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HSAB-driven regioselectivity difference in the Lewis-acid catalyzed reactions of 2-*C*-substituted glycals with sulfur and oxygen nucleophiles: direct versus allylic substitution

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ABSTRACT

A remarkable regioselectivity difference in the Lewis-acid catalyzed reactions of 2-*C*-acteoxymethyl glycals with thiophenols and phenols has been observed. The reaction with thiophenols led to *preferential* formation of a new class of compounds viz. 2-*C*-arylthiomethyl glycals via direct attack at the *C*-2 side chain primary carbon bearing the leaving group. In contrast, phenols were reported to afford *predominantly* 2-*C*-methylene-*O*-aryl glycosides via allylic attack at the anomeric carbon. The observed results correlate well with the HSAB principle proposed earlier for similar type of reactions with simple glycals. In addition, formation of an unusual bis-thioarylated product in presence of an excess of thiophenol is also reported.

1. Introduction

Carbohydrates are ubiquitous in nature and play vital roles in various physiological functions and biological processes, such as cell proliferation, cell adhesion, cell–cell interactions etc.[1] In order to understand the precise roles of carbohydrates in biological systems, it is essential to isolate complex oligosaccharides in pure and homogeneous forms. However, this has become a formidable task due to the existence of oligosaccharides in micro-heterogeneity forms and hence it has been realized that chemical synthesis is the viable alternative to obtain homogeneous oligosaccharides in large quantities.[2] Oligosaccharides are generally synthesized through glycosylation reaction of a protected glycosyl donor and an aglycon in presence of a promoter or an activator.[2,3] In this context, thioglycosides have received immense attention of chemists due to their unique and dual reactivity of acting both as glycosyl donors as well as acceptors.[2–4] Furthermore, their high stability, long shelf-life, remarkable tolerance towards various chemical manipulations coupled with their facile activation with thiophilic reagents under mild conditions make them the preferred choice of glycosyl donors in oligosaccharide synthesis. Conventional synthesis of thioglycosides involves a Lewis-acid catalyzed nucleophilic displacement of a suitable leaving group by thiols at the anomeric carbon of sugars.[4] Among the various thioglycosides that have been investigated, 2,3-unsaturated thioglycosides enjoyed immense applications in carbohydrate chemistry, as the unsaturation allowed the introduction of a variety of functionalities through chemical transformations.[5]

The most common method to access 2,3-unsaturated thioglycosides is through the acid catalyzed Ferrier rearrangement of glycals with thiols (Scheme 1).[6] This rearrangement was reported to be condition dependant resulting in the formation of two regioisomeric products, namely, 2,3-dideoxy-hex-2-enothiopyranosides **2** and 3-deoxy-3-alkylthio-hex-2-enitols **3**, the former being the kinetic product and the latter the thermodynamic one (Scheme 1). The product distribution, however, could be tuned towards either one of them by properly defining the reaction conditions.[6] Complete equilibration of the kinetic to the thermodynamic product could be effected in presence of a Lewis acid,[6,7] longer reaction time or even during chromatographic purification of **2** over silica gel.[8] On the other hand, literature reports on the *exclusive* formation of 2,3-dideoxy-hex-2-enothiopyranoside **2** are also quite abundant.[9] A

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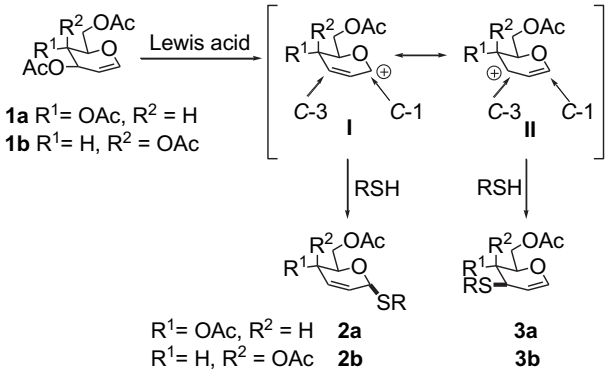
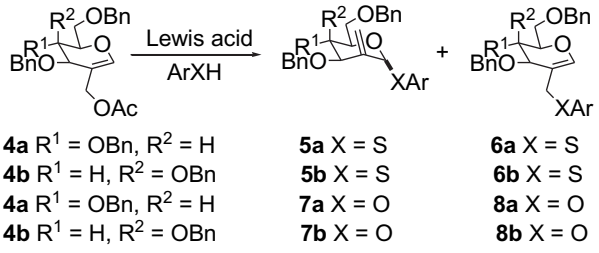
plausible explanation based on Pearson's HSAB (Hard Soft Acid Base) concept was proposed by Priebe and Zamojski for the formation of the regioisomers under different reaction conditions.[6]



Scheme 1. Lewis-acid catalyzed reactions of thiols with glycals.

As a part of our research on the use of unsaturated carbohydrates for the synthesis of small natural and unnatural biologically active compounds, we became interested in exploring the Lewis-acid catalyzed reaction of 2-*C*-acetoxymethyl glycals **4** with thiophenols. Surprisingly, a thorough literature search revealed that this reaction remained uninvestigated so far, although similar reaction with phenols has been explored in detail by several groups.[10] Interest in this research arose not only from the synthetic point of view, but from its mechanistic aspect as well, as this reaction is also expected to yield two regioisomeric products. If the reaction proceeds in a similar fashion as phenols react, one would expect the formation of the 2-*C*-methylene arylthioglycosides **5**. On the other hand, sulfur being a soft nucleophile, an HSAB-driven reaction would give rise to 2-*C*-arylthiomethyl glycals **6** as the major products. Formation of either or both of them is advantageous as these are versatile substrates for further synthetic exploitations. Experimental results of the Lewis-acid catalyzed reaction of 2-*C*-substituted glycals with thiophenols are quite suggestive of the influence of HSAB principle. The reaction afforded predominantly *hitherto unreported* 2-*C*-arylthiomethyl glycals **6a** via direct attack at the *C*-2 side chain primary carbon bearing the leaving group with only a trace amount (not isolable in pure forms) of products **5** arising out of Ferrier rearrangement. In contrast, phenols were reported to afford *predominantly* 2-*C*-methylene-*O*-aryl glycosides **7** via allylic attack at the anomeric carbon (Scheme 2) under acidic conditions. Further, unusual formation of a dithioarylated derivative **28** in presence of an excess of thiophenol that further supports the HSAB concept is also reported in this article.

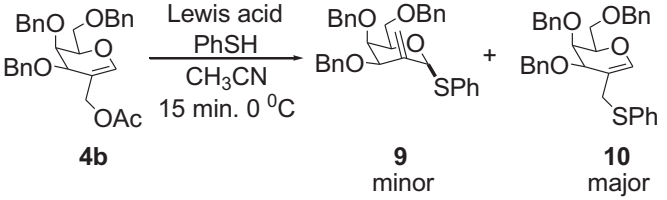


Scheme 2. Lewis-acid catalyzed reactions of thiophenols and phenols with 2-*C*-acetoxymethyl glycals **4a** and **4b**.

2. Results and discussion

The required starting materials, namely, 3,4,6-tri-*O*-benzyl-2-*C*-acetoxymethyl glycals **4a** and **4b**, were prepared according to the literature reported procedure.[11] In a preliminary experiment, compound **4b** was treated with 1.0 equiv of thiophenol in the presence of 20 mol % of $BF_3 \cdot Et_2O$ at 0 °C in acetonitrile as the solvent and the progress of the reaction was monitored by TLC. The reaction was found to be complete in 15 min as indicated by the disappearance of the spot due to the starting material and appearance of a new spot in TLC. The product was purified by column chromatography over silica gel. Analysis of the ^1H NMR spectrum of the product revealed the presence of only one olefinic proton in the molecule (that resonated at δ 6.14 as a singlet) indicating the formation of 2-*C*-phenylthiomethyl galactal **10**. This was further supported by its ^{13}C NMR spectrum, which displayed a signal at δ 108.7 (resonating as a singlet in its off-resonance spectrum) and another signal at δ 141.6 (resonating as a doublet in its off-resonance spectrum) due to the β-olefinic and α-olefinic carbons of the enol–ether moiety of **10**, respectively. On the other hand, the Ferrier rearranged product **9** should display two signals in the olefinic region in its ^1H NMR spectrum for the two terminal *exo*-methylene protons and two signals in the ^{13}C NMR spectrum (a singlet and a triplet in the off-resonance spectrum) for the olefinic carbons as well. The possibility of an intramolecular equilibration/isomerization of an initially formed **9** to **10** during purification by column chromatography over silica gel[8] was ruled out as the ^1H NMR spectrum of the *crude reaction mixture* itself showed the presence of **10** as the major product (≥90%), along with a very small amount (≤10%) of Ferrier rearranged product **9**. Similar results were obtained irrespective of the nature of the Lewis acid (Table 1), although $InCl_3$ was found to be the best among them in terms of mildness of the reaction and yield (Table 1, entry 3). Hence, all subsequent reactions were performed with $InCl_3$. Change in the reaction conditions, such as temperature, solvent, amount of the catalyst etc. did not bring about any significant change in the product formation.

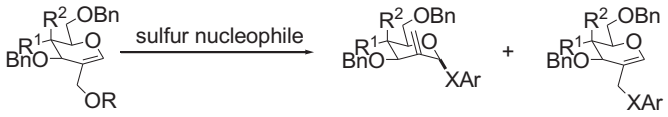
Table 1
Reaction of 2-*C*-acetoxymethyl galactal **4b** with thiophenol in presence of 20 mol % of catalyst



Entry	Catalyst	Isolated yield of **10** (%)
1	$BF_3 \cdot Et_2O$	62
2	$BiCl_3$	68
3	$InCl_3$	87
4	$ZnCl_2$	70
5	CAN	72

In order to study the effect of leaving group on the regiochemical outcome, the reaction was performed with substrates (**11**, **12** and **13**) possessing relatively poor leaving groups, such as methoxy, benzyloxy and a free hydroxyl group etc. at the *C*-2 side chain carbon. Hardly any difference was noticed in the reactivity as compared to the acetyl case (Table 2, entries 1–4). Even the reaction of 2-*C*-hydroxymethyl galactal **13** with thiophenol under Mitsunobu condition followed a similar trend (Table 2, entry 5) affording only the 2-*C*-thiophenylmethyl galactal **10** in 66% yield. The generality of $InCl_3$ catalyzed reaction was tested with a few substituted thiophenols. In all the cases, 2-*C*-arylthiomethyl galactals, **14**–**17**, were obtained as the major products and in high yields (Table 2, entries 6–9). Change in the nucleophilicity of sulfur derivatives have often been shown to alter the regioselectivity of

Table 2
Reaction of 2-*C*-substituted glycals with sulfur nucleophiles under different conditions



4a,4b,11-13 **9** **10, 14-21**

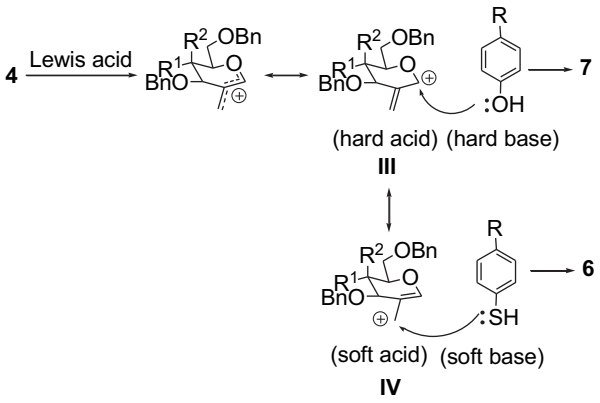
Entry	Substrate	R	R^1	R^2	Nucleophile	Reaction conditions[a]	X	Ar	Product[b]	Yield[c] %
1	**4b**	Ac	H	OBn	C_6H_5SH	A	S	C_6H_5	**10**	87
2	**11**	Me	H	OBn	C_6H_5SH	A	S	C_6H_5	**10**	62
3	**12**	Bn	H	OBn	C_6H_5SH	A	S	C_6H_5	**10**	70
4	**13**	H	H	OBn	C_6H_5SH	A	S	C_6H_5	**10**	56
5	**13**	H	H	OBn	C_6H_5SH	B	S	C_6H_5	**10**	66
6	**4b**	Ac	H	OBn	*p*-CH_3–C_6H_4–SH	A	S	*p*-CH_3–C_6H_4	**14**	84
7	**4b**	Ac	H	OBn	*p*-OCH_3–C_6H_4–SH	A	S	*p*-OCH_3–C_6H_4	**15**	84
8	**4b**	Ac	H	OBn	*p*-Cl–C_6H_4–SH	A	S	*p*-Cl–C_6H_4	**16**	85
9	**4b**	Ac	H	OBn	*p*-Br–C_6H_4–SH	A	S	*p*-Br–C_6H_4	**17**	80
10	**4b**	Ac	H	OBn	$PhSO_2Na$	C	SO_2	C_6H_5	**18**	84
11	**4a**	Ac	OBn	H	C_6H_5SH	A	S	C_6H_5	**19**	78
12	**4a**	Ac	OBn	H	*p*-CH_3–C_6H_4–SH	A	S	*p*-CH_3–C_6H_4	**20**	80
13	**4a**	Ac	OBn	H	*p*-OCH_3–C_6H_4–SH	A	S	*p*-OCH_3–C_6H_4	**21**	82

[a] A: $InCl_3$ (20 mol %), (substituted) thiophenols (1 equiv), CH_3CN, 0 °C, 15 min; B: Ph_3P (1.5 equiv), DEAD (1.5 equiv), thiophenol (1 equiv). dry benzene, 0 °C, 30 min; C: $InCl_3$ (20 mol %), $PhSO_2Na$ (1.1 equiv), CH_3CN, room temperature, 1 h.
[b] In all these cases, the 2-*C*-methylene-thioglycosides, such as **9**, were obtained only in very small quantities that were not isolated.
[c] Isolated yields after column chromatography.

organic reactions. In view of this, it was of interest to study the reaction with another sulfur based nucleophile and hence readily available sodium benzensulfinate was chosen for this purpose. $InCl_3$ catalyzed reaction of compound **4b** with sodium benzenesulfinate was also found to adopt the same pathway as thiophenols. The reaction afforded the 2-*C*-phenylsulfonylmethyl galactal **18** in 84% yield (Table 2, entry 10). Extension of this acid-catalyzed substitution reaction to 2-*C*-acetoxymethyl glucal **4a** with various substituted thiophenols also delivered the same type of products **19**–**21**, respectively, in high yields (Table 2, entries 11–13).

The acid-catalyzed reaction of compounds **4a** and **4b** or similar systems with phenols has been the subject of research interest of several groups, including us, for almost the past two decades.[10] Ferrier rearrangement was the main reaction in all the examples reported, affording the 2-*C*-methylene-*O*-aryl-glycosides **7**, through the attack of the phenols at the anomeric carbon.[10b,f–h] In some cases, the reaction proceeded further, under the reaction conditions, resulting in the formation of pyrano[2,3-*b*]benzopyrans.[10a,c–e,i] In contrast to the behaviour of phenols, our present research reveals that thiophenols prefer to attack at the *C*-2 side chain primary carbon bearing the leaving group rather than at the anomeric carbon. These intriguing results can be best rationalized based on the concept of HSAB.[12–15] It has been known in literature that, in many organic reactions, the reactivities of sulfur compounds do not parallel with their oxygen analogues, persumably because of the difference in their hard/soft character.[15e,16] Priebe and Zamojski had pioneered in proposing the HSAB concept to rationalize the behaviour of thiols towards glycals **1** in the presence of an acid (Scheme 1),[6] which was subsequently substantiated by other groups as well.[7,8]

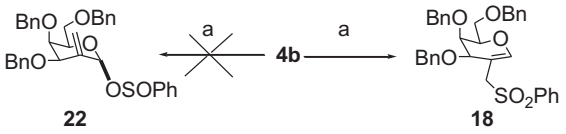
In a similar way, one can rationalize the regiochemical outcome in the present case based on HSAB concept. The formation of resonating allylic carbocations **III** and **IV** in the acid-catalyzed reactions of **4a** and **4b** has been well established by us as well as by other groups.[10,17b] As per the HSAB concept, carbocation **III** with a positive charge on *C*-1 is a 'hard acid' while **IV** with a positive charge on the side chain primary carbon is soft in nature. Phenols being 'hard bases' prefer to react with the 'hard acid' (carbocation **III**) resulting in the formation of kinetically favoured 2-*C*-methyelene glycosides **7**. Thiophenols, which are classified as 'soft bases' react with 'soft acid' (carbocation **IV**) to afford directly the thermodynamic products, namely, 2-*C*-arylthiomethylglycals, such as **6** (Scheme 3).



Scheme 3. HSAB based rationalization for the regioselective formation of compounds **7** and **6**, respectively, with phenols and thiophenols.

An interesting example is the $InCl_3$ catalyzed reaction of sodium benzenesulfinate with compound **4b** (Scheme 4). Sodium benzenesulfinate is an ambident nucleophile having both sulfur and oxygen atoms as nucleophilic sites.[18] Based on the HSAB concept and literature precedence, this reaction was expected to result either in the formation of sulfone **18** (soft–soft combination) or sulfinate ester **22** (hard–hard pair). It is likely that exclusive formation of **18** (Table 2, entry 10) under the given reaction condition is probably due to the synergistic effect of both HSAB concept and thermodynamic parameter. The formation of sulfone **18** was inferred from two strong bands that appeared in its IR spectrum at 1308 and 1149 cm^{-1} due to asymmetric and symmetric stretching frequencies of the S=O bond of sulfonyl group. Further, the appearance of a signal at δ 55.9 (t) in its ^{13}C NMR spectrum is in accordance with the expected value for the side chain methylene carbon at *C*-2 position of **18**.

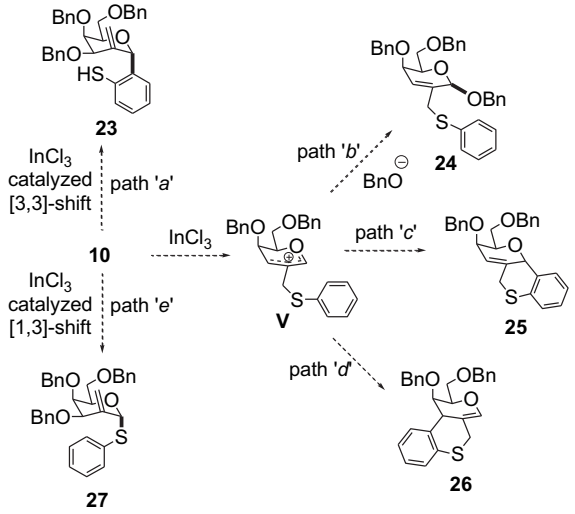
With a variety of 2-*C*-thioarylmethyl glycals in hand, it appeared worthwhile to explore their chemistry and hence, compound **10** was exposed further to $InCl_3$ catalyst. Our curiosity for such an investigation arose from the fact that this simple reaction could



[a] **4b** (1 equiv.), $PhSO_2Na$ (1.1 equiv.), $InCl_3$ (20 mol%), CH_3CN, 0 °C, 1 h.

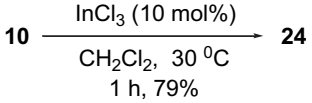
Scheme 4. $InCl_3$ catalyzed reaction of compound **4b** with sodium benzensulfinate.

possibly lead to five different products through various mechanistic pathways as outlined in Scheme 5. Path '*a*' involves an $InCl_3$ catalyzed thio-Claisen rearrangement resulting in the formation of 2-*C*-methylene-*C*-aryl glycoside **23**. Alternatively, $InCl_3$ catalyzed 1,3-alkoxy migration,[17a] (through the intermediate allylic carbocation **V**) would lead to 2,3-unsaturated glycoside **24** (path '*b*'). On the other hand, intramolecular Friedel–Crafts type alkylation of the carbocation **V** might give rise to regioisomeric tetrahydrothiochromeno pyrans **25** (path '*c*') and/or **26** (path '*d*'). Path '*e*' represents an $InCl_3$ catalyzed 1,3-transposition of thiophenyl group to give 2-*C*-methylene-thioglycoside **27**.



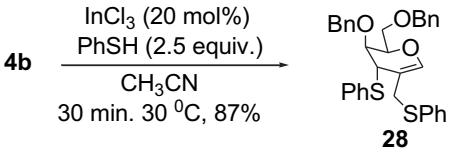
Scheme 5. Possible mechanistic pathways for the reaction of compound **10** with $InCl_3$.

Experimental results clearly revealed that among the various possibilities, 1,3-alkoxy migration (path '*b*') was the *only* reaction of choice and compound **24** was formed, under the experimental condition, as a single product in 1 h in 79% yield as an anomeric mixture in a ratio of 10:1 (Scheme 6). The preferential 1,3-benzyloxy migration (path '*b*') over intramolecular Friedel–Crafts type alkylations (path '*c*' or '*d*') is note worthy. A similar type of 1,3-alkoxy migration reaction from *C*-3→*C*-1 in simple glycals have been reported earlier by us and others, and is in accordance with the HSAB principle.[17]



Scheme 6. $InCl_3$ catalyzed 1,3-alkoxy migration of compound **10** to **24**.

Based on the above observation, it was expected that addition of an external 'soft' nucleophile in the above reaction (path '*b*') should result in the attack of the soft nucleophile at *C*-3 position rather than at *C*-1 position of the carbocation **V**. In order to verify our hypothesis, thiophenol itself was chosen as a 'soft' base and compound **4b** was treated with an excess of thiophenol in presence of $InCl_3$ as a catalyst. It was expected that this reaction should result in the formation of a dithioarylated compound, such as **28**. Indeed, as anticipated, reaction of glycal **4b** with 2.5 equiv of thiophenol in presence of 20 mol % of $InCl_3$ afforded the dithioarylated compound **28** in 87% yield, as a single diastereomer in 30 min (Scheme 7) thereby providing further support for the HSAB concept.



Scheme 7. Synthesis of dithioarylated compounds **28**.

3. Conclusions

In conclusion, a new class of thioarylated glycals has been prepared through a Lewis-acid catalyzed reaction of 2-*C*-substituted glycals with thiophenols. A rationale for the observed regioselectivity based on HSAB concept has been provided. $InCl_3$ catalyzed facile 1,3-benzyloxy migration and formation of a novel dithioarylated compound provide further support for HSAB principle. 2-*C*-Thioarylmethyl glycals reported here are ideal substrates to be exploited for thermal [3,3]-sigmatropic (thio-Claisen) rearrangement as well as novel glycosyl donors for the synthesis of unsaturated oligosaccharides. Research in these directions is currently underway in our lab.

4. Experimental section

4.1. General considerations

All solvents were purified by standard procedures. Thin-layer chromatography (TLC) was performed on Merck silica gel precoated on aluminium plates. Flash column chromatography was performed on 230–400 mesh silica gel. Melting points are uncorrected. 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). IR spectra were taken over the 4000–400 cm^{-1} range as KBr pellets on a Nicolet (Madison, USA) FTIR spectrophotometer (Model Protégé 460). All the ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker Spectrospin DPX FT-NMR spectrometer. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as internal standard. Mass spectra were recorded with an Applied Biosystems Q-Star and Bruker Microtof-Q-II instruments.

4.2. General procedure for the $InCl_3$ catalyzed reaction of glycals 4a and 4b with substituted thiophenols

Glycal **4a** or **4b** (1 equiv) was taken in a flame-dried three-necked round bottomed flask and dissolved with 10 mL of dry acetonitrile. Thiophenol or substituted thiophenol (1 equiv) was added to it and stirred for 5 min under argon atmosphere. Anhydrous $InCl_3$ (20 mol %) was then added to the reaction mixture. The progress of the reaction was monitored by TLC. After 15 min, when TLC indicated the disappearance of the starting material, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with chloroform (3×50 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by column chromatography over silica gel using hexane/ethyl acetate mixture as an eluent to obtain 2-*C*-arylthiomethyl glycals **10**, **14**–**17**, **19**–**21**.

*4.2.1. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-thiophenyl methyl-D-lyxo-hex-1-enitol (**10**).* Obtained in 87% yield (3.6 g) as a colourless solid from the reaction of **4b** (3.76 g, 7.7 mmol) with thiophenol (0.874 mL, 7.7 mmol) in presence of $InCl_3$ (20 mol %, 0.34 g, 1.54 mmol). Mp 64 °C; R_f (10% EtOAc/hexane) 0.65; $[\alpha]_D^{28}$ +130 (*c* 0.18, $CHCl_3$); ν_{max} (KBr) 3062, 3025, 2916, 2873, 1654, 1595, 1486, 1451, 1409, 1345, 1306, 1214, 1147, 1089, 1025, 901, 868, 804, 733, 695, 603 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.35–7.17 (20H, m, aromatic), 6.14 (1H, s), 4.84–4.78 (2H, m), 4.63–4.58 (2H, m), 4.48 (1H, d, *J*=11.7 Hz), 4.40–4.36 (2H, m), 4.11 (1H, m), 3.96 (1H, m), 3.75–3.60 (3H, m), 3.47 (1H, d, *J*=13.2 Hz); δ_C (75 MHz, $CDCl_3$) 141.6, 138.2, 138.1, 137.8, 135.9, 130.8, 128.7, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 108.7, 75.6, 73.36 (2× CH_2), 73.31, 71.7, 71.5, 68.1, 34.7; HRMS (ESI): $[M+Na]^+$, found 561.2092. $C_{34}H_{34}O_4SNa$ requires 561.2076.

*4.2.2. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-methyl-thiophenyl)methyl-D-lyxo-hex-1-enitol (**14**).* Obtained in 84% yield (0.415 g) as a colourless solid from the reaction of **4b** (0.44 g, 0.90 mmol) with *p*-methylthiophenol (0.111 g, 0.90 mmol) in presence of $InCl_3$ (20 mol %, 0.039 g, 0.18 mmol). Mp 70 °C; R_f (10% EtOAc/hexane) 0.51; $[\alpha]_D^{28}$ +156 (*c* 0.20, $CHCl_3$); ν_{max} (KBr) 3058, 3027, 2867, 1657, 1449, 1373, 1347, 1314, 1224, 1185, 1149, 1101, 1027, 953, 906, 858, 738, 691, 608 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.33–7.01 (19H, m, aromatic), 6.07 (1H, s), 4.83–4.77 (2H, m), 4.62–4.58 (2H, m), 4.47 (1H, d, *J*=11.7 Hz), 4.39–4.35 (2H, m), 4.11 (1H, m), 3.95–3.93 (1H, m), 3.75–3.61 (3H, m), 3.40 (1H, d, *J*=13.5 Hz), 2.28 (3H, s); δ_C (75 MHz, $CDCl_3$) 141.4, 138.3, 138.1, 137.8, 136.6, 132.0, 131.6, 129.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 109.0, 75.6, 73.4 (2× CH_2), 73.3, 71.7 (2× CH), 68.1, 35.4, 21.0; HRMS (ESI): $[M+Na]^+$, found 575.2256. $C_{35}H_{36}O_4SNa$ requires 575.2232.

*4.2.3. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-methoxythiophenyl)methyl-D-lyxo-hex-1-enitol (**15**).* Obtained in 84% yield (0.415 g) as a colourless solid from the reaction of **4b** (0.43 g, 0.88 mmol) with *p*-methoxythiophenol (0.108 mL, 0.88 mmol) in presence of $InCl_3$ (20 mol %, 0.038 g, 0.17 mmol). Mp 76 °C; R_f (10% EtOAc/hexane) 0.32; $[\alpha]_D^{28}$ +177.6 (*c* 0.21, $CHCl_3$); ν_{max} (KBr) 3032, 2911, 2878, 1656, 1585, 1488, 1452, 1346, 1288, 1242, 1145, 1090, 1026, 901, 867, 815, 733, 695, 609 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.53–7.23 (17H, m, aromatic), 6.75 (2H, d, *J*=8.4 Hz, aromatic), 5.98 (1H, s), 4.83–4.79 (2H, m), 4.63–4.59 (2H, m), 4.49–4.35 (3H, m), 4.10 (1H, m), 3.95 (1H, m), 3.74–3.58 (6H, m, with the signal of OCH_3 proton merged), 3.31 (1H, d, *J*=13.2 Hz); δ_C (75 MHz, $CDCl_3$) 159.1, 141.3, 138.3, 138.1, 137.8, 134.5, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 125.7, 114.3, 109.0, 75.6, 73.3 (3× CH_2), 71.8 (2× CH), 68.1, 55.1, 36.6; HRMS (ESI): $[M+Na]^+$, found 591.2200. $C_{35}H_{36}O_5SNa$ requires 591.2176.

*4.2.4. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-chlorothiophenyl)methyl-D-lyxo-hex-1-enitol (**16**).* Obtained in 85% yield (0.430 g) as a colourless solid from the reaction of **4b** (0.435 g, 0.89 mmol) with *p*-chlorothiophenol (0.128 g, 0.89 mmol) in presence of $InCl_3$ (20 mol %, 0.039 g, 0.17 mmol). Mp 60 °C; R_f (10% EtOAc/hexane) 0.36; $[\alpha]_D^{28}$ +151.2 (*c* 0.16, $CHCl_3$); ν_{max} (KBr) 3062, 3029, 2915, 2875, 1653, 1570, 1459, 1410, 1374, 1345, 1308, 1217, 1146, 1088, 1017, 900, 867, 812, 734, 693, 604 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.42–7.15 (19H, m, aromatic), 6.16 (1H, s), 4.84 (1H, d, *J*=12.0 Hz), 4.82 (1H, d, *J*=12.0 Hz), 4.63 (1H, d, *J*=9.9 Hz), 4.60 (1H, d, *J*=9.9 Hz), 4.52–4.38 (3H, m), 4.12 (1H, br s), 4.0–3.98 (1H, m), 3.75–3.55 (3H, m), 3.45 (1H, d, *J*=13.2 Hz); δ_C (75 MHz, $CDCl_3$) 141. 7, 138.1, 138.0, 137.7, 134.4, 132.3, 132.0, 128.8, 128.3, 128.1, 127.9, 127.8, 127.7, 127.69, 127.66, 108.4, 75.6, 73.4 (2× CH_2), 73.2, 71.7, 71.2, 68.0, 34.9; HRMS (ESI): $[M+Na]^+$, found 595.1689. $C_{34}H_{33}O_4SCl$ Na requires 595.1680.

*4.2.5. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-bromothiophenyl)methyl-D-lyxo-hex-1-enitol (**17**).* Obtained in 80% yield (0.470 g) as a colourless solid from the reaction of **4b** (0.460 g, 0.942 mmol) with *p*-bromothiophenol (0.178 g, 0.942 mmol) in presence of $InCl_3$ (20 mol %, 0.041 g, 0.18 mmol). Mp 60 °C; R_f (10% EtOAc/hexane) 0.44; $[\alpha]_D^{28}$ +141.4 (*c* 0.21, $CHCl_3$); ν_{max} (KBr) 3061, 3030, 2907, 2865, 1661, 1461, 1414, 1373, 1345, 1217, 1184, 1089, 901, 811, 744, 693 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.38–7.21 (17H, m, aromatic), 7.13–7.10 (2H, m, aromatic), 6.16 (1H, s), 4.84–4.77 (2H, m), 4.62–4.55 (2H, m), 4.48 (1H, d, *J*=12.0 Hz), 4.40–4.34 (2H, m), 4.10 (1H, m), 3.96 (1H, m), 3.74–3.61 (3H, m), 3.44 (1H, d, *J*=13.2 Hz); δ_C (75 MHz, $CDCl_3$) 141. 8, 138.17, 138.10, 137.7, 132.1, 131.7, 128.3, 127.9, 127.8, 127.76, 127.70, 120.3, 108.4, 75.6, 73.4, 73.3, 73.2, 71.8 (2× CH), 68.1, 34.7; HRMS (ESI): $[M]^+$, found 639.1176. $C_{34}H_{33}O_4SBrNa$ requires 639.1175.

*4.2.6. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-thiophenylmethyl-D-arabino-hex-1-enitol (**19**).* Obtained in 78% yield (0.184 g) as a colourless viscous liquid from the reaction of **4a** (0.215 g, 0.440 mmol) with thiophenol (0.045 mL, 0.44 mmol) in presence of $InCl_3$ (20 mol %, 0.019 g, 0.088 mmol). R_f (10% EtOAc/hexane) 0.55; $[\alpha]_D^{28}$ +56.8 (*c* 0.70, $CHCl_3$); ν_{max} (KBr) 3061, 3030, 2916, 2864, 1659, 1582, 1483, 1450, 1361, 1288, 1242, 1091, 918, 740, 695, 614 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.36–7.17 (20H, m, aromatic), 6.19 (1H, s), 4.77–4.53 (6H, m), 4.40 (1H, d, *J*=4.8 Hz), 4.13–4.05 (1H, m), 3.95 (1H, m), 3.79–3.61 (3H, m), 3.47 (1H, d, *J*=13.5 Hz); δ_C (75 MHz, $CDCl_3$) 142.3, 138.2, 137.8, 135.7, 131.1, 129.1, 128.7, 128.4, 128.36, 128.31, 127.8, 127.67, 127.61, 126.5, 108.6, 76.5, 74.4, 74.3, 73.3, 73.0, 72.7, 67.9, 34.6; HRMS (ESI): $[M+Na]^+$, found 561.2055. $C_{34}H_{34}O_4SNa$ requires 561.2070.

*4.2.7. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-methyl-thiophenyl)methyl-D-arabino-hex-1-enitol (**20**).* Obtained in 80% yield (0.345 g) as a colourless viscous liquid from the reaction of **4a** (0.382 g, 0.782 mmol) with *p*-methylthiophenol (0.097 g, 0.782 mmol) in presence of $InCl_3$ (20 mol %, 0.034 g, 0.15 mmol). R_f (10% EtOAc/hexane) 0.44; $[\alpha]_D^{28}$ +8.16 (*c* 0.60, $CHCl_3$); ν_{max} (KBr) 3029, 2917, 2861, 1658, 1599, 1494, 1454, 1371, 1302, 1241, 1208, 1096, 1031, 906, 806, 740, 699 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.37–7.23 (17H, m, aromatic), 7.10–7.08 (2H, m), 6.13 (1H, s), 4.89–4.83 (2H, m), 4.68–4.64 (2H, m), 4.55–4.40 (3H, m), 4.16 (1H, br s), 4.00 (1H, m), 3.77–3.65 (3H, m), 3.44 (1H, d, *J*=13.2 Hz), 2.34 (3H, s); δ_C (75 MHz, $CDCl_3$) 141.4, 138.3, 138.1, 137.8, 136.6, 131.9, 131.7, 129.54, 128.3, 127.9, 127.85, 127.80, 127.68, 127.60, 109.0, 75.6, 73.3 (3× CH_2), 71.7 (2× CH), 68.1, 35.5, 21.0; HRMS (ESI): $[M+K]^+$, found 591.2000. $C_{35}H_{36}O_4SK$ requires 591.1966.

*4.2.8. 1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-C-(p-methoxythiophenyl)methyl-D-arabino-hex-1-enitol (**21**).* Obtained in 82% yield (0.308 g) as a colourless viscous liquid from the reaction of **4a** (0.322 g, 0.659 mmol) with *p*-methoxythiophenol (0.081 mL, 0.659 mmol) in presence of $InCl_3$ (20 mol %, 0.029 g, 0.13 mmol). R_f (10% EtOAc/hexane) 0.28; $[\alpha]_D^{28}$ +117.5 (*c* 0.90, $CHCl_3$); ν_{max} (KBr) 3061, 3030, 2920, 2861, 1659, 1593, 1493, 1456, 1361, 1286, 1243, 1172, 1095, 1032, 825, 740, 698 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.34–7.27 (17H, m, aromatic), 6.81–6.79 (2H, m), 6.05 (1H, s), 4.81–4.70 (4H, m), 4.62 (2H, m), 4.47 (1H, d, *J*=4.8 Hz), 4.12 (1H, m), 3.99 (1H, m), 3.79–3.71 (5H, m with the signal of OCH_3 merged), 3.57 (1H, d, *J*=13.2 Hz), 3.34 (1H, d, *J*=13.2 Hz); δ_C (75 MHz, $CDCl_3$) 159.2, 142.1, 138.3, 137.92, 137.90, 134.9, 128.45, 128.42, 128.3, 127.9, 127.8, 127.7, 127.6, 125.6, 114.3, 108.9, 76.5, 74.3, 74.2, 73.4, 73.1, 72.7, 68.0, 55.2, 36.5; HRMS (ESI): $[M]^+$, found 591.2196. $C_{35}H_{36}O_5SNa$ requires 568.2176.

4.3. Synthesis of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-benzenesulfonyl-D-lyxo-hex-1-enitol (18)

Glycal **4b** (0.45 g. 0.922 mmol) was taken in a flame-dried three-necked round bottomed flask and dissolved with 10 mL of dry

acetonitrile. Sodium benzenesulfinate (0.166 g, 1.01 mmol) was added to it and stirred for 5 min under argon atmosphere. Anhydrous $InCl_3$ (0.040 g, 0.18 mmol) was then added to the reaction mixture. The progress of the reaction was monitored by TLC. After 1 h, when TLC indicated the disappearance of the starting material, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with chloroform (3×50 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by column chromatography over silica gel using hexane/ethyl acetate mixture (5:1) as an eluent to obtain **18** as a colourless low melting solid in 84% yield (0.440 g). R_f (30% EtOAc/hexane) 0.33; $[\alpha]_D^{28}$ −71.4 (*c* 0.56, $CHCl_3$); ν_{max} (KBr) 3063, 3032, 2924, 2862, 1648, 1587, 1450, 1399, 1366, 1308, 1246, 1209, 1149, 742, 691 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.80–7.24 (20H, m, aromatic), 6.13 (1H, s), 4.83–4.71 (2H, m), 4.57–4.35 (5H, m), 4.17–4.13 (2H, m), 3.98 (1H, m), 3.68–3.56 (2H, m), 3.46 (1H, d, *J*=12.0 Hz); δ_C (75 MHz, $CDCl_3$) 146.7, 138.4, 137.9, 137.6, 133.5, 129.0, 128.2, 127.7, 101.4, 75.9, 73.8, 73.3, 73.1, 72.8, 69.9, 68.0, 55.9; HRMS (ESI): $[M+Na]^+$, found 593.1981. $C_{34}H_{34}O_6SNa$ requires 593.1974.

4.4. Synthesis of benzyl-4,6-di-*O*-benzyl-2,3-dideoxy-2-*C*-thiophenylmethyl-D-*threo*-hex-2-enopyranoside (24)

Compound **10** (0.250 g, 0.464 mmol) was taken in a flame-dried three-necked round bottomed flask and dissolved with 10 mL of dry dichloromethane. After 5 min, anhydrous $InCl_3$ (0.010 g, 0.046 mmol) was added to the reaction mixture and it was stirred under argon atmosphere. The progress of the reaction was monitored by TLC. After 1 h, when TLC indicated the disappearance of the starting material, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with chloroform (3×50 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by column chromatography over silica gel using hexane/ethyl acetate mixture (15:1) as an eluent to obtain **24** as an anomeric mixture in a ratio of 10:1. Yield 79% (0.198 g). Colourless viscous liquid. R_f (10% EtOAc/hexane) 0.32; Specific rotation reported here is for the anomeric mixture. $[\alpha]_D^{28}$ −59.4 (*c* 0.70, $CHCl_3$); ν_{max} (KBr) 3031, 2916, 2864, 1585, 1486, 1452, 1379, 1101, 1030, 951, 740, 697 cm^{-1}; ^1H and ^{13}C NMR values reported here are due α-anomer only from a mixture of anomers (10:1). δ_H (300 MHz $CDC1_3$) 7.35–7.10 (20H, m, aromatic), 5.86 (1H, d, *J*=5.1 Hz), 5.36 (1H, s), 4.83 (1H, d, *J*=11.4 Hz), 4.66–4.53 (3H, m), 4.39 (1H, d, *J*=11.7 Hz), 4.25–4.18 (2H, m), 3.85–3.69 (3H, m), 3.59 (2H, br s); δ_C (75 MHz, $CDCl_3$) 138.4, 138.3, 137.8, 137.3, 135.3, 130.5, 128.8, 128.37, 128.30, 128.2, 127.7, 127.58, 127.52, 126.9, 126.6, 124.1, 94.2, 73.3, 70.0, 69.8, 69.6, 69.4, 67.4, 36.7; HRMS (ESI): $[M+Na]^+$ found 561.2075. $C_{34}H_{34}O_6SNa$ requires 561.2112.

4.5. Synthesis of 1,5-anhydro-4,6,-di-*O*-benzyl-2,3-didoexy-3-thiophenyl-2-thiophenylmethyl-D-lyxo-hex-1-enitol (28)

Glycal **4b** (0.160 g, 0.327 mmol) was taken in a flame-dried three-necked round bottomed flask and dissolved with 10 mL of dry acetonitrile. Thiophenol (0.084 mL, 0.82 mmol) was added to it and stirred for 5 min under argon atmosphere. Anhydrous $InCl_3$ (0.014 g, 0.065 mmol) was then added to the reaction mixture. The progress of the reaction was monitored by TLC. After 30 min, when TLC indicated the disappearance of the starting material, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with chloroform (3×50 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by column chromatography over silica gel using hexane/ethyl acetate mixture as an eluent to obtain dithioarylated compounds **28** as a colourless low melting solid in 87% yield (0.152 g). R_f (10% EtOAc/hexane) 0.68; $[\alpha]_D^{28}$ −123 (*c* 0.60, $CHCl_3$); ν_{max} (KBr) 3054, 2908, 2862, 1655, 1443, 1422, 1409, 1373, 1251, 1194, 1145, 1099, 1057, 1024, 925, 785, 697 cm^{-1}; δ_H (300 MHz $CDC1_3$) 7.41–6.91 (20H, m, aromatic), 6.39 (1H, s), 4.57–4.37 (4H, m), 4.16 (1H, br s), 4.04 (1H, dd, *J*=12.0, 1.8 Hz), 3.89 (1H, d, *J*=14.1 Hz), 3.74–3.59 (3H, m), 3.52–3.47 (1H, m); δ_C (75 MHz, $CDCl_3$) 143.8, 137.8, 135.9, 134.4, 132.7, 131.0, 129.2, 128.8, 128.2, 127.6, 126.6, 105.7, 73.2, 72.7, 71.8, 70.8, 69.2, 43.9, 36.5; HRMS (ESI): $[M+Na]^+$, found 563.1694 $C_{33}H_{32}O_3S_2Na$ requires 563.1691.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.122.

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