Insertion of a D-Glucosamine Residue into the α-Cyclodextrin Skeleton; A Model Synthesis of 'Chimera Cyclodextrins'

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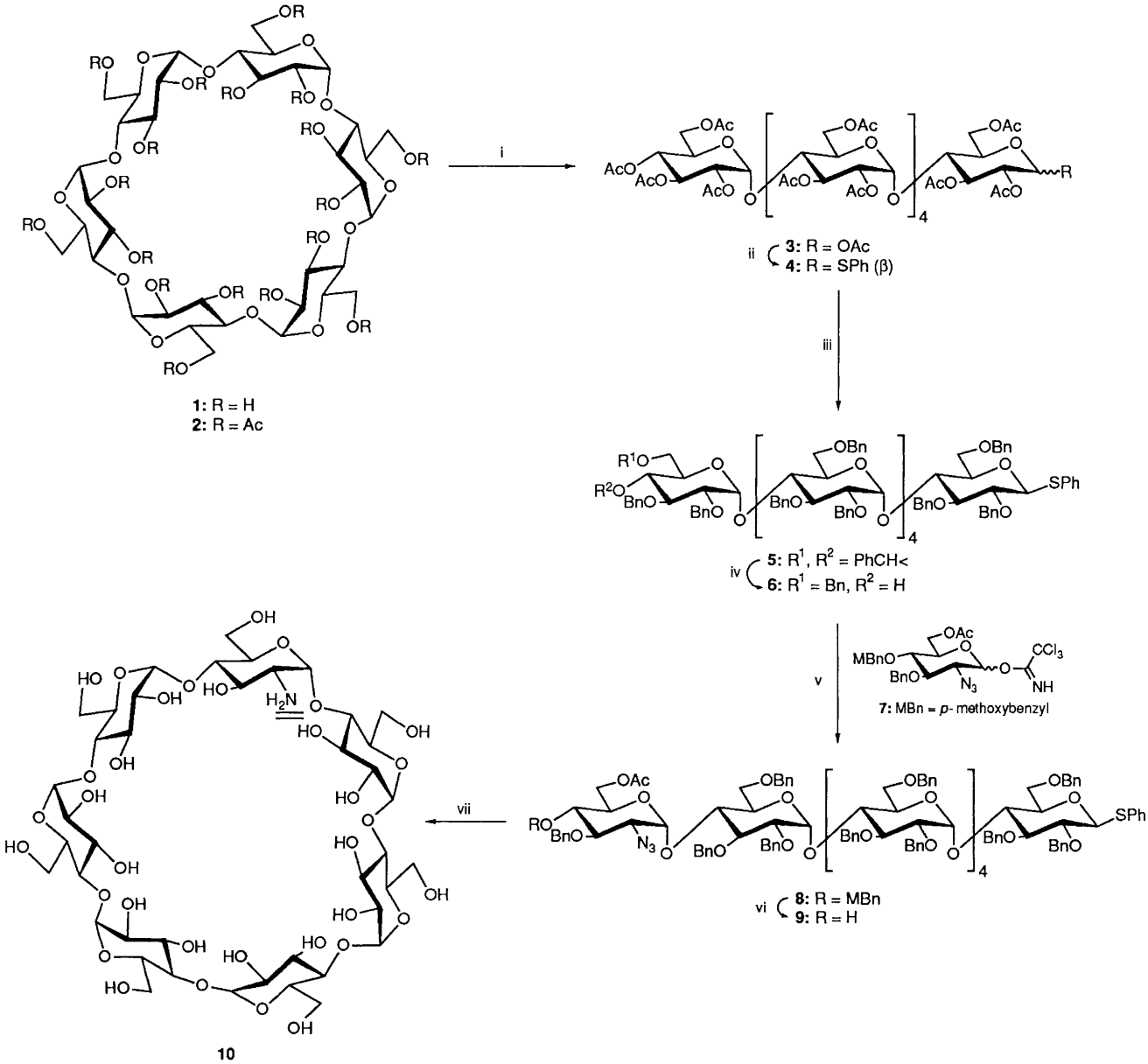
Efficient conversion of α-cyclodextrin peracetate **2** into icosa-*O*-acetylmaltohexaose **3** by acetolytic fission of one glycosidic linkage, a series of manipulations including coupling with a 2-azido-2-deoxy-D-glucopyranose derivative, recyclization and final work-up (catalytic hydrogenolysis *etc.*) gave a novel β-cyclodextrin analogue **10** containing a D-glucosamine residue as a monosaccharide component.

Although numerous investigations have been performed on the chemical modification of cyclodextrins (CDs), prompted mainly by the interest in their inclusion properties,[1] the reaction patterns employed have been quite limited owing to the structural characteristics of CDs. The extreme congestion of the hydroxy groups in CDs and difficulty in differentiation between monosaccharide components severely reduced the yields and regioselectivites of these reactions. Recently reported chemical[2] and enzymatic syntheses[3] of cyclic oligosaccharides using small building blocks do not seem to be of practical utility, because they take many laborious reaction steps or are restrictive in terms of the structure of the starting materials. The present communication describes the procedure of a widely applicable novel modification of α-CDs that includes fission of the ring, coupling with a heterogeneous sugar unit and recyclization.



Scheme 1 *Reagents and conditions*: i, Ac_2O–conc. H_2SO_4 (49:1, v:v), 50–60 °C, 20 h, 47%; ii, NaOMe–MeOH; Ac_2O–NaOAc, 130 °C; $PhSSiMe_3$–ZnI_2, [$(CH_2Cl)_2$], room temp., 20 h, 84%; iii, NaOMe–MeOH; $PhCH(OMe)_2$–TsOH dimethylformamide (DMF), 60 °C, 20 mmHg, 15 h; BnBr–NaH (DMF), 74%; iv, BH_3·Me_3N–$AlCl_3$–molecular sieves 4 Å (THF), room temp., 2 days, 67%; v, **7** (2 equiv.), Me_3SiOTf–molecular sieves AW-300 (Et_2O), −15 °C, 3 h, 39%; vi, DDQ (aq. CH_2Cl_2), 0 °C, 5 h, 65%; vii, MeOTf–molecular sieves 4 Å (Et_2O), room temp., 2 days; NaOMe–MeOH; H_2–Pd/C ($MeOC_2H_4OH$–0.1 mol dm^{-3} HCl), 39%

We found that acetolysis of α-CD peracetate[4] **2** could be controlled to give icosa-*O*-acetylmaltohexaose **3** as a result of the fission of only one glycosidic bond. This observation was in contrast to the direct acetolysis of α-CD **1** which gives a complex mixture of products, owing to the uncontrollable exothermic nature of the reaction. Thus, **2** was treated with Ac_2O–conc. H_2SO_4 (49 : 1, v : v) at 50–60 °C for 20 h, giving **3**† (α : β = 5.3 : 1) in 46% yield together with unchanged **2** in 47% yield. The yield of **3** based on the starting material consumed was 87%. This acetolysis was also applicable to β- and γ-CD peracetates,[4] giving maltoheptaose and maltooctaose peracetates in 41 and 52% yields with recovery of the starting materials in 49 and 37% yields, respectively.

Both terminals of the acyclic hexasaccharide derivative **3** were modified efficiently to give **6**, one of the key intermediates, as shown in Scheme 1. Lewis acid-catalysed thioglycosidation[5] of **3** (α : β = 1 : 5) with $PhSSiMe_3$–ZnI_2, gave the phenyl β-thioglycoside **4** {84%; $[\alpha]_D^{23}$ +112° (*c* 0.21, $CHCl_3$)}, which was converted to the 4⁶,6⁶-*O*-benzylidene derivative **5** {74%; $[\alpha]_D^{23}$ +52° (*c* 0.24, $CHCl_3$)} by de-*O*-acetylation followed by selective benzylidenation and benzylation. Reductive ring opening of the benzylidene acetal[6] with BH_3·Me_3N–$AlCl_3$ in tetrahydrofuran (THF) afforded the 4⁶-hydroxy derivative **6** {67%; $[\alpha]_D^{23}$ +77° (*c* 0.24, $CHCl_3$)}.

Among many candidates for the heterogeneous monosaccharide unit to be inserted, D-glucosamine was first chosen as a model. Its precursor, a 2-azido-2-deoxy-D-glucose derivative,‡ was prepared starting from D-mannose and activated as a glycosyl donor by conversion into the corresponding trichloroacetimidate **7**. Coupling between **6** and **7** was conducted in Et_2O according to the Schmidt procedure,[7] giving the desired heptasaccharide **8** {$[\alpha]_D^{23}$ +74° (*c* 0.14, $CHCl_3$)} in 39% yield based on **6**. After removal of the *O*-*p*-methoxybenzyl group by 2,3-dichloro-5,6-dicyano-1,4-benzo quinone (DDQ) oxidation, the resulting 4-hydroxy derivative **9** underwent recyclization.[7] Thus, treatment of **9** with MeOTf (Tf = SO_2CF_3) in Et_2O gave the fully protected cyclic heptasaccharide§ in 41% yield.[8] Finally, de-*O*-acetylation followed by hydrogenolysis with 10% Pd/C gave the expected 'chimera β-CD' **10**,¶ which kept the D-glucosamine residue as a constituent, in 70% yield. The solubility of **10** was dependent on pH; it was 4.4 times more soluble than a usual β-CD in water and 12 times, in 0.1 mol dm^{-3} HCl.

The present procedure can be adapted to give wide variety of 'chimera CDs', by modification of the acyclic intermediate and by choice of the sugar unit to be inserted in the ring.

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

‡ The precursor, 6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-D-glucopyranose {m.p. 111–112 °C (EtOH); $[\alpha]_D^{23}$ +50.6° (*c* 0.20, $CHCl_3$)}, was synthesized from known 1,6-anhydro-2,3-*O*-benzylidene-β-D-mannose (M. Kloosterman, M. P. de Nijs and J. H. van Boom, *J. Carbohydr. Chem.*, 1986, **5**, 215) *via* 1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-β-D-glucopyranose. This preparation will be reported elsewhere.

§ *Selected spectra data*: $[\alpha]_D^{23}$ +55° (*c* 0.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 1.88 (s, 3H), 4.70 (d, 1H, *J* 3.5 Hz), 4.96 (d, 1H, *J* 3.0 Hz), 4.98 (d, 1H, *J* 3.0 Hz), 5.06 (d, 1H, *J* 3.5 Hz), 5.41 (d, 1H, 3.9 Hz) and 5.48 (d, 1H, *J* 3.7 Hz); IR ν_{max}/cm^{-1} (film) 1735 and 2080.

¶ *Selected spectral data* for **10**: $[\alpha]_D^{23}$ +146° (*c* 0.18, H_2O); ^1H NMR (400 MHz, D_2O), δ 2.80 (dd, 1H, *J* 4.0, 9.6 Hz, H-2 of GlcN), 4.93 (d, 1H, *J* 4.0 Hz, H-1 of GlcN) and 4.98–5.04 (m, 6H, 6 × H-1 of Glc); in D_2O–DCl δ 3.34 (dd, 1H, *J* 3.4, 10.7 Hz, H-2 of GlcN), 4.04 (t, 1H, *J* 8.6 Hz, H-3 of GlcN), 4.95–4.98 (m, 6H, 6 × H-1 of Glc) and 5.19 (d, 1H, *J* 3.4 Hz, H-1 of GlcN).