Tetrahedron 64 (2008) 9821–9827

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of the mixed acetal segment of *S*-glyceroplasmalopsychosine

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ARTICLE INFO

Article history:
Received 31 May 2008
Received in revised form 6 August 2008
Accepted 7 August 2008
Available online 12 August 2008

Dedicated to Professor Klaus Grohmann, our friend and colleague, on the occasion of his retirement from Hunter College of CUNY

Keywords:
Glyceroplasmalopsychosine
Mixed acetal
Conversion of carbohydrate to non-carbohydrate asymmetric molecules
Heterogeneous Wittig reaction
Olefin metathesis
Wilkinson's catalyst

ABSTRACT

In this report the concept of converting carbohydrate to non-carbohydrate asymmetric molecules has been successfully exploited. The mixed acetal segment of glyceroplasmalopsychosine, a novel glycolipid, has been synthesized in a stereospecific manner using two simple sugar units. The glycosidation reaction between these two monosaccharides ensured the correct acetal stereocenter of the target molecule. Either olefin metathesis or heterogeneous Wittig reactions were used for constructing the long aliphatic chain of glyceroplasmalopsychosine.

1. Introduction

Long chain aldehydes, hexadecanal, and octadecanal, with or without a double bond, are collectively called plasmal.[1,2] They are a common component of a novel type of glycosphingolipid (GSL) in which a plasmal is conjugated to two hydroxyl groups of psychosine or galactosylceramide through a cyclic acetal linkage. These were originally isolated from human brain white matter and are termed, respectively, plasmalopsychosine (PLPS)[3] **1** and plasmalocerebroside.[4] Recently Hikita[5] et al. have isolated a novel glycolipid 'glyceroplasmalopsychosine' **2** from the white matter of bovine brain. This unique glycolipid contains a glycerol moiety, a plasmal, and psychosine where the plasmal is conjugated to the primary hydroxyl group of the glycerol and the 6-hydroxyl of the psychosine by an acetal linkage.[6,7] Glyceroplasmalopsychosine exists as a pair of stereoisomers whose structures depend on the mode of plasmal conjugation, i.e., the way that *O*-plasmal conjugate is linked at C1 at two primary hydroxyl groups at glycerol and galactose. The structures of both the isomers, which differ with respect to the asymmetric C-1 carbon of the aldehyde are shown in Figure 1.

Glyceroplasmalopsychosine is the most recent cationic sphingolipid extracted from the white matter of bovine brain. Although glyceroplasmalopsychosine is characterized by properties similar to those of PLPS, it has certain properties distinct from them due to the presence of an additional polar group, i.e., glycerol. The glycerol residue may interact with galactosyl residue to achieve steric stability, such that axes of two aliphatic chains, sphingosine and plasmal, are oriented in parallel regardless of the C1 stereoisomer of plasmal. NMR data indicate that two stereoisomers with regard to the asymmetric C1 carbon of plasmal in glyceroplasmalopsychosine are detected in a ratio of ~1:1 whereas those of PLPS are found exclusively in only one form[8] ('*endo* type'). This may reflect a difference in stability of the plasmal linkage in these two compounds, i.e., the linkage in glyceroplasmalopsychosine is much more unstable than that in PLPS.

The observation that glyceroplasmalopsychosine showed no cytotoxic effect but only weak protein kinase C (PKC) inhibition in contrast with strong cytotoxicity as well as PKC inhibitory activity of psychosine,[3] presented interesting questions concerning the function of the glycerol and fatty aldehyde chain of glycolipid on the membrane surface.

The intriguing biological properties and the challenge of constructing the acetal linkage in a stereospecific manner make glyceroplasmalopsychosine an interesting synthetic target. Herein we report the first synthesis of the mixed acetal segment of *S*-glyceroplasmalopsychosine **2A**.

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0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.023

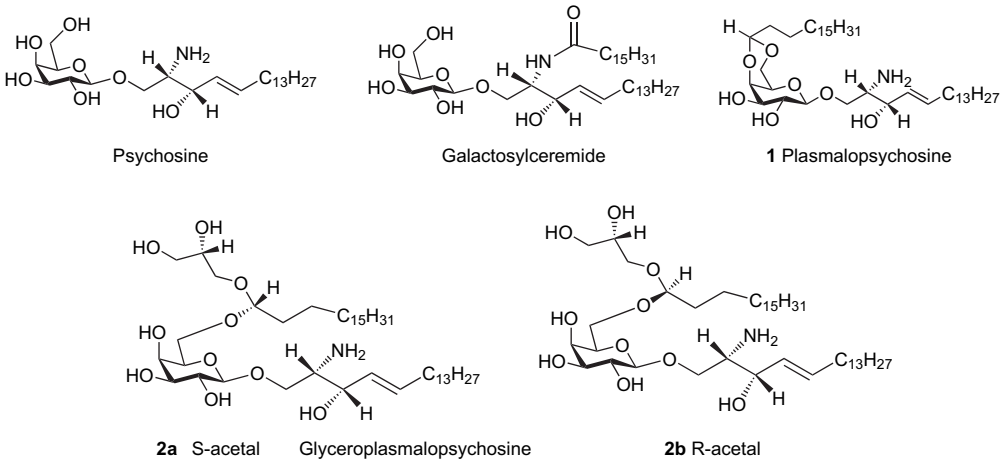


Figure 1. Structures of psychosine, galactosylceramide, *endo* form of 4,6-PLPS (**1**), and both isomers of glyceroplasmalopsychosine (**2a** and **2b**).

2. Results and discussion

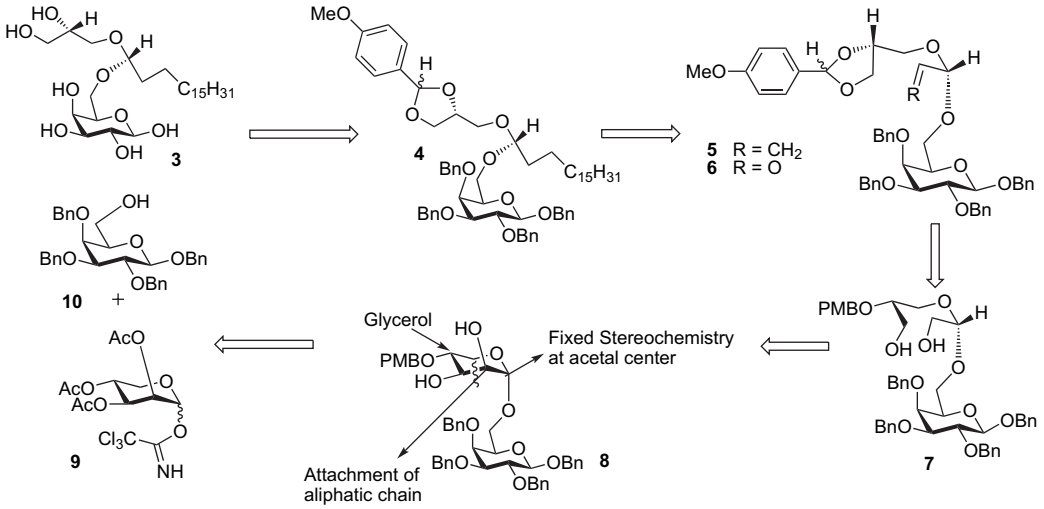
Our retrosynthetic approach outlined in Scheme 1 is a classic example of conversion of a carbohydrate to an asymmetric non-carbohydrate molecule where chiral centers of the carbohydrate are incorporated into the non-carbohydrate product. We envisioned that the disaccharide **8** is a suitable intermediate for the target compound **3** in that it may be elaborated to several of the important functionalities of **3**.

In particular the glycerol and acetal moieties could be derived from this disaccharide **8**. We reasoned that oxidative cleavage of the C2–C3 bond of the lyxose unit in **8** and reduction of the product would lead to diol **7** in which the C3, C4, and C5 of the lyxose unit corresponds to the C1, C2, and C3, respectively, of the glycerol and the C1 of the lyxose would now be converted to the acetal center with a 2-carbon aliphatic chain. We hoped that the acetal stereochemistry would be controlled by the C2 protecting group in the lyxose donor during glycosidation reaction. So out of three existing stereocenters of the lyxose donor we would exploit two, one for retaining the glycerol stereochemistry and the other to influence the glycosidation. The disaccharide **8** would be obtained from the two monosaccharides, a lyxose donor **9** and a galactose acceptor **10**. After protecting the hydroxyl group of the glycerol in **7**, the required 16-carbon aliphatic chain would be stitched to the existing aliphatic chain possibly by doing aldehyde chemistry or by alkene chemistry. Conversion of the resulting 18-carbon chain to the saturated aliphatic chain and global deprotection would then furnish the desired final product **3**.

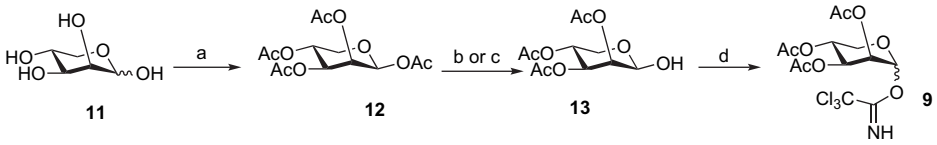
Our synthesis began with the preparation of D-lyxose trichloroacetimidate donor **9**[9] from commercially available D-lyxose. Acetylation of **11** followed by regioselective deacetylation of the anomeric acetate using hydrazinium acetate produced the lactol **13** in 64% yield. The yield improved slightly by using benzyl amine in THF.[10] The trichloroacetimidation of lactol **13** smoothly furnished the trichloroacetimidate **9** as a mixture of two anomers in 82% yield (Scheme 2).

The synthesis of galactose acceptor **10** started from peracetylated galactose **14**, which was glycosylated with benzyl alcohol under BF_3-etherate catalysis to give β-glycoside **15** in 75% yield.[11] Deacetylation using $NaOCH_3$ followed by selective protection of the primary OH with TIPS gave compound **17**.[12] Benzyl protection of remaining OH groups of **17** followed by the removal of silyl protection furnished the desired galactose derivative **10** in very good overall yield (Scheme 3).

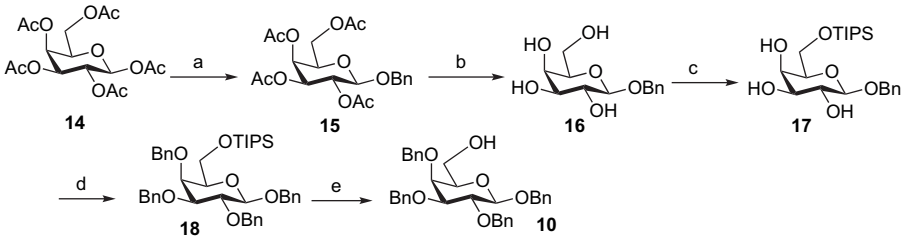
With both the coupling partners in hand, we were ready for the key glycosidation step. Condensation of lyxose trichloroacetimidate donor **9** and galactose acceptor **10** in the presence of catalytic amount of TMSOTf produced exclusively α-glycoside **19** in 86%



Scheme 1. Retrosynthetic analysis of *S*-glycero-*S*-plasmalgalactose.



Scheme 2. Synthesis of lyxose donor **9**. Reagents and conditions: (a) Ac_2O, DMAP, EtOAC; (b) $NH_2NH_2{\cdot}HOAc$, DMF, 2 h, 64%; (c) benzyl amine, THF, 72%; (d) CCl_3CN, DCM, 2 h, 82%.



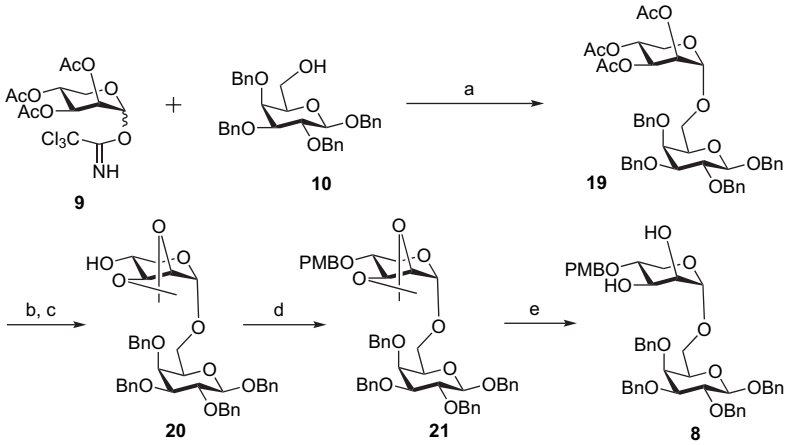
Scheme 3. Synthesis of galactose acceptor **10**. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, BnOH, DCM, −78 °C, 75%; (b) $NaOCH_3$, MeOH; (c) TIPSCl, imidazole, DMF, 87%; (d) NaH, BnBr, DMF, TBAI, 76%; (e) TBAF, THF, 92%.

yield.[13] The protecting group manipulation started with deprotection of acetates groups in **19**, followed by regioselective formation of the lyxose C2–C3 acetonide **20** by exploiting the cis relationship between these OH groups. The free C4 hydroxyl group in lyxose unit of **20** was then protected as PMB ether to produce **21** in very high overall yield. The deblocking of acetonide using 9:1 AcOH/H_2O furnished the desired diol **8** in 83% yield (Scheme 4).

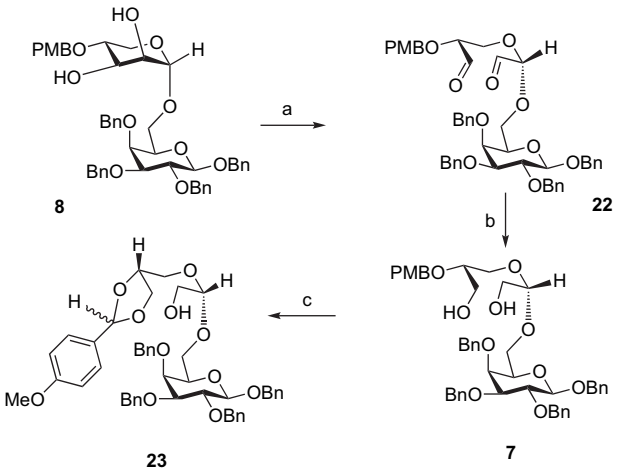
With the desired diol **8** in hand, the next key step was oxidative cleavage of the C2–C3 bond of the lyxose unit of **8**. Sodium metaperiodate has been an attractive and popular reagent for the oxidative cleavage of vicinal diols into dicarbonyls. Use of silica gel supported sodium metaperiodate[14] in oxidative cleavage has many advantages such as running the reaction in dichloromethane and without the need of purification. When the diol **8** was subjected to the oxidative cleavage using silica gel supported metaperiodate, dialdehyde **22** was obtained in quantitative yield. The dialdehyde **22** was then immediately reduced with $NaBH_4$ to furnish the diol **7** in 90% yield over two steps (Scheme 4). The neutral conditions employed in oxidative cleavage and subsequent reactions ensured that there was no epimerization at the acetal center evident from the proton and carbon NMR.

The key intermediate compound **7** has now all the important functionalities of the target molecule **3**. It has the required acetal stereocenter along with 2-carbon aliphatic chain and the glycerol moiety with correct C2 stereochemistry. The primary OH of glycerol unit of **7** was then protected as *p*-methoxy benzylidene[15] by treatment with DDQ in presence of molecular sieves. This reaction afforded the desired product **23** as a mixture of two diastereomers (formed due to the attack of glycerol primary OH from two faces of the carbocation at the benzylic carbon) in 72% yield (Scheme 5).

Our next objective was the elongation of the 2-carbon acetal chain, which was unveiled by the periodate cleavage to the18-carbon aliphatic chain of the natural product. Olefin metathesis[16] and Wittig reactions are the two options we employed. The required aldehyde **6** was prepared using Dess–Martin reagent[17] where primary alcohol **23** was oxidized to aldehyde **6** in quantitative yield. The choice of Dess–Martin reagent as oxidizing reagent is particularly important to ensure that no epimerization occurred at the acetal center during oxidation. For the olefin cross-metathesis, the required terminal alkene **5** can be prepared by two methods. In the first method, Tebbe olefination[18] produced the required terminal olefin **5** in a modest 30% yield. In the second



Scheme 4. Preparation of key intermediate compound-diol **8**. Reagents and conditions: (a) TMSOTf, 4 Å molecular sieves, DCM, 82%; (b) NaOMe, MeOH, 94%; (c) DMP, *p*-TsOH, acetone, 97%; (d) PMBCl, NaH, DMF, 94%; (e) AcOH/H_2O (9:1), 60 °C, 90%.



Scheme 5. Oxidative cleavage followed by reduction and protection. Reagents and conditions: (a) silica gel supported $NaIO_4$, DCM, 2 h, quant; (b) $NaBH_4$, MeOH, quant; (c) DDQ, DCM, 4 Å molecular sieves, 72%.

method, exposing the aldehyde **6** to heterogeneous Wittig reaction[19] with PPh_3MeBr using K_2CO_3 as base with a crown ether phase transfer catalyst, the terminal olefin **5** was obtained in 75% yield. The terminal olefin **5** was subjected to cross-metathesis with 1-heptadecene to produce the internal alkene **25** as a mixture of isomers in 78% yield. Encouraged by the simplicity and cleanliness of the heterogeneous Wittig reaction, we then prepared the 17-carbon phosphonium salt **24** following the literature method.[20] When aldehyde **6** was subjected to the heterogeneous Wittig protocol using phosphonium salt **24**, compound **25** was obtained as a mixture of isomers in 75% yield (Scheme 6).

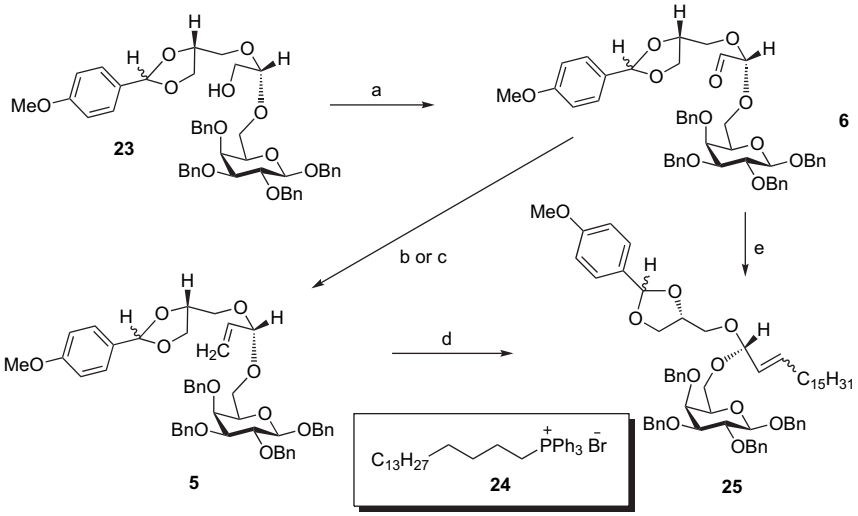
The reduction of the internal double bond of **25** was achieved by hydrogenation using Wilkinson's catalyst[21,22] to produce compound **4** in quantitative yield (Scheme 7).

For global deprotection of **25** to produce the target compound **3**, we subjected **25** to hydrogenolysis and hydrogenation using $Pd(OH)_2$ as catalyst. Although our attempt to get a pure analytical sample of the product was unsuccessful, the mass spectra confirmed the presence of product **3** (Scheme 8).

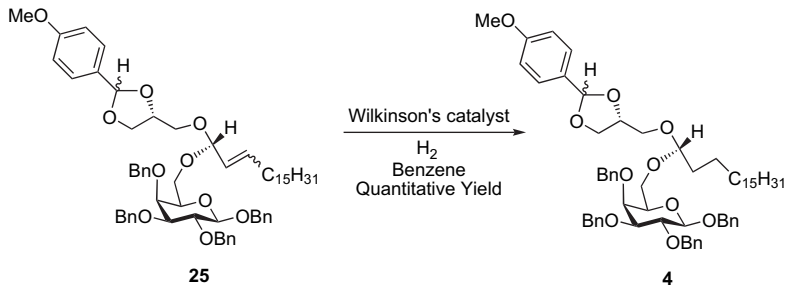
We have completed a building block that can, in principle, be used for the total synthesis of glyceroplasmalopsychosine. We note that the mixed acetal is very sensitive in our hands and may not survive the conditions required for completion of the synthesis (deprotection, activation of the anomeric hydroxyl, and glycosyl transfer to a sphingosine). Thus, a modified plan, which places a removable electron-withdrawing group adjacent to the acetal center to stabilize it until every segment of the final product is assembled has become our preferred route.

3. Conclusion

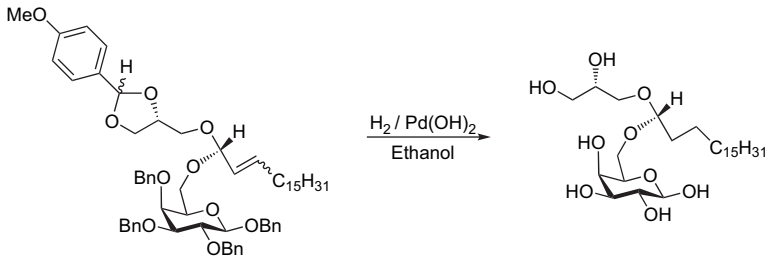
In conclusion, we have synthesized the mixed acetal segment of glyceroplasmalopsychosine in a stereospecific manner. All the key reactions including glycosidation, oxidative cleavage, oxidation, metathesis, and heterogeneous Wittig reaction took place in very



Scheme 6. Preparation of internal alkene **25**. Reagents and conditions: (a) Dess–Martin periodinane, DCM, 1 h, quant; (b) Tebbe reagent, 0.5 M in toluene, THF, pyridine, 30%; (c) PPh_3MeBr, K_2CO_3, alumina, crown-6, THF, 70 °C, 1 h, 75%; (d) 1-heptadecene, second generation Grubbs catalyst, DCM, 78%; (e) **24**, K_2CO_3, alumina, crown-6, THF, 70 °C, 1 h, 75%.



Scheme 7. Preparation of mixed acetal **4**.



Scheme 8. Attempted synthesis of the final product **3**.

good yield ensuring that the product is a pure material of known configuration with respect to the acetal stereocenter.

4. Experimental

4.1. General information

NMR spectra were recorded at 300 MHz or 500 MHz (^{1}H) and 75 MHz or 125 MHz (^{13}C) in deuterated solvent. The assignment of proton and carbon NMR peaks was supported by routine COSY and for some cases by NOESY spectra. All air-moisture sensitive reactions were performed under a positive pressure of dry nitrogen. All solvents and reagents were purified prior to use according to standard laboratory procedures. Low temperatures were recorded as bath temperatures. Thin layer chromatography analyses were carried out on precoated aluminum sheets of silica gel 60 F_{254}. UV light and vanillin, potassium permanganate or phosphomolybdic acid spray was used to visualize the components on the TLC plates. Flash column chromatography was carried out with silica gel 60 (230–400 mesh), using ACS reagent grade petroleum ether, ethyl acetate, methylene chloride, hexane, chloroform, and ethyl ether.

4.1.1. 1,2,3,4-Tetra-O-benzyl-6-O-(2,3,4-tri-O-acetyl-α-D-lyxopyranosyl)-β-D-galactopyranoside: ***19***

2,3,4-Tri-*O*-acetyl-D-lyxopyranosyl trichloroacetimidate **9** (0.56 g, 1.35 mmol) and 1,2,3,4-tetra-*O*-benzyl-β-D-galactopyranoside **10** (0.69 g, 1.3 mmol) were dried together under high vacuum for 2 h. To the flask containing the donor, acceptor, and some 4 Å molecular sieves, 15 mL anhydrous DCM was added and the resulting mixture was stirred for 1 h. TMSOTf (5 μL, 0.02 mmol) was added dropwise at −25 °C with N_2 protection. The reaction mixture was stirred for 3 h, during which time the temperature was gradually warmed to ambient temperature. Then the mixture was neutralized with Et_3N and filtered, concentrated to dryness to afford the crude disaccharide, which was subjected to silica gel chromatography (1:5 ethyl acetate/petroleum ether) to yield 716 mg product **19** as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.34 (m, 20H), 5.38 (dd, *J*=9.8, 3.4 Hz, 1H), 5.25 (m, 1H), 5.20 (m, 1H), 5.0 (m, 3H), 4.89–4.80 (m, 3H), 4.7 (dd, *J*=18.1, 12.0 Hz, 2H), 4.55 (d, *J*=9.7 Hz, 1H), 4.53 (d, *J*=1.8 Hz, 1H), 3.99–3.89 (m, 3H), 3.87 (d, *J*=2.5 Hz, 1H), 3.76 (m, 1H), 3.62 (dd, *J*=9.7, 2.8 Hz), 3.58 (m, 1H), 3.40 (dd, *J*=9.5, 5.6 Hz, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.9 (2), 169.8, 138.8, 138.6, 138.5, 137.6, 129.1, 128.6, 128.5 (2), 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 102.8, 97.4, 82.6, 79.7, 75.4, 74.6, 73.8, 73.7, 73.3, 71.1, 69.7, 68.8, 67.1, 66.9, 60.0, 21, 20.9 (2). HRMS calcd for $C_{45}H_{50}NaO_{13}$ [M^++Na] 821.3149, found 821.3109.

4.1.2. 1,2,3,4-Tetra-O-benzyl-6-O-(α-D-lyxopyranosyl)-β-D-galactopyranoside

To a stirred solution of **19** (1.15 g, 1.44 mmol) in 90 mL of anhydrous methanol was added 1.2 mL of 0.5 M $NaOCH_3$ solution. The reaction mixture was stirred for 12 h and then neutralized with 1 N HCl. Removal of the solvent afforded the crude product, which was purified by flash column chromatography (EtOAc) to give the pure product (908 mg, 94% yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.25 (m, 20H), 4.95 (m, 3H), 4.82–4.72 (m, 3H), 4.65 (t, *J*=11.5 Hz, 2H), 4.46 (m, 2H), 3.91 (t, *J*=9 Hz, 1H), 3.82–3.80 (m, 3H), 3.73 (m, 2H), 3.64 (br s, 1H), 3.54 (m, 3H), 3.49–3.46 (m, 1H), 2.45 (d, *J*=5 Hz, 1H), 2.13 (d, *J*=3.5 Hz, 1H), 2.07 (d, *J*=3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.8, 138.6, 137.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 103.0, 100.2, 82.6, 79.8, 75.4, 74.5, 73.7, 73.2, 72.0, 71.2, 70.5, 68.0, 66.7, 63.1. HRMS calcd for $C_{39}H_{44}NaO_{10}$ [M^++Na] 695.2832, found 695.2771.

4.1.3. 1,2,3,4-Tetra-O-benzyl-6-O-(2,3-O-isopropylidene-α-D-lyxopyranosyl)-β-D-galactopyranoside: ***20***

To a stirred suspension of above compound (1 g, 1.48 mmol) in 15 mL of acetone was added 4.5 mL of dimethoxypropane and 50 mg of *p*-toluenesulfonic acid. After 12 h, at room temperature 60 mL of 1:1 hexane–diethyl ether was added, and the solution was washed once with aqueous sodium bicarbonate solution and twice with water, and concentrated in vacuo. The resulting material was chromatographed (1:1 ethyl acetate/petroleum ether) over silica gel to yield colorless oil (1.02 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.33 (m, 20H), 5.04–4.9 (m, 3H), 4.86–4.69 (m, 5H), 4.63 (d, *J*=2.4 Hz, 1H), 4.5 (d, *J*=7.7 Hz, 1H), 4.25 (m, 1H), 4.03 (m, 2H), 3.97 (dd, *J*=9.7, 7.7 Hz, 1H), 3.90 (dd, *J*=11.5, 3.7 Hz, 1H), 3.86–3.82 (m, 2H), 3.78 (dd, *J*=11.3, 4.6 Hz, 1H), 3.57 (dd, *J*=9.8, 2.8 Hz, 1H), 3.54 (m, 1H), 3.44 (dd, *J*=9.5, 6.0 Hz, 1H), 3.18 (d, *J*=8.4 Hz, 1H), 1.54 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.8, 138.6, 138.5, 137.8, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 109.6, 102.9, 98.7, 82.5, 79.8, 76.1, 75.4, 74.5, 74.3, 73.6, 73.3, 71.1, 67.5, 67.2, 63.5, 27.6, 25.7. HRMS calcd for $C_{42}H_{48}NaO_{10}$ [M^++Na] 735.3145.35, found 735.3156.

4.1.4. 1,2,3,4-Tetra-O-benzyl-6-O-(2,3-O-isopropylidene-4-O-PMB-α-D-lyxopyranosyl)-β-D-galactopyranoside: ***21***

Compound **20** (1.0 g, 1.4 mmol) was azeotroped with toluene (3×10 mL), dried under vacuum for 1 h, and dissolved in DMF (8 mL). The solution was cooled to 0 °C, sodium hydride (112 mg, 2.8 mmol, 60% dispersion in mineral oil) was added, and the reaction mixture was stirred for 1 h. After addition of PMBCl (0.43 g, 2.8 mmol), the solution was warmed to room temperature and stirred for 12 h. the reaction was quenched by the dropwise addition of water. The aqueous layer was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash silica gel chromatography (1:4 EtOAc/petroleum ether) afforded the pure product **21** (1.09 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–5.32 (m, 22H), 6.9 (m, 2H), 5.04–4.99 (m, 3H), 4.87–4.60 (m, 8H), 4.53 (d, *J*=7.7 Hz, 1H), 4.23 (t, *J*=5.7 Hz, 1H), 3.98 (dd, *J*=9.7, 7.7 Hz, 1H), 3.94–3.91 (m, 2H), 3.89 (dd, *J*=8.0, 4.3 Hz, 1H), 3.8 (s, 3H), 3.66–3.58 (m, 4H), 3.56–3.50 (m, 2H), 1.56 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.5, 138.9, 138.7, 137.8, 130.5,

129.5, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 114.0, 109.3, 103.0, 98.5, 82.7, 79.9, 75.5, 75.4, 74.5, 74.4, 73.6, 73.4, 73.2, 71.9, 71.1, 66.4, 59.7, 55.5, 28.3, 26.6. HRMS calcd for $C_{50}H_{56}NaO_{11}$ [M^++Na] 855.3720, found 855.3731.

4.1.5. 1,2,3,4-Tetra-O-benzyl-6-O-(4-O-PMB-α-D-lyxopyranosyl)-β-D-galactopyranoside: ***8***

A solution of **21** (1.1 g, 1.32 mmol) in AcOH/H_2O (10:1, 20 mL) was heated to 60 °C for 1.5 h. The reaction was cooled to room temperature and then concentrated to give a white solid, which was purified by silica gel chromatography (3:2 EtOAc/petroleum ether) to furnish the pure product **22** (940 mg, 90%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.25 (m, 22H), 6.88 (m, 2H), 5.01–4.97 (m, 3H), 4.85–4.76 (m, 3H), 4.70 (d, J=11.90 Hz, 1H), 4.66 (d, J=12.1 Hz, 1H), 4.60–4.53 (m, 2H), 4.50 (m, 1H), 3.95 (dd, J=9.7, 7.9 Hz, 1H), 3.87–3.82 (m, 2H), 3.69 (m, 1H), 3.57 (m, 2H), 3.47 (m, 2H), 2.58 (d, 1H), 2.39 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.6, 138.9, 138.6, 137.7, 130.3, 129.5, 128.6, 128.5, 128.4 (2), 128.3 (2), 128.1, 127.8, 127.7, 127.6, 114.2, 103.0, 99.7, 82.7, 79.9, 75.4, 75.2, 74.5, 73.7, 73.5, 73.3, 72.4, 71.1, 70.7, 70.4, 66.6, 61.1, 55.5. HRMS calcd for $C_{47}H_{52}NaO_{11}$ [M^++Na] 815.3407, found 815.3378.

4.2. Procedure for glycol cleavage oxidation

To a vigorously stirred suspension of silica gel supported reagent (2.0 g) in DCM (5 mL) in a 25 mL round-bottomed flask was added a solution of the vicinal diol (1 mmol) in DCM (5 mL). The reaction was monitored by TLC until disappearance of the starting material (generally 2–3 h). The mixture was filtered through a sintered glass funnel and the silica gel was thoroughly washed with chloroform (3×10 mL). Removal of the solvent from the filtrate afforded the aldehyde that was pure enough for the following step.

4.3. $NaBH_4$ reduction

The resulting aldehyde from the oxidative cleavage was dissolved in dry MeOH (5 mL/mmol of aldehyde). To the cooled solution (0 °C) of the aldehyde in MeOH, $NaBH_4$ (excess) was added and the reaction mixture was allowed to attain room temperature slowly. The mixture was stirred overnight and was diluted with H_2O. The reaction mixture was extracted with chloroform and the organic layer was washed with water. The combined organic phases dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash silica gel chromatography afforded the pure product.

4.4. Diol 7 (prepared from oxidative cleavage of 8 followed by reduction)

The oxidative cleavage of **8** afforded the crude aldehyde **22**, which was immediately reduced with $NaBH_4$ to afford the diol **6** (from 500 mg of **8** yield 451 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.27 (m, 22H), 6.90 (m, 2H), 5.0–4.93 (m, 3H), 4.84–4.75 (m, 3H), 4.66 (d, J=11.9 Hz, 2H), 4.59 (m, 2H), 4.52 (d, J=7.7 Hz, 1H), 4.49 (m, 1H), 3.94 (dd, J=9.7, 7.7 Hz, 1H), 3.87 (dd, J=9.8, 6.4 Hz, 1H), 3.81 (m, 6H), 3.66–3.62 (m, 3H), 3.55–3.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.6, 138.8, 138.6, 137.7, 130.1, 129.6, 128.5, 128.4 (2), 128.3, 128.1, 127.8, 127.7, 127.6, 114.2, 103.2, 102.9, 83.9, 82.6, 82.2, 79.8, 77.8, 75.5, 74.6, 73.8, 73.6, 72.1, 71.4, 66.2, 66.1, 62.3, 62.1, 55.5. HRMS calcd for $C_{47}H_{54}NaO_{11}$ [M^++Na] 817.3564, found 817.3544.

4.5. *p*-Methoxy benzylidene derivative: 23

Molecular sieves (3 g) were finely ground and suspended in dichloromethane (15 mL). Compound **7** (1.11 g, 1.4 mmol) in dichloromethane (15 mL) was added and the mixture was cooled to 0 °C. DDQ (0.35 g, 1.55 mmol) in THF (3 mL) was added slowly. The mixture was stirred for 3 h and filtered over Celite and concentrated under reduced pressure. The residue was chromatographed (3:2 ethyl acetate/petroleum ether) to give the product **23** (798 mg, 72%) as colorless oil. ^{1}H NMR (500 MHz) δ: 7.45–7.29 (m, 22H), 6.92 (m, 2H), 5.8 (s, 1H), 5.03–4.95 (m, 3H), 4.85–4.75 (m, 3H), 4.69 (d, J=2.9 Hz, 1H), 4.65 (d, J=3.6 Hz, 1H), 4.54–4.51 (m, 2H), 4.39 (m, 1H), 4.09 (m, 1H), 3.94 (m, 2H), 3.89 (m, 1H), 3.81 (m, 3H), 3.67 (dd, J=10.4, 5.8 Hz, 1H), 3.57–3.52 (m, 4H), 3.46 (dd, J=9.9, 5.6 Hz, 1H), 2.35 (t, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.1, 139.1, 139.0, 138.9, 138.0, 129.5, 129.3, 129.2, 129.0 (2), 128.9 (2), 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 114.4, 105.0, 104.3, 103.5, 82.8, 80.1, 75.9, 75.7, 74.8, 73.9, 73.8, 73.7, 71.7, 68.6, 68.0, 66.2, 66.1, 62.5, 55.8. HRMS calcd for $C_{47}H_{52}NaO_{11}$ [M^++Na] 815.3407, found 815.3360.

4.6. Dess–Martin oxidation

Dess–Martin periodinane (1.3 equiv) was added to a solution of alcohol in DCM (4 mL/0.2 mmol of alcohol) under nitrogen. The reaction mixture was stirred at room temperature for 1 h, to generate a milky suspension. When all starting materials were consumed, a 10% solution of sodium hydrosulfite in a solution of saturated aqueous $NaHCO_3$ was added slowly to suspensions and stirred until two separate layer formed. The aqueous layer was extracted with DCM (3×10 mL). The combined organic phases were dried over $NaSO_4$, filtered, and concentrated to give the crude aldehyde **6** as a colorless oil, which was used for the next step without further purification.

4.7. Procedure for heterogeneous Wittig reaction

Alkylphosphonium salt (1.2 equiv) was ground with anhydrous oven dried K_2CO_3 (1.2 equiv) and basic alumina. THF (10 mL/mmol of aldehyde) was added to the flask followed by the solution of aldehyde in THF (10 mL/mmol) and some crystals of crown-6 ether. The color of the mixture turned yellow immediately after the addition of the aldehyde, which was refluxed at 70 °C for 1–2 h. After all the starting materials were consumed, the reaction mixture was allowed to come to the room temperature. The solids were filtered and washed with THF. The combined solvents were concentrated and the residue was subjected to chromatography to produce the pure product in good yield.

The alkene **25** was prepared by heterogeneous Wittig reaction given above in 70% yield calculated from the crude aldehyde **6** (from 60 mg of aldehyde **6**: yield 53 mg, 70%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.24 (m, 22H), 6.85 (m, 2H), 5.76 (s, 1H), 5.68 (m, 1H), 5.43 (m, 1H), 5.25 (m, 1H), 5.0–4.94 (m, 3H), 4.79–4.73 (m, 3H), 4.65 (m, 2H), 4.48 (m, 1H), 4.34 (m, 1H), 4.06 (m, 1H), 3.94–3.88 (m, 2H), 3.8 (m, 1H), 3.77 (s, 3H), 3.68 (m, 1H), 3.54 (m, 3H), 2.10 (m, 2H), 1.25 (aliphatic chain), 0.87 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.1, 139.1, 138.7, 138.6, 137.8, 136.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 126.6, 114.3, 104.8, 103.4, 99.1, 82.8, 80.1, 75.8, 75.3, 75.1, 74.7, 73.6, 73.3, 71.1, 68.3, 68.1, 65.8, 65.2, 65.0, 55.5, 32.5, 30.3, 29.9, 29.6, 28.5, 23.0, 14.7. HRMS calcd for $C_{63}H_{86}NO_{10}$ [M^++NH_4^+] 1016.6252, found 1016.6248.

4.8. Wilkinson's hydrogenation product, mixed acetal: 4

To the solution of alkene **25** (20 mg, 0.015 mmol) in 1 mL of anhydrous benzene was added Wilkinson's catalyst (15 mg). The resulting mixture was stirred overnight under an atmosphere of H_2 (balloon) after which the solution was evaporated to dryness in vacuo. The residue was purified by column chromatography (10: 1, PE/EtOAc) to afford the pure product (15 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 22H), 6.89 (m, 2H), 5.77 (s, 1H), 5.02–4.94 (m, 3H), 4.81–4.73 (m, 3H), 4.67–4.62 (m, 2H), 4.51–4.43 (m, 2H), 4.36 (t, 1H), 4.07 (m, 1H), 3.95–3.90 (m, 2H), 3.87 (m, 1H), 3.82–3.78 (m, 4H),

3.68–3.61 (m, 1H), 3.56–3.49 (m, 3H), 1.56 (m, 2H), 1.27 (aliphatic chain), 0.91 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.1, 139.3, 139.1, 138.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 114.3, 104.9, 104.2, 103.5, 82.9, 80.2, 75.8, 75.3, 75.4, 74.9, 74.2, 74.1, 74.0, 73.9, 73.7, 71.5, 68.6, 68.4, 66.5, 65.8, 65.7, 55.8, 33.7, 32.5, 30.3, 30.2, 30.0, 29.9, 25.2, 23.3, 14.7. HRMS calcd for $C_{63}H_{88}NO_{10}$ [M^++NH_4^+] 1018.6408, found 1018.6401.

Acknowledgements

The research was supported by NIH grant GM60271 to CUNY. The Hunter Chemistry Department infrastructure is supported by RCMI NIH RR03037.

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