

# On the Direct Epoxidation of Glycals: Application of a Reiterative Strategy for the Synthesis of $\beta$ -Linked Oligosaccharides

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**Abstract:** The use of dimethyldioxirane for the first direct epoxidation of glycals is described. The products of such reactions, 1,2-anhydro sugars, are employed in the stereospecific construction of  $\beta$ -linked oligosaccharides. A key element is the use of glycals with nonparticipating protecting groups to avoid complications.

The possibility of using 1,2-anhydro sugars (cf. **1**) as glycosyl donors in reactions has been recognized, but not extensively exploited.<sup>1,2</sup> The syntheses of systems **1** from suitably functionalized and differentiated hexose derivatives has been accomplished in certain cases,<sup>3,4</sup> but has not been widely developed. Perhaps owing to a lack of broad availability of such oxiranes, the transformation implicit in eq 1 (Figure 1) has not been systematically investigated or generalized (NuH is a nucleophile).<sup>5</sup>

We have been studying the use of glycals (cf. **2**) as starting materials for glycoside formation. The symbolism X in eq 2 (Figure 1) covers two possibilities. In one instance X represents a nonisolable (onium) intermediate arising from attack of E<sup>+</sup> upon **2**.<sup>6</sup> Alternatively, X might represent an isolable compound that subsequently reacts with NuH. With respect to the latter formulation, the obvious possibility of direct epoxidation of glycals to produce 1,2-anhydro sugars (**1**) was considered. Previous attempts to achieve this reaction using per acids did not lead to isolable epoxide.<sup>7</sup> Instead, there were obtained products that corresponded to reaction of an initially formed 1,2-anhydro sugar, which reacted with either solvent or acid, RCO<sub>2</sub>H (derived from reduction of the per acid RCO<sub>3</sub>H). Accordingly, we have evaluated the use of anhydrous 3,3-dimethyldioxirane (**3**) as an epoxidant.<sup>8</sup> The byproduct, acetone, generated from a successful reaction would not be expected to react with system **1**. Our results are described here.<sup>9</sup>

Dimethyldioxirane (**3**) prepared according to the procedure of Murray and co-workers<sup>8c</sup> was used as a solution in acetone. Reaction of tri-*O*-acetylglucal **4** with **3** in methylene chloride/acetone at 0 °C followed by solvolysis in methanol afforded a mixture of products, which was not separated. *We reasoned that selectivity might be improved both in epoxidation and in subsequent glycosylation reactions if the protecting groups were of a nonparticipatory nature.* Toward this end glycals **5** and **6** were employed as substrates (Figure 2). In the event, a stereospecific reaction ensued with each of these substrates. The workup simply consists of evaporation of the volatiles. While the NMR spectra of the crude product did not rigorously define the stereochemical sense of epoxidation, this point was established by a sequence of methanolysis followed by acetylation. In a similar way, the galactal-derived system, **10**,<sup>10</sup> cleanly gave rise to  $\alpha$ -oxirane **11**.

The first synthesis of a  $\beta$ -epoxide by direct epoxidation using the Murray system<sup>8c</sup> was carried out with the allal derivative **12**.<sup>11,12</sup> Compound **13** was obtained in 98% yield. A mixture (ca. 1:1) of oxiranes **15** and **16** was generated by epoxidation of the gual derivative **14**.<sup>11</sup> An early experiment designed to probe the possibility of hydroxyl directivity on this type of epoxidation<sup>13</sup> indicated relatively little effect. Thus, reaction of the C<sub>3</sub>-free hydroxy version of **14** gave only a small difference in the product ratio obtained relative to that with the protected system.

With a general route to these epoxides in hand, we probed their value as glycosyl donors. The first experiments involved methyl glycoside formation by dissolution of the epoxide in methanol (Figure 3). Reactions were complete within 2 h at room temperature. The resultant methoxyhydrins were acetylated with acetic anhydride in pyridine at 0 °C. *In each instance methanolysis had occurred with clean inversion of configuration in excellent yield.*

We have begun to examine the usefulness of such oxiranes as glycosyl donors in the construction of oligosaccharides. This type of reaction had been studied in the past in a limited way<sup>5,14</sup> and had been attended by low yields. In these early experiments we

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(8) For a history of the use of this compound, including a few examples of epoxidation of simple model olefins, cf. inter alia: (a) Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820. (b) Edwards, J. O.; Pater, R. H.; Curci, R.; Furia, F. D. *Photochem. Photobiol.* **1979**, *30*, 63. (c) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (d) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (e) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311. (f) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437. (g) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzou, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

(9) A very recent and important paper by Harris and co-workers deals with the use of **3** in the synthesis of the ultimate carcinogen from aflatoxin B<sub>1</sub>. Also described in the Harris disclosure is the epoxidation of the parent dihydrofuran and dihydropyran. See: Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 1988.

(10) Tris-*O*-(*tert*-butyldimethylsilyl)galactal was prepared in ca. 80% overall yield from tri-*O*-acetylgalactal by the two-step sequence: (a) MeOH, catalytic NaOMe, (b) TBS-Cl, Et<sub>3</sub>N, DMF.

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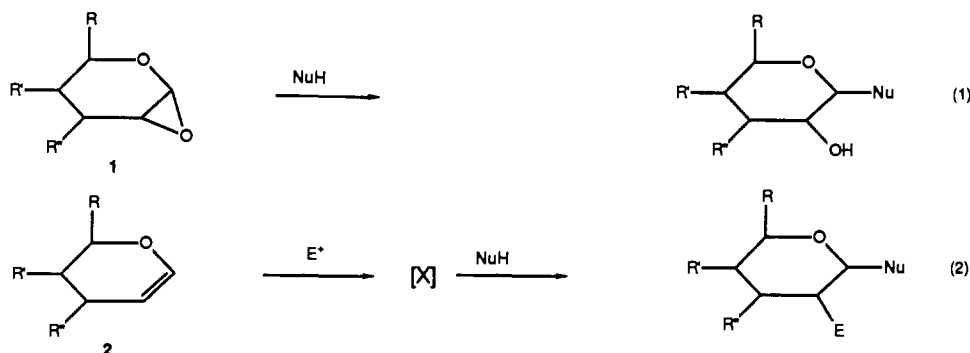


Figure 1.

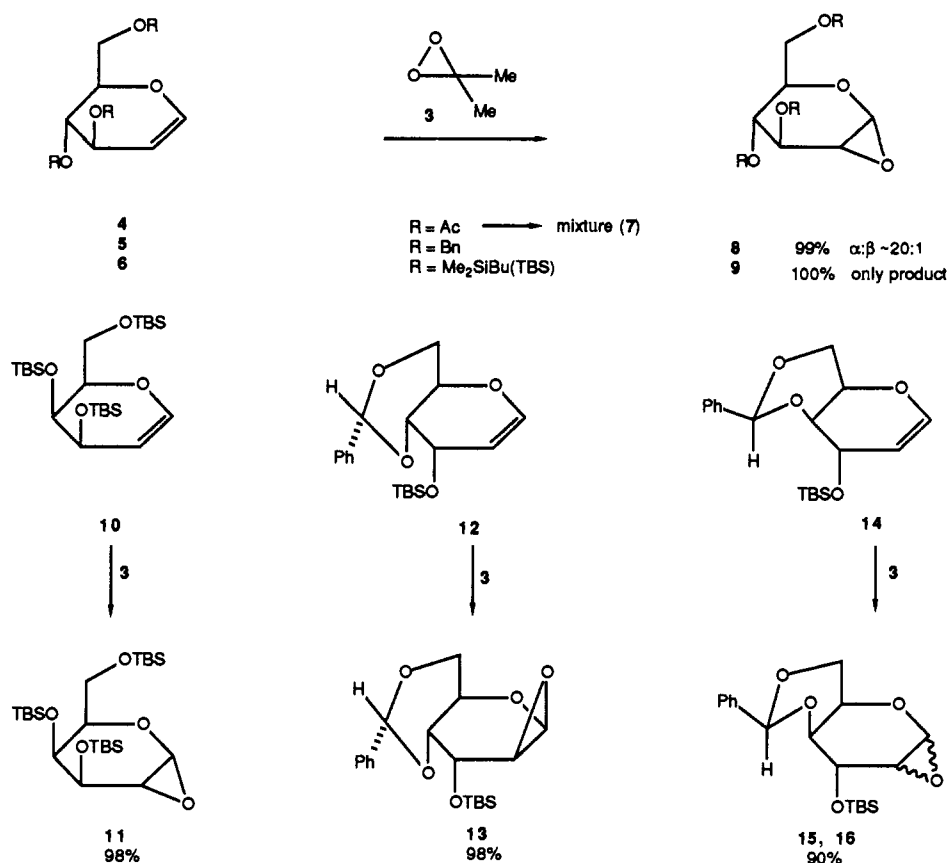


Figure 2.

have used anhydrous zinc chloride as the catalyst in tetrahydrofuran from  $-78^\circ\text{C}$  to room temperature for 24 h. Two encouraging cases have already been demonstrated. Reaction of epoxide **8** with diisopropylidene galactose derivative **21** afforded cleanly disaccharide **22a**. Similar reaction of **8** with differentiated glucal **23**<sup>15</sup> afforded **24a**. The yields based on consumed glycosyl acceptor are 80–90%. However, the yields based on reacted epoxide are only ca. 50–58%. In a separate experiment it was shown that epoxide **8** is substantially consumed upon exposure to anhydrous zinc chloride under these conditions ( $-78^\circ\text{C}$ ). In each case, the glycosylation reaction was essentially stereospecific with formation of a  $\beta$ -glycosidic bond. This was firmly proven by <sup>1</sup>H NMR analysis of acetylated derivatives **22b** and **24b**. Benzylation of **24a** followed by reiteration of the sequence gave epoxide **25** and trisaccharide **26a**. We attribute the much greater success of these glycosylation reactions both in terms of stereospecificity and of yield (relative to the classical Brigl's<sup>3,5</sup> anhydride case) to the absence of participating groups in the epoxide substrate.

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In addition to their utility in oligosaccharide construction, the 1,2-anhydro sugars synthesized as described above will be useful glycosylating agents for the formation of lipid conjugates. For instance, reaction of **8** with menthol (**27**) gives **28a** (Figure 4). Likewise, the cholesterol conjugate **30a** is formed upon reaction of **8** with cholesterol (**29**). As before, the structures of the glycosides were proven by analysis of the respective acetates **28b** and **30b**.

In summary, we have described the first general, high-yield, one-step conversion of glycols to 1,2-anhydro sugars. We have also demonstrated that the epoxide linkage at the anomeric center can be displaced with clean inversion of configuration to form oligosaccharides and other conjugates with  $\beta$ -glycosidic linkages at temperatures as low as  $-78^\circ\text{C}$ . Possibilities of a reiteratable and automatable scheme for oligosaccharide synthesis via oxidative coupling of glycols in the fashion suggested by these and earlier results<sup>6</sup> are currently being evaluated.

#### Experimental Section

**General Procedure for Epoxidation.** The glycal (0.1 mmol) was dissolved in 1.0 mL of  $\text{CH}_2\text{Cl}_2$ , and the resulting solution was cooled to  $0^\circ\text{C}$ . A solution of dimethyldioxirane **3** in acetone (1.2 equiv, ca. 0.05 M) was added dropwise. The reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h

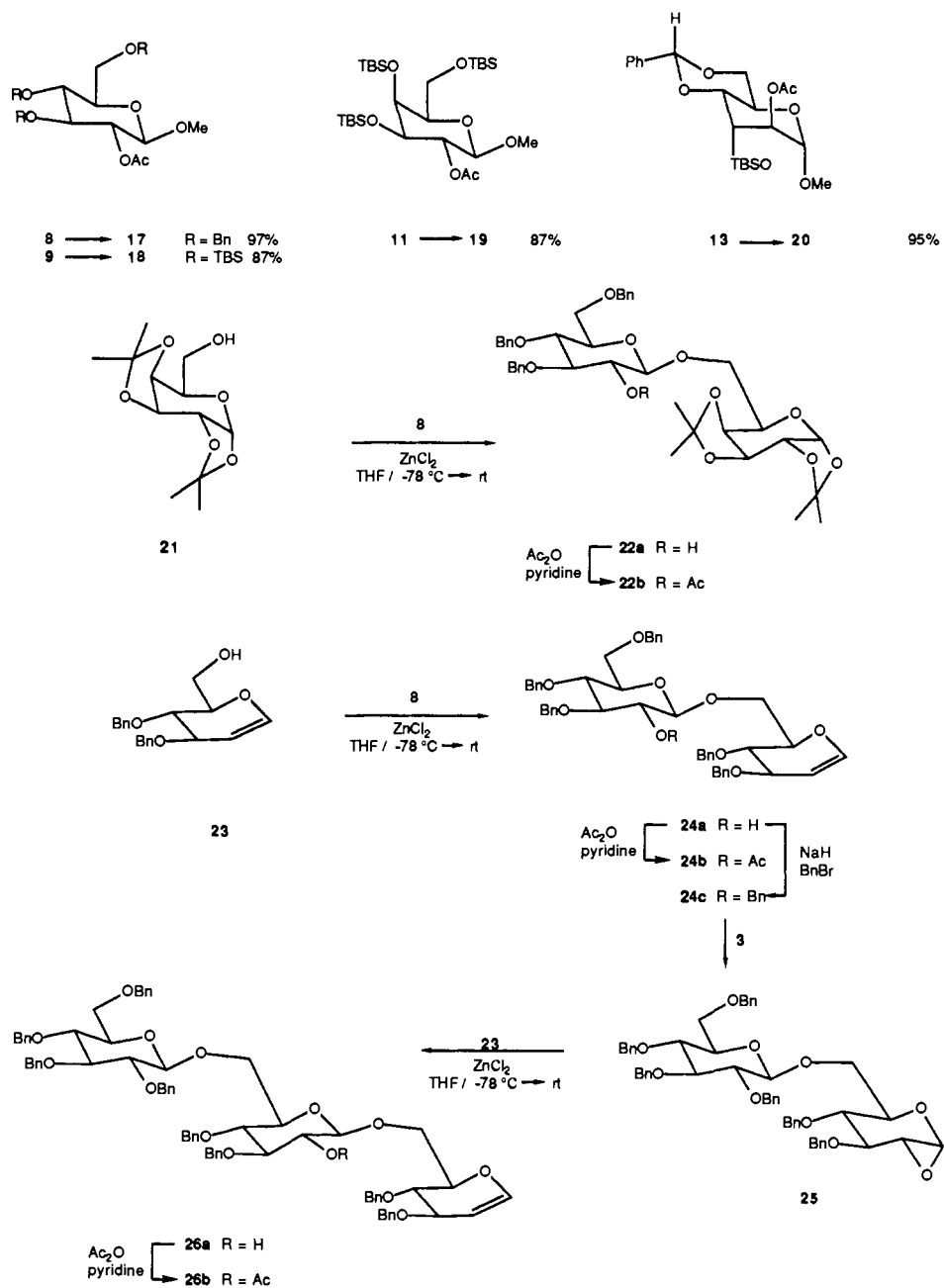


Figure 3.

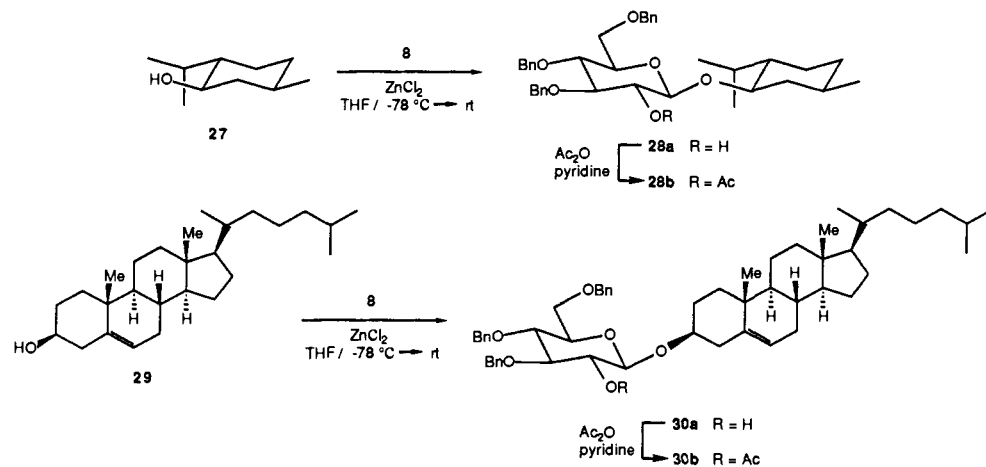


Figure 4.

or until TLC indicated complete consumption of the glycol. The solution was evaporated with a stream of dry N<sub>2</sub> and the residue was dried in vacuo to afford the 1,2-anhydro sugar(s) in quantitative yield.

**1,2-Anhydro-3,4,6-tri-*O*-benzyl- $\alpha$ -D-glucopyranose (8):**  $[\alpha]_D^{25} +29.2^\circ$  (*c* 0.96, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2990, 2900, 2840, 1714, 1440, 1245, 1090 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.4–7.1 (m, 15 H), 5.00 (br d, 1 H, *J* = 1.96 Hz), 4.88–4.50 (m, 6 H), 3.99 (d, 1 H, *J* = 7.62 Hz), 3.85–3.60 (m, 4 H), 3.10 (d, 1 H, *J* = 1.96 Hz); MS (20 eV) *m/z* 432, 341, 325, 181, 91.

**1,2-Anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)- $\alpha$ -D-glucopyranose (9):**  $[\alpha]_D^{25} +23.6^\circ$  (*c* 0.87, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2958, 2935, 2860, 1475, 1262, 1145, 1110, 845 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  4.90 (d, 1 H, *J* = 2.20 Hz), 3.98 (d, 1 H, *J* = 6.52 Hz), 3.82–3.76 (m, 2 H), 3.60–3.43 (m, 2 H), 2.92 (d, 1 H, *J* = 2.45 Hz), 0.95 (s, 9 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.21 (s, 3 H), 0.15 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 6 H); MS (20 eV) *m/z* 505, 447, 374, 315, 241, 171, 129.

**1,2-Anhydro-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)- $\alpha$ -D-galactopyranose (11):**  $[\alpha]_D^{25} +25.0^\circ$  (*c* 1.01, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2960, 2935, 2860, 1472, 1260, 1184, 1160, 1148, 1100, 845 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  4.89 (d, 1 H, *J* = 2.63 Hz), 3.85 (br s, 2 H), 3.80–3.40 (m, 3 H), 2.92 (br s, 1 H), 0.96 (s, 9 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS (20 eV) *m/z* 505, 487, 469, 447, 445, 374, 373, 357, 331, 316, 315, 273, 241, 213, 211, 171.

**1,2-Anhydro-4,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)- $\beta$ -D-altropyranose (13):**  $[\alpha]_D^{25} +29.0^\circ$ ; (*c* 0.94, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2930, 2905, 2835, 1458, 1420, 1245, 1150, 1135, 1110, 1090, 1010, 830, 819 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.52–7.30 (m, 5 H), 5.50 (s, 1 H), 4.91 (d, 1 H, *J* = 2.52 Hz), 4.63 (t, 1 H, *J* = 2.50 Hz), 4.31 (dd, 1 H, *J* = 10.03, 5.25 Hz), 3.92 (dd, 1 H, *J* = 9.85, 3.09 Hz), 3.61 (t, 1 H, *J* = 10.26 Hz), 3.21 (t, 1 H, *J* = 2.53 Hz), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H); MS (20 eV) *m/z* 364, 307, 215, 202, 201, 183, 171, 155, 145, 143, 129, 117, 105.

**General Procedure for Methanolysis and Acetylation.** The 1,2-anhydro sugar (0.1 mmol) was dissolved in 1.0 mL of anhydrous MeOH, and the solution was stirred at room temperature for 2 h or until TLC indicated complete consumption of the starting material. The MeOH was removed in vacuo to afford a quantitative yield of methyl glycoside(s). The methyl glycoside(s) was dissolved in 1.0 mL of pyridine, and the resulting solution was cooled to 0 °C. Acetic anhydride (1.0 mL) was added dropwise, and the mixture was then stirred at 0 °C for 3 h or until TLC indicated the disappearance of starting material. The mixture was added slowly to 20 mL of saturated NaHCO<sub>3</sub> followed by extraction with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated to afford the acetylated products, which were purified by silica gel chromatography.

**Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- $\beta$ -D-glucopyranoside (17):**  $[\alpha]_D^{25} +4.90^\circ$  (*c* 0.49, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2990, 1730, 1440, 1360, 1225, 1080, 1050 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.42–7.10 (m, 15 H), 5.00 (t, 1 H, *J* = 8.58 Hz), 4.88–4.76 (m, 2 H), 4.73–4.50 (m, 4 H), 4.30 (d, 1 H, *J* = 7.85 Hz), 3.83–3.62 (m, 4 H), 3.49 (s, 3 H), 3.55–3.43 (m, 1 H), 1.98 (s, 3 H); MS (20 eV) *m/z* 469, 415, 383, 309, 277, 217, 205, 187, 181, 163, 127, 91. Anal. Calcd for C<sub>39</sub>H<sub>34</sub>O<sub>7</sub>: C, 71.13; H, 6.76. Found: C, 71.51; H, 6.95.

**Methyl 2-*O*-acetyl-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)- $\beta$ -D-glucopyranoside (18):**  $[\alpha]_D^{25} -23.9^\circ$  (*c* 1.05, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2940, 2915, 2845, 1735, 1465, 1255, 1110, 845 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  4.72 (dd, 1 H, *J* = 6.90, 3.40 Hz), 4.60 (d, 1 H, *J* = 6.66 Hz), 3.92–3.65 (m, 5 H), 3.47 (s, 3 H), 2.07 (s, 3 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.14 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 9 H); MS (20 eV) *m/z* 521, 489, 461, 447, 429, 415, 401, 374, 373, 357, 347, 379, 315, 301, 273, 255, 231, 213, 175. Anal. Calcd for C<sub>27</sub>H<sub>58</sub>O<sub>7</sub>Si<sub>3</sub>: C, 56.01; H, 10.10. Found: C, 56.59; H, 9.59.

**Methyl 2-*O*-acetyl-3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)- $\beta$ -D-galactopyranoside (19):**  $[\alpha]_D^{25} -0.4^\circ$  (*c* 1.00, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 2940, 2910, 2840, 1740, 1470, 1370, 1255, 1110, 1080, 840 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  5.28 (dd, 1 H, *J* = 9.70, 7.39 Hz), 4.34 (d, 1 H, *J* = 7.74 Hz), 3.98 (d, 1 H, *J* = 1.81 Hz), 3.80–3.70 (m, 2 H), 3.63 (dd, 1 H, *J* = 9.92, 2.27 Hz), 3.45 (s, 3 H), 3.39 (t, 1 H, *J* = 7.09 Hz), 2.09 (s, 3 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.10 (s, 9 H), 0.07 (s, 6 H); MS (20 eV) *m/z* 549, 521, 461, 429, 389, 375, 347, 315, 301, 287, 273, 261, 255, 245, 231, 229, 213, 197, 189, 175, 147, 117, 89. Anal. Calcd for C<sub>27</sub>H<sub>58</sub>O<sub>7</sub>Si<sub>3</sub>: C, 56.01; H, 10.10. Found: C, 56.28; H, 9.99.

**Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)- $\alpha$ -D-altropyranoside (20):**  $[\alpha]_D^{25} +71.2^\circ$  (*c* 0.59, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3005, 2910, 2840, 1735, 1370, 1240, 1143, 1105, 1045, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.56–7.15 (m, 5 H), 5.59 (s, 1 H), 4.86 (d, 1 H, *J* = 3.00 Hz), 4.57 (s, 1 H), 4.45–4.28 (m, 2 H), 4.07 (br t, 1 H, *J* = 1.95 Hz), 3.90–3.72 (m, 2 H), 3.37 (s, 3 H), 2.14 (s, 3 H), 0.93 (s,

9 H), 0.11 (s, 3 H), 0.04 (s, 3 H); MS (20 eV) *m/z* 381, 349, 322, 321, 289, 275, 243, 233, 215, 185, 169, 159, 149, 145, 121, 117, 105; HRMS (CI) calculated for C<sub>27</sub>H<sub>34</sub>O<sub>7</sub>Si 438.2074, found 438.2079.

***O*-(3,4,6-Tri-*O*-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,2,3,4-di-*O*-isopropylidene- $\alpha$ -D-galactopyranose (22a).** Epoxide 8 (37.7 mg, 0.0873 mmol) was dissolved in 0.15 mL of THF, and the resulting solution was cooled to –78 °C. A solution of 34.0 mg (0.136 mmol) of compound 21 in 0.15 mL of THF was added followed by the dropwise addition of 0.15 mL of a 1.0 M solution of ZnCl<sub>2</sub> in ether. The reaction mixture was stirred at –78 °C for 1.5 h and then warmed to room temperature over the course of 2 h. After being stirred at room temperature for 20 h, the mixture was added to 25 mL of saturated NaHCO<sub>3</sub> and extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was chromatographed on silica gel, eluting with hexanes/EtOAc (7:3), to afford 34.8 mg of disaccharide 22a (58%, 82% based on 21) as well as 19.7 mg of unreacted 21:  $[\alpha]_D^{25} -44.4^\circ$  (*c* 3.25, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3010, 2905, 1496, 1388, 1258, 1170, 1080, 1010 cm<sup>-1</sup>; <sup>1</sup>H NMR (490 MHz, CDCl<sub>3</sub>)  $\delta$  7.50–7.13 (m, 15 H), 5.56 (d, 1 H, *J* = 4.96 Hz), 5.03 (d, 1 H, *J* = 11.27), 4.85 (d, 1 H, *J* = 10.80 Hz), 4.81 (d, 1 H, *J* = 11.17 Hz), 4.67–4.59 (m, 2 H), 4.58–4.50 (m, 2 H), 4.40–4.30 (m, 4 H), 4.23 (dd, 1 H, *J* = 7.96, 1.69 Hz), 4.10 (dd, 1 H, *J* = 11.15, 3.44 Hz), 4.04 (m, 1 H), 3.80–3.68 (m, 3 H), 3.67–3.58 (m, 3 H), 3.50 (m, 1 H), 2.97 (s, 1 H), 1.55 (s, 3 H), 1.46 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H); <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>)  $\delta$  138.90, 138.23, 138.17, 128.29, 127.90, 127.79, 127.62, 127.55, 127.46, 109.50, 108.77, 104.03, 96.29, 84.61, 77.32, 77.18, 75.17, 74.97, 74.82, 73.49, 71.20, 70.74, 70.47, 69.36, 68.94, 67.85, 26.01, 25.95, 24.92, 24.37; FAB MS *m/z* 692, 677, 447, 433, 405, 351, 325, 313, 253, 235, 224, 223, 221, 191, 181, 177. Anal. Calcd for C<sub>39</sub>H<sub>48</sub>O<sub>11</sub>: C, 67.61; H, 6.98. Found: C, 67.79; H, 7.28.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,2,3,4-di-*O*-isopropylidene- $\alpha$ -D-galactopyranose (22b).** Disaccharide 22a (36 mg, 0.0520 mmol) was dissolved in 1.0 mL of pyridine, and the solution was cooled to 0 °C. Acetic anhydride (0.5 mL) was added and the solution was stirred at 0 °C for 3 h, after which time it was added slowly to 25 mL of saturated NaHCO<sub>3</sub> and extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, concentrated, and flash chromatographed on silica gel (eluting with hexanes/EtOAc, 8:2) to afford 32.1 mg (84%) of 22b:  $[\alpha]_D^{25} -30.1^\circ$  (*c* 1.02, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3010, 2920, 1745, 1455, 1380, 1235, 1080 cm<sup>-1</sup>; <sup>1</sup>H NMR (490 MHz, CDCl<sub>3</sub>)  $\delta$  7.40–7.18 (m, 15 H), 5.52 (d, 1 H, *J* = 4.96 Hz), 5.03 (t, 1 H, *J* = 8.54 Hz), 4.83–4.77 (m, 2 H), 4.69 (d, 1 H, *J* = 11.40 Hz), 4.64 (d, 1 H, *J* = 12.17 Hz), 4.60–4.55 (m, 3 H), 4.45 (d, 1 H, *J* = 8.02 Hz), 4.29 (dd, 1 H, *J* = 4.90, 2.40 Hz), 4.20 (dd, 1 H, *J* = 7.97, 1.75 Hz), 4.07 (dd, 1 H, *J* = 11.26, 3.52 Hz), 3.94 (m, 1 H), 3.78–3.67 (m, 4 H), 3.64 (dd, 1 H, *J* = 11.25, 7.39 Hz), 3.49 (dt, 1 H, *J* = 9.17, 3.13 Hz), 2.04 (s, 3 H), 1.53 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H); FAB MS *m/z* 757 (M + Na<sup>+</sup>).

***O*-(3,4,6-Tri-*O*-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (24a).** Epoxide 8 (49.4 mg, 0.114 mmol) was dissolved in 0.15 mL of THF, and the resulting solution was cooled to –78 °C. A solution of glycol 23 (55.8 mg, 0.171 mmol) in 0.15 mL of THF was added followed by the dropwise addition of 0.25 mL of a 1.0 M solution of ZnCl<sub>2</sub> in ether. The mixture was stirred at –78 °C for 1 h and then allowed to warm to room temperature over the course of 1 h. After being stirred at room temperature for 18 h, the mixture was added to 25 mL of saturated NaHCO<sub>3</sub>, which was then extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was chromatographed on silica gel (eluting with hexanes/EtOAc, 7:3) to give 48.7 mg of compound 24a (56%, 81% based on 23) along with 30.0 mg of unreacted 23:  $[\alpha]_D^{25} -5.9^\circ$  (*c* 2.97, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3015, 3000, 2860, 1645, 1490, 1450, 1353, 1228, 1070, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (490 MHz, CDCl<sub>3</sub>)  $\delta$  7.41–7.17 (m, 25 H), 6.42 (dd, 1 H, *J* = 6.11, 0.91 Hz), 4.95 (d, 1 H, *J* = 11.29 Hz), 4.91 (dd, 1 H, *J* = 6.19, 2.91 Hz), 4.87–4.80 (m, 3 H), 4.72–4.52 (m, 6 H), 4.29 (d, 1 H, *J* = 7.28 Hz), 4.21–4.16 (m, 3 H), 3.87 (dd, 1 H, *J* = 11.92, 7.14 Hz), 3.77 (dd, 1 H, *J* = 7.49, 5.75 Hz), 3.76–3.68 (m, 2 H), 3.64–3.57 (m, 3 H), 3.46 (m, 1 H), 2.51 (s, 1 H); <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>)  $\delta$  144.43, 138.75, 138.23, 128.55, 128.43, 128.35, 127.93, 127.87, 127.76, 127.70, 127.64, 127.55, 103.55, 99.88, 84.53, 76.29, 75.33, 75.03, 74.97, 74.74, 74.65, 74.41, 73.53, 73.29, 70.41, 68.97, 68.68; FAB MS *m/z* 758, 652, 651, 545, 447, 443, 433, 398, 346, 325, 307.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (24b).** Compound 24a (21.2 mg, 0.0280 mmol) was dissolved in 1.0 mL of pyridine and cooled to 0 °C. Acetic anhydride (1.0 mL) was added, and the mixture was stirred for 1 h at 0 °C followed by 2 h at room temperature. The mixture was added slowly to 25 mL of saturated NaHCO<sub>3</sub>, which was then extracted with 3  $\times$  10 mL of EtOAc. The combined

extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel, eluting with hexanes/EtOAc (8:2), gave 16.5 mg (74%) of compound **24b**:  $[\alpha]_D^{25} +7.3^\circ$  (*c* 1.65,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3020, 3000, 2860, 1740, 1642, 1490, 1450, 1360, 1230, 1060  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.18 (m, 25 H), 6.38 (dd, 1 H, *J* = 6.17, 0.90 Hz), 5.05 (t, 1 H, *J* = 8.54 Hz), 4.87 (dd, 1 H, *J* = 6.19, 2.93 Hz), 4.82–4.78 (m, 3 H), 4.71–4.52 (m, 7 H), 4.43 (d, 1 H, *J* = 7.94 Hz), 4.15–4.08 (m, 3 H), 3.84 (dd, 1 H, *J* = 11.37, 6.13 Hz), 3.78–3.64 (m, 5 H), 3.48 (m, 1 H), 1.93 (s, 3 H); FAB MS *m/z* 823 (*M* + *Na*<sup>+</sup>). Anal. Calcd for  $\text{C}_{49}\text{H}_{52}\text{O}_{10}$ : C, 73.48; H, 6.54. Found: C, 73.61; H, 6.55.

**O-(2,3,4,6-Tetra-O-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,5-anhydro-3,4-di-O-benzyl-2-deoxy-D-arabino-hex-1-enopyranose (24c)**. A solution of disaccharide **24a** (30.2 mg, 0.0398 mmol) in 0.2 mL of DMF was added dropwise to a suspension of 60% NaH (3.0 mg) in 0.1 mL of DMF at 0 °C. After stirring at 0 °C for 1 h, 10 mL of benzyl bromide was added, and the mixture was stirred for another 1 h at 0 °C followed by 1 h at room temperature. The mixture was added to 15 mL of saturated  $\text{NaHCO}_3$ , which was then extracted with 3  $\times$  5 mL of EtOAc. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Purification by flash chromatography on silica gel (eluting with hexanes/EtOAc, 8:2) gave 29.6 mg (88%) of compound **24c**:  $[\alpha]_D^{25} +13.9^\circ$  (*c* 0.825,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3010, 3000, 2860, 1680, 1495, 1453, 1230, 1070  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.15 (m, 30 H), 6.42 (d, 1 H, *J* = 6.17 Hz), 5.02 (d, 1 H, *J* = 10.95 Hz), 4.94 (d, 1 H, *J* = 10.90 Hz), 4.90 (dd, 1 H, *J* = 6.18, 3.03 Hz), 4.85–4.77 (m, 2 H), 4.76–4.72 (m, 2 H), 4.65–4.59 (m, 3 H), 4.57–4.51 (m, 3 H), 4.42 (d, 1 H, *J* = 7.80 Hz), 4.26–4.18 (m, 2 H), 4.15 (m, 1 H), 3.89 (dd, 1 H, *J* = 10.96, 6.40 Hz), 3.79 (dd, 1 H, *J* = 7.30, 5.67 Hz), 3.76–3.58 (m, 4 H), 3.50 (t, 1 H, *J* = 8.24 Hz), 3.43 (m, 1 H); FAB MS *m/z* 849 (*M* + *Na*<sup>+</sup>). Anal. Calcd for  $\text{C}_{54}\text{H}_{56}\text{O}_9$ : C, 76.39; H, 6.65. Found: C, 75.91; H, 6.93.

**O-(2,3,4,6-Tetra-O-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-O-(3,4-di-O-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,5-anhydro-3,4-di-O-benzyl-2-deoxy-D-arabino-hex-1-enopyranose (26a)**. Disaccharide **24c** (42.3 mg, 0.0499 mmol) was dissolved in 1.0 mL of  $\text{CH}_2\text{Cl}_2$ , and the resulting solution was cooled to 0 °C. A solution of **3** (0.10 M, 0.75 mL) was added dropwise. After stirring at 0 °C for 0.5 h, the volatiles were removed in vacuo, giving 44.9 mg of compound **25**.<sup>16</sup> Epoxide **25** (40.0 mg, 0.0463 mmol) was dissolved in 0.20 mL of THF and cooled to -78 °C. A solution of glycol **23** in 0.15 mL of THF was added, followed by a solution of  $\text{ZnCl}_2$  in ether (1.0 M, 0.12 mL). The mixture was stirred at -78 °C for 1 h and allowed to warm to room temperature over the course of 2 h. After being stirred for 10 h at room temperature, the mixture was added to 25 mL of saturated  $\text{NaHCO}_3$  and extracted with 3  $\times$  10 mL of EtOAc. The combined extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel gave 17.4 mg of trisaccharide **26a** (32%, 57% based on 16.0 mg of recovered **23**):  $[\alpha]_D^{25} +3.88^\circ$  (*c* 0.825,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3690, 3035, 3010, 1240, 1072, 813, 710  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.5–7.14 (m, 40 H), 6.38 (d, 1 H, *J* = 6.20 Hz), 4.98–4.93 (m, 2 H), 4.89 (d, 1 H, *J* = 10.97 Hz), 4.86 (dd, 1 H, *J* = 6.14, 2.90 Hz), 4.84–4.72 (m, 7 H), 4.65–4.50 (m, 7 H), 4.44 (d, 1 H, *J* = 7.77 Hz), 4.26 (m, 1 H), 4.20 (dd, 1 H, *J* = 11.13, 1.40 Hz), 4.16–4.12 (m, 2 H), 4.02 (m, 1 H), 3.78–3.68 (m, 4 H), 3.65–3.55 (m, 5 H), 3.53–3.40 (m, 3 H), 2.45 (s, 1 H); FAB MS *m/z* 1123 (*M* + *Na*<sup>+</sup> - *Bn*).

**O-(2,3,4,6-Tetra-O-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-O-(2-O-acetyl-3,4-di-O-benzyl- $\beta$ -D-glucopyranosyl)-(1 $\rightarrow$ 6)-1,5-anhydro-3,4-di-O-benzyl-2-deoxy-D-arabino-hex-1-enopyranose (26b)**. Trisaccharide **26a** (16.0 mg, 0.0136 mmol) was dissolved in 0.5 mL of pyridine and cooled to 0 °C. Acetic anhydride (0.5 mL) was added, and the mixture was stirred at 0 °C for 3 h. The solution was added slowly to 15 mL of saturated  $\text{NaHCO}_3$  and extracted with 3  $\times$  5 mL of EtOAc. The combined extracts were dried over  $\text{MgSO}_4$ , filtered, concentrated, and filtered through silica to afford 16.1 mg (96%) of compound **26b**:  $[\alpha]_D^{25} +7.0^\circ$  (*c* 0.99,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3005, 2992, 2860, 1742, 1453, 1358, 1240, 1070  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.17 (m, 40 H), 6.35 (dd, 1 H, *J* = 6.14, 0.94 Hz), 5.07 (dd, 1 H, *J* = 9.38, 8.02 Hz), 4.95 (d, 1 H, *J* = 11.06 Hz), 4.90 (d, 1 H, *J* = 10.94 Hz), 4.84–4.80 (m, 2 H), 4.79–4.65 (m, 5 H), 4.64–4.49 (m, 8 H), 4.48 (d, 1 H, *J* = 7.81 Hz), 4.38 (d, 1 H, *J* = 7.93 Hz), 4.19 (br d, 1 H, *J* = 10.43 Hz), 4.14–4.09 (m, 2 H), 3.93 (m, 1 H), 3.78–3.55 (m, 10 H), 3.48–3.42 (m, 2 H), 1.89 (s, 3 H); FAB MS *m/z* 1255 (*M* + *Na*<sup>+</sup>). Anal. Calcd for  $\text{C}_{76}\text{H}_{80}\text{O}_{15}$ : C, 74.01; H, 6.54. Found: C, 73.81; H, 6.81.

**l-Menthyl 3,4,6-Tri-O-benzyl- $\beta$ -D-glucopyranoside (28a)**, Epoxide **8** (43.1 mg, 0.10 mmol) and *l*-menthol (**27**; 23.4 mg, 0.15 mmol) were dissolved in 0.25 mL of THF, and the resulting solution was cooled to

-78 °C. A solution of  $\text{ZnCl}_2$  in ether (1.0 M, 0.20 mL) was then added dropwise. The solution was stirred at -78 °C for 1 h and then allowed to warm to room temperature over a period of 2 h. After being stirred at room temperature for 10 h, the mixture was added to 25 mL of saturated  $\text{NaHCO}_3$  and extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel (eluting with hexanes/EtOAc, 85:15) gave 25.8 mg (43%) of compound **28a**:  $[\alpha]_D^{25} -41.7^\circ$  (*c* 2.57,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 2995, 2935, 2900, 2845, 1493, 1452, 1350, 1110, 1060  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43–7.20 (m, 15 H), 4.96 (d, 1 H, *J* = 11.40 Hz), 4.89–4.82 (m, 2 H), 4.64–4.53 (m, 3 H), 4.34 (d, 1 H, *J* = 7.75 Hz), 3.75–3.69 (m, 2 H), 3.66–3.58 (m, 2 H), 3.56–3.44 (m, 3 H), 2.31 (d sept, 1 H, *J* = 6.97, 2.14 Hz), 2.07 (br d, 1 H, *J* = 12.28 Hz), 1.71–1.64 (m, 2 H), 1.44–1.33 (m, 1 H), 1.31–1.22 (m, 1 H), 1.08–0.85 (m, 10 H), 0.82 (d, 3 H, *J* = 6.88 Hz); FAB MS *m/z* 588 (*M*<sup>+</sup>), 587, 547, 443, 433, 415, 369, 346, 341, 325, 313, 271, 253, 235, 225. Anal. Calcd for  $\text{C}_{37}\text{H}_{48}\text{O}_6$ : C, 75.48; H, 8.22. Found: C, 74.94; H, 8.19.

**l-Menthyl 2-O-Acetyl-3,4,6-tri-O-benzyl- $\beta$ -D-glucopyranoside (28b)**, To a solution of **28a** (16.9 mg, 0.0287 mmol) in 1.0 mL of pyridine at 0 °C was added 0.5 mL of acetic anhydride. The mixture was stirred at 0 °C for 2 h, after which it was slowly added to 25 mL of saturated  $\text{NaHCO}_3$  and extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel (eluting with hexanes/EtOAc, 9:1) gave 15.9 mg (88%) of **28b**:  $[\alpha]_D^{25} -22.64^\circ$  (*c* 0.795,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3020, 3005, 2955, 2920, 2865, 1740, 1452, 1352, 1230, 1060  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30–7.21 (m, 15 H), 4.94 (t, 1 H, *J* = 8.57 Hz), 4.83–4.78 (m, 2 H), 4.68 (d, 1 H, *J* = 11.41 Hz), 4.65–4.60 (m, 2 H), 4.55 (d, 1 H, *J* = 12.12 Hz), 4.41 (d, 1 H, *J* = 8.02 Hz), 3.76–3.64 (m, 4 H), 3.46 (m, 1 H), 3.39 (dt, 1 H, *J* = 10.61, 4.23 Hz), 2.36–2.27 (d sept, 1 H, *J* = 6.96, 2.44 Hz), 1.96 (s, 3 H), 2.68–2.59 (m, 2 H), 2.40–2.28 (m, 2 H), 2.25–2.18 (m, 1 H), 0.91 (d, 3 H, *J* = 6.54 Hz), 0.88 (d, 3 H, *J* = 7.09 Hz), 0.79 (d, 3 H, *J* = 6.85 Hz); FAB MS *m/z* 653 (*M* + *Na*<sup>+</sup>).

**Cholesteryl 3,4,6-Tri-O-benzyl- $\beta$ -D-glucopyranoside (30a)**, Cholesterol (**29**; 60.8 mg, 0.157 mmol) and epoxide **8** (45.4 mg, 0.105 mmol) were dissolved in 0.3 mL of THF, and the resulting solution was cooled to -78 °C. A solution of  $\text{ZnCl}_2$  in ether (1.0 M, 0.3 mL) was added dropwise, and the mixture was stirred at -78 °C for 1 h. The mixture was allowed to warm to room temperature over a period of 2 h and then stirred for a further 6 h. The mixture was added to 25 mL of saturated  $\text{NaHCO}_3$ , which was then extracted with 3  $\times$  10 mL of EtOAc. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel (eluting with hexanes/EtOAc, 8:2) gave 44.3 mg of compound **30a** (52%, 83% based on 35.7 mg of recovered **29**):  $[\alpha]_D^{25} -15.2^\circ$  (*c* 1.55,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3570, 3010, 3000, 2930, 2860, 1710, 1470, 1455, 1365, 1273, 1115, 1068  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.14 (m, 15 H), 5.40–5.35 (m, 1 H), 4.95 (d, 1 H, *J* = 11.31 Hz), 4.87–4.82 (m, 2 H), 4.64–4.54 (m, 3 H), 4.36 (d, 1 H, *J* = 7.64 Hz), 3.75 (dd, 1 H, *J* = 10.78, 1.83 Hz), 3.67 (dd, 1 H, *J* = 10.82, 5.04 Hz), 3.64–3.47 (m, 5 H), 2.36 (dd, 1 H, *J* = 4.70, 2.14 Hz), 2.31–2.25 (m, 2 H), 2.06–1.96 (m, 3 H), 1.90–1.81 (m, 2 H), 1.71–1.22 (m, 14 H), 1.21–1.15 (m, 7 H), 1.02 (s, 3 H), 0.93 (d, 3 H, *J* = 6.52 Hz), 0.90–0.87 (m, 6 H), 0.69 (s, 3 H); FAB MS *m/z* 818 (*M*<sup>+</sup>). Anal. Calcd for  $\text{C}_{54}\text{H}_{74}\text{O}_6$ : C, 79.18; H, 9.10. Found: C, 78.94; H, 9.22.

**Cholesteryl 2-O-Acetyl-3,4,6-tri-O-benzyl- $\beta$ -D-glucopyranoside (30b)**, To a solution of compound **30a** (19.3 mg, 0.0236 mmol) in 1.0 mL of pyridine at 0 °C was added 0.5 mL of acetic anhydride. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The reaction mixture was slowly added to 15 mL of saturated  $\text{NaHCO}_3$ , which was then extracted with 3  $\times$  5 mL of EtOAc. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography on silica gel, eluting with hexanes/EtOAc (9:1), gave 14.2 mg (70%) of **30b**:  $[\alpha]_D^{25} +2.70^\circ$  (*c* 0.705,  $\text{CHCl}_3$ ); IR ( $\text{CHCl}_3$ ) 3020, 2950, 1740, 1450, 1380, 1230, 1060  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (490 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.17 (m, 15 H), 5.34 (m, 1 H), 4.97 (t, 1 H, *J* = 8.20 Hz), 4.84–4.78 (m, 2 H), 4.67 (d, 1 H, *J* = 11.41 Hz), 4.62 (d, 1 H, *J* = 12.20 Hz), 4.60–4.56 (m, 2 H), 4.44 (d, 1 H, *J* = 7.97 Hz), 3.75 (dd, 1 H, *J* = 10.88, 1.85 Hz), 3.71–3.63 (m, 3 H), 3.53–3.45 (m, 2 H), 2.28–2.17 (m, 2 H), 2.08–1.92 (m, 6 H), 1.89–1.81 (m, 2 H), 1.68–1.23 (m, 14 H), 1.20–0.99 (m, 12 H), 0.97–0.83 (m, 12 H), 0.69 (s, 3 H); FAB MS *m/z* 883 (*M* + *Na*<sup>+</sup>). Anal. Calcd for  $\text{C}_{56}\text{H}_{76}\text{O}_7$ : C, 78.10; H, 8.89. Found: C, 77.84; H, 9.07.

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(16) Compound **25** exists as a 9:1 mixture of  $\alpha$ - and  $\beta$ -epoxides and was used without purification.

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Registry No. 3, 74087-85-7; 5, 55628-54-1; 6, 79999-47-6;  $\alpha$ -8, 74372-90-0; 9, 121654-00-0; 10, 121702-69-0; 11, 121654-01-1; 12, 121702-70-3; 13, 121654-02-2; 17, 82231-32-1; 18, 121654-03-3; 19,

121654-04-4; 20, 121654-05-5; 21, 4064-06-6; 22a, 40246-33-1; 22b, 51532-76-4; 23, 58871-10-6; 24a, 121654-06-6; 24b, 121654-07-7; 24c, 121654-08-8; 25, 121654-09-9; 26a, 121654-10-2; 26b, 121654-11-3; 27, 2216-51-5; 28a, 121654-12-4; 28b, 121654-13-5; 29, 57-88-5; 30a, 121654-14-6; 30b, 121654-15-7.

## Synthesis of the ABC Ring System of Brevetoxin B

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**Abstract:** A synthesis of the ABC ring framework of brevetoxin B is described. The optically active intermediate **2** representing the ABC ring system and equipped with appropriate functionality for further elaboration is constructed from glucal triacetate. The reported stereocontrolled construction proceeds via key intermediates **38** and **45**, which serve as efficient cyclization precursors sequentially leading from a monocyclic to a bicyclic and finally to the desired tricyclic system. The synthesis demonstrates the applicability of the recently developed 6-endo-hydroxy epoxide activation method for the construction of tetrahydropyran systems. The stereochemistry of the final product was confirmed by an X-ray crystallographic analysis of the crystalline derivative **50**.

Among the toxins associated with the phenomenon of the "red tide" catastrophes,<sup>2</sup> brevetoxin B (**1**,<sup>3</sup> Scheme I) holds a prominent position as the first member of this new class of marine natural products to be structurally elucidated and as one of the most potent neurotoxins ( $IC_{50} = 16 \mu\text{g}/\text{mL}$ ) of its class. This novel compound produced by *Ptychodiscus brevis* Davis (*Gymnodinium breve* Davis) was structurally defined by the groups of Nakanishi and Clardy using spectroscopic and X-ray crystallographic techniques.<sup>3</sup> Since then, a number of other brevetoxin structures appeared,<sup>4</sup>

Brevetoxin B (**1**) has a novel polycyclic structure, never encountered in nature before. Its unusual molecular framework contains 11 rings fused together by trans fusions and 23 stereogenic centers. Each ring contains an oxygen in a pattern that points to an intriguing, as yet unknown, biogenesis.<sup>5</sup> The polycyclic skeleton is rigid except at the region of the oxepane-oxepane junction. The oxocene ring introduces an approximately 30° turn away from the main axis of the remaining backbone. The 11 oxygen-containing rings are in a ladderlike shape, 30 Å long, 6 Å wide, and 6 Å high.

This fascinating molecule exerts its biological effects by activating sodium channels and causing repetitive firings in neurons.<sup>6</sup> It binds to a receptor different from that of tetrodotoxin and

saxitoxin, two other marine toxins.<sup>6</sup> The precise nature of its binding site, however, is presently unknown.

Brevetoxin B (**1**) presents an attractive synthetic target<sup>7</sup> for a number of reasons. This novel and complex structure would almost certainly require new synthetic technology and a carefully designed strategy before yielding to total synthesis. In addition, synthetic fragments and analogues may prove useful in elucidating the puzzling biosynthetic pathways leading to this class of compounds; they may also shine light on their mode of action. Finally, the scarcity of these compounds coupled with the environmental hazards they cause provides further justification for a research program directed toward their synthesis. A number of years ago we decided to embark on such a program, and in this series of papers, we detail stereoselective constructions of the tetrahydropyran systems of brevetoxin B (**1**), beginning with the ABC framework.

### Retrosynthetic Analysis

A potentially useful retrosynthetic analysis of brevetoxin B (**1**) is shown in Scheme I. Disconnection of the indicated strategic bonds and a number of standard functional group interchanges disassemble the medium-size rings and lead to the three fragments **2**, **3**, and **4**. These disconnections allow for a highly convergent synthesis involving intermediates containing only tetrahydropyran rings and thus considerably simplify the synthetic problem at hand.

The constructions of fragments ABC (**2**, this article), FG (**3**),<sup>8</sup> and IJK (**4**)<sup>9</sup> were based on the synthetic technology described in previous papers.<sup>7a,10</sup> Scheme II outlines the retrosynthetic analysis of the ABC ring system of brevetoxin B (**1**) as the hydroxycarboxylic acid protected as a *p*-methoxybenzyl ether (**2**). Thus, rupture of the indicated bonds in structure **2** (Scheme II) and simple functional group manipulations lead to hydroxy epoxide **5**, which can be retrosynthetically converted to the  $\alpha,\beta$ -unsaturated

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