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Intramolecular Benzyl Protection Delivery: A Practical Synthesis of DMDP and DGDP from D-Fructose

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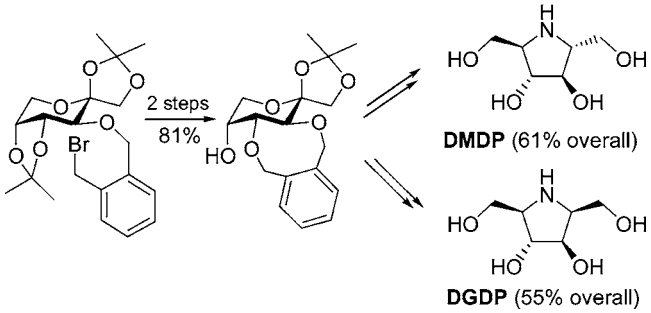
ABSTRACT



A two-step protection of 1,2-diols as the corresponding *o*-xylylene cyclic ethers, involving an intramolecular ring-closing O-benzylation reaction, has been developed to overcome the problems associated to regioselective benzylation reactions. The strategy has been applied to the high-yielding synthesis of the pyrrolidine glycosidase inhibitors DMDP and DGDP.

Benzyl ethers occupy a prominent position among the battery of hydroxyl protecting groups currently employed in organic chemistry. They can be introduced in high yield, remain stable under the acidic or basic conditions used during manipulation of other protecting groups such as esters, silyl ethers, carbamates, or acetals, and can be removed in a later step under mild conditions by catalytic hydrogenation. O-Benzylation of polyol systems generally proceeds, however, with low regioselectivity, which is a quite serious drawback frequently encountered in carbohydrate chemistry.[1,2] The preparation of the natural polyhydroxylated pyrrolidines 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **1**) and 2,5-dideoxy-2,5-imino-D-glucitol (DGDP, **2**) from D-fructose typically illustrates this limitation. Compounds **1** and **2** are potent inhibitors of several glycosidases[3] and have been used as starting materials for the preparation of other polyhydroxyalkaloids of the pyrrolizidine family.[4] A convenient synthetic strategy for accessing **1** and **2** has been

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(1) Regioselective benzylation of carbohydrate derivatives has been achieved, to a certain extent, via transient protection with silyl ether or stannylidene acetal groups. See, for example: (a) Lee, J.-C.; Chang, S.-W.; Liao, C.-C.; Chi, F.-C.; Chen, C.-S.; Wen, Y.-S.; Wangn, C.-C.; Kulkarni, S. S.; Puranik, R.; Liu, Y.-H.; Hung, S.-C. *Chem. Eur. J.* **2004**, *10*, 399. (b) Halila, S.; Benazza, M.; Demailly, G. *J. Carbohydr. Chem.* **2001**, *20*, 467.

(2) Some remarkable preparations of partially benzylated carbohydrate derivatives have been accomplished by an alternative strategy involving regioselective O-debenzylation. See, for example: (a) Bistri, O.; Sinaÿ, P.; Sollogoub, M. *Tetrahedron Lett.* **2005**, *46*, 7757. (b) Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sinaÿ, P. *Chem. Eur. J.* **2004**, *10*, 2960. (c) Roizel, B. C.; Cabianca, E.; Rollin, P.; Sinaÿ, P. *Tetrahedron* **2002**, *58*, 9579. (d) Pearce, A. J.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3610.

(3) Legler, G. In *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999; p 31.

(4) (a) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527. (b) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1465. (c) García-Moreno, M. I.; Rodríguez-Lucena, D.; Ortiz Mellet, C.; García Fernández, J. M. *J. Org. Chem.* **2004**, *69*, 3578.

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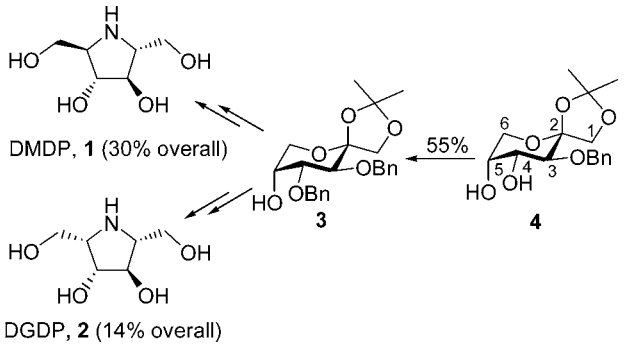
published that involves the 3,4-di-*O*-benzylated D-fructopyranose derivative **3** as a pivotal intermediate.[5−7] Although the hydroxyl group at position C-3 can be easily discriminated at an early stage in the reaction sequence, O-regioselective benzylation of the equatorial OH-4 in the presence of the axial OH-5 in the monobenzylated precursor **4** is troublesome, affording the desired vicinal di-*O*-benzyl ether in rather modest yield. Alternative preparations of **3** require multistep reaction sequences.[8] This handicap in the regioselective *O*-benzylation is largely responsible for the low overall yields in the preparation of **1** and **2** from **3** (30% and 14%, respectively; Scheme 1).

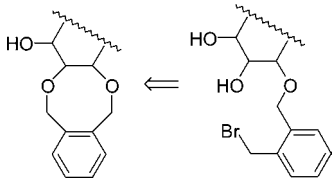
Scheme 1. Synthesis of DMDP and DGDP from Selectively Benzylated D-Fructose Derivatives[a]



[a] For reagents and conditions, see ref 5.

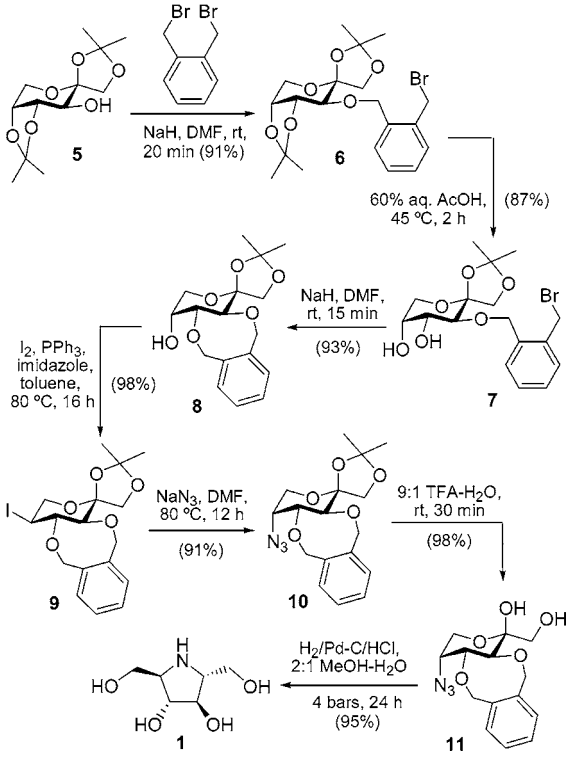
Inspired by the concept of intramolecular delivery of vicinal functionality,[9] we conceived a strategy for the selective O-xylylation of 1,2-diols involving an intramolecular ring-closing O-benzylation reaction of a hydroxyl group by a benzylating moiety previously installed at the neighboring oxygen atom. We reasoned that this tactic would enjoy improved regioselectivity compared to the corresponding intermolecular O-benzylation reaction. Geometrical considerations suggested that the *o*-xylylene tether would provide the appropriate distance restriction to favor 1,2- versus 1,3-*O*-(*o*-xylylene) protection.[10] Moreover, protection of a vicinal diol segment by a cyclic xylylene group, instead of two independent benzyl ethers, results in a considerable efficiency improvement in terms of atom economy[11] (Scheme 2). The potential that this strategy holds for hydroxyl group manipulation is demonstrated here by its application to the high yielding syntheses of **1** and **2**.

Scheme 2. Retrosynthetic Analysis of the Intramolecular Benzyl Delivery Strategy for the Selective Protection of 1,2-Diols



Our synthetic route started from 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose **5**,[12] which was transformed into the corresponding 3-*O*-(2-bromomethyl)benzyl ether **6** by reaction with excess of commercial α,α′-dibromoxylene. Selective acid-catalyzed hydrolysis of the 4,5-*O*-isopropylidene group provided diol **7**, which was activated by treatment with sodium hydride in *N*,*N*-dimethylformamide. Formation of a fused eight-membered ring involving OH-4, to give the key intermediate **8**, readily took place under these conditions (Scheme 3). No traces of the 3,5-*O*-(*o*-xylylene) positional isomer or intermolecular reaction products were observed, which is in stark contrast with the low selectivity of the classical intermolecular benzylation reaction.

Scheme 3. Synthesis of DMDP via Intramolecular Benzyl Delivery



(5) (a) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1503. (b) Izquierdo, I.; Plaza, M. T.; Robles, R.; Franco, F. *Carbohydr. Res.* **2001**, *330*, 301.

(6) For selected examples of alternative recent syntheses, see: (a) Liu, J.; Numa, M. M. D.; Liu, H.; Huang, S.-J.; Sears, P.; Shikhamn, A. R.; Wong, C.-H. *J. Org. Chem.* **2004**, *69*, 6273. (b) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999. (c) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7023. (d) Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393.

(7) For a very interesting approach to the synthesis of selectively functionalized DMDP derivatives, see: (a) Wrodnigg, T. A.; Stütz, A. E.; Withers, S. G. *Tetrahedron* **1997**, *38*, 5463. (b) Wrodnigg, T. A.; Withers, S. G.; Stütz, A. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1063. (c) Wrodnigg, T. A.; Dines, F.; Gruber, C.; Häusler, H.; Lundt, I.; Rupitz, K.; Steiner, A. J.; Stütz, A. E.; Tarling, C. A.; Withers, S. G.; Wölfrer, H. *Bioorg. Med. Chem.* **2004**, *38*, 3485.

(8) Tatibouët, A.; Lefoix, M.; Nadolny, J.; Martin, O. R.; Rollin, P.; Yang, J.; Holman, G. D. *Carbohydr. Res* **2001**, *333*, 327.

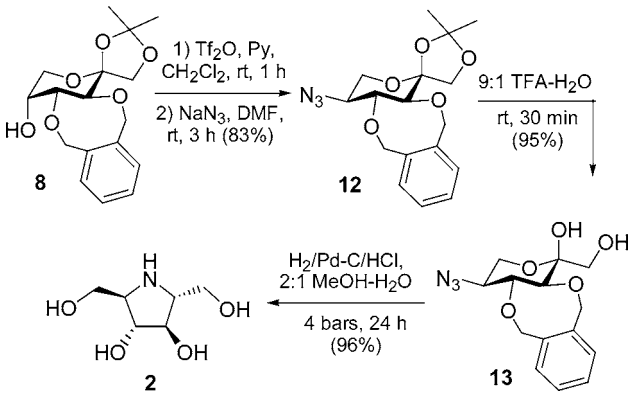
(9) Knapp, S. *Chem Soc. Rev.* **1999**, *28*, 61.

Compound **8** is well-suited for further elaboration at C-5 in order to access polyhydroxylated pyrrolidines.[13] Thus, double inversion involving iodination with the iodine−imidazole−triphenylphosphine system, followed by nucleophilic displacement of the halogen atom in the L-*sorbo* intermediate **9** with azide anion, afforded the corresponding 5-azido-5-deoxy-β-D-fructopyranose derivative **10**. Cleavage of the anomeric acetonide group by treatment with 90% aqueous trifluoroacetic acid provided the reducing azidosugar **11**, possessing a substitution profile of stereochemical complementarity to DMDP. Catalytic hydrogenation of **11** at 4 bar in the presence of HCl provoked simultaneous removal of the cyclic *o*-xylylene protecting group, reduction of the azido group into the corresponding amine, intramolecular addition of the amino group to the latent aldehyde group of the monosaccharide and steroselective reduction of the resulting imine, to give the target C_2-symmetric pyrrolidine **1** as the corresponding hydrochloride in a one-pot transformation (Scheme 3).

It is noteworthy that, in addition to the expected increase in the regioselectivity of the vicinal diol protection step, the use of the cyclic *o*-xylylene protecting group results in a dramatic improvement of the nucleophilic substitution reactions at the neighboring C-5 center as compared with the di-*O*-benzyl derivative **3**. Thus, using identical reaction conditions, the iodination yield goes up from 48% to 98% (for **9**) and the subsequent azide anion displacement increases from 85% to 91% (for **10**). Probably, in the cyclic arrangement the aromatic ring is forced to occupy the space between the positions involved in the benzyl ether linkages, therefore releasing steric hindrance at the vicinity of this region. The preparation of **1** from the diacetonide D-fructose precursor **5** was accomplished in seven steps and 61% overall yield.

The synthesis of the epimeric pyrrolidine **2** requires a precursor having the L-*sorbo* configuration. Trifluoromethanesulfonylation of OH-5 in **8** and subsequent nucleophilic displacement by azide provided the requested azidosugar **12** in 83% yield (to be compared with a 72.5% yield for a similar two-step transformation in **3**).[14] Trifluoroacetic acid catalyzed cleavage of the anomeric isopropylidene group to give the reducing derivative **13** followed by catalytic hydrogenation afforded the target compound **2**, as the corresponding hydrochloride, in six steps and 55% overall yield from **5** (Scheme 4).

Scheme 4. Synthesis of DGDP



In summary, the concept of intramolecular delivery of benzyl protection is here demonstrated by the regioselective preparation of the 3,4-*O*-(*o*-xylylene)-D-fructose derivative **8** from the monobenzyl-protected diol **7**. The new methodology provides alternative opportunities for selective diol protection and for reactivity control. These favorable features have been translated into highly efficient preparations of the natural glycosidase inhibitors DMDP and DGDP.[15]

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Supporting Information Available: Experimental details and characterization data for compounds **6**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The *o*-xylylene tether has been previously used as a rigid spacer to connect two different monosaccharide moieties during the stereocontrolled synthesis of spirodisaccharides. See: (a) Rubio, E. M.; García-Moreno, M. I.; Balbuena, P.; Ortiz Mellet, C.; Fernández García, J. M. *Org. Lett.* **2005**, *7*, 729. (b) Rubio, E. M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **2003**, *5*, 873.

(11) Trost, B. M. *Science* **1991**, *247*, 1471.

(12) Compound **5** can be prepared in one step from commercially available D-fructose by reaction with acetone in the presence of sulfuric acid (45% yield). See: Lichtenthaler, F. W. *Carbohydr. Res.* **1998**, *313*, 69.

(13) For early, but remarkable, examples on the manipulation of D-fructose at C-5, see: (a) Murphy, D. *J. Chem. Soc. C* **1967**, 1732. (b) Armenakian, A.; Mahmood, M.; Murphy, D. *J. Chem. Soc., Perkin I* **1972**, 63. (c) Chmielewski, M.; Whistler *J. Org. Chem.* **1975**, *40*, 639.

(14) For a discussion on the influence of polar and steric factors on the nucleophilic displacement of sulfonate esters, see: Richardson, A. C. *Carbohydr. Res.* **1969**, *10*, 395.

(15) The fact that efficient methods to access L-fructose have been recently reported additionally broadens the scope of this approach to access unnatural polyhydroxypyrrolidine derivatives. See: Franke, D.; Machajewski, T.; Hsu, C.-C.; Wong, C.-H. *J. Org. Chem.* **2003**, *68*, 6828.