SYNTHESIS OF β- AND ISO-β-CYCLOAWAODORIN

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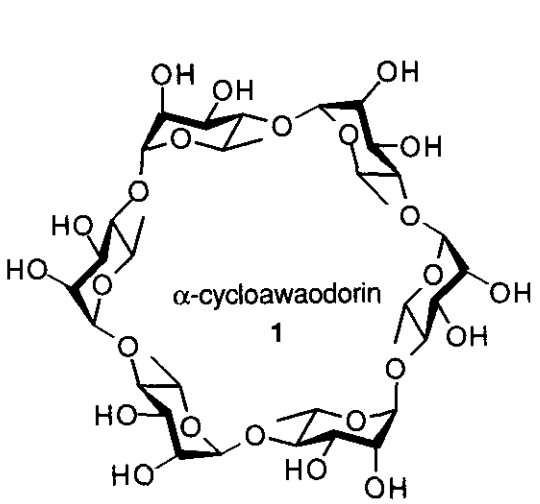
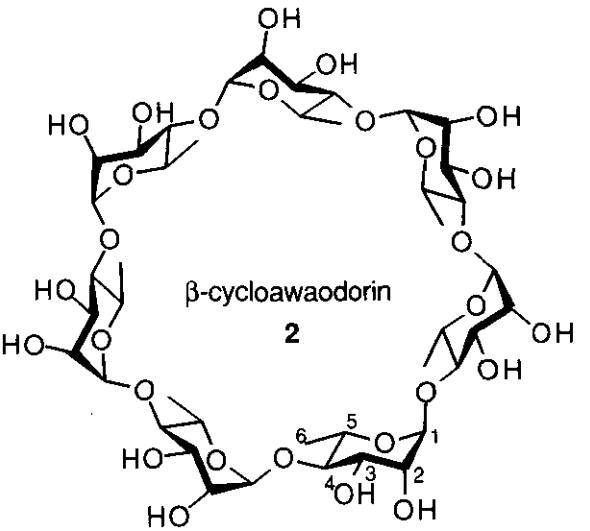
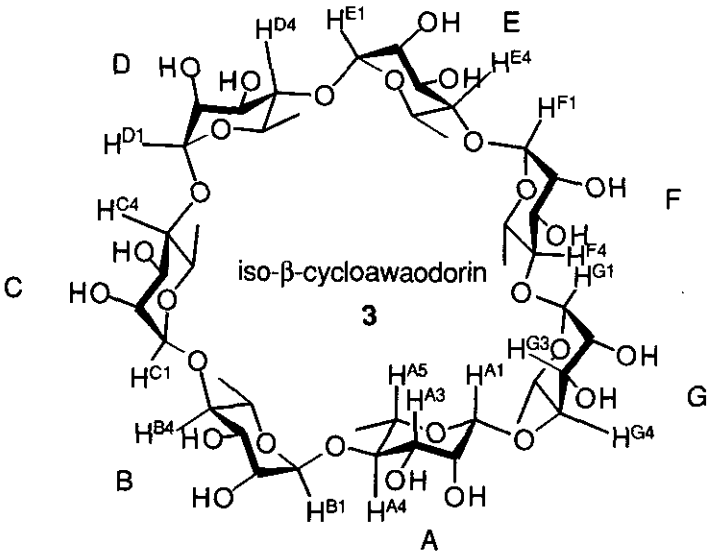
Abstract-Cyclic heptamers of L-rhamnose, β-cycloawaodorin and a stereoisomer, have been prepared by means of α-selective thermal glycosylation and DMTST induced cycloglycosylation. These novel oligosaccharides have characterized by nmr experiments as well as high resolution FAB mass spectra.

In 1991, we have reported the first cyclooligosaccharide of L-series, cyclo-L-rhamnohexaose (**1**), and named it α-cycloawaodorin.[1] The synthesis has been achieved using α-selective thermal glycosylation to extend the L-rhamnose chain by the way of [3 + 3] route. An alternative [*n* + 1] route has been developed to give rhamnose hexamer efficiently.[2] Novel cyclic L-rhamnose pentamer has also been prepared recently.[3] Herein we wish to describe the synthesis and characterization of cyclic L-rhamnose heptamer, β-cycloawaodorin (**2**), and its stereoisomer (**3**) by means of α-selective thermal glycosylation[4] and DMTST induced cycloglycosylation. Synthesis of cyclic heptaose, cyclo-D-mannohexaose, has been reported by Ogawa and co-workers.[5]

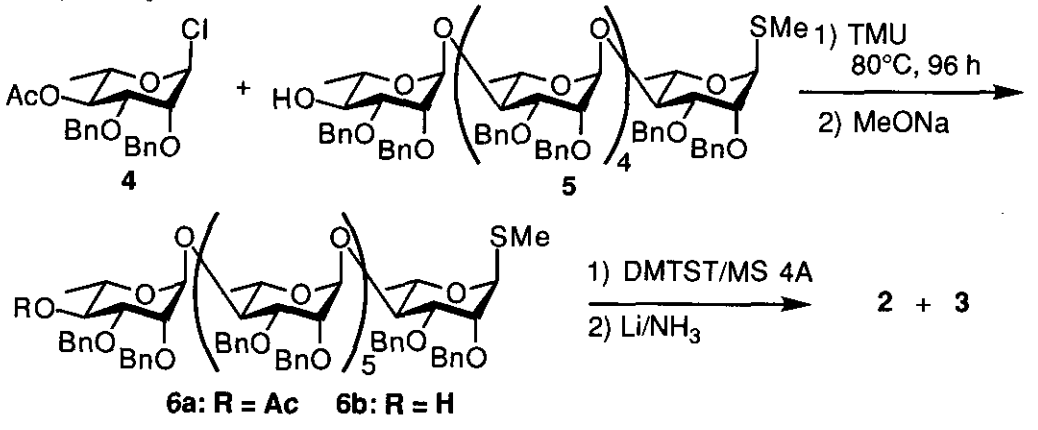




Dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.



A dried neat mixture of L-rhamnosyl chloride (**4**) (3 equiv), L-rhamnose hexamer (**5**),[2] and tetramethylurea (TMU, 3 equiv) was heated at 80°C for 96 h.[4] An α-coupling product (**6a**) was obtained in 85% yield with complete stereoselectivity. The acetyl group was hydrolyzed by the treatment with NaOMe to give heptamer(**6b**) quantitatively. The 600 MHz ^{1}H nmr of **6b** showed seven sets of anomeric protons as well as seven sets of *sec*-methyl groups. The dichloromethane solution of the heptamer (**6b**)(1.8 x 10^{-4} M) was slowly added by using syringe drive to a solution of excess dimethylthiomethylsulfonium triflate (DMTST, 37 equiv) in dichloromethane in the presence of 4A ms powder during a period of 24 h at room temperature, and the mixture was stirred for an additional 30 h. Column chromatography of the crude product afforded cyclization products as a mixture of stereoisomers. It was subjected to Li/NH_3 reduction to cleave fourteen benzyl groups simultaneously to afford deprotection products quantitatively. Catalytic hydrogenation required very long reaction period for this cleavage due to the low solubility of the substrate. Therefore isomeric two compounds were easily separated at this stage by ODS column chromatography. A product (**2**)(Rf value 0.2 by MeOH-H_2O 2:1), $[\alpha]_D^{22}$ -44.1° (*c* 0.6, MeOH), showed molecular formula $C_{42}H_{70}O_{28}$ based on the high resolution FAB mass spectrum,[6] that corresponds to rhamnose cyclic heptamer.



^{1}H Nmr in D_2O showed that this compound is simple monomeric pattern (Figure I). ^{13}C Nmr also supports that this product is the symmetrical cyclic rhamnose heptamer, namely β-cycloawaodorin.[7] Another product (**3**)(Rf value 0.8), $[\alpha]_D^{22}$ -27.5°; (*c* 0.5, MeOH), also afforded molecular formula $C_{42}H_{70}O_{28}$ based on the high resolution FAB mass spectrum.[8] However the nmr spectrum of this compound was very complicated (Figure II).[9] According to COSY and TOCSY experiments, most of proton signals were assigned. Particularly the consecutive three rhamnose units G, A, and B were assigned completely. ROE relationships of H^{A4} with H^{B1}, H^{B4} with H^{C1}, H^{C4} with H^{D1}, H^{D4} with H^{E1}, H^{E4} with H^{F1}, and H^{F4} with H^{G1} were observed on ROESY. Although no relationship was detected between H^{G4} and H^{A1}, a cross peak between H^{G3} and H^{A1} suggested the cyclic structure of **3**. Most of carbon signals were also assigned by HMQC experiments, and the cyclic structure of **3** was also confirmed by detecting cross peaks between H^{A4} and C^{B1}, H^{B4} and C^{C1}, H^{C4} and C^{D1}, H^{D4} and H^{E1}, H^{E4} and C^{F1}, H^{F4} and C^{G1}, and H^{G4} and C^{A1} on HMQC. ROE cross peaks of H^{A1} with H^{A3} and H^{A5} indicate β-glycosidic linkage between rhamnoses G and A. Therefore **3** is also cyclic L-rhamnose heptamer and stereoisomeric with **2** at one of the anomeric centers. Thus we named this compound as iso-β-cycloawaodorin.

Figure I. 600 MHz ^{1}H Nmr of β-Cycloawaodorin (**2**) in D_2O

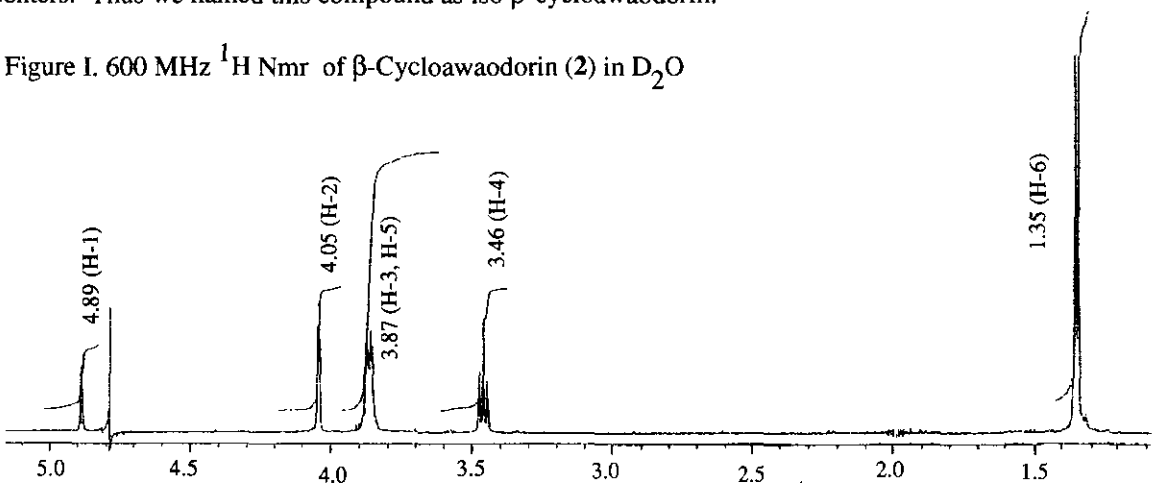
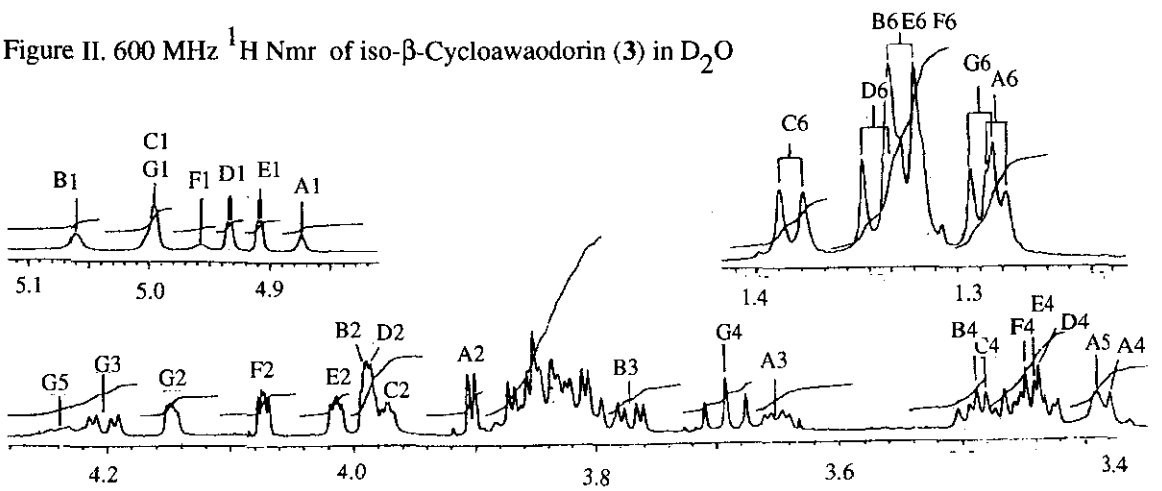


Figure II. 600 MHz ^{1}H Nmr of iso-β-Cycloawaodorin (**3**) in D_2O



The observed low selectivity of the cycloglycosylation of **6b** to give **2** and **3** (3.2:1) is surprising in comparison with the cycloglycosylations to give α-cycloawaodorin (hexamer) or cyclo-L-rhamnopentaose those were completely controlled to give α-glycosides. Linear glycosylations to give rhamnose oligomer by thermal glycosylation were always 100% α-selective,[2] and even Schmidt's imidate method affords α selectivity of 6:1 to 15:1.[3] Conformation analysis and the experiment dealing with the inclusion chemistry of cycloawaodorins are currently undertaking.

REFERENCES AND NOTES

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3. M. Nishizawa, H. Imagawa, E. Morikuni, S. Hatakeyama, and H. Yamada, *Chem. Pharm. Bull.*, 1994, **42**, 1365.
4. M. Nishizawa, Y. Kan, W. Shimomoto, and H. Yamada, *Tetrahedron Lett.*, 1990, **31**, 2431.
5. M. Mori, Y. Ito, J. Uzawa, and T. Ogawa, *Tetrahedron Lett.*, 1990, **31**, 3191.
6. HR ms (FAB) of **2**: *m/z* 1045.3930, calcd for $C_{42}H_{70}O_{28}Na$ 1045.3956 ($M^+ + Na$).
7. ^{13}C Nmr of **2** in D_2O (50 MHz): 17.3 (C-6) 68.5 (C-5), 69.7 (C-3), 70.4 (C-2), 83.6 (C-4), 102.6 (C-1, J_{CH} = 167.9 Hz) (assignment based upon HSQC).
8. HR ms (FAB) of **3**: *m/z* 1023.4180, calcd for $C_{42}H_{71}O_{28}$ 1023.4135 ($M^+ + H$).
9. ^{13}C Nmr of **3** in D_2O (150 MHz): 16.8 (G-6), 17.0, 17.1, 17.2, 17.4, 17.8 (C-6), 21.4 (A-6), 64.7, (G-3), 67.7 (D-5), 67.9 (B-5), 68.4 (C-5, E-5), 68.6 (G-5), 68.7 (F-5), 69.6 (D-3, E-3), 70.3, 70.3, 70.4 (A-5, B-2), 70.6 (B-3), 70.8 (E-2), 71.1 (G-2), 71.3 (A-2), 73.7 (A-3), 78.4 (G-4), 81.3 (E-4), 82.0 (A-4), 82.2 (F-4), 82.8 (B-4), 83.6 (D-4), 84.1 (C-4), 95.0 (A-1), 101.9 (D-1), 102.1 (E-1), 102.2 (C-1), 102.3 (B-1), 102.4 (F-1), 102.8 (G-1).

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