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OFox imidates as versatile glycosyl donors for chemical glycosylation†,‡

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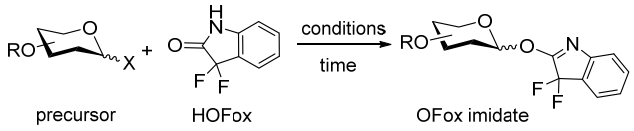
Previously we communicated 3,3-difluoroxindole (HOFox) – mediated glycosylations wherein 3,3-difluoro-3*H*-indol-2-yl (OFox) imidates were found to be key intermediates. Both the *in-situ* synthesis from the corresponding glycosyl bromides and activation of the OFox imidates could be conducted in a regenerative fashion. Herein, we extend this study with the main focus on the synthesis of various OFox imidates and their investigation as glycosyl donors for chemical 1,2-*cis* and 1,2-*trans* glycosylation.

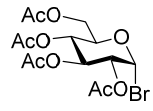
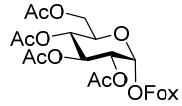
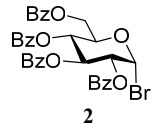
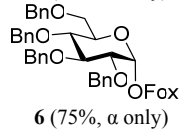
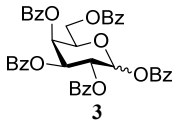
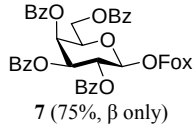
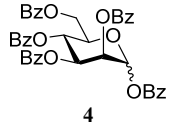
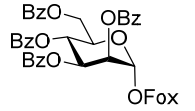
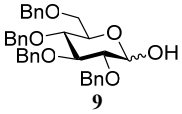
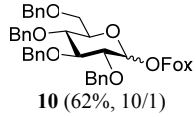
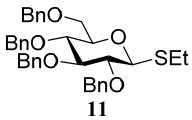
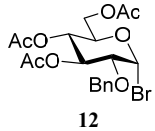
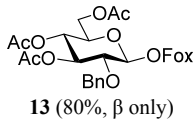
Practically all complex carbohydrates are connected via *O*-glycosidic linkages, but obtaining these linkages by chemical methods remains challenging. Many methods for glycoside synthesis have been developed.[1] However, the complexity of glycosylation reactions constantly calls for further improvement.[2] A majority of all glycosylations are performed with thioglycosides[3] and *O*-trichloroacetimidates (TCAI),[4] but *N*-phenyl trifluoroacetimidates (PTFAI) introduced by Yu and co-workers[5] have also been gaining a considerable niche amongst methods used for chemical glycosylation. Inspired by excellent results achieved with the PTFAI donors, we decided to investigate the 3,3-difluoro-3*H*-indol-2-yl (OFox) leaving group that represents a hybrid structure between PTFAI and *S/O*-benzoxazolyl (SBox/OBox) leaving groups developed by our laboratory.[6] While investigating approaches to the synthesis of OFox imidates, we discovered that these new compounds can be generated and glycosylated in a regenerative fashion *in situ*. This created the basis to exploring 3,3-difluoroxindole (HOFox)-mediated regenerative glycosylations wherein the OFox imidates were found to be key intermediates.[7] Described herein is a continuation of this study with the main focus on the synthesis of various OFox imidates and their investigation as glycosyl donors for chemical glycosylation.

3,3-Difluoroxindole aglycone (HOFox) can be synthesized from the commercially available Isatin with diethylaminosulfur trifluoride (DAST) in anhydrous CH_2Cl_2 at room temperature,[7-8] but there is a variety of approaches that might be suitable as well.[9] Based on previous syntheses of imidates and thioimidates of similar structure we decided to react HOFox with different glycosyl halides (**1**[10] or **2**,[11] X = Br, Table 1) that were used either directly or obtained *in situ* from the corresponding benzoates (**3** or **4**, X = Bz). It was observed that all anomeric substitutions proceeded stereoselectively providing either 1,2-*trans* or 1,2-*cis*-linked OFox imidates **5-8** in 75-84% yields (entries 1-4, Table 1). Also investigated was the synthesis using hemiacetal **9**[12] (X = OH) as the starting material. This transformation was performed via the corresponding chloride (X = Cl) and resulted in the formation of per-benzylated OFox imidate **10** in 62% yield (entry 5). We also demonstrated that thioglycoside **11**[13] can be converted into OFox imidate **10** in 95% yield in the presence of *N*-iodosuccinimide (entry 6). The synthesis of 2-benzyl-3,4,6-tri-*O*-acetylated OFox imidate **13** was performed from the corresponding bromide **12**[14] in 80% yield (entry 7). The formation of OFox imidates in all cases was confirmed by detecting changes in the ^{19}F NMR signals from -112.4 ppm for 3,3-difluoro-2-oxindole to -121 to -122 ppm for the coupled product.[15] Interestingly, the formation of side products such as *N*-glycosides or 1,2-dehydro derivatives (glycals) seen in other imidate syntheses[16] was practically absent in the case of OFox imidates.

Table 1. Synthesis of 3,3-difluoro-3*H*-indol-2-yl (OFox) imidates



precursor HOFox OFox imidate

Entry	Precursor	Conditions	Product (yield, α/β ratio)
1	 **1**	HOFox, Ag_2O, DIPEA, toluene, rt, 6 h	 **5** (80%, α only)
2	 **2**	HOFox, Ag_2O, DIPEA, CH_2Cl_2, rt, 10 h	 **6** (75%, α only)
3	 **3**	i) 33% HBr/AcOH, CH_2Cl_2; ii) HOFox, Ag_2O, DIPEA, CH_2Cl_2, 0 °C to rt, 6 h	 **7** (75%, β only)
4	 **4**	i) 33% HBr/AcOH, CH_2Cl_2, ii) HOFox, Ag_2O, DIPEA, CH_2Cl_2, rt, 2.5 h	 **8** (84%, α only)
5	 **9**	i) $SOCl_2$, DMF, CH_2Cl_2; ii) HOFox, Ag_2O, DIPEA, CH_2Cl_2, rt, 8 h	 **10** (62%, 10/1)
6	 **11**	NIS, HOFox, CH_2Cl_2, rt, 1 h	**10** (95%, 9.0/1)
7[a]	 **12**	HOFox, Ag_2O, DIPEA, CH_2Cl_2, 0 °C, 40 min	 **13** (80%, β only)

[a] – reactions at rt for prolonged time (5 h) lead to the exclusive formation of the corresponding α-linked OFox imidate (81% yield)

With success in synthesizing a variety of OFox imidates, we turned our attention to studying the glycosidation of per-acylated

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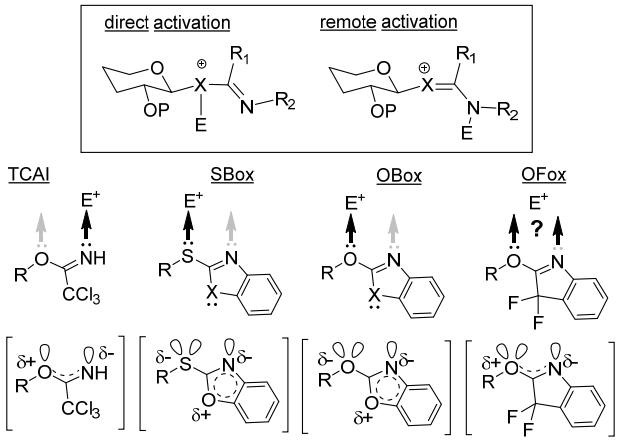
compounds **5-8** with selected representative glycosyl acceptors **14-17**. A majority of leaving groups in carbohydrate chemistry, even the most reactive ones, would not depart on their own. Instead, the leaving group departure is typically affected via the interaction with electrophilic promoters. Resultantly, the leaving group ability is enhanced and it departs as neutral species or a complex.[2c] For the glycosyl imidate series, the activation can take place either directly, via the anomeric atom (oxygen or sulfur), or remotely, via the nitrogen atom as depicted in Figure 1. For instance, it has become common knowledge that TCAI donors are activated via the remote nitrogen.[2c]

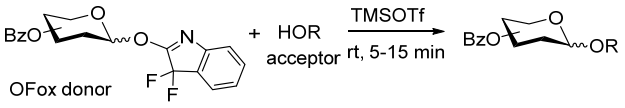
Figure 1. Direct vs. remote activation of S- and O-imidates

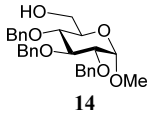
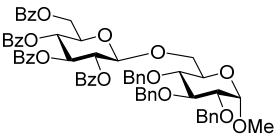
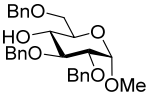
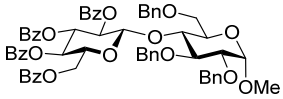
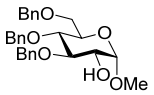
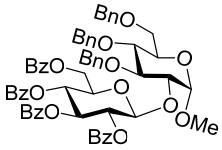
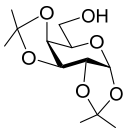
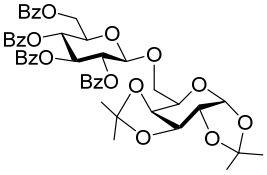
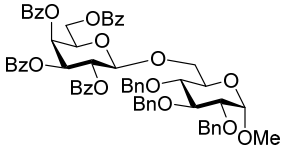
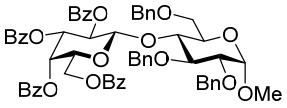
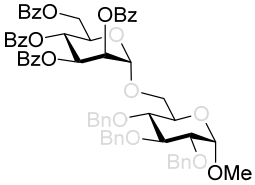
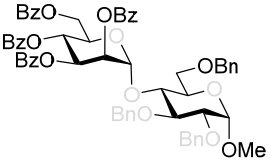


In principle, the activation mode can be determined by means of isolation and characterization of the departed aglycone that represents the leaving group-promoter conjugate. As previously shown in our laboratory, S-thiazolinyl donors are activated via the remote nitrogen.[17] In strong contrast, bicyclic leaving groups SBox or OBox are activated via the anomeric sulfur or oxygen atom, respectively (Figure 1).[18] This is due to the propensity of the benzoxazolyl group to retain the aromaticity of its heterocyclic ring, which otherwise would have been disrupted if the activation were taking place via the endocyclic nitrogen. In regards to the OFox imidates, the five-membered ring is non-aromatic, therefore, our working hypothesis was that the activation of the OFox leaving group takes place via the remote nitrogen atom. However, regardless of the activator used (vide infra), the isolation of the departed leaving group as an elusive OFox-promoter conjugate was proven impossible at this stage. All glycosylation reactions with OFox imidates, even deactivated per-O-benzoylated ones, were completed in a matter of minutes in the presence of a catalytic amount of the promoter. Instead, only "free" HOFox could be isolated from the reaction medium because the departed aglycone would release the activator creating the basis for exploring the HOFox mediated regenerative glycosylation disclosed previously.[7]

It has been previously demonstrated that the activation of O-imidoyl glycosyl donors TCAI, PTFAI, OBox) can be accomplished in the presence of the catalytic amount of promoters including TMSOTf,[19] BF_3-Et_2O,[20] *p*-TsOH,[21] $Bi(OTf)_3$,[22] $Yb(OTf)_3$,[23] $Sm(OTf)_3$,[23] AgOTf,[24] MeOTf,[6b] Among these, TMSOTf is arguably the most commonly used promoter. Hence, our initial focus has been centered on examining the effect of this activator on OFox glycosides. Unfortunately, the reaction of per-acetylated OFox donor **5** with glycosyl acceptor **14**[25] in the presence of TMSOTf gave low yields for the formation of the corresponding disaccharide (<50% yield).

Table 2. Glycosylation with per-benzoylated OFox donors **6-8**



Entry	Donor	Acceptor	Product (yield)
1	**6**	 **14**	 **18** (94%)
2	**6**	 **15**	 **19** (86%)
3	**6**	 **16**	 **20** (93%)
4	**6**	 **17**	 **21** (90%)
5	**7**	**14**	 **22** (98%)
6	**7**	**15**	 **23** (98%)
7	**8**	**14**	 **24** (93%)
8	**8**	**15**	 **25** (90%)

We note that the low yield is mainly attributed to high rates of the competing acetyl migration to the C-6 of the glycosyl acceptor. Similarly to our previous study with OBox imidates,[6b] we were able to overcome this issue by performing this

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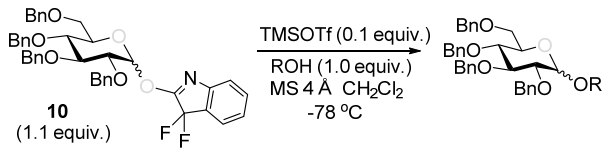
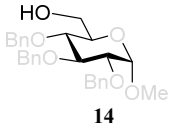
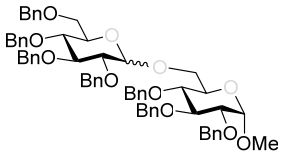
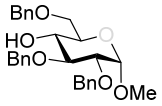
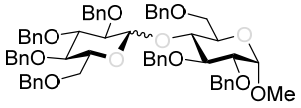
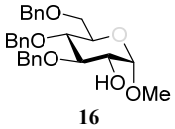
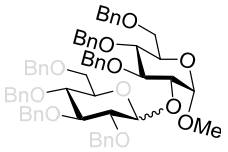
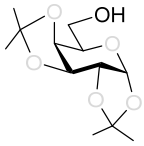
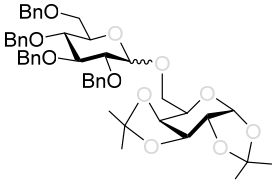
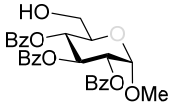
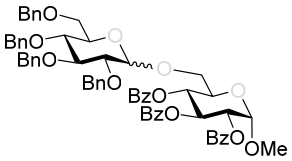
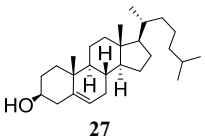
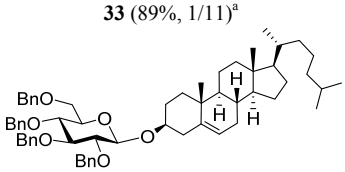
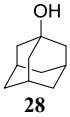
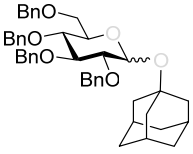
glycosylation reaction using $SnCl_4$ as an activator. This reaction led to the formation of the corresponding disaccharide in a respectable 80% yield. Nevertheless, to avoid complications related to the competing acetyl migration, further study was conducted with per-benzoylated OFox imidates of the D-gluco, D-galacto, and D-manno series (**6-8**). All glycosylations summarized in Table 2 proceeded smoothly in the presence of TMSOTf (0.1 equiv. to donor), completed in minutes and provided excellent yields for the formation of disaccharides **18-25** (86% and higher). Complete 1,2-*trans* stereoselectivity due to the participatory effect of the 2-*O*-benzoyl substituent was recorded in each case.

We were then bound to extend the scope of the OFox glycosylation methodology to per-benzylated OFox imidate **10** with the intention of gaining access to 1,2-*cis* glycosidic linkage. For this study, we chose TMSOTf as the promoter and a set of structurally diverse glycosyl acceptors (**14-17**, **26-28**) ranging from highly reactive primary alcohols to sterically hindered and/or less reactive alcohols. All reactions were performed at -78 °C due to the anticipated high reactivity of **10**. The results of this study are summarized in Table 3. Glycosidation of donor **10** with primary acceptor **14** gave glycoside **29** in 94% yield and a nearly complete β-selectivity (α/β = 1/24, entry 1). Reactions with secondary acceptors **15**[25] and **16**[25] were still β-selective and disaccharides **30** and **31** were obtained in high yields over 90% and moderate selectivity (up to α/β = 1/4-6, entries 2 and 3). Along similar lines, glycosylations with other primary acceptors **17** and **26**[26] as well as more sterically hindered alcohols, cholesterol **27** and adamantanol **28**, were all β-selective. The respective products **32-35** were obtained in high yields (85-89%) and high 1,2-*trans* selectivity (up to complete β, entries 4-7). It is noteworthy that the high β-selectivity obtained from glycosyl donors without the neighboring participating acyl group is relatively rare. While rather unexpected, these glycosylations indicate that OFox glycosyl donor **10** can be used to obtain β-linked glycosides in high yields and selectivities.

Encouraged by the high selectivity and overall high reactivity of OFox imidates, we decided to explore the effect that different experimental conditions and factors may have on stereoselectivity. The effect of solvents on the stereoselectivity of glycosylation has been studied for a long time and resulted in a good level of understanding of the modes by which solvents may affect the reaction. For instance, it has been shown that nitrilic solvents strongly favor the formation of equatorial (β-D) glycosides, whereas ethereal solvents are often beneficial for the synthesis of axial (α-D) glycosides.[27] As aforementioned, glycosylation of per-O-benzylated OFox donor **10** with primary glycosyl acceptor **14** in the presence of TMSOTf (10 mol %) at -78 °C produced disaccharide **29** in 94% yield and excellent β-selectivity (α/β = 1/24, entry 1, Table 3). A similar result was obtained with the reduced amount of TMSOTf to 5 mol % (entry 1, Table 4). With the exploration of the solvent effect on the stereoselectivity of glycosidation of OFox donors in mind, the reaction in CH_2Cl_2 (entry 1) was chosen as the benchmark. Along this study, we also investigated the temperature effect of glycosylation with OFox imidates with the anticipation that low temperatures will favor the equatorial (kinetic) product, whereas high temperature would be beneficial for axial (thermodynamic) product.

Table 3. TMSOTf-promoted glycosidation of OFox donor **10** with acceptors **14-17**, **26-28.**



Entry	Acceptor	Product (yield, α/β ratio)
1	 **14**	 **29** (94%, 1/24)[a]
2	 **15**	 **30** (94%, 1/4.0)[a]
3	 **16**	 **31** (90%, 1/6.0)[a]
4	 **17**	 **32** (85%, 1/12)[a]
5	 **26**	 **33** (89%, 1/11)[a]
6	 **27**	 **34** (86%, β only)
7	 **28**	 **35** (88%, 1/23)

[a] – the β-selectivity of these reactions could be further enhanced by using EtCN as the reaction solvent (*vide infra*)

Glycosylation of per-O-benzylated OFox donor **10** with primary glycosyl acceptor **14** in the presence of TMSOTf (5 mol %) at -40 °C produced disaccharide **29** in an excellent yield of 94%, but the β-selectivity was significantly reduced (α/β = 1/8.0, entry 2, Table 4). A similar glycosylation of per-O-benzylated OFox donor **10** performed at rt produced disaccharide **29** in an excellent yield of 93%, but practically no stereoselectivity (α/β =

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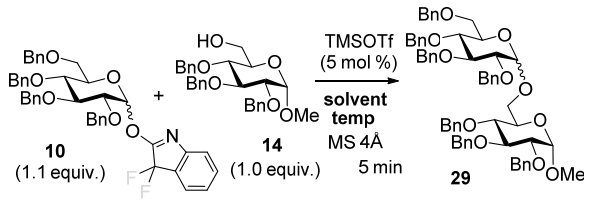
1/1.2, entry 3, Table 4). The β-selectivity was enhanced by changing the reaction solvent from CH_2Cl_2 to CH_3CN. Under these reaction conditions disaccharide **29** was obtained in 87% yield (α/β = 1/14, entry 4). Interestingly, when a solvent mixture of CH_2Cl_2/CH_3CN (1/2, v/v) was used a decreased in stereoselectivity in comparison to the results achieved with both of these solvents individually was recorded (α/β = 1/6.0, entry 5).

Table 4. The solvent and temperature effects on glycosidation of OFox donor **10**.



Entry	Solvent	Temp	Yield of **29**	α/β ratio
1	CH_2Cl_2	-78 °C	94%	1/24
2	CH_2Cl_2	-40 °C	97%	1/8.0
3	CH_2Cl_2	rt	93%	1/1.2
4	CH_3CN	-40 °C	87%	1/14
5	CH_2Cl_2/CH_3CN (1/2, v/v)	-40 °C	96%	1/6.0
6	CH_2Cl_2/CH_3CN/EtCN (1/2/1, v/v/v)	-78 °C	99%	β only
7	EtCN	-78 °C	99%	β only
8	Et_2O	-78 °C	84%	1/5.0
9	Et_2O	50 °C	81%	1.6/1

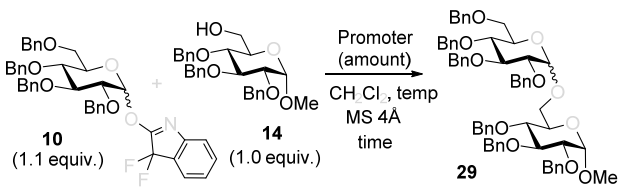
The use of acetonitrile as the reaction solvent has its limitations because the reactions cannot be cooled below -40 °C. Therefore, to achieve direct comparison of excellent β-selectivity (α/β = 1/24, entry 1) obtained in CH_2Cl_2 at -78 °C we incorporated propionitrile (EtCN) in our study. To our delight, when CH_3CN was used either as an additive or neat, disaccharide **29** was obtained in a nearly quantitative yield and complete β-stereoselectivity (entries 6 and 7). Along similar lines, the effect of diethyl ether as the reaction solvent was also investigated. Since diethyl ether favors the formation of α-glucosides, we observed reduced β-stereoselectivity in reactions at -78 °C (α/β = 1/5.0, entry 8). The same reaction performed at higher temperatures of 50 °C, gave disaccharide **29** with preferential α-stereoselectivity (α/β = 1.6/1, entry 9). A similar result was obtained using THF as the reaction solvent (not shown).

With the establishment of the effect of EtCN on stereoselectivity, we decided to reevaluate reactions performed earlier, particularly those where somewhat lower β-stereoselectivity was recorded, Table 3, entries 2-6 in particular. Thus, the synthesis of **30** yielded enhanced α/β selectivity from 1/4.0 to 1/12; **31** from 1/6.0 to 1/15; **32** from 1/12 to β-only; and **33** from 1/11 to 1/18 with practically the same yield.

A result of this study confirmed that OFox imidates adequately respond to the solvent and temperature effects. A similar trend to that established for other classes of glycosyl donors was also observed herein. As an expansion of this study, we decided to investigate whether other Lewis acid activators would provide further enhancement of the methodology. A study dedicated to the activation of OFox imidate **10** using other promoters is summarized in Table 5. Glycosylation using TMSOTf as the promoter has been used as the benchmark (entry 1). Using BF_3-Et_2O, $Cu(OTf)_2$ or MeOTf as promoters gave very comparable results (entries 2-4) to those achieved with TMSOTf. All of these reactions proceeded with a nearly complete β-selectivity for the formation of disaccharide **29**, which is rather uncommon for benzylated glycosyl donors.

When metal salt-based promoters AgOTf or $PdCl_2$ were used, the reactions became much slower, did not proceed to completion even in 24-36 h (entries 5 and 6). $Bi(OTf)_3$-promoted reactions were swift (entry 7), but the stereoselectivity has dropped in all cases of metal promoter-based activations. To reinforce this finding further, we were curious to investigate whether OFox imidate **10** is capable of providing α-stereoselectivity. For this purpose we chose trimethylsilyl perchlorate ($TMSClO_4$) as an activator because our independent study showed that perchlorates typically outperform other counter ions and provide superior α-selectivity.[28] Thus, reaction in the presence of $TMSClO_4$ in diethyl ether gave disaccharide **29** in 75% yield in enhanced α-selectivity (α/β = 5.0/1, entry 9). A similar stereoselectivity albeit a reduced yield was achieved using diethyl ether/1,4-dioxane (1/1, v/v) as a solvent mixture (not shown).

Table 5. The effect of promoter on the stereoselectivity of glycosidation of OFox donor **10**.



Entry	Promoter (equiv.)	Temp, time	Yield of **29**	α/β ratio
1	TMSOTf (0.05 equiv.)	-78 °C, 5 min	94%	1/24
2	BF_3-OEt_2 (0.1 equiv.)	-78 °C, 5 min	93%	1/20
3	$Cu(OTf)_2$ (0.2 equiv.)	-78 °C, 5 min	97%	β only
4	MeOTf (0.2 equiv.)	-78 °C, 10 min	91%	1/>25
5	AgOTf (0.5 equiv.)	rt, 24 h	71%	1/1.6
6	$PdCl_2$ (0.3 equiv.)	rt, 36 h	57%	1/1.7
7	$Bi(OTf)_3$ (0.1 equiv.)	-78 °C, 5 min	85%	1/7
8[a]	$TMSClO_4$ (0.1 equiv.)[a]	rt, 5 min	75%	5.0/1

[a] – Et_2O was used as the reaction solvent

As a result of the preliminary screening of reaction conditions; we conclude that reactions in the presence of 5 mol % of TMSOTf in either CH_2Cl_2 or EtCN at -78 °C are the most effective reaction conditions for glycosidation of OFox imidate **10**. Since per-benzylated OFox donor **10** was β-selective, in the expansion of our studies we decided to investigate whether other common O-imidates behave similarly under essentially the same reaction conditions. For these studies we acquired similarly protected TCAI and PTFAI **36** and **37**, respectively.

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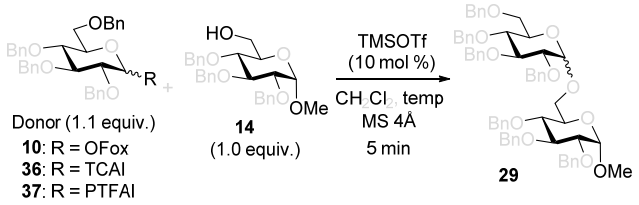
Glycosidations of **10** with acceptor **14** in the presence of TMSOTf either at -78 °C or ambient temperature were used as the benchmark (entries 1 and 2, Table 6). Coupling of all three glycosyl donors **10**, **36**,[29] and **37**[5a] with acceptor **14** produced disaccharide **29** in 5 min at either temperature in comparable yields and stereoselectivities. Comparable results were obtained in BF_3-OEt_2 promoted glycosylations (not shown). Nevertheless, the highest β-stereoselectivity amongst all was achieved with OFox donor **10** at -78 °C (entry 1).

Table 6. Comparative investigation of glycosylations with *O*-imidates **10**, **36**, and **37.**



Entry	Donor	Temp.	Yield of **29**	Ratio, α/β
1	**10**	-78 °C	94%	1/24
2	**10**	rt	93%	1/1.2
3	**36**	-78 °C	92%	1/15
4	**36**	rt	94%	4.0/1
5	**37**	-78 °C	70%	1/4.4
6	**37**	rt	91%	1/2.2

Since per-benzylated OFox donor **10** was generally very β-selective, in the expansion of our studies to obtaining 1,2-*cis* glycosides we wanted to investigate whether OFox imidates with other protecting groups would be more suitable for our purpose. For instance, we were particularly interested in investigating glycosyl donors with the superdisarming 2-O-benzyl-3,4,6-tri-O-acyl protecting group pattern. In the unrelated study, thioglycoside donors equipped with this protecting group pattern allowed us to obtaining complete α-selectivities, whereas glycosyl donors with multiple benzyl groups gave much lower stereoselectivity.[30] For this purpose, OFox imidate **13** was subjected to exploratory glycosylations. Since both α-**13** and **β-13** could be obtained individually (*vide supra*), first we wanted to look into the possible effect of the anomeric group orientation on the stereoselectivity of glycosylations. As a result of this experimentation, we determined that either **α-13** or **β-13** is capable of providing the corresponding disaccharide **38** in a practically identical yield of 88-89%. Most noteworthy, complete α-stereoselectivity was achieved in both cases (Table 7, entries 1 and 2). In this context, although perbenzylated OFox donor **10** was used as the anomeric mixture (α/β = 10/1), a test reaction with pure α-**10** gave essentially the same result: disaccharide **29** was obtained in 94% yield with excellent selectivity of α/β = 1/24. This study helps to exclude the uncertainty arising from the impact of the differential anomeric orientation between donors **10** (used as α-mainly) and donor **13** that is used as β-only due to the readiness of its synthesis. Irrespective of the orientation of the OFox group of the glycosyl donor, essentially the same stereoselectivity was achieved.

Being encouraged by excellent stereoselectivity achieved with 2-OH acceptor **16**, we moved on to explore other glycosyl acceptors. For instance, 4-OH acceptor **15** also provided complete α-stereoselectivity, but the corresponding disaccharide **39** was isolated in a modest yield of 70% (entry 3). The outcome of this coupling could be improved by using excess donor 13 (1.8 equiv. in respect to the acceptor) necessary to overcome the mismatch between the highly reactive OFox donor and hindered 4-OH acceptor. As a result, disaccharide **39** was obtained in 99% yield, still with complete α-stereoselectivity (entry 4). Upon further exploration of this approach, we noticed that other, more reactive glycosyl acceptors may lead to a reduced stereoselectivity. Thus, glycosylation of 3-OH acceptor **40** produced disaccharide **41** in 79% yield an a reduced stereoselectivity of α/β = 10/1 (entry 5). Since all reactions with the OFox imidate donors are quite swift, we assumed that slowing the reaction would help to gain a better control of the outcome in general, and stereoselectivity in particular. This was attempted by diluting the reaction mixture. All previous reactions have been performed under the standard dilution, typical for glycosylation reactions, 50 mM concentration of the donor. Since the donor-acceptor ratio may vary, we standardized the reaction conditions by maintaining the concentration of the glycosyl acceptor, 45 mM for glycosylations with 1.1 equiv. excess of the donor. When the glycosylation between donor **13** and acceptor **40** was performed at 9 mM concentration of the latter, five-fold dilution in respect to the standard conditions used previously, a significant enhancement of stereoselectivity was recorded. Thus, disaccharide **41** was obtained in 72% yield and α/β = 20/1 (entry 6). The impact of the five-fold dilution on the reaction rate was modest, but the reaction did not proceed to completion, and the unreacted acceptor **40** was still remaining even after 18 h. This was addressed by upping the amount of the donor to 1.5 equiv. As a result, disaccharide **41** was obtained in 80% yield, and excellent stereoselectivity was maintained (α/β = 21/1, entry 7).

Further drop in stereoselectivity was observed with the highly reactive primary acceptor **14**. Under normal concentration (45 mM of **14**) disaccharide **42** was obtained in 88% with very poor stereoselectivity α/β = 1.7/1 (entry 8). Repeating this reaction at low concentration (9 mM of **14**) immediately boosted stereoselectivity to α/β = 6.0/1 and disaccharide **42** was isolated in 78% yield (entry 9). Since this five-fold dilution had practically no effect on the rate of the reaction, we continued experimenting and performed the coupling at 4.5 mM concentration of acceptor **14**. Again, no visible rate reduction was detected and disaccharide **42** was isolated in 86% with further enhancement in stereoselectivity α/β = 9.0/1 (entry 10). Experiments with further dilution (up to 1.5 mM of **14**) required the increased amount of donor **13** (1.5 equiv.) to maintain high rates and yields. As a result, disaccharide **42** was obtained in 30 min in 95% yield with an improved stereoselectivity α/β = 12/1 (entry 11). Finally, we investigated glycosyl acceptor **26** with the anticipation that the decreased nucleophilicity due to multiple ester protecting groups would help to obtain high stereoselectivity. Indeed, glycosylation of **26** under the regular concentration conditions gave disaccharide **43** in 89% α/β = 5.2/1 (entry 12), which was a three-fold enhancement for stereoselectivity obtained with acceptor **14** under the same reaction conditions (compare with entry 8). This outcome could be further improved in high dilution conditions, 9 mM of **26**, which led to the formation of disaccharide **43** in 96% yield and excellent stereoselectivity α/β = 18/1 (entry 13).

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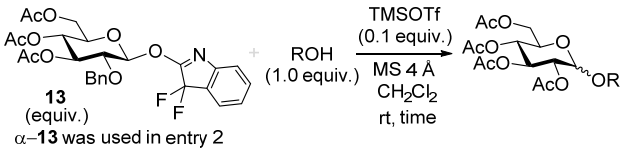
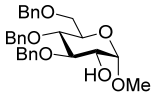
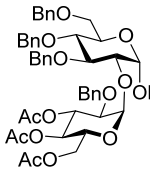
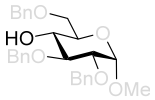
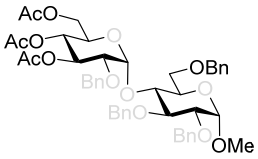
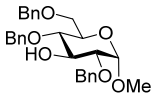
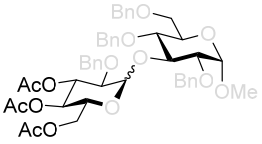
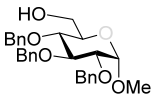
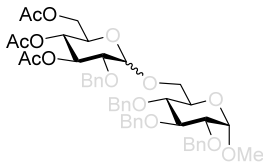
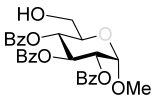
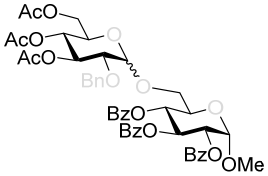
Table 7. Investigation of the stereoselectivity of glycosidation of OFox donor **13**



α–**13** was used in entry 2

Entry	**13** (equiv.)	ROH (conc.)	Product (time, yield, α/β ratio)
1	1.10	 **16** (45 mM)	 **38** (15 min, 88%, α only)
2	1.10[a]	**16** (45 mM)	**38** (15 min, 89%, α only)
3	1.10	 **15** (45 mM)	 **39** (5 min, 70%, α only)
4	1.80	**15** (45 mM)	**39** (5 min, 99%, α only)
5	1.10	 **40** (45 mM)	 **41** (5 min, 79%, 10/1)
6	1.10	**40** (9 mM)	**41** (18 h, 72%, 20/1)[b]
7	1.50	**40** (9 mM)	**41** (5 min, 80%, 21/1)
8	1.10	 **14** (45 mM)	 **42** (5 min, 88%, 1.7/1)
9	1.10	**14** (9 mM)	**42** (5 min, 78%, 6.8/1)
10	1.10	**14** (4.5 mM)	**42** (5 min, 86%, 9.0/1)
11	1.50	**14** (1.5 mM)	**42** (30 min, 95%, 12/1)
12	1.10	 **26** (45 mM)	 **43** (5 min, 89%, 5.2/1)
13	1.10	**26** (9.0 mM)	**43** (10 min, 96%, 18/1)

[a] – α-configured OFox donor (**α-13**) was used for comparison; [b] – the reaction did not go to completion even after 18 h

Interestingly, further dilution led to decreased stereoselectivity, thus, reaction performed at 4.5 mM of **26** gave disaccharide **43** with selectivity α/β = 7.2/1 (no details are provided). In a further attempt to enhance the stereoselectivity, we also explored the solvent effect on the glycosylations with donor **13**. However, the effect of reaction solvents that typically favor the formation of axially oriented products, such as 1,4-dioxane, diethyl ether, THF or toluene, used either neat or in combination with halogenated solvents, dichloromethane, 1,2-dichloroethane or chloroform was negligible (no details have been provided).

For conducting the comparative hydrolytic stability studies, per-benzoylated OFox glycosyl donor **6** was compared with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **44**[6b, 31] and 2,3,4,6-tetra-*O*-benzoyl-α,β-D-glucopyranosyl *N*-phenyltrifluoroacetimidate **45**.[5a] These studies summarized in Table 8 were performed in the presence of various Lewis acids in wet $ClCH_2CH_2Cl$ and quantitative estimates were made at 1, 16 and 24 h time points and are based on the accumulation of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose **46**, as observed by TLC. Thus, in the presence of BF_3-OEt_2 as the activator OFox imidate **6** underwent a nearly quantitative hydrolysis in 1 h, whereas TCAI **44** and PTFAI **45** counterparts showed 50% and 40% hydrolysis, respectively, in 1h of reaction (Table 8, entries 1-3). Imidates **44** and **45** were still present even after 24 h.

On the other hand, practically no hydrolysis in cases of all three imidates took place in the presence of $Bi(OTf)_3$ (0.1 equiv., entries 4-6). In a similar series of experiments, we determined that PTFAI **45** showed the highest stability in comparison with the OFox donor **6** and TCAI counterpart **44** under MeOTf-mediated activation conditions (entries 7-9). Conversely, we found out that under $PdCl_2$ mediated reactions OFox donor **6** shows the highest stability followed by TCAI donor **44** with PTFAI counterpart **45** being the least stable (entries 10-12).

Conclusions

A new class of compounds, OFox imidates, with various protecting groups have been synthesized in high yields from a variety of precursors. The OFox imidates are very reactive and depending on the protecting groups employed are suitable as glycosyl donors for the synthesis of 1,2-cis and 1,2-trans glycosides. These glycosylations show notable features such as operational simplicity, rapid reaction times, high yields and excellent stereocontrol in presence of Lewis acids used in catalytic amounts. Achieving high levels of β-stereoselectivity with per-benzylated OFox donors is an uncommon event in carbohydrate chemistry and the use of propionitrile as the reaction solvent can further enhance the stereoselectivity suggesting the solvent participation during glycosylation. High α-selectivities could also be achieved by using OFox of the superdisarmed series, particularly at high dilution conditions. This study complements a new regenerative concept for chemical glycosylation that proceeds via reactive glycosyl OFox intermediates and activation thereof in the catalytic fashion in situ. Very recently, we reported a high utility of donor **6** in HPLC-assisted automated oligosaccharide synthesis, which, however, was outperformed by more traditional TCAI imidates and showed similar efficacy to that of phosphates.[32] The exploration of both glycosylation pathways in application to the synthesis of oligosaccharides in solution and using solid-phases is currently underway in our laboratory.

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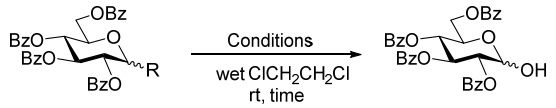
Table 8. Comparative hydrolytic stability study of OFox imidates, TCAI, and PTFAI.



46

6: R = OFox
44: R = TCAI
45: R = PTFAI

Entry	Donor	Conditions	% of hemiacetal **46** formed after		
			1 h	16 h	24 h
1	**6**	BF_3-Et_2O (0.1 equiv.)	quant.	---	---
2	**44**	BF_3-Et_2O (0.1 equiv.)	50	60	60
3	**45**	BF_3-Et_2O (0.1 equiv.)	40	50	50
4	**6**	$Bi(OTf)_3$ (0.1 equiv.)	0	0	0
5	**44**	$Bi(OTf)_3$ (0.1 equiv.)	0	0	0
6	**45**	$Bi(OTf)_3$ (0.1 equiv.)	0	0	0
7	**6**	MeOTf (1.0 equiv.)	0	quant.	---
8	**44**	MeOTf (1.0 equiv.)	0	0	20
9	**45**	MeOTf (1.0 equiv.)	0	0	0
10	**6**	$PdCl_2$ (0.1 equiv.)	0	0	50
11	**44**	$PdCl_2$ (0.1 equiv.)	0	10	quant.
12	**45**	$PdCl_2$ (0.1 equiv.)	0	70	quant.

Experimental

General. The reactions were performed using commercial reagents and the ACS grade solvents used for reactions were purified and dried in accordance with standard procedures. Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254}. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH_2Cl_2 and 1,2-dichloromethane (DCE) were distilled from CaH_2 directly prior to application. Molecular sieves (3 or 4 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C for 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-1020' polarimeter. ^{1}H NMR spectra were recorded at 300, 500 or 600 MHz, ^{13}C NMR spectra were recorded at 75, 125 or 150 MHz. The ^{1}H NMR chemical shifts are referenced to the signal of the residual $CHCl_3$ (δ_H = 7.27 ppm) for solutions in $CDCl_3$. The ^{13}C NMR chemical shifts are referenced to the central signal of $CDCl_3$ (δ_C = 77.23 ppm) for solutions in $CDCl_3$. The ^{19}F NMR chemical shifts are referenced to $CFCl_3$ (δ_F = 0 ppm) for solutions in $CDCl_3$. HRMS determinations were made with the use of a mass spectrometer with FAB ionization and ion-trap detection.

Synthesis of 3,3-difluoroxindole (HOFox, 3,3-difluoroindolin-2-one). HOFox was obtained from Isatin and DAST as previously described. Analytical data were in accordance with that previously reported.[8]

Synthesis of glycosyl donors

Method A. A typical procedure for the preparation from glycosyl bromides. A mixture of a glycosyl bromide (**1**, **2** or **12**, 0.15 mmol) and freshly activated molecular sieves (3 Å, 300 mg) in dry CH_2Cl_2 (1.0 mL) or toluene (1.0 mL) was stirred under argon for 1 h at rt. After that, 3,3-difluorooxindole (25.7 mg, 0.15 mmol), Ag_2O (105 mg, 0.45 mmol), and DIPEA (39.7 µL, 0.23 mmol) were added and the resulting mixture was stirred for 40 min - 10 h at the temperature indicated in Table 1. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~40 mL) was washed with 1% aq. NaOH (2 x 15 mL) and water (2 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the corresponding OFox imidates **5**, **6** or **13** in yields listed in Table 1.

Method B. A typical procedure for the preparation from pentabenzoates via glycosyl bromides. A 33% solution of HBr in AcOH (0.10 mL, 1.7 mmol) was added to a solution of a 1,2,3,4,6-penta-*O*-benzoyl-D-galacto or mannopyranose (**3** or **4**, 100 mg, 0.14 mmol) in dry CH_2Cl_2 (0.2 mL) and the resulting mixture was stirred under argon for 2-4 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (~40 mL) and washed with cold sat. aq. $NaHCO_3$ (2 x 15 mL) and cold water (2 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue containing crude glycosyl bromide (0.14 mmol) was dried under high vacuum for 4 h. After that, freshly activated molecular sieves (3 Å) and dry CH_2Cl_2 (1.4 mL) were added and the resulting mixture was stirred under argon for 1 h at rt. The resulting mixture was cooled to 0 °C in case of galactosyl bromide (rt for mannosyl bromide). 3,3-Difluorooxindole (26.7 mg, 0.16 mmol), Ag_2O (99.2 mg, 0.43 mmol) and DIPEA (37.4 µL, 0.21 mmol) were added and the resulting mixture was stirred for 2.5-6 h as indicated in Table 1. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~40 mL) was washed with 1% aq. NaOH (2 x 15 mL) and water (2 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the corresponding OFox imidates **7** or **8** in yields listed in Table 1.

Method C. A typical procedure for the preparation from hemiacetals via glycosyl chlorides. $SOCl_2$ (81.1 µL, 1.11 mmol) was added dropwise to a solution of hemiacetal **9** (0.20 g, 0.37 mmol) in dry CH_2Cl_2 (2.0 mL) and dry DMF (14.3 µL) and the resulting mixture was stirred under argon for 7 h at rt. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (~30 mL) and washed with sat. aq. $NaHCO_3$ (2 x 15 mL) and cold water (2 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue containing crude glycosyl halide (0.37 mmol) was dried under high vacuum for 4 h. Freshly activated molecular sieves (3 Å, 600 mg) and dry CH_2Cl_2 (2.0 mL) were added and the resulting mixture was stirred under argon for 1 h at rt. After that, 3,3-difluorooxindole (69 mg, 0.41 mmol), Ag_2O (258 mg, 1.11 mmol), and diisopropylethylamine (DIPEA, 97 µL, 0.56 mmol) were added and the resulting mixture was stirred for 8 h. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~40 mL) was washed with 1% aq. NaOH (2 x 15 mL) and water (2 x 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the corresponding OFox imidate **10** in 62% yield.

Method D. A typical procedure for the preparation from thioglycosides. A mixture of thioglycoside **11** (29 mg, 0.05 mmol) and freshly activated molecular sieves (4 Å, 100 mg) in dry CH_2Cl_2 (1.0 mL) was stirred under argon for 1 h at rt. After that, *N*-iodosuccinimide (NIS, 22.4 mg, 0.10 mmol) was added and the resulting mixture was stirred for 10 min. HOFox (8.55 mg, 0.05 mmol) was added and the reaction mixture was stirred for 1h at rt. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~20 mL) was washed with $NaHCO_3$ (5 mL) and water (2 x 5 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford OFox imidate **10** in 95% yield.

3,3-Difluoro-3*H*-indol-2-yl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (5). The title compound was obtained from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1**[10] by Method A in 62% yield as a white foam. Analytical data for **5**: R_f = 0.42 (ethyl

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acetate/ hexanes, 1/1, v/v); $[\alpha]_D^{21}$ +5.2 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 1.96, 1.97, 1.98, 2.01 (4 s, 12H, 4 x $COCH_3$), 3.95 (m, 1H, H-5), 4.15 (dd, 1H, $J_{5,6a}$ = 2.3 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.30 (dd, 1H, $J_{5,6b}$ = 4.3 Hz, H-6b), 5.17-5.32 (m, 3H, H-2, 3, 4), 5.95 (m, 1H, H-1), 7.14-7.40 (m, 4H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 20.4, 20.6 (x 2), 20.7, 61.4, 67.6, 70.3, 72.4, 72.9, 96.6, 120.5 (x 2), 123.3 (x 2), 126.2, 126.8, 133.6, 150.0, 169.3, 169.4, 170.2, 170.8 ppm; ^{19}F n.m.r.: δ, -122.4 (s, 1F, CF_2^a), -122.3 (s, 1F, CF_2^b) ppm; HR-FAB MS $[M+H]^+$ calculated for $C_{22}H_{23}F_2NO_{10}$ 500.1290, found 500.1361.

3,3-Difluoro-3*H*-indol-2-yl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (6). The title compound was obtained from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **2**[11] by Method A in 75% yield as a pale yellow foam. Analytical data for **6**: R_f = 0.41 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{23}$ +45.8 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 4.48 (dd, 1H, $J_{5,6a}$ = 4.7 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.64 (m, 2H, $J_{5,6b}$ = 2.3 Hz, H-5, 6b), 5.69 (dd, 1H, $J_{2,3}$ = 10.2 Hz, H-2), 5.83 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 6.31 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3), 6.82 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 7.05-7.99 (m, 24H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 62.4, 68.6, 70.1, 70.3, 70.6, 94.8, 120.6, 123.2, 126.0, 126.5, 128.3, 128.4 (x 2), 128.4 (x 2), 128.5 (x 4), 128.6 (x 2), 128.8, 129.1, 129.5, 129.7 (x 2), 129.8 (x 2), 130.0 (x 4), 133.1, 133.4, 133.5, 133.6, 133.7, 150.1, 165.2, 165.5, 165.6, 166.0 ppm; ^{19}F n.m.r.: δ, -121.8 (s, 1F, CF_2^a), -121.6 (s, 1F, CF_2^b) ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{31}F_2NO_{10}Na^+$ 770.1813, found 770.1800.

3,3-Difluoro-3*H*-indol-2-yl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (7). The title compound was obtained from 1,2,3,4,6-penta-*O*-benzoyl-D-galactopyranose **3** by Method B in 75% yield as a white foam. Analytical data for **7**: R_f = 0.39 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{22}$ +2.7 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 4.51 (dd, 1H, $J_{5,6a}$ = 5.9 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6a), 4.63 (m, 1H, H-5), 4.72 (dd, 1H, $J_{5,6b}$ = 6.6 Hz, H-6b), 5.75 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 6.11 (m, 2H, H-2, 4), 6.34 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 7.14-8.14 (m, 24H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 61.8, 67.6, 68.9, 71.4, 72.7, 97.4, 120.4, 123.6, 124.7, 125.4, 128.3, 128.6 (x 4), 128.7, 128.8, 128.9 (x 2), 129.0, 129.2 (x 2), 129.4, 129.9 (x 9), 130.1 (x 2), 133.3, 133.5, 133.6, 133.8, 165.1, 165.5 (x 2), 166.0 ppm; ^{19}F n.m.r.: δ, -122.2 (s, 2F, CF_2); HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{31}F_2NO_{10}Na^+$ 770.1813, found 770.1791.

3,3-Difluoro-3*H*-indol-2-yl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (8). The title compound was obtained from 1,2,3,4,6-penta-*O*-benzoyl-D-mannopyranose **4** by Method B in 84% yield as a white foam. Analytical data for **8**: R_f = 0.43 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{21}$ -5.3 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 4.52 (dd, 1H, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.62 (m, 1H, H-5), 4.70 (dd, 1H, $J_{5,6b}$ = 2.2 Hz, H-6b), 6.02 (dd, 1H, $J_{2,3}$ = 3.3 Hz, H-2), 6.07 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3), 6.24 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 6.64 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 7.16-8.09 (m, 24H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 62.5, 66.2, 69.0, 69.6, 71.5, 96.0, 121.0, 123.5, 125.5, 126.4, 126.8, 128.4, 128.5 (x 2), 128.6 (x 2), 128.7 (x 2), 128.8, 128.9 (x 2), 128.9, 129.0, 129.2, 129.8, 129.9 (x 2), 130.0 (x 2), 130.1 (x 4), 133.2, 133.6, 133.8, 134.0, 138.1, 165.2, 165.5, 165.6, 166.1 ppm; ^{19}F n.m.r.: δ, -121.8 (s, 1F, CF_2^a), -121.5 (s, 1F, CF_2^b); HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{31}F_2NO_{10}Na^+$ 770.1813, found 770.1814.

3,3-Difluoro-3*H*-indol-2-yl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside (10). The title compound was obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **9**[12] by Method C in 62% yield (α/β = 10/1) as a white foam. The title compound was also obtained from ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **11**[13] by Method D in 95% yield (α/β = 1/9.0). Analytical data for α-**10**: R_f = 0.43 (ethyl acetate/hexanes, 1/4, v/v); ^{1}H n.m.r. (300 MHz): δ, 3.66 (dd, 1H, $J_{5,6a}$ = 1.8 Hz, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.79 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 3.79 (dd, 1H, $J_{5,6b}$ = 3.3 Hz, H-6b), 3.83 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 4.01 (m, 1H, H-5), 4.13 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.52 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.69 (dd, 2H, ^2J = 10.5 Hz, CH_2Ph), 4.73 (s, 2H, CH_2Ph), 4.93 (dd, 2H, ^2J = 10.9 Hz, CH_2Ph), 6.50 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 7.11-7.42 (m, 24H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 68.1, 73.2, 73.5, 73.6 (x 2), 75.2, 75.3, 79.4, 81.5, 99.8, 117.4, 120.4, 123.3, 125.7, 127.8, 127.9, 128.0 (x 4), 128.0 (x 2), 128.1 (x 7), 128.6 (x 8), 133.6, 137.9, 138.0, 138.2, 138.8 ppm; ^{19}F n.m.r.: δ, -121.3 (s, 2F, CF_2) ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{39}F_2NO_6Na^+$ 714.2643, found 714.2645.

3,4,6-Tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide (12). The title compound was obtained from 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzyl-D-glucopyranose[33] in 90% yield as a white foam as previously described.[14] Analytical data for **12**: R_f = 0.43 (ethyl acetate/hexanes, 2/3, v/v); ^{1}H n.m.r. (300 MHz): δ, 1.96, 1.98, 2.00 (3s, 9H, 3 x $COCH_3$), 3.57 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.12 (m, 1H, $J_{5,6a}$ = 4.1 Hz, H-6a), 4.22 (m, 1H, H-5), 4.27 (dd, 1H, $J_{5,6b}$ = 4.0 Hz, $J_{6a,6b}$ = 12.6 Hz, 6b), 4.63 (dd, 2H, ^2J = 12.3 Hz, CH_2Ph), 5.06 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.48 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 6.34 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1) ppm; ^{13}C n.m.r. (75 MHz): δ, 20.8, 20.9 (x 2), 61.3, 67.3, 72.2 (x 2), 72.9, 76.5, 89.2, 128.1 (x 2), 128.5, 128.8 (x 2), 137.0, 169.9, 170.1, 170.7 ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{19}H_{23}BrO_8Na^+$ 481.0474, found 481.0483.

3,3-Difluoro-3*H*-indol-2-yl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-β-D-glucopyranoside (β-13). The title compound was obtained from **12** by Method A at 0 °C in 80% yield as a white foam. Analytical data for **β-13**: R_f = 0.39 (ethyl acetate/hexanes, 2/3, v/v); $[\alpha]_D^{26}$ +13.7 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 1.95, 2.03, 2.07 (3s, 9H, 3 x $COCH_3$), 3.80 (dd, 1H, $J_{2,3}$ = 7.9 Hz, H-2), 3.95 (m, 1H, H-5), 4.14 (dd, 1H, $J_{5,6a}$ = 2.3 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.34 (dd, 1H, $J_{5,6b}$ = 4.4 Hz, H-6b), 4.74 (dd, 2H, ^2J = 11.6 Hz, CH_2Ph), 5.11 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.27 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.94 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 7.18-7.49 (m, 9H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 20.7 (x 2), 20.8, 61.5, 67.9, 72.6, 73.6, 74.7, 77.6, 99.1, 120.6, 123.3, 126.2, 128.1 (x 2), 128.3 (x 3), 128.5 (x 3), 133.7, 137.1, 150.3, 169.7, 170.0, 170.7 ppm; ^{19}F n.m.r.: δ, -122.0 (d, 2F, CF_2) ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{27}H_{27}F_2NO_9Na^+$ 570.1552, found 570.1562.

3,3-Difluoro-3*H*-indol-2-yl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranoside (α-13). The title compound was obtained from 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide **12** by Method A at rt in 81% yield as a white foam. Analytical data for **α-13**: R_f = 0.38 (ethyl acetate/hexanes, 2/3, v/v); $[\alpha]_D^{25}$ +101.4 (*c* = 1.0, $CHCl_3$); ^{1}H n.m.r. (300 MHz): δ, 2.02, 2.03, 2.05 (3 s, 9H, 3 x $COCH_3$), 3.81 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 4.06 (dd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 12.4 Hz, H-6a), 4.18 (m, 1H, H-5), 4,29 (dd, 1H, $J_{5,6b}$ = 4.1 Hz, H-6b), 4.67 (s, 2H, CH_2Ph), 5.11 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 5.57 (d, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 6.45 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 7.17-7.40 (m, 9H, aromatic) ppm; ^{13}C n.m.r. (75 MHz): δ, 20.7 (x 2), 20.8, 61.4, 67.8, 69.8, 71.4, 73.3, 75.7, 95.0, 120.4, 123.3, 125.9, 126.8, 127.9 (x 3), 128.2, 128.6 (x 3), 133.5, 137.2, 150.4, 168.7, 169.8, 170.1 ppm; ^{19}F n.m.r.: δ, -121.6 (s, 1F, CF_2^a), -121.5 (s, 1F, CF_2^b); HR-FAB MS $[M+Na]^+$ calculated for $C_{27}H_{27}F_2NO_9Na^+$ 570.1552, found 570.1569.

2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl trichloroacetimidate (36). The title compound was obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **9**[12] in 62% yield as a white foam as previously described.[29] Analytical data for α-**36**: R_f = 0.43 (ethyl acetate/hexanes, 1/4 v/v); ^{1}H n.m.r. (300 MHz): δ, 3.67 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.74-3.80 (m, 3H, H-2, 4, 6b), 3.99 (m, 1H, $J_{5,6a}$ = 1.9 Hz, H-5), 4.05 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 4.53 (dd, 2H, ^2J = 12.0 Hz, CH_2Ph), 4.71 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 4.73 (dd, 2H, ^2J = 10.7 Hz, CH_2Ph), 4.84 (dd, 2H, ^2J = 10.6 Hz, CH_2Ph), 6.50 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 7.12-7.33 (m, 20H, aromatic), 8.57 (s, 1H, NH) ppm; ^{13}C n.m.r. (75 MHz): δ, 68.1, 73.0, 73.2, 73.6, 75.5, 75.8, 79.5, 81.5, 91.4, 94.5, 127.8 (x 3), 127.9 (x 2), 128.0, 128.1 (x 2), 128.2 (x 4), 128.5 (x 5), 128.6 (x 4), 137.9, 138.1, 138.2, 138.7, 161.4 ppm; HR-ESI MS $[M+Na]^+$ calculated for $C_{36}H_{36}Cl_3NO_6Na^+$ 706.1506, found 706.1500.

2,3,4-Tri-*O*-benzyl-α,β-D-glucopyranosyl *N*-phenyltrifluoroacetimidate (37). The title compound was obtained from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **9**[12] by adapting previously published procedure.[5a] K_2CO_3 (55 mg, 0.55 mmol) in acetone (1.5 mL) was added to a mixture of **9** (150 mg, 0.28 mmol)

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and 2,2,2,-trifluoro-*N*-phenylethanimidoyl chloride (89.4 µL, 0.55 mmol) and the resulting mixture was stirred for 3 h at rt. The solids were filtered off through a pad of Celite and the solvent was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound in 72% yield as a white amorphous solid. Analytical data for β-**37**: R_f = 0.5 (ethyl acetate/hexanes, 1/4, v/v); ^{1}H n.m.r. (500 MHz): δ, 3.56-3.95 (m, 6H, H-2, 3, 4, 5, 6a, 6b), 4.58 (dd, 2H, ^2J = 9.5 Hz, CH_2Ph), 4.69 (dd, 2H, ^2J = 12.2 Hz, CH_2Ph), 4.88 (s, 2H, CH_2Ph), 5.00 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 5.74 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 6.78-7.50 (m, 25H, aromatic); ^{13}C n.m.r. (75 MHz): δ, 73.6, 75.3, 75.4, 75.8 (x 2), 75.9 (x 2), 75.8, 81.1, 84.7, 119.5, 124.5, 127.9, 128.0 (x 2), 128.1 (x 3), 128.2 (x 3), 128.4 (x 2), 128.6 (x 6), 128.7 (x 6), 128.9 (x 2), 137.9, 138.1 (x 2), 138.5, 143.6 ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{40}F_3NO_6Na^+$ 734.2705, found 734.2720.

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (44). The title compound was obtained from 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose **46** in 83% yield as a white foam as previously described.[31] Analytical data for **44** was in accordance with that reported previously.[6b]

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl N-phenyltrifluoroacetimidate (45). The title compound was obtained from 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose **46** by adapting the previously published procedure.[5a] K_2CO_3 (0.54 g, 5.46 mmol) in acetone (20 mL) was added to a mixture of **46** (2.17 g, 3.64 mmol) and 2,2,2,-trifluoro-*N*-phenylethanimidoyl chloride (0.7 mL, 4.37 mmol) and the resulting mixture was stirred for 5 h at rt. The solids were filtered off through a pad of Celite and the solvent was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound in 86% yield as a white foam. Analytical data for α-**45**: R_f = 0.5 (ethyl acetate/hexanes, 3/7, v/v); $[\alpha]_D^{27}$ +49.4 (*c*= 1.0, $CHCl_3$); ^{1}H n.m.r. (500 MHz): δ, 4.51 (dd, 1H, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.69 (m, 1H, H-5), 4.77 (dd, 1H, $J_{5,6b}$ = 1.8 Hz, H-6b), 5.67 (dd, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 5.93 (dd, 1H, $J_{4,5}$ = 10.1 Hz, H-4), 6.30 (m, 3H, H-3, aromatic), 6.92 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 7.00-8.15 (m, 25H, aromatic) ppm; ^{13}C n.m.r. (125 MHz): δ, 62.4, 68.6, 70.0, 70.5, 70.8, 92.3, 119.1, 124.4, 128.6 (x 2), 128.7 (x 5), 128.8 (x 5), 128.9, 129.7, 129.9 (x 2), 130.0 (x 8), 133.3, 133.4, 133.7, 133.8, 142.8, 143.0, 165.2, 165.4, 165.7, 166.1; ^{19}F n.m.r.: δ, -65.51 (s, 3F, CF_3) ppm; HR-FAB MS $[M+Na]^+$ calculated for $C_{42}H_{32}F_3NO_{10}Na^+$ 790.1876, found 790.1886.

Synthesis of disaccharides

A typical glycosylation procedure and the synthesis of glycosides. A mixture of glycosyl donor (0.11 mmol or as indicated in Tables), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 or 4 Å, 90 mg) in CH_2Cl_2 (0.5 mL) or other solvent or amount required for high dilution experiments as indicated in Tables was stirred under argon for 1 h at rt. The mixture was cooled to -78 °C or other temperature as indicated in Tables, promoter (0.0055-0.11 mmol) was added, and the resulting mixture was stirred for the time as indicated in Tables. The solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (~40 mL) was washed with 1% aq. NaOH (2 x 10 mL) and water (2 x 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate - hexane gradient elution) to afford a glycoside derivative in yields listed in Tables.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (18). The title compound was obtained from donor **6** and acceptor **14**[25] as a clear film in 94% yield. Analytical data for **18** were essentially the same as reported previously.[25]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (19). The title compound was obtained from donor **6** and acceptor **15**[25] as a clear film in 86% yield. Analytical data for **19** were essentially the same as reported previously.[25]

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (20). The title compound was obtained from donor **6** and acceptor **16**[25] as a clear film in 93% yield. Analytical data for **20** were essentially the same as reported previously.[25]

6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (21). The title compound was obtained from donor **6** and acceptor **17** in 90% yield. Analytical data for **21** were essentially similar as reported previously.[16a]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (22). The title compound was obtained from donor **7** and acceptor **14**[25] as a clear film in 98% yield. Analytical data for **22** were essentially the same as reported previously.[34]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (23). The title compound was obtained from donor **7** and acceptor **15**[25] as a clear film in 98% yield. Analytical data for **23** were essentially the same as reported previously.[16a]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (24). The title compound was obtained from donor **8** and acceptor **14**[25] as a clear film in 93% yield. Analytical data for **24** were essentially the same as reported previously.[16a]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (25). The title compound was obtained from donor **8** and acceptor **15**[25] as a clear film in 90% yield. Analytical data for **25** were essentially the same as reported previously.[35]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (29). The title compound was obtained from donor **10** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **14**[25] in 57-99% yield (α/β ranging from 5.0/1 to β-only, see Tables). Analytical data for **29** was in accordance with that reported previously.[36]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (30). The title compound was obtained from donor **10** and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **15**[25] in CH_2Cl_2 or EtCN in 94% (α/β = 1/4) or 92% yield (α/β = 1/12), respectively. Analytical data for **30** was in accordance with that reported previously.[37]

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (31). The title compound was obtained by Method A from donor **10** and methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **16**[25] in CH_2Cl_2 or EtCN in 90% (α/β = 1/6.0) or 88% yield (α/β = 1/15), respectively. Analytical data for **31** was in accordance with that reported previously.[16a]

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (32). The title compound was obtained by Method A from donor **10** and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **17** in CH_2Cl_2 or EtCN as a clear film in 85% yield (α/β = 1/12) or 89% yield (β only), respectively. Analytical data for **32** was in accordance with that reported previously.[38]

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (33). The title compound was obtained from donor **10** and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **26**[26] in CH_2Cl_2 or EtCN as a clear film in 89% yield (α/β = 1/11) or 87% yield (α/β = 1/18), respectively. Analytical data for **33** was in accordance with that reported previously.[37]

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(3β)-Cholest-5-en-3-yl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (34). The title compound was obtained from donor **10** and (3β)-cholest-5-en-3-ol **27** as a white amorphous solid in 86% yield (β-only). Analytical data for **34** was in accordance with that reported previously.[39]

1-Adamantyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (35). The title compound was obtained from donor **10** and 1-adamantol **28** as a white amorphous solid in 88% yield (α/β = 1/23). Analytical data for **35** was in accordance with that reported previously.[39]

Methyl 2-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (38). The title compound was obtained from donor α-**13** or donor β-**13** and acceptor **16**[25] as a clear film in 89% or 88% yield (α only), respectively. Analytical data for **38** was in accordance with that reported previously.[16a]

Methyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (39). The title compound was obtained from donor **13** and acceptor **15**[25] as a clear film in 70% or 99% yield (α only). Analytical data for **39** was in accordance with that reported previously.[16a]

Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (41). The title compound was obtained from donor **13** and acceptor **40**[25] as a clear film in 72-80% yield (α/β = 10-21/1). Analytical data for **41** was in accordance with that reported previously.[40]

Methyl 6-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (42). The title compound was obtained from donor **13** and acceptor **14**[25] as a clear film in 78-95% yield (α/β = 1.7-12/1). ^{1}H n.m.r. (300 MHz): δ, 1.96, 1.97, 2.00 (3s, 9H, 3 x $COCH_3$), 3.35 (s, 3H, OCH_3), 3.37-3.42 (m, 1H, H-2), 3.48 (dd, 1H, $J_{2',3'}$ = 9.9 Hz, H-2'), 3.56 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.61-3.81 (m, 3H, H-5, 6a, 6b), 3.89-4.01 (m, 3H, $J_{5',6b'}$ = 4.4 Hz, H-3, 5', 6a'), 4.14 (dd, 1H, $J_{6a',6b'}$ = 12.5 Hz, H-6b'), 4.45-4.82 (m, 7H, H-1, 3 x CH_2Ph), 4.85-4.98 (m, 4H, $J_{1',2'}$ = 3.5 Hz, H-1', 4', CH_2Ph), 5.39 (dd, $J_{3',4'}$ = 9.7 Hz, 1H, H-3'), 7.16-7.36 (m, 20H, aromatic) ppm; ^{13}C n.m.r. (150 MHz): δ, 21.0, 55.4, 62.1, 66.4, 67.3, 68.8, 70.5, 71.9, 72.5, 73.5, 75.2, 75.9, 76.6, 77.8, 80.0, 82.3, 97.0, 98.2, 127.8 (x 3), 127.9 (x 3), 128.1 (x 3), 128.2 (x 3), 128.6 (x 3), 137.9, 138.3, 138.6, 138.9, 170.3, 170.6, 170.8. The remaining analytical data for **42** was in accordance with that reported previously.[16a]

Methyl 6-*O*-(3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (43). The title compound was obtained from donor **13** and acceptor **26**[26] as a clear film in 89-96% yield (α/β = 5.2-18/1). Analytical data for **43** was in accordance with that reported previously.[18]

Notes and references

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