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Stereoselective synthesis of 2-*C*-methylene glycosides and disaccharides via direct allylic substitution of hydroxy group in benzylated glycals

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ABSTRACT

$InCl_3$ efficiently catalyzes allylic substitution of the hydroxy group of 2-*C*-hydroxymethyl glycals to afford a diversity of 2-*C*-methylene alkyl and aryl glycosides as well as disaccharides in high yields. This protocol surpasses the existing methods for the synthesis of 2-*C*-methylene glycosides as it obviates the need for functionalizing the allylic hydroxy group of glycals. The interest of this methodology relies on the extremely mild conditions required even with a free hydroxyl group at the allylic position of the glycals and that too only with a catalytic amount of $InCl_3$. The reaction is fast (30 min.), stereoselective and is compatible with a variety of oxygenated nucleophiles including those possessing acid-labile groups. A mechanistic investigation on the direct formation of an α,α-(1→1)linked disaccharide derivative from 2-*C*-hydroxymethyl galactal reveals that the reaction proceeds through a *domino* Ferrier rearrangement followed by a facile 1,3-alkoxy migration.

1. Introduction

Over the last one decade, 2-*C*-methylene glycosides have emerged as versatile chiral intermediates in organic synthesis owing to the facile synthetic maneuverability of their exocyclic double bond into a variety of functional groups. 2-*C*-Methylene glycosides have found applications in the total synthesis of natural and biologically important molecules, such as aracyclohexenyl-adenine,[1] polyenes,[2] *C*-disaccharides,[3] cyclophellitol,[4] and restricticin.[5] Chmielewski et al. have utilized 2-*C*-methylene hydroperoxides, synthesized from 2-*C*-methlyene glycosides, as chiral catalysts in enantioselective epoxidation reactions.[6] Very recently, Vankar and Gupta have reported the synthesis of 2-*C*-methylene aza sugars enroute their synthetic approach toward novel glycosidase inhibitors.[7] Some of these aza sugars show promising and selective inhibition properties against glycosidases. The *exo*-methylene group of 2-*C*-methylene glycosides has also been shown to be a key functionality of molecules involved in mechanism-based inactivation of ribonucleotide diphosphate reductase.[8] In view of these vast applications, there has been a considerable interest in the synthesis of 2-*C*-methylene glycosides in recent years. So far, only two general methodologies are available for synthesis of 2-*C*-methylene glycosides. The conventional Wittig reaction of 2-keto glycosides to the corresponding 2-*C*-methylene glycosides has practical limitations due to the sensitivity of the reaction conditions employed.[1–5,9] A simple and a more convenient approach involving Ferrier rearrangement of 2-*C*-acetoxymethyl glycals **1a** developed by Balasubramanian et al.[10] (Scheme 1) was largely exploited by a number of other groups due to its simplicity.[11] Sinou et al. and Vankar et al. have reported a palladium catalyzed approach to 2-*C*-methylene glycosides from the carbonates of 2-*C*-hydroxymethyl glycals **1b**.[11c,d] Hotha et al. recently exploited the alkynophilic behavior of $AuCl_3$ to obtain 2-*C*-methylene glycosides from the corresponding 2-*C*-propargyloxymethyl glycals **1c**.[11a] Obviously, all these latter methodologies[10,11] require an additional step of protecting and/or functionalizing the hydroxy group of 2-*C*-hydroxymethyl glycals **1d**, and further activating them to undergo Ferrier rearrangement. In addition, some of these methodologies suffer from limitations, such as substrate instability,[12] expensive catalysts, longer reaction times (1–16 h),[11a] lack of stereoselectivity, and requirement of stoichiometric or even more amounts of catalysts. To our knowledge, except for a very recent report on a facile transformation of 2-*C*-hydroxymethyl glycals **1d** to pyrano[2,3-*b*]benzopyrans, via tandem Ferrier rearrangement-intramolecular cyclization, mediated by trifluroacetic acid,[13] there is no report on direct Ferrier rearrangement of 2-*C*-hydroxymethyl glycals with oxygen nucleophiles especially under *catalytic* conditions.

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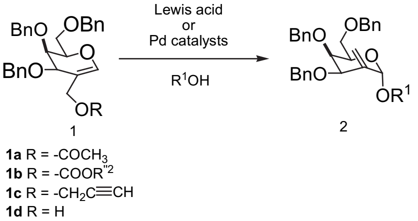


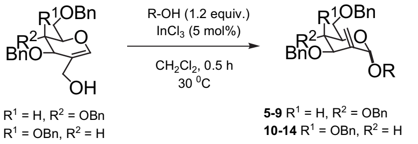
Scheme 1. Synthesis of 2-*C*-methylene glycosides through Ferrier type rearrangement.

Direct substitution of hydroxy group in alcohols by nucleophiles always remains a challenging task in organic chemistry due to their poor leaving group ability. An equimolar or an excess of an acid is generally required to perform this transformation which precludes their use with nucleophiles possessing acid-labile groups. As a consequence, alcohols are normally converted into good leaving groups, such as acetates, halides, tosylates etc., before being reacted with a nucleophile.[14] This process inevitably requires an additional step of pre-activating the hydroxyl group and in addition produces a stoichiometric amount of salt waste. Even so, catalytic activation of alcohols is much more difficult to realize and hence great emphasis has been given in recent years to develop catalytic version of this transformation. Successful attempts in this direction include the use of transition metal complexes of Cu,[15] Mo,[16] Ru,[17] Pd,[18] Re,[19] Au,[20] and salts of La, Sc and Hf [21] as catalysts. Several Lewis acids, such as $FeCl_3$,[22] $AuCl_3$,[23] $BiCl_3$,[24] $Bi(OTf)_3$,[25] $BiBr_3$,[26] I_2,[27] $InCl_3$,[28] $InBr_3$ [29] have also been reported to catalyze direct substitution of hydroxy group with various carbon, nitrogen, and oxygen nucleophiles. Nucleophilic substitution of hydroxy group catalyzed by a Brønsted acid has also been reported.[30] Noteworthy is that all these examples dealt with the direct substitution of the hydroxy group of only reactive alcohols, such as allylic, benzylic or propargylic alcohols.

Given this background, we reasoned that glycals bearing a free hydroxy group at the allylic position are ideal substrates to be exploited for catalytic allylic substitution of hydroxy group. Such a methodology would obviate the need for an additional step of protecting the hydroxyl group and use of expensive chemicals to further activate them. Since water being the only by-product from such a reaction, it would be environmentally benign. A recent report of Baba et al. on direct allylic substitution of alcohols with carbon nucleophiles using $InCl_3$ at high temperatures[31] prompted us to explore the catalytic behavior of $InCl_3$ toward glycals possessing a free hydroxyl group the allylic position. Our initial success in this direction leading to a facile and stereoselective synthesis of 2,3-unsaturated glycosides has been recently communicated.[32] Subsequently, we had investigated the versatility of this catalytic transformation with 2-*C*-hydroxymethyl glycals in presence of a wide array of oxygen nucleophiles. In this paper, we report the first example of a direct *catalytic* allylic substitution of the free hydroxy group of 2-*C*-hydroxymethyl glycals by oxygen nucleophiles. The reaction proceeds at ambient temperature yielding a variety of 2-*C*-methylene alkyl and aryl glycosides as well as disaccharides. A mechanistic investigation on the one-pot conversion of 2-*C*-hydroxymethyl galactal to an α,α-(1→1)linked disaccharide derivative,[33] confirms that the reaction proceeds through a *domino* Ferrier rearrangement followed by a stereoselective 1,3-alkoxy migration pathway.

2. Results and discussion

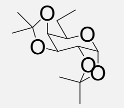
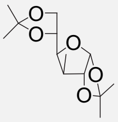
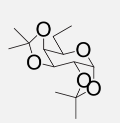
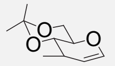
Following our earlier procedure,[32] initially, we treated 3,4,6-tri-*O*-benzyl-2-*C*-hydroxymethyl glucal **3**, obtained in two steps from tri-*O*-benzyl-D-glucal,[10,11] with methanol (1.2 equiv) in presence of 5 mol % of $InCl_3$. The progress of the reaction was monitored by TLC, which indicated a complete consumption of the starting material in just 30 min and appearance of a new spot. Upon purification by column chromatography over silica gel and careful analysis, the product was indeed identified as methyl glycoside **5**, obtained in 88% yield. (Scheme 2, Entry 1, Table 1). The anomeric configuration of the isolated product was identified as α by detailed NMR NOE analysis.[33,34] Quite significantly, the reaction rate, isolated yield and anomeric selectivity of this reaction were found to be superior than the synthesis of **5** from the Ferrier rearrangement of 2-*C*-acetoxymethyl glucal with methanol as reported by Balasubramanian et al.[10b] and Ghosh et al.[11b] It is worth mentioning that while it requires 30 mol % of $InCl_3$ and 1 h reaction time to realize the Ferrier rearrangement of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glucal with methanol,[11b] just 5 mol % of $InCl_3$ was sufficient to carry out the same reaction in 30 min. and that too with hydroxy as the leaving group. This clearly indicates that hydroxy group, as compared to an acetoxy group, has a better affinity toward $InCl_3$. Even with $BF_3 \cdot Et_2O$, a strong Lewis acid, the reaction of 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glucal with methanol required a much longer time (2 h).[10b] Encouraged with the success, the generality of the reaction was tested with benzyl and allyl alcohols as nucleophiles (Scheme 2, Entries 2 and 3, Table 1). In these examples also, the reaction was successful and the corresponding 2-*C*-methylene glycosides **6** and **7** were obtained in good yields. Extension of this reaction to sugar nucleophiles (Scheme 2, Entries 4 and 5, Table 1) resulted in the formation of unsaturated disaccharides **8** and **9** in high yields and anomeric selectivity, with the isopropylidene group remaining intact under the reaction condition. Similarly, the $InCl_3$ catalyzed reaction of 2-*C*-hydroxymethyl galactal **4** with a variety of alcohols also proceeded smoothly to afford the corresponding 2-*C*-methylene galactosides, in just 30 min (Scheme 2; Entries 6–10, Table 1). Notable and an interesting example among them is the $InCl_3$ catalyzed reaction of 2-*C*-hydroxmethyl galactal **4** (possessing a primary allylic hydroxyl group) with 4,6-*O*-isopropylidene-D-glucal (Entry 10, Table 1) (possessing a secondary allylic hydroxyl group). In this case, as both the reactants have a free hydroxyl group at the allylic position one may expect the formation of two types of products **14** (Entry 10, Table 1) and **15** (Fig. 1). However, the reaction was found to be highly selective leading to an exclusive formation of the unsaturated disaccharide **14**, obtained from the reaction of 4,6-*O*-isopropylidene-D-glucal as a glycosyl acceptor and galactal **4** as a glycosyl donor. Formation of the other compound **15** (Fig. 1) was not observed as evidenced from the ^1H NMR spectrum of the product. This selectivity may be attributed to the greater coordinating tendency of $InCl_3$ toward a primary allylic hydroxy group over the secondary allylic one. The double unsaturation present in compound **14** provides scope for further synthetic manipulations toward complex carbohydrates.



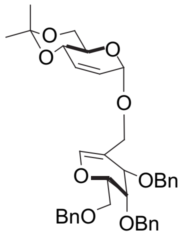
Scheme 2. Synthesis of 2-*C*-methylene glycosides via $InCl_3$ catalyzed Ferrier rearrangement of 2-*C*-hydroxymethyl glycals **3** and **4**.

It is well documented in literature that Lewis acid ($BF_3 \cdot Et_2O$[35] or $InCl_3$[11b]) catalyzed or Brønsted acid (trifluoroacetic acid) mediated[13] Ferrier rearrangement of 2-*C*-acetoxymethyl glycals **1a** or 2-*C*-hydroxymethyl glycals **3** or **4** afforded directly chiral pyrano[2,3-*b*]benzopyrans **17** through a domino Ferrier

Table 1
Synthesis of 2-*C*-methylene glycosides via $InCl_3$ catalyzed Ferrier rearrangement of 2-*C*-hydroxymethyl glycals **3** and **4**

Entry	Reactant	R	Product	Yield[b] (%)	Ratio[c] (α:β)
1	**3**	CH_3–	**5**[a]	88	95:5 (100)
2	**3**	$C_6H_5CH_2$–	**6**[a]	85	80:20 (67:33)
3	**3**	$–CH_2CH{=}CH_2$	**7**[a]	85	82:18 (90:10)
4	**3**		**8**	79	83:17 (92:8)
5	**3**		**9**	73	83:17 (90:10)
6	**4**	CH_3–	**10**[a]	92	93:7 (96:4)
7	**4**	$C_6H_5CH_2$–	**11**[a]	93	89:11 (88:12)
8	**4**	$–CH_2CH{=}CH_2$	**12**[a]	80	91:9 (100)
9	**4**		**13**	82	91:9 (100)
10	**4**		**14**	87	89:11(100)

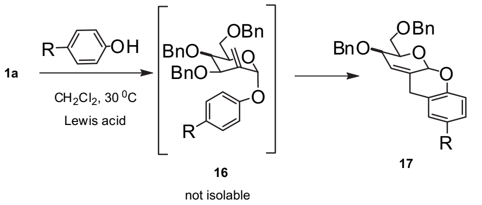
[a] Spectral data are consistent with literature reported values (see Ref. 33).
[b] Isolated yields after column chromatography.
[c] Anomeric ratios were obtained from ^1H NMR spectra of the crude product; values in parenthesis refer to the anomeric ratio of the products obtained after column chromatography.



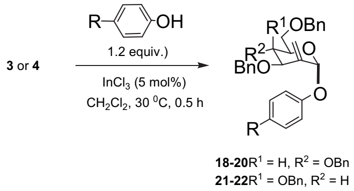
15

Figure 1. Structure of compound **15**.

rearrangement–intramolecular cyclization (Scheme 3). Except for a couple of examples reported by Vankar and Gupta,[11c] in none of the other cases, the intermediate 2-*C*-methylene aryl glycosides **16** could be isolated. The Mitsunobu approach[34] reported earlier for the synthesis of 2-*C*-methylene aryl glycosides lacked stereo and regioselectivity and also required an excess of Ph_3P (2.2 equiv) and DEAD (2.4 equiv). In carbohydrate chemistry, 2,3-unsaturated aryl glycosides have served as useful precursors for palladium catalyzed stereoselective synthesis of *C*-glycosides and *C*-aryl glycosides.[36] On the contrary, the chemistry of 2-*C*-methylene aryl glycosides remains largely unexplored mainly due to the paucity of convenient methods for their synthesis. Thus, there is a need for the development of a simple and a reliable methodology in order to unravel the synthetic potential of 2-*C*-methylene aryl glycosides. With this aim, we investigated the $InCl_3$ catalyzed reaction of 2-*C*-hydroxymethyl glucal **3** with phenol. As in the case of alcohols, the reaction of 2-*C*-hydroxymethyl glucal with phenol in presence of 5 mol % of $InCl_3$, was also found to be very facile. The reaction was over in half an hour affording the 2-*C*-methylene aryl glycoside **18** in 84% yield with an anomeric ratio of 90:10, the α-anomer being the major one (Scheme 4; Entry 1, Table 2). Under this condition, formation of pyrano[2,3-*b*]benzopyran such as **17** was not observed. The reaction was found to be general with unsubstituted as well as with a few substituted phenols and the 2-*C*-methylene aryl glycosides were isolated in high yields. The reaction of 2-*C*-hydroxymethyl galactal **4** with phenols also proceeded with equal ease (Scheme 4; Table 2, Entries 4 and 5). Noteworthy is that earlier attempts to obtain 2-*C*-methylene aryl glycosides by conventional Ferrier rearrangement were all unsuccessful.[11b,35] With a view of investigating the further reactivity of 2-*C*-methylene aryl glycosides with $InCl_3$, we then exposed the isolated 2-*C*-methylene aryl glycoside **22** to 5 mol % of $InCl_3$ in CH_2Cl_2. Glycoside **22** underwent a smooth intramolecular cyclization, under this condition, to afford pyrano[2,3-*b*]benzopyran **23** in 3 h (Scheme 5). The tunability of the reaction condition toward the desired product (either toward the 2-*C*-methylene aryl glycoside or pyrano[2,3-*b*]benzopyran) thus highlights the added advantage of the present protocol.



Scheme 3. Literature synthesis of pyrano[2,3-*b*]benzopyrans through a domino Ferrier rearrangement–intramolecular cyclization.[11b,13,35]

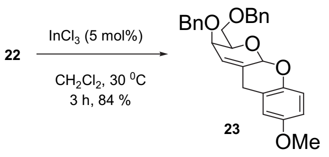


Scheme 4. Synthesis of 2-*C*-methylene aryl glycosides via $InCl_3$ catalyzed Ferrier rearrangement of 2-*C*-hydroxymethyl glycals **3** and **4** with phenols.

Table 2
Synthesis of 2-*C*-methylene aryl glycosides via $InCl_3$ catalyzed Ferrier rearrangement of 2-*C*-hydroxymethyl glycals **3** and **4** with phenols

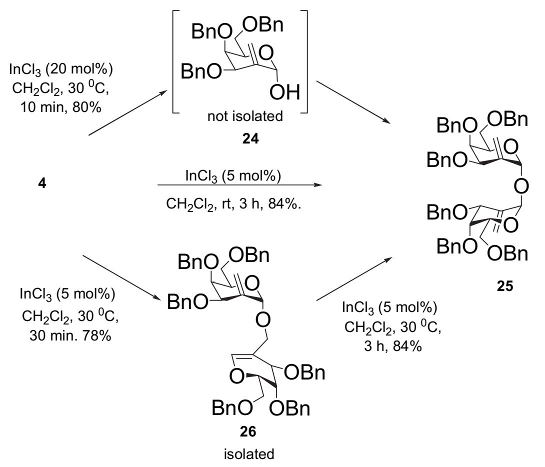
Entry	Reactant	R′	Product	Yield[b] (%)	Ratio[c](α:β)
1	**3**	–H	**18**	84	89:11(90:10)
2	**3**	–Me	**19**[a]	78	81:19 (88:12)
3	**3**	–OMe	**20**[a]	82	81:19 (93:7)
4	**4**	–Me	**21**[a]	81	100 (100)
5	**4**	–OMe	**22**[a]	88	88:12 (90:10)

[a] Spectral data are consistent with literature reported values (see Ref.34).
[b] Isolated yields after column chromatography.
[c] Anomeric ratios were obtained from ^1H NMR spectra of the crude products; values in parenthesis refer to the anomeric ratio of the products obtained after column chromatography.



Scheme 5. Synthesis of pyrano[2,3-*b*]benzopyran **23** from 2-*C*-methylene aryl glycoside **22**.

Previously, we had reported a facile and rapid one-pot conversion of 2-*C*-hydroxymethyl galactal **4** to an α,α-(1→1)linked disaccharide derivative **25** in presence of 20 mol % of $InCl_3$ (Scheme 6).[33] Initially, 1,3-alkoxy migration followed by an in-situ glycosidation reaction was believed to be the reaction pathway as the intermediate **24** could not be isolated. In order to have an insight in to the exact mechanistic pathway, the reaction was re-investigated with 5 mol % of $InCl_3$. Thus, when 2-*C*-hydroxymethyl galactal **4** was treated with 5 mol % of $InCl_3$ in dry CH_2Cl_2, the starting material was completely consumed in 0.5 h. Interestingly, the ^1H NMR spectrum of the product isolated from the reaction was different from that of α,α-(1→1)linked disaccharide derivative **25** observed earlier. After careful analysis of the ^1H NMR and ^{13}C NMR spectral data, the product was identified to be a disaccharide **26** arising out of self Ferrier rearrangement of one molecule of 2-*C*-hydroxymethyl galactal with another one (Scheme 6). Subsequently, the disaccharide **26** on exposure to an additional 5 mol % of $InCl_3$ underwent a stereoselective 1,3-alkoxy migration reaction[33] affording the α,α-(1→1)linked disaccharide **25** derivative in 3 h, in an isolated yield of 84%, whose spectral data were identical with the compound reported earlier. Alternatively, reaction of 2-*C*-hydroxymethyl galactal **4** with 5 mol % of $InCl_3$ yielded directly the α,α-(1→1)linked disaccharide derivative **25** in 3 h, in 84% yield. These experiments clearly reveal that the direct formation of the α,α-(1→1)linked disaccharide derivative from 2-*C*-hydroxymethyl galactal **4** proceeds through an initial Ferrier rearrangement followed by a stereoselective 1,3-alkoxy migration and not via the pathway earlier thought of.



Scheme 6. Direct formation of the α,α-(1→1)linked disaccharide derivative via Ferrier rearrangement followed by 1,3-alkoxy migration: A mechanistic investigation.

3. Conclusions

In conclusion, we have demonstrated for the first time that $InCl_3$ efficiently catalyzes a direct allylic substitution of hydroxy group of 2-*C*-hydroxymethyl glycals with a wide array of oxygen nucleophiles. Synthetic significance of the present protocol is that it demonstrates that prior protection of the allylic hydroxy groups of glycals is not a pre-requisite to realize Ferrier rearrangement successfully. Since only 5 mol % of the $InCl_3$ is required, the reaction condition is mild thus making it compatible for glycosyl acceptors having acid-labile groups, which is not the case with most of the literature available routes. The methodology is simple, void of expensive chemicals and versatile resulting in the formation of a wide variety of unsaturated alkyl glycosides, aryl glycosides as well as disaccharides. Stereoselectivity of the reaction is comparable with other methods and even higher in some cases. The methodology paves way for the isolation of 2-*C*-methylene aryl glycosides for which no reliable method is available. Initial Ferrier rearrangement followed by a stereoselective 1,3-alkoxy migration has been shown to be the mechanistic pathway for the direct formation of the α,α-(1→1)linked disaccharide derivative from 2-*C*-hydroxymethyl galactal. We strongly believe that the simplicity of the methodology reported here would spur on further research activities in the area of unsaturated glycosides.

4. Experimental

4.1. General considerations

All solvents were purified using standard procedures. Thin-layer chromatography (TLC) was performed on Merck silica gel precoated on aluminum plates. Flash column chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on 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 within the range 4000–400 cm^{-1} as KBr pellets on a Nicolet (Madison, USA) FTIR spectrophotometer (Model Protege 460). All the ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker Spectrospin DPX FT NMR. Chemical shifts are reported as δ values (ppm) relative to internal standard Me_4Si. Mass spectra were recorded using Applied Biosystems Q-Star instrument.

4.1.1. 6-O-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-D-arabino-hexopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***8***. Glycal **3** (220 mg, 0.493 mmol) was stirred with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (153 mg, 0.591 mmol) in presence of 5 mol % of anhydrous $InCl_3$ (5.4 mg, 0.024 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (30% EtOAc/Hexane) to give the title compound **8** (268 mg, 79%) as a colorless liquid. The product was obtained a mixture of anomers (α:β=92:8) from which the anomers were not separated. R_f (30% EtOAc/Hexane) 0.43; Specific rotation reported here is for the anomeric mixture; $[\alpha]_D^{28}$ −2.6 (*c* 1.20, $CHCl_3$); υ_{max} (KBr) 3061, 3030, 2986, 2911, 1663, 1495, 1455, 1375, 1312, 1253, 1210, 1071, 1003, 916, 858, 740, 698 cm^{-1}; δ_H and δ_C values reported here correspond to the signals of only α-anomer taken from a mixture of α and β anomers; δ_H (300 MHz, $CDCl_3$) δ 7.36–7.15 (15H, m, aromatic), 5.52 (1H, d, *J*=4.5 Hz, H-1), 5.29 (1H, s, H-7a′), 5.24 (1H, s, H-1′), 5.14 (1H, s, H-7b′), 4.86 (1H, d, *J*=10.5 Hz, OCH_2Ph), 4.76 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.70 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.64 (1H, d, *J*=12.6 Hz, OCH_2Ph), 4.58–4.43 (4H, m), 4.31–4.22 (2H, m), 4.00–3.98 (2H, m), 3.70–3.61 (5H, m), 1.52 (3H, s, $(CH_3)_2C$), 1.43 (3H, s, $(CH_3)_2C$), 1.32 (6H, s, $(CH_3)_2C$); δ_C (75 MHz, $CDCl_3$) 142.2, 138.3, 138.3, 138.1, 128.4, 128.2, 127.9, 127.8, 127.6, 127.6, 127.5, 110.7, 109.2, 108.5, 101.1, 96.2, 81.1, 79.8, 74.9, 73.4, 73.3, 71.7, 70.8, 70.5, 68.5, 65.6, 65.3, 29.1, 25.9, 24.9, 24.5; HRMS (ESI): $[M+Na]^+$ found: 711.3138. $C_{40}H_{48}O_{10}Na$ requires 711.3145.

4.1.2. 3-O-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-D-arabino-hexopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose ***9***. Glycal **3** (197 mg, 0.441 mmol) was stirred with 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (137 mg, 0.529 mmol) in presence of 5 mol % of anhydrous $InCl_3$ (4.8 mg, 0.022 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (30% EtOAc/Hexane) to give the title compound **9** (220 mg, 73%) as a colorless liquid. The product was obtained as mixture of anomers (α:β=90:10) from which the anomers were not separated. R_f (30% EtOAc/Hexane) 0.38; Specific rotation reported here is for the anomeric mixture; $[\alpha]_D^{28}$ 17.3 (*c* 0.80, $CHCl_3$); υ_{max} (KBr) 3062, 3030, 2986, 2929, 1612, 1495, 1455, 1373, 1322, 1252, 1214, 1072, 1030, 850, 742, 699, 633 cm^{-1}; δ_H and δ_C values reported here correspond to the signals of only α-anomer taken from a mixture of α and β anomers; δ_H (300 MHz, $CDCl_3$) δ 7.41–7.20 (15H, m, aromatic), 5.88 (1H, d, *J*=3.0 Hz, H-1), 5.53 (1H, s, H-1′), 5.32 (1H, s, H-7a′), 5.19 (1H, s, H-7b′), 4.90 (1H, d, *J*=10.5 Hz, OCH_2Ph), 4.80 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.74 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.70–4.64(2H, m), 4.56–4.50 (2H, m) 4.44–4.38 (2H, m), 4.24–4.10 (3H, m), 4.04–3.99 (2H, m), 3.84–3.63 (3H, m), 1.53 (3H, s, $(CH_3)_2C$), 1.45 (3H, s, $(CH_3)_2C$), 1.38 (3H, s, $(CH_3)_2C$), 1.29 (3H, s, $(CH_3)_2C$); δ_C (75 MHz, $CDCl_3$) 141.5, 138.1, 138.0, 138.0, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 111.9, 111.0, 109.2, 105.2, 101.8, 83.8, 81.5, 80.9, 79.6, 79.5, 75.0, 73.5, 73.4, 72.3, 68.7, 67.7, 26.8, 26.7, 26.1, 25.4; HRMS (ESI): $[M+Na]^+$ found: 711.3165. $C_{40}H_{48}O_{10}Na$ requires 711.3145.

4.1.3. 6-O-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-D-lyxo-hexopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***13***. Glycal **4** (220 mg, 0.493 mmol) was stirred with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (153 mg, 0.591 mmol) in presence of 5 mol % of anhydrous $InCl_3$ (5.4 mg, 0.024 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (30% EtOAc/Hexane) to give the title compound **13** (280 mg, 82%) as a colorless liquid. The product was obtained as a pure α-anomer. R_f (30% EtOAc/Hexane) 0.41; $[\alpha]_D^{28}$ −5.3 (*c* 0.60, $CHCl_3$); υ_{max} (KBr) 3061, 3030, 2986, 2922, 1734, 1608, 1494, 1455, 1374, 1305, 1252, 1211, 1163, 1070, 1001, 912, 811, 743, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.23 (15H, m, aromatic), 5.51 (1H, d, *J*=5.1 Hz, H-1), 5.40 (1H, s, H-7a′), 5.26 (1H, s, H-1′), 5.24 (1H, s, H-7b′), 4.89 (1H, d, *J*=11.7 Hz, OCH_2Ph), 4.71–4.57 (4H, m), 4.48–4.37 (3H, m), 4.31–4.29 (1H, m), 4.24–4.17 (2H, m), 4.00 (2H, br s), 3.77–3.73 (2H, m), 3.56–3.54 (2H, m), 1.51 (3H, s, $(CH_3)_2C$), 1.41 (3H, s, $(CH_3)_2C$), 1.32 (6H, s, $(CH_3)_2C$); δ_C (75 MHz, $CDCl_3$) 140.7, 138.7, 138.4, 138.1, 128.4, 128.3, 128.3, 128.1, 127.8, 127.6, 127.5, 127.1, 111.5, 109.2, 108.5, 101.1, 96.3, 78.1, 75.3, 74.0, 73.3, 71.6, 71.0, 70.6, 70.5, 69.0, 65.8, 65.4, 26.1, 25.9, 24.9, 24.5; HRMS (ESI): $[M+Na]^+$ found: 711.3125. $C_{40}H_{48}O_{10}Na$ requires 711.3145.

4.1.4. 1,5-Anhydro-3-O-(3,4,6-tri-O-benzyl-2-deoxy-2-C-methylene-D-lyxo-hexopyranosyl)-2-deoxy-4,6-O-isopropylidene-D-arabino-hex-1-enitol ***14***. Glycal **4** (300 mg, 0.672 mmol) was stirred with 4,6-*O*-isopropylidene-D-glucal (150 mg, 0.807 mmol), in presence of 5 mol % of anhydrous $InCl_3$ (7.0 mg, 0.0336 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (30% EtOAc/Hexane) to give the title compound **14** (360 mg, 87%) as a colorless liquid. The product was obtained as a pure α-anomer. R_f (30% EtOAc/Hexane) 0.33; $[\alpha]_D^{28}$ −5.5 (*c* 0.20, $CHCl_3$); υ_{max} (KBr) 3029, 2922, 2858, 1640, 1456, 1370, 1309, 1267, 1230, 1155, 1099, 1004, 868, 744, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 7.37–7.23 (15H, m, aromatic), 6.28 (1H, dd, *J*=6.0, 1.5 Hz, H-1), 5.65 (1H, s, H-1′), 5.39 (1H, s, H-7a′), 5.20 (1H, s, H-7b′), 4.89 (1H, d, *J*=12.0 Hz, OCH_2Ph), 4.73–4.60 (4H, m), 4.50–4.38 (4H, m), 4.17 (1H, t, *J*=6.3 Hz), 4.02–3.91 (3H, m), 3.84–3.75 (2H, m), 3.59–3.57 (2H, m), 1.51 (3H, s, $(CH_3)_2C$), 1.39 (3H, s, $(CH_3)_2C$); δ_C (75 MHz, $CDCl_3$) 144.6, 140.9, 138.6, 138.4, 138.0, 128.4, 128.4, 128.4, 128.1, 127.8, 127.7, 127.5, 127.1, 111.3, 102.7, 101.4, 99.5, 78.2, 75.2, 74.0, 73.5, 72.9, 71.7, 70.9, 69.6, 69.3, 61.7, 29.0, 19.2; HRMS (ESI): $[M+Na]^+$ found: 637.2767. $C_{37}H_{42}O_8Na$ requires 637.2777.

4.1.5. Phenyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-methylene-D-arabino-hexopyranoside ***18***. Glycal **3** (210 mg, 0.45 mmol) was stirred with phenol (50.8 mg, 0.540 mmol), in presence of 5 mol % anhydrous $InCl_3$ (4.9 mg, 0.022 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (10% EtOAc/Hexane) to give the title compound **18** (198 mg, 84%) as a colorless liquid. The product was obtained as mixture of anomers (α:β=90:10) from which the anomers were not separated. R_f (10% EtOAc/Hexane) 0.30; Specific rotation reported here is for the anomeric mixture; $[\alpha]_D^{28}$ 24.0 (*c* 0.50, $CHCl_3$); υ_{max} (KBr) 3063, 3031, 2922, 2858, 1740, 1593, 1492, 1455, 1403, 1359, 1320, 1220, 1100, 1033, 980, 922, 845, 744, 696 cm^{-1}; δ_H and δ_C values reported here correspond to the signals of only α-anomer taken from a mixture of α and β anomers; δ_H (300 MHz, $CDCl_3$) 7.41–6.98 (20H, m, aromatic), 5.89 (1H, s, H-1), 5.39 (1H, s, H-7a), 5.24 (1H, s, H-7b), 4.89 (1H, d, *J*=10.8 Hz, OCH_2Ph), 4.83 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.77 (1H, d, *J*=11.4 Hz, OCH_2Ph), 4.64–4.58 (2H, m), 4.51 (1H, d, *J*=10.8 Hz, OCH_2Ph), 4.41 (1H, d, *J*=12.0 Hz, OCH_2Ph), 4.07–4.04 (1H, m), 3.81–3.68 (2H, m), 3.60 (1H, dd, *J*=10.5, 1.5 Hz, H-6); δ_C (75 MHz, $CDCl_3$) 156.3, 141.4, 138.2, 137.9, 129.7, 129.4, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.6, 127.5, 122.1, 116.7, 111.4, 99.8, 81.0, 79.6, 75.0, 73.5, 73.3, 72.1, 68.4; HRMS (ESI): $[M+Na]^+$ found: 545.2282. $C_{34}H_{34}O_5Na$ requires 545.2304.

4.1.6. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(3,4,6-tri-O-benzyl-2-deoxy-2-C-methylene-α-D-lyxo-hexopyranosyloxy)-methyl-D-lyxo-hex-1-enitol ***26***. Glycal **4** (135 mg, 0.302 mmol) was stirred with 5 mol % of anhydrous $InCl_3$ (3.3 mg, 0.0235 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature for 30 min after which the reaction mixture was quenched with water and extracted with chloroform (2×50 mL). The organic layer was dried over sodium sulfate, filtered and then concentrated. The crude product was purified by column chromatography (20% EtOAc/Hexane) to give the title compound **26** (104 mg, 78%) as a colorless liquid. Product was obtained as a pure α-anomer. R_f (20% EtOAc/Hexane) 0.25; $[\alpha]_D^{28}$ 3.3 (*c* 0.30, $CHCl_3$); υ_{max} (KBr) 3030, 2918, 2866, 1658, 1500, 1456, 1357, 1254, 2094, 1012, 913, 742, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.24 (30H, m, aromatic), 6.39 (1H, s, H-1), 5.36 (1H, s, H-7a′), 5.18 (1H, s, H-1′), 5.13 (1H, s, H-7b′), 4.89 (1H, d, *J*=11.7 Hz, OCH_2Ph), 4.78 (1H, d, *J*=12.0 Hz, OCH_2Ph), 4.75 (1H, d, *J*=11.1 Hz, OCH_2Ph), 4.70–4.60 (4H, m), 4.57 (1H, d, *J*=11.1 Hz, OCH_2Ph), 4.50 (1H, d, *J*=11.7 Hz, OCH_2Ph), 4.40–4.31 (5H, m), 4.25 (1H, m), 4.19 (1H, m), 4.09 (1H, t, *J*=6.3 Hz), 3.94 (2H, br s), 3.86–3.75 (2H, m), 3.66 (1H, dd, *J*=10.2, 4.2 Hz, H-6), 3.51–3.49 (2H, m); δ_C (75 MHz, $CDCl_3$) 143.7, 141.1, 138.6, 138.4, 138.10, 138.0, 137.9, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.1, 111.0, 108.9, 98.9, 78.1, 75.7, 75.2, 74.0, 73.5, 73.4, 73.1, 71.4, 71.3, 70.7, 69.3, 68.1, 64.2; HRMS (ESI): $[M+Na]^+$ found: 897.3974. $C_{56}H_{58}O_9Na$ requires 897.3979.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **5**–**14**; **18**–**22** and **26**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.11.082.

References and notes

1. Horvath, A.; Ruttens, B.; Herdewijn, P. *Tetrahedron Lett.* **2007**, *48*, 3621–3623.
2. Mehta, G.; Pallavi, K. *Tetrahedron Lett.* **2004**, *45*, 3865–3867.
3. Rekai, E. D.; Rubinstenn, G.; Mallet, J.-M.; Sinaÿ, P.; Müller, S. N.; Giese, B. *Synlett* **1998**, 831–834.
4. Jung, M. E.; Choe, S. W. T. *J. Org. Chem.* **1995**, *60*, 3280–3328.
5. Jendrzejewski, S.; Ermann, P. *Tetrahedron Lett.* **1993**, *34*, 615–618.
6. (a) Hamann, H.-J.; Chmielewski, M.; Mostowicz, D.; Liebscher, J. *ARKIVOC* **2007**, 17–20; (b) Kosnik, W.; Stachulski, A. V.; Chmielewski, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1975–1981; (c) Hamann, H.-J.; Hoft, E.; Mostowicz, D. M.; Mishnev, A.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1997**, *53*, 185–192.
7. Gupta, P.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 1925–1933.
8. (a) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 812–819; (b) Baker, C. H.; Banzon, J. M.; Bollinger, J. M.; Stubbe, J.; Samano, V.; Robins, M. J.; Lippert, B.; Jarvi, E.; Resvick, R. *J. Med. Chem.* **1991**, *34*, 1879–1884.
9. (a) Wong, G.; Fraser-Reid, B. *Can. J. Chem.* **1994**, *72*, 69–74; (b) Sarda, P.; Olesker, A.; Lukacs, G. *Carbohydr. Res.* **1992**, *229*, 161–165.
10. (a) Ramesh, N. G.; Balasubramanian, K. K. *Eur. J. Org. Chem.* **2003**, 4477–4487; (b) Booma, C.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1993**, 1394–1395.
11. (a) Kashyap, S.; Vidadala, S. R.; Hotha, S. *Tetrahedron Lett.* **2007**, *48*, 8960–8962; (b) Ghosh, R.; Chakraborty, A.; Maiti, D. K.; Puranik, V. G. *Tetrahedron Lett.* **2005**, *46*, 8047–8051; (c) Gupta, A.; Vankar, Y. D. *Tetrahedron* **2000**, *56*, 8525–8531; (d) Bouoit, S.; Goux, C.; Sinou, D. *Carbohydr. Lett.* **1997**, *2*, 267–272.
12. One difficulty often encountered by us is the purification of 2-*C*-acetoxylmethyl-glycals **1a**. 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-life of more than a couple of days even at low temperatures. Such a rearrangement on furanose-derived 2-*C*-(acetoxymethyl)-glycals has already been reported. See: (a) Wolf, J.; Monneret, C.; Pontikis, R.; Florent, J.-C. *Eur. J. Org. Chem.* **1998**, 2417–2423; (b) Pontikis, R.; Wolf, J.; Monneret, C.; Florent, J.-C. *Tetrahedron Lett.* **1995**, *36*, 3523–3526.
13. Santhi, M.; Balasubramanian, K. K.; Bhagavathy, S. *Carbohydr. Res.* **2009**, *344*, 521–525.
14. (a) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574; (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729.
15. (a) Yadav, J. S.; Reddy, B. V. S.; Rao, T. S.; Rao, K. V. R. *Tetrahedron Lett.* **2008**, *49*, 614–618; (b) Yang, X.; Knochel, P. *Chem. Commun.* **2006**, 2486–2488; (c) Kundu, A.; Roy, S. *Organometallics* **2000**, *19*, 105–107; (d) Ishii, T.; Kawamura, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Hitomi, T. *J. Org. Chem.* **1987**, *52*, 4418–4420.
16. (a) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591; (b) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2751–2764.
17. Gruber, S.; Zaitsev, A. B.; Worle, M.; Pregosin, P. S. *Organometallics* **2009**, *28*, 3437–3448.
18. (a) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650; (b) Gan, K.-H.; Jhong, C.-J.; Yang, S.-C. *Tetrahedron* **2008**, *64*, 1204–1212; (c) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2006**, *4*, 1278–1283; (d) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627–3629; (e) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737; (f) Yamamoto, Y.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1995**, 2013–2014.
19. (a) Ohri, R. V.; Redosevich, A. T.; Hrovt, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501–2504; (b) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325–1327; (c) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760–15761; (d) Sherry, B. D.; Redosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077.
20. Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664–10665.
21. Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161–5167.
22. (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501–1507; (b) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065–4069; (c) Zhan, Z.-p.; Yu, J.-L.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem.* **2006**, *71*, 8298–8301.
23. Kothandaraman, P.; Rao, W.; Zhang, X.; Chan, P. W. H. *Tetrahedron* **2009**, *65*, 1833–1838.
24. De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 8345–8350.
25. (a) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, *9*, 825–828; (b) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003–9005; (c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 4861–4864.
26. Lian, Y.; Hinkle, R. J. *J. Org. Chem.* **2006**, *71*, 7071–7074.
27. (a) Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Yadav, J. S. *Synlett* **2008**, *7*, 1045–1049; (b) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, *72*, 8588–8590.
28. Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516–8522.
29. Yadav, J. S.; Sunitha, V.; Reddy, B. V. S.; Das, P. P.; Gyanchander, E. *Tetrahedron Lett.* **2008**, *49*, 855–857.
30. (a) Kan, S. B. J.; Matsubara, R.; Berthiol, F.; Kobayashi, S. *Chem. Commun.* **2008**, 6354–6356; (b) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337; (c) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841–1845.
31. (a) Baba, A.; Yasuda, M.; Nishimoto, Y.; Saito, T.; Onishi, Y. *Pure Appl. Chem.* **2008**, *80*, 845–854; (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793–796.
32. Nagaraj, P.; Ramesh, N. G. *Tetrahedron Lett.* **2009**, *50*, 3970–3973.
33. Nagaraj, P.; Ramesh, N. G. *Eur. J. Org. Chem.* **2008**, 4607–4614.
34. Ramesh, N. G.; Balasubramaniam, K. K. *Tetrahedron* **1995**, *51*, 255–272.
35. Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1993**, *34*, 6757–6760.
36. (a) Chaguir, B.; Brakta, M.; Bolitt, V.; Lhoste, P.; Sinou, D. *J. Carbohydr. Chem.* **1992**, *11*, 609–625; (b) Bolitt, V.; Chaguir, B.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 2481–2484; (c) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890–1896; (d) Brakta, M.; Le Borgne, F.; Sinou, D. *J. Carbohydr. Chem.* **1987**, *6*, 307–311.