Regioselective access to 3^{I}-*O*-substituted-β-cyclodextrin derivatives†

Nicolas Masurier,[ab] Olivier Lafont,[b] Romain Le Provost,[ab] David Lesur,[c] Patrick Masson,[d] Florence Djedaïni-Pilard[c] and François Estour*[ab]

Received (in Cambridge, UK) 24th July 2008, Accepted 10th November 2008
First published as an Advance Article on the web 5th December 2008
DOI: 10.1039/b812325j

Formation of a copper(II)–β-cyclodextrin (β-CD) complex in an aqueous medium allowed the regioselective introduction into the oligosaccharide of a benzyl or a bromo-allyl substituent at O-3.

Much effort has focused recently on the development and synthesis of artificial enzymes.[1] In order to build biomimetic structures, cyclodextrins (CDs) are extremely attractive components and present several advantages in preparing active scavengers.[2] The presence of the secondary hydroxy groups of glucose at C-2 and C-3 located on the most open face of the CD torus, and the presence of the primary C-6 alcohols on the other face, have been exploited for introducing functional chemical groups.[3] This transformed the oligosaccharide into a truly reactive molecule towards a substrate.[4] Recently, active catalytic scavengers towards organophosphorus poisons were obtained by introducing a 2-iodosobenzoic residue on a secondary alcohol located in position 2 of β-CD **1**.[5] Because the facial position of a reactive group influences the catalytic scavenger efficiency,[6] monofunctionalization of the other secondary alcohol in position 3 with benzyl derivatives had also to be investigated. Alcohols in position 3 are the least reactive hydroxy groups in CDs and, therefore, they are the most difficult to substitute regioselectively. Only a few examples of 3-modified CD have been published.[7] Jindřich and Tišlèrová recently reported a novel direct synthesis of 3^{I}-*O*-cinnamyl-β-CD in aqueous sodium hydroxide which offered further modification possibilities.[8] Jindřich's methodology was applied with benzyl bromide as electrophile. Treatment of β-CD **1** with benzyl bromide (1.1 equiv.) and NaOH (2.2 equiv.) led to compound **6b** in 29% yield with some regioselectivity. But a large amount of polysubstituted by-products is also formed (21% yield). This relatively high yield of polysubstitution was unavoidable in order to obtain the desired compound **6b**.

Herein, we describe the monobenzylation of β-CD **1** at O-3, using temporary complexation of some secondary hydroxy groups. Formation of a copper(II)–β-CD complex **2** induced a distortion of the oligosaccharide cavity by a diagonal link between copper ions and oxygen atoms (at C-2 and C-3) on adjacent glucopyranose units. This was likely due to a complex structure containing two aquo-copper(II) ions for each molecule of β-CD.[9] Such a complex was assumed to modify the reactivity of CD alcohol functions. The synthesis of this complex being performed in aqueous sodium hydroxide, this strategy had the advantage of allowing formation of the copper complex and of deprotonating hydroxy groups for subsequent substitution reaction in the same reaction medium.

Benzyl bromide **3** was first used as a model electrophile to investigate the best experimental conditions for the monosubstitution of β-CD at O-3.

The selectivity at O-3 was strictly dependent on the amount of the electrophile used. With eight equivalents of electrophile (Table 1, Entry A), the single 3^{I}-*O*-benzyl-β-CD **6b** was isolated with a satisfactory yield of 38% after decomplexation and easy separation from polysubstituted derivatives which are formed in a lower yield (9.5%). In the presence of a smaller amount of benzyl bromide **3** (six to two equivalents, Table 1, Entries B–D), the total yield of substitution was lower. It should be pointed out that the proportion of 2-monosubstituted β-CD (compound **6a**) increased when the concentration of benzyl bromide **3** decreased (Table 1, Entries B–D). The great increase of benzyl bromide **3** significantly increased the formation of disubstituted compounds as by-products (9.5% yield with 8 equiv. of reactant **3**), but four times less polysubstituted derivatives than the desired compound **6b** are obtained. When the reaction was carried out without $CuSO_4$ (Scheme 1, Table 1, Entry E), it was not possible to obtain a good selectivity in favour of position 3 against position 2. Under less basic conditions (Table 1, Entry F), the three regioisomers respectively monobenzylated at O-2 (compound **6a**), O-3 (compound **6b**) and O-6 were detected. Thus, the amount of the base reagent was then not sufficient to quantitatively give the Cu complex. This last assumption was supported by the importance of the reaction time for β-CD complexation with Cu^{II}. When time was increased (70 min instead of 10 min) and with only two equivalents of benzyl bromide (Table 1, Entry G), the selectivity was better. In addition to distortion of the oligosaccharide cavity in the copper–β-CD complex,[9a] steric hindrance caused by copper ions could also modify the electrophile approach and make more difficult the reactivity of the 2-OH which are oriented toward the cavity center in the CD structure. The selective substitution of the 3-O position was then improved.

Identification of monosubstituted β-CD regioisomers was carried out from samples of 2^{I}-*O*- and 3^{I}-*O*-benzyl-β-CDs **6a** and **6b** after final purification by preparative HPLC.†‡ Electrospray ionization mass spectrometry (ESI-MS) experiments provided evidence that both compounds **6a** and **6b** were

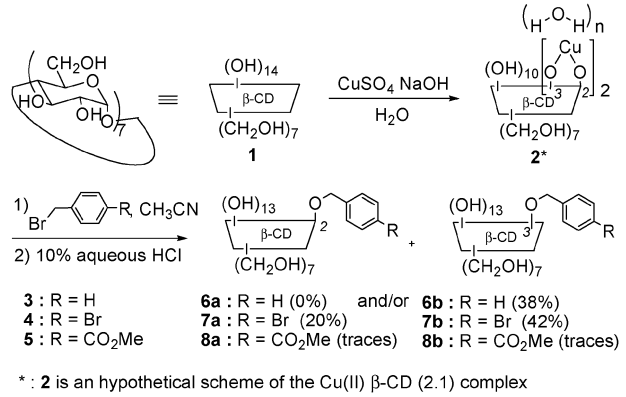
[a] *UMR 6014 CNRS, rue Tesnière, 76821 Mont-Saint-Aignan Cedex, France. E-mail: francois.estour@univ-rouen.fr; Fax: +33-235-522-971; Tel: +33-235-522-451*
[b] *Université de Rouen, UFR de Médecine-Pharmacie, Laboratoire de Pharmacochimie, 22 boulevard Gambetta, 76183 Rouen Cedex 1, France*
[c] *Laboratoire des Glucides, UMR CNRS 6219, Université Picardie Jules Verne, 33 rue St-Leu, 80039 Amiens, France*
[d] *Unité d'Enzymologie, Centre de Recherche du Service de Santé des Armées, 24 avenue des Maquis du Grésivaudan, BP 87, 38702 La Tronche, France*

† Electronic supplementary information (ESI) available: Experimental procedures, NMR data, identification of regioisomers, NMR spectra for representative products. See DOI: 10.1039/b812325j

Table 1 Influence of experimental parameters on the monobenzylation of β-CD

Entry	NaOH (equiv.[a])	Complexation time (min)	Benzyl bromide (equiv.[a])	Total substitution yield (%)	Relative percentage of disubstitution	Relative percentage of monosubstitution[b]
A	25	10	8	47.5	9.5	38[d]
B	25	10	6	27	Traces	27[e]
C	25	10	4	27	Traces	27[e]
D	25	10	2	9	Traces	9[e]
E[c]	25	—	8	32	8	24[e]
F	10	10	2	5.5	Traces	5.5[f]
G	25	70	2	21	Traces	21[d]

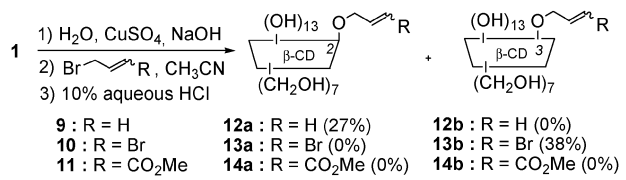
[a] Equiv. = molar equivalents *versus* β-CD. [b] All percentages were determined from an isolated product (or a mixture of isomers) after silica gel chromatography; detection of monosubstituted compounds was carried out by electrospray mass spectrometry and ^{13}C NMR (by the specific chemical shift of the signal which corresponds to the carbon in β-position of the substituted carbon). [c] Experiment E was realized without $CuSO_4$. [d] At O-3 (**6b**). [e] At O-2 (**6a**) and O-3 (**6b**). [f] At O-2 (**6a**), O-3 (**6b**) and O-6.



Scheme 1 Regioselective benzylation at O-3.

monobenzylated. 2D NMR experiments were carried out to determine the location of the substituent in each compound. A HMQC correlation between the proton signals of H-6 (3.66–3.55 ppm) and the signal of C-6 at 59.70 ppm for all glucose units showed that no substitution occurred at O-6 in either case. The 2-*O* substitution in compound **6a** was proved by the specific downfield-shifted value of signal of C-2′ (79.33 ppm) and by the presence of an HMBC correlation between the benzylic protons signal (4.82 and 4.74 ppm) and the carbon signal C-2′. By comparison, the compound **6b** was then identified as the 3-O isomer.

In order to study the scope of 3^{I}-*O*-substitution reactions, this new methodology (*i.e.* 25 equiv. of sodium hydroxide, 8 equiv. of halide *versus* β-CD and complexation time of 70 min) was extended to several substituted benzyl and allyl derivatives (Schemes 1 and 2, Table 2). When the benzyl group bore an electron withdrawing ester function in the *para* position of the nucleus, only traces of monobenzylated derivatives **8a–8b** were detected and no formation of polysubstituted products was observed. On the other hand, when the benzyl group bore an



Scheme 2 Regioselective allylation of β-CD.

electron donor halogen atom in the *para* position of the nucleus, the overall yield of the reaction was the highest (95%) and 42% of the 3-*O*-monosubstituted derivative **7b** was obtained. The corresponding 2^{I}-*O*-substituted β-CD **7a** was also formed in a lower yield (20%). These results highlighted the great importance of the electrophile nature of the substituent on the reaction result. The more the cationic intermediate was stabilized, the more the substitution was favoured. Reactivity of position O-3 was slightly improved by the presence of a bromine atom on the aromatic ring (42% yield for compound **7b** against 38% for compound **6b**). The bromine atom favoured also monosubstitution at O-2 (20%), and it increased also the disubstitution yield (33%).

In the case of allyl bromides (Scheme 2, Table 2) which have a reactivity similar to that of benzyl halides and which are widely used in CDs chemistry,[10] the best efficiency was obtained when the allylic position was substituted by another bromine atom (compound **10**). Efficiency and selectivity of the substitution were also dependent on electrophile amounts as it was the case with benzyl bromide **3**. With eight equivalents of reactant **10**, the total substitution yield was 85% against 41% with unsubstituted allylic compound **9** (Table 2). This best efficiency was mainly in favour of the polysubstitution in this case (30.5% of disubstituted compounds and 16.5% of trisubstituted compounds). No substitution of β-CD was observed when a carboxymethyl group was in the allylic position (compound **11**). Contrary to what was observed with the benzyl bromide reactant **3**, monosubstitution of β-CD by unsubstituted allyl bromide **9** occurred only in the O-2 position and not in the O-3 position. The smaller size of the allyl bromide group compared to that of the benzyl bromide group allowed the approach of 2-OH despite the steric hindrance caused by the copper ions. Even if the 2-OH were oriented towards the cavity of the copper oligosaccharide complex, their relative position likely allowed a higher reactivity with the electrophile substrate. The presence of an additional bromine atom on the electrophile reagent (compound **10**) was unfavourable to substitution at O-2. Bromine being quite bulky, the steric hindrance caused by two halogen atoms did not allow a suitable entry of compound **10** into the cavity of the copper(II)–β-CD complex. Thus, in this case, the monosubstitution occurred at O-3 to give compound **13b** in 38% yield after purification. Although the starting material (compound **10**) was marketed as a mixture of *cis* (40%) and *trans* (60%) isomers, only the *trans* diastereomer (compound **13b**†) could be detected for monosubstitution at O-3. This stereoselectivity was

Table 2 Efficiency of the substitution of β-CD

Method	Electrophile reagent	Total substitution yield (%)	Polysubstitution yield (%)	Monosubstitution yield at O3/at O2 (%)
A[a] Benzylic reagents	**3**	47.5	9.5	38/0
	4	95	33	42/20
	5	Traces	0	Traces
Allylic reagents	**9**	41	14	0/27
	10	85	47	38/0
	11	0	0	0/0
B[b] Benzylic reagents	**3**	23	0	0/23
	4	32	5	8/19
	5	29	9	0/20
Allylic reagents	**9**	29	4	0/25
	10	35	5	0/30
	11	13	0	0/13

[a] H_2O, $CuSO_4$, NaOH; [b] EtONa, DMSO.

presumably due to steric hindrance, the *trans* isomer being less bulky than the *cis*.

A new methodology based on a temporary copper(II)–β-CD complexation allowed the synthesis of 3^I-*O*-derivatives using bulky electrophilic reagents as benzylic compounds **3**, **4** or a bulky allylic reagent **10**. Monosubstitution isolated yields (38–42%) were higher than those obtained at O-2 with a previous method using dimethyl sulfoxide as solvent and sodium ethoxide as a basic agent (Method B, Table 2).[5c] Method B was previously described for introducing a benzylic moiety at O-2 and it was extended here to allylic compounds. The quite common 2^I-*O*-substituted derivatives were generally obtained when the substitution reaction was carried out in dimethyl sulfoxide. In contrast to that, the paramount interest of the new method A based on a temporary complexation of some secondary hydroxy groups in aqueous medium is to mainly obtain 3^I-*O*-substituted derivatives, such as versatile intermediates **6b** and **13b** easy to use in CD chemistry. Compound **6b** which is obtained from cheap and commercially available β-CD, is an important intermediate to access 3-hydroxy permethylated β-CD as a good precursor for a wide variety of monofunctionalized 'permethyl' β-CDs used in chromatography.[11] Compound **13b** contains a halogeno alkenyl substituent which is particularly convenient for palladium-catalyzed coupling reactions. It could then serve as a versatile intermediate to access CD dimers.[12] And finally, this new methodology will soon be applied to the synthesis of functionalized CDs displaying catalytic scavenger properties against xenobiotics and toxicants such as potent nerve agents and organophosphorus pesticides.

This work was supported by DGA (a–DGA/CNRS fellowships to N.M. and R.L.P. b–DSP/STTC contract PEA010807 to F.E./O.L. and P.M), and ANR (contract BLAN06-1_134538). The authors thank C. Dubouilh and A. Martinet for excellent technical assistance, and they also acknowledge B. Brasme, J.C. Debouzy and B. Lefèvre for hepful compound analysis.

Notes and references

‡ Final purification by HPLC was used for analytical reasons. O-3 Regioisomers can be isolated with a satisfactory degree of purity by a common procedure (*i.e.* chromatography on silica gel column followed by a recrystallization) described in the ESI.†

1 (*a*) R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997; (*b*) E. Engeldinger, D. Armspach and D. Matt, *Chem. Rev.*, 2003, **103**, 4147.
2 (*a*) T. A. Gadosy and O. S. Tee, *Can. J. Chem.*, 1996, **74**, 745; (*b*) O. S. Tee, M. Bozzi, N. Clement and T. A. Gadosy, *J. Org. Chem.*, 1995, **60**, 3509.
3 (*a*) D. Gallois-Montbrun, N. Thiebault, V. Moreau, G. Le Bas, J.-C. Archambault, S. Lesieur and F. Djedaïni-Pilard, *J. Inclusion Phenom. Macrocyclic Chem.*, 2007, **57**, 131; (*b*) B. Perly, S. Moutard and F. Djedaini-Pilard, *PharmaChem*, 2005, **4**, 4; (*c*) A. RaufKhan, P. Forgo, K. J. Stine and V. T. D'Souza, *Chem. Rev.*, 1998, **98**, 1977.
4 (*a*) D. Yuan, K. Ohta and K. Fujita, *Chem. Commun.*, 1996, 821; (*b*) M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao and S. Tani, *J. Am. Chem. Soc.*, 2001, **123**, 10760; (*c*) C. Rousseau, F. Ortega-Caballero, L. U. Nordstrom, B. Christensen, B. E. Petersen and M. Bols, *Chem.–Eur. J.*, 2005, **11**, 5094.
5 (*a*) N. Masurier, F. Estour, M.-T. Froment, B. Lefèvre, J.-C. Debouzy, B. Brasme, P. Masson and O. Lafont, *Eur. J. Med. Chem.*, 2005, **40**, 615; (*b*) R. Ramaseshan, S. Sundarrajan, L. Yingjun, R. S. Barhate, N. L. Lala and S. Ramakrishna, *Nanotechnology*, 2006, **17**, 2947; (*c*) N. Masurier, F. Estour, B. Lefèvre, B. Brasme, P. Masson and O. Lafont, *Carbohydr. Res.*, 2006, **341**, 935.
6 B. Siegel, A. Pinter and R. J. Breslow, *J. Am. Chem. Soc.*, 1977, **99**, 2309.
7 (*a*) K. Fugita, T. Tahara, T. Imoto and T. Koga, *J. Am. Chem. Soc.*, 1986, **108**, 2030; (*b*) S. Tian, P. Forgo and V. T. D'Souza, *Tetrahedron Lett.*, 1996, **37**, 8309; (*c*) D. Q. Yuan, T. Tahara, W. H. Chen, Y. Okabe, C. Yang, Y. Yagi, Y. Nogami, M. Fukudome and K. Fujita, *J. Org. Chem.*, 2003, **68**, 9456.
8 J. Jindřich and I. Tišlèrová, *J. Org. Chem.*, 2005, **70**, 9054.
9 (*a*) Y. Matsui, T. Kurita, M. Yagi, T. Okayma, K. Mochida and Y. Date, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2187; (*b*) P. K. Bose and P. L. Polavarapu, *Carbohydr. Res.*, 2000, **323**, 63; (*c*) O. Egyed and V. Weiszfeiler, *Vib. Spectrosc.*, 1994, **7**, 73.
10 (*a*) B. B. Ghera, F. Fache and H. Parrot-Lopez, *Tetrahedron*, 2006, **62**, 4807; (*b*) O. Bistri, P. Sinaÿ and M. Sollogoub, *Chem. Commun.*, 2006, 1112.
11 H. Cousin, P. Cardinael, H. Oulyadi, X. Pannecoucke and J.-C. Combret, *Tetrahedron: Asymmetry*, 2001, **12**, 81.
12 (*a*) O. Bistri, T. Lecourt, J.-M. Mallet, M. Sollogoub and P. Sinay, *Chem. Biodiversity*, 2004, **1**, 12–137; (*b*) A. Binello, B. Rubaldo, A. Barge, R. Cavalli and G. Cravotto, *J. Appl. Polym. Sci.*, 2008, **107**, 2549.