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A novel stereoselective carbon-chain extension reaction at the C-6 position of 1,6-anhydropyranose

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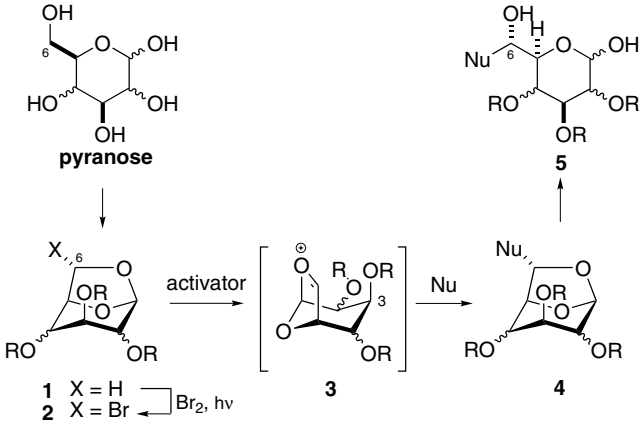
Abstract—6-Bromo-1,6-anhydro-D-mannose triacetate reacted with a variety of carbon nucleophiles such as allylsilane, silylacetylenes, propargylsilane, and aromatic compounds in the presence of silver triflate to give the corresponding chain extended products at C-6 in high *exo*-selectivities. The product obtained from the reaction with propargylsilane was efficiently transformed into a naturally occurring heptopyranose derivative found in bacterial lipopolysaccharide.

Stereoselective carbon-chain elongation of carbohydrate is of great importance, because various sugars have been employed as chiral starting materials, the so-called chiral pool, for the syntheses of many optically active compounds.[1] Carbon-chain extension at the anomeric position (at C-1) has been extensively studied as '*C*-glycosidation' to establish a variety of useful stereoselective reactions.[2] On the other hand, carbon-chain extension at the C-6 position of pyranose has been carried out by alkylation of the aldehyde with carbon nucleophiles such as Grignard reagents and other organometallic reagents. However, the stereoselectivities depend on the kind of carbohydrate, protective group of the hydroxyl function, nucleophile, etc.[3]

In this laboratory, *C*-glycosidation of glycals with silylacetylenes has been extensively studied to establish a reliable methodology for highly stereoselective synthesis of 'sugar acetylene' and its wide application.[4] On the other hand, levoglucosenone, a 1,6-anhydropyranose derivative prepared from pyrolysis of cellulose, has been employed as a useful chiral starting material.[5] Both methodologies have been applied to the syntheses of complex natural products such as indole alkaloids,[6] tautomycin,[7] and tetrodotoxins.[8] In the course of these studies, we considered that readily prepared 6-bromo-1,6-anhydropyranose **2** would serve as a substrate for carbon-chain extension reaction at the C-6 position; the 6-bromide **2** would react with a nucleophile (Nu) in the presence of an activator to afford adduct **4** (Scheme 1). This process was anticipated to proceed in a highly stereoselective manner, because of the steric environment of the bicyclo[3.2.1] system around the C-6 position as well as steric hindrance of the axial alkoxy group at the C-3 position. Opening the 1,6-anhydro ring of the product **4** under acidic conditions would regenerate pyranose **5** bearing a carbon chain at the C-6 position.



Scheme 1. Stereoselective C–C bond-forming reaction at the C-6 position through 1,6-anhydropyranose intermediate.

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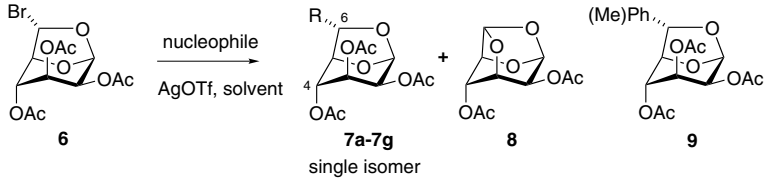
6-Bromo-1,6-anhydropyranose derivatives **2** were previously studied as the substrate for radical reactions at the C-6 position by Ohrui, Meguro,[9] and Fraser-Reid.[10] We disclose herein a highly stereoselective C–C bond formation at the C-6 position through an oxonium cation intermediate **3** generated from 6-bromo-1,6-anhydropyranose **2**.[11]

6-Bromo-1,6-anhydro-D-mannose triacetate **6** was prepared from photobromination of 1,6-anhydromannose triacetate[12] by the Ferrier procedure,[13] and employed as a substrate for the reaction with allyltrimethylsilane (Scheme 2 and Table 1). After extensive examination of the conditions, we found a practical condition whereby 2 equiv of allyltrimethylsilane and 1 equiv of AgOTf in dichloromethane at 0 °C gave a mixture of **7a**[14] and tricyclic product **8**[15] in 63% and 16% yield, respectively (entry 1).[16] The diastereomeric product of **7a** at the C-6 position could not be detected. The *S*-configuration (*exo*-stereochemistry) of the C-6 position of the product **7a** was confirmed by observing NOESY correlation between H-4 and H-6.[17] The solvent used in this reaction proved critical to the success of the reaction; when CH_3CN or *i*-PrCN was employed as a solvent, the reaction was greatly retarded and gave the product **7a** in very low yields (ca. 30%). The reaction in an aromatic solvent such as benzene or toluene gave arylated product **9** as a major product instead of the desired product **7a**.

In order to expand the highly stereoselective reaction, various nucleophiles listed in Table 1 were examined. The reaction with silylacetylene such as phenyltrimethylsilylacetylene and trimethylsilylheptyne gave the corresponding adduct **7b** and **7c** in 59% and 47% yield, respectively (entries 2 and 3). The reaction with propargyltrimethylsilane also proceeded under the same conditions to afford allenylated product **7d** in 62% yield (entry 4). In the case of electron-rich aromatics as the nucleophile, the reaction in CH_2Cl_2 gave a complex mixture. In contrast, *i*-PrCN was an effective solvent to give the corresponding product **7e** and **7f** in good yields (entries 5 and 6). In both cases, 2 equiv of AgOTf was necessary to consume the bromide **6**. Furan, an important nucleophile as an equivalent of carboxylic acid, reacted with **6** in *i*-PrCN at 0 °C to afford **7g** in good yield (entry 7), while the reaction with TMS–CN, a conventional alternative to carboxylic acid, gave a complex mixture under the same conditions.

To demonstrate further usefulness of this reaction, we carried out a concise synthesis of the peracetate **11** of L-glycero-D-manno-heptopyranose (L-D-Hepp), a common component of bacterial lipopolysaccharide,[18] from the product **7d** (Scheme 3). Ozonolysis of **7d** was followed by reduction with $NaBH_4$ to give alcohol **10**[19] in good overall yield. Acetylation of **10** and subsequent acetolysis afforded L-D-Hepp hexaacetate **11** as an anomeric mixture ($\alpha/\beta = 11{:}3$).[20,21]

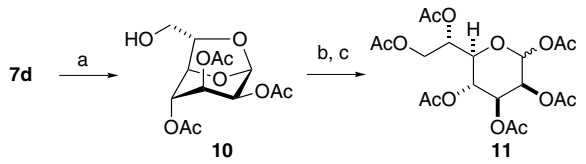
In summary, we have developed a new highly stereoselective C–C bond-forming reaction at the C-6 position of 1,6-anhydro-D-mannose with various nucleophiles and demonstrated a facile synthesis of the heptose derivative. Since a variety of other 1,6-anhydropyranose and 1,5-anhydrofuranose derivatives[22] is available, this reaction should be useful for the synthesis of carbohydrate-related compounds as well as other complex



Scheme 2.

Table 1. Reaction of 6-bromo-1,6-anhydro-D-mannose triacetate **(6)** with various nucleophiles

Entry	Nucleophiles (equiv)	Conditions			Product (**7a**–**g**)		**8** yield (%)
		AgOTf	Solvents	Temperature	R=	Yield (%)	
1	CH_2=$CHCH_2$− TMS (2 equiv)	1 equiv	CH_2Cl_2	0 °C	**7a** CH_2=$CHCH_2$	63	16
2	Ph−C≡C− TMS (5 equiv)	1 equiv	CH_2Cl_2	0 °C	**7b** Ph−C≡C	59	20
3	$Me(CH_2)_4$−C≡C− TMS (5 equiv)	1 equiv	CH_2Cl_2	0 °C	**7c** $Me(CH_2)_4$−C≡C	47	15
4	H−C≡C−CH_2− TMS (5 equiv)	1 equiv	CH_2Cl_2	0 °C	**7d** CH_2=C=CH	62	7
5	*p*-Methylanisole (5 equiv)	2 equiv	*i*-PrCN	rt	**7e** 2-Methoxy-5-methylbenzene	74	Trace
6	1,4-Dimethoxybenzene (5 equiv)	2 equiv	*i*-PrCN	rt	**7f** 2,5-Dimethoxybenzene	76	Trace
7	Furan (5 equiv)	4 equiv	*i*-PrCN	0 °C	**7g** 2-Furyl	66	Trace



Scheme 3. Synthesis of L-D-Hepp hexaacetate. Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C; $NaBH_4$, EtOH, −78 to 0 °C (76%); (b) Ac_2O, py; (c) concd H_2SO_4, Ac_2O (91% in two steps).

natural products. Further studies along this line are currently under way in our laboratory.

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14. Spectroscopic data of **7a**. IR (KBr) ν_{max} 2960, 1744, 1373, 1228, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (3H, s, OAc), 2.14 (3H, s, OAc), 2.15 (3H, s, OAc), 2.24–2.42 (2H, m, H-7, 7′), 4.28 (1H, br s, H-5), 4.43 (1H, t, $J = 6.5$ Hz, H-6), 4.82 (1H, br t, $J = 1.5$ Hz, H-4), 5.00 (1H, dd, $J = 5.5$, 2 Hz, H-2), 5.12 (1H, m, H-9), 5.16 (1H, m, H-9′), 5.28 (1H, dq, $J = 5.5$, 1.5 Hz, H-3), 5.46 (1H, br s, H-1), 5.74–5.84 (1H, m, H-8). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 20.8, 20.9, 39.1, 66.6, 67.6, 71.4, 75.6, 76.8, 99.9, 118.4, 133.0, 169.4, 169.6 (x2). $[\alpha]_D^{29}$ −121° (*c* 0.475, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.87; H, 6.23.
15. Spectroscopic data of **8**. IR (KBr) ν_{max} 2998, 1743, 1375, 1235, 1071 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (3H, s, OAc), 2.20 (3H, s, OAc), 4.42–4.47 (1H, m, H-3), 4.72 (1H, br t, $J = 1.5$ Hz, H-2), 4.80–4.86 (2H, m, H-4, 5), 5.54 (1H, t, $J = 1.5$ Hz, H-1), 5.85 (1H, br d, $J = 3$ Hz, H-6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 20.8, 64.8, 72.3, 74.9, 75.7, 101.0, 101.3, 170.2, 170.3. FAB-MS 245 (M^++H). HRMS (FAB) calcd for $C_{10}H_{13}O_7$ 245.0661, found 245.0651 (M^++H). $[\alpha]_D^{28}$ −126° (*c* 0.975, $CHCl_3$).
16. Experimental: To an ice-cold solution of the bromide **2** (111 mg, 0.302 mmol) and allyltrimethylsilane (0.096 mL, 0.604 mmol) in CH_2Cl_2 (1.5 mL) was added AgOTf (78 mg, 0.302 mmol). After stirring at 0 °C for 60 min, the reaction was quenched with satd $NaHCO_3$ solution. The resulting mixture was filtered through a pad of Super-Cel and the residue was washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (x3). The combined organic layer was washed with satd $NaHCO_3$ solution (x1) and brine (x1), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g, AcOEt/hexane = 1:2) to give a mixture of the allylated product **7a** and byproduct **8** (75 mg). Since chromatographic separation of these two products was difficult, the yields of **7a** and **8** were calculated to be 63% and 16%, respectively from integration values of the ^1H NMR spectra.
17. The configuration of the C-6 position was determined by NOESY correlation between H-4 and H-6, and/or the coupling constant between the protons at H-5 and H-6; J H5-H6$_{exo}$ = ca. 1 Hz; J H5-H6$_{endo}$ = ca. 6 Hz.
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19. Spectroscopic data of **10**. IR (KBr) ν_{max} 3589–3351, 2966, 1744, 1233, 1049 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (3H, s, OAc), 2.16 (3H, s, OAc), 2.17 (3H, s, OAc), 3.62 (2H, br d, $J = 6$ Hz, H-7, 7′), 4.44 (1H, td, $J = 1.5$, 1 Hz, H-5), 4.51 (1H, td, $J = 6$, 1 Hz, H-6), 4.86 (1H, br t, $J = 1.5$ Hz, H-4), 5.03 (1H, dd, $J = 5.5$, 2 Hz, H-2), 5.30 (1H, dq, $J = 5.5$, 1.5 Hz, H-3), 5.48 (1H, br t, $J = 1.5$ Hz, H-1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 20.7, 20.8, 63.6, 66.5, 67.5, 71.4, 75.4, 76.2, 99.9, 169.5, 169.6, 169.7 HRMS (FAB) calcd for $C_{13}H_{19}O_9$ 319.1029, found 319.1027 (M^++H). $[\alpha]_D^{27}$ −105° (*c* 1.86, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 49.07; H, 5.81.

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