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SYNTHESES OF HEPARIN SACCHARIDES

Stereospecific synthesis of derivatives of 2-amino-2-deoxy-4-O-(α-D-glucopyranuronosyl)-D-glucose

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The synthesis of ethyl 2-amino-2-deoxy-4-O-(β-D-glucopyranuronosyl)-D-glucopyranoside has recently been reported$^{1)}$. We now wish to report a part of our synthetic work on heparin saccharides. In the present paper, the synthesis of simple derivatives of 2-amino-2-deoxy-4-O-(α-D-glucopyranuronosyl)-D-glucose$^{2)}$ by two different routes is described.

A) By reaction of 3,4,6-tri-O-acetyl-1,2-anhydro-α-D-glucopyranose (1) with the amino sugar 2

Reaction$^{3)}$ of benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-6-O-p-tolylsulfonyl-α-D-glucopyranoside (2-a)* [mp 122-123°, $[\alpha]_D^{25}$ = +83.1° (c 0.30, $CHCl_3$)] with 1 in boiling toluene for 3 days, gave disaccharide 3 (yield: 23 %), $[\alpha]_D^{25}$ = +114.4° (c 0.94, $CHCl_3$). Deacetylation of 3, followed by treatment with an excess of sodium iodide in boiling 2-pentanone for 8 h, gave in good yield the 6-iodide 4, mp 133-134°, $[\alpha]_D^{25}$= +122° (c 1.0, $CHCl_3$). Compound 4 in aqueous p-dioxane was oxidized with oxygen in the presence of platinum catalyst$^{4)}$ (3 days at 65°, pH 9.5), and the crude uronic acid was converted into its methyl ester 5, by treatment with ethereal diazomethane (yield: 33 %), mp 117-118°, $[\alpha]_D^{25}$ = +100° (c 0.40, $CHCl_3$). Treatment of 5 with an excess of silver acetate

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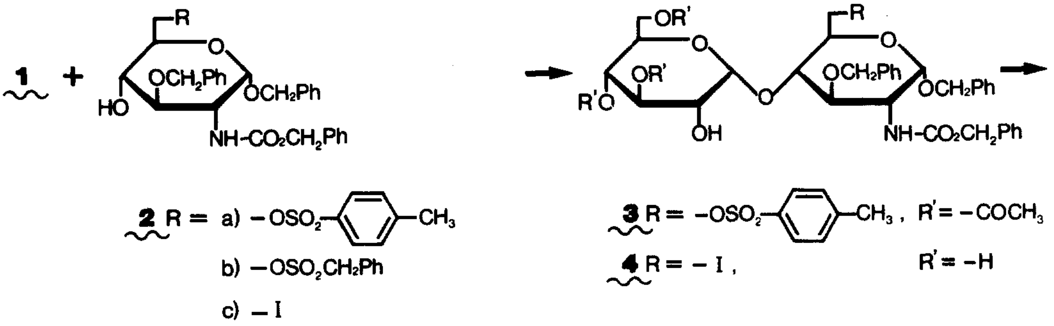
*All new compounds gave satisfactory analytical values.



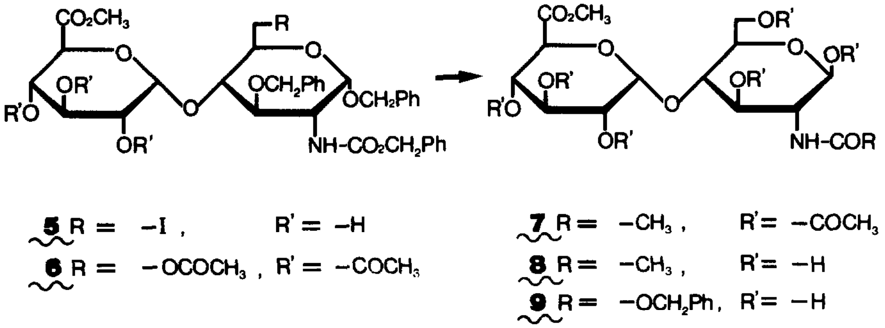
2 R = a) $-OSO_2-$ $-CH_3$

b) $-OSO_2CH_2Ph$

c) $-I$

3 R = $-OSO_2-$ $-CH_3$, R' = $-COCH_3$

4 R = $-I$, R' = $-H$



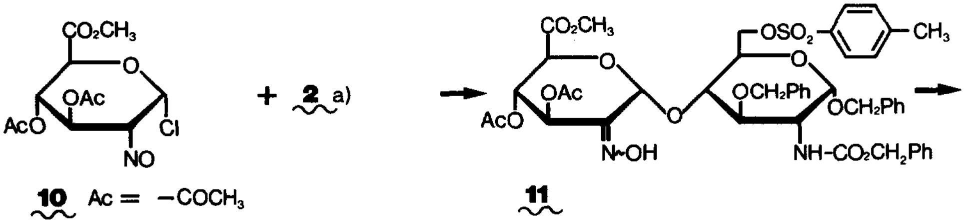
5 R = $-I$, R' = $-H$

6 R = $-OCOCH_3$, R' = $-COCH_3$

7 R = $-CH_3$, R' = $-COCH_3$

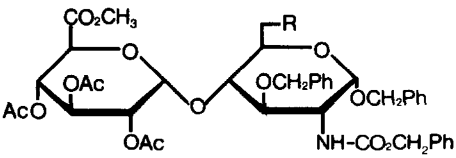
8 R = $-CH_3$, R' = $-H$

9 R = $-OCH_2Ph$, R' = $-H$



10 Ac = $-COCH_3$

11



12 R = $-OSO_2-$ $-CH_3$

13 R = $-I$

in acetic anhydride and pyridine for 12 h at 70° gave in good yield the acetylated disaccharide 6, mp 101-102°, $[\alpha]_D^{25}$ = +125.1° (c 0.94, $CHCl_3$); nmr ($CDCl_3$): δ 5.61 (1 H, d, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.43 (1 H, t, H-3' or H-4'), 5.15 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ = $J_{4',5'}$ = 8.0 Hz, H-3' or H-4') ppm.

Compound 6 was hydrogenolyzed, and the product was acetylated to give a good yield of 2-acetamido-1,3,6-tri-O-acetyl-2-deoxy-4-O-(methyl 2,3,4—tri-O-acetyl-α-D-glucopyranosyluronate)-β-D-glucopyranose (7), mp 184-185°, $[\alpha]_D^{25}$ = +74.8° (c 0.90, $CHCl_3$); nmr ($CDCl_3$): δ 5.65 (1 H, d, $J_{1,2}$ = 8.5 Hz, H-1), 5.54 (1 H, d, $J_{1',2'}$ = 3.5 Hz, H-1'), 5.41 (1 H, t, $J_{3',4'}$ = 9.5 Hz, H-3'), 4.87 (1 H, q, $J_{2',3'}$ = 10.0 Hz, H-2') ppm. De-O-acetylation of 7 with sodium methoxide in methanol afforded a quantitative yield of 2-acetamido-2-deoxy-4-O-(methyl α-D-glucopyranosyluronate)-D-glucose (8), mp 149-150° (dec), $[\alpha]_D^{25}$ = $+82 \longrightarrow +96°$ (c 1.65, MeOH).

In another experiment, disaccharide 6 was hydrogenolyzed, and the product was N-acylated with benzyl chloroformate, followed by de-O-acetylation, to give a good yield of 2-[1-(benzyloxy)formamido]-2-deoxy-4-O-(methyl α-D-glucopyranosyluronate)-D-glucose (9), mp 189-190°, $[\alpha]_D^{25}$ = $+97.6 \longrightarrow +86.3°$ (c 0.89, H_2O).

B) By condensation of methyl 3,4-di-O-acetyl-1-chloro-1,2-dideoxy-2-nitroso-α-D-glucopyranuronate (10) with the amino sugar 2-a)

Condensation of 2-a) with 10 [mp 111-112°, $[\alpha]_D^{25}$ = +145.9° (c 0.95, $CHCl_3$)] in N,N-dimethylformamide at room temperature for 7 days, gave benzyl 3-O-benzyl-2-[1-(benzyloxy)formamido]-2-deoxy-4-O-(methyl 3,4-di-O-acetyl-2-hydroxyimino-α-D-*arabino*- hexopyranosyluronate)-6-O-p-tolylsulfonyl-α-D-glucopyranoside (11), (yield: 58 %), mp 158-159°, $[\alpha]_D^{25}$ = +115.1° (c 0.97, $CHCl_3$); nmr ($CDCl_3$): δ 8.49 (1 H, s, = NO$\underline{H}$), 6.37 (1 H, s, H-1'), 5.77 (1 H, d, $J_{3',4'}$ = 9.5 Hz, H-3'), 5.29 (1 H, t, $J_{4',5'}$ = 9.5 Hz, H-4') ppm. Hydrolysis of the hydroxyimino sugar 11 with levulinic acid and hydrochloric acid, followed by reduction with sodium borohydride and acetylation,[5] gave a good yield of disaccharide 12,

$[\alpha]_D^{25}$ = +114.7° (c 0.63, $CHCl_3$); nmr ($CDCl_3$): δ 5.40 (1 H, t, $J_{3',4'} = J_{4',5'}$ = 8.0 Hz, H-3' or H-4'), 5.38 (1 H, d, $J_{1',2'}$ = 4.2 Hz, H-1'), 5.16 (1 H, t, H-3' or H-4'), 4.88 (1 H, q, $J_{2',3'}$ = 8.0 Hz, H-2') ppm. Disaccharide 12 was treated with an excess of sodium iodide in boiling 2-pentanone for 7 h, to give the 6-iodide 13, mp 147-148°, $[\alpha]_D^{25}$ = +118.5° (c 0.95, $CHCl_3$). Treatment of compound 13 with silver acetate as described for 5, gave the acetylated disaccharide 6.

The disaccharides obtained by the two routes were shown to be identical by comparison of their mp, optical rotation, ir- and nmr-spectra, and behaviour in thin-layer chromatography.

Polycondensation of disaccharide 8 in N,N-dimethylformamide in the presence of polyphosphate esters as catalyst$^{6)}$, followed by sulfation, gave products which were shown to possess anticoagulant and antilipaemic activity.

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