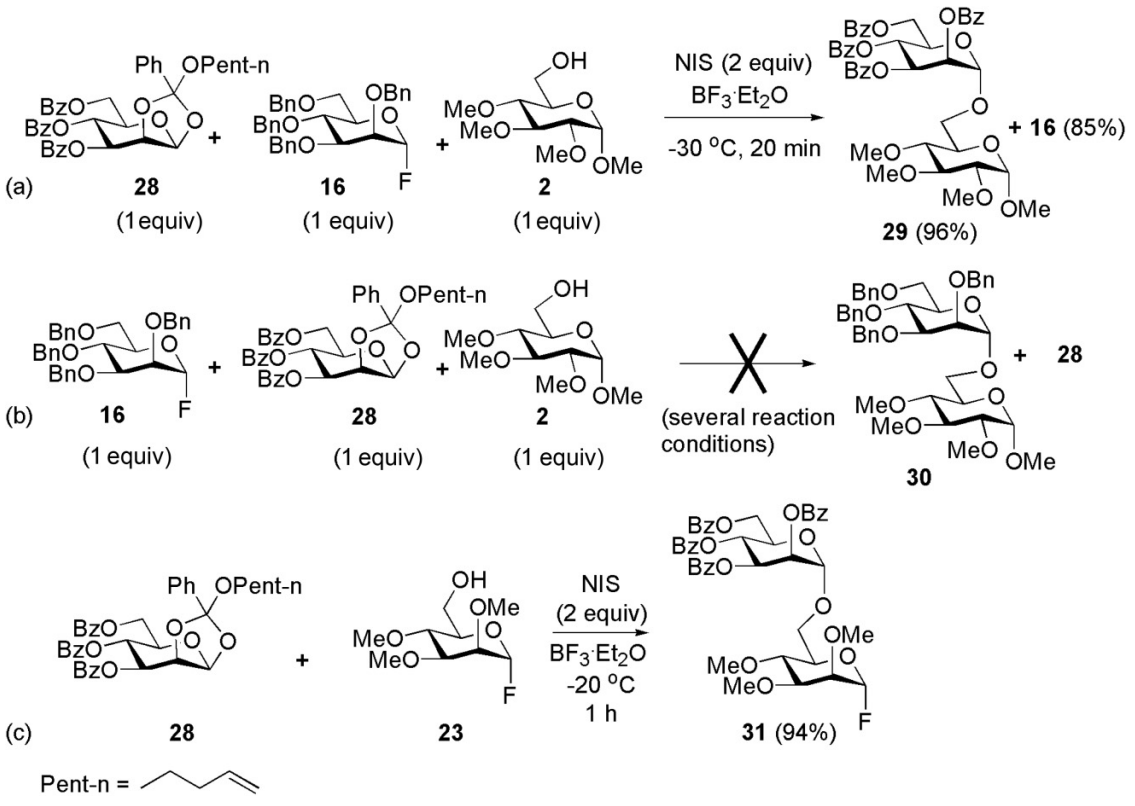
n-Pentenyl orthoesters (NPOEs) are ~15 kcal (1 cal = 4.184 J) more reactive than the corresponding NPG,[24] and on that basis, they should serve as better progenitors of glycosyl fluorides. This possibility was tested by presenting acceptor **2** (1 equiv) to equimolar amounts of NPOE **28** and the armed fluoride **16** along with NIS (2 equiv) and $BF_3{\cdot}OEt_2$. After 20 min at −30 °C, glycosylation had occurred by the NPOE only to give the tetrabenzoylated disaccharide **29** in a 96% yield (Scheme 3*a*), with the glycosyl fluoride being recovered to the extent of 85%.

This result suggested that the NPOE was the superior donor under the conditions used in Scheme 3*a*. Attempts were made to enforce glycosylation of acceptor **2** by armed glycosyl fluoride **16**, in the presence of NPOE **28**, by the use of various fluorophilic agents, but all failed to produce disaccharide **30** (Scheme 3*b*). These experiments confirmed that activation of a glycosyl fluoride in the presence of an NPOE is highly unlikely.

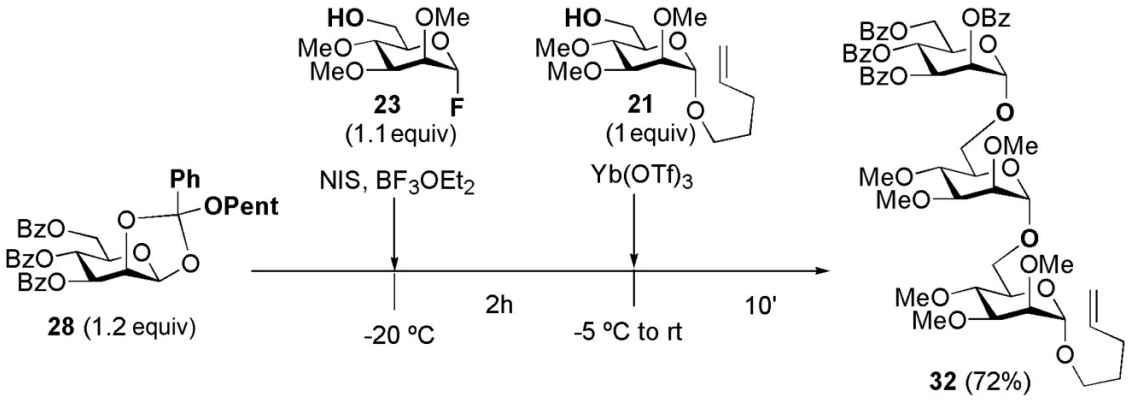
Accordingly, chemoselective coupling of NPOE **28** with the glycosyl fluoride acceptor **23** went smoothly (Scheme 3*c*) to give disaccharide **31** in a 94% yield.

In view of the foregoing results, a one-pot synthesis using three reactants (**21**, **23**, and **28**), each of which is a potential donor, and two of which (**21** and **23**) are potential acceptors, is shown in Scheme 4. Thus, glycosyl fluoride **23** served as acceptor to NPOE donor **28** under NIS/$BF_3{\cdot}OEt_2$ activation at −20 °C. After 2 h, NPG **21** was presented, as an acceptor, for glycosylation by the putative disaccharide under activation by $Yb(OTf)_3$ at room temperature. After 10 min, the

Scheme 3. Competition experiments for the chemoselective activation of *n*-Pentenyl orthoesters (NPOEs) in the presence of glycosyl fluorides.



Scheme 4. One-pot synthesis of trisaccharide **32**.



n-pentenyl trisaccharide **32** was obtained in a 72% yield as a single (α,α,α) isomer.

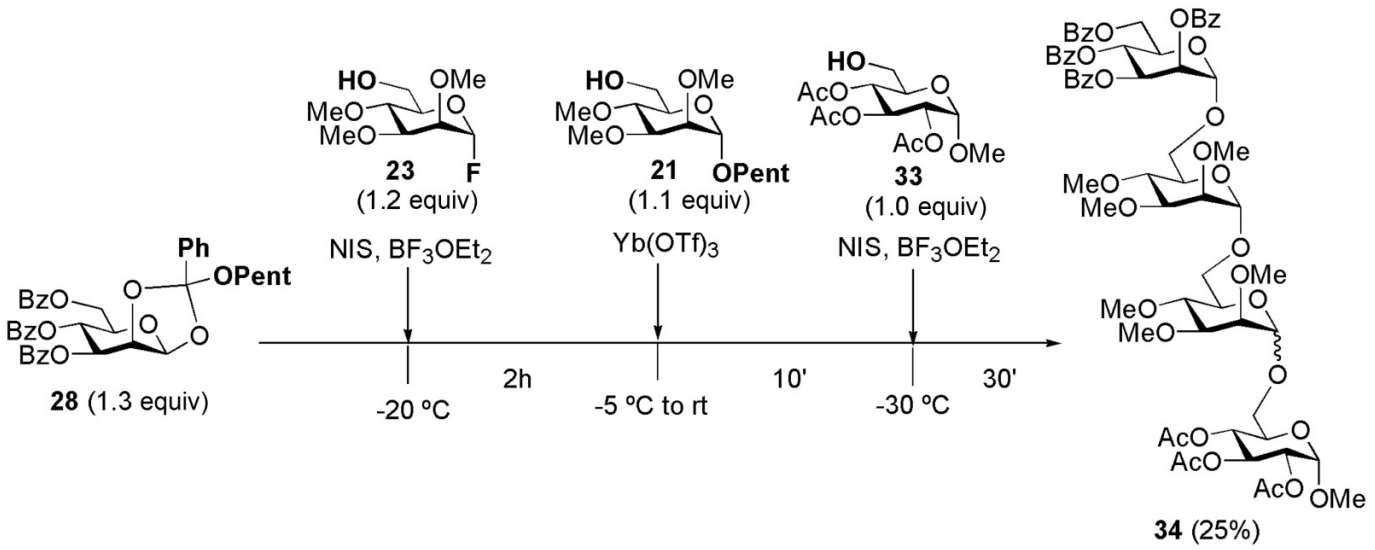
Along this line, and taking full advantage of the knowledge gained in this work, a further extension could be made to the one-pot synthesis in Scheme 4. Thus, in Scheme 5, methyl glucoside **33** was added (to **23** and **21**) as a third acceptor, which resulted in the one-pot synthesis of linear tetrasaccharide **34** (obtained as an α/β mixture). The low yield in this transformation was ascribed to the poor reactivity of acetylated acceptor **33** towards the intermediate *n*-pentenyl trisaccharide donor. In this sense, a considerable amount of hemiacetal arising from the trisaccharide was observed in the reaction mixture.

Glycosyl fluorides from furanosyl 1,2-orthoesters

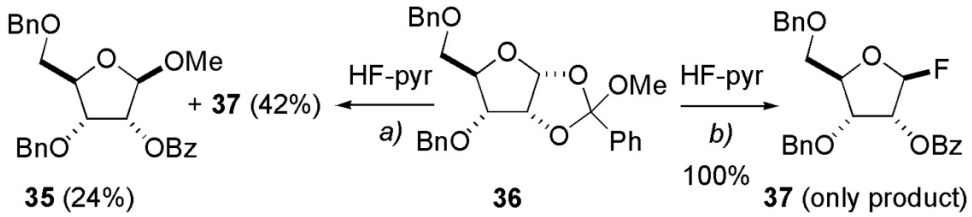
We were interested to see whether the previously discussed transformations of pyranosyl NPOEs could be extended to recently described furanosyl counterparts.[25,26]

Our exploratory work revealed the need for a different operational procedure than that used with the pyranose systems because the furanosyl substrates are much more acid-sensitive. It is crucial that a solution of the furanosyl orthoester in CH_2Cl_2 be added to the reaction mixture of HF–pyridine in CH_2Cl_2 rather than in the reverse order. Otherwise, with NPOE **36**, for example, rearrangement to the corresponding alkyl glycoside **35** was an important reaction course compared with that of the desired glycosyl fluoride **37** (Scheme 6).

Scheme 5. One-pot synthesis of tetrasaccharide **34**.



Scheme 6. Transformation of 1,2-orthoester **36** to furanosyl fluoride **37** by treatment with HF–pyridine complex. (*a*) Addition of HF–pyridine complex to a solution of **36** in CH_2Cl_2. (*b*) Addition of **36** to a precooled solution of HF–pyridine in CH_2Cl_2.



With this precaution implemented, the *ribo*-NPOE **38a** gave the fluoride **44** quantitatively in ~10 min (Table 3, entry *i*). The dibenzoyl and dibenzyl arabino substrates, **39a** and **40a**, respectively, behaved similarly, affording fluorides **45** and **46** in 95% and 91% yields, respectively (Table 3, entries *ii* and *iii*). These results suggested that the nature of the protecting groups at O3 and O5 did not have a major effect on the formation of the glycosyl fluorides.

The partially protected analogs with a free C3–OH gave distinctly different results. The arabino-NPOE **41** was converted to the fluoride **47** in a 91% yield (Table 3, entry *vii*). In contrast, the ribo counterpart **42** gave only a 53% yield of fluoride **48** (Table 3, entry *viii*).

Not surprisingly, a free C5–OH was unacceptable. Thus, diol **43** furnished the 1,5-anhydro derivative **49** upon treatment with HF–pyridine (Table 3, entry *ix*).

The use of these furanosyl fluorides with other donors for orthogonal coupling leading to oligofuranosides was tested as shown in Scheme 7. Glycosyl fluoride **47**, when presented to NPOE **38a** under activation with NIS/Yb(OTf)$_3$, gave a product that was presumed to be disaccharide **50**. This was directly treated with NPG **51** under activation of $BF_3{\cdot}OEt_2$, which led to trisaccharide **52**.

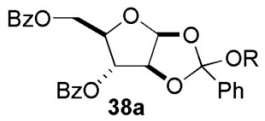
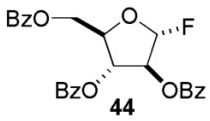
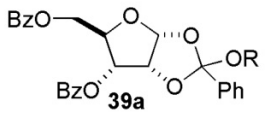
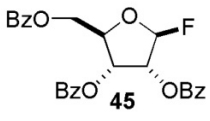
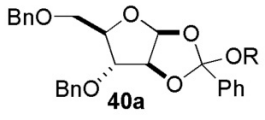
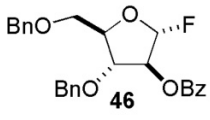
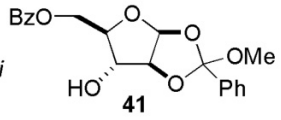
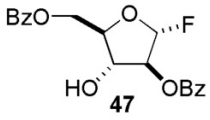
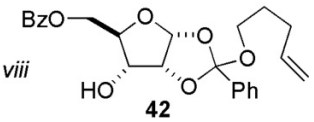
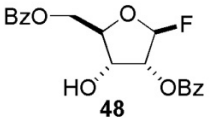
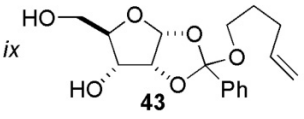
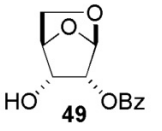
Conclusion

NPGs and NPOEs can be transformed into glycosyl fluorides by a variety of methods, which involve the use of electrophilic iodonium and nucleophilic fluoride. In the case of NPGs, Barluenga's reagent gives good yields of glycosyl fluorides when HF–pyridine complex is used as an additional fluoride source. NPOEs can be activated by a combination of electrophilic iodonium (Barluenga's reagent) and HBF_4 or by action of HF–pyridine complex in which acidic triggering of the pentenyl moiety is accompanied by the fluoride nucleophile present in Olah's reagent. Furthermore, the ensuing glycosyl fluorides form a semiorthogonal pair of glycosyl donors when confronted with NPGs.

Experimental section

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained for solutions in $CDCl_3$ using either a 300, 400, or a 500 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were assigned with the assistance of two-dimensional (2D) correlation spectroscopy (COSY) and 2D heteronuclear single quantum correlation (HSQC) experiments. Optical rotations were determined for solutions in chloroform at 25 °C. Column chromatography was performed on silica gel (230−400 mesh). TLC was conducted in precoated Kiesel gel 60 F_{254} (Merck). Detection was first by UV light (254 nm), then charring with a 1:20:4 solution of sulfuric acid / acetic acid / H_2O. All solvents were purified by distillation over drying agents or by elution through a PURE SOLV purification system. A time-of-flight (TOF) mass analyzer was used for the HR-MS. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium

Table 3. Reaction of 1,2-orthoesters **38**−**43** with HF–pyridine complex in CH_2Cl_2.

Entry	Substrate	HF–pyridine (equiv)	Product	Yield (%)
i	 **38a**	20	 **44**	95
ii	**38b**	20	**44**	79
iii	 **39a**	20	 **45**	100
iv	**39b**	20	**45**	100
v	 **40a**	40	 **46**	91
vi	**40b**	40	**46**	93
vii	 **41**	20	 **47**	91
viii	 **42**	20	 **48**	53
ix	 **43**	20	 **49**	40

Note: R = *n*-pentenyl for series **a**; R = Me for series **b**.

sulfate was used for drying solutions. (NPGs) **1**, **5**–**8**, **14**–**15**, and **21**, pyranose orthoester **28**, and furanose orthoesters **36** and **38**–**43** were prepared following previously described procedures.[27] The exchange of substituents at the different hydroxyl groups was carried out following routine procedures.[28]

Attempted glycosylation of compound 2 with NPG 1, mediated by IPy_2BF_4

A solution of IPy_2BF_4 (74.4 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) under argon and cooled to −78 °C was treated with tetrafluoroboric acid (27 μL, 0.24 mmol). After 5 min, a solution of the NPG **1** (122 mg, 0.23 mmol) and the glycosyl acceptor **2** (23.6 mg, 0.11 mmol) dissolved in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at −78 °C for 30 min after which time it was allowed to warm to −30 °C and then stirred for an additional 2 h. The reaction mixture was then diluted with dichloromethane (30 mL) and washed with 10% aqueous sodium thiosulphate containing sodium bicarbonate and water. The organic layer was dried and concentrated and the ensuing residue was purified by flash chromatography (hexane/EtOAc, 8:2 to 1:1) to provide fluoride **4**[29] (72 mg, 60%) and disaccharide **3** (27 mg, 35%).

*Methyl 2,3,4-tri-*O*-methyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (3)*

^{1}H NMR (300 MHz) δ: 7.34−7.15 (m, 20H), 5.02 (d, J = 11.1 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 9.9 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 10.9 Hz, 1H), 4.48 (m, 1H), 4.20 (m, 1H), 3.78–3.37 (m, 12H), 3.62 (s, 3H), 3.50 (s, 3H), 3.47 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (75 MHz) δ: 138.5, 138.4, 138.2, 138.1, 128.4 (×2), 128.3 (×6), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.7 (×2), 127.6 (×2), 127.5 (×2), 103.9, 97.3, 84.8, 83.4, 82.1, 81.7, 79.8, 77.9, 75.7, 75.0 (×2), 74.9, 73.4, 69.8, 69.0, 68.8, 60.8, 60.4, 58.9, 55.1. Anal. calcd for $C_{44}H_{54}O_{11}$ (758.37): C 69.64, H 7.17; found: C 69.30, H 7.35.

*2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (4)*

$[\alpha]_D$ +10.7 (*c* 0.53, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.15–7.31 (m, 20H), 5.56 (dd, J = 53.2, 2.6 Hz, 1H), 4.98–4.45 (m, 8H), 3.99 (t, J = 9.6 Hz, 1H), 3.94 (m, 1H) 3.79 (m, 1H), 3.65 (m, 1H), 3.57 (ddd, J = 25.7, 9.6, 2.6 Hz, 1H). Atmospheric pressure ionization and electrospray ionization (API–ES) positive: 565.2 $(M + Na)^+$. Anal. calcd for $C_{34}H_{35}O_5F$ (542.65): C 75.26, H 6.50; found: C 75.3, H 6.64.

General procedure A — IPy_2BF_4-mediated transformation of NPGs to glycosyl fluorides

A solution of IPy_2BF_4 (44.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) under argon and cooled to −40 °C was treated with tetrafluoroboric acid (13 μL, 0.12 mmol). After 5 min, a solution of the NPG or orthoester (0.10 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added. When all the starting material disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography.

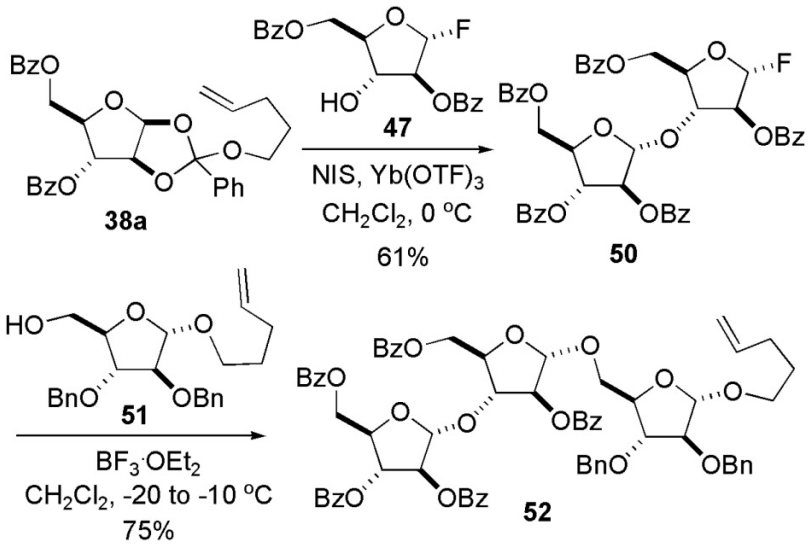
General procedure B — Reaction of partially unprotected NPGs with IPy_2BF_4/HBF_4

A solution of IPy_2BF_4 (44.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) under argon and cooled to −40 °C was treated with tetrafluoroboric acid (13 μL, 0.12 mmol). After 5 min, a solution of the NPG (0.10 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added. When all the starting material disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography.

General procedure C — IPy_2BF_4/HF–pyridine-mediated transformation of partially unprotected NPGs to glycosyl fluorides

A solution of IPy_2BF_4 (74.2 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) was cooled to −40 °C. HF–pyridine complex (5, 10, or 20 mmol) was then added and the resultant solution was stirred for 5 min. A solution of the NPG (0.1 mmol) in dry CH_2Cl_2 (2 mL) was then added dropwise. The resultant solution was

Scheme 7. Stepwise synthesis of trisaccharide **52**.



stirred for 20 min at −40 °C. The reaction was then diluted with methylene chloride (20 mL) and the resultant solution was carefully added to an aqueous solution containing $NaHCO_3$ and $Na_2S_2O_3$. The resulting layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc) afforded the corresponding glycosyl fluorides.

General procedure D — HF–pyridine mediated transformation of 1,2-orthoesters to glycosyl fluorides

A solution of the 1,2-orthoester (1 equiv) in dry CH_2Cl_2 (5 mL/mmol) was added to a solution of HF–pyridine (20 equiv unless otherwise specified) in dry CH_2Cl_2 (1 mL/mmol) under argon and cooled to −40 °C. After 5−10 min, when all the starting material had disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched by saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography eluting with a mixture of hexane and ethyl acetate to afford the pure products.

*2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl fluoride (10)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (**5**; 60.8 mg, 0.2 mmol). Silica gel chromatography (hexane/EtOAc, 7:3) provided pure **10** (50 mg, quantitative yield). ^{1}H NMR (300 MHz) δ: 5.66 (dd, J = 53.3, 2.6 Hz, 1H), 3.80–3.75 (m, 1H), 3.64 (s, OMe, 3H), 3.62–3.38 (m, 3H), 3.54 (s, OMe, 3H), 3.53 (s, OMe, 3H), 3.40 (s, OMe, 3H), 3.28 (t, J = 9.4 Hz, 1H), 3.19 (ddd, J = 25.6, 9.4, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 104.9 (d, J = 224.8 Hz), 82.7, 81.2 (d, J = 24.6 Hz), 78.2, 72.3 (J = 4.0 Hz), 70.2, 60.9, 60.5, 59.1 (×2). API-ES positive: 477.3 $(2M + H)^+$. Anal. calcd for $C_{10}H_{19}O_5F$ (238.12): C 50.41, H 8.04; found: C 50.30, H 8.28.

*2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl fluoride (11a)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside (**6a**; 60.8 mg, 0.2 mmol). Silica gel chromatography (hexane/EtOAc, 7:3) provided **11a** (45 mg, 94%). $[\alpha]_D$ +28.7 (c 1.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.65 (dd, J = 1.6, 50.2 Hz, 1H), 3.76−3.58 (m, 6H), 3.51 (s, OMe, 3H), 3.50 (s, OMe, 3H), 3.49 (s, OMe, 3H), 3.39 (s, OMe, 3H). ^{13}C NMR (75 MHz) δ: 105.5 (d, J = 220.8 Hz), 80.4 (d, J = 2.0 Hz), 75.8 (d, J = 34.6 Hz), 75.4, 73.6 (d, J = 2.5 Hz), 60.6, 59.5, 59.2, 58.0. API-ES positive: 477.3 $(2M + H)^+$, 261.1 $(M + Na)^+$. Anal. calcd for $C_{10}H_{19}O_5F$ (238.12): C 50.41, H 8.04; found: C 50.17, H 7.96.

*6-*O*-tert-Butyldiphenylsilyl-2,3,4-*O*-tri-*O*-methyl-α-D-mannopyranosyl fluoride (11b)*

This compound was prepared according to General procedure A from *n*-pentenyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-*O*-tri-*O*-methyl-α-D-mannopyranoside (**6b**; 53 mg, 0.1 mmol). Silica gel chromatography (hexane/EtOAc, 8:2) provided **11b** (39.3 mg, 85%). $[\alpha]_D$ +26.5 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.75−7.69 (m, 5H), 7.43–7.35 (m, 5H), 5.72 (dd, J = 50.5, 1.9 Hz, 1H), 3.97 (dd, J = 11.5, 3.4 Hz, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.85 (dd, J = 11.5, 1.7 Hz, 1H), 3.74 (m, 1H), 3.67−3.63 (m, 1H), 3.57 (s, 3H), 3.56 (m, 1H), 3.55 (s, 3H), 3.54 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (75 MHz) δ: 135.9 (×2), 135.6 (×2), 133.8, 133.3, 129.5 (×2), 127.6 (×2), 127.5 (×2), 105.6 (d, J = 219.4 Hz), 80.4, 75.9, 75.0, 74.8, 62.3, 60.7, 58.9, 57.9, 26.7 (×3), 19.4. API-ES positive: 480.3 $(M + NH_4)^+$, 485.3 $(M + Na)^+$. Anal. calcd for $C_{25}H_{35}O_5FSi$ (462.22): C 64.9, H 7.63; found: C 65.02, H 7.58.

*2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl fluoride (12a)*

This compound was prepared according to General procedure A from *n*-pentenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**7a**; 60.8 mg, 0.1 mmol). Silica gel chromatography (hexane/EtOAc, 9:1) provided pure **12a** (51 mg, 94%).[30] $[\alpha]_D$ +25.9 (c 0.56, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.35–7.18 (20H, m), 5.60 (d, J = 50.6 Hz, 1H), 4.88 (d, J =

10.8 Hz, 1H), 4.81 (d, J = 12.3 Hz, 1H), 4.70–4.63 (4H, m), 4.56–4.53 (2H, m), 4.08 (t, J = 9.7 Hz, 1H), 3.93–3.88 (3H, m), 3.79 (dd, J = 11.0, 4.5 Hz, 1H), 3.72 (d, J = 10.9 Hz, 1H). API-ES positive: 565.3 $(M + Na)^+$. Anal. calcd for $C_{34}H_{35}FO_5$: C 75.26, H 6.50; found: C 75.16, H 6.45.

2-O-Benzoyl-3,4,6-O-tri-O-benzyl-α-D-mannopyranosyl fluoride (12b)

This compound was prepared according to General procedure A from *n*-pentenyl 2-*O*-benzoyl-3,4,6-*O*-tri-*O*-benzyl-α-D-mannopyranoside (**7b**; 44.6 mg, 0.12 mmol). Silica gel chromatography (hexane/EtOAc, 9:1) provided **12b** (50 mg, 90%). ^{1}H NMR (300 MHz) δ: 8.08–8.06 (m, 2H), 8.05 (m, 1H), 7.56–7.19 (m, 17H), 5.75 (dd, J = 49.3, 1.7 Hz, 1H), 5.74 (t, J = 2.4 Hz, 1H), 4.89 (d, J = 10.5 Hz, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.21–3.96 (m, 3H), 3.91 (dd, J = 11.2, 3.6 Hz, 1H), 3.80 (dd, J = 11.2, 1.5 Hz, 1H). ^{13}C NMR (75 MHz) δ: 165.3, 138.1, 138.0, 137.5, 133.4, 129.9 (×2), 128.5 (×2), 128.4 (×5), 128.3 (×3), 128.0 (×2), 127.9 (×2), 127.8, 127.7, 127.5 (×2), 105.5 (d, J = 219.3 Hz), 77.2, 75.3, 73.9 (d, J = 2.5 Hz), 73.4, 73.2, 71.8, 68.3, 67.2 (d, J = 40.0 Hz). API-ES positive: 579 $(M + Na)^+$. Anal. calcd for $C_{34}H_{33}O_6F$ (556.23): C 73.36, H 5.98; found: C 73.54, H 5.86.

2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranosyl fluoride (13)

A solution of IPy_2BF_4 (55.8 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was cooled to −78 °C and HBF_4 (16 μL, 0.15 mmol) was added. After 5 min of stirring, a solution of *n*-pentenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**8**; 66.4 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) was added. The stirring was maintained at −78 °C for 30 min before $BF_3{\cdot}OEt_2$ (13 μL, 0.1 mmol) was added. The reaction mixture was then warmed to room temperature over 20 min and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated sodium bicarbonate, and water. The organic layer was then dried and concentrated and the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to provide pure **13** (45 mg, 75%). $[\alpha]_D$ −29.7 (*c* 1.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.14–7.26 (m, 20H), 6.22 (t, J = 10.1 Hz, 1H), 5.96–5.86 (m, 2H), 5.86 (dd, $J_{1,2}$ = 43.1, 1.8 Hz, 1H), 4.79 (dd, J = 12.3, 2.2 Hz, 1H), 4.61 (m, 1H), 4.49 (dd, J = 12.3, 3.8 Hz, 1H). API-ES positive: 622.1 $(M + Na)^+$. Anal. calcd for $C_{34}H_{27}O_9F$ (598.57): C 68.22, H 4.55; found: C 68.14, H 4.43.

Reaction of *n*-pentenyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (14)

Application of General procedure B to partially protected NPG **14** (77.8 mg, 0.15 mmol) followed by flash chromatography (hexane/EtOAc, 8:2) afforded glycosyl fluoride **16** (28.5 mg, 42%) followed by disaccharide **17** (19.5 mg, 15%).

3,4,6-Tri-O-benzyl-α-D-mannopyranosyl fluoride (16)

$[\alpha]_D$ +9.3 (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.29–7.29 (m, 15H), 5.59 (dd, J = 49.4, 1.6 Hz, 1H), 4.75 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 10.8 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.03 (m, 1H), 3.91–3.78 (m, 3H), 3.70 (dd, J = 10.9, 3.4 Hz, 1H), 3.62 (dd, J = 10.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz) δ: 138.0, 137.9, 137.5, 128.6 (×2), 128.4 (×2), 128.3 (×2), 128.1, 127.9 (×2), 127.88 (×2), 127.85 (×2), 127.7, 127.6, 107.2 (d, J = 217.3 Hz), 79.0 (d, J = 1.8 Hz), 75.2, 73.5, 73.3 (d, J = 2.9 Hz), 73.2, 72.4, 68.2, 67.1 (d, J = 39.7 Hz). ^{19}F NMR (376 MHz) δ: −141.0 (d, J = 49.4 Hz). API-ES positive: 475.1 $(M + Na)^+$. Anal. calcd for $C_{27}H_{29}O_5F$ (452.51): C 71.66, H 6.46; found: C 71.54, H 6.34.

3,4,6-Tri-O-benzyl-2-O-(3,4,6-tri-O-benzyl-D-mannopyranosyl)-α-D-mannopyranosyl fluoride (17)

$[\alpha]_{Hg}$ (435 nm) +38.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.25–7.08 (m, 30H), 5.63 (dd, J = 50.4, 1.3 Hz, 1H), 5.05 (bs, 1H), 4.87–4.48 (m, 14H), 4.11 (m, 2H), 3.91–3.72 (m, 8H). Anal. calcd for $C_{54}H_{57}O_{10}F$ (884.39): C 73.28, H 6.49; found: C 73.14, H 6.34.

Reaction of *n*-pentenyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranose (15)

Application of General procedure B to partially protected NPG **15** (77.8 mg, 0.15 mmol) followed by flash chromatography (hexane/EtOAc, 8:2) afforded glycosyl fluoride **18** (27 mg, 40%) followed by disaccharide **19** (20 mg, 15%). When NPG **15** (38.9 mg, 0.075 mmol) was subjected to the General procedure C with 10 equiv of HF–pyridine followed by flash chromatography (hexane/EtOAc, 8:2), glycosyl fluoride **18** was exclusively obtained (32 mg, 94%).

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl fluoride (18)

$[\alpha]_D$ +71.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.28–7.08 (m, 15H), 5.54 (dd, J = 53.8, 2.3 Hz, 1H), 4.84 (d, J = 11.3 Hz, 1H), 4.75 (d, J = 11.1 Hz, 2H), 4.55 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 3.98 (m, 1H), 3.81–3.76 (m, 4H), 3.70 (dd, J = 10.8, 1.8 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.2, 137.8, 137.6, 128.5 (×2), 128.4 (×3), 127.9 (×3), 127.84 (×3), 127.81 (×3), 127.7, 107.1 (d, J = 224.0 Hz), 81.9, 76.6, 75.4, 74.9, 73.5, 73.0 (d, J = 3.4 Hz), 72.3 (d, J = 25.6 Hz), 67.7. ^{19}F NMR (376 MHz) δ: −151.2 (dd, J = 53.8, 24.6 Hz). API-ES positive: 475.1 $(M + Na)^+$. Anal. calcd for $C_{27}H_{29}O_5F$ (452.51): C 71.66, H 6.46; found: C 71.60, H 6.48.

3,4,6-Tri-O-benzyl-2-O-(3,4,6-tri-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranosyl fluoride (19)

^{1}H NMR (300 MHz) δ: 7.37–7.07 (m, 30H), 5.76 (dd, J = 53.5, 1.5 Hz, 1H), 5.07 (d, J = 2.1 Hz, 1H), 4.93 (d, J = 11.2 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 10.7 Hz, 1H), 4.83 (d, J = 10.4 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 4.76 (d, J = 10.5 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 10.7 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 10.9 Hz, 1H), 4.34 (d, J = 12.1 Hz, 1H), 3.97–3.90 (m, 3H), 3.84–3.68 (m, 7H), 3.47 (dd, J = 11.1, 2.8 Hz, 1H), 3.40 (dd, J = 10.7, 1.2 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.5, 138.4, 137.9, 137.8, 137.6 (×2), 128.5 (×4), 128.4 (×2), 128.3 (×2), 128.3 (×2), 128.2 (×2), 128.1 (×2), 128.0 (×2), 127.9 (×4), 127.8, 127.8, 127.7 (×2), 127.7 (×2), 127.6 (×2), 127.6, 127.5, 104.1 (d, J = 226.6 Hz), 96.5, 82.9, 79.8, 77.1, 76.1, 75.2, 75.1, 74.9 (d, J = 26.5 Hz), 74.8, 73.5, 73.3, 72.9 (d, J = 3.6 Hz), 72.6, 70.8, 67.8, 67.7. API-ES positive: 886.3 $(M + H)^+$. Anal. calcd for $C_{54}H_{57}O_{10}F$ (884.39): C 73.28, H 6.49; found: C 73.2, H 6.48.

4-Fluor-5-iodo-pentyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside (20)

Mixture of diastereomers (1:1). ^{1}H NMR (300 MHz) δ: 7.30–7.08 (m, 15H), 4.82 (d, J = 1.5 Hz, 1H), 4.75 (d, J =

10.8 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 10.8 Hz, 1H), 4.39 (m, 1H), 3.94 (m, 1H), 3.82−3.61 (m, 5H), 3.42− 3.34 (m, 1H), 3.24 (d, J = 5.4 Hz, 1H), 3.18 (d, J = 5.4 Hz, 1H), 1.85−1.52 (m, 4H). ^{13}C NMR (75 MHz) δ: 138.4 (×2), 138.1, 128.8 (×2), 128.6 (×2), 128.5 (×2), 128.2 (×2), 128.1 (×2), 128.0 (×3), 127.9, 127.8, 99.5, 99.4, 93.3, 90.9, 80.4, 75.4, 74.5, 73.7, 72.3, 71.4, 69.2, 68.6, 67.2, 32.0, 31.7, 25.0, 6.9, 6.6. Anal. calcd for $C_{32}H_{38}O_6FI$ (664.54): C 57.84, H 5.76; found: C 57.73, H 7.64.

n-*Pentenyl 2,3,4-tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (24a)*

To a stirred solution of fluoride **12a** (54.2 mg, 0.1 mmol), NPG **21** (29 mg, 0.1 mmol), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (5 mL) was added ytterbium(III) trifluoromethanesulfonate (62 mg, 0.1 mmol). Stirring was maintained for 10 min, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 7:3) to give disaccharide **24a** (55.2 mg, 68%). $[\alpha]_D$ +37.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.32−7.06 (m, 20H), 5.71 (ddt, J = 17.1, 10.4, 6.6 Hz, 1H), 5.04 (s, 2H), 4.86−4.96 (m, 1H), 4.81 (d, J = 10.9 Hz, 1H), 4.73 (bs, 1H), 4.65 (s, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 3.85−3.26 (m, 14H), 3.42 (s, 3H), 3.41 (s, 3H), 3.36 (s, 3H), 2.06−1.97 (m, 2H), 1.61−1.52 (m, 2H). ^{13}C NMR (75 MHz) δ: 138.7, 138.6, 138.5, 138.4, 137.9, 128.3 (×2), 128.2 (×6), 127.8 (×2), 127.7 (×2), 127.6 (×2), 127.5 (×2), 127.4 (×2), 127.3 (×2), 114.9, 98.0, 96.6, 81.4, 79.9, 77.1, 76.1, 74.9, 74.8 (×2), 73.2, 72.3, 71.8, 71.7, 71.4, 69.2, 66.9, 65.9, 60.8, 58.8, 57.6, 30.3, 28.5. API-ES positive: 830.5 $(M + NH_4)^+$, 835.2 $(M + Na)^+$, 859.5 $(M + 2Na)^+$. Anal. calcd for $C_{48}H_{60}O_{11}$ (812.98): C 70.91, H 7.44; found: C 71.06, H 7.37.

n-*Pentenyl 2,3,4-tri*-O-*methyl-6*-O-*(2*-O-*benzoyl-,3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (24b)*

To a stirred solution of fluoride **12b** (27.8 mg, 0.05 mmol), NPG **21** (14.5 mg, 0.05 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added ytterbium(III) trifluoromethanesulfonate (62 mg, 0.1 mmol). Stirring was maintained for 10 min, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 7:3) to give disaccharide **24b** (31 mg, 75%). $[\alpha]_D$ +13.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.06 (m, 2H), 7.57−7.17 (m, 18H), 5.80 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 5.73 (m, 1H), 5.09 (d, J = 1.8 Hz, 1H), 5.05−4.95 (m, 2H), 4.88 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 12.3 Hz, 1H), 4.76 (d, J = 12.9 Hz, 1H), 4.54 (m, 3H), 4.12−4.10 (m, 1H), 3.96 (m, 1H), 3.91 (dd, J = 10.8, 3.6 Hz, 1H), 3.81−3.57 (m, 8H), 3.51 (s, 6H), 3.51 (s, 3H), 3.46−3.37 (m, 2H). ^{13}C NMR (75 MHz) δ: 165.4, 138.6, 138.5, 138.0, 137.9, 132.9, 130.0, 129.9 (×3), 128.3 (×2), 128.29 (×2), 128.24 (×2), 128.21 (×2), 128.1 (×2), 127.8 (×2), 127.6, 127.5 (×2), 127.4, 114.9, 98.1, 96.5, 81.4, 78.3, 76.3, 75.1, 74.2, 73.3, 71.5, 71.4, 71.0, 69.0, 68.7, 67.0, 66.7, 60.8, 58.8, 57.5, 30.3, 28.6. API-ES positive: 844.3 $(M + NH_4)^+$, 872 $(M + 2Na)^+$. Anal. calcd for $C_{48}H_{58}O_{12}$ (826.39): C 69.71, H 7.07; found: C 69.61, H 6.94.

2,3,4-Tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzyl-D-glucopyranosyl)-α- and -β-D-glucopyranosyl fluoride (25)

To a stirred solution of pentenyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**; 122 mg, 0.2 mmol) and 2,3,4-tri-*O*-methyl-α-D-glucopyranosyl fluoride (**22**; 34.8 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) under argon was added IDCP (234 mg, 0.5 mmol) in one portion. The solution was stirred for 2 h and then the mixture was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2 to 1:1) gave disaccharide **25*α*** (51 mg, 45%) followed by disaccharide **25*β*** (50 mg, 45%). α-Anomer: $[\alpha]_D$ +37.5 (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.30−7.05 (m, 20H), 5.48 (dd, J = 53.3, 2.7 Hz, 1H), 4.98 (d, J = 17.4 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 16.7 Hz, 1H), 4.61 (d, J = 17.2 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.42 (bs, 1H), 4.40 (d, J = 12.1 Hz, 1H), 3.91 (t, J = 9.2 Hz, 1H), 3.80−3.39 (m, 9H), 3.56 (s, 3H), 3.48 (s, 3H), 3.38 (s, 3H), 3.24 (t, J = 9.5 Hz, 1H), 2.93 (ddd, J = 25.7, 9.5, 2.7 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.8, 138.5, 138.2, 137.9, 128.3 (×5), 127.9 (×3), 127.8 (×3), 127.7 (×3), 127.6 (×2), 127.5 (×2), 127.3 (×2), 104.9 (d, J = 226.3 Hz), 94.4, 82.9, 81.8, 81.2 (d, J = 24.8 Hz), 80.1, 78.4, 77.5, 75.6, 75.1, 73.4, 72.3, 72.4 (d, J = 3.5 Hz), 70.3, 68.4, 66.0, 60.8, 60.6, 59.1. API-ES positive: 764.3 $(M + NH_4)^+$, 769.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{51}FO_{10}$ (746.86): C 69.15, H 6.88; found: C 69.35, H 6.65. β-Anomer: $[\alpha]_D$ +17.5 (*c* 0.45, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.29−7.08 (m, 20H), 5.60 (dd, J = 53.3, 2.6 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 9.3 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 10.8 Hz, 1H), 4.37 (d, J = 7.7 Hz, 1H), 4.13 (dd, J = 11.0, 1.7 Hz, 1H), 3.83 (ddd, J = 10.0, 4.5, 1.6 Hz, 1H), 3.70−3.40 (m, 8H), 3.56 (s, 3H), 3.47 (s, 3H), 3.39 (s, 3H), 3.18 (t, J = 9.6 Hz, 1H), 3.11 (ddd, J = 25.7, 9.6, 2.7 Hz, 1H). ^{13}C NMR (75 MHz) δ: 138.5, 138.3, 138.1, 137.9, 128.4 (×2), 128.33 (×2), 128.32 (×2), 128.31 (×2), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.7, 127.6 (×2), 127.57, 127.56, 127.55, 104.8 (d, J = 226.4 Hz), 103.7, 84.8, 82.8, 81.9, 81.3 (d, J = 24.8 Hz), 78.5, 77.8, 75.7, 75.0, 74.9, 74.8, 73.4, 72.2 (d, J = 3.9 Hz), 68.9, 68.1, 60.9, 60.5, 59.1. API-ES positive: 769.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{51}FO_{10}$ (746.86): C 69.15, H 6.88; found: C 69.3, H 6.93.

2,3,4-Tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*methyl-D-mannopyranosyl)-α- and -β-D-mannopyranosyl fluoride (26a)

To a stirred solution of fluoride **23** (22 mg, 0.1 mmol), NPG **6a** (30 mg, 0.1 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added $I(coll)_2ClO_4$ (117 mg, 0.25 mmol). Stirring was maintained for 1 h, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated aqueous sodium bicarbonate, and water. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 2:8)

to give disaccharide **26aα** (20 mg, 44%) followed by disaccharide **26aβ** (19 mg, 44%). α-Anomer: $[\alpha]_D$ +26.8 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.65 (dd, *J* = 50.4, 2.1 Hz, 1H), 5.03 (d, *J* = 1.8 Hz, 1H), 3.91 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.74−3.70 (m, 2H), 3.67−3.65 (m, 3H), 3.61 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.52 (s, 3H), 3.49 (s, 3H), 3.46 (s, 3H), 3.40 (s, 3H), 3.58−3.44 (m, 6H). ^{13}C NMR (75 MHz) δ: 105.4 (d, *J* = 221.3 Hz), 97.3, 81.1, 80.6 (d, *J* = 1.6 Hz), 76.8, 76.3, 75.7 (d, *J* = 34.1 Hz), 75.1, 73.7 (d, *J* = 2.2 Hz), 71.6, 71.3, 65.9, 60.9, 60.6, 59.4, 59.2, 58.8, 57.9, 57.7. API-ES positive: 465.2 $(M + Na)^+$. Anal. calcd for $C_{19}H_{35}FO_{10}$ (442.47): C 51.57, H 7.97; found: C 51.64, H 8.03. β-Anomer: $[\alpha]_D$ −20.1 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 5.66 (dd, *J* = 50.4, 1.8 Hz, 1H), 4.48 (bs, 1H), 4.22 (dd, *J* = 11.1, 1.5 Hz, 1H), 3.87−3.82 (m, 1H), 3.73−3.70 (m, 2H), 3.65 (s, 3H), 3.52 (s, 3H), 3.51 (s, 6H), 3.49 (s, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 3.67−3.25 (m, H), 3.18 (dd, *J* = 8.7, 3.3 Hz, 1H). API-ES positive: 465.2 $(M + Na)^+$. Anal. calcd for $C_{19}H_{35}FO_{10}$ (442.47): C 51.57, H 7.97; found: C 51.39, H 8.15.

6-O-tert-*Butyldiphenylsilyl-2,3,4-tri*-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*methyl-*D *mannopyranosyl-α- and -β-*D*-mannopyranosyl fluoride (26b)*

To a stirred solution of fluoride **23** (22 mg, 0.1 mmol), NPG **6b** (52.8 mg, 0.1 mmol), and 4 Å molecular sieves (25 mg) in CH_2Cl_2 (3 mL) was added $I(coll)_2ClO_4$ (117 mg, 0.25 mmol). Stirring was maintained for 1 h, then the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with 10% aqueous sodium thiosulfate containing sodium bicarbonate, saturated aqueous sodium bicarbonate, and water. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/AcOEt, 1:1) to give disaccharide **26bα** (32 mg, 48%) followed by disaccharide **26bβ** (16 mg, 24%). α-Anomer: $[\alpha]_D$ +43.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.76−7.71 (m, 4H), 7.42−7.34 (m, 6H), 5.66 (dd, *J* = 50.4, 1.5 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 3.95−3.83 (m, 4H), 3.76−3.66 (m, 4H), 3.57−3.46 (m, H), 3.53 (s, 6H), 3.51 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (75 MHz) δ: 135.9 (×2), 135.6 (×2), 134.1, 133.6, 129.4 (×2), 127.5 (×2), 127.4 (×2), 105.4 (d, *J* = 220.9 Hz), 96.8, 81.2, 80.5 (d, *J* = 1.6 Hz), 76.7, 76.1, 75.6 (d, *J* = 34.0 Hz), 75.2, 73.8 (d, *J* = 2.0 Hz), 73.0, 65.5, 63.3, 60.9, 60.6, 59.3, 58.3, 57.9, 57.6, 26.7 (×3), 19.4. API-ES positive: 684.3 $(M + NH_4)^+$. Anal. calcd for $C_{34}H_{51}FO_{10}Si$ (666.85): C 61.24, H 7.71; found: C 61.09, H 7.65. β-Anomer: $[\alpha]_D$ −9.5 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.78−7.70 (m, 4H), 7.42− 7.35 (m, 6H), 5.69 (dd, *J* = 50.4, 1.8 Hz, 1H) 4.48 (bs, 1H), 4.25 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.95 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.91−3.85 (m, 1H), 3.76 (d, *J* = 3.3 Hz, 1H), 3.72 (m, 1H), 3.65 (s, 3H), 3.62−3.55 (m, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.48 (s, 6H), 3.44 (t, *J* = 9.3 Hz, 1H), 3.25−3.22 (m, 1H), 3.19 (dd, *J* = 9.3, 3.0 Hz, 1H), 1.05 (s, 9H). API-ES positive: 684.3 $(M + NH_4)^+$. Anal. calcd for $C_{34}H_{51}FO_{10}Si$ (666.85): C 61.24, H 7.71; found: C 61.15, H 7.84.

2,3,4-Tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranosyl fluoride (27)*

A solution of *n*-pentenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**8**; 79.7 mg, 0.12 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 22.4 mg, 0.1 mmol), NIS (44.8 mg, 0.2 mmol), and 4 Å molecular sieves (25 mg) in anhydrous CH_2Cl_2 (3 mL) was stirred under argon for 10 min at room temperature. Then the reaction was cooled to −30 °C and BF_3OEt_2 (15 μL, 0.12 mmol) was added. After 30 min, the reaction was diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was a complex mixture of compounds from which disaccharide **27** could be purified by flash chromatography (hexane/AcOEt, 7:3; 20 mg, 25%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.0−7.15 (m, 20H), 6.04 (t, *J* = 10.0 Hz, 1H), 5.87 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.70 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.64 (dd, *J* = 50.3, 1.8 Hz, 1H), 5.14 (d, *J* = 1.6 Hz, 1H), 4.67−4.58 (m, 1H), 4.47−4.39 (m, 2H), 3.96 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.87−3.78 (m, 2H), 3.67 (m, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.53−3.42 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4 165.3, 165.2, 133.4 (×2), 133.1, 133.0, 129.9, 129.8 (×4), 129.7 (×2), 129.6 (×2), 129.4, 129.1, 128.9, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 105.3 (d, *J* = 220.8 Hz), 98.0, 80.5, 75.5 (d, *J* = 34.0 Hz), 75.4, 73.7, 70.3, 69.9, 68.8, 67.1, 66.9, 62.8, 60.9, 59.4, 57.8. API-ES positive: 825.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{43}FO_{14}$ (802.79): C 64.33, H 5.40; found: C 64.47, H 5.49.

Methyl 2,3,4-tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranoside (29)*

A stirred solution of **28** (57.5 mg, 0.087 mmol), **16** (47 mg, 0.087 mmol), and **2** (20 mg, 0.087 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to −30 °C and then NIS (38.7 mg, 0.173 mmol) and $BF_3{\cdot}OEt_2$ (1.1 μL, 0.0087 mmol) were added. The solution was stirred for 20 min and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 3:2 to 1:1) gave recovered **16** (40 mg, 85%) and disaccharide **29** (68 mg, 96%). $[\alpha]_D$ +4.3 (*c* 3.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.05−7.17 (m, 20H), 6.02 (t, *J* = 10.0 Hz, 1H), 5.85 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.67 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.14 (d, *J* = 1.4 Hz, 1H), 4.74 (d, *J* = 3.5 Hz, 1H), 4.68 (dd, *J* = 11.9, 2.0 Hz, 1H), 4.48 (ddd, *J* = 9.9, 4.3, 2.0 Hz, 1H), 4.39 (dd, *J* = 11.9, 4.6 Hz, 1H), 3.91 (dd, *J* = 11.0 Hz, 5.4 Hz, 1H), 3.79 (dd, *J* = 10.9, 1.4 Hz, 1H), 3.69−3.63 (m, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 3.49 (m, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.11 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.05 (m, 1H). ^{13}C NMR (75 MHz) δ: 166.4, 165.7, 165.6, 165.5, 133.7 (×2), 133.4, 133.3, 130.2, 130.1 (×2), 129.9 (×6), 129.6 (×2), 129.3 (×4), 129.2 (×2), 128.8, 128.7, 128.6, 97.7, 97.5, 83.8, 82.0, 79.8, 70.6, 70.2, 70.0, 69.2, 67.2, 66.8, 63.1, 61.1, 60.8, 59.3, 55.4. API-ES positive: 837.2 $(M + Na)^+$. Anal. calcd for $C_{44}H_{46}O_{15}$ (814.83): C 64.86, H 5.69; found: C 65.02, H 5.73.

2,3,4-Tri-O-*methyl-6*-O-*(2,3,4,6-tetra*-O-*benzoyl-α-*D*-mannopyranosyl)-α-*D*-glucopyranosyl fluoride (31)*

A stirred solution of NPOE **28** (66.4 mg, 0.1 mmol) and fluoride **23** (22.4 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to −20 °C and then NIS (44.8 mg, 0.2 mmol) and $Yb(OTf)_3$ (62 mg, 0.1 mmol) were added. The solution was stirred for 1 h and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was

dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 3:2 to 1:1) gave disaccharide **31** (75 mg, 94%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.0−7.15 (m, 20H), 6.04 (t, *J* = 10.0 Hz, 1H), 5.87 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.70 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.64 (dd, *J* = 50.3, 1.8 Hz, 1H), 5.14 (d, *J* = 1.6 Hz, 1H), 4.67−4.58 (m, 1H), 4.47−4.39 (m, 2H), 3.96 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.87−3.78 (m, 2H), 3.67 (m, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.53−3.42 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4, 165.3, 165.2, 133.4 (×2), 133.1, 133.0, 129.9, 129.8 (×4), 129.7 (×2), 129.6 (×2), 129.4, 129.1, 128.9, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 105.3 (d, *J* = 220.8 Hz), 98.0, 80.5, 75.5 (d, *J* = 34.0 Hz), 75.4, 73.7, 70.3, 69.9, 68.8, 67.1, 66.9, 62.8, 60.9, 59.4, 57.8. API-ES positive: 825.2 $(M + Na)^+$. Anal. calcd for $C_{43}H_{43}FO_{14}$ (802.79): C 64.33, H 5.40; found: C 64.47, H 5.49.

One-pot assembly of trisaccharide 32

A mixture of NPOE **28** (73 mg, 0.11 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 22.4 mg, 0.1 mmol), and 4 Å molecular sieves in CH_2Cl_2 (4 mL) was stirred under argon at −20 °C for 10 min. Then NIS (24.6 mg, 0.11 mmol) and $Yb(OTf)_3$ (68.2 mg, 0.11 mmol) were added. The reaction mixture was stirred at −20 °C for 1 h, after which *n*-pentenyl-2,3,4-tri-*O*-methyl-α-D-mannopyranoside (**21**; 26.1 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was allowed to warm to room temperature and then $Yb(OTf)_3$ (68.2 mg, 0.11 mmol) was added. Upon stirring for 10 min, the reaction was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 1:1) gave trisaccharide **32** (69 mg, 72%). $[\alpha]_D$ −2.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.31−7.79 (m, 8H), 7.61−7.22 (m, 12H), 6.10 (t, *J* = 9.9 Hz, 1H), 5.96 (dd, *J* = 10.2, 3.3 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.5, 6.6 Hz, 1H), 5.76 (m, 1H), 5.26 (d, *J* = 1.8 Hz, 1H), 5.12 (d, *J* = 1.0 Hz, 1H), 5.03−4.92 (m, 2H), 4.88 (bs, 1H), 4.71−4.68 (m, 1H), 4.57−4.47 (m, 2H), 4.05−3.97 (m, 2H), 3.91−3.87 (m, 1H), 3.81−3.35(m, 11H), 3.58 (s, 3H), 3.56 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H), 2.11−2.04 (m, 2H), 1.69−1.60 (m, 2H). ^{13}C NMR (75 MHz) δ: 166.2, 165.4, 165.2, 165.1, 137.9, 133.3, 133.2, 132.9, 129.9, 129.8 (×2), 129.77 (×2), 129.73 (×2) 129.6 (×2), 129.5, 129.2, 129.0, 128.5 (×2), 128.4 (×2), 128.3 (×2), 128.2 (×2), 114.9, 97.6, 96.9, 96.6, 81.39, 81.38, 77.1, 76.6, 76.3, 75.8, 71.4, 71.1, 70.4, 69.9, 68.7, 67.1, 67.0 (×2), 66.0, 62.9, 60.8, 60.7, 58.7, 58.6, 57.5, 57.4, 30.3, 28.6. API-ES positive: 1090.3 $(M + NH_4)^+$, 1095.4 $(M + Na)^+$. Anal. calcd for $C_{57}H_{68}O_{20}$ (1073.14): C 63.80, H 6.39; found: C 63.93, H 6.51.

One-pot assembly of tetrasaccharide 34

A mixture of NPOE **28** (88.4 mg, 0.133 mmol), 2,3,4-tri-*O*-methyl-α-D-mannopyranosyl fluoride (**23**; 27.1 mg, 0.12 mmol), and 4 Å molecular sieves in CH_2Cl_2 (4 mL) was stirred under argon at −20 °C for 10 min. Then NIS (29.8 mg, 0.133 mmol) and $Yb(OTf)_3$ (82.5 mg, 0.133 mmol) were added. The reaction mixture was stirred at −20 °C for 1 h, after which *n*-pentenyl-2,3,4-tri-*O*-methyl-α-D-mannopyranoside (**21**;31.9 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added. The reaction was allowed to warm to room temperature and then $Yb(OTf)_3$ (41.2 mg, 0.066 mmol) was added. Upon stirring for 30 min, the acceptor **33** (32 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added and the reaction was cooled to −30 °C. Then NIS (24.6 mg, 0.11 mmol) and $BF_3(OEt)_2$ (3.8 μL, 0.03 mmol) were added. After 12 h, the reaction was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 2:8) yielded tetrasaccharide **34** (32.6 mg, 25%). Major isomer, selected signals: ^{1}H NMR (300 MHz) δ: 5.25 (d, *J* = 1.8 Hz, 1H), 5.11 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 2.5 Hz, 1H), 4.91 (bs, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 3.50 (s, 6H), 3.47 (s, 3H), 3.44 (s, 3H), 3.35 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz) δ: 97.7, 96.9, 96.8, 96.6. Electrospray ionization (ESI)-HR-MS: 1324.5055 $(M + NH_4)^+$, 1329.4602 $(M + Na)^+$. Anal. calcd for $C_{65}H_{78}O_{28}$ (1306.46): C 59.72, H 6.01, O 34.27; found: C 59.88, H 6.09.

Methyl 3,5-di-O-benzyl-2-O-benzoyl-β-D-ribofuranoside (35)

To a solution of 1,2-orthoester **36** (80 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) at −40 °C under argon was added a solution of HF–pyridine (10.27 mL, 1.78 mmol) in dry CH_2Cl_2 (2 mL). After 10 min, when all the starting material had disappeared, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched by saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl. The resultant organic phase was dried, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc, 8:2) to yield fluoride **37** (33 mg, 42%) followed by methyl glycoside **35** (19 mg, 24%). For **35**: $[\alpha]_D$ +32.0 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.10−8.07 (m, 3H), 7.61−7.23 (m, 12H), 5.45 (d, *J* = 4.3 Hz, 1H), 5.04 (s, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.36 (m, 1H), 4.24 (m, 1H), 3.61 (ddd, *J* = 16.6, 10.5, 4.6 Hz, 2H), 3.38 (s, 3H, OMe). ^{13}C NMR (75 MHz) δ: 165.6, 138.2, 137.4, 133.3, 129.9 (×2), 129.6, 128.4 (×2), 128.3 (×4), 128.0 (×2), 127.8, 127.6 (x 2), 127.5, 106.3, 80.5, 77.9, 74.2, 73.2, 73.0, 71.2, 55.1. API-ES positive: 471.5 $(M + Na)^+$.

3,5-Di-O-benzyl-2-O-benzoyl-β-D-ribofuranosyl fluoride (37)

Following General procedure D, a solution of HF–pyridine (40 equiv, 6 mmol, 0.9 mL) was treated with orthoester **36** (70 mg, 0.16 mmol) to afford, after flash chromatography (hexane/EtOAc, 9:1), compound **37** (72 mg, quantitative yield) as a colorless oil. $[\alpha]_D$ +44.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.10−8.07 (m, 3H), 7.61−7.23 (m, 12H), 5.85 (d, *J* = 61.9 Hz, 1H), 5.60 (t, *J* = 4.0 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.48−4.40 (m, 1H), 4.35−4.30 (m, 1H), 3.74 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.60 (dd, *J* = 11.0, 5.4 Hz, 1H). ^{13}C NMR (75 MHz) δ: 165.5, 134.0, 133.9, 133.5 (×2), 130.1 (×2), 130.0 (×4), 128.8 (×2), 128.7 (×2), 128.6 (×2), 112.6 (d, *J* = 225.2 Hz, C-1), 82.8 (d, *J* = 2.3 Hz, C-3), 75.1, 74.6, 71.2, 64.2, 29.9. ^{19}F NMR (376 MHz) δ: 115.1 (m). API-ES positive: 459.2 $(M + Na)^+$. Anal. calcd for $C_{26}H_{25}FO_5$ (436.47): C 71.55, H 5.77; found: C 71.43, H 5.64.

***2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl fluoride (44)*[31]**

Following General procedure D, a solution of HF–pyridine (3.0 mmol, 0.45 mL) was treated with orthoester **38a** (80 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **12** (66 mg, 95%) as a colorless oil. In a different run, orthoester **38b** (80 mg, 0.17 mmol) was subjected to the same reaction conditions to obtain fluoride **44** (62 mg, 79%). $[\alpha]_D$ −53.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03−7.90 (m, 5H), 7.56, 7.17 (m, 10H), 5.95 (d, *J* = 58.4 Hz, 1H), 5.63 (bd, *J* = 6.1 Hz, 1H), 5.52 (m, 1H), 4.80−4.74 (m, 2H), 4.62 (dd, *J* = 12.9, 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 166.1, 165.0, 133.8, 133.7, 133.1, 129.9 (×2), 129.8 (×2), 129.7 (×2), 129.4, 128.6 (×3), 128.5 (×2), 128.4, 128.3 (×2), 112.4 (d, *J* = 226.5 Hz, C-1), 84.4, 80.8 (d, *J* = 40.0 Hz, C-2), 76.5, 63.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −124.7 (dd, *J* = 58.5, 6.0 Hz). API-ES positive: 487.3 $(M + Na)^+$. Anal. calcd for $C_{26}H_{21}FO_7$ (464.44): C 67.24, H 4.56; found: C 67.18, H 4.43.

2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl fluoride (45)

Following General procedure D, a solution of HF–pyridine (3.0 mmol, 0.45 mL) was treated with orthoester **39a** (80 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **45** (70 mg, quantitative yield) as a colorless oil. In a different run, orthoester **39b** (80 mg, 0.17 mmol) was subjected to the same reaction conditions to obtain fluoride **45** (77 mg, quantitative yield). $[\alpha]_D$ +105.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10−7.87 (m, 5H), 7.63−7.31 (m, 10H), 5.98 (d, *J* = 61.0 Hz, 1H), 5.93−5.86 (m, 2H), 4.87 (m, 1H), 4.78 (dd, *J* = 12.1, 3.8 Hz, 1H), 4.59 (dd, *J* = 12.1, 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.4, 165.5, 165.2, 134.0, 133.9, 133.5, 130.1 (×2), 130.4 (×2), 130.2 (×2), 129.7, 128.9, 128.8 (×3), 128.7 (×2), 128.6 (×2), 112.3 (d, *J* = 226.3 Hz, C-1), 81.1 (d, *J* = 2.7 Hz, C-3), 74.9 (d, *J* = 36.2 Hz, C-2), 71.2, 64.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −116.0 (bd, *J* = 65.0 Hz). API-ES positive: 487.3 $(M + Na)^+$. Anal. calcd for $C_{26}H_{21}FO_7$ (464.44): C 67.24, H 4.56; found: C 67.13, H 4.49.

3,5-Di-O-benzyl-2-O-benzoyl-α-D-arabinofuranosyl fluoride (46)

Following General procedure D, a solution of HF–pyridine (3.6 mmol, 0.53 mL) was treated with orthoester **40a** (60 mg, 0.12 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **46** (51 mg, 91%) as a colorless oil. In a different run, orthoester **40b** (40 mg, 0.09 mmol) was subjected to the same reaction conditions to obtain fluoride **46** (39 mg, 93%). $[\alpha]_D$ +14.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.98−7.95 (m, 3H), 7.64−7.28 (m, 12H), 5.90 (d, *J* = 59.0 Hz, 1H, 1-H), 5.54 (dd, *J* = 7.1, 1.1 Hz, 1H, 2-H), 4.84 (d, *J* = 12.3 Hz, 1H, –OCH_2Ph), 4.65 (d, *J* = 12.3 Hz, 1H, –OCH_2Ph), 4.61−4.58 (m, 1H, 4-H), 4.12 (dd, *J* = 4.6, 1.1 Hz, 1H, 3-H) 3.68 (dd, *J* = 10.8, 4.5 Hz, 1H, 5a-H), 3.62 (dd, *J* = 10.8, 6.0 Hz, 1H, 5b-H). ^{13}C NMR (75 MHz) δ: 165.4, 137.9, 137.5, 133.9, 130.1 (×2), 129.2, 128.8 (×2) 128.7 (×2), 128.6 (×2), 128.2 (×3), 128.0, 127.9 (×2), 113.2 (d, *J* = 225.4 Hz, 1-C), 85.4, 82.3, 80.7 (d, *J* = 39.2 Hz, 2-C), 73.7, 72.6, 69.1. ^{19}F NMR (376 MHz) δ: −123.5 (dd, *J* = 59.1, 7.0 Hz). API-ES positive: 459.2 $(M + Na)^+$. Anal. calcd for $C_{26}H_{25}FO_5$ (436.47): C 71.53, H 5.77; found: C 71.39, H 5.59.

2,5-Di-O-benzoy1-α-D-arabinofuranosyl fluoride (47)

Following General procedure D, a solution of HF–pyridine (3.06 mmol, 0.45 mL) was treated with orthoester **41** (34 mg, 0.09 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **47** (29 mg, 91%). $[\alpha]_D$ +52.1 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.04 (m, 4H), 7.59−7.41 (m, 6H), 6.00 (d, *J* = 60.0 Hz, 1H), 5.32 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.72−4.50 (m, 3H), 4.33 (dd, *J* = 5.8, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 166.8, 166.4, 134.2, 133.5, 130.1 (×2), 130.0 (×2), 129.7, 128.9 (×2), 128.8, 128.6 (×2), 113.2 (d, *J* = 223.9 Hz, C-1), 86.1 (d, *J* = 39.0 Hz, C-2), 84.3, 77.0, 63.5, 30.0. ^{19}F NMR (376 MHz) δ: −121.9 (dd, *J* = 59.8, 11.3 Hz). API-ES positive: 383.4 $(M + Na)^+$. Anal. calcd for $C_{19}H_{17}FO_6$ (360.33): C 63.33, H 4.76; found: C 63.17, H 4.51.

2,5-Di-O-benzoyl-1-β-D-ribofuranosyl fluoride (48)

Following General procedure D, a solution of HF–pyridine (1.82 mmol, 0.27 mL) was treated with orthoester **42** (57 mg, 0.15 mmol) to afford, after flash chromatography (hexane/EtOAc, 8:2), compound **48** (29 mg, 53%). $[\alpha]_D$ +30.4 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.03−8.00 (m, 2H), 7.65−7.30 (m, 8H), 6.01 (d, *J* = 59.7 Hz, 1H), 5.32 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.69 (m, 2H), 4.54 (m,1H), 4.33 (dd, *J* = 5.8, 2.6 Hz, 1H). ^{13}C NMR (75 MHz) δ: 166.5, 166.2, 132.9, 132.0, 128.9 (×2), 128.7 (×2), 127.7 (×2), 127.4 (×2), 111.9 (d, *J* = 223.9 Hz, C-1), 84.8 (d, *J* = 39.0 Hz, C-2), 82.8, 75.9, 62.2, 28.7. ^{19}F NMR (376 MHz) δ: −115.7 (bd, *J* = 60.7 Hz). API-ES positive: 383.3 $(M + Na)^+$. Anal. calcd for $C_{19}H_{17}FO_6$ (360.33): C 63.33, H 4.76; found: C 63.21, H 4.63.

1,5-Anhydro-2-O-benzoyl-β-D-ribofuranose (49)

Following General procedure D, a solution of HF–pyridine (40 equiv, 8.8 mmol, 1.31 mL) was treated with orthoester **43** (60 mg, 0.22 mmol) to afford, after flash chromatography (hexane/EtOAc, 1:1), compound **49** (21 mg, 40%). $[\alpha]_D$ −27.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 8.09−8.04 (m, 2H), 7.63−7.44 (m, 3H), 5.35 (d, *J* = 4.6 Hz, 1H), 5.13 (s, 1H), 4.95 (m, 1H), 4.02 (m, 2H), 3.83 (m, 1H), 2.16 (d, 1H, OH). ^{13}C NMR (75 MHz) δ: 166.2, 133.6, 129.8 (×2), 129.3, 128.5 (×2), 104.5, 82.7, 77.2, 69.7, 66.6. API-ES positive: 473.3 $(2M + H)^+$, 495.3 $(2M + Na)^+$. Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C 61.01, H 5.12; found: C 60.87, H 4.98.

2,5-Di-O-benzoyl-3-O-(2,3,5-tri-O-benzoyl-α-D-arabino-furanosyl)-α-D-arabinofuranosyl fluoride (50)

A stirred solution of NPOE **38a** (100 mg, 0.198 mmol) and fluoride **47** (74 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) under argon was cooled to 0 °C and then NIS (85.5 mg, 0.38 mmol) and $Yb(OTf)_3$ (58.9 mg, 0.10 mmol) were added. The solution was stirred for 1 h and then quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution. The separated organic extract was dried, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2) gave disaccharide **50** (86 mg, 61%). $[\alpha]_D$ −6.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 8.13−7.93 (m, 10H), 7.60−7.21 (m, 15H), 6.00 (d, *J* = 58.1 Hz, 1H, 1-H), 5.72 (s, 1H, 1′-H), 5.63 (s, 1H, 2-H), 5.59 (d, *J* = 1.6 Hz, 1H, 3′-H), 5.57 (d, *J* = 6.6 Hz, 1H, 2-H), 4.78−4.53 (m, 7H). ^{13}C NMR (100 MHz) δ: 166.1, 166.0, 165.6, 165.3, 165.2, 133.7, 133.6, 133.5, 133.2, 133.1, 130.0 (×4), 129.9 (×2), 129.8, 129.7 (×2), 129.6 (×2), 129.5, 129.3, 128.9, 128.8,

128.7 (×2), 128.6 (×2), 128.5 (×2), 128.4 (×2), 128.3 (×2), 112.6 (d, J = 225.2 Hz), 105.6, 84.2, 82.2, 81.7, 81.3 (d, J = 40.2 Hz), 79.9, 77.4, 63.7, 63.0. API-ES positive: 827.5 $(M + Na)^+$. Anal. calcd for $C_{45}H_{37}O_{13}F$ (804.77): C 67.16, H 4.63; found: C 67.07, H 4.39.

***n*-Pentenyl-2,3-di-O-benzyl-5-O-[2,5-di-O-benzoyl-3-O-(2,3,5-tri-O-benzoyl-α-D-arabino-furanosyl)-α-D-arabino-furanosyl]-α-D-arabino-furanoside (52)**

To a stirred solution of fluoride **50** (8 mg, 0.01 mmol) and NPG **51** (8 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C was added $BF_3{\cdot}Et_2O$ (0.9 μL, 0.00710 mmol). The reaction was allowed to warm to −10 °C and then stirred for an additional 4 h after which time it was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate. The organic extract was dried, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2) to give trisaccharide **52** (9 mg, 75%). $[\alpha]_D$ +22.2 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz) δ: 8.13−7.93 (m, 10H), 7.60−7.15 (m, 25H), 5.75 (m, 1H), 5.72 (s, 1H, 1-H), 5.60 (d, J = 1.5 Hz, 1H, 2′-H), 5.53 (dd, J = 3.9, 0.7 Hz, 1H, 1-H), 5.45 (d, J = 1 Hz, 1H, 2″-H), 5.34 (s, 1H, 1-H), 4.98 (d, J = 1.3 Hz, 1H), 4.91 (m, 2H), 4.74−4.42 (m, 11H), 4.21 (dt, J = 6.6, 4.2 Hz, 1H, 4-H), 4.04 (dd, J = 6.6, 3.4 Hz, 1H, 3-H), 3.99 (dd, J = 3.4, 1.5 Hz, 1H, 2-H), 3.90 (dd, J = 11.2, 4.6 Hz, 1H, 5-H), 3.75 (dd, J = 11.2, 3.9 Hz, 1H), 3.68 (m, 1H), 3.34 (m, 1H), 2.06 (m, 2H), 1.60 (m, 2H). ^{13}C NMR (125 MHz) δ: 166.1 (d), 166.0, 165.6, 165.3, 165.2, 138.2, 137.9, 137.6, 133.5, 133.4, 133.3, 133.1, 132.9, 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.2, 129.1, 128.4 (×2), 128.3 (×2), 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 114.7, 106.1, 106.0, 105.0, 88.2, 83.4, 82.0, 81.9, 81.6, 81.1, 80.6, 80.0, 77.7, 77.6, 72.2, 71.9, 66.9, 66.3, 63.7, 63.2, 30.3, 28.7. HR-MS: 1205.4127 $(M + Na)^+$. Anal. calcd for $C_{69}H_{66}O_{18}$ (1182.42): C 70.04, H 5.62; found: C 69.94, H 5.49.

Acknowledgements

B.F.R. thanks the National Science Foundation (grant No. CHE 0717702) for financial support. This research has been supported with funds from the Ministerio de Ciencia e Innovación and Comunidad de Madrid (grant Nos. CTQ2009-10343 and S2009/PPQ-1752, respectively). We also thank Ms. M. Rodríguez (Instituto de Química Orgánica General (IQOG)) for skillful technical support.

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