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STEREOSELECTIVITY OF CYCLOGLYCOSYLATION IN *MANNO*OLIGOSE SERIES DEPENDS ON CARBOHYDRATE CHAIN LENGTH: SYNTHESES OF *MANNO* ISOMERS OF β- AND γ- CYCLODEXTRINS

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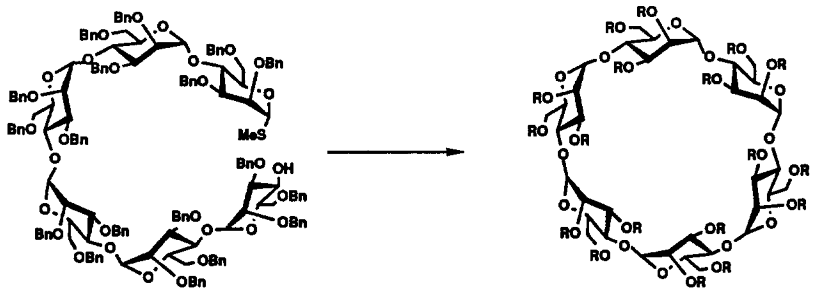
Abstract: Syntheses of *manno* isomer of β- and γ-cyclodextrins were achieved for the first time employing methylthioglycosides of α-(1→4) linked mannoheptaose and mannooctaose.

Recently we reported[1] an efficient and stereoselective cycloglycosylation of thioglycoside 1 into completely benzylated cyclomannohexaose 2 in 92% yield which was subsequently deprotected into *manno* isomer 3 of α-cyclodextrin. In continuation of our project on cyclooligoglycose synthesis, we report here first syntheses of *manno* isomers (6 and 11) of β- and γ-cyclodextrins.

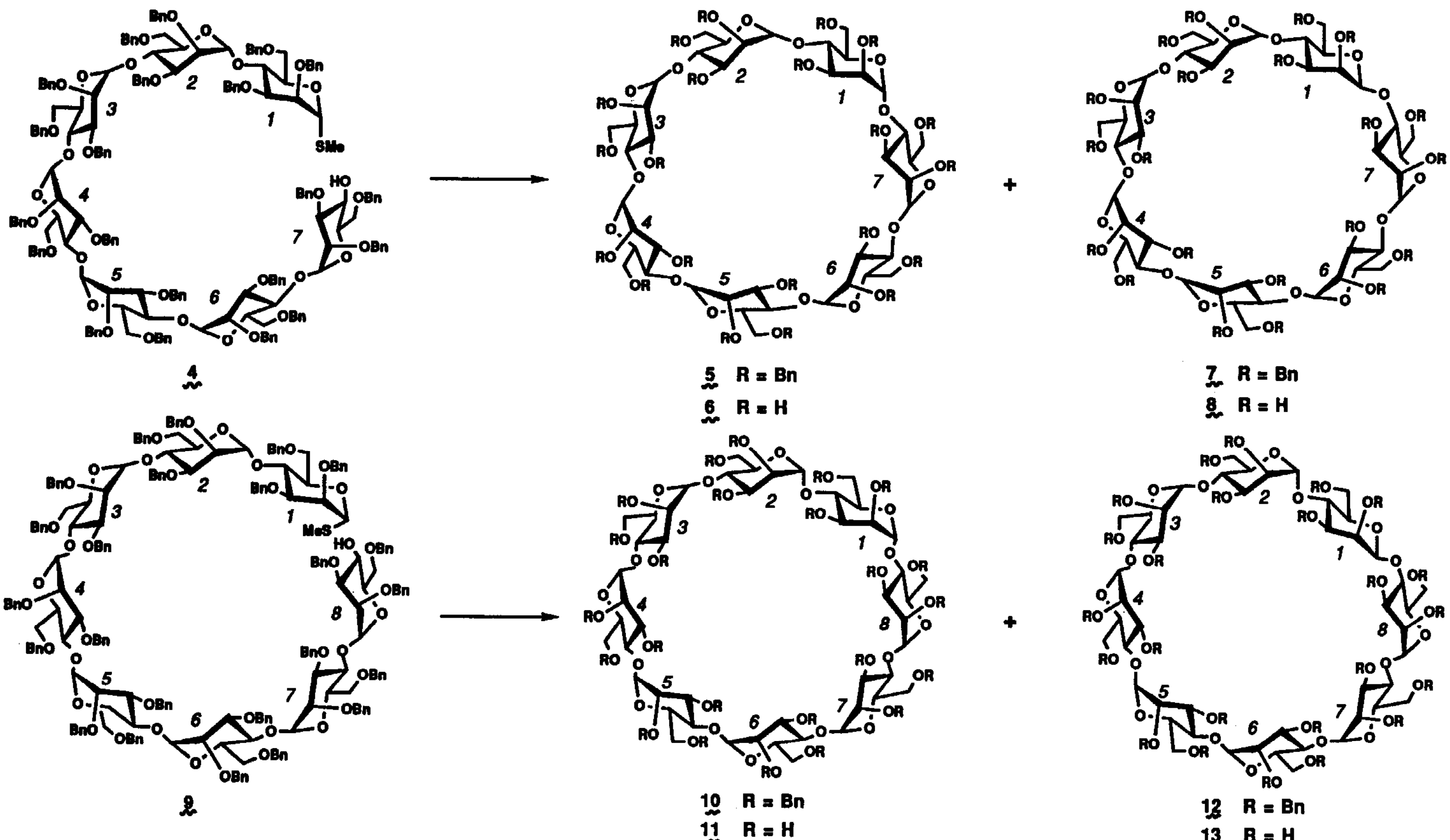


1

2 R = Bn
3 R = H

Cycloglycosylation of 4 in the presence of PhSeOTf[2] in $(ClCH_2)_2$ at -22° afforded 5[3] and 7 in 46 and 33% yield which were then hydrogenolysed in the presence of 20% $Pd(OH)_2/C$ in 12:1:1 MeOH-EtOAc-H_2O to give 6 and 8, respectively. Similarly, cycloglycosylation of 9 afforded 10 and 12 in 53 and 25% yield which were again quantitatively deprotected to 11 and 13, respectively.

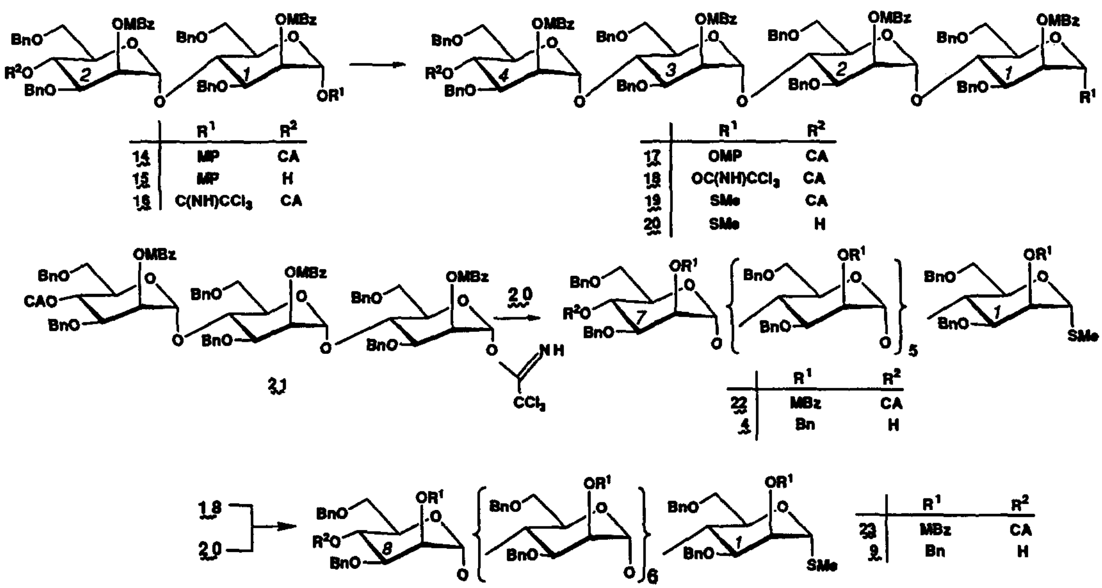
The structures of the α-(1→4) linked product 5 and the β-(1→4) linked product 7 were deduced from ^1H and ^{13}C-n.m.r. data measured in $CDCl_3$. A signal for H-1 and C-1 of 5 was observed, respectively, at δ 5.033 as a singlet and at δ 100.8 with a value of $^1J_{C,H}$ 164 Hz, in agreement with C_7 symmetry of the molecule. For the compound 7, we observed signals for seven anomeric protons at δ 5.283 (s, 1H), 5.061 (d, 1.5 Hz, 2H), 5.050 (s, 1H), 5.012 (d, 1.5 Hz, 1H), 4.990 (d, 1.5 Hz, 1H) and 4.574 (s, 1H). Among these signals for anomeric protons, a signal at δ 4.574 could be assigned for $H\text{-}1^1$ with β-D configuration by ^1H-^{13}C heteronuclear multiple quantum coherence (HMQC)[4] which revealed a corresponding signal for $C\text{-}1^1$ at δ 96.67 with $^1J_{C,H}$ 154 Hz[5] as well as the signals for $C\text{-}1^{2\sim7}$ with α-D configuration at δ 101.86, 101.21, 100.94, 100.87, 100.83 and 99.08 ($^1J_{C,H}$ ~170 Hz[5]). The assignment of configuration for the newly introduced glycosidic linkage in 10 and 12 was also made by ^1H-^{13}C HMQC measurements. These experimental results showed that cycloglycosylations of α-(1→4)-linked thio-mannooligosides 1, 4, and 9 in the presence of PhSeOTf afforded a high yield (80~90%) of cyclization products but the



Scheme 1

stereoselectivity of cycloglycosylation depends heavily on the chain length of the oligosaccharides employed. The α/β ratios of the products were as follows: only α for **1**, 1.4/1 for **4**, and 2.1/1 for **9**.

The key intermediates **4** and **9** were prepared starting from the protected mannobiosyl derivatives **14**[1] and **15**[1]. Conversion of **14** into trichloroacetimidate **16** was performed in two steps (*1* CAN in 4:1 MeCN-H_2O[6], *2* CCl_3CN[7], DBU in $(CH_2Cl)_2$, overall 74%). TMSOTf[8] promoted glycosylation of **15** with **16** in $(ClCH_2)_2$ at -20° afforded the mannotetraosyl derivative **17** in 85% yield. Conversion of **17** into a glycosyl donor **18** was accomplished in two steps (overall 64%) as in the case of **14**. Treatment of **18** with Bu_3SnSMe[9] in the presence of $BF_3{\cdot}OEt_2$ gave an 88% yield of **19** which was converted into a glycosyl acceptor **20** in 95% yield by treatment with $(NH_2)_2CS$ in EtOH[10].



Scheme 2 (CA = $ClCH_2CO$, MBZ = 4-MeBz, MP = 4-MeOPh)

Having prepared necessary mannotetraosyl donor **18** and acceptor **20**, glycosylation of **20** with the known mannotriosyl donor **21**[1] in the presence of TMSOTf afforded a 66% yield of mannoheptaosyl derivative **22** which was then converted into a key intermediate **4** in 5 steps (*1* $(NH_2)_2CS$ in EtOH, *2* $EtOCH{=}CH_2$, PPTS in $(ClCH_2)_2$, *3* NaOMe in 1:3 THF-MeOH, *4* BnBr, NaH in DMF, *5* Amberlyst 15 (H^+) in 1:1 CH_2Cl_2-MeOH, overall 64%). Similarly, glycosylation of **20** with mannotetraosyl donor **18** in the presence of TMSOTf gave a 62% yield of mannooctaosyl derivative **23** which was then converted in 5 steps into another key intermediate **9** in 57% overall yield in a same reaction sequence as described for **4**.

Crucial cycloglycosylations of **4** and **9** were achieved in high yield but with low stereocontrol as described already. Reasonable explanation for these interesting experimental observations has remained to be done.

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Reference and Notes

1) M. Mori, Y. Ito, and T. Ogawa, *Tetrahedron Lett.*, **30** 1273 (1989); *idem.*, *Carbohydr. Res.*, **192** 131 (1989).

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3) Physical data for key compounds are described below. Values of $[\alpha]_D$ and $\delta_{H,C}$ were measured for $CHCl_3$ and $CDCl_3$ solutions, respectively, at 23±3°, unless noted otherwise. **4**: $[\alpha]_D$ -1.3° (c 0.8); δ_H 5.327 (d, 3H, 2.1 Hz), 5.300 (s, 2H) and 5.284 (s, 2H) for 7 x H-1, 2.169 (s, SMe); δ_C 99.9 ($^1J_{CH}$ 171 Hz, 2 x C-1), 99.7 ($^1J_{CH}$ 173 Hz, 4 x C-1), 82.7 (C-1^{1}), 13.8 (SMe). **5**: $[\alpha]_D$ -36.7° (c 0.5). **6**: $[\alpha]_D$ +47.4° (c 0.3, H_2O); δ_H (D_2O, 50°) 4.941 (d, 2.1 Hz, H-1), 4.039 (dd, 2.1 and 3.4 Hz, H-2), 3.924 (dd, 3.4 and 8.9 Hz, H-3), 3.897 (dd, 2.4 and 12.5 Hz, H-6), 3.857 (dd, 4.6 and 12.5 Hz, H-6), 3.792 (ddd, 2.4, 4.6 and 8.9 Hz, H-5), 3.736 (t, 8.9 Hz, H-4). **7**: $[\alpha]_D$ -29.4° (c 0.5). **8**: $[\alpha]_D$ +50.0° (c 0.3, H_2O); δ_H (D_2O, 50°) 5.195 (d, 2.4 Hz), 5.005 (d, 2.6 Hz), 4.987 (d, 1.8 Hz), 4.962 (d, 2.0 Hz), 4.950 (d, 2.1 Hz), and 4.934 (d, 2.1 Hz) for 6 x H-1, 4.930 (s, H-1^{1}). **9**: $[\alpha]_D$ -1.6° (c 0.3); δ_H 5.330 (s, 4H), 5.299 (s, 2H) and 5.281 (s, 2H) for 8 x H-1, 2.169 (s, SMe); δ_C 99.9 ($^1J_{CH}$ 171 Hz, 2 x C-1), 99.7 ($^1J_{CH}$ 170 Hz, 5 x C-1), 82.7 (C-1^{1}), 13.8 (SMe). **10**: $[\alpha]_D$ -40.7° (c 1.7); δ_H 5.073 (d, 1.5 Hz, H-1). **11**: $[\alpha]_D$ +27.2° (c 0.3, H_2O); δ_H (D_2O, 50°) 4.981 (d, 2.1 Hz, H-1). **12**: $[\alpha]_D$ -42.9° (c 1.0); δ_H (HMQC) 5.316, 5.255, 5.163, 5.073 (2H), 5.051 and 5.042 (6s, 7 x H-1), 4.887 (s, H-1^{1}); δ_C (HMQC) 97.4 ($^1J_{CH}$ 157 Hz, C-1^{1}), 100.4~100.8($^1J_{CH}$ ~170 Hz, 7 x C-1). **13**: $[\alpha]_D$ +61.9° (c 0.2, H_2O); δ_H (D_2O, 50°) 5.185 (d, 2.1 Hz), 5.105 (d, 1.8 Hz), 5.084 (d, 2.1 Hz), 5.063 (d, 1.8 Hz), 4.997 (d, 1.8 Hz), 4.989 (d, 2.1 Hz) and 4.975 (d, 1.8 Hz) for 7 x H-1, 4.950 (s, H-1^{1}). **16**: $[\alpha]_D$ -16.3° (c 0.9); δ_H 8.743 (s, C=NH), 6.404 (d, 1.8 Hz, H-1^{1}), 5.719 and 5.702 (2dd, 1.8 and 3.1 Hz, H-2^{1,2}), 5.608 (d, 1.8 Hz, H-1^{2}), 2.385 and 2.376 (2s, 2 x PhMe). **17**: $[\alpha]_D$ -33.5° (c 4.4); δ_H 5.597 (d, 1.8 Hz, 2 x H-1), 5.578 (d, 1.5 Hz, H-1), 5.528 (d, 1.5 Hz, H-1), 5.470 (t, 10.0 Hz, H-4^{4}); δ_C 99.3 (C-1), 98.9 (2 x C-1), 96.9 (C-1^{1}), 55.5 (OMe). **18**: $[\alpha]_D$ -30.6° (c 0.9); δ_H 8.778 (s, C=NH), 6.430 (d, 2.0 Hz, H-1^{1}), 5.584 (s, 2 x H-1), 5.530 (d, 1.8 Hz, H-1), 5.476 (t, 10.0 Hz, H-4^{4}). **19**: $[\alpha]_D$ -34.0° (c 1.5); δ_H 5.591 (d, 1.8 Hz, H-1), 5.529 (s, 2 x H-1), 5.477 (t, 10.0 Hz, H-4^{4}), 5.333 (d, 2.0 Hz, H-1^{1}); δ_C 99.3 (C-1), 98.9 (2 x C-1), 83.8 (C-1^{1}). **20**: $[\alpha]_D$ -40.4° (c 1.0); δ_H 5.579 (d, 1.8 Hz, H-1), 5.528 (s, 2 x H-1), 5.333 (d, 1.8 Hz, H-1^{1}); δ_C 99.3 (3 x C-1), 83.8 (C-1^{1}). **22**: $[\alpha]_D$ -42.1° (c 0.8); δ_H 5.596 (d, 1.5 Hz, H-1), 5.584 (s, 2 x H-1), 5.563 (d, 1.5 Hz, H-1), 5.560 (d, 1.8 Hz, H-1), 5.543 (s, H-1), 5.473 (t, 10.0 Hz, H-4^{7}), 5.331 (s, H-1^{1}); δ_C 98.8 (6 x C-1), 83.9 (C-1^{1}). **23**: $[\alpha]_D$ -50.4° (c 0.8); δ_H 5.595 (2H), 5.579 (2H), 5.561, 5.553, 5.541, (5d, 1.5~1.8 Hz, 7 x H-1), 5.472 (t, 10.0 Hz, H-4^{8}), 5.329 (d, 1.2 Hz, H-1^{1}).

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