Carbohydrate Synthesis

DOI: 10.1002/anie.200502742

Short De Novo Synthesis of Fully Functionalized Uronic Acid Monosaccharides**

*Mattie S. M. Timmer, Alexander Adibekian, and Peter H. Seeberger**

Dedicated to Professor Albert Eschenmoser on the occasion of his 80th birthday

The biological importance of carbohydrates in a host of fundamental cellular processes has dramatically increased the demand for pure, synthetically derived oligosaccharides.[1] Over the past 100 years, chemical methods for the assembly of all classes of carbohydrates have been developed. This has resulted in sophisticated glycosylation reactions that allow the formation of even the most difficult glycosidic linkages with a high degree of selectivity.[2] More recently, automated methods for the rapid combination of monosaccharide building blocks on a solid phase were reported.[3] The time required to assemble an oligosaccharide has been reduced more than 100-fold, and as a result, the need for substantial quantities of and rapid access to fully functionalized building blocks has increased.

[*] Dr. M. S. M. Timmer, A. Adibekian, Prof. Dr. P. H. Seeberger
Laboratory for Organic Chemistry
Swiss Federal Institute of Technology (ETH) Zürich
ETH Hönggerberg HCI F315
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
Fax: (+41) 44-633-1235
E-mail: seeberger@org.chem.ethz.ch

[**] This research was supported by the ETH Zürich, a Niels–Stensen Postdoctoral Fellowship (to M.T.) and a Kekulé Fellowship from the Fonds dre Chemischen Industrie (to A.A.). We thank Professor D. Seebach for helpful discussions.

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

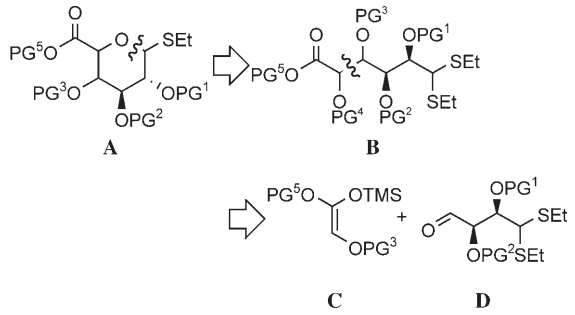
A typical monosaccharide building block used in oligosaccharide assembly is equipped with different protecting groups that mask the hydroxy and amine functions and an anomeric leaving group that can be activated to induce the formation of a glycosidic linkage. These differentially protected and functionalized monosaccharides have traditionally been accessed from naturally occurring sugar starting materials through a series of protection-deprotection maneuvers. Such a process establishes the desired protecting group pattern and typically requires 6–20 steps depending on the sugar, the protecting group pattern, and the anomeric leaving group.[4]

To avoid these lengthy procedures for producing building blocks for the assembly of larger structures, efforts have been directed at the synthesis of orthogonally protected hexose monosaccharides from noncarbohydrate precursors.[5] The landmark syntheses of hexoses by Masamune, Sharpless, and co-workers[6] were enabled by the ability of new synthetic methods to introduce specific stereogenic centers selectively. The aldol reaction has also proved to be a particularly useful tool in the creation of hexoses from simple precursors. Mukaiyama and co-workers[7] reported a stereoselective synthesis of pentoses and hexoses through the use of silyl enol ethers in aldol condensations to furnish partially protected pentoses and hexoses. Unfortunately, these fundamental explorations were not investigated further than the initial proof of concept. Recently, proline-catalyzed aldol reactions were used to fashion aldo- and ketohexose precursors for Mukaiyama-type aldol reactions, which were then used to synthesize partially protected glucose, mannose, and allose monosaccharides.[8] The yields and selectivities reported for these transformations, although excellent, were highly dependent on the specific protecting groups that were chosen.

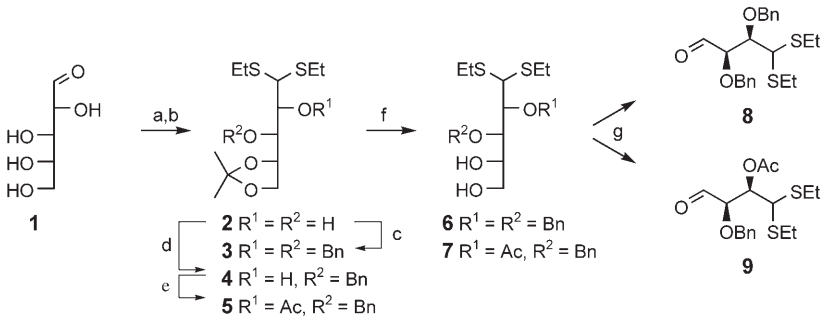
Oligosaccharide assembly requires monosaccharide building blocks that contain orthogonal protecting-group patterns and a readily activated anomeric leaving group. Herein we report a convergent route to orthogonally protected D-glucuronic and L-iduronic acid thioglycoside building blocks, which are commonly used in the assembly of heparin oligosaccharides.[9] This approach relies on the selective Mukaiyama-type aldol reaction[10] that unifies a silyl enol ether and a thioacetal-containing aldehyde (derived from the chiral pool).

Retrosynthetic analysis of the uronic acids **A** (Scheme 1) revealed that the fully protected uronic acid thioglycosides could be obtained through cyclization of the linear hexoses **B**. The open-chain hexoses can be formed, in turn, through a Mukaiyama-type aldol reaction of an appropriately protected ketene acetal **C** with a thioacetal-containing aldehyde **D**.

Synthesis of the key thioacetal aldehydes **8** and **9** commenced with readily available L-arabinose (**1**; Scheme 2). The aldehyde was converted into the corresponding thioacetal by reaction with ethanethiol in the presence of hydrochloric acid.[11] Subsequent protection of the 4,5-diol with 2,2-dimethoxypropane furnished the crystalline acetonide **2**.[12] At this stage, the protecting-group patterns for the C2 and C3 hydroxy groups were selected. The reaction of **2** with NaH, in the presence of excess benzyl bromide, afforded



Scheme 1. Retrosynthetic analysis of uronic acid thioglycosides. PG = protecting group, TMS = trimethylsilyl.



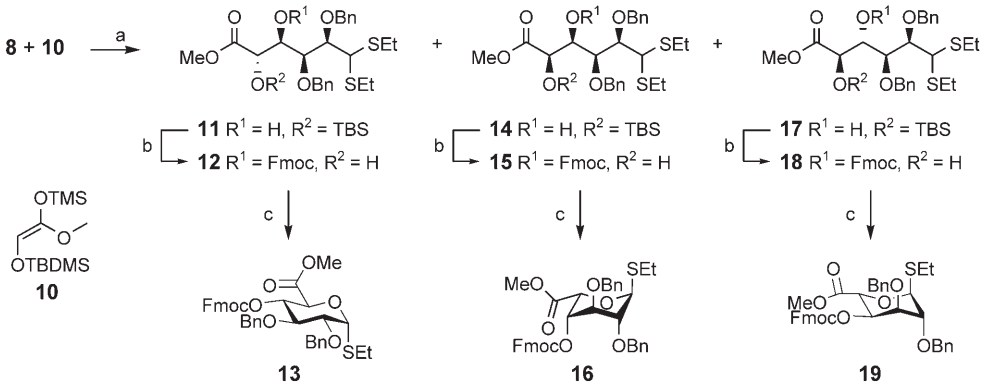
Scheme 2. Synthesis of differentially protected thioacetal aldehydes from L-arabinose: a) EtSH, conc. aq. HCl, 10 min, 77%; b) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate (cat.), acetone, 1.5 h, 81%; c) BnBr, TBAI (cat.), NaH, DMF, 0°C, 4 h; d) nBu_2SnO, toluene, Dean–Stark trap; then BnBr, CsF, TBAI (cat.), DMF; e) Ac_2O, pyridine, 46% (two steps); f) $AcOH/H_2O$ (1:1, v/v), 50°C, 1 h, **6**: 62% (two steps: c and f), **7**: 92%; g) $NaIO_4$, H_2O/THF, 0°C, 15 min, **8**: 82%, **9**: 80%. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, TBAI = tetrabutylammonium iodide.

$BF_3{\cdot}Et_2O$ mediated aldol reaction[13] of aldehyde **8** with silyl enol ether **10**[14] gave a 1:1:1 mixture of three products as was determined by analysis of the ^1H NMR spectrum of the crude product mixture. The three individual aldol products were isolated by column chromatography and identified after conversion into the corresponding thiopyranosides. The free hydroxy groups of **11**, **14**, and **17** were first transformed into 9-fluorenylmethyl carbonates followed by cleavage of the silyl ether in the presence of pyridine·HF to obtain the alcohols **12**, **15**, and **18**, respectively, in good overall yields. Although initial attempts to effect cyclization under various acidic conditions proved to be challenging, NIS-promoted activation of the thioacetal led to the formation of pyranose carbohydrates **13**, **16**, and **19**, respectively, in quantitative yields.

At this stage, the absolute configurations of the pyranoses were established by the ^1H NMR coupling patterns of the carbohydrate ring protons. For compound **13**, the large coupling constants ($J = 8$–10 Hz) between 2-H, 3-H, 4-H, and 5-H provided the evidence to assign the *gluco* configuration. The *ido* configuration of **16** was assigned based on the characteristically small coupling constants ($J = 1$–3 Hz) for protons 2-H to 5-H. This configuration was further corroborated by the W coupling, $^4J_{2,4} = 1.0$ Hz, which is typical of a 2,4-diaxial-substituted pyranose. The coupling pattern for the less common altruronic acid **19** was in full accordance with the reported coupling constants for altroses.[15] Notably, no trace of the *galacto* uronic acid, the fourth possible isomer, was found. This absence can be rationalized through the assumption of a nonchelating, open-chain transition state that allows only the three C–C bond formations observed and not the sterically demanding *Si*, *Si* attack that would lead to the *galacto* isomer.

Once the absolute configurations of the aldol products had been determined, the selectivity of the aldol reaction was dibenzylarabinoside **3**, whereas formation of a tin ketal of the diol **2** and subsequent monobenzylation gave **4**. After acetylation of the remaining hydroxy group in **4**, selectively protected **5** was isolated in 46% overall yield together with 45% of the 2-*O*-benzyl-3-*O*-acetyl regioisomer. Deprotection of the acetal groups in **3** and **5** was followed by sodium periodate mediated cleavage of the resulting vicinal diols to form the desired aldehydes **8** and **9** in very good overall yields. Notably, these two key intermediates are derived from cheap, commercially available starting materials (L-arabinose) through straightforward and high-yielding transformations that are readily scalable.

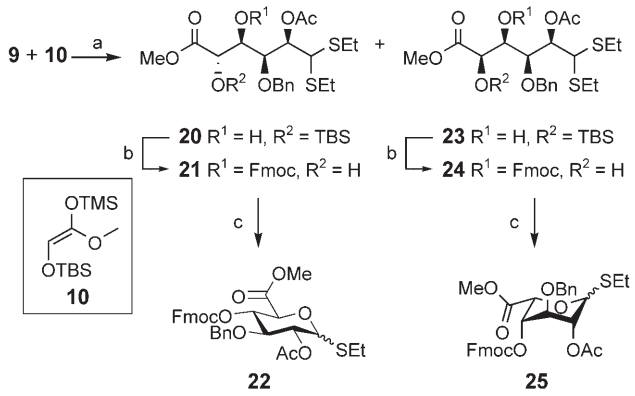
After this efficient route for the synthesis of thioacetal aldehydes was established, the aldol reaction/cyclization sequence was explored (Scheme 3). The



Scheme 3. Synthesis of L-glucuronic acid, L-iduronic acid, and L-altruronic acid building blocks: a) Method A: $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 15 min, 93% (**11**/**14**/**17** = 1:1:1); Method B: $MgBr_2{\cdot}Et_2O$, toluene, −78→−30°C, 1 h, quant. (only **11**); b) 1. FmocCl, pyridine, 2 h; 2. HF·pyridine, THF, 16 h, **12**: 83%, **15**: 89%, **18**: 84% (two steps); c) NIS, CH_2Cl_2, 15 min, quant. (**13**, **16**, and **19**). Fmoc = 9-fluorenylmethoxycarbonyl, NIS = *N*-iodosuccinimide.

explored further. It has been shown previously that stereoselectivities can be significantly improved by the use of metal Lewis acids in a chelation-controlled Mukaiyama-type aldol reaction.[13] We envisaged that Felkin–Anh addition of a silyl enol ether to a aldehyde, in an open transition state, should preferentially furnish a glucuronic acid. Indeed, the $MgBr_2{\cdot}Et_2O$-promoted aldol reaction of the aldehyde **8** and the silyl enol ether **10** (Method B, Scheme 3) afforded glucuronic acid **11** in quantitative yield as a single diastereomer.

The $BF_3{\cdot}Et_2O$-mediated aldol reaction between the selectively protected aldehyde **9** and ketene acetal **10** was also examined (Scheme 4). Surprisingly, analysis of the crude



Scheme 4. Synthesis of selectively protected D-glucuronic and L-iduronic acid building blocks. a) Method A: $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 15 min, 95% (**20**/**23** = 3:2); Method B: $MgBr_2{\cdot}Et_2O$, toluene, −78 → −30 °C, 1 h, 98% (only **20**); b) 1. FmocCl, pyridine, 2 h; 2. HF·pyridine, THF, 16 h, **21**: 79%, **24**: 76% (two steps); c) NIS, CH_2Cl_2, 15 min, quant. (**22** and **25**), (α/β = 1:1).

reaction mixture by ^1H NMR spectroscopy showed a 3:2 ratio of two diastereomers, and only traces of a third. Separation of the individual isomers followed by protecting-group manipulations and NIS-mediated cyclization led to the isolation of the pyranoses **22** and **25**. Through comparison of the ^1H NMR coupling constants with those of the pyranosides **13** and **16**, thioglycoside **22** was identified as D-glucuronic acid and **25** as L-iduronic acid. Finally, the $BF_3{\cdot}Et_2O$-mediated aldol reaction between **9** and **10** (analogous to the reaction of **8** and **10**) led to the formation of the *gluco*-configured product as the only detectable diastereomer (Method B, Scheme 4).

In conclusion, a highly convergent route to orthogonally protected D-glucuronic and L-iduronic acid thioglycoside building blocks has been developed. Rapid access to substantial quantities of monosaccharides that contain practical protecting group patterns and a readily activatable anomeric leaving group will greatly facilitate oligosaccharide assembly by using automated methods. The construction of heparin analogues and the development of efficient routes to further carbohydrate building blocks are currently under investigation.

Received: August 4, 2005
Published online: November 3, 2005

Keywords: aldol reaction · carbohydrates · thioglycosides · uronic acids

[1] a) A. Varki, *Glycobiology* **1993**, *3*, 97–130; b) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683–720; c) R. Roy, *Drug Discovery Today* **2004**, *1*, 327–336; D. M. Ratner, E. W. Adams, B. R. Su, J. O'Keefe, M. Mrksich, P. H. Seeberger, *ChemBioChem* **2004**, *5*, 379–382; d) D. H. Dube, C. R. Bertozzi, *Nat. Rev. Drug Discovery* **2005**, *4*, 477–488; e) D. B. Werz, P. H. Seeberger, *Chem. Eur. J.* **2005**, *11*, 3194–3206.

[2] For recent reviews on oligosaccharide synthesis, see: a) S. Hanessian, *Preparative Carbohydrate Chemistry*, Marcel Dekker, New York, **1997**; b) *Carbohydrates in Chemistry and Biology, Vol. 1* (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, **2000**; c) B. Davies, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2137–2160; d) P. J. Garegg, *Adv. Carbohydr. Chem. Biochem.* **2004**, *59*, 69–113.

[3] a) T. Kanemitsu, O. Kanie, *Trends Glycosci. Glycotechnol.* **1999**, *11*, 267–276; b) P. H. Seeberger, W. C. Haase, *Chem. Rev.* **2000**, *100*, 4349–4394; c) O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Science* **2001**, *291*, 1523–1527; d) P. Sears, C.-H. Wong, *Science* **2001**, *291*, 2344–2350; e) O. J. Plante, E. R. Palmacci, R. B. Andrade, P. H. Seeberger, *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554; f) P. H. Seeberger, *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*, Wiley, New York, **2001**; g) T. Kanemitsu, O. Kanie, *Comb. Chem. High Throughput Screening* **2002**, *5*, 339–360; h) O. J. Plante, P. H. Seeberger, *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 521–525.

[4] a) T. Ogawa, *Chem. Soc. Rev.* **1994**, *23*, 397–407; b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1380–1419; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1482–1522; c) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195–1220.

[5] For recent reviews on de novo synthesis of carbohydrates, see: a) R. R. Schmidt, *Pure Appl. Chem.* **1987**, *59*, 415–424; b) A. Kirschning, M. Jesberger, K.-U. Schoning, *Synthesis* **2001**, 507–540.

[6] S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949.

[7] a) T. Mukaiyama, I. Shiina, S. Kobayashi, *Chem. Lett.* **1990**, *12*, 2201–2204; b) T. Mukaiyama, H. Anan, I. Shiina, S. Kobayashi, *Bull. Soc. Chim. Fr.* **1993**, *130*, 388–394.

[8] a) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1755; b) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235–1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212.

[9] For a recent review, see: C. Noti, P. H. Seeberger, *Chem. Biol.* **2005**, *12*, 731–756.

[10] a) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509; b) T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331.

[11] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 677.

[12] F. L. van Delft, A. R. P. M. Valentijn, G. A. van der Marel, J. H. van Boom, *J. Carbohydr. Chem.* **1999**, *18*, 165–190.

[13] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

[14] K. Hattori, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 5301–5303.

[15] C. Altona, C. A. G. Haasnoot, *Org. Magn. Reson.* **1980**, *13*, 417–429.

