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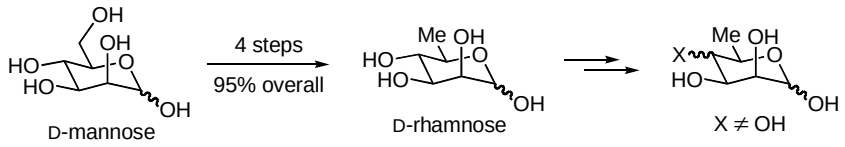

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An efficient synthesis of selectively functionalized D-rhamnose derivatives

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ABSTRACT

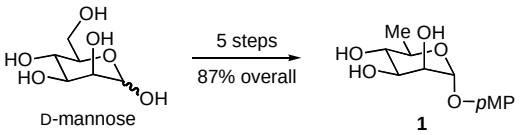
D-Rhamnose is an important component of bacterial lipopolysaccharides. This paper describes a short and highly efficient synthesis of D-rhamnose from D-mannose. The synthesis of selectively C-4 modified D-rhamnosides and 6-deoxy-D-talosides as potential building blocks for complex oligosaccharide synthesis is also discussed.

Bacterial cell surface carbohydrates are now widely recognized as playing an essential role in disease progression and host defense mechanisms. Lipopolysaccharides (LPS) are the major component of Gram-negative outer cell membranes, and are known to be intimately involved in pathogenesis in both animals and plants.[1] Of particular importance is the O-antigen component of the LPS, which is displayed towards the external environment by the bacterium, and is known to be associated with host-pathogen cross-talk.[2]

The role of bacterial LPS, and specifically O-antigens, in disease has prompted a number of investigations into the chemical structure of these carbohydrate antigens, with a view to both understanding their role in pathogenesis and also using these antigenic structures to develop vaccines.[3] As our knowledge of the specific monomers present in these carbohydrate antigens grows, so too does the need for efficient chemical syntheses of the building blocks required to construct appropriate oligosaccharides for vaccine development and pathogenicity studies. In this regard, 6-deoxy-D-hexoses are of interest, since these sugars are found in a number of important pathogens, including genera such as *Burkholderia*, *Helicobacter*, *Pseudomonas*, *Xanthomonas*, *Citrobacter*, and *Bacillus*.[4,5]

Despite the importance of 6-deoxy-D-hexoses, access to appropriate synthetic compounds as building blocks is limited by their availability. 6-Deoxy-D-mannosides, or D-rhamnosides, are of particular interest. Whilst the precise role of this deoxy sugar remains unclear, it does appear that D-rhamnose is a key component of the LPS of certain human pathogens as well as several phytopathogenic organisms.[6] Given that D-rhamnose is not present in humans, this rare sugar is an ideal template for drug discovery strategies and vaccine development.

Although D-rhamnose is commercially available, its cost is prohibitively expensive for large-scale synthetic chemistry. Several chemical syntheses of D-rhamnosides have been reported,[7-10] however, in general these methods are not readily applicable to the large scale approaches that are necessary for gaining access to appropriate building blocks for oligosaccharide synthesis. A significant advancement in D-rhamnose chemistry was reported by the Roy group in 2007,[11] wherein they synthesized the D-rhamnoside **1** in five steps from D-mannose. Importantly, this work was able to be carried out on a large scale, affording the D-rhamnoside **1** in 87% overall yield from D-mannose.[11] We report here our efforts towards the synthesis of D-rhamnose, and specifically functionalized D-rhamnosides that may serve as useful building blocks for oligosaccharide synthesis.



Our synthesis of D-rhamnose is shown in Scheme 1. Treatment of D-mannose with benzyl alcohol under acidic conditions[12] gives exclusively the α-benzyl-glycoside **2** in high yield (98%). Regioselective iodination of the primary alcohol in **2** was achieved in high yield (98%) using Mitsunobu conditions.[9,11] Confirmation that the iodide was attached to C-6 in **3** was obtained by noting the change in the ^{13}C NMR chemical

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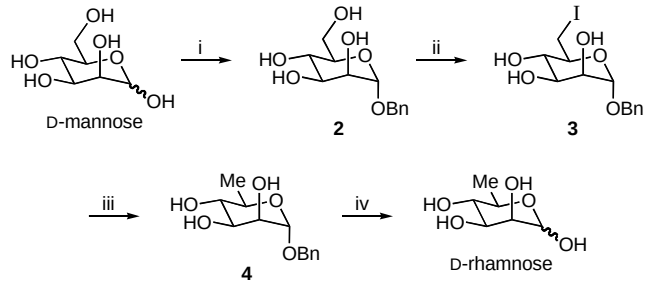
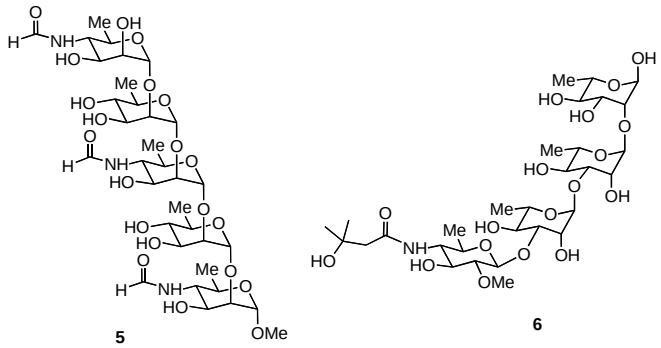
shift of C-6 from δ 60.7 in **2** to δ 7.4 in **3**, consistent with the expected shielding effect of iodine. Reduction of the iodide in **3** using catalytic hydrogenation gave the expected D-rhamnoside **4** in quantitative yield. The structure of **4** was confirmed by ^{1}H NMR spectroscopy, most notably by the presence of a 3-proton doublet at δ 1.26. Significantly, the three-step conversion of D-mannose to the rhamnoside **4** can be routinely carried out on a 10 g scale.



Scheme 1. Reagents and conditions: i) BnOH, AcCl, 50 °C for 1.5 h, then rt for 12 h, 98%; ii) PPh_3, I_2, imidazole, THF, reflux, 2 h, 98%; iii) H_2 (g), $Pd(OH)_2$ on C, EtN^iPr_2, MeOH, rt, 6 h, 100%; iv) H^+ resin, H_2O, 80 °C, 12 h, 100%.

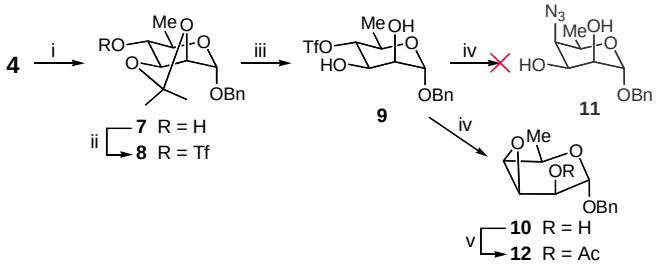
To complete the synthesis of D-rhamnose itself, the α-benzyl-glycoside in **4** can be removed in quantitative yield by exposure of **4** to acidic resin in water at 80 °C for 12 hours.

Having established a highly efficient synthesis of the D-rhamnoside **4**, we next examined the usefulness of this compound as a building block for possible oligosaccharide synthesis. In Nature, D-rhamnose is usually linked (1→2) or (1→3) with another D-Rha*p*, or linked (1→6) or (1→4) to other hexoses, notably Man and Gal.[4] Of particular interest in our work was selective functionalisation at C-4 of D-rhamnose; C-4 modified D-rhamnose derivatives could serve as useful building blocks in efforts to incorporate specifically modified rhamnose derivatives into polysaccharide-based conjugate vaccines, such as the rhamnose-containing analogue **5**[13] of the *Bacillus anthracis* tetrasaccharide **6**.[10,14] In addition, functionalisation with epimerization at C-4 would produce 6-deoxy-talosides,[15] which could also serve as useful synthetic intermediates.



Our initial strategy towards C-4 modified derivatives of **4** was focused on introducing nitrogen-based functionality. Given that the C-2 and C-3 hydroxys in **4** are *cis*- with respect to each other, they are ideally arranged to use a cyclic protecting group, thereby leaving the C-4 hydroxy free for selective functionalisation. After some refinement of reaction conditions, we found that treatment of the benzyl rhamnoside **4** with 2,2-dimethoxypropane and acetone in the presence of *p*-TsOH and 4 Å molecular sieves gave the desired 2,3-*O*-isopropylidene derivative **7** in quantitative yield (Scheme 2). In order to gain access to C-4 modified 6-deoxy-talosides, we reasoned that a potential strategy could involve direct displacement of a good leaving group at C-4 in **7**. Accordingly, exposure of **7** to triflic anhydride at low temperature proceeded smoothly, with successful incorporation of the triflate group at C-4 confirmed by examination of the ^{1}H NMR spectrum of **8** which showed the expected deshielding of the H-4 proton from δ 3.42 in **7** to δ 4.57 in **8**. Unfortunately, all attempts at nucleophilic displacement of the triflate group in **8** with sodium azide failed, with highly complex reaction mixtures being obtained in each instance. An examination of the literature revealed that attempted nucleophilic displacement of the 4-*O*-sulfonate group in 6-deoxy-2,3-*O*-isopropylidene pyranosides such as **8** resulted in an unusual rearrangement to give furanoside products with the nucleophile attached to C-5.[16-18] It has been suggested[16,19] that the ring contraction occurs through an initial S_N2-like process whereby the ring oxygen attacks C-4, due to the fact that the C-5 ring oxygen bond is *trans*-antiparallel to the C-4 sulfonate group. The complexity of our reaction mixture would be consistent with this type of rearrangement.

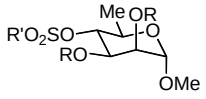
We reasoned that our inability to successfully displace the triflate group in **8** was probably due to steric hindrance and ring strain, since the 2,3-*O*-isopropylidene group adds rigidity into the system and also sterically blocks the face that the incoming nucleophile is attacking from. This observation is supported by the fact that the analogous epimeric C-4 triflate to **8**, with the triflate in an axial orientation, can be readily displaced by sodium azide, to give the C-4 equatorial azido product.[9] In an attempt to overcome these potential steric problems, the triflate **8** was deprotected to give the diol **9** (Scheme 2).



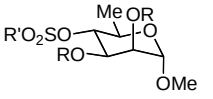
Scheme 2. Reagents and conditions: i) 2,2-dimethoxypropane: acetone (1:1), *p*-TsOH, 4 Å sieves, 30 min, 100%; ii) Tf_2O, pyridine, -78 °C to 0 °C, 83%; iii) dil. HCl, 95%; iv) NaN_3, DMF, 60 °C, 4 h, 98%; v) Ac_2O, pyridine, 0 °C to rt, 15 h, 95%.

Interestingly, initial attempts at base-promoted displacement of the triflate in **9** with sodium azide in DMF at elevated temperature resulted in the rapid formation of the 3,4-anhydro derivative **10** as the major product, rather than the anticipated *talo*-configured product **11** (Scheme 2). Using trimethylsilyl azide as the nucleophile also failed to furnish the desired product **11**, returning unreacted starting material **9**. Proof that the 3,4-anhydro derivative **10** had indeed been formed during the treatment of **9** with sodium azide was obtained from careful analysis of the spectroscopic data and comparison with related literature compounds.[19,20] Most notably, a molecular mass of *m/z* 259 (M+Na) was consistent with the loss of triflic acid from **9**, whilst the change in the magnitude of the coupling between H-4 and H-5 (from J = 9.6 Hz in **9** to 4.2 Hz in **10**) and H-3 and H-2 (from J = 3.6 Hz in **9** to 4.5 Hz in **10**) was consistent with the formation of the 3,4-anhydro system. Additionally, acetylation of the product **10** gave compound **12** which contained a single acetyl group at C-2, confirming that the anhydro ring in **10** was formed between C-3 and C-4. Deliberate formation of the 3,4-anhydro derivative **10** was achieved by treating the triflate **9** with K_2CO_3 in MeOH,[19,21] resulting in quantitative formation of **10**.

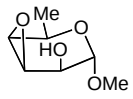
It is generally considered that direct nucleophilic displacement reactions at C-4 of *manno*-configured pyranosides such as **9** is difficult, since the β-*trans*-axial group at C-2 can sterically hinder the approaching nucleophile, and can also cause unfavourable polar interactions.[18,22,23] This apparent difficulty has prompted some to avoid this transformation completely, and opt instead for an oxidation - oximation - reduction strategy in order to introduce an axial nitrogen-based functionality at C-4 when starting with a *manno*-configured sugar.[20] In a comprehensive study on the nucleophilic displacement of 4-sulfonyloxy groups in D-*manno*-configured sugars (e.g. **13**), Cicero *et al.* showed that the nature of the other substituents played an important role in the outcome of the displacement reactions.[22] For example, attempted thiocyanate displacement of the C-4 sulfonate group in **14** resulted in attack at C-4 by the C-2 benzyloxy substituent, followed by benzoyl migration to give a mixture of the three possible dibenzoate products.[22] Interestingly, in the absence of protecting groups at C-2 and C-3, attempted thiocyanate displacement of the C-4 sulfonate in **15** gave a mixture of both the *talo*- and *manno*-configured C-4 thiocyano derivatives, presumably via a 3,4-anhydro transition state.[22]



13 R = H or Bz
R' = *p*-MePh or *p*-NO_2Ph



14 R = Bz, R' = *p*-NO_2Ph
15 R = H, R' = *p*-NO_2Ph

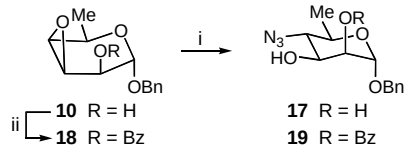


16

The α-methyl glycoside analogue **16** of **10** has been used as a key intermediate in the synthesis of 4-amino-4-deoxy-D-rhamnose.[21] In that work, the authors deliberately prepared the 3,4-anhydro derivative **16** by treating the corresponding 4-*O*-mesylate-rhamnoside with sodium hydroxide. Treatment of **16** with either sodium azide or ammonia in MeOH resulted in predominant attack at C-3, whilst the use of aqueous dimethylamine gave a 12:1 mixture favouring attack at C-3 over C-4.[21] Interestingly, introduction of a benzoyl protecting group on the C-2 hydroxy in **16** resulted in a complete change in the regiochemical outcome of azide opening, with the predominant product resulting from attack at C-4.[21] This finding was rationalized on the conformation of the anhydro sugar, and the preference for a transition state that favours a *trans*-diaxial opening of the epoxide. It was reasoned that the sterically demanding group at C-2 would result in destabilization of the half-chair conformation that favours attack at C-3, thus promoting attack at C-4.[21] Several other examples of the nucleophilic opening of anhydro sugars have been reported, and in many of these papers both the regio- and stereochemical outcome of the opening can be controlled by varying either the type of nucleophile being used or by alteration of hydroxy protecting groups.[19,20,24-26]

For our 3,4-anhydro derivative **10**, nucleophilic attack at C-3 would result in a *ido*-configured sugar, whilst nucleophilic attack at C-4 would return a *manno*-configured sugar. Unfortunately however, in our hands the anhydro sugar **10**, or the 2-acetyl analogue **12**, were surprisingly robust compounds. Exposure of **10** or **12** to NaN_3 in DMF for extended reaction times and at elevated temperature failed to produce any products, returning unreacted starting material in all cases. Treatment of **12** with NaN_3 in the presence of either NH_4Cl in aqueous MeOH[20] or $CeCl_3$ in aqueous acetonitrile[27] also resulted in recovered starting material. Non-nitrogen based nucleophiles, including methoxide and sodium acetate, also failed to react with **10**.

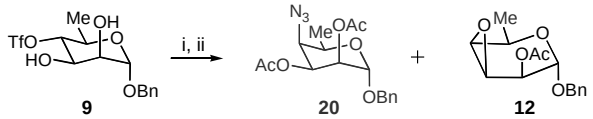
The use of Lewis acids in conjunction with $TMSN_3$ appears to be a mild and highly regioselective method for opening epoxy alcohols.[24,25,28] A postulated benefit of using the Lewis acid is that the epoxide oxygen coordinates to the metal of the Lewis acid. Accordingly, exposure of **10** to $TMSN_3$ and BF_3•OEt_2 provided the 4-azido-D-rhamnoside **17** in a modest 26% yield (Scheme 3), together with several other minor products. In an attempt to improve this outcome, we decided to protect the hydroxy group in **10** prior to epoxide opening. Treatment of **10** with either acetic anhydride or benzoyl chloride, under standard conditions, gave the corresponding C-2 esters **12** and **18**, respectively, in high yield. Interestingly, whilst exposure of **12** to $TMSN_3$ / BF_3•OEt_2 gave a complex mixture of products (similar to the outcome with **10**), reaction of **18** under the same conditions gave the 4-azido-D-rhamnoside **19** in a 59% yield. Proof that epoxide opening had occurred via nucleophilic attack at C-4, resulting in the D-rhamnoside **19**, was obtained from examination of the ^{1}H NMR data. In particular, the magnitude of the coupling between H-4 and H-3 (J = 9.6 Hz) is consistent with a *trans*-diaxial coupling, whilst H-3 also shows a coupling to an exchangeable OH proton, clearly indicating that the newly formed hydroxy group from epoxide opening is attached to C-3.



10 R = H
18 R = Bz
17 R = H
19 R = Bz

Scheme 3. Reagents and conditions: i) $TMSN_3$, BF_3•OEt_2, rt, 1 h; ii) BzCl, pyridine, rt, 98%.

Having shown that we could successfully generate 4-azido *manno*-configured D-rhamnosides from 3,4-anhydro compounds such as **10** and **18**, we returned to our original strategy involving direct displacement of the C-4 triflate group in **9**, with a view to generating C-4 modified sugars with a *talo*-configuration (i.e. an axial C-4 substituent). Our original experiments had shown that the 3,4-anhydro derivative **10** formed quite readily from the 4-triflate **9**, being present (by T.L.C. analysis) in the reaction mixture even after a few minutes. We therefore reasoned that lowering the reaction temperature may limit the formation of **10**. Accordingly, treatment of **9** with NaN_3 in DMF at 0 °C for 30 minutes resulted in a mixture of two products with similar mobility on silica gel. To assist with separation of these two components, the crude reaction mixture was acetylated prior to chromatographic purification. In that way the desired 4-azido *talo*-configured derivative **20** was isolated in a respectable 62% yield (based on **9)** together with the 3,4-anhydro derivative **12** (35%) (Scheme 4).



9 **20** **12**

Scheme 4. Reagents and conditions: i) NaN_3, DMF, 0 °C, 30 min; (ii) Ac_2O, pyridine, 0 °C to rt, 15 h.

At this stage we have not been able to prevent completely the formation of the 3,4-anhydro derivative **10**, but our experiments have shown that milder conditions reduce substantially the proportion of 3,4-anhydro sugar being formed. Further studies in this regard will be reported in due course.

In conclusion, our four step synthesis of D-rhamnose from D-mannose represents the most efficient route for preparing D-

rhamnose reported to date. Importantly, the type of chemistry employed means that the four steps can be routinely carried out on a large scale, making this an attractive route for those requiring multi-gram quantities of this valuable 6-deoxy sugar. Additionally, our syntheses of the 4-azido rhamnoside **19** and the 4-azido taloside **20** are important, since these compounds have obvious application as building blocks in studies aimed at generating novel compounds for developing conjugate vaccines or as probes for carbohydrate-binding proteins associated with various bacterial virulence factors.

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References and notes

1. (a) Holst, O.; Molinaro, A. *Microbial Glycobiology: Structures, Relevance and Applications*, Moran, A. P. (ed), Academic Press, London, 2009. (b) Lukácová, M.; Barák, I.; Kazár, J. *Clin. Microbiol. Infect.* **2008**, *14*, 200-206. (c) Pier, G. B. *Int. J. Med. Microbiol.* **2007**, *297*, 277-295. (d) Schweda, E. K.; Richards, J. C.; Hood, D. W.; Moxon, E. R. *Int. J. Med. Microbiol.* **2007**, *297*, 297-306. (e) Silipo, A.; Erbs, G.; Shinya, T.; Dow, J. M.; Parrilli, M.; Lanzetta, R.; Shibuya, N.; Newman, M.-A.; Molinaro, A. *Glycobiology* **2010**, *20*, 406-419. (f) Erbs, G.; Jensen, T. T.; Silipo, A.; Grant, W.; Dow, J. M.; Molinaro, A.; Parrilli, M.; Newman, M.-A. *Microbes Infect.* **2008**, *10*, 571-574. (g) Silipo, A.; Molinaro, A.; Sturiale, L.; Dow, J. M.; Erbs, G.; Lanzetta, R.; Newman, M.-A.; Parrilli, M. *J. Biol. Chem.* **2005**, *280*, 33660-33668.
2. (a) Lerouge, I.; Vanderleyden, J. *FEMS Microbiol. Rev.* **2002**, *26*, 17-47. (b) Lukacova, M.; Barak, I.; Kazar, J. *Clin. Microbiol. Infect.* **2008**, *14*, 200-206. (c) Amano, K.-i. *Trends Glycosci. Glycotechnol.* **2002**, *14*, 105-114. (d) Preston, A.; Mandrell, R. E.; Gibson, B. W.; Apicella, M. A. *Crit. Rev. Microbiol.* **1996**, *22*, 139-180.
3. (a) Holst, J.; Martin, D.; Arnold, R.; Huergo, C. C.; Oster, P.; O'Hallahan, J.; Rosenqvist, E. *Vaccine* **2009**, *27*, B3-B12. (b) Schild, S.; Nelson, E. J.; Camilli, A. *Infect. Immun.* **2008**, *76*, 4554-4563. (c) Ellis, T. N.; Kuehn, M. J. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 81-94.
4. (a) Kocharova, N. A.; Katzenellenbogen, E.; Zatonsky, G. V.; Gamian, A.; Brzozowska, E.; Shashkov, A. S.; Knirel, Y. A. *Carbohydr. Res.* **2010**, *345*, 2571-2573. (b) Karapetyan, G.; Kaczynski, Z.; Iacobellis, N. S.; Evidente, A.; Holst, O. *Carbohydr. Res.* **2006**, *341*, 930-934. (c) Cimmino, A.; Marchi, G.; Surico, G.; Hanuszkiewicz, A.; Evidente, A.; Holst, O. *Carbohydr. Res.* **2008**, *343*, 392-396. (d) Comegna, D.; Bedini, E.; Parrilli, M. *Tetrahedron* **2008**, *64*, 3381-3391. (e) Winn, A. M.; Wilkinson, S. G. *Carbohydr. Res.* **1996**, *294*, 109-115. (f) Molinaro, A.; Silipo, A.; Lanzetta, R.; Newman, M-A.; Maxwell Dow, J.; Parrilli, M. *Carbohydr. Res.* **2003**, *338*, 277-281. (g) Yokota, S.; Kaya, S.; Sawada, S.; Kawamura, T.; Araki, Y.; Ito, E. *Eur. J. Biochem.* **1987**, *167*, 203-209. (h) Kocharova, N. A.; Knirel, Y. A.; Widmalm, G.; Jansson, P.-E.; Moran, A. P. *Biochemistry* **2000**, *39*, 4755-4760.
5. Daubenspeck, J. M.; Zeng, H.; Chen, P.; Dong, S.; Steichen, C. T.; Krishna, N. R.; Pritchard, D. G.; Turnbough, Jr. C. L. *J. Biol. Chem.* **2004**, *279*, 30945-30953.
6. (a) Zdorovenko, E. L.; Valueva, O. A.; Kachala, V. V.; Shashkov, A. S.; Kocharova, N. A.; Knirel, Y. A.; Kutkowska, J.; Turska-Szewczuk, A.; Urbanik-Sypniewska, T.; Choma, A.; Russa, R. *Carbohydr. Res.* **2009**, *344*, 2519-2527. (b) Cimmino, A.; Marchi, G.; Surico, G.; Hanuszkiewicz, A.; Evidente, A.; Holst, O. *Carbohydr. Res.* **2008**, *343*, 392-396. (c) Karapetyan, G.; Kaczynski, Z.; Iacobellis, N. S.; Evidente, A.; Holst, O. *Carbohydr. Res.* **2006**, *341*, 930-934.
7. (a) Tsvetkov, Y. E., Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1989**, *193*, 75-90. (b) Ramm, M.; Lobe, M.; Hamburger, M. *Carbohydr. Res.* **2003**, *338*, 109-112. (c) Bedini, E.; Carabellese, A.; Corsaro, M. M.; De Castro, C.; Parrilli, M. *Carbohydr. Res.* **2004**, *339*, 1907-1915. (d) Bedini, E.; Carabellese, A.; Barone, G.; Parrilli, M. *J. Org. Chem.* **2005**, *70*, 8064-8070. (e) Ley, S. V.; Owen, D. R.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2805-2806. (f) Zou, W.; Sen, A. K.; Szarek, W. A.; MacLean, D. B. *Can. J. Chem.* **1993**, *71*, 2194-2200. (g) Crich, D.; Bowers, A. A. *Org. Lett.* **2006**, *8*, 4327-4330. Crich, D.; Li, L. *J. Org. Chem.* **2009**, *74*, 773-781.
8. Dhénin, S. G. Y.; Moreau, V.; Morel, N.; Nevers, M.-C.; Volland H.; Créminon, C.; Djedaïni-Pilard, F. *Carbohydr. Res.* **2008**, *343*, 2101-2110.
9. Bundle, D. R.; Gerken, M.; Peters, T. *Carbohydr. Res.* **1988**, *174*, 239-251.
10. Dhénin, S. G. Y.; Moreau, V.; Nevers, M.-C.; Créminon, C.; Djedaïni-Pilard, F. *Org. Biomol. Chem.* **2009**, *7*, 5184-5199.
11. Fauré, R.; Shiao, T. C.; Damerval, S.; Roy, R. *Tetrahedron Lett.* **2007**, *48*, 2385-2388.
12. Winnik, F. M.; Carver, J. P.; Krepinsky, J. J. *J. Org. Chem.* **1982**, *47*, 2701-2707.
13. Kihlberg, J.; Bundle, D. R. *Carbohydr. Res.* **1991**, *216*, 67-78.
14. Werz, D. B.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6315-6318.
15. 6-Deoxy-D-talosides have been found in some pathogenic bacteria, see for example: (a) Forsberg, L. S.; Carlson, R. W. *J. Biol. Chem.* **2008**, *283*, 16037-16050. (b) Zähringer, U.; Rettenmaier, H.; Moll, H.; Senchenkova, S. N.; Knirel, Y. A. *Carbohydr. Res.* **1997**, *300*, 143-151. (c) Perry, M. B.; Maclean, L. M.; Brisson, J.-R.; Wilson, M. E. *Eur. J. Biochem.* **1996**, *242*, 682-688. (d) Shibuya, N.; Amano, K.; Azuma, J.-i.; Nishihara, T.; Kitamura, Y.; Noguchi, T.; Koga, T. *J. Biol. Chem.* **1991**, *266*, 16318-16323.
16. Hanessian, S. *Chem. Commun.* **1966**, 796-798.
17. Stevens, C. L.; Glinski, R. P.; Taylor, K. G.; Blumbergs, P.; Sirokman, F. *J. Am. Chem. Soc.* **1966**, *88*, 2073-2074.
18. Capon, B. *Chem. Rev.* **1969**, *69*, 407-498.
19. Banaszek, A.; Zaitsev, V. *Tetrahedron: Asymmetry* **2004**, *15*, 299-306.
20. Tsvetkov, Y. E.; Shashkov, A. S.; Knirel, Y. A.; Zähringer, U. *Carbohydr. Res.* **2001**, *335*, 221-243.
21. Stevens, C. L.; Glinski, R. P.; Taylor, K. G.; Blumbergs, P.; Gupta, S. K. *J. Am. Chem. Soc.* **1970**, *92*, 3160-3168.
22. Cicero, D.; Varela, O.; de Lederkremer, R. M. *Carbohydr. Res.* **1991**, *211*, 295-308.
23. Richardson, A. C. *Carbohydr. Res.* **1969**, *10*, 395-402.
24. Banaszek, A.; Janisz, B. *Tetrahedron: Asymmetry* **2000**, *11*, 4693-4700.
25. Janairo, G.; Kowollik, W.; Voelter, W. *Liebigs Ann. Chem.* **1987**, 165-167.
26. Popsavin, V.; Benedekovic, G.; Popsavin, M.; Sreco, B.; Djokovic, D. *Carbohydr. Res.* **2005**, *340*, 1866-1871.
27. Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343-345.
28. (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557-1560. (b) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599-602.

Supplementary Material

Full experimental details and spectroscopic characterization of all compounds is provided, along with copies of ^{1}H NMR data of several key compounds.