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Unexpected Stereocontrolled Access to 1α,1′β-Disaccharides from Methyl 1,2-Ortho Esters

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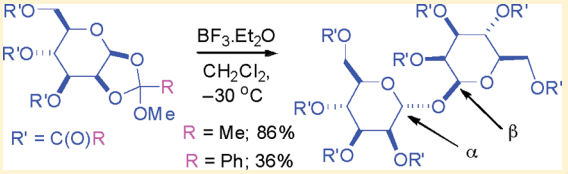
Supporting Information

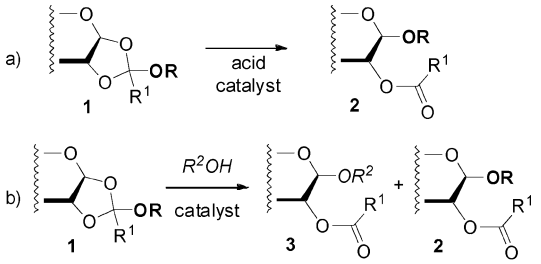
ABSTRACT: Mannopyranose-derived methyl 1,2-orthoacetates (R = Me) and 1,2-orthobenzoates (R = Ph) undergo stereoselective formation of 1α,1′β-disaccharides, upon treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2, rather than the expected acid-catalyzed reaction leading to methyl glycosides by way of a rearrangement−glycosylation process of the liberated methanol.



Alkyl 1,2-ortho esters, first introduced in glycosylation studies by Kochetkov and co-workers,[1−4] have been recently revitalized[5] with the advent of *n*-pentenyl ortho esters (NPOEs)[6−8] and can be considered as valuable, multifaceted substrates in oligosaccharide[9] assembly.[10,11]

Alkyl 1,2-ortho esters (e.g., **1**, Scheme 1a) undergo a facile acid-catalyzed rearrangement to glycosides.[12,13] In this context,

Scheme 1. Transformations Involving Alkyl 1,2-Ortho Esters



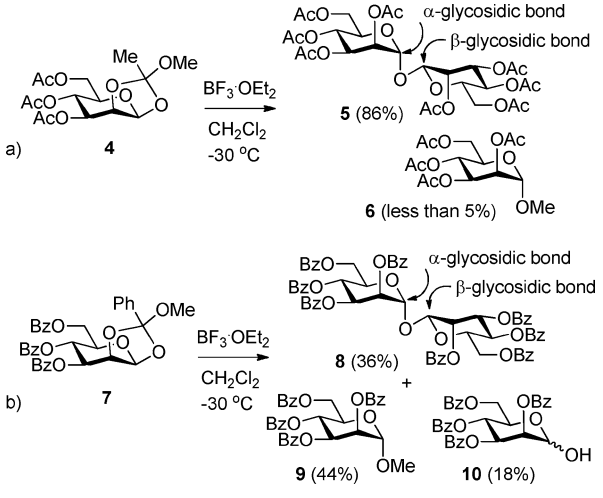
R = alkyl, *n*-pentenyl, propargyl

n-pentenyl glycosides are routinely prepared in our laboratories by acid-catalyzed rearrangement of NPOEs.[14] However, their use in "direct" glycosylation protocols[15,16] is compromised by the *competing glycosylation issue* depicted in Scheme 1b, where the leaving group (OR) can compete with the glycosyl acceptor (R^2OH) to give a mixture of glycosides (e.g., **2** and **3**, Scheme 1b).[17] Along these lines, the success of NPOEs[2] as glycosyl donors rests in the fact that by way of halonium, rather than acid, activation the pentenyloxy moiety (Scheme 1b, R = *n*-pentenyl) is extruded as a non-nucleophilic 2-(halomethyl)-tetrahydrofuran,[18,19] thus reducing the amount of rearranged glycoside (e.g., **2**).

Along these lines, it could be anticipated that methyl 1,2-ortho esters (**1**, R = Me) should be useful precursors for methyl glycosides by acid-catalyzed rearrangement, i.e. **1** → **2** (R = Me). In this paper we disclose that some methyl 1,2-mannopyranosyl ortho esters lead upon treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2, in a completely stereocontrolled manner, to 1α,1′β-mannose disaccharides rather than to the expected methyl mannopyranosides.[20] This unexpected outcome has been studied, and a reaction pathway that accounts for the observed experimental results is advanced.

In an attempt to prepare methyl mannopyranoside **6**, we treated the mannose-derived methyl 1,2-orthoacetate **4** with $BF_3{\cdot}Et_2O$. To our surprise, 1α,1′β-mannose disaccharide **5** was isolated in 86% yield, and no significant amount (<5%) of methyl mannopyranoside **6** could be observed (Scheme 2a).[21]

Scheme 2. Reaction of Methyl Ortho Esters 4 and 7 with $BF_3{\cdot}Et_2O$ (3 equiv) in CH_2Cl_2 at −30 °C



In contrast, treatment of 1,2-orthobenzoate **7** with $BF_3{\cdot}Et_2O$ did afford the methyl mannopyranoside **9** in 44% yield (Scheme 2b).

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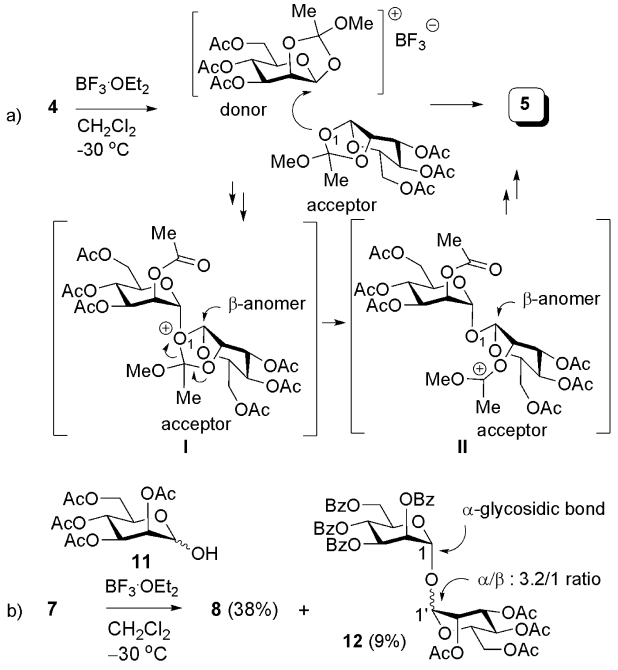
However, 1α,1′β-mannose disaccharide **8** was also observed (36%), along with hemiacetal **10**. The configurations at C-1 and C-1′ in compounds **5** and **8** were unambiguously assigned on the basis of their $^{1}J_{C1,H1}$ coupling constants.[22,23]

Several aspects of these transformations could be regarded as remarkable: (i) the unexpected formation of 1,1′-disaccharides **5** and **8** in appreciable amounts, (ii) the complete stereocontrol in their formation (along with the β stereochemistry on one of the monosaccharide components), and (iii) the absence of methyl mannopyranoside **6** in the reaction of methyl ortho ester **4**.

With respect to item ii, the α-anomeric configurations of disaccharide products **5** and **8** are consistent with the well-known 1,2-trans-directing effect of ortho ester glycosyl donors. Because of the latter effect, the anomeric β configurations in **5** and **8** must be seen as "unusual", therefore inviting speculation that the β configuration was retained from the ortho ester progenitor **4** or **7**. Thus, a reaction pathway is suggested in Scheme 3, where the ortho ester serves as both donor and

Scheme 3. Proposed Rationalization for the Entirely Stereocontrolled Formation of 1α,1′β-Disaccharides from 1,2-Ortho Esters and a Supporting Experiment



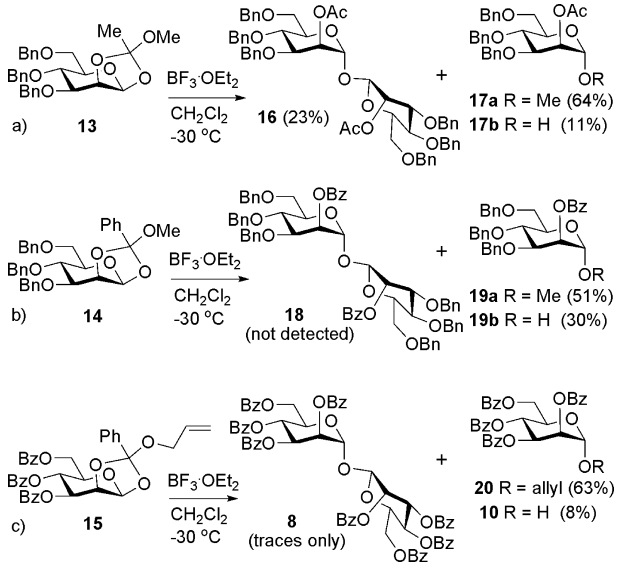
acceptor, going through intermediates **I** and then **II**, establishing inverted (α) and retained (β) configurations consecutively in disaccharide products **5** and **8**.[24]

In order to discard the formation of 1α,1′β-disaccharides by direct glycosylation of an in situ formed hemiacetal (e.g., **10**) by the ortho ester,[25] we conducted the experiment depicted in Scheme 3b. Accordingly, methyl orthobenzoate **7** was treated with $BF_3{\cdot}Et_2O$ in the presence of hemiacetal **11**, to give a mixture of 1α,1′β-disaccharide **8** and 1,1′-disaccharides **12** in 38 and 9% yield, respectively.[26,27]

The formation of **12** as an anomeric mixture, with the α,α' isomer predominating, is in agreement with the stereochemical preference for α orientation displayed by hemiacetal mannopyranose glycosyl acceptors in 1,1′-disaccharide formation.[28,29] On the basis of this evidence, we rule out the participation of hemiacetal species in the glycosylation events leading to 1,1′-disaccharides in Scheme 2.

To gain insight into the formation of these 1,1′-disaccharides, we examined the mannose ortho esters shown in Scheme 4.

Scheme 4. Reaction of Ortho Esters 13–15 with $BF_3{\cdot}Et_2O$



There were striking differences in results obtained from the tri-*O*-acetyl and tri-*O*-benzyl orthoacetate analogues **4** and **13**, respectively. With respect to the methyl orthoacetate **4** rearrangement products, compound **6** was "not observed" in Scheme 2a, whereas the analogous compound **17a** was the major product in Scheme 4a. On the other hand, whereas disaccharide **5** had been the major product in Scheme 2a, analogue **16**[30] was a minor product in Scheme 4a.

The effect of the alkoxy moiety on the reaction was tested by replacing methoxy with allyloxy in orthobenzoate **15** (Scheme 4c). This change also resulted in a reduced yield of 1,1′ disaccharide **8** (compare Scheme 2b with Scheme 4c).

According to the results in Scheme 4, the protecting groups in the pyranose ring and the nature of the alkoxy moiety of the ortho ester play an important role in the formation of 1,1′-disaccharides. Better yields are observed for methyl ortho esters on acyl-substituted pyranoses.

We have also studied the effect of different acids on methyl orthoacetate **4**. Thus, treatment of **4** with $Yb(OTf)_3$ and $HgBr_2$ in acetonitrile led to hemiacetal **11** in 91% and 42% yields, respectively, although in the latter case a considerable amount of unreacted ortho ester **4** (45%) was also recovered (Scheme 5a,b). The use of commercially available acid-washed molecular sieves under microwave irradiation[11,31] proved to be the method of choice for the preparation of methyl mannopyranoside **6** (90% yield, Scheme 5c). Finally, according to precedents,[32] reaction of **4** with TMSOTf led to a mixture of **6** (4.5%), and methyl di- and trisaccharides **21** and **22** (46% and 21%, respectively) (Scheme 5d).

As mentioned above, in addition to the unexpected formation of 1α,1′β-disaccharide **5**, an additional issue of interest in the reaction of **4** was the fate of the "supposedly" released methanol in the reaction medium, since no rearranged methyl mannoside **6**[15] had been observed (see Scheme 2a).

Our rationalization of these observations rests on the analysis of the commonly accepted reaction pathway for the reaction of

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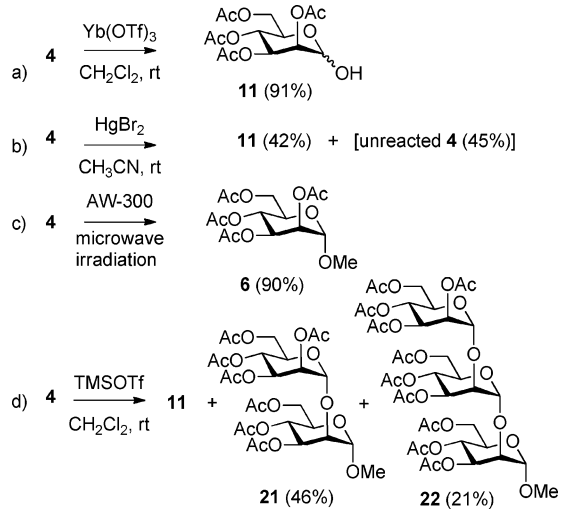
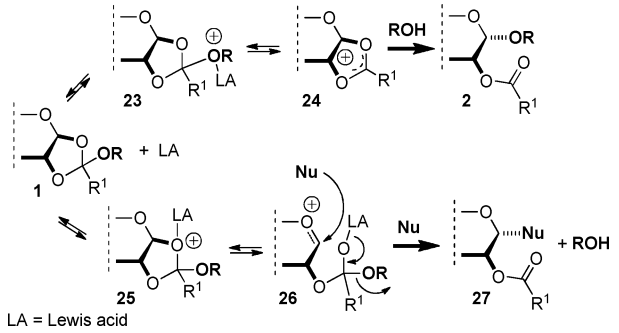
Scheme 5. Reaction of Methyl Ortho Ester 4 under Different Conditions



1,2-ortho esters with Lewis acids (Scheme 6).[3,4,33−36] Accordingly, the formation of alkyl mannosides by rearrangement would invoke coordination of the Lewis acid (LA) with OR (e.g., **1** → **23**, Scheme 6), followed by bond cleavage to dioxolenium **24**[37] and subsequent glycosylation of the extruded ROH to give **2**.

Scheme 6. Proposed Reaction Pathway for the Formation of 1α,1′β-Disaccharides 5 and 8 from Ortho Ester 1



However, Lewis acid activation could also take place at *O*-1 (e.g., **1** → **25**, Scheme 6),[3,4,33−36] and the results obtained in this work could be explained if $BF_3{\cdot}Et_2O$ activation of methyl ortho esters proceeds through intermediate **25** and then oxocarbenium ion **26**, which is susceptible to reaction with an "external nucleophile". The methoxy residue (OR, R = Me) is then extruded subsequently. As indicated by **I** (Scheme 2a), we propose that the "external nucleophile" can be the anomeric oxygen of an ortho ester.

We sought support of the foregoing analysis by treating ortho ester **7** in the usual way, except that 1.0 equiv of CD_3OD was included, with the expectation that it could scavenge any oxocarbenium ion **26**. Indeed, deuteriomethyl mannopyranoside **9** was isolated (85% deuterium content) and formation of the 1,1′-disaccharide **8** was thwarted.

In summary, some mannose-derived methyl 1,2-orthoacetates and 1,2-orthobenzoates react in the presence of $BF_3{\cdot}Et_2O$ to give 1α,1′β-disaccharides in a completely stereocontrolled manner. The construction of this type of saccharide bridge is a challenging process, and this 1α,1′β-disaccharide unit has been found in the antibiotic everninomicin 13,384-1,[38] which has shown antibacterial properties against drug-resistant pathogens.[39] On the other hand, a reaction pathway in which the cyclic ortho ester acts as a nucleophile has been put forward to account for the β-stereochemistry of one of the components. A reaction course in which coordination of the 1,2-ortho ester with the Lewis acid takes place at *O*-1, e.g. **25**, rather than at the exocyclic OR, e.g. **23**, could explain this outcome. Synthetic implications of these findings in glycosylation studies are under consideration in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. ^1H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ using a 300, 400, or 500 MHz spectrometer. Optical rotations were determined for solutions in chloroform at 25 °C. Column chromatography was performed on silica gel (230−400 mesh). TLC was conducted in precoated Kieselgel 60 F254 (Merck). Detection was first by UV light (254 nm) and then charring with a 1/20/4 solution of sulfuric acid/acetic acid/H_2O. All solvents were purified by distillation over drying agents or by elution through a PURE SOLV purification system. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions. Microwave irradiation was performed with a single-mode Discovery System from CEM Corp. Methyl orthoacetate **4**[40,41] and methyl orthobenzoates **7**[42] and **15**[43] were prepared from tetra-*O*-acetyl-α-D-mannopyranosyl bromide[44] and tetra-*O*-benzoyl-α-D-mannopyranosyl bromide[12] following a published procedure.[41] Ortho esters **13** and **14** were prepared from **4** and **7**, respectively, as previously described.[45]

Reaction of Ortho Esters with $BF_3{\cdot}OEt_2$: General Procedure. A solution of the corresponding 1,2-ortho ester, in dry CH_2Cl_2 under argon at −30 °C, was treated with $BF_3{\cdot}Et_2O$. After 5−15 min, when all the starting material had disappeared, Et_3N was added and the resulting mixture was vigorously stirred. The reaction mixture was then concentrated, without heating, and the crude product was purified by flash chromatography.

(2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl)-2,3,4,6-tetra-O-acetyl-β-D-mannopyranoside (5). Following the general procedure, the 1,2-ortho ester **4** (50 mg, 0.14 mmol) was treated with $BF_3{\cdot}Et_2O$ (50 μL, 0.42 mmol). After 5 min, Et_3N (59 μL, 0.42 mmol) was added, and the residue was purified by flash chromatography (hexane/EtOAc, 1/1) to yield compound **5** (41 mg, 86%). Data for **5**: $[\alpha]_D$ = +15.6° (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 2.16 (s, 3 H), 2.23 (s, 3 H), 3.69 (ddd, *J* = 9.8, 5.8, 2.5 Hz, 1 H), 4.09 (m, 1 H), 4.17 (dd, *J* = 12.3, 5.9 Hz, 1 H), 4.24 (dd, *J* = 12.3, 2.5 Hz, 1 H), 4.26−4.28 (m, 1 H), 4.28 (dd, *J* = 12.7, 2.8 Hz, 1 H), 4.87 (d, *J* = 1.3 Hz, 1 H), 5.05 (dd, *J* = 10.0, 3.4 Hz, 1 H), 5.09 (d, *J* = 1.8 Hz, 1 H), 5.17 (dd, *J* = 2.9, 1.9 Hz, 1 H), 5.22 (t, *J* = 9.9 Hz, 1 H), 5.33−5.39 (m, 2 H), 5.49 (dd, *J* = 3.4, 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8 (×4), 20.9 (×2), 21.0, 62.0, 62.7, 65.6, 65.7, 68.7 (×2), 69.2, 69.6, 70.7, 73.2, 97.8 (dd, *J* = 157.4, 2.1 Hz, C_β), 98.2 (dd, *J* = 174.6, 4.3 Hz, C_α), 169.7 (×2), 169.9, 170.0, 170.1, 170.5, 170.8, 170.9; API-ES positive 701.1 $(M + Na)^+$. Anal. Calcd for $C_{28}H_{38}O_{19}$ (678.59): C, 49.56; H, 5.64; O, 44.80. Found: C, 49.47; H, 5.50.

(2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranosyl)-2,3,4,6-tetra-O-benzoyl-β-D-mannopyranoside (8). Following the general procedure, a solution of the 1,2-ortho ester **7** (61.1 mg, 0.1 mmol) was treated with $BF_3{\cdot}Et_2O$ (38 μL, 0.3 mmol). After 5 min, Et_3N (42 μL, 0.3 mmol) was added, and the residue was purified by flash chromatography (hexane/EtOAc, 8/2) to yield the 1α,1′β-disaccharide **8** (21 mg, 36%), methyl mannopyranoside **9**[46] (27 mg, 44%), and hemiacetal **10**[47] (11 mg, 18%). Data for **8**: $[\alpha]_D$ = −54.3° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (m, 1 H), 4.34 (dd, *J* = 12.3, 2.4 Hz, 1 H), 4.44 (dd, *J* = 12.3, 4.0 Hz, 1 H), 4.55 (m, 1 H), 4.68 (dd, *J* = 12.4, 2.1 Hz, 1 H), 4.93 (dd, *J* = 12.2, 2.3 Hz, 1 H), 5.36 (s, 1 H), 5.51 (s, 1 H), 5.67−5.70 (m, 3 H), 6.08−6.20 (m, 3 H), 7.20−8.15 (m, 40 H); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ 62.2, 62.3, 66.4 (×2), 69.7 (×2), 69.9, 70.0, 71.6, 73.3, 97.6 (d, J = 174.9 Hz, C_α), 98.1 (d, J = 158.4 Hz, C_β), 128.3 (×3), 128.4 (×3), 128.5 (×3), 128.6 (×6), 128.7 (×3), 128.8, 128.9, 129.1, 129.2, 129.3, 129.5, 129.8 (×3), 129.9 (×3), 130.0 (×6), 130.1, 130.2 (×3), 133.1 (×2), 133.3, 133.4, 133.5 (×2), 133.6, 133.7, 165.1, 165.2, 165.3, 165.4, 165.6, 165.7, 166.1 (×2). ESI-HRMS: 1192.3578 $(M+NH_4)^+$; Anal. Calcd for $C_{68}H_{54}O_{19}$ (1174.32): C, 69.50; H, 4.63; O, 25.87; Found C, 69.61; H, 4.67.

*(2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranosyl)-2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside and (2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranosyl)-2,3,4,6-tetra-O-acetyl-β-D-mannopyranoside (**12**).* To a stirred solution of the 1,2-ortho ester **7** (91.6 mg, 0.15 mmol) and hemiacetal **11**[48] (52.2 mg, 0.15 mmol) was added $BF_3{\cdot}Et_2O$ (57 μL, 0.45 mmol). After 5 min, Et_3N (63 μL, 0.45 mmol) was added and the resulting residue was purified by flash chromatography (hexane/EtOAc, 8/2 to 7/3) to give **8** (34 mg, 38%) and 1,1′-disaccharides **12** (1α, 1′α/1α, 1′β; 3.2/1 ratio) (12.4 mg, 9%) along with other compounds such as 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride (14 mg, 16%), methyl glycoside **9** (29 mg, 32%), and unchanged starting material **11** (30 mg, 57%). Selected data for **12** are as follows. Major isomer: 1α,1′α-disaccharide ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, J = 1.3 Hz, 1H, H-1′), 5.46 (dd, J = 1.3, 3.5 Hz, 1H, H-2′), 5.46 (d, J = 1.8 Hz, 1H, H-1), 5.72 (dd, J = 1.8, 3.4 Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.17 (d, J = 173.8 Hz, C-1α), 93.49 (d, J = 173.3 Hz, C-1′α). Minor isomer: 1α,1′β-disaccharide ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (d, J = 1.2 Hz, 1H, H-1′), 5.38 (d, J = 1.8 Hz, 1H, H-1), 5.60 (dd, J = 1.2, 3.3 Hz, 1H, H-2′), 5.64 (d, J = 1.8, 3.3 Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 97.84 (d, J = 156.7 Hz, C-1′β), 98.10 (d, J = 175.3 Hz, C-1α). Anal. Calcd for $C_{48}H_{46}O_{19}$ (926.86): C, 62.20; H, 5.00; O, 32.80. Found: C, 62.30; H, 5.10.

*(2-O-acetyl-3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-2-O-acetyl-3,4,6-tetra-O-benzyl-β-D-mannopyranoside (**16**).* Following the general procedure, the 1,2-ortho ester **13** (50.6 mg, 0.1 mmol) was treated with $BF_3{\cdot}Et_2O$ (38 μL, 0.3 mmol). After 10 min, Et_3N (42 μL, 0.3 mmol) was added, and the residue was purified by flash chromatography (hexane/EtOAc 8/2), to yield 1α,1β′-disaccharide **16** (11 mg, 23%) along with methyl glycoside **17a** (32 mg, 64%) and hemiacetal **17b** (6 mg, 11%). Data for **16**: $[\alpha]_D$ = +19.3° (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.07 (s, 3H), 3.38 (ddd, J = 9.7, 4.3, 2.6 Hz, 1H), 3.52 (dd, J = 10.8, 1.9 Hz, 1H), 3.56 (dd, J = 9.3, 3.3 Hz, 1H), 3.58−3.68 (m, H), 3.86−3.92 (m, 2H), 3.99−4.02 (m, 1H), 4.25 (d, J = 12.1 Hz, 1H), 4.38 (d, J = 15.0 Hz, 1H), 4.39 (d, J = 15.0 Hz, 1H), 4.41 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 15.0 Hz, 1H), 4.46 (d, J = 15.0 Hz, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.50 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 1.0 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.79 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 1.8 Hz, 1H), 5.23 (dd, J = 1.9, 2.9 Hz, 1H), 5.53 (dd, J = 1.0, 3.2 Hz, 1H), 7.08−7.25 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.5, 68.0, 68.5, 68.7, 69.3, 71.7, 72.0, 72.4, 73.4, 73.5, 74.1, 74.2, 75.2, 75.3, 75.9, 77.8, 80.2, 98.2, 98.3, 127.6 (x2), 127.7 (×2), 127.8 (×3), 127.9 (×3), 128.0 (×3), 128.2 (×3), 128.3 (×2), 128.4 (×4), 128.5 (×4), 128.6 (×4), 137.6, 138.0, 138.3, 138.4, 138.5, 138.7, 170.5, 170.6; ESI-HRMS 989.4203 $(M + Na)^+$. Anal. Calcd for $C_{58}H_{62}O_{13}$ (966.4190): C, 72.03; H, 6.46; O, 21.51. Found: C, 72.25; H, 6.33.

*Methyl 2-O-Benzoyl-3,4,6-tetra-O-benzyl-α-D-mannopyranoside (**19a**) and 2-O-Benzoyl-3,4,6-tetra-O-benzyl-α-D-mannose (**19b**).* Following the general procedure, the 1,2-ortho ester **14** (56.8 mg, 0.1 mmol) was treated with $BF_3{\cdot}Et_2O$ (38 μL, 0.3 mmol). After 10 min Et_3N (42 μL, 0.3 mmol) was added and the resulting residue was concentrated and purified by flash chromatography (hexane/EtOAc 7/3) to yield methyl glycoside **19a** (29 mg, 51%) and hemiacetal **19b** (17 mg, 30%). Data for **19a**: $[\alpha]_D$ = +1.9° (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.71 (dd, J = 1.5, 10.2 Hz, 1H), 3.76 (m, 1H), 3.81 (m, 1H), 3.99 (m, 2H), 4.46 (d, J = 10.9 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.78 (d, J = 2.2 Hz, 1H), 4.80 (d, J = 10.2 Hz, 1H), 5.54 (bt, J = 2.2 Hz, 1H), 7.10−8.01 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.1, 69.0, 69.2, 71.5, 71.6, 73.5, 74.4, 75.3, 78.3, 98.9, 127.5 (×2), 127.6 (×2), 127.7 (×4), 128.0 (×2), 128.1 (×2), 128.4 (×3), 128.5 (×4), 130.0, 133.2, 138.1, 138.5 (×2), 165.8; API-ES positive 591.3 $(M + Na)^+$. Anal. Calcd for $C_{35}H_{36}O_7$ (568.24): C, 73.92; H, 6.38; O, 19.69. Found: C, 73.87; H, 6.30. Data for **19b**: 3.74−3.83 (m, 2H), 3.96 (m, 1H), 4.09−4.19 (m, 2H), 4.53 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.88 (d, J = 12.0 Hz, 1H), 5.35 (bs, 1H), 5.63 (dd, J = 1.9, 3.0 Hz, 1H), 7.18−8.08 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.8 (×2), 71.8, 71.9, 73.7, 74.9, 75.3, 77.9, 92.8, 127.7 (×3), 127.8 (×3), 128.1 (×3), 128.4 (×4), 128.5 (×4), 130.1 (×3), 133.2, 138.3, 138.6, 138.7, 165.9; API-ES positive 573.6 $(M + Na)^+$. Anal. Calcd for $C_{34}H_{34}O_7$ (554.62): C, 73.63; H, 6.18; O, 20.19. Found: C, 73.51; H, 6.12.

*Allyl 2,3,4,6-Tetra-O-benzoyl-α-D-mannopyranoside (**20**).* Following the general procedure, 1,2-ortho ester **15** (63.6 mg, 0.1 mmol) was treated with $BF_3{\cdot}Et_2O$ (38 μL, 0.3 mmol). After 10 min, Et_3N (42 μL, 0.3 mmol) was added and the resulting residue was concentrated and purified by flash chromatography (hexane/EtOAc 7/3) to yield allyl glycoside **20**[49] (40 mg, 63%), hemiacetal **10** (5 mg, 8%), and 1α,1β′-disaccharide **8** (2 mg, 2%).

Reaction of Methyl Ortho Ester 4 with Different Acids. *Reaction with $Yb(OTf)_3$.* To a stirred solution of methyl ortho ester **4** (100 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (4 mL), at room temperature, was added $Yb(OTf)_3$ (515 mg, 0.83 mmol). After $5^1/_2$ h all the starting material has disappeared and the reaction mixture was treated with Et_3N (700 μL). The crude mixture was concentrated and purified by flash chromatography (hexane/EtOAc 7/3) to yield hemiacetal **11** (87 mg, 91%).

Reaction with $HgBr_2$. Methyl ortho ester **4** (100 mg, 0.28 mmol) in anhydrous CH_3CN (4 mL) at room temperature was treated with $HgBr_2$ (302.4 mg, 0.84 mmol). After 12 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 over Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc 7/3) to yield hemiacetal **11** (41 mg, 42%).

Reaction with AW-300. A solution of methyl ortho ester **4** (50 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (4 mL) was treated with acid molecular sieves AW-300 (1.6 mm pellets, 1 g). After it was heated for 2 h at 50 °C under MW irradiation, the crude mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc 7/3) to afford methyl glycoside **6** (46 mg, 90%).

Reaction with TMSOTf. To a stirred solution of methyl ortho ester **4** (100 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (4 mL) at −30 °C was added TMSOTf (158 μL, 0.84 mmol). After 5 min, 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 over Na_2SO_4, filtered, and concentrated.

The resulting residue was purified by silica gel flash column chromatography (hexane/EtOAc, 1/1) to yield methyl glycoside **6** (4.6 mg, 4.5%), methyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-mannopyranoside **21**[50] (42.4 mg, 46%), and trisaccharide **22** (19 mg, 21%). Data for **22**: $[\alpha]_D$ = +2.0° (*c* 0.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.02 (s, 3H), 2.03 (s, 6H), 2.05 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 3.41 (s, 3H), 3.89 (m, 1H), 4.01 (m, 1H), 4.06−4.19 (m, 8H), 4.23 (dd, J = 4.8, 12.0 Hz, 1H), 4.86 (bs, 1H), 4.94 (bs, 1H), 5.09 (d, J = 1.6 Hz, 1H), 5.24−5.32 (m, 6H), 5.38 (dd, J = 3.2, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8 (×4), 20.9 (×4), 21.0 (×2), 55.4, 62.3, 62.4, 62.7, 66.3, 66.4, 68.5, 68.6, 69.4, 69.6, 69.7, 69.8, 70.5, 76.7, 77.4, 99.3, 99.5, 99.9, 169.5, 169.6 (×2), 169.8, 169.9, 170.2, 170.3, 170.6, 170.9, 171.0; ESI-HRMS 956.3215 $(M + NH_4)^+$. Anal. Calcd for $C_{39}H_{54}O_{26}$ (938.8305): C, 49.89; H, 5.80; O, 44.31. Found: C, 49.71; H, 5.77.

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Reaction of Methyl Ortho Ester 7 in the Presence of CD_3OD. Following the general procedure, to a solution of the 1,2-ortho ester **7** (50 g, 0.08 mmol) in dry CH_2Cl_2 (3 mL), under argon and cooled to −30 °C, was added CD_3OD (3.33 μL, 0.08 mmol), and this mixture was treated with $BF_3{\cdot}Et_2O$ (31 μL, 0.25 mmol). After 5 min, when all the starting material had disappeared, Et_3N (1 mL) was added and the resulting mixture was vigorously stirred. The residue was concentrated and purified by flash chromatography (hexane/EtOAc, 8/2) to yield deuteriomethyl mannopyranoside **9** (22 mg, 48% yield, 85% deuterium content) and hemiacetal **10** (12 mg, 24%).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron Lett.* **1964**, *5*, 289−293.

(2) Kochetkov, N. K. *Tetrahedron* **1987**, *43*, 2389−2436.

(3) Kong, F. *Carbohydr. Res.* **2007**, *342*, 345−373.

(4) Fraser-Reid, B.; López, J. C. Orthoesters and Related Derivatives. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: New York, 2008; Chapter 5.1.

(5) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934.

(6) Lu, J.; Fraser-Reid, B. *Chem. Commun.* **2005**, 862−864.

(7) Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894−5898.

(8) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; López, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449−2463.

(9) McReynolds, K. D.; Gervay-Hague, J. *Chem. Rev.* **2007**, *107*, 1533−1552.

(10) Marotte, K.; Sanchez, S.; Bamhaoud, T.; Prandi, J. *Eur. J. Org. Chem.* **2003**, 3587−3598, and references cited therein.

(11) Ravidà, A.; Liu, X.; Kovacs, L.; Seeberger, P. H. *Org. Lett.* **2006**, *8*, 1815−1818, and references cited therein.

(12) They have become substrates of choice in the preparation of *n*-pentenyl glycosides: Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345−7354.

(13) Ortho esters have also been employed in the synthesis of glycosyl phosphates.[11] *Thio or seleno glycosides*: (a) Sanchez, S.; Bamhaoud, T.; Prandi, J. *Eur. J. Org. Chem.* **2002**, 3864−3873. *S-thiazolinyl glycosides*: (b) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123−7126. (c) Pornsuriyasak, P.; Demchenko, A. V. *Chem. Eur. J.* **2006**, *12*, 6630−6646. *Glycosyl fluorides*: (d) López, J. C.; Ventura, J.; Uriel, C.; Gómez, A. M.; Fraser-Reid, B. *Org. Lett.* **2009**, *11*, 4128−4131.

(14) *n*-Pentenyl glycosides are readily obtained by rearrangement of NPOEs mediated by $Yb(OTf)_3$ in CH_2Cl_2, from 0 °C to room temperature. For the first report on the use of $Yb(OTf)_3$ in NPOE chemistry, see: Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett.* **2002**, *43*, 6953−6955.

(15) "Two-stage" glycosylation strategies that make use of ortho ester intermediates have been described: Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6−C9.

(16) See also: Kong, F. *Curr. Org. Chem.* **2003**, *7*, 841−865, and references cited therein.

(17) For early strategies to overcome this problem, see: Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Snyatkova, V. J. *Carbohydr. Res.* **1971**, *16*, 17−27.

(18) Llera, J. M.; López, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 2997−2998.

(19) Propargyl ortho esters that also release a non-nucleophilic species have been recently described: Vidadala, S. R.; Thadke, S. A.; Hotha, S. *J. Org. Chem.* **2009**, *74*, 9233−9236, and references cited therein.

(20) Castillón and co-workers have reported the use $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to induce the rearrangement of ortho ester intermediates to glycolipids; see: (a) Morales-Serna, J. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 443−446. (b) Morales-Serna, J. A.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 3831−3836.

(21) Careful inspection of a blowout of the anomeric region in the ^1H NMR spectrum of the reaction of **4** with $BF_3{\cdot}Et_2O$ showed the presence of some methyl mannopyranoside **6** (<5%), although it could not be isolated.

(22) Duus, J. Ø.; Gotfredsen, C. H.; Bock., K. *Chem. Rev.* **2000**, *100*, 4589−4614.

(23) $^1J_{C1,H1}$ Coupling constants: **5**, C-1α $^1J_{C1,H1}$ = 174.6 Hz, C-1β $^1J_{C1,H1}$ = 157.4 Hz; , C-1α $^1J_{C1,H1}$ = 174.9 Hz, C-1β $^1J_{C1,H1}$ = 158.4 Hz.

(24) In this context, Nicolaou et al. described a related stereocontrolled construction of 1,1′-disaccharides comprising a β-mannoside structure in which a five-membered-ring stannane was used to fix the anomeric oxygen in the desired β configuration; see: Nicolaou, K. C.; van Delf, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodríguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057−9058.

(25) Hemiacetals have been used as glycosyl acceptors in the preparation of 1,1′-disaccharides; see: Wang, W.; Kong, F. Z. *Tetrahedron Lett.* **1999**, *40*, 1361−1364, and references cited therein.

(26) Other compounds such as hemiacetal **11** (57%), methyl mannopyranoside **9** (32%), and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl fluoride (16%) were also isolated from the reaction media.

(27) ^{13}C NMR $^1J_{C1,H1}$ coupling constants, disaccharides **12** (1α,1′α/1α,1′β, 3.2/1 ratio): major isomer, 93.17 (d, $^1J_{C1,H1}$ = 173.8 Hz, C-1), 93.49 (d, $^1J_{C1,H1}$ = 173.3 Hz, C-1′); minor isomer, 98.10 (d, $^1J_{C1,H1}$ = 175.3 Hz, C-1, 97.84 (d, $^1J_{C1,H1}$ = 156.7 Hz, C-1′).

(28) Nishizawa, M.; Garcia, D. M.; Noguchi, Y.; Komatsu, K.; Hatakeyama, S.; Yamada, H. *Chem. Pham. Bull.* **1994**, *42*, 2400−2402.

(29) Yoshimura, J.; Hara, K.; Sato, T.; Hashimoto, H. *Chem. Lett.* **1983**, 319−320.

(30) ^{13}C NMR $^1J_{C1,H1}$ coupling constants, disaccharide **16**: 98.16 (d, $^1J_{C1,H1}$ = 156.2 Hz, C-1), 98.30 (d, $^1J_{C1,H1}$ = 172.5 Hz, C-1′.

(31) For the recent use of acid-washed molecular sieves in glycosylation, see: Morales-Serna, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2009**, 3849−3852, and references cited therein.

(32) Zhu, Y.; Kong., F. *Synlett* **2001**, 1217−1220.

(33) Bochkov, A. F.; Zaikov, G. E. *The Chemistry of the O-Glycosidic Bond*; Pergamon Press: New York, 1979; p 210.

(34) Garegg, P. J.; Konradsson, P.; Kvarnstrom, I.; Norberg, T.; Svensson, S. C. T.; Wigilius, B. *Acta Chem. Scand., Ser. B* **1985**, *39*, 569−577.

(35) Garegg, P. J.; Kvarnstrom, I. *Acta Chem. Scand., Ser. B* **1976**, *30*, 655−658.

(36) Crich, D.; Dai, Z.; Gastaldi, S. *J. Org. Chem.* **1999**, *64*, 5224−5229.

(37) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem. Eur. J.* **2003**, *9*, 4687−4692.

(38) Ganguly, A. K.; Pramanik, B.; Chan, T. C.; Sarre, O.; Liu, Y.-T.; Morton, J.; Girijavallabhan, V. M. *Heterocycles* **1989**, *28*, 83−88.
(39) Nicolaou, K. C.; Fylaktakidou, K. C.; Mitchell, H. J.; van Delf, F. L.; Rodríguez, R. M.; Conley, S. R.; Jin, Z. *Chem. Eur. J.* **2000**, *6*, 3166−3184.
(40) Beignet, J.; Tiernan, J.; Woo, C. H.; Kariuki, B. M.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341−6356.
(41) Wei, S.; Zhao, J.; Shao, H. *Can. J. Chem.* **2009**, *87*, 1733−1737.
(42) Hoelemann, A.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8071−8088.
(43) Anas, S.; Sajisha, V. S.; Rajan, R.; Kumaran, R. T.; Radhakrishnan, K. V. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 553−560.
(44) Lóbrega, C.; Vázquez, J. T. *Tetrahedron: Asymmetry* **2003**, *14*, 2793−2801.
(45) For compound **13**, see ref 40, and for compound **14**, see ref 42.
(46) Esmurziev, A; Simic, N; Sundby, E.; Hoff, B. H. *Magn. Reson. Chem.* **2009**, *47*, 449−452.
(47) Mbadugha, B. N. A.; Menger, F. M. *Org. Lett.* **2003**, *5*, 4041−4044.
(48) Tosin, M.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4107−4117.
(49) Pakulski, Z. *Synthesis* **2003**, 2074−2078.
(50) Szurmai, Z.; Balatoni, L.; Lipták, A. *Carbohydr. Res.* **1994**, *254*, 301−309.