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A Hybrid Cavitand Made by Capping Permethylated α-Cyclodextrin with Cyclotriveratrylene

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A hybrid C_3-symmetric cavitand **1**, in which permethylated α-cyclodextrin (PM α-CDX) is capped with cyclotriveratrylene (CTV), has been prepared in 8 % yield by intramolecular cyclization of a vanillyl alcohol derivative attached to the primary rim of the CDX platform. The reaction proceeds diastereoselectively ($dr \approx 6:1$), the chirality of the α-glucopyranosyl units controlling the chirality of the CTV component. Interestingly, in polar solvents, **1** shows self-complexation properties as the primary methoxy groups of the CDX component are directed towards the CTV cavity.

Introduction

Cavitands were defined by Cram and co-workers as "synthetic organic compounds that contain enforced cavities large enough to accommodate simple molecules or ions".[1] However, nowadays the name "cavitand" is usually given to compounds that derive from four-fold symmetric resorcin[4]arenes by linking the phenolic oxygen atoms to small carbon (e.g., methylenic)[2] or heteroatom (e.g., phosphonito)[3] bridging units. Deep-cavity cavitands result from the bridging of these resorcinol-derived oxygen atoms with aromatic subunits that form vertical "walls".[4,5] Self-folding systems represent the most advanced version of these latter receptors, their C_{4v} cone conformation being stabilized by a seam of intra-annular hydrogen bonds, as in the case of resorcin[4]arene itself. Deep-cavity cavitands are unique molecular containers because, in spite of their open end, exchange between complexed and free guest species can be slow on the NMR timescale.[5a] Besides, cyclodextrins (CDX) have been considered as natural cavitands[1b] and cryptophanes,[6] made from two cone-shaped cyclotriveratrylene (CTV) cyclophanes, have also been included in the original cavitand class of compounds.[1b,7] Considering the host–guest properties of cryptophanes[6b,6c] and cyclodextrins,[8] the former involving van der Waals interactions, the latter solvophobic effects, and the symmetry matching between C_3-symmetric CTVs and C_6-symmetric α-CDX, we envisaged that capping[9] the narrow rim of α-CDX with CTV would produce a deep-cavity C_3-symmetric cavitand[5] having the shape of a shuttlecock and the potential ability to bind substrates with a greater variety of interactions than separated cryptophanes and cyclodextrins. Such a system is reminiscent of calix[6]cryptamides in which the small rim of calix[6]arene is capped with CTV through amide bridges.[10] In addition, CDX-based cavitands that feature organic[11] or metallo-organic[12] bridges endowed with catalytic properties have been reported. We now disclose our synthetic efforts to obtain the aesthetically pleasing CDX/CTV hybrid receptor, which turned out to be accessible in two steps from known reaction precursors.

Results and Discussion

Two synthetic strategies can be considered for preparing a cavitand from CDX and CTV, either coupling of the functionalized separate components (strategy A) or construction of the CTV-derived subunit by using the CDX platform as a template (strategy B). Both strategies were tested and only the second produced the target hybrid cavitand. Note that cryptophanes are also most efficiently synthesized by constructing the second CTV component on a presynthesized CTV platform,[13] the tripod/tripod coupling strategy affording lower yields.[14] We used permethylated (PM) α-CDX rather than genuine α-CDX because the former lends itself easily to selective discrimination of three out of the six primary alcohol functions by using the trityl protection technique[15] and also because it shows better flexibility and water solubility than the latter.[16] The direct CDX precursor used in strategy A was the known mesylate derivative **3**[17] of tris(hydroxymethyl) PM α-CDX (**2**; Figure 1). It was obtained in 94% isolated yield by reaction of **2** with mesyl chloride in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP). However, upon reaction of **3** with cyclotriphenolene (**4**)[18] in the presence of caesium carbonate in DMF at 70 °C and under high dilution conditions (2×10^{-3} M) we were unable to detect any trace

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of cavitand. This was quite surprising as we had deliberately chosen the sterically unhindered cyclotriphenolene (**4**) as CTV precursor. However, the tripod/tripod coupling can also produce misdirected products resulting from unwanted [2+2] condensation that cannot be corrected to the desired [3+3] product when the reaction involved is irreversible.[19] Therefore we directed our efforts towards the synthesis of a CDX/CTV hybrid cavitand by using strategy B.

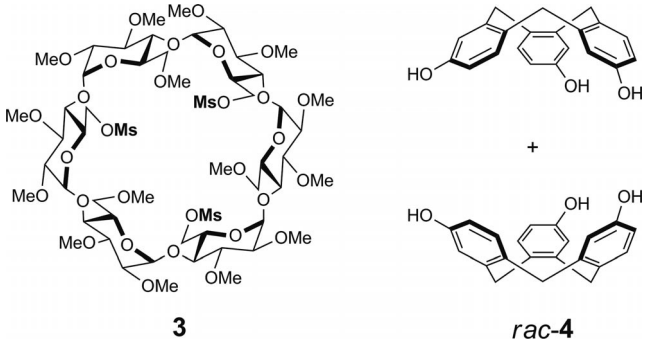


Figure 1. Chemical structures of PM α-CDX **3** and CTV **4** precursors used for the tripod/tripod coupling strategy A.

The chemical structures of the two possible diastereomers of target cavitand **1** are shown in Figure 2. In this molecule three oxygen atoms at the narrow rim of the CDX platform are connected to three oxygen atoms of the CTV subunit through ethylene bridges, as in cryptophane A.[13a] Cavitand **1** was synthesized according to Scheme 1. The precursor of the CTV cap is the vanillyl alcohol derivative **5**, which was prepared according to literature procedures.[20] In the subsequent step, triol **2** was treated with a four-fold excess of sodium hydride in DMF at room temperature followed by the addition of the same amount of iodo derivative **5**. Twice as much reagent was used as mono- and disubstituted intermediates were still present after 12 h of reaction. The direct precursor **6** of cavitand **1** was finally obtained in 49% yield after column chromatography.

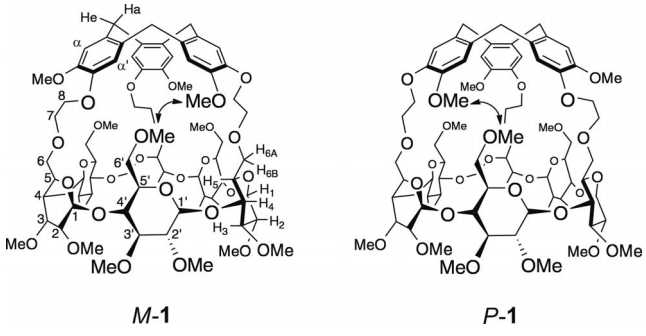
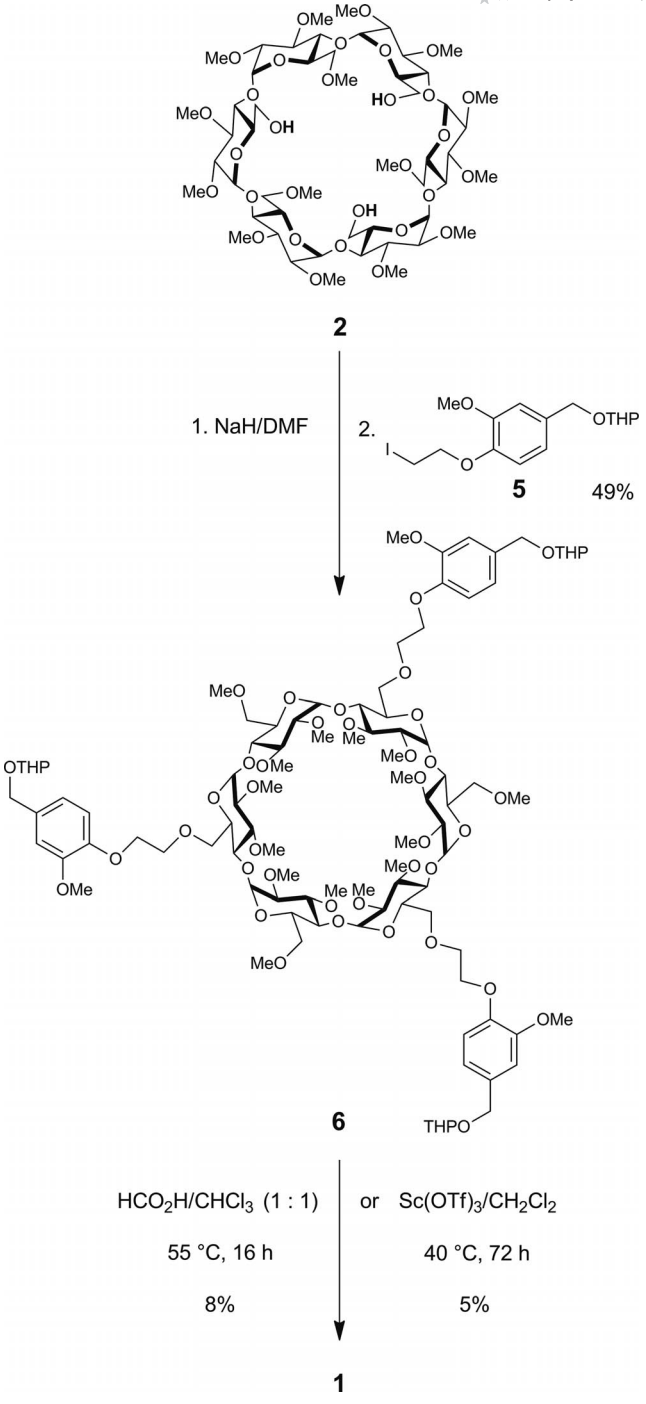


Figure 2. Chemical structures of the two diastereomers of cavitand **1**. The atom numbering is shown for the diastereomer *M*-**1**. The double-ended arrows indicate through-space interactions, as shown by 2D ROESY $^1H/^1H$ NMR spectroscopy.

As this compound combines the asymmetric carbon atom of the THP protecting group and the enantiopure CDX platform, it should exist as four diastereomers. At least two diastereomers are formed as the ^1H NMR spectrum shows splitting of the singlet of the 2′-OCH_3 substituents at 3.405 and 3.403 ppm, and splitting of several signals in the $^{13}C\{^1H\}$ NMR spectrum in [D_6]acetone (see Figures S5 and S6 in the Supporting Information). Intramolecular cyclization (Scheme 1) was performed following two different reported procedures, that is, either under classic formic acid conditions[7,21] or by the recently developed Lewis acid catalysis method using $Sc(OTf)_3$.[22] First, precursor **6**



Scheme 1. Two-step preparation (strategy B) of cavitand **1** from PM α-CDX (**2**) and vanillyl alcohol derivative **5**.

(2.0×10^{-3} M) was heated in a 1:1 mixture of HCOOH and chloroform at 55 °C[23] and the reaction was followed by MALDI-TOF mass spectrometry. Examination of the sequence of spectra (see Figures S27 and S28 in the Supporting Information) showed that the signal of precursor **6** (as sodium adduct) disappeared after 8 h giving rise to signals at *m*/*z* = 1691.6 and 1783.7, which correspond, respectively, to the sodium adducts of cavitand **1** and intermediate **7** (see Figure 3). The maximum **1**:**7** ratio was observed after 32 h, but the signals of the CDX-containing compounds disappeared after 56 h reaction, which points to a complete degradation of the CDX backbone.[24] However, monitoring of the reaction by ^{1}H NMR spectroscopy led to less optimistic conclusions as degradation products that were not detected by mass spectrometry were clearly apparent in the ^{1}H NMR spectrum recorded after 24 h (see Figure S29 in the Supporting Information). In preparative runs, the heating of **6** (1.1×10^{-3} M) in a 1:1 mixture of HCOOH and chloroform at 55 °C for 3 h allowed us to isolate cavitand **1** in 4% yield after careful column chromatography and the yield of isolated product increased to 8% by extending the reaction time to 16 h. A higher temperature and longer reaction time, which have otherwise been shown to improve the yield of the cyclization reaction,[25] as expected led to the breaking up of the CTV backbone (MALDI-TOF MS). In fact, the major product (**7**), isolated in 39% yield after 3 h (49% yield after 16 h), results from the dimerization of two vanillyl alcohol pendants, the unreacted benzyl alcohol functions being left as formate esters (Figure 3). This is attested by ESI-MS, which shows a signal at *m*/*z* = 1783.76 corresponding to the sodium adduct, and ^{1}H NMR spectroscopy, which shows narrow triplets due to the formate hydrogen atoms between 8.3 and 8.5 ppm (see Figures S21 and S25 in the Supporting Information). In fact, there are four of these signals, which have pairwise relationships, as expected for the two possible diastereomers **7a** and **7b** shown in Figure 3. Integration of these signals gives a ratio of 65:35 for the major and minor diastereomers of **7**. Such covalent capture of a cyclization intermediate in the template-directed formation of a CTV is unprecedented. To the best of our knowledge, no such intermediates have been observed in the course of cryptophane synthesis. Their isolation in significant yield points to the difficult nature of the cyclization reaction in this case. Employing $Sc(OTf)_3$ in dichloromethane at reflux for 48 h only slightly improved the isolated yield of **1** (5%), but changing the solvent to acetonitrile, again at reflux, produced only traces of the desired product.

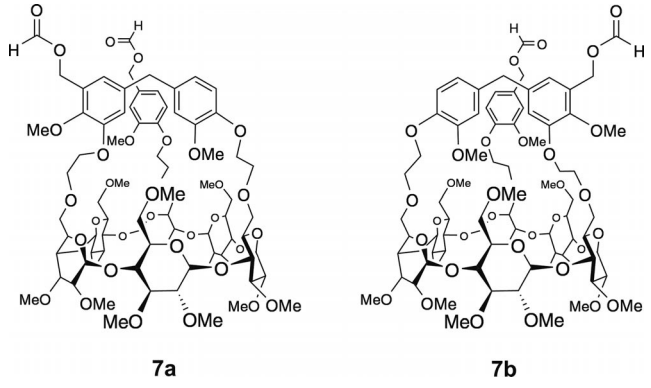


Figure 3. Chemical structures of diastereomers **7a** and **7b**.

Cavitand **1** was characterized by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy (see the Supporting Information). The main peak in the ESI mass spectrum corresponds to the sodium adduct (*m*/*z* = 1691.74). The ^{1}H NMR spectrum in [D_6]acetone is reproduced in Figure 4. The signals were fully assigned by use of 2D ^{1}H NMR techniques (^{1}H–^{1}H COSY and ROESY, ^{1}H–^{13}C HSQC and HMBC) and it is clearly seen that the CTV and CDX components are present in a 1:1 ratio. The signals of the latter are split, the doublets of 1-H and 1′-H excepted, which indicates that the symmetry of the PM α-CDX platform has been lowered from C_6 to C_3 upon conjugation with CTV, as expected. This is confirmed by the ^{13}C NMR spectrum

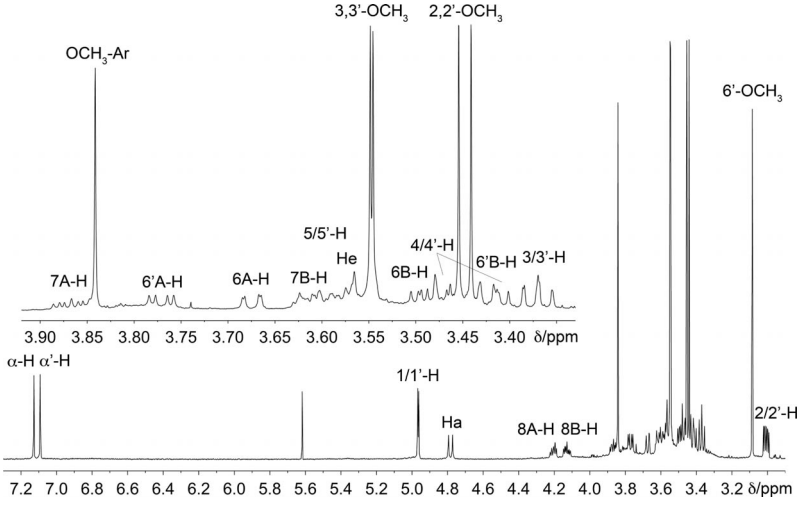


Figure 4. ^{1}H NMR spectrum ([D_6]acetone, 600 MHz) of cavitand **1**.

in which all the signals of the CDX component are split (see Figures S13 and S14 in the Supporting Information). In fact, the most interesting feature of the NMR spectra is that they correspond to a single species as in theory two diastereomers are expected to form depending on the direction of cyclization of the vanillyl alcohol derived fragment (Figure 2). In fact, the two diastereomers can be distinguished in the ^{1}H NMR spectrum of the crude reaction mixture by the signals of the α-H and α′-H protons at δ = 7.15 and 7.11 ppm for the minor diastereomer, and at 7.12 and 7.09 ppm for the major diastereomer, the ratio of the latter to the former being $dr \approx 6{:}1$. This indicates that the reaction is diastereoselective to a certain extent, however, the slightly less polar minor diastereomer could not be isolated in pure form by column chromatography as it is always accompanied by the major isomer. Note, the synthesis of cryptophanes on a CTV platform is also diastereoselective as it produces either D_3- or C_{3h}-symmetric stereoisomers depending on the nature of the bridges connecting the CTV platform and the vanillyl alcohol derived endgroups.[6a] The diastereoselectivity of the cyclization reaction could stem from the fact that the asymmetry of cyclodextrins is amplified by permethylation.[26] Interestingly, the primary methoxy groups at C-6′ are shielded by –0.233 ppm (in [D$_6$]acetone) on switching from triol **2** to cavitand **1**, whereas the secondary methoxy groups (at C-2/2′ and C-3/3′) show an upfield shift of less than 0.05 ppm. Moreover, shielding of 6′-OCH$_3$ is increased by an additional –0.194 ppm in the presence of only around 5% H$_2$O. These observations suggest that the 6′-OCH$_3$ groups are directed towards the CTV cavity of the receptor rather than the outside of the PM α-CDX component in these polar, hydrophilic solvents. Remarkably, shielding as strong as –1.72 ppm has been noted in the case of a cryptophane with *endo* methyl carboxylate groups.[27] Examination of the 2D ^{1}H–^{1}H ROESY spectrum of cavitand **1** in [D$_6$]acetone shows remarkable correlations, for example, α-H/OCH$_3$(Ar) and α′-H/8A,8B-H. However, the only intercomponent through-space correlation is much weaker and involves the CTV OCH$_3$(Ar) and the PM α-CDX 6′-OCH$_3$ groups (see Figure S20 in the Supporting Information).

Reports on the complexation properties of PM α-CDX are relatively scarce. These compounds have been shown, in particular, to host aromatic guests[8] and this property has been recently used for the generation of [2]rotaxane dimers by self-association of singly modified species.[28] Besides, polyrotaxanes made from the threading of PM α-CDX onto polyTHF have been reported.[29] The unexpected self-complexation of hybrid compound **1** is reminiscent of the behaviour of PM α-CDX, which is bowl-shaped in the solid state, because glucose subunits A and D are strongly tilted inwards. As a consequence, the corresponding 6′-OCH$_3$ moieties are oriented towards the cavity axis and form van der Waals contacts with each other, closing the narrow rim of the CDX cavity.[30] This could account for the inability of this receptor to form a host–guest complex with, for example, decanoic acid even in 20% (v/v) water in acetone.[31]

Conclusions

We have shown that PM α-CDX can be used as a platform for the covalently templated cyclotrimerization of a vanillyl alcohol derivative attached to its primary rim. The reaction proceeds in low yield but diastereoselectively, the chirality of the CDX template controlling the direction of cyclization of the CTV precursor. As the primary 6′-OCH$_3$ substituents are probably responsible for the poor cyclization yields and complexation properties of **1**, we are now concentrating our efforts towards the synthesis of a true α-CDX/CTV hybrid lacking the methoxy substituents.

Experimental Section

General Methods: Mass spectra were obtained either in MALDI-TOF reflectron mode by using dithranol (1,8-dihydroxy-9(10*H*)-anthracene) as a matrix or in ESI mode. Column chromatographic separations were carried out by using 0.035–0.070 mm or 0.075–0.200 mm silica gel 60. Analytical TLC was performed on silica gel TLC plates with F-254 indicator. Solvents were dried and distilled prior to use: DMF from CaH_2, CH_2Cl_2 from P_2O_5, pyridine from KOH. All other commercially available chemicals were used without further purification. 2-[4-(2-Iodoethoxy)-3-methoxybenzyloxy]-tetrahydropyran (**5**) was prepared from vanillyl alcohol.[20] 2^{I},2^{II},2^{III},2^{IV},2^{V},2^{VI},3^{I},3^{II},3^{III},3^{IV},3^{V},3^{VI},6^{II},6^{IV},6^{VI}-Pentadeca-*O*-methyl-α-cyclodextrin (**2**) was prepared according to literature procedures.[15]

2^{I},2^{II},2^{III},2^{IV},2^{V},2^{VI},3^{I},3^{II},3^{III},3^{IV},3^{V},3^{VI},6^{II},6^{IV},6^{VI}-Pentadeca-*O*-methyl-6^{I},6^{III},6^{V}-tri-*O*-methylsulfonyl-α-cyclodextrin (3): 4-(Dimethylamino)pyridine (0.301 g, 2.46 mmol) and methanesulfonyl chloride (0.410 g, 3.58 mmol) were added successively to a solution of **2** (1.185 g, 1.00 mmol) in pyridine (13 mL). The mixture was stirred for 22 h at room temperature whereupon brine (50 mL) was added. Then the mixture was extracted with ethyl acetate (4 × 40 mL). The combined organic layers were washed twice with 1 M HCl (2 × 30 mL), twice with 1 M NaOH (2 × 30 mL) and dried with magnesium sulfate. After evaporating the solvent under reduced pressure the crude product was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 4:96) to give compound **3** as a colourless solid (1.329 g, 0.938 mmol) in 94% yield. ^{1}H NMR (500 MHz, [D$_6$]acetone, 300 K): δ = 5.10 (d, $J_{H,H}$ = 3.5 Hz, 3 H, 1′-H), 5.08 (d, $J_{H,H}$ = 3.5 Hz, 3 H, 1-H), 4.61 (dd, $J_{H,H}$ = 11.5, 4.4 Hz, 3 H, 6A-H), 4.54 (dd, $J_{H,H}$ = 11.5, 1.9 Hz, 3 H, 6B-H), 4.01 (ddd, $J_{H,H}$ = 9.6, 4.4, 1.9 Hz, 3 H, 5-H), 3.92 (ddd, $J_{H,H}$ = 9.7, 5.8, 1.4 Hz, 3 H, 5′-H), 3.85 (dd, $J_{H,H}$ = 10.8, 1.4 Hz, 3 H, 6′A-H), 3.76 (dd, $J_{H,H}$ = 10.8, 5.8 Hz, 3 H, 6′B-H), 3.60 (s, 9 H, 3- or 3′-OCH$_3$), 3.58 (s, 9 H, 3- or 3′-OCH$_3$), 3.53–3.39 (m, 12 H, 4/4′-H, 3/3′-H), 3.48 (s, 9 H, 2- or 2′-OCH$_3$), 3.47 (s, 9 H, 2- or 2′-OCH$_3$), 3.36 (s, 9 H, 6′-OCH$_3$), 3.17 (s, 9 H, SO_2CH_3), 3.12 (dd, $J_{H,H}$ = 9.4, 3.5 Hz, 3 H, 2-H), 3.07 (dd, $J_{H,H}$ = 9.9, 3.5 Hz, 3 H, 2′-H) ppm. ^{13}C NMR (150 MHz, [D$_6$]acetone, 300 K): δ = 100.72, 99.85 (C-1/1′), 83.64, 83.18, 82.95, 82.59, 82.33, 82.05 (C-2/2′, C-3/3′, C-4/4′), 72.95 (C-6′), 72.27 (C-5′), 70.86 (C-6), 70.54 (C-5), 61.91, 61.81 (3/3′-OCH$_3$), 59.13 (6′-OCH$_3$), 58.34, 57.89 (2/2′-OCH$_3$), 37.54 (SO_2CH_3) ppm. HRMS (ESI): calcd. for $C_{54}H_{96}NaO_{36}S_3$ [M + Na]$^+$ 1439.47356; found 1439.46916.

Compound 6: Sodium hydride (60% w/w in oil, 0.144 g, 3.60 mmol) was added to a solution of **2** (0.347 g, 0.293 mmol) and the mixture was stirred for 1 h. Tetrahydropyran **5** (1.38 g, 3.52 mmol) was then added and the mixture was stirred overnight at room temperature.

As TLC analysis indicated the presence of remaining starting material as well as the mono- and disubstituted derivatives, another portion of sodium hydride (60% w/w in oil, 0.143 g, 3.58 mmol) was added followed by the addition of **5** (1.378 g, 3.51 mmol) 1 h later and the mixture was stirred for 22 h at room temperature. The same procedure was repeated once with sodium hydride (60% w/w in oil, 0.161 g, 4.03 mmol) and **5** (0.365 g, 0.931 mmol). The reaction was stirred for a further 24 h. The solvent was then evaporated under reduced pressure and the residue was extracted with CH_2Cl_2. The organic layer was washed with water, brine and dried with magnesium sulfate. After evaporating the solvent under reduced pressure the crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, gradient from 6:94 to 1:9) to afford compound **6** as a colourless solid (0.285 g, 0.144 mmol) in 49% yield. ^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 6.89 (s, 3 H, β′-H), 6.86 (s, 6 H, α′-H, α-H), 5.07 (d, $J_{H,H}$ = 3.0 Hz, 3 H, 1- or 1′-H), 5.04 (d, $J_{H,H}$ = 3.3 Hz, 3 H, 1- or 1′-H), 4.70 [d, $J_{H,H}$ = 11.7 Hz, 3 H, $ArCH_2(A)$], 4.67 (t, $J_{H,H}$ = 3.6 Hz, 3 H, 9-H), 4.42 [d, $J_{H,H}$ = 11.7 Hz, 3 H, $ArCH_2(B)$], 4.16 (m, 6 H, 8A/B-H), 4.10 (dd, $J_{H,H}$ = 10.8, 3.1 Hz, 3 H, 6A-H), 3.90 (m, 9 H, 13A-H, 7A/B-H), 3.83 (s, 9 H, OCH_3-Ar), 3.82–3.67 (m, 21 H, 6B-H, 6′A/B-H, 5/5′-H, 4/4′-H), 3.64 (s, 9 H, 3- or 3′-OCH_3), 3.62 (s, 9 H, 3- or 3′-OCH_3), 3.53 (m, 9 H, 13B-H, 3/3′-H), 3.48 (s, 9 H, 2- or 2′-OCH_3), 3.43 (s, 9 H, 2- or 2′-OCH_3), 3.33 (s, 9 H, 6′-OCH_3), 3.15 (dd, $J_{H,H}$ = 10.0, 3.3 Hz, 3 H, 2- or 2′-H), 3.11 (dd, $J_{H,H}$ = 9.2, 3.0 Hz, 3 H, 2- or 2′-H), 1.85 (m, 3 H, 10A-H), 1.72 (m, 3 H, 11A-H), 1.58 (m, 12 H, 10B-H, 11B-H, 12A/B-H) ppm. ^1H NMR (600 MHz, $[D_6]$acetone, 300 K): δ = 6.97 (d, $J_{H,H}$ = 1.9 Hz, 3 H, α-H), 6.94 (d, $J_{H,H}$ = 8.2 Hz, 3 H, α′-H), 6.87 (m, 3 H, β′-H), 5.07 (d, $J_{H,H}$ = 3.2 Hz, 3 H, 1-H), 4.99 (d, $J_{H,H}$ = 3.4 Hz, 3 H, 1′-H), 4.66 (t, $J_{H,H}$ = 3.4 Hz, 3 H, 9-H), 4.64 [d, $J_{H,H}$ = 11.7 Hz, 3 H, $ArCH_2(A)$], 4.40 [d, $J_{H,H}$ = 11.7 Hz, 3 H, $ArCH_2(B)$], 4.20–4.15 (m, 6 H, 8A-H, 7A-H), 4.13–4.09 (m, 3 H, 8B-H), 3.91–3.79 (m, 15 H, 13A-H, 6A/B-H, 5/5-H′), 3.83 (s, 9 H, OCH_3-Ar), 3.74–3.67 (m, 12 H, 7B-H, 6′A/B-H, 4′-H), 3.58 (s, 9 H, 3- or 3′-OCH_3), 3.56 (s, 9 H, 3- or 3′-OCH_3), 3.48 (m, 3 H, 13B-H), 3.46 (s, 9 H, 2- or 2′-OCH_3), 3.405 and 3.403 (2 s, 9 H, 2- or 2′-OCH_3), 3.40 (m, 9 H, 3/3′-H, 4-H), 3.31 (s, 9 H, 6′-OCH_3), 3.04 (dd, $J_{H,H}$ = 9.9, 3.4 Hz, 3 H, 2′-H), 2.99 (m, 3 H, 2-H), 1.81 (m, 3 H, 11A-H), 1.67 (m, 3 H, 10A-H), 1.52 (m, 12 H, 10B-H, 11B-H, 12A/B-H) ppm. ^{13}C NMR (150 MHz, $[D_6]$acetone, 300 K): δ = 150.61, 150.60 (C-γ), 149.11 (C-γ′), 132.51, 132.50 (C-β), 121.13, 121.12 (C-β′), 114.56, 114.54 (C-α′), 113.31, 113.28 (C-α), 100.44 (C-1′), 99.74, 99.73 (C-1), 98.09, 98.08 (C-9), 83.32 (C-4), 83.17, 83.12 (C-2/2′), 82.56 (C-4′), 82.51, 82.48 (C-3/3′), 72.76 (C-6′), 72.27 (C-5′), 71.79 (C-5), 70.52, 70.51 (C-7), 70.41 (C-6), 69.13, 69.10 (C-8), 69.07, 69.06 ($ArCH_2$), 62.29, 62.28 (C-13), 61.82, 61.72 (3/3′-OCH_3), 58.90 (6′-OCH_3), 58.20, 57.82 (2′-OCH_3), 57.81 (2-OCH_3), 56.36 (OCH_3-Ar), 31.37 (C-10), 26.31 (C-12), 20.10 (C-11) ppm. HRMS (ESI): calcd. for $C_{96}H_{150}NaO_{42}$ $[M + Na]^+$ 1997.94939; found 1997.95692.

Compound 7: See the preparation of cavitand **1** below. Characterization: HRMS (ESI): calcd. for $C_{83}H_{124}NaO_{40}$ $[M + Na]^+$ 1783.75611; found 1783.76066. ^1H NMR (600 MHz, $[D_6]$acetone, 300 K): see the Supporting Information.

Synthesis of Cavitand 1

Procedure A: Formic acid (92 mL) was added in one portion to a solution of precursor **6** (0.386 g, 0.195 mmol) in chloroform (92 mL) under nitrogen. The reaction mixture was gently stirred at 55 °C and monitored by ^1H NMR and MALDI-TOF MS. After 16 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted into CH_2Cl_2. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ to remove traces of formic acid. The solvent was then evaporated under reduced pressure and the residue purified twice by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 3:97) to provide first intermediate **7** as a mixture of diastereomers **7a** and **7b** (0.169 g, 49%) followed by cavitand **1** as a colourless solid (23.2×10^{-3} g, 1.39×10^{-2} mmol) in 8% yield.

Procedure B: A solution of precursor **6** (0.300 g, 0.152 mmol) in CH_2Cl_2 (20 mL) was added to a stirred suspension of scandium triflate (0.076 g, 0.154 mmol) in CH_2Cl_2 (38 mL) at reflux over a period of 25–30 h through a syringe pump. After complete addition, the reaction mixture was stirred at 40 °C for a further 48 h. The dark solution was then poured into water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried with magnesium sulfate. After evaporating the solvent under reduced pressure the crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 3:97) to afford cavitand **1** as a colourless solid (12.7×10^{-3} g, 7.61×10^{-3} mmol) in 5% yield. ^1H NMR (600 MHz, $[D_6]$acetone, 300 K): δ = 7.13 (s, 3 H, α-H), 7.09 (s, 3 H, α′-H), 4.97 (d, $J_{H,H}$ = 3.3 Hz, 6 H, 1/1′-H), 4.78 (d, $J_{H,H}$ = 13.5 Hz, 3 H, Ha), 4.20 (ddd, $J_{H,H}$ = 11.4, 5.0, 4.5 Hz, 3 H, 8A-H), 4.13 (ddd, $J_{H,H}$ = 11.4, 7.2, 4.1 Hz, 3 H, 8B-H), 3.87 (ddd, $J_{H,H}$ = 11.9, 7.0, 4.0 Hz, 3 H, 7A-H), 3.84 (s, 9 H, OCH_3-Ar), 3.77 (dd, $J_{H,H}$ = 11.7, 4.1 Hz, 3 H, 6′A-H), 3.67 (dd, $J_{H,H}$ = 10.4, 1.4 Hz, 3 H, 6A-H), 3.64–3.56 (m, 12 H, 7B-H, He, 5/5′-H), 3.55 (s, 9 H, 3- or 3′-OCH_3), 3.55 (s, 9 H, 3- or 3′-OCH_3), 3.50 (dd, $J_{H,H}$ = 10.4, 1.4 Hz, 3 H, 6B-H), 3.48–3.46 (m, 3 H, 4- or 4′-H), 3.45 (s, 9 H, 2- or 2′-OCH_3), 3.44 (s, 9 H, 2- or 2′-OCH_3), 3.43–3.40 (m, 6 H, 4- or 4′-H, 6′B-H), 3.37 (td, $J_{H,H}$ = 4.4, 8.9 Hz, 6 H, 3/3′-H), 3.09 (s, 9 H, 6′-OCH_3), 3.02 (dd, $J_{H,H}$ = 5.3, 3.3 Hz, 3 H, 2- or 2′-H), 3.00 (dd, $J_{H,H}$ = 5.2, 3.3 Hz, 3 H, 2- or 2′-H) ppm. ^{13}C NMR (150 MHz, $[D_6]$acetone, 300 K): δ = 149.6 (C-γ), 147.7 (C-γ′), 134.1 (C-β), 133.0 (C-β′), 117.6 (C-α′), 114.8 (C-α), 100.4, 100.2 (C-1/1′), 83.6 (C-4 or -4′), 83.38, 83.36 (C-2/2′), 82.9 (C-4 or -4′), 82.34, 82.26 (C-3/3′), 72.4, 72.3 (C-5/5′), 71.8 (C-6′), 70.8 (C-6), 69.3 (C-8), 69.1 (C-7), 61.79, 61.76 (3/3′-OCH_3), 58.8 (6′-OCH_3), 58.0, 57.9 (2/2′-OCH_3), 56.5 (OCH_3-Ar), 36.4 ($ArCH_2$) ppm. HRMS (ESI): calcd. for $C_{81}H_{120}NaO_{36}$ $[M + Na]^+$ 1691.74515; found 1691.74451.

MALDI-TOF MS Studies: Formic acid (10 mL) was added in one portion to a solution of precursor **6** (0.042 g, 0.0213 mmol) in chloroform (10 mL) under nitrogen. Aliquots (0.1 mL) were withdrawn from time to time, neutralized with $NaHCO_3$ and extracted into dichloromethane (see Figures S26 and S27 in the Supporting Information).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **1**, **3** and **6**. ^1H NMR spectrum of compound **7**. ^1H–^1H COSY and ROESY, and ^1H–^{13}C HSQC and HMBC NMR spectra of compounds **1** and **6**. ESI-HRMS spectra of compounds **1**, **3**, **6** and **7**. MALDI-TOF and ^1H NMR spectra recorded during the formation of compound **1** (procedure A).

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[1] a) J. R. Moran, S. Karbach, D. J. Cram, *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828; b) D. J. Cram, *Science* **1983**, *219*, 1177–1187.

[2] D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson, R. C. Helgeson, *J. Am. Chem. Soc.* **1988**, *110*, 2229–2237.
[3] R. Pinalli, M. Suman, E. Dalcanale, *Eur. J. Org. Chem.* **2004**, 451–462.
[4] D. J. Cram, H.-J. Choi, J. A. Bryant, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7748–7765.
[5] a) D. M. Rudkevich, J. Rebek Jr, *Eur. J. Org. Chem.* **1999**, 1991–2005; b) S. M. Biros, J. Rebek Jr, *Chem. Soc. Rev.* **2007**, *36*, 93–104.
[6] a) A. Collet, *Tetrahedron* **1987**, *43*, 5725–5759; b) A. Collet, J.-P. Dutasta, B. Lozach, *Bull. Soc. Chim. Belg.* **1990**, *99*, 617–633; c) T. Brotin, J.-P. Dutasta, *Chem. Rev.* **2009**, *109*, 88–130.
[7] J. Canceill, M. Cesario, A. Collet, J. Guilhem, C. Pascard, *J. Chem. Soc., Chem. Commun.* **1985**, 361–363.
[8] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875–1977.
[9] a) E. Engeldinger, D. Armspach, D. Matt, *Chem. Rev.* **2003**, *103*, 4147–4173; b) T. Lecourt, J.-M. Mallet, P. Sinaÿ, *C. R. Chim.* **2003**, *6*, 87–90.
[10] S. Le Gac, I. Jabin, *Chem. Eur. J.* **2008**, *14*, 548–557.
[11] L. G. Marinescu, M. Bols, *Angew. Chem.* **2006**, *118*, 4706; *Angew. Chem. Int. Ed.* **2006**, *45*, 4590–4593.
[12] D. Armspach, D. Matt, *C. R. Chim.* **2011**, *14*, 135–148.
[13] a) J. Gabard, A. Collet, *J. Chem. Soc., Chem. Commun.* **1981**, 1137–1139; b) J. Canceill, L. Lacombe, A. Collet, *C. R. Acad. Sci., Ser. II* **1984**, *298*, 39–42.
[14] D. J. Cram, M. E. Tanner, S. J. Keipert, C. B. Knobler, *J. Am. Chem. Soc.* **1991**, *113*, 8909–8916.
[15] J. Boger, D. G. Brenner, J. R. Knowles, *J. Am. Chem. Soc.* **1979**, *101*, 7630–7631.
[16] D. Armspach, D. Matt, *Inorg. Chem.* **2001**, *40*, 3505–3509, and references cited therein.
[17] Reported trimesylate **3** has not been characterized in the literature, see ref.[15] and the Supporting Information.
[18] a) H. A. Fogarty, P. Berthault, T. Brotin, G. Huber, H. Desvaux, J.-P. Dutasta, *J. Am. Chem. Soc.* **2007**, *129*, 10332–10333; b) T. Traoré, L. Delacour, S. Garcia-Argote, P. Berthault, J.-C. Cintrat, B. Rousseau, *Org. Lett.* **2010**, *12*, 960–962; c) T. Traoré, L. Delacour, N. Kotera, G. Merer, D.-A. Buisson, C. Dupont, B. Rousseau, *Org. Process Res. Dev.* **2011**, *15*, 435–437.
[19] L. Krejčí, M. Buděšínský, I. Císařova, T. Kraus, *Chem. Commun.* **2009**, 3557–3559.
[20] J. Canceill, L. Lacombe, A. Collet, *J. Am. Chem. Soc.* **1985**, *107*, 6993–6996.
[21] A. S. Lindsey, *J. Chem. Soc.* **1965**, 1685–1692.
[22] T. Brotin, V. Roy, J.-P. Dutasta, *J. Org. Chem.* **2005**, *70*, 6187–6195.
[23] M. Darzac, T. Brotin, L. Rousset-Arzel, D. Bouchu, J.-P. Dutasta, *New J. Chem.* **2004**, *28*, 502–512.
[24] Heating **2** in $CHCl_3/HCO_2H$ (50:50) at 55 °C for 6 h did not lead to the degradation of the CDX backbone, but as expected resulted in partial esterification of the primary alcohol functions.
[25] P. A. Hill, Q. Wei, T. Troxler, I. J. Dmochowski, *J. Am. Chem. Soc.* **2009**, *131*, 3069–3077.
[26] K. Kano, K. Yoshiyasu, S. Hashimoto, *J. Chem. Soc., Chem. Commun.* **1989**, 1278–1279.
[27] C. E. O. Roesky, E. Weber, T. Rambusch, H. Stephan, K. Gloe, M. Czugler, *Chem. Eur. J.* **2003**, *9*, 1104–1112.
[28] T. Fujimoto, A. Nakamura, Y. Inoue, Y. Sakata, T. Kaneda, *Tetrahedron Lett.* **2001**, *42*, 7987–7989.
[29] N. Kihara, K. Hinoue, T. Takata, *Macromolecules* **2005**, *38*, 223–226.
[30] T. Steiner, W. Saenger, *Angew. Chem.* **1998**, *110*, 3628; *Angew. Chem. Int. Ed.* **1998**, *37*, 3404–3407.
[31] H. Sun, C. L. D. Gibb, B. C. Gibb, *Supramol. Chem.* **2008**, *20*, 141–147.

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