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Methyl 1,2-Orthoesters as Useful Glycosyl Donors in Glycosylation Reactions: A Comparison with *n*-Pent-4-enyl 1,2-Orthoesters

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Dedicated to Professor Dr. Serafín Valverde (IQOG-CSIC) on the occasion of his retirement

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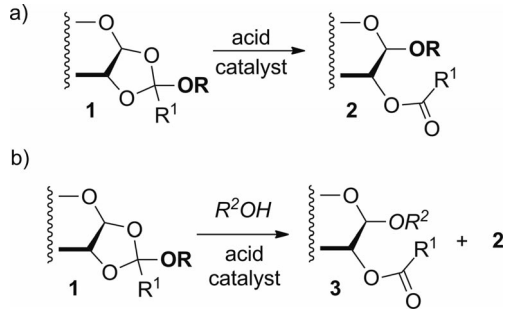
Mannopyranose-derived methyl 1,2-orthoacetates (R = Me) and -benzoates (R = Ph) can function as glycosyl donors – upon $BF_3{\cdot}Et_2O$ activation in CH_2Cl_2 – in glycosylation reactions with monosaccharide acceptors to afford disaccharides in good yields. In the process, glycosylation is preferred to acid-catalyzed rearrangement leading to methyl mannopyranosides. Methyl 1,2-orthoesters can be also used in regioselective glycosylation protocols with monosaccharide diols, in which they display good regioselectivity.

Introduction

The biological importance of oligosaccharides and glycoconjugates is now generally recognized.[1] Most carbohydrates found in nature exist as polysaccharides, glycoconjugates, or glycosides, in which sugar units are attached to one another or to aglycons through *O*-glycosidic bonds.[2] The stereoselective formation of *O*-glycosidic bonds is therefore the key process in most glycoside syntheses.[3] Over the years a variety of methods for the construction of interglycosidic bonds have been introduced. The most popular glycosylation donors include glycosyl trichloroacetimidates,[4] fluorides,[5] and sulfoxides,[6] as well as *n*-pent-4-enyl glycosides[7] and thioglycosides.[8] As well as these established donors, a variety of additional glycosyl donors have also been used in glycosylation protocols; examples include glycosyl bromides,[9] glycals,[10] glycosyl phosphates,[11] glycosyl phosphites,[12] glycosyl iodides,[13] thiazolyl thioglycosides,[14] benzoxazolyl thioglycosides,[15] 2′-carboxybenzyl (CB) glycosides,[16] glycosyl pent-4-enoates,[17] glycosyl benzyl and aryl phthalates,[18] and glycosyl *ortho*-alkynylbenzoates.[19]

Our research groups have recently been interested in the use of glycosyl 1,2-orthoesters as glycosyl donors. Glycosyl 1,2-orthoesters, such as **1** (Scheme 1), were first encountered by Emil Fischer and co-workers in 1920,[20] although it required 10 years before the then unusual structure was elucidated independently by Freudenberg,[21] Braun,[22] Haworth,[23] and their co-workers. The structural assignment was facilitated by observation of the acid-catalyzed rearrangement **1**→**2** (Scheme 1, a), in which the alkoxy residue was transferred from the orthoester to the anomeric center. This stereoselective process indicated that orthoesters such as **1** could function as glycosyl donors, and this feature played a seminal role in Isbell's discovery of neighboring-group participation.[24,25]



Scheme 1. Transformations involving alkyl 1,2-orthoesters.

In spite of this promising beginning, the use of 1,2-orthoesters as glycosyl donors was impeded by the process summarized in Scheme 1 (b). Under acid catalysis conditions, the departing alkoxy entity (**OR**) competed with the intended acceptor (R^2OH) for the anomeric center, resulting in a mixture of glycosides **2** and **3**.

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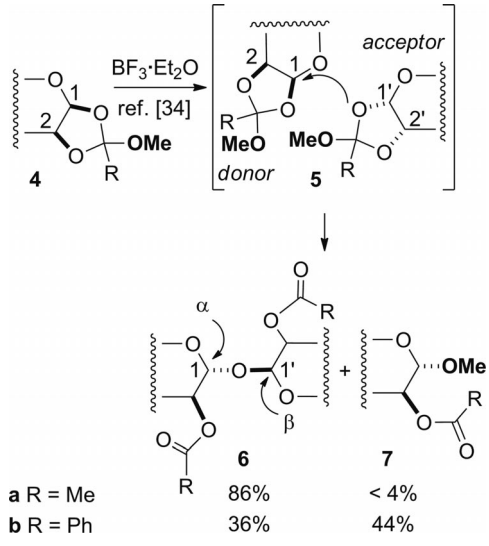
Extensive studies by Kotchetkov and co-workers directed towards overcoming this dilemma by modifying the orthoester leaving group did not solve the fundamental problem.[26,27] However the results were instructive, and led to much innovative chemistry.[28]

Fraser-Reid and co-workers introduced *n*-pent-4-enyl orthoesters (NPOEs, **1**, **R** = *n*-pent-4-enyl)[29] as useful glycosyl donors, the success of which is based on activation by halonium ion in a process in which the liberated pent-4-enyloxy moiety is trapped as a non-nucleophilic 2-(halomethyl)tetrahydrofuran.[30,31] The intended glycosyl acceptor therefore faces no significant competition.

On the other hand, the acid-catalyzed rearrangement **1**→**2** is a well-known process that has been successfully applied to the preparation of *trans*-(1–2) glycosides.[32] Indeed in our groups the method of choice for preparing *n*-pent-4-enyl glycosides (e.g., **2**, **R** = *n*-pent-4-enyl) requires preparation and rearrangement of the corresponding NPOEs (e.g., **1**, R = *n*-pent-4-enyl).[33]

In light of these precedents, we were surprised by the exceptional course of the reaction shown in Scheme 2.[34] The methyl mannopyranose orthoacetate **4a**, upon treatment with $BF_3{\cdot}Et_2O$, gave 1α,1′β-disaccharide **6a** (R = CH_3) with minor amounts of the expected methyl mannopyranose **7a** (R = CH_3). The corresponding orthobenzoate **4b** behaved similarly, although the proportions of products **6b** and **7b** were very different.



Scheme 2. An "unusual" reaction pathway for methyl orthoesters.

Clearly, self-coupling of two molecules of **4** had occurred, and the α/β orientations of compounds **6** provided vital mechanistic clues. The α-oriented anomeric centers in compounds **6** indicated that the *manno* orthoesters **4** functioned as glycosyl donors. In contrast, the β-orientations in compounds **6** implied that the *C*1–*O*1 bonds in precursors **4** had been preserved during the coupling. One equivalent of a compound **4** thus served as the donor, whereas another equivalent served as the acceptor.

The data in Scheme 2 showed that the self-coupling tendency was greater with orthoacetates than with the corresponding orthobenzoates. It was thus of interest to see whether or not this tendency could be reduced so that methyl orthoacetates could serve as glycosyl donors in acid-catalyzed reactions without the intrusion of self-condensation or acid-catalyzed rearrangement. Along these lines, we reasoned that the presence of external nucleophiles in the reaction media could lead to different glycosyl coupling derivatives.

In this work we have evaluated the potential of methyl 1,2-orthoesters (MeOEs) as glycosyl donors with monosaccharide alcohols as nucleophiles, and disclose here that MeOEs can be used as glycosyl donors and that they display good regioselectivities in glycosylation reactions with diol-acceptors leading to disaccharides.

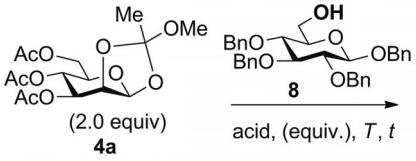
Results and Discussion

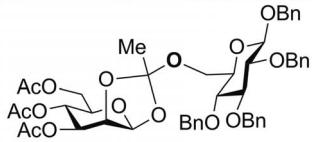
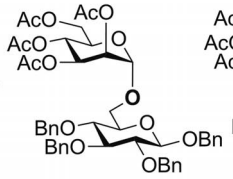
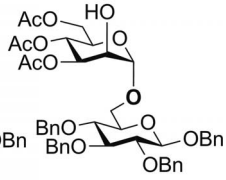
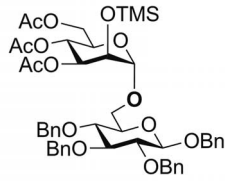
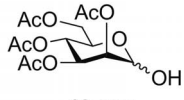
Glycosylation of Monosaccharide Acceptors with MeOEs

Initial glycosylation experiments were performed with MeOE **4a** (Table 1, 2.0 equiv.) and benzyl glycoside **8** in the presence of different acid promotors. The use of $Yb(OTf)_3$[35] (0 °C, 30 min) resulted in the formation of mixed orthoester **9** (99% yield), whereas extended reaction times (12 h) led to reduced yields of rearranged disaccharides **10a** and **11**, as well as hydrolysis and rearrangement products arising from **4a** (Table 1, Entries *i* and *ii*, respectively). When TMSOTf was used as the promoter, 2′-*O*-trimethylsilyl disaccharide **12** was obtained (80% yield, Table 1, Entry *iii*).[36] Finally, the use of *p*TsOH did not yield any disaccharide **10a** and resulted in the formation of hemiacetal **13** (Table 1, Entry *iv*).

In line with our previous observations,[34] $BF_3{\cdot}Et_2O$ proved to be the best acid promoter for employment in glycosylation reactions with MeOEs (see Table 2). In this context, the results obtained in a study directed towards optimization of the amounts of $BF_3{\cdot}Et_2O$, together with the MeOE/glycosyl acceptor ratios in these glycosylation reactions, are displayed in Table 2. According to these, the best results in the glycosylation of benzyl glucopyranoside **8** with MeOEs **4a** and **4b** were obtained with the use of an excess of $BF_3{\cdot}Et_2O$ (3.0 equiv.) when compared with the use of catalytic amounts of acid (0.05 equiv.) (Table 2, compare Entry *i* with Entries *ii* and *iii* and Entries *iv* and *v* with Entries *vi* and *vii*). On the other hand, the use of 2 equiv. of MeOE proved to be beneficial in increasing the observed yield of disaccharide **10**, when compared with the use of equimolar amounts of MeOE (Table 2, compare Entries *ii* and *iii* and Entries *iv* and *v*). From the data in Table 2, it also seems that methyl orthobenzoate **4b** gave slightly better yields of disaccharide **10** than orthoacetate **4a** (compare Entry *i* in Table 2 with Entry *iv*, Entry *ii* with Entry *vi*, and Entry *iii* with Entry *vii*). Comparison of Entries *vi* and *vii* in Table 2 shows that a twofold excess of MeOE **4b** might be obviated when highly reactive glycosyl acceptors are glycosylated.

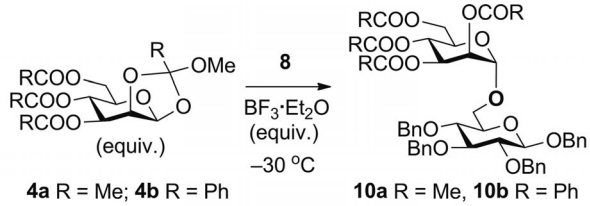
Table 1. Glycosylation of benzyl glucoside **8** with MeOE **4a** in the presence of different acid promotors.



Entry	Reaction conditions	Product(s), yield (%)
i	Yb(OTf)$_3$, (4.0), 0 °C, 30 min	 **9** (99)
ii	Yb(OTf)$_3$, (1.0), 0 °C, 12 h	 **10a** (17)[a]  **11** (<10)[a]
iii	TMSOTf, (3.0), –30 °C, 1 h	 **12** (80)
iv	*p*TsOH, (2.0), r.t., 1 h	 **13** (69)

[a] Other minor compounds were isolated, see Exp. Sect. for details.

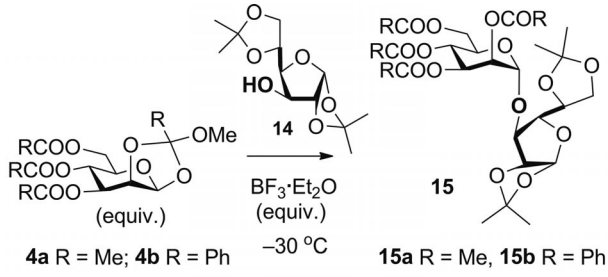
Table 2. Glycosylation of benzyl glucoside **8** with MeOEs **4a** and **4b**.



Entry	Orthoester (equiv.)	$BF_3{\cdot}Et_2O$ (equiv.)	Product	Yield (%)
i	**4a** (1)	0.05	**10a**	–[a]
ii	**4a** (1)	3.0	**10a**	40[b]
iii	**4a** (2)	3.0	**10a**	92[b]
iv	**4b** (1)	0.05	**10b**	43[b]
v	**4b** (2)	0.05	**10b**	54[b]
vi	**4b** (1)	3.0	**10b**	93[b]
vii	**4b** (2)	3.0	**10b**	95[b]

[a] Complex reaction mixture. [b] Other minor compounds were also isolated; see Exp. Sect. for details.

Table 3. Glycosylation of diacetone glucose **14** with MeOEs **4a** and **4b**.



Entry	Orthoester (equiv.)	$BF_3{\cdot}Et_2O$ (equiv.)	Product	Yield (%)
i	**4a** (2)	3.0	**15a**	–[a]
ii	**4b** (1)	3.0	**15b**	53[b]
iii	**4b** (2)	3.0	**15b**	70[b]

[a] Complex reaction mixture. [b] Other minor compounds were isolated; see Exp. Sect. for details.

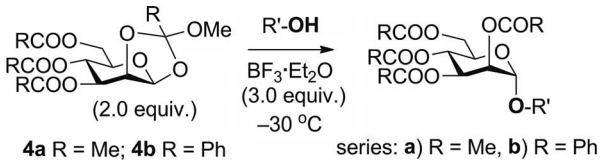
Glycosyl coupling of secondary hydroxy groups, represented by diacetone glucose **14** (Table 3), worked relatively well with orthobenzoate **4b** to give disaccharide **15b** (Table 3, Entries *ii* and *iii*), but failed when orthoacetate **4a** was used as the glycosyl donor (Table 3, Entry *i*). In these examples, the use of a twofold excess of MeOE **4b** resulted in a moderate yield increase from 53 to 70% in the formation of **15b** (Table 3, Entries *ii*, *iii*).

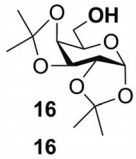
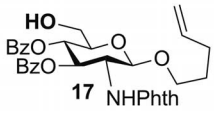
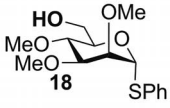
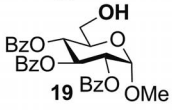
To complete this study, we selected glycosyl acceptors **16**–**19** (Table 4) and treated them with MeOEs **4a** or **4b** (2.0 equiv.) in CH_2Cl_2 at –30 °C in the presence of $BF_3{\cdot}Et_2O$ (3.0 equiv.) to give disaccharides **20**–**23**.

Under these reaction conditions, good to excellent yields of disaccharides were obtained (Entries *i*–*viii*, Table 4). A low yield of disaccharide **23a** was observed in the reaction between **4a** and tribenzoyl derivative **19** (Entry *vii*, Table 4). In keeping with our previous observations, methyl orthobenzoate **4b** consistently gave slightly better yields of disaccharides **20** to **23** than orthoacetate **4a** (see Entries *i* through *viii*, Table 4), although we do not at present have an explanation to account for these results.

The observed glycosylation byproducts arose from the orthoester employed (2.0 equiv.) and in the case of glycosylations with **4b** included variable amounts of the corresponding methyl mannopyranoside **7b** (12–28%, relative to MeOE), most likely arising from acid rearrangement of the excess MeOE employed. Small amounts of 1α,1′β-disaccharides could also be observed.[37]

Table 4. Glycosylation of monosaccharides **16**–**19** with MeOEs **4a** and **4b**.



Entry	Orthoester	Acceptor (R'-**OH**)	Product(s)	Yield (%)
i	**4a**	 **16**	**20a**	82[a]
ii	**4b**	**16**	**20b**	99[a]
iii	**4a**	 **17**	**21a**	87[a]
iv	**4b**	**17**	**21b**	92[a]
v	**4a**	 **18**	**22a**	73[a]
vi	**4b**	**18**	**22b**	95[a]
vii	**4a**	 **19**	**23a**	40[a]
viii	**4b**	**19**	**23b**	99[a]

[a] Other minor compounds were also isolated; see Exp. Sect. for details.

Glycosylation of Monosaccharide Diol Acceptors with MeOEs – A Comparative Regioselectivity Study

As a continuation of our interest in the study of regioselective glycosylation strategies,[38] we examined the behavior of methyl orthobenzoate **4b** towards monosaccharides **25**–**27**, containing primary/secondary diol pairs. The results obtained are displayed in Table 5, in which previous data from glycosylations of the same monosaccharide-diols with NPOE **24**[39] have also been included for purposes of comparison.

Treatment of glucose-derived diol **25** with **4b** at –30 °C (Table 5, Entry *i*) led to a mixture of the two possible disaccharides **28** (32%) and **29** (9%), as well as the doubly glycosylated trisaccharide product **30** (13%). When the reaction was repeated at –50 °C, slightly better regioselectivity was observed, with disaccharide **28** being obtained in higher yield (Table 5, Entry *ii*). With the NPOE **24** (Table 5, Entry *iii*) preferential glycosylation at the primary 6-OH group gave **28** as the only disaccharide, albeit with some trisaccharide **30**.

Glycosylation of the analogous *manno* diol **26** with MeOE **4b**, at –30 °C, gave significantly different results (Table 5, Entry *iv*). Only one of the two possible disaccharides was obtained (**31**, 35%), along with traces of trisaccharide **32** (3%). Again, improved regioselective formation of the major product **31** was observed when the reaction was repeated at –50 °C (Table 5, Entry *v*), with both products being obtained in better yields (41% and 5%, respectively). With the NPOE **24** (Table 5, Entry *vi*) preferential glycosylation at the primary 6-OH group gave **31** as the only disaccharide, and with no evidence of the trisaccharide **32**.[39]

Three experiments designed to evaluate the influence of the iodonium ion on the regioselective glycosylation of diol **26** with NPOE **24** were then devised. In the first two experiments (Table 5, Entries *vii, viii*) the amount of NIS used earlier (Entry *vi*) was reduced to 1.0 equiv., whereas in the third experiment, NIS was omitted altogether (Table 5, Entry *ix*).

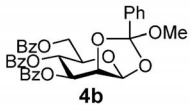
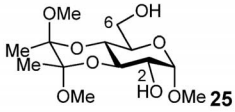
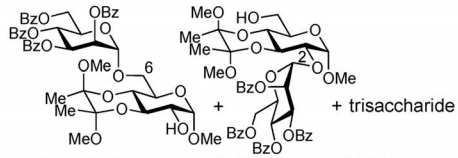
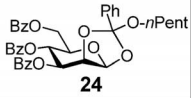
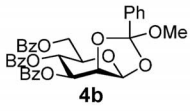
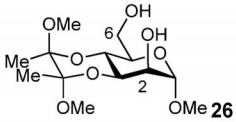
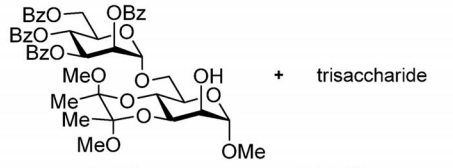
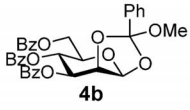
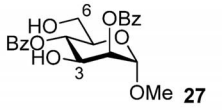
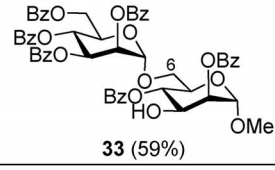
Comparison of Entries *viii* and *ix* make it clear that iodonium ion has a salutary effect on regioselective glycosylation. The yield of disaccharide **31** in the purely acid-catalyzed process (Entry *ix*) was raised from 40% in Entry *ix* to 50% in Entry *viii* by addition of one equivalent of iodonium. The effectiveness of iodonium vis-à-vis acid catalysis was further emphasized by comparing the results in Entries *vii* and *viii*. Substantial reduction of the $BF_3{\cdot}Et_2O$ concentration caused the formation of **31** to increase from 50% to 65%. The last result emphasizes the catalytic role that Lewis acids have on NIS in the production of iodonium ion.

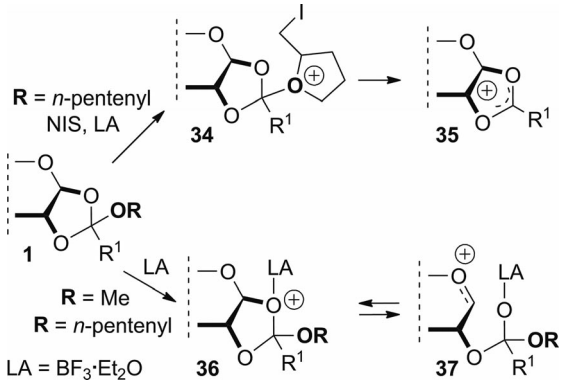
Finally, glycosylation of diol **27** with **4b** at either –30 or –50 °C (Table 5, Entries *x* and *xi*) led to a single disaccharide **33** (49% and 50%, respectively) resulting from glycosylation of the primary OH group. Similar behavior towards diol **27** had also been observed for NPOE **24** (Table 5, Entry *xii*).[39]

A Proposed Explanation for the Regioselective Discrimination of MeOEs versus NPOEs

Our explanation for the differences in regioselectivity displayed by MeOEs and NPOEs is based on the assumption of differences in the activation of NPOEs and MeOEs, as illustrated in Scheme 3. NPOEs are remotely activated with iodonium ion and activity is transmitted to the **OR** residue (**R** = *n*-pent-4-enyl), as in furanylium ion **34**, which gives rise to dioxolenium ion **35**.[40] On the other hand, we postulate that acid activation of MeOEs with $BF_3{\cdot}Et_2O$ takes place preferentially at the glycosyl oxygen (O-1) leading to **36** and thence **37**. In the latter, the alkoxy moiety (**R** = methyl) is still connected to the remains of the donor species (i.e., **37**, Scheme 3). These two cationic intermediates, **35** and **37**, might then display different regioselectivities towards the hydroxy groups of the acceptor, with the dioxolenium ion **35** being more regiochemically demanding.[41] Indeed, some of the experiments displayed in Table 5 were designed to evaluate this hypothesis: glycosylation of diol **26** with NPOE **24**, upon iodonium activation, thus led exclusively to disaccharide **31** (64%, Table 5, Entry *vi*).

Table 5. Regioselective glycosylation of diols **25**–**27** with methyl orthobenzoate **4b** and with *n*-pent-4-enyl orthoester **24** in CH_2Cl_2.

Entry	Donor	Diol acceptor	Promotor (equiv.)	Products
i	 **4b**	 **25**	$BF_3{\cdot}Et_2O$ (2.0), –30 °C	 **28** (32%) **29** (9%) **30** (13%)
ii	**4b**	**25**	$BF_3{\cdot}Et_2O$(2.0), –50 °C	**28** (39%) **29** (8%) **30** (7%)
iii	 **24**	**25**	$BF_3{\cdot}Et_2O$ (0.3), NIS (2.0), –30 °C, (ref. [39])	**28** (50%) **29** (--) **30** (10%)
iv	 **4b**	 **26**	$BF_3{\cdot}Et_2O$ (2.0), –30 °C	 **31** (41%) **32** (5%)
v	**4b**	**26**	$BF_3{\cdot}Et_2O$ (2.0), –50 °C	**31** (41%) **32** (5%)
vi	**24**	**26**	$BF_3{\cdot}Et_2O$ (0.3), NIS (2.0), –30 °C (ref. 39)	**31** (64%)
vii	**24**	**26**	$BF_3{\cdot}Et_2O$ (0.3), NIS (1.0), –30 °C	**31** (65%) **32** (7%)
viii	**24**	**26**	$BF_3{\cdot}Et_2O$ (2.0), NIS (1.0), –30 °C	**31** (50%) **32** (10%)
ix	**24**	**26**	$BF_3{\cdot}Et_2O$ (2.0), **no NIS**, –30 °C	**31** (40%) **32** (6%)
x	 **4b**	 **27**	$BF_3{\cdot}Et_2O$ (2.0), –30 °C	 **33** (59%)
xi	**4b**	**27**	$BF_3{\cdot}Et_2O$ (2.0), –50 °C	**33** (50%)
xii	**24**	**27**	$BF_3{\cdot}Et_2O$ (0.3), NIS (2.0), –30 °C (ref. 39)	**33** (43%)



Scheme 3. Proposed reaction intermediates from NPOEs (1 **R** = *n*-pent-4-enyl) and MeOEs (1, **R** = Me) upon activation with NIS/$BF_3{\cdot}Et_2O$ (iodonium ion) or $BF_3{\cdot}Et_2O$.

Upon $BF_3{\cdot}Et_2O$ activation (no NIS present), however, these reactants gave a product distribution (Table 5, Entry *ix*) of **31** (40%) and **32** (6%). Most notably, this product distribution was also obtained on $BF_3{\cdot}Et_2O$-mediated glycosylation of diol **26** with MeOE **4b** [**31** (41%), **32** (5%), Table 5, Entry *v*].

Conclusions

In summary, mannose-derived methyl 1,2-orthoacetates and -orthobenzoates are useful glycosyl donors in glycosidation protocols on activation with $BF_3{\cdot}Et_2O$. The reaction works better with stoichiometric amounts of $BF_3{\cdot}Et_2O$ (two or three equivalents could be used without significant difference), and use of a twofold excess of a MeOE normally results in increased disaccharide yields. MeOEs could also be used in regioselective glycosyl couplings with regioselectivity sometimes similar to that displayed by NPOEs. An explanation for these observations has been advanced, in which different cationic species arising from MeOEs (acti-

vation at O-1) and NPOEs (chemoselective remote iodonium activation at the *n*-pent-4-enyl residue) might result in different regiochemical preferences. Even though similar transformations have already been carried out with NPOEs, the use of MeOEs might have the advantage of the low cost of methanol in relation to that of *n*-pent-4-enyl alcohol. Experiments to test these regiochemical issues are underway and will be reported in due course.

Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were obtained with solutions in $CDCl_3$ and a 300, 400 or 500 MHz spectrometer. Optical rotations were determined with solutions in chloroform. Column chromatography was performed on silica gel (230–400 mesh). TLC was conducted on precoated Kieselgel 60 F254 plates (Merck). Detection was achieved first with UV light (254 nm) and then by charring with a solution of sulfuric acid/acetic acid/H_2O (1:20:4). All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used to dry solutions. Methyl orthoacetate **4a**,[42] methyl orthobenzoate **4b**,[42] and *n*-pent-4-enyl orthoester **24**[33] were prepared as described previously. Acceptors **8**,[43] **19**,[44] **21**–**22**,[45] and **23**[46,47] were prepared by published procedures.

Pent-4-enyl 3,4-Di-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (17): Tetrabutylammonium fluoride (52 mg, 2 mmol) was added to a cooled (0 °C) solution of pent-4-enyl 3,4-di-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside[48] (700 mg, 1 mmol) in THF (20 mL). The reaction mixture was stirred for 3 h and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 7:3) to give pent-4-enyl 3,4-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**17**, 498 mg, 85%). $[\alpha]_D$ = +13.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (qd, *J* = 13.8, 7.1 Hz, 1 H), 1.86–1.95 (m, 2 H), 3.52 (dt, *J* = 9.7, 6.7 Hz, 1 H), 3.75 (dd, *J* = 13.1, 4.8 Hz, 1 H), 3.86–3.94 (m, 3 H), 4.55 (dd, *J* = 10.9, 8.4 Hz, 1 H), 4.73–4.82 (m, 2 H), 5.52 (t, *J* = 9.5 Hz, 1 H), 5.54 (d, *J* = 8.4 Hz, 1 H), 5.61 (ddd, *J* = 16.9, 6.6, 3.7 Hz, 1 H), 6.33 (dd, *J* = 10.9, 9.2 Hz, 1 H), 7.25–7.96 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 29.9, 55.0, 61.5, 69.4, 70.3, 71.1, 98.4, 114.9, 123.7, 128.4, 128.6, 128.7, 128.8, 129.9, 130.1, 131.5, 133.4, 133.8, 134.3, 137.8, 165.8, 166.2 ppm. API-ES positive: 608.7 $[M + Na]^+$. $C_{33}H_{31}NO_9$ (585.6): calcd. C 67.68, H 5.34; found C 67.70, H 5.38.

Phenyl 2,3,4-Tri-*O*-methyl-1-thio-α-D-mannopyranoside (18): Sodium hydride (566 mg, 23.6 mmol) was added at 0 °C to a stirred solution of phenyl 6-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-mannopyranoside[49] (2 g, 3.9 mmol) in dry THF (15 mL). After 15 min, methyl iodide (1.46 mL, 23.6 mmol) was added, the reaction mixture was allowed to reach room temperature, and stirring was then continued for 12 h. The mixture was diluted with Et_2O and washed successively with saturated aqueous NH_4Cl and brine. The organic phase was dried and concentrated, and the crude mixture was purified by flash chromatography (hexane/EtOAc 8:2) to give phenyl 6-*O*-*tert*-butyldiphenylsilyl-2,3,4-tri-*O*-methyl-1-thio-α-D-mannopyranoside (1.77 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 9 H), 3.50 (s, 3 H), 3.51–3.55 (m, 1 H), 3.56 (s, 3 H), 3.58 (s, 3 H), 3.77 (t, *J* = 9.4 Hz, 1 H), 3.86–3.92 (m, 1 H), 3.91 (dd, *J* = 3.4, 1.7 Hz, 1 H), 4.00–4.09 (m, 2 H), 5.71 (d, *J* = 1.2 Hz, 1 H), 7.25–7.78 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 26.9 (×3), 57.7, 57.8, 60.8, 63.3, 74.2, 76.5, 78.9, 82.0, 84.8, 127.2, 127.6 (×2), 127.7 (×2), 129.1 (×2), 129.6, 131.1 (×2), 135.4, 135.7 (×2), 136.1 (×2) ppm.

A sample of this material (553 mg, 1 mmol) was dissolved in THF (20 mL), cooled to 0 °C and then treated with tetrabutylammonium fluoride (52 mg, 2 mmol). The reaction mixture was stirred for 3 h and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 6:4) to give phenyl-2,3,4-tri-*O*-methyl-1-thio-α-D-mannopyranoside (**18**, 283 mg, 90%). $[\alpha]_D$ = +156.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 3 H), 3.50 (m, 1 H), 3.53 (s, 3 H), 3.57 (s, 3 H), 3.77 (dd, *J* = 11.8, 4.6 Hz, 1 H), 3.84 (dd, *J* = 11.9, 2.9 Hz, 1 H), 3.85 (m, 2 H), 4.04 (m, 1 H), 5.61 (d, *J* = 1.3 Hz, 1 H), 7.28–7.49 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.7, 58.3, 60.7, 62.0, 73.2, 76.5, 78.8, 81.7, 85.1, 127.6, 129.1 (×2), 131.7 (×2), 134.1 ppm. API-ES positive: 337.0 $[M + Na]^+$. $C_{15}H_{22}O_5S$ (314.4): calcd. C 57.30, H 7.05; found C 57.23, H 7.15.

Glycosylation Reaction of Methyl Orthoester 4a in the Presence of Different Acid Catalysts

With $Yb(OTf)_3$: A dry mixture of the methyl orthoester **4a** (50 mg, 0.138 mmol) and acceptor **8** (37.3 mg, 0.069 mmol) was dissolved in dry CH_2Cl_2 (3 mL mmol^{-1}), the solution was cooled to 0 °C, and $Yb(OTf)_3$ (344 mg, 0.552 mmol) was added. After 30 min all the starting material had disappeared and the reaction mixture was treated with Et_3N (500 μL). The crude mixture was concentrated and purified by flash chromatography (hexane/EtOAc 7:3) to yield mixed orthoester **9** (60 mg, 99%). $[\alpha]_D$ = –17 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 2.05 (s, 3 H), 3.39 (ddd, *J* = 9.3, 5.2, 1.9 Hz, 1 H), 3.47 (m, 1 H), 3.51 (t, *J* = 9.0 Hz, 1 H), 3.57–3.66 (m, 3 H), 3.74 (dd, *J* = 12.0, 1.9 Hz, 1 H), 4.12 (dd, *J* = 15.0, 2.7 Hz, 1 H), 4.21 (dd, *J* = 12.2, 4.9 Hz, 1 H), 4.43–4.47 (m, 2 H), 4.59 (d, *J* = 10.8 Hz, 1 H), 4.63 (d, *J* = 11.8 Hz, 1 H), 4.68 (d, *J* = 10.9 Hz, 1 H), 4.74 (d, *J* = 10.9 Hz, 1 H), 4.81 (d, *J* = 10.9 Hz, 1 H), 4.88 (d, *J* = 9.3 Hz, 1 H), 4.89 (d, *J* = 2.1 Hz, 1 H), 4.92 (d, *J* = 9.1 Hz, 1 H), 5.09 (dd, *J* = 9.9, 3.9 Hz, 1 H), 5.26 (t, *J* = 9.7 Hz, 1 H), 5.36 (d, *J* = 2.7 Hz, 1 H), 7.32–7.37 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8 (×2), 20.9, 24.7, 61.9, 62.6, 65.7, 70.5, 71.2, 71.6, 74.0, 75.0, 75.8 (×2), 76.6, 77.8, 82.4, 84.8, 97.5, 102.5, 124.3, 127.7, 127.8, 127.9, 128.0 (×2), 128.2 (×2), 128.3 (×4), 128.5 (×4), 128.6 (×4), 137.5, 138.4, 138.5, 138.7, 169.6, 170.4, 170.8 ppm. API-ES positive: 894.3 $[M + Na]^+$. $C_{48}H_{54}O_{15}$ (870.93): calcd. C 66.19, H 6.25, O 27.56; found C 66.24, H 6.30.

In a different run, orthoester **4a** (50 mg, 0.138 mmol), acceptor **8** (37.3 mg, 0.069 mmol), and $Yb(OTf)_3$ (86 mg, 0.138 mmol) were allowed to react at 0 °C for 12 h. The reaction mixture was then treated with Et_3N (500 μL). The crude mixture was then concentrated and purified by flash chromatography (hexane/EtOAc 7:3) to yield disaccharide **10a** (10 mg, 17%), disaccharide **11** (5 mg, <10%), hemiketal **13** (16 mg, 33%) and methyl 3,4,6-tri-*O*-acetyl-α-D-mannopyranose (8 mg, 18%).

Compound 11: $[\alpha]_D$ = +22 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 3.47–3.51 (m, 2 H), 3.48 (dd, *J* = 7.9, 1.2 Hz, 1 H), 3.66 (t, *J* = 9.0 Hz, 1 H), 4.01 (ddd, *J* = 9.6, 4.4 Hz, 1 H), 4.07 (dd, *J* = 12.3, 2.2 Hz, 1 H), 4.21 (dd, *J* = 12.3, 4.4 Hz, 1 H), 4.51 (d, *J* = 7.8 Hz, 1 H), 4.60 (d, *J* = 11.3 Hz, 1 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 4.72 (d, *J* = 11.3 Hz, 1 H), 4.77 (d, *J* = 10.9 Hz, 1 H), 4.91–4.97 (m, 5 H), 5.29 (dd, *J* = 9.8, 3.0 Hz, 1 H), 5.34 (t, *J* = 9.8 Hz, 1 H), 7.26–7.40 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 20.9, 21.1, 62.4, 66.3, 66.6, 68.4, 69.4, 71.2, 71.7, 74.3, 75.1 (×2), 75.9, 78.0, 82.5, 84.9, 99.6, 102.4, 127.8 (×2), 127.9 (×2), 128.0 (×4), 128.1 (×2), 128.3 (×2), 128.5 (×4), 128.6 (×4), 137.4, 138.1, 138.4, 138.5,

169.9 (×2), 170.9 ppm. API-ES positive: 846.3 $[M + NH_4]^+$, 851.3 $[M + Na]^+$. $C_{46}H_{52}O_{14}$ (828.89): calcd. C 66.65, H 6.32, O 27.02; found C 66.70, H 6.38.

Reaction in the Presence of TMSOTf: TMSOTf (50 μL, 0.276 mmol) was added at –30 °C to a stirred solution of methyl orthoester **4a** (50 mg, 0.138 mmol) and acceptor **8** (37.3 mg, 0.069 mmol) in anhydrous CH_2Cl_2 (3 mL). After 1 h, the reaction mixture was diluted with CH_2Cl_2 and quenched by addition of 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 with Na_2SO_4, filtered, and concentrated.

The resulting residue was purified by silica gel flash column chromatography (hexane/EtOAc 85:15) to yield silylated disaccharide **12** (49 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.14 (s, 9 H), 1.93 (s, 6 H), 2.04 (s, 3 H), 3.42–3.55 (m, 3 H), 3.66 (t, J = 8.9 Hz, 1 H), 3.76 (dd, J = 11.5, 2.0 Hz, 1 H), 3.81 (dd, J = 11.8, 5.1 Hz, 1 H), 3.96 (ddd, J = 9.8, 4.8, 2.6 Hz, 1 H), 4.04–4.11 (m, 2 H), 4.13 (dd, J = 12.3, 2.5 Hz, 1 H), 4.50 (d, J = 7.8 Hz, 1 H), 4.63 (d, J = 12.6 Hz, 1 H), 4.66 (d, J = 12.2 Hz, 1 H), 4.72 (d, J = 10.7 Hz, 1 H), 4.75 (d, J = 12.9 Hz, 1 H), 4.80 (d, J = 2.0 Hz, 1 H), 4.91–4.98 (m, 4 H), 5.22 (dd, J = 9.9, 3.0 Hz, 1 H), 5.33 (t, J = 9.9 Hz, 1 H), 7.27–7.39 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.05, 20.7, 21.0, 26.8, 62.2, 65.9, 66.5, 68.8, 69.7, 70.9, 71.5, 74.4, 74.9, 75.0, 75.8, 77.8, 82.3, 84.7, 100.5, 102.3, 127.7 (×2), 127.8 (×2), 127.9 (×4), 128.2 (×2), 128.3 (×2), 128.4 (×4), 128.5 (×4), 137.3, 138.0, 138.3, 138.4, 169.6, 170.1, 172.8 ppm. API-ES positive: 924.3 $[M + Na]^+$. $C_{49}H_{60}O_{14}Si$ (901.07): calcd. C 65.31, H 6.71, O 24.86, Si 3.12; found C 65.37, H 6.77.

Reaction in the Presence of TsOH: A solution of methyl orthoester **4a** (50 mg, 0.138 mmol) and acceptor **8** (37.3 mg, 0.069 mmol) in anhydrous CH_2Cl_2 (3 mL) was treated with *p*-toluenesulfonic acid (47.5 mg, 0.276 mmol). After it had been stirred for 2 h at room temp., the reaction mixture was treated with Et_3N (500 μL, 3.6 mmol) and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc 1:1) to afford hemiketal **13**[50] (33 mg, 69%).

Glycosylation Reactions of Methyl Orthoesters 4a and 4b with Monosaccharides 8 and 14 – Optimization of Reaction Conditions: A dry mixture of the 1,2-orthoester **4a** or **4b** (number of equivalents shown in Table 2 and Table 3) and the corresponding acceptor (**8** or **14**) was dissolved in dry CH_2Cl_2 (5 mL mmol^{-1}), the solution was cooled to –30 °C, and $BF_3{\cdot}Et_2O$ (number of equivalents shown in Table 2 and Table 3) was added. After TLC analysis indicated full disappearance of the starting materials, the reaction was quenched by addition of 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 with Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography. The yields of the corresponding pure disaccharide always refer to the acceptor employed in each case. On the other hand, when two equiv. of donor were used, byproducts arising from the orthoester transformation are detected in the reaction. In some instances these byproducts were quantified and characterized, and included the corresponding 1α,1′β-disaccharide (i.e., **6**) and methyl glycoside (i.e. **7**).[34]

Benzyl 6-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (10a): This compound was prepared from orthoester **4a** (100 mg, 0.276 mmol), benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside **8** (75 mg, 0.138 mmol) and $BF_3{\cdot}Et_2O$ (289 μL, 0.81 mmol). Purification by flash chromatography (hexane/EtOAc 7:3) afforded **10a** (111 mg, 92%). $[\alpha]_D$ = +28.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 1.96 (s, 3 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 3.40–3.51 (m, 3 H), 3.64 (t, J = 8.8 Hz, 1 H), 3.73 (m, 2 H), 4.01–4.05 (m, 1 H), 4.05 (dd, J = 12.4, 2.1 Hz, 1 H), 4.20 (dd, J = 12.4, 4.9 Hz, 1 H), 4.49 (d, J = 7.8 Hz, 1 H, 1 H), 4.56 (d, J = 11.3 Hz, 1 H), 4.64 (d, J = 11.9 Hz, 1 H), 4.69 (d, J = 10.9 Hz, 1 H), 4.74 (d, J = 10.9 Hz, 1 H), 4.87 (d, J = 1.6 Hz, 1 H), 4.90 (d, J = 10.9 Hz, 1 H), 4.91 (d, J = 10.0 Hz, 1 H), 4.92 (d, J = 11.6 Hz, 1 H), 4.94 (d, J = 10.8 Hz, 1 H, 1 H), 5.26 (t, J = 10.1 Hz, 1 H), 5.28 (dd, J = 3.4, 1.8 Hz, 1 H), 5.36 (dd, J = 10.1, 3.4 Hz, 1 H), 7.22–7.37 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 20.8, 20.9, 21.0, 62.4, 66.1, 66.7, 68.6, 69.2, 69.5, 71.1, 74.1, 74.9, 75.0, 75.8, 78.0, 82.4, 84.8, 97.5, 102.3, 127.7, 127.8, 127.9 (×5), 128.0 (×2), 128.2 (×2), 128.4 (×2), 128.5 (×2), 128.6 (×4), 137.4, 138.0, 138.4, 138.5, 169.8, 169.9, 170.0, 170.7 ppm. API-ES positive: 888.3 $[M + NH_4]^+$. $C_{48}H_{54}O_{15}$ (870.93): calcd. C 66.19, H 6.25, O 27.56; found C 66.23, H 6.22.

Benzyl 6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (10b): This compound was prepared from orthoester **4b** (122 mg, 0.20 mmol), benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**8**, 54 mg, 0.10 mmol) and $BF_3{\cdot}Et_2O$ (71 μL, 0.60 mmol). Purification by flash chromatography (hexane/EtOAc 8:2) afforded **10b** (106.3 mg, 95%). $[\alpha]_D$ = –19.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49–3.60 (m, 2 H), 3.62–3.70 (m, 1 H), 3.75 (t, J = 8.9 Hz, 1 H), 3.88–3.93 (m, 1 H), 3.96 (dd, J = 10.9, 6.5 Hz, 1 H), 4.46 (dd, J = 12.1, 4.2 Hz, 1 H), 4.53–4.57 (m, 1 H), 4.63–4.85 (m, 6 H), 4.97–5.09 (m, 4 H), 5.19 (d, J = 1.6 Hz, 1 H), 5.81 (dd, J = 2.9, 1.6 Hz, 1 H), 6.01 (dd, J = 10.1, 3.2 Hz, 1 H), 6.16 (t, J = 10.1 Hz, 1 H), 7.23–7.65 (m, 30 H), 7.85–8.18 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.8, 67.0, 67.1, 69.1, 70.2, 70.5, 71.3, 74.2, 75.0, 75.1, 75.8, 78.2, 82.4, 84.9, 97.7, 102.4, 127.7, 127.8, 127.9 (×2), 128.0 (×3), 128.2 (×2), 128.3 (×2), 128.4 (×2), 128.5 (×6), 128.6 (×8), 128.7 (×4), 129.0, 129.3, 129.5, 129.8 (×2), 129.9 (×4), 130.0 (×2), 130.1, 133.2, 133.3, 133.4, 133.5, 137.4, 138.1, 138.5, 138.7, 165.4, 165.5, 165.6, 166.2 ppm. API-ES positive: 1141.6 $[M + Na]^+$. $C_{68}H_{62}O_{15}$ (1119.2): calcd. C 72.97, H 5.58, O 21.44; found C 72.98, H 5.53.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-glucofuranose (15b):[51] This compound was prepared from orthoester **4b** (183 mg, 0.3 mmol), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**14**, 39 mg, 0.15 mmol) and $BF_3{\cdot}Et_2O$ (320 μL, 0.90 mmol). Purification by flash chromatography (hexane/EtOAc 7:3) afforded **15b** (88 mg, 70%), along with methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (**7b**, 27 mg, 15%), 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride (25 mg, 0.14%), and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (7 mg, 4%). For **15b**:[51] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.12–7.26 (m, 20 H), 6.06 (t, J = 10.0 Hz, 1 H), 6.02 (d, J = 2 3.0 Hz, 1 H), 5.88 (dd, J = 3.3, 10.0 Hz, 1 H), 5.76 (dd, J = 1.7, 3.3 Hz, 1 H), 5.41 (d, J = 1.7 Hz, 1 H), 4.73–4.69 (m, 2 H), 4.56–4.51 (m, 2 H), 4.44 (d, J = 2.8 Hz, 1 H), 4.35–4.30 (m, 1 H), 4.23 (dd, J = 6.2, 8.6 Hz, 1 H), 4.11 (dd, J = 2.8, 8.8 Hz, 1 H), 4.01 (dd, J = 4.0, 8.6 Hz, 1 H, 6-H), 1.50 (s, 3 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H) ppm.

Glycosylation Reactions of Methyl Orthoesters 4a and 4b with Monosaccharides 16–19 – General Procedure: A dry mixture of the appropriate 1,2-orthoester (2.0 equiv.) and the appropriate acceptor (1.0 equiv.) in toluene (5 mL) was azeotroped to dryness, and subsequently kept overnight under high vacuum. This mixture was then dissolved in dry CH_2Cl_2 (5 mL mmol^{-1}), the solution was cooled to –30 °C, and $BF_3{\cdot}Et_2O$ (3.0 equiv.) was added. After TLC analysis indicated full disappearance of the starting materials, the reaction was quenched by addition of 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 resulting organic phase was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography to afford the corresponding pure disaccharide. The yields shown for each compound refer to the acceptor employed in each case. On the other hand, because two equiv. of donor were used, byproducts arising from the orthoester transformation were commonly detected in the reaction. In some instances these byproducts were quantified and characterized, and included the corresponding 1α,1′β-disaccharide (i.e., **6**) and methyl glycoside (i.e., **7**).

6-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-1:2,3:4-di-*O*-isopropylidene-α-D-galactopyranoside (20a):[52] This compound was prepared from orthoester **4a** (100 mg, 0.28 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**16**, 36 mg, 0.138 mmol) by the general procedure for glycosylation. Purification by flash chromatography (hexane/EtOAc 6:4) afforded **20a** (67 mg, 82%), the spectroscopic data for which are identical to those described previously.[52] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 6 H), 1.41 (s, 3 H), 1.55 (s, 3 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 2.15 (s, 3 H), 3.70 (dd, J = 10.2, 6.4 Hz, 1 H), 3.78 (dd, J = 10.2, 6.2 Hz, 1 H), 3.94–3.96 (m, 1 H), 4.06–4.11 (m, 2 H), 4.24 (dd, J = 7.9, 1.7 Hz, 1 H), 4.29–4.33 (m, 2 H), 4.61 (dd, J = 7.9, 2.4 Hz, 1 H), 4.86 (d, J = 1.2 Hz, 1 H), 5.22–5.34 (m, 3 H), 5.49 (d, J = 5.0 Hz, 1 H) ppm.

6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl)-1:2,3:4-di-*O*-isopropylidene-α-D-galactopyranoside (20b):[53] This compound was prepared by the general method from orthoester **4b** (171 mg, 0.28 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**16**, 20 mg, 0.138 mmol). Purification by flash chromatography (hexane/EtOAc 7:3) afforded **20b** (63 mg, 99%) along with methyl glycoside **7b**[34] (48 mg, 28%) and 1α,1′β-disaccharide **6b**[34] (39 mg, 12%). The spectral data for **20b** are in agreement with those described previously.[53] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.43 (s, 3 H), 1.63 (s, 3 H), 3.90 (dd, J = 10.4, 6.0 Hz, 1 H), 3.98 (dd, J = 10.4, 6.3 Hz, 1 H), 4.07–4.17 (m, 1 H), 4.32–4.39 (m, 2 H), 4.51 (dd, J = 12.1, 3.9 Hz, 1 H), 4.57–4.64 (m, 1 H), 4.65–4.73 (m, 2 H), 5.17 (d, J = 1.8 Hz, 1 H), 5.57 (d, J = 5.0 Hz, 1 H), 5.75 (dd, J = 3.2, 1.8 Hz, 1 H), 5.92 (dd, J = 10.1, 3.3 Hz, 1 H), 6.14 (t, J = 10.0 Hz, 1 H), 7.24–7.62 (m, 12 H), 7.83–8.14 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 25.1, 26.1, 26.3, 63.0, 66.8, 66.9, 67.7, 68.9, 70.3, 70.5, 70.8 (×2), 71.1, 96.5, 98.0, 108.9, 109.6, 128.4 (×2), 128.5 (×4), 128.7 (×2), 129.2, 129.3, 129.5, 129.8 (×2), 129.9 (×4), 130.0 (×2), 130.1, 133.1, 133.2, 133.5 (×2), 165.5 (×2), 165.6, 166.3 ppm.

Pent-4-enyl 3,4-Di-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (21a): This compound was prepared from orthoester **4a** (100 mg, 0.276 mmol) and pent-4-enyl 3,4-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**17**, 81 mg, 0.138 mmol) by the general procedure for glycosylation. Purification by flash chromatography (hexane/EtOAc 6:4) afforded **21a** (112 mg, 87%). $[\alpha]_D$ = +42.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (dq, J = 13.9, 7.5 Hz, 2 H), 1.90 (m, 2 H), 1.98 (s, 3 H), 2.01 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 3.54 (dt, J = 9.8, 6.6 Hz, 1 H), 3.67 (dd, J = 10.8, 2. 3 Hz, 1 H), 3.88–4.03 (m, 4 H), 4.13 (ddd, J = 9.3, 6.6, 2.3 Hz, 1 H), 4.20 (dd, J = 12.1, 5.1 Hz, 1 H), 4.56 (dd, J = 10.8, 8.4 Hz, 1 H), 4.77 (m, 1 H), 4.85 (d, J = 1.6 Hz, 1 H), 5.26 (t, J = 10.0 Hz, 1 H), 5.27 (dd, J = 3.5, 1.7 Hz, 1 H), 5.38 (dd, J = 10.1, 3.5 Hz, 1 H), 5.53 (dd, J = 10.1, 9.3 Hz, 1 H), 5.54 (d, J = 8.4 Hz, 1 H), 5.62 (ddt, J = 17.0, 10.3, 6.7 Hz, 1 H), 6.27 (dd, J = 10.8, 9.2 Hz, 1 H), 7.25–7.95 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 20.8 (×2), 21.0, 28.6, 29.9, 54.9, 62.2, 66.1, 66.6, 68.6, 69.0, 69.3, 69.4, 70.3, 71.2, 72.8, 97.4, 98.3, 114.9, 123.6, 128.4, 128.5, 128.6, 128.7, 129.8, 129.9, 131.5, 133.3, 133.6, 134.3, 137.7, 165.3, 165.7, 169.8, 170.0, 170.7 ppm. API-ES positive: 938.2 $[M + Na]^+$. $C_{47}H_{49}NO_{18}$ (915.9): calcd. C 61.63, H 5.39, N 1.53, O 31.44; found C 61.65, H 5.37, N 1.45.

Pent-4-enyl 3,4-Di-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (21b): This compound was prepared by the general method from orthoester **4b** (94 mg, 0.15 mmol) and pent-4-enyl 3,4-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**17**, 44.5 mg, 0.076 mmol). Purification by flash chromatography (hexane/EtOAc 8:2) afforded **21b** (81.3 mg, 92%) along with methyl glycoside **7b**[34] (16 mg, 17%) and 1α,1β-disaccharide **6b**[34] (26 mg, 15%). For **21b**: $[\alpha]_D$ = –12.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.60 (m, 2 H), 1.78–1.85 (m, 2 H), 3.55 (dt, J = 9.8, 6.5 Hz, 1 H), 3.70 (dd, J = 10.5, 1.7 Hz, 1 H), 3.92 (dt, J = 9.8, 6.1 Hz, 1 H), 4.03 (dd, J = 10.5, 6.4 Hz, 1 H), 4.13 (m, 1 H), 4.27 (dd, J = 12.0, 4.7 Hz, 1 H), 4.37 (ddd, J = 9.6, 4.6, 2.2 Hz, 1 H), 4.47 (d, J = 8.8 Hz, 1 H), 4.49 (t, J = 10.9 Hz, 1 H), 4.63 (m, 2 H), 5.04 (d, J = 1.3 Hz, 1 H), 5.52 (d, J = 8.4 Hz, 1 H), 5.42–5.56 (m, 1 H), 5.65 (dd, J = 3.2, 1.7 Hz, 1 H), 5.88 (dd, J = 10.1, 3.2 Hz, 1 H), 5.98 (t, J = 9.9 Hz, 1 H), 6.23 (dd, J = 10.1, 9.9 Hz, 1 H), 7.16–8.03 (m, 35 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7, 30.0, 55.1, 62.8, 66.9, 67.0, 69.1, 69.4, 70.1, 70.4, 70.5, 71.4, 73.0, 97.6, 98.4, 114.9, 123.7, 128.4 (×4), 128.5 (×4), 128.6 (×8), 128.7 (×4), 128.8 (×2), 129.2 (×2), 129.3, 129.4, 129.8 (×4), 129.9 (×8), 131.6 (×2), 133.1, 133.2, 133.3, 133.5, 133.6, 134.3, 137.8, 165.4 (×3), 165.6, 165.8, 166.2 ppm. API-ES positive: 1187.1 $[M + Na]^+$. $C_{67}H_{57}NO_{18}$ (1164.2): calcd. C 69.12, H 4.94, N 1.20; found C 69.20, H 4.90, N 1.22.

Phenyl 6-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-methyl-1-thio-α-D-mannopyranoside (22a): This compound was prepared from orthoester **4a** (100 mg, 0.276 mmol) and phenyl 2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside (**18**, 50 mg, 0.138 mmol) by the general procedure for glycosylation. Purification by flash chromatography (hexane/EtOAc 6:4) afforded **17a** (65 mg, 73%). $[\alpha]_D$ = +81.4 (c = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.14 (s, 3 H), 3.46 (s, 3 H), 3.48 (m, 1 H), 3.49 (m, 1 H), 3.52 (s, 3 H), 3.56 (s, 3 H), 3.75 (dd, J = 11.1, 1.8 Hz, 1 H), 3.86 (t, J = 1.9 Hz, 1 H), 3.91 (dd, J = 11.1, 5.8 Hz, 1 H), 4.04 (ddd, J = 9.4, 5.0, 2.1 Hz, 1 H), 4.11 (dd, J = 12.2, 2.2 Hz, 1 H, 1 H), 4.15–4.22 (m, 1 H), 4.26 (dd, J = 12.2, 5.1 Hz, 1 H), 4.93 (d, J = 1.5 Hz, 1 H), 5.27 (t, J = 9.8 Hz, 1 H), 5.31 (dd, J = 3.2, 1.5 Hz, 1 H), 5.35 (dd, J = 9.8, 3.2 Hz, 1 H), 5.59 (d, J = 1.9 Hz, 1 H), 7.24–7.51 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 20.9 (×2), 21.1, 57.6, 58.1, 61.0, 62.4, 66.4, 67.2, 68.5, 69.1, 69.6, 72.0, 76.5, 78.4, 81.7, 84.7, 97.9, 127.7, 129.3 (×2), 131.6 (×2), 134.5, 169.7, 169.9, 170.0, 170.8 ppm. API-ES positive: 667.2 $[M + Na]^+$. $C_{29}H_{40}O_{14}S$ (664.68): calcd. C 54.03, H 6.25, S 4.97; found C 54.07, H 6.27, S 4.79.

Phenyl 6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-methyl-1-thio-α-D-mannopyranoside (22b): This compound was prepared by the general method from orthoester **4b** (168 mg, 0.28 mmol) and phenyl 2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside (**18**, 50 mg, 0.138 mmol). Purification by flash chromatography (hexane/EtOAc 7:3) afforded **22b** (117 mg, 95%). $[\alpha]_D$ = +7.8 (c = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3 H), 3.47–3.49 (m, 2 H), 3.48 (s, 3 H), 3.53 (s, 3 H), 3.82 (m, 2 H), 4.01 (dd, J = 11.0, 6.0 Hz, 1 H), 4.23 (m, 1 H), 4.41 (m, 2 H), 4.59 (dd, J = 13.7, 4.3 Hz, 1 H), 5.13 (d, J = 1.8 Hz, 1 H), 5.58 (d, J =

1.5 Hz, 1 H), 5.70 (dd, *J* = 3.3, 1.8 Hz, 1 H), 5.86 (dd, *J* = 10.1, 3.3 Hz, 1 H), 6.04 (t, *J* = 9.7 Hz, 1 H), 7.01–7.57 (m, 17 H), 7.72–8.09 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.7, 58.1, 61.1, 63.0, 67.1, 67.7, 68.9, 70.2, 70.5, 72.2, 76.7, 78.5, 81.9, 85.0, 98.1, 127.9, 128.5, 128.6, 128.7, 128.8, 129.2, 129.4 (×2), 129.7, 130.0 (×2), 130.1 (×2), 130.2, 132.1 (×2), 133.2, 133.3, 133.6, 133.7, 134.5, 165.3, 165.4, 165.7, 166.4 ppm. API-ES positive: 915.2 $[M + Na]^+$. $C_{49}H_{48}O_{14}S$ (892.9): calcd. C 65.91, H 5.42; found C 65.88, H 5.38.

Methyl 6-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (23a):[54] This compound was prepared from orthoester **4a** (50 mg, 0.14 mmol) and methyl 2,3,4 tri-*O*-benzoyl-α-D-mannopyranosyl (**19**, 35 mg, 0.07 mmol) by the general procedure for glycosylation. Purification by flash chromatography (hexane/EtOAc 6:4) allowed the isolation of **23a** (23 mg, 40%) along with methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**7a**, 5 mg, 10%), and unchanged methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl (**19**, 5 mg, 14%), together with a lower running mixture of compounds appearing as a single spot on tlc. Acetylation of this mixture (consisting of partially de-*O*-acetylated materials) resulted after additional chromatography (hexane/EtOAc 6:4) in the isolation of 1α,1′β-disaccharide **6a** (8 mg, 17%) and disaccharide **23a** (7 mg, 12%). Spectral data for **23a** are in agreement with those described previously.[54] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.79 (m, 6 H), 7.48–7.19 (m, 9 H), 6.08 (t, *J* = 9.6 Hz, 1 H), 5.45 (t, *J* = 9.9 Hz, 1 H), 5.31 (dd, *J* = 10.2, 3.3 Hz, 1 H), 5.19 (m, 4 H), 4.77 (s, 1 H), 4.21 (m, 1 H), 4.12 (dd, *J* = 12.0, 5.4 Hz, 1 H), 3.97 (m, 2 H), 3.83 (dd, *J* = 10.8, 6.3 Hz, 1 H), 3.58 (dd, *J* = 10.8, 1.8 Hz, 1 H), 3.43 (s, 3 H), 2.07, 1.984, 1.978, 1.92 (4s, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 170.8, 170.1, 169.9, 166.0, 165.5, 133.7, 133.5, 133.3, 130.15, 130.08, 129.9, 129.4, 129.3, 129.0, 128.7, 128.6, 128.5, 97.6, 97.1, 72.3, 70.7, 69.7, 69.2, 68.9, 68.5, 66.7, 66.3, 62.6, 55.8, 21.0, 20.93, 20.87 ppm.

Methyl 6-*O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (23b):[53] This compound was prepared by the general method from orthoester **4b** (100 mg, 0.163 mmol) and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**19**, 41.5 mg, 0.082 mmol). Purification by flash chromatography (hexane/EtOAc 8:2) afforded **23b** (90 mg, 99%), the spectroscopic data for which are identical to those described previously.[53] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3 H), 3.74 (dd, *J* = 10.8, 1.8 Hz, 1 H), 4.07 (dd, *J* = 10.6, 6.2 Hz, 1 H), 4.31–4.40 (m, 2 H), 4.51 (ddd, *J* = 9.7, 4.6, 1.8 Hz, 1 H), 4.60 (dd, *J* = 12.2, 2.0 Hz, 1 H), 5.13 (d, *J* = 1.2 Hz, 1 H), 5.24 (dd, *J* = 10.2, 3.7 Hz, 1 H), 5.31 (d, *J* = 3.7 Hz, 1 H), 5.56 (t, *J* = 9.9 Hz, 1 H), 5.74 (dd, *J* = 2.9, 1.8 Hz, 1 H), 5.96 (dd, *J* = 10.1, 3.1 Hz, 1 H), 6.07 (t, *J* = 10.0 Hz, 1 H), 6.19 (t, *J* = 9.8 Hz, 1 H), 7.24–8.10 (m, 35 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8, 62.8, 66.5, 66.9, 68.4, 69.1, 69.4, 70.1, 70.4, 72.2, 97.0, 97.5, 128.4 (×3), 128.5 (×3), 128.6 (×4), 128.7 (×2), 128.9, 129.2 (×2), 129.3, 129.4, 129.8 (×4), 129.9 (×4), 130.1 (×3), 133.1, 133.2 (×2), 133.4, 133.5 (×2), 133.6, 165.4, 165.5 (×2), 165.6, 165.8, 165.9, 166.2 ppm.

Glycosylation Reactions of Diol Acceptors 25–27 with Methyl Orthobenzoate 4b – General Procedure: A dry mixture of **4b** (1.0 equiv.) and the appropriate diol (1.0 equiv.) in toluene (5 mL) was azeotroped to dryness and subsequently kept overnight under high vacuum. This mixture was then dissolved in dry CH_2Cl_2 (5 mL mmol^{-1}), the solution was cooled to the appropriate temperature (–30 °C or –50 °C), and $BF_3{\cdot}Et_2O$ (2.0 equiv.) was added. After TLC analysis indicated full disappearance of the starting materials (usually 10 min), the reaction was quenched by addition of 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 resulting organic phase was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel column chromatography.

Glycosidation of Diol 25 with 4b: In two different experiments, orthobenzoate **4b** (92 mg, 0.15 mmol) was treated with diol **25** (46 mg, 0.15 mmol) at –30 °C or –50 °C. After workup and column chromatography (hexane/EtOAc 7:3), trisaccharide **30**[39] (19 mg, 13% and 16 mg, 7%, respectively), and a single spot containing an inseparable mixture of disaccharides **28**[39] and **29**[39] (55 mg, 41%, ratio **28/29** 3.0:1; and 63 mg, 47%, ratio **28/29** 4.8:1, respectively) were isolated.

Glycosidation of Diol 26 with 4b: In two different experiments, orthobenzoate **4b** (92 mg, 0.15 mmol) was treated with diol **26** (46 mg, 0.15 mmol) at –30 °C or –50 °C. After workup and column chromatography (hexane/EtOAc 7:3), trisaccharide **32**[39] (7 mg, 3% and 13 mg, 5% respectively), and disaccharide **31**[39] (47 mg, 35% and 56 mg, 41%, respectively) were obtained.

Glycosidation of Diol 27 with 4b: In two different experiments, orthobenzoate **4b** (92 mg, 0.15 mmol) was treated with diol **27** (60 mg, 0.15 mmol) at –30 °C or –50 °C. After workup and column chromatography (hexane/EtOAc 7:3), disaccharide **33**[39] (72 mg, 49% and 74 mg, 50%, respectively) was obtained.

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

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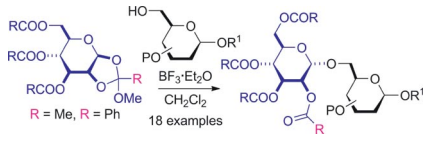
Methyl 1,2-orthoesters are useful glycosyl donors upon acid activation with boron trifluoride etherate. They react smoothly with monosaccharide alcohols or diols, leading to disaccharides in good to excellent yields. When monosaccharide diols are used as glycosyl acceptors, good regioselectivity in the glycosyl coupling is observed.



Keywords: Carbohydrates / Glycosylation / Glycosyl donors / Regioselectivity

