Regioselective synthesis and zone selective deprotection of [60]fullerene tris-adducts with an *e,e,e* addition pattern†

Florian Beuerle, Nikos Chronakis and Andreas Hirsch*

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***D*$_{3h}$-symmetrical tripodal tris(malonate) tethers have been used for the synthesis of [60]fullerene tris-adducts with an *e,e,e* addition pattern bearing topologically distinct polar and equatorial addend zones that can selectively be deprotected.**

The cyclopropanation of the [60]fullerene cage *via* the Bingel reaction can theoretically lead to the formation of eight regioisomeric bis-adducts[1] whereas, in the case of tris-adducts this number increases to 46.[2] In 1994,[1] we reported the synthesis and characterization of [60]fullerene tris-adducts *via* the stepwise nucleophilic cyclopropanation of the [6,6] bonds of the fullerene sphere. Tris-adducts with three-fold rotational symmetry like *trans*-3,*trans*-3,*trans*-3 and *e,e,e* were isolated, but this method required tedious chromatographic separations and purifications.

The concept of tethered systems[3] connecting the reactive malonate groups has been proved a powerful tool to control the regioselectivity of tris-additions on C_{60}. In 1999, Diederich[4] reported the regioselective synthesis of C_3-symmetrical tris-adducts by using a cyclotriveratrylene (CTV) tether connecting the malonate reactive groups. In this work, the all-*trans*-3 and all-*e* tris-adducts were isolated in 11% and 9% yields respectively, while the regioselective synthesis of C_{60} tris-adducts with rotational symmetry in good yields was demonstrated in an elegant way by utilizing cyclo-[*n*]-alkylmalonate[5] tethers with variable alkyl spacers connecting the malonate groups. Despite the improvements in the regioselective synthesis of C_{60} tris-adducts, the tether approaches mentioned showed two disadvantages that should be taken into consideration. In contrast to the cyclo-[*n*]-alkylmalonates, the CTV tether required multiple synthetic steps whereas, in both cases the tethers do not offer the possibility of further structural tuning. Specifically, the tethered functionalized tris-adducts of C_{60} can be only subjected to hydrolytic removal of the tether to afford the water soluble hexaacids of C_{60}. Further functionalization of the hexaacids was not possible due to decarboxylation phenomena.

It becomes obvious, that a new approach should be addressed for the synthesis of derivatized [60]fullerene tris-adducts that fulfils the following requirements: a) facile synthesis of tris(malonate) tethers, b) tunability of their structure by means of topologically distinct addend zones bearing protected functional groups, and c) subsequent selective chemical transformations *i.e.*, deprotection of the functional groups. For this purpose, we have developed the synthesis of tripodal tris(malonate) tethers where, the malonate reactive groups are connected *via* alkyl spacers with a benzene core, described as the focal point of the tether. The second ester moiety of each malonate is terminated by another protecting group. The concept of the newly designed tethers is demonstrated in Fig. 1. The tris-adducts derived from the Bingel cyclopropanation of C_{60} with this family of tethers possess two distinct addend zones namely, polar zone A and equatorial zone B. Zone A represents the focal point of the tether where the hydroxyl terminal groups of the alkyl spacers located in the pole of C_{60} are connected/protected with a benzene core. Zone B includes the *tert*-butyl ester functional groups terminating the alkyl substituents of the malonic ester moieties around the equator of C_{60}. The selective deprotection of the addends in zone A or B is expected to provide facile access to the direct synthesis of the C_{60} tris-adducts I and II, respectively. As was mentioned before, these structurally novel tris-adducts are not accessible starting from the *e,e,e* tris(malonic acid) of C_{60}. Finally, the fullerene cage can also be regarded as a reactive zone, taking into account the possibility of further functionalization in targeting hexa-adducts, as well as the fact that, to a certain extent, it retains the unique electronic properties of a fullerene molecule.

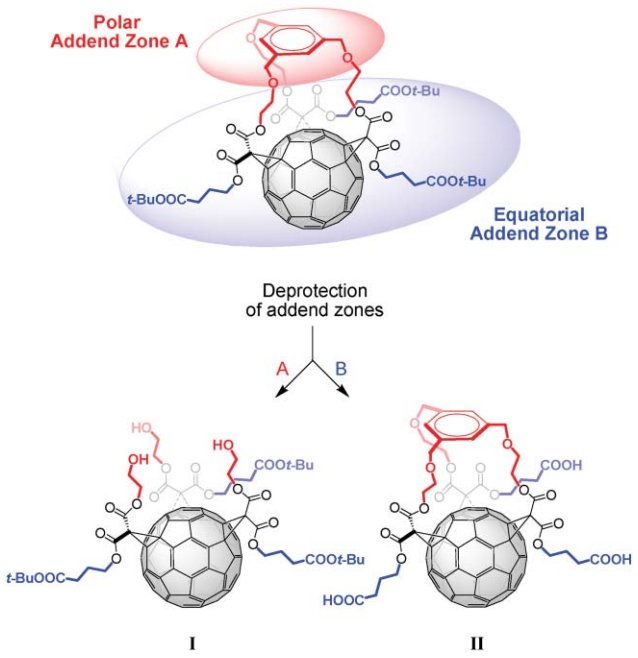

Fig. 1 Topologically distinct polar (A) and equatorial (B) addend zones and selective deprotection of the remote sites.

Institut für Organische Chemie der Universität Erlangen, Henkestrasse 42, D-91054 Erlangen, Germany. E-mail: andreas.hirsch@chemie.uni-erlangen.de; Fax: (+49) 9131 8526864; Tel: (+49) 9131 8522537

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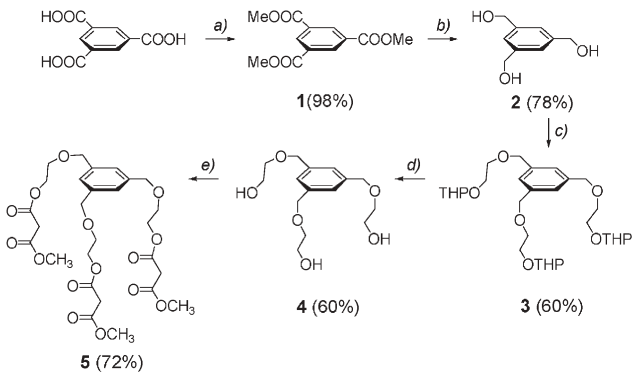
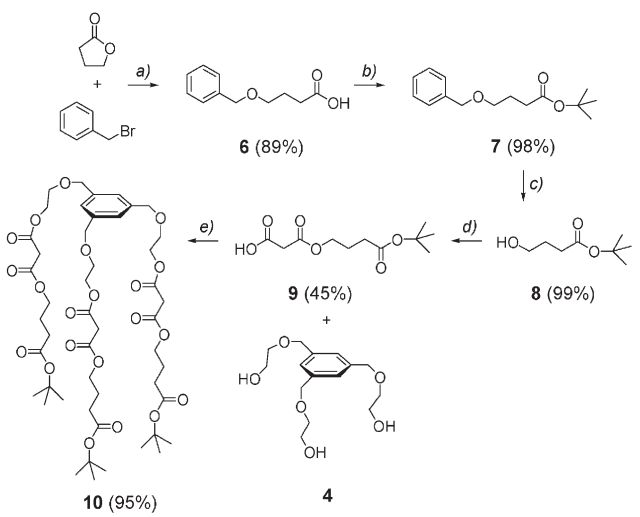
The synthesis of the first example of such a tripodal tether (**5**) is shown in Scheme 1. Triol **4** was synthesized starting from benzene-1,3,5-tricarboxylic acid according to a literature procedure.[6] Treatment of **4** with methyl 3-chloro-3-oxopropionate in the presence of pyridine in CH_2Cl_2, followed by flash column chromatographic purification, afforded pure **5** in 72% yield.

Targeting tripodal tethers bearing easily removable protective groups in the side chains, we performed the synthesis of tether **10** (Scheme 2), where the malonic ester moieties are further elongated with C_3 alkyl chains terminated by *tert*-butyl ester groups. In this case, selective hydrolysis of the ester moieties or focal deprotection (debenzylation) of the formed tris-adducts of C_{60} can give a facile access to structurally different derivatives. For this purpose, *tert*-butyl 4-hydroxybutyrate[7] (**8**) was prepared (Scheme 2) and then subjected to a DCC monoesterification reaction with malonic acid to yield the mono-protected diacid **9**. Three-fold esterification of triol **4** with acid **9** by using DCC and DMAP in CH_2Cl_2, afforded the tether **10** in 95% isolated yield.



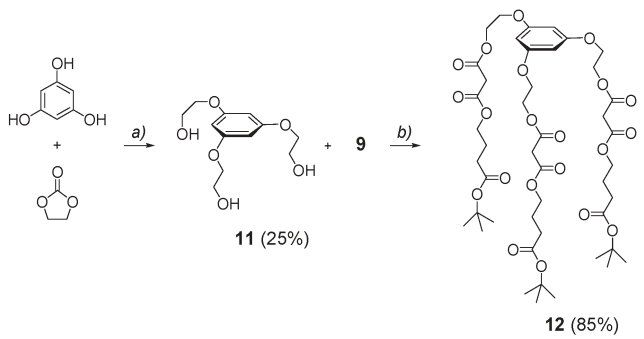
Scheme 1 Synthesis of the tripodal tether **5**; *a)* H_2SO_4, MeOH, reflux; *b)* $LiAlH_4$, THF; *c)* $BrCH_2CH_2OTHP$, THF, reflux, 7 days; *d)* HCl, CH_2Cl_2–MeOH, 1:1, rt; *e)* $ClC(O)CH_2CO_2CH_3$, C_5H_5N, CH_2Cl_2, 0 °C → rt.



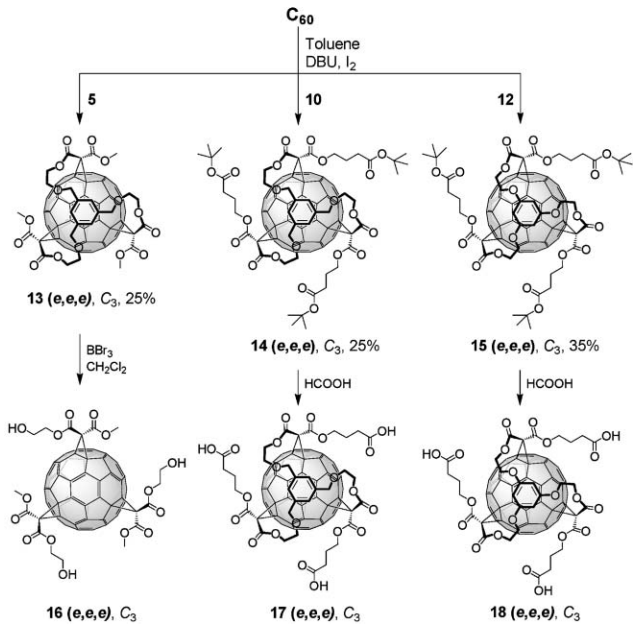
Scheme 2 Synthesis of the tripodal tether **10**: *a)* toluene, NaOH, reflux; *b)* isobutene, H_2SO_4, CH_2Cl_2; *c)* H_2, Pd/C, toluene; *d)* $CH_2(CO_2H)_2$, DCC, CH_2Cl_2, 0 °C → rt; *e)* DCC, DMAP, CH_2Cl_2, 0 °C → rt.

Molecular modelling studies showed that replacement of the focal benzyl site by a phenyl group favors the regioselective formation of the *e*,*e*,*e* fullerene tris-adduct. It is postulated that the reduction of the tether length is responsible for the increased calculated thermodynamic stability of the *e*,*e*,*e* regioisomer over other isomers such as, for example, the *trans*-3,*trans*-3,*trans*-3. Consequently, tether **10** was modified by replacing the benzyloxy protective group with phenoxy, thus shortening each spacer by one carbon atom. For this purpose, triol **11** was synthesized in one step[8] followed by a DCC esterification reaction with acid **9** (Scheme 3). The reaction was performed in THF, as **11** was insoluble in CH_2Cl_2 and, after chromatographic purification, tether **12** was obtained in pure form in 85% yield.

We then investigated the Bingel functionalization of C_{60} with the D_{3h}-symmetrical tether **5**. The reaction was carried out at a concentration of 0.55 mmol L^{-1} of C_{60} in toluene, in the presence of I_2 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Flash column chromatographic separation of the crude mixture (SiO_2, toluene–EtOAc, 70:30) afforded two fractions, which were further analyzed by FAB-MS and HPLC. The first, least polar fraction, showed the expected 1315 *m*/*z* molecular ion in the FAB-MS spectrum, thus confirming that the three-fold Bingel cyclopropanation occurred successfully on C_{60}. The HPLC elugram consisted of one peak but ^1H and ^{13}C NMR analysis revealed that this fraction was a mixture of tris-adducts, not separable by chromatographic methods. The second, most polar fraction consisted of a single tris-adduct and was formed in 55% relative yield. The structure of **13** was assigned by comparison of its UV/Vis spectra with those of previously reported *e*,*e*,*e* tris-adducts.[1,4,5,9] The ^1H and ^{13}C NMR spectroscopic data were in agreement with an *e*,*e*,*e* addition pattern (Scheme 4). In the fullerene spectral region between 140 and 148 ppm, 17 of the 18 expected signals for the sp^2 carbon atoms of the fullerene are observed, indicating a C_3 symmetry. The signal at 146.64 ppm is of double intensity. In addition, two signals for the fullerene sp^3 carbons at 69.72 and 70.65 ppm, and one signal for the bridgehead sp^3 C-atoms at 52.56 ppm are present in the spectrum while, the carbonyl C-atoms show two absorptions at 163.20 and 163.82 ppm. The ^1H NMR spectra (Fig. 2) shows a singlet absorption at 7.08 ppm for the phenylic protons and two doublets at 4.43 and 4.50 ppm for the diastereotopic benzylic hydrogens, while it is worth noting that the two diastereotopic methylenic protons H_a and $H_{a'}$ experience totally different chemical environments reflected in the large difference between their chemical shifts (0.53 ppm). These protons resonate at 4.23



Scheme 3 Synthesis of the tripodal tether **12**: *a)* $NBu_4^+Br^-$, DMF, 150 °C, 14 h; *b)* DCC, DMAP, THF, 0 °C → rt.



Scheme 4 Tether directed remote functionalization of C_{60} with the tripodal tris(malonate) tethers and subsequent selective deprotection of the polar and equatorial addend zones.

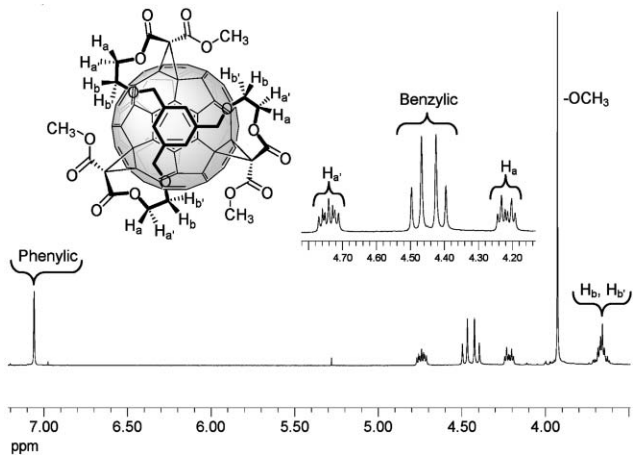


Fig. 2 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13**.

and 4.76 ppm, correspondingly. Tris-adduct **13** was isolated in pure form (SiO_2, toluene–EtOAc, 70:30) as a cherry-red solid, in 25% yield.

The Bingel cyclopropanation of C_{60} with the D_{3h}-symmetrical tether **10** was carried out under the same experimental conditions used in the reaction of C_{60} with tether **5**. Tether **10** showed similar regioselectivity, leading to the formation of a mixture of non-separable tris-adducts eluted in a single fraction (SiO_2, toluene–EtOAc, 70:30) and the *e*,*e*,*e* regioisomer **14**, which was formed in 55% relative yield (Scheme 4). Tris-adduct **14** was isolated in 25% yield and characterized by ^{1}H, ^{13}C NMR and UV/Vis spectroscopy, and FAB-MS.

An improved enhancement in the regioselectivity of the Bingel tris-addition was observed when C_{60} was treated with the tripodal tether **12** in toluene, in the presence of I_2 and DBU. The reaction afforded with complete regioselectivity the C_3-symmetrical *e*,*e*,*e* tris-adduct **15** (Scheme 4) which was purified by flash column chromatography on SiO_2 using a mixture of toluene–EtOAc, 80:20, as eluent. The addition pattern was unambiguously assigned by ^{1}H, ^{13}C NMR, and UV/Vis spectroscopy and **15** was isolated in pure form in 35% yield.

With the successfully synthesized and characterized *e*,*e*,*e* tris-adducts **13**, **14**, and **15** in hand, we attempted in the next step the selective deprotection of the distinct addend zones. The deprotection of the benzyloxy moiety[10] of tris-adduct **13** (focal deprotection) was carried out in the present of a Lewis acid as it had been reported that removal of the *O*-benzyl groups of sugar fullerene derivatives by palladium catalyzed hydrogenolysis, afforded a complex mixture due to decomposition of C_{60}.[11] A rapid reaction was observed on the addition of BBr_3 to a solution of **13** in CH_2Cl_2 at −70 °C, and the formed *e*,*e*,*e* triol **16** (Scheme 4) was isolated by flash column chromatography (SiO_2, CH_2Cl_2–CH_3OH, 95:5). The FAB-MS showed the expected M^+ molecular ion at *m*/*z* 1201, whereas the UV/Vis spectrum was in full agreement with the *e*,*e*,*e* addition pattern. Furthermore, the treatment of tris-adducts **14**, **15** with formic acid led to the hydrolysis of the *tert*-butyl ester groups to form the corresponding tris-acids **17** and **18** respectively, as demonstrated by FAB-MS and UV/Vis spectroscopy.

In conclusion, we have synthesized a new family of tripodal D_{3h}-symmetrical tris(malonate) tethers and investigated their regioselectivity in the Bingel cyclopropanation of C_{60}. Tuning of the spacer length allows for a significant improvement in selectivity for *e*,*e*,*e* regioisomer formation whereas selective deprotection of the topologically distinct polar and equatorial addend zones provides facile synthetic access to appealing building blocks for further selective functionalization.

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