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De Novo Approach to 2-Deoxy-β-glycosides: Asymmetric Syntheses of Digoxose and Digitoxin[1]

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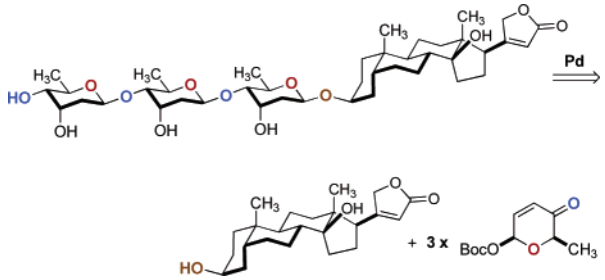

A highly enantioselective and straightforward route to trisaccharide natural products digoxose and digitoxin has been developed. Key to this approach is the iterative application of the palladium-catalyzed glycosylation reaction, reductive 1,3-transposition, diastereoselective dihydroxylation, and regioselective protection. The first total synthesis of natural product digoxose was accomplished in 19 total steps from achiral 2-acylfuran, and digitoxin was fashioned in 15 steps starting from digitoxigenin **2** and pyranone **8**β. This flexible synthetic strategy also allows for the preparation of mono- and disaccharide analogues of digoxose and digitoxin.

Introduction

The cardiac glycoside digitoxin (**1**) (Figure 1), an extract from the leaves of *Digitalis purpurea* (purple foxglove), has long been used to slow the heart rate while increasing the contractility of the heart muscle (inotropic activity). It has been widely prescribed for congestive heart failure and cardiac arrhythmia for over 200 years. However, extensive care must be taken when treating patients with digitoxin, because the typical therapeutic dose (14−26 ng mL^{-1}) is dangerously close to the toxic dose (>35 ng mL^{-1}).[2] Digitoxin has also been shown to possess potential anticancer activities.[3] Structurally, digitoxin is the combination of two natural products, the aglycon digitoxigenin (**2**)[4] and the trisaccharide digoxose (**3**).[5] Oligosaccharides are known to play important roles in many pharmacologically important antibiotics, vaccines, and antitumor agents.[6] For instance, while the digitoxigenin is considered to be the

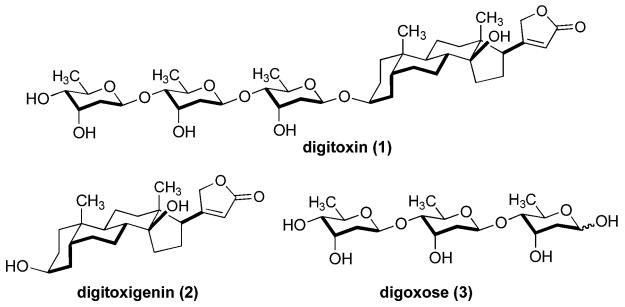

FIGURE 1. Digitoxin, digoxose, and digitoxigenin.

(1) This paper is dedicated to a dear friend and former colleague, Professor Wayland Noland, on the occasion of his 80th birthday.

(2) Greeff, K. Cardiac Glycosides, Part 1: Experimental Pharmacology. In *Handbook of Experimental Pharmacology*; Springer-Verlag: Berlin, New York, 1981; Vol. 56.

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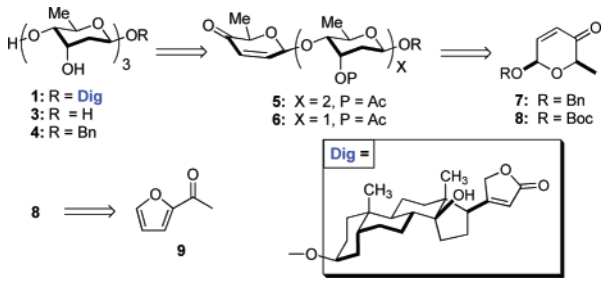
pharmacophore portion of digitoxin **1**, the aglycon **2** is inactive without the attachment of digoxose trisaccharide **3**. Thus, it is reasonable to assume that by manipulating the sugar portion, the resulting analogues may have improved activities. An excellent example of the interplay between carbohydrate structure and biological activity can be seen in the digitoxin neoglycoside library constructed by Thorson and co-workers.[7] Several of these digitoxigenin monosaccharide analogues showed improved anticancer activity yet lower cardiotoxicity.[7] In an effort to differentiate the effects of carbohydrate substitution versus neoglycoside substitution on activity, we desired access to digitoxin and its bis- and monosaccharide analogues as well as the free sugar digoxose and its mono- and disaccharide.

The stereocontrolled synthesis of 2-deoxy-β-glycosides is difficult as a result of the missing control element at the C-2 position.[8,9] The use of the participation of an attached C-3 group to control the anomeric stereochemistry had been shown to be unreliable.[10] To date, the most direct method involved an S_N2 substitution of an α-D-glycopyranosyl donor and alcohol acceptor.[11] The selectivity of this method, however, is highly dependent on the protecting-group manipulation (activation) of the pyranose donor and the reactivity of the acceptor.[12] Their use is also limited by the low availability of corresponding monosaccharides in nature. Other strategies utilized equatorial C-2 heteroatom neighboring groups (Br,[13] I,[14] SAr,[15] SePh,[16]

SCHEME 1. Digitoxin/Digoxose Retrosynthesis



OAc,[17] and NHCHO[18]) to control the anomeric stereochemistry, which after glycosylation need to be reductively removed using radical tin-hydride chemistry. Similarly the Barton-type deoxygenation of C-2 hydroxyl groups has been used in combination with nucleophilic opening of anomeric epoxides.[19] This challenge of stereocontrolled synthesis of 2-deoxy β-glycosides is evident in the two previous syntheses of the tris-1,4-linked 2,6-dideoxy-β-D-allose portion of digitoxin. While there has been no synthesis of the natural product digoxose (**3**), there have been two syntheses of digitoxin (**1**), a carbohydrate approach by Wiesner and co-workers and a de novo approach by McDonald and co-workers.[20,21] Herein we describe the full account of our successful de novo approach to 2-deoxy-β-*allo*-glycosides and its application to syntheses of β-linked 1,4-oligosaccharide natural products digoxose (**3**) and digitoxin (**1**).[22] This de novo methodology (Scheme 1) features the iterative use of a β-selective palladium-catalyzed glycosylation reaction[23] and subsequent chemo- and stereoselective transformations for the diastereoselective installation of the C-3/C-4 hydroxy groups and regioselective C-3 protection, which we believe resulted in a more efficient and flexible route in terms of number of steps and stereocontrol compared with the previous approaches.[24]

Results and Discussion

Approach to β-Pyranones. Previously, we have shown that α-glycosyl donors, such as α-Boc-pyranones **8**α and **15**α, can be oligomerized and subsequently transformed into α-linked oligosaccharides.[23d] Because these oligosaccharides are prepared from achiral acylfurans, such as **9** and **10**, we call this a de

(5) The attempts at the selective hydrolysis of digitoxin to form digoxose (**3**) has been futile, only the monosaccharide digitoxose was isolated. Surprisingly, **3** can be isolated from the dried twigs of *Orthenthera viminea*, see: Tiwari, K. N.; Khare, N. K.; Khare, A.; Khare, M. P. *Carbohydr. Res.* **1984**, *129*, 179−187.

(6) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (c) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84. (d) Marzabadi, C. H.; Frank, R. W. *Tetrahedron* **2000**, *56*, 8385−8417. (e) Kirschning, A.; Jesberger, M.; Schoning, K. U. *Synthesis* **2001**, 507−540. (f) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624. (g) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344−2350. (h) He, X.; Liu, H.-W. *Annu. Rev. Biochem.* **2002**, *71*, 701−754.

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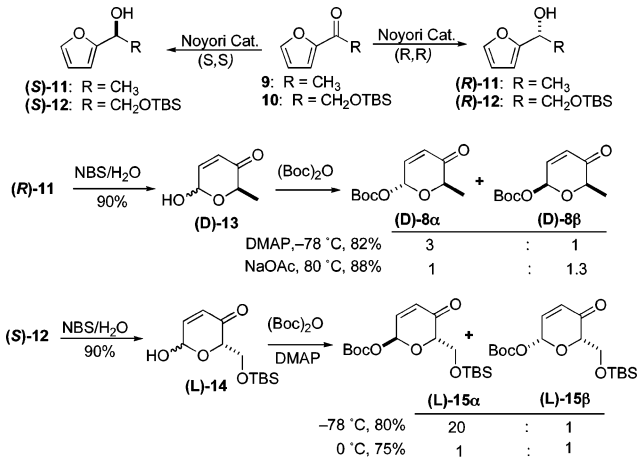
(21) In contrast, McDonald and coworkers are able to use his methodology to prepare an all-alpha analogue of digitoxin with high stereocontrol, see: McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

(22) For the communication of our initial approach to **1** see: Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339−4342.

(23) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8715. (c) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337. For its application in the de novo synthesis of a-linked 1,4- and 1,6-oligosaccharides, see: (d) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429.

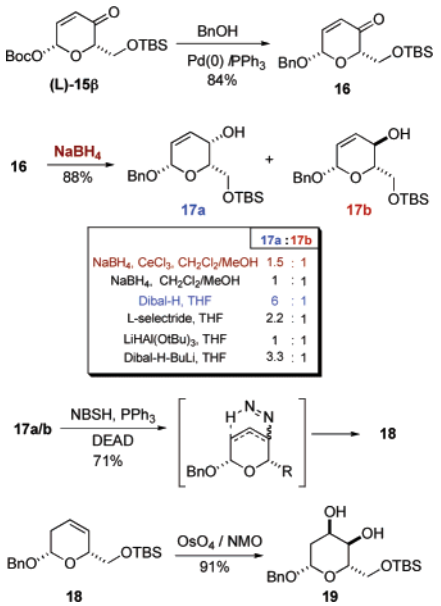
(24) In both the Wiesner and McDonald syntheses of digitoxin at least one of the three glycosidic bonds was assembled with poor stereoselectivity; see ref 20.

SCHEME 2. De Novo Pyranone Synthesis



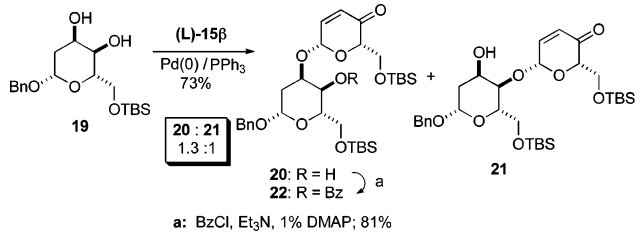
novo approach. By employing an enantioselective Noyori reduction,[25,26] an Achmatowicz oxidation, and diastereoselective acylation, the acylfurans can be converted into α-Boc-pyranones **8**α and **15**α (Scheme 2).[27] Alternatively, the Boc protection can be preformed at an elevated temperature ($(Boc)_2O$/NaOAc in benzene at 80 °C) such that β-pyranones **8**β and **15**β can be isolated in ∼50% yields from Achmatowicz products **13** and **14**, and the ratio of β-pyranones to α-pyranones at these higher temperatures can be as high as 1.3:1 (Scheme 2). As with α-pyranones **8**α and **15**α, β-pyranones **8**β and **15**β can be converted via palladium(0) catalysis into their corresponding mixed acetal pyranones with complete retention of stereochemistry (i.e., **8** to **7** and **15**β to **16**, Scheme 1 and 3).

SCHEME 3. Synthesis of 2-Deoxy-L-allose 19



Approach to 2-Deoxy-β-glycosides. With a practical route to the β-pyranones glycosyl donors, we next turned our attention toward the preparation of 2-deoxy-β-L-allose, which started with the palladium-catalyzed glycosylation (5 mol % Pd(0)/10% PPh_3) of BnOH with the β-pyranone **15**β[27] to form the β-benzyloxy pyranone **16** in 84% yield as a single diastereomer (Scheme 3). Ketone reduction of pyranone **16** with $NaBH_4$[28] gave a mixture of allylic alcohols **17a** and **17b** in 88% yield with the diastereomeric ratio of ca. 1.5:1, respectively. Fortunately, both diastereomers **17a/b** could be used in the next reaction. The diastereomeric ratio of alcohols could be improved with the use of DibalH (dr = 6:1); however, because of the slightly lower yields, we preferred to use the operationally simpler Luche procedure ($NaBH_4/CeCl_3$, −78 °C; 88% 1.5:1). Applying the Myers' reductive rearrangement conditions[29] (NBSH, PPh_3/DEAD, NMM, −30 °C to rt) to the mixture of allylic alcohols **17** cleanly provided olefin **18** in 71% yield. Finally, exposing olefin **18** to the Upjohn conditions[30] (OsO_4/NMO) gave exclusively the diol **19** in 91% yield.[31]

SCHEME 4. Pd(0)-Catalyzed Glycosylation of 2-Deoxy-L-allose 19



With the successful synthesis of 2-deoxy-L-allose **19**, we next investigated the synthesis of allo-disaccharides using the same strategy (Scheme 4). Our attempts at the regioselective glycosylation of diol **19** using pyranones **15**β were not promising, giving a mixture of C-3 and C-4 glycosylated product **20** and **21** in a ratio of ca. 1.3:1. The regiochemistry of glycosylation was assigned by coupling constant analysis of the benzoate **22** from the major isomer **20**. Because of the inability of our palladium glycosylation methodology to differentiate the equatorial alcohol from the axial alcohol in **19**, we decided to incorporate a selective protection step and applied this methodology toward oligosaccharides (vide infra).

Synthesis of Digoxose and Digitoxin. Encouraged by these promising results toward the synthesis of 2-deoxy-L-allose **19**, we next investigated the use of this approach for the synthesis of digitoxose **25a**. Thus, palladium-catalyzed glycosylation of pyranone **(D)-8**β with benzyl alcohol provided the pyranone **7a** in 85% yield as a single diastereomer (Scheme 5). The Luche reduction of pyranone **7a** gave a mixture of allylic alcohols **23a** in 85% yield. Reductive rearrangement of allylic alcohols **23a** provided olefin **24a** in 84% yield. Dihydroxylation of **24a** using the Upjohn conditions (OsO_4/NMO)[30] gave exclusively the diol **25a** in 92% yield.[31] Using the same strategy starting from the digitoxigenin and β-pyranone **(D)-8**β, the digitoxigenin mono-

(25) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

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(27) For the preparation of Boc-protected pyranones, see ref 26. (a) Babu, R. S.; O'Doherty, G. A. *J. Carb. Chem.* **2005**, *24*, 169−177. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921−3924.

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(29) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841−4844. (c) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507. (d) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774.

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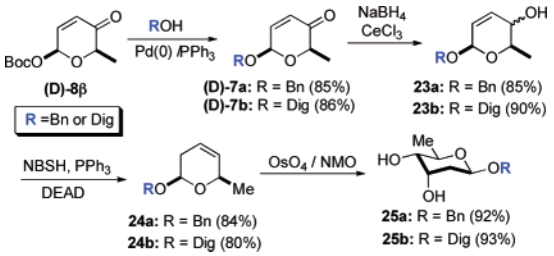
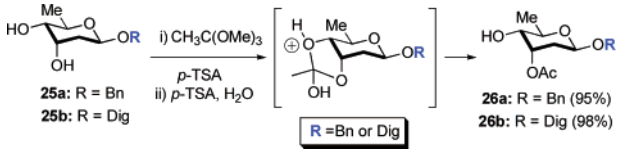
(31) No minor diastereomer was detected by ^1H NMR.

SCHEME 5. Synthesis of Digitoxose and Digitoxin Monosaccharides 25a/b



digitoxoside **25b** was prepared with similar efficiency.[32,33] It is worth noting that both the tertiary alcohol and the butenolide ring of the aglycon were left untouched and thus compatible to the palladium-catalyzed glycosylation and subsequent transformation.

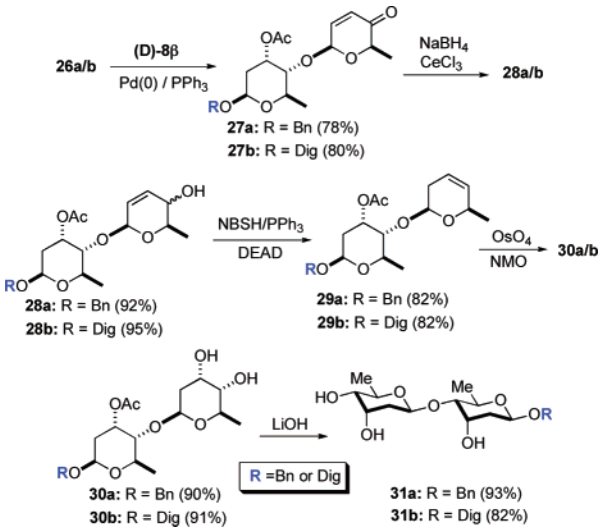
SCHEME 6. Regioselective Protection of Diol 25



To prepare the digitoxose disaccharide, a regioselective protection of diols **25a/b** was needed. This was achieved by the formation of an orthoester and regioselective ring opening (Scheme 6).[34] Specifically, the diol **25a** was treated with trimethyl orthoacetate and catalytic *p*-toluenesulfonic acid to form an orthoester intermediate, which upon regiospecific acid hydrolysis ($TsOH/H_2O$) opened to the kinetically preferred axial acetate **26a** in excellent yield (95%). In the case of digitoxigenin monodigitoxoside **25b**, the reaction works as well as when using **25a**. The tertiary alcohol, the butenolide ring of the aglycon, and glycosidic bond were compatible with the acidic condition. The remaining equatorial alcohol was then ready to serve as a glycosyl acceptor for a second Pd(0)-catalyzed glycosylation.

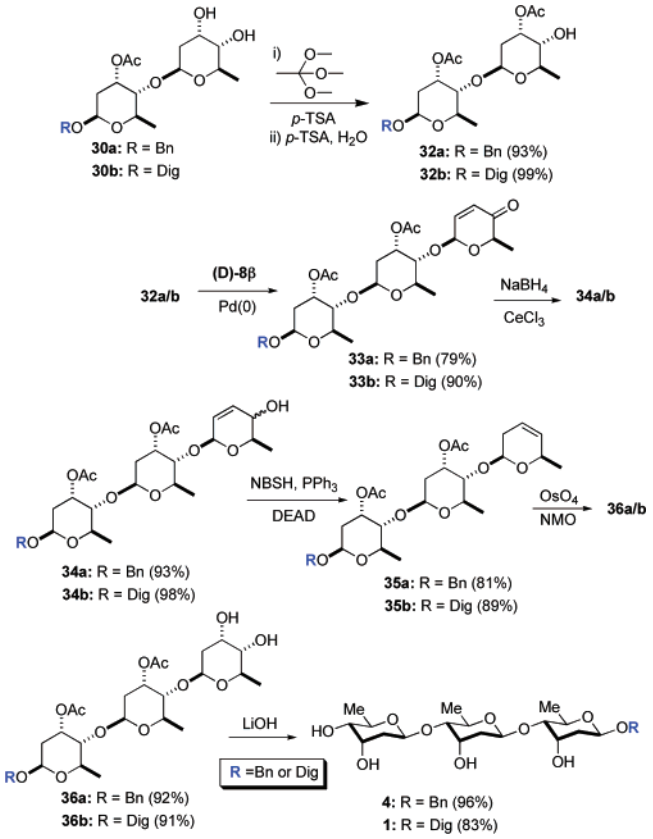
We next explored the potential for the synthesis of β-linked 1,4-oligosaccharides via glycosylation of the C-4 secondary alcohol in **26a/b**.[35] Applying the same palladium-catalyzed glycosylation conditions to **26a/b** (2 equiv of pyranone **(D)-8**β, with 5% Pd(0)/10% PPh_3) afforded the C-4 disaccharides **27a/b** with complete stereocontrol at the anomeric center in 78% and 80% yields, respectively (Scheme 7). Once again, the 1,2-reduction of the keto-group in pyranone **27a/b** under Luche conditions provided a mixture of allylic alcohols **28a/b** (~1:1), which when exposed to the Myers' reductive 1,3-allylic transposition conditions provided olefin **29a/b** in 82% yield. Finally, applying the Upjohn conditions to **29a/b** gave exclusively the dihydroxylated products **30a/b** in 90% and 91% yield, respectively.[31] The digitoxose disaccharide and digitoxin disaccharide **31a/b** were fashioned by deprotection of the acetate-protecting groups in **30a/b** in 93% and 82% yield, respectively.

SCHEME 7. Synthesis of Digitoxin and Digitoxose Disaccharides



Gratifyingly, the preparation of trisaccharide occurred with the same efficiency and high degree of stereocontrol as with the disaccharides **31a/b** (Scheme 7). Thus, regioselective protection of the C-3 axial alcohol in diol **30a/b** provided the equatorial alcohol **32a/b** which were subjected to the pyranone **(D)-8**β under Pd(0) catalyst to fashion the 1,4-linked trisaccharides **33a/b** in 79% and 90% yield, respectively (Scheme 8). When enone **33a/b** were subjected to Luche reduction, a mixture

SCHEME 8. Synthesis of Digitoxin and Digitoxose Trisaccharides 1 and 4



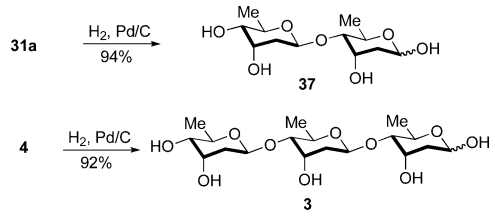
(32) Mono- and bisdigtoxosides have been prepared by gradual degradation of digitoxin; see: (a) Satoh, D., Aoyama, K. *Chem. Pharm. Bull.* **1970**, *18*, 94−98. (b) Templeton, F. J.; Setiloane, P.; Kumar, V. P. S.; Yan, Y.; Zeglam, H. T.; LaBella, F. S. *J. Med. Chem.* **1991**, *34*, 2778−2782. Our synthetic material **25b** and **31b** have physical and spectral data identical with those of the degraded products in the terms of ^1H NMR, ^{13}C NMR, optical rotation, and melting point.

(33) The nomenclature of compounds **25b** and **31b** was used according to ref 32.

(34) (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754−1769. (b) Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res.* **1994**, *251*, 33−67.

(35) For glycosylation at the C-4 position, we found that the best yields were obtained when a 2:1 ratio of glycosyl donor to acceptor was used.

SCHEME 9. Synthesis of Digoxose Bisdigitoxoside 37 and Digoxose 3



of allylic alcohols **34a/b** was obtained in 93% and 98% yields, respectively. The alcohols **34a/b** were then reductively rearranged to corresponding olefin **35a/b** in 81% and 89% yield, respectively. The trisaccharides **4** and **1** were prepared with high yield and complete stereocontrol by dihydroxylation of olefins in **35a/b** followed by deprotection of acetate groups in **36a/b**. The synthetic material **1** has physical and spectral data identical to those of the commercially available natural product **1**[36,37] (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).

Finally the digoxose bisdigitoxoside **37** and natural product digoxose **3** were prepared by hydrogenolysis of the anomeric benzyl group (H_2, Pd/C), which gave synthetic material with physical and spectral data identical to those of the isolated natural product **3** (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).[37,38]

Conclusions

In conclusion, a highly enantioselective route to digitoxin (**1**) and digoxose (**3**) as well as corresponding mono- and disaccharides (**25a**, **25b** and **31b**, **37**) has been developed. Key to the success of this approach is the iterative use of the palladium-catalyzed glycosylation reaction, Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective protection. Digoxose (**3**) was enantioselectively prepared in 16 steps and 12% overall yield from pyranone **8**β (19 steps from achiral 2-acylfuran), which constitutes the first total synthesis of **3**. The digitoxin (**1**) was achieved in 15 steps from digitoxigenin **2** and β-pyranone **8**, which is not only the shortest but also the most stereocontrolled synthesis so far.[39] This approach is equally amenable for the synthesis of the diastereomeric L-sugar digitoxin analogues. The uses of this strategy for the synthesis of these various analogues are ongoing and will be reported in due course.

Experimental Section[40]

(2*R*,6*R*)-2-Methyl-6-(phenylmethoxy)-2*H*-pyran-3(6*H*)-one (7a). A CH_2Cl_2 (3 mL) solution of Boc pyranone **8**β (716 mg, 3.14 mmol) and benzyl alcohol (678 mg, 6.28 mmol) was cooled to 0 °C. A CH_2Cl_2 (2 mL) solution of $Pd_2(DBA)_3$·$CHCl_3$ (81 mg, 2.5 mol %) and PPh_3 (82 mg, 10 mol %) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, quenched with 10 mL of saturated aqueous $NaHCO_3$, extracted (3 × 10 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 8% EtOAc/hexanes to give **7a** (582 mg, 2.67 mmol, 85%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ −41.8 (*c* 1.20, $CHCl_3$); IR (thin film, cm^{-1}) 2933, 1698, 1453, 1373, 1163, 1057, 1023, 903, 800, 733, 697; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.92 (dd, J = 10.3, 2.0 Hz, 1H), 6.14 (dd, J = 10.3, 1.6 Hz, 1H), 5.40 (m, 1H), 4.95 (d, J = 11.7 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.24 (q, J = 6.9 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 196.8, 146.4, 136.8, 128.5 (2C), 128.1(3C), 128.0, 94.3, 75.2, 70.1, 17.2; HRCIMS calcd for $[C_{13}H_{14}O_3Na^+]$ 241.0835, found 241.0843.

(2*R*,6*R*)-3,6-Dihydro-2-methyl-6-(phenylmethoxy)-2*H*-pyran-3-ol (23a). A CH_2Cl_2 (2 mL) solution of enone **7a** (435 mg, 2.0 mmol) and $CeCl_3$ in MeOH solution (1.7 mL) was cooled to −78 °C. $NaBH_4$ (75 mg, 2.0 mmol) was added, and the reaction mixture was stirred at −78 °C for 3 h. The reaction mixture was diluted with Et_2O (5 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to give allylic alcohols **23a** (374 mg, 1.70 mmol, 85%) as a viscous oil (diastereomeric ratio I:II = 1.5:1, inseparable by silica gel chromatography): R_f (40% EtOAc/hexanes) = 0.30; IR (thin film, cm^{-1}) 3397, 2978, 2933, 2869, 1498, 1455, 1378, 1053, 1010, 808, 738, 698; ^{1}H NMR (600 MHz, $CDCl_3$) (**isomer I**) δ 7.35 (m, 5H), 6.16 (ddd, J = 10.2, 5.4, 1.2 Hz, 1H), 5.86 (d, J = 10.2 Hz, 1H), 5.14 (ddd, J = 1.8, 1.8, 1.2 Hz, 1H), 4.92 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 3.75 (qd, J = 6.0, 2.4 Hz, 1H), 3.68 (m, 1H), 2.0 (d, J = 10.2 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H); (**isomer II**) δ 7.30 (m, 5H), 5.95 (ddd, J = 10.2, 2.4, 1.8 Hz, 1H), 5.79 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 5.18 (ddd, J = 1.8, 1.8, 1.2 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 3.90 (m, 1H), 3.64 (dq, J = 6.6, 6.0 Hz, 1H), 2.10 (d, J = 6.6 Hz, 1H), 1.38 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) (**isomer I**) δ 137.5, 131.3, 130.6, 128.4 (2C), 127.9 (2C), 127.7, 97.0, 71.4, 69.9, 64.7, 16.6; (**isomer II**) δ 137.7, 132.1, 128.7, 128.3 (2C), 127.9 (2C), 127.6, 95.5, 74.4, 69.2, 68.3, 17.8; HRCIMS calcd for $[C_{13}H_{16}O_3Na^+]$ 243.0992, found 243.0983.

***cis*-3,6-Dihydro-6-methyl-2-(phenylmethoxy)-2*H*-pyran (24a).** A flask was charged with dry *N*-methyl morpholine (NMM) 3.0 mL and triphenyl phosphine (1.45 g, 5.54 mmol) and was cooled to −30 °C under Ar atmosphere. Diethylazodicarboxylate (0.8 mL, 5.05 mmol) was added and the reaction was stirred for 5 min. Allylic alcohol **23a** (370 mg, 1.68 mmol) was added in a 1 M solution of NMM and the reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (1.02 g, 5.05 mmol). The reaction was stirred at −30 °C for 2 h and was monitored by TLC. Upon consumption of starting material, the mixture was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with Et_2O (10 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 2% Et_2O/hexanes to give product **24a** (293 mg, 1.44 mmol, 84%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.48; $[\alpha]_D^{21}$ −128.5 (*c* 1.80, $CHCl_3$); IR (thin film, cm^{-1}) 2973, 2927, 1453, 1366, 1158, 1080, 1028, 880, 777, 733. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.69 (ddd, J = 10.2, 4.8, 2.4 Hz, 1H), 5.60 (ddd, J = 10.2, 1.2, 1.2 Hz, 1H), 4.95 (d, J = 12.0 Hz, 1H), 4.75 (dd, J = 9.0, 3.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.35 (m, 1H), 2.27 (dddd, J = 17.4, 8.4, 3.6, 2.4 Hz, 1H), 2.19 (dddd, J = 17.4, 6.6, 2.4, 1.2 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ137.9, 130.9, 128.3 (2C), 127.9 (2C), 127.6, 122.5, 97.7, 70.6, 69.8, 30.9, 21.1; HRCIMS calcd for $[C_{13}H_{16}O_2Na^+]$ 227.1042, found 227.1045.

(36) Digitoxin purchased from Acros was used to do the comparison.

(37) Stereochemical assignments were made by coupling constant analysis and verified by the synthesis of known natural products **1** and **3**.

(38) We found our synthetic digoxose had higher optical rotation and melting points ($[\alpha]_D^{21}$ = +40.0 (*c* 0.35, MeOH), mp 210−212 °C) than the literature values ($[\alpha]_D^{21}$ = +36.25 (*c* 0.70, MeOH); mp 171−174 °C), which is probably just an indication of purity.

(39) The synthesis by McDonald and co-workers prepares digitoxin in 18 steps and experiences poor stereocontrol in the installation of the final glycosidic bond; see ref 20d.

(40) Presented in this experimental section are the procedures and spectral data for all new compounds. Complete experimental procedures and spectral data for all compounds are presented in Supporting Information.

Phenylmethyl 2,6-Dideoxy-β-D-ribo-hexopyranoside (25a). To a CH_2Cl_2 (3 mL) solution of olefin **24a** (291 mg, 1.43 mmol) at 0 °C was added a solution of 50% (w/v) of *N*-methyl morpholine *N*-oxide/water (0.67 mL). Crystalline OsO_4 (3.6 mg, 1 mol %) was added and the reaction was stirred for 3 h. The reaction was quenched by adding EtOAc and saturated $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 35% EtOAc/hexanes. Pure fractions were combined and concentrated to afford diol **25a** as a viscous oil (313 mg, 1.31 mmol, 92%): R_f (50% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ −85.9 (*c* 1.30, $CHCl_3$); IR (thin film, cm^{-1}) 3426, 2883, 1496, 1454, 1364, 1164, 1137, 1072, 1007, 867, 731, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.90 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.09 (m, 1H), 3.74 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (m, 1H), 2.51(s, 1H), 2.35 (s, 1H), 2.12 (ddd, *J* = 13.8, 3.6, 2.4 Hz, 1H), 1.78 (ddd, *J* = 13.8, 9.0, 3.0 Hz, 1H), 1.33(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.7, 128.4 (2C), 127.9 (2C), 127.7, 96.9, 73.0, 70.5, 69.5, 67.9, 37.7, 18.1; HRCIMS calcd for $[C_{13}H_{18}O_4Na^+]$ 261.1097, found 261.1087.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-β-D-ribo-hexopyranoside (26a). A round-bottom flask containing a 0.5 M solution of diol **25a** (300 mg, 1.26 mmol) in benzene (2.5 mL) was stirring at room temperature. To this solution were added trimethylorthoacetate (0.8 mL, 6.29 mmol) and a catalytic amount of *p*-toluenesulfonic acid (12 mg, 63 μmol). The reaction was allowed to stir until starting material is gone. The solvent was removed under reduced pressure and the residue was dissolved in 3 mL of THF/H_2O (1:1,v/v) solution. Then *p*-toluenesulfonic acid (600 mg, 3.15 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched by adding EtOAc and saturated $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 30% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **26a** (335 mg, 1.20 mmol, 95%): R_f (50% EtOAc/hexanes) = 0.38; $[\alpha]_D^{21}$ −52.4 (*c* 1.40, $CHCl_3$); IR (thin film, cm^{-1}) 3471, 2975, 2934, 1740, 1498, 1455, 1372, 1242, 1164, 1075, 1006, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.29 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.91 (d, *J* = 12.0 Hz ,1H), 4.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.73 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.46 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.14 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.10 (s, 3H), 1.87 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.2, 137.5, 128.3(2C), 127.8 (2C), 127.7, 97.0, 72.2, 71.0, 70.4, 70.3, 35.6, 21.1, 18.0; HRCIMS calcd for $[C_{15}H_{20}O_5Na^+]$ 303.1203, found 303.1201.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[(2*R*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (27a). A CH_2Cl_2 (0.8 mL) solution of Boc pyranone **8***β* (337 mg, 1.48 mmol) and alcohol **26a** (207 mg, 0.74 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.4 mL) solution of $Pd_2(DBA)_3{\cdot}CHCl_3$ (19 mg, 2.5 mol %) and PPh_3 (20 mg, 10 mol %) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 22% EtOAc/hexanes to give enone **27a** (228 mg, 0.58 mmol, 78%) as a viscous oil: R_f (30% EtOAc/hexanes) = 0.23; $[\alpha]_D^{21}$ +20.0 (*c* 0.55, $CHCl_3$); IR (thin film, cm^{-1}) 2931, 1739, 1698, 1454, 1373, 1256, 1242, 1155, 1050, 1004, 787, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.89 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.13 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.44 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.83 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.16 (q, *J* = 6.6 Hz, 1H), 3.96 (dq, *J* = 9.0, 6.6 Hz, 1H), 3.55 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.19 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.06 (s, 3H), 1.85 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.2, 170.1, 146.3, 137.6, 128.8, 128.4 (2C), 127.8 (2C), 127.7, 97.1, 97.0, 79.4, 75.2, 70.5, 69.4, 69.3, 35.6, 21.2, 18.3, 16.3; HRCIMS calcd for $[C_{21}H_{26}O_7Na^+]$ 413.1571, found 413.1558.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[(2*R*,6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (28a). A CH_2Cl_2 (0.6 mL) solution of enone **27a** (228 mg, 0.584 mmol) and $CeCl_3$ in MeOH solution (0.6 mL) was cooled to −78 °C. $NaBH_4$ (22 mg, 0.585 mmol) was added and the reaction mixture was stirred at −78 °C for 3 h. The reaction mixture was diluted with Et_2O (5 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 35% EtOAc/hexanes to give allylic alcohols **28a** (211 mg, 0.538 mmol, 92%) as a viscous oil (diastereometric ratio I:II = 1.6:1, inseparable by silica gel chromatography): R_f (40% EtOAc/hexanes) = 0.15; IR (thin film, cm^{-1}) 3471, 2980, 2934, 2875, 1740, 1498, 1455, 1372, 1243, 1154, 1057, 1009, 736, 698; ^1H NMR (600 MHz, $CDCl_3$) (**isomer I**) δ 7.28 (m, 5H), 6.17 (dd, *J* = 10.2, 5.4 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.57 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.15 (m, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.84 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.91 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.70 (dq, *J* = 1.8, 6.0 Hz, 1H), 3.60 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.47 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.27 (d, *J* = 14.4 Hz, 1H), 2.10 (ddd, *J* = 14.4, 4.8, 2.4 Hz, 1H), 2.05 (s, 3H), 1.87 (ddd, *J* = 14.4, 9.6, 2.4 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); (**isomer II**) δ 7.34 (m, 5H), 5.96 (d, *J* = 10.2 Hz, 1H), 5.78 (d, *J* = 10.2 Hz, 1H), 5.42 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.18 (m, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.80 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.86 (m, 2H), 3.64 (dq, *J* = 6.6, 6.0 Hz, 1H), 3.45 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.06 (s, 3H), 1.83 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.63 (d, *J* = 7.8 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) (**isomer I**) δ 170.3, 137.67, 131.8, 128.4, 128.2 (2C), 127.7 (3C), 98.3, 97.21, 78.2, 71.5, 70.51, 70.1, 69.3, 64.4, 35.9, 21.28, 18.1, 16.7; (**isomer II**) δ 170.2, 137.65, 132.9, 129.3, 128.37 (2C), 127.8 (3C), 97.5, 97.16, 78.1, 74.5, 70.49, 69.8, 69.4, 68.5, 35.8, 21.25, 18.3, 18.2; HRCIMS calcd for $[C_{21}H_{28}O_7Na^+]$ 415.1727, found 415.1726.

Phenylmethyl 3-*O*-Acetyl−2,6-dideoxy-4-*O*-[(2*S*,6*R*)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-β-D-ribo-hexopyranoside (29a). A flask was charged with dry NMM 0.9 mL and triphenyl phosphine (465 mg, 1.78 mmol) and was cooled to −30 °C under Ar atmosphere. Diethylazodicarboxylate (0.25 mL, 1.61 mmol) was added and the reaction was stirred for 5 min. Allylic alcohol **28a** (195 mg, 0.50 mmol) was added in a 1 M solution of NMM and the reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (328 mg, 1.61 mmol). The reaction was stirred at −30 °C for 2 h and was monitored by TLC. Upon consumption of starting material, the reaction was warmed to room temperature and stirred for another 2 h. The reaction mixture was diluted with Et_2O (10 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 8% EtOAc/hexanes to give product **29a** (156 mg, 0.41 mmol, 82%) as a viscous oil: R_f (15% EtOAc/hexanes) = 0.31; $[\alpha]_D^{21}$ +4.0 (*c* 0.5, $CHCl_3$); IR (thin film, cm^{-1}) 2974, 2927, 1742, 1453, 1367, 1243, 1156, 1090, 1065, 1044, 781, 698. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.63 (dddd, *J* = 9.6, 4.8, 2.4, 2.4 Hz, 1H), 5.55 (ddd, *J* = 10.2, 2.4, 1.2 Hz, 1H), 5.55 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.81 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.69 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.28 (m, 1H), 3.93 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.38 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.20 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.18 (ddd, *J* = 17.4, 7.2, 4.2 Hz, 1H), 2.13 (ddd, *J* = 17.4, 6.6, 3.0 Hz, 1H), 2.07-(s, 3H), 1.84 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.3,

137.7, 131.2, 128.4 (2C), 127.8 (2C), 127.7, 122.2, 100.3, 97.2, 79.2, 70.9, 70.5, 69.9, 69.4, 35.7, 30.9, 21.3, 20.8, 18.2; HRCIMS calcd for $[C_{21}H_{28}O_6Na^+]$ 399.1778, found 399.1773.

Phenylmethyl 3-*O*-Acetyl-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (30a). To a CH_2Cl_2 (3 mL) solution of olefin **29a** (148 mg, 0.39 mmol) at 0 °C was added a solution of 50% (w/v) *N*-methyl morpholine *N*-oxide/water (0.11 mL). Crystalline OsO_4 (1.2 mg, 1 mol %) was added and the reaction was stirred for 3 h. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 60% EtOAc/hexanes. Pure fractions were combined and concentrated to afford diol **30a** (145 mg, 0.35 mmol, 90%): R_f (70% EtOAc/hexanes) = 0.18; $[\alpha]_D^{21}$ +1.6 (*c* 1.35, $CHCl_3$); IR (thin film, cm^{-1}) 3436, 2972, 2932, 2879, 1741, 1370, 1247, 1165, 1066, 1012, 868, 740, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.38 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.84 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.79 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.05 (m, 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.67 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.35 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.24 (ddd, *J* = 9.0, 6.6, 3.6 Hz, 1H), 2.54 (s, 1H), 2.33(d, *J* = 5.4 Hz, 1H), 2.16 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.08 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 2.06 (s, 3H), 1.82 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.68 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.31(d, *J* = 6.0 Hz, 3H), 1.22(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 137.6, 128.3 (2C), 127.8 (2C), 127.7, 98.6, 97.2, 79.4, 72.7, 70.5, 69.7, 69.3, 69.2, 68.0, 37.6, 35.6, 21.3, 18.2, 17.9; HRCIMS calcd for $[C_{21}H_{30}O_8Na^+]$ 433.1833, found 433.1826.

Phenylmethyl 2,6-Dideoxy-4-*O*-[2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (31a). To a MeOH/H_2O (0.1 mL, 1:1, 1 M) solution of diol **30a** (6 mg, 14.6 μmol) at room temperature was added LiOH (0.35 mg, 14.6 μmol) and the reaction was stirred for 3 h. The reaction was quenched by adding EtOAc and saturated aquous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 65% EtOAc/hexanes. Pure fractions were combined and concentrated to afford triol **31a** (5 mg, 13.6 μmol, 93%) as a white solid: R_f (80% EtOAc/hexanes) = 0.28; mp 145−145.5 °C; $[\alpha]_D^{21}$ −44.0 (*c* 0.20, $CHCl_3$); IR (thin film, cm^{-1}) 3437, 2962, 2931, 2886, 1454, 1405, 1368, 1164, 1068, 1011, 868, 735, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.92 (m, 1H), 4.91 (m, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.26 (dddd, *J* = 6.6, 3.6, 3.6, 1.8 Hz, 1H), 4.12 (dddd, *J* = 5.4, 4.2, 3.0, 2.4 Hz, 1H), 3.82 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.67 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.30 (ddd, *J* = 9.6, 6.6, 3.0 Hz, 1H), 3.26 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.96 (m, *J* = 2.4, 1.8, 1.2 Hz, 1H), 2.28 (d, *J* = 1.2 Hz, 1H), 2.17 (ddd, *J* = 14.4, 4.2, 2.4 Hz, 1H), 2.13 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1H), 1.96 (d, *J* = 6.6 Hz, 1H), 1.79 (m, 1H), 1.75 (m, 1H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.28(d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 128.4 (2C), 127.9 (2C), 127.6, 98.3, 97.1, 82.7, 72.8, 70.6, 69.5, 68.3, 68.2, 66.3, 37.9, 36.6, 18.2, 18.1; HRCIMS calcd for $[C_{19}H_{28}O_7Na^+]$ 391.1727, found 391.1726.

Phenylmethyl 3-*O*-Acetyl-4-*O*-[3-*O*-acetyl-2,6-dideoxy-*β*-D-ribo-hexopyranosyl]-2,6-dideoxy-*β*-D-ribo-hexopyranoside (32a). A round-bottom flask containing a 0.5 M solution of diol **30a** (140 mg, 0.34 mmol) in benzene (0.6 mL) was stirred at room temperature. To this solution were added trimethylorthoacetate (0.13 mL, 1.02 mmol) and a catalytic amount of *p*-toluenesulfonic acid (3.2 mg, 17 μmol). The reaction was allowed to stir until starting material was gone. The solvent was removed under reduced pressure and the residue was dissolved in 0.8 mL of THF/H_2O (1:1,v/v) solution. Then *p*-toluenesulfonic acid (97 mg, 0.51 mmol) was added. Stirring was continued until hydrolysis was complete as seen by TLC. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 45% EtOAc/hexanes. Pure fractions were combined and concentrated to afford compound **32a** (143 mg, 0.32 mmol, 93%) as a white solid: R_f (80% EtOAc/hexanes) = 0.48; mp 105−106 °C; $[\alpha]_D^{21}$ +14.8 (*c* 1.15, $CHCl_3$); IR (thin film, cm^{-1}) 3475, 2972, 2932, 2879, 1741, 1370, 1243, 1165, 1068, 1009, 947, 870, 704; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.39 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.25 (ddd, *J* = 3.6, 3.0, 2.4 Hz, 1H), 4.89 (d, *J* = 12.0 Hz ,1H), 4.79 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.74 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.65 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.36 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.35 (ddd, *J* = 9.0, 3.0, 3.0 Hz, 1H), 2.17 (ddd, *J* = 14.4, 3.6, 1.8 Hz, 1H), 2.13 (s, 3H), 2.08 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.05 (s, 3H), 1.81 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.78 (ddd, *J* = 14.4, 9.6, 3.0 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.4, 137.8, 128.6 (2C), 128.2 (2C), 127.9, 98.8, 97.4, 79.8, 72.2, 71.3, 70.7, 70.4, 69.7, 69.5, 36.1, 35.8, 21.5, 21.4, 18.4, 18.1; HRCIMS calcd for $[C_{23}H_{32}O_9Na^+]$ 475.1938, found 475.1926.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2*R*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (33a). A CH_2Cl_2 (0.3 mL) solution of Boc pyranone **8***β* (228 mg, 0.62 mmol) and alcohol **32a** (141 mg, 0.31 mmol) was cooled to 0 °C. A CH_2Cl_2 (0.2 mL) solution of $Pd_2(DBA)_3{\cdot}CHCl_3$ (16 mg, 2.5 mol %) and PPh_3 (16 mg, 10 mol %) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 33% EtOAc/hexanes to give enone **33a** (138 mg, 0.25 mmol, 79%) as a white solid: R_f (40% EtOAc/hexanes) = 0.18; mp 95−96 °C; $[\alpha]_D^{21}$ +43.0 (*c* 0.3, $CHCl_3$); IR (thin film, cm^{-1})2980, 1740, 1702, 1454, 1372, 1243, 1158, 1055, 1006; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.87 (dd, *J* = 10.2, 1.2 Hz, 1H), 6.11 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.40 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.39 (m, 2H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.79 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.74 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.88 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.86 (dq, *J* = 9.0, 6.0 Hz, 1H), 3. 45 (dd, *J* = 9.6, 3.0 Hz, 1H), 3. 34 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.15 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.11 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.81 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.76 (ddd, *J* = 14.4, 9.0, 3.0 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 170.1, 170.07, 146.2, 137.6, 128.7, 128.3 (2C), 127.8 (2C), 127.7, 98.7, 97.1, 97.07, 79.6, 79.2, 75.1, 70.5, 69.64, 69.60, 69.2, 69.0, 35.9, 35.7, 21.24, 21.20, 18.2, 18.0, 16.3; HRCIMS calcd for $[C_{29}H_{38}O_{11}Na^+]$ 585.2306, found 585.2299.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2*R*,6*R*)-5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl]-*β*-D-ribo-hexopyranosyl]-*β*-D-ribo-hexopyranoside (34a). A CH_2Cl_2 (0.3 mL) solution of enone **33a** (138 mg, 0.245 mmol) and $CeCl_3$ in MeOH solution (0.3 mL) was cooled to −78 °C. $NaBH_4$ (10 mg, 0.25 mmol) was added and the reaction mixture was stirred at −78 °C for 3 h. The reaction mixture was diluted with Et_2O (5 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexanes to give allylic alcohols **34a** (374 mg, 1.70 mmol, 85%) as a viscous oil (diastereometric ratio I:II = 1.4:1, inseparable in chromatography): R_f (60% EtOAc/hexanes) = 0.25; IR (thin film, cm^{-1}) 3478, 2972, 2932, 2874, 1742, 1371, 1243, 1156, 1059, 1010; ^1H NMR (600 MHz, $CDCl_3$) (**isomer I**) δ 7.33 (m, 5H), 6.15 (dd, *J* = 10.2, 6.0, Hz, 1H), 5.72 (d, *J* = 9.6 Hz, 1H), 5.54 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 5.40 (ddd, *J* = 3.6, 3.0, 3.0 Hz, 1H), 5.12 (m, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.788 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.75 (dd, *J* = 9.6, 1.8 Hz, 1H), 4.551 (d, *J* = 12.0 Hz, 1H), 3.88 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.87 (m, 1H), 3.77 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.68 (qd, *J* = 6.0, 1.8 Hz, 1H), 3.58 (dd, *J* =

11.4, 5.4 Hz, 1H), 3.39 (dd, J = 9.6, 3.0 Hz, 1H), 3.34 (dd, J = 9.6, 3.6 Hz, 1H), 2.16 (ddd, J = 14.4, 3.6, 2.4 Hz, 1H), 2.08 (s, 3H), 2.069 (s, 3H), 2.02 (ddd, J = 14.4, 3.0, 2.4 Hz, 1H), 1.79 (ddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.72 (ddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.70 (s, 1H), 1.31 (d, J = 6.6 Hz, 3H), 1.25 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H); (**isomer II**) δ 7.33 (m, 5H), 5.94 (ddd, J = 10.8, 1.8, 1.8 Hz, 1H), 5.86 (d, J = 10.2 Hz, 1H), 5.75 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 5.39 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 5.38 (ddd, J = 3.0, 3.0, 2.4 Hz, 1H), 5.13 (m, 1H), 4.88 (d, J = 12.0 Hz, 1H), 4.783 (dd, J = 9.6, 2.4 Hz, 1H), 4.71 (dd, J = 9.6, 1.8 Hz, 1H), 4.548 (d, J = 12.0 Hz, 1H), 3.87 (m, 1H), 3.83 (dq, J = 9.6, 6.0 Hz, 1H), 3.54 (dq, J = 6.6, 6.0 Hz, 1H), 3.35 (m, 2H), 2.32 (d, J = 11.4 Hz, 1H), 2.16 (ddd, J = 14.4, 3.6, 2.4 Hz, 1H), 2.09 (s, 3H), 2.056 (s, 3H), 2.02 (ddd, J = 14.4, 3.0, 2.4 Hz, 1H), 1.81 (ddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.76 (ddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.29 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) (**isomer I**) δ 170.1 (2C), 133.0 (2C), 131.7, 128.1 (2C), 127.7 (3C), 98.75 (2C), 98.24, 98.22, 79.5, 77.8, 71.4, 69.9, 69.7, 69.2, 69.1, 64.4, 36.0, 35.7, 21.30, 21.28, 18.18, 18.03, 17.9; (**isomer II**) δ 170.3 (2C), 137.6 (2C), 129.2, 128.3 (2C), 127.8 (3C), 98.72, 97.6, 97.2 (2C), 79.6, 78.0, 74.5, 70.5, 70.2, 69.6, 69.3, 68.4, 35.9, 35.6, 21.28, 21.26, 18.17, 18.16, 16.7; HRCIMS calcd for [$C_{29}H_{40}O_{11}$-Na^+] 587.2463, found 587.2453.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-2,6-dideoxy-4-*O*-[(2*S*,6*R*)-3,6-dihydro-6-methyl-2*H*-pyran-2-yl]-β-D-ribo-hexopyranosyl]-β-D-ribo-hexopyranoside (35a). A flask was charged with dry NMM 0.4 mL and triphenyl phosphine (191 mg, 0.73 mmol) and was cooled to −30 °C under Ar atmosphere. Diethylazodicarboxylate (0.1 mL, 0.66 mmol) was added, the reaction was stirred for 5 min, allylic alcohols **34a** (125 mg, 0.22 mmol) was added in a 1 M solution of NMM, and the reaction mixture was stirred for 10 min, followed by addition of *o*-nitrobenzenesulfonyl hydrazide (NBSH) (135 mg, 0.66 mmol). The reaction was stirred at −30 °C for 4 h and was monitored by TLC. Upon consumption of starting material, the reaction was warmed up to room temperature and stirred for another 2 h. The reaction mixture was diluted with Et_2O (10 mL), quenched with 5 mL of saturated aqueous $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexanes to give product **35a** (97 mg, 0.18 mmol, 81%) as a white solid: R_f (50% EtOAc/hexanes) = 0.44; mp 101−101.5 °C; $[\alpha]_D^{21}$ +38.0 (*c* 0.9, $CHCl_3$); IR (thin film, cm^{-1}) 2981, 2932, 2871, 1742, 1368, 1243, 1157, 1090, 1067, 1008, 704; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.62 (dddd, J = 10.2, 4.8, 2.4, 2.4 Hz, 1H), 5.53 (ddd, J = 9.6, 1.2, 1.2 Hz, 1H), 5.41 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 5.37 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.78 (dd, J = 9.6, 1.8 Hz, 1H), 4.71 (dd, J = 9.6, 1.8 Hz, 1H), 4.65 (dd, J = 8.4, 3.6 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.25 (m, 1H), 3.87 (dq, J = 9.0, 6.0 Hz, 1H), 3.84 (dq, J = 9.6, 6.0 Hz, 1H), 3.34 (dd, J = 9.6, 3.6 Hz, 1H), 3.28 (dd, J = 9.6, 3.6 Hz, 1H), 2.14 (m, 4H), 2.11 (s, 3H), 2.06 (s, 3H), 1.81 (dddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.74 (dddd, J = 14.4, 9.6, 3.0 Hz, 1H), 1.30 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.3, 170.1, 137.6, 131.1, 128.3 (2C), 127.8 (2C), 127.7, 122.2, 100.3, 98.8, 97.2, 79.5, 78.9, 70.9, 70.5, 70.1, 69.7, 69.3, 69.2, 35.9, 35.7, 30.9, 21.33, 21.26, 20.8, 18.2, 18.0; HRCIMS calcd for [$C_{29}H_{40}O_{10}Na^+$] 571.2514, found 571.2525.

Phenylmethyl 3-*O*-Acetyl-2,6-dideoxy-4-*O*-[[3-*O*-acetyl-4-*O*-[2,6-dideoxy-β-D-ribo-hexopyranosyl]-2,6-dideoxy-β-D-ribo-hexopyranosyl]-β-D-ribo-hexopyranoside (36a). To a CH_2Cl_2 (0.6 mL) solution of olefin **35a** (94 mg, 0.17 mmol) at 0 °C was added a solution of 50% (w/v) *N*-methyl morpholine *N*-oxide/water (80 μL). Crystalline OsO_4 (0.4 mg, 1 mol %) was added and the reaction was stirred for 3 h. The reaction was quenched by adding EtOAc and saturated $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 60% EtOAc/hexanes. Pure fractions were combined and concentrated to afford alcohol **36a** (92 mg, 0.16 mmol, 92%) as a white solid: R_f (80% EtOAc/hexanes) = 0.25; mp 167−167.5 °C; $[\alpha]_D^{21}$+35.0 (*c* 1.45, $CHCl_3$); IR (thin film, cm^{-1}) 3455, 2972, 2932, 2880, 1741, 1370, 1244, 1162, 1065, 1011, 869, 704; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.39 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 5.34 (ddd, J = 3.0, 3.0, 3.0 Hz, 1H), 4.88 (d, J = 12.0 Hz, 1H), 4.81 (dd, J = 9.6, 1.8 Hz, 1H), 4.78 (dd, J = 9.6, 1.8 Hz, 1H), 4.70 (dd, J = 9.6, 1.8 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.05 (m, 1H), 3.86 (dq, J = 9.0, 6.0 Hz, 1H), 3.80 (dq, J = 9.0, 6.0 Hz, 1H), 3.65 (dq, J = 9.0, 6.0 Hz, 1H), 3.33 (dd, J = 9.6, 3.0 Hz, 1H), 3.27 (dd, J = 9.6, 3.6 Hz, 1H), 3.23 (ddd, J = 9.6, 6.0, 3.6 Hz, 1H), 2.47 (s, 1H), 2.25 (d, J = 6.6 Hz, 1H), 2.15 (ddd, J = 14.4, 3.6, 1.8 Hz, 1H), 2.09 (s, 3H), 2.08 (ddd, J = 14.4, 3.0, 1.8 Hz, 1H), 2.06 (ddd, J = 14.4, 3.0, 1.8 Hz, 1H), 2.05 (s, 3H), 1.80 (ddd, J = 14.4, 9.6, 2.4 Hz, 1H), 1.72 (ddd, J = 14.4, 9.6, 3.0 Hz, 1H), 1.66 (ddd, J = 13.8, 9.6, 3.0 Hz, 1H), 1.29 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.2, 137.6, 128.3(2C), 127.8 (2C), 127.7, 98.8, 98.7, 97.2, 79.5, 79.2, 72.7, 70.5, 69.9, 69.7, 69.3 (2C), 69.1, 68.0, 37.6, 35.9, 35.6, 21.3, 21.2, 18.2, 17.9 (2C); HRCIMS calcd for [$C_{29}H_{42}O_{12}Na^+$] 605.2568, found 605.2580.

Phenylmethyl 2,6-Dideoxy-4-*O*-[[2,6-dideoxy-β-D-ribo-hexopyranosyl]-2,6-dideoxy-β-D-ribo-hexopyranosyl]-β-D-ribo-hexopyranoside (4). To a MeOH/H_2O (0.3 mL, 1:1, 1 M) solution of alcohol **36a** (14 mg, 24 μmol) at room temperature was added LiOH (2.5 mg, 60 μmol) and the reaction was stirred for 3 h. The reaction was quenched by adding EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated. It was purified by a silica gel column using 75% EtOAc/hexanes. Pure fractions were combined and concentrated to afford **4** (11.5 mg, 23 μmol, 96%) as a white solid: R_f (80% EtOAc/hexanes) = 0.18; mp 120−121 °C; $[\alpha]_D^{21}$ −13.3 (*c* 0.60, $CHCl_3$); IR (thin film, cm^{-1}) 3424, 2927, 2886, 1455, 1369, 1318, 1163, 1130, 1068, 1012, 869, 733, 699; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.91 (dd, J = 9.6, 3.0 Hz, 1H), 4.90 (m, 2H), 4.88 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.25 (m, 2H), 4.12 (ddd, J = 3.6, 3.6, 2.4 Hz, 1H), 3.83 (dq, J = 9.6, 6.0 Hz, 1H), 3.81(dq, J = 9.0, 6.0 Hz, 1H), 3.76 (dq, J = 9.6, 6.0 Hz, 1H), 3.30 (m, 1H), 3.26 (dd, J = 9.6, 3.0 Hz, 1H), 3.20 (dd, J = 9.6, 3.0 Hz, 1H), 2.99 (s, 1H), 2.95 (s, 1H), 2.33 (s, 1H), 2.16 (ddd, J = 13.8, 3.6, 2.4 Hz, 1H), 2.14 (ddd, J = 14.4, 3.0, 2.4 Hz, 1H), 2.11 (ddd, J = 13.8, 3.0, 2.4 Hz, 1H), 2.03 (s, 1H), 1.78 (ddd, J = 14.4, 9.0, 3.0 Hz, 1H), 1.74 (m, 2H), 1.28 (d, J = 6.6 Hz, 6H), 1.22 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 128.3 (2C), 127.9 (2C), 127.6, 98.30, 98.26, 97.1, 82.6, 82.2, 72.7, 70.6, 69.5, 68.32, 68.26, 68.1, 66.4, 66.2, 37.8, 36.7, 36.6, 18.2 (2C), 18.1; HRCIMS calcd for [$C_{25}H_{38}O_{10}$-Na^+] 521.2357, found 521.2360.

***O*-2,6-Dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-D-ribo-hexose (37).** To an EtOH (2 mL) solution of **31a** (15.6 mg, 42 μmol) under H_2 atmosphere at room temperature was added Pd/C (8 mg) and the reaction was stirred for 6 h. The reaction mixture was filtered through a pad of Celite using MeOH. The filtrate was concentrated and purified by a silica gel column using 1% MeOH/EtOAc. Pure fractions were combined and concentrated to afford digoxose bisdigitoxide **37** (11 mg, 39.5 μmol, 94%) as a white solid: R_f (10% MeOH/EtOAc) = 0.18; mp 132−135 °C; $[\alpha]_D^{21}$ +56.7 (*c* 0.80, MeOH); IR (thin film, cm^{-1}) 3426, 2930, 1376, 1319, 1165, 1132, 1068, 1014, 992, 869, 729; ^{1}H NMR (600 MHz, $CD_3OD/CDCl_3$) (β) δ 5.03 (dd, J = 9.6, 1.8 Hz, 1H), 4.84 (dd, J = 9.6, 2.4 Hz, 1H), 4.17 (ddd, J = 3.6, 3.0, 2.4 Hz, 1H), 3.98 (m, 1H), 3.78 (dq, J = 9.0, 6.0 Hz, 1H), 3.69 (dq, J = 9.0, 6.0 Hz, 1H), 3.15 (dd, J = 9.0, 3.0 Hz, 1H), 3.13 (dd, J = 9.0, 3.0 Hz, 1H), 2.04 (m, 2H), 1.61 (ddd, J = 13.8, 9.6, 3.0 Hz, 1H), 1.67 (m, 1H), 1.20 (d, J = 6.0 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H); (α) 5.01 (d, J = 3.0 Hz, 1H), 4.87 (dd, J = 9.6, 1.8 Hz, 1H), 4.26 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 4.07 (dq, J = 9.6, 6.0 Hz, 1H), 3.97 (m, 1H), 3.68 (dq, J = 9.6, 6.0 Hz, 1H), 3.18 (dd, J = 9.0,

3.0 Hz, 1H), 3.14 (dd, J = 9.0, 3.0 Hz, 1H), 2.06 (m, 2H), 1.80 (ddd, J = 14.4, 3.0, 3.0 Hz, 1H), 1.68 (m, 1H), 1.19 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD/$CDCl_3$) (β) δ 98.56, 91.4, 82.4, 72.46, 69.59, 68.0, 67.62, 66.3, 37.76, 37.69, 17.92, 17.86; (α) δ98.58, 91.5, 82.2, 72.44, 69.60, 67.6, 66.9, 61.6, 37.74, 34.3, 17.93, 17.7; HRCIMS calcd for [$C_{12}H_{22}O_7Na^+$] 301.1263, found 301.1255.

***O*-2,6-Dideoxy-β-D-ribo-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-D-ribo-hexose (3).** To an EtOH (0.3 mL) solution of **4** (11 mg, 22 μmol) under H_2 atmosphere at room temperature was added Pd/C (6 mg) and the reaction was stirred for 6 h. The reaction mixture was filtered through a pad of Celite using MeOH. The eluent was concentrated and purified by a silica gel column using 2% MeOH/EtOAc. Pure fractions were combined and concentrated to afford digoxose **3** (8 mg, 20 μmol, 92%) as a white solid: R_f (10% MeOH/EtOAc) = 0.29; mp 210−212 °C; $[\alpha]_D^{21}$ +40.0 (*c* 0.35, MeOH); IR (thin film, cm^{-1}) 3425, 2929, 1376, 1319, 1231, 1165, 1133, 1067, 1013, 992, 869, 729; ^{1}H NMR (600 MHz, CD_3OD/$CDCl_3$) (β) δ 5.04 (dd, J = 9.6, 2.4 Hz, 1H), 4.845 (dd, J = 9.6, 1.8 Hz, 1H), 4.841 (dd, J = 9.6, 1.8 Hz, 1H), 4.18 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 4.17 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 3.98 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 3.78 (m, *2*H), 3.69 (dq, J = 9.0, 6.0 Hz, 1H), 3.16 (dd, J = 9.6, 3.0 Hz, 1H), 3.147 (dd, J = 9.6, 3.0 Hz, 1H), 3.144 (dd, J = 9.6, 3.0 Hz, 1H), 2.16 (m, 3H), 1.65 (m, 3H), 1.213 (d, J = 6.6 Hz, 3H), 1.175 (d, J = 6.6 Hz, 3H), 1.165 (d, J = 6.6 Hz, 3H); (α) 5.01 (d, J = 3.0 Hz, 1H), 4.87 (dd, J = 10.2, 2.4 Hz, 1H), 4.848 (dd, J = 9.6, 2.4 Hz, 1H), 4.26 (ddd, J = 3.6, 3.0, 3.0 Hz, 1H), 4.06 (m, 2H), 3.77 (m, *2*H), 3.70 (dq, J = 9.0, 6.0 Hz, 1H), 3.19 (dd, J = 9.6, 3.0 Hz, 1H), 3.137 (dd, J = 9.6, 3.0 Hz, 1H), 3.140 (m, 1H), 2.06 (m, 3H), 1.64 (m, 3H), 1.216 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.160 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD/$CDCl_3$) (β) δ 98.6, 98.5, 91.4, 82.4, 82.19, 82.17, 72.5, 69.64, 68.2, 67.6, 66.9, 66.15, 37.75 (2C), 36.61, 17.95 (2C), 17.75; (α) δ 98.6, 98.5, 91.5, 82.21, 82.19, 82.17, 69.63, 68.0, 66.4, 66.18, 66.16, 61.50, 37.71, 36.62, 34.3, 17.95, 17.93, 17.90; HRCIMS calcd for [$C_{18}H_{32}O_{10}Na^+$] 431.1889, found 431.1888.

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

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