

# Rapid Synthesis of L-Idosyl Glycosyl Donors from $\alpha$ -Thioglucosides for the Preparation of Heparin Disaccharides

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**Abstract:** A new methodology for the synthesis of the most challenging heparin building block has been developed. Orthogonally protected L-idosyl glycosyl donors were prepared by C5 epimerization of the corresponding thioglucosides using the hydroboration/oxidation method followed by a 4,6-acetal formation. The  $\alpha$ -anomeric configuration was crucial and the bulky C4 substituent was advantageous for the high L-ido diastereoselectivity. The 4,6-arylmethylene group proved to be a directing element in glycosylation thereby stereoselective  $\alpha$ -idosylation could be achieved by using idosyl donors without a C-2 participating group.

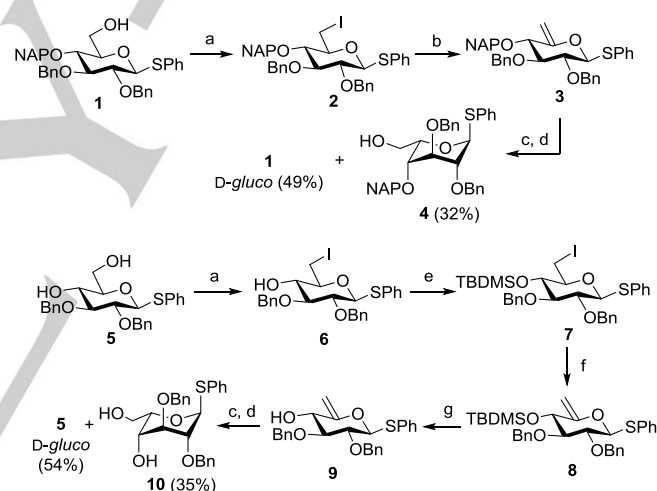
Heparin and heparan sulfates (H/HS) are highly sulfated linear glycosaminoglycan (GAG) polysaccharides, consisting of alternating N-glucosamine and hexuronic acid units, specifically either D-glucuronic acid or its C5 epimer L-iduronic acid (IdoA). GAGs interact with a variety of proteins and thereby play important roles in a diverse set of biological processes including blood coagulation, cell growth control, inflammation, tumor metastasis and viral infection.<sup>[1]</sup> The synthesis of specific GAG oligosaccharides or their mimetics as biological probes and potential new therapeutics is an area of great current interest.<sup>[2]</sup> One lasting challenge in heparin/HS synthesis is the efficient preparation of L-idose or IdoA building blocks, as these sugars are not readily available. Various methods have been explored for their synthesis,<sup>[3]</sup> involving epimerization at C5 of D-glucose<sup>[4]</sup> or D-glucuronic acid derivatives,<sup>[5]</sup> isomerisation of unsaturated sugars,<sup>[6]</sup> and homologation of tetroses or pentoses.<sup>[7]</sup> However, the idose derivatives obtained by these routes are generally not applicable directly in heparin/HS syntheses and further multistep transformation is required to turn them to properly functionalized glycosyl donors.

Recently, Bols and co-workers published a general method for the preparation of all eight L-hexoses as the thioglycoside donors, ready for glycosylations.<sup>[8]</sup> While this method, based on iridium-catalyzed CH-activation of the corresponding 6-deoxy L-hexopyranosides, is highly attractive for most rare L-sugars, in the specific case of L-idose the synthesis of the corresponding 6-deoxy precursor requires fourteen steps from L-rhamnose, including epimerizations at C2 and C3,<sup>[8b]</sup> making the whole process particularly lengthy and low-yielding.

We envisaged a rapid, cost-friendly and scalable synthesis of orthogonally protected L-idose thioglycoside donors by diastereoselective hydroboration of 5-hexenopyranosides obtained from the corresponding thioglucosides. The

hydroboration/oxidation is a well-elaborated method for C5 isomerisation of  $\alpha$ -O-glycosides,<sup>[6a,b]</sup> however, it has not been applied on thioglucosides, probably due to the sensitivity of sulfur towards oxidation and non-trivial synthesis of  $\alpha$ -thioglycosides. Herein, we present the first application of this approach for direct synthesis of orthogonally protected thio-idosides and utilization of them in the synthesis of heparin-related disaccharides.

Although it is known that the  $\alpha$ -anomeric configuration of O-glycosyl 5-enopyranosides is crucial for the high L-ido-selectivity of hydroboration, initially, we tested the viability of this procedure on  $\beta$ -thioglucosides which are available more easily than the  $\alpha$ -congeners (Scheme 1).



**Scheme 1.** Synthesis of L-idose starting from  $\beta$ -D-thioglucosides **1** and **5**: a) toluene, PPh<sub>3</sub>, I<sub>2</sub>, imidazole, 75 °C, 30 min (**2**: 80%, **6**: 79%); b) DMF, NaH, 0 °C to rt, 24 h (66%); c) THF, BH<sub>3</sub>·THF, 0 °C, 1.5 h; d) 30% H<sub>2</sub>O<sub>2</sub>, 2M NaOH, 0 °C to rt, 50 min; e) CH<sub>2</sub>Cl<sub>2</sub>, 2,6-lutidine, TBDMSOTf, 0 °C to rt, 2 h (84%); f) THF, t-BuOK, 0 °C, 30 min (85%); g) THF, TBAF, 0 °C to rt, 2 h (97%).

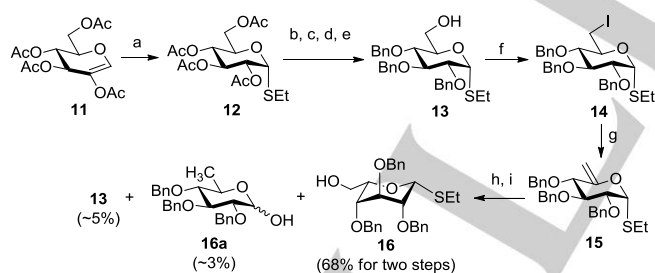
iodination of **1**<sup>[9]</sup> followed by dehydrohalogenation of **2** with sodium hydride gave 6-deoxy- $\beta$ -D-xylo-hex-5-enopyranoside **3** which was then subjected to hydroboration/oxidation. To our great satisfaction, the reactions proceeded cleanly and with high efficacy. The standard oxidation conditions (i.e. H<sub>2</sub>O<sub>2</sub>, NaOH) reported for O-glycosides proved to be well suited for thioglucosides as oxidation of the anomeric thioacetal functionality was not observed. As expected, the corresponding D-glucoside **1** was formed as the major product, nevertheless, the desired L-ido thioglycoside **4** was also obtained in 32% isolated yield. Recently, Łopatkiewicz and Młynarski have demonstrated that hydroboration stereoselectivity can be substantially influenced by the C4 protective group.<sup>[10]</sup> They have found that small C4-substituents or free 4-OH group are

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favorable, while bulky C-4 substituents are unfavorable for L-idose isomer formation. Hence, in the hope of achieving a higher L-idose ratio, 5-enopyranoside **9** with a free 4-OH group was prepared starting from diol **5**<sup>[11]</sup> via routine transformations including selective iodination of the primary position followed by silylation of **6**, dehydrohalogenation of **7** and desilylation of **8**. Although hydroboration/oxidation of **9** proceeded with an excellent 89% combined yield, the ratio of the L-ido diastereoisomer, unfortunately, did not increase. We assume that the excess borane-THF complex reacts with the 4-OH group of **9** forming a borinic ester at position C4 which exhibits a shielding effect on the bottom face of the pyranose ring upon hydroboration, similarly to that of the 4-O-NAP group in compound **3**.

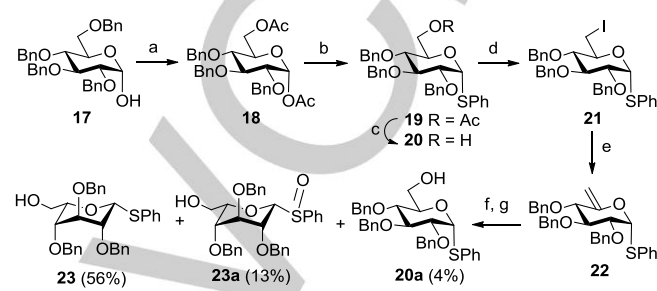
Having established that hydroboration/oxidation of  $\beta$ -thioglycosides occurred with high efficacy we studied the isomerisation of the  $\alpha$ -anomers. Ethyl 1-thioglycoside **12** was prepared with exclusive  $\alpha$ -selectivity in 87% yield by photoinduced hydrothiolation of the peracetylated 2-hydroxyglycal **11** as previously reported<sup>[12]</sup> (Scheme 2). Deacetylation of **12** followed by selective 6-O-tritylation, benzylation and subsequent detritylation gave **13** which was transformed to 5-enopyranoside **15** via dehydrohalogenation of **14** with sodium hydride. Hydroboration/oxidation of **15** afforded the desired L-idose isomer **16** in a good yield of 68% over two steps. Interestingly, the oxidation reaction was not as clean as in the case of the  $\beta$ -phenylthio congeners **3** and **9**, some polar degradation products and small amount of apolar by-products were detected by TLC monitoring of the reaction. The main components of the apolar by-products, isolated as an inseparable mixture of compounds, were identified, after acetylation and a subsequent chromatographic separation, as **13**, the D-*gluco* isomer of the major product, and the 6-deoxy-D-glucose derivative **16a**.



**Scheme 2.** Synthetic route to L-idose starting from ethylthio  $\alpha$ -D-glucopyranoside **12**: a) Ref. 12, EtSH, DPAP, hv, rt, 3 x 15 min (87%); b) NaOMe, MeOH, rt, 24 h; c) pyr, TrCl, DMAP, 0 °C to rt, 24 h; d) DMF, NaH, BnBr, 0 °C to rt, 24 h; e) CH<sub>2</sub>Cl<sub>2</sub>, 90% TFA, rt, 30 min (70% over four steps); f) toluene, PPh<sub>3</sub>, I<sub>2</sub>, imidazole, 75 °C, 30 min (76%); g) DMF, NaH, 0 °C to rt, 24 h (78%); h) THF, BH<sub>3</sub>·THF, 0 °C, 1.5 h; i) H<sub>2</sub>O<sub>2</sub>, 2M NaOH, 0 °C to rt, 50 min.

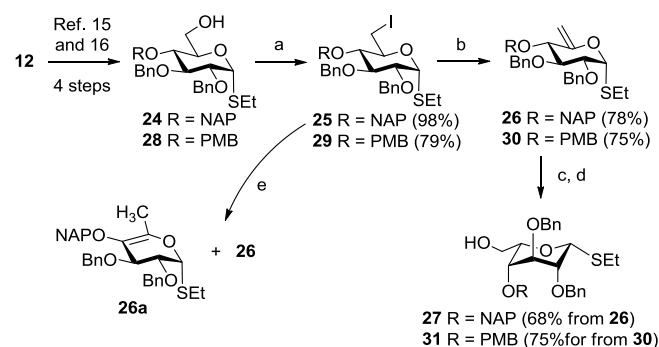
In order to test whether the formation of by-products could be suppressed by changing the alkylthio aglycone into an aryl one, the phenylthio glucoside **21** was prepared and subjected to the isomerisation process (Scheme 3). After partial acetylation of **17**<sup>[13]</sup> the obtained **18** was reacted with thiophenol in the presence of Lewis acid resulting in **19** as an  $\alpha$ : $\beta$  mixture in an

8:1 ratio. Zemplén deacetylation of **19** followed by iodination and subsequent chromatographic purification provided the pure  $\alpha$ -anomer of **21** in 71% yield over two steps. Dehydrohalogenation of **21** with sodium hydride followed by hydroboration and oxidation of the obtaining **22** provided the desired L-idose **23** in 56% yield along with its sulfoxide derivative **23a** (13%) and glucose isomer **20** (4%). Although sulfoxide **23a**, formed by over-oxidation of **23**, can also be used as a glycosyl donor<sup>[14]</sup> no benefits were found using phenyl aglycone instead of ethyl.



**Scheme 3.** Synthesis of L-idose via hydroboration-oxidation of phenylthio  $\alpha$ -enoglycopyranoside **22**: a) Ac<sub>2</sub>O, AcOH, H<sub>2</sub>SO<sub>4</sub>, 0 °C, 30 min; b) CH<sub>2</sub>Cl<sub>2</sub>, PhSH, BF<sub>3</sub>·Et<sub>2</sub>O, 0 °C to rt 2 h (63% over two steps); c) MeOH, NaOMe, rt, 24 h; d) THF, imidazole, Ph<sub>3</sub>P, I<sub>2</sub>, 75 °C, 30 min (71% over two steps); e) DMF, NaH, 0 °C to rt, 24 h (72%); f) THF, BH<sub>3</sub>·THF, 0 °C, 1.5 h; g) 30% H<sub>2</sub>O<sub>2</sub>, 2M NaOH, 0 °C to rt, 50 min.

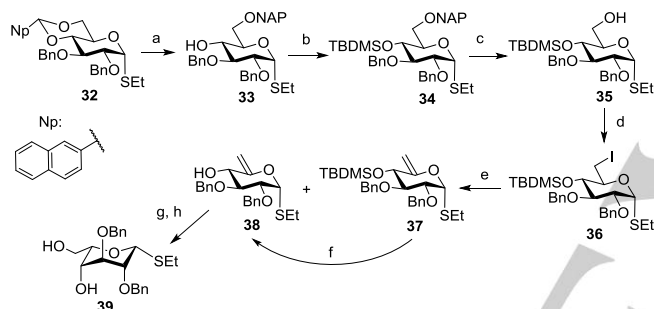
Next, we we turned our attention to the synthesis of orthogonally protected idosyl thioglycosides, useful as building blocks in glycosylation reactions (Scheme 4). Hence, compound **24**<sup>[15]</sup> bearing the 2-naphthylmethyl group at C4 position was prepared and converted to enopyranoside **26** via sodium hydride mediated elimination of the 6-iodo derivative **25**. The two-step isomerisation process of **26** resulted in the desired idose derivative **27** in 68% yield over two steps. Improving the dehydroiodination of **25** by using potassium *tert*-butoxide instead of NaH was unsuccessful, because this reaction led to the formation of an inseparable 1:2 mixture of **26** and **26a**. Subjecting this mixture to the hydroboration/oxidation process, **26a** having an endocyclic double bond remained unchanged.



**Scheme 4.** Hydroboration-oxidation of orthogonally protected  $\alpha$ -thioglycosides: a) toluene, PPh<sub>3</sub>, I<sub>2</sub>, imidazole, 75 °C, 30 min; b) DMF, NaH, 0 °C to rt, 24 h; c) THF, BH<sub>3</sub>·THF, 0 °C, 1.5 h; d) 30% H<sub>2</sub>O<sub>2</sub>, 2 M NaOH, 0 °C to rt, 50 min; e) THF, *t*-BuOK, 0 °C, 30 min (97%, **26a** : **26**, 2:1).

The iodination and subsequent elimination reaction were also performed on compound **28**<sup>[16]</sup> bearing 4-*O*-*p*-methoxybenzyl ether as a temporary protecting group. We were pleased to find that hydroboration/oxidation of the obtaining enopyranoside **30** having the bulky 4-OPMB group gave rise to the desired idose derivative **31** in an excellent 75% yield.

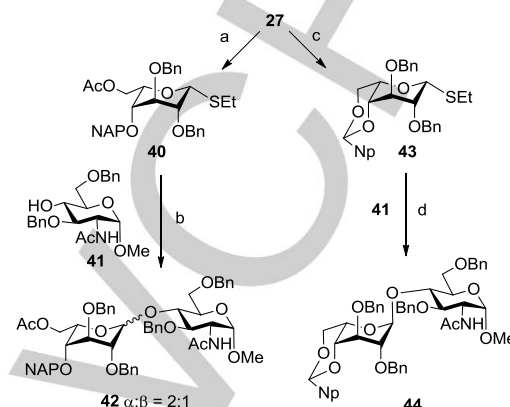
We investigated if the isomerisation process could be further improved by applying a 4-OH derivative in the hydroboration step (Scheme 5). Compound **32**<sup>[15]</sup> was converted to **33** by reductive cleavage of the 4,6-acetal ring using the Garegg method.<sup>[17]</sup> The freed 4-OH group was temporarily protected by silylation to afford **34** which was transformed to the 6-OH derivative **35** by oxidative cleavage of the NAP ether using DDQ. Iodination followed by sodium hydride mediated dehydroiodination of the obtained **36** gave **37** along with its desilylated derivative **38** in 36% and 14% yields, respectively. Treatment of **37** with TBAF afforded enopyranoside **38** in 61% yield. Unfortunately, hydroboration/oxidation of **38** having a free hydroxyl group at position C4 proceeded with low efficacy resulting in the desired idose derivative only in a 41% yield.



**Scheme 5.** Hydroboration-oxidation of 5-enopyranoside **38** with a free 4-OH group: a) THF,  $(\text{CH}_3)_3\text{N}\cdot\text{BH}_3$ ,  $\text{AlCl}_3$ , rt, 30 min (64%); b)  $\text{CH}_2\text{Cl}_2$ , 2,6-lutidine, TBDMSOTf, 0 °C to rt, 2.5 h (75%); c)  $\text{CH}_2\text{Cl}_2$ ,  $\text{H}_2\text{O}$ , DDQ, rt, 30 min (87%); d) toluene,  $\text{PPh}_3$ ,  $\text{I}_2$ , imidazole, 75 °C, 30 min (99%); e) DMF, NaH, rt, 24 h (**37**: 36%, **38**: 14%); f) THF, TBAF, 0 °C to rt, 2 h (61%); g) THF,  $\text{BH}_3$ :THF, 0 °C, 1.5 h, h) 30%  $\text{H}_2\text{O}_2$ , 2M NaOH, 0 °C to rt, 50 min (41% over two steps).

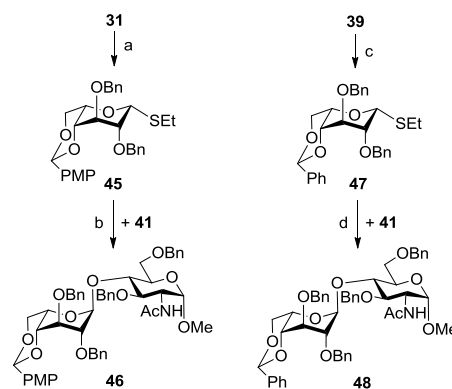
With the functionalized idosyl thioglycosides **27**, **31** and **39** in hand, stereoselective synthesis of heparinoid disaccharides was attempted. First, compound **27** was acetylated and the obtaining **40** was reacted with the aminoglycoside acceptor **41**<sup>[18]</sup> (Scheme 6). Unfortunately, the glycosylation occurred with a low  $\alpha$ -stereoselectivity affording an inseparable 2:1 mixture of the  $\alpha$ - and  $\beta$ -linked disaccharide **42** in 51% yield. The moderate yield of coupling can be explained by the low reactivity of the 4-OH group of *N*-acetylglucosamine.<sup>[19]</sup> To investigate whether a 4,6-*O*-acetal had a beneficial effect on the stereochemical outcome of glycosylation, compound **27** was converted to the corresponding 4,6-*O*-(2-naphthyl)methylene derivative **43** by oxidative ring closure<sup>[20]</sup> with DDQ (Scheme 6). To our great delight, reaction of **41** with the donor **43** led to exclusive formation of disaccharide **44** with the required  $\alpha$ -interglycosidic linkage. It is well-known from the works by Crich and co-workers that the 4,6-benzylidene acetal of a donor is a control element in glycosylations permitting stereoselective 1,2-*cis*- $\beta$  glycosidic bond formation in the mannopyranose series<sup>[21]</sup> and 1,2-*cis*- $\alpha$

glycosylation in the gluco- and galactopyranose series.<sup>[22]</sup> However, to the best of our knowledge, the directing effect of the 4,6-acetal group has not been exploited for stereoselective 1,2-*trans*- $\alpha$  glycosylations in the lack of a C2 participating group.



**Scheme 6.** Synthesis of heparin-related disaccharides using idosyl donors obtained from **27**: a) pyr,  $\text{Ac}_2\text{O}$ , 0 °C to rt, 24 h (81%); b)  $\text{CH}_2\text{Cl}_2$ , NIS, TfOH, -50 to +5 °C, 4 h, (51%); c)  $\text{CH}_2\text{Cl}_2$ , DDQ, rt, 2 h (61%); d)  $\text{CH}_2\text{Cl}_2$ , NIS, AgOTf, -10 °C to rt, 3 h (52%).

A similar glycosylation strategy was pursued with the idosyl thioglycosides **31** and **39** (Scheme 7.). The oxidative cyclization of **31** gave **45** in 77% yield. Coupling of **45** with **41** also proceeded with full  $\alpha$ -stereoselectivity giving the heparinoid disaccharide **46** in 51% yield. Finally, diol **39** was benzylidened and the obtained 4,6-*O*-acetal derivative **47** was coupled with **41** to result in the desired disaccharide **48** with exclusive  $\alpha$ -stereoselectivity.



**Scheme 7.**  $\alpha$ -Selective glycosylations with 4,6-*O*-acetal-protected thiodisides: a)  $\text{CH}_2\text{Cl}_2$ , DDQ, rt, 1.5 h (77%); b)  $\text{CH}_2\text{Cl}_2$ , NIS, AgOTf, *sym*-collidine, -10 °C to rt, 3 h (51%); c) DMF,  $\text{PhCH}(\text{OMe})_2$ , *p*-TSA, 50 °C, 1 h (80%); d)  $\text{CH}_2\text{Cl}_2$ , NIS, AgOTf, -10 °C to rt, 3 h (53%).

In conclusion, a short route to L-idosyl glycosyl donors was developed from properly functionalized  $\alpha$ -thioglycosides. The



key steps include C5 epimerization by hydroboration/oxidation of the corresponding 5-enopyranosides followed by a 4,6-*O*-acetal formation of the obtained 6-hydroxy or 4,6-dihydroxy L-idosides. We demonstrated that the 4,6-arylmethylene group has a directing effect on the stereochemistry of glycosylation reaction, which can be exploited in the stereoselective formation of the  $\alpha$ -L-idosidic bond in the lack of a C2 participating group. Importantly, idose or iduronic acid donors with a C-2 participating group have found exclusive application in heparin syntheses, hitherto. Our results pave the way to designing new, more diverse protecting group strategies for the synthesis of H/HS oligosaccharides. Moreover, the obtained thiodosides can be oxidised into the corresponding L-iduronic acids in a chemo- and regioselective manner using the TEMPO/BAIB<sup>[23]</sup> reagent combination and this oxidative transformation can easily be performed at an oligosaccharide level as well.<sup>[24]</sup> The optimization of our epimerization and glycosylation procedures and their application in the synthesis of heparin oligosaccharides are in progress.

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## COMMUNICATION

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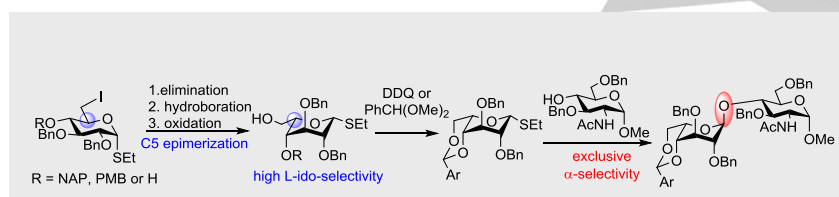
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Layout 2:

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Synthesis of L-idopyranosyl glycosyl donors starting from  $\alpha$ - and  $\beta$ -thio-D-glucopyranosides *via* the corresponding 5-enopyranosides were studied for the first time. Hydroboration of the  $\alpha$ -configured 5-enopyranosides proceeded with very high L-ido stereoselectivity. After a 4,6-O-acetal formation, the obtained idosyl thioglycosides proved to be useful as donors in the synthesis of heparin-related disaccharides.

Mihály Herczeg, Fruzsina Demeter,  
Tímea Balogh, Viktor Kelemen and  
Anikó Borbás\*

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Rapid Synthesis of L-Idosyl Glycosyl  
Donors from  $\alpha$ -Thiogluco-sides for the  
Preparation of Heparin Disaccharides