Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5411–5413

TETRAHEDRON LETTERS

Synthesis of symmetrically modified α-cyclodextrins: an efficient and easy method

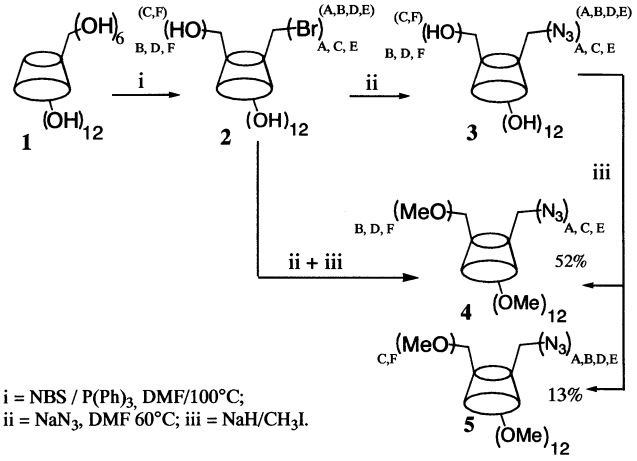
Romain Heck,[a] L. Jicsinszky[b] and Alain Marsura[a,*]

[a]*UMR CNRS 7565-UHP, GEVSM, Faculté de Pharmacie, 5 rue A. Lebrun, F-54001 Nancy Cedex, France*
[b]*Cyclolab Ltd, PO Box 435, H-1525 Budapest, Hungary*

Received 31 March 2003; revised 14 May 2003; accepted 26 May 2003

Abstract—Efficient and simple synthetic methods of designed specific synthons of cyclodextrins are fundamental for the further development of more sophisticated supramolecular devices. Here, a new two step synthesis was proposed for the obtention of the $6^A,6^C,6^E$-triazido-$6^A,6^C,6^E$-trideoxy-$6^B,6^D,6^F$-tri-*O*-methylhexakis-(2,3-di-*O*-methyl)cyclomaltohexaose on a large scale. © 2003 Elsevier Science Ltd. All rights reserved.

In our opinion synthesis of cyclodextrin (Cd) specific synthons should be considered as very important particularly in the conception of new supramolecular devices. So, as it was obvious in this case, the cyclodextrin core plays the role of an organizing template for building more sophisticated structures,[1] finding efficient methods which readily offer large scale of carefully designed and selectively functionalized Cds becomes a true priority. Regarding the literature one can see that only a few methods exist to perform efficient selective functionalized Cd key synthons on a large scale. Recently, in this sense, a first good synthesis of pure A–D disusbstituted β-Cd in a very high yield was reported in the literature.[2] As far as we know, until today only two methods have been reported in the literature for the synthesis of the ^{A,C,E} triazidopermethyl-α-Cd by Boger[3] (overall yield 20%, from α-Cd) and Coleman group (overall yield 18%, from α-Cd).[4] In this work the authors decribed a five step synthesis based on an α-Cd multiple tritylation first step, giving a complex mixture of all the position isomers from which the $6^A,6^C,6^E$-tritrityl-α-Cd (23%)[3] was separated after random chromatographic purifications. In addition, two major problems are also attached and are sometimes, a sudden unexplained poor reproducibility of the reaction which led to unworkable amounts of the desired isomer and the lack of data concerning the $6^A,6^C,6^E$-triazido-$6^A,6^C,6^E$-trideoxy-$6^B,6^D,6^F$-tri-*O*-methylhexakis-(2,3-di-*O*-methyl)cyclomaltohexaose characterization.



Scheme 1. *Reagents and conditions*: (i) NBS/$P(Ph)_3$, DMF/100°C; (ii) NaN_3, DMF, 60°C; (iii) NaH/CH_3I.

The aim of the present work is to propose an improved method for a scale-up obtention of the $6^A,6^C,6^E$-triazido-$6^A,6^C,6^E$-trideoxy-$6^B,6^D,6^F$-tri-*O*-methylhexakis-(2,3-di-*O*-methyl)cyclomaltohexaose (Scheme 1) in two (or three) steps of synthesis from the α-Cd, in a fairly good yield and without heavy purification and separation steps. The first reaction (limitation step) describes the direct bromination of freshly dried α-Cd **1** by NBS into DMF giving after one crystallization the mixture of ^{A,C,E}-tribromo, ^{A,B,D,E}-tetrabromo isomer **2** and small amounts of α-Cd (81%).[5] The mixture of the crude bromomethyl Cds is readily transformed into the final $6^A,6^C,6^E$ - triazido - $6^A,6^C,6^E$ -trideoxy-$6^B,6^D,6^F$ - tri - *O*-methylhexakis-(2,3-di-*O*-methyl)cyclomaltohexaose **4**

* Corresponding author. Tel.: 33-(0)3-8368-2324; fax: 33-(0)3-8368-2345; e-mail: alain.marsura@pharma.uhp-nancy.fr

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01313-3

after an azidation/methylation 'one pot' reaction. The pure final product **4** was obtained after extraction of the solid residue by ether and a simple crystallization in CH_3CN (overall yield 50%). Finally, to obtain pure isomer **5** formed in the reaction as minor product it was necessary to chromatograph the solid residue resulting from extraction. Pure **5** was obtained in 13% yield after crystallization in CH_3CN. The azidation step and methylation step could be performed separately, but it appears that there is no difference in comparison to the 'one pot' procedure.

Analysis of **4** and **5** by FTIR, ^{13}C NMR, elemental analysis and ESI-MS are in agreement with the proposed structure.[6] The positive mode ESI mass spectrum of **4** in MeOH shows the presence of the molecular ion at $[M+H]^+$ 1258.4 amu along with the substitution of one azido group by methoxy group that gives a $[M-N_3+OCH_3]^+$ ion at 1247.4 amu. This substitution does not occur if recording the spectrum in acetone. Characterization and assignments of the signals have been made from an HMBC experiment of compound **4**.[7] The ^{13}C NMR spectrum exhibits the expected very high symmetry, the two C-1 signals at 100.5 ppm are not resolved, as C-2, C-3 at 81.7 ppm and C-6 at 62.2 ppm. The other signals (C-4, C-5) show the expected symmetry doubling (Fig. 1). These results confirm that **4** is the desired isomer in high purity. ^1H NMR spectrum also shows that the symmetry of the cyclodextrin was maintained, and the three kinds of methoxy groups C-2, C-3 and C-6 at 3.66, 3.51 and 3.42 ppm respectively.

In conclusion the simple procedure outlined here provides an interesting access to large quantities of a selectively modified cyclodextrin difficult to obtain until now and which becomes suitable for advanced applications in the field of supramolecular designed devices conception.

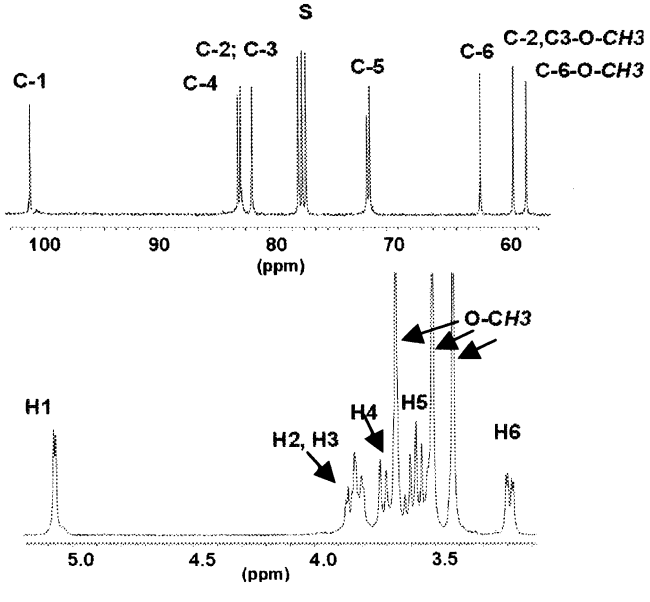


Figure 1.

Acknowledgements

We are grateful to the MRES, to the CNRS and to the Région Lorraine for the financial support. Cyclolab Ltd (Hungary) for the generous gift of Cyclodextrins. The authors wish to thank Mrs. N. Marshall for correcting the manuscript.

References

1. (a) Heck, R.; Dumarcay, F.; Marsura, A. *Chem. Eur. J.* **2002**, *8*, 2438–2445; (b) Charbonnier, F.; Marsura, A.; Roussel, K.; Kovacs, J.; Pinter, I. *Helv. Chim. Acta* **2001**, *84*, 535–551.
2. Pearce, A. J.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3610–3612.
3. Boger, J.; Brenner, D. G.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7630–7631.
4. (a) Ling, C. C.; Coleman, A. W.; Miocque, M. *Angew. Chem. Int. Ed.* **1992**, *31*, 1381–1383; (b) Ling, C. C.; Coleman, A. W.; Miocque, M. *Carbohydr. Res.* **1992**, *223*, 287–291.
5. The yield of 81% represents the yield of the precipitated crude material after sonication which is a mixture of tri and tetrabromo derivatives along variable amounts of starting α-Cd.
6. Structures of all compounds were assigned by ^1H and ^{13}C NMR on a Bruker-DRX 400 spectrometer, FTIR spectra were recorded on a Bruker-Vector 22 spectrometer. Mass-spectra were recorded on an ESI-MS Plateform Micromass Platform spectrometer. Elemental analyses were obtained with a EuroEA-Vector analyzer. The solvents were purified by standard methods.
7. **Hexakis-6^A,6^C,6^E-tribromocyclomaltohexaose and hexakis-6^A,6^B,6^D,6^E-tetrabromocymaltohexaose 2**. 20 mmol of freshly dried α-cyclodextrin (20 g) is dissolved in freshly distilled dimethylformamide (80 mL, previously flushed for 20 min with argon) at room temperature. First *N*-bromosuccinimide (8 equiv., 29.3 g), then triphenylphosphane (5.65 equiv., 29.69 g) is added in one portion to the solution at room temperature. The reaction temperature increases up to 100°C at the end of triphenylphosphine addition. The reaction mixture is immersed into a preheated (80–85°C) oil-bath and stirred for 3 h at 80–85°C. The reaction can be monitored by TLC (silica gel dioxane/NH_4OH 10/7). The reaction mixture is poured onto icy water (800 mL), sonicated for 30 min and allowed to stand for crystallization (overnight). The yellow solid is filtered, washed with water (3×100 mL, pH 2–3, 3–4, 4–5), dried under reduced pressure at moderate temperature (40–45°C) in the presence of P_2O_5. The mother liquor is concentrated to 300 mL, toluene (10 mL) is then added and the mixture is sonicated for 30 min at max 35°C, then allowed to crystallize for one week. The formed solid is filtered off, washed with water (3×25 mL), and dried as above. The product is used for the next step without further purification. TLC (SiO_2, dioxane/NH_4OH 10/7) R_f: tribromo 0.57; tretrabromo 0.63.
6^A,6^C,6^E-Triazido-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-methyl-hexakis-(2,3-di-*O*-methyl)cyclomaltohexaose 4 (Method A). 23.85 mmol of sodium azide (13.4 equiv., 1.55 g) is added

to a solution of 2 g of crude product **2** in freshly distilled DMF (previously flushed for 20 min with argon). The mixture is stirred at 60°C under argon for 24 h. The solution is cooled to room temperature, NaH is added to the solution (excess, 5 g), the mixture is stirred for 1 h then CH_3I is added dropwise to the mixture (temperature should remain below 35°C). The mixture is stirred for 19 h. Excess of NaH is destroyed with MeOH, the solution is concentrated under reduced pressure until a yellow-brown paste is obtained. 800 mL of $CHCl_3$ is added, the white precipitate is filtered off over fritted and thoroughly washed with $CHCl_3$. The yellow solution obtained is evaporated to dryness. The residue is dissolved in a minimum of warm acetonitrile and allowed to crystallize at 4°C for 24 h. The white crystals obtained are filtered off and washed with hexane. Pure compound **4** was obtained as white crystals. Yield (%) 50 (1.26 mmol, 1.58 g) TLC (SiO_2, CH_2Cl_2/dioxane 25/75): R_f: 0.85. IR (KBr), $\nu = 2833$ (CH_3O); 2102 (N_3). ^{1}H NMR ($CDCl_3$): $\delta = 5.07$ (d, H_1, 6H); 3.83 (m, H_2, H_3, 12H); 3.71(d, H_4, 6H); 3.66 (s, OCH_3, 18H); 3.58 (m, H_5, 6H); 3.51 (s, OCH_3, 18H); 3.42 (s, OCH_3, 18H); 3.18 (dd, H_6, 6H). ^{13}C NMR ($CDCl_3$): $\delta = 100.5$ (C_1); 82.9, 82.6 (C_4); 81.7 (C_2, C_3); 71.9, 71.6 (C_5); 62.2 (C_6); 59.4 ($C_{2,3}$-O-CH$_3$); 58.2 (C_6-O-CH$_3$). ESIMS (MeOH): m/z: 1258.4 $[M+H]^+$; 1247.4 $[M-N_3+OMe]^+$. ESIMS (CH_3COCH_3): m/z 1315.3 $[M+CH_3COCH_3]^+$; 1257.7 $[M]^+$. Anal. calcd for $C_{51}H_{91}N_2O_{27}$ (1164.27): C, 52.61; H, 7.88; N, 2.41. Found: C, 52.35; H, 7.85; N, 2.22. (Azides are thermically decomposed with considerable loss of molecular nitrogen which is not detected by the apparatus. This explains that we are unable to dose more than two residual nitrogens in the compound).

6^A,6^C,6^E-Triazido-6^A,6^C,6^E-trideoxy-6^B,6^D,6^F-tri-*O*-methyl-hexakis-(2,3-di-*O*-methyl)cyclomaltohexaose 4 and 6^A,6^B,6^D,6^E-tetraazido-6^A,6^B,6^D,6^E-tetradeoxy-6^C,6^F-di-*O*-methyl-hexakis-(2,3-di-*O*-methyl)cyclomaltohexaose 5 (Method B). 23.85 mmol of sodium azide (13.4 equiv., 1.55 g) is added to a solution of 2.0 g of **2** in freshly distilled DMF (previously flushed for 20 min with argon). The mixture is stirred at 60°C under argon for 72 h. The mixture is cooled to room temperature, remaining salts are filtered over a sintered glass. The filtrate is evaporated until an oily paste is obtained, methanol is added and the solution is evaporated to dryness. The residue is dried under vacuum. The crude mixture of **hexakis-6^A,6^C,6^E-triazidocyclomaltohexaose and hexakis-6^A,6^B,6^D,6^E-tetrazidocyclomaltohexaose 3** is used for the next step without further purification.

NaH (excess, 6 g) is added to a solution of the treated residue containing the hexakis-6^A,6^C,6^E-triazidocyclomaltohexaose and hexakis-6^A,6^B,6^D,6^E-tetrazidocyclomaltohexaose (2.77 g). The mixture is stirred for 1 h then CH_3I is added dropwise to the mixture (temperature should remain below 35°C). The mixture is stirred for 16 h. Excess of NaH is destroyed with MeOH, the solution is concentrated under reduced pressure until a yellow-brown paste is obtained. 800 mL of $CHCl_3$ is added, the white precipitate is filtered off over a sintered glass and thoroughly washed with $CHCl_3$. The yellow solution obtained is evaporated to dryness. CH_2Cl_2 is added to the residue and salts are filtered, the filtrate is evaporated to dryness. Ether is added to the residue, the precipitate is filtered over a sintered glass. The solid residue is chromatographed over a silicagel column (dioxane/CH_2Cl_2 75/25) to separate pure 6^A,6^B,6^D,6^E-tetraazido-6^A,6^B,6^D,6^E-tetradeoxy-6^C,6^F-di-*O*-methylhexakis-(2,3-di-*O*-methyl)cyclomaltohexaose **5** as a white powder, yield (%) 13 (0.32 mmol, 0.410 g). ^{1}H NMR (DMSO-d_6): $\delta = 4.97$ (d, H_1, 2H); 4.64 (d, H_1, 4H); 4.33 (m, H_6, 4H); 3.81–3.84 (m, H_6, 8H); 3.77–3.71 (m, H_5, 1H); 3.56–3.51 (m, H_5, 4H); 3.49 (s, 3H, O-CH_3); 3.45–3.43 (m, H_4, 4H); 3.37 (s, 3H, O-CH_3); 3.35–3.26 (m, H_2, H_3, 12H); 3.23 (s, 3H, O-CH_3); 3.15 (dd, H_5, 1H); 3.02 (dd, H_4, 2H). ^{13}C NMR (DMSO-d_6): $\delta = 99.47$ (C_1); 91.54 (C_1); 82.5, 82.4 (C_4); 81.9 (C_2, C_3); 71.1, 70.8 (C_5); 66.0, 63.6 (C_6); 61.8, 58.7, 58.1 (O-CH$_3$). ESIMS (MeOH): m/z: 1270.4 $[M+H]^+$; 1247.4 $[M-2N_3+2OMe]^+$.

The ether phase was evaporated to dryness and the residue is dissolved in a minimum of warm acetonitrile and allowed to crystallize at 4°C for 24 h. The white crystals obtained are filtered off, washed with hexane. Pure product **4** is obtained as white crystals; yield (%) 52 (1.31 mmol, 1.65 g).