

Regio- and stereoselective synthesis of enantiomerically pure [60]fullerene tris-adducts with an inherently chiral *e,e,e* addition pattern†

Nikos Chronakis and Andreas Hirsch*

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The synthesis and flash column chromatographic separation of enantiomerically pure tris-adducts of C₆₀ with an *e,e,e*-addition pattern is achieved *via* cyclopropanation with chiral D₃-symmetrical cyclo-tris(malonate) tethers.

The synthesis and characterization of [60]fullerene tris-adducts with an inherently chiral addition pattern is a challenging topic in the area of fullerene chemistry.^{1–6} Enantiomerically pure C₆₀ tris-adducts represent attractive building blocks for the construction of chiral macromolecular architectures such as dendrimers and spherical amphiphiles.⁷

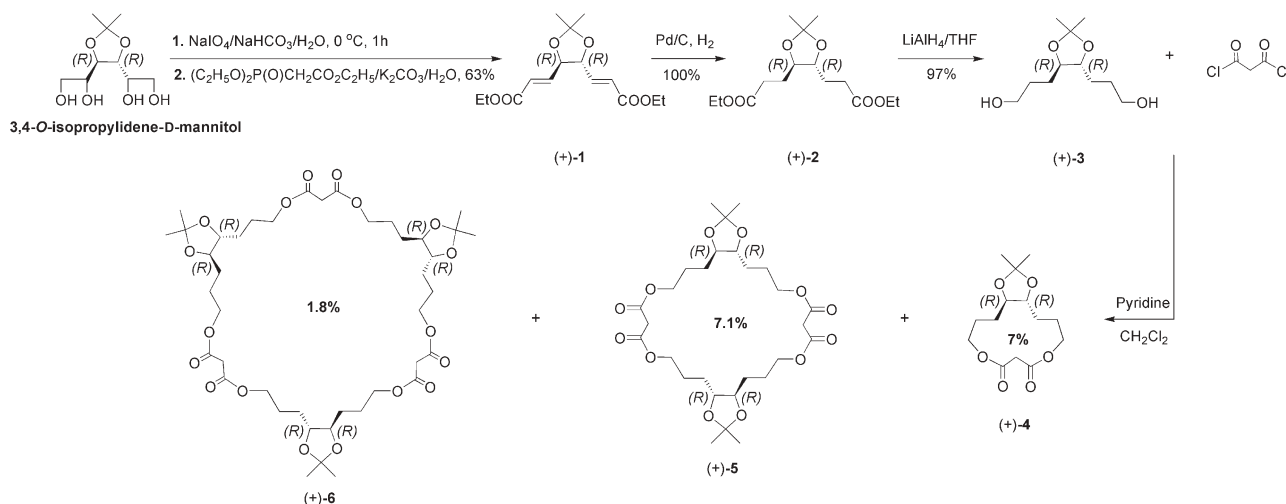
The utilization of chiral bis(malonate) tethers for the synthesis of enantiomerically pure [60]fullerene bis-adducts with an inherently chiral addition pattern was firstly reported by Diederich.⁸ Furthermore, chiral bis-adducts were also synthesized by this method, using [4 + 2] and [3 + 2] cycloadditions.⁹ Up to now, pure enantiomers of inherently chiral tris-adducts of C₆₀ have been synthesized by stepwise nucleophilic cyclopropanation of the [6,6] double bonds with diethyl bromomalonate and enantiomeric separation of the racemic mixture of the inherently chiral tris-adducts by means of preparative chromatography (HPLC) on

chiral stationary phases.³ In addition, enantiomerically pure tris-adducts of C₆₀ were obtained by cyclopropanation of the [6,6] bonds of the fullerene cage with C₂-symmetrical bis(oxazolines) and subsequent HPLC chromatographic separation of the corresponding diastereomers on achiral stationary phases.^{4,6} In these cases, only poor regio- and diastereoselectivities were observed, while tedious preparative HPLC chromatographic separations were required. Previous results on the regioselective synthesis of C₆₀ tris-adducts showed that the tether-directed approach, in which macrocyclic malonates bearing achiral alkyl spacers as linkers between the malonate groups,^{10,11} is a superior method to control triple additions to C₆₀. However, only racemic mixtures of C₆₀ adducts with an inherently chiral addition pattern were obtained.

We report here the synthesis and the facile separation by column chromatography on SiO₂, of the pure enantiomers of a [60]fullerene tris-adduct with an *e,e,e* addition pattern, by using chiral cyclo-malonate tethers. For this purpose, we synthesized a new family of enantiomerically pure macrocyclic malonates [bis- and tris-, (+)-**5** and (+)-**6**], with chiral C₈-spacers connecting the reactive malonate groups (Scheme 1). Sequential treatment of 3,4-*O*-isopropylidene-D-mannitol with aqueous sodium periodate and triethyl phosphonoacetate in the presence of potassium carbonate in the same aqueous media, afforded the bis-(*E*)-unsaturated ester (+)-**1** in 63% overall yield.¹² Catalytic hydrogenation of (+)-**1** using Pd/C in ethyl acetate, followed by LiAlH₄ reduction of the ester moieties, yielded the corresponding

Institut für Organische Chemie der Universität Erlangen, Henkestrasse 42, D-91054 Erlangen, Germany. E-mail: andreas.hirsch@chemie.uni-erlangen.de; Fax: (+49) 91318526864; Tel: (+49) 9131 8522537

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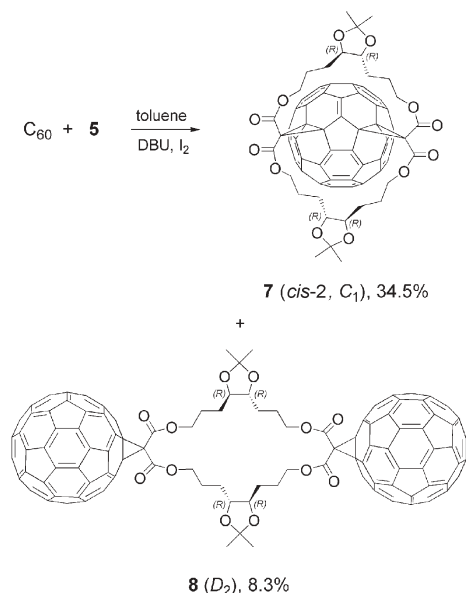


Scheme 1 Synthesis of the enantiomerically pure macrocyclic mono-, bis- and tris(malonate)s (**4–6**) bearing C₈-spacers.

optically active diol (+)-**3**. The condensation of (+)-**3** with malonyl dichloride was carried out at a concentration of $\approx 15 \text{ mmol L}^{-1}$ of the diol in CH_2Cl_2 , in the presence of pyridine as a base. The FAB mass spectrum of the crude reaction mixture revealed the formation of macrocyclic structures with up to eight repetition units. Macrocycles (+)-**4**, (+)-**5**, and (+)-**6** were isolated successfully by flash column chromatography on SiO_2 , by using a mixture of CH_2Cl_2 -EtOAc (70:30) as an eluent. The order of elution correlates the number of repetition units; (+)-**4** is eluted first, followed by the larger rings (+)-**5** and (+)-**6**. The D_2 -symmetrical dimeric ring (+)-**5** was obtained in pure form as a white solid (7.1% isolated yield), while the D_3 -symmetrical trimeric macrocycle (+)-**6** was isolated in a 1.8% yield as a highly viscous colourless oil.

First, we investigated the Bingel functionalization of C_{60} with the chiral cyclo-bis(malonate) tether (+)-**5**. The modified Bingel¹³ reaction of (+)-**5** with C_{60} was performed under high dilution conditions ($6.6 \times 10^{-4} \text{ M}$ for C_{60}) and, after flash column chromatographic separation of the crude reaction mixture (SiO_2 , toluene-EtOAc, 80:20), the *cis*-2 bis-adduct **7** and the bis(methanofullerene) derivative **8** were isolated in pure form in 34.5% and 8.3% yield, respectively (Scheme 2). The structure of bis-adduct **7** was assigned by comparison of its UV/Vis spectrum^{2,14} with that of known *cis*-2 bis-adducts, while the ^1H and ^{13}C NMR spectra depicted molecular C_1 symmetry. As a consequence, the Bingel functionalization of C_{60} with macrocycle (+)-**5** was proved to be completely regioselective, leading to the exclusive formation of the *cis*-2 regioisomer, but not appropriate to achieve an inherently chiral addition pattern.

According to our previous results,¹⁰ the cyclopropanation of C_{60} with the chiral cyclo-tris(malonate) (+)-**6** is expected to lead to the preferential formation of tris-adducts with threefold rotational symmetry, namely *cis*-1,*cis*-1,*cis*-1, *e,e,e*, *trans*-3,*trans*-3,*trans*-3, and *trans*-4,*trans*-4,*trans*-4. The formation of other tris-adducts is energetically disfavoured because of an unequal distribution of strain energy within the tether. The all-*cis*-1 regioisomer is excluded due to steric hindrance of the addends. The all-*trans*-3 and all-*e* are inherently chiral. An *e,e,e* tris-adduct of C_{60} was formed as a major

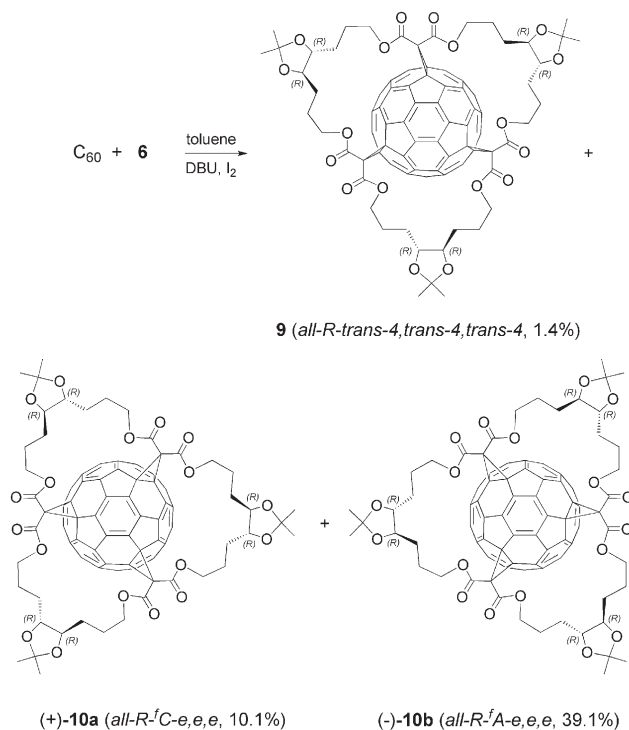


Scheme 2 Bis-functionalization of C_{60} with the cyclo-bis(malonate) **5**.

product on utilizing a tris(malonate) tether bearing achiral C_8 -alkyl chains as spacers. Macrocycle (+)-**6** reacted cleanly with C_{60} in the presence of I_2 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene, to afford three fullerene tris-adducts (Scheme 3). The relative yields of the raw products of the reaction (HPLC) are 5%, 21%, and 74% for **9**, (+)-**10a**, and (–)-**10b**. The R_f values (SiO_2 , toluene-EtOAc, 80:20) were found to be 0.37, 0.32, and 0.24, respectively. The crude mixture was separated successfully by flash column chromatography on SiO_2 , using a mixture of toluene-EtOAc (80:20) as eluent. The least polar tris-adduct **9** eluted first from the column and exhibits an olive-green colour, characteristic for the *trans*-4,*trans*-4,*trans*-4 addition pattern with C_{3v} symmetry.¹⁰ Its structure was ascertained by comparison of its UV/Vis spectra with that of a known all-*trans*-4 tris-adduct,¹⁰ as well as from the NMR spectroscopic data which support a C_3 symmetry of the whole molecule. Adduct **9** was isolated in pure form in a 1.4% yield.

Tris-adducts (+)-**10a** and (–)-**10b** eluted separately as the second and the third products from the silica gel column (toluene-EtOAc, 80:20) and were isolated in pure form in 10.1% and 39.1% yield, respectively. It should be noted here that no preparative HPLC was required for further purification, showing that the difference in polarity is sufficient enough for classical column chromatographic separation. Both isomers exhibit a cherry-red colour in solution and their structural assignment was accomplished by ^1H NMR, ^{13}C NMR and UV/Vis spectroscopy, and by mass spectrometry.

The FAB-MS (NBA) of (+)-**10a** and (–)-**10b** show the expected $[\text{M}^+ + 1]$ molecular ion at 1574 m/z , confirming that the threefold cyclopropanation of the fullerene core was successful. Their UV/Vis spectra are identical and of equal similarity with those of tris-adducts with an *e,e,e* addition pattern synthesized and



Scheme 3 Synthesis of the *trans*-4,*trans*-4,*trans*-4 (**9**) and the enantiomerically pure *e,e,e* (**10a**), (**10b**) tris-adducts.

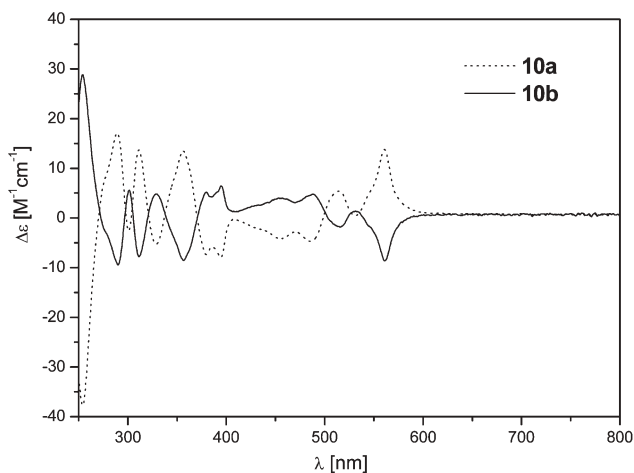


Fig. 1 CD spectra (CHCl₃) of the all-*R*^f-*A*-*e,e,e*-**10b** (solid line) and all-*R*^f-*C*-*e,e,e*-**10a** (dotted line) tris-adducts.

characterized previously.^{2,4,6,10} The ¹³C NMR spectrum of the major adduct (–)-**10b** is in complete agreement with the proposed structure. In the fullerene spectral region between 140 and 148 ppm, 15 of the 18 expected signals for the sp² carbon atoms of the fullerene are observed, indicating a C₃ molecular symmetry. The three missing signals are attributed to closely overlapping resonances. In addition, two signals for the fullerene sp³ carbons at 70.50 and 71.12 ppm, and one signal for the bridgehead sp³ C atoms at 54.18 ppm are present in the spectrum, while the carbonyl C atoms show two absorptions at 162.39 and 162.92 ppm. The methylene carbon atoms of the tether part show six absorptions as a set of three pairs, while the stereogenic methine carbons appear as two distinct peaks at 80.17 and 80.36 ppm. Finally, the methyl carbons of the isopropylidene moiety resonate at 27.10 and 27.22 ppm and the quaternary carbons appear at 108.22 ppm. The pattern of the ¹³C NMR spectrum of tris-adduct (+)-**10a** is similar to that of (–)-**10b**, showing only minor differences in the chemical shifts of the observed peaks. In addition, 16 resolved signals for the sp² fullerene carbons between 140 and 148 ppm can be clearly observed. This fact testifies that (+)-**10a** and (–)-**10b** compose a pair of diastereomers whose inherently chiral addition pattern has an enantiomeric relationship. The formation of the tris-adducts (+)-**10a** and (–)-**10b** is diastereoselective with a *de* value of 55% (HPLC), favouring the formation of (–)-**10b**.

The fact that (+)-**10a** and (–)-**10b** have an enantiomeric inherently chiral *e,e,e* addition pattern is clearly reflected in their circular dichroism (CD) spectra (Fig. 1), which show almost perfect mirror-image behaviour and pronounced Cotton effects. The chiroptical properties depend mainly on the chiral arrangement of the conjugated π-electron system within the fullerene core and not so much on the nature of the tether. Moreover, the CD spectra of the newly synthesized tris-adducts are identical to those of enantiomerically pure [60]fullerene adducts with an *e,e,e* addition pattern, synthesized previously^{3,4,6} by non-tethered

methods, and serve as fingerprints for the addition pattern and the absolute configuration. By direct comparison of the spectroscopic data, the configurations of (+)-**10a** and (–)-**10b** were unambiguously determined. Thus, the minor product formed in the tris-cyclopropanation of C₆₀ with tether (+)-**6** having an *e,e,e* addition pattern was assigned as the (*R,R,R,R,R,R*)-^f*C* isomer (+)-**10a**, while the major as the (*R,R,R,R,R,R*)-^f*A* (–)-**10b**. Finally, the specific rotation values [α]_D were measured in chloroform and found to be +1275° and –1389° for tris-adducts (+)-**10a** and (–)-**10b**, respectively.

In conclusion, we have developed a new method for the synthesis of enantiomerically pure tris-adducts of C₆₀ with an *e,e,e* inherently chiral addition pattern. The utilization of the optically active *D*₃-symmetrical cyclo-tris(malonate) tether (+)-**6** was proved highly regioselective for the all-*e* addition pattern and afforded the ^f*C*- and ^f*A*-enantiomers in good yields. Separation and purification was achieved by flash column chromatography on SiO₂.

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