2000

Novel synthetic and characterisation strategies towards a-Fulleryl amino acids

Glenn A. Burley

University of Wollongong

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Novel Synthetic and Characterisation Strategies Towards α-Fulleryl Amino Acids

Glenn A. Burley, B.Med.Chem (Hons.)

A thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

Department of Chemistry
University of Wollongong
Wollongong, AUSTRALIA

October, 2000
For Jo
This work described in this thesis does not contain any material which has been accepted for the award of any degree or diploma in this or any other University and to the best of my knowledge and belief contains no material previously published by any other person, except where due reference has been acknowledged.
Sections of the work described in this thesis have been reported in the following publications:


Acknowledgements

My supervisors, Steve and Paul for their personal and professional support.

To Graham Ball at the UNSW who showed me that sitting around an NMR spectrometer adorned in Bhuddist prayer flags, talking about premier league soccer, brit pop and the mullet haircut count is a pretty grouse way to spend an afternoon.

To my parents for their love and tireless commuting between the gong and the homeland.

Members of the G06 lab. who have made most of the last four years a humorous experience with the exception of the Triple J/Power FM radio wars.

To Trudy and Tien, two very special friends who helped calm the waters during the stormy episodes.

Chris “around the corner and not over the top mate” Mitchell for making fumehood 3 a very humorous place to work.

The guys at Corrimal Leagues Rangers Soccer club for being themselves. A special mention for Ranger Mark Beaton who showed me that ego is not a dirty word.

And finally some of the most important people that I have to thank are unibar staff members Davo “the machine”, Gassy, Aido and Maxi for hours of entertainment. Without alcohol and those times I don’t think this thesis would have gotten past this page.
### List of Abbreviations

<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-azobisisobutyronitrile</td>
</tr>
<tr>
<td>AO</td>
<td>atomic orbital</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere(s)</td>
</tr>
<tr>
<td>bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2’-bipyridyl</td>
</tr>
<tr>
<td>t-bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization (in mass spectrometry)</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>D</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>El</td>
<td>electron impact (in mass spectrometry)</td>
</tr>
<tr>
<td>ESR</td>
<td>electron spin spectroscopy</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>hr</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond coherence</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethyphosphoric triamide</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (in NMR)</td>
</tr>
<tr>
<td>L</td>
<td>litre(s)</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
</tbody>
</table>
\( \mu \) micro

m multiplet (spectral), milli

M moles per litre

Me methyl

MeCN acetonitrile

MeOH methanol

MHz megahertz

min minute(s)

mM millimoles per litre

MO molecular orbital

mol mole(s)

MS mass spectrometry

m/z mass to charge ratio (in mass spectrometry)

NBS \( N \)-bromosuccinimide

NMR nuclear magnetic resonance

nOe nuclear Overhauser effect

NOESY nuclear Overhauser effect spectroscopy

Nu nucleophile

ppm parts per million (in NMR)

Pr propyl

i-Pr isopropyl

q quartet (spectral)

\( R_f \) retention factor (in chromatography)

RT room temperature

s singlet (spectral)

SET single electron transfer

\( S_{N1} \) unimolecular nucleophilic substitution

\( S_{N2} \) bimolecular nucleophilic substitution

\( t \) triplet (spectral)

TBDMS \( \text{tert-butyldimethylsilyl} \)

TFA trifluoroacetic acid

THF tetrahydrofuran

TLC thin layer chromatography

TMS trimethylsilyl, tetramethylsilane

Torr \( 1 \text{mm Hg}, 1/760 \text{atm.} \)

TS transition state

UV ultraviolet

vis visible
Abstract

Chapter 1 of this thesis describes the structure and reactivity of the most common member of the new family of carbon allotropes, [60]fullerene. Although originally thought to be an unreactive “superaromatic” molecule, [60]fullerene is susceptible to a diverse number of reactions. [60]Fullerene and many [60]fullerene derivatives, such as fulleryl amino acids also exhibit a wide range of biological activities.

One of the most useful reactions known in fullerene chemistry is the Bingel cyclopropanation. This facile reaction enables access to a wide range of cyclopropanated fullerene derivatives (or methanofullerenes) in acceptable yields and under mild conditions. To date, such cyclopropanation reactions were confined to malonate-derived starting materials.

Chapter 2 reports the synthesis of a number of novel cyclopropanated [60]fullerene derivatives that were prepared from [60]fullerene and readily available N-(diphenylmethyleneglycinate) esters using Bingel reaction conditions. Although deprotection of the N-terminus or C-terminus of these protected methanofullerenes was not forthcoming, a novel reductive ring-opening of these methanofullerenes was discovered to yield a new class of α-fulleryl glycine derivatives. Although deprotection of these derivatives was also unsuccessful, this new reductive ring-opening technique provided access to a new range of fullerene derivatives.

In chapter 3, the synthetic strategy described in chapter 2 was extended to produce multifunctionalised [60]fullerenes by utilising tether-directed synthesis. The resultant tethered bis-N-(diphenylmethyleneglycinate) esters afforded [60]fullereryl bisadducts of unexpected regiochemistries when compared to cognate tethered bismalonic esters. The unexpected regiochemistry of the major products was
unambiguously confirmed by $^{13}$C-$^{13}$C connectivity experiments using the 2D INADEQUATE experiment.

In an effort to provide insight into the observed regiochemical differences of the tethered bis-$N$-(diphenylmethyleneglycinate) esters and their cognate tethered bismalonic esters, mechanistic and computational studies were conducted to investigate the mechanism of $N$-(diphenylmethyleneglycinate) ester addition under Bingel reaction conditions. No definitive conclusion was made as to why the observed regiochemistries between the two tethered systems differed. A mixed malonate $N$-(diphenylmethyleneglycinate) ester tether was synthesised in an effort to determine the fundamental factors governing the regiochemistry of addition. Unfortunately no bisadduct was observed under double Bingel reaction conditions. Under mono-Bingel reaction conditions however, a cyclopropanation occurred exclusively at the $N$-(diphenylmethyleneglycinate) ester site, providing evidence of this site being significantly more reactive than its malonic ester counterpart. This study was reported in chapter 4.

Chapter 5 reports the results of attempts at the double reductive ring opening reaction of the bis-$N$-(diphenylmethyleneglycinate) ester fulleryl adducts. Under reductive ring-opening conditions, an unexpected ring-opened monoadduct rather than the expected double ring-opened bisadduct was formed. This unexpected product is thought to arise via the elimination of one of the substituents much akin to a retro-Bingel-type reaction. This reaction was shown to be tether-independent by the formation of the corresponding elimination ring-opened monoadduct from a non-tethered bismethanofullerene precursor.
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Introduction
1.1. Fullerenes: The Third Allotrope of Carbon

In 1985, the scientific community was first exposed to a third and novel form of carbon; a soccer ball-shaped molecule of 60 carbons comprising alternate single and double carbon-carbon bonds. Some schematic representations of the structure of this compound, [60]fullerene, are shown in Figure 1.1.

\textbf{Figure 1.1:} Schematic representations of [60]fullerene (a) chemical structure diagram, (b) PM3-optimised tube model, (c) space filling model, and (d) Schlegel diagram with IUPAC numbering system.
Kroto and co-workers named the newest carbon allotrope, buckminsterfullerene; after the architect Buckminsterfuller whose giant icosahedral structures resembled the proposed structure, with the addition of the suffix *ene* to indicate the unsaturated nature of the molecule. Since the discovery of C\textsubscript{60}, or [60]fullerene, a number of homologues have been found. The next stable homologue is the football-shaped C\textsubscript{70} (or [70]fullerene) followed by a range of higher fullerenes (e.g. C\textsubscript{76}, C\textsubscript{78}, C\textsubscript{82}, C\textsubscript{84}). It was not until 1991 that a method for the purification of fullerenes in macroscopic quantities was discovered, opening up the possibility of synthetic fulleryl chemistry to the scientific community.\textsuperscript{3,4} This allowed the unprecedented three-dimensional architecture of [60]fullerene to be investigated more closely in relation to its structure and reactivity.

1.2. [60]Fullerene Structure

The systematic nomenclature of the parent C\textsubscript{60} is [5,6]-fullerene-60-I\textsubscript{h}.\textsuperscript{5} The numbers 5 and 6 denote that C\textsubscript{60} consists of pentagons and hexagons, the number 60 indicates the number of carbon atoms, and I\textsubscript{h} denotes the icosahedral symmetry. For [5,6]-fullerene-60-I\textsubscript{h}, there exists only one stable isomer which further simplifies the name to [60]fullerene. An unambiguous description of such derivatives requires the introduction of a simple numbering system for the C-atoms comprising the sphere.\textsuperscript{6} Figure 1.1d shows a two-dimensional representation of [60]fullerene (Schlegel diagram). Numbering begins in a clockwise, spiral fashion commencing in a hexagon and working outwards. The icosahedral symmetric [60]fullerene comprises of 12 pentagons and 20 hexagons. [60]Fullerene is the smallest structure to obey the isolated pentagon rule (IPR), which states, "stabilised fullerene structures are formed when all pentagons are isolated by hexagons. Destabilised fullerene structures are formed by the presence of adjacent pentagons".\textsuperscript{4,6} Another structural aspect of fullerenes is in the alternating bond
Chapter 1: Introduction

Lengths. Bonds at the junction of two hexagons (6,6-bonds, 1.355 Å) are shorter than bonds at the junction of a hexagon and a pentagon (5,6-bonds, 1.467 Å)\(^*\). The lowest energy structure of [60]fullerene has the double bonds placed at the 6,6-bond junctions, and the single bonds placed at the 5,6-bond junctions. Topologically, each hexagon in [60]fullerene exhibits cyclohexatriene character and each pentagon, [5]radialene character (Figure 1.2). Consequently, the structure and chemical reactivity of [60]fullerene is comparable to an electron deficient alkene.

![Cyclohexatriene and [5]radialene substructure of [60]fullerene.](image)

**Figure 1.2:** Cyclohexatriene and [5]radialene substructure of [60]fullerene.

1.3. [60]Fullerene Reactivity

A general overview of the chemical reactivity of [60]fullerene is shown in Scheme 1.1. The major groups of reactions are presented, including cycloadditions, reduction reactions (hydride and electron transfer), nucleophilic and radical additions.\(^5\)-\(^9\) Much of the chemistry has been recently reviewed and thus only selected examples have been shown in this introduction.\(^8\)

---

\(^*\) Bond lengths presented were experimentally derived from X-ray crystallographic data.\(^7\)
1.3.1 Cycloadditions

Among the various reactions available for derivatisation of [60]fullerene, cycloaddition reactions are the most numerous. The electron deficient carbon sphere is an excellent dienophile and dipolarophile resulting in stable [6,6]-cycloadducts.⁵⁻¹³ Among the most important cycloaddition reactions are [4+2] cycloadditions with [60]fullerene acting as the dienophile (e.g. Diels-Alder reactions).¹⁶⁻²¹ [3+2] Cycloadditions with 1,3-dipoles,⁵ thermally or photochemically induced [2+2] cycloadditions¹⁵,²²⁻³⁰ and carbene-derived [2+1] cycloadditions³¹⁻³⁴ are shown in the general Scheme 1.2.
1.3.2. Nucleophilic Additions

The electron deficient [60]fullerene readily reacts with carbon nucleophiles (e.g. organolithium and Grignard reagents) to form arylated and alkylated [60]fullerene adducts (Scheme 1.3).\textsuperscript{36-37} For example, the reaction of ethylmagnesium bromide (6.8 equiv.) with [60]fullerene in toluene solution results in the instantaneous precipitation of the corresponding [60]fulleryl salt (EtC$_6$O$_{60}$MgBr).\textsuperscript{35} Protonation yields 1-ethyl-1,2-dihydrofullerene, C$_{60}$EtH (1) in 80% yield from HPLC analysis. The more reactive organolithium compound, methyllithium, required only 1.2 molar equiv. to obtain a maximum yield of 47% for the 1,2-dihydrofullerene [(C$_{60}$MeH), (2)]. Other alkyl derivatives, for example (3) and (4), have also been prepared by this method.
It has been well documented that primary and secondary amines undergo nucleophilic additions to the electron deficient [60]fullerene to form multiple adducts. The reaction of [60]fullerene with neat amines such as propylamine, leads to the formation of green solutions. Following this reaction by EPR spectroscopy revealed an initial mixture of [60]fulleryl and ammonium radicals, whose concentration decreased over time as the solution turns from green to chestnut brown. These observations suggested a stepwise mechanism involving electron transfer/recombination steps (Scheme 1.4) rather than a direct nucleophilic addition to [60]fullerene. The initial electron transfer step is from the amine to [60]fullerene to form the fulleryl radical anion. The next step is radical recombination to form green zwitterionic intermediates (Scheme 1.4). The final rate-determining step involves proton transfer from the nitrogen to the fulleryl ring to yield the product (5).

Isomerically pure di-aminated products such as (6) were obtained by the reaction of secondary diamines, such as piperazine, with [60]fullerene at reaction temperatures between 0°C and 100°C (Scheme 1.5).
1.3.3. Reduction

Theoretical calculations of the molecular orbitals of [60]fullerene revealed comparatively low energy and triply degenerate lowest unoccupied molecular orbitals \([\text{LUMO}], \text{(Figure 1.3)}\)\(^{43-49}\) which indicated that [60]fullerene is electronegative and thus susceptible to reduction.

Indeed experimental evidence (cyclic voltammetry, differential pulse voltammetry) supports the theoretical calculations showing [60]fullerene being reduced in a facile, stepwise and reversible fashion up to the hexa-anion (Figure 1.4).\(^{50-51}\)
Chapter 1: Introduction

Potential (Volts vs Fc/Fc+)

Figure 1.4: Reduction of [60]fullerene in MeCN/toluene at -10°C using (a) cyclic voltammetry and (b) differential pulse voltammetry.52

The electrochemically generated fulleride anions can be used to synthesise organodihydrofullerene derivatives, by quenching of these anions with electrophiles, such as alkyl halides53 Deaerated benzonitrile solutions of [60]fullerene have been exhaustively electrolysed in the presence of tetra-n-butylammonium perchlorate (TBAP) to give the dianion C_{60}^{2-}. Treatment of a solution of this dianion with an excess of methyl iodide afforded the organodihydrofullerene, C_{60}(CH_3)_2 as a 1.4:1 mixture of the 1,2 (7) and 1,4 isomers (8), (Scheme 1.6). Increasing the steric bulk of the incoming electrophiles (e.g. benzoyl chloride) can force the exclusive formation of the 1,4-isomer.
The reaction of [60]fullerenes with the Lewis acid borane has been used to synthesise hydrogenated [60]fullerenes (Scheme 1.7).\textsuperscript{34} The addition of one pair of hydrogens, after quenching the hydroborated derivative (9) with acetic acid, occurred exclusively across the 6,6-fusion (1,2 isomer formed) to form the 1,2-dihydrofullerene (10).

1.3.4. Oxidation and Reactions with Electrophiles

Although the reduction of fullerenes is much more facile than its oxidation, several oxidative functionalisations of [60]fullerene have been reported. Mixtures of $C_{60}O_n$ can be generated by bulk electrolysis of [60]fullerene in the presence of air\textsuperscript{49-50} while photooxygenation results in the formation of $C_{60}O$ (11) in 7% yield (Scheme 1.8).\textsuperscript{59,60}
The reaction of [60]fullerene with a stoichiometric amount of osmium tetroxide in the presence of pyridine leads to the osmylated monoadduct (12) in 75% yield.\textsuperscript{61,63} When heated under vacuum in the absence of air, (12) reverts to [60]fullerene (Scheme 1.9).

Halogenation of [60]fullerene can be achieved via a variety of methods to form polyhalogenated products. Polychlorination of [60]fullerene was carried out either by allowing a slow stream of chlorine gas to react with solid [60]fullerene at elevated temperatures (250-400°C)\textsuperscript{64} or by treatment of solid [60]fullerene with liquid chlorine at -35°C.\textsuperscript{55} Isomerically pure C\textsubscript{60}Cl\textsubscript{6} (13) was obtained by the reaction of benzene solutions of [60]fullerene with ICl at room temperature.\textsuperscript{65} Treatment of a carbon disulfide solution of [60]fullerene with bromine afforded C\textsubscript{60}Br\textsubscript{8} (14) in 80% yield\textsuperscript{66}.
1.3.5 Radical Additions

The electron deficient [60]fullerene sphere readily reacts with radicals that are generated under either photochemical or thermal conditions. In situ generation of simple organic radicals in the presence of [60]fullerene such as \( R^* \) via UV irradiation of a radical initiator (e.g. di-tert-butylperoxide in the presence of RH) or from the homolysis of alkyl halides or alkyl mercury compounds, form \( \text{RC}_{60}^* \) adducts as observed by ESR (Scheme 1.10).^{67-71}

Scheme 1.10

\[
\begin{align*}
(\text{CH}_3)_3\text{COOC(CH}_3)_3 & \xrightarrow{\text{UV}} 2(\text{CH}_3)_3\text{CO}^* + \text{RH} \rightarrow R^* \\
\text{RX} & \xrightarrow{\text{UV}} R^*
\end{align*}
\]

\( X = \text{halogen, HgR} \)

Stable 1,2-[60]dihydrofullerol adducts can be obtained via thermolysis of an excess of tributyltin hydride in the presence of benzene solutions of [60]fullerene over 4 hr.^{35} Prolonged reaction times resulted in a lowering in the concentration of the 1,2-monoadduct and an increase in multiple addition adducts.

1.4. Fulleryl Amino Acids

An intensely investigated area of fullerene chemistry is the biological activity of [60]fullerene derivatives. Combining the properties of biomolecules (such as water solubility and precise secondary/tertiary structure)^{73} with particular physical properties of fullerenes (sensitisation of singlet oxygen; electron acceptor characteristics)^{73,74} to give novel bioactive molecules has been investigated by several research groups. For example, [60]fullerene derivatives covalently tethered to peptides and proteins have
been the goal of a number of research groups concerned with the application of [60]fullerene-peptide conjugates to biological problems.\textsuperscript{75-80} This section will report current progress in the preparation and applications of fulleryl amino acids and related derivatives.

1.4.1 Preparation of Fulleryl Amino Acids

Fulleryl amino acid and peptide derivatives have commonly been prepared by the initial attachment of a versatile handle widely used in amino acid chemistry (such as hydroxyl, amino or carboxylic acid functional groups) to [60]fullerene followed by a coupling to a protected amino acid or peptide. The addition of [4-tert-butoxycarbonylphenyl]diazomethane (15) to [60]fullerene and subsequent deprotection of the ester (16) afforded the carboxylic acid (17). This acid was the first example of a fulleryl derivative with a convenient handle that was utilised for peptide functionalisation (Scheme 1.11).\textsuperscript{24} Coupling of (17) to the pentapeptide H-(L-Ala-Alb)\textsubscript{2}-L-Ala-OMe via the acyl chloride (18) yielded the first fulleryl peptide (19). Using this versatile synthons (17), a range of peptide-fullerene derivatives was prepared.
Alkyl diazoacetates, for example (20) and (21), were shown to be just as effective in producing another versatile synthon, methanofullerene carboxylic acid (24) (Scheme 1.12). The acid (24) was readily coupled to peptides under standard DCC coupling conditions. Thermal addition of diazoamides (27) produced directly the methanofullerene carboxamides, (28)-(31) including the protected fulleryl peptide derivatives, (30) and (31) (Scheme 1.13).
Scheme 1.12

Hydrolysis and subsequent reduction of the [4+2]-cycloadduct (33) formed the racemic alcohol (35) which is another versatile synthon for the preparation of fulleryl amino acid derivatives (Scheme 1.14). Coupling of glutamate and alanine derivatives to (35), via DCC-mediated esterification, produced the amino acid derivatives (36) and (37), respectively, in high yields.
Photolysis of aminoesters (38) in the presence of aerated solutions of [60]fullerene readily form proline-like fullerene derivatives (41) (Scheme 1.15).\textsuperscript{82,83,84b} The initial key step in these photoreactions is presumed to be the formation of a $\alpha$-carbon-centred radical (39), which attacks the [60]fullerene. The presence of oxygen in the reaction vessel appears to accelerate this photoreaction. Interestingly, photolysis of the corresponding amino acids with [60]fullerene results in photolytic decarboxylation and the formation of the 1,2-dihydro[60]fullerene derivative (47) (Scheme 1.16).\textsuperscript{84}
The proposed mechanism was assumed to be similar to the reaction pathway of the amino ester (Scheme 1.15), involving the formation of the carboxyl radical (44). Decarboxylation of (44) forms the aminomethyl radical (45), which undergoes addition to [60]fullerene and H-abstraction from the environment to yield (47).
1.4.2 Fulleroproline: The First True Fulleryl α-Amino Acid

The [60]fullerene adducts introduced in the previous section present examples of fulleryl amino acid derivatives. However none of these derivatives mimics the structure of true amino acids found in nature of the general structure shown in compound (48).

The synthesis of the first fulleryl C-substituted α-amino acid was achieved by the reaction of azomethine ylides with [60]fullerene to form proline ring-fused products that
are more commonly known as fulleroprolines (Fpr), (Scheme 1.17). The Prato group has used either thermal ring opening of electron deficient aziridines (51) or the condensation of aminoesters (49) with aldehydes (50) to produce azomethine ylides in situ\textsuperscript{6,7} These reactions are versatile in that a variety of substituted fulleroproline derivatives can be obtained using different aldehydes and amino esters.

**Scheme 1.17**

\[
\begin{align*}
R_1\text{NHCH}_2\text{COOR}_2 \quad (49) & \xrightarrow{\Delta} R_2\text{OOC}_N\overset{\ominus}{\text{R}_1} \text{H} \text{H} \xrightarrow{\Delta} R_3\text{COOR}_2 \\
+ \quad R_3\text{CHO} \quad (50) & \quad \text{C}_{60} \\
& \quad R_1 = R_2 = R_3 = H = (Fpr)
\end{align*}
\]

Fpr derivatives can be prepared with the pyrrolidine nitrogen protected (Scheme 1.18) or unprotected (Scheme 1.19).\textsuperscript{75} Selective deprotection of the \(N\)-protecting group (either trityl or \(p\)-methoxybenzyl) in (54) was achieved in the presence of a methyl ester group using trifluoroacetic acid (TFA) (Scheme 1.18). This allowed Fpr to be incorporated into peptides, via coupling of the free amine of (55) with unprotected C-terminal peptides.
The unprotected adduct (58) could not be isolated as a pure solid due to the reactivity of the free amino group, but could be stored in the dark and in dilute solutions.\textsuperscript{75,87,89} Compound (58), however, can be used to prepare either \(N\)-terminal peptides [(61) and (62)] or \(C\)-terminal peptides [(63) and (64)] as mixtures of diastereoisomers as shown in Scheme 1.19.
1.5. Methanofullerenes

One of the most important synthetic fullerene building blocks are fused cyclopropanated fullerenes, or methanofullerenes. Their synthetic accessibility as well as their structural diversity and conformational rigidity make methanofullerenes one of the most versatile of all [60]fullerene derivatives.
Chapter 1: Introduction

1.5.1 The Synthesis of Methanofullerenes

The synthetic methods currently used to produce methanofullerenes can be divided into two categories. The addition of "free" carbenes and diazo compounds to \([60]\)fullerene via \([2+1]\) and \([3+2]\) cycloadditions respectively, provide an effective route for methanofullerene formation. Reactions that proceed via an addition/elimination mechanism, such as the Bingel cyclopropanation provide the most popular route for methanofullerene formation.

1.5.1.1 Cycloaddition Reactions to \([60]\)Fullerene

The addition of diphenyl diazomethane to a toluene solution of \([60]\)fullerene at RT provided the first example of a methanofullerene as an isomeric mixture of methanofullerene (6,6 closed) and methanoannulene (5,6 open) products (Scheme 1.20).\(^90^,91\) Investigations into the mechanism of diazomethane addition with \([60]\)fullerene revealed diphenyl diazomethane adds initially as a \([1,3]\)-dipole to \([60]\)fullerene, forming the pyrazine intermediate (65), followed by thermal extrusion of nitrogen to form a mixture of methanofullerene [(67), (1,2-closed)] and methanoannulene [(66), (1,6-open)] products. Under photochemical or prolonged thermal (48 hr) conditions, the intermediate (65) gave almost exclusively the thermodynamically more stable methanofullerene product (67).

Thermal addition of other diazo compounds to \([60]\)fullerene such as diazoacetates and diazomalonates provides substituted methanofullerenes, which have handles for further synthetic modification (Scheme 1.21).\(^33^,91^,94\)
The 1,2-dihydro-61-(carboxy)methano-[60]fullerene (24) can be obtained either from the tert-butyl ester (68) or the O-glycolic ester (69), followed by ester deprotection of the adducts (70) and (71) respectively. The synthetic utility of (24) was demonstrated by its DCC-mediated esterification to produce the methanofullerene peptides (72) and (73). Analogous reactions using diazoamides have also been carried out. The preparation of methanofullerene derivatives by prolonged thermolysis with diazoamide derivatives [(27a-d)] provided the protected fulleryl amino acid derivatives (28)-(31), (Scheme 1.13).
Singlet carbenes add exclusively across 6,6-fusion bonds of [60]fullerene to form methanofullerenes. As a result of the potential biological activity of amphiphilic water-soluble [60]fullerene derivatives, the isomerically pure fullerene-sugar conjugates (77) and (78) were prepared from the thermal addition of the corresponding diazirines (74) and (75) via carbene addition of (76) to [60]fullerene, in 55% and 54% yield, respectively (Scheme 1.22).
Other examples of carbene [2+1] cycloadditions to [60]fullerene include the pyrolysis of sodium trichloroacetate, and thermolysis of oxadiazoles, cyclopropene acetals and tosylhydrazone lithium salts in the presence of [60]fullerene.16-19

1.5.1.2 Methanofullerene Formation via Addition/Elimination Mechanisms

The susceptibility of [60]fullerene to nucleophilic attack was demonstrated in section 1.3.2, by the addition of Grignard, organolithium and amines to the carbon sphere. [60]Fullerene reacts with stabilised α-halocarbanions at room temperature to give methanofullerenes [(80)-(88)].94-101 This reaction, more commonly known as the Bingel cyclopropanation,99 is formulated as an addition of the stabilised α-halocarbanion to [60]fullerene, followed by intramolecular displacement of the halide by the anionic centre generated on the [60]fullerene sphere (79). This reaction results in an isomerically pure methanofullerene product, and has become one of the most widely used reactions in fullerene chemistry (Table 1.1).
This reaction has been further refined using malonic esters where the *in situ* generation of bromomalonates leads to an efficient and reliable one-pot reaction. The versatility of the Bingel cyclopropanation reaction is illustrated by the diverse range of substituents that have been used (Scheme 1.23). Deprotection of the ester moieties in malonate-derived methanofullerenes provides access to the versatile methanofullerene dicarboxylic acid (92), (Scheme 1.24).
The addition of sulfonium and phosphonium ylides to [60]fullerene at RT also yields methanofullerene products (85)-(88) in moderate yield (Table 1.1).100,101
1.6. Regioselective Multiple Additions to [60]Fullerene: The Evolution of [60]Fullerene Chemistry

The realisation of the full potential of [60]fullerene relies heavily on the development of new synthetic and spectroscopic techniques in order to exploit the unique 3-dimensional structure of [60]fullerene as a novel 3-dimensional template. To harness the unique physical properties of [60]fullerene in a range of disciplines, for example, the biological and material sciences, the production of chemical "handles" or synthons in defined positions on the [60]fullerene sphere is required. Methanofullerenes have been introduced as an effective rigid scaffold for the positioning of such substituents. The development of methods for the selective multiple functionalisation of [60]fullerene provides access to an unprecedented variety of 3D building blocks for organic chemistry, which complement the present repertoire of 2D acetylenic, olefinic and benzenoid components for the construction of tailor made functional molecules and polymers. A wide range of synthetic protocols exists for the formation of [60]fullerene monoadducts. In contrast, sequential multiple functionalisation of [60]fullerene has been problematic as regioisomeric product mixtures are produced, requiring tedious chromatographic separations. Several studies of multiple addition reactions, such as the multiple Bingel addition of diethyl malonate under Bingel reaction conditions to [60]fullerene have been conducted. These studies produced a complex mixture of regioisomeric bisadditions (see section 3.3 for details), as shown in Scheme 1.25, for the non-regioselective cyclopropanation of the methanofullerene (80).
1.6.1 Regioselective Functionalisation of [60]Fullerene using Tethers

The use of rigid molecular spacers or tethers allows regioselective construction of fullerene derivatives with addition patterns that are difficult to obtain with untethered reagents.\textsuperscript{12,104,107-125} A general method for the synthesis of tether-derived multifunctionalised derivatives is illustrated in Scheme 1.26. The initial attachment of a reactive group (R.G.1) to the [60]fullerene, anchors the tether-reactive group conjugate, thereby allowing the second reactive group (R.G.2) to add to a kinetically or thermodynamically favourable site on the carbon sphere.

For example, tethered bismalonate derivatives from ortho, meta and para benzenedimethanols, produce bisadducts via double Bingel cyclopropanation reactions with high regioselectivity and in acceptable yields (Scheme 1.27).\textsuperscript{117} Double Diels-
Alder cycloadducts using α,ω-dioxamethylene tethers also proved effective for regioselective functionalisation (Scheme 1.28).\textsuperscript{126-128}

Scheme 1.27

\begin{equation}
\text{(a) C}_{60}, \text{DBU (5 equiv.), I}_2 \text{ (2 equiv.)}
\end{equation}
Tether-derived multifunctionalisation has also been used to successfully attach different anchors to the [60]fullerene surface as illustrated in Scheme 1.29. The initial Bingel derived cyclopropanation product of [60]fullerene and (102), was subjected to Diels-Alder reaction conditions to produce the pure trisadduct (103) in which functionalisation occurred exclusively at the \( e \) (equatorial) position.²⁰⁻¹²⁻¹³

Although tether-directed multifunctionalisation is an effective method for the control of regioselectivity, the scope of this method has been generally limited to malonate-derived cyclopropanations, nitrene and Diels-Alder reactions, with identical
reactive groups, directed towards the construction of symmetrical systems. Other tethered reactions, such as tethered non-malonate Bingel cyclopropanations have yet to be explored as methods for the regioselective multifunctionalisation of [60]fullerene.

1.7. Characterisation of Multifunctionalised [60]Fullerene Derivatives

As was stated in section 1.5, a wide range of synthetic protocols exist for the formation of [60]fullerene monoadducts; however very few procedures exist for the production of multiple [60]fullerene adducts. Characterisation of [60]fullerene derivatives has involved the use of traditional spectroscopic methods such as 1D $^1$H and $^{13}$C NMR spectroscopy, mass spectrometry and UV/vis spectrometry (for a more detailed explanation of these techniques and their application to bisadduct characterisation see section 3.4). However as [60]fullerene chemistry evolves to more complex systems, such as non-symmetrical, higher-order derivatives, these traditional techniques will become insufficient for unequivocal structural characterisation.

Two techniques that provide unequivocal structural characterisation are X-ray crystallography and 2D NMR spectroscopy. Crystal structures have proven to be the most widely used of these techniques for the unequivocal characterisation of mono- and multifunctionalised [60]fullerene derivatives. However this technique is limited by the relative difficulty in obtaining suitable crystals for analysis. Compared with X-ray crystallography, 2D NMR spectroscopy of fullerenes has had limited investigation. Since [60]fullerene derivatives primarily consists of carbon, the powerful $^{13}$C-$^{13}$C connectivity experiments such as 2D-INADEQUATE and C-C TOCSY experiments can provide equivalent information to crystal structures. The
Achilles' heel of this technique is the extreme insensitivity of these experiments at normal $^{13}$C enrichment, requiring isotopically enriched ($^{13}$C) samples.

In contrast to the numerous examples of [60]fullerene crystal structures in the literature, only two studies of [60]fullerene derivatives by 2D NMR spectroscopy have been reported. The mono-osmylated derivative (12) and four regioisomeric bis-osmylated adducts $C_{60}[\text{OsO}_4\text{py}_2]_2$ have been investigated using isotopically enriched materials.61,158 Using the 2D INADEQUATE experiments, the carbon spheres of (12) and four of the [60]fullerene derivatives of $C_{60}[\text{OsO}_4\text{py}_2]_2$ were fully characterised.

![Structure](image)

(12)

### 1.8. Project Aims

The initial aim of this project was to prepare the protected cyclopropyl amino acid (105) from the reaction of [60]fullerene and readily available N-(diphenylmethylene glycinate) esters (104) under Bingel cyclopropanation conditions. It was expected that the selective deprotection of (105) would yield either the free amino ester or the N-protected amino acid that could be coupled to peptides to give novel fulleryl peptides. Complete deprotection should provide the amino acid (106) (Scheme 1.30). It was planned that the conformation of the synthesised fulleryl peptides would be studied using a series of 2D NMR experiments.
These studies would then be extended to the synthesis of protected bincyclopropyl amino acids using different tethered protected bis-α-iminoglycines (T) under double Bingel cyclopropanation conditions. Selective deprotection of these structures would produce derivatives such as (107) (Scheme 1.31), that could in principle be coupled to two different peptides.

Another aim of this project was to develop spectroscopic and computational methodologies in order to unambiguously characterise the multifunctionalised [60]fullerene derivatives as well as to theoretically predict the regiochemical outcomes of the synthesised tethered bisaddition products obtained in this project. Using 2D NMR spectroscopy, the INADEQUATE experiment will be used in an attempt to characterise all carbons in the [60]fullerene sphere in both mono- and multifunctionalised [60]fullerene architectures via $^{13}$C-$^{13}$C connectivities.
Chapter 2:

Acyclic $\alpha$-Fulleryl Amino Acids
Chapter 2: Acyclic α-Fulleryl Amino Acids

To date, the only true α-fulleryl amino acid that has been prepared, has been fulleroproline (Fpr); albeit a [60]fullerene-fused proline derivative.\textsuperscript{75,129-161} The synthesis of an acyclic α-substituted amino acid, for example α-fulleryl glycine (Fgly), akin to the majority of natural amino acids, has not yet been realised.

This chapter describes the synthesis of a protected version of (Fgly) through an unexpected novel reductive ring-opening reaction of a methanofullerene derivative. The initial aim of this work was to prepare the fulleryl cyclopropane amino acid (106), and its mono- and diprotected derivatives using the one pot Bingel cyclopropanation methodology developed by Hirsch and Camps,\textsuperscript{102} using readily available \(N\)-(diphenylmethylene glycinate) esters.

2.1 The Bingel Cyclopropanation Beyond Malonates

The Bingel cyclopropanation reaction (section 1.5.1.2) has been widely used in fullerene chemistry to form malonate-derived methanofullerenes [(Table 1.1), (Scheme 1.23)].\textsuperscript{99} However, the use of these conditions to form protected methanofullereryl amino acids using \(N\)-(diphenylmethylene glycinate) esters had not been explored prior to this study; thus cyclopropanation was attempted using \(N\)-(diphenylmethylene glycinate) esters under Bingel conditions. In a typical reaction, a solution of [60]fullerene, and commercially available (108) or (109) in chlorobenzene was treated successively with
carbon tetrabromide (1.0 molar equiv.) and DBU (2.2 molar equiv.) under a nitrogen atmosphere for 1 hr. Purification of the crude products by flash column chromatography afforded the desired methanofullerenes, (110) or (111), as brown amorphous solids in 46% and 72% yields, respectively (Scheme 2.1).

Scheme 2.1

The $^1$H NMR spectrum of (110) revealed a loss of the methylene resonance ($\delta$ 4.21) associated with the $N$-(diphenylmethyleneglycinate) ester (108) as a result of cyclopropanation. The aromatic region of these methanofullerene derivatives exhibit three distinct resonances associated with the diphenyl imine protons, ortho ($H_a, \delta$ 8.05), meta ($H_b, \delta$ 7.42) and para ($H_x, \delta$ 7.31) to the site of substitution (Figure 2.1). Of these resonances, the ortho protons exhibit a characteristic downfield shift of approximately 0.3 ppm compared to the corresponding starting material, indicative of the diphenyl imine moiety being in close proximity to the electron deficient fullerene sphere.
Figure 2.1: $^1$H NMR (400 MHz, C$_6$D$_6$/CS$_2$; 6:4) spectrum of (110) with expansion of the aromatic region. Aromatic protons labeled $H_a$, $H_b$ and $H_x$ shift downfield with respect to the corresponding starting material. This downfield shift is attributed to the electron deficient fullerene sphere being in close proximity to the diphenylimine moiety, illustrated by the dashed lines from $H_a$ to the fullerene $\pi$ system adjacent to the site of substitution.

The $^{13}$C NMR spectrum of (110) comprises 28 resonances arising from the fullerene core (Figure 2.2). Literature examples of related compounds reveal two possible structures can, in principle, be considered; methanofullerene or methanoannulene (section 1.5.1.1). Methanofullerene and methanoannulene derivatives with different bridgehead substituents are $C_5$ symmetrical, exhibiting 32 fullerene $^{13}$C NMR resonances. Distinguishing between these two isomers can be achieved by inspection of the bridgehead carbon resonance (Figure 2.3).
Chapter 2: Acyclic α-Fulleryl Amino Acids

Figure 2.2: $^{13}$C NMR (100 MHz, C$_6$D$_6$/CS$_2$: 6:4) spectrum of (110) with expansion of the bridgehead carbon (δ 96.3) and fulleryl sp$^3$ carbons (δ 84.2, δ 83.3).

![Figure 2.2](image)

Figure 2.3: Chemical shifts for the bridgehead C-atoms for isomers, methanofullerene (112) and methanoannulene (113).

![Figure 2.3](image)

The $^{13}$C NMR chemical shift of the methano bridge C-atom is sensitive to local ring currents that differ greatly in methanofullerene and methanoannulene derivatives. In the case of methanofullerenes, the bridgehead carbons generally resonate between δ 70-90, depending on the nature of the R group substituents (Table 2.1), while in
methanoannulene derivatives the bridgehead carbons appear between δ 130-150. Compounds (110) and (111) were identified as possessing “closed” methanofullerene structures rather than the “open” methanoannulene structures by the presence of bridgehead carbon resonances at δ 92.9 and δ 96.3 respectively. This is approximately 20 ppm downfield to that of the corresponding diethyl malonate methanofullerene (80), due to the electronegative nature of the imino nitrogen adjacent to the bridgehead carbon.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>(δ) Bridgehead Carbon (Cₐ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(114)</td>
<td>-CN</td>
<td>-CN</td>
<td>67.9</td>
</tr>
<tr>
<td>(115)</td>
<td>-CN</td>
<td>-CO₂Et</td>
<td>69.7</td>
</tr>
<tr>
<td>(80)</td>
<td>-CO₂Et</td>
<td>-CO₂Et</td>
<td>71.6</td>
</tr>
<tr>
<td>(116)</td>
<td>-H</td>
<td>-NO₂</td>
<td>70.4</td>
</tr>
<tr>
<td>(110)</td>
<td>-N=CPh₂</td>
<td>-CO₂Bu</td>
<td>92.9</td>
</tr>
<tr>
<td>(111)</td>
<td>-N=CPh₂</td>
<td>-CO₂Et</td>
<td>96.3</td>
</tr>
</tbody>
</table>

Table 2.1 Bridgehead carbon ¹³C NMR chemical shifts of selected methanofullerenes with the general formula C₆ᵣ(R₁)R₂.¹³

The fullerene region of the ¹³C NMR spectrum of (111) is expanded in Figure 2.4. Typically, a C₅ symmetrical fullerene derivative with different bridgehead substituents exhibit 32 sp² resonances with four half-intensity peaks. In the case of (111), only 28 out of 32 sp² resonances were observed at 100 MHz, with only two out of the four half-intensity resonances (shown by red circles) being identified due to peak overlap. Half-intensity peaks arise from the existence of carbon atoms on the plane of symmetry (C₁₈, C₂₇, C₃₆ and C₄₅) as illustrated in Figure 2.5. An additional fullerene peak was observed at δ 82.7. This was assigned as the fullerene sp³ carbon at the site of substitution on the fullerene core.
**Figure 2.4:** $^{13}$C NMR of the fullerene sp$^2$ region of (111), exhibiting 28 out of the 32 possible resonances. Red circles identify half-intensity resonances.

**Figure 2.5:** Schlegel diagram of (110) showing IUPAC numbering of the fullerene core. Red circles identify carbons on the symmetry plane (C18, C27, C36 and C45).
Chapter 2: Acyclic α–Fulleryl Amino Acids

The MALDI-TOF spectrum of (111) displayed a molecular ion at m/z 985 as well as a fragment ion at m/z 817 corresponding to the loss of a diphenyl carbene fragment. 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 [60]fullerene dimer under MALDI-TOF conditions. Dimerisation is assumed to proceed via the carbene (117) undergoing a [1+2] cycloaddition with [60]fullerene to give (118) (Scheme 2.2).

Scheme 2.2

![Scheme 2.2](image)

(111) \( m/z \ 985 \)

(117) \( m/z \ 1452 \)

2.2 Deprotection of Amino Acid Derivatives

Selective deprotection of (110) and (111) to give the corresponding free amino and carboxylic acid derivatives respectively would allow direct incorporation of [60]fullerene into peptide sequences using conventional coupling reactions as shown in the general scheme of Scheme 2.3.
The diphenylimine moiety is known for its lability in acidic media.\textsuperscript{166} Despite literature precedent, treatment of (110) with 1M HCl at RT failed to hydrolyse the imine, with a quantitative recovery of the starting material. Table 2.2 summarises the range of hydrolysis reaction conditions attempted on compound (110). Harsher acidic conditions (entry 7) gave rise to the partial formation of a polar product (analytical TLC analysis). Longer reaction times did not result in further conversion to this unknown product. \textsuperscript{1}H NMR analysis of this product was difficult due to its poor yield and solubility. Hydrolysis using 6M HCl/dioxane at reflux (entry 8) however resulted in the formation of a dark brown precipitate (Scheme 2.4).
Both $^1$H and $^{13}$C NMR spectra could not be acquired due to the extreme insolubility of this compound in both water and organic solvents. Mass spectrometry analysis was also unsatisfactory. Without adequate spectroscopic evidence of (106), it is difficult to say if the fully hydrolysed fulleryl amino acid (106) was indeed formed. The insolubility of this unknown product could be equated to the formation of large aggregates with hydrophilic ends facing outward, and leaving the hydrophobic fulleryl moiety within the centre.

![Scheme 2.4](image)

### Table 2.2: Attempted imine acid-hydrolysis conditions on compound (110).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Reaction Temp.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl (1 M)</td>
<td>two-phase (CHCl$_3$/1M HCl)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>2</td>
<td>HCl (1 M)</td>
<td>single-phase (1M HCl in THF)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>3</td>
<td>HCl (2 M)</td>
<td>single-phase (1M HCl in THF)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>4</td>
<td>HCl (2 M)</td>
<td>single-phase (1M HCl in THF)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>single-phase (TFA:DCM; 1:1)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>6</td>
<td>TFA</td>
<td>single-phase (TFA:DCM; 1:1)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>7</td>
<td>$p$-toluene sulfonic acid</td>
<td>toluene</td>
<td>reflux</td>
<td>trace amounts of unknown product formed</td>
</tr>
<tr>
<td>8</td>
<td>HCl (6 M)</td>
<td>single-phase (dioxane:6M HCl)</td>
<td>reflux</td>
<td>uncharacterisable product formed</td>
</tr>
</tbody>
</table>
Deprotection of the ester moiety of (110) was attempted using the following sets of acidic conditions (entries 1-3; Table 2.3). All acid hydrolysies conditions that were attempted did not provide the free carboxylic acid. An attempted base hydrolysis of (111) using lithium hydroxide (entry 4; Table 2.3) also returned unreacted starting material.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>R Group</th>
<th>Reaction Conditions</th>
<th>Reaction Temperature</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>'Bu</td>
<td>TFA:DCM (1:1)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>'Bu</td>
<td>TFA:DCM (1:1)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>3</td>
<td>p-toluene sulfonic acid</td>
<td>'Bu</td>
<td>toluene</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>4</td>
<td>LiOH</td>
<td>Et</td>
<td>1M LiOH/MeOH/dioxane</td>
<td>RT</td>
<td>starting material</td>
</tr>
</tbody>
</table>

Table 2.3: Attempted ester hydrolysis conditions on compounds (110) and (111).

Difficulties in hydrolysing methanofullerene carboxylic esters have been observed in the literature; presumably the bulky fullerene hinders the approach of nucleophilic reagents (e.g. OH⁻) to the carbonyl carbon. In the case of Isaacs and Diederich, a methanofullerene carboxylic acid has been realised via the boron tribromide (BBr₃) deprotection of a O-ethylglycolic ester moiety. A boron tribromide deprotection was attempted on the ethyl ester (111), but was unsuccessful and thus efforts were directed towards the synthesis of the N-(diphenylmethylene) glycinate O-ethylglycolic ester (128) (Scheme 2.5).
The diphenylimino O-ethylglycolic ester (128) was synthesised in four steps by the esterification of N-tert-butoxycarbonyl glycine (123) with ethyl bromoacetate in the presence of excess potassium carbonate, followed by TFA mediated deprotection of the N-tert-butoxycarbonyl group to afford the trifluoroacetate salt (126). Finally, transimination was achieved by using benzophenone imine to form (127). Reaction of (127) under Bingel reaction conditions in the presence of [60]fullerene, afforded the...
methanofullerenne (128) in 46% yield. The addition of BBr₃ to a dichloromethane solution of (128) afforded the free carboxylic acid (129) in 51% yield as a moderately soluble material. ¹H NMR analysis of (129) revealed aromatic resonances corresponding to the ortho (δ 8.08, d, J = 10.6 Hz), meta (δ 7.55, t, J = 7.3 Hz) and para (δ 7.43, t, J = 7.3 Hz) protons of the diphenyl imine moiety accompanied by the disappearance of resonances associated with the O-ethylglycolic ester functionality. A mass spectrum of (129) was unsuccessful and because of its low solubility, a ¹³C NMR analysis prevented confirmation of (129).

The reactivity of the tentatively assigned free carboxylic acid (129) was explored using a DCC-mediated amidation reaction in an attempt to form the peptide derivative (130) (Scheme 2.5). Reaction of (129) and ethyl phenylglycinate in the presence of a catalytic amount of DMAP and DCC (1.3 equiv.) in THF afforded a brown fraction after flash chromatography. ¹H NMR analysis revealed a complex mixture of compounds for this single brown fraction.

2.3 Characterisation of Methanofullerenes (80) and (111) using the 2D INADEQUATE Experiment

2.3.1 The 2D INADEQUATE Experiment

The INAQEQUATE experiment gives responses only from homonuclear coupled systems (e.g. ¹³C-¹³C satellites not ¹³C-¹²C or ¹²C-¹³C) by exploiting the property known as multiple quantum coherence.¹⁶⁷ Multiple quantum coherences can be distinguished from single quantum coherences as:

(a) multiple quantum coherences can only occur in coupled spin systems (such as ¹³C-¹³C couplings
(b) multiple quantum coherences have different phase properties from single-quantum coherences.

Multiple quantum coherence can be visualised by analogy with the single-quantum coherence. An isolated spin-1/2 nucleus (e.g. $^{13}\text{C}^{12}\text{C}$) in a field has two energy levels, labeled $\alpha$ (low energy) and $\beta$ (high energy) shown in Figure 2.6.

![Energy level diagram for a single spin in a magnetic field.](image)

**Figure 2.6:** Energy level diagram for a single spin in a magnetic field.

The energy separation between these levels is related to the absorption frequency $\nu$ by the equation $\Delta E = h\nu$. A single quantum transition occurs when a spin is promoted from the lower to the upper level by absorption of an appropriate quantum of energy. This transition is detected indirectly by detection of the evolution of the magnetisation in the $xy$ plane.

Similarly, two spins which are $J$-coupled (e.g. an AX spin system) have four available energy levels as shown in Figure 2.7. In addition to the set of single quantum transitions there is also a double-quantum transition, which connects $\alpha\alpha$ to $\beta\beta$, and a zero quantum transition which connects $\alpha\beta$ to $\beta\alpha$. These transitions, which are not normally observed, are only present in $J$-coupled systems. Magnetisation can be forced to evolve at the double quantum (or zero quantum) frequency during a period which follows an appropriate preparation sequence. The pulse sequence that generates suitable double-quantum coherences between two coupled spins in the INADEQUATE
The experiment is shown in Figure 2.8a. The addition of an incremented time \( t_1 \) and a fourth 90° pulse completes the 2D INADEQUATE sequence (Figure 2.8b).

Figure 2.7: Energy level diagram for a pair of coupled spins.

\[ \begin{array}{c}
\text{(a)} \\
\begin{array}{c}
\text{90°} \\
\tau = \frac{1}{4J_{cc}} \\
\text{180°} \\
\tau = \frac{1}{4J_{cc}} \\
\text{90°}
\end{array}
\end{array} \]

\[ \begin{array}{c}
\text{(b)} \\
\begin{array}{c}
\text{90°} \\
\tau = \frac{1}{4J_{cc}} \\
\text{180°} \\
\tau = \frac{1}{4J_{cc}} \\
\text{90°} \\
\tau = \frac{1}{4J_{cc}} \\
\text{90°}
\end{array}
\end{array} \]

Figure 2.8: (a) The portion of the INADEQUATE pulse sequence that generates double quantum coherence. (b) The 2D INADEQUATE pulse sequence where \( t_1 \) is an incremented time delay.

A second Fourier transformation, in this case applied on the intensity variation of the satellite signals gives the double-quantum frequency of the AX spin system. Since this frequency is equal for all four signals of an AX spin system, the satellite signals, appear in the same row of the two-dimensional spectrum, though with differing phase.
The projection of the contours of a two-dimensional INADEQUATE spectrum onto the x-axis of a coordinate system gives the chemical shifts of the satellite signals, whereas the y-axis projects the double-quantum frequencies of the different AX spin system.

2.3.2 Application of 2D INADEQUATE in [60] Fullerene Chemistry

The attractiveness of the INADEQUATE for structural investigations of [60] fullerene derivatives is the lack of hydrogens that are normally abundant in organic compounds. This feature prevents structural analysis of these derivatives by $^1$H NMR spectroscopy as well as 2D heteronuclear experiments such as HSQC and HMBC. Using the INADEQUATE experiment, all structural information, such as connectivity patterns and bond information derived from $^1J_{CC}$ can be obtained.

The 2D INADEQUATE pulse sequence was employed for the first time on a $^{13}$C-enriched example of the osmylated derivative (12). The 17 sets of carbons in the $C_{2v}$-symmetric (12) were assigned on the basis of their connectivities. Three types of carbons were identified on the basis of $^1J_{CC}$. The $C(sp^3)$-$C(sp^3)$ bonds (~48 Hz), the longer 5,6 bonds (54-57 Hz) and the shorter 6,6 bonds (65-71 Hz).61,62,158

The potential of the 2D INADEQUATE technique for unequivocal structural characterisation of [60] fullerene derivatives is enormous. The advantages of this technique are as follows:

- Unequivocal structural assignment of all carbons in the [60] fullerene sphere regardless of symmetry and functionalisation.
- Information can be gained on the nature of C-C bonds and how substituents and increasing functionalisation affect them.
• A non-destructive technique that enables sample recovery and thus potentially further synthetic use.

The biggest drawback of this technique as mentioned already is the extreme insensitivity at normal enrichment. Coupled with the relative insolubility of [60]fullerene derivatives for use at normal enrichment, isotopically \(^{13}\text{C}\) enriched samples are mandatory. Another disadvantage of this technique is the relative small frequency window of the fullerene sp\(^2\) carbons which increases the instances of peak overlap. The most severe case of this is in non-symmetrical systems when potentially 58 sp\(^2\) carbons are situated in a small frequency window (typically 132-155 ppm).

2.3.3 Methanofullerenes (80) and (111)

2D INADEQUATE experiments were performed on the diester (80) and compound (111) on \(^{13}\text{C}\) enriched samples (see chapter 6 for acquisition details). While (80) is a known compound, no 2D experiments have been performed on this compound, and this study was undertaken to assist in the analysis of (111) and more complex derivatives. The 1D \(^{13}\text{C}\) NMR spectrum of isotopically enriched (80) showed 17 fulleryl peaks consistent with a \(C_{2v}\)-symmetrical [60]fullerene derivative (Figure 2.9). Fulleryl resonances are distinguished from non-fulleryl resonances by the presence of \(^{13}\text{C}-^{13}\text{C}\) coupled satellites situated either side of a central resonance peak. Of the 17 peaks, four peaks were expected to be approximately half the intensity of the other 13 peaks. The four half-intensity peaks were observed at \(\delta\) 145.08, \(\delta\) 144.92, \(\delta\) 143.37, and \(\delta\) 72.06 (Figure 2.9). Assignment of the carbon sphere was achieved on the basis of the one-bonded \(^{13}\text{C}-^{13}\text{C}\) connectivities. Half-intensity sp\(^2\) peaks (\(\delta\) 145.08, \(\delta\) 144.92, and \(\delta\) 143.37) were assigned to carbons C55(C60), C18(C27), and C36(C45) respectively,
which were located on the mirror planes (Figure 2.10, Figure 2.11). Although the half-intensity peak at δ 144.92 was difficult to assign due to peak overlap, it was identified as corresponding to C18(C27) by a correlation to another half-intensity carbon, C36(C45) with a coupling typical for a 6,6-ring fusion (\(^\text{1}J_{CC} = 69\) Hz). The remaining half-intensity resonance located upfield at δ 72.06 was assigned to the fulleryl sp\(^3\) carbon, C1(C2) that correlated to a single carbon, C6(C3,C9,C12) with a coupling typical for sp\(^2\)-sp\(^3\) bonds \(^{1}J_{CC} = 44\) Hz). Carbon 55(C60) was assigned to the half-intensity resonance located at δ 145.08 on the basis of exhibiting only one correlation to C54(C51) (δ 145.47) (Figure 2.10, Figure 2.11).

\[\text{EtO} \begin{array}{c} \text{O} \\ \text{Et} \end{array} \]

\((80)\)

**Figure 2.9:** \(^{13}\)C NMR (150 MHz, CS\(_2\):CDCl\(_3\); 7:3) spectrum of 10\(^{\%}\) \(^{13}\)C-enriched (80) showing the fulleryl sp\(^3\) region. Half-intensity resonances identified by red circles. The fourth half-intensity resonance located at δ 72.06 as omitted for clarity.
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Resonances δ 144.92 and δ 145.37 were assigned to C18(C27) and C36(45), identified by a correlation between these two carbons with a coupling constant of 69 Hz, consistent with a 6,6-ring fusion (Figure 2.10). Carbons 18(C27) and 36(C45) exhibit an additional correlation to C19(C17,C26,C28) and C37(C35,C44,C46) respectively with observed coupling constant for $^{1}J_{C_{36}C_{37}}$ typical for a 5,6 fusion (55 Hz). The coupling constant for $^{1}J_{C_{18}C_{19}}$ was not first order due to the closeness of the peaks, thus no coupling constant value was obtained. The bonding of all carbons revealed the retention of the [5]radialene and cyclohexatriene substructures of the parent [60]fullerene.

Starting from C1(C2), $^{13}$C-$^{13}$C connectivities provided the complete assignment of the carbon sphere. Resonances corresponding to C21(C15,C24,C30) (δ 141.22) and C39(C33,C42,C48) (δ 142.48) were identified from their coupling to three full-intensity peaks (C21/C22; C21/C20; C21/C7; C39/C38; C39/C22; C39/C40), while C6(C3,C9,C12), C19(C17,C26,C28) and C37(C35,C44,C46) coupled with two full-intensity peaks (C6/C5; C6/C7; C19/C18; C19/C20; C37/C38; C37/C53) and one half-intensity peak (C6/C1; C19/C18; C37/C36) (Figure 2.10c). The remaining carbons comprised of only two correlations due to their positions relative to the plane of symmetry. Interestingly, the carbon directly adjacent to the functionalisation site (C6) appears most downfield of the main “cluster” of carbons, whereas the carbon correlating to C6 on a 6,6 ring fusion C5 is located the most upfield of the main cluster of carbons. A table of the complete assignment of all carbons in compound (80) is shown in Appendix 2.1.
Figure 2.10: 2D INADEQUATE spectrum (150 MHz, CS$_2$:CDCl$_3$; 7:3) of (80) showing (a) the fulleryl sp$^2$ region and (b) correlations of C18 and C54 to C36 and C55 respectively.
Figure 2.11: (a) Schlegel diagram of (80) with the IUPAC numbering system taken from Thilgen et al. (1997).168 (b) Schematic representation of the carbon sphere with half-intensity resonances in red.
The corresponding 1D $^{13}$C NMR spectrum of isotopically enriched (111) showed 26 out of the expected 31 fulleryl peaks for a $C_5$-symmetrical [60]fullerene derivative (Figure 2.12). The corresponding $^{13}$C NMR spectrum of (111) at normal enrichment exhibited 28 resonances as a consequence of no line broadening due to $^{13}$C-$^{13}$C couplings (Figure 2.4). Three of the four half-intensity peaks were identified at $\delta$ 146.95, $\delta$ 146.81 and $\delta$ 141.77, while the sp$^2$ fulleryl carbon was located at $\delta$ 82.73.

Figure 2.12: $^{13}$C NMR (150 MHz, CS$_2$: CDCl$_3$; 7:3) spectrum of 10% $^{13}$C-enriched (111) showing the fulleryl sp$^2$ region. Half-intensity resonances identified by red circles. The fulleryl sp$^3$ resonance located at $\delta$ 82.73 is omitted for clarity.
Attempted assignment of the [60]fullerene core of compound (111) began by the correlation of the fulleryl sp$^3$ carbon C1(C2) at $\delta$ 82.73 to the fulleryl sp$^2$ carbon resonances at $\delta$ 153.07 and $\delta$ 148.45 either side of the substitution site C3(C6) and C12(C9). The INADEQUATE experiment cannot distinguish which of these carbons lie underneath the diphenyl imine or ester moieties respectively, however, C9(C12) is most likely to correspond to the resonance at $\delta$ 148.45 underneath the ester moiety, which is consistent with the corresponding resonance at $\delta$ 145.82 for C6 in compound (80) (Figure 2.11). Thus C3(C6) in (111) was assigned to the isolated downfield resonance located at $\delta$ 153.07. Such a downfield shift of almost 5 ppm would most likely arise from spatial communication between the diphenyl imine moiety and the [60]fullerene core close to the site of substitution. Two additional correlations were identified for carbons C3 [C3/C4 ($^1J_{CC} = 57$ Hz); C3/C14 ($^1J_{CC} = 72$ Hz)] and C12 [C12/C11 ($^1J_{CC} = 57$ Hz); C12/C13 ($^1J_{CC} = 72$ Hz)], however due to peak overlap the resonance at $\delta$ 145.02 corresponding to C4 could not unambiguously be assigned. The positioning of C14 in the five membered ring adjacent to the site of substitution was confirmed by this resonance exhibiting three correlations [(C14/C3 ($^1J_{CC} = 72$ Hz); C14/C13 ($^1J_{CC} = 54$ Hz); C14/C15 ($^1J_{CC} = 57$ Hz)]. Assignment of the five-membered ring adjacent to the site of substitution is complete by the observation of a correlation between C13 and C14 with a small $^1J_{CC}$ of 54 Hz. Further assignments were prevented by the overlapped C4 resonance, and further overlapped peaks at $\delta$141.71 corresponding to C15.

Figure 2.13 illustrates a Schlegel diagram of (111) indicating the carbons that could be assigned. Of the assignable peaks, the most significant deviations in the [60]fullerene core of compound (111) is the unexplainable bonding arrangement. For compound (80), the [5]radialene substructure of the [60]fullerene core was retained.
(Figure 2.11b) with large $^1J_{CC}$ values (68-72 Hz) observed for carbons at the 6,6 fusions, and small $^1J_{CC}$ values (54-57 Hz) observed for carbons at the 5,6 fusions. In contrast, compound (111) revealed large $^1J_{CC}$ values in the 5,6-ring fusion, and smaller $^1J_{CC}$ values for a 6,6, ring fusions. This sort of bonding is the complete opposite of what has been experimentally observed for pristine [60]fullerene as well as in compound (80) and the osmylated compound (12) where [50]radialene and cyclohexatriene substructures were observed. However, since the complete carbon sphere of (111) could not be characterised, such bonding type cannot be substantiated. A table of the assignments of carbons in compound (111) is shown in Appendix 2.2.

$X = \text{CO}_2\text{Et}; Y = \text{N}=\text{CPh}_2$

**Figure 2.13:** Schlegel diagram of (111) with the IUPAC numbering system as per Thilgen 	extit{et al.} (1997).
2.3.4 [60] Fullerene Cage Topology of (80)

Using the 2D INADEQUATE experiment, all fulleryl carbons in (80) were unambiguously assigned (Appendix 2.1). Information concerning the bond lengths in compound (80) was obtained by correlating geometry optimised (PM3) bond lengths to measured $^1J_{CC}$ values (Figure 2.14). A corresponding correlation of bond lengths with measured $^1J_{CC}$ values for compound (111) was not carried out due to incomplete characterisation. These measured values and the bond lengths calculated from the PM3 forcefield, were consistent with the [5]radialene substructure of the [60]fullerene cage in (80). A good correlation was obtained between the measured $^1J_{CC}$ values and the calculated bond lengths. Compound (80) displayed three types of bond lengths, consistent with the observed bond length types of the monosmylated product (12) derived from both X-ray crystallographic analysis and $^1J_{CC}$ values. The smallest observed $^1J_{CC}$ value (44 Hz) corresponded to the sp$^3$-sp$^2$ bond located at the site of substitution. Such a bond length was slightly longer than the sp$^3$-sp$^2$ bond of the monosmylated derivative (12) which observed a $^1J_{CC}$ value of 48 Hz, indicative of (80) causing slightly more distortion due to the formation of a ring-fused cyclopropyl ring [for compound (80)] rather than a ring-fused cyclohexyl ring for compound (12).

The C-C bonds with larger $^1J_{CC}$ values (67-73 Hz) and calculated shorter bond lengths corresponded to 6,6 ring-fused bonds. Of these bond types, those in close proximity to the site of functionalisation (C5-C6), were noticeably shorter still (see A in Figure 2.14).
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Figure 2.14: 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 (80).

The second type of C-C bonds were those associated with 5,6 ring fused carbons. These carbon bond lengths were shown to be similar, indicative of little deviation occurring in 5,6 ring fusions upon monofunctionalisation of the [60]fullerene core. This observation of 5,6 bond lengths was also observed in the monosmylated product using both X-ray-derived bond lengths and $^1J_{CC}$-derived values. The [60]fullerene topology reveals that the most significant distortions of the [60]fullerene sphere upon monoaddition occur at the site of addition with the molecule adopting a distorted teardrop structure (Figure 2.15) with elongation along an axis through the site of substitution and the corresponding trans-$\perp$ bond.
Figure 2.15: Schematic representation of the cage distortion of (80) due to cyclopropanation. Arrows represent the direction of distortion. The most significant distortion was observed in the 5,6 bond (shown as bond A, which also corresponds to A in Figure 2.14).

2.4 Reductive Ring-opening

Due to a lack of reactivity in hydrolysing the diphenylimine moiety of (110) and (111), an alternate deprotection method was considered. The initial strategy was to hydrogenate the diphenyl imine of (110) to the corresponding amine (131). Subsequent cleavage of the resulting benzhydryl amino group in (131) using palladium black in the presence of formic acid,\textsuperscript{169,170} should afford the primary amine (106) (Scheme 2.6).
Hydrogenation of the diphenyl imine (110) over Pd/C under a hydrogen atmosphere proved to be incompatible with methanofullerene (110) due to adherence of the fullerene sphere to Pd/C. Reduction of (110) or (111) using sodium borohydride resulted in an uncharacterisable polar compound whereas the milder reductant, sodium cyanoborohydride, yielded not the reduced product (131), rather the unexpected ring opened 1,2-dihydro[60]fullerylglycine derivatives (133) and (134), respectively (Scheme 2.7).

Initially, the reductive ring-opening was attempted under protic conditions (pH 4), using acetic acid; however for reasons not completely understood, reductive ring-opening was confined to only the tert-butyl ester (110). A more reliable method was developed that involved treating (110) or (111) initially with boron trifluoride diethyl etherate (5.0 equiv.) and then treatment of the Lewis acid activated imine with sodium
cyanoborohydride. This method consistently yielded (133) or (134) respectively, accompanied by the formation of free [60]fullerene (~12%) and N-(diphenylmethyl)glycine ester (~8%) (Table 2.4).

<table>
<thead>
<tr>
<th>R Group</th>
<th>Starting Material</th>
<th>Product Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protic Acid (AcOH)</td>
</tr>
<tr>
<td>'Bu</td>
<td>(110)</td>
<td>(133) (44)</td>
</tr>
<tr>
<td>Et</td>
<td>(111)</td>
<td>(134) (0)</td>
</tr>
<tr>
<td>menthyl</td>
<td>(135)</td>
<td>(135) (0)</td>
</tr>
</tbody>
</table>

Table 2.4: Reductive ring-opening conditions and respective yields.

2.4.1 Mechanism of Ring-opening

The proposed mechanism of this novel ring-opening under protic acid conditions is shown in Scheme 2.8. This process may not necessarily be concerted, and the protonation steps may occur at different stages of the pathway. The first step in the reaction pathway is activation of the diphenyl imine functionality under protic acid conditions to form an iminium cation (136). The first equivalent of hydride then attacks this activated iminium carbon, resulting in migration of the imine double bond to the Cα position (137), with subsequent ring-opening, forming the fulleryl anion intermediate A. The driving force for such a ring-opening must be the stabilisation of the incipient fulleryl carbanion by delocalisation over the electron deficient [60]fullerene sphere. Such reductive ring-opening of cyclopropane amino esters and acids is known when a β-electron-withdrawing group is present on the ring that can stabilise a developing carbanionic centre.171
The mechanism for the corresponding Lewis acid promoted reductive ring-opening is assumed to proceed via a different but related pathway (Scheme 2.9). Initial complexation of BF$_3$ with the imino nitrogen, activates the imino carbon to hydride attack (138). This results in migration of the imine double bond to C$_a$ with subsequent formation of the fulleryl carbanion, analogous to that shown in Scheme 2.8. At this stage, the fulleryl anion (A) (Scheme 2.9) can be complexed with a second equivalent of BF$_3$, thus forming a bis-BF$_3$ intermediate (B), that can be in equilibrium with the corresponding free anion (C). The free anion (C) can then eliminate the addend to form free [60]fullerene and eventually (140). Alternatively, the complexed anion (B) can be protonated upon aqueous work-up to form the observed ring opened product (133).
This Lewis-acid derived mechanism can also explain the different by-products produced compared to the protic acid catalysed reaction. Significant amounts of free [60]fullerene and \( N \)-(diphenylmethyl)glycinate ester are formed, most probably as a result of elimination of the addend from the intermediate fulleryl anion (C) (Scheme 2.9).

To explore the mechanism of the Lewis-acid activated ring-opening, corresponding ring-opening experiments were performed using deuterium labeled...
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sodium cyanoborohydride (NaCNBD$_3$) followed by an aqueous (H$_2$O) workup. Such an experiment could give insight towards the origin of the proton source for the fullerene proton (H$_a$). Reduction of (110) with sodium cyanoborodeuteride in the presence of boron trifluoride diethyl.etherate followed by an aqueous workup, afforded the ring opened compound (141) in 38% yield. $^1$H NMR analysis revealed 42% deuterium incorporation at both the H$_a$ and H$_p$ positions, consistent with the proposed mechanism (Scheme 2.10); however no insight into the origin of the fulleryl proton (H$_x$) 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$_2$O as the quenching agent (Scheme 2.10). No incorporation of deuterium was observed in the product by $^1$H NMR of (142), indicative that the proton source is unlikely to arise from either the cyanoborohydride or the aqueous workup for H$_x$ but perhaps from adventitious water in the glassware.

Scheme 2.10

The ring-opening of methanofullerene derivatives have been previously observed in spiroannelated methanofullerenes, such as (143), whereupon a one-electron reduction causes a homolytic cleavage of one of the bonds in the cyclopropane ring (Scheme 2.11). This ring-opening however could only be observed transiently using EPR spectroscopy before proceeding irreversibly to an unknown product.$^{172}$
2.5 Characterisation of the Ring Opened Products

The $^1$H NMR spectrum of the ring-opened product (133), revealed a three proton coupled spin system at $\delta$ 5.27 (H$_B$, d, $J$ 4.0 Hz), $\delta$ 4.83 (H$_A$, d, $J$ 15.6 Hz) and $\delta$ 3.61 (NH, dd, $J$ 15.6, 4.0 Hz) (Figure 2.16a). A singlet resonance at $\delta$ 6.85 was assigned to the fulleryl proton (H$_x$). This was consistent with the chemical shifts of fulleryl protons identified in the literature (Table 2.5). For 1,2-C$_{60}$HR or 1,4-C$_{60}$HR derivatives, fulleryl protons characteristically fall in the 5-7 ppm region depending upon the position of the R group (C2 versus C4). The increased steric bulk of the R group, results in a downfield shift in the fullerene proton. In the case of our ring opened product (133), the R group is quite large and, according to trends from Table 2.4, should fall in the ~6.80-7.00 ppm region for a 1,2-organodihydrofullerene. The chemical shift observed was $\delta$ 6.85.
Figure 2.16: Expansion plots of the ring-opened product (133). (a) $^1$H NMR (400 MHz, C$_6$D$_6$/CS$_2$; 80:20) revealing $^1$H resonances, H$_a$, H$_b$, H$_x$ and NH (tert-butyl resonance at δ1.55 was omitted for clarity), and (b) fullerene region in the $^{13}$C NMR (400 MHz, C$_6$D$_6$/CS$_2$; 80:20), revealing 47 sp$^2$ resonances, indicative of a fullerene adduct possessing no plane of symmetry. The full compliment of 58 sp$^2$ resonances is not observed due to overlap.
Table 2.5: Fulleryl proton (H_x) chemical shifts of selected 1,2 organodihydrofullerenes with the general formula C_{60}(H)R\textsuperscript{84} Chemical shifts reported in CDCl\textsubscript{3}.

The fullerene region of the $^{13}$C NMR spectrum of (133) is shown in Figure 2.16b, and reveals 47 of the possible 58 sp\textsuperscript{2} resonances, indicative of a fulleryl adduct possessing no plane of symmetry. Closer inspection of the fulleryl sp\textsuperscript{2} section reveals that a number of resonances exist in defined clusters 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 observed.

Protonation of the carbanion (B) (Scheme 2.9) could give rise to both the 1,2 or 1,4 adducts, (133) and (144). The 1,4 addition pattern is usually preferred for sterically demanding addends\textsuperscript{173} The addend of the ring opened anion may present sufficient steric hindrance to force the protonation step into the 4-position to form (144). Thus, to identify whether a 1,2 or a 1,4 substituted product was formed, 2D NMR experiments were undertaken.
2.5.1 2D NMR Experiments on Organodihydrofullerenes

HSQC and HMBC experiments were used to identify the addition pattern by examining the $^1H-^{13}C$ couplings between $H_\alpha$ and C$_{\alpha}$, as well as $H_\alpha$ and C$_\chi$. The HSQC identified carbons C$_{\alpha}$, C$_{\beta}$ and C$_\chi$ by one bond $^1H-^{13}C$ correlations to $H_\alpha$, $H_\beta$ and $H_\chi$ respectively (Figure 2.17).

Figure 2.17: HSQC (400 MHz, C$_6$D$_6$:CS$_2$; 1:1) spectrum of ring opened product (133) revealing $^1J_{HC}$ couplings for $H_\alpha/C_{\alpha}$, $H_\beta/C_{\beta}$, and $H_\chi/C_{\chi}$.  

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Figure 2.18: 8 Hz optimised HMBC (600 MHz, C₆H₆; CS₂; 1:1) expansion plots of (133) revealing (a) $^3J_{HC}$ for $H_x \rightarrow C_\alpha$ and (b) $^3J_{HC}$ for $H_\alpha \rightarrow C_x$. Proton in question is coloured red while the carbon in question is coloured in green.
The HMBC experiment identified a 3-bond $^1H-^{13}C$ correlation between $H_x$ and $C_\alpha$ (Figure 2.18a). A corresponding 3-bond correlation between $H_\alpha$ and $C_x$ also confirmed the 1,2-addition pattern (Figure 2.18b). A 1,4 substitution pattern would not show such correlations since this would represent coupling over 5 bonds between $H_x/C_\alpha$ and $H_\alpha/C_x$.

An interesting finding from the HMBC experiment conducted on (133), emerged on closer inspection of the correlations between $H_x$ and the fullerene sp² region. A 2 Hz optimised HMBC experiment was performed, allowing long-range $^1H-^{13}C$ correlations to be observed. It was found that the single proton resonance of $H_x$ correlated to 20 fullerene sp² carbons; i.e. one third of the fullerene sphere was identified from a single proton resonance (Figure 2.19).

![HMBC spectrum Figure 2.19](image_url)

**Figure 2.19:** 2 Hz optimised HMBC (600 MHz, $C_6H_6$; CS$_2$; 1:1) spectrum of (133) showing 20 correlations from $H_x$ into the fullerene sp² core.
Particular resonance clustering were apparent after closer inspection of the nature of the coupling between Hx and the fullerene sp² carbons. Of the correlations between Hx and the fullerene sp² carbons, the most downfield resonances δ 154.44 and δ 153.66, 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 diastereotopic pairs as a consequence of the stereogenicity of Cα. These were assigned the carbons alpha to the functionalisation site, but on the same hemisphere as Hx (red circles in Figure 2.20). The more upfield diastereotopic pair of this cluster of four carbons were assigned to C6 or C9 at δ 153.07 or δ 152.38 respectively. These assignments were identified by a $^3J_{HC}$ of 6.0 Hz. These carbons were assigned as being alpha to the functionalisation site, but in the same hemisphere as the addend (green circles in Figure 2.20). Unequivocal assignment of the diastereotopic pairs of C3, C12 and C6, C9 could not be determined using the HMBC experiment.

Consistent with the most downfield carbon pairs C3/C12 and C6/C9, the most upfield carbons C4/C11 and C13/C14 also exist as diastereotopic pairs due to the formation of a chiral centre at the Cα position. Although these carbons cannot be assigned unequivocally by the HMBC experiment alone, there appears to be a trend in the nature of fullerene sp² $^{13}$C NMR chemical shifts directly in the vicinity of functionalisation. Fullerene sp² carbons alpha to the functionalisation site (C3, C6, C9 and C12) appear to exist downfield compared with the remaining fullerene sp² population (red and green circles, Figure 2.20).
Chapter 2: Acyclic $\alpha$-Fulleryl Amino Acids

Figure 2.20: Schlegel diagram of the ring opened adduct (133). C3 and C12 were identified by a $^2J_{HC}$ coupling to H$_x$ (red circles). C6 and C9 were identified by a $^3J_{HC}$ coupling to H$_x$ (green circles). Blue-circled carbon atoms are those beta to the site of functionalisation but could not be unambiguously determined from HMBC experiments to be C4, C5, C10, C11 or C7, C8, C13, C14.

Carbons located at the most upfield section of the fullerene sp$^2$ region (δ 137.30-136.58) were assigned to either C4/C11 or C13/C14 by a $^3J_{HC}$ of 6.0 Hz. Fullerene sp$^2$ carbons beta to the site of functionalisation (C4/C12, or C13/C14) appear to exist upfield compared with the remaining fullerene sp$^2$ population (blue circles, Figure 2.20). This "upfield/downfield" effect on fulleryl sp$^2$ carbons directly in the vicinity of the functionalisation was also seen in the case of ring-closed methanofullerene adduct (80) in section 2.3.3 using the 2D INADEQUATE experiment.

2.6 Deprotection of 1,2-Dihydrofullerylglycine Derivatives

Selective deprotection of the ring opened 1,2-dihydrofullerylglycine derivatives was attempted by exposing the ester group to a variety of acidic and basic conditions (Scheme 2.12). In all cases, a quantitative recovery of the starting material resulted (Table 2.6) except when a solution of (133) was heated at reflux in 6M HCl/dioxane.
(entry 4), which resulted in an insoluble brown precipitate. Acquisition of $^1$H NMR, $^{13}$C NMR and mass spectra of this precipitate was not possible due to its extreme insolubility.

Scheme 2.12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Reaction Temperature</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>single-phase (TFA:DCM; 1:1)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>single-phase (TFA:DCM; 1:1)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>3</td>
<td>p-toluene sulfonic acid</td>
<td>toluene</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>4</td>
<td>6M HCl</td>
<td>single-phase (dioxane:6M HCl)</td>
<td>reflux</td>
<td>uncharacterisable product formed</td>
</tr>
</tbody>
</table>

Table 2.6: Attempted ester hydrolysis conditions on compound (133).

Deprotection of the benzhydryl moiety of (133) via reduction (Table 2.7) also resulted in a quantitative recovery of the starting material. An alternate strategy was the activation of the secondary amine via the attempted formation of a carbamate (146) (Scheme 2.13). Attempts to prepare the carbamates (146) did not result in a product, most likely due to the reduced nucleophilicity of the secondary amine as a result of the electron withdrawing nature of the [60]fullerene sphere. Further efforts to selectively deprotect (133) were not pursued.

Scheme 2.13
### Table 2.7: Attempted deprotection conditions on compound (133).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
<th>Reaction Temp.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd black/HCO₂H</td>
<td>THF/McOH (1:1)</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>2</td>
<td>Pd black/HCO₂H</td>
<td>THF/McOH (1:1)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>3</td>
<td>Pd hydroxide/C</td>
<td>THF</td>
<td>RT</td>
<td>starting material</td>
</tr>
<tr>
<td>4</td>
<td>di-tert-butyl dicarbonate</td>
<td>NEt₃ THF/McOH (1:1)</td>
<td>reflux</td>
<td>starting material</td>
</tr>
<tr>
<td>5</td>
<td>CICO₂CH₂Cl₃</td>
<td>NEt₃ CHCl₃</td>
<td>reflux</td>
<td>starting material</td>
</tr>
</tbody>
</table>

2.7 Attempted Stereoselective Ring-opening

After the successful addition of diphenylimino esters to form achiral methanofullerene derivatives, interest turned to the formation of chiral methanofullerenes derived from chiral diphenylimino esters. It was hoped that substituting simple esters on N-diphenylmethyleneglycinate derivatives with chiral esters such as the menthyl ester (151) might induce a stereoselective ring-opening (Scheme 2.14). The synthesis of such chiral esters would allow us to observe if any diastereoselectivity could be obtained in the ring-opening reaction.

The chiral (+)-menthyl N-diphenylmethyleneglycinate (150) was prepared by DCC-mediated esterification of N-tert-butoxycarbonylglycine with (+)-menthol to afford (148) in 84% yield. Deprotection of (148) using TFA yielded the amine salt (149). Benzophenone imine mediated transimination yielded (+)-menthyl N-
diphenylmethylene glycinate (150) in 76%. The chiral methanofullerene derivative (151) was prepared in 31% yield under standard Bingel reaction conditions described in section 2.1. The \(^1\)H NMR spectrum of (151) exhibited all characteristics typical for a \(N\)-diphenylmethylene glycinate moiety being attached to [60]fullerene.

Scheme 2.14

\[
\text{BocHN} \quad \text{OH} \quad (123) \quad + \quad \overset{\text{DMAP (cat.), DCC (1.1 equiv.)}}{\xrightarrow{\text{THF}}} \quad \text{Ph}_2\text{C}=\text{NH} \quad \overset{\text{DCM}}{\xrightarrow{\text{Ph}_2\text{C}=\text{NH}}} \quad \text{Ph} \quad \overset{\text{N}}{\xrightarrow{\text{OR}}} \quad \text{OR}'
\]

\[\text{CH}_3\quad \overset{TFA}{\text{(-t-) menthol}} \quad (148) \quad R = \text{Boc, 84}\% \quad (149) \quad R = \text{H}_2\cdot\text{CF}_2\text{CO}_2, 55\%\]

\((+)-\text{menthol} \quad (150) \quad 76\% \quad C_{60} \cdot \text{DBU (2.1 equiv., CBr}_4 (1 \text{ equiv.)}}\]

The \(^{13}\)C NMR of (151) comprised 37 out of the expected 58 fulleryl sp\(^2\) resonances. A lack of a plane of symmetry in such chiral fullerene derivatives should, in theory cause non-equivalence in the fullerene carbon skeleton. This should allow 58 sp\(^2\) fulleryl carbons to be observed. However only 37 resonances were observed due to extensive overlap of peaks.

Reductive ring-opening was attempted to see if any diastereoselectivity in the reduction could be achieved using the chiral menthyl ester (151). Diastereoselectivity would arise from the second equivalent of hydride attacking the newly formed planar
iminium carbonyl carbon (A) (Scheme 2.9). If the approach of hydride on (A) is more sterically favoured to one side of the plane of the iminium group, then a diastereomeric excess should be achieved. Ring-opening of (151) was achieved using typical BF₃·diethyl etherate/sodium cyanoborohydride conditions forming the corresponding ring opened product (152). ¹H NMR analysis of (152) revealed the formation of a 1:1 mixture of diastereomers by inspection of the integration of the corresponding fullerene protons at δ 6.91 and δ 6.88 for each diastereomer (Figure 2.21).

Figure 2.21: ¹H NMR (400 MHz, C₆D₆/CS₂; 6:4) spectrum of (152) with expansion of the diastereotopic fulleryl protons (δ 6.91 and δ 6.88).

A possible explanation for such a lack of diastereoselectivity in the ring-opening of (151), could be that the source of chirality (the menthylation ester) is too far removed from
the site of nucleophilic attack by hydride on the iminium carbon. While other chiral auxiliaries were considered, no further studies in this area were pursued.

2.8 Concluding Remarks

The formation of a series of methanofullerenyl amino acid derivatives were synthesised using conventional Bingel reaction conditions. Although deprotection of the ring closed derivatives (110) and (111) did not yield the corresponding cyclic fulleryl amino acid, a novel cyanoborohydride mediated reductive ring-opening reaction was discovered. This reaction provided access to a range of substituted dihydrofullerene derivatives. Furthermore, by taking advantage of the acidity of the fulleryl proton (pKₐ 5.4), more highly functionalised [60]fullerenes could potentially be synthesised using base-catalysed chemistry.

The formation of the reductive ring-opened compounds has paved the way for the characterisation of more highly functionalised [60]fullerenes using 2D NMR techniques such as the 2D INADEQUATE experiment.
Chapter 3:
Unexpected Regiochemistry of Tethered Bis-N-(diphenylmethyleneglycinato) [60] Fullerene derivatives: Synthesis and Characterisation using 2D NMR Spectroscopy
3.1. Isomerism of Multifunctionalised [60]Fullerene Derivatives

[60]Fullerene is comprised of 30 reactive double bonds. These bonds are arranged in a precise three-dimensional array, resulting in a configurationally rigid molecule. Such configurational rigidity causes a number of regio- and stereoisomeric functionalisation patterns to arise in higher order, or multifunctionalised [60]fullerene derivatives. The isomerism found in these derivatives can be divided into three broad categories: regioisomerism (section 3.1.1), stereoisomerism (section 3.1.2) and [60]fullerene adducts with a chiral functionalisation pattern (section 3.1.3).168

3.1.1 Regioisomerism

In the formation of bis-methanofulleryl adducts, there are nine possible addition sites for functionalisation, assuming the reaction occurs across 6,6-fused bonds (Figure 3.1).5,9,12,18,105,106,109,117,130,131,141,164,176-180 The basis for the positional algorithm is the contiguous numbering of carbon atoms of a [60]fullerene derivative in a spiral fashion.168 If the second addition occurs in the same hemisphere as the first, it is assigned the cis regiochemistry with the numbering scheme (cis-1, cis-2, cis-3) increasing as the second addend retreats from the first site of addition. Trans regioisomers occur in the opposing hemisphere with the numbering scheme (trans-1, trans-2, trans-3, trans-4) increasing as the second addend approaches the first site of addition (Figure 3.1).

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In parent fullerenes, not every individual bond is labelled, but rather sets of bonds (with identical regiochemical environment). Each bond of a given set can be transferred into any other by spectroscopically determined (from the number of NMR-derived fulleryl $^{13}$C resonances) symmetry operations. Non-tethered regioisomeric methanofullerene bisadducts from cis-2 to trans-2 are either $C_5$ (characterised by plane of symmetry through [60]fullerene) or $C_2$ (characterised by an axis of symmetry) symmetry (Figure 3.2).

Table 3.1 presents the relationship between the symmetry for each regioisomer with the number of expected $^{13}$C NMR resonances for that symmetry operation of bismethanofullerene. Regiochemical assignment however, is not unequivocal using 1D $^{13}$C NMR due to several groups of regioisomers possessing identical symmetry. In addition to this drawback, the frequency range of fulleryl sp$^2$ resonances is small (132-155 ppm), thus increasing the probability of overlapping resonances, often making symmetry-based assignments difficult.
Figure 3.2: Schlegel and schematic diagrams of typical (a) \(C_5\)-symmetrical methanofullerene bisadducts, for example cis-2, containing a plane of symmetry, and (b) \(C_2\)-symmetrical methanofullerene bisadducts, for example cis-3 (one enantiomer shown), containing an axis of symmetry.
### Table 3.1: Summary of regioisomeric assignments for methanofullerene bisadducts, the number of observed fulleryl $^{13}$C resonances, and corresponding symmetry operations determined from $^{13}$C NMR spectra.

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$N^\circ$ of Fulleryl $^{13}$C Resonances</th>
<th>$N^\circ$ of 1/2 Intensity $^{13}$C Resonances</th>
<th>Symmetry Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-1</td>
<td>32</td>
<td>4</td>
<td>$C_s$</td>
</tr>
<tr>
<td>cis-2</td>
<td>32</td>
<td>4</td>
<td>$C_s$</td>
</tr>
<tr>
<td>cis-3</td>
<td>30</td>
<td>0</td>
<td>$C_2$</td>
</tr>
<tr>
<td>e-face</td>
<td>60</td>
<td>0</td>
<td>$C_s$</td>
</tr>
<tr>
<td>e-edge</td>
<td>60</td>
<td>0</td>
<td>$C_s$</td>
</tr>
<tr>
<td>trans-1</td>
<td>8</td>
<td>0</td>
<td>$D_{2h}$</td>
</tr>
<tr>
<td>trans-2</td>
<td>30</td>
<td>0</td>
<td>$C_2$</td>
</tr>
<tr>
<td>trans-3</td>
<td>30</td>
<td>0</td>
<td>$C_2$</td>
</tr>
<tr>
<td>trans-4</td>
<td>32</td>
<td>4</td>
<td>$C_s$</td>
</tr>
</tbody>
</table>

3.1.2 Stereoisomerism

Multifunctionalised fullerene derivatives having different substituents can possess several stereoisomeric forms. For example, in the case of *cis*-1, *cis*-2 and *trans*-4 bis-methanofullerenyl adducts having two different bridgehead substituents ($R$ and $R'$), there exists two $C_s$-symmetrical (*in*-in and *out*-out) and one $C_1$-symmetrical (*in*-out or *out*-in) diastereomers where the *in*-isomer has both "like" substituents occupying the space between the two methano groups.\textsuperscript{117,118} For the corresponding *cis*-3, *trans*-3 and *trans*-2 bisadducts, there exists two $C_2$-symmetrical (*in*-in and *out*-out) and one $C_1$-symmetrical (*in*-out) diastereomers (Figure 3.3).
3.1.3 **Chirality of [60]Fullerene: Configurational Descriptors of [60]Fullerene Derivatives with a Chiral Functionalisation Pattern**

[60]Fullerene derivatives can possess chirality that arises from a specific addition to an achiral parent fullerene (e.g. pristine [60]fullerene). In a three dimensional model of [60]fullerene, the path defining the C-atom numbering traces a helix, and, therefore, is chiral. Consequently, two geometrically equivalent, mirror-symmetric numbering schemes can be applied to an achiral parent fullerene (Figure 3.4). Therefore, by tracing a path from C1 to C2 to C3, a clockwise (C) or an anticlockwise (A) motion is defined, where the superscript "f" refers to fullerene."
Figure 3.4: Schlegel diagrams of [60]fullerene with enantiomeric numbering schemes according to Godly and Taylor (1993). Since pristine [60]fullerene is achiral, both numbering schemes are equivalent in this case. The red arrow indicates the path of numbering commencement.
Fullerene multifunctionalisation patterns can be defined as inherently chiral if there exists two enantiomeric species for a single regiochemistry (or stereochemical arrangement), regardless of the addends. Only the $C_2$-symmetrical regioisomers, $\text{cis}-3$, $\text{trans}-3$ and $\text{trans}-2$, exhibit such isomerism. For example, the $\text{cis}-3$ tetraethyl ester (157) exists as both the optically active $'^C$ and $'^A$ enantiomers (Figure 3.5). The numbering scheme adopted for such enantiomers will lead to the lowest set of locants for a given regiochemistry.

Figure 3.5: Two enantiomers of the $C_2$-symmetrical bisadduct (157). The bisadduct (157) can exist as clockwise ($'^C$) or anticlockwise ($'^A$) enantiomers.

3.2. Non-Tethered Multifunctionalisation of $[60]$Fullerene: Regiochemical Outcomes

3.2.1 Literature Examples of Double Bingel Cyclopropanations, Nitrene and Azomethine Ylide Additions

Systematic investigations on the regioselectivity of multiple 1,2-additions to $[60]$fullerene reveal intrinsic chemical properties of these carbon spheres. A comprehensive study of the formation of bisadducts was conducted separately by the groups of Hirsch$^{141}$ and Wilson$^{181}$ with two identical as well as with two different addends.
Chapter 3: Unexpected Regiochemistry

Figure 3.6: Relative yields of the isolated regioisomeric bisadducts of: (a) \( C_{62}(\text{COOEt})_4 \), (b) \( C_{60}(\text{NCOOEt})_2 \), (c) bis(\(N\)-methylpyrrolidine)-\(C_{60}\), and (d) \( C_{61}(\text{COOEt})_2-(\text{NCOOEt}) \). Red columns depict major regioisomeric yield, while the green column represent other significant regioisomeric yields. Black columns represent minor regioisomeric yields.
For these two-fold additions to [60]fullerene (Figure 3.6), the product distributions revealed the following characteristics:

(a) product distributions were not statistical (statistically the regiochemical ratio should be for example trans-1: e-face: trans-2; 1:2:4).

(b) three-membered ring bisadducts exhibit preference for the e, followed by trans-3 positions, while trans-2, trans-3, trans-4 and cis-3 are the major isomers for the azomethine bisaddition.

(c) cis-1 isomers are formed only if the steric requirement of the addends allow their suitable arrangement in close proximity.

(d) cis-1 adducts are the major products when their formation is possible. Bisadduct formation is less regioselective if more drastic reactive conditions are used. This is evident from a comparison of the two-fold nitrene and azomethine additions, that require reflux conditions with the diethyl bromomalonate additions that occur at RT. For a comparative analysis of the regioselectivities of these two-fold additions to [60]fullerene, the relative yields of the various bisadducts are represented in Figure 3.6. Hirsch et al. revealed the shortest and thus most reactive bonds, independent of the nature of the addend in 1,2 monoadducts, were situated at the cis-1, e-edge, e-face positions, according to AM1 calculations. It was concluded that product distributions of two-fold additions to [6,6] bonds on the [60]fullerene sphere were a consequence of enhanced frontier orbitals at these positions, i.e. the electronics of the fullerene monoadduct were the major force behind the product distribution. Regioselectivity of addition was found to be highest for the room temperature bismalonate addition (Figure 3.6a), whereas the least regioselective bisaddition was the bispyrrolidine reaction (Figure 3.6c), formed under refluxing conditions.
3.2.2 Non-Tethered Bisosmylations: The use of the 2D INADEQUATE Experiment for Regiochemical Assignment

A detailed investigation of the regiochemistry of [60]fullerene bisosmylation revealed five regioisomers $C_{60}[\text{OsO}_4(t\text{-bupy})_2]$ that were separated and isolated by preparative HPLC (Scheme 3.1).\(^{158}\)

**Scheme 3.1**

Using $^{13}$C-enriched [60]fullerene samples, the five regioisomers were converted to their 4-t-butylpyridyl analogues and the structure of four of these were analysed by 2D INADEQUATE experiments (Figure 3.7).

**Figure 3.7:** Regioisomers of the respective bisosmylation products obtained according to Scheme 3.1. Bold lines indicate sites of substitution.\(^{158}\)
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As was the case of the monoosmylated product described in section 2.3.2, three categories of $J_{CC}$ were observed. These were 48 Hz, 54-57 Hz, and 65-71 Hz, corresponding to three different types of C-C bonds present, sp$^2$-sp$^3$ bonds, 5-6 bonds and 6,6 bonds respectively.\textsuperscript{52,158}

Although the solubility of the trans-1 regioisomer was too low for NMR analysis, the remaining regioisomers possessed sufficient solubility for analysis. These four regioisomers possessed either $C_5$ or $C_2$ symmetry operations, characterised by a plane or axis of symmetry, respectively. Analysis revealed the retention of the [5]radialene structure, characterised by alternating 6,6-double and 5,6-single bonds in all bisadducts identified. The regiochemistry of each isomer was identified by determining the number of connectivities from the sp$^3$ functionalised carbon to the sp$^3$ carbons situated either on the plane or adjacent to the plane or axis of symmetry. Using this method of analysis, assignment of the four soluble regioisomers was achieved.\textsuperscript{158}

3.2.3 Additions of Non-Tethered N-(Diphenylmethyleneglycinate) Esters

Additions to [60]Fullerene

Studies are too few to definitively determine the factors responsible for product distribution in non-tethered bisadditions to [60]fullerene. For example, Hirsch et al.\textsuperscript{141} suggested that the [60]fullerene electronics of the Bingel monoadduct was the determining factor in the product distribution of the resultant bisadduct.\textsuperscript{141} The less regioselective double azomethine ylide and nitrene additions were explained by the differing reaction conditions used.\textsuperscript{182} However, the question of whether the difference in regiochemistry is a function of the difference in reaction mechanism between the different types of reactive intermediates (anions, nitrenes, 1,3-dipoles) has not been
addressed. In this study the product distribution of non-malonate double Bingel
cyclopropanations were investigated by sequential addition of \( N \)-
(diphenylmethyleneglycinate) esters.

In a typical reaction, a solution of [60]fullerene, and iminoester (109) (2 equiv.) in
chlorobenzene was treated successively with carbon tetrabromide (2 equiv.) and DBU
(3.5 equiv.) under a nitrogen atmosphere for 1 hr (Scheme 3.2). Purification of the
crude products by silica gel and eluting with DCM:petroleum spirit (90:10), afforded
two brown fractions.

Scheme 3.2

\[
\begin{align*}
\text{Ph} = \text{N} - \text{O} - \text{Et} & \quad \text{2 equiv.} \\
\text{in-out} & \quad \text{in-in}
\end{align*}
\]

\(^1\)H NMR analysis revealed the probable formation of at least 7 compounds in the first
fraction and 4 compounds in the second fraction, based on the number of methylene
ester quartets present. Since the addends of the \( N \)- (diphenylmethyleneglycinate) ester
were different, three possible stereoisomers (\textit{in-in}, \textit{in-out}, and \textit{out-out}) could form for
each regioisomer, leading to the complex mixture of compounds produced (Scheme
3.2). To obtain an insight into the regiochemistry of \( N \)- (diphenylmethyleneglycinate)
ester bisadditions under Bingel cyclopropanation conditions, a tedious HPLC separation
would be required but this was not pursued.
3.3. Regioselective Multifunctionalisation of [60]Fullerene using Tethered Bis-N-(diphenylmethyleneglycinate) Diesters

3.3.1 Synthesis of Tethered N-(Diphenylmethyleneglycinate) Diesters

The tethered bis-N-(diphenylmethyleneglycinate) diesters (170), (171), and (172) were synthesised according to the procedure illustrated in Scheme 3.3. DCC-mediated bis-esterification of ortho, meta, and para benzenedimethanol, afforded the bisglycine esters (164), (165) and (166), respectively.

Scheme 3.3

\[
\begin{align*}
\text{(a) DMAP (cat.), DCC (2.1 equiv.), } & \text{N-tert-butoxycarbonylglycine, DCM;} \\
\text{(b) TFA} & \\
\text{(c) Ph}_2\text{C}=\text{NH (2 equiv.), DCM} \\
\end{align*}
\]

Deprotection of the N-tert-butoxycarbonyl (Boc) group using TFA afforded the corresponding ammonium trifluoroacetate salts (167), (168) and (169). Transimination was achieved by treating a DCM suspension of the ammonium trifluoroacetate salts with benzophenone imine for 24 hr. Washing the organic layer with brine and concentration in vacuo afforded the transiminated diesters (170), (171) and (172) in 89%, 76% and 73% yields, respectively. Compound (170) was a pale oil, while (171)
and (172) were white amorphous solids. Compounds (170), (171) and (172) exhibited similar $^1$H and $^{13}$C NMR spectra, typified by that illustrated in Figure 3.8 for compound (171).

![Figure 3.8: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of (171) with an expansion of the aromatic region. x denoted H$_2$O resonance.](image)

The $^1$H NMR spectrum of (171) (Figure 3.8) comprised two singlet resonances at $\delta$ 3.17 and $\delta$ 5.09 for the acidic methylene and benzyl resonances respectively. In addition to these two resonances, aromatic resonances corresponding to the aromatic tether ($\delta$ 7.1-7.3) as well as three resonances corresponding to the diphenyl imine protons ($\delta$ 7.4-7.6) were present.

3.3.2 Double Bingel Cyclopropanation with Bis-N-
(Diphenylmethylene glycinate) Diesters

The individual double Bingel cyclopropanation reactions of (170), (171) and (172) with [60]fullerene were attempted using carbon tetrabromide (2.0 equiv.) and DBU (3.5 equiv.) (Scheme 3.4). These reactions typically took 1 hr to reach completion. The
reaction mixtures were stirred at RT, and monitored by analytical TLC. Purification required elution of the crude reaction mixture through two silica gel columns with DCM:petroleum spirit (90:10) as the eluent.

Scheme 3.4

(a) DBU (4.5 equiv), CBr₄ (2 equiv), C₆H₅Cl

3.3.2.1 Ortho Bis-N-(Diphenylmethyleneglycinate Diester Addition to [60]Fullerene

Under double Bingel reaction conditions, the ortho tethered bis-N-(diphenylmethyleneglycinate diester (170), did not afford a bisadduct, unlike the corresponding ortho bismalonate tether (Scheme 3.4). Analytical TLC revealed significant amounts of unreacted [60]fullerene and a polar species. ¹H NMR analysis of this polar species indicated a complex mixture that was difficult to characterise.

The lack of a resultant bisadduct was assumed to be due to the reactive intermediate formed in the bis-N-(diphenylmethyleneglycinate) diester system, undergoing the intramolecular addition proposed in Scheme 3.5. This hypothesis was
investigated by taking (170) and using standard double Bingel reaction conditions in the absence of [60]fullerene. $^1$H NMR and CI-MS analysis of this reaction revealed no discernable products, including (177), and thus it was assumed that a polymeric material had been formed.

Scheme 3.5

\[
\text{DBU (4.5 equiv.) } \quad \text{CB}_{\text{r}4} (2 \text{ equiv.}) \quad \text{C}_6\text{H}_5\text{Cl} \quad \text{Ph} = \text{Ph}^- \quad \text{N} \quad \text{Ph} \quad \text{Ph}^- \quad \text{N} = \text{CPh}_2 \\
\text{(170) } \quad \text{(177)}
\]

3.3.2.2 *Meta Bis-N-(Diphenylmethylene glycinate) Diester Addition to [60]Fullerene*

Exposing [60]fullerene and the *meta* tether (171), to double Bingel cyclopropanation conditions resulted in two regioisomers in an 80:20 mixture in the crude reaction mixture (based on $^1$H NMR analysis). These regiosomers could be separated by column chromatography and final recrystallisations yielded pure (173) and (174) in 28% and 9%, yields respectively. The MALDI-TOF spectrum of both (173) and (174) displayed a molecular ion at $m/z$ 1298 and fulleryl anion at $m/z$ 720.

The $^1$H NMR spectra of (173) and (174) revealed a loss of the methylene resonance ($\delta$ 3.17) associated with the $N$-(diphenylmethylene glycinate) ester (171) as a result of cyclopropanation (Figure 3.9). Tether macrocyclisation induces the benzyl protons to become diastereotopic and these appeared as doublets [$\delta$ 5.06 and 5.71 ppm; $J = 11.2$ Hz for (173); $\delta$ 5.41 and $\delta$ 5.32; $J = 11.0$ Hz for (174)] in contrast to the singlet resonance ($\delta$ 5.09) of the starting material (171).
Figure 3.9: Expanded sections of the $^1$H NMR (400 MHz, CDCl$_3$) spectrum of (a) (173) and (b) (174).
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The aromatic region of these methanofullerene derivatives exhibited a doubling up of resonances as a result of macrocyclisation. As with the monocyclopropanated derivatives, the ortho protons exhibit a characteristic downfield shift [(δ 7.92, 2H, d, J = 8.4 Hz and δ 8.04, 2H, d, J = 8.4 Hz for (173); δ 8.17, 2H, d, J = 7.6 Hz, δ 8.21, 2H, d, J = 7.6 Hz for (174)] compared to those corresponding protons in the starting material [(171), (δ 7.64, 4H, dd, J = 8.4, 1.6 Hz)].

The $^{13}$C NMR spectrum of (173) comprised 29 sp$^2$ fullerene resonances with three distinct half-intensity $^{13}$C resonances (shown in red in Figure 3.10b), characteristic of a $C_s$ symmetrical [60]fullerene derivative. The lack of a fourth half-intensity resonance was most likely due to peak overlap (see section 3.5). Two fulleryl sp$^3$ resonances (δ 81.8, δ 81.5) and one cyclopropane bridgehead carbon (δ 97.1) were observed, indicative of (173) possessing a single plane of symmetry (Figure 3.10a). Compound (174) exhibited a $^{13}$C NMR spectrum typical of a $C_2$-symmetrical compound, exhibiting 28 sp$^2$ resonances in the fulleryl region (Figure 3.10) and two sp$^3$ resonances. A plane of symmetry present for both (173) and (174) is indicative of the presence of either in-in (with respect to the diphenyl imine moieties) or out-out stereoisomers, however due to the large steric bulk of the diphenyl imine moiety, the former isomer is highly unlikely.

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Figure 3.10: $^{13}$C NMR (100 MHz, CDCl$_3$) of (173) showing (a) full spectrum with expansion of the bridgehead carbon and two fullerene sp$^3$ resonances and (b) expansion of the sp$^2$ fulleryl region showing half-intensity resonances (red circles).
3.3.2.3 Para Bis-N-(Diphenylmethylene glycinate) Diester Addition to [60]Fullerene

For the corresponding para tether (172), double Bingel cyclopropanation conditions also afforded two regioisomers in an 80:20 mixture in the crude reaction mixture (based on $^1$H NMR analysis) with a final yield of 33% and 8% for (175) and (176), respectively, after column chromatography and recrystallisation.

Similar to the meta bisaddition series described in the previous section, the MALDI-TOF spectrum of (175) and (176) displayed a molecular ion at $m/z$ 1298 and fulleryl anion at $m/z$ 720. The $^1$H NMR spectra of (175) and (176) revealed a loss of the methylene resonance ($\delta$ 3.17) associated with the N-(diphenylmethylene glycinate) diester (172) as a result of cyclopropanation. Diastereotopic benzyl doublets for (175) (Figure 3.12) and (176) appeared at $\delta$ 5.21 and $\delta$ 5.58 ($J = 11.6$ Hz), and at $\delta$ 5.17 and $\delta$ 5.72 ($J = 13.4$ Hz) respectively, compared to the singlet resonance for the
corresponding protons (δ 5.09) of the starting material (172). The aromatic region of these methanofullerene derivatives exhibit a doubling up of resonances as a result of macrocyclisation. The aromatic ortho protons exhibit a characteristic downfield shift at δ 8.16 (2H, d, J = 8.4 Hz) and δ 8.21 (2H, d, J = 8.4 Hz) for (175) and δ 7.92 (2H, d, J = 9.6 Hz) and δ 8.02 (2H, d, J = 9.6 Hz) for (176), compared to the corresponding protons in the starting material (δ 7.64, 4H, dd, J = 8.4, 1.6 Hz).

Figure 3.12: Expanded section of the $^1$H NMR (400 MHz, CDCl$_3$) spectrum of (175).

Due to the extreme insolubility of (175), a $^{13}$C NMR spectrum could not be acquired. The $^{13}$C NMR spectrum of (176), however, revealed a $C_s$ symmetrical compound comprising 29 sp$^2$ fullerene resonances with three distinct half-intensity $^{13}$C resonances virtually identical to (173), shown in Figure 3.10. Similar to the case of the

* A range of solvents (C$_6$D$_6$, (CD$_3$)$_2$SO, CS$_2$, $d_4$-dichlorobenzene) were tried in an effort to increase the solubility of (175); however these were ineffective.
$^{13}$C NMR of (176), the lack of a fourth half-intensity resonance was most likely due to peak overlap. Two fullerene sp$^3$ resonances (δ 82.1, δ 82.0) and one cyclopropane bridgehead carbon (δ 96.7) were observed, indicative of (176) possessing a single plane of symmetry.

3.4. Attempted Assignment of Bisadduct Regiochemistry using Current Spectroscopic Techniques

The regiochemistry of the tethered bismalonate derivatives illustrated in Scheme 1.27 were determined empirically from their symmetry, derived from the number of $^{13}$C resonances in their 1D $^{13}$C NMR spectra, in addition to comparative analysis of their UV/vis spectra with that of their non-tethered bisadduct analogues. Unfortunately for this study, no such non-tethered analogues were available to assist in the structure determination of (173)-(176).

3.4.1 $^{13}$C NMR Analysis and Possible Bisaddition Regiochemistry

The $^{13}$C NMR spectra for the regioisomeric bisadducts in both the meta and para series are summarised in Table 3.2. To confirm the symmetries of these bisadditions and possibly identify the fourth half-intensity resonance for compound (173), transesterification (K$_2$CO$_3$, EtOH/THF) to form the diethyl ester was performed (Scheme 3.6). This would remove the ipso $^{13}$C resonance, associated with the benzene dimethanol tether from the spectra as well as possibly shifting the fulleryl sp$^2$ resonances, enabling the fourth half-intensity peak to be identified. To a solution of (173) or (174) in a minimum volume of THF/EtOH (1:1) was added 10 molar equivalents of K$_2$CO$_3$ (Scheme 3.6, Scheme 3.7). The mixture was stirred at RT for 2 hr.
or until complete consumption of starting material was observed by analytical TLC.

Column chromatography (DCM eluent) yielded the bis-diethyl esters (178) and (179) in 51% and 49% yield, respectively.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Fullerene $^{13}$C Resonances</th>
<th>$\text{N}^\circ$ of $\frac{1}{2}$ Intensity $^{13}$C Resonances</th>
<th>Symmetry Operation</th>
<th>Possible Regiochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(173)</td>
<td>31</td>
<td>3</td>
<td>$C_s$</td>
<td>cis-1, cis-2, trans-4</td>
</tr>
<tr>
<td>(174)</td>
<td>30</td>
<td>0</td>
<td>$C_2$</td>
<td>cis-3, trans-3, trans-2</td>
</tr>
<tr>
<td>(175)</td>
<td>30</td>
<td>0</td>
<td>$C_2$</td>
<td>cis-3, trans-3, trans-2</td>
</tr>
<tr>
<td>(176)</td>
<td>31</td>
<td>3</td>
<td>$C_s$</td>
<td>cis-1, cis-2, trans-4</td>
</tr>
</tbody>
</table>

Table 3.2: Summary of $^{13}$C data, number of half-intensity resonances observed in the [60]fullerene region, symmetry operations and regioisomers satisfying the corresponding symmetry operations.

Scheme 3.6
Compounds (178) and (179) exhibited resonances associated with an ethyl ester [δ 1.41, 3H, t, J = 6.8 Hz; δ 3.48, 2H, q, J = 6.8 Hz for (178); δ 1.42, 3H, t, J = 6.9 Hz; δ 3.49, 2H, q, J = 6.9 Hz for (179)] and aromatic protons [δ 7.90, 2H, dd, J = 7.2 Hz, 1.2 Hz, δ 8.06, 2H, dd, J = 7.6 Hz, 1.2 Hz for (178); δ 8.25, 2H, d, J = 7.6 Hz, δ 8.09, 2H, d, J = 7.6 Hz for (179)]. The $^{13}$C NMR spectrum for the fulleryl regions of (178) and (179) were virtually identical to their tethered parent compounds, with the exception that the benzenedimethanol ipso carbon resonance was absent. While the major regioisomer for the para bisaddition series (175), was too insoluble to obtain a $^{13}$C NMR spectrum, its transesterified product (180) (Scheme 3.8) was sufficiently soluble for NMR spectral acquisition. For a comparative analyses, the transesterified minor para bisadduct (181), was also synthesised from (176) and characterised by $^{13}$C NMR (Scheme 3.9).
Scheme 3.8

Transesterification of (175) and (176) using identical conditions described for the meta bisaddition series yielded (180) and (181) in yields of 32% and 42%, respectively. Compound (180) exhibits $C_2$ symmetry, characterised by 30 sp$^2$ resonances, whereas (181) exhibits $C_s$ symmetry, characterised by 29 sp$^2$ resonances, three of which are half-intensity. Interestingly, the $^1$H NMR and $^{13}$C NMR spectra of (178) were found to be identical to that of (181), indicating that they have originated from compounds of the same regiochemistry. In summary, based on these 1D $^{13}$C NMR studies, compounds (173) and (176) have the same regiochemistry and are either cis-2 or trans-4 isomers, whereas compounds (174) and (175) have different regiochemistries and can be either cis-3, trans-3 or trans-2.
3.4.2 Attempted Regiochemical Assignment of Bisadditions using UV-vis Spectrophotometry

Regioisomer assignments for the bismalonate addition series (Scheme 1.27) were made by direct comparison of the UV/vis spectra of the tetraethyl malonate series as shown in Figure 3.13. According to Hirsch et al.\textsuperscript{141} UV/vis spectra of bisadducts “depend mostly on the addition pattern rather than on the nature of the addend”.\textsuperscript{141} Therefore the UV/vis spectra of compounds (173), (174), (175) and (176) should display comparable UV/vis spectra for a particular addition pattern. Figure 3.14 shows the UV/vis spectra for both regioisomers in the meta and para N-(diphenylmethylene glycinate) diester bisaddition series.

![UV/vis spectra](image)

**Figure 3.13:** UV/vis spectra (in DCM) for all regioisomeric bisadditions of the general formula C_6O(CO_2Et)_3.\textsuperscript{141}
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Figure 3.14: UV/vis spectra of (a) (173), (b) (174), (c) (175) and (d) (176) in DCM.

The UV/vis spectrum of compound (173), exhibits a shoulder at 430 nm in conjunction with a shallow shoulder at 490 nm. Two weak absorbances were also observed at 630 and 690 nm. This appears to be consistent with the trans-4 regiochemistry of the bismalonate derivative in Figure 3.13; however the similarities between the UV/vis traces of the trans-4 and cis-3 regioisomers do not enable these regioisomers to be unambiguously assigned. The UV/vis trace of the cis-3 isomer (174) showed similar characteristics in the 400-500 nm region to the cis-2 bismalonate as illustrated in Figure 3.13, however there was a distinct lack of weak absorbances situated in the 600-700 nm region. Compound (176) exhibited an identical UV/vis trace to that of (173), consistent with previous $^{13}$C NMR studies (section 3.3.1). Therefore the regiochemical assignment for (173) and (176) is likely to be trans-3. Compound (174) exhibited shallow shoulder
absorbances at 420 and 480 nm as well as weak absorbance peaks located at 630 and 690 nm. In comparison with Figure 3.12, (174) appears to exhibit characteristics of both cis-2 and cis-3 regiochemistry. The most likely regiochemical assignment for (174) would be the C2-symmetrical cis-3 regioisomer, based on 13C NMR analysis and in conjunction with UV/vis spectrometry.

The UV/vis spectrum of (175) exhibits a deep trough at 440 nm with two shoulder absorbances at 490 nm and 500 nm, bearing resemblance to the trans-3 regioisomer in Figure 3.13. The 1H NMR of compounds (174) and (175) show a distinct difference in chemical shifts for the aromatic and ethyl ester proton resonances, suggestive that both (174) and (175) are different regioisomers. The only alternative regiochemistry for the C2 symmetric (175) would be trans-3 or trans-2.

Such similarity in UV/vis spectra for two distinct regioisomers (174) and (175) questions Hirsch's theory that UV/vis spectra of regioisomeric bisadditions "depend mostly on the addition pattern rather than on the nature of the addend". Contrary to this claim, deviations in the UV/vis spectra have been observed in other bis-adducts, such as bis(N-methylpyrrolidine)-C60. Bismalonates and bis(N-methylpyrrolidines)-C60 that possess the same regiochemistry exhibit unique UV/vis spectra (Figure 3.15), suggestive that the addend substitution may significantly affect UV/vis spectra. Thus UV/vis spectra cannot be used as a definitive characterisation tool for the assignment of bisaddition regiochemistry. In conclusion, Table 3.3 summarises the tentative assignment of regiochemistry for the meta and para bisaddition series based on 1D 13C NMR and UV/vis studies.
Figure 3.15: UV/vis spectra of regioisomeric bisadducts (a) $C_{62}(CO_2Et)_4$, (b) bis(N-methylpyrrrolidine)-$C_{60}$ and (c) (173/176), (174), and (175).
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<table>
<thead>
<tr>
<th>Compound</th>
<th>Tentative Assignment of Regiochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>(173)</td>
<td>trans-4</td>
</tr>
<tr>
<td>(174)</td>
<td>cis-3</td>
</tr>
<tr>
<td>(175)</td>
<td>trans-3</td>
</tr>
<tr>
<td>(176)</td>
<td>trans-4</td>
</tr>
</tbody>
</table>

Table 3.3: Summary of regiochemical assignments for the *meta* and *para* bisaddition series.

3.5. Regiochemical Assignment of Bisadditions using 2D-INADEQUATE Experiments

The use of conventional $^{13}$C NMR symmetry and comparative UV/vis analysis techniques are not sufficient for unambiguous structure determination. Due to ambiguity associated with regiochemical assignments of bisadducts (173), (174), (175), and (176), difficulties in obtaining suitable crystals for X-ray crystallographic analysis, confirmation of the regiochemistry of (173) and (175) was achieved by the use of the 2D INADEQUATE experiment (see Appendix 3.1 for acquisition and processing parameters).

3.5.1 2D INADEQUATE Study of (173)

Unlike the ring-closed monoaadducts (80) and (111) where the plane of symmetry bisects the site of substitution, the symmetry operations of the bisadducts (173) and (175) occur at a site removed from the site of substitution. As described in section 3.1.1, the symmetry operations of bisadducts correspond to characteristic $^{13}$C NMR spectra in the fullerene $sp^2$ region. The $C_5$-symmetrical bisadduct (173) comprises 31 observed fulleryl peaks corresponding to two fulleryl $sp^3$ carbons and 29 fulleryl $sp^2$ carbons (Figure 3.16).
Figure 3.16: $^{13}$C NMR (150 MHz, CS$_2$/CDCl$_3$; 7:3) of $^{13}$C enriched (173) showing half-intensity resonances (red circles) and ipso carbon resonances (green circles).
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The half-intensity peaks provide the exact location of a plane of symmetry for (173). Thus regiochemical assignment can be achieved by identifying correlations from the half-intensity peaks (located on the symmetry plane) to the fulleryl sp\textsuperscript{3} carbons (locating the site of substitution). Fulleryl resonances are easily distinguished from non-fulleryl resonances by the presence of \textsuperscript{13}C-\textsuperscript{13}C coupled satellites situated either side of a central resonance peak. Thus, resonances located at δ 133.1, δ 132.2 and δ 131.9 were assigned as the ipso carbons corresponding to the aromatic tether and diphenyl imine moieties (Figure 3.16).

The full 2D INADEQUATE spectrum of (173) is shown in Figure 3.17. As was observed in the \textsuperscript{13}C NMR of the natural abundance sample of (173) (Figure 3.10), only three out of the four half-intensity sp\textsuperscript{2} resonances were observed for a \textit{C}_\text{S} symmetrical compound. The fourth half-intensity resonance was shown to arise at δ 150.6 from the fortuitous overlap of one full-intensity peak and one half-intensity peak. Confirmation of this overlap was observed by the number of correlations to the peak at δ 150.6. Resonances lying either side of the symmetry plane observe three correlations, while resonances situated on or directly adjacent to the plane of symmetry, experience two correlations. The peak at δ 150.6 showed five correlations; i.e. three correlations arising from a resonance removed from the plane of symmetry, and two correlations arising from a resonance lying on or directly adjacent to the plane of symmetry. One of these correlations was to the half-intensity resonance at δ 145.7 with a \textit{J}_{C,C} of 68 Hz, typical for a 6,6 fused bond, thus confirming the presence of the fourth half-intensity resonance at δ 150.6.
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3.5.1.1 Assignment of Regiochemistry

The three regiochemical possibilities for compound (173) with $C_5$ symmetry are cis-1, cis-2 and trans-3. The three aforementioned regioisomers would be expected to show two, one and three bond separations respectively, between a fulleryl sp$^3$ hybridised carbon and its nearest half-intensity carbon situated on the plane of symmetry. The 2D INADEQUATE experiment (Figure 3.18a) revealed a three bond connectivity (Figure 3.18b) between C1 (sp$^3$ carbon) and C19 (half-intensity peak), providing unequivocal evidence for its trans-4 regiochemistry. Starting from C19, correlations were observed to the other half-intensity peak (C20) with a relatively large coupling constant ($^1J_{C,C} = 66.8$ Hz), typical for 6,6 ring fusion carbons. Carbon-19 also displayed a correlation to C5 with a smaller $^1J_{C,C}$ value (57 Hz), typical for 5,6 ring fusion carbons. Carbon-5

Figure 3.17: 2D INADEQUATE (150 MHz, CS$_2$/CDCl$_3$; 7:3) spectrum of (173).
showed correlations to C6 ($J_{C-C} = 73$ Hz) and C4 ($J_{C-C} = 53$ Hz), consistent with their 6,6 and 5,6 ring fusion portions, 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. Complete chemical shifts, peak assignments and carbon-carbon coupling constants for (173) are shown in Appendix 3.1.

The characteristic “upfield-downfield” effect (section 2.5.1) was also observed for compound (173). The most downfield resonances, $\delta$ 150.6 and $\delta$ 149.6 were identified as C6/C36 and C9/C52 respectively, characterised by a typical sp$^3$-sp$^3$ coupling of 45 Hz to C1/C35. The most upfield resonances were assigned to C4 ($\delta$ 129.17), C10 ($\delta$ 147.13), C5 ($\delta$ 136.25) and C11 ($\delta$ 136.24) respectively by correlations to C3 ($J_{C-C} = 70$ Hz), C9 ($J_{C-C} = 73$ Hz) and C12 ($J_{C-C} = 71$ Hz) respectively. The remaining carbons adjacent to the site of functionalisation (C3 and C12), were assigned resonances that were situated in the “main pack” of fulleryl sp$^2$ resonances ($\delta$ 143.7 and $\delta$ 146.6 for C3 and C12 respectively), rather than downfield of the main pack (i.e. not situated near C6 and C9). Such deviations in chemical shift is suggestive of differing [60]fullerene topology not observed in the corresponding methanofullerenes (80) and (111).
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Figure 3.18: (a) 2D INADEQUATE fulleryl sp² expansion showing relevant correlations confirming trans-4 regiochemistry. (b) Schlegel diagram of (173) showing connectivities (green) from the site of substitution (C1) to the half-intensity peak (C29, red circle). Numbering system has been adopted from Thilgen et al. (1997).
3.5.2 2D INADEQUATE of (180)

Due to insolvency problems of (175), the $^{13}$C-$^{13}$C connectivity experiments were conducted using the transesterified sample (180). The $C_2$-symmetrical bisadduct (180) comprised of 30 observed fulleryl peaks; two fulleryl sp$^3$ carbons and 28 fulleryl sp$^2$ carbons. Unlike the $^{13}$C NMR of (173), no half-intensity peaks exist in $C_2$-symmetrical adducts, since the symmetry axis bisects two sets of bonds (at the point of entry and exit on each side of the ball) rather than a symmetry plane passing through two sets of bonds (as is the case for $C_5$-symmetrical compounds) (Figure 3.2). However, the point at which the symmetry axis bisects two bonds on the [60]fullerene core results in magnetic equivalence of the carbon nuclei directly either side of the axis, and is identifiable by two correlations rather than three correlations observed for the remaining resonances. Therefore the positional relationship of these resonances relative to the fulleryl sp$^3$ carbons (i.e. sites of functionalisation) provides the exact location of functionalisation relative to the symmetry axis.

The 2D INADEQUATE spectrum of the fulleryl sp$^2$ region (180) is shown in Figure 3.19. To aid 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.
3.5.1.2 Assignment of Regiochemistry

The three possible regioisomers that have a $C_2$-axis of symmetry are cis-3, trans-3 and trans-2 (section 3.1.1). The three aforementioned regioisomers would be expected to show one, two and three bond separations respectively, between a fulleryl sp$^3$ hybridised carbon and its nearest carbon exhibiting two correlations (i.e. the carbon bond at which the axis of symmetry is bisected). The 2D INADEQUATE experiment revealed a two bond connectivity (Figure 3.20) between C2 (sp$^3$ carbon) and C14 (peak exhibiting two correlations). Starting from C2 (sp$^3$ carbon), correlations were observed to resonances corresponding to C3 and C12 with $J_{CC}$ of 42Hz and 40Hz typical for sp$^3$, sp$^2$ ring fusion carbons. Carbon-3 exhibited correlations to C4 with a large $J_{CC}$ (71 Hz) consistent with a 6,6-fusion and to C14, a carbon with only two correlations, with a smaller $J_{CC}$ (58 Hz), providing unequivocal evidence for its trans-3 regiochemistry.
Figure 3.20: (a) 2D INADEQUATE fulleryl sp² expansions showing relevant correlations confirming trans-3 regiochemistry. * on C14 denotes resonance containing two correlations. (b) Schlegel diagram of one enantiomer of (180) showing connectivities (green) from the site of substitution (C1) 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. Numbering system according to Thilgen et al. (1997).
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The other two-correlation resonance (at the point of exit of symmetry axis) was identified as C39(C40). These resonances exhibit a five bond connectivity to the sp$^3$ carbon C50. Complete chemical shifts, peak assignments and carbon-carbon coupling constants for (180) are shown in Appendix 3.2.

3.5.3 [60] Fullerene Cage Topology of (173) and (180)

Using the 2D INADEQUATE and C-C TOCSY experiments, all fulleryl carbons in (173) and (180) were unambiguously assigned (Appendix 3.1 and Appendix 3.2). Information concerning the bond lengths in compounds (173) and (180) was obtained by correlating geometry optimised (PM3) bond lengths to measured $^1J_{C-C}$ values (Figure 3.21). These measured values, and the bond lengths calculated from the PM3 forcefield, were consistent with the [5]radialene substructure of the [60]fullerene cage in both (173) and (180) (Figure 3.21). In fact, a good correlation was obtained between the measured $^1J_{C-C}$ values and the calculated bond lengths (Figure 3.21). Both compounds (173) and (180) displayed three types of bond lengths, similar to those identified for (80) and (111). The C-C bonds with larger $^1J_{C-C}$ values (67-73 Hz) and calculated shorter bond lengths (1.37-1.39Å) corresponded to 6,6 ring-fused bonds. Of these bond types, those in close proximity to the site of functionalisation, were noticeably shorter still (see A, B, C, D in Figures 3.20 and 3.21) for both structures. The second type of fulleryl sp$^2$ C-C bonds displayed smaller $^1J_{C-C}$ (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 bonds, longer than normal bond lengths were identified for (173) (see F and G in Figure 3.21a and Figure 3.22a) and (180) (see E for Figure 3.21b and Figure 3.22b) close to the site of functionalisation. Unusually compound (173) displays
a significantly shorter 5,6 ring fusion bond (Figure 3.21a) close to the site of functionalisation. This shortened 5,6 bond-length was not observed in compound (180), most likely due to the more remote functionalisation pattern (trans-3) of (180) compared to compound (173) (trans-4).

(a)

Figure 3.21: Plot of calculated (PM3) carbon-carbon bond lengths (Å) versus $J_{C-C}$ (Hz) showing three groupings of carbon bonds: 6,6 ring fusion, 5,6 ring fusions and sp$^2$-sp$^3$ carbon bonds for (a) (173) and (b) (180).
The second type of C-C bonds were those associated with 5,6 ring fused carbons. A number of these carbons in (173) exhibited a bond shortening, depicted by a corresponding increase in $^1J_{C-C}$ (59 Hz versus the average of 55 Hz; for C3-C14 shown in green in Figure 3.22a), however no shortening was observed in these corresponding bonds for (180). Other 5,6 ring fused bonds showed a lengthening, characterised by
smaller $^{1}J_{C-C}$ values (53 Hz versus the average 55 Hz) and calculated longer C-C bond lengths (1.47 Å). The fulleryl cage of (173) exhibits comparatively more distortion when compared to (180), most likely as a consequence of the closer proximity of the functionalised sites in (173) and the removal of the effects of the tether in (180). 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 fulleryl sp$^{3}$ carbons. The shortening of bonds local to sites of substitution has been noted before from X-ray analysis of 1,2-difunctionalised [60]fullerenes as well as in earlier studies of methanofulleryl monoadducts (80) and (111) due to geometrical distortion of the [60]fullerene cage to a teardrop-like structure with elongation along an axis through the poles. This effect is manifested in bisadduct (173) 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.

3.6. Concluding Remarks

Using tether-directed syntheses, a series of [60]fulleryl bis-N-(diphenylmethyleneglycinate) esters using meta and para benzenedimethanol as a rigid tether were synthesised using conventional Bingel reaction conditions. The regiochemistry of the resultant bisadducts deviated significantly from the analogous bismalonate tethers. Conventional methods for the regiochemical assignment of [60]fullerene bisadducts were insufficient for the unequivocal assignment of the regiochemistry of the bis-N-(diphenylmethyleneglycinate) esters [60]fulleryl derivatives.
and therefore 2D INADEQUATE experiments were undertaken on the major regioisomeric bisadducts.

Such significant differences in regiochemistry between this study and those of Nierengarten et. al.\textsuperscript{117} may arise from the different stereoelectronic properties of the reactive intermediates involved or from the differences in the steric bulk of the diphenylimine moiety in the bis-N-(diphenylmethylene)glycinate ester system compared to the ethyl ester in the tethered bismalonate system. In an attempt to explain such differences in regiochemistry of the two systems, molecular modeling studies were undertaken and will be described in the proceeding chapter.
Chapter 4:
Computational and Mechanistic Investigations of N-(diphenylmethyleneglycinate) [60]Fullerene Derivatives
The bisadditions using bis-N-(diphenylmethyleneglycinate) diester tethered benzenedimethanols to [60]fullerene gave products with unexpected regiochemistry compared to their corresponding bismalonate addition products (Chapter 3). There have been no literature reports concerning whether the regiochemical outcome of tethered reactions is solely dependent upon the stereoelectronic requirements of the reactive addend, the mechanism of addition or steric factors or some combination of these factors. In an effort to gain insight into why such different regiochemistry was observed, mechanistic and computational investigations were initiated into the nature of the reactive intermediates, the mechanism of cyclopropanation and how these factors relate to the observed differences in regiochemistry.

4.1. Mechanistic Studies of Cyclopropanation

There is significant literature precedent concerning the mechanism of cyclopropanation of [60]fullerene using malonate esters. These reactions are thought to proceed via addition of a bromomalonate anion to [60]fullerene with initial formation of a fulleryl anion, followed by intramolecular SN2 cyclopropanation, yielding the methanofullerene (80) (Scheme 1.23). However no literature precedent exists for the mechanism of N-(diphenylmethyleneglycinate) ester cyclopropanation. An alternative possibility from the established nucleophilic mechanism of the malonic ester is for the deprotonated α-haloester to undergo α-elimination of the halide to give the corresponding carbene (182) which undergoes [2+1] cycloaddition across the [6-6] bond of fullerene (Scheme 4.1). Carbenes are known to react with [60]fullerene (Scheme 1.22). It is yet to be concluded that methanofullereryl N-(diphenylmethyleneglycinate) esters formed under Bingel reaction conditions proceed via an ionic mechanism or a [2+1] cycloaddition. To gain a greater insight into the
mechanistic nature of this reaction, experiments were conducted using both malonate and N-(diphenylmethyleneglycinate) esters with non [60] fullerene molecules that are known to react with carbenes (e.g. alkenes) and carbanions (e.g. \( \alpha,\beta \)-unsaturated ketones).

**Scheme 4.1:** Possible mechanism for the methanofullerene formation of N-(diphenylmethyleneglycinate) ester via carbene [2+1] cycloaddition.

\[ \text{DBU (2equiv.)} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{Et} \quad \text{DBU (2equiv.)} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{Et} \]

(109)

4.1.1 Reactions with Alkenes

The \( \pi \)-electron system of alkenes acts as a source of electrons for electrophiles such as radicals and carbenes. Thus a simple alkene, such as cyclohexene (184), readily traps highly reactive electrophilies, such as dichloromethylene (Cl\(_2\)C:, 183) to yield the bicyclo[4.1.0]heptane (185) (Scheme 4.2). Alternatively, the electron-rich \( \pi \)-system of alkenes does not normally react with nucleophiles, such as enolate anions. Using cyclohexene as a known carbene acceptor, the presence of carbenes was investigated using Bingel reaction conditions in the presence of either diethyl malonate or N-diphenylmethyleneglycinate tert-butyloxycarbonyl ester.
Scheme 4.2

\[
\text{Cl}_2\text{C} = \text{C} + \text{C} = \text{C} \quad \xrightarrow{[2+1] \text{cycloaddition}} \quad \text{Cl}_2\text{C} = \text{C} - \text{C} = \text{C}
\]

Diethyl malonate, under Bingel cyclopropanation conditions exhibited no cyclopropanated product in the presence of cyclohexene at -78 °C, 0 °C or at RT (Scheme 4.3). Similarly, N-diphenylmethyleneglycinate tert-butyl ester under Bingel cyclopropanation conditions revealed no cyclopropanated product at the same temperatures.

Scheme 4.3

Thus it can be concluded that under Bingel cyclopropanation conditions, the formation of carbene intermediates are unlikely in the presence of traditional alkenes, such as cyclohexene.

4.1.2 Reactions with α,β- Unsaturated Ketones

The π-electron system of the double bond in α,β-unsaturated ketones is conjugated with the carbonyl carbon, causing the β-carbon to be electrophilic, and thus susceptible to nucleophiles. Alternatively, the electron-deficient nature of α,β-unsaturated ketones ensures that these substrates do not normally react with other electron deficient species such as carbenes. Using 2-cyclopenten-1-one as a known
Michael acceptor, the nucleophilicity of diethyl malonate and \(N\)-diphenylmethylene glycinate, ethyl ester was investigated under Bingel cyclopropanation conditions. Using Bingel conditions, diethyl malonate in the presence of 2-cyclopenten-1-one (188), afforded the cyclopropanated product (189) (Scheme 4.4).\(^9^9\)

Scheme 4.4

\[
\begin{align*}
\text{C}_6\text{H}_{10} \quad \text{CO}_2\text{Et} & \quad \text{CBr}_4, \text{DBU} \quad \text{toluene} \\
\text{Scheme 4.4} & \\
\end{align*}
\]

Changing the leaving group from bromo- to chloro- in the monohalogenated malonate (190), and the Michael acceptor, resulted in not the cyclopropanated product but the Michael adduct (191) exclusively (Scheme 4.5).\(^9^{90}\)

Scheme 4.5

\[
\begin{align*}
\text{C}_6\text{H}_{10} \quad \text{CO}_2\text{Me} & \quad \text{NaH} \quad \text{OMe} \\
\text{Scheme 4.5} & \\
\end{align*}
\]

When Bingel conditions were adopted in the presence of \(N\)-diphenylmethylene glycinate ethyl ester and 2-cyclopenten-1-one, no Michael adduct (194) was observed by \(^1\text{H}\) NMR and mass spectrometry at \(-78 \, ^\circ\text{C}, 0 \, ^\circ\text{C}\) or RT. However mass spectrometry showed the formation of molecular ion \((m/z \, 531)\) that may correspond to the possible formation of the \(N\)-diphenylmethylene glycinate ethyl ester dimer (192/193) (Scheme 4.6). No corresponding dimer was observed for the malonate example; however a
malonate dimer (195) was observed under similar conditions in the absence of a Michael acceptor (Scheme 4.7).

Scheme 4.6

\[
\begin{align*}
\text{EtO}_2\text{C} & \text{N=Ph}_2 \\
\text{Ph}_2\text{C=NC} & \text{CO}_2\text{Et} \\
\text{Ph}_2\text{C}=\text{N} & \text{N=Ph}_2 \\
\text{EtO}_2\text{C} & \text{N=Ph}_2 \\
\end{align*}
\]

Scheme 4.7

\[
\begin{align*}
\text{EtO}_2\text{C} & \text{O} \quad \text{EtO}_2\text{C} \\
\text{EtO}_2\text{C} & \text{Br} \quad \text{EtO}_2\text{C} \\
\end{align*}
\]

For the formation of the tentatively assigned \textit{N}-diphenylmethyleneglycinate ester (192/193), a nucleophilic or carbene derived mechanism is feasible (Scheme 4.8). The proposed mechanism of the corresponding malonate dimer (Scheme 4.7) in the literature\textsuperscript{190} revealed a nucleophilic/elimination derived mechanism; thus no conclusive
evidence was obtained concerning the mechanism of the N-diphenylmethyleneglycinate ester under Bingel conditions.

Scheme 4.8

In summary, mechanistic studies reconfirm the literature precedent of the nucleophilic nature of malonic esters under Bingel cyclopropanation conditions. However, insight into the mechanism of N-(diphenylmethyleneglycinate) esters under Bingel cyclopropanation conditions were inconclusive. Thus no conclusions from these mechanistic studies can be drawn to explain differences in the observed regiochemistry of tethered bismalonic esters and tethered bis-N-(diphenylmethyleneglycinate) esters, as summarised in Table 4.1.
<table>
<thead>
<tr>
<th>Regiochemistry of Products (% yield)</th>
<th>Tethered Bismalonate Esters</th>
<th>Tethered N-(diphenylmethyleneglycinate) Esters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>meta</strong></td>
<td>R = <img src="image" alt="meta structure" /></td>
<td><img src="image" alt="meta structure" /></td>
</tr>
<tr>
<td><strong>para</strong></td>
<td>R = <img src="image" alt="para structure" /></td>
<td><img src="image" alt="para structure" /></td>
</tr>
<tr>
<td>cis-2 (32)</td>
<td><img src="image" alt="cis-2 structure" /> (97)</td>
<td><img src="image" alt="cis-2 structure" /> (98) (99)</td>
</tr>
<tr>
<td>trans-4 (33) major</td>
<td><img src="image" alt="trans-4 major structure" /> (173)</td>
<td><img src="image" alt="trans-4 major structure" /> (174) (176)</td>
</tr>
<tr>
<td>e (8) minor</td>
<td><img src="image" alt="e minor structure" /> (174)</td>
<td><img src="image" alt="e minor structure" /> (176)</td>
</tr>
<tr>
<td>cis-3 (9) minor</td>
<td><img src="image" alt="cis-3 minor structure" /> (175)</td>
<td><img src="image" alt="cis-3 minor structure" /> (176)</td>
</tr>
<tr>
<td>trans-4 (8) minor</td>
<td><img src="image" alt="trans-4 minor structure" /> (173)</td>
<td><img src="image" alt="trans-4 minor structure" /> (176)</td>
</tr>
</tbody>
</table>

Table 4.1: Double Bingel cyclopropanation of tethered bismalonate esters and tethered bis-N-(diphenylmethyleneglycinate) esters.

4.2. Computational Studies

4.2.1 Electronics of Tethered Monoaddition Intermediates

The electronic properties of the [60]fullerene sphere of different methanofullerene adducts were examined at the AM1 level of computations. Any observed differences could enable insight into the differences in reactivity and thus differences in observed...
Chapter 4: Computational investigations

regiochemistry of the tethered bisadducts shown in Table 4.1. Table 4.2 reveals the calculated bond lengths of the corresponding monoadducts (80)\textsuperscript{180} and (111) are essentially the same with the exception of the cis-l bond. However, when these calculated bond lengths are compared to bond lengths determined from X-ray crystallography\textsuperscript{141}, the calculated bond lengths do not accurately match the experimentally determined values for compound (80), thus definitive correlations of calculated bond lengths between compounds (80) and (111) cannot be considered accurate.

<table>
<thead>
<tr>
<th>Bond Type</th>
<th>$\text{EtO}_2C_6\text{CO}_2\text{Et}$</th>
<th>$\text{Ph}_2\text{C}=\text{N}_2\text{CO}_2\text{Et}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-1</td>
<td>1.385</td>
<td>1.394</td>
</tr>
<tr>
<td>trans-2</td>
<td>1.385</td>
<td>1.391</td>
</tr>
<tr>
<td>trans-3</td>
<td>1.385</td>
<td>1.395</td>
</tr>
<tr>
<td>trans-4</td>
<td>1.384</td>
<td>1.386</td>
</tr>
<tr>
<td>e-face</td>
<td>1.384</td>
<td>1.394</td>
</tr>
<tr>
<td>e-edge</td>
<td>1.384</td>
<td>1.384</td>
</tr>
<tr>
<td>cis-3</td>
<td>1.386</td>
<td>1.389</td>
</tr>
<tr>
<td>cis-2</td>
<td>1.387</td>
<td>1.406</td>
</tr>
<tr>
<td>cis-l</td>
<td>1.375</td>
<td>1.379</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.564</td>
<td>1.606</td>
</tr>
</tbody>
</table>

Table 4.2: Comparative 6,6-bond lengths (Å) of [60]fullerene monoadducts determined by semiempirical (AM1) or X-ray crystallography\textsuperscript{141}.
Chapter 4: Computational investigations

The comparable frontier orbitals in monoadducts (80) and (111) are presented in Figure 4.1. The LUMO coefficients in a precursor molecule are expected to influence the product distribution of nucleophilic additions, whereas the HOMO coefficients are expected to influence the product distributions of electrophilic additions (e.g. carbenes).

(a) (b)

Figure 4.1: AM1-calculated frontier orbitals of (111): (a) HOMO (b) HOMO-1 (c) LUMO (d) LUMO+1
The molecular orbital structure of (80) and (111) exhibit the following characteristics:

In the HOMO, the higher coefficients are located at the e-edge bonds, followed by the cis-1 bonds. The molecular orbital structure of (80) for HOMO-1 exhibits enhanced coefficient orbitals located in a diagonal belt going from cis-2 to trans-3, the highest coefficients are located in the e-face, cis-3 and cis-2 positions, consistent with the findings of Hirsch et al. The HOMO-1 coefficients for (111) were found to be essentially the same as those of (80) (Figure 4.1a,b).

The highest LUMO coefficients were found at e-edge, followed by trans-3 and cis-2 for both (111) and (80) (Figure 4.1c,d). Enhanced LUMO+1 coefficients were located at the e-edge position, followed by cis-1 and trans-2 for both compounds. Only in the LUMO+2 do the trans-1, trans-4 and cis-3 bonds exhibit enhanced orbital coefficients. Such observations in the LUMO for both compounds is directly comparable to that observed by Hirsch et al. The energies of the HOMO, HOMO-1, HOMO-2, LUMO, LUMO+1, LUMO+2 are essentially the same for both compounds (Table 4.3).

Thus in conclusion, semi-empirical calculations indicate that the effect of methanofullerene monofunctionalisation and its effect on the electronics of the [60]fullerene sphere appears to be addend independant. This conclusion is in agreement with the studies conducted by Hirsch et al. who concluded that the regiochemistry of non-tethered bisadducts are due to “typical cage distortions of [60]fullerene are in general responsible for the characteristic molecular orbitals”. The electronics of the [60]fullerene sphere for both (80) and (111) are virtually identical, and such characteristics appear to not play a role in determining the difference in regiochemistry of tethered bismalonic versus tethered bis-N-(diphenylmethylene)glycinate) esters. Therefore the characteristics of the tethered molecule (steric, electronic) or the reactive
intermediate must determine the regioselectivity. To provide insight into why the difference in regiochemistry is observed between bismalonic and bis-N-(diphenylmethylene glycinate) esters semi-empirical calculations were conducted on bisaddition systems.

<table>
<thead>
<tr>
<th></th>
<th>Molecular Orbital Energies (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EtO₂C₄H₁₂CO₂Et</td>
</tr>
<tr>
<td></td>
<td>(80)</td>
</tr>
<tr>
<td>HOMO</td>
<td>-9.43</td>
</tr>
<tr>
<td>HOMO-1</td>
<td>-9.55</td>
</tr>
<tr>
<td>HOMO-2</td>
<td>-9.57</td>
</tr>
<tr>
<td>LUMO</td>
<td>-2.92</td>
</tr>
<tr>
<td>LUMO+1</td>
<td>-2.83</td>
</tr>
<tr>
<td>LUMO+2</td>
<td>-2.72</td>
</tr>
</tbody>
</table>

**Table 4.3:** Calculated overall molecular orbital energies for (80) and (111).

**4.2.2 Semi-Empirical Calculations of Bisadducts**

The results of AM1 semi-empirical calculations of the heats of formation of bisadducts for the *meta* and *para* bisaddition series of both tethered bismalonic esters and bis-N-(diphenylmethylene glycinate) esters are summarised in Table 4.4 and Table 4.5 respectively. In both the *meta* and *para* bisadditions, the *cis*-1, *trans*-2 and *trans*-1 positions were not modelled due to both steric constraints and tether length (Table 4.4). Calculations for the bismalonic esters show a slight preference for the *cis*-2 and *cis*-3 bonds for the *meta* series. The corresponding *para* bisaddition series reveals no
thermodynamically preferable regiochemistry for cis-2, cis-3, trans-4 or e bonds. The more remote trans-3 regiochemistry displayed significantly higher final heats of formation in both the meta and para series. Thus, the final heats of formation of the theoretically-derived tethered malonic esters show no thermodynamic preference for the experimentally observed tethered malonic esters.

Calculations on the corresponding tethered bis-N-(diphenylmethyleneglycinate) ester meta and para series indicated little regiochemical preference, with the trans-3 product seemingly highly unlikely, although this is the major regioisomer in the case of the para tether (Table 4.5). Therefore, like the tethered malonic acid series, semi-empirical-derived heats of formations of the final structures do not provide any insight for the observed regioselectivity in tethered reactions shown in Table 4.1.

<table>
<thead>
<tr>
<th>Regiochemistry</th>
<th>Heat of Formation ( (\Delta H_r, \text{kcal.mol}^{-1}) )</th>
<th>Regiochemistry</th>
<th>Heat of Formation ( (\Delta H_r, \text{kcal.mol}^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-2</td>
<td>712</td>
<td>cis-2</td>
<td>717</td>
</tr>
<tr>
<td>cis-3</td>
<td>713</td>
<td>cis-3</td>
<td>717</td>
</tr>
<tr>
<td>e</td>
<td>717</td>
<td>e</td>
<td>716</td>
</tr>
<tr>
<td>trans-4</td>
<td>721</td>
<td>trans-4</td>
<td>717</td>
</tr>
<tr>
<td>trans-3</td>
<td>764</td>
<td>trans-3</td>
<td>787</td>
</tr>
</tbody>
</table>

Table 4.4: Calculated (AM1) Heats of Formation \( (\Delta H_r, \text{kcal.mol}^{-1}) \) for meta and para bisadditions of tethered bismalonic esters.
4.2.3 Influence of Tether Ring Strain on the Thermodynamics of Final Bisadducts

To investigate the extent that tethered ring strain contributes to the final heats of formation of each bisadduct, the C-C bond between the aromatic tether and benzyl carbon was broken for computational studies. In breaking this bond, there will be a relief of tether ring strain and therefore the extent of the decrease in energy can provide an indication of whether tether ring strain is a significant factor in determining the overall final energy of a compound (Figure 4.2).¹⁹¹

Table 4.5: Calculated (AM1) Heats of Formation (ΔHₚ, kcal.mol⁻¹) for meta and para bisadditions of tethered bis-N-(diphenylmethyleneglycinate) esters.

<table>
<thead>
<tr>
<th>Regiochemistry</th>
<th>Heat of Formation (ΔHₚ, kcal.mol⁻¹)</th>
<th>Regiochemistry</th>
<th>Heat of Formation (ΔHₚ, kcal.mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-2</td>
<td>1044</td>
<td>cis-2</td>
<td>1058</td>
</tr>
<tr>
<td>cis-3</td>
<td>1041</td>
<td>cis-3</td>
<td>1050</td>
</tr>
<tr>
<td>e</td>
<td>1042</td>
<td>e</td>
<td>1043</td>
</tr>
<tr>
<td>trans-4</td>
<td>1044</td>
<td>trans-4</td>
<td>1045</td>
</tr>
<tr>
<td>trans-3</td>
<td>1452</td>
<td>trans-3</td>
<td>1099</td>
</tr>
</tbody>
</table>

Figure 4.2: The contribution of ring strain can be analysed by breaking a bond that is involved in the ring in question. By comparing the heats of formation for the starting (ring-closed) and ring-opened molecules, the contribution of ring strain to the final heat of formation can be calculated. Two hydrogens replace the valencies that contributed to the broken bond. Cleaved structures have hydrogens occupying empty valencies.
Table 4.3 shows the heats of formation of both the bismalonate and bis-N-(diphenylmethyleneglycinate) esters at each regiochemical site. When comparing each regioisomer with the corresponding heat of formation of the tethered system (Table 4.4 and Table 4.5), ring strain only contributes to approximately 1-3% of the overall heat of formation, with the exception of the trans-3 regioisomers where ring strain was contributing to approximately 8-10% of the final heat of formation. Thus ring strain is not a significant factor in determining the regiochemistry.

<table>
<thead>
<tr>
<th>Cleaved Bismalonate</th>
<th>Cleaved Bis-N-(Diphenylmethyleneglycinate) Ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regiochemistry</td>
<td>Heat of Formation (ΔH_f, kcal.mol^{-1})</td>
</tr>
<tr>
<td>cis-2</td>
<td>698</td>
</tr>
<tr>
<td>cis-3</td>
<td>701</td>
</tr>
<tr>
<td>e</td>
<td>701</td>
</tr>
<tr>
<td>trans-4</td>
<td>709</td>
</tr>
<tr>
<td>trans-3</td>
<td>696</td>
</tr>
</tbody>
</table>

Table 4.6: Calculated (AM1) Heats of Formation (ΔH_f, kcal.mol^{-1}) for cleaved bismalonate and bis-N-(diphenylmethyleneglycinate) esters.

4.2.4 Coordinate Driving

One method that allows depiction of a reaction pathway for nucleophilic S_N2 reactions is coordinate driving. The coordinate driving dialogue using the Spartan©191 program allows the construction of a collection of molecules by varying a one-dimensional sequence (e.g. displacement, angle). For example, the S_N2 reaction of bromide with methyl chloride (Scheme 4.9) passes through a transition state (TS) in which both entering and leaving groups are associated with the central carbon in a trigonal bipyramidal geometry.
Here, the overall negative charge is thought of as delocalized throughout the entire molecule. Using the coordinate driving dialogue, the distance between the incoming bromide nucleophile and the electron deficient central carbon of methyl chloride is examined as a function of displacement in the reaction coordinate. A transition state is obtained when the heat of formation reaches a maximum (Figure 4.3). The transition state is also indicative of the interception of charge changing from the entering group to the leaving group.

Figure 4.3: Coordinate driving of methyl chloride as a function of the C-Br displacement. Plot of molecule versus heat of formation (blue line). Plot of electrostatic charge of the entering (Br) (pink line) and leaving (Cl) (aqua line) group versus molecule.
The location of transition states may provide information relating to the regiochemical outcome of tethered double Bingel cyclopropanations. The Bingel cyclopropanation is most likely an intermolecular nucleophilic reaction comprising the initial formation of the fulleryl anion which then undergoes an intramolecular SN2 nucleophilic attack of the electron deficient carbon of the α-haloester (Scheme 4.10).

Scheme 4.10

![Scheme 4.10](image)

Analogous to the SN2 reaction of bromide with methyl chloride (Scheme 4.9), the Bingel cyclopropanation will pass through a transition state with the carbon of the α-haloester possessing an approximate trigonal bipyramidal geometry (TS1).

![TS1](image)

Using the coordinate driving dialogue, the transition states of the second Bingel cyclopropanation for each regiochemical bond was obtained by driving the distance between the incipient fulleryl anion (C1), and the electron deficient carbon (C2) of the α-haloester moiety (Scheme 4.11).
Scheme 4.11

\[
\begin{align*}
&\text{in} \\
&\text{(TS1)-in} \\
&\text{(TS1)-out} \\
&\text{out}
\end{align*}
\]

\[R = \begin{cases} 
\text{phenyl} \\
\text{CO}_2\text{Et}, \text{N=CPh}_2
\end{cases}\]

\[R' = \text{CO}_2\text{Et}, \text{N=CPh}_2\]
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Starting from an arbitrary distance of 2.50Å, the C1-C2 distance was driven using equal intervals to a distance typical for a cyclopropyl bond of a methanofullerene (1.52Å). Since each regiochemical site of functionalisation contains two carbon atoms, the newly formed fulleryl anion was situated in or out, relative to the first site of functionalisation. Thus for each regiochemical bond, the creation of two coordinate driving dialogues was required (Scheme 4.11).

4.2.5 Comparative Analysis of Coordinate Driving Dialogues of Meta

Tethered Bismalonic Ester and Bis-N-(diphenylmethyleneglycinate) Ester

For the meta tethered bismalonic ester series, the cis-2, cis-3, e, and trans-4 bonds were subjected to coordinate driving based-studies using the AM1 theoretical model due to their calculated relative low heats for formation of the final bisaddition products (Table 4.4). Table 4.7 shows the initial energy for the C1-C2 bond distance equal to 2.5Å and the transition state energies.

These calculations revealed a preference for the cis-2 and e positions when the fulleryl anions (C1) are both located at the in positions. Looking at the reaction profile (Figure 4.4) the electrostatic charges of both entering and leaving groups for cis-2 (in) intersect at the crest of the energy profile, thus confirming the transition state at 683 kcal.mol\(^{-1}\). The most stable transition state structure (cis-2 (in)) correlates directly with the exclusive formation of the cis-2 regiosiomer. Looking at the comparative initial energies of the cis-2 (in) and e (in) revealed no significant preference for either regioisomer, indicative of both cis-2 (in) and e (in) isomers being thermodynamically favourable.
<table>
<thead>
<tr>
<th>Positional Relationship</th>
<th>Energy at C1-C2 distance of 2.5 Å</th>
<th>Energy of Transition State (kcal.mol⁻¹)</th>
<th>C1-C2 Distance at the Transition State (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-2 (in)</td>
<td>649</td>
<td>683</td>
<td>1.88</td>
</tr>
<tr>
<td>cis-2 (out)</td>
<td>661</td>
<td>695</td>
<td>1.85</td>
</tr>
<tr>
<td>cis-3 (in)</td>
<td>657</td>
<td>693</td>
<td>1.85</td>
</tr>
<tr>
<td>cis-3 (out)</td>
<td>665</td>
<td>697</td>
<td>1.85</td>
</tr>
<tr>
<td>e (in)</td>
<td>651</td>
<td>685</td>
<td>1.85</td>
</tr>
<tr>
<td>e (out)</td>
<td>666</td>
<td>694</td>
<td>1.95</td>
</tr>
<tr>
<td>trans-4 (in)</td>
<td>668</td>
<td>727</td>
<td>1.79</td>
</tr>
<tr>
<td>trans-4 (out)</td>
<td>661</td>
<td>699</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Table 4.7: Heats of Formation (kcal.mol⁻¹) and corresponding C1-C2 distances for calculated transition states obtained from AM1-derived coordinate driving for the meta tethered bismalonic ester series.

However no experimentally observed bisadduct with e regiochemistry was reported despite the energy of the e (in) transition state being very similar to cis-2 (in) (683 kcal.mol⁻¹ for cis-2 (in) versus 685 kcal.mol⁻¹ e (in)). This is an unusual observation, when considering the LUMO coefficients of the [60]fullerene sphere which are expected to influence nucleophilic additions. As described in section 6.2.1, the highest LUMO coefficients exist in the e and the cis-2 positions. Thus computational methods do not explain why the e bisadduct is not experimentally observed, despite this position being both thermodynamically and electronically favourable.
In comparison, the meta bis-N-(diphenylmethylene glycinate) ester series revealed the lowest energy transition state occurred at the cis-3 (in) position followed by the trans-4 (out) position (Table 4.8). Experimentally observed regiochemistry for the meta bis-N-(diphenylmethylene glycinate) ester series revealed the trans-4 and cis-3 as the major and minor regioisomers, respectively (Table 4.1). Although the e (out) position has a comparable transition state energy to the cis-3 (in) and trans-4 (out) positions, the e (out) position has a high initial energy relative to these other positions, making such a regiochemistry unfavourable, typified by a lack of this experimentally observed regiochemistry (Table 4.1). In contrast the initial energies of the cis-3 (in) and trans-4 (out) structures are significantly lower than that of e (out), and thus these regioisomers
are more favourable. This is reflected by their experimentally observed regiochemistry (Table 4.1).

<table>
<thead>
<tr>
<th>Positional Relationship</th>
<th>Energy at C1-C2 distance of 2.5 Å</th>
<th>Energy of Transition State (kcal.mol⁻¹)</th>
<th>C1-C2 Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-2 (in)</td>
<td>998</td>
<td>1030</td>
<td>1.96</td>
</tr>
<tr>
<td>cis-2 (out)</td>
<td>1006</td>
<td>1041</td>
<td>1.96</td>
</tr>
<tr>
<td>cis-3 (in)</td>
<td>966</td>
<td>1018</td>
<td>1.85</td>
</tr>
<tr>
<td>cis-3 (out)</td>
<td>1001</td>
<td>1034</td>
<td>1.84</td>
</tr>
<tr>
<td>e (in)</td>
<td>993</td>
<td>1029</td>
<td>1.85</td>
</tr>
<tr>
<td>e (out)</td>
<td>997</td>
<td>1021</td>
<td>1.95</td>
</tr>
<tr>
<td>trans-4 (in)</td>
<td>1001</td>
<td>1026</td>
<td>1.84</td>
</tr>
<tr>
<td>trans-4 (out)</td>
<td>966</td>
<td>1023</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Table 4.8: Heats of Formation (kcal.mol⁻¹) and corresponding C1-C2 distances for calculated transition states obtained from AM1-derived coordinate driving for the meta tethered bis-N-(diphenylmethyleneglycinate) ester series.

The cis-2 (in) position was shown to be the most stable transition state for the meta bismalonic ester series. This was consistent with the experimentally observed findings (Table 4.1). This result is also reflected in the observation of the highest LUMO coefficients occurring at the cis-2 position for monoadducts (Figure 4.1c). The corresponding cis-2 (in) position for the meta bis-N-(diphenylmethyleneglycinate) ester series revealed a transition structure that was 7 kcal.mol⁻¹ higher in energy as well as an initial energy 32 kcal.mol⁻¹ higher in energy. The most stable transition structures, cis-3 (in) and trans-4 (out) are consistent with the experimentally observed trans-4 (major) and cis-3 (minor) bisadducts. However, at these regiochemical sites, the LUMO and LUMO+1 coefficients are small; thus if N-(diphenylmethyleneglycinate) esters are proceeding via nucleophilic addition, the electronics of the [60]fullerene sphere is not significantly contributing to the regiochemical outcome. Conversely, the HOMO-1

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frontier orbitals coefficients are high for the trans-4 and cis-3 positions. HOMO coefficients influence the product distribution of electrophilic additions and thus cyclopropanation of \(N\)-(diphenylmethyleneglycinate) esters may proceed via the [2+1] carbene addition as shown in Scheme 4.1 since electrophiles, such as carbenes are influence by HOMO coefficients. Another possible explanation for the regiochemical differences between meta bismalonic ester and meta bis-\(N\)-(diphenylmethyleneglycinate) ester could be the steric hindrance of the aromatic rings of the diphenyl imine moiety. This can be reflected in the high transition state energies of the cis-2 position coordinate driving dialogues for the meta bis-\(N\)-(diphenylmethyleneglycinate) ester. Thus, in summary, it is not clear why the tethered bis-\(N\)-(diphenylmethyleneglycinate) diester system shows regiochemical preference for the trans-4 and cis-3 positions if the system proceeded via a nucleophilic addition mechanism. The validity of the theoretical model itself may well be questionable and a more reliable ab initio molecular orbital based model should be employed.

4.2.6 Comparitive Analysis of Coordinate Driving Dialogues of Para Tethered Bismalonic Ester and Bis-N-(diphenylmethyleneglycinate) Ester

For the \textit{para} tethered bismalonic and bis-\(N\)-(diphenylmethyleneglycinate) diester series, the cis-3, e, \textit{trans}-4 and \textit{trans}-3 bonds were subjected to coordinate driving based-studies due to their calculated relative low heats of formation for the final bisaddition products (Table 4.4). Table 4.9 shows the initial energy for the C1-C2 bond distance of 2.5\(Å\) and transition state energies for each bond of the \textit{para} tethered bismalonic ester regioisomers.
There is a preference for the $e$ and trans-4 regioisomers when the fulleryl anions (C1) are both located at the in positions. Both of these energetically favourable structures correlate directly with the experimentally observed regioisomers (98) (trans-4) and (99) (e). Looking at the comparative initial energies of the cis-3 (in), $e$ (in) and trans-4 (in) intermediates revealed no significant energetic preference for either regioisomer, however the transition state of cis-3 (in) is 7 kcal.mol$^{-1}$ higher than that for trans-4 (in) which could explain why no experimentally observed cis-3 regioisomer is formed.

<table>
<thead>
<tr>
<th>Positional Relationship</th>
<th>Energy at C1-C2 distance of 2.5 Å</th>
<th>Energy of Transition State (kcal.mol$^{-1}$)</th>
<th>C1-C2 Distance at the Transition State (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-3 (in)</td>
<td>653</td>
<td>694</td>
<td>1.85</td>
</tr>
<tr>
<td>cis-3 (out)</td>
<td>677</td>
<td>704</td>
<td>1.84</td>
</tr>
<tr>
<td>$e$ (in)</td>
<td>648</td>
<td>682</td>
<td>1.85</td>
</tr>
<tr>
<td>$e$ (out)</td>
<td>669</td>
<td>696</td>
<td>1.96</td>
</tr>
<tr>
<td>trans-4 (in)</td>
<td>654</td>
<td>687</td>
<td>1.85</td>
</tr>
<tr>
<td>trans-4 (out)</td>
<td>659</td>
<td>696</td>
<td>1.85</td>
</tr>
<tr>
<td>trans-3 (in)</td>
<td>729</td>
<td>754</td>
<td>1.74</td>
</tr>
<tr>
<td>trans-3 (out)</td>
<td>690</td>
<td>753</td>
<td>2.07</td>
</tr>
</tbody>
</table>

Table 4.9: Heats of Formation (kcal.mol$^{-1}$) and corresponding C1-C2 distances for calculated transition states obtained from AM1-derived coordinate driving for the para tethered bismalonic ester series.

When considering the LUMO coefficients of the [60]fullerene sphere, LUMO coefficients are quite small in the cis-3 positions while being high in the $e$ and trans-4 positions (Figure 4.1). Thus in combination with coordinate driving studies and studying the electronics of [60]fullerene monoadducts, the experimentally observed regiochemistry of the para series tethered bismalonate correlates directly with the
computational studies. However, in the corresponding meta series of the tethered bismalonate system, no explanation for the lack of experimentally observed e regioisomer is provided (Table 4.6).

In comparison, the para bis-N-(diphenylmethyleneglycinate) ester series reveal the lowest initial energy as well as transition state energy occurring at the trans-4 (in) position followed by the trans-3 (out) position (Table 4.10).

<table>
<thead>
<tr>
<th>Positional Relationship</th>
<th>Energy at C1-C2 distance of 2.5 Å (kcal.mol⁻¹)</th>
<th>Energy of Transition State (kcal.mol⁻¹)</th>
<th>C1-C2 Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-3 (in)</td>
<td>1001</td>
<td>1031</td>
<td>1.85</td>
</tr>
<tr>
<td>cis-3(out)</td>
<td>1021</td>
<td>1048</td>
<td>1.96</td>
</tr>
<tr>
<td>e (in)</td>
<td>992</td>
<td>1033</td>
<td>1.85</td>
</tr>
<tr>
<td>e (out)</td>
<td>1001</td>
<td>1024</td>
<td>1.96</td>
</tr>
<tr>
<td>trans-4 (in)</td>
<td>997</td>
<td>1030</td>
<td>1.85</td>
</tr>
<tr>
<td>trans-4 (out)</td>
<td>990</td>
<td>1020</td>
<td>1.85</td>
</tr>
<tr>
<td>trans-3 (in)</td>
<td>1066</td>
<td>1092</td>
<td>1.85</td>
</tr>
<tr>
<td>trans-3 (out)</td>
<td>984</td>
<td>1023</td>
<td>1.78</td>
</tr>
</tbody>
</table>

Table 4.10: Heats of Formation (kcal.mol⁻¹) and corresponding C1-C2 distances for calculated transition states obtained from AM1-derived coordinate driving for the para tethered bis-N-(diphenylmethyleneglycinate) ester series.

Experimentally observed regiochemistry for the para bis-N-(diphenylmethyleneglycinate) ester series reveal (175) (trans-3) and (176) (trans-4) as major and minor regioisomers respectively (Table 4.1). Thus in the para bis-N-(diphenylmethyleneglycinate) ester series, the computationally favourable regioisomers (Table 4.10) correlate directly with the experimentally observed regioisomers (Table 4.1).

Analysis of the electronics at the trans-3 site revealed significant LUMO coefficients (Figure 4.1) typical for a nucleophilic-based mechanism. Corresponding
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HOMO coefficients at the trans-3 site are negligible. Such a result is contradictory to the meta bis-N-(diphenylmethyleneglycinate) ester series where the regiochemical bonds of the observed bisadducts revealed high HOMO coefficients, giving evidence for an electrophilic-based mechanism. Therefore, in conclusion coordinate driving dialogues provide evidence for the observed regiochemistry of tethered bismalonate and the para series of bis-N-(diphenylmethyleneglycinate) [60]fullerene derivatives, however the coordinate driving dialogues provided no insight into the observed regiochemistry of the meta series of the tethered bis-N-(diphenylmethyleneglycinate) ester. Since the mechanism of tethered bis-N-(diphenylmethyleneglycinate) ester addition to [60]fullerene is not known and the validity of the theoretical model itself is questionable, a carbene-derived transition state computational study using a more reliable ab initio molecular orbital based model should be employed, however this is beyond the scope of this thesis.

4.3. Reactivity of Malonate versus N-(Diphenylmethyleneglycinate) Ester

To gain insight into the reactivity of the malonate system versus the N-(diphenylmethyleneglycinate) system, the tethered mixed malonate N-(diphenylmethyleneglycinate) ester (199) was synthesised according to Scheme 4.12. Monoesterification of 1,3-benzenedimethanol using methyl malonyl chloride and triethylamine yielded (196) in 93% yield. DCC-mediated esterification of (196) afforded the mixed malonic-glycine ester (197). Deprotection of the N-tert-butoxycarbonyl (Boc) group using TFA afforded the corresponding ammonium trifluoroacetate salt (198). Transimination was achieved by treating a DCM/MeCN suspension of the ammonium trifluoroacetate salts with benzophenone imine for 24 hr. Washing the organic layer with brine and concentration in vacuo afforded the
transiminated ester (199) in 44% yield. The aromatic region of the $^1$H NMR of (199) comprised of protons corresponding to the diphenyl imine protons (ortho, $\delta$ 7.81, 4H, d, $J = 7.2$ Hz; meta, $\delta$ 7.48, 4H, t, $J = 7.2$ Hz; $\delta$ 7.44, m), as well as the benzyl protons ($\delta$ 5.19, s, 2H; $\delta$ 5.17, s, 2H) and methylene resonances corresponding to methylene protons between the malonic ester ($\delta$ 3.43, s, 2H) and $N$-(diphenylmethyleglycinate) ester ($\delta$ 4.26, s, 2H), respectively.

Compound (199) was subjected to double Bingel reaction conditions in the presence of [60]fullerene to afford no discernable product. However when (199) was subjected to mono-Bingel reaction conditions in the presence of [60]fullerene, the monocyclopropanated product (200) was obtained exclusively in 19% yield after flash column chromatography using DCM as eluent. The corresponding cyclopropanated adduct at the malonic ester site (201) was not observed. The $^1$H NMR spectra of (200) revealed a loss of the methylene resonance ($\delta$ 4.26) associated with the $N$-(diphenylmethyleglycinate) ester of (199) as a result of cyclopropanation (Figure 4.5). The methylene resonance associated with the acidic methylene protons between the malonic ester was observed at $\delta$ 3.42. The aromatic protons associated with the diphenyl imine moiety exhibited the characteristic downfield shift ($\delta$ 8.08, $\delta$ 7.51, $\delta$ 7.39) of a mono-cyclopropanated [60]fullerene derivative.
Scheme 4.12

\[
\begin{align*}
\text{HO-} & \text{OH} \xrightarrow{\text{Cl, NEt}_3, \text{THF}} \text{MeO} \xrightarrow{\text{O, OMe}} \text{MeO} \xrightarrow{\text{O, OMe}} \text{Cl} \\
& \quad 88\%
\end{align*}
\]

\[
\begin{align*}
\text{OMe MeO'} \xrightarrow{\text{BocHN-NH, DMAP(cat.), DCC (1.1 equiv.), THF}} \text{DMAP(cat.), DCC (1.1 equiv.), THF} \\
& \quad 19\%
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \xrightarrow{\text{O, OMe}} \text{O=O} \xrightarrow{\text{PhC=NH, DCM}} \text{MeO} \xrightarrow{\text{O, OMe}} \text{O=O} \\
& \quad 44\%
\end{align*}
\]

\[
\begin{align*}
\text{OMe MeO'} \xrightarrow{TFA} \text{OMe MeO'} \\
& \quad (197) \quad R = \text{Boc, 64\%} \\
& \quad (198) \quad R = \text{H}_2\text{CO}_3\text{CO}_2, 60\%
\end{align*}
\]

\[
\begin{align*}
\text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.}) \xrightarrow{\text{Ph=O, C=O, OMe}} \text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.}) \\
& \quad 19\%
\end{align*}
\]

\[
\begin{align*}
\text{Ph=O, C=O, OMe} \xrightarrow{\text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.})} \text{Ph=O, C=O, OMe} \\
& \quad \text{unknown structure}
\end{align*}
\]

\[
\begin{align*}
\text{Ph=O, C=O, OMe} \xrightarrow{\text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.})} \text{Ph=O, C=O, OMe} \\
& \quad \text{unknown structure}
\end{align*}
\]

\[
\begin{align*}
\text{Ph=O, C=O, OMe} \xrightarrow{\text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.})} \text{Ph=O, C=O, OMe} \\
& \quad \text{unknown structure}
\end{align*}
\]

\[
\begin{align*}
\text{Ph=O, C=O, OMe} \xrightarrow{\text{C}_{60}, \text{DBU (2.1 equiv.), CBr}_4 (1 \text{ equiv.})} \text{Ph=O, C=O, OMe} \\
& \quad \text{unknown structure}
\end{align*}
\]
Chapter 4: Computational investigations

Figure 4.5: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of (200). Resonance at $\delta$ 5.27 corresponds to DCM.

The $^{13}$C NMR spectrum of (200) (Figure 4.6) comprised of 32 fullerene resonances with two distinct half-intensity $^{13}$C resonances, characteristic of $C_5$ symmetrical [60]fullerene derivative. A single fulleryl $sp^3$ resonance ($\delta$ 82.9) and one cyclopropane bridgehead carbon ($\delta$ 95.9) were observed, indicative of (200) possessing a single plane of symmetry. MALDI mass spectrometry exhibited a molecular ion at $m/z$ 1077 in addition to $m/z$ 720 associated with free [60]fullerene.
Such exclusive formation of Bingel cyclopropanation at the site between the $N$-(diphenylmethyleneglycinate) ester is indicative of the increased reactivity of this site over the corresponding methylene malonic ester site. This may be due to the enhanced acidity of the methylene protons associated with the iminoglycine moiety. In an effort to investigate if regioselectivity arises from the second reactive group, a second Bingel cyclopropanation was attempted on compound (200). On the basis of the observation of the cis-2 regioisomer (97) being formed from (94) and [60]fullerene under double Bingel cyclopropanation conditions, it was assumed that compound (200) when subjected to Bingel cyclopropanation conditions would afford the corresponding cis-2 bisadduct (201).
The resultant $^1$H NMR spectrum (Figure 4.7) of the Bingel cyclopropanation of (200) after column chromatography revealed three singlets at $\delta$ 3.97 (3H), $\delta$ 5.30 (2H) and $\delta$ 5.43 (2H) corresponding to a methyl ester and two benzyl peaks respectively.

![NMR Spectrum](image)

**Figure 4.7: $^1$H NMR (300 MHz, CDCl$_3$) spectrum of the unknown product according to Scheme 4.12.**

The aromatic region exhibited virtually identical features to that of compound (200) i.e. (ortho, $\delta$ 7.92, 4H, d, $J = 7.2$ Hz; meta, $\delta$ 7.40, 4H, t, $J = 7.2$ Hz; $\delta$ 7.31, m), indicative
of the diphenylimine moiety in close vicinity with the [60]fullerene sphere. The $^1$H NMR spectrum shown in Figure 4.7 does not exhibit features expected for a compound such as (201), such as diastereotopic benzyl protons that would arise from macrocyclisation. This feature has been observed in both tethered bismalonic (96-99)$^{117}$ and bis-$N$-(diphenylmethylene glycinate) esters (173-176) (section 3.3.2).

The $^{13}$C NMR spectrum of the Bingel cyclopropanation product of (200) (Figure 4.8) revealed a $C_5$-symmetrical product comprising of 29 fulleryl $sp^2$ resonances, two of which were clearly observed half-intensity resonances (shown by red circles in Figure 4.8b). An upfield shift of two of the $^{13}$C resonances in the carbonyl region from $\delta$ 166.1 and $\delta$ 166.4 to $\delta$ 163.4 and and $\delta$ 163.6 respectively may indicate differing chemical environment as a consequence of functionalisation within close vicinity to these carbonyl resonances. The $^{13}$C NMR in the $\delta$ 60-100 region reveals a resonance at $\delta$ 95.8 indicative of the retention of the cyclopropane bridgehead carbon attached to the diphenylimine moiety (inset, Figure 4.8a). Two resonances at $\delta$ 81.6 and $\delta$ 82.4 are indicative of fulleryl $sp^3$ resonances. The corresponding region of the $^{13}$C NMR spectrum of (200) revealed a single fulleryl $sp^3$ resonance at $\delta$ 82.9 (Figure 4.6) thus a second chemical functionalisation of the [60]fullerene core may have occurred. A resonance at $\delta$ 70.9 is indicative of a bridgehead carbon attached to a malonic ester$^{4,10,12,13,180}$ and thus in combination with the presence of a second fulleryl $sp^3$ resonance, there is evidence of a second Bingel cyclopropanation occurring. However structure (201) is again ruled out as a possible product candidate by the presence of a symmetry plane. Compound (201) would not possess a plane of symmetry and would be expected to observe 56 fulleryl $sp^2$ and four $sp^3$ carbons respectively.
Figure 4.8: $^{13}$C NMR (75 MHz, CDCl$_3$) spectrum of the unknown product according to Scheme 4.12. (a) Full spectrum with an expansion of the δ 60-100 region. (b) Expansion of the fulleryl sp$^2$ region showing half-intensity fulleryl sp$^2$ carbon (red circles).
Another possible structure would be the dimer (202); however for the formation of such a compound, a significant amount of [60]fullerene would have to be present. $^{13}$C NMR analysis of the starting material (200) shown in Figure 4.6 shows no large $^{13}$C resonance at δ 143 corresponding to free [60]fullerene thus the formation of this compound is highly unlikely from a synthetic point of view.

Finally, a third, more synthetically feasible structure is compound (203). Such a compound could form via a mechanism shown in Scheme 4.7 where the α-halocarbanion attacks the electrophilic site of the α-halomalonic ester, followed by elimination of hydrogen bromide to form the dimer (203).

Indeed the $^1$H NMR satisfies compound (203); however the $^{13}$C NMR reveals a $^{13}$C resonance at δ 70.9 which is typical for a methanofullerene bridgehead carbon of a malonic ester methanofullerene. In addition to this, the fulleryl sp$^3$ carbons exist at δ 80.9 and δ 82.3 which also do not satisfy the dimer (203). Therefore in conclusion, no definative structure for the second Bingel cyclopropanation of (200) could be assigned.
4.4. Concluding Remarks

A series of computational calculations were conducted in an effort to provide insight in the differences in the experimentally observed regiochemistry of tethered bismalonates and bis-N-(diphenylmethyleneglycinate) ester. Although no definitive insights could be obtained into the regiochemical differences in these two systems, synthetically it was demonstrated that the reactivity of the N-(diphenylmethyleneglycinate) ester is significantly higher than malonic esters under Bingel cyclopropanation conditions. Such an observation can provide access to a range of [60]fullerene derivatives that have the ability to be selectively cyclopropanated under conventional Bingel conditions. In conclusion, a more comprehensive computational and mechanistic study of the possible reactive intermediates (e.g. carbene) of the tethered bis-N-(diphenylmethyleneglycinate) ester under Bingel reaction conditions is required in an effort to determine the differences in regiochemistry.
Chapter 5:
Double Reductive Ring Opening of Bis-N-(Diphenylmethylene)glycinate [60]Fullerene Derivatives.
This chapter will discuss the results of the reductive ring-opening reactions of a series of bisadducts (173)-(175), (178) that were described in Chapter 3 and two new non-symmetrically tethered bismethanofullerenes whose synthesis is also described in this chapter.

5.1. Possible Structures Formed from the Double Reductive Ring Opening

Originally it was envisaged that the double reductive ring-opening reaction of the tethered bisadducts (173)-(175) would yield a double reductive ring-opened product as illustrated in the general structure in Figure 5.1.

The formation of a doubly reductive ring-opened product like that shown in Figure 5.1 could, in theory, produce a range of isomeric products due to the stereogenicity of the chiral Cα/Cα carbons as well as the positioning of the fulleryl protons Hx/Hx with respect to each other. As an example, Figure 5.2 illustrates the possible isomeric products that would arise from the double ring opening of (173), with respect to the relative positioning of the fullerene protons. The nomenclature devised to accommodate such structures is based on the geometric (in-out) isomerism117 introduced in section 3.1.2. Each of these ring-opened compounds can also differ in the stereochemistry at both stereogenic Cα/Cα atoms, as well as the positioning of the fulleryl protons (Hx/Hx) relative to the tethered substituent (Figure 5.2).
Chapter 5: Double Reductive Ring Opening

Stereogenicity of $C_\alpha$ Fulleryl proton $H$-in with respect to tether

Figure 5.1: Generalised structure of a double reductive ring opened bisadduct showing the possible types of isomerism present.

If both fulleryl hydrogens ($H_x / H_{x'}$) exist at a maximum distance from each other (determined by the number of bonds from one fulleryl hydrogen to the other), the ring-opened bisadduct (204) is designated the $H,H$-out configuration. Conversely, if both fulleryl hydrogens exist at a minimal distance relative to each other, the resulting bisadduct (205) is designated the $H,H$-in configuration (determined by the number of bonds between the two fulleryl protons).

The formation of a third grouping is also theoretically possible. This group of structures, named $H,H$-in-out (206) and $H,H$-out-in (207), would have one fulleryl hydrogen facing away from the tethered substituent, while the remaining fulleryl hydrogen exists between the tethered functionalised sites on the carbon sphere and *visa versa*. 
Figure 5.2: Possible structures from the double reductive ring-opened reaction of (173).
5.1.1 Double Reductive Ring Opening

In a typical reaction, a DCM solution of (173), (174) or (175) was treated at 0°C with boron trifluoride diethyl etherate (5.0 equiv) for 30 min followed by the addition of dry MeCN and solid sodium cyanoborohydride (10 equiv). After 30 min, the reaction mixture was quenched with distilled water and extracted in DCM. Purification of the crude reaction mixture by flash column chromatography (90:10; DCM/petroleum spirit) afforded the 1-substituted-1,2-dihydro-[60]fullerenes (208) in 42%, and 44% yield from (173) and (174), respectively, and (209) in 31% yield from (175) (Table 5.1). The formation of free [60]fullerene was thought to have been accompanied by the formation of the reduced addend (210)-(211). A $^1$H NMR of the crude reaction mixtures were not undertaken however due to the small scale of the reactions and flash chromatography did not yield any reduced addend (210) or (211).

Scheme 5.1
Chapter 5: Double Reductive Ring Opening

<table>
<thead>
<tr>
<th>Starting Compound</th>
<th>Product Yields (%)</th>
<th>Reductive Ring-Opened Product</th>
<th>[60] Fullerene</th>
</tr>
</thead>
<tbody>
<tr>
<td>(173)</td>
<td>(208)</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>(174)</td>
<td>(208)</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>(175)</td>
<td>(209)</td>
<td>37</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 5.1: Yields of the double ring opening products ((208)-(209)] from the ring closed tethered bisadducts [(173)-(175)].

5.1.2 Spectroscopic Analysis of (208)

UV/vis spectrum (Figure 5.3) of (208) revealed a distinct absorbances at 430 nm, 640 nm and 705 nm that was also observed for the ring-opened monoaddition product (133).

![UV/vis spectrum](image)

**Figure 5.3:** UV/vis spectrum of (208) in DCM showing characteristic absorbances at 430, 640 and 705nm.
Analysis of the $^1$H NMR spectrum of (208) revealed a solitary major singlet resonance corresponding to a single fulleryl proton (H*) at $\delta$ 6.84 (Figure 5.4a). The presence a weak intensity resonance at $\delta$ 6.94 may correspond to the presence of a fulleryl proton of a minor isomeric ring opened product such as the 1,4-isomer (1:40; minor:major regioisomeric ratio). An upfield shift of the aromatic protons of the benzhydryl moiety was consistent with the chemical transformation of the imine to the secondary amino functionality (Figure 5.5).

The addend region of (208) revealed two doublets at $\delta$ 5.41 and $\delta$ 5.24 ($J = 11.9$ Hz) corresponding to the diastereotopic benzylic protons (H/H'). The benzylic protons (H) resonate as a singlet of integration of two protons at $\delta$ 5.08, whereas the singlet of integration of two protons at $\delta$ 3.40 was identified as the methylene protons (H). A singlet resonance of integration of one proton arising at $\delta$ 4.84 corresponds to the benzhydryl resonance (H). A three proton coupled spin system was identified as $H_\alpha$ ($\delta$ 4.97, d, $J = 12.3$ Hz), $H_\beta$ ($\delta$ 5.24, d, $J = 2.5$ Hz), and NH ($\delta$ 3.67, dd, $J = 12.3$, 2.5 Hz). The corresponding double reductive ring-opened bisadducts shown in Figure 5.2 were ruled out as possible structures, due to the presence of the three singlet resonances ($H_\alpha$, $H_\beta$, and H), corresponding to the formation of the mono ring-opened product (208). These deviate from the expected two fulleryl proton resonances that would be observed for the ring-opened bisadducts (204)-(207).
Figure 5.4: $^1$H NMR (600 MHz, CDCl$_3$/CS$_2$; 80:20) of (208) with expansions of (a) the aromatic region and (b) region corresponding to the reduced addend. The NH resonance is not shown. X denotes DCM impurity.
Figure 5.5: $^1$H NMR (400 MHz, CDCl$_3$/CS$_2$; 80:20) spectrum of showing the aromatic regions of (a) ring closed (173) and (b) ring opened (208).

Consistent with the $^{13}$C NMR of the corresponding ring-opened monoadduct (208) (section 2.4), the $^{13}$C NMR spectrum of the fulleryl sp$^2$ region of (133) revealed a structure lacking a plane of symmetry (Figure 5.6). This was consistent with the fulleryl sp$^2$ carbons of the [60]fullerene sphere being diastereotopic with respect to the newly formed chiral centre. Such observations were consistent with the reductive ring-opened product (133) (see section 2.4 for details). A single set of fulleryl sp$^3$ resonances at C$_x$ (δ 58.9), and C' (δ 67.3) were observed in addition to resonances corresponding to the addend C$_a$ (δ 70.4), C$_b$ (δ 66.3) C$_d$ (δ 67.8), C$_e$ (δ 66.2), C$_f$ (δ 47.5) and C$_y$ (δ 66.5). If the reductive ring-opening of (173) afforded any of the ring-opened bisadduct structures
shown in Figure 5.2, then two sets of fulleryl sp³ carbons would be expected. Thus, spectroscopic analysis reveals the formation of the ring-opened monoadduct via a chemical retro-Bingel-type reaction.\(^{149,192,193}\) Similar reductive cleavages of both malonate-derived mono- and bis-methanofullerenes have been observed both chemically\(^{193}\) and electrochemically\(^{149,192}\) as shown in Scheme 5.2.

(a)

![Image of 13C NMR spectrum](image)

(b)

![Image of expanded NMR spectrum](image)

**Figure 5.6:** \(^{13}\)C NMR (150 MHz, CDCl\(_3\)/CS\(_2\); 80:20) of (208) with expansions of (a) fulleryl sp² region and (b) region corresponding to the tethered addend.
Scheme 5.2: The retro-Bingel reaction can cleave methanofullerene cyclopropanes either electrochemically by a two-electron controlled potential electrolysis or chemically using a magnesium-mercury amalgam.

5.1.3 2D NMR Experiments on (208)

2D NMR experiments were undertaken for unambiguous confirmation of the structure of compound (208). A NOESY (700ms) experiment on (208) at 600 MHz revealed an intense nOe from Hx to Ha accompanied by a slightly weaker nOe from Hx to NH (Figure 5.7). The presence of such nOe’s is indicative of the close spatial arrangement of Ha with respect to Hx and NH for (208).

The HSQC experiment enabled the identification of aromatic, Cα, Cβ, Cζ and benzyl (C66') resonances by the observation of $^1J_{HC}$ couplings (Figure 5.8). The $^{13}$C NMR resonances corresponding to the diastereotopic benzyl carbons, C66' appeared at δ 67.3, ($^1J_{HC} = 132$ Hz), and the carbons corresponding to Cα at δ 70.4 ($^1J_{HC} = 128$ Hz), and Cβ at δ 66.3 ($^1J_{HC} = 120$ Hz) for (208). The carbon resonance, Cx, shown in Figure 5.8, was located at δ 58.9 ($^1J_{HC} = 143$ Hz) for (208).
Figure 5.7: NOESY (700ms, 600MHz, CDCl₃/CS₂ 6:4) spectrum of (208) showing nOe's from Hₓ to Hα and Hₓ to NH.
Figure 5.8: HSQC (600 MHz, CDCl₃:CS₂; 1:1) spectrum of the ring opened product (208) revealing ¹J_HC couplings for Hₓ/Cₓ, Hᵧ/Cᵧ, and Hₛ,ₜ/Cₛ.

The identification of the C₇ (δ 68.1) resonance was confirmed by a ²J_HC coupling from both Hₓ (δ 6.84) and Hₐ (δ 4.97), consistent with the corresponding HMBC correlation of the 1,2-addition monoadduct (133) (Figure 2.16). The one fulleryl proton resonance allowed for correlations into the fulleryl sp² region which were identical to that observed for (133) (Figure 2.17). This is illustrated in Figure 5.9, which shows an expansion of the correlations between Hₓ and the fulleryl sp² region of (208). The "upfield-downfield" effect described in Chapter 2 is again observed in (208) with fulleryl sp² carbons alpha to the functionalisation site, but on the same hemisphere as Hₓ (red circles in Figure 2.18) being observed the most downfield. The more upfield pair of this cluster of four carbons was assigned to C₆ or C₉ at δ 153.07 or δ 152.38 respectively. These assignments were identified by a ³J_HC of 6.0 Hz. These carbons
were assigned as being alpha to the functionalisation site, but in the same hemisphere as the addend (green circles in Figure 2.18).

![Figure 5.9: 2Hz Optimised HMBC (600 MHz, CDCl₃:CS₂; 1:1) spectrum of the ring opened product (208) revealing correlations from the fulleryl proton (Hₓ) into the fullerene sp² region. See the corresponding Schlegel diagram in Figure 2.18.](image)

5.1.4 Possible Mechanisms for the Double Reductive Ring-Opening Reactions

In theory, the double reductive ring opened product (208) could arise from the intermediates (A), (B) or (C) shown in Scheme 5.3. The driving force for the mono-elimination of the tether from these intermediates is thought to be the increase in conjugation in the [60]fullerene ring system of the final product.
Scheme 5.3: Possible intermediates that could arise from the double reductive ring-opening of (173).

The rate of monoelimination (akin to a retro-Bingel reaction) appears to be much faster than the rate of elimination of the entire addend as determined by the relative yields of recovered [60]fullerene and (208) after flash chromatography.

5.1.5 Double Reductive Ring Opening of (174) and (175)

The product of the double reductive ring opening of (174) (Scheme 5.4) using reaction conditions described in section 5.1 afforded, after flash column chromatography, a brown band with identical polarity as (208) according to analytical TLC. The corresponding $^1$H NMR and $^{13}$C NMR spectrum of the double reductive ring-opening of (174) revealed the formation of (208); i.e. an identical compound was formed to that from the double reductive ring-opening of (173).
Scheme 5.4

\[
\text{Scheme 5.5}
\]

\[R = \text{Ph}
\]

\[\text{1}^1\text{H NMR and }^{13}\text{C NMR analysis of the double reductive ring-opening of (175) (Scheme 5.5) revealed an almost identical spectrum to (208). The aromatic region in both the }^1\text{H NMR and }^{13}\text{C NMR spectrum differed slightly due to differences in the nature of the aromatic tether.}
\]

The UV/vis spectra of the ring opened compound (209) (Figure 5.10) revealed a characteristic absorbance at 430 nm, in addition to absorbances at 640 nm and 705 nm consistent with (208) (Figure 5.3).
5.2. Non-symmetrical Tethered Additions: Efforts Directed towards the Formation of Chemically Non-equivalent Fulleryl Protons

Initially it was envisaged that by breaking the symmetry of the [60]fullerene bis-adducts, the ring-opened products shown in Figure 5.1 would be more readily characterised. Breaking the symmetry of the tethered system shown in Figure 5.11 is possible by substitution at three possible positions.

Figure 5.10: UV/vis spectra of ring opened compound (209) in DCM.
Figure 5.11: Potential sites (identified by black arrows) on a bis N-(diphenylmethyleneglycinate) ester for the induction of non-symmetry.

This could be achieved by adding a substituent to the central aromatic ring, or to one of the diphenyl imine aromatic rings, or by substitution of one of the benzyl protons with another functionality. From a synthetic point of view, starting with a non-symmetrical aromatic diol would be the most direct strategy. The 1,3-naphthyldimethanol diester (219) was proposed as a feasible tether that would satisfy the non-symmetrical criteria (Scheme 5.6).

The non-symmetrical bis-N-(diphenylmethyleneglycinate) tether (219) was synthesised according to the procedure illustrated in Scheme 5.6. Dibromination of 1,3-dimethylnaphthalene (213), followed by nucleophilic displacement using sodium acetate yielded the diacetyloxylated derivative (215) in 48% yield. Deprotection of the acetyl ester using potassium carbonate in methanol afforded the known 1,3-naphthalenedimethanol (216) in 43% yield. This procedure was an improvement on that published in the procedure. DCC-mediated esterification of 1,3-naphthalenedimethanol with N-tert-butoxycarbonylglycine, afforded the biglycine ester (217). Deprotection of the N-tert-butoxycarbonyl group using TFA afforded the corresponding ammonium trifluoroacetate salt (218). Transimination was achieved by
treating a DCM/MeCN (1:1) suspension of the ammonium trifluoroacetate salts with benzophenone imine for 24 hr. Washing the organic layer with brine and concentration in vacuo afforded the transiminated diester (219) in 51% yield as a pale yellow oil.

Scheme 5.6

(i) NBS, AIBN, \( \text{hv} \); (ii) \( \text{NaOAc}, \text{HMPA/DMF} \); (iii) \( \text{K}_2\text{CO}_3/\text{MeOH} \); (iv) \( N\text{-tert-butoxycarbonylglycine (2 equiv.), DMAP (0.1 equiv.), DCC (2.2 equiv.)} \); (v) TFA; (vi) \( \text{Ph}_2\text{C}=\text{NH (2 equiv.), DCM/MeCN} \); (vii) DBU (4.5 equiv.), CBr\(_4\) (2 equiv.), C\(_6\)H\(_5\)Cl

(iii) \( \text{Pr} \cdot \text{Ph}, \text{Pr} \), \( \text{Ph} \cdot \text{RHiOC}0 \cdot \text{J}^\text{NHR} \)

(213)  \( \rightarrow \)  (214)  \( \rightarrow \)  (215)  \( \rightarrow \)  (216)  

(217). \( R = \text{'Boc.} \) 82%

(218). \( R = \text{H}_2\text{C}^\text{F}_3\text{CO}_2^\text{O} \) 70%

(220), \( \text{trans-4} \) 9%

(221), \( \text{cis-3} \) 5%
The $^1$H NMR spectrum of (219) (Figure 5.12) comprised of two singlet resonances at $\delta 4.25$ (2H) and $\delta 4.28$ (2H) corresponding to the acidic methylene protons. The benzyl resonances were located at $\delta 5.32$ (s, 2H) and $\delta 5.62$ (s, 2H) respectively. In addition to these aliphatic resonances, aromatic resonances corresponding to the naphthyl tether and resonances corresponding to the diphenyl imine protons were present in the $\delta 7.0$-7.9 region.

The double Bingel cyclopropanation reaction of (219) with [60]fullerene was attempted using conditions according to section 3.3.2 (Scheme 3.5). The reaction mixture was stirred at RT, and monitored by analytical TLC. Purification required elution through two silica gel columns with DCM:petroleum spirit (90:10), to afford the two regioisomers (220) and (221) in 9% and 5% yields, respectively.

![Figure 5.12: $^1$H NMR (400 MHz, CDCl$_3$) spectrum of (219).](image-url)
The MALDI-TOF spectrum of both (220) and (221) displayed a molecular ion at 
$m/z$ 1348 and fulleryl anion at $m/z$ 720. The $^1$H NMR spectra of (220) and (221)
revealed the loss of methylene resonances associated with the $N$-(diphenylmethylene
glycinate) ester (219) as a result of cyclopropanation (Figure 5.13). The non-symmetrical
nature of the naphthyl tether induced the four benzyl protons to 
become diastereotopic and appear as four doublets ($\delta$ 6.42, $\delta$ 6.02, $\delta$ 5.24, $\delta$ 5.04, $J =
11.6$ Hz) for (220) and ($\delta$ 6.12, $\delta$ 5.84, $\delta$ 5.37, $\delta$ 5.21, $J = 11.6$ Hz) for (221)). The 
aromatic region revealed a complex region of naphthyl tethered and diphenylimine 
proton resonances between $\delta$ 7.0-8.4.

The $^{13}$C NMR spectrum of both (220) and (221) comprised 56 sp\(^2\) fullerene
resonances corresponding to the non-symmetrical nature of the [60]fullerene core as a
consequence of a lack of a plane or axis of symmetry. In addition to the fulleryl 56 sp\(^2\)
resonances observed for both non-symmetrical bisadducts, four fulleryl sp\(^3\) resonances
[$\delta$ 81.9, $\delta$ 81.7, $\delta$ 81.5, $\delta$ 81.3 for (220); $\delta$ 82.4, $\delta$ 81.92, $\delta$ 81.89, $\delta$ 81.88 for (221)] and
two cyclopropane bridgehead carbons [$\delta$ 97.1, $\delta$ 96.7 for (220); $\delta$ 96.6, $\delta$ 95.9 for (221)]
were observed. The corresponding transesters of (220) and (221), displayed identical
UV/vis, $^1$H NMR and $^{13}$C NMR spectra to regioisomers (178) and (179), indicative of
(220) and (221) possessing identical regiochemistry to (178) (trans-4) and (179) (cis-3)
respectively (Scheme 5.7, Scheme 5.8).
Figure 5.13: $^1$H NMR (400 MHz, CDCl$_3$) spectrum of (a) (220) and (b) (221).
The double reductive ring opening reaction was attempted on compounds (220) and (221) using the conditions described in section 5.1 afforded free [60]fullerene (12%) and (222/223) in a combined yield of 46% after purification by flash column chromatography (DCM) (Scheme 5.9). Efforts to separate compounds (222) and (223) by HPLC, however, were unsuccessful.

$^1$H NMR analysis of (222/223) revealed a 60:40 ratio of compounds (Figure 5.14), however, even after 2D NMR analysis using NOESY and HMBC experiments, the major and minor compounds could not be ascertained. The 60:40 ratio was 176
observed in both $^1$H NMR and $^{13}$C NMR spectra between cognate resonances. Two fullereryl proton resonances were situated at $\delta$ 6.82 and $\delta$ 6.78 (Figure 5.14). The aromatic region revealed a complex mass of resonances corresponding to the benzhydryl groups and the naphthyl ring. The diasterotopic benzyl doublets ($H_b$/$\delta$/$\delta$/$\delta$/$\delta$) were identified at $\delta$ 5.88, $\delta$ 5.70, $\delta$ 5.62 and $\delta$ 5.32, each with an integration of one proton and a coupling of 12.0 Hz. The three proton spin coupled spectrum corresponded to the reduced addend protons $H_a/c$ ($\delta$ 4.95, $\delta$ 4.94 ppm, d, $J = 8.1$ Hz), $H_{b/C'}$ ($\delta$ 5.26, $\delta$ 5.22 ppm, d, $J = 2.2$ Hz), and NH/NH' ($\delta$ 3.60 ppm, dd, $J = 8.1, 2.2$ Hz). The reduced, cleaved addend portion consisted of singlet resonances at $\delta$ 5.44 ($H_{a/c}$), $\delta$ 4.82, $\delta$ 4.78 ($H_{y/y'}$), $\delta$ 3.38, $\delta$ 3.34 ($H_{y/c}$).

Scheme 5.9

![Scheme 5.9](image)
Chapter 5: Double Reductive Ring Opening

Figure 5.14: $^1$H NMR (400 MHz, CDCl$_3$) spectrum of (222/223) showing an expansion of the fulleryl proton region.

The $^{13}$C NMR spectrum of (222/223) revealed a total of 68 resonances in the fulleryl sp$^2$ region. Taking into account the ipso resonances associated with both the free and cleaved naphthyl rings (12 in total), 56 out of the expected 112 fulleryl sp$^2$ resonances were observed. Using the HSQC, experiment, $C_{\alpha \beta \gamma}$ (δ 70.1), $C_{\beta \gamma}$ (δ 66.6, δ 65.5), $C_{\gamma \gamma}$ (δ 58.8, δ 58.6), $C_{\gamma \gamma}$ (δ 66.3) and the benzyl carbons, $C_{66}$ (δ 67.4, δ 65.2) and $C_{77}$ (δ 66.55, δ 66.49) were identified by $^1$J$_{HC}$ couplings. Using the HMBC experiment, $C_{\gamma \gamma}$ (δ 67.6, δ 67.5) was identified by a $^2$J$_{HC}$ from $C_{\gamma \gamma}$ and hence confirming the 1,2-addition pattern of (220/221).

Thus, from spectroscopic analysis, reductive ring-opening of both symmetrical and non-symmetrical tethered bis-N-(diphenylmethylene)glycinate) esters afforded ring opened monoadducts (204)-(205) and (222/223).
5.3. Influence of Tether on Ring Opening

To test the influence of the tether on the double reductive ring-opening reaction, a double reductive ring opening was conducted on the diethyl ester (178) that was prepared from the base-catalysed transesterification of (173) as shown in Scheme 3.6 (section 3.4). If the tether was a significant influence in the formation of the monoelimination product (204), then the absence of the tether should, in theory, enable the formation of one or more of the possible isomers proposed in Figure 5.2. However if the resulting double reductive ring-opening of (178) results in the formation of the known monoadduct (134), then the driving force of the double reductive ring-opening is the elimination of one addend of a bisadduct.

Treatment of (178) under reaction conditions described in section 5.1, resulted in the ring opened ethyl ester (134) being isolated as a major product in 51% yield (Scheme 5.10). The $^1$H NMR analysis revealed the formation of (134) accompanied by the formation of a minor product (minor:major; approximately 1:20 according to proton integration).

Scheme 5.10
The major product exhibited $^1$H NMR and $^{13}$C NMR resonances that were identical to those of the corresponding addend resonances of the ring-opened ethyl ester (134).

Therefore, from the formation of the corresponding ring-opened adduct (134) from the non-tethered bisadduct (178) it can be concluded that the presence of the tether is not the driving force in the monoelimination of one of the addends. The proposed reasoning behind the elimination of the second addend is most likely the formation of the corresponding dianion (A/B) (Scheme 5.3). The rate of elimination of one of these addends appears to be higher than the corresponding elimination of both addends on the basis of recovered monoadduct (204) compared with recovered free [60]fullerene (Table 5.1).

5.4. Concluding Remarks

Using the reductive ring-opening synthetic methodology discussed in chapter 2, reductive ring-opening reactions were conducted on tethered and non-tethered bis-$N$-(diphenylmethyleneglycinate) bisadducts in an effort to synthesise the corresponding ring-opened bisadduct analogues. Such ring-opened products were not forthcoming, and the corresponding ring-opened monoadducts (204), (205), and (222/223) were formed from the corresponding tethered bisadducts (173/174), (175) and (220/221) respectively. Such monoelimination of one cyclopropane ring from each bisadduct is much akin to the electrochemical/chemical retro-Bingel reaction, where a malonate-derived bismethanofullerene can have single cyclopropane selectively cleaved under reductive conditions. Thus, under much milder chemical conditions, a selective reductive elimination reaction of $N$-(diphenylmethyleneglycinate) ester methanofullerenes has been discovered which could lead to further application in fullerene chemistry.
Investigations into the influence of the tether in elimination of one cyclopropane were conducted on the non-tethered bisadduct (178). Under reductive ring-opening conditions using the bisadduct (178), the corresponding ring-opened monoadduct (134) was formed as the major product. Thus it was concluded that the tether has little influence on elimination of one of the cyclopropanes, rather the formation of the corresponding dianion intermediate.
Conclusions
This thesis has demonstrated the synthetic versatility of the Bingel cyclopropanation reaction to provide a range of novel protected methanofullerenyl amino acids, including compounds (110) and (111) (Chapter 2).

A range of deprotection techniques were employed, with no success in providing their free N-terminal or C-terminal derivatives. Complete deprotection of (110) or (111) to give the fulleryl amino acid (106) gave a product that could not be characterised.

A novel reductive ring-opening reaction was discovered during efforts directed towards the deprotection of compounds (110) and (111) that yielded a new class of α-fulleryl glycine derivatives, such as (133) and (134).
Although deprotection of (133) and (134) was unsuccessful, these compounds may serve as useful starting materials to prepare more highly functionalised [60]fullerenes by taking advantage of the acidity of the fulleryl proton (pKₐ 5.4) using base-catalysed chemistry.

Chapter 3 reported an extension of the Bingel cyclopropanation using N-(diphenylmethyleneglycinate) esters to produce multifunctionalised [60]fullerene by utilising tether-directed synthesis. The tethered bis-N-(diphenylmethyleneglycinate) esters afforded [60]fulleryl bisadducts of unexpected regiochemistries when compared to tethered bismalonates. For example, the compounds (173) and (97) had different regiochemistries.

![Chemical structures](image)

The regiochemistry of the major products of tethered bis-N-(diphenylmethyleneglycinate) esters, (173) and (175) [the latter via the formation of the transesterified diethylester (180)] were unambiguously characterised using ¹³C-¹³C connectivities using the 2D INADEQUATE experiment.

In an effort to explain such significant differences in regiochemistry between cognate tethered bis-N-(diphenylmethyleneglycinate) ester and bismalonic ester, computational studies were conducted and reported in chapter 4. No definitive conclusions were made concerning the mechanism of N-(diphenylmethyleneglycinate) ester addition to [60]fullerene under Bingel reaction conditions or to the differences in
observed regiochemistry. The reactivity of the $N$-(diphenylmethyleneglycinate) site was shown to be significantly more reactive than its malonic ester site by reacting the mixed malonate $N$-(diphenylmethyleneglycinate) ester tether (199) with [60]fullerene under mono-Bingel conditions. The resultant monocyclopropanated adduct (200), from reaction at the $N$-(diphenylmethyleneglycinate) ester site, was obtained exclusively.

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2 \quad \text{Ph} \\
\text{O} & \quad \text{O} \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{Cyclopropanation} \\
\text{[60]Fullerene} & \quad \text{MeO} \\
\end{align*}
\]

Reductive ring-opening of the tethered bis-$N$-(diphenylmethyleneglycinate) ester fullerene bisadducts gave, for example in the case of (173), the unexpected ring-opened monoadduct (208) rather than the expected double ring-opened bisadduct (204).

\[
\begin{align*}
\text{Ph}_2\text{HCHN} & \quad \text{H} \quad \text{CO}_2 \\
\text{H} & \quad \text{O}_2\text{C} \quad \text{N} \quad \text{Ph} \\
\text{H} & \quad \text{Ph} \\
\end{align*}
\]

Compounds like (208) were thought to arise via the elimination of one of the substituents much akin to the retro-Bingel reaction. This reaction was shown to be tether-independent by the formation of the corresponding elimination of the ring-opened monoadduct from a non-tethered bismethanofullerene precursor. Such a reaction could be potentially used as a mild method for selectively removing methano groups from [60]fullerenes.
Chapter 6:
Experimental
Reagents and solvents were purchased reagent-grade and used without further purification. Toluene and THF were distilled from sodium benzophenone ketyl. DCM was distilled from phosphorus pentoxide. MeCN was distilled from potassium carbonate. Fullerene was purchased from MER Corporation Tucson, Arizona AZ 85706. USA. 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) purchased from Merk. 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 quadrupole via a direct insertion technique and an electron beam energy of 70eV 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. ¹H 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. ¹³C 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 CDCl₃, D₂O, C₆D₆ were obtained commercially (Sigma-Aldrich or Cambridge) 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% ¹³C-enriched samples of (80), (110), (173) and (180) were performed on a Bruker DMX 600 spectrometer fitted with a
Bruker TXI-XYZ $^1$H/$^13$C/$^{15}$N probe. The sample (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 was 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 x 8192 Total points were collected in t1 and t2 respectively. A recycle delay of 9 seconds and 16 scans per increment were employed.

Computer modelling was performed on a Silicon Graphics O2 Workstation using the Spartan© Semi-empirical (AM1 and PM3) program: SGI/V5.1.1. Geometry optimisation model: RHF/AM1 and RHF/PM3 were used for semi-empirical calculations. Coordinate driving program: RHF/AM1 using an initial C1-C2 distance of 2.5Å. The C1-C2 distance was driven to 1.52 Å over ten interval steps.

tert-Butyl 61-diphenylmethyldieneamino -1,2-methano[60]fullerene-61-carboxylate (110)

DBU (0.184 mL, 1.22 mmol) was added at RT to a solution containing [60]fullerene (0.220 g, 0.306 mmol), carbon tetrabromide (0.132 g, 0.397 mmol) and N-(diphenylmethylene)glycinate tert-butyl ester (0.106 g, 0.397 mmol) in toluene (250 mL). The solution was stirred for 2 hr. The crude material was filtered through a short plug of silica gel (5cm), eluting first with toluene (to retrieve unreacted [60]fullerene) and then with DCM. Column chromatography eluting with (90:10; DCM/petroleum spirit) and recrystallisation from DCM/diethyl ether provided (110) as a brown amorphous solid (0.143 g, 46%). UV/vis (DCM): 430nm (18000), 610nm (1800), 690nm (8000). $^1$H NMR (CDCl$_3$, 300MHz): 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).
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$^{13}$C NMR (CDCl$_3$, 75MHz): $\delta$ 162.43, 153.69, 149.26, 147.75, 146.64, 146.18 (2 x C), 146.07, 145.65, 145.52, 145.36, 145.12, 144.47, 143.29, 143.06, 142.70, 142.62, 142.17 (2 x C), 142.15, 141.68 (2 x C), 140.04, 139.47, 136.78, 134.99, 130.02, 128.57, 96.04, 84.25, 82.56, 30.30. MS(ES) (+ve ion mode): m/z 1013 (M$^+$), 720 (C$_{60}$).

Ethyl 61-diphenylmethylideneamino-1,2-methano[60]fullerene-61-carboxylate (III)

DBU (0.847 mL, 5.62 mmol.) was added at RT to a solution containing [60]fullerene (1.00 g, 1.38 mmol), carbon tetrabromide (0.500 g, 1.51 mmol) N-(diphenylmethylene glycinate) ethyl ester (0.408 g, 1.53 mmol) in chlorobenzene (900 mL). The solution was stirred for 2 hr. 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 recrystallisation from DCM/diethyl ether provided (111) as black crystals (0.992 g, 72%). UV/vis (DCM): 430nm (18000), 610nm (1800), 690nm (800). $^1$H NMR (CDCl$_3$, 400MHz): $\delta$ 1.54 (t, 3H, J= 6.8 Hz), 4.62 (q, 2H, J= 6.8 Hz), 7.40 (t, 2H, J= 8.0 Hz), 7.50 (t, 4H, J= 8.0 Hz), 8.07 (d, 4H, J= 8.0 Hz). $^{13}$C NMR (CDCl$_3$, 75MHz): $\delta$ 159.17, 157.38, 150.15, 145.52, 144.48, 144.04, 143.90, 143.33, 142.90, 142.76, 142.36 (2 x C), 142.07, 141.79 (2 x C), 141.13, 139.93, 139.68 (2 x C), 139.33 (2 x C), 138.78 (2 x C), 138.27, 136.69, 136.11, 133.67, 131.56, 126.97, 125.31, 92.93, 79.83, 60.04, 11.26. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 985 (M$^-$), 720 (C$_{60}$).

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Ethoxycarbonylmethyl N-(tert-butoxycarbonyl) glycinate (125)

Potassium carbonate (1.58 g, 114 mmol) was added to a solution containing N-tert-butoxycarbonyl glycine (1.00 g, 5.71 mmol) and ethyl bromoacetate (0.953 g, 5.71 mmol) in DMF (15 mL) at RT and the mixture was stirred overnight. The reaction mixture was diluted with diethyl ether (50 mL) and the resultant precipitate was removed by gravity filtration. The filtrate was washed with saturated ammonium chloride solution (2 x 20 mL), followed by brine (20 mL). The organic layer was dried (MgSO₄), and concentrated in vacuo to afford (125) as a bright yellow oil (0.848 g, 57%). ¹H NMR (CDCl₃, 400 MHz): δ 1.29 (t, 3H, J = 8 Hz), 1.45 (s, 9H), 4.04 (d, 2H, J = 4 Hz), 4.23 (q, 2H, J = 8 Hz), 4.67 (s, 2H), 5.11 (s, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ 169.9, 167.3, 155.1, 80.4, 70.0, 61.6, 42.6, 28.6, 14.0. MS(CI): m/z 262 (M+1).

Ethoxycarbonylmethyl glycine. trifluoroacetate salt (126)

The ester (125) (0.848 g, 3.25 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (126) (0.488 g, 55%) as a colourless oil. ¹H NMR (D₂O, 300 MHz): δ 1.32 (t, 3H, J = 8 Hz), 4.67 (s, 2H), 3.91 (s, 2H). MS(CI): m/z 162 (RNH₃⁺).
**Ethoxycarbonylmethyl N-diphenylmethylidenglycinate (127)**

To a suspension of (126) (0.827 g, 3.01 mmol) in DCM/MeCN (20 mL/10 mL) was added benzophenone imine (0.545 g, 3.01 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to yield (127) as a white amorphous solid (0.526 g, 54%). $^1$H NMR (CDCl₃, 400 MHz): $\delta$ 1.30 (t, 2H, $J = 5.7$ Hz), 4.15 (s, 2H), 4.25 (q, 2H, $J = 5.7$ Hz), 4.69 (s, 2H), 7.34 (d, 2H, $J = 7.2$ Hz), 7.59 (t, 4H, $J = 7.2$ Hz), 7.71 (d, 4H, $J = 7.2$ Hz). $^{13}$C NMR (CDCl₃, 100 MHz): $\delta$ 173.2, 137.5, 132.4, 130.0, 128.2, 61.5, 60.5, 60.1, 14.1. MS(CI): $m/z$ 326 (M+1).

**Ethoxycarbonylmethyl 61-diphenylmethylideneamino-1,2-methano[60]fullerene-61-carboxylate (128)**

DBU (0.087 mL, 0.583 mmol) was added at RT to a solution containing [60]fullerene (0.200 g, 0.278 mmol), carbon tetrabromide (0.101 g, 0.305 mmol) and (127) (0.099 g, 0.306 mmol) in chlorobenzene (120 mL). The solution was stirred for 2 hr. 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 recrystallisation from DCM/diethyl ether provided (128) as a brown amorphous solid (0.130 g, 46%). UV/vis (DCM): $\lambda_{max}$ 430 nm (18000), 610 nm (1800), 690 nm (800). $^1$H NMR (CDCl₃, 300 MHz): $\delta$ 1.34 (t, 3H, $J = 8$ Hz), 4.23 (q, 2H, $J = 8$ Hz), 4.78 (s, 2H), 7.40 (t, 2H, $J = 8.0$ Hz), 7.50 (t, 4H, $J = 8.0$ Hz), 8.12 (d, 4H, $J = 8.0$ Hz). $^{13}$C NMR (CDCl₃, 75 MHz): $\delta$ 165.8, 161.2, 159.2, 152.9,
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148.1, 147.5, 146.9, 146.8, 146.2, 145.8, 145.6, 145.3, 145.2, 144.9, 144.7, 144.04, 144.00, 142.8, 142.6, 142.5, 142.2, 141.7, 141.6, 141.5, 141.1, 140.6, 139.6, 139.0, 136.6, 134.5, 129.6, 128.3, 128.2, 95.9, 82.7, 62.0, 61.6, 14.0. MALDI-MS (-ve ion mode, 9-nitroanthracene): m/z 1043 (M-), 720 (C\textsubscript{60}).

61-Diphenylmethylideneamino-1,2-methano[60]fullerene-61-carboxylic acid (129)

Boron tribromide (0.034 g, 0.0134 mmol) was added at 0°C to a solution containing (128) (0.014 g, 0.00134 mmol) in DCM (10 mL) under a nitrogen atmosphere. The solution was allowed to warm to RT and stirred for a further 3 hr. The reaction mixture was quenched with 1M HCl (10 mL). The organic layer was washed with brine (10 mL), dried (MgSO\textsubscript{4}) and concentrated in vacuo. The reaction mixture was redissolved in DCM and precipitated with diethyl ether to afford (129) (0.007 g, 51%) as a brown amorphous solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ 7.46 (t, 2H, J= 8.0 Hz), 7.59 (t, 4H, J= 8.0 Hz), 8.24 (d, 4H, J= 8.0 Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): too insoluble for acquisition. MALDI-MS (-ve ion mode, 9-nitroanthracene): m/z 720 (C\textsubscript{60}).

tert-Butyl 1,2-dihydro-α-diphenylmethy lamino-[60]fullerene acetate (133)

Sodium cyanoborohydride (0.005 g, 79.57 μmol) was added at RT over a 5 min period to an acidified solution (adjusted to pH 4 with glacial acetic acid) of (110) (0.02 g, 19.74 μmol) in THF (20 mL)/MeOH (5 mL). The pH of the brown solution was maintained at pH 4 by further addition of glacial acetic acid. Upon no further change in pH, the reaction mixture was stirred for a further 2 hr and

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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 (MgSO₄) and concentrated *in vacuo*. Column chromatography, eluting with toluene/hexane (1:1) provided (133) as a brown amorphous solid (0.0078 g, 39%). UV/vis (DCM) 410 nm (sh, 5000), 440 nm (3000). ¹H NMR (CDCl₃, CS₂ (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). ¹³C NMR (CDCl₃, CS₂ (60:40), 75 MHz): δ 170.98, 154.44, 153.66, 153.07, 152.38, 147.71, 147.45, 147.42, 146.89, 146.71, 146.64, 146.59, 146.52, 146.41, 146.10, 146.04, 145.92, 146.82, 146.76, 145.66, 146.63, 145.00, 144.76, 144.74, 143.69, 143.47, 142.92, 142.69, 142.59, 142.38, 141.98, 141.92, 141.84, 141.76, 140.68, 139.77, 139.64, 137.30, 136.85, 136.64, 136.58, 129.24, 129.14, 128.56, 127.93, 127.65, 82.81, 76.89, 68.18, 66.68, 58.80, 28.43. MS(ES) (+ve ion mode): m/z 1017 (M⁺), 720 (C₆₀).

*Boron trifluoride diethyl etherate (0.072 g, 508 µmol)* was added dropwise over 1 min to a solution of (111) (0.050 g, 50.76 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, 79.57 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 (MgSO₄) and concentrated in vacuo. Column chromatography using flash silica gel and eluting with toluene/hexane (1:1) provided (134) (0.029 g, 58%) as a brown amorphous solid.

UV/vis (DCM): 410nm (sh, 5000), 440nm (3000). ¹H NMR (CD₆D₆, CS₂ (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). ¹³C NMR (CD₆D₆, CS₂ (60:40), 75 MHz): δ 17184, 154.38, 153.46, 152.86, 151.95, 147.76, 147.41, 147.39, 147.38, 146.73, 146.71, 146.68, 146.47, 145.99, 145.97, 145.95, 145.72, 145.71, 145.00, 144.73, 143.63, 143.51, 143.49, 143.34, 142.94, 142.74, 142.62, 142.36, 142.01, 141.99, 141.91, 140.89, 140.75, 139.97, 139.68, 137.45, 136.81, 136.72, 136.51, 129.27, 129.15, 128.57, 127.99, 70.81, 68.13, 66.75. 61.84, 58.08. 14.88. MALDI-MS: (-ve ion mode, 9-nitroanthracene): $m/z$ 720 (C₆D₆).

l-Menthyl N-tert-butoxycarbonylglycininate (148)

To a solution of (+)-menthol (2.05 g, 13.1 mmol), N-tert-butoxycarbonylglycine (2.29 g, 13.1 mmol) and DMAP (0.160 g, 1.39 mmol) in THF (20 mL) was added DCC (2.97 g, 14.4 mmol). The mixture was stirred overnight at RT and then filtered and concentrated in vacuo. The crude product was redissolved in DCM (100 mL) and washed with 0.1M HCl (20 mL), 0.1M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was then dried, and concentrated in vacuo. Flash column chromatography (silica gel), eluting with DCM/MeOH (98/2) provided (148) (3.43 g, 84%) as a pale yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 0.81 (d, 3H, J = 6.9 Hz), 0.91 (d, 3H, J = 4.5 Hz), 0.93 (d, 3H, J = 5.1 Hz), 1.49 (s, 1H), 1.66 (m, 2H), 1.84 (m, 1H), 1.96 (m, 1H), 2.17 (pd, 1H, 192
\[ J = 6.9, 2.7 \text{ Hz}, 3.41 (\text{td}, 1H, J = 10.5, 4.2 \text{ Hz}), 3.89 (\text{d}, 1H, J = 5.4 \text{ Hz}), 4.01 (\text{d}, 2H, J = 5.1 \text{ Hz}), 4.75 (\text{td}, 1H, J = 10.8, 4.2 \text{ Hz}), 5.03 (\text{bs}, 1H). \]

\[ ^{13}C \text{ NMR (CDCl}_3, 75 \text{ MHz}): \delta 171.01, 156.00, 79.83, 77.39, 45.78, 42.23, 40.17, 34.02, 31.35, 26.51, 23.83, 22.02, 20.52, 16.68. \text{ MS(CI): } m/z 314 (M+1). \]

\[ l\text{-Menthyl glycinate.trifluoroacetate salt (149)} \]

The ester (148) (3.43 g, 10.96 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (149) (1.98 g, 55%) as a colourless oil. \[ ^1H \text{ NMR (D}_2\text{O, 400 MHz): } \delta 0.65 (\text{d}, 3H, J = 7.2 \text{ Hz}), 0.79 (\text{d}, 3H, J = 6.8 \text{ Hz}), 0.81 (\text{d}, 3H, J = 6.4 \text{ Hz}), 1.39 (\text{m}, 3H), 1.61 (\text{m}, 3H), 1.72 (\text{pd}, 1H, J = 6.9, 2.7 \text{ Hz}), 3.41 (\text{td}, 1H, J = 10.5, 4.2 \text{ Hz}), 3.82 (\text{s}, 2H), 4.75 (\text{td}, 1H J=10.8, 4.2 \text{ Hz}). \text{ MS(CI): } m/z 214 (RNH}_3^+). \]

\[ l\text{-Menthyl N-Diphenylmethylidene glycinate (150)} \]

To a suspension of (149) (1.98 g, 6.07 mmol) in DCM (20 mL) was added benzophenone imine (1.10 g, 6.07 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO\(_4\)) and concentrated in vacuo to yield (150) (1.74 g, 76%) as a viscous, pale yellow oil. \[ ^1H \text{ NMR (CDCl}_3, 400 \text{ MHz): } \delta 0.75 (\text{d}, 3H, J = 6.8 \text{ Hz}), 0.86 (\text{d}, 3H, J = 193 \text{ Hz}), 1.74 (\text{m}, 3H), 1.84 (\text{d}, 3H, J = 1.7 \text{ Hz}), 4.12 (\text{d}, 2H, J = 5.1 \text{ Hz}). \]
4.8 Hz), 0.89 (d, 3H, J=6.4 Hz), 1.35 (m, 3H), 1.66 (m, 3H), 1.85 (pd, 1H, J=6.4, 2.4 Hz), 2.01 (m, 1H), 4.20 (s, 2H), 4.77 (td, 1H, J=10.8, 4.4 Hz), 7.18 (m, 3H), 7.33 (m, 3H), 7.42 (t, 1H, J=7.2 Hz), 7.45 (m, 1H), 7.65 (d, 1H, J=7.2 Hz), 7.81 (d, 1H, J=7.2 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 171.05, 137.57, 134.81, 132.43, 131.99, 130.24, 130.09, 128.23, 128.07, 79.83, 77.37, 45.78, 42.23, 40.18, 34.04, 31.44, 26.55, 23.88, 22.03, 20.53, 16.66. HRMS(CI) calculated for C₂₅H₃₁N₂O₂⁺ requires 378.2433, found 378.2422 (M+1).

l-Menthyl 60-diphenylmethylideneamino-1,2-methano[60]fullerene-60-carboxylate (151)

DBU (0.114 mL, 0.764 mmol) was added at RT to a solution containing [60]fullerene (0.25 g, 0.347 mmol), carbon tetrabromide (0.126 g, 0.382 mmol) and (150) (0.157 g, 0.417 mmol.) in chlorobenzene (200 mL). The solution was stirred for 2 hr. 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 recrystallisation from DCM/diethyl ether provided (151) (0.117 g, 31%) as a brown amorphous solid. UV/vis (DCM): 410nm (sh, 5000), 440nm (3000). ¹H NMR (CDCl₃, 300 MHz): δ 0.83 (d, 3H, J=6.9 Hz), 0.92 (d, 3H, J=6.9 Hz), 0.98 (d, 3H, J=6.9 Hz), 1.25 (m, 3H), 1.59 (m, 2H), 1.78 (bd, 1H, J=12.3 Hz), 2.01 (pd, 1H, 6.9, 2.4 Hz), 2.24 (bd, 1H, J=11.7 Hz), 5.10 (td, 1H, J=11.1, 4.5), 7.36 (m, 6H), 7.47 (t, 2H J=7.8 Hz), 8.03 (d, 2H, J=7.8 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 161.66, 160.58, 153.04, 152.94, 148.48, 148.29, 147.25, 146.96, 146.82, 146.68, 146.14, 145.68, 145.56, 145.16, 145.01, 144.86, 144.61, 143.95, 142.75, 142.52, 142.16, 141.64, 141.57, 141.16, 141.10, 140.94, 140.76, 139.47, 139.01, 138.87, 136.38, 136.33, 134.59,
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134.24, 129.46, 128.13, 128.06, 128.00, 95.78, 82.74, 82.60, 77.31, 46.82, 40.62, 34.17, 31.53, 26.70, 23.85, 22.02, 20.52, 16.61. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 1096 (M), 720 (C₆₀).

l-Menthyl 1,2-dihydro-α-diphenylmethylamino-[60]fullerene-1-acetate (152)

Boron trifluoride diethyl etherate (0.0129 g, 91.30 μmol) was added dropwise over 1 min to a solution of (151) (0.050 g, 50.76 μmol.) in DCM (20 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (10 mL) was added. Sodium cyanoborohydride (0.016 g, 254 μmol) was added to the reaction mixture which was stirred for 90 min and then concentrated in vacuo. The crude product was redissolved in chloroform (100 mL) and washed with saturated ammonium chloride solution (10 mL), followed by saturated sodium bicarbonate (10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. Column chromatography, eluting with toluene/hexane (1:1) provided (152) as a 1:1 diastereomeric mixture (0.022 g, 40%). UV/vis (DCM): 410nm (sh, 5000), 440nm (3000). ¹H NMR (C₆D₆, CS₂ (60:40), 300 MHz): δ 0.73 (d, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 7.2 Hz), 0.90 (d, 3H, J = 6.3 Hz), 0.94 (d, 3H, J = 6.3 Hz), 1.03 (d, 3H, J = 7.2 Hz), 1.09 (d, 3H, J = 7.2 Hz), 1.35 (m, 3H), 1.76 (m, 3H), 1.82 (td, 1H, J = 6.3, 2.4 Hz), 2.12 (bd, 2H), 2.17 (td, 1H, J = 6.3, 2.4 Hz), 2.38 (m, 2H), 3.68 (bd, 2H), 4.95 (td, 1H, J = 11.2, 4.4 Hz), 4.99 (s, 1H), 5.11 (td, 1H, J = 11.2, 4.4 Hz), 5.27 (s, 1H), 5.31 (s, 1H), 6.96 (s, 1H), 6.98 (s, 1H), 7.36 (m, 4H), 7.46 (m, 3H), 7.63 (d, 1H, J = 8.4 Hz), 7.65 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz). ¹³C NMR (C₆D₆, CS₂ (60:40), 75 MHz): δ 170.98, 154.44, 153.66, 153.07, 152.38, 147.71, 147.45, 147.42, 146.89, 146.71, 146.64, 146.59, 146.52, 146.41, 146.10, 146.04, 145.92, 146.82, 146.76, 145.66,
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146.63, 145.00, 144.76, 144.74, 143.69, 143.47, 142.92, 142.69, 142.59, 142.38, 141.98, 141.92, 141.84, 141.76, 140.68, 139.77, 139.64, 137.30, 136.85, 136.64, 136.58, 129.24, 129.14, 128.56, 127.93, 127.65, 82.81, 77.31, 76.89, 68.18, 58.80, 46.82, 40.62, 34.17, 31.53, 26.70, 23.85, 22.02, 20.52, 16.61. MALDI-TOF (-ve ion mode, 9-nitroanthracene): \( m/z \) 720 (C_{60}).

\[ 1,2\text{-Bis[(N-tert-butoxycarbonyl)acetoxyethyl]benzene (164)} \]

To a solution of 1,2-benzene dimethanol (1.500 g, 10.9 mmol), \textit{N}-tert-butoxycarbonyl glycine (3.810 g, 21.7 mmol) and DMAP (0.266 g, 2.18 mmol) in THF (20 mL) was added DCC (4.72 g, 22.9 mmol). The mixture was stirred overnight and then filtered, and the filtrate concentrated in vacuo. The crude product was redissolved in DCM (100 mL) and washed with 0.1M HCl (20 mL), 0.1M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was dried, and concentrated in vacuo. Flash column chromatography (silica gel), eluting with DCM/MeOH (98/2) provided (164) (3.840 g, 73%) as a pale yellow oil. \(^1\)H NMR (CDCl_3, 300 MHz): \( \delta \) 1.44 (s, 18H), 3.93 (bd, 4H, \( J = 6.0 \) Hz), 5.19 (bs, 2H), 5.26 (s, 4H), 7.38 (m, 4H). \(^1^3\)C NMR (CDCl_3, 75 MHz): \( \delta \) 170.19, 156.12, 132.23, 128.98, 127.31, 79.73, 64.68, 42.12, 28.09. MS(CI): \( m/z \) 453 (M+1).
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1,3-Bis[(N-tert-butoxycarbonyl)acetoxymethyl]benzene (165)

To a solution of 1,3-benzene dimethanol (3.500 g, 25.2 mmol), N-tert-butoxycarbonyl glycine (8.870 g, 50.6 mmol) and DMAP (0.924 g, 7.56 mmol) in THF (20 mL) was added DCC (10.92 g, 52.9 mmol). The mixture was stirred overnight and then filtered, and the filtrate concentrated in vacuo. The crude product was redissolved in DCM (100 mL) and washed with 0.1 M HCl (20 mL), 0.1 M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was dried, and concentrated in vacuo. Flash column chromatography (silica gel), eluting with DCM/MeOH (98/2) provided (165) (8.100 g, 69%) as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.44 (s, 18H), 3.94 (bd, 4H, $J$ = 4.2 Hz), 5.09 (bs, 2H), 5.16 (s, 4H), 7.32 (m, 4H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 170.20, 156.12, 132.20, 128.80, 127.11, 127.31, 79.72, 64.53, 42.15, 28.09. MS(CI): m/z 453 (M+1).

1,4-Bis[(N-tert-butoxycarbonyl)acetoxymethyl]benzene (166)

To a solution of 1,4-benzene dimethanol (5.00 g, 36.0 mmol), N-tert-butoxycarbonyl glycine (12.60 g, 71.9 mmol) and DMAP (0.879 g, 7.19 mmol) in THF (20 mL) was added DCC (15.59 g, 75.5 mmol). The mixture was stirred overnight and then filtered, and the filtrate concentrated in vacuo. The crude product was redissolved in DCM (100 mL) and washed with 0.1 M HCl (20 mL), 0.1 M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was dried, and concentrated in vacuo. Flash column chromatography (silica gel), eluting with DCM/MeOH (98/2) provided (166) (14.29 g, 86%) as a white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.42 (s, 18H), 3.91 (bd, 4H, $J$ = 5.2 Hz), 5.12 (bs, 2H), 5.14 (s, 4H), 7.33
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\( ^{13} \text{C NMR (CDCl}_3, 75 \text{ MHz): } \delta 170.20, 156.12, 132.27, 127.31, 79.72, \ 64.53, 42.15, 28.09. \text{ MS(Cl): m/z 453 (M+1).} \)

1,2-Bis[acetoxyethylglycinate]benzene.bistrifluoracetate salt (167)

The ester (164) (3.840 g, 8.49 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (167) (3.61 g, 89%) as a colourless oil. \( ^{1} \text{H NMR (D}_2\text{O, 300 MHz): } \delta 3.68 (s, 4H), \ 5.23 (s, 4H), 7.31 (m, 4H). \text{ MS(Cl): m/z 253 (RNH}_3^{+}). \)

1,3-Bis[acetoxyethylglycinate]benzene.bistrifluoracetate salt (168)

The ester (165) (8.100 g, 17.9 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (168) (7.35 g, 86%) as a colourless oil. \( ^{1} \text{H NMR (D}_2\text{O, 400 MHz): } \delta 3.81 (s, 4H), \ 5.18 (s, 4H), 7.31 (m, 4H). \text{ MS(Cl): m/z 253 (RNH}_3^{+}). \)
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1,4-Bis[acetoxyethylglycinate]benzene.bistrifluoracetate salt (169)

The ester (166) (14.29 g, 31.6 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (169) (13.59 g, 90%) as a colourless oil. ¹H NMR (D₂O, 400 MHz): δ 3.81 (s, 4H), 5.21 (s, 4H), 7.31 (s, 4H). MS(CI): m/z 253 (M+1).

1,2-Bis[(N-diphenylmethylidene)acetoxy)methyl]benzene (170)

To a suspension of (167) (3.83 g, 8.01 mmol) in DCM (20 mL) was added benzophenone imine (2.90 g, 16.02 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to yield (170) (3.90 g, 89%) as a viscous yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 4.22 (s, 4H), 5.27 (s, 4H), 7.13 (m, 8H), 7.35 (m, 4H), 7.39 (m, 4H), 7.42 (m, 4H), 7.64 (dd, 4H, J = 8.4, 1.6 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 172.07, 170.34, 139.16, 134.37, 129.85, 128.79, 128.74, 128.10, 127.63, 64.07, 55.56. HRMS(CI) calculated for C₃₈H₃₂N₂O₄⁺H⁺ requires 581.2440, found 581.2427 (M+1).
1,3-Bis[(N-diphenylmethylidene)acetoxy)methyl]benzene (171)

To a suspension of (168) (15.80 g, 33.1 mmol) in DCM (20 mL) was added benzophenone imine (11.99 g, 66.2 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo and recrystallized from diethyl ether to yield (171) (14.59 g, 76%) as a white amorphous solid. ¹H NMR (CDCl₃, 400 MHz): δ 4.17 (s, 4H), 5.09 (s, 4H), 7.13 (m, 8H), 7.35 (m, 4H), 7.39 (m, 4H), 7.42 (m, 4H), 7.64 (dd, 4H, J= 8.4, 1.6 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 171.89, 170.26, 139.00, 137.39, 135.96, 132.27, 130.38, 129.89, 128.61, 128.12, 66.07, 55.42. HRMS(CI) calculated for C₃₈H₃₂N₂O₄+H⁺ requires 581.2440, found 581.2398 (M+1).

1,4-Bis[(N-Diphenylmethylidene)acetoxy)methyl]benzene (172)

To a suspension of (169) (8.60 g, 17.9 mmol) in DCM (20 mL) was added benzophenone imine (6.49 g, 35.8 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo and recrystallized diethyl ether to yield (172) as a white amorphous solid (7.57 g, 73%). ¹H NMR (CDCl₃, 400 MHz): δ 4.17 (s, 4H), 5.09 (s, 4H), 7.13 (m, 8H), 7.35 (m, 4H), 7.39 (m, 4H), 7.42 (m, 4H), 7.64 (dd, 4H, J= 8.4, 1.6 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 171.96, 170.29, 137.40, 132.27, 129.89, 128.56, 128.13, 127.93, 66.00,
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55.45. HRMS(Cl) calculated for C_{39}H_{32}N_{2}O_{4}+H^{+} requires 581.2440, found 581.2440 (M+1).

endo,endo-(m-Phenylenedimethyl) 61,62-bis (N-diphenylmethylideneamino)-1,2:34,35-bis(methano)[60]fullerene-61,62 -dicarboxylate (173) and endo,endo-(m-
Phenylenedimethyl) 61,62-bis(N-diphenylmethylideneamino)-1,2:16,17-
bis(methano)[60]fullerene-61,62 -dicarboxylate (174)

DBU (0.45 mL, 3.01 mmol) was added at RT to a solution containing
[60]fullerene (0.43 g, 0.5975 mmol), carbon tetrabromide (0.54 g, 1.42 mmol) and (171)
(0.47 g, 0.810 mmol) in chlorobenzene (200 mL). The solution was stirred for 2 hr. 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 recrystallisation from
DCM/diethyl ether provided (173) (0.245 g, 32%) and (174) (0.079 g, 9%) as brown
amorphous solids.

(173): UV/vis (DCM): 320nm (15000), 630nm
(250), 690nm (150). \(^1\)H NMR (CDCl\(_3\), 400 MHz):
\(\delta 5.06\) (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): \(\delta 68.04, 81.47, 81.80, 97.06, 127.93, 128.04,
128.32, 129.36, 129.60, 136.42, 137.66, 138.92, 139.61, 140.60, 140.94, 141.27,
141.33, 141.39, 141.54, 142.10, 142.48 (ipso), 143.64, 143.92, 145.63, 145.68, 145.75,
145.80, 145.98, 146.03 (1C), 146.65, 146.75, 146.82, 147.40, 148.62, 148.99 (1C),
149.89, 150.88, 160.71, 161.25. MALDI-TOF (-ve ion mode, 9-nitroanthracene): \(m/z\)
1296 (M\(^-\)), 720 (C\(_{60}^+\)).
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(174): UV/vis (DCM): 320nm (19000), 430nm (sh, 1700), 450nm (sh, 1400), 640nm (280), 695nm (190). 1H NMR (CDCl3, 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). 13C NMR (CDCl3, 100 MHz): δ 68.46, 81.83, 82.38, 96.02, 128.32, 128.56, 129.64, 129.94, 131.37, 134.55, 134.77, 138.49, 139.24, 140.71, 141.02, 141.20, 141.84, 143.36, 143.46, 143.98, 144.06, 144.11, 144.30, 144.42, 144.70, 144.92, 145.00, 145.92 (1C), 147.28, 147.38, 147.51, 147.80, 148.55, 148.86, 149.01, 149.21, 150.93, 153.44, 154.37, 161.03, 161.14. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 1296 (M), 720 (C80-).

endo,endo-(p-Phenylenedimethyl) 61,62-bis (N-diphenylmethylideneamino)-1,2:3,4,3,5-bis(methano)[60]fullerene-61,62 -dicarboxylate (175) and endo,endo-(p-Phenylenedimethyl) 61,62-bis (N-diphenylmethylideneamino)-1,2:3,4,3,5-bis(methano)[60]fullerene-61,62 -dicarboxylate (176)

DBU (0.45 mL, 3.01 mmol) was added at RT to a solution containing [60]fullerene (0.43 g, 0.597 mmol), carbon tetrabromide (0.54 g, 1.42 mmol) and (172) (0.47 g, 0.810 mmol) in chlorobenzene (200 mL). The solution was stirred for 2 hr. The crude material was filtered through a short plug of silica (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 recrystallisation from DCM/diethyl ether provided (175) (0.287 g, 37%) and (176) (0.078 g, 10%) as brown amorphous solids.
(175): UV/vis (DCM): 330nm (15000), 430nm (sh, 180), 620nm (210), 690nm (80). 1H NMR (CDCl3, 400 MHz): δ 5.21 (d, 2H, J = 11.6 Hz), 5.58 (d, 2H, J = 11.6 Hz), 7.16 (d, 2H J = 4.4 Hz), 7.39 (d, 2H, 4.4 Hz), 7.51 (m, 8H), 7.62 (t, 4H, J = 7.2 Hz), 8.16 (d, 4H, J = 7.2 Hz), 8.21 (d, 4H, J = 7.2 Hz). 13C NMR (CDCl3, 100 MHz): too insoluble to obtain adequate spectrum. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 1296 (M), 720 (C60).

(176): UV/vis (DCM): 320nm (19000), 640nm (210), 695nm (180). 1H NMR (CDCl3, 400 MHz): δ 5.17 (d, 2H J = 14.4 Hz), 5.72 (d, 2H, J = 14.4 Hz), 7.29 (m, 4H), 7.40 (m, 4H), 7.46 (t, 4H, J=10.0 Hz, 1.6 Hz), 7.55 (t, 4H, J=9.6 Hz), 7.92 (d, 4H, J=9.6 Hz), 8.02 (d, 4H, J=9.6 Hz). 13C NMR (CDCl3, 100 MHz): δ 67.85, 86.75, 83.04, 96.74, 128.07, 128.20, 128.38, 129.62, 129.71, 134.19, 135.62, 136.22, 137.26, 138.37, 139.76, 140.66, 141.22, 141.542, 143.98, 144.13, 145.49, 145.76, 145.97, 146.83, 146.92, 147.36, 147.58, 148.89, 150.31, 151.01, 160.67, 161.25. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 1296 (M), 720 (C60).

Diethyl endo,endo-61,62-bis (N-diphenylmethyldeneamino)-1,2:34,35-bis(methano)60 fullerene-61,62 -dicarboxylate (178)

Solid potassium carbonate (0.211 g, 1.53 mmol) was added to a solution of (173) (0.170 g, 0.131 mmol) in THF:EtOH (2:1, 100 mL) and the mixture was stirred at RT for 1.5 hr. The mixture was then
filtered and the solvent was removed \textit{in vacuo}. Column chromatography (flash silica gel, DCM:petroleum spirit 90:10) followed by recrystallisation (chloroform/diethyl ether) yielded (178) (82 mg, 51\%) as a brown amorphous solid. UV/\textit{vis} (DCM): 440\nm (1100), 470\nm (sh, 650), 690\nm (470). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.41 (t, 6H, \textit{J}=6.8 \text{Hz}), 4.48 (q, 4H, \textit{J}=6.8 \text{Hz}), 7.29 (t, 4H, \textit{J}=7.2 \text{Hz}), 7.38 (t, 4H, \textit{J}=8.0 \text{Hz}), 7.46 (t, 4H, \textit{J}=7.2 \text{Hz}), 7.56 (t, 4H, \textit{J}=8.0 \text{Hz}), 7.90 (dd, 2H, \textit{J}=7.2 \text{Hz, 1.2 Hz}), 8.06 (dd, 2H, \textit{J}=7.6 \text{Hz, 1.2 Hz}$. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.16, 160.53, 151.40, 151.02 (2 x C), 150.06, 148.83, 148.72 (2 x C), 147.83, 147.57, 147.24, 146.76 (2 x C), 146.67, 146.58, 146.35, 145.97, 145.78, 145.75, 145.70, 143.93, 142.26, 142.00 (2 x C), 141.88, 141.55, 141.43, 140.78, 140.67, 140.05, 139.04, 136.76, 136.55, 134.03, 131.41, 129.75, 129.62, 128.36, 128.18, 128.14, 96.64, 82.01, 81.45, 62.99, 14.17. MALDI-TOF (-ve ion mode, 9-nitroantracene): \textit{m/z} 1250 (M$^-$), 720 (C$_{60}^-$).

\textit{Diethyl endo,endo-61,62-bis (N-diphenylmethylideneamino)-1,2:16,17-bis(methano)[60]fullerene-61,62 -dicarboxylate (179)}

Solid potassium carbonate (0.211 g, 1.53 mmol) was added to a solution of (174) (0.165 g, 0.127 mmol) in THF:EtOH (2:1) (100 mL) and the mixture was stirred at RT for 1.5 hr. The mixture was then filtered and the solvent was removed \textit{in vacuo}. Column chromatography (flash silica gel, DCM:petroleum spirit 90:10) followed by recrystallisation (chloroform/diethyl ether) yielded (179) (78 mg, 49\%) as a brown amorphous solid. UV/\textit{vis} (DCM): 320\nm (19000), 430\nm (sh,1700), 450\nm (sh, 1400), 640\nm (280), 695\nm (190). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.42 (t, 6H, \textit{J}=8.0 \text{Hz}), 4.48 (q, 4H, \textit{J}=8.0 \text{Hz}), 7.36 (t, 4H, \textit{J}=8.0 \text{Hz}), 7.49 (m, 4H), 7.63 (t, 4H, \textit{J}=8.0 \text{Hz}), 8.09 (d, 4H, \textit{J}=8.0 \text{Hz})
8.0 Hz), 8.25 (d, 4H, \( J = 8.0 \) Hz). \(^{13}\)C NMR (\( \text{CDCl}_3, 100 \) MHz): \( \delta 167.81, 162.24, 160.46, 154.21, 153.58, 151.43, 148.73, 148.71, 148.60, 148.57, 147.95, 147.94, 147.84, 147.43, 145.62, 145.25, 145.08, 144.94, 144.54, 144.17, 143.91, 143.88, 143.40, 142.39, 141.85, 141.54, 141.08, 140.83, 140.49, 139.28, 138.45, 136.34, 135.01, 130.96, 130.05, 129.89, 128.80, 128.54, 128.32, 95.91, 82.35, 81.88, 68.11, 62.44, 17.14. MALDI-TOF (-ve ion mode, 9-nitroanthracene): \( m/z \) 1250 (M), 720 (\( \text{C}_{60} \)).

**Diethyl endo,endo-61,62-bis (N-diphenylmethyldieneamino)-1,2;33,50-bis(methano)[60]fullerene-61,62 -dicarboxylate (180)**

Solid potassium carbonate (0.098 g, 0.71 mmol) was added to a solution of (175) (0.039 g, 0.003 \( \mu \)mol) in THF:EtOH (2:1) (100 mL) and the mixture was stirred at RT for 1.5 hr. The mixture was then filtered and the solvent was removed in vacuo. Column chromatography (flash silica gel, DCM/petroleum spirit 90:10) followed by recrystallisation (chloroform/diethyl ether) yielded (180) (0.012 g, 32%) as a brown amorphous solid.

UV/vis (DCM): 330nm (15000), 430nm (sh, 180), 620nm (210), 690nm (80). \(^1\)H NMR (300 MHz, \( \text{CDCl}_3 \)): \( \delta 1.42 \) (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, \( \text{CDCl}_3 \)): \( \delta 162.23, 160.50, 154.27, 153.57, 151.53, 148.77, 148.70, 148.67, 148.56, 147.98, 147.95, 147.90, 147.44, 145.66, 145.20, 145.01, 144.95, 144.53, 144.12, 143.98, 143.94, 143.49, 142.34, 141.89, 141.52, 141.09, 140.89, 140.49, 139.21, 138.48, 136.37, 135.06, 130.04, 129.83, 128.50,
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128.34, 128.29, 95.94, 82.33, 81.88, 63.01, 14.17. MALDI-TOF (-ve ion mode, 9-nitroanthracene): \( m/z \) 1250 (\( M^- \)), 720 (\( C_{60}^- \)).

**Diethyl endo,endo-61,62-bis (N-diphenylmethylideneamino)-1,2:34,35-bis(methano)[60]fullerene-61,62 -dicarboxylate (181)**

Solid potassium carbonate (0.025 g, 0.18 mmol) was added to a solution of (176) (0.02 g, 0.02 mmol) in THF:EtOH (2:1) (100 mL) and the mixture was stirred at RT for 1.5 hr. The mixture was then filtered and the solvent was removed in vacuo. Column chromatography (flash silica gel, DCM/petroleum spirit 90:10) followed by recrystallisation (chloroform/diethyl ether) yielded (181) (8 mg, 42%) as a brown amorphous solid. 320nm (19000), 640nm (210), 695nm (180). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 1.41 (t, 6H, \( J = 6.9 \) Hz), 4.48 (q, 4H, \( J = 6.9 \) Hz), 7.29 (t, 2H, \( J = 6.9 \) Hz), 7.39 (t, 2H, \( J = 7.5 \) Hz), 7.46 (t, 4H, \( J = 7.5 \) Hz), 7.56 (t, 4H, \( J = 7.5 \) Hz), 7.90 (d, 4H, \( J = 7.5 \) Hz), 8.06 (d, 4H, \( J = 7.5 \) Hz). \(^1\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 162.26, 160.64, 151.45, 151.06 (1xC), 150.11, 148.88, 148.77 (1xC), 147.90, 147.62, 147.30, 146.76, 146.69, 146.62, 146.41, 146.02, 145.80, 145.79, 145.72, 143.99, 142.30, 142.00 (2 x C), 141.92, 141.59, 141.49, 140.88, 140.76, 140.09, 139.10, 138.44, 138.38, 134.02, 131.60, 129.89, 129.34, 127.68, 128.53, 96.73, 82.10, 81.95, 63.01, 14.21. MALDI-TOF (-ve ion mode, 9-nitroanthracene): \( m/z \) 1250 (\( M^- \)), 720 (\( C_{60}^- \)).
trans (E) Diethyl 2,3-bis(N,N-diphenylmethylidene) butendioate (192) and cis (Z) Diethyl 2,3-bis(N,N-diphenylmethylidene) butendioate (193)

DBU (1.12 mL, 7.49 mmol) was added at RT to a solution containing N-(diphenylmethylenglycinate) ethyl ester (1.00 g, 3.75 mmol) and carbon tetrabromide (g, 3.75 mmol) and in toluene (250 mL). The solution was stirred for 3 hr and washed with brine (2 x 50 mL). The organic layer was then dried (MgSO₄) and concentrated in vacuo to yield a bright orange oil. ¹H NMR and ¹³C NMR analysis of the crude mixture did not reveal the presence of (192/193); however a molecular ion for (192/193) was observed using MS(Cl). MS(Cl): m/z 531 (M+).

3-Hydroxymethylphenylmethyl methyl malonate (196)

A solution of methyl malonyl chloride (0.487 g, .24 mmol) in THF (24 mL) was added dropwise to a solution containing 1,3-benzene dimethanol (0.500 g, 3.60 mmol) and pyridine (0.285 g, 3.60 mmol) in THF (30 mL) over a 30 min period at 0°C (ice bath). The solution was stirred for a further 3 hr at RT and then diluted with DCM (150 mL) and washed with ammonium chloride solution (2 x 50 mL). The organic layer was then dried (MgSO₄) and concentrated in vacuo to yield (196) (0.711 g, 83%) as a colourless oil. ¹H NMR (CDCl₃, 300 MHz): 3.02 (bs, 1H), 3.41 (s, 2H), 3.81 (s, 3H), 4.66 (s, 2H), 5.16 (s, 2H), 7.32 (m, 4H). MS(Cl): m/z 238 (M+).

3'-[Methoxycarbonyl(acetoxyethyl)] phenyl-l'-methyl N-tert-butoxycarbonyl glycinate (197)
To a solution of (196) (0.750 g, 2.98 mmol), N-tert-butoxycarbonyl glycine (0.955 g, 2.98 mmol) and DMAP (0.036 g, 0.298 mmol) in THF (10 mL) was added DCC (0.737 g, 3.57 mmol) and the mixture was stirred overnight, filtered and the filtrate was concentrated in vacuo. The crude product was redissolved in DCM (100 mL) and washed with 0.1M HCl (20 mL), 0.1M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was dried (MgSO₄), and concentrated in vacuo. Flash column chromatography (SiO₂), eluting with DCM/MeOH (98/2) provided (197) (0.766 g, 64%) as a pale yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 1.44 (s, 9H), 3.42 (s, 2H), 3.81 (s, 3H), 3.91 (d, 2H, J= 6.3 Hz), 5.17 (s, 2H), 5.18 (s, 2H), 5.40 (bs, 1H), 7.38 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz): δ 170.03, 166.12, 155.57, 135.60, 135.57, 135.53, 127.90, 127.65, 127.59, 79.51, 66.42, 66.20, 61.26, 42.13, 41.18, 27.97, 13.70. MS(ES): m/z 379 (M⁺).

3'-[Methoxycarbonyl(acetoxymethyl)] phenyl-1'-methyl glycinate trifluoroacetate salt (198)

The ester (197) (2.35 g, 5.95 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (198) (1.46 g, 60%) as a colourless oil. CI(MS): m/z 296 (RN⁺H₂).
3'-[Methoxycarbonyl(acetoxymethyl)] phenyl-1'-methyl N-(diphenylmethylideneamino) glycinate (199)

To a suspension of (198) (1.45 g, 3.55 mmol) in DCM/MeCN (20 mL:10 mL) was added benzophenone imine (0.643 g, 3.55 mmol) and the reaction mixture was stirred vigorously for 24 hr before being filtered and concentrated in vacuo. The yellow oil was then redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO\textsubscript{4}) and concentrated in vacuo to yield (199) as a viscous, pale yellow oil (0.72 g, 44%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 3.42 (s, 2H), 3.73 (s, 3H), 4.26 (s, 2H), 5.17 (s, 2H), 5.19 (s, 2H), 7.17 (m, 1H), 7.35 (s, 2H), 7.44 (m, 5H), 7.49 (m, 4H), 7.81 (d, 2H, \( J = 8.0 \) Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta \) 171.94, 170.38, 166.66, 166.18, 139.17, 137.52, 136.15, 135.86, 135.56, 130.46, 128.70, 128.25, 128.06, 127.60, 66.83, 66.07, 55.66, 52.50, 41.20. MS(CI): \textit{m/z} 460 (M+1).

3'-[Methoxycarbonyl(acetoxymethyl)] phenyl-1'-methyl-61[N-(diphenylmethylideneamino)-1,2-methano[60]fullerene-61-carboxylate (200)

DBU (0.041 mL, 0.278 mmol) was added at RT to a solution of [60]fullerene (0.100 g, 0.139 mmol), carbon tetrabromide (0.046 g, 0.139 mmol) and (199) (0.066 g, 0.139 mmol) in chlorobenzene (120 mL). The solution was stirred for 2 hr. 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 recrystallisation from
DCM/diethyl ether provided (200) (0.031 g, 19%) as a brown amorphous solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.40 (s, 2H), 3.81 (s, 3H), 5.17 (s, 2H), 5.58 (s, 2H), 7.38 (m, 5H), 7.49 (m, 5H), 8.08 (d, 4H, $J=7.2$). $^{13}$C NMR (75 MHz, CDCl$_3$): 166.60, 166.58, 162.41, 160.66, 153.40, 148.58, 147.61, 147.37 (1xC), 147.23 (1xC), 146.66, 146.22, 146.09, 145.66, 145.40, 145.37, 145.12, 144.42, 143.24, 143.03, 142.98, 142.68, 142.58, 142.11, 142.09, 142.06, 141.55, 141.15, 139.94, 139.41, 137.07, 136.12, 135.29, 134.83, 129.98, 129.31, 129.05, 128.86, 128.78, 128.67, 128.64, 96.25, 83.13, 83.11, 68.39, 67.00, 61.85, 41.79. MALDI-TOF (-ve ion mode, 9-nitroanthracene): $m/z$ 1177 ($M^-$), 720 (C$_{68}$).

$3'[(Diphenylmethylamino)acetoxymethyl]phenyl-1'-methyl)-1,2-dihydro-\alpha$-diphenylmethylamino-[60]fullerene acetate (208)

Boron trifluoride.diethyl etherate (0.104 g, 732.80 μmol) was added dropwise over 1 min to a solution of (173) (0.095 g, 73.19 μmol) in DCM (100 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (50 mL) was added. Sodium cyanoborohydride (0.046 g, 732.80 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, eluting with DCM/hexane (90:10) provided [60]fullerene (0.006 g, 12%) and (208) (0.043 g, 42%) as a brown amorphous solid. UV/vis (DCM) 330nm (sh, 15000),
435 nm (3000). $^1$H NMR (CDCl$_3$ CS$_2$ (80:40), 600 MHz): $\delta$ 3.37 (s, 2H), 3.66 (dd, 1H, $J$ = 12.3, 2.7 Hz), 4.84 (s, 1H), 4.98 (d, 1H, $J$ = 12.3 Hz), 5.07 (s, 2H), 5.24 (d, 1H, $J$ = 11.9 Hz), 5.28 (d, 1H, $J$ = 2.7 Hz), 5.41 (d, 1H $J$ = 11.9 Hz), 6.84 (s, 1H), 7.20 (m, 10H), 7.30 (m, 8H), 7.41 (t, 2H, $J$ = 7.9 Hz), 7.47 (t, 2H, $J$ = 7.6 Hz), 7.64 (d, 2H, $J$ = 7.8 Hz), 7.74 (d, 2H, $J$ = 7.8 Hz). $^{13}$C NMR (CDCl$_3$ CS$_2$ (80:40), 600 MHz): $\delta$ 172.39, 172.31, 154.03, 152.99, 152.17, 151.05, 147.50, 147.20, 147.07, 146.97, 146.43, 146.43, 146.38, 146.33, 146.25, 146.19, 146.18, 146.16, 145.88, 145.75, 145.71, 145.58, 145.44, 145.42, 145.35 (2 x C), 145.31, 145.22, 144.74, 144.68, 144.38, 144.35, 143.17, 143.13, 143.11, 142.63, 142.58, 142.56, 142.43, 142.23, 142.14, 142.09, 142.06, 142.04, 142.01, 141.72, 141.70, 141.54, 141.49, 141.47, 140.39, 140.37, 139.62, 139.23, 137.34, 136.43, 136.32, 136.14, 135.45, 129.32, 129.12, 129.07, 129.04, 128.91, 128.71, 128.04, 127.68, 127.29, 127.26, 70.38, 67.74, 67.32, 66.56, 66.35, 66.09, 58.87, 49.08. MS(ES): m/z 1327 (M+23), 720 (C$_{60}$).

$3'(\text{Diphenylmethylamino})\text{acetoxy methyl}1' -\text{methyl}) -1,2\text{-dihydro-} \alpha\text{-diphenylmethylamino-}[60]\text{fullerene acetate (208)}$

Boron trifluoride.diethyl etherate (0.055 g, 385.4 µmol) was added dropwise over 1 min to a solution of (173) (0.050 g, 38 µmol) in DCM (50 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (25 mL) was added. Sodium cyanoborohydride (0.029 g, 462 µmol) was added to the reaction mixture which was stirred for 90 min and 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 (MgSO₄) and concentrated in vacuo. Column chromatography, eluting with DCM/hexane (90:10) provided [60]fullerene (0.004 g, 14%) and (208) (0.022 g, 44%) as a brown amorphous solid. Spectral data were identical to (208) as described above.

4'[(Diphenylmethylamino)acetoxyethyl]phenyl-1'-methyl)-1,2-dihydro-α-diphenylmethylamino-[60]fullerene acetate (209)

Boron trifluoride-diethyl etherate (0.207 g, 1.46 mmol) was added dropwise over 1 min to a solution of (175) (0.160 g, 146 μmol) in DCM (200 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (100 mL) was added. Sodium cyanoborohydride (0.092 g, 1.46 mmol) 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 (30 mL), followed by saturated sodium chloride solution (30 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. Column chromatography, eluting with DCM/hexane (90:10) provided [60]fullerene and (205) (0.059 g, 37%) as a brown amorphous solid. UV/vis (DCM) 330nm (sh, 15000), 435nm (300). ¹H NMR (CDCl₃ CS₂ (80:40), 600 MHz): δ 3.67 (bd, J = 12.0 Hz), 4.98 (d, J = 12.0 Hz), 5.24 (d, J = 11.9 Hz), 5.28 (bs), 5.42 (d, J = 11.9 Hz), 6.85 (s), 7.23 (8H), 7.32 (m, 8H), 7.42 (t, 2H, J = 8.0 Hz), 7.47 (t, 2H, J = 8.0 Hz), 7.65 (d, 2H, J = 7.2 Hz), 7.74 (d, 2H, J = 7.2 Hz). ¹³C NMR (CDCl₃ CS₂ (80:40), 400 MHz): 172.39, 172.31, 154.06, 153.01, 152.15, 151.03, 147.51, 147.22, 147.08, 147.00, 146.44, 146.42, 146.34,
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\[ \begin{align*}
146.27, 146.24, 146.18, 145.87, 145.77, 145.61, 145.47, 145.44, 145.36, 145.33,  \\
145.24, 144.75, 144.69, 144.38, 143.37, 143.58, 143.20, 143.18, 142.65, 142.60,  \\
142.44, 142.25, 142.16, 142.10142.08, 142.07, 142.05, 141.73, 141.71, 141.50, 141.49,  \\
141.39, 140.39, 139.62, 139.23, 137.38, 136.33, 136.27, 136.18, 135.18, 129.09,  \\
128.92, 128.51, 128.23, 128.05, 127.69, 127.37, 127.31, 70.39, 67.74, 67.32, 66.56,  \\
66.35, 66.09, 58.87, 49.08.
\end{align*} \]

1,3-Dibromomethylnaphthalene (214)

\[
\text{N-bromosuccinimide (1.23 g, 6.91 mmol) was added to a solution of 1,3-dimethylnaphthalene (0.5 mL, 3.14 mmol) in carbon tetrachloride (30 mL) and the mixture was photolysed using a 500W mercury visible lamp under an atmosphere of nitrogen for 1 hr. The reaction mixture was allowed to cool, and the resultant precipitate was filtered and the solution was concentrated in vacuo to afford (214) (0.980 g, 100%) as a light brown solid.}^{195} \]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): } & \delta 4.64 (s, 2H), 4.94 (s, 2H), 7.60 (m, 3H), 7.83 (bs, 1H), 7.85 (d, 1H, } J = 7.8 \text{ Hz), 8.13 (d, 1H, } J = 8.4 \text{ Hz). MS(CI): } m/z 314 (M^+) \text{ Br} \\
\text{316} \text{ Br.}
\end{align*}
\]

1,3-Bis(acetoxymethyl)naphthalene (215)

\[
\text{Sodium acetate (0.772 g, 9.42 mmol) was added to a solution of (214) (0.970 g, 3.14 mmol) in DMF/HMPA (75 ml/5 mL) and the reaction mixture was left to stir for 48 hr at 40°C. The reaction mixture was diluted with diethyl ether/hexane (1:1, 100 mL) and washed several times with water. The organic layer was dried (MgSO\textsubscript{4}) and}
\]

213
concentrated in vacuo. Column chromatography (DCM/hexane; 90/10) yielded (214) (0.410 g, 48%) as a white amorphous solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.12 (s, 3H), 2.13 (s, 3H), 5.26 (s, 2H), 5.56 (s, 2H), 7.53 (m, 3H), 7.82 (s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.98 (d, 1H, J = 8.4 Hz). $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 170.81, 170.78, 133.53, 132.79, 132.06, 131.20, 128.77, 128.50, 127.27, 126.91, 126.37, 123.39, 66.07, 64.26, 20.96, 20.94. MS(CI): m/z 272 (M$^+$).

$^1$,3-Bis(hydroxymethylnaphthalene (216)

Solid potassium carbonate (2.44 g, 17.6 mmol) was added to a solution of (215) (0.400 g, 1.47 mmol) in methanol (20 mL) and the mixture stirred at RT under an atmosphere of nitrogen for 3 hr. The reaction mixture was filtered, diluted with DCM (100 mL) and washed with saturated ammonium chloride solution (2 x 30 mL), followed by brine (30 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo to afford (216) as a pale yellow oil (0.119 g, 43%). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.94 (bs, 2H), 4.48 (s, 2H), 4.78 (s, 2H), 7.38 (m, 2H), 7.43 (s, 1H), 7.64 (m, 2H), 7.75 (m, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 137.51, 136.61, 133.38, 130.18, 128.44, 126.02, 125.92, 125.48, 123.87, 123.08, 64.74, 62.51. MS(CI): m/z 188 (M$^+$).

$^1$,3-Bis[(N-tert-butoxycarbonyl)acetoxymethyl]naphthalene (217)

To solution of (216) (0.119 g, 0.638 mmol), N-tert-butoxycarbonylglycine (0.224 g, 1.28 mmol) and DMAP (0.016 g, 0.128 mmol) in THF (10 mL) was added DCC (0.016 g, 0.128 mmol) and the mixture was stirred overnight at RT.
before being filtered, and concentrated in vacuo. The reaction mixture was redissolved in DCM (100 mL) and washed with 0.1M HCl (20 mL), 0.1M sodium carbonate solution (20 mL) and brine (20 mL). The organic layer was then dried (MgSO4), and concentrated in vacuo. Flash column chromatography (silica gel), eluting with DCM/MeOH (98/2) provided (217) (0.262 g, 82%) as a pale yellow oil. 1H NMR (CDCl3, 300 MHz): δ 1.43 (s, 9H), 1.44 (s, 9H), 3.96 (d, 2H, J= 6.3 Hz), 3.99 (d, 2H, J= 6.9 Hz), 5.08 (bs, 2H), 5.34 (s), 5.64 (s), 7.56 (m, 3H), 7.84 (s, 1H), 7.88 (dd, 1H, J= 7.2, 2.4 Hz), 7.97 (d, 1H, J= 7.2 Hz). 13C NMR (CDCl3, 75 MHz): δ 170.19, 155.67, 133.28, 132.04, 131.41, 131.00, 128.66, 127.07, 126.99, 126.34, 123.13, 79.72, 66.51, 64.71, 42.21, 42.12, 28.09. MS(CI): m/z 503 (M+1).

1,3-Bis[acetoxyethylglycinate]naphthalene.bistrifluoracetate salt (218)

The ester (217) (0.262 g, 0.521 mmol) was added to neat TFA (5.0 mL) and the reaction mixture was stirred for 1 hr and then concentrated in vacuo. The reaction mixture was redissolved in distilled water (10 mL) and washed several times with diethyl ether (10 mL). The aqueous layer was retained and freeze-dried overnight to yield (218) as a pale yellow oil (0.194 g, 70%). 1H NMR (D2O, 300 MHz): δ 3.84 (s, 2H), 3.89 (s, 2H), 5.36 (s, 2H), 5.67 (s, 2H), 7.57 (m, 3H), 7.91 (d, 1H, J= 1.8 Hz), 7.94 (bs, 1H), 8.01 (d, 1H, J= 8.1 Hz). MS(CI): m/z 303 (RNH3+).
1,3-Bis[[(N-Diphenylmethylidene)acetoxy]methyl]naphthalene (219)

Benzophenone imine (0.130 g, 0.719 mmol) was added to a solution of (218) (0.194 g, 0.359 mmol) in DCM/MeCN (20 mL; 10 mL) and the mixture was stirred overnight at RT. The reaction mixture was then filtered and concentrated in vacuo. The yellow oil was redissolved in diethyl ether (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to yield a viscous yellow oil (219) (0.115 g, 51%).

\(^1\)H NMR (CDCl₃, 300 MHz): \(\delta\) 4.25 (s, 2H), 4.28 (s, 2H), 5.32 (s, 2H), 5.62 (s, 2H), 7.11 (m, 4H), 7.15 (m, 4H), 7.34 (m, 2H), 7.40 (m, 4H), 7.50 (m, 4H), 7.57 (t, 2H, \(J = 6.8\) Hz), 7.64 (t, 2H, \(J = 8.0\) Hz), 7.80 (d, 4H, \(J = 8.0\) Hz). \(^1\)C NMR (CDCl₃, 75 MHz): \(\delta\) 172.04, 170.42, 139.18, 137.54, 135.79, 133.50, 132.33, 131.81, 131.18, 130.54, 130.03, 128.76, 128.25, 128.03, 127.54, 126.92, 126.36, 123.58, 66.35, 64.63, 55.57.

HRMS (CI) calculated for C₄₂H₃₄N₂O₄+H\(^+\) requires 631.25968, found 631.25933 (M\(^+\)).

endo,endo-(1',3'-Naphthylendimethyl) 61,62-bis (N-diphenylmethylideneamino)-1,2:34,35-bis(methano)[60]fullerene-61,62-dicarboxylate (220) and endo,endo-(1,3-naphthylendimethyl) 61,62-bis (N-diphenylmethylideneamino)-1,2:16,17-bis(methano)[60]fullerene-61,62-dicarboxylate (221)

DBU (0.175 mL, 1.17 mmol) was added at RT to a solution containing [60]fullerene (0.200 g, 0.278 mmol), carbon tetrabromide (0.184 g, 0.556 mmol) and (219) (0.193 g, 0.306 mmol) in chlorobenzene (200 mL). The solution was stirred for 2 hr. The crude material was filtered through a short plug (5 cm) of silica gel, eluting first with toluene (to retrieve unreacted [60]fullerene) and then with DCM. Column chromatography eluting with (90:10; DCM/petroleum spirit) and recrystallisation from
DCM/diethyl ether provided (220) (0.0343 g, 9%) and (221) (0.019 g, 5%) as brown amorphous solids.

(220): UV/vis (DCM): 440nm (170000), 470nm (sh, 150000), 630nm (3000), 690nm (2300). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.05 (d, 1H, $J$ = 11.2 Hz), 5.24 (d, 1H, $J$ = 11.6 Hz), 6.04 (d, 1H, $J$ = 11.2 Hz), 6.43 (d, 1H, $J$ = 11.6 Hz), 7.25 (m, 17H), 7.35 (t, 1H, $J$ = 7.2 Hz), 7.42 (td, 1H, $J$ = 7.2, 1.2 Hz), 7.52 (t, 1H, $J$ = 7.2 Hz), 7.55 (td, 1H, $J$ = 7.2, 1.2 Hz), 7.79 (d, 1H $J$ = 1.0 Hz), 7.85 (d, 1H, $J$ = 7.2 Hz), 7.86 (d, 1H, $J$ = 7.2 Hz), 7.99 (d, 1H, $J$ = 7.2 Hz), 8.00 (d, 1H, $J$ = 7.2 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.75, 160.78, 160.62, 160.52, 151.16, 150.77, 150.70, 149.82, 149.60, 148.90, 148.51, 148.39, 147.34, 147.27, 146.75, 146.70, 146.62, 146.55, 146.35, 146.20, 145.80, 145.68, 145.66, 145.56, 145.48, 145.22, 145.06, 144.72, 144.63, 144.25, 143.61, 143.48, 142.31, 141.98, 141.97, 141.95, 141.33, 141.24, 141.22, 141.14, 141.04, 140.92, 140.85, 140.76, 140.55, 139.62, 139.58, 138.60, 137.49, 137.45, 137.16, 136.48, 136.44, 133.76, 133.59, 133.49, 133.16, 131.54, 131.48, 130.97, 130.71, 129.63, 129.49, 129.43, 129.37, 129.06, 128.29, 128.22, 128.07, 128.02, 127.92, 126.92, 123.26, 97.16, 96.65, 81.93, 81.66, 81.47, 81.25, 67.96, 65.08. MALDI-TOF (-ve ion mode, 9-nitroanthracene): $m/z$ 1346 (M), 720 (C$_{60}$).

(221): UV/vis (DCM): 440nm (sh, 130000), 460nm (80000), 490nm (sh, 60000), 630nm (1000), 690nm (4000). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.23 (d, 1H, $J$ = 15.6 Hz), 5.40 (d, 1H, $J$ = 15.2 Hz), 5.87 (d, 1H, $J$ = 15.6 Hz), 6.16 (d, 1H, $J$ = 15.2 Hz).
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7.09 (d, 1H, J = 2.0 Hz), 7.37 (tt, 1H, J = 9.2, 2.0 Hz), 7.51 (m, 17H), 7.62 (tt, 1H, J = 10.8, 2.0 Hz), 7.77 (d, 1H, J = 10.4 Hz), 7.90 (td, 1H, J = 10.8, 1.3 Hz), 8.03 (d, 1H, J = 10.0 Hz), 8.14 (d, 1H, J = 10.0 Hz), 8.22 (d, 1H, J = 10.0 Hz), 8.27 (d, 1H, J = 10.0 Hz). 13C NMR (75 MHz, CDCl3): δ 161.38, 161.22, 161.11, 160.75, 154.15, 153.83, 153.68, 153.46, 151.09, 150.76, 148.97, 148.96, 148.94, 148.78, 148.77, 148.64, 148.29, 147.91, 147.80, 147.60, 147.50, 147.32, 147.27, 147.20, 146.93, 144.99, 144.92, 144.84, 144.68, 144.49, 144.35, 144.25, 144.19, 144.05, 144.02, 144.00, 143.68, 143.40, 143.08, 142.90, 141.79, 141.76, 141.39, 141.25, 141.09, 141.03, 140.95, 140.67, 140.46, 139.18, 138.72, 138.69, 138.22, 135.22, 134.99, 134.81, 134.05, 134.05, 133.36, 132.69, 131.61, 130.32, 130.13, 130.00, 129.92, 129.90, 129.74, 129.62, 129.24, 128.55, 128.48, 128.33, 128.23, 127.95, 126.91, 123.39, 96.59, 95.92, 82.35, 81.94, 81.89, 81.78, 68.54, 66.57. MALDI-TOF (-ve ion mode, 9-nitroanthracene): m/z 1346 (M—), 720 (C60).

3'-[(Diphenylmethyl(amino)acetoxymethyl)naphthyl 1,2-dihydro-α-diphenylmethylamino-[60]fullerene acetate (222) and 1'-[(Diphenylmethyl(amino)acetoxymethyl)naphthyl 1,2-dihydro-α-diphenylmethylamino-[60]fullerene acetate (223)

Boron trifluoride diethyl etherate (0.095 g, 0.668 μmol.) was added dropwise over 1 min to a solution of (220/221) (0.090 g, 66.8 μmol) in DCM (200 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (100 mL) was added. Sodium cyanoborohydride (0.042 g, 0.668 mmol) 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 (30 mL), followed by saturated sodium bicarbonate solution (30 mL). The organic layer was dried (MgSO4) and concentrated in vacuo.
Column chromatography, eluting with DCM/hexane (90:10) provided [60]fullerene (0.006 g, 12%) and (222/223) (0.042 g, 42%).

UV/vis (DCM): 330nm (sh, 15000), 435nm (3000). $^1$H NMR (C$_6$D$_6$, CS$_2$ (60:40), 400 MHz)(where possible the resonances of the major isomer are shown with a *): δ 3.36 (s, 2H), 3.40 (s, 2H), 3.64 (bs, 2H), 4.83* (d, 2H, $J = 12.4$ Hz), 4.97 (bt, 2H), 5.23 (m, 4H), 5.35 (d, 1H, $J = 11.6$ Hz), 5.50 (s, 2H), 5.63 (d, 2H, $J = 11.6$ Hz), 5.72 (s, 1H, $J = 12.4$ Hz), 5.89 (d, 1H, $J = 12$ Hz), 6.78 (s, 1H), 6.83* (s, 1H), 7.16 (m, 14H), 7.38 (m, 55H), 7.40 (m, 30H). $^{13}$C NMR (C$_6$D$_6$, CS$_2$ (60:40), 75 MHz): δ 172.31, 172.24, 172.13, 153.81, 153.79, 152.78, 152.69, 151.81, 151.69, 150.84, 150.82, 147.36, 147.06, 146.93, 146.91, 146.88, 146.73, 146.70, 146.25, 146.28, 146.11, 146.10, 146.04, 145.62, 145.59, 145.52, 145.48, 145.39, 145.37, 145.29, 145.21, 145.20, 145.18, 145.08, 145.06, 144.59, 144.52, 144.22, 144.30, 144.26, 143.41, 143.02, 142.98, 142.93, 142.49, 142.42, 142.39, 142.28, 142.24, 142.06, 142.02, 142.01, 141.95, 141.86, 141.84, 141.64, 141.56, 141.29, 141.22, 141.17, 141.13, 141.11, 141.06, 140.26, 140.23, 140.18, 140.05, 139.25, 139.16, 138.98, 138.74, 137.17, 137.06, 136.40, 136.21, 136.19, 136.10, 135.96, 135.90, 133.66, 133.44, 132.44, 132.27, 131.90, 131.87, 131.64, 131.43, 130.49, 129.98, 129.01, 128.83, 128.50, 128.48, 128.26, 128.91, 128.16, 128.11, 128.00, 127.92, 127.62, 127.28, 127.25,
127.20, 126.64, 123.45, 123.36, 70.21, 67.69, 67.58, 67.41, 66.51, 66.30, 66.19, 65.25, 64.41, 58.81, 58.62, 49.02, 48.95. MALDI-MS: (-ve ion mode, 9-nitroanthracene): \textit{m/z} 720 (C$_{60}$).

\textit{Ethyl 1,2-dihydro-\alpha-diphenylmethylamino-[60]fullerene acetate (134) from Diethyl endo,endo-61,62-bis (N-diphenylmethylideneamino)-1,2:34,35-bis(methano)[60]fullerene-61,62-dicarboxylate (178)}

Boron trifluoride diethyl etherate (0.111 g, 779 \textmu mol) was added dropwise over 1 min to a solution of (178) (0.082 g, 65.6 \textmu mol) in DCM (50 mL) at 0°C. The reaction mixture was allowed to warm to RT over a 30 min period when MeCN (25 mL) was added. Sodium cyanoborohydride (0.049 g, 779 \textmu mol) was added to the reaction mixture which was stirred for 90 min, and then concentrated \textit{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 \textit{in vacuo}. Column chromatography, using flash silica gel eluting with toluene/hexane (1:1) provided (134) (0.033 g, 51 \%) as a brown amorphous solid. Spectral data were identical to (134) as described above.
References
References


References

References


References


224


225

226
References

(139) Diederich, F. Chimia 1993, 47, 449.
References


(189) Ung, A., University of Wollongong, personal communication 2000.


Appendices
Appendix 2.1: 2D INADEQUATE peak assignments of $^{13}$C-enriched (80).

<table>
<thead>
<tr>
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<td>6 (44.1)</td>
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* two correlations
** half-intensity resonances
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<td>147.31</td>
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**Appendix 2.2: 2D INADEQUATE peak assignments of $^{13}$C-enriched (110).**
<table>
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<th>Peak</th>
<th>Chemical Shift ($\delta$, ppm)</th>
<th>Carbon Number</th>
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<td>24</td>
<td>139.39</td>
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<td>(3) 56.4, (7) 67.2, (21) 56.8</td>
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<td>138.72</td>
<td>26,60</td>
<td>(14) 56.4, (15) 67.6</td>
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* = peak has two resonances. One full intensity and one half intensity
One full intensity and one half-intensity.
** = cross peaks not observed due to the closeness of the chemical shifts i.e. 2nd order coupling. Peaks positioning consistent with structure model.
Appendix 3.2: 2D INADEQUATE peak assignments of $^{13}$C-enriched (180).

<table>
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<td>Chemical Shift (δ, ppm)</td>
<td>IUPAC Carbon Number</td>
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* denotes resonance having two correlations