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SYNTHESIS OF HEPARIN SACCHARIDES[1]—V

ANOMERIC O-BENZYL DERIVATIVES OF L-IDOPYRANOSYLURONIC ACID

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Dedicated to Professor GABOR FODOR, West Virginia University, Morgantown, on his 60th birthday

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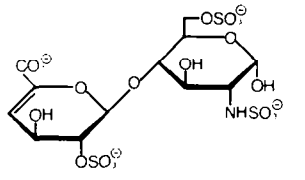
Abstract—Derivatives of the anomeric benzyl L-idopyranosides and L-idopyranosiduronates have been synthesized from D-glucose as models for conformation studies. The two key reactions in the synthesis are: (a) inversion of configuration at C(5) of the D-glucofuranose derivative **4**, and (b) catalytic oxidation of the L-idopyranosides **19**, and **22** to uronic acids.

2-Amino-2-deoxy-D-glucose and D-glucuronic acid have long been known as constituents of heparin,[2] whereas the presence of L-iduronic acid has been recognized only in the last decade.[3] It has been unequivocally established that L-iduronic acid is an integral constituent of heparin of various sources,[4] and does not originate from chondroitin sulfuric acid-B ("β-Heparin") which accompanies heparin in mammalian tissues.[5]

The configuration of the glycosidic linkage of the L-idopyranosyluronic acid residue in heparin is believed to be alpha as in disaccharides **1**[6] and **2**[7] released by chemical[8] and enzymatic degradation of heparin.



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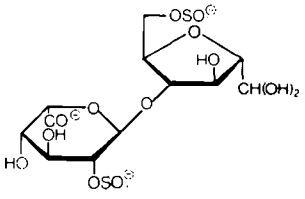

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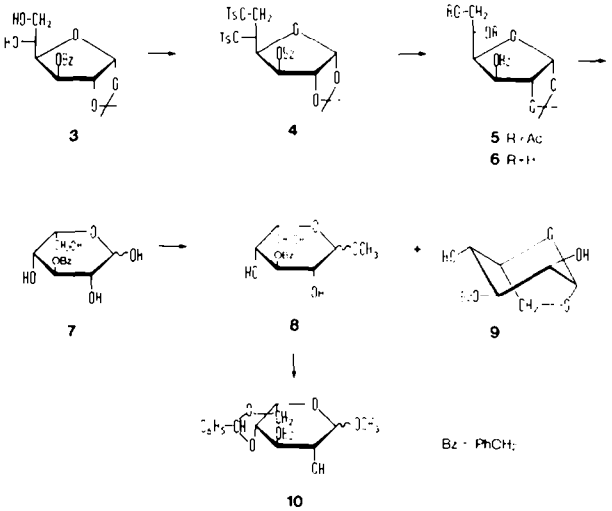
Disaccharide **1** has been isolated in good yield by degradation of heparin with Flavobacterium heparinum,[9] and its structure has been assigned on the basis of its NMR spectrum.[6] However, structural assignment has proved to be very difficult in the absence of reference models. Furthermore, the above enzyme possesses only a restricted stereospecificity,[10] so that the unsaturated disaccharide **1** might originate as well from D-glucuronic acid as from L-iduronic acid.

We now wish to report the synthesis of derivatives of the anomeric benzyl L-idopyranosiduronic acids as references and as models for conformation studies.[11] The conversion of D-glucuronic acid into L-iduronic acid by epimerization[12] has proved to be unpractical for synthesis on a preparative scale. An alternative approach, consisting of inverting the configuration at C(5) of a suitable D-glucofuranose derivative, was therefore chosen.

The starting material for this synthesis was 3 - O - benzyl - 1,2 - O - isopropylidene - α - D - glucofuranose (**3**), readily available from D-glucose in three steps.[13] Compound **3** was treated with *p*-toluenesulfonyl chloride in pyridine to give the 5,6-di-O-*p*-toluenesulfonate **4**, which on treatment with potassium acetate in acetic anhydride gave the 5,6-diacetate **5**. De-O-acetylation of **5** afforded crystalline 3 - O - benzyl - 1,2 - O - isopropylidene-β - L - idofuranose (**6**). The isopropylidine protecting group of **6** was then hydrolyzed with dilute sulfuric acid to give a good yield of 3-O-benzyl-L-idose (**7**) as a syrup.



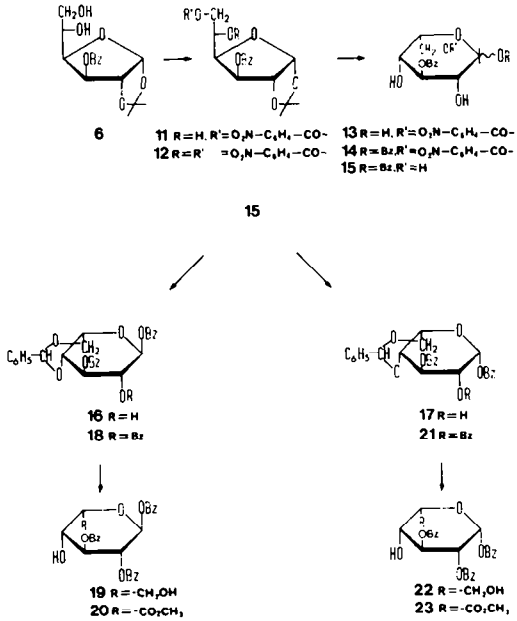
Glycosidation of **7** with methanol in the presence of Dowex-50 (H^+) provided only a low yield of methyl glycoside **8** as a syrup. The major product of the glycosidation was characterized as the anhydro sugar **9**. A crystalline 4,6-O-benzylidene derivative (**10**) was obtained on reaction of **8** with benzaldehyde and zinc chloride. On the other hand, attempted glycosidation of **7** with benzyl alcohol under identical reaction conditions gave **9** exclusively.

The C(6) OH group of **6** had therefore to be protected, in order to prevent the formation of the anhydro sugar. *p*-Nitrobenzoylation of **6** produced a crystalline 6-O-*p*-nitrobenzoyl derivative **11** in good yield, together with

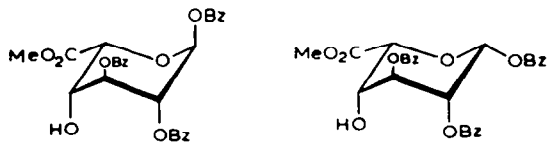
some 5,6-di-O-*p*-nitrobenzoate **12**. The C(1) and C(2) OH groups of **11** were subsequently deblocked by hydrolysis with aqueous acetic acid to give 3 - O - benzyl - 6 - O - (*p* - nitrobenzoyl) - L - idopyranose (**13**). Treatment of this compound with benzyl alcohol and hydrochloric acid provided the benzyl glycoside **14**. The *p*-nitrobenzoyl protecting group of **14** was then removed by reaction with a catalytic amount of sodium methoxide in methanol to give benzyl 3-O-benzyl-L-idofuranoside (**15**). Resolution of the anomeric mixtures **14** and **15** proved to be difficult at these stages. The corresponding 4,6-O-benzylidene derivative, obtained by treatment of **15** with benzaldehyde in the presence of zinc chloride, proved to be a more suitable derivative for anomeric resolution. The anomeric mixture was easily separated by column chromatography, and both anomers (**16** and **17**) were isolated in crystalline form.

Benzylation of **16** with benzyl chloride in the presence of potassium hydroxide afforded the 2,3-di-O-benzyl ether **18** in high yield. The C(4) and C(6) OH groups of **18** were subsequently deblocked by hydrolysis with aqueous acetic acid to give **19**. This compound was oxidized in water at 50° and pH 7.5–8.1 with oxygen in the presence of platinum followed by esterification of the crude uronic acid with diazomethane, whereby crystalline methyl (benzyl 2,3 - di - O - benzyl - α - L - idopyranosid)uronate (**20**) was obtained.

The corresponding β-anomer **23** was prepared from **17** by the same sequence of reactions as described for the α-anomer.



The presence of w-type couplings between the pairs of protons H–C(1)/H–C(3) and H–C(2)/H–C(4) in the NMR spectrum of **20** was consistent with on equatorial arrangement of these protons, thus confirming the α configuration of its glycosidic linkage. In contrast, no w-pattern between protons H–C(1) and H–C(3) was observed in the spectrum of the β-anomer **23**, as indicated by the pressence of proton H–C(1) as a doublet. On the other hand, the magnitude of the coupling constants between the ring protons in these compounds indicated that both anomers adopt a 1C(L) conformation (**24** and **25**) almost exclusively.[14] In this conformation,[15] the benzyloxy



groups at C(2) and C(3) are axially oriented, whereas the methoxycarbonyl groups at C(5) are equatorially oriented.

EXPERIMENTAL

General methods. M.ps were determined on a Büchi (Flawil, Switzerland) m.p. apparatus and are not corrected. Spectral measurements were performed in the Physical Chemistry Department of Hoffmann–La Roche using the following instruments: NMR: Varian HA 100. Chemical shifts are given in ppm relative to TMS (= 0 ppm) as internal standard, coupling constants J in Hz. IR.: Beckmann IR 9 spectrometer. Optical rotations: Perkin–Elmer polarimeter Model 141. Precoated silica gel plates F 254 (Merck) were used for TLC. The spots were observed by spraying with 10% H_2SO_4 and subsequent heating. For the column chromatography silica gel (30–70 mesh/0.2–0.5 mm) of Merck was used.

3 - O - *Benzyl* - 1,2 - O - *isopropylidene* - 5,6 - *di* - O - (p - *tolysulfonyl*) - α - D - *glucofuranose* (**4**). A soln of **3** (7.6 g; 57 mmol)[13] in pyridine (40 ml) was treated at RT with *p*-toluenesulfonyl chloride (38 g; 200 mmol) in chloroform (60 ml). After 16 hr standing at RT, the mixture was evaporated to dryness. The residue was dissolved in 150 ml dichloromethane, and the extract was washed with cold 3N HCl, 5% $NaHCO_3$aq and water, then dried over Na_2SO_4 and evaporated to dryness. The residue was extracted with 3 × 200 ml boiling hexane to remove unreacted *p*-toluenesulfonyl chloride. The crystalline residue was suspended in 100 ml isopropyl ether, filtered off, washed with isopropyl ether and recrystallized from EtOAc/petroleum ether: yield 25 g (72%), m.p. 97–98°, $[\alpha]_D^{25} = -4.1°$ (*c* = 1.3, chloroform) (Found: C, 58.23; H, 5.46; S, 10.24. Calc. for $C_{40}H_{34}O_{10}S_2$: C, 58.24; H, 5.54; S, 10.36%).

3-O-*Benzyl*-1,2-O-*isopropylidene*-β-L-*idofuranose* (**6**). A mixture of **4** (24.4 g; 39 mmol) Ac_2O (200 ml) and KOAc (34 g) was refluxed for 8 hr under stirring. The mixture was evaporated to dryness and the residue was extracted with 1 l of ether. The ether extract was evaporated to dryness and the mixture was fractionated on a column (300 g) of silica gel with dichloromethane as developer. The syrupy diacetate **5** was dissolved in MeOH (150 ml) and 1% NaOMe (14 ml) was added. After 16 hr standing at RT, the soln was neutralized with CO_2 and evaporated to dryness. The residue was chromatographed on silica gel (150 g) with dichloromethane/ether 4:1 as developer. Evaporation of the eluate left crystalline material, which was recrystallized from EtOAc/petroleum ether: yield 5.5 g (44.7%), m.p. 86–87°, $[\alpha]_D^{25} = -61°$ (*c* = 0.26, chloroform) (Found: C, 61.98; H, 6.99. Calc. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15%).

3-O-*Benzyl*-L-*idose* (**7**). Compound **6** (33.7 g, 109 mmol) was stirred in 0.1 N H_2SO_4 at 100° for 3 hr. The cooled soln was neutralized with $BaCO_3$, filtered, and the filtrate evaporated to dryness. The residue was dried by repeated evaporation with alcohol/benzene and chromatographed on silica gel (600 g). Elution with $CHCl_3$/MeOH 9:1 gave **7** as a glass: yield 20.3 g (69.3%).

Reaction of 3-O-*benzyl*-L-*idose* (**7**) *with methanol/Dowex*-50(H^+). A soln of **7** (3.0 g; 11.1 mmol) in MeOH (60 ml) was treated with Dowex-50(H^+) (1.5 g) and the mixture was refluxed for 20 hr under stirring. The ion-exchange resin was filtered off and washed with MeOH. The filtrate was evaporated to dryness and the mixture was fractionated on a silica gel column (100 g). Elution with EtOAc gave 1,6-*anhydro*-3-O-*benzyl*-β-L-*idopyranose* (**9**): yield 1.58 g (56.5%), m.p. 155–156° (EtOAc/petroleum ether), $[\alpha]_D^{25} = +67.3°$ (*c* = 0.21, EtOAc) (Found: C, 61.76; H, 6.30. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39%). Acetylation of **9** with Ac_2O in pyridine gave the corresponding 2,4-di-O-acetate, m.p. 76–77° (isopropyl ether/petroleum ether),

$[\alpha]_D^{25} = +57.1°$ ($c = 0.72$, chloroform) (Found: C, 60.91; H, 5.95. Calc. for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99%). Elution with EtOAc/MeOH 9:1 gave *methyl* 3-O-*benzyl*-L-*idopyranoside* (**8**) as a syrup: yield 0.17 g (5.3%) (Found: C, 59.44; H, 7.22; CH_3O, 10.65. Calc. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09; CH_3O, 10.92%).

Methyl 3 - O - *benzyl* - 4,6 - O - *benzylidene* - L - *idofuranoside* (**10**). A mixture of **8** (2.0 g; 7.05 mmol) benzaldehyde (10 ml) and anhyd $ZnCl_2$ (1.5 g) was shaken at RT for 16 hr. The mixture was treated with 20 ml water and extracted with 4 × 30 ml dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4 and evaporated to dryness. Crystallization and recrystallization from MeOH/petroleum ether gave pure product: yield 0.6 g (23%), m.p. 154–155°, $[\alpha]_D^{25} = -81.6°$ (C = 0.44, chloroform) (Found: C, 67.61; H, 6.52. Calc. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50).

3 - O - *Benzyl* - 1,2 - O - *isopropylidene* - 6 - O - (p - *nitrobenzoyl*) - β - L - *idofuranose* (**11**). A soln of **6** (168 g; 0.54 mol) pyridine (3.5 l) was treated with 121.6 g (0.65 mol) of *p*-nitrobenzoyl chloride in 2.5 l of benzene under ice-cooling and stirring. After 15 hr standing at RT, the mixture was concentrated to a small volume (1 l), and treated with 2.5 l dichloromethane. The soln was washed with cold 3N HCl, 10% $NaHCO_3$aq and water, then dried over Na_2SO_4 and evaporated to an oil (290 g). The components of the mixture were separated on a silica gel column (2.3 kg) by development with benzene/ether 9:1. The minor component was shown to be the ($c = 0.95$, chloroform) (Found: C, 59.31; H, 4.71; N, 4.54. Calc. for $C_{30}H_{28}N_2O_{12}$: C, 59.21; H, 4.64; N, 4.60%). Recrystallization of the major component from EtOAc/petroleum ether gave **11**: yield 138.6 g (56%), m.p. 93–94°, $[\alpha]_D^{25} = -52.5°$ ($c = 0.68$, chloroform) (Found: C, 59.85; H, 5.59; N, 2.87. Calc. for $C_{21}H_{25}NO_9$: C, 60.12; H, 5.48; N, 3.05%).

3 - O - *Benzyl* - 6 - O - (p - *nitrobenzoyl*) - L - *idopyranose* (**13**). An amount of **11** (168 g; 365 mmol) was suspended in 60% aqueous acetic acid (3.5 l) and the mixture was refluxed for 4 hr under stirring, whereupon soln occurred. The soln was concentrated nearly to dryness, and the acid and water were removed by repeated evaporation with benzene/EtOH, to give an amorphous solid; yield 121 g (79%). The crude product (1 g) was purified by column chromatography on silica gel (50 g). Elution was effected with CH_2Cl_2/EtOH 19:1 to give a syrup: yield 0.8 g (Found: C, 57.33; H, 5.13; N, 3.30. Calc. for $C_{20}H_{21}NO_9$: C, 57.28; H, 5.05; N, 3.34%).

Benzyl 3 - O - *benzyl* - 6 - O - (p - *nitrobenzoyl*) - L - *idopyranoside* (**14**). Crude **13** (120 g, 286 mmol) was dissolved in 3 l benzyl alcohol containing 1.5% HCl, and the soln was heated at 60° for 3.5 hr. The clear soln was allowed to stand at RT for 16 hr, neutralized with $CaCO_3$, filtered and evaporarated (75°, 0.01 Torr) to a syrup. The crude product was purified by column chromatography on silica gel (3 kg). Elution with benzene/EtOAc 3:1 gave a syrup: yield 120 g (58.8%), $[\alpha]_D^{25} = -23.2°$ ($c = 0.84$, chloroform) (Found: C, 63.81; H, 5.37; N, 2.69. Calc. for $C_{27}H_{27}NO_9$: C, 63.65; H, 5.34; N, 2.75%).

Benzyl 3 - O - *benzyl* - 4,6 - O - *benzylidene* - α (**16**) *and* β - L - *idopyranoside* (**17**). Compound **14** (165.8 g, 325 mmol) was dissolved in MeOH (4 l) containing Na (1.5 g), and the soln was allowed to stand for 20 min at RT. The soln was neutralized with CO_2, concentrated to a small volume (400 ml), filtered and evaporated to a syrup. Methyl *p*-nitrobenzoate was removed by extraction with 10 × 600 ml petroleum ether. The crude syrup (**15**, 107.5 g) was treated with benzaldehyde (600 ml) and $ZnCl_2$ (100 g), and the mixture was shaken at RT for 40 hr. The mixture was treated with water (100 ml) and extracted with ether/hexane 1:1 (1 l). The extract was washed with 3 × 200 ml water, dried over $NaSO_4$ and evaporated to dryness (123.8 g, 85%). The anomeric mixture (10 g) was fractionated on a column (200 g) of Florisil. Development with benzene gave a crystalline product, which was recrystallized from isopropyl ether (**16**): yield 2.8 g (28% from **14**), m.p. 109°, $[\alpha]_D^{25} = -91.2°$ ($c = 0.16$, chloroform) (Found: C, 72.03; H, 6.19. Calc. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29%). Development with benzene/ethyl acetate 9:1 gave a crystalline product, which was recrystallized from EtOAc/petroleum ether (**17**): yield 3.6 g (36% from **14**), m.p. 151°, $[\alpha]_D^{25} = +72.2°$ ($C = 0.70$, chloroform) (Found: C, 72.11; H, 6.18%).

Benzyl 2,3 - *di* - O - *benzyl* - 4,6 - O - *benzylidene* - α - L - *idopyranoside* (**18**). A mixture of **16** (15 g; 33.5 mmol) benzyl chloride (45 ml) and powdered KOH(15 g) was heated at 120° for 3.5 hr under stirring. The mixture was cooled and treated with 100 ml ice-water. The crystalline product was filtered off, successively washed with water and petroleum ether, and dried: yield 16.4 g (91.1%). Recrystallization from isopropyl ether afforded pure product, m.p. 145–146°, $[\alpha]_D^{25} = -80.2°$ ($c = 2.0$, chloroform) (Found: C, 75.81; H, 6.31. Calc. for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36%).

Benzyl 2,3 - *di* - O - *benzyl* - 4,6 - O - *benzylidene* - β - L - *idopyranoside* (**21**). The title compound was prepared in 91% yield from **17** by the method described for **18**. Syrup, $[\alpha]_D^{25} = +47.2°$ ($c = 0.39$ chloroform) (Found: C, 76.10; H, 6.36%).

Benzyl 2,3 - *di* - O - *benzyl* - α - L - *isopyranoside* (**19**). An amount of **18** (16.4 g; 30.5 mmol) was suspended in 60% aqueous AcOH (600 ml) and the mixture was heated for 3 hr at 100° under stirring. The soln was concentrated nearly to dryness, and the acid was removed by repeated evaporation with alcohol/benzene. The crystalline residue was recrystallized from isopropyl ether: yield 11.2 g (81.8%), m.p. 71–72°, $[\alpha]_D^{25} = -58.7°$ ($c = 0.74$, chloroform) (Found: C, 72.02; H, 6.90. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71%).

Benzyl 2,3 - *di* - O - *benzyl* - β - L - *idopyranoside* (**22**). Syrup, yield = 86%, $[\alpha]_D^{25} = +91.8°$ ($c = 0.58$, chloroform) (Found: C, 71,74; H, 6.71%).

Methyl (*benzyl* 2,3 - *di* - O - *benzyl* - α - L - *idopyranosid*)*uronate* (**20**). Compound **19** (3,3 g; 8.25 mmol) was dissolved in 100 ml water. The soln was treated with Pt (1 g, obtained by catalytic reduction of PtO_2), and O_2 was bubbled through the mixture under stirring at 50°, while the pH was maintained at 7.5–8.1 by the addition of 10% $NaHCO_3$aq. After 15 hr the reaction was complete. The catalyst was removed and the soln was adjusted to pH 2 under cooling by the dropwise addition of H_2SO_4. The mixture was extracted with 3 × 100 ml ether, and the combined extracts were dried over Na_2SO_4 and evaporated to a syrup. The crude acid was dissolved in 50 ml dry MeOH and the soln was treated with an excess of a soln of diazomethane in ether. After 10 min at RT the soln was evaporated to dryness, and the residue was chromatographed on a silica gel column (50 g), by development with benzene/ether 9:1. Crystallization and recrystallization from isopropyl ether/petroleum ether gave pure product: yield 2.1 g (42.8%), m.p. 65–66°, $[\alpha]_D^{25} = -29.5°$ ($c = 0.72$, chloroform). IR.: 3500 (–OH), 1748 cm^{-1}(C=O, ester). NMR (C_6D_6): 5.15 (br. s, $J_{1,2} \sim J_{1,3} \sim 0.5$–1.5, H–C(1)); 4.95 (d, $J_{4,5} \sim 1.6$, H–C(5)); ~4.25 (H–C(4), masked by other signals; 3.81 (ddd, $J_{1,2} \sim 0.5$–1.5, $J_{2,3} \sim J_{3,4} \sim 3.3$, H–C(3)); 3.65 (d, $J_{4,OH} = 11.6$, OH); 3.57 (ddd, $J_{1,2} \sim 0.5$–1.5, $J_{2,3} \sim 3.3$, $J_{2,4} \sim 0$–1.0, H–C(2)) (Found: C, 70.42; H, 6.50; OCH_3, 6.54. Calc. for $C_{28}H_{30}O_7$: C, 70.28; H, 6.32; OCH_3, 6.49%).

Methyl (*benzyl* 2,3 - *di* - O - *benzyl* - β - L - *idopyranosid*)*uronate* (**23**). The product was obtained as a glass: yield 28.5%, $[\alpha]_D^{25} = +113.6°$ ($c = 0.12$, chloroform). IR.: 3510 (–OH), 1750 cm^{-1} (C=O, ester). NMR. (C_6D_6): 4.87 (d, $J_{1,2} \sim 1.2$, H–C(1)) ~4.55 (H–C(5), masked by other signals); ~4.2(H–C(4), masked by other signals); 3.83 (dd, $J_{2,3} \sim 3.8$, $J_{3,4} \sim 1.2$, H–C(3)): 3.58 (dd, H–C(2)) (Found: C, 70.23; H, 6.41; CH_3O, 6.48%).

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