Sequential ring closing/opening metathesis for the highly selective synthesis of a triply bifunctionalized α-cyclodextrin†

Olivia Bistri, Pierre Sinaÿ and Matthieu Sollogoub*

Received (in Cambridge, UK) 21st July 2005, Accepted 22nd November 2005
First published as an Advance Article on the web 12th December 2005
DOI: 10.1039/b510329k

Metathesis versatility has been exploited to reveal the cyclic directionality of cyclodextrins and to selectively synthesise a unique cyclodextrin bearing three pairs of orthogonal protecting groups on its primary rim.

The design and synthesis of artificial enzymes is a long-standing goal for chemists.[1] Cyclodextrins (CDs) are very appropriate candidates for this purpose as they have both a hydrophobic cavity to host the substrate and many functionalities to transform it.[2] It was however rapidly shown that they have only limited catalytic activity, and that functionalities other than hydroxyl groups should be introduced onto CDs. Progress in the design of CD-based artificial enzymes was then tightly connected to the possibility of selectively functionalizing CDs. Breslow's utilization[3] and improvement[4] of Tabushi's capping[5] to synthesise a model of ribonuclease followed by Tabushi's synthesis of a carbonic anhydrase model[6] and the resulting emulation, are nice illustrations of this fact. We recently proposed a method for the bifunctionalization of CDs[7,8] which was used by Bols[9] to create artificial enzymes that catalyse glycoside hydrolysis more efficiently than non functionalized CDs.[10]

A step further relies on more sophisticated modifications such as hetero-bifunctionalization, which allow three points recognition of asymmetric species[11] and have been shown to give rise to strong asymmetric induction in the catalysis of an amination reaction.[12] Only very few reports on hetero-bifunctionalization have been published, and they all rely on sulfonate displacement,[13] only compatible with a certain number of functionalities. In our case a perbenzylated CD is selectively deprotected by diisobutylaluminium hydride (DIBAL-H) to form the diol **1** in excellent yield; a large number of functionalizations can then be performed. A challenging step forward is the duplication of this process to obtain a CD with a set of three pairs of orthogonal protecting groups on its primary rim.

When the allyl-protected CD **2** was exposed to the action of DIBAL-H, a mixture of three compounds was obtained: the starting diol **1** resulting from an A,D-type bis-deallylation (51%), and two regioisomeric diols **3** and **4**, both products of the same type of bis-debenzylation, isolated in noticeably different proportions (**3** : **4**, 18% : 9%) (Scheme 1).[14] One goal was reached as we observed the first example of a CD bearing three pairs of orthogonal functionalities on its primary rim, but the synthesis of a single compound remained a challenge at this point.

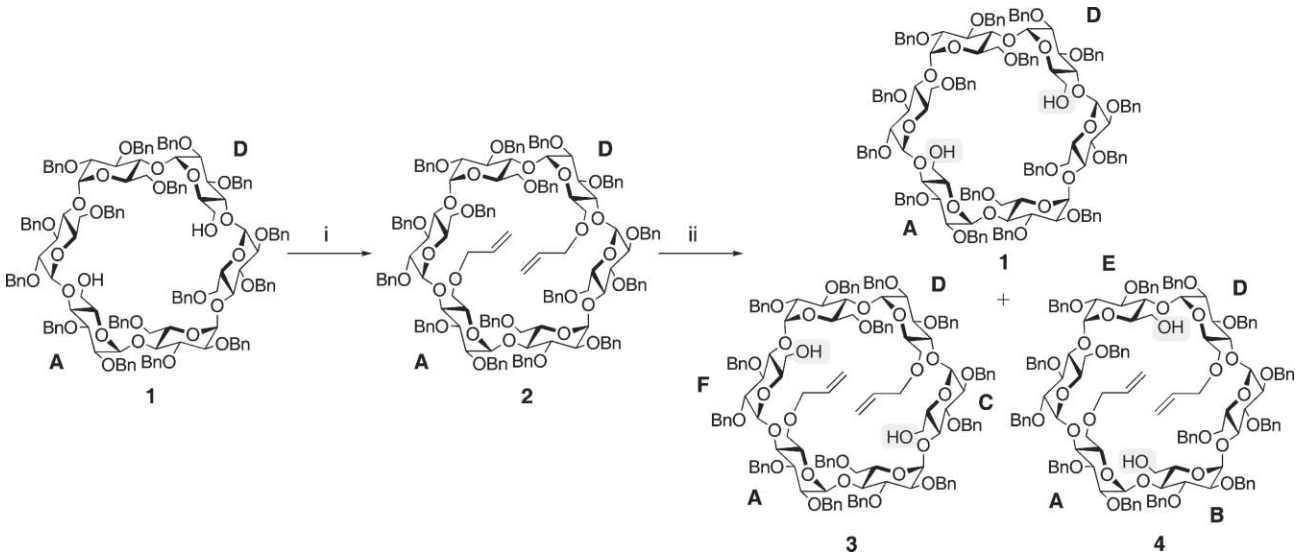
During the elucidation of the de-*O*-benzylation reaction mechanism,[8] we showed that a tetramethylene-capped CD could be regioselectively de-*O*-benzylated. The bridge was remarkably untouched because the oxygen atoms bearing it are oriented inside the cavity; this feature also makes the endocyclic oxygen atoms of the two sugars clockwise to the 6^A,6^D-capped glucosides (view from the primary rim) more available for complexation, thus inducing their de-*O*-benzylation on position 6.

The tetramethylene-capping of the CD was performed through a Ring Closing Metathesis (RCM) using Grubbs'^{I} initiator,[15] followed by a saturation of the double bond making the cap inert to further chemical transformation. According to our mechanism[8] the lack of reactivity of the cap should be independent of the presence of the double bond, even though we just showed that allyl groups were preferentially cleaved by DIBAL-H over benzyl groups. Furthermore keeping the double bond would enable us to restore the allyl protecting group through a Ring Opening Metathesis (ROM).

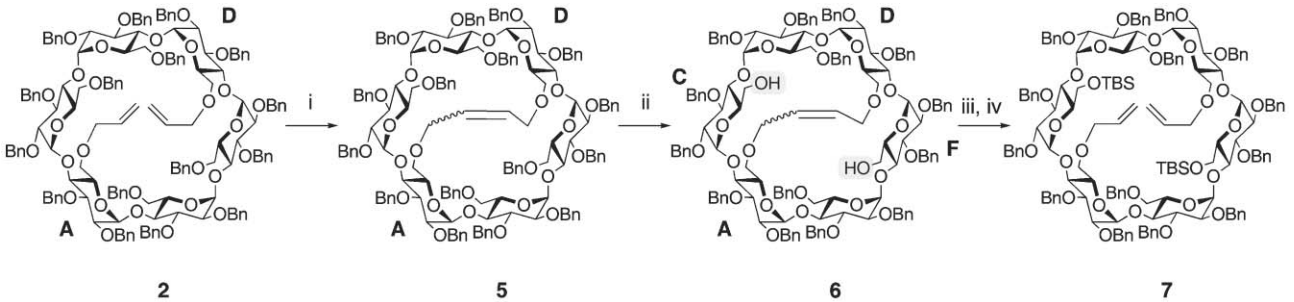
Consequently, the di-*O*-allylated compound **2** was reacted with Grubbs'^{I} catalyst to obtain, through RCM, the capped CD **5** (92%) as an inseparable mixture of *E* and *Z* isomers (1 : 1). This mixture was submitted to the action of DIBAL-H under standard conditions, to solely give, much to our delight, the 6^C,6^F-diol **6** in 84% yield. As hoped, not only did we turn off de-*O*-allylation, but we also obtained a single regioisomer (Scheme 2).[14] The final task was the recovery of a unique CD with a set of three pairs of orthogonal protecting groups on its primary rim. This aim was easily achieved by protecting the formed diol **6** with *tert*-butyldimethylsilyl (TBS) groups (95% yield), and re-opening the bridge over the CD through a ROM using Grubbs^I catalyst under an atmosphere of ethylene to give **7** in 70% yield, thus restoring allyl protection (Scheme 2).

In addition to the synthesis of a unique macrocyclic molecule containing three pairs of orthogonal protecting groups on one of its rims, we also confirmed our hypothesis concerning the mechanism of our reaction. Indeed, the bridge is untouched by DIBAL-H whatever its reactivity towards Lewis acids, meaning that the orientation of the C-6/O-6 bond towards the inside of the cavity induced by the capping through RCM in compound **5** prevents the aluminium atom complexing to the oxygen atom bearing it (O-6^A and O-6^D), which is not the case with an allyl group in CD **2**. Furthermore, this change in orientation in **5** of allyloxy functions also induces an easier approach of aluminium reagent on the sugar units C, F, and their subsequent debenzylation, whereas the approach of aluminium on units B, E is

Ecole Normale Supérieure, Département de Chimie, Institut de chimie moléculaire (FR 2769), UMR 8642: CNRS-ENS-UPMC Paris 6, 24 rue Lhomond, 75231, Paris Cedex 05, Paris, France.
E-mail: sollo@ens.fr; Fax: 33 144323397; Tel: 33 144323335
† Electronic supplementary information (ESI) available: experimental section. See DOI: 10.1039/b510329k



Scheme 1 Action of DIBAL-H on bis-allylated CD **2**. *Reagents and conditions*: i) AllBr, NaH, DMF, RT, 2 h, 95%; ii) DIBAL-H, toluene, 50 °C, 2 h, 79% (**1** : **3** : **4**, 51 : 18 : 9).



Scheme 2 Closing the bridge induces the regioselective de-*O*-benzylation, opening the bridge delivers the triply bifunctionalized CD **7**. *Reagents and conditions*: i) Grubbs^{I}, 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) 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%.

hampered by the O-6^{C} and O-6^{F} benzyl groups. This selectivity is due to the cyclic directionality of the CD, which is, so-to-say, deciphered by the aluminium reagent and revealed by the RCM reaction. (Fig. 1)

In conclusion, we present here an original use of metathesis by sequentially performing an RCM and an ROM to reversibly cap a CD, preventing allyl deprotection and inducing regioselective synthesis of a unique CD **7** with a set of three pairs of orthogonal protecting groups on its primary rim.

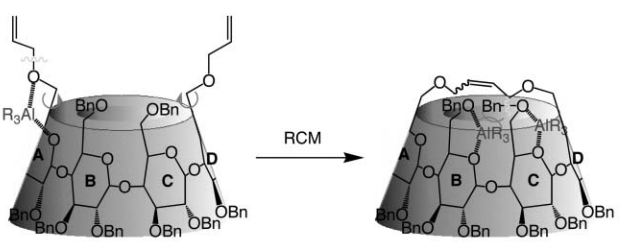


Fig. 1 RCM-induced change of orientation of O-6^{A} and O-6^{D} allows 6^{C},6^{F} regioselective cleavage of benzyl groups.

Notes and references

1 W. B. Motherwell, M. J. Bingham and Y. Six, *Tetrahedron*, 2001, **57**, 4663–4686.
2 R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997–2011; I. Tabushi, *Acc. Chem. Res.*, 1982, **15**, 66–72.
3 R. Breslow, J. B. Doherty, G. Guillot and C. Lipsey, *J. Am. Chem. Soc.*, 1978, **100**, 3227–3229.
4 E. Anslyn and R. Breslow, *J. Am. Chem. Soc.*, 1989, **111**, 5972–5973.
5 I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, *J. Am. Chem. Soc.*, 1976, **98**, 7855–7856; I. Tabushi, K. Yamamura and T. Nabeshima, *J. Am. Chem. Soc.*, 1984, **106**, 5267–5270.
6 I. Tabushi, Y. Kuroda and A. Mochizuki, *J. Am. Chem. Soc.*, 1980, **102**, 1152–1153.
7 A. J. Pearce and P. Sinaÿ, *Angew. Chem., Int. Ed.*, 2000, **39**, 3610–3612.
8 T. Lecourt, A. J. Pearce, A. Herault, M. Sollogoub and P. Sinaÿ, *Chem. Eur. J.*, 2004, **10**, 2960–2971; O. Bistri, P. Sinaÿ and M. Sollogoub, *Tetrahedron Lett.*, 2005, **46**, 7757–7760.
9 F. Ortega-Caballero, C. Rousseau, B. Christensen, T. E. Petersen and M. Bols, *J. Am. Chem. Soc.*, 2005, **127**, 3238–3239; C. Rousseau, N. Nielsen and M. Bols, *Tetrahedron Lett.*, 2004, **45**, 8709–8711.
10 T. Ohe, Y. Kajiwara, T. Kida, W. Zhang, Y. Nakatsuji and I. Ikeda, *Chem. Lett.*, 1999, 921–922.
11 E. Rizzarelli and G. Vecchio, *Coord. Chem. Rev.*, 1999, **188**, 343–364; M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875–1917.
12 I. Tabushi, Y. Kuroda, M. Yamada and H. Higashimura, *J. Am. Chem. Soc.*, 1985, **107**, 5545–5546.

13 I. Tabushi, T. Nabeshima, H. Kitaguchi and K. Yamamura, *J. Am. Chem. Soc.*, 1982, **104**, 2017–2019; D.-Q. Yuan, T. Yamada and K. Fujita, *Chem. Commun.*, 2001, 2706–2707; E. Fasella, S. D. Dong and R. Breslow, *Bioorg. Med. Chem.*, 1999, **7**, 709–714; M. Fukudome, D.-Q. Yuan and K. Fujita, *Tetrahedron Lett.*, 2005, **46**, 1115–1118; K. Fujita, A. Matsunaga, H. Yamamura and T. Imoto, *J. Org. Chem.*, 1988, **53**, 4520–4522.
14 The structure of this product was determined by chemical transformations into the tetramethylated capped-CD described in ref. 8.
15 R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450.

