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First Syntheses of Disaccharides by Use of Cycloaddition in a Key Step

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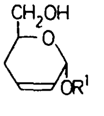
Summary *O*-α-D-altrosyl-(1 → 3)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose, and its *O*-α-L-altrosyl and *O*-β-L-altrosyl analogues have been prepared in 35, 42, and *ca.* 38% yields from the products of the cycloaddition of butyl glyoxylate to 3-*O*-(buta-1,3-dienyl)-1,2;5,6-di-*O*-isopropylidene-β-glucofuranose.

RECENTLY we suggested a new reaction sequence for disaccharide synthesis, which could be divided into three main steps: (i) synthesis of a dienyl ether of a monosaccharide, (ii) cycloaddition, and (iii) functionalization.[1] The first two steps of the synthesis were carried out when *O*-(2,3,4-trideoxy-α-D-glycero-hex-2-enopyranosyl)-(1 → 3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, (**1**) and its α-L-glycero (**2**) and β-L-glycero (**3**) analogues were prepared in yields of 12·5, 25 and 27% respectively from 'diacetone-glucose.'[1] We now report the conversion of (**1**) into the protected derivative (**7**) of *O*-α-D-altropyranosyl-(1 → 3)-D-glucose, in 34% overall yield, thus achieving a practical synthesis of a completely functionalized disaccharide.

Epoxidation of (**1**) with benzonitrile and hydrogen peroxide[2] gave two compounds readily separated by chromatography (Et_2O);† the less polar epoxide (**4**) was an amorphous powder (52%), b.p. 160 °C at 0·01 mm Hg, $[\alpha]_D^{20}$ + 18·4°, and the other (**5**) was crystalline (8%) m.p. 144 °C (from MeOH–C_6H_{12}), $[\alpha]_D^{20}$ + 18·5°. Reaction of the epoxide (**4**) with selenophenol, and consecutive treatment with hydrogen peroxide,[3] afforded the allylic alcohol (**6**), (76%), m.p. 153 °C (from MeOH–Et_2O), $[\alpha]_D^{20}$ + 21·6°. *Cis*-hydroxylation with one molar equivalent of osmium tetroxide,[4] followed by chromatography (15% MeOH in $CHCl_3$) then gave the tetrol (**7**) as an amorphous powder (95%), $[\alpha]_D^{20}$ + 40·2° ($CHCl_3$). The tetra-4-nitrobenzoate (**8**) was obtained crystalline (87%) m.p. 126—128 °C (from $MeCO_2Et$–EtOH), $[\alpha]_D^{20}$ − 6°.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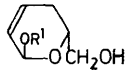
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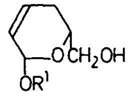
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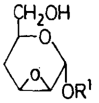
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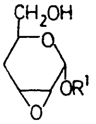
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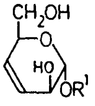
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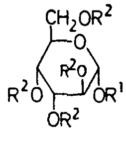
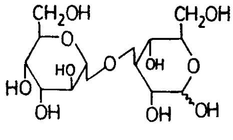
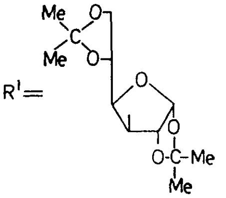

(7) R^2 =H

(8) R^2 =p-$NO_2C_6H_4CO$


(9)



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† Unless otherwise stated, chromatography was performed on silica gel columns, optical rotations were measured in dichloromethane (*c ca.* 1%) and new compounds gave satisfactory analyses.

Hydrolysis of the ketal functions in (**7**) with a mixture of a 1% solution of water in trifluoroacetic acid (0·6 ml), and $CHCl_3$ (4 ml), for 2 h at room temperature, gave the free disaccharide (**9**) which was purified by chromatography ($MeCO_2Et$–Pr^iOH–H_2O, 3 : 3 : 2). The white powder obtained by freeze-drying of an aqueous solution still contained about 1% inorganic contaminant. However, hydrolysis with 0·6 M sulphuric acid for 90 min at 100 °C gave a solution containing glucose and altrose as the only component sugars, shown by paper ($MeCO_2Et$–C_5H_5N–H_2O, 2 : 1 : 2) and thin-layer (silica gel; $MeCO_2Et$–Pr^iOH–H_2O, 3 : 3 : 2) chromatography. The solution was brought to pH 5 with a 1 M citrate buffer and D-glucose was removed by fermentation with bakers yeast. From the remaining solution, a conventional derivatization procedure allowed the isolation of D-altrose dibenzyl dithioacetal, m.p. 120—121 °C, alone or mixed with an authentic sample, $[\alpha]_D^{20} + 38°$ (*c* 0·74, pyridine), lit.[5] m.p. 119—120°, $[\alpha]_D^{20} + 39·8°$ (*c* 1·75, pyridine).

In the same manner, compound (**2**) was converted to *O*-α-L-altropyranosyl-(1 → 3)-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose, $[\alpha]_D^{20} - 108°$ ($CHCl_3$) (42%), and hydrolysed to L-altrose (dibenzyl dithioacetal, m.p. 120 °C, $[\alpha]_D^{20} - 38·7°$). *O*-β-L-altropyranosyl-(1 → 3)-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose, $[\alpha]_D^{20} + 1·7°$ ($CHCl_3$), was also prepared from (**3**) in 38% yield and hydrolysed to L-altrose (dibenzyl dithioacetal, m.p. 120°, $[\alpha]_D^{20} - 37·0°$).

These are the first instances, as far as we know, of disaccharide syntheses not involving some kind of activation of the anomeric carbon of one component sugar. One useful feature of this method may be the possibility of stepwise introduction of functions, which may dispense with the use of protecting groups for higher oligosaccharide synthesis.

In the course of this work, we have also achieved total synthesis of D- and L-altrose.

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