Tetrahedron: *Asymmetry* 19 (2008) 2240–2245

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of polyenyl derivatives of permethylated β-cyclodextrin

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ARTICLE INFO

Article history:
Received 17 July 2008
Accepted 19 September 2008
Available online 15 October 2008

ABSTRACT

Polyenyl derivatives of permethylated 6-amino-6-deoxy-β-cyclodextrin were obtained by polycondensation of acetaldehyde on permethylated 6-amino-6-deoxy-β-cyclodextrin. The acetaldehyde was provided by enzymatic hydrolysis of vinyl laurate or used directly. The mechanism of this polycondensation reaction between an acetaldehyde and modified cyclodextrins is discussed. The immobilised lipase of *Mucor miehei* appeared to increase the rate of this unexpected reaction, as well as permethylated 6-amino-6-deoxy-β-cyclodextrin for the water uptake to form the enamine. This polymerisation-type reaction was optimised to obtain a permethylated 6-*N*-decapentaenyl-6-deoxy-β-cyclodextrin as the main product.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides which are obtained by enzymatic degradation of starch. The best known CDs are composed of six (α-CD), seven (β-CD) or eight (γ-CD) α-(1→4) linked D-glucopyranosides. The hydrophobic, size-selective toroidal cavity is well known to incorporate a large range of hydrophobic molecules.[1] This property has been studied to vectorise drugs.[1] CDs have been modified with hydrophobic moieties (cholesterol for example) to target membranes.[2] Aliphatic chains have also been grafted on β-CD to incorporate these vectors in lipidic bilayers.[3,4] We were also interested in polyenyl grafted CDs because polyenyl moeities are able to interact with fungal cell membranes. Such compounds could have interesting applications as anti-fungal agents of the polyene macrolide antibiotic class.[5–7]

Among hydrolases, lipases are the most widely used enzymes for biocatalysis.[8] These hydrolytic enzymes are able to catalyse synthetic reactions with carbohydrates, lipids and peptides in non-aqueous media and are often used for enantioselective reactions.[9] Several examples of transesterification using vinyl esters are described in the literature.[10,11] Concerning β-CD as a substrate, hydrolase-catalysed transesterification with vinyl laurate leads to a mixture of acetylated compounds.[12] The by-product of the latter reaction is acetaldehyde resulting from the tautomerisation of the released vinyl alcohol. Acetaldehyde has been reported to deactivate some lipases and special care was undertaken to prevent deactivation: working in an open reactor or using trapping agents such as hydrogen sulfite.[10,11,13] In previous work, we reported that the reaction of permethylated 6-amino-6-deoxy-β-cyclodextrin and vinyl esters catalysed by various lipases in organic solvents led to acyl permethylated β-CD. Using specific experimental conditions such as an open reactor, this amidification reaction proceeded in good yield.[14] In a closed reactor, we observed the synthesis of new, interesting compounds by the reaction between permethylated 6-amino-6-deoxy-β-cyclodextrin and acetaldehyde. Herein we report the latter reaction and optimize the conditions to obtain previously unknown compounds.

2. Results and discussion

The chemo-enzymatic synthesis of polyenyl compounds was studied from permethylated 6-amino-6-deoxy-β-cyclodextrin **1** by two different routes (Scheme 1). The β-CD derivative **1** was obtained in a classical way.[15–19]

For the different lipases (*Candida rugosa, Mucor miehei* and *Candida antartica*) used in a free or immobilised form, crude reaction mixtures were monitored using electrospray ionisation mass spectrometry (ESI-MS). Since vinyl laurate is used as a substrate, acetaldehyde is produced during the lipase catalysed transesterification. In a closed reactor, all enzymes led to these polyenyl compounds as by-products by reaction between **1** and acetaldehyde to form Schiff base as already shown with alcohols to form hemiacetals by Isaksson et al.[20]

An optimisation of the reaction was carried out to give only one main compound **5**. The immobilised *M. miehei* lipase (Lipozyme®) was selected because it could be removed easily from the medium by simple filtration. Using vinyl laurate, work-up of the reaction proved very troublesome, because vinyl laurate and lauric acid were present in a large excess. In order to simplify the purification

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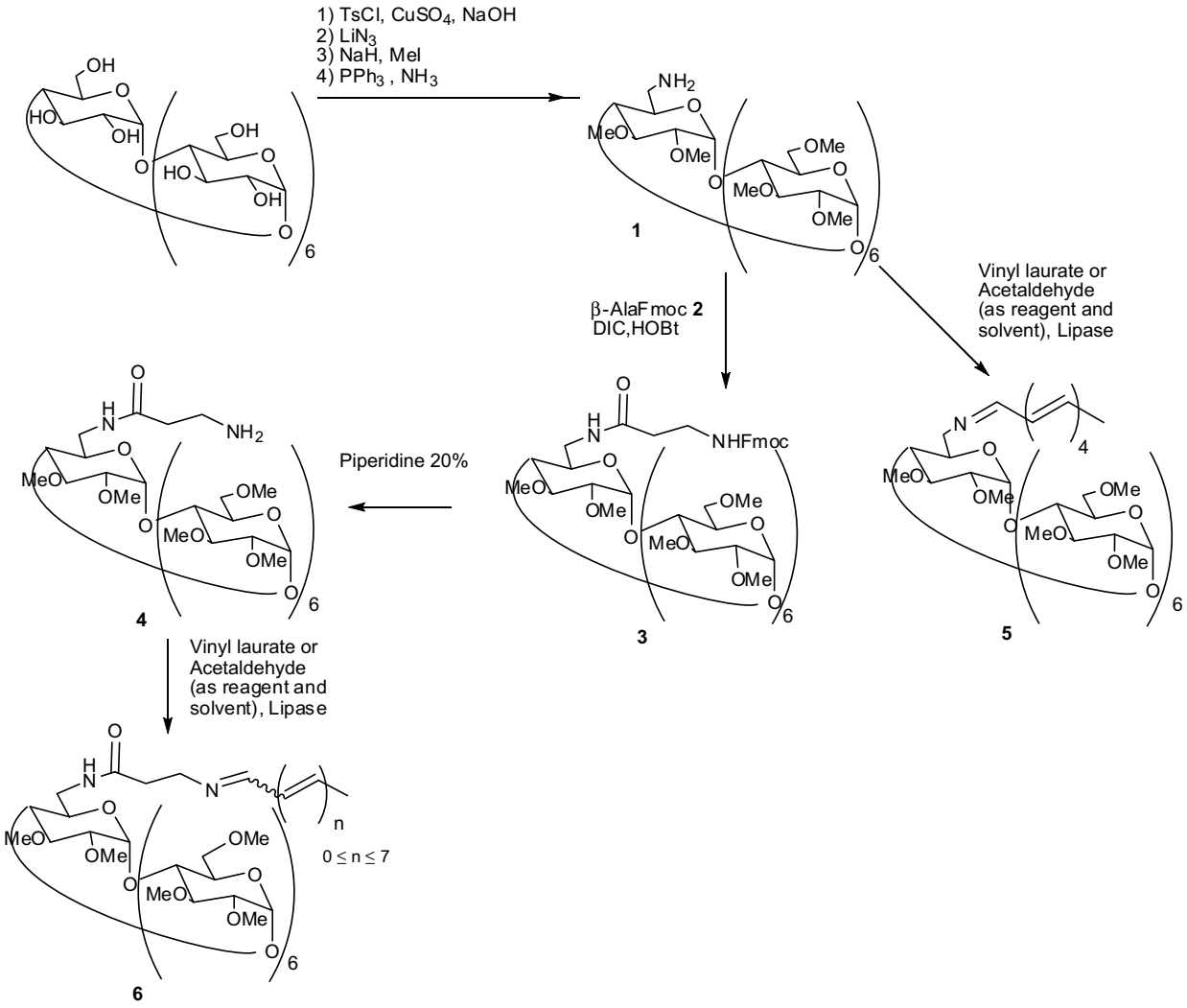
doi:10.1016/j.tetasy.2008.09.017



Scheme 1. Routes to polyenic compounds via enzymatic synthesis.

process and to elucidate the mechanism of this polycondensation, we used the acetaldehyde directly as both substrate and solvent in this reaction. Under these conditions, this reaction led to complete conversion and **5** was obtained in 20% yield after purification (Scheme 1). As expected, the concentration of **5** increased with time and the reaction is remarkably faster when acetaldehyde is used as both solvent and substrate rather than when it results from the hydrolysis of vinyl laurate. When, using vinyl esters, this reaction is in competition with lipase-catalysed amidification which is predominant.[14] It should be noted that the continuous evolution of **5** can be observed by MS, even when the CD substrate consumption has stopped. Moreover the disappearance of **1** over the first 2 h is faster than the increase of **5**. This indicates that the formation of CD derivatives bearing a shorter polyenyl chain occurs during the first steps of synthesis.

Product **5** was difficult to isolate, as is usual with such polyenyl compounds. After semi-preparative HPLC, a complete characterisation was realised. The ESI mass spectrum (Fig. 1A) showed abundant $[M+H]^+$ (m/z 1544.77) and $[M+H+Na]^{2+}$ (m/z 783.86) ions. Good agreement was found between the experimental isotopic pattern of the obtained HRMS $[M+H]^+$ ion of **5** and the one predicted by theoretical means, as shown in Figure 1B.

Moreover if the starting-compound **1** offered no chromophore, **5** exhibited an UV absorbance at 270 nm ($\varepsilon = 3880\ L\ mol^{-1}\ cm^{-1}$) in acetonitrile, which is consistent with a $\pi \rightarrow \pi^*$ transition. The IR spectrum of **5** was recorded, and absorption bands were observed between 1600 and 1720 cm^{-1} which correspond to C=C or C=N stretching assignments. Finally, ^1H NMR spectroscopy (Fig. 2) was performed on **5** and the specific signals of vinylic protons were observed in range from 6.0 to 7.3 ppm with coupling constants of 14.5–15.5 Hz which could indicate that the main compound was the *E*-isomer. Moreover, both quadruplets with 1.7 and 6.9 Hz could be assigned to H_α and H_β of the methyl group of **5** in the main non-tautomerised form. This hypothesis is in agreement with the absence of the methylene group and the presence of a methyl group at 19.3 ppm on a DEPT 135 spectrum.

We postulate that these results are consistent with the nucleophilic attack of the amino group on the acetaldehyde, followed by the dehydration step and tautomerisation to lead to an enamine which then reacts with another molecule of acetaldehyde (Scheme 2).

Per-deuterated acetaldehyde was used to provide further evidence for the proposed polycondensation mechanism. The MS spectrum of the crude mixture was realized (Fig. 3).

According to the proposed mechanism (Scheme 2), 11 D were expected to be incorporated leading to a theoretical $[M+H]^+$ ion at m/z 1556.9 (Fig. 3C). The experimental results showed that there are indeed mainly five acetaldehydes-d_4, which are condensed on the amino group of compound **5** (Fig. 3G). Nevertheless, contributions at m/z 1557.9 showed that the H on nitrogen could be

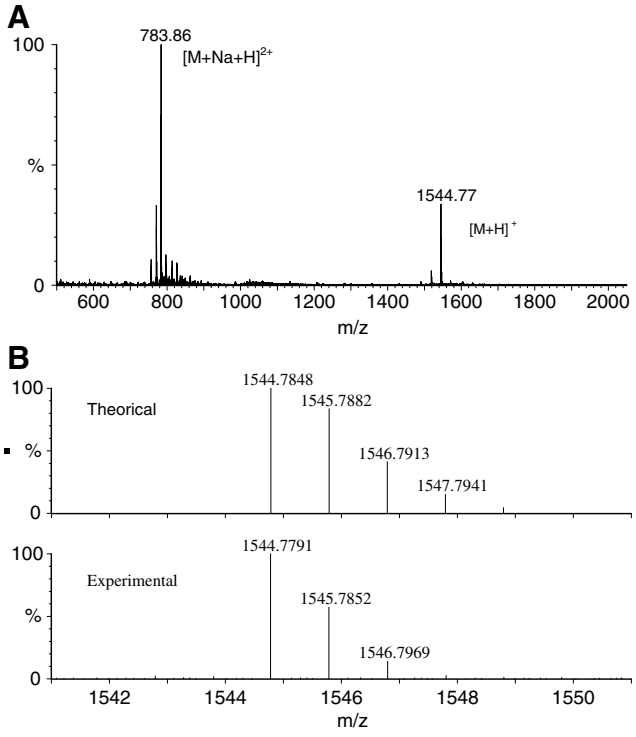


Figure 1. (A) ESI-HRMS spectrum (Q-TOF) of **5**. (B) Theoretical (top) and experimental (bottom) isotopic patterns for the $[M+H]^+$ ion of **5**.

exchanged by D in the medium. Moreover, the polyenic chain is sensitive to D/H exchanges to lead to more or less deuterated compounds.

In order to study the influence of the CD on the synthesis, we carried out this reaction with alternative amines, such as ethylamine or butylamine. In the presence of acetaldehyde and an enzyme, no polycondensation was observed with these amines, whereas butylamine reacted with vinyl esters to form amidification product only, without any deactivation of the lipase. It can be concluded that in absence of the permethylated-β-CD derivative **1**, the polycondensation reaction is not favoured. We could suppose that permethylated-β-CD participates to the dehydration. Indeed, the yield of **5** depended on the hydration of **1** and the best results were obtained with carefully dried CD. Furthermore, modified cyclodextrins, and particularly the permethylated β-CD, are already known as protecting agents for enzymes. They maintain the native protein structure in an organic medium, by acting as a pre-treatment when co-lyophilised with the enzyme prior to reactions.[21–25] In other reports,[21–23,25] permethylated β-CD was used to prevent possible damage during lyophilisation of the enzyme before reactions. Compound **1** is thus essential for this reaction, as already described in other enzymatic reactions.[25] In order to determine the influence of the proximity of the cylodextrin from the reaction centre, the synthesis of analogue of **1** with a β-alanine as a spacer arm, was carried out. The β-alanine amino function was protected by a Fmoc group. It was then coupled to permethylated 6-amino-6-deoxy-β-CD **1** in the presence of DIC as a coupling agent. After deprotection of the Fmoc group, compound **4** was used as a substrate in the polycondensation reaction (Scheme 1). As observed by MS, even when the amino group is not close to the CD, the polycondensation occurred but led to a mixture of polyenyl compounds **6**. It appears that the CD has to be close to the amine to control the formation of the main product with **5** ethylene groups.

Finally, we became interested in the enzyme action, which hydrolyzes vinyl esters to provide acetaldehyde; experimental observations showed that it could improve the reaction even if acetaldehyde is used as substrate and solvent. Reaction in the presence or absence of the dedicated enzyme was monitored by LC/MS. We focused on the formation of main compound **5** but we also observed the formation of other products of polycondensation with 1, 2, 3 and 4 ethylene units, as already shown for vinyl laurate[14] but only in very small amounts. The conversion proceeded faster ($Vi = 5.3 \times 10^{-2}$ nM/min) in the presence of lipase than without it ($Vi = 3.2 \times 10^{-2}$ nM/min) and the final concentration of **5** after a 4 days reaction was increased 2-fold (19.3 nM and 9.7 nM) with or without enzyme, respectively. This could be due to protein acid base catalysis.

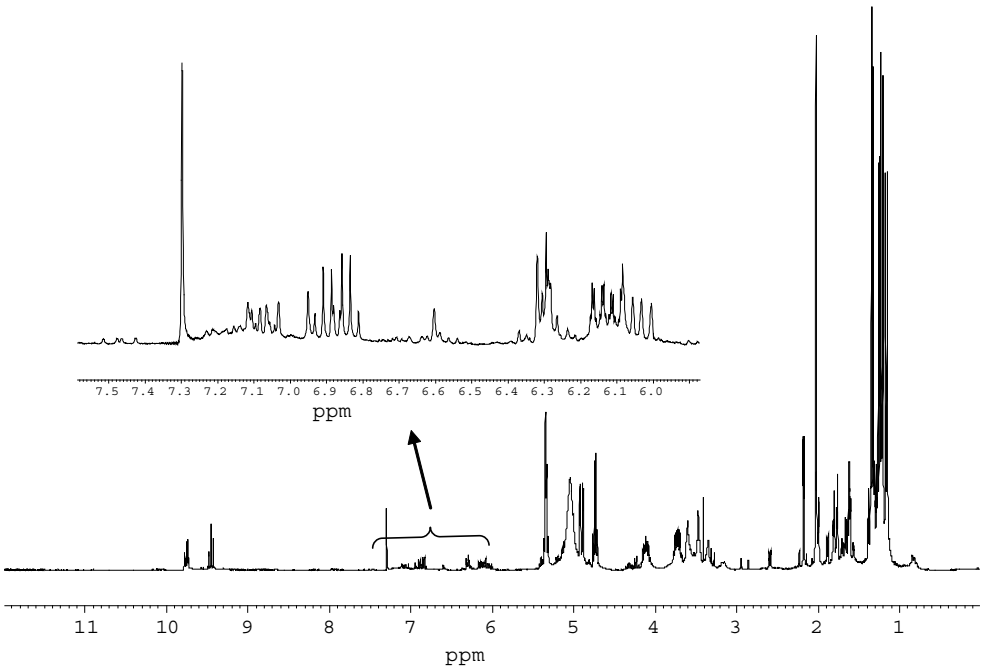
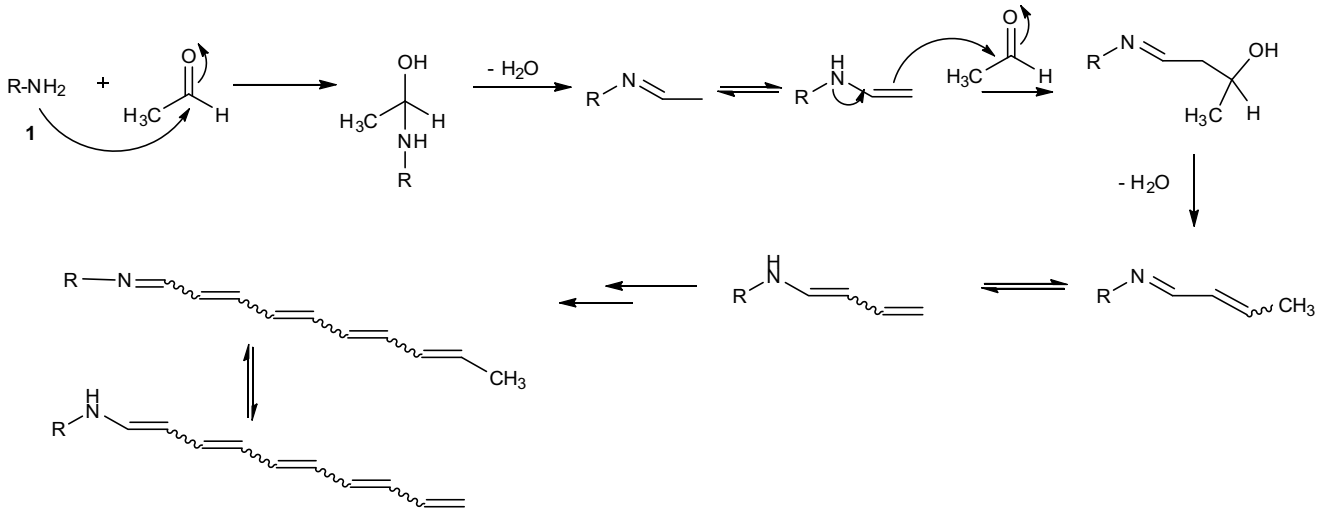


Figure 2. ^1H NMR spectrum (300 MHz, $CDCl_3$) of crude **5** obtained from acetaldehyde, compound **1** and Lipozyme® in closed reactor conditions.



Scheme 2. Proposed mechanism of polycondensation of acetaldehyde on **1**.

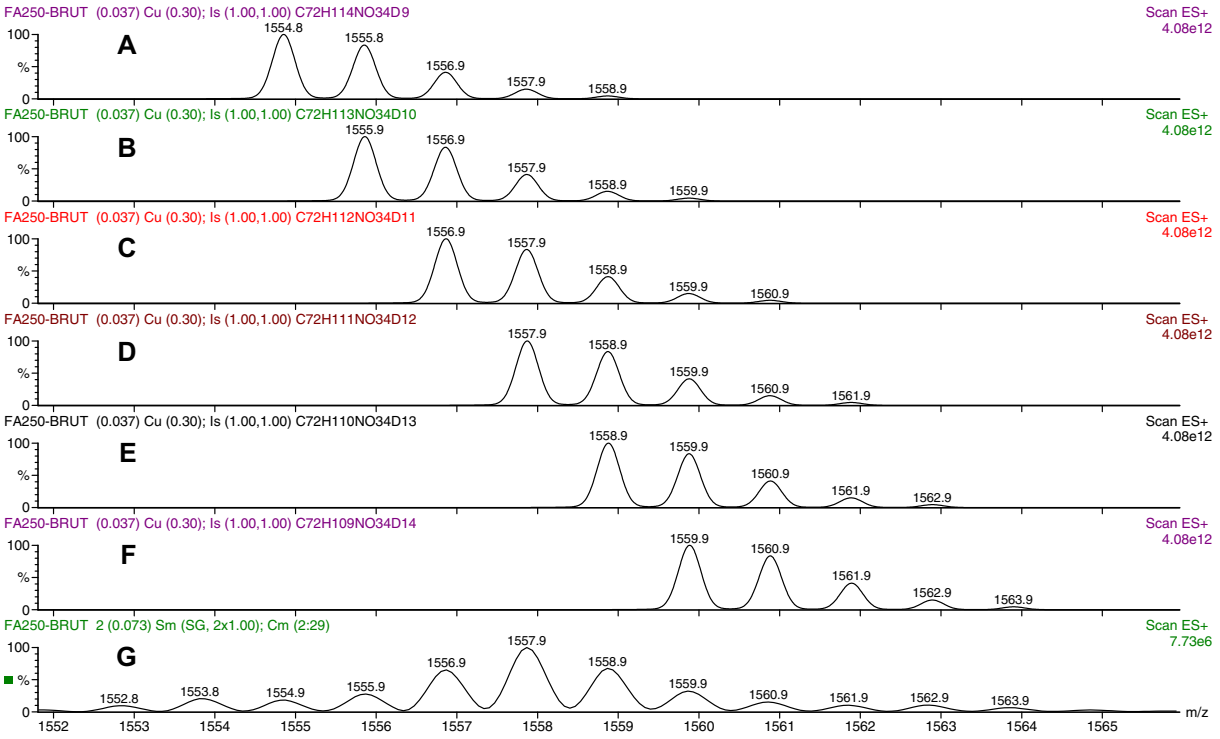


Figure 3. Experimental isotopic pattern obtained for the $[M+H]^+$ ion of deuterated compound **5** (G) compared to simulations with the incorporation of, respectively 9, 10, 11, 12, 13, and 14 deuterium atoms (A, B, C, D, E, F).

3. Conclusion

This chemo-enzymatic way seems to be a very promising approach for an original and efficient synthesis of polyenyl CD derivative as a new vector for therapeutic applications.

4. Experimental

4.1. Chemicals

Native β-cyclodextrin was obtained by Wacker Chemicals (Germany). Vinyl laurate (99% purity) and Lipozyme® were purchased from Fluka Chemie GmbH (Germany). Acetaldehyde (99% purity) was purchased from Aldrich (Germany). The acetaldehyde-d_4 (99% D atom) was purchased from Acros (Belgium). Other chemicals and enzymes were purchased from Sigma, Acros (Belgium) and Fluka Chemie GmbH (Germany). All the solvents employed for the reactions were distilled once before use. Deuterated solvents were purchased from Eurisotop (France).

4.2. Spectroscopic analysis

Stepwise control of the reactions has been readily achieved using ESI-MS in the positive ion mode using a ZQ 4000 quadrupole mass spectrometer (Waters-Micromass, Manchester, UK). High-resolution electrospray mass spectra (ESI-HRMS) in the positive

ion mode were obtained on a Q-TOF *Ultima Global* instrument (Waters-Micromass, Manchester, UK). Data acquisition and processing were performed with MASSLYNX 4.0 software.

Structure elucidation of the final products was readily achieved using standard ^{1}H, ^{13}C, COSY, and HSQC NMR experiments performed at 500.13 MHz or 300.13 MHz using Bruker DRX 500 or DMX 300 spectrometers. Me_4Si was used as the internal standard. Measurements were performed at 298 K. ^{1}H NMR data spectra were collected using 16 K data points. Samples were dissolved in $CDCl_3$. Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter, using a sodium lamp (λ = 589 nm) at 20 °C. IR spectra were recorded using a Nicolet Avatar 320ft-IR spectrometer with an O.M.N.I. Sampler and UV ones with Cary 50 Bio UV–Vis. spectrometer from Varian.

4.3. Chromatographic separations

Analytical TLC was performed using Silica Gel 60 F_{254} plates (Merck, Germany) (eluent: CH_2Cl_2/MeOH 9:1) followed by charring with vanillin–H_2SO_4.

LC/MS conditions: A symmetry® C_{18}-bonded silica column (4.6 × 150 mm, 5 μm, Waters) was used, elution was performed at 0.8 mL min^{-1} using an isocratic eluent of methanol (100%). The effluent from the column was directed towards the ESI source of the ZQ 4000 instrument. LC/ESI-MS data were recorded in the positive ion mode. The source and desolvation temperatures were kept at 120 and 250 °C, respectively. Nitrogen was used as a drying and nebulising gas at flow rates of 450 and 100 L/h, respectively. The capillary voltage was 2 kV and a cone voltage of 100 V was used. Scanning was performed in the range 250–1850 Da at a scan rate of 1.5 s/scan.

For kinetic studies, β-CD$(OMe)_{21}$ was chosen as the internal standard (C = 0.015 mg mL^{-1}). Aliquots (200 μL) were taken, filtered off and diluted.

4.4. Preparation of cyclodextrin derivatives used as an acceptor

4.4.1. 6^{I}-Amino-6^{I}-deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis(2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose 1

Compound **1** was obtained in four steps from the native cyclodextrin, as already described in the literature.[15,16] It was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 (v/v), R_f 0.50) with 30% yield. Analytical data were identical with literature.[15,16]

Compound **1** must be freeze-dried for 24 h and then dried under reduced pressure at 35 °C in presence of P_2O_5 overnight before being used in next reactions.

4.4.2. 6^{I}-[*N*-(9-Fluorenemethyloxycarbonyl)-amido-β-alanyl]-6^{I}-deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis (2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose 3

Under an N_2 atmosphere, Fmoc-β-Ala-OH **2** (65 mg, 0.21 mmol, 1.5 equiv) was dissolved in anhydrous *N,N*-dimethylformamide (DMF) (10 mL) at room temperature. To this solution, *N,N′*-diisopropylcarbodiimide (DIC) (0.22 mL, 2.1 mmol, 10 equiv) and hydroxybenzotriazole (HOBt) (189 mg, 2.1 mmol, 10 equiv) were added. The reaction mixture was stirred for 2 h at room temperature and then, a solution of **1** (200 mg, 0.14 mmol, 1 equiv) in chloroform (6 mL) and triethylamine was added. The reaction was carried out overnight at room temperature and under N_2. The solvent was removed by evaporation under reduced pressure and the residue was purified by dialysis against deionized water over 24 h (Spectra/Por, MWCO 1000 Da, diameter 24 mm, 4.6 mL/cm) to give after evaporation the compound **3** as a yellow oil (120 mg, 50%). R_f 0.54 (CH_2Cl_2/MeOH 9:1 (v/v)); $[\alpha]_D^{20} = +9.8$ (c 0.5, MeOH); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.4 (2H; $CH_{2\alpha}$), 2.9–3.9 (m, 44H; $CH_{2\beta}$, $H_{2\,CD}^{I–VII}$, $H_{3\,CD}^{I–VII}$, $H_{4\,CD}^{I–VII}$, $H_{5\,CD}^{I–VII}$, $H_{6\,CD}^{I–VII}$), 3.4 (s, 21H; $OCH_{3(2)}$), 3.5 (s, 21H; $OCH_{3(3)}$), 3.6 (s, 18H; $OCH_{3(6)}$), 4.2 (1H; CH_{Fmoc}), 4.4 (2H; CH_{2Fmoc}), 5–5.3 (7H; $H_{1\,CD}^{I–VII}$), 5.7 (1H; NH_{CD}), 6.3 (1H; NH_{Fmoc}), 7.3–7.9 (m; 8H; CH_{arom}); δ_C (75 MHz, $CDCl_3$, TMS) 36.1 (1C; $CH_{2\alpha}$), 37.4 (1C; $CH_{2\beta}$), 40.2 (1C; $C_{6}^{I}{}_{CD}$), 47.4 (1C; CH_{Fmoc}), 58.6 (7C; $OCH_{3(2)}$), 59.2 (7C; $OCH_{3(3)}$), 59.6 (6C; $OCH_{3(6)}$), 67.0 (1C; CH_{2Fmoc}), 71.4 (6C; $C_{6\,CD}^{II–VII}$), 71.7 (7C; $C_{5\,CD}^{I–VII}$), 81.6 (7C; $C_{4\,CD}^{I–VII}$), 81.9 (7C; $C_{2\,CD}^{I–VII}$), 82.2 (7C; $C_{3\,CD}^{I–VII}$), 99.2 (7C; $C_{1\,CD}^{I–VII}$), 120.1 (2C; CH_{arom}), 125.2 (2C; CH_{arom}), 127.2 (2C; CH_{arom}), 127.9 (2C; CH_{arom}), 141.5 (2C; C_{arom}), 144.1 (2C; C_{arom}), 155.7 (1C; OCONH), 171.8 (1C; CONH); HRMS (ESI): m/z: 1729.7917 ($[M+Na]^+$), ($C_{80}H_{126}N_2O_{37}Na$ requires 1729.7937).

4.4.3. 6^{I}-Amido-β-alanyl-6^{I}-deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis(2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose 4

The compound **3** (180 mg, 0.11 mmol, 1 equiv) was dissolved in 20% piperidine solution in chloroform (1.5 mL) at room temperature under vigorous stirring. The reaction mixture was heated at reflux for 1 h and then allowed to warm to room temperature. The solvent was removed by evaporation under reduced pressure and the crude product was purified by dialysis against deionized water during 24 h (Spectra/Por, MWCO 1000 Da, diameter 24 mm, 4.6 mL/cm) to give after evaporation compound **4** as a yellow oil (88 mg, 54%). R_f 0.51 (CH_2Cl_2/MeOH 95:5 (v/v)) $[\alpha]_D^{20} = +78$ (c 0.29, MeOH); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.6 (2H; $CH_{2\alpha}$), 3.2–3.8 (44H; $CH_{2\beta}$, $H_{2\,CD}^{I–VII}$, $H_{3\,CD}^{I–VII}$, $H_{4\,CD}^{I–VII}$, $H_{5\,CD}^{I–VII}$, $H_{6\,CD}^{I–VII}$), 3.4 (s, 21H; $OCH_{3(2)}$), 3.5 (s, 21H; $OCH_{3(3)}$), 3.7 (s, 18H; $OCH_{3(6)}$), 5.2 (7H; $H_{1\,CD}^{I–VII}$), 6.5 (1H; NH_{CD}); δ_C (75 MHz, $CDCl_3$, Me_4Si) 33.7 (1C; $CH_{2\alpha}$), 37.4 (1C; $CH_{2\beta}$), 40.4 (1C; $C_{6}^{I}{}_{CD}$), 58.5 (7C; $OCH_{3(2)}$), 59.1 (7C; $OCH_{3(3)}$), 61.5 (6C; $OCH_{3(6)}$), 71.4 (6C; $C_{6\,CD}^{II–VII}$), 71.6 (7C; $C_{5\,CD}^{I–VII}$), 80.5 (7C; $C_{4\,CD}^{I–VII}$), 81.5 (7C; $C_{2\,CD}^{I–VII}$), 82.1 (7C; $C_{3\,CD}^{I–VII}$), 98.9 (7C; $C_{1\,CD}^{I–VII}$), 171.4 (1C; CONH); HRMS (ESI): m/z: 1485.7365 ($[M+H]^+$), ($C_{65}H_{117}N_2O_{35}$ requires 1485.7437).

4.5. *N*-(6^{I}-Deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis(2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose)-decatetra-3,5,7,9-en-1-imine 5

Modified cyclodextrin **1** (100 mg) was dissolved in acetaldehyde (25 mL). The reaction was initiated by adding immobilized *M. miehei* lipase (Lipozyme®, 100 mg, 42 U/g) and carried out at 25 °C under magnetic stirring and atmospheric pressure over 24 h. The reaction was stopped by filtering off the biocatalyst and evaporating acetaldehyde under reduced pressure. Then, purification by semi-preparative HPLC (Symmetry® C_{18}-bonded silica column (19 × 250 mm, 5 μm), 20 mL min^{-1}, acetonitrile/water (90:10 to 100:0 in 50 min) was performed to isolate final product **5** as a yellow oil (21.8 mg, 20%) R_f 0.50 (CH_2Cl_2/MeOH 9:1 (v/v)) $[\alpha]_D^{20} = +10$ (c 0.3, $CHCl_3$); λ_{max} (CH_3CN)/nm 270 (ε dm^3 mol^{-1} cm^{-1} 3880); ν_{max} (KBr)/cm^{-1} = 1600–1720 (C=C); δ_H (300 MHz, $CDCl_3$, Me_4Si) 2.05 (dd, 3H, J = 1.7 and 6.9 Hz, CH_3), 3.2–3.9 (m, 42H, $H_{2\,CD}^{I–VII}$, $H_{1\,CD}^{I–VII}$, $H_{4\,CD}^{I–VII}$, $H_{5\,CD}^{I–VII}$, $H_{6\,CD}^{I–VII}$), 3.4 (s, 21H, $OCH_{3(2)}$), 3.5 (s, 21H, $OCH_{3(3)}$), 3.6 (s, 18H, $OCH_{3(6)}$), 5.0–5.2 (7H; $H_{1\,CD}^{I–VII}$), 6.05 (dd, 1H, J = 8.3 and 14.6 Hz, CH=), 6,12 (ddq, 1H, J = 8.3, 1.7 and 15.3 Hz, CH_{β}=), 6.3 (m, 2H, CH=).6.6 (m, 1H, CH=), 6.9 (ddq, 1H, J = 6.9, 15.3 and 13.6Hz, CH_{α}=), 6.95 (m, 1H; CH=), 7.0–7.2 (m, 2H; CH=); δ_C (125 MHz, $CDCl_3$, Me_4Si) 19.3 (1C, CH_3), 40.4 (1C, $C_{6\,CD}^{I}$), 58.9 (7C, $OCH_{3(2)}$), 59.1 (7C, $OCH_{3(3)}$), 61.0 (6C, $OCH_{3(6)}$), 71.4 (6C, $C_{6\,CD}^{II–VII}$), 71.6 (7C, $C_{5\,CD}^{I–VII}$), 81.5 (7C, $C_{4\,CD}^{I–VII}$), 82.0 (7C, $C_{2\,CD}^{I–VII}$), 82.1 (7C, $C_{3\,CD}^{I–VII}$), 93 (1C, CH=), 99.0 (7C, $C_{1\,CD}^{I–VII}$), 119 (1C, CH=), 130 (2C, CH_{α}= and CH=), 135 (4C, CH_{β}= and 3 CH=), 154 (1C, CH=); HRMS (ESI): m/z: 1544.7791 ($[M+H]^+$), ($C_{72}H_{122}NO_{34}$ requires 1544.7848).

Acknowledgements

This work was supported by the Conseil Régional de Picardie under the scientific 'IBFBIO' program. The authors are also grateful

to Dr. Serge PILARD and Dr. David LESUR for the electrospray MS and HRMS analyses and for valuable comments, and to Dr. Dominique Cailleu and M. David Mathiron for help in NMR experiments.

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