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The Stereoselective Synthesis of Cyclomaltopentaose. A Novel Cyclodextrin Homologue with D.P. Five.

Toshio Nakagawa*, Koji Ueno, Mariko Kashiwa, and Junko Watanabe

Department of Chemistry, Yokohama City University,
22-2 Seto, Kanazawa-ku, Yokohama 236, Japan

Abstract: *A key intermediate* **15** *was prepared via successive glycosidations of 1,6-anhydro maltose derivative* **8** *with glycosyl donors* **6** *and then with* **11**, *cyclized under a diluted condition, and deprotected to give the title compound. Every glycosidation, including the cyclization, is likely to proceed stereoselectively by participation of the N-phenylcarbamoyl group at O-6 of* **6**, **11** *and* **15**.

Cyclodextrins, known as cyclic malto-oligosaccharides with a degree of polymerization (dp) ≥ 6, are produced from starch by elaboration of amylase of Bacillus macerans[1]. The chemical synthesis of those with dp 6 and 8 was reported first by Ogawa and Takahashi[2], and that of mono-2-deoxy analogues with dp 6 and 7 by Kuzuhara and his coworkers[3]. Although a cyclodextrin analogue having dp 5, cyclo-α-(1→4)-manno-pentaose, has been recently described[4], none of cyclodextrin homologues having dp ≤ 5 is known; Sundararajan and Rao[5] described in 1970 its reason to be "steric overlaps" on the basis of non-bonded interaction energy calculations using molecular mechanics. On the other hand, a CPK model of the titled dp 5 homologue **1** whose α-D-glucopyranose residues have the usual $^4C_1$ conformation can be set up, suggesting that **1** should be enough to exist. Indeed, we have successfully synthesized **1** using stereoselective glycosidations participated by the *N*-phenylcarbamoyl group at the *O*-6 position[6a,b] of glycosyl donors **6**, **11** and **15**, as the followings.

Ethyl 1-thio-β-D-glucopyranoside **2**, easily prepared by treatment of β-D-glucopyranose pentaacetate with EtSH in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2[7] followed by Zemplén deacetylation (overall yield ~90%), was treated with $PhCH(OMe)_2$ in the presence of $MeSO_3H$ in MeCN to afford 4,6-*O*-benzylidene derivative **3** (86%, mp 129-130°C, from EtOAc / hexane)[8], which was di-*O*-benzylated with NaH / $PhCH_2Br$ in DMF to give compound **4** (89%, mp 129 -130°C, from EtOH / hexane)[8]. After removal of the benzylidene group of **4** by heating in 60% aqueous AcOH, the resulting **5** (mp 66.5-67.5°C, from PhMe / hexane)[8] was reacted in dry pyridine with PhNCO(1.15 mol equiv.) and then *in-one-pot* with Ac_2O to give glycosyl donor **6** (overall yield 90% from **4**; mp 128.5-129°C, from PhMe / hexane)[8].

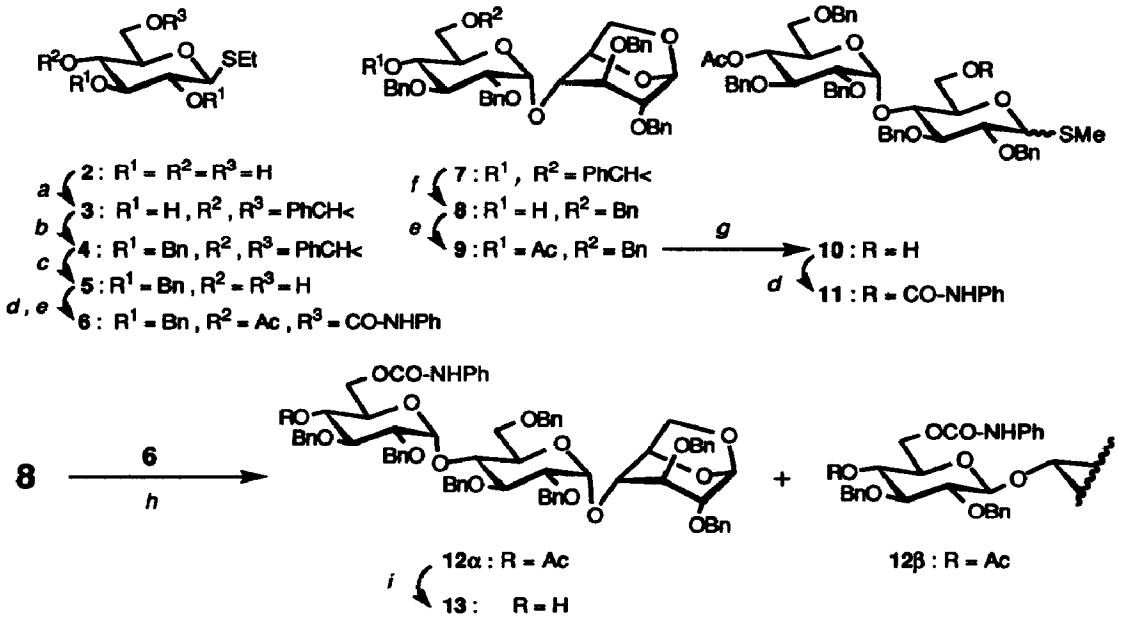
1,6-Anhydro-2,2',3,3'-tetra-*O*-benzyl-4',6'-*O*-benzylidene-β-maltose **7**[9], derived from 1,6-anhydro-β-maltose[10], was treated with $Me_3N{\cdot}BH_3$ / $MeSO_3H$ in THF to give glycosyl acceptor **8**[11] which was acetylated to 4'-*O*-acetate **9** (59% overall yield, mp 98.5-99.5°C, from PhMe / hexane)[8]. The selective thiolysis of the anhydro ring of **9** was carried out by modified Hanessian's method[12] using Me_3SiSMe / ZnI_2 in 1,2-dichloroethane (DCE) to give, after silica gel column chromatography eluted with 7:1 PhMe-EtOAc, methyl

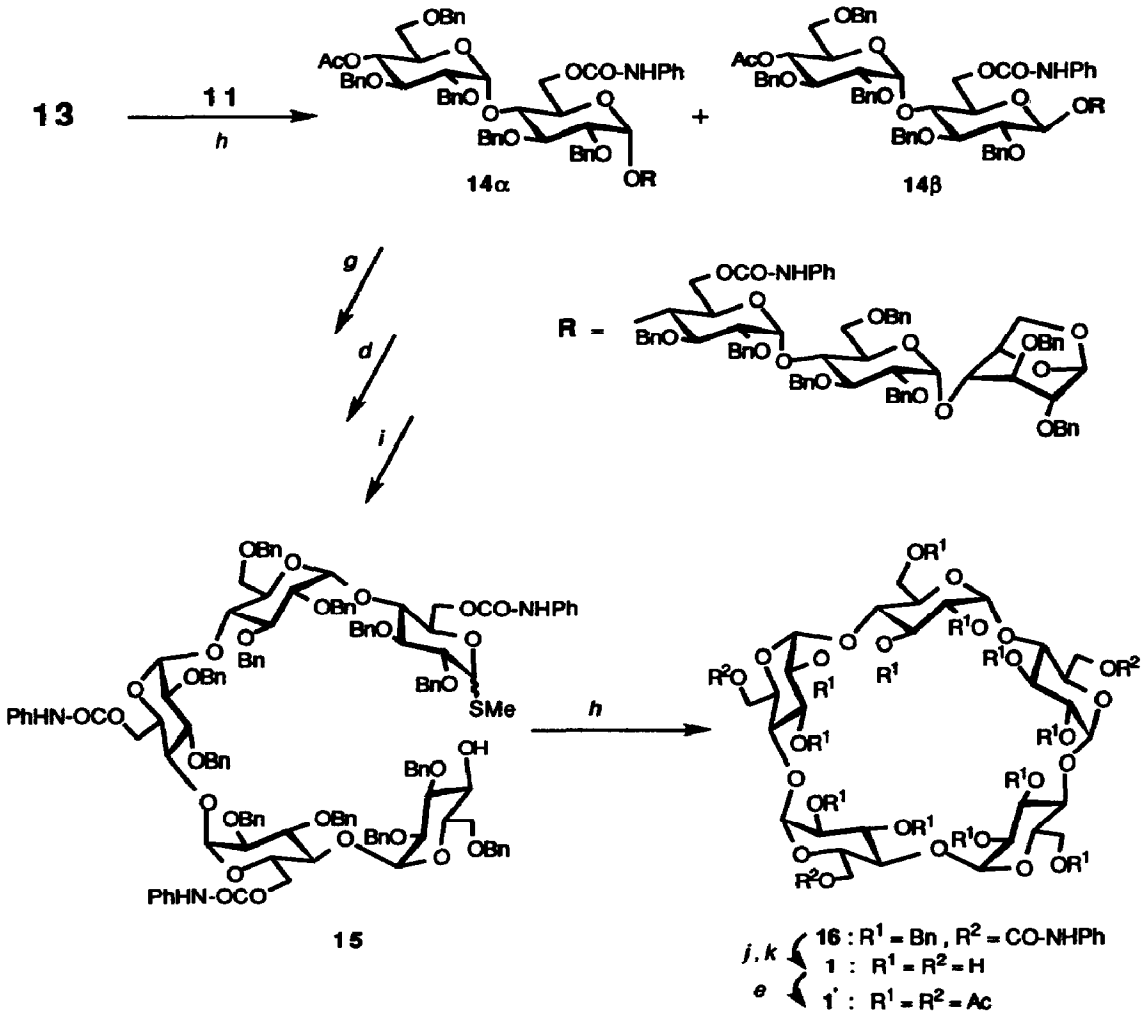
1-thio-α,β-maltoside **10** (75%, α/β = 3/2)[8]. Treatment of **10** with PhNCO in pyridine yielded another glycosyl donor **11** (~100%)[8].

Coupling of **8** with **6** (1.20 mol equiv.) was carried out in the presence of methyl triflate (MeOTf, 3.00 mol equiv.) and powdered molecular sieves 4A in DCE under argon atmosphere at room temperature, giving a α,β-mixture of trisaccharide **12** which was separated by column chromatography on silica gel eluted with 5:1 PhMe-EtOAc to **12α** (75%, R_f[13a] 0.55)[8] and **12β** (18%, R_f[12a] 0.48)[8]. Deacetylated derivative **13**, obtained from **12α**, was coupled with glycosyl donor **11** (1.26 mol equiv.) and worked up (elution with 10:1 PhMe-EtOAc) to give pentasaccharide **14α** (49%, R_f[13b] 0.56)[8] and **14β** (12%, R_f[13b] 0.43)[8].

By similar treatments as **9**→**11**, followed by deacetylation, **14α** gave a key intermediate **15** (7:5 α,β-mixture, overall yield 62%, R_f[13c] 0.2)[8]. Into a stirred solution of MeOTf (2.16×10^{-4} mol) in DCE (5 ml) in the presence of powdered molecular sieves 4A(800 mg) was added a solution of **15** (7.18×10^{-5} mol/ 7 ml) in DCE dropwise over 2.5 h under argon atmosphere at room temperature and the stirring was continued overnight, yielding the expected cyclopentaose derivative **16** (27%, R_f[13d] 0.66)[8], which was separated from other products [R_f[13d] 0.69, 0.46 and 0.15; tentatively assigned as β-linkaged isomer of **16** (10%), glycal derivative of **15**(40%) and hydrolysate of **15** (2%) at C-1, respectively][8] by repeated silica gel column chromatographies, eluted with 15:1 PhMe-EtOAc and then with 4:1 hexane-EtOAc. Removal of the *N*-phenylcarbamoyl groups of **16** (NaOMe-*i*PrOH-THF, refluxed) followed by hydrogenolysis (H_2-Pd(OH)$_2$ / MeOH-EtOAc) to give the title compound **1** (amorphous, ~quant.)[8,14], which was also characterized as per-*O*-acetate **1'** [8,15]. Positive and negative FAB-MS for **1** gave prominent peaks at m/z 832 ($M-H+Na^+$) and 809($M-H^+$), respectively.

Establishing a facile route to a preparative scale of **1** is now under way in our laboratory.





Abbreviations: Bn = $PhCH_2$, DEC = $ClCH_2CH_2Cl$

Reagents and conditions: *a*) $PhCH(OMe)_2$-$MeSO_3H$ / MeCN; *b*) NaH-BnBr / DMF; *c*) 60% aqueous AcOH, Δ; *d*) Ph-N=C=O / pyridine; *e*) Ac_2O / pyridine; *f*) $Me_3N{\cdot}BH_3$-$MeSO_3H$ / THF-molecular sieves 4A; *g*) Me_3SiSMe-ZnI_2 / DCE; *h*) MeOTf / THF-molecular sieves 4A; *i*) NaOMe / MeOH-THF (5:1); *j*) NaOMe / *i*PrOH-THF (5:1), Δ; *k*) 20% $Pd(OH)_2$-C / MeOH-AcOEt (5:1).

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7. A similar reaction using $ZrCl_4$ as a catalyst was recently reported by the following two groups:
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   (b) Takeo, K.; Maki, K.; Wada,Y.; Kitamura, S. *ibid*, **1993**, *245*, 81-96.
8. All new compounds were characterized by ^{1}H-NMR spectra. Crystalline compounds with mp recorded gave satisfactory elemental analysis. Values of $[\alpha]_D$ were measured at 25°C for $CHCl_3$ solutions unless noted otherwise: Compound **1**: + 99° (H_2O, *c* 0.075); **1'**: + 65° (*c* 0.22); **3** : −59° (*c* 1.00); **4** : −41° (*c* 0.99); **5** : −35° (*c* 1.10); **6** : −4.2° (*c* 0.95); **8** : + 4.1° (*c* 1.13); **9** : + 2.4° (*c* 1.00); **12α**: + 29° (*c* 1.45); **12β**: + 3.2° (*c* 1.05); **13** : + 16° (*c* 0.54); **14α**: + 49° (*c* 2.12); **14β**: + 37° (*c* 0.80); **16** : + 42° (*c* 1.19).
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13. Thin-layer chromatography was carried out using aluminum sheets silica gel 60 F_{254} (E.Merck, Darmstadt, Germany); Elution with toluene-EtOAc in the ratio of: (a) 5:1; (b) 7:1; (c) 10:1; (d) 6:1.
14. ^{1}H-NMR(270MHz, D_2O) for **1**: δ 5.048 (1H, d, *J* = 2.97 Hz, H-1), 4.008 (1H, dd, *J* = 9.89, 8.26 Hz, H-3), 3.927-3.800 (3H, br.m, H-5, H-6, H-6'), 3.618-3.569 (2H, m, H-2, H-4).
15. ^{1}H-NMR(270MHz, $CDCl_3$) for **1'**: δ 5.482 (1H, dd, *J* = 9.57, 7.59 Hz, H-3), 5.018 (1H, d, *J* = 3.30 Hz, H-1), 4.855 (1H, dd, *J* = 9.57, 3.30 Hz, H-2), 4.396 (2H, br.d, *J* = 2.97 Hz, H-6, H-6'), 4.210 (1H, br.dt, *J* = 8.25, 2.97 Hz, H-5), 3.833 (1H, dd, *J* = 8.25, 7.59 Hz, H-4), 2.135 (3H, s, Ac), 2.076 (3H, s, Ac), 2.069 (3H, s, Ac).

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