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A HIGHLY EFFICIENT AND STEREOSELECTIVE CYCLOGLYCOSYLATION. SYNTHESIS OF CYCLO{→4)-[α-Man-(1→4)]5-α-Man-(1→}, A MANNO ISOMER OF α-CYCLODEXTRIN

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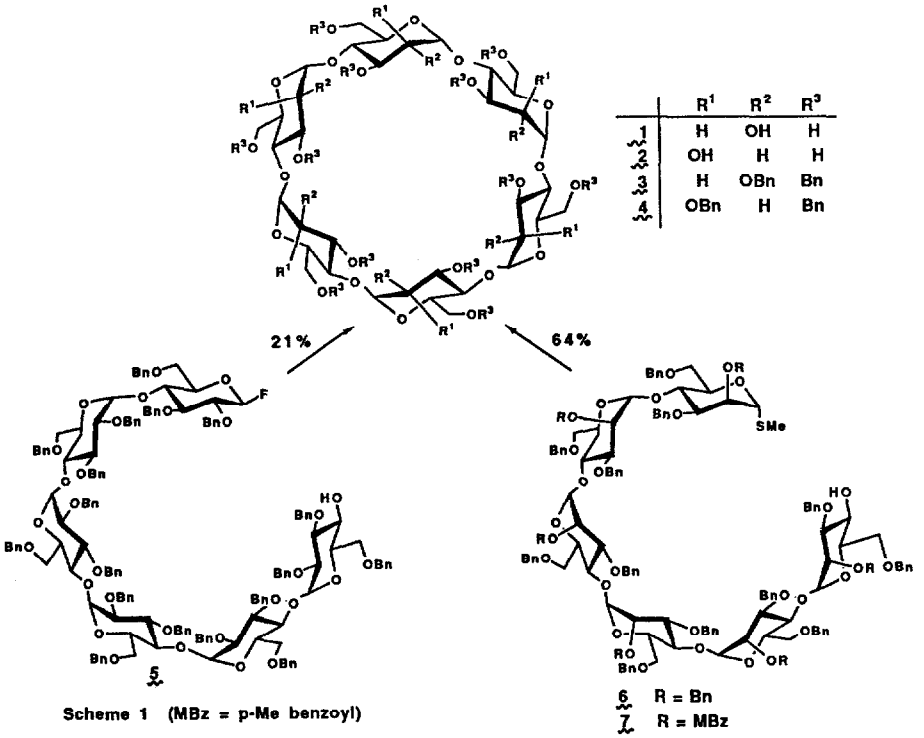
Abstract: Stereocontrolled synthesis of a *manno* isomer of α-cyclodextrin was achieved for the first time employing PhSeOTf promoted cycloglycosylation of octadeca-O-benzyl-α-Man-(1→4)-{α-Man-(1→4)}4-α-Man-1→SMe.

Cycloglycosylations leading to the formation of cyclooligosaccharides have been reported only in few cases[1]. In the field of cyclooligosaccharides, synthetic studies have mostly been directed to the functional group manipulations[2] of cyclodextrins (cyclomaltooligoses). Recently we reported a first chemical synthesis[3] of α-cyclodextrin (cyclomaltohexaose) 1 via octadeca-O-benzylether 3 that was prepared in 21% yield by $SnCl_2$-AgOTf[4] promoted cycloglycosylation of the key intermediate 5. Efficiency of cycloglycosylation depended on the ring size and in the case of cyclomaltooctaose (γ-cyclodextrin) cycloglycosylation of the corresponding maltooctaosyl fluoride under the same condition could be achieved only in 8.4% yield[5].



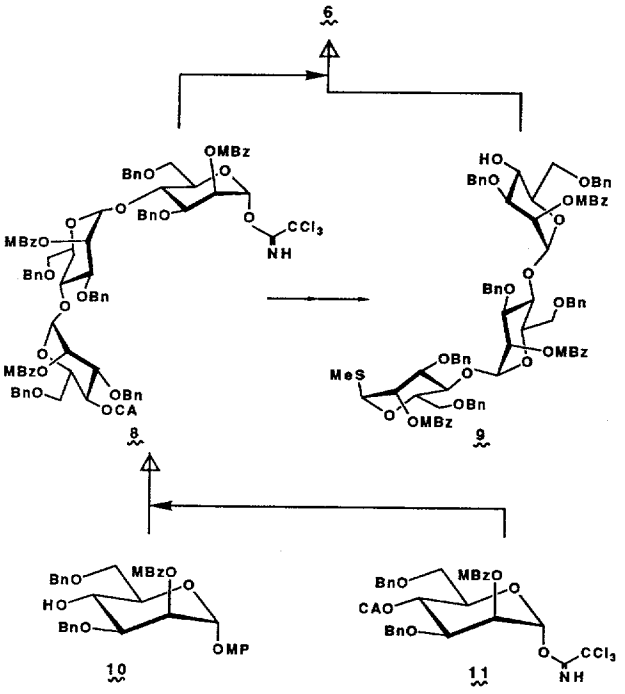
	R^1	R^2	R^3
1	H	OH	H
2	OH	H	H
3	H	OBn	Bn
4	OBn	H	Bn

Scheme 1 (MBz = p-Me benzoyl)

6 R = Bn
7 R = MBz

In close connection with these synthetic studies on cyclooligosaccharides, we report here an efficient and practical cycloglycosylation of a mannohexaosyl methylthioglycoside 6 that led to a stereocontrolled synthesis of the unnatural cyclooligosaccharide, cyclo α-(1→4)-linked

mannohexaose **2**, a *manno* isomer of α-cyclodextrin. Thus PhSeOTf promoted[6] cycloglycosylation of methylthioglycoside **6** proceeded at -20° in $(CH_2Cl)_2$ to afford a 64% yield of octadeca-O-benzyl cyclomannohexaose **4**[7], which was smoothly hydrogenolized in the presence of 10% Pd-C in MeOH to give desired **2**[7]. Surprisingly, use of *p*-methyl benzoyl group as an O-2 stereocontrolling auxiliary[8] in place of an O-2 benzyl group in compound **6** deteriolated the smooth cycloglycosylation. Attempted cycloglycosylation of compound **7** gave multiple products under various conditions. A reasonable explanation for this unexpected observation has remained to be made.

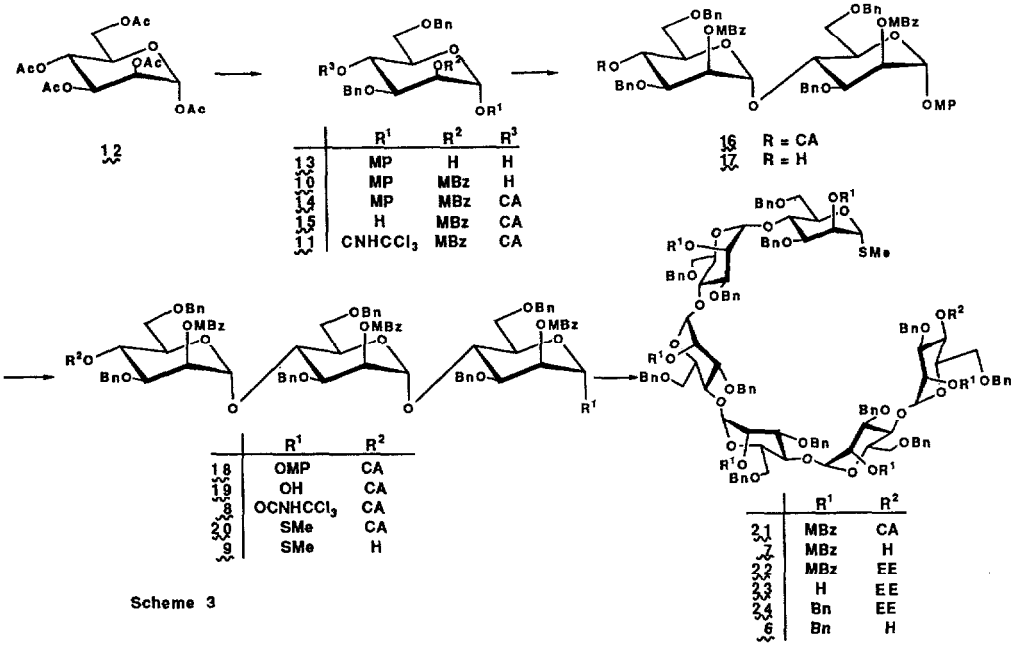


Scheme 2 (CA = $ClCH_2CO$, MP = p-MeOPh)

The two key intermediates **6** and **7** were synthesized according to Scheme 2 by employing a mannotriaosyl donor **8** carrying *p*-methyl benzoyl group at O-2 as a stereocontrolling auxiliary and a mannotriaosyl acceptor **9**, which in turn were prepared starting from monosaccharide synthons **10** and **11**.

A glycosyl acceptor **10**[7] was designed to carry p-methoxyphenyl group for the purpose of temporary protection of the anomeric hydroxy function and was prepared in 4 steps in 54% overall yield from pentaacetyl mannose **12** via **13**[7] (1 p-MeOPhOH-CF_3SO_3H in $(CH_2Cl)_2$, 2 NaOMe in MeOH, 3 $(Bu_3Sn)_2O$[9] then BnBr-Bu_4NBr[10], 4 p-MeBzCl in pyridine at -20°). Conversion of **10** into a mannosyl donor **11** was performed in a straightforward manner in 3 steps via **14**[7] in 50% overall yield (1 $(ClCH_2CO)_2O$-$NaHCO_3$[11] in DMF, 2 $(NH_4)_2Ce(NO_3)_6$ in 4:1 CH_3CN-H_2O[12], 3 CCl_3CN-DBU in $(CH_2Cl)_2$[13]). TMSOTf promoted glycosylation[14] of the glycosyl acceptor **10** with the trichloroacetimidate **11** according to Schmidt[13] in the presence of powdered molecular sieves 4A proceeded stereoselectively to give an 87% yield of α-(1→4) linked mannobioside **16**[7], which was treated with $(NH_2)_2CS$ in EtOH[15] to give selectively dechloroacetylated product **17**[7] in 98% yield. The mannobiosyl glycosyl acceptor **17** was smoothly converted into mannotriaosyl glycosyl donor **8**[7] in 3 steps in 56% overall yield via **18**[7] and **19**[7] (1 **11**, TMSOTf and MS4A in $(CH_2Cl)_2$ at -20°, 2 $(NH_4)_2Ce(NO_3)_6$ in 4:1 CH_3CN-H_2O, 3 Cl_3CCN-DBU in $(CH_2Cl)_2$ at -20°). Mannotriaosyl glycosyl donor **9**[7] was obtained from **8** in 2 steps in 78% overall yield via **20**[7] (1 Bu_3SnSMe[16]-BF_3•Et_2O in $(CH_2Cl)_2$, 2 $(NH_2)_2CS$ in EtOH).

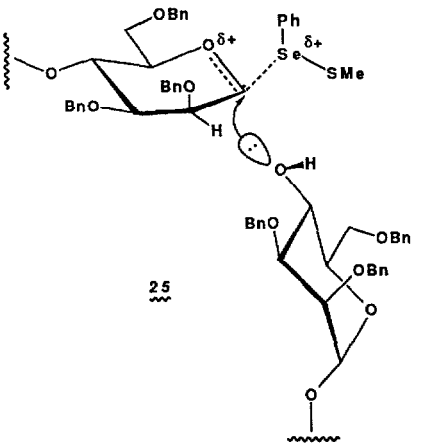
Having both glycosyl donor **8** and acceptor **9** prepared in a stereocontrolled way, coupling between them was examined in the presence of TMSOTf to afford an 87% yield of mannohexaosyl derivative **21**[7] which was then dechloroacetylated to give an 81% yield of the designed key intermediate **7**[7]. Available procedures for the activation of thioglycoside **7** by use of thiophilic reagents failed to give any isolable amount of cyclyzation product. Therefore, completely



Scheme 3

benzylated derivative **6** was chosen as an alternative key intermediate for cycloglycosylation. Replacement of O-2 *p*-methyl benzoyl groups of **7** into O-2 benzyl groups was achieved in 4 steps to give **6**[7] in 75% overall yield via **22**[7] and **23**[7], (1 $EtOCH{=}CH_2$ and PPTS in $(CH_2Cl)_2$, 2 NaOMe in MeOH, 3 BnBr and NaH in DMF, 4 Amberlyst 15 resin in 1:1 $CHCl_3$-MeOH).

Crucial cycloglycosylation of **6** was achieved successfully as already described. A higher efficiency of the cycloglycosylation for *manno* compound **6** compared with that for *gluco* isomer **5** may not be explained only by the difference of anomeric learing groups. The *manno* configuration at the reducing-end residue of the "intimate ion-pair"[17] intermediate **25** might play important role for this result.



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In summary, an efficient synthesis of a *manno* isomer of α-cyclodextrin was excecuted in 3.4% overall yield in 21 steps from readily obtainable pentaacetylmannopyranose **12** by use of PhSeOTf promoted cycloglycosylation of the key thioglycoside **6**.

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7 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 25°, unless noted otherwise. **2**: $[\alpha]_D$ +26.5° (c 0.2, H_2O); $\delta_H(D_2O)$ 4.926 (d, 2.4 Hz, H-1), 4.009 (t, 3 Hz, H-2), 3.944 (dd, 2.5, 11.3 Hz, H-6), 3.925 (dd, 3.4, 9.0 Hz, H-3), 3.880 (dd, 5.2, 12.2 Hz, H-6), 3.787 (ddd, 9.5, 2.4, 4.9 Hz, H-5), 3.703 (t, 9.0 Hz, H-4). **4**: $[\alpha]_D$ -2.8° (c 0.3); δ_H 5.043 (d, 1.5 Hz, H-1); δ_C 100.9 ($^1J_{CH}$ 165 Hz, C-1). **6**: $[\alpha]_D$ -2.1° (c 0.8); δ_H 5.333 (bs, H-1 x 2), 5.290 (bs, H-1 x 4), 2.172 (s, SCH_3). **7**: $[\alpha]_D$ -52.6° (c 0.9); δ_H 5.572 (bs, H-1), 5.562 (bs, H-1 x 2), 5.546 (bs, H-1 x 2), 5.331 (d, 1.5 Hz, H-1a), 2.220 (s, SCH_3); δ_C 99.4, 99.1, 99.0, 98.9, 98.8 (C-1bcdef), 83.9 ($^1J_{CH}$ 164 Hz, C-1a). **8**: $[\alpha]_D$ -21.2° (c 0.7); δ_H 6.420 (d, 2.1 Hz, H-1a), 5.571 (d, 1.8 Hz, H-1 x 2), 5.484 (t, 10.0 Hz, H-4c), 3.723 (s, CH_2Cl). **9**: $[\alpha]_D$ -25.5° (c 0.4); δ_H 5.545 (d, 1.5 Hz, H-1), 5.510 (d, 1.8 Hz, H-1), 5.324 (d, 1.5 Hz, H-1a), 2.208 (s, SCH_3); δ_C 99.4 ($^1J_{CH}$ 175 Hz, C-1bc), 83.8 ($^1J_{CH}$ 169 Hz, C-1a). **10**: $[\alpha]_D$ +10.5° (c 0.8); δ_H 5.747 (dd, 1.8, 3.1 Hz, H-2), 5.565 (d, 1.8 Hz, H-1), 3.758 (s, OCH_3). **11**: $[\alpha]_D$ -20.1° (c 1.9); δ_H 6.414 (d, 1.2 Hz, H-1); δ_C 95.1 ($^1J_{CH}$ 179 Hz, C-1), 40.6 ($COCH_2Cl$). **13**: $[\alpha]_D$ +73.9° (c 1.9); δ_H 5.467 (d, 1.5 Hz, H-1), 3.745 (s, OCH_3). Acetylation of **13** gave diacetate: δ_H 5.523 (dd, 1.8, 3.4 Hz, H-2), 5.331 (t, 9.8 Hz, H-4). **14**: $[\alpha]_D$ -3.0° (c 0.5); δ_H 5.733 (dd, 1.8, 3.1 Hz, H-2), 5.610 (t, 9.8 Hz, H-4), 3.804 and 3.771 (2d, 14.7 Hz, CH_2Cl). **16**: $[\alpha]_D$ -3.2° (c 1.4); δ_H 5.632 (d, 1.8 Hz, H-1), 5.558 (d, 1.8 Hz, H-1), 5.480 (t, 10.0 Hz, H-4b); δ_C 99.2 ($^1J_{CH}$ 175 Hz, C-1), 96.9 ($^1J_{CH}$ 175 Hz, C-1). **17**: $[\alpha]_D$ -11.7° (c 1.9); δ_H 5.628 (d, 1.8 Hz, H-1), 5.554 (d, 1.8 Hz, H-1), 4.429 (t, 10 Hz, H-4a), 4.110 (t, 10.0 Hz, H-4b). **18**: $[\alpha]_D$ -26.4° (c 1.1); δ_H 5.582 (d, 1.8 Hz, H-1 x 2), 5.563 (d, 1.8 Hz, H-1), 5.468 (t, 10.0 Hz, H-4c). **19**: δ_H 5.556 (d, 1.8 Hz, H-1), 5.506 (bs, H-1), 5.480 (t, 10.0 Hz, H-4c), 5.382 (bs, H-1a). **20**: $[\alpha]_D$ -18.2° (c 0.6); δ_H 5.564 (d, 1.5 Hz, H-1), 5.514 (d, 1.8 Hz, H-1), 5.476 (t, 10.0 Hz, H-4c), 5.326 (d, 1.5 Hz, H-1a), 2.216 (s, SCH_3). **21**: $[\alpha]_D$ -42.6° (c 0.9); δ_H 5.587 (bs, H-1 x 2), 5.565 (bs, H-1 x 2), 5.548 (d, 1.8 Hz, H-1), 5.476 (t, 9.8 Hz, H-4f), 5.336 (d, 1.5 Hz, H-1a). **22**: δ_H 5.330 (s, H-1a), 2.219 (s, SCH_3). **23**: δ_H 5.244 (d, 1.5 Hz, H-1a), 2.151 (s, SCH_3).

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