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SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4137–4139

Expeditious selective synthesis of primary rim tri-differentiated α-cyclodextrin

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Received 6 March 2006; revised 11 April 2006; accepted 14 April 2006

Abstract—An expeditious synthesis of a cyclodextrin with three pairs of functionalities on its primary rim is presented. Compared to the previous one, this improved synthetic route yields the product in four steps and 70% yield, instead of six steps and 35% yield; it also bypasses two metathesis reactions and avoids the use of tin reagent.

Given their lampshade shape and multi-functionality, cyclodextrins (CDs) have long been pointed out as potential artificial enzymes.[1] The fulfilment of this goal critically depends on the effective differentiation of the various hydroxyl groups; indeed, as soon as efficient methods became available, they have been exploited to build up enzyme models.[2] The current methods give access to homo-mono-, bi- or tri-functionalised CDs.[3] A much more difficult challenge consists in their efficient hetero-oligo-functionalisation. A few methods of hetero-bi-functionalisation are now available;[4] among them, we have recently discovered a process of double hetero-tri-functionalisation of the primary rim of CDs.[5,6]

Our method originates in the understanding of a remarkable de-*O*-benzylation reaction promoted by diisobutylaluminium hydride (DIBAL-H) that allows a very efficient access to diol **1** based on the high sensitivity of the reagent to steric hindrance.[7] A so-called bascule-bridge strategy was then delineated to yield, in six steps and 35% yield, a CD **7** with three pairs of functionalities on its primary rim.[5] Those steps include the capping of the CD via bis-allylation of CD **1**, and subsequent ring-closing metathesis (RCM) of CD **2** into capped-CD **3**. The change in steric hindrance on the primary rim of the CD induced by this capping allows a remarkable regioselective de-*O*-benzylation. The formed diol **4** is protected by silyl groups, and the allyl protection is restored through ring-opening metathesis (ROM) to yield CD **6**. Compound **7** can then be obtained by de-*O*-allylation. We also recently discovered that it is possible to shorten this synthesis via a one step Pd-catalysed formal reduction of the unsaturated cap in **5** into the desired diol **7**.[8] We would now like to disclose an expeditious synthesis of CD **7**, also based on the same concept, that is to say the regiodirecting role of a cap (Scheme 1).

Our original capping strategy was based on the RCM reaction; we now took advantage of the capping reaction described by Bols et al.,[9] using a slightly different protocol to introduce the methallyl function.[10] The previously observed regioselective de-*O*-benzylation of CD **3** was due to a change induced by the tetracarbonated capping; we thus anticipated a similar reactivity with methallyl capped-CD **9**. *Upon reaction with DIBAL-H, capped-CD **9** indeed nicely afforded diol **10** as a single product in 90% yield*,[10] hence demonstrating the compatibility of this cap with our methodology (Scheme 2).

We next had to show that this methallyl-cap could also play the role of a temporary protecting group and be efficiently cleaved. For this purpose, we used Pd^0 chemistry. We envisaged to produce a symmetric π-allyl from a methallylic diether in the presence of a Lewis acid; its reduction would regenerate a methallyl ether, which in

Keywords: Aluminium; Diisobutylaluminium hydride (DIBAL-H); Cyclodextrins; Selectivity.
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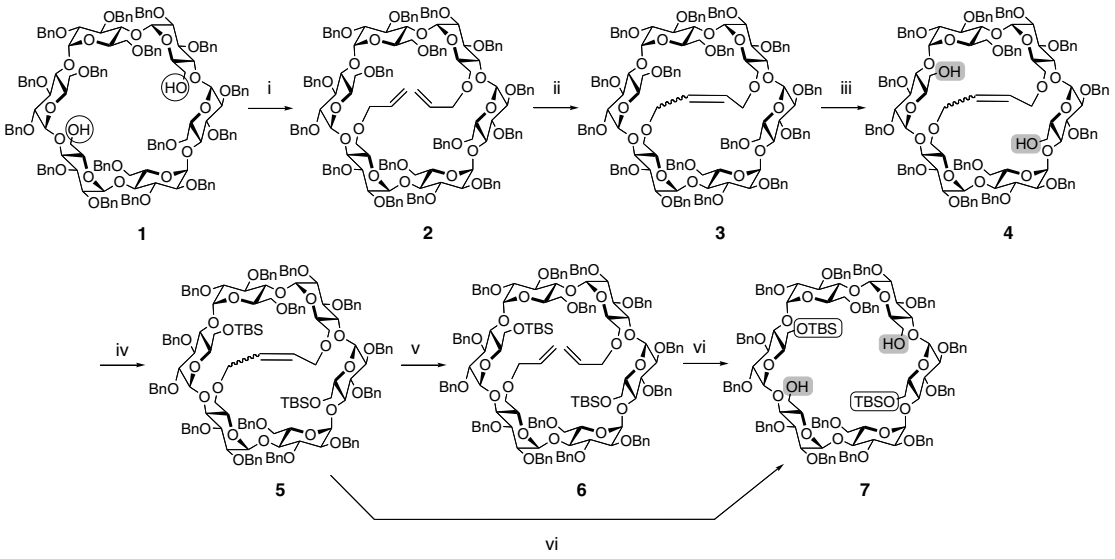
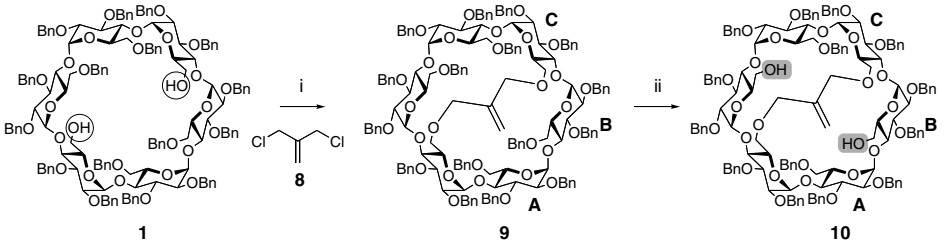
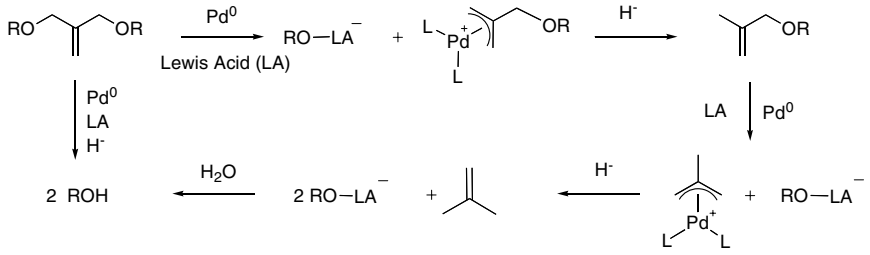
doi:10.1016/j.tetlet.2006.04.065



Scheme 1. Synthesis of the triply bifunctionalised CD **7**. Reagents and conditions: (i) AllBr, NaH, DMF, rt, 1 h, 91% (ii) Grubbs^{I}, CH_2Cl_2, reflux, 1.5 h then $Pb(OAc)_4$, rt, 3 h, 92%; (iii) DIBAL-H, toluene, 50 °C, 1 h, 84% ; (iv) TBSOTf, pyr, CH_2Cl_2, rt, 2 h, 95%; (v) Grubbs^{I}, $CH_2{=}CH_2$, CH_2Cl_2, rt 3 days then $Pb(OAc)_4$, rt, 3 h, 70%; (vi) $Pd(PPh_3)_4$, $ZnCl_2$, Bu_3SnH, THF, reflux, 12 h, 75%.



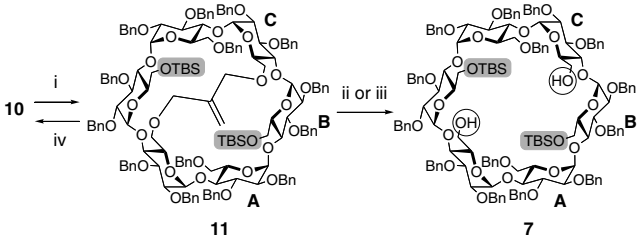
Scheme 2. Synthesis and regioselective de-*O*-benzylation of capped-CD **9**. Reagents and conditions: (i) **8**, NaH, rt, 2 h, 92%; (ii) DIBAL-H, toluene, 50 °C, 1 h, 90%.



Scheme 3. Pd-catalysed cap-removal.

its turn is deprotected according to the same mechanism to afford the two alcohols ROH (Scheme 3).

Hence, CD **10** was first silylated into CD **11** and submitted to the action of Pd^0 in the presence of zinc chloride and tributyltin hydride (see also Scheme 1)[8] to afford the desired CD **7** in 67% yield. Since the drawback of this protocol being the use of tin derivatives which are toxic and always difficult to eliminate, we decided to use triethylsilane instead. The simple replacement of tin hydride by the silane in the same protocol nicely afforded the desired CD **7** in 88% yield.[10] It is worth noting that the use of BF_3-OEt_2, instead of zinc chloride, only produced the desilylated compound **10** (Scheme 4).



Scheme 4. Synthesis of the triply bifunctionalised CD **7**. Reagents and conditions: (i) TBSOTf, pyr, CH_2Cl_2, rt, 2 h, 95%; (ii) $Pd(PPh_3)_4$, $ZnCl_2$, Bu_3SnH, THF, reflux, 12 h, 67% ; (iii) $Pd(PPh_3)_4$, $ZnCl_2$, Et_3SiH, THF, reflux, 6 h, 88% ; (iv) $Pd(PPh_3)_4$, BF_3-OEt_2, Et_3SiH, THF, 0 °C, 3 h.

In conclusion, we now offer a very efficient entry to the triply modified CD **7**, paving the way to its further use. Compared to our previous protocol,[5,8] it is operationally much simpler, higher yielding (70% overall yield, instead of 35%), and circumventing the use of expensive, unhandy and toxic reagents.

Acknowledgements

The authors would like to warmly thank Dr. Anny Jutand for a generous supply of $Pd(PPh_3)_4$ and advice on its use, as well as Cyclolab (Hungary) for a gift of α-CD.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.065.

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