Glycosylation with 2′-Carboxybenzyl Glycosides as Glycosyl Donors: Scope and Application to the Synthesis of a Tetrasaccharide

Kwan Soo Kim,* Sung Soo Kang, Yong Sung Seo, Hyo Jin Kim, Yong Joo Lee, Kyu-Sung Jeong

Department of Chemistry, Yonsei University, Seoul 120-749, Korea
Fax +82(2)3647050; E-mail: kwan@yonsei.ac.kr

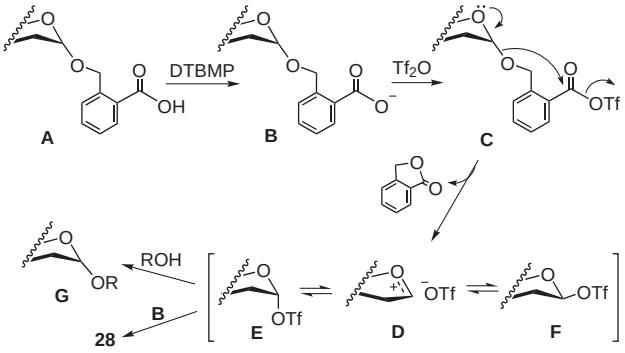
Received 17 March 2003

Dedicated to the late Professor Ray Lemieux in admiration of his many seminal contributions to carbohydrate chemistry.

Abstract: Glycosylation of 2′-carboxybenzyl (CB) 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**3**), CB 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**4**), and CB 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**5**) as glycosyl donors with various glycosyl acceptors provided corresponding disaccharides in high yields. The present CB glycoside methodology was successfully applied to the efficient construction of the tetrasaccharide **41**.

Key words: carbohydrates, oligosaccharide synthesis, glycosylations, CB glycosides, BCB glycosides

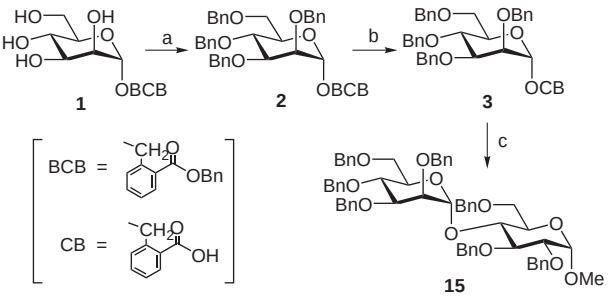
Development of efficient and stereoselective glycosylation methodologies has been one of the major concerns in synthetic organic chemistry in recent years due to the biological significance of complex oligosaccharides and glycoconjugates.[1] Although several glycosylation methodologies based on quite efficient glycosyl donors such as thioglycosides,[2] glycosyl sulfoxides,[3] glycals,[4] glycosyl trichloroacetimidates,[5] *n*-pentenyl glycosides,[6] and glycosyl fluorides[7] have been available, there still remains a need for more efficient and generally applicable new glycosylation methodologies. In fact, there have been recent reports on development of new glycosylation methods based on devising new glycosyl donors and employing new activation systems for existing glycosyl donors.[8] We have also recently reported the 2′-carboxybenzyl (CB)[9] glycoside **A** in Scheme 1 as a novel type of glycosyl donors for the stereoselective β-mannopyranosylation[10] and 2-deoxyglycosylation.[11] Lactonization of the glycosyl triflate **C**, which was derived from the CB glycoside **A**, was the driving force for the facile generation of the oxocarbenium **D** for the glycosylation as shown in Scheme 1. In our previous work, only the CB mannopyranoside having the 4,6-*O*-benzylidene protective group has been subjected to the glycosylation reaction and just two examples of glycosylation with CB glucopyranosides have been reported.[10] Therefore, to explore the scope of this CB glycoside methodology, we further carried out glycosylation reactions with new CB mannopyranosides and CB glucopyranosides. In addition, in order to demonstrate the applicability of the CB glycoside methodology to oligosaccharide synthesis, we report the construction of a



Scheme 1

tetrasaccharide employing the pair of the 'latent' 2′-(benzyloxycarbonyl)benzyl (BCB) glycoside and the 'active' CB glycoside.

The CB tetrabenzylmannoside **3**[12] was prepared by selective hydrogenolysis of BCB tetrabenzylmannoside **2**, which was obtained from the known BCB mannoside **1**[10] as shown in Scheme 2. The CB tetrabenzylglucoside **4** was prepared in an analogous fashion while the CB 4,6-*O*-benzylideneglucoside **5** (Figure 1)was synthesized by the known procedure.[10]



Scheme 2 *Reagents and conditions* a) NaH, BnBr, DMF, r.t., 2 h, 80%; b) H_2, Pd/C, NH_4OAc, MeOH, r.t., 1 h, 94%; c) **3**, DTBMP, Tf_2O, 4 Å MS, CH_2Cl_2, –78 ºC, 10 min, then **9**, –78 ºC to 0 ºC, 3 h, 75%.

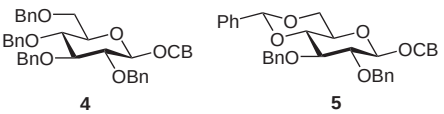
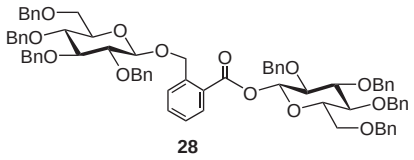


Figure 1

Synlett 2003, No. 9, Print: 11 07 2003.
Art Id.1437-2096,E;2003,0,09,1311,1314,ftx,en;S05103ST.pdf.

Glycosylation of the CB tetrabenzylmannoside **3** with the glycosyl acceptors **6**–**11** was carried out under the standard reaction condition (condition A) by the following sequence: (i) stirring the solution of **3** (60 mg, 1.0 equiv) and 2,6-di-*t*-butyl-4-methylpyridine (DTBMP, 2.4 equiv) in the presence of 4A molecular sieves (MS) for 20 min at room temperature in CH_2Cl_2 (8 mL), (ii) addition of Tf_2O (1.2 equiv) to this solution at –78 ºC and stirring the solution for 10 min, (iii) addition of the glycosyl acceptor (2.0 equiv) and stirring the reaction mixture for further 1 h at –78 ºC and allowing to warm over 2 h to 0 ºC, and (iv) quenching the reaction by addition of aqueous $NaHCO_3$. Glycosylation of CB mannoside **3** with primary alcohol acceptors **6**–**8** gave the mixtures of α- and β-disaccharides **12**–**14** (Table 1, entries 1–3) while reaction of **3** with secondary alcohol acceptors **9**–**11** afforded exclusively α-disaccharides **15**–**17** in good yields (Scheme 2 and Table 1, entries 3–6). This result indicates that not only 4,6-*O*-benzylidene-protected CB mannosides but also CB mannosides with other protective groups are efficient mannosyl donors.



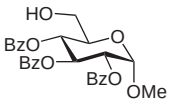
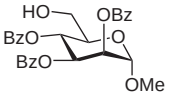
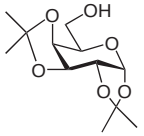
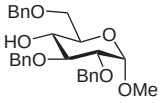
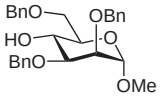
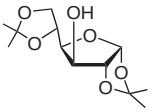
28

Figure 2

Glycosylations of the CB tetrabenzylglucoside **4** and of the CB 4,6-*O*-benzylideneglucoside **5** with various glycosyl acceptors were also carried out under the standard reaction condition (condition A) as described above for the CB mannoside **3**. Reaction of the benzyl-protected glucose donor **4** with the glycosyl acceptor **6** under the reaction condition A afforded a mixture of α- and β-disaccharides **18** in 76% yield along with the self-condensed ester **28** (Figure 2), which must be derived from two molecules of the glycosyl donor **4**, in 22% yield (Table 2, entry 1). Glycosylation of **4** with other glycosyl acceptors **7** and **11** gave also the mixtures of α- and β-disaccharides along with the self-condensed ester **28** (Table 2, entries 2 and 3). However, glycosylation of the 4,6-*O*-benzylidene-protected glucose donor **5** with glycosyl acceptors **6**, **7**, **9**, and **11** afforded exclusively the α-disaccharides **21**, **22**, **23**, and **24**, respectively, in high yields but formation of the self-condensed ester was not observed (Table 2, entries 4–7). It is noteworthy that glycosylation of the 4,6-*O*-benzylidene-protected glucose donor **5** provided only α-disaccharides regardless of what kind of glycosyl acceptors were used, primary or secondary alcohols. In fact, it has been previously reported that the selective α-glucopyranosylation could be achieved by employing the 4,6-*O*-benzylidene-protected glycosyl sulfoxides and thioglycosides as glycosyl donors.[13]

Formation of the self-condensed ester **28** probably resulted from the coupling between the carboxylate anion **B**, which was generated by deprotonation of the CB glycoside **A** by DTBMP, and the oxocarbenium ion **D** or the C-1 triflate intermediate **E** or **F** as shown in Scheme 1. Generation of a substantial amount of ester **28** led us to postulate that the conversion of the carboxylate **B** into **C** was slower than the formation of **D** by the lactonization of **C**. We envisaged that if the concentration of **B** was kept at a minimum during glycosylation, the formation of the ester **28** would be suppressed. We, therefore, ran the glycosylation reaction with the reversal of the order of addition of the reactants. Thus, glycosylation of the CB tetrabenzylglucoside **4** with various glycosyl acceptors **6**–**11** was carried out under the modified reaction condition (condition B) by the following sequence: (i) stirring the solution of the glycosyl acceptor (2 equiv) and DTBMP (2.4 equiv) in the presence of 4Å MS for 20 min at room temperature in CH_2Cl_2 (3 mL), (ii) addition of Tf_2O (1.2 equiv) to this solution at –78 ºC, (iii) addition of **4** (60 mg, 1.0 equiv) in CH_2Cl_2 (4 mL) dropwise to this solution over a period of 10 min and stirring the reaction mixture for further 1 h at

Table 1 Glycosylation of the CB Mannoside **3** as the Glycosyl Donor under the Standard Condition (Condition A)[a]

Entry	Glycosyl Acceptor	Product	Yield (%)	Ratio (α/β)
1	 **6**	**12**	87	1.3:1
2	 **7**	**13**	91	1.1:1
3	 **8**	**14**	65	1.6:1
4	 **9**	**15**	75	α only
5	 **10**	**16**	73	α only
6	 **11**	**17**	77	α only

[a] To a solution of the donor were added sequentially Tf_2O and then the acceptor at –78 ºC.

Table 2 Glycosylation of the CB Glycosides **4** and **5** as Glycosyl Donors under the Standard Condition (Condition A)[a]

Entry	Donor	Acceptor	Product	Yield (%)	Ratio (α/β)	Ester **28** (%)
1	**4**	**6**	**18**	76	1:2	22
2	**4**	**7**	**19**	73	1:3	22
3	**4**	**11**	**20**	77	1:1	16
4	**5**	**6**	**21**	87	α only	0
5	**5**	**7**	**22**	85	α only	0
6	**5**	**9**	**23**	80	α only	0
7	**5**	**11**	**24**	85	α only	0

[a] To a solution of the donor were added sequentially Tf_2O and then the acceptor at –78 ºC.

–78 ºC and allowing to warm over 2 h to 0 ºC, and (iv) quenching the reaction by addition of aqueous $NaHCO_3$. Glycosylation of **4** with **6** under the condition B provided exclusively the disaccharide **18** (α/β = 1:2.5) in 93% yield without formation of ester **28** (Table 3, entry 1). Reaction of **4** with other acceptors **7**–**11** under the condition B also gave exclusively disaccharides in high yields without the ester **28** (Table 3, entries 2–6).

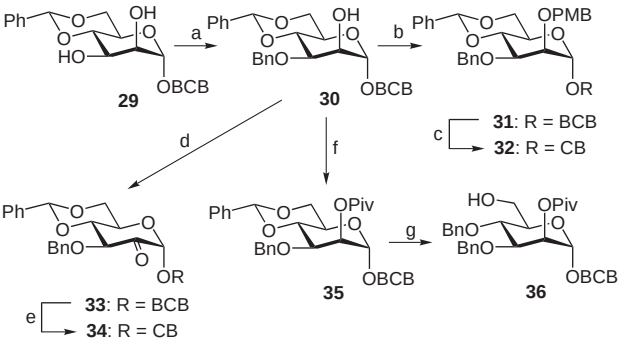
Then we applied this CB glycoside methodology to the synthesis of the protected tetrasaccharide **41**, which we designed as an analog of the tetrasaccharide repeating unit of the O-antigen polysaccharide from the *E. coli* lipopolysaccharide. Monosaccharide building blocks **32**, **34**, and **36** were synthesized from a common starting material **30**, which was prepared by selective benzylation of the diol **29** using dibutyltin oxide (Scheme 3). *p*-Methoxybenzylation of **30** and the subsequent selective hydrogenolysis of **31** gave the CB glycoside **32**. Oxidation of **30** with PDC and the hydrogenolysis of the resulting ketone **33** afforded another CB glycoside **34**. Pivaloylation of **30** and the subsequent reductive cleavage of the benzylidene acetal **35** with borane-dibutylboron triflate[14] provided the alcohol **36**. Glycosylation of the glycosyl donor **32** and acceptor **30** was carried out under the standard condition to afford exclusively the β-disaccharide **37** in 91% yield and removal of the PMB group in **37** with DDQ gave the alcohol **38** as shown in Scheme 4. Again, it has been demonstrated that CB mannopyranosides having the 4,6-O-benzylidene group and a C-2 nonparticipating group are extremely useful mannosyl donors for the stereoselective β-mannopyranosylation.

Glycosylation of the ketone glycosyl donor **34** with acceptor **36**, on the other hand, was conducted under the different reaction condition in order to obtain the α-disaccharide **39** because the β-disaccharide was found to be the major product under the standard condition. Thus, a solution of **34**, **36**, and DTBMP in the presence of 4A MS was stirred at room temperature for 30 min and cooled down to –40 ºC. Triflic anhydride was added to this solution and the reaction mixture was stirred for further 1 h at –40 ºC and allowed to warm to 10 ºC to afforded a mixture of the α-disaccharide **39** and its anomeric β-disaccharide (4:1) in 74% yield. The latent BCB disaccharide **39** was converted into the active CB disaccharide **40** by the selective debenzylation. Finally, the coupling of two disaccharides **40** and **38** was carried out by addition of Tf_2O to a

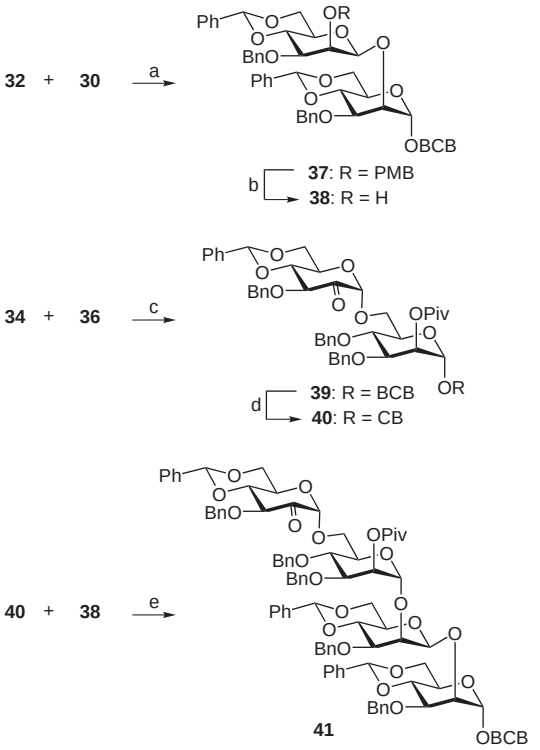
Table 3 Glycosylation of the CB Glycoside **4** as the Glycosyl Donor under the Modified Condition (Condition B)[a]

Entry	Acceptor	Product	Yield (%)	Ratio (α/β)
1	**6**	**18**	93	1:2.5
2	**7**	**19**	92	1:2.3
3	**8**	**25**	92	1:1.3
4	**9**	**26**	87	1:1.6
5	**10**	**27**	86	1:1.2
6	**11**	**20**	96	1.4:1

[a] To a solution of the acceptor and Tf_2O was added dropwise the donor at –78 ºC.



Scheme 3 *Reagents and conditions* a) Bu_2SnO, MeOH, reflux, 1 h, then BnBr, DMF, 90 ºC, 3 h, 84%; b) PMBCl, NaH, DMF, r.t., 1.5 h, 83%; c) H_2, Pd/C, NH_4OAc, MeOH, r.t., 1 h, 91%; d) PDC, CH_2Cl_2, 4 Å MS, r.t., 8 h, 72%; e) same as c), 92%; f) PivCl, DMAP (cat.), Et_3N, CH_2Cl_2, r.t, 1 h, 86%; g) BH_3, Bu_2BOTf (cat.), THF, 0 ºC to r.t., 1 h, then Et_3N, 2 h, 88%.



Scheme 4 *Reagents and conditions* a) **32**, DTBMP, Tf_2O, 4 Å MS, CH_2Cl_2, –78 ºC, 10 min, then **30**, –78 ºC to 0 ºC, 3 h, 91%; b) DDQ, CH_2Cl_2–H_2O (18:1), r.t., 9 h, 83%; c) **34**, **36**, DTBMP, 4 Å MS, CH_2Cl_2, –40 ºC, then Tf_2O, –40 ºC to 0 ºC, 3 h, 74% (α/β = 4:1); d) H_2, Pd/C, NH_4OAc, MeOH, r.t., 1 h, 87%; e) **38**, **40**, DTBMP, 4 Å MS, CH_2Cl_2, –40 ºC, then Tf_2O, –40 ºC to 0 ºC, 3 h, 75%.

stirred solution of the glycosyl donor **40**, acceptor **38**, and DTBMP in the presence of 4 Å MS at –40 ºC to afford exclusively the desired α-tetrasaccharide **41**[15] in 75% yield. This result indicates that the participating group at C-2 is working well in the CB glycosides and the present methodology could be applied for the construction of more complex important oligosaccharides.

In summary, we have shown that CB glycosides having various protective groups can be employed as efficient glycosyl donors and demonstrated the power of the CB glycoside methodology in oligosaccharide synthesis by presenting the efficient construction of a tetrasaccharide.

Acknowledgement

This work was support by a grant (2001-1-0064) from Yonsei University.

References

(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.
(2) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
(3) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
(4) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
(5) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.
(6) Fraser-Reid, B.; Madsen, R. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, **1997**, 339.
(7) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799.
(8) For recent examples of new glycosyl donors and activating systems, see: (a) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545. (b) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766. (c) Hinklin, R. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **2001**, *123*, 3379. (d) Davis, B. J.; Ward, S. J.; Rendle, P. M. *Chem. Commun.* **2001**, 189.
(9) The 2′-carboxybenzyl (CB) glycoside seems to be the more appropriate name than the 2-(hydroxycarbonyl)benzyl (HCB) glycoside, which was used in our earlier publication. See, ref. 10
(10) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477.
(11) Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem. Int. Ed.* **2003**, *42*, 459.
(12) The compound **3** has been prepared previously by a different method. See: Scheffler, G.; Schmidt, R. R. *J. Org. Chem* **1999**, *64*, 1319.
(13) For discussions on α-glucopyranosylation, see: Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926.
(14) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355.
(15) A solution of **40** (32 mg, 0.035 mmol, 1.0 equiv), **38** (39 mg, 0.042 mmol, 1.2 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (21 mg, 0.11 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL) in the presence of 4A molecular sieves was stirred for 30 min at room temperature and cooled to –40 ºC, then Tf_2O (8.8 μL, 0.055 mmol, 1.5 equiv) was added. The reaction mixture was stirred at –40 ºC 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 in vacuo. The residue was purified by silica gel flash column chromatography (33% ethyl acetate in hexane) to afford compound **41** (44 mg, 75%): colorless oil, R_f = 0.37 (33% ethyl acetate in hexane); $[\alpha]_D^{20}$ = +46.3 (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 3.38–3.47 (m, 2 H), 3.56–3.63 (m, 2 H), 3.69 (dd, *J* = 3.0 Hz, 5.0 Hz, 1 H), 3.83–3.91 (m, 5 H), 4.00–4.11 (m, 5 H), 4.14 (dd, *J* = 2.5 Hz, 5.0 Hz, 1 H), 4.22–4.35 (m, 6 H), 4.39–4.47 (m, 2 H), 4.52–4.65 (m, 5 H), 4.70–4.82 (m, 5 H), 4.92 (d, *J* = 6.0 Hz, 1 H), 5.00–5.12 (m, 3 H), 5.29 (m, 1 H), 5,33 (s, 2 H), 5.53 (s, 1 H), 5.59 (s, 1 H), 5.61 (s, 1 H), 7.06–7.55 (m, 46 H), 7.68 (dd, *J* = 3.7 Hz, 3.7 Hz, 1 H), 7.94 (d, *J* = 3.7 Hz, 1 H), 8.00 (d, *J* = 3.7 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.3, 39.0, 64.9, 66.7, 67.8, 68.1, 68.4, 68.6, 69.1, 69.6, 70.0, 70.8, 71.4, 72.7, 73.9, 74.4, 74.7, 76.7, 78.6, 80.1, 97.3, 98.0, 98.8, 100.9, 101.4, 101.5, 101.6, 125.8, 125.9, 126.0, 126.1, 127.3, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 129.0, 134.0, 137.7, 146.5, 166.7, 177.1, 194.6; Anal. Calcd for $C_{100}H_{102}O_{24}$: C, 71.16; H, 6.09. Found: C, 71.15; H, 6.11; MALDI-TOF MS Calcd for 1725.7761 (M + K). Found 1725.7712.