# InCl<sub>3</sub>-Catalyzed Rapid 1,3-Alkoxy Migration in Glycal Ethers: Stereoselective Synthesis of Unsaturated $\alpha$ -O-Glycosides and an $\alpha$ , $\alpha$ -(1 $\rightarrow$ 1)-Linked Disaccharide

Paramathevar Nagaraj<sup>[a]</sup> and Namakkal G. Ramesh\*<sup>[a]</sup>

Dedicated to Dr. Antonius J. H. Klunder

Keywords: Carbohydrates / Glycosylation / Lewis acids / Glycosides / Disaccharides

InCl<sub>3</sub> catalyzes a facile stereoselective 1,3-migration of allylic ethers of glycals to afford 2-*C*-methylene- and 2,3-unsaturated- $\alpha$ -O-glycosides in high yields. The reaction is rapid (10 min), requires only 20 mol-% of the catalyst, and is compatible with acid-labile functional groups such as epoxides and acetals. This methodology provides a convenient alter-

native to the Ferrier rearrangement. A direct synthesis of an  $\alpha, \alpha$ -(1 $\rightarrow$ 1)-linked disaccharide derivative by a domino process is also reported.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

#### Introduction

The rapidly growing interest in understanding the role of oligosaccharides in various biological processes, coupled with the formidable task of isolating them from natural sources, provide organic chemists with tremendous scope for the development of new and efficient strategies for stereoselective construction of glycosidic linkages.<sup>[1]</sup> Furthermore, glycosides possessing additional synthetically maneuverable functionalities offer added advantages and allow easy access to more complex molecules. In this context, 2,3-unsaturated glycosides have enjoyed widespread applications in organic synthesis for the last four decades, as their unsaturation allowed the introduction of a variety of functionalities.<sup>[2]</sup> In recent years, 2-C-methylene glycosides, a class of unsaturated glycosides with an exo-methylene group at C2, have gained immense importance as versatile intermediates in the synthesis of natural products and biologically important compounds such as restricticin,<sup>[3]</sup> cyclophellitol,<sup>[4]</sup> C-disaccharides,<sup>[5]</sup> carbohydrates from polyenes,<sup>[6]</sup> and ara-cyclohexenyl-adenine.<sup>[7]</sup> 2-C-Methylene hydroperoxides synthesized from 2-C-methylene glycosides have been used as chiral catalysts for enantioselective epoxidation reactions.<sup>[8]</sup> The 2-C-methylene group is also a key structural feature of molecules involved in mechanism-

Fax: +91-11-26582037

based inactivation of ribonucleotide diphosphate reductase.  $\ensuremath{^{[9]}}$ 

Conventionally, 2-C-methylene glycosides 2 are accessed through Wittig reactions of the corresponding 2-keto glycosides 1 [Equation (1)].<sup>[3,4,7,10]</sup> In certain cases it has been reported that the Wittig reaction is very sensitive to the conditions employed.<sup>[3,4]</sup> An alternative and simple approach to 2-C-methylene glycosides 2 using a "New Ferrier system" first developed by Balasubramanian et al.<sup>[11]</sup> and subsequently exploited by others<sup>[12-14]</sup> generally involves an acid-catalyzed (Lewis or Brønsted) substitution with allylic rearrangement of 2-C-acetoxymethyl glycals 3 [Equation (2)] or 2-C-(propargyloxymethyl)-glycals. Some of these methodologies suffer from certain disadvantages such as substrate instability,<sup>[15,16]</sup> longer reaction times (1-16 h), lack of stereoselectivity in some examples, and requirement for stoichiometric or even larger amounts of catalysts. During the course of our research on 2-C-substituted sugars, we encountered a facile route to the synthesis of 2-C-methylene glycosides through InCl<sub>3</sub>-catalyzed 1,3-alkoxy migration in glycal ethers, which we report here. The reaction is general, rapid, stereoselective, yielding only the  $\alpha$ -anomers, and also compatible with acid-labile groups such as epoxides and acetals. A novel InCl<sub>3</sub>-catalyzed one-pot stereoselective synthesis of an  $\alpha, \alpha$ -(1 $\rightarrow$ 1)-linked disaccharide has also been accomplished.

#### **Results and Discussion**

In the last decade, InCl<sub>3</sub> has found wide application as a mild Lewis acid in organic chemistry.<sup>[17]</sup> In carbohydrate

WILEY

 <sup>[</sup>a] Department of Chemistry, Indian Institute of Technology – Delhi, Hauz Khas, New Delhi 110016, India

E-mail: ramesh@chemistry.iitd.ac.in

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



chemistry, it is mainly used as a catalyst for glycosylation reactions through the coupling of glycosyl donors with a variety of nucleophiles,<sup>[12,18]</sup> and its use in a 1,3-migration reaction, to the best of our knowledge, has not been reported so far. With this background, we investigated the reaction between 3,4,6-tri-O-benzyl-2-C-methoxymethyl galactal 6a and InCl<sub>3</sub> (Scheme 1). When compound 6a was initially exposed to 50 mol-% of anhydrous InCl<sub>3</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at room temperature, we were pleasantly surprised to observe that the starting material was completely consumed within 10 min and that the reaction afforded an 88% yield of a single product that was characterized as methyl 2-C-methylene- $\alpha$ -O-glycoside 8a. Subsequently, after few experiments, we observed that just 20 mol-% of InCl<sub>3</sub> was sufficient to bring about this reaction without any change in the reaction time, yield, or stereoselectivity. The  $\alpha$ -anomeric stereochemistry was confirmed by detailed <sup>1</sup>H NMR NOE studies.[19]



Scheme 1. InCl<sub>3</sub>-catalyzed 1,3-migration of ether 6a.

The facile nature of the reaction prompted us to investigate the efficiency of various Lewis acids in effecting this reaction. From Table 1, it is quite clear that while this reaction has been achieved with a variety of Lewis acids – such as anhydrous BiCl<sub>3</sub>, ZnCl<sub>2</sub>, and CAN, etc. – InCl<sub>3</sub> was the best among them in terms of yield. Interestingly, with BF<sub>3</sub>·Et<sub>2</sub>O, a more popular and more commonly used Lewis acid, only a complex mixture was obtained. Furthermore, use of CH<sub>3</sub>CN instead of CH<sub>2</sub>Cl<sub>2</sub> as a solvent, while equally

Table 1. Effect of Lewis acids on [1,3]-migration in ether **6a** to afford the 2-*C*-methylene glycoside **8a**.

Entry	Lewis acid	mol-%	Time (min)	Yield (%)[a]
1	InCl <sub>3</sub>	20	10	88
2	$ZnCl_2$	20	10	73
3	CAN <sup>[b]</sup>	20	10	69
4	BiCl <sub>3</sub>	20	10	63
5	BF <sub>3</sub> ·Et <sub>2</sub> O	20	10	complex mixture

[a] Isolated yield after column chromatography. [b] Ceric ammonium nitrate.

effecting the InCl<sub>3</sub>-mediated transformation in 10 min, resulted, however, in a lower yield of the product (68%).

Intrigued by the simplicity and success, we prepared several hitherto unknown glycal ethers<sup>[20,21]</sup> possessing diverse functional groups (**6a–g**, **7a–c**) from the corresponding alcohols **4** and **5**,<sup>[22]</sup> and the InCl<sub>3</sub>-mediated 1,3-migration reaction was tested on them (Scheme 2, Table 2). In all cases the allylic rearrangement occurred rapidly with just 20 mol-% of anhydrous InCl<sub>3</sub>, affording the corresponding 2-*C*-methylene glycosides (**8a–g**, **9a–c**) exclusively as their  $\alpha$ -anomers in high yields. The reaction works with equal ease in both the galactal (Entries 1–7; Table 2) and the glucal series (Entries 8–10; Table 2). Comparison of a few ex-

Table 2. Synthesis of glycal ethers 6 and 7 and their allylic rearrangement catalyzed by  $InCl_3$ .

Entry	R-OH	Time	Ether	R <sup>3</sup>	Yield <sup>[a]</sup>	Glycoside <sup>[b]</sup>	Cat.[c]	Yield <sup>[a]</sup>
		(h)			(%)			(%)
1	4	4	6a	$CH_3$	77	8a <sup>[d]</sup>	InCl <sub>3</sub>	88
							ZnCl <sub>2</sub>	73
2	4	4	6b	$CH_2CH_3$	70	8b <sup>[d]</sup>	InCl <sub>3</sub>	89
3	4	5	6c	CH <sub>2</sub> CH=CH <sub>2</sub>	70	8c	InCl <sub>3</sub>	73
							ZnCl <sub>2</sub>	60
4	4	4	6d	$CH_2 - C \equiv CH$	73	8d	InCl <sub>3</sub>	83
5	4	8	6e	CH <sub>2</sub> CH(OCH <sub>3</sub> )	257	8e	InCl <sub>3</sub>	64
6	4	10	6f <sup>[e]</sup>	CH <sub>2</sub> -CH-CH <sub>2</sub>	70	8f <sup>[c]</sup>	InCl <sub>3</sub>	70
				- <sub>2</sub> /- 0			ZnCl <sub>2</sub> <sup>[f]</sup>	-
7	4	4	6g	CH <sub>2</sub> Ph	74	$8g^{[d]}$	InCl <sub>3</sub>	91
			-				$ZnCl_2$	78
8	5	4	7a	$CH_3$	55	9a <sup>[d]</sup>	InCl <sub>3</sub>	67
9	5	8	7b <sup>[e]</sup>	CH <sub>2</sub> -CH-CH <sub>2</sub>	56	9b <sup>[e]</sup>	InCl <sub>3</sub>	60
				- <sub>2</sub> / -			ZnCl <sub>2</sub> <sup>[f]</sup>	-
10	5	5	7c	CH <sub>2</sub> Ph	70	<b>9c</b> <sup>[d]</sup>	InCl <sub>3</sub>	72

[a] Isolated yields after column chromatography. [b] In all cases, only  $\alpha$ -anomer was obtained. [c] All the reactions were performed with 20 mol-% of anhydrous catalyst in dry CH<sub>2</sub>Cl<sub>2</sub> at room temperature over 10 min. [d] The spectroscopic data were consistent with the literature values<sup>[11,12,13,14]</sup>. [e] Racemic epichlorohydrin was used for the etherification, and the 1:1 diastereomeric mixtures of **6f** and **7b** were subjected to subsequent allylic rearrangement without separation. [f] A complex mixture was obtained.



Scheme 2. Synthesis of glycal ethers (6 and 7) and their InCl<sub>3</sub>-catalyzed allylic rearrangement.



amples carried out with 20 mol-% of anhydrous  $ZnCl_2$  displayed the catalytic superiority of  $InCl_3$  (Entries 1, 3, 6, 7, and 9; Table 2).

In order to demonstrate the functional group compatibility, ethers bearing acid-labile groups such as epoxides (**6f** and **7b**) and an acetal (**6e**) were synthesized and subjected to the InCl<sub>3</sub>-mediated reaction. Gratifyingly, the alkoxy migration reaction occurred very readily to afford the corresponding 2-*C*-methylene glycosides (**8f**, **9b**, and **8e**) in good yields and with the acid labile groups remaining intact. In view of the literature background that InCl<sub>3</sub> rapidly catalyzed the rearrangement of epoxides to carbonyl compounds,<sup>[23]</sup> the preference for the 1,3-migration reaction over the epoxide rearrangement in the case of compounds **6f** and **7b** merits special mention. It is noteworthy that ZnCl<sub>2</sub> failed to bring about the expected allylic rearrangements of compound **6f** and **7b**, resulting in complex mixtures.

A plausible mechanism for the 1,3-migration reaction with the observed  $\alpha$ -stereoselectivity is given in Scheme 3. Initial coordination of InCl<sub>3</sub> with the side-chain alkoxy group at C-2 of 6 (to afford intermediate I) followed by its departure would result in the formation of a highly stabilized anomeric carbocation **II**. It is likely that the anomeric carbocation II would be stabilized not only by the ring oxygen atom but also by the remote oxygen atom of the C-6benzyloxy group, thereby sterically blocking the  $\beta$ -face for attack of the departing alkoxy group and thus resulting in exclusive formation of  $\alpha$ -anomers. Stereoselective glycosylation reactions through the anchimeric assistance of remote acyl, ester, or carbamate groups are well documented in the literature.<sup>[24]</sup> It has also been reported that esters are better stereodirecting agents than alkoxy groups. However, most of these reports have dealt with saturated pyranosides, except for the one by Srivastava et al.,<sup>[24a]</sup> who observed such remote stereocontrol in an endocyclic unsaturated sugar. In the present case, in order to find out whether the exclusive formation of  $\alpha$ -anomers in all these examples is influenced by the remote stereocontrolling effect of the C-6 benzyloxy group, semiempirical AM1 calculations were performed with HyperChem.<sup>[25]</sup> First of all, AM1 calculations indicate that the preferred low-energy conformation of compound **6a** is  ${}^{5}H_{4}$  (with a minimum calculated energy of -7.0 kcal), in which the (pseudo)axial C-6 benzyloxy group positions itself close to the anomeric carbon, with a spatial distance of 2.91 Å between the C-6 benzyloxy oxygen atom and the anomeric carbon (Figure 1). In the carbocation II, this spatial distance decreases to 2.74 Å, presumably due to the interaction between the lone pair of electrons on the oxygen atom of the *C*-6 benzyloxy group and the positive charge at the anomeric carbon (Figure 1). Such an interaction would not only provide additional stability for II, but would also sterically block the  $\beta$ -face for attack of the nucleophile. On the other hand, the spatial distance between the oxygen atom of the *C*-3 benzyloxy group and the anomeric carbon increases from 3.28 Å in **6a** to 3.39 Å in carbocation II. Preliminary AM1 calculations are thus suggestive of a possible involvement of the *C*-6 benzyloxy group in stereodirecting the glycosylation step, resulting in exclusive formation of  $\alpha$ -anomers. However, detailed mechanistic investigations taking the effect of solvents, temperature, reagents,



 ${}^{5}H_{4}$  conformation of compound **6a** 



Figure 1. Low-energy conformations of compound 6a and carbocation II. Hydrogens are omitted for clarity.



Scheme 3. Putative mechanism for stereoselective formation of  $\alpha$ -glycosides 8 and 9.

### FULL PAPER

reaction conditions, etc. into account would need to be done to explain the observed stereoselectivity unambiguously.

A novel and interesting observation was the direct synthesis of an  $\alpha, \alpha$ -(1 $\rightarrow$ 1)-linked disaccharide 11 as a single diastereomer in 80% yield in just 10 min (Scheme 4) when alcohol 4 itself was exposed to a catalytic amount of anhydrous InCl<sub>3</sub>. The formation of the disaccharide was suggested by the absence of any OH stretching frequency in its IR spectrum, as well as the absence of any exchangeable proton in its <sup>1</sup>H NMR spectrum. This was further supported by the ESI HRMS data, which showed a peak at 879.3998 { $[M + Na]^+$ } due to the formation of the disaccharide. The  $C_2$  symmetry of the molecule was evidenced from its <sup>13</sup>C NMR spectrum, which displayed signals corresponding to only half the number of carbon atoms. The  $\alpha,\alpha$ -anomeric stereochemistry was confirmed by detailed <sup>1</sup>H NMR NOE studies. It is likely that the reaction proceeds through an initial [1,3]-migration of alcohol 4 to give the hemiacetal 10, which could not be isolated under the reaction conditions, followed by a rapid in situ glycosylation reaction resulting directly in the stereoselective formation of an  $\alpha, \alpha$ -(1 $\rightarrow$ 1)-linked disaccharide 11. To the best of our knowledge, formation of an  $\alpha, \alpha$ -(1 $\rightarrow$ 1)-linked disaccharide through such a domino process has no precedence. Given the biological significance of trehalose  $\{\alpha, \alpha - (1 \rightarrow 1) - 1\}$ glucoside} and its analogues,<sup>[26]</sup> the one-pot synthesis of compound 11 reported here assumes synthetic significance.



Scheme 4. Domino one-pot synthesis of disaccharide 11.

An earlier report by Descotes and Martin<sup>[27]</sup> on the BF<sub>3</sub>·Et<sub>2</sub>O-catalyzed rearrangement of 3,4,6-tri-O-benzyl-Dglucal 12 to the 2,3-unsaturated  $\alpha$ -benzyl glycoside 14 prompted us to examine this reaction with InCl<sub>3</sub> as a catalyst. As in our earlier cases, treatment of 12 with 20 mol-% of InCl<sub>3</sub> proceeded with equal feasibility to afford 14 in 64% yield, as an anomeric mixture in a 5:1 ratio.<sup>[28,29]</sup> InCl<sub>3</sub> also mediated a rapid transformation of 3,4,6-tri-O-benzyl-D-galactal 13 into the glycoside 15 as a single anomer in 77% yield (Scheme 5).<sup>[30]</sup> Interestingly, with ZnCl<sub>2</sub> as a catalyst, the above reactions again proved to be futile. It is worth mentioning that Ferrier rearrangements of protected galactals are not as easy reactions as those of protected glucals,<sup>[31]</sup> and the methodology reported here for the synthesis of 2,3-unsaturated galactoside through [1,3]-alkoxy migration should prove to be synthetically attractive.



Scheme 5. InCl<sub>3</sub>-catalyzed synthesis of 2,3-unsaturated glycosides 14 and 15.

#### Conclusions

In conclusion, we report a new strategy for the synthesis of relatively less well explored unsaturated glycosides – namely, 2-*C*-methylene glycosides – for which only a few methods are available in the literature. The reaction is highly stereoselective, affording only the  $\alpha$ -anomers in all cases. This methodology, while providing a convenient alternative to the Ferrier rearrangement, is also explicitly simple to perform. We have also demonstrated the synthesis of some unique 2-*C*-methyleneglycosides such as **8e**, **8f**, and **9b** that are not accessible by the existing methods. The stereoselective formation of the  $\alpha,\alpha-(1\rightarrow 1)$ -linked disaccharide derivative **11** in one-pot fashion is synthetically quite interesting and is likely to spur further interest in this area.

#### **Experimental Section**

General Considerations: All solvents were purified by standard procedures. Thin-layer chromatography (TLC) was performed on Merck silica gel pre-coated on aluminium plates. Flash column chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on an Autopol II or an Autopol V (Rudolph Research Flanders, New Jersey) instrument. All the rotations were measured at 589 nm (sodium D line). Melting points of the compounds are uncorrected. IR spectra were taken over the 4000– 400 cm<sup>-1</sup> range as KBr pellets on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model protégé 460). All the <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 300 MHz Bruker Spectrospin DPX FT-NMR spectrometer. Chemical shifts are reported as  $\delta$  values (ppm) relative to Me<sub>4</sub>Si as internal standard. Mass spectra were recorded with a Waters Micro Mass Q-TOF or an Applied Biosystems O-Star instrument.

**Typical Procedure for the Synthesis of Ethers 6 and 7:** Alcohol 4 or  $5^{[22]}$  (1.0 g, 2.2 mmol) was dissolved in dry DMF (5.0 mL), and the mixture was cooled to 0 °C. Sodium hydride (0.131 g, 3.3 mmol, 60% in paraffin oil) was added. After 5 min, alkyl halide (3.3 mmol) was added, and the reaction mixture was stirred at room temperature for the specified time. After completion, the reaction mixture was quenched with water and extracted with ethyl acetate (4×50 mL). The organic layer was washed with saturated sodium hydrogen carbonate solution, followed by water, and was then dried with sodium sulfate, filtered, and concentrated. Column chromatography of the crude reaction mixture with hexane/ethyl acetate (5:1) as an eluent afforded ethers 6 or 7, respectively.



1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-methoxymethyl-Dlyxo-hex-1-enitol (6a): Compound 6a (0.80 g, 77% yield) was obtained as a colorless liquid by treatment of glycal 4 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and methyl iodide (0.213 mL, 3.3 mmol) over 4 h.  $[a]_{D}^{28} = +11.5 (c = 0.33, \text{CHCl}_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.32–7.23 (m, aromatic, 15 H), 6.39 (s, 1 H, 1-H), 4.81 (d, J = 11.7 Hz, 1 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.64 (d, J = 11.4 Hz, 1 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.40 (d, J = 12.0 Hz, 1 H), 4.26 (m, 2 H), 4.14 (d, J = 11.1 Hz, 1 H), 3.96 (t, J = 3.3 Hz, 1 H), 3.80–3.78 (m, 1 H), 3.68 (dd, J = 10.5, 4.2 Hz, 1 H), 3.59 (d, J = 10.5 Hz, 1 H), 3.23 (s, 3 H, OCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.8 (C-1), 138.4, 138.0, 137.9, 137.7, 128.7, 128.4, 127.8, 127.7, 127.6, 127.4, 127.3 (Caryl), 109.7 (C), 75.4 (OCH), 73.2 (OCH<sub>2</sub>), 73.0 (OCH<sub>2</sub>), 72.8 (OCH<sub>2</sub>), 72.2 (OCH), 71.6 (OCH), 69.8 (OCH<sub>2</sub>), 67.8  $(OCH_2)$ , 56.8  $(OCH_3)$  ppm. IR (KBr):  $\tilde{v} = 2870$ , 1663, 1455, 1350, 1088, 952, 907, 741, 698 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{29}H_{32}NaO_5 [M + Na]^+$  483.2147; found 483.2145.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-ethoxymethyl-D-lyxohex-1-enitol (6b): Compound 6b (0.74 g, 70% yield) was obtained as a colorless liquid by treatment of glycal 4 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and ethyl iodide (0.268 mL, 3.3 mmol) over 4 h.  $[a]_{D}^{28} = +13.6$  (c = 0.22, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.39–7.26 (m, 15 H, aromatic), 6.44 (s, 1 H, 1-H), 4.87 (d, J = 11.7 Hz, 1 H), 4.84 (d, J = 11.7 Hz, 1 H), 4.72 (d, J =15.0 Hz, 1 H), 4.70 (d, J = 11.7 Hz, 1 H), 4.56 (d, J = 11.7 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 4.33 (m, 1 H), 4.20 (d, J = 10.8 Hz, 1 H), 4.02 (t, J = 3.6 Hz, 1 H), 3.86 (dd, J = 10.5, 3.5 Hz, 1 H), 3.80-3.71 (m, 2 H), 3.54-3.35 (m, 3 H), 1.21 (t, J = 7.2 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.4 (C-1), 138.3, 137.8, 137.6, 127.9, 127.5, 127.4, 127.3, 127.2, 127.1 (Carvl), 109.9 (C), 75.2 (OCH), 73.0 (OCH<sub>2</sub>), 72.8 (2×OCH<sub>2</sub>), 72.7 (OCH<sub>2</sub>), 72.1 (OCH), 70.6 (OCH), 67.7 (OCH<sub>2</sub>), 64.5 (OCH<sub>2</sub>), 14.8  $(OCH_2CH_3)$  ppm. IR (KBr):  $\tilde{v} = 2969, 2863, 1663, 1489, 1454,$ 1353, 1091, 741, 698 cm<sup>-1</sup>. HRMS (ESI): calcd. for C<sub>30</sub>H<sub>34</sub>NaO<sub>5</sub> [M + Na]<sup>+</sup> 497.2304; found 497.2304.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(prop-2'-enyloxy)methyl-D-lyxo-hex-1-enitol (6c): Compound 6c (0.76 g, 70% yield) was obtained as a colorless liquid by treatment of glycal 4 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and allyl bromide (0.287mL, 3.3 mmol) over 5 h.  $[a]_{D}^{28} = +20.0 \ (c = 0.28, \text{ CHCl}_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.40–7.28 (m, aromatic, 15 H), 6.45 (s, 1 H, 1-H), 6.00-5.87 (m, 1 H), 5.30 (d, J = 17.1 Hz, 1 H), 5.21(d, J = 10.5 Hz, 1 H), 4.87 (d, J = 12.0 Hz, 1 H), 4.86 (d, J =11.4 Hz, 1 H), 4.71 (d, J = 11.4 Hz, 1 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.47 (d, J = 12.0 Hz, 1 H), 4.35 (m, 2 H), 4.25 (d, J = 11.1 Hz, 1 H), 4.04–3.97 (m, 4 H), 3.64–3.56 (m, 2 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 143.0 (C-1), 138.6, 138.19, 137.9, 134.8, 128.1, 127.87, 127.81, 127.67, 127.60, 127.4 (Carvl), 116.9 (=CH<sub>2</sub>), 110.0 (C), 75.7 (OCH), 73.4 (OCH<sub>2</sub>), 73.2 (OCH<sub>2</sub>), 73.0 (OCH<sub>2</sub>), 72.3 (OCH), 71.0 (OCH), 70.3 (OCH<sub>2</sub>), 68.0  $(OCH_2)$ , 67.7  $(OCH_2)$  ppm. IR (KBr):  $\tilde{v} = 2861$ , 1662, 1456, 1348, 1183, 1071, 922, 741, 698 cm<sup>-1</sup>. HRMS (ESI): calcd. for C<sub>31</sub>H<sub>34</sub>NaO<sub>5</sub> [M + Na]<sup>+</sup> 509.2304; found 509.2298.

**1,5-Anhydro-3,4,6-tri-***O***-benzyl-2-deoxy-2***-C***-(**2',2'-**dimethoxy-ethoxy)methyl-D***-lyxo***-hex-1-enitol (6e):** Compound **6e** (0.672 g, 57% yield) was obtained as a colorless liquid by treatment of glycal **4** (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and  $\alpha$ -chloro-acetaldehyde dimethyl acetal (0.398 mL, 3.3 mmol) over 8 h. [a]<sub>D</sub><sup>28</sup> = +97.1 (c = 0.35, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.34-7.24 (m, aromatic, 15 H), 6.39 (s, 1 H, 1-H), 4.808 (d, J = 12.0 Hz, 1 H), 4.801 (d, J = 11.7 Hz, 1 H), 4.66 (d, J = 11.7 Hz, 1 H), 4.62

(d, J = 12.0 Hz, 1 H), 4.53–4.38 (m, 3 H), 4.29–4.25 (m, 3 H), 3.96 (t, J = 3.6 Hz, 1 H), 3.83–3.63 (m, 3 H), 3.45–3.40 (m, 2 H), 3.35 [s, 6 H, C(OMe)<sub>2</sub>] ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 143.2$  (C-1), 138.7, 138.1, 138.0, 128.3, 128.2, 127.89, 127.85, 127.69, 127.64, 127.5 (C<sub>aryl</sub>), 109.7 (C), 102.6 [CH(OCH<sub>3</sub>)<sub>2</sub>], 75.7 (OCH), 73.5 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 73.1 (OCH<sub>2</sub>), 72.4 (OCH), 71.0 (OCH), 69.0 (OCH<sub>2</sub>), 68.7 (OCH<sub>2</sub>), 68.1 (OCH<sub>2</sub>), 53.7 (OCH<sub>3</sub>), 53.6 (OCH<sub>3</sub>) ppm. IR (KBr):  $\tilde{v} = 2928$ , 2867, 1671, 1497, 1449, 1390, 1256, 1191, 1091, 743, 699 cm<sup>-1</sup>. HRMS (ESI): calcd. for C<sub>32</sub>H<sub>38</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 557.2515; found 557.2528.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(2',3'-epoxypropyloxy)methyl-D-lyxo-hex-1-enitol (6f): Compound 6f (0.78 g, 70%) yield) was obtained as a colorless liquid by treatment of glycal 4 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and epichlorohydrin (0.263 mL, 3.3 mmol) over 10 h. The spectroscopic data and specific rotation reported are for a 1:1 mixture of diastereomers.  $[a]_{D}^{28} = +20.0 \ (c = 0.22, \text{ CHCl}_3).$ <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta =$ 7.33–7.19 (m, aromatic, 30 H), 6.38 (s, 2 H, 1-H), 4.80 (d, J =12.0 Hz, 2 H), 4.78 (d, J = 11.4 Hz, 2 H), 4.64 (d, J = 11.4 Hz, 2 H), 4.61 (d, J = 12.0 Hz, 2 H), 4.50 (d, J = 11.7 Hz, 2 H), 4.40 (d, J = 11.7 Hz, 2 H), 4.26–4.20 (m, 6 H), 3.96 (m, 2 H), 3.83–3.51 (m, 8 H), 3.28–3.21 (m, 2 H), 3.06 (m, 2 H), 2.71 (t, J = 4.2 Hz, 2 H), 2.51 (m, 2 H) ppm. <sup>13</sup>C NMR(75 MHz, CDCl<sub>3</sub>):  $\delta$  = 143.2 (C-1), 143.1, 138.5, 138.0, 137.8, 128.2, 127.77, 127.71, 127.59, 127.52, 127.3 (C<sub>arv1</sub>), 109.6 (C), 75.6 (OCH), 73.3 (OCH<sub>2</sub>), 73.1 (OCH<sub>2</sub>),73.0 (OCH<sub>2</sub>), 72.2 (OCH), 70.9 (OCH), 69.9 (OCH<sub>2</sub>), 69.6 (OCH<sub>2</sub>), 68.8 (OCH<sub>2</sub>), 68.6 (OCH<sub>2</sub>), 68.0 (OCH<sub>2</sub>), 50.6 (OCH), 44.18 (OCH<sub>2</sub>), 44.12 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v}$  = 2922, 2863, 2361, 1663, 1456, 1347, 1185, 1088, 742, 698 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{31}H_{34}NaO_6 [M + Na]^+$  525.2253; found 525.2242.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-benzyloxymethyl-Dlyxo-hex-1-enitol (6g): Compound 6g (0.89g, 74% yield) was obtained as a colorless low-melting solid by treatment of glycal 4 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and benzyl chloride (0.381 mL, 3.3 mmol) over 4 h.  $[a]_D^{28} = +27.5 (c = 0.16, CHCl_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.37–7.24 (m, aromatic, 20 H), 6.39 (s, 1 H, 1-H), 4.80 (d, J = 11.7 Hz, 1 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.60 (d, J = 11.4 Hz, 1 H), 4.57 (d, J = 11.7 Hz, 1 H), 4.53–4.35 (m, 4 H), 4.27–4.24 (m, 2 H), 3.95 (t, J = 3.3 Hz, 1 H), 3.83–3.53 (m, 3 H) ppm. <sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):  $\delta = 143.2$  (C-1), 138.6, 138.4, 138.1, 138.0, 128.36, 128.30, 127.8, 127.7, 127.6, 127.5, 126.9 (Caryl), 110.0 (C), 75.7 (OCH), 73.6 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 73.1 (OCH<sub>2</sub>), 72.5 (OCH), 71.5 (OCH<sub>2</sub>), 71.1 (OCH), 68.1 (OCH<sub>2</sub>), 67.9 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v}$  = 2903, 2861, 1658, 1453, 1346, 1211, 1172, 1094, 890, 735, 690, 602, 468 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{35}H_{36}NaO_5 [M + Na]^+$ 559.2460; found 559.2430.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-methoxymethyl-Darabino-hex-1-enitol (7a): Compound 7a (0.56 g, 55% yield) was obtained as a colorless liquid by treatment of glycal 5 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and methyl iodide (0.213 mL, 3.3 mmol) over 4 h.  $[a]_{D}^{28} = +34.5 (c = 0.39, \text{CHCl}_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.30–7.24 (m, aromatic, 15 H), 6.47 (s, 1 H, 1-H), 4.73 (d, J = 11.7 Hz, 1 H), 4.63–4.53 (m, 5 H), 4.20– 4.17 (m, 3 H), 3.89 (t, J = 6.3 Hz, 1 H), 3.80 (dd, J = 10.5, 5.7 Hz, 1 H), 3.70 (dd, J = 10.5, 3.3 Hz, 1 H), 3.59 (d, J = 11.4 Hz, 1 H),3.25 (s, 3 H, OCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 143.7 (C-1), 138.4, 138.0, 137.9, 128.48, 128.42, 127.89, 127.85, 127.77, 127.70 (Carvl), 109.7 (C), 76.6 (OCH), 74.3 (OCH), 73.8 (OCH), 73.4 (OCH<sub>2</sub>), 73.1 (OCH<sub>2</sub>), 72.8 (OCH<sub>2</sub>), 70.0 (OCH<sub>2</sub>), 68.2 (OCH<sub>2</sub>), 56.9 (OCH<sub>3</sub>) ppm. IR (KBr):  $\tilde{v}$  = 2923, 2862, 1666, 1455, 1362, 1168, 1089, 740, 699 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{29}H_{32}NaO_5 [M + Na]^+ 483.2147$ ; found 483.2152.

## FULL PAPER

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(2',3'-epoxypropyloxy)methyl-D-arabino-hex-1-enitol (7b): Compound 7b (0.624 g, 56% yield) was obtained as a colorless liquid by treatment of glycal 5 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and epichlorohydrin (0.263 mL, 3.3 mmol) over 8 h. The spectroscopic data and specific rotation reported are for a 1:1 mixture of diastereomers.  $[a]_{D}^{28} = +32.5 \ (c = 0.22, \text{ CHCl}_3).$ <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta =$ 7.29–7.24 (m, aromatic, 30 H), 6.46 (s, 2 H, 1-H), 4.72 (d, J =11.4 Hz, 2 H), 4.64-4.52 (m, 10 H), 4.30-4.15 (m, 6 H), 3.88 (t, J = 5.4 Hz, 2 H), 3.79–3.64 (m, 6 H), 3.53 (m, 2 H), 3.36–3.24 (m, 2 H), 3.10 (m, 2 H), 2.75 (m, 2 H), 2.55 (m, 2 H) ppm. <sup>13</sup>C NMR  $(75 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 143.9 (\text{C-1}), 143.8 (\text{C-1}), 138.3, 137.9, 128.5,$ 128.47, 128.41, 127.8, 127.7, 127.6 (Carvl), 109.4 (C), 109.3 (C), 76.6 (OCH), 76.5 (OCH), 73.9 (OCH), 73.7 (OCH), 73.4 (OCH<sub>2</sub>), 73.0 (OCH<sub>2</sub>), 72.79 (OCH<sub>2</sub>), 72.76 (OCH<sub>2</sub>),71.2 (OCH<sub>2</sub>),69.58 (OCH<sub>2</sub>), 69.53 (OCH<sub>2</sub>), 69.4 (OCH<sub>2</sub>), 68.8 (OCH<sub>2</sub>), 68.6 (OCH<sub>2</sub>), 68.2 (OCH<sub>2</sub>), 50.9 (OCH), 50.7 (OCH), 44.36 (OCH<sub>2</sub>), 44.32  $(OCH_2)$  ppm. IR (KBr):  $\tilde{v} = 2863$ , 1958, 1879, 1813, 1723, 1666, 1487, 1456, 1361, 1253, 1169, 914, 847, 743, 699, 607, 473 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{31}H_{34}NaO_6$  [M + Na]<sup>+</sup> 525.2253; found 525.2249.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-benzyloxymethyl-Darabino-hex-1-enitol (7c): Compound 7c (0.82 g, 70% yield) was obtained as a colorless liquid by treatment of glycal 5 (1.0 g, 2.2 mmol) with NaH (0.131 g, 3.3 mmol) and benzyl chloride (0.381 mL, 3.3 mmol) over 4 h.  $[a]_{D}^{28} = +36.1 (c = 0.10, \text{ CHCl}_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.31–7.25 (m, aromatic, 20 H), 6.50 (s, 1 H, 1-H), 4.75 (d, J = 11.4 Hz, 1 H), 4.66–4.63 (m, 3 H), 4.60– 4.52 (m, 3 H), 4.39 (d, J = 11.7 Hz, 1 H), 4.34–4.24 (m, 3 H), 3.94 (t, J = 5.4 Hz, 1 H), 3.76 (m, 3 H) ppm. <sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):  $\delta = 143.6$  (C-1), 138.3, 138.2, 137.88, 137.85, 128.6, 128.3, 128.2, 128.1, 128.0, 127.75, 127.73, 127.6, 127.5, 127.4 (Carvl), 109.5 (C), 76.4 (OCH), 74.0 (OCH), 73.7 (OCH), 73.3 (OCH<sub>2</sub>), 72.9 (OCH<sub>2</sub>),72.6 (OCH<sub>2</sub>), 70.8 (OCH<sub>2</sub>) 68.1 (OCH<sub>2</sub>), 67.5  $(OCH_2)$  ppm. IR (KBr):  $\tilde{v} = 2860, 1664, 1456, 1361, 1169, 1067,$ 740, 697 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{35}H_{36}NaO_5$  [M + Na]<sup>+</sup> 559.2460; found 559.2467.

General Procedure for InCl<sub>3</sub>-Mediated [1,3]-Migrations in Glycal Ethers 6 and 7 to form 8 and 9: Glycal ether 6 or 7 (1 mmol) was dissolved in dry  $CH_2Cl_2$  (5 mL) and dried with activated molecular sieves (4 Å) in order to remove any moisture if present. The solution was then transferred by syringe to a dry three-necked round-bottomed flask (flame-dried and cooled under argon). Anhydrous InCl<sub>3</sub> (0.2 mmol) was added to the reaction mixture in one lot, and the reaction mixture was quenched with water and extracted with chloroform (3 × 50 mL). The combined organic layer was washed with water, dried with sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography with hexane/ethyl acetate (5:1) mixture as an eluent to provide 2-*C*-methylene glycosides 8 or 9, respectively.

Methyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methylene-α-D-*lyxo*-hexopyranoside (8a): Compound 8a (0.22 g, 88% yield) was obtained by treatment of ether 6a (0.250 g, 0.54 mmol) with anhyd. InCl<sub>3</sub> (0.022 g, 0.108 mmol) over 10 min. Colorless liquid. [*a*]<sub>D</sub><sup>28</sup> = +5.6 (*c* = 0.53, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.36–7.23 (m, aromatic, 15 H), 5.43 (s, 1 H), 5.28 (s, 1 H), 5.10 (s, 1 H, 1-H), 4.91 (d, *J* = 11.7 Hz, 1 H), 4.72 (d, *J* = 12.0 Hz, 1 H), 4.65 (d, *J* = 13.5 Hz, 1 H), 4.61 (d, *J* = 13.5 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.43–4.39 (m, 2 H), 4.09 (t, *J* = 6.3 Hz, 1 H), 3.97 (m, 1 H), 3.62–3.54 (m, 2 H), 3.38 (s, 3 H, OMe) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 140.7 (C-2), 138.5, 138.3, 138.0, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 127.4, 127.0 ( $C_{aryl}$ ), 111.5 (=CH<sub>2</sub>), 102.5 (C-1), 78.0 (OCH), 75.4 (OCH), 73.9 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 71.5 (OCH<sub>2</sub>), 70.6 (OCH), 69.3 (OCH<sub>2</sub>), 54.7 (OCH<sub>3</sub>) ppm. IR (KBr):  $\tilde{v} = 2910$ , 2359, 1597, 1454, 1358, 1194, 1092, 1055, 966, 916, 740, 698 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{29}H_{32}NaO_5$  [M + Na]<sup>+</sup> 483.2147; found 483.2186.

Prop-2-enyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-a-D-lyxohexopyranoside (8c): Compound 8c (0.175g, 76% yield) was obtained by treatment of ether 6c (0.230 g, 0.47 mmol) with anhyd. InCl<sub>3</sub> (0.020 g, 0.094 mmol) over 10 min. Colorless liquid.  $[a]_{D}^{28} =$ +16 (c = 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta = 7.36-7.21$ (m, aromatic, 15 H), 5.97-5.84 (m, 1 H), 5.40 (s, 1 H), 5.28-5.14 (m, 4 H), 4.89 (d, J = 12.0 Hz, 1 H), 4.71 (d, J = 12.0 Hz, 1 H), 4.63 (d, J = 11.7 Hz, 1 H), 4.61 (d, J = 12.0 Hz, 1 H), 4.49–4.37 (m, 3 H), 4.19-4.09 (m, 2 H) 4.04-3.97 (m, 2 H), 3.54-3.50 (m, 2 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 140.7 (C-2), 138.6, 138.3, 138.0, 134.0, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.59, 127.49, 127.44, 127.0 (Carvl), 117.2 (=CH<sub>2</sub>), 111.4 (=CH<sub>2</sub>), 100.6 (C-1), 78.1 (OCH), 75.4 (OCH), 73.9 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 71.5 (OCH<sub>2</sub>), 70.7 (OCH), 69.3 (OCH<sub>2</sub>), 67.7 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v} = 2917, 2862, 2359, 1597, 1492, 1455, 1358, 1149, 1093, 1022,$ 740, 698 cm<sup>-1</sup>. HRMS (ESI) calcd. for  $C_{31}H_{34}NaO_5$  [M + Na]<sup>+</sup> 509.2304; found 509.2291.

Prop-2-ynyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-a-D-lyxohexopyranoside (8d): Compound 8d (0.165 g, 83% yield) was obtained by treatment of ether 6d (0.200 g, 0.413 mmol) with anhyd. InCl<sub>3</sub> (0.018 g, 0.082 mmol) over 10 min. Colorless liquid.  $[a]_{D}^{28} =$ +20.8 (c = 0.5, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 7.36$ -7.20 (m, aromatic, 15 H), 5.45 (s, 1 H, 1-H), 5.38 (s, 1 H), 5.31 (s, 1 H), 4.90 (d, J = 12.0 Hz, 1 H), 4.71 (d, J = 12.0 Hz, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 4.61 (d, J = 12.0 Hz, 1 H), 4.46 (d, J =12.0 Hz, 1 H), 4.44–4.37 (m, 2 H), 4.23 (m, 2 H), 4.09 (t, J =6.6 Hz, 1 H), 3.98 (m, 1 H), 3.54 (m, 2 H), 2.39 (t, J = 2.4 Hz, 1 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 140.0 (C-2), 138.5, 138.3, 137.9, 128.4, 128.38, 128.34, 128.1, 127.9, 127.7, 127.6, 127.55, 127.51, 127.0 (Caryl), 112.4 (=CH<sub>2</sub>), 100.1 (C-1), 79.0 (C), 78.0 (=CH), 75.2 (OCH), 74.5 (OCH<sub>2</sub>), 74.0 (OCH<sub>2</sub>), 73.4 (OCH<sub>2</sub>), 71.6 (OCH<sub>2</sub>), 71.1 (OCH), 69.1 (OCH<sub>2</sub>), 54.0 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v} = 2919, 2861, 1636, 1455, 1358, 1092, 1028, 740, 696 \text{ cm}^{-1}.$ HRMS (ESI): calcd. for  $C_{31}H_{32}NaO_5$  [M + Na]<sup>+</sup> 507.2140; found 507.2139.

(2',2'-Dimethoxy)ethyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylenea-D-lyxo-hexopyranoside (8e): Compound 8e (0.18 g, 64% yield) was obtained by treatment of ether 6e (0.280 g, 0.524 mmol) with anhyd. InCl<sub>3</sub> (0.022 g, 0.104 mmol) over 10 min. Colorless liquid.  $[a]_{\rm D}^{28}$  = +9.3 (c = 0.6, CHCl\_3). <sup>1</sup>H NMR (300MHz, CDCl\_3):  $\delta$  = 7.36-7.21 (m, aromatic, 15 H), 5.41 (s, 1 H, 1-H), 5.26 (s, 1 H), 5.22 (s, 1 H), 4.89 (d, J = 11.7 Hz, 1 H), 4.70 (d, J = 12.0 Hz, 1 H), 4.63–4.57 (m, 2 H), 4.53 (t, J = 5.4 Hz, 1 H), 4.48–4.37 (m, 3 H), 4.15 (t, J = 6.3 Hz, 1 H), 3.98 (m, 1 H), 3.66 (dd, J = 11.1, 6.3 Hz, 1 H), 3.59-3.49 (m, 3 H), 3.35 (s, 3 H, OCH<sub>3</sub>), 3.32 (s, 3 H, OCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 140.6 (C-2), 138.6, 138.4, 138.0, 128.48, 128.44, 128.3, 128.1, 127.8, 127.7, 127.5, 127.1 (Carvl), 111.9 (=CH<sub>2</sub>), 102.6 (C-1), 101.9 (OCH), 78.0 (OCH), 75.3 (OCH), 74.0 (OCH<sub>2</sub>), 73.4 (OCH<sub>2</sub>), 71.6 (OCH<sub>2</sub>), 70.8 (OCH), 69.4 (OCH), 66.8 (OCH<sub>2</sub>), 53.9 (OCH<sub>3</sub>), 53.7  $(OCH_3)$  ppm. IR (KBr):  $\tilde{v} = 2918$ , 1633, 1496, 1454, 1403, 1358, 1325, 1192, 1107, 1072, 1031, 973, 919, 738, 697 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{32}H_{38}NaO_7 [M + Na]^+ 557.2515$ ; found 557.2540.

2',3'-Epoxypropyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene- $\alpha$ -D*lyxo*-hexopyranoside (8f): Compound 8f (0.19 g, 70% yield) was obtained by treatment of ether 6f (0.270 g, 0.53 mmol) with anhyd. InCl<sub>3</sub> (0.022 g, 0.106 mmol) over 10 min. Colorless liquid; the spectroscopic data and specific rotation reported are for a 1:1 mixture of diastereomers.  $[a]_{D}^{28} = +7.5$  (c = 0.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 7.37–7.21 (m, aromatic, 30 H) 5.42 (s, 2 H),5.27 (s, 2 H), 5.24 (s, 1 H), 5.23 (s, 1 H), 4.90 (d, J = 11.7 Hz, 2 H), 4.73–4.58 (m, 6 H), 4.50–4.37 (m, 6 H), 4.14 (d, J = 4.2 Hz, 2 H), 3.97-3.69 (m, 4 H), 3.63-3.47 (m, 6 H), 3.18-3.16 (m, 2 H), 2.77-2.73 (m, 2 H), 2.58-2.55 (m, 2 H) ppm. <sup>13</sup>C NMR (75 MHz,  $CDCl_3$ )  $\delta = 140.4$  (C-2), 138.5, 138.3, 138.0, 128.3, 128.0, 127.6,  $127.5, 127.0 (C_{arvl}), 111.9 (2 \times = CH_2), 101.8 (C-1), 101.5 (C-1), 77.9$ (OCH), 75.3 (OCH), 74.0 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 71.6 (OCH<sub>2</sub>), 70.8 (OCH), 70.7 (OCH), 69.4 (OCH<sub>2</sub>), 69.2 (OCH<sub>2</sub>), 68.3 (OCH<sub>2</sub>), 67.5 (OCH<sub>2</sub>), 50.5 (OCH), 50.2 (OCH), 44.5 (OCH<sub>2</sub>) ppm. IR (KBr): v = 2919, 2861, 1635, 1491, 1456, 1358, 1249, 1206, 1092, 740, 697 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{31}H_{34}NaO_6$  [M + Na]<sup>+</sup> 525.2253; found 525.2255.

2',3'-Epoxypropyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-a-Darabino-hexopyranoside (9b): Compound 9b (0.130 g, 56% yield) was obtained by treatment of allyl ether **7b** (0.230 g, 0.45 mmol) with anhyd. InCl<sub>3</sub> (0.020 g, 0.090 mmol) over 10 min. Colorless liquid; the spectroscopic data and specific rotation reported are for a 1:1 mixture of diastereomers.  $[a]_{D}^{28} = +10.5 (c = 0.40, CHCl_3)$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.41–7.16 (m, aromatic, 30 H) 5.33 (s, 2 H), 5.23–5.19 (m, 4 H), 4.89 (d, J = 10.8 Hz, 2 H),4.76 (m, 4 H), 4.62-4.44 (m, 8 H), 3.98 (m, 2 H), 3.88-3.49 (m, 10 H), 3.20-3.19 (m, 2 H), 2.81 (t, J = 5.4 Hz, 2 H), 2.79-2.61 (m, 2 H) ppm.<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 141.9 (C-2), 138.2, 138.0, 128.7, 128.5, 128.3, 128.3, 127.9, 127.8, 127.6 ( $C_{aryl}$ ), 111.1 (2×=CH<sub>2</sub>), 101.6 (C-1), 101.5 (C-1), 81.0 (OCH), 77.9 (OCH), 75.0 (OCH<sub>2</sub>), 73.5 (OCH<sub>2</sub>), 73.46 (OCH<sub>2</sub>), 73.43 (OCH<sub>2</sub>), 71.78 (OCH<sub>2</sub>), 71.70 (OCH), 68.8 (OCH<sub>2</sub>), 68.7 (OCH), 68.3 (OCH<sub>2</sub>), 67.4 (OCH<sub>2</sub>), 50.5 (OCH), 50.2 (OCH), 44.67 (OCH<sub>2</sub>), 44.62 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v} = 2921, 2862, 1633, 1455, 1359, 1258, 1208, 1105, 1029, 740,$ 697 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{31}H_{34}NaO_6 [M + Na]^+$ 525.2253; found 525.2259.

3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-a-D-lyxo-hexopyranosyl 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-a-D-lyxo-hexopyranoside (11): Alcohol 4 (0.280 g, 0.673 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL), and the mixture was dried with activated molecular sieves (4 Å) in order to remove any moisture if present. The solution was then transferred by syringe to a dry three-necked round-bottomed flask (flame-dried and cooled under argon). Anhydrous InCl<sub>3</sub> (0.028 g, 0.134 mmol) was added to the mixture, and the reaction was allowed to proceed under argon. After 10 min, the reaction mixture was quenched with water and extracted with chloroform  $(3 \times 50 \text{ mL})$ . The combined organic layer was washed with water, dried with sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography with a hexane/ ethyl acetate (5:1) mixture as an eluent to provide compound 11 (0.140 g, 80% yield) as a colorless liquid.  $[a]_{D}^{28} = +33.7$  (c = 0.64, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.41–7.26 (m, aromatic, 15 H), 5.56 (s, 1 H), 5.39 (s, 1 H), 5.32 (s, 1 H), 4.93 (d, J = 12.0 Hz, 1 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.66 (d, J = 12.0 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.450 (d, J = 11.7 Hz, 1 H), 4.43 (d, J =11.7 Hz, 1 H), 4.34 (d, J = 2.1 Hz, 1 H), 4.12 (t, J = 6.6 Hz, 1 H), 4.01 (d, J = 1.8 Hz, 1 H), 3.59–3.56 (m, 2 H) ppm. <sup>13</sup>C NMR  $(75 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 140.3 \text{ (C-2)}, 138.5, 138.3, 138.0, 128.7,$ 128.5, 128.3, 128.1, 127.6, 127.57, 127.51, 127.0 (C<sub>aryl</sub>), 111.4 (=CH<sub>2</sub>), 97.04 (C-1), 77.8 (OCH), 75.2 (OCH), 74.0 (OCH<sub>2</sub>), 73.3 (OCH<sub>2</sub>), 71.4 (OCH<sub>2</sub>), 71.2 (OCH), 69.2 (OCH<sub>2</sub>) ppm. IR (KBr):  $\tilde{v} = 2918, 2864, 1642, 1491, 1455, 1358, 1246, 1208, 1095, 956,$ 740, 696 cm<sup>-1</sup>. HRMS (ESI): calcd. for  $C_{56}H_{58}NaO_9$  [M + Na]<sup>+</sup> 897.3979; found 897.3998.



**Supporting Information** (see also the footnote on the first page of this article): Spectral data for compounds **6d**, **8b**, **8g**, **9a**, **9c**, **14**, **15** (p. S4–S6), copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra (p. S7–S52).

#### Acknowledgments

We are grateful to the Council of Scientific and Industrial Research, New Delhi, India for financial support. PN thanks CSIR, India and IIT Delhi for a research fellowship. We also thank Dr. N. Pant, Department of Chemistry, IIT-Delhi for his assistance in performing AM1 calculations.

- For very recent reviews on glycosylation methods see: a)
   A. F. G. Bonget, A. V. Demchenko, *Carbohydr. Res.* 2007, 342, 374–406; b)
   P. Fügedi, in *Organic Chemistry of Sugars*, CRC Press LLC, Florida, 2006, p. 90–151.
- [2] For reviews see: a) R. J. Ferrier, J. O. Hoberg, Adv. Carbohydr. Chem. Biochem. 2003, 58, 55–119; b) W. Priebe, G. Grynkiewicz, Glycoscience 2001, 1, 749–783; c) B. Fraser-Reid, Acc. Chem. Res. 1996, 29, 59–66; d) B. Fraser-Reid, Acc. Chem. Res. 1985, 18, 347–354; e) B. Fraser-Reid, Acc. Chem. Res. 1975, 8, 192–201.
- [3] S. Jendrzejewski, P. Ermann, *Tetrahedron Lett.* 1993, 34, 615–618.
- [4] M. E. Jung, S. W. T. Choe, J. Org. Chem. 1995, 60, 3280-3328.
- [5] E. D. Rekai, G. Rubinstenn, J.-M. Mallet, P. Sinaÿ, S. N. Müller, B. Giese, Synlett 1998, 831–834.
- [6] G. Mehta, K. Pallavi, Tetrahedron Lett. 2004, 45, 3865–3867.
- [7] A. Horvath, B. Ruttens, P. Herdewijn, *Tetrahedron Lett.* 2007, 48, 3621–3623.
- [8] a) H.-J. Hamann, M. Chmielewski, D. Mostowicz, J. Liebscher, *ARKIVOC* 2007, 17–20; b) W. Kosnik, A. V. Stachulski, M. Chmielewski, *Tetrahedron: Asymmetry* 2005, 16, 1975–1981; c) H.-J. Hamann, E. Hoft, D. M. Mostowicz, A. Mishnev, Z. Urbanczyk-Lipkowska, M. Chmielewski, *Tetrahedron* 1997, 53, 185–192.
- [9] a) A. Matsuda, K. Takenuki, M. Tanaka, T. Sasaki, T. Ueda, J. Med. Chem. 1991, 34, 812–819; b) C. H. Baker, J. M. Banzon, J. M. Bollinger, J. Stubbe, V. Samano, M. J. Robins, B. Lippert, E. Jarvi, R. Resvick, J. Med. Chem. 1991, 34, 1879– 1884.
- [10] a) G. Wong, B. Fraser-Reid, *Can. J. Chem.* 1994, 72, 69–74; b)
   P. Sarda, A. Olesker, G. Lukacs, *Carbohydr. Res.* 1992, 229, 161–165.
- [11] a) N. G. Ramesh, K. K. Balasubramanian, *Eur. J. Org. Chem.* 2003, 4477–4487; b) C. Booma, K. K. Balasubramanian, *J. Chem. Soc., Chem. Commun.* 1993, 1394–1395.
- [12] a) R. Ghosh, A. Chakraborty, D. K. Maiti, V. G. Puranik, *Tetrahedron Lett.* 2005, *46*, 8047–8051; b) A. Gupta, Y. D. Vankar, *Tetrahedron* 2000, *56*, 8525–8531.
- [13] For palladium-catalyzed transformations of carbonates of 2-C-hydroxymethyl glycals to 2-C-methylene-O-glycosides see: S. Bouoit, C. Goux, D. Sinou, Carbohydr. Lett. 1997, 2, 267–272.
- [14] For a very recently reported AuCl<sub>3</sub>-catalyzed Ferrier-type rearrangement of 2-*C*-(propargyloxy)-methylglycals see: S. Kashyap, S. R. Vidadala, S. Hotha, *Tetrahedron Lett.* 2007, 48, 8960–8962.
- [15] One difficulty often encountered by us is the purification of 2-C-(acetoxylmethyl)-glycals 3. They tend to rearrange or decompose during chromatographic purification over silica gel, sometimes resulting in poor yields. If purified very carefully, they do not have shelf-lives of more than a couple of days even at low temperatures; see also ref. 16.
- [16] Such a rearrangement on furanose-derived 2-C-(acetoxymethyl)-glycals has already been reported. See: a) J. Wolf, C. Monneret, R. Pontikis, J.-C. Florent, *Eur. J. Org. Chem.* 1998, 2417–2423; b) R. Pontikis, J. Wolf, C. Monneret, J.-C. Florent, *Tetrahedron Lett.* 1995, *36*, 3523–3526.

## FULL PAPER

- [17] For reviews: a) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Curr. Org. Chem.* 2003, 7, 1661–1689; b) R. Ghosh, *Ind. J. Chem. B* 2001, 40, 550–557; c) B. C. Ranu, *Eur. J. Org. Chem.* 2000, 2347–2356.
- [18] For some recent examples see: a) J. S. Yadav, B. V. S. Reddy, M. Sreenivas, G. Satheesh, *Synthesis* 2007, 1712–1716; b) S. K. Das, K. A. Reddy, V. L. N. R. Krovvidi, K. Mukkanti, *Carbohydr. Res.* 2005, 340, 1387–1392; c) S. B. Boga, K. K. Balasubramanian, *ARKIVOC* 2004, *VIII*, 87–102; d) R. Ghosh, A. Chakroborty, S. Maiti, *ARKIVOC* 2004, *XIV*, 1–9.
- [19] Irradiation of the signal at  $\delta = 5.10$  ppm due to H-1 of **8a** resulted in an enhancement of the signal due to one of the *exo*-methylene olefinic protons at  $\delta = 5.28$  ppm and vice versa. This confirms that that anomeric proton of **8a** is in the equatorial position and that the methoxy group is in the axial position. For details of the assignment of anomeric configurations of similar compounds by NOE experiments, see: N. G. Ramesh, K. K. Balasubramanian, *Tetrahedron* **1995**, *51*, 255–272.
- [20] Unlike the 2-C-(acetoxymethyl)-glycals **3**, all ethers **6a**–g, **7a–c** reported in this manuscript are relatively stable and can be stored in a refrigerator for longer times.
- [21] While our work was in progress, 2-*C*-(propargyloxymethyl)-galactal (**6d**) was reported by Hotha et al.; see ref. 14.
- [22] Alcohols 4 and 5 were each prepared in two steps from the readily available tri-O-benzyl-D-galactal and tri-O-benzyl-Dglucal, respectively, by Vilsmeier–Haack formylation followed by reduction. See: N. G. Ramesh, K. K. Balasubramanian, *Tetrahedron Lett.* **1991**, *32*, 3875–3878 and also refs. 11–14, 19.
- [23] For InCl<sub>3</sub>-promoted rearrangements of epoxides to carbonyl compounds: B. C. Ranu, U. Jana, J. Org. Chem. 1998, 63, 8212–8216.
- [24] a) R. N. de Oliveira, A. C. N. de Melo, R. M. Srivastava, D. Sinou, *Heterocycles* 2006, 68, 2607–2613; b) N. Ustyuzhanina, B. Komarova, N. Zlotina, V. Krylov, A. Gerbst, Y. Tsvetkov, N. Nifantiev, *Synlett* 2006, 921–923; c) C. de Meo, M. N. Kamat, A. V. Demchenko, *Eur. J. Org. Chem.* 2005, 706–711; d)

I. A. I. Ali, E. S. H. El Ashry, R. R. Schmidt, *Eur. J. Org. Chem.* **2003**, 4121–4131; e) A. V. Demchenko, E. Rousson, G.-J. Boons, *Tetrahedron Lett.* **1999**, 40, 6523–6526; f) J. Hirsch, M. Koóš, P. Kováč, *Carbohydr. Res.* **1998**, *310*, 145–149 and references cited in these articles.

- [25] Geometry optimization and AM1 calculations were performed with HyperChem. version 7.5: HyperChem<sup>™</sup> professional 7.5. Hypercube, Inc. 1115 NW 4<sup>th</sup> St., Gainesville, FL 32601, USA. The minimum energies reported for compound **6a** and cation **II** were based on conformational search.
- [26] For some very recent reports on the synthesis and structural aspects of trehalose analogues see: a) H.-M. Kim, Y.-K. Chang, S.-I. Ryu, S.-G. Moon, S.-B. Lee, J. Mol. Catal. B 2007, 49, 98–103; b) R. Namme, T. Mitsugi, H. Takahashi, S. Ikegami, Eur. J. Org. Chem. 2007, 3758–3764; c) F. L. Lin, H. H. Van, C. R. Bertozzi, Carbohydr. Res. 2007, 342, 2014–2030; d) F. Alberto, V. A. Chapa, X. Chen, A. J. Diaz, P. S. Cremer, J. Am. Chem. Soc. 2007, 129, 10567–10574.
- [27] G. Descotes, J.-C. Martin, Carbohydr. Res. 1977, 56, 168-172.
- [28] Guthrie et al. obtained an anomeric mixture of 14 under the conditions reported by Descotes in ref. 27. Please see: R. D. Guthrie, R. W. Irvine, *Carbohyr. Res.* 1980, *82*, 225–236.
- [29] For the synthesis of 14 by a Ferrier-type rearrangement, see:
  a) S. Kashyap, S. Hotha, *Tetrahedron Lett.* 2006, 47, 2021–2023;
  b) H. Kim, H. Men, C. Lee, *J. Am. Chem. Soc.* 2004, 126, 1336–1337.
- [30] For an InCl<sub>3</sub>-catalyzed Ferrier-type rearrangement of an allylic carbonate to 15, within 2 min under microwave irradiation at 150 °C, see H.-C. Lin, C.-C. Chang, J.-Y. Chen, C.-H. Lin, *Tetrahedron Asymm.* 2005, *16*, 297–301.
- [31] a) A. A.-H. Abdel-Rahman, G. A. Winterfeld, M. Takhi, R. R. Schmidt, *Eur. J. Org. Chem.* 2002, 713–717; b) B. Shanmuga-sundaram, A. K. Bose, K. K. Balasubramanian, *Tetrahedron Lett.* 2002, 43, 6795–6798.

Received: May 7, 2008 Published Online: August 5, 2008