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SYNTHESIS OF CYCLO-L-RHAMNOPENTAOSE

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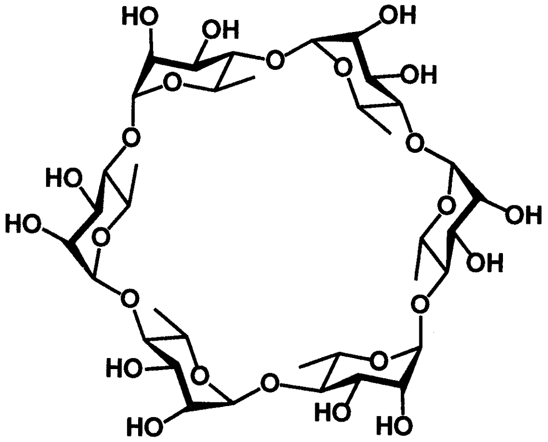
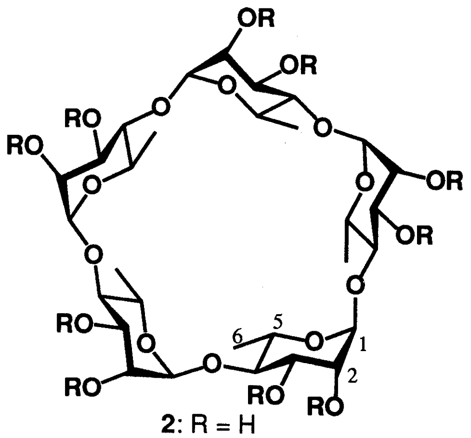
A novel L-series cyclooligosaccharide, cyclo-L-rhamnopentaose, has been synthesized by means of successive glycosylation by Schmidt's imidate method and DMTST induced cycloglycosylation.

KEYWORDS cyclo-L-rhamnopentaose; cyclooligosaccharide; imidate; glycosylation; DMTST

Recently we reported the synthesis of the first L-series cyclooligosaccharide, cyclo-L-rhamnohexaose (**1**),[2, 3] based on an α-selective thermal rhamnosylation, and named it α-cycloawaodorin. Although the thermal glycosylation developed in our group is a convenient procedure to give rhamnoside with extremely high α-selectivity,[4, 5] it requires very long reaction period when the reaction has to be carried out at relatively lower temperature around 70 to 80°C in the case for sensitive substrates. In the present study, we tried to couple rhamnose residue successively by using Schmidt's imidate method[6] and prepared L-rhamnose pentamer. It was cyclized by dimethyl(methylthio)sulfonium triflate (DMTST) in moderate yield. Therefore we would like to describe herein the synthesis and characterization of cyclo-L-rhamnopentaose (**2**). Recently syntheses of cyclo-D-mannopentaose[7] as well as cyclomaltopentaose[8] were recorded.

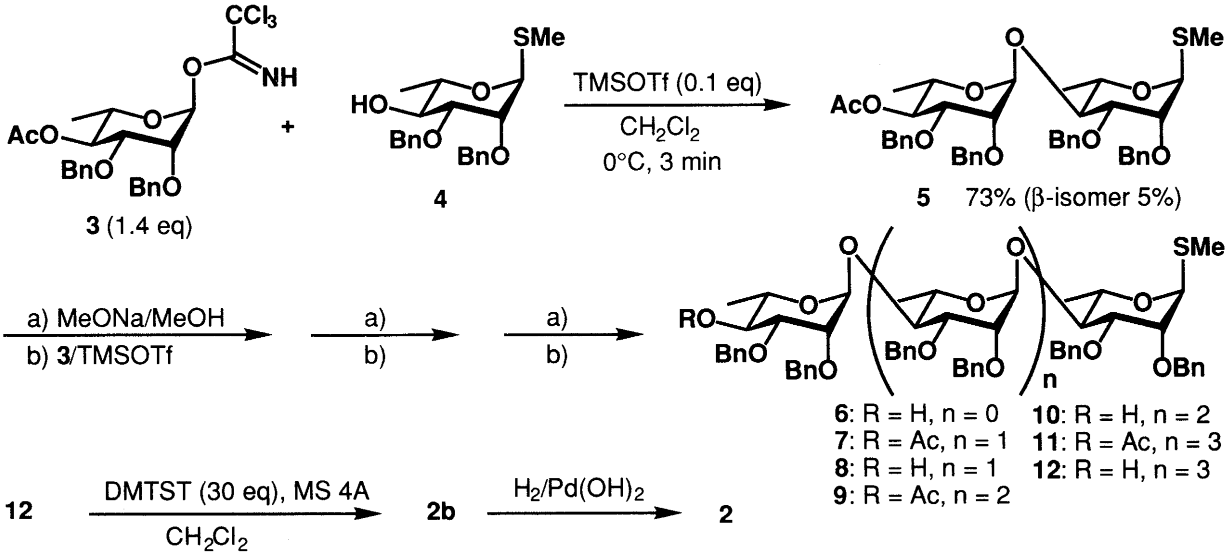


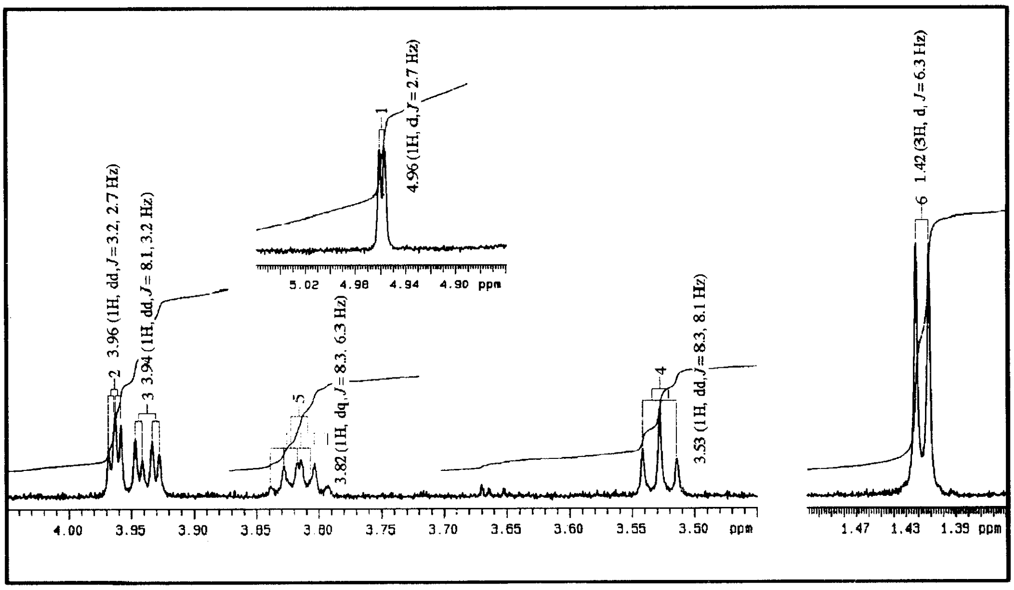
1



2: R = H
2b: R = Bn

A mixture of 2,3-di-*O*-benzyl-4-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetoimidate (**3**) and *S*-methyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside (**4**) was treated with 0.1 eq of TMSOTf in dichloromethane at 0°C for 3 min to give an α-dimer **5** in 73% yield along with 5% of β-isomer after column chromatography. Hydrolysis of the acetyl group of **5** by MeONa afforded an alcohol **6** quantitatively. Glycosylation of **6** with **3** under analogous conditions afforded a trimer **7** in 71% yield together with 6% of β-isomer. Hydrolysis and further rhamnosylation with **3** afforded a mixture of a tetramer **9** and its β-isomer. After hydrolysis of the acetyl group, α-tetramer **10** was obtained in 70% yield along with 8% of β-isomer. The imidate **3** was condensed again to give pentamers containing **11** in 79% yield. Since purification at this stage was very difficult, acetyl group was cleaved and purification was done by using HPLC to give pentamer alcohol **12** in 87% yield and 9% of β-isomer.[9] Diluted dichloromethane solutions of **12** (2×10^{-4} M) and DMTST (30 eq) were slowly mixed together at room temperature by using syringe drive over a period of 20 h and the mixture was stirred for an additional 24 h to give cyclic pentamer **2b**, $[\alpha]_D^{22}$ +5.6° (*c* 0.6, $CHCl_3$), in 20% yield after ODS column chromatography eluted with MeOH.[9] Upon $Pd(OH)_2$ catalyzed hydrogenolysis of **2b** in methanol/ethyl acetate/water (12:1:1) provided cyclo-L-rhamnopentaose (**2**), $[\alpha]_D^{22}$ -17.6° (*c* 0.4, MeOH), after final purification with ODS column chromatography eluted with MeOH-H_2O (1:3). ^1H and ^{13}C NMR of **2** appeared as an essentially rhamnose monomer pattern. Each signal appeared sharper than hexamer at room temperature, reflecting the conformational rigidity. Finally, the size of this molecule was confirmed by determining FAB mass spectrum. A peak observed at *m/z* 753 was attributed to $(M + Na)^+$ ion, and $(M + K)^+$ ion was observed at *m/z* 769 supporting the structure of rhamnose pentamer. No trace signal was detected around *m/z* 1460 that corresponds to rhamnose decamer.





^{1}H NMR of Cyclo-L-rhamnopentaose (**2**) in D_2O at 600 MHz (Room Temperature)

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REFERENCES AND NOTES

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9) Although the separation of α and β isomers of dimers or trimers were easily carried out by column chromatography, tetramers were hard to separate. Pentamers were not separable by column chromatography.

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