# 2-(Hydroxycarbonyl)benzyl Glycosides: A Novel Type of Glycosyl Donors for Highly Efficient β-Mannopyranosylation and Oligosaccharide Synthesis by Latent-Active Glycosylation

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**Abstract:** 2-(Benzyloxycarbonyl)benzyl (BCB) glycosides were prepared by coupling of the corresponding tetraacetylglycosyl bromides and benzyl 2-(hydroxymethyl)benzoate. The BCB glycosides were converted almost quantitatively into the corresponding 2-(hydroxycarbonyl)benzyl (HCB) glycosides by selective hydrogenolysis of the benzyl ester functionality without affecting the benzylidene acetal and the benzyl ether. Treatment of the HCB 4,6-*O*-benzylidenemannopyranoside **4** with triflic anhydride in the presence of di-*tert*-butylmethylpyridine and subsequent addition of the glycosyl acceptor having a primary hydroxyl group afforded exclusively the disaccharide of the β-mannopyranosyl linkage. Glycosylation of the compound **4** with secondary and tertiary alcohols also provided β-mannopyranosides as the major products. Glycosylation of the HCB 4,6-*O*-cyclohexylidenemannoside **5** with primary alcohols was also highly β-selective, and the HCB 2,3-*O*-cyclohexylidenemannoside **6** exhibited the moderate β-selectivity. On the other hand, unlike the HCB mannosides, the HCB 4,6-*O*-benzylideneglucoside **7** gave exclusively the disaccharides of the α-glycopyranosyl linkage in the glycosylation with primary alcohols. The latent BCB−disaccharide **23**, which was obtained from the HCB mannoside **4** as the donor and the BCB glucoside **12** as the acceptor by the present glycosylation method, was converted into the active HCB−disaccharide **39** by selective hydrogenolysis. Repetitive glycosylation of the donor **39** with the same acceptor **12** afforded the BCB−trisaccharide **40**. Other BCB−trisaccharides **42** and **46** were also efficiently synthesized by employing the present methodology.

## Introduction

A great deal of effort has been devoted to the development of efficient and stereoselective glycosylation methodologies[1] in recent years due to the biological significance of glycoconjugates.[2] Devising new glycosyl donors and developing new activating systems for existing donors have led to major advances in this field. Thioglycosides,[3] glycosyl sulfoxides,[4] glycals,[5] glycosyl trichloroacetimidates,[6] *n*-pentenyl glycosides,[7] and glycosyl fluorides[8] have been the most widely used glycosyl donors for the synthesis of various important oligosaccharides. One of the challenges in the glycoside synthesis has been the stereospecific formation of the 1,2-*cis*-β-D-mannopyranosyl linkage. Several diverse and innovative strategies for the β-mannopyranosylation[9] have been developed including the recent indirect intramolecular aglycone delivery approach.[10] More recently, Crich et al. have developed a direct approach for the formation of β-mannopyranosides by the $S_N2$-like displacement of the intermediate α-triflates[11] generated from glycosyl sulfoxides or thioglycosides.[12] Another recent focus in this field has been the development of sequential glycosylation strategies for the efficient construction of oligosaccharides.[13] The success of sequential glycosylation depends on the fine-tuning of the reactivity of the anomeric leaving group by employing either different anomeric leaving groups or identical leaving groups having different protective groups in glycosyl donors.[14] Another known strategy for the rapid assembly of oligosaccharides is the latent-active glycosylation method in which a stable anomeric group is converted into a good leaving group by a simple transformation.[15] In fact, the latent-active glycosylation strategy has certain advantages over the other strategies since it does not require the tuning of the anomeric leaving group so that the glycosyl donor and the acceptor could

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(1) For a review on the glycosylation, see: Toshima K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(2) Varki, A. *Glycobiology* **1993**, *3*, 97−130.

(3) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205.

(4) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882. (b) Gildersleeve, J.; Pascal, R. A., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961−5969.

(5) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419.

(6) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.

(7) Fraser-Reid, B.; Madsen, R. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 339−356.

(8) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799−822.

(9) For reviews of β-mannopyranosylation, see: (a) Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis;* Khan, S. H., O'Neil, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp 251−276. (b) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471−1491.

(10) For selected references of the intramolecular aglycon delivery approach for β-mannosylation, see: (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376−9377. (b) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. (c) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767. (d) Ziegler, T.; Lemanski, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3129−3132.

(11) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(12) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4507. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (d) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348. (e) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067−4069.

(13) For a review on strategies in oligosaccharide synthesis, see: Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121.

10.1021/ja015842s CCC: $20.00 
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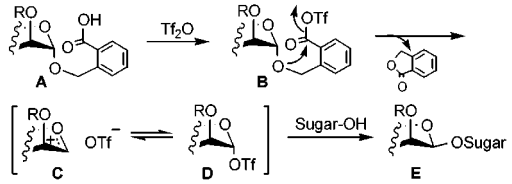
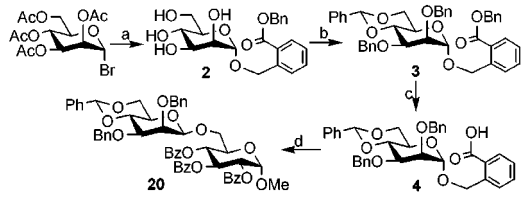
**Scheme 1**



**Scheme 2**[a]

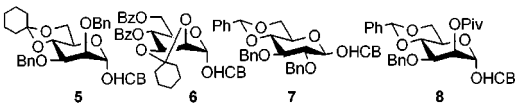


[a] (a) (i) benzyl 2-(hydroxymethyl)benzoate (**1**), $HgBr_2$, $Hg(CN)_2$, $CH_3CN$ (86%); (ii) NaOMe, MeOH (93%); (b) (i) $PhCH(OMe)_2$, CSA, DMF (70%); (ii) BnBr, NaH, DMF (80%); (c) $H_2$ (balloon), Pd/C, 3.5 equiv $NH_4OAc$, MeOH (95%); (d) $Tf_2O$, DTBMP, 4 Å MS, $CH_2Cl_2$, −78 °C, then **9**, −78 to 0 °C (91%).

be prepared from a common building block and the sequential glycosylation could be carried out employing a single glycosylation method. Herein we introduce 2-(hydroxycarbonyl)-benzyl (HCB) glycosides as a novel type of glycosyl donors that is useful for the $\beta$-mannopyranosylation but also very effective for the efficient construction of oligosaccharides by the latent-active glycosylation strategy. We envisioned that treatment of the HCB mannoside **A** with $Tf_2O$ in the presence of di-*tert*-butlymethylpyridine (DTBMP) would induce the lactonization of **A** via the mixed anhydride **B** to generate phthalide and the oxocarbenium ion **C**, which might be in equilibrium with the α-triflate **D** as shown in Scheme 1. Subsequent reaction of **C** or **D** with the glycosyl acceptor would provide the $\beta$-mannopyranoside **E**.

## Results and Discussion

Differentially protected HCB manno- and glucopyranosides **4**−**8** were efficiently prepared starting from the corresponding acetylated glycosyl bromides and crystalline benzyl 2-(hydroxymethyl)benzoate (**1**), which was readily obtained in large quantities from inexpensive phthalide. For example, the synthetic sequence for the HCB mannoside **4** is shown in Scheme 2. Coupling of the tetraacetylmannosyl bromide and **1** followed by deacetylation of the resulting tetraacetylmannoside afforded the 2-(benzyloxycarbonyl)benzyl (BCB) mannoside **2**, of which benzylidenation and subsequent benzylation afforded the protected BCB mannoside **3**. Selective hydrogenolysis of the benzyl ester functionality in the compound **3** in the presence of the benzylidene acetal and the benzyl ether, which was the crucial step for the efficient preparation of the HCB glycosides, was readily achieved by just addition of 3.5 equiv of ammonium acetate to provide the desired HCB mannoside **4** in 95% yield.[16] The amount of ammonium acetate does not have to be accurate and thus hydrogenolysis of other BCB glycosides with 1−4 equiv of ammonium acetate also gave the HCB glycosides in almost quantitative yields. The HCB glycosides **5**−**8** were also prepared in an analogous fashion and could be stored at room temperature for a few months without any change.



Glycosylation was carried out by the following sequence: (i) stirring the solution of 1 equiv of the HCB glycoside and 2 equiv of DTBMP in the presence of 4 Å molecular sieves (MS) for 30 min at room temperature in $CH_2Cl_2$, (ii) addition of 1 equiv of $Tf_2O$ to this solution at −78 °C and stirring the solution for 10 min, (iii) addition of 2 equiv of the glycosyl acceptor and stirring the reaction mixture for further 1 h at −78 °C and allowing to warm over 2 h to 0 °C, and (iv) quenching the reaction by addition of aqueous $NaHCO_3$. Glycosylation of **4** with primary alcohols **9**−**13** was so efficient that the reaction virtually completed in 1 h at −78 °C to afford only $\beta$-mannosides in high yields (Scheme 2 and entries 1−5 in Table 1). The highly $\beta$-selective mannosylation of **4** was also achieved with the secondary alcohols **14**−**16** and with the hindered tertiary alcohol **17** (entries 6−9). These results indicate that the present HCB glycoside method for the $\beta$-mannopyranosylation is comparable to the Crich−Kahne sulfoxide method in terms of the yield and the stereoselectivity. For comparison, the glycosylation results by the sulfoxide method were also listed in Table 1 [(d) of entries 2, 6, and 8]. Unlike the sulfoxide method for $\beta$-mannopyranosylation,[12a] toluene was also found to be a good solvent in the present method [(b) of entry 1]. The presence of the cyclic 4,6-acetal in mannosyl donors has been recognized as one of the necessary factors for the improvement of the $\beta$-selectivity in mannosylation: Crich et al. have suggested that the 4,6-benzylidene group stabilizes the intermediate α-triflate to give selectively the $\beta$-mannopyranosides via the $S_N2$-like displacement,[11] while Ito et al. reported the 4,6-cyclohexylidene group was the better protecting group than the benzylidene group.[17] The present result indicates that the glycosylation with the HCB 4,6-*O*-cyclohexylidenemannoside **5** was also highly $\beta$-selective but $\beta$-selectivity was somewhat reduced compared to its benzylidene counterpart **4** when the secondary alcohol **14** and the tertiary alcohol **17** were employed as glycosyl acceptors (entries 12−16). It is notable that the glycosylation of the HCB 2,3-*O*-cyclohexylidenemannoside **6**, which does not contain the cyclic 4,6-acetal group, with glycosyl acceptors afforded also $\beta$-mannosyl disaccharides as the major products (entries17 and 18).[18] The present HCB glycoside protocol could be applied to not only the mannosylation but also the glucosylation. Thus, glycosylation of **7** with acceptors **9** and **11** provided α-glucosides as the major products (entries 19 and 20).[19]

When the mannosylation was performed with the reversal of the order of addition of the reactants, for example, when $Tf_2O$

(14) For selected references on the sequential glycosylation, see: (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. An. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Mehta, S.; Pinto, B. M. *Tetrahedron Lett.* **1991**, *32*, 4435−4438. (c) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581. (d) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919−7920. (e) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292−2294. (f) Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073−12074. (g) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Bassov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (h) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414−417.

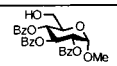
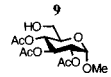
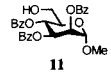
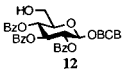
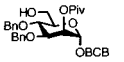
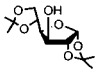
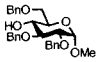
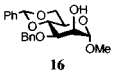
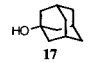
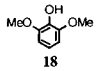
(15) (a) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053−6056. (b) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593−3596. (c) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262−4271. (d) Boons, G.-J.; Heskamp, B.; Hout, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *33*, 2845−2847.

(16) For suppression effect of $NH_4OAc$ on the hydrogenolysis of benzyl ethers, see: Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465−3468.

(17) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102−1104.

(18) On the other hand, glycosylation of HCB 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside, which neither contains the 2,3-acetal nor the 4,6-acetal, with the acceptor **10** gave the α-disaccharide as the major product ($\beta/\alpha$ = 1:1.3).

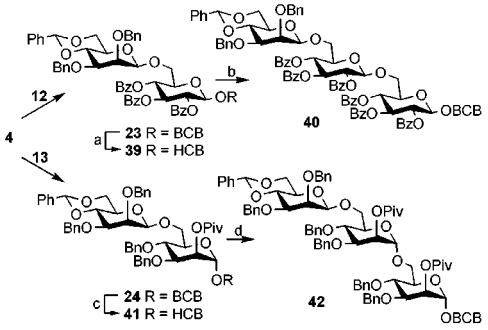
**Table 1.** Glycosylation with HCB Glycosides **4**, **5**, **6**, and **7** in $CH_2Cl_2$

| Entry | Glycosyl Donor | Glycosyl Acceptor | Product | Yield (%)[a] | Ratio (β/α)[a] |
|---|---|---|---|---|---|
| 1 | **4** |  **9** | **20** | 91 (95)[b] {91}[c] | β only (20:1)[b] {16:1}[c] |
| 2 | **4** |  **10** | **21** | 95 {95}[d] | β only {>25:1}[d] |
| 3 | **4** |  **11** | **22** | 91 | β only |
| 4 | **4** |  **12** | **23** | 85 | β only |
| 5 | **4** |  **13** | **24** | 83 | β only |
| 6 | **4** |  **14** | **25** | 91 {88}[e] {99}[d] | >20:1[e] {8:1}[e] {19:1}[d] |
| 7 | **4** |  **15** | **26** | 93 | 16:1 |
| 8 | **4** |  **16** | **27** | 96 {96}[d] | 17:1 {15:1}[d] |
| 9 | **4** |  **17** | **28** | 90 | >20:1[e] |
| 10 | **4** |  **18** | **29** | 89 | 4:1 |
| 11 | **4** + its β-anomer (1:3) | **9** | **20** | 81 | β + 17% of an ester |
| 12 | **5** | **9** | **30** | 83 | β only |
| 13 | **5** | **11** | **31** | 91 | β only |
| 14 | **5** | **14** | **32** | 93 | 9:1 |
| 15 | **5** | **17** | **33** | 90 | 8:1 |
| 16 | **5** | **18** | **34** | 87 | 6:1 |
| 17 | **6** | **9** | **35** | 95 | 5:1 |
| 18 | **6** | **11** | **36** | 76 | 5:1 |
| 19 | **7** | **9** | **37** | 87 | α only |
| 20 | **7** | **11** | **38** | 85 | α only |
| 21 | **7** + its α-anomer (1:3.5) | **9** | **37** | 93 | α only |

[a] Determined after isolation. [b] In toluene as a solvent. [c] $Tf_2O$ was added to the mixture of the glycosyl donor and the acceptor. [d] The result by the Crich−Kahne sulfoxide method, see ref 12d. [e] After isolation of most of β-anomer, the ratio of the remaining β/α mixture was determined by $^1H$ NMR.

was added to the mixture of **4** and **9**, the β-mannoside **20** was still the major product (91%, β/α = 16:1, [(c) of entry 1] and addition of $Tf_2O$ to the mixture of **4** and **14** afforded also β-mannoside **25** as the major product (88%, β/α = 8:1, [(c) of entry 6]. We also examined the relative reactivity and stereoselectivity in the glycosylation of the α-anomer **4** and its β-anomer and of the β-anomer **7** and its α-anomer. The β-anomer of the HCB mannoside **4** exhibited almost same stereoselectivity but much lower reactivity compared to its α-anomer **4** so that the esterification between a portion of the β-anomer and the acceptor alcohol **9** occurred faster than the glycosylation to produce a substantial amount of an ester (entry 11). In the case of the HCB glucoside **7**, the stereoselectivity of both anomers was almost same, but the β-anomer **7** was also less reactive than its α-anomer although the glycosylation of both anomers proceeded smoothly without formation of the ester (entry 21).[20] We also observed the generation of phthalide with the disappearance of the starting HCB glycoside as soon as $Tf_2O$ was added to the HCB glycoside at −78 °C in the absence of the acceptor. On the basis of the aforementioned results, we think that the reaction mechanism of the present glycosylation would be as shown in Scheme 1. Yet, it is difficult to say whether β-mannosylation would occur only through $S_N2$-like displacement of the α-triflate **D** by the acceptor[11] or by direct attack of the acceptor to the oxocarbenium ion **C**.[21]

**Scheme 3**[a]




[a] (a) $H_2$ (balloon), Pd/C, 1 equiv $NH_4OAc$, MeOH (92%); (b) $Tf_2O$, DTBMP, 4 Å MS, $CH_2Cl_2$, −45 °C, then **12**, −45 to 0 °C (72%); (c) $H_2$ (balloon), Pd/C, 3.5 equiv $NH_4OAc$, MeOH (94%); (d) $Tf_2O$, DTBMP, 4 Å MS, $CH_2Cl_2$, −78 °C, then **13**, −78 to 0 °C (73%).

The successful glycosylation of the HCB glycoside **4** with the BCB glycosides **12** and **13** indicated that the sequential glycosylation for oligosaccharide synthesis would be possible employing this methodology since the resulting BCB disaccharide could be used for another glycosylation after selective removal of the benzyl ester linkage. In fact, the stable ("latent") BCB disaccharide **23**,[22] obtained from **4** and **12**, was readily converted into the "active" HCB glycoside **39** in 92% yield by the selective hydrogenolysis. Repetitive glycosylation of **39** with the same glycosyl acceptor **12** provided the BCB trisaccharide **40** in 72% yield as shown in Scheme 3. Similarly, the BCB trisaccharide **42** was also efficiently prepared from **4** and **13** via the latent BCB disaccharide **24** and the active HCB disaccharide **41**. Finally, we also prepared the trisaccharide **46** from the HCB glycoside **8** and the methyl glycoside **43** via disaccharides **44** and **45** in 74% overall yield in three steps by the conventional protection-deprotection method as shown in Scheme 4.

## Conclusions

In conclusion, we described the synthesis of novel HCB glycosides and the highly efficient and stereoselective procedure for the β-mannopyranosylation employing the HCB mannopyranoside with triflic anhydride. The present HCB glycoside method for β-mannopyranosylation was found to be comparable

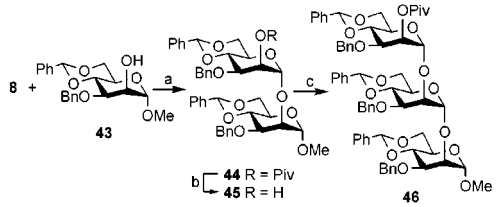
(19) For the α-glucopyranosylation employing glycosyl sulfoxides and thioglycosides, see: Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930.

(20) The higher reactivity of the α-anomer could be attributed to the higher nucleophilicity of the anomeric oxygen or the weaker anomeric C−O bond due to the anomeric effect, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 4−53.

(21) For a recent suggestion of direct attack on the oxocarbenium by the glycosyl acceptor in β-mannopyranosylation, see: Weingart, R.; Schimidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753−8758.

(22) The BCB glycosides are inert not only under the present glycosylation conditions but also toward various Lewis acids and glycosylation promoters except toward TMSOTf above room temperature.

**Scheme 4**[a]




[a] (a) **8**, $Tf_2O$, DTBMP, 4 Å MS, $CH_2Cl_2$, −78 °C, then **43**, −78 to 0 °C (90%); (b) NaOMe, MeOH, reflux (99%); (c) **8**, $Tf_2O$, DTBMP, 4 Å MS, $CH_2Cl_2$, −78 °C, then **45**, −78 to 0 °C (83%).

to the thioglycoside and the glycosyl sulfoxide methods in terms of stereoselectivity. We also found that not only 4,6-acetals but also the 2,3-*O*-cyclohexylidene-protecting group in the HCB mannopyranoside facilitated the formation of $\beta$-mannopyranosides. α-Glucopyranosides were produced as the major product in the glycosylation of the HCB 4,6-*O*-benzylideneglucoside. The power of the present methodology was demonstrated by the efficient synthesis of trisaccharides employing the pair of the latent BCB glycoside and the active HCB glycoside.

## Experimental Section

**Benzyl 2-(Hydroxymethyl)benzoate (1).** A suspension of phthalide (10 g, 74.6 mmol) on an aqueous 1 N NaOH (75 mL) was stirred at 100 °C for 1 h. The reaction mixture was concentrated in vacuo, coevaporated with toluene, and dried under high vacuum to give a white solid. The solution of the resulting solid sodium salt and benzyl bromide (8.87 mL, 74.6 mmol) in DMF (50 mL) was stirred at room temperature for 1 h. After being quenched with water (100 mL), the reaction mixture was extracted with EtOAc (2 × 200 mL). The combined organic layer was washed with saturated aqueous $NH_4Cl$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (25% ethyl acetate in hexane) to afford the pure **1** (16.8 g, 93%): white solid, mp 62−64 °C; $R_f$ = 0.33 (25% ethyl acetate in hexane); IR ($CHCl_3$ film) 3270, 1710, 1262, 736 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.83 (t, $J$ = 7.3 Hz, 1 H), 4.79 (d, $J$ = 7.3 Hz, 2 H), 5.37 (s, 2 H), 7.36−7.53 (m, 8 H), 8.05 (dd, $J$ = 1.2, 6.6 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 64.9, 67.3, 128.0, 128.4, 128.6, 128.8, 128.9, 130.5, 131.4, 133.3, 135.7, 143.3, 167.9. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.35; H, 5.84.

**2-(Benzyloxycarbonyl)benzyl α-D-Mannopyranoside (2).** To a stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (5.0 g, 12.2 mmol) in the presence of 4 Å MS in acetonitrile (25 mL) at 0 °C were added mercury (II) bromide (5.28 g, 14.7 mmol, 1.2 equiv), mercury (II) cyanide (3.70 g, 14.7 mmol, 1.2 equiv), and finally the compound **1** (3.25 g, 13.4 mmol, 1.1 equiv). After stirring at 0 °C for further 20 min, the reaction mixture was filtered, and the filtrate was concentrated. The resulting oil was dissolved in $CH_2Cl_2$ (50 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (33% ethyl acetate in petroleum ether) to afford 2-(benzyloxycarbonyl)benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (6.0 g, 86%): $R_f$ = 0.25 (33% ethyl acetate in petroleum ether); $[\alpha]^{20}_D$ = +52.4 ($c$ = 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.01 (s, 3 H), 2.04 (s, 3 H), 2.09 (s, 3 H), 2.16 (s, 3 H), 4.03−4.14 (m, 2 H), 4.31 (dd, $J$ = 5.1, 12.3 Hz, 1 H), 4.96 (d, $J$ = 1.5 Hz, 1 H), 4.98 (d, $J$ = 13.8 Hz, 1 H), 5.18 (d, $J$ = 13.8 Hz, 1 H), 5.33 (s, 2 H), 5.33 (t, $J$ = 9.9 Hz, 1 H), 5.38 (dd, $J$ = 1.5, 3.3 Hz, 1 H), 5.44 (dd, $J$ = 3.3, 9.9 Hz, 1 H), 7.30−7.46 (m, 6 H), 7.56 (td, $J$ = 8.1, 1.5 Hz, 1 H), 7.63 (dd, $J$ = 0.6, 8.1 Hz, 1 H), 8.01 (dd, $J$ = 1.5, 8.1 Hz, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.7 (3), 20.9, 62.3, 66.1, 66.8, 67.8, 68.7, 69.3, 69.5, 97.5, 127.6, 127.8, 128.1, 128.2, 128.3, 128.6, 130.8, 132.7, 135.9, 139.0, 166.4, 169.7, 169.9, 170.0, 170.6. Anal. Calcd for $C_{29}H_{32}O_{12}$: C, 60.83; H, 5.63. Found: C, 60.88; H, 5.68.

To a solution of 2-(benzyloxycarbonyl)benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (5.0 g, 8.73 mmol) in MeOH (50 mL) was added NaOMe (94 mg, 1.74 mmol). After stirring at room temperature for further 20 min, the reaction mixture was neutralized with DOWEX CCR-3 ($H^+$ mode) and concentrated to give the title compound **2** (3.28 g, 8.11 mmol, 93%), which was used for the next step without purification.

**2-(Benzyloxycarbonyl)benzyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (3).** A solution of the compound **2** and benzaldehyde dimethylacetal (1.34 mL, 8.93 mmol, 1.1 equiv) in the presence of camphor sulfonic acid (56 mg, 0.24 mmol, 0.03 equiv) in DMF (30 mL) was stirred at 50 °C for 4 h. After being quenched with saturated aqueous $NaHCO_3$ (100 mL), the reaction mixture was extracted with EtOAc (3 × 70 mL). The combined organic layer was washed with saturated aqueous $NH_4Cl$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (50% ethyl acetate in hexane) to afford 2-(benzyloxycarbonyl)benzyl 4,6-*O*-benzylidene-α-D-mannopyranoside (2.80 g, 70%): white solid, mp 129−131 °C; $R_f$ = 0.28 (50% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +55 ($c$ = 1.4, $CHCl_3$); IR ($CHCl_3$ film) 3378, 3244, 2911, 1715, 1256, 1064, 742 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 2.68 (brs, 2 H), 3.77−3.98 (m, 3 H), 4.08−4.16 (m, 2 H), 4.25 (dd, $J$ = 3.0, 8.7 Hz, 1 H), 4.95 (d, $J$ = 13.5 Hz, 1 H), 4.97 (d, $J$ = 1.5 Hz, 1 H), 5.14 (d, $J$ = 13.5 Hz, 1 H), 5.34 (s, 2 H), 5.52 (s, 1 H), 7.34−7.60 (m, 13 H), 8.01 (dd, $J$ = 1.0, 7.7 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 63.4, 66.8, 67.6, 68.7, 68.8, 70.9, 78.9, 100.1, 102.2, 126.3, 127.4, 127.9, 128.3, 128.6, 129.2, 130.8, 132.5, 135.8, 137.2, 139.5, 166.7. Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73. Found: C, 68.28; H, 5.74.

To a solution of 2-(benzyloxycarbonyl)benzyl 4,6-*O*-benzylidene-α-D-mannopyranoside (2.50 g, 5.08 mmol, 1 equiv) and benzyl bromide (1.45 mL, 12.2 mmol, 2.4 equiv) in DMF (15 mL) was added NaH (0.49 g, 12.2 mmol, 2.4 equiv) at 0 °C, and then the ice bath was removed. After stirring at room temperature for 1 h, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with saturated aqueous $NH_4Cl$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (20% ethyl acetate in hexane) to afford the compound **3** (2.73 g, 80%): $R_f$ = 0.40 (20% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +50.8 ($c$ = 4.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.83−3.91 (m, 3 H), 4.03 (dd, $J$ = 3.3, 10.2 Hz, 1 H), 4.21−4.32 (m, 2 H), 4.66 (d, $J$ = 12.0 Hz, 1 H), 4.74 (d, $J$ = 12.3 Hz, 1 H), 4.81 (d, $J$ = 12.0 Hz, 1 H), 4.85 (d, $J$ = 12.3 Hz, 1 H), 4.91 (d, $J$ = 14.1 Hz, 1 H), 4.94 (d, $J$ = 1.5 Hz, 1 H), 5.07 (d, $J$ = 14.1 Hz, 1 H), 5.28 (s, 2 H), 5.64 (s, 1 H), 7.26−7.51 (m, 23 H), 7.98 (dd, $J$ = 1.2, 7.8 Hz, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 64.5, 66.7, 67.4, 68.8, 73.2, 73.4, 76.3, 76.4, 79.2, 99.1, 101.4, 126.0, 127.3, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 128.6, 128.8, 130.7, 132.5, 135.8, 137.7, 138.5, 138.6, 139.6, 166.6. Anal. Calcd for $C_{42}H_{40}O_8$: C, 74.98; H, 5.99. Found: C, 74.87; H, 5.92.

**2-(Hydroxycarbonyl)benzyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (4).** Compound **3** (2.0 g, 2.97 mmol, 1 equiv) was stirred under hydrogen atmosphere using a balloon in the presence of Pd/C (10%, 221 mg, 0.07 equiv) and ammonium acetate (801 mg, 10.39 mmol, 3.5 equiv) in MeOH (100 mL) at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (50% ethyl acetate in hexane) to afford the title compound **4** (1.66 g, 96%): white solid, mp 81−82 °C; $R_f$ = 0.40 (50% ethyl acetate in hexane); $[\alpha]^{20}_D$ = +62.6 ($c$ = 2.5, $CHCl_3$); IR ($CHCl_3$ film) 3070, 3034, 2915, 1695, 1101, 746 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.86−3.88 (m, 2 H), 3.91 (dd, $J$ = 1.8, 3.3 Hz, 1 H), 4.06 (dd, $J$ = 3.3, 10.2 Hz, 1 H), 4.25−4.30 (m, 2 H), 4.67 (d, $J$ = 12.0 Hz, 1 H), 4.74 (d, $J$ = 12.3 Hz, 1 H), 4.81 (d, $J$ = 12.3 Hz, 1 H), 4.86 (d, $J$ = 12.0 Hz, 1 H), 4.92 (d, $J$ = 14.4 Hz, 1 H), 4.99 (d, $J$ = 1.8 Hz, 1 H), 5.12 (d, $J$ = 14.4 Hz, 1 H), 5.64 (s, 1 H), 7.24−7.56 (m, 18 H), 8.07 (dd, $J$ = 1.2, 7.8 Hz, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 64.7, 67.6, 68.9, 73.3, 73.6, 76.4, 76.5, 79.2, 99.3, 101.6, 126.2, 127.5, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 128.9, 131.7, 133.4, 137.8, 138.2, 138.7, 140.5, 172.1. Anal. Calcd for $C_{35}H_{34}O_8$: C, 72.15; H, 5.88. Found: C, 72.15; H, 5.84.

**General Procedure for the Glycosylation Employing HCB Glycosides.** A solution of the HCB glycoside (0.10 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (0.20 mmol, 2 equiv) in $CH_2Cl_2$ (6 mL) in the presence of 4 Å MS was stirred for 30 min at room temperature and cooled to −78 °C. After addition of $Tf_2O$ (0.10 mmol, 1 equiv), the solution was stirred at −78 °C for 10 min, and then the glycosyl acceptor (0.20 mmol, 2 equiv) was added. The reaction mixture was stirred at −78 °C for further 1 h and allowed to warm over 2 h to 0 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the organic phase was washed with brine, dried ($MgSO_4$), concentrated, and purified by silica gel flash column chromatography.

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**Supporting Information Available:** Synthetic procedure for **5**−**8** and for **39**−**46** and spectral data for **12**, **13**, and **20**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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