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Regioselective benzoylation of sugars mediated by excessive Bu_2SnO: observation of temperature promoted migration

Zhiyuan Zhang and Chi-Huey Wong*

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

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Abstract—Regioselective benzoylation of carbohydrates using an excess of dibutyltin oxide (Bu_2SnO) at increased reaction temperatures has been developed for the synthesis of several glycoside benzoates with one or two free hydroxyl groups, including galactosides, glucosides, mannosides and lactosides in high yields. These compounds are useful as building blocks for the synthesis of complex saccharides and derivatives.

1. Introduction

Oligosaccharides with immense molecular diversity can be created from a few common monosaccharides through a linear or branched connection between each multifunctional sugar unit. However, creating such a high degree of molecular diversity requires the design of building blocks with orthogonal protecting groups for use in glycosylation reactions. Development of new methods for the synthesis of carbohydrate building blocks for this application is thus of current interest.

Recently, the use of organotin reagents such as tributyltin oxide, $(Bu_3Sn)_2O$, or dibutyltin oxide, Bu_2SnO, has been widely explored.[1–4] Regioselective alkylation,[5,6] silylation,[7] acylation[8–10] and even regioselective glycosylation[11–13] have been reported with such reagents. It is believed that the reactivity of a hydroxyl group can be enhanced by forming a stannylene complex and, in most cases, the stannylene complex of a sugar exists as cyclic acetals, which can be selectively protected with an alkyl or acyl group. Most of the studies, however, use a stoichiometric or slightly excessive amount of the tin reagent. Our interest in this subject is to exploit the use of excess organotin reagents to mediate the regioselective protection of the hydroxyl groups of a sugar to give a product with one free hydroxyl group, as these building blocks are useful for selective glycosylation.

As suggested by previous studies,[3] if the galactoside shown in Fig. 1 is treated with 3 equiv. of Bu_2SnO followed by 3 equiv. of BzCl, it is expected to generate the stannylene intermediate **A** and then give the 2,3,6-tri-*O*-benzoyl product **B**. To our surprise, some unexpected results were observed (Table 1). For example, *p*-methoxyphenyl β-D-galactoside **1**[14] was first treated with 3 equiv. of Bu_2SnO in toluene–benzene (1:1) followed by azeotropic removal of water to give a clear solution of the stannylene complex. Treatment of this complex with 3 equiv. of BzCl at room temperature, however, gave only the diprotected 3,6-*O*-dibenzoyl derivative **10** in 93% yield (Table 1). This result appears to be consistent with an early study with 1.5 equiv. of $(Bu_3Sn)_2O$ and 3 equiv. of BzCl at room temperature.[10] We thought that a higher temperature might facilitate additional benzoylation. Therefore, in a second experiment the tin complex was treated with 3 equiv. of BzCl at 100°C. While additional benzoylation was observed, the 3,4,6-tri-OBz derivative **11** was obtained in 86% yield instead of the expected 2,3,6-derivative. It is known that, in general, the 2-OH position is more reactive than the 4-OH in a β-galactoside series,[15] even in the tin complex case.[10]

To confirm this unusual regioselectivity, galactosides **2** and **3** were also tested under this condition, and compounds **13** and **14** were obtained with the same selectivity in 89 and 91% yield, respectively (Table 1, entries 3 and 4). We were excited by these results, since there was no known synthetic method that would give this type of compound in few steps. To further study these reactions, we carefully followed the reaction at room temperature by TLC. We observed that the 3,6-di-OBz derivative **10** was first formed after only a few minutes. When the tin complex was treated with 2.2 equiv. of benzoyl chloride at room temperature followed by 100°C, a new spot with low R_f appeared after approximately 10 min, then disappeared during the formation of the 3,4,6-tri-Obz derivative **11**. We finally isolated the first intermediate and confirmed by NMR and high-resolution mass spectrometry this to be the 4,6-*O* dibenzoate **12**.

Keywords: sugar; glycoside; benzoylation; regioselective.

* Corresponding author. Tel.: +1-619-784-2487; fax: +1-619-784-2409; e-mail: wong@scripps.edu

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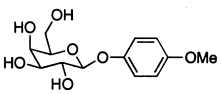
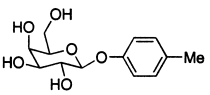
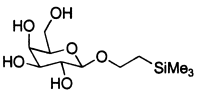
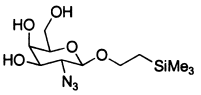
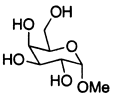
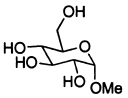
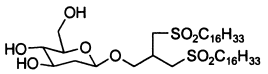
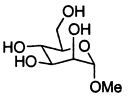
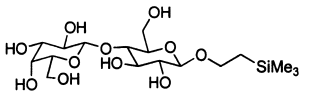
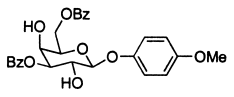
Table 1. Benzoylations using Bu_2SnO

Starting material	Entry	Bu_2SnO (equiv.)	BzCl (equiv.)	Temperature (°C)	Reaction time	Products (yield)
1 	1	3.0	3.3	22	5 h	**10** (93%)
	2	3.0	3.3	100	30 min	**11** (93%)
	3	3.0	2.2	22, then 100	2 h, then 30 min	**12** (75%), **11** (20%)
2 	4	3.0	2.2	100	30 min	**13** (88%)
3 	5	3.0	2.2	100	30 min	**14** (85%)
4 	6	2.0	3.3	22	5 h	**15** (90%)
	7	2.0	2.2	80	3 h	**15** (23%), **16** (46%)
5 	8	3.0	3.3	45	2.5 h	**17** (42%), **18** (29%), **19** (12%)
6 	9	3.0	3.2	100	5 min	**20** (91%), **21** (6%)
7 	10	3.0	3.3	90	20 min	**22** (85%)
8 	11	3.0	3.3	90	20 min	**23** (89%), **24** (6%), **25** (2%)
	12	3.0	2.2	22, then 100	2 h, then 30 min	**24** (74%), **23** (20%)
9 	13	6	10	120	2 h	**26** (86%)
	14	7	10	120	7 h	**27** (85%)



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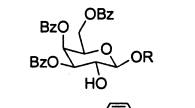
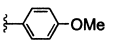
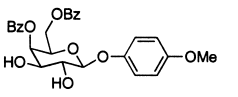


11, R = 

14, R = 



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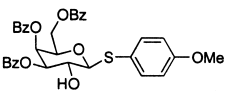

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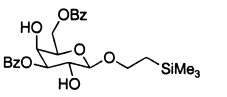

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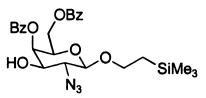

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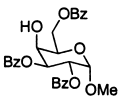

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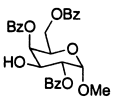

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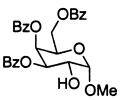

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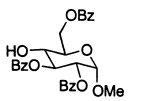

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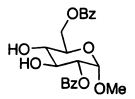

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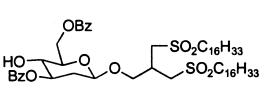

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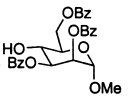

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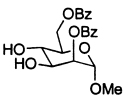

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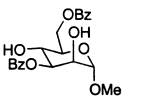

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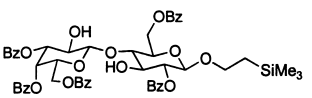

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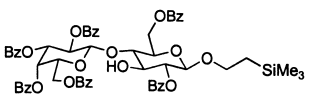


27

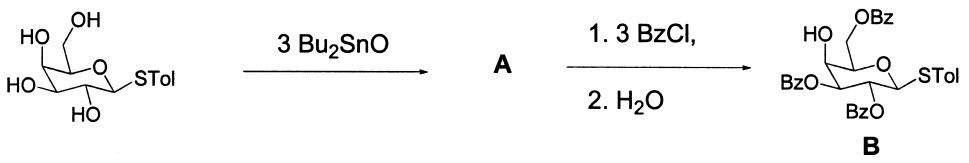


Figure 1.

As proposed in Fig. 2, it is possible that the galactoside intermediate **A** was formed after reaction with 3 equiv. of Bu_2SnO. As stannylene complexes have different dimer and polymer forms,[3,16] we assume that the R′ group may be another tin moiety or sugar residue. The 3-*O* and 6-*O* positions of intermediate **A** are perhaps more reactive and readily benzoylated to give the 3,6-di-*O*-benzoyl derivative with a structure like compound **C**. This intermediate will then give the diprotected product **10**. Under higher temperature, two pathways from intermediate **C** may be possible. One is a slow benzoylation reaction at the 2-*O*-position to give products **B** and **H** through intermediate **G**, which is often isolated in a small amount in each reaction. Another is a faster migration reaction, where the benzoyl group at 3-*O* migrates to the 4-*O*-position, presumably with an aid from the tin group at the 2-O position to give the newly formed 2,3-*O* stannylene acetal **D**. Further benzoylation would occur at the 3-*O* position as the 3-*O* position is more reactive than the 2-*O* position to give the hydrolyzed product **F** through intermediate **E**.

In order to further support this migration mechanism, we performed additional experiments. First, we treated compound **1** (Table 1) with 3 equiv. of Bu_2SnO, followed by 2.2 equiv. of BzCl at room temperature to form the 3,6-OBz intermediate **10** (see Fig. 2, **C**). Raising the reaction temperature to 100°C gave 4,6-di-benzoate **12** in 75% along with 20% of 3,4,6-OBz **11**. This example shows that higher temperature is necessary for the migration. To support the hypothesis involving the assistance from the tin moiety at the 2-*O* position of intermediate **C** (Fig. 1), 2-(trimethylsilyl)ethyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside[17] was treated with 1 equiv. of Bu_2SnO in refluxing benzene. After 10 h, only about 50% of the migrated product was formed. Moreover, when a complex of 2-azido-2-deoxy galactoside **4** and 2 equiv. of Bu_2SnO was treated with 3 equiv. of BzCl at room temperature, 3,6-di-benzoate **15** was obtained in 90% yield and with 2 equiv. of BzCl at 70–90°C for 1.5–3 h the migrated product **16** was obtained in 45% yield along with ~20% of compound **15**. All these examples show that the migration of Bz- from position 3-*O* to 4-*O* is very slow without the anchimeric effect from the tin moiety at the 2-*O* position.

The galactosides discussed above are β-linked compounds; however, a result from Ogawa's group indicated a different reaction pattern with an α-galactopyranoside.[8] Treatment of methyl α-galactopyranoside **5** with 1.5 equiv. of $(Bu_3Sn)_2O$ and 3 equiv. of BzCl gave a mixture of different di-OBz and tri-OBz compounds, and the 2,3,6-tri-OBz **17** was isolated in 40% yield as the major product. We obtained a mixture using 3 equiv. of Bu_2SnO and 3.3 equiv. of BzCl under a higher temperature (45°C) condition. Three major products, 2,3,6-tri-OBz **17**, 2,4-6-tri-OBz **18** and 3,4,6-tri-OBz **19** were isolated in 42, 29 and 12, respectively (entry 8). A possible explanation for this is that a stannylene acetal at the 2-*O* position coordinates with the α-anomeric oxygen and reduces the extent of the 3-*O* to 4-*O* benzoyl migration (Scheme 1). In this case, the 2-*O* seems more reactive towards benzoylation than its β-isomer, consequently slowing down the 3-*O* to 4-*O* migration. In addition, compound **17** was synthesized in 65% yield by a direct benzoylation using 4.2 equiv. of BzCl in pyridine.[15]

A glucoside is a 4-epimer of galactoside. Ogawa et al. systematically studied the reactions of an α-glucoside with

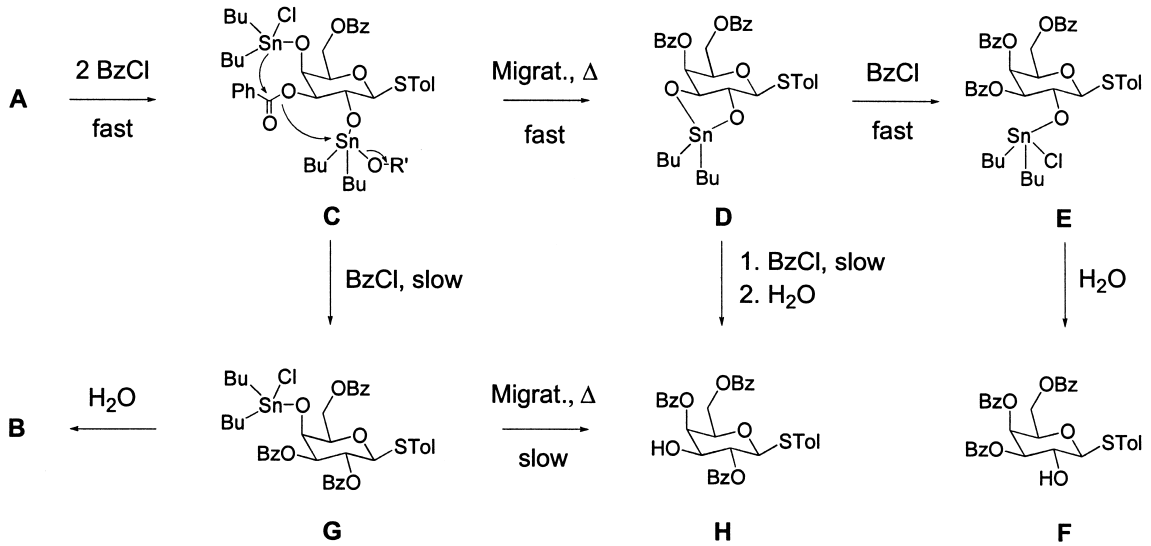
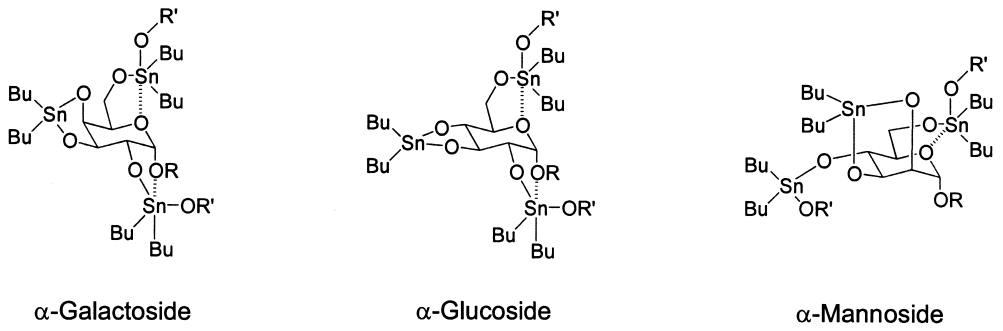


Figure 2. Note: R′ is not identified (could be another tin moiety or another sugar).



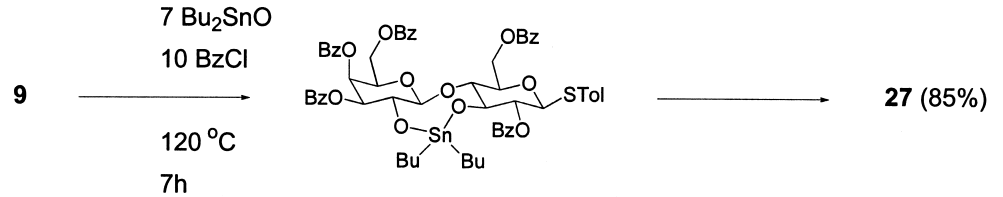
Scheme 1.

different ratios of $(Bu_3Sn)_2O$ to BzCl.[10] They found that 1.5 equiv. of $(Bu_3Sn)_2O$ and 2–3 equiv. of BzCl gave 2,6-di-OBz **21** in 73–82%. A larger excess of $(Bu_3Sn)_2O$ and BzCl gave the 2,3,6-*O*-tri-benzoate **20** in 63%. A higher yield (90%) was obtained with a modified procedure.[18] We hypothesized that the stannylene complex of an α-glucoside with 3 equiv. of Bu_2SnO may be similar to the α-galactoside case. With our high temperature procedure, the methyl α-glucoside **6** was treated with 3 equiv. of Bu_2SnO, followed by 3.2 equiv. of BzCl at 70°C to give 2,3,6-*O*-tri-OBz **20** in 91% yield. TLC analysis of the reaction showed that the intermediate 2,6-di-OBz **21** was formed first. Based on these results, the reactivities of these hydroxy groups as tin derivatives in the α-glucoside seem to be 6-*O*>2-*O*>3-*O*>4-*O*, a trend similar to those found under imidazole benzoate treatment.[19] This high regioselectivity makes this method attractive for preparation of tri-benzoates. We have also applied this procedure to the modification of 2-deoxy globotriosyl neo-glycosyl lipid.[20] We treated the 2-deoxy glucosyl lipid **7** (entry 10) with 3 equiv. of Bu_2SnO followed by 2.4 equiv of BzCl at 100°C for 5 min, giving the desired 3,6-dibenzoate in 85% yield.

Another model structure studied was a methyl α-mannoside, 2-epimer of a glucoside. Based on the stannylene complex, we expected that the migration reaction would be involved in the benzolation process. Indeed, treatment of α-methyl mannoside **8** with 3 equiv. of Bu_2SnO followed by 3 equiv. of 3.3 BzCl at 90°C for 15 min gave the product 2,3,6-tri-OBz mannoside **23** in 89% yield. The 2,6-di-OBz **24** and 3,6-di-OBz **25** were also isolated in 6 and 3%, respectively. Using 2.2 equiv. of BzCl gave 3,6-*O*-di-OBz **24** in 61% yield which is comparable to a reported result (66%).[10] Taking advantage of the observation, we treated the stannylene complex (3 equiv. of Bu_2SnO) with BzCl (2.2 equiv.) at room temperature for 2 h, then a higher temperature (100°C) for 20 min. We were able to isolate the 2,6-diester **24** in 74% yield together with 20% of the 2,3,6-tri-OBz **23**. This procedure thus enables us to prepare three different partially protected building blocks by varying the amount of BzCl and temperature.

We have found an interesting trend under these conditions. In a pyranoside structure, when an equatorial hydoxy group is *cis* to an adjacent axial hydroxy group, this equatorial hydoxy group is much more reactive than another equatorial hydoxy group which is *trans* to an adjacent equatorial hydroxyl group. For instance, the 3-*O* group is more reactive than the 2-*O* group in the β-galactoside series, the 2-*O* group is more reactive than the 3-*O* and 4-*O* groups in the α-glucoside, and the 3-*O* group is more reactive than the 4-*O* group in the α-mannoside series.

Encouraged by these results, the disaccharide lactoside **9** was chosen as the substrate for multiple stannylation. We treated compound **9** with 6 equiv. of Bu_2SnO, followed by 9 equiv. of BzCl at 120°C for 2 h, and we isolated a major product (86% yield). The ^1H NMR spectrum of this product indicated the structure 2,6,3′,4′,6′-*O*-penta-benzoyl lactosyl-pyranoside **26**. In another experiment, lactoside **9** was treated with 7 equiv. of Bu_2SnO, followed by 10 equiv. of BzCl at 120°C for a longer reaction time (7 h). Surprisingly, a new product, 2,6,2′,3′,4′,6′-hexa-benzoate **27** was isolated in 85% yield. The mechanisms in these two cases are unclear. Perhaps, with a longer reaction time and lager excess of Bu_2SnO at high temperature, an 8-membered stannylene acetal from the 3-*O* and 2′-*O* position of the **26** is formed (Scheme 2), but further studies are needed to understand the mechanism. The speculated existence of 3,2′-*O*-stannylene complex is based on the known structure of 3,2′-*O*-benzylidene lactoside.[21] In the newly formed stannylene complex, the 2′-*O* position may be less hindered towards benzoylation to give the hexabenzoate **27**. This result is different from Ogawa's early result, where they treated a free lactose with slightly more than 3 equiv. of $(Bu_3Sn)_2O$ and 6.6 equiv. of BzCl at 45°C for 2 days and 2,6,3′6′-tetra-OBz lactose was isolated in 72% yield. In their procedure, no migration reaction is involved.[10] Therefore,



Scheme 2.

the high temperature induced migration procedure is crucial for the syntheses of compounds **26** and **27**.

In summary, we have observed a different migration pattern in organotin-mediated benzoylations at high temperature using excess amounts of $(Bu_3Sn)_2O$ and BzCl. We have used this method in preparation of building blocks that normally require many steps with traditional synthesis. High regioselectivities have been found in different sugar structures including galactosides, glucosides, mannosides, and even a disaccharide. The conditions used in this study represent a new method for the synthesis of partially benzoylated glycosides. The mechanisms of these transformations described above are speculative and require further investigation.

2. Experimental

2.1. Data for compounds

2.1.1. *p*-Methoxylphenyl 3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (11). A suspended mixture of *p*-methoxylphenyl β-D-galactopyranoside[14] (100 mg, 0.350 mmol) and Bu_2SnO (266 mg, 1.04 mmol) in toluene–benzene (1:1, 40 mL) was refluxed for 20 min. Approximately 30 mL solvent was azeotropicly removed using a Dean–stark apparatus under Ar, then the hot solution (~100°C) was treated with benzoyl chloride (130 μL, 1.12 mmol). After being stirred for 1 h at this temperature, the reaction mixture was diluted with EtOAc (50 mL), cooled to 0°C and filtered through Celite. The solid cake was washed with cold (0°C) EtOAc, and concentrated. Chromatography of the residue (hexane–EtOAc, 4:1 to 2:1 to 1:1) gave **11** (242 mg, 93%) as a foam: ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.20–7.26 (m, 15H), 7.07 and 6.73 (d, each 2H, J=9.0 Hz), 5.93 (d, 1H, J=3.4 Hz, H-4), 5.47 (dd, 1H, J=3.4, 10.1 Hz, H-3), 5.02 (d, 1H, J=7.8 Hz, H-1), 4.62 (dd, 1H, J=7.7, 11.3 Hz, H-6), 4.49–4.30 (m, 3H), 3.75 (s, 3H, OCH_3). Selected ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.4, 166.3, 166.0, 155.6, 150.9, 118.6, 114.5, 102.6, 73.2, 71.6, 69.7, 68.1, 62.3, 55.6.

2.1.2. *p*-Methoxylphenyl 4,6-di-*O*-benzoyl-β-D-galactopyranoside (12). A suspended mixture of *p*-methoxylphenyl β-D-galactopyranoside (50 mg, 0.175 mmol) and Bu_2SnO (133 mg, 0.52 mmol) in toluene–benzene (1:1, 40 mL) was refluxed for 20 min. Approximately 30 mL solvent was azeotropically removed using a Dean–stark apparatus under Ar, then the solution (about 50°C) was treated with benzoyl chloride (45 μL, 0.38 mmol). After being stirred for 1 h at this temperature, the reaction mixture was heated to 100°C for 30 min, then diluted with EtOAc (50 mL), cooled to 0°C and filtered through Celite. The solid cake was washed with cold (0°C) EtOAc, and concentrated. Chromatography of the residue (toluene–acetone, 20:1 then 5:1) gave **11** (33 mg, 32%) and compound **12** (57 mg, 66%). Compound **12** had: ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.12–8.00 (m, 4H), 7.60–7.38 (m, 6H), 7.01 and 6.68 (bd, each 2H, J=9.1 Hz), 5.68 (d, 1H, J=2.8 Hz, H-4), 4.80 (d, 1H, J=7.4 Hz, H-1), 4.55–4.40 (m, 2H, H-6), 4.14–3.90 (m, 3H, H-2, H-5, H-3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (62 MHz, $CDCl_3$), δ 166.39, 166.03, 155.49, 150.98, 133.55, 133.25, 1330.05, 129.73, 129.08, 128.49, 128.40, 118.43, 114.43, 102.14, 77.50, 76.99, 72.35, 71.69, 69.91, 62.65, 55.53.

2.1.3. *p*-Methylphenyl 3,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (13).[22] *p*-Methylphenyl 1-thio-β-D-galactopyranoside[23] (100 mg, 0.350 mmol) was treated with Bu_2SnO (266 mg, 1.04 mmol), then BzCl (130 μL, 1.12 mmol) at 100°C as described in the synthesis of compound **11**. Chromatography of the residue (hexane–EtOAc, 4:1 to 2:1 to 1:1) furnished **13** (192 mg, 91.7%) as a syrup: $[\alpha]_D^{22}=+150°$ (c 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$), δ 5.91 (d, 1H, J=3.1 Hz, H-4), 5.43 (dd, 1H, J=3.3, 9.7 Hz, H-3), 4.720 (d, 1H, J=9.6 Hz, H-1), 4.29 (bt, 1H, J=6.5 Hz, H-5), 4.62 (dd, 1H, J=6.6 Hz, H-6) 4.37 (dd, 1H each, J=11.5 Hz, H-6′), 4.03 (t, 1H, J=9.6 Hz, H-2), 2.38 (s, 3H, Me); ^{13}C NMR (62 MHz, $CDCl_3$) δ 165.98, 165.90, 165.29, 88.26, 74.97, 74.47, 68.59, 67.34, 62.45, 21.28.

2.1.4. 2-(Trimethylsilyl)ethyl 3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (14). 2-(Trimethylsilyl)ethyl β-D-galactopyranoside[17] (150 mg, 0.535 mmol) was treated with Bu_2SnO (400 mg, 1.6 mmol), followed by BzCl (205 μL, 1.77 mmol) at 80°C as described in the preparation of **11**. Work up and chromatography (AcOEt–hexanes, 4:1 to 2:1) gave compound **14** (271 mg, 86%): $[\alpha]_D^{25}=+1.4°$ (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) partial data, δ 5.91 (dd, 1H, J=1.0, 3.4 Hz, H-4), 5.41 (dd, 1H, J=3.5, 10.2 Hz, H-3), 4.66 (dd, 1H, J=68, 11.2 Hz, H-6a), 4.57 (d, 1H, J=7.8 Hz, H-1), 4.38 (dd, 1H, J=6.6, 11.2 Hz, H-6b), 0.05 (s, 9H, $SiMe_3$); HRMS ($M+Na^+$) calcd for $C_{32}H_{36}O_9SiNa$: 615.2026, found 615.2010.

2.1.5. 2-(Trimethylsilyl)ethyl 2-azido-2-deoxy-3,6-di-*O*-benzoyl-β-D-galactopyranoside (15) and 2-(trimethylsilyl)ethyl 2-azido-2-deoxy-4,6-di-*O*-benzoyl-β-D-galactopyranoside (16). *Method a*. 2-(Trimethylsilyl)ethyl 2-azido-2-deoxy-β-D-galactopyranoside[24] (50 mg, 0.175 mmol) was treated with Bu_2SnO (107 mg, 0.438 mmol), followed by BzCl (60 μL, 0.524 mmol) at room temperature as described in the preparation of **11**. Work up and chromatography (AcOEt–hexanes, 4:1 to 2:1) gave compound **15** (77 mg, 89%) and compound **16** (6 mg, 7%).

Compound **15**: $[\alpha]_D^{25}=+27.6°$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) partial data, δ 4.98 (dd, 1H, J=10.7, 3.2 Hz, H-3), 4.66 (dd, 1H, J=6.8, 11.5 Hz, H-6), 4.53 (dd, 1H, J=6.4, 11.5 Hz, H-6), 4.46 (d, 1H, J=8.1 Hz, H-1), 4.20 (m, 1H), 2.51 (d, 1H, J=5.3 Hz, OH), 0.03 (s, 9H, $SiMe_3$); HRMS ($M+Na^+$) calcd for $C_{25}H_{31}O_7SiNa$: 536.1829, found 536.1820.

Compound **16** had: $[\alpha]_D^{25}=-20.0°$ (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) partial data, δ 5.65 (dd, 1H, J=1.0, 3.4 Hz, H-4), 4.58 (dd, 1H, J=6.9, 11.4 Hz, H-6), 4.43 (d, 1H, J=7.9 Hz, H-1), 4.37 (dd, 1H, J=6.4, 11.4 Hz, H-6), 3.78 (dd, 1H, J=3.4, 10.3 Hz, H-3), 0.04 (s, 9H, $SiMe_3$); HRMS ($M+Na^+$) calcd for $C_{25}H_{31}O_7SiNa$: 536.1829, found 536.1825.

Method b. 2-(Trimethylsilyl)ethyl 2-azido-2-deoxy-β-D-galactopyranoside (50 mg, 0.175 mmol) was treated with

Bu_2SnO (96 mg, 0.386 mmol), followed by BzCl (45 μL, 0.385 mmol) at 90°C as described in the preparation of **11**. Work up and chromatography (AcOEt–hexanes, 4:1 to 2:1) gave compound **15** (20 mg, 23%) and compound **16** (41 mg, 47%).

2.1.6. Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (17),[10] methyl 2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (18)[19] and methyl 3,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (19).[25] Methyl α-D-galactopyranoside (50 mg, 0.257 mmol) was treated with Bu_2SnO (200 mg, 0.80 mmol), followed by BzCl (120 μL, 1.03 mmol) at 45°C for 2.5 h as described in the preparation of **11**. Chromatography (AcOEt–hexanes, 3:1 to 1:1) gave compound **17** (38 mg, 42%), **18** (55 mg, 29%) and **19** (18 mg, 14%).

Compound **17** had: ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.10–7.96 (m, 6H), 7.62–7.3 (m, 9H), 5.76 (dd, 1H, J=2.9, 10.7 Hz, H-3), 5.67 (dd, 1H, J=3.3, 10.7 Hz, H-2), 5.14 (d, 1H, J=3.3 Hz, H-1), 4.68 (dd, 1H, J=6.0, 11.4 Hz, H-6), 4.62 (dd, 1H, J=6.7, 11.4 Hz, H-6), 4.39 (m, 2H), 3.45 (s, 3H, OCH_3), 2.55 (d, 1H, J=4.2 Hz, OH).

Compound **18** had: ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.16–8.01 (m, 6H), 7.64–7.3 (m, 9H), 5.83 (d, 1H, J=3.5 Hz, H-4), 5.40 (dd, 1H, J=3.7, 10.3 Hz, H-2), 5.20 (d, 1H, J=3.7 Hz, H-1), 4.6–4.35 (m, 4H), 3.45 (s, 3H, OCH_3).

Compound **19** had: ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.10–7.20 (m, 15H), 5.91 (d, 1H, J=3.3 Hz, H-4), 5.57 (dd, 1H, J=3.3, 10.3 Hz, H-3), 5.05 (d, 1H, J=3.8 Hz, H-1), 4.58 (dd, 1H, J=6.8, 10.3 Hz, H-6), 4.63–4.22 (m, 4H), 3.54 (s, 3H, OCH_3).

2.1.7. Methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (20)[10] and methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (21).[10] Methyl α-D-glucopyranoside (100 mg, 0.524 mmol) was treated with Bu_2SnO (400 mg, 1.60 mmol), followed by BzCl (200 μL, 1.72 mmol) at 100°C for 30 min as described in the preparation of **11**. Chromatography of the residue (AcOEt–hexanes, 3:1 to 1:1) gave compound **20** (233 mg) in 91% yield: ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.10 (m, 2H), 7.97 (m, 4H), 7.65 (m, 1H), 7.51–7.33 (m, 8H), 5.78 (dd, 1H, J=9.5, 10.0 Hz, H-3), 5.26 (dd, 1H, J=4.0, 10.0 Hz, H-2), 5.14 (d, 1H, J=4.0 Hz, H-1), 4.78 (dd, 1H, J=5.0, 12.5 Hz, H-6), 4.62 (dd, 1H, J=2.5, 12.5), 4.11 (ddd, 1H, J=2.5, 4.5, 10.0 Hz, H-5), 3.87 (t, 1H, J=10.0 Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3$), δ 167.3, 166.9, 165.9, 133.4, 133.3, 129.8, 129.79, 128.4, 128.39, 128.38, 73.8, 71.3, 70.0, 69.7, 63.4, 55.4. Further elution gave compound **21** (12.7 mg, 6.8%): ^{1}H NMR (250 MHz, $CDCl_3$), δ 8.08 (m, 4H), 7.59–7.25 (m, 6H), 5.05 (d, 1H, J=3.7 Hz, H-1), 4.95 (dd, 1H, J=3.7, 9.9 Hz, H-2), 4.79 (dd, 1H, J=5.0, 12.5 Hz, H-6a), 4.53 (dd, 1H, J=2.5, 12.5 Hz, H-6b), 4.20 (t, 1H, J=9.9 Hz), 3.95 (m, 1H, H-5), 3.59 (t, 1H, J=10.0 Hz, H-4), 3.40 (s, 3H); ^{13}C NMR (62 MHz, $CDCl_3$), δ 167.3, 133.4, 129.9, 129.8, 128.4, 79.3, 73.7, 71.5, 70.6, 69.6, 63.6, 55.4.

2.1.8. 3-(Hexadecylsulfonyl)-2-[(hexadecylsulfonyl)-methyl]propyl 3,6-di-*O*-benzoyl-2-deoxy-α-D-arabino-hexopyranoside (22). Yield 84%, see Ref. 20. $[\alpha]_D^{22}=-2.7°$ (c 1.0, $CHCl_3$); ^{1}H NMR data ($CDCl_3$): δ 5.15 (m, 1H), 4.77 (dd, 1H, J=12.2, 4.2 Hz), 4.72 (dd, 1H, J=9.6, 1.9 Hz), 4.63 (dd, 1H, J=12.1, 2.0 Hz), 4.02, 3.96 (dd, 1H each, J=10.0, 5.0, 4.8 Hz), 2.45 (ddd, 1H, J=12.3, 5.1, 1.7 Hz), 0.88 (t, 6H, J=6.6 Hz); HRMS calcd for $C_{56}H_{92}O_{11}S_2Na$ (M+Na): 1027.5979; found: 1027.5958.

2.1.9. Methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (23).[10] Methyl α-D-mannopyranoside (100 mg, 0.524 mmol) was treated with Bu_2SnO (400 mg, 1.60 mmol), followed by BzCl (200 μL, 1.72 mmol) at 100°C as described in the preparation of **11**. The residue was chromatographed (AcOEt–hexanes, 3:1 to 1:1) to give compound **23** (232 mg) in 89% yield: ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.12, 7.98 and 7.9 (bd, 2H each, J=7.6 Hz), 7.65–7.29 (m, 9H), 5.64–5.55 (m, 2H, H-2 and H-3), 4.92 (d, 1H, J=1.6 Hz, H-1), 4.86 (dd, 1H, J=4.0, 12.0 Hz, H-6a), 4.66 (dd, 1H, J=4.0, 12.0 Hz, H-6b), 4.31 (ddd, 1H, J=5.1, 9.5, 9.5 Hz, H-4), 3.48 (w, 3H, OCH3), 3.07 (d, 1H, J=5.1 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.82, 166.53, 165.29, 133.32, 133.22, 133.02, 129.76, 129.72, 129.66, 128.42, 128.25, 98.59, 72.51, 71.11, 70.40, 66.13, 63.36, 55.25.

2.1.10. Methyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside (24).[10] Methyl α-D-mannopyranoside (50 mg, 0.257 mmol) was treated with Bu_2SnO (200 mg, 0.80 mol) as described in the preparation of **11**. To the mixture at room temperature was added BzCl (66 μL, 0.56 mmol) and stirred for 3 h. The mixture was brought to 100°C and stirred for 1 h. Work up and chromatography (AcOEt–hexanes, 3:1 to 1:1) gave compound **24** (78 mg, 76%):^{1}H NMR (500 MHz, $CDCl_3$), δ 8.11 and 7.91 (bd, 2H each, J=7.9 Hz), 7.61 and 7.50 (bt, 1H each, J=7.5 Hz), 7.46 and 7.24 (t, 2H each, J=7.6 Hz), 5.37 (dd, 1H, J=1.5, 3.0 Hz, H-2), 4.89 (dd, 1H, J=2.6, 12.1 Hz, H-6), 4.86 (d, 1H, J=1.5 Hz, H-1), 4.53 (dd, 1H, J=1.4, 12.1 Hz, H-6b), 4.16 (bs, 1H, H-3), 3.91 (m, 2H, H-4, H-5), 3.44 (s, 3H, OCH_3).

2.1.11. Methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside (25).[10] Methyl α-D-mannopyranoside (50 mg, 0.257 mmol) was treated with Bu_2SnO (200 mg, 0.80 mol) as described in the preparation of **11**. To the mixture at room temperature was added BzCl (91 μL, 0.77 mmol) and stirred for 3 h. The residue was worked up and chromatographed (AcOEt–hexanes, 3:1 to 1:1) to give compound **25** (92 mg, 88%):^{1}H NMR (400 MHz, $CDCl_3$), δ 8.10 (d, 4H, J=7.9 Hz), 7.59 (m, 2H), 7.46 (m, 4H), 5.38 (dd, 1H, J=3.2, 9.7 Hz, H-3), 4.82 (d, 1H, J=1.8 Hz, H-1), 4.79 (dd, 1H, J=4.7, 12.0 Hz, H-6a), 4.61 (dd, 1H, J=2.3, 12.0 Hz, H-6b), 4.20 (m, 1H), 4.11 (ddd, 1H, J=5.0, 10.0, 10.0 Hz, H-4), 4.01 (dddd, 1H, J=2.0, 4.4, 10.0 Hz, H-5), 3.46 (s, 3H, OCH_3), 3.07 and 2.07 (d, 1H each, J=5.3, 4.7 Hz, OH).

2.1.12. 2-(Trimethylsilyl)ethyl 2,6-di-*O*-benzoyl-4-*O*-(3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-β-D-glucopyranoside (26). 2-(Trimethylsilyl)ethyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside[17] (50 mg, 0.113 mmol) was treated with Bu_2SnO (169 mg, 0.678 mmol), followed by BzCl (118 μL, 1.01 mmol) at 120°C for 2 h as described in the preparation of **11**. Work up and chromatography (toluene–ether, 30:1) gave compound **26** (93.5 mg, 86%): $[\alpha]_D^{25}=+38.2°$ (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)

partial data, δ 5.87 (d, 1H, J=3.4 Hz, H-4′), 5.40 (dd, 1H, J=3.4, 10.2 Hz, H-3′), 5.26 (dd, 1H, J=8.1, 9.6 Hz, H-2), 4.71 (d, 1H, J=7.8 Hz, H-1′), 4.65 (d, 1H, J=8.0 Hz, H-1), −0.08 (s, 9H, $SiMe_3$); ^{13}C NMR (75 MHz, $CDCl_3$) partial data, δ 167.0, 166.2, 165.9, 165.4, 165.3, 104.7, 100.3, 82.7, 73.9, 73.6, 73.1, 73.0, 69.7, 68.2, 67.4, 17.9, −1.5; HRMS ($M+Na^+$) calcd for $C_{52}H_{54}O_{16}SiNa$: 985.3079, found 985.3057.

2.1.13. 2-(Trimethylsilyl)ethyl 2,6-di-*O*-benzoyl-4-*O*-(2,3,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-β-D-glucopyranoside (27). 2-(Trimethylsilyl)ethyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (50 mg, 0.113 mmol) was treated with Bu_2SnO (183 mg, 0.734 mmol), followed by BzCl (160 μL, 1.13 mmol) at 120°C for 7 h as described in the preparation of **11**. Work up and chromatography (toluene–ether, 30:1) gave compound **27** (102 mg, 85%): $[\alpha]_D^{25}=+79.9°$ (c 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) partial data, δ 5.97 (d, 1H, J=3.2 Hz, H-4′), 5.91 (dd, 1H, J=8.1, 10.5 Hz, H-2′), 5.60 (dd, 1H, J=3.4, 10.5 Hz, H-3′), 5.25 (dd, 1H, J=8.1, 9.5 Hz, H-2), 5.04 (d, 1H, J=7.8 Hz, H-1′), 4.61 (d, 1H, J=8.1 Hz, H-1), −0.14 (s, 9H, $SiMe_3$); HRMS ($M+Na^+$) calcd for $C_{59}H_{58}O_{17}SiNa$: 1089.334, found 1089.3340.

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