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Synthesis and Orthogonal Functionalization of [60]Fullerene *e,e,e*-Trisadducts with Two Spherically Defined Addend Zones

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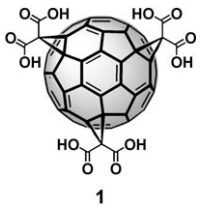
Abstract: *e,e,e*-Trisadducts **13** and **15** have been prepared by a highly regioselective threefold cyclopropanation of tripodal malonates **10** and **12** with C_{60}. The yield and regioselectivity depend on the length and structure of the tethers that connect the malonate units to the focal benzene core of **13**–**15**. As a consequence of the template-directed synthesis, all *e,e,e*-trisadducts were formed as *in/out* isomers exclusively and contain two spherically well-defined addend zones with equatorial and polar orientation, respectively. By variation of the outer malonate termini of the tethers, selective functionalization of the equatorial addend zone could be achieved, thus leading to fine-tuning of intermolecular interactions, such as solubility or aggregation phenomena. After removal of the focal benzene moiety in **14** and **15**, selective functionalization of the polar addend zone could be achieved. Strong intramolecular hydrogen-bonding networks of the polar substituents in the polar addend zone could be observed by ^{1}H NMR spectroscopic analysis. By orthogonal functionalization of both addend zones, fullerene derivatives **44**–**48** could be synthesized as one single *in/out* isomer, thus greatly enhancing the potential of *e,e,e*-trisadducts as building blocks in supramolecular architectures.

Keywords: cyclopropanation · fullerenes · regioselectivity · trisadducts

Introduction and Background

Shortly after their discovery[1] and accessibility in macroscopic amounts,[2] fullerenes were identified as versatile molecular building blocks due to unprecedented chemical and physical properties.[3–11] On one hand, intrinsic properties such as hydrophobicity, pronounced stacking interactions with other conjugated π systems, and their unrivalled electronic properties make C_{60} and its derivatives promising candidates for functional components in supramolecular aggregates. On the other hand, fullerenes can serve as versatile templates that can arrange several addends in a spherically well-defined manner. Well-established exohedral functionalization protocols provided access to a large variety of defined fullerene derivatives with tunable chemical and materials properties.[12] An example is the threefold cyclopropanation of C_{60} that leads to C_3 symmetrical trisadducts with an all equatorial *e,e,e*-addition pattern, which represents a fundamental structural motif in fullerene chemistry.[12] The most prominent *e,e,e*-trisadduct is the trismalonic acid **1**, which we synthesized in 1994.[13] This compound exhibits pronounced solubility in water and shows very promising activities as an antioxidant or neuroprotective agent both in cultured central nervous system (CNS) cells and in whole animal models.[14–19] The toxicity of this trisadduct due to facile metabolic decarboxylation,[20] however, requires the design of new structural analogues as potential drug candidates. In another context, fullerene compounds with an *e,e,e*-addition pattern allow ready access to amphiphilic [3:3]hexakisadducts.[21,22] Based on *e,e,e*-trisadducts with lipophilic addends, such as cyclo[*n*]alkylmalonate macrocycles, new prototypes of functional amphiphiles were readily obtained by the subsequent threefold addition of malonates with hydrophilic side chains. These amphiphiles aggregate to structurally persistent micelles in water and consist of exactly six molecules arranged in a highly symmetrical fashion as determined by cryo-transmission electron microscopy (cryo-TEM).[23]



1

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The bisfunctionalization of C_{60} is elegantly controllable by tether-directed remote approaches,[12,24–26] whereas the highly regioselective synthesis of C_{60} trisadducts, which are suitable for subsequent functionalization still remains a more challenging task. For threefold additions, the number of theoretically possible regioisomers raises from 8 to 46, thus making it almost impossible to obtain pure isomers after a threefold cyclopropanation without any preorganization of the malonates or by applying stepwise procedures. The first success in this direction was accomplished by the stepwise addition of segregated malonates and the separation of several trisadducts with a defined addition pattern, such as *e*,*e*,*e* or *trans*-3,*trans*-3,*trans*-3.[27] By switching from achiral malonates to chiral bisoxazolines addends, we could isolate inherently chiral *e,e,e*-trisadducts in an enantiomerically pure form.[28] In a one-step synthesis of *e*,*e*,*e*-trisadducts starting from pristine C_{60} through a tethered approach, the final C_3 symmetry of the product should be reflected in the malonate precursor to avoid unfavorable strain energy within the resulting trisadduct. Following this strategy, the first one-pot synthesis of an *e*,*e*,*e*-trisadduct was achieved by Diederich and co-workers in 1999 after treating a C_3-symmetrical tripodal malonate based on a cyclotriveratrylene core with C_{60}.[29] We developed an efficient concept in 2002 that utilized flexible cyclo[3]alkylmalonates for the selective formation of trisadducts. When cyclo[3]octylmalonate was employed as an addend, the *e*,*e*,*e*-adduct was obtained as a single regioisomer in good yield.[30] We also introduced optically active diols into the alkyl chains, thus achieving diastereoselectivity for the threefold cyclopropanation, and isolated the two diasteroisomers with the corresponding enantiomorphic *e*,*e*,*e*-addition patterns.[31] Despite this success, one major point still has not been satisfactorily solved so far, namely, the development of trisadducts that can be readily and selectively further functionalized both at the fullerene core and the attached addends. We recently reported a first conceptual step to accomplish this goal.[32] By using tripodal malonate tethers, we could synthesize a new class of *e*,*e*,*e*-trisadduct in good yield with two distinct addend zones, which potentially can be used for further side-chain modification. We recently demonstrated the potential of some water-soluble representatives as pharmaceutical agents by investigating their antioxidant[33] and superoxide-quenching[34] activities in vitro and neuroprotective activity[20] in vivo. Herein, we report for the first time on the development of an entire family of *e*,*e*,*e*-trisadducts that can be readily and specifically functionalized in two spherically well-defined addend zones. As a consequence, a multitude of functional fullerene derivatives with a defined three-dimensional structure and widely tunable properties has been made available. Due to the presence of the redox- and photoactive fullerene core combined with the features brought in by the very versatile combination of functionalities within the separately addressable polar and equatorial addend zones, this compound class has great potential for both biomedical and materials applications.

Results and Discussion

Regioselective formation of *e,e,e*-trisadducts based on tripodal malonate tethers: To achieve straightforward access to a great variety of structurally tunable *e,e,e*-trisadducts containing diverse functionalities, a synthetic concept that fulfills the following aspects has to be implemented: 1) the use of readily accessible precursors that preorganize the malonate units in an appropriate manner, 2) highly regioselective cyclopropanation reactions that lead to *e*,*e*,*e*-trisadducts in good yields, 3) the facile removal of the structural template by appropriate deprotection strategies, 4) the possibility of further functionalization of deprotected derivatives, and 5) complete control of *in*/*out* isomerism[35] in case of asymmetrically substituted malonates. Based on these considerations, we chose a 1,3,5-trisubstituted benzene core as the most prominent structural template. The corresponding threefold symmetry should be compatible with the C_3 symmetry of the *e*,*e*,*e*-trisadducts, and favorable π–π interactions between the aromatic ring and the fullerene surface were supposed to facilitate sufficient preorganization of the reaction partners. On each side arm, malonate units are connected through a short ethylene spacer. The second terminus of the malonate groups can be used for further functionalization (Figure 1). After a highly regioselective trisaddition, the structural template can be removed by using appropriate deprotection techniques. Due to the template-assisted synthesis, the two different side arms of each malonate unit are thereby spherically well arranged as one single *in*/*out* isomer (Figure 1). The three free side chains of the tripodal malonate tether are topologically well oriented and define an equatorial addend zone in which selective functionalization is possible. After removal of the aromatic template, the remaining malonate termini define a second functionalizable and spatially well-arranged region, that is, the polar addend zone. Therefore, this sequence allows us to independently address two sterically well-added regions of *e*,*e*,*e*-trisadducts.

Based on these conceptual considerations, we synthesized three trisalcohols **2**, **8**, and **9** as template precursors (Scheme 1). Compound **2** was obtained in one step from phloroglucinol and ethylene carbonate catalyzed by tetrabutylammonium bromide in DMF.[36] The ethylene spacer units are thereby directly connected to the benzene core by phenyl ether linkages. As a precursor for **8** and **9**, 1,3,5-trisbromomethylbenzene **5** was used.[37,38] Quantitative esterification of trimesic acid with methanol under acidic conditions led to trisester **3**, which was then reduced with lithium aluminum hydride in THF to trisalcohol **4**. Final bromination was achieved by the use of phosphorus tribromide in diethyl ether, thus yielding **5** in good yield. The incorporation of the ethylene units was accomplished by using a slightly modified procedure.[39] Monoprotection of ethylene glycol with dihydropyran under acidic catalysis gave **6** in 59% yield. Deprotonation of **6** with NaH in dry THF and subsequent nucleophilic substitution of the bromine atoms of **5** led to the THP-protected trisalcohol **7**. The deprotected triol **8** was obtained after quantitative acetal cleavage with

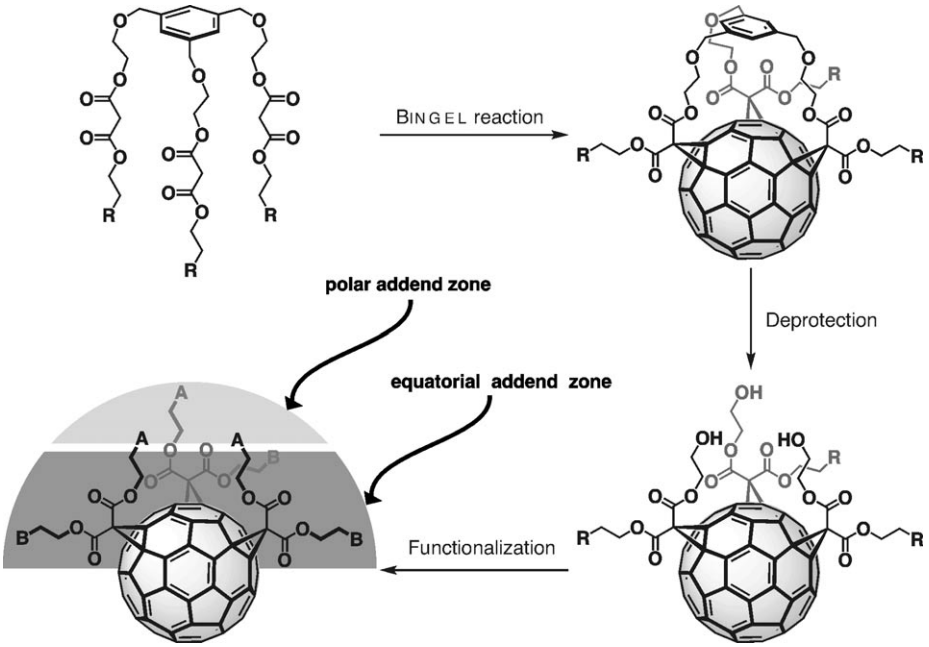
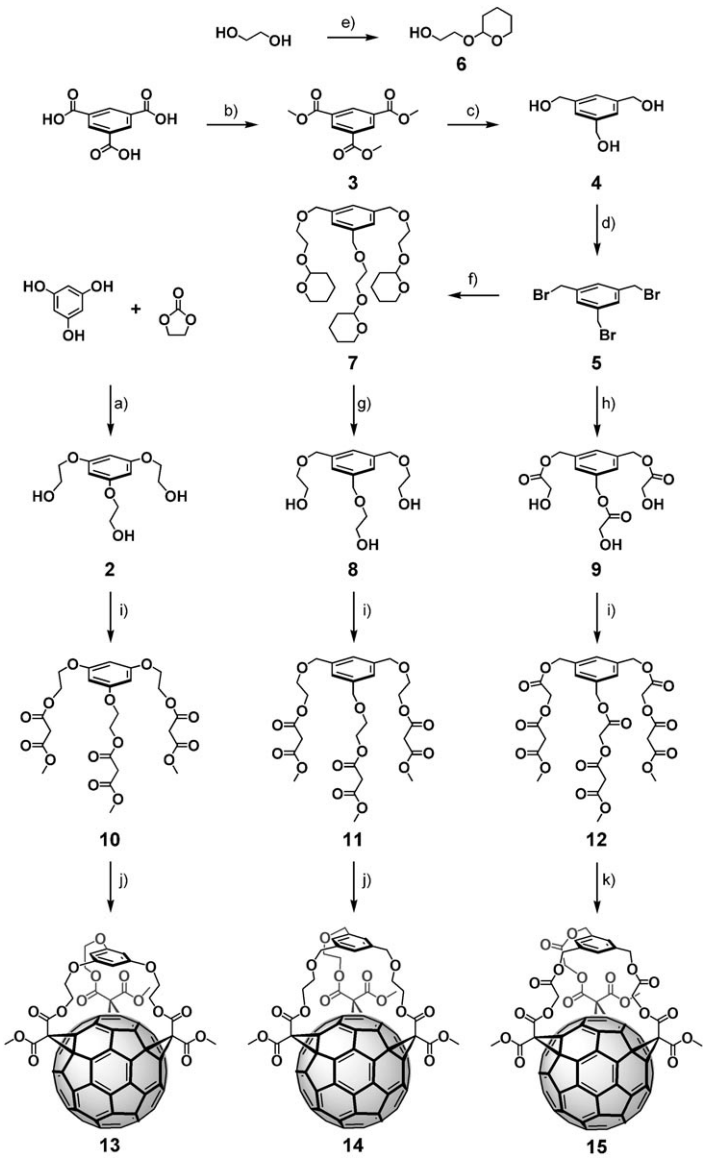


Figure 1. General concept for the synthesis of *e*,*e*,*e*-trisadducts with two spherically defined addend zones.

HCl in CH_2Cl_2/MeOH.[39] Tripodal alcohol **9** was synthesized by a threefold nucleophilic substitution with glycolic acid. Altogether three types of trismalonate have been made available that differ either in the chain length or connection to the focal point with respect to the used tether. According to the above-mentioned concept, suitable deprotection strategies would therefore create different kinds of functionality, for example, hydroxy or carboxyl groups, within the polar addend zone. To investigate the regioselectivity of a threefold Bingel reaction with respect to the individual tether system, malonates **10**, **11**, and **12**, each containing a methyl ester as the second terminus, were synthesized (Scheme 1). All the three tripodal malonates were readily accessible by a threefold condensation of malonic acid monomethylester chloride with the appropriate tripodal building block **2**, **8**, or **9** in the presence of pyridine. Purification by column chromatography on silica gel afforded **10**, **11**, and **12** in good yield. Subsequently, the final triscyclopropanation of C_{60} was carried out (Scheme 1). To avoid the formation of polymeric material, the reactions were carried out under high-dilution conditions. The best yields of the macrocyclization products **13**–**15** were obtained for fullerene concentrations of around 0.5 mmol L^{-1}. In the case of **10**, treatment with iodine and DBU in toluene and subsequent separation by column chromatography afforded only one main fraction that showed the expected protonated molecular ion peak (*m*/*z* 1274) for **13** in the MALDI-TOF mass spectrum. As demonstrated by the HPLC elugrams, this fraction consisted of one single regioisomer and its addition pattern could be assigned as *e*,*e*,*e* by comparison with the UV/Vis spectra and ^{1}H and ^{13}C NMR spectroscopic data with those of previously reported *e*,*e*,*e*-trisadducts.[27,29,30,40] The reaction proceeded with complete regioselectivity. Only traces of lower addition products, for example, mono- and bisadducts were formed and were removed by flash chromatography. Therefore, *e*,*e*,*e*-trisadduct **13** could be isolated in pure form in 29% yield. For the tether system **11** with elongated spacer side chains, the same threefold cyclopropanation afforded two main fractions, which both exhibited the molecular-ion peak for trisadducts (*m*/*z* 1315) in the FAB-mass-spectrometric spectra, after separation by column chromatography on silica gel. The HPLC elugram of the first, less-polar fraction consisted of one dominant peak and the UV/Vis spectra of which matched those of previously reported *trans*-3,*trans*-3,*trans*-3-trisadducts.[30,40] ^{1}H and ^{13}C NMR spectroscopic analysis, however, revealed that this fraction was a mixture of trisadducts. Separation by chromatographic methods could not be achieved. The second, more-polar fraction consisted of a single trisadduct and was formed in 55% relative yield. By comparing the UV/Vis spectra of this second fraction with those of known *e*,*e*,*e*-trisadducts, the *e*,*e*,*e*-addition pattern of **14** could be clearly assigned. As a matter of fact, this regioisomer could be isolated from the reaction mixture by one simple column-chromatographic step and was obtained in 23% yield. For tether **12** with its malonate side chains attached by benzylic esters instead of benzylic ethers, surprisingly no favored reactions could be detected under the standard cyclopropanantion conditions successfully applied for **10** and **11**. By using iodine as a halogenation reagent and DBU as a base, only small amounts of multiple adducts could be observed and most of the C_{60} remained unreacted. TLC analysis, however, indicated the complete conversion of the starting malonate **12** and a brownish precipitate was formed. This lack of sufficient conversion is probably due to the enhanced reactivity of benzylic esters towards nucleophilic substitution. The presence of iodine or iodide ions generated in situ during the reaction probably led to substantial ester cleavage and therefore degradation of the malonate. Indeed, by using CBr_4 as a bromination reagent in situ and the even more non-nucleophilic phophazene base P_1-*t*Bu instead of DBU led to slow conversion of C_{60} into *e*,*e*,*e*-isomer **15** as the only trisadduct. Several separation steps with column chromatography were required in the purification, after which **15** was obtained in 8% yield.

The ^{1}H NMR spectra of **13**, **14**, and **15** are represented in Figure 2. Due to the inherent chirality of the *e*,*e*,*e*-addition pattern, the protons of the side chains (2) and (3) become diastereotopic, thus giving rise to pronounced splitting pat-



Scheme 1. Synthesis of the *e*,*e*,*e*-trisadducts **13**–**15** based on tripodal malonate tethers: a) $Bu_4^+Br^-$, DMF, 150 °C, 14 h (24%); b) H_2SO_4, MeOH, reflux, 12 h (98%); c) $LiAlH_4$, THF, RT, 12 h (78%); d) PBr_3, Et_2O, RT, 12 h (80%); e) DHP, PPTS, RT, 14 h (58%); f) **6**, NaH, THF, reflux, 12 h (60%); g) HCl, CH_2Cl_2/MeOH (1:1), RT, 14 h (90%); h) glycolic acid, DBU, MeCN, RT, 12 h (83%); i) methyl malonyl chloride, pyridine, THF, 0 °C→RT, 24 h (**10**: 80%, **11**: 75%, **12**: 81%); j) C_{60}, I_2, DBU, toluene, RT, 12 h (**13**: 29%, **14**: 23%); k) C_{60}, CBr_4, P_1-*t*Bu, toluene, RT, 48 h (8%). DHP = dihydropyran, PPTS = pyridinium *para*-toluenesulfonate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

terns. In the spectral region of the ABCD spin system of the ethylene side chains of **13**, four signals are exhibited due to the diastereotopicity of both CH_2 groups. Each CH_2 group splits into one doublet and one triplet with a diastereotopic shift of $J = 0.16$ and 0.34 Hz, respectively, as demonstrated by 2D NMR spectroscopic analysis (^1H–^1H COSY, HETCOR). A closer analysis of the coupling constants revealed that there are two geminal couplings of each proton with its diastereotopic counterpart ($^2J_{2,2'} = 11.9$, $^2J_{3,3'} = 11.7$ Hz) and one strong vicinal coupling between protons (2′) and (3) ($^3J_{2',3} = 10.0$ Hz). In contrast, the other vicinal coupling constants are comparatively small ($^3J_{2,3} = 1.7$, $^3J_{2,3'} = 2.0$, $^3J_{2',3'} = 1.8$ Hz) and only visible as small shoulders and splittings at higher resolution. These observations strongly indicate that the spherical structure of **13** is very rigid with almost no rotational degree of freedom around the C–C bonds in the ethylene chains, even in solution. If the geometry of these ethylene groups is fixed in the staggered conformation shown in Figure 2, the individual vicinal coupling constants can be estimated by using the relation developed by Karplus.[41,42] For this staggered conformation, the Karplus curve predicts one large vincinal coupling constant $^3J_{2',3}$ of around 10–12 Hz ($\phi_{2',3} = 180°$) and small coupling constants in the range 2–3 Hz for $^3J_{2,3}$, $^3J_{2,3'}$, and $^3J_{2',3'}$ each with $\phi = 60°$. Indeed, this finding is in perfect agreement with the experimental observations, thus giving very strong evidence for the postulated rigid structure of **13**. In contrast, the more flexible structure of the capping benzene moiety due to the longer side chains in **14** is reflected in its ^1H NMR spectrum as well. Whereas the two protons of the CH_2 group (2) nearest to the fullerene core exhibit two multiplets with a diastereotopic splitting of $\Delta\delta = 0.53$ ppm, the chemical environment of the two other methylene protons (3) is very similar since they give rise to only one multiplet. For the benzylic protons (4), there are also two doublets with a small diastereotopic shift of $\Delta\delta = 0.07$ ppm. By changing the linkage from benzylic ethers to benzylic esters as exemplified in **15**, the flexibility of the attached benzene core is again diminished. This outcome can be evidenced by an increased splitting of $\Delta\delta = 0.38$ ppm for the two diastereotopic benzylic protons (4), thus showing doublets at $\delta = 5.04$ and 5.46 ppm, respectively. The remaining methylene groups (2) also split up in two doublets with a shift of $\Delta\delta = 0.33$ ppm. Therefore, these spectroscopic data nicely mirror the effects of small structural changes within the tether systems on the flexibility and selectivity of the resulting fullerene adduct.

Selective functionalization of the equatorial addend zone: One possibility for targeting *e*,*e*,*e*-trisadducts bearing various functional groups on the periphery is to modify the equatorial addend zone. This modification can in principle be achieved by a simple variation of the monofunctionalized malonic acid derivative in threefold esterifications that lead to tripodal malonate tethers such as **10**, **11**, or **12**. As the most suitable template for such an approach, we chose **2** because the highest yield for the threefold cyclopropanation was obtained for **10**. Condensation reactions of the Meldrum acid (i.e., 2,2-dimethyl-1,3-dioxane-4,6-dione) with suitable alcohols resulted in the formation of the monofunctionalized malonic acids **16** and **17** (Scheme 2). Whereas **16** was obtained by simple melting equivalent amounts of the Meldrum acid and dodecanol in quantitative yield, the synthesis of **17** had to be carried out in toluene as the solvent and an aqueous workup was required probably due to the enhanced sensitivity of the bromide compounds at higher temperatures. To introduce carboxylic acids as functional groups in

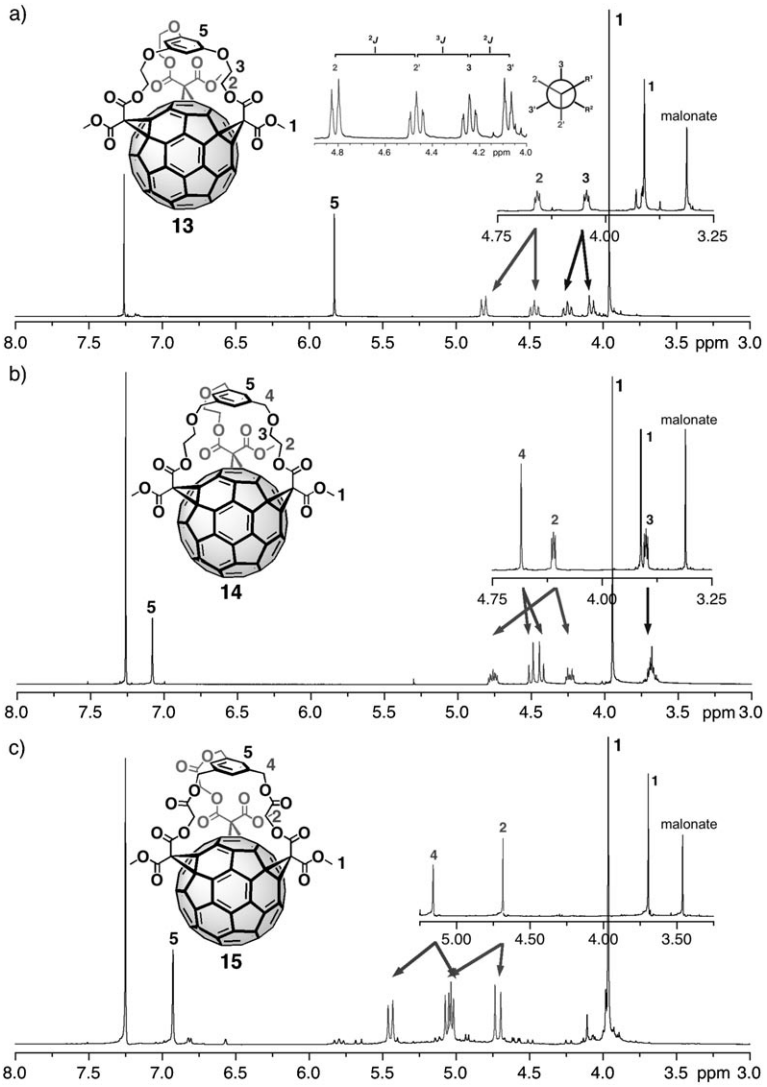
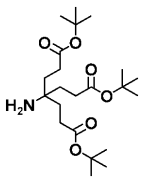


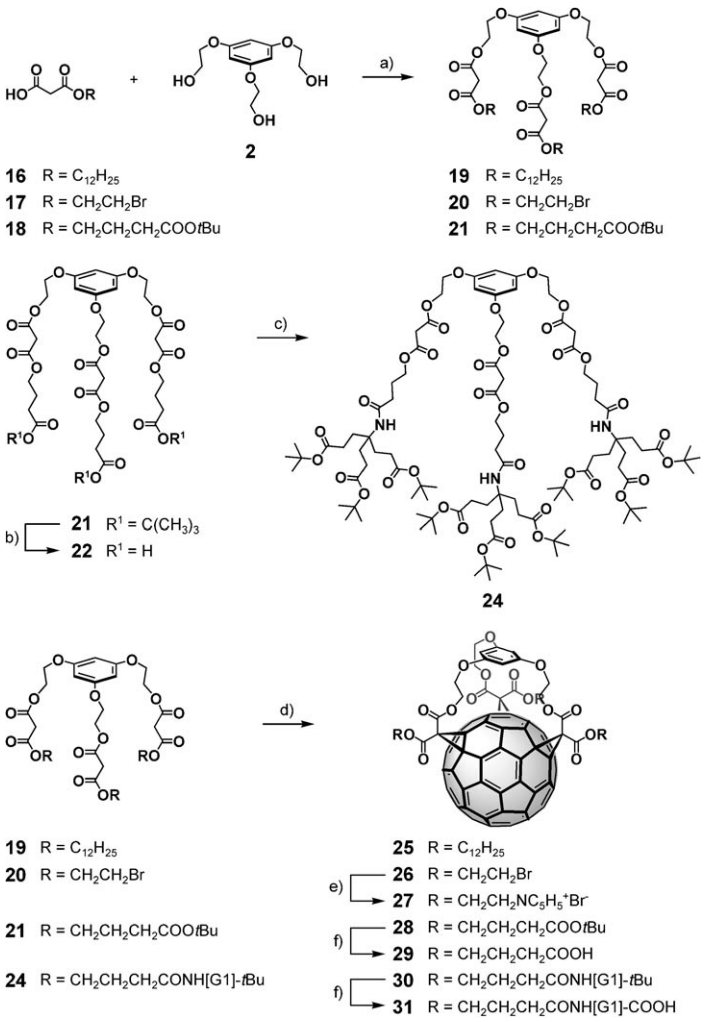
Figure 2. ^{1}H NMR spectra (400 MHz, RT, $CDCl_3$) of *e*,*e*,*e*-trisadducts a) **13**, b) **14**, and c) **15**. Insets represent the spectra of the free malonates, respectively.

the equatorial addend zone, the *tert*-butyl-protected butanoic acid derivative **18** was synthesized according to reported procedure.[32,43] With the malonic acid derivatives **16**–**18** in hand, the synthesis of tripodal malonate tethers **19**–**21** was straightforward (Scheme 2). Threefold esterification with trisalcohol **2** and the appropriate malonic acid derivative under modified Steglich conditions in THF gave trismalonates **19**–**21** in good yield. To obtain satisfactory yields for the cyclopropanation reactions of malonates bearing sterically demanding groups, the introduction of spacer groups between the malonate and the bulky group turned out to be necessary. Therefore, **21** with three C_4 spacer units at the malonate termini was chosen as a precursor for the *e*,*e*,*e*-trisadducts containing bulky groups in the equatorial addend zone. Acidic deprotection of the *tert*-butyl esters by means of formic acid provided the triscarboxylic acid **22** in almost quantitative yield as a versatile building block for further functionalization. For example, the treatment of **22** with the Newkome first-generation amino dendrimer **23** [44] in the presence of EDC and DMAP in CH_2Cl_2 afforded the dendritic malonate **24** containing nine *tert*-butyl-protected acid groups.



23

With trismalonates **19**–**21** and **24** in hand, a series of tethers could be synthesized all bearing various kinds of functional group, for example, alkyl chains, dendritic moieties, protected carboxylic acids, or bromides, at their peripheral side arms. Because the reactive malonate groups of these tethers are connected in the same manner to the focal benzene template as in **10**, the same regioselectivity for a threefold cyclopropanation reaction as for **13** was expected. To synthesize the corresponding *e*,*e*,*e*-trisadducts, cyclopropanations of C_{60} with the D_{3h}-symmetrical tethers **19**–**21** and **24** were carried out under the same experimental conditions as those used for the synthesis of **13**. All tethers showed similar regioselectivity, thus leading to the formation of the respective *e*,*e*,*e*-trisadduct as the only regioisomer that was eluted in one single fraction during purification by column chromatography of the reaction mixture with mixtures of toluene/EtOAc as the eluent. Trisadducts **25**, **26**, **28**, and **30** could be isolated in 35–40% yield and were characterized by FAB mass spectrometric, ^{1}H and ^{13}C NMR spectroscopic, and UV/Vis spectroscopic analysis. The structure of the side chains attached to the malonate units did not significantly influence the regioselectivity and yield for the threefold cyclopropanation, thus making **2** an ideal building block for the synthesis of functionalized *e*,*e*,*e*-trisadducts. Further functionalization of the equatorial addend zone could be achieved by means of appropriate chemical conversions. To introduce positive charges within the equatorial addend zone, trisbromide **26** was heated in pyridine at 60°C (Scheme 2). After stirring overnight, the fully quarternized product was precipitated. Coevaporation of the precipitate with toluene and several reprecipitations from a solution of

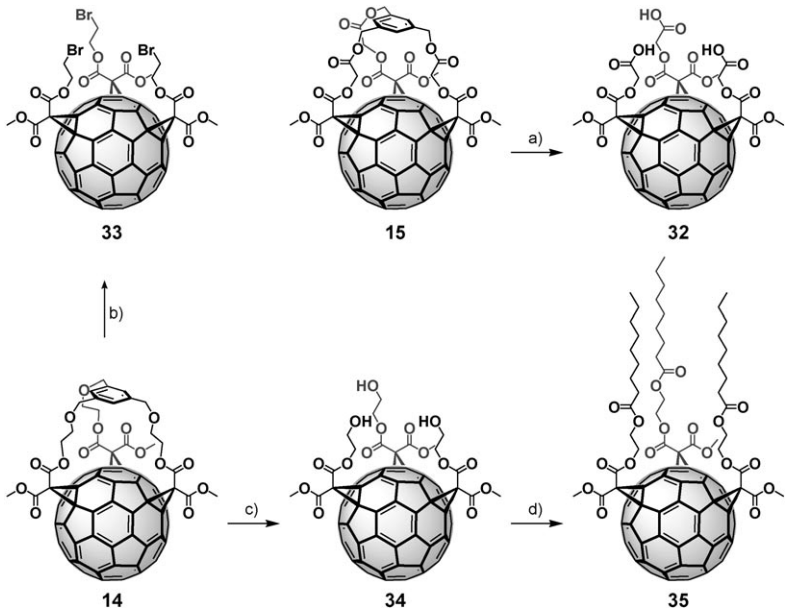


Scheme 2. Selective functionalization of the equatorial addend zone: a) DCC, DMAP, THF, 0°C→RT, 48 h (**19**: 81%, **20**: 55%, **21**: 85%; b) HCOOH, RT, 18 h (99%); c) **23**, EDC, HOBt, DMAP, CH_2Cl_2, 0°C→RT, 48 h (64%); d) C_{60}, I_2, DBU, toluene, RT, 12 h (**25**: 45%, **26**: 32%, **28**: 35%, **30**: 33%); e) pyridine, 60°C, 14 h (91%); f) HCOOH, CH_2Cl_2, RT, 24 h (95%). DCC = *N*,*N*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide; HOBt = 1-hydroxybenzotriazole.

methanol induced by the addition of diethyl ether yielded cationic *e*,*e*,*e*-trisadduct **27** in 90% yield. Deprotection of the *tert*-butyl-protected tris- and nonakisacids **28** and **30** was achieved by stirring in formic acid at room temperature for several days (Scheme 2). Structural characterization of all these compounds was achieved by NMR and UV/Vis spectroscopic and mass-spectrometric analysis.

In summary, a variety of functional groups was introduced into the equatorial addend zone by a simple variation of the second malonate terminus. Derivatives containing alkyl chains **25** or dendritic moieties **30** are versatile building blocks and precursors for supramolecular ensembles and functional groups such as bromide **26** or protected carboxylic acid **28**, thus facilitating further functionalization. Furthermore, polar or charged derivatives such as **27**, **29**, or **31** turned out to be interesting candidates for biomedical applications.[20,33,34] Concerning their water solubility, the triscationic fullerene derivative **27** is very soluble over the whole pH range and even in nonbuffered water, whereas trisacid **29** is very soluble in water at pH 8 or higher due to complete deprotonation. Furthermore, polar dendritic derivative **31** bearing nine carboxylic acid groups on its periphery is well soluble in aqueous solutions at pH 7 due to the increased number of polar groups. In contrast, amphiphilic monoadducts containing one dendritic branch with three carboxylic acids are virtually insoluble, even under basic conditions.[33] This outcome correlates well with the generalized observation that at least three ionic charges with an appropriate arrangement at the fullerene surface or some combination of net charging and other polar moieties is required for sufficient water solubility.[33,45–49]

Selective functionalization of the polar addend zone: For the selective functionalization of the polar addend zone, the focal benzene moiety has to be removed first. In principle, this removal could be achieved through suitable disconnection reactions that cleave the ether or ester bonds in **13**–**15**. Unfortunately, it was not possible to cleave all the phenylic ether bonds of **13** in a preparative manner, even when trying with a large variety of ether-cleaving reagents. Treatment of **13** with BBr_3 in CH_2Cl_2[50] resulted in complete decomposition of the fullerene compound, as indicated by a strong color change. The use of $LiI/SiCl_4/BF_3{\cdot}OEt_2$,[51] BCl_3,[52] $BCl_3/NBu_4^+Br^-$[53], or HBr/H_3CCOOH as ether-cleaving reagents showed no conversion of the reactant even after several days and at higher temperatures. In contrast, after heating a solution of **13** and NaI in HBr/H_3CCOOH (1:1) and $CHCl_3$ to reflux, cleavage of one ether bond could be detected by mass-spectrometric analysis, but this deprotection was reversible. However, longer reaction times caused gradual deprotection of the methyl esters after 2–3 days. This lack of deprotection is probably due to a decreased reactivity of the ether compounds because of the 1,3,5-trisalkoxy-substitution pattern and the very rigid capped structure. This very strong preorganization can be assumed to favor reclosing the tethered system after cleavage of one out of three ether linkages. In contrast, the more reactive benzylic ether and ester groups in **14** and **15** were shown to be much more labile. The drawback of lower yield in the regioselective threefold cyclopropanation is thereby overcompensated by the favorable disconnection properties of these functionalities. Whereas hydrogenation of benzylic ethers seemed to be unsuitable for fullerene derivatives due to partial hydrogenation of the fullerene surface,[54] other common ether-cleaving reagents smoothly cleaved these protecting groups in the presence of fullerenes. The benzylic ester groups of **15** were cleaved by stirring a solution in CH_2Cl_2 in the presence of HBr/H_3CCOOH (Scheme 3). Aqueous workup and reprecipitation from $CHCl_3$ with pentane yielded the triscarboxylic acid **32** in reasonable yield. Depending on the reaction conditions, the benzylic ethers of **14** were cleaved to yield alcohol or bromide derivatives



Scheme 3. Selective functionalization of the polar addend zone: a) HBr/CH_3COOH, CH_2Cl_2, RT, 14 h (86%); b) CTAB, HBr/H_2O, $CHCl_3$, reflux, 7 days (77%); c) BCl_3, CH_2Cl_2, 0°C, 12 h (75%); d) nonanoyl chloride, pyridine, CH_2Cl_2, 0°C→RT, 48 h (94%). CTAB = cetyltrimethylammonium bromide.

(Scheme 3). Heating a two-phase system of $CHCl_3$ and 48% HBr in water with **14** and the phase-transfer catalyst CTAB[55] to reflux for seven days gave tribromide **33** in reasonable yield. Furthermore, treating a solution of **14** in CH_2Cl_2 with boron trichloride and subsequent aqueous workup led to the formation of triol **34** in good yield (Scheme 3). Depending on the starting materials and the applied reaction conditions, functionalities such as bromide, hydroxy, and carboxyl groups were introduced into the polar addend zone that could be further chemically modified in subsequent transformations. As an example, the acid chloride coupling of **34** with nonanoyl chloride in the presence of pyridine in CH_2Cl_2 resulted in the formation of the *e*,*e*,*e*-trisadduct **35** in good yield (Scheme 3).

Because of their proximal alignment within the polar region of the fullerene surface, these functional groups exhibit close contact with each other, thus influencing the chemical behavior significantly. For example, the solubility of trisacids **29** and **32** in aqueous and organic media strongly depends on the spherical arrangement of their polar groups. Trisadduct **29** exhibits three carboxylic groups well distributed in the equatorial addend zone. It is very soluble in buffered water at pH 8 or in the presence of $NaHCO_3$ but is virtually insoluble in apolar organic solvents such as CH_2Cl_2 or $CHCl_3$. In contrast, **32** with three acid groups located in the polar addend zone is reasonably soluble in organic media in the fully protonated form. In aqueous phases, solubility could only be achieved under basic conditions (pH > 10). A reasonable explanation for these differences is the establishment of favorable intramolecular hydrogen-bonding interactions due to the close contact of the functional groups in the polar addend zone. On closer investigation, the ^{1}H NMR spectra of **32** and **34** were recorded in polar and apolar solvents, respectively. Spectra recorded in protic media such as methanol or dipolar aprotic solvents such as THF show the expected two triplets for the ethylene units (2) and (3) in **34** and one singlet for the methylene groups (2) of **32** (Figure 3). However, in the case of pure $CDCl_3$ as the solvent, comparable splitting patterns to those for the capped precursors **14** and **15** (Figure 2) were observed. The protons of the CH_2 groups directly attached to the malonates (2) in **34** split into two multiplets at $\delta = 4.29$ and 4.54 ppm with a diastereotopic shift of $\Delta\delta = 0.25$ ppm. The corresponding signal for **32** splits into an unstructured multiplet in the range $\delta = 4.5$–5.0 ppm. These NMR spectroscopic data provide strong evidence for an inherent structural rigidity of the attached side arms in the polar region for **32** and **34** in apolar solvents such as $CHCl_3$. This finding can most likely be rationalized by an intramolecular hydrogen-bonding system that fixes the three polar functionalities together in a ring-like structure with threefold symmetry. The very weak, broad, and almost undetectable bands for the OH stretching vibrations in the IR spectra of **32** and **34** are further hints for strong intramolecular hydrogen bonding. In contrast, fullerene derivatives with carboxylic acids in the equatorial addend zone showed broad OH stretching bands at $\tilde{\nu} = 3500\ cm^{-1}$ (see Figure S1 in the Supporting Information for the spectra). For both *e*,*e*,*e*-trisadducts, the thermodynamical feasibility of such intramolecular hydrogen-bonding networks could be evidenced by molecular modeling on the PM3-level.[56] The calculated minimum structures and schematic representations of the respective bonding motifs are depicted in Figure 3. Both the hydroxy and carboxyl groups are thereby connected by three hydrogen bonds in cyclic structures containing six and twelve atoms, respectively. In comparison to its covalently bridged precursor **14**, the splitting for the diastereotopic ester protons in **34** is significantly smaller ($\Delta\delta = 0.53$ and 0.25 ppm, respectively), thus indicating the expected higher degree of flexibility for the supramolecular system. Thereby, effective intramolecular complexation of the polar groups avoids unfavorable interactions with the solvent in apolar media, thus explaining the great discrepancies in solubilities of **29** and **32** in organic media. In polar or protic solvents, the intramolecular hydrogen bonds are broken and the flexibility of the side arms is drastically enhanced, which is evidenced by the disappearance of the diastereotopic splitting in the NMR spectra.

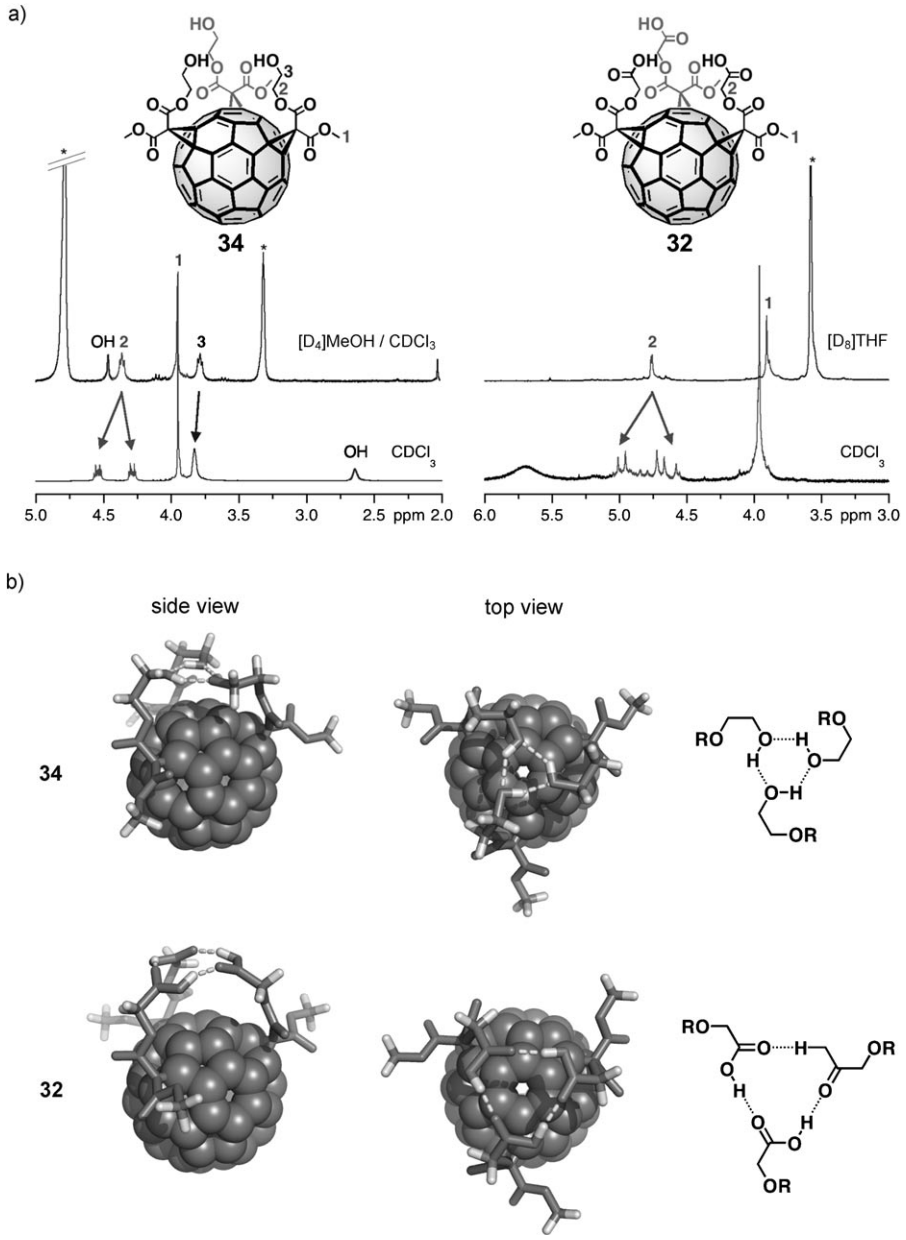
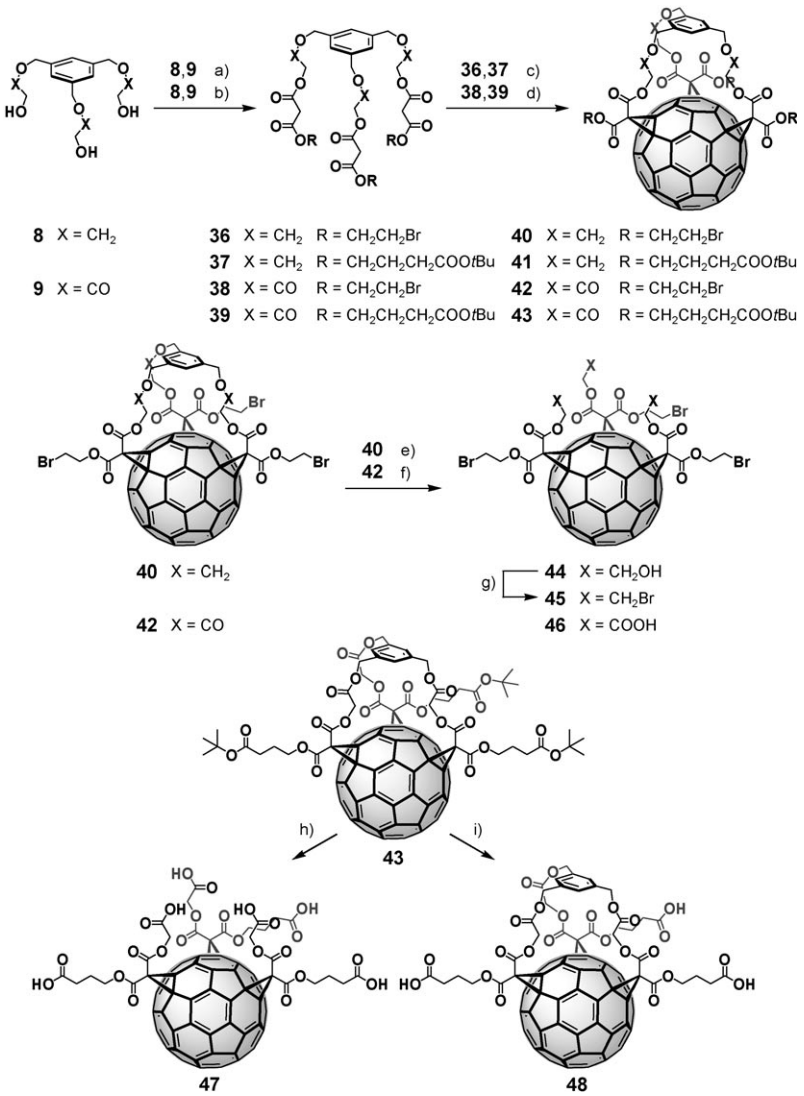


Figure 3. a) ^{1}H NMR spectra (300 MHz, RT) of *e,e,e*-trisadducts **34** (left) and **32** (right) in polar and apolar solvents (top: $[D_4]$MeOD/$CDCl_3$ and $[D_8]$THF; bottom: $CDCl_3$). b) Energy-minimized structures for intramolecular hydrogen bonding in the polar addend zone for **64** (top) and **62** (bottom) and schematic representations of the respective binding motif.

Orthogonal functionalization of both addend zones: To target the orthogonal functionalization of both addend zones, a suitable combination of both functionalization of the equatorial addend zone and facile template deprotection followed by further chemical transformation of the polar addend zone is required. For this purpose, tether building blocks **8** and **9** were chosen as focal templates capable of being readily deprotected after addition to C_{60}. Standard esterification reactions of the monofunctionalized malonic acids **17** and **18** with DCC and DMAP afforded the tripodal malonate tethers **36–39**, which exhibit benzylic ether or ester linkages and bromides or *tert*-butyl-protected acids on the periphery (Scheme 4). In the case of bromoethyl-functionalized side chains, the use of EDC as a coupling agent significantly improved the yield and reaction time as well as the ease of purification because removal of the formed *N,N*-dicyclohexylurea (DCU) appeared to be very difficult with DCC as the activating reagent. Based on the individual linkage of the side chains to the central benzene ring, malonates **36–39** were subjected to a threefold cyclopropanation with C_{60} by using either iodine and DBU or CBr_4 and the phosphazene base P_1-*t*Bu for halogenation in situ, as it was described for the tether systems **11** and **12**, respectively (Scheme 4). The trisadducts **40–43** could be obtained with comparable regioselectivity and yield as the parent adducts **14** and **15**. Benzylic ether-linked compounds **40** and **41** could be isolated in 25–30% yield as the major regioisomers beside other trisadducts. On the other hand, **42** and **43** containing benzylic esters as connecting units were isolated in up to 10% yield as the only characterizable fullerene adducts. Again, the regioselectivity and isolation of the favored *e,e,e*-trisadducts appeared to be independent of the chemical nature of the attached side chains that utilized **8** and **9** as highly versatile building blocks for the preparation of *e,e,e*-trisadducts in the same manner as **2**. For the successful deprotection and removal of the structural template, the appropriate synthetic protocols developed for **14** and **15** were applied to the equatorially functionalized derivatives as well. The reaction of **40** with boron trichloride in CH_2Cl_2 afforded the mixed bromoalcohol **44** in good yield. Subsequent bromination with the aid of HBr and the phase-transfer catalyst CTAB in a biphasic $H_2O/CHCl_3$ mixture resulted in the formation of hexabromide **45** in an almost quantitative yield. The treatment of **42** with HBr/H_3CCOOH in CH_2Cl_2 and subsequent aqueous workup afforded trisbromoacid **46** in good yield (Scheme 4). Therefore, the deprotection of **40** and **42** could be achieved without any problems because the bromide



Scheme 4. Orthogonal functionalization of both addend zones: a) **17**, EDC, DMAP, THF, 0 °C→RT, 48 h (**36**: 89 %, **38**: 28 %; b) **18**, DCC, DMAP, THF, 0 °C→RT, 48 h (**37**: 95 %, **39**: 48 %); c) C_{60}, I_2, DBU, toluene, RT, 12 h (**40**: 32 %, **41**: 25 %); d) C_{60}, CBr_4, P_1-*t*Bu, toluene, RT, 48 h (**42**: 7 %, **43**: 8 %; e) BCl_3, CH_2Cl_2, 0 °C, 12 h (76 %); f) Br/CH_3COOH, CH_2Cl_2, RT, 14 h (75 %); g) CTAB, HBr/H_2O, $CHCl_3$, reflux, 7 days (77 %); h) HBr/CH_3COOH, CH_2Cl_2, RT, 14 h (79 %); i) HCOOH, CH_2Cl_2, RT, 24 h (97 %).

groups in the equatorial addend zone appeared to be inert under the applied reaction conditions. Thus, the orthogonally functionalized *e*,*e*,*e*-trisadducts **44**, **45**, and **46** all bearing bromide groups in the equatorial addend zone and alcohol, bromide, or carboxylic acid groups in the polar addend zone could be synthesized and fully characterized by using standard analytical methods, such as mass spectometric, NMR spectroscopic, and UV/Vis spectroscopic analysis. In case of trisadducts **41** and **43**, the presence of *tert*-butyl-protected acid groups in the equatorial addend zone turned out to be very crucial in terms of a facile removal of the focal benzene moiety. Because all the synthetic protocols for the sufficient deprotection of **14** and **15** required activation of the ether or ester bonds by Bronsted or Lewis acid reagents, such as BCl_3 or HBr, cleavage without affecting the protected carboxylic acids could not be achieved in any case. Due to the very high sensitivity of *tert*-butyl-protected carboxylic acids towards acidic reagents, deprotection of the *tert*-butyl esters always occurred instantaneously under reaction conditions associated with the precipitation of the free acids in reaction media such as CH_2Cl_2 or $CHCl_3$. The subsequent or removal in situ of the capped moiety was therefore greatly hampered in the case of **40** and could not be achieved in a preparative manner. For **43**, complete cleavage of both benzylic and *tert*-butyl esters could be achieved by stirring in a mixture of CH_2Cl_2 and HBr/H_3CCOOH at room temperature to afford hexaacid **47** in almost quantitative yield (Scheme 4). Because the cleavage of the benzylic esters is supposed to proceed through an S_N2 pathway, these groups were anticipated to be stable under acidic conditions in the absence of strong nucleophiles. As a matter of fact, the treatment of **43** in CH_2Cl_2 with formic acid resulted in the exclusive deprotection of the *tert*-butyl esters and the formation of trisacid **48**. Thus, depending on the reaction conditions, carboxylic acids could be selectively generated in both addend zones, thus leading to versatile building blocks **47** and **48**, which are capable of being further functionalized in subsequent synthetic steps.

By appropriate orthogonal functionalization, both the inter- and intramolecular effects of selective equatorial and polar functionalization, respectively, should be combined in a concise manner (Figure 4). For fullerene derivatives of this type, these two effects might interact in a very elegant manner to lead to versatile supramolecular building blocks that can efficiently bind appropriate guest molecules and simultaneously control their chemical environment and aggregation processes.

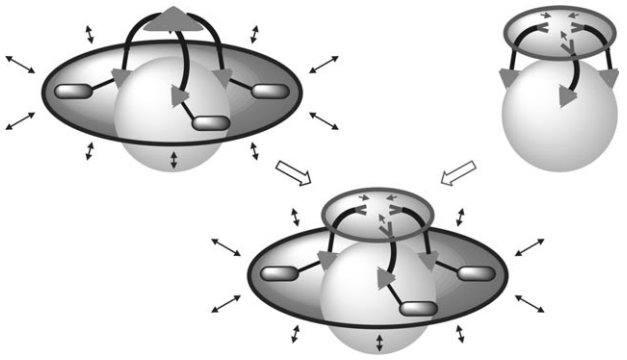


Figure 4. Combination of inter- and intramolecular interactions by orthogonal functionalization of both addend zones.

Conclusions and Outlook

In conclusion, it was possible to show that the introduced concept of tripodal malonate tethers is a very powerful tool for synthesizing *e*,*e*,*e*-trisadducts with good regioselectivity and control over *in*/*out* isomerism. Both the equatorial and polar addend zones of these novel fullerene derivatives were shown to be selectively functionalizable in an orthogonal fashion, thus giving access to unique classes of molecules not accessible by any other known synthetic procedures. Furthermore, it could be shown that the selective functionalization of both addend zones influences the chemical and physical properties of the respective *e*,*e*,*e*-trisadducts in a different fashion. Whereas variations in the equatorial region effectively impact the intermolecular interactions, modifications in the polar region are dominated by intramolecular forces. Owing to the rigid structure and close preorganization of substituents in the polar addend zone, these derivatives are ideal candidates for supramolecular hosts capable of complexing metal ions or hydrogen-bonding systems. In the case of different functionalities in these two distinct addend zones, the corresponding fullerene derivatives are the first example of a novel class of *e*,*e*,*e*-trisadducts that exhibit asymmetrically substituted malonate addends in a spherically well-defined manner. Further functionalization by means of suitable chemical transformations of these molecular building blocks will give access to a great diversity of molecular structures with a defined arrangement of different functionalities. Up to now, no other synthetic methods have been reported that can synthesize fullerene derivatives of such a type. Thereby, well-directed modifications for both addend regions may lead to novel tailor-made building blocks that can control both close interactions with appropriate guest systems within the polar region and intermolecular interplay by fine-tuning the equatorial belt. The combination of the functionalities brought by the addition chemistry introduced herein with the redox properties of the remaining π system of the fullerene core makes such derivatives promising candidates for a variety of applications, such as redox-active components for new molecule-based materials.

Experimental Section

Chemicals: All the chemicals were purchased from chemical suppliers and used without further purification. All the analytical-reagent-grade solvents were purified by distillation. Dry solvents were prepared by using customary procedures.[58] Thin layer chromatography (TLC) was carried out on Riedel-de Haen silica gel F254 and Merck silica gel 60 F254. Detection was performed by using a UV lamp and iodine chamber. Flash column chromatography (FC) was carried out on Merck silica gel 60 (230–400 mesh, 0.04–0.063 nm). A Shimadzu liquid chromatograph LC-10 with a Bus module CBM-10A, autoinjector SIL-10A, two pumps LC-10AT, and diode array detector was used for analytical HPLC. The HPLC-grade solvents were purchased from SDS or Acros Organics. The HPLC analytical column was a Nucleosil 5Lm, 200×4 mm from Macherey–Nagel, Düren. The UV/Vis spectra were recorded on a Shimadzu UV-3102 PC UV/Vis/NIR scanning spectrophotometer, and the absorption maxima λ_{max} are given in nm. The mass spectra were recorded on a Micromass Zabspec in the FAB (LSIMS) mode on a matrix of 3-nitrobenzyl alcohol and on a Shimadzu AXIMA Confidence MALDI-TOF mass spectrometer using a nitrogen UV laser at 50 Hz at a 337-nm wavelength on a matrix of 2,5-dihydroxybenzoic acid (DHB), sinapinic acid (SIN), or 2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB). The NMR spectra were recorded on JEOL JNM EX 400, JEOL JNM GX 400, and Bruker Avance 300 spectrometers. The chemical shifts are given in ppm relative to trimethylsilane (TMS). The resonance multiplicities are indicated as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and m = multiplet; nonresolved, or broad (br). Elemental analysis (CHN) was succeeded by combustion and gas-chromatographic analysis on an EA 1110 CHNS analyzer (CE Instruments). References to previously reported precursors are given in the main text. The synthetic procedures and characterization details of **11**, **14**, **18**, **21**, **28**, **29**, **37**, and **41**[32] and **17**, **20**, **26**, and **27**[33] have been reported recently. The synthetic procedures and full characterization details for **12**, **25**, **30**, **36**, **38**–**40**, and **42**–**48** are given in the Supporting Information.

2-(Tetrahydro-2*H*-pyran-2-yloxy)ethanol (6): 2,3-Dihydro-2*H*-pyran (DHP; 10.8 mL, 119 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise to a solution of ethylene glycol (10.0 mL, 179 mmol, 1.5 equiv) and PPTS (0.45 g, 0.15 equiv) in CH_2Cl_2 (250 mL) over 1 h. After the reaction mixture was stirred overnight and the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, hexanes/THF 3:1 and 1:1). Removal of the solvents and drying under high vacuum gave **6** as a colorless oil (10.2 g, 69.4 mmol, 58%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): δ = 1.48 (m, 4H; CH_2), 1.73 (m, 2H; CH_2), 3.11 (s, 1H; OH), 3.48 (m, 1H), 3.65 (m, 4H; OCH_2), 3.86 (m, 1H; OCH_2), 4.52 (m, 1H; OHCO) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): δ = 19.7 (1C; CH_2), 25.0 (1C; CH_2), 30.5 (1C; CH_2), 61.9 (1C; CH_2OH), 62.9 (1C; OCH_2), 70.4 (1C; OCH_2), 99.9 (1C; OHCO) ppm; MS (FAB, NBA): *m*/*z*: 147 $[M+H]^+$; elemental analysis (%) calcd for $C_7H_{14}O_3$: C 57.51, H 9.65; found C 57.21, H 9.93.

1,3,5-Tris-(2-hydroxy-1-oxo)ethoxymethyl benzene (9): DBU (2.05 mL, 13.8 mmol, 3.3 equiv) was added to a solution of **5** (1.50 g, 4.20 mmol, 1 equiv) and glycolic acid (1.05 g, 13.8 mmol, 3.3 equiv) in acetonitrile (20 mL). The reaction mixture was stirred at ambient temperature overnight. After the removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (SiO_2, acetonitrile). Removal of the solvent and drying under high vacuum gave **9** as a colorless solid (1.20 g, 3.51 mmol, 83%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): δ = 2.39 (s, br, 3H; OH), 4.20 (s, 6H; CH_2OH), 5.21 (s, 6H; Ar-CH_2), 7.32 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): δ = 60.7 (3C; CH_2OH), 66.4 (3C; Ar-CH_2), 128.5 (3C; ArC-H), 136.3 (3C; Ar*C*-CH_2), 173.1 (3C; CO) ppm; MS (FAB, NBA): *m*/*z*: 342 $[M]^+$; elemental analysis (%) calcd for $C_{15}H_{18}O_9$: C52.63, H 5.30; found C 51.52, H 5.40. m.p. 115–117 °C.

1,3,5-Tris-(2-methylmalonyl)ethoxybenzene (10): Methyl malonyl chloride (2.10 mL, 19.6 mmol, 5.1 equiv) in THF (15 mL) was added dropwise at 0 °C to a solution of **2** (1.00 g, 3.87 mmol, 1 equiv) and dry pyridine (2.10 mL, 25.8 mmol, 6.7 equiv) in dry THF (35 mL). The reaction mixture was slowly warmed and stirred at room temperature overnight. Af-

terwards, the precipitated pyridinum salts were removed by filtration. The filtrate was evaporated and the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 97:3) to give **10** as a pale yellow oil (1.73 g, 3.10 mmol, 80%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 3.43$ (s, 6H; $OCCH_2CO$), 3.72 (s, 9H; OCH_3), 4.12 (t, $^3J = 4.7$ Hz, 6H; Ar-OCH_2), 4.47 (t, $^3J = 4.7$ Hz, 6H; Ar-OCH_2CH_2), 6.09 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): $\delta = 41.1$ (3C; $OCCH_2CO$), 52.5 (3C; OCH_3), 63.6 (3C; Ar-OCH_2CH_2), 65.7 (3C; Ar-OCH_2), 94.6 (3C; ArC-H), 160.2 (3C; ArC-O), 166.4, 166.8 (6C; $OCCH_2CO$) ppm; MS (MALDI-TOF, without matrix): m/z: 581 $[M+Na]^+$; elemental analysis (%) calcd for $C_{24}H_{30}O_{15}\cdot 0.5\,CH_2Cl_2$: C48.97, H 5.20; found C 49.40, H 5.57.

***e,e,e*-Trisadduct 13**: C_{60} (500 mg, 0.693 mmol, 1 equiv) was dissolved in degassed, dry toluene (1200 mL). After complete dissolution of the fullerene was obtained, iodine (580 mg, 2.28 mmol, 3.3 equiv) and malonate **10** (360 mg, 0.645 mmol, 0.95 equiv) were added. Afterwards, a solution of DBU (670 µL, 4.49 mmol, 6.5 equiv) in toluene (500 mL) was added dropwise over 4 h. After stirring overnight at ambient temperature, the reaction mixture was subjected directly to flash column chromatography with toluene as the eluent. After elution of traces of starting material C_{60} with toluene, the eluent was changed to toluene/EtOAc (8:2) to isolate the product. Final reprecipitation from $CHCl_3$ with pentane gave **13** as a red solid (238 mg, 0.187 mmol, 29%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 3.96$ (s, 9H; OCH_3), 4.08 (d, $^2J = 11.6$ Hz, 3H; Ar-OCH_2), 4.24 (dd, $^2J = 11.6$, $^3J = 10.0$ Hz, 3H; Ar-OCH_2), 4.47 (dd, $^2J = 12.0$, $^3J = 10.0$ Hz, 3H; Ar-OCH_2CH_2), 4.81 (d, $^2J = 12.0$ Hz, 3H; Ar-OCH_2CH_2), 5.83 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): $\delta = 52.7$ (3C; $OCCCO$), 53.9 (3C; OCH_3), 65.8 (3C; Ar-OCH_2CH_2), 66.1 (3C; Ar-OCH_2), 69.4, 70.7 (6C; C_{60} sp^3), 94.2 (3C; ArC-H), 141.0, 141.0, 141.7, 142.0, 142.7, 143.3, 143.7, 144.2, 145.2, 145.8, 146.0, 146.3, 146.5, 146.6, 146.8, 146.9, 146.9, 147.0 (54C; C_{60} sp^2), 160.3 (3C; ArC-O), 163.1, 163.4 (6C; $OCCCO$) ppm; MS (MALDI-TOF, SIN): m/z: 1274 $[M+H]^+$, 1297 $[M+Na+H]^+$; UV/Vis (CH_2Cl_2): $\lambda_{max} = 252.5$, 281.5, 305 (sh), 380.5 (sh), 480.5, 565 (sh) nm.

***e,e,e*-Trisadduct 15**: C_{60} (500 mg, 0.693 mmol, 1 equiv) was dissolved in thoroughly degassed toluene (1100 mL) under nitrogen. After complete dissolution was obtained, CBr_4 (760 mg, 2.29 mmol, 3.3 equiv) and malonate **12** (416 mg, 0.647 mmol, 0.95 equiv) were added. Afterwards, a solution of P_1-*t*Bu (615 µL, 2.42 mmol, 3.5 equiv) in toluene (250 mL) was added dropwise over 4 h. The reaction mixture was stirred at room temperature and monitored by TLC analysis. After completion of conversion, the mixture was subjected directly to column chromatography with toluene as the eluent. After elution of traces of starting material C_{60}, the eluent was changed to toluene/EtOAc (7:3) to isolate the crude product. For final purification, the residue was subjected to multiple column-chromatographic steps (SiO_2, CH_2Cl_2/EtOAc 8:2). Reprecipitation from $CHCl_3$ with pentane yielded **15** as a red solid (70.2 mg, 0.051 mmol, 8%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 3.97$ (s, 9H; OCH_3), 4.73 (d, $^2J = 15.7$ Hz, 3H; $OCCH_2O$), 5.04 (d, $^2J = 12.8$ Hz, 3H; Ar-CH_2), 5.06 (d, 3H; $^2J = 15.7$ Hz, $OCCH_2O$), 5.46 (d, $^2J = 12.8$ Hz, 3H; Ar-CH_2), 6.94 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): $\delta = 51.8$ (3C; $OCCCO$), 54.0 (3C; OCH_3), 63.0 (3C; $OCCH_2O$), 66.1 (3C; Ar-CH_2), 69.2, 70.3 (6C; C_{60} sp^3), 126.0 (3C; ArC-H), 135.8 (3C; Ar*C*-CH_2), 140.6, 141.0, 141.4, 142.0, 142.8, 143.47, 144.4, 144.9, 145.4, 145.7, 145.9, 146.3, 146.5, 146.5, 146.7, 146.8, 147.0, 147.3 (54C; C_{60} sp^2), 163.5, 163.6 (6C; $OCCCO$), 166.8 (3C; $OCCH_2O$) ppm; MS (FAB, NBA): m/z: 1358 $[M+H]^+$; UV/Vis (CH_2Cl_2): $\lambda_{max} = 252$, 280, 305 (sh), 381 (sh), 480, 565 (sh) nm.

1,3,5-Tris-(2-dodecylmalonyl)ethoxybenzene (19): DCC (6.99 g, 33.8 mmol, 3.5 equiv) was added to a solution of trisalcohol **2** (2.50 g, 9.68 mmol, 1 equiv) and DMAP (421 mg, 3.45 mmol, 0.35 equiv) in dry THF at 0°C in an inert gas atmosphere. The reaction mixture was warmed up slowly, stirred at room temperature for several days, and monitored by TLC analysis. After completion of the reaction, the solution was filtered and the solvent was evaporated under vacuum. The residue was dissolved in a small amount of ethyl acetate and filtered again for several times to remove the remaining DCU. The crude product was purified by flash column chromatography (SiO_2, toluene/EtOAc 9:1) to yield **19** as a colorless solid (7.99 g, 7.82 mmol, 81%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.9$ Hz, 9H; CH_3), 1.25 (m, 54H; CH_2), 1.60 (m, 6H; $COOCH_2CH_2CH_2$), 3.43 (s, 6H; $OCCH_2CO$), 4.12 (m, 12H; $COOCH_2CH_2CH_2$, Ar-OCH_2CH_2), 4.47 (t, $^3J = 4.7$ Hz, 6H; Ar-OCH_2), 6.09 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): $\delta = 14.0$ (3C; CH_3), 22.6, 25.7, 28.4, 29.1, 29.3, 29.4, 29.5, 29.6, 31.8 (30C; CH_2), 41.3 (3C; $OCCH_2CO$), 63.5 (3C; $ArOCH_2CH_2$), 65.7 (3C; Ar-OCH_2), 65.8 (3C; $COOCH_2CH_2CH_2$), 94.6 (3C; ArC-H), 160.4 (3C; Ar*C*-CH_2), 166.5, 166.7 (6C; $OCCH_2CO$) ppm; MS (FAB, NBA): m/z: 1021 $[M]^+$; elemental analysis (%) calcd for $C_{57}H_{96}O_{15}$: C67.03, H 9.47; found C 67.63, H 9.72.

1,3,5-Tris-[2′-(3″-amido[G1]-*tert*-butyl)propylmalonyl]ethoxybenzene 24: Malonate **21** (990 mg, 1.05 mmol) was dissolved in formic acid (10 mL) and stirred at ambient temperature overnight. After removal of the solvent under reduced pressure, the crude product was mixed with toluene and distilled several times to remove the remaining traces of formic acid. Drying under high vacuum gave trisacid **22** as a yellow viscous oil (810 mg, 1.04 mmol, 99%). Complete deprotection was checked by ^{1}H NMR spectroscopic analysis and the product was used without further purification in the next synthetic step.

H_2N-[G1] **23** (1.82 g, 4.39 mmol, 4 equiv), butan-1-ol (0.52 g, 3.84 mmol, 3.5 equiv), and DMAP (70 mg, 0.55 mmol, 0.5 equiv) were added to a solution of trisacid **22** (850 mg, 1.10 mmol, 1 equiv) in dry CH_2Cl_2 (50 mL). The solution was cooled to 0°C and EDC (740 mg, 3.84 mmol, 3.5 equiv) was added. The reaction mixture was slowly warmed up and stirred at room temperature for two days. After completion of the reaction was detected by TLC analysis, the organic phase was washed with water (3× 25 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc 1:1) to yield **24** as a colorless cerac eous solid (1.38 g, 700 mmol, 64%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 1.43$ (s, 81H; $C(CH_3)_3$), 1.97 (m, 24H; $CH_2CH_2COOC(CH_3)_3$, CH_2CH_2CONH), 2.20 (m, 24H; $CH_2COOC(CH_3)_3$, CH_2CONH), 3.45 (s, 6H; $OCCH_2CO$), 4.14 (m, 6H; Ar-OCH_2), 4.18 (t, $^3J = 6.2$ Hz, 6H; $CH_2CH_2CH_2CONH$), 4.49 (m, 6H; Ar-OCH_2CH_2), 6.00 (s, 3H; NH), 6.10 (s, 3H; Ar-H) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): $\delta = 24.6$ (3C; CH_2CH_2CONH), 28.0 (27C; $C(CH_3)_3$), 29.7 (9C; $CH_2CH_2COOC(CH_3)_3$), 29.8 (9C; $CH_2COOC(CH_3)_3$), 33.2 (3C; CH_2CONH), 41.4 (3C; $OCCH_2CO$), 57.4 (3C; $CONHC$), 63.6 (3C; $ArOCH_2CH_2$), 64.7 (3C; $CH_2CH_2CH_2CONH$), 66.0 (3C; Ar-OCH_2), 80.7 (9C; $C(CH_3)_3$), 86.7 (3C; ArC-H), 160.3 (3C; ArC-O), 166.3, 167.0 (6C; $OCCH_2CO$), 171.3 (3C; CONH), 173.0 (9C; $COOC(CH_3)_3$) ppm; MS (FAB, NBA): m/z: 1462 $[M-9\,C_4H_8]^+$, 1967 $[M]^+$, 1990 $[M+Na]^+$; elemental analysis (%) calcd for $C_{99}H_{159}N_3O_{36}$: C60.44, H 8.15, N 2.14; found C 60.52, H 8.27, N 2.18.

***e,e,e*-Trisadduct 31**: Trisadduct **30** (75 mg, 28.0 µmol) was dissolved in CH_2Cl_2 (10 mL) and formic acid (5 mL) was added. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC analysis. The solvent was removed under vacuum and traces of formic acid were removed by repeated coevaporation with toluene and THF. Reprecipitation from THF with pentane gave **31** as a red solid (54 mg, 24.8 µmol, 95%). ^{1}H NMR (400 MHz, RT, [D_8]THF): $\delta = 1.99$ (m, 24H; CH_2CH_2COOH; CH_2CH_2CONH), 2.23 (m, 24H; CH_2COOH; CH_2CONH), 3.9–4.7 (m, 15H; Ar-OCH_2CH_2, $CH_2CH_2CH_2CONH$), 4.82 (m, 3H; Ar-OCH_2CH_2), 6.59 (m, 6H; Ar-H; NH), 10.86 (s, br, 9H; COOH) ppm; ^{13}C NMR (100.5 MHz, RT, [D_8]THF): $\delta = 23.6$ (3C; CH_2CH_2CONH), 30.4 (9C; CH_2CH_2COOH), 30.7 (9C; CH_2COOH), 32.9 (3C; CH_2CONH), 54.6 (3C; $OCCCO$), 57.9 (3C; $CONHC$), 64.1 (3C; Ar-OCH_2CH_2), 98.9 (3C; ArC-H), 141.6, 143.0, 144.3, 144.9, 146.1, 146.6, 147.1, 147.1, 147.5, 147.5, 147.8, 148.0 (54C; C_{60} sp^2), 159.0 (3C; ArC-O), 161.9, 162.2 (6C; $OCCCO$), 171.8 (3C; CONH), 175.0 (9C; COOH) ppm; MS (MALDI-TOF, SIN): m/z: 2178 $[M+H]^+$; UV/Vis (DMSO): $\lambda_{max} = 281$, 305 (sh), 380 (sh), 481, 565 (sh) nm.

***e,e,e*-Trisadduct 32**: Trisadduct **15** (65 mg, 47.9 µmol) was dissolved in CH_2Cl_2 (10 mL) and 33% HBr in H_3CCOOH (5 mL) was added. The reaction mixture was stirred at ambient temperature and the progress of the reaction was monitored by TLC analysis. After complete conversion,

CH_2Cl_2 (15 mL) was added and the organic phase was washed with water (3×10 mL). After drying over $MgSO_4$ and removal of the solvent, the residue was dissolved in a small amount of THF and the insoluble by-product 1,3,5-trisbromobenzene was removed by filtration. Reprecipitation from THF with pentane gave **32** as a red solid (51.2 mg, 41.2 μmol, 86%). ^{1}H NMR (400 MHz, RT, [D$_8$]THF): δ=3.03 (s, br, 3H; COOH+H_2O), 3.91 (s, 9H; OCH_3), 4.76 (m, 6H; CH_2) ppm; ^{13}C NMR (100.5 MHz, RT, [D$_8$]THF): δ=46.4 (3C; OC*C*CO), 54.2 (3C; OCH_3), 63.2 (3C; CH_2), 71.6, 72.4 (6C; C_{60} sp^3), 142.0, 142.9, 143.0, 143.3, 144.7, 144.8, 145.3, 146.5, 146.7, 146.9, 147.4, 147.7, 147.8, 148.0, 149.2 (54C; C_{60} sp^2), 163.4, 164.0 (6C; O*C*CCO), 168.6 (COOH) ppm; MS (MALDI-TOF, DHB): *m/z*: 1245 $[M+3H]^+$, 1268 $[M+3H+Na]^+$, 1291 $[M+3H+2Na]^+$; UV/Vis (CH_2Cl_2): λ_{max}=250, 285, 308 (sh), 380 (sh), 480, 570 (sh) nm.

***e*,*e*,*e*-Trisadduct 33**: Trisadduct **14** (100 mg, 76.0 μmol) was dissolved in $CHCl_3$ (20 mL) and mixed with a 48% HBr in water (20 mL). After adding hexadecyltrimethylammonium bromide (85.0 mg), the biphasic system was heated to reflux for several days. The progress of the reaction was monitored by TLC analysis. After quantitative conversion, $CHCl_3$ (30 mL) and water (30 mL) were added. After separation of the phases, the organic layer was extracted with a saturated aqueous $NaHCO_3$ solution (2×30 mL) and water (30 mL). After drying over $MgSO_4$ and removal of the solvent, the residue was purified by flash column chromatography (SiO_2, toluene/ethyl acetate 9:1). Reprecipitation from $CHCl_3$ with pentane gave **33** as a red solid (81.2 mg, 58.5 μmol, 77%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): δ=3.54 (t, ^3J=5.9 Hz, 6H; CH_2Br), 3.94 (s, 9H; OCH_3), 4.57 (t, ^3J=5.9 Hz, 6H; CH_2CH$_2$Br) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): δ=27.7 (3C; CH_2Br), 52.3 (3C; OC*C*CO), 53.9 (3C; OCH_3), 66.0 (3C; *C*H$_2$CH$_2$Br), 69.8, 70.5 (6C; C_{60} sp^3), 141.0, 141.5, 141.9, 142.5, 143.5, 144.4, 144.7, 145.0, 145.4, 145.7, 146.0, 146.3, 146.5, 146.6, 146.7, 146.7, 146.9, 147.0 (54C; C_{60} sp^2), 162.4, 162.9 (O*C*C*O*) ppm; MS (MALDI-TOF, DCTB): *m/z*: 1391 $[M+H]^+$, 1602 $[M+Na]^+$; UV/Vis (CH_2Cl_2): λ_{max}=251, 280, 306 (sh), 380 (sh), 480, 565 (sh) nm.

***e*,*e*,*e*-Trisadduct 34**: Trisadduct **14** (208 mg, 158 μmol, 1 equiv) was dissolved in dry CH_2Cl_2 (100 mL) under nitrogen and cooled to 0°C. Afterwards, a solution of BCl_3 (480 μL 1 M solution in hexane, 480 μmol, 3 equiv) in CH_2Cl_2 (20 mL) was added dropwise over 20–30 min. The progress of deprotection was monitored by TLC analysis. After completion of the reaction, a saturated aqueous $NaHCO_3$ solution (50 mL) was added and the biphasic mixture was stirred for 30 min. The organic layer was separated, washed with water (50 mL), and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5). Reprecipitation from $CHCl_3$ with pentane gave **34** as a red solid (142 mg, 118 μmol, 75%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): δ=2.64 (s, br, 3H; OH), 3.83 (m, 6H; CH_2OH), 3.95 (s, 9H; OCH_3), 4.29 (m, 3H; CH_2CH$_2$OH), 4.54 (m, 3H; CH_2CH$_2$OH) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): δ=52.6 (3C; OC*C*CO), 53.9 (3C; OCH_3), 60.5 (3C; CH_2OH), 68.1 (3C; *C*H$_2$CH$_2$OH), 69.9, 70.6 (6C; C_{60} sp^3), 141.0, 141.9, 142.2, 142.3, 142.9, 143.3, 144.2, 144.3, 144.3, 145.7, 146.0, 146.3, 146.4, 146.4, 146.6, 146.7, 146.7, 146.8 (54C; C_{60} sp^2), 163.3, 163.8 (6C; O*C*CCO) ppm; MS (FAB, NBA): *m/z*: 720 $[C_{60}]^+$, 1201 $[M]^+$; UV/Vis (CH_2Cl_2): λ_{max}=251, 282, 305 (sh), 380 (sh), 480, 565 (sh) nm.

***e*,*e*,*e*-Trisadduct 35**: Trisadduct **34** (173 mg, 144 μmol, 1 equiv) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to 0°C. Subsequently, nonanoyl chloride (116 μL, 650 μmol, 4.5 equiv) and dry pyridine (46 μL, 650 μmol, 4.5 equiv) were added. The reaction mixture was slowly warmed up and stirred for three days at room temperature. The progress of the reaction was monitored by TLC analysis and in case of incomplete acylation, additional nonanoyl chloride and pyridine were added. After evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1) to give **35** as a red solid (220 mg, 135 μmol, 94%). ^{1}H NMR (400 MHz, RT, $CDCl_3$): δ=0.87 (t, ^3J=6.9 Hz, 9H; CH_2CH_3), 1.26 (m, 30H; CH_2), 1.59 (m, $OOCCH_2CH_2$), 2.29 (t, ^3J=7.6 Hz, 6H; $OOCCH_2CH_2$), 3.93 (s, 9H; OCH_3), 4.32 (t, ^3J=4.7 Hz, 6H; $COOCH_2CH_2O$), 4.44 (m, 3H; $COOCH_2CH_2O$), 4.50 (m, 3H; $COOCH_2CH_2O$) ppm; ^{13}C NMR (100.5 MHz, RT, $CDCl_3$): δ=14.0 (CH_2CH_3), 22.6, 24.7, 29.1, 29.2, 31.7, 33.9 (21C; CH_2), 52.3 (3C; OC*C*CO), 53.7 (3C; OCH_3), 61.2 (3C; $COOCH_2CH_2O$), 64.5 (3C; $COOCH_2CH_2O$), 69.8, 70.6 (6C; C_{60} sp^3), 141.0, 141.6, 141.9, 142.6, 142.7, 143.5, 144.4, 144.9, 145.1, 145.4, 145.7, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.1 (54C; C_{60} sp^2), 163.1, 163.6 (O*C*C*O*), 173.6 (3C; $OOCCH_2CH_2O$) ppm; MS (MALDI-TOF, SIN): *m/z*: 1622 $[M]^+$, 1645 $[M+Na]^+$; UV/Vis (CH_2Cl_2): λ_{max}=250, 285, 305 (sh), 380 (sh), 480, 565 (sh) nm.

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