A study towards the regioselective synthesis of the *e*,*e*,*e* trisadduct of C_{60} *via* the [4+2] Diels-Alder reaction with tethers bearing *ortho*-quinodimethane precursors

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Dedicated to Professor Michael Orfanopoulos on the occasion of his 67th birthday

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Abstract

The regioselective synthesis of an *e*,*e*,*e* trisadduct of C_{60} *via* the Diels-Alder reaction with *ortho*-quinodimethanes has been attempted employing the tether-directed remote functionalization approach. Opened-structure tether **10** and macrocyclic tethers **16** and **21** were synthesized for this purpose. The functionalization of C_{60} afforded inseparable mixtures of regiomeric trisadducts and the regioselective formation of the *e*,*e*,*e* trisadduct was not feasible even when the more preorganized tethers **16** and **21** were employed. The *in situ* thermal generation of *ortho*-quinodimethanes from the 1,2-bis(bromomethyl)benzene precursors requires high temperatures and is followed by fast, irreversible cycloaddition with C_{60} to afford thermally stable products, which prevents the achievement of high regioselectivities.

Keywords: [60]Fullerene, Diels-Alder, cycloaddition, *ortho*-quinodimethanes, addition pattern, [4+2] trisadduct

Introduction

The fascinating properties of [60]fullerene have inspired chemists to design and synthesize derivatives with specific function and unique architectures targeting future applications in advanced nanoscale materials and devices.[1,2] For synthetic chemists, the limited solubility of C_{60} in common organic solvents has been an obstacle but at the same time triggered an enormous development of its covalent chemistry.[3] Functionalization methods such as the Bingel reaction, the Prato reaction and the Diels-Alder cycloaddition are powerful tools for the construction of well-defined fullerene materials.[1-3] While single additions on C_{60} deliver one regioisomer (all

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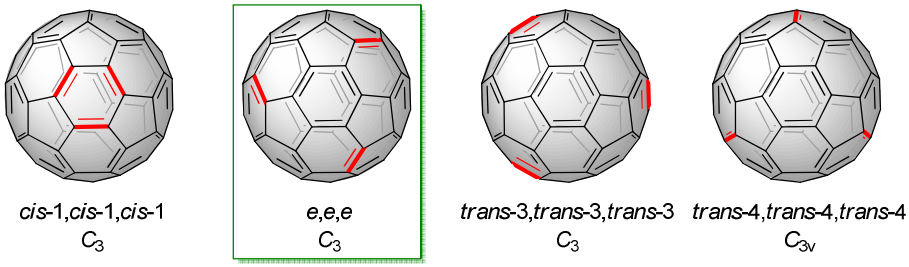
double bonds are equivalent), the double and triple covalent attachment of addends leads to the formation of different regioisomers with the number increasing to 46 for trisadducts. The multi-functionalization of C_{60} became one of the first targets in fullerene chemistry and following the tether-directed remote functionalization concept introduced by Diederich,[4] there has been a significant increase of research activity in this area.

A challenging topic in the areas of fullerene chemistry, material and biological sciences is the regioselective synthesis of [60]fullerene trisadducts with C_3-symmetrical addition patterns (Scheme 1). The well-defined three-dimensional molecular architecture combined with the unique physicochemical properties of the fullerene chromophore render this family of molecules candidates for future applications. Apart from the aesthetically pleasing architecture, this family of trisadducts showed pronounced biological activity and were investigated as potent drugs for numerous diseases.[2] The strong antioxidant character of these compounds[2] together with their potential to act as platforms for the construction of functional supramolecules (*e.g.*, lipofullerenes, dendrofullerenes)[5] have set the development of synthetic methods for the regioselective triple additions on C_{60} a highly desirable target.



Scheme 1. The four possible C_3-symmetrical addition patterns of C_{60}.

The tether-directed remote functionalization method has been successfully applied for the synthesis of C_3-symmetrical trisadducts of C_{60} by the groups of Diederich,[6] Hirsch,[7-12] Nierengarten[13-15] and ours.[16-18] Opened- and closed-structure tethers equipped with three malonate groups were utilized for this purpose and all possible C_3-symmetrical addition patterns have been accessed except the *cis*-1,*cis*-1,*cis*-1 (all-*cis*-1) which is not energetically favored owing to the steric hindrance of the addends. In all these cases, the covalent functionalization was performed by the Bingel cyclopropanation of the reactive [6,6]-double bonds of C_{60}, a widely used derivatization method in fullerene chemistry.

A disadvantage of the Bingel reaction is the reversibility under reductive (chemical and electrochemical) conditions[19-21] [Scheme 2, (a)], a limiting factor for possible applications of C_{60} trisadducts in electron transfer processes mimicking the photosynthetic system. To overcome this problem, Diels-Alder cycloadditions can be employed that lead to the formation of stable fullerene cycloadducts, at least under reductive conditions. A cycloadduct of C_{60} [Scheme 2, (b)] derived from the Diels-Alder addition of a diene to C_{60} is, however, sensitive to oxidation which

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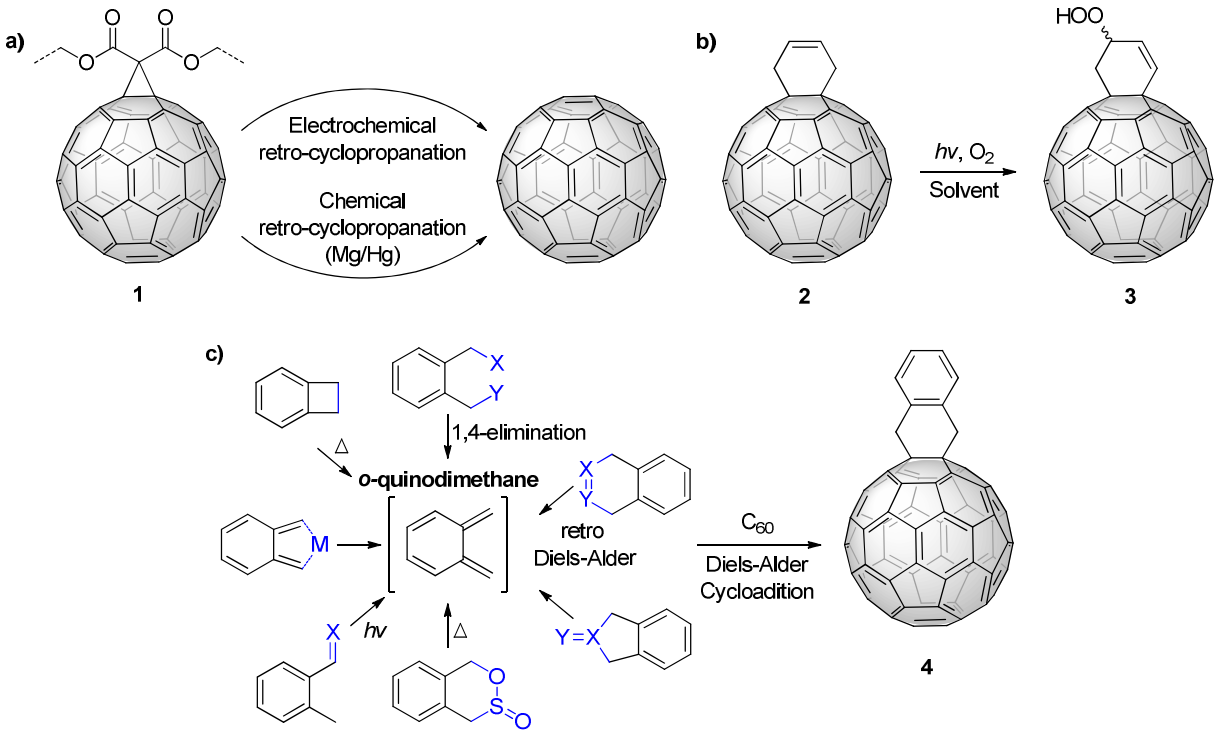
proceeds *via* the "ene" reaction of singlet oxygen ($^1O_2$)[22] with the double bond of the cyclohexene ring to afford the corresponding allylic hydroperoxide **3**.[23-25] The fullerene core acts as a photosensitizer and thus, adducts of this kind should be handled in the dark. This problem can be tackled if *ortho*-quinodimethanes are used as dienes [Scheme 2, (c)] and in such a case the corresponding cycloadducts **4** are thermally and photochemically stable. While a plethora of C_{60} monoadducts have been reported in the literature using *ortho*-quinodimethanes as reactive dienes,[26,27] there are only a few reports on the synthesis of bisadducts.[28,29]



Scheme 2. (a) Reversibility of the Bingel cyclopropanation of C_{60}, (b) photooxidation of C_{60} cycloadducts with $^1O_2$ and (c) synthesis of *ortho*-quinodimethanes and Diels-Alder cycloaddition with C_{60}.

With respect to the trisadducts, to the best of our knowledge, there are no reports on either stepwise or tether-directed regioselective synthesis of a Diels-Alder trisadduct of C_{60} employing *ortho*-quinodimethanes as reactive dienes. The synthesis of the *equatorial*,*equatorial*,*equatorial* (*e*,*e*,*e*) trisadduct derived from the stepwise Diels-Alder reaction of 9,10-dimethylanthracene with C_{60} is the only example of [4+2] trisadduct reported by Kräutler in 2008.[30]

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Results and Discussion

Our interest was focused on the regioselective synthesis of a redox-stable and singlet oxygen insensitive trisadduct of C_{60}, functionalized by the [4+2] Diels-Alder reaction with *ortho*-quinodimethanes. Specifically, we designed *e,e,e* trisadduct **5** (Figure 1) which is expected to be thermally stable and inert to $^1O_2$ photooxidation owing to the presence of the aromatic benzenes formed during the cycloaddition reactions. The choice of the *e* addition pattern was not accidental as it is well documented that it is favored over the others (*cis* and *trans*).[31,32] For the synthesis of trisadduct **5** we employed the tether-directed remote functionalization method utilizing C_3-symmetrical tethers equipped with *ortho*-quinodimethane precursor moieties for the three-fold Diels-Alder reaction on the fullerene sphere.

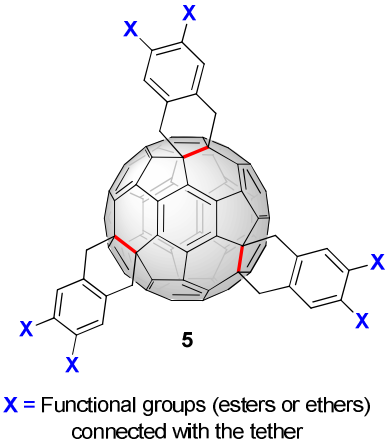

Figure 1. The designed *e,e,e* trisadduct of C_{60} functionalized with tethers bearing *ortho*-quinodimethane precursors.

The reports of Hirsch[9-12] and Nierengarten[13,14] on the synthesis of *e,e,e* trisadducts of C_{60} with tripodal tethers equipped with malonate moieties, prompted us to design opened-structure tether **10** bearing *ortho*-quinodimethane precursors covalently connected to the phloroglucinol focal point *via* two-carbon alkyl chains (Scheme 3). Bromoethanol was firstly protected as a THP ether[33] followed by a three-fold Williamson etherification with phloroglucinol to afford tripodal protected alcohol **7**. The highest yield of **7** (70%) was obtained when the reaction was carried out in acetone heated at reflux, and by using K_2CO_3 as a base in the presence of 18-crown-6. Subsequent cleavage of the protecting groups using *p*-TSA furnished triol **8** which has been synthesized before in one step by the reaction of phloroglucinol with ethylene carbonate.[34] This stepwise, protection-deprotection strategy offers the possibility of synthesizing similar tethers differing in the length of the alkyl spacers connecting the reactive groups with phloroglucinol. This can be accomplished by employing the appropriate bromoalcohols with variable number of carbon atoms, which in the case of ethylene carbonate is limited to two. In the last step, triol **8** was subjected to a three-fold esterification with acid **9**[35] using DCC and

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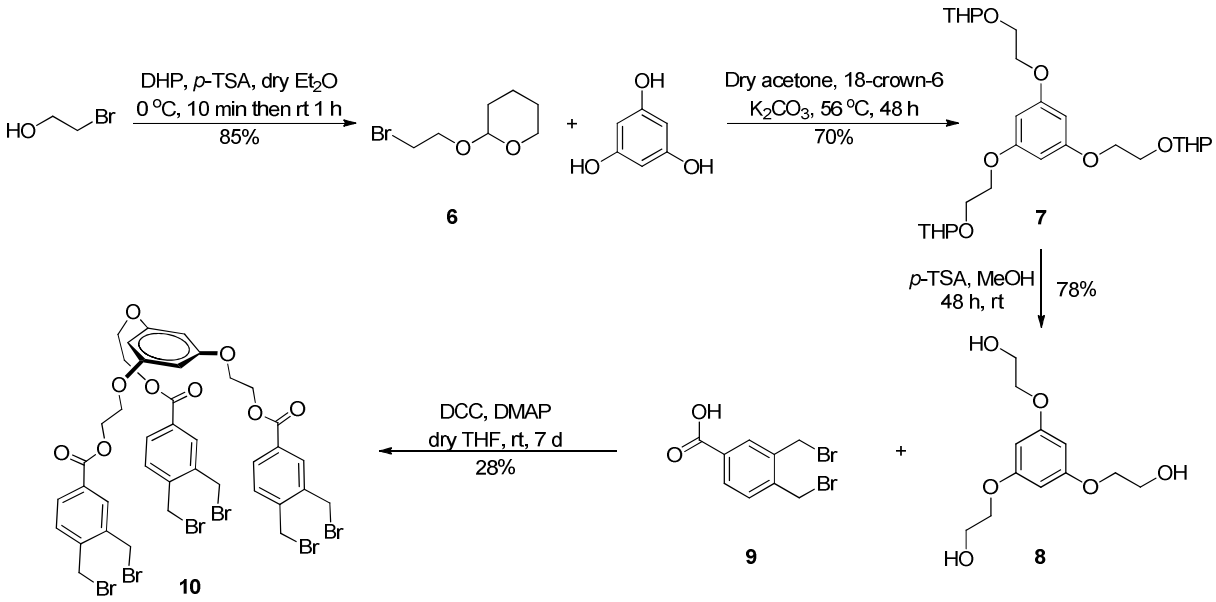
DMAP, in THF solvent. Tether **10** was isolated by column chromatography in 28% yield and characterized by NMR spectroscopy and MALDI-TOF mass spectrometry.



Scheme 3. Synthesis of tripodal tether **10**.

We next investigated the remote three-fold Diels-Alder functionalization of C_{60} with tether **10** under the experimental conditions used for the generation of *ortho*-quinodimethanes from the corresponding 1,2-bis(bromomethyl)benzene precursors (Scheme 4). The reaction was carried out under high dilution conditions (C_{60} concentration 10^{-5} mol/L), in toluene solvent and by using KI/18-crown-6 as the 1,4-debrominating reagent. As the 1,4-elimination step requires high temperature, the reaction mixture was refluxed at 110 ^{o}C and the progress of the reaction was monitored by TLC, HPLC and MALDI-TOF. According to the HPLC elugram of the crude mixture (see Supplementary Material), the regioselective formation of a specific trisadduct was not observed but instead, the reaction led to the formation of an unseparable mixture of fullerene adducts. In the MALDI-TOF spectrum (see Supplementary Material), the dominant peak at 1368 *m/z* corresponding to the $[M-H]^-$ ion confirmed that the three-fold Diels-Alder reaction was successful and the reaction products were trisadducts of C_{60}.The lack of regioselectivity in the remote functionalization of C_{60} with tether **10** can be attributed to the open structure of the tripodal tether and thus, to an insufficient preorganization of the reactive groups. Furthermore, for adducts formed from opened-structure tethers, *in-out* stereoisomerism[36,37] has been observed which is attributed to the relative orientation of the ester moieties connecting the reactive groups with phloroglucinol. As a consequence, a specific addition pattern is represented by a number of stereoisomers and in the case of *e,e,e* trisadduct **5**, there are four possible (Figure 2). According to PM3 calculations,[38] the *in-in, out-in, out-out* stereoisomer was the most thermodynamically stable.

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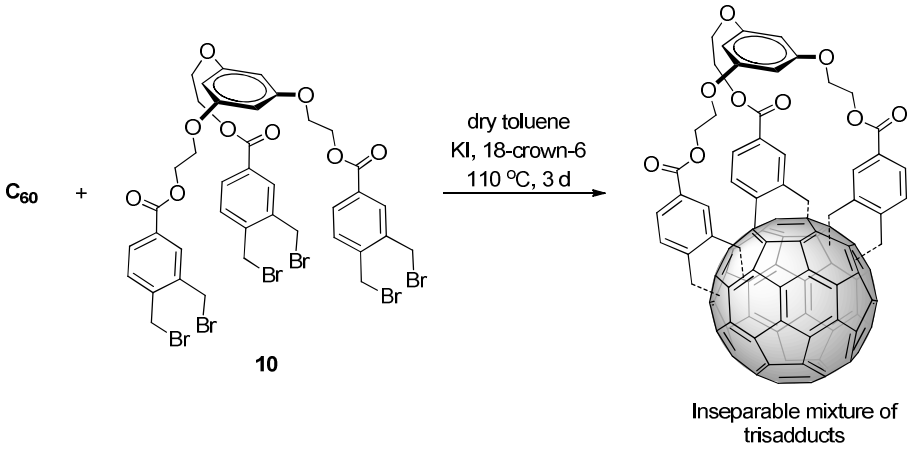

Scheme 4. Remote [4+2] functionalization of C_{60} with tether **10**.

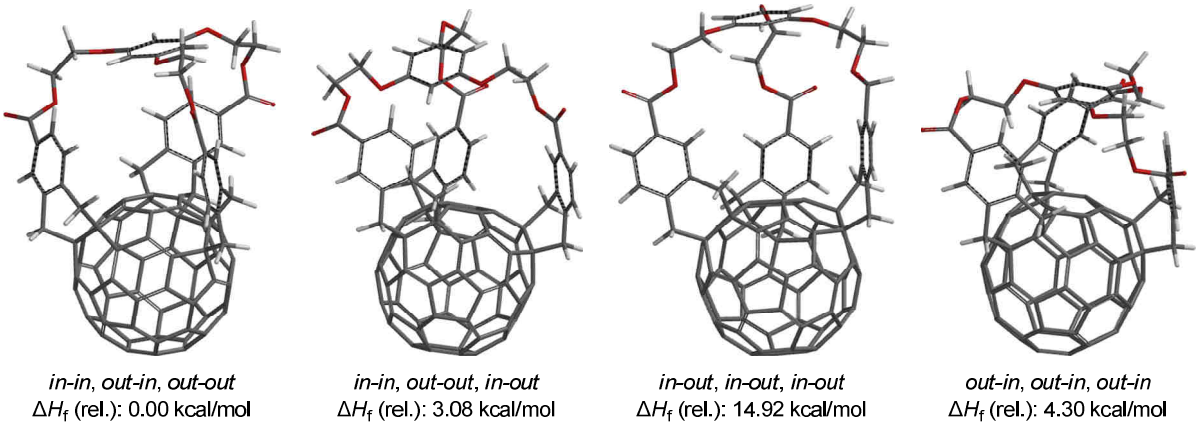

Figure 2. The four possible stereoisomers of *e,e,e* trisadduct **5** and their PM3 calculated ΔH_f energies.

The remote functionalization of C_{60} with *cyclo*-[*n*]-malonate tethers[7,8,15-18] has been proved advantageous in the regioselective synthesis of cyclopropanated fullerene multi-adducts, compared to the acyclic tether analogues. In addition, when macrocyclic tethers are used, the *in-out* stereoisomerism cannot operate due to the restricted flexibility of the reactive groups. With this in mind, we designed macrocyclic tether **16** (Scheme 5) where the *ortho*-quinodimethane precursors are well-preorganized as they are incorporated in a macrocyclic system. For the synthesis of **16**, pyrocatechol was firstly mono-protected as a benzyl ether[39,40] and subjected to a Williamson etherification with 1,5-dichloropentane to afford **12** in very good yield. Deprotection of the benzyl ethers by hydrogenation furnished diol **13** which was allowed to react with dichloride **14** derived from the two-fold Williamson etherification of pyrocatechol with 1,5-dichloropentane. The cesium-templated intermolecular cyclization of **13** and **14** led to the exclusive formation of macrocycle **15** isolated in 50% yield after column chromatography.

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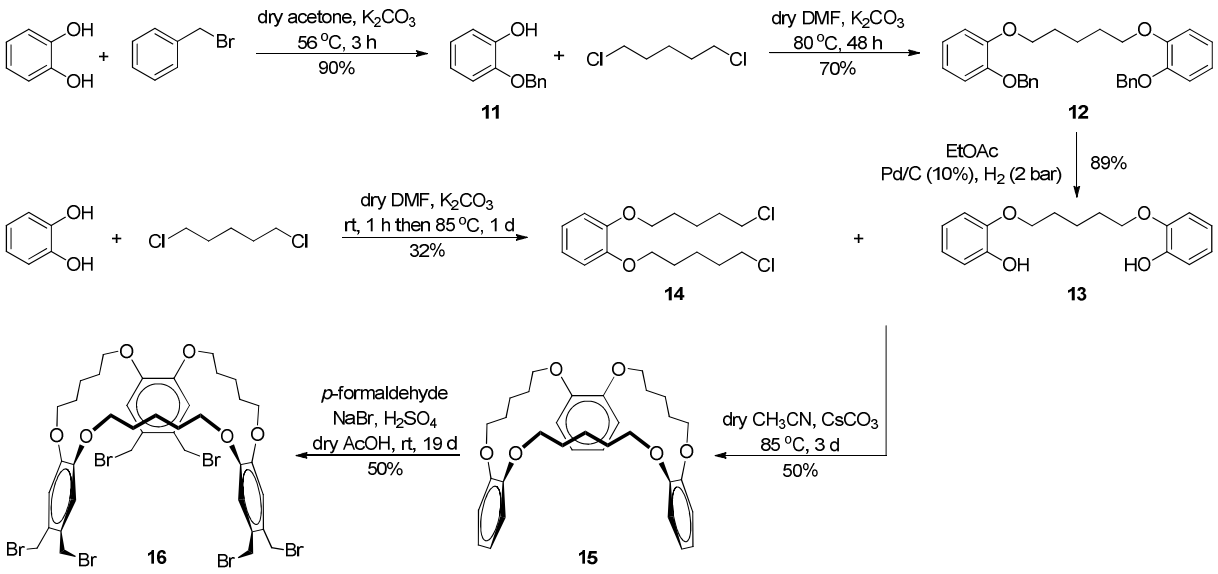

Scheme 5. Synthesis of macrocyclic tether **16**.

Finally, the benzylic bromide groups on the aromatic rings were installed in a one-pot, two-step process. A six-fold electrophilic aromatic substitution with formaldehyde followed by the *in situ* substitution of hydroxyl groups with bromine atoms led to the successful synthesis of tether **16** (isolated in 50%). Its structural assignment was accomplished by ^{1}H, ^{13}C NMR, IR spectroscopies and by MALDI-TOF mass spectrometry.

The remote functionalization of C_{60} with tether **16** was then investigated under high dilution conditions (C_{60} concentration 10^{-5} mol/L), in toluene and by using KI/18-crown-6 for the generation of the reactive *ortho*-quinodimethane dienes. In the MALDI-TOF spectrum (see Supplementary Material) of the crude reaction mixture the intense peak at 1334 *m/z* corresponding to the $[M+H]^+$ ion confirmed the successful formation of trisadducts of C_{60}. HPLC analysis (see Supplementary Material) revealed the non-regioselective behavior of tether **16** in the remote Diels-Alder cycloaddition reaction which led to an inseparable mixture of trisadducts. Attempts to separate at least some major adducts by column chromatography failed.

In tether **16**, the *ortho*-quinodimethane precursors are connected with C5 alkyl chains which prefer an *anti* confirmation. This might render the adoption of a concave geometry difficult, leading to an inappropriate orientation of the reactive groups and consequently to the poor regioselectivity of the Diels-Alder remote functionalization of C_{60}. With this assumption in mind, we modified the tether's structure by replacing the alkyl chains with glycol moieties. Thus, we designed tether **21** which was synthesized following the same synthetic strategy (Scheme 6) with that for tether **16**. To introduce the glycol groups, we employed in the Williamson etherification steps bis(2-chloroethyl)ether instead of 1,5-dichloropentane. Compounds **18**[41] and **19**[42] were synthesized according to literature reports while, **17**[41] and **20**[43] are known compounds in the literature but they were synthesized following our approach. Worthy of note was that the higher

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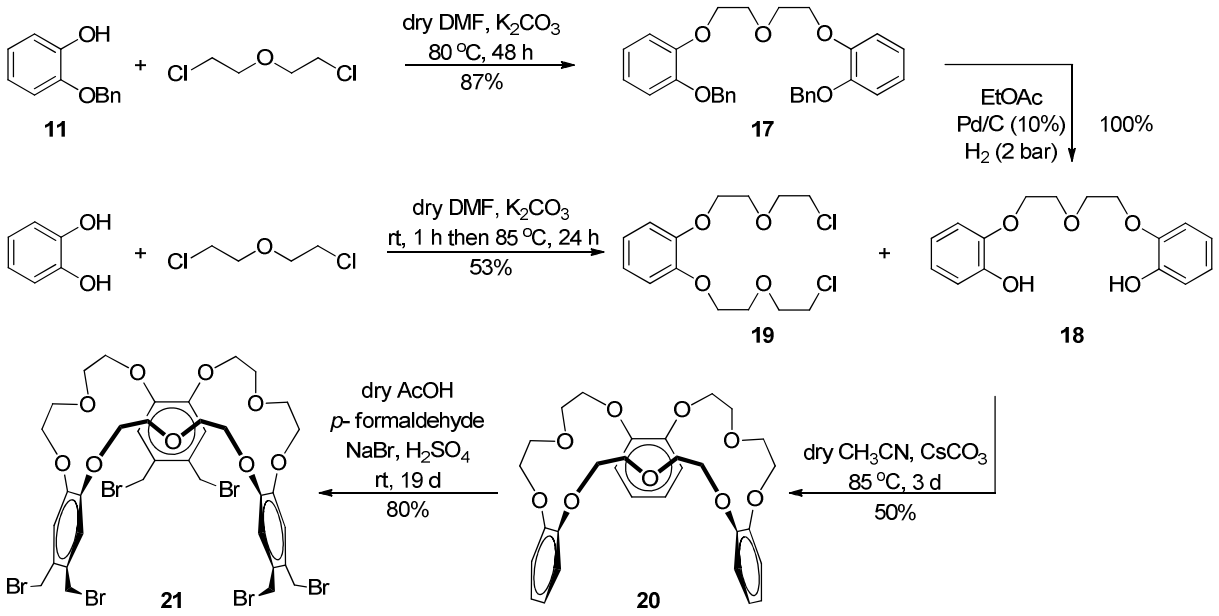
yields of these synthetic steps may be attributed to the presence of the glycol groups which helped improve the solubility of the intermediates. Thus, tether **21** was synthesized in very good overall yield and its structure was assigned by NMR spectroscopy and MALDI-TOF mass spectrometry.



Scheme 6. Synthesis of macrocyclic tether **21**.

The three-fold Diels-Alder functionalization of C_{60} with tether **21** was successful as confirmed from the MALDI-TOF spectrum (see Supplementary Material) of the crude reaction mixture which showed a clear peak at 1339 *m/z* corresponding to the $[M^+]$ ion of C_{60} trisadducts. Unfortunately, HPLC analysis (see Supplementary Material) revealed that the remote functionalization of C_{60} was not regioselective, and column chromatographic separation of any of the formed trisadducts was not feasible.

As the Diels-Alder remote functionalization of C_{60} with macrocyclic tethers **16** and **21** was non-regioselective, we focused our attention on the 1,4-debromination of the 1,2-bis(bromomethyl)benzene precursors of the tethers leading to the formation of the reactive *ortho*-quinodimethanes. In all cases, KI/18-crown-6 was used as the source of I^- which acts as the 1,4-elimination reagent preceding the cycloaddition reaction with C_{60}. To exclude the possibility that K^+ also binds into the macrocyclic cavity of **16** and especially of **21** which bears glycol chains rigidifying the structure of the macrocyclic rings, we tested different iodine salts. As such, we repeated the reactions of C_{60} with tethers **16** and **21** in toluene heated at 110 °C, by using $Et_4N^+I^-$ and CsI as debrominating reagents. The reactions were monitored by HPLC and MALDI-TOF but in all cases, non-separable mixtures of C_{60} trisadducts were formed. At temperatures lower

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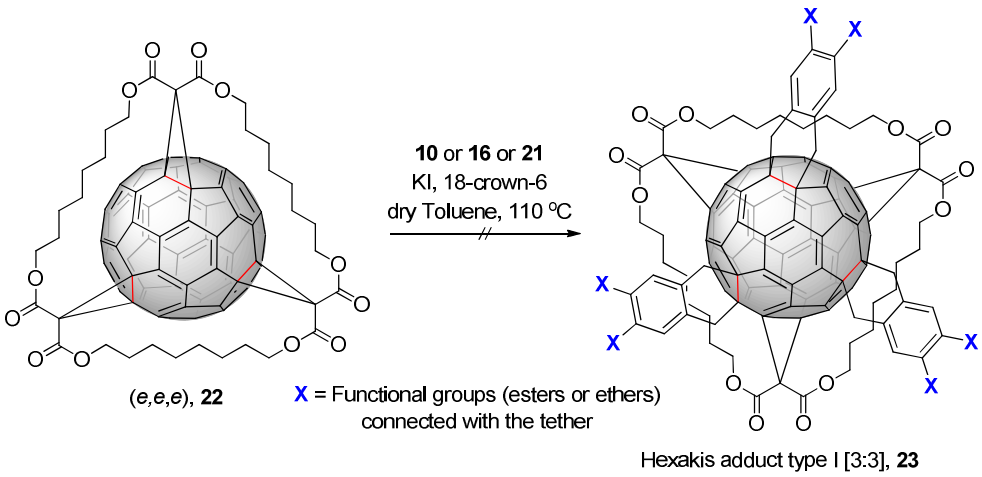
than 110 °C the formation of *ortho*-quinodimethanes from the corresponding 1,2-bis(bromo-methyl)benzene precursors was notably suppressed.

In the three-fold Diels-Alder reaction of C_{60} with tethers **10**, **16** and **21**, thirty double bonds of the fullerene skeleton are available for functionalization and the possible trisadducts that can be formed are 46. The final approach of our study focused on finding a way to reduce the number of possible regioisomers and obtain a better understanding regarding the regioselective behavior of the synthesized tethers. As such, we chose as a starting material a synthetically valuable derivative of C_{60} namely, *e*,*e*,*e* trisadduct **22** (Scheme 7). In the trisadduct **22**, one hemisphere of the fullerene core is protected by the *cyclo*-[3]-octyl malonate moiety and thus, the number of double bonds available for functionalization is reduced to half in comparison with the parent C_{60}. In case that the synthesized tethers will react in a regioselective manner with trisadduct **22** and succeed in accessing the *e*,*e*,*e* addition pattern, hexakis adduct **23** (Scheme 7) was expected to form. Such hexaadducts of C_{60} are called type I [3:3][44] and the addends are located at the octahedral sites of the fullerene sphere. Apart from their unique architecture, hexakis adducts derived from the functionalization of the six *e* double bonds of C_{60} are very attractive structures in the synthesis of functional fullerene materials.[45-50] Trisadduct **22** was synthesized according to the literature[7] and the remote functionalization with tethers **10**, **16** and **21** was investigated in toluene heated at 110 °C and by using KI/18-crown-6 as the 1,4-debrominating reagent. The crude reaction mixtures were analyzed with the aid of TLC, HPLC and MALDI-TOF mass spectrometry. The successful formation of hexakis adducts was confirmed by the measured MALDI-TOF spectra but according to the HPLC elugrams, the regioselective formation of a specific hexaadduct did not occur. The Diels-Alder functionalization reactions of the trisadduct **22** with tethers **10**, **16** and **21** furnished inseparable mixtures of fullerene hexakis adducts and, as such, the targeted hexakis adduct **23** could not be isolated.



Scheme 7. Remote Diels-Alder functionalization of *e*,*e*,*e* trisadduct **22** with tethers **10**, **16** and **21**.

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Conclusions

Summarizing, the results derived from the present study on the regioselective tether-directed synthesis of an *e,e,e* trisadduct of C_{60} *via* the [4+2] Diels-Alder reaction with *ortho*-quinodimethanes, we designed and synthesized three novel C_3-symmetrical tethers equipped with 1,2-bis(bromo-methyl)benzene moieties. Under the appropriate experimental conditions, these groups lead to the *in situ* formation of the corresponding *ortho*-quinodimethanes *via* an 1,4-elimination transformation. Tether **10** has an open structure, while **16** and **21** are macrocyclic molecules where the *ortho*-quinodimethane precursors are better preorganized as they are linked with alkyl and glycol chains, respectively. The three-fold [4+2] cycloaddition reactions of tethers **10**, **16** and **21** with C_{60} were carried out under high dilution conditions, in toluene heated at 110 ^{o}C and by using different 1,4-debrominating reagents. In all cases, inseparable mixtures of regiomeric trisadducts were formed and the regioselective formation of the targeted *e,e,e* trisadduct was not feasible even when the more preorganized tethers **16** and **21** were employed. The results of the present study lead to the conclusion that the [4+2] cycloaddition of *ortho*-quinodimethanes with the C_{60} is a kinetically controlled reaction. The *in situ* thermal generation of *ortho*-quinodimethanes from the corresponding 1,2-bis(bromomethyl)benzene precursors requires high temperatures (110 ^{o}C) and is followed by the fast, irreversible [4+2] cycloaddition reaction with C_{60} to afford thermally stable products. To reduce the number of possible regioisomeric trisadducts, the tether-directed remote [4+2] functionalization was also investigated with *e,e,e* trisadduct **22** towards the synthesis of hexakis adduct **23** functionalized at the octahedral sites of the fullerene. Also in this case, tethers **10**, **16** and **21** reacted in a non-regioselective manner strengthening the conclusion that the *in situ* thermal formation of *ortho*-quinodimethanes from 1,2-bis(bromomethyl)benzene precursors followed by the fast and irreversible [4+2] cycloaddition prevents the achievement of high regioselectivities even if the reactive groups are incorporated in well-preorganized molecular systems.

Experimental Section

General. All starting materials were purchased from commercial sources and used without further purification. The solvents were dried using standard techniques. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F_{254} (Merck) aluminium plates. After development, TLC plates were stained with potassium permanganate ($KMnO_4$). Products were isolated by column chromatography (silica gel 60, particle size 0.04-0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance III 500 Ultrashield Plus 500 MHz spectrometers. The chemical shifts are given in ppm relative to the appropriate solvent peak as a standard reference. The resonance multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), or combinations of these. Broad resonances are designated with br. Peak assignments were aided by ^{1}H-^{13}C HSQC,

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whenever necessary. High resolution (EI) mass spectra were recorded on a Thermo Finnigan Mat 95 instrument. High resolution MALDI-TOF mass spectra were recorded on a Bruker Autoflex III Smartbeam instrument. UV/vis spectra were recorded on a Shimadzu UV-3600 spectrometer. IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer. The spectra were measured as a film on NaCl plates. Melting points (mp) were determined on a Stuart Scientific SMP10 apparatus and were uncorrected. 1-(2-Tetrahydropyranyloxy)-2-bromoethane (**6**),[33] 3,4-bis(bromomethyl)benzoic acid (**9**),[35] 2-(benzyloxy)phenol (**11**),[39,40] 2,2'-[oxybis(ethane-2,1-diyloxy)]diphenol (**18**),[41] 1,2-bis[2-(2-chloroethoxy)ethoxy]benzene (**19**)[42] and *e,e,e* trisadduct **22**[7] were synthesized according to the literature.

2,2',2''-[Benzene-1,3,5-triyltris(oxyethane-2,1-diyloxy)]tris(tetrahydro-2*H*-pyran) (7). In a 100 mL three-necked round bottom flask equipped with gas inlet, condenser and magnetic stirrer, phloroglucinol (0.16 g, 1.23 mmol) was dissolved under a nitrogen atmosphere in dry acetone (50 mL) followed by the addition of 1-(2-tetrahydropyranyloxy)-2-bromoethane (**6**) (1.29 g, 6.16 mmol), K_2CO_3 (3.40 g, 24.60 mmol) and 18-crown-6 (0.33 g, 1.23 mmol). The reaction mixture was stirred for 48 h at 56 °C. The solution was concentrated and the residue was partitioned between equal volumes of dichloromethane and water. The organic layer was separated, washed with water, brine and dried ($MgSO_4$). The crude mixture was adsorbed on SiO_2 and chromatographed on a SiO_2 column (*n*-Hexane/EtOAc/CH_2Cl_2, 6:3:1) to afford the title compound **7** as a yellowish oil (0.46 g, 70%). R_f 0.55 (SiO_2, *n*-Hexane/EtOAc/CH_2Cl_2, 6:3:1, stain: $KMnO_4$); IR (NaCl, evap. film, ν_{max}, cm^{-1}): 2941, 2872, 1598, 1454, 1415, 1382, 1352, 1323, 1284, 1259, 1240, 1201, 1168, 1138, 1126, 1076, 1035, 1020, 985, 964, 931, 906, 871, 813; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.51-1.66 (12H, m, CH_2), 1.71-1.76 (3H, m, CH_2), 1.81-1.86 (3H, m, CH_2), 3.50-3.54 (3H, m, CH_2), 3.77-3.81 (3H, m, CH_2), 3.87-3.91 (3H, m, CH_2), 3.99-4.03 (3H, m, CH_2), 4.06-4.13 (6H, m, ArO-CH_2), 4.69 (3H, t, ^3J 3.5 Hz, Ar *H*), 6.14 (3H, s, Ar *H*); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ_C 19.4 (3C, *C*H_2), 25.4 (3C, *C*H_2), 30.5 (3C, *C*H_2), 62.2 (3C, *C*H_2), 65.7 (3C, *C*H_2), 67.4 (3C, ArO-*C*H_2), 94.5 (3C, 3 × *ortho*-Ar*C*H), 99.0 (3C, O*C*HO), 160.6 (3C, 3 × *meta*-Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 240 (3667), 267 (651) ε/$dm^3mol^{-1}cm^{-1}$; HRMS (EI^+): *m/z* calcd for $C_{27}H_{42}O_9$ $[M]^+$ 510.2823; found 510.2809.

1,3,5-Tris[(2'-hydroxy)ethoxy]benzene (8).[34] In a 25 mL three-necked round bottom flask equipped with condenser and magnetic stirrer, the tris(tetrahydro-2*H*-pyran) **7** (0.17 g, 0.33 mmol) was dissolved in dry methanol (10 mL) followed by the addition of *p*-TSA (0.01 g, 0.03 mmol). The resulting mixture was stirred for 48 h at room temperature. The solution was concentrated and the crude mixture was adsorbed on SiO_2 and chromatographed on a SiO_2 column (CH_2Cl_2/MeOH/*n*-Hexane, 8:1:1) to give the title compond **8** as a colorless solid (0.06 g, 78%). R_f 0.29 (SiO_2, CH_2Cl_2/MeOH/*n*-Hexane, 8:1:1, stain: $KMnO_4$). ^{1}H, ^{13}C NMR resonances, IR absorptions and mass spectrometric data were in good agreement with that reported in the literature.

Benzene-1,3,5-triyltris(oxyethane-2,1-diyl)tris[3,4-bis(bromomethyl)benzoate] (10). In a dry 250 mL three-necked round bottom flask equipped with gas inlet and magnetic stirrer, 1,3,5-

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tris[(2'-hydroxy)ethoxy]benzene (**8**) (1.00 g, 3.87 mmol), 3,4-bis(bromomethyl)benzoic acid (**9**) (5.97 g, 19.52 mmol), DCC (4.01 g, 19.40 mmol) and DMAP (0.19 g, 1.54 mmol) were dissolved under a nitrogen atmosphere in dry THF (100 mL). The reaction mixture was stirred for 7 d at room temperature. The solution was concentrated and the residue was diluted with EtOAc (30 mL) and stored at -20 ^{o}C for 12 h. The crude mixture was filtered under reduce pressure and the filtrate was adsorbed on SiO_2 and chromatographed on a SiO_2 column (CH_2Cl_2, 100%) to afford the title compound **10** as a colorless solid (1.22 g, 28%). R_f 0.60 (SiO_2, CH_2Cl_2, 100%, stain: $KMnO_4$); mp 100-101 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 2953, 2874, 1720, 1611, 1593, 1454, 1414, 1369, 1330, 1296, 1274, 1217, 1189, 1155, 1125, 1107, 1076, 1028, 818, 772, 760; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ_H 4.27 (6H, t, ^{3}J 6.5 Hz, ArOCH_2), 4.65 (18H, apparent t, CH_2Br and CH_2OCO), 6.19 (3H, s, Ar *H*), 7.44 (3H, d, *J* 8.0 Hz, Ar *H*), 7.97 (3H, dd, *J* 1.5, 1.5 Hz, Ar *H*), 8.03 (3H, d, *J* 2.0 Hz, Ar *H*); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ_C 28.7 (3C, Ar*C*H$_2$Br), 29.2 (3C, Ar*C*H$_2$Br), 63.6 (3C, C*H*$_2$OCOAr), 66.0 (3C, ArO*C*H$_2$), 94.8 (3C, 3 × *ortho*-Ar*C*-H), 130.6 (3C, Ar*C*-H), 130.7 (3C, Ar*C*-H), 131.3 (3C, Ar*C*-H), 132.3 (3C, Ar*C*-H), 136.9 (3C, Ar*C*-H), 141.6 (3C, Ar*C*-H), 160.5 (3C, CH$_2$O*C*OAr), 165.4 (3C, 3 × *meta*-Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 246 (40876), 298 (3630) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (MALDI-TOF, positive mode, HCCA matrix): *m/z* calcd for $C_{39}H_{36}O_9(^{79}Br)_3(^{81}Br)_3Na$ $[M+Na]^+$ 1150.7297; found 1150.7265.

1,1'-[Pentane-1,5-diylbis(oxy)]bis[2-(benzyloxy)benzene] (12). In a dry 250 mL three-necked round bottom flask equipped with gas inlet, condenser and magnetic stirrer, 2-(benzyloxy)phenol (**11**) (3.00 g, 15.00 mmol), 1,5-dichloropentane (0.96 mL, 7.50 mmol) and K_2CO_3 (4.14 g, 30.00 mmol) were dissolved under a nitrogen atmosphere in dry DMF (55 mL). The reaction mixture was stirred at 80 ^{o}C for 48 h. DMF was removed under reduced pressure and the resulting mixture was partitioned between equal volumes of EtOAc and water. The organic layer was separated, washed with water, brine and dried ($MgSO_4$). The crude mixture was chromatographed on a SiO_2 column (CH_2Cl_2/*n*-Hexane, 7:3) to afford product **12** as a colorless solid (2.39 g, 70%). R_f 0.29 (SiO_2, CH_2Cl_2/*n*-Hexane, 7:3, stain: $KMnO_4$); mp 72-74 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 3063, 3034, 2943, 2907, 2856, 1589, 1506, 1464, 1450, 1384, 1329, 1288, 1252, 1217, 1121, 1051, 1034, 1024, 928, 907, 856, 827, 733; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.66-1.74 (2H, m, CH$_2$CH_2CH$_2$), 1.86-1.96 (4H, m, ArOCH$_2$CH_2CH$_2$), 4.04 (4H, t, ^{3}J 6.5 Hz, ArOCH_2CH$_2$), 5.12 (4H, s, ArCH_2OAr), 6.83-6.94 (8H, m, Ar *H*), 7.28-7.36 (6H, m, Ar *H*), 7.45 (4H, d, *J* 7.0 Hz, Ar *H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 22.7 (1C, ArOCH$_2$CH$_2$*C*H$_2$), 29.0 (2C, ArOCH$_2$*C*H$_2$CH$_2$), 69.0 (2C, ArO*C*H$_2$CH$_2$), 71.3 (2C, Ar*C*H$_2$OAr), 114.1, 128.4 (18C, Ar*C*-H), 137.5, 149.4 (6C, Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 240 (6709), 277 (5380) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (EI$^+$): *m/z* calcd for $C_{31}H_{32}O_4$ $[M]^+$ 468.2295; found 468.2285.

2,2'-[Pentane-1,5-diylbis(oxy)]diphenol (13). A mixture of 1,1'-[pentane-1,5-diylbis(oxy)]-bis[2-(benzyloxy)benzene] (**12**) (2.37 g, 5.07 mmol) and a catalytic amount of 10% Pd/C were dissolved in EtOAc (100 mL) and hydrogenated under a H_2 atmosphere (2 bar) for 2 h at room temperature. The reaction mixture was filtered through a Celite® pad and the filtrate was

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evaporated to dryness to afford the title compound **13** (1.24 g, 89%) as a colorless solid. mp 98-100 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 3356, 2949, 1611, 1593, 1505, 1479, 1467, 1404, 1382, 1356, 1307, 1261, 1250, 1232, 1219, 1109, 1049, 1018, 847, 783, 746, 737; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.62-1.72 (2H, m, $CH_2CH_2CH_2$), 1.86-1.96 (4H, m, $ArOCH_2CH_2$), 4.09 (4H, t, ^{3}J 6.5 Hz, $ArOCH_2$), 5.68 (2H, s, ArOH), 6.83-6.90 (6H, m, Ar H), 6.93-6.96 (2H, m, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 22.7 (1C, $ArOCH_2CH_2CH_2$), 28.9 (2C, $ArOCH_2CH_2CH_2$), 68.5 (2C, $ArOCH_2CH_2CH_2$), 111.7, 114.6, 120.1, 121.5 (8C, ArC-H), 145.75, 145.79 (4C, ArC-O); UV/vis ($CHCl_3$) nm/λ_{max}: 239 (2690), 276 (5463) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (EI$^+$): *m/z* calcd for $C_{17}H_{20}O_4$ [M]$^+$ 218.1356; found 218.1354.

1,2-Bis[(5-chloropentyl)oxy]benzene (14). In a dry 250 mL three-necked round bottom flask equipped with gas inlet, condenser and magnetic stirrer, pyrocatechol (3.00 g, 27.27 mmol), 1,5-dichloropentane (7.30 mL, 57.27 mmol) and K_2CO_3 (9.40 g, 30.00 mmol) were dissolved under a nitrogen atmosphere in dry DMF (55 mL). The reaction mixture was stirred at 85 ^{o}C for 24 h and then it was partitioned between equal volumes of dichloromethane and water. The organic layer was separated, washed with water, brine and dried ($MgSO_4$). The crude mixture was chromatographed on a SiO_2 column (CH_2Cl_2, 100%) to afford the title compound **14** as a yellowish oil (2.73 g, 32%). R_f 0.9 (SiO_2, CH_2Cl_2, 100%, stain: $KMnO_4$); IR (NaCl, evap. film, ν_{max}, cm^{-1}): 2949, 1631, 1573, 1515, 1479, 1467, 1404, 1381, 1256, 1229, 1089, 1019, 837, 763, 746, 717; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.62-1.68 (4H, m, $OCH_2CH_2CH_2CH_2CH_2Cl$), 1.82-1.90 (8H, m, $OCH_2CH_2CH_2CH_2CH_2Cl$), 3.57 (4H, t, ^{3}J 7.0 Hz, CH_2Cl), 4.01 (4H, t, ^{3}J 6.5 Hz, $ArOCH_2$), 6.89 (4H, s, Ar H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ_C 23.6 (2C, $OCH_2CH_2CH_2CH_2CH_2Cl$), 28.6, 32.4 (4C, $OCH_2CH_2CH_2CH_2CH_2Cl$), 45.0 (2C, CH_2Cl), 68.8 (2C, $ArOCH_2CH_2$), 114.0, 121.2 (4C, ArC-H), 149.0 (2C, ArC-O); UV/vis ($CHCl_3$) nm/λ_{max}: 239 (3012), 277(2826) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (EI$^+$): *m/z* calcd for $C_{16}H_{24}Cl_2O_2$ [M]$^+$ 318.1148; found 318.1162.

7,8,9,10,18,19,20,21,29,30,31,32-Dodecahydro-6*H*,17*H*,28tribenzo[*b*,*k*,*t*][1,4,10,13,19,22]-hexaoxacycloheptacosine (15). In a dry 500 mL three-necked round bottom flask equipped with gas inlet, condenser, dropping funnel and magnetic stirrer, $CsCO_3$ (2.03 g, 6.24 mmol) was stirred in dry acetonitrile (140 mL) at 85 ^{o}C for 1 h. Subsequently, a solution of the diol **13** (0.60 g, 2.08 mmol) and dichloride **14** (0.66 g, 2.08 mmol) in dry acetonitrile (140 mL) were added dropwise over a period of 9 h. The reaction mixture was heated at 85 ^{o}C for additional 3 d. The mixture was allowed to cool at room temperature, diluted with dichloromethane and concentrated under reduced pressure. The resulting mixture was partitioned between equal volumes of dichloromethane and 0.5 N KOH (H_2O/MeOH, 6:4, v/v). The organic layer was separated, washed with water, brine and dried ($MgSO_4$). The crude mixture was adsorbed on SiO_2 and chromatographed on a SiO_2 column (CH_2Cl_2, 100%) to give the title compound **15** as a colorless solid (0.556 g, 50%). R_f 0.33 (SiO_2, CH_2Cl_2, 100%, stain: $KMnO_4$); mp 60-63 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 3647, 2927, 1593, 1506, 1469, 1452, 1358, 1330, 1288, 1256, 1219, 1127, 1093, 1053, 1031, 964, 941, 924, 779, 741; ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.71- 1.78 (6H, m, $ArOCH2CH_2CH_2$), 1.86-1.95 (12H, m, $ArOCH_2CH_2$), 4.04 (12H, t, ^{3}J 6.0 Hz,

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ArOC*H*$_2$), 6.91 (12H, s, Ar *H*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ^{o}C): δ_C 22.8 (3C, ArOCH$_2$C*H*$_2$CH$_2$), 29.0 (6C, ArOCH$_2$*C*H$_2$), 69.2 (6C, ArO*C*H$_2$CH$_2$), 114.6, 121.2 (12C, Ar*C*-H), 149.3 (6C, Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 240 (6333), 278 (6967) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (EI$^+$): *m/z* calcd for $C_{33}H_{42}O_6$ [M]$^+$ 534.2976; found 534.2967.

2,3,13,14,24,25-Hexakis(bromomethyl)-7,8,9,10,18,19,20,21,29,30,31,32-dodecahydro-6*H*,17*H*,28*H*-tribenzo[*b*,*k*,*t*][1,4,10,13,19,22]hexaoxacycloheptacosine (16). In a dry 100 mL three-necked round bottom flask equipped with gas inlet and magnetic stirrer, compound **15** (0.08 g, 0.15 mmol), *p*-formaldehyde (0.20 g, 6.75 mmol), sulfuric acid (8.0 mL, 150.00 mmol) and NaBr (1.02 g, 9.90 mmol) were stirred in dry acetic acid (45 mL) for 19 d. The mixture was poured into cold water and was extracted with toluene. The solvent was evaporated under reduced pressure and the brown solid was washed (EtOH) and dried under high vacuum to give the title compound **16** as a light brown solid (0.08 g, 50%). mp 184-186 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 3312, 2926, 1607, 1597, 1504, 1462, 1358, 1301, 1284, 1267, 1222, 1204, 1114, 1090, 1064, 1047, 947, 906, 846, 777, 727, 702; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ_H 1.67-1.69 (6H, m, ArOCH2CH$_2$C*H*$_2$), 1.85-1.88 (12H, m, ArOCH$_2$C*H*$_2$), 4.01 (12H, t, ^3J 6.0 Hz, ArOC*H*$_2$), 4.59 (12H, s, ArC*H*$_2$Br), 6.82 (6H, s, Ar *H*); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ_C 22.9 (3C, ArOCH$_2$C*H*$_2$CH$_2$), 28.7 (6C, Ar*C*H$_2$Br), 30.8 (6C, ArOCH$_2$*C*H$_2$), 69.3 (6C, ArO*C*H$_2$CH$_2$), 116.1 (6C, Ar*C*-H), 129.2 (6C, Ar*C*-O), 149.6 (6C, Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 244 (56711), 281 (21512) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (MALDI-TOF, positive mode, HCCA matrix): *m/z* calcd for $C_{39}H_{48}O_6(^{79}Br)_3(^{81}Br)_3Na$ [M+Na]$^+$ 1114.8388; found 1114.8333.

1,1'-[Oxybis(ethane-2,1-diyloxy)]bis[2-(benzyloxy)benzene] (17).[41] Compound **17** was synthesized following the method used for the synthesis of 1,1'-[pentane-1,5-diylbis(oxy)]bis[2-(benzyloxy)benzene] (**12**). In dry DMF (55 mL), **11** (3.00 g, 15.00 mmol), 2-chloroethyl ether (0.88 mL, 7.50 mmol) and K_2CO_3 (4.14 g, 30.00 mmol) were dissolved. The crude mixture was chromatographed on a SiO_2 column to afford the title compound **17** as a colorless solid (3.07 g, 87%). ^{1}H, ^{13}C NMR resonances, IR absorptions and mass spectrometry data were in good agreement with that reported in the literature.

6,7,9,10,17,18,20,21,28,29,31,32-Dodecahydrotribenzo[*b*,*k*,*t*][1,4,7,10,13,16,19,22,25]nona-oxacycloheptacosine (20).[43] Compound **20** was synthesized following the method used for the synthesis of compound **15**. In dry acetonitrile (150 mL), $CsCO_3$ (2.00 g, 6.21 mmol) was stirred at 85 ^{o}C for 1 h. Subsequently, a solution of diol **18** (0.60 g, 2.07 mmol) and dichloride **19** (0.67 g, 2.07 mmol) in dry acetonitrile (150 mL) were added dropwise over a period of 9 h. The mixture was chromatographed on a SiO_2 column to give the title compound **20** as a colorless solid (0.56 g, 50%). ^{1}H, ^{13}C NMR resonances, IR absorptions and mass spectrometry data were in good agreement with that reported in the literature.

2,3,13,14,24,25-Hexakis(bromomethyl)-6,7,9,10,17,18,20,21,28,29,31,32-dodecahydrotri-benzo[*b*,*k*,*t*][1,4,7,10,13,16,19,22,25]nonaoxacycloheptacosin (21). Compound **21** was synthesized following the method used for the synthesis of the tether **16**. A mixture of the nona-oxacycloheptacosine **20** (0.50 g, 0.92 mmol), *p*-formaldehyde (1.30 g, 41.40 mmol), sulfuric acid (50.0 mL, 920.00 mmol) and NaBr (6.26 g, 60.72 mmol, 66.0) were dissolved in dry acetic acid

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(250 mL) to give the title compound **21** as a light brown solid (0.80 g, 80%). mp 185-188 ^{o}C; IR (NaCl, evap. film, ν_{max}, cm^{-1}): 3406, 2929, 2873, 1602, 1522, 1452, 1355, 1279, 1238, 1195, 1125, 1083, 1051, 955, 901, 870, 754, 733; ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C): δ_H 3.91 (12H, t, ^{3}J 4.5 Hz, $ArOCH_2CH_2$), 4.14 (12H, t, ^{3}J 4.5 Hz, $ArOCH_2$), 4.56 (12H, s, $ArCH_2Br$), 6.86 (6H, s, Ar *H*); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C): δ_C 30.5 (6C, $ArCH_2Br$), 69.4 (6C, $ArOCH_2CH_2$), 70.0 (6C, $ArOCH_2CH_2$), 116.8 (6C, Ar*C*-H), 129.7 (6C, Ar*C*-O), 149.4 (6C, Ar*C*-O); UV/vis ($CHCl_3$) nm/λ_{max}: 241 (49929), 273 (22425) ε/dm^{3}mol^{-1}cm^{-1}; HRMS (MALDI-TOF, positive mode, HCCA matrix): *m/z* calcd for $C_{36}H_{42}O_9(^{79}Br)_3(^{81}Br)_3Na$ $[M+Na]^+$ 1120.7765; found 1120.7714.

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