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Regioselectivity in Tether-Directed Remote Functionalization – The Addition of a Cyclotriveratrylene-Based Trimalonate to C_{60} Revisited

Agnieszka Kraszewska,[a] Pablo Rivera-Fuentes,[a] Gwénaël Rapenne,[b] Jeanne Crassous,[c] Ana G. Petrovic,[d] José Lorenzo Alonso-Gómez,[d] Elisa Huerta,[e] François Diederich,[a] and Carlo Thilgen*[a]

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The Bingel addition of a trimalonate derived from a chiral, cyclotriveratrylene (CTV)-based tripodal tether to C_{60} was reinvestigated. The present use of enantiomerically pure (*P*)- and (*M*)-configured CTV units in the tether allowed the isolation of a total of four enantiomerically pure C_3-symmetric tris-adducts of [60]fullerene (two from each CTV enantiomer). With the support of NMR and UV/Vis spectroscopy, electronic (ECD) and vibrational (VCD) circular dichroism spectroscopic analysis (comparison to ECD data of known compounds and to ECD and VCD data calculated by TD-DFT or ZINDO methods as part of this work) allowed a definitive determination of the following structural features for all four CTV-C_{60} conjugates: (i) The constitution of the fullerene addition pattern, (ii) its absolute configuration, and (iii) the absolute configuration of the CTV moiety. It is concluded that the triple Bingel addition proceeded with complete regioselectivity and negligible diastereoselectivity, affording only the *trans*-3,*trans*-3,*trans*-3 fullerene addition pattern in both enantiomeric forms, whereas the previously reported *e*,*e*,*e* motif was not formed.

Introduction

The chirality of fullerenes and fullerene derivatives has remained a fascinating topic since the isolation of the first chiral fullerene, C_{76}, in 1991.[1–3] Besides inherently chiral pristine carbon cages such as C_{76}-D_2,[3] C_{78}(1)-D_3,[4] or C_{84}(22)-D_2,[5] there are chiral derivatives of achiral parent fullerenes resulting from the relative arrangement of addends on the fullerene surface. The corresponding fullerene functionalization patterns are either inherently chiral (the chirality of such fullerene derivatives does not depend on identity/non-identity relationships between addends) or non-inherently chiral (a prerequisite for chirality, in this case, is the non-identity between two addends at least). Chiral derivatives of achiral parent fullerenes may also have their stereogenic element(s) located exclusively in the addend(s). Such stereogenic elements can be combined with a chiral functionalization pattern of an achiral or a chiral parent fullerene.[1,2,6–9]

An undirected threefold addition to 6,6-bonds of C_{60} can, in principle, yield 46 regioisomeric products, many of which are chiral. Although some of the possible tris-adducts are generally favored in a given reaction,[10–12] product mixtures often contain a considerable number of regioisomers that are difficult to separate.[13] Cyclopropanation of regioisomerically pure *trans*-3 and *e* bis-adducts preferentially afforded racemic tris-adducts with the inherently chiral *trans*-3,*trans*-3,*trans*-3 and *e*,*e*,*e* functionalization patterns, respectively.[14] Their resolution was achieved by high-performance liquid chromatography (HPLC) with a chiral stationary phase (CSP).[15] Stepwise cyclopropanation of C_{60} with chiral and enantiopure diisoxazolinylmethanes, partly in combination with malonates, provided diastereoisomeric tris-adducts of C_{60} with enantiomeric functionalization patterns, which were separated and chiroptically investigated.[11,12]

A very efficient strategy for the selective synthesis of fullerene bis- and multi-adducts with a defined functionalization pattern is the tether-directed remote functionalization,[16–18] which was first applied to fullerene chemistry by Diederich and co-workers.[19] The generation of specific fullerene functionalization patterns results from the size and the geometry of the tether that interconnects the individual reactive groups.

Various effective tethers have been developed that allow all the bis-functionalization patterns of C_{60} to be targeted, making the desired products accessible with high regioselectivity and, in certain cases, high stereoselectivity.[17] Good regioselectivities were achieved in Bingel-type tether-di-

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[a] Laboratorium für Organische Chemie, ETH Zürich,
Hönggerberg, HCI, 8093 Zürich, Switzerland
Fax: +41-44-6321109
E-mail: thilgen@org.chem.ethz.ch
[b] CNRS, CEMES, BP 94347,
29 rue J. Marvig, 31055 Toulouse, France
[c] Sciences Chimiques de Rennes, UMR CNRS 6226, Université Rennes 1,
Campus de Beaulieu, 35042 Rennes, France
[d] Department of Chemistry, Columbia University,
New York, NY 10027, USA
[e] Institute of Chemical Research of Catalonia (ICIQ),
Av. Països Catalans 16, 43007 Tarragona, Spain

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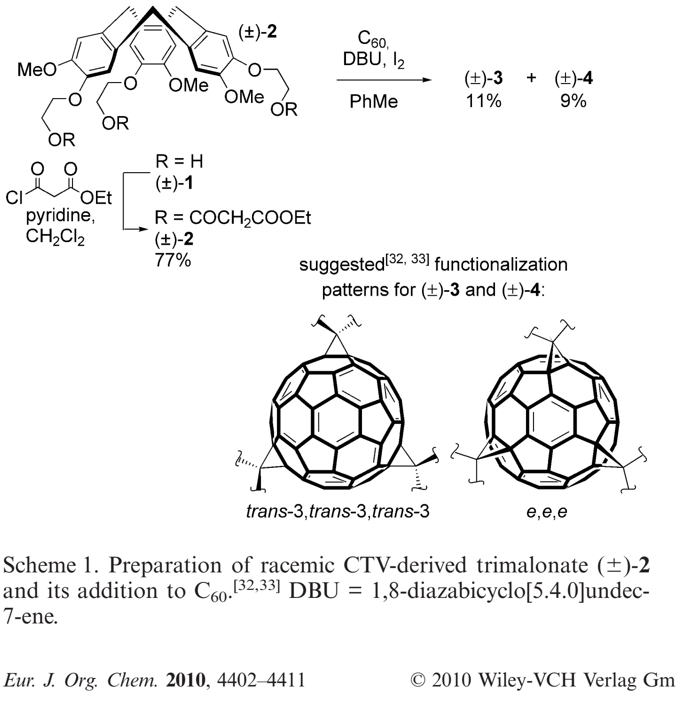
rected remote functionalizations by using spacers derived from xylene,[20,21] porphyrins,[22] or crown ethers.[23,24] For bis-adducts of C_{60} with an inherently chiral functionalization pattern (*cis*-3, *trans*-3, and *trans*-2), excellent stereoselectivities were obtained with optically pure dimalonates including tethers derived from threitol[20,21] or the Tröger base.[25,26] The latter also performed very well in the directed multi-functionalization of [70]fullerene.[27]

Tethers that can be used for directed triple additions to fullerenes remain rare. The first conjugate including three reactive groups was attached stepwise to C_{60}. It had a linear overall geometry and initial anchoring of a central malonate unit was followed by two Diels–Alder reactions at the termini, yielding a tris-adduct with the C_{2v}-symmetrical *e*,*e*,*trans*-1 addition pattern.[19] Racemic, C_3-symmetrical adducts of C_{60} with the inherently chiral *e*,*e*,*e* addition pattern were obtained by Hirsch and co-workers through addition of achiral tripodal conjugates having trimalonates linked to a benzene-1,3,5-trimethylene or a benzene-1,3,5-trioxy core.[28,29] Addition of the macromonocycle tris(octamethylene) cyclotrimalonate to C_{60} provided the C_3-symmetrical *e*,*e*,*e* tris-adduct in high yields, and the achiral C_{3v}-symmetrical *trans*-4,*trans*-4,*trans*-4 derivative as a minor product.[30] A chiral cyclotrimalonate with enantiomerically pure spacer units derived from D-mannitol afforded C_3-symmetrical adducts in a 4:1 ratio as separable diastereoisomers with enantiomeric *e*,*e*,*e* fullerene addition patterns.[31]

The tripodal tether developed by Diederich and co-workers for the tris-functionalization of C_{60} is based on the cyclotriveratrylene (CTV) scaffold (Scheme 1). The corresponding reactant is C_3-symmetrical and has three pendent "arms" with malonates as reactive groups at their ends. In 1999, the CTV-derived racemic triol (±)-**1** was transformed into the corresponding trimalonate (±)-**2**, which was added to C_{60} to afford two racemic products, (±)-**3** and (±)-**4** (Scheme 1).[32,33]



Scheme 1. Preparation of racemic CTV-derived trimalonate (±)-**2** and its addition to C_{60}.[32,33] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Both products showed C_3 symmetry, as reflected by the number of signals in their ^{13}C NMR spectra. Accordingly, their fullerene addition patterns had to have threefold rotational symmetry and, after exclusion of the sterically overcrowded *cis*-1,*cis*-1,*cis*-1 motif, (±)-**3** and (±)-**4** were assigned, at the time, as racemic *trans*-3,*trans*-3,*trans*-3 and *e*,*e*,*e* regioisomers, respectively (Scheme 1). The addends of the *trans*-3,*trans*-3,*trans*-3 pattern are arranged on an equatorial belt, dividing the fullerene sphere into equal halves, whereas they lie on a "polar circle" in the product with the *e*,*e*,*e* pattern.

This assignment[32,33] appeared to be further supported by the comparison of the UV/Vis spectra and the colors of the two compounds with data reported for known tris-adducts, as well as by the ^{13}C NMR chemical shifts of the cyclopropane carbon atoms.[14]

Appraisal of an alternative assignment for (±)-**3** and (±)-**4** as diastereoisomeric racemic mixtures originating from the four possible combinations of: (i) the enantiomers [(*P*) or (*M*)][34] of the conformationally chiral CTV unit, and (ii) the enantiomeric forms ($^{\mathrm{f,s}}C$ or $^{\mathrm{f,s}}A$) of one and the same inherently chiral fullerene functionalization pattern (either *trans*-3,*trans*-3,*trans*-3 or *e*,*e*,*e*) would have required the use of an enantiomerically pure CTV-malonate conjugate [either (+)-**2** or (–)-**2**], which was not available at the time. In the absence of chiroptical information, analysis of the experimental data of racemic compounds alone could not indisputably determine whether the two isolated products were regioisomers or diastereoisomers. For this reason, we repeated the work with the enantiomerically pure CTV-derived trimalonates (+)-**2** and (–)-**2** to obtain optically pure tris-adducts and to study them by electronic (ECD) and vibrational (VCD) circular dichroism spectroscopy, which are important tools for the determination of the absolute configuration and also of the fullerene functionalization pattern.

Resolution of the CTV-Derived Tether Moiety and Synthesis of the CTV-C_{60} Conjugates

The racemic CTV-derived triol (±)-**1**[35] (Scheme 1) was separated into the enantiomers (–)-**1** and (+)-**1** by HPLC with an (*S*,*S*)-Whelk-*O*1 chiral stationary phase (Regis; hexane/MeOH, 1:9 as eluent; Figure 1).

The enantiomerically pure triols (–)-**1** and (+)-**1** were transformed into the corresponding CTV-derived trimalonates (–)-**2** and (+)-**2**, respectively, by esterification with methyl 3-chloro-3-oxopropanoate at room temperature (Scheme 1).[33] It is known that the barrier for enantiomer interconversion of chiral CTV derivatives (conformational enantiomers) is in the order of 26–27 kcal mol^{-1}, and appreciable racemization may already occur at ambient temperature.[36,37] To avoid racemization of trimalonates (–)-**2** and (+)-**2** in the course of the Bingel reaction with C_{60}, the enantiomer interconversion process was studied beforehand by ECD spectroscopy (see the Supporting Information). The decrease in intensity of a significant Cotton effect at

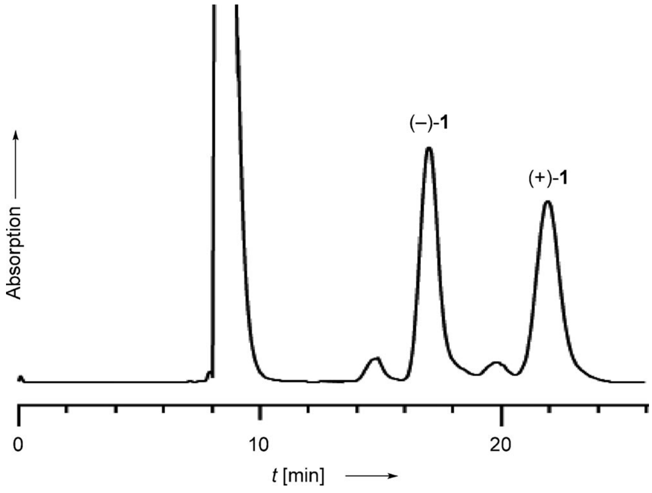
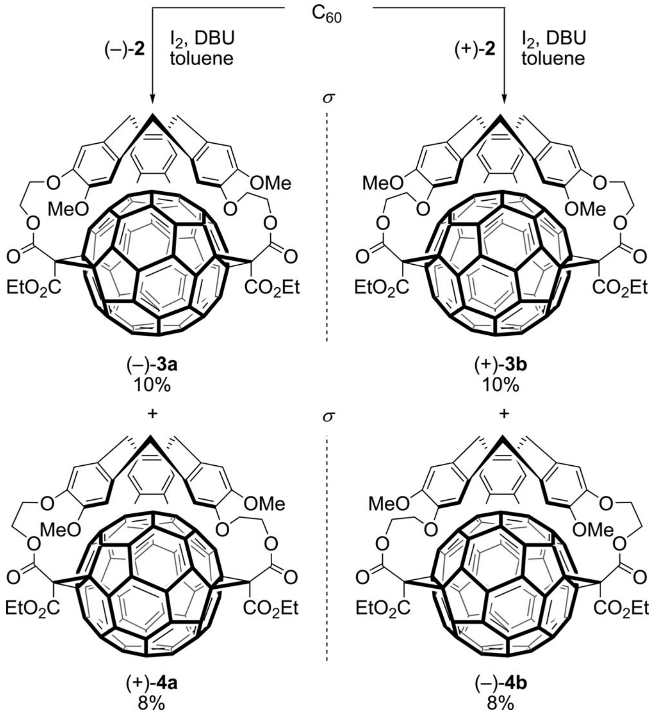


Figure 1. Resolution of (±)-**1** by HPLC on an (*S*,*S*)-Whelk-*O*1 CSP (Regis). Column dimensions: 21.1 × 250 mm; injection: 0.2 mL of a solution of (±)-**1** in DMF/methanol (1:1, *c* = 5 mg mL^{-1}); flow rate: 9 mL min^{-1} (hexane/methanol, 1:9); UV/Vis detection at 238 nm. Retention times: 17.03 min for (–)-**1**, 21.95 min for (+)-**1**, 8.4 min for DMF, 14.80 and 19.80 min for isomers of different geometry (not isolated).

275 nm was used to determine the rate constant k_1 of enantiomer interconversion at different temperatures. From these data, the half-lifetimes were calculated, showing that expeditious handling of the CTV-derived trimalonates (–)-**2** and (+)-**2** ($t_{1/2} \approx 8$ d at 30 °C) is possible at room temperature without significant racemization.

The CTV-malonate conjugates (–)-**2** and (+)-**2** were individually subjected to triple Bingel addition with C$_{60}$ (Scheme 2). In each case, the reaction afforded two products [(–)-**2** + C$_{60}$ → (–)-**3a** + (+)-**4a**; (+)-**2** + C$_{60}$ → (+)-**3b** + (–)-**4b**], which could be separated on unmodified silica gel.



Scheme 2. Two product mixtures, (–)-**3a** + (+)-**4a** and (+)-**3b** + (–)-**4b**, obtained by addition of (–)-**2** and (+)-**2**, respectively, to C$_{60}$.

The ^{1}H and ^{13}C NMR spectra of (–)-**3a** and (+)-**3b** on one hand, and those of (+)-**4a** and (–)-**4b** on the other hand, are in agreement with the data previously obtained for products (±)-**3** and (±)-**4**, respectively (Scheme 1).[32,33] Furthermore, the UV/Vis spectra of all four adducts were identical and did not exhibit the slight difference reported previously (see the Supporting Information).[32,33]

Complete Structure Elucidation: Determination of the Fullerene Functionalization Pattern and the Absolute Configurations of CTV-C$_{60}$ Conjugates (–)-3a, (+)-3b, (+)-4a, and (–)-4b

Tris-adducts (–)-**3a**, (+)-**3b**, (+)-**4a**, and (–)-**4b** have three structural features that can, in principle, be assigned by ECD spectroscopy, i.e., the configuration of the CTV moiety, the functionalization pattern of the fullerene, and their absolute configuration (Figure 2).

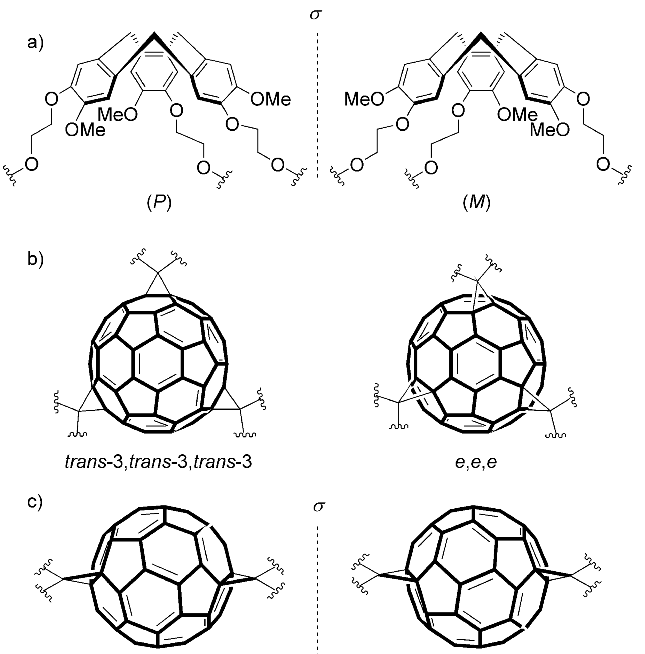
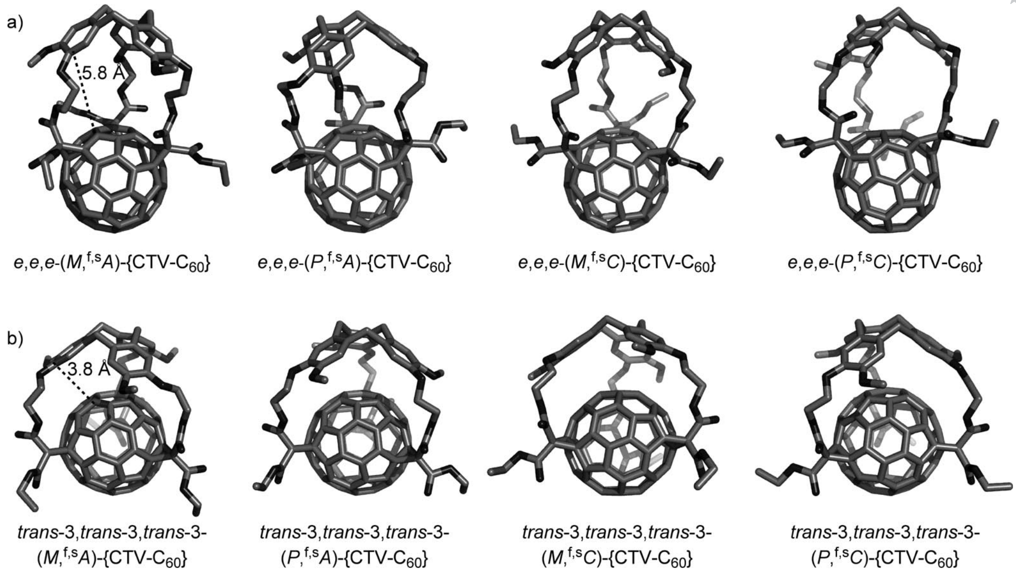


Figure 2. Three structural features relevant to the constitutional and configurational characterization of the obtained tris-adducts of C$_{60}$ [(–)-**3a**, (+)-**3b**, (+)-**4a**, and (–)-**4b**]: (a) configuration of the CTV moiety [(*P*) or (*M*)]; (b) fullerene functionalization pattern (*trans*-3,*trans*-3,*trans*-3 or *e*,*e*,*e*), and (c) configuration of the fullerene functionalization pattern [($^{\mathrm{f,s}}A$) or ($^{\mathrm{f,s}}C$)], shown here for the *trans*-3,*trans*-3,*trans*-3 functionalization pattern only. The cyclopropane rings can be considered as angled blades of a propeller, the shaft of which coincides with the C_3 axis of the molecule. As expected for mirror images, the inclination angle of the blades is positive for one enantiomer and negative for the other.

The possible combination of two chiral functionalization patterns (*trans*-3,*trans*-3,*trans*-3 or *e*,*e*,*e*) and the chiral CTV moiety leads to a total of eight ($2^3 = 8$) isomeric CTV-C$_{60}$



e,e,e-(M,$^{f,s}A$)-{CTV-C_{60}} *e,e,e*-(P,$^{f,s}A$)-{CTV-C_{60}} *e,e,e*-(M,$^{f,s}C$)-{CTV-C_{60}} *e,e,e*-(P,$^{f,s}C$)-{CTV-C_{60}}

trans-3,*trans*-3,*trans*-3-(M,$^{f,s}A$)-{CTV-C_{60}} *trans*-3,*trans*-3,*trans*-3-(P,$^{f,s}A$)-{CTV-C_{60}} *trans*-3,*trans*-3,*trans*-3-(M,$^{f,s}C$)-{CTV-C_{60}} *trans*-3,*trans*-3,*trans*-3-(P,$^{f,s}C$)-{CTV-C_{60}}

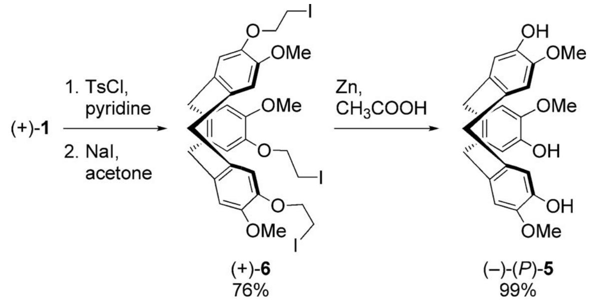
Figure 3. Structural candidates for the four isolated CTV-C_{60} conjugates ({CTV-C_{60}}). (a) Tris-adducts with an *e,e,e* functionalization pattern; (b) tris-adducts with a *trans*-3,*trans*-3,*trans*-3 functionalization pattern. All structures are optimized at the AM1 level of theory. The distances between CTV-C_{ar} and $C_{fullerene}$ are longer than 5.8 Å for the *e,e,e* tris-adducts and around 3.8 Å for the *trans*-3,*trans*-3,*trans*-3 tris-adducts.

conjugates (Figure 3), which have to be assessed as candidates for the four isolated compounds (–)-**3a**, (+)-**3b**, (+)-**4a**, and (–)-**4b**.

The contacts between the electron-rich CTV aromatic rings and the electron-deficient fullerene surface are of particular interest. The closest CTV-$C_{ar}\cdots C_{fullerene}$ distance in the *trans*-3,*trans*-3,*trans*-3 adduct is 3.8 Å, whereas it is much longer (5.8 Å) in the calculated structure of the *e,e,e* tris-adduct (Figure 3).

Configuration of the CTV Moiety

For the determination of the absolute configuration of the CTV unit, CTV-derived triethanol (+)-**1** (cf. Scheme 1) was de-hydroxyethylated to cyclotriguaiacylene [(–)-**5**], the absolute configuration of which is known (Scheme 3).[38] Great care was taken in each step to keep the temperature below 30 °C to avoid discernible racemization of the enantiomerically pure CTV derivatives.



Scheme 3. Chemical correlation between the absolute configurations of (+)-**1** (cf. Scheme 1) and (–)-**5** by transformation of CTV-derived triethanol (+)-**1** into cyclotriguaiacylene (–)-**5**, which is known as (–)-(P)-**5**.[38]

Because its direct iodination was not successful, CTV-derived triethanol (+)-**1** was first transformed into the corresponding tritosylate, which was then subjected to nucleophilic substitution with NaI, affording CTV-derived triiodide (+)-**6**.[39] Cleavage of the iodoethyl groups with zinc in acetic acid yielded cyclotriguaiacylene (–)-**5**,[34] which, according to Collet and co-workers, has the absolute configuration (P).[38] By assuming a retention of configuration in all steps (Scheme 3) and by taking into account a change in the Cahn–Ingold–Prelog (CIP) priorities[40,41] of the substituents on transition from (+)-**6** to (–)-(P)-**5**, the absolute configuration of the starting material (+)-**1** could be assigned as (M) and, accordingly, (–)-**1** has the absolute configuration (P). Based on the chemical correlation between (+)-**2** and (+)-**1** on one hand, and between (–)-**2** and (–)-**1** on the other hand (cf. Scheme 1), the absolute configurations of the trimalonates added to C_{60} were thereby established as (+)-(M)-**2** and (–)-(P)-**2**.

This assignment was confirmed by comparison of the experimental ECD spectra of (+)-**2** with data calculated for (M)-**2**. Due to the complex conformational space of the CTV-derived trimalonate, a conformational search for (M)-**2** was performed by using mixed-torsional/low-mode conformational sampling with the force field MMFF implemented in MacroModel 9.5.[42] The conformational search was ensued by optimization of all non-redundant conformers at the B3LYP/6-31G(d)//AM1 level of theory. This refinement yielded three structures within an energy window of 3 kcal mol^{-1} above the global minimum (Figure 4). Even when many conformers might have been overlooked in this search, the conformation of the malonate chains is not expected to contribute significantly to the chiroptical properties in the measured range.

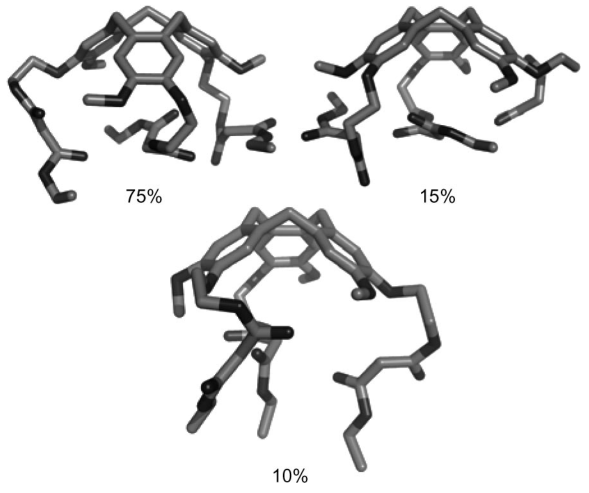


Figure 4. Low-energy conformers of (*M*)-**2** and their relative populations in a Boltzmann ensemble.

The ECD spectra of these conformers were calculated by using time-dependent density functional theory (TD-DFT) with Gaussian 03.[43] The spectrum of (*M*)-**2** was simulated as the Boltzmann-weighted sum of the individual spectra of the three conformers. The resulting spectrum was redshifted by 0.25 eV to facilitate the comparison with the experimental data of (+)-**2** (Figure 5).

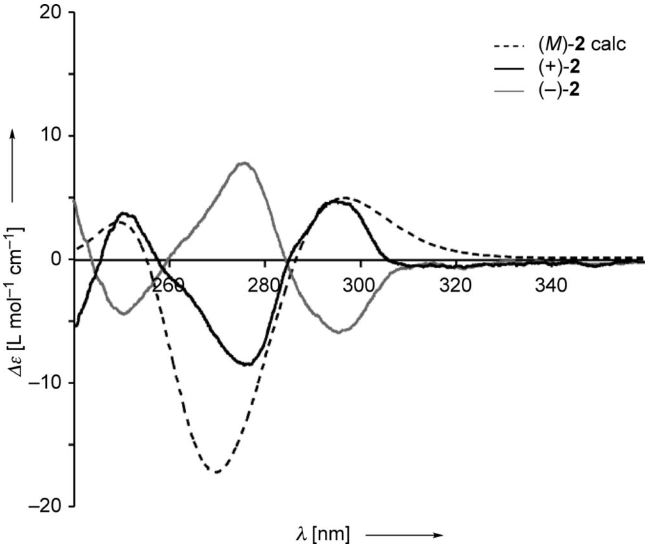


Figure 5. Experimental ECD spectra (CH_2Cl_2) of CTV-derived trimalonates (+)-**2** (black solid line) and (–)-**2** (gray solid line), and the spectrum calculated for (*M*)-**2** [TD-B3LYP/6-31G(d) (black dashed line); for details see the Supporting Information].

In accord with the chemical correlation method (see above), a comparison of the calculated spectrum to the experimental traces suggests that the absolute configuration of the CTV-derived trimalonates is (+)-(*M*)-**2** and (–)-(*P*)-**2**. This assignment is in agreement with that of previously reported chiral CTV derivatives, the absolute configuration of which was assigned by using the exciton couplet model and the concept of spectroscopic moments (SM).[44] Even when the SM of the malonate side chains of **2** is not known, it can be expected to be smaller than that of the methoxy group, due to conformational effects,[45] allowing a comparison between our system and those previously assigned.[46]

Vibrational circular dichroism (VCD) spectroscopy was used as another cross-validation method for the assignment of the absolute configuration of the CTV moieties of (+)-**2** and (–)-**2**.[47,48] The VCD spectrum of (*M*)-**2** was simulated as the Boltzmann-weighted sum of the individual spectra of the three conformers found above (Figure 4).

Seven Cotton effects were used to compare and correlate experimental (0.042 M solution in CCl_4) with computed VCD spectra (Figure 6). The aggregation of the CTV-derived trimalonate **2** at this concentration was studied by ^{1}H NMR and IR spectroscopy (see the Supporting Information). Cotton effects A to G are associated with vibrations that are nearly independent of the conformation of the malonate side chains (see the Supporting Information) and are, therefore, useful for the assignment of the absolute configuration of the CTV moiety. The signs of the calculated Cotton effects for the conformational ensemble of (*M*)-**2** match those in the spectrum measured for (+)-**2**. Therefore, the absolute configuration determined by VCD is in agreement with that assigned by chemical correlation and by ECD (see above).

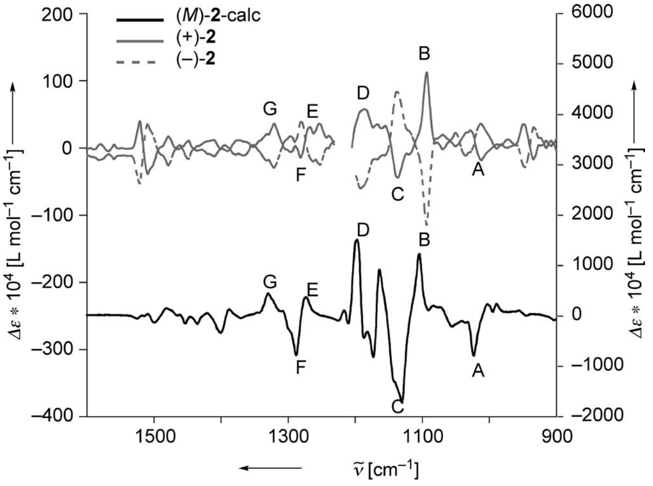


Figure 6. Experimental VCD spectra (0.042 M, CCl_4) of (+)-**2** (gray solid line) and (–)-**2** (gray dashed line), and the VCD trace calculated for (*M*)-**2** (black solid line). The calculated frequencies were scaled by the basis-set-specific factor 0.97. The region between 1200 and 1240 cm^{-1} is omitted due to intense solvent (CCl_4) absorption. IR spectra and further details can be found in the Supporting Information.

Assignment of the Fullerene Functionalization Pattern and the Absolute Configurations of Tris-Adducts (–)-3a, (+)-3b, (+)-4a, and (–)-4b

The four isolated tris-adducts have pairwise mirror-image-shaped ECD spectra (Figure 7), arising from two pairs of enantiomers [(–)-(*P*)-**3a**/(+)-(*M*)-**3b** and (+)-(*P*)-**4a**/(–)-

(*M*)-**4b**], as expected from the Bingel addition to C_{60} of two enantiomeric trimalonates [(–)-(*P*)-**2** and (+)-(*M*)-**2**]. Furthermore, the spectra of adducts (–)-(*P*)-**3a** and (+)-(*P*)-**4a**, as well as those of (+)-(*M*)-**3b** and (–)-(*M*)-**4b**, are also nearly mirror-image-shaped, whereas the ECD traces are virtually identical for (–)-(*P*)-**3a** and (–)-(*M*)-**4b** on one hand and (+)-(*M*)-**3b** and (+)-(*P*)-**4a** on the other, showing only slight differences between 300 and 350 nm. This is indicative of an enantiomeric relationship between the residual fullerene chromophores (main chiroptical contributors) in pairs of tris-adducts resulting from addition to C_{60} of the same enantiomer of trimalonate **2** [(–)-(*P*)-**2** → (–)-(*P*)-**3a** + (+)-(*P*)-**4a**, and (+)-(*M*)-**2** → (+)-(*M*)-**3b** + (–)-(*M*)-**4b**]. In other words, each of these product pairs is composed of two diastereoisomers – not regioisomers as previously reported. The diastereoisomers of each pair have identical CTV moieties and enantiomeric fullerene functionalization patterns. The 5:4 ratio, in which they were isolated (Scheme 2), leads to the conclusion that the tether-directed remote functionalization of C_{60} by trimalonates (–)-(*P*)-**2** or (+)-(*M*)-**2** takes place with almost no diastereoselectivity.

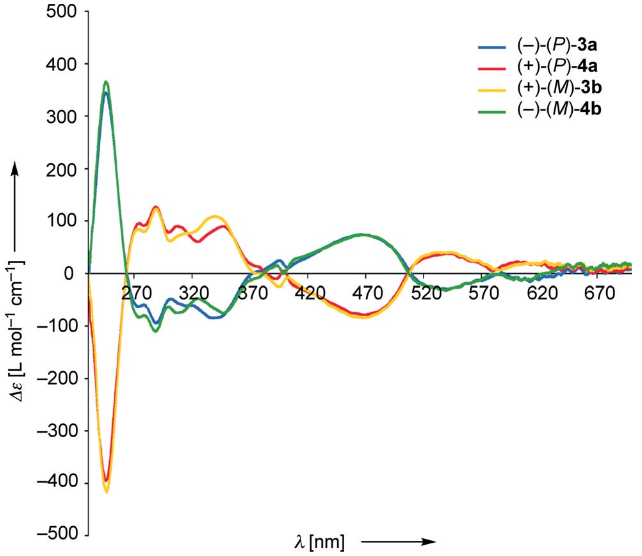


Figure 7. ECD spectra (CH_2Cl_2) of the four isolated tris-adducts (–)-(*P*)-**3a**, (+)-(*P*)-**4a**, (+)-(*M*)-**3b**, and (–)-(*M*)-**4b**, resulting from addition of enantiopure CTV-derived trimalonates (–)-(*P*)-**2** and (+)-(*M*)-**2** to C_{60}.

The regioselectivity of the triple Bingel addition (formation of the *trans*-3,*trans*-3,*trans*-3 vs. the *e*,*e*,*e* fullerene functionalization pattern) can be ascertained by comparing the ECD data of tris-adducts **3a/b** and **4a/b** to those of previously reported adducts, as well as by quantum mechanical calculations. According to Hirsch and co-workers,[11,12] the fullerene addition pattern can easily be recognized by typical fingerprints in the ECD spectrum. The Cotton effects of the four CTV-C_{60} conjugates (**3a/b**, **4a/b**) in the region between 650 and 400 nm exactly match those ascribed to a *trans*-3,*trans*-3,*trans*-3 functionalization pattern.[12,15] Because the fingerprints reported by Grimme, Hirsch, and coworkers[12] are practically independent of the nature of the tether, it is clear that all four products (**3a/b**, **4a/b**) isolated in the present work are stereoisomers with the *trans*-3,*trans*-3,*trans*-3 functionalization pattern. Calculations using the semi-empirical ZINDO method (for details see the Supporting Information) nicely reproduce the intense bisignated Cotton effects in the region between 400 and 600 nm, thereby confirming the *trans*-3,*trans*-3,*trans*-3 fullerene addition pattern.

In addition to its *trans*-3,*trans*-3,*trans*-3 constitution, the configuration of the inherently chiral fullerene functionalization pattern [$({}^{\mathrm{f,s}}A)$ or $({}^{\mathrm{f,s}}C)$] could also be determined by comparing the calculated ECD spectra to the experimental traces of the CTV-C_{60} conjugates **3a/b** and **4a/b**. Computations were carried out for the *trans*-3,*trans*-3,*trans*-3 tris-adducts with the absolute configurations $(P,{}^{\mathrm{f,s}}A)$ and $(P,{}^{\mathrm{f,s}}C)$ (Figure 8; for the structures see Figures 3 and 9).

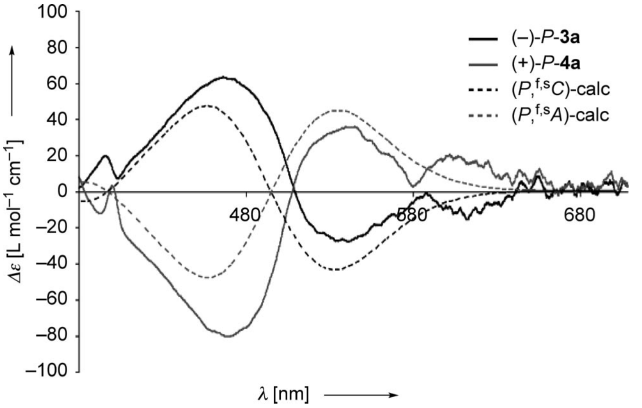


Figure 8. Experimental ECD spectra of tris-adducts (–)-(*P*)-**3a** and (+)-(*P*)-**4a** in the region between 600 and 400 nm (solid lines) and data calculated for *trans*-3,*trans*-3,*trans*-3 CTV-C_{60} conjugates with the absolute configurations $(P,{}^{\mathrm{f,s}}A)$ and $(P,{}^{\mathrm{f,s}}C)$ (dashed lines).

As can clearly be seen in Figure 8, the calculated spectra (dashed lines) show the expected Cotton effects in the region between 600 and 400 nm with opposite signs for opposite configurations [$({}^{\mathrm{f,s}}A)$ and $({}^{\mathrm{f,s}}C)$] of the fullerene addition pattern, despite the configuration of the CTV moiety being the same [(*P*)] in both cases. This reflects the fact the residual fullerene chromophore is the main chiroptical contributor in the CTV-C_{60} conjugates.

Comparison of the calculated and experimental ECD traces, in combination with all the above information, finally leads to a full structural assignment including both constitution and absolute configuration of all four tris-adducts, which can be denominated as (–)-$(P,{}^{\mathrm{f,s}}C)$-**3a**, (+)-$(M,{}^{\mathrm{f,s}}A)$-**3b**, (+)-$(P,{}^{\mathrm{f,s}}A)$-**4a**, and (–)-$(M,{}^{\mathrm{f,s}}C)$-**4b** (Figure 9).

Conclusions

The reinvestigation of the addition of a CTV-based trimalonate to C_{60} led to a structure reassignment of two of the four obtained products. In each case, ECD and VCD spectroscopy, in combination with calculated data, allowed a complete determination of the constitution and absolute

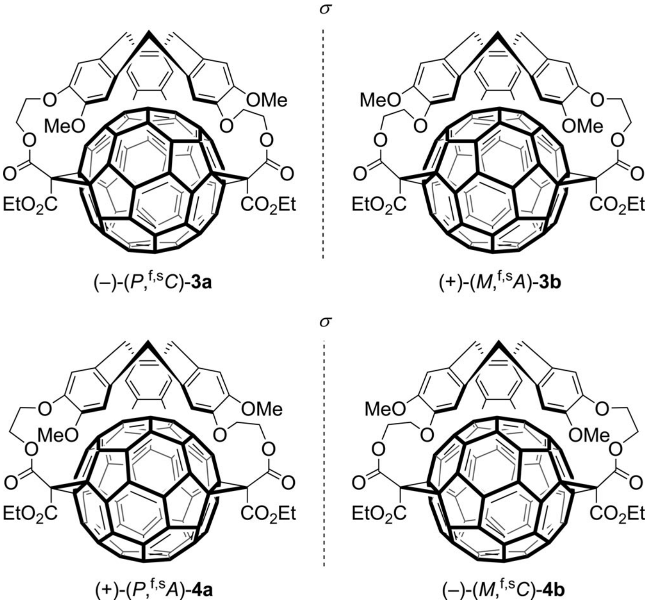


Figure 9. Full structural assignment of the four isolated CTV-C_{60} conjugates, including the fullerene addition pattern (*trans*-3,*trans*-3,*trans*-3 in all cases), its configuration [($^{\mathrm{f,s}}A$) or ($^{\mathrm{f,s}}C$)], and the configuration of the CTV moiety [(P) or (M)].

configuration of the fullerene functionalization pattern, in addition to the absolute configuration of the enantiomerically pure CTV moiety of the precursors and, therefore, of the products. It was demonstrated that the addition of the CTV-tethered trimalonate proceeds with complete regioselectivity, providing products with the *trans*-3,*trans*-3,*trans*-3 fullerene addition pattern exclusively. On the other hand, the diastereoselectivity of the reaction was negligible, as reflected by the 5:4 ratio in which the diastereoisomeric products were isolated. The AM1-optimized structures shown in Figure 3 suggest an explanation for this remarkable regioselectivity. In the *trans*-3,*trans*-3,*trans*-3 adducts, the electron-rich aromatic rings of the CTV moiety are interacting much more closely and strongly with the electron-deficient fullerene surface than in the *e*,*e*,*e* tris-adducts. Such energetically favorable "templating" interactions between the tether and the carbon sphere are presumably also effective in the transition states of the tethered second and third Bingel cyclopropanations, favoring the formation of the regioisomers that are actually isolated.

Experimental Section

General Methods: Reagent-grade reagents and solvents were purchased from Acros, Aldrich, Baker, Fluka, Merck, or MTR Ltd. and used as received. CH_2Cl_2 was freshly distilled from CaH_2, and toluene from Na under N_2. Thin-layer chromatography was conducted on glass sheets coated with SiO_2 60 F_{254} obtained from Merck; visualization was achieved with a UV lamp at 254 nm. Column chromatography was carried out with SiO_2 (Silica Flash 60, Silicycle, particle size 40–63 µm, 230–400 mesh) and distilled technical solvents. HPLC was performed with a Merck–Hitachi LaChrom D-Line system equipped with a D-7000 Interface, L-7100 pump, L-7200 auto sampler, and L-7400 UV detector. UV/Vis spectra were recorded with a Varian Cary-5 spectrophotometer (shoulders indicated as sh, ε reported in $\mathrm{L\,mol^{-1}\,cm^{-1}}$ in parentheses), ECD spectra with a Jasco J-715 spectropolarimeter ($\Delta\varepsilon$ reported in $\mathrm{L\,mol^{-1}\,cm^{-1}}$ in parentheses). VCD and IR spectra were recorded with a commercial Fourier-transform VCD spectrometer (chiral IR), in the range 2000–900 $\mathrm{cm^{-1}}$. VCD spectra were recorded from a 0.042 M solution (CCl_4) with 1 h data collection time, dual photoelastic modulator set to 1400 $\mathrm{cm^{-1}}$ and resolution to 8 $\mathrm{cm^{-1}}$. The sample was held in a variable pathlength cell with BaF_2 windows and pathlength setting at 260 µm. The spectrum of the solvent (IR and VCD) was subtracted from that of the sample, which was measured under the same conditions. Experimental details on the calculation of ECD and VCD spectra are given in the Supporting Information. ^{1}H and ^{13}C NMR spectra were measured with a Varian Gemini 300, Varian Mercury 300, or a Bruker DRX500 spectrometer at 298 K; chemical shifts (δ) are reported in ppm relative to the signal of tetramethylsilane (TMS). Residual solvent signals were used as an internal reference. Coupling constants (J) are given in Hz. Mass spectra were measured by the MS Service of the Laboratorium für Organische Chemie at the ETH Zurich: HR-ESI spectra with a Waters Micromass AutoSpec-Ultima and HR-MALDI-TOF spectra with a Bruker Daltonics UltraFlex II spectrometer by using a DCTB {2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]-malononitrile} matrix and Ultramark 1621 for calibration. All CTV derivatives, with the exception of the C_{60} adducts, were handled at $T \leq 30$ °C. The nomenclature of non-fullerene compounds follows the suggestions of the ACD-Name 9.0 (ACD/Labs) program. The core numbering and stereodescriptors of fullerene derivatives follow the systematic IUPAC system.[9]

(–)-(*P*)-2,2′,2′′-[(3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo-[*a*,*d*,*g*]cyclononene-2,7,12-triyl)tris(oxy)]triethanol [(–)-(*P*)-1] and (+)-(*M*)-2,2′,2′′-[(3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo-[*a*,*d*,*g*]cyclononene-2,7,12-triyl)tris(oxy)]triethanol [(+)-(*M*)-1]: A racemic mixture of (±)-**1**[35] was separated by preparative HPLC on an (*S*,*S*)-Whelk-*O*1 CSP column (Regis): 21.1 × 250 mm; flow rate = 9 $\mathrm{mL\,min^{-1}}$; hexane/methanol (1:9); injection: 0.2 mL of a solution of (±)-**1** in DMF/methanol (1:1, c = 5 $\mathrm{mg\,mL^{-1}}$); UV/Vis detection at 238 nm. Up to 32 mg of each enantiomer was obtained as colorless solid after several injections. The analytical data are in agreement with those reported previously.[35]

(–)-(*P*)-1: t_R = 17.03 min. $[\alpha]_{365}^{20}$ = –22 (1 $\mathrm{mg\,mL^{-1}}$, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 22 °C): δ = 3.41 (d, $^{3}J_{H,H}$ = 13.7 Hz, 3 H, *eq*.-$C_{Ar}CHH'C_{Ar}$), 3.71 (s, 9 H, OCH_3), 3.70–3.73 (m, 6 H, CH_2OH), 3.96–4.11 (m, 6 H, OCH_2), 4.61 (d, $^{3}J_{H,H}$ = 13.5 Hz, 3 H, *ax*.-$C_{Ar}CHH'C_{Ar}$), 6.90 (s, 3 H, ArH), 6.93 (s, 3 H, ArH) ppm. ^{13}C NMR (100 MHz, CD_3OD, 22 °C): δ = 36.75, 56.83, 61.76, 72.25, 115.20, 117.28, 133.89, 134.48, 148.09, 149.50 ppm. IR (neat): $\tilde{\nu}$ = 3524 (br.), 2936 (br.), 1609, 1513, 1482, 1458, 1400, 1344, 1262, 1219, 1195, 1142, 1090, 897, 853, 743, 624 $\mathrm{cm^{-1}}$. UV/Vis (MeOH): λ (ε) = 205 (62800), 232 (28100), 291 (8800) nm. CD (MeOH): λ ($\Delta\varepsilon$) = 252 (+2.0), 275 (+2.7), 293 (–2.5) nm. HRMS (ESI+): calcd. for $C_{30}H_{36}NaO_9^+$ [M + Na]$^+$ 563.2252; found 563.2242.

(+)-(*M*)-1: t_R = 21.95 min. $[\alpha]_{365}^{20}$ = +22 (1 $\mathrm{mg\,mL^{-1}}$, MeOH). CD (MeOH): λ ($\Delta\varepsilon$) = 253 (–1.8), 275 (–3.1), 294 (+2.8) nm.

(–)-1,1′,1′′-Triethyl (*P*)-3,3′,3′′-[(3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triyl)tris(oxy-2,1-ethanediyl)] Trimalonate [(–)-(*P*)-2] and (+)-1,1′,1′′-Triethyl (*M*)-3,3′,3′′-[(3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-

2,7,12-triyl)tris(oxy-2,1-ethanediyl)] Trimalonate [(+)-(*M*)-2]: Compounds (–)-(*P*)-**2** and (+)-(*M*)-**2** were obtained from (–)-(*P*)-**1** and (+)-(*M*)-**1**, respectively, according to a literature procedure.[33]

(–)-(*P*)-2: Yield: 40 mg (76%) from (–)-(*P*)-**1** (32 mg, 0.06 mmol) as a pale-yellow oil. R_f = 0.08 (SiO_2; heptane/EtOAc, 1:1). $[\alpha]^{20}_{365}$ = –32 (2.7 mg mL^{-1}, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 9 H, CH_2CH_3), 3.38 (s, 6 H, $COCH_2CO$), 3.55 (d, $^3J_{H,H}$ = 13.9 Hz, 3 H, *eq*.-$C_{Ar}CHH'C_{Ar}$), 3.82 (s, 9 H, OCH_3), 4.18 (q, $^3J_{H,H}$ = 7.1 Hz, 12 H, CH_2CH_2), 4.39–4.51 (m, 6 H, CH_2CH_3), 4.73 (d, $^3J_{H,H}$ = 13.7 Hz, 3 H, *ax*.-$C_{Ar}CHH'C_{Ar}$), 6.86 (s, 3 H, Ar*H*), 6.92 (s, 3 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 14.00, 36.39, 41.38, 56.27, 61.55, 63.65, 67.58, 114.16, 117.31, 131.86, 133.52, 146.51, 148.85, 166.30, 166.61 ppm. IR: $\tilde{\nu}$ = 2935 (br.), 1725, 1607, 1509, 1445 (br.), 1397, 1369, 1329, 1260, 1217, 1185, 1140, 1089, 1028, 947, 854, 743, 623 cm^{-1}. UV/Vis (CH_2Cl_2): λ (ε) = 234 (34300), 292 (11900) nm. CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 250 (–4.4), 275 (+7.6), 295 (–6.0) nm. HRMS (ESI+): calcd. for $C_{45}H_{54}NaO_{18}^+$ [M + Na]$^+$ 905.3202; found 905.3205.

(+)-(*M*)-2: Yield: 37 mg (71%) from (+)-(*M*)-**1** (32 mg, 0.06 mmol) as a pale-yellow oil. $[\alpha]^{20}_{365}$ = +36 (2.8 mg mL^{-1}, CH_2Cl_2). CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 250 (+3.6), 275 (–8.5), 295 (+4.6) nm.

The addition of (–)-(*P*)-**2** and (+)-(*M*)-**2** to C_{60} was performed according to a literature procedure. The analytical data are in agreement with those reported.[33]

(–)-*out*,*out*,*out*-Triethyl (*P*)-[3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triyltris(oxy-2,1-ethanediyl)] (^{f,s}*C*)-Tricyclopropa[1,9:34,35:43,57](C_{60}-*I*$_h$)[5,6]fullerene-3′,3′,3′′,3′′,3′′′,3′′′-hexacarboxylate [(–)-(*P*,^{f,s}*C*)-3a]: Yield: 5.0 mg (10%) of a cherry-red solid obtained from C_{60} (23 mg, 0.032 mmol) and (–)-(*P*)-**2** (25 mg, 0.032 mmol). ^1H NMR (500 MHz, $CDCl_3$, 22 °C): δ = 1.42 (t, $^3J_{H,H}$ = 7.2 Hz, 9 H, CH_2CH_3), 3.37 (d, $^3J_{H,H}$ = 13.9 Hz, 3 H, *eq*.-$C_{Ar}CHH'C_{Ar}$), 3.63 (s, 9 H, OCH_3), 3.98–4.05 (m, 3 H), 4.12–4.15 (m, 3 H), 4.41–4.50 (m, 6 H, CH_2CH_3), 4.57–4.62 (m, 6 H), 5.33 (d, $^3J_{H,H}$ = 12.1 Hz, 3 H, *ax*.-$C_{Ar}CHH'C_{Ar}$), 6.55 (s, 3 H, Ar*H*), 6.61 (s, 3 H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 22 °C): δ = 14.10, 37.06, 50.64, 53.40, 55.43, 63.32, 64.66, 71.14, 71.65, 112.16, 113.20, 132.12, 132.67, 138.17, 140.15, 140.61, 141.50, 141.65, 142.66, 142.99, 143.74, 144.68, 144.99, 145.53, 145.68, 145.75, 145.98, 146.33, 146.70, 147.08, 147.59, 147.89, 148.37, 163.54, 164.12 ppm. IR: $\tilde{\nu}$ = 2921, 2852, 1741 (br.), 1605, 1513, 1456 (br.), 1396, 1368, 1256 (br.), 1221, 1146, 1092, 1059, 1020, 944, 870, 800, 731, 700, 626 cm^{-1}. UV/Vis (CH_2Cl_2): λ (ε) = 238 (187000), 296 (79000), 405 (sh, 8600), 466 (7100) nm. CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 247 (+341), 275 (sh, –66), 290 (–96), 315 (sh, –64), 339 (–86), 397 (+22), 467 (+72), 542 (–32), 613 (–18) nm. HRMS (MALDI-TOF): calcd. for $^{12}C_{105}H_{48}O_{18}^+$ [M]$^+$ 1596.2835; found 1596.2878.

(+)-*out*,*out*,*out*-Triethyl (*M*)-[3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triyltris(oxy-2,1-ethanediyl)] (^{f,s}*A*)-Tricyclopropa[1,9:34,35:43,57](C_{60}-*I*$_h$)[5,6]fullerene-3′,3′,3′′,3′′,3′′′,3′′′-hexacarboxylate [(+)-(*M*,^{f,s}*A*)-3b]: Yield: 4.6 mg (10%) of a cherry-red solid from C_{60} (20 mg, 0.028 mmol) and (+)-(*M*)-**2** (19 mg, 0.025 mmol). CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 247 (–419), 274 (sh, +81), 290 (+120), 315 (sh, +74), 341 (+107), 396 (–28), 469 (–87), 545 (+38), 611 (+18) nm.

(+)-*out*,*out*,*out*-Triethyl (*P*)-[3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triyltris(oxy-2,1-ethanediyl)] (^{f,s}*A*)-Tricyclopropa[1,9:34,35:43,57](C_{60}-*I*$_h$)[5,6]fullerene-3′,3′,3′′,3′′,3′′′,3′′′-hexacarboxylate [(+)-(*P*,^{f,s}*A*)-4a]: Yield: 3.9 mg (8%) of a cherry-red solid from C_{60} (23 mg, 0.032 mmol) and (–)-(*P*)-**2** (25 mg, 0.032 mmol). ^1H NMR (500 MHz, $CDCl_3$, 22 °C): δ = 1.40 (t, $^3J_{H,H}$ = 7.1 Hz, 9 H, CH_2CH_3), 3.39 (d, $^3J_{H,H}$ = 14.0 Hz, 3 H, *eq*.-$C_{Ar}CHH'C_{Ar}$), 3.58 (s, 9 H, OCH_3), 4.11–4.20 (m, 6 H), 4.48 (q, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_2CH_3), 4.66 (d, $^3J_{H,H}$ = 13.7 Hz, 3 H, *ax*.-$C_{Ar}CHH'C_{Ar}$), 4.81–4.84 (m, 3 H), 4.94–4.98 (m, 3 H), 6.53 (s, 3 H, Ar*H*), 6.56 (s, 3 H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 22 °C): δ = 14.21, 51.09, 53.40, 55.26, 63.30, 65.55, 70.69, 70.76, 111.97, 112.96, 131.66, 132.32, 140.64, 140.89, 141.41, 141.57, 141.89, 142.07, 142.70, 144.11, 144.59, 144.60, 144.80, 145.23, 145.75, 146.03, 146.96, 147.16, 147.35, 147.45, 148.33, 163.56, 164.95 ppm. IR: $\tilde{\nu}$ = 2921, 2852, 1742 (br.), 1606, 1512, 1457 (br.), 1368, 1257, 1221, 1146, 1092, 1059, 1020, 944, 870, 800, 731, 709, 626 cm^{-1}. UV/Vis (CH_2Cl_2): λ (ε) = 238 (193000), 296 (83000), 405 (sh, 9100), 466 (7200) nm. CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 246 (–397), 272 (sh, +85), 289 (+124), 309 (+87), 348 (+87), 378 (sh, +11), 400 (+3), 470 (–81), 540 (+35), 602 (+20) nm. HRMS (MALDI-TOF): calcd. for $^{12}C_{105}H_{48}O_{18}^+$ [M]$^+$ 1596.2835; found 1596.2826.

(–)-*out*,*out*,*out*-Triethyl (*M*)-[3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triyltris(oxy-2,1-ethanediyl)] (^{f,s}*C*)-Tricyclopropa[1,9:34,35:43,57](C_{60}-*I*$_h$)[5,6]fullerene-3′,3′,3′′,3′′,3′′′,3′′′-hexacarboxylate [(–)-(*M*,^{f,s}*C*)-4b]: Yield: 3.4 mg (8%) of a cherry-red solid from C_{60} (20 mg, 0.028 mmol) and (+)-(*M*)-**2** (19 mg, 0.025 mmol). CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 246 (+363), 275 (sh, –86), 289 (–112), 309 (–77), 348 (–77), 378 (–11), 400 (–3), 468 (+71), 541 (–35), 600 (–15) nm.

(+)-(*M*)-2,7,12-Tris(2-iodoethoxy)-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene [(+)-(*M*)-6]: To a solution of (+)-(*M*)-**1** (39 mg, 0.092 mmol) in pyridine (3 mL), TsCl (211 mg, 1.10 mmol) was added at –20 °C. The mixture was stirred at –20 °C for 4 h, then poured into an ice/water mixture (20 mL), which was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. The crude product was dissolved in acetone, NaI (500 mg) was added, and the mixture was stirred for 20 h. The solvent was removed, and the residue was dissolved in EtOAc. The organic layer was washed with satd. aq. $NaHCO_3$ solution and with brine. The combined aqueous phases were extracted with EtOAc, the combined organic phases dried with $MgSO_4$, and the solvent was evaporated. Column chromatography (SiO_2; heptane/EtOAc, 9:1 → 7:3) afforded (+)-(*M*)-**6** (48 mg, 76%) as a pale-yellow solid. R_f = 0.82 (SiO_2; heptane/EtOAc, 7:3). $[\alpha]^{20}_{D}$ = +94 (1.1 mg mL^{-1}, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 3.36 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, CH_2I), 3.55 (d, $^3J_{H,H}$ = 13.8 Hz, 3 H, *eq*.-$C_{Ar}CHH'C_{Ar}$), 3.86 (s, 9 H, OCH_3), 4.26 (t, $^3J_{H,H}$ = 7.4 Hz, 6 H, OCH_2), 4.74 (d, $^3J_{H,H}$ = 13.7 Hz, 3 H, *ax*.-$C_{Ar}CHH'C_{Ar}$), 6.84 (s, 3 H, ArH), 6.89 (s, 3 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 1.56, 36.40, 56.34, 70.82, 113.87, 117.59, 131.77, 133.68, 145.82, 148.90 ppm. UV/Vis (CH_2Cl_2): λ (ε) = 233 (34400), 293 (10900) nm. CD (CH_2Cl_2): λ ($\Delta\varepsilon$) = 249 (+7.0), 279 (–10.9), 295 (+12.4) nm.

(–)-(*P*)-3,8,13-Trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triol [(–)-(*P*)-5]: (+)-(*M*)-**6** (36 mg, 0.041 mmol) was suspended in concd. AcOH (4 mL), Zn powder (400 mg) was added, and the mixture was stirred for 2 h. Further Zn powder (200 mg) and concd. AcOH (2 mL) were added, and stirring was continued until the CTV-derived triiodide was consumed (reaction monitored by TLC). The product was extracted with EtOAc, and the organic layer was washed with H_2O, dried with $MgSO_4$, and the solvent was evaporated in vacuo. After drying (*T* = 22 °C, 10^{-2} mbar), (–)-(*P*)-**5** (17 mg, 99%) was obtained as a colorless powder, which still contained traces of AcOH. The analytical data are in agreement with those reported previously.[49] $[\alpha]^{20}_{365}$ = –98 (1.0 mg mL^{-1}, MeOH). ^1H NMR (300 MHz, CD_3OD, 22 °C): δ =

3.42 (d, $^{3}J_{\mathrm{H,H}}$ = 13.7 Hz, 3 H, *eq*.-$\mathrm{C_{Ar}}C\mathit{H}\mathrm{H'C_{Ar}}$), 3.81 (s, 9 H, $\mathrm{OC}H_3$), 4.66 (d, $^{3}J_{\mathrm{H,H}}$ = 13.6 Hz, 3 H, *ax*.-$\mathrm{C_{Ar}CH}H'\mathrm{C_{Ar}}$), 6.83 (s, 3 H, Ar*H*), 6.86 (s, 3 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $\mathrm{CD_3OD}$, 22 °C): δ = 36.79, 56.59, 114.50, 117.61, 132.64, 134.17, 145.81, 147.47 ppm. IR: $\tilde{\nu}$ = 3493 (br.), 2923 (br.), 1594, 1510, 1443, 1361, 1269, 1210, 1174, 1138, 1082, 1011, 938, 884, 850, 744, 620 cm^{-1}. UV/Vis (MeOH): λ (ε) = 205 (58800), 230 (21800), 293 (8200) nm. CD (MeOH): λ ($\Delta\varepsilon$) = 249 (–8.3), 279 (+2.7), 299 (–3.9) nm. HRMS (ESI–): calcd. for $\mathrm{C_{24}H_{23}O_6^-}$ [M – H$^-$] 407.1495; found: 407.1494.

Supporting Information (see footnote on the first page of this article): NMR and mass spectra of **3a**, **4a**, **3b**, and **4b**; determination of activation energy (E_a) and enthalpy ($\Delta H^{\ddagger}$) of the thermal racemization of **2**; details on the calculations of electronic (ECD) and vibrational (VCD) circular dichroism spectra.

Acknowledgments

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