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Diastereoselective Synthesis of Fulleropyrrolidines from Suitably Functionalized Chiral Cyclobutanes

Beatriz M. Illescas and Nazario Martín*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, E-28040 Madrid, Spain

Jordi Poater

Afdeling Theoretische Chemie, Scheikundig Laboratorium der Vrije Universiteit, De Boelelaan 1083, NL-1081 HV Amsterdam, The Netherlands

Miquel Solà

Institut de Química Computacional and Departament de Química, Universitat de Girona, Campus de Montilivi, 17071 Girona, Catalonia, Spain

Gemma P. Aguado and Rosa M. Ortuño

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

nazmar@quim.ucm.es

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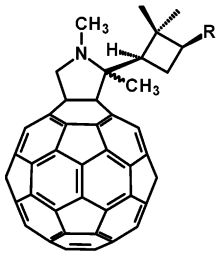
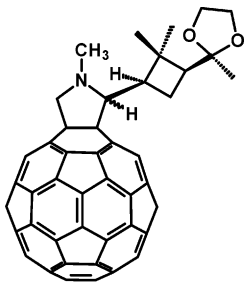


7a: R = CH_2OCH_2Ph
7b: R = $CO_2{}^tBu$



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The first diastereoselective synthesis of fulleropyrrolidines endowed with diastereomerically pure functionalized cyclobutanes is reported. The new C_{60}-based cyclobutane derivatives **7a**,**b** and **9** are suitably functionalized for further incorporation into peptide surrogates.

Since the discovery of fullerenes in 1985, different studies with fullerene derivatives have shown that they exhibit several types of biological activities, both in vitro and in vivo, that can be exploited for medicinal purposes.[1] The exceptionally hydrophobic nature and spherical shape of C_{60} make it a very interesting pharmacophore in the search of novel biologically active molecules. In this regard, some fullerene derivatives have shown a broad range of promising biological activities,[1] especially in fields such as photodynamic therapy,[2] inhibition of HIV-protease,[3] neuroprotection,[4] and apoptosis.[1] Among the different classes of chemically modified fullerenes, fullerene-based amino acids and peptides are particularly interesting, both for structural studies and biological applications (Chart 1).

Despite the large amount of fullerene derivatives reported in the last few years, the number of chiral C_{60}-based compounds is still low.[5] Chiral monoadducts of C_{60} have been synthesized from asymmetric[6] or C_2-symmetric[7] molecules. Inherently asymmetric bisadducts of C_{60} with C_2-symmetry have also been reported.[8] Among the different chiral addends linked to C_{60}, amino acids have played an important role as potential candidates to be incorporated in nonnatural C_{60}-based peptide analogues. A series of fullero-peptides containing amino acid **4** have been successfully obtained by solid-phase synthesis, thus paving the way to the extension of this methodology to different classes of biologically relevant peptides.[9] We had previously reported the synthesis of the first fullerene derivatives bearing enantiomerically pure cyclopropane amino acids (**5**) in which both amino and carboxyl groups are suitably protected (Chart 1).[10]

The cyclobutane ring has been shown to be an efficient inducer of secondary structures when incorporated into α-,[11] β-,[12] and γ-peptides.[13] Otherwise, the cyclobutane

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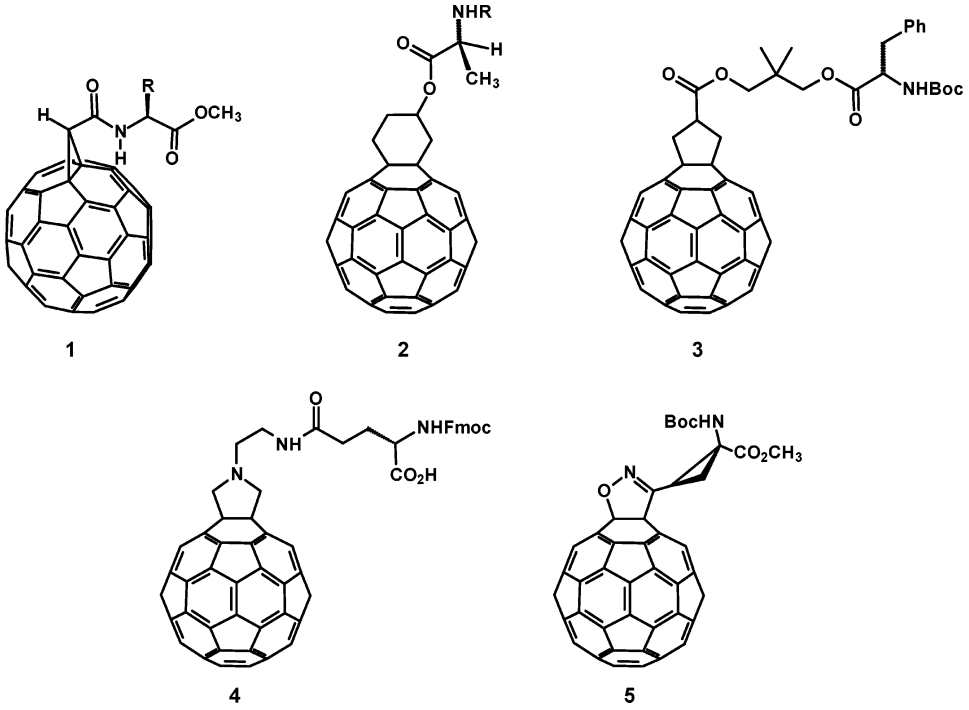
CHART 1

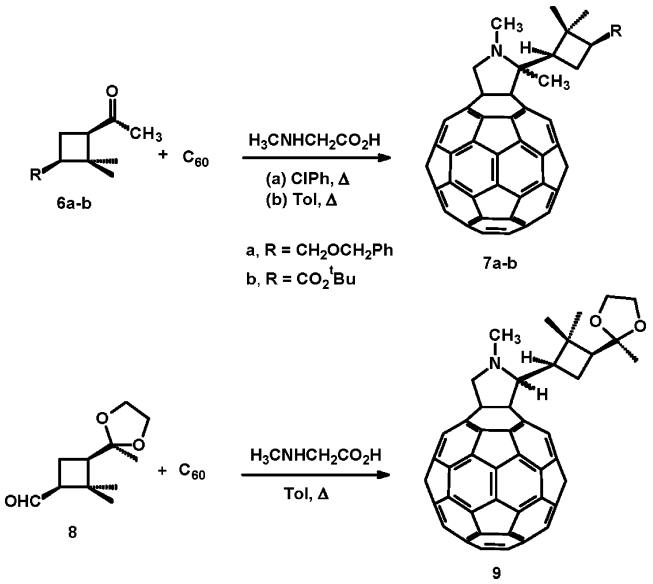


unit is present in the molecular structure of natural[14] or designed[15] amino acids and peptides with biological activities as well as in other bioactive products such as carbocyclic nucleosides.[16]

In this paper, we report the synthesis of new C_{60}-based cyclobutane derivatives suitably functionalized for their further incorporation into peptide surrogates. Prepared compounds **6a**,**b** and **8** are precursors to polyfunctional amino acids with conformationally constrained structures, according to convenient protocols previously described in our laboratory.[17] These compounds (**6a**,**b** and **8**) were synthesized from (−)-*cis*-pinononic acid prepared by oxidation of (−)-verbenone,[17a] involving the reaction with *t*-BuOH to afford *tert*-butyl ester **6b**,[17d] or by selective transformations of the carboxyl group, namely, reduction to alcohol and subsequent benzylation leading to **6a**,[17f] or reduction to aldehyde **8**.[17a]

The synthesis of new fullerene derivatives **7a**,**b** and **9** was carried out by 1,3-dipolar cycloaddition of the in situ-generated azomethine ylides to C_{60} by following Prato's procedure.[18] Thus, a mixture of the corresponding carbonyl compound (**6a**,**b** or **8**), C_{60}, and sarcosine was refluxed in chlorobenzene (**7a**) or toluene (**7b** and **9**) for 22−24 h (**7a** and **9**) or 4 days (**7b**) (Scheme 1). Whereas the reaction with the methyl ketone **6a** was carried out in chlorobenzene, no reaction was observed in this solvent with methyl ketone **6b**. 1,2-Dichlorobenzene was also employed, but the yield on **7b** was lower (4%) than in toluene. A remarkable decrease in yield is observed in the 1,3-dipolar cycloaddition reaction when a methyl ketone is employed (13% for **7a** and 9% for **7b**) instead of an aldehyde (27% for **9**) for the generation of the corresponding azomethine ylide and their further transformation into the respective fulleropyrrolidines.

SCHEME 1



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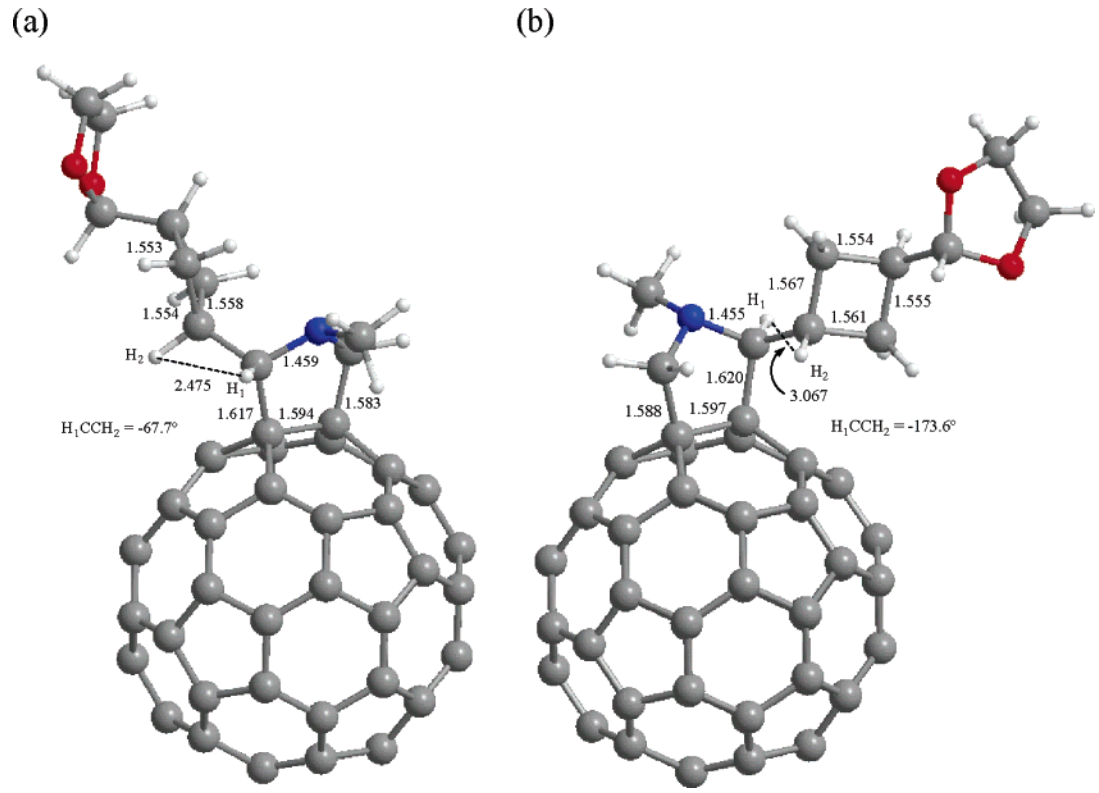

FIGURE 1. BP86 molecular structure of the cis (a) and trans (b) isomers of compound **9** with the most relevant bond lengths.

Interestingly, the ^{1}H NMR spectra of these compounds (**7a**,**b** and **9**) show the presence of one of the possible isomers with diastereomeric excesses over 90%. Thus, the cyclization to afford the pyrrolidine ring, which takes place with the generation of a new stereogenic center, was highly diastereoselective. We had previously observed a high stereoselectivity in the synthesis of fulleropyrrolidine-based cyclopropane amino acids[10] as well as in other fulleropyrrolidines bearing the biologically active 1,4-dihydropyridine ring.[19] The origin of the diastereoselectivity in this latter reaction has been analyzed recently by some of us using quantum mechanical calculations.[19c] We have found that the high stereoselectivity achieved in this reaction is due to energy barrier differences of about 4 kcal mol^{-1}, and it must be attributed to the steric hindrance caused by the bulky organic addend attached to the 1,3-dipole.

Compounds **7a** and **7b** show in the ^{1}H NMR spectra the signals of the pyrrolidine protons at δ 5.28 and 4.88 (**7a**) and δ 5.24 and 4.88 (**7b**) as doublets (J = 12.8 Hz; geminal hydrogens). The *N*-methyl protons appear at δ 3.48 (**7a**) and 3.45 (**7b**), and the methyl group attached to C-2 of the pyrrolidine ring is observed at δ 2.23 (**7a**) and 2.26 (**7b**).

For compound **9**, the pyrrolidine protons appear at δ 4.98 and 4.83 as doublets (J = 12.6 Hz; geminal hydrogens) and δ 4.86 (CH−N) as a doublet by coupling with the adjacent cyclobutane proton (J = 11.7 Hz).

The ^{13}C NMR spectra of compounds **7a**,**b** and **9** show a high number of signals, which indicates a lack of symmetry in these structures. The signals of the 6,6-ring junction of the C_{60} framework appear together with pyrrolidine carbons and the remaining sp^3 carbons of the compounds (δ 17.10−85.83). UV−vis spectra show the typical weak absorption band at 430−433 nm of dihydrofullerenes, thus confirming the [6,6]-closed character of the molecules.

BP86/DZP calculations (see Computational Details in Supporting Information) have been performed for the cis and trans isomers of compound **9**, in which the two geminal methyl groups on the cyclobutane ring have been substituted by hydrogen atoms, to determine their molecular structure and relative stability. The BP86/DZP-optimized molecular structures of the two isomers are depicted in Figure 1. The distance between the pyrrolidine proton H_1 and the cyclobutane proton H_2 is 2.475 and 3.012 Å and the $\angle H_1CCH_2$ dihedral angle is −67.7 and −173.6° for the cis and trans isomers, respectively. According to our BP86/DZP calculations, the trans isomer is 1.4 kcal mol^{-1} more stable than the cis isomer. BP86/TZ2P//BP86/DZP results also confirm that the trans isomer is the most stable, but only by 1.0 kcal mol^{-1}. Although the energy difference is rather small, our results point out that the trans formation is preferred from a thermodynamic point of view. Therefore, the product observed is likely to be the trans isomer of compound **9**. This result is further supported by BP86/TZ2P//BP86/DZP calculations of the nuclear spin−spin coupling constant between the pyrrolidine proton H_1 and the cyclobutane proton H_2, J_{H1H2}, for the two isomers. At the BP86/TZ2P//BP86/DZP level of theory, J_{H1H2} is 1.3

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Hz for the cis isomer of Figure 1a and 10.9 Hz for the trans isomer. The large difference between the cis and trans J_{H1H2} computed value and the fact that the calculated J_{H1H2} for the trans isomer is quite close to the experimental value (J = 11.7 Hz) let us unambiguously identify the compound obtained as the trans isomer.

In summary, we report herein the first diastereoselective synthesis of fulleropyrrolidines endowed with diastereomerically pure substituted cyclobutanes that are efficient inducers of secondary structures when they are contained in peptidic chains. Provided that fullerene derivatives have previously been incorporated into different peptides,[9] the results now reported pave the way to the incorporation of the new modified fulleropyrrolidines into peptide surrogates in the search of novel and unexpected structural and biological properties.

Experimental Section

7a. *Procedure.* To a solution of C_{60} (70 mg, 0.097 mmol) in chlorobenzene (20 mL) the methyl ketone **6a** (25 mg, 0.101 mmol) and sarcosine (35 mg, 0.388 mmol) were added. The mixture was refluxed for 24 h. The solvent was removed under reduced pressure, and the solid residue thus obtained was purified by column chromatography, using cyclohexane/toluene 1/1 as the eluent. An additional purification was accomplished by washing the solid two times with methanol: yield 13% (28% based on recovered C_{60}); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.30 (m, 5H, HAr), 5.28 (d, 1H, J = 12.8 Hz), 4.88 (d, 1H, J = 12.8 Hz), 4.53 (AB, 2H), 3.60 (t, 2H, J = 8.2 Hz), 3.48 (m, 4H), 2.32 (m, 1H), 2.23 (s, 3H), 1.92 (m, 2H), 1.45 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.7, 156.18, 155.81, 154.80, 146.80, 146.62, 146.56, 146.15, 145.93, 145.84, 145.72, 145.65, 145.50, 145.28, 145.11, 144.95, 144.83, 144.72, 144.42, 144.28, 143.23, 143.18, 142.82, 142.67, 142.61, 142.53, 142.25, 142.16, 142.13, 141.99, 141.73, 141.66, 140.26, 140.08, 139.65, 138.64, 135.94, 135.25, 135.00, 134.51, 128.35, 127.57, 127.49, 85.83, 79.46, 75.94, 73.07, 70.91, 70.39, 50.08, 44.68, 41.60, 39.76, 32.95, 29.69, 27.44, 17.45; FTIR (KBr) ν 2920, 2851, 1634, 1455, 1374, 1071, 576, 527 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 255, 317, 430 nm; MS *m/z* 993 (M^+).

7b. *Procedure.* To a solution of C_{60} (144 mg, 0.2 mmol) in toluene (80 mL) the methyl ketone **6b** (48 mg, 0.21 mmol) and sarcosine (71 mg, 0.8 mmol) were added. The mixture was refluxed for 4 days. The solvent was removed under reduced pressure, and the solid residue thus obtained was purified by column chromatography, using cyclohexane and cyclohexane/toluene (1/1 and 1/2) as eluents. An additional purification was accomplished by washing the solid two times with methanol: yield 9% (30% based on recovered C_{60}); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.24 (d, 1H, J = 12.8 Hz), 4.88 (d, 1H, J = 12.8 Hz), 3.64 (dd, 1H, J_1 = 11.5 Hz and J_2 = 7.7 Hz), 3.45 (s, 3H), 2.75 (dd, 1H, J_1 = 10.3 Hz and J_2 = 7.4 Hz), 2.50 (m, 1H), 2.26 (s, 3H), 1.89 (m, 1H), 1.64 (s, 3H), 1.50 (s, 9H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.50, 147.28, 147.24, 146.97, 146.60, 146.38, 146.32, 146.30, 146.11, 146.20, 145.91, 145.87, 145.75, 145.70, 144.88, 144.83, 144.72, 143.66, 143.62, 143.51, 143.13, 143.06, 142.98, 142.67, 142.63, 142.54, 142.43, 142.38, 142.23, 142.16, 142.11, 142.02, 140.70, 140.53, 140.15, 135.51, 135.11, 134.90, 80.65, 79.80, 76.18, 70.91, 68.18, 49.91, 47.46, 47.03, 40.14, 32.96, 30.11, 28.75, 25.39, 18.65; FTIR (KBr) ν 2922, 2851, 1724, 1458, 1366, 1238, 1151, 1070, 527 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 262, 320, 433, 703 nm; MS *m/z* 973 (M^+).

9. *Procedure.* To a solution of C_{60} (144 mg, 0.2 mmol) in toluene (80 mL) the aldehyde (40 mg, 0.20 mmol) and sarcosine (71 mg, 0.8 mmol) were added. The mixture was refluxed for 22 h. The solvent was removed under reduced pressure, and the solid residue thus obtained was purified by column chromatography, using toluene as the eluent. An additional purification was accomplished by washing the solid two times with methanol: yield 27% (46% based on recovered C_{60}); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.98 (d, 1H, J = 12.6 Hz), 4.86 (d, 1H, J = 11.7 Hz), 4.83 (d, 1H, J = 12.6 Hz), 4.05−3.96 (m, 2H), 3.91−3.82 (m, 2H), 3.54 (s, 3H), 3.02−2.96 (m, 1H) 2.33 (dd, 1H, J_1 = 11.0 Hz, J_2 = 7.8 Hz), 2.20−2.10 (m, 2H), 1.56 (s, 3H), 1.53 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.88, 156.69, 156.62, 154.30, 146.80, 146.76, 146.69, 146.31, 146.03, 145.99, 145.89, 145.85, 145.84, 145.83, 145.81, 145.53, 145.50, 145.19, 145.13, 145.07, 145.05, 145.03, 145.01, 144.43, 144.37, 144.35, 144.32, 143.19, 143.12, 142.63, 142.59, 142.57, 142.26, 142.24, 142.21, 142.20, 142.19, 142.16, 142.15, 142.14, 142.06, 141.90, 141.88, 141.78, 141.71, 140.22, 140.21, 139.70, 139.56, 135.99, 135.48, 134.96, 134.62, 132.33, 109.85, 81.95, 79.23, 70.31, 65.40, 63.53, 49.96, 44.89, 43.30, 40.72, 32.12, 29.69, 26.35, 23.70, 17.10; FTIR (KBr) ν 2922, 2853, 1655, 1638, 1605, 1458, 1248, 1175, 1036, 527 cm^{-1}; UV−vis ($CHCl_3$) λ_{max} 256, 317, 432, 703 nm; MS *m/z* 945 (M^+).

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Supporting Information Available: Computational details, BP86-optimized *xyz* coordinates of the cis and trans isomers of compound **9**, and ^{1}H and ^{13}C NMR spectra of new fullerene derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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