Tetrahedron: *Asymmetry* 22 (2011) 609–612

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

1-*C*-Alkyl imino-D-xylitol and -L-arabinitol derivatives obtained via nucleophilic addition to pentose-derived *N*-*tert*-butanesulfinyl imines: sugar- versus chiral auxiliary-induced stereoselectivity

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ARTICLE INFO

Article history:
Received 14 February 2011
Accepted 28 February 2011
Available online 12 April 2011

ABSTRACT

The stereoselective synthesis of 1-*C*-alkyl iminosugars in the D-*xylo* and L-*arabino* series as potential drugs for the treatment of lysosomal diseases has been achieved. The key step involves nucleophilic addition to pentodialdofuranose-derived imines generated using enantiopure *tert*-butanesulfinamide. Depending on the pentofuranose configuration and structure, the stereoselectivity of this reaction was found to be controlled either by the sugar moiety or by the stereogenic sulfur center.

1. Introduction

Recently, pharmacological chaperone therapy (PCT)[1] has emerged as a promising therapeutic option for the treatment of glycosphingolipid lysosomal storage disorders.[2,3] This small group of a dozen inherited diseases, also known as glycosphingolipidoses, are characterized by the deficiency of glycosidases involved in the catabolism of glycosphingolipids in the lysosome. The chaperone therapy is based on the ability of competitive inhibitors to enhance the residual hydrolytic activity of the mutant enzyme at sub-inhibitory concentrations.[1] Reversible competitive inhibitors are believed to induce or stabilize the proper conformation of the defective enzyme, thus preventing its degradation by the 'quality control' mechanism in the endoplasmic reticulum.[4] The normal trafficking to lysosomes of the mutant enzyme, which is still catalytically active, is restored and the residual enzyme activity is consequently enhanced in these organelles. Most of the pharmacological chaperones identified, to date, for the treatment of glycosphingolipidoses are iminosugars. Isofagomine (Plicera™) and 1-deoxygalactonojirimycin (Amigal™) **1** are currently being evaluated in clinical trials for the treatment of Gaucher and Fabry diseases, respectively (Fig. 1).[5] In a search for a chaperone-based therapy for glycosphingolipidoses,[6,7] we have recently identified α-1-*C*-nonyl-iminoxylitol **2** (α-C_9-DIX, Fig. 1), as an efficient pharmacological chaperone for the treatment of Gaucher disease: this compound is able to increase, by a factor of ~2, the residual cellular activity of β-glucocerebrosidase (GCase) in N370S fibroblasts from Gaucher patients at a nanomolar sub-inhibitory concentration (10 nM).[7] Moreover, α-C_9-DIX **2** is highly selective and displays no inhibition toward α-glucosidases, including lysosomal and intestinal α-glucosidases.

2. Results and discussion

The identification of α-1-*C*-alkyl-iminoxylitol was reached by way of structure–activity relationship studies taking *N*-alkyl-1-deoxynojirimycin (DNJ) derivatives, such as **3**, as a starting point for optimization (Fig. 1). This provided the basis for a new paradigm in the design of highly selective glycolipid hydrolases inhibitors: removal of the 5-CH_2OH group of *N*-butyl-DNJ and a shift of the alkyl chain from the endocyclic nitrogen atom to C-1 in the α-position lead to selective nM inhibitors of human GCase. Based on these results, our first objective was to extend the scope of this structural modification to inhibitors of other lysosomal glycosidases. Our prime target was β-galactocerebrosidase, which cleaves βGalCer, and the mutations of which are at the origin of Krabbe's disease (globoid cell leukodystrophy).[8] α-1-*C*-Alkyl-imino-L-arabinitols mimic the *galacto* configuration of the substrate and could therefore be powerful inhibitors of this enzyme and thus be useful as pharmacological chaperones.[9] In addition, this family of compounds could also have a favorable effect on other lysosomal glycosidases such as α-galactosidase A (Fabry disease) or β-galactosidase (G_{M1}-gangliosidosis). It is important to note that no treatment is currently available for Krabbe's disease. In this context, we designed synthetic strategies toward 1-*C*-alkyl-iminosugars in the L-*arabino* series to target Krabbe's disease, and in the D-*xylo* series to improve our initial synthetic sequence.[7] These syntheses hinged on nucleophilic addition to pentodialdofuranose-derived

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doi:10.1016/j.tetasy.2011.02.024

N-tert-butanesulfinyl imines (Ellman's imines). Ellman's chiral auxiliary[10] was expected to provide stereocontrol in the key imine chain extension step, which controls the α- versus β-configuration at the pseudo-anomeric center in the final product. Furthermore, the addition of Grignard reagents to *N-tert*-butanesulfinyl imines proceeds generally very efficiently in good yields and high diastereoselectivity.[10,11]

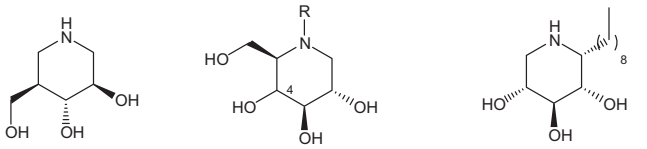
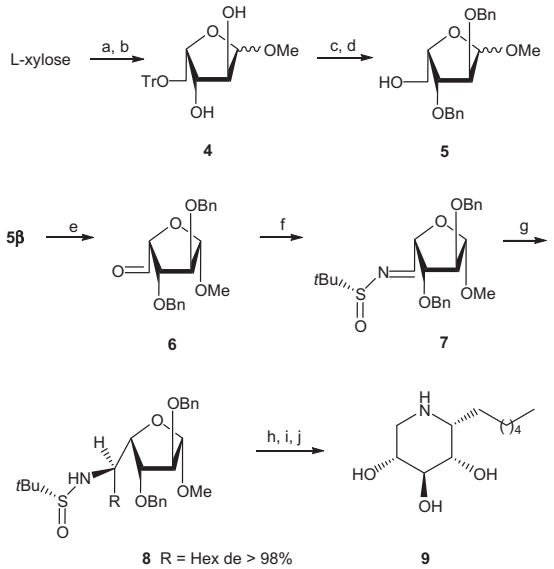


Figure 1.

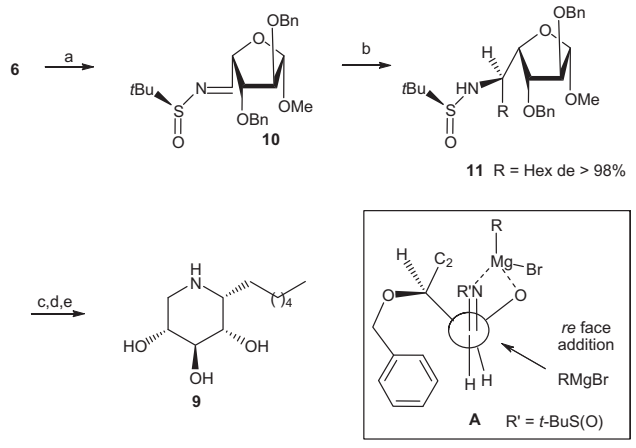
The synthesis of the C-alkylated iminoxylitols began with the improved preparation of aldehyde **6**, by furanoside formation,[12] tritylation at the primary position, benzylation, detritylation and Dess–Martin oxidation (Scheme 1).[13] At the stage of **5**, the anomers were separated and the synthesis continued with the major one **5β**. Condensation of **6** with (*R*)-*tert*-butanesulfinamide in dry dichloromethane in the presence of anhydrous $CuSO_4$ afforded imine **7**. The nucleophilic addition of hexylmagnesium bromide to this imine provided the expected amine **8** as a single diastereoisomer in 73% yield. It is noteworthy that similar reactions performed with less reactive L-xylose-derived *N*-benzyl imines led to much lower yields.[7] The configuration of the newly created stereocenter was unambiguously established to be (*R*) at the stage of the piperidine products. The formation of the piperidine ring via intramolecular reductive amination of the unmasked aminoxylose derived from **8** proved more difficult. Removal of the sulfinyl group was realized using methanolic HCl. Hydrolysis of the glycosidic bond, intramolecular reductive amination and cleavage of the benzyl groups were performed in a one-pot process by treatment of **8** with aqueous HCl in 1,4-dioxane followed by hydrogenolysis. Following this procedure, α-C_6-DIX **9** was obtained in 28% overall yield from **8**. The one-pot process was particularly difficult to optimize, which was in contrast to our observations in the sorbofuranose series.[14] This may be explained by the relative instability of the intermediate cyclic hemiaminal under aqueous acidic conditions.[15] The influence of Ellman's chiral auxiliary on the stereochemical outcome of the imine chain extension step was evaluated by performing the same synthetic sequence using (*S*)-*tert*-butanesulfinamide (Scheme 2). The addition of hexylmagnesium bromide to **10**, the epimer of imine **7**, was again found to proceed in good yield and high diastereoselectivity from the *re* face of the imine **10**. This indicated that the stereoselectivity of the addition step is likely to be controlled by the sugar moiety and is independent of the configuration at the stereogenic sulfur center.

The high stereoselectivity of the addition of the organometallic species to the *re* face of imines **7** and **10** can be rationalized by the chelated intermediate **A** involving as ligands the nitrogen atom of the *N*-sulfinyl imine and the ring oxygen atom of the xylofuranose moiety (Scheme 2).[16] In furanoid systems, it is well established that the endocyclic oxygen acts as a coordinating Lewis base in the additions of organometallic reagents to pentodialdo-furanose derivatives.[17] Such chelation seems to counterbalance the possible chair-transition state intermediate **B** (Fig. 2) proposed by Ellman in which the magnesium atom of the Grignard reagent is chelated to the oxygen atom of the sulfinyl imine.[10] Based on these results, we decided to extend the synthesis to the 1-*C*-alkyl-imino-L-arabinitols using racemic *tert*-butanesulfinamide (Scheme 3).

In addition, the L-*lyxo* precursor **14** was designed to carry a benzyl glycoside to facilitate the cleavage of this group during the one-pot intramolecular reductive amination step. The synthesis of this intermediate from commercially available D-gulono-γ-lactone is based on the optimization of known reaction sequences (Scheme 3).[18] The reaction of D-gulonolactone with an excess of acetone under acidic conditions followed by treatment with DIBAL-H afforded hemiacetal **12** which was converted into a separable mixture of the two anomers of benzyl furanosides **13**. The synthetic sequence was continued with the major anomer **13β**. Regioselective deprotection of the 5,6-*O*-isopropylidene acetal and subsequent oxidative cleavage[19] of the resulting diol provided



Scheme 1. Reagents and conditions: (a) HCl (33 mM), MeOH, reflux; (b) TrCl (1.2 equiv), pyridine, reflux, 68%; (c) NaH (4 equiv), BnBr (4 equiv), DMF, 0 °C to rt, 69%; (d) 80% AcOH, 70 °C, 80%; (e) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 0 °C to rt, quant.; (f) (*R*)-*tert*-butanesulfinamide (1.2 equiv), anhyd $CuSO_4$, CH_2Cl_2, 48%; (g) hexylmagnesium bromide (4 equiv), toluene, −78 °C to rt, 73%; (h) HCl (3 mM), MeOH, rt, quant.; (i) 0.4 M HCl/dioxane (1/1), 75 °C; (j) H_2, 10% Pd/C, rt, 28% (two steps).



Scheme 2. Reagents and conditions: (a) (*S*)-*tert*-butanesulfinamide (1.2 equiv), anhyd $CuSO_4$, CH_2Cl_2, 66%; (b) hexylmagnesium bromide (4 equiv), toluene, −78 °C to rt, 53%; (c) HCl (3 mM), MeOH, rt, quant.; (d) 0.4 M HCl/dioxane (1/1), 75 °C; (e) H_2, 10% Pd/C, rt, 30% (two steps).

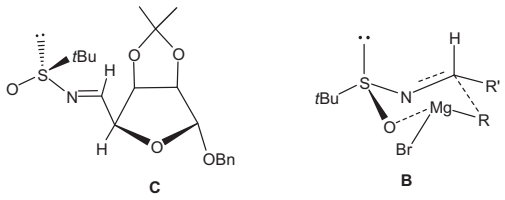
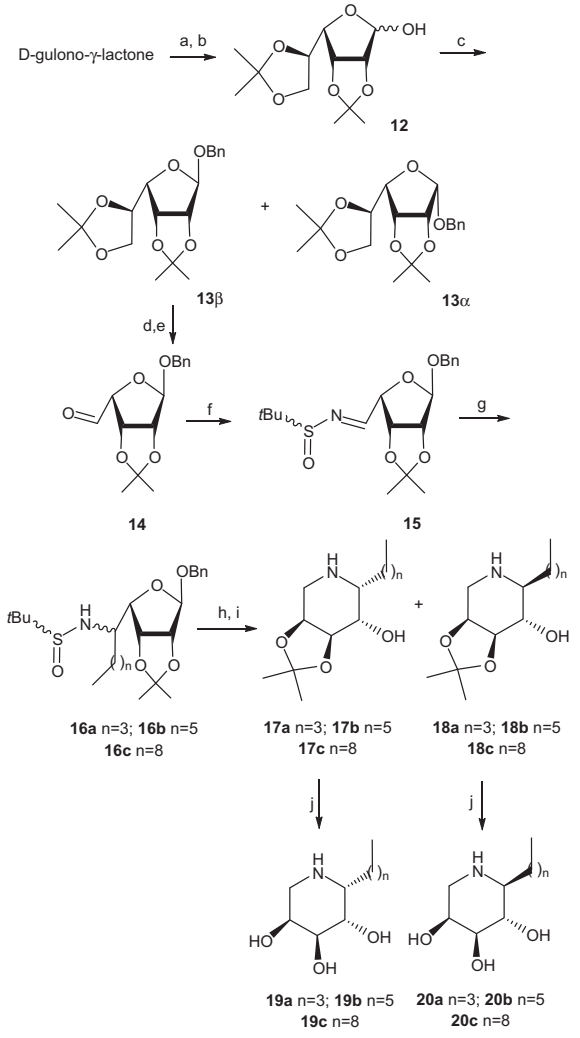
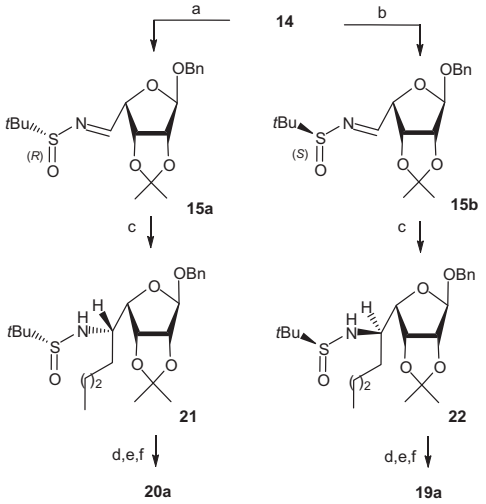


Figure 2.



Scheme 3. Reagents and conditions: (a) acetone, H_2SO_4, anhyd $CuSO_4$, rt, 97%; (b) DIBAL-H (3 equiv), CH_2Cl_2, −78 °C, 86%; (c) NaH (2 equiv), BnBr (2 equiv), TBAI (cat.), DMF, 76% (**13β**), 16% (**13α**); (d) 70% AcOH, rt, 94%; (e) $NaIO_4$ on SiO_2, CH_2Cl_2, 0 °C, quant.; (f) *tert*-butanesulfinamide (1.2 equiv), anhyd $CuSO_4$, CH_2Cl_2, 80%; (g) alkylmagnesium bromide (4 equiv), toluene, −78 °C to rt, 76% (**16a**), 73% (**16b**), 64% (**16c**); (h) HCl (3 mM), MeOH, rt; (i) H_2, 10% Pd/C, *i*PrOH–AcOH (100/1), rt, 46% (**17a**), 19% (**18a**), 39% (**17b**), 18% (**18b**), 49% (**17c**), 20% (**18c**) (two steps); (j) Dowex 50WX8 (H^+), dioxane/H_2O (1/1), rt, quant.

aldehyde **14** in 94% yield over two steps. Condensation of **14** with racemic *tert*-butanesulfinamide afforded the key imine intermediate **15**. The nucleophilic addition of various organomagnesium reagents to sulfinyl imine **15** proceeded with acceptable to good yields. However, in contrast to the results obtained with sulfinyl imines **7** and **10**, a significant loss in stereoselectivity was observed.[20] The one-pot deprotection (*tert*-butanesulfinyl and benzyl groups) and intramolecular reductive amination were performed on a mixture of diastereoisomers **16** using hydrogen over palladium on carbon under mild acidic conditions (Scheme 3). This one-pot process was found to be quite efficient as 1-*C*-alkyl iminosugars **17** and **18** were obtained in 57–69% yields (for **17** and **18**). The pseudo-α- and -β-epimers were separated by flash chromatography and deprotected in quantitative yields to afford 1-*C*-alkyl-imino-L-arabinitols **19** and **20**. Having optimized the key one-pot process of our strategy, we attempted to rationalize the low diastereoselectivity observed for the addition to sulfinyl imine **15**. The loss of stereocontrol observed at C5 suggested that, contrary to the D-*xylo* series, the stereoselectivity of the addition step was not controlled by the sugar moiety, but might be dependent on the configuration at the stereogenic sulfur center. To validate this hypothesis, we studied the nucleophilic addition to the (S_R)- and (S_S)-epimers of sulfinyl imines **15a** and **15b** (Scheme 4). The reaction performed with 4 equiv of butylmagnesium bromide was found to be highly diastereoselective; the stereoselectivity was thus controlled by the configuration at the sulfur center. Sulfinyl amines **21** and **22** were converted to α- and β-1-*C*-butyl-imino-L-arabinitols **20a** and **19a**, respectively, according to the synthetic sequence described in Scheme 4. The marked difference of stereocontrol in the L-*xylo* and L-*lyxo* series may be explained as follows: the results obtained with xylofuranose-derived imines **8** and **10** clearly indicated that the chelation of the magnesium ions to the nitrogen atom of the imine and the endocyclic ring oxygen atom as in intermediate **A** is favored over the chair-transition state intermediate **B** involving the oxygen atom of the sulfinyl imine as the ligand (Fig. 2).



Scheme 4. Reagents and conditions: (a) (*R*)-*tert*-butanesulfinamide (1.2 equiv), anhyd $CuSO_4$, CH_2Cl_2, 74%; (b) (*S*)-*tert*-butanesulfinamide (1.2 equiv), anhyd $CuSO_4$, CH_2Cl_2, 77%; (c) butylmagnesium bromide (4 equiv), toluene, −78 °C to rt, 66% **21**, 78% **22**; (d) HCl (3 mM), MeOH, rt; (e) H_2, 10% Pd/C, *i*PrOH/AcOH (100/1), rt; (f) Dowex 50WX8 (H^+), dioxane/H_2O (1/1), rt, 83% **19a**, 69% **20a** for the three steps.

In the L-*lyxo* series, the 2,3-*O*-isopropylidene acetal induces strong conformational constraints and steric effects. As a result, the conformation of the imine around the sp^2–sp^3 bond required for chelation becomes less favorable, and the system adopts an 'open' conformation such as **C**, which favors sulfinyl imine-induced stereocontrol by a transition state as illustrated in **B**.

3. Conclusion

In conclusion, we have developed an efficient, stereocontrolled access to α- or β-1-*C*-alkyl-imino-L-arabinitols. The key step involves the nucleophilic addition to pentose-derived imines generated from enantiopure *tert*-butanesulfinamide. A comparison with results obtained in the D-*xylo* series indicated that, depending on

the pentose structure, the stereoselectivity of the addition step was controlled either by the sugar moiety or by the configuration at the stereogenic sulfur center. The evaluation of these iminosugars as chaperones for the treatment of glycosphingolipidoses is currently in progress.

Acknowledgments

Financial support of this study by grants from ANR (07MRAR-015-01), CNRS and the French Department of Research is gratefully acknowledged. One of us (F.O.) thanks the CNRS and Région Centre for a fellowship.

References

1. (a) Fan, J.-Q. In *Iminosugars: from Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, 2007; pp 225–247; (b) Fan, J.-Q. *Trends Pharmacol. Sci.* **2003**, *24*, 355; (c) Fan, J.-Q. *Biol. Chem.* **2008**, *389*, 1; (d) Yu, Z.; Sawker, A. R.; Kelly, J. W. *FEBS J.* **2007**, *274*, 4944; (e) Suzuki, Y.; Ogawa, S.; Sakakibara, Y. *Perspect. Med. Chem.* **2009**, *3*, 7; (f) Parenti, G. *EMBO Mol. Med.* **2009**, *1*, 268.
2. A special issue of *Philosophical Transactions: Biological Sciences* has been devoted to the glycolipids in cell biology: *Philos. Trans. R. Soc. London, Ser. B* **2003**, *358*, 845.
3. (a) Winchester, B.; Vellodi, A.; Young, E. *Biochem. Soc. Trans.* **2000**, *28*, 150; (b) Gregersen, N. *J. Inherit. Metab. Dis.* **2006**, *29*, 456; (c) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532; (d) Neufeld, E. F. *Annu. Rev. Biochem.* **1991**, *60*, 257; (e) Kolter, T.; Sandhoff, K. *Biochim. Biophys. Acta* **2006**, *1758*, 2057; (f) Raas-Rothschild, A.; Pankova-Kholmyansky, I.; Kacher, Y.; Futerman, A. H. *Glycoconjugate J.* **2004**, *21*, 295; (g) Wennekes, T.; van den Berg, R. J. B. H. N.; Boot, R. G.; van der Marel, G. A.; Overkleeft, H. S.; Aerts, J. M. F. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8848.
4. (a) Yam, G. H.-F.; Zuber, C.; Roth, J. *FASEB J.* **2005**, *19*, 12; (b) Kornhaber, G. J.; Tropak, M. B.; Maegawa, G. H.; Tuske, S. J.; Coales, S. J.; Mahuran, D. J.; Hamuro, Y. *ChemBioChem* **2008**, *9*, 2643; (c) Ulloa-Aguirre, A.; Janovick, J. A.; Brothers, S. P.; Conn, P. M. *Traffic* **2004**, *5*, 821.
5. Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discovery Today* **2011**, *16*, 107.
6. See for example: (a) Yu, L.; Ikeda, K.; Kato, A.; Adachi, I.; Godin, G.; Compain, P.; Martin, O. R.; Asano, N. *Bioorg. Med. Chem.* **2006**, *14*, 7736; (b) Boucheron, C.; Toumieux, S.; Compain, P.; Martin, O. R.; Ikeda, K.; Asano, N. *Carbohydr. Res.* **2007**, *342*, 1960; (c) Schönemann, W.; Gallienne, E.; Compain, P.; Ikeda, K.; Asano, N.; Martin, O. R. *Bioorg. Med. Chem.* **2010**, *18*, 2645.
7. Compain, P.; Martin, O. R.; Boucheron, C.; Godin, G.; Yu, L.; Ikeda, K.; Asano, N. *ChemBioChem* **2006**, *7*, 1356.
8. (a) Suzuki, K.; Suzuki, Y. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *66*, 302; (b) Svennerholm, L.; Mansson, J. E. *J. Lipid Res.* **1980**, *21*, 53.
9. Lee, W. C.; Kang, D.; Causevic, E.; Herdt, A. R.; Eckman, E. A.; Eckman, C. B. *J. Neurosci.* **2010**, *30*, 5489.
10. For a review see: Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
11. Charette, A. B. In *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010; pp 1–49.
12. Augestad, I.; Berner, E. *Acta Chem. Scand.* **1954**, *8*, 251.
13. Cuzzupe, A. N.; Di Florio, R.; Rizzacasa, M. A. *J. Org. Chem.* **2002**, *67*, 4392.
14. Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960.
15. Bordier, A.; Compain, P.; Martin, O. R.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 47.
16. For related results in pyranoid systems see: Risseeuw, M. D. P.; Mazurek, J.; van Langenvelde, A.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Org. Biomol. Chem.* **2007**, *5*, 2311.
17. (a) Inch, T. D. *Adv. Carbohydr. Chem. Biochem.* **1972**, *27*, 191; (b) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.
18. Buchanan, J. G.; Moorhouse, S. J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2258; (b) Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, *59*, 572; (c) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3994; (d) Chen, F.-E.; Zhao, J.-F.; Xiong, F.-J.; Xie, B.; Zhang, P. *Carbohydr. Res.* **2007**, *342*, 2461.
19. Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
20. The diastereomeric excess of the addition reaction could not be precisely determined by NMR spectra at this stage. In our hands, the mixture of diastereoisomers **16** proved difficult to separate by flash chromatography on silica gel.