Cyclic Dimerization of 1,2-Unsaturated Maltotriose Derivatives with Iodinium Addition; One-pot Preparation of a Fully Methylated $2^A,2^D$-Dideoxy-$2^A,2^D$-diiodocyclohexasaccharide

Nobuo Sakairi and Hiroyoshi Kuzuhara*

The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

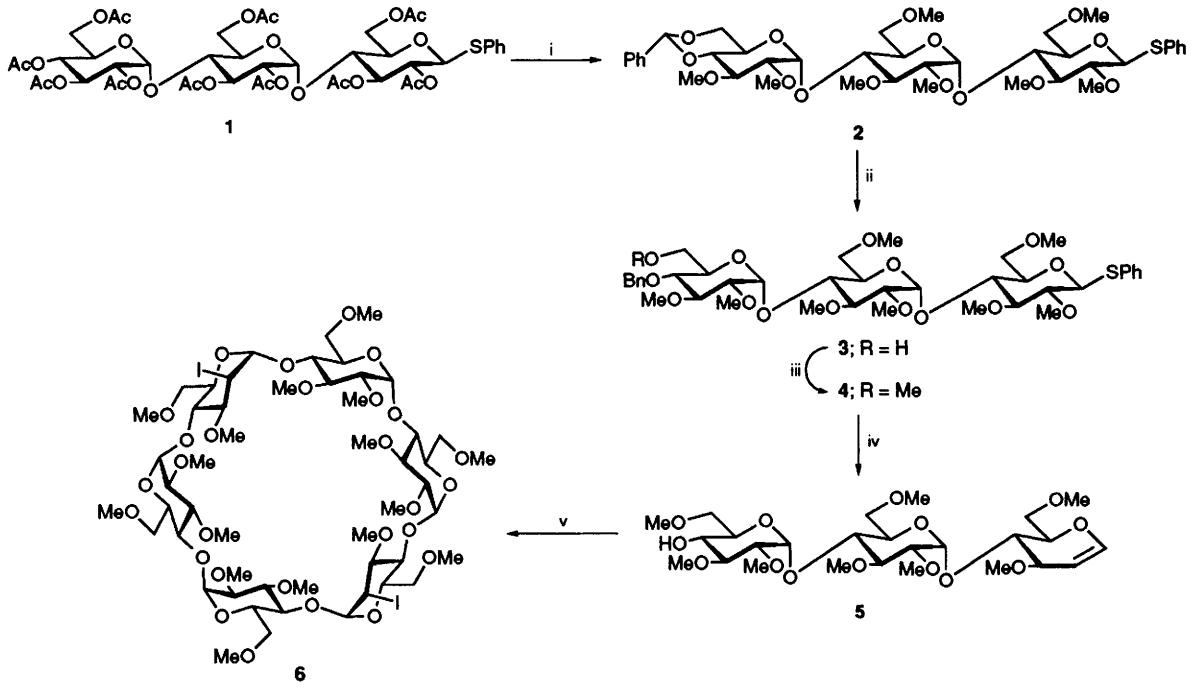
Iodonium ion treatment of 1,2-unsaturated octa-*O*-methylmaltotriose having a sole hydroxy group at the 4″-position results in dimerization of the trisaccharide derivative with simultaneous cyclization, giving a fully methylated cyclohexasaccharide consisting of four α-D-glucopyranosyl residues and two 2-deoxy-2-iodo-α-D-mannopyranosyl residues.

Regio- and/or stereo-selective modification of cyclodextrins (CDs) have attracted much attention for both academic and industrial applications.[1] The characteristic structural feature of CDs, however, has narrowed the possibilities of such modification.

Recently, we succeeded in the cycloglycosidation of 1,2-unsaturated maltohexaose derivatives with iodonium addition, giving mono(2-deoxy-2-iodo)cyclohexasaccharides.[2] Here we describe the one-pot synthesis of a $2^A,2^D$-dideoxy-$2^A,2^D$-diiodocyclohexasaccharide derivative starting from a trisaccharide glycal derivative by the extended application of the previous methodology. Thus, iodonium ion treatment of the trisaccharide starting material brought about simultaneous dimerization and cyclization to give a cyclic diiodo compound with two-fold symmetry.

The key trisaccharide glycal **5** was prepared from the thioglycoside **1**† {$[\alpha]_D^{24}$ + 58 (*c* 0.24, $CHCl_3$)} derived from the known undeca-*O*-acetyl-β-maltotriose[3] by the Lewis acid catalysed thioglycosideration as shown in Scheme 1. Thus, **1**

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



Scheme 1 *Reagents and conditions*: i, NaOMe–MeOH; $PhCH(OMe)_2$–TsOH, *N*,*N*-dimethylformamide (DMF), 60 °C, 20 mmHg, 6 h; $(MeO)_2SO_2$–NaH, DMF, room temp., overall 74%; ii, $LiAlH_4$–$AlCl_3$, Et_2O–CH_2Cl_2, room temp., 3 h, 93%; iii, $(MeO)_2SO_2$–NaH, DMF–THF, room temp., 88%; iv, lithium naphthalenide (8 equiv.), THF, −80 °C → room temp., overnight, 96%; v, IDCP (5 equiv.) molecular sieves 4 A, CH_2Cl_2, room temp., 1 day, 33%

was subjected to de-*O*-acetylation followed by *O*-benzylidenation and *O*-methylation, giving the 4,6-*O*-benzylidene derivative **2** {$[\alpha]_D^{28}$ + 74 (*c* 0.24, $CHCl_3$)}. Reductive ring opening of the benzylidene acetal under the conditions of Lipták *et al.*[4] afforded the 6″-hydroxy derivative **3** {$[\alpha]_D^{28}$ + 71 (*c* 0.22, $CHCl_3$)}, which was readily methylated to give the 4″-*O*-benzyl derivative **4** {$(\alpha]_D^{28}$ + 88 (*c* 0.49, $CHCl_3$)} in 82% overall yield. Upon treatment with an excess of lithium naphthalenide[5] under slighlty vigorous condition (−80 °C to room temp. overnight, in tetrahydrofuran (THF) under an argon atmosphere), **4** underwent a radical reductive elimination at the C-1 and C-2 positions with concomitant de-*O*-benzylation at C-4″ to give the desired hydroxy glycal **5**‡ {$[\alpha]_D^{28}$ + 143 (*c* 0.26, $CHCl_3$)} in almost quantitative yield.

Compound **5** was treated with iodonium di (*sym*-collidine) perchlorate[6] (IDCP) in the presence of 4 A molecular sieves in CH_2Cl_2 at room temp. for 1 day. TLC of the reaction mixture showed that more than 3 compounds were produced, one of which moved faster on TLC than the starting material. The fast-moving product§ {$[\alpha]_D^{28}$ + 101 (*c* 0.27, $CHCl_3$)} was isolated as an amorphous powder in moderate yield by extractive work-up followed by column chromatography on silica gel (benzene–acetone, 3:1 v/v). Fast atom bombardment mass spectrometry (FABMS) of the product showed *m/z* 1439.3 $[M + Na]^+$ and 1289.3 $[M - I]^+$ signals and determined that the product was a dimer of the trisaccharide. ^1H and ^{13}C NMR spectroscopy revealed a simple pattern compatible with regular trisaccharide repeating units, which consisted of two α-D-glucopyranosyl residues [δ_H 5.05 (d, *J* 3.4 Hz, 1-H), 5.03 (d, *J* 3.3 Hz, 1-H) and δ_C 99.8, 99.7 (C-1)] and a 2-deoxy-2-iodo-α-D-mannopyranosyl residue [δ_H 5.21 (s, 1-H-1) and δ_C 104.6 (C-1)]. Therefore, the product was elucidated as the 2^A,2^D-dideoxy-2^A,2^D-diiodocyclohexasaccharide **6**; yield of cyclization was 33%.

The cyclic hexasaccharide **6** possessed the ability to form a host–guest complex. Thus, the UV–VIS absorption spectrum of methyl orange in aqueous solution (3×10^{-5} mol dm^{-3}) at pH 1.0 showed a peak at 505 nm with a molar extinction coefficient of ε 3.3×10^4 dm^3 mol^{-1} cm^{-1}, which decreased to ε 2.4×10^4 dm^3 mol^{-1} cm^{-1} by addition of **6** (1×10^{-3} mol dm^{-3}). The observed strong hypochromic effect suggested that **6** accommodated the methyl orange molecule in its cavity.[7]

By selective modification of the acyclic maltotriose starting material,[3,8] the methodology presented here allows the efficient preparation of finely designed cyclohexasaccharides, which might be useful for construction of novel enzyme mimics or receptor models.

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‡ Selected ^1H NMR (400 MHz, $CDCl_3$) data: δ 2.86 (s, 1 H, OH), 3.22 (dd, 1 H, *J*, 3.5, 9.8 Hz, 2-H), 3.29 (dd, 1 H, *J* 3.4, 9.8 Hz, 2-H), 3.32, 3.35, 3.39, 3.40, 3.49, 3.52, 3.58, 3.63 (8 × s, 8 × 3H, 8 × Me), 4.83 (dd, 1 H, *J* 2.5, 6.3 Hz, 2^1-H), 5.59 (d, 1 H, *J* 3.9 Hz, 1-H), 5.66 (d, 1 H, *J* 3.9 Hz, 1-H-1), and 6.44 (d, 1 H, *J* 5.9 Hz, 1^1-H).

§ *Selected spectral data*: ^1H NMR (400 MHz, $CDCl_3$); δ 3.15 (dd, 2 H, *J* 3.4, 9.8 Hz, 2-H), 3.18 (dd, 2 H, *J* 3.1, 9.5 Hz, 2-H), 3.38, 3.39, 3.41, 3.46, 3.47, 3.62, 3.63 (s, Me), 3.84 (dd, 2 H, *J* 4.0, 10.7 Hz, 6-H), 3.91 (dd, 2 H, *J* 4.3, 10.3 Hz, 6-H), 4.57 (br d, 2 H, *J* 4.3 Hz, 2^1, 2^4-H), 5.03 (d, 2H, *J* 3.4 Hz, 1-H), 5.05 (d, 2 H, *J* 3.4 Hz, 1-H), and 5.21 (br s, 2 H, 1^1, 1^4-H); ^{13}C NMR (67.8 MHz, $CDCl_3$); δ 33.2, 57.6, 57.9, 58.0, 59.0, 59.1, 59.2, 61.0, 61.7, 70.7, 70.9, 71.1, 72.0, 73.2, 77.2, 80.3, 80.8, 81.0, 81.2, 82.0, 82.1, 82.5, 99.7, 99.8 and 104.6.