Efficient Synthesis of Doubly Connected Primary Face-to-Face Cyclodextrin Homo-Dimers

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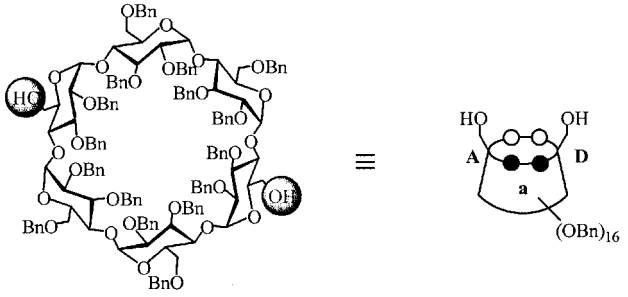
"Head-to-head" type α- and β-cyclodextrin homo-dimers in which the two primary rims are doubly ligated through alkyl chains have been synthesised in high yield by acyclic diene metathesis (ADM), followed by ring-closing metathesis (RCM).

Introduction

Cyclodextrins (CDs) are naturally occurring cyclic oligomers of α-1,4-linked D-glucose units with a unique shape resembling a bottomless flowerpot.[1] This chemical structure features a hydrophobic cavity that can encapsulate various guest molecules to produce supramolecular inclusion complexes.[2,3] During the last twenty years or so, a large number of cyclodextrin dimers have been synthesised.[4] These dimers have the capability for much stronger binding of chemical species than the corresponding CD monomer.

An interesting but uncommon sub-class of such duplexes is made up of doubly bridged CD platforms.[5] It is foreseeable that the imposed mutual orientation of the two CDs in such a duplex, in relation to the conformationally much more mobile singly bridged dimers, might generate novel physical properties. In 1979, Tabushi et al.[5a] synthesised a doubly head-to-head (H,H) bridged duplex for the first time, the overall yield from β-CD being about 2.5%. Although the overall precise yield was somewhat difficult to extract from the published data, the elegant doubly-linked occlusive and aversive CDs studied by Breslow et al.[5b,5c] suffer from the same drawback. Finally, a doubly tethered H,H methylated β-CD was recently prepared by Kuroda et al.[5d] in about 2% yield from β-CD. The H,H dimers were obtained and studied as mixtures of the possible isomers, which could not be separated even by HPLC.[5a,5d] In each of these three cases the overall yield is dramatically eroded by the difficulty involved in preparing the starting regiospecifically bifunctionalised CD in pure form. This limitation is also associated to some extent with the synthesis of singly connected dimers. We have recently discovered a very powerful and expeditious method for the preparation of AD diols from fully benzylated α- or β-CDs.[6] As illustrated in Scheme 1, with α-CD as an example, a truncated cone is commonly used to represent the CD torus, so that the AD type diol **1α** is conveniently depicted as shown on the right part of the scheme, clearly presenting the primary rim, which is that intended to be manipulated.



1α

Scheme 1. Structure (left) and simplified (right) representation of the AD diol **1α**

In this work we would like to demonstrate how the diols **1α** and **1β** can be efficiently converted into homo-dimeric CDs. They can be described as two CDs nicely orientated in a "head-to-head" (HH) fashion through a double polyalkyl chain ligation, as schematically depicted in Scheme 2. It should be noted that head-tail nomenclature suffers from disparity. Some authors define the secondary hydroxy rim as the head,[7a] whereas others, including us, prefer to identify the primary hydroxy site of the CD as the head.[7b]

About the Ring Nomenclature of Substituted β-Cyclodextrins

We would first like to discuss some aspects of the nomenclature of the substituted β-CD derivatives used in this work. The ABCDEFG naming system for β-cyclodextrin was originally introduced by Breslow.[8,9] The IUPAC rules now require the use of superscript roman numbers (I, II, III…) for labelling of the glucoses, but it is currently still a

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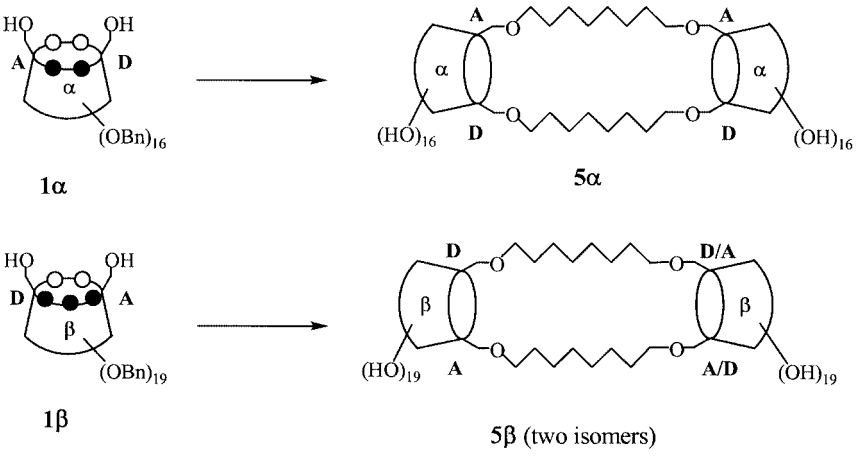
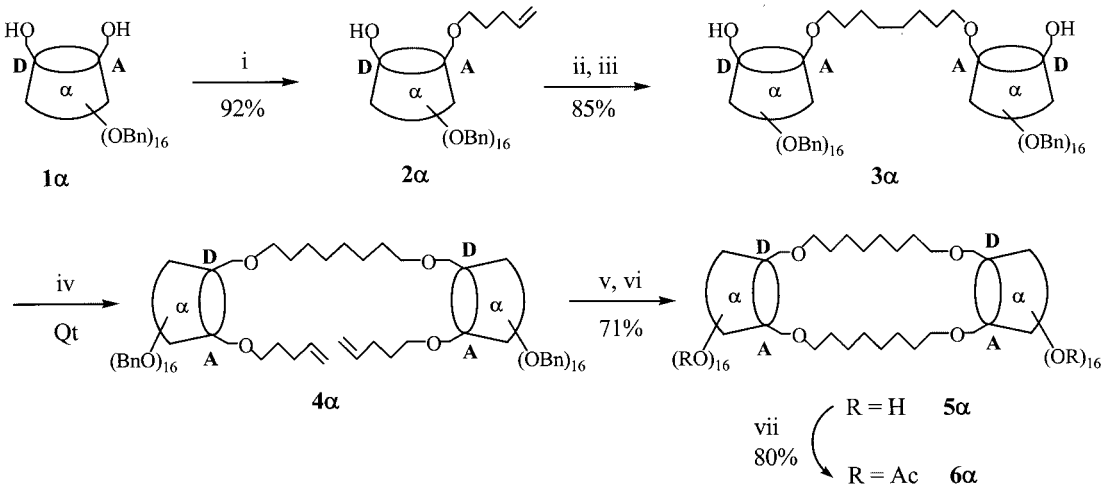


Scheme 2. Two representative examples of a new type of CD-duplexes



Scheme 3. Reagents and conditions: i: 5-bromopent-1-ene (1.7 equiv.), *t*BuOK (1.7 equiv.), THF, 18-crown-6 (0.1 equiv.), room temp., 18 h; ii: $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), CH_2Cl_2 (10^{-1} M), reflux, 6 h then $Pb(OAc)_4$, room temp. overnight; iii: H_2, PtO_2, EtOAc, room temp., 3 h; iv: 5-bromopent-1-ene (6 equiv.), NaH (6 equiv.), DMF, room temp.; v: $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (10 mol %), CH_2Cl_2 (10^{-3} M), reflux, 3 h then $Pb(OAc)_4$, room temp. overnight (87%); vi: H_2, PtO_2, EtOAc, 3 h then Na, liq NH_3/THF (1:1), −33 °C, 1 h (82%); vii: Ac_2O, pyridine, DMAP, room temp., 18 h

common usage to use superscript letters (A, B, C…). The isomer called $6^A,6^D$ is that in which the substituted glucose units are separated by two (and three) unsubstituted glucoses. The original notation, accepted in Chemical Abstracts, for glucose rings refers to a view from the secondary side and named A, B, C, D, E, F, and G clockwise. However, as already pointed out by Tabushi,[10] a view from the primary side is just much more convenient to draw in our case. This would imply a counter-clockwise naming (that is, going from A to B in a counter-clockwise fashion), to keep in agreement with IUPAC rules. In the case of β-cyclodextrin derivatives unsymmetrically disubstituted with two different groups, it is necessary to define A. Faced with this problem, Fujita[11] proposed that the glucose unit A should indicates the one bearing the heavier substituent. Although not specified in this letter, we understood that the "heavier" should be taken in the sense of Cahn, Ingold, and Prelog (*R*,*S*).

To extend this nomenclature and for the sake of simplicity, we propose to assimilate a fully substituted β-CD, such as a perbenzylated or a permethylated one, to a β-CD and compare only the two modified substituents.

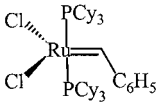
In the case of diol **1β**, by selecting the shortest route OH→OH, the glucose unit named as A, although only "prodifferentiated", is now unambiguously determined. The efficient monopentenylation of **1β** occurs either on the A or the D position to give isomers A,D and A,E, respectively.

Results and Discussion

Chemical Synthesis of the α-CD Doubly Ligated Dimer 5α

A remarkably selective monopentenylation of the diol **1α** was achieved in 92% yield, under the conditions detailed in Scheme 3 (see Exp. Sect.). Compound **2α** is a highly differ-

entiated α-CD derivative expeditiously obtained in three steps and in over 70% yield from natural α-cyclodextrin. This triple differentiation confers a privileged position on compound **2α**, for a variety of transformations into a variety of CD-based molecules. As an example, the conversion into the neoglycolipid type duplex **5α** is now described. In our original piece of work on α-CD duplexes,[12] compound **2α** was first *tert*-butyldimethylsilylated, and then subjected to an acyclic diene metathesis (ADM). Some authors have noted that the presence of an unprotected free alcohol in the molecule significantly lowers the yield of the ADM.[13,14] In some other cases, however, the efficient ADM was compatible with the presence of free hydroxy groups.[15] The alcohol **2α** was now directly subjected to ADM in dichloromethane, by use of Grubbs catalyst **G** as depicted in Scheme 4.



G

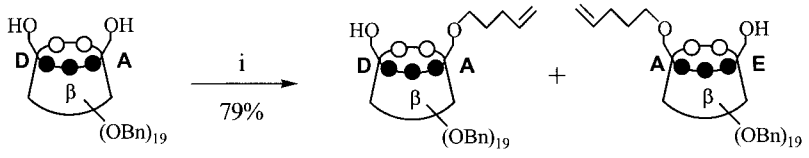
Scheme 4. The Grubbs catalyst **G** used in this work to achieve both acyclic diene metathesis (ADM) and ring-closing metathesis (RCM)

As proposed by Paquette et al.,[16] we used lead tetraacetate to remove all coloured impurities effectively and to deliver colourless CD derivatives suitably pure for further use.

No attempt was made to evaluate the *Z*/*E* ratio, since the first bridge between the two CD platforms is directly saturated to give the expected dimer **3α**. After dipentenylation of this dimer, the diene **4α** underwent efficient (87%) ring-closing metathesis (RCM), and the double bond was then again directly reduced in ethyl acetate with dihydrogen and PtO_2 as a catalyst. Final multi-*O*-debenzylation was best achieved with sodium in liquid ammonia/THF to give the expected duplex **5α** in high yield. The compound **5α** is D_2 symmetrical and was further characterised as the corresponding D_2 symmetrical peracetate **6α**.

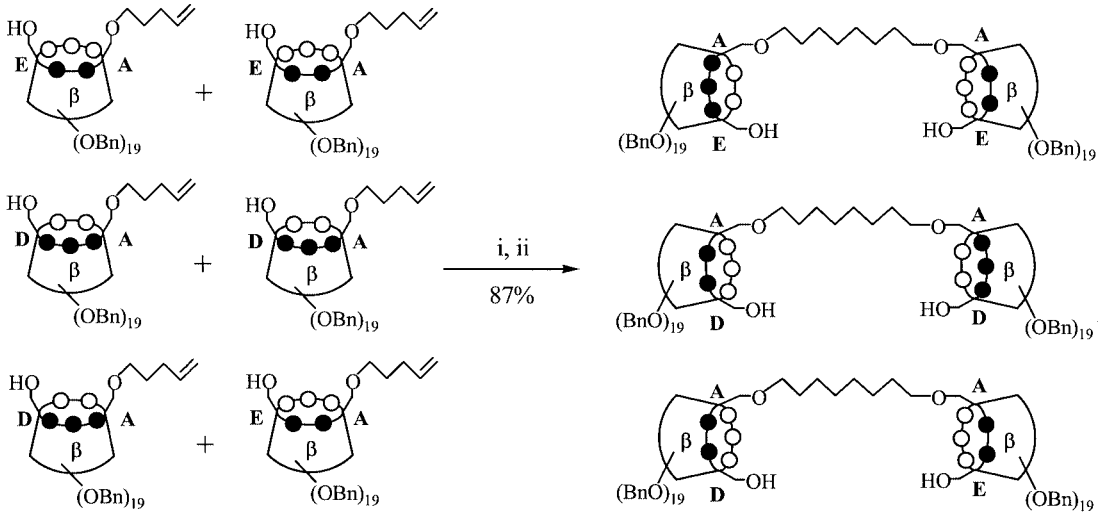
Chemical Synthesis of the β-CD Doubly Ligated Dimer 5β

The α-CD had been selected as a simple model, for symmetry reasons, with which to establish the strategy, which was now extended to the much more interesting β-CD. When the mono-*O*-pentenylation of **1β** was attempted as described previously (see Scheme 3), the isolated yield of **2β** was only 66%, due to extensive formation of bis-pentenylated derivative. The use of NaH as a base did not improve the yield (62%). Finally, it was found that the use of potassium hydride in the presence of tetrabutylammonium iodide



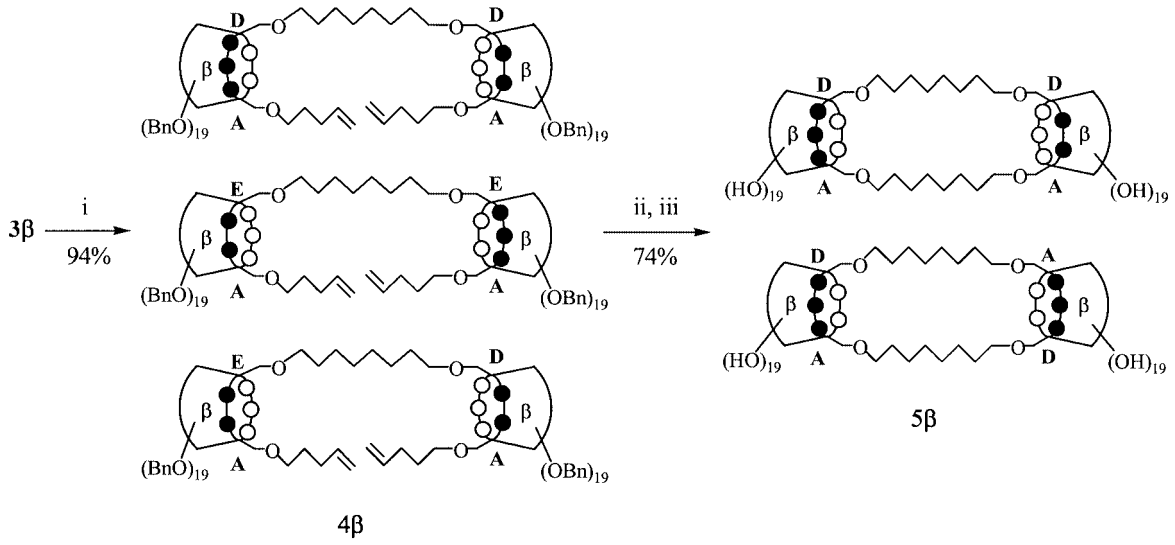
1β **2β**

Scheme 5. Reagents and conditions: i: 5-bromopent-1-ene (1.7 equiv.), KH (1.7 equiv.), THF, nBu$_4$NI (0.1 equiv.), room temp., 18 h



2β **3β**

Scheme 6. Reagents and conditions: i: $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %), CH_2Cl_2 (10^{-1} M), reflux, 6 h then $Pb(OAc)_4$, room temp. overnight; ii: H_2, PtO_2, EtOAc, room temp., 3 h



Scheme 7. Reagents and conditions: i: 5-bromopent-1-ene (6 equiv.), NaH (6 equiv.), DMF, room temp.; ii: $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (10 mol %), CH_2Cl_2 (10^{-3} M), reflux, 3 h then $Pb(OAc)_4$, room temp. overnight (87%); iii: H_2, PtO_2, EtOAc, 3 h then Na, liq NH_3/THF (1:1), −33 °C, 1 h (85%)

gave a satisfactory yield (79%). Compounds **2β** was obtained as an inseparable mixture of the two (AD and AE) isomers (Scheme 5).[17]

Dimerisation of **2β** by ADM in dichloromethane, followed by selective reduction of the double bond, gave the dimer **3β** in 87% yield (Scheme 6). The diol **3β** was an inseparable mixture of the three possible isomers.

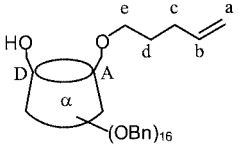
After di-*O*-pentenylation of **3β**, the diene **4β** (three isomers) underwent efficient (87%) ring-closing metathesis (RCM). The double bond was reduced and final multi-*O*-debenzylation was achieved to give the expected duplex **5β** in 74% yield over two steps (Scheme 7). The doubly connected homo-dimer **5β** was obtained as mixture of two isomers, which were not separable at this stage.

With these duplexes to hand, we have studied[18] the reticulation of an amphiphilic polymer made up of a chitosane backbone bearing hydrophobic adamantyl residues.[19] Preliminary results show a strong reticulation of the polymer by **5β**, resulting in a large increase in the viscosity, and quite unique rheological behaviour. Further studies to explore this behaviour are underway, and a detailed account of these physical properties will be published elsewhere.

Experimental Section

General Remarks: Optical rotations were measured at 20±2 °C with a Perkin−Elmer Model 241 digital polarimeter, in a 10 cm, 1 mL cell. Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained with a JMS-700 spectrometer. MALDI mass spectra were recorded on a PerSeptive Biosystems Voyager Elite (Framingham, MA, USA) time-of-flight mass spectrometer. This instrument was equipped with a nitrogen laser (337 nm), a delayed extraction and a reflector. PEG standards were used to calibrate the mass scale by use of the two points calibration software 3.07.1 from PerSeptive Biosystems. The matrix, 2,5-dihydroxybenzoic acid (2,5-DHB), was from Sigma (France) and was used without further purification. ESI mass spectra were recorded with a Q-TOF1 (Micromass) time-of-flight mass spectrometer with a sample cone of 40 V. Elemental analyses were performed by the Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. ^{1}H NMR spectra were recorded with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ or D_2O at ambient temperature. Assignments were aided by COSY experiments. ^{13}C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ or D_2O, with adoption of 77.00 ppm for the central line of $CDCl_3$. Assignments were aided by the J-mod technique and HMQC experiments. Reactions were monitored by thin-layer chromatography (TLC) on a precoated silica gel 60 F_{254} plate (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230−400 mesh, E. Merck).

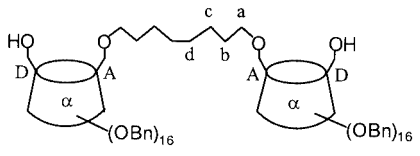
2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^B,6^C,6^E,6^F-Hexadecakis-*O*-benzyl-6^A-*O*-pentenyl-α-cyclodextrin (2α): *t*BuOK (51 mg, 456 μmol), 18-crown-6 (11 mg, 42 μmol), and 5-bromopent-1-ene (54 μL, 455 μmol) were added to a stirred solution of diol **1α** (1 g, 414 μmol) in dry THF (20 mL), under argon at room temp. More *t*BuOK and 5-bromopent-1-ene (0.3 equiv. each) were added twice. The reaction was monitored by TLC (cyclohexane/EtOAc, 3:1) and the system was stirred until complete disappearance of the starting material and formation of the major product (ca 18 h). The reaction mixture was quenched with MeOH (10 mL) and concentrated. A solution of the residue in dichloromethane (100 mL) was washed with aq. sat. NH_4Cl (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography (cyclohexane/EtOAc, 4:1) on silica gel gave **2α** (945 mg, 92%) as a white foam.



$[\alpha]_D^{20}$ = +34 ($CHCl_3$, c = 1.0). R_f = 0.36 (cyclohexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (q, $^3J_{d,c}$ = $^3J_{d,e}$ = 7.0 Hz, 2 H, d-H, d′-H), 2.04 (m, 2 H, c-H, c′-H), 2.82 (t, $^3J_{OH,6}$ =

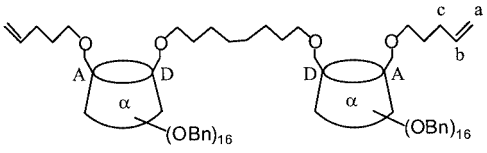
$^3J_{OH,6'}$ = 5.5 Hz, 1 H, OH), 3.19−3.27 (m, 1 H, e-H), 3.38−3.52 (m, 7 H, 4 × 2-H, 2 × 6-H, e′-H), 3.57 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 6.5 Hz, 1 H, 2-H), 3.60 (dd, $^3J_{2,1}$ = 3.7, $^3J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 3.66 (m, 2 H, 2 × 6-H), 3.75 (m, 2 H, 2 × 6-H), 3.83−4.00 (m, 14 H, 3-H, 6 × 4-H, 4 × 5-H, 3 × 6-H), 4.07−4.26 (m, 10 H, 5 × 3-H, 2 × 5-H, 3 × 6-H), 4.34−4.59 (m, 18 H, 18 × CHPh), 4.72 (d, ^2J = 12.1 Hz, 2 H, 2 × CHPh), 4.81−4.98 (m, 13 H, 4 × 1-H, a-H, 8 × CHPh), 5.01 (ddd, $^3J_{a',b}$ = 16.8, $^4J_{a',c}$ = $^4J_{a',c'}$ = 1.6 Hz, 1 H, a′-H), 5.19 (d, ^2J = 11.0 Hz, 1 H, CHPh), 5.24 (d, ^2J = 10.6 Hz, 1 H, CHPh), 5.36 (d, ^2J = 10.6 Hz, 1 H, CHPh), 5.42 (d, ^2J = 10.5 Hz, 1 H, CHPh), 5.52 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, 1-H), 5.55 (d, $^3J_{1,2}$ = 3.7 Hz, 1 H, 1-H), 5.76 (dddd, $^3J_{b,a'}$ = 16.8, $^3J_{b,a}$ = 10.3, $^3J_{b,c'}$ = $^3J_{b,c}$ = 5.6 Hz, 1 H, b-H), 7.15−7.32 (m, 80 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9 (C-d), 30.2 (C-c), 61.3 (C-e), 68.8, 68.9, 69.2, 69.3, 69.4, 69.7 (6 × C-6), 71.2, 71.25 (2 × C-5), 71.3 (OCH_2Ph), 71.35, 71.6, 71.7, 71.8, (4 × C-5), 72.3 (2 × OCH_2Ph), 72.9, 72.95, 73.1, 73.2, 73.25, 73.3, 73.35, 73.4, 74.5 (9 × OCH_2Ph), 75.3 (CH), 75.8 (2 × OCH_2Ph), 76.0 (OCH_2Ph), 76.1 (CH), 76.2 (OCH_2Ph), 77.9, 78.3, 79.0, 79.1, 79.3, 79.5 (6 × C-2), 80.1, 80.2, 80.4, 80.7 (4 × CH), 80.8 (2 × CH), 81.0, 81.1, 81.3, 81.4 (4 × CH), 97.9 (2 × C-1), 97.95, 98.0, 98.3, 98.7 (4 × C-1), 114.9 (C-a), 126.6−128.4 (80 × CH-aromatic), 138.0 (C-b), 137.8, 137.9, 138.0, 138.05, 138.1, 138.15, 138.2, 138.3, 138.4, 138.5, 139.1, 139.15, 139.2, 139.25, 139.3, 139.35 (16 × C-arom. quat.) ppm. MS (FAB, NBA): *m*/*z* (%) = 2505.0 (100) [M + Na]$^+$. $C_{153}H_{164}O_{30}$ (2483): calcd. C 74.01, H 6.66; found C 74.07, H 6.81.

α-Cyclodextrin Diol Dimer 4α: Grubbs catalyst **G** (6.5 mg, 8 μmol) was added under argon at room temp. to a solution of **2α** (400 mg, 161 μmol) in degassed dichloromethane (2 mL). The reaction mixture was heated at reflux for 6 h. $Pb(OAc)_4$ (5 mg, 1.5eq/Ru) was added to the cooled (room temp.) solution, and the reaction mixture was stirred overnight and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 4:1 then 3:1) to give the unsaturated homo-dimer: MS (MALDI-TOF): *m*/*z* (%) = 4957.2 (100) [M + Na]$^+$. A mixture of this product and PtO_2 (140 mg) in EtOAc (15 mL) was stirred under H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite® and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 2.5:1), to give **3α** (338 mg, 85% over two steps) as a white foam.



$[\alpha]_D^{20}$ = +33 ($CHCl_3$, *c* = 1.0). R_f = 0.17 (cyclohexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.0−1.1 (m, 2 H, c-H), 1.2−1.3 (m, 4 H, b-H, c′-H), 1.45−1.55 (m, 4 H, b′-H, d-H), 1.7−1.8 (m, 2 H, d′-H), 2.71 (t, $^3J_{OH,6}$ = 5.4 Hz, 2 H, OH), 3.21 (dd, ^2J = 15.7, $^3J_{a,b}$ = 7.1 Hz, 2 H, a-H), 3.42−3.55 (m, 14 H, 4 × 2-H, 2 × 6-H, a′-H), 3.58 (2 × dd, 4 H, $^3J_{2,3}$ = 9.5, $^3J_{2,3}$ = 9.7 Hz, 2 × 2-H), 3.66 (m, 4 H, 6-H), 3.74 (m, 4 H, 6-H), 3.82−4.04 (m, 28 H), 4.07−4.25 (m, 20 H), 4.34−4.60 (m, 38 H, CHPh), 4.69 (d, ^2J = 12.2 Hz, 2 H, CHPh), 4.74 (d, ^2J = 12.2 Hz, 2 H, CHPh), 4.83−4.97 (m, 18 H, 3 × 1-H, 6 × CHPh), 5.02 (d, $^3J_{1,2}$ = 3.4 Hz, 2 H, 1-H), 5.02 (d, ^2J = 11.2 Hz, 2 H, CHPh), 5.18 (d, ^2J = 11.0 Hz, 2 H, CHPh), 5.25 (d, ^2J = 10.7 Hz, 2 H, CHPh), 5.34 (d, ^2J = 10.7 Hz, 2 H, CHPh), 5.39 (d, ^2J = 10.7 Hz, 2 H, CHPh), 5.46 (d, $^3J_{1,2}$ = 3.6 Hz, 2 H, 1-H), 5.49 (d, $^3J_{1,2}$ = 3.6 Hz, 2 H, 1-H), 7.17−7.31 (m, 160 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6 (C-d), 29.8 (C-c), 29.9 (C-b), 61.4 (C-a), 69.8, 68.9, 69.2, 69.25, 69.3, 69.5 (6 × C-6), 71.2, 71.3, 71.4, 71.6, 71.7, 71.8 (6 × C-5), 72.1 (OCH_2Ph), 72.4 (2 × OCH_2Ph), 72.8, 72.9, 73.0, 73.1 (4 × OCH_2Ph), 73.2 (2 × OCH_2Ph), 73.3, 73.4 (2 × OCH_2Ph), 74.7 (2 × OCH_2Ph), 75.75, 75.8 (2 × OCH_2Ph), 75.9 (2 × CH), 76.1 (OCH_2Ph), 78.0, 78.5, 78.9, 79.1, 79.2, 79.4 (6 × C-2), 79.8, 79.9, 80.1, 80.6, 80.7, 80.75, 81.0, 81.1, 81.2, 81.3 (10 × CH), 97.8, 97.9, 98.0, 98.1, 98.3, 98.8 (6 × C-1), 126.7−128.3 (80 × CH-aromatic), 137.85, 137.90, 137.95, 138.0, 138.1, 138.15, 138.2, 138.3, 138.4, 138.5, 139.1, 139.15 (12 × C-arom. quat.), 139.2 (2 × C-arom. quat.), 139.3, 139.4, (2 × C-arom. quat.) ppm. MS (MALDI-TOF): *m*/*z* (%) = 4959.3 (100) [M + Na]$^+$. $C_{304}H_{326}O_{60}$ (4940): calcd. C 73.92, H 6.65; found C 73.78, H 6.83.

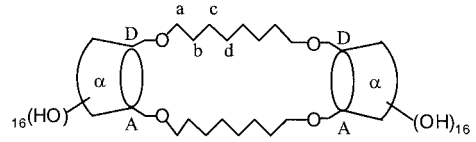
α-Cyclodextrin-bis(pentenyl) Dimer 4α: NaH (60% in oil, 7 mg, 175 μmol) was added slowly, under argon at room temp., to a solution of **3α** (198 mg, 39 μmol) in dry DMF (10 mL). After 1 h, 5-bromopent-1-ene (19 μL, 155 μmol) was added. More NaH and 5-bromopent-1-ene (3 equiv.) were added twice. Stirring was continued until complete disappearance of the starting material (ca 24 h). The reaction mixture was quenched with MeOH (2 mL), diluted with aq. sat. NH_4Cl (15 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography of the residue (cyclohexane/EtOAc, 5:1) on silica gel gave **4α** (204 mg, 100%) as a colourless oil.



$[\alpha]_D^{20}$ = +34 ($CHCl_3$, *c* = 1.0). R_f = 0.49 (cyclohexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45−1.55 (m, 8 H, 2 × CH_2), 1.48−1.58 (m, 4 H, CH_2), 1.68−1.75 (m, 4 H, CH_2), 2.00−2.17 (m, 4 H, c-H), 3.23−3.32 (m, 4 H, 2 × OCH_2), 3.35−3.47 (m, 6 H, 6-H, 2 × OCH_2), 3.50−3.60 (m, 18 H, 6 × 2-H, 3 × 6-H), 3.63 (br. d, ^2J = 11.0 Hz, 4 H, 2 × 6-H), 3.89 (br. d, $^3J_{5,4}$ = 9.4 Hz, 4 H, 2 × 5-H), 3.95−4.24 (m, 44 H, 6 × 3-H, 6 × 4-H, 4 × 5-H, 6 × 6-H), 4.36−4.63 (m, 40 H, 20 × CHPh), 4.90−4.98 (m, 12 H, 6 × CHPh), 4.99−5.12 (m, 8 H, 2 × 1-H, 2 × a-H) 5.15 (d, $^3J_{1,2}$ = 3.0 Hz, 4 H, 2 × 1-H), 5.17−5.26 (m, 12 H, 2 × 1-H, 4 × CHPh), 5.32 (d, ^2J = 10.8 Hz, 4 H, 2 × CHPh), 5.80 (dddd, $^3J_{b,a}$ = 16.8, $^3J_{b,a'}$ = 10.3, $^3J_{b,c'}$ = $^3J_{b,c}$ = 5.6 Hz, 2 H, b-H), 7.16−7.30 (m, 160 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (CH_2), 26.9 (CH_2), 28.8 (CH_2), 30.1 (CH_2), 30.3 (CH_2), 68.9, 68.95, 69.0, 69.3, 69.35, 69.4 (6 × C-6), 70.9 (OCH_2), 71.4, 71.45, 71.5 (6 × C-5), 71.7 (OCH_2), 72.6 (2 × OCH_2Ph), 72.65, 72.7 (2 × OCH_2Ph), 72.8 (2 × OCH_2Ph), 73.3 (2 × OCH_2Ph), 73.35 (2 × OCH_2Ph), 75.25, 75.3 (2 × OCH_2Ph), 75.6 (2 × OCH_2Ph), 75.7 (OCH_2Ph), 78.4 (2 × CH), 78.7 (2 × CH), 79.0, 79.1 (2 × CH), 79.2 (2 × CH), 79.3, 79.4, 79.6, 79.7 (4 × CH), 80.9 (4 × CH), 81.0, 81.1 (2 × CH), 98.5 (C-1), 98.55 (3 × C-1), 98.6 (2 × C-1), 114.7 (C-a), 126.8−128.3 (80 × CH-aromatic), 138.0, 138.05 (2 × C-arom. quat.), 138.1 (C-b), 138.15, 138.2, 138.25, 138.3, 138.35 (5 × C-arom. quat.), 138.4 (3 × C-arom. quat.), 139.3 (4 × C-arom. quat.), 139.35 (2 × C-arom. quat.) ppm. MS (MALDI-TOF): *m*/*z* (%) = 5095.4 (100) [M + Na]$^+$. $C_{314}H_{342}O_{60}$ (5076): calcd. C 74.30, H 6.79; found C 74.68, H 7.11.

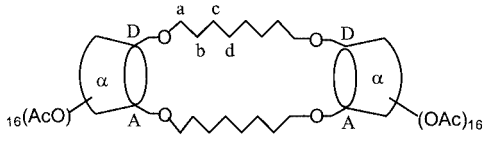
Duplex-α-cyclodextrin 5α: Grubbs catalyst **G** (2 mg, 2.4 μmol) was added under argon at room temp. to a stirred solution of **4α** (119 mg, 23 μmol) in degassed dichloromethane (25 mL). The reac-

tion mixture was heated at reflux for 3 h. $Pb(OAc)_4$ (1.5 mg, 1.5eq/Ru) was added to the cooled solution (room temp.). The reaction mixture was stirred overnight at room temp., and concentrated. Chromatography of the residue (cyclohexane/EtOAc, 5:1) on silica gel afforded the unsaturated duplex: MS (MALDI-TOF): *m/z* (%) = 5067.3 (100) $[M + Na]^+$. A mixture of this product and PtO_2 (30 mg) in EtOAc (5 mL) was stirred under H_2 atmosphere for 3 h, filtered through Celite® and concentrated. The residue was dissolved in a mixture of THF/NH_3 (1:1, 10 mL) at −78 °C. Small pieces of Na (excess) were added. The blue solution was heated at reflux for 1 h (−33 °C), carefully quenched with *i*PrOH (10 mL) and concentrated. A solution of the residue in water (15 mL) was neutralised with IR-120 H^+ resin, diluted with EtOAc (15 mL), stirred vigorously for 30 minutes, and filtered. The organic layer was separated and extracted with water (3 × 10 mL), and the combined aqueous layers were concentrated. The residue was purified by chromatography on Sephadex G25 column (water) to give **5α** (35 mg, 71% over three steps) as a white powder.



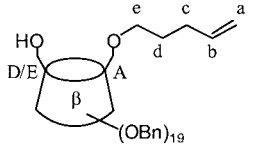
$[\alpha]_D^{20}$ = +122 (MeOH, *c* = 0.5). ^1H NMR (400 MHz, D_2O): δ = 1.25−1.35 (m, 16 H, c-H, d-H), 1.50−1.60 (m, 8 H, b-H), 3.41 (t, $^3J_{4,3} = {}^3J_{4,5}$ = 9.8 Hz, 4 H, 4-H), 3.49 (t, $^3J_{a,b} = {}^3J_{a,b'}$ = 6.5 Hz, 8 H, a-H), 3.51−3.69 (m, 28 H, 3 × 2-H, 4-H, 3 × 6-H), 3.71−4.01 (m, 40 H, 3 × 3-H, 4-H, 3 × 5-H, 3 × 6-H), 4.99 (d, $^3J_{1,2}$ = 3.5 Hz, 4 H, 1-H), 5.01 (d, $^3J_{1,2}$ = 4.0 Hz, 4 H, 1-H), 5.02 (d, $^3J_{1,2}$ = 3.8 Hz, 4 H, 1-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 25.7, 29.1, 29.15 (C-b, C-c, C-d), 60.5 (2 × OCH_2), 70.1 (OCH_2), 71.0 (CH), 71.8 (OCH_2), 71.9 (2 × CH), 71.95 (CH), 72.3 (2 × CH), 73.4, 73.5, 73.8 (3 × CH), 81.1, 81.2, 82.4 (3 × CH), 101.2, 101.8, 102.0 (3 × C-1) ppm. MS (MALDI-TOF): *m/z* (%) = 2187.7 (100) $[M + Na]^+$. MS (ESI-TOF): *m/z* (%) = 1104.38 (100) $[M - 2 H + 2 Na]^{2+}$.

Peracetylated Duplex-α-cyclodextrin 6α: A mixture of **5α** (10 mg, 4.6 μmol), pyridine (50 μL), and DMAP (cat.) in Ac_2O (2 mL) was stirred at rt. overnight, and concentrated. Column chromatography of the residue on silica gel (acetone/cyclohexane, 1.5:1) afforded **6α** (11 mg, 80%).



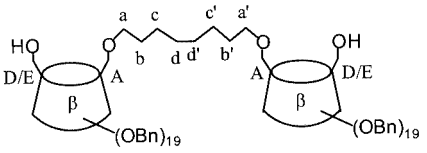
$[\alpha]_D^{20}$ = +93 ($CHCl_3$, *c* = 0.5). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (m, 16 H, c-H, d-H), 1.65 (m, 8 H, b-H), 2.02−2.34 (8 × s, 96 H, 8 × CH_3CO-), 3.86−3.91 (m, 8 H, a-H), 3.75−3.80 (m, 4 H, 6-H), 3.82−3.98 (m, 16 H, 3 × 4-H, 6-H), 4.05−4.12 (m, 4 H, 5-H), 4.13−4.29 (m, 12 H, 2 × 5-H, 6-H), 4.31−4.38 (m, 4 H, 6-H), 4.55−4.62 (m, 8 H, 2 × 6-H), 4.76 (dd, $^3J_{2,3}$ = 10.0, $^3J_{2,1}$ = 3.4 Hz, 4 H, 2-H), 4.80 (dd, $^3J_{2,3}$ = 10.6, $^3J_{2,1}$ = 3.7 Hz, 4 H, 2-H), 4.86 (dd, $^3J_{2,3}$ = 10.6, $^3J_{2,1}$ = 3.3 Hz, 4 H, 2-H), 5.02 (d, $^3J_{1,2}$ = 3.4 Hz, 4 H, 1-H), 5.05 (d, $^3J_{1,2}$ = 3.3 Hz, 4 H, 1-H), 5.27 (d, $^3J_{1,2}$ = 3.7 Hz, 4 H, 1-H), 5.41 (dd, $^3J_{3,2}$ = 10.0, $^3J_{3,4}$ = 8.6 Hz, 4 H, 3-H), 5.57 (dd, $^3J_{3,2}$ = 10.5, $^3J_{3,4}$ = 9.25 Hz, 4 H, 3-H), 5.82 (dd, $^3J_{3,2}$ = 10.6, $^3J_{3,4}$ = 9.2 Hz, 4 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7−20.9 (CH_3CO), 25.8, 29.2, 29.4 (C-b, C-c, C-d), 63.1, 63.2 (2 × OCH_2), 68.1, 69.9 (2 × CH), 70.1 (2 × CH), 70.2, 71.1, 71.4, 71.7 (4 × CH), 71.9 (2 × OCH_2), 72.6, 75.1, 77.7, 78.0 (4 × CH), 95.9, 96.4, 96.7 (3 × C-1), 168.8, 169.3, 169.4, 170.3, 170.4, 170.45, 170.8, 171.2 (8 × CH_3CO) ppm. MS (MALDI-TOF): *m/z* (%) = 3532.1 (100) $[M + Na]^+$. $C_{152}H_{212}O_{92}$ (3511): calcd. C 51.99, H 6.09; found C 52.26, H 6.02.

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^E,6^F,6^G-Octadecakis-*O*-benzyl-6^A-*O*-pentenyl-β-cyclodextrin (2β): KH (30% dispersion in mineral oil, 480 mg, 3.59 mmol) and nBu_4NI (241 mg, 653 μmol) were added at 0 °C to a stirred solution of diol **1β** (9.309 g, 3.27 mmol) in dry THF (300 mL). After 10 min at room temp., 5-bromopent-1-ene (425 μL, 3.59 μmol) was added and the reaction was monitored by TLC (cyclohexane/EtOAc, 3:1). More KH and 5-bromopent-1-ene were added twice in small portions (0.3 equiv.). Stirring was continued until the complete disappearance of the starting material (ca 18 h). The reaction mixture was carefully quenched with MeOH (50 mL) and concentrated. The residue was dissolved in dichloromethane (500 mL), washed with aq. sat. NH_4Cl (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated. Compound **2β** (7.529 g, 79%) was obtained as a white foam after silica gel chromatography (cyclohexane/EtOAc, 3:1).



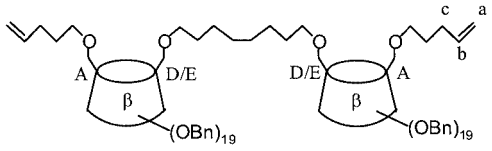
R_f = 0.35 (cyclohexane/EtOAc, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (br. q, ^3J = 7.0 Hz, 2 H, d-H, d′-H), 2.09 (m, 2 H, c-H, c′-H), 2.59 (m, 1 H, OH), 3.30−3.34 (m, 1 H, e-H), 3.37−3.79 (m, 15 H, 7 × 2-H, 7 × 6-H, e′-H), 3.84−4.17 (m, 28 H, 7 × 3-H, 7 × 4-H, 7 × 5-H, 7 × 6-H), 4.38−4.62 (m, 24 H, 24 × CHPh), 4.69−4.87 (m, 8 H, 7 × CHPh), 4.95−5.15 (m, 9 H, 4 × CHPh, 2 × a-H, 3 × 1-H), 5.17−5.31 (m, 5 H, 3 × CHPh, 2 × 1-H), 5.36−5.39 (m, 1 H, 1-H), 5.42 (m, 1 H, 1-H), 5.74−5.88 (2 × dddd, $^3J_{b,a'}$ = 15.0, $^3J_{b,a}$ = 10.1, $^3J_{b,c'} = {}^3J_{b,c}$ = 5.5 Hz, 1 H, b-H), 7.13−7.31 (m, 95 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 28.75 (C-d), 30.2 (C-c), 61.4, 68.5, 68.7, 69.1−69.5, 70.8, 70.9 (OCH_2), 71.2−71.8 (C-5), 72.4−72.8 (OCH_2Ph), 73.1−73.4 (OCH_2Ph), 74.6−75.8 (OCH_2Ph), 78.1−79.8 (CH), 80.7−81.0 (C-3), 97.8−98.8 (C-1), 114.75, 114.8 (C-a), 127.3−128.3 (CH-aromatic), 137.7, 137.9 (C-arom. quat.), 138.0 (C-b), 138.1−138.4 (C-arom. quat.), 138.8−139.3 (C-arom. quat.) ppm. MS (FAB, NBA): *m/z* (%) = 2937.9 (100) $[M + Na]^+$. $C_{180}H_{192}O_{35}$ (2915): calcd. C 74.15, H 6.64; found C 74.02, H 6.76.

β-Cyclodextrin Diol Dimer 3β: Grubbs catalyst **G** (89 mg, 108 μmol) was added under argon at room temp. to a stirred solution of **2β** (6.294 g, 2.159mmol) in degassed dichloromethane (25 mL). The reaction mixture was heated at reflux for 7 h. $Pb(OAc)_4$ (72 mg, 1.5 equiv./Ru) was added to the cooled solution (room temp.). The reaction mixture was stirred under argon overnight and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 4:1 then 3:1) to give the unsaturated homodimer: MS (MALDI-TOF): *m/z* (%) = 5826.1 (100) $[M + Na]^+$. A mixture of this product and PtO_2 (1.79 g) in EtOAc (220 mL) was stirred under H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite® and concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 2.5:1), to give **3β** (5.451 g, 87% over two steps) as a white foam.



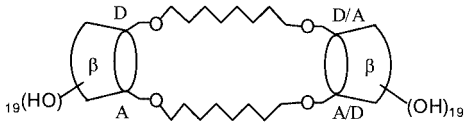
R_f = 0.18 (cyclohexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28−1.32 (m, 4 H, d-H, d′-H), 1.62−1.71 (m, 8 H, c-H, c′-H, b-H, b′-H), 2.48 (br. s, 2 H, OH), 3.20−3.38 (2m, 4 H, a-H, a′-H), 3.39−4.12 (m, 84 H), 4.31−4.62 (m, 46 H, CHPh), 4.63−4.84 (m, 18 H), 4.90−5.06 (m, 8 H), 5.07−5.26 (m, 14 H), 5.32−5.45 (m, 4 H), 7.16−7.31 (m, 190 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2−26.9 (CH_2), 29.7−30.1 (CH_2), 61.5 (OCH_2), 68.6−69.2 (OCH_2), 71.1−71.9 (CH), 72.5−73.3 (O*CH*$_2$Ph), 74.8−75.9 (O*CH*$_2$Ph), 78.4−79.8 (CH), 80.7−81.1 (CH), 97.8−98.9 (C-1), 127.4−128.2 (CH-aromatic), 137.7−138.4 (C-arom. quat.), 138.8−139.3 (C-arom. quat.) ppm. MS (MALDI-TOF): *m*/*z* (%) = 5828.0 (100) [M + Na]$^+$. $C_{358}H_{382}O_{70}$ (5804): calcd. C 74.07, H 6.63; found C 73.98, H 6.82.

β-Cyclodextrin-bis(pentenyl) Dimer 4β: NaH (60% in oil, 83 mg, 2.07 mmol) was added slowly, under argon at room temp., to a solution of **3β** (2.015 g, 345 μmol) in dry DMF (30 mL). After 1 h, 5-bromopent-1-ene (250 μL, 2.07 mmol) was added. More NaH and 5-bromopent-1-ene (3 equiv. each) were added twice. Stirring was continued until complete disappearance of the starting material (ca 24 h). The reaction was quenched with MeOH (5 mL), diluted with aq. sat. NH_4Cl (60 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Chromatography of the residue (cyclohexane/EtOAc, 4:1) on silica gel gave **4β** (1.992 g, 94%) as a colourless oil.



R_f = 0.56 (cyclohexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19−1.36 (m, 12 H, CH_2), 1.41−1.52 (m, 2 H, CH_2), 1.53−1.62 (m, 2 H, CH_2), 1.96−2.13 (m, 4 H, c-H), 3.21−3.39 (m, 8 H, O*CH*$_2$-CH_2), 3.40−3.69 (m, 28 H), 3.84−4.15 (m, 58 H), 4.37−4.59 (m, 46 H, CHPh), 4.63−4.84 (m, 14 H), 4.92−5.31 (m, 32 H), 5.72−5.83 (br. dddd, $^3J_{b,a'}$ = 17.0, $^3J_{b,a}$ = 10.0, $^3J_{b,c'}$ = $^3J_{b,c}$ = 5.0 Hz, 2 H, b-H), 7.10−7.31 (m, 190 H, aromatic-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 28.7, 28.8 (CH_2), 29.7−29.8 (CH_2), 30.2 (CH_2), 69.3−69.5 (OCH_2), 70.7, 70.8 (OCH_2), 71.3−71.4 (CH), 71.6 (OCH_2), 72.5−73.2 (O*CH*$_2$Ph), 75.0−75.7 (O*CH*$_2$Ph), 77.8−79.3 (CH), 80.8−81.0 (CH), 98.2−98.6 (C-1), 114.7, 114.8 (C-a), 126.9−128.3 (CH-aromatic), 138.0, 138.05 (C-b), 138.1−138.4 (C-arom. quat.), 139.1−139.3 (C-arom. quat.) ppm. MS (MALDI-TOF): *m*/*z* (%) = 5964.1 (100) [M + Na]$^+$. $C_{368}H_{398}O_{70}$ (5941): calcd. C 74.40, H 6.75; found C 74.29, H 6.87.

Duplex-β-cyclodextrin 5β: Grubbs catalyst **G** (5 mg, 6 μmol) was added under argon at room temp. to a stirred solution of **4β** (345 mg, 58 μmol) in degassed dichloromethane (58 mL). The reaction mixture was heated at reflux for 3 h. $Pb(OAc)_4$ (4 mg, 1.5eq/Ru) was added to the cooled solution (room temp.). The reaction mixture was stirred under argon overnight and concentrated. Chromatography of the residue (cyclohexane/EtOAc, 5:1) on silica gel afforded the unsaturated duplex: MS (MALDI-TOF): *m*/*z* (%) = 5935.9 (100) [M + Na]$^+$. A mixture of this product and PtO_2 (100 mg) in EtOAc (20 mL) was stirred under H_2 atmosphere for 3 h, filtered through Celite®, and concentrated. The residue was dissolved at −78 °C in a mixture of THF/NH_3 (1:1, 20 mL). Small pieces of Na (excess) were added. The blue solution was heated at reflux for 1 h (−33 °C), carefully quenched with *i*PrOH (10 mL) and concentrated. A solution of the residue in water (25 mL) was neutralised with IR-120 H^+ resin, diluted with EtOAc (25 mL), stirred vigorously for 30 minutes, and filtered. The organic layer was separated and extracted with water (3 × 15 mL), and the combined aqueous layers were concentrated. The residue was purified by chromatography on Sephadex G25 column (water) to give **5β** (107 mg, 74% over three steps) as a white powder.



^{1}H NMR (400 MHz, D_2O): δ = 1.22−1.57 (m, 24 H, CH_2), 3.35−4.11 (m, 106 H, 2-H, 3-H, 4-H, 5-H, 6-H, OCH_2), 5.02−5.18 (m, 14 H, 1-H) ppm. ^{13}C NMR (100 MHz, D_2O):[20] δ = 29.0 (CH_2) 60.2 (OCH_2), 71.8−73.7 (CH), 102.2−102.3 (C-1) ppm. MS (MALDI-TOF): *m*/*z* (%) = 2512.1 (100) [M + Na]$^+$. MS (ESI-TOF): *m*/*z* (%) = 1267.98 (100) [M − 2H+2Na]$^{2+}$.

Acknowledgments

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