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One-Pot Synthesis of Dimannopyranosylbenzene (or Pyridine) and Dimannosyl-1,8-diaminooctane

Y.G. LEE[1], J.H. SONG[1], S.H. JUNG[2], E.J. LEE[1], E.S. LEE[1], D.H. LEE[1], D.I. JUNG[1,*] and J.T. HAHN[3]

[1]Department of Chemistry, Dong-A University, Saha-Gu, Busan 604-714, South Korea
[2]Center for Drug Discovery Technologies, Korea Research Institute of Chemical Technology, 100 Jang Dong, Yuseong, Deajeon 305-343, South Korea
[3]Department of Beautycare, Young-Dong University, Chungcheongbuk-do 370-701, South Korea

*Corresponding author: Fax: +82 51 2007259; Tel: +82 51 2007249; E-mail: dijung@dau.ac.kr

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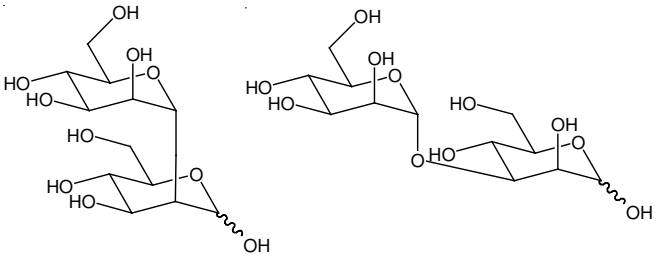
The one-pot synthesis of divalent of mannose disaccharides, of potential use as anti-infective agents against enterobacteria infections, is described. We report one-pot synthesis of dimannopyranosylbenzenes (**6**, **7**, **8**), dimannosyl-2,6-diamino-pyridine (**9**) and dimannosyl-1,8-diaminooctane (**10**). But the reaction of 8-(2-amino-pyridin-3-yl)-8-azabicyclo[3.2.1]octane-3-one (**11**) as a monoamine and D-(+)-mannose did not occur. The results implied that compound **12** is not produced due to steric hindrance of tropane ring.

Key Words: Dimannopyranosylbenzene, Dimannosyl-2,6-diaminopyridine, Dimannosyl-1,8-diaminooctane, Antiinfective agent.

INTRODUCTION

Glycoproteins and glycolipids are widely expressed on cell surfaces and participate in many molecular recognition and binding processes in both healthy and diseased states[1]. In particular, some bacterial surface proteins demonstrate specific binding for carbohydrates expressed on human cells and such interactions form an essential part of the infection pathway. It has been demonstrated that administration of synthetic or natural carbohydrate derivatives can disrupt this infective pathway, so long as the administered derivatives have a high affinity for the bacterial lectins[2]. In such cases, the bacteria are no longer able to interact with the host and therefore pass through the body without initiating infection. Such therapeutic agents have been termed anti-infective agents. A number of antiinfective agents occur naturally, for example, human breast milk contains numerous soluble oligosaccharides that provide newborn babies with a mechanism for aborting infection processes[3]. However, there is also considerable interest in the synthesis of non-natural carbohydrate based antiinfective agents[4]. In particular, flexible multivalent arrays of receptor carbohydrates are considered of interest, due to their enhanced activity resulting from the cluster effect[5]. As part of a programme directed towards the inhibition of infections caused by enterobacteria (for example some *E. coil* and *S. suis* strains), that naturally adhere *via* type 1 fimbriae to high-branched mannose chains[6-8], we required access to multivalent arrays of mannose saccharides. Although the natural hosts display complex mannose saccharides, it has already been demonstrated that multivalent arrays of mannose monosaccharides[9,10], as well as Man α-12-Man and Man α-1,3-Man disaccharide (Fig. 1)[11], are effective for inhibiting the carbohydrate-lectin interaction.



Man α-1,2-Man Man α-1,3-Man

Fig. 1. Man α-1,2-Man and Man α-1,3-Man

The synthesis of carbohydrate based therapeutics is often complicated by the necessity for extensive protection/deprotection strategies. Therefore the aim of this research was to establish a short and efficient route to multivalent arrays of mannose saccharides, with minimal dependence on protecting groups. Our attention thus focused on the development of a one-pot strategy involving condensation[12] of a series of divalent amines with unprotecred mannose mono and disaccharides.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicon oxide (silica gel

60 F_{254}) and compounds were visualized using a UV lamp. ^1H NMR and ^{13}C NMR spectra were obtained with Bruker AC 200 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

N,N-Di-(D-mannopyranosyl)-1,2-diaminobenzene (6): Yield 15 %; m.p. 112-116 ºC; $[\alpha]_D^{20}$ -93.52 (c 0.007, H_2O); ^1H NMR (D_2O, 500 MHz) δ 6.97-7.04 (m, 4H), 4.91 (s, 2H), 4.10 (d, *J* = 3.5 Hz, 2H), 3.92 (dd, *J* = 1.0, 11.0 Hz, 2H), 3.75-3.71 (m, 4H), 3.64 (t, *J* = 10.9 Hz, 2H), 3.46-3.49 (m, 2H); ^{13}C NMR (DMSO, 50 MHz) δ 135.6, 120.5, 115.7, 83.1, 79.2, 75.7, 72.8, 68.3, 62.5; MS (MALDI-TOF), m/z 455.119 [M + Na^+]; Anal. calcd. (%) for $C_{18}H_{28}N_2O_{10}$: C, 50.00; H, 6.53; N, 6.48. Found (%): C, 49.82; H, 6.43; N, 6.40.

N,N-Di-(D-mannopyranosyl)-1,3-diaminobenzene (7): Yield 82 %; m.p. 195-200 ºC; $[\alpha]_D^{20}$ -70.35 (c 0.001, H_2O); ^1H NMR (D_2O, 500 MHz) δ 6.78 (t, *J* = 7.8 Hz, 1H), 6.13 (m, 3H), 4.64 (s, 2H), 3.11-3.65 (m, 12H); ^{13}C NMR (DMSO, 50 MHz) δ 149.3, 131.4, 106.3, 101.5, 83.9, 80.2, 76.9, 73.5, 69.5, 63.6; MS (MALDI-TOF), m/z 455.257 [M + Na^+]; anal. calcd. (%) for $C_{18}H_{28}N_2O_{10}$: C, 50.00; H, 6.53; N, 6.48. Found (%): C, 49.77; H, 6.50; N, 6.43.

N,N-Di-(D-mannopyranosyl)-1,4-diaminobenzene (8): Yield 86 %; m.p. 194-197 ºC; $[\alpha]_D^{20}$ -94.55 (c 0.001, H_2O); ^1H NMR (DMSO, 200 MHz) δ 6.54 (d, *J* = 7.7 Hz, 4H), 4.66 (s, 2H), 3.13-3.78 (m, 12H); ^{13}C NMR (DMSO, 50 MHz) δ 138.1, 114.9, 82.3, 77.2, 74.6, 71.4, 67.2, 61.3; MS (MALDI-TOF), m/z 455.257 [M + Na^+]; anal. calcd. (%) for $C_{18}H_{28}N_2O_{10}$: C, 50.00; H, 6.53; N, 6.48. Found (%): C, 49.88; H, 6.46; N, 6.41.

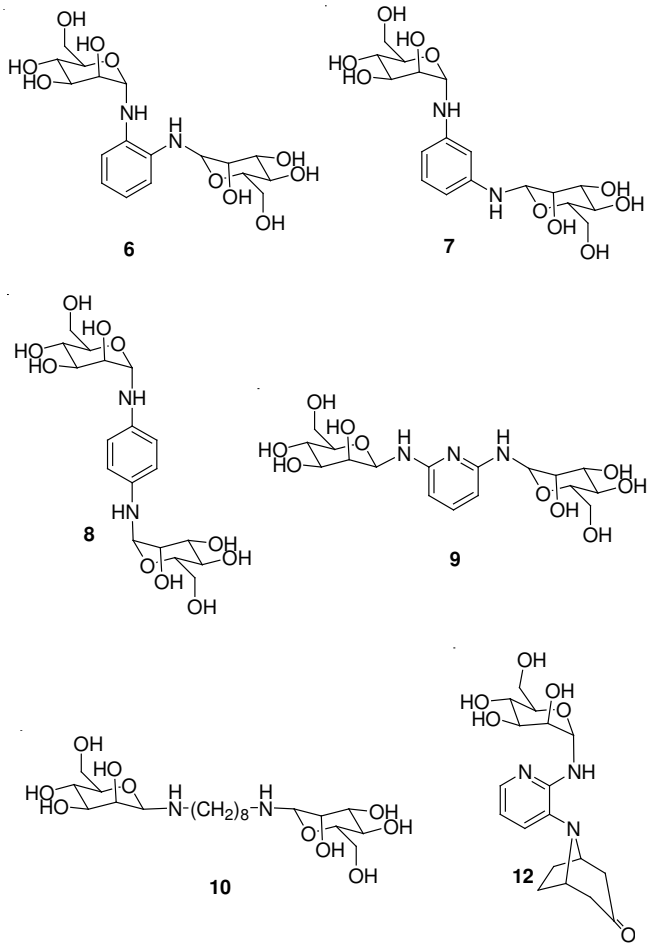
N,N-Di-(D-mannopyranosyl)-2,6-diaminopyridine (9): Yield 80 %; m.p. 194-197 ºC; $[\alpha]_D^{20}$ -59.94 (c 0.001, H_2O); ^1H NMR (DMSO, 200 MHz) δ 7.20 (t, *J* = 7.8 Hz, 1H), 5.91 (d, *J* = 7.9 Hz, 2H), 4.96 (s, 2H), 3.28-3.78 (m, 12H); ^{13}C NMR (DMSO, 50 MHz) δ 155.9, 138.6, 96.9, 79.6, 78.2, 74.5, 71.1, 67.0, 61.2; MS (MALDI-TOF), m/z 456.593 [M + Na^+]; anal. calcd. (%) for $C_{17}H_{27}N_3O_{10}$: C, 47.11; H, 6.28; N, 9.70. Found (%): C, 47.01; H, 6.20; N, 9.45.

N,N-Di-(D-mannopyranosyl)-1,8-diaminooctane (10): Yield 88 %; m.p. 122-114 ºC; $[\alpha]_D^{20}$ -12.71 (c 0.008, H_2O); ^1H NMR (D_2O, 500 MHz) δ 4.23 (s, 2H), 3.94 (dd, *J* = 2.0, 10.0 Hz, 2H), 3.88 (d, *J* = 2.5 Hz, 2H), 3.72-3.64 (m, 4H) 3.55 (t, *J* = 10.9 Hz, 2H), 3.32-3.37 (m, 2H), 2.90-2.69 (m, 2H), 2.63-2.69 (m, 2H), 1.49-1.52 (m, 4H), 1.34 (s, 8H); ^{13}C NMR (DMSO, 50 MHz) δ 87.5, 87.1, 78.1, 77.8, 74.9, 74.5, 71.7, 71.3, 67.8, 61.7, 44.9, 30.0, 29.1, 26.9; MS (MALDI-TOF), m/z 491.649 [M + Na^+]; anal. calcd. (%) for $C_{20}H_{40}N_2O_{10}$: C, 51.27; H, 8.60; N, 5.98. Found (%): C, 51.17; H, 8.43; N, 5.92.

RESULTS AND DISCUSSION

In this paper, one-pot synthesis of dimannopyranosylbenzenes, dimannopyranosyl-2,6-diaminopyridine and dimannosyl-1,8-diaminooctane from diaminobenzene and dimannosyl-1,8-diaminooctane in anhydrous methanol are reported.

An experimental procedure for the synthesis of N,N-di-(D-mannopyranosyl)-1,2-diaminobenzene (**6**) is as follows: A mixture of 1,2-diaminopyridine (**1**) (0.54 g, 5 × 10^{-3} mol), D-(+)-mannose (1.82 g, 1 × 10^{-2} mol) and anhydrous MeOH (60 mL) was stirred at -20 ºC for 50 h. After *ca.* 3 h, precipitation of the target derivative commenced. However, the reaction was left to stir at room temperature overnight and then cooled to 4 ºC and stored at this temperature for 48 h. Simple filteration of the precipitate thus formed then afforded N, N-di-(D-mannopyranosyl)-1,2-diaminobenzene **6** (10.18 g, 9 %) as a light yellow crystalline solid.



Structures of dimannopyranosylbenzenes, dimannopyranosyl-2,6-diaminopyridine and dimonopynanosyl-1,8-diaminooctane

A one-pot synthesis of N,N-di-(D-mannopyranosyl)-1,3-diaminobenzene (**7**) (1.77 g, 82 %) and N,N-di-(D-mannopyranosyl)-1,4-diaminobenzene (**8**) (1.73 g, 80 %) was executed in similar reaction. It is supposed that the major reason of low yield for **6** is the steric hindrance of mannopyranosyl group.

In case of the synthesis of N,N-di-(D-mannopyranosyl)-2,6-diaminopyridine (**9**), to a stirred solution of 2,6-diaminopyridine (**4**) (0.54 g, 5 × 10^{-3} mol), D-(+)-mannose (1.82 g, 1 × 10^{-2} mol) and anhydrous MeOH (60 mL) was added conc. HCl (0.5 mL). The reaction mixture was stirred at room temperature for 34 h. After stirring, it was stored at 4 ºC for 30 h to precipitate product. The crude precipitate was re-crystallized by dimethyl sulfoxide and methanol to give **9** as a pink powder (1.73 g, 80 %).

N,N-Di-(D-mannopyranosyl)-1,8-diaminooctane (**10**) was synthesized by the reaction of 1,8-diaminooctane (**8**) (0.72 g, 5 × 10^{-3} mol) and D-(+)-mannose (1.82 g, 1 × 10^{-2}

mol) with anhydrous MeOH (80 mL). The reaction mixture was stirred at room temperature for 12 h. After stirring, it was stored at 4 ºC for 24 h to precipitate product. The crude precipitate was re-crystallized by MeOH to give **10** (2.06 g, 88 %) as a white powder.

Interestingly, the condensation reaction of diamines, to produce divalent derivatives, has proved successful (Table-1).

TABLE-1
YIELDS OF PRODUCTS

Diamine	Saccharide	Product	Yield (%)*
1	D-(+)-Mannose	**6**	15
2	D-(+)-Mannose	**7**	82
3	D-(+)-Mannose	**8**	86
4	D-(+)-Mannose	**9**	48
5	D-(+)-Mannose	**10**	88
11	D-(+)-Mannose	**12**	–

*Isolated yields.

But the reaction of monoamine like **11** and D-(+) mannose with HCl in anhydrous MeOH did not occur. It is suggested that the compound **12** is not produced due to steric hindrance of tropane ring.

These results illustrated that in all cases, it was possible to form the divalent saccharide derivatives in one pot without any need for protecting group manipulations[13]. It is also interested to note that targets incorporation Man α-1,2-Man and Man α-1,3-Man disaccharides, as well as a glycodendrimers[14], could be prepared using this direct approach. The ability of these divalent derivatives to inhibit infections caused by *E. coil* is currently being assessed.

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