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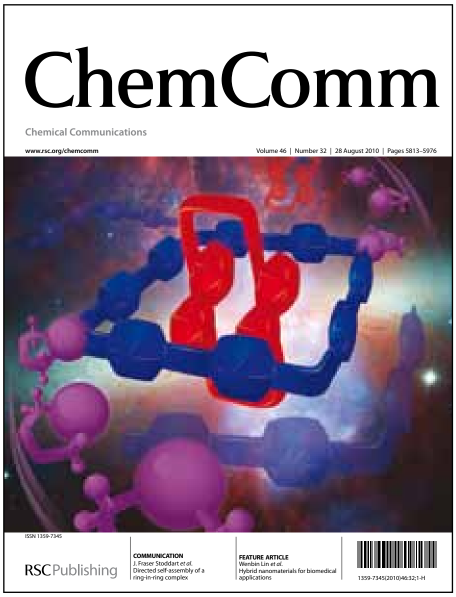

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ARTICLE TYPE

The first one-pot synthesis of a chiral pentakis-adduct of C_{60} utilising a opened-structure malonate tether†

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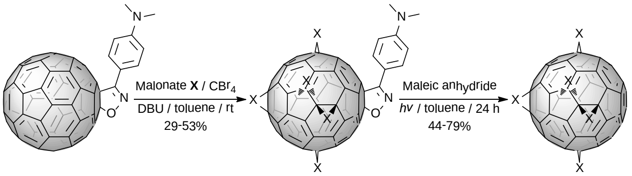
A pentakis-adduct of C_{60} with an incomplete octahedral addition pattern was synthesised in a one-pot procedure using a tether equipped with five malonate moieties. The five-fold Bingel cyclopropanation of C_{60} was completely regioselective and afforded a chiral, C_2-symmetric pentakis-adduct which was easily separated by column chromatography on SiO_2.

The arrangement of functional organic moieties in a stereochemically well-defined orientation in space requires a highly symmetric and reactive organic scaffold with a three-dimensional structure. Absolute control of the reactions employed for the covalent connection of the desired addends is another important issue targeting novel materials with specific properties and function. [60]Fullerene is the only organic molecule that fulfils these requirements and the development of strategies for the regioselective synthesis of multi-adducts has flourished the literature with unprecedented structures with potential applications in biological and materials science.[1]

Pentakis-adducts of C_{60} with an incomplete octahedral addition pattern[2] (Scheme 1, **3**) represent molecular building blocks with unique importance in storing and transferring structural and functional information. The five addends bound on the *equatorial* (*e*) double bonds located at the octahedral sites of the fullerene sphere can be endowed with a specific structural or functional property which can be transferred to another organic molecule *via* the ligation on the unreacted double bond at the remaining octahedral site. This activated [6,6] double bond can be selectively functionalised with a wide range of molecules, in a completely regioselective manner as has been well-established in the literature both theoretically and experimentally.[3,4]

The first synthesis of a cyclopropanated pentakis-adduct of C_{60} was reported in 1994, by Hirsch.[3] Starting from an *e,e,e* tris-adduct and employing stepwise Bingel[5] additions followed by preparative HPLC separations, a pentakis-adduct equipped with malonate ester moieties was successfully isolated and fully characterised. An improved synthesis was published in 1996 by the same group[6] where 9,10-dimethylanthracene (DMA) was used as a template in order to activate the *e* bonds at the octahedral sites of a C_{60} triazoline mono-adduct. Bingel cyclopropanation with an excess of diethyl 2-bromomalonate afforded the corresponding hexakis-adduct and subsequent thermal removal of the triazoline group furnished a pentakis-adduct which was separated by preparative HPLC. In 1997, Diederich[7] reported the synthesis of pentakis-adducts of C_{60} starting from a tethered *e,e,trans-1* tris-adduct and by performing selective *e* additions. The synthesised pentakis-adducts functionalised both with Bingel and Diels-Alder reactions were isolated by column chromatography. In a different approach, Duarte-Ruiz et al.,[8] cyclopropanated an *e,e,e* tris-adduct of C_{60} bearing three anthracene addends with diethyl 2-bromomalonate. An unstable pentakis-adduct, due to the lability of the attached anthracene groups, was subsequently isolated by column chromatography and characterised. Finally, the most efficient synthesis of pentakis-adducts of C_{60} with an incomplete octahedral addition pattern was reported in 2012, by Hirsch.[2] Bingel nucleophilic cyclopropanations of a series of malonates at the *e* bonds of isoxazoline monoadduct **1** (Scheme 1) led to the successful synthesis of hexakis-adducts **2**. Subsequent deprotection of the isoxazoline moiety under irradiation with light furnished the C_{2v}-symmetric pentakis-adducts **3** which were isolated by column chromatography. The overall yield of the sequence starting from C_{60} (over three steps: cycloaddition/five-fold Bingel cyclopropanation/retro-cycloaddition) was in the range of 8-13%.



1 **2** **3**

Scheme 1 Protection-deprotection strategy for the synthesis of pentakis-adducts of C_{60} reported by Hirsch.[2]

Our recent report[9] on the synthesis of a stable e_{edge},e_{face},*trans*-1 tris-adduct of C_{60} *via* a three-fold Bingel reaction with a tether bearing three malonate groups incorporated in a well preorganized molecular system, stimulated us to attempt the synthesis of a pentakis-adduct of C_{60} with an incomplete octahedral addition pattern in a one-pot procedure, *via* a five-fold Bingel cyclopropanation with an appropriate tether. The realisation of this quite challenging task was based on our previous report[10] where a tripodal tether with a phenoxy focal

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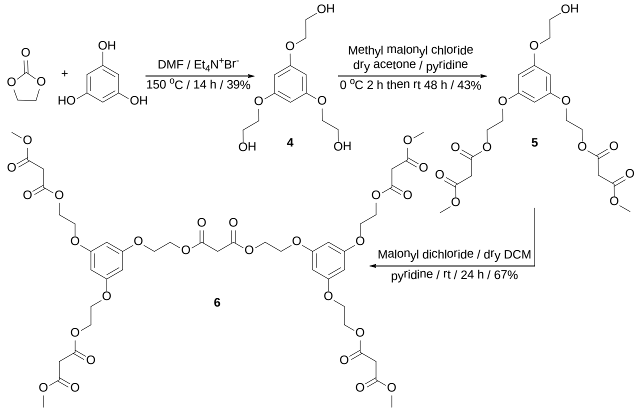
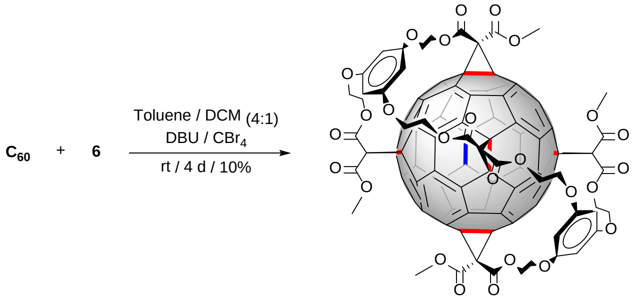
point was designed and successfully afforded an *e,e,e* tris-adduct of C_{60}. As the *e,e,e* addition pattern is part of the addition pattern of the targeted pentakis-adduct, we designed tether **6** (Scheme 2), featuring similar structural characteristics with the tripodal tether employed for the synthesis of the *e,e,e* tris-adduct but bearing five reactive malonate groups.



Scheme 2 Synthesis of tether **6**.

In the first step of our synthetic approach (Scheme 2), triol **4** was synthesised according to a literature procedure[11] followed by a two-fold esterification with methyl malonyl chloride. The reaction led to the formation of the mono-, bis- and tris-esterified products and thus, we optimised the reaction parameters (solvent, stoichiometry, concentration) in an effort to obtain the highest possible yield for the desired bis-ester **5**. Under the optimised conditions, the best yield for **5** was 43% while, the two by-products (mono- and tris-ester) were also isolated by column chromatography and fully characterised (see ESI†). In the last step, **5** was allowed to react with malonyl dichloride, in DCM solvent and in the presence of pyridine as a base to afford tether **6** which was isolated in 67% yield after purification with column chromatography on SiO_2.

In the next step, the one-pot, five-fold Bingel cyclopropanation of C_{60} with tether **6** was investigated (Scheme 3). The remote functionalisation was carried out in a mixture of toluene/DCM (4:1) as a solvent due to the insolubility of **6** in pure toluene. High dilution conditions were employed in order to avoid the attachment of more than one C_{60} molecules on the same tether and the reaction was performed in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base and a large excess of carbon tetrabromide.[12] TLC and HPLC monitoring of the reaction progress revealed the formation of a single fullerene adduct which was isolated by flash column chromatography on SiO_2 using a mixture of toluene/EtOAc (8:2) as an eluent. Pentakis-adduct **7** was isolated as an orange solid, in 10% yield after column chromatography and precipitation from DCM/pentane. It has to be highlighted here that the obtained yield is considered very satisfactory taking into account that the overall yield (over three steps) of the synthetic procedure introduced by Hirsch[2] ranged between 8-13%. The structural assignment of **7** was accomplished by ^{1}H-, ^{13}C NMR, UV-Vis spectroscopy and by MALDI-TOF mass spectrometry.



7

Scheme 3 Synthesis of pentakis-adduct **7**. Bonds in red denote the reacted double bonds of C_{60} while the blue represents the unreacted [6,6] double bond at the remaining octahedral site.

In the MALDI-TOF mass spectrum (positive mode, DCTB matrix) of the purified product **7**, the $[M+Na]^+$ ion at 1718 *m/z* (see ESI†) was clearly observed confirming that the five-fold Bingel cyclopropanation of C_{60} was successful and led to the formation of a pentakis-adduct. The incomplete octahedral addition pattern was unambiguously assigned with the aid of UV-Vis spectroscopy. In the UV-Vis spectrum of pentakis-adduct **7** (see ESI†), the pattern of absorptions in the region between 250-600 nm was identical with that of previously synthesized pentakis-adducts.[2]

NMR spectroscopy was crucial for the assignment of the proposed structure and molecular symmetry of pentakis-adduct **7** and the spectra were easily recorded due to the pronounced solubility of the compound in common organic solvents such as $CHCl_3$. In the ^{1}H NMR spectrum of **7**, all hydrogens were clearly observed but a complete assignment was difficult due to the diastereotopicity of the methylenic hydrogens induced by the covalent binding of the tether on the fullerene sphere. Nevertheless, the ^{13}C NMR spectrum was fully informative and provided an accurate assignment of the pure compound's structure. Specifically, in the ^{13}C NMR spectrum of **7** (Fig. 1), 24 signals for the *sp*^{2} carbons of the fullerene skeleton were observed in the region between 149-138 ppm clearly indicating a C_2-symmetric structure. This was further confirmed by the presence of five signals between 164-162 ppm corresponding to the ten carbonyl carbons, three signals for the six Ar*C*-O aromatic carbons at 160.35, 160.25 and 160.21 ppm, three distinct peaks at 94.28, 94.17, 94.10 ppm attributed to the six Ar*C*-H aromatic carbon atoms and five peaks at around 69 ppm characteristic for the ten fullerene *sp*^{3} carbons. Furthermore, all the other resonance signals in the ^{13}C NMR spectra were in full accordance with the C_2 symmetry of adduct **7** (for detailed ^{13}C NMR spectroscopic data see ESI†).

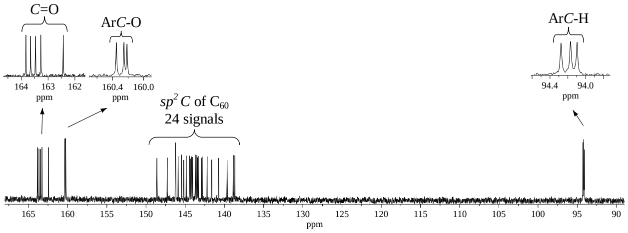


Fig. 1 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of pentakis-adduct **7** in the region 90-170 ppm.

Pentakis-adduct **7** possesses a C_2 axis of symmetry intersecting the unreacted double bond and its *trans*-1 cyclopropanated one located in the opposite hemisphere (Scheme 3). As a

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consequence, the molecule has axial chirality which results from the helicity adopted by the tether upon cyclopropanation of the five double bonds of C_{60}. The spherical structure of C_{60} and the achiral incomplete octahedral addition pattern built up by the five double bonds which are cyclopropanated, lock the tether molecule in a helically chiral arrangement and thus, pentakis-adduct **7** exists as a pair of enantiomers. Following the CIP rules[13] and with the aid of 3D-models, we have set an axis passing from the phenoxy groups of the tether and we observed the helicity of the organic chain connecting them, regarding its handedness (Fig. 2). This operation results in two enantiomeric forms namely, right-handed (*P*) and left-handed (*M*).

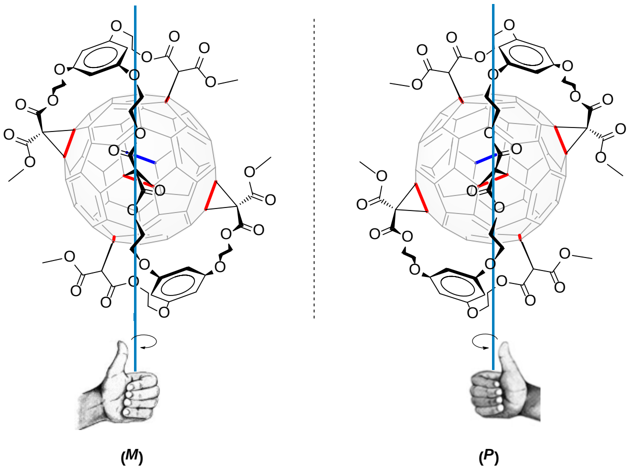
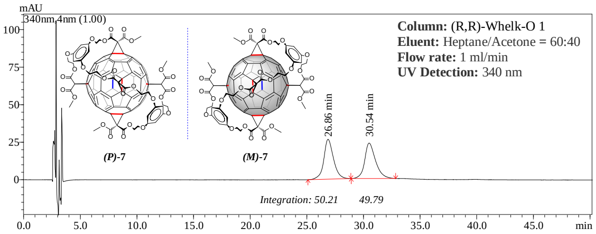


Fig. 2 Representation of the *P* and *M* enantiomers of pentakis-adduct **7**.

The chirality of pentakis-adduct **7** prompted us to attempt the resolution of the *P*- and *M*-enantiomers with the aid of analytical HPLC. For this purpose, we used a chiral Whelk-O 1 analytical column and a mixture of heptane/acetone (60:40) as an eluent. Under these conditions, a baseline separation was achieved for the racemic mixture (*P*)-**7**/(*M*)-**7**, as shown is Fig. 3. Small quantities (~0.5 mg) of each enantiomer were isolated in pure form by analytical HPLC in order to measure their circular dichroism (CD) spectra. As the concentration of the solutions could not be determined accurately due to the limited isolated quantities of (*P*)-**7** and (*M*)-**7**, the specific optical rotation values were not measured. The enantiomeric relationship of (*P*)-**7**/(*M*)-**7** resulting from the axial chirality of pentakis-adduct **7** was clearly reflected in their CD spectra (Fig. 4). The measured spectra showed mirror-image behaviour but the absolute configuration (*P* or *M*) of the first (26.86 min) and second eluted (30.54 min) enantiomer cannot be assigned at the moment without the aid of theoretical calculations.



Column: (R,R)-Whelk-O 1
Eluent: Heptane/Acetone = 60:40
Flow rate: 1 ml/min
UV Detection: 340 nm

Fig. 3 HPLC analytical resolution of the *(P)*-**7** and *(M)*-**7** enantiomers.

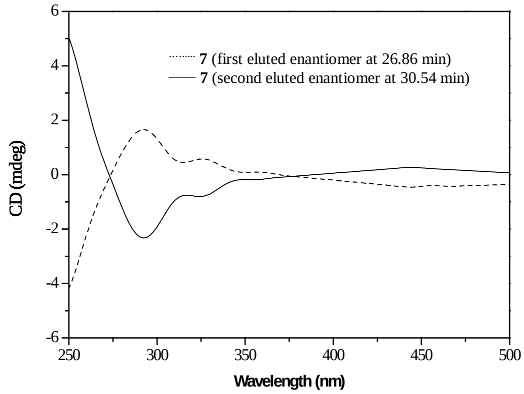


Fig. 4 CD spectra of the *P* and *M* enantiomers of pentakis-adduct **7**.

In conclusion, we have designed and synthesised a opened-structure tether equipped with five malonate moieties in an effort to target, for the first time, the one-pot synthesis of a pentakis-adduct of C_{60} with an incomplete octahedral addition pattern. The remote functionalisation of C_{60} with tether **6** was successful and afforded pentakis-adduct **7** in a completely regioselective manner. Isolation and purification was easily carried out by column chromatography on SiO_2 and **7** was obtained in 10% yield, as an orange solid. Its solubility was very good in common organic solvents and allowed a complete spectroscopic characterisation. Adduct **7** has axial chirality due to the helicity of the anchored tether and is the first chiral pentakis-adduct of C_{60}. Thus, it exists as a pair of enantiomers namely, (*P*)-**7** and (*M*)-**7** which were resolved by analytical HPLC on a chiral column. Isolation of the pure enantiomers allowed the measurement of their circular dichroism spectra which showed a perfect mirror-image pattern.

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