A Straightforward Access to Cyclotriveratrylene Analogues with C1-Symmetry: Toward the Synthesis of Monofunctionalizable Cryptophanes

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A Straightforward Access to Cyclotriveratrylene Analogues with C_1-Symmetry: Toward the Synthesis of Monofunctionalizable Cryptophanes

Gaëlle Milanole,[a] Bo Gao,[a] Emilie Mari,[b] Patrick Berthault,[b] Grégory Pieters*,[a] and Bernard Rousseau*,[a]

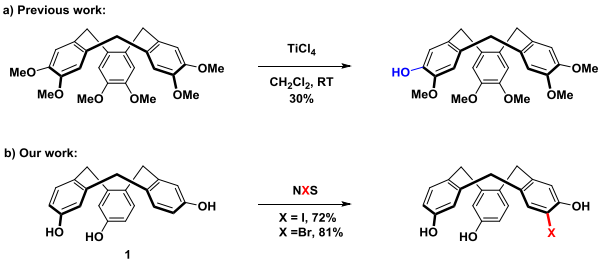
Abstract: A straightforward and practical access to various C_1-symmetric cyclotriveratrylene derivatives from a monohalogenated cyclotriphenolene is described. This unique scaffold can also be used as a precursor for the rapid construction of monofunctionalizable cryptophane-based biosensors for hyperpolarized ^{129}Xe MRI.

Introduction

Cyclotriveratrylenes (CTVs) are versatile macrocyclic host molecules with a rigid bowl-shaped lipophilic and electron-rich cavity favoring the binding of guest molecules in a non-covalent way.[1] In the last decades, CTVs and their analogues have received considerable interest in a wide range of applications such as selective fullerene separation,[2] formation of liquid crystals[3] and organogels,[4] anion sensing,[5] metallo-supramolecular assemblies[6] and for their fluorescence properties.[7]

Since the early 1980s, CTVs are also known as highly valuable precursors for the synthesis of cryptophanes.[8] These cage-molecules made of two CTV units connected by alkylenedioxy linkers exhibit outstanding properties for xenon encapsulation.[9] These host-guest assemblies have proven to be powerful systems for the hyperpolarized ^{129}Xe NMR-based biosensing approach, in which a biological ligand is grafted on a particular site of the cryptophane.[10] Unfortunately, the high symmetry of these cryptophanes proved to be a drawback to control the reactivity of a particular position with respect to other equivalent sites: complex mixtures are reported, complicating the purification steps and preventing the production of large quantities of biosensor required for *in vivo* experiments. For this reason, the efficient introduction of a single chemical functionality on the aromatic rings of a symmetrical cryptophane needs to be addressed. Herein, we have focused our attention on the monofunctionalization of a CTV scaffold. To the best of our knowledge, only few C_1-symmetric CTV derivatives have been described in the literature.[11] For example, one reported method involves a selective demethylation to furnish a single hydroxyl moiety with a low yield, then exploited to introduce a functional group (Scheme 1a).[11b]

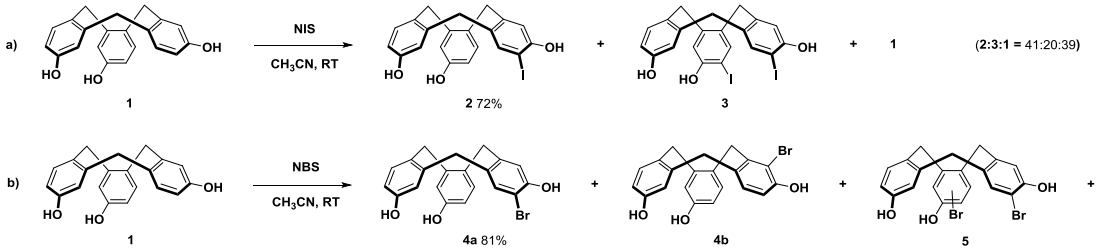
In this context, we describe here a new and alternative strategy to access novel C_1-symmetric CTV analogues based on the monohalogenation of cyclotri-phenolene **1** (Scheme 1b). These CTV backbones appear to be valuable precursors for designing monofunctionalized cryptophane-based biosensors.



Scheme 1. A New Strategy to Access C_1-symmetric CTVs

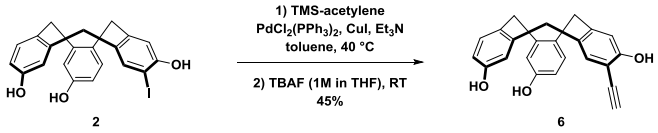
Results and Discussion

Synthesis of C_1-Symmetric CTV Derivatives. CTV **1** was obtained in two steps using a simple and scalable procedure elaborated by our group (40g-scale within 3 days).[12] Mono-iodation of compound **1** using *N*-iodosuccinimide in acetonitrile gave rise to a mixture of mono-iodinated CTV **2** along with di-iodinated CTV **3** and cyclotriphenolene **1** (Scheme 2a). Purification by chromatography on silica gel efficiently provided the expected mono-iodinated CTV **2** in a 72% isolated yield (yield based on recovered starting material). It is noteworthy that unreacted cyclotriphenolene **1** was easily recovered. We were pleased to observe that the iodation takes place in a perfectly regioselective manner. Indeed, the ^{1}H NMR spectrum of CTV **2** unambiguously shows that iodination occurs at the *ortho* position of a phenoxy ring as outlined in Scheme 2a (two singlets in the aromatic area at 7.74 and 7.00 ppm). Alternatively, we investigated the synthesis of mono-brominated scaffold **4** by a similar procedure using *N*-bromosuccinimide (Scheme 2b). Surprisingly, the expected CTV **4** was obtained as a mixture of two regioisomers, easily separated on silica gel to afford **4a** and **4b** in 81% overall yield based on recovered starting material. Di-brominated CTV **5** was also observed. Most CTVs reported so far are substituted by electron-donating functions and only a few examples of CTVs substituted by electron-withdrawing groups or π-extended conjugated systems have been reported.[7a,13] Indeed, CTV analogues are synthesized by an acid-catalyzed trimerization of 3,4-disubstituted benzyl alcohol compounds. The efficiency of this aromatic electrophilic substitution reaction (SE_{Ar}) is mainly owed to the nature of 3- and 4-substituents which should be electron donors to strongly activate the aromatic ring. In our attempts to demonstrate the high potential of CTV **2** as a perfect key intermediate to extend the C_1-symmetric CTV family, we studied the introduction of electron-withdrawing or conjugated functions using either organolithium or cross-coupling chemistry.



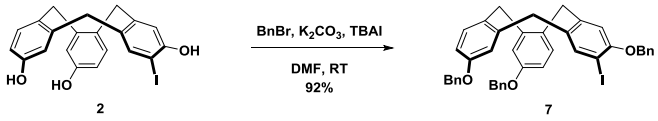
Scheme 2. Synthesis of Monohalogenated CTV Derivatives

We decided to focus our study on iodinated derivative **2** for its expected higher reactivity in pallado-catalyzed reactions than the corresponding brominated compound **4a**.[14]
First, CTV-phenylacetylene **6** was prepared through palladium-catalyzed Sonogashira coupling of **2** with trimethylsilylacetylene (Scheme 3). Classical conditions using $PdCl_2(PPh_3)_2$ as a catalyst, CuI as a co-catalyst, excess of Et_3N and toluene as solvent, followed by a TBAF-mediated desilylation led to CTV **6** in 45% overall yield.



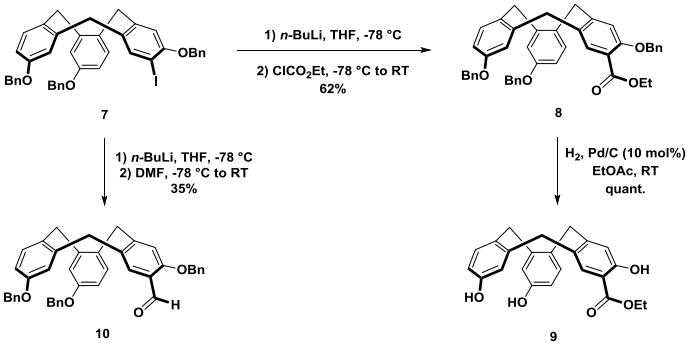
Scheme 3. Sonogashira Coupling from **2**

We then turned our attention toward organolithium chemistry to introduce diverse electron-withdrawing groups. For that purpose, benzylation of phenolic moieties was initially carried out to protect the alcohol functionalities and to improve the solubility of mono-iodinated CTV in THF. Treatment of CTV **2** with benzyl bromide, K_2CO_3 and catalytic amount of TBAI led efficiently to the protected CTV **7** in 92% yield (Scheme 4).



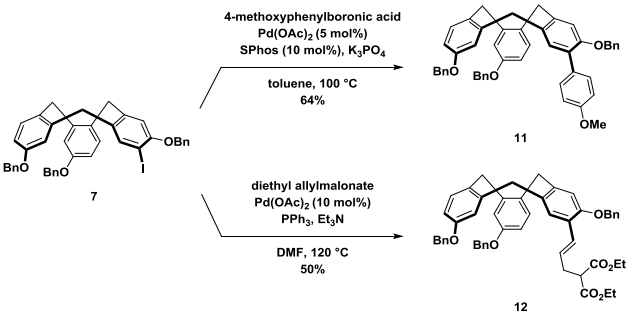
Scheme 4. Synthesis of Derivative **7**

A halogen-metal exchange with *n*-BuLi at low temperature, followed by addition of ethyl chloroformate, converted CTV **7** to the corresponding ester **8** (Scheme 5). Then, removal of the benzyl protecting groups by hydrogenolysis over Pd/C in EtOAc led to CTV **9** in 62% yield over two steps. Alternatively, reaction of the organolithium intermediate with DMF afforded the expected aldehyde **10** in 35% yield (Scheme 5).



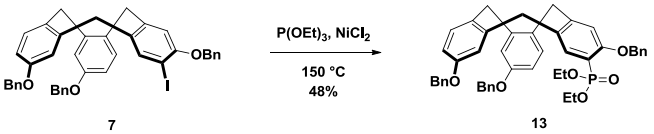
Scheme 5. Introduction of Electron-Withdrawing Groups using Organolithium Chemistry

Then, the reactivity of CTV **7** in classical conditions of Suzuki-Miyaura coupling was explored as outlined in Scheme 6. Thus, cross-coupling with 4-methoxyphenylboronic acid using $Pd(OAc)_2$ as catalyst, SPhos as ligand and anhydrous K_3PO_4 as base in refluxing toluene gave rise to CTV **11** in 64% yield (Scheme 6). The palladium-catalyzed Heck vinylation of iodinated CTV **7** was also investigated. Treatment with diethyl allylmalonate in the presence of $Pd(OAc)_2$, PPh_3 and Et_3N in refluxing DMF provided the π-extended conjugated CTV **12** in 50% yield (Scheme 6).



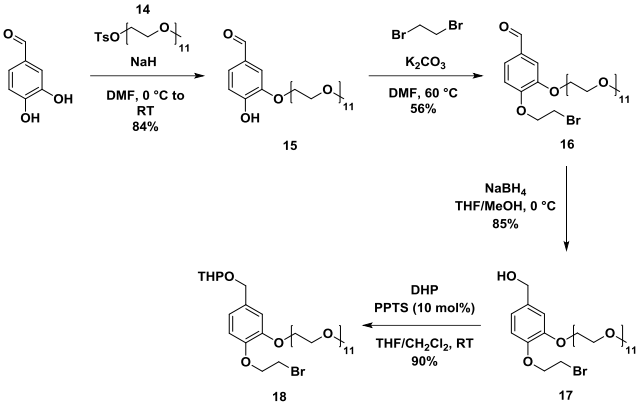
Scheme 6. Suzuki-Miyaura and Heck Cross-Coupling of **7**

Finally, a Michaelis-Arbuzov reaction was successfully achieved using thiethylphosphite and nickel(II) chloride at 150 °C, leading to the expected CTV **13** bearing a phosphonate moiety in 48% yield (Scheme 7).



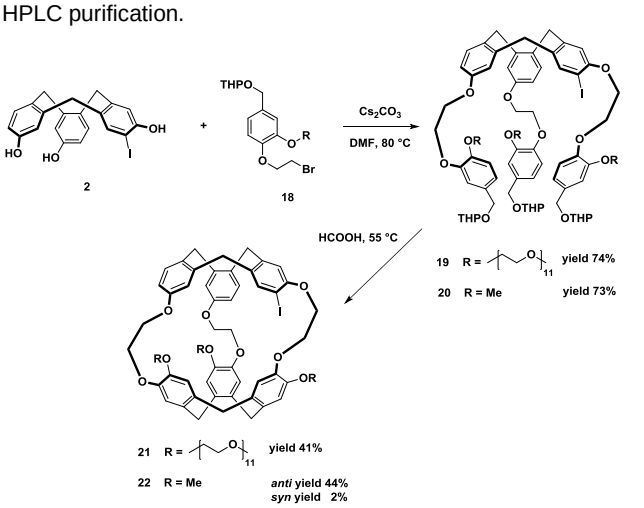
Scheme 7. Michaelis-Arbuzov Reaction from **7**

Synthesis of a Water-Soluble Monofunctionalizable Cryptophane. As part of our on-going research program dedicated to the efficient synthesis of a functionalizable water-soluble cryptophane,[15] we decided to explore the potentiality of C_1-symmetric CTV **2** as a universal platform to access a wide range of original ^{129}Xe MRI-based biosensors bearing a single functionality. To date, the concept of cryptophane-xenon assemblies as ^{129}Xe NMR biosensing systems has not been extended to *in vivo* experiments owing to the limiting factor of scale. Indeed, a selective functionalization is required to introduce the recognition antenna of the biological target. Unfortunately, the high symmetry of cryptophane cores provides complex mixtures along with complicated purification steps, thus leading to unsatisfying yields and small quantities of biosensors. As a result, the construction of new cryptophane congeners from C_1-symmetric CTVs described above is expected to provide two essential advantages: 1) diverse cryptophanes on a larger scale through the efficient monohalogenation of CTV **1** at the early stage of the synthetic strategy; 2) introduction of a specific biological antenna facilitated by taking advantage of the single functional group. Moreover, most biosensors described in the literature are based on cryptophanol-A.[10b,f,h-m] However, the limited solubility of this hydrophobic cryptophane core in biological media results in the biosensor's uptake by biological membranes[16] and formation of self-organized systems,[10i] hampering their use for *in vitro* or *in vivo* experiments. In this context, there is an urgent and unmet need to develop straightforward synthetic methods leading to simultaneously hydrophilic and C_1-symmetric cryptophane congeners. Recently, two water-soluble cryptophanes bearing a single functionality on their skeleton have been reported by Brotin *et al*.[17] Herein, we describe the synthesis of one such cryptophane obtained from the C_1-symmetric CTV **2** and containing three poly(ethylene glycol) (PEG) chains as water-soluble moieties. To the best of our knowledge, this is the first time that introduction of a mono-functionality at the early stage of cryptophane synthesis is reported. The synthetic pathway started with the regioselective substitution of a phenol group of 3,4-dihydroxybenzaldehyde[18] by a tosyl-functionalized PEG monomethyl ether **14** of eleven repeated units (M_n 550) providing compound **15** in 84% yield (Scheme 8). An S_N2 type reaction was performed in the presence of 1,2-dibromoethane and potassium carbonate to give rise to compound **16** in 56% yield. Reduction of the aldehyde function with $NaBH_4$ at low temperature afforded the corresponding primary alcohol **17** in excellent 85% yield. Finally, protection of the alcohol function by a tetrahydropyranyl acetal led to compound **18** in 90% yield.



Scheme 8. Synthesis of compound **18**

With pegylated linker **18** in hand, we applied the so-called *template method* to afford the expected cryptophane in two steps (Scheme 9).[8] Deprotonation of CTV **2** with Cs_2CO_3, followed by treatment with compound **18** in DMF, led to the *tris*-functionalized intermediate **19** in 74% yield. Subsequent cyclotrimerization of this preorganized precursor with formic acid occurred affording the final compound **21** in a satisfying yield (41%) after preparative HPLC purification.



Scheme 9. Synthesis of Cryptophanes **21** and **22**

NMR spectroscopic studies: In order to evaluate the xenon encapsulation properties of the new water-soluble cage, a purified sample of cryptophane **21** was then submitted to hyperpolarized ^{129}Xe NMR experiments. Two different ^{129}Xe NMR signals were observed (see ^{129}Xe NMR spectra in SI), with chemical shifts of 60 and 75 ppm, attributed to the presence of *anti* and *syn* forms in the sample (difficult to separate because of the high polarity of the PEG chains). In order to confirm this hypothesis, the synthesis of cryptophane **22** was undertaken (Scheme 9). *Syn* and *anti* form were successfully separated and both forms showed satisfying encapsulation properties in tetrachloroethane, with xenon chemical shifts of 78 and 74 ppm, respectively (see ^{129}Xe NMR spectra in SI). Because of their ease of preparation and functionalization, we believe that the molecular cages described here can be considered as useful platforms for the construction of various cryptophane-based ^{129}Xe MRI biosensors.

Conclusion

In summary, we propose a new strategy for the straightforward synthesis of a monofunctionalized CTV from cyclotriphenolene. This C_1-symmetric compound is a perfect platform to add new members bearing electron-withdrawing or π-extended conjugated systems to the CTV family. Moreover, these valuable compounds open the way to a wide range of original cryptophanes for ^{129}Xe MRI biosensors. As an example, we describe a short and scalable synthetic route to a water-soluble C_1-symmetric cryptophane bearing an iodine atom. The single functionality on the aromatic scaffold is expected to allow the easy introduction of recognition antennas for various biosensing applications, avoiding the purification of complex statistical mixtures usually generated from C_3 or D_3-symmetric congeners.

Experimental Section

General Information. All reactions were conducted in oven-dried glassware under a nitrogen atmosphere. All moisture sensitive reactants were handled under a nitrogen atmosphere. Organic solvents were used without further purification. THF was distilled over sodium/benzophenone under a nitrogen atmosphere and CH_2Cl_2 over CaH_2. Thin-layer chromatography (TLC) were performed on Merck 60 F254 silica gel plates, using UV light as a visualizing agent and ethanolic solution of phosphomolybdic acid and heat as developing agents. Flash column chromatography purifications were carried out by silica gel columns (particules size: 0.040-0.063 mm) or by Combiflash® chromatography on a RediSep apparatus using “pre-packed” silica cartridges. Infrared spectra (IR) were recorded on a Perkin Elmer system 2000 FT-IR spectrophotometer. Absorption bands are reported as wavelength numbers (cm^{-1}). ^1H NMR (400.13 MHz), ^{13}C NMR (100.62 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, d) downfield from residual solvent peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t) or broad singulet (bs). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). ^{129}Xe NMR spectra were recorded on a Bruker Avance II 500 MHz equipped with 5 mm HNX and broadband inverse probeheads. Accurate calibration of the temperature was made using a methanol sample. Prior the introduction of the hyperpolarized noble gas, the solutions were degassed through helium bubbling or using several freeze-pump-thaw cycles. Electrospray mass spectra were recorded using an ESI/TOF Mariner Mass Spectrometer. High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier. Unless otherwise noted, all other commercially available reagents were used without further purification.

Compound (2): In a 250 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, cyclotriphenolene **1** (300 mg, 0.942 mmol) was dissolved in CH_3CN (100 mL). *N*-iodosuccinimide (212 mg, 0.942 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. Then, the orange solution was quenched with water and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (50 mL), washed with water (20 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x15 mL), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a brownish solid. The resulting crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **2** as a pale yellow solid (184 mg, 72%, yield based on recovered starting material). R_f 0.22 (Cyclohexane/EtOAc: 6/4); MS (ESI positive mode): m/z 462.0 $[M+NH_4]^+$; MS (ESI negative mode): m/z 443.1 $[M-H]^-$, 887.2 $[2M-H]^-$; IR (neat): 3286, 1687, 1606, 1585, 1496, 1476, 1443, 1395, 1233, 1147, 964, 867, 741, 633, 491 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{21}H_{18}IO_3$: 445.029519; found: 445.029435; ^1H NMR (400.13 MHz, acetone-d_6): δ 8.68 (bs, 1H), 8.10 (bs, 1H), 8.02 (bs, 1H), 7.74 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 2.6 Hz, *J* = 8.2 Hz, 1H), 6.56 (dd, *J* = 2.6 Hz, *J* = 8.2 Hz, 1H), 4.74 (d, *J* = 13.3 Hz, 3H), 3.55 (m, 3H); ^{13}C NMR (100.62 MHz, acetone-d_6): δ 156.9, 155.9, 143.3, 142.6, 141.9, 141.0, 134.3, 132.0, 131.7, 131.6, 131.0, 117.2, 117.0, 114.8, 114.6, 82.0, 36.7, 36.4, 36.1.

Compounds (4a) and (4b): In a 250 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, cyclotriphenolene **1** (100 mg, 0.314 mmol) was dissolved in CH_3CN (35 mL). *N*-bromosuccinimide (56 mg, 0.942 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. Then, the orange solution was quenched with water and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (30 mL), washed with water (15 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x10 mL), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a brownish solid. The resulting crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **4a** and **4b** as white solids (**4a**: 41.2 mg, 45%; **4b**: 32.4 mg, 36%, yields based on recovered starting material).

Isomer 4a: R_f 0.42 (Cyclohexane/EtOAc: 1/1); MS (ESI positive mode): m/z 414.0 $[M+NH_4]^+$; MS (ESI negative mode): m/z 397.1 $[M-H]^-$, 793.4 $[2M-H]^-$; IR (neat): 3295, 2989, 2916, 1686, 1604, 1496, 1476, 1439, 1400, 1227, 1146, 1108, 1089, 964, 868, 798, 742, 634 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{21}H_{18}BrO_3$: 397.043383; found: 397.043203; ^1H NMR (400.13 MHz, acetone-d_6): δ 7.53 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.05 (s, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.89 (d, *J* = 2.6 Hz, 1H), 6.58 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 2.6 Hz, *J* = 8.2 Hz, 1H), 4.76 (m, 3H), 3.57 (m, 3H); ^{13}C NMR (100.62 MHz, acetone-d_6): δ 156.9, 153.2, 142.6, 142.4, 141.9, 134.8, 133.8, 132.1, 131.8, 131.6, 131.0, 118.4, 117.2, 117.0, 114.8, 114.6, 108.1, 36.7, 36.3, 36.2.

Isomer 4b: R_f 0.38 (Cyclohexane/EtOAc: 1/1); MS (ESI positive mode): m/z 398.9 $[M+H]^+$; MS (ESI negative mode): m/z 396.1 $[M-H]^-$; IR (neat): 3254, 1689, 1585, 1497, 1470, 1438, 1235, 1148, 966, 867, 745, 711, 632, 555, 492 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{21}H_{18}BrO_3$: 397.043383; found: 397.042726; ^1H

NMR (400.13 MHz, acetone-d_6): δ 8,53 (bs, 1H), 8.08 (s, 1H), 8.07 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.59 (dd, *J* = 2.6 Hz, *J* = 8.2 Hz, 1H), 6.51 (dd, *J* = 2.7 Hz, *J* = 8.6 Hz, 1H), 4.82 (m, 3H), 4.38 (d, *J* = 14.2 Hz, 1H), 3.65 (d, *J* = 13.7 Hz, 1H), 3.55 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (100.62 MHz, acetone-d_6): δ 156.9, 153.8, 143.7, 142.0, 141.3, 134.1, 132.6, 132.4, 131.6, 131.5, 130.6, 117.4, 117.2, 115.2, 114.9, 114.1, 38.0, 37.1, 34.3.

Compound (6): In a 10 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **2** (40 mg, 0.090 mmol), copper iodide (3.4 mg, 0.018 mmol) and bis-(triphenylphosphine)palladium(II) dichloride (12.6 mg, 0.018 mmol) were dissolved in toluene (2.5 mL). Subsequently, anhydrous triethylamine (628 µL, 4.50 mmol) and trimethylsilylacetylene (38 µL, 0.270 mmol) were added. The reaction mixture was stirred for 24 hours at 40 °C. The reaction was cooled to room temperature and concentrated *in vacuo*. The brown crude oil was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford 3-((trimethylsilyl)ethynyl)-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triol as a pale yellow solid (23.5 mg). Then, this intermediate was dissolved in THF (2 mL) under nitrogen atmosphere, and a 1M TBAF solution in THF (0.198 mL, 0.198 mmol) was added slowly. The resulting solution was stirred at room temperature overnight until complete disappearance of starting material. The reaction mixture was dissolved in EtOAc (15 mL) and H_2O (5 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x10 mL), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford **6** as a yellowish solid (18.2 mg, 45% over two steps). R_f 0.36 (Cyclohexane/EtOAc: 1/1); MS (ESI positive mode): m/z 343.1 $[M+H]^+$, 685.4 $[2M+H]^+$; MS (ESI negative mode): m/z 341.2 $[M-H]^-$; IR (neat): 3272, 2921, 2853, 1693, 1606, 1494, 1444, 1230, 1194, 1148, 1090, 965, 868, 743 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{23}H_{19}O_3$: 343.132871; found: 343.133002; ^{1}H NMR (400.13 MHz, acetone-d_6): δ 8.17 (s, 1H), 8.06 (s, 1H), 8.02 (s, 1H), 7.41 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 6.91 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.58-6.54 (m, 2H), 4.77 (m, 3H), 3.69 (s, 1H), 3.56 (m, 3H); ^{13}C NMR (100.62 MHz, acetone-d_6): δ 158.0, 157.0, 144.3, 142.7, 142.0, 135.6, 132.3, 132.0, 131.9, 131.6, 130.9, 117.5, 117.3, 117.1, 114.8, 114.7, 108.7, 83.0, 80.7, 36.8, 36.7, 36.4.

Compound (7): In a 100 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **2** (280 mg, 0.630 mmol), potassium carbonate (1.74 g, 12.60 mmol) and tetrabutylammonium iodide (69.8 mg, 0.189 mmol) were dissolved in DMF (55 mL). Subsequently, benzyl bromide (1.48 mL, 12.60 mmol) was added and the reaction mixture was stirred overnight at room temperature until complete disappearance of starting material (monitored by TLC). The pale yellow suspension was diluted with EtOAc (70 mL) and water (30 mL). The aqueous layer was separated and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting yellow crude oil was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **7** as a white solid (414.2 mg, 92%). R_f 0.65 (Cyclohexane/EtOAc: 8/2); MS (ESI positive mode): m/z 731.9 $[M+NH_4]^+$; IR (neat): 3059, 3028, 2986, 2908, 2887, 2851, 1607, 1497, 1375, 1254, 1231, 1026, 731, 694 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{42}H_{36}IO_3$: 715.170369; found: 715.170512; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.50-7.33 (m, 15H), 7.21 (d, *J* = 8.6 Hz, 1H), 7.00-6.97 (m, 2H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.78 (s, 1H), 6.74 (dd, *J* = 2.6 Hz, *J* = 8.6 Hz, 1H), 6.64 (dd, *J* = 2.6 Hz, *J* = 8.6 Hz, 1H), 5.22-5.02 (m, 6H), 4.69 (m, 3H), 3.58 (m, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.6, 157.5, 155.8, 141.3, 140.8, 140.5, 140.3, 137.1, 137.0, 136.7, 133.6, 131.8, 131.1, 130.6, 128.6, 128.5, 128.0, 127.8, 127.7, 127.5, 127.3, 126.8, 116.4, 116.2, 114.3, 113.2, 113.1, 84.5, 71.0, 70.1, 69.9, 36.4, 36.1.

Compound (8): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **7** (20 mg, 0.028 mmol) was dissolved in THF (4.25 mL). The reaction mixture was cooled to -78 °C and *n*-BuLi (2.5 M in THF, 56 µL, 0.140 mmol) was added dropwise. The resulting yellow solution was stirred at -78 °C for 15 min. Then, freshly distilled ethyl chloroformate (80 µL, 0.840 mmol) was added and the mixture was stirred at -78 °C for 2 hours and at room temperature for 2 hours. Upon completion, the pale yellow solution was quenched with a saturated NH_4Cl aqueous solution at 0 °C. The mixture was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **8** as a white solid (11.3 mg, 62%). R*f* 0.35 (Cyclohexane/EtOAc: 8/2); MS (ESI positive mode): m/z 661.5 [M+H]+, 1339.2 $[2M+NH_4]^+$; IR (neat): 3033, 2963, 2921, 2870, 1699, 1606, 1496, 1453, 1410, 1378, 1248, 1148, 1027, 729, 693 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{45}H_{41}O_5$: 661.294851; found: 661.295026; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.49-7.30 (m, 15H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.93 (s, 1H), 6.72 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 2.7 Hz, *J* = 8.6 Hz, 1H), 5.25-5.02 (m, 6H), 4.75 (m, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 3.65 (m, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.2, 157.7, 157.6, 156.7, 145.5, 141.1, 140.4, 137.0, 133.6, 131.8, 131.4, 131.1, 130.8, 130.7, 128.6, 128.5, 128.0, 127.9, 127.7, 127.6, 127.4, 126.9, 119.6, 116.3, 116.2, 115.6, 113.3, 113.2, 70.9, 70.0, 60.8, 36.7, 36.5, 36.4, 14.3.

Compound (9): A solution of **8** (11.2 mg, 0.017 mmol) and palladium (10% wt. on carbon, 1.8 mg, 0.002 mmol) in EtOAc (2 mL) was stirred under an atmospheric pressure of hydrogen at room temperature for 16 hours, until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to afford **9** (6.5 mg, quantitative). No further purification was needed. R_f 0.58 (Cyclohexane/EtOAc: 1/1); MS (ESI positive mode): m/z 391.2 $[M+H]^+$, 408.3 $[M+NH_4]^+$, 798.6 $[2M+NH_4]^+$; MS (ESI negative mode): m/z 389.3 $[M-H]^-$, 779.6 $[2M-H]^-$; IR (neat): 3380, 3355, 2920, 2851, 1674, 1618, 1582, 1493, 1463, 1376, 1263, 1213, 1147, 788, 741, 492 cm^{-1}; HRMS (ESI positive mode) calcd. for

$C_{24}H_{23}O_5$: 391.154000; found: 391.154017; ^{1}H NMR (400.13 MHz, acetone-d_6): δ 10.47 (s, 1H), 8.09 (s, 1H), 8.07 (s, 1H), 7.90 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.04 (s, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.60 (d, *J* = 1.1 Hz, 1H), 6.58 (d, *J* = 1.1 Hz, 1H), 4.81 (m, 3H), 4.39 (m, 2H), 3.62 (m, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.62 MHz, acetone-d_6): δ 170.7, 160.9, 157.1, 157.0, 150.5, 142.8, 141.8, 132.3, 132.2, 132.1, 131.8, 130.2, 119.0, 117.2, 117.1, 114.9, 114.8, 111.9, 62.2, 36.9, 36.8, 36.6, 14.6.

Compound (10): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **7** (20 mg, 0.028 mmol) was dissolved in THF (4.25 mL). The reaction mixture was cooled to -78 °C and *n*-BuLi (2.5 M in THF, 56 µL, 0.140 mmol) was added dropwise. The resulting yellow solution was stirred at -78 °C for 15 min. Then, *N,N*-dimethylformamide (65 µL, 0.840 mmol) was added and the mixture was stirred at -78 °C for 2 hours and at room temperature for 2 hours. Upon completion, the pale yellow solution was quenched with a saturated NH_4Cl aqueous solution at 0 °C. The mixture was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **10** as a white solid (6.0 mg, 35%). R_f 0.55 (Cyclohexane/EtOAc: 7/3); MS (ESI positive mode): m/z 617.5 $[M+H]^+$, 1251.6 $[2M+NH_4]^+$; MS (ESI negative mode): m/z 615.5 $[M-H]^-$; IR (neat): 3058, 3026, 2919, 2855, 1672, 1603, 1494, 1453, 1248, 1025, 729, 692 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{43}H_{37}O_4$: 617.268636; found: 617.268918; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.84 (s, 1H), 7.43-7.35 (m, 15H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 2.7 Hz, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 5.27-5.00 (m, 6H), 4.74 (m, 3H), 3.65 (m, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 189.1, 159.5, 157.7, 157.6, 148.4, 141.2, 140.1, 137.0, 136.9, 136.3, 132.1, 131.6, 131.0, 130.7, 130.1, 128.8, 128.5, 128.1, 127.9, 127.5, 127.3, 127.1, 123.9, 116.3, 116.0, 114.5, 113.6, 113.3, 70.5, 70.1, 70.0, 36.9, 36.6, 36.3.

Compound (11): In a 10 mL round-bottom flask equipped with a septum, a magnetic stirrer and a reflux condenser under nitrogen atmosphere, **7** (16.0 mg, 0.022 mmol), 4-methoxyphenylboronic acid (6.8 mg, 0.045 mmol), SPhos (0.9 mg, 2.25 µmol), palladium acetate (0.25 mg, 1.12 µmol) and anhydrous tripotassium phosphate (14.3 mg, 0.068 mmol) were dissolved in toluene (1.0 mL). The reaction mixture was stirred overnight at 100 °C until complete disappearance of starting material (monitored by TLC). Subsequently, the mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting brownish solid was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **11** as a pale yellow solid (10.0 mg, 64%). R_f 0.31 (Cyclohexane/EtOAc: 9/1); IR (neat): 3027, 2919, 2853, 1608, 1492, 1452, 1377, 1250, 1027, 833, 730, 693 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{49}H_{43}O_4$: 695.315867; found: 695.315586; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.41-7.28 (m, 16H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.96-6.93 (m, 4H), 6.71 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 5.12-5.00 (m, 6H), 4.79 (d, *J* = 13.6 Hz, 3H), 3.87 (s, 3H), 3.65 (m, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.5, 157.6, 157.4, 154.2, 141.0, 140.9, 139.6, 137.5, 137.2, 137.1, 132.3, 131.9, 131.7, 131.6, 131.0, 130.8, 130.8, 129.6, 128.6, 128.5, 128.4, 127.9, 127.5, 127.4, 126.8, 116.5, 116.2, 114.9, 113.4, 113.2, 113.0, 70.6, 70.1, 70.0, 55.3, 36.7, 36.5, 36.4.

Compound (12): In a 10 mL round-bottom flask equipped with a septum, a magnetic stirrer and a reflux condenser under nitrogen atmosphere, **7** (20.0 mg, 0.028 mmol), palladium acetate (0.7 mg, 2.8 µmol) and triphenylphosphine (14.7 mg, 0.056 mmol) were dissolved in DMF. Then, triethylamine (19 µL, 0.140 mmol) was added and diethyl allylmalonate (55 µL, 0.280 mmol) was added slowly. The reaction mixture was stirred overnight under reflux until complete disappearance of starting material (monitored by TLC). Subsequently, the mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting brownish solid was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **11** as a white solid (11.2 mg, 50%). R_f 0.35 (Cyclohexane/EtOAc: 8/2); MS (ESI positive mode): m/z 804.6 $[M+NH_4]^+$; IR (neat): 3030, 2986, 2920, 2862, 1727, 1605, 1496, 1453, 1248, 1149, 1025, 857, 734, 695 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{52}H_{51}O_7$: 787.362930; found: 787.363256; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.45-7.31 (m, 15H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.99 (m, 2H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.80 (s, 1H), 6.69 (m, 2H), 6.62 (dd, *J* = 2.6 Hz, *J* = 8.4 Hz, 1H), 6.13 (m, 1H), 5.14-5.00 (m, 6H), 4.72 (m, 3H), 4.13 (m, 4H), 3.60 (m, 3H), 3.45 (t, *J* = 7.5 Hz, 1H), 2.79 (m, 2H), 1.20 (2t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100.62 MHz, CDCl3): δ 168.9, 157.6, 157.4, 154.4, 140.9, 140.8, 140.0, 137.3, 137.2, 131.8, 131.6, 131.4, 131.0, 130.7, 128.6, 127.9, 127.8, 127.6, 127.5, 127.3, 127.1, 126.0, 125.3, 116.3, 116.2, 113.9, 113.1, 113.0, 70.4, 70.0, 61.3, 52.2, 36.6, 36.5, 32.7, 14.1.

Compound (13): In a sealed tube equipped with a magnetic stirrer under nitrogen atmosphere, **7** (10.0 mg, 0.014 mmol) and anhydrous nickel chloride (3.6 mg, 0.028 mmol) were dissolved in triethylphosphite (0.5 mL). The reaction mixture was stirred for 5 days at 150 °C until complete disappearance of starting material. Subsequently, the mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford **13** as a yellow solid (4.8 mg, 48%). R_f 0.35 (Cyclohexane/EtOAc: 1/1) ; MS (ESI positive mode): m/z 725.6 $[M+H]^+$, 1450.3 $[2M+H]^+$; IR (neat): 3030, 2980, 2924, 1603, 1496, 1245, 1021, 966, 732, 695 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{46}H_{46}O_6P$: 725.302652; found: 725.303277; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.88 (d, *J* = 15.2 Hz, 1H), 7.48-7.31 (m, 15H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 6.6 Hz, 1H), 6.70 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1H), 6.62 (dd, *J* = 2.1 Hz, *J* = 8.2 Hz, 1H), 5.26-5.00 (m, 6H), 4.74 (m, 3H), 4.08 (m, 4H), 3.64 (m, 3H), 1.26 (m, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.7, 157.6, 146.2, 141.2, 140.4, 137.0, 136.7, 131.6, 131.0, 130.7, 130.5, 128.6, 128.5, 127.9, 127.8, 127.7, 127.4, 127.3, 126.8, 116.2, 116.0, 113.5, 113.2, 70.2, 69.9, 63.6, 63.5, 36.8, 36.5, 36.3, 16.2, 16.1.

Compound (15): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, sodium hydride 95% (225.0 mg, 9.39 mmol) was suspended in DMF (2.5 mL) and the resulting suspension was cooled to 0 °C. Then, 3,4-dihydroxybenzaldehyde (618.3 mg, 4.47 mmol), previously dissolved in DMF (2.5 mL), was added dropwise and the yellow solution was stirred at 0 °C for 30 min. Subsequently, **14** (3.00 g, 4.47 mmol), previously dissolved in DMF (2.5 mL), was added slowly and the reaction mixture was stirred at room temperature overnight. Upon completion, the mixture was concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (50 mL) and a 1M HCl aqueous solution was added until pH 2. The aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting brownish oil was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to afford **15** as a pale yellow oil (2.40 g, 84%). R_f 0.55 (CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 637.4 $[M+H]^+$, 654.4 $[M+NH_4]^+$; MS (ESI negative mode): m/z 635.5 $[M-H]^-$; IR (neat): 3504, 2870, 1682, 1588, 1512, 1442, 1349, 1292, 1251, 1093, 948, 847, 633 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{30}H_{53}O_{14}$: 637.342983; found: 637.343011; ^1H NMR (400.13 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.40 (m, 2H), 6.99 (d, *J* = 7.7 Hz, 1H), 4.22 (t, *J* = 4.2 Hz, 2H), 3.86 (t, *J* = 4.2 Hz, 2H), 3.72 (m, 2H), 3.68-3.63 (m, 36H), 3.53 (t, *J* = 4.2 Hz, 2H), 3.37 (s, 3H), 3.09 (bs, 1H); ^{13}C NMR (100.62 MHz, CDCl*3*): δ 190.7, 153.6, 146.8, 129.2, 127.9, 115.7, 112.1, 71.8, 70.5, 70.4, 70.3, 70.2, 69.2, 68.8, 59.0.

Compound (16): In a 100 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **15** (2.40 g, 3.77 mmol) was dissolved in DMF (28 mL). Potassium carbonate (625.0 mg, 4.52 mmol) and 1,2-dibromoethane (1.3 mL, 15.1 mmol) were added and the resulting yellow suspension was stirred at 60 °C overnight. Upon completion, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting brownish oil was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to afford **16** as a yellowish oil (1.57 g, 56%). R_f 0.53 (CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 745.3 $[M+H]^+$; IR (neat): 3579, 2867, 1686, 1595, 1586, 1509, 1435, 1348, 1266, 1096, 947, 849 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{32}H_{56}BrO_{14}$: 743.284795; found: 743.284780; ^1H NMR (400.13 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.45 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.39 (t, *J* = 6.4 Hz, 2H), 4.22 (t, *J* = 4.7 Hz, 2H), 3.89 (t, *J* = 4.4 Hz, 2H), 3.75 (m, 2H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.62 (m, 36H), 3.53 (m, 2H), 3.36 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 190.7, 153.3, 149.3, 130.8, 126.3, 113.4, 112.2, 71.8, 70.9, 70.6, 70.5, 70.4, 69.4, 68.9, 58.9, 28.6.

Compound (17): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **16** (775.0 mg, 1.04 mmol) was dissolved in THF (2.5 mL) and the reaction mixture was cooled to 0 °C. Subsequently, sodium borohydride (39.4 mg, 1.04 mmol) and MeOH (0.250 mL) were added slowly. The resulting colorless solution was stirred at 0 °C for 30 min until complete disappearance of starting material (monitored by TLC). Upon completion, the reaction mixture was quenched with a 1M HCl aqueous solution and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford **17** as a colorless oil (660.5 mg, 85%). The crude product was engaged in the next step without further purification. R_f 0.48 (CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 762.3 $[M+NH_4]^+$; IR (neat): 3467, 2867, 1607, 1591, 1510, 1455, 1427, 1349, 1262, 1097, 949, 851, 568 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{32}H_{61}BrNO_{14}$: 762.326994; found: 762.327166; ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.82 (m, 2H), 4.52 (s, 2H), 4.24 (t, *J* = 6.4 Hz, 2H), 4.12 (t, *J* = 4.8 Hz, 2H), 3.80 (t, *J* = 4.9 Hz, 2H), 3.67 (m, 2H), 3.61-3.54 (m, 38H), 3.49 (m, 2H), 3.31 (s, 3H), 2.75 (bs, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.1, 147.0, 135.8, 119.7, 116.0, 113.5, 71.7, 70.6, 70.4, 70.3, 69.7, 69.5, 68.6, 64.3, 58.8, 29.4.

Compound (18): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **17** (600.0 mg, 0.81 mmol) was dissolved in THF (2 mL). Then, 3,4-dihydro-2H-pyran (147 µL, 1.62 mmol) and pyridinium p-toluenesulfonate (20.4 mg, 0.08 mmol) previously dissolved in CH_2Cl_2 (0.4 mL) were added. The reaction mixture was stirred at room temperature overnight until complete disappearance of starting material. Subsequently, the crude was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting yellowish oil was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to afford **18** as a colorless oil (601.6 mg, 90%). R_f 0.55 (CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 846.4 $[M+NH_4]^+$; IR (neat): 2867, 1511, 1455, 1349, 1264, 1099, 1033, 949, 868, 852 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{37}H_{69}BrNO_{15}$: 846.384509; found: 846.384788; ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.81 (s, 1H), 4.60 (m, 2H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.22 (t, *J* = 4.8 Hz, 2H), 4.09 (t, *J* = 4.8 Hz, 2H), 3.82 (m, 1H), 3.79 (t, *J* = 4.8 Hz, 2H), 3.66 (m, 2H), 3.58-3.54 (m, 40H), 3.46 (t, *J* = 4.8 Hz, 2H), 3,29 (s, 3H), 1.79-1.44 (m, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.0, 147.2, 132.4, 120.8, 116.0, 114.3, 97.3, 71.6, 70.5, 70.4, 70.3, 70.2, 69.6, 69.4, 68.6, 68.2, 61.9, 58.7, 30.2, 29.3, 25.2, 19.3.

Compound (19): In a 25 mL round-bottom flask equipped with a septum and a magnetic stirrer under nitrogen atmosphere, **2** (20.0 mg, 0.045 mmol) and cesium carbonate (58.6 mg, 0.180 mmol) were dissolved in DMF (7 mL). The pale yellow suspension was stirred at 80 °C for 15 min. Then, **18** (130.7 mg, 0.158 mmol) previously dissolved in DMF (1 mL), was added dropwise and the reaction mixture was stirred at 80 °C for 24 hours. Upon completion, the mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resulting residue was taken up in CH_2Cl_2, filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to afford a brownish oil. The crude was

purified by preparative TLC (CH_2Cl_2/MeOH 95:5) and the expected compound **19** was obtained as a brownish oil (90.9 mg, 74%). R_f 0.41(CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 1388.9 ([M+2Na]/2 + 21); IR (neat): 3516, 2867, 1715, 1640, 1510, 1454, 1349, 1252, 1098, 1034, 948, 851, 814, 536 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.27-7.20 (m, 2H), 7.03-6.85 (m, 12H), 6.69-6.54 (m, 2H), 4.73-4.58 (m, 9H), 4.41 (d, *J* = 11.9 Hz, 3H), 4.36-4.15 (m, 12H), 3.90-3.80 (m, 9H), 3.63-3.54 (m, 120H), 3.37 (s, 9H), 1.86-1.52 (m, 18H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.5, 157.4, 149.1, 148.2, 141.6, 141.1, 140.6, 140.4, 134.6, 134.1, 132.2, 132.1, 131.9, 131.4, 131.3, 130.9, 121.5, 121.3, 121.0, 116.3, 115.5, 115.3, 115.1, 114.8, 114.5, 114.3, 113.0, 97.7, 93.4, 84.6, 71.9, 71.5, 70.6, 69.7, 69.6, 68.8, 68.7, 68.2, 66.5, 62.3, 59.1, 36.5, 36.2, 30.6, 29.8, 25.5, 19.5.

Compound (20): 2-((4-(2-bromoethoxy)-3-methoxy benzyl)oxy)tetrahydro-2H-pyran (465 mg, 1.35 mmol) was added to a stirred solution of **2** (100 mg, 0.23 mmol) and cesium carbonate (440 mg, 1.35 mmol) in dry DMF (15 mL). The solution was heated for 3 days at 80 °C under nitrogen. The solvent was stripped off and the residue was extracted with dichloromethane / water. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to leave an oily residue. A purification by chromatography on silica gel (cyclohexane/EtOAc 100:0 to 70:30) afforded product **20** as a pale yellow solid (207 mg, 73%). R_f 0.48 (Cyclohexane/EtOAc 8/2); MS (ESI positive mode): m/z 846.4 $[M+NH4]^+$; IR (neat): 2944, 1609, 1516, 1478, 1234, 1136, 1026, 794, 741, 549 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{66}H_{77}INaO_{15}$: 1259.419940; found: 1259.419582. ^1H NMR (400.13 MHz, CDC_{l3}): δ 7.72 (s, 1H), 7.30-7.24 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.96-6.85 (m, 11H), 6.69 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H), 6.64 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H), 4.77-4.63 (m, 9H), 4.44 (d, *J* = 11.8 Hz, 3H), 4.41-4.21 (m, 12H), 3.97-3.89 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.66-3.58 (m, 3H), 3.58-3.50 (m, 3H), 1.92-1.79 (m, 3H), 1.78-1.68 (m, 3H), 1.68-1.47 (m, 12H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.3, 156.0, 149.5, 147.4, 141.4, 140.9, 140.4, 140.2, 134.0, 131.6, 131.2, 131.0, 130.6, 120.5, 120.4, 116.2, 114.3, 114.0, 113.8, 113.8, 112.9, 112.8, 113.0, 111.9, 97.5, 84.5, 68.6, 68.1, 67.6, 66.2, 62.2, 55.9, 55.8, 36.3, 36.0, 30.5, 25.3, 19.4.

Compound (21): In a 50 mL round-bottom flask equipped with a septum and a magnetic stirrer, **19** (40.0 mg, 0.015 mmol) was dissolved in formic acid (20 mL). The reaction mixture was slowly stirred at 55 °C for 3 hours. Subsequently, the colorless solution was allowed to cool to room temperature and concentrated *in vacuo*. The brownish crude oil was purified by preparative HPLC (water/acetonitrile 100:0 to 0:100) to afford **21** as a yellow oil (14.5 mg, 41%). R_f 0.50 (CH_2Cl_2/MeOH: 9/1); MS (ESI positive mode): m/z 1347.6 ± 22, $[(M+2H)/2]^+$; IR (neat): 3062, 3031, 2981, 2925, 2867, 2231, 1603, 1496, 1454, 1286, 1246, 1021, 966, 732, 695, 646 cm^{-1}. ^1H NMR (400.13 MHz, CDC_{l3}): δ 7.21-6.39 (m, 12H), 4.64-4.47 (m, 3H), 4.44-4.03 (m, 12H), 3.97-3.41 (m, 141H), 3.37 (s, 9H). For this compound, the ^1H NMR spectrum interpretation is extremely difficult due to the presence of two forms (syn/anti) of the cryptophane (confirmed by the synthesis of **22**) and 3 PEG11 substituents (All attempts of separation of this two forms have not been successful). Nevertheless, the water solubility of this compound and the presence of syn and anti forms of this cryptophane have been demonstrated by the ^{129}Xe NMR spectrum included in the Supporting Information.

Compound (22)-*anti*: In a 250 mL round-bottom flask equipped with a septum and a magnetic stirrer, **20** (105 mg, 0.085 mmol) was dissolved in formic acid (100 mL). The reaction mixture was slowly stirred at 55 °C for 5 hours and kept stirring in the room temperature for 18 h. Subsequently, the colorless solution was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (cyclohexane/chloroform 100:0 to 50:50) afforded product ***22-anti*** as a white solid (35 mg, 44%). R_f 0.25 ($CHCl_3$/EtOAc: 9/1); MS (ESI positive mode): m/z 948.7, $[M+NH_4]^+$; IR (neat): 2231, 1005, 948, 884, 733, 700, 626, 530 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{51}H_{48}IO_9$: 931.233758; found: 931.233085; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 6.82 (s, 1H), 6.79-6.72 (m, 2H), 6.70 (s, 1H), 6.66 (s, 3H), 6.62 (s, 1H), 6.46 – 6.34 (m, 2H), 4.69-4.46 (m, 6H), 4.44 (t, *J* = 9.4 Hz, 2H), 4.42-4.04 (m, 10H), 3.99-3.89 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.57-3.36 (m, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.4, 156.5, 156.3, 148.7, 148.4, 147.2, 147.0, 146.5, 141.8, 141.0, 140.3, 139.9, 136.2, 134.3, 132.9, 132.7, 132.2, 131.5, 130.8, 130.6, 122.0, 120.1, 119.1, 119.0, 116.6, 116.5, 114.8, 114.0, 113.1, 112.0, 111.8, 87.7, 77.7, 66.6, 65.4, 65.1, 56.7, 56.5, 55.9, 36.3, 36.1, 35.9.

Compound (22)-*syn*: In a 250 mL round-bottom flask equipped with a septum and a magnetic stirrer, **20** (105 mg, 0.085 mmol) was dissolved in formic acid (100 mL). The reaction mixture was slowly stirred at 55 °C for 5 hours and kept stirring in the room temperature for 18 h. Subsequently, the colorless solution was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (cyclohexane/chloroform 100:0 to 50:50). Then the fraction containing targeted product was purified by preparative TLC (chloroform/EtOAc 90:10) to afford the expected compound ***22-syn*** as a white solid (2 mg, 2%). R_f 0.44 ($CHCl_3$/EtOAc: 9/1); MS (ESI positive mode): m/z 948.7, $[M+NH_4]^+$; IR (neat): 2231, 1005, 948, 884, 733, 700, 626, 530 cm^{-1}; HRMS (ESI positive mode) calcd. for $C_{51}H_{48}IO_9$: 931.233758; found: 931.233400; ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.76-6.64 (m, 6H), 6.61 (d, *J* = 2.4 Hz, 1H), 4.69-4.46 (m, 6H), 4.45-4.17 (m, 7H), 4.15-4.06 (m, 1H), 4.05-3.91 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76-3.68 (m, 1H), 3.61-3.53 (m, 1H), 3.52-3.37 (m, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.7, 157.0, 156.6, 150.1, 149.5, 149.3, 147.2, 146.3, 146.2, 141.7, 140.7, 140.0, 140.0, 137.6, 134.7, 134.3, 134.0, 132.2, 132.1, 131.5, 131.3, 130.8, 130.7, 128.8, 121.8, 121.5, 121.3, 119.3, 118.9, 118.6, 114.2, 114.0, 113.6, 112.8, 88.1, 71.4, 71.2, 70.7, 69.2, 68.1, 65.8, 56.1, 38.7, 36.2, 30.9, 30.4, 29.7, 28.9, 23.7, 23.0, 14.1, 11.0.

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