Cycloglycosidation of 1,2-Unsaturated Maltohexaose and Maltoheptaose Derivatives with Iodonium Addition. Conversion of α- and β-Cyclodextrins into Mono(2-deoxy) Derivatives *via* Acyclic Intermediates

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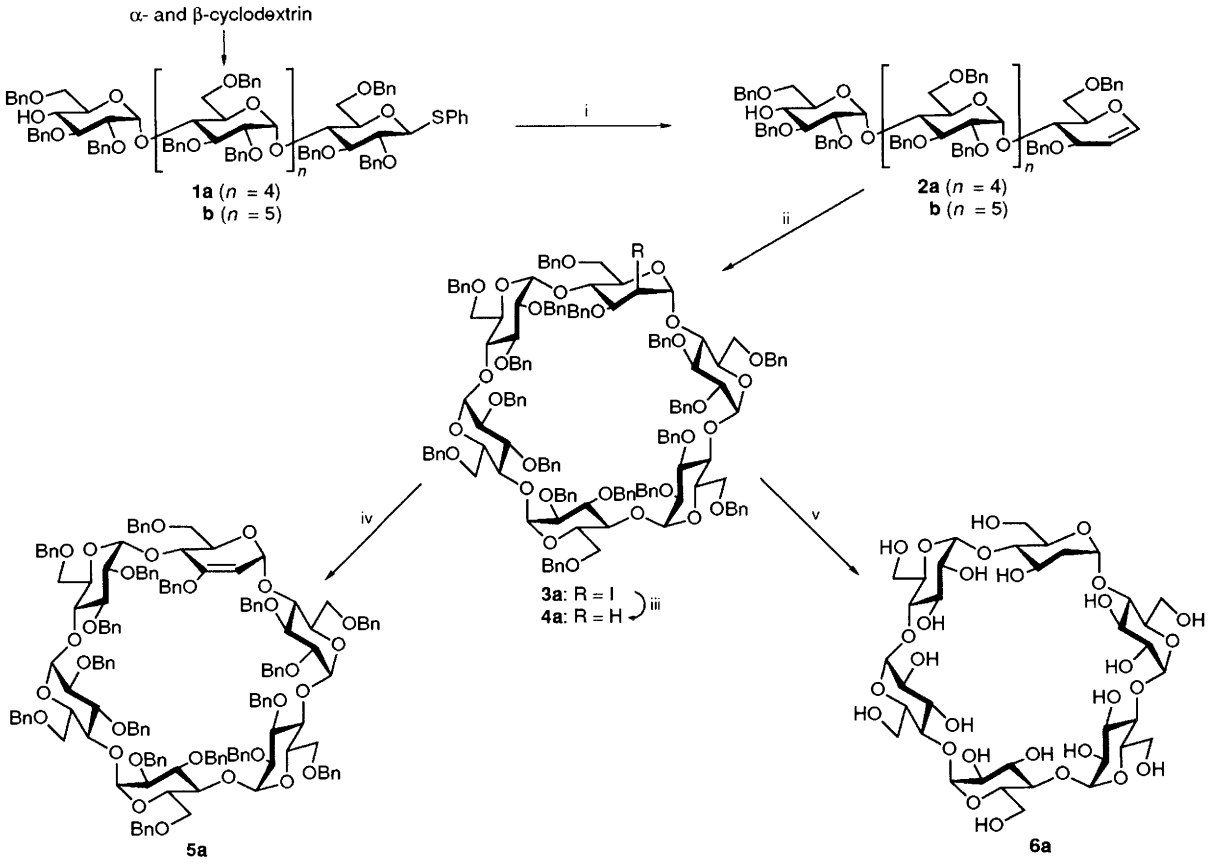
Iodonium ion treatment of 1,2-unsaturated heptadeca-*O*-benzylmaltohexaose and icosa-*O*-benzylmaltoheptaose derivatives derived from α- and β-cyclodextrins brought about their recyclization by intramolecular glycosidation, giving mono(2-deoxy-2-iodo)-α- and -β-cyclodextrin derivatives, which were converted into mono(2-deoxy)-α- and -β-cyclodextrins by radical reduction.

In our previous communication[1] we reported a new methodology for insertion of a heterogeneous sugar unit into the α-cyclodextrin (α-CD) skeleton, which included efficient fission of the starting α-CD ring, coupling with a heterogeneous monosaccharide residue, and recyclization *via* activation of a thioglycoside. In this process, a linear thioglycoside derivative **1a**, that has only one hydroxy group at C-4 of the non-reducing end, served as a crucial substrate for the above chain elongation. The potential utility of **1a** and its heptasaccharide homologue **1b**† for preparation of further new types of modified CDs has also been recognized. This communication describes a novel cycloglycosidation process employing **1a** and **1b** as key precursors and subsequent preparations of mono(2-deoxy)-α-CD **6a** and -β-CD **6b**, as well as a 2,3-unsaturated α-CD derivative **5a** that is indicative of a wide range of further manipulations. In this work we achieved a one-step conversion of **1a** and **1b** into their glycal analogues, and their subsequent cyclization *via* glycosidation initiated by iodonium addition. The choice of this route was stimulated by recent results on the conversion of thioglycosides into the corresponding glycals[2] and the successful use of glycals as glycosyl donors in the preparation of linear oligosaccharides;[3] the glycosyl donors for cycloglycosidation so far have been limited to glycosyl fluorides,[4] bromide,[5] and thioglycosides.[1,6]

Treatment of the phenyl 1-thio-β-maltohexaoside **1a** with a tetrahydrofuran (THF) solution of lithium naphthalenide,[2] freshly prepared by ultrasonication of a mixture of lithium and

† This compound {$[\alpha]_D^{24}$ +69 (*c* 0.34, $CHCl_3$)} was prepared from β-cyclodextrin by the same method as for the synthesis of **1a** (ref. 1). The preparation will be reported elsewhere.



Scheme 1 *Reagents and conditions*: i, lithium naphthalenide, THF, −80 °C; ii, IDCP–molecular sieves 4A, CH_2Cl_2, 0 °C; iii, Ph_3SnH–AIBN, toluene, 80 °C, 5 min, 68%; iv, $KOBu^t$, THF, room temp., 2 h, 87%; v, H_2, 10% Pd/C, aqueous $MeOC_2H_4OH$, room temp., 87% (Bn = $PhCH_2$)

naphthalene, under argon at −80 °C afforded the glycal **2a**‡ {72%; $[\alpha]_D^{22}$ +71 (*c* 0.39, $CHCl_3$)}. The stereoselective intramolecular glycosidation of **2a** was successfully attained through addition of I^+ to the 1,2-double bond to form onium species and subsequent nucleophilic attack by the terminal hydroxy group. Thus, **2a** was treated with iodonium di-*sym*-collidine perchlorate[7] (IDCP) in the presence of 4 A molecular sieves in CH_2Cl_2 at 0 °C to give solely the cyclic hexasaccharide **3a** {48%; $[\alpha]_D^{21}$ +41 (*c* 0.10, $CHCl_3$)}, the structure of which was determined mainly on the basis of ^1H NMR spectroscopy.§ The very small coupling constants observed ($J_{1^1,2^1}$ = *ca.* 0, $J_{2^1,3^1}$ < 2 Hz) suggested the *manno*-configuration of the 2-deoxy-2-iodohexopyranose unit. Furthermore, the anomeric configuration was later assigned as α, when **3a** was converted into the 2^1-deoxy derivative **4a**. Similarly, the heptasaccharide **1b** was converted to **2b** {65%, $[\alpha]_D^{24}$ +99 (*c* 0.42, $CHCl_3$)} and then treated with IDCP, giving the cyclic heptasaccharide **3b** {25%; $[\alpha]_D^{22}$ +47 (*c* 0.21, $CHCl_3$)}.

A couple of further manipulations were undertaken on the hexasaccharide **3a**. On treatment with $KOBu^t$ in THF at room temperature, **3a** underwent smooth elimination of HI, giving the 2,3-unsaturated derivative **5a**§ {$[\alpha]_D^{24}$ +77 (*c* 0.24, $CHCl_3$)} in excellent yield. On the other hand, attempts to reduce **3a** with tri-n-butyltin hydride (Bu^n_3SnH)–2,2′-azoisobutyronitrile (AIBN) failed and gave an intractable mixture, whereas use of triphenyltin hydride (Ph_3SnH)–AIBN as the reducing agent gave good results. Thus, **3a** was treated with Ph_3SnH–AIBN in toluene under argon atmosphere at 80 °C to give the 2^1-deoxy derivative **4a** {68%; $[\alpha]_D^{22}$ +61 (*c* 0.12, $CHCl_3$)}. Its 500 MHz ^1H NMR spectrum in C_6D_6 showed signals assignable to the methylene protons at δ 1.71 (ddd, 1H, $J_{1^1,2^1ax}$ 2.8, $J_{2^1ax,2^1eq}$ 11.2, $J_{2^1ax,3^1}$ 8.0 Hz, H-2^1ax) and 2.19 (dt, 1H, $J_{1^1,2^1eq}$ 3.0, $J_{2^1ax,2^1eq}$ = $J_{2^1eq,3^1}$ = 11.6 Hz, H-2^1eq), indicating the α-configuration of the glycosidic linkage. Catalytic hydrogenolysis of **4a** with 10% Pd/C in aqueous 2-methoxyethanol gave mono(2-deoxy)-α-CD **6a**§ {87%; $[\alpha]_D^{24}$ +143 (*c* 0.21, H_2O)}. In a similar way, treatment of the mono(2-deoxy-2-iodo)-heptasaccharide **3b** homologue of **3a** with Ph_3SnH–AIBN followed by de-*O*-benzylation afforded the mono(2-deoxy)-β-CD **6b**§ {$[\alpha]_D^{24}$ +150 (*c* 0.24, H_2O)}. It is interesting that the solubilities of **6a** and **6b** in water at 25 °C were 1.2 and 1.5 times as large as those of parent CDs despite the fact that they have fewer hydrophilic groups.

‡ All new compounds gave satisfactory spectral data and elemental analyses.

§ Selected 500 MHz ^1H NMR data: **3a** (C_6D_6): δ 3.28–3.31 (m, 1H, H-3^1), 3.43 (dd, 1H, *J* 2.9, 8.3 Hz, H-2), 3.50 (dd, 1H, *J* 3.2, 7.9 Hz, H-2), 3.52 (dd, 1H, *J* 3.2, 7.9 Hz, H-2), 3.55 (dd, 1H, *J* 2.9, 7.9 Hz, H-2), 3.57 (dd, 1H, *J* 2.9, 8.3 Hz, H-2), 4.97 (d, 1H, *J* 3.2 Hz, H-1), 5.17 (d, 1H, *J* 2.9 Hz, H-1), 5.20 (d, 1H, *J* 2.9 Hz, H-1), 5.27 (d, 1H, *J* 2.9 Hz, H-1), 5.40 (d, 1H, *J* 3.2 Hz, H-1), 5.58 (s, 1H, H-1^1): **5a** (C_6D_6): δ 4.81 (d, 1H, *J* 4.1 Hz, H-2^1), 4.99 (m, 2H, H-1, 1/2 × CH_2Ph), 5.10 (m, 2H, H-1, 1/2 × CH_2Ph), 5.15 (d, 1H, *J* 2.5 Hz, H-1), 5.24 (m, 2H, H-1, 1/2 × CH_2Ph), 5.57 (d, 1H, *J* 3.0 Hz, H-1), 5.67 (d, 1H, *J* 4.0 Hz, H-1^1): **6a** (D_2O): δ 1.65 (dt, 1H, *J* 2.1, 11.6 Hz, H-2^1ax), 2.26 (ddd, 1H, *J* 1.5, 4.5, 11.6 Hz, H-2^1eq), 3.43 (t, 1H, *J* 9.5 Hz, H-4^1), 3.51 (brt, 5H, *J* 8.6 Hz, H-4^{2-6}), 3.57 (brd, 5H, *J ca.* 9.8 Hz, H-2^{2-6}), 3.89 (brt, 5H, *J* 9.5 Hz, H-3^{2-6}), 4.10 (m, 1H, H-3^1), 500 (brs, 5H, H-1^{2-6}), 5.06 (brs, 1H, H-1^1): **6b** (D_2O): δ 1.60 (dt, 1H, *J* 3.2, 12.4 Hz, H-2^1ax), 2.20 (dd, 1H, *J* 4.6, 12.7 Hz, H-2^1eq), 3.45 (brt, 6H, *J* 9.0 Hz, H-4^{2-7}), 3.51 (brd, 6H, *J* 8.9 Hz, H-2^{2-7}), 3.82 (brt, 6H, *J* 9.5 Hz, H-3^{2-7}), 4.03 (ddd, 1H, *J* 4.8, 8.3, 11.5 Hz, H-3^1), 4.94 (m, 6H, H-1^{2-7}), 5.00 (brs, 1H, H-1^1).

Compounds like **3a,b** and **5a** are expected to be of use as intermediates for preparation of wide range of modified CDs.

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