

## Novel Synthesis of L-Iduronic Acid Using Trehalose as the Disaccharidic Starting Material

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### Abstract

For the preparation of L-iduronic acid, trehalose was converted into a derivative of a novel disaccharide,  $\beta$ -L-idopyranosyl  $\beta$ -L-idopyranoside, through diastereoselective hydroboration of the 5, 5'-di-eno intermediate. The 6- and 6'-hydroxy groups were then oxidized in two steps to give a disaccharide composed of 2 units of L-iduronate moieties, which underwent acidic cleavage of the glycosidic bond to give the target compound.

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L-Iduronic acid is a common key component of three important mammalian glycosaminoglycans, namely, heparin, heparan sulfate, and dermatan sulfate. The iduronate residue in those glycosaminoglycans has a unique conformational flexibility like a kind of molecular hinge, which has been considered to bring about their potent binding ability [1]. A great need for L-iduronic acid in bioorganic studies has prompted the chemical syntheses of itself and its precursor, L-idose, that is not readily accessible in nature. Most of those synthetic methods involved a selective inversion of the configuration at C-5 of D-*gluco* derivatives in various ways as shown in the following: nucleophilic displacement of the sulfonate group in D-glucofuranose [2-4] or D-glucofuranuronic acid derivatives [5, 6], epimerization of di-*O*-alkylidene derivatives of D-glucopyranuronate [7] and radical reduction of a 5-bromo compound derived from D-glucopyranuronate [8]. Diastereoselective hydroboration of methyl  $\alpha$ -D-*xylo*-hex-5-enopyranosides derived from methyl  $\alpha$ -D-glucopyranosides was another convenient route for construction of the L-*ido* configuration [9, 10, 11]. In this methodology, the axially oriented aglycone plays an essential role to produce preferably the *ido* configuration by impeding an attack of borane reagents from the  $\alpha$  side.

This communication describes the synthetic conversion of  $\alpha,\alpha$ -trehalose into a derivative of a novel disaccharide,  $\beta$ -L-idopyranosyl  $\beta$ -L-idopyranoside, by applying the above diastereoselective hydroboration methodology to the disaccharidic dieno system and further transformation into the corresponding disaccharidic uronate by oxidation of the 6 and 6' hydroxy groups followed by acidic fission of the disaccharide for the production of L-iduronic acid.

Recently, a highly efficient production of  $\alpha,\alpha$ -trehalose ( $\alpha$ -D-glucopyranosyl  $\alpha$ -D-glucopyranoside) from starch has been established by utilizing microbial enzymes newly found [12]. As a result, this inexpensive disaccharide has become an attractive starting material for the preparation of L-iduronic acid.

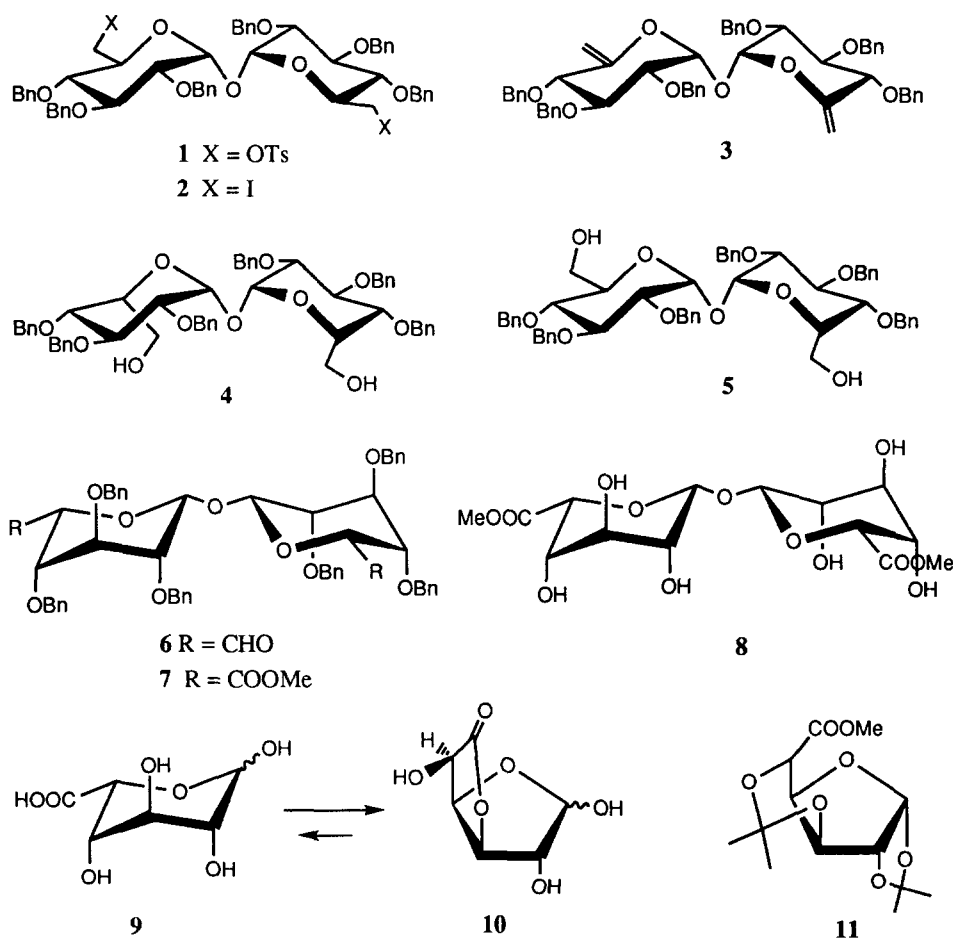
The known 2,2',3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-tosyl-trehalose (**1**) [13] was treated in *N,N*-dimethylformamide (DMF) with NaI, giving the 6,6'-dideoxy-6,6'-diiodo derivative (**2**)<sup>1</sup>, glass,  $[\alpha]_{\text{D}}^{29} +102^\circ$  (c 1.20,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.14 (dd, 2H,  $J_{6a,6b(6a',6b')} = 10.8$  Hz,  $J_{5,6a(5',6a')} = 2.7$  Hz, H-6a,6a'), 3.22 (dd, 2H,  $J_{5,6b(5',6b')} = 4.5$  Hz, H-6b,6b'), in almost quantitative yield. Dehydrohalogenation of **2** into the 5,5'-dieno derivative was the first difficulty to be overcome. Jacquinet et al. [11] reported the successful dehydrohalogenation of methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in DMF, giving the corresponding 5-eno derivative in 74% yield. In contrast to such monosaccharide chemistry, treatment of **2** with DBU in DMF or THF gave only poor yields (less than 10%) of the expected alkene. Although the yields were somewhat improved (about 26%) by treatment with AgF in pyridine, isolation of the expected compound from the accompanying products was very hard. When **2** was treated with potassium *t*-butoxide at  $-20^\circ\text{C}$  in THF, migration of the double bond took place from the *exo* into the *endo* position, giving a 4,4'-dieno derivative in 88% yield. The efficient preparation of the expected 5,5'-dieno compound was finally achieved by employing NaH as a base. Thus, **2** was treated with large excess of NaH in DMF at  $0^\circ\text{C} \rightarrow \text{r.t.}$  for 12 h, giving *O*-(2,3,4-tri-*O*-benzyl-6-deoxy- $\alpha$ -D-xylo-hex-5-enopyranosyl)-(1 $\rightarrow$ 1)-2,3,4-tri-*O*-benzyl-6-deoxy- $\alpha$ -D-xylo-hex-5-enopyranoside **3** in 96% yield as a syrup:  $[\alpha]_{\text{D}}^{25} -16^\circ$  (c 1.01,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.01 (brd, 2H,  $J_{3,4(3',4')} = 9.0$  Hz,  $J_{4,6a(4',6a')} < 1.0$  Hz,  $J_{4,6b(4',6b')} < 1.0$  Hz, H-4,4'), 4.73 (brs, 2H, H-6a,6a'), 4.91 (brs, 2H, H-6b,6b'), 5.51 (d, 2H,  $J_{1,2(1',2')} = 3.4$  Hz, H-1,1').

The 5- and 5'-eno groups of **3** next underwent hydroboration reaction with borane methylsulfide ( $\text{BH}_3\cdot\text{SMe}_2$ ) or 9-borabicyclo[3,3,1]nonane (9-BBN). When **3** was treated with  $\text{BH}_3\cdot\text{SMe}_2$  in THF and then with  $\text{H}_2\text{O}_2$  in a basic medium in the regular manner, two products were isolated in 64% and 18% yields. NMR analyses disclosed that the major product was the desired compound, *O*-(2,3,4-tri-*O*-benzyl- $\beta$ -L-idopyranosyl)-(1 $\rightarrow$ 1)-2,3,4-tri-*O*-benzyl- $\beta$ -L-idopyranoside **4**:  $[\alpha]_{\text{D}}^{32} +1.5^\circ$  (c 0.89,  $\text{CHCl}_3$ ),  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.52 (dd, 2H,  $J_{1,2(1',2')} = 3.7$  Hz,  $J_{2,3(2',3')} = 9.6$  Hz, H-2,2'), 3.72 (dd, 2H,  $J_{3,4(3',4')} = 9.4$  Hz,  $J_{4,5(4',5')} = 6.3$  Hz, H-4,4'), 3.80 (dd, 2H,  $J_{6a,6b(6a',6b')} = 11.9$  Hz,  $J_{5,6a(5',6a')} = 3.6$  Hz, H-6a,6a'), 3.94 (t, 2H, H-3,3'), 4.09 (t, 2H,  $J_{5,6b(5',6b')} = 11.3$  Hz, H-6b,6b'), 4.16 (ddd, 2H, H-5,5'), 4.58 (d, 2H, H-1,1'). The structure of the minor product was also confirmed by NMR spectrum, which revealed a combination of D-*gluco* and L-*ido* moieties as in **5**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) D-*gluco* moiety  $\delta$  3.53 (dd, 1H,  $J_{1,2} = 3.1$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.54 (t, 1H,  $J_{3,4} = 9.6$  Hz,  $J_{4,5} = 9.8$  Hz, H-4); L-*ido* moiety  $\delta$  3.48 (dd, 1H,  $J_{1,2} = 2.4$  Hz,  $J_{2,3} = 9.5$  Hz, H-2), 3.72 (dd, 1H,  $J_{3,4} = 9.4$  Hz,  $J_{4,5} = 6.3$  Hz, H-4). A similar reaction with **3** using 9-BBN

1. All compounds with the specific rotation data gave satisfactory results of elemental analyses.

gave **4** and **5** in 83% and 10% yields, respectively. Although the ratio of **4**/**5** was remarkably improved by using 9-BBN, the separation of **4** from cis-1,5-cyclooctanediol derived from 9-BBN was rather laborious.

Oxidation of **4** into the corresponding uronic acid did not proceed smoothly at first. All attempts for the direct oxidation using  $\text{CrO}_3$  in acetone- $\text{H}_2\text{SO}_4$  (Jones oxidation),  $\text{CrO}_3$  in acetic acid-water, or pyridinium dichromate in DMF resulted in decomposition of the product. Therefore, our attention was directed towards a two-step oxidation like  $-\text{CH}_2\text{OH} \rightarrow -\text{CHO} \rightarrow -\text{COOH}$ . Thus, **4** was treated at  $-60^\circ\text{C}$  for 2.5 h in  $\text{CH}_2\text{Cl}_2$  with dimethyl sulfoxide (DMSO)-oxalyl chloride and then with triethyl amine (Swern oxidation) [14] and the resulting dialdehyde **6** was quickly extracted with diethyl ether. After evaporation of the extract at below  $5^\circ\text{C}$ , the intermediate **6** immediately underwent Jones oxidation and the subsequent treatment with diazomethane, giving methyl [*O*-(methyl 2,3,4-tri-*O*-benzyl- $\beta$ -L-idopyranosyluronate)-(1 $\rightarrow$ 1)-2,3,4-tri-*O*-benzyl- $\beta$ -L-idopyranosid]uronate **7** in 71% overall yields from **4**:  $[\alpha]_{\text{D}}^{28} +101^\circ$  (c 1.42,  $\text{CHCl}_3$ ),  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.66 (s, 6H, 2 x



COOCH<sub>3</sub>), 3.68 (m, 4H, H-3,3', H-4,4'), 3.72 (brs, 2H,  $J_{1,2(1',2')} = 1.3$  Hz, H-2,2'), 4.50 (d, 2H,  $J_{4,5(4',5')} = 1.7$  Hz, H-5,5'), 5.36 (d, 2H, H-1,1'). When treatment with DMSO-SO<sub>3</sub>·pyridine-Et<sub>3</sub>N was employed instead of Swern oxidation, the subsequent Jones oxidation and esterification gave **7** in only 37% yield, being accompanied with 24% yield of a by-product. NMR examination indicated that the by-product was formed by epimerization of one of the aldehyde groups of **6**. All benzyl groups were removed from **7** by catalytic hydrogenation over palladium hydroxide on carbon in acetic acid, giving methyl [*O*-(methyl β-L-idopyranosyluronate)-(1→1)-β-L-idopyranosid]uronate **8** in 94% yield as a glass:  $[\alpha]_{\text{D}}^{29} +122^\circ$  (c 0.35, MeOH), <sup>1</sup>H NMR (D<sub>2</sub>O) δ 3.77 (s, 6H, 2 x COOCH<sub>3</sub>), 3.82 (dd, 2H,  $J_{1,2(1',2')} = 1.0$  Hz,  $J_{2,3(2',3')} = 3.8$  Hz, H-2,2'), 3.94 (dd, 2H,  $J_{3,4(3',4')} = 4.0$  Hz,  $J_{4,5(4',5')} = 2.0$  Hz, H-4,4'), 4.13 (t, 2H, H-3,3'), 4.67 (d, 2H, H-5,5'), 5.27 (d, 2H, H-1,1').

At the final stage, **8** underwent simultaneous cleavage of the glycosidic bond and the ester bonds under acidic conditions. As previously noted in the literature [15], the free iduronic acid exists in equilibrium with its lactone even in water solution. When **8** was heated at 120 °C for 10 h in water with Amberlite IR-120B (H<sup>+</sup>), a mixture of L-iduronic acid **9** and α,β-L-idofuranurono-3,6-lactone **10** was formed. On evaporation of the mixture solution, most of **9** converted to **10**: <sup>1</sup>H NMR (D<sub>2</sub>O) α-anomer δ 4.35 (s, 1H, H-2), 4.45 (brs, 1H,  $J_{4,5} < 1$  Hz, H-5), 4.88 (brd, 1H,  $J_{3,4} = 5.7$  Hz, H-4), 5.11 (d, 1H, H-3), 5.42 (s, 1H, H-1); β-anomer δ 4.36 (brd, 1H,  $J_{1,2} = 4.3$  Hz,  $J_{2,3} < 1$  Hz, H-2), 4.53 (d, 1H,  $J_{4,5} = 3.0$  Hz, H-5), 4.87 (dd, 1H, H-4), 5.01 (brd, 1H, H-3), 5.48 (d, 1H, H-1). The structure of **9** and **10** was confirmed by their transformation into the known crystalline derivative of L-iduronic acid. Treatment of **10** (+ a little amount of **9**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave methyl 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranuronate **11**, mp. 117 °C,  $[\alpha]_{\text{D}}^{22} +7.8^\circ$  (c 0.52, CHCl<sub>3</sub>), which showed good agreement with the data reported in the literature [7], mp. 119 °C,  $[\alpha]_{\text{D}}^{26} +7.6^\circ$  (c 0.5, CHCl<sub>3</sub>).

In conclusion, an efficient synthesis of L-iduronic acid was established starting from the inexpensive disaccharide, trehalose.

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