Tetrahedron Letters, Vol.28, No.14, pp 1569-1572, 1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE SYNTHESIS OF THE HEPTOSE REGION OF THE GRAM-NEGATIVE BACTERIAL CORE OLIGOSACCHARIDES

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Summary: Disaccharides linked α (1-3) and α (1-7) and a trisaccharide linked α (1-7) and α (1-3) have been synthesized from suitably blocked L-glycero-D-mannoheptose derivatives using the trichloroacetimidate approach.

The synthesis of oligosaccharides constituing parts of bacterial lipopolysaccharides attracts the attention of many laboratories.[1-4]

Structural studies have revealed that the heptose region of the core oligosaccharides isolated from many Gram-negative bacteria is composed of two [linked α(1-3), 1] or, more often, of three [linked α(1-7) and α(1-3), 2] L-glycero-D-mannoheptose (LD-Hepp) units.[5]

L α D-Hepp-(1-3)-L αβ D-Hepp

1

L α D-Hepp-(1-7)-L αD-Hepp-(1-3)-L αβ D-Hepp

2

L α D-Hepp-(1-7)-L αβ D-Hepp

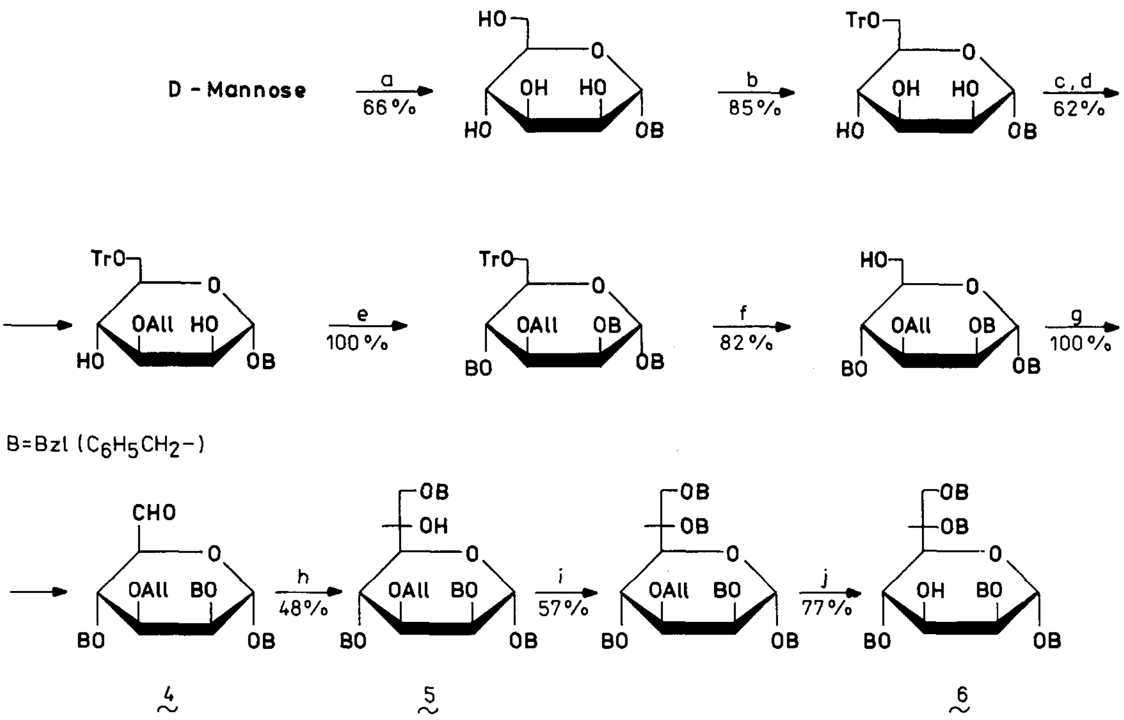
3

We wish to present the first syntheses of 1 and 2, and of α(1-7) linked L-glycero-D-mannoheptobiose (3).

The suitably blocked L-glycero-D-mannoheptoses were obtained by one-carbon atom homologation at C-6 of D-mannose.[6]

The synthesis of benzyl 2,4,6,7-tetra-O-benzyl-L-glycero- α-D-mannoheptopyranoside (6) representing the future reducing part of 1 is shown in Scheme 1.

Scheme 1[7]



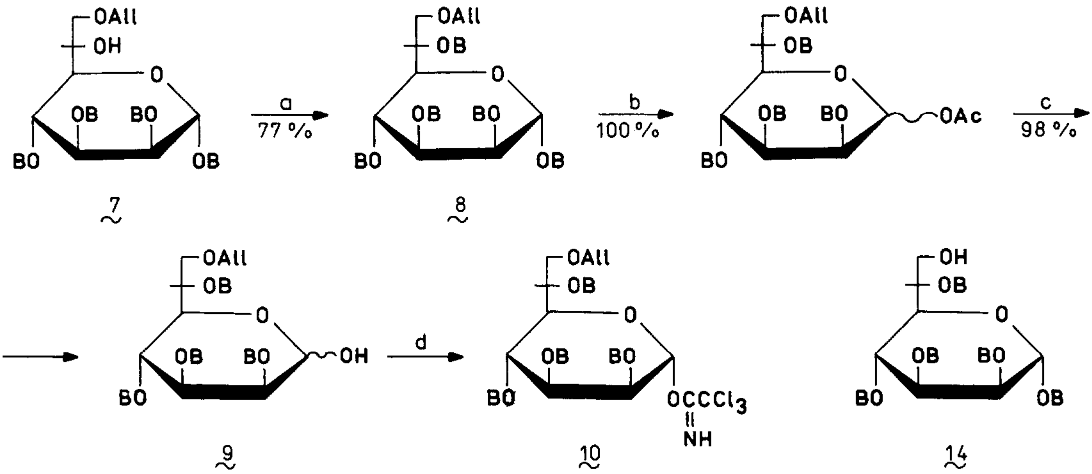
a. BzlOH, HCl (CH$_3$COCl). b. TrCl, Py. c. Bu$_2$SnO, MeOH. d. AllBr, DMF.
e. NaH, BzlBr, DMF. f. HBF$_4$, CH$_3$CN-Et$_2$O 3:1. g. (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$.
h. PhCH$_2$OCH$_2$MgCl, THF, -30°—r.t. i. NaH, BzlBr, DMF. j. Pd/C, TsOH, MeOH-H$_2$O.

The reaction of 4 with benzyloxymethyl magnesium chloride led to two C-6 stereoisomeric heptosides in 28:1 proportion. The prevailing stereoisomer 5 - readily isolated by column chromatography - had the desired L configuration at C-6.[8] It is worth of mentioning that the formation of 5 could be predicted on the basis of Cram's cyclic model of asymmetric 1,2-induction.

The synthesis of the non-reducing partner 9 for coupling with 6 is shown in Scheme 2.

Heptose 9 was converted according to Schmidt[9] into trichloroacetimidate 10 which was condensed with 6 in the presence of anh. p-toluenesulfonic acid to yield the α-linked heptobiose 11 as the single product in 50% yield. Deallylation of 11 (Pd/C, TsOH, MeOH--H$_2$O, 88%) gave 12. Exhaustive debenzylation (Pd/C, H$_2$, EtOH, 99%) of 12 furnished 1 as a mixture of α and β anomers in the reducing part.[10]

Scheme 2[7]

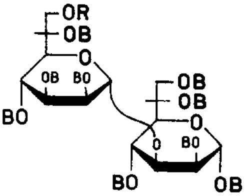


a. NaH, BzlBr, DMF. b. Ac_2O, H_2SO_4, AcOEt. c. NH_3, MeOH. d. NaH, CCl_3CN.

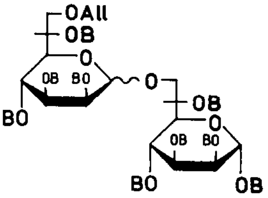
The trisaccharide was obtained by condensation of 10 with 12 in the presence of anh. p-toluenesulfonic acid. Single α-linked product 13 was obtained in 52% yield. Deallylation of 13 followed by debenzylation (as for 11) gave the free trisaccharide 2 in 44% yield.[11]

For the synthesis of 3 heptoside 8 was deallylated to furnish 14; its condensation with 10 gave a mixture of α and β linked disaccharides (15 and 16) in 3.5:1 proportion in 91% overall yield. These products were separated by column chromatography. Full deprotection of pure 15 and 16 gave free disaccharide 3 and its β-linked stereoisomer 17.[12]

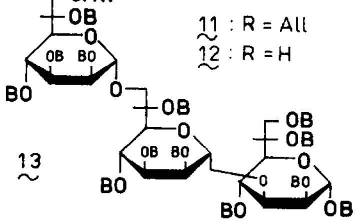
These syntheses demonstrate the utility of the new homologation of D-mannose to L-glycero-D-mannoheptose for the preparation of properly blocked units for further oligosaccharide synthesis. Also, the utility of the recently elaborated trichloroacetimidate method[13] for the construction of oligosaccharides is worth of stressing.



11 : R = All
12 : R = H



15 : α-linkage
16 : β-linkage



13

LβD-Hepp-(1-7)-LαβD-Hepp

17

Acknowledgment. This work was financed from the Grant No.MR-I.12.1.7.4. Authors are grateful to Drs. G. Lukacs and Y. A. Knirel for the help with ^{13}C-NMR spectra.

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6. K. Dziewiszek and A. Zamojski, Carbohydr. Res., 150, 163 (1986).

7. All compounds depicted in the Scheme had correct elemental analyses and spectral (IR and ^{1}H-NMR) data.

8. Full deprotection of 5 gave free heptose in 38% yield. Its reaction with ethanethiol in hydrochloric acid gave diethyldithioacetal, m.p. 199-200°, $[\alpha]_D$ +8.4° (c 1.8, pyridine). M. Teuber, R. D. Bevill, and M. J. Osborn, Biochemistry, 7, 3303 (1968) give for diethyldithioacetal of LD-Hepp: m.p. 202-203°, $[\alpha]_D$ +10.2° (c 1.2, pyridine).

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10. 1: $[\alpha]_D^{21}$ -9.6° (c 1.2, water). ^{13}C-NMR (100 MHz, D_2O): δ 103.4 (C-1'α), 102.0 (C-1'β), 95.3 (C-1α), 95.2 (C-1β), 81.3 (C-3β), 78.9 (C-3α), 76.5 (C-5β), 73.0 (C-5α), 72.5 (C-5'), 71.7 (C-3', C-2β), 71.2 (C-2', C-6β), 70.8 (C-2α), 70.1 (C-6α), 69.9 (C-6'), 67.3 (C-4'), 67.1 (C-4α), 66.8 (C-4β), 64.1 (C-7α, C-7'), 64.0 (C-7β).

11. 2: $[\alpha]_D^{16}$ +47.5° (c 2.8, water). ^{13}C-NMR (100 MHz, D_2O): δ 103.6 (C-1'α), 103.3 (C-1'β), 101.5 (C-1''α), 95.2 (C-1α), 94.9 (C-1β), 81.2 (C-3β), 78.9 (C-3α), 75.7 (C-5β), 73.3 (C-5'), 72.5 (C-5'', C-3''), 72.0 (C-5α), 71.7 (C-3', C-2β), 71.2 (C-2'', C-2', C-2α), 70.1 (C-6'', C-6α), 70.0 (C-6', C-6β), 68.5 (C-7'), 67.3 (C-4'', C-4'), 67.1 (C-4α), 67.0 (C-4β), 64.3 (C-7'', C-7α and β).

12. 3: $[\alpha]_D^{18}$ +38.0° (c 1.1, water). ^{13}C-NMR (75 MHz, D_2O): δ 101.6 (C-1'), 95.4 (C-1α), 95.2 (C-1β), 76.0 (C-5β), 74.5 (C-3β), 72.7 (C-5'), 72.5 (C-5α, C-2β), 72.4 (C-3'), 72.1 (C-2α), 71.8 (C-3α), 71.2 (C-2'), 70.2 (C-6'), 69.9 (C-6α), 69.6 (C-6β), 68.6 (C-7α), 68.4 (C-7β), 67.5 (C-4α, C-4'), 67.1 (C-4β), 64.3 (C-7').

    17: ^{13}C-NMR (75 MHz, D_2O): δ 101.5 (C-1'), 95.5 (C-1α), 95.2 (C-1β), 76.0 (C-5'), 75.8 (C-5β), 74.6 (C-3β), 74.5 (C-3'), 72.5 (C-2β), 72.2 (C-2α), 72.0 (C-2'), 71.8 (C-5α), 71.6 (C-6α and β), 70.3 (C-6'), 68.3 (C-4'), 67.8 (C-7β), 67.6 (C-4α), 67.4 (C-7α), 67.3 (C-4β), 64.2 (C-7').

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(Received in UK 20 January 1987)