Syntheses of D- and L-Mannose, Gulose, and Talose via Diastereoselective and Enantioselective Dihydroxylation Reactions

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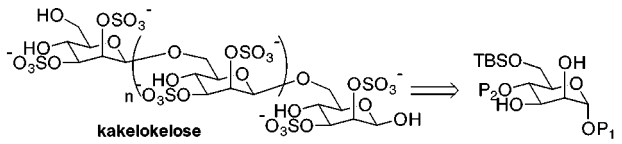
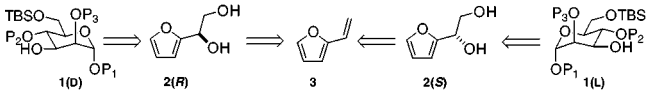
The de novo enantioselective synthesis of the hexoses stands as a challenge to asymmetric catalysis.[1] Despite some germinal efforts toward the hexoses, notably by Masamune/Sharpless (epoxidation),[2] Danishefsky (Diels−Alder),[3] Johnson/Hudlicky (enzymatic desymmetrization),[4] and Wong/Sharpless (osmium/enzyme),[5] there still does not exist a practical, nonenzymatic route to the hexoses.[6] As part of our program aimed at investigating the biological role of oligosaccharides, we are interested in the synthesis of analogues of the anti-HIV agent kakelokelose (Scheme 1). Kakelokelose is a polysulfated β-oligomannosugar, isolated as an oligomer from the Pacific tunicate *Didemnum molle*. It has been proposed that the biologically active form is an oligosaccharide.[7] We are particularly interested in studying oligosaccharide analogues of the all D-, all L-, and mixed D,L-oligosugar structures. Consequently, we required an efficient approach to both D- and L-mannose. The ideal route would allow for the synthesis of other mixed D- and L-oligosaccharides, such as the D-mannose-L-gulose portion of bleomycin.[8] Herein, we would like to present our discovery of an expeditious route to mannose, gulose, or talose using Sharpless's dihydroxylation reaction to set the D- or L-configuration depending on the ligand used.

We have targeted differentially protected D- and L-mannose **1** as building blocks for the assembly of analogues of kakelokelose (Scheme 1). We desired a route in which the synthetic efficiency is better than traditional protection/deprotection strategies from mannose and is amenable to both D- and L-mannose. The ideal synthesis should also start from a commercially available starting material that is even cheaper than D-mannose.[9,10] The strategy outlined below has led to a highly stereocontrolled synthesis of D- or L-mannose in only five steps and in approximately 39% yield from furfural (Scheme 2). Our approach relies upon the use of

Scheme 1



Scheme 2



catalytic asymmetric osmium chemistry on vinylfuran **3** developed by Ogasawara[11] and augments the earlier work of Achmatowicz.[12]

To accomplish this goal we, as have others, recognized that substituted furyl alcohols possess the proper C-5 stereochemistry for the hexopyranoses.[13] Crucial to this approach is a simple three-step route toward pyranone **6b** (Scheme 3). We envision **6b** as the linchpin molecule that will be amenable for the synthesis of all the possible stereoisomers of the hexoses. A key part of this sequence is our ability to convert furfural into an ether solution of vinylfuran.[14] This one-step in situ process for the generation of vinylfuran constitutes a significant improvement in terms of overall efficiency. A 2 M solution of vinylfuran can be used directly in the *t*-BuOH/H_2O AD-mix reaction mixture developed by Sharpless.[12,15] The $(DHQ)_2$Phal ligand gave an 85% yield of (*R*) diol **2(*R*)** from furfural in 90% ee.[16] The $(DHQD)_2$Phal ligand afforded (*S*) diol **2(*S*)** in an 85% yield with a 92% ee.[17] The absolute configuration is based upon the Sharpless mnemonic[15] and Mosher ester analysis.[18] Diol **2** can be selectively protected with TBSCl (90%) to give furan **5**, which smoothly rearranges to hemiacetal **6a** when oxidized with NBS.[19] Hemiacetal **6a** exists as an equilibrating mixture of anomers, diastereomerically enriched mixtures of **6a** equilibrate to a (1:1) mixture of anomers in deuterated chloroform. Our hopes of taking advantage of the difference in reactivities of axial versus equatorial anomeric alcohols were realized when hemiacetal **6a** was treated with benzoyl chloride at −78 °C to produce pyranone **6b** (>20:1 ratio of diastereomers). This result appears to be general for acid chlorides as pivaloyl chloride (>10:1) showed similar selectivity, whereas TBSCl gave approximately a 1:1 mixture

(1) For a good review: Zamoiski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.

(2) Sharpless, K. B.; Masamune, S. *Science* **1983**, *220*, 949.

(3) For a review, see: (a) Danishefsky, S. J. *Chemtracts* **1989**, 273. For improved catalysis, see: (b) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405.

(4) (a) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *58*, 7185−7194. (b) Hudlicky, T.; Pitzer, K. K.; Stabile, M. R.; Thorpe, A. J.; Whited, G. M. *J. Org. Chem.* **1996**, *61*, 4151−4153.

(5) Henderson, I.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 558−561.

(6) Recently Wong has developed a route to a mixture of glucose and fructose using an enzymatic process: Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443−73.

(7) Riccio, R.; Kinnel, R. B.; Bifulco, G.; Scheur, P. J. *Tetrahedron Lett.* **1996**, *37*, 1979.

(8) For a recent total synthesis of bleomycin, see: (a) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647−5656. (b) Boger, D. L.; Honda, T.; Menezes, R. F.; Colletti, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5631−5646. (c) Boger, D. L.; Teramoto, S.; Zhou, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 7344−7356.

(9) According to the Aldrich catalog, on a per gram basis D-mannose cost 35 times more than furfural and for L-mannose the cost ratio is 4000.

(10) Furfural is commercially produced by Great Lakes Chemical. For a convenient laboratory procedure, see: Adams, R.; Voorhees, V. *Organic Syntheses*; Wiley: New York, 1921; Collect. Vol. I, p 280.

(11) (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165. (b) Grapsas, I.; K.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823.

(12) Ogasawara has previously demonstrated the asymmetric dihydroxylation of vinylfuran and applied it toward the synthesis of D- and L-levoglucosenone: (a) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synlett* **1996**, 971. (b) Taniguchi, T.; Ohnishi, H.; Ogasawara, K. *Chem. Commun.* **1996**, 1477−1478.

(13) For a good review, see: Hudlicky, T.; Entwistle, D. A.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195.

(14) This in situ use of vinylfuran allows for much higher yields of diol **7**. Wittig technology provides vinylfuran in yields on the order of 10%. Previous practical approaches to vinylfuran involve a four-step sequence from furfural that involves a stoichiometric Cu-promoted decarboxylation of 3-furylpropanoic acid, see: Schmidt, U.; Werner, J. *Synthesis* **1986**, 986.

(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(16) Although we were concerned about an adverse solvent effect caused by the presence of ether, Ogasawara has observed identical ee's in *t*-BuOH/H_2O; see ref 12a.

(17) The (*R*) diol **7** has been prepared on a half mole scale with no reduction of enantioselectivity. Similarly the (*S*) diol **7** has been prepared on a quarter mole scale.

(18) (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1975**, *38*, 2143. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363.

(19) Georgiadis, M. P.; Couladoures, E. A. *J. Org. Chem.* **1986**, *51*, 2725 and ref 11b.

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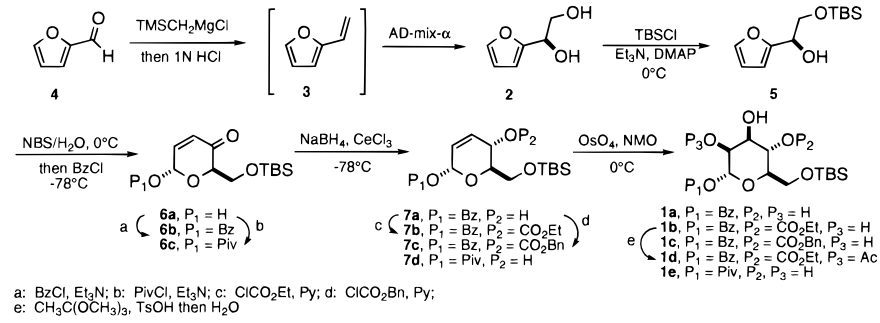
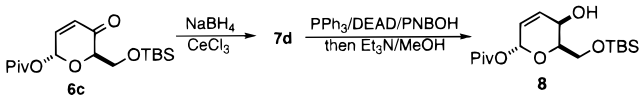
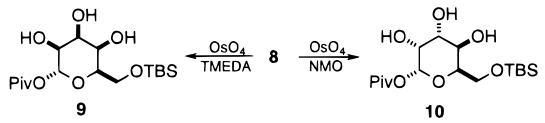
Scheme 3



Scheme 4



Scheme 5



of anomers.[20] Pyranone **6b** was easily purified by filtering through silica gel and isolated as a single diastereomer in a 56% yield from **2**. With the two stereocenters of **6b** introduced, the molecule was poised for introduction of the remaining functionality of the hexoses (Scheme 3).

Pyranone **6b** was stereoselectively reduced under the Luche conditions ($NaBH_4/CeCl_3$, −78 °C)[21] to give alcohol **7a**[22] as the only observable stereoisomer (>95%), which can be protected without purification to give ethyl carbonate **7b** or benzyl carbonate **7c**, each in 80% yield. Three partially protected mannosugars were produced via a completely diastereoselective dihydroxylation reaction of **7a**, **7b**, or **7c** in ∼90% yield in each case (Scheme 3).[23] A differentially protected mannose was easily achieved upon treatment of diol **1b** with trimethyl orthoacetate to form a cyclic ortho ester in situ, which was hydrolyzed to the axial acetate **1d**. The differentiated mannosugar **1d** was formed in a 62% yield with a regioselectivity greater than 25:1.[24]

The C-4 isomer of **7d**, allylic alcohol **8**, can also be easily produced by performing a Mitsunobu reaction on **7d** (Scheme 4). Key to this transformation is the selective hydrolysis of a *p*-nitrobenzoyl ester in the presence of the anomeric ester. Although this operation can be performed on benzoate **6b**, more reproducible results are observed when pivolate **6c** is used. Reduction of pyranone **6c** under the Luche conditions yielded allylic alcohol **7d** as a single diastereomer in 95% yield. Exposure of **7d** to the Mitsunobu reaction conditions (PPh_3, DEAD, *p*-nitrobenzoic acid (PNBOH)) yielded a *p*-nitrobenzoic ester (65%) which was selectively hydrolyzed with Et_3N in MeOH to yield the axial alcohol **8** (90%).[25]

Finally, access to **8** extends this versatile synthetic strategy to other hexoses, as illustrated by the synthesis of protected talose **9** and gulose **10** (Scheme 5). Treatment of allylic alcohol **8** with OsO_4/NMO in *t*-BuOH/H_2O afforded an 80% yield of the protected gulose isomer **10**.[26] Amazingly, the protected talose isomer **9** can be selectively produced upon treatment of **8** with the TMEDA adduct of OsO_4 (80%).[27] Unfortunately for this system, the hydroxy-directed delivery of a cis diol requires an axial alcohol; exposure of **7a** to the identical conditions only yielded the mannose isomer **1a**. The relative configurations of **1a**, **9**, and **10** were determined by examining relevant coupling constants and NOE's from a series of ^1H NMR, $^1H,^1H$-COSY, and ^1H NOE experiments. The relative and absolute configurations of the gulose sugar **10** were confirmed by single-crystal X-ray analysis (see Supporting Information).

In summary, we have developed a practical five-step synthesis of both D- and L-mannose from furfural (39% yield). This route is amenable to multigram scale preparation. Similarly we have also extended this methodology to D- and L-gulose and D- and L-talose in comparable yields (19%). We are currently investigating an epoxide ring opening approach to the other isomers of the hexoses. We feel this new route to L-sugars will be very beneficial for the synthesis of natural and unnatural oligosaccharides.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The selective benzoylation allows for the simple purification of **6b** without resorting to tedious chromatographic separation. BzCl at room temperature with excess Et_3N gave a 4:1 mixture of isomers, whereas 1 equiv of Et_3N gave a 1:1 mixture. Achmatowicz has previously shown that molecules related to **6a** gave a 1:1 mixture of methoxy anomers with MeOH/acid; see ref 11a.

(21) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226.

(22) Mosher ester analysis of **7a** showed that recrystallized enone **6b** had significantly increased enantioexcess (>96% ee).

(23) For a review of diastereoselection in the osmium-catalyzed dihydroxylation reaction, see: Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

(24) A mixture of axial and equitorial acetates was produced upon treatment of **1c** with 1 equiv of Ac_2O which allowed for easy detection of the > 25:1 mixture by ^1H NMR.

(25) (a) Martin, S. P.; Dodge, J. A.*Tetrahedron Lett.* **1991**, *32*, 3017. (b) Grynkiewicz, G. *Pol. J. Chem.* **1979**, *53*, 2501. (c) Mitsunobu, O. *Compr. Org. Synth.* **1991**, *6*, 1.

(26) For a recent eight-step synthesis of gulose from L-xylose, see: Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261. Dondoni appraises L-gulose at $2000/g.

(27) Less than 5% of the gulose isomer was formed. These conditions were chosen for the hydroxy-directed delivery of a cis diol. See: Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.