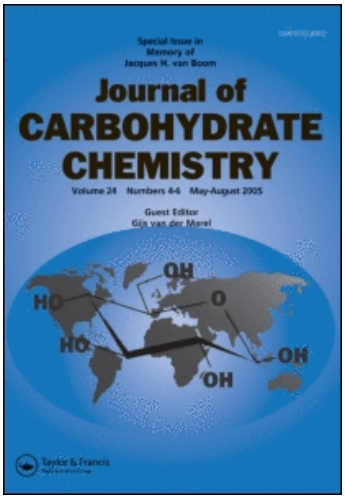


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# Efficient Chemical Syntheses of Branched Cyclomalto-Oligosaccharides Using the Trichloroacetimidate Method

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## ABSTRACT

Glycosylation using the trichloroacetimidate method was investigated in order to synthesize branched cyclomalto-oligosaccharides (cyclodextrins, CDs). We examined the chemical syntheses of galactosyl CDs, directly β-linked to the CD ring, which could not be synthesized by enzyme catalyzed reactions. We prepared 6-*O*-(D-galactosyl)-γCD and 6-*O*-(D-mannosyl)-γCD as basic model compounds using a combination of protecting groups on the glycosyl donor, catalysts to synthesize imidate derivatives, and catalysts for glycosylation. The configurational isomers were determined by HPLC and NMR spectroscopy.

*Key Words:* Glycosylation; Galactosyl-γCD; Mannosyl-γCD.

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## INTRODUCTION

Hetero-branched cyclodextrins (CDs) having various kinds of oligosaccharide components of glycoproteins or glycolipids on their side chains are expected to be useful as drug carriers in targeted drug delivery systems. Their model hetero-branched CDs having heterogeneous sugars as galactose or mannose were synthesized by transglycosylation or the reverse action of several enzymes such as β-galactosidases, α-galactosidases, and α-mannosidases. β-Galactosidases from microorganisms such as *Bacillus circulans*, *Aspergillus oryzae*, and *Penicillium multicolor* and α-galactosidase as *Mortierella vinacea* synthesize hetero-branched CDs, which have galactose residues linked only to the side chains of the branched CDs. These enzymes do not catalyze synthesis of galactosyl CDs, that is, galactose is not directly linked to the CD ring. However, α-galactosidase from coffee bean and α-mannosidase from jack bean can bind galactosyl and mannosyl residues directly to the CD ring, respectively, by transglycosylation or reverse action.[1–3]

Here we examine the chemical syntheses of glycosyl CDs, directly β-linked to the CD ring, which cannot be synthesized by enzyme catalyzed reactions, by preparing 6-*O*-(D-galactosyl)-γCD and 6-*O*-(D-mannosyl)-γCD as basic model compounds using the trichloroacetimidate method (Figure 1).

The glycosylation reaction presented by Schmidt et al.[4] in 1980 and in 1994[5] surpassed the conventional imidate method.[6] This method allows very convenient and facile preparation of sugar donors on a small scale. It can give high yields of trichloroacetimidates with an anomeric hydroxyl group that reacts with trichloroacetonitrile in the presence of base, e.g., potassium carbonate, sodium hydride, or 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU).[7,8] Irrespective of the protecting group on OH-2, the thermodynamically stable α-imidate can be obtained using sodium hydride or DBU. Using potassium carbonate gives β-imidate, which is much more subject to kinetic control. There are several variations of this method.[9–11]

| | R | R' |
|---|---|---|
| **1** | H | DTr |
| **2** | Ac | DTr |
| **3** | Ac | H |
| **4** | Ac | X |
| **5** | Ac | Y |
| **6** | Ac | D-galactopyranosyl |
| **7** | H | α-D-galactopyranosyl |
| **8** | H | β-D-galactopyranosyl |
| **9** | Ac | Z |
| **10** | H | α-D-mannopyranosyl |

DTr: dimethoxytrityl
X: 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl
Y: 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl
Z: 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl

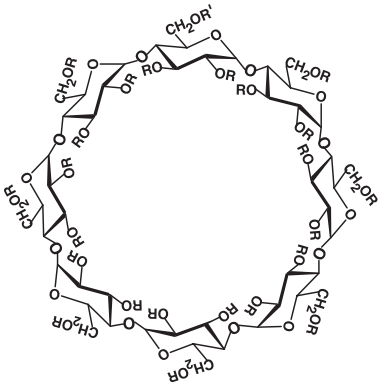

***Figure 1.*** Structures of compounds **1**–**10**.





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Many studies have been done using the glycosylation method and have shown that anomer formation is influenced not only by the catalyst, but also by the solvent, temperature, glycosyl donor type, and other factors. In general, without neighboring-group participation of a protecting group such as a benzyl or azido group on OH-2,

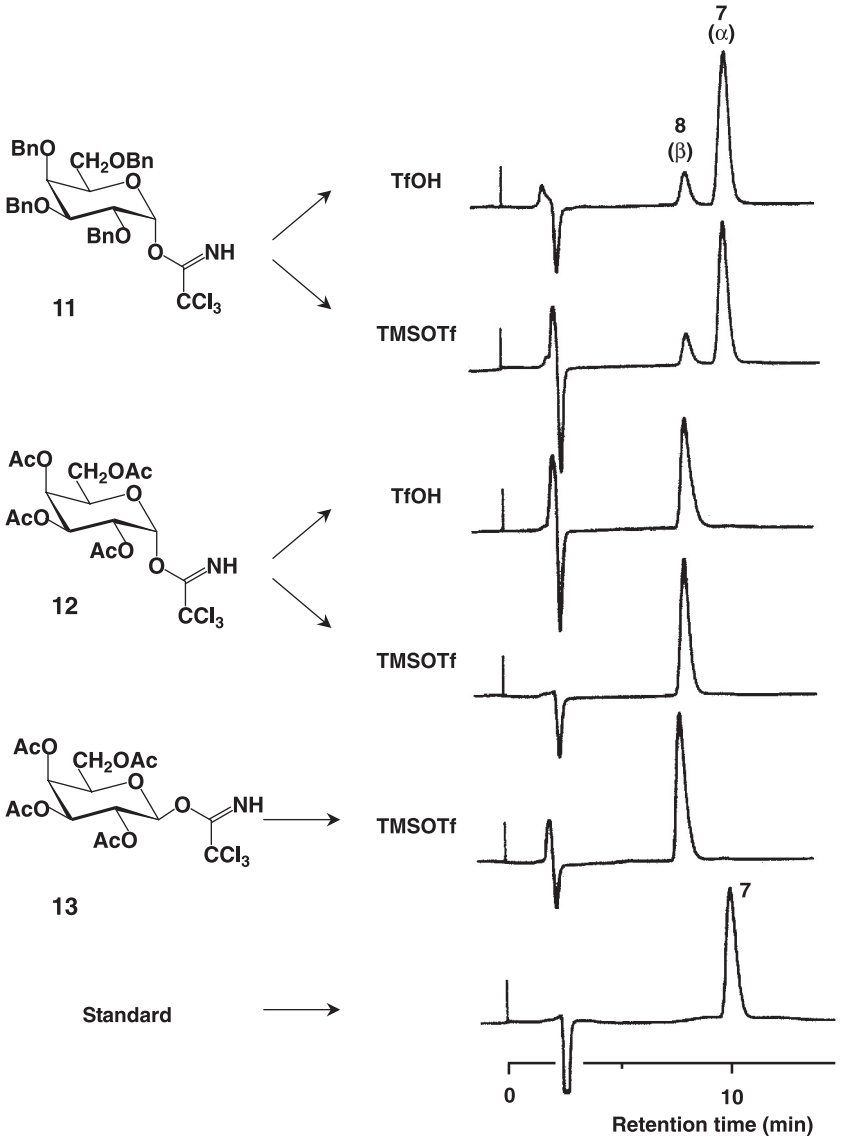


***Figure 2.*** Elution profiles of 6-*O*-(α-D-galactosyl)-γCD (**7**) and 6-*O*-(β-D-galactosyl)-γCD (**8**) resulting from the galactosylation with the benzyl (**11**) or acetyl (**12**, **13**) protected imidate donors in the presence of TfOH or TMSOTf. Chromatographic conditions: column, Hikarisil C18-4D (150 × 4.6 mm i.d.); eluent, 3:97 methanol-water; flow rate, 0.8 mL/min; detector, Shodex RI-71; temperature, 30°C.

glycosylation of R′OH with α-imidate using boron trifluoride etherate as the catalyst in dichloromethane affords the β-glycoside derivatives.[12,13] With trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst in dichloromethane or diethyl ether, β-imidates afford α-anomers.[14,15] With neighboring-group participation of the acyl protecting group such as acetyl, benzoyl, and pivaloyl on OH-2,[16,17] or protection of a 2-amino group with the phthaloyl group,[18,19] the reactions of both β-imidate and α-imidate with R′OH and boron trifluoride etherate or TMSOTf as a catalyst in dichloromethane give the β-anomers.

## RESULTS AND DISCUSSION

To synthesize 6-*O*-(D-galactosyl)-γCD, acetylation of 6-*O*-dimethoxytrityl-γCD (**1**)[20] with acetic anhydride in pyridine for 5 h at 100°C, followed by *O*-dedimethoxytritylation with boron trifluoride etherate in dichloromethane, afforded the galactosyl acceptor, (2,3-di-*O*-acetyl)heptakis(2,3,6-tri-*O*-acetyl)-γCD (**3**). Galactosyla-

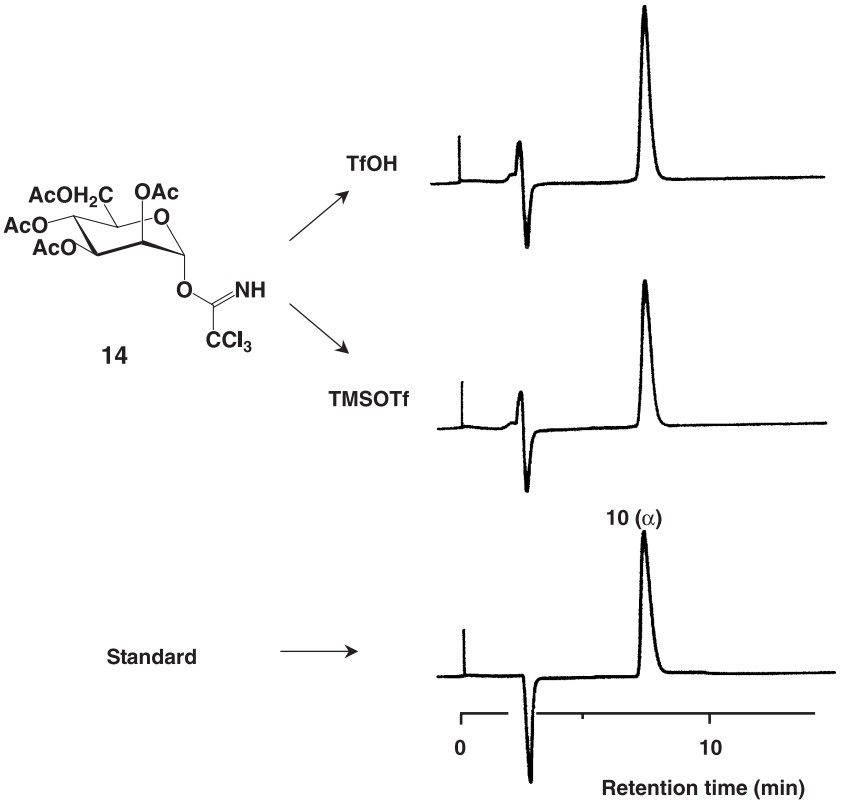


***Figure 3.*** Elution profiles of 6-*O*-(α-D-mannosyl)-γCD (**10**) resulting from the mannosylation with the acetyl protected α-imidate donor (**14**) in the presence of TfOH or TMSOTf. Chromatographic conditions as in Figure 2.





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tion of **3** was performed with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate (**11**)[9] or 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl trichloroacetimidate (**12**[21–23] and **13**[21,22]) in the presence of trifluoromethanesulfonic acid (TfOH) or TMSOTf (Figure 2). The resulting benzyl protected galactosyl-γCD (**4**) was treated with Pd-C/$H_2$ in methanol, and the product (**6**) and the acetyl protected galactosyl-γCD (**5**) were *O*-deacetylated with methanolic sodium methoxide, giving the corresponding galactosyl-γCDs (**7** and **8**). Figure 2 shows the elution profiles of the resulting galactosyl-γCDs and the authentic α-D-galactosyl-γCD (**7**)[2] which was obtained by an enzymatic synthesis. Compound **7** was the favored product over β-D-galactosyl-γCD (**8**) when the benzyl protected α-imidate donor (**11**) was employed in the presence of either TfOH or TMSOTf as a catalyst, yielding a ratio of α-anomer (**7**) to β-anomer (**8**) of 5:1. The glycosylation with the acetyl protected α-imidate donor (**12**), however, gave **8** as a single product. Similarly the reaction of **3** with the acetyl protected β-imidate donor (**13**) in the presence of TMSOTf afforded **8**.

As expected from the α/β selectivity in galactosylation reactions, mannosylation of **3** with 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl trichloroacetimidate (**14**)[24,25] in the presence of TfOH or TMSOTf as a catalyst gave only the α-anomer (**10**)[26] (Figure 3).

NMR spectral data were recorded for 10% solutions in $D_2O$ at 50°C with a Jeol GSX-500 spectrometer. Chemical shifts are expressed in ppm downfield from the signal of $Me_4Si$ referenced to external 1,4-dioxane (67.40 ppm). We have previously reported partial assignments of $^{13}C$ NMR spectra of compounds **7**[2] and **10**.[26] Here, the $^{13}C$ resonances of all carbons in the spectra of **7**, **8**, and **10** were assigned using $^1H$-$^1H$ COSY and $^1H$-$^{13}C$ COSY methods (Figure 4). The measurements were the same as those reported in the previous paper.[27]

## CONCLUSION

We obtained the desired branched cyclomalto-oligosaccharide directly β-galactosylated to the CD ring by a chemical synthesis of 6-*O*-(β-D-galactosyl)-γCD, which could not be synthesized by an enzyme catalyzed reaction. Both the acetyl protected α- and β-D-galactopyranosyl trichloroacetimidates with neighboring-group participation at OH-2, in the presence of TfOH or TMSOTf as a catalyst in dichloromethane, gave the 6-*O*-(β-D-galactosyl)-γCD as a single product.

In general, one feature of the glycosylation reaction using the trichloroacetimidate method is inversion of the anomer without neighboring-group participation at OH-2. However, little anomer inversion occurred in our experiments with TfOH or TMSOTf in dichloromethane.

## EXPERIMENTAL

**General methods.** TLC was performed on Silica Gel 60 plates (E. Merck). Centrifugal chromatography was performed with a Harrison Centrifugal Thin-Layer Chromatotron, Model 7924. HPLC was conducted with a Tri Rotar SR-1 or 880-PU pump (Jasco), and an SE-61 or 71 refractive index monitor (Showa Denko). The columns used were YMC-Pack SH-343-ODS (250 × 20 mm i.d.), Hikarisil C18-4D (150 × 4.6 mm





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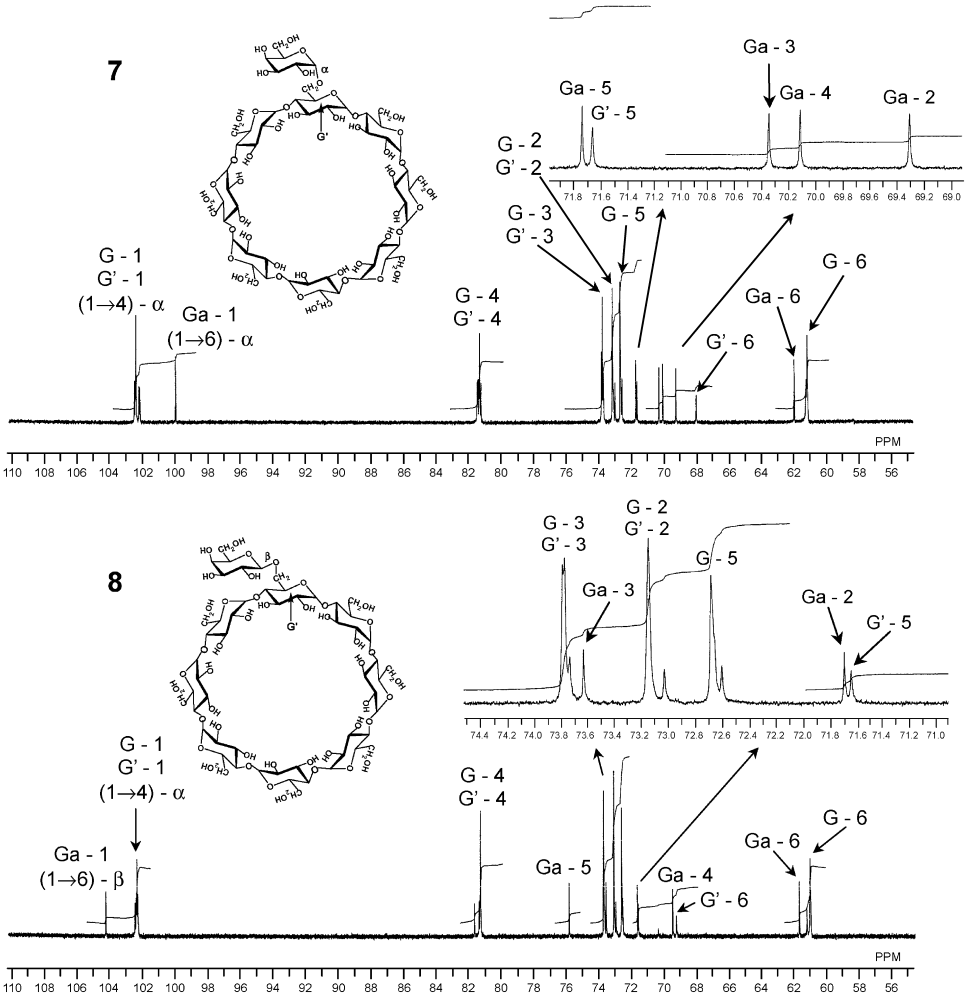


***Figure 4.*** $^{13}C$ NMR spectra of 6-*O*-(α-D-galactosyl)-γCD (**7**), 6-*O*-(β-D-galactosyl)-γCD (**8**) and 6-*O*-(α-D-mannosyl)-γCD (**10**) measured in $D_2O$ at 125.65 MHz.

i.d.), TSKgel Amide-80 (300 × 7.8 mm i.d.), and YMC-Pack A-323 ODS (250 × 10 mm i.d.). A Shimadzu Chromatopac C-R3A digital integrator was used for quantitative analyses. NMR spectra were recorded with a Jeol GSX-500 spectrometer in $D_2O$.

**(2,3-Di-*O*-acetyl)heptakis(2,3,6-tri-*O*-acetyl)cyclomaltooctaose (3).** Compound **1** (1,022 mg) was acetylated with acetic anhydride (30 mL) in dry pyridine (50 mL) for 5 h at 100°C, and the mixture was concentrated. The residue was extracted with chloroform, and the extract was washed sequentially with water, aqueous sodium hydrogen carbonate, and water, then dried, and concentrated to a syrup **2** (1,508 mg, 92.0%). To a solution of **2** (629 mg) in dry dichloromethane (40 mL) in an ice-water bath was added 47% boron trifluoride etherate in ether (600 μL) with stirring. The





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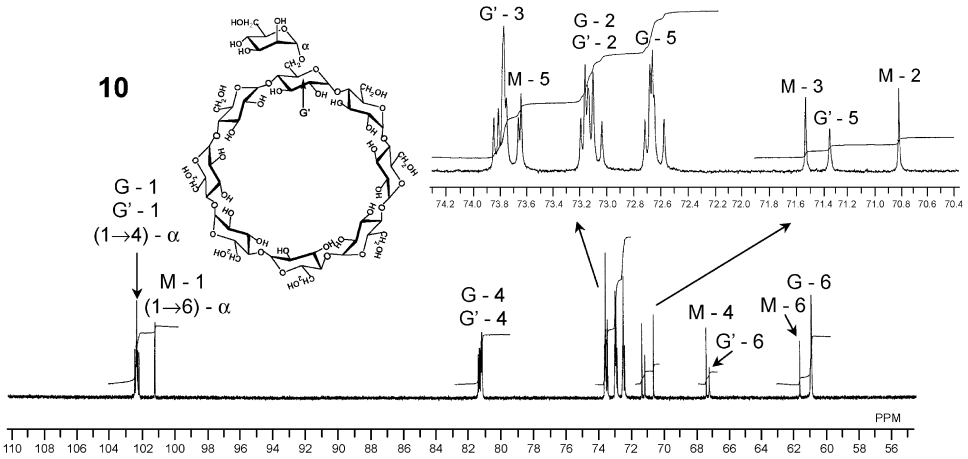


***Figure 4.*** Continued.

stirring was continued at room temperature for 2 h, then the mixture was diluted with chloroform and was poured into ice water. The chloroform layer was separated and washed as described above. Centrifugal chromatography (2:1→2:3 hexane-acetone) of the residue gave **3** (460 mg, 82.9%).

**Galactosyl trichloroacetimidates (11,[9] 12,[21–23] and 13[21,22]).** To a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactose (1,395 mg) in absolute dichloromethane (7 mL) was added DBU (80 μL) and trichloroacetonitrile (3 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was mixed with chloroform, washed with water, then dried, and concentrated to a syrup 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate (**11**, 1,958 mg). Work-up in a similar manner as above gave 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate (**12**, 2,008 mg) from 2,3,4,6-tetra-*O*-acetyl-D-galactose (1,391 mg). 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl trichloroacetimidate (**13**, 1,901 mg) was also synthesized from 2,3,4,6-tetra-*O*-acetyl-D-galactose (1,412 mg) using potassium carbonate (2,680 mg) as a catalyst.

**Galactosylation of 3.** Mixtures of **3**, galactosyl trichloroacetimidate (**11**, **12** or **13**), and dry powdered molecular sieves 4 Å × (MS-4 Å, 2.0 g) in dry dichloromethane (20–30 mL) were stirred under nitrogen at −20°C. A solution of trifluoromethanesulfonic acid (TfOH) or trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane (1–2 mL) was added. After stirring for 1 h at −20°C, triethylamine (1–2 mL) was added to the mixture, which was diluted with chloroform, filtered through Celite, washed sequentially with 1 M sulfuric acid, aqueous sodium hydrogencarbonate, and water, then dried, and concentrated. Centrifugal chromatography with hexane-acetone of the residue afforded chromatographically pure 6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-γCD peracetate (**4**) or 6-*O*-(2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl)-γCD peracetate (**5**). The experimental conditions and the results are summarized in Table 1.

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***Table 1.*** Galactosylation conditions and products.

| | Galactosyl acceptor | | Galactosyl donor | | Catalyst | | Product | | |
|---|---|---|---|---|---|---|---|---|---|
| Entry | Compound | mg (μmol) | Compound | mg (mmol) | Compound | μL (mmol) | Compound | mg | Yield (%)[a] |
| 1 | **3** | 316 (140) | **11** | 1958 (2.86) | TfOH | 80 (0.90) | **4** | 195 | 50.2 |
| 2 | **3** | 253 (112) | **11** | 1309 (1.91) | TMSOTf | 110 (0.61) | **4** | 235 | 75.5 |
| 3 | **3** | 230 (102) | **12** | 990 (2.01) | TfOH | 80 (0.90) | **5** | 243 | 91.8 |
| 4 | **3** | 217 (96) | **12** | 2008 (4.08) | TMSOTf | 268 (1.48) | **5** | 116 | 46.7 |
| 5 | **3** | 220 (97) | **13** | 965 (1.96) | TMSOTf | 250 (1.38) | **5** | 94 | 37.4 |

[a]Based on acceptor.

***Table 2.*** Deprotection conditions and products.

| | Debenzylation | | | | | Deacetylation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | mg | | |
| Entry | Compound | mg (μmol) | Pd-C (mg) | Product | mg | Compound | mg (μmol) | $CH_3ONa$ (mL) | Product | α | β | (α:β) |
| 1 | **4** | 195 (70) | 500 | **6** | 143 | **6** | 143 (59) | 10 | **7** > **8** | 70 | 14 | (5:1) |
| 2 | **4** | 235 (84) | 700 | **6** | 181 | **6** | 181 (75) | 10 | **7** > **8** | 87 | 17 | (5:1) |
| 3 | | | | | | **5** | 243 (94) | 10 | **8** | | 86 | |
| 4 | | | | | | **5** | 116 (45) | 10 | **8** | | 61 | |
| 5 | | | | | | **5** | 94 (36) | 6 | **8** | | 50 | |

***Table 3.*** Mannosylation conditions and products.

| | Mannosyl acceptor | | Mannosyl donor | | Catalyst | | Product | | |
|---|---|---|---|---|---|---|---|---|---|
| Entry | Compound | mg (μmol) | Compound | mg (mmol) | Compound | μL (mmol) | Compound | mg | Yield (%)[a] |
| 6 | **3** | 230 (102) | **14** | 1060 (2.15) | TfOH | 150 (1.70) | **9** | 226 | 85.7 |
| 7 | **3** | 203 (90) | **14** | 530 (1.08) | TMSOTf | 50 (0.28) | **9** | 180 | 77.4 |

[a]Based on acceptor.

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**6-*O*-(α-D-Galactopyranosyl)-γCD (7) and 6-*O*-(β-D-galactopyranosyl)-γCD (8).** Solutions of **4** and 10% Pd-C (500–700 mg) in methanol (20–25 mL) were stirred under hydrogen at room temperature, then filtered, and concentrated, to give **6**. Compounds **5** and **6** were individually treated with methanolic 0.05 M sodium methoxide (6–10 mL) for 1 h at room temperature, neutralized with Amberlite IR-120B ($H^+$) resin, filtered, and concentrated. The desired compounds **7** and **8** were isolated from each product, respectively, by HPLC. The detailed conditions of the reactions are listed in Table 2.

**Mannosyl trichloroacetimidate (14[24,25]).** To a solution of 2,3,4,6-tetra-*O*-acetyl-D-mannose (2.96 g) in absolute dichloromethane (15 mL) were added DBU (240 μL) and trichloroacetonitrile (8.6 mL), and the mixture was stirred at 0°C for 1 h. The reaction mixture was mixed with chloroform, washed with water, then dried, and concentrated to a syrup, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl trichloroacetimidate (**14**, 4.24 g).

**Mannosylation of 3.** A mixture of **3**, **14**, and dry powdered MS-4 Å (2.0 g) in dry dichloromethane (30 mL) was stirred under nitrogen at −20°C. A solution of TfOH (150 μL) or TMSOTf (50 μL) in dichloromethane (1–2 mL) was added. After stirring for 1 h at −20°C, triethylamine (1 mL) was added to the mixture, which was diluted with chloroform, filtered through Celite, washed sequentially with 1 M sulfuric acid, aqueous sodium hydrogencarbonate, and water, then dried, and concentrated. Centrifugal chromatography with hexane-acetone of the residue afforded chromatographically pure 6-*O*-(2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl)-γCD peracetate (**9**). The experimental conditions and the results are summarized in Table 3.

**6-*O*-(α-D-Mannopyranosyl)-γCD (10).** Compound **9** (entry 6; 226 mg, entry 7; 180 mg) was treated with methanolic 0.05 M sodium methoxide (10 mL) for 1 h at room temperature, neutralized with Amberlite IR-120B ($H^+$) resin, filtered, and concentrated (entry 6; 141 mg, entry 7; 118 mg). The desired compound **10** was isolated from each product, respectively, by HPLC.

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