Acylketene [4 + 2] Cycloadditions: Divergent de Novo Synthesis of 2,6-Dideoxy Sugars

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Received August 13, 1992

The synthetic methodology demonstrated herein provides a divergent, de novo synthetic pathway to 2,6-dideoxy carbohydrates. Pyranone **2**, which was prepared by [4 + 2] cycloaddition of the acylketene generated from dioxinone **1** with butyl vinyl ether, was converted in a straightforward manner to *arabino*-hexopyranosides olivoside **11** and oleandroside **12**, and branched sugars olivomycoside **14** and chromoside B **15**, with near complete control of relative stereochemistry at the three newly introduced stereogenic centers. Olivoside **11** proved to be a pivotal intermediate for elaboration to the ribo, lyxo, and xylo families of 2,6-dideoxy carbohydrates. Selective Mitsunobu inversion at C3 of **11** provided ready access to the *ribo*-pyranoside digitoxoside **17**, whereas selective inversion at C4 of **11** or **12** via the intermediacy of the O^4-trifluoromethanesulfonate ester gave rise to the *lyxo*-pyranosides olioside **23** and diginoside **21**, respectively. A high-yielding sequence of reactions for the elaboration of **11** to *lyxo*-anhydro sugar **25** furnished an intermediate for the direct conversion to the *xylo*-pyranosides boivinoside **30** and sarmentoside **31** by a regioselective epoxide opening.

Introduction

Deoxy and branched sugars are widely distributed among plants, fungi, and bacteria. Naturally occurring antibiotic and antitumor agents isolated from these sources are often embellished with a variety of such highly modified sugars.[2] Among the structural classes of carbohydrates found as the glycosidic component(s) of these natural products, the 2,6-dideoxy substitution pattern is frequently encountered[2] (cf. Figure 1), being present in such medicinally important agents as aureolic acids,[3a] anthracycline antibiotics,[3b] and cardiac glycosides.[3c] The de novo synthesis of carbohydrates from acyclic precursors has remained a significant and extensive focus of many research groups,[4] and although numerous methods have appeared for the construction of deoxysugars using preexisting carbohydrate frameworks,[5] these methods can be lengthy and suffer from lack of generality. Herein, we report the development of efficient, stereocontrolled synthetic approaches to each member of the 2,6-dideoxy hexopyranoside family of carbohydrates. The *arabino*-, *ribo*-, *xylo*-, and *lyxo*-hexopyranose sugars whose syntheses are detailed herein are shown in Figure 1.

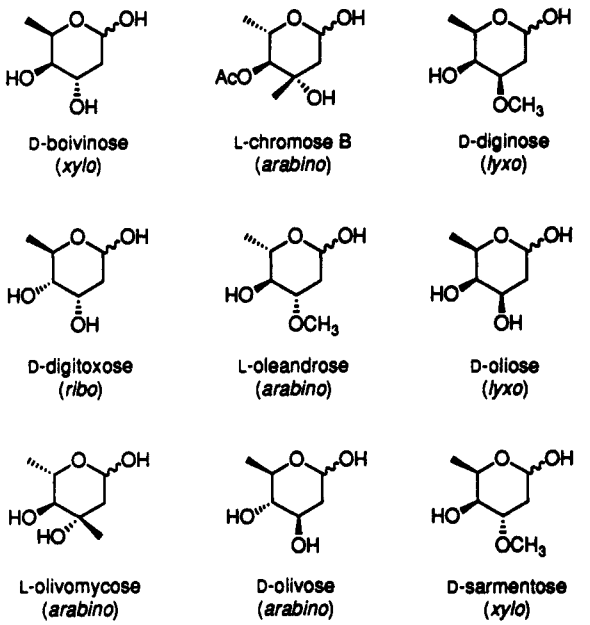
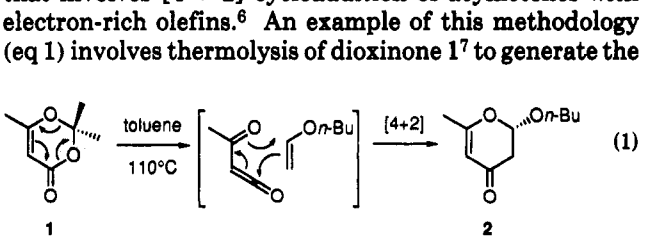


Figure 1.

We recently communicated a method for the one-step construction of 2,3-dihydro-4*H*-pyran-4-one ring systems that involves [4 + 2] cycloaddition of acylketenes with electron-rich olefins.[6] An example of this methodology (eq 1) involves thermolysis of dioxinone **1**[7] to generate the



(1)

1 **2**

intermediate acylketene via a cycloreversion reaction. The reactive acylketene undergoes in situ [4 + 2] cycloaddition with butyl vinyl ether to afford dihydropyranone **2** in good

(1) Recipient of a Camille and Henry Dreyfus Foundation Distinguished New Faculty Award (1989–1994) and an American Cancer Society Junior Faculty Research Award (1991–1993).

(2) Williams, N. R.; Wander, J. D. In *The Carbohydrates*; Pigman, W., Horton, D., Wander, J. D., Eds.; Academic Press: New York, 1980; Vol. IB, p 761. Mallams, A. K. In *Carbohydrate Chemistry*; Kennedy, J. F., Ed.; Clarendon Press: Oxford, 1988; p 73.

(3) (a) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979. (b) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288. (c) Reichstein, T.; Weiss, E. *Adv. Carbohydr. Chem.* **1962**, *17*, 65.

(4) *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series 386; Washington, D.C., 1989. Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 415. Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250. McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohdr. Chem. Biochem.* **1982**, *40*, 1. Danishefsky, S. J. *Acc. Chem. Res.* **1981**, *14*, 400. Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395.

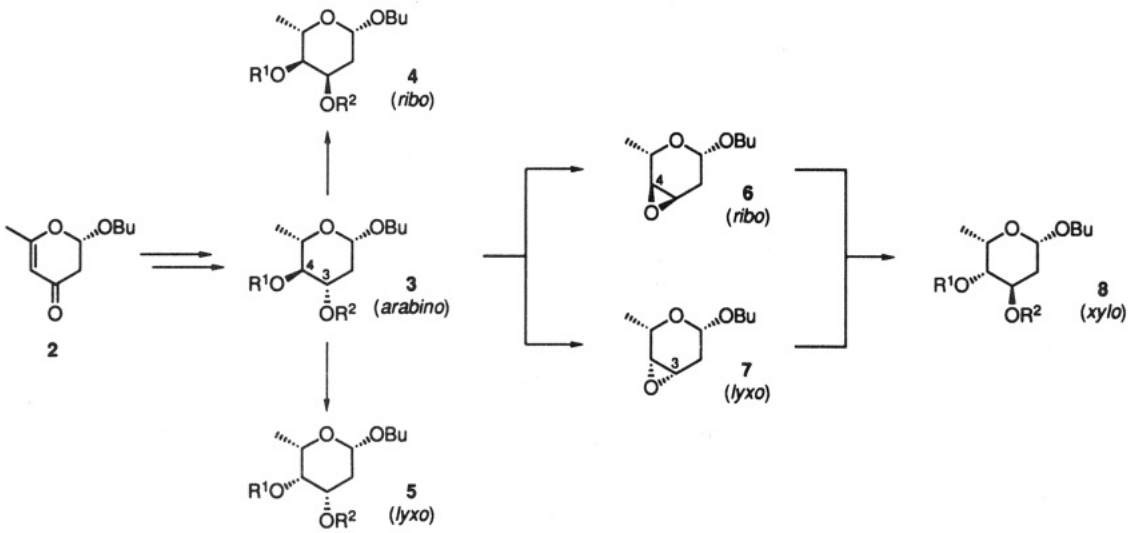
(5) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: Oxford, 1983. Baggett, N. In *Carbohydrate Chemistry*; Kennedy, J. F., Ed.; Clarendon Press: Oxford, 1988; p 381. Brimacombe, J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 236.

(6) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1990**, *31*, 3677.

(7) Commercially available from Aldrich Chemical Co. and MTM Lancaster Synthesis, Ltd.

0022-3263/93/1958-0385$04.00/0

Scheme I



yields.[6] Cycloadduct **2** appeared ideally suited to serve as a platform for elaboration to more functionally and stereochemically evolved pyranoid systems. Herein, we provide full details of our studies on the use of **2** for the divergent de novo synthesis of a wide range of biologically important 2,6-dideoxy carbohydrates.

Implementation of this cycloaddition methodology[6] in the de novo synthesis of biologically interesting 2,6-dideoxy carbohydrates is illustrated in Scheme I. In this divergent tactic, pyranone **2** serves as a template upon which the oxygen and carbon functionality of the targeted carbohydrates is introduced in a regio- and diastereoselective manner. It was envisioned that carbohydrates of the arabino configuration (**3**) would be available directly from pyranone **2** by a diastereoselective 1,2-reduction of the carbonyl group followed by a stereoselective hydroboration of the resulting allylic alcohol. *arabino*-Pyranosides **3**, in turn, would serve a pivotal role as precursors to carbohydrates of the ribo, lyxo, and xylo configurations. Conversion of **3** to *ribo*-pyranosides **4** could be achieved directly by selective inversion of configuration at C3. Conversely, selective configurational inversion at C4 would provide *lyxo*-pyranosides **5**. Sugars possessing the xylo substitution pattern could be accessed by a double inversion at both C3 and C4 of **3**. In principle, this could be achieved through the intermediacy of either the *ribo*-(**6**) or *lyxo*-anhydropyranoside **7** by regioselective (stereoelectronically controlled) epoxide opening at C4 of **6** or C3 of **7** to provide access to *xylo*-pyranosides **8**. Thus, all four stereochemical families of 2,6-dideoxy sugars are available from the single, readily constructed pyranone **2**.

Results

Analysis of **2** by ^{1}H NMR and molecular modeling (PCMODEL) revealed that the 2,3-dihydro-4*H*-pyran-4-one ring system adopts the conformation shown in Figure 2, wherein the anomeric alkoxy group exists in a pseudoaxial conformation (*n*-Bu replaced by CH_3 to simplify calculations). This is clearly evidenced by the values of the geminal ^{1}H NMR coupling constants measured for C2-H of **2** ($J_{2,3}$ = 5.8, 3.9 Hz),[6] which are indicative of a pseudoequatorial hydrogen and thus a pseudoaxial alkoxy group. Addition of a nucleophile in a 1,2-manner to the C4-carbonyl was predicted to occur selectively from the β-face of **2**, anti to the anomeric alkoxy group, resulting

Figure 2.

in a product bearing C2,C4-syn stereochemistry. This prediction was to provide the cornerstone of our stereocontrolled synthetic approach to 2,6-dideoxy carbohydrates as it provided an effective method for stereochemical communication from C2 to C4; subsequent manipulations would further transfer this stereochemistry to C5 and C6.

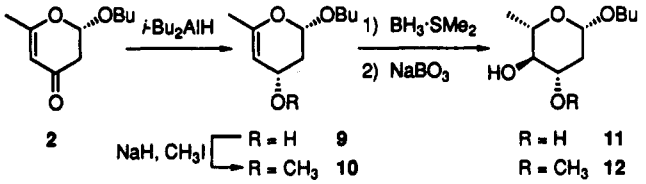
***arabino*-Pyranosides.** The above strategy was implemented in the total syntheses of olivoside **11** and oleandroside **12**, 2,6-dideoxy-*arabino*-hexopyranosides that occur in mithramycin[8e] and avermectin,[12g] respectively. Stereoselective 1,2-reduction of the C4-carbonyl of **2** with diisobutylaluminum hydride (1.8 equiv, toluene, 0 °C) occurred with 10:1 face selectivity to afford unstable allylic alcohol **9** in 96% crude isolated yield. *n*-Butyl β-DL-olivoside (**11**)[8,9] was obtained in 68% yield from crude **9** through hydroboration (2 equiv of BH_3·SMe_2, THF, 0–26 °C) and oxidation ($NaBO_3$, 26 °C)[10a] in a process that occurred with complete stereo- and regioselectivity.[10b] O-Methylation of **9** (5 equiv of NaH, 5 equiv of CH_3I, 5:1

(8) (a) Toshima, K.; Yoshida, T.; Mukaiyama, S.; Tatsuta, K. *Carbohydr. Res.* **1991**, *222*, 173. (b) Hatakeyama, S.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1986**, *27*, 4485. (c) Schmidt, R. R.; Maier, M. *Ibid.* **1985**, *26*, 2065. (d) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5093. (e) Bakhaeva, G. P.; Berlin, Y. A.; Boldyreva, E. F.; Chuprunova, O. A.; Kolosov, M. N.; Soifer, V. S.; Vasiljeva, T. E.; Yartseva, I. V. *Tetrahedron Lett.* **1968**, 3595.

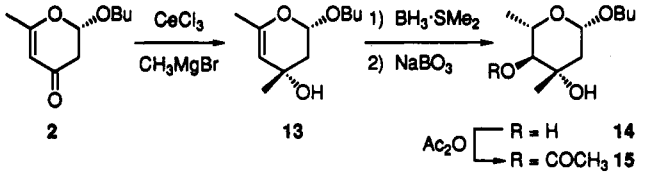
(9) The *n*-butyl glycoside of **11** could be removed hydrolytically by treatment with 5% HCl/THF (1:20) at reflux (2 h) to afford α- and β-DL-olivose (48:52), which exhibited ^{1}H NMR spectra identical with published data.[8d]

(10) (a) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483. (b) Brown, H. C.; Gallivan, R. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2906. Brown, H. C.; Sharp, R. L. *Ibid.* **1968**, *90*, 2915. Anselmi, C.; Catelani, G.; Monti, L. *Gazz. Chim. Ital.* **1983**, *113*, 167.

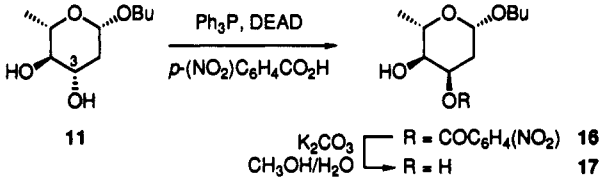
THF/DMF)[11] provided methyl ether **10** (94%), and hydroboration followed by oxidation afforded *n*-butyl β-DL-oleandroside (**12**)[8a,b,12] in 84% yield. The syntheses of **11** and **12** are exceptionally efficient, proceeding from readily available **2** in two or three steps, respectively, with excellent control of relative stereochemistry using the intrinsic conformational and stereoelectronic biases of the reaction substrates.



Sugars branched at C3 can be prepared in a similar manner. Thus, the total synthesis of olivomycoside **14** and chromoside B **15** was achieved from pyranone **2**. Addition of methylcerium dichloride[13] ($CeCl_3$, CH_3MgBr, THF, 0 °C) to **2** occurred selectively in a 1,2-fashion and afforded tertiary alcohol **13** in 78% yield with 7:1 diastereoselectivity. In contrast, the addition of CH_3Li or CH_3MgBr to **2** proved low yielding and afforded ring-opened products resulting from α-hydrogen abstraction. Hydroboration and oxidation of **13** under standard conditions afforded *n*-butyl β-DL-olivomycoside (**14**),[8a,14] a component of olivomycin,[14c] in 55% yield and in two steps from **2**. Selective acylation of the secondary alcohol of **14** with acetic anhydride afforded *n*-butyl β-DL-chromoside B (**15**), which is found in chromomycin,[15] in quantitative yield. Branched sugars **14** and **15** are thereby available from pyranone **2** in two or three steps, respectively.



***ribo*-Pyranosides.** Conceptually, a direct and efficient construction of 2,6-dideoxy carbohydrates of the *ribo*-hexopyranose family can be achieved by selective configurational inversion at C3 of an *arabino*-pyranoside such as **11**. Illustrative of the success of this strategy is the total synthesis of digitoxoside **17**. Selective inversion at the less sterically hindered C3-alcohol was efficiently accomplished using a Mitsunobu reaction[16a] employing the conditions of Martin and Dodge.[16b] Thus, treatment of *arabino*-pyranoside **11** with *p*-nitrobenzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate (toluene, 26 °C)[16b] afforded the selectively protected *ribo*-pyranoside **16** in 75% yield. Hydrolysis of the benzoate ester of **16** (K_2CO_3, CH_3OH/H_2O, 26 °C) afforded *n*-butyl β-DL-digitoxoside (**17**),[8a,b,17] a component of kijanimicin,[17d] in 71% yield.



***lyxo*-Pyranosides.** In a strategy similar to that used for the synthesis of 2,6-dideoxy-*ribo* sugars, selective inversion of configuration at C4 of an *arabino*-pyranoside would provide direct access to members of the *lyxo*-pyranoside family. In practice, this strategy suffers from two problems: (1) inversion of configuration at the C4 stereogenic center by nucleophilic displacement is inherently more difficult due to the more sterically crowded environment at this center, and (2) displacement of a leaving group at C4 vs C3 is disfavored on stereoelectronic grounds due to a destabilizing antiparallel dipole alignment of the pyran C–O bond and the C4-leaving group bond in the reaction transition state.[18] The success of this strategy depended on the combination of an excellent leaving group and a highly reactive nucleophile.

The selectively protected *arabino*-pyranosides **12** and **18** were used as substrates for C4-inversion. *O*-Benzyl ether **18** was prepared from olivoside **11** by treatment with *n*-Bu_2SnO followed by selective O^3-alkylation with benzyl bromide,[19] and oleandroside **12** was prepared as described previously. Acylation of **12** and **18** with trifluoromethanesulfonic anhydride (pyridine, 0 °C) quantitatively afforded the triflate esters **19** and **20**, respectively, which were used without purification. Treatment of triflates **19** and **20** with excess potassium superoxide[20] (DMF, 18-crown-6, 0 °C) effected clean inversion of configuration at C4 providing *n*-butyl β-DL-diginoside (**21**),[21] which is found in cardiac glycosides,[21c] and *n*-butyl 3-*O*-benzyl-β-DL-olioside (**22**) in 59% and 62% yield, respectively. Hydrogenolysis of the *O*-benzyl ether of **22** (Pd black, 1 atm H_2, CH_3OH) afforded *n*-butyl β-DL-olioside (**23**),[8d] a component of chromomycin,[15] in 97% yield. The use of the corresponding O^4-methanesulfonate esters of **12** and **18** in S_N2 displacement reactions was unsuccessful[22] and led to sulfur-oxygen bond cleavage upon reaction with

(11) Coggins, J. R.; Benoiton, N. L. *Can. J. Chem.* **1971**, *49*, 1968.
(12) (a) Ford, M. J.; Ley, S. V. *Synlett.* **1990**, 771. (b) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967. (c) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489. (d) Berti, G.; Catelani, G.; Colonna, F.; Monti, L. *Tetrahedron* **1982**, *38*, 3067. (e) Ohzeki, M.; Mizoguchi, T.; Koga, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 2676. (f) Yasuda, S.; Matsumoto, T. *Tetrahedron* **1973**, *29*, 4087. (g) Albers-Schoñberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216.
(13) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392 and references cited therein.
(14) (a) Hatakeyama, S.; Sugawara, K.; Takano, S. *Tetrahedron Lett.* **1991**, *32*, 4513. (b) Fuganti, C.; Grasselli, P.; Marinoni, G. Ibid. **1979**, *20*, 1161. (c) Berlin, Y. A.; Esipov, S. E.; Kolosov, M. N.; Shemyakin, M. M.; Brazhnikova, M. G. *Ibid.* **1964**, 3513.
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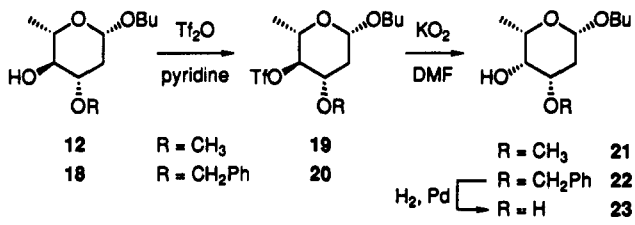
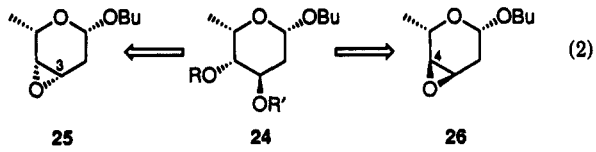
(16) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(17) (a) Fujisawa, T.; Kojima, E.; Itoh, T.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 6089. (b) Fronza, G.; Fuganti, C.; Grasselli, P.; Servi, S. *Ibid.* **1985**, *26*, 4961. (c) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Ibid.* **1982**, *23*, 4143. (d) Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938.
(18) Richardson, A. C. *Carbohydr. Res.* **1969**, *10*, 395.
(19) Monneret, C.; Gagnet, R.; Florent, J.-C. *J. Carbohydr. Chem.* **1987**, *6*, 221. For a review see: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(20) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, *37*, 3183.
(21) (a) Herczegh, P.; Kovaćs, I.; Sztaricskai, F. J. *Tetrahedron* **1991**, *47*, 1541. (b) Mukaiyama, T.; Yamada, T.; Suzuki, K. *Chem. Lett.* **1983**, 5. (c) Renkonen, O.; Schindler, O.; Reichstein, T. *Helv. Chim. Acta* **1959**, *42*, 182.

KO_2. The combination of triflates **19** and **20** with less reactive nucleophiles[23] proved equally unsuccessful.



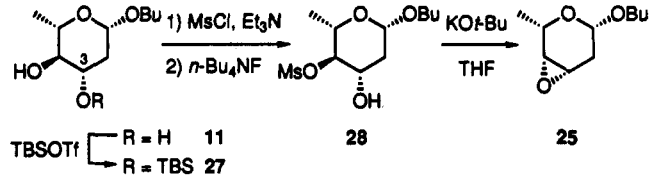
***xylo*-Pyranosides.** Construction of the *xylo*-pyranose ring system from an *arabino*-pyranose (cf. Scheme I) necessitates configurational inversion at both the C3 and C4-stereogenic centers. The proposed synthesis of *xylo*-pyranoside **24** (eq 2) was envisioned to occur through the



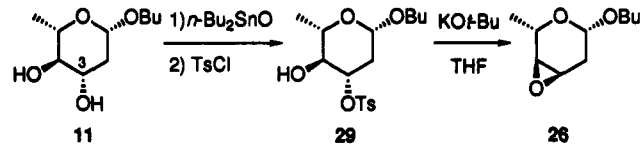
(2)

intermediacy of either the *lyxo*-epoxide **25** or the *ribo*-epoxide **26**; in principle, both epoxides converge to the same C3,C4-trans-1,2-diol array as a result of the stereoelectronic requirement for trans-diaxial epoxide opening.[24] *lyxo*-Epoxide **25** was anticipated to react with nucleophiles at C3 to afford **24**, whereas *ribo*-epoxide **26** was proposed to react at C4, likewise to afford **24**. Thus, an effectual synthesis of *xylo*-pyranosides was envisioned to require an efficient synthesis of **25** or **26**, most appropriately starting with readily available olivoside **11**.

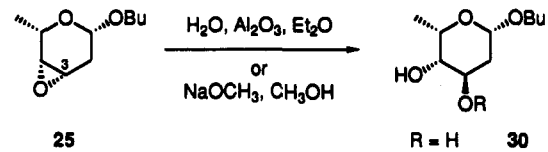
A high-yielding synthesis of *lyxo*-epoxide **25** was achieved starting from olivoside **11**. Initial efforts at selective protection of the C3-hydroxyl group of **11** as the acetate ester or trimethylsilyl ether were unsuccessful, whereas reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) under carefully controlled conditions (1 equiv, 2,6-lutidine, CH_2Cl_2, −20 °C) selectively afforded the O^3-silyl ether **27** in 83% yield. Acylation of the remaining C4-hydroxyl group of **27** with methanesulfonyl chloride (Et_3N, CH_2Cl_2, −20 °C, 89%) followed by fluoride-promoted removal of the silyl ether (*n*-Bu_4NF, THF, 0 °C, 98%) afforded the O^4-methanesulfonate **28**, surprisingly without cyclization occurring under the basic reaction conditions. Cyclization of **28** was achieved by treatment with potassium *tert*-butoxide (THF, 0 °C), providing *lyxo*-epoxide **25** in 98% yield. The elaboration of epoxide **25** was achieved efficiently in four steps from **11** in 71% overall yield. A strategy for the synthesis of **25** based on the formation of the O^3,O^4-dimethanesulfonate ester of **11** followed by regioselective O^3-sulfonate cleavage and subsequent epoxide formation was unsuccessful.[25a]



A two-step synthesis of *ribo*-epoxide **26** was developed starting from olivoside **11**. Since acylation of the C3-hydroxyl group of **11** with methanesulfonyl chloride or *p*-toluenesulfonyl chloride proved nonselective, a strategy that relied on the directing influence of a cyclic stannylene acetal[19] for acylation of the C3-hydroxyl group of **11** was selected. Treatment of **11** with di-*n*-butyltin oxide (toluene, 110 °C) with azeotropic removal of water afforded the intermediate stannylene acetal,[19] which was not isolated, but was treated directly with *p*-toluenesulfonyl chloride in the presence of *n*-Bu_4NI (toluene, 25 °C) to provide O^3-toluenesulfonate **29** in 98% yield. Cyclization of **29** was initiated by treatment with potassium *tert*-butoxide (THF, 0 °C) and afforded *ribo*-epoxide **26** in 89% yield. The construction of epoxide **26** was effected in two steps from **11** in 87% overall yield. Treatment of **11** with the Mitsunobu reagent system (Ph_3P, $EtO_2CN{=}NCO_2Et$) did not effect cyclization to **26**.[25b]



lyxo-Epoxide **25** reacted with nucleophiles with complete regioselectivity and afforded products that resulted from *exclusive* attack at C3, as predicted by stereoelectronic arguments. Thus, treatment of *lyxo*-epoxide **25** with H_2O preadsorbed on Al_2O_3 (Et_2O, 26 °C)[26] afforded *n*-butyl β-DL-boivinoside (**30**)[8d,27] in 67% yield, and treatment of **25** with sodium methoxide in methanol (70 °C) afforded *n*-butyl β-DL-sarmentoside (**31**)[21a] in 90% yield. These sugars both occur as components of the cardiac glycosides.[27c,28]



Distressingly, although not surprisingly,[29] *ribo*-epoxide **26** proved completely nonselective in its reactions with nucleophiles under acidic and basic conditions and af-

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(29) This lack of regiocontrol in the nucleophilic oxirane opening reactions of *ribo*-pyranosides related to **26** is well precedented: Martin, A.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1983**, *113*, 189.

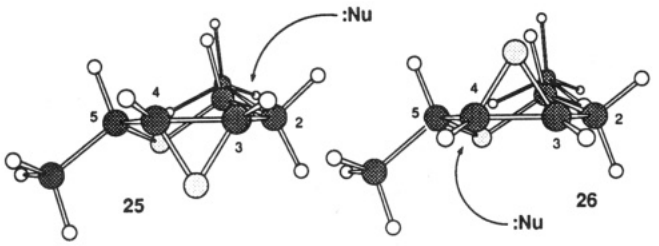
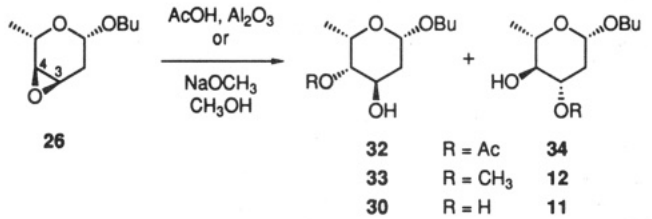


Figure 3.

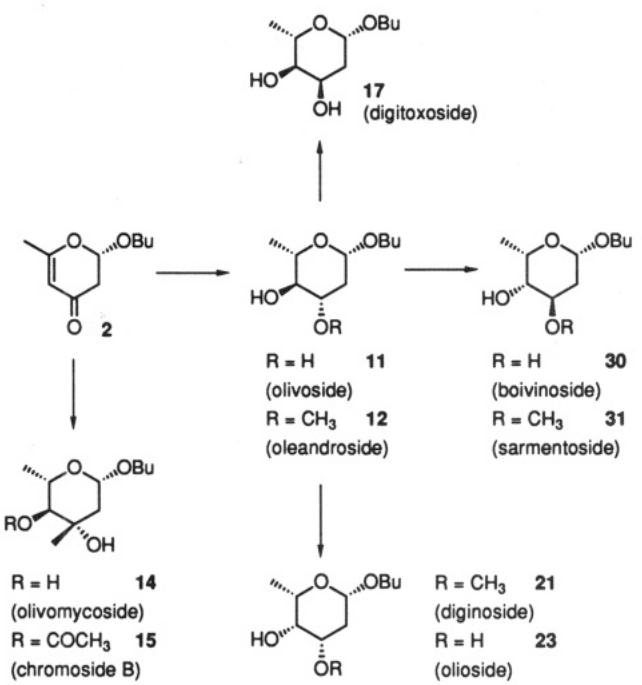
forded products that resulted from attack at *both* C3 and C4. For instance, reaction of **26** with acetic acid preadsorbed on Al_2O_3 (Et_2O, 26 °C)[26] effected slow epoxide opening to afford *n*-butyl 4-*O*-acetyl-β-DL-boivinoside (**32**) and "recovered," C3-opened *n*-butyl 3-*O*-acetyl-β-DL-olivoside (**34**) along with the corresponding diols **30** and **11** in low yields (≤10% each). Likewise, treatment of **26** with sodium methoxide in methanol (80 °C) afforded both the O^4-methyl ether **33** and *n*-butyl β-DL-oleandroside (**12**) in about a 1:1 ratio in low yield (≤10%) and recovered epoxide **26**. Even strong nucleophiles such as azide reacted with **26** nonselectively and required forcing conditions (5 equiv of NaN_3, DMF, 100 °C, 12 h) to convert a significant proportion of **26** to ring-opened products (21% combined yield of isomeric azides). Reaction of **26** with methanol in the presence of $BF_3{\cdot}OEt_2$ (25 °C) produced a complex mixture of products. Unfortunately, and despite the short and high-yielding route to *ribo*-epoxide **26**, we were forced to abandon this component of our strategy for the synthesis of *xylo*-pyranosides.



The lack of regioselectivity in the nucleophilic opening of *ribo*-epoxide **26** and the complete control of regiochemistry observed in reactions of *lyxo*-epoxide **25** can be interpreted[29] by examination of molecular models of the minimum energy conformers of these compounds[30] (Figure 3). Stereoelectronic requirements for trans-diaxial epoxide opening[24] would lead to the prediction that **25** should react with nucleophiles at C3, whereas **26** should react at C4, as illustrated in Figure 3. This prediction is substantiated for reactions of **25**, where there is no obvious hindrance to the anti approach of a nucleophile to C3, and reactions proceed by the most stereoelectronically favored pathway. However, with epoxide **26**, anti approach of a nucleophile to C4 is hindered in the transition state by a severe eclipsing interaction with the proximal methyl group at C5, and reaction occurs partially by the less stereoelectronically favored pathway at C3. These observations[29] likewise explain the sluggish reactivity of **26**, since nucleophilic attack at either C4 or C3 must occur by an energetically disfavored (i.e., sterically or stereoelectronically, respectively) transition state.

(30) These minimum energy conformations were generated using the program PCMODEL (MMX forcefield). These calculated conformations were consistent with experimentally determined conformations obtained through analysis of ^1H NMR coupling constants, which were indicative of an equatorial anomeric alkoxyl group. For epoxide **25**, $J_{1,2_{ax}}$ = 9.3 Hz and $J_{1,2_{eq}}$ = 4.0 Hz (calculated: J = 9.7, 3.1 Hz based on dihedral angles of 166° and 50°, respectively). For epoxide **26**, $J_{1,2_{ax}}$ = 9.0 Hz and $J_{1,2_{eq}}$ = 2.8 Hz (calculated: J = 9.8, 2.3 Hz for dihedral angles of 172° and 54°, respectively).

Scheme II



Discussion

The methodology demonstrated herein provides a divergent, de novo synthetic pathway to all four families of 2,6-dideoxy carbohydrates (Scheme II). Pyranone **2**, prepared by [4 + 2] cycloaddition of the acylketene generated from dioxinone **1** with butyl vinyl ether,[6] served as a template upon which the oxygen and carbon functionality of the target molecules was introduced in a highly stereocontrolled manner. Pyranone **2** was converted in 2–3 steps to *arabino*-hexopyranosides olivoside **11**, oleandroside **12**, and branched sugars olivomycoside **14** and chromoside B **15**. Introduction of three new stereogenic centers occurred with near-complete control of relative stereochemistry, thereby providing ready access to stereochemically and functionally complex carbohydrates with extraordinary efficiency. Olivoside **11** proved to be the pivotal intermediate for elaboration to the ribo, lyxo, and xylo families of 2,6-dideoxy carbohydrates. Inversion of configuration at C3 of **11** using a Mitsunobu reaction provided ready access to the *ribo*-pyranoside digitoxoside **17**, whereas inversion at C4 of **11** or **12** via the intermediacy of the O^4-trifluoromethanesulfonate ester gave rise to the *lyxo*-pyranosides olioside **23** and diginoside **21**, respectively. A high-yielding sequence of reactions converted **11** to *lyxo*-anhydro sugar **25**, which underwent stereoelectronically controlled epoxide ring opening to afford the *xylo*-pyranosides boivinoside **30** and sarmentoside **31**. These efficient and direct reaction protocols permitted the divergent total synthesis of a wide assortment of biologically important 2,6-dideoxy hexopyranosides.

Experimental Section

(2*R,4*R**)-2-*n*-Butoxy-4-hydroxy-6-methyl-2,3-dihydro-4*H*-pyran (9).** A solution of **2** (861 mg, 4.7 mmol) in toluene (10 mL) under N_2 at 0 °C was treated with a solution of *i*-Bu_2AlH (1.5 M in toluene, 6.0 mL, 9.0 mmol) over a period of 5 h. The

reaction mixture was stirred at 0 °C for an additional 1 h and was quenched at 0 °C by the addition of saturated aqueous sodium potassium tartrate (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the organic extracts were washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **9** (838 mg, 870 mg theoretical, 96%) as an unstable yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3 H, C4′-H), 1.26–1.35 (m, 2 H, C3′–H), 1.44–1.55 (m, 2 H, C2′-H), 1.72 (apparent t, J = 0.9 Hz, 3 H, C6-CH_3), 1.87 (ddd, J = 14.4, 5.0, 2.7 Hz, 1 H, C3-H_{ax}), 2.13 (apparent dq, J = 14.4, 1.8 Hz, 1 H, C3-H_{eq}), 3.00 (d, J = 11.2 Hz, 1 H, C4-OH), 3.42 (dt, J = 9.6, 6.6 Hz, 1 H, C1′-H), 3.68 (dt, J = 9.6, 6.4 Hz, 1 H, C1′-H), 3.85–3.90 (m, 1 H, C4-H), 4.90 (apparent d, J = 5.5 Hz, 1 H, C5-H), 5.16 (dd, J = 2.7, 1.8 Hz, 1 H, C2-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 101.7, 97.7, 68.8, 60.1, 34.7, 32.0, 20.3, 19.6, 14.1; IR (neat) ν_{max} 3560, 2934, 1679, 1384, 1314, 1213, 1116, 1058, 908, 862 cm^{-1}; EIMS m/e (relative intensity) 186 (M^+, 30), 169 (40), 113 (30), 100 (60), 85 (60), 56 (base); HRMS m/e calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1248.

***n*-Butyl 2,6-Dideoxy-β-DL-*arabino*-hexopyranoside (*n*-Butyl β-DL-Olivoside) (11).**[8] A solution of **9** (179.3 mg, 0.96 mmol) in THF (2 mL) under N_2 at 0 °C was treated dropwise with BH_3·SMe_2 (2.0 M in THF, 1.0 mL, 1.9 mmol). The reaction mixture was allowed to warm to 26 °C over 3 h and was stirred at 26 °C for 12 h. The reaction mixture was quenched by the addition of water (2 mL), $NaBO_3$·H_2O[10a] (580 mg, 5.8 mmol) was added, and the slurry was stirred vigorously at 26 °C for 4 h. The reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined extracts were neutralized with 5% aqueous HCl, washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (8 × 2 cm silica, 30–60% EtOAc/hexanes) to afford **11**[8] (134.5 mg, 196.7 mg theoretical, 68%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.29 (d, J = 6.1 Hz, 3 H, C6-H), 1.32–1.38 (m, 2 H, C3′-H), 1.51–1.63 (m, 3 H, C2-H_{ax}, C2′-H), 2.14 (ddd, J = 9.5, 5.0, 1.9 Hz, C2-H_{eq}), 3.06 (apparent t, J = 8.8 Hz, 1 H, C4-H), 3.24 (dq, J = 9.1, 6.1 Hz, 1 H, C5-H), 3.40 (dt, J = 9.5, 6.9 Hz, 1 H, C1′-H), 3.47 (br s, 2 H, C3-OH and C4-OH), 3.58 (ddd, J = 11.7, 8.5, 5.0 Hz, 1 H, C3-H), 3.84 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.43 (dd, J = 9.8, 1.9 Hz, 1 H, C1-H); ^{13}C NMR (125 MHz, benzene-d_6) δ 100.0, 78.1, 72.2, 71.9, 68.8, 39.8, 32.3, 19.7, 18.1, 14.1; IR ($CDCl_3$) ν_{max} 3590, 3446, 2962, 2936, 2875, 1371, 1170, 1069 cm^{-1}; EIMS m/e (relative intensity) 203 (M^+ – H, 5), 173 (5), 160 (5), 131 (40), 113 (20), 104 (30), 101 (90), 73 (30), 57 (base); HRMS m/e calcd for $C_{10}H_{20}O_4$ – H 203.1283, found 203.1283.

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.72; H, 9.83.

(2*R,4*R**)-2-*n*-Butoxy-4-methoxy-6-methyl-2,3-dihydro-4*H*-pyran (10).** A slurry of **9** (1.85 g, 9.9 mmol) and sodium hydride (1.19 g, 49.8 mmol) in THF/DMF (5:1, 30 mL) under N_2 at 26 °C was treated dropwise, over 45 min, with CH_3I (3.1 mL, 49.8 mmol) at a rate sufficient to maintain a vigorous reaction.[11] The reaction mixture was cooled to 0 °C, quenched by the addition of water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with water (20 mL) and saturated aqueous NaCl (20 mL) and were dried ($MgSO_4$) and concentrated in vacuo to afford **10** (1.88 g, 1.99 g theoretical, 94%) as an unstable yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3 H, C4′-H), 1.32–1.38 (m, 2 H, C3′-H), 1.54–1.62 (m, 2 H, C2′-H), 1.75 (apparent t, J = 1.0 Hz, 3 H, C6-CH_3), 1.88 (ddd, J = 13.4, 7.2, 6.9 Hz, 1 H, C3-H_{ax}), 2.10 (ddd, J = 13.4, 6.5, 2.5 Hz, 1 H, C3-H_{eq}), 3.29 (s, 3 H, OCH_3), 3.48 (dt, J = 9.7, 6.9 Hz, 1 H, C1′-H), 3.82 (dt, J = 9.7, 6.9 Hz, 1 H, C1′-H), 3.89–3.92 (m, 1 H, C4-H), 4.71 (apparent d, J = 3.0 Hz, 1 H, C5-H), 4.94 (dd, J = 7.2, 2.5 Hz, 1 H, C2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 98.4, 97.7, 70.5, 68.9, 55.4, 33.2, 31.6, 19.9, 19.2, 13.9; IR (neat) ν_{max} 2934, 1677, 1386, 1267, 1136, 1094, 1044, 871 cm^{-1}.

***n*-Butyl 2,6-Dideoxy-3-*O*-methyl-β-DL-*arabino*-hexopyranoside (*n*-Butyl β-DL-Oleandroside) (12).**[8a,b,12] A solution of **10** (963 mg, 4.8 mmol) in THF (20 mL) under N_2 at 0 °C was treated dropwise with BH_3·SMe_2 (0.91 mL, 9.6 mmol). The reaction mixture was allowed to warm to 26 °C over 2 h and was quenched by the addition of water (5 mL). Sodium perborate monohydrate[10a] (1.92 g, 19.3 mmol) was added, and the slurry was stirred vigorously for 12 h. Workup as described for **11** afforded **12**[8a,b,12] (0.88 g, 1.05 g theoretical, 84%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.31 (d, J = 6.2 Hz, 3 H, C6-H), 1.33–1.38 (m, 2 H, C3′-H), 1.43 (ddd, J = 12.3, 11.3, 9.8 Hz, 1 H, C2-H_{ax}) 1.53–1.58 (m, 2 H, C2′-H), 2.30 (ddd, J = 12.3, 4.5, 2.0 Hz, 1 H, C2-H_{eq}), 2.60 (br s, 1 H, C4-OH), 3.12 (apparent t, J = 8.7 Hz, 1 H, C4-H), 3.17 (ddd, J = 11.3, 8.6, 4.5 Hz, 1 H, C3-H), 3.28 (dq, J = 8.9, 6.2 Hz, 1 H, C5-H) 3.36 (s, 3 H, OCH_3), 3.41 (dt, J = 9.5, 6.9 Hz, 1 H, C1′-H), 3.85 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.42 (dd, J = 9.8, 2.0 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.7, 80.8, 75.6, 71.6, 69.2, 56.2, 35.2, 31.7, 19.2, 17.9, 13.9; IR ($CDCl_3$) ν_{max} 3452, 2935, 2874, 1377, 1169, 1073, 989, 905 cm^{-1}; EIMS m/e (relative intensity) 217 (M^+ – H, 5), 201 (5), 174 (10), 145 (20), 118 (20), 101 (30), 87 (20), 74 (base), 58 (40); HRMS m/e calcd for $C_{11}H_{22}O_4$ – H 217.1440, found 217.1446.

Anal. Calcd. for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.54; H, 10.18.

(2*R,4*R**)-2-*n*-Butoxy-4-hydroxy-4,6-dimethyl-2,3-dihydro-4*H*-pyran (13).** Precooled (0 °C) THF (10 mL) was added to finely ground anhydrous $CeCl_3$ (739 mg, 3.0 mmol, Strem) under N_2 at 0 °C, and the stirred suspension was allowed to warm to 26 °C overnight. The suspension was recooled to 0 °C, CH_3MgBr (2.91 M in Et_2O, 0.69 mL, 2.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h.[13] A solution of **2** (177 mg, 1.0 mmol) in THF (1 mL) was added, and stirring was continued for 1 h at 0 °C. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **13** (150 mg, 202 mg theoretical, 78%) as an unstable yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H, C4′-H), 1.21 (d, J = 1.1 Hz, 3 H, C4-CH_3), 1.29–1.39 (m, 2 H, C3′-H), 1.48–1.56 (m, 2 H, C2′-H), 1.74 (d, J = 1.0 Hz, 3 H, C6-CH_3), 1.83 (apparent dd, J = 14.2, 2.8 Hz, 1 H, C3-H_{ax}), 2.08 (apparent dt, J = 14.2, 1.9 Hz, 1 H, C3-H_{eq}), 3.46 (dt, J = 9.5, 6.3 Hz, 1 H, C1′-H), 3.68 (br s, 1 H, C4-OH), 3.72 (dt, J = 9.5, 6.5 Hz, 1 H, C1′-H), 4.78 (br s, 1 H, C5-H), 5.18 (dd, J = 2.8, 1.9 Hz, 1 H, C2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 106.5, 97.6, 68.4, 63.6, 40.0, 31.6, 28.7, 19.8, 19.3, 13.8; IR (neat) ν_{max} 3550, 2932, 1680, 1385, 1308, 1226, 1117, 1006, 897 cm^{-1}.

***n*-Butyl 2,6-Dideoxy-3-*C*-methyl-β-DL-*arabino*-hexopyranoside (*n*-Butyl β-DL-Olivomycoside) (14).**[8a,14] A solution of **13** (45.7 mg, 0.23 mmol) in THF (1 mL) under N_2 at 0 °C was treated with BH_3·SMe_2 (43 μL, 0.46 mmol). The reaction mixture was stirred at 0 °C for 1 h and then was allowed to warm to 26 °C over 1 h. Sodium perborate monohydrate[10a] (140 mg, 1.38 mmol) was added, and the slurry was stirred vigorously for 4 h. Workup as described for **12** followed by purification by flash chromatography (8 × 2 cm silica, 45% EtOAc/hexanes) afforded **14**[8a,14] (27.4 mg, 49.8 mg theoretical, 55%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.25 (s, 3 H, C3-CH_3), 1.30 (d, J = 6.0 Hz, 3 H, C6-H), 1.32–1.38 (m, 2 H, C3′-H), 1.50–1.60 (m, 2 H, C2′-H), 1.70 (dd, J = 12.7, 9.7 Hz, 1 H, C2-H_{ax}), 1.96 (dd, J = 12.7, 2.1 Hz, 1 H, C2-H_{eq}), 2.51 (s, 1 H, C3-OH), 2.79 (d, J = 3.8 Hz, 1 H, C4-OH), 3.21 (dd, J = 9.4, 3.8 Hz, 1 H, C4-H), 3.32 (dq, J = 9.4, 6.0 Hz, 1 H, C5-H), 3.39 (dt, J = 9.4, 6.9 Hz, 1 H, C1′-H), 3.83 (dt, J = 9.4, 6.7 Hz, 1 H, C1′-H), 4.47 (dd, J = 9.7, 2.1 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.3, 79.5, 72.1, 70.9, 69.2, 45.2, 31.7, 20.5, 19.2, 18.4, 13.9; IR (neat) ν_{max} 3404, 2960, 1378, 1120, 1073, 668 cm^{-1}.

***n*-Butyl 4-*O*-Acetyl-2,6-dideoxy-3-*C*-methyl-β-DL-*arabino*-hexopyranoside (*n*-Butyl β-DL-Chromoside B) (15).**[15] A solution of **14** (24 mg, 0.1 mmol) in pyridine/THF (1:1, 4 mL) under N_2 at 26 °C was treated with catalytic DMAP and acetic anhydride (50 μL, 0.5 mmol), and the reaction mixture was stirred for 4 h. The reaction was quenched by the addition of water (1 mL) and was extracted with EtOAc (3 × 8 mL). The combined extracts were washed with saturated aqueous NaCl (8 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (7 × 2 cm silica, 10–20% EtOAc/hexanes) to afford **15**[15] (29 mg, 29 mg theor., 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H, C4′-H), 1.20 (d, J = 6.2 Hz, 3 H, C6-H), 1.21 (s, 3 H, C3-CH_3), 1.26–1.39

(m, 2 H, C3′-H), 1.49–1.58 (m, 2 H, C2′-H), 1.76 (dd, J = 13.1, 9.2 Hz, 1 H, C2-H_{ax}), 2.01 (dd, J = 13.1, 2.2 Hz, 1 H, C2-H_{eq}), 2.09 (s, 3 H, CO_2CH_3), 2.75 (s, 1 H, C3-OH), 3.38 (dt, J = 9.4, 6.8 Hz, 1 H, C1′-H), 3.48 (dq, J = 9.1, 6.2 Hz, 1 H, C5-H), 3.82 (dt, J = 9.4, 6.7 Hz, 1 H, C1′-H), 4.48 (dd, J = 9.2, 2.2 Hz, 1 H, C1-H), 4.55 (d, J = 9.1 Hz, 1 H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 99.2, 80.1, 71.0, 69.6, 69.1, 45.3, 31.7, 21.4, 21.0, 19.2, 18.4, 13.9; IR (neat) ν_{max} 3470, 2960, 2874, 1745, 1373, 1237, 1162, 1096, 1060, 1009, 861 cm^{-1}; EIMS m/e (relative intensity) 259 (M^+ – H, 5), 199 (10), 187 (base), 169 (20), 143 (50); HRMS m/e calcd for $C_{13}H_{24}O_5$ – H 259.1545, found 259.1543.

***n*-Butyl 2,6-Dideoxy-3-*O*-(4-nitrobenzoyl)-β-DL-*ribo*-hexopyranoside (16).** A solution of **11** (18.3 mg, 0.09 mmol) in toluene (3 mL) under N_2 at 26 °C was treated sequentially with triphenylphosphine (47 mg, 0.18 mmol), diethyl azodicarboxylate (28 μL, 0.18 mmol), and 4-nitrobenzoic acid (30 mg, 0.18 mmol), and the reaction mixture was stirred for 30 min.[16b] Hexane (10 mL) was added, and the reaction mixture was filtered. The filtrate was diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (2 × 7 cm silica, 5–30% EtOAc/hexanes) to afford **16** (23.7 mg, 31.7 mg theoretical, 75%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.32–1.38 (m, 2 H, C3′-H), 1.35 (d, J = 6.2 Hz, 3 H, C6-H), 1.52–1.59 (m, 2 H, C2′-H), 1.93 (ddd, J = 14.4, 9.5, 2.9 Hz, 1 H, C2-H_{ax}), 2.22 (ddd, J = 14.4, 3.5, 2.0 Hz, 1 H, C2-H_{eq}), 3.44 (dt, J = 9.3, 6.9 Hz, C1′-H), 3.58 (dd, J = 9.3, 3.0 Hz, 1 H, C4-H), 3.84 (dq, J = 9.3, 6.2 Hz, 1 H, C5-H), 3.91 (dt, J = 9.3, 6.7 Hz, 1 H, C1′-H), 4.81 (dd, J = 9.5, 2.0 Hz, 1 H, C1-H), 5.59 (apparent dd, J = 6.3, 3.1 Hz, 1 H, C3-H), 8.20 (d, J = 9.0 Hz, 2 H, ArH), 8.30 (d, J = 9.0 Hz, 2 H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 135.7, 131.2, 124.1, 98.3, 96.5, 73.1, 72.8, 70.8, 69.6, 36.2, 32.1, 19.6, 18.5, 14.3; IR ($CDCl_3$) ν_{max} 3600, 2963, 1725, 1607, 1531, 1349, 1276, 1078, 1012, cm^{-1}; CIMS (NH_3), m/e (relative intensity) 354 (M^+ + H, 10), 343 (30), 336 (10), 326 (20), 297 (90), 280 (base), 262 (40), 250 (30); HRMS m/e calcd for $C_{17}H_{23}NO_7$ – OC_4H_9 280.0821, found 280.0820.

***n*-Butyl 2,6-Dideoxy-β-DL-*ribo*-hexopyranoside (*n*-Butyl β-DL-Digitoxoside) (17).**[8a,b,17] A solution of **16** (48.2 mg, 0.14 mmol) in CH_3OH/H_2O (30:1, 5 mL) at 26 °C was treated with K_2CO_3 (21 mg, 0.15 mmol) and the reaction mixture was stirred for 1.5 h. The reaction was concentrated in vacuo, diluted with EtOAc (10 mL), washed with saturated aqueous NaCl (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (1 × 6 cm silica, 10–40% EtOAc/hexanes) to afford **17**[8a,b,17] (19.9 mg, 28.0 mg theoretical, 71%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H, C4′-H), 1.27 (d, J = 6.3 Hz, 3 H, C6-H), 1.30–1.41 (m, 2 H, C3′-H), 1.48–1.59 (m, 2 H, C2′-H), 1.70 (ddd, J = 13.9, 9.5, 2.9 Hz, 1 H, C2-H_{ax}), 2.07 (ddd, J = 13.9, 3.6, 2.1 Hz, 1 H, C2-H_{eq}), 2.43 (br s, 2 H, C3-OH and C4-OH), 3.28 (dd, J = 9.3, 3.2 Hz, 1 H, C4-H), 3.41 (dt, J = 9.5, 6.9 Hz, 1 H, C1′-H), 3.70 (dq, J = 9.3, 6.3 Hz, 1 H, C5-H), 3.84 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.08 (apparent q, J = 3.2 Hz, 1 H, C3-H), 4.77 (dd, J = 9.5, 2.1 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.7, 73.1, 69.4, 69.2, 68.0, 37.8, 31.7, 19.2, 18.1, 13.9; IR (neat) ν_{max} 3418, 2960, 2934, 1373, 1074, 1016, 867 cm^{-1}; EIMS m/e (relative intensity) 203 (M^+ – H, 5), 190 (10), 172 (10), 157 (10), 131 (base), 113 (80), 69 (60), 57 (40); HRMS m/e calcd for $C_{10}H_{20}O_4$ – H 203.1283, found 203.1283.

***n*-Butyl 2,6-Dideoxy-3-*O*-methyl-β-DL-*lyxo*-hexopyranoside (*n*-Butyl β-DL-Diginoside) (21).**[21] A solution of **12** (83.0 mg, 0.38 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (2 mL) under N_2 at 0 °C was treated with trifluoromethanesulfonic anhydride (77 μL, 0.46 mmol), and the reaction mixture was stirred at 0 °C for 35 min. The reaction was quenched by the addition of water (4 mL), and the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with 5% aqueous HCl (3 mL) and saturated aqueous NaCl (5 mL) and were dried ($MgSO_4$) and concentrated in vacuo to afford the triflate **19**, which was used immediately without further purification.

A solution of KO_2 (108 mg, 1.52 mmol) and 18-crown-6 (400 mg, 1.52 mmol) in DMSO (0.5 mL) under N_2 at 0 °C was treated with a solution of triflate **19** in DMSO (0.3 mL).[20] The reaction mixture was stirred at 0 °C for 35 min and then at 26 °C for 30 min. The reaction was quenched by the addition of water (2 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (1 × 7 cm silica, 20–30% EtOAc/hexanes) to afford **21**[21] (48.9 mg, 83.0 mg theoretical, 59%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.28–1.41 (m, 2 H, C3′-H), 1.34 (d, J = 6.5 Hz, 3 H, C6-H), 1.51–1.61 (m, 2 H, C2′-H), 1.66 (apparent dt, J = 12.5, 9.8 Hz, 1 H, C2-H_{ax}), 1.75 (br s, 1 H, C4-OH), 2.00 (dddd, J = 12.5, 5.2, 2.2, 0.7 Hz, 1 H, C2-H_{eq}), 3.32 (ddd, J = 12.1, 5.2, 3.1 Hz, 1 H, C3-H), 3.37–3.46 (m, 2 H, C5-H) and C1′-H), 3.38 (s, 3 H, OCH_3), 3.68 (apparent d, J = 3.0 Hz, 1 H, C4-H), 3.88 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.37 (dd, J = 9.7, 2.2 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.0, 77.9, 69.0, 67.2, 55.5, 31.7, 19.2, 16.7, 13.9; IR (neat) ν_{max} 3440, 2935, 1378, 1102, 1032, 982 cm^{-1}; HRMS m/e calcd for $C_{11}H_{22}O_4$ – H 217.1440, found 217.1436.

***n*-Butyl 3-*O*-Benzyl-2,6-dideoxy-β-DL-*arabino*-hexopyranoside (18).** A solution of **11** (299 mg, 1.47 mmol) in toluene (30 mL) under N_2 was treated with di-*n*-butyltin oxide (440 mg, 1.76 mmol), and the reaction mixture was warmed at reflux with continuous removal of water using a Dean-Stark trap for 4 h.[19] The reaction mixture was cooled to 26 °C, treated with *n*-Bu_4NI (271 mg, 0.73 mmol) and benzyl bromide (0.26 mL, 2.20 mmol), and warmed at reflux for 14 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (3 × 10 cm silica, 0–30% EtOAc/hexanes) to afford **18** (370 mg, 431 mg theoretical, 86%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3 H, C4′-H), 1.32 (d, J = 6.0 Hz, 3 H, C6-H), 1.34–1.38 (m, 2 H, C3′-H), 1.51–1.61 (m, 3 H, C2-H_{ax} and C2′-H), 2.33 (ddd, J = 12.6, 4.7, 1.9 Hz, 1 H, C2-H_{eq}), 2.43 (d, J = 1.7 Hz, 1 H, C4-OH), 3.21 (ddd, J = 9.1, 8.3, 1.7 Hz, 1 H, C4-H), 3.27 (dq, J = 9.1, 6.0 Hz, 1 H, C5-H), 3.36–3.41 (m, 1 H, C3-H), 3.42 (dt, J = 9.3, 6.9 Hz, 1 H, C1′-H), 3.87 (dt, J = 9.3, 6.7, Hz, 1 H, C1′-H), 4.42 (dd, J = 9.8, 1.9 Hz, 1 H, C1-H), 4.56 (ABq, J = 11.5 Hz, $\Delta\nu$ = 113.9 Hz, 2 H, CH_2Ph), 7.24–7.36 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.6, 127.9, 127.8, 99.7, 79.0, 75.7, 71.6, 70.7, 69.2, 36.0, 31.7, 19.3, 17.9, 13.9; IR ($CDCl_3$) ν_{max} 3458, 2933, 2872, 1496, 1455, 1370, 1073, 904 cm^{-1}; EIMS m/e (relative intensity) 294 (M^+, 5), 250 (5), 220 (10), 193 (5), 150 (15), 91 (base); HRMS m/e calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1835.

***n*-Butyl 3-*O*-Benzyl-2,6-dideoxy-β-DL-*lyxo*-hexopyranoside (22).** A solution of **18** (84.6 mg, 0.29 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (2 mL) under N_2 at 0 °C was treated with trifluoromethanesulfonic anhydride (58 μL, 0.35 mmol), and the reaction mixture was stirred for 30 min. Workup as described for **19** afforded triflate **20**, which was used without further purification.

A solution of KO_2 (61 mg, 0.86 mmol) and 18-crown-6 (152 mg, 0.57 mmol) in DMSO (0.4 mL) under N_2 at 0 °C was treated with a solution of the triflate **20** in DMSO (0.3 mL).[20] The reaction mixture was stirred at 0 °C for 25 min and then at 26 °C for 30 min. Workup as described for **21** and purification by flash chromatography (1 × 7 cm silica, 20–30% EtOAc/hexanes) afforded **22** (52.1 mg, 84.6 mg theoretical, 62%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.30–1.38 (m, 2 H, C3′-H), 1.33 (d, J = 6.5 Hz, 3 H, C6-H), 1.50–1.60 (m, 2 H, C2′-H), 1.77 (apparent dt, J = 12.2, 9.8 Hz, 1 H, C2-H_{ax}), 1.99 (dddd, J = 12.5, 5.1, 2.2, 0.5 Hz, 1 H, C2-H_{eq}), 2.19 (br s, 1 H, C4-OH), 3.36–3.43 (m, 2 H, C5-H) and C1′-H), 3.50 (ddd, J = 12.2, 5.1, 3.1 Hz, 1 H, C3-H), 3.67 (apparent d, J = 3.0 Hz, 1 H, C4-H), 3.87 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.34 (dd, J = 9.8, 2.2 Hz, 1 H, C1-H), 4.59 (ABq, J = 12.1, $\Delta\nu$ = 6.3 Hz, 2 H, CH_2Ph), 7.25–7.36 (m, 5 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.5, 127.9, 127.7, 99.9, 75.5, 70.4, 69.8, 68.9, 67.7, 31.9, 31.7, 19.3, 16.8, 13.9; IR (neat) ν_{max} 3483, 2935, 1455, 1370, 1172, 1089, 982, 738, 699 cm^{-1}; HRMS m/e calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1835.

***n*-Butyl 2,6-Dideoxy-β-DL-*lyxo*-hexopyranoside (*n*-Butyl β-DL-Olioside) (23).**[8d,22] A solution of **22** (55 mg, 0.19 mmol) in dry CH_3OH (2 mL) at 26 °C was treated with palladium black (5 mg), and the reaction mixture was placed under 1 atm of H_2 for 2 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo to afford **23**[8d,22] (37.0 mg, 38.2 mg theoretical, 97%) as a colorless oil: ^{1}H NMR (300

MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H, C4′-H), 1.29 (d, J = 6.5 Hz, 3 H, C6-H), 1.29–1.40 (m, 2 H, C3′-H), 1.49–1.60 (m, 3 H, C2-H_{ax} and C2′-H), 2.00 (ddd, J = 12.7, 5.2, 2.2 Hz, 1 H, C2-H_{eq}), 2.40 (br s, 2 H, C3-OH and C4-OH), 3.31–3.48 (m, 2 H, C5-H and C1′-H), 3.51 (apparent d, J = 3.3 Hz, 1 H, C4-H), 3.66 (ddd, J = 12.0, 5.2, 3.2 Hz, 1 H, C3-H), 3.86 (dt, J = 9.5, 6.6 Hz, 1 H, C1′-H), 4.35 (dd, J = 9.8, 2.2 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.1, 70.5, 69.3, 69.0, 67.3, 35.1, 31.7, 19.2, 16.7, 13.9; IR (neat) ν_{max} 3384, 2936, 1374, 1044, 982 cm^{-1}; HRMS m/e calcd for $C_{10}H_{20}O_4$ – H 203.1283, found 203.1288.

n-Butyl 3,4-Anhydro-2,6-dideoxy-β-DL-*lyxo*-hexopyranoside (25). A solution of **28** (605 mg, 2.15 mmol) in THF (20 mL) under N_2 at 0 °C was treated with potassium *tert*-butoxide (240 mg, 3.22 mmol), and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in Et_2O (20 mL), and the solution was washed with water (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford **25** (390 mg, 399 mg theoretical, 98%) as a colorless oil that was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H, C4′-H), 1.23–1.35 (m, 2 H, C3′-H), 1.38 (d, J = 6.5 Hz, 3 H, C6-H), 1.48–1.58 (m, 2 H, C2′-H), 1.90 (dd, J = 15.2, 9.3 Hz, 1 H, C2-H_{ax}), 2.03 (ddd, J = 15.2, 5.3, 4.0 Hz, 1 H, C2-H_{eq}), 2.89 (d, J = 4.0 Hz, 1 H, C4-H), 3.24 (dd, J = 5.3, 4.0 Hz, 1 H, C3-H), 3.33 (dt, J = 9.4, 6.7 Hz, 1 H, C1′-H), 3.81 (dt, J = 9.4, 6.7 Hz, 1 H, C1′-H), 3.94 (q, J = 6.5 Hz, 1 H, C5-H), 4.36 (dd, J = 9.3, 4.0 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.7, 68.4, 68.3, 52.5, 49.9, 31.7, 29.5, 19.2, 17.9, 13.9; IR (neat) ν_{max} 2934, 1360, 1174, 1107, 1056, 1023, 809 cm^{-1}; EIMS m/e (relative intensity) 185 (M^+ – H, 5) 169 (5), 142 (30), 130 (60), 113 (80), 84 (base); HRMS m/e calcd for $C_{10}H_{18}O_3$ – H 185.1178, found 185.1180.

n-Butyl 2,6-Dideoxy-3-O-(*p*-toluenesulfonyl)-β-DL-*arabino*-hexopyranoside (29). A solution of **11** (181 mg, 0.89 mmol) in toluene (25 mL) under N_2 was treated with di-*n*-butyltin oxide (265 mg, 1.06 mmol), and the reaction mixture was warmed at reflux with removal of water using a Dean-Stark trap for 2.5 h.[19] The reaction mixture was cooled to 26 °C, treated with *n*-Bu_4NI (164 mg, 0.44 mmol) and *p*-toluenesulfonyl chloride (254 mg, 1.33 mmol), and stirred at 26 °C for 16 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (3 × 10 cm silica, 10–40% EtOAc/hexanes) to afford **29** (314 mg, 318 mg theoretical, 98%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3 H, C4′-H), 1.20–1.36 (m, 2 H, C3′-H), 1.30 (d, J = 5.7 Hz, 3 H, C6-H), 1.46–1.55 (m, 2 H, C2′-H), 1.72 (apparent dt, J = 12.2, 9.7 Hz, 1 H, C2-H_{ax}), 2.14 (ddd, J = 12.6, 5.5, 2.0 Hz, 1 H, C2-H_{eq}), 2.42 (s, 3 H, ArCH_3), 2.59 (br s, 1 H, C4-OH), 3.20–3.30 (m, 2 H, C4-H and C5-H), 3.37 (dt, J = 9.4, 6.8 Hz, 1 H, C1′-H), 3.80 (dt, J = 9.4, 6.6 Hz, 1 H, C1′-H), 4.37 (dd, J = 9.7, 2.0 Hz, 1 H, C1-H), 4.44 (ddd, J = 10.4, 8.5, 5.5 Hz, 1 H, C3-H), 7.33 (d, J = 8.2 Hz, 2 H, ArH), 7.79 (d, J = 8.2 Hz, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 133.4, 130.0, 127.8, 98.8, 81.8, 74.2, 71.4, 69.4, 37.3, 31.6, 21.7, 19.2, 17.8, 13.9; IR (neat) ν_{max} 3463, 2936, 1360, 1177, 1073, 959, 908, 829 cm^{-1}; EIMS m/e (relative intensity) 357 (M^+ – H, 5) 284 (5), 257 (10), 214 (10), 173 (15), 155 (45), 91 (30), 56 (base); HRMS m/e calcd for $C_{17}H_{26}O_6S$ – H 357.1372, found 357.1381.

n-Butyl 3,4-Anhydro-2,6-dideoxy-β-DL-*ribo*-hexopyranoside (26). A solution of **29** (314 mg, 0.88 mmol) in THF (3 mL) under N_2 at 0 °C was treated with potassium *tert*-butoxide (128 mg, 1.14 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of water (3 mL) and was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with saturated aqueous NaCl (8 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **26** (145 mg, 163 mg theoretical 89%) as a colorless oil, which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3 H, C4′-H), 1.26–1.36 (m, 2 H, C3′-H), 1.39 (d, J = 6.9 Hz, 3 H, C6-H), 1.47–1.57 (m, 2 H, C2′-H), 1.77 (ddd, J = 14.5, 9.0, 2.1 Hz, 1 H, C2-H_{ax}), 2.23 (apparent dt, J = 14.5, 2.3 Hz, 1 H, C2-H_{eq}), 2.94 (d, J = 4.2 Hz, 1 H, C4-H), 3.34 (dt, J = 9.5, 6.8 Hz, 1 H, C1′-H), 3.36–3.37 (m, 1 H, C3-H), 3.78 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.00 (q, J = 6.9 Hz, 1 H, C5-H), 4.43 (dd, J = 9.0, 2.8 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.0, 70.7, 69.2, 55.2, 53.3, 31.7, 31.3, 19.4, 19.2, 13.9; IR (neat) ν_{max} 2959, 2873, 1372, 1162, 1110, 1079, 1013, 873 cm^{-1}; CIMS (NH_3) m/e (relative intensity) 187 (M^+ + H, 10), 147 (10), 130 (base), 113 (75); HRMS m/e calcd for $C_{10}H_{18}O_3$ – H 185.1178, found 185.1177.

n-Butyl 2,6-Dideoxy-β-DL-*xylo*-hexopyranoside (n-Butyl β-DL-Boivinoside) (30).[8d,27] A slurry of chromatography-grade Al_2O_3 (7.5 g/mmol substrate, 1.6 g) in Et_2O (2 mL) under N_2 at 26 °C was treated with water (10 wt %, 0.16 mL) and stirred for 15 min.[26] A solution of **25** (40.0 mg, 0.22 mmol) in Et_2O (0.5 mL) was added to the Al_2O_3 slurry, and the reaction mixture was stirred for 7 h at 26 °C. The reaction was quenched by the addition of CH_3OH (5 mL) and was allowed to stand at 26 °C for 3 h. The mixture was filtered through a pad of Celite (CH_3OH wash), and the filtrate was concentrated in vacuo to afford **30**[8d,27] (28.7 mg, 43.9 mg theoretical, 67%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H, C4′-H), 1.23 (d, J = 6.6 Hz, 3 H, C6-H), 1.26–1.39 (m, 2 H, C3′-H), 1.49–1.58 (m, 2 H, C2′-H), 1.72–1.86 (m, 2 H, C2-H), 2.46 (br s, 2 H, C3-OH, C4-OH), 3.27 (apparent d, J = 2.7 Hz, 1 H, C4-H), 3.41 (dt, J = 9.5, 6.9 Hz, 1 H, C1′-H), 3.85 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 4.01 (dq, J = 6.6, 1.0 Hz, 1 H, C5-H), 4.08 (apparent dd, J = 6.7, 3.3 Hz, 1 H, C3-H), 4.71 (dd, J = 8.5, 3.4 Hz, 1 H, C1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.9, 71.1, 69.4, 69.4, 69.2, 34.3, 32.1, 19.6, 16.8, 14.3; IR ($CDCl_3$) ν_{max} 3418, 2935, 1379, 1171, 1042, 1003, 977, 931 cm^{-1}; EIMS m/e (relative intensity) 203 (M^+ – H, 5), 187 (5), 160 (15), 131 (50), 101 (base); HRMS m/e calcd for $C_{10}H_{20}O_4$ – H 203.1283, found 203.1288.

n-Butyl 2,6-Dideoxy-3-O-methyl-β-DL-*xylo*-pyranoside (n-Butyl β-DL-Sarmentoside) (31).[21a] A solution of **25** (39.6 mg, 0.21 mmol) in CH_3OH (0.5 mL) under N_2 was treated with $NaOCH_3$ (4.37 M in CH_3OH, 0.49 mL, 2.1 mmol), and the reaction mixture was warmed at 80 °C (bath temperature) for 1.5 h in a sealed vial. After cooling to 26 °C, the reaction was quenched by the addition of water (1 mL) and was extracted with CH_2Cl_2 (3 × 8 mL). The combined extracts were washed with saturated aqueous NaCl (8 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **31**[21a] (41.6 mg, 46.4 mg theoretical, 90%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3 H, C4′-H), 1.24 (d, J = 6.6 Hz, 3 H, C6-H), 1.29–1.41 (m, 2 H, C3′-H), 1.51–1.61 (m, 2 H, C2′-H), 1.70 (ddd, J = 14.4, 9.7, 3.3 Hz, 1 H, C2-H_{ax}), 1.89 (dddd, J = 14.4, 3.2, 2.3, 0.9 Hz, 1 H, C2-H_{eq}), 3.37–3.38 (m, 1 H, C4-H), 3.37 (s, 3 H, OCH_3), 3.41 (dt, J = 9.5, 6.9 Hz, 1 H, C1′-H), 3.56 (apparent q, J = 3.2 Hz, 1 H, C3-H), 3.87 (dt, J = 9.5, 6.7 Hz, 1 H, C1′-H), 3.92 (dq, J = 6.6, 1.2 Hz, 1 H, C5-H), 4.62 (dd, J = 9.7, 2.3 Hz, 1 H, C1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.8, 78.3, 69.1, 69.0, 68.1, 57.0, 31.8, 30.7, 19.3, 16.5, 13.9; IR (neat) ν_{max} 3417, 2935, 1372, 1171, 1096, 1038 cm^{-1}; EIMS m/e (relative intensity) 217 (M^+ – H, 5), 174 (5), 145 (5), 118 (10), 101 (20), 74 (base), 58 (50); HRMS m/e calcd for $C_{11}H_{22}O_4$ – H 217.1438, found 217.1440.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (ACS-PRF No. 22781-G1). We also thank the Camille and Henry Dreyfus Foundation (NF-89-18), the National Institutes of Health (S07-RR07160), and the American Cancer Society (JFRA-319) for their support of this work. We thank Molecular Design Ltd. for the use of their synthetic database. NMR spectra were obtained on instruments purchased with funds from the National Science Foundation (CHE-8411172 and CHE-8904942) and the National Institutes of Health (S10-RR02425).

Supplementary Material Available: General experimental procedures, detailed experimental procedures, and spectral characterization for **2**, **27**, **27-O-methanesulfonate**, and **28** and photocopies of ^1H or ^{13}C NMR spectra of **9**, **10**, **13–18**, **21–23**, and **25–31** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.