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Stereocontrolled α-Galactosylation under Cooperative Catalysis

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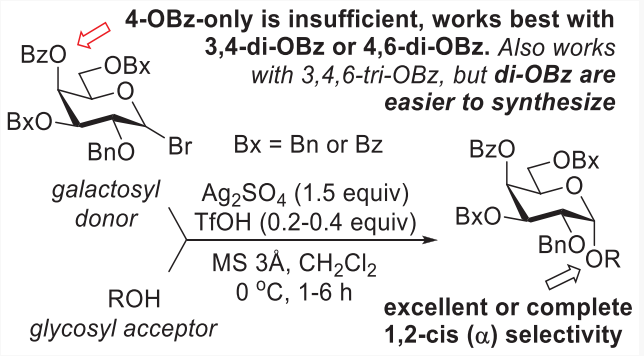
ABSTRACT: A recent discovery of a cooperative catalysis comprising a silver salt and an acid led to a dramatic improvement in the way glycosyl halides are glycosidated. Excellent yields have been achieved, but the stereoselectivity achieved with 2-*O*-benzylated donors was poor. Reported herein is our first attempt to refine the stereoselectivity of the cooperatively catalyzed galactosylation reaction. Careful optimization of the reaction conditions along with studying effects of the remote protecting groups led to excellent stereocontrol of α-galactosylation of a variety of glycosyl acceptors with differentially protected galactosyl donors.



INTRODUCTION

Construction of the biologically relevant glycans has been a great challenge since the first chemical glycosidations of glycosyl halides performed by Michael,[1] Koenigs−Knorr,[2] and Fischer.[3] A rigorous study of chemical glycosylation gave straightforward access to many 1,2-trans glycosidic linkages that can be reliably achieved with the aid of a neighboring participating ester group at C-2.[4−7] Conversely, there is no universal method for installing 1,2-cis glycosidic linkages.[8] Early work by Helferich, Zemplen, and others has enhanced our understanding of the synthesis of 1,2-cis glycosides with glycosyl halides as donors.[9−12] However, these studies did not lead to practical application in the synthesis of complex oligosaccharides. Since then, many improvements for the construction of 1,2-cis glycosides with glycosyl halides have emerged: employing bases as acid scavengers,[2,13−16] alcoholysis of glycosyl halides with or without halide additives,[17−19] halide-ion catalyzed glycosylation,[20−22] conversion of anomeric halides to positively charged leaving groups,[23,24] β- to α-glycoside anomerization,[25−27] *in situ* generation and glycosylation of glycosyl bromides from thioglycosides,[28] bromine-promoted glycosylation,[29,30] etc.

Due to their general instability, low reactivity profile, and the requirement for excess toxic reagents for their activation, glycosyl halides have been superseded by other glycosyl donors at the forefront of modern oligosaccharide synthesis. In recent years, imidates, thioglycosides, and phosphates were found to be more advantageous.[8] Many current methods employed for 1,2-cis glycosylation rely on these glycosyl donors in combination with other effects including steric factors,[31,32] remote participation,[33−37] chiral auxiliaries,[38−41] H-bond-mediated aglycone delivery (HAD),[42] modification of catalysts,[43−45] or glycosylation modulators.[46,47] In spite of these significant advancements, completely stereocontrolled 1,2-cis glycosylation remains a notable challenge in chemical synthesis.[8]

Recently, glycosyl chlorides have been progressively gaining interest after Ye[48] and Jacobsen[49] reported organocatalyzed activation for the α- and β-stereoselective glycosidation, respectively. A new method for highly stereoselective 1,2-cis glycosylation with glycosyl bromides has also been recently reported.[16] However, glycosidation of glycosyl halides may be very slow, even at elevated temperatures. Recently, our group has introduced a cooperative catalysis approach for the activation of glycosyl halides.[50] An acid and a silver salt applied together have changed the fate of glycosyl halides by leading to a drastically reduced glycosylation reaction time to as low as 2 min and a dramatic increase in the yields of glycosides.[51] However, our previous cooperatively catalyzed reactions were nonstereoselective, and reported herein is our first attempt to investigate 1,2-cis α-stereoselective galactosylation.

RESULTS AND DISCUSSION

In the effort to investigate 1,2-cis stereoselective glycosylation we chose to focus on galactosyl bromide donors. One of the driving forces for this selection is the fact that the HAD method that gives excellent *syn*-selectivity in application to β-mannosides[52] and α-glucosides[53] cannot be applied to α-

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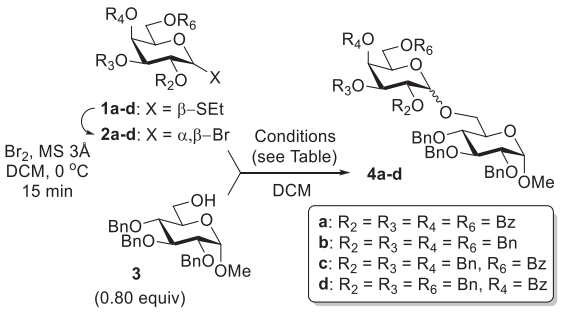
galactosides because all remote substituents are pointing upward (*anti*). Another motivation to investigate α-galactosylation was due to the very unexpected β-stereoselectivity observed in our recent work with galactosyl bromides.[50] Glycosidation of per-benzoylated bromide **2a** generated from the corresponding thioglycoside **1a** with glycosyl acceptor **3**[54] provided disaccharide **4a** with complete β-stereoselectivity due to the participation of a 2-*O*-benzoyl neighboring group (Table 1, entry 1). This glycosylation was performed in the presence of Ag_2O (3.0 equiv) and TMSOTf (0.25 equiv).[50] However, when galactosyl bromide **2b** generated from per-benzylated thioglycoside precursor **1b**, was coupled with glycosyl acceptor **3**, rather unexpectedly disaccharide **4b** was obtained in 96% yield with a nearly complete β-stereoselectivity (α/β = 1:20, entry 2). This glycosylation was performed in the presence of Ag_2O (3.0 equiv) and TMSOTf (0.10 equiv).[50] With a general idea of developing universal reaction conditions that would be applicable to all kinds of substrates, we repeated glycosidation of **2b** in the presence of Ag_2O (3.0 equiv) using the larger amount of TMSOTf (0.25 equiv). Strikingly, increasing the amount of TMSOTf resulted in a complete loss of stereoselectivity and a significant reduction of the yield of **4b** that dropped to 71% (entry 3).

Table 1. Comparative Glycosidation of Galactosyl Bromides 2a−d and Optimization of the Reaction Conditions



Entry	Donor	Conditions	Product, yield, α/β
1[50]	2a	Ag_2O (3.0 equiv), TMSOTf (0.25 equiv), 0 °C→rt, 10 min	**4a**, 99%, β-only
2[50]	2b	Ag_2O (3.0 equiv), TMSOTf (0.10 equiv), 0 °C→rt, 15 min	**4b**, 96%, 1:20
3	2b	Ag_2O (3.0 equiv), TMSOTf (0.25 equiv), 0 °C→rt, 15 min	**4b**, 71%, 1.0:1
4	2c	Ag_2O (3.0 equiv), TMSOTf (0.25 equiv), 0 °C→rt, 1 h	**4c**, 84%, 1:3.0
5	2d	Ag_2O (3.0 equiv), TMSOTf (0.25 equiv), 0 °C→rt, 3 h	**4d**, 80%, 2.9:1
6	2d	Ag_2O (3.0 equiv), TfOH (0.15 equiv), −10 °C, 1.5 h	**4d**, 72%, 5.0:1
7	2d	Ag_2O (3.0 equiv), TfOH (0.15 equiv), −30 °C, 2 h	**4d**, 82%, 11:1
8	2d	Ag_2O (3.0 equiv), TfOH (0.20 equiv), −50 °C, 3 h	**4d**, 67%, 11:1
9	2d	Ag_2SO_4 (1.0 equiv), TfOH (0.20 equiv), −30 °C → rt, 18 h	**4d**, 95%, 11:1
10	2d	Ag_2SO_4 (1.5 equiv), TfOH (0.20 equiv), −10 °C, 1 h	**4d**, 92%, 11.5:1
11	2d	Ag_2SO_4 (1.5 equiv), TfOH (0.20 equiv), 0 °C→rt, 1 h	**4d**, 87%, 6.0:1

Methods for enhancing α-stereoselectivity of galactosylation exist. Among these, utilizing the remote protecting group participation appealed to us as a promising next step toward improving the stereoselectivity. Previous studies demonstrated that acyl groups at various remote positions may have a profound effect on the stereoselectivity of glycosylation.[55−58] To understand the effects of remote substituents on cooperatively catalyzed galactosylations, we obtained thioglycosides **1c** and **1d**, equipped with a 6-OBz and 4-OBz substituent, respectively. The corresponding galactosyl bromides **2c** and **2d** were generated *in situ* and activated in the presence of Ag_2O (3.0 equiv) and TMSOTf (0.25 equiv). Glycosidation of 6-OBz bromide **2c** with acceptor **3** was largely disappointing because it produced disaccharide **4c** in a good yield of 84% albeit preferential β-stereoselectivity (α/β = 1:3.0, entry 4). Encouragingly, galactosyl bromide **2d** afforded disaccharide **4d**[56] in 80% yield with a marginal shift toward α-stereoselectivity (α/β = 2.9:1, entry 5). From these results, it was apparent that only the benzoyl group at the C-4 position offers a promising structural feature for the galactosyl donor favoring α-1,2-cis stereoselectivity.

To enhance the utility of this galactosylation we then endeavored to optimize the reaction conditions bearing the following considerations. We note that some reactions were accompanied by a competing silyl transfer to the glycosyl acceptor that explains compromised yields of disaccharides seen in a number of experiments. Hence, we replaced TMSOTf with trifluoromethanesulfonic acid (TfOH), which provided comparable results in our previous study,[51] to avoid the silyl transfer side reaction. All previous reactions were conducted at 0 °C followed by slowly bringing the reaction temperature to ambient. Hence, we wondered if modifying the reaction temperature would offer a better means for the stereocontrol. After preliminary screening, we found that the reaction of galactosyl bromide **2d** with glycosyl acceptor **3** in the presence of Ag_2O (3.0 equiv) and TfOH (0.15 equiv) at −10 °C affords disaccharide **4d** in 72% yield with a further improved α-stereoselectivity (α/β = 5.0:1, entry 6). A decrease in temperature to −30 °C produced disaccharide **4d** in a respectable yield and even higher stereoselectivity (82%, α/β = 11:1, entry 7). Further cooling to −50 °C (or −70 °C) did not enhance the stereoselectivity but led to a decreased yield (67%, α/β = 11:1, entry 8).

We then endeavored to change the source of the silver promoter and replaced silver(I) oxide with silver(I) sulfate (Ag_2SO_4). After preliminary screening, we noticed that the same stereoselectivity albeit with a much higher yield could be achieved in the presence of only 1.0 equiv of Ag_2SO_4, along with 0.20 equiv of TfOH. Thus, disaccharide **4d** was produced in an excellent yield of 95% and high stereoselectivity (α/β = 11:1, entry 9). This reaction was much slower than the previous experiments. As a matter of fact, it was not proceeding at −30 °C during the initial 5 h. When the external cooling was removed, the reaction required an additional 13 h to complete. The subsequent experiment was performed with a larger amount of Ag_2SO_4 (1.50 equiv) and at higher reaction temperature (−10 °C). As a result, disaccharide **4d** was produced in only 1 h in an excellent yield of 92% and with a similar stereoselectivity (α/β = 11.5:1, entry 10). A further increase in the starting reaction temperature to 0 °C followed by warming to room temperature produced disaccharide **4d** in a similar yield, but the stereoselectivity dropped (87%, α/β = 6.0:1, entry 11). Nevertheless, we chose this latter experiment as the benchmark for our subsequent study. This choice was driven by experimental convenience as opposed to low

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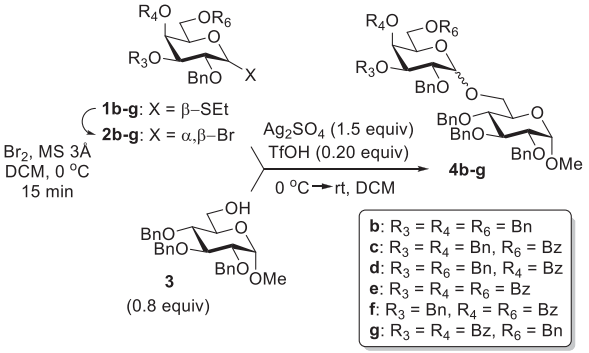
temperature experiments that are more tedious to set up and maintain.

Under the established reaction conditions, with the addition Ag_2SO_4 (1.5 equiv) and TfOH (0.20 equiv) and a starting reaction temperature of 0 °C which was allowed to warm to room temperature, whereas 4-OBz donor **4d** showed good stereoselectivity (α/β = 6.0:1, Table 2, entry 1), galactosyl

Table 2. Comparative Glycosidation of Galactosyl Bromides 2b−g under Optimized Reaction Conditions



Entry	Donor	Time	Product, yield, α/β
1	**2d** (4-OBz)	1 h	**4d**, 87%, 6.0:1
2	**2b** (all-OBn)	1.5 h	**4b**, 87%, 1:1.2
3	**2c** (6-OBz)	1 h	**4c**, 75%, 1:2.7
4	**2e** (3,4,6-OBz)	1 h	**4e**, 97%, α-only
5	**2f** (4,6-OBz)	30 min	**4f**, 93%, 33:1
6	**2g** (3,4-OBz)	2 h	**4g**, 96%, α-only

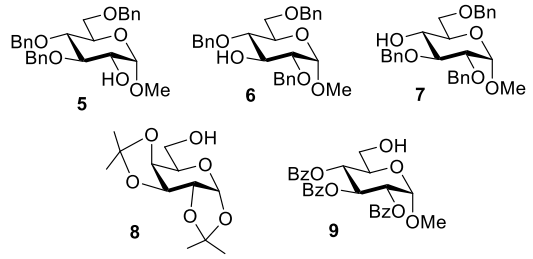
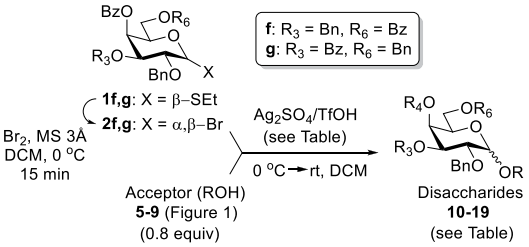
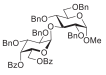
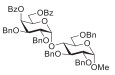
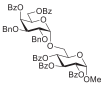
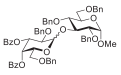
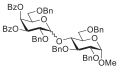
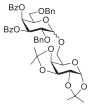
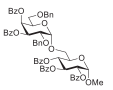


Figure 1. Standard glycosyl acceptors **5−9** for broadening the scope of α-galactosylation

bromides **2b** and **2c** failed. Thus, per-OBn bromide **2b** and 6-OBz bromide **2c** produced the respective disaccharides **4b** and **4c** in good yields albeit with preferential β-stereoselectivity (α/β = 1/1.2−2.7, entries 2 and 3). These results reinforce our previous assumption that the 4-OBz group is essential for achieving preferential α-stereoselectivity. To elaborate on this, we obtained a further series of differentially polybenzoylated ethylthio galactosides **1e−g**. The corresponding bromides were then generated *in situ* followed by their glycosidation with acceptor **3**. Galactosyl bromide donor **2e** equipped with three benzoyl substituents at C-3, -4, and -6 provided disaccharide **4e** in 97% yield with complete α-stereoselectivity (entry 4). Although galactosyl bromide **2e** is equipped with the electronically superdisarming protecting group pattern,[59] the reaction readily completed within 1 h. Glycosidation of 4,6-OBz galactosyl bromide **2f** was faster, and the corresponding disaccharide **4f** was smoothly produced in only 30 min in 93% yield and with nearly complete stereoselectivity (α/β = 33/1, entry 5). Glycosidation of 3,4-OBz galactosyl bromide **2g** was slower (2 h), but the corresponding disaccharide **4g** was smoothly produced in 96% yield with complete α-stereoselectivity (entry 6).

Table 3. Expanding the Scope of Glycosidation of Donors 2f and 2g with Acceptors 5−9



Entry	Donor + Acceptor	Equiv Ag_2SO_4/ TfOH, time	Product, yield, α/β
1	**2f** + **5**	1.50/0.20, 3 h	 **10**, 91%, α-only
2	**2f** + **6**	1.50/0.40, 6 h	 **11**, 73%, α-only
3	**2f** + **7**	1.50/0.40, 6 h	 **12**, 49%, α-only
4	**2f** + **8**	1.50/0.20, 1 h	 **13**, 68%, 11:1
5	**2f** + **9**	1.50/0.20, 1 h	 **14**, 87%, α-only
6	**2g** + **5**	1.50/0.20, 2 h	 **15**, 93%, >25:1
7	**2g** + **6**	1.50/0.40, 6 h	 **16**, 70%, >25:1
8	**2g** + **7**	1.50/0.40, 6 h	 **17**, 65%, >25:1
9	**2g** + **8**	1.50/0.20, 2 h	 **18**, 75%, >25:1
10	**2g** + **9**	1.50/0.20, 2 h	 **19**, 97%, α-only

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Excellent yields and α-stereoselectivity achieved with galactosyl bromide donors **2e−g** and primary glucosyl acceptor **3** prompted us to broaden the scope of the cooperatively catalyzed 1,2-cis glycosylation. For this study, we selected dibenzoylated galactosyl bromides **2f** and **2g** due to the ease of their preparation from the corresponding cyclic acetal/ketal-protected precursors. We also chose a series of glycosyl acceptors including secondary alcohols **5**−**7**[54] and primary alcohols of differential reactivity, highly reactive diacetone galactose **8**, and electronically deactivated compound **9**[60] (Figure 1). Results for reactions between glycosyl donors **2f** and **2g** and different glycosyl acceptors **5**−**9** are listed in Table 3. Glycosylation between donor **2f** and 2-OH acceptor **5** was very efficient in the presence of Ag_2SO_4 (1.5 equiv) and TfOH (0.20 equiv) at 0 °C to rt. As a result, disaccharide **10** was obtained in 3 h in 91% yield and with complete α-stereoselectivity (entry 1). Glycosidation of donor **2f** with the less reactive 3- and 4-OH acceptors **6** and **7** was slower, and to enhance the utility we increased the amount of TfOH to 0.40 equiv. As a result, disaccharides **11** and **12** were obtained in 6 h in 73% and 49% yield, respectively, with complete α-stereoselectivity in both cases (entries 2 and 3).

Glycosidations of donor **2f** with differently protected primary acceptors were performed using 0.20 equiv of TfOH. Under these reaction conditions, diacetone galactose acceptor **8** gave disaccharide **13**[58] in 68% yield and good α-selectivity (α/β = 11/1, entry 4). Glycosylation of a much less reactive benzoylated 6-OH acceptor **9** with donor **2f** gave disaccharide **14** in 87% yield and with complete α-stereoselectivity (entry 5). A practically identical trend was observed during glycosylations with 3,4-OBz protected bromide **2g** (Table 3). All glycosylations were rather swift (2−6 h), and the respective disaccharide derivatives **15**−**19** were produced in good yields of 65−97% with practically complete stereoselectivity in all cases (α/β > 25/1 to α-only, entries 6−10).

In conclusion, combined effects of the cooperative catalysis and remote participation of benzoyl groups led us to develop a powerful new method for stereocontrolled α-galactosylation. This method has the following four (conservatively estimated) advantages in comparison with the known methods. First, the ease of the synthesis of glycosyl donors and a rapid *in situ* conversion to the corresponding bromides. Second, no specialized protecting groups are required; only altering positions of common benzyl and benzoyl groups provide high to exclusive α-stereoselectivity. Third, the reaction duration is relatively short, and the reaction can be conducted at ambient temperature without losing stereoselectivity. Fourth, promoter systems are stable, not environment sensitive, and commonly available. Further development of the methodology and its application to the stereoselective synthesis of biologically relevant molecules are currently underway in our laboratory.

EXPERIMENTAL SECTION

General. The reactions were performed using commercially available reagents. CH_2Cl_2 used for reactions was distilled from CaH_2 prior to the application. Other ACS-grade solvents used for reactions were purified and dried according to standard procedures. Prior to the initial application, silver salts were coevaporated with toluene (×2), dried *in vacuo* in the dark. Column chromatography was performed on silica gel 60 (70−230 mesh); reactions were monitored using Thin-Layer Chromatography (TLC) on Kieselgel 60 F_{254}. TLC was examined under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. Molecular sieves (3 Å) used for reactions were crushed and activated under vacuum for 8 h at 390 °C in the first instance, and then for 2−3 h at 390 °C directly prior to application. Optical rotations were measured by a Jasco P2000 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. ^{1}H NMR was calibrated to tetramethylsilane (TMS, δ_H = 0 ppm) in $CDCl_3$. ^{13}C NMR was calibrated to the central signal of $CDCl_3$ (δ_C = 77.00 ppm) in $CDCl_3$. HRMS analysis was performed using an Agilent 6230 ESI TOF LC/MS mass spectrometer.

Synthesis of Thioglycoside Donors. *Ethyl 2,3,4,6-Tetra-O-benzoyl-1-thio-β-D-galactopyranoside (**1a**).* **1a** was synthesized as previously reported,[61] and its analytical data were in accordance with those reported previously.[61]

*Ethyl 2,3,4,6-Tetra-O-benzyl-1-thio-β-D-galactopyranoside (**1b**).* **1b** was synthesized as previously reported,[28] and its analytical data were in accordance with those reported previously.[28]

*Ethyl 6-O-Benzoyl-2,3,4-tri-O-benzyl-1-thio-β-D-galactopyranoside (**1c**).* A solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**20**,[62] 2.34 g, 4.73 mmol) in pyridine (40 mL) was cooled to 0 °C. Benzoyl chloride (0.82 mL, 7.09 mmol) was added dropwise followed by the addition of 4-dimethylaminopyridine (DMAP, 115.6 mg, 0.95 mmol), the external cooling was removed, and the resulting mixture was stirred under argon for 16 h at rt. Afterward, the reaction was quenched with MeOH (∼10 mL), the volatiles were removed under reduced pressure, and the residue was coevaporated with toluene (4 × 10 mL). The resulting residue was dissolved in CH_2Cl_2 (∼40 mL) and washed with 1 N aq. HCl (15 mL), sat. aq. $NaHCO_3$ (15 mL), and water (2 × 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane 10% gradient elution) to afford the title compound as a white amorphous solid (2.25 g, 3.75 mmol, 80% yield). Analytical data for **1c**: R_f = 0.65 (EtOAc/hexanes, 3/7, v/v); $[\alpha]^{23}_D$ −13.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.99−7.88 (m, 2H, aromatic), 7.62−7.50 (m, 1H, aromatic), 7.48−7.15 (m, 17H, aromatic), 5.01 (d, 1H, ^2J = 11.7 Hz, C*H*Ph), 4.90 (d, 1H, ^2J = 10.2 Hz, C*H*Ph), 4.77 (dd, 4H, 4 × C*H*Ph), 4.54−4.42 (m, 2H, $J_{1,2}$ = 9.7, $J_{6a,6b}$ = 11.2 Hz, H-1, 6a), 4.31 (dd, 1H, H-6b), 3.93−3.82 (m, 2H, $J_{2,3}$ = 9.3 Hz, H-2, 4), 3.70 (m, 1H, $J_{5,6a}$ = 6.9, $J_{5,6b}$ = 6.0 Hz, H-5), 3.61 (dd, 1H, $J_{3,4}$ = 2.8 Hz, H-3), 2.85−2.63 (m, 2H, SCH_2CH_3), 1.29 (t, 3H, SCH_2CH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ, 166.1, 138.2, 138.1 (×2), 133.1 129.7, 129.6 (×3), 128.4 (×2), 128.3 (×5), 128.2 (×2), 127.8, 127.7 (×2), 127.6 (×3), 85.3, 84.1, 78.4, 75.9, 75.8, 74.3, 73.2 (×2), 63.5, 24.9, 15.1 ppm; HR-FAB MS $[C_{36}H_{38}O_6SNa]^+$ calcd for 621.2281, found 621.2290.

*Ethyl 4-O-Benzoyl-2,3,6-tri-O-benzyl-1-thio-β-D-galactopyranoside (**1d**).* A solution of ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (**21**,[63] 1.50 g, 3.03 mmol) in pyridine (20 mL) was cooled to 0 °C. Benzoyl chloride (0.53 mL, 4.55 mmol) was added dropwise followed by addition of DMAP (74.5 mg, 0.61 mmol), the external cooling was removed, and the resulting mixture was stirred under argon for 16 h at rt. Afterward, the reaction was quenched with MeOH (∼5 mL), the volatiles were removed under reduced pressure, and the residue was coevaporated with toluene (3 × 5 mL). The resulting residue was dissolved in CH_2Cl_2 (∼20 mL) and washed with 1 N aq. HCl (8 mL), sat. aq. $NaHCO_3$ (8 mL), and water (2 × 8 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane 10% gradient elution) to afford the title compound as a white amorphous solid (1.63 g, 2.73 mmol, 90% yield). Analytical data for **1d**: R_f = 0.60 (EtOAc/hexanes, 3/7, v/v); $[\alpha]^{23}_D$ +13.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.16−8.05 (m, 2H, aromatic), 7.59−7.14 (m, 18H, aromatic), 5.90 (br. d, 1H, H-4), 4.77 (dd, 2H, ^2J = 10.2 Hz, CH_2Ph), 4.70 (dd, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.54 (d, 1H, $J_{1,2}$ = 9.1 Hz, H-1), 4.47 (dd, 2H, ^2J = 11.7 Hz, CH_2Ph), 3.84 (m, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5), 3.72 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 3.71−3.59 (m, 2H, $J_{6a,6b}$ = 9.4 Hz, H-3, 6a), 3.53 (dd, 1H, H-6b), 2.79 (m, 2H, SCH_2CH_3), 1.34 (t, 3H, SCH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$ at 75 MHz): δ 165.6, 137.9, 137.6, 137.4, 133.1, 129.9 (×2), 129.7, 128.4

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(×4), 128.3 (×5), 128.2, 128.0 (×2), 127.8 (×2), 127.7 (×2), 127.6, 85.3, 81.0, 77.6, 75.9, 75.8, 73.6, 71.6, 68.2, 67.3, 24.8, 15.0 ppm; HR-FAB MS $[C_{36}H_{38}O_6SNa]^+$ calcd for 621.2297, found 621.2290.

*Ethyl 3,4,6-Tri-O-benzoyl-2-O-benzyl-1-thio-β-D-galactopyranoside (**1e**).* A solution of ethyl 2-*O*-benzyl-1-thio-β-D-galactopyranoside (**22**,[64] 1.17 g, 3.72 mmol) in pyridine (20 mL) was cooled to 0 °C. Benzoyl chloride (2.59 mL, 22.33 mmol, 6.0 equiv) was added dropwise, followed by the addition of DMAP (90.4 mg, 0.74 mmol, 0.2 equiv). The external cooling was removed, and the resulting mixture was stirred under argon for 16 h at rt. Afterward, the reaction was quenched with MeOH (∼8 mL), the volatiles were removed under reduced pressure, and the residue was coevaporated with toluene (3 × 5 mL). The resulting residue was dissolved in CH_2Cl_2 (∼30 mL) and washed with 1 N aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (2 × 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane 10% gradient elution) to afford the title compound as a white amorphous solid (2.28 g, 3.64 mmol, 98%). Analytical data for **1e**: R_f = 0.70 (EtOAc/hexanes, 3/7 v/v); $[\alpha]^{23}_D$ +103.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.03 (m, 4H, aromatic), 7.81 (d, 2H, aromatic), 7.71−7.37 (m, 7H, aromatic), 7.38−7.07 (m, 7H, aromatic), 5.93 (br d, 1H, H-4), 5.48 (dd, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 4.85 (d, 1H, ^2J = 10.6 Hz, C*H*Ph), 4.75 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.67−4.57 (m, 2H, ^2J = 11.0, $J_{5,6a}$ = 6.3 Hz, H-5, C*H*Ph), 4.35 (dd, 1H, $J_{6a,6b}$ = 11.4 Hz, H-6a), 4.23 (dd, 1H, H-6b), 3.95 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 2.96−2.72 (m, 2H, S*CH*$_2$CH$_3$), 1.37 (t, 3H, SCH$_2$*CH*$_3$) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 166.0, 165.4, 165.3, 137.2, 133.5, 133.2, 133.1, 129.9 (×2), 129.7 (×2), 129.6 (×2), 129.4, 129.3, 129.2, 128.5, 128.4 (×2), 128.3, 128.2 (×5), 127.8, 85.7, 77.2, 76.2, 75.6, 74.5 (×2), 68.7, 62.2, 25.4, 15.2 ppm; HR-FAB MS $[C_{36}H_{34}O_8S + Na]^+$ calcd for 649.1867, found 649.1878.

*Ethyl 4,6-Di-O-benzoyl-2,3-di-O-benzyl-1-thio-β-D-galactopyranoside (**1f**).* A solution of ethyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (**23**,[63] 1.06 g, 2.62 mmol) in pyridine (20 mL) was cooled to 0 °C. Benzoyl chloride (0.91 mL, 7.86 mmol, 3.0 equiv) was added dropwise, followed by the addition of DMAP (64.0 mg, 0.52 mmol, 0.2 equiv). The external cooling was removed, and the resulting mixture was stirred under argon for 16 h at rt. Afterward, the reaction was quenched with MeOH (∼8 mL), the volatiles were removed under reduced pressure, and the residue was coevaporated with toluene. The resulting residue was dissolved in CH_2Cl_2 (∼20 mL) and washed with 1 N aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), and water (2 × 10 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane 10% gradient elution) to afford the title compound as a white amorphous solid (1.43 g, 2.33 mmol, 90%). Analytical data for **1f**: R_f = 0.75 (EtOAc/hexanes, 3/7, v/v); $[\alpha]^{23}_D$ +10.8 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.20−8.08 (m, 2H, aromatic), 8.03 (dd, 2H, aromatic), 7.58 (m, 2H, aromatic), 7.53−7.16 (m, 14H, aromatic), 5.90 (dd, 1H, H-4), 4.86 (d, 1H, ^2J = 11.3 Hz, C*H*Ph), 4.79 (dd, 2H, ^2J = 10.1 Hz, CH_2Ph), 4.62−4.52 (m, 3H, $J_{6a,6b}$ = 10.6 Hz, H-1, 6a, C*H*Ph), 4.36 (dd, 1H, H-6b), 4.02 (m, 1H, $J_{5,6a}$ = 7.2, $J_{5,6b}$ = 6.3 Hz, H-5), 3.73 (m, 2H, $J_{2,3}$ = 9.1, $J_{3,4}$ = 2.8 Hz, H-2, 3), 2.94−2.63 (m, 2H, S*CH*$_2$CH$_3$), 1.34 (t, 3H, SCH$_2$*CH*$_3$) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 166.1, 165.7, 137.9, 137.5, 133.3, 133.2, 130.0 (×3), 129.7 (×3), 129.5 (×2), 128.5, 128.4 (×2), 128.3 (×5), 128.0 (×2), 127.8, 127.7, 85.4, 80.9, 77.6, 75.9, 74.6, 71.9, 67.3, 62.8, 25.0, 15.1 ppm; HR-FAB MS $[C_{36}H_{36}O_7S + Na]^+$ calcd for 635.2074, found 635.2068.

*Ethyl 3,4-Di-O-benzoyl-2,6-di-O-benzyl-1-thio-β-D-galactopyranoside (**1g**).* A solution of ethyl 2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (**24**,[65] 3.10 g, 7.66 mmol) in pyridine (50 mL) was cooled to 0 °C. Benzoyl chloride (2.67 mL, 22.9 mmol, 3.0 equiv) was added dropwise, followed by the addition of DMAP (187 mg, 1.53 mmol, 0.2 equiv). The external cooling was removed, and the resulting mixture was stirred under argon for 16 h at rt. Afterward, the reaction was quenched with MeOH (∼10 mL), the volatiles were removed under reduced pressure, and the residue was coevaporated with toluene. The resulting residue was dissolved in CH_2Cl_2 (∼40 mL) and washed with 1 N aq. HCl (15 mL), sat. aq. $NaHCO_3$ (15 mL), and water (2 × 15 mL). The organic phase was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane 10% gradient elution) to afford the title compound as a clear syrup (4.22 g, 6.89 mmol, 90%). Analytical data for **1g**: R_f = 0.75 (EtOAc/hexanes, 3/7, v/v); $[\alpha]^{23}_D$ +126.0 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.06−7.93 (m, 2H, aromatic), 7.86−7.74 (m, 2H, aromatic), 7.61 (d, 1H, aromatic), 7.53−7.42 (m, 3H, aromatic), 7.37−7.05 (m, 12H, aromatic), 5.88 (d, 1H, H-4), 5.43 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 4.83 (d, 1H, ^2J = 10.6 Hz, C*H*Ph), 4.69 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.61 (d, 1H, ^2J = 10.6 Hz, C*H*Ph), 4.51 (d, 1H, ^2J = 11.8 Hz, C*H*Ph), 4.40 (d, 1H, ^2J = 11.8 Hz, C*H*Ph), 4.04 (m, 1H, $J_{5,6a}$ = 6.2 Hz, H-5), 3.89 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.72−3.48 (m, 2H, H-6a, 6b), 2.93−2.76 (m, 2H, S*CH*$_2$CH$_3$), 1.38 (t, 3H, SCH$_2$*CH*$_3$) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.4 (×2), 137.5, 137.3, 133.3, 133.0, 129.8 (×3), 129.6 (×3), 129.5, 128.4 (×2), 128.3 (×2), 128.2 (×5), 127.7 (×3), 127.6, 85.7, 76.4, 76.0, 75.5, 74.7, 73.5, 68.9, 68.0, 25.3, 15.0 ppm; HR-FAB MS $[C_{36}H_{36}O_7S + Na]^+$ calcd for 635.2074, found 635.2078.

Synthesis of Disaccharides. *A General Procedure for Bromination of Thioglycosides followed by Glycosylation.* A mixture containing a thioglycoside precursor (0.047−0.050 mmol), which was dried *in vacuo* for 45 min, and activated molecular sieves (3 Å, 90 mg) in freshly distilled CH_2Cl_2 (1.0 mL) was stirred under argon for 30 min at rt. The resulting mixture was cooled to 0 °C, Br_2 (0.062−0.065 mmol, 1.3 equiv) was added, and the reaction mixture was stirred under argon for 15 min at 0 °C. Afterward, the volatiles were removed under reduced pressure, and the residue was dried *in vacuo* for 30 min. A silver salt (1.50 equiv) and a glycosyl acceptor (0.038−0.040 mmol, 0.80 equiv) were added, and the resulting mixture was dried in *vacuo* for 1.5 h. Freshly distilled CH_2Cl_2 (1.0 mL) was added, and the resulting mixture was stirred under argon for 10 min at rt. The mixture was cooled to the temperature specified in tables, TMSOTf or TfOH (0.20−0.40 equiv) was added, and the resulting mixture was stirred under argon for the time and temperature specified in tables. Afterward, the solids were filtered off through a pad of Celite and rinsed successively with CH_2Cl_2. The combined filtrate (∼25 mL) was washed with water (2 × 10 mL). The organic phase was separated, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to yield a corresponding disaccharide derivative in a yield and with a stereoselectivity specified in Tables 1−3 and below.

*Methyl 6-O-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4a**).* **4a** was obtained as described previously,[50] and its analytical data were consistent with those reported previously.[66]

*Methyl 6-O-(2,3,4,6-Tetra-O-benzyl-α/β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4b**).* **4b** was obtained as a colorless amorphous solid from galactosyl bromide donor **2b** and acceptor **3** by the general glycosylation method (35 mg, 0.035 mmol, 87% yield, α/β = 1:1.2). The analytical data for **4b** were consistent with those reported previously.[67]

*Methyl 6-O-(6-O-Benzoyl-2,3,4-tri-O-benzyl-α/β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4c**).* **4c** was obtained as a colorless foam from galactosyl bromide donor **2c** and acceptor **3** by the general glycosylation method (34 mg, 0.034 mmol, 75% yield, α/β = 1:2.7). Analytical data for **4c**: R_f = 0.50 (EtOAc/hexane, 3/7, v/v); Selected ^{1}H NMR data for α-**4c** ($CDCl_3$ at 300 MHz): δ 4.94 (d, H-1′), 4.49 (d, H-1), 4.05 (dd, H-2′), 3.89 (dd, H-3), 3.22 (dd, H-2) ppm; Selected ^{1}H NMR data for β-**4c** ($CDCl_3$ at 300 MHz): δ 4.58 (d, $J_{1,2}$ = 3.5 Hz, H-1), 4.33 (d, H-1′), 3.98 (dd, H-3) 3.90 (dd, H-2′), 3.52 (dd, H-3′), 3.48 (dd, H-2) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 166.0 (×2), 138.8, 138.6, 138.5, 138.3, 138.2, 138.1 (×2), 133.1, 133.0, 129.9, 129.7, 129.5 (×2), 128.4, 128.3 (×2), 128.2 (×2), 128.1, 127.9 (×2), 127.8, 127.7, 127.6 (×2), 127.5, 127.4, 104.1, 97.8, 97.5, 97.4, 82.2, 81.9, 80.0, 79.7, 79.1, 78.2, 78.0, 77.2,

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75.6, 75.1, 74.9, 74.8, 74.5, 74.4, 73.3 (×2), 73.2, 73.1, 72.7, 72.0, 70.0, 69.8, 68.6, 66.2, 64.0, 63.1, 55.1, 54.9 ppm; HR-FAB MS $[C_{62}H_{64}O_{12} + Na]^+$ calcd for 1023.4290, found 1023.4312.

*Methyl 6-O-(4-O-Benzoyl-2,3,6-tri-O-benzyl-α/β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4d**).* **4d** was obtained from thioglycoside donor **2d** and acceptor **3** by the general glycosylation method (35 mg, 0.035 mmol, 87% yield, α/β = 6.0:1). The analytical data for **4d** were consistent with those reported previously.[56]

*Methyl 6-O-(3,4,6-Tri-O-benzoyl-2-O-benzyl-α-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4e**).* **4e** was obtained from galactosyl bromide donor **2e** and acceptor **3** by the general glycosylation method (38 mg, 0.037 mmol, 97% yield). Analytical data for **4e**: R_f = 0.30 (EtOAc/hexane, 3/10, v/v); $[\alpha]^{23}_D$ +117.8 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.94 (m, 4H, aromatic), 7.80 (d, 2H, aromatic), 7.66−7.05 (m, 29H, aromatic), 5.88 (d, 1H, H-4′), 5.72 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, H-3′), 5.16 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1′), 4.94 (2 d, 2H, ^2J = 10.9, ^2J = 11.2 Hz, 2 × C*H*Ph), 4.81 (d, 1H, ^2J = 10.9 Hz, C*H*Ph), 4.71 (d, 1H, ^2J = 12.2 Hz, C*H*Ph), 4.65−4.54 (m, 5H, $J_{1,2}$ = 3.4 Hz, H-1, 4 × C*H*Ph), 4.53−4.36 (m, 2H, $J_{5',6a'}$ = 4.1, $J_{6a',6b'}$ = 10.2 Hz, H-5′, 6a′), 4.29 (dd, 1H, H-6b′), 4.11 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2′), 3.98 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 3.89−3.71 (m, 3H, $J_{5,6a}$ = 6.8, $J_{6a,6b}$ = 12.4 Hz, H-5, 6a, 6b), 3.55−3.28 (m, 5H, $J_{2,3}$ = 3.4 Hz, H-2, 4, OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.9, 165.4 (×2), 138.7, 138.3, 138.0, 137.7, 133.3, 133.1, 133.0, 129.7 (×2), 129.6 (×5), 129.3, 128.4 (×9), 128.3 (×5), 128.1 (×2), 127.9 (×3), 127.8 (×3), 127.7 (×3), 127.6, 127.5, 97.7, 97.2, 82.0, 79.8, 77.8, 75.6, 75.0, 73.2, 73.0, 72.3, 70.1, 70.0, 69.5, 66.8, 66.1, 62.7, 55.1 ppm; HR-FAB MS $[C_{62}H_{60}O_{14} + Na]^+$ calcd for 1051.3875, found 1051.3890.

*Methyl 6-O-(4,6-Di-O-benzoyl-2,3-di-O-benzyl-α-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4f**).* **4f** was obtained from galactosyl bromide donor **2f** and acceptor **3** by the general glycosylation method (36 mg, 0.035 mmol, 93% yield, α/β = 33:1). Analytical data for ***α*-4f**: R_f = 0.55 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +80.4 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.10−7.91 (m, 4H, aromatic), 7.64−7.49 (m, 2H, aromatic), 7.47−7.10 (m, 29H, aromatic), 5.80 (br d, 1H, H-4′), 5.03 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 4.95 (d, 1H, ^2J = 10.9 Hz, C*H*Ph), 4.86−4.74 (m, 4H, ^2J = 12.3 Hz, 4 × C*H*Ph), 4.69 (d, 1H, ^2J = 12.0 Hz, C*H*Ph), 4.67−4.61 (dd, 2H, ^2J = 11.9 Hz, CH_2Ph), 4.59 (d, 1H, C*H*Ph), 4.52 (dd, 2H, $J_{1,2}$ = 3.4, ^2J = 12.0 Hz, H-1, C*H*Ph), 4.41−4.28 (m, 3H, H-5′, 6a′, 6b′), 4.03 (dd, 1H, $J_{3',4'}$ = 2.9 Hz, H-3′), 3.98−3.87 (m, 2H, $J_{2',3'}$ = 10.0 Hz, $J_{3,4}$ = 9.2 Hz, H-2′, 3), 3.83−3.69 (m, 3H, H-5, 6a, 6b), 3.38 (dd 1H, H-4), 3.32−3.19 (m, 4H, $J_{2,3}$ = 9.5 Hz, H-2, OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.9, 165.7, 138.7, 138.4, 138.3, 138.1, 137.9, 133.1 (×2), 129.9 (×2), 129.7, 129.6, 129.5 (×2), 128.4 (×7), 128.3 (×5), 128.2 (×4), 127.9 (×3), 127.8 (×3), 127.7 (×2), 127.6 (×3), 127.5, 127.4, 97.5 (×2), 82.0, 79.9, 78.0, 75.6, 75.1, 75.0, 74.8, 73.1, 72.9, 71.6, 70.0, 68.6, 67.1, 66.1, 63.2, 54.9 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4094.

*Methyl 6-O-(3,4-Di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**4g**).* **4g** was obtained from galactosyl bromide donor **2g** and acceptor **3** by the general glycosylation method (37 mg, 0.036 mmol, 96% yield). Analytical data for **4g**: R_f = 0.60 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +132.5 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.88 (d, 2H, aromatic), 7.80 (d, 2H, aromatic), 7.59 (dd, 1H, aromatic), 7.54−7.10 (m, 30H, aromatic), 5.83 (d, 1H, H-4′), 5.70 (dd, 1H, $J_{3',4'}$ = 2.9 Hz, H-3′), 5.19 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 4.96 (dd, 2H, ^2J = 11.0 Hz, CH_2Ph), 4.83 (d, 1H, ^2J = 11.0 Hz, C*H*Ph), 4.71 (2 d, 2H, ^2J = 11.2, ^2J = 12.3 Hz, 2 × C*H*Ph), 4.59 (m, 4H, H-1, 3 × C*H*Ph,), 4.46 (d, 1H, ^2J = 11.9 Hz, C*H*Ph), 4.40−4.31 (m, 2H, H-5′, C*H*Ph), 4.13−4.02 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2′), 3.99 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 3.92−3.75 (m, 3H, H-5, 6a, 6b), 3.63 (dd, 1H, H-4), 3.58−3.30 (m, 6H, $J_{2,3}$ = 9.3 Hz, H-2, 6a', 6b', OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.4 (×2), 138.7, 138.3, 138.1, 137.8, 137.6, 133.1, 132.8, 129.7 (×3), 129.6 (×3), 128.4 (×7), 128.3 (×3), 128.2 (×3), 128.1, 128.0, 127.9 (×4), 127.8 (×4), 127.7, 127.6 (×2), 127.5 (×4), 97.9, 97.4, 82.0, 79.8, 77.7, 75.6, 75.0, 73.3, 73.2, 72.1, 70.4, 70.2, 69.8, 68.3, 67.6, 66.1, 55.1 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4096.

*Methyl 2-O-(4,6-Di-O-benzoyl-2,3-di-O-benzyl-α-D-galactopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside (**10**).* **10** was obtained from galactosyl bromide donor **2f** and acceptor **5** by the general glycosylation method (35 mg, 0.034 mmol, 91% yield). Analytical data for **10**: R_f = 0.50 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +81.9 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.09−7.89 (m, 4H, aromatic), 7.60−7.52 (m, 1H, aromatic), 7.47−7.03 (m, 30H, aromatic), 5.33 (d, 1H, H-4′), 4.96 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′), 4.92 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 4.74 (m, 6H, ^2J = 11.1, ^2J = 12.4 Hz, 6 × C*H*Ph), 4.60−4.43 (m, 4H, 4 × C*H*Ph), 4.39 (dd, 1H, $J_{5',6a'}$ = 3.5, $J_{5',6b'}$ = 8.1 Hz, H-5′), 4.22−4.02 (m, 2H, $J_{3,4}$ = 9.2 Hz, H-3, 6a′), 4.00−3.88 (m, 3H, $J_{3',4'}$ = 2.9 Hz, H-2, 3′, 6b′), 3.88−3.73 (m, 3H, H-2′, 5, 6a), 3.69 (m, 1H, H-6b), 3.60 (dd, 1H, H-4), 3.47 (s, 3H, OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.8, 165.6, 138.7, 138.5, 138.0, 137.9, 137.8, 133.1, 132.9, 129.8 (×5), 129.7, 129.6, 128.4 (×9), 128.3 (×3), 128.2 (×2), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.7 (×2), 127.6, 127.5, 127.2 (×2), 96.3, 94.9, 80.7, 78.4, 77.2, 76.0, 75.6, 74.9, 74.6, 74.1, 73.6, 73.3, 71.8, 70.1, 68.5 (×2), 66.9, 63.3, 55.0, 53.4 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4096.

*Methyl 3-O-(4,6-Di-O-benzoyl-2,3-di-O-benzyl-α-D-galactopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (**11**).* **11** was obtained from galactosyl bromide donor **2f** and acceptor **6** by the general glycosylation method (28 mg, 0.028 mmol, 73% yield). Analytical data for **11**: R_f = 0.40 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +85.7 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.13−8.00 (m, 2H, aromatic), 8.00−7.88 (m, 2H, aromatic), 7.55 (m, 2H, aromatic), 7.41 (m, 5H, aromatic), 7.35−7.10 (m, 18H, aromatic), 7.10−6.90 (m, 6H, aromatic), 5.58 (br d, 2H, $J_{1',2'}$ = 3.4 Hz, H-1′, 4′), 5.00 (d, 1H, ^2J = 11.7 Hz, C*H*Ph), 4.84 (m, 2H, $J_{5',6a'}$ = 7.6, $J_{5',6b'}$ = 6.8, ^2J = 10.9 Hz, H-5′, C*H*Ph), 4.78−4.67 (m, 2H, $J_{1,2}$ = 3.4, ^2J = 11.6 Hz, H-1, C*H*Ph), 4.65−4.38 (m, 7H, 7 × C*H*Ph), 4.33 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.22 (dd, 1H, $J_{6a',6b'}$ = 12.0 Hz, H-6a′), 4.13 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, H-3′), 4.00 (dd, 1H, H-6b′), 3.90 (dd, 1H, $J_{2',3'}$ = 10.2 Hz, H-2′), 3.83 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.78−3.54 (m, 4H, H-2, 5, 6a, 6b), 3.31 (s, 3H, OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 166.2, 165.7, 138.3, 137.9, 137.7 (×2), 137.6, 133.0, 132.7, 130.0 (×3), 129.8 (×2), 129.7, 128.4 (×9), 128.3 (×5), 128.2 (×2), 128.1 (×3), 128.0 (×3), 127.8, 127.6, 127.5, 127.4, 127.2, 126.7 (×3), 97.8, 97.3, 78.8, 78.7, 76.5, 74.8, 74.0, 73.9, 73.4, 72.7, 71.7, 69.7, 68.8, 68.2, 66.6, 63.8, 55.0 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4096.

*Methyl 4-O-(4,6-Di-O-benzoyl-2,3-di-O-benzyl-α-D-galactopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (**12**).* **12** was obtained from galactosyl bromide donor **2f** and acceptor **7** by the general glycosylation method (19 mg, 0.019 mmol, 49% yield). Analytical data for **12**: R_f = 0.45 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +34.6 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.99 (m, 4H, aromatic), 7.57 (m, 2H, aromatic), 7.49−7.05 (m, 29H, aromatic), 5.70 (br d, 2H, $J_{1',2'}$ = 3.2 Hz, H-1′, 4′), 5.00−4.64 (m, 5H, ^2J = 11.8 Hz, 5 × C*H*Ph), 4.61−4.47 (m, 4H, $J_{1,2}$ = 3.2 Hz, H-1, 3 × C*H*Ph), 4.43 (2 d, 2H, ^2J = 9.1, ^2J = 11.6 Hz, 2 × C*H*Ph), 4.37−4.27 (m, 1H, H-6a′), 4.22−3.97 (m, 3H, $J_{5',6a'}$ = 5.3 Hz, H-3, 5′, 6a′), 3.96−3.79 (m, 4H, $J_{2',3'}$ = 10.2 Hz, H-2′, 3′, 4, 5), 3.64 (dd, 2H, $J_{6a,6b}$ = 10.0 Hz, H-6a, 6b), 3.52 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 3.39 (s, 3H, OCH_3) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$ at 75 MHz): δ 165.9, 165.7, 139.0, 137.9 (×2), 137.8, 133.1 (×2), 129.8 (×2), 129.6 (×5), 129.0, 128.4 (×9), 128.3, 128.1 (×5), 127.9 (×3), 127.8, 127.7, 127.6 (×2), 127.5, 127.4, 127.0, 126.7, 126.5, 125.2, 97.6, 97.5, 81.7, 79.9, 76.1, 74.2, 73.7, 73.6, 73.3, 73.1, 71.9, 69.3 (×2), 69.2, 68.3, 67.4, 63.1, 55.1 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4096.

*6-O-(4,6-Di-O-benzoyl-2,3-di-O-benzyl-α/β-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**13**).* **13** was obtained from galactosyl bromide donor **2f** and acceptor **8** by the general glycosylation method (21 mg, 0.026 mmol, 68% yield, α/β = 11.0:1). The analytical data for **13** were consistent with those reported previously.[58]

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*Methyl 2,3,4-Tri-O-benzoyl-6-O-(4,6-di-O-benzoyl-2,3-di-O-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside (**14**).* **14** was obtained from galactosyl bromide donor **2f** and acceptor **9** by the general glycosylation method (35 mg, 0.033 mmol, 87% yield). Analytical data for **14**: R_f = 0.40 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +100.31 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.14–7.77 (m, 10H, aromatic), 7.66–7.14 (m, 25H, aromatic), 6.05 (dd, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 5.85 (d, 1H, H-4′), 5.24 (dd, 1H, H-4), 5.13 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.94 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 4.89–4.80 (m, 3H, $J_{1',2'}$ = 3.5 Hz, H-1′, 2 × C*H*Ph), 4.67 (d, 2H, ^2J = 11.2 Hz, 2 × C*H*Ph), 4.47–4.36 (m, 2H, $J_{5',6b'}$ = 8.5 Hz, H-5′, 6a′), 4.30–4.20 (m, 2H, H-5, 6b′), 4.12 (dd, 1H, $J_{3',4'}$ = 2.8 Hz, H-3′), 3.99–3.84 (m, 2H, $J_{2',3'}$ = 10.0, $J_{6a,6b}$ = 10.6 Hz, H-2′, 6a), 3.58 (d, 1H, H-6b), 3.28 (s, 3H, OCH_3) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.9, 165.7, 165.6, 165.5, 165.3, 138.2, 137.8, 133.4, 133.2 (×2), 133.0, 129.9 (×4), 129.8, 129.7 (×4), 129.6, 129.5 (×2), 129.1, 129.0, 128.7, 128.5 (×2), 128.4 (×3), 128.3 (×2), 128.2 (×6), 128.1 (×3), 127.8 (×3), 127.7, 127.5, 97.4, 96.4, 75.3, 74.6, 73.4, 71.9, 71.6, 70.4, 69.3, 68.7, 68.1, 67.3, 66.0, 63.3, 55.2 ppm; HR-FAB MS $[C_{62}H_{56}O_{16} + Na]^+$ calcd for 1079.3461, found 1079.3471.

*Methyl 2-O-(3,4-Di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-3,4,6-tri-O-benzyl-α-D-glucopyranoside (**15**).* **15** was obtained from galactosyl bromide donor **2g** and acceptor **5** by the general glycosylation method (36 mg, 0.035 mmol, 93% yield). Analytical data for **15**: R_f = 0.45 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +209.2 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.93–7.79 (m, 4H, aromatic), 7.64–7.06 (m, 31H, aromatic), 5.85 (dd, 1H, $J_{3',4'}$ = 3.3 Hz, H-3′), 5.62 (br d, 1H, H-4′), 5.13 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 5.04–4.82 (m, 4H, $J_{1,2}$ = 3.4, ^2J = 11.1 Hz, H-1, 3 × C*H*Ph), 4.73 (d, 1H, ^2J = 12.4 Hz, C*H*Ph), 4.63 (d, 2H, ^2J = 12.2 Hz, 2 × C*H*Ph), 4.53 (m, 3H, $J_{5',6a'}$ = 6.8, $J_{5',6b'}$ = 5.3, ^2J = 12.0 Hz, H-5′, CH_2Ph), 4.21–4.06 (m, 4H, $J_{2',3'}$ = 10.5 Hz, H-2′, 3, CH_2Ph), 3.93 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 3.86–3.56 (m, 4H, H-4, 5, 6a, 6b), 3.46 (s, 3H, OCH_3), 3.38 (dd, 1H, $J_{6a',6b'}$ = 10.4 Hz, H-6a′), 3.17 (dd, 1H, H-6b′) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.4, 165.3, 138.2, 138.0 (×2), 137.8, 133.1, 132.8, 129.8, 129.7, 129.6 (×2), 128.5 (×3), 128.4 (×8), 128.3 (×2), 128.2 (×4), 128.0, 127.9 (×5), 127.8 (×2), 127.7 (×4), 127.3 (×3), 127.2, 96.4, 94.8, 80.6, 78.2, 75.0, 74.7, 73.5, 73.0, 72.7, 72.5, 70.4, 70.2, 69.8, 68.4, 68.3, 67.0, 55.0 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4190, found 1037.4095.

*Methyl 3-O-(3,4-Di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (**16**).* **16** was obtained from galactosyl bromide donor **2g** and acceptor **6** by the general glycosylation method (27 mg, 0.027 mmol, 70% yield). Analytical data for **16**: R_f = 0.50 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +114.4 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.84 (dd, 4H, aromatic), 7.64–6.90 (m, 31H, aromatic), 5.92 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, H-3′), 5.74 (dd, 2H, $J_{1',2'}$ = 3.3 Hz, H-1′, 4′), 5.03–4.85 (m, 2H, $J_{5',6a'}$ = 6.1, $J_{5',6b'}$ = 6.7, ^2J = 11.8 Hz, H-5′, C*H*Ph), 4.78 (d, 1H, ^2J = 11.3 Hz, C*H*Ph), 4.68–4.42 (m, 3H, $J_{1,2}$ = 3.7 Hz, H-1, CH_2Ph), 4.52–4.40 (m, 4H, 4 × C*H*Ph), 4.38–4.17 (m, 3H, $J_{3,4}$ = 9.1, ^2J = 12.0 Hz, H-3, CH_2Ph), 4.12 (dd, 1H, $J_{2',3'}$ = 10.7 Hz, H-2′), 3.88–3.57 (m, 5H, H-2, 4, 5, 6a, 6b), 3.50 (dd, 1H, $J_{6a',6b'}$ = 10.1 Hz, H-6a′), 3.34 (d, 1H, H-6b′), 3.31 (s, 3H, OCH_3) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.5, 165.4, 138.4, 138.0, 137.8, 137.7, 137.2, 133.0, 132.8, 129.9, 129.8, 129.7 (×2), 129.6 (×2), 128.7 (×2), 128.6 (×2), 128.3 (×5), 128.2 (×4), 128.1 (×4), 128.0 (×4), 127.8 (×2), 127.7 (×2), 127.6, 127.5, 127.2, 127.1, 126.6, 97.7, 97.5, 78.9, 78.6, 77.2, 76.1, 73.5 (×2), 73.4, 73.2, 72.8, 70.5, 70.3, 69.6, 68.3, 67.1, 55.0 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4094.

*Methyl 4-O-(3,4-Di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (**17**).* **17** was obtained from galactosyl bromide donor **2g** and acceptor **7** by the general glycosylation method (25 mg, 0.025 mmol, 65% yield). Analytical data for **17**: R_f = 0.45 (EtOAc/hexanes, 3/7, v/v); $[\alpha]^{23}_D$ +114.0 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.90–7.83 (m, 2H, aromatic), 7.80–7.72 (m, 2H, aromatic), 7.63–7.56 (m, 1H, aromatic), 7.51–7.38 (m, 3H, aromatic), 7.35–7.23 (m, 18H, aromatic), 7.17–6.94 (m, 9H, aromatic), 5.84 (br. d, 2H, $J_{1',2'}$ = 3.6 Hz, H-1′, 4′), 5.70 (dd, 1H, $J_{3',4'}$ = 2.4 Hz, H-3′), 5.05 (d, 1H, ^2J = 11.9 Hz, C*H*Ph), 4.84 (d, 1H, ^2J = 11.9 Hz, CH_2Ph), 4.74–4.38 (m, 7H, $J_{1,2}$ = 3.6 Hz, H-1, 6 × C*H*Ph), 4.32–4.22 (m, 2H, ^2J = 12.6 Hz, H-5′, C*H*Ph), 4.14–4.07 (m, 3H, H-3, 4, C*H*Ph), 4.01 (dd, 1H, $J_{2',3'}$ = 10.6 Hz, H-2′), 3.97–3.85 (m, 2H, $J_{5,6b}$ = 9.2 Hz, H-5, 6a), 3.70 (dd, 1H, H-6b), 3.60 (dd, 1H, $J_{2,3}$ = 9.3 Hz, H-2), 3.45–3.29 (m, 5H, H-6a′, 6b′, OCH_3) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.5, 165.3, 139.2, 138.4, 138.2, 138.0, 137.9, 137.8, 137.7, 137.5, 137.3, 137.2, 133.0, 132.8, 129.7, 129.6, 128.7, 128.5, 128.3 (×2), 128.2, 128.1 (×2), 128.0 (×2), 127.8 (×3), 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.9, 126.6, 126.5, 97.7, 97.6, 97.3, 81.8, 80.1, 78.9, 78.7, 76.1, 74.2, 73.4, 73.2, 73.0, 72.8, 70.5, 70.3, 70.1, 69.6, 69.4, 69.0, 68.3, 68.1, 67.8, 67.1, 55.1 ppm; HR-FAB MS $[C_{62}H_{62}O_{13} + Na]^+$ calcd for 1037.4083, found 1037.4095.

*6-O-(3,4-Di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-glucopyranose (**18**).* **18** was obtained from galactosyl bromide donor **2g** and acceptor **8** by the general glycosylation method (23 mg, 0.028 mmol, 75% yield). Analytical data for **18**: R_f = 0.45 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +58.6 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 7.90 (d, 2H, aromatic), 7.82 (d, 2H, aromatic), 7.64–7.56 (m, 1H, aromatic), 7.53–7.39 (m, 3H, aromatic), 7.36–7.11 (m, 12H, aromatic), 5.88 (d, 1H, H-4′), 5.74 (dd, 1H, $J_{3',4'}$ = 2.8 Hz, H-3′), 5.54 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 5.18 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 4.70–4.57 (m, 3H, $J_{3,4}$ = 8.0 Hz, H-3, 5′, C*H*Ph), 4.54–4.37 (m, 4H, ^2J = 12.0 Hz, H-4, 3 × C*H*Ph), 4.32 (dd, 1H, $J_{2,3}$ = 2.3 Hz, H-2), 4.14–4.05 (m, 2H, $J_{2',3'}$ = 10.5, $J_{5,6a}$ = 6.0, $J_{5,6b}$ = 8.0 Hz, H-2′, 5), 3.92 (dd, 1H, $J_{6a,6b}$ = 10.0 Hz, H-6a), 3.87–3.75 (m, 1H, H-6b), 3.62–3.48 (m, 2H, H-6a′, 6b′), 1.61, 1.46, 1.37, 1.24 (4 s, 12H, 4 × CH_3) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.4 (×2), 137.8, 137.6, 133.1, 132.8, 129.8, 129.7 (×3), 129.6 (×2), 128.4 (×2), 128.2 (×6), 128.1, 127.6 (×4), 127.5, 109.0, 108.7, 97.7, 96.2, 77.2, 73.4, 73.3, 72.1, 70.6 (×2), 70.5, 70.2, 69.8, 68.1, 67.6, 66.7, 65.9, 26.0, 24.9, 24.5 ppm; HR-FAB MS $[C_{46}H_{50}O_{13} + Na]^+$ calcd for 833.3144, found 833.3152.

*Methyl 2,3,4-Tri-O-benzoyl-6-O-(3,4-di-O-benzoyl-2,6-di-O-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside (**19**).* **19** was obtained from galactosyl bromide donor **2g** and acceptor **9** by the general glycosylation method (39 mg, 0.037 mmol, 97% yield). Analytical data for **19**: R_f = 0.35 (EtOAc/hexane, 3/7, v/v); $[\alpha]^{23}_D$ +154.7 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ at 300 MHz): δ 8.11–7.75 (m, 10H, aromatic), 7.67–7.09 (m, 25H, aromatic), 6.18 (dd, 1H, $J_{3,4}$ = 8.7 Hz, H-3), 5.87 (br d, 1H, H-4′), 5.77 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, H-3′), 5.52 (dd, 1H, H-4), 5.27 (dd, 2H, $J_{1,2}$ = 3.4, $J_{2,3}$ = 10.8 Hz, H-1, 2), 4.98 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′), 4.76–4.28 (m, 6H, $J_{5,6a}$ = 7.3, $J_{5,6b}$ = 9.1, ^2J = 12.4 Hz, H-5, 5′, 4 × C*H*Ph), 4.11 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, H-2′), 3.96 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, H-6a), 3.65 (d, 1H, H-6b), 3.57–3.39 (m, 5H, H-6a′, 6b′, OCH_3) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$ at 75 MHz): δ 165.7 (×2), 165.4, 165.3 (×2), 137.8, 137.6, 133.4, 133.3, 133.1, 133.0, 132.8, 129.9 (×5), 129.8, 129.7 (×2), 129.6 (×5), 129.1, 129.0, 128.8, 128.3 (×4), 128.2 (×8), 128.1 (×2), 127.9, 127.7, 127.5 (×2), 127.4, 97.4, 96.7, 73.5, 73.2, 72.8, 72.1, 70.4, 70.2, 69.8, 69.6, 68.5, 68.0, 67.6, 66.7, 55.6 ppm; HR-FAB MS $[C_{62}H_{56}O_{16} + Na]^+$ calcd for 1079.3461, found 1079.3471.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01279.

Characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In loving memory of Kyle Dewayne Robert Hill and Lester Gene Shadrick.

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