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Development of Functionalized Cyclotriveratrylene Analogues: Introduction of Withdrawing and π-Conjugated Groups

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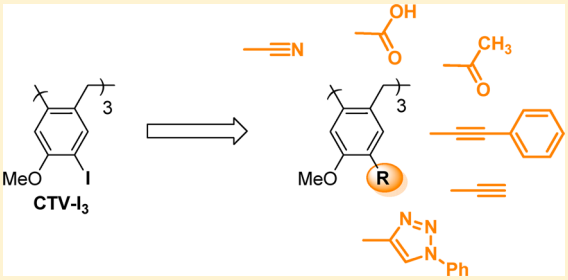
Supporting Information

ABSTRACT: Cyclotriveratrylene analogues (CTVs) are supramolecular bowl-shaped molecules known for their ability to complex organic and organometallic guests, to form liquid crystals, polymers, or nanostructures. In this Article, we report the synthesis of new cyclotriveratrylene analogues with fluorescence properties in which various electron-withdrawing or π-extended conjugated groups are appended to the wide rim ortho to the methoxy-donating groups. Synthetically, these functionalized CTVs cannot be obtained as CTVs with electron-rich functions by the typical method (i.e., the trimerization of the corresponding benzyl alcohol) but are prepared from a common key intermediate, the C_3-triiodocyclotriveratrylene (CTV-I_3), in good yields. Despite the synthetic difficulties encountered due to the presence of three reactive centers, we have demonstrated the possibility of performing Sonogashira coupling and Huisgen cycloaddition reactions directly to the CTV core for the first time. CTVs with π-extended conjugated groups reveal interesting fluorescence profiles. More broadly, this study utilizes CTV-I_3 to introduce novel functionalities into CTVs to keep exploring their potential applications.



INTRODUCTION

Since the discovery of the bowl-shaped cyclotriveratrylene macrocycle a century ago, its analogues have attached much attention[1,2] for their complexing properties (for metals,[3−6] fullerenes,[7−9] and small organic molecules guests[10]) and as materials to form liquid crystals,[11] gelators,[12] dendrimers,[13] or nanostructures.[14,15] Like the cyclotriveratrylene parent, which is prepared from veratryl alcohol, cyclotriveratrylene analogues (hereafter designed CTVs) are typically synthesized by aromatic electrophilic substitution of appropriate benzyl alcohols. This reaction is really efficient when two electron-donating groups are present in meta and para positions of the benzyl alcohol (R_1, R_2 in Figure 1). Nevertheless, this strategy has some limitations as soon as these positions are substituted by either deactivating electron-withdrawing groups or aromatic groups. Indeed, in such cases, the trimerization is not efficient, or formation of byproduct during the trimerization process is observed. Thus, most of the synthesized CTVs bear electron-rich functions on their wide rim, in particular, ethers (R_1 and R_2 = alkyl ether, Figure 1), and only few examples of CTVs with aromatic or electron-withdrawing groups have been reported in the literature.[7,14,15] However, the latter are of interest to widen the family of CTVs and to access, in particular, extended-cavity CTVs with properties other than those with ether side-arms. For example, aryl-extended rigid CTVs (R_1 = OMe, R_2 = Ar, Figure 1) have much larger and deeper cavities and more appropriate shapes to form nanotubes or to interact with C_{60}.[7,14] We also recently showed that CTVs presenting electron-withdrawing groups near donating ones (R_1 = OMe, R_2 = $PO(OH)_2$, OPO(OLi)Bu, Figure 1) led to fluorescent CTVs of interest as fluorescent probes.[10,16]

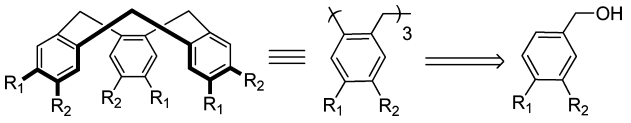


Figure 1. Typical synthesis and structure of cyclotriveratrylene analogues.

In this context, to extend the CTV family, the trihalogenated CTVs (R_1 = OMe, R_2 = Br, I, Figure 1), the syntheses of which were reported a few years ago,[17−19] are attractive intermediates. In particular, the cavitands with rigid arms (R_1 = OMe, R_2 = Py, Ar, Figure 1) have been obtained via Suzuki−Miyaura coupling reactions[7,14] from the C_3-tribromoyclotriveratrylene, CTV-

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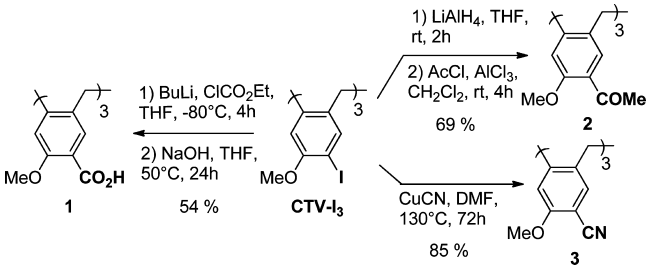
Br_3[17,18] (R_1 = OMe, R_2 = Br, Figure 1). In the present work, we have focused our attention on the iodo analogue C_3-triiodocylotriveratrylene CTV-I_3[19] (R_1 = OMe, R_2 = I, Figure 1). Indeed, iodo aryl groups are expected to be better substrates than bromo aryl ones, especially in cross-coupling reactions.[20,21] In a recent report, we have reconsidered the synthesis of CTV-I_3, and with 47% overall yield in only three steps, we can now prepare this intermediate in gram scale,[16] as compared to the synthesis of CTV-Br_3, which is described in only 10% overall yield.[17,18] We have also shown that it could be efficiently used in an Arbusov–Michaelis reaction to prepare a phosphorylated CTV, CTV-$(PO(OH)_2)_3$ (R_1 = OMe, R_2 = $PO(OH)_2$, Figure 1). To date, this CTV-I_3 has been underused, and only one example (R_1 = OMe, R_2 = CHO) has been reported in the literature.[15] In this work, we propose then to further exploit the reactivity of the aryl iodides of CTV-I_3 to synthesize CTVs that cannot be obtained by direct trimerization of the corresponding benzyl alcohol derivatives, that is, CTVs substituted by electron-withdrawing and π-extended conjugated groups ortho to the methoxy-donating ones. Through various examples reported herein, this study highlights the potential of CTV-I_3 as a key intermediate in the chemistry of CTVs to introduce novel functionalities.

RESULTS AND DISCUSSION

CTV-I_3 was first employed to access CTVs **1** and **2**, bearing carboxyl or ketone functions (Scheme 1). To get the CTV **1**

Scheme 1. Synthesis of CTVs Bearing Withdrawing Groups

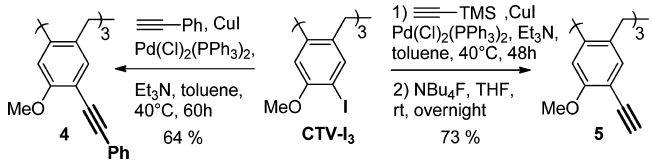


with three carboxyl groups, CTV-I_3 was engaged in a halogen metal exchange with *n*-BuLi at low temperature. The organolithium intermediate formed reacted with ethylchloroformate in THF to give, after ester hydrolysis, CTV **1** with 54% yield. The yield is similar to those reported in the literature using DMF as electrophile (R_1 = OMe, R_2 = CHO, Figure 1), confirming the potential of the iodinated intermediate to introduce electrophilic substituents on the CTV core.[15] Moreover, by taking advantage of the carboxyl group functionalization, CTV **1** appears as an interesting precursor to append diverse side-arms to the wide rim of CTVs.

CTV **2** with ketone arms was synthesized in 69% yield via a Friedel–Crafts reaction after reduction of the CTV-I_3 by lithium aluminum chloride.[19] Obviously in this last case, we do not take direct advantage of the reactivity of the iodo aryl groups of CTV-I_3 because they are reduced before the electrophilic substitution. The interest of CTV-I_3 is indirect and lies in the easy access to the hydrogenated CTV intermediate, CTV-H_3, that can be subjected to efficient Friedel–Crafts substitutions thanks to its methoxy activating groups and thus lead to new functionalized CTVs.

To test the reactivity of CTV-I_3 in transition metal-catalyzed cross-coupling reactions, we first performed the cyanation of the aryl iodides using the Rosenmund–von Bran reaction (Scheme 1). The reaction in DMF as solvent was proved efficient, and the cyanylated CTV **3** was obtained in an excellent yield of 85%. Next, we explored CTV-I_3 in cross-coupling Sonogashira reactions (Scheme 2). Classical con-

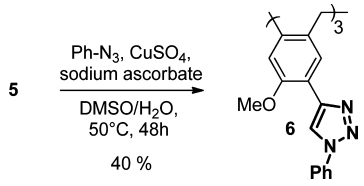
Scheme 2. Sonogashira Couplings from CTV-I_3



ditions for Sonogashira couplings using ethynylbenzene or trimethyl-silylacetylene as alkynylated reagents were employed. The corresponding CTVs **4** and **5** were obtained in 64% and 73%, respectively (after hydrolysis of the silyl groups in case of **5**). These are the first examples of Sonogashira couplings on a CTV scaffold, and the good yields obtained attest to the efficiency of this kind of organometallic cross coupling from CTV-I_3.

Diverse CTVs could be further obtained by Sonogashira couplings from CTV-I_3 by using a variety of alkynes and aromatic alkynes diversily substituted. CTVs with π-conjugation extension as in **4** could be of interest in particular for their fluorescence properties. CTV **5** or its silylated precursor could also be employed as intermediates in additional organometallic couplings or in alkyne-based chemistry. As an example, we engaged CTV **5** in a copper(I)-mediated alkyne–azide cycloaddition (CuAAC) reaction with phenylazide as a prototype of organic azides (Scheme 3). CTV **6** was obtained

Scheme 3. Example of Cu(I)-Catalyzed Huisgen 1,3-Dipolar Cycloaddition from 5



in 40% yield using the classical combination of sodium ascorbate and $CuSO_4$ as Cu(I) source in a mixture of water/dimethylsulfoxyde to dissolve the starting material **5**. This example shows the feasibility of using "click chemistry" to functionalize CTVs directly onto their aromatic core, and thus the possibility of taking advantage of the versatility of this chemoselective ligation to introduce different entities on the CTV core. Moreover, the 1,2,3-triazole-1,4-diyl entity formed in the CuAAC has been recently studied and proved as a π-linker.[22] Using "click chemistry" from **5** is also a way to extend the conjugation in the CTV core, as do the Sonogashira couplings using aryl acetylenes.

In our research group, we are interested in developing fluorescent CTVs. Therefore, we wanted to investigate the spectroscopic properties of the CTVs **1**–**3** with electron-withdrawing conjugated groups and the CTVs **4** and **6** with π-extended conjugated groups (Table 1). This study was performed in DMSO.

It is noteworthy that CTV-I_3 that absorbs light with a maximum at 300 nm (ε = 12 × 10^4 M^{-1} cm^{-1}) is not

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Table 1. Spectroscopic Characterizations of the CTVs

CTV	$\lambda_{abs\ max}$ (nm)	ε (10^4 M^{-1} cm^{-1})	$\lambda_{em\ max}$ (nm)	$\Delta\lambda^a$ (nm)	$\Phi_F{}^b$ (%)	τ (ns)
CTV **1**	302	5.1	348	46	8	1
CTV **2**	318	7.4	520	183	<1	0.09
CTV **3**	310	6.4	334	24	16	2
CTV **4**	320	4.9	355	35	63	1.5
CTV **6**	302	3.2	377	75	<1	0.9
$CTV(PO(OH)_2)_3{}^c$	297	7.1	317	20	13.5	2.7

[a] $\Delta\lambda$ = Stokes shift. [b] Relative quantum yields are measured using 7-methoxycoumarin-4-acetic acid as a reference (Φ_F = 0.18 in methanol).[23] [c] This compound, previously described,[18] is studied here in DMSO.

fluorescent. The fact that nonradiative pathways of de-excitation are very strong when aromatic groups are substituted by heavy atoms like iodine atoms is consistent with this observation.[24]

For the CTVs **1**−**3**, if the nature of the electron-withdrawing groups introduced on the CTV core has only a minor influence on the absorption properties, it affects more significantly the emission properties. Indeed, **2** shows only a faint emission, while CTVs **1** and **3** are fluorescent with moderate fluorescent quantum yields of 16% and 8% respectively. Concerning the maximum emission wavelength (λ_{em}), both **1** and **3** show longer values than CTV-$(PO(OH)_2)_3$, attesting an effect of the relative strength of the electron-withdrawing groups on the bathochromic shift of the λ_{em}. Nevertheless, CTV **1** with λ_{em} at 348 nm and Stokes displacement of 46 nm is the most interesting one considering further applications as probes. Indeed, its λ_{em} and its fluorescent quantum yield, although it is moderate, are retained in aqueous buffer at neutral pH. Therefore, we evaluated the complexing properties of **1** toward ammonium species in phosphate buffer, and the preliminary results showed a slight preference of **1** for acetylcholine (Figure S1, Supporting Information).

CTV **2** bearing ketone groups is a special case with a high bathochromic shift associated with a very low fluorescent quantum yield. Similar behaviors for aromatic ketones are mentioned in the literature and are correlated to low-lying n−π^* transition states of weak energy that induce red-shifted emissions and strengthen the intersystem crossing and the nonradiative pathways of de-excitation, quenching the fluorescence.[24]

In CTVs **4** and **6**, by extending π conjugation, we expected a shift of the absorption and emission maxima to longer wavelengths and better fluorescence quantum yields than CTVs **2** and **3**. This is the case for CTV **4** prepared by Sonogashira coupling. This one absorbs at 320 nm, and presents a higher red-shift (λ_{em} at 355 nm) and a superior quantum yield of 63%, as compared to the moderate ones obtained for CTVs **1** and **2**. Concerning CTV **6** with triazole units, it shows the longest-wavelength emission of this series (about 20 nm bathochromically shifted as compared to **4**). The very low quantum yield obtained for **6** does not question the ability of the triazole to act as a π-linker and its potential to get fluorescent CTVs. Indeed, by exploring the literature about the fluorescence properties of some triazole clicked compounds, it seems that the value of quantum yield is very dependent on the electron-donor or -withdrawing character of the clickable azido and alkyne subunits.[25,26] In our case, the use of phenylazides with donating groups could overcome this weakness and is under investigation.

CONCLUSION

In summary, through this work, we enhance the CTV family with new CTVs functionalized by electron-withdrawing and π-extended conjugated groups. These groups are directly attached onto the CTV aromatic core, enabling one to keep the very interesting rigid and stable structure of CTVs. All of the compounds are prepared in maximum three steps from the CTV-I_3 intermediate with good yields considering that for each step three reaction sites are present on the CTV squeleton. In terms of fluorescence properties, CTVs with π-extended conjugated groups are the most promising ones. More broadly, this study proves the potential of CTV-I_3 as a key intermediate in the chemistry of CTVs to introduce novel functionalities and thus to keep exploring the interest of CTVs in many applications. In particular, the opportunity to perform Sonogashira couplings and Huisgen cycloadditions, two reactions with wide scopes, opens new routes toward functionalized CTVs.

EXPERIMENTAL SECTION

General Experimental Details. Commercially available reagents were used without purification. Dichloromethane was freshly distilled from CaH_2 and tetrahydrofuran from sodium benzophenone ketyl under nitogen atmosphere. Anhydrous *N*,*N*-dimethylformamide was kept under argon atmosphere and used without further purification. Melting points were measured using a melting point bench and are uncorrected. NMR spectra were recorded on a 400 MHz (^1H frequency) spectrometer. Chemical shifts are reported using tetramethylsilane or the residual solvent peak as internal reference for ^1H or for ^{13}C. Infrared spectra were recorded on a FT-IR spectrometer in the range 4000−1000 cm^{-1}. UV/vis and fluorescence spectra were recorded in DMSO at 298 K. Molar extinction coefficients were obtained in the range of 10^{-4}−10^{-7} M in DMSO. The data curve absorbance versus concentration was fitted with a linear curve-fitting equation (with interception at 0 for x = 0) implemented within Origin. The fluorescence quantum yields were obtained by using 7-methoxycoumarin-4-acetic acid in methanol as a reference (ϕ_{ref} = 0.18). Time-resolved fluorescence experiments were performed using a frequency-tripled Nd:YAG laser (355 nm, 8 ns pulse) for excitation. Right-angle detection was used to collect the luminescence spectra using a gated CCD camera and spectrograph at variable delays.

3,8,13-Trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]-cyclononene-2,7,12-tricarboxylic Acid (1). CTV-I_3[15] (400 mg, 0.54 mmol) was dissolved in 25 mL of dried THF under argon atmosphere. The reaction mixture was cooled to −80 °C, and then butyllithium (1.95 mL of 2.5 M in hexane solution, 4.9 mmol, 9 equiv) was added slowly. The reaction was allowed to warm to 0 °C for 1 h, and then to room temperature for 1 h. The reaction was cooled to −80 °C again before the addition of ethyl chloroformate (2 mL, 20.8 mmol, 39 equiv). Next, the reaction was allowed to warm to room temperature. After 3 h at room temperature, the reaction mixture was cooled to 0 °C, and 80 mL of saturated $NH_4Cl_{(aq)}$ was added slowly. The crude mixture was extracted with ethyl acetate (3 × 100 mL). Next, the organic phases were washed with water, before being dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was finally purified by column chromatography on silica gel (dichloromethane/ethyl acetate first from 0 to 25% ethyl acetate). The intermediate ester CTV was obtained as a white solid (170 mg, 55% yield): mp 130 °C; δ_H (400 MHz, $CDCl_3$) 7.83 (s, 3H), 6.97 (s, 3H), 4.77 (d, J = 13.6 Hz, 3H), 4.29 (m, 6H), 3.88 (s, 9H), 3.73 (d, J = 13.6 Hz, 3H), 1.33 (t, J = 6.8 Hz, 9H); δ_C (100 MHz, $CDCl_3$) 165.8, 158.3, 145.4, 133.6, 130.2, 119.1, 113.7, 60.8, 56.3, 36.5, 14.4; ν_{max} (neat)/cm^{-1} 2977, 2932, 2901, 2859, 2832, 1723, 1692, 1609, 1503, 1403,

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1389, 1244, 1196, 1110, 1058, 1020; HRMS (ESI, positive mode) calcd for $C_{33}H_{36}O_9$, Na adduct 599.2258, found 599.2275. This intermediate (60 mg, 0.1 mmol) was dissolved in 6 mL of THF. A 5 M sodium hydroxide solution (4 mL, 20 mmol, 200 equiv) was added, and the solution was allowed to react at 50 °C for 24 h. The reaction mixture was cooled to room temperature, and the THF was removed under vacuum. A 37% HCl solution was added to the crude to reach pH < 1. The precipitate formed was collected and rinsed twice with 0.1 M HCl, followed by 0.01 M HCl. The solid obtained was dried under vacuum at 50 °C overnight. The CTV **1** was obtained as a beige solid (50 mg, 98% yield): mp decomposition from 255 °C; δ_H (400 MHz, DMSO-d_6) 12.38 (s, 3H), 7.848 (s, 3H), 7.23 (s, 3H), 4.84 (d, J = 13.2 Hz, 3H), 3.78 (d, J = 13.2 Hz, 3H), 3.77 (s, 9H); δ_C (100 MHz, DMSO-d_6) 166.9, 156.7, 145.1, 132.5, 130.8, 119.9, 113.7, 55.9, 34.9; ν_{max} (neat)/cm^{-1} 3490, 3231, 2925, 2859, 2839, 1709, 1602, 1492, 1458, 1406, 1334, 1317, 1285, 1155, 1055, 983; HRMS (ESI, TOF, negative mode) calcd for $C_{27}H_{23}O_9$, 491.1347, found 491.1356.

*1-(7,12-Diacetyl-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo-[a,d,g]cyclononen-2-yl)-1-ethanone (**2**).* CTV-I_3 was reduced by $LiAlH_4$ using the reported procedure.[2] The reduced CTV-H_3 (1.07 g, 2.97 mmol) was dissolved in 107 mL of dried dichloromethane under nitrogen atmosphere, at 0 °C. The aluminum chloride (2.14 mg, 16.05 mmol, 5.4 equiv) and acetyl chloride (3.15 mL, 44.5 mmol, 15 equiv) were added. After 20 min at 0 °C, the reaction was allowed to warm to room temperature. After 4 h at room temperature, 210 mL of HCl 1 M, which has been cooled to 0 °C, was added to the reaction mixture. The crude was extracted with dichloromethane (3 × 120 mL). Next, the organic phases were washed with distilled water up to neutrality of the water phase. The organic phase was dried with anhydrous magnesium sulfate and concentrated under vacuum. The solid was rinsed with diethyl ether and dried under vacuum. Finally, the solid obtained was purified by column chromatography on silica gel, using dichloromethane/ethyl acetate (9/1) as eluent, to give CTV **2** as a white solid (1.0 g, 70% yield): mp decomposition over 265 °C; δ_H (400 MHz, $CDCl_3$) 7.82 (s, 3H), 6.97 (s, 3H), 4.73 (d, J = 13.6 Hz, 3H), 3.88 (s, 9H), 3.75 (d, J = 13.6 Hz, 3H), 2.52 (s, 9H); δ_C (100 MHz, $CDCl_3$) 198.9, 158.4, 146.0, 132.4, 130.5, 126.7, 113.2, 56.9, 36.5, 32.1; ν_{max} (neat)/cm^{-1} 2997, 2918, 2849, 2835, 1664, 1599, 1492, 1392, 1262, 1231, 1151, 1048, 1004; HRMS (FAB with NBA matrix) calcd for $C_{31}H_{30}O_6$, 487.212, found 487.211.

*3,8,13-Trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]-cyclononene-2,7,12-tricarbonitrile (**3**).* CTV-I_3 (250 mg, 0.34 mmol) was dissolved in 12 mL of dried DMF under nitrogen atmosphere, and copper cyanide (250 mg, 5.6 mmol, 17 equiv) was added. The reaction was warmed to 130 °C. After 24 and 48 h, 250 mg of copper cyanide was added again to the mixture. After 3 days, the reaction was allowed to cool to room temperature. The crude was poured into 250 mL of 1 M HCl. The precipitate formed was filtered and washed with 200 mL of 1 M HCl, followed by saturated $NH_4Cl_{(aq)}$ up to neutrality of the water phase, and then with ether. The solid obtained was dissolved in hot dichloromethane and filtered through silica gel. After evaporation under vacuum of the dichloromethane, CTV **3** was obtained as a white solid (125 mg, 85% yield): mp decomposition over 265 °C; δ_H (400 MHz, DMSO-d_6) 8.08 (s, 3H), 7.46 (s, 3H), 4.88 (d, J = 13.6 Hz, 3H), 3.90 (s, 9H), 3.775 (d, J = 13.6 Hz, 3H); δ_C (100 MHz, DMSO-d_6) 159.6, 147.2, 135.4, 131.4, 113.5, 99.1, 56.7, 34.9; ν_{max} (neat)/cm^{-1} 2933, 2851, 2223, 1605, 1566, 1498, 1459, 1391, 1309, 1274, 1209, 1138, 1074, 1002; MALDI-MS (with a dithranol + AgTFA matrix) calcd for $C_{27}H_{21}N_3O_3$, Ag adduct 542.06, found 542.02.

*2,7,12-Trimethoxy-3,8,13-tris(2-phenylethynyl)-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (**4**).* CTV-I_3 (200 mg, 0.27 mmol) and ethynylbenzene (267 μL, 2.4 mmol, 9 equiv) were dissolved in 8 mL of toluene and 2 mL of dried triethylamine, under argon atmosphere. After 20 min of argon sparging, copper iodide (30.8 mg, 0.016 mmol, 0.6 equiv) and bis(triphenylphosphine)palladium(II) dichloride (114 mg, 0.16 mmol, 0.6 equiv) were added, and the solution was heated to 40 °C under argon atmosphere. After 60 h, the solution was cooled to room temperature and was evaporated under vacuum. The crude was purified by chromatography on silica gel, using cyclohexane/dichloromethane (1/1) as eluent, to give CTV **4** as a white powder (114 mg, 64% yield): mp decomposition over 253 °C; δ_H (400 MHz, $CDCl_3$) 7.53 (br, 6H), 7.46 (s, 3H), 7.31 (br, 9H), 6.87 (s, 3H), 4.69 (d, J = 13.6 Hz, 3H), 3.91 (s, 9H), 3.62 (d, J = 13.6 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 159.0, 141.5, 135.0, 131.8, 131.0, 128.4, 128.2, 123.8, 112.6, 111.6, 93.2, 85.8, 56.3, 36.7; ν_{max} (neat)/cm^{-1} 3033, 2969, 2937, 2851, 2822, 1591, 1502, 1481, 1441, 1391, 1295,1242, 1199, 1071, 1003; HRMS (ESI, TOF, positive mode) calcd for $C_{48}H_{36}O_3$, Na adduct 683.2565, found 683.2556.

*2,7,12-Triethynyl-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo-[a,d,g]cyclononene (**5**).* CTV-I_3 (300 mg, 0.406 mmol) and trimethylsilylacetylene (509 μL, 3.65 mmol, 9 equiv) were dissolved in 12 mL of toluene under argon atmosphere. After 20 min of argon sparging, copper iodide (46.4 mg, 0.24 mmol, 0.6 equiv), bis-(triphenylphosphine)palladium(II) dichloride (171 mg, 0.24 mmol, 0.6 equiv), and dried triethylamine 3 mL were added, and the solution was heated to 40 °C under argon atmosphere. After 48 h, the solution was cooled to room temperature and evaporated under vacuum. The crude was purified by chromatography on silica gel, using cyclohexane/dichloromethane (7/3) as eluent, to give trimethyl(2-{3,8,13-trimethoxy-7,12-bis[2-(trimethylsilyl)ethynyl]-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononen-2-yl}ethynyl)silane as a white powder (200 mg, 77% yield). This intermediate (200 mg, 0.308 mmol) was dissolved in 10 mL of dried THF under nitrogen atmosphere. Tetrabutylammonium fluoride (4.62 mL of 1 M in THF, 4.62 mmol, 15 equiv) was added, and the solution was allowed to react at 25 °C under argon atmosphere overnight. The THF was evaporated under vacuum, and distilled water (150 mL) was added to the crude. This one was extracted three times (100 mL) with dichloromethane. The organic phases were washed with water, dried with anhydrous magnesium sulfate, and concentrated under vacuum. The solid obtained was rinsed with diethyl ether and dried under vacuum. CTV **5** was obtained as a white powder (127 mg, 95% yield): mp decomposition over 200 °C; δ_H (400 MHz, DMSO-d_6) 7.64 (s, 3H), 7.19 (s, 3H), 4.75 (d, J = 13.2 Hz, 3H), 4.12 (s, 9H), 3.78 (d, J = 13.2 Hz, 3H), 3.66 (s, 3H); δ_H (100 MHz, DMSO-d_6) 158.8, 142.4, 135.0, 131.2, 112.6, 109.2, 83.9, 80.1, 55.9, 34.9; ν_{max} (neat)/cm^{-1} 3276, 2929, 2847, 2098, 1606, 1559 1492, 1463, 1388, 1199, 1134, 1074; HRMS (ESI, TOF, positive mode) calcd for $C_{30}H_{24}O_3$, Na adduct 455.1617, found 455.1637.

*1-Phenyl-4-[3,8,13-trimethoxy-7,12-bis(1-phenyl-1H-1,2,3-triazol-4-yl)-10,15-dihydro-5H-tribenzo[a,d,g]cyclononen-2-yl]-1H-1,2,3-triazole (**6**).* CTV **5** (30 mg, 0.069 mmol) and 1-azidobenzene (74.4 mg, 0.062 mmol, 9 equiv) were dissolved in 5 mL of DMSO/water (2/3) under argon atmosphere. After 20 min of argon sparging, copper sulfate (17 mg, 0.014 mmol, 1.5 equiv) and sodium ascorbate (41 mg, 0.02 mmol, 3 equiv) were added, and the solution was heated to 50 °C under argon atmosphere. After 48 h, the solution was cooled to room temperature, and 50 mL of distilled water was added. The crude was extracted with dichloromethane. The organic phases were dried with anhydrous magnesium sulfate and concentrated under vacuum. The solid was rinsed with diethyl ether and then dried under vacuum at 40 °C overnight. CTV **6** was obtained as a yellow powder (22 mg, 40% yield): mp decomposition over 265 °C; δ_H (400 MHz, $CDCl_3$) 8.48 (s, 3H), 8.32 (s, 3H), 7.77 (d, J = 7.4 Hz, 6H), 7.5 (t, J = 7.4 Hz, 6H), 7.4 (t, J = 7.4 Hz, 3H) ; δ_C (100 MHz, $CDCl_3$) 154.8, 143.8, 141.2, 137.4, 131.6, 129.8, 129.0, 128.5, 120.7, 120.5, 117.7, 112.6, 55.98, 36.8; ν_{max} (neat)/cm^{-1} 2919, 2851, 1595, 1495, 1463, 1420, 1378, 1256, 1235, 1149, 1113, 1031; HRMS (ESI, TOF, positive mode) calcd for $C_{48}H_{39}N_9O_3$, Na adduct 812.3068, found 812.3053.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds, and fluorescence titration data of **1** in the presence of choline and acetylcholine. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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