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One-pot synthesis of multivalent arrays of mannose mono- and disaccharides

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Abstract—The one-pot synthesis of multivalent arrays of mannose mono- and disaccharides, of potential use as anti-infective agents against enterobacteria infections, is described.

1. Introduction

It is now accepted that 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 anti-infective 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 anti-infective 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. coli* and *S. suis* strains), that naturally adhere via type 1 fimbriae to high-branched mannose chains,[6] 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,[7] as well as Man α-1,2-Man and Man α-1,3-Man disaccharides,[8] are effective for inhibiting the carbohydrate-lectin interactions.

2. Results and discussion

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 of a series of multivalent (di- to hexavalent) amines with unprotected mannose mono- and disaccharides. Interestingly, the condensation reaction of mono- and diamines with wood pulp disaccharides, to produce divalent derivatives, had previously proved successful.[9] A series of reactions was therefore performed to establish the utility of this methodology for accessing multivalent arrays of mannose mono- and disaccharides (Table 1). A representative example utilizing ethylenediamine and D-mannose is illustrated below (Scheme 1). Examples of other amine and saccharide substrates employed are illustrated in Fig. 1 and Table 1. In all cases the reactions were effected by dissolving

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Table 1.

Saccharide	Amine	Yield of product (%)
D-Mannose	Ethylenediamine	77
D-Mannose	1,2-Propanediamine	64
D-Mannose	1,3-Propanediamine	68
D-Mannose	1,4-Butanediamine	53
D-Mannose	Tris(2-aminoethyl)amine	56
D-Mannose	Pentaerythrityl tetraamine	47
D-Mannose	Hexavalent dendrimer[12]	56
Man α-1,2-Man	Ethylenediamine	39
Man α-1,3-Man	Ethylenediamine	43
Man α-1,2-Man	Hexavalent dendrimer[12]	35
Man α-1,3-Man	Hexavalent dendrimer[12]	37

the multivalent amine and either D-mannose or Man-α-1,2-Man or Man-α-1,3-Man in anhydrous methanol, and stirring the reaction mixture at room temperature.[10] After approximately one hour, precipitation of the target multivalent derivatives commenced. However, the reactions were left to stir at room temperature overnight, and then cooled to 4°C and stored at this temperature for 24 hours. Simple filtration of the precipitates thus formed then afforded the desired targets.[11]

Pleasingly these results illustrate that in all cases it was possible to form the multivalent saccharide derivatives in one pot without any need for protecting group manipulations. It is interesting to note that targets incorporating Man α-1,2-Man and Man α-1,3-Man disaccharides, as well as a glycodendrimers,[13] could be prepared using this direct approach. Conversion yields varied from excellent to moderate, with the lower yields corresponding to the reactions of higher valent amines with the mono- and disaccharides. However, in these latter cases it should be noted that up to six condensation reactions were occurring within the one-pot.

The ability of these multivalent derivatives to inhibit infections caused by *E. coli* is currently being assessed.

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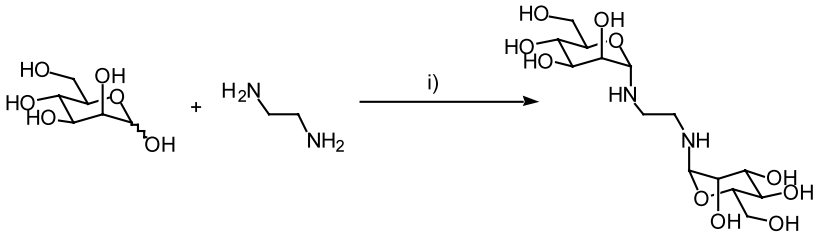

Scheme 1. Representative example of the condensation methodology. (i) Anhydrous methanol, room temperature, then 4°C.

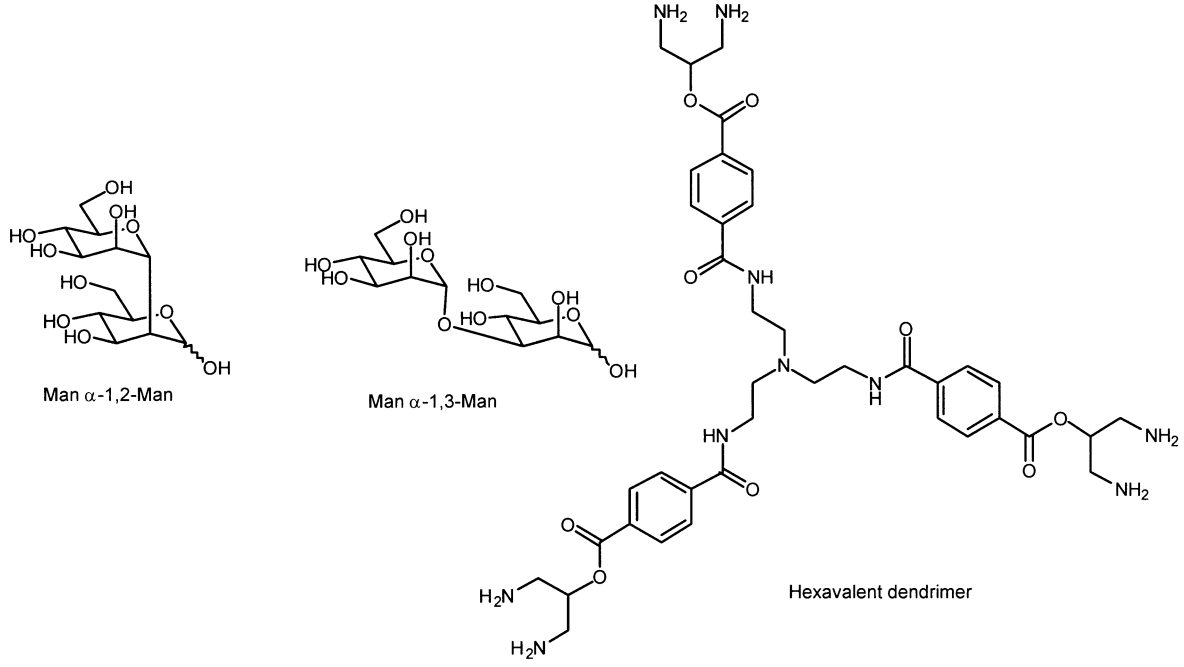

Figure 1.

References

1. For a recent review, see: Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–601 and references cited therein.
2. For example, see: Zopf, D.; Roth, S. *Lancet* **1996**, *347*, 1017–1021.
3. Mouricout, M.; Petit, J. M.; Carias, J. R.; Julien, R. *Infect. Immun.* **1990**, *58*, 98–106.
4. Mulvey, G.; Kitov, P. I.; Marcato, P.; Bundle, D. R.; Armstrong, G. D. *Biochimie* **2001**, *83*, 841–847.
5. Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–327.
6. (a) Ofek, I.; Sharon, N. *Curr. Top. Microbiol. Immunol.* **1990**, *151*, 91–114; (b) Ofek, I.; Mirelman, D.; Sharon, N. *Nature* **1977**, *265*, 623–625; (c) Ofek, I.; Beachey, E. H. *Infect. Immun.* **1978**, *22*, 247–254.
7. For example, see: (a) Ashton, P. R.; Hounsell, E. F.; Jayaraman, N.; Nilsen, T. M.; Spencer, N.; Stoddart, J. F.; Young, M. *J. Org. Chem.* **1998**, *63*, 3429–3437; (b) Corbell, J. B.; Lundquist, J. J.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 95–111.
8. Firon, N.; Ofek, I.; Sharon, N. *Infect. Immun.* **1984**, *43*, 1088–1090.
9. MacLeod, J. M. *Carbohydr. Res.* **1979**, *75*, 71–81.
10. Representative procedure and data: Ethylenediamine (0.39 mL, 6.48 mmol) was dissolved in anhydrous methanol (7 mL) and the mixture stirred at room temperature under a nitrogen atmosphere. To this was added D-mannose (2.10 g, 11.66 mmol). After 5 minutes the D-mannose was seen to dissolve and after 1 hour a colourless solid precipitated out of the solution. Further anhydrous methanol (7 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was then cooled to 4°C and stored for 24 hours at this temperature. The precipitate was then filtered off, washed with ice-cold methanol and dried in vacuo (using a drying piston) for 48 hours at 40°C. This yielded *N,N-di-α-D-mannopyranosyl ethylenediamine* as a colourless powder (1.77 g, 77%). Mp 152.8–153.4°C; $[\alpha]_D^{20}$ −10.74 (*c* 3.55, H_2O); ν_{max} (KBr, cm^{-1}) 3510, 3311, 2931, 2885, 2841, 1618, 1136, 995, 696; δ_H (400 MHz, D_2O) 4.03 (2H, s, H-1, H-1′), 3.71 (2H, dd, *J* 2.5, 12.0, H-6, H-6′), 3.68 (2H, d, *J* 3.5, H-2, H-2′), 3.49 (2H, dd, *J* 6.5, 12.0, H-6, H-6′), 3.42 (2H, dd, *J* 3.5, 9.5, H-3, H-3′), 3.32 (2H, t, *J* 9.5, H-4, H-4′), 3.10–3.14 (2H, m, H-5, H-5′), 2.61–2.81 (4H, m, 2×H_a, 2×H_b); δ_C (100 MHz, D_2O) 89.5 (2×CH), 80.0 (2×CH), 76.6 (2×CH), 73.6 (2×CH), 69.9 (2×CH), 64.0 (2×CH_2), 47.1 (2×CH_2); *m/z* (FAB) 385 ($M+H^+$, 22%); Found 385.1832, $C_{14}H_{29}O_{10}N_2$ requires 385.1822.
11. All compounds were subjected to ^1H and ^{13}C NMR, IR, *m/z* and either HRMS or elemental analysis and were shown to be analytically pure. The anomeric configurations of the targets were determined by extensive NMR analysis.
12. Hayes, W.; Romagnoli, B.; Harwood, L. M.; Philp, D.; Price, D. W.; Smith, M. synthesis of the dendrimer has been submitted for publication in *Tetrahedron*.
13. For a recent review of glycodendrimers, see: Röckendorf, N.; Lindhorst, T. K. *Top. Curr. Chem.* **2001**, *217*, 201–238.