(Patterson) methods. Hydrogen atoms were localized and refined in the riding mode. The crystal was mounted on a glass fiber. $Os_3O_{30}C_{82}H_{72}$ ($M_r = 1788.00$); $Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å, graphite monochromator; $2\Theta_{max} = 22.50°$, monoclinic $C2/c$; $a = 54.641(5)$, $b = 11.7486(10)$, $c = 33.250(3)$ Å, $\beta = 120.447(3)°$, $V = 18401(3)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.291$ g cm^{-3}, $\mu = 41.79$ mm^{-1}, absorption correction: SADABS; 12021 reflections were measured and all reflections with ($I = 2\sigma(I)$) observed, $R = 0.0747$, $R_w = 0.1710$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-143392 (**2a**) and CCDC-143393 (**4a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[14] The C–C triple bond length in diphenylacetylene is 1.198 Å. A. Mavridis, I. Moustakali-Mavridis, *Acta Crystallogr. Sect. B* **1977**, *33*, 3612.

[15] U. H. F. Bunz, V. Enkelmann, *Chem. Eur. J.* **1999**, *5*, 263.

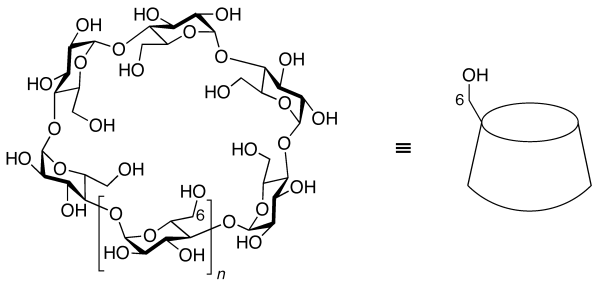
[16] A. J. Berresheim, M. Müller, K. Müllen, *Chem. Rev.* **1999**, *99*, 1747; M. Müller, C. Kübel, K. Müllen, *Chem. Eur. J.* **1998**, *4*, 2099; R. Goddard, M. W. Haenel, W. C. Herndon, C. Krüger, M. Zander, *J. Am. Chem. Soc.* **1995**, *117*, 30.

[17] X. Qiao, M. A. Padula, D. M. Ho, N. J. Vogelaar, C. E. Schutt, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1996**, *118*, 741.

Diisobutylaluminum-Promoted Regioselective De-*O*-benzylation of Perbenzylated Cyclodextrins: A Powerful New Strategy for the Preparation of Selectively Modified Cyclodextrins**

Alan J. Pearce and Pierre Sinaÿ*

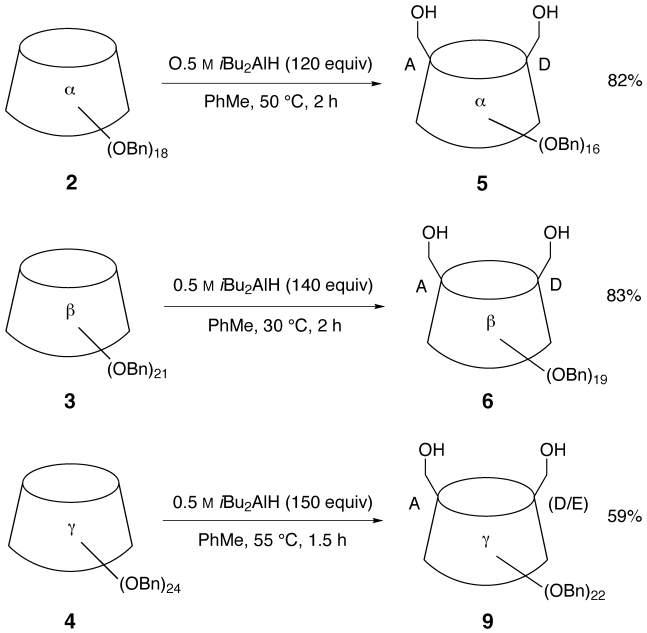
Cyclodextrins (CDs) **1** and their derivatives are of great importance in supramolecular chemistry,[1] analytical chemistry,[2] as artificial enzymes,[3] drug delivery systems,[4] and modifiers of chemical reactions (Scheme 1).[5] The preparation of selectively modified cyclodextrins for these applications remains a crucial challenge in organic synthesis despite considerable effort and several well defined protocols.[6] Traditional methods may be classified[6a] as a) "long", involving lengthy protection and deprotection steps; b) "clever", where the chemistry of cyclodextrin is exploited to get the desired product by the shortest route; and c) "sledgehammer", where indiscriminate reaction leads to complex product mixtures and lengthy separation. A far more elegant alternative approach is the regioselective deprotection of perfunctionalized cyclodextrins,[7] thus combining the advantageous aspects of the first two methods mentioned above.



Scheme 1. Schematic structural representation of CDs.

We recently reported that triisobutylaluminum (TIBAL) led to highly regioselective mono-de-*O*-benzylation of perbenzylated mono- and disaccharide derivatives.[8] Herein, we report the first regioselective de-*O*-benzylation of perbenzylated CDs by application of this methodology.

Perbenzylated CDs **2**–**4** were prepared by direct benzylation of CDs **1** in DMSO with benzyl chloride and NaH, in excellent yield using the method of Sato et al.[9] When α-CD(OBn)$_{18}$ (**2**) was treated with excess diisobutylaluminum (DIBAL)[10] in toluene at 50 °C we observed formation of a single product **5** of di-*O*-debenzylation in 82% yield (Scheme 2). The structure of **5** was identified as the AD



Scheme 2. Highly regioselective DIBAL-promoted di-*O*-debenzylation affords AD diols in excellent yield.

regioisomer by ^{1}H and ^{13}C NMR spectroscopy, which indicated high C_2 symmetry, and was further confirmed by chemical degradation using the "hex-5-enose method" as described below. The regioselectivity of this di-*O*-debenzylation is remarkable. Statistical calculations indicate that for di-*O*-deprotection of α-CD(OBn)$_{18}$ (**2**) 27 regioisomers are possible, of which, we obtain only one in excellent yield.

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[**] The authors thank the European Community for a TMR Marie Curie Research Training Grant (no. ERBFMBICT983225) to A.J.P.

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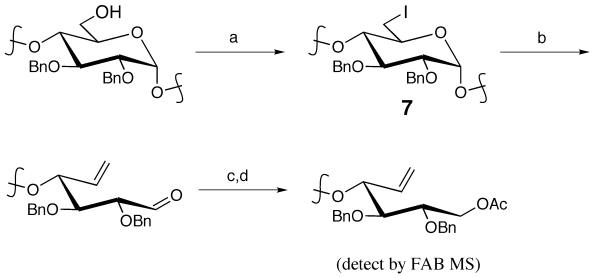
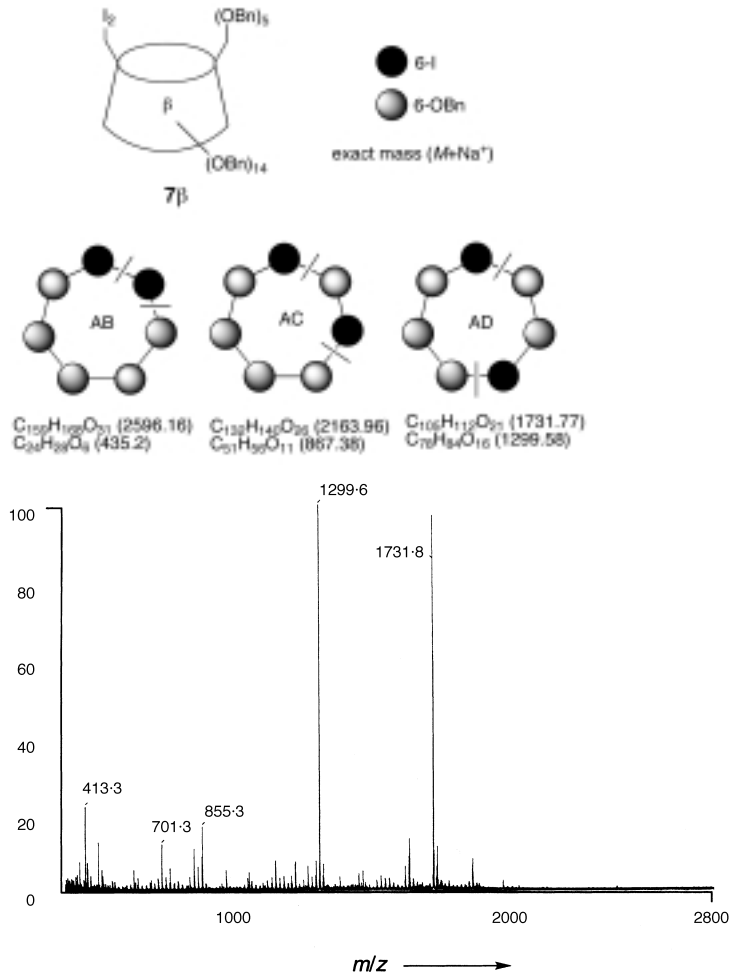
Similarly, β-CD(OBn)$_{21}$ (**3**) underwent smooth di-*O*-debenzylation with excess DIBAL to give a single diol **6** in 83% yield (Scheme 2). We obtain only one of 33 possible regioisomers as product, indicating the high regioselectivity of the di-*O*-debenzylation process. The regiochemistry of **6** was not assignable using a combination of TOCSY-ROESY NMR experiments[11] as the low symmetry of **6** led to extensive overlapping in spectra. However, the structure of **6** was established using the "hex-5-enose method" (Scheme 3).[12]



Scheme 3. The "hex-5-enose degradation" method. Reagents: a) I_2, PPh_3, imidazole, toluene, 62% for **7*α***, 85% for **7*β***, 81% for **7*γ***; b) Zn, *n*PrOH, H_2O, reflux, 1 h; c) $NaBH_4$, MeOH, H_2O; d) Ac_2O, pyridine.

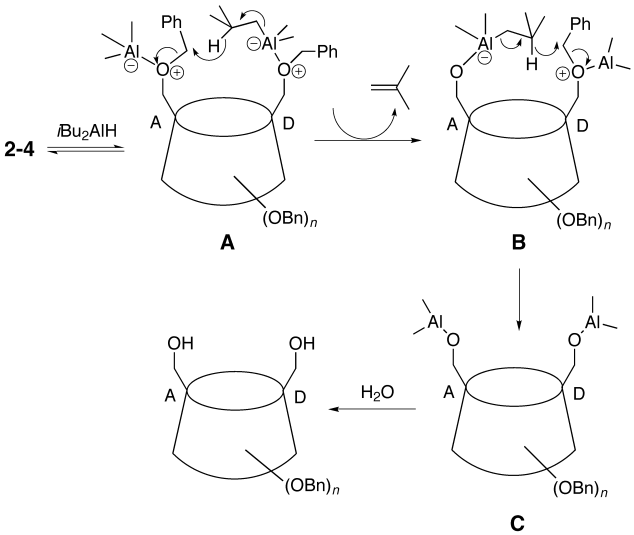
Thus, **6** was converted to the (bis)iodide **7*β*** using Garegg's conditions[13] and subsequently fragmented by using activated zinc, then reduced with $NaBH_4$, and acetylated. Analysis of the products **8** by FAB MS identified only the two fragments arising from the AD regioisomer **7*β*** and hence the diol **6** was assigned as the AD regioisomer accordingly (Scheme 4).



Scheme 4. Structural confirmation (by FAB MS) of **7*β*** (and **6**) by the "hex-5-enose degradation".

DIBAL-promoted di-*O*-debenzylation of γ-CD(OBn)$_{24}$ (**4**) gave a mixture of AD/AE diols **9** in 59% yield (see Scheme 2) after analysis and assignment by the "hex-5-enose method".

A proposed mechanism for this de-*O*-benzylation is shown in Scheme 5. In the presence of a large excess of the Lewis acidic DIBAL, coordination of the perbenzylated CD may lead to the product-productive intermediate **A**. Hydride transfer from the ate complex[14] at position D to the proximal and activated benzyl at position A may then occur affording **B**. The aluminate complex at A remains an activated hydride donor and subsequently "directs" a second hydride transfer back to the correctly disposed and activated benzyl group at D. Hydrolysis of intermediate **C** on work-up affords the observed diol products.



Scheme 5. Postulated mechanism of the DIBAL-promoted de-*O*-benzylation.

This method is particularly powerful given that the derivatives obtained in preparative yield are selectively protected and therefore suitable for direct further functionalization. The synthetic utility of the selective protection in **5** is highlighted in Scheme 6. Allylation of **5**, followed by ring-closing metathesis[15] using the Grubbs' initiator and hydrogenolysis gave the unusual rigidly AD-capped α-cyclodextrin **10** in 80% yield from **5**. Methylation of **5** followed by hydrogenolysis gave the AD-bis-methylated α-cyclodextrin **11** in 82% yield (from **5**). Derivatives **10** and **11** also maintained the high C_2 symmetry in NMR spectra.

Careful modification of the reaction conditions also allowed access to products of mono-de-*O*-benzylation. Thus, when α-CD(OBn)$_{18}$ (**2**) was treated with excess DIBAL under

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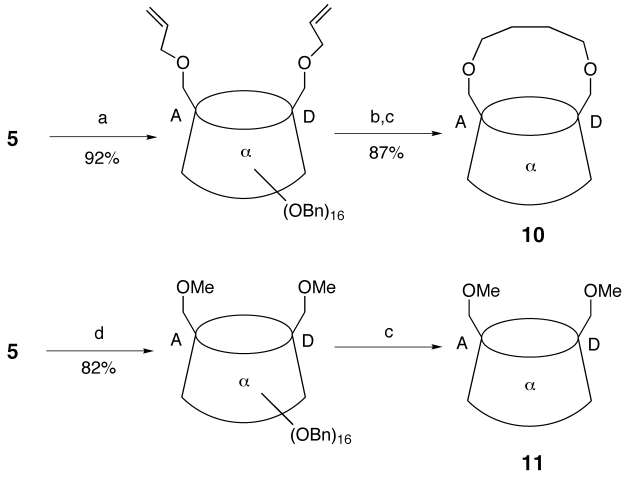
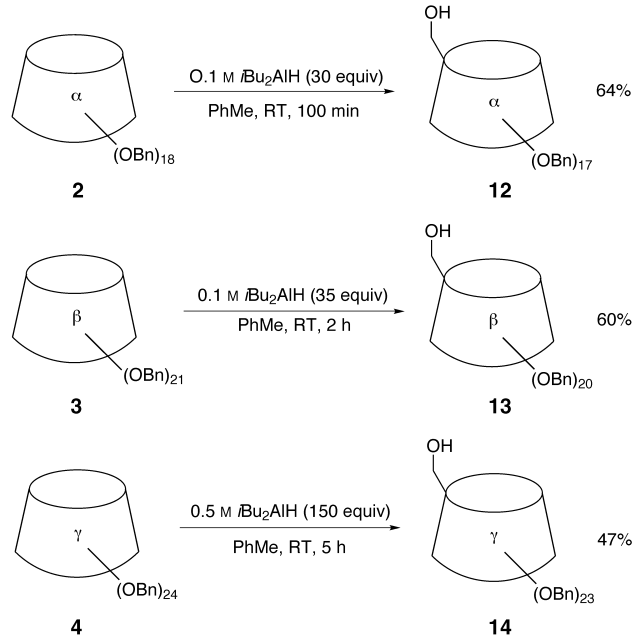


Scheme 6. AD-modified cyclodextrins. Reagents: a) NaH, allylBr, DMF, RT; b) 6 mol% $[Cl_2(PCy_3)_2Ru{=}CHPh]$, PhH, 60 °C, 4 h; c) Pd/C, EtOAc, MeOH, RT, 48 h, quant; d) NaH, MeI, DMF, RT.

dilute conditions at room temperature we isolated the mono-debenzylated product **12**[16] in 64% yield together with **5** (21%) and recovered **2** (13%) (Scheme 7). Using these



Scheme 7. DIBAL-promoted regioselective mono-de-*O*-benzylation occurs exclusively at the primary torus of CDs.

conditions, the β-CD$(OBn)_{21}$ (**3**) gave the mono-debenzylated product **13** in 60% yield together with diol **6** (27%) and recovered starting material **3** (12%). Finally, in the case of γ-CD$(OBn)_{24}$ (**4**), DIBAL-promoted debenzylation gave the alcohol **14** in 47% yield along with diol **9** (25%) and recovered **4** (10%).

In conclusion we have demonstrated that DIBAL-promoted de-*O*-benzylation of perbenzylated cyclodextrins occurs with remarkably high regioselectivity, giving access to either mono-6-*O*-debenzylated or AD-di-*O*-debenzylated derivatives, which are selectively protected for direct further functionalization. This very simple method gives access to large quantities of selectively modified cyclodextrins suitable for advanced applications. We are currently exploring further applications of this powerful de-*O*-alkylation process.

Experimental Section

DIBAL (62.0 mL, 93.0 mmol, 1.5 M in toluene) was added to a stirred solution of **3** (2.0 g, 0.7 mmol) in anhydrous toluene (140 mL) at room temperature under argon. The reaction mixture was heated at 30 °C for 2 h, after which time TLC (EtOAc/cyclohexane = 1/3) indicated no starting material ($R_f = 0.5$) but a major product ($R_f = 0.3$). The mixture was cooled to 0 °C, water (100 mL) was carefully added dropwise, and the mixture was stirred vigorously at room temperature for 15 min. The mixture was filtered (Celite) into a separating funnel washing thoroughly with hot EtOAc (3 × 200 mL). The organic layer was washed with brine (150 mL), dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, 20–25% EtOAc in cyclohexane) to afford **6** as a colorless foam (1.6 g, 83%), $[\alpha]_D^{22} = +34$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.61$ (d, $^3J(1,2) = 3.7$ Hz, 1H; H-1), 5.56 (d, $^3J(1,2) = 3.8$ Hz, 1H; H-1), 5.04 (d, $^3J(1,2) = 3.5$ Hz, 1H; H-1), 5.02 (d, $^3J(1,2) = 3.4$ Hz, 1H; H-1), 5.00 (d, $^3J(1,2) = 4.0$ Hz, 1H; H-1), 4.98 (d, $^3J(1,2) = 3.7$ Hz, 1H; H-1), 4.89 (d, $^3J(1,2) = 3.3$ Hz, 1H; H-1), 2.78 (brs, 1H; OH), 2.69 (brs, 1H; OH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 99.2$, 99.1, 98.4, 98.2, 98.0, 97.6, 97.4 (7 × d, 7C; C-1A-G), 69.3, 69.15, 69.1, 69.0, 68.7 (5 × t, 5C; C-6BCEFG), 61.5 (2 × t, 2C; C-6AD); MS (FAB): m/z (%): 2868.1 (100) $[M\mathrm{Na}^+]$.

Received: May 30, 2000 [Z 15199]

[1] G. Wenz, *Angew. Chem.* **1994**, *106*, 851; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803–822.
[2] S. Li, W. C. Purdy, *Chem. Rev.* **1992**, *92*, 1457–1470.
[3] R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997–2011.
[4] K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013–2033.
[5] K. Uekama, F. Hirayama, T. Irie, *Chem. Rev.* **1998**, *98*, 2045–2076.
[6] a) A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977–1996; b) A. P. Croft, R. A. Bartsch, *Tetrahedron* **1983**, *39*, 1417–1474; c) R. Breslow, J. W. Canary, M. Varney, S. T. Waddell, D. Yang, *J. Am. Chem. Soc.* **1990**, *112*, 5212–5219; d) I. Tabushi, K. Yamamura, T. Nabeshima, *J. Am. Chem. Soc.* **1984**, *106*, 5267–5270; e) I. Tabushi, K. Shimokawa, K. Fujita, *Tetrahedron Lett.* **1977**, 1527–1530.
[7] The classical acetolysis of primary benzyl ethers has been applied to perbenzylated CDs, see: P. Angibeaud, J.-P. Utille, *Synthesis* **1991**, 737–738.
[8] M. Sollogoub, S. K. Das, J.-M. Mallet, P. Sinaÿ, *C. R. Acad. Sci. Ser. 2* **1999**, 441–448.
[9] T. Sato, H. Nakamura, Y. Ohno, T. Endo, *Carbohydr. Res.* **1990**, *199*, 31–35.
[10] De-*O*-alkylation of ethers using TIBAL or DIBAL has been reported, see: E. Winterfeldt, *Synthesis* **1975**, 617–630. Indeed, when **2** was treated with TIBAL in toluene at 55 °C de-*O*-benzylation to **5** also occurred but in only 52% yield—hence all de-*O*-benzylations have been performed with DIBAL.
[11] H.-J. Schneider, F. Hacket, V. Rüdiger, *Chem. Rev.* **1998**, *98*, 1755–1785.
[12] a) T. Tanimoto, M. Tanaka, T. Yuno, K. Koizumi, *Carbohydr. Res.* **1992**, *223*, 1–10; b) T. Tanimoto, T. Sakaki, K. Koizumi, *Chem. Pharm. Bull.* **1993**, *41*, 866–869; c) G. O. Aspinall, L. Khondo, J. A. Kinnear, *Carbohydr. Res.* **1988**, *179*, 211–221; d) G. O. Aspinall, R. C. Carpenter, L. Khondo, *Carbohydr. Res.* **1987**, *165*, 281–298.
[13] P. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866–2869.
[14] Initial hydride transfer is illustrated to occur from the *i*Bu group, consistent with the tentative observation of isobutene evolution when DIBAL is added to the reaction mixture.
[15] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450.
[16] Previously prepared by multistep synthesis during the de novo synthesis of α-CD: Y. Takahashi, T. Ogawa, *Carbohydr. Res.* **1987**, *169*, 127–149.

  1433-7851/00/3920-3612 $ 17.50+.50/0