ORGANIC LETTERS

2005
Vol. 7, No. 21
4709−4712

Synthesis of α-D-Idoseptanosyl Glycosides Using an *S*-Phenyl Septanoside Donor

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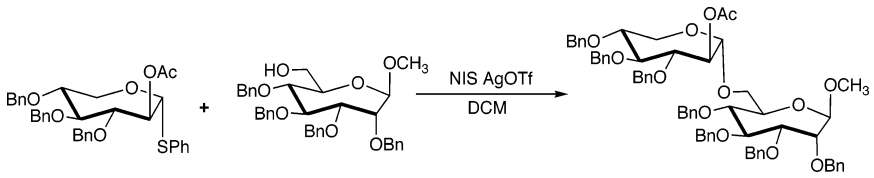
Received August 8, 2005

ABSTRACT



An *S*-phenyl α-D-idoseptanoside donor was used in the selective preparation of a series of α-D-idoseptanosyl glycosides. Glycosylation of a methyl *β*-D-*glycero*-D-guloseptanoside acceptor with the new donor constituted the first synthesis of a septanose disaccharide.

A growing appreciation for the role of carbohydrates in biological processes has spurred the development of analogues that can serve as tools for glycobiology.[1] We have been interested in utilizing seven-membered ring (septanose) carbohydrates as analogues of natural pyranose sugars for the investigation of protein−carbohydrate interactions.[2] Septanoses may be able to effectively adopt distorted conformations in glyco-enzyme binding sites[3] or be used to define new types of protein−carbohydrate interactions.[4] The synthesis and characterization of septanose carbohydrates, however, has received only limited attention relative to the naturally occurring furanose and pyranose ring forms.[5] A challenge central to the synthesis of any class of oligo- or polysaccharide is the formation of the glycosidic linkages between saccharide units.[6] Herein we report the efficient and selective synthesis of a variety of α-D-idoseptanosyl glycosides from an *S*-phenyl septanoside donor. The new donor was activated under mild conditions and formed α-septanosides in good yields. Glycosylation of a methyl septanoside acceptor using the new donor provided an α-1,7-linked diseptanoside; this is the first reported synthesis of a disaccharide containing a septanose residue at both the reducing and nonreducing end of the structure.

Previously, glycosylations using anomeric chlorides[7] or acyclic chloro-thioethyl acetals[8] as septanosyl donors were reported. Additionally, we have investigated the glycal-like reactivity of the D-xylose based oxepine **1**.[9] Epoxidation of **1**, using DMDO, formed the *β*-1,2-anhydroseptanose **2**,

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(1) (a) Gruner, S. A. W.; Locardi, E.; Lohof, W.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357. (c) Koeller, K. M.; Wong, C. H. *Nat. Biotech.* **2000**, *18*, 835.

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(3) (a) Martínez-Mayora, K.; Medina-Franco, J. L.; Marı̈, S.; Cañada, F. J.; Rodríguez-Garcia, E.; Vogel, P.; Li, H.; Blériot, Y.; Sinaÿ, P.; Jiménez-Barbero, J. *Eur. J. Org. Chem.* **2004**, 4119. (b) Li, H.; Blériot, Y.; Chantereau, C.; Mallet, J.-M.; Sollogoub, M.; Zhang, Y.; Rodríguez-Garcia, E.; Vogel, P.; Jiménez-Barbero, J.; Sinaÿ, P. *Org. Biomol. Chem.* **2004**, *2*, 1492. (c) Morís-Varas, F.; Qian, X.-H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647.

(4) (a) Benner, S. A.; Sismour, A. M. *Nat. Rev. Genet.* **2005**, *6*, 533. (b) Benner, S. A. *Nature* **2003**, *421*, 118.

(5) Pakulski, Z. *Pol. J. Chem.* **1996**, *70*, 667.

(6) (a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137. (b) Toshima, K.; Tatsuda, K. *Chem. Rev.* **1993**, *93*, 1503.

(7) Micheel, F.; Suckfüll, F. *Ann. Chim.* **1933**, *507*, 138.

(8) McAuliffe, J. C.; Hindsgaul, O. *Synlett* **1998**, 307.

(9) (a) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carbohydr. Res.* **2004**, *339*, 1163. (b) $^3J_{H1,H2}$ values of these 1,2-*trans* glycoside products were between 6.6 and 8.4 Hz.

10.1021/ol051912e CCC: $30.25
Published on Web 09/23/2005

which was reacted with nucleophiles to give septanosides such as **3** (Figure 1). Although this method was relatively

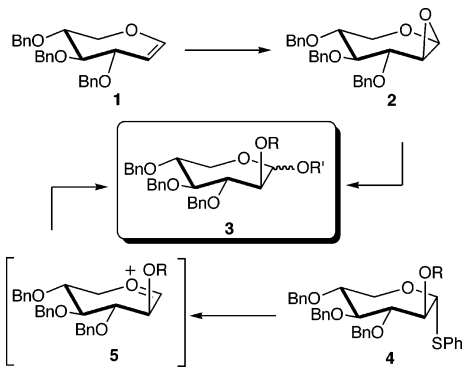
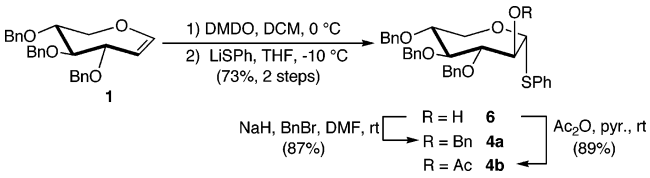


Figure 1. Glycosylation strategies for the preparation of septanosyl glycosides.

efficient for the preparation of simple (-OCH_3, -O*i*Pr) septanosides, with di-*O*-isopropylidene-α-D-galactose (**10**) as the acceptor only a modest yield (45%) of the pyranosyl septanoside resulted along with poor anomeric selectivity (3:2 α:*β*). At the outset of this investigation, we endeavored to improve the yield and selectivity of such glycosylations using more elaborate acceptors.

Several factors made *S*-phenyl α-D-idoseptanoside **4** (Figure 1) an attractive donor for the preparation of septanosyl glycosides. *S*-Phenyl septanosides would be analogous to the broadly utilitized *S*-phenyl pyranosides in "normal" glycosylation reactions. We reasoned that activation of the *S*-phenyl group under standard conditions would produce an oxonium such as **5** that could be attacked by a nucleophile to give septanosides such as **3**. Participatory protecting groups (R = Ac) on the C2 oxygen could also be utilized to enhance the selectivity for the formation of the α-septanoside. The preparation of **4** (Scheme 1) utilized

Scheme 1. Synthesis of **4**



oxepine **1** as a starting material. Epoxidation of **1** with DMDO and exposure to the lithium salt of thiophenol in THF gave *S*-phenyl septanoside **6** (73%) as reported.[9] The C2 alcohol of **6** was thereafter protected as either the benzyl ether (**4a**) or the acetate (**4b**) in 87% and 89% yields, respectively. Attempts at improving the yield of donors **4a** and **4b** from **1** by forming the thiophenyl septanoside and protecting C2 in a two-step, one-pot procedure were not successful.

Having established a synthetic route to *S*-phenyl septanosides **4a** and **4b**, we next explored their ability to serve as donors for glycosylation reactions. Activation using *N*-iodosuccinimide (NIS) and silver triflate in the presence of a series of alcohol acceptors **7**−**12** (Table 1) afforded the corresponding septanosides (**13**−**18**) in moderate to very good yields with a high degree of stereocontrol in the formation of the α-glycosides.[10] Table 1 collects information on the specific glycosylation reactions. The stereochemistry of the anomeric center was assigned on the basis of the similarity of the product C1 chemical shifts and $^3J_{H1,H2}$ coupling constants to our previously reported α-D-idoseptanosides.[9] In general, the donors **4a** and **4b** provided the product glycosides with similar efficiency, although the yields using **4b** were consistently lower than those with **4a**. Also, the activation[11] of **4a** occurred rapidly at −40 °C, whereas reactions using **4b** often were allowed to warm to −25 °C before activation was noted. These observations are consistent with a slight deactivation of donor **4b** due to the acetate group at C2.[12]

Simple alcohol acceptors such as **7** and **8** gave exclusively the corresponding α-glycosides in very good yields (entries 1−4). Peculiar among this group of reactions was the glycosylation of **7** using the acetate-protected donor **4b** (entry 2). The main product of this reaction (**13b**) was accompanied by a side product corresponding to the deacetylated glycoside in 14% yield.[13] This material most likely arises from a transesterification reaction between **13b** and the excess acceptor **7** that is present in the reaction mixture. Factors that likely contributed to the transesterification are (i) excess acceptor present in the glycosylations (2−3 equiv) and (ii) the higher reaction temperature relative to glycosylations involving **4a**. Donor **4b** was also used to glycosylate 4-*tert*-butylphenol (**9**) as acceptor to provide the aryl glycoside **15** (entry 5). Glycosylation of 2,6-dimethylphenol (not shown) with **4b** was unsuccessful, presumably as a result of steric hindrance of the phenolic hydroxyl group.

Readily available carbohydrate alcohols **10**−**12** were next investigated (entries 6−11). Di-*O*-isopropylidene galactose (**10**), a primary alcohol, gave a high yield of the α-septanoside product **16**. The preparation of this pyranosyl septanoside is a significant improvement on our previous oxidative glycosylation reaction[9] in terms of both yield (79% versus 45%) and selectivity (α only versus 3:2 α:*β*). Reactions with more hindered secondary alcohol groups on di-*O*-isopropylidene glucose (**11**) and methyl 2,3,6-tri-*O*-benzyl-D-glucoside (**12**) gave moderate yields of the corresponding glycosides **17** and **18**. The lower yields in these examples are attributed to steric congestion around the nucleophilic hydroxyl groups of the acceptors. Results for the glycosylation of **11** with either donor were unique in giving mixtures (α/*β*) of glycoside products. In fact, glycosylation of **11** with a donor

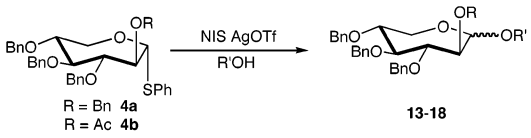
(10) (a) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155. (b) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *Org. Lett.* **2001**, *3*, 607.

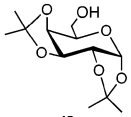
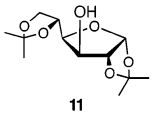
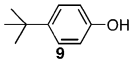
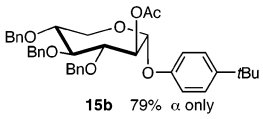
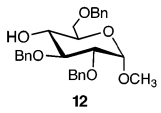
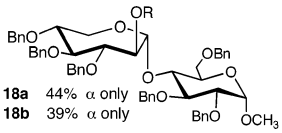
(11) Activation here was estimated by the disappearance of donor by TLC and color change (to magenta) of the reaction mixture.

(12) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275.

(13) NMR spectra of the material isolated are in Supporting Information.

Table 1. Glycosylations with *S*-Phenyl Septanosides **4a** and **4b**[a]



entry	donor	acceptor (R'OH)	product (yield, α/β)[b,c]	entry	donor	acceptor (R'OH)	product (yield, α/β)[b,c]
1 2	**4a** **4b**	1-decanol **7**	R = Bn **13a** 77% α only R = Ac **13b**[d] 60% α only	6 7	**4a** **4b**	 **10**	R = Bn **16a** 79% α only R = Ac **16b** 79% α only
3 4	**4a** **4b**	 **8**	R = Bn **14a** 77% α only R = Ac **14b** 71% α only	8 9	**4a** **4b**	 **11**	R = Bn **17a** 57% 10:1 R = Ac **17b** 55% 1:1
5	**4b**	 **9**	 **15b** 79% α only	10 11	**4a** **4b**	 **12**	 R = Bn **18a** 44% α only R = Ac **18b** 39% α only

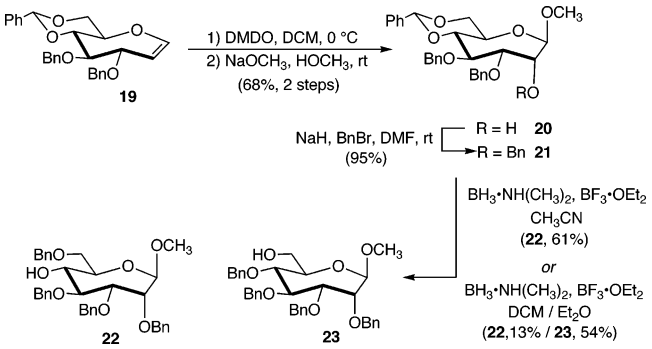
[a] Reaction conditions: *S*-phenyl glycoside **4a** or **4b** (0.1 mmol), alcohol (0.15−0.3 mmol), 4 Å molecular sieves, *N*-iodosuccinimide (0.13 mmol), and silver triflate (0.03 mmol) in 3 mL of CH_2Cl_2 for 30 min at −40 to −25 °C. [b] Characterization data is in Supporting Information. [c] Stereochemistry based on δ C1 and $^3J_{H1,H2}$. [d] 14% yield of **13b** lacking the C2 acetate was also recovered in this reaction.

lacking a participatory group at C2 (**4a**) was more selective (10:1 α:β) than with the acetate-protected donor **4b** (1:1). This result leaves open the question of the participatory nature of the C2 acetate group in this system and is further complicated by the low nucleophilicity of acceptor **11**. In total, the new donors are useful reagents for the selective preparation of a variety of novel α-septanosides.

Encouraged by these results, we undertook the synthesis of a disaccharide composed solely of septanose residues as an extended demonstration of the donating capability of *S*-phenyl septanosides. To the best of our knowledge, diseptanosides with a septanose at the reducing and nonreducing end have not been previously described in the literature.

Oxepine **19** served as a starting material for the preparation of methyl septanoside acceptors **22** and **23** (Scheme 2).

Scheme 2. Preparation of Septanoside Acceptors **22**/**23**



Epoxidation of **19** with DMDO was followed by attack with $NaOCH_3/CH_3OH$ to give the methyl β-septanoside **20** in 68% yield over two steps; the assignment of β-stereochemistry was based on the high selectivity observed in the epoxidation reaction,[14] S_N2-like opening of the α-1,2-anhydroseptanose, and comparison of the NMR data of the hydrogenolysis product of **20**, which was found to be that of the known methyl β-D-*glycero*-D-guloseptanoside.[15] Protection of the C2 hydroxyl group gave benzyl ether **21** (95%). Regioselective functionalization of 4,6-*O*-benzylidenes is precedented for pyranoses, and similar reaction conditions were utilized to open the 5,7-*O*-benzylidene ring of methyl septanoside **21**. Reduction of **21** with lithium aluminum hydride (LAH) in the presence of aluminum chloride in DCM/Et_2O gave a mixture of **22** (13%) and **23** (42%).[16] A slightly better yield was obtained using $BH_3{\cdot}NH(CH_3)_2$ as reductant with $BF_3{\cdot}Et_2O$ in DCM/Et_2O, giving **22** and **23** in 13% and 55%, respectively.[17,18] Changing the solvent to acetonitrile under these reaction conditions gave the C5 hydroxy material (**22**) in 61% yield.

(14) The parameters that govern the selectivity in epoxidation of carbohydrate-based oxepines is currently under investigation.

(15) DeMatteo, M.; Snyder, N. L.; Morton, M.; Baldisseri, D. M.; Hadad, C. M.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 24.

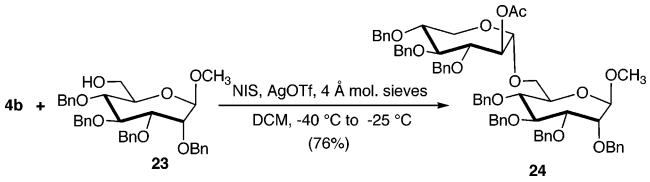
(16) Liptak, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1.

(17) (a) Fukase, K.; Fukase, Y.; Oikawa, M.; Liu, W.; Suda, Y.; Kusamoto, S. *Tetrahedron* **1998**, *54*, 4033. (b) Toone, E. J.; Debenham, S. S. *Tetrahedron: Asymmetry* **2000**, *11*, 384.

(18) Reduction of the glycosidic linkage under the $BH_3{\cdot}NH(CH_3)_2/BF_3{\cdot}OEt_2$ reaction conditions to form an acyclic methyl ether was also observed. NMR spectra of the product of this overeduction are provided in Supporting Information.

Methyl septanosides **22** and **23** were then tested as acceptors in glycosylations under the established reaction conditions. The inspiration for preparing diseptanosides was based on two major factors. First, we were interested in evaluating diseptanosides as ligands for carbohydrate binding proteins. Second, the synthesis of diseptanosides is a step toward the preparation of larger linear and branched oligoseptanosides. Attempts at glycosylation of **22** with either **4a** or **4b** to form the 1,5-linked diseptanoside were unsuccessful.[19] The inability to effect this glycosylation is a limitation and may be ascribed to poor nucleophilicity of the C5 hydroxyl group of **22**, similar to that of acceptor **12**. On the other hand, glycosylation of **23** with **4b** under the conditions established for the other acceptors gave the α-1,7-linked diseptanoside **24** (76%) (Scheme 3). The yield of this reaction

Scheme 3. Preparation of α-1,7-Linked Diseptanoside **24**



is comparable to the glycosylations using di-*O*-isopropylidene-α-D-galactose (**10**), the primary alcohol acceptor in the pyranose series (Table 1).

(19) No disaccharide product was observed in an attempted glycosylation of **22** using donor **4b** under NBS activation in dry DCM at room temperature.

In conclusion, we have introduced *S*-phenyl α-D-idoseptanoside (**4**) as a donor for septanose glycosylations. A number of alcohols were glycosylated, with **4** affording the corresponding idoseptanosides in good yields and high selectivity in forming the α-anomer. An α-1,7-linked diseptanoside (**24**) was synthesized from **4b** and methyl septanoside acceptor **23**. This is the first reported preparation of a disaccharide where both the reducing and nonreducing unit are composed of septanose carbohydrates and highlights the utility of the donor. On the basis of the general ability to transform oxepines into *S*-phenyl septanosides, we anticipate that a wide variety of septanosyl glycosides should be accessible by this strategy. Progress on these fronts will be reported in due course.

Acknowledgment. Financial support was provided by the Petroleum Research Fund administered by the American Chemical Society and the University of Connecticut.

Supporting Information Available: Complete crystallographic data for the structural analysis of oxepine **19** have been deposited in the Cambridge Crystallographic Data Centre (CCDC), no. 280201. Copies of this information may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44-1223-336033. Web: www.ccdc.cam.ac.uk/conts/retrieving/html. Email: deposit@ccdc.cam.ac.uk). General experimental procedures and characterization data for all compounds not previously reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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