Pd-catalysed Capping Removal on a Tri-differentiated α-Cyclodextrin

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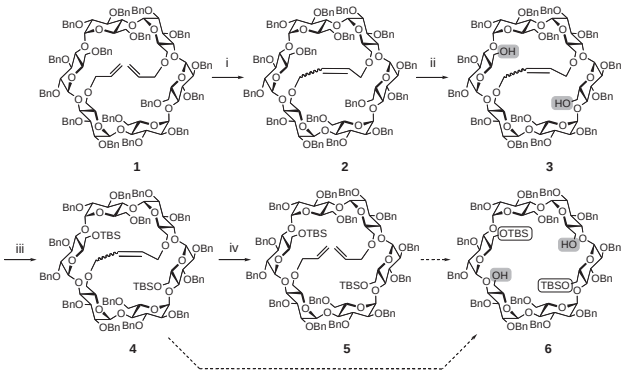
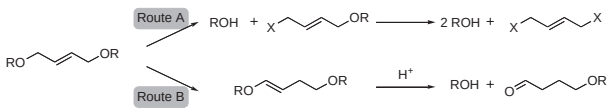
A chemically novel palladium-catalysed sequential double de-O-allylation to produce a diol is presented and applied to the efficient removal of a cap on a polyfunctionalized cyclodextrin.

Cyclodextrins (CDs) have promised to become enzyme models for a very long time,[1] but with only moderate success until now. It clearly appears that the rational design of such compounds is restricted by the limited possibility to selectively functionalize those polyhydroxylated compounds.[2] It is particularly critical for this purpose to be able to introduce, at will, a set of different functional groups on CDs; but only a few methods of polyfunctionalization have been developed so far. Hetero-bifunctionalization of the primary rim was achieved starting from monofunctionalized CD[3] but most of the time yielding a mixture of compounds; a more sophisticated method is using sulfonate capping of CDs.[4] It is only very recently that the CD was hetero-bifunctionalized on its secondary rim.[5]

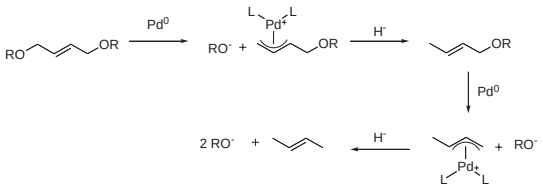


Scheme 1. Synthesis of the triply bifunctionalized CD **6**. Reagents and conditions: i) Grubbs[I] catalyst [bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride], CH_2Cl_2, reflux, 1.5 h then $Pb(OAc)_4$, rt, 3 h, 92%; ii) DIBAL-H, toluene, 50 °C, 1 h, 84%; iii) *t*-butyldimethylsilyl triflate (TBSOTf), pyr, CH_2Cl_2, rt, 2 h, 95%; iv) Grubbs[I], $CH_2{=}CH_2$, CH_2Cl_2, rt, 3 days then $Pb(OAc)_4$, rt, 3 h, 70%.

The understanding of the mechanism[6] of de-O-benzylation reaction of perbenzylated sugars[7] allowed us to selectively synthesize the unique CD **5** having three pairs of orthogonal protecting groups.[8] This synthesis was conceptually based on a conformational change on CD **1** induced by a reversible capping via ring closing metathesis (RCM) to form capped CD **2**. This modification allowed the selective de-O-benzylation into CD **3**. In one option, the cap was then suppressed by the reverse ring opening metathesis (ROM) of disilylated CD **4** to restore the starting allyl protection in CD **5**, which in turn can be converted into diol **6** by classical de-O-allylation. Another option would be the one-step removal of the temporary cap in CD **4** to directly provide the diol **6** (Scheme 1).



Scheme 2. De-O-allylation methods leading to one or two alcohols.



Scheme 3. Pd-catalysed double de-O-allylation.

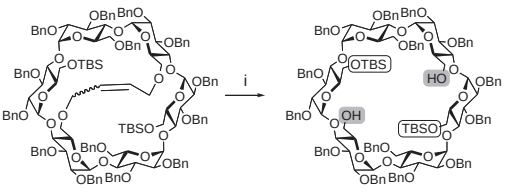
This direct conversion would, on one hand, alleviate the synthesis and on the other hand materialize a new chemical process, that is the double de-O-allylation shown in Scheme 2 route A. It is therefore necessary to restore the allyl ether function after the first deprotection. All classical de-O-allylation methods involving an isomerization of the double bond followed by hydrolysis of the formed enol ether, as illustrated on Scheme 2 (route B), are obviously not suitable in our case.

For this purpose, we reasoned that the palladium-catalysed hydrogenolysis of allyl carboxylates and allyl aryl ethers[9] could be a possible solution to this chemical problem. Indeed, a first hydrogenolysis, through the formation of a π-allyl and hydride reduction, would lead to a new allylic ether ready for a second Pd-assisted cleavage (Scheme 3).

In the case of an alkyl allyl ether, $Pd(PPh_3)_4$ alone does not allow the formation of a π-allyl, and the addition of a Lewis acid such as zinc chloride, which has occasionally been used as an accelerator,[10] was found essential in our case. On this basis, $Pd(PPh_3)_4$ (0.1 equiv.) was added to a solution of **4** in degassed THF. The reaction mixture was treated by a degassed 1 M solution of $ZnCl_2$ (15 equiv.) in THF and stirred at room temperature under argon for 10 min. Bu_3SnH (15 equiv.) was slowly added and the reaction mixture was refluxed under argon for 20 h to afford after purification 75% yield of CD **6**[11] (Scheme 4).

We believe that the critical role of zinc chloride in this reaction is twofold. First, it should promote the required formation of a π-allyl by facilitating ether cleavage; second, it activates tributylstannane.

In conclusion, we have developed a Pd-catalysed double de-O-allylation, which fulfils our specific goals. Furthermore, we hope that this reaction will also show that this double allyl



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Scheme 4. Direct synthesis of diol **6** through double de-O-allylation. Reagents and conditions: i) $Pd(PPh_3)_4$, $ZnCl_2$, Bu_3SnH, THF, rt → reflux, 12 h, 75%.

function can be seen as an original diol protecting group, or as a temporary tether between two alcohols.

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References and Notes

1 I. Tabushi, *Acc. Chem. Res.* **1982**, *15*, 66; R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997.
2 A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977.
3 K. Fujita, A. Matsunaga, Y. Ikeda, T. Imoto, *Tetrahedron Lett.* **1985**, *26*, 6439; K. Fujita, A. Matsunaga, H. Yamamura, T. Imoto, *J. Org. Chem.* **1988**, *53*, 4520; K. Fujita, H. Yamamura, T. Imoto, *Tetrahedron Lett.* **1991**, *32*, 6737; K. Fujita, H. Yamamura, Y. Egashira, T. Imoto, *Tetrahedron Lett.* **1992**, *33*, 3511; T. Lecourt, J.-M. Mallet, P. Sinaÿ, *Eur. J. Org. Chem.* **2003**, 4553.
4 I. Tabushi, T. Nabeshima, H. Kitaguchi, K. Yamamura, *J. Am. Chem. Soc.* **1982**, *104*, 2017; I. Tabushi, Y. Kuroda, M. Yamada, H. Higashimura, R. Breslow, *J. Am. Chem. Soc.* **1985**, *107*, 5545; D.-Q. Yuan, T. Yamada, K. Fujita, *Chem. Commun.* **2001**, 2706; E. Fasella, S. D. Dong, R. Breslow, *Bioorg. Med. Chem.* **1999**, *7*, 709.
5 M. Fukudome, Y. Sugimoto, D.-Q. Yuan, K. Fujita, *Chem. Commun.* **2005**, 3168; M. Fukudome, D.-Q. Yuan, K. Fujita, *Tetrahedron Lett.* **2005**, *46*, 1115.
6 T. Lecourt, A. J. Pearce, A. Herault, M. Sollogoub, P. Sinaÿ, *Chem. Eur. J.* **2004**, *10*, 2960; O. Bistri, P. Sinaÿ, M. Sollogoub, *Tetrahedron Lett.* **2005**, *46*, 7757.
7 M. Sollogoub, S. K. Das, J.-M. Mallet, P. Sinaÿ, *C. R. Acad. Sci., Ser. IIc: Chim.* **1999**, 441; A. J. Pearce, P. Sinaÿ, *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3610.
8 O. Bistri, P. Sinaÿ, M. Sollogoub, *Chem. Commun.* **2006**, 1112.
9 F. Guibe, Y. Saint M'leux, *Tetrahedron Lett.* **1981**, *22*, 3591; O. Dangles, F. Guibé, G. Balavoine, S. Lavielle, A. Marquet, *J. Org. Chem.* **1987**, *52*, 4984; R. Beugelmans, S. Bourdet, A. Bigot, J. Zhu, *Tetrahedron Lett.* **1994**, *35*, 4349.
10 K. Ganguly, J. L. McCormick, A. K. Saksena, P. R. Das, T.-M. Chan, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1209; M. J. Broadhurst, S. J. Brown, J. M. Percy, M. E. Prime, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3217; S. Chandrasekhar, Ch. R. Reddy, R. J. Rao, *Tetrahedron* **2001**, *57*, 3435.
11 $Pd(PPh_3)_4$ (53 mg, 46 μmol) was added to a solution of **4** (1.15 g, 460 μmol) in degassed THF (12 mL). The reaction mixture was treated by a degassed 1 M solution of $ZnCl_2$ in THF (6.9 mL, 6.9 mmol) and stirred at rt under argon for 10 min. Bu_3SnH (1.85 mL, 6.9 mmol) was slowly added and the reaction mixture was refluxed under argon for 20 h. Solvents were removed in vacuo and the residue was dissolved in toluene and purified by silica gel flash chromatography (cyclohexane/AcOEt, 4:1) to give diol **6** (849 mg, 75%). $[\alpha]^{20}_D$ +43° ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.96 (s, 9H, $(CH_3)_3Si$), 3.42 (dd, $^3J_{2,1} = 3.5$ Hz, $^3J_{2,3} = 9.6$ Hz, 1H, H-2), 3.51–3.57 (m, 2H, 2 × H-2), 3.62–3.75 (m, 2H, 2 × H-6), 3.78–3.87 (m, 4H, 2 × H-4, H-5, H-6), 3.90 (brd, $^2J = 11.0$ Hz, 1H, H-6), 3.93–4.05 (m, 4H, H-4, 2 × H-5, H-6), 4.09 (t, $^3J_{3,2} = {}^3J_{3,4} = 9.7$ Hz, 1H, H-3), 4.11 (t, $^3J_{3,2} = {}^3J_{3,4} = 9.5$ Hz, 1H, H-3), 4.21 (dd, $^2J = 11.5$ Hz, $^3J_{6,5} = 4.1$ Hz, 1H, H-6), 4.27 (dd, $^3J_{3,2} = 7.8$ Hz, $^3J_{3,4} = 9.7$ Hz, 1H, H-3), 4.32 (d, $^2J = 12.6$ Hz, 1H, CHPh), 4.38 (d, $^2J = 12.6$ Hz, 1H, CHPh), 4.47 (d, $^2J = 12.0$ Hz, 1H, CHPh), 4.52 (d, $^2J = 11.9$ Hz, 1H, CHPh), 4.62 (d, $^2J = 12.7$ Hz, 1H, CHPh), 4.65 (d, $^2J = 12.2$ Hz, 2H, 2 × CHPh), 4.73 (d, $^3J_{1,2} = 3.4$ Hz, 1H, H-1), 4.80 (d, $^2J =$ 10.6 Hz, 2H, 2 × CHPh), 4.84 (d, $^2J = 11.2$ Hz, 1H, CHPh), 4.87 (d, $^2J = 10.9$ Hz, 1H, CHPh), 4.92 (d, $^2J = 10.3$ Hz, 1H, CHPh), 4.98 (d, $^3J_{1,2} = 3.3$ Hz, 1H, H-1), 5.20 (d, $^2J = 10.8$ Hz, 1H, CHPh), 5.49 (d, $^2J = 10.3$ Hz, 1H, CHPh), 5.68 (d, $^3J_{1,2} = 3.8$ Hz, 1H, H-1), 7.10–7.33 (m, 35H, CH arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.2 (CH_3Si), −5.0 (CH_3Si), 18.5 ($(H_3C)_3\underline{C}Si$), 26.0 ($(H_3\underline{C})_3CSi$), 61.9, 63.1, 69.6 (3 × C-6), 71.2 (C-5), 72.0 (C-5), 72.2 (CH_2Ph), 72.7 (C-5), 72.8, 73.3, 73.4 (3 × CH_2Ph), 74.0 (CH_2Ph), 74.05 (C-4), 76.1, 76.2 (2 × CH_2Ph), 77.9 (C-2), 79.0 (C-2), 79.7 (C-2), 80.6 (C-3), 80.65 (C-4), 80.8 (C-3), 81.7 (C-3, C-4), 97.3 (C-1), 97.7 (C-1), 98.3 (C-1), 126.5–128.3 (35 × CH arom.), 137.8, 138.0, 138.3, 138.5, 139.2, 139.25, 139.3 (7 × Cquat. arom.). FAB MS: m/z $[MNa]^+ = 2485.2$. Anal. Calcd for $C_{146}H_{172}O_{30}Si_2$: C, 71.19; H, 7.04%. Found, C, 70.81; H, 7.04%.

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