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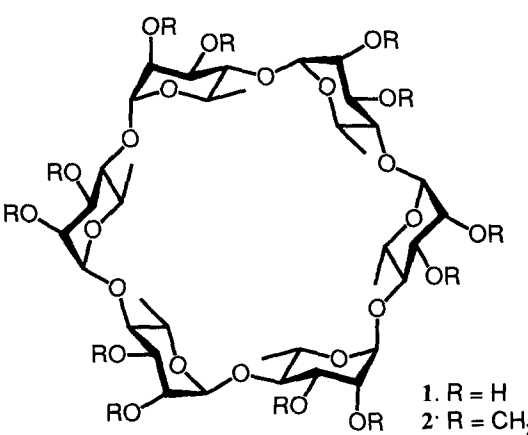
TOTAL SYNTHESIS OF CYCLO-L-RHAMNOHEXAOSE BY A STEREOSELECTIVE THERMAL GLYCOSYLATION

Mugio NISHIZAWA,* Hiroshi IMAGAWA, Yukiko KAN, and Hidetoshi YAMADA

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-Cho, Tokushima 770, Japan

Abstract: The first cyclooligosaccharide of L series, cyclo-L-rhamnohexaose, have been synthesized from L-rhamnose by α-selective thermal glycosylation and PhSeOTf promoted cycloglycosylation.

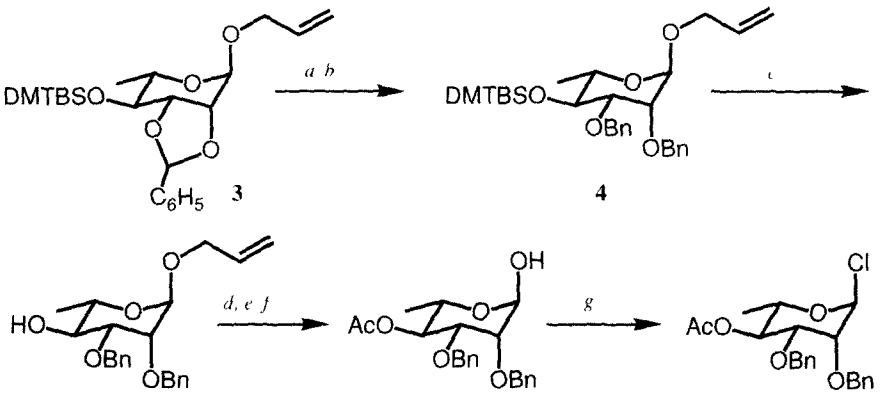
Significant attentions have been focused on the inclusion chemistry of cyclodextrins and the related compounds,[1] and synthetic studies of cyclooligosaccharides are continued intensively. For example, Ogawa and co-workers reported the total synthesis of cyclodextrins[2-4] and a manno isomer of cyclodextrins[5-7] by means of phenylselenyl triflate promoted cycloglycosylations. Synthesis of 1-3β linked cycloglucohexaose was reported by Collins' group.[8] Modification of α-cyclodextrin into trimethyl,[9] 1,3-anhydro,[10] and a chimera analog[11] have also reported recently. However, cyclooligosaccharides available today are only limited to D series. As we have developed a novel thermal glycosylation procedure,[12,13] which can be applied to rhamnosylation with high α-selectivity,[14] we designed the synthesis of cyclo-L-rhamnohexaose (**1**), the first cyclooligosaccharide of L series. Herein described is the total synthesis of **1**, which would open a new dimension of the inclusion chemistry.



1. R = H
2· R = $CH_2C_6H_5$ (Bn)

L-Rhamnose monohydrate was successively protected by allyl alcohol (1-OH),[15] benzaldehyde dimethylacetal (2,3-OH), and *tert*-butyldimethylsilyl chloride (4-OH), to give **3** in 54% overall yield. DIBAL reduction of **3**[16] in dichloromethane afforded a mixture of 2- and 3-benzylethers in a ratio of 5:3, which was then

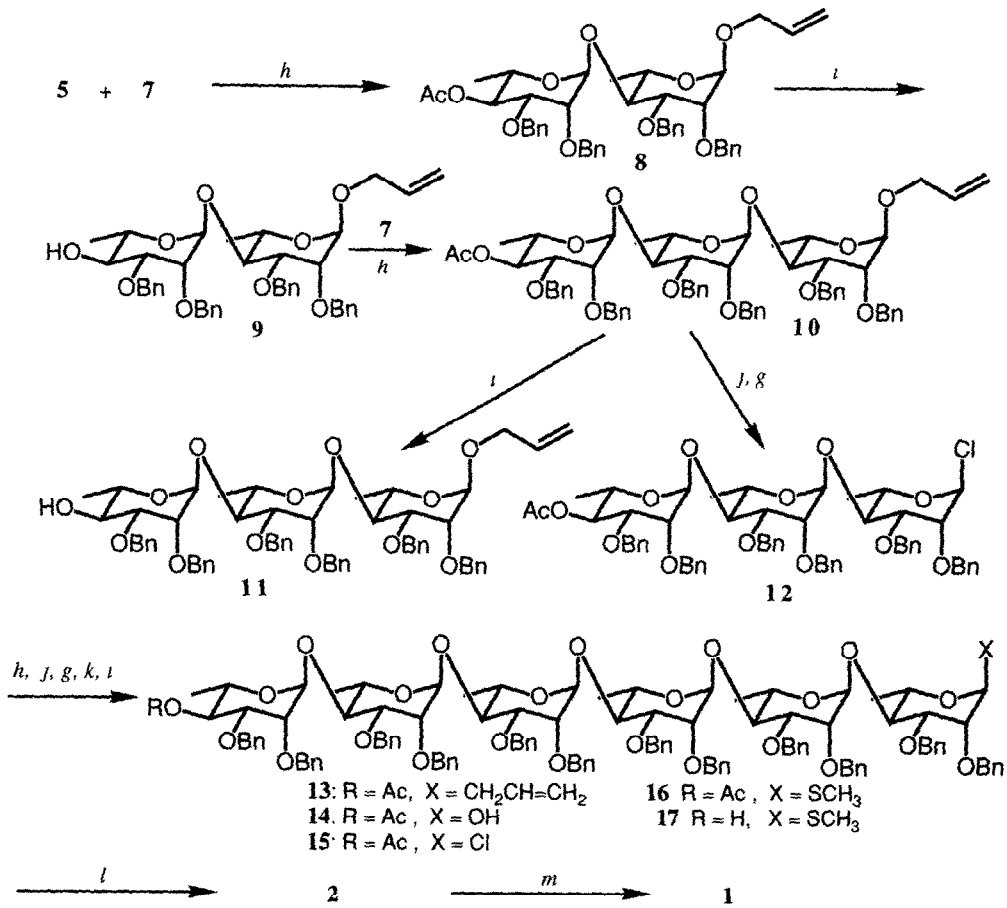
benzylated by benzyl bromide and NaH in DMF-THF (1:3) to give allyl 2,3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-α-L-rhamnopyranoside (**4**), $[\alpha]_D^{23}$ -44.6° (*c* 1.5, $CHCl_3$), in 88% yield. The silyl group of **4** was cleaved by aqueous hydrogen fluoride in acetonitrile to give the alcohol **5**, $[\alpha]_D^{23}$ -2.6° (*c* 2.1, $CHCl_3$), in 92% yield. After acetylation, allyl group was removed in two steps to the hemiacetal **6** in 97% yield. Rhodium complex catalyzed isomerization of double bond into 1,2-position followed by an oxidative hydrolysis using H_2O_2-SeO_2 in acetonitrile and phosphate buffer. The chlorination of **6** with $SOCl_2$ afforded the rhamnosyl chloride **7**, $[\alpha]_D^{17}$ -75.6° (*c* 4.8, $CHCl_3$), in 97% yield.



[a] DIBAL/CH_2Cl_2 [b] $C_6H_5CH_2Br$/NaH/DMF/THF [c] aq HF/CH_3CN [d] Ac_2O/C_5H_5N
[e] $[(C_6H_5)_3P]_3RhCl$ (0.005 eq)/$(C_6H_5)_3P$ (0.2 eq)/C_2H_5OH-C_6H_6-H_2O (7.3:1), reflux, 1 h
[f] SeO_2/H_2O_2/CH_3CN-pH 7 phosphate buffer [g] $SOCl_2$/CH_2Cl_2-DMF (1 drop)

Thermal glycosylation of **5** with chloride **7** (1.4 equiv) was achieved by heating the mixture at 70°C for 15 h in the presence of α-methylstyrene (3 equiv), the acid scavenger, giving rise to a single stereoisomer of the α-1,4-disaccharide **8**, $[\alpha]_D^{18}$ -15.7° (*c* 2.6, $CHCl_3$), in 60% yield.[17,18] Hydrolysis of the acetyl group in **8** yielded the alcohol **9**, $[\alpha]_D^{17}$ -5.1° (*c* 1.7, $CHCl_3$), which was again subjected to the thermal rhamnosylation with **7** (1.4 equiv) under the similar conditions (40 h),[17] to give the trimer **10**, $[\alpha]_D^{18}$ -8.1° (*c* 2.9, $CHCl_3$), in 52% yield. While methanolysis of **10** afforded the trimer alcohol **11**, $[\alpha]_D^{17}$ +4.0° (*c* 1.2, $CHCl_3$), in 78% yield, the $PdCl_2$ catalyzed hydrolysis and subsequent chlorination of **10** yielded the trimer chloride **12**, $[\alpha]_D^{18}$ -25.1° (*c* 0.7, $CHCl_3$), in 80% yield. The thermal coupling of **11** and **12** (1.2 equiv) for 24 h at 70°C and an additional 1.5 h at 90°C in the presence of α-methylstyrene (3 equiv) afforded the hexamer **13**, $[\alpha]_D^{18}$ +2.5° (*c* 0.6, $CHCl_3$), in 60% yield. The hexamer **13** was successively subjected to the deprotection at the anomeric center by $PdCl_2$/aq AcOH (to **14** in 76% yield), chlorination [to **15**, $[\alpha]_D^{22}$ -7.4° (*c* 0.5, $CHCl_3$), in 73% yield], *S*-methylation [to **16** (α/β 2:3) in 88% yield], and hydrolysis of acetyl group to give hexamer alcohol **17** $[\alpha]_D^{18}$ +20.3° (*c* 1.1,

$CHCl_3$), in 79% yield.



^{h} α-methylstyrene (3 equiv) 70℃, 15-40h ^{i} CH_3ONa/CH_3OH ^{J} $PdCl_2$ (1.2 eq)/AcOH-H_2O, (20:1) room temp, 9h. ^{k} $(C_4H_9)_3SnSCH_3/BF_3$/molecular sieves AW-300/CH_2Cl_2, 0℃, 1 h. ^{l} C_6H_5SeOTf/molecular sieves-4A/$(CH_2Cl)_2$. ^{m} $H_2/Pd(OH)_2/CH_3OH$-$CH_3CO_2C_2H_5$-H_2O (12:1:1).

The hexamer alcohol **17** was treated at -20℃ for overnight with phenylselenyl triflate in 1,2-dichloroethane in the presence of molecular sieves 4A,[6] and the cyclization product **2**, $[\alpha]_D^{22}$ +30.3° (*c* 0.15, $CHCl_3$), was isolated as colorless crystals, mp 139-141℃, in 23% yield after silica gel column chromatography. This product exhibited sharp monomer-like ^1H and ^{13}C NMR spectra in $CDCl_3$.[19] Upon hydrogenolysis of **2** in the presence of 20%$Pd(OH)_2$-C, the first cyclooligosaccharide of L-series, α-cyclo-L-rhamnohexaose (**1**) $[\alpha]_D^{23}$ -18.5° (*c* 0.085, CH_3OH), was obtained in 72% yield as amorphous solid. The structure of **1** was verified on

the basis of FAB mass spectrum of m/z 899 $(M + Na)^+$ and 915 $(M + K)^+$ as well as ^1H and ^{13}C NMR spectra in D_2O [20] Studies including the detailed characterization of **1** and its possibility as a host compound of inclusion chemistry are in progress.[21]

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17. Thermal coupling of **5** and **7** at 120°C for 2 h with or without α-MS sometimes afforded much higher yield, however those conditions were not effective for larger scales (2 ~ 3 mmol)
18. NMR chemical shifts along with coupling constants in parenthesis (Hz) of anomeric protons and carbons in $CDCl_3$ are as follows: **5**, δ 4.86 (1.64) and δ 97.0 (167.3), **7**, δ 6.09 (br s) and δ 91.3 (181.7); **8**, δ 4.83 (1.65), 5.31 (1.65), and δ 96.8 (168.4), 99.8 (172.1); **9**, δ 4.84 (1.1), 5.23 (br s), and δ 97.0 (165.8), 99.8 (170.2); **10**, δ 4.85 (1.65), 5.28 (1.65), 5.30 (1.65), and δ 99.08 (168.8), 99.59 (176.1), 99.84 (171.7); **11**, δ 97.0 (170.2), 99.6 (170.2), 99.7 (170.2), **12**, δ 5.29 (2H, br s), 6.06 (1.64), and δ 91.4 (183.1), 99.6 (172.8), 99.7 (172.8). **13**, δ 4.86 (br s), 5.27-5.31 (5H, complex), and δ 97.0, 99.2, 99.3, 99.4, 99.7, **15**, δ 5.26 (2H, br s), 5.29 (1H, br s), 5.31 (2H, br s), 6.07 (1.47), and δ 91.5, 99.3, 99.4, 99.4, 99.8, 99.8; **16**, δ 84.8 (137.8), 85.7 (149.6), 99.4 (176.1), 99.4 (176.1), 99.6 (173.1), 99.8 (176.1), **17**, δ 84.8 (135.5), 85.7 (149.6), 99.4 (170.0), 99.4 (170.0), 99.4 (170.0), 99.7 (172.0), 99.7 (172.0).
19. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectrum of **2** in $CDCl_3$ δ 1.44 (18H, d, J = 6.1 Hz), 3.56 (6H, t, J = 8.8 Hz), 3.76 (6H, dd, J = 8.8, 2.4 Hz), 3.81 (12H, m), 4.25 (6H, d, J = 12.1 Hz), 4.31 (6H, d, J = 12.1 Hz), 4.48 (6H, d, J = 12.1 Hz), 4.53 (6H, d, J = 12.1 Hz), 4.92 (6H, s), 7.15-7.26 (60H, m), and δ18.4q, 68.5d, 71.5t, 72.5t, 76.7d, 78.4d, 100.9d (J_{CH} = 163.8 Hz), 127.0d, 127.4d, 127.5d, 127.6d, 127.6d, 128,0d, 128.1d, 128.3d, 128.3d, 138.3s, 138.4s
20. ^1H (600 MHz) and ^{13}C (150 MHz) NMR spectrum of **1** in D_2O (*tert*-butyl alcohol as internal standard at δ 1.25 and δ 32.25, respectively): δ 1.39 (18H, d, J = 6.4 Hz), 3.48 (6H, t, J = 9.0 Hz), 3.88 (6H, m), 3.89 (6H dd, J = 9.0, 2.6 Hz), 4.01 (6H t, J = 2.6 Hz), 4.91 (6H, d, J = 2.6 Hz), and δ 20.0q, 70.9d, 72.5d, 73.0d, 104.8d
21. We propose the common name "α-cycloawaodorin" to **1**, the first cyclooligosaccharide of L-series, in connection with the area where the compound has been prepared

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