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Synthesis and Stereoselective Glycosylation of D- and L-*glycero-β*-D-*manno*-Heptopyranoses

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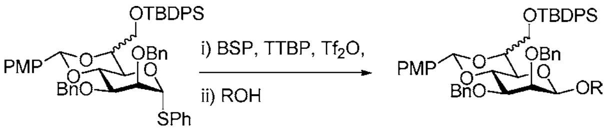
ABSTRACT



A method for the direct stereocontrolled synthesis of D- and L-*glycero-β*-D-*manno*-heptopyranosides such as those found in the repeating unit of the O-specific polysaccharide from the CNCTC 113/92 LPS (serotype 54) is described. The method relies on the presence of a 4,6-*O*-benzylidene acetal to effect stereocontrol at the anomeric center; the configuration at C6 (L- or D-*glycero*) is of minimal importance.

Well-defined syntheses of complex oligosaccharides and glycoconjugates corresponding to native bacterial structures are essential tools for investigation of the immunological response against polysaccharides.[1] Heptoses of the L-*glycero*-D-*manno* and D-*glycero*-D-*manno* configurations are common constituents of the inner and outer core regions of lipopolysaccharides (LPS) and are found in many pathogenic bacteria.[2] The synthesis of higher carbon sugars has been investigated for more than a century,[3] and several methods have been developed;[2−4] however, less attention has been devoted to their stereocontrolled incorporation into glycosidic bonds. Most LPS heptosides have the α-anomeric configuration,[2] and syntheses of several complex oligosaccharides containing α-L,D- or α-D,D-heptopyranosides (Hep*p*) have been achieved by Oscarson and co-workers.[1,5]

The structure of the core LPS from *Plesimonas shigelloides* O54 (strain CNCTC 113/92) was recently elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, monosaccharide analysis, and immunological methods.[6] Interestingly, the O-specific polysaccharide of this strain was found to be composed of a hexasaccharide repeating unit (Figure 1) containing two unusual *β*-linked heptose units. The presence of the two *β*-linkages in this immunological lipopolysaccharide prompted the investigation

-4)-D-β-D-Hep*p*-(1-3)-6d-β-D-Hep*p*-(1-4)-α-L-Rha*p*-(1-4)-β-D-Glc*p*NAc-(1-
| |
3   2-O-Ac
|
1-α-L-Rha*p*-(4-1)-β-D-Gal*f*

Figure 1. Repeating unit of the O-specific polysaccharide from CNCTC 113/92 LPS (serotype 54).

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(1) Oscarson, S. *Carbohydr. Polym.* **2001**, *44*, 305.

(2) Zamyatina, A.; Gronow, S.; Puchberger, M.; Graziani, A.; Hofinger, A.; Kosma, P. *Carbohydr. Res.* **2003**, *338*, 2571.

(3) Györgydeák, Z.; Pelyvás, I. F. *Monosaccharide Sugars—Chemical Synthesis by Chain Elongation, Degradation and Epimerization*; Academic Press: San Diego, 1998.

(4) (a) Brimacombe, J. S.; Kabir, A. B. K. M. S. *Carbohydr. Res.* **1986**, *152*, 329 and references therein. (b) Boons, G. J. P. H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1989**, *30*, 229. (c) Jørgensen, M.; Iversen, E. H.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4625 and references therein. (d) Read, J. A.; Ahmed, R. A.; Morrison, J. P.; Coleman, W. G., Jr.; Tanner, M. E. *J. Am. Chem. Soc.* **2004**, *126*, 8878.

(5) (a) Oscarson, S.; Ritzen, H. *Carbohydr. Res.* **1994**, *254*, 81. (b) Ekeloef, K.; Oscarson, S. *J. Carbohydr. Chem.* **1995**, *14*, 299. (c) Bernlind, C.; Oscarson, S. *Carbohydr. Res.* **1997**, *297*, 251. (d) Bernlind, C.; Oscarson, S. *J. Org. Chem.* **1998**, *63*, 7780. (e) Bernlind, C.; Bennett, S.; Oscarson, S. *Tetrahedron: Asymmetry* **2000**, *11*, 481. (f) Segerstedt, E.; Manerstedt, K.; Johansson, M.; Oscarson, S. *J. Carbohydr. Chem.* **2004**, *23*, 443.

(6) (a) Niedziela, T.; Lukasiewicz, J.; Jachymek, W.; Dzieciatkowska, M.; Lugowski, C.; Kenne, L. *J. Biol. Chem.* **2002**, *277*, 11653. (b) Czaja, J.; Jachymek, W.; Niedziela, T.; Lugowski, C.; Aldova, E.; Kenne, L. *Eur. J. Biochem.* **2000**, *267*, 1672.

10.1021/ol050224s CCC: $30.25

which we now report into stereocontrolled β-glycosidation in D,D-heptoses and the related L,D-epimers.

Our interest in these molecules was further spurred by the insight that their study might yield into the underlying reasons for the beneficial influence of the 4,6-*O*-benzylidene acetal on the stereocontrolled preparation of β-mannosides.[7] Originally, working in the gluco series, Fraser-Reid and coworkers suggested that trans-fused 4,6-*O*-benzylidene protecting groups restrict the flexibility of the pyranose ring, resulting in an oxacarbenium ion intermediate with a computed (PM3) 20° twist in the ideally syn coplanar C5−O5−C1−C2 system.[8a] In a subsequent paper, differential solvation was also computed to be of significance in these so-called torsional disarming effects.[8b] More recently, Bols and coworkers provided experimental evidence in support of the notion that the disarming effect of the 4,6-*O*-acetal group is mainly due to the locking of the C5−C6 bond in the deactivated *tg*-conformation.[9] We hypothesized that the inclusion of either an extra axial C-6 substituent, as in the 4,6-*O*-benzylidene-protected L-*glycero*-D-*manno*-heptoses, or a corresponding equatorial substituent, as in the D-*glycero*-D-*manno* series, would influence both torsional and solvation considerations differently, whereas the *tg* conformation of the C5−C6 bond would be unchanged. Comparisons of either reactivity or stereoselectivity between the two diastereomeric series might therefore provide support for one or other of the two conflicting rationales for the 4,6-*O*-benzylidene group effect.

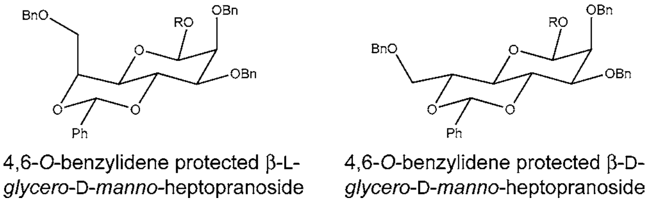
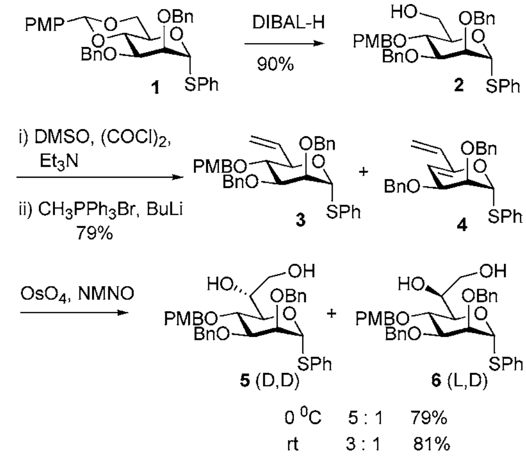


Figure 2. L- and D-glycero-D-manno-heptopyranosides.

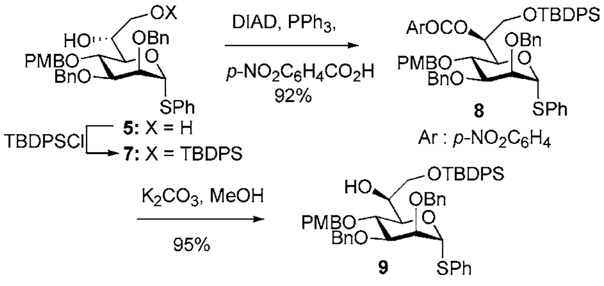
The synthesis of a diastereomeric glycosyl donor pair (Scheme 1) began with the known 4,6-*O*-*p*-methoxybenzylidene-protected thiomannoside **1**,[10] which was regioselectively opened to the primary alcohol **2** exclusively in 90% yield with DIBAL-H in dichloromethane.[11] Comparable results were obtained with scandium triflate-catalyzed, BH_3−THF-mediated reduction;[12] all other standard protocols[13] gave mixtures of isomers and considerable cleavage of the acid-labile *p*-methoxybenzyl group. Swern oxidation[14] of **2** gave the corresponding unstable[15] aldehyde, which was carried on to the next step, Wittig olefination,[14] without purification.

Scheme 1. Synthesis of Heptoses **5** and **6**



The yield (65%) of the olefination product **3** was compromised by the concomitant formation of diene **4** in 14% yield.[16] Use of the Nysted reagent[17] for this transformation also generated compound **4**, along with compound **3**, however, in higher yield, whereas the Petasis reagent[18] gave predominantly decomposition products. Treatment of olefin **3** with OsO_4 (5 mol %) and NMNO at 0 °C and room temperature furnished diols **5** and **6** in 5:1 and 3:1 diastereomeric ratios and in 79 and 81% yields, respectively. The stereochemical outcome of this dihydroxylation follows Kishi's empirical rule;[19] the relatively poor diastereoselectivity starting from the sugar with 2,3-erythro configuration is also consistent with literature precedent.[4c] Asymmetric dihydroxylation was also unsatisfactory for this transformation in our hands.[15,20] Silylation of **5** gave the primary silyl ether **7**, which, when subjected to the Mitsunobu protocol,[15] afforded the inverted ester **8**. Removal of the ester function then gave more significant quantities of the L,D-series in the form of the silyl ether **9** (Scheme 2).

Scheme 2. Inversion of Configuration at C6



Compound **7** was converted uneventfully to the D-*glycero*-D-*manno*-heptothioglycoside **10** by oxidative ring closure with DDQ in 84% yield (Scheme 3).[21]

In the diasteromeric series, however, cyclization of silyl ether **9** was comparatively slow due to the developing 1,3-

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[7] (a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9051. (b) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115.

[8] (a) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434. (b) Andrews, C. W.; Rodebaugh, R. Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280.

[9] Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205.

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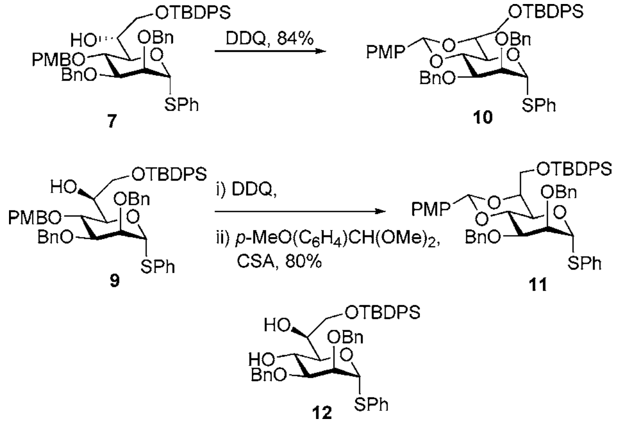
[11] (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033.

[12] Wang, C.-C.; Luo, S.-Y.; Shie, C.-R.; Hung, S.-C. *Org. Lett.* **2002**, *4*, 847. Note: This method gave 84% yield but generated more diol compared to the DIBAL-H reaction.

Scheme 3. Preparation of Glycosyl Donors **10** and **11**



diaxial interaction in the acetal ring. As a consequence, oxidative cleavage of the PMB group was a competing reaction, resulting in the formation of diol **12** in 48% yield along with the desired L-*glycero*-D-*manno*-heptothioglycoside **11** in 43% yield. In the face of this difficulty, a protocol was devised whereby the crude reaction mixture from treatment of **9** with DDQ was treated with *p*-methoxybenzylaldehyde dimethyl acetal and catalytic CSA to give **11** in 80% yield over two steps (Scheme 3).

At this stage, the NOE correlations indicated in Figure 3 served to confirm both the configuration at C6 in compounds **10** and **11**, as well as the equatorial nature of the *p*-methoxyphenyl group in the two acetals.

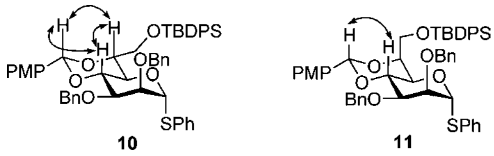
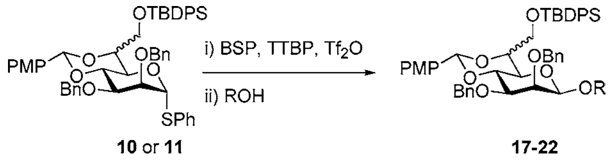


Figure 3. Diagnostic NOE correlations for donors **10** and **11**.

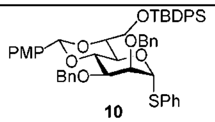
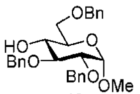
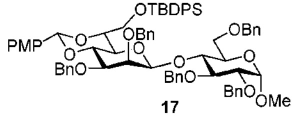
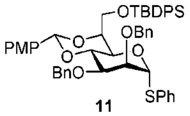
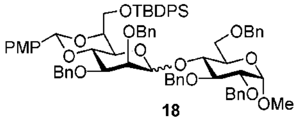
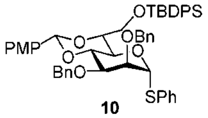
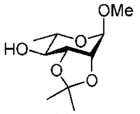
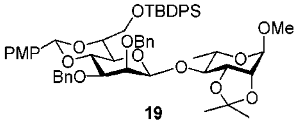
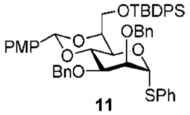
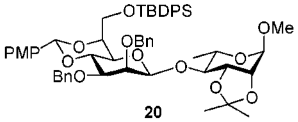
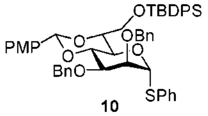
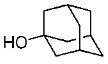
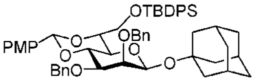
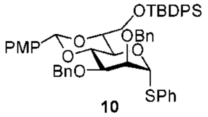
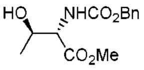
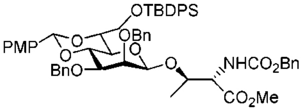
A series of glycosylation reactions were then conducted with donors **10** and **11** with thioglycoside activation by means of 1-benzenesulfinyl piperidine and trifluoromethanesulfonic anhydride (BSP/Tf_2O)[7a] in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[22] in dichloromethane at −60 °C prior to the addition of the acceptor alcohols (Scheme 4).

Scheme 4. Glycosylation with the BSP/Tf_2O Couple



All couplings were highly *β*-selective and proceeded in high yields (Table 1). A minor exception to the otherwise

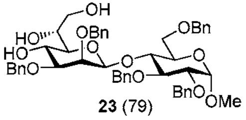
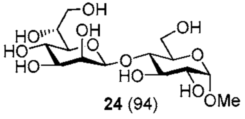
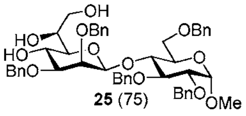
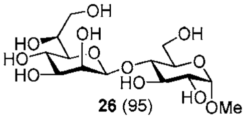
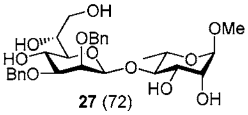
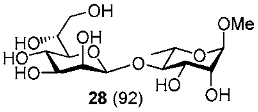
Table 1. Diastereoselective Glycosidation Reactions

entry	donor	acceptor	product	% yield (β:α ratio)
1	 **10**	 **13**	 **17**	81 (1:0)
2	 **11**		 **18**	86 (8:1)
3	 **10**	 **14**	 **19**	88 (1:0)
4	 **11**		 **20**	85 (1:0)
5	 **10**	 **15**	 **21**	88 (1:0)
6	 **10**	 **16**	 **22**	89 (1:0)

exclusive β-selectivity was observed in the coupling of donor **11** to the glucose-4-OH acceptor **13** (Table 1, entry 2). This may represent a small difference in reactivity between the two donors, which only becomes apparent with less reactive acceptors such as **13**.[23] The assignment of anomeric stereochemistry in all glycosides was made on the basis of $^1J_{CH}$ coupling constants.[24] Furthermore, in all products arising from donors **10** and **11**, a relatively upfield chemical shift (δ 3.25 to 3.50 in $CDCl_3$) of the heptose H5 resonance was observed, as is characteristic of 4,6-*O*-benzylidene-protected β-mannosides.[25]

Finally, attention was turned to deprotection (Table 2). Thus, glycosides **17**, **18*β***, and **19** were first exposed to TBAF in THF. This was followed by benzylidene acetal and acetonide removal with catalytic CSA in refluxing methanol. Finally, hydrogenolysis over Pd/C afforded the fully deprotected disaccharides, whose anomeric stereochemistry was again confirmed by determination of the $^1J_{CH}$ coupling constants.

Table 2. Final Deprotections

cmpd	partial deprotection (% yield)[a]	final product (% yield)[b]
17	 **23** (79)	 **24** (94)
18β	 **25** (75)	 **26** (95)
19	 **27** (72)	 **28** (92)

[a] Treatment with TBAF in THF followed by camphorsulfonic acid in methanol, both at room temperature. [b] Hydrogenolysis over Pd/C in methanol.

In summary, a method for the stereocontrolled synthesis of both β-D-*glycero*-D-*manno*- and β-L-*glycero*-D-*manno*-heptopyranosides has been established. We anticipate that this work will open the way for the synthesis of most β-linked heptopyranosides, including those in the polysaccharide repeating unit illustrated in Figure 1. Furthermore, it has been established that the stereochemistry of substitution at the 6-position has little effect on the stereoselectivity of these 4,6-*O*-alkylidene acetal-controlled glycosidation reactions. This observation is most consistent with Bols' interpretation of the benzylidene acetal effect, namely, the locking of the C5−C6 bond in the *tg* conformation.

Acknowledgment. We thank the NIGMHS for financial support (GM 57335).

Supporting Information Available: Full experimental details and charcterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Note: epimerization at C5 was also observed but was substantially eliminated by carrying out the reaction at low temperature.

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