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Tetrahedron
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Tetrahedron 60 (2004) 12163–12168

Synthesis of novel highly water-soluble 2:1 cyclodextrin/fullerene conjugates involving the secondary rim of β-cyclodextrin

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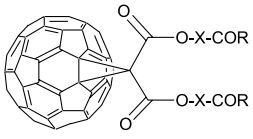
Received 11 August 2004; revised 6 October 2004; accepted 7 October 2004

Available online 28 October 2004

Abstract—Two novel fullerene[60]-cyclodextrin conjugates have been prepared, they display the highest solubility in water reported to date. This is the first synthesis of such conjugates in which the linker is attached to the secondary rim of β-CD.

1. Introduction

The recently described 2:1 cyclodextrin–fullerene conjugates **1** (Fig. 1)[1,2] display high solubility in water, an adequate property for their use in biological systems.[3]



1a R= NH-PMBCD ; X= $(CH_2)_{11}$

1b R= NH-PMBCD ; X= CH_2

1c R= NH-PMBCD ; X= CH_2-CH_2-O-CH_2

1d R= NH-PMGCD ; X= CH_2-CH_2-O-CH_2

Figure 1. The 2:1 CD-C_{60} conjugates linked via the primary rim of the β- or γ-CD.

Since cyclodextrins and permethylcyclodextrins are not toxic, these molecules seem well adapted to study the application to biological problems of the very attractive photo-, electro-chemical and physical properties of fullerenes.[3–5] It was postulated that these conjugates could be present in water equilibria between conformers such as **A**, **B** and **C** (Fig. 2); **A** and **B** could form micelle-like aggregates, while **C** could exist as a non-associated species.[1]

As expected, these compounds were very soluble in water: UV and NMR spectra showed the presence of aggregates; and the 'internal complexation' conformer **C** was not detected. Although this high solubility is convenient for application to biological systems, micellar aggregation may induce chemical,[6–9] electrochemical[10,11] or photophysical[12,13] properties differing from those of the isolated fullerene molecule (see however[14]). It thus seems worthwhile to try new structural modifications in order to obtain cyclodextrin–fullerene conjugates that would be highly water-soluble

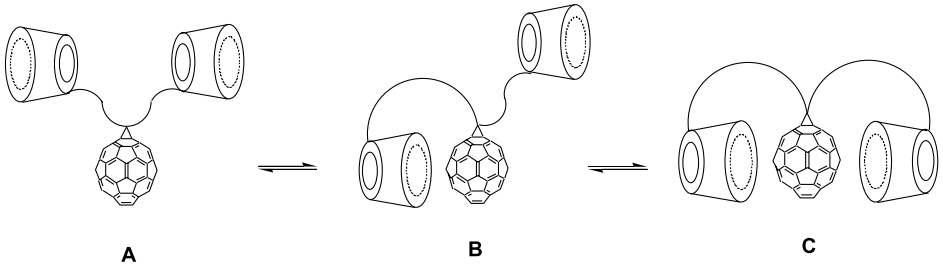


Figure 2. Postulated equilibria of the CD-C_{60} conjugates in water.

Keywords: C_{60}; Conjugate; Cyclodextrin; Fullerene; Synthesis.
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0040–4020/$ - see front matter
doi:10.1016/j.tet.2004.10.015

and, even at the highest concentration, would exist mainly in the form of the internal complex.

Because of the much easier availability of the primary carbon derivatives,[15] the two moieties of all the cyclodextrin–fullerene conjugates reported so far,[1,2,16,17] are linked via the primary external rim of the β- or γ-CD. As suggested previously,[1,2] a possible way to favour internal complexation vs. micelle formation could be to connect the fullerene to the cyclodextrin through the larger secondary rim, in order to favour a conformation D of the internal complex similar to the one (E) found by calculations on the (γ-CD)-fullerene 2:1 complex[18] (Fig. 3).

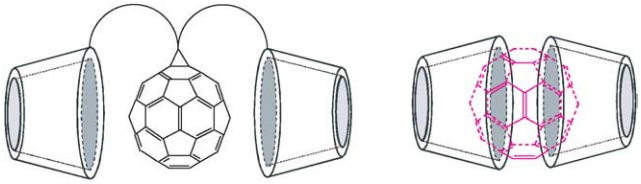
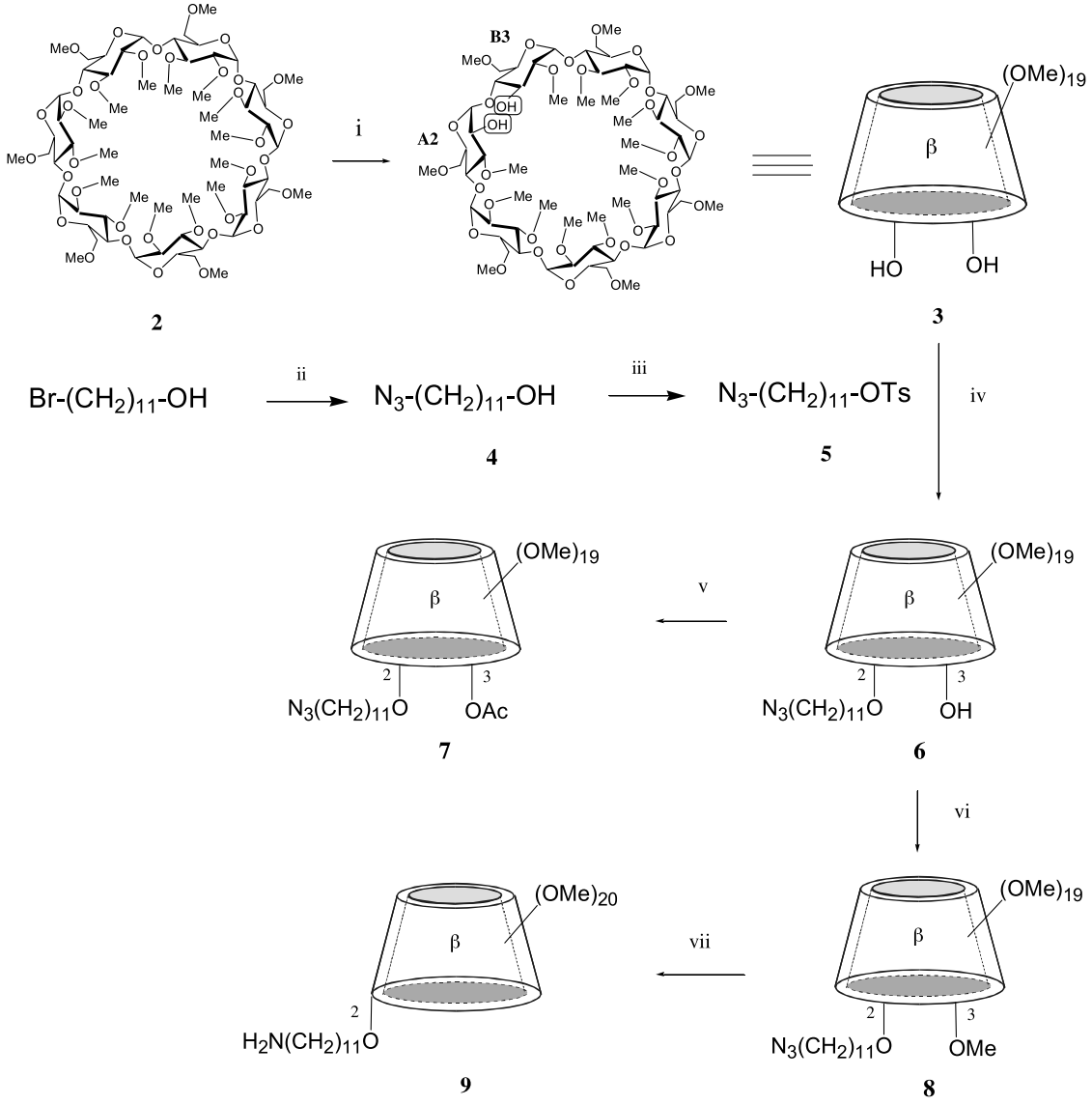


Figure 3. CD-C_{60} conjugate D and γ-CD/C_{60} 2:1 complex E.

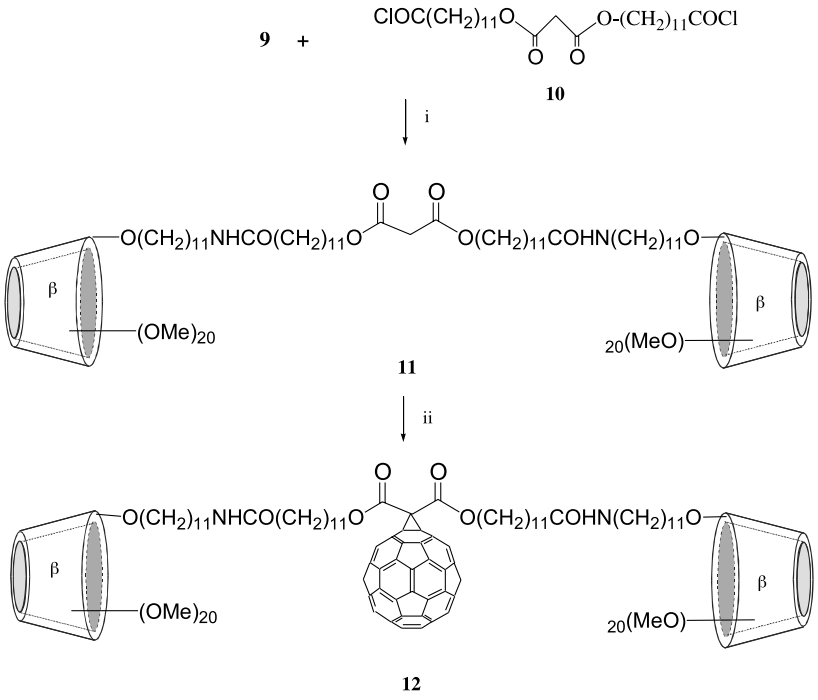
We present here two examples of fullerene–cyclodextrin conjugates in which the linker is attached to the secondary rim. This is indeed the first preparation of such conjugates through what may be a general method. In order to allow flexibility, we have chosen two long linkers consisting of 24 and 14 atoms, respectively. Permethylated β-cyclodextrin (PMBCD) **2** was selected for a better solubility in water compared to the native β-CD.

2. Results and discussion

The key intermediate of this synthesis is a methylated β-CD **3** having specifically located hydroxyl groups available on the secondary rim. The traditional methods for selectively



Scheme 1. Reagents and conditions: (i) DIBAL, 0 °C, 18 h (56%); (ii) NaN_3, DMF, 80 °C, 15 h (94%); (iii) TsCl, Et_3N, CH_2Cl_2, rt, 24 h (94%); (iv) NaH, DMF, 80 °C, 15 h (71%); (v) Ac_2O, Py, 40 °C, 15 h (68%); (vi) MeI, NaH, THF, 66 °C, 5 h (70%); (vii) $HS(CH_2)_3SH$, Et_3N, MeOH, rt, 28 h (95%).



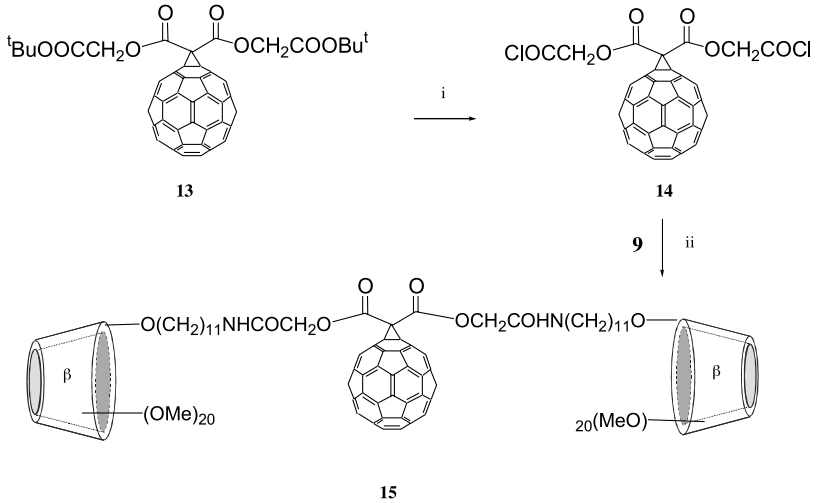
Scheme 2. Reagents and conditions: (i) Et_3N, CH_2Cl_2, rt, 7 h (84%); (ii) C_{60}, CBr_4, DBU, toluene, rt, 24 h (29%).

modified methylated CDs proceeds usually through a temporary regioselective protection of specific hydroxyl groups of the native CD, followed by *O*-methylation and final removal of the protective groups to unmask the required hydroxyl functions. We recently introduced a conceptually new way to obtain directly such compounds.[19–21] This alternative approach is based on the efficient selective de-*O*-alkylation of a fully alkylated α or β-CD, using commercially available diisobutylaluminum hydride (DIBAL-H) as a regioselective chemical 'scalpel'.[22]

Thus (Scheme 1) β-CD A2,B3-diol **3** was regioselectively prepared from the commercially available permethylated β-CD in 56% yield, and condensed with azidotosylate **5**, obtained from bromoundecanol through azidoalcohol **4**, to afford azidoalkyl β-CD **6** in good yield and as a single isomer. The structure of compound **6** was confirmed from the ^{1}H NMR spectrum of derivative **7**, readily obtained from **6** by acetylation; the H-3 of the glucose unit B displayed a deshielded signal at 5.41 ppm (dd, $J_{2,3}=J_{3,4}=10.0$ Hz), indicating that alkylation of **6** took place at position 2. The remaining OH of compound **6** was then methylated to give azidoalkyl permethylated β-CD **8**, which, after treatment by propane dithiol in the presence of triethyl amine,[23] gave aminoalkyl β-CD derivative **9** in 95% yield.

Condensation of **9** with malonic ester diacylchloride **10**[1] gave compound **11**, which through the Hirsch–Bingel reaction[24] with C_{60} afforded, after 24 h at room temperature, the target compound **12**, identified as a methanofullerene mono-adduct (Scheme 2).

The second conjugate was prepared in a slightly modified



Scheme 3. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 4 h; then $(COCl)_2$, CH_2Cl_2, reflux, 21 h. (ii) Et_3N, CH_2Cl_2, rt, 18 h (70%).

way: aminocyclodextrin **9** was reacted with the fullerene diacylchoride **14**, prepared from **13**[1] in the presence of triethylamine, to give conjugate **15** in 70% yield (Scheme 3).

The conjugates **12** and **15** are very soluble in dichloromethane and in chloroform and have a very high solubility in water at 20 °C, greater than 7×10^{-2} M for **12** and 9×10^{-2} M for **15**: clear solutions were obtained after dissolving **12** (32 mg) in water (100 μL), and **15** (35 mg) in water (100 μL). To our knowledge, these are the highest solubilities in neutral water for fullerene derivatives.[4,25]

As for the previously reported CD-C_{60} conjugates, aggregates are present in water solutions: the NMR spectra of **12** and **15** are much broader in water than in chloroform. The UV spectra of dichloromethane solutions of **12** and **15** are not distinguishable from those of **1c**. In water solution, these three compounds have slightly different UV spectra; none of these spectra display the absorption peak at 430 nm observed in dichloromethane solutions, a critical indication of the presence of aggregates.[26–28]

Similarly, water solutions (concentrations 10^{-4}–10^{-5} M) of these conjugates did not show any circular dichroism in the absorption bands of C_{60}, although induced circular dichroism has been observed for a γ-CD/C_{60} complex.[29,30]

3. Conclusion

We have reported here the first preparation of CD-C_{60} conjugates in which the connection is achieved through the secondary rim of the CD. These molecules display the highest solubility in water reported to date. Like most water-soluble fullerenes derivatives[31] (see however[25]) these conjugates are aggregated in water solution. Since it is possible that the affinity of β-CD for the fullerene moiety is not sufficient to induce this type of complexation, work is in progress towards conjugates connected to γ-CD, now[2] through the secondary rim.

4. Experimental

4.1. General procedures

Optical rotations were measured at 20±2 °C with a Perkin Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Chemical Ionisation Mass Spectra (CI-MS ammonia) and Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained with a JMS-700 spectrometer. Elemental analyses were performed by Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. NMR spectra were recorded on a Bruker Avance 250 spectrometer or a Bruker DRX 400 spectrometer at ambient temperature. ^{1}H NMR chemical shifts are referenced to residual protic solvent ($CDCl_3$, $\delta_H=7.30$) or the internal standard TMS ($\delta_H=0.00$). ^{13}C NMR chemical shifts are referenced to the solvent signal ($\delta_c=77.0$ for the central line of $CDCl_3$). Reactions were monitored by thin-layer chromatography (TLC) on a pre-coated silica gel 60 F_{254} plate (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulphuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck).

4.1.1. 11-Azido-1-undecanol (4). A mixture of the 11-bromo-1-undecanol (100 mg, 0.40 mmol), NaN_3 (78 mg, 1.20 mmol) in dry DMF (3 mL) was stirred at 80 °C overnight under argon. The DMF was removed by evaporation under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with water and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by chromatography on silica gel, eluted by CH_2Cl_2 to give the compound **4** as a yellowish syrup (80 mg, 94%). $R_f=0.39$ (CH_2Cl_2/MeOH 50:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.61 (t, $J=6.5$ Hz, 2H, CH_2O), 3.25 (t, $J=6.9$ Hz, 2H, CH_2N_3), 2.12 (s, 1H, OH), 1.61–1.28 (m, 18H, 9×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.83 (CH_2–OH), 51.45 (CH_2–N_3), 32.73, 29.54, 29.44, 29.40, 29.12, 28.81, 26.68, 25.74 (9C, 9×CH_2); MS (ESI): *m/z* 235.8 (100%, M+Na^+); Anal. Calcd for $C_{11}H_{23}ON_3$: C, 61.92; H, 10.89; N, 19.70. Found: C, 61.79; H, 10.84; N, 19.86.

4.1.2. 11-Azido-1-undecanyl tosylate (5). To a solution of **4** (194 mg, 0.91 mmol), TsCl (262 mg, 1.37 mmol) in dry CH_2Cl_2 (4 mL) was added triethylamine (0.4 mL, 2.73 mmol) under argon, the reaction mixture was stirred at room temperature for 24 h. After diluted with CH_2Cl_2, washed with brine, water, dried over $MgSO_4$ and evaporated, the residue was purified by flash-chromatography, eluting with 1:1 cyclohexane/CH_2Cl_2 to offer **5** as a colourless syrup (313 mg, 94%): $R_f=0.39$ (cyclohexane/CH_2Cl_2 1:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.79 (d, 2H, $J_{a,b}=8.3$ Hz, 2×Ph-$H_{2,2'}$), 7.35 (d, 2H, $J_{a,b}=8.1$ Hz, 2×Ph-$H_{3,3'}$), 4.02 (t, $J=6.5$ Hz, 2H, CH_2O), 3.26 (t, $J=6.9$ Hz, 2H, CH_2N_3), 2.45(s, 3H, Ph-CH_3), 1.69–1.23 (m, 18H, 9×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.47 (Ph-C_1), 132.95 (Ph-C_4), 129.62 (Ph-$C_{2,2'}$), 127.64 (Ph-$C_{3,3'}$), 70.51 (CH_2–OH), 51.22 (CH_2–N_3), 29.18, 29.13, 29.11, 28.89, 28.66, 28.61, 28.57, 26.47, 25.09 (9C, 9×CH_2), 21.39 (Ph-CH_3); MS (ESI): *m/z* 390.0 (100%, M+Na^+); Anal. Calcd for $C_{18}H_{29}O_3N_3S$: C, 58.81; H, 7.97; N, 11.43. Found: C, 58.73; H, 7.99; N, 11.30.

4.1.3. Azidoalkyl β-CD (6). A mixture of **3** (423 mg, 0.30 mmol), NaH (60%, 18 mg, 0.45 mmol) in dry DMF (5 mL) under argon was stirred at room temperature for 1 h. Compound **5** (133 mg, 0.36 mmol) was dissolved with dry DMF (2 mL) and added to the above mixture at room temperature, then the reaction mixture was stirred at 80 °C overnight. MeOH was added dropwise to quench the reaction and the solvent was removed by evaporation. After dissolved with CH_2Cl_2, washed with brine and water, dried over $MgSO_4$ and concentrated, the crude product was purified by column chromatography (cyclohexane/acetone 3:2) to afford **6** (342 mg, 71%) as a white amorphous solid: $R_f=0.36$ (cyclohexane/acetone 3:2); $[\alpha]_D=+132$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16–5.12 (m, 4H, 4×H_1), 5.11 (d, 1H, $J_{1,2}=3.6$ Hz, H_1), 5.08 (d, 1H, $J_{1,2}=3.6$ Hz, H_1), 4.97 (d, 1H, $J_{1,2}=3.6$ Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.19, 99.77, 99.68, 99.32, 98.99, 98.85, 98.76 (7C, 7×C_1), 83.32, 82.29, 82.19, 82.03, 81.97, 81.69, 81.64, 81.61, 81.59, 81.47, 81.45, 81.25, 81.19, 80.79, 80.36, 80.21, 80.09, 70.96, 70.91, 70.87, 70.82, 69.99

(28C, 7×C_2, C_3, C_4, C_5), 72.98, 71.40, 71.36, 71.30, 71.10 (8C, CH_2O+7×C_6), 61.81, 61.61, 61.48, 61.41, 61.38, 61.36, 59.00, 58.94, 58.91, 58.90, 58.56, 58.52, 58.49, 58.46, 58.41, 58.35 (19C, 19×OMe), 51.41 (CH_2N_3), 29.60, 29.47, 29.39, 29.37, 29.26, 29.06, 28.76, 26.64, 25.64 (9C, 9×CH_2); MS (FAB): *m/z* 1618.8 (75%, M+Na^+); Anal. Calcd for $C_{72}H_{129}O_{35}N_3$: C, 54.16; H, 8.14; N, 2.63. Found: C, 54.40; H, 8.42; N, 2.56.

4.1.4. Azidoalkyl permethylated β-CD (8). A mixture of **6** (90 mg, 0.056 mmol), NaH (60%, 11.3 mg, 0.28 mmol) in dry THF (2 mL) under argon was stirred at room temperature for 1 h. After CH_3I (17.5 μL, 0.28 mmol) added, the reaction mixture was stirred at 66 °C for 5 h, MeOH was added dropwise to quench the reaction and the solvent was removed by evaporation. The residue dissolved with CH_2Cl_2, washed with brine, water, dried ($MgSO_4$), concentrated, and purified by flash-chromatographed (eluent: cyclohexane/acetone 2:1) to give **8** (63 mg, 70%) as a white amorphous solid: R_f=0.42 (cyclohexane/acetone 3:2); $[\alpha]_D$=+122 (*c* 2.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19–5.16 (m, 4H, 4×H_1), 5.14 (2d, 2H, $J_{1,2}$=3.5 Hz, 2×H_1), 5.08 (d, 1H, $J_{1,2}$=3.4 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.94, 98.93, 98.89, 98.86, 98.83 (7C, 7×C_1), 82.03, 81.95, 81.92, 81.77, 81.75, 81.68, 81.64, 81.61, 81.50, 80.86, 80.41, 80.36, 80.12, 80.02, 79.94, 79.81, 71.00, 70.87, 70.82, 70.74 (28C, 7×C_2,C_3,C_4,C_5), 71.49, 71.42, 71.35, 71.26, 71.16 (8C, CH_2O+7×C_6), 61.61, 61.49, 61.37, 61.34, 61.31, 58.93, 58.91, 58.90, 58.62, 58.58, 58.48, 58.39, 58.33 (20C, 20×OMe), 51.41 (1C, CH_2N_3), 30.09, 30.00, 29.53, 29.43, 29.41, 29.08, 28.76, 26.65, 25.90 (9C, 9×CH_2); MS (FAB): *m/z* 1632.9 (100%, M+Na^+); Anal. Calcd for $C_{73}H_{131}O_{35}N_3 \cdot H_2O$: C, 53.81; H, 8.25; N, 2.58. Found: C, 53.83; H, 8.40; N, 2.24.

4.1.5. Aminoalkyl permethylated β-CD (9). To a solution of **8** (285 mg, 0.18 mmol) in dry MeOH (8 mL) were added 1,3-propanedithiol (0.8 mL) and triethylamine (0.8 mL) under argon, the mixture was stirred at room temperature for 28 h. A white precipitate was formed. After filtration and washing with MeOH, the filtrate was concentrated. The residue was flash chromatographed, eluting with 6:1 ethyl acetate/MeOH, then 3:3:2 ethyl acetate/isopropanol/H_2O to afford **9** (265 mg, 95%) as a white amorphous solid: R_f=0.43 (ethyl acetate/isopropanol/H_2O 3:3:2); $[\alpha]_D$=+133 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19–5.16 (m, 4H, 4×H_1), 5.14 (2d, 2H, $J_{1,2}$=3.5 Hz, 2×H_1), 5.08 (d, 1H, $J_{1,2}$=3.5 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.77, 98.75, 98.69, 98.67 (7C, 7×C_1), 81.85, 81.76, 81.72, 81.62, 81.59, 81.54, 81.32, 80.72, 80.22, 80.02, 79.90, 79.85, 79.69, 79.64, 70.93, 70.82, 70.74, 70.68, 70.6 (28C, 7×C_2,C_3,C_4,C_5), 71.38, 71.28, 71.19, 71.14, 71.02, 70.88 (8C, CH_2O+7×C_6), 61.49, 61.36, 61.35, 61.25, 61.21, 61.19, 58.84, 58.80, 58.54, 58.52, 58.50, 58.43, 58.31, 58.27 (20C, 20×OMe), 39.48 (CH_2NH_2), 29.89, 29.47, 29.43, 29.38, 29.30, 29.00, 28.18, 26.37, 25.83 (9C, 9×CH_2); MS (FAB): *m/z* 1606.8 (20%, M+Na^+), 1584.9 (35%, M+H^+); Anal. Calcd for $C_{73}H_{133}O_{35}N \cdot 3H_2O$: C, 53.49; H, 8.56; N, 0.85. Found: C, 53.41; H, 8.43; N, 1.06.

4.1.6. Malonic acid bis-(11-carboxy-undecyl) acid chloride (10). To a solution of Malonic acid bis-(11-carboxy-undecyl) acid (122 mg, 0.24 mmol) in dry CH_2Cl_2 (5 mL) in ice-bath under argon was added oxalyl chloride (0.063 mL, 0.73 mmol). The mixture was stirred under reflux for 18 h. After the solvent was removed in vacuum, the compound **10** (135 mg, dark blue solid) was obtained and used without further purification.

4.1.7. Permethylated β-CD dimer (11). To a solution of **9** (360 mg, 0.23 mmol) in dry CH_2Cl_2 (12 mL) in ice-bath under argon were added triethylamine (79 μL, 0.57 mmol) and **10** (61 mg, 0.11 mmol, dissolved with 3 mL CH_2Cl_2). The mixture was stirred at room temperature for 7 h. After removal of the solvent, the residue was flash chromatographed, eluting with 8:1 ethyl acetate/MeOH to provide **11** (343 mg, 84%) as a white amorphous solid. R_f=0.52 (EtOAc/isopropanol/H_2O 6:3:1); $[\alpha]_D$=+121 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (t, 2H, *J*=5.5 Hz, 2×NH), 5.19–5.16 (m, 8H, 8×H_1), 5.14 (2d, 4H, $J_{1,2}$=3.6 Hz, 4×H_1), 5.08 (d, 2H, $J_{1,2}$=3.4 Hz, 2×H_1), 4.15 (t, 4H, *J*=6.8 Hz, 2×CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.96, 166.62 (4C, 2×CO–NH, 2×CO–O), 98.90, 98.86, 98.84, 98.82, 98.80 (14C, 14×C_1), 82.00, 81.91, 81.88, 81.75, 81.72, 81.65, 81.61, 81.58, 81.47, 80.84, 80.38, 80.34, 80.11, 80.08, 79.99, 79.89, 79.78, 70.98, 70.85, 70.79, 70.71 (56C, 14×C_2,C_3,C_4,C_5), 71.47, 71.39, 71.31, 71.23, 71.21, 71.13, 66.42, 65.57 (18C, 2×OCH_2, 2×*C*H_2OCO, 14×C_6), 61.59, 61.46, 61.34, 61.31, 61.29, 58.91, 58.87, 58.59, 58.56, 58.46, 58.36, 58.30 (40C, 40×OMe), 41.62, 39.42, 36.81 (5C, OOC–*C*H_2–COO, 2×*C*H_2–NH–CO, 2×*C*H_2–CO–NH), 29.97, 29.61, 29.54, 29.50, 29.48, 29.43, 29.41, 29.36, 29.27, 29.24, 29.10, 28.35, 26.86, 25.89, 25.74, 25.68 (36C, 36×CH_2); MS (FAB): *m/z* 3655.6 (100%, M+Na^+); Anal. Calcd for $C_{173}H_{310}O_{76}N_2 \cdot H_2O$: C, 56.88; H, 8.63; N, 0.77. Found: C, 56.66; H, 8.51; N, 0.91.

4.1.8. 2:1 β-Cyclodextrin/fullerene[60] conjugate (12). To a solution of **11** (263 mg, 0.07 mmol), C_{60} (252 mg, 0.35 mmol) and CBr_4 (58 mg, 0.18 mmol) in dry toluene (25 mL) was added DBU (26 μL, 0.18 mmol) under argon, the mixture was stirred at room temperature for 24 h. The reaction mixture was directly flash chromatographed, eluting first with toluene to remove the excess C_{60}, then 3:2 cyclohexane/acetone to afford **12** as a dark-red solid (88 mg, 29%); $[\alpha]_D$=+10 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (t, 2H, *J*=5.6 Hz, 2×NH), 5.18–5.14 (m, 8H, 8×H_1), 5.13 (2d, 4H, $J_{1,2}$=3.5 Hz, 4×H_1), 5.07 (d, 2H, $J_{1,2}$=3.4 Hz, 2×H_1), 4.50 (t, 4H, *J*=6.5 Hz, 2×CH_2OOC); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.93, 163.60 (4C, 2×COO–, 2×CONH–), 145.28, 145.16, 145.09, 145.08, 144.78, 144.59, 144.57, 144.50, 143.78, 142.98, 142.92, 142.89, 142.10, 141.81, 140.84, 138.90 (C_{60}-sp^2C), 98.91, 98.87, 98.85, 98.83, 98.81 (14C, 14×C_1), 82.01, 81.92, 81.89, 81.75, 81.73, 81.65, 81.62, 81.58, 81.48, 80.85, 80.38, 80.35, 80.13, 80.08, 80.00, 79.90, 79.79, 70.98, 70.86, 70.79, 70.72 (56C, 14×C_2, C_3, C_4, C_5), 71.48, 71.40, 71.32, 71.24, 71.22, 71.14, 67.39, 39.42, 36.82 (23C, 14×C_6, 2×$COOCH_2$, 2×OCH_2, 2×C_{60}-sp^3C, 2×CH_2–NH, bridgehead C), 61.59, 61.45, 61.34, 61.31, 61.29, 58.91, 58.88, 58.59, 58.57, 58.55, 58.46, 58.36, 58.30 (40C, 40×OMe), 29.99, 29.63, 29.56, 29.50, 29.44, 29.33, 29.30, 29.26, 29.14, 28.50, 26.89, 26.81, 25.90, 25.76 (38C, 38×CH_2); MS (FAB): *m/z* 4375.0 (60%,

$M+Na^+$); Anal. Calcd for $C_{233}H_{308}O_{76}N_2 \cdot 10H_2O$: C, 61.72; H, 7.31; N, 0.62. Found: C, 61.44; H, 7.07; N, 0.96.

4.1.9. 2:1 β-Cyclodextrin/fullerene[60] conjugate (15). To a solution of **14** (20.5 mg, 0.021 mmol) in dry CH_2Cl_2 (2 mL) under argon in ice-bath was added triethylamine (11.8 μL) and **9** (66.6 mg, 0.042 mmol, dissolved with 3 mL of CH_2Cl_2). The mixture was stirred at room temperature for 18 h. After concentration at 30 °C, the residue was purified by flash chromatography, eluting with 3:2 cyclohexane/acetone to provide **15** (60 mg, 70%) as a dark-red solid. R_f= 0.5 (cyclohexane/acetone 1:1); $[\alpha]_D = +5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (t, 2H, J=5.7 Hz, 2× NH), 5.18–5.14 (m, 8H, 8×H_1), 5.13 (2d, 4H, $J_{1,2}$=3.5 Hz, 4×H_1), 5.06 (d, 2H, $J_{1,2}$=3.4 Hz, 2×H_1), 4.96 (s, 4H, 2× $OCCH_2COO$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.59, 162.44 (4C, 2×COO–, 2×CONH–), 145.27, 145.18, 144.92, 144.81, 144.69, 144.65, 144.40, 144.33, 143.79, 143.04, 142.93, 142.09, 141.70, 140.98, 139.01 (C_{60}–sp^2C), 98.89, 98.84, 98.82, 98.80, 98.76 (14C, 14×C_1), 81.99, 81.90, 81.87, 81.73, 81.63, 81.59, 81.55, 81.44, 80.84, 80.36, 80.34, 80.14, 80.05, 79.96, 79.85, 79.78, 70.97, 70.87, 70.84, 70.77, 70.70 (56C, 14×C_2, C_3, C_4, C_5), 71.47, 71.38, 71.30, 71.23, 71.20, 71.12, 66.50, 39.63 (23C, 14× C_6, 2×COO*C*H_2, 2×OCH_2, 2×C_{60}–sp^3C, 2×CH_2–NH, bridgehead C), 61.60, 61.45, 61.44, 61.33, 61.29, 61.27, 58.91, 58.86, 58.57, 58.55, 58.46, 58.34, 58.29 (40C, 40× OMe), 29.97, 29.56, 29.52, 29.50, 29.46, 29.44, 29.29, 26.92, 26.80, 25.89 (18C, 18×CH_2); MS (FAB): *m/z* 4094.5 (20%, $M+Na^+$); Anal. Calcd for $C_{213}H_{268}O_{76}N_2 \cdot 8H_2O$: C, 60.67; H, 6.79; N, 0.66. Found: C, 60.36; H, 6.95; N, 0.87.

Acknowledgements

We thank Cyclolab (Hungary) for a generous supply of starting material (PMBCD). Financial support from the CNRS and the ENS is gratefully acknowledged.

References and notes

1. Filippone, S.; Heimann, F.; Rassat, A. *Chem. Commun.* **2002**, 1508–1509.
2. Filippone, S.; Rassat, A. *C. R. Chimie* **2003**, *6*, 83–86.
3. Da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
4. Bosi, S.; Da Ros, T.; Spalluto, G.; Prato, M. *Eur. J. Med. Chem.* **2003**, *38*, 913–923.
5. Jensen, A. W.; Wilson, S. R.; Schuster, D. I. *Bioorg. Med. Chem.* **1994**, *4*, 767–779.
6. Bhattacharyya, K. *Acc. Chem. Res.* **2003**, *36*, 95–101.
7. Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2771.
8. Cordes, E. H. *Pure Appl. Chem.* **1978**, *50*, 617–625.
9. Cordes, E. H.; Dunlop, R. B. *Acc. Chem. Res.* **1969**, *2*, 329–337.
10. Cardona, C. M.; Mendoza, S.; Kaifer, A. E. *Chem. Soc. Rev.* **2000**, *29*, 37–42.
11. Bersier, P. M.; Bersier, J.; Klingert, B. *Electroanalysis* **1991**, *3*, 443–455.
12. Gehlen, M. H.; Deschryver, F. C. *Chem. Rev.* **1993**, *93*, 199–221.
13. Turro, N. J.; Barton, J. K.; Tomalia, D. A. *Acc. Chem. Res.* **1991**, *24*, 332–340.
14. Guldi, D. M.; Hungerbuhler, H.; Asmus, K. D. *J. Phys. Chem. B* **1999**, *103*, 1444–1453.
15. Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
16. Yuan, D. Q.; Koga, K.; Kourogi, Y.; Fujita, K. *Tetrahedron Lett.* **2001**, *42*, 6727–6729.
17. Samal, S.; Geckeler, K. E. *Chem. Commun.* **2000**, 1101–1102.
18. Bonnet, P.; Bea, I.; Jaime, C.; Morin-Allory, L. *Supramol. Chem.* **2003**, *15*, 251–260.
19. Wang, W.; Pearce, A. J.; Zhang, Y.; Sinaÿ, P. *Tetrahedron: Asymmetry* **2001**, *12*, 517–523.
20. Du Roizel, B.; Baltaze, J.-P.; Sinaÿ, P. *Tetrahedron Lett.* **2002**, *43*, 2371–2373.
21. Luo, X.; Chen, Y.; Huber, J. G.; Zhang, Y.; Sinaÿ, P. *C. R. Chimie* **2004**, *7*, 25–28.
22. Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sinaÿ, P. *Chem. Eur. J.* **2004**, *10*, 2960–2971.
23. Zhang, Y.; Iwabuchi, K.; Nunomura, S.; Hakomori, S. *Biochemistry* **2000**, *39*, 2459–2468.
24. Camps, X.; Hirsch, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1595–1596.
25. Hao, J. C.; Li, H. G.; Liu, W. M.; Hirsch, A. *Chem. Commun.* **2004**, 602–603.
26. Bensasson, R. V.; Bienvenüe, E.; Dellinger, M.; Leach, S.; Seta, P. *J. Phys. Chem.* **1994**, *98*, 3492–3500.
27. Bensasson, R. V.; Bienvenüe, E.; Fabre, C.; Janot, J. M.; Land, E. J.; Leach, S.; Leboulaire, V.; Rassat, A.; Roux, S.; Seta, P. *Chem. Eur. J.* **1998**, *4*, 270–278.
28. Quaranta, A.; Mcgarvey, D. J.; Land, E. J.; Brettreich, M.; Burghardt, S.; Schönberger, H.; Hirsch, A.; Gharbi, N.; Moussa, F.; Leach, S.; Gottinger, H.; Bensasson, R. V. *Phys. Chem. Chem. Phys.* **2003**, *5*, 843–848.
29. Priyadarsini, K. I.; Mohan, H.; Mittal, J. P. *Fullerene Sci. Tech.* **1995**, *3*, 479–493.
30. Kohler, G.; Grabner, G.; Klein, C. T.; Marconi, G.; Mayer, B.; Monti, S.; Rechthaler, K.; Rotkiewicz, K.; Viernstein, H.; Wolschann, P. *J. Inclusion Phenom. Macrocyclic Chem.* **1996**, *25*, 103–108.
31. For example, Nakamura, E.; Isobe, H. *Acc. Chem. Res.* **2003**, *36*, 807–815.