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Remote Functionalization of C_{60} with Enantiomerically Pure *cyclo*-[2]-Malonate Tethers Bearing C12 and C14 Spacers: Synthetic Access to Bisadducts of C_{60} with the Inherently Chiral trans-3 Addition Pattern

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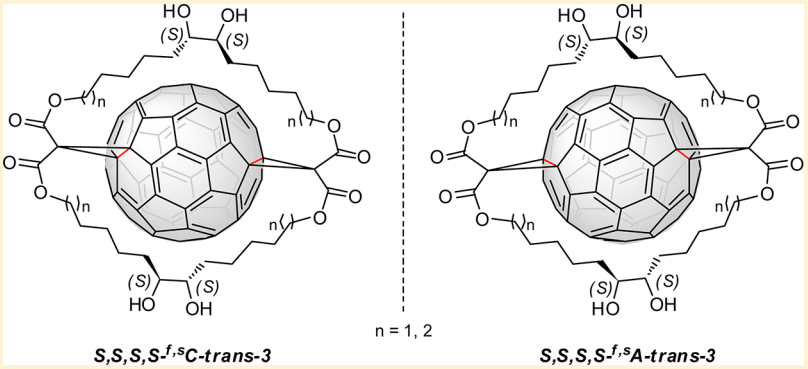
Supporting Information



ABSTRACT: In this Article, we describe the synthesis of two optically pure diols bearing a 1,2-diol moiety masked as an isopropylidene acetal group and long alkyl chains comprised of 12 and 14 carbon atoms, respectively. The synthetic methodology that was developed offers a general way for the synthesis of optically pure diols with long alkyl chains. Diols (−)-**4** and (−)-**9** were subjected to a condensation reaction with malonyl dichloride to afford two *cyclo*-[2]-malonate tethers that were separated by column chromatography in optically pure form. The bismalonates (−)-**4b** and (−)-**9b** proved to be excellent tethers for the regioselective Bingel functionalization of C_{60}, furnishing in a regioselective manner the corresponding $^{f,s}C$ and $^{f,s}A$ trans-3 bisadducts with low diastereoselectivity but in very good to excellent total yields. In both cases, the formed trans-3 bisadducts were isolated in pure form by simple column chromatography and were fully characterized. The successful acetal deprotection of the synthesized trans-3 bisadducts afforded quantitatively the corresponding polyalcohols, which represent novel chiral fullerene compounds equipped with glycol moieties.

INTRODUCTION

Enantiomerically pure organic compounds are essential in life, and the development of synthetic methodologies aiming to access them still remains a great challenge for organic chemists. Although [60]fullerene is an achiral molecule, it can be easily equipped with the property of chirality by functionalizing its double bonds with chiral addends. By taking advantage of the 30 reactive double bonds of C_{60} that are localized at the junctions of two hexagons,[1] different regioisomeric multiadducts can be constructed. If the addends are located at specific positions on the fullerene sphere, then adducts endowed with the property of inherent chirality can be formed.[2] After the first monoaddition on the fullerene cage, eight regioisomeric bisadducts (for identical addends) are possible because of the nonequivalent double bonds located in both hemispheres.[3] The C_2-symmetrical addition patterns cis-3, trans-2, and trans-3 are inherently chiral, which is a property exclusively attributed to the functionalization pattern and is characterized by the chirality of the π system of the fullerene chromophore.[2] Thus, the synthesis of enantiomerically pure bisadducts of C_{60} with an inherently chiral addition pattern has attracted great attention because of their possible applications in enantioselective synthesis, in chiral recognition, and in the construction of chiral macromolecular architectures. Investigations and synthetic efforts focused on this exciting area over the last 15 years have been reviewed in detail by Thilgen and Diederich.[4] The above-mentioned target was approached by the following ways: (1) The stepwise addition of achiral addends on C_{60} followed by the subsequent separation of the $^{f,s}C$ and $^{f,s}A$ enantiomers[5] 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, racemic, or enantiomerically pure tethers equipped with the reactive groups responsible for the addition reactions on the double bonds of the fullerene sphere. The inherently chiral trans-2 and trans-3 addition patterns of C_{60} have attracted particular attention because of

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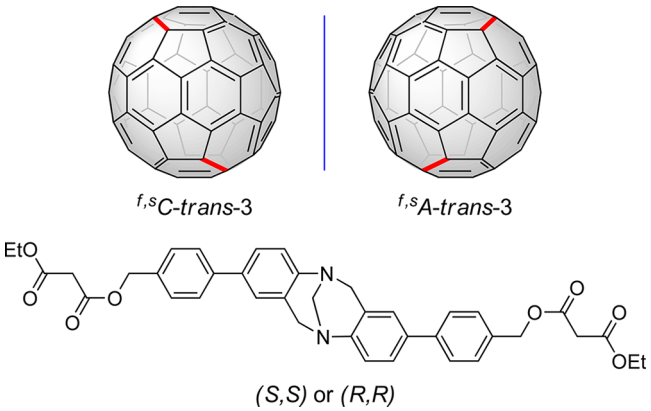
the fact that the chiral tethers required for the synthesis of the $^{f,s}C$ and $^{f,s}A$ enantiomers should have large and rigid structures. In a pioneering work, Diederich and co-workers[7] employed bismalonate tethers bearing the Tröger base motif as a spacer. Bingel addition of an optically pure 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.[6] By using the pure enantiomers of a more extended Tröger tether (with enantiomeric separation on chiral HPLC column), the isolation of the pure enantiomers of the trans-3 bisadducts was achieved after their separation by preparative HPLC on a Bucky Clutcher column (Scheme 1).

Scheme 1. ^{f,s}Clockwise and ^{f,s}Anticlockwise Enantiomers of the trans-3 Bisadduct of C_{60} and the Tröger's Base Tether Employed by Diederich[7] for Their Synthesis



The remote Bingel bis-functionalization of C_{60} was completely regioselective for the trans-3 addition pattern and afforded only bisadducts with an in−out configuration.[7] This work provided a major contribution to the synthesis of enantiopure bisadducts of C_{60} with the trans-3 addition pattern via the tether-directed remote functionalization concept. However, 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 the fullerene products cannot be further derivatized because the tethers located on the fullerene core are not equipped with additional reactive groups.

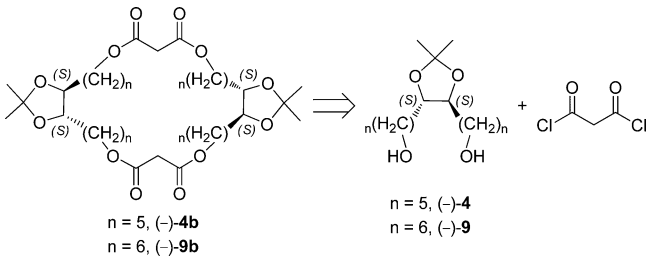
Stimulated by the challenge of establishing a procedure for the synthesis and isolation of the pure enantiomers of C_{60} bisadducts with the inherently chiral trans-3 addition pattern but without the need of preparative HPLC for the enantiomeric separation of the chiral tether or the formed fullerene adducts, we communicated recently[8] the synthesis of enantiomerically pure bisadducts of C_{60} with the inherently chiral trans-3 addition pattern using an optically pure *cyclo*-bismalonate tether derived from (−)-dimethyl-2,3-*O*-isopropylidene-L-tartrate. The concept of *cyclo*-[*n*]-malonate tethers, introduced by Hirsch,[9] has been successfully employed for the regioselective remote functionalization of C_{60}. We also reported on the further derivatization of the isolated enantiomerically pure bisadducts resulting from the promising properties of the trans-3 addition pattern.[8] 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}.

Now, we wish to present a complete study on the synthesis of enantiomerically pure bisadducts of C_{60} with the inherently chiral trans-3 addition pattern with the aid of two enantiopure *cyclo*-bismalonate tethers bearing spacers comprised of 12 and 14 carbon atoms, respectively. The experimental results have also allowed us to draw conclusions regarding the advantages and disadvantages of each tether on the basis of the number of synthetic steps required in each case, the ease of the separation and purification procedures, the regioselectivities of the Bingel twofold cyclopropanation of C_{60}, and the yield of the fullerene products formed. The key synthetic intermediates to access the enantiopure *cyclo*-bismalonates employed in this study are optically pure diols bearing a 1,2-diol moiety masked as an isopropylidene acetal group and long alkyl chains with 12 and 14 carbon atoms. Thus, we developed and present here an efficient and general methodology for the synthesis of these synthetically valuable chiral compounds in enantiopure form.

RESULTS AND DISCUSSION

Following our previous work on the regio- and diastereoselective tris-functionalization of C_{60} with an enantiopure *cyclo*-trismalonate tether derived from 3,4-*O*-isopropylidene-D-mannitol[11] and the report of Hirsch[9a] where achiral *cyclo*-[2]-dodecylmalonate was allowed to react with C_{60} under Bingel conditions and afforded completely regioselectivly a trans-3 bisadduct of C_{60} in 56% yield, we designed two optically pure *cyclo*-[2]-malonate esters with C12 and C14 spacers connecting the reactive malonate groups, respectively. If these tethers are selective for the trans-3 addition pattern of C_{60}, then it is expected to convert the two enantiomeric forms of the inherently chiral trans-3 addition pattern into diastereomeric; thus, their successful separation and isolation should in principle be feasible by simple column chromatography. The synthesis of *cyclo*-[2]-malonate esters can be realized by the condensation reaction of the appropriate enantiopure diol with malonyl dichloride under the optimized conditions reported earlier[12] (Scheme 2).

Scheme 2. Retrosynthesis of the Optically Pure *cyclo*-[2]-Malonate Tethers Bearing C12 and C14 Spacers



Synthesis of Enantiomerically Pure Diols Bearing C12 and C14 Alkyl Spacers. Our initial investigation was focused on the synthesis of optically pure diols bearing a 1,2-diol moiety masked as an isopropylidene acetal group and long alkyl chains composed of 12 and 14 carbon atoms, respectively. In our first approach, we investigated the nucleophilic substitution reaction of the ditosylate[13] and diiodide[14] derived from (−)-2,3-*O*-isopropylidene-D-threitol (Scheme 3) with Grignard and acetylide nucleophiles bearing C4 and C5 alkyl chains terminated by alcohol groups protected as THP or TBDMS ethers. In all cases, the reactions afforded complicated mixtures where the desired product could barely be detected by mass

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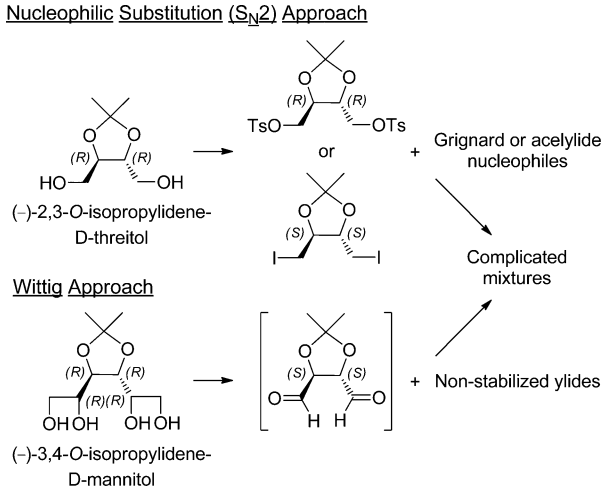
Scheme 3. Approaches to the Synthesis of Optically Pure Diols Bearing Long Alkyl Spacers



spectrometry. Thus, we changed our strategy and focused our efforts on the Wittig olefination reaction. The versatile chiral synthon (−)-3,4-*O*-isopropylidene-D-mannitol was first subjected to oxidative cleavage (with $NaIO_4$ or $Pb(OAc)_4$)[14,15] to afford the corresponding dialdehyde (Scheme 3) that cannot be isolated[15b,16] but should be used in situ in the Wittig step. To achieve the introduction of the alkyl chains, we employed nonstabilized ylides bearing four and five carbon atoms terminated by an ester moiety that can be easily transformed to an alcohol. The resulting reaction mixtures were again complicated, and only traces of the product could be detected with the aid of mass spectrometry.

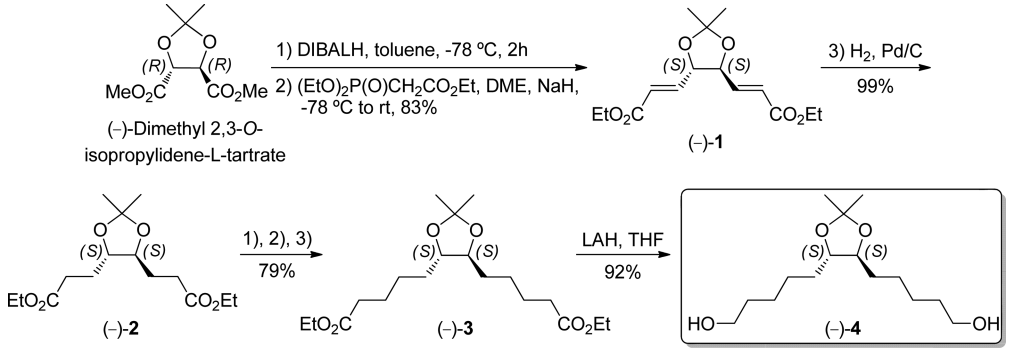
The synthesis of the optically pure diol (−)-**4** bearing a C12 spacer was finally performed via a five-step synthetic route[8] and is illustrated in Scheme 4. In a one-pot two-step transformation, (−)-dimethyl-2,3-*O*-isopropylidene-L-tartrate was reduced with DIBAL-H followed by the in situ Wittig−Horner reaction with triethyl phosphonoacetate to afford unsaturated diester (−)-**1** in 83% overall yield. This sequential transformation has been reported before[17] and served in our case as a general methodology for the elongation of alkyl chains terminated by an ester moiety by two carbon atoms. Each side chain of (−)-**2**, derived from hydrogenation of the double bonds of diester (−)-**1**, was subsequently elongated by two more carbon atoms via the same sequence (DIBAL-H reduction/Wittig−Horner/hydrogenation), and saturated diester (−)-**3** was obtained in very good overall yield. Finally, reduction of the ester moieties with LAH in THF solvent furnished optically pure diol (−)-**4** in 92% yield.

For the synthesis of optically pure diol (−)-**9** bearing a C14 alkyl spacer (Scheme 5), we started from unsaturated diester (−)-**2** that bears an eight-carbon chain and requires the elongation of each side chain by three carbon atoms. First, (−)-**2** was treated with LAH in THF to furnish diol (−)-**5** in 98% yield. Swern oxidation of diol (−)-**5** under inert conditions[18] afforded the optically pure dialdehyde (−)-**6** that proved to be stable during chromatography on SiO_2 and was isolated as a yellowish oil in 77% yield (Scheme 5). According to the literature,[19] dialdehydes that do not contain stabilizing α substituents are usually unstable. For this reason, they are further manipulated directly after their isolation or their in situ formation without further purification. However, dialdehyde (−)-**6** seemed to be quite stable and could be stored for several weeks at 0 °C without showing signs of decomposition.

The next step of our synthetic approach involves the twofold Wittig reaction of dialdehyde (−)-**6** with a three-carbon ylide bearing a terminal functional group that can be transformed to an alcohol. For this purpose, we synthesized a series of phosphonium salts starting from the corresponding organic precursor reagents (Scheme 6) and tested them in the Wittig reaction with dialdehyde (−)-**6**. Phosphonium salt **10a** was synthesized following a general experimental procedure[20] by the reaction of methyl-3-bromopropionate with PPh_3 in 94% yield. Treatment of **10a** with *n*-BuLi or KHMDS at −78 °C failed to generate the corresponding ylide because the phosphonium salt remained glued and completely unreacted at the bottom of the flask, which most probably resulted from the insolubility of this waxy material in THF. An extensive search of the literature revealed only limited reports where the employment of phosphonium salt **10a** in Wittig reactions is mentioned.[21] In general, it seems that salt **10a** is not preferred as a three-carbon synthon for the elongation of a carbon chain under Wittig olefination conditions. Therefore, three-carbon phosphonium salt **11a** was employed that possesses a terminal hydroxyl group (Scheme 6).

According to the literature,[22] onefold Wittig reactions were carried out successfully using the specific phosphonium salt, and the corresponding products were obtained in good-to-high yields. Phosphonium salt **11a** was synthesized in 94% yield by the reaction of 3-bromopropanol with PPh_3[22a] and treated with the optically pure dialdehyde (−)-**6** under Wittig conditions. The reaction led to the formation of a complicated mixture consisting of unidentified products from which the desired diol could not be detected. Literature reports[22a,23] mention that a

Scheme 4. Synthesis of Optically Pure Diol (−)-4 Bearing a C12 Alkyl Spacer



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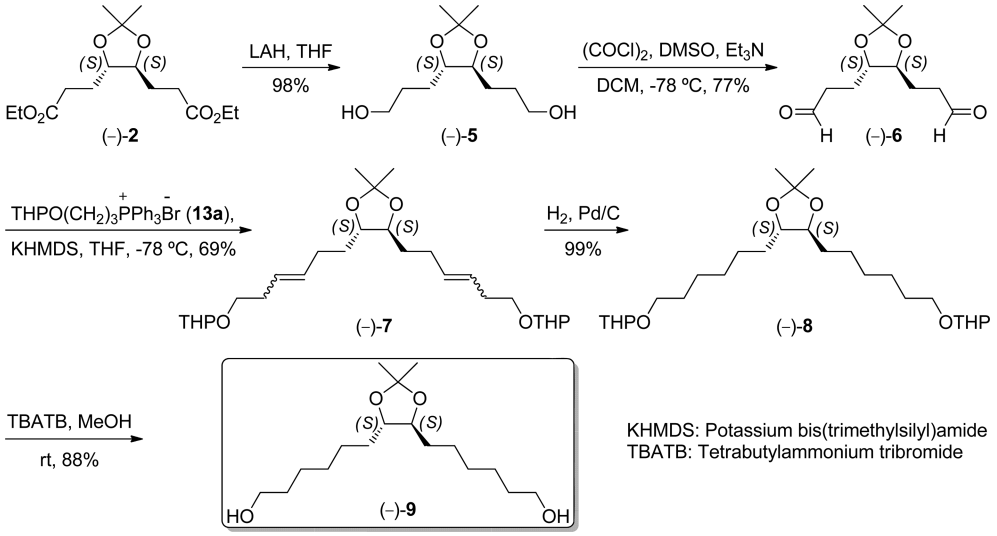
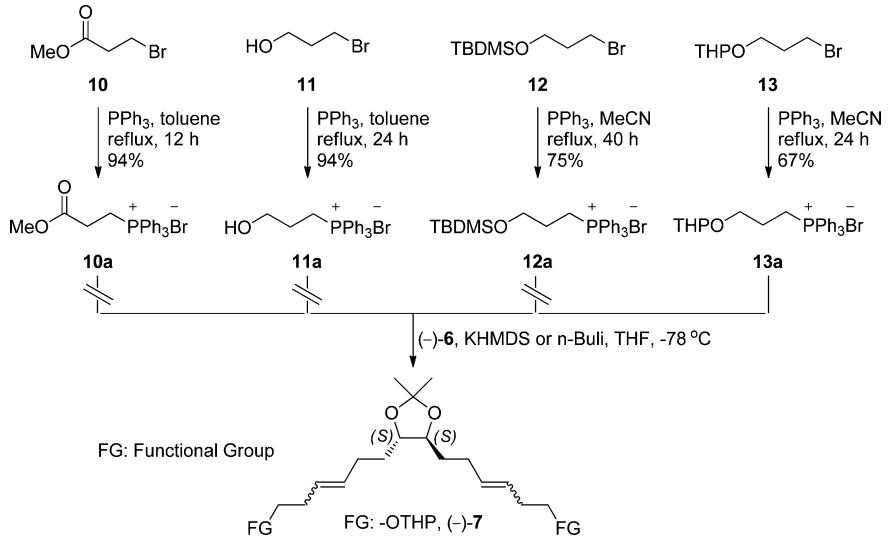
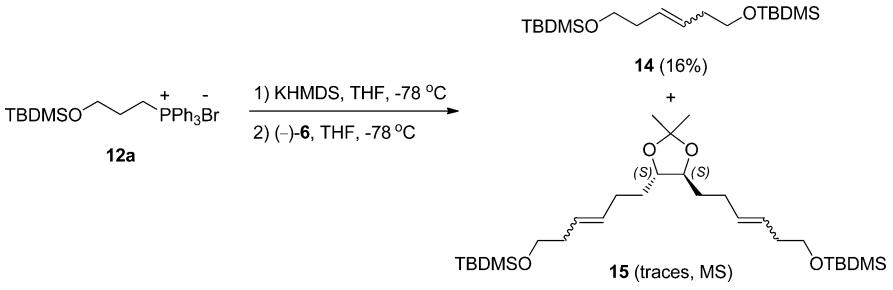
Scheme 5. Synthesis of Optically Pure Diol (−)-9 Bearing a C14 Alkyl Spacer



Scheme 6. Three-Carbon Phosphonium Salts Employed in the Wittig Reaction with Aldehyde (−)-6



Scheme 7. Wittig Reaction of Dialdehyde (−)-6 with the Ylide Derived from Phosphonium Salt 12a



temporary masking of the hydroxyl group present in **11a** favors the formation of the Z isomer of the Wittig product with high isomeric purity and overall yield. With this in mind, we decided to follow the same strategy in an attempt to achieve a less complicated reaction mixture and therefore manage to isolate and elucidate the structure of the main products. As such, phosphonium salt **11a** was treated with *n*-BuLi at 0 °C followed by the addition of TMSCl in the reaction mixture. The mixture was cooled at −78 °C, and a solution of dialdehyde (−)-**6** in THF was added dropwise. The reaction progress was monitored by TLC, but again the formation of a complicated mixture seemed to be inevitable. However, it could not be confirmed whether the in situ TMS protection of the hydroxyl group in phosphonium salt **11a** had occurred effectively. Thus, a conclusion concerning the influence of the protected phosphonium salt in the Wittig reaction progress could not be safely made. To test this approach further, we decided to ensure the protection of the hydroxyl group of salt **11a** prior to

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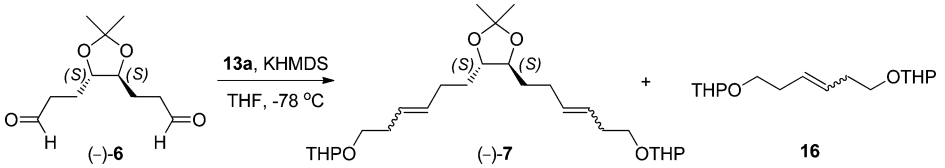
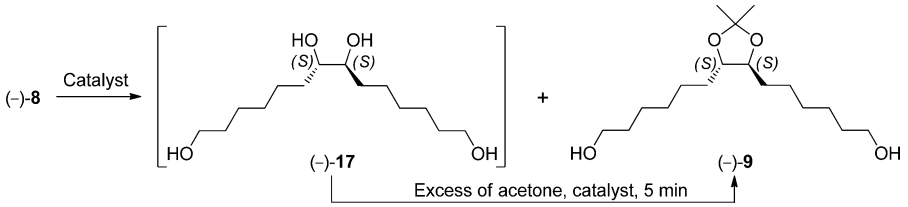
Table 1. Optimization of the Wittig Reaction of Dialdehyde (−)-6 with the Ylide Derived from Phosphonium Salt 13a Regarding the Equivalents of the Salt



entry	(−)-6 (equiv)	13a (equiv)	yield of (−)-7 (%)	yield of 16 (%)[a]
1	1	3	44	14
2	1	5	52	15
3	1	6	69	13

[a]Relative to **13a**.

Table 2. Optimization of the Twofold THP Deprotection of (−)-8



entry	catalyst	solvent	conditions	time	yield of (−)-9 (%)
1	PTSA	MeOH	rt	24 h	[a]
2	PTSA	MeOH	50 °C	24 h	[a]
3	Amberlyst 15	MeOH	rt	24 h	[a]
4	Amberlyst 15	MeOH	50 °C	24 h	[a]
5	PPTS	MeOH	rt	48 h	44
6	PPTS	MeOH	50 °C	48 h	55
7	I_2	MeOH	60 °C/microwave	10 min	58
8	TBATB	MeOH	rt	2.5 h	88
9	$MgBr_2{\cdot}Et_2O$	Et_2O	rt	4 d	90

[a]Complicated mixture.

the Wittig reaction. For this purpose, the protection of 3-bromopropanol was performed first followed by the reaction with PPh_3 to produce the corresponding protected phosphonium salt **12a** (Scheme 6). As the chosen protecting group will have to be deprotected selectively leaving the isopropylidene acetal moiety intact, we first synthesized the TBDMS-protected 3-bromopropanol[24a] that was reacted with PPh_3 to produce phosphonium salt **12a** in 75% yield.[24b] The twofold Wittig reaction of optically pure dialdehyde (−)-**6** with the phosphonium ylide of salt **12a** was then carried out (Scheme 7). Surprisingly, the reaction afforded olefin **14** as the main product that was separated and isolated in 16% yield, whereas mass spectrometric measurement of the crude reaction mixture revealed only traces of desired Wittig product **15**.

It is known that nonstabilized ylides can autoxidatively self-condense to afford symmetrical olefins when exposed to an oxidative reagent. Efficient oxidants for this purpose are molecular oxygen,[25a,b] $NaIO_4$,[25c] $(PhO)_3PO_3$,[25d] *N*-camphorsulfonyloxaziridine,[25e] and $VO(acac)_2$.[25f] The oxidative coupling reaction proceeds through the in situ formation of the corresponding aldehyde upon treatment of the ylide with the oxidant. The aldehyde further reacts with a second ylide molecule via a standard Wittig reaction to afford the symmetrical olefin. To exclude the presence of oxygen, the Wittig transformation was repeated under strict inert conditions by repeatedly degassing the solvent prior to the reaction and by using high-purity inert gases. In all cases, the formation of olefin **14** as the main product was unavoidable, whereas desired product **15** was only detectable with the aid of mass spectrometry. Such byproducts have been reported in the literature,[26] but the mechanism of their formation has not been clarified.

Our efforts then turned to the alteration of the protecting group of the phosphonium salt from TBDMS ether to THP ether. The reaction of 3-bromopropanol with DHP in the presence of PTSA yielded quantitatively THP ether **13**, which was allowed to react with PPh_3 in CH_3CN to furnish the corresponding phosphonium salt **13a** in 67% yield (Scheme 6).[27] The twofold Wittig reaction of the ylide derived from phosphonium salt **13a** with optically pure dialdehyde (−)-**6** was carried out using 3 equiv of the salt, affording two main products that were isolated as one fraction by column chromatography on SiO_2 (Table 1). Because the R_f values of the two compounds were almost identical regardless of the solvent system used, their separation by column chromatography on SiO_2 or Al_2O_3 was not possible. This problem was efficiently confronted by employing the silver ion chromatography technique,[28] which is based on the ability of an unsaturated organic compound to reversibly form charge-transfer complexes with silver. Even though such complexes are unstable, this method can be efficiently utilized in chromatographic techniques for the separation of olefins possessing uneven double bonds. The order of elution depends on the number of the double bonds present in the molecules. The

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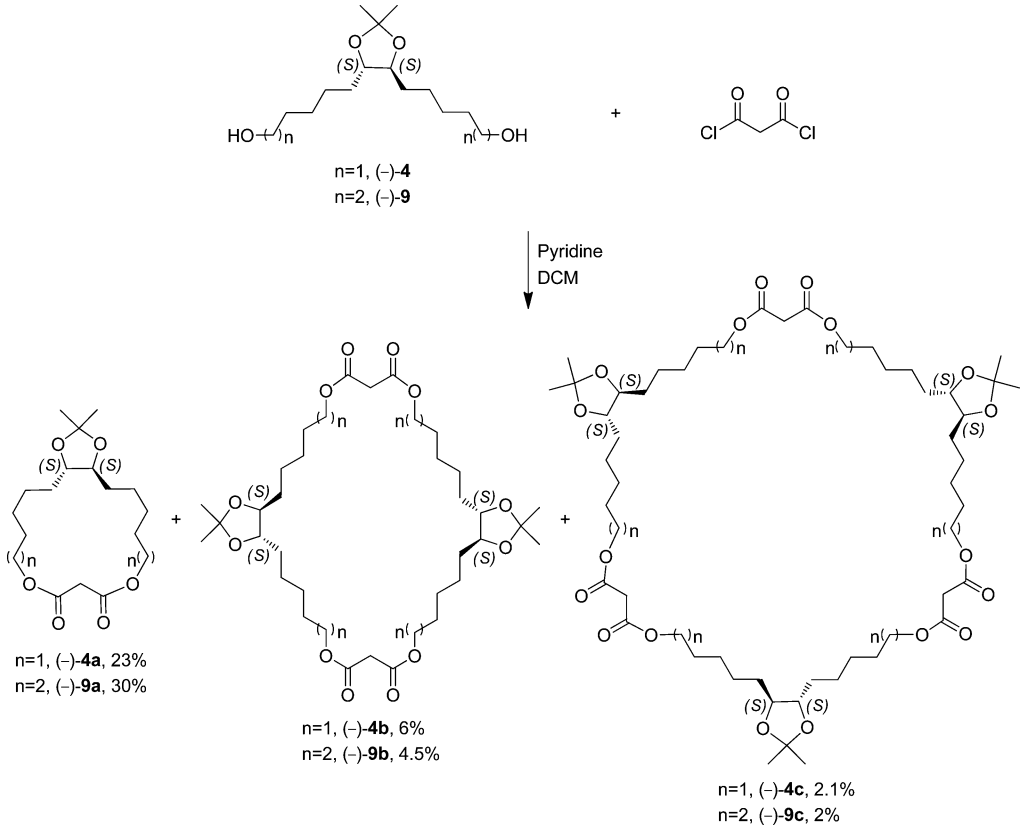
Scheme 8. Cyclization Reaction of the Enantiopure Diols (−)-4 and (−)-9 with Malonyl Dichloride



more double bonds the substrate has the longer the retention time is by the Ag−SiO_2 stationary phase. This separation approach is widely used in lipid chemistry, and several silver ion chromatographic techniques have been successfully developed so far.[28] The successful separation of products (−)-7 and **16** (Table 1) was achieved by column chromatography (SiO_2 impregnated with silver nitrate)[29] using a mixture of DCM/EtOAc (11:5) as the eluent. Olefin **16** was eluted first followed by desired Wittig product (−)-7. However, the yield of product (−)-7 (44%, Table 1, entry 1) was moderate; thus, the Wittig reaction was repeated using 5 and 6 equiv of the phosphonium salt.

As shown in Table 1, the optimum yield of product (−)-7 (69%) was achieved when 6 equiv of salt **13a** were employed, whereas the yield of byproduct **16** did not change significantly. Further optimization of the reaction conditions was not necessary at this point because the yield of product (−)-7 (69%) was satisfactory for a twofold Wittig reaction; furthermore, a larger wasteful stoichiometry of **13a** was not desired.

The final step for the synthesis of optically pure diol (−)-**9** bearing a 14-carbon chain was the double THP deprotection of (−)-**8** (Scheme 5). Although the specific THP deprotection was presumed to be a straightforward process, several acidic catalysts had to be explored to find the optimum conditions. The results are summarized in Table 2. To our surprise, double THP deprotection of (−)-**8** was always accompanied by the formation of fully deprotected product (−)-**17** regardless of the catalyst used. The complete deprotection of (−)-**8** was observed even in the presence of catalysts such as TBATB and $MgBr_2{\cdot}Et_2O$ that do not affect the isopropylidene acetal groups according to the literature.[30] As a result, the yield of desired diol (−)-**9** dropped significantly. This problem was efficiently circumvented by adding an excess of acetone to the mixture after the reaction was completed. By this approach, fully deprotected product (−)-**17** was transformed in situ back to optically pure diol (−)- **9** (Table 2). As illustrated in Table 2, the employment of PTSA and Amberlyst 15 as catalysts either at rt or at 50 °C led to complicated mixtures (Table 2, entries 1−4). Among the other catalysts screened, TBATB and $MgBr_2{\cdot}Et_2O$ afforded the best yields for diol (−)-**9** (Table 2, entries 8 and 9). However, TBATB was the catalyst of choice because of its associated ease of handling and workup.[30a] In addition, a significantly shorter reaction time was required. The specific reaction was performed in MeOH solvent by stirring the reaction mixture at rt for 2.5 h followed by the addition of an excess of acetone and additional stirring for 5 min. By this approach, diol (−)-**9** was isolated in 88% yield.

Synthesis of the Enantiopure *cyclo*-[2]-Malonate Tethers. With diols (−)-**4** and (−)-**9** available on a large scale, the next step toward the synthesis of the corresponding optically pure *cyclo*-[*n*]-malonate esters was a one-pot condensation reaction with malonyl dichloride. Following the optimized general experimental procedure,[9a] the condensation reactions of diols (−)-**4** and (−)-**9** with malonyl dichloride were performed in separate experiments under high dilution conditions in DCM solvent and in the presence of pyridine as a base. After stirring at rt overnight, the macrocyclic products were separated from polymeric material and pyridine salts by filtration over a short pad of SiO_2 using a 1:1 mixture of DCM/EtOAc as the eluent. The oligo-malonates were isolated as one fraction, and they were subsequently separated and purified by column chromatography with the elution sequence being proportional to the increasing size of the macrocyclic rings. As

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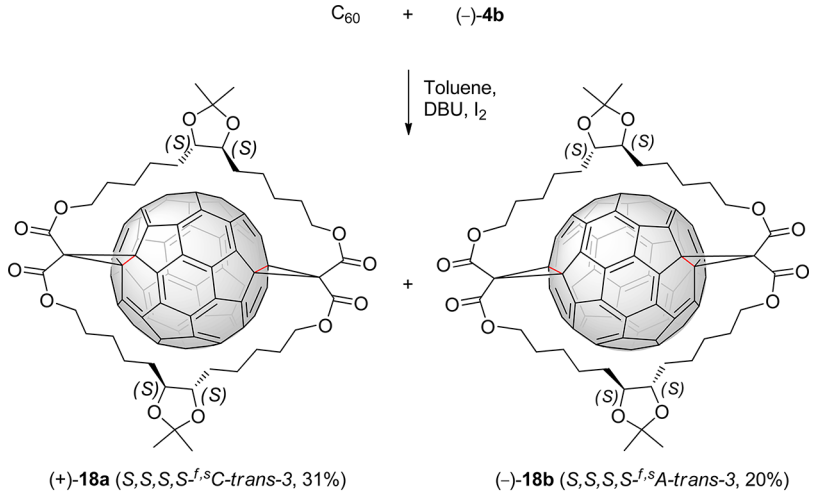
Scheme 9. Synthesis of the Enantiomerically Pure trans-3 Bisadducts of C_{60} Utilizing C12-Bismalonate Tether (−)-4b.[8]



we have already reported,[8] the condensation reaction of optically pure C12-diol (−)-**4** with malonyl dichloride (Scheme 8) afforded corresponding monomalonate (−)-**4a** as a yellowish oil in 23% yield, bismalonate (−)-**4b** as a waxy white solid in 6% yield, and trismalonate (−)-**4c** as a yellowish oil in 2.1% yield. The separation and isolation of the macrocyclic compounds was accomplished by column chromatography using a mixture of DCM/EtOAc/Hexane in a 8:2:4 ratio. The cyclization reaction of C_{14}-diol (−)-**9** with malonyl dichloride led to the formation of mono- (−)-**9a**, bis- (−)-**9b**, and trismalonate (−)-**9c** in 30, 4.5, and 2% yields, respectively. Their separation was accomplished by column chromatography on SiO_2 (DCM/EtOAc/hexane = 8:2:3). Mono- and trismalonate esters (−)-**9a** and (−)-**9c** were obtained as yellowish oils, whereas bismalonate (−)-**9b** was isolated as a waxy white solid. It should be mentioned that the purification procedure for the macrocyclic oligo-malonates bearing C14 spacers turned out to be very difficult, and tedious chromatographic separations were required in comparison to those used for the corresponding C12 analogues shown in Scheme 8. This indicates that the length of the alkyl spacer of diol (−)-**9**, composed 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. The cyclization reactions illustrated in Scheme 8 favored the formation of the monomeric rings, whereas the corresponding dimeric and trimeric products were obtained in significantly lower yields. Furthermore, when C14 diol (−)-**9** was employed the yield of corresponding monomalonate (−)-**9a** was higher compared with that of (−)-**4a**, whereas the yield of bismalonate ester (−)-**9b** was lower compared with that of (−)-**4b**. Both families of the enantiomerically pure *cyclo*-[*n*]-malonate esters were isolated in pure form and were fully characterized. According to the literature,[9a,12] an interesting feature of macrocyclic bismalonate esters resulting from condensation reactions of α,ω-diols with malonyl dichloride is their pronounced ability to crystallize, forming columnar structures with molecular channels in the solid state. However, all attempts to obtain X-ray-quality crystals of optically pure bismalonate esters (−)-**4b** and (−)-**9b**, either by slow evaporation of the solvent or by slow diffusion of pentane into their DCM solutions, failed.

Synthesis of Enantiomerically Pure Bisadducts of C_{60} with the Inherently Chiral trans-3 Addition Pattern. To reach our initial target, which is the synthesis of enantiomerically pure bisadducts of C_{60} with the inherently chiral trans-3 addition pattern utilizing the *cyclo*-[2]-malonate tethers (−)-**4b** and (−)-**9b**, we carried out the remote bis-functionalization of C_{60} under the experimental conditions of the modified Bingel cyclopropanation reaction. According to our recent report,[8] *cyclo*-[2]-malonate tether (−)-**4b** reacted in a regioselective manner with C_{60} to afford bisadducts (+)-**18a** and (−)-**18b**, which were separated by column chromatography (Scheme 9). After an extensive screening of eluent systems, the fullerene adducts were successfully separated using a mixture of PhCl/DCM/MeCN (65:30:5), which resulted in an R_f value of 0.27 for (+)-**18a** and 0.31 for (−)-**18b**. Precipitation from DCM/pentane afforded (+)-**18a** and (−)-**18b** as dark-red/brown solids in a 31 and 20% yield, respectively. The Bingel functionalization of C_{60} with tether (−)-**4b** showed low diastereoselectivity with a de value of 20%, favoring the formation of (+)-**18a**. Bisadducts (+)-**18a** and (−)-**18b** were characterized by ^{1}H and ^{13}C NMR, UV−vis spectroscopy, and MALDI−TOF mass spectrometry. Their enantiomeric relationship resulting from the inherent chirality of the trans-3 addition pattern and their absolute configuration were confirmed by CD spectroscopy. Finally, the specific optical rotation values, $[\alpha]_D^{25}$, were measured in $CHCl_3$ and were found to be +1295 for clockwise isomer (+)-**18a** and −1314 for anticlockwise (−)-**18b**. In our recent work,[8] we also reported the successful acetal deprotection of synthesized bisadducts (+)-**18a** and (−)-**18b**, which afforded quantitatively the corresponding polyalcohols that 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.

Our primary goal, which was the synthesis and isolation of the pure enantiomers of the inherently chiral trans-3 bisaddition pattern of C_{60} without the need for preparative HPLC, was successfully accomplished. The enantiopure $^{f,s}C$ and $^{f,s}A$ trans-3 bisadducts were formed regioselectively by employing C_{12}-bismalonate ester (−)-**4b** as a tether and were isolated

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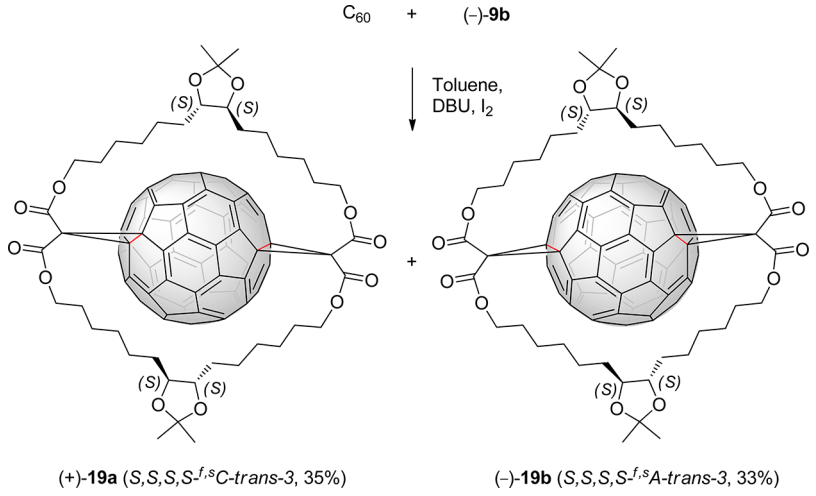
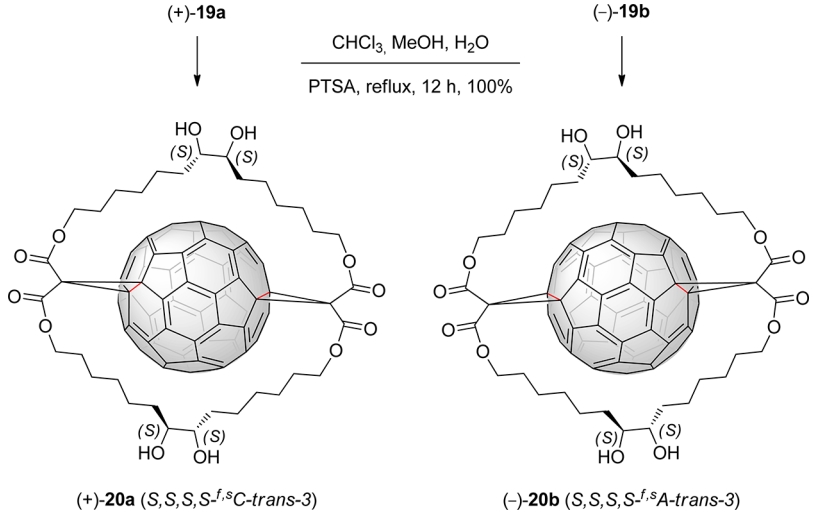
Scheme 10. Synthesis of the Enantiomerically Pure trans-3 Bisadducts of C_{60} Utilizing C14-Bismalonate Tether (−)-9b



Scheme 11. Synthesis of the Enantiomerically Pure trans-3 Derivatives of C_{60} (+)-20a and (−)-20b



by column chromatography in a remarkable 51% total yield. These results prompted us to investigate whether larger C_{14}-bismalonate ester (−)-**9b** is a more advantageous tether than (−)-**4b** and to complete our study that is focused on the investigation of this family of tethers in the regioselective synthesis of enantiomerically pure trans-3 bisadducts of C_{60}.

C_{14}-bismalonate ester (−)-**9b** and C_{60} were allowed to react under modified Bingel conditions, and monitoring the reaction progress by TLC revealed the formation of two major products (Scheme 10). To achieve a satisfactory difference in their R_f values, a variety of solvent mixtures were screened, and the successful separation of the two products was accomplished by employing a mixture of toluene/EtOAc in a 10:0.5 ratio. It has to be mentioned that the separation procedure of the formed products was much easier compared to that of trans-3 bisadducts (+)-**18a** and (−)-**18b** derived from the remote functionalization of C_{60} with bismalonate tether (−)-**4b**. Precipitation from DCM/hexane afforded bisadducts (+)-**19a** and (−)-**19b** as dark-red/brown solids in a 35 and 33% yield, respectively. The total yield of (+)-**19a** and (−)-**19b** was 68%, which is an excellent value for a twofold Bingel cyclopropanation of C_{60}. To the best or our knowledge, this is the highest yield obtained so far for a one-pot bis-cyclopropanation of fullerene C_{60} via the tether-directed remote-functionalization concept. This demonstrates undoubtedly that C_{14}-bismalonate ester (−)-**9b** is in fact a superior tether compared to C_{12}-analogue (−)-**4b** with regard to the yield and the ease of separation of the formed enantiomerically pure trans-3 bisadducts. By HPLC analysis of the crude reaction mixture, the relative yields of (+)-**19a** and (−)-**19b** were found to be 60 and 40%, respectively, whereas the de value of the reaction was calculated to be 20%, favoring the formation of (+)-**19a**. The MALDI−TOF spectra of (+)- **19a** and (−)-**19b** were measured in negative mode using DCTB as a matrix, and in both cases the M^- molecular ion at 1457 m/z was clearly observed (Supporting Information).

The C_2-symmetrical structure of bisadducts (+)-**19a** and (−)-**19b** is clearly reflected in their ^1H and ^{13}C NMR spectra (Supporting Information). In particular, the ^{13}C NMR spectra of both adducts displayed the expected 28 signals for the sp^2 fullerene carbons in the region between 137 and 148 ppm, whereas the carbonyl carbons showed 2 signals at around 164 ppm. Two absorptions corresponding to the stereogenic methine carbon atoms were observed at around 80 ppm, whereas the sp^3 carbon atoms of the fullerene core appeared as two distinct peaks at 71 to 72 ppm. The peak at 53 ppm is also

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characteristic and corresponds to the bridgehead sp^3 carbon atoms.

The trans-3 addition pattern of bisadducts (+)-**19a** and (−)-**19b** was unambiguously confirmed by their UV−vis spectra (Supporting Information), which were found to be identical to those of trans-3 bisadducts (+)-**18a** and (−)-**18b** that were synthesized utilizing C_{12}-bismalonate (−)-**4b**. The absolute configuration of bisadducts (+)-**19a** and (−)-**19b** was determined by a direct comparison of their recorded CD spectra (Supporting Information) with the data reported in the literature[6b,31] and were assigned as ^{fs}C and ^{fs}A, respectively. The spectra showed mirror image behavior and strong Cotton effects due to the chirality of the fullerene chromophore.

To this end, trans-3 bisadducts (+)-**19a** and (−)-**19b** were subjected in separate experiments to a twofold acetal deprotection using *p*-toluenesulfonic acid (PTSA) as a catalyst. The reactions proceeded cleanly to quantitatively afford the fully deprotected products (+)-**20a** and (−)-**20b** (Scheme 11), which were easily isolated by flash column chromatography on SiO_2 using a 10:1 mixture of toluene/MeOH as the eluent. The enantiomerically pure trans-3 fullerene polyalcohols were fully characterized by NMR, UV−vis, CD spectroscopy, and MALDI−TOF mass spectrometry (Supporting Information).

Acetal deprotection of trans-3 bisadducts (+)-**19a** and (−)-**19b** does not affect the addition pattern of the fullerene core; therefore, the UV−vis and CD spectra (Supporting Information) of corresponding polyalcohols (+)-**20a** and (−)-**20b** were identical to those of protected adducts (+)-**19a** and (−)-**19b**. In the ^{13}C NMR spectra of bisadducts (+)-**20a** and (−)-**20b** (Supporting Information), the cleavage of the isopropylidene acetal groups was clearly demonstrated by the absence of the two signals corresponding to the bridgehead sp^3 carbon atoms and the methyl carbons of the 1,2-acetonide five-membered rings that should absorb at approximately 110 and 27 ppm, respectively. In addition, the stereogenic methine carbon atoms were shifted at higher field and observed at around 74 ppm, whereas the sp^3 carbon atoms of the fullerene core appeared as two distinct peaks at 71 to 72 ppm. Furthermore, the ^{13}C NMR spectra of both adducts displayed the expected (for a C_2-symmetrical structure) 28 signals for the sp^2 fullerene carbons in the region between 137 and 148 ppm, whereas the carbonyl carbons showed two signals at around 164 ppm.

Finally, a facile and less time-consuming procedure to obtain pure (+)-**20a**, (−)-**20b**, or the trans-3 fullerene polyalcohols derived from the acetal deprotection of (+)-**18a** and (−)-**18b**[8] was achieved when the mixtures of the enantiomerically pure trans-3 derivatives were not separated after the Bingel functionalization of C_{60} with tethers (−)-**4b** and (−)-**9b** but were purified only from an excess of reagents and polymeric material on a short plug (SiO_2, PhMe/EtOAc). Then, the mixtures were subjected to acetal deprotection, and the final separation of the inherently chiral trans-3 polyalcohols was easily carried out by column chromatography on SiO_2 using the appropriate solvent mixtures as eluents.

CONCLUSIONS

We have described the synthesis of two optically pure diols bearing a 1,2-diol moiety masked as an isopropylidene acetal group and long alkyl chains composed of 12 and 14 carbon atoms, respectively. The synthetic methodology that was developed offers a general way for the synthesis of optically pure diols with long alkyl chains utilizing classical organic transformations. The condensation reactions of optically pure diols (−)-**4** and (−)-**9** with malonyl dichloride gave access to two novel families of enantiopure *cyclo*-[*n*]-malonate esters bearing long alkyl spacers connecting the malonate moieties. The only major drawback of this method is the low total yields of the macrocyclic products resulting from the statistical nature of the specific reactions. These yields could be improved by templated synthesis or by designing alternative synthetic pathways involving multistep protection/deprotection chemistry. However, our primary goal was to gain quick access to the specific optically pure macrocyclic oligo-malonate ester families to test their ability to serve as efficient tethers for the regioselective synthesis of the inherently chiral trans-3 bisadducts of C_{60} via Bingel cyclopropanation. Enantiopure bismalonates (−)-**4b** and (−)-**9b** were excellent tethers for the regioselective Bingel functionalization of C_{60} and led to the regioselective formation of the corresponding ^{fs}C and ^{fs}A trans-3 bisadducts with low diastereoselectivity but with very good to excellent total yields. Noteworthy is the combined yield of the trans-3 bisadducts resulting from the cyclopropanation of C_{60} with C_{14}-tether (−)-**9b**, which reached a remarkable value of 68%. This clearly demonstrates the superior efficiency of the specific tether compared to C_{12}-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 (−)-**19a** and (−)-**19b**, derived from the remote functionalization of C_{60} with C_{14}-tether (−)-**9b**, was easier compared to those formed when C_{12}-tether (−)-**4b** was used, crediting this *cyclo*-malonate tether with an additional advantage. Finally, the successful acetal deprotection of the synthesized bisadducts afforded quantitatively the corresponding polyalcohols that 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.

EXPERIMENTAL SECTION

General Remarks. All starting materials were purchased from commercial sources and used without further purification. The solvents were dried using appropriate standard procedures. Column chromatography was carried out using silica gel 60H (40−60 nm, 230−300 mesh). Thin-layer chromatography (TLC) was carried out on aluminum plates coated with $HF_{254/366}$ silica gel. Visualization was accomplished with a 254 nm ultraviolet (UV) light source and/or by immersion in potassium permanganate ($KMnO_4$) or phosphomolybdic acid (PMA) solutions followed by heating. ^1H and ^{13}C NMR spectra were recorded on 300 and 500 MHz spectrometers. Residual nondeuterated solvent was used as the internal standard for ^1H NMR spectra, and a carbon signal of the solvent was used as the internal standard for ^{13}C NMR spectra. Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane (TMS). The resonance multiplicity patterns are described as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), or a combination of these. Coupling constants (J) are quoted in hertz (Hz). Peak assignments were aided by $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, DEPT-135, and/or DEPT-90 when necessary. Low-resolution (EI) mass spectra were recorded on a GCMS instrument with a direct inlet probe. High-resolution mass spectra were recorded on a MALDI−TOF instrument using DCTB as a matrix or on an ESI mass spectrometer. UV−vis and IR spectrometers were used for the measurements of the corresponding spectra. IR spectra were measured as a film on NaCl plates, and bands are given in cm^{-1}. Analytical

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HPLC measurements were performed using a SiO_2 column (250 × 4 mm, silica gel 100−5, 5 μm) at a flow rate of 1 mL/min and UV detection at 340 nm. A CEM Discover Microwave Reactor was used for microwave experiments, and reaction temperatures were controlled using standard IR thermometry. Optical rotations were measured on a polarimeter, and circular dichroism (CD) spectra were recorded on a CD spectrometer. Melting points (mp) were uncorrected.

Compounds (−)-**1**,[8] (−)-**2**,[8] (−)-**3**,[8] (−)-**4**,[8] (−)-**4a**,[8] (−)-**4b**,[8] (−)-**4c**,[8] **12**,[24a] **13**,[27] **10a**,[20] **11a**,[22a] **12a**,[24b] and **13a**[27] were prepared according to literature procedures.

*(4S,5S)-4,5-Bis(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan (−)-**5**.* In a dry 50 mL three-necked round-bottomed flask equipped with a gas inlet, dropping funnel, and magnetic stirrer, $LiAlH_4$ (0.38 g, 0.01 mol) was added in dry THF (30 mL). The mixture was cooled to 0 °C and stirred vigorously for 15 min. A solution of diester (−)-**2** (1.52 g, 5.03 mmol) in dry THF (10 mL) was added dropwise, and the mixture was left stirring overnight at rt. Subsequently, the mixture was cooled to 0 °C and 0.40 mL of H_2O was very carefully added dropwise. The reaction mixture was then held at 66 °C for 15 min followed by cooling to 0 °C, and 0.40 mL of a 15% aqueous solution of NaOH were added dropwise. The mixture was again held at 66 °C for 15 min followed by cooling to 0 °C, and 1.20 mL of H_2O was added dropwise. Subsequently, the mixture was held at 66 °C until the formation of a characteristic white precipitate was observed, which was then removed by filtration. The filtrate was dried over $MgSO_4$. Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a SiO_2 column (100% EtOAc) to give diol (−)-**5** (1.06 g, 97%) as a colorless oil. R_f = 0.24 (SiO_2, 100% EtOAc, stain = $KMnO_4$). $[\alpha]_D^{25}$ (c = 0.33 g/100 mL, $CHCl_3$) −28.2. IR (NaCl, evap. film) cm^{-1} ν_{max} 3335, 2984, 2936, 2868, 1447, 1435, 1420, 1369, 1337, 1317, 1240, 1219, 1180, 1163, 1094, 1018, 968, 949, 887, 856, 835, 804, 779, 756, 735. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 3.68 (br s, 4H, 2 × CH_2CH_2OH), 3.65−3.63 (m, 2H, 2 × $OCHCH_2$), 2.13 (br s, 2H, 2 × CH_2OH), 1.77−1.70 (m, 6H, 3 × CH_2), 1.56−1.51 (m, 2H, CH_2), 1.40 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 108.3 ($(CH_3)_2C$), 80.9 ($OCHCH_2$), 62.6 (CH_2CH_2OH), 29.5 (CH_2), 29.4 (CH_2), 27.2 ($(CH_3)_2C$). HRMS (ESI$^+$): $[M + H]^+$ calcd for $C_{11}H_{23}O_4$, 219.1591; found, 219.1581.

*3,3′-[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dipropanal (−)-**6**.* In a dry 500 mL three-necked round-bottomed flask equipped with a gas inlet, dropping funnel, and magnetic stirrer, $(COCl)_2$ (2.22 mL, 0.027 mol) was added in 140 mL of dry DCM under an Ar atmosphere. The mixture was cooled to −78 °C, and a solution of dry DMSO (3.50 mL, 0.049 mol) in dry DCM (25 mL) was added dropwise. The resulting reaction mixture was stirred for 0.5 h at −78 °C followed by the dropwise addition of a solution of diol (−)-**5** (1.95 g, 8.95 mmol) in dry DCM (20 mL) at the same temperature. The mixture was again left stirring for 0.5 h at −78 °C. Subsequently, dry Et_3N (12.5 mL, 0.089 mol) was added dropwise at the same temperature. The resulting mixture was stirred for 1 h with the temperature at −78 °C, and then it was warmed slowly to 0 °C over a period of 1 h. The mixture was stirred at the same temperature for 0.5 h and subsequently diluted with 250 mL of dry toluene. Filtration and evaporation of the solvent under vacuum at a temperature not exceeding 35 °C afforded a crude mixture that was then mixed with 250 mL of dry hexane. The resulting mixture was filtered, and the solvent was carefully evaporated under vacuum with the temperature at 35 °C. Chromatography (SiO_2, hexane/EtOAc = 6:4) of the resulting crude mixture afforded dialdehyde (−)-**6** (1.48 g, 77%) as a colorless oil. R_f = 0.22 (SiO_2, hexane/EtOAc = 6:4, stain = PMA). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (br s, 2H, 2 × CH_2CHO), 3.67−3.59 (m, 2H, 2 × $OCHCH_2$), 2.73−2.55 (m, 4H, 2 × CH_2CHO), 2.04−1.93 (m, 2H, CH_2), 1.82−1.70 (m, 2H, CH_2), 1.35 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6 (CH_2CHO), 108.5 ($(CH_3)_2CO$), 79.5 ($OCHCH_2$), 40.2 (CH_2CHO), 27.1 ($(CH_3)_2C$), 24.7 (CH_2). MS (EI) m/z: $[M - CH_3]^+$ 199.

*2,2′-{[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis[hex-3-ene-6,1-diyloxy]}bis(tetrahydro-2H-pyran) (−)-**7** and 1,6-Di-(tetrahydropyran)hex-3-ene **16**.* In a dry 500 mL three-necked round-bottomed flask equipped with a gas inlet, dropping funnel, and magnetic stirrer, a 0.5 M solution of KHMDS in toluene (60 mL, 0.03 mol) was added dropwise to a suspension of phosphonium salt **13a** (15.00 g, 0.03 mol) in dry THF (200 mL) at −78 °C. The solution of the formed ylide was left stirring for 20 min at the same temperature followed by the dropwise addition of a solution of dialdehyde (−)-**6** (1.07 g, 5 mmol) in dry THF (20 mL). The resulting reaction mixture was warmed to rt and stirred at the same temperature overnight. Filtration and evaporation of the solvent afforded a crude mixture that was chromatographed on SiO_2 (EtOAc/hexane = 1:5) to give a fraction consisting of compound (−)-7 and olefin **16**. The two products were separated and isolated in pure form by silver ion chromatography (Ag−SiO_2, DCM/EtOAc = 11:5).

*2,2′-{[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis[hex-3-ene-6,1-diyloxy]}bis(tetrahydro-2H-pyran) (−)-**7**.* Colorless oil (1.61 g, 69%). R_f = 0.36 (SiO_2, hexane/EtOAc = 5:1, stain = PMA) and 0.07 (Ag−SiO_2, DCM/EtOAc = 11:5, stain = PMA). IR (NaCl, evap. film) cm^{-1} ν_{max} 3013, 2943, 2868, 1755, 1720, 1692, 1445, 1389, 1352, 1271, 1202, 1128, 1074, 982, 906, 870, 814, 737. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50−5.39 (m, 4H, 2 × CH=CH), 4.59 (apparent t, J = 3.4 Hz, 2H, 2 × $OCHO$), 3.90−3.82 (m, 2H, OCH_2), 3.78−3.68 (m, 2H, OCH_2), 3.64−3.57 (m, 2H, 2 × $OCHCH_2$), 3.53−3.46 (m, 2H, OCH_2), 3.44−3.36 (m, 2H, OCH_2), 2.40−2.33 (m, 4H, 2 × CH_2), 2.25−2.13 (m, 4H, 2 × CH_2), 1.86−1.49 (m, 16H, 8 × CH_2), 1.37 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7 (CH=CH), 126.5 (CH=CH), 107.9 ($(CH_3)_2C$), 98.7 (OCHO), 80.2 ($OCHCH_2$), 67.0 (OCH_2), 62.3 (OCH_2), 32.8 (CH_2), 30.7 (CH_2), 27.9 (CH_2), 27.3 ($(CH_3)_2C$), 25.5 (CH_2), 24.0 (CH_2), 19.6 (CH_2). HRMS (ESI$^+$): $[M + Na]^+$ calcd for $C_{27}H_{46}O_6Na$, 489.3187; found, 489.3181.

*1,6-Di(tetrahydropyran)hex-3-ene **16**.* Colorless oil (0.91 g, 13% relative to phosphonium salt **13a**). R_f = 0.36 (SiO_2, hexane/EtOAc = 5:1, stain = PMA) and 0.22 (Ag−SiO_2, DCM/EtOAc = 11:5, stain = PMA). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56−5.46 (m, 2H, CH=CH), 4.59 (apparent t, J = 3.6 Hz, 2H, 2 × $OCHO$), 3.91−3.83 (m, 2H, OCH_2), 3.78−3.70 (m, 2H, OCH_2), 3.53−3.37 (m, 4H, 2 × OCH_2), 2.41−2.35 (m, 4H, 2 × CH_2), 1.87−1.49 (m, 12H, 6 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.7 (CH=CH), 98.7 (OCHO), 67.0 (OCH_2), 62.3 (OCH_2), 30.7 (CH_2), 28.1 (CH_2), 25.5 (CH_2), 19.6 (CH_2). HRMS (ESI$^+$): $[M + Na]^+$ calcd for $C_{16}H_{28}O_4Na$, 307.1880; found, 307.1869.

*2,2′-{[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(hexane-6,1-diyloxy)}bis(tetrahydro-2H-pyran) (−)-**8**.* Unsaturated diol (−)-7 (1.52 g, 3.26 mmol) was dissolved in EtOH (30 mL) and hydrogenated under an H_2 atmosphere (hydrogen pressure 2.5 bar) using 10% Pd/C (70 mg) as a catalyst for 0.5 h at rt. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness to afford saturated diester (−)-**8** (1.52 g, 99%) as a colorless oil. R_f = 0.7 (SiO_2, hexane/EtOAc = 1:1, stain = PMA). $[\alpha]_D^{20}$ (c = 0.46g/100 mL, $CHCl_3$) −13.4. IR (NaCl, evap. film) cm^{-1} ν_{max} 2936, 2860, 1454, 1441, 1377, 1367, 1352, 1323, 1283, 1259, 1240, 1200, 1184, 1161, 1136, 1121, 1078, 1064, 1024, 986, 905, 868, 845, 814, 785, 729. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (br s, 2H, 2 × $OCHO$), 3.87 (apparent t, J = 9.5 Hz, 2H, OCH_2), 3.75−3.70 (m, 2H, OCH_2), 3.58 (br s, 2H, 2 × $OCHCH_2$), 3.51−3.50 (m, 2H, OCH_2), 3.49−3.36 (m, 2H, OCH_2), 1.85−1.80 (m, 2H, CH_2CHO), 1.73−1.69 (m, 2H, CH_2CHO), 1.60−1.50 (m, 22H, 11 × CH_2), 1.37 (br s, 16H, $(CH_3)_2C$ and 5 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.7 ($(CH_3)_2C$), 98.8 (OCHO), 81.0 ($OCHCH_2$), 67.6 (OCH_2), 62.3 (OCH_2), 32.9 (CH_2), 30.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 27.3 ($(CH_3)_2C$), 26.1 (CH_2), 25.5 (CH_2), 19.7 (CH_2). HRMS (ESI$^+$): $[M + Na]^+$ calcd for $C_{27}H_{50}O_6Na$, 493.3500; found, 493.3493.

*6,6′-[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dihexan-1-ol (−)-**9**.* In a 100 mL single-necked round-bottomed flask equipped with a magnetic stirrer, saturated THP-protected diol (−)-**8** (4.11 g, 8.73 mmol) and TBATB (0.85 g, 1.75 mmol) were dissolved in 35 mL of MeOH. After stirring at rt for 2.5 h, an excess of acetone was added, and the reaction mixture was stirred for 5 min. The mixture was subsequently diluted with EtOAc and washed with a 5% aqueous solution of sodium bisulfite. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Column

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chromatography (SiO_2, EtOAc/DCM = 9:1) of the crude residue afforded diol (−)-**9** (2.32 g, 88%) as a colorless oil. R_f = 0.35 (SiO_2, EtOAc/DCM = 9:1, stain = PMA); $[\alpha]_D^{20}$ (*c* = 0.296g/100 mL, $CHCl_3$) −29.3. IR (NaCl, evap. film) cm^{-1} ν_{max} 3339, 2984, 2932, 2858, 1456, 1435, 1377, 1369, 1339, 1286, 1240, 1219, 1173, 1097, 1074, 1055, 941, 878, 854, 802, 723, 705. ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.6 Hz, 4H, 2 × CH_2OH), 3.58 (apparent t, *J* = 3.0 Hz, 2H, 2 × $OCHCH_2$), 1.60−1.48 (m, 12H, 5 × CH_2 and 2 × CH_2OH), 1.37 (br s, 16H, $(CH_3)_2C$ and 5 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.8 ($(CH_3)_2C$), 80.9 ($OCHCH_2$), 62.9 (CH_2OH), 32.8 (CH_2), 32.6 (CH_2), 29.4 (CH_2), 27.3 ($(CH_3)_2C$), 26.1 (CH_2), 25.5 (CH_2). HRMS (ESI^+): $[M + H]^+$ calcd for $C_{17}H_{35}O_4$, 303.2530; found, 303.2526.

*(7S,8S)-Tetradecane-1,7,8,14-tetraol (−)-**17**.* White solid. R_f = 0.11 (SiO_2, EtOAc/DCM = 10:1, stain = PMA); $[\alpha]_D^{25}$ (*c* = 0.102g/100 mL, CH_3OH) −34.2. IR (NaCl, evap. film) cm^{-1} ν_{max} 3381, 2914, 2846, 2361, 2336, 1728, 1601, 1456, 1387, 1111, 1067, 717, 687, 665, 432, 413. ^1H NMR (300 MHz, CD_3OD) δ 3.50 (t, *J* = 6.6 Hz, 4H, 2 × CH_2OH), 3.34−3.30 (m, 2H, 2 × $OCHCH_2$), 1.49−1.24 (m, 20H, 10 × CH_2). ^{13}C NMR (75 MHz, CD_3OD): δ 75.3 ($OCHCH_2$), 63.0 (CH_2OH), 33.9 (CH_2), 33.6 (CH_2), 30.7 (CH_2), 27.1 (CH_2), 26.9 (CH_2). HRMS (ESI^+): $[M + Na]^+$ calcd for $C_{14}H_{30}O_4Na$, 285.2036; found, 285.2039.

*Synthesis of cyclo-Malonates (−)-**9a**, (−)-**9b**, and (−)-**9c**.* In a dry 500 mL three-necked round-bottomed flask equipped with a gas inlet, dropping funnel, and magnetic stirrer, diol (−)-**9** (1.10 g, 3.64 mmol) was dissolved under an argon atmosphere in dry DCM (240 mL) followed by the addition of pyridine (0.59 mL, 7.28 mmol). Subsequently, a solution of malonyl dichloride (0.71 mL, 7.28 mmol) in dry DCM (120 mL) was added dropwise over a period of 2 h. After stirring for 1 day at rt, the mixture was concentrated, absorbed on SiO_2, and chromatographed on a short column (SiO_2, DCM/EtOAc = 1:1) to remove polymeric material and pyridine salts. The isolated mixture was then evaporated and separated by column chromatography (SiO_2, DCM/EtOAc/hexane = 8:2:3) to give *cyclo*-[1]-malonate (−)-**9a**, *cyclo*-[2]-malonate (−)-**9b**, and *cyclo*-[3]-malonate (−)-**9c**. The order of elution was (−)-**9a**, (−)-**9b**, and (−)-**9c**.

*cyclo-[1]-Malonate (−)-**9a**.* Yellowish oil (0.40 g, 30%). R_f = 0.58 (SiO_2, DCM/EtOAc/hexane = 8:2:3, stain = $KMnO_4$); $[\alpha]_D^{25}$ (*c* = 0.11g/100 mL, $CHCl_3$) −10.2. IR (NaCl, evap. film) cm^{-1} ν_{max} 2982, 2934, 2858, 1751, 1736, 1460, 1412, 1373, 1323, 1254, 1221, 1153, 1092, 1051, 1003, 914, 881. ^1H NMR (300 MHz, $CDCl_3$) δ 4.22−4.09 (m, 4H, 2 × OCH_2CH_2), 3.69−3.62 (m, 2H, 2 × $OCHCH_2$), 3.37 (s, 2H, $COCH_2CO$), 1.68−1.62 (m, 8H, 4 × CH_2), 1.42−1.38 (m, 18H, $(CH_3)_2C$ and 6 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C=O), 107.5 ($(CH_3)_2C$), 80.4 ($OCHCH_2$), 65.6 (CH_2O), 42.0 ($COCH_2CO$), 32.3 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 27.2 ($(CH_3)_2C$), 25.1 (CH_2), 24.8 (CH_2). HRMS (ESI^+): $[M + Na]^+$ calcd for $C_{20}H_{34}O_6Na$, 393.2248; found, 393.2261.

*cyclo-[2]-Malonate (−)-**9b**.* Waxy white solid (60.7 mg, 4.5%). R_f = 0.41 (SiO_2, DCM/EtOAc/hexane = 8:2:3, stain = PMA). mp 85 °C; $[\alpha]_D^{25}$ (*c* = 0.15g/100 mL, $CHCl_3$) −20.6. IR (NaCl, evap. film) cm^{-1} ν_{max} 2982, 2930, 2857, 1730, 1468, 1435, 1406, 1389, 1377, 1367, 1342, 1290, 1248, 1211, 1194, 1175, 1115, 1103, 1067, 1026, 1016, 987, 951, 897, 879, 854, 820, 723. ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, *J* = 6.7 Hz, 8H, 4 × OCH_2CH_2), 3.57 (br s, 4H, 4 × $OCHCH_2$), 3.36 (s, 4H, 2 × $COCH_2CO$), 1.70−1.61 (m, 8H, 4 × CH_2), 1.51 (br s, 12H, 6 × CH_2), 1.37 (br s, 32H, 2$(CH_3)_2C$ and 10 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C=O), 107.8 ($(CH_3)_2C$), 80.8 ($OCHCH_2$), 65.5 (CH_2O), 41.8 ($COCH_2CO$), 32.9 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 27.3 ($(CH_3)_2C$), 26.0 (CH_2), 25.7 (CH_2). HRMS (MALDI−TOF): $[M + Na]^+$ calcd for $C_{40}H_{68}O_{12}Na$, 763.4603; found, 763.4589.

*cyclo-[3]-Malonate (−)-**9c**.* Colorless oil (26.6 mg, 2%). R_f = 0.28 (SiO_2, DCM/EtOAc/hexane = 8:2:3, stain = PMA); $[\alpha]_D^{20}$ (*c* = 0.205g/100 mL, $CHCl_3$) −22.6. IR (NaCl, evap. film) cm^{-1} ν_{max} 2984, 2932, 2858, 1751, 1734, 1464, 1377, 1329, 1248, 1151, 1103, 1047, 889, 667. ^1H NMR (500 MHz, $CDCl_3$) δ 4.14 (t, *J* = 6.5 Hz, 12H, 6 × OCH_2CH_2), 3.57 (br s, 6H, 6 × $OCHCH_2$), 3.36 (s, 6H, 3 × $COCH_2CO$), 1.68−1.63 (m, 12H, 6 × CH_2), 1.51 (br s, 18H, 9 × CH_2), 1.37 (br s, 48H, 3$(CH_3)_2C$ and 15 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7 (C=O), 107.8 ($(CH_3)_2C$), 80.9 ($OCHCH_2$), 65.5 (CH_2O), 41.7 ($COCH_2CO$), 32.9 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 27.3 ($(CH_3)_2C$), 26.0 (CH_2), 25.7 (CH_2). HRMS (MALDI−TOF): $[M + Na]^+$ calcd for $C_{60}H_{102}O_{18}Na$, 1133.6958; found, 1133.6975.

*Synthesis of Bisadducts (+)-**19a** and (−)-**19b**.* In a dry 100 mL three-necked round-bottomed flask equipped with a gas inlet, dropping funnel, and magnetic stirrer, C_{60} (31 mg, 0.04 mmol) was dissolved in dry toluene (31 mL) under an argon atmosphere. Subsequently, macrocycle (−)-**9b** (29 mg, 0.039 mmol) and iodine (20 mg, 0.08 mmol) were added followed by the dropwise addition of a solution of DBU (0.02 mL, 0.16 mmol) in dry toluene (12 mL) over a period of 1 h. The solution was stirred at rt for 1 day, and the crude reaction mixture was subjected to flash column chromatography on SiO_2. Unreacted C_{60} and other impurities were eluted with toluene and the eluent was changed to toluene/EtOAc = 8:2. Diastereomers (+)-**19a** and (−)-**19b** were obtained as a mixture and were separated by column chromatography on SiO_2 using a 10:0.5 mixture of toluene/EtOAc as the eluent. Precipitation from DCM/hexane afforded (+)-**19a** and (−)-**19b** in pure form.

*(S,S,S,S-^{f,s}C-trans-3) (+)-**19a**.* Dark-red solid (22 mg, 35%). R_f = 0.45 (SiO_2, toluene/EtOAc = 10:0.5). HPLC: retention time = 9.93 min (toluene/EtOAc = 95:5). $[\alpha]_D^{20}$ (*c* = 0.0081g/100 mL, $CHCl_3$) +1062. ^1H NMR (500 MHz, $CDCl_3$) δ 4.80−4.76 (m, 2H, OCH_2CH_2), 4.53−4.43 (m, 4H, 2 × OCH_2CH_2), 4.40−4.36 (m, 2H, OCH_2CH_2), 3.45−3.42 (m, 2H, 2 × $OCHCH_2$), 3.39−3.36 (m, 2H, 2 × $OCHCH_2$), 1.83−1.16 (m, 52H, 2$(CH_3)_2C$ and 20 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.18 (C=O), 164.06 (C=O), 147.29, 147.15, 147.08, 146.84, 146.73, 146.63, 146.49, 146.32, 146.17, 146.04, 145.59, 145.45, 144.70, 144.42, 144.32, 143.97, 143.69, 143.68, 143.58, 142.85, 142.64, 142.08, 141.99, 141.88, 141.59, 140.19, 138.57, 137.65 (sp^2 *C* of C_{60}), 107.61 ($(CH_3)_2C$), 80.78 ($OCHCH_2$), 80.74 ($OCHCH_2$), 71.92 (sp^3 *C* of C_{60}), 71.62 (sp^3 *C* of C_{60}), 67.64 (CH_2CH_2O), 67.22 (CH_2CH_2O), 53.33 (COCCO), 33.22 (CH_2), 32.65 (CH_2), 29.66 (CH_2), 29.01 (CH_2), 28.96 (CH_2), 28.40 (CH_2), 27.27 ($(CH_3)_2C$), 27.18 ($(CH_3)_2C$), 26.62 (CH_2), 26.54 (CH_2), 25.97 (CH_2), 25.87 (CH_2). UV−vis ($CHCl_3$) λ_{max} nm (ε/dm^3 mol^{-1} cm^{-1}) 317 (45 094), 380 (11 803), 400 (6510), 411.5 (5446), 423 (4541), 482.5 (3554), 573 (1498), 633 (536), 688 (174). CD ($CHCl_3$) 286 nm ($\Delta\varepsilon$ = −87.2), 347.6 (−44.2), 391.0 (30.4), 403.8 (22.9), 417.4 (10.8), 447.6 (47.8), 521.0 (−27.0), 580.4 (11.8), 614.6 (−3.4), 664.4 (−7.3). HRMS (MALDI−TOF, negative mode, DCTB): $[M]^-$ calcd for $C_{100}H_{64}O_{12}$, 1457.4426; found, 1457.4368.

*(S,S,S,S-^{f,s}A-trans-3) (−)-**19b**.* Dark-red solid (20.7 mg, 33%). R_f = 0.52 (SiO_2, toluene/EtOAc = 10:0.5). HPLC: retention time = 11.92 min (toluene/EtOAc = 95:5). $[\alpha]_D^{20}$ (*c* = 0.0074g/100 mL, $CHCl_3$) −1094. ^1H NMR (500 MHz, $CDCl_3$) δ 4.86−4.81 (m, 2H, OCH_2CH_2), 4.61−4.56 (m, 2H, OCH_2CH_2), 4.39−4.34 (m, 4H, 2 × OCH_2CH_2), 3.45 (br s, 4H, 4 × $OCHCH_2$), 1.85−1.10 (m, 52H, 2$(CH_3)_2C$ and 20 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.08 (C=O), 163.87 (C=O), 147.29, 147.15, 147.11, 146.69, 146.64, 146.48, 146.38, 146.29, 146.26, 145.89, 145.51, 145.47, 144.69, 144.41, 144.32, 143.92, 143.70, 143.56, 143.54, 142.88, 142.63, 142.41, 142.13, 142.01, 141.65, 140.18, 138.52, 137.71 (sp^2 *C* of C_{60}), 107.72 ($(CH_3)_2C$), 80.65 ($OCHCH_2$), 80.46 ($OCHCH_2$), 71.82 (sp^3 *C* of C_{60}), 71.53 (sp^3 *C* of C_{60}), 67.30 (CH_2CH_2O), 67.21 (CH_2CH_2O), 52.90 (COCCO), 32.93 (CH_2), 32.59 (CH_2), 29.39 (CH_2), 29.12 (CH_2), 28.75 (CH_2), 28.61 (CH_2), 27.30 ($(CH_3)_2C$), 27.25 ($(CH_3)_2C$), 26.25 (CH_2), 26.08 (CH_2), 25.98 (CH_2), 25.91 (CH_2). UV−vis ($CHCl_3$) λ_{max} nm (ε/dm^3 mol^{-1} cm^{-1}) 315 (32 737), 378 (8803), 401 (4153), 411 (3497), 423 (3005), 482 (2587), 575 (1058), 629 (453), 688 (167). CD ($CHCl_3$) 285.8 nm ($\Delta\varepsilon$ = 90.8), 347.4 (45.2), 390.8 (−27.2), 404.2 (−19.3), 417.2 (−6.9), 446.4 (−42.3), 521.6 (25.6), 580.2 (−8.4), 610.0 (2.3), 668.0 (10.7); HRMS (MALDI−TOF, negative mode, DCTB): $[M]^-$ calcd for $C_{100}H_{64}O_{12}$, 1457.4426; found, 1457.4495.

*Synthesis of Bisadduct (S,S,S,S-^{f,s}C-trans-3) (+)-**20a**.* In a 15 mL two-necked round-bottomed flask equipped with a condenser, gas

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inlet, and magnetic stirrer, (+)-**19a** (20 mg, 1.37×10^{-5} mmol) was dissolved in $CHCl_3$ (3 mL) followed by the addition of MeOH (1 mL). Subsequently, PTSA was added to the reaction mixture (5.1 mg, 0.027 mmol) followed by the addition of a few drops of H_2O. The mixture was held overnight at 70 °C. The solution was then extracted with H_2O, dried over Na_2SO_4, and filtered. The filtrate was evaporated and chromatographed on a SiO_2 column (toluene/MeOH = 10:1) to afford (+)-**20a**. Precipitation from $CHCl_3$/pentane afforded (+)-**20a** (18.9 mg, 100%) as a red solid in pure form. R_f = 0.28 (SiO_2, toluene/MeOH = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79−4.75 (m, 2H, OCH_2CH_2), 4.54−4.49 (m, 2H, OCH_2CH_2), 4.48−4.43 (m, 2H, OCH_2CH_2), 4.41−4.37 (m, 2H, OCH_2CH_2), 3.29−3.25 (m, 2H, 2 × $OCHCH_2$), 3.21−3.20 (m, 2H, 2 × $OCHCH_2$), 2.11 (apparent d, J = 5.5 Hz, 2H, 2 × CH_2OH), 1.89−1.66 (m, 10H, 4 × CH_2 and 2 × OH), 1.47−1.18 (m, 32H, 16 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.17 (C=O), 163.82 (C=O), 147.26, 147.15, 147.03, 146.70, 146.50, 146.48, 146.39, 146.28, 146.20, 146.00, 145.58, 145.46, 144.64, 144.40, 144.29, 143.93, 143.67, 143.64, 143.53, 142.91, 142.60, 142.41, 142.19, 141.98, 141.66, 140.24, 138.33, 137.53 (sp^2 C of C_{60}), 73.91 ($HOCHCH_2$), 73.78 ($HOCHCH_2$), 71.89 (sp^3 C of C_{60}), 71.64 (sp^3 C of C_{60}), 67.56 (CH_2CH_2O), 67.47 (CH_2CH_2O), 53.04 (COCCO), 33.75 (CH_2), 33.31 (CH_2), 29.01 (CH_2), 28.91 (CH_2), 28.64 (CH_2), 28.41 (CH_2), 26.35 (CH_2), 26.14 (CH_2), 25.81 (CH_2), 25.52 (CH_2). UV−vis ($CHCl_3$) λ_{max} nm (ε/dm^3 mol^{-1} cm^{-1}) 315 (46 229), 380 (11 803), 400 (6510), 411.5 (5462), 423 (4541), 483 (3553), 574 (1483), 629 (579), 687 (177). CD ($CHCl_3$) 285.8 nm ($\Delta\varepsilon$ = −66.9), 347.0 (−33.6), 391.2 (25.6), 403.8 (19.7), 417.6 (9.9), 446.4 (38.6), 521.8 (−18.5), 577.0 (10.7), 614.4 (−6.5), 680.6 (−10.11). HRMS (MALDI−TOF, negative mode, DCTB): $[M]^-$ calcd for $C_{94}H_{56}O_{12}$, 1376.3766; found, 1376.3794.

*Synthesis of Bisadduct (S,S,S,S-^{f,s}A-trans-3) (−)-**20b**.* (−)-**19b** (18 mg, 1.23×10^{-5} mol) was subjected to the acetal deprotection reaction following the procedure described for the synthesis of (+)-**19a** to give (−)-**20b** (17 mg, 100%) as a red solid after column chromatography (SiO_2, toluene/MeOH = 10:1). R_f = 0.27 (SiO_2, toluene/MeOH = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80−4.76 (m, 2H, OCH_2CH_2), 4.66−4.61 (m, 2H, OCH_2CH_2), 4.40−4.32 (m, 4H, 2 × OCH_2CH_2), 3.25 (br s, 2H, 2 × $OCHCH_2$), 3.18 (br s, 2H, 2 × $OCHCH_2$), 2.39 (br s, 2H, 2 × CH_2OH), 1.97 (br s, 2H, 2 × CH_2OH), 1.82−1.07 (m, 40H, 20 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.90 (C=O), 163.75 (C=O), 147.25, 147.12, 147.04, 146.68, 146.48, 146.43, 146.34, 146.33, 146.03, 145.65, 145.46, 145.37, 144.68, 144.40, 144.32, 143.92, 143.70, 143.54, 143.41, 142.92, 142.61, 142.53, 142.27, 142.01, 141.67, 140.27, 138.61, 137.76 (sp^2 C of C_{60}), 73.88 ($HOCHCH_2$), 73.85 ($HOCHCH_2$), 71.82 (sp^3 C of C_{60}), 71.60 (sp^3 C of C_{60}), 67.41 (CH_2CH_2O), 66.95 (CH_2CH_2O), 52.61 (COCCO), 33.73 (CH_2), 33.27 (CH_2), 28.76 (CH_2), 28.71 (CH_2), 28.50 (CH_2), 28.12 (CH_2), 26.11 (CH_2), 25.96 (CH_2), 25.82 (CH_2), 25.20 (CH_2); UV−vis ($CHCl_3$) λ_{max} nm (ε/dm^3 mol^{-1} cm^{-1}) 315 (27 761), 378 (7702), 398 (4689), 412 (3750), 422 (3322), 488 (2496), 573 (941), 627 (430), 690 (187). CD ($CHCl_3$) 286.2 nm ($\Delta\varepsilon$ = 73.3), 346 (39.2), 390.8 (−22.1), 403.6 (−16.2), 416.2 (−8.5), 447.0 (−35.8), 520.4 (19.3), 582.0 (−8.5), 618.8 (4.1), 671.0 (5.1). HRMS (MALDI−TOF, negative mode, DCTB): $[M + 1]^-$ calcd for $C_{94}H_{56}O_{12}$, 1377.3800; found, 1377.3743.

*Synthesis of Bisadducts (+)-**20a** and (−)-**20b** from (+)-**19a**/(−)-**19b**.* In a 25 mL two-necked round-bottomed flask equipped with a condenser, gas inlet, and magnetic stirrer, a mixture of (+)-**19a**/(−)-**19b** (45 mg, 3.08×10^{-5} mol) as obtained from the Bingel reaction of C_{60} with (−)-**9b** was dissolved in $CHCl_3$ (6 mL) followed by the addition of MeOH (2 mL). Subsequently, PTSA (14 mg, 0.072 mmol) and a few drops of H_2O were added, and the reaction mixture was held overnight at 70 °C. The solution was then extracted with H_2O, dried over Na_2SO_4, and filtered. The filtrate was evaporated and flash chromatographed on a SiO_2 column (toluene/EtOAc/MeOH = 4:4:1) to afford (+)-**20a** (25.5 mg, 100%) and (−)-**20b** (17.0 mg, 100%) as red solids.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR data of compounds (−)-**5**, (−)-**6**, (−)-**7**, **16**, (−)-**8**, (−)-**9**, (−)-**9a**, (−)-**9b**, (−)-**9c**, (−)-**17**, (+)-**19a**, (−)-**19b**, (+)-**20a**, and (−)-**20b**. UV−vis spectra of compounds (+)-**19a**, (−)-**19b**, (+)-**20a**, and (−)-**20b**. CD spectra of compounds (+)-**19a**, (−)-**19b**, (+)-**20a** and (−)-**20b**. High-resolution MALDI−TOF spectra of compounds (+)-**19a**, (−)-**19b**, (+)-**20a**, and (−)-**20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Michael Orfanopoulos on the occasion of his 65th birthday.

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