One-pot regioselective synthesis of $2^I,3^I$-*O*-(*o*-xylylene)-capped cyclomaltooligosaccharides: tailoring the topology and supramolecular properties of cyclodextrins†

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Received (in Austin, TX, USA) 16th April 2007, Accepted 15th May 2007
First published as an Advance Article on the web 8th June 2007
DOI: 10.1039/b705644c

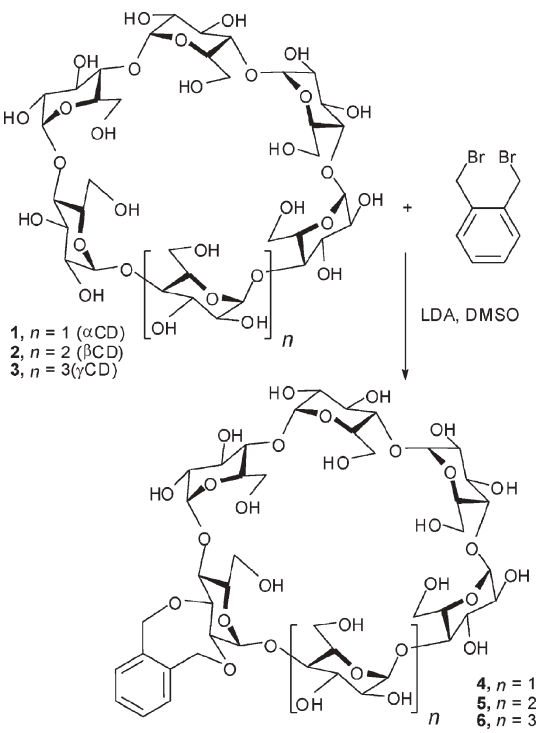
The α,α′-dibromo-*o*-xylylene cap has been installed at the secondary hydroxyls of a single glucopyranosyl residue in cyclodextrins in one pot and with total regioselectivity; the resulting cyclic ether acts as a removable hinge, allowing selective elaboration of the secondary face and modulating both the self-association and the inclusion capabilities of the hosts.

Applications of cyclomaltooligosaccharide (cyclodextrin, CD) derivatives in fields such as site-specific drug delivery,[1] artificial enzymes,[2] catalysis,[3] molecular machines[4] or supramolecular sensing[5] critically depend on the development of efficient methods to manipulate their topology and recognition features with the environment.[6] Despite intense efforts, most of the current methods are restricted to the mono-, per- or oligofunctionalization at the primary hydroxyl rim. Regioselective modification at two hydroxyls offers the opportunity to graft a set of pendant ("flexible caps") or two-point bridging groups ("rigid caps") appropriately arranged to act cooperatively in complexation, chelation or catalysis.[7] A guest-sensitive group linked through a bidentate hinge at the cavity entrance may additionally act as a functional element to modulate aggregation and inclusion capabilities. Although the wider secondary rim shows a very high interest for such goals, the difficulties associated with primary *vs.* secondary hydroxyl reactivity competition as well as positional isomerism makes difunctionalization at this face a far more complicated challenge.[8]

Herein we report the successful one-pot regioselective differentiation of both secondary hydroxyls of a single D-glucopyranosyl residue in CDs by using α,α′-dibromo-*o*-xylene as a complementary group for the *trans*-diequatorial 1,2-diol segment.[9] Treatment of CDs **1–3** with the above reagent in DMSO in the presence of lithium diisopropylamide (LDA) afforded the corresponding $2^I,3^I$-*O*-(*o*-xylylene) derivatives **4–6** in 28–33% yield after a simple silica gel column chromatography (Scheme 1).

The regioselectivity of this direct di-*O*-etherification reaction is remarkable. Statistical calculations indicate that 27, 33 and 36 regioisomers are possible for di-*O*-protection of α, β and γCD, respectively, of which only one is obtained in the three cases. Only traces of the products of monosubstitution at the primary position O-6 were detected by HPLC and MS (secondary *vs.* primary position reaction ratio >20 : 1).

The combination of free and xylylene-protected hydroxyls in the CD platform, formally equivalent to a regioselective di-*O*-benzylation at the wider secondary rim, offers new and very versatile possibilities to introduce molecular diversity in a controlled manner.[10] The method is particularly powerful given that removal of the *o*-xylylene group can be effected cleanly and quantitatively, after elaboration of some or all the other hydroxyls, by standard hydrogenolysis to regenerate the diol with the original



Scheme 1 One-pot synthesis of the $2^I,3^I$-*O*-(*o*-xylylene-capped) cyclodextrin derivatives **4–6**.

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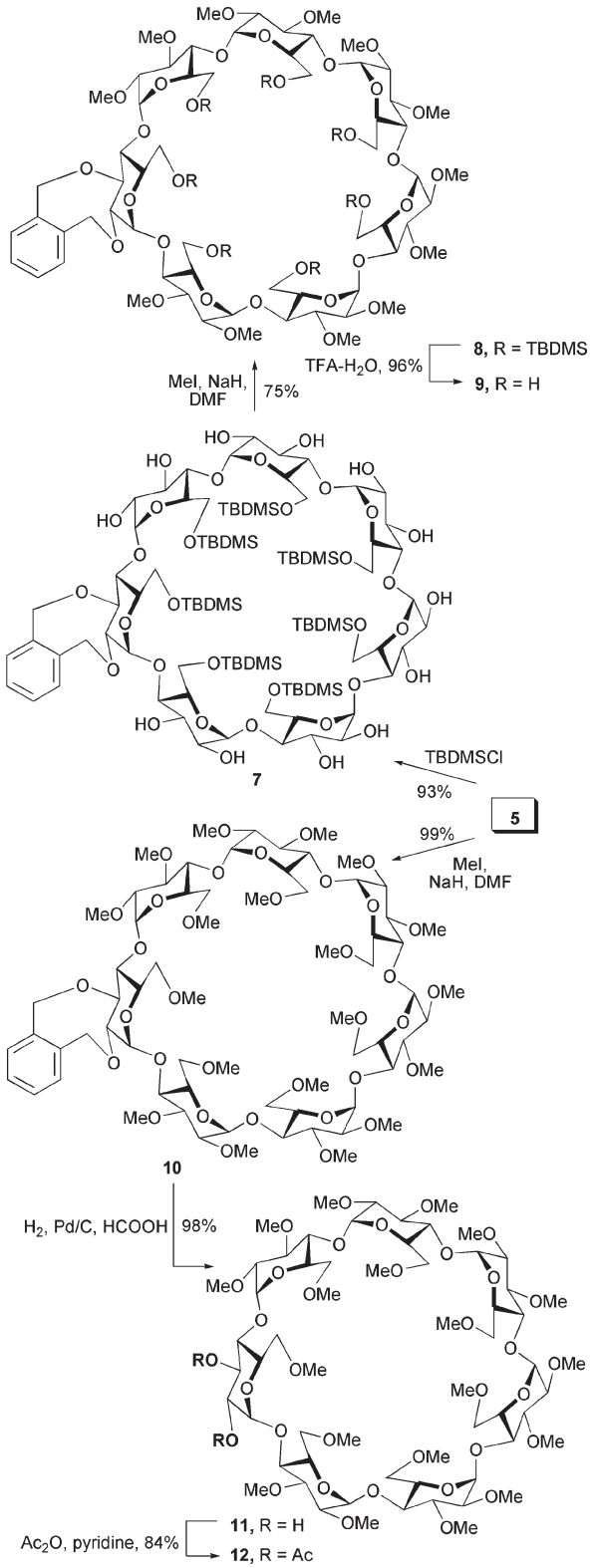
† Electronic supplementary information (ESI) available: Experimental details, copies of the NMR spectra and procedures for evaluation of aggregation and complexing properties. See DOI: 10.1039/b705644c

configurational pattern. The synthetic utility of the selective protection in the βCD series is highlighted in Scheme 2.

Silylation of the primary hydroxyl groups of **5** (→**7**), subsequent methylation of the secondary hydroxyls (→**8**) and hydrolysis of the silyl ether groups afforded the face-differentiated derivative **9**. Direct methylation of **5** afforded the $2^{I},3^{I}$-*O*-(*o*-xylylene)-capped TRIMEB (per-*O*-Me βCD; R = Me in **11**) analogue **10**, which after hydrogenolysis provided **11** having two vicinal free OH groups at the secondary face suitable for further functionalization. Acetylation yielded the corresponding diacetate **12**, whose ^{1}H NMR spectrum showed the expected lowfield shift of the H-2^{I} and H-3^{I} resonances.



Scheme 2 Synthesis of selectively modified β-cyclodextrin derivatives *via* the corresponding $2^{I},3^{I}$-*O*-(*o*-xylylene) derivative **5**.

Molecular modeling‡ suggested that the mobility of the aromatic ring in xylylene-capped derivatives is considerably restricted as compared with monosubstituted compounds, the unsaturated cyclic diether acting as a hinge that prevents self-inclusion. Accordingly, NOE experiments for **10** at low (<1 mM) concentration in D_2O indicated through-space relationships between the aromatic protons and methyl groups, in agreement with a prevalent "capped" conformation with the xylylene moiety lying over the wider rim of the CD torus. Dynamic ^{1}H NMR evidenced, however, the existence of fast chemical exchange processes, suggesting a temperature dependent conformational change from the "capped" to the "open" arrangement. Variable-concentration NMR spectra unambiguously pointed to an aggregation phenomena associated to that conformational change. The process was fully reversible and was disrupted in $CDCl_3$ solution, supporting the hydrophobic nature of the interactions at work. From the chemical shift variations of spectra recorded at 25 °C for different concentrations, an association number $n = 2$ was derived (Fig. 1).[11]

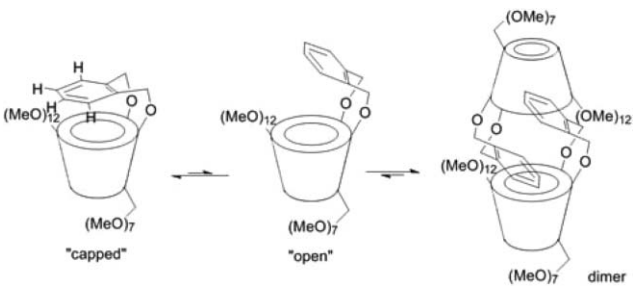


Fig. 1 Schematic representation of the conformational and aggregation equilibria for compound **10**.

Fluorescent decay measurements (λ_{ex} = 260 nm; λ_{em} = 288 nm) further supported the existence of an enthalpy-driven monomer/dimer equilibrium. Thus, in addition to a short lifetime component (0.1–0.4 ns), due to an small solvent scattering contribution, two other main components of 3.5–5 and 8–15 ns, ascribable to the monomer and dimer species, respectively, were identified. The dimerization equilibrium constant ($K = 200 \pm 85$ M^{-1} at 25 °C) was obtained from nonlinear regression analysis of the plot of the intensity weighted average lifetime (τ) against concentration of **10**. A standard van't Hoff analysis for K values obtained in the 5–45 °C temperature range yielded $\Delta H^{\circ} = -22.7 \pm 4.4$ kJ mol^{-1} and $\Delta S^{\circ} = -34 \pm 15$ J K^{-1} mol^{-1} (Fig. 2).

The monomer/dimer equilibrium is fast at room temperature in the NMR time scale, meaning that a fast "capping"/"opening" of the wider entrance to the cavity also operates, thereby endowing these hinged CDs with an additional selection mechanism against guests. In a proof-of-principle study, the association constant (K_{as})

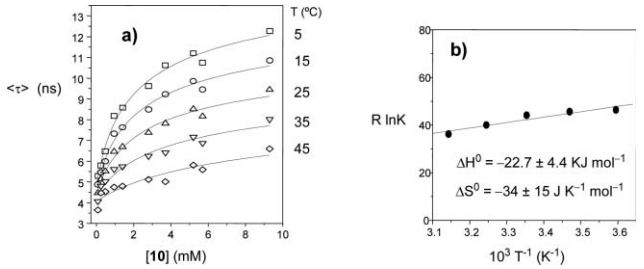


Fig. 2 Average lifetimes as a function of total concentration of **10** to determine *K* at different temperatures (a) and linear van't Hoff plot for the monomer-to-dimer equilibrium (b).

for the **10**: octyl β-D-glucopyranoside (OG) complex showed a three-fold increase as compared with the corresponding complex between TRIMEB and OG (350 ± 10 *vs.* 115 ± 2 M^{-1}, respectively),[12] which must be attributed, essentially, to specific interactions implying the xylylene cap. The observation of NOE contacts between aromatic protons in the host and sugar protons in OG strongly supports this assumption (Fig. 3).[13]

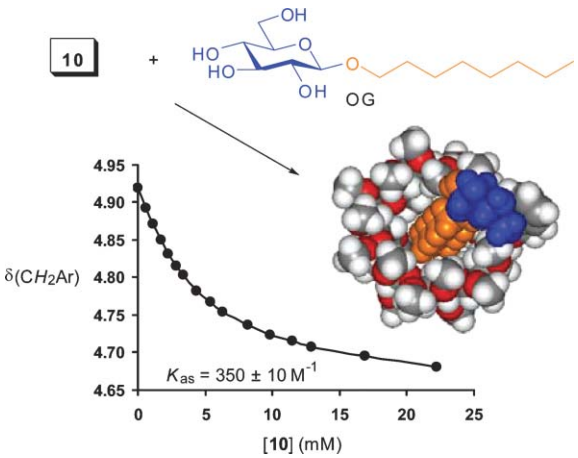


Fig. 3 Binding isotherm for the **10**: OG complex. A three-dimensional model is depicted.

In summary, we have reported the first successful preparation of $2^I,3^I$-*O*-capped CDs. The incorporation of the *o*-xylylene group to the vicinal diol system is effected in one-pot with high regioselectivity. The resulting selectively protected derivatives are important intermediates for selective difunctionalization of CDs at the secondary face and can be considered as a new type of hinged receptors for molecular recognition.

This work was supported by the Spanish MEC (contract numbers CTQ2006-15515-C02-01/BQU, CTQ2004-05854/BQU and CTQ2005-04710/BQU), the Junta de Andalucía (P06-FQM-01601), the Comunidad de Madrid (S-055/MAT/0227) and the Conseil Régional de Picardie (IBFBio).

Notes and references

‡ Calculations were performed with the MACROMODEL 6.0 package and the GB/SA continuous solvent model for water.

1 (*a*) A. Vargas-Berenguel, F. Ortega-Caballero and J. M. Casas-Solva, *Mini-Rev. Org. Chem.*, 2007, **4**, 1; (*b*) J. M. García Fernández, C. Ortiz Mellet and J. Defaye, *J. Inclusion Phenom. Macrocycl. Chem.*, 2006, **56**, 149; (*c*) K. Hattori, A. Kenmoku, T. Mizuguchi, D. Ikeda, M. Mizuno and T. Inazu, *J. Inclusion Phenom. Macrocycl. Chem.*, 2006, **56**, 9; (*d*) J. M. Benito, M. Gómez-García, C. Ortiz Mellet, I. Baussanne, J. Defaye and J. M. García Fernández, *J. Am. Chem. Soc.*, 2004, **126**, 10355; (*e*) N. Mazzaglia, D. Forde, D. Garozzo, P. Malvagna, B. J. Ravoo and R. Darcy, *Org. Biomol. Chem.*, 2004, **2**, 957; (*f*) C. Ortiz Mellet, J. Defaye and J. M. García Fernández, *Chem.–Eur. J.*, 2002, **8**, 1982; (*g*) K. Takahashi, *Chem. Rev.*, 1998, **98**, 2013.

2 (*a*) J. Bjerre, T. H. Fenger, L. G. Marinescu and M. Bols, *Eur. J. Org. Chem.*, 2007, 704; (*b*) H. L. Zen, B. Zhao and Z. B. Wang, *J. Inclusion Phenom. Macrocycl. Chem.*, 2006, **56**, 17; (*c*) L. G. Marinescu and M. Bols, *Angew. Chem., Int. Ed.*, 2006, **45**, 4590; (*d*) C. Rousseau, F. Ortega-Caballero, L. U. Nordstrom, B. Christensen, T. E. Petersen and M. Bols, *Chem.–Eur. J.*, 2005, **11**, 5094; (*e*) F. Ortega-Caballero, C. Rousseau, B. Christensen, T. E. Petersen and M. Bols, *J. Am. Chem. Soc.*, 2005, **127**, 3238; (*f*) R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997.

3 (*a*) Z.-Y. Dong, S.-Z. Mao, K. Liang, J.-Q. Liu, G.-M. Luo and J.-C. Shen, *Chem.–Eur. J.*, 2006, **12**, 3575; (*b*) F. Hapiot, S. Tilloy and E. Monflier, *Chem. Rev.*, 2006, **106**, 767; (*c*) C. Jeunesse, D. Armspach and D. Matt, *Chem. Commun.*, 2005, 5603.

4 (*a*) R. J. Coulston, H. Onagi, S. F. Lincoln and C. J. Easton, *J. Am. Chem. Soc.*, 2006, **128**, 14750; (*b*) H. Tian and Q. C. Wang, *Chem. Soc. Rev.*, 2006, **35**, 364; (*c*) G. Wenz, B. H. Han and A. Muller, *Chem. Rev.*, 2006, **106**, 782.

5 (*a*) Y. Liu, N. Zhang, Y. Chen and L. H. Wang, *Org. Lett.*, 2007, **9**, 315; (*b*) A. Yamauchi, Y. Sakashista, K. Hirose, T. Hayashita and I. Suzuki, *Chem. Commun.*, 2006, 4312; (*c*) Y. Liu and Y. Chen, *Acc. Chem. Res.*, 2006, **39**, 681; (*d*) N. Smiljanic, V. Moreau, D. Yockot, J. M. Benito, J. M. García Fernández and F. Djedaïni-Pilard, *Angew. Chem., Int. Ed.*, 2006, **45**, 5465.

6 A. R. Khan, P. Forgo, K. J. Stine and V. T. D'Souza, *Chem. Rev.*, 1998, **98**, 1977.

7 E. Engeldinger, D. Armspach and D. Matt, *Chem. Rev.*, 2003, **103**, 4147.

8 The recorded examples generally imply prior selective protection of the primary face and/or statistic sulfonylation. Alternatively, the use of rigid disulfonyl reagents has been attempted. In both cases, however, further transformations lead to compounds that do not keep the initial D-gluco configuration at the corresponding monosaccharide subunits. For selected references, see: (*a*) D.-Q. Yuang, T. Tahara, W.-H. Chen, Y. Okabe, C. Yang, Y. Yagi, Y. Nogami, M. Fukudome and K. Fujita, *J. Org. Chem.*, 2003, **68**, 9456; (*b*) K. Teranishi, *Tetrahedron*, 2003, **59**, 2519; (*c*) K. Teranishi, *J. Inclusion Phenom. Macrocycl. Chem.*, 2002, **44**, 313. A remarkable exception is the selective bis(demethylation) of permethylated α and βCD by reaction with DIBAL. See: (*d*) B. du Roizel, J.-P. Baltaze and P. Sinaÿ, *Tetrahedron Lett.*, 2002, **43**, 2371.

9 (*a*) P. Balbuena, E. M. Rubio, C. Ortiz Mellet and J. M. García Fernández, *Chem. Commun.*, 2006, 2610; (*b*) M. I. García-Moreno, M. Aguilar, C. Ortiz Mellet and J. M. García Fernández, *Org. Lett.*, 2006, **8**, 297.

10 For a noteworthy example of double differentiation at the primary face of CDs, see: (*a*) T. Lecourt, A. Herault, A. J. Pearce, M. Sollogoub and P. Sinaÿ, *Chem.–Eur. J.*, 2004, **10**, 2960; (*b*) A. J. Pearce and P. Sinaÿ, *Angew. Chem., Int. Ed.*, 2000, **112**, 3756.

11 Additional NMR studies confirmed the head-to-head (HH) architecture for the dimer species as depicted in Fig. 1.

12 In both cases the 1 : 1 stoichiometry was confirmed by Job's plots.

13 Preliminary inclusion complex studies for **10** and D,L-2-(4-isobutylphenyl)propionic acid (ibuprofen, IB), have been additionally carried out. NMR titration experiments evidenced an almost ten-fold increase in the association constant for the 1 : 1 **10**·IB complex (K_{as} = 1.5 × 10^4 M^{-1}) as compared with the corresponding TRIMEB·IB complex (K_{as} = 2.0 × 10^3 M^{-1}). Although the current data are not conclusive, π–π stacking might be responsible for the observed stability enhancement. For selected references on the complexation of IB by βCD derivatives, see: (*a*) K. Hussein, M. Türk and M. A. Wahl, *Pharm. Res.*, 2007, **24**, 585; (*b*) M. Charoenchaitrakool, F. Dehghani and N. R. Foster, *Int. J. Pharm.*, 2002, **239**, 103; (*c*) P. Mura, G. P. Bettinetti, A. Manderioli, M. T. Faucci, G. Bramanti and M. Sorrenti, *Int. J. Pharm.*, 1998, **166**, 189. For a remarkable βCD derivative complex stability enhancement through π–π stacking involving aromatic substituents, see: (*d*) T. Yamanoi, N. Kobayashi, K. Takahashi and K. Hattori, *Lett. Drug Des. Discov.*, 2006, **3**, 188.

