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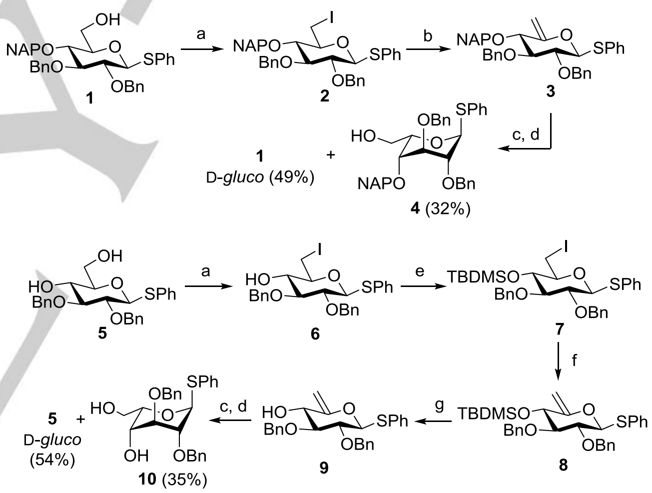
Rapid Synthesis of L-Idosyl Glycosyl Donors from α-Thioglucosides for the Preparation of Heparin Disaccharides

Mihály Herczeg,[a] Fruzsina Demeter,[a] Tímea Balogh,[a] Viktor Kelemen[a] and Anikó Borbás[a]*

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 α-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 α-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.[1] The synthesis of specific GAG oligosaccharides or their mimetics as biological probes and potential new therapeutics is an area of great current interest.[2]
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,[3] involving epimerization at C5 of D-glucose[4] or D-glucuronic acid derivatives,[5] isomerisation of unsaturated sugars,[6] and homologation of tetroses or pentoses.[7] 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.[8] 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,[8b] 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 α-*O*-glycosides;[6a,b] however, it has not been applied on thioglycosides, probably due to the sensitivity of sulfur towards oxidation and non-trivial synthesis of α-thioglycosides. Herein, we present the first application of this approach for direct synthesis of orthogonally protected thioidosides and utilization of them in the synthesis of heparin-related disaccharides.
Although it is known that the α-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 β-thioglucosides which are available more easily than the α-congeners (Scheme 1).



Scheme 1. Synthesis of L-idose starting from β-D-thioglucosides **1** and **5**: a) toluene, PPh_3, I_2, imidazole, 75 °C, 30 min (**2**: 80%, **6**: 79%); b) DMF, NaH, 0 °C to rt, 24 h (66%); c) THF, $BH_3{\cdot}THF$, 0 °C,1.5 h; d) 30% H_2O_2, 2M NaOH, 0 °C to rt, 50 min; e) CH_2Cl_2, 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**[9] followed by dehydrohalogenation of **2** with sodium hydride gave 6-deoxy-β-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_2O_2, NaOH) reported for *O*-glycosides proved to be well suited for thioglycosides 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 Mlynarski have demonstrated that hydroboration stereoselectivity can be substantially influenced by the C4 protective group.[10] They have found that small C4-substituents or free 4-OH group are

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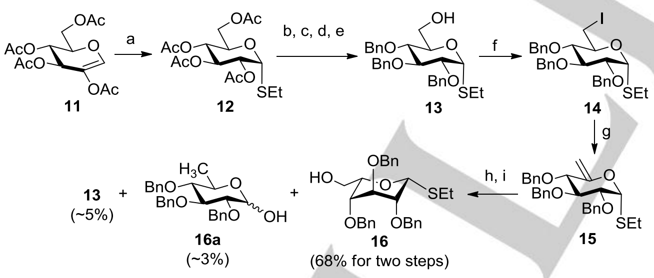
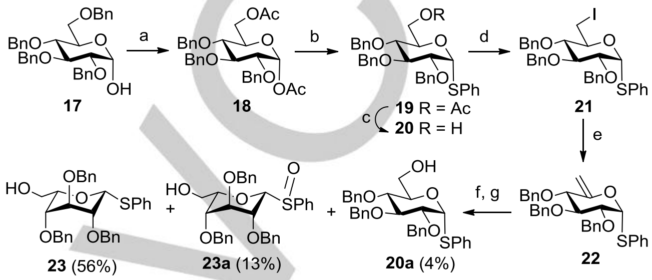
favorable, while bulky C-4 substituents are unfavorable for L-idose isomer formation. Hence, in the hope of achieving a higher L-idose ratio, 5-enopyranoside **9** with a free 4-OH group was prepared starting from diol **5**[11] *via* routine transformations including selective iodination of the primary 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 β-thioglycosides occurred with high efficacy we studied the isomerisation of the α-anomers. Ethyl 1-thioglucoside **12** was prepared with exclusive α-selectivity in 87% yield by photoinduced hydrothiolation of the peracetylated 2-hydroxyglycal **11** as previously reported[12] (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 β-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**.



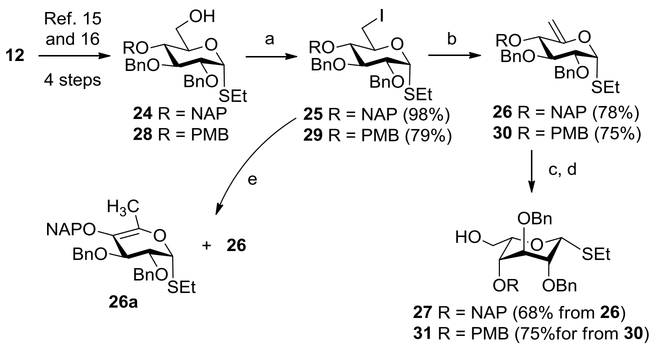
Scheme 2. Synthetic route to L-idose starting from ethylthio α-D-glucopyranoside **12**: a) Ref. 12, EtSH, DPAP, hv, rt, 3 x 15 min (87%); b) NaOMe, MeOH, rt, 24 h; c) pyr, TrCl, DMAP, 0 °C to rt, 24 h; d) DMF, NaH, BnBr, 0 °C to rt, 24 h; e) CH_2Cl_2, 90% TFA, rt, 30 min (70% over four steps); f) toluene, PPh_3, I_2, imidazole,75 °C, 30 min (76%); g) DMF, NaH, 0 °C to rt, 24 h (78%); h) THF, BH_3·THF, 0 °C, 1.5 h; i) H_2O_2, 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 acetolysis of **17**[13] the obtained **18** was reacted with thiophenol in the presence of Lewis acid resulting in **19** as an α:β mixture in an 8:1 ratio. Zemplén deacetylation of **19** followed by iodination and subsequent chromatographic purification provided the pure α-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[14] no benefits were found using phenyl aglycone instead of ethyl.



Scheme 3. Synthesis of L-idose *via* hydroboration-oxidation of phenylthio α-enoglycopyranoside **22**: a) Ac_2O, AcOH, H_2SO_4, 0 °C, 30 min; b) CH_2Cl_2, PhSH, BF_3·Et_2O, 0 °C to rt 2 h (63% over two steps), c) MeOH, NaOMe, rt, 24 h d) THF, imidazole, Ph_3P, I_2, 75 °C, 30 min (71% over two steps); e) DMF, NaH, 0 °C to rt, 24 h (72%); f) THF, BH_3·THF, 0 °C, 1.5 h; g) 30% H_2O_2, 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**[15] bearing the 2-napthylmethyl 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 α-thioglucosides: a) toluene, PPh_3, I_2, imidazole, 75 °C, 30 min; b) DMF, NaH, 0 °C to rt, 24 h; c) THF, BH_3·THF, 0 °C, 1.5 h; d) 30% H_2O_2, 2 M NaOH, 0 °C to rt, 50 min, e) THF, *t*-BuOK, 0 °C, 30 min (97%, **26a** : **26**, 2:1).

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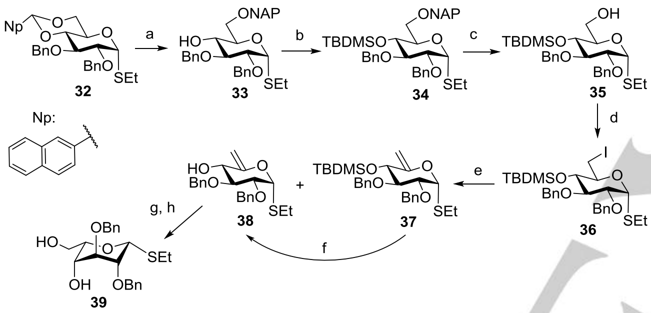
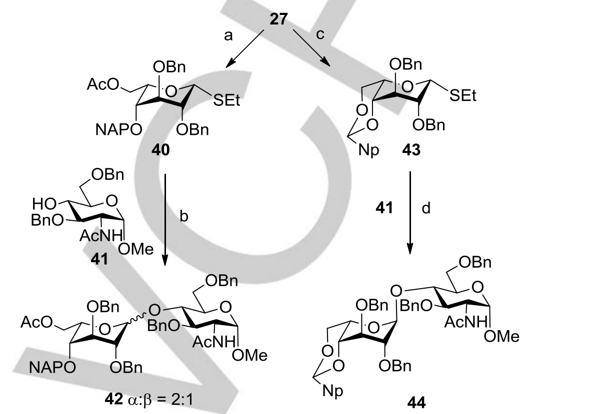
The iodination and subsequent elimination reaction were also performed on compound **28**[16] bearing 4-*O*-*p*-methoxybenzyl ether as a temporary protecting group. We were pleased to find that hydroboration/oxidation of the obtaining enopyranoside **30** having the bulky 4-OPMB group gave rise to the 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**[15] was converted to **33** by reductive cleavage of the 4,6-acetal ring using the Garegg method.[17] 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.



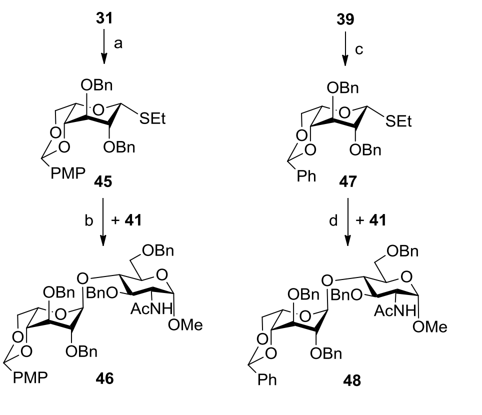
Scheme 5. Hydroboration-oxidation of 5-enopyranoside **38** with a free 4-OH group: a) THF, $(CH_3)_3N\cdot BH_3$, $AlCl_3$, rt, 30 min (64%); b) CH_2Cl_2, 2,6-lutidine, TBDMSOTf, 0 °C to rt, 2.5 h (75%); c) CH_2Cl_2, H_2O, DDQ, rt, 30 min (87%); d) toluene, PPh_3, I_2, imidazole, 75 °C, 30 min (99%); e) DMF, NaH, rt, 24 h (**37**: 36%, **38**: 14%); f) THF, TBAF, 0 °C to rt, 2 h (61%); g) THF, $BH_3\cdot THF$, 0 °C, 1.5 h, h) 30% H_2O_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**[18] (Scheme 6). Unfortunately, the glycosylation occurred with a low α-stereoselectivity affording an inseparable 2:1 mixture of the α- and β-linked disaccharide **42** in 51% yield. The moderate yield of coupling can be explained with the low reactivity of the 4-OH group of *N*-acetylglucosamine.[19] To investigate whether a 4,6-*O*-acetal had a beneficial effect on the stereochemical outcome of glycosidation, compound **27** was converted to the corresponding 4,6-*O*-(2-naphthyl)methylene derivative **43** by oxidative ring closure[20] 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 α-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-β glycosidic bond formation in the mannopyranose series[21] and 1,2-cis-α glycosidation in the gluco- and galactopyranose series.[22] 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-α glycosylations in the lack of a C2 participating group.



Scheme 6. Synthesis of heparin-related disaccharides using idosyl donors obtained from **27**: a) pyr, Ac_2O, 0 °C to rt, 24 h (81%); b) CH_2Cl_2, NIS, TfOH, -50 to +5 °C, 4 h, (51%); c) CH_2Cl_2, DDQ, rt, 2 h (61%); d) CH_2Cl_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 α-stereoselectivity giving the heparinoid disaccharide **46** in 51% yield. Finally, diol **39** was benzylidenated and the obtained 4,6-*O*-acetal derivative **47** was coupled with **41** to result in the desired disaccharide **48** with exclusive α-stereoselectivity.



Scheme 7. α-Selective glycosylations with 4,6-*O*-acetal-protected thioidosides: a) CH_2Cl_2, DDQ, rt, 1.5 h (77%); b) CH_2Cl_2, NIS, AgOTf, *sym*-collidine, -10 °C to rt, 3 h (51%); c) DMF, $PhCH(OMe)_2$, *p*-TSA, 50 °C, 1 h (80%); d) CH_2Cl_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 α-thioglucosides. 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 α-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 thioidosides can be oxidised into the corresponding L-iduronic acids in a chemo- and regioselective manner using the TEMPO/BAIB[23] reagent combination and this oxidative transformation can easily be performed at an oligosaccharide level as well.[24]
The optimization of our epimerization and glycosylation procedures and their application in the synthesis of heparin oligosaccharides are in progress.

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Keywords: thioglycosides • L-idose • glycosylation • stereoselective • heparin

[1] a) B. Casu, U. Lindahl, *Adv. Carbohydr. Chem. Biochem*. **2001**, *57*, 159–206; b) N. S. Gandhi, R. L. Mancera, *Chem. Biol. Drug Des*. **2008**, *72*, 455–482.

[2] Selected ref.: a) M. Herczeg, L. Lázár, Z. Bereczky, K. E. Kövér, I. Timári, J. Kappelmayer, A. Lipták, S. Antus, A. Borbás, A. *Chem. Eur. J*. **2012**, *18*, 10643 –10652; b) S. U. Hansen, G. J. Miller, G. C. Jayson, J. M. Gardiner, *Org Lett.* **2013**, *15*, 88–91. c) C.-H. Chang, L. S. Lico, T.-Y. Huang, S.-Y. Lin, C.-L. Chang, S. D. Arco, S.-C. Hung, *Angew. Chem. Int. Ed*. **2014**, *53*, 9876–9879; d) P. C. Tyler, S. E. Guimond, J. E. Turnbull, O. V. Zubkova, *Angew. Chem. Int. Ed*. **2015**, *54*, 2718–2723; e) M. Baráth, S. U. Hansen, C. E. Dalton, G. C. Jayson, G. J. Miller, J. M. Gardiner, *Molecules*, **2015**; *20*, 6167–6180; f) E. Mező, D. Eszenyi, E. Varga, M. Herczeg, A. Borbás, *Molecules* **2016**, *21*, 1497; g) N. V. Sankaranarayanan, R. Tamara, T. R. Strebel, R. S. Boothello, K. Sheerin, A. Raghuraman, F. Sallas, P. D. Mosier, N. D. Watermeyer, S. Oscarson, U. R. Desai, *Angew. Chem. Int. Ed*. **2017**, *56*, 2312–2317; h) C. Zong, A. Venot, X. Li, W. Lu, W. Xiao, J.-S. L. Wilkes, C. L. Salanga, T. M. Handel, L. Wang, M. A. Wolfert, G. J. Boons, *J. Am. Chem. Soc*. **2017**, *139*, 9534-9543; i) G. Łopatkiewicz, S. Buda, J. Mlynarski, *J. Org. Chem*. **2017**, *82*, 12701–12714.

[3] a) F. Vito, *Adv. Carbohydr. Chem. Biochem*. **2015**; *57*,159–206; b) T. G. Frihed, M. Bols, C. M. Pedersen, *Chem. Rev*. **2015**, *115*, 3615-3676.

[4] Selected ref.: a) J. C. Jacquinet, M. Petitou, P. Duchaussoy, I. Lederman, J. Choay, G. Torri, P. Sinaÿ, *Carbohydr. Res*. **1984**, *130*, 221–241; b) J.-C. Lee, X.-A. Lu, S. S. Kulkarni, Y.-S. Wen, S.-C. Hung, *J. Am. Chem. Soc*. **2004**, *126*, 476–477; c) J. Tatai, G. Osztrovszky, M. Kajtár-Peredy, P. Fügedi, *Carbohydr. Res*. **2008**, *343*, 596–606; d) M. Herczeg, L. Lázár, A. Mándi, A. Borbás, I. Komáromi, A. Lipták, S. Antus, *Carbohydr. Res*. **2011**, *346*, 1827–1836; e) H. Takahashi, Y. Hitomi, Y. Iwai, S. Ikegami, *J. Am. Chem. Soc*. **2000**, *122*, 2995–3000.

[5] Selected ref.: a) T. Chiba, P. Sinaÿ, *Carbohydr. Res*. **1986**, *151*, 379–389; b) W. Ke, D. M. Whitfield, M. Gill, S. Larocque, S.-H. Yu, *Tetrahedron Lett*. **2003**, *44*, 7767–7770; c) S. Salamone, M. Boisbrun, C. Didierjean, Y. Chapleur, *Carbohydr. Res*. **2014**, *386*, 99–105; d) X. Cao, Q. Lv, D. Li, H. Ye, X. Yan, X. Yang, H. Gan, W. Zhao, L. Jin, P. Wang, J. Shen, *Asian J. Org. Chem*. **2015**, *4*, 899–902.

[6] Selected ref.: a) L. Rochepeau-Jobron, J.-C. Jacquinet, *Carbohydr. Res*. **1997**, *303*, 395–406; b) H. Takahashi, N. Miyama, H. Mitsuzuka, S. Ikegami, *Synthesis* **2004**, *18*, 2991-2994; c) H. G. Bazin, M. W. Wolff, R. J. Linhardt, *J. Org. Chem*. **1999**, *64*, 144–152.

[7] Selected ref.: a) M. S. M. Timmer, A. Adibekian, P. H. Seeberger, *Angew. Chem. Int. Ed*. **2005**, *44*, 7605–7607; b) A. Adibekian, P. Bindschädler, M. S. M. Timmer, C. Noti, N. Schützenmeister, P. H. Seeberger, *Chem. Eur. J*. **2007**, *13*, 4510–4522; c) S. U. Hansen, M. Barath, B. A. B. Salameh, R. G. Pritchard, W. T. Stimpson, J. M. Gardiner, G. C. Jayson, *Org. Lett*. **2009**, *11*, 4528–4531; d) A. Dondoni, A. Marra, A. Massi, *J. Org. Chem*. **1997**, *62*, 6261–6267; e) A. Lubineau, O. Gavard, J. Alais, D. Bonnaffé, *Tetrahedron Lett*. **2000**, *41*, 307–311.

[8] a) T. G. Frihed, C. M. Pedersen, M. Bols, *Angew. Chem. Int. Ed*. **2014**, *53*, 13889–13893; b) T. G: Frihed, C. M. Pedersen, M. Bols, *Eur. J. Org. Chem*. **2014**, 7924–7939.

[9] M. Herczeg, L. Lázár, M. Ohlin, A. Borbás, *Carbohydrate Chemistry: Proven Synthetic Methods*, G. van der Marel, J. Codée, Eds.; CRC Press, **2014**, *Vol. 2*, pp 9-20.

[10] G. Łopatkiewicz, J. Mlynarski, *J. Org. Chem*. **2016**, *81*, 7545–7556.

[11] M. Trumtel, P. Tavecchia, A. Veyrieres, P. Sinay, *Carbohydr. Res*. **1990**, *202*, 257–275.

[12] L. Lázár, M. Csávás, M. Herczeg, P. Herczegh, A. Borbás, *Org. Lett*. **2012**, *14*, 4650−4653.

[13] R. Eby, S. J. Sondheimer, C. Schuerch, *Carbohydr. Res*. **1979**, *73*, 273–276.

[14] D. Kahne, D. Walker, Y. Chen, D. V. Engen, *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882.

[15] M. Herczeg, E. Mező, D. Eszenyi, L. Lázár, M. Csávás, I. Bereczki, S. Antus, A. Borbás, *Eur. J. Org. Chem*. **2013**, *25*, 5570–5573.

[16] E. Mező, M. Herczeg, D. Eszenyi, A. Borbás, *Carbohydr. Res*. **2014**, *388*, 19–29.

[17] a) M. Ek, P. J. Garegg, H. Hultberg, S. Oscarson, *J. Carbohydr. Chem*. **1983**, *2*, 305–311; b) A. Borbás, Z. B. Szabó, L. Jánossy. L. Szilágyi, A. Bényei, A. Lipták, *Tetrahedron*, **2002**, *58*, 5723–5732.

[18] S. S. Rana, J. J. Barlow, K. L. Matta, *Carbohydr. Res.* **1983**, *113*, 257-271.

[19] a) D. Crich, V. Dudkin, *J. Am. Chem. Soc*. **2001**, *123*, 6819-6825; b) L. Liao, F.-I. Auzanneau, *Org. Lett*. **2003**, *5*, 2607-2610.

[20] a) Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett*. **1982**, *23*, 889-892; b) H. Kim, H. M. R. Hoffmann, *Eur. J. Org. Chem*. **2000**, 2195-2201.

[21] a) D. Crich, S. Sun, *J. Org. Chem*. **1996**, *61*, 4506–4507; b) D. Crich, S. Sun, *J. Org. Chem*. **1997**, *62*, 1198–1199.

[22] a) D. Crich, W. Cai, *J. Org. Chem*. **1999**, *64*, 4926–4930; b) H. N. Yu, J Furukawa, T. Ikeda, C.-H. Wong, *Org. Lett.* **2004**, *6*, 723-726; c) A. Vibert, C. Lopin-Bon, J.-C. Jacquinet, *Chem. Eur. J*. **2009**, *15*, 9561-9578; d) M. Moumé-Pymbock, T. Furukawa, S. Mondal, D. Crich, *J. Am. Chem. Soc*. **2013**, *135*, 14249–14255.

[23] L. J. van den Bos, J. D. C. Codée, J. C. van der Toorn, T. J. Boltje, J. H. van Boom, H. S. Overkleeft, G. A. van der Marel, *Org. Lett*. **2004**, *6*, 2165–2168.

[24] a) J. D. C. Codée, A. E. Christina, M. T. C. Walvoort, H. S. Overkleeft, G. A. van der Marel, *Top. Curr. Chem*. **2011**, *301*, 253–289; b) M. Herczeg, E. Mező, D. Eszenyi, S. Antus, A. Borbás, *Tetrahedron* **2014**, *70*, 2919-2927.

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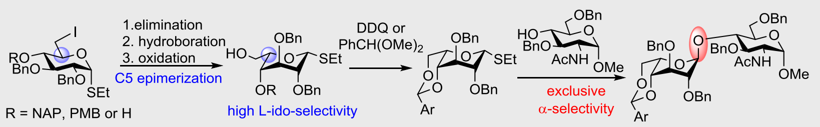

Synthesis of L-idopyranosyl glycosyl donors starting from α- and β-thio-D-glucopyranosides *via* the corresponding 5-enopyranosides were studied for the first time. Hydroboration of the α-configured 5-enopyranosides proceeded with very high L-*ido* stereoselectivity. After a 4,6-*O*-acetal formation, 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 α-Thioglucosides for the Preparation of Heparin Disaccharides