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Abstract
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Keywords
Reductive, ring, opening, reactions, diphenyldihydrofullerenylpyrroles, CMMB

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Reductive ring-opening reactions of diphenyldihydrofullerenylpyrroles

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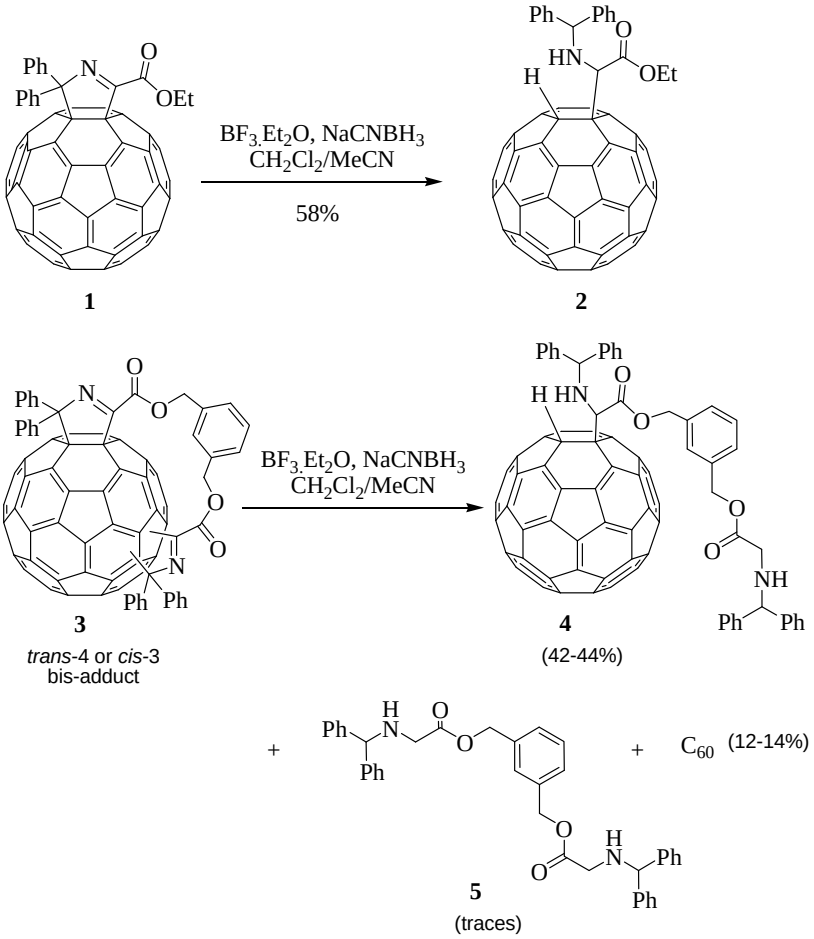
Abstract: The reductive ring-opening reaction conditions for the simple [60]fullerenyldihydropyrrole **1** have been optimized to include acetic acid in the reaction mixture to rapidly protonate the anionic intermediate. Under these conditions the ring-opened dihydrofullerene **2** was obtained in 68% yield. Under slightly modified conditions and at -78 ^{o}C the reductive bis-ring-opening of the tethered *trans*-4 isomer **3** provided the novel racemic bis-dihydrofullerenyl derivative **7**.

Keywords: Dihydrofullerenes, Ring opening, Amino acids, Fullerenyldihydropyrroles.

The synthesis of [60]fullerenyl amino acids has been the focus of many groups around the globe.[1] From a materials science and medicinal chemistry perspective, these are important targets potentially serving as central hubs in architecturally defined nanostructures or 3D-templates in drug design.[2] To date [60]fullerenyl amino acids and peptide derivatives have been prepared by the initial attachment of a handle to fullerene followed by coupling to a protected amino acid or peptide.[3] Notably, the only true α-[60]fullerenyl amino acid synthesized thus far is [60]fulleroproline; albeit a [60]fullerene-fused proline derivative.[4] The synthesis of acyclic α-[60]fullerenyl amino acids such as α-[60]fullerenyl glycine, akin to the majority of natural amino acids has remained elusive. We recently reported that the reductive ring-opening reaction of the diphenylfullerenyldihydropyrrole **1** gave the protected α-[60]fullerenyl glycinate **2** (Scheme 1).[5,6] Here we report our efforts towards the extension of the reductive ring-opening reactions of diphenylfullerenyldihydropyrroles from *mono*- to *bis*-substituted fullerenyl systems.

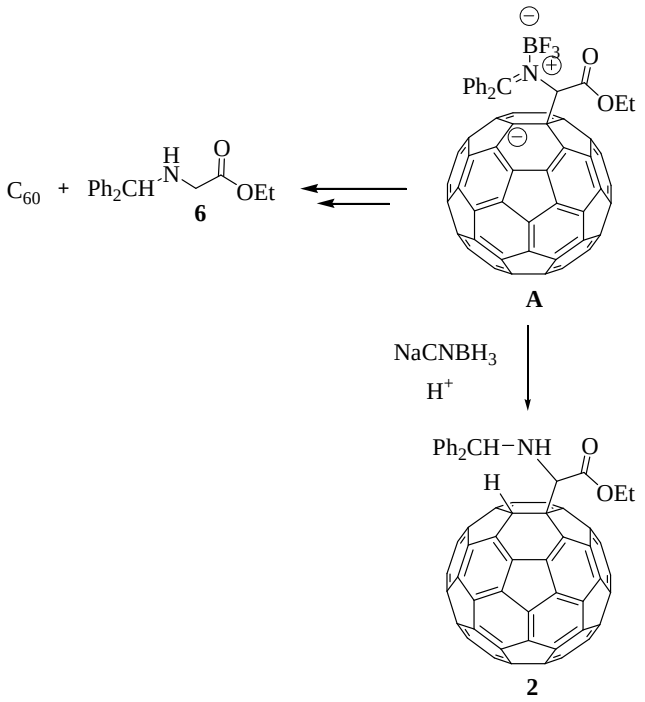
The reductive ring-opening reaction conditions previously established in our laboratory are sufficient for the simple [60]fullerenyldihydropyrrole **1**, however optimisation of these reaction conditions was required to allow for use in more complicated systems. For example, when the *trans*-4 or *cis*-3 bis-adducts of **3** were subjected to standard ring-opening reaction conditions the analogous dihydrofullerene compounds **4**, as well as the reduced addend **5** and C_{60} were obtained rather than the desired bis-dihydrofullerenyl derivatives (*e.g.* **7**, Scheme 3.).[5] Hence a comprehensive study was conducted to optimize the conditions for reductive ring opening of **1** before using this methodology on structurally more complex compounds (Table 1, Supporting Information).



Scheme 1:

Under our previously published reductive ring opening reaction conditions[5] **2** was isolated in 58% yield along with a significant quantity of pristine fullerene.[7] The latter product was expected to arise from collapse of the anionic intermediate **A** (Scheme 2) to form C_{60} and eventually the reduced addend **6**. As a modification of the published procedure, glacial acetic acid was additionally added at the beginning of the reaction to quench the proposed anionic intermediate **A** *in situ.* By systematically varying the amounts of acetic acid, reducing agent and the Lewis acid ($BF_3.OEt_2$) and varying the reaction temperature, solvent and concentration (see Supporting Information for details) the yield of **2** was increased from 58% to 68%. The best reaction conditions found involved the addition of $BF_3.OEt_2$ (10 equiv.) to a 0.5 mg/mL solution of **1** in THF at 0 ^{o}C, followed by the addition of $NaCNBH_3$ (10 equiv.) and glacial acetic acid

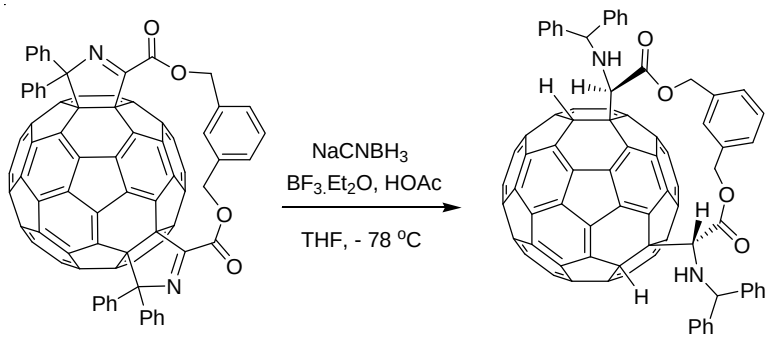
(60 equiv.). The solution was stirred for 45 min leading to an increased yield of the protected α-[60]fullerenyl glycine **2** (68%) together with 13% of C_{60}.[8]



Scheme 2:

The extension of the optimised conditions developed for the reductive ring-opening of the monoadduct **1** to the *trans*-4 bis-adduct **3** did not represent an efficient method for the generation of the analogous bis-ring-opened product **7**, but rather led to the isolation of the dihydrofullerenyl derivative **4** in an increased yield of 68%, reduced addend **5** (8%) and C_{60} (Scheme 1). Notably, traces of what was speculated to be the bis-dihydrofullerenyl derivative **7** were evident from TLC analysis of the reaction mixture, This analysis showed two products, speculated to be the racemate (*R,R* and *S,S*) and the *meso* forms (*R,S*)/(*S,R*) of **7** (Scheme 3). When this reaction was conducted at -78 ^{o}C however, TLC analysis indicated almost complete conversion to the compounds of interest, speculated to be *rac*- and *meso*-**7** (Scheme 3).[9] The remaining

component of the reaction mixture appeared as unknown baseline material. Purification of the crude reaction mixture by flash silica gel chromatography delivered the racemic bis-dihydrofullerenyl derivative *rac*-**7** in 9% yield. None of the *meso* form of **7** was isolated. Further elution provided the known dihydrofullerenyl derivative **4** (62%) and the reduced addend **5** (10%). Our results suggest that *rac*-**7** is more stable than *meso*-**7**. However, it appeared that **7** was unstable to the work-up and/or isolation processes and decomposed to form **4**. In order to determine the cause of decomposition of **7** to **4**, both the work-up and isolation procedures were systematically investigated, the results of which indicated that the primary cause for degradation was when the work-up temperatures exceeded 0 ^{o}C.



trans-4 **3**

(*RS,RS*)-**7**

+ **4** (62%) + **5** (10%)

Scheme 3

Analysis of the ^{1}H NMR spectrum of *rac*-**7** showed two singlets at 6.24 and 6.61 ppm, both with relative integrations of 1H, indicative of the fullerenyl protons (H_F, Figure 1). In conjunction with the gCOSY spectrum the four resonances corresponding to the diastereotopic benzylic protons (H_D and H_E) were assigned as the four 1H doublets; J = 11.1 Hz for the coupled resonances at 5.76 and 4.57 ppm and J = 11.7 Hz, for the coupled resonances at 5.50 and 4.66 ppm. Further evidence for the structure of *rac*-**7** was the pair of 1H doublet of doublets at 3.21 (J = <1, 13.8 Hz) and 3.52 ppm (J = <1, 13.8 Hz) assigned as the NH resonances (H_B). Analysis of the gCOSY spectrum clearly showed cross-peaks from the NH resonance at 3.21 ppm to the 1H doublet resonance at 4.62 ppm (H_C, J = 13.8 Hz), whilst the NH resonance at 3.52 ppm was coupled to 4.53 ppm (H_C), (J = 13.8 Hz). An additional correlation from each NH resonance was also shown to the 1H doublets (J < 1 Hz) at 5.16 and 5.24 ppm (2 x H_A), this three spin system was consistent with the proposed structure. Further confirmation of the structure of *rac*-**7** was provided by analysis of the negative ion ESI mass spectrum, which showed a peak at *m/z* 1303 (100%) assigned as the molecular ion $(M-H)^-$.

Interestingly, the *meso* compound was not isolated and was speculated to have decomposed during work-up. Since a symmetry plane would bisect the substitution sites of *meso*-**7**, the ^{1}H NMR spectrum of this compound would be relatively simple compared to the *rac*-**7**, which does not possess any symmetry elements (Figure 1).

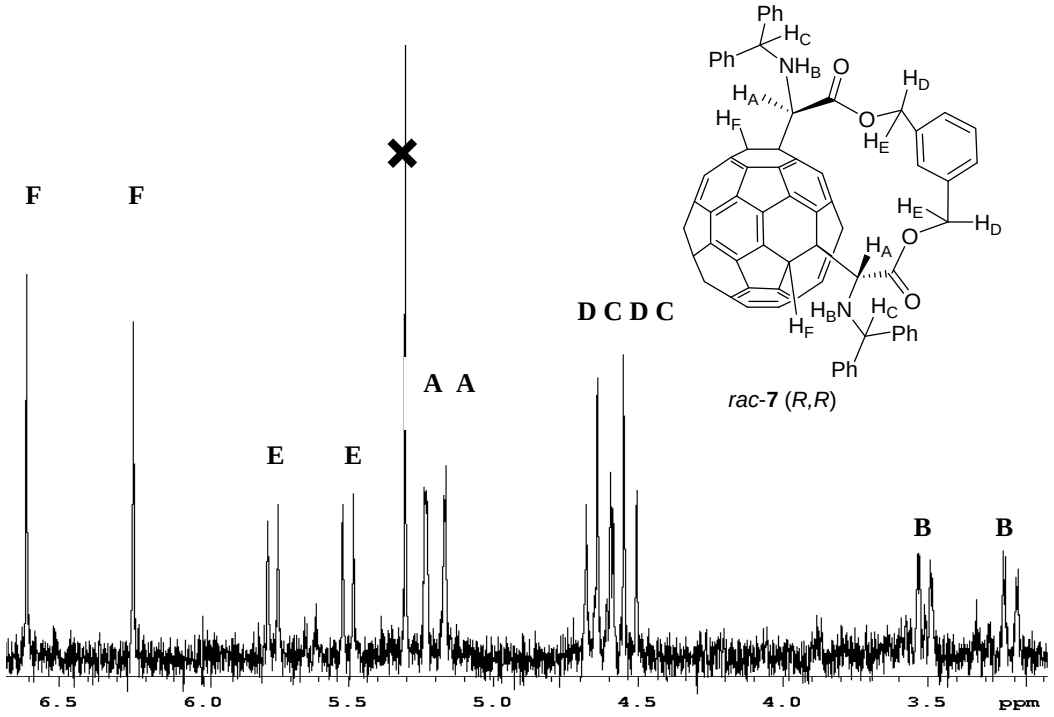


Figure 1: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of the bis-dihydrofullerenyl derivative *rac*-**7**, proton assignments were determined in conjunction with analysis of the gCOSY spectrum. X denotes the CH_2Cl_2 resonance, the (*R*,*R*) enantiomer is inset.

In conclusion, the reductive ring opening reaction conditions for the simple [60]fullerenyldihydropyrrole **1** have been optimized to include acetic acid in the reaction mixture to rapidly protonate the anionic intermediate. Under these conditions the dihydrofullerene **2** was obtained in 68% yield. Under slightly modified conditions, and at -78 ^{o}C, the reductive bis-ring opening of the tethered *trans*-4 isomer of **3** provided the novel racemic bis-dihydrofullerenylderivative **7**. Efforts to further increase the yield of this

compound and to use it in the synthesis of bis-fullerenyl peptides will be reported in due course.

Acknowledgements

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(8) To a solution of **1** (0.030 g, 0.030 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC under an atmosphere of nitrogen was added dropwise boron trifluoride.diethyl etherate (0.043 g, 0.30 mmol) over

1 min. The reaction mixture was stirred for 15 min then THF (20 mL), sodium cyanoborohydride (0.019 g, 0.30 mmol) and glacial acetic acid (0.1 mL) were added and the solution was stirred for a further 30 min. The reaction mixture was then concentrated in vacuo, the residue redissolved in CH_2Cl_2 (40 mL) and washed with a saturated NH_4Cl solution (10 mL). The organic phase was collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was then subjected to silica gel column chromatography, elution with toluene/hexanes (1 : 1) to afford **2** (0.020 g, 68%) as a brown amorphous solid. The spectral data was identical to that reported. [5,6]

(9) Boron trifluoride.diethyl etherate (0.057 g, 0.40 mmol) was added dropwise over 1 min to a solution of *trans*-4 **3** (0.050 g, 39 μmol) in THF (30 mL) at -78 ^oC under an atmosphere of argon. The reaction mixture was stirred for 10 min then sodium cyanoborohydride (0.025 g, 0.40 mmol) and glacial acetic acid (0.1 mL) were added to the reaction mixture, which was stirred for 15 min at –78 ^oC. CH_2Cl_2 (50 mL) was added and the reaction mixture was quenched with ice water. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure (at 0 ^oC) then, subjected to flash silica gel chromatography. Elution with CH_2Cl_2/hexanes (3 : 2), afforded the title compound **7** (0.0043 g, 9%) as a brown amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.21 (dd, 1H, *J* = <1, 13.8 Hz, NH), 3.52 (dd, 1H, *J* = <1, 13.5 Hz, NH), 4.53 (d, 1H, *J* = 13.8 Hz, C<u>H</u>Ph_2), 4.57 (d, 1H, *J* = 11.1 Hz, OC<u>H_2</u>), 4.62 (d, 1H, *J* = 13.8 Hz, C<u>H</u>Ph_2), 4.66 (d, 1H, *J* = 11.7 Hz, OC<u>H_2</u>), 5.16 (d, 1H, J < 1 Hz, NCHCO_2), 5.24 (d, 1H, J < 1 Hz, NCHCO_2), 5.50 (d, 1H, *J* = 11.7 Hz, OC<u>H_2</u>), 5.76 (d, 1H, *J* = 11.1 Hz, OC<u>H_2</u>), 6.24 (s, 1H, $C_{60}H$), 6.61 (s, 1H, $C_{60}H$), 6.78 (d, 1H, *J* = 8.0 Hz, ArH), 6.96 (m, 3H, ArH), 7.16 (d, 1H, *J* = 8.0 Hz, ArH), 7.33 (t, 2H, *J* = 7.3 Hz, ArH), 7.45 (m, 6H, ArH), 7.58 (m, 3H, ArH), 7.65 (d, 2H, *J* = 7.0 Hz, ArH), 7.72 (d, 2H, *J* = 7.0 Hz, ArH), 7.80 (d, 2H, *J* = 7.0 Hz, ArH), 7.88 (d, 2H, *J* = 7.0 Hz, ArH). ESI-MS (-ve): *m/z* 1303 (100%, M-H).

Further elution with CH_2Cl_2/hexanes (7 : 3) provided **4** (0.031 g, 62%) as a brown solid. The spectral data was identical to that reported.[5] Further elution with CH_2Cl_2/hexanes (7 : 3) furnished **5** as a white powder (0.0018 g, 10%). This compound has only been reported in a PhD thesis.[7] ^1H NMR ($CDCl_3$, 300 MHz): δ 2.33 (bs, 2H, 2 x NH), 3.42 (s, 4H, 2 x C<u>H_2</u>NH), 4.87 (s, 2H, 2 x C<u>H</u>Ph_2), 5.15 (s, 4H, 2 x benzylC<u>H_2</u>), 7.38-7.19 (m, 24H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 49.0 ($NHCH_2$), 66.1 (<u>C</u>HPh_2), 66.5 (benzyl<u>C</u>H_2), 127.0 (ArC2; 127.2 (ArC4,6), 127.3 (ArC4',4"), 128.5 (ArC3',3",5',5"), 128.6 (ArC2',2",6',6"), 129.3 (ArC5), 135.8 (ArC1,3), 143.1 (ArC1',1"), 172.4 (CO). ESI-MS (+ve): *m/z* 585 (100%, MH^+).