JOC Article
pubs.acs.org/joc

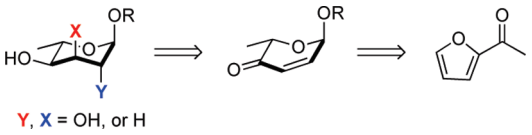
De Novo Asymmetric Synthesis of an α-6-Deoxyaltropyranoside as Well as its 2-/3-Deoxy and 2,3-Dideoxy Congeners

Mingde Shan, Yalan Xing, and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

george.odoherty@mail.wvu.edu

Received May 9, 2009



A highly divergent de novo asymmetric synthesis of benzyl α-6-deoxyaltropyranoside, benzyl α-ascarylopyranoside, benzyl α-amicetopyranoside, and benzyl α-digitoxopyranoside has been achieved via a common pyranone intermediate. The routes rely upon a palladium(0)-catalyzed glycosylation reaction and corresponding post-glycosylation transformations. The control of the absolute and relative stereochemical configuration came from a Noyori reduction of 2-acylfuran and subsequent diastereoselective introduction of other stereogenic centers.

Introduction

Deoxysugars are a common structural motif in biologically active natural products.[1] Among the deoxysugars, the 6-deoxysugars are the most prevalent followed by sugars with deoxygenation at the C-2 and C-3 positions. The removal of the hydroxyl groups in sugars along with the use of unusual stereochemistry imparts resistance to most glycosidases and thus conveys improved metabolic stability.[1] Examples of nature's reliance of these structural motifs are seen in the use of α-6-deoxyaltrose as the main constituent of some bacterial lipopolysaccharides,[2] as well as the use of α-2,6- and α-3,6-dideoxyaltrose (i.e., α-digitoxose and α-ascarylose) in biologically active natural products such as jadomycin B[3] and daumone,[4] respectively.[5]

Over the last 10 years, there has been considerable effort made toward the synthesis of monosaccharides from achiral starting materials.[6] In this regard, we have reported a de novo asymmetric synthesis of carbohydrates using achiral acylfurans **1** (Scheme 1).[7] Our approach used a Noyori reduction, an Achmatowicz reaction, and a Pd(0)-catalyzed glycosylation (**2** to **3**) to prepare pyranone intermediate **3**,[7−9] which via post-glycosylation transformations were converted into the corresponding carbohydrates (e.g., **3** to **4**, **5** and **6**).[7,9] This method has allowed for the stereoselective synthesis of a variety of sugars, including rare sugars, aminosugars, and even unnatural sugars.[10]

(1) (a) Johnson, D. A.; Liu, H.-w. *Comprehensive Natural Products Chemistry*; Elsevier: Amsterdam, NY, 1999; Vol. 3, pp 311−365. (b) Thibodeaux, C.; Melancüon, C. E. III; Liu, H.-w. *Nature* **2007**, *446*, 1008–1016. (c) Kren, V.; Martinkova, L. *Curr. Med. Chem.* **2001**, *8*, 1303–1328.

(2) Gorshkova, R. P.; Kalmykova, E. N.; Isakov, V. V.; Ovodov, Y. S. *Eur. J. Biochem.* **1985**, *150*, 527–531.

(3) (a) Doull, J. L.; Singh, A. K.; Hoare, M.; Ayer, S. W. *J. Ind. Microbiol.* **1994**, *13*, 120–125. (b) Jakeman, D. L.; Borissow, C. N.; Graham, C. L.; Timmons, S. C.; Reid, T. R.; Syvitski, R. T. *Chem. Commun.* **2006**, 3738–3740.

(4) (a) Jeong, P.-Y.; Jung, M.; Yim, Y.-H.; Kim, H.; Kim, K.; Paik, Y.-K. *Nature* **2005**, *433*, 541–545. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921–3924. (c) Baiga, T. J.; Guo, H.; Xing, Y.; O'Doherty, G. A.; Parrish, A.; Dillin, A.; Austin, M. B.; Noel, J. P.; La Clair, J. J. *ACS Chem. Biol.* **2008**, *3*, 294–304.

(5) For a recent approach to 2,6-dideoxysugars, see: (a) Hou, D.; Lowary, T. L. *J. Org. Chem.* **2009**, *74*, 2278–2289. For approaches to 3,6-dideoxysugars, see: (b) Weigel, T. M.; Liu, H.-w. *Tetrahedron Lett.* **1988**, *29*, 4221–4224 and ref 4b.

(6) (a) Zamoiski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1. (b) Ernst, B., Hart, G. W., Sinay, P., Eds. *Carbohydrates in Chemistry and Biology*; Wiley-VCH: New York, 2000. (c) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B. *Science* **1983**, *220*, 949–951. (d) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755.

(7) (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982–2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17–36. For its use in oligosaccharide synthesis, see: (c) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429. (d) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 3015–3019. (e) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745–748. (f) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206–5208. (g) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 2283–2286.

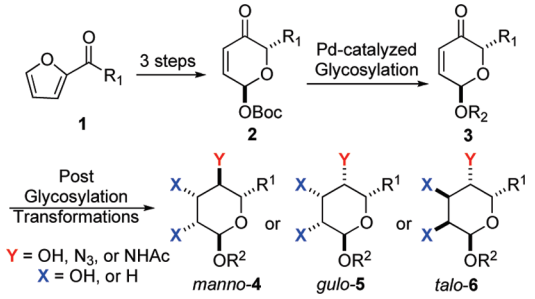
(8) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849–1851.

(9) (a) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605–1608. (b) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149–5152. (c) Guppi, S. R.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 4966–4969.

(10) (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 3899–3992. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771–1774. (c) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 4151–4155.

DOI: 10.1021/jo9009722 Published on Web 07/16/2009

SCHEME 1. De Novo Approach to Carbohydrate



These approaches primarily rely on the osmium-catalyzed dihydroxylation reaction for the *syn*-addition of two hydroxyl groups across the C-2/C-3 pyran double bond, which has been used to prepare D- or L-sugars with *manno-*, *gulo-*, and *talo*-stereochemistry.[9,10] A related dihydroxylation on the C-3/C-4 pyran double bond provided the sugars with *galacto-* and *allo*-stereochemistry.[10,11] By combining this approach with protection/inversion reactions, this route has also been used to access to the *gluco*-stereoisomers.[12]

As part of our efforts to expand upon this methodology, we have been investigating epoxidation/nucleophilic ring-opening reactions for the net *anti*-addition of hydroxyl groups across the C-2/C-3 pyran double bond. Herein we describe our successful application of this new post-glycosylation transformation for the de novo synthesis of four deoxysugar targets (i.e., benzyl pyranosides with α-*altro*-stereochemistry as well as its 2-deoxy (α-digitoxose), 3-deoxy (α-ascarylose), and 2,3-dideoxy (α-amicetose) congeners) (Figure 1).

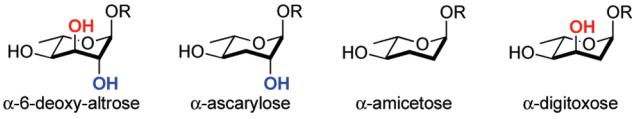


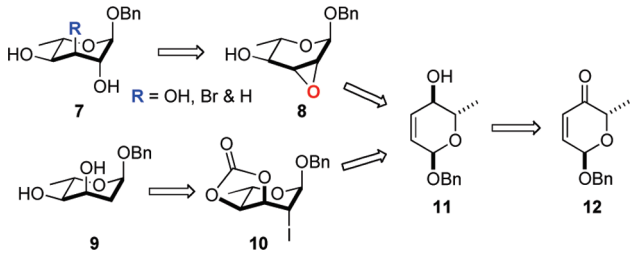
FIGURE 1. Targeted rare sugar pyranosides.

Results and Discussion

Retrosynthetically, we envisioned both α-6-deoxyaltropyranoside and α-3,6-dideoxyaltropyranoside **7** as being derived from the *trans*-diaxial opening of epoxide **8** with either a formal hydroxy or hydride nucleophile, respectively (Scheme 2). Epoxide **8** could be prepared by epoxidation of pyran **11**, which in turn could be prepared by a ketone reduction of pyranone **12**. The regioisomeric 2-deoxysugars could be prepared by switching the order of *trans*-diaxial addition of oxygen and halogen across pyran **11**. Thus, the α-digitoxose **9** should come from the radical reduction of iodocarbonate **10**, which in turn could be prepared from pyran **11** (Scheme 2). Because our route began with the Noyori reduction of acylfuran, it is amenable to the synthesis of either D- or L-enantiomer of these sugars.[13]

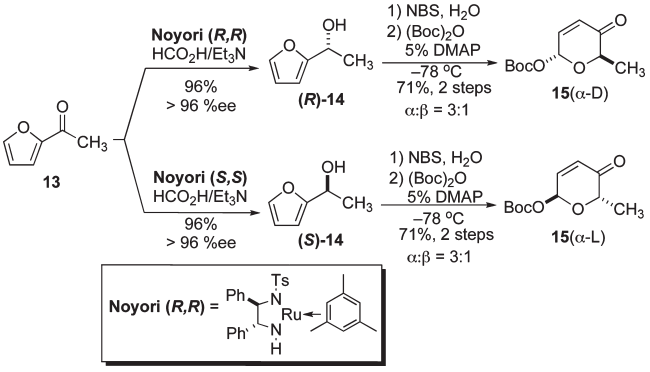
As we have previously reported,[13b] the Noyori reduction of acylfuran **13**, with formic acid/triethylamine as hydride source,

SCHEME 2. Retrosynthetic Analysis



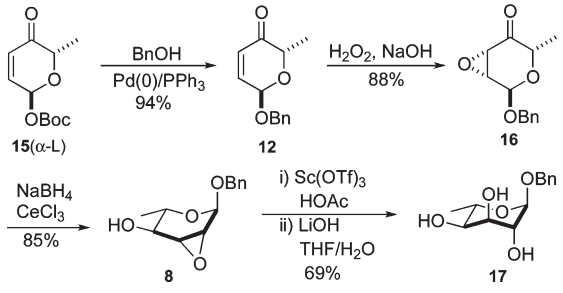
produced either enantiomer of furfuryl alcohol **14** in 96% yield with high enantiomeric excess (> 96% ee).[13] An Achmatowicz rearrangement transformed the furfuryl alcohol to pyranone in 91% yield. The hemiacetal was then protected as *tert*-butyl carbonate **15** at low temperature in 78% yield with 3:1 ratio of α- and β-diastereomers (Scheme 3).

SCHEME 3. De Novo Synthesis of α-Boc-pyranone



Our proposed synthesis of a α-6-deoxyaltropyranoside started with the attempted epoxidation of pyran **11**. Unfortunately, our efforts to epoxidize allylic alcohol **11** were not satisfactory. So, we decided to reverse the reduction/oxidation sequence. These efforts began with our Pd(0)-catalyzed glycosylation reaction to diastereoselectively install the anomeric benzyloxy group with complete α-selectivity (Scheme 4). Similarly, treating pyranone **12** with hydrogen peroxide in the presence of a catalytic amount of base (10 mol % of $NaOH/H_2O_2$) diastereoselectively installed the epoxide **16** in 88% yield.[4b] In an equally diastereoselective fashion, the ketone **16** was reduced with $NaBH_4$ (−78 to −20 °C) to form the equatorial alcohol **8** in 85% yield.

SCHEME 4. Synthesis of α-6-Deoxyaltropyranoside

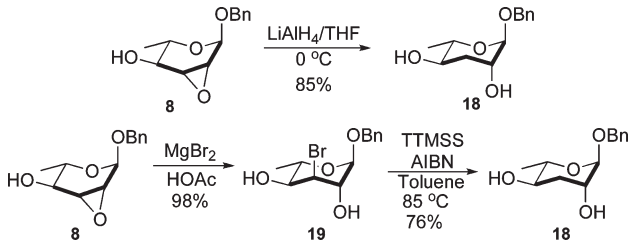


With the alcohol in hand, we turned our attention to the epoxide ring opening with acetic acid. After investigating the use of a variety of Lewis acids, we found $Sc(OTf)_3$ gave the

(11) (a) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339–4342. (b) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485–2493.
(12) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033–4036.
(13) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522. (b) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407–6411.

best results. In practice, treatment of epoxide **8** with $Sc(OTf)_3$ in HOAc afforded an inseparable mixture of acetates which presumably resulted from acid-catalyzed ester migration of the initial epoxide ring-opening product. This mixture was directly hydrolyzed with LiOH in aqueous THF to produce α-6-deoxyaltrose **17** in 69% yield. The stereochemistry of the ring opening was confirmed by analysis of the corresponding proton/proton coupling constants at C-2, C-3, and C-4 positions of **17** (see the Supporting Information).

SCHEME 5. Synthesis of α-Ascarylopyranoside

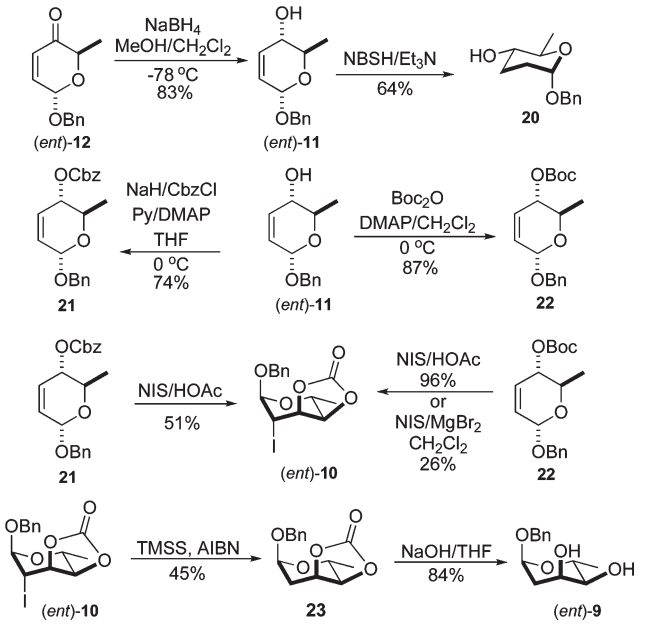


As we previously reported,[4b] epoxide **8** was converted into the α-ascarylose sugar **18** in 85% yield using $LiAlH_4$ (Scheme 5). This same regioselective Lewis acid promoted ring-opening reaction can also be used for 3-deoxysugars to provide a less basic alternative to our previously reported $LiAlH_4$ method.[4b] Simply switching the Lewis acid to $MgBr_2 \cdot Et_2O$ promoted a regioselective opening to form bromide **19**. The axial bromide in **19** was cleanly removed to give **18** in 76% yield, using an AIBN-promoted tris-(trimethylsilyl)silane (TTMSS) radical reduction.

Using our previously reported NBSH diimide procedure (o-$NO_2PhSO_2NHNH_2/Et_3N$),[10a,10b] the D-amicetose **20** was prepared from pyran (*ent*)-**11**, which was easily prepared by a reduction of pyranone (*ent*)-**12** (Scheme 6). A related regioisomeric halohydrin could be used to prepare the 2-deoxypyranoside, α-digitoxose **9**. This was accomplished by replacing the epoxide opening with a *trans*-diaxial iodocarbonate formation. This has been most commonly accomplished using $I(collidine)_2ClO_4$ as the electrophilic reagent.[14] We believed a more economical method would employ the cheaper NIS. These efforts began with the conversion of the allylic alcohol (*ent*)-**11** into the Cbz- and Boc-allylic carbonates **21** and **22**, respectively.

Because of the electron-deficient nature of the pyran double bonds in the carbonates **21** and **22**, it was not surprising that they did not react with NIS in CH_2Cl_2. This changed upon the addition of Lewis acids, such as 1 equiv of $MgBr_2 \cdot Et_2O$ (26% yield) and 30 mol % of $LiClO_4$ (< 10% yield), albeit in low yields. An even more efficient conversion occurred when the solvent was changed from CH_2Cl_2 to AcOH. Thus, simply exposing the Boc-carbonate **22** to 2.5 equiv of NIS in acetic acid without any Lewis acid, provided an excellent yield of the desired iodocarbonate (*ent*)-**10** (96%).[15] This improved reactivity was also found for the Cbz-carbonate **21**, although it gave the iodo-carbonate (*ent*)-**10** in significantly lower yield (51%). The iodine in iodocarbonate (*ent*)-**10** was reduced by tris(trimethylsilyl)silane

SCHEME 6. Synthesis of 2,3,6-Trideoxy- and 2,6-Dideoxy-D-sugars



(TTMSS) under radical condition in 45% yield. Finally, the cyclic carbonate was hydrolyzed with NaOH in aqueous THF afforded desired α-digitoxose (*ent*)-**9** in 84% yield.

In summary, a highly enantio- and diastereoselective procedure for the preparation of various C-2, C-3, and C-6 deoxypyranosides has been developed. Our approach to these sugars provides rapid and practical access to these rare and naturally occurring sugars, which should be of use for further natural product synthesis. Critical to the success of this synthesis was the use of the Pd(0)-catalyzed glycosylation and corresponding post-glycosylation transformations. It is also worth noting that our method is structurally divergent in that it produces four different sugar congeners from the same advanced intermediate. We believe that this approach will be particularly useful for medicinal chemistry. Finally, by selecting either enantiomeric form of the Noyori catalyst (*R*,*R*) or (*S*,*S*), our strategy is also amenable to the synthesis of both D- or L-forms of these sugars. Our efforts to apply these postglycosylation reactions in oligosaccharide settings will be reported in due course.

Experimental Section[16]

(1*R*,2*R*,4*S*,6*S*)-2-(Benzyloxy)-4-methyl-3,7-dioxabicyclo[4.1.0]-heptan-5-one (16). To the solution of pyranone **12** (220 mg, 1.0 mmol) in methanol (3 mL) at 0 °C was added dropwise 30% aqueous hydrogen peroxide (0.26 mL, 2.5 mmol), followed by aqueous sodium hydroxide (0.1 mL, 0.5 M). The reaction mixture was stirred at rt for 4 h, and then the reaction mixture was extracted with diethyl ether. The extracts were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give epoxide **16** (207 mg, 0.88 mmol, 88%) as a colorless oil: R_f (20% EtOAc/hexane) 0.47; $[\alpha]^{20}_D$ −59.3 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) ν 3034, 2937, 1726, 1455, 1369,

(14) (a) Pauls, H. W.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1985**, *4*, 1–14. (b) Martin, S. F.; Zinke, P. W. *J. Org. Chem.* **1991**, *56*, 6600–6606.

(15) To the best of our knowledge, this is the first successful use of NIS to convert allyl carbonate to an iodo-cyclic carbonate.

(16) Experimental procedures for the synthesis of all new compounds are presented in the Experimental Section. Complete experimental procedures and spectral data for the remaining compounds are presented in the Supporting Information.

1256, 1146, 1060, 996, 859, 699; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.30 (d, J = 1.2 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.17 (q, J = 6.9 Hz, 1H), 3.59 (dd, J = 3.9, 1.2 Hz, 1H), 3.46 (d, J = 4.0 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 203.1, 136.6, 128.7, 128.4, 128.2, 93.3, 93.2, 72.0, 70.8, 53.8, 53.1; HRMS calcd for $[C_{13}H_{14}O_4 + Na]^+$ 257.0784, found 257.0784.

(1*R*,2*R*,4*S*,5*S*,6*R*)-2-(Benzyloxy)-4-methyl-3,7-dioxabicyclo-[4.1.0]heptan-5-ol (8). To a solution of epoxide **16** (672 mg, 2.87 mmol) in CH_2Cl_2 (3 mL) was added a solution of $CeCl_3$/MeOH (3 mL, 0.4 M). The mixture was cooled to −78 °C. $NaBH_4$ (130 mg, 3.4 mmol) was added, and the reaction mixture was stirred at −78 to −20 °C for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O, and the organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give epoxide **8** (576 mg, 2.44 mmol, 85%) as a colorless oil: R_f (80% EtOAc/hexane) 0.47; $[\alpha]^{20}_D$ −62.8 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) ν 3430, 2911, 1454, 1370, 1241, 1114, 1054, 980, 848, 805, 738, 698; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.03 (s, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 3.58 (dq, J = 9.0, 6.0 Hz, 1H), 3.45 (d, J = 9.0 Hz, 1H), 3.23 (d, J = 3.6 Hz, 1H), 3.12 (d, J = 3.6 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 128.8, 128.4, 128.3, 94.5, 70.3, 68.0, 65.8, 56.1, 50.5, 18.5; HRMS calcd for $[C_{13}H_{16}O_4 + H]^+$ 237.1121, found 237.1121.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Benzyloxy)-6-methyltetrahydro-2*H*-pyran-3,4,5-triol (17). To a round-bottom flask were added epoxide **8** (13 mg, 0.055 mmol), HOAc (0.5 mL), and $Sc(OTf)_3$ (5 mg, 0.01 mmol). The reaction solution was stirred for 1 h at rt. The reaction mixture was diluted with EtOAc, and saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with EtOAc, and the EtOAc layer was washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in THF/H_2O (0.4 mL, 3:1) at rt, and lithium hydroxide monohydrate (5 mg, 0.13 mmol) was added to the solution. The reaction mixture was stirred at rt for 5 h, and then the reaction mixture was directly loaded onto a silica gel column to give α-6-deoxyaltrose **17** (9.6 mg, 0.038 mmol, 69%) as a colorless oil: R_f (EtOAc) 0.49; $[\alpha]^{20}_D$ −73.3 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) ν 3384, 2930, 1455, 1375, 1259, 1127, 1061, 1014, 970, 852, 737, 698; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.81 (s, 1H), 4.75 (d, J = 12 Hz, 1H), 4.55 (d, J = 12 Hz, 1H), 3.98 (dd, J = 3.6, 1.8 Hz, 1H), 3.89 (dd, J = 3.6, 3.6 Hz, 1H), 3.79 (dq, J = 9.0, 6.0 Hz, 1H), 3.51 (dd, J = 9.6, 3.6 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 128.9, 128.6, 128.4, 99.0, 70.9, 70.1, 69.8, 69.6, 65.8, 17.8; HRMS calcd for $[C_{13}H_{18}O_5 + Na]^+$ 277.1046, found 277.1047.

(2*R*,3*S*,4*S*,5*S*,6*S*)-2-(Benzyloxy)-4-bromo-6-methyltetrahydro-2*H*-pyran-3,5-diol (19). To a round-bottom flask were added epoxide **8** (96 mg, 0.41 mmol), HOAc (0.5 mL), and $MgBr_2 \cdot Et_2O$ (106 mg, 0.41 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc, and saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with EtOAc, and the organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give bromide **19** (137 mg, 0.4 mmol, 98%) as a colorless oil: R_f (50% EtOAc/hexane) 0.28; $[\alpha]^{20}_D$ −57.2 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) ν 3402, 2919, 1718, 1454, 1245, 1055, 994, 739; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.80 (d, J = 12.0 Hz, 1H), 4.72 (d, J = 3.6 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.35 (dd, J = 6.0, 3.6 Hz, 1H), 4.12 (dd, J = 6.0, 3.6 Hz, 1H), 4.08 (qd, J = 6.6, 6.6 Hz, 1H), 3.67 (dd, J = 6.0, 3.6 Hz, 1H), 1.27 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2, 128.4, 127.8, 127.7, 99.0, 71.8, 70.4, 69.8, 68.5, 56.0, 16.9; HRMS calcd for $[C_{13}H_{17}BrO_4 + Na]^+$ 339.0202, found 339.0204.

(2*R*,3*R*,5*R*,6*S*)-2-(Benzyloxy)-6-methyltetrahydro-2*H*-pyran-3,5-diol (18). To a solution of bromide **19** (17 mg, 0.05 mmol) in dry toluene (0.5 mL) were added tris(trimethylsilyl)silane (TTMSS) (0.033 mL, 0.1 mmol) and AIBN (4 mg, 0.025 mmol) at 0 °C. At this stage, the reaction mixture was degassed using a freeze−pump−thaw technique three times. The reaction mixture was then stirred at 80 °C for 4 h under Ar. The mixture was directly loaded onto silica gel column for purification to give α-ascarylose **18** (10 mg, 0.038 mmol, 76%) as a colorless oil.

Alternative Procedure for 18. To a round-bottom flask were added epoxide **8** (23 mg, 0.094 mmol), THF (0.5 mL), and $LiAlH_4$ (7.1 mg, 0.19 mmol) at 0 °C. The reaction solution was stirred for 30 min at 0 °C. Water was added dropwise to quench the reaction, and then the mixture was extracted with EtOAc. The organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give α-ascarylose **18** (19 mg, 0.08 mmol, 85%) as a colorless oil: R_f (60% EtOAc/hexane) 0.17; $[\alpha]^{20}_D$ −90.8 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) ν 3405, 2935, 1718, 1686, 1256, 1123, 1080, 995; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.74 (d, J = 12.0 Hz, 1H), 4.68 (s, 1H), 4.53 (d, J = 12.0 Hz, 1H), 3.91 (dd, J = 4.8, 3.0 Hz, 1H), 3.70 (dq, J = 9.6, 6.0 Hz, 1H), 3.61 (ddd, J = 10.8, 9.0, 4.2 Hz, 1H), 2.09 (ddd, J = 13.2, 3.6, 3.6 Hz, 1H), 1.89 (ddd, J = 13.2, 11.4, 3.0 Hz, 1H), 1.30 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.4, 128.5, 127.9, 127.8, 98.2, 69.8, 69.0, 68.8, 68.1, 35.2, 17.7; HRMS calcd for $[C_{13}H_{18}O_4 + H]^+$ 239.0202, found 239.0204.

(2*R*,3*S*,6*S*)-6-(Benzyloxy)-2-methyltetrahydro-2*H*-pyran-3-ol (20). To a solution of allylic alcohol (*ent*)-**11** (40 mg, 0.18 mmol) in *N*-methylmorpholine (NMM) (0.5 mL) was added *o*-nitrobenzenesulfonyl hydrazide (NBSH) (118 mg, 0.54 mmol) followed by addition of Et_3N (100 μL). The mixture was stirred at rt for 1 day, and then more NBSH (60 mg, 0.27 mmol) was added and the mixture stirred at rt overnight. At 0 °C, the reaction mixture was diluted with ethyl acetate and washed with 1 M HCl (aq). The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was subsequently washed with saturated aqueous $NaHCO_3$ and saturated brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography. Elution with hexane/EtOAc (3.5:1, v/v) afforded the dideoxysugar **20** (26 mg, 64%) as a clear oil: R_f (hexanes/EtOAc, 2:1 v/v) 0.24; $[\alpha]^{20}_D$ + 133.2 (*c* 1.26, $CHCl_3$); IR (thin film, cm^{-1}) ν 3419 (broad), 3071, 3037, 2936, 2891, 1501, 1453, 1350, 1227, 1123, 1045, 982; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38−7.33 (m, 4H), 7.29 (m, 1H), 4.84 (dd, J = 3.0, 1.2 Hz, 1 H), 4.71 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1H), 3.66 (dq, J = 9.0, 6.0 Hz, 1H), 3.29 (dddd, J = 9.6, 9.0, 5.4, 4.8 Hz, 1 H), 1.88 (m, 2H), 1.80 (m, 2H), 1.45 (d, J = 4.8 Hz, OH), 1.27 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.1, 128.4, 127.8, 127.6, 95.5, 72.2, 69.6, 68.6, 29.6, 27.7, 17.9; HRMS calcd for $[C_{13}H_{18}O_3 + Na]^+$ 245.1148, found 245.1148.

Benzyl (2*R*,3*S*,6*S*)-6-(Benzyloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ylcarbonate (21). A solution of allylic alcohol (*ent*)-**11** (224 mg, 1.03 mmol) in CH_2Cl_2 (4 mL) at rt was added 60% NaH (220 mg, 5.5 mmol) in CH_2Cl_2 (4 mL), which was washed with hexane before use. Then n-Bu_4NI (369 mg, 1 mmol) was added to the mixture followed by the addition of DMAP (61 mg, 0.5 mmol). The reaction mixture was stirred at rt for 2 h. It was then diluted with Et_2O and washed with saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O twice. The combined organic layer was then washed with saturated aqueous $NaHCO_3$ and saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography, and

elution with hexane/EtOAc (15:1, v/v) afforded the carbonate **21** (270 mg, 74%) as a colorless viscous oil: R_f (hexanes/EtOAc, 3:1 v/v) 0.44; $[\alpha]^{20}_D$ +96.1 (*c* 4.48, $CHCl_3$); IR (thin film, cm^{-1}) ν 3032, 2979, 2936, 1747, 1497, 1456, 1382, 1250, 1049, 1020, 962; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.41−7.34 (m, 9H), 7.31(m, 1H), 5.96 (d, J = 10.2 Hz, 1 H), 5.85 (ddd, J = 9.6, 2.4, 1.8 Hz, 1 H), 5.21 (d, J = 12.6 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 5.08 (brs, 1H), 4.94 (ddd, J = 9.0, 3.0, 1.8 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.05 (dq, J = 9.6, 6.6 Hz, 1H), 1.24 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.7, 137.9, 135.0, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6, 93.6, 74.7, 70.1, 69.8, 64.7, 17.8; HRMS calcd for $[C_{21}H_{22}O_5 + Na]^+$ 377.1359, found 377.1362.

***tert*-Butyl (2*R*,3*S*,6*S*)-6-(Benzyloxy)-2-methyl-3,6-dihydro-2*H*-pyran-3-ylcarbonate (22).** A solution of allylic alcohol (*ent*)-**11** (519 mg, 2.38 mmol) and DMAP (14.5 mg, 0.119 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added a solution of Boc_2O (778 mg, 3.57 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was then stirred at rt for 1 h. It was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$ at 0 °C. The mixture was stirred at 0 °C for 20 min and then was extracted with Et_2O, and the aqueous layer was extracted again with Et_2O. The pooled organic layer was subsequently washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography, and elution with hexane/EtOAc (20:1, v/v) afforded the carbonate **22** (663 mg, 87%) as a white solid: mp 60−62 °C; R_f (hexanes/EtOAc, 3:1 v/v) 0.60; $[\alpha]^{20}_D$ +88.6 (*c* 2.99, $CHCl_3$); IR (thin film, cm^{-1}) ν 2982, 2935, 1732, 1455, 1370, 1336, 1317, 1286, 1269, 1254, 1154, 1094, 1049, 1028, 969; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.38−7.32 (m, 4H), 7.29 (m, 1H), 5.93 (d, J = 10.2 Hz, 1 H), 5.82 (ddd, J = 10.8, 2.4, 1.8 Hz, 1 H), 5.06 (brs, 1H), 4.86 (ddd, J = 9.0, 3.0, 1.8 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.01 (dq, J = 9.0, 6.0 Hz, 1H), 1.50 (s, 9H), 1.22 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.1, 138.1, 129.7, 128.4, 127.9, 127.8, 127.6, 93.7, 82.6, 73.5, 70.1, 64.9, 27.7, 17.8; HRMS calcd for $[C_{18}H_{24}O_5 + Na]^+$ 343.1516, found 343.1517.

(3a*R*,4*R*,6*S*,7*S*,7a*R*)-6-(Benzyloxy)-7-iodo-4-methyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-2-one ((*ent*)-10). To a solution of allyl carbonate **22** (285 mg, 0.90 mmol) in HOAc (3 mL) was added NIS (320 mg, 1.42 mmol) at rt. It was stirred at rt for 12 h, more NIS (230 mg, 1.0 mmol) was added, and the mixture was stirred at rt for another 12 h. The reaction mixture was diluted with EtOAc, cooled to 0 °C, and quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the organic layer was washed subsequently with saturated aqueous $Na_2S_2O_3$ and saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography, and elution with hexane/EtOAc (5:1, v/v) afforded the iodocarbonate (*ent*)-**10** (335 mg, 95%) as a white solid: mp 80.5−82.5 °C; R_f (hexanes/EtOAc, 3:1 v/v) 0.38; $[\alpha]^{20}_D$ +52.0 (*c* 2.65, $CHCl_3$); IR (thin film, cm^{-1}) ν 3030, 2980, 2935, 1839, 1806, 1497, 1454, 1347, 1331, 1147, 1087, 1053, 1021, 970; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.39−7.34 (m, 4H), 7.32 (m, 1H), 5.16 (d, J = 5.4 Hz, 1 H), 4.96 (dd, J = 8.4, 7.8 Hz, 1 H), 4.76 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.40 (dd, J = 9.0, 7.8 Hz, 1H), 4.21 (dd, J = 8.4, 6.0 Hz, 1H), 4.05 (dq, J = 9.0, 6.6 Hz, 1H), 1.35 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.9, 136.6, 128.5, 128.1, 127.9, 101.0, 78.7, 77.1, 70.2, 64.0, 21.0, 18.6; HRMS calcd for $[C_{14}H_{15}IO_5 + Na]^+$ 412.9856, found 412.9859.

Alternative Procedure for (*ent*)-10. To a solution of allyl carbonate **22** (31.8 mg, 0.1 mmol) and NIS (33.8 mg, 0.15 mmol) in CH_2Cl_2 (0.8 mL) was added $MgBr_2 \cdot Et_2O$ (25.8 mg, 0.1 mmol) at rt. It was stirred at rt for 12 h, then more NIS (22.5 mg, 0.1 mmol) was added, and the mixture was stirred at rt for another 24 h. The reaction mixture was diluted with EtOAc, cooled to 0 °C, and quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the organic layer was washed subsequently with saturated aqueous $Na_2S_2O_3$ and saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, a crude ^1H NMR experiment showed that the ratio of product and remaining starting material is 2:1. Then the residue was subjected to silica gel column chromatography, and elution with hexane/EtOAc (7:1, v/v) afforded iodocarbonate (*ent*)-**10** (10.1 mg, 26%).

Second Alternative Procedure for (*ent*)-10. A solution of allyl carbonate **21** (35.4 mg, 0.10 mmol) in HOAc (3 mL) was added NIS (33.8 mg, 0.15 mmol) at rt. It was stirred at rt for 12 h, then more NIS (22.5 mg, 0.1 mmol) was added, and the mixture was stirred at rt for another 24 h. Once again, more NIS (22.5 mg, 0.1 mmol) was added, and the mixture was stirred at rt for an additional 24 h. The reaction mixture was diluted with EtOAc, and cooled to 0 °C, and quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the organic layer was washed subsequently with saturated aqueous $Na_2S_2O_3$ and saturated brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography. Elution with hexane/EtOAc (7:1, v/v) afforded the iodocarbonate (*ent*)-**10** (20 mg, 51%).

(3a*R*,4*R*,6*S*,7a*S*)-6-(Benzyloxy)-4-methyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-2-one (23). To a solution of iodocarbonate (*ent*)-**10** (59 mg, 0.15 mmol) in toluene (2 mL) was added tris(trimethylsilyl)silane (TTMSS) (70 μL, 0.22 mmol) and then solid AIBN (5 mg, 0.03 mmol) was quickly added in one portion at 0 °C. The system was then cooled to approximately −50 °C, degassed with vacuum, and refilled with Ar. This procedure was repeated three times, and then the mixture was heated to 75 °C for 40 min. The reaction mixture was cooled to rt and then directly loaded onto silica gel column. Elution with hexane/EtOAc (3:1, v/v) afforded carbonate **23** (17.8 mg, 45%) as a colorless viscous oil: R_f (hexanes/EtOAc, 2:1 v/v) 0.29; $[\alpha]^{20}_D$ +129.5 (*c* 0.93, $CHCl_3$); IR (thin film, cm^{-1}) ν 3035, 2975, 2940, 1798, 1454, 1356, 1175, 1152, 1066, 1036, 1023, 919; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.36−7.27 (m, 5H), 4.92 (dd, J = 5.4, 4.8 Hz, 1 H), 4.78 (ddd, J = 7.2, 7.2, 6.0 Hz, 1 H), 4.71 (d, J = 12.6 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.26 (dd, J = 9.0, 7.8 Hz, 1H), 4.01 (dq, J = 9.0, 6.0 Hz, 1H), 2.31 (ddd, J = 15.0, 5.4, 5.4 Hz, 1H), 2.19 (ddd, J = 15.0, 7.2, 4.8 Hz, 1 H), 1.31 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.3, 137.2, 128.5, 127.8, 127.7, 94.2, 77.0, 72.5, 69.3, 63.3, 30.7, 18.5; HRMS calcd for $[C_{14}H_{16}O_5 + Na]^+$ 287.0890, found 287.0890.

(2*R*,3*S*,4*S*,6*S*)-6-(Benzyloxy)-2-methyltetrahydro-2*H*-pyran-3,4-diol ((*ent*)-9)[17]. To a solution of carbonate **23** (16 mg, 0.06 mmol) in THF (2 mL) was added 2 M NaOH (1 mL). The mixture was stirred at rt for 1 h. It was then diluted with EtOAc and passed through a pad of Celite, eluting with EtOAc/MeOH (3:1, v/v). The eluent was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography, and elution with hexane/EtOAc (1.5:1, v/v) afforded the α-digitoxose (*ent*)-**9** (12 mg, 84%) as a colorless oil: R_f (hexanes/EtOAc, 1:1 v/v) 0.25; $[\alpha]^{20}_D$ +107.5 (*c* 1.2, $CHCl_3$); IR (thin film, cm^{-1}) ν 3461 (broad), 3090, 3065, 3033, 2975, 2918, 1497, 1454, 1407, 1235, 1148, 1120, 1101, 1054, 1010, 970; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.39−7.35 (m, 2H), 7.34−7.30 (m, 3H), 4.97 (d, J = 3.6 Hz, 1 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.50 (d, J = 11.4 Hz, 1H), 3.96 (brs, 1 H), 3.77 (dq, J = 9.6, 6.0 Hz, 1H), 3.45 (brs, OH), 3.16 (dd, J = 10.2, 3.6 Hz, 1H), 2.48 (brs, OH), 2.22 (ddd, J = 15.0, 3.0, 1.2 Hz, 1H), 1.94

(17) (a) Current, S.; Sharpless, K. B. *Tetrahedron Lett.* **1978**, *19*, 5075–5078. (b) Koepper, S.; Thiem, J. *J. Carbohydr. Chem.* **1987**, *6*, 57–85.

(ddd, $J = 15.0, 3.6, 3.6$ Hz, 1H), 1.33 (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 136.9, 128.6, 128.1, 127.9, 96.4, 72.6, 69.5, 67.3, 64.7, 35.1, 17.8.

Acknowledgment. We are grateful to the NSF (CHE-0749451) and the ACS-PRF (47094-AC1) for the support of our research program and NSF-EPSCoR (0314742) for a 600 MHz NMR at WVU. A dissertation fellowship to M.S. from WVU's Office of Graduate Study and Life is greatly appreciated.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.