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A Facile Access to Enantiomerically Pure [60]Fullerene Bisadducts with the Inherently Chiral *Trans*-3 Addition Pattern

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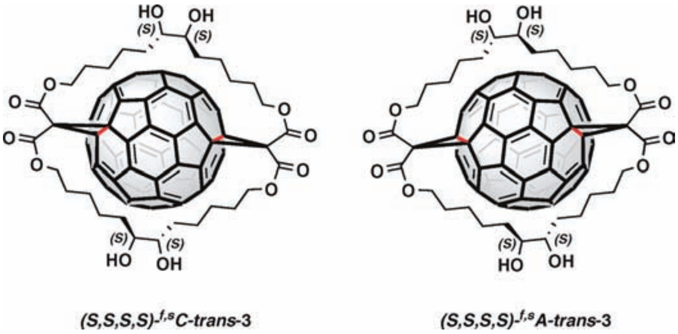
ABSTRACT



The Bingel reaction between C_{60} and an enantiopure bismalonate tether equipped with two acetonide moieties led to the synthesis and successful column chromatographic isolation of the enantiomerically pure $^{f,s}C$ and $^{f,s}A$ bisadducts with the inherently chiral *trans*-3 addition pattern. Acidic deprotection of the acetonide groups gave access to novel chiral fullerene compounds which combine the inherent chirality of the fullerene core with the functional glycol groups located on the tether.

The spherical structure of C_{60} combined with the reactivity of its double bonds has led to a tremendous growth in research on the design and synthesis of molecular building blocks equipped with functional groups with a well-defined orientation in the three dimensions. After the first monoaddition on the fullerene cage, eight regioisomeric bisadducts (for identical addends) are possible due to the nonequivalent double bonds located in both hemispheres.[1] The regioselective synthesis of all possible [60]fullerene bisadducts was one of the first targets in fullerene chemistry, and the tether-directed remote functionalization, introduced by Diederich,[2] has been applied successfully to give synthetic access to all bis-addition patterns with remarkable regioselectivity.[3] The C_2-symmetric addition patterns *cis*-3, *trans*-2, and *trans*-3 are inherently chiral, a property which is exclusively attributed to the functionalization pattern and characterized by the chirality of the π-system of the fullerene chromophore.[4] Thus, the synthesis of the enantiomerically pure bisadducts of C_{60} with an inherently chiral addition pattern has attracted great attention due to their possible applications in enantioselective synthesis and/or chiral recognition. Investigations and synthetic efforts focused on this exciting area in the past 15 years have been reviewed in detail by Thilgen and Diederich.[5] The above-mentioned target was approached in the following ways: (1) the stepwise addition of achiral addends on C_{60} and the subsequent separation of the $^{f,s}C$ and $^{f,s}A$ enantiomers[6] of the inherently chiral bisadducts by means of preparative HPLC on chiral stationary phases, (2) the stepwise addition of enantiomerically pure addends followed by the separation of the corresponding diastereomers on achiral stationary phases, and (3) the tether-directed remote functionalization of C_{60} utilizing chiral,

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(1) Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 437.

(2) Isaacs, L.; Haldimann, R. F.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2339.

(3) (a) Thilgen, C.; Sergeyev, S.; Diederich, F. *Top. Curr. Chem.* **2004**, *248*, 1. (b) Thilgen, C.; Diederich, F. *C. R. Chim.* **2006**, *9*, 868.

(4) Thilgen, C.; Gosse, I.; Diederich, F. *Top. Stereochem.* **2003**, *23*, 1.

(5) Thilgen, C.; Diederich, F. *Chem. Rev.* **2006**, *106*, 5049.

(6) (a) Hirsch, A.; Lamparth, I.; Schick, G. *Liebigs Ann.* **1996**, 1725. (b) Thilgen, C.; Herrmann, A.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 183.

10.1021/ol200816z

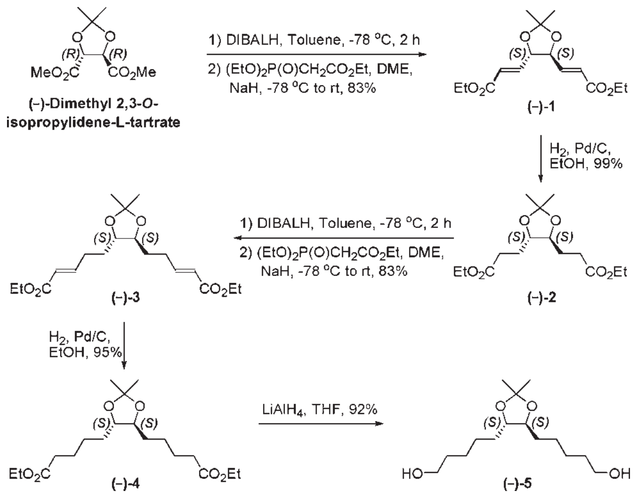
racemic, or enantiomerically pure tethers equipped with the reactive groups responsible for the addition reactions on the double bonds of the fullerene sphere. Apart from the widely used Bingel nucleophilic cyclopropanation,[7] [2 + 2], [3 + 2], and [4 + 2] cycloadditions[5] have been employed as methods of derivatization of C_{60}.

The inherently chiral *trans*-2 and *trans*-3 addition patterns have attracted particular attention due to the fact that the chiral tethers required for the synthesis of the $^{f,s}C$ and $^{f,s}A$ enantiomers should have large and rigid structures. In a pioneering work, Diederich and co-workers[8] employed bismalonate tethers bearing the Tröger base motif as a spacer. The Bingel addition of an optically pure Tröger tether to C_{60}, after separation of the racemic mixture by preparative HPLC on a chiral stationary phase, afforded the enantiomerically pure *trans*-2 bisadducts with complete regioselectivity and excellent diastereoselectivity. By using the pure enantiomers of a more extended Tröger tether (enantiomeric separation on chiral HPLC column) the isolation of the pure enantiomers of the *trans*-3 bisadducts was achieved after their separation by means of preparative HPLC on a Bucky Clutcher column. The remote Bingel bis-functionalization of C_{60} was completely regioselective for the *trans*-3 addition pattern and afforded only the bisadducts with an *in*–*out* configuration.[9]

Stimulated by the challenge of establishing a procedure for the synthesis and isolation of the pure enantiomers of C_{60} bisadducts with the inherently chiral *trans*-3 addition pattern, without the need of preparative HPLC for the enantiomeric separation of the chiral tether or the formed fullerene adducts, we decided to explore the feasibility of optically pure bismalonate tethers to reach this target. We also focused our efforts on the further derivatization of the enantiomerically pure bisadducts due to the promising properties of the *trans*-3 addition pattern. For example, Nishimura et al.[10] reported the construction of helical arrays of C_{60} molecules along a polymer backbone using an optically active *trans*-3 bisadduct of C_{60}.

The concept of *cyclo*-[*n*]-malonate tethers, introduced by Hirsch,[11] has been successfully employed for the regioselective remote functionalization of C_{60}. When the achiral *cyclo*-[2]-dodecylmalonate was allowed to react with C_{60} under the Bingel conditions, the *trans*-3 bisadduct was formed regioselectively in 56% yield. Following our previous work on the regio- and diastereoselective trisfunctionalization of C_{60} with an enantiopure cyclo-trismalonate tether derived from 3,4-*O*-isopropylidene-D-mannitol,[12] we designed the optically active bismalonate tether **(−)-7** (Scheme 2). The synthesis of tether **(−)-7** can be realized by the cyclization reaction of malonyl dichloride with the appropriate enantiomerically pure diol, as described previously.[13]

Scheme 1. Synthesis of the Optically Pure Diol **(−)-5**



Enantiopure diol **(−)-5** with a spacer connecting the hydroxyl groups comprised of 12 carbon atoms and equipped with an acetonide moiety was synthesized as shown in Scheme 1. In a one-pot, two-step transformation, (−)-dimethyl-2,3-*O*-isopropylidene-L-tartrate was reduced with DIBALH followed by a Wittig–Horner reaction with triethyl phosphonoacetate to afford the (*E*,*E*)-unsaturated ester **(−)-1** in 83% overall yield.[14] Catalytic hydrogenation of **(−)-1** using Pd/C in ethanol quantitatively yielded the saturated ester **(−)-2** which was subjected to the same sequence of reactions to give the saturated ester **(−)-4** in very good yield. It has to be mentioned here that the applied sequential treatment (DIBALH reduction, Wittig–Horner olefination, catalytic hydrogenation) offers a general and efficient method for the elongation of alkyl chains of bis-esters by two carbon atoms and will be discussed in detail elsewhere. In the final step, reduction of the ester moieties with LAH in THF solvent afforded the desired optically pure diol **(−)-5** in 92% isolated yield.

The condensation of **(−)-5** with malonyl dichloride (Scheme 2) was carried out following the experimental procedure reported earlier.[11a,13] Separation by column chromatography on SiO_2 using a mixture of CH_2Cl_2–EtOAc–hexane (4:1:2) as an eluent afforded the mono-**(−)-6**, bis-**(−)-7**, and trismalonate **(−)-8** in 23%, 6%, and 2.1% yields, respectively. The new family of enantiomerically pure *cyclo*-[*n*]-malonates (*n* = 1, 2, 3) bearing identical spacers consisted of 12 carbon atoms was characterized by

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(7) Bingel, C. *Chem. Ber.* **1993**, *126*, 1957.

(8) (a) Sergeyev, S.; Diederich, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 1738. (b) Sergeyev, S.; Schär, M.; Seiler, P.; Lukoyanova, O.; Echegoyen, L.; Diederich, F. *Chem.—Eur. J.* **2005**, *11*, 2284.

(9) (a) Nierengarten, J.-F.; Habicher, T.; Kessinger, R.; Cardullo, F.; Diederich, F.; Gramlich, V.; Gisselbrecht, J.-P.; Boudon, C.; Gross, M. *Helv. Chim. Acta* **1997**, *80*, 2238. (b) Bourgeois, J.-P.; Seiler, P.; Fibbioli, M.; Pretsch, E.; Diederich, F.; Echegoyen, L. *Helv. Chim. Acta* **1999**, *82*, 1572.

(10) Nishimura, T.; Tsuchiya, K.; Ohsawa, S.; Maeda, K.; Yashima, E.; Nakamura, Y.; Nishimura, J. *J. Am. Chem. Soc.* **2004**, *126*, 11711.

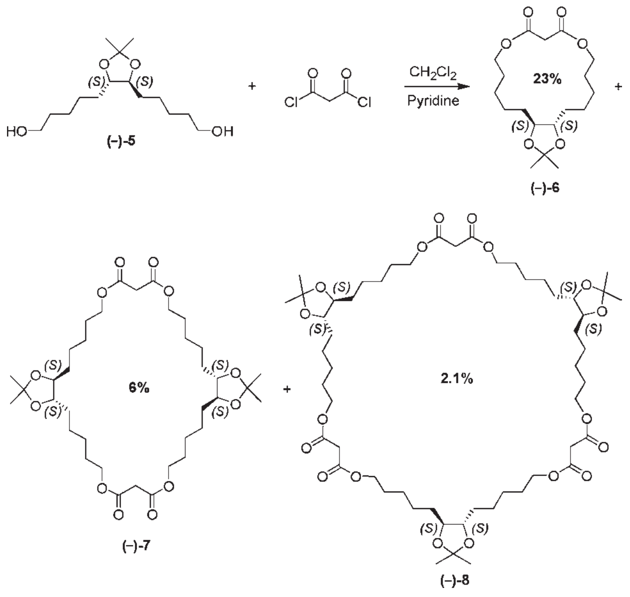
(11) (a) Reuther, U.; Brandmüller, T.; Donaubauer, W.; Hampel, F.; Hirsch, A. *Chem.—Eur. J.* **2002**, *8*, 2261. (b) Chronakis, N.; Hirsch, A. *C. R. Chim.* **2006**, *9*, 862.

(12) Chronakis, N.; Hirsch, A. *Chem. Commun.* **2005**, 3709.

(13) Chronakis, N.; Brandmüller, T.; Kovacs, C.; Reuther, U.; Donaubauer, W.; Hampel, F.; Fischer, F.; Diederich, F.; Hirsch, A. *Eur. J. Org. Chem.* **2006**, 2296.

(14) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.

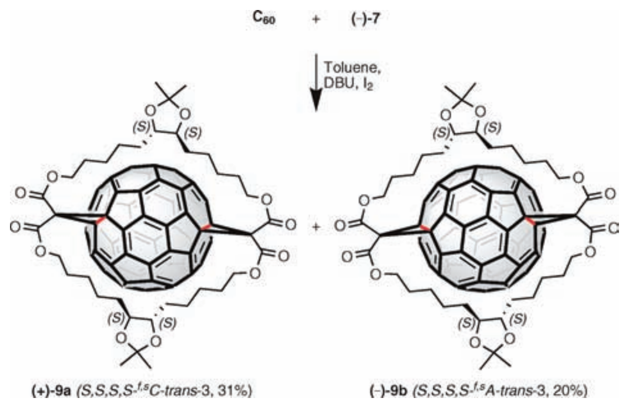
Scheme 2. Synthesis of Enantiomerically Pure *cyclo*-[*n*]-Malonates with C12 Spacers



^{1}H, ^{13}C NMR, IR spectroscopies and by mass spectrometry (see Supporting Information).

Next, bismalonate **(−)-7** was reacted with C_{60} in the presence of I_2 and DBU in toluene, to afford in a regioselective manner two bisadducts (Scheme 3). The largest difference in the R_f values of the two bisadducts on SiO_2 [0.31 for **(−)-9b** and 0.27 for **(+)-9a**] was found by using a mixture of PhCl−CH_2Cl_2−MeCN in a 65:30:5 ratio. The relative yields of **(+)-9a** and **(−)-9b** in the crude reaction mixture were calculated as 60% and 40%, respectively by integrating the corresponding peaks in the HPLC elugram. Successful separation of the formed bisadducts was achieved by column chromatography (SiO_2) using the above-mentioned solvent mixture as an eluent. The MALDI-TOF mass spectra of **(+)-9a** and **(−)-9b** showed the expected M^- molecular ion at 1401 m/z, thus confirming that the 2-fold Bingel cyclopropanation of the fullerene core was successful. Their UV−vis spectra were identical and characteristic for the *trans*-3 addition pattern as confirmed by comparison with previously reported *trans*-3 C_{60} bisadducts.[15] In the ^{13}C NMR spectrum of **(+)-9a** (Figure 1), 27 of the 28 expected signals for the sp^2 carbons of the fullerene skeleton were observed in the region between 138 and 148 ppm. This indicates a C_2 symmetry which was further confirmed by the presence of two signals at 163.33 and 164.59 ppm corresponding to the carbonyl carbons, one signal for the quaternary carbons at 108.16 ppm, two distinct peaks for the stereogenic methine carbon atoms at 80.69 and 81.14 ppm, two signals at 71.52 and 72.79 ppm characteristic for the fullerene sp^3 carbons, and a single absorption at 53.34 ppm attributed to the bridgehead sp^3 carbon atoms. The pattern of the ^{13}C NMR spectrum of bisadduct **(−)-9b** (Figure 1) was similar to that of **(+)-9a**, showing only minor differences in the chemical shifts of the observed peaks. In the fullerene spectral region between 138 and 148 ppm (sp^2 fullerene carbons) 28 signals were observed, clearly reflecting the C_2 symmetry of **(−)-9b**. Bisadducts **(+)-9a** and **(−)-9b** compose a pair of diastereomers with an enantiomeric relationship between the fullerene cores due to the inherent chirality of the *trans*-3 addition pattern. The Bingel functionalization of C_{60} with tether **(−)-7** showed low diastereoselectivity with a dr value of 20% (HPLC), favoring the formation of **(+)-9a**.

Scheme 3. Synthesis of the Enantiomerically Pure Bisadducts **(+)-9a** and **(−)-9b** with the Inherently Chiral *trans*-3 Addition Pattern



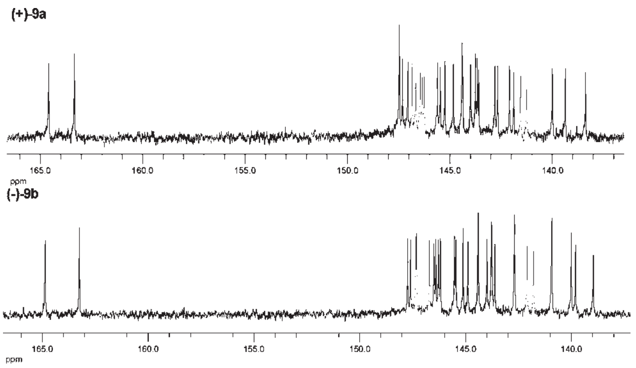


Figure 1. ^{13}C NMR spectra (75 MHz, $CDCl_3$) of **(+)-9a** and **(−)-9b** in the region 148−165 ppm (sp^2 fullerene and C=O carbons).

The circular dichroism (CD) spectra of the isolated **(+)-9a** and **(−)-9b** (Figure 2) show a mirror-image behavior due to the enantiomeric relationship of the carbon cores, with strong Cotton effects originating from the fullerene chromophore. The spectra are identical to those of previously synthesized enantiomerically pure bisadducts with the *trans*-3 addition pattern,[8b,15d,16] while the absolute

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(15) (a) Djojo, F.; Herzog, A.; Lamparth, I.; Hampel, F.; Hirsch, A. *Chem.—Eur. J.* **1996**, *2*, 1537. (b) Lu, Q.; Schuster, D. I.; Wilson, S. R. *J. Org. Chem.* **1996**, *61*, 4764. (c) Nierengarten, J.-F.; Habicher, T.; Kessinger, R.; Cardullo, F.; Diederich, F.; Gramlich, V.; Gisselbrecht, J.-P.; Boudon, C.; Gross, M. *Helv. Chim. Acta* **1997**, *80*, 2238. (d) Djojo, F.; Hirsch, A. *Chem.—Eur. J.* **1998**, *4*, 344.

configurations of **(+)-9a** and **(−)-9b** were assigned as $^{f,s}C$ and $^{f,s}A$, respectively by direct comparison with the reported CD spectroscopic data. Finally, the specific rotation values $[\alpha]_D^{25}$ were measured in chloroform and found to be +1295° for the clockwise isomer **(+)-9a** and −1314° for the anticlockwise **(−)-9b**.

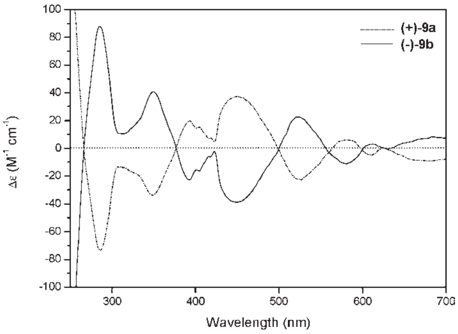
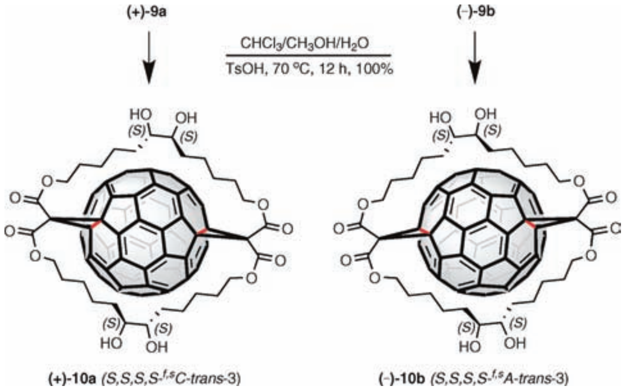


Figure 2. CD spectra of **(+)-9a** and **(−)-9b** in $CHCl_3$.

The successful synthesis and isolation of bisadducts **(+)-9a**, **(−)-9b** prompted us to attempt the acid-catalyzed deprotection of both acetal groups incorporated in the tether. Among the acidic reagents tested, TsOH showed the best behavior, in a mixture of $CHCl_3$−MeOH (3:1) which contained a few drops of water. In separate experiments, **(+)-9a**, **(−)-9b** were treated under these conditions by heating the reaction mixtures at 70 °C for 12 h (Scheme 4). Monitoring of the reaction progress by TLC showed a clean and quantitative transformation into the corresponding bisadducts **(+)-10a** and **(−)-10b** which were easily isolated by column chromatography (SiO_2, PhMe−MeOH, 9:1). The structures of **(+)-10a** and **(−)-10b** were unambiguously assigned by ^1H, ^{13}C NMR, UV/vis, CD spectroscopies and by MALDI-TOF mass spectrometry (see Supporting Information).

Scheme 4. Deprotection of Bisadducts **(+)-9a** and **(−)-9b**



Finally, a facile and less time-consuming procedure to obtain pure **(+)-10a** and **(−)-10b** was achieved when the mixture of **(+)-9a/(−)-9b** was not separated after the Bingel functionalization of C_{60} with **(−)-7** but only purified from an excess of reagents and polymeric material on a short plug (SiO_2, PhMe−EtOAc, 8:2). Then, it was subjected to acetal deprotection and the final separation of **(+)-10a** and **(−)-10b** was easily carried out by column chromatography on SiO_2 (PhMe−EtOAc−MeOH, 4:4:1).

In conclusion, the enantiomerically pure *trans*-3 bisadducts **(+)-9a**, **(−)-9b** were successfully synthesized and separated by column chromatography utilizing the bismalonate tether **(−)-7**. Acetal deprotection afforded bisadducts **(+)-10a** and **(−)-10b**, equipped with glycol moieties and, thus, offering the potential for further derivatization targeting functional fullerene materials with the inherently chiral *trans*-3 addition pattern.

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Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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