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Carbohydrate Research 342 (2007) 1876–1887
Carbohydrate RESEARCH

# Synthesis of a bicyclic analog of L-iduronic acid adopting the biologically relevant $^2S_0$ conformation

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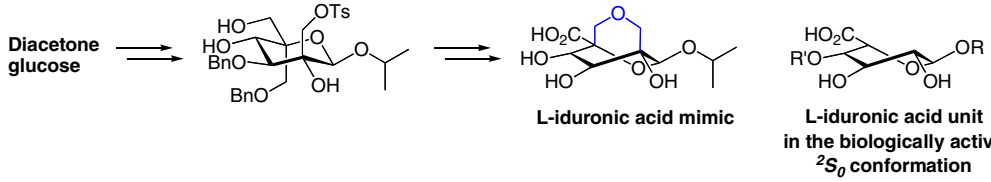
Received 30 January 2007; received in revised form 14 February 2007; accepted 21 February 2007
Available online 25 February 2007

**Abstract**—The synthesis of a bicyclic analogue of the naturally occurring α-L-iduronic acid locked in a biologically active $^2S_0$ skew-boat conformation is disclosed. The desired $^2S_0$ conformation has been obtained by tethering the C-2 and C-5 carbon atoms of the sugar ring with a dimethyloxy bridge and confirmed by NMR and molecular modeling. The new mimic displays the exact hydroxyl pattern of α-L-iduronic acid, a major monosaccharide component of glycosaminoglycans and thus represents a closer mimic of the latter, compared to previously reported bicyclic analogs.

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*Keywords:* Conformation; Glycosaminoglycans; Heparin; Iduronic acid; Scaffold

## 1. Introduction

The conformation of L-iduronic acid residues in glycosaminoglycans (GAGs) such as heparin, heparan sulfate, and dermatan sulfate was earlier the cause of a long controversy.[1,2] Thanks to the availability of well defined synthetic oligosaccharides, it has been unambiguously demonstrated that such residues are in equilibrium between three conformations: $^1C_4$, $^4C_1$, and $^2S_0$.[3] This unique conformational flexibility emerged as a new concept for explaining the recognition and biological properties of GAGs containing L-iduronic acid.[4] More specifically, NMR studies[5] on the synthetic pentasaccharide **1**[6] (Fig. 1), representing the antithrombin binding site of heparin and containing only one L-iduronic acid residue, suggested a large contribution of the unusual $^2S_0$ skewboat conformer[7] in such a pentamer where it is adjacent to a 3-O-sulfonated aminosugar residue.[4a]

To establish a correlation between conformation and antithrombotic activity, the total synthesis of the three pentasaccharides **2**–**4** was achieved,[8] in which the L-iduronic acid residue was conformationally locked, either in a $^1C_4$ , $^4C_1$ or $^2S_0$ form. In these compounds, several hydroxyl groups and all the *N*-sulfonates were replaced by methoxy groups and *O*-sulfonates, respectively, a change that greatly simplified the synthetic route but

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doi:10.1016/j.carres.2007.02.025

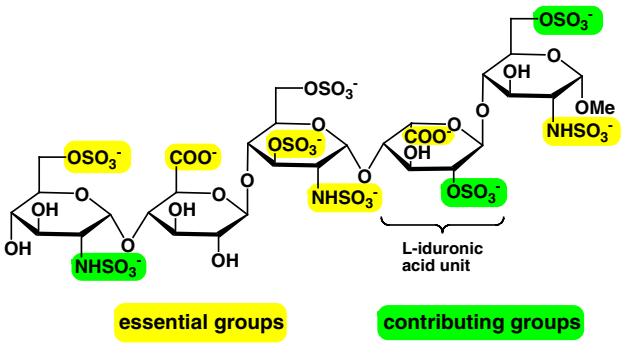


**Figure 1.** Structure of pentasaccharide **1** with essential and contributing groups (reproduced from Petitou and van Boeckel).[12b]

which did not affect their biological activity.[9,10] It was concluded that antithrombin-bound L-iduronic acid adopts the $^2S_0$ skewboat conformation, which thus governs the antithrombotic activity of heparin (Fig. 2). Another pentasaccharide, **5**, containing a slightly more flexible L-iduronic acid unit was later prepared.[11] In these first- and second-generation pentamers **3** and **5**, respectively, and as the logical result of the selected synthetic strategy, the hydroxyl group at C-2 of the parent L-iduronic acid was missing. In the specific case of antithrombin mediated activity, this substituent was shown not to be essential, albeit contributing to an increase of the activity;[12] actually, the effect of the missing substituent is compensated by the sulfate group located at C-3 of the D-glucosamine unit.[13] In the more general context of GAGs biological studies, the synthesis of a closer mimic of L-iduronic acid locked around the $^2S_0$ conformation and retaining all the hydroxyl groups is of interest and is disclosed in this piece of work. Our selected new third-generation scaffold **6** has its oxygen atom of the bridging unit moved one atom away from C-2, to generate a stable structure of ether type (Fig. 2).

## 2. Results and discussion

### 2.1. First approach

The first approach started from the known D-glucose derivative **7**[14] available from diacetone glucose. The choice of the isopropyl group as the anomeric substituent was imposed by the poor glycosylation step of the thiophenyl glycosyl donor with methanol. Alkene **7** was ozonolyzed and further reduced with $LiAlH_4$ to yield primary alcohol **8** in 70% yield. O-Benzylation followed by silyl group removal with TBAF afforded alcohol **9**. The required stereoselective installation of a latent leaving group at position 2 while retaining a D-*gluco* configured scaffold having two extra substituents at positions 2 and 5 was performed as follows. Swern oxidation of alcohol **9** furnished the corresponding ketone, which was directly used without purification and treated with vinyl magnesium bromide to afford the allylic alcohol **10** as a single product in 75% yield, the stereochemistry at C-2 for this compound being not firmly established at this stage.[‡] Ozonolysis followed by reduction with $NaBH_4$ yielded diol **11** (37% yield over two steps, unoptimized). Regioselective tosylation at the primary position afforded tosylate **12**, from which the isopropylidene group was removed under mild acidic conditions to furnish triol **13** in excellent yield.

The key cyclization step was then achieved by treatment of triol **13** under basic conditions with NaH in dry DMF to afford **14** in a modest 20% yield along with more polar unidentified products. Its structure was firmly established as follows: hydrogenolysis of the benzyl groups and subsequent per-acetylation of the crude compound afforded a crystalline compound **15**, the X-ray structure of which was solved (Fig. 3).[§] The structure of tetracetate **15** clearly indicates that the bicyclic compound **14** arises from displacement of the tosyl group at C-2 in **13** by the OH group at C-4. This in turn demonstrates addition of the Grignard reagent from the α-face of the transient ketone yielding the undesired D-*manno* configured isomer, **10**. As described by Ley and co-workers in a paper that appeared after we undertook this research,[15] the stereoselectivity of the addition of the Grignard reagent can be rationalized by the β-configuration of the anomeric substituent in the ketone favoring a trans addition at C-2 (see Scheme 1).

### 2.2. Second approach

Another route, based on the dihydroxylation of an exomethylene installed at C-2, was envisioned to provide the desired D-*gluco* configured stereoisomer (Scheme 2). Cis dihydroxylation of *C*-alkylidene carbohydrates with $OsO_4$ has been shown to proceed from the less hindered face of the olefin.[16] In our case, the isopropylidene group and the β-anomeric isopropyl group should favor a dihydroxylation from the α face of the sugar ring to produce the desired D-*gluco* stereoisomer.

[‡] NOE experiments gave ambiguous results on this structure.

[§] Selected crystal structure data for **15**; crystal system orthorhombic; space group $P2_12_12_1$; $Z = 4$; cell parameters: $a = 10.485(5)$, $b = 14.231(10)$, $c = 14.836(10)$, $\alpha = 90$, $\beta = 90$, $\gamma = 90$; radiation (Mo Kα) $\lambda = 0.71069$ Å; 193 variables for 1169 reflections; final $R = 0.1142$, $R_W = 0.1327$; crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 604630. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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