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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, β-L-idopyranosyl β-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.

Keywords: conformation; diastereoselection; elimination reaction; oxidation

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-glucofuranuronate [7] and radical reduction of a 5-bromo compound derived from D-glucopyranuronate [8]. Diastereoselective hydroboration of methyl α-D-*xylo*-hex-5-enopyranosides derived from methyl α-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 α side.

This communication describes the synthetic conversion of α,α-trehalose into a derivative of a novel disaccharide, β-L-idopyranosyl β-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.

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

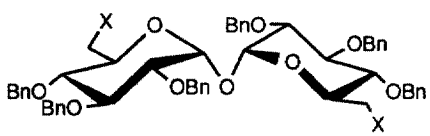
The known 2,2',3,3',4,4'-hexa-*O*-benzyl-6,6'-di-*O*-tosyl-trehalose (**1**) [13] was treated in *N*,*N*-dimethylformamide (DMF) with NaI, giving the 6,6'-dideoxy-6,6'-diiodo derivative (**2**)[1], glass, $[\alpha]_D^{29}$ +102° (c 1.20, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 3.14 (dd, 2H, $J_{6a,6b(6a',6b')}$ = 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-α-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 °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 °C → r.t. for 12 h, giving *O*-(2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranosyl)-(1→1)-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside **3** in 96% yield as a syrup: $[\alpha]_D^{25}$ -16° (c 1.01, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 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 (BH_3•SMe_2) or 9-borabicyclo[3,3,1]nonane (9-BBN). When **3** was treated with BH_3•SMe_2 in THF and then with H_2O_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-β-L-idopyranosyl)-(1→1)-2,3,4-tri-*O*-benzyl-β-L-idopyranoside **4**: $[\alpha]_D^{32}$ +1.5° (c 0.89, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 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**: ^1H NMR ($CDCl_3$) D-*gluco* moiety δ 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 δ 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

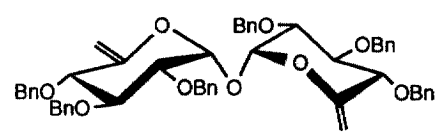
1. All compounds with the specific rotation data gave satisfactory results of elemental analyses.

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 CrO_3 in acetone-H_2SO_4 (Jones oxidation), 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 -CH_2OH → -CHO → -COOH. Thus, **4** was treated at -60 °C for 2.5 h in CH_2Cl_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 °C, the intermediate **6** immediately underwent Jones oxidation and the subsequent treatment with diazomethane, giving methyl [*O*-(methyl 2,3,4-tri-*O*-benzyl-β-L-idopyranosyluronate)-(1→1)-2,3,4-tri-*O*-benzyl-β-L-idopyranosid]uronate **7** in 71% overall yields from **4**: $[\alpha]_D^{28}$ +101° (c 1.42, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 3.66 (s, 6H, 2 x



1 X = OTs
2 X = I



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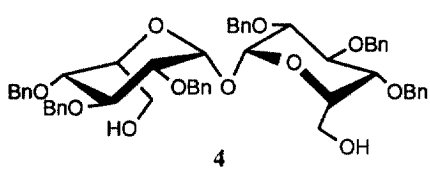

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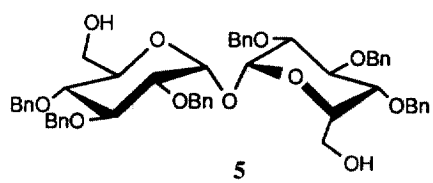
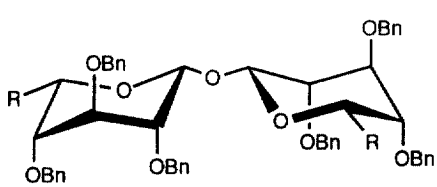
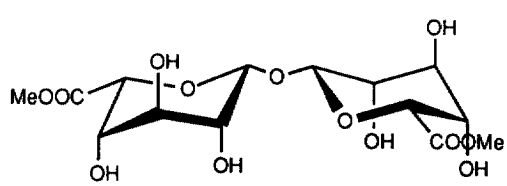


5



6 R = CHO
7 R = COOMe



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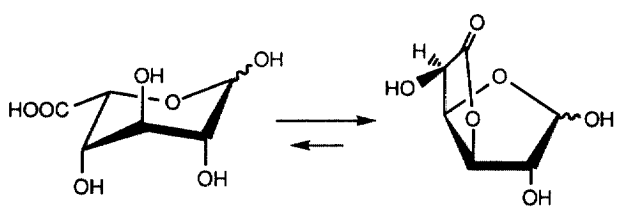
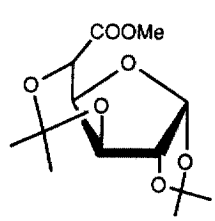


9 **10**



11

$COOCH_3$), 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_3•pyridine-Et_3N 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: $[\alpha]_D^{29}$ +122° (c 0.35, MeOH), ^1H NMR (D_2O) δ 3.77 (s, 6H, 2 x $COOCH_3$), 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^+), 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**: ^1H NMR (D_2O) 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, $[\alpha]_D^{22}$ +7.8° (c 0.52, $CHCl_3$), which showed good agreement with the data reported in the literature [7], mp. 119 °C, $[\alpha]_D^{26}$ +7.6° (c 0.5, $CHCl_3$).

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

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