JOC*Article*

RCM-Based Synthesis of a Variety of β-*C*-Glycosides and Their in Vitro Anti-Solid Tumor Activity

Maarten H. D. Postema,*[,1] Jared L. Piper, and Russell L. Betts

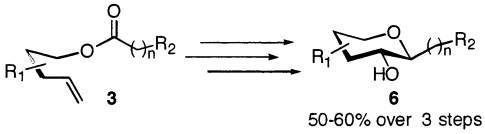
Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Frederick A. Valeriote* and Halina Pietraszkewicz

Josephine Ford Cancer Center, Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan 48203

mpostem1@hfhs.org; fvaleri1@hfhs.org

Received September 2, 2004



The synthesis of a number of biologically relevant *C*-glycosides has been carried out through the use of an esterification−ring-closing metathesis (RCM) strategy. The required acid precursors were readily prepared via a number of standard chemical transformations followed by dehydrative coupling of these acids with several olefin alcohols **1** to yield the precursor esters **3** in excellent yield. Methylenation of the esters **3** was followed by RCM and in situ hydroboration−oxidation of the formed glycals to furnish the protected β-*C*-glycosides **6** in good overall yield. Several examples were converted to the corresponding *C*-glycoglycerolipids **17** and subsequently screened against solid-tumor cell lines for in vitro differential cytotoxicity.

Introduction

A wide variety of synthetic strategies[2] have been developed for the attachment of carbon-based groups, including alkyl, aryl, and glycosyl, to the anomeric carbon of carbohydrates.[3−6] By definition, *C*-glycosides are compounds in which the interglycosidic oxygen atom has been replaced by a carbon atom to produce a stable glycoside derivative that is not prone to enzymatic or chemical hydrolysis, Figure 1. The aryl class of *C*-glycosides is particularly important due to the existence of a number of naturally occurring compounds that contain this motif, many of which possess interesting and potentially useful biological activity.[7,8] Included within this class are the

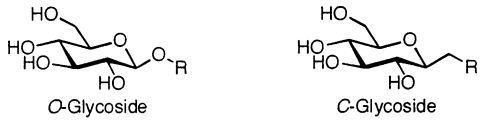


FIGURE 1. *O*-Glycoside versus *C*-glycoside.

C-saccharide derivatives[9] which are carbon analogues of *O*-saccharides.

To be suitable stable mimics of *O*-glycoside, *C*-glycosides must possess conformations that are similar to those of the parent *O*-glycoside or adopt conformations that still elicit a biological response or recognition event. The debate regarding the validity of *C*-saccharides as accurate conformational mimics of *O*-saccharides is ongoing and has yet to be resolved.[10−12] It is known, however, that the K_i values for *O*- and *C*-lactose for the competitive inhibition of β-galactosidase are within 2 μm of one

(1) Present Address: Josephine Ford Cancer Center, Department of Internal Medicine, Henry Ford Health System, One Ford Place, OFP-1D25, Detroit, MI 48202.

(2) Postema, M. H. D. *C-Glycoside Synthesis*; 1st ed.; CRC Press: Boca Raton, 1995; p 379.

(3) Postema, M. H. D.; Calimente, D. In *Glycochemistry: Principles, Synthesis and Applications*; Wang, P. G., Bertozzi, C., Eds.; Marcel Dekker: New York, 2000; pp 77−131.

(4) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959.

(5) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1−54.

(6) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83.

(7) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−195.

(8) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, 103−137.

(9) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133−1167.

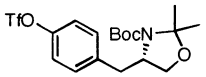
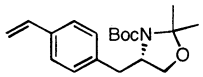
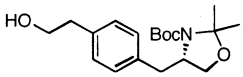
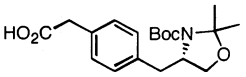
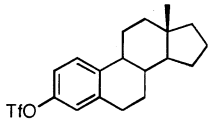
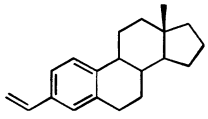
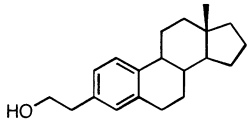
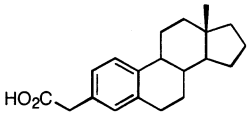
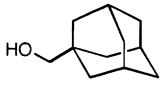
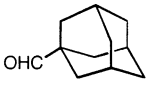
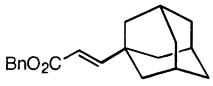
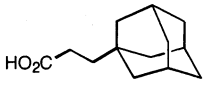
(10) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160−2169.

(11) Asensio, J. L.; Espinosa, J. F.; Dietrich, H.; Cañada, F. J.; Schmidt, R. R.; Martín-Lomas, M.; André, S.; Gabius, H.-J.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1999**, *121*, 8995−9000.

(12) Rubinstenn, G.; Sinaÿ, P.; Berthault, P. *J. Chem. Phys. A* **1997**, *101*, 2536−2540 and references therein.

10.1021/jo040254t CCC: $30.25
Published on Web 12/29/2004

TABLE 1. Synthesis of Carboxylic Acids 2[a]

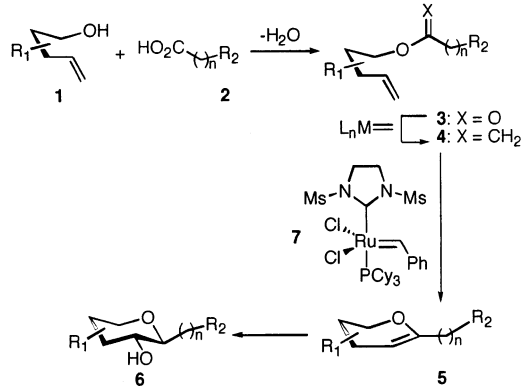
entry	precursor **8**	precursor **9**	precursor **10**	acid **2**
1	 **8b**, 86%	 **9b**, 80%[b]	 **10b**, 94%[c]	 **2b**, 93%[d]
2	 **8c**, 94%	 **9c**,81%[b]	 **10c**, 95%[c]	 **2c**, 91%[d]
3	 **8d**	 **9d**, 95%	 **10d**, 88%[e]	 **2d**, 90%[f]

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Stille coupling with $(Ph_3P)_4Pd$, $Bu_3SnCH{=}CH_2$ and LiCl.[29,31] [c] 9-BBN; NaOOH. [d] Swern [O] followed by $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene. [e] Wittig reaction carried out with $Ph_3P{=}CHCO_2Bn$ in CH_2Cl_2. [f] Hydrogenation carried out with H_2, Pd/C.

another.[13] Several groups[14−17] have convincingly shown that the substitution of the interglycosidic oxygen atom with a carbon atom does not greatly alter biological activity. Given the vast biological functions that carbohydrates perform,[18] it stands to reason that stable analogues of these derivatives could be useful as biological probes or enzyme inhibitors.

In this paper, we present full details of our ring-closing metathesis-based (RCM) methodology for the preparation of biologically relevant *β-C*-glycosides[19] and the corresponding *β-C*-glycoglycerolipids. Our goal has always been the development of a general approach for the synthesis of *C*-glycosides,[20] *β-C*-disaccharides,[21,22] *β-C*-trisaccharides,[23] and a branched *β-C*-tetrasaccharide.[24] Our generic synthetic approach to *C*-glycoside synthesis is shown below in Scheme 1 and begins with the dehydrative coupling of the generic olefin alcohol **1** with a suitable carbohydrate-based acid such as **2** to provide ester **3**, Scheme 1. Methylenation[25] (**3** → **4**) is followed by RCM with the second-generation Grubbs' catalyst **7**[26]

SCHEME 1. RCM Approach to *β-C*-Glycosides



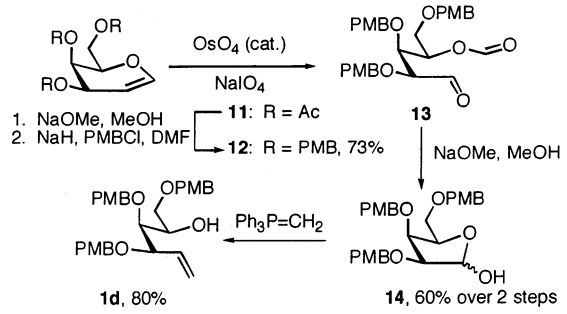
to generate the *C*-glycal **5**. Hydroboration[27,28] of the formed double bond then affords the gluco-*β-C*-glycoside **6**. This work also features the preparation of a variety of different olefin alcohols that serve to further expand the scope of this methodology.

Results and Discussion

Preparation of the various acids (Table 1) proceeded smoothly with many of the required carboxylic acids having been described previously. The synthesis of the aromatic tyrosine-based acid **2b** (entry 1) began with triflation[29] of the corresponding phenol[30] to produce **8b** in 86% yield that was coupled with tributylvinyltin under standard Stille coupling[29,31] conditions to provide **9b** in good overall yield. Hydroboration with 9-BBN and subsequent oxidative workup gave primary alcohol **10b** that was transformed to the target acid **2b** using Swern's procedure followed by Pinnick oxidation[32] (entry 1).

(13) Espinosa, J. F.; Montero, E.; Vian, A.; Garcia, J. L.; Dietrich, H.; Schmidt, R. R.; Martín-Lomas, M.; Imberty, A.; Cañada, F. J.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1998**, *120*, 1309−1318 and references therein.
(14) Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432−9436.
(15) Wang, J.; Kovac, P.; Sinaÿ, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1998**, *308*, 191−193.
(16) Tsuruta, O.; Yuasa, H.; Kurono, S.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 807−810.
(17) Yang, G.; Franck, R. W.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **2001**, *3*, 197−200.
(18) *Glycochemistry. Principles, Synthesis and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Marcel Dekker Inc.: New York, 2001.
(19) Postema, M. H. D.; Piper, J. L. *Org. Lett.* **2003**, *5*, 1721−1723.
(20) Postema, M. H. D.; Calimente, D. *J. Org. Chem.* **1999**, *64*, 1770−1771.
(21) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061−6068.
(22) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755−4759.
(23) Postema, M. H. D.; Piper, J. L.; Komanduri, V.; Liu, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1608−1615.
(24) Piper, J. L.; Postema, M. H. D. *J. Org. Chem.* **2004**, *69*, 7395−7398.
(25) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.
(26) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(27) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926−927.
(28) Schmidt, R. R.; Preuss, R.; Betz, R. *Tetrahedron Lett.* **1987**, *28*, 6591−6594.
(29) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.
(30) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385−1393.
(31) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

SCHEME 2. Synthesis of Olefin Alcohol 1d



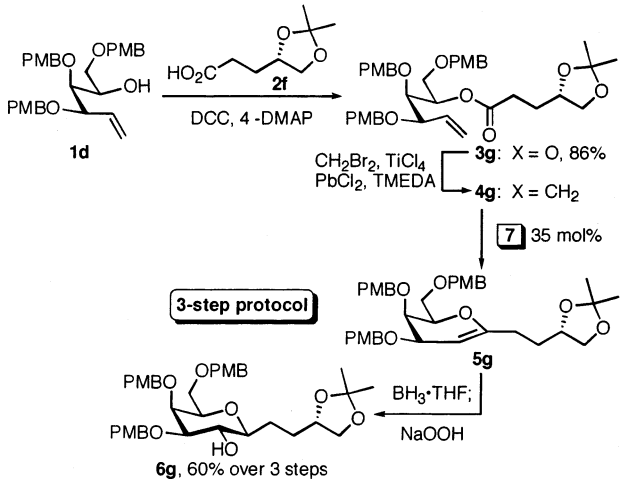
Similar chemistry (entry 2) was used to prepare steroid-based acid **2c** from the reduced[33] and suitably functionalized precursor **8c**.

The adamantyl-based acid **2d** (entry 3) was prepared using Wittig olefination of aldehyde **9d** followed by concomitant olefin reduction and debenzylation.

To make the methodology more versatile, it was necessary to introduce a different protecting group on the hydroxyls of the olefin alcohol. The *p*-methoxybenzyl (PMB) group seemed to be an ideal candidate since it is easily removed under mild oxidative conditions. We could not employ the same procedure for the preparation of the benzyl-protected olefin alcohol because the final step of the sequence,[34] an acidic hydrolysis of an anomeric methyl group, is incompatible with the PMB group (not shown). The synthesis began with the exchange of the acetates on tri-*O*-acetyl-D-galactal (**11**) for PMB to afford **12**. Lemieux–Johnson cleavage[20,35] of the cyclic enol ether gave formyl aldehyde **13**. Removal of the formate ester revealed lactol **14** that was subsequently exposed to an excess[36] of $Ph_3P{=}CH_2$ to deliver the target olefin alcohol **1d**, Scheme 2.

With the required olefin alcohols and acids in hand, the esterification–RCM sequence was examined. DCC-mediated coupling of alcohol **1d** and acid **2f**[37] proceeded smoothly to afford ester **3g** in 84% yield. Ester **3g** was converted to β-*C*-glycoside **6g** using our recently developed three-step protocol.[38] Takai methylenation[25] of ester **3g** generated acyclic enol ether **4g** which was subsequently exposed to 35 mol % of the second-generation Grubbs catalyst **7**[26] in hot toluene to provide the intermediate glycal **5g**. Regioselective hydroboration[27,28] with an excess of $BH_3{\cdot}THF$ was followed by oxidative quench (H_2O_2, NaOH) of the intermediate organoborane to afford the target β-*C*-glycoside **6g** in 60% yield over three steps, Scheme 3. The stereochemistry of the hydroboration was verified by acetylation of **6g** and examination of the proton NMR data ($J_{1,2} = J_{2,3} = 9.5$ Hz). This three-step protocol efficiently provided the target *C*-glycoside **6a**, a building block for the synthesis of β-*C*-glycoglycerolipids, in good overall yield.

SCHEME 3. Synthesis of β-*C*-Glycoside 6g via the Three-Step Protocol[39]



A variety of diverse β-*C*-glycoconjugates (**6a**–**k**) were prepared using this methodology as outlined in Table 2. The esters were produced (**1** + **2** → **3**) in good yield using a DCC-mediated coupling. Esters **3a**–**k** were exposed to our three-step protocol to deliver the target β-*C*-glycosides **6a**–**k** in 49–60% overall yield for the three steps. Entries 1–3 are three benzylic β-*C*-glycosides. Compound **6a** (entry 1) is a carbon analogue of a phenolic glycoside. Compound **6b** (entry 2) is a stable carbon analogue of the *O*-linked amino acid glycoside of tyrosine. In this example, the Boc group on the nitrogen was found to be compatible with the methylenation chemistry even in the presence of an excess of the Takai reagent. Entry 3 is a stable mimic of an aromatic sterol glycoside. Entry 4 represents a *C*-glycoside that carries a very lipophilic group at the anomeric center. It is noteworthy that the shorter chain variant (minus the two methylene spacers) could not be converted to the corresponding β-*C*-glycoside, since methylenation gave only recovered ester (not shown). Presumably, the steric bulk of the adamantyl group hinders methylenation. Compound **6e** (entry 5) is a stable analogue of a saturated sterol glycoside, and the corresponding acid **2e** is known.[40] Compounds **6f**–**j** (entries 6–10) are precursors to *C*-glycoside analogues of *O*-glycoglycerolipids. In the latter case, the hydroboration step was replaced by a stereoselective reduction[41,42] of the formed cyclic enol ether (and concomitant removal of the benzyl ethers) followed by exhaustive benzylation of the formed triol. Certain *O*-glycoglycerolipids have been found to possess antitumor activity,[43,44] and the corresponding *C*-glycoside analogues could provide stable mimics of these compounds, vide infra. The protected β-*C*-glycoside serine analogue was also prepared (entry 11) and could potentially serve as a building block for β-*C*-ceramide synthesis.[45] The precursor acid **2k** is known.[43,44]

(32) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(33) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301–3303.
(34) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516.
(35) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976–2985.
(36) Freeman, F.; Robrage, K. D. *Carbohydr. Res.* **1987**, *171*, 1–11.
(37) Chida, N.; Tobe, T.; Okada, S.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1992**, *1064–1066*.
(38) Postema, M. H. D.; Piper, J. L.; Liu, L.; Shen, J.; Faust, M.; Andreana, P. *J. Org. Chem.* **2003**, *68*, 4748–4754.
(39) The configuration of the secondary alcohol on the glycerol side chain was drawn incorrectly in our original communication.
(40) Golebiewski, W. M.; Keyes, R. F.; Cushman, M. *Bioorg. Med. Chem.* **1996**, *4*, 1637–1648.
(41) Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903–5906.
(42) Dubois, E.; Beau, J.-M. *Carbohydr. Res.* **1992**, *228*, 103–120.
(43) Siddiqui, M. A.; Marquez, V. E.; Driscoll, J. S.; Barchi, J. *Tetrahedron Lett.* **1994**, *35*, 3263–3266.
(44) Markidis, T.; Kokotos, G. *J. Org. Chem.* **2001**, *66*, 1919–1923.

TABLE 2. Preparation of β-*C*-Glycosides[a]

Entry	Ester **3** / Enol Ether **4**	*C*-Glycoside **6**[b,c]
1	**3a**: X = O, 86% **4a**: X = CH_2	**6a**, 55%
2	**3b**: X = O, 82% **4b**: X = CH_2	**6b**, 59%
3	**3c**: X = O, 82% **4c**: X = CH_2	**6c**, 52%
4	**3d**: X = O, 93% **4b**: X = CH_2	**6d**, 60%
5	**3e**: X = O, 91% **4e**: X = CH_2	**6e**, 50%
6	**3f**: R = Bn, X = O, 97% **4f**: R = Bn, X= CH_2	**6f**: R = Bn, 57%
7	**3g**: R = PMB, X = O, 84% **4g**: R = PMB, X= CH_2	**6g**: R = PMB, 53%
8	**3h**: R = Bn, X = O, 94% **4h**: R = Bn, X= CH_2	**6h**: X = OH, R = Bn, 57%
9	**3i**: R = PMB, X = O, 87% **4i**: R = PMB, X= CH_2	**6i**: X = OH, R = PMB, 50%
10		**6j**: X = H, R = PMB, 25%[d]
11	**3k**: X = O, 85% **4k**: X = CH_2	**6k**, 50%

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Yields are for three steps; Takai methylenation, RCM (20 mol % of **7**) and hydroboration−oxidative workup. [c] Stereochemistry at C-1 and C-2 determined by acetylation and analysis of the H-2 coupling constant in ^{1}H NMR. [d] In this case, the yield is over four steps starting from **3h** (methylenation, RCM, hydrogenation (H_2, Pd/C), and alkylation (NaH, PMBCl)).

There exists a very large number of sphingolipids that possess a wide variety of interesting biological properties[46,47] with ceramides being one subclass of this family. Sakakibara[48,49] has demonstrated that some derivatives demonstrate antitumor activity, Figure 2.

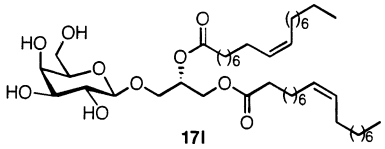
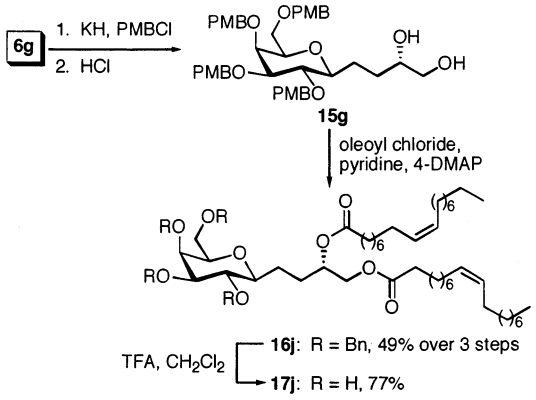


FIGURE 2. *O*-Glycoglycerolipid with antitumor activity.

SCHEME 4. β-*C*-Glycoglycerolipid Preparation



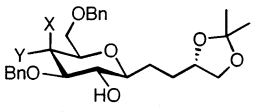
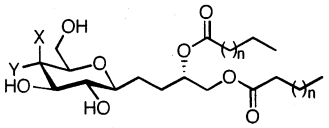
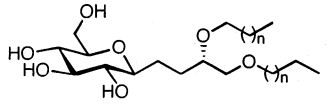
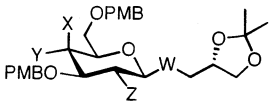
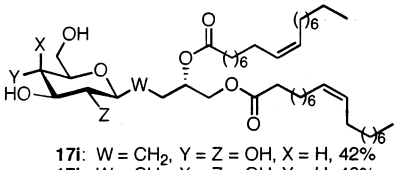
We were curious to determine if in vivo stable *C*-glycoside analogues of these glycolipid derivatives would exhibit differential cytotoxicity against solid tumor versus normal or leukemic cells. There has been considerable interest in this general area, and several groups[50−52] have carried out studies[17,53] related to the present work.

A small library of analogues were prepared from **6f**−**j** and for biological testing by simply protecting *O*-2 as a benzyl ether, removing the acetonide and then installing the appropriate long-chain fragments, Scheme 4. The secondary hydroxyl was protected as a *p*-methoxybenzyl ether, and the acetonide was removed to give **15g**. Acylation of the resulting diol with stearic anhydride then provided **16j** that was subsequently deblocked, under reductive conditions, to afford the target structure **17j**, Scheme 4. Selective acylation of the primary alcohol was possible if a stoichiometric amount of the carboxylic acid chloride was employed. This method allowed for the synthesis of a variety of analogues differing only in side chain length. The present approach is very flexible and convergent and allows quick access to a variety of analogues.

Table 3 illustrates the analogues that were prepared. Entries 1−6 are all acylated analogues with chain lengths from C-18 to C-28. Entries 7 and 8 are deoxygenated variations of entries 1−6. Installation of the oleoyl side chain necessitated the use of a PMB blocked β-*C*-glycoside and the gluco, galacto and 2-deoxygluco variants were all prepared (entries 9−11). Finally, the *O*-derivative[48,49] with the oleoyl side chain **17l** was prepared along literature guidelines for comparative purposes.

(45) For example, s. C., M.; Postema, M. H. D.; Valeriote, F. A.; Pietraszkiewicz, H. *Tetrahedron Lett.* **2004**, *45*, 7791−7794.
(46) Byun, H. S.; Bittman, R. *Phospholipids Handb.* **1993**, 97−140.
(47) Kundu, S. K. In *Glycoconjugates: Composition, Structure and Function*; Allen, H. J., Kisailus, E. C., Eds.; Marcel Dekker: New York, 1992; pp 203−262.
(48) Nagatsu, A.; Watanabe, M.; Ikemoto, K.; Hashimoto, M.; Murakami, N.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A.; Yazawa, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1619−1622.
(49) Shirahashi, H.; Murakami, N.; Watanabe, M.; Nagatsu, A.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A. *Chem. Pharm. Bull.* **1993**, *41*, 1664−1666.
(50) Cipolla, L.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163−6170.
(51) Gurjar, M. K.; Reddy, R. *Carbohydr. Lett.* **1997**, *2*, 293−298.
(52) Dondoni, A.; Perrone, D.; Turturici, E. *J. Org. Chem.* **1999**, *64*, 5557−5564.
(53) Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **1999**, *1*, 2149−2151.

TABLE 3. Synthesis of *β-C*-Glycoglycerolipids 17[a]

Entry	RCM Product **6**	*C*-Glyco*glycero*lipid **17**[b]
		
1	**6f**: X = OBn, Y = H	**17a**: X = OH, Y = H, n = 15, 47%
2	**6h**: Y = OBn, X = H	**17b**: Y = OH, X = H, n = 15, 46%
3	**6f**: X = OBn, Y = H	**17c**: X = OH, Y = H, n = 18, 48%
4	**6h**: Y = OBn, X = H	**17d**: Y = OH, X = H, n = 18, 52%
5	**6f**: X = OBn, Y = H	**17e**: X = OH, Y = H, n = 25, 51%
6	**6h**: Y = OBn, X = H	**17f**: Y = OH, X = H, n = 25, 50%
		
7	**6h**: Y = OBn, X = H	**17g**: n = 15, 15%
8	**6h**: Y = OBn, X = H	**17h**: n = 18, 15%
		
9	**6i**: W = CH_2, Y = OPMB, X = H, Z = OH	**17i**: W = CH_2, Y = Z = OH, X = H, 42%
10	**6g**: W = CH_2, X = OPMB, Y = H, Z = OH	**17j**: W = CH_2, X = Z = OH, Y = H, 46%
11	**6j**: W = CH_2, Y = OPMB, X = H, Z = H[c]	**17k**: W = CH_2, Y = OH, X = Z = H, 46%
12	**6l**: W = O, Y = Z = OPMB, X = H	**17l**: W = O, Y = Z = OH, X = H[d]

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Yields are for four steps: Protection of O-2 (NaH, BnBr/KH, PMBCl, TBAI), acetonide removal (*p*-TsOH, MeOH), acylation ($(RCO)_2O$ or RCOCl, pyridine, 4-DMAP/RCO_2H, DCC, 4-DMAP), and debenzylation (H_2, Pd/C). In the case of entries 7 and 8, the acylation step was substituted by alkylation with NaH, R-Br, and *n*-Bu_4NI. [c] Prepared by selective hydrogenation of the product glycal **5h** followed by benzylation. [d] Prepared along the guidelines described by Sakakibara.[48]

TABLE 4. In Vitro Antitumor Activity of Glycoglycerolipids 17

entry	compd	μg/disk	$_{C38}\Delta S_{L1210}$	$_{C38}\Delta S_{CFU}$
1	**17a**		50	
2	**17b**		50	
3	**17c**		50	
4	**17d**		50	
5	**17e**	100	**600**	**700**
6	**17f**	75	**250**	**300**
7	**17g**		0	
8	**17h**		0	
9	**17i**	145	**250**	**300**
10	**17j**		0	
11	**17k**		0	
12	**17l**	180	**550**	**750**

The disk-diffusion-based anti-solid tumor assay that was employed to determine the differential anti-solid tumor activity relies upon differences in cytotoxicity between normal or leukemia and solid tumor cells. The differential cytotoxicity is quantified by zone units. A value of 0 indicates there was no cell killing with a maximum kill of 1200 representing the point at which all the cells on the plate have been killed. A zone difference *between two different cell lines* of **250 units** or more is considered a hit in the assay and is bolded in Table 4. A zone difference of 250 units or more means the agent is selectively toxic against solid tumor cells versus either leukemia ($_{C38}\Delta S_{L1210}$) or normal cells ($_{C38}\Delta S_{CFU}$).

The compounds were screened[54] against a variety of solid tumor cell lines in vitro and the results are outlined in Table 4. Using this assay, it was discovered that three compounds demonstrated selectivity against solid tumor cells. Both long-chain derivatives **17e** and **17f** showed activity against colon 38 solid tumor cells showing differentials of 600 and 250 zone units. More importantly, they exhibited selectivity against the solid tumor C38 cells versus normal murine cells (entries 5 and 6). We expected that analogue **17j** of the Sakakibara compound **17l** would be the most active. However, the gluco variant of that compound, **17i**, possessed differential cytotoxicity activity in vitro exhibiting a difference of 300 zone units between colon 38 versus normal cells and a difference of 250 units for C38 versus leukemia. This suggests that the replacement of the oxygen atom with a carbon atom has altered the conformation and effected the binding conformation of the sugar. Noteworthy is that the 2-deoxy analogue **17k**, a compound easily accessed by our methodology, was inactive and seemingly indicated that the *C*-2 hydroxyl is critical for biological activity. The active compounds are selective, but not potent, given the relatively large amount of material that has to be placed on the filter disk. In this assay, the range for normal cytotoxic agents is approximately 0.01−5.0 μg/disk.[55]

(54) Corbett, T. H.; Valeriote, F. A.; Polin, L.; Panchapor, C.; Pugh, S.; White, K.; Lowichick, N.; Knight, J.; Bissery, M.-C.; Wozniak, A.; LoRusso, P.; Biernat, L.; Polin, D.; Knight, L.; Biggar, S.; Looney, D.; Demchick, L.; Jones, J.; Jones, L.; Blair, S.; Palmewr, K.; Essenmacher, S.; Lisow, L.; Mattes, L. C.; Cavenaugh, P.; Rake, J.; Baker, L. In *Cytotoxic Anticancer Drugs: Models and Concepts for Drug Discovery and Development*; Kluwer Academic Publishers: Boston, 1992; pp 35−87.

(55) For example, to achieve zone values in the range of 500 units, 0.01 μg of Taxol or 1 μg of adriamycin must be applied to the filter disk.

The corresponding oleoyl *O*-derivative **17l** gave interesting results showing excellent differential cytoxocity exhibiting $_{C38}\Delta S_{L1210}$ = 550 and $_{C38}\Delta S_{CFU}$ = 750 zone units. These numbers are significantly superior to the data from the corresponding *β*-*C*-analogue **17i**, seemingly indicating that the oxygen linkage is important for differential anti-solid tumor activity.

The synthesis of *β*-*C*-glycosides by our esterification−RCM approach has proven to be an effective means of gaining access to a diverse array of *β*-*C*-glycosides. The use of the second-generation Grubbs catalyst **7** in our one-pot approach makes the synthesis of these compounds practical. A small library of *β*-*C*-glycoglycerolipids were screened for antitumor activity, and several compounds demonstrated differential cytotoxicity in vitro.

Experimental Section[56]

2,3,5-Tri-*O*-(4-methoxybenzyl)-D-lyxofuranoside. To a solution of 3,4,6-tri-*O*-(4-methoxybenzyl)-D-galactal[57] (320 mg, 0.73 mmol) in THF (6 mL) and H_2O (2 mL) was added osmium tetraoxide (0.1 mL, 4% in H_2O), and the resulting mixture turned from light tan to black within 10 min. At this point, $NaIO_4$ (390 mg, 1.83 mmol) was added in four portions, and the resulting solution was then stirred for 18 h at ambient temperature, at which point TLC (silica, 25% Et_2O−hexanes) showed the reaction was complete. The reaction was quenched with saturated $Na_2S_2O_3$ (10 mL), and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give crude 2,3,5-tri-*O*-(4-methoxybenzyl)-4-*O*-formyl-D-lyxose (324 mg, 84% crude yield) as a white solid. Due to instability of the resultant product, the crude material was azeotroped with benzene (3 × 10 mL) and then dissolved in THF/MeOH (10 mL, 1:1). To this solution was added a solution of NaOMe (50 mg, 0.90 mmol) in THF (1.0 mL). After 1 min, TLC (silica, 40% EtOAc−hexanes) showed the deformylation reaction was complete. The reaction was diluted with saturated ammonium chloride (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were washed with brine, dried, and filtered to give crude lactol as a yellow oil. Flash chromatography on silica gel using 15 → 25% EtOAc−hexanes gave the galacto lactol (190 mg, 60% over two steps) as an inseparable mixture (1:1, ^{1}H NMR, 500 MHz) of anomers (R_f = 0.22, TLC, silica 25% EtOAc−hexanes, ^{1}H NMR (500 MHz)), colorless oil, data for one isomer only: $[\alpha]^{26}_D$ (*c* = 1.00, CH_2Cl_2); FT-IR (neat) 3429 (br), 2950, 2851, 1608, 1584, 1514, 1456, 1304, 1229, 1007, 808, 709 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of anomers, data for major isomer only) *δ* 7.34−7.20 (m, 6 H, Ar*H*), 6.92−6.82 (m, 6 H, Ar*H*), 5.29 (dd, 1 H, *J* = 10.5, 4.0 Hz, *H*-1), 4.76 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.66 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.53 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.52 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.52 (d, 1 H, *J* = 11 Hz, OC*H*$_2$-Ar), 4.44 4.52 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.34 (br d, 1 H, *J* = 12 Hz, O*H*), 4.15−4.07 (m, 2 H, *H*-3, *H*-4), 3.97 (dd, 1 H, *J* = 4.5, 4.5 Hz, *H*-2), 3.79 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 3.79 (s, 3 H, OC*H*$_3$), 3.68−3.64 (m, 2 H, 2 × *H*-5); ^{13}C NMR (125 MHz) *δ* 159.1, 159.1, 158.9, 129.6, 129.2, 129.1, 129.1, 129.1, 113.6, 113.5, 113.5, 99.7, 95.3, 82.9, 78.7, 77.9, 76.5, 73.6, 72.9, 71.2, 68.6, 54.9, 54.9, 54.9; HRMS(FAB) calcd for $C_{29}H_{34}O_8Na$ (M)$^+$ 533.2146, found 533.2119.

2,3,5-Tri-*O*-(4-methoxybenzyl)-1,2-dideoxy-D-*lyxo*-hex-1-enitol (1d). LiHMDS (0.43 mL, 1 M solution in THF, 0.43 mmol) was added via syringe over 3 min to a cool (0 °C) and stirred suspension of methyltriphenylphosphonium bromide (124 mg, 0.49 mmol) in dry THF (2 mL). The resulting orange solution was allowed to warm to ambient temperature over 15 min and then cooled back to 0 °C. A solution of the lyxo-lactol (100 mg, 0.195 mmol) in THF (2 mL) was then added in one portion via syringe. The resulting mixture was then warmed to 60 °C for 1 h, at which point TLC (silica, 40% EtOAc−hexanes) showed no starting material remained. The solution was cooled to 0 °C, diluted with ether (20 mL), and quenched with saturated ammonium chloride (5 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined ethereal layers were washed with ammonium chloride (1 × 10 mL) and brine (1 × 10 mL), dried, filtered, and concentrated. Flash chromatography of the residue over silica gel gave olefin alcohol **1d** (80 mg, 80%) as a pure (R_f = 0.32, TLC, silica 40% EtOAc−hexanes, ^{1}H NMR (500 MHz, $CDCl_3$)), pale yellow oil: $[\alpha]^{26}_D$ = −33.9 (*c* = 1.00, CH_2Cl_2); FT-IR (neat) 3010 (br), 2973, 2897, 2845, 1619, 1503, 1474, 1321, 1310, 1240, 1041, 803 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.27−7.21 (m, 4 H, Ar*H*), 7.19−7.15 (m, 2 H, Ar*H*), 6.89−6.82 (m, 6 H, Ar*H*), 5.92 (ddd, 1 H, *J* = 17.5, 11, 7.5 Hz, *H*-2), 5.32 (d, 1 H, *J* = 11.5, Hz, *H*-1), 5.30 (d, 1 H, *J* = 17 Hz, *H*-1), 4.58 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ph), 4.56 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ph), 4.46 (d, 1 H, *J* = 12 Hz, OC*H*$_2$Ph), 4.41 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ph), 4.38 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ph), 4.33 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$-Ph), 4.03 (m, 2 H, *H*-3, *H*-5), 3.80 (s, 3 H, OC*H*$_3$), 3.79 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 3.56 (dd, 1 H, *J* = 6.0, 3.0 Hz, *H*-4), 3.46 (m, 2 H, 2 × *H*-6), 2.88 (d, 1 H, *J* = 5.5 Hz, O*H*); ^{13}C NMR (125 MHz) *δ* 159.2, 159.1, 159.1, 135.7, 130.1, 130.1, 130.0, 129.8, 129.4, 129.4, 129.4, 119.1, 113.7, 113.7, 113.6, 80.1, 79.4, 73.3, 72.9, 70.6, 70.3, 69.6, 55.9, HRMS(FAB) calcd for $C_{30}H_{36}O_7Na$ (M)$^+$ 531.2353, found 531.2334.

Ester 3g. 4-DMAP (132 mg, 1.08 mmol) and DCC (535 mg, 2.60 mmol) were added in one portion to a dry solution of acid **2f**[2] (452 mg, 2.60 mmol) and olefin alcohol **1d** (1.1 g, 2.16 mmol) in dry CH_2Cl_2 (5 mL). The resulting solution was then stirred for 18 h at ambient temperature, at which point TLC (40% EtOAc−hexanes) showed the reaction was complete. The reaction mixture was diluted with ether (20 mL) and filtered by gravity through cotton to remove most of the formed dicyclohexylurea. The resulting organic solution was washed with NH_4Cl (1 × 30 mL), dried, and concentrated under reduced pressure. Flash chromatography of the residue over silica gel using 30 → 40% EtOAc−hexanes gave ester **3g** (1.23 g, 84%) as a pure (R_f = 0.33, TLC, silica, 30% EtOAc−hexanes; ^{1}H NMR (500 MHz, $CDCl_3$)) oil: $[\alpha]^{26}_D$ = −9.0 (*c* = 1.00, $CHCl_3$); FT-IR (neat) 3323, 2944, 2839, 1730, 1619, 1584, 1462, 1509, 1240, 1036, 816 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.26−7.16 (m, 6 H, Ar*H*), 6.87−6.80 (m, 6 H, Ar*H*), *5*.87 (ddd, 1 H, *J* = 17.5, 10.5, 7.5 Hz, *H*-2), 5.36 (dd, 1 H, *J* = 10.5, 1.5 Hz, *H*-1), 5.7 (ddd, 1 H, *J* = 4.0, 4.0, 4.0 Hz, *H*-5), 5.30 (dd, 1 H, *J* = 17.5, 1.0 Hz, *H*-1), 4.62 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.46 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.45 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.40 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.36 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.20 (d, 1 H, *J* = 10.5 Hz, OC*H*$_2$Ar), 4.05 (dddd, 1 H, *J* = 12.5, 12.5, 6.0, 6.0 Hz, *H*-9), 3.98 (dd, 1 H, *J* = 8.0, 6.0 Hz, *H*-10), 3.84−3.80 (m, 1 H, *H*-3), 3.79 (s, 6 H, 2 × OC*H*$_3$), 3.79 (s, 3 H, OC*H*$_3$), 3.73 (dd, 1 H, *J* = 6.5, 3.5 Hz, *H*-4), 3.55−3.45 (m, 3 H, 2 × *H*-6, *H*-10), 2.41 (ddd, 1 H, *J* = 16.5, 7.5, 7.5 Hz, *H*-7), 2.28 (ddd, 1 H, 15.5, 7.5, 7.5 Hz, *H*-7), 1.96 (m, 1 H, *H*-8), 1.74−1.66 (s, 1 H, *H*-8), 1.38 (s, 3 H, C(C*H*$_3$)$_2$), 1.30 (s, 3 H, C(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) d 172.5, 159.2, 159.2, 159.1, 135.8, 130.3, 130.2, 129.9, 129.8, 129.6, 129.4, 119.5, 113.7, 113.7, 113.7, 113.6, 108.9, 94.7, 79.6, 78.7, 74.9, 74.1, 72.7, 71.4, 69.9, 69.0, 67.8, 55.2, 30.3, 286,

(56) For a description of general methods, see ref 21.

(57) This compound was prepared in the same fashion as the corresponding gluco derivative; see: Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758−8762.

26.9, 25.6; HRMS (EI) calcd for $C_{38}H_{48}O_{10}Na$ $(M)^+$ 687.3140, found 687.3151.

***C*-Glycoside (6g).** A solution of titanium tetrachloride (3.8 mL, 2 M in CH_2Cl_2, 7.67 mmol) was added to cool (0 °C) THF (4 mL). The resulting mixture was stirred for 30 min at which point TMEDA (2.23 mL, 14.8 mmol) was added in one portion. The resulting yellow-brown suspension was allowed to warm to ambient temperature and stirred for 30 min. At this point, zinc dust (1.09 g, 16.65 mmol) and lead(II) chloride (13 mg, 0.045 mmol) were added in one portion, and stirring at ambient temperature was continued for 10 min. A solution of ester **3g** (300 mg, 0.45 mmol) and dibromomethane (0.29 mL, 4.19 mmol) in THF (3 mL) was then added via cannula to the reaction flask in one portion. The mixture was stirred at 60 °C for 1 h, cooled to 0 °C, and then quenched by the addition of saturated potassium carbonate (1.0 mL). The resulting mixture was stirred for 30 min (while warming to ambient temperature), diluted with ether (20 mL), and stirred vigorously for 15 min. The resulting mixture was filtered through basic alumina using 3% triethylamine−ether as the eluent. The greenish-blue precipitate that resulted was crushed (mortar and pestle) and thoroughly extracted by vigorous stirring over diethyl ether (15−20 mL) for 30 min. The combined ethereal extracts were concentrated in vacuo, azeotroped with benzene (3 × 20 mL), and redissolved in dry toluene (14 mL). After the crude enol ether was degassed thoroughly under nitrogen atmosphere for 20 min, the first aliquot (1/4) of catalyst **7** (134 mg, 0.158 mmol, 35 mol %) was added and heated to 60 °C. The remaining catalyst was added in three equivalent portions over the next 3 h, and upon completion, the solution was cooled to 0 °C, BH_3·THF (4.5 mL, 1 M in THF, 4.5 mmol) was added, and the resulting mixture was stirred at this temperature for 3 h until TLC indicated the reaction was complete. NaOH (25 mL, 1 M, 25 mmol) and hydrogen peroxide (25 mL, 30% in water, 0.20 mol) were added sequentially dropwise, and the solution was allowed to warm to room temperature over 2 h at which point TLC showed a clean product spot. The solution was extracted with ether (3 × 15 mL), and the combined ethereal extracts were washed with brine (1 × 10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue over silica using 30→40% EtOAc−hexanes gave **6g** (175 mg, 60% over three steps) as a pure (R_f = 0.36, TLC, silica, 40% EtOAc−hexanes; ^{1}H NMR (500 MHz, $CDCl_3$)) oil: $[\alpha]^{26}_D$ = +28.7 (*c* = 1.00, $CHCl_3$); FT-IR (neat) 3450 (br), 2915, 2853, 1612, 1513, 1246, 1173, 1078, 1033, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.20 (m, 6 H, Ar*H*), 6.88−6.86 (m, 4 H, Ar*H*), 6.85−6.81 (m, 2 H, Ar*H*), 4.76 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.63 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.54 (d, 1 H, *J* = 12 Hz, OC*H*$_2$Ar), 4.43 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.37 (d, 1 H, *J* = 12 Hz, OC*H*$_2$Ar), 4.36 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.08 (dddd, 1 H, *J* = 13, 13, 6.0, 6.0 Hz, *H*-9), 4.00 (dd, 1 H, *J* = 8.0, 7.5 Hz, *H*-10), 3.96 (app d, 1 H, *J* = 2.0 Hz, *H*-4), 3.80 (s, 6 H, 2 × OC*H*$_3$), 3.77 (s, 3 H, OC*H*$_3$), 3.70 (dd, 1 H, *J* = 10, 10 Hz, *H*-2), 3.54−3.48 (m, 4 H, *H*-5, 2 × *H*-6, *H*-10), 3.31 (dd, 1 H, *J* = 9.5, 2.0 Hz, *H*-3), 3.12 (dd, 1 H, *J* = 8.5, 8.5, 1.5 Hz, *H*-1), 2.30 (br s, 1 H, O*H*), 1.93−1.82 (m, 2 H, *H*-7, *H*-8), 1.63−1.51 (m, 2 H, *H*-7, *H*-8), 1.38 (s, 3 H, C(C*H*$_3$)$_2$), 1.32 (s, 3 H, C(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 159.3, 159.1, 130.7, 129.9, 129.8, 129.7, 129.6, 129.3, 114.0, 113.8, 113.6, 108.5, 83.8, 79.6, 77.2, 75.9, 73.9, 73.1, 71.9, 71.1, 70.5, 69.4, 68.5, 55.2, 55.2, 29.4, 27.8, 26.9, 25.7; HRMS (FAB) calcd for $C_{37}H_{48}O_{10}Na$ $(M)^+$ 675.3140, found 675.3183.

Diol 15g. The hydroborated product **6g** (100 mg, 0.15 mmol) was dissolved in DMF (2 mL) and added dropwise into a stirring solution of KH (72 mg, 0.535 mmol, 35% dispersion in mineral oil) and DMF (2 mL) at 0 °C. After 10 min, *p*-methoxybenzyl chloride (62 μL, 1.07 mmol) was added dropwise, followed by a catalytic amount of TBAI (20 mg). The reaction was stirred for 30 min, warmed to room temperature, and allowed to stir for an additional 1 h. This mixture was diluted with Et_2O (10 mL), quenched by the addition of water (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (1 × 15 mL), dried, and concentrated. Flash chromatography of the residue over silica using 20 → 30% EtOAc−hexanes gave the fully protected *C*-glycoside (101 mg, 86%) as a pure (R_f = 0.33, TLC, silica, 40% EtOAc−hexanes; ^{1}H NMR (400 MHz, $CDCl_3$), (HRMS (FAB) calcd for $C_{45}H_{56}O_{11}Na$ $(M)^+$ 795.3715, found 795.3761)) clear oil that was taken to the next step without further characterization. The usual procedure for acetonide methanolysis was followed using *p*-TsOH (5 mg), MeOH−CH_2Cl_2 (1:1, 3 mL), the acetonide (65 mg, 0.084 mmol), and Et_3N (1 mL) for quench. After the usual workup, flash chromatography over silica using 2 → 4% CH_2Cl_2−MeOH gave diol **15g** (50 mg, 81%, 70% over two steps) as a pure (R_f = 0.31, TLC, silica, 3% CH_2Cl_2−MeOH; ^{1}H NMR (500 MHz, $CDCl_3$)) white solid: mp = 100−101 °C; $[\alpha]^{26}_D$ = −10.6 (*c* = 1.00, $CHCl_3$); FT-IR (neat) 3419 (br), 2999, 2931, 2864, 1612, 1586, 1513, 1464, 1301, 1244, 1173, 1090, 1031, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2 H, Ar*H*), 7.23−7.19 (m, 6 H, Ar*H*), 6.90−6.82 (m, 8 H, Ar*H*), 4.87 (d, 1 H, *J* = 10 Hz, OC*H*$_2$Ar), 4.84 (d, 1 H, *J* = 11 Hz, OC*H*$_2$Ar), 4.68 (d, 1 H, *J* = 12 Hz, OC*H*$_2$Ar), 4.62 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.56 (d, 1 H, *J* = 10.5 Hz, OC*H*$_2$Ar), 4.54 (d, 1 H, *J* = 12.0 Hz, OC*H*$_2$Ar), 4.40 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.32 (d, 1 H, *J* = 11.5 Hz, OC*H*$_2$Ar), 3.82 (dd, 1 H, *J* = 3.0, 3.0 Hz, *H*-4), 3.81 (s, 3 H, OC*H*$_3$), 3.80 (s, 6 H, 2 × OC*H*$_3$), 3.79 (s, 3 H, OC*H*$_3$), 3.70−3.64 (m, 1 H, *H*-9), 3.61 (dd, 1 H, *J* = 9.0, 9.0 Hz, *H*-2), 3.53 (dd, 1 H, *J* = 9.0, 2.5 Hz, *H*-3), 3.53−3.47 (m, 3 H, *H*-5, *H*-6, *H*-10), 3.36 (dd, 1 H, *J* = 10.5, 7.5 Hz, *H*-10), 3.27 (dd, 1 H, *J* = 8.0, 4.0 Hz, *H*-6), 3.21 (ddd, 1 H, *J* = 9.0, 9.0, 1.5 Hz, *H*-1), 3.21 (bs, 1 H, O*H*), 2.16−2.02 (m, 2 H, *H*-7, O*H*), 1.64−1.52 (m, 2 H, *H*-7, *H*-8), 1.50−1.43 (m, 1 H, *H*-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 159.3, 159.2, 159.2, 130.5, 130.4, 130.4, 129.9, 129.8, 129.7, 129.7, 129.2, 113.8, 113.8, 113.7, 113.6, 84.4, 80.4, 78.3, 75.1, 73.8, 73.2, 72.9, 72.1, 69.2, 66.8, 55.2, 30.9, 28.5; HRMS (FAB) calcd for $C_{42}H_{52}O_{11}Na$ $(M)^+$ 755.3402, found 755.3354.

***C*-Glycoglycerolipid (17j).** Oleoyl chloride (271 μL, 0.82 mmol) was added in one portion to a pyridine (2 mL) solution of diol **15g** (100 mg, 0.136 mmol) and 4-DMAP (8.5 mg, 0.068 mmol). The solution was stirred for 18 h at ambient temperature and then concentrated in vacuo. Flash chromatography of the residue over silica using 25−30% EtOAc−hexanes gave **16j** (121 mg, 71%) as a pure (R_f = 0.22, TLC, silica, 25% EtOAc−hexanes; ^{1}H NMR (500 MHz, $CDCl_3$)) yellow oil. The product was then taken directly to the next step. TFA (5 drops) was added to a solution of **16j** (25 mg, 0.022 mmol) in CH_2Cl_2 (2.0 mL), and the reaction was stirred for 1 h at ambient temperature. At this point TLC analysis (silica, first 30% EtOAc−hexanes then 5% MeOH−CH_2Cl_2) indicated the reaction was almost complete and upon concentration in vacuo the reaction went to completion. Flash chromatography of the residue over silica gel using 5 → 10% MeOH−CH_2Cl_2 gave **17j** (19 mg, 77%) as a pure (R_f = 0.21, TLC, silica, 10% MeOH−CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$)) white solid: mp = 41−42 °C; $[\alpha]^{26}_D$ = +3.4 (*c* = 1.00, CH_2Cl_2); FT-IR (neat) 3600−3300 (b), 2921, 2852, 1736, 1463, 1245, 1168, 1088, 1052, 722 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38−5.27 (m, 5 H, 4 × C=C−H, *H*-9), 4.31 (dd, 1 H, *J* = 12.0, 3.5 Hz, *H*-10), 4.08−4.04 (m, 1 H, *H*-4), 3.97 (dd, 1 H, *J* = 11.5, 7.0 Hz, *H*-10), 3.92−3.82 (m, 2 H, 2 × *H*-6), 3.80−3.72 (s, 1 H, O*H*), 3.57 (dd, 1 H, *J* = 9.0, 9.0 Hz, *H*-2), 3.48−3.44 (m, 1 H, *H*-3), 3.42 (dd, 1 H, *J* = 4.0, 4.0 Hz, *H*-5), 3.24 (ddd, 1 H, *J* = 9.5, 2.0, 2.0 Hz, *H*-1), 3.11 (s, 1 H, O*H*), 3.00 (s, 1 H, O*H*), 2.73 (s, 1 H, O*H*), 2.33−2.26 (m, 4 H, 2 × C(O)C*H*$_2$), 2.03−1.98 (m, 8 H, 4 × C*H*$_2$), 1.97−1.88 (m, 1 H, *H*-7), 1.82−1.68 (m, 2 H, 2 × *H*-8), 1.68−1.55 (m, 5 H, *H*-7, 2 × C*H*$_2$), 1.35−1.24 (m, 40 H, 20 × C*H*$_2$), 0.88 (t, 6 H, *J* = 6.5 Hz, 2 × C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.8, 130.0, 130.0, 129.7, 129.7, 79.3, 77.3, 77.1, 75.5,

71.1, 71.1, 65.2, 63.9, 34.5, 34.1, 31.9, 29.7, 29.7, 29.5, 29.3, 29.2, 29.2, 29.2, 29.1, 29.1, 27.2, 27.2, 26.6, 26.2, 25.0, 24.8, 22.7, 14.1; HRMS (FAB) calcd for $C_{46}H_{84}O_9Na$ $(M)^+$ 803.6008, found 803.6008.

Acknowledgment. We thank Mr. Mani Raj Chaulagain and Mr. Venu Komanduri for the preparation of some of the starting materials. Acknowledgment is made to the NSF (CHE-0132770) for support of this research.

Supporting Information Available: Experimental procedures and spectral data listing for all the major compounds along with copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040254T