First Synthesis of a Digitalis Saponin. Demonstration of the Scope and Limitations of a Convergent Scheme for Branched Oligosaccharide Synthesis by the Logic of Glycal Assembly

John T. Randolph[†,‡] and Samuel J. Danishefsky*[,†,‡,§,||]

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511, Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, Box 106, New York, New York 10021, and Department of Chemistry, Columbia University, New York, New York 10027

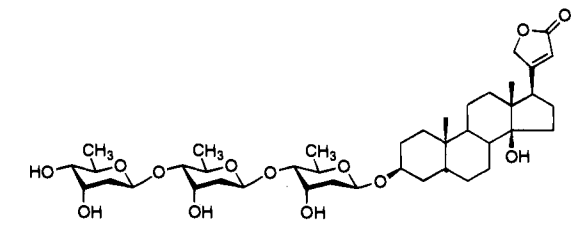
Received December 16, 1994[⊗]

Abstract: The synthesis of complex glycosides, with branching at C_2, is demonstrated. The key element involves the use of a 1,2-oxirane donor. Upon glycosylation, a C_2 hydroxyl is exposed to serve as the acceptor in the next glycosylation. Branching at C_2 with a β-linked glycoside at C_1 was not achievable with epoxy **23** donor, but was accomplished with fluoro donor **25**, in turn derived from **23**. (See **19** + **18** → **20**; **20** + **25** → **26**. Compound **26** was deprotected to complete the first total synthesis of a natural saponin, desgalactotigonin (**3**)). A limitation in stereospecifity in the use of donor **23** and monoprotected galactal acceptor **28** was also encountered.

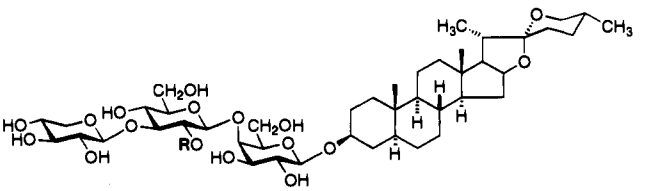
Background and Strategy

Steroidal glycosides constitute a structurally and biologically diverse class of molecules which has been isolated from a wide variety of both plant and animal species. Members of this class of biomolecules have received considerable recent attention due to their exhibited physiological and pharmacological activities. These include the marine saponins, which are responsible for the toxicity of sea cucumbers and starfishes.[1] Another important class of steroid glycosides is comprised of the cardenolides. These compounds are isolated from the purple foxglove (*Digitalis purpurea* L.) and have been used to treat cardiac disorders for over two centuries.[2] Structural characteristics of these so-called cardiac glycosides (cf. digitoxin, **1**) include the C_{17}–β butenolide substituent and the C_{14}–β tertiary hydroxyl in the aglycon, as well as the β–1→4 linked digitoxose (2,6-dideoxy-D-erythropyranose) units attached at C_3 of the steroid. The cardiac glycosides have been the object of extensive synthetic studies.[3] Such studies were no doubt influenced by the desire to improve the therapeutic index of these dangerously toxic pharmaceutical agents.

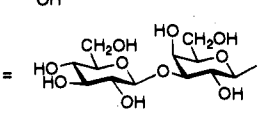
Another important group of steroidal glycosides isolated from *D. purpurea* L. are the saponins, which include tigonin, **2**, and desgalactotigonin, **3**. These structures are characterized by the presence of a spiroketal linkage at C_{21} in the aglycon and a branched oligosaccharide pattern which is more complex than that found in the cardenolides. Numerous other digitalis saponins, bearing the same structural similarities described for tigonins **2** and **3**, have also been identified.[4] Although these



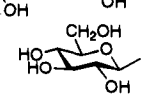
1: Digitoxin



2: Tigonin; R =



3: Desgalactotigonin; R =



compounds lack demonstrated cardiotonic activity, some members of this class have therapeutic potential as antiviral[5] and antitumor[6] agents. Furthermore, digitalis saponins have found

[†] Yale University.

[‡] Sloan-Kettering Institute for Cancer Research.

[§] Columbia University.

[||] Current address at Sloan-Kettering Institute for Cancer Research and at Columbia University.

[⊗] Abstract published in *Advance ACS Abstracts*, April 1, 1995.

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(3) For recent reviews, see: (a) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799. (b) Theim, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 315. See also: (c) Kihara, M.; Yoshioka, K.; Deffo, T.; Fullerton, D. S. *Tetrahedron* **1984**, *40*, 1121. (d) Weisner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300. (e) Hashimoto, T.; Rathore, H.; Satoh, D.; Hong, G.; Griffin, J. F.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 997. (f) Templeton, J. F.; Kumar, V. P. S.; Cote, D.; Elliott, D.; Kim, R. S.; LaBella, F. S. *J. Med. Chem.* **1987**, *30*, 1502. (g) Templeton, J. F.; Setiloane, P.; Kumar, V. P. S.; Yan, Y.; Zeglam, T. H.; LaBella, F. S. *J. Med. Chem.* **1991**, *34*, 2778.

(4) (a) Tschesche, R.; Wulff, G. *Tetrahedron* **1963**, *19*, 621. (b) Kawasaki, T.; Nishioka, I. *Chem. Pharm. Bull.* **1964**, *12*, 1311. (c) Yang, Y. M.; Lloyd, H. A.; Pannell, L. K.; Fales, H. M.; Macfarlane, R. D.; McNeal, C. J.; Ito, Y. *Biomed. Mass Spectrom.* **1986**, *13*, 439.

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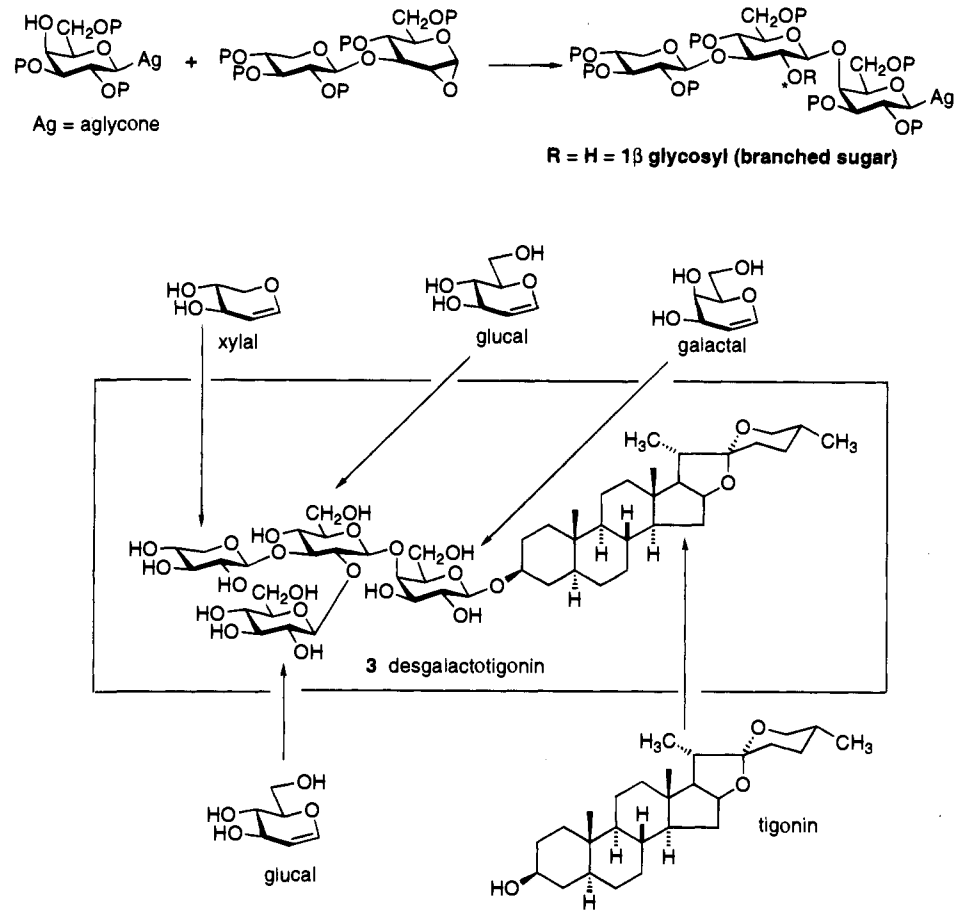
Scheme 1. A Strategy for the Assembly of Digitalis Saponins



use as biological detergents for the solubilization and isolation of membrane receptors.[7]

Synthetic efforts directed toward some of the more interesting saponin structures reflect the ever-expanding knowledge into their biological significance.[8] The extreme difficulties associated with the purification of closely related saponins provides synthesis with a realistic opportunity to contribute to the availability of homogeneous saponins. Our interest in this area has focused on the digitalis saponins. Although several of the sapogenins (aglycons) have been prepared in the laboratory by partial synthesis,[9] the carbohydrate sectors of these glycoconjugates have received very little attention.[10] We focused on this region of the saponins. Our goal was to develop general synthetic methodology which might provide simplified access to these carbohydrate domains.[11] We considered the possibility that the carbohydrate region could be assembled in toto and fashioned to serve as a glycosyl donor for delivery to an aglycon acceptor. Alternatively, a suitable carbohydrate building block might be attached to the aglycon and the remaining carbohydrate building blocks attached to such a framework.

While the goal structures are interesting from a biological standpoint, we came to the problem with an additional agenda, i.e. that of probing the limits of the concept of "glycal assembly". We have been finding that glycals are versatile units for synthesizing oligosaccharides and other glycoconjugates.[12] The saponin problem was seen to be an opportunity for important expansion of the glycal method to the glycosylation of hindered acceptor centers and to the synthesis of branched sugars.

Our strategy for assembling digitalis saponins contemplated taking full advantage of the synthetic potential of 1,2-anhydro sugar donors. In the key step (Scheme 1), a protected tigogenyl galactopyranoside is glycosylated at the axial $C_{4'}$ hydroxyl center using a 1,2-anhydro sugar disaccharide, obtained by epoxidation of the corresponding glycal. The trisaccharide product obtained possesses a uniquely free hydroxyl group, resulting from epoxide opening, at the 2″ position. Hopefully, this position might be subsequently glycosylated with a suitable donor (possibly another 1,2-anhydro sugar) to provide the desired branched oligosaccharide pattern of **2** and **3**. *The attractiveness of this concept was that the very glycosylation by the glucal derived epoxide sets the stage for identifying the acceptor center for*

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(6) (a) Bersuker, I. B.; Dimoglo, A. S.; Choban, I. N.; Lazur'evskii, G. V.; Kintya, P. K. *Khim.-Farm. Zh.* **1983**, *17*, 1467. (b) Murayama, M. JP 04 230 696, 1992. *Chem. Abstr.* **1993**, *118*, 124958.

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(8) See for example: (a) Yamada, H.; Nishizawa, M. *Synlett* **1993**, 54. (b) Bing, H.-X.; Jiand, Z.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1993**, 853. (c) Zehavi, U.; Ziv-Fecht, O.; Levy, M.; Naim, M.; Evron, R.; Polacheck, I. *Carbohydr. Res.* **1993**, *244*, 161. (d) Bing, H. X.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 817. (e) Jiang, Z.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 975.

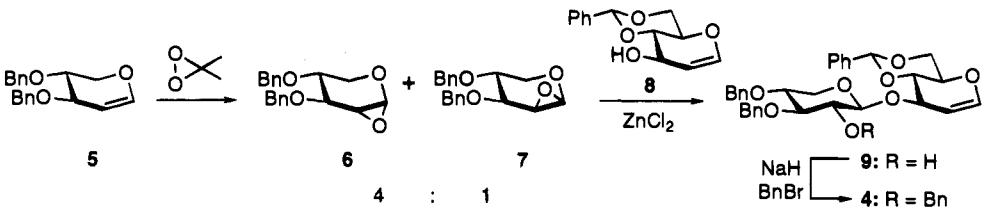
(9) See for example: Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1959**, *81*, 3161. (b) Mazur, Y.; Danieli, N.; Sondheimer, F. *J. Am. Chem. Soc.* **1960**, *82*, 5889.

(10) For an alternative approach to the synthesis of the tetrasaccharide lycotetraose, a common pattern of the digitalis saponins, see: (a) Takeo, K.; Nakaji, T.; Shinmitsu, K. *Carbohydr. Res.* **1984**, *133*, 275.

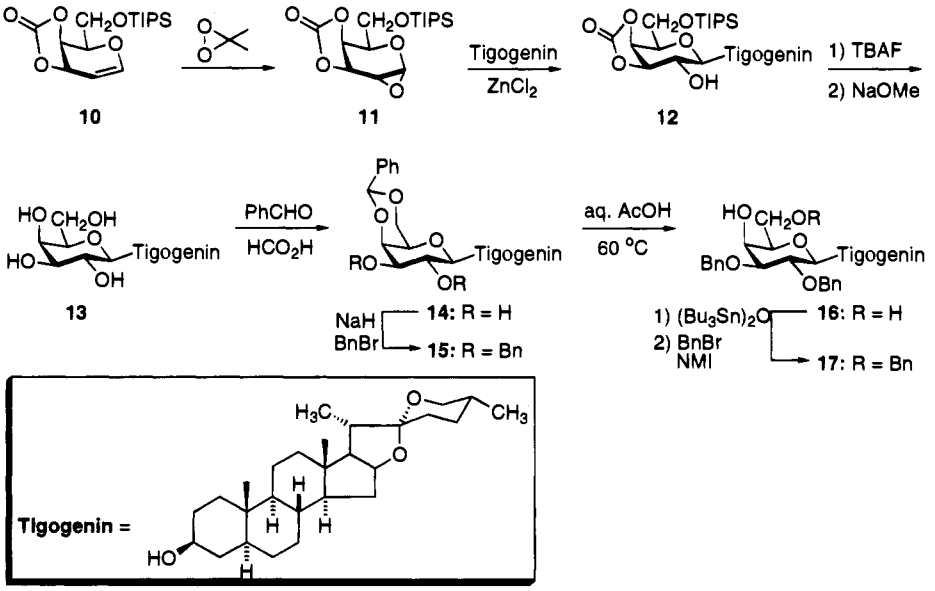
(11) For a recent review on glycosidation methods and applications to the synthesis of natural products, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(12) For a recent review on the use of glycals for oligosaccharide synthesis, see: Bilodeau, M. T.; Danishefsky, S. J. In *Coupling of Glycals: A New Strategy for the Rapid Assembly of Oligosaccharides*, in press.

Scheme 2



Scheme 3



branching. The described strategy has been successfully put into practice in a synthesis of the naturally occurring saponin desgalactotigonin, **3**.[13] As a result of this study, the potentialities and apparent limitations of the glycal come in to sharper focus.

Results and Discussion

3,4-Di-*O*-benzyl-D-xylal, **5**, was prepared by known methods.[14] Epoxidation of compound **5** using 3,3-dimethyldioxirane[15] gave a 4:1 mixture of the desired α to β epoxides **6** and **7**, respectively, as determined by ^{1}H NMR analysis (Scheme 2). The stereochemical outcome of this conversion is noteworthy. Thus, the absence of a substituent at C_5 of the pyranose leads to a considerable erosion in α stereoselectivity in the oxygen transfer reaction. It will be recalled that 3,4,6-tri-*O*-benzyl-D-glucal gives an α:β ratio of epoxides in excess of 20:1.[16]

The mixture of xylal derived epoxides reacted with D-glucal derivative **8**[17] in the presence of zinc chloride to provide, in 65% yield, a mixture of **9** and the α-lyxo disaccharide resulting from glycosylation via β-epoxide **7**. This mixture was benzylated to provide **4**, which was obtained in pure form using a combination of silica gel chromatography and subsequent crystallization.

Since we were concerned that glycosylation of tigogenin with a donor derived from the entire tetracyclic domain might be problematic, we elected to pursue a segmental approach. The sterol was to be galactosylated with a monosaccharide. Accordingly, D-galactal derivative **10**[18] was subjected to epoxidation with 3,3-dimethyldioxirane to give **11.** The latter served to galactosylate tigogenin giving a 89% yield of **12**. The high selectivities, both in epoxidation and in galactosylation are attributable to the conformational rigidity imposed by the cyclic carbonate. Simple deprotection of compound **12** using tetra-*n*-butylammonium fluoride (TBAF) followed by addition of sodium methoxide gave D-galactoside **13** in 98% yield.

An early strategy for exposing the $C_{4'}$ position of **13** to function as the acceptor center involved attempts to selectively benzylate the $C_{2'}$ and $C_{3'}$ equatorial hydroxyl groups and the primary $C_{6'}$ hydroxyl through mediation by stannyl ethers. In the event, reaction of **13** with excess bis(tributyltin) oxide in refluxing toluene with azeotropic water removal (Dean–Stark trap) provided the presumed tin ether derivative which was treated with benzyl bromide in the presence of either tetra-*n*-butylammonium bromide or 1-methylimidazole (NMI).[20] However, the major product obtained under these methods was the 3,6-dibenzyl derivative. Attempts to effect tin ether mediated benzylation at $C_{2'}$ using refluxing xylene led to a mixture of the desired 2,3,6-tribenzyl and 3,6-dibenzyl galactosides. However, the yield was quite low due to extensive decomposition as well as the formation of the perbenzylated galactopyranoside.

A rather more fruitful route started with benzylidenation of the $C_{4'}$ and $C_{6'}$ hydroxyls of **13**, thereby providing **14** in 88% yield (Scheme 3). In this derivative, we could focus on the simpler problem of bis benzylation of the only free hydroxyls,

(13) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 8473.
(14) Weygand, F. *Methods Carbohydr. Chem.* **1962**, *1*, 182.
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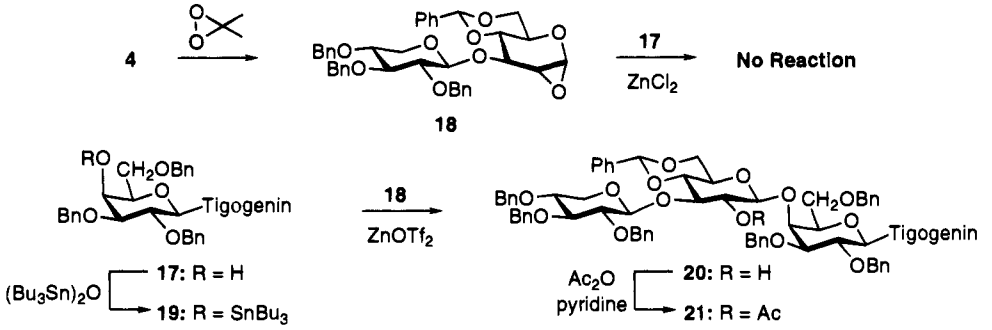
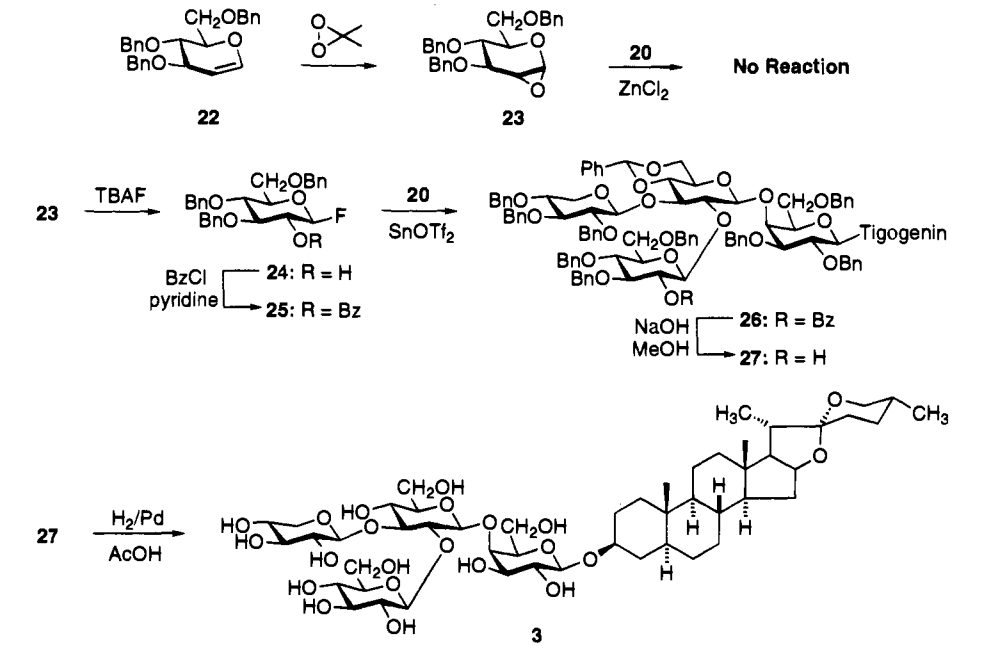
(20) Fernandez-Mayoralas, A.; Martin-Lomas, M. *Carbohydr. Res.* **1986**, *154*, 93.

Scheme 4



Scheme 5



i.e. those at $C_{2'}$ and $C_{3'}$. This was, in fact accomplished as shown in 77% yield.

Attempts to reductively open the benzylidene acetal to give the 6-benzyl derivative using the method of Garegg et al.,[21] led to concomitant reductive cleavage of the spiroketal linkage in the aglycon. Therefore, the benzylidene group was removed by acidic hydrolysis to provide **16** (92% yield), which was readily regioselectively monobenzylated at $C_{6'}$ via stannylation to give **17** (91% yield).

We now faced the critical stage wherein bicyclic glycal **4** was to be attached to the steroidal galactoside **17** at its $C_{4'}$ axial hydroxyl group. Toward this goal, epoxidation of glycal **4** was accomplished with 3,3-dimethyldioxirane to give glycosyl donor **18** (Scheme 4). Attempts to glycosylate **17** with **18** in the presence of zinc chloride failed to provide the desired trisaccharide product. However, stannylative coupling proved to be feasible. Thus, treatment of **17** with bis(tributyltin) oxide followed by reaction of the presumed **19** with **18** under mediation by zinc triflate afforded **20** in a 46% yield from **4** (94% yield based upon recovered **17**).[22] The stereochemical outcome of this glycosidation was confirmed upon acetylation to give **21**. ^{1}H NMR analysis of **21** showed a signal for the $C_{2''}$ hydrogen at δ 5.14 (dd, 1 H, $J_{1,2} \approx J_{2,3} = 8.4$ Hz), indicating that the desired β-linkage was obtained. *This reaction was a significant advance for the glycal method of assembly in that it demonstrated that under suitable conditions glycal epoxides can function as effective donors even with hindered (axial) acceptors.*

We now sought to effect the final glycosylation with the uniquely identified $C_{2''}$-hydroxyl on the benzylidene glucose moiety. Again, we hoped to use glycal epoxide methodology. The stage for this probe was set by treatment of glucal **22**, with 3,3-dimethyldioxirane. This reaction indeed provided the 1,2-anhydro derivative **23**. However, all attempts to glycosylate **20** using **23** as the donor in the presence of zinc chloride or via stannylation chemistry failed to provide the desired tetrasaccharide product. A variety of attempts to bring about such coupling led to destruction of donor and recovery of acceptor. Reluctantly, we concluded, that under the catalyst–promoter conditions thus far practiced, a 1,2-anhydroglucose derivative was not a sufficiently reactive donor to introduce the required branch in the hindered benzylidene glucose sector.

We then investigated whether an anomeric fluoro donor would succeed where the oxirane had apparently failed. Accordingly, compound **23** was subjected to the action of TBAF to afford **24**[23] (Scheme 5). Benzoylation of **24** provided **25**. Our choice of this protecting group for C_2 was made in order to foster β selectivity through participation during subsequent glycosidation. Happily, **20** reacted with **25** in the presence of stannous triflate to give tetrasaccharide **26** in 54% yield.[24]

(21) (a) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2371.

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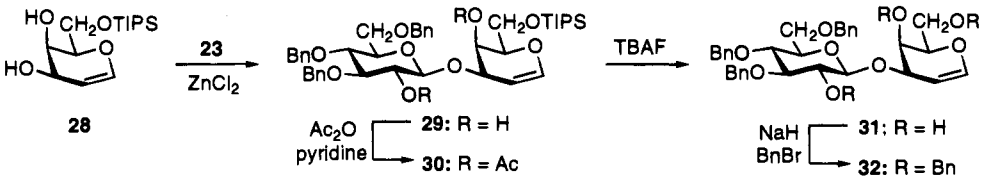
(23) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *206*, 361.

Scheme 6



The deprotection phase proved to be quite straightforward. Debenzoylation of **26** gave **27**, which was subjected to catalytic hydrogenolysis using palladium black to give desgalactotigonin, **3** (94% yield from **26**).[25] *Thus, although oxirane 23 did not serve as a competent donor, the anomeric fluoride armed with a directing benzoate at C_2 (see 25), readily derived from 23, functioned to complete the required array.*

Several attempts to obtain an authentic sample of pure desgalactotigonin from various authors brought forth either highly impure material or no material at all. Thus, our structure assignment must rest on the detailed characterization of our purely synthetic material. NMR analysis at each coupling of sugars or of sugar with aglycon established that the glycosidations had occurred as expected. Detailed NMR analysis of **3** located all of the anomeric protons, and the overall molecular formula is supported by mass spectroscopy. In addition, the optical rotation, melting point, and ^{13}C NMR spectrum of our synthetic material were in closer agreement with those reported.[25] The first total synthesis of a naturally occurring saponin had been achieved.

We have also prepared a disaccharide glycal which is, in principle, suitable for use in building more complex saponins (*cf.* **2**). Regioselective glycosylation at C_3 of **28** using **23** gave disaccharide **29** in 46% yield (Scheme 6).[26] The stereochemical assignment of **29** was confirmed by acetylation to give **30**. ^1H NMR analysis of **30** showed a signal at δ 5.43 (d, 1 H, $J = 4.6$ Hz, H_4) and at δ 4.98 (dd, 1 H, $J_{1,2} \approx J_{2,3} = 8.5$ Hz, $H_{2'}$). Desilylation of **29** using TBAF gave **31**, which was benzylated to give **32** (62% yield from **29**). Studies to evaluate the applicability of donors derived from **32** for the synthesis of complex saponins are planned.

Conclusion

In summary, the logic of glycal assembly has been shown to be applicable to the synthesis of branched oligosaccharides and glycoconjugates. The application described here to the synthesis of the digitalis saponin desgalactotigonin, **3**, attests to the conciseness and simplification of blocking group manipulations which are available through the glycal assembly method. We were in a position to apply the logic implemented above to the synthesis of more extensively branched systems such as are encountered in the human blood group determinants.

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR. ^1H NMR spectra were obtained on a General Electric QE Plus NMR (300 MHz) and are reported in parts per million (δ) relative to $SiMe_4$ (0.00 ppm) or to pyridine-d_5 (7.20 ppm) as an internal reference, with coupling constants (J) reported in hertz. ^{13}C NMR spectra were obtained at 75 MHz and are reported in δ relative to $CDCl_3$ (77.00 ppm) or to pyridine-d_5 (123.50 ppm) as an internal reference, with coupling constants (J) reported in hertz. High-resolution mass spectra were recorded on a Kratos MS-80RFA mass spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter using a 1 dm cell at the reported temperatures and concentrations.

Chemicals used were reagent grade and used as supplied except where noted. Pyridine, benzene, and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under N_2. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under N_2. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate–ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on E. Merck silica gel 60 (40–63 μm).

Synthesis of 2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl-(1→3)-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol (4). D-Xylal derivative **5**[14] (2.00 g, 6.75 mmol), which had been azeotropically dried with benzene, was dissolved in 60 mL of anhydrous CH_2Cl_2 under N_2 and cooled to −10 °C. A solution of 3,3-dimethyldioxirane[15] (90 mL, ~8 mmol) was added, and the mixture was stirred at −10 °C for 30 min, at which time TLC indicated no trace of **5**. The solvents were evaporated to give a mixture of **6** and **7**, which was dried in vacuo. D-Glucal derivative **8**[17] (2.45 g, 10.5 mmol), which had been azeotropically dried with benzene, was dissolved in 40 mL of anhydrous THF and added via cannula to the flask containing **6** and **7** under N_2. The stirred solution was cooled to −78 °C, and 3.5 mL of 1.0 M $ZnCl_2$ in Et_2O was added. The reaction mixture was allowed to warm to rt over ~4 h and stirred for 16 h. The mixture was treated with 150 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to provide a crude product which was chromatographed on silica gel (2:3 EtOAc:hexanes) to give **9**, which was still contaminated with the undesired (α-lyxo) isomer as a minor component. This slightly crude material (2.40 g, 4.39 mmol) was dissolved in 30 mL of anhydrous DMF under N_2, and NaH (0.25 g of a 60% suspension in mineral oil, 6.25 mmol) was added. After the suspension was stirred for 20 min at rt, BnBr (0.80 mL, 6.7 mmol) was added. The reaction mixture was stirred for 10 h, treated with 5 mL of MeOH, stirred for an additional 15 min, and then partitioned between EtOAc (100 mL) and H_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product was chromatographed on silica gel (1:4 EtOAc:hexanes). The product disaccharide (2.32 g, 54% from **5**) was obtained as a 6:1 mixture of **4**:α-lyxo isomer as indicated by ^1H NMR. This mixture crystallized from Et_2O:hexanes to give pure **4**: mp 134–6 °C; TLC: $R_f = 0.33$ (1:3 EtOAc:hexanes); $[\alpha]^{22}_D = -44.8°$ (c 1.0, $CHCl_3$); FTIR (thin film) 3062, 3029, 2913, 2856, 1647, 1452, 1401, 1368, 1237, 1217, 1165, 1107, 1070, 1027, 985, 747, 694; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.26 (m, 20 H, Ar*H*), 6.38 (d, 1 H, $J = 6.0$ Hz, H_1), 5.57 (s, 1 H, PhC*H*O_2), 4.93–4.82 (m, 5 H, 2 × PhCH_2, H_2), 4.77–4.67 (m, 2 H, PhCH_2), 4.58 (d, 1 H, $J = 8.5$ Hz, H_3), 4.53 (d, 1 H, $J = 7.6$ Hz, $H_{1'}$), 4.36 (dd, 1 H, $J = 2.8$ Hz, $J = 8.5$ Hz, H_5), 4.00 (ψt, 1 H, $J = 8.4$ Hz, H_4), 3.95–3.80 (m, 3 H, $H_{5'}$, $H_{6,6a}$), 3.65–3.52 (m, 2 H, $H_{5'}$, $H_{3'}$), 3.39 (ψt, 1 H, $J = 8.1$ Hz, $H_{2'}$), 3.10 (dd, 1 H, $J = 9.9$ Hz, $J = 11.1$ Hz, $H_{4'}$); ^{13}C NMR ($CDCl_3$) δ 144.90, 138.64, 138.12, 137.20, 129.00, 128.42, 128.31, 128.20, 127.90, 127.81, 127.58, 126.11, 102.39, 101.43, 83.92, 81.94, 78.60, 77.84, 75.55, 75.00, 73.85, 73.33, 68.83, 68.28, 63.91; HRMS (FAB) calcd for $C_{39}H_{40}O_8$Na 659.2621, found m/z 659.2675 (M + Na).

(24) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 6221.
(25) Nagumo, S.; Kishi, S.; Inoue, T.; Nagai, M. *Yakugaku Zasshi* **1991**, *111*, 306.
(26) In addition to compound **29**, the α glycoside product was also obtained and was readily removed by silica gel chromatography. The β:α ratio was approximately 3:1.
(27) For a review of methods for activating glycosyl fluorides, see ref 11, pp 1505–1507.
(28) See the following two papers in this issue. We note that the α epoxide from tribenzylglucal is the most problematic of our glycosyl donors. Furthermore 6-monoprotected glycals reacting at C_3 are the most reactive and least selective of our acceptors. Thus, the combination used to reach **29** is, for us, a worst case scenario.

Synthesis of Tigogenyl 3′,4′-Di-*O*-carbonyl-6′-*O*-(trilsopropylsilyl)-β-D-galactopyranoside (12). D-Galactal derivative **10**[18] (1.90 g, 5.78 mmol) was azeotropically dried with benzene and dissolved in 50 mL of anhydrous CH_2Cl_2 under N_2. The solution was cooled to 0 °C, and 100 mL of 3,3-dimethyldioxirane solution (~9 mmol of dioxirane) was added. The reaction mixture was stirred at 0 °C for 40 min, at which time TLC (1:1 EtOAc:hexanes) indicated complete conversion to epoxide **11**. Solvents were removed by evaporation with a dry N_2 stream, and **11** was dried in vacuo. Tigogenin (3.20 g, 7.68 mmol), which had been azeotropically dried with toluene, was dissolved in 50 mL of anhydrous THF and added, via cannula, to the flask containing **11** under N_2. The vigorously stirred solution was cooled to −78 °C, and 6.0 mL of 1.0 M $ZnCl_2$ in Et_2O was added. The mixture was allowed to warm to rt over ~4 h and stirred for an additional 8 h, at which time TLC (1:1 EtOAc:hexanes) indicated no trace of **11**. The reaction mixture was treated with 100 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified by silica gel chromatography (1:9 EtOAc:CH_2Cl_2). Compound **12** was obtained as a colorless solid (3.90 g, 89% based upon **10**): TLC $R_f = 0.62$ (1:1 EtOAc:hexanes); $[\alpha]^{22}_D = -70.0°$ (*c* 1.0, $CHCl_3$); FTIR (thin film) 3444 (OH), 2942, 2866, 1804 (C=O), 1462, 1380, 1241, 1173, 1073, 981, 898, 882, 756, 683; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (d, 1 H, $J = 6.4$ Hz, $H_{4'}$), 4.66 (ψt, 1 H, $J = 6.5$ Hz, $H_{3'}$), 4.51 (d, 1 H, $J = 6.7$ Hz, $H_{1'}$), 4.36 (m, 1 H, $J = 7.0$ Hz, H_{16}), 3.95−3.84 (m, 3 H, $H_{5'}$, $H_{6'a}$), 3.72−3.56 (m, 2 H, $H_{2'}$, H_3), 3.45 (m, 1 H, $J = 3.1$ Hz, $J = 11$ Hz, $H_{27equat}$), 3.33 (ψt, 1 H, $J = 11$ Hz, $H_{27axial}$), 3.28 (d, 1 H, $J = 3.1$ Hz, OH), 1.95 (m, 1 H), 1.89−1.40 (m, 15 H), 1.35−1.18 (m, 5 H), 1.15−1.00 (m, 24 H), 0.93 (d, 3 H, $J = 6.9$ Hz, CH_3), 0.90−0.80 (m, 2 H), 0.80 (s, 3 H, CH_3), 0.76 (d, 3 H, $J = 6.5$ Hz, CH_3), 0.74 (s, 3 H, CH_3), 0.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.15, 109.19, 98.54, 80.74, 77.94, 77.73, 74.43, 72.13, 71.38, 66.72, 62.04, 61.84, 56.56, 54.24, 44.53, 41.49, 40.45, 39.91, 36.81, 35.59, 34.94, 33.98, 32.13, 31.78, 31.63, 31.23, 30.16, 29.01, 28.64, 28.59, 20.91, 17.80, 17.63, 17.04, 16.38, 14.39, 14.04, 12.19, 11.73; HRMS (FAB) calcd for $C_{43}H_{73}O_9Si$ 761.5024, found *m/z* 761.5010 (M + H).

Synthesis of Tigogenyl β-D-Galactopyranoside (13). To a solution of galactoside **12** (3.75 g, 4.93 mmol) in 70 mL of THF was added 10.0 mL of 1.0 M TBAF in THF. The reaction mixture was stirred for 2 h at rt, at which time 10 mL of MeOH and 100 mg of NaOMe was added. After stirring an additional 2 h at rt, the solvents were removed in vacuo and the crude product was purified by silica gel chromatography (1:9 MeOH:CH_2Cl_2). Compound **13** was obtained as a colorless solid (2.80 g, 98%) which crystallized from MeOH: mp = 247−51 °C (dec); TLC $R_f = 0.13$ (1:9 MeOH:CH_2Cl_2); $[\alpha]^{22}_D = -61.8°$ (*c* 1.0, pyridine); FTIR (KBr) 3427 (OH), 2931, 1630, 1453, 1377, 1243, 1154, 1057, 983, 899; ^{1}H NMR (300 MHz, pyridine-d_5): δ 6.92 (br s, 1 H, OH), 6.62 (br s, 1 H, OH), 6.35 (br s, 1 H, OH), 5.08 (br s, 1 H, OH), 4.94 (d, 1 H, $J = 7.5$ Hz, $H_{1'}$), 4.58 (d, 1 H, $J = 2.7$ Hz, $H_{4'}$), 4.56−4.41 (m, 4 H), 4.21 (dd, 1 H, $J = 2.7$ Hz, $J = 9.3$ Hz, $H_{3'}$), 4.13 (ψt, 1 H, $J = 5.3$ Hz, $H_{5'}$), 3.56 (m, 1 H, $J = 4.7$ Hz, H_3), 3.62−3.45 (m, 2 H, $H_{27.27a}$), 2.12−1.90 (m, 3 H), 1.88−1.74 (m, 2 H), 1.73−1.46 (m, 11 H), 1.47−1.32 (m, 5 H), 1.13 (d, 3 H, $J = 6.6$ Hz, CH_3), 1.24−0.96 (m, 3 H), 0.81 (s, 3 H, CH_3), 0.92−0.76 (m, 2 H), 0.68 (d, 3 H, $J = 4.9$ Hz, CH_3), 0.65 (s, 3 H, CH_3), 0.50 (m, 1 H, $J = 3$ Hz, $J = 7.9$ Hz); ^{13}C NMR (pyridine-d_5) δ 109.18, 102.69, 81.09, 76.98, 76.94, 75.40, 72.67, 70.32, 66.83, 62.99, 62.57, 56.44, 54.39, 44.56, 41.96, 40.73, 40.13, 37.17, 35.79, 35.24, 34.83, 32.38, 32.10, 31.78, 30.57, 30.00, 29.23, 28.91, 21.26, 17.31, 16.60, 15.01, 12.28; HRMS (FAB) calcd for $C_{33}H_{55}O_8$ 579.3897, found *m/z* 579.3895 (M + H).

Synthesis of Tigogenyl 4′,6′-*O*-Benzylidene-β-D-galactopyranoside (14). A mixture of compound **13** (2.07 g, 3.58 mmol), benzaldehyde (8 mL), and HCO_2H (8 mL) was stirred at 0 °C under N_2 for 30 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified by silica gel chromatography (1:19 MeOH:CH_2Cl_2). Compound **14** was obtained as a colorless solid (2.10 g, 88%): TLC $R_f = 0.41$ (1:9 MeOH:CH_2Cl_2); $[\alpha]^{22}_D = -88.8°$ (*c* 1.0, $CHCl_3$); FTIR (thin film) 3390 (OH), 2928, 2861, 1450, 1367, 1243, 1171, 1082, 1050, 899, 754; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.47 (m, 2 H, Ar*H*), 7.40−7.34 (m, 3 H, Ar*H*), 5.54 (s 1 H, PhC*H*), 4.44−4.34 (m, 2 H, $H_{1'}$, H_{16}), 4.32 (d, 1 H, $J = 12.5$ Hz, $H_{6'}$), 3.77−3.63 (m, 3 H), 3.51−3.43 (m, 2 H), 3.37 (ψt, 1 H, $J = 10.8$ Hz, $H_{27axial}$), 2.54 (br s, 2 H, 2 × OH), 2.05−1.80 (m, 3 H), 1.80−1.39 (m, 14 H), 1.38−1.19 (m, 5 H), 1.18−1.02 (m, 2 H), 0.96 (d, 3 H, $J = 6.9$ Hz, CH_3), 0.94−0.86 (m, 2 H), 0.83 (s, 3 H, CH_3), 0.79 (d, 3 H, $J = 6.3$ Hz, CH_3), 0.76 (s, 3 H, CH_3), 0.64 (m, 1 H, $J = 3$ H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 137.48, 129.15, 128.17, 126.38, 109.22, 101.37, 100.42, 80.80, 77.92, 75.33, 72.71, 71.72, 69.21, 66.81, 66.58, 62.13, 56.24, 54.31, 44.70, 41.56, 40.53, 40.00, 36.94, 35.74, 35.03, 34.27, 32.24, 31.73, 31.32, 30.26, 29.23, 28.74, 28.68, 20.99, 17.11, 16.46, 14.47, 12.33; HRMS (FAB) calcd for $C_{40}H_{59}O_8$ 667.4210, found *m/z* 667.4213 (M + H).

Synthesis of Tigogenyl 4′,6′-*O*-Benzylidene-2′,3′-di-*O*-benzyl-β-D-galactopyranoside (15). To a solution of **14** (2.00 g, 3.00 mmol) in 30 mL of anhydrous DMF under N_2 was added NaH (0.35 g of a 60% suspension in mineral oil, 8.8 mmol). The suspension was stirred at rt for 30 min before BnBr (1.0 mL, 8.4 mmol) was added. The reaction mixture was stirred at rt 8 h, after which time 5 mL of MeOH was added and stirring was continued for an additional 15 min. The mixture was partitioned between EtOAc (100 mL) and H_2O (2 × 100 mL), and the organic layers were combined and dried ($MgSO_4$) and concentrated to give a crude product which was purified by silica gel chromatography (1:4 EtOAc:hexanes). Compound **15** was obtained as a colorless solid (1.95 g, 77%): TLC $R_f = 0.25$ (1:3 EtOAc:hexanes); $[\alpha]^{22}_D = -33.0°$ (*c* 1.0, $CHCl_3$); FTIR (thin film): 2929, 2862, 1452, 1366, 1173, 1095, 1059, 1018, 903, 738, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.52 (m, 2 H, Ar*H*), 7.43−7.24 (m, 13 H, Ar*H*), 5.48 (s, 1 H, PhC*H*O_2), 4.94 (d, 1 H, $J = 10.8$ Hz, PhC*H*), 4.83−4.70 (m, 3 H, 3 × PhC*H*), 4.50 (d, 1 H, $J = 7.7$ Hz, $H_{1'}$), 4.39 (m, 1 H, $J = 7.4$ Hz, H_{16}), 4.27 (d, 1 H, $J = 11.6$ Hz, $H_{6'}$), 4.08 (d, 1 H, $J = 3.5$ Hz, $H_{4'}$), 3.99 (d, 1 H, $J = 11.3$ Hz, $H_{6'}$), 3.81 (dd, 1 H, $J = 7.9$ Hz, $J = 9.5$ Hz, $H_{2'}$), 3.66 (m, 1 H, H_3), 3.53 (dd, 1 H, $J = 3.6$ Hz, $J = 9.7$ Hz, $H_{3'}$), 3.48 (m, 1 H, $H_{27equat}$), 3.37 (ψt, 1 H, $J = 10.8$ Hz, $H_{27axial}$), 3.28 (s, 1 H, $H_{5'}$), 2.03−1.92 (m, 2 H), 1.86 (m, 1 H, $J = 6.8$ Hz), 1.80−1.40 (m, 14 H), 1.38−1.19 (m, 5 H), 1.19−1.00 (m, 2 H), 0.96 (d, 3 H, $J = 6.9$ Hz, CH_3), 0.98−0.84 (m, 2 H), 0.83 (s, 3 H, CH_3), 0.78 (d, 3 H, $J = 6.3$ Hz, CH_3), 0.76 (s, 3 H, CH_3), 0.63 (m, 1 H, $J = 3.4$ H, $J = 11.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 138.93, 138.48, 137.87, 128.81, 128.47, 128.26, 128.19, 128.06, 127.56, 127.46, 126.48, 109.21, 101.49, 101.23, 80.80, 79.27, 78.61, 78.38, 75.26, 74.06, 71.99, 69.30, 66.79, 66.24, 62.13, 56.25, 54.32, 44.71, 41.55, 40.53, 40.01, 36.96, 35.73, 35.03, 34.52, 32.24, 31.73, 31.32, 30.25, 29.44, 28.73, 28.69, 20.98, 17.11, 16.46, 14.48, 12.32; HRMS (FAB) calcd for $C_{54}H_{71}O_8$ 847.5150, found *m/z* 847.5126 (M + H).

Synthesis of Tigogenyl 2′,3′-Di-*O*-benzyl-β-D-galactopyranoside (16). A mixture of **15** (0.50 g, 0.59 mmol) in 15 mL of 80% aqueous AcOH was vigorously stirred at 60 °C for 48 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give a crude product which was purified by silica gel chromatography (1:1 EtOAc:hexanes). Compound **16** was obtained as a colorless solid (0.41 g, 92%): TLC $R_f = 0.28$ (2:1 EtOAc:hexanes); $[\alpha]^{22}_D = -37.5°$ (*c* 0.4, $CHCl_3$); FTIR (thin film) 3455 (OH), 2929, 1597, 1450, 1368, 1067; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10 H, Ar*H*), 4.92 (d, 1 H, $J = 10.0$ Hz, PhC*H*), 4.76−4.67 (m, 3 H, 3 x PhC*H*), 4.48 (d, 1 H, $J = 7.7$ Hz, $H_{1'}$), 4.38 (m, 1 H, $J = 7.4$ Hz, H_{16}), 3.98−3.92 (m, 2 H), 3.82−3.74 (m, 1 H), 3.64 (m, 1 H, H_3), 3.62 (ψt, 1 H, $J = 7.5$ Hz, $H_{2'}$), 3.51−3.42 (m, 3 H), 3.37 (ψt, 1 H, $J = 10.9$ Hz, $H_{27axial}$), 2.61 (br s, 1 H, OH), 2.18 (br s, 1 H, OH), 2.00−1.89 (m, 2 H), 1.85 (m, 1 H, $J = 6.9$ Hz), 1.78−1.40 (m, 14 H), 1.38−1.14 (m, 5 H), 1.14−0.96 (m, 2 H), 0.95 (d, 3 H, $J = 6.9$ Hz, CH_3), 0.95−0.85 (m, 2 H), 0.82 (s, 3 H, CH_3), 0.78 (d, 3 H, $J = 6.3$ Hz, CH_3), 0.75 (s, 3 H, CH_3), 0.63 (m, 1 H, $J = 4.1$ H, $J = 12.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 138.58, 137.79, 128.46, 128.28, 128.15, 127.91, 127.81, 127.62, 109.22, 101.89, 80.81, 80.48, 78.97, 78.87, 75.21, 73.90, 72.54, 67.45, 66.81, 62.52, 62.15, 59.24, 54.29, 44.65, 41.57, 40.54, 40.00, 36.93, 35.70, 35.05, 34.65, 32.21, 31.74, 31.34, 30.26, 29.64, 28.76, 28.64, 21.00, 17.11, 16.46, 14.48, 12.29; HRMS (FAB) calcd for $C_{47}H_{67}O_8$ 759.4836, found *m/z* 759.4855 (M + H).

Synthesis of Tigogenyl 2′,3′,6′-Tri-*O*-benzyl-β-D-galactopyranoside (17). A solution of **16** (0.34 g, 0.45 mmol) and bis(tributyltin) oxide (0.35 mL, 0.69 mmol) in 8 mL of anhydrous toluene under N_2 was stirred at reflux for 8 h with azeotropic removal of water (Dean−

Stark trap). To the mixture were added BnBr (0.16 mL, 1.35 mmol) and 1-methylimidazole (35 μL, 0.45 mmol), and the mixture was stirred at reflux for an additional 16 h. Solvents were removed in vacuo, and the residue was partitioned between H_2O (25 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified by chromatography on silica gel (1:4 EtOAc:hexanes). Compound **17** was obtained as a colorless solid (0.35 g, 91%) TLC R_f = 0.58 (2:3 EtOAc:hexanes); $[\alpha]^{22}_D = -23.7°$ (*c* 1.0, $CHCl_3$) FTIR (thin film): 3420 (OH), 3065, 3033, 2930, 1454, 1376, 1366, 1174, 1157, 1097, 1076, 1029, 1007, 981, 911, 732, 699, 648; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.25 (m, 15 H, Ar*H*), 4.952 (d, 1 H, *J* = 11.0 Hz, PhC*H*), 4.78−4.72 (m, 3 H, 3 × PhC*H*), 4.60 (s, 2 H, PhCH_2), 4.49 (d, 1 H, *J* = 7.7 Hz, $H_{1'}$), 4.41 (m, 1 H, *J* = 7.5 Hz, H_{16}), 4.02 (d, 1 H, *J* = 2.9 Hz, $H_{4'}$), 3.85−3.46 (m, 8 H), 3.39 (ψt, 1 H, *J* = 10.7 Hz, $H_{27axial}$), 2.42 (br s, 1 H, OH), 2.06−1.95 (m, 2 H), 1.88 (m, 1 H, *J* = 6.8 Hz), 1.71−1.42 (m, 13 H), 1.42−1.20 (m, 6 H), 1.20−0.98 (m, 2 H), 0.98 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.94−0.83 (m, 2 H), 0.85 (s, 3 H, CH_3), 0.81 (d, 3 H, *J* = 6.4 Hz, CH_3), 0.78 (s, 3 H, CH_3), 0.68 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.75, 138.14, 137.99, 128.36, 128.18, 128.10, 127.75, 127.64, 127.50, 109.15, 101.95, 80.79, 79.11, 78.75, 75.12, 73.63, 73.20, 72.39, 69.33, 66.95, 66.80, 62.28, 56.30, 54.40, 44.73, 41.61, 40.56, 40.06, 37.00, 35.71, 35.11, 34.68, 32.25, 31.76, 31.39, 30.28, 29.63, 28.81, 28.69, 21.02, 17.09, 16.44, 14.45, 12.30; HRMS (FAB) calcd for $C_{54}H_{72}O_8$Na 871.5125, found *m/z* 871.5144 (M + Na).

Synthesis of Tigogenyl 4′-*O*-(Tributyltin)-2′,3′,6′-tri-*O*-benzyl-β-D-galactopyranoside (19). Compound **17** (0.33 g, 0.39 mmol) and bis(tributyltin) oxide (0.10 mL, 0.20 mmol) in 5 mL of *o*-xylene under N_2 was stirred at reflux for 36 h with azeotropic removal of water (Dean−Stark trap). The reaction mixture was cooled to 60 °C, and the solvents were removed by evaporation with a dry N_2 stream. Crude **19** was dried in vacuo and used without further purification.

Synthesis of Tigogenyl 2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→4)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (20). To a solution of **4** (0.18 g, 0.28 mmol) in 5 mL of anhydrous CH_2Cl_2 at 0 °C under N_2 was added 5 mL of 3,3-dimethyldioxirane solution (~0.45 mmol). The reaction solution was stirred at 0 °C for 30 min, at which time TLC (1:2 EtOAc:hexanes) indicated complete conversion to give **18**. The solvents were evaporated using a dry N_2 stream, and **18** was dried in vacuo. To the flask containing **18** under N_2 was added $Zn(OTf)_2$ (0.15 g, 0.42 mmol). The flask was cooled to 0 °C and compound **19**, prepared as described above, was added as a solution in 3 mL of anhydrous THF. The mixture was allowed to warm to rt and stirred for 24 h, at which time TLC (1:1 EtOAc:hexanes) indicated no further improvement in reaction progress. The reaction was quenched with 20 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified by chromatography on silica gel (1:3 EtOAc:hexanes). Two major fractions were obtained, the more polar of which was unreacted **17** (0.21 g, 0.25 mmol). Compound **20** was obtained as a colorless solid (0.20 g, 46% from **4**, 94% based upon recovered **17**): TLC R_f = 0.67 (2:3 EtOAc:hexanes); $[\alpha]^{22}_D = -28.1°$ (*c* 1.4, $CHCl_3$); FTIR (thin film) 3365 (OH), 3065, 3030, 2935, 2864, 1453, 1368, 1361, 1174, 1098, 1074, 1028, 982, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.22 (m, 35 H, Ar*H*), 5.51 (s, 1 H, PhC*H*O_2), 5.05 (d, 1 H, *J* = 11.0 Hz, PhC*H*), 4.94 (d, 1 H, *J* = 10.8 Hz, PhC*H*), 4.90−4.76 (m, 4 H), 4.72−4.62 (m, 5 H), 4.61−4.43 (m, 8H), 4.39 (m, 1 H, *J* = 7.5 Hz, H_{16}), 4.18−4.11 (m, 2 H), 4.08 (s, 1 H, OH), 4.03−3.84 (m, 4 H), 3.84−3.27 (m, 13 H), 3.14 (dd, 1 H, *J* = 8.6 Hz, *J* = 11.6 Hz), 2.03−1.80 (m, 3 H), 1.79−1.39 (m, 13 H), 1.38−1.19 (m, 6 H), 1.18−1.00 (m, 2 H), 0.96 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.94−0.79 (m, 2 H), 0.82 (s, 3 H, CH_3), 0.79 (d, 3 H, *J* = 6.3 Hz, CH_3), 0.76 (s, 3 H, CH_3), 0.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.81, 138.66, 138.40, 138.27, 137.27, 137.24, 128.90, 128.47, 128.35, 128.31, 128.22, 127.87, 127.76, 127.69, 127.40, 126.07, 109.22, 105.98, 103.44, 101.76, 101.30, 83.39, 81.80, 80.81, 80.30, 79.87, 79.49, 79.16, 78.70, 77.99, 77.94, 77.20, 75.53, 75.28, 74.28, 73.89, 73.53, 73.31, 72.97, 72.47, 68.58, 68.47, 66.80, 66.64, 63.57, 62.14, 56.25, 54.30, 44.64, 41.56, 40.53, 40.02, 36.92, 35.69, 35.04, 34.56, 32.21, 31.73, 31.33, 30.26, 29.67, 29.53, 28.75, 28.65, 20.99, 17.12, 16.46, 14.48, 12.30; HRMS (FAB) calcd for $C_{93}H_{112}O_{17}$Na 1523.7797, found *m/z* 1523.7869 (M + Na).

Synthesis of 2′-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl Fluoride (25). To a solution of **22** (0.50 g, 1.20 mmol) in 20 mL of anhydrous CH_2Cl_2 under N_2 at 0 °C was added 20 mL of 3,3-dimethyldioxirane solution (~1.8 mmol). After stirring for 30 min at 0 °C, the solvents were evaporated using a dry N_2 stream, and **23** was dried in vacuo. To the flask containing **23** under N_2 was added 20 mL of THF and 5.0 mL of 1.0 M TBAF in THF (dried over 4 Å molecular sieves prior to use). The mixture was stirred at rt for 12 h and then partitioned between H_2O (50 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product was chromatographed on silica gel (1:9 EtOAc:CH_2Cl_2) to provide **24**. The slightly crude material was dissolved in 3 mL of anhydrous pyridine under N_2, and benzoyl chloride (0.25 mL, 2.20 mmol) was added. The mixture was stirred at rt for 6 h, solvents were removed in vacuo, and the residue was partitioned between saturated aqueous NH_4Cl (50 mL) and EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product was purified by silica gel chromatography (1:4 EtOAc:hexanes). Compound **25** was crystallized from Et_2O:hexanes to give colorless needles (0.38 g, 57% from **22**): mp = 90−2 °C; TLC R_f = 0.35 (1:2 EtOAc:hexanes); $[\alpha]^{22}_D = +64.4°$ (*c* 1.1, $CHCl_3$); FTIR (thin film) 3031, 2872, 1782 (C=O), 1597, 1451, 1362, 1263, 1067, 700; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, 2 H, *J* = 7.6 Hz, Ar*H*), 7.51 (t, 1 H, *J* = 7.6 Hz, Ar*H*), 7.43 (t, 2 H, *J* = 7.6 Hz, Ar*H*), 7.37−7.25 (m, 8 H, Ar*H*), 7.20−7.12 (m, 7 H, Ar*H*), 5.43 (dd, 1 H, *J* = 5.8 Hz, *J* = 54.1 Hz, H_1), 5.40 (m, 1 H, *J* = 7.0 Hz, *J* = 15.6 Hz, H_2), 4.79 (d, 1 H, *J* = 10.9 Hz, PhC*H*), 4.73 (s, 2 H, PhCH_2), 4.64 (d, 1 H, *J* = 12.2 Hz, PhC*H*), 4.58 (d, 1 H, *J* = 10.7 Hz, PhC*H*), 4.56 (d, 1 H, *J* = 12.2 Hz, PhC*H*), 3.94 (ψt, 1 H, *J* = 8.7 Hz, H_4), 3.85 (ψt, 1 H, *J* = 7.8 Hz, H_3), 3.80−3.73 (m, 3 H, H_5, $H_{6,6a}$); ^{13}C NMR ($CDCl_3$) δ 164.97, 137.76, 137.60, 137.40, 134.48, 133.39, 130.49, 129.79, 129.18, 128.81, 128.37, 128.29, 127.94, 127.79, 127.68, 106.71 (d, *J* = 217.8 Hz), 81.34 (d, *J* = 6.4 Hz), 76.56, 74.97, 74.81, 74.25, 73.53, 72.93 (d, *J* = 28.3 Hz); HRMS (FAB) calcd for $C_{34}H_{34}O_6F$ 557.2339, found *m/z* 557.2341 (M + H).

Synthesis of Tigogenyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→3)]-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→4)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (26). A mixture of **20** (0.40 g, 0.27 mmol) and **25** (0.30 g, 0.54 mmol), which had been azeotropically dried using benzene, was dissolved in 6 mL of anhydrous Et_2O and added via cannula to a flask containing $Sn(OTf)_2$ (220 mg, 0.53 mmol) and powdered 4 Å molecular sieves (1.0 g) under N_2 at 0 °C. The mixture was allowed to warm to rt and stirred for 48 h before being partitioned between saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (3 × 50 mL). The organic layers were dried ($MgSO_4$) and concentrated, and the crude product was purified by silica gel chromatography (1:2 EtOAc:hexanes). Compound **26** was obtained as a colorless solid (0.29 g, 54% based upon **20**): TLC R_f = 0.37 (1:2 EtOAc:hexanes); $[\alpha]^{22}_D = -16.5°$ (*c* 1.4, $CHCl_3$); FTIR (thin film) 3064, 3031, 2927, 2867, 1732 (C=O), 1453, 1362, 1267, 1096, 1072, 1028, 749, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2 H, *J* = 7.4 Hz, ArH), 7.45−7.00 (m, 53 H, Ar*H*), 5.44 (ψt, 1 H, *J* = 8.7 Hz, H_2 glucose), 5.39 (s, 1 H, PhC*H*O_2), 5.10 (d, 1 H, *J* = 12 Hz, PhC*H*), 5.02−4.92 (m, 3 H), 4.90−4.76 (m, 3 H), 4.70−4.35 (m, 16 H), 4.12−4.01 (m, 2 H), 3.99−3.91 (m, 3 H), 3.85−3.77 (m, 2 H), 3.75−3.32 (m, 14 H), 3.22 (m, 1 H, *J* = 4.8 Hz), 2.76 (dd, 1 H, *J* = 9 Hz, *J* = 12 Hz), 2.04−0.55 (m, 39 H); ^{13}C NMR ($CDCl_3$) δ 164.79, 139.44, 138.87, 138.76, 138.34, 138.28, 138.06, 137.47, 132.81, 130.22, 130.05, 129.85, 128.69, 128.31, 128.22, 128.02, 127.88, 127.72, 127.63, 127.51, 127.38, 127.29, 126.12, 109.19, 102.16, 102.07, 101.10, 101.00, 99.03, 83.17, 83.07, 81.89, 81.66, 76.05, 75.50, 74.93, 74.75, 74.62, 74.53, 74.32, 74.07, 73.54, 73.27, 73.17, 72.76, 72.35, 69.87, 69.70, 68.89, 66.83, 65.48, 62.89, 62.24, 56.30, 54.37, 44.68, 41.62, 40.57, 40.07, 36.98, 35.70, 35.10, 34.76, 32.25, 31.77, 31.40, 30.31, 29.78, 29.69, 28.81, 28.69, 21.03, 17.11, 16.47, 14.48, 12.32; HRMS (FAB) calcd for $^{13}C^{12}C_{126}H_{144}O_{23}$Na 2061.0029, found *m/z* 2061.0075 (M + Na).

Synthesis of Tigogenyl β-D-Glucopyranosyl)-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside (3).

A solution of compound **26** (220 mg, 108 μmol) in 5 mL of 1% NaOH in MeOH was stirred at 40 °C for 36 h, at which time TLC (1:9 EtOAc: toluene) indicated complete conversion to **27** ($R_f = 0.24$). The mixture was partitioned between H_2O (20 mL) and EtOAc (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified on silica gel using 1:9 EtOAc: toluene. Compound **27** (207 mg, 107 μmol) and Pd black (50 mg) were suspended in 10 mL of 1:1 AcOH:MeOH, placed under H_2 (1 atm), and stirred at rt for 48 h. The mixture was filtered through Celite and thoroughly rinsed with pyridine. The rinsings were concentrated to give a crude product which was purified by C-18 reverse-phase silica gel chromatography (3:2 dioxane:water). Compound **3** was obtained as a colorless solid (105 mg, 94% from **26**): TLC mp 277−280 °C (dec); TLC $R_f = 0.45$ (65:35:10 $CHCl_3$:MeOH:H_2O); $[\alpha]^{22}_D = -49.6°$ (*c* 0.9, pyridine); FTIR (KBr) 3380 (OH), 2930, 1635, 1449, 1376, 1156, 1073, 1040, 981, 897; ^{1}H NMR (300 MHz, pyridine-d_5) δ 8.38 (br d, 1 H, OH), 7.46 (br s, 1 H, OH), 7.29 (br s, 1 H, OH), 7.13 (br s, 1 H, OH), 7.06 (br d, 1 H, OH), 7.01 (br d, 1 H, OH), 6.92 (br s, 1 H, OH), 6.80 (br t, 1 H, CH_2OH), 6.38 (br t, 1 H, CH_2OH), 6.07 (br t, 1 H, CH_2OH), 5.58 (d, 1 H, $J = 7.5$ Hz, anomeric H), 5.42 (s, 1 H, OH), 5.22 (d, 1 H, $J = 7.7$ Hz, anomeric H), 5.19 (d, 1 H, $J = 7.9$ Hz, anomeric H), 5.09 (1 H, OH), 4.88 (d, 1 H, $J = 7.6$ Hz, anomeric H), 4.77 (m, 1 H, $J = 9.7$ Hz), 4.58 (d, 1 H, $J = 1.4$ Hz, H_4 galactose), 4.57−4.47 (m, 3 H), 4.46−4.32 (m, 4 H), 4.27−3.77 (m, 15 H), 3.76 (ψt, 1 H, $J = 10.1$ Hz), 3.58 (dd, 1 H, $J = 10.1$ Hz, $H_{27equat}$), 3.49 (ψt, 1 H, $J = 10.3$ Hz, $H_{27axial}$), 2.05−1.87 (m, 3 H), 1.81−0.70 (m, 29 H), 0.67 (d, 3 H, J = 5.0 Hz, CH_3), 0.60 (s, 3 H, CH_3), 0.46 (m, 1 H, $J =$ 1.8 Hz, $J = 10$ Hz); ^{13}C NMR (pyridine-d_5) δ 109.17, 104.64, 104.47, 102.22, 86.64, 81.00, 79.61, 78.34, 78.13, 77.41, 77.26, 75.77, 75.17, 75.10, 74.72, 72.78, 70.72, 70.42, 70.05, 67.00, 66.71, 62.76, 62.59, 62.05, 60.43, 56.25, 54.21, 44.46, 41.81, 40.59, 39.96, 37.00, 35.60, 35.06, 34.60, 32.20, 31.91, 31.61, 30.38, 29.69, 29.05, 28.72, 21.09, 17.14, 16.44, 14.85, 12.12; HRMS (FAB) calcd for $C_{50}H_{82}O_{22}Na$ 1057.5196, found *m/z* 1057.5241 (M + Na).

Synthesis of 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-1,5-anhydro-2-deoxy-6-*O*-(triisopropylsilyl)-D-*lyxo*-hex-1-enitol (29). Compound **22** (1.00 g, 2.40 mmol) was azeotropically dried with benzene and dissolved in 20 mL of anhydrous CH_2Cl_2 under N_2. The solution was cooled to 0 °C and 40 mL of 3,3-dimethyldioxirane solution (~3.6 mmol) was added. The mixture was stirred at 0 °C for 40 min, and the solvents were evaporated using a dry N_2 stream to give **23**, which was dried in vacuo. Compound **23** was placed under N_2 and a solution of **28** (1.10 g, 3.64 mmol) in 15 mL of anhydrous THF was added via cannula. The solution was cooled to −78 °C, and 4.0 mL of a 1.0 M solution of $ZnCl_2$ in Et_2O was added. The resultant mixture was allowed to slowly warm to rt over ~4 h and then stirred for 16 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product which was purified by silica gel chromatography (1:2 EtOAc:hexanes). Compound **29** was obtained as a colorless solid (0.81 g, 46% based upon **22**): TLC $R_f = 0.39$ (2:3 EtOAc:hexanes); $[\alpha]^{22}_D = -3.1°$ (*c* 1.2, $CHCl_3$); FTIR (thin film) 3430 (OH), 3031, 2942, 2865, 1651 (C=O), 1497, 1454, 1360, 1239, 1111, 1063, 883, 792, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.14 (m, 15 H, Ar*H*), 6.41 (d, 1 H, $J = 6.2$ Hz, H_1), 4.93 (d, 1 H, $J = 11.3$ Hz, PhC*H*), 4.86−4.78 (m, 2 H, 2 × PhC*H*), 4.72 (m, 1 H, $J = 6.3$ Hz, H_2), 4.63−4.44 (m, 4 H, 3 × PhC*H*, $H_{1'}$), 4.20 (m, 1 H, H_3), 4.02 (m, 1 H), 3.96−3.88 (m, 2 H), 3.70−3.56 (m, 4 H), 3.48 (m, 1 H), 3.33 (br s, 1 H, OH), 3.01 (br s, 1 H, OH), 1.18−1.02 (m, 21 H, TIPS); ^{13}C NMR ($CDCl_3$) δ 145.23, 138.43, 137.85, 137.71, 128.20, 127.76, 127.55, 101.56, 98.94, 84.18, 76.99, 76.64, 74.98, 74.80, 74.04, 73.26, 73.04, 68.49, 63.67, 62.11, 17.79, 11.69; HRMS (FAB) calcd for $C_{42}H_{58}O_9SiNa$ 757.3748, found *m/z* 757.3760 (M + Na).

Synthesis of 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-1,5-anhydro-2-deoxy-4,6-di-*O*-benzyl-D-*lyxo*-hex-1-enitol (32). To a solution of **29** (0.73 g, 0.99 mmol) in 10 mL of THF was added 1.1 mL of a 1.0 M solution of TBAF in THF. The mixture was stirred at rt for 2 h and partitioned between EtOAc (50 mL) and H_2O (2 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the crude product was chromatographed on silica gel using EtOAc to give **31** ($R_f = 0.23$, EtOAc). Compound **31** (0.56 g, 0.97 mmol) was dissolved in 20 mL of anhydrous DMF under N_2, and NaH (0.15 g of a 60% suspension in mineral oil, 3.75 mmol) was added. The mixture was stirred at rt for 1 h, and BnBr (0.45 mL, 3.80 mmol) was added. The reaction mixture was stirred at rt for 16 h, 5 mL of MeOH was added, and stirring was continued for an additional 1 h. The mixture was partitioned between EtOAc (50 mL) and H_2O (2 × 50 mL), the organic layer was dried ($MgSO_4$) and concentrated, and the crude product was purified by chromatography on silica gel (1:4 EtOAc: hexanes). Compound **32** was obtained as a colorless gum (0.51 g, 62% from **29**): TLC $R_f = 0.65$ (1:2 EtOAc:hexanes); $[\alpha]^{22}_D = -27.7°$ (*c* 1.5, $CHCl_3$); FTIR (thin film) 3024, 2860, 1647, 1496, 1453, 1357, 1234, 1088, 1069, 1028, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.12 (m, 30 H, Ar*H*), 6.40 (dd, 1 H, $J = 1.0$ Hz, $J = 6.0$ Hz, H_1), 5.03 (d, 1 H, $J = 12.1$ Hz, PhC*H*), 5.00−4.91 (m, 2 H, 2 × PhC*H*), 4.87−4.77 (m, 3 H, 2 × PhC*H*, H_2), 4.68 (d, 1 H, $J = 12.0$ Hz, PhC*H*), 4.67 (d, 1 H, $J = 10.8$ Hz, PhC*H*), 4.62−4.47 (m, 5 H, 3 × PhC*H*, H_3, $H_{1'}$), 4.40 (d, 1 H, $J = 11.9$ Hz, PhC*H*), 4.31 (d, 1 H, $J = 11.9$ Hz, PhC*H*), 4.13 (ψt, 1 H, $J = 6.1$ Hz), 4.03 (m, 1 H), 3.77−3.58 (m, 5 H), 3.54−3.44 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.43, 138.73, 138.50, 138.23, 137.96, 137.93, 137.83, 128.26, 128.10, 127.90, 127.69, 127.54, 127.35, 102.78, 100.06, 84.57, 82.25, 77.70, 75.72, 75.57, 74.92, 74.76, 74.61, 73.56, 73.34, 73.23, 72.08, 71.45, 69.07, 68.74; HRMS (FAB) calcd for $C_{54}H_{56}O_9Na$ 871.3822, found *m/z* 871.3830 (M + Na).

Acknowledgment. This research was supported by National Institutes of Health (N.I.H. grant no. AI 16943). An NIH National Resarch Service Award Postdoctoral Fellowship to J.T.R. is gratefully acknowledged.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **12**−**17**, **20**, **26**, **29**, and **32**; D_2O exchange for compound **3** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA944053Q