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Supporting information

Iron(III) Chloride-Catalyzed Activation of Glycosyl Chlorides

Scott A. Geringer and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri – St. Louis One University Boulevard, St. Louis, Missouri 63121, USA Fax: (+) 1-314-516-5342;E-mail: <u>demchenkoa@umsl.edu</u>

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General Experimental

Column chromatography was performed on silica gel 60 (70-230 mesh), reactions were monitored by TLC on Kieselgel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH₂Cl₂ and ClCH₂CH₂Cl (1,2-DCE) were distilled from CaH₂ directly prior to application. Anhydrous DMF was used as it is. Molecular sieves (4 Å), used for reactions, were crushed and activated *in vacuo* at 390 °C during 8 h in the first instance and then for 2-3 h at 390 °C directly prior to application. Optical rotations were measured at 'Jasco P-2000' polarimeter. ¹H NMR spectra were recorded in CDCl₃ at 300 or 600 MHz.

Synthesis of Glycosyl Chloride Donors

2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosyl chloride (1). A solution of oxalyl chroride (621.1



mg, 4.89 mmol) in dichloromethane (2.0 mL) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzyl-D-glucopyranose (881.8 mg, 1.63 mmol) in dichloromethane (6.0 mL) and DMF (2.0 mL) and the resulting mixture was stirred under argon for 30 min at 0 °C. The external cooling was then removed and the reaction mixture was allowed to slowly warm to rt and

stirred for additional 1 h at rt. After that, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate and hexane (10 mL, 1/1, v/v) and passed through a pad of silica gel (10 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (100 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 98% yield (899.1 mg, 1.59 mmol). Analytical data for **1** was essentially the same as reported previously.¹

2,3,4,6-Tetra-*O*-benzyl- α -D-galactopyranosyl chloride (10). Thionyl chloride (302.8 mg, 2.54 BnO OBn BnO OBn BnO OBn BnO OCl OBn OCl OBn OBn OCl OCl OBn OCl OCl OBn OCl OCl OBn OCl O

acetate and hexane (75 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 95% yield (451.0 mg, 0.81 mmol). Analytical data for **10** was essentially the same as reported previously.¹

2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl chloride (15). A solution of oxalyl chroride (322.6 mg, 2.54 mmol) in dichloromethane (6.5 mL) was added dropwise to a stirring solution of 2,3,4,5-tetra-O-benzyl-D-mannopyranose (458.1 mg, 0.847 mmol) in 1,2-dichloroethane (5.0 mL) and DMF (0.1 mL) and the resulting mixture was stirred under argon for 30 min at 0 °C. The external cooling was then removed and the reaction mixture was allowed to slowly warm to rt and

stirred for additional 1 h at rt. After that, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate and hexane (5 mL, 1/1, v/v) and passed through a pad of silica gel (5 g). The pad of silica gel was washed with a mixture of ethyl acetate and hexane (100 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a clear oil in 95% yield (452mg, 0.81 mmol). Analytical data for **15** was essentially the same as reported previously.²

2,3,4,6-Tetra-*O***-benzoyl-** β **-D-glucopyranosyl chloride (20).** Thionyl chloride (106.85 mg, 0.898 mmol) was added dropwise to a stirring solution of 2,3,4,5-tetra-*O*-benzoyl-D-glucopyranose (242.8 mg, 0.45 mmol) in 1,2-dichloroethane (5.0 mL) and DMF (0.1 mL) and the resulting mixture was stirred under argon for 1 h at 0 °C. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in a mixture of ethyl acetate and hexane (5 mL, 1/1, v/v) and passed

through a pad of silica gel (3.5 g). The pad of silica gel was washed with a

mixture of ethyl acetate and hexane (50 mL, 1/1, v/v) and the combined eluate was concentrated *in vacuo* to afford the title compound as a white foam in 98% yield (276.8 mg, 0.44 mmol). Analytical data for **20** was essentially the same as reported previously.³

Synthesis of Disaccharides

General procedure for glycosidation of glycosyl chlorides in the presence of FeCl₃. A mixture of glycosyl chloride donor (0.05 mmol), glycosyl acceptor (0.025 mmol) and molecular sieves (4 Å, 60 mg) in dichloromethane (1.0 mL) was stirred under argon for 1 h at rt. The mixture was then cooled to 0 °C, FeCl₃ (0.01 mmol) was added, and the reaction mixture was stirred for the time specified in Table 1 of the article. If the reaction was incomplete after 3 h at 0 °C, the external cooling was removed, the reaction mixture was allowed to slowly warm to rt, and stirred for additional 13 h at rt. After that, the solid was filtered off through a pad of Celite and rinsed successively with dichloromethane. The combined filtrate (~30 mL) was washed with sat. aq. NaHCO₃ (10 mL) and water (2 x 10 mL). The organic phase was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/toluene gradient elution). If necessary, further purification was accomplished by size-exclusion column chromatography on Sephadex LH20 (methanol/ dichloromethane, 1/1, v/v, isocratic elution). Anomeric ratios were determined by comparison of integral intensities of their respective signals in the ¹H NMR spectra of anomeric mixtures.



Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (3). The title compound was obtained from donor 1 and acceptor 2⁴ under the general glycosylation method as a colorless foam in 67% yield ($\alpha/\beta = 1.1/1$). Analytical data for 3 was in accordance with that previously reported.⁵

Methyl 2,4,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (5). The title compound was obtained from donor 1 and acceptor 4⁴ under the general glycosylation method as an oil in 47% yield of 5 ($\alpha/\beta = 1.2/1$). Analytical data for 5 was in accordance with previously reported values.⁶



Methyl 2,4,6-tri-O-benzyl-3-O-(2,3,4,6-tetra-O-benzyl- α/β -D-glucopyranosyl)- α -D-glucopyranoside (7). The title compound was obtained from donor 1 and acceptor 6⁴ under the general glycosylation method as an oil in 60% yield of 7($\alpha/\beta = 1.5/1$). Analytical data for 7 was in accordance with previously reported values.⁷





Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-galactopyranosyl)- α -D-glucopyranoside (11). The title compound was obtained from donor 10 and acceptor 2 under the general glycosylation method as an oil in 88% yield of 11 ($\alpha/\beta = 1/1.4$). Analytical data for 11 was in accordance with previously reported values.⁹



Methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl- α/β -D-galactopyranosyl)- α -D-glucopyranoside (12). The title compound was obtained from donor 10 and acceptor 4 under the general glycosylation method as an oil in 57% yield of 12 ($\alpha/\beta = 1.6/1$). Analytical data for 12 was in accordance with previously reported values.¹⁰



Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-galactopyranosyl)- α -D-glucopyranoside (13). The title compound was obtained from donor 10 and acceptor 6 under the general glycosylation method as an oil in 80% yield of 13 ($\alpha/\beta = 1.3/1$). Analytical data for 13 was in accordance with previously reported values.¹¹



Methyl 3,4,6-tri-O-benzyl-2-O-(2,3,4,6-tetra-O-benzyl- α/β -D-galactopyranosyl)- α -D-glucopyranoside (14). The title compound was obtained from donor 10 and acceptor 8 under the general glycosylation method as an oil in 90% yield of 14 ($\alpha/\beta = 1/2.7$). Analytical data for 14 was in accordance with previously reported values.¹²



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl- α/β -D-mannopyranosyl)- α -D-glucopyranoside(16). The title compound was obtained from donor 15 and acceptor 5 under the general glycosylation method as an oil in 80% yield of 16 (α/β = 4.5/1). Analytical data for 16 was in accordance with previously reported values.¹³



Methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl- α -D-mannopyranosyl)- α -D-glucopyranoside (17). The title compound was obtained from donor 15 and acceptor 6 under the general glycosylation method as an oil in 66% yield of 17. Analytical data for 17 was in accordance with previously reported values.¹⁴

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl- α -D-mannopyranosyl)- α -D-glucopyranoside (18). The title compound was obtained from donor 15 and acceptor under the general glycosylation method as an oil in 56% yield of 18. Analytical data for 18 was in accordance with previously reported values.¹⁵

Methyl 3,4,6-tri-O-benzyl-2-O-(2,3,4,6-tetra-O-benzyl- α/β -D-mannopyranosyl)- α -D-glucopyranoside (19). The title compound was obtained from donor 15 and acceptor 8 under the general glycosylation method as an oil in 95% yield of 19 ($\alpha/\beta = 2.6/1$). Analytical data for 19 was in accordance with previously reported values.⁸

Methyl 6-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-2,3,4-tri-O-benzyl- α -D-glucopyranoside (21). The title compound was obtained from donor 20 and acceptor 5 under the general glycosylation method as an oil in 98% yield of 21. Analytical data for 21 was in accordance with previously reported values.¹⁶



Methyl 4-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-2,3,6-tri-O-benzyl- α -D-glucopyranoside (22). The title compound was obtained from donor 20 and acceptor 6 under the general glycosylation method as an oil in 80% yield of 22. Analytical data for 22 was in accordance with previously reported values.¹⁶



Methyl 3-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-2,4,6-tri-O-benzyl- α -D-glucopyranoside (23). The title compound was obtained from donor 20 and acceptor 7 under the general glycosylation method as an oil in 52% yield of 23. Analytical data for 23 was in accordance with previously reported values.⁴



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Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (24).

The title compound was obtained from donor **20** and acceptor **8** under the general glycosylation method as an oil in 73% yield of **24**. Analytical data for **24** was in accordance with previously reported values.¹⁷

References

- (1) Gómez, A. M.; Pedregosa, A.; Casillas, M.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2009**, *2009*, 3579.
- (2) Matsuoka, K.; Terabatake, M.; Umino, A.; Esumi, Y.; Hatano, K.; Terunuma, D.; Kuzuhara, H. *Biomacromol.* **2006**, *7*, 2274.
- (3) Encinas, L.; Chiara, J. L. J. Comb. Chem. 2008, 10, 361.
- (4) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V. Org. Lett. 2010, 12, 5628.
- (5) Eby, R.; Schuerch, C. Carbohydr. Res. 1975, 39, 33.
- (6) Pougny, J. R.; Nassr, M. A. M.; Naulet, N.; Sinay, P. Nouveau J. Chem. 1978, 2, 389.
- (7) Chiba, H.; Funasaka, S.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 2003, 76, 1629.
- (8) Ito, Y.; Ogawa, T.; Numata, M.; Sugimoto, M. Carbohydr. Res. 1990, 202, 165.
- (9) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. Tetrahedron 1991, 47, 9985.
- (10) Wegmann, B.; Schmidt, R. R. J. Carbohydr. Chem. 1987, 6, 357.
- (11) Kobashi, Y.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 2005, 78, 910.
- (12) Premathilake, H. D.; Demchenko, A. V. Beilstein J. Org. Chem. 2012, 8, 597.
- (13) Hotha, S.; Kashyap, S. J. Am. Chem. Soc. 2006, 128, 9620.
- (14) Nguyen, H. M.; Chen, Y. N.; Duron, S. G.; Gin, D. Y. J. Am. Chem. Soc. 2001, 123, 8766.
- (15) Jayakanthan, K.; Vankar, Y. D. Carbohydr. Res. 2005, 340, 2688.
- (16) Garcia, B. A.; Gin, D. Y. J. Am. Chem. Soc. 2000, 122, 4269.
- (17) Pornsuriyasak, P.; Demchenko, A. V. Chem. Eur. J. 2006, 12, 6630.











NMR Spectra of known disaccharides















































