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Synthesis of Iduronic Acid Building Blocks for the Modular Assembly of Glycosaminoglycans

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Abstract: The modular synthesis of glycosaminoglycans requires straightforward methods for the production of large quantities of protected uronic acid building blocks. In particular, the preparation of fully differentiated iduronic acids has proven particularly challenging. An efficient route to methyl 3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-idopyranosiduronate **6** from diacetone glucose in nine steps and 36% overall yield is described. Idopyranosiduronate **6** is useful as a glycosyl acceptor and as an intermediate that may be further elaborated into iduronic acid trichloroacetimidate glycosyl donors for the assembly of glycosaminoglycan structures as illustrated here.

L-Iduronic acid is found naturally as a component of the glycosaminoglycans heparin, heparan, and dermatan. While these biopolymers are known to have diverse biological function, the structure−activity relationships remain poorly understood.[1,2] Access to defined glycosaminoglycan sequences through a general, modular synthesis would be a significant asset to the biochemical studies of these compounds.

Glycosaminoglycan synthesis requires large quantities of differentially protected iduronic acid molecules and necessitates concise and efficient methods for the production of iduronic acid synthons. Since iduronic acid itself is not commercially available, syntheses of iduronic acid derivatives from a variety of starting materials, including idose,[3] glucose,[4,5] glycals,[6] and glucuronic acid,[7] have been developed. While L-idose is very costly, rendering it an undesirable starting material, syntheses with other starting materials require the inversion of the C-5 stereocenter on a D-gluco sugar. Few methods reported for this inversion have realized full selectivity for the desired configuration. Syntheses from idose to procure iduronic acid building blocks used in the synthesis of large heparin structures have been reported, but remain lengthy and involve several steps that produce multiple products.[3] Methods for the completely selective conversion of 5-aldopentoses to iduronic acid derivatives[8] and for the selective silylation of the anomeric hydroxyl of iduronic acids[9] have been described, but have not been incorporated into the synthesis of iduronic acid monosaccharide building blocks. Here we report a short synthetic route to iduronic acid building blocks through the conversion of diacetone glucose to the key intermediate methyl 3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-idopyranosiduronate **6**. This iduronic acid derivative can serve as a glycosyl acceptor or can be readily converted to fully differentiated iduronic acid trichloroacetimidate glycosyl donors. The synthesis described incorporates a number of past chemistries through improved and simplified procedures, and requires only a few purification steps.

Commercially available diacetone glucose **1** was transformed to diol **2** through benzylation and selective acetal cleavage (Scheme 1).[5] Treatment of **2** with aqueous sodium periodate adsorbed onto silica yielded aldehyde **3**[10,11] that was used without purification. Reaction of **3** with freshly prepared trithiophenylmethylithium afforded L-idose-configured thioortho ester in high yield with no D-glucose product detectable.[8] The reaction products were treated directly with $CuCl_2$/CuO to effect the cleavage of the thioortho ester to the furanose methyl ester **4**, along with small amounts of the corresponding phenylthioester. Stirring the crude product mixture with K_2CO_3 in methanol converted this byproduct to the desired methyl ester **4**. Removal of the isopropylidene group from furanose **4** by reaction with 90% TFA (aq) yielded the crystalline 3-*O*-benzyl iduronic methyl ester **5** in its pyranose form.[12]

Installation of a 1,2-isopropylidene onto **5** locked the sugar in the $^1C_4$ pyranose form and afforded key intermediate **6**.[12] Use of highly reactive 2-methoxypropene[13,14] to form the desired isopropylidene acetal prevented opening of the sugar ring and thus the trapping of thermodynamically more stable furanose isomers. Partial hydrolysis of the crude product mixture with acidic resin in methanol produced the desired product **6** in 48% yield from **4**, along with recovered **5** (36%). The synthesis of **6** from diacetone glucose was achieved in nine steps and 36% overall yield (56% assuming complete resubmission of **5**). Only three chromatographic steps were required in this synthetic sequence; additionally, the procedures for the transformation of **3** to **4** and **5** to **6** have been

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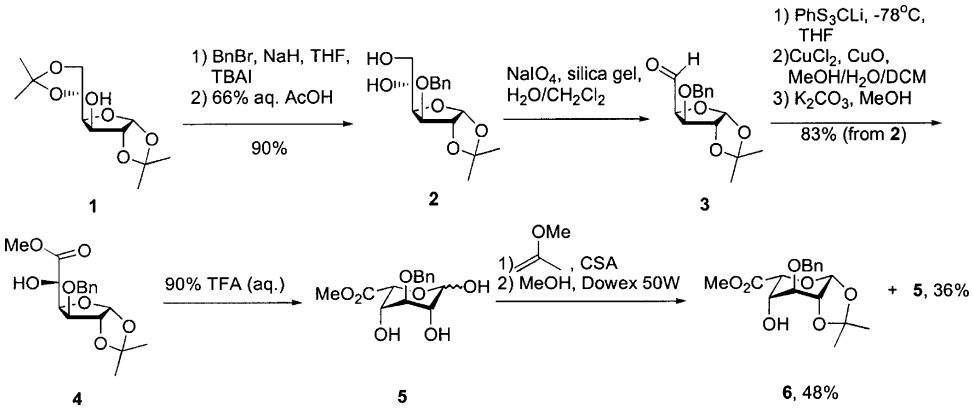
SCHEME 1



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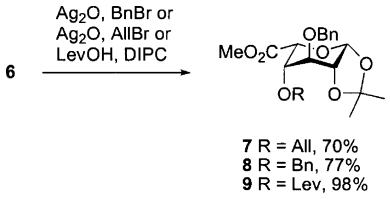

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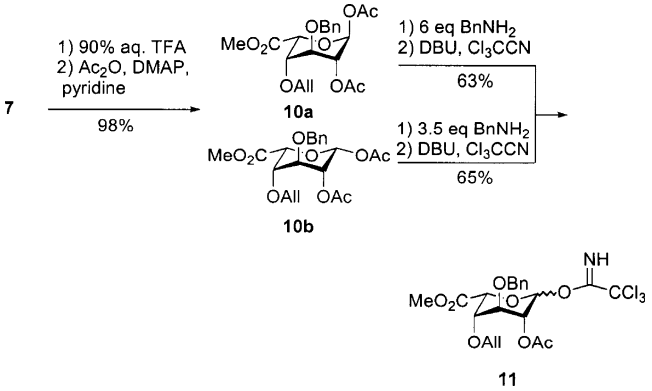

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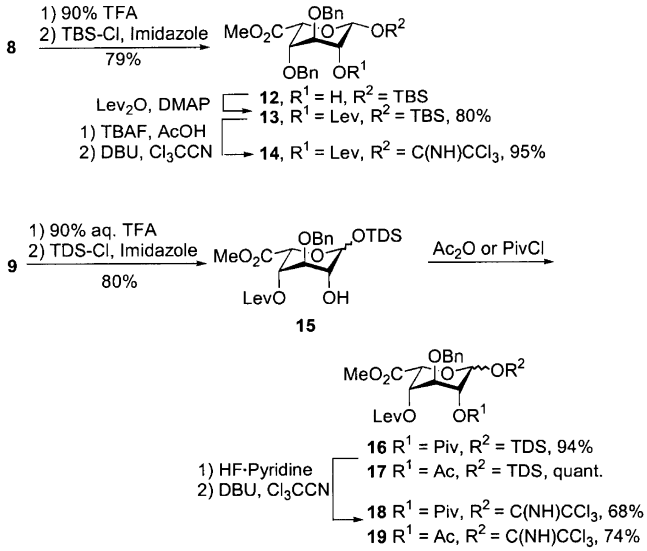

simplified from those previously reported and the yields improved.[8,12]

L-iduronic acid derivative **6** may serve as a glycosyl acceptor in the synthesis of disaccharide modules,[5] or may be converted into a variety of iduronic acid trichloroacetimidate glycosyl donors. The introduction of different protecting groups, including silyl ethers, esters, and alkyl ethers, on the C-4 hydroxyl can be readily achieved.[5] Silylation can be effected through the use of silyl triflates, esterification through acid anhydrides, and DMAP. Alkylation poses more of a challenge, as the C-5 stereocenter of **6** may epimerize in the presence of strong base, but was accomplished with silver oxide and the corresponding alkyl bromide (Scheme 2).

Differential protection of the C-1 and C-2 hydroxyls was achieved through two routes. One option capitalized on the faster rate of cleavage of anomeric acetates over other ester protecting groups.[15] Treatment of **7** with aqueous TFA to effect isopropylidene cleavage, followed by acetylation of the crude material, afforded **10a** and **10b** (Scheme 3). These anomers were separated and exposed to benzylamine to cleave the anomeric acetate selectively. Since **10a** and **10b** react at different rates under these conditions, better yields were obtained by treating these isomers separately. The resultant lactol was transformed to glycosyl trichloroacetimidate **11** by reaction with trichloroacetonitrile and DBU.

The second route to differentially protected iduronic acid derivatives from **6** was the selective formation of anomeric silyl ethers.[9] After protection of the C-4 hydroxyl, the isopropylidenes of **8** and **9** were cleaved with aqueous TFA (Scheme 4). Both **8** and **9** were exposed to a silyl chloride at low temperature to selectively protect the C-1 hydroxyl and produce **12** and **15**, respectively. The steric bulk of the C-4 protecting group required the adjustment of reaction conditions to achieve good yield and selectivity. The larger benzyl group allowed use of *tert*-butyldimethylsilyl chloride (TBS−Cl) as the silylating agent. The smaller levulinate ester required lower temperatures and the bulkier thexyldimethylsilyl chloride (TDS−Cl) to achieve good selectivity.

Further elaboration of **12** by introduction of a levulinate ester on the C-2 hydroxyl afforded **13**. Cleavage of the anomeric silyl ether yielded lactol, which was con-

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verted to trichloroacetimidate **14**. Similarly, product **15** was converted to its pivaloyl ester **16** and acetate ester **17**. The anomeric thexyl ethers were cleaved with HF·pyridine, and the lactols converted to the corresponding trichloroacetimidates **18** and **19**.

The synthesis of compound **6** in 36% overall yield in nine steps from diacetone glucose is significantly shorter than the previous route,[12] allowing for the rapid production of multigram quantities of iduronic acid building blocks. Key intermediate **6** may be elaborated through selective anomeric hydroxyl silylation or selective acetate cleavage to produce a variety of iduronic acid derivatives, including the glycosyl donors **11**, **14**, **18**, and **19**, using chemistry readily adaptable to other protecting group schemes. The chemistry presented offers for the first time a general, high-yielding, and easily scaleable route to iduronic acid synthons for glycosaminoglycan assembly, addressing a long-standing obstacle in the convenient production of these compounds.

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Supporting Information Available: Experimental procedures and characterization data for all compounds not previously reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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