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Abstract

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Keywords

Fullerenes, NMR spectroscopy, Regioselectivity, bisadducts, fullerenyl amino acids, CMMB

Disciplines

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Regioselective synthesis of novel *e*-edge-[60]fullerenylmethanodihydropyrroles and 1,2-dihydromethano[60]fullerenes

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Abstract: Treatment of a tethered *N*-(diphenylmethylene)glycinate-malonate derivative with [60]fullerene under Bingel conditions yielded an *e*-edge-[60]fullerenylmethanodihydropyrrole adduct in a regioselective manner. The regiochemical outcome was independent of the order of addition of either the *N*-(diphenylmethylene)glycinate or the malonate moieties. This new bis-adduct was also prepared in ^{13}C enriched form allowing for its unequivocal structural characterization by 2D INADEQUATE NMR experiments. Ring-opening of the dihydropyrrole functionality of the bisadducts under reductive conditions gave exclusively novel dihydromethano[60]fullerene derivatives.

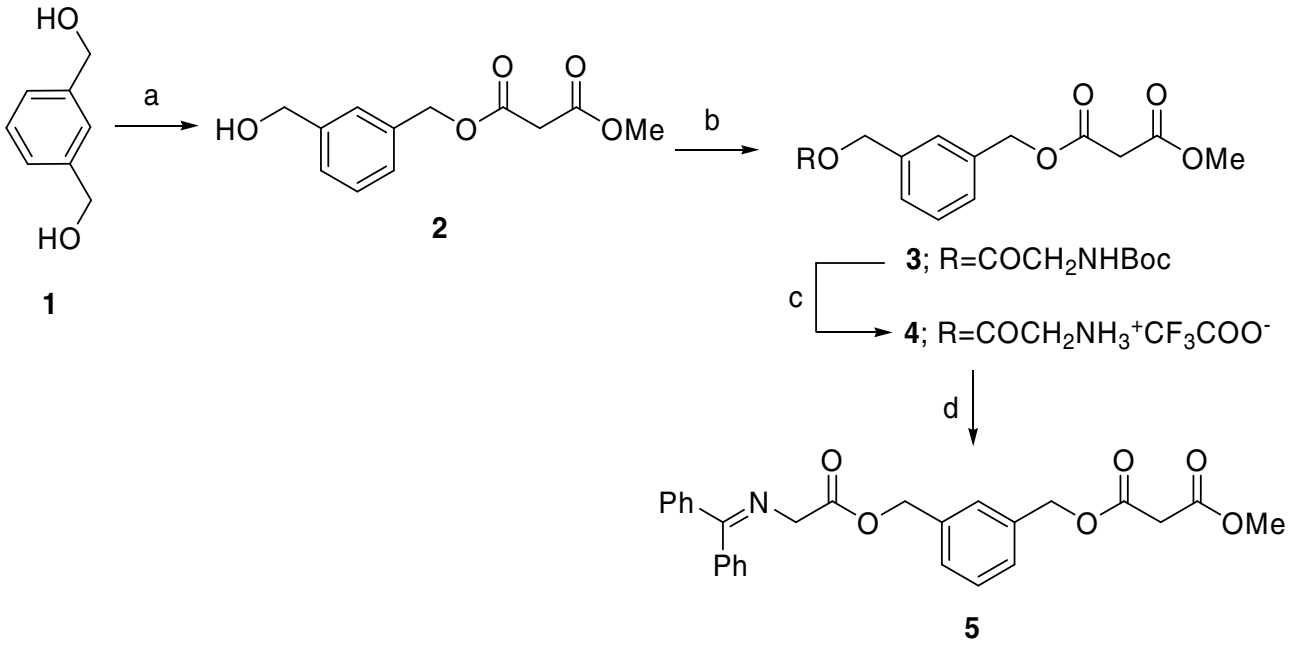
Introduction

The Bingel reaction of activated methylenes (WCH_2W') and [60]fullerene is used extensively to produce methano[60]fullerenes, ($C_{60}CW(W')$),[1,2] including tethered examples to produce bis-adducts.[3] We recently reported that the addition of *N*-(diphenylmethylene)glycinate esters under these

conditions, and their corresponding tethered analogs, gave [60]fullerenyldihydropyrroles and the corresponding bis-adducts, respectively.[4-8] The tether used was 1,3-benzene dimethanol and the regiochemical outcome was *trans*-4 and *cis*-3 in a 3 : 1 ratio. The corresponding bis-malonate derivative, linked by the identical tether, yielded exclusively the *cis*-2 bis-methano[60]fullerene.[9] Given the differences in regiochemistry using an identical tether, we decided to examine the regiochemical outcome of a mixed-tethered system utilizing 1,3-benzene dimethanol to tether a *N*-(diphenylmethylene)glycinate and a malonate unit.

Results and Discussion

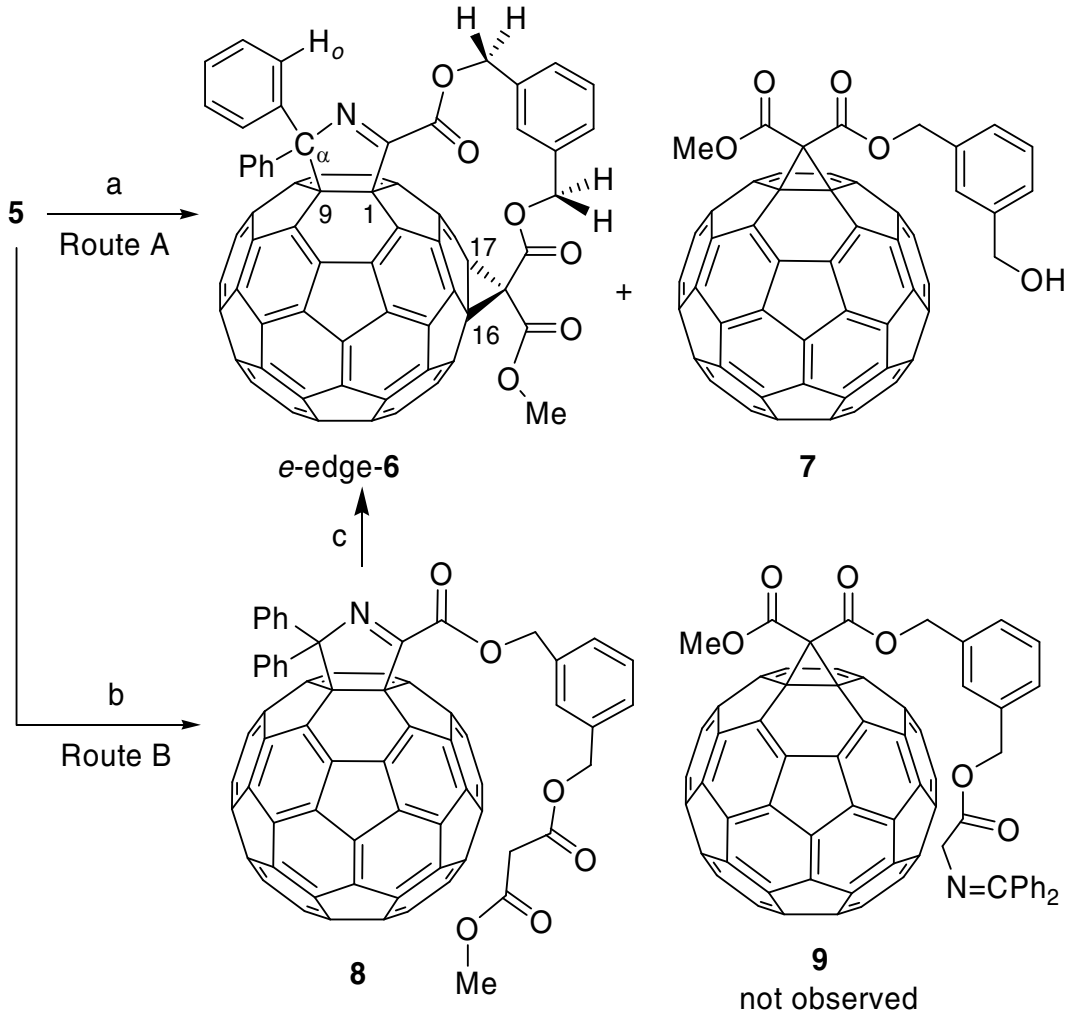
The required mixed-tethered system **5** (Scheme 1) was prepared by treating 1,3-benzene dimethanol **1** with methyl malonyl chloride, followed by DCC mediated esterification giving the mixed malonic-glycine ester **3**. Deprotection using TFA then afforded the ammonium trifluroacetate salt **4**, which was treated with benzophenone imine in a trans-imination reaction to give the desired mixed-tethered system **5**.



Scheme 1. Synthesis of the mixed-tethered system **5**. a) methyl malonyl chloride, triethylamine, THF, r.t., 3 h, 83%; b) *N*-Bocglycine, DMAP, DCC, THF, r.t., 18 h, 64%; c) TFA, r.t., 1 h, 60%; d) benzophenone imine, DCM/MeCN, r.t., 24 h, 44%.

The reaction of **5** with [60]fullerene under Bingel conditions using CBr_4 (2 equiv) and DBU (4 equiv) gave the *e*-edge-[60]fullerenylmethanodihydropyrrole **6** in a yield of 30%, with no evidence of additional regioisomers being formed (Route A, Scheme 2). In addition, a small quantity of the

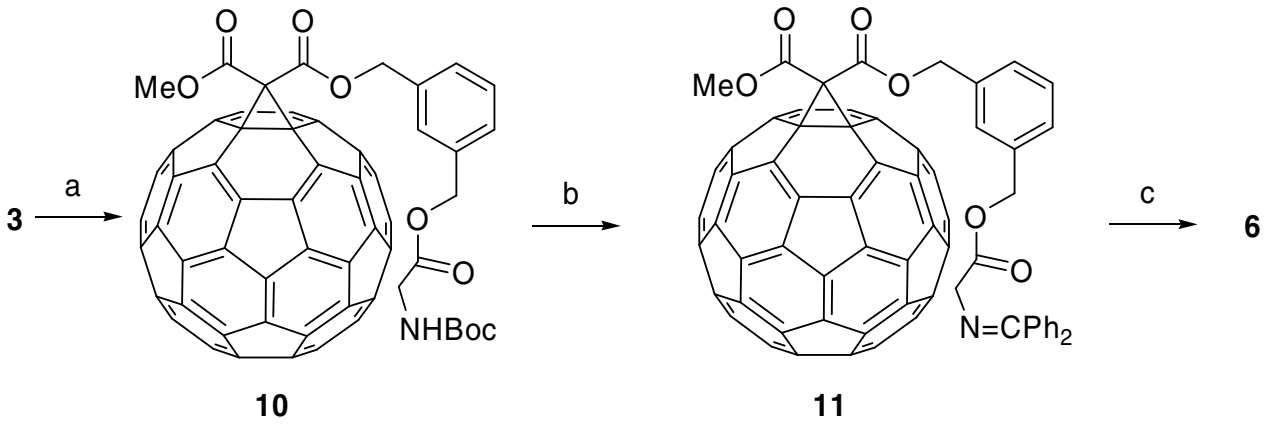
hydrolysed adduct **7** was also isolated. The structure of this bis-adduct was unequivocally determined by 2D INADEQUATE NMR experiments (see later discussion). Repeating this reaction using CBr_4 (1 equiv) and DBU (2 equiv) resulted in exclusive formation of a mono-adduct, the [60]fullerenyldihydropyrrole **8**, with no evidence for the formation of the methano[60]fullerene **9** (Route B, Scheme 2). Such select formation of a single adduct is indicative of the increased reactivity of the methylene associated with the iminoglycine moiety over the corresponding methylene of the malonic ester. Subsequent cyclisation of **8**, under Bingel conditions, also led to regioselective formation of the *e*-edge-bis-adduct **6**, with no evidence of additional regioisomers.



Scheme 2. Synthesis of the mono and bis-adducts, **8** and **6**, respectively. a) C_{60} (1 equiv), CBr_4 (2 equiv), DBU (4 equiv), toluene, r.t., 18 h, 30%. b) C_{60} (1 equiv), CBr_4 (1 equiv), DBU (2 equiv), toluene, r.t., 2 h, 19%. c) CBr_4 (1 equiv), DBU (2 equiv), toluene, r.t., 18 h, 20%.

In order to investigate the regiochemical outcome of the reverse order of addition, it was necessary to attach the malonyl portion to [60]fullerene using the precursor **3**. The resulting methano[60]fullerene

10 was isolated in 32% yield and was then deprotected and treated with benzophenone imine to give **11**. Subsequent cyclisation under Bingel conditions again yielded solely the *e*-edge-bis-adduct **6** (Scheme 3).



Scheme 3. Alternative synthesis of the mixed-tethered compound **6**. a) C_{60} (1 equiv), CBr_4 (1 equiv), DBU (2 equiv), toluene, r.t., 18 h, 32%; b) i) TFA, DCM, 18 h, ii) benzophenone imine, THF, r.t., 62% from **10**; c) C_{60} (1 equiv), CBr_4 (1 equiv), DBU (2 equiv), toluene, r.t., 1 h, 30%.

In order to further facilitate the identification of the bis-adduct **6**, and to confirm its symmetry, a trans-esterification reaction was performed at r.t. with an excess of $MeOH/K_2CO_3$ to provide the trimethyl ester **12** in 40% yield (Scheme 4). The relative position of the cyclopropane and dihydropyrrole rings on the fullerene cage of **6** and **12** was determined based on their C_S molecular symmetry, deduced from analysis of their ^1H and ^{13}C NMR spectra. The structure of the tethered adduct **6** was unambiguously established by 2D INADEQUATE NMR experiments on ^{13}C enriched material.[11-13] The ^1H NMR spectrum of **6** showed three singlets at δ 4.03 (3H), 5.37 (2H) and 5.52 (2H) corresponding to the methyl ester and the two sets of benzylic methylene protons, respectively. The equivalence of the methylene protons on the individual benzylic carbons indicated a plane of symmetry that bisects the tether, the cyclopropane ring and the dihydropyrrole ring (see Figure 1). This feature was key to the unambiguous indentification of the structure **6**. In related tethered bis-malonate and tethered bis-*N*-diphenylmethyleneglycinate ester [60]fullerene adducts, these benzylic protons are usually diastereotopically split into pairs of doublets arising from a lack of a corresponding plane of symmetry.[8,9] The ^1H NMR spectrum of **12** showed three singlets at δ 4.01 (3H), 4.02 (3H) and 4.13 (3H), corresponding to three sets of non-equivalent methyl ester protons. The ^{13}C NMR spectra of **6** and **12** showed 29 fulleryl sp^2 resonances, two of which where clearly half-intensity resonances (C-52 and C-60, Figure 1), indicating C*s*-symmetry for both bis-adducts. The sp^3 C atoms of the fullerene cage located on the mirror plane gave rise to two half-intensity signals, which

appeared at δ 81.2 and 82.9 (C-9 and C-1, respectively) and δ 81.9 and 82.6, for **6** and **12**, respectively. The HMBC spectrum of **6** showed a strong 3-bond correlation from the *ortho*-phenyl protons (H_O) to the dihydropyrrole sp^3 quaternary carbon at δ 95.9 (C_α, see Scheme 2 for numbering) and a weaker 4-bond correlation to the fullerenyl sp^3 carbon at δ 81.2 (C-9). The full-intensity signal at δ 69.8 was assigned to the malonic cyclopropyl sp^3 carbons (C-16 and C-17).[13] Similar correlations were observed in the HMBC spectra of **12**.

As further confirmation of the *e*-edge-regiochemistry, compound **6** was synthesized starting from 20-30 % ^{13}C-enriched fullerene, and 2D-INADEQUATE NMR experiments were conducted. Assignment of the carbon sphere was achieved on the basis of one-bonded ^{13}C-^{13}C connectivities and examination of the carbon-carbon coupling ($^1J_{CC}$) values knowing typical values for C (sp^2)-C (sp^3) bonds (~48 Hz), the longer 5,6 ring-fused bonds (53-59 Hz) and the shorter 6,6 ring-fused bonds (65-71 Hz).[11-13] This analysis facilitated the unambiguous characterisation of the entire fullerene sphere (Figure 1 and Table 1). For example, a four bond sequential connectivity was observed from the sp^3 carbon at δ 69.8 (C-16/17, malonate site) to the sp^3 carbon at δ 82.9 (C-1, dihydropyrrole site). These results confirmed that the second addition occurred at the *e*-edge position (Figure 1) and allowed the subsequent analysis of the entire sphere (Table 1). The UV-vis spectra of **6** and **12** showed two absorbance bands in DCM solution at 424 and 451 nm and 424 and 455 nm, respectively, consistent with an *e*-edge-[60]fullerene bis-adduct.[10a]

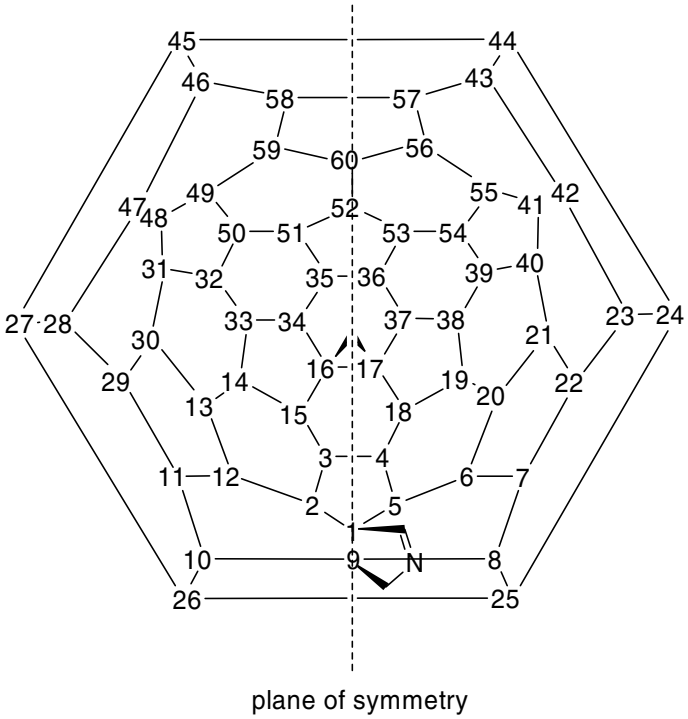


Figure 1. Schlegel diagram of bis-adduct **6** (the tether is removed for clarity).

Table 1: 2D-INADEQUATE NMR analysis (200 MHz, $CDCl_3$) of bis-adduct **6.**

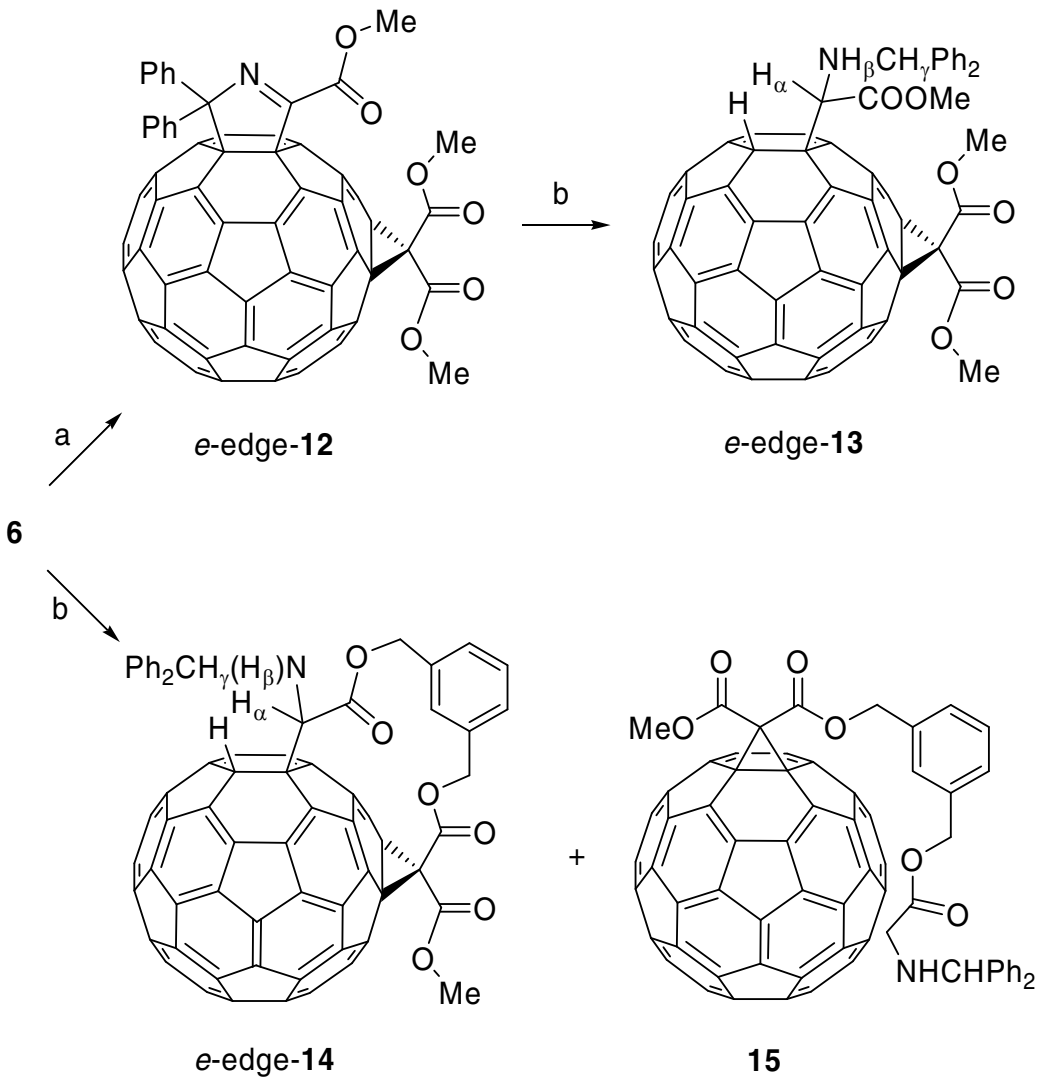
Carbon Number	δ (ppm)	Single Bond Correlation (Carbon number) $^1J_{C\text{-}C}$/Hz[e)]
1	82.92	(2) 36.0
2,5	146.71	(1) 36.0, (3) 59.5, (6) 70.5
3,4	141.99	(2) 59.5, (15) 71.5
6,12	139.55	(2) 70.5, (7) 56.5, (13) 56.5
7,11	137.49	(6) 56.5, (8) 71.5, (22) 59.0
8,10	155.68	(7) 71.5, (9) 40.5, (25) 60.0
9	81.19	(8) 40.5
13,20	137.80	(6) 56.5, (14) 69.0, (21) 55.0
14,19	145.49	(13) 69.0, (15) 57.5
15,18	142.94	(3) 71.5, (14) 57.5, (16) 54.0
16,17	69.84	(15) 54.0, (34) 54.0
21,30	144.21	(13) 55.0, (22) 56.0,(31) 71.0
22,29	141.80	(7) 59.0, (23) 70.0, (21) 56.0
23,28	144.91	(42) 55.0, (22) 70.0, (24) 56.5
24,27	141.32	(23) 56.5, (25) 69.0, (44) 58.0
25,26	146.07	(8) 60.0, (24) 69.0
31,40	142.93	(21) 71.0, (32) [b)], (41) 59.0
32,39	142.66	(31) [b)], (33) 67.5, (50) 59.0
33,38	145.28	(32) 67.5, (34) 57.5
34,37	143.01	(16) 54.0, (33) 57.5, (35) 72.0
35,36	139.44	(34) 72.0, (51) 59.0
41,48	145.45	(42) 70.0, (31) 59.0, (49) 58.0
(42,47) [a)]	144.26	(23) 55.0, (41) 70.0
(43,46) [a)]	144.26	[c)]
44,45	144.16	(24) 58.0
49,55	146.81	(41) 58.0, (56) 69.0
50,54	146.85	(32) 59.0, (51) 70.0
51,53	144.35	(50) 70.0, (52) 59.0
52	148.51	(51) 59.0, (60) 69.0
56,59	147.84	(57) 59.5, (60) 53.5
57,58	144.19	(56) 59.5
60	147.14	(52) 69.0, (56) 53.5

[a)] Coincidental peaks. [b)] Unable to obtain coupling constant due to peak proximity. [c)] Unable to obtain correlations due to peak proximity. [d)] The shift assignments for several very closely spaced peaks may be reversed as they become overlapped in the ^{13}C labeled sample. Specifically this applies to the following combinations: 21,30/42,47/43,46/57,58/44,45; 50,54/49,55; 14,19/41,48; 15,18/31,40. Reversing any or all of these shift assignments never leads to a different structure however. [e)] *J* values measured to +/- 0.5 Hz.

We previously demonstrated that mono- and bis-[60]fullerenyldihydropyrroles undergo reductive ring-opening reactions upon treatment with boron trifluoride-diethyl etherate, and sodium

cyanoborohydride to give novel dihydromethano[60]fullerene derivatives.[8] Treatment of **12** with boron trifluoride-diethyl etherate, acetic acid and an excess of sodium cyanoborohydride for few minutes accomplished a reductive ring-opening reaction to provide **13** in 40% yield, as well as the known methanofullerene, $C_{60}C(CO_2Me)_2$. The ^{1}H NMR spectrum of **13** revealed a two proton coupled spin system at δ 3.41 (1H, d, *J* = 12 Hz, NH) and 4.66 (1H, d, *J* = 12 Hz, H_α) with a singlet resonance at δ 5.16 for H_γ to the fullerene cage (Scheme 4). The singlet resonance at δ 6.36 corresponded to the fullerenyl proton. The ^{13}C NMR spectrum of **13** revealed 56 sp^2 resonances indicative of a fullerenyl bis-adduct possessing no plane of symmetry. The addend and the fullerene sp^3 carbons were assigned by HSQC and HMBC experiments with the former allowing the assignments of the ^{1}H-^{13}C coupling for the fullerenyl proton and the sp^3 fullerenyl carbon at δ 58.7. Other correlations allowed the assignment of the dihydropyrrole carbons, C_α and C_γ at δ 71.3 and 66.5, respectively. The HMBC spectrum reveals a strong 2-bond correlation from H_α to the fullerene sp^3 carbon bearing the glycine substituent at δ 67.3. There were also three moderately strong 3-bond correlations; i) from the fullerenyl proton to C_α, ii) from H_α to the sp^3 fullerenyl methine carbon; and iii) from H_γ to C_α. The remaining two sp^3 fullerenyl carbons appeared at δ 69.9 and 70.0 and were identified as part of the cyclopropane ring. The bridgehead carbon of the malonate site was not observed due to overlap with the three methoxy signals.

Reductive ring-opening of **6** required a larger excess of sodium cyanoborohydride (30 equiv) and longer reaction times (18 h) and yielded **14** and **15** in yields of 50% and 10%, respectively (Scheme 4). Compound **14** exhibited no plane of symmetry with the ^{1}H NMR spectrum of **14** revealing a single fullerenyl proton at δ 6.10 and two sets of diastereotopic benzyl methylene resonances at δ 5.74 and 5.69 (*J* = 11 Hz) and at δ 4.80 and 4.68 (*J* = 11 Hz). A singlet resonance corresponding to H_γ was observed at δ 5.18. A two proton coupled spin system was identified as H_α (δ 4.53, d, *J* = 13 Hz) and the NH (δ 3.37, d, *J* = 13 Hz).



Scheme 4. Reductive ring-opening reactions of bis-adducts **6** and **12**. a) K_2CO_3, THF/MeOH (10 : 1), r.t., 18 h, 40%; b) $BF_3.(OEt_2)_2$, HOAc, $NaCNBH_3$, DCM, r.t., 15 min, 40% from **12**, 18 h, 50% from **6**.

In conclusion, a novel *e*-edge-[60]fullerenylmethanodihydropyrrole adduct **6** has been prepared in an exclusive manner using a mixed-tethered system. The regiochemical outcome was found to be independent of the order of addition of either the *N*-(diphenylmethylene)glycinate or the malonate moieties. Ring-opening of the dihydropyrrole functionality of the bisadduct under reductive conditions gave a novel dihydromethano[60]fullerene derivative **14**. The trans-esterified derivative **12** also provided a novel dihydromethano[60]fullerene derivative **13** upon reductive ring-opening. The mixed tethered-system **5** gave a different regiochemical outcome (exclusively the *e*-edge-isomer) to the corresponding symmetrical tethered systems comprising a bis-malonate (*cis*-2 isomer) or a bis-iminoglycine (*trans*-4 and *cis*-3, 3 : 1). These differences indicate that these regiochemical outcomes are not dependent on the nature of the tether alone, but must incorporate additional factors including

the mechanism of each reaction, the orientation of the tether based upon the first addend, and the electronic nature of the mono-substituted-fullerenyl changing the likely kinetic and thermodynamic outcomes of subsequent additions.[10] The first step in the cyclization reactions of the mono-adducts **8** and **11** to give the bis-adduct **6,** was expected to involve the addition of an α-bromoenolate anion to a mono-substituted-[60]fullerene. This initial step may be reversible, however, the final step, attack of a fullerenyl anion on either the bromomalonate or the bromoiminoglycinate moiety would be expected to be irreversible and thus under kinetic control. Clearly both cyclizations favor formation of the *e*-edge-regioisomer in the second reaction step, independent of the nature of the first addend. We are currently preparing other mixed bis- and tris-tethered systems to probe the factors that affect the regiochemical outcomes in these regioselective tethered-reactions.

Experimental Section (the supporting information provides general and specific preparative and spectroscopic details and copies of the ^{13}C NMR, INADEQUATE and HBMC spectra of **6** and ^{13}C NMR spectra of **12** and **13**.

Acknowledgments

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[4] In earlier papers we reported that the addition of *N*-(diphenylmethylene)glycinate esters to [60]fullerene under Bingel conditions gave, methano[60]fullerenyl iminoesters and that tethered bis-*N*-(diphenylmethylene)glycinate esters, derived from *meta*- and *para*-benzenedimethanol scaffolds, gave the corresponding bis-methano[60]fullerenyl iminoesters.[5-8] We have recently performed INADEQUATE NMR experiments on a methano[60]fullerenyl iminoester and discovered that [60]fullerenyldihydropyrroles are formed in these reactions. A correction paper has been accepted for publication.[14]

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