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The journey of L-tartaric acid in the world of enantiomerically pure bis- and trisadducts of C₆₀ with the inherently chiral *trans*-3 and *all-trans*-3 addition patterns

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Abstract

Inherently chiral multi-adducts of [60]fullerene represent unique chiral molecular tectons featuring fascinating optoelectronic properties. Herein we discuss the most recent progress in the synthesis of enantiomerically pure bis- and trisadducts of C₆₀ with the inherently chiral *trans*-3 and *all-trans*-3 addition patterns utilizing *cyclo*-[n]-malonate tethers derived from (–)-dimethyl-2,3-*O*-isopropylidene-L-tartrate. Some future perspectives regarding the investigation of these chiral building blocks in modern areas of research are discussed.

Introduction

The discovery of molecular chirality by Pasteur in 1848¹ has been recognized as a landmark in the birth and development of molecular chemistry. Nowadays, chirality remains a beehive of remarkable research activity and this is readily proved by the number of published papers dedicated to this topic. The asymmetrical tetrahedral carbon proposed by Le Bel² and van't Hoff in 1874³ is not considered anymore the only source of chirality in the molecular world. As chirality is rigidly connected with symmetry, other kinds such as planar and axial chirality⁴ are well documented in the literature. It is really fascinating how fast chirality is being integrated in all modern research areas (e.g.

supramolecular chemistry, nanotechnology)⁵ revealing its universal and fundamental role which also plays in life.

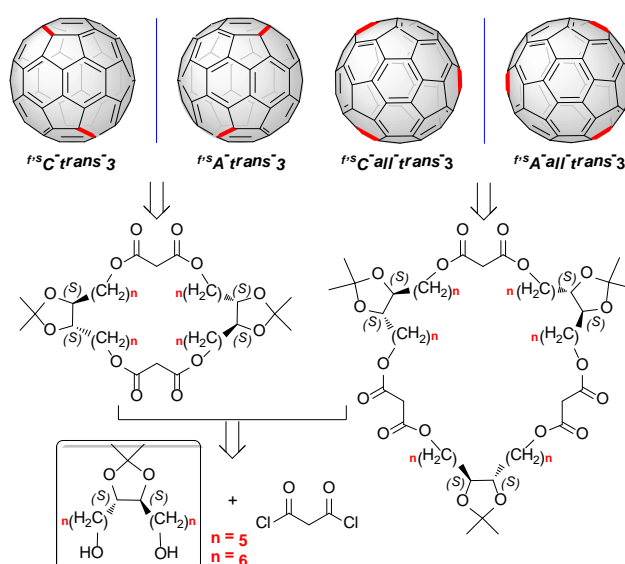
The discovery of fullerenes in 1985⁶ was another landmark in the history of chemistry. Although the most abundant fullerene C₆₀ is achiral, the simplest way to produce chiral derivatives is the functionalization of the double bonds with chiral addends. A glycoconjugate of C₆₀ was the first reported⁷ enantiomerically pure derivative of this kind. As chirality in fullerenes is a very attractive and important topic in the fields of medicinal chemistry and material science, stereoselective additions on C₆₀ have been recently developed by Martín⁸ employing metal-catalysed processes and organocatalytic methods. In the context of multiple additions on C₆₀, an exciting area in fullerene chemistry emerged when the first bis-osmylated *trans*-2 and *trans*-3 bisadducts were isolated in enantiomerically pure form and their circular dichroism (CD) spectra were recorded.⁹ Their chirality originates from the geometric arrangement of the addends and not from the presence of stereogenic centers in the added groups. In one enantiomer, the π -electron cloud of the fullerene core adopts a helically chiral arrangement which has a mirror-image relationship with the π -cloud of the other enantiomer. This kind of chirality is called inherent chirality¹⁰ and resembles the one met in helicenes.¹¹ For the configuration of the enantiomers of an inherently chiral fullerene adduct, the descriptors ^{f,s}C and ^{f,s}A are used. What is really amazing with these unique molecular tectons is the large magnitude of their specific rotations and the strong Cotton effects attributed to the chirality of the π -electron system. The fullerene chemists were now in front of a big challenge: to achieve the synthesis and isolation of enantiomerically pure C₆₀ multi-adducts with an inherently chiral addition pattern in macroscopic quantities. The marriage between chirality and multiple addition chemistry

on C₆₀ had already given birth to novel molecular structures endowed with exceptional chirality.

Synthesis of enantiomerically pure bis- and trisadducts of C₆₀ with the inherently chiral *trans*-3 and *all-trans*-3 addition patterns.

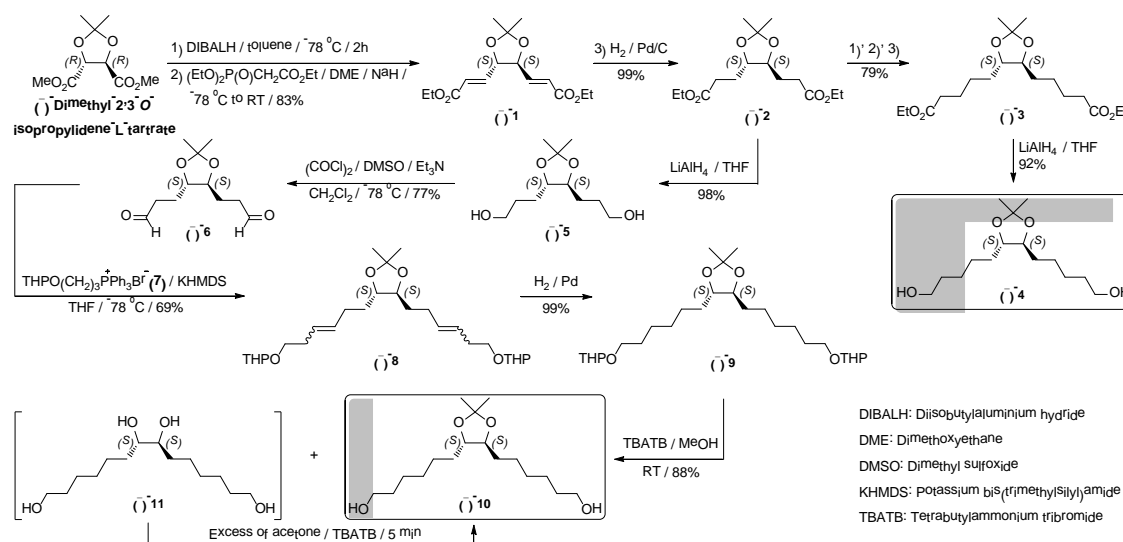
Fascinated by the three-dimensional chirality of the inherently chiral [60]fullerene derivatives, we dedicated part of our research on the synthesis, isolation and characterization of enantiopure bis- and trisadducts of C₆₀ with an inherently chiral addition pattern. In 2005, we reported the synthesis of enantiomerically pure trisadducts of C₆₀ with the inherently chiral *e,e,e* (*all-e*) addition pattern utilizing an enantiopure *cyclo*-trimalonate tether derived from 3,4-*O*-isopropylidene-D-mannitol.¹² The synthesis and isolation of the pure enantiomers of the inherently chiral *trans*-3 and *trans*-3,*trans*-3,*trans*-3 (*all-trans*-3) addition patterns of C₆₀ still represent challenging tasks. This is due to the fact that the optically pure tethers required for this purpose should have extended structures and at the same time the reactive groups should be well-preorganized. Diederich *et al.*, reported the synthesis of the ^{*f,s*}C and ^{*f,s*}A enantiomers of a *trans*-3 bisadduct by employing a bismalonate tether based on the Tröger's base motif¹³ and a few years later, the ^{*f,s*}C and ^{*f,s*}A enantiomers of an *all-trans*-3 trisadduct utilizing a rigid CTV-derivative equipped with three malonate ester moieties.¹⁴ However, in both cases, preparative HPLC was required for the successful separation of the two enantiomeric forms of the tether and/or the formed fullerene adducts. Moreover, apart from transesterification, these fullerene products cannot be further derivatized since the tethers located on the fullerene are not equipped with additional reactive groups.

Our purpose was to establish a general methodology, capable to give access to macroscopic quantities of these compounds without the need of preparative HPLC for their isolation and purification. We also desired the installation of functional groups in the fullerene adducts as their incorporation in molecular assemblies would offer new opportunities in the construction of chiral, fullerene-containing materials. Thus, we designed two families of optically pure *cyclo*-[*n*]-malonate esters with C12 and C14 spacers connecting the malonate groups which were utilized in the Bingel functionalization of C₆₀ targeting the regioselective formation of the inherently chiral *trans*-3 and *all-trans*-3 fullerene adducts (**Scheme 1**). Following the general strategy for the separation of enantiomers, the enantiopure tethers will convert the two enantiomers of an inherently chiral addition pattern into diastereomers and thus, their separation should in principle be feasible by column chromatography. The synthesis of *cyclo*-[*n*]-malonate esters can be realized by the condensation reaction of the appropriate enantiopure diol with malonyl dichloride, under the optimized conditions reported in the literature¹⁵ (**Scheme 1**).



Scheme 1 Optically pure *cyclo*-[*n*]-malonate esters designed to target the inherently chiral *trans*-3 and *all-trans*-3 addition patterns of C₆₀. (Single column)

The choice of the chiral isopropylidene acetal functionality in the designed tethers was not accidental as (–)-dimethyl-2,3-*O*-isopropylidene-L-tartrate is a commercially available and versatile chiral pool synthon which can be employed as a chiral inductor and at the same time carries the acetonide group which upon deprotection liberates the 1,2-diol moiety. Thus, our second target regarding the post-functionalization of the inherently chiral fullerene derivatives could be reached by using this simple derivative of L-tartronic acid. Starting from this reagent we had to prepare the corresponding diols with different chain length and this is illustrated in **Scheme 2** where the synthesis of the optically pure diols bearing C12 and C14 spacers connecting the hydroxyl groups is presented. In order to reach this synthetic methodology which offers a general way for the synthesis of optically pure diols equipped with the chiral isopropylidene acetal moiety and bearing long alkyl chains, numerous alternatives have been investigated. At this point we would like to highlight the most important findings



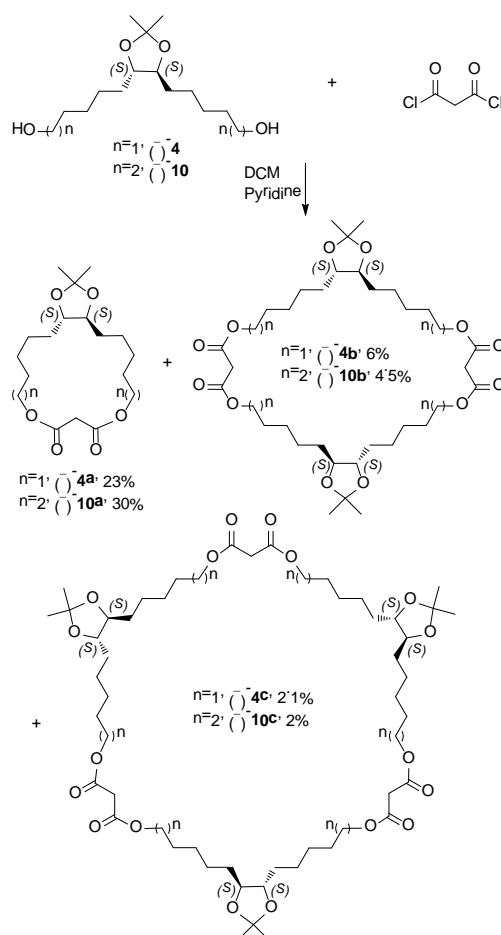
Scheme 2 Synthesis of optically pure diols bearing C12 and C14 spacers. (Double column)

and draw some general conclusions derived from this study. Starting from (–)-dimethyl-2,3-*O*-isopropylidene-L-tartrate, the sequence DIBALH reduction/*in situ* Wittig-Horner olefination with triethyl phosphonoacetate/catalytic hydrogenation afforded in very

good overall yield diester (–)-**2** with each carbon chain elongated by two carbon atoms. The same sequence was applied starting from (–)-**2** to yield with the same efficiency diester (–)-**3** endowed with two more carbon atoms in each chain. Finally, reduction of (–)-**3** with LiAlH_4 furnished the optically pure diol (–)-**4** with a C12 alkyl spacer connecting the hydroxyl groups. In order to access the enantiopure diol (–)-**10** (Scheme 2) which bears a longer alkyl spacer (C14), we started from diester (–)-**2**. Reduction with LiAlH_4 followed by a Swern oxidation afforded the optically pure dialdehyde (–)-**6** which was stable during chromatography on SiO_2 and could be stored for several weeks at 0 °C without signs of decomposition. Dialdehydes which do not contain stabilizing α -substituents are usually unstable¹⁶ and they are further manipulated directly after their isolation or their *in situ* generation, without further purification. A two-fold Wittig olefination with a three-carbon ylide was subsequently required in an effort to achieve elongation of each carbon chain in (–)-**6** by three carbon atoms. Among a diversity of phosphonium ylides screened, the THP-protected ylide derived from phosphonium salt **7** was the best choice and afforded the C14 unsaturated THP-protected diol (–)-**8** in excellent yield for a two-fold Wittig transformation. Hydrogenation of the double bonds led to the protected enantiopure diol (–)-**9** which is the precursor of the targeted diol (–)-**10**. Although the THP-deprotection is presumed to be a straightforward process, several acidic catalysts had to be explored in order to find the optimum conditions for the two-fold THP-deprotection of (–)-**9**. Tetrabutylammonium tribromide (TBATB) was the catalyst of choice based on its associated ease of handling and work-up¹⁷ and the significantly shorter reaction time required. To our surprise, with most catalysts, the THP-deprotection of (–)-**9** was accompanied by the deprotection of the acetonide group. That was also observed with TBATB¹⁷ which according to the literature does not affect the isopropylidene acetal groups. This problem was efficiently circumvented by adding

excess of acetone into the mixture, after the reaction was completed. This way, the fully deprotected product (–)-**11** was transformed *in situ* back to the desired optically pure diol (–)-**10**. To this end, the developed methodology gives access to enantiomerically pure diols equipped with a masked 1,2-diol moiety and long alkyl chains connecting the free hydroxyl groups. We hope that apart from the purpose they served in our research, these functional enantiopure building blocks will be also important in other areas such as asymmetric synthesis and chiral recognition.

With diols (–)-**4** and (–)-**10** available in large scale, the next step was the condensation reaction with malonyl dichloride towards the synthesis of the optically pure *cyclo*-[n]-malonate esters (**Scheme 3**). Following the optimized general



Scheme 3 Synthesis of the enantiopure *cyclo*-[n]-malonates bearing C12 and C14 spacers. (Single column)

experimental procedure,¹⁵ the macrocyclization reactions were performed under high dilution conditions, in CH₂Cl₂ solvent and in the presence of pyridine as a base. The formed *cyclo*-[n]-malonates (n=1,2,3) were separated by column chromatography on SiO₂ and were fully characterized. As expected according to previous studies,¹⁵ the cyclization reactions favored the formation of the monomeric products compared to the corresponding dimers and trimers. The purification procedure of the oligo-malonates with C14 spacers required repeated chromatographic separations compared to the corresponding C12-analogues. This indicates that the length of the alkyl spacer of diol (–)-**10** comprised of 14 carbon atoms might represent the limit for the successful separation and isolation of such optically pure macrocyclic oligo-malonates esters resulting from the condensation reaction of malonyl dichloride with diols bearing a chiral 1,2-acetonide core. In conclusion, the successful condensation reactions of the optically pure diols (–)-**4** and (–)-**10** with malonyl dichloride have undoubtedly demonstrated the feasibility of this versatile one-step procedure which allowed synthetic access to two novel families of enantiopure *cyclo*-[n]-malonate esters bearing long alkyl chains. The only major drawback is the low yields of the bis- and trismalonates due to the statistical nature of the specific reactions. These yields could be improved by applying templated synthesis or by designing alternative synthetic pathways involving multi-step protection/deprotection chemistry.

The enantiopure bismalonates (–)-**4b** and (–)-**10b** were excellent tethers for the regioselective Bingel functionalization of C₆₀ and led to the regioselective formation of the corresponding ^{f,s}C- and ^{f,s}A-*trans*-3 bisadducts with low diastereoselectivity but with very good to excellent total yields (**Scheme 4**).¹⁸ Noteworthy is the combined isolated yield of bisadducts (+)-**13a** and (–)-**13b** resulting from the cyclopropanation of C₆₀ with C14-tether (–)-**10b** which reached the remarkable value of 68%. This clearly

demonstrates the superior efficiency of the specific tether compared to the C12-analogue (–)-**4b**. In both cases, the formed *trans*-3 bisadducts were isolated in pure form by column chromatography and were fully characterized. The separation of bisadducts (+)-**13a** and (–)-**13b** was more easy compared to (+)-**12a** and (–)-**12b**, crediting C14-*cyclo*-malonate tether (–)-**10b** with an additional advantage. In **Figure 1**, the CD spectra of the enantiopure *trans*-3 bisadducts (+)-**13a** and (–)-**13b** are presented. The spectra show perfect mirror-image behaviour due to the enantiomeric relationship of the carbon cores with strong Cotton effects originating from the chirality of the π -electron system.

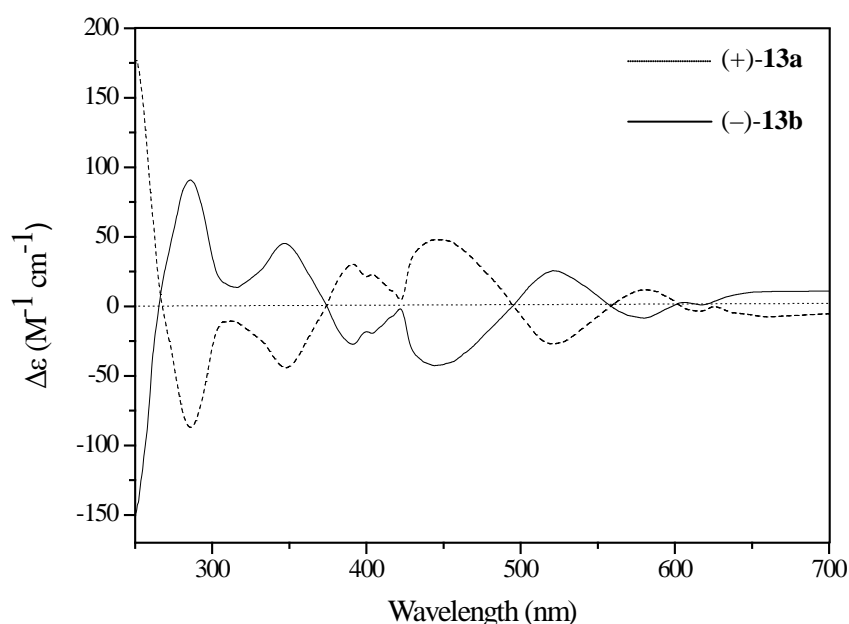
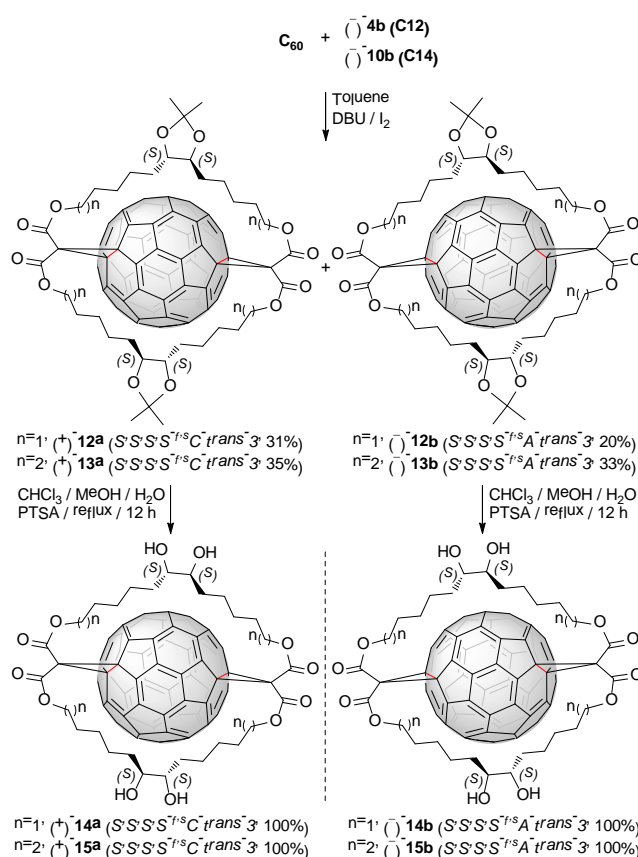


Figure 1 CD spectra (CHCl_3) of the isolated (+)-**13a** and (–)-**13b**. (Single column)

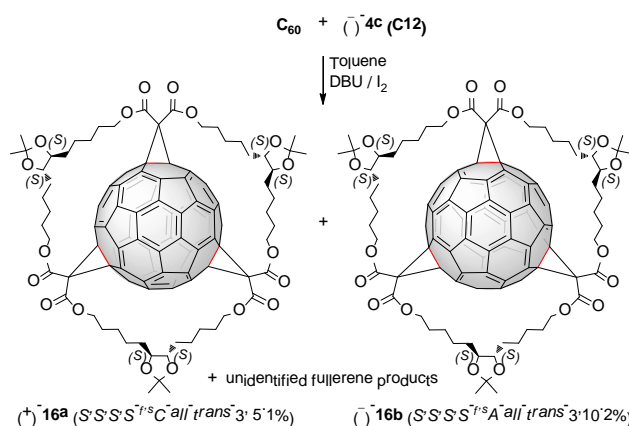
The acetal deprotection of the synthesized *trans*-3 bisadducts was successfully carried out by using *p*-toluenesulfonic acid (PTSA) as a catalyst to afford in quantitative yields the corresponding poly-alcohols (**Scheme 4**) which represent novel chiral fullerene compounds equipped with glycol moieties. This offers the potential for further derivatization of the specific compounds targeting the construction of enantiopure

functional fullerene materials equipped with fascinating chiroptical properties resulting from the inherently chiral *trans*-3 addition pattern of the fullerene chromophore.



Scheme 4 Synthesis and deprotection of enantiomerically pure *trans*-3 bisadducts of C_{60} . (Single column)

In contrast to bismalonates $(-)-4b$ and $(-)-10b$, the regioselectivity of the Bingel tris-cyclopropanation of C_{60} with tethers $(-)-4c$ and $(-)-10c$ was poor. C14-trismalonate ester $(-)-10c$ afforded an inseparable mixture of several fullerene products and thus, the remote functionalization was investigated with C12-trismalonate ester $(-)-4c$. The reaction proceeded with poor regioselectivity to afford the targeted *all-trans*-3 trisadducts $(+)-16a$ and $(-)-16b$ in low isolated yields (**Scheme 5**). However, their



Scheme 5 Synthesis of enantiomerically pure *all-trans*-3 trisadducts of C_{60} . (Single column)

separation and purification was achieved by column chromatography on SiO_2 without the need of preparative HPLC. The poor regioselectivity of tether $(-)-4c$ and the low isolated yields of the $^{f,s}C$ and $^{f,s}A$ trisadducts $(+)-16a$ and $(-)-16b$ are additional proofs for the difficulty in accessing the *all-trans*-3 addition pattern. Nevertheless, the L-tartrate derived tether $(-)-4c$ revealed an unexpected stereoisomerism in the trisadducts formed. According to the ^{13}C NMR data, the isolated *all-trans*-3 trisadducts $(+)-16a$ and $(-)-16b$ have a C_2 symmetry instead of a C_3 . A new stereoisomerism was considered in order to explain the symmetry of the formed products which was attributed to the spatial arrangement of spacers in the tether and this is discussed in detail in our recently published work.¹⁹

Conclusions and outlook

Pasteur's investigation on the crystallization of racemic sodium ammonium tartrate in aqueous solution set the basis of an extraordinarily wide research area with a scientific but at the same time a philosophical character due to the unanswered questions regarding the origin of homochirality in living organisms. Although these questions may never find their answers, the science of chemistry has shed light to a plethora of

questions regarding chirality and how does it operate through the interactions of the different enantiomeric forms of a chiral molecule with a molecular or a supramolecular entity. The common element of our contribution in the area of chirality and Pasteur's studies is the key molecule L-tartaric acid. We have employed a simple derivative of this chiral natural product namely, (–)-dimethyl-2,3-*O*-isopropylidene-L-tartrate, in a journey where chirality was amplified during the construction process of larger molecular tectons such as *cyclo*-[n]-malonates and inherently chiral bis- and trisadducts of C₆₀. Our efforts have been fruitful in the development of a general methodology for the synthesis of enantiopure diols equipped with the isopropylidene acetal moiety and bearing long alkyl chains but their cyclization reactions with malonyl dichloride toward the synthesis of chiral *cyclo*-[n]-malonates have to be improved regarding the yields of the higher macrocycles (**Scheme 3**). A multi-step, protection/deprotection synthetic strategy cannot be excluded from our future plans but we consider the use of templates a more elegant method. The template effect is not expected to operate by using alkali metal cations due to the lack of oxygen atoms in the diol spacers and this has been also confirmed experimentally.²⁰ We have started to consider now the use of covalent templates which can bring the diol molecules in close proximity with a stoichiometry determined by which macrocycle is desired. This could be accomplished by the covalent connection of the diols with carbonyl compounds *via* the 1,2-diol moiety (acetal formation) which is liberated upon deprotection of the acetonide group. After the cyclization with malonyl dichloride has been accomplished, the template can be easily released under mild acidic conditions and the 1,2-diol groups can be re-protected as acetals to afford the *cyclo*-malonate tethers. Apparently, the template removal and the re-protection step can be carried out in a one-pot procedure.

The deprotection of the enantiomerically pure *trans*-3 fullerene bisadducts (**Scheme 4**) has been already investigated and the synthesis of inherently chiral fullerene bisadducts with functional 1,2-diol moieties is a target that has been reached. We believe that the acetal deprotection will also work efficiently with the synthesized trisadducts of C₆₀. Although the yield of the enantiopure *all-trans*-3 trisadducts (**Scheme 5**) is low and their synthesis requires multiple steps, the ^{f,s}C- and ^{f,s}A-enantiomers of a structurally identical (regarding the tether) *all-e* trisadduct¹² of C₆₀ were obtained in very good yields and without the aid of preparative HPLC. Taking into account that the 1,2-diol moieties of the deprotected bis- and trisadducts of C₆₀ with an inherently chiral addition pattern can serve as recognition sites for a plethora of organic groups, unexplored topics such as chiral recognition and development of catalysts for asymmetric synthesis await investigation. Furthermore, the ability of C₆₀ and its derivatives to produce singlet oxygen (¹O₂) upon irradiation,²¹ renders the synthesized inherently chiral fullerene poly-alcohols promising candidates as chiral photosensitizers.²¹ Prochiral alkenes with allylic hydrogens and functional groups which can bind the 1,2-diol moieties *via* non-covalent interactions (hydrogen bonds) can be photooxidized with ¹O₂ generated by the fullerene core, under irradiation. Studies on the enantioselectivity of the "ene" reaction²¹ leading to the formation of chiral allylic hydroperoxides are currently underway in our group.

Acknowledgements

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