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Synthesis and Characterization of Mono- and Bis-methano[60]fullerenyl Amino Acid Derivatives and Their Reductive Ring-Opening Retro-Bingel Reactions

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Received May 10, 2002

The addition of *N*-(diphenylmethylene)glycinate esters ($Ph_2C{=}NCH_2CO_2R$) **3**−**6** to [60]fullerene under Bingel conditions gives, respectively, the methano[60]fullerenyl iminoesters **7**−**10**. Upon treatment of **7**−**9** with sodium cyanoborohydride, in the presence of a protic or a Lewis acid, a novel reductive ring-opening reaction occurred to give the corresponding 1,2-dihydro[60]fullerenyl glycine derivatives **11**−**13**. Using tethered bis-*N*-(diphenylmethylene)glycinate esters **33** and **34** derived from *m*- and *p*-benzenedimethanol scaffolds, the corresponding bis-methano[60]fullerenyl iminoesters **35**−**38** were synthesized under double Bingel reaction conditions. The *m*-benzenedimethanol derivative **33** gave the *trans*-4 (**35**) and *cis*-3 (**36**) regioisomeric bisadducts in a ratio of 80:20. The analogous para-tethered derivative **34** afforded the *trans*-3 (**37**) and *trans*-4 (**38**) regioisomers in a 80:20 ratio. The regiochemistry of the major bisadducts **35** and **37** (via the trans-esterified **39**) were unequivocally determined using 2D INADEQUATE and C−C TOCSY NMR experiments. The regiochemistry of these bis-additions were unexpected on the basis of literature precedents. These results unequivocally show that the regiochemistry of tethered bis-additions is not solely dependent on the nature of the tether. A mixture of the *trans*-4 and *cis*-3 nonsymmetrical bisadducts **45** and **46** was obtained from the double-Bingel cyclopropanation of a bis-*N*-(diphenylmethylene)glycinate tether based on a 1,3-naphthyldimethanol scaffold. The regiochemistry of these compounds (**45** and **46**) was identified by correlation with the diethyl esters **40** and **47**, prepared by trans-esterification of **35**/**45** and **36**/**46**, respectively. The INADEQUATE and molecular modeling experiments allowed topological mapping of the fullerene surfaces of the bis-methano[60]fullerenes **38** and **42**. Reductive ring-opening reactions on the tethered bis-methano[60]fullerenes **35**−**37**, **45**, and **46** gave none of the expected bis-fullerenylglycinates rather the reductive ring-opening-retro-Bingel products, the 1,2-dihydro[60]fullerenylglycinates **48**, **49**, **52**, and **53**. These compounds resulted from the reductive ring-opening of one methanoimino ester moiety and a retro-Bingel reaction of the other. Under analogous reductive ring-opening-retro-Bingel conditions, the non-tethered bis-methano[60]fullerene **40** afforded the 1,2-dihydro[60]fullerenylglycinate **12**. Thus, it was concluded that the tether was not the driving force for the reductive elimination of one of the methano groups.

Introduction

The pioneering investigations into the chemical reactivity of [60]fullerene[1−8] have provided a precedent toward the design and synthesis of novel and sophisticated architectures that may have applications in medicinal chemistry and the material sciences.[9−11] The incorporation of biomolecular principles (such as water solubility and precise secondary/tertiary structure) with the unique physicochemical properties of fullerenes (sensitization of singlet oxygen; electron acceptor characteristics) have produced molecular structures with a variety of biological activities.[12] For example, in 1993, Friedman and co-workers recognized the fullerene sphere can be accommodated inside the cylindrical hydrophobic cavity of HIV protease.[13] In an additional illustration, in vitro studies of water-soluble [60]fullerene derivatives containing hydrophilic functionalities demonstrated the

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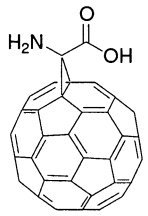
10.1021/jo025928j CCC: $22.00
Published on Web 10/31/2002

ability of [60]fullerenes to inhibit acutely and chronically affected peripheral blood mononuclear cells with an EC_{50} of 7 μM.[13,14]

As part of a program aimed at the investigation of the potential applications of [60]fullerene derivatives, we have proposed a method for the synthesis of protected versions of the mono- and disubstituted fullerenyl α-amino acids **1** and **2**. Derivatives of these compounds have been obtained via the Bingel cyclopropanation methodology using readily available *N*-(diphenylmethylene)glycinate esters.[15−17] Systematic protection/deprotection of the carboxylate and amino functionalities of these protected amino acids should allow the incorporation of α-fullerenyl amino acids into biological macromolecules using conventional peptide coupling methods. The resultant fullerenyl-containing structures would have unique electron acceptor properties as well as interesting structural features and biological activities. Indeed, there are reports of polypeptide chains being terminally tagged with fullerenes,[18] while the insertion of the fullerene spheroid into peptide chains has been demonstrated using fulleroproline.[9,19−23] The proposed α-fullerenyl amino acids **1** and **2**, however, would be expected to produce new and interesting biomolecular structures and were therefore deemed worthy targets for synthesis.



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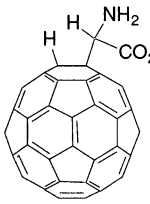
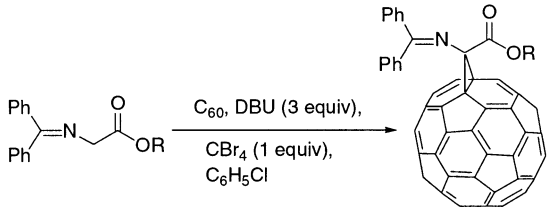


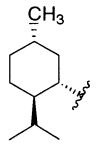
2

From the outset of our studies, we aimed to produce the methano[60]fullerenyl α-amino acid **1** or suitably protected versions of this molecule. Although our efforts toward the realization of **1** were thwarted, this paper reports on the serendipitous discovery of a novel reductive ring-opening reaction of methano[60]fullerenes and the synthesis of a fully protected version of the [60]-fullerenylglycine **2**, a true α-fullerenyl amino acid. We also report the synthesis of a series of bismethano[60]-fullerene amino acid derivatives via tether-directed remote functionalization, yielding products of unexpected regiochemistry. The unequivocal characterization of these novel fullerenyl derivatives was made using the powerful 2D-INADEQUATE suite of experiments to map out important $^{13}C-^{13}C$ connectivity patterns. Additionally, the reductive ring-opening reactions of these bisadducts are also described.

SCHEME 1

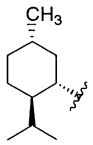


3 R = ^{t}Bu
4 R = Et
5 R =



6 R = EtO_2CCH_2-

7 R = ^{t}Bu
8 R = Et
9 R =



10 R = EtO_2CCH_2-

TABLE 1. Yields of the Bingel Cyclopropanation Products 7−10 from *N*-(Diphenylmethylene) Glycinate Esters 3−6

compd	R group	yield (%)
7	^{t}Bu	46
8	Et	72
9	(+)-menthyl	31
10	*O*-glycolic	46

Synthesis of Mono- and Bis-methano[60]-fullerenyl Imino Esters

The reaction of [60]fullerene with active methylene components (CH_2WW') in the presence of base and a halogenating agent (the Bingel reaction)[24] is a general and versatile method for preparing methano[60]fullerenes of the general formula $C_{61}WW'$ (where W is an electron-withdrawing group). While malonic esters have generally been employed,[25] we have found that under Bingel conditions the reaction of [60]fullerene with *N*-(diphenylmethylene)glycinate esters **3**−**6** efficiently provides the corresponding methano[60]fullerenyl imino esters **7**−**10** (Scheme 1).

Thus treatment of a mixture of [60]fullerene and the individual *N*-(diphenylmethylene)glycinate esters **3**−**6** with 1.0 molar equiv of carbon tetrabromide and 3.0 molar equiv of base (DBU) for 30 min afforded the methano[60]fullerene derivatives **7**−**10**, respectively, after purification by silica gel column chromatography (Table 1). A significant difference in the reaction times was observed for Bingel adducts arising from *N*-(diphenylmethylene)glycinate esters (30 min) versus the corresponding malonate esters (8 h),[26] suggestive of the greater acidity of the *N*-(diphenylmethylene)glycinate ester methylene protons and their cognate α-bromo derivatives.

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The ^{13}C NMR spectrum of **7** comprised 28 resonances arising from the sp^2 carbons of the fullerene core. Three of these carbons were half the intensity of the remaining fullerenyl sp^2 carbons, indicative of C_s symmetry.[27] Compounds **7**−**10** were identified as possessing "closed" methano[60]fullerene structures rather than the "open" methanoannulene structures by the presence of bridgehead carbon resonances between δ 93 and 96.[28,29] ^{13}C NMR resonances located between δ 82 and 83 were assigned to the fullerenyl sp^3 carbons at the site of substitution on the fullerene core. The ESMS spectrum of **7** displayed a molecular ion (M^+) at *m*/*z* 1013 while the MALDI-TOF spectrum of **8** displayed a molecular ion at *m*/*z* 985. An unusual peak was also observed at *m*/*z* 1452 in a number of MALDI-TOF spectra. This ion was attributed to the formation of a methano[60]fullerene dimer under MALDI-TOF conditions.[30,31]

The diphenylimine moiety is known for its lability in acidic media;[32] however, following the literature methods, treatment of **7** with 1 M HCl at room temperature resulted in a quantitative recovery of the starting material. This was attributed to the electron-withdrawing nature of the [60]fullerene sphere making the imino nitrogen less basic and thus less susceptible to protonation under these reaction conditions. This effect was also observed in fulleropyrrolidines for which it has been found that the nitrogen has a far reduced nucleophilicity and basicity compared to its pyrrolidine analogue.[33] Harsher acidic conditions gave rise to products that were difficult to characterize due to the extreme insolubility of these organic compounds in both water and organic solvents. An attempted base hydrolysis of **8** using lithium hydroxide in a mixture of THF/MeOH/H_2O (10:5:1) at room temperature for 24 h also returned unreacted starting material. Treatment of the *O*-ethyl glycolic ester **10** with BBr_3[34] in dichloromethane solution afforded a moderately soluble material that was also difficult to characterize.

Reductive Ring-Opening of *N*-(Diphenylmethylene)glycinate Methano[60]fullerene Esters

Due to a lack of reactivity in hydrolyzing the diphenylimine moiety of **7** and **8**, an alternate deprotection method was considered. The initial strategy was to reduce the diphenyl imine group of **7**/**8** to its corresponding secondary amine and subsequently cleave the resulting benzhydryl amino group using catalytic transfer hydrogenation[35] to afford the free primary amine.

SCHEME 2

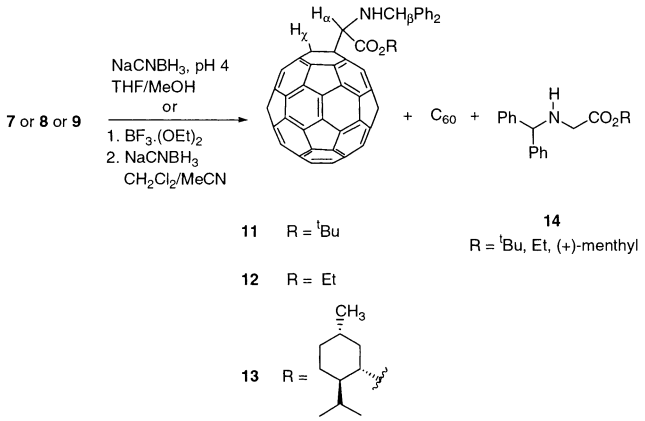

TABLE 2. Yields of Reductive Ring-Opening Products Shown in Scheme 2

	product yields (%)		
starting compds	reductive ring-opening	[60]fullerene	**14**
7	**11** (39)	9	*a*
8	**12** (58)	12	8
9	**13** (40)[b]	10	*a*

[a] Due to the small scale of this reaction, isolation of **14** proved difficult. [b] The product was a 1:1 mixture of diastereomers.

Hydrogenation of **7** and **8** over Pd/C under a hydrogen atmosphere provided only unreacted starting material. Reduction of **7** using sodium borohydride resulted in an uncharacterizable polar compound whereas the milder reductant, sodium cyanoborohydride, adjusted to pH 4 with glacial acetic acid,[36] yielded not the reduced secondary amine but rather the unexpected ring-opened 1,2-dihydro[60]fullerenylglycine derivative **11** (Scheme 2).

Unfortunately, this reductive ring opening using glacial acetic acid proved unreliable. However, treatment of **7**−**9** with boron trifluoride·diethyl etherate (5.0 molar equiv) followed by the addition of sodium cyanoborohydride consistently yielded the ring-opened products **11**−**13**, respectively (Table 2), accompanied by the formation of free [60]fullerene (9−12%). From the reductive ring opening of **8**, the reduced addend **14** (R = ^{t}Bu) was also isolated (Table 2). Reductive ring opening of the chiral methano[60]fullerene **9** was attempted to investigate whether a diasteroselective reaction could take place. ^1H NMR analysis of **13**, however, revealed the formation of a 1:1 diastereomeric mixture of ring-opened products from integration of the corresponding fullerenyl protons at δ 6.91 and 6.88 for each diastereomer.

The proposed mechanism of this novel ring opening under protic acid conditions is shown in Scheme 3. This process may not necessarily be concerted, and the protonation steps may occur at different stages of the pathway. The first step is activation of the diphenyl imine functionality under protic acid conditions to form an iminium cation **15**. The first equivalent of hydride then attacks the activated iminium carbon, with subsequent cyclopropyl ring opening (see **16**) giving rise to the

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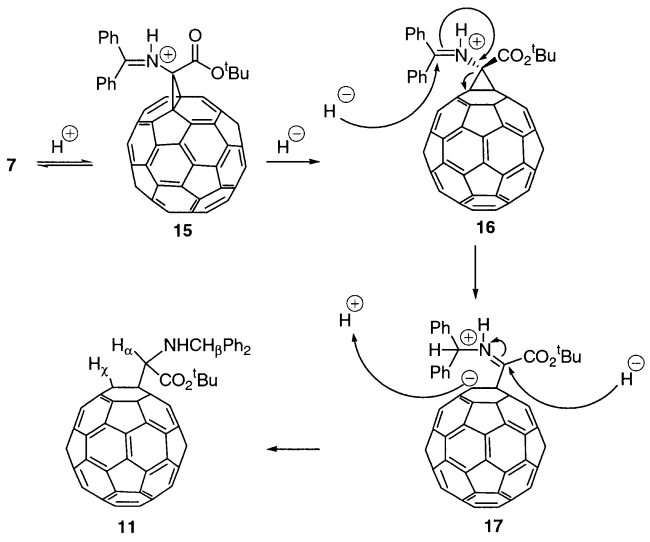
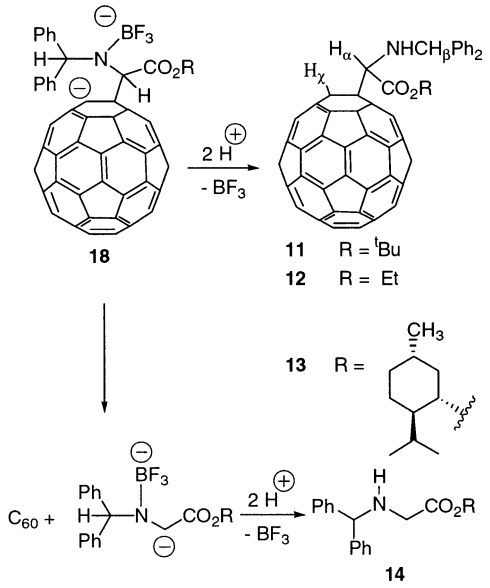
SCHEME 3



SCHEME 4

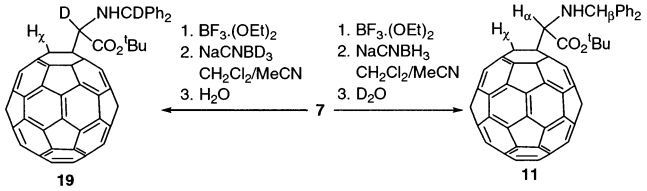


fullerenyl anion intermediate **17**. The driving force for such a ring opening is assumed to be the release of ring strain and the stabilization of the incipient fullerenyl carbanion **17** by the electron-deficient fullerene sphere. Such ring opening of cyclopropane amino esters and acids is known when a β-electron-withdrawing group is present on the ring that can stabilize a developing carbanionic center.[37]

The mechanism for the corresponding Lewis acid promoted reductive ring-opening is assumed to proceed via a different but related pathway (Scheme 4). The corresponding expected intermediate fullerenyl carbanion **18** can be protonated to give **11**−**13** or undergo elimination of the addend to form free [60]fullerene and eventually **14**.

To explore the mechanism of this Lewis-acid activated ring opening, corresponding ring-opening experiments were performed using deuterium-labeled sodium cyanoborohydride ($NaCNBD_3$) followed by an aqueous (H_2O) workup. Such an experiment could give insight toward the origin of the proton source for the fullerenyl proton (H_χ). Reduction of **7** with sodium cyanoborodeuteride in the presence of boron trifluoride.diethyl etherate followed by an aqueous workup afforded the ring-opened compound **19** in 38% yield (Scheme 5). ^{1}H NMR analysis revealed 42% deuterium incorporation at both the H_α and H_β positions, consistent with our proposed mechanism. However, no insight into the origin of the fullerenyl proton (H_χ) was obtained. To examine if the proton source arose from the workup conditions, a Lewis-acid-mediated ring opening was performed using sodium cyanoborohydride with D_2O as the quenching agent (Scheme 5). ^{1}H NMR analysis showed no incorporation of deuterium in **11** after purification by column chromatography using silica gel. Recently, we have found that related 1,2-dihydrofullerene compounds undergo rapid exchange of the fullerenyl proton (or deuteron, H_χ) upon silica gel chromatography thus possibly explaining the lack of deuterium incorporation in the latter experiment.[38] This result was understandable and consistent with the known relatively high acidity of 1,2-dihydro[60]fullerene derivatives; for example, 1,2-C_{60}(^{t}Bu)H has a pK_a of 5.7.[39]

SCHEME 5



The ring opening of methano[60]fullerene derivatives has been previously observed in spiroannelated methano[60]fullerenes whereupon a one-electron reduction causes a homolytic cleavage of one of the bonds in the cyclopropane ring. This ring opening, however, could only be observed transiently using EPR spectroscopy before proceeding irreversibly to an unknown product.[40]

Characterization of the Ring-Opened Products

The ^{1}H NMR spectrum of the ring-opened product **11** revealed a three-proton coupled spin system at δ 5.27 (H_β, d, J = 4.4 Hz), 4.83 (H_α, d, J = 15.6 Hz), and 3.61 (NH, dd, J = 15.6, 4.4 Hz). A singlet resonance at δ 6.84 was assigned to the fullerenyl proton (H_χ). This was consistent with the chemical shifts of fullerenyl protons identified in the literature.[41] The fullerenyl sp^2 region of the ^{13}C NMR spectrum of **11** revealed 47 of the possible 58 sp^2 resonances, indicative of a fullerenyl adduct possessing no symmetry elements. Closer inspection of the fullerenyl sp^2 section revealed a number of defined clusters of resonances in particular regions of the ^{13}C NMR spectrum. For example, both an upfield (δ 136−138) and a downfield (δ 152−155) cluster of four resonances were

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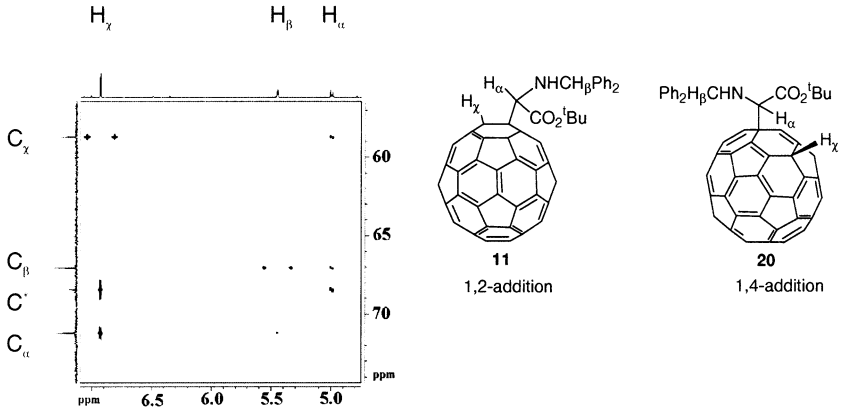


FIGURE 1. 8 Hz optimized HMBC (600 MHz, C_6H_6/CS_2 1:1) expansion plots of **13** revealing $^3J_{HC}$ for $H_\chi \rightarrow C_\alpha$ and $^3J_{HC}$ for $H_\alpha \rightarrow C_\chi$. These assignments were identified by a $^3J_{HC}$ of 6.0 Hz.

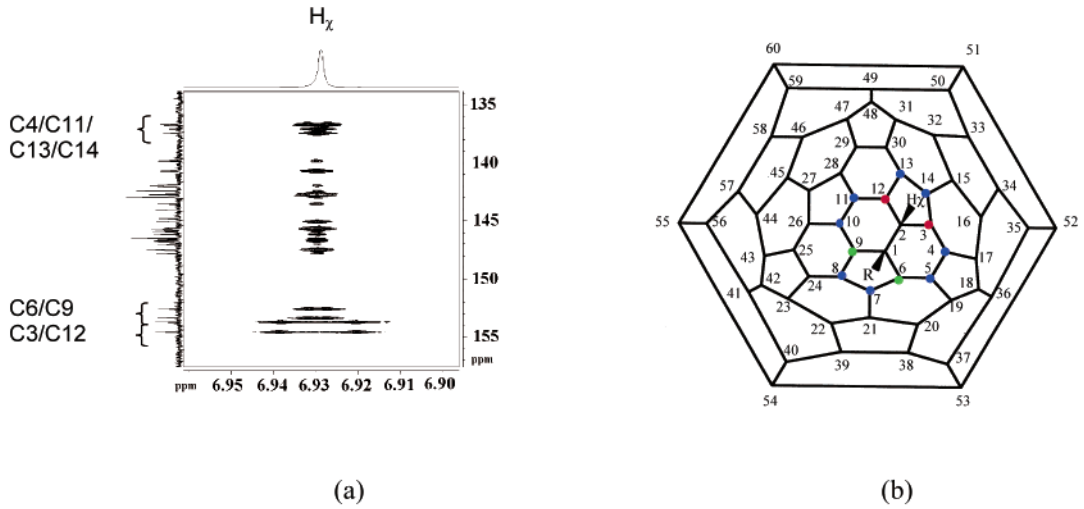


FIGURE 2. (a) 2 Hz optimized HMBC (600 MHz, C_6H_6/CS_2 1:1) spectrum of **11** showing 20 correlations from H_χ into the fullerene sp^2 core. (b) Schlegel diagram of the ring-opened adduct **11**. C3 and C12 were identified by a $^2J_{HC}$ coupling to H_χ (red circles). C6 and C9 were identified by a $^3J_{HC}$ coupling to H_χ (green circles). Blue-circled carbon atoms are those β to the site of functionalization but could not be unambiguously determined from HMBC experiments to be C4, C5, C10, C11 or C7, C8, C13, C14.

observed relative to that for the main cluster of peaks between δ 142−147.

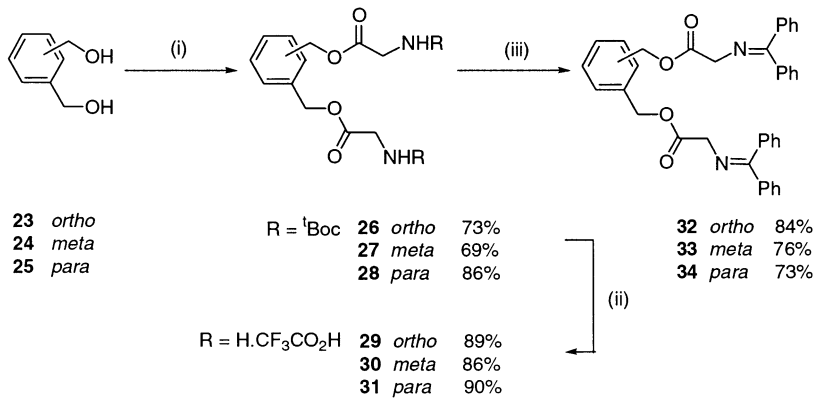
The HMBC experiment identified a three-bond $^1H-^{13}C$ correlation between H_χ and C_α (Figure 1). A corresponding three-bond correlation between H_α and C_χ also confirmed the 1,2-addition pattern. A 1,4 substitution pattern (**20**) would not show such correlations since this would represent coupling over five bonds between H_χ/C_α and H_α/C_χ. A 2 Hz optimized HMBC experiment was also performed on **11**, allowing long-range $^1H/^{13}C$ correlations to be observed. Interestingly, it was found that the single proton resonance of H_χ correlated to 20 fullerene sp^2 carbons; i.e., one-third of the fullerene sphere was identified from a single proton resonance (Figure 2a).

Particular resonance clustering was apparent after closer inspection of the nature of the coupling between H_χ and the fullerenyl sp^2 carbons. Of the correlations between H_χ and the fullerenyl sp^2 carbons, the most downfield resonances δ 154.4 and 153.7, with the largest J_{HC} values, were assigned to C3 or C12, respectively. These carbons both had a $^2J_{HC}$ of 10.8 Hz and exist as a diastereotopic pair as a consequence of the stereogenicity of C_α. These were assigned the carbons α to the functionalization site, and adjacent to H_χ (red circles in Figure 2b).

The more upfield diastereotopic pair of this cluster of four carbons was assigned C6 or C9 at δ 153.1 or 152.4, respectively. These carbons were assigned as being α to the functionalization site, but in the same hemisphere as the addend (green circles in Figure 2b). Unequivocal assignment of the individual carbons of the diastereotopic pairs could not be determined using the HMBC experiment. The most upfield group of carbons C4/C11 and C13/C14, were also found to exist as diastereotopic pairs due to the stereotopic center at the C_α position. Although these carbons could not be assigned unequivocally by the HMBC experiment alone, there appeared to be a trend in the nature of fullerene sp^2 ^{13}C NMR chemical shifts directly in the vicinity of functionalization. Fullerene sp^2 carbons α to the functionalization site (C3, C6, C9 and C12) appear to exist downfield when compared with the remaining fullerene sp^2 population (red and green circles, Figure 2b).

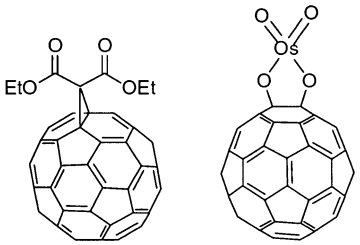
The group of four upfield fullerenyl sp^2 carbons (δ 137.3−136.6) were assigned to either C4/C11 or C13/C14 from their $^3J_{HC}$ of 6.0 Hz. This "upfield/downfield" effect

SCHEME 6[a]



[a] Reagents: (i) DMAP (cat.), DCC (2.1 equiv), *N*-*tert*-butoxycarbonlyglycine, CH_2Cl_2; (ii) TFA; (iii) $Ph_2C{=}NH$ (2 equiv), CH_2Cl_2.

of fullerenyl sp^2 carbons α and β to the site of functionalization has also been observed in the methano[60]-fullerene adduct **21** and has been reported for some fullerene−organometallic complexes, for example the osmium derivative **22**, using the 2D INADEQUATE experiment.[42−44]



21 **22**

[60]Fullerene Bisfunctionalization using Tethered Bis-*N*-(diphenylmethyleneglycinate) Esters

In principle, the bis-cyclopropanation of [60]fullerene using tethered bis-*N*-(diphenylmethylene)glycinate esters followed by our reductive ring-opening methodology would allow protected bis-amino acid functionalities to be incorporated into precise locations on the surface of the fullerene sphere. To produce regioselective multifunctionalized fullerenyl amino acids, a tether-directed methodology was adopted.[1,45] The tethers chosen for bisfunctionalization of [60]fullerene were the benzenedimethanols **23**−**25** that have been used extensively by the Diederich group for the malonate-derived biscyclopropanation of [60]fullerene.[46] The tethered bis-*N*-(diphenylmethylene)glycinate diesters **32**−**34** were synthesized as shown in Scheme 6. DCC-mediated bis-esterification of *o*-, *m*-, and *p*-benzenedimethanol (**23**−**25**) afforded the bisglycine esters **26**−**28**, respectively. These were converted to their respective ammonium trifluoroacetate salts **29**−**31** by treatment with TFA.

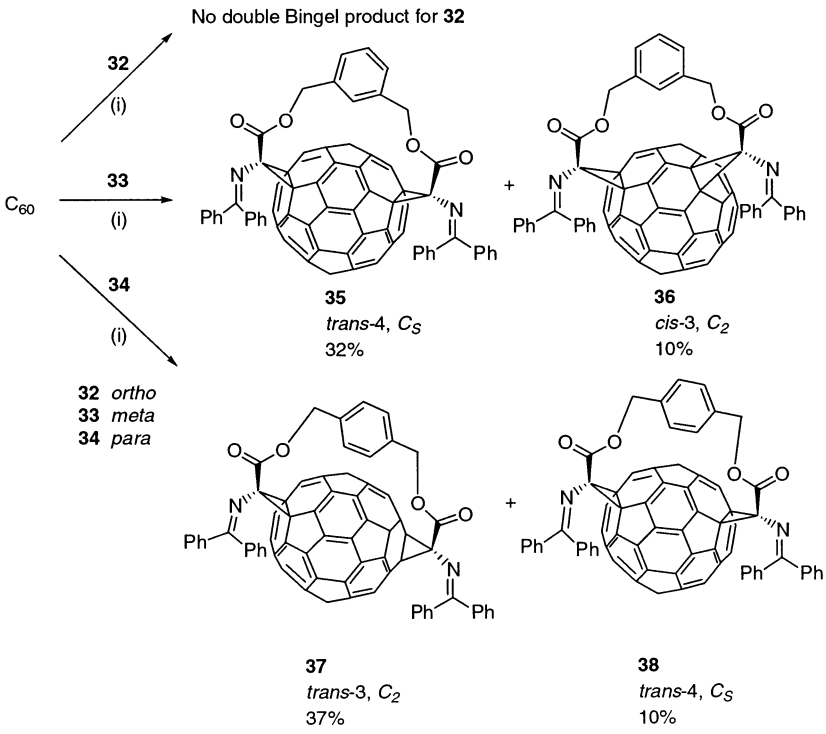
Treating a suspension of these salts in dichloromethane (DCM) with benzophenone imine for 24 h afforded the transiminated diesters **32**, **33**, and **34** in 84, 76, and 73% yields, respectively.

The individual double Bingel cyclopropanation reactions of **32**, **33**, and **34** with [60]fullerene were attempted using carbon tetrabromide (2.0 molar equiv) and DBU (3.5 molar equiv) (Scheme 7). These reactions typically took 1 h to reach completion on the basis of TLC analysis. Purification required elution of the crude reaction mixture through two silica gel columns with DCM/petroleum spirit (90:10) as the eluent. Under these conditions, the reactions using ortho-tethered bis-*N*-(diphenylmethylene)glycinate diester **32** did not afford a characterizable product.

Earlier work has shown that tethered bis-malonate esters undergo regioselective bis-cyclopropanation reactions with [60]fullerene under Bingel conditions.[46] For example, both the ortho- and meta-substituted tethered bismalonate analogues of **32** and **33** gave exclusively the *cis*-2 regioisomer as determined by comparative UV−vis spectroscopy and from its symmetry by 1D ^{13}C NMR spectroscopy. The corresponding para isomer afforded predominantly the *trans*-4 adduct. In contrast, we have found that treatment of [60]fullerene with our bisimino ester **33** gives, under similar reaction conditions, two regioisomeric adducts **35** and **36** in a ratio of 80:20 from ^1H NMR analysis of the crude reaction mixture. These compounds were readily separated by column chromatography to afford **35** and **36** in 32 and 10% yields, respectively (Scheme 7). The ^1H NMR of pure samples of **35** and **36** showed resonances for the two pairs of diastereotopic methylene protons [δ 5.06 and 5.71, J = 11.2 Hz for **35**; δ 5.41 and 5.31, J = 11.0 Hz for **36**] consistent with a tethered bis-methano[60]fullerene structure. ^{13}C NMR spectroscopy revealed 31 peaks associated with the fullerenyl sp^2 carbons in **35**, consistent with its C_s-symmetry; three of these carbons were identified as being of half-intensity compared to the remaining carbons.[27] The ^{13}C NMR spectrum of **36** revealed 30 full-intensity peaks associated with the fullerenyl sp^2 carbons, typical of a molecule exhibiting C_2-symmetry. Furthermore, the MALDI-TOF spectrum of **35** and **36** showed a characteristic parent molecular ion at *m*/*z* 1296. The UV−

(42) Hawkins, J. M.; Loren, S.; Meyer, A.; Nunlist, R. *J. Am. Chem. Soc.* **1991**, *113*, 7770−7771.
(43) Hawkins, J. M.; Meyer, A.; Lewis, T. A.; Bunz, U.; Nunlist, R.; Ball, G. E.; Ebbesen, T. W.; Tanigaki, K. *J. Am. Chem. Soc.* **1992**, *114*, 7954−7955.
(44) Burley, G. A.; Keller, P. A.; Pyne, S. G.; Ball, G. E. *Magn. Reson. Chem.* **2001**, *39*, 466−470.
(45) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170−177.
(46) Nierengarten, J. F.; Habicher, T.; Kessinger, R.; Cardullo, F.; Diederich, F.; Gramlich, V.; Gisselbrecht, J. P.; Boudon, C.; Gross, M. *Helv. Chim. Acta* **1997**, *80*, 2238−2276.

SCHEME 7[a]



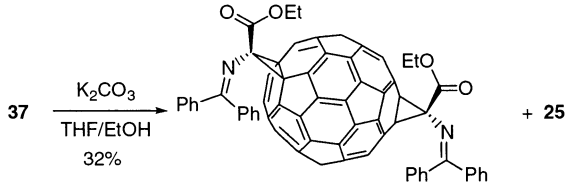
[a] Reagents: (i) DBU (3.5 equiv), CBr_4 (2 rquiv), C_6H_5Cl.

vis spectrum of **35** showed bands between 400 and 800 nm that suggested a *trans*-4 structure,[47] but this conclusion was not definitive due to the lack of adequate reference compounds. The corresponding UV−visible spectrum for **36** exhibited characteristics of both a *cis*-2 and a *cis*-3 bis-methano[60]fullerene,[47] therefore rendering regiochemical assignment by UV−visible spectroscopy as not definitive.

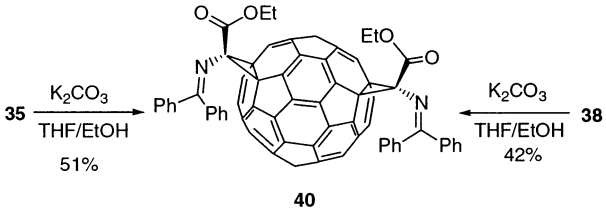
Treatment of [60]fullerene with **34** under Bingel conditions afforded two regioisomers in an 80:20 ratio from ^{1}H NMR analysis with the isolated yields of **37** and **48** being 37 and 10%, respectively. The MALDI-TOF spectra for both **37** and **38** showed a characteristic parent ion at *m*/*z* 1296, consistent with the MALDI-TOF spectra of compounds **35** and **36**. Both compounds **37** and **38** exhibited characteristics in their ^{1}H NMR spectra of a tethered bismethano[60]fullerene [doublets at δ 5.21 and 5.58, J = 11.6 Hz for **37**; doublets at δ 5.17 and 5.72, J = 14.4 Hz for **38**]. Due to the extreme insolubility of **38**, a ^{13}C NMR spectrum could not be acquired[48] however transesterification of **38** using K_2CO_3 in a 1:1 mixture of THF/EtOH afforded **39** that was readily soluble in a range of organic solvents (Scheme 8).

The ^{13}C NMR of **39** indicated that it had C_2-symmetry, characterized by 30 full-intensity sp^2 resonances, whereas **38** had C_s-symmetry, characterized by 29 sp^2 resonances, three being half-intensity.[27] The bis-methano[60]fullerene adducts **35**−**38** all exhibited a single cyclopropyl bridgehead carbon (ca. δ 96) and two fullerenyl sp^3 carbons (ca. δ 82) in their ^{13}C NMR spectra.

SCHEME 8



SCHEME 9



The UV−vis spectrum of **39** had characteristic bands in the 400−800 nm region that beared resemblance to a *trans*-3 bis-methano[60]fullerene, which was consistent with its C_2-symmetry. The corresponding UV−vis spectrum for **38** revealed an almost identical spectrum to that of **35**. Both **35** and **38** possess C_s-symmetry, suggesting identical regiochemistry. This was confirmed by their transesterification reactions to form the same bis-methano-[60]fullerene **40** (Scheme 9).

The similarity in the UV−vis spectra for the two distinct regioisomers **36** and **38** gave rise to ambiguities in the assignment of the absolute regiochemistry. Such ambiguities have been noted elsewhere[49] and the assignment of regiochemistries based upon comparative techniques has its limitations when no suitable comparison can be made, e.g., higher order substitution patterns. In

(47) Djojo, F.; Herzog, A.; Lamparth, I.; Hampel, F.; Hirsch, A. *Chem.*−*Eur. J.* **1996**, *2*, 1537−1547.

(48) A range of solvents (C_6D_6, $(CD_3)_2SO$, CS_2, dichlorobenzene-d_4) were tried in an effort to increase the solubility of **40**; however, these were ineffective.

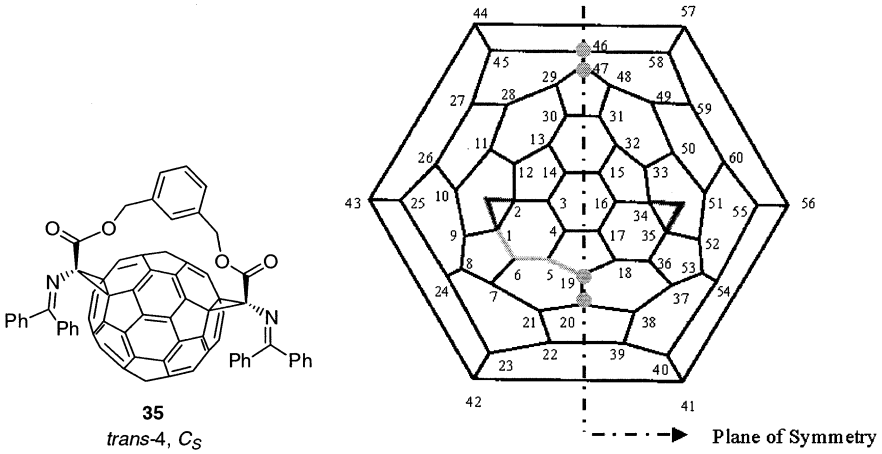


FIGURE 3. Schlegel diagram of **35**, showing the carbon numbering system and key connectivities (gray lines) from NMR. The carbon atoms that lie on the plane of symmetry (C19, C20, C46, C47) are identified by gray circles. The tether moiety on the Schelgel diagram has been removed for clarity. Numbering system according to Thilgen et al.[50]

our case, UV−vis spectroscopy could not be used as a *definitive* characterization tool in this study for the assignment of the regiochemistry of the bisadducts **35**−**38** and unequivocal evidence for their structures came from 2D INADEQUATE experiments.

2D INADEQUATE Experiments

As discussed earlier, ^{13}C NMR spectroscopy revealed 31 peaks associated with the fullerenyl carbons in **35**. The resonance at δ 150.9 was shown to arise from the fortuitous overlap of one full-intensity peak and one-half-intensity peak. Hence, **35** has 32 unique fullerene carbons, four of which are half-intensity peaks (labeled as gray circles in Figure 3), indicative of a bis-methano-[60]fullerene with C_s-symmetry. To distinguish between the three possible structural isomers, *cis*-1, *cis*-2, and *trans*-4, INADEQUATE experiments were performed on a 10% ^{13}C enriched sample of **35**.

The assignment of the regiochemistry of the bis-methano[60]fullerene **35** was achieved by identifying correlations from the half-intensity peaks (located on the symmetry plane) to the fullerenyl sp^3 carbons (locating the site of substitution). The above-mentioned three possible regioisomers would be expected to show two, one and three-bond separations, respectively, between a fullerenyl sp^3 hybridized carbon and its nearest carbon on the plane of symmetry (i.e., half-intensity peak). These experiments revealed a three-bond connectivity (shown as gray lines in Figure 3) between C1 (sp^3 carbon) and C19 (half-intensity peak) providing unequivocal evidence for its *trans*-4 structure. Starting from C19, correlations were observed to the other half-intensity peak (C20) with a relatively large coupling constant ($^1J_{CC} = 67$ Hz) typical for 6,6 ring fusion carbons and one to C5 with a smaller $^1J_{CC}$ (57 Hz) typical for 6,5 ring fusion carbons.[42] Carbon-5 showed correlations to C6 ($^1J_{CC} = 73$ Hz) and C4 ($^1J_{CC} = 53$ Hz), consistent with their 6,6 and 5,6 ring fusion positions, as well as to C19. Carbon-6 showed a correlation to the sp^3 carbon C1, unequivocally confirming the position of the cyclopropane ring relative to the plane of symmetry. Further corroborative evidence for this structure was the observation that C4 showed only two correlations (to C3 and C5) consistent with the magnetic equivalence of C4 and C17 due to their positions relative to the plane of symmetry. The complete assignment for the fullerenyl carbons of **35** is summarized in Table 3.

Due to the insolubility of **37** the ^{13}C-^{13}C connectivity experiments were conducted on its transesterified prod-

TABLE 3. Chemical Shifts (δ), Peak Assignments, and Carbon−Carbon Coupling Constants ($^1J_{CC}$) for the [60]fullerene Cage of 35[a]

carbon no.	chemical shift (δ, ppm)	$^1J_{CC}$ (Hz) (carbon no.)
1, 35	81.4	(2)**, (6) 44, (9) 44
2, 34	81.3	(1)**, (3) 40, (12) 41
3, 16	145.7	(2) 41, (4) 70, (14) 59
4, 17	129.0	(3) 70, (5) 53
5, 18	136.2	(4) 53, (6) 73, (19) 57
6*, 36	150.6	(1) 45, (5) 73, (7) 57
7, 37	146.5	(6) 57, (8)**, (21) 67
8, 53	146.4	(7)**, (9) 56, (24) 67
9, 52	149.6	(1) 45, (8) 56, (10) 72
10, 51	147.1	(9) 72, (11) 53, (26) 57
11, 50	136.2	(10) 53, (12) 71, (28) 57
12, 33	146.6	(11) 71, (13) 56, (2) 41
13, 32	145.3	(12) 56, (14) 54, (30) 68
14, 15	143.5	(13) 54, (15) 59
19#	142.2	(5) 57, (20) 67
20#	148.7	(19) 67, (21) 56
21, 38	139.4	(7) 67, (20) 56, (22) 57
22, 39**	141.1	(21) 57, (23)**
23, 40**	141.3	(22)**, (24)**, (42) 56
24, 54	140.9	(8) 67, (23)**, (25) 56,
25, 55	141.9	(24) 56, (26) 68, (43) 56
26, 60	143.4	(10) 57, (25) 68, (27) 55
27, 59	148.3	(26) 55, (28) 55, (44/45) 68
28, 59	140.3	(11) 57, (27) 55, (29) 68
29, 48	145.3	(28) 68, (30) 56, (47) 54
30, 31	138.7	(29) 56, (13) 68
42, 41	141.8	(23)**, (43) 55
43, 56	145.5	(25) 56, (42) 55, (44/45)**
44, 57	145.5	(11)**, (45)**
45, 58	145.5	(27) 68, (44)**, (46) 56
46*#	150.6	(45) 56, (47) 68
47#	145.7	(46) 68, (29) 57

[a] Key: *Denotes peak has two resonances; one full intensity and one-half intensity. **Denotes coupling not first order. Peaks positioning consistent with structure model. #Denotes half-intensity peaks.

(49) Pasimeni, L.; Hirsch, A.; Lamparth, I.; Herzog, A.; Maggini, M.; Prato, M.; Corvaja, C.; Scorrano, G. *J. Am. Chem. Soc.* **1997**, *119*, 12896−12901.

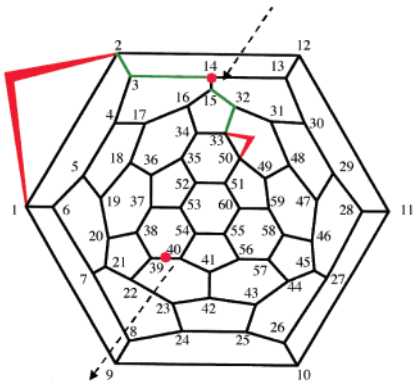


FIGURE 4. Schlegel diagram of one enantiomer of **39** showing connectivities (green) from the site of substitution (C2) to the magnetically equivalent carbons (C14 and C15). Axis of symmetry is shown in red while red dots signify entry and exit of the axis of symmetry. The methano substitutents on the Schelgel diagram have been removed for clarity. Numbering system according to Thilgen et al.[50]

uct **39** using a ^{13}C enriched sample. The ^{13}C NMR of the C_2-symmetrical bisadduct **39** comprised 30 observed fullerenyl peaks; two fullerenyl sp^3 carbons and 28 fullerenyl sp^2 carbons (Figure 4). No half-intensity peaks were observed, since the axis of symmetry in **39** bisects two sets of bonds (at the point of entry and exit on each side of the fullerene sphere) in C_2-symmetrical adducts, rather than a symmetry plane passing through two sets of bonds as in **35**. To aid the assignment of resonances close together, a series of ^{13}C-^{13}C TOCSY experiments were conducted, enabling the identification of $^{2-5}J_{CC}$ couplings.[43]

The three possible regioisomers that have a C_2-axis of symmetry are the *cis*-3, *trans*-3, and *trans*-2 isomers. These regioisomers would be expected to show one, two, and three bond separations, respectively, between a fullerenyl sp^3-hybridized carbon and its nearest carbon exhibiting two correlations (i.e., the carbon bond at which the axis of symmetry is bisected). The 2D INADEQUATE experiments revealed a two-bond connectivity between C2 (sp^3 carbon) and C14 (a peak exhibiting two correlations). Starting from C2 (sp^3 carbon), correlations were observed to resonances corresponding to C3 and C12 with $^1J_{CC}$ of 42 and 40 Hz, respectively, typical for couplings between sp^3 and sp^2 ring fusion carbons. Carbon-3 exhibited correlations to C4, with a large $^1J_{CC}$ (71 Hz) consistent with a 6,6-fusion, and to C14, a carbon with only two correlations, with a smaller $^1J_{CC}$ (58 Hz), providing unequivocal evidence for the *trans*-3 regiochemistry of **39** (Figure 4). The other two-correlation resonance (at the point of exit of symmetry axis) was identified as C39 (C40). These resonances showed a five-bond connectivity to the sp^3 carbon C50. Complete chemical shifts, peak assignments, and carbon−carbon coupling constants for **39** are shown in Table 4.

Topology of Bis-methano[60]fullerene Derivatives 35 and 49

Using 2D INADEQUATE experiments, all fullerenyl carbons in **35** and **39** were unambiguously assigned (Tables 3 and 4). Both compounds displayed three

TABLE 4. Chemical Shifts (δ), Peak Assignments, and Carbon−Carbon Coupling Constants ($^1J_{CC}$) for the [60]Fullerene Cage of 39

carbon no.	chemical shift (δ, ppm)	$^1J_{CC}$ (Hz) (carbon no.)
9, 51	153.9	(1, 50) 44; (7/8, 59/60); 57; (10, 52) 72
6, 49	153.3	(1, 50) 44; (7/8, 59/60) 57; (5, 48) 72
12, 34	151.2	(13, 16) 58; (11, 35) 71; (2, 33) 40
20, 46	148.5	(21, 58) 57; (38, 45) 56; (19, 47)
13,16	148.5	(12, 34) 58; (14, 15) 55; (17, 30) 67
18, 29	145.4	(19, 47); (28, 36) 67; (17, 30) 55
3, 32	148.3	(14, 15) 58; (4, 31) 71; (2, 33) 42
7/8, 59/60	147.6	(7/8, 59/60) N/A; (21, 58) 68; (6, 49) 57; (25, 55); (9, 51) 57
7/8, 59/60	147.6	(7/8, 59/60) N/A; (21, 58) 68; (6, 49) 57; (25, 55); (9, 51) 57
37, 27	147.6	(26, 53); (38, 45) 67; (28, 36) 55
25, 54	147.2	(40, 43) 56; (24, 55) 56; (26, 53) 67
14*, 15	145.4	(3, 32) 58; (13, 16) 55
39, 44	144.9	(38, 45) 56; (22, 57) 56; (40, 43) 68
23, 56	144.7	(22, 57) 68; (24, 55); (41, 42) 56
26, 53	144.6	(10, 52) 57; (27, 37); (25, 54) 67
38, 45	144.3	(20, 46) 56; (39, 44) 56; (27, 37) 67
22, 57	143.8	(21, 58) 56; (39, 44) 56; (23, 56)
24, 55	143.7	(7/8, 59/60); (25, 54) 56; (23, 56)
19, 47	143.6	(5, 48) 57; (18, 29); (20, 46)
40, 43	143.2	(41, 42) 56; (39, 44) 68; (25, 54) 56
11, 35	142.0	(12, 34) 71; (28, 36) 57; (10, 52) 54
41*, 42	141.6	(40, 43) 56; (23, 56) 56
21, 58	141.3	(22, 57) 56; (7/8, 59/60) 68; (20, 46) 57
28, 36	140.2	(11, 35) 57; (27, 37) 55; (18, 29) 67
10, 52	138.9	(11, 35) 54; (26, 53) 57; (9, 51) 72
17, 30	138.2	(4, 31) 57; (18, 29) 55; (13, 16) 67
4, 31	136.0	(17, 30) 57; (5, 48) 54; (3, 32) 71
5, 48	134.9	(4, 31) 54; (19, 47) 57; (6, 49) 72
1, 50	81.9	(9, 51) 44; (6, 49) 44; (30) N/A
2, 33	81.6	(12, 34) 40; (3, 32) 42; (1, 50) N/A

*Denotes resonance having two correlations.

types of bond lengths, consistent with the observed bond length types of analogous fullerene derivatives derived from both X-ray crystallographic analysis and $^1J_{CC}$ values.[42,44,51] The smallest observed $^1J_{CC}$ value (44 Hz) corresponded to the sp^3−sp^2 bond located at the site of substitution.

Information concerning the bond lengths in compounds **35** and **39** was obtained by correlating geometry-optimized (PM3)[52] bond lengths to measured $^1J_{CC}$ values (Figure 5). These measured values and calculated bond lengths were consistent with the [5]radialene substructure of the [60]fullerene cage in both **35** and **39** (Figure 6). In fact, a good correlation was obtained between the measured $^1J_{CC}$ values and the calculated bond lengths (Figure 5). The C−C bonds with larger $^1J_{CC}$ values (67−73 Hz) and calculated shorter bond lengths (1.37−1.39 Å) corresponded to 6,6 ring-fused bonds. Of these bond types, those in close proximity to the site of functionalization were noticeably shorter still (see A−D in Figure 5a,b) for both structures. The second type of fullerenyl sp^2 C−C bonds displayed smaller $^1J_{CC}$ (53−58 Hz) and calculated larger bond lengths (1.42−1.48 Å) corresponded to 5,6 ring-fused bonds. Of these 5,6 ring-fused

(50) Thilgen, C.; Herrmann, A.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 183−199.
(51) Paulus, E. F.; Bingel, C. *Acta Crystallogr., Sect. C*: *Cryst. Struct. Commun.* **1995**, *C51*, 143−146.
(52) Spartan Semiempirical (PM3) program: SGI/V5.1.1

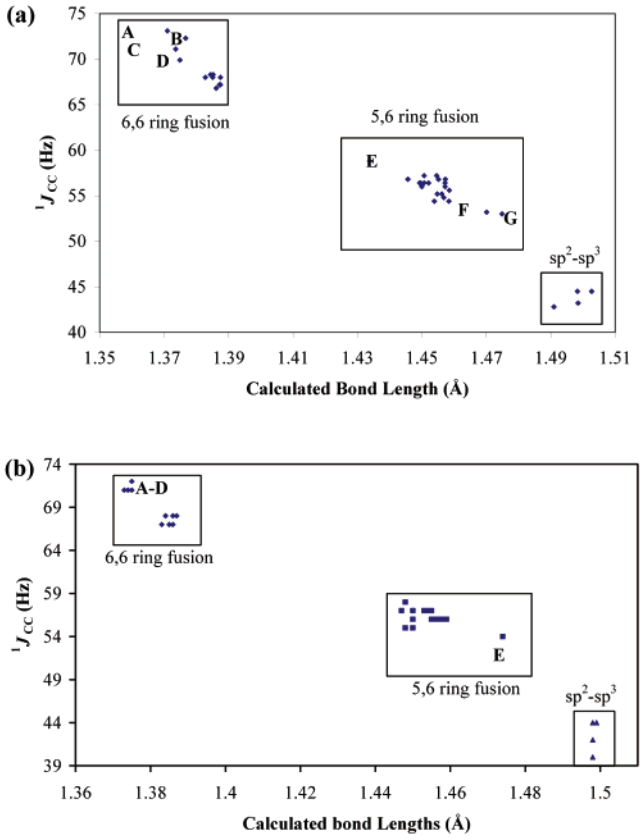


FIGURE 5. Plot of calculated (PM3) carbon−carbon bond lengths (Å) versus $^1J_{CC}$ (Hz) showing three groupings of carbon bonds: 6,6 ring fusion, 5,6 ring fusions, and sp^2-sp^3 carbon bonds for (a) **35** and (b) **39**.

bonds, longer than normal bond lengths were identified for **35** (see F and G in Figure 5a and Figure 6a) and **39** (see E for Figures 5b and 6b) close to the site of functionalization. Uniquely, compound **35** displays a significantly shorter 5,6 ring fusion bond (bond **E**, Figure 5a) close to the site of functionalization. This shortened 5,6 bond-length was not observed in compound **39**, most likely due to the more remote functionalization pattern (*trans*-3) of **39** compared to compound **35** (*trans*-4).

The second type of C−C bonds were those associated with 5,6 ring fused carbons. A number of these carbons in **35** exhibited a bond shortening, depicted by a corresponding increase in $^1J_{CC}$ (59 Hz versus the average of 55 Hz; for C3−C14 shown in green in Figure 6a), however no shortening was observed in these corresponding bonds for **39**. Other 5,6 ring fused bonds showed a lengthening, characterized by smaller $^1J_{CC}$ values (53 Hz versus the average 55 Hz) and calculated longer C−C bond lengths (1.47 Å). The fullerenyl cage of **35** exhibits comparatively more distortion when compared to **39**, most likely as a consequence of the closer proximity of the functionalized sites in **35** and the removal of the effects of the tether in **39**. This is indicative of the changed topology of the [60]-fullerene surface with an alternating lengthening and shortening of the bonds proximal to each cyclopropyl unit to compensate for the induced distortion arising from the longer sp^3 bonds. This effect is clearly most prominent in the region between the two sets of fullerenyl sp^3 carbons. The shortening of bonds local to sites of substitution has been noted before from X-ray analysis of 1,2-difunctionalized [60]fullerenes as well as in earlier studies of mono-methano[60]fullerenyl adducts due to geometrical distortion of the [60]fullerene cage to a teardrop-like structure with elongation along an axis through the poles.[5] This effect is manifested in the calculated structure of **35** with elongation occurring along two axes, each bisecting a cyclopropyl ring. This results in an increased concavity of the [60]fullerene cage topology in the region between the two substituents.

In summary, the regiochemistry of bisadducts **35** and **39** were unequivocally assigned as *trans*-4 and *trans*-3, respectively, using 2D INADEQUATE experiments. Compound **39** was synthesized via transesterification of **37** thus the regiochemistry of **37** is also *trans*-3. The tethered bisadduct **38** was also assigned as *trans*-4 as a result of the transesterification of **35** and **39** affording the same product **40** (Scheme 9). Although **36** was not assigned unequivocally by $^{13}C-^{13}C$ connectivity experiments, it is most likely to have the *cis*-3 structure based on its C_2 symmetry and the relative energy of its calculated structure.

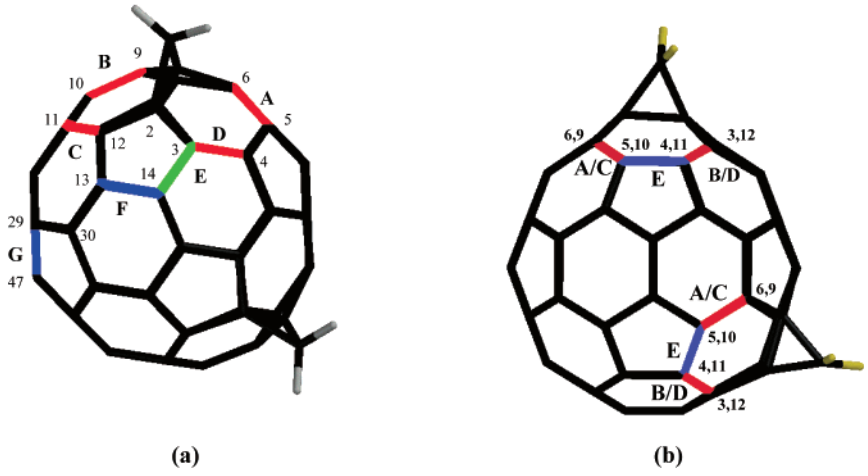
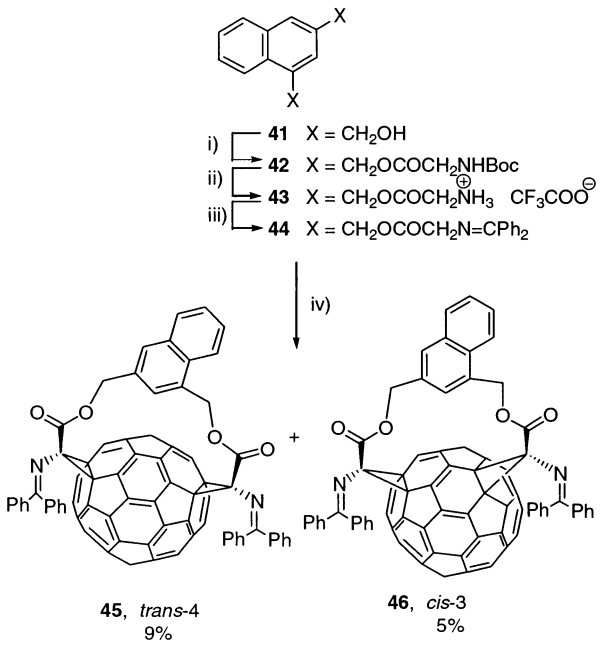


FIGURE 6. Semiempirical (PM3) structures of (a) **35** and (b) **39** showing shorter 6,6 bonds (in red), longer 5,6 bond (in green), and shorter 5,6 bonds (in blue). The tethering group has been removed for clarity.

SCHEME 10[a]



[a] Reagents: (i) *N*-*tert*-butoxycarbonylglycine (2 equiv), DMAP (0.1 equiv), DCC (2.2 equiv); (ii) TFA; (iii) $Ph_2C{=}NH$ (2 equiv), CH_2Cl_2/MeCN; (iv) C_{60} (1 equiv), DBU (4.5 equiv), CBr_4 (2 equiv), C_6H_5Cl.

Nonsymmetrical Tethered [60]Fullerene Bis-addition

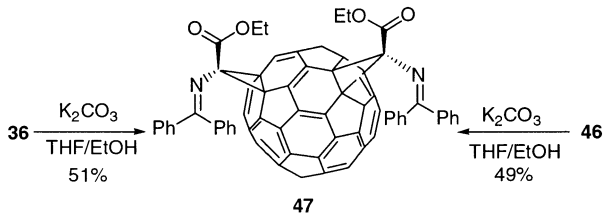
As an extension of these studies, we examined the use of a novel naphthyl tether in an effort to break the symmetry of the resultant [60]fullerene bisadducts. This was expected to make the resulting ring-opened products more readily characterized. The nonsymmetrical bis-*N*-(diphenylmethylene)glycinate tether **44** was synthesized according to the procedure illustrated in Scheme 10.

The double-Bingel cyclopropanation reaction of **44** with [60]fullerene was attempted using conditions described above for the synthesis of **35**−**39**. Purification of the crude reaction products required elution through two silica gel columns with DCM/petroleum spirit (90:10) to afford the two regioisomers **45** and **46** in yields of 9 and 5%, respectively.

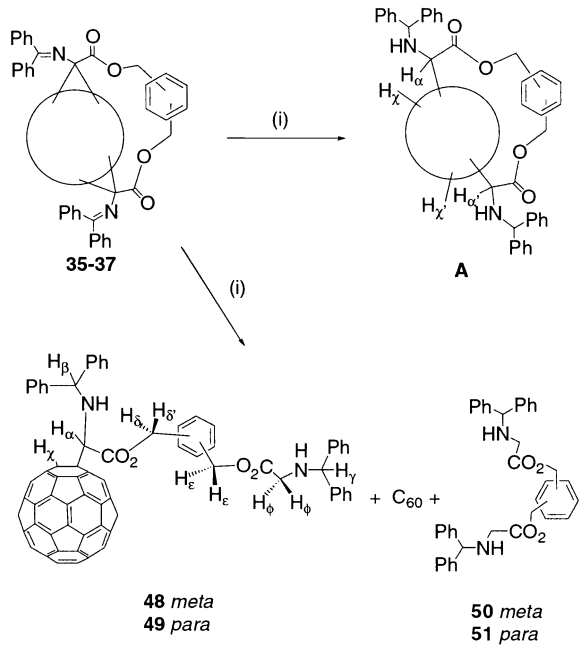
The MALDI-TOF spectrum of both **45** and **46** displayed a molecular ion at *m*/*z* 1346 and fullerenyl anion at *m*/*z* 720. The ^{1}H NMR spectrum of **45** and **46** showed resonances for the four pairs of diastereotopic benzyl protons (δ 6.43, 6.04, 5.24, 5.05, *J* ca. 11 Hz for **45**; δ 6.16, 5.87, 5.40, 5.23, *J* ca. 15 Hz for **46**). The aromatic region revealed a complex region of naphthyl tethered and diphenylimine proton resonances between δ 7.0−8.4. The ^{13}C NMR spectra of both **45** and **46** comprised 56 sp^2 fullerene resonances corresponding to the nonsymmetrical nature of the [60]fullerene core as a consequence of a lack of symmetry. In addition to the fullerenyl 56 sp^2 resonances observed for both nonsymmetrical bisadducts, four fullerenyl sp^3 resonances (δ 81.9, 81.7, 81.5, 81.3 for **45**; δ 82.4, 81.9, 81.89, 81.88 for **46**) and two cyclopropane bridgehead carbons (δ 97.1, 96.7 for **45**; δ 96.6, 95.9 for **46**) were observed.

The UV−vis, ^{1}H NMR, and ^{13}C NMR spectra of the corresponding trans esters, **40** and **47**, of **45** (Scheme 9) and **46** (Scheme 11), respectively, displayed identical spectra to the transesters of **35** and **36**, indicative of **45** and **46** possessing identical regiochemistry to **35** (*trans*-4) and **39** (*cis*-3), respectively.

SCHEME 11



SCHEME 12[a]



[a] Reagents: (i) (1) $BF_3{\cdot}(OEt_2)$, 0 °C, (2) $NaCNBH_3$, CH_2Cl_2/MeCN.

Ring-Opening Retro-Bingel Reactions of Tethered Bis-methano[60]fullerenes

The double-reductive ring opening of the tethered bisadducts **35**−**37**, in direct analogy to the monoadduct **7** (Scheme 5), was anticipated to produce the corresponding double ring-opened product **A** (Scheme 12). Treatment of **35**−**37** under the typical reductive conditions yielded the unexpected monoadducts **48** and **49** and [60]-fullerene. These compounds arise formally from a tandem reductive ring-opening retro-Bingel reaction and a double-retro-Bingel reaction, respectively. Similar reductive retro-Bingel reactions of both malonate-derived mono- and bis-methano[60]fullerenes have been observed both chemically[53] and electrochemically.[54−60] However, the conditions reported here are milder compared to these reports and should therefore be more applicable to complex systems containing multiple functionalities. The product yields are summarized in Table 5.

Compounds **50** and **51** were not isolated due to the small scale of these reactions however, based on the recovery of [60]fullerene and the isolation of **16** in the reductive ring-opening of **14**, the formation of **50** and **51**

TABLE 5. Yields of the Double-Ring-Opening Products 48/49 from the Ring-Closed Tethered Bisadducts 35−37

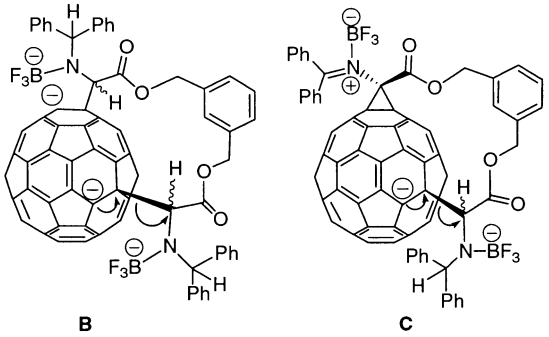
	product yields (%)	
starting material	reductive ring-opened product	[60]fullerene
35	**48** (42)	(12)
36	**49** (44)	(14)
37	**50** (31)	(12)

was assumed**.** The monofunctionalized structure of **48** and **49** was evident from the UV−vis spectra of these compounds. Both compounds **48** and **49** displayed absorbances at 430, 640, and 705 nm. The absorbance at 430 nm was also found in the UV−vis spectra of the 1,2-dihydrofullerenes **11**−**13** as well as other related derivatives reported elsewhere.[61] The ^{1}H NMR spectrum of **48** revealed a one proton singlet at δ 6.84 that corresponded to a single fullerene proton (H_χ). The addend region of **48** revealed two doublets at δ 5.41 and 5.24 (J = 11.9 Hz) corresponding to the diastereotopic benzyl protons (H_δ/$H_{\delta'}$). The other benzylic protons (H_ϵ) resonated as a two proton singlet at δ 5.07, whereas the two proton singlet at δ 3.37 was identified as corresponding to the methylene protons (H_ϕ). A singlet one proton resonance at δ 4.84 corresponded to the benzhydryl resonance (H_γ). A three proton coupled spin system was identified as H_α (δ 4.98, d, J = 12.3 Hz), H_β (δ 5.28, d, J = 2.7 Hz) and NH (δ 3.66, dd, J = 12.3, 2.6 Hz). The ^{13}C NMR spectrum of the fullerenyl sp^2 region of **48**, like that of **11**, revealed a structure lacking a plane of symmetry due to the newly formed stereogenic carbon at C61 (60_α). A single set of fullerenyl sp^3 resonances at C_χ (δ 58.9), and C1 (δ 67.3) were observed in addition to resonances corresponding to the addend C_α (δ 70.4), C_β (δ 66.4) C_δ (δ 67.7), C_ϵ (δ 66.1), C_ϕ (δ 49.1), and C_γ (δ 66.6). These carbons were readily assigned from HSQC and HMBC experiments.

Similarly, double reductive ring-opening reaction of compounds **45** and **46** afforded **52** and **53** in a combined yield of 42% and free [60]fullerene (12%) (Scheme 13). Although **52** and **53** could not be separated by HPLC, ^{1}H NMR analysis revealed a 60:40 ratio of compounds, although the major and minor compounds could not be unequivocally ascertained, even after 2D NMR analysis using NOESY and HMBC experiments. The 60:40 ratio was observed in both ^{1}H NMR and ^{13}C NMR spectra between cognate resonances (resonances for the major isomer are indicated below with a *). Two fullerenyl proton resonances were situated at δ 6.83* and 6.78. The diastereotopic benzyl doublets ($H_{\delta/\delta'}$) were identified at δ 5.89, 5.72, 5.63*, and 5.35*, each with a coupling of about 12 Hz. The three proton spin coupled spectrum corresponded to the reduced addend protons H_α (δ 4.95 m), $H_{\beta/\beta'}$ (δ 5.23, m, 2H), and NH/NH′ (δ 3.64, bs, 2H). The reduced, cleaved addend portion consisted of singlet resonances at δ 5.44 (H_ϵ), δ 4.82*, 4.78 (H_γ), and δ 3.38, 3.34* (H_ϕ).

Proposed Mechanism of Reductive Ring-Opening Reactions

In principle, the product **48** could arise from the anionic intermediates **B** or **C**. The driving force for monoelimination of the tether from either structure might be the relief of ring strain upon expulsion of one arm of the tether. In the case of **B**, a further driving force may be the conversion of a fullerenyl dianion intermediate to a thermodynamic more stable fullerenyl monoanionic system. Clearly, the rate of monoelimination of the addend is much faster than the rate of elimination of the entire addend as indicated by the relative isolated yields of **48** versus [60]fullerene (Table 5).



To examine the influence of the tether on this ring opening-retro-Bingel reaction, the diethyl ester **40** was subjected to similar reduction conditions to those described for **35**−**37**. This reaction yielded the ring-opened-retro-Bingel product **12** in 51% yield and a small amount of [60]fullerene (10%) (Scheme 14). In comparison, the mono-ester **12** was also prepared in 58% yield from reductive ring opening of the methano[60]fullerene **8** (Scheme 14).

Conclusions

In conclusion, we have demonstrated the synthetic versatility of the Bingel cyclopropanation reaction beyond malonate additions to [60]fullerene, providing a range of novel protected methano[60]fullerenyl amino acids derivatives. Using tethered bisimino esters, the regiochemistry of the [60]fullerenyl bisadducts provided unique and unexpected regiochemistry when compared to their tethered bismalonate counterparts. This study clearly demonstrates that much has yet to be understood about tethered fullerene reactions before generalizations on regiochemical outcomes can be made. These differences in regiochemistry may indicate that these reactions proceed via different mechanisms and experiments are in progress to understand these differences.

Additionally, a novel ring-opening reaction and a tandem reductive ring-opening retro-Bingel reaction were discovered, yielding a new class of 1,2-dihydro[60]-fullerenylglycine derivatives. Although deprotection of

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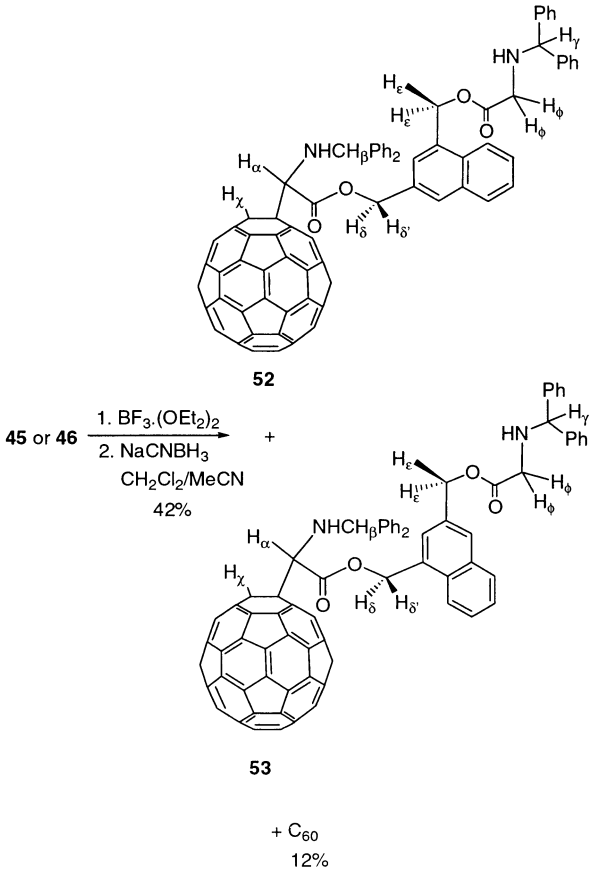
SCHEME 13



the [60]fullerenylglycine derivatives has so far been unsuccessful, methods for the selective deprotection of these compounds is currently under investigation. Furthermore, we have demonstrated the importance of 2D INADEQUATE NMR experiments for the unequivocal assignment of the regiochemistry of [60]fullerenyl bisadducts which are more superior than the more widely used comparative techniques (UV−visible). These experiments also provided useful topological information of the [60]-fullerenyl sphere upon functionalization. Such techniques will be invaluable in future studies of multifunctionalized [60]fullerenes.

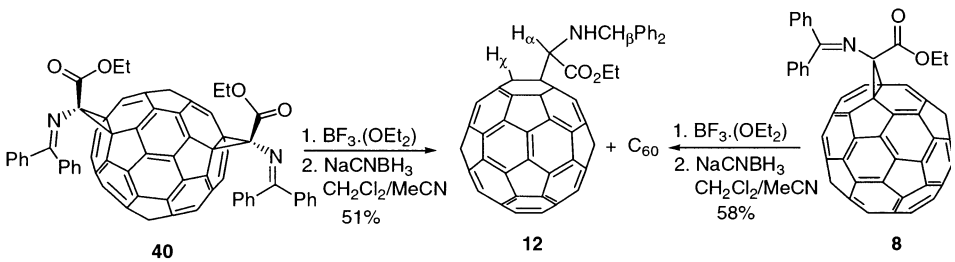
Experimental Section

Toluene and THF were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) was distilled from phosphorus pentoxide. Acetonitrile (MeCN) was distilled from potassium carbonate. [60]Fullerene and 10% ^{13}C-enriched [60]fullerene were purchased from MER Corp., Tucson, AZ 85706. Compounds **3** and **4** were purchased from a commercial supplier. All reactions were performed in standard glassware under an inert atmosphere of nitrogen. Evaporation and concentration in vacuo were done at water-aspirator pressure, and compounds were dried at 10^{-2} Torr. Flash column chromatography was performed using silica 60 (230−400 mesh, 0.040−0.063 mm). Petroleum spirit refers to a hydrocarbon fraction with a boiling point of 40−60 °C.

UV−vis spectra were recorded on a Shimadzu UV-1601 (λ_{max} in nm (ϵ)). Mass spectral data were recorded on a Shimadzu QP-5000 for MS(CI) data. MS(ES) were recorded on a VG Quattro-triple quadrapole via a direct insertion technique and an electron beam energy of 70 eV and a source temperature of 200 °C. High-resolution mass spectra (CI) were obtained using a QTOF mass spectrometer. MALDI-TOF spectra were recorded on a Bruker BIFLEX mass spectrometer in the negative ion mode using 9-nitroanthracene as matrix. ^{1}H NMR spectra were acquired on a Varian Unity 300 or 400 spectrometer at 300.1 and 399.9 MHz, respectively, or a Bruker DMX-600 spectrometer at 600.2 MHz. ^{13}C NMR spectra were acquired on Varian Unity 300 or 400 spectrometer at 75.4 and 100.0 MHz, respectively, or a Bruker DMX-600 spectrometer at 150.9 MHz. Deuterated solvents $CDCl_3$, D_2O, C_6D_6 were obtained commercially and were greater than 99.5 atom % d. All chemical shifts are reported relative to TMS (δ 0.00). The 2D INADEQUATE experiments for 10% ^{13}C-enriched samples of **35** and **39** were performed on a Bruker DMX 600 spectrometer fitted with a Bruker TXI-XYZ ^{1}H/^{13}C/^{15}N probe. The samples (ca. 16 mg for each compound) were dissolved in CS_2/$CDCl_3$ (6:4) (ca. 250 μL) in a Shigemi tube, and the spectra were recorded at 288 K. A standard pure phase (States-TPPI) double quantum spectrum with power-gated proton decoupling was employed. A spectral width of 13020.8 Hz was used in both dimensions resulting in deliberate folding in F1, which will not cause any ambiguity of peak assignments. 2048 × 8192 Total points were collected in t1 and t2, respectively. A recycle delay of 9 s and 16 scans per increment were employed. Computer modeling was performed on a Silicon Graphics O2 Workstation using the Spartan Semiempirical (AM1 and PM3) program: SGI/V5.1.1. Geometry optimization model: RHF/AM1 and RHF/PM3 were used for semiempirical calculations.

Bingel Reactions. *tert*-Butyl 61-Diphenylmethylideneamino-1,2-methano[60]fullerene-61-carboxylate (7). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.18 mL, 1.2 mmol) was added at rt to a solution containing [60]fullerene (0.22 g, 0.31 mmol), carbon tetrabromide (0.13 g, 0.397 mmol), and **3** (0.11 g, 0.40 mmol) in toluene (250 mL). The solution was stirred for 2 h. The crude material was filtered through a short plug of silica gel (5 cm), eluting first with toluene (to retrieve unreacted [60]fullerene) and then with DCM. Column chromatography eluting with (90:10 DCM/petroleum spirit) and recrystallization from DCM/diethyl ether provided **7** as a brown amorphous solid (0.14 g, 46%). UV−vis (DCM): 430 (18 000), 610 (1800), 690 (800) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60 (s, 9H), 7.31 (t, 2H J = 7.5 Hz), 7.42 (t, 4H, J = 7.5 Hz), 8.05 (d, 4H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.4, 153.7, 149.3, 147.8, 146.6, 146.2 (2 × C), 146.1, 145.7, 145.5, 145.4, 145.1, 144.5, 143.3, 143.06, 142.7, 142.6, 142.2 (2 × C), 142.1, 141.7 (2 × C), 140.0, 139.5, 136.8, 135.0, 130.0,

SCHEME 14



128.6, 96.0, 84.3, 82.6, 30.3. MS (ES) (+ve ion mode): *m*/*z* 1013 (M^+), 720 (C_{60}).

***endo,endo*-(*m*-Phenylenedimethyl)-61,62-bis-(*N*-diphenylmethylideneamino)-1,2:34,35-bis(methano)[60]-fullerene-61,62-dicarboxylate (35) and *endo,endo*-(*m*-Phenylenedimethyl)-61,62-bis-(*N*-diphenylmethylideneamino)-1,2:16,17-bis(methano)[60]fullerene-61,62-dicarboxylate (36).** DBU (0.45 mL, 3.01 mmol) was added at rt to a solution containing [60]fullerene (0.43 g, 0.60 mmol), carbon tetrabromide (0.54 g, 1.42 mmol), and **33** (0.47 g, 0.81 mmol) in chlorobenzene (200 mL). The solution was stirred for 2 h. The crude material was filtered through a short plug of silica gel (5 cm), eluting first with toluene (to retrieve unreacted [60]fullerene) and then with DCM. Column chromatography eluting with (90:10 DCM/petroleum spirit) and recrystallization from DCM/diethyl ether provided **35** (0.25 g, 32%) and **36** (0.08 g, 10%) as brown amorphous solids. **35**. UV−vis (DCM): 320 (15 000), 630 (250), 690 (150) nm. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.06 (d, 2H, J = 11.2 Hz), 5.71 (d, 2H, J = 11.2 Hz), 7.07 (t, 1H, J = 7.6 Hz), 7.14 (s, 1H), 7.30 (t, 2H, J = 7.6 Hz), 7.40 (t, 4H, J = 7.2 Hz), 7.46 (t, 4H, J = 7.2 Hz), 7.55 (t, 4H, J = 7.2 Hz), 7.92 (d, 4H, J = 8.4 Hz), 8.04 (d, 4H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.0, 81.5, 81.8, 97.1, 127.9, 128.0, 128.3, 129.4, 129.6, 136.4, 137.7, 138.9, 139.6, 140.6, 140.9, 141.27, 141.3, 141.4, 141.5, 142.1, 142.5 (ipso), 143.6, 143.9, 145.6, 145.68, 145.8, 145.8, 145.9, 146.0, 146.7, 146.8, 146.82, 147.4, 148.6, 149.0, 149.9, 150.9, 160.7, 161.3. MALDI-TOF (−ve ion mode, 9-nitroanthracene): *m*/*z* 1296 (M^-), 720 (C_{60}^-). **36**. UV−vis (DCM): 320 (19 000), 430 (sh, 1700), 450 (sh, 1400), 640 (280), 695 (190) nm. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.31 (d, 2H, J = 11.2 Hz), 5.41 (d, 2H, J = 11.2 Hz), 6.95 (s, 1H), 7.18 (m, 3H), 7.23 (t, 4H, J = 7.6 Hz), 7.37 (dd, 4H, J = 7.2 Hz, 1.6 Hz), 7.50 (dd, 4H, J = 7.6 Hz, 1.2 Hz), 7.62 (t, 4H, J = 8.4 Hz), 8.17 (d, 4H, J = 7.6 Hz), 8.21 (d, 4H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.5, 81.8, 82.4, 96.0, 128.3, 128.6, 129.6, 129.9, 131.4, 134.6, 134.8, 138.5, 139.2, 140.7, 141.0, 141.2, 141.8, 143.4, 143.5, 143.9, 144.1, 144.11, 144.3, 144.4, 144.7, 144.9, 145.0, 145.9, 147.3, 147.4, 147.5, 147.8, 148.6, 148.9, 149.0, 149.2, 150.9, 153.4, 154.4, 161.0, 161.1. MALDI-TOF (−ve ion mode, 9-nitroanthracene): *m*/*z* 1296 (M^-), 720 (C_{60}^-).

Transesterifications. Diethyl *endo,endo*-61,62-Bis(*N*-diphenylmethylideneamino)-1,2:33,50-bis(methano)[60]-fullerene-61,62-dicarboxylate (39). Solid potassium carbonate (0.010 g, 0.71 mmol) was added to a solution of **37** (0.04 g, 0.003 mmol) in THF/EtOH (2:1) (100 mL), and the mixture was stirred at rt for 1.5 h. The mixture was then filtered, and the solvent was removed in vacuo. Column chromatography (flash silica gel, DCM/petroleum spirit 90:10) followed by recrystallization (chloroform/diethyl ether) yielded **39** (0.012 g, 32%) as a brown amorphous solid. UV−vis (DCM): 330 (15 000), 430 (sh, 180), 620 (210), 690 (80) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, 6H, J = 6.9 Hz), 4.49 (q, 4H, J = 6.9 Hz), 7.37 (t, 4H, J = 7.5 Hz), 7.49 (m, 4H, J = 7.5 Hz), 7.64 (t, 4H, J = 7.5 Hz), 8.09 (d, 4H, J = 7.5 Hz), 8.25 (d, 4H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 160.5, 154.3, 153.6, 151.5, 148.8, 148.7, 148.67, 148.6, 147.98, 147.95, 147.9, 147.4, 145.7, 145.2, 145.1, 145.0, 144.5, 144.1, 144.0, 143.9, 143.5, 142.3, 141.9, 141.5, 141.1, 140.9, 140.5, 139.2, 138.5, 136.4, 135.1, 130.0, 129.8, 128.5, 128.34, 128.3, 95.9, 82.3, 81.9, 63.0, 14.2. MALDI-TOF (−ve ion mode, 9-nitroanthracene): *m*/*z* 1250 (M^-), 720 (C_{60}^-).

Reductive Ring-Opening Reactions. *tert*-Butyl 1,2-Dihydro-α-diphenylmethylamino[60]fullerenyl Acetate (11). Sodium cyanoborohydride (0.005 g, 80 μmol) was added at rt over a 5 min period to an acidified solution (adjusted to pH 4 with glacial acetic acid) of **7** (0.02 g, 20 μmol) in THF (20 mL)/MeOH (5 mL). The pH of the brown solution was maintained at pH 4 by the further addition of glacial acetic acid. Upon no further change in pH, the reaction mixture was stirred for a further 2 h and concentrated in vacuo. The reaction mixture was redissolved in chloroform (20 mL) and washed with saturated ammonium chloride solution (10 mL), followed by saturated sodium bicarbonate solution (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography, eluting with toluene/hexane (1:1), provided **11** as a brown amorphous solid (0.008 g, 39%). UV−vis (DCM) 410 (sh, 5000), 440 (3000) nm. ^{1}H NMR (C_6D_6/CS_2 60:40, 400 MHz): δ 1.52 (s, 9H), 3.61 (dd, 1H, J = 15.6, 4.4 Hz), 4.83 (d, 1H, J = 15.6 Hz), 5.27 (d, 1H, J = 4.4 Hz), 6.84 (s, 1H), 7.20 (m, 2H), 7.28 (t, 2H, J = 10.4 Hz), 7.33 (t, 2H, J = 10.4 Hz), 7.56 (d, 2H, J = 10.4 Hz), 7.66 (d, 2H, J = 10.4 Hz). ^{13}C NMR (C_6D_6, CS_2 (60:40), 75 MHz): δ 171.0, 154.4, 153.7, 153.1, 152.4, 147.7, 147.5, 147.4, 146.9, 146.7, 146.64, 146.6, 146.5, 146.4, 146.1, 146.0, 145.9, 146.82, 146.8, 145.7, 146.6, 145.0, 144.8, 144.7, 143.7, 143.5, 142.9, 142.7, 142.6, 142.4, 142.0, 141.9, 141.8, 141.76, 140.7, 139.8, 139.6, 137.3, 136.9, 136.64, 136.6, 129.2, 129.1, 128.6, 127.9, 127.7, 82.8, 76.9, 68.2, 66.7, 58.8, 28.4. MS (ES) (+ve ion mode): *m*/*z* 1017 (M^+), 720 (C_{60}).

Ethyl 1,2-Dihydro-α-diphenylmethylamino[60]-fullerenyl Acetate (12). Boron trifluoride·diethyl etherate (0.072 g, 508 μmol) was added dropwise over 1 min to a solution of **8** (0.050 g, 51 μmol) in DCM (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to rt over a 30 min period when MeCN (25 mL) was added. Sodium cyanoborohydride (0.005 g, 80 μmol) was added to the reaction mixture, which was stirred for 90 min and then concentrated in vacuo. The reaction mixture was redissolved in chloroform (100 mL) and washed with saturated ammonium chloride solution (10 mL), followed by saturated sodium bicarbonate solution (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography using flash silica gel and eluting with toluene/hexane (1:1) provided **12** (0.029 g, 58%) as a brown amorphous solid. UV−vis (DCM): 410 (sh, 5000), 440 (3000) nm. ^{1}H NMR (C_6D_6/CS_2 60:40, 400 MHz): δ 1.19 (t, 3H, J = 7.2 Hz), 3.59 (bs, 1H), 4.23 (q, 2H, J = 7.2 Hz), 4.94 (s, 1H), 5.26 (s, 1H), 6.84 (s, 1H), 7.20 (m, 2H), 7.28 (t, 2H, J = 10.4 Hz), 7.33 (t, 2H, J = 10.4 Hz), 7.56 (d, 2H, J = 10.4 Hz), 7.66 (d, 2H, J = 10.4 Hz). ^{13}C NMR (C_6D_6, CS_2 (60:40), 75 MHz): δ 171.8, 154.4, 153.5, 152.9, 152.0, 147.8, 147.4, 147.39, 147.38, 146.73, 146.71, 146.7, 146.5, 146.0, 145.97, 145.95, 145.72, 145.7, 145.0, 144.7, 143.6, 143.5, 143.49, 143.3, 143.0, 142.7, 142.6, 142.4, 142.0, 141.99, 141.9, 140.9, 140.8, 140.0, 139.7, 137.5, 136.8, 136.7, 136.5, 129.3, 129.2, 128.6, 128.0, 70.8, 68.1, 66.8. 61.8, 58.1, 14.9. MALDI-MS: (−ve ion mode, 9-nitroanthracene): *m*/*z* 720 (C_{60}).

3′-[(Diphenylmethyl(amino)acetoxymethyl]naphthyl-1,2-dihydro-α-diphenylmethylamino[60]fullerenyl Acetate (52) and 1′-[(Diphenylmethyl(amino)acetoxymethyl]naphthyl-1,2-dihydro-α-diphenylmethylamino-[60]-fullerenyl Acetate (53). The title compound was prepared from boron trifluoride·diethyl etherate (0.095 g, 668 μmol), (**45**/**46**) (0.090 g, 67 μmol), and sodium cyanoborohydride (0.04 g, 0.67 mmol) using a procedure analogous to that described above for the synthesis of **12** to yield [60]fullerene (0.006 g, 12%) and (**52**/**53**) (0.042 g, 42%). UV−vis (DCM): 330 (sh, 15 000), 435 (3000) nm. ^{1}H NMR (C_6D_6/CS_2 60:40, 400 MHz) (where possible the resonances of the major isomer are shown with a *, integration values are relative values for each isomer): δ 3.34* (s, 2H), 3.38 (s, 2H), 3.64 (bs, 2H), 4.78 (s, 2H), 4.82* (s, 2H), 4.95 (bd, 2H, J = 8.1 Hz), 5.23 (m, 2H), 5.35* (d, 1H, J = 11.6 Hz), 5.44 (s, 2H), 5.63* (d, H, J = 11.6 Hz), 5.72 (d, J = 12.4 Hz), 5.89 (d, 1H, J = 12 Hz), 6.78 (s, 1H), 6.83* (s, 1H), 7.16 (m, 14H), 7.38 (m, 55H), 7.70 (m, 30H). ^{13}C NMR (C_6D_6, CS_2 (60:40), 75 MHz): δ 172.3, 172.2, 172.1, 153.81, 153.8, 152.78, 152.7, 151.8, 151.7, 150.84, 150.8, 147.4, 147.1, 146.93, 146.91, 146.9, 146.73, 146.7, 146.3, 146.28, 146.11, 146.1, 146.0, 145.6, 145.59, 145.5, 145.48, 145.4, 145.37, 145.3, 145.21, 145.2, 145.18, 145.1, 145.0, 144.6, 144.5, 144.3, 144.26, 144.2, 143.4, 143.0, 142.98, 142.9, 142.5, 142.4, 142.39, 142.3, 142.2, 142.1, 142.02, 142.01, 142.0, 141.9, 141.8, 141.6, 141.5, 141.3, 141.2, 141.17, 141.13, 141.11, 141.1, 140.3,

140.2, 140.18, 140.1, 139.3, 139.2, 139.0, 138.7, 137.2, 137.1, 136.4, 136.2, 136.19, 136.1, 136.0, 135.9, 133.7, 133.4, 132.4, 132.3, 131.9, 131.87, 131.6, 131.4, 130.5, 130.0, 129.0, 128.8, 128.5, 128.48, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.3, 127.25, 127.2, 126.6, 123.5, 123.4, 70.2, 67.7, 67.6, 67.4, 66.5, 66.51, 66.3, 66.2, 65.3, 64.4, 58.8, 58.6, 49.0, 48.9. MALDI-MS: (−ve ion mode, 9-nitroanthracene): *m*/*z* 720 (C_{60}).

Ethyl 1,2-Dihydro-α-diphenylmethylamino[60]-fullerenyl Acetate (12) from Diethyl *endo,endo*-61,62-Bis-(*N*-diphenylmethylideneamino)-1,2:34,35-bis(methano)-[60]fullerene-61,62-dicarboxylate (40). The title compound was prepared from boron trifluoride·diethyl etherate (0.111 g, 779 μmol), **40** (0.082 g, 66 μmol), and sodium cyanoborohydride (0.049 g, 779 μmol) using a procedure analogous to that described above for the synthesis of **12** from **8** yielded **12** (0.033 g, 51%) as a brown amorphous solid. Spectral data were identical to the synthesis of **12** from **8** as described above.

Acknowledgment. We thank the Australian Research Council for financial support and for a Ph.D. scholarship to G.A.B.

Supporting Information Available: Experimental procedures for the synthesis of compounds **6**, **8**−**10**, **13**, **27**−**34**, **40**, and **42**−**49**. ^{1}H and/or ^{13}C NMR data of [60]fullerene derivatives **7**, **8**, **11**, **13**, **35**−**37**, **45**−**46**, **48**, and **52**/**53**. UV−vis spectra of **35**−**39** and **48**. INADEQUATE spectra of **35** and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025928J