Pergamon

*Tetrahedron Letters*, Vol. 38, No. 31, pp. 5419-5422, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01204-5

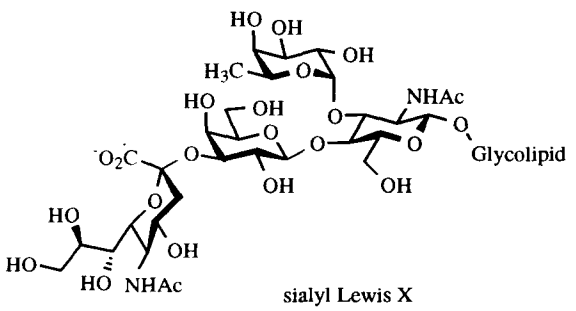
# One-pot Synthesis of 1-Allyl- and 1-Allenyl-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glycosides from Methyl Tetra-*O*-benzyl-α-D-glycosides

Shang-Cheng Hung, Chun-Cheng Lin and Chi-Huey Wong*

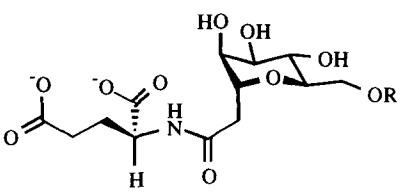
Department of Chemistry, The Scripps Research Institute,
10550 North Torrey Pines Road, La Jolla, CA 92037, USA

***Abstract:*** *A one-pot synthesis of 1-allyl- and 1-allenyl-6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glycosides from the corresponding methyl per-benzyl-α-D-glycosides and allyl trimethylsilane or propargyl trimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate followed by addition of acetic anhydride in good yields was described.*


Recent efforts directed toward the development of sialyl Lewis X tetrasaccharide mimetics[1-3] have led to the discovery of a series of 6-*O*-alkyl-α-C-mannopyranosides[2g] which are superior to the parent carbohydrates as drug candidates for the treatment of inflammatory diseases. The synthesis of these mimetics often requires the preparation of 1-allyl-6-hydroxy-α-D-mannopyranoside from mannose pentaacetate through a five-step process and chromatographic separation of anomeric isomers.[4] Here we report a one-pot synthesis of 1-allyl- and 1-allenyl-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glycosides from the corresponding methyl per-benzyl-α-D-glycosides



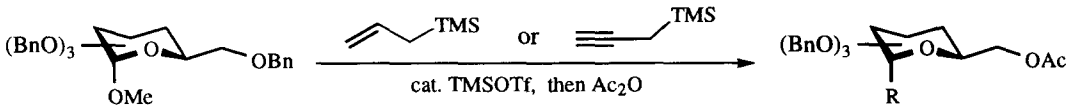

sialyl Lewis X




R = long chain alkyl group

sialyl Lewis X mimetics

with allyl trimethylsilane or propargyl trimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[5] followed by addition of acetic anhydride. This new process is based on the previous observation that methyl 2,3,4,6-tetra-*O*-benzyl-α-D-pyranosides can be converted to the corresponding 6-*O*-acetyl[6] or 1,6-di-*O*-acetyl pyranosides[7] using acetic anhydride under acid-catalyzed conditions.




R = allyl or allenyl

We found that under the afore mentioned C-allylation condition the 6-OBn group can be converted to the 6-OAc group concurrently in the presence of acetic anhydride. It appears that this process is quite general as indicated in Table 1.[8] It is noted that the electron-riched allyl or allenyl group can survive under this condition. The mechanism of the highly regio-selective conversion at 6-position is not clear. Perhaps the less hindered primary benzyl ether of compound **7** first reacted with acetic anhydride in the presence of TMSOTf to give the cationic intermediate **8**, triflate and AcOTMS (see Scheme 1). The intermediate **8** then reacted with AcOTMS to afford product **9** and another cationic intermediate **10** which reacted with $TfO^-$ to regenerate TMSOTf. Alternatively, TMSOTf may activate the benzyl ether group first, followed by reaction with acetic anhydride in the presence of the released $TfO^-$.

As demonstrated, the procedure described here is an easy and effective method for the synthesis of 6-acetyl-C-linked glycosides which are useful building blocks for the synthesis of various C-glycosides with modification at C-6 position.

**Scheme 1**

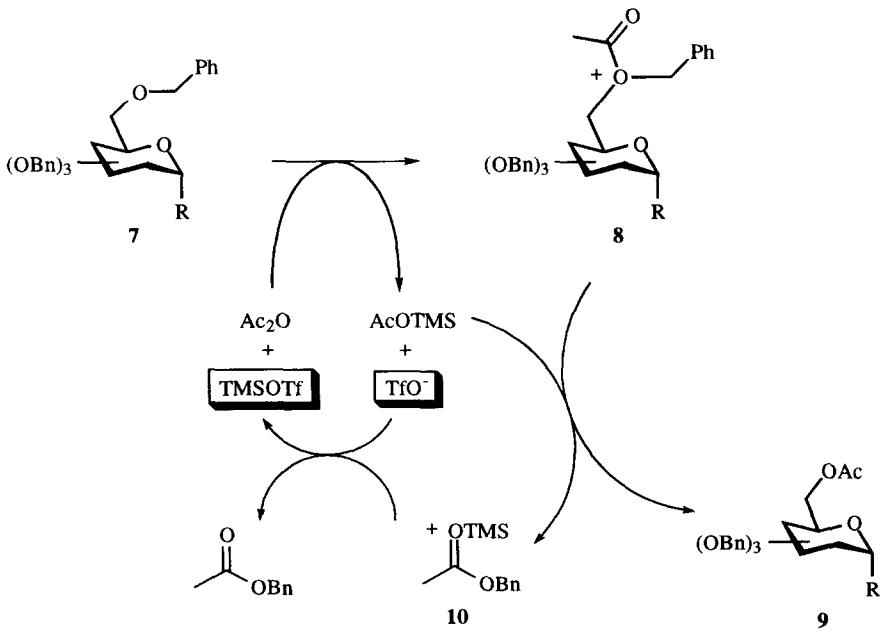
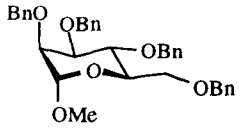
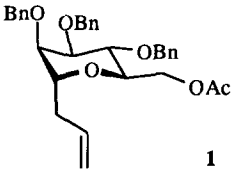
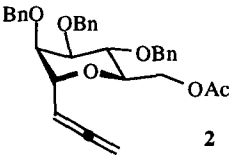
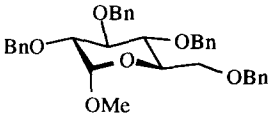
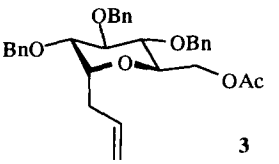
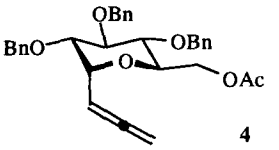
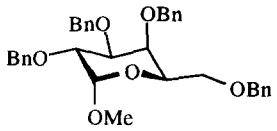
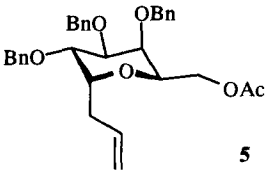
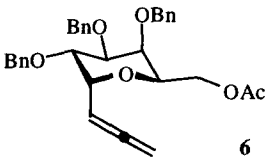


**Table 1.** One-pot synthesis of 1-allyl- or 1-allenyl-6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glycosides from the corresponding methyl per-benzylglycosides.

| starting material | condition | product | yield |
|---|---|---|---|
|  | A |  **1** | 83% |
| | B |  **2** | 72% |
|  | A |  **3** | 77% |
| | B |  **4** | 64% |
|  | A |  **5** | 80% |
| | B |  **6** | 75 % |

A: allyl trimethylsilane, cat. TMSOTf, $CH_3CN$, 0 °C to 25 °C; then $Ac_2O$.
B: propargyl trimethylsilane, cat. TMSOTf, $CH_3CN$, 0 °C to 25 °C; then $Ac_2O$.

**General Procedure.** To a solution of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glycoside (0.69 mmol) in $CH_3CN$ (1.4 mL) was added allyltrimethylsilane or propargyltrimethylsilane (1.45 mmol) followed by the addition of TMSOTf (0.35 mmol) at 0 °C under argon. The reaction was kept stirring under the same temperature overnight and the mixture was added acetic anhydride (1 mL) drop by drop. After 5 min, the reaction was diluted with $CH_2Cl_2$ (10 mL) and the resulting solution was quenched by sat'd $NaHCO_3$. The aqueous phase was

extracted with $CH_2Cl_2$ (2 x 10 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography. The isolated yields of products were shown in Table 1.

**References and Notes**


1. Lasky, L. A. *Annu. Rev. Biochem.* **1995**, *64*, 113.
2. a) Hiruma, K.; Kajimoto, Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 9265. b) Wu, S.-H.; Shimazaki, M.; Lin, C.-C.; Qiao, L.; Moree, W. J.; Weitz-Schmidt, G.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 88. c) Marron, T. G.; Woltering, T. J.; Weitz-Schmidt, G.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 9037. d) Woltering, T. J.; Weitz-Schmidt, G.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 9041. e) Cappi, M. W.; Wilna, J. M.; Qiao, L.; Marron, T. G.; Weitz-Schmidt, G.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2346. f) Lin, C.-C.; Shimazaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzèn, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826. g) Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc.* in press.
3. a) Dupre, B.; Bui, H.; Scott, I. L.; Market, R. V.; Keller, K. M.; Beck, P. J.; Kogan, T. P. *Bioorg. & Med. Chem. Lett.* **1996**, *6*, 569. b) Spevak, W.; Foxall, C.; Charych, D. H.; Dasgupta, F.; Nagy, J. O. *J. Med. Chem.* **1996**, *39*, 1018. c) Ohmoto, H.; Nakamura, K.; Inoue, T.; Kondo, N.; Inoue, Y.; Yoshino, K.; Kondo, H. *J. Med. Chem.* **1996**, *39*, 1339.
4. Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.
5. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737.
6. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894.
7. Shah, R. N.; Baptista, J.; Perdomo, G. R.; Carver, J. P.; Krepinsky, J. J. *J. Carbohydr. Chem.* **1987**, *6*, 645.
8. Spectra data of products are shown below. **1.** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 15 H), 5.72 (ddt, *J* = 17.0, 10.3, 6.9 Hz, 1 H), 5.04-5.00 (m, 2 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 4.63-4.53 (m, 5 H), 4.39 (dd, *J* = 11.6, 6.4 Hz, 1 H), 4.25 (dd, *J* = 11.6, 2.8 Hz, 1 H), 4.07 (ddd, *J* = 10.5, 5.9, 2.2 Hz, 1 H), 3.83-3.75 (m, 3 H), 3.62 (dd, *J* = 4.4, 2.7 Hz, 1 H), 2.38-2.27 (m, 2 H), 2.05 (s, 3 H). **2.** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 15 H), 5.14 (dt, *J* = 5.8, 3.2 Hz, 1 H), 4.96 (d, *J* = 12.0 Hz, 1 H), 4.76-4.70 (m, 4 H), 4.64-4.59 (m, 2 H), 4.58 (d, *J* = 10.8 Hz, 1 H), 4.56 ( d, *J* = 12.0 Hz, 1 H), 4.36 (dd, *J* = 11.8, 2.2 Hz, 1 H), 4.29 (dd, *J* = 11.8, 5.3 Hz, 1 H), 3.92 ( t, *J* = 9.0 Hz, 1 H), 3.88 (dd, *J* = 3.1, 2.2 Hz, 1 H), 3.84 (dd, *J* = 9.0, 3.1 Hz, 1 H), 3.77 (ddd, *J* = 9.0, 5.3, 2.2 Hz, 1 H), 2.07 (s, 3 H). **3.** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 15 H), 5.77 (ddt, *J* = 17.2, 10.4, 6.6 Hz, 1 H), 5.12-5.04 (m, 2 H), 4.95 (d, *J* = 10.8 Hz, 1 H), 4.86 (d, *J* = 10.8 Hz, 1 H), 4.81 (d, *J* = 10.8 Hz, 1 H), 4.70 (d, *J* = 11.6 Hz, 1 H), 4.62 (d, *J* = 11.6 Hz, 1 H), 4.55 (d, *J* = 10.8 Hz, 1 H), 4.22-4.21 (m, 2 H), 4.11-4.07 (m, 1 H), 3.82 (t, *J* = 9.1 Hz, 1 H), 3.73 (dd, *J* = 9.1, 5.8 Hz, 1 H), 3.69 (dt, *J* = 10.0, 3.8 Hz, 1 H), 3.45 (dd, *J* = 10.0, 9.1 Hz, 1 H), 2.50-2.46 (m, 2 H), 2.02 (s, 3 H). **4.** $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 15 H), 5.44 (q, *J* = 6.3 Hz, 1 H), 4.97 (d, *J* = 11.8 Hz, 1 H), 4.89-4.85 (m, 2 H), 4.87 (d, *J* = 10.7 Hz, 1 H), 4.81 (d, *J* = 11.8 Hz, 1 H), 4.73-4.71 (m, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.55 (d, *J* = 10.7 Hz, 1 H), 4.26 (dd, *J* = 11.9, 1.9 Hz, 1 H), 4.22 (dd, *J* = 11.9, 4.5 Hz, 1 H), 3.88 (ddd, *J* = 9.6, 4.2, 1.9 Hz, 1 H), 3.84 (t, *J* = 9.6 Hz, 1 H), 3.75 (dd, *J* = 9.6, 5.8 Hz, 1 H), 3.47 (t, *J* = 9.6 Hz, 1 H), 2.03 (s, 3 H). **5.** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 15 H), 5.71 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 5.07-4.98 (m, 2 H), 4.76-4.72 (m, 1 H), 4.71 (d, *J* = 12.1 Hz, 1 H), 4.61, 4.57 (ABq, *J* = 11.8 Hz, 2 H), 4.60 (d, *J* = 12.1 Hz, 1 H), 4.51, 4.46 (ABq, *J* = 11.9 Hz, 2 H), 4.22 (dd, *J* = 12.4, 2.9 Hz, 1 H), 4.13-4.10 (m, 1 H), 4.04 (ddd, *J* = 8.7, 5.9, 2.9 Hz, 1 H), 3.98 (dd, *J* = 5.0, 2.9 Hz, 1 H), 3.76 (dd, *J* = 5.6, 2.9 Hz, 1 H), 3.60 (bs, 1 H), 2.40-2.24 (m, 2 H), 2.05 (s, 3 H). **6.** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 15 H), 5.39 (dt, *J* = 6.8, 5.6 Hz, 1 H), 4.84 (d, *J* = 11.7 Hz, 1 H), 4.82 (dd, *J* = 6.8, 1.5 Hz, 1 H), 4.80 (dd, *J* = 6.8, 1.5 Hz, 1 H), 4.75-4.72 (m, 3 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.61 ( d, *J* = 11.7 Hz, 1 H), 4.29 (dd, *J* = 11.7, 8.5 Hz, 1 H), 4.15 (dd, *J* = 11.7, 4.0 Hz, 1 H), 4.06-4.02 (m. 2 H), 3.91 (t, *J* = 2.7 Hz, 1 H), 3.71 (dd, *J* = 8.5, 2.8 Hz, 1 H), 2.00 (s, 3 H).


(*Received in USA* 15 *April* 1997; *revised* 6 *June* 1997; *accepted* 11 *June* 1997)