Study of the Regioselectivity of Intra- and Intermolecular Glycosylations of Mannoside Diol Acceptors

M. Belén Cid,*[1] Serafín Valverde,* J. Cristobal López, Ana M. Gómez, Mercedes García[2]

Instituto de Química Orgánica General, Juan de la Cierva 3, 28006 Madrid, Spain
Fax +34(91)4973966; E-mail: Belen.cid@uam.es

Received 25 October 2005

Abstract: The intramolecular glycosylation of thiomannoside donors linked through C6′ by a phthaloyl group to C3 of a diol mannoside acceptor is described. The unexpected results led us to undertake a systematic analysis of the factors affecting the regioselectivity of the intermolecular process. The substituents on the diol mannoside acceptor have been found to play an important role.

Key words: glycosylation, regioselectivity, stereoselectivity

The interest in carbohydrate derivatives is increasing because of their function in many biological processes.[3] The preparation of complex oligosaccharides still requires enormous effort by synthetic organic chemists, and strategies that avoid protecting group manipulations through regioselective processes would be a tremendous advance.[3c] As a part of our program directed at developing regio- and stereoselective glycosylation methods based on intramolecular glycosylation[4] we applied this approach to the synthesis of a trimannan branched at C3 and C6, through a combined intramolecular-intermolecular one-pot glycosylation with minimal hydroxyl group protection.[4d] On the other hand, recent work by Fraser-Reid and coworkers[5b,6] has shown that the, normally overlooked, substituent at O-2 plays an important role in determining the regioselectivity on the glycosylation of diols. In this work we have drawn the attention to the, normally unnoticed, substituents at O-6 and O-3 in a mannoside-2,4-diol. Furthermore, we have compared intramolecular with intermolecular glycosylation processes.

The synthesis of mannosides branched at the C2 and C4 positions has been less studied than that of the 6,3- and 6,2-substituted oligomannosaccharides; however, some interesting results regarding regioselectivity have been published.[5] For example, position 4 of acceptors **4a** and **4b** is glycosylated in a regioselective manner, respectively, by donors **1** and **3**, which have participating groups at C2 (Figure 1).[5a] In contrast, when donor **2** with a non-participating group is used, the C2 hydroxyl group of the mannose acceptor **4a** undergoes complete regioselective glycosylation.[5b] It has also been shown that glucosamine donors with phthalimide as the participating protecting group at C2 also react regioselectively with the C4 hydroxyl group of the acceptor.[7]

SYNLETT 2005, No. 7, pp 1095–1100
Advanced online publication: 14.04.2005
DOI: 10.1055/s-2005-865228; Art ID: D31804ST

The results of our investigations into the regioselectivity of the equivalent reaction in the context of intramolecular glycosylation appeared to complement to those described previously for intermolecular processes and led us to undertake a thorough examination of the factors involved.

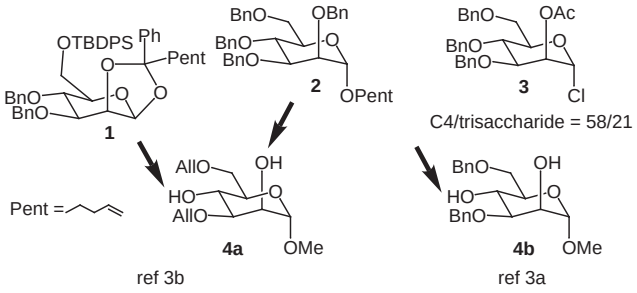


Figure 1 Regioselective glycosylations of mannoside acceptors **4** and donors with participating (**1** and **3**) and non-participating (**2**) groups

We first investigated the regioselectivity of glycoside donors in reactions with mannose diol acceptors analogous to **4** in an intramolecular glycosylation of diols **5** (Figure 2). The effects of both participating and non-participating groups at position C2 of the donors were analyzed. The C6′ and C3 positions were chosen as the anchoring sites for the donor and acceptor, respectively. In order to analyze the regioselectivity of the process for C4 and C2, the hydroxyl group at C6 of the acceptor was protected as a TBDPS group. Previous experience led us to use thioglycosides as the glycosyl donors and a phthaloyl group as the linker.[4]

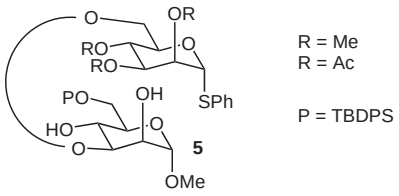
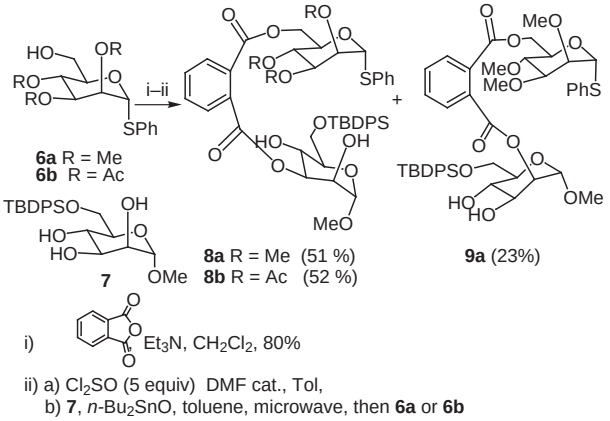


Figure 2 General structure of intramolecular glycosylation precursors

Precursors **6a**,**b** and **7** were used as the mannosyl donors[8,4d] and acceptor,[9] respectively, and were prepared from mannose following reported procedures. The (6′-3) and (6′-2) diester phthaloyl derivatives **8** and **9** were obtained from **6** by acylation, formation of the corre-

sponding acid chloride and coupling with the dialkylstannylene derivative of **7** prepared by microwave irradiation as described previously by us (Scheme 1).[4d] The acetylated donor **6b** furnished the (6′-3) linked diester **8b** in 52% yield and the permethylated derivative gave a 70:30 mixture of the (6′-3) and (6′-2) diesters **8a** and **9a**, which could be separated readily by flash chromatography.[10]



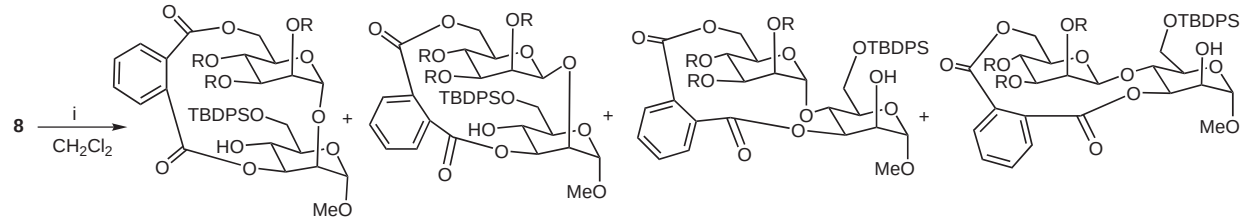
Scheme 1

The intramolecular glycosylation of diester **8a**, which bears the fully methylated donor, was studied under two different sets of reaction conditions (Table 1). When NIS was used as the only promoter (entry 1) the β(1-2) disaccharide **11a** was isolated in 39% yield and the α(1-2), α(1-4) and β(1-4) disaccharides **10a**, **12a** and **13a** were obtained after acetylation in 6, 8 and 8% yield, respectively. The NIS/AgOTf system (entry 2) led to a mixture of the α(1-2), β(1-2), α(1-4) and β(1-4) disaccharides (**10a**/**11a**/**12a**/**13a** = 21:37:37:5) in 62% yield. The intramolecular glycosylation of diol **8b** took place upon treatment with NIS/AgOTf (entry 3) to give a 75:25 mixture of the α(1-2) and α(1-4) disaccharides **10b** and **12b** in 46% yield.[11]

The formation of different ratios of stereoisomers depending on the activation procedure (NIS/TfOTMS or TfOMe) was also observed by Ziegler and co-workers when studying intramolecular (1-4) glycosylation of 3′- and 6′-linked mannoside donors with different acceptors.[12] Although several methods have been described recently for the preparation of β-mannosides in an intermolecular manner,[13] an intramolecular approach has once again proved to be a complementary alternative for the formation of this difficult kind of linkage.[14]

The result obtained in the glycosylation reaction of diester **8b** (entry 3) contrasts with those observed by Fraser-Reid and Ogawa, who observed the opposite regioselectivity in the intermolecular glycosylation of donors **1** and **3** bearing participating substituents at C2 with acceptors **4a** and **4b** (Figure 1).[5] An important difference between the intermolecular glycosylations studied by Ogawa and Fraser-Reid (Figure 1) and the intramolecular version studied by us (Table 1) lies in the protecting groups of the acceptor moiety. Since various factors, such as the type and position of the bridging group between the glycosyl donor and acceptor, can influence the regio- and stereoselectivity of intramolecular glycosylations, these results are difficult to rationalize. Therefore, with the aim of determining whether the intramolecular nature of the process was the only factor responsible for the different regioselectivity observed, several intermolecular glycosylations were carried out and are summarized in Table 2.

Table 1 Intramolecular Glycosylation

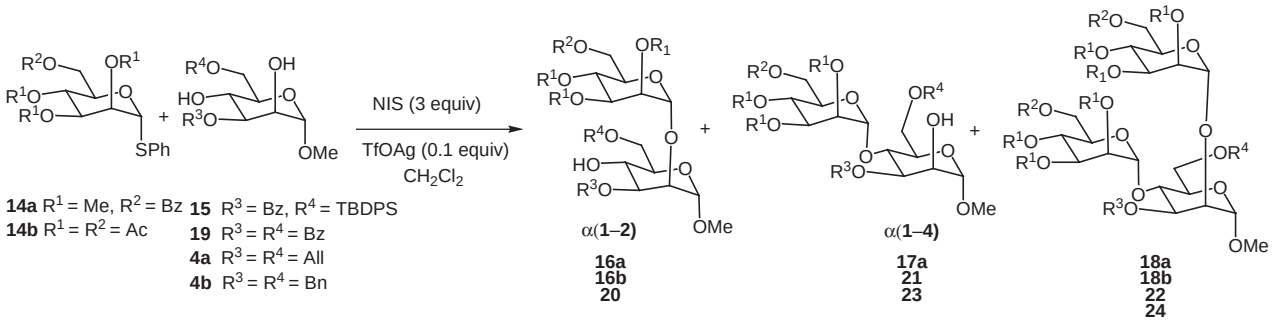


i) Method A: NIS (3 equiv), r.t., 48 h; method B: NIS (3 equiv), TfOAg (0.1 equiv), –40 °C to r.t., 24 h; method C: NIS (3 equiv), TfOAg (1 equiv), 0 ºC, 10 min.

Entry	Substrate	Conditions (yield, %)	Ratio of products			
			α(1-2) **10**	β(1-2) **11**	α(1-4) **12**	β(1-4) **13**
1	R = Me **8a**	Method A (61)[a]	10 (6%)	64 (39)	13 (8)	13 (8)
2	R = Me **8a**	Method B (62)	21	37	37	5
3	R = Ac **8b**	Method C (46)	75		25	

[a] Yields given for acetylated products.

Table 2 Intermolecular Glycosylations



14a R^1 = Me, R^2 = Bz
14b R^1 = R^2 = Ac
15 R^3 = Bz, R^4 = TBDPS
19 R^3 = R^4 = Bz
4a R^3 = R^4 = All
4b R^3 = R^4 = Bn

16a 16b 20 | **17a 21 23** | **18a 18b 22 24**

Entry	Substrates (donor/acceptor)	Conditions	Yield of glycosylation (%)		
			α(1-2)	α(1-4)	Trisaccharide
1	R^1 = Me, R^2 = Bz (**14a**)/ R^3 = Bz, R^4 = TBDPS (**15**)	0 °C to r.t., 48 h	12 (**16a**/**17a** = 3:1)		3 (**18a**)
2	R^1 = R^2 = Ac (**14b**)/ R^3 = Bz, R^4 = TBDPS (**15**)	0 °C to r.t., 1 h	23 (**16b**)	–	21 (**18b**)
3	R^1 = R^2 = Ac (**14b**)/ R^3 = R^4 = Bz (**19**)	0 °C to r.t., 20 min (38%)[a]	26 (**20**)	22 (**21**)	5 (**22**)
4	R^1 = R^2 = Ac (**14b**)/ R^3 = R^4 = Bz (**19**)	–40 °C to 0 °C, 3 h (23%)[a]	19 (**20**)	28 (**21**)	21 (**22**)
5	R^1 = R^2 = Ac (**14b**)/ R^3 = R^4 = All (**4a**)	–40 °C to 0 °C, 24 h	Complex mixture		
6	R^1 = R^2 = Ac (**14b**)/ R^3 = R^4 = Bn (**4b**)	–35 °C to 0 °C, 6 h 30 min (26%)[a]	–	51 (**23**)	12 (**24**)

[a] Recovered acceptor.

Donors **14a** and **14b**, prepared following standard procedures,[15] were chosen as analogues of diesters **8a** and **8b**, respectively, and used in equivalent intermolecular glycosylations. Mannosyl acceptor **15** presents maximum similarity with the acceptor used in the intramolecular version of the reaction.[16]

The glycosylation reaction of the armed donor **14a** with acceptor **15** afforded an inseparable 3:1 mixture of α(1-2) and α(1-4) disaccharides **16** and **17** in a poor 12% yield; the corresponding trisaccharide **18a** formed by double glycosylation was also isolated in 3% yield (entry 1).[17] In spite of the low yield, the tendency towards reaction at the C2 position is in agreement with the result obtained by Fraser-Reid with donor **2** (Figure 1).[5b] This result also illustrates the influence of the protecting groups on the acceptor in the reactivity of the diol system when compared to the results obtained with acceptor **4a**.[5b] Comparison between Table 1 (entries 1 and 2) and Table 2 (entry 1), where similar glycosyl acceptors gave strikingly different yield of disaccharides, indicate that the intramolecular glycosylation process is clearly superior, avoids the formation of trisaccharides and allows the reaction to be carried out in the absence of TfOAg. A plausible consequence of this is that the intramolecular strategy could be specially well suited for coupling unreactive glycosyl partners.

The reaction of the disarmed donor **14b** with acceptor **15** afforded the α(1-2) disaccharide **16b** and trisaccharide **18b** in 23 and 21% yield, respectively; 19% of acceptor **15** was recovered (entry 2). The regioselectivity observed in this case was lower than that of the analogous intramolecular process (entry 3, Table 1). This result is also in contrast with the regioselectivity observed with glycosyl donors **1** and **3**, with participating groups at C2, for the C4 position of the mannosyl acceptors **4** (Figure 1).[5] This observation seems to indicate that the preference for C2 over C4 in the intramolecular reaction (entry 3, Table 1) could in part be a consequence of the different substituents on the acceptor and not only an effect of the intramolecular nature of the process.

We reasoned that the volume of the bulky TBDPS protecting group at C6 of the acceptor could be responsible for this poor regioselectivity, and it was substituted for a benzoyl group. Nevertheless, the reaction of the disarmed donor **14b** with acceptor **19**[18] gave all three possible glycosylation products. Mixtures of the α(1-2) disaccharide **20**, α(1-4) regioisomer **21** and trisaccharide **22** were formed in different ratios depending on the reaction conditions (entries 3 and 4).

With the aim of determining unambiguously whether the leaving group of the glycosyl donor or the nature of the

substituents on the acceptor were responsible for this different reactivity, the acceptors **4a** and **4b** used by Ogawa and Fraser-Reid were prepared,[19] and their glycosylation reaction with disarmed donor **14b** studied. The allylated acceptor **4a** gave a complex mixture of products, as the allyl groups also react under the reaction conditions (entry 5). Nevertheless, the benzylated acceptor **4b** showed a clear tendency to undergo glycosylation at the C4 position when it reacts with the thioglycoside donor **14b**, affording **23** and trisaccharide **24** in 51 and 12% yield, respectively (entry 6). Therefore, the results in Table 2 (entries 4 and 6) clearly illustrate how the mere switch from a benzoyl to a benzyl protecting group at O-3 and O-6 of the acceptor has an important influence on the regiochemistry of the process.

In summary, it has been shown that the intramolecular glycosylation of the studied mannoside diol acceptors is a reliable alternative when the intermolecular approach gives poor yields providing complementary stereoselectivities. The presence of the anchoring spacer avoids the undesired trisaccharides obtained in the intermolecular glycosylation of polyol systems. It has also been demonstrated that subtle changes in the substituents on the glycosyl acceptor have a very important effect on the regiochemistry of glycosylation reactions.

Acknowledgment

This research was supported by the Dirección General de Investigación Científica y Técnica (Grant BQU2002-00120). MBC thanks MCyT (Ministerio de Ciencia y Tecnología) for a Ramón y Cajal contract and Nicole Frost for proof reading this manuscript.

References

(1) Present address: Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco 28049, Spain.
(2) Present address: DDW-Medicinal Chemistry II, GlaxoSmithKline, 28770 Tres Cantos, Madrid, Spain.
(3) (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (b) Varki, A. *Glycobiology* **1993**, *3*, 97. (c) *Carbohydrates in Chemistry and Biology*, Vol. 1-4; Ernst, B.; Hart, G. W.; Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, **2000**. (d) *Glycoscience*, Vol. 1-3; Fraser-Reid, B.; Tatsuta, K.; Thiem, J., Eds.; Springer-Verlag: Berlin, Heidelberg, **2001**.
(4) (a) Valverde, S.; Gómez, A. M.; Hernandez, A.; Herradón, B.; López, J. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2005. (b) Valverde, S.; Gómez, A. M.; López, J. C.; Herradón, B. *Tetrahedron Lett.* **1996**, *37*, 1105. (c) Valverde, S.; García, M.; Gómez, A. M.; López, J. C. *Synlett* **2000**, 22. (d) Valverde, S.; García, M.; Gómez, A. M.; López, J. C. *Chem. Commun.* **2000**, 813.
(5) (a) Ogawa, T.; Sasajima, K. *Carbohydr. Res.* **1981**, *93*, 67. (b) Anikumar, G.; Nair, L. G.; Fraser-Reid, B. *Org. Lett.* **2000**, *2*, 2587.
(6) (a) Fraser-Reid, B.; López, J. C.; Radhakrishanan, K. V.; Mach, M.; Schlueter, U.; Gómez, A. M.; Uriel, C. *Can. J. Chem.* **2002**, *80*, 1075. (b) Fraser-Reid, B.; López, J. C.; Radhakrishanan, K. V.; Mach, M.; Schlueter, U.; Gómez, A. M.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198. (c) Fraser-Reid, B.; Anilkumar, G. N.; Nair, L. G.; Radhakrishanan, K. V.; López, J. C.; Gómez, A. M.; Uriel, C. *Aust. J. Chem.* **2002**, *55*, 123. (d) Fraser-Reid, B.; López, J. C.; Radhakrishanan, K. V.; Nandakumar, M. V.; Gómez, A. M.; Uriel, C. *Chem. Commun.* **2002**, 2104. (e) López, J. C.; Gómez, A. M.; Uriel, C.; Fraser-Reid, B. *Tetrahedron Lett.* **2003**, *44*, 1417. (f) Uriel, C.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Synlett* **2003**, 2203. (g) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387.
(7) (a) Arnap, J.; Haraldsson, M.; Lönngren, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 535. (b) Ogawa, T.; Nakabayashi, S. *Agric. Biol. Chem.* **1981**, *45*, 2329.
(8) Lemanski, G.; Ziegler, T. *Tetrahedron* **2000**, *56*, 563.
(9) Arias-Perez, M. S.; Santos, M. J. *Tetrahedron* **1996**, *52*, 10785.
(10) **General Method for the Formation of Diesters 8 and 9.** A solution of **6a** or **6b**, phthalic anhydride (2 equiv) and Et_3N (5 equiv) in 20 mL of CH_2Cl_2 was stirred at r.t. for 4 h. Then, a sat. solution of NH_4Cl was added, the mixture was stirred for 15 min, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give the corresponding triethylamine salt. This salt was dissolved in toluene and treated with $SOCl_2$ (5 equiv) and 3 drops of DMF, and the mixture was stirred under reflux for 4 h. The reaction mixture was then co-evaporated with toluene several times under vacuum to give the corresponding acid chloride as a yellow oil, which was treated with a solution of the tin derivative (1.1 equiv) prepared as follows: methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (**7**) was dissolved in anhyd toluene in an Erlenmeyer flask, then dibutyltin oxide (1.1 equiv) was added. The suspension was heated in a microwave oven (domestic microwave oven LG intellowave 700 W) for periods of 2 min until the solid was completely dissolved. The solution was allowed to reach r.t., then was added to the freshly prepared acid chloride, and the mixture was stirred for 20 h. Silica gel was then added, the slurry was stirred for 1 h, the solvent was evaporated under vacuum, and the solid was directly loaded into a column for flash chromatography.
Phenyl 2,3,4-tri-*O*-methyl-6-*O*-[methyl-*O*-(6-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranos-3-yloxy)-2-carbonylbenzoyl]-1-thio-α-D-mannopyranoside (8a): $[\alpha]_D$ +36 (*c* 0.63, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.11 (m, 19 H, Ar), 5.65 (d, 1 H, *J* = 1.2 Hz, $H_{1'}$), 5.27 (dd, 1 H, *J* = 9.8, 3.1 Hz, H_3), 4.72 (d, 1 H, *J* = 1.3 Hz, H_1), 4.53 (m, 2 H, $H_{5'}$ and $H_{6'}$), 4.31 (m, 2 H, $H_{4'}$ and H_2), 4.11 (td, 1 H, *J* = 9.7, 2.6 Hz, H_4), 3.97 (dd, 1 H, *J* = 9.3, 4.9 Hz, H_6), 3.91 (dd, 1 H, *J* = 9.3, 4.9 Hz, H_6), 3.89 (br t, 1 H, *J* = 1.2 Hz, $H_{2'}$), 3.79 (dt, 1 H, *J* = 9.7, 4.9 Hz, H_5), 3.53–3.41 (m, 2 H, $H_{3'}$ and $H_{6'}$), 3.54 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.14 (d, 1 H, *J* = 2.6 Hz, C_4OH), 2.91 (d, 1 H, *J* = 4.7 Hz, C_2OH), 1.05 (s, 9 H, 3 Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8 (CO), 167.2 (CO), 135.5 (2 CH), 134.0, 133.1, 133.0, 132.2, 131.1, 130.6, 129.7, 139.6, 129.1, 129.0, 127.6, 127.3, 100.6, 84.1, 81.5, 78.1, 77.0, 76.4, 71.7, 70.5, 68.3, 66.7, 64.8, 64.8, 61.0, 58.0, 57.5, 54.8, 26.8 (3 C), 19.1 (C). MS (ES): *m/z* (%) = 894 (100) [M + 18], 899 (75) [M + 23].

Phenyl 2,3,4-tri-*O*-acetyl-6-*O*-[methyl-*O*-(6-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranos-3-yloxy)-2-carbonylbenzoyl]-1-thio-α-D-mannopyranoside (8b): $[\alpha]_D$ +32.2 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, 1 H, *J* = 7.8 Hz, Ar), 7.68–7.51 (m, 7 H, Ar), 7.45–7.19 (m, 9 H, Ar), 7.14–7.11 (m, 2 H, Ar), 5.43–5.41 (m, 2 H, $H_{1'}$, $H_{2'}$), 5.35 (t, 1 H, *J* = 9.9 Hz, $H_{4'}$), 5.26 (m, 1 H, H_3), 5.22 (dd, 1 H, *J* = 9.9, 3.1 Hz, $H_{3'}$), 4.65 (d, 1 H, *J* = 1.5 Hz, H_1), 4.54 (ddd, 1 H, *J* = 9.9, 7.8, 3.5 Hz, $H_{5'}$), 4.35 (dd, 1 H, *J* = 7.8, 3.5 Hz, $H_{6'a}$ and $H_{6'b}$), 4.20 (m, 1 H, H_2), 4.0 (dt, 1 H, *J* = 9.7, 2.8 Hz, H_4), 3.91 (dd, 1 H, *J* = 10.7, 4.7 Hz, H_{6a}), 3.85 (dd, 1 H, *J* = 10.7, 5.3 Hz, H_{6b}), (m, 1 H, H_5) 3.41 (s, 3 H, OMe), 3.14 (d, 1 H, *J* = 2.9 Hz, C_4-OH), 2.88 (d, 1 H, *J* = 4.7 Hz, C_2-OH), 2.02 (s, 3 H, Me), 1.94 (s, 3 H, Me), 1.93 (s, 3 H, Me), 0.98 (s, 9 H, *t*-Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.0 (CO), 169.7 (2 × CO), 167.6 (CO), 167.1 (CO), 135.6, 131.8, 130.7, 129.7, 129.5, 129.4, 129.2, 128.0, 127.7, 100.7, 86.6, 77.0, 71.9, 70.9, 69.4, 69.2, 68.6, 66.9, 66.5, 64.9 (C-6), 63.9 (C-6), 54.8 (OMe), 26.8 (*t*-Bu), 20.7 (2 × Me), 20.6 (Me), 19.2. ESI^+ $[M + Na]^+$: 983.6; ESI^- $[M + Cl]^-$: 995.4.

(11) **Procedure for Intramolecular Glycosylation Reactions. Method A**: diester **8a** was co-evaporated 3 times with toluene, 4 Å molecular sieves were added, and the residue was dried under vacuum for 3 h. The mixture was dissolved in CH_2Cl_2 under argon, and NIS (3 equiv) was added as solid under a stream of argon at r.t. The reaction mixture was stirred for 48 h, then $NaHCO_3$ and $Na_2S_2O_3$ were added as solids. The mixture was stirred at r.t. for 30 min, then filtered through a short pad of celite, the solvent was evaporated, and the crude product was purified by flash chromatography.
Method B: as for method A, but with the addition of 0.1 equiv of TfOAg after the addition of NIS. In this case the reaction mixture was stirred at –40 °C for 2 h, was left to reach r.t. over a period of 12 h, and was then stirred at r.t. for a further 4 h.
Method C: as for method A, but with the addition of 1 equiv of TfOAg after the addition of NIS and stirring the reaction mixture at 0 °C for 10 min.
Methyl *O*-(2′,3′,4′-tri-*O*-methyl-α-D-mannopyranosyl)-(1-2)-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside-3,6′-phthalate (10a): $[\alpha]_D$ +43 (*c* 0.21, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, 1 H, *J* = 6.6, 2.2 Hz, Ar), 7.58–7.33 (m, 13 H, Ar), 5.57 (d, 1 H, *J* = 4.4, $H_{1'}$), 5.32 (dd, 1 H, *J* = 10.2, 3.4 Hz, H_3), 4.78–4.74 (m, 2 H, H_1 and $H_{6'}$), 4.58 (m, 1 H, H_2), 4.43–4.33 (m, 2 H, $H_{6'}$ and H_4), 4.12 (m, 2 H, 2 H_6), 3.83 (m, 1 H, $H_{5'}$), 3.78 (dt, *J* = 9.3, 4.1 Hz, 1 H, H_5), 3.53–3.51 (m, 1 H, $H_{2'}$), 3.50 (s, 3 H, OMe), 3.45–3.35 (m, 2 H, $H_{4'}$ and $H_{3'}$), 3.41 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 2.82 (d, 1 H, *J* = 3.5 Hz, C_4OH), 1.08 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1 (CO), 168.0 (CO), 136.1 (4 CH), 133.5, 133.4, 132.9, 132.8, 132.0, 131.4, 130.5, 130.1, 129.7, 128.8, 128.1 (2 CH), 128.0 (2 CH), 101.4 (C_1, J_{C-H} = 166 Hz), 98.0 ($C_{1'}$, J_{C-H} = 175 Hz), 80.6 ($C_{2'}$), 78.9 ($C_{4'}$), 77.6 (C_3), 76.0 ($C_{3'}$), 74.6 ($C_{5'}$), 73.0 (C_5), 71.8 (C_2), 66.8 (C_4), 66.3 (C_6), 64.8 ($C_{6'}$), 60.5 (OMe), 59.1 (OMe), 58.0 (OMe), 55.1 (OMe), 28.9 (C), 27.2 (3Me). After treatment with pyridine–Ac_2O: ^1H NMR (300 MHz, $CDCl_3$): δ = 5.55 (t, 1 H, *J* = 10.0 Hz, H_4). MS (ES): *m/z* (%) = 809 (14) [M + 1], 826 (100) [M + 18], 831 (28) [M + 23].
Methyl *O*-(2′,3′,4′-tri-*O*-methyl-β-D-mannopyranosyl)-(1-2)-4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside-3,6′-phthalate (11a): $[\alpha]_D$ –19 (*c* 1.07, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.62 (m, 5 H, Ar), 7.56–7.28 (m, 9 H, Ar), 5.45 (dd, 1 H, *J* = 16.0, 4.8 Hz, H_3), 5.36 (t, 1 H, *J* = 15.0, H_4), 5.07 (dd, 1 H, *J* = 16.0, 6.0 Hz, $H_{6'}$), 4.77 (d, 1 H, *J* = 2.7 Hz, H_1), 4.67 (d, 1 H, *J* = 1.6 Hz, $H_{1'}$), 4.49 (dd, 1 H, *J* = 15.0, 2.7 Hz, H_2), 4.22 (dd, 1 H, *J* = 16.0, 2.7 Hz, $H_{6'}$), 3.88 (ddd, 1 H, *J* = 13.3, 5.9, 3.8 Hz, H_5), 3.73 (m, 2 H, 2 H_6), 3.71 (dd, 1 H, *J* = 4.2, 1.6 Hz, $H_{2'}$), 3.59 (s, 3 H, OMe), 3.53 (dd, 1 H, *J* = 13.5, 13 Hz, $H_{4'}$), 3.46 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44–3.37 (m, 1 H, $H_{5'}$), 3.19 (dd, 1 H, *J* = 13.0, 4.2, $H_{3'}$), 1.96 (s, 3 H, Me), 1.02 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (CO), 168.8 (CO), 167.4 (CO), 136.0 (2 CH), 136.0 (2 CH), 134.2, 133.6, 131.9, 131.6, 130.6, 130.1, 128.5, 128.1 (2 CH), 128.0 (2 CH), 99.3 (C_1, J_{C-H} = 168 Hz), 98.6 ($C_{1'}$, J_{C-H} = 156 Hz), 83.1 ($C_{3'}$), 76.0 ($C_{4'}$, $C_{2'}$), 73.3 ($C_{5'}$), 71.9, 71.8, 71.6 (C_3, C_2 and C_5), 67.6 (C_4), 63.4 (C_6), 62.0 ($C_{6'}$), 61.4 (OMe), 61.1 (OMe), 57.3 (OMe), 55.2 (OMe), 27.0 (3 Me), 21.1 (Me), 19.6 (C). MS (ES): *m/z* (%) = 809(7) [M + 1], 826 (100) [M + 18], 831 (63) [M + 23].
Methyl *O*-(2′,3′,4′-tri-*O*-methyl-α-d-mannopyranosyl)-(1-4)-2-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside-3,6′-phthalate (12a): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dd, 1 H, *J* = 7.4, 1.1 Hz, Ar), 7.75–7.35 (m, 13 H, Ar), 5.89 (dd, 1 H, *J* = 10.7, 3.6 Hz, H_3), 5.68 (t, 1 H, *J* = 2.2 Hz, H_2), 5.19 (d, 1 H, *J* = 3.7 Hz, $H_{1'}$), 5.04 (d, 1 H, *J* = 9.3 Hz, H_6 or $H_{6'}$), 4.72 (d, 1 H, *J* = 2.2 Hz, H_1), 5.58 (t, 1 H, *J* = 10.3 Hz, H_4), 4.04 (dd, 1 H, *J* = 10.7, 3.0, H_6 or $H_{6'}$), 3.96–3.85 (m, 5 H, 2 H_6 or 2 $H_{6'}$, $H_{5'}$ H_5 and $H_{4'}$), 3.51 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.30 (m, 1 H, $H_{2'}$), 3.27 (s, 3 H, OMe), 3.19 (dd, 1 H *J* = 9.3, 5.5 Hz, $H_{3'}$), 2.17 (s, 3 H, Me), 1.05 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (CO), 168.2 (CO), 165.5 (CO), 135.7 (2 CH), 135.6 (2 CH), 135.2, 133.5, 133.3, 132.4, 131.2, 130.0, 129.7, 129.6, 127.6 (2 CH), 127.6 (2 CH), 98.2 (C_1, J_{C-H} = 172 Hz), 92.6 ($C_{1'}$, J_{C-H} = 160 Hz), 79.2 ($C_{2'}$), 77.1 ($C_{3'}$), 71.1, 69.8, 69.7, 69.2, 68.8 (H_4), 64.9 (CH_2), 62.3 (CH_2), 59.2 (OMe), 58.2 (OMe), 57.9 (OMe), 55.3 (OMe), 26.7 (3 Me), 20.7 (Me), 19.4 (C). After desilylation of **12** with TBAF and treatment with pyridine–Ac_2O: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.6 (C_1, J_{C-H} = 177 Hz), 93.3 ($C_{1'}$, J_{C-H} = 166 Hz). MS (ES): *m/z* (%) = 809 (2) [M + 1], 826 (100) [M + 18], 831 (40) [M + 23].
Methyl *O*-(2′,3′,4′-tri-*O*-methyl-β-D-mannopyranosyl)-(1-4)-2-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside-3,6′-phthalate (13a): $[\alpha]_D$ –15 (*c* 0.17, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.30 (m, 14 H, Ar), 5.69 (dd, 1 H, *J* = 6.3, 3.7 Hz, H_3), 5.46 (t, 1 H, *J* = 3.7 Hz, H_2), 4.95 (dd, 1 H, *J* = 11.5, 2.7 Hz, $H_{6'}$), 4.78 (d, 1 H, *J* = 4.7 Hz, H_1), 4.41 (s, 1 H, $H_{1'}$), 4.28 (dd, 1 H, *J* = 9.8, 6.3 Hz, H_4), 4.12 (dd, 1 H, *J* = 11.5, 6.6 Hz, $H_{6'}$), 4.00–3.88 (m, 2 H, 2 H_6), 3.85–3.78 (m, 1 H, H_5), 3.52 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.50–3.26 (m, 2 H, $H_{5'}$ and $H_{2'}$), 3.34 (t, 1 H, *J* = 8.8 Hz, $H_{4'}$), 3.01 (dd, 1 H, *J* = 8.8, 2.9 Hz, $H_{3'}$), 2.07 (s, 3 H, Me), 1.09 (s, 9 H, 3 Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (CO), 167.8 (CO), 167.1 (CO), 136.4 (2 CH), 136.1 (2 CH), 134.3, 133.6, 133.1, 131.8, 131.7, 131.3, 130.4, 129.6, 128.3 (2 CH), 128.2 (2 CH), 102.4 ($C_{1'}$, J_{C-H} = 157 Hz), 99.1 (C_1, J_{C-H} = 172 Hz), 83.8 ($C_{3'}$), 77.1 ($C_{4'}$), 76.8 ($C_{5'}$), 74.9 (C_4), 74.0 (C_3), 73.8 ($C_{2'}$), 72.1 (C_5), 70.2 (C_2), 64.1 ($C_{6'}$), 63.7 (C_6), 61.8 (OMe), 61.2 (OMe), 57.9 (OMe), 55.7 (OMe), 27.1 (3 Me), 21.4 (Me), 19.7 (C). MS (ES): *m/z* (%) = 809 (5) [M + 1], 826 (100) [M + 18], 831 (16) [M + 23].
Methyl *O*-(2′,3′4′-tri-*O*-acetyl-α-d-mannopyranosyl)-(1-2)-α-D-mannopyranoside-3,6′-phthalate: formed by treatment of **10b** with TBAF. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.93 (m, 1 H, Ar), 7.55–7.50 (m, 3 H, Ar), 5.69 (d, 1 H, *J* = 4.7 Hz, $H_{1'}$), 5.33 (dd, 1 H, *J* = 10.6, 3.7 Hz, H_3), 5.24 (dd, 1 H, *J* = 7.0, 3.8 Hz, $H_{3'}$), 5.06–5.00 (m, 2 H, $H_{2'}$,

$H_{4'}$), 4.78 (dd, 1 H, J = 12.3 , 5.0 Hz, $H_{6'a}$), 4.73 (d, 1 H, J = 1.3 Hz, H_1), 4.46 (dd, 1 H, J = 3.5, 1.2 Hz, H_2), 4.28–4.22 (m, 2 H, H_4, $H_{6'b}$), 4.17–4.14 (m, 1 H, $H_{5'}$), 3.82–3.78 (m, 2 H, H_{6a} and H_{6b}), 3.64 (ddd, 1 H, J = 9.7, 6.7, 3.4 Hz, H_5), 3.34 (s, 3 H, OMe), 2.81 (d, 1 H, J = 5.3 Hz, C_4OH), 2.01 (s, 3 H, Me), 2.00 (s, 3 H, Me), 1.78 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7 (CO), 165.5 (CO), 165.1 (CO), 163.7 (CO), 162.6 (CO), 128.7 (C), 127.7, 126.6, 126.4, 124.7 (C), 123.4, 96.6, 89.1, 72.9, 72.7, 72.5, 72.1, 68.8, 68.4, 68.3, 65.5, 64.4, 63.8, 60.6, 60.4, 57.4, 50.6 (OMe), 16.3 (2 × Me), 15.9 (Me).

Methyl *O*-(2′,3′4′-tri-*O*-acetyl-α-D**-mannopyranosyl)-(1-4)-α-D-mannopyranoside-3,6′-phthalate**: formed by treatment of **12b** with TBAF. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (m, 1 H, Ar), 7.62 (dt, 1 H, J = 7.5, 1.5 Hz, Ar), 7.55 (dt, 1 H, J = 7.5, 1.5 Hz, Ar), 7.43 (m, 1 H, Ar), 5.70 (dd, 1 H, J = 10.7, 3.5 Hz, H_3), 5.33 (dd, 1 H, J = 10.0, 3.3 Hz, $H_{3'}$), 5.33 (s, 1 H, $H_{1'}$), 5.24 (t, 1 H, J = 10.0 Hz, $H_{4'}$), 5.01 (dd, 1 H, J = 3.3, 1.5 Hz, $H_{2'}$), 4.83 (dd, 1 H, J = 11.5, 1.2 Hz, $H_{6'a}$), 4.75 (d, 1 H, J = 2.0 Hz, H_1), 4.41–4.34 (m, 2 H, H_2, H_4), 4.20 (br t, 1 H, J = 10.0 Hz, $H_{5'}$), 3.95–3.87 (m, 3 H, $H_{6'b}$, H_{6a}, H_{6b}), 3.83– 3.77 (m, 1 H, H_5), 3.38 (s, 3 H, OMe), 2.16 (s, 3 H, Me), 2.10 (s, 3 H, Me), 2.08 (s, 3 H, Me), 2.07 (s, 3 H, Me), 2.11 (s, 3 H, Me), 2.06 (s, 3 H, Me), 1.96 (s, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (CO), 165.8 (CO), 165.3 (CO), 164.2 (CO), 160.7 (CO), 130.5 (C), 128.3, 125.8, 125.6, 123.1, 122.9 (C), 95.8, 87.5, 66.5, 66.4, 66.2, 66.0, 64.4, 64.2, 63.5, 61.7, 59.2 (C_6), 57.3 (C_6), 51.1 (OMe), 16.4 (Me), 16.2 (Me), 16.1 (Me). After treatment with pyridine–Ac_2O: ^1H NMR (300 MHz, $CDCl_3$): δ = 5.56 (m, 1 H, H_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.2 ($J_{C\text{-}H}$ = 170 Hz), 91.7 ($J_{C\text{-}H}$ = 167 Hz).

(12) (a) Ziegler, T.; Lemanski, G. *Angew. Chem. Int. Ed.* **1998**, 3129. (b) Ziegler, T.; Lemanski, G. *Eur. J. Org. Chem.* **1998**, 163. (c) Ziegler, T.; Lemanski, G.; Rakoczy, A. *Tetrahedron Lett.* **1995**, *36*, 8973.

(13) (a) Abel-Rahman, A. A.-H.; Jonke, S.; El Ashry El, S. H.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2972. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. (c) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477.

(14) (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. (b) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447. (c) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102. (d) Fairbanks, A. J. *Synlett* **2003**, 1945. (e) Abdel-Rahman, A. A. H.; El Ashry El, S. H.; Schmidt, R. R. *Carbohydr. Res.* **2002**, *337*, 195. (f) For a review of intramolecular glycosylation see: Jung, K.-H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423.

(15) Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010.

(16) Methyl 3-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (**15**) was prepared starting from methyl-α-D-mannopyranoside by silylation of the C6 hydroxyl group followed by benzoylation of the dialkylstannylene derivative formed by microwave irradiation. This compound had been prepared previously by: Chung, S.-K.; Yu, S.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1461.

(17) Intermolecular glycosylations were carried out following procedure B, previously described for an intramolecular glycosylation reaction using 1 equiv each of the corresponding glycosyl donor and acceptor, at the temperature and for the reaction times specified in the text. The structures of all oligosaccharides were assigned by means of 2D NMR spectroscopy (COSY, HMQC) and mass spectrometry. Regioisomers were identified based on variations in the ^1H chemical shift of the free hydroxyl groups after acetylation. The assignment of the configuration (α or β) was based on the CH coupling constant at the anomeric center (J_{CH} ≈ 160Hz for β-mannosides and J_{CH} ≈ 170 Hz for α-mannosides).

(18) Compound **19** was synthesized from methyl-α-D-mannopyranoside under standard benzoylation conditions in the presence of two equivalents of benzoyl chloride. This methylmannoside **19** had been previously prepared by: Meyers, H. V.; Ojika, M.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1990**, *197*, 15.

(19) Alais, J. O.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 377.