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Diastereoselective lithium salt-assisted 1,3-dipolar cycloaddition of azomethine ylides to the fullerene C_{60}

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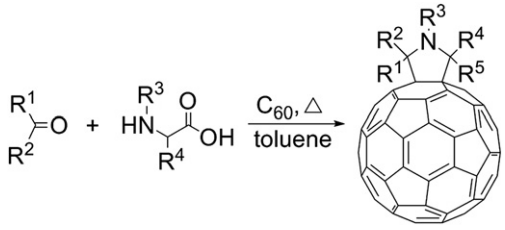
ABSTRACT

An efficient method for the diastereoselective synthesis of 5-substituted 3,4-fulleroproline esters based on the lithium salt-assisted cycloaddition of azomethine ylides has been developed. A series of the fulleroproline esters containing either electron donating or electron withdrawing substituents was prepared with high yields and diastereoselectivities provided by the *S-trans*-configuration of ylide generated in situ from the corresponding Schiff base in the presence of a lithium salt and base. This method provides easy preparation of 3,4-fulleroproline derivatives suitable for fullerene-based peptide synthesis.

1. Introduction

Physical and chemical properties of organic fullerene derivatives depend on their moieties. This attracts much attention to elaboration of methods, which could allow the preparation of compounds possessing desirable moieties with high yields. Among possible application areas for fullerenes modified by attaching of organic groups are organic electronics[1] and medicine.[2] Encouraging biological properties, such as *anti*-HIV activity and ability to inhibit enzymes, DNA cleavage, neuroprotective, antioxidant, and antimicrobial activities were discovered for several fullerene derivatives.[3]

One of the promising classes of fullerene derivatives is fulleropyrrolidines. The simplest path to these compounds is the Prato reaction involving 1,3-dipolar cycloaddition of azomethine ylides to C_{60}.[4] Azomethine ylides are generated in situ from either aldehydes or ketones and α-amino acids under reflux. This method allows the introduction of different substituents in three positions of the pyrrolidine ring by varying reagents (Scheme 1). A convenient α-amino acid usually employed is *N*-methylglycine and the reaction leads to the formation of the corresponding 5-substituted *N*-methyl-3,4-fulleropyrrolidines with moderate yields 30–40%.[5] Using of *N*-unsubstituted α-amino acids gives 3,4-fulleropyrrolidines with a lower yields.[6,7] When using an ester of an amino acid and aldehyde, the ester remains attached to the pyrrolidine ring so that 3,4-fulleroprolines (hereinafter Fpr, using the three-letter code for amino acids[5]) are formed.[8] The better yields (57–78%) of Fpr derivatives were achieved by thermal addition of α-imino acid esters to C_{60}.[9]



Scheme 1. General scheme of the Prato reaction.

Other methods of azomethine ylide generation based on thermal opening of the aziridine ring[10] and *N*-methoxymethyl-*N*-[(trimethylsilyl)-methyl]amine derivatives desilylation[11] are not widely used starting chemicals are difficult to access. Substituted Fpr derivatives were obtained by rearrangement of ethyl fullerenyl[60]glycinate imines in very mild conditions (rt, 16 h) with the moderate yields (14–64%).[12] The formation of fulleropyrrolidines was also observed during radical cycloaddition of secondary or tertiary amines to fullerene with low yields.[13]

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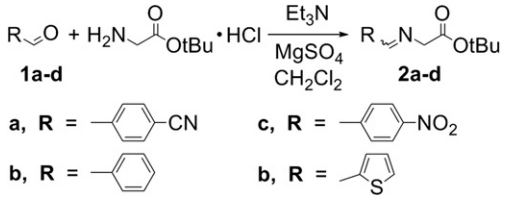
Further improvement of the Fpr yields can be achieved by employing of metal-assisted azomethine ylide cycloaddition. In contrast to the classical thermal condition often resulted in formation of diastereomeric mixture of products, low temperature metal-mediated azomethine ylide cycloaddition leads to higher yields and diastereoselectivity.[14,15] For example, pyrrolidine derivatives were prepared by imine cycloaddition to alkenes in the presence of lithium[16] or silver (I)[17] salts with high yields (50–96%) at ambient temperature. Recently effective synthetic methodology of chiral fulleropyrrolidines preparation based on this approach was proposed.[18] Controlled chiral functionalization of fullerene was achieved by the reaction of imines and fullerene in the presence of silver (I) and copper (II) salts together with a chiral ligand with excellent yields (25–88%) and diastereomeric and enantiomeric excesses at low temperatures.

Here, we report an efficient method of fulleroprolines' synthesis via the lithium salt-assisted cycloaddition of azomethine ylides generated from Schiff bases.

2. Results and discussion

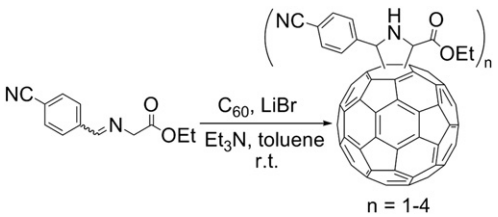
The Schiff bases **2a–d** were synthesized according to the standard procedure[19] by condensation of the corresponding aldehydes **1a–d** and glycine *tert*-butyl ester (Scheme 2). The prepared imines were used for subsequent reactions without any separation or additional purification.



Scheme 2. Preparation of the imines 2a–d.

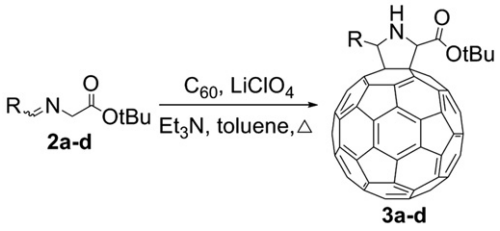
Lithium salt-assisted cycloaddition of azomethine ylides to alkenes are usually carried out during 24 h at room temperature. Reactions can be performed in homogeneous (LiBr solution in THF) regimes as well as in heterogeneous regimes (suspension of LiBr or AgOAc in toluene).

Initially, we used a suspension of LiBr in toluene. The low solubility of fullerene in polar solvents made us carry out a reaction in toluene instead of THF. *N*-(4-Cyanobenzyliden)glycine ethyl ester reacts with fullerene C_{60} in the presence of LiBr and triethylamine during 24 h at room temperature yielding compound mixture of mono- and polycycloadducts (Scheme 3). MALDI mass-spectrometry data indicate addition of up to four substituted pyrrolidine moieties to the fullerene cage. Formation of the products in the presence of LiBr even at the room temperature confirms metal-mediated azomethine ylide mechanism of cycloaddition. However heterogeneity of the reaction media results in the low conversion of the fullerene (41%) and the low selectivity. Therefore lithium perchlorate more soluble in nonpolar reaction media[20] was used as a catalyst in the following reactions.



Scheme 3. Reaction of *N*-(4-cyanobenzyliden)glycine ethyl ester with fullerene C_{60} in presence of lithium bromide.

Reaction of fullerene and the corresponding imines **2a–d** in the presence of a base (Et_3N) and lithium perchlorate under reflux for 5 h leads to compounds **3a–d** (Scheme 4) in quite high yields (55–73%, see Table 1). In contrast to LiBr-assisted cycloaddition, formation of polyadducts in considerable quantities is not observed.



Scheme 4. Reaction of imines with fullerene C_{60} in the presence of lithium perchlorate.

Table 1
Yields and diastereomeric ratios of the substituted Fpr derivatives **3a–d**

Comp.	R	Yield, %	*cis*/*trans*
3a	NC–	73	3:1
3b	–	64	2:1
3c	O_2N–	61	5:1
3d	S	55	2:1

To find out whether the aforementioned two-stage technique of fullerene derivatization can be simplified, additional experiments were carried out. The main idea of the suggested one-stage procedure consists of in situ imine formation. Refluxing of glycine *tert*-butyl ester, aldehyde and fullerene C_{60} in the presence of Et_3N and lithium perchlorate gives the target compounds with the lower yields in comparison with the two-stage technique. Furthermore, product mixture contains small quantity of *N*-ethyl-2,5-dimethyl-3,4-fulleropyrrolidine formed by radical addition of triethylamine to the fullerene.[13] We found that formation of such by-products can be suppressed by using sterically hindered 4-methylmorpholine instead of Et_3N.

MALDI mass-spectrometry analysis of compounds **3a–d** revealed some differences between negative and positive mass-spectra modes. In negative mode, molecular ions and C_{60}^- fragmentary ion were observed in contrast to positive mode containing peaks of the corresponding protonated acids being free of molecular ions' peaks. It can be explained by protonation of the ester group by the DCTB matrix with subsequent elimination of *tert*-butyl fragment under ionization and laser irradiation.[21]

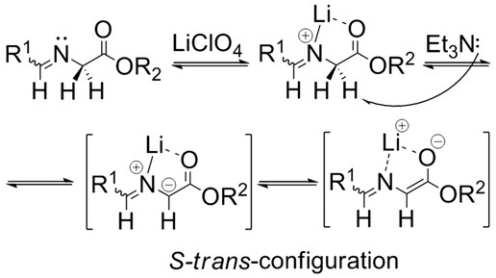
HPLC analysis (*Cosmosil Buckyprep* column, 4.6 I.D.mm×25 cm, and toluene as eluent, 1 or 2 mL min^{-1}) of the synthesized compounds showed that each of the compositions **3a–d** is presented by two isomers. Isomer ratios are given in Table 2 (assignment of diastereomers is discussed below). Isolation of pure individual diastereomers was performed by means of semipreparative HPLC (*Cosmosil Buckyprep*, 10 I.D.mm×25 cm, toluene, 4.6 mL min^{-1}).

Table 2
Chemical shifts of protons H^1 and H^2 of pyrrolidine ring **3a–d** compounds

Compound			3a	3b	3c	3d
NMR shift, ppm	*trans*-	H^1	6.57	6.54	6.62	6.84
		H^2	5.70	5.76	5.71	5.69
	cis-	H^1	5.89	5.86	5.93	6.17
		H^2	5.56	5.57	5.56	5.55

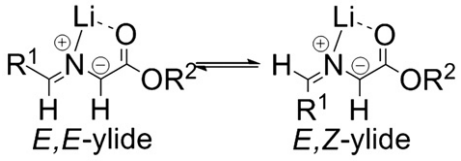
The ^{1}H NMR spectroscopic data reveal presence of both *cis*- and *trans*-isomers of compounds **3a**–**d**. The structural assignment was performed on the basis of correlations found in the work,[9] namely, the larger difference in chemical shift values of H^1 and H^2 (the proton labeling are given in the Scheme 7) as well as their downfield shift for the *trans*-isomer with respect to the *cis*-isomer. The signal assignments are given in Table 2. Interestingly, the chemical shift of *tert*-butyl groups' protons also appeared to be sensitive to the product configuration: it equals 1.51 ppm for the *cis*- and 1.57 ppm for the *trans*-isomer.

Obviously, the observed diastereoselectivity is related to the mechanism of $4\pi+2\pi$ concerted cycloaddition of metallo-1,3-dipole to the double bond.[22] The key stage of the process is electrocyclic addition of the azomethine ylide in distinct configuration to the fullerene cage. Apparently, the configuration of the azomethine ylide in the presence of lithium perchlorate is strongly fixed owing to coordination of lithium by both nitrogen and oxygen atoms of initial Schiff base (see Scheme 5). Subsequent deprotonation under base action leads to the *S*-*trans*-configuration of the ylide.[23]



Scheme 5. Formation of azomethine ylide in the *S*-*trans*-configuration.

The azomethine ylide can exist in two equilibrium *E*,*E*- and *E*,*Z*-configurations, wherein the *E*,*E*-configuration is thermodynamically more stable (Scheme 6).[23]

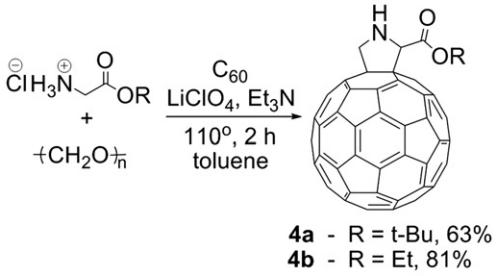


Scheme 6. Equilibrium of *E*,*E*- and *E*,*Z*-forms of azomethine ylide.

The formation of particular diastereomers of Fpr depends on the configuration of the reacting ylide. Thus, addition of either the *E*,*E*- or *E*,*Z*-azomethine ylide to the fullerene results in *cis*- or *trans*-diastereomer formation, respectively (Scheme 7). The yields of *cis*-Fprs exceed those of the *trans*-isomer due to the lower thermodynamic stability of *E*,*Z*-configuration of azomethine ylide.

It can be seen from Table 1 that the *cis*/*trans*-isomers ratio values for compounds **3a**,**c** containing electron withdrawing groups exceed those for derivatives with electron donor groups (**3b**,**d**). The stabilization of *E*,*E*-conformation of ylide by electron withdrawing substituent[23] R^1 makes more preferable formation of the *cis*-isomer as a major product.

We carried out the synthesis of Fpr esters **4a** and **4b** (1,5-unsubstituted Fpr *tert*-butyl and ethyl esters correspondingly) by generating the Schiff base in situ. A toluene solution containing paraformaldehyde, glycine ethyl (or *tert*-butyl) ester hydrochloride, fullerene C_{60}, lithium perchlorate and Et_3N was heated at reflux for 2 h (Scheme 8). Compounds **4a**,**b** were found to be stable and were isolated in 63% and 81% yields, correspondingly, and were characterized by HPLC, MALDI MS, and ^{1}H NMR spectroscopy.



Scheme 8. Preparation of Fpr esters.

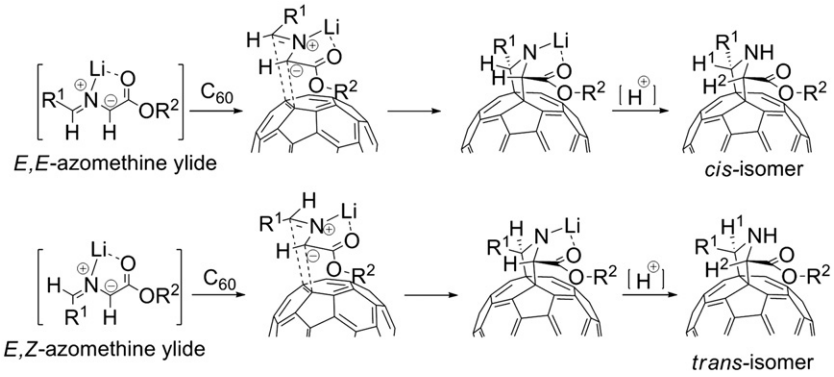
An earlier application of the Prato reaction to C_{60} aimed at **4a** gave only a 33% yield of the latter[8] while synthesis of Fpr ethyl ester **4b** by the reaction between C_{60} and perhydrotriazine derivative for 32 h at 90 °C resulted in 77% yield.[9]

In summary, a method of lithium salt-assisted cycloaddition of azomethine ylides known and widely used for alkenes was successfully applied to the fullerene C_{60}. This method appears to be an attractive tool for the synthesis of fulleroproline derivatives with both electron withdrawing and donor groups owing to quite high yield in comparison with the Prato reaction.

3. Experimental

3.1. Instrumentation

IR spectra were recorded on *Bruker Tensor* 27 spectrometer. ^{1}H NMR spectra were recorded on *Bruker Avance-400* (frequency 400 MHz) for chloroform-*d* solutions with TMS as an internal standard (δ_{TMS}=0.00 ppm). MALDI mass-spectra were obtained on *Bruker AutoFlex* spectrometer in both negative and positive ion modes, using DCTB (2-*trans*-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenilyden]malononitrile) as a matrix. High-performance liquid chromatography analysis was carried out on an *Agilent* 1100



Scheme 7. Mechanism for the formation of *cis*- and *trans*-diastereomers of the 5-substituted Fpr.

liquid chromatograph using a *Cosmosil Buckyprep* column (4.6 I.D.mm×25cm) with toluene as an eluent (1 or 2 mL min^{-1}). Preparative separation of diasteromeric products was performed on Waters chromatograph using a *Cosmosil Buckyprep* column (10 I.D.mm×25cm) with toluene as an eluent (4.6 mL min^{-1}). High resolution mass-spectra were obtained on *Bruker Apex-Ultra* FT ICR ESI MS spectrometer in positive mode. The samples were prepared in acetonitrile containing formic acid (0.1%), the analyte/solvent ratio was 1:100. The AC Tune mix G2421A mixture was used for calibration.

3.2. General procedure for preparation of iminoesters 2a–d

To a solution of glycine *tert*-butyl ester hydrochloride (28 mg, 0.17 mmol) and the corresponding aldehyde **1a–d** (0.17 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (23 μL, 0.17 mmol) and magnesium sulfate (33 mg, 0.34 mmol). The mixture was stirred at room temperature overnight. Then the mixture was filtered, toluene (20 mL) was added, and the solvent was evaporated to a half of the volume. The obtained imines were used in the next step without further purification.

3.3. General procedure for synthesis of Fpr derivatives 3a–d

A mixture of fullerene C_{60} (100 mg, 0.14 mmol), iminoester **2a–d** (0.17 mmol), lithium perchlorate (18 mg, 0.17 mmol), and triethylamine (23 μL, 0.17 mmol) in toluene (120 mL) was heated under reflux for 5 h. Purification by flash column chromatography (toluene, subsequently ethyl acetate–toluene mixture (v/v) 17/83) gave Fpr derivatives **3a–d** as an diastereomer mixtures. Individual diastereomers of **3a–d** were isolated by means of HPLC (*Cosmosil Buckyprep*, 10 I.D.mm×25 cm, toluene as an eluent, 4.6 mL min^{-1}) as brown solids.

*3.3.1. cis-5-(4-Cyanophenyl)-3,4-fulleroproline tert-butyl ester (cis-**3a**).* Yield 74 mg (55%); HPLC, 2 mL min^{-1}: t_R 3.47 min; ν_{max}(ATR IR) 2976, 2228, 1737, 1609, 1455, 1428, 1368, 1257, 1228, 1152, 1094, 1066, 832, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.2 Hz, Ar), 7.78 (2H, d, *J* 8.2 Hz, Ar), 5.89 (1H, s, C*H*Ar), 5.56 (1H, s, C*H*COO), 1.53 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 964 (71, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 909 (30, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 965.1294. $C_{74}H_{17}N_2O_2$ requires 965.1290.

*3.3.2. trans-5-(4-Cyanophenyl)-3,4-fulleroproline tert-butyl ester (trans-**3a**).* Yield 24 mg (18%); HPLC, 2 mL min^{-1}: t_R 3.01 min; ν_{max}(ATR IR) 2974, 2924, 2851, 2228, 1729, 1608, 1456, 1368, 1229, 1152, 1069, 1037, 836, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.06 (2H, d, *J* 8.2 Hz, Ar), 7.74 (2H, d, *J* 8.2 Hz, Ar), 6.57 (1H, s, C*H*Ar), 5.70 (1H, s, C*H*COO), 1.57 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 964 (71, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 909 (30, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 965.1294. $C_{74}H_{17}N_2O_2$ requires 965.1290.

*3.3.3. cis-5-Phenyl-3,4-fulleroproline tert-butyl ester (cis-**3b**).* Yield 53 mg (41%); HPLC, 1 mL min^{-1}: t_R 4.38 min; ν_{max}(ATR IR) 2923, 2853, 1735, 1456, 1369, 1247, 1151, 1043, 950, 841, 757, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 7.3 Hz, Ar), 7.47–7.43 (2H, t, *J* 7.9 Hz, Ar), 7.39–7.35 (1H, t, *J* 7.6 Hz, Ar), 5.86 (1H, s, C*H*Ar), 5.57 (1H, s, C*H*COO), 1.51 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 939 (27, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 884 (2, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 940.1336. $C_{73}H_{18}NO_2$ requires 940.1338.

*3.3.4. trans-5-Phenyl-3,4-fulleroproline tert-butyl ester (trans-**3b**).* Yield 30 mg (23%); HPLC, 1 mL min^{-1}: t_R 3.94 min; ν_{max}(ATR IR) 2973, 2910, 1730, 1455, 1368, 1230, 1153, 1029, 965, 839, 752, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 7.3 Hz, Ar), 7.45–7.41 (2H, t, *J* 7.9 Hz, Ar), 7.37–7.33 (1H, t, *J* 7.3, Ar), 6.54 (1H, s, C*H*Ar), 5.76 (1H, s, C*H*COO), 1.56 (9H, s, *t*-Bu); *m*/*z* (MALDI-TOF MS NI) 939 (27, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 884 (7, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 940.1336. $C_{73}H_{18}NO_2$ requires 940.1338.

*3.3.5. cis-5-(4-Nitrophenyl)-3,4-fulleroproline tert-butyl ester (cis-**3c**).* Yield 68 mg (50%); HPLC, 2 mL min^{-1}: t_R 2.95 min; ν_{max}(ATR IR) 2975, 2927, 2854, 1732, 1603, 1522, 1345, 1229, 1152, 907, 855, 839, 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* 8.5 Hz, Ar), 8.03 (2H, d, *J* 8.5 Hz, Ar), 5.93 (1H, s, C*H*Ar), 5.56 (1H, s, C*H*COO), 1.51 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 984 (66, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 929 (25, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 985.1188. $C_{73}H_{17}N_2O_4$ requires 985.1188.

*3.3.6. trans-5-(4-Nitrophenyl)-3,4-fulleroproline tert-butyl ester (trans-**3c**).* Yield 15 mg (11%); HPLC, 2 mL min^{-1}: t_R 2.65 min; ν_{max}(ATR IR) 2975, 2927, 2856, 1730, 1602, 1522, 1345, 1230, 1152, 908, 855, 839, 731 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.29 (2H, d, *J* 8.5 Hz, Ar), 8.11 (2H, d, *J* 8.5 Hz, Ar), 6.62 (1H, s, C*H*Ar), 5.71 (1H, s, C*H*COO), 1.56 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 984 (90, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 929 (8, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 985.1188. $C_{73}H_{17}N_2O_4$ requires 985.1188.

*3.3.7. cis-5-(2-Thienyl)-3,4-fulleroproline tert-butyl ester (cis-**3d**).* Yield 47 mg (36%); HPLC, 1 mL min^{-1}: t_R 2.95 min; ν_{max}(ATR IR) 2974, 2925, 2852, 1729, 1455, 1429, 1368, 1216, 1152, 834, 754, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.46 (1H, d, *J* 4.0 Hz, Ar), 7.38–7.37 (1H, dd, *J* 0.6, 4.9 Hz, Ar), 7.11–7.09 (1H, dd, *J* 3.7, 4.9 Hz, Ar), 6.17 (1H, s, C*H*Ar), 5.55 (1H, s, C*H*COO), 1.50 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 945 (37, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 890 (3, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 946.0899. $C_{71}H_{16}NO_2S$ requires 946.0902.

*3.3.8. trans-5-(2-Thienyl)-3,4-fulleroproline tert-butyl ester (trans-**3d**).* Yield 25 mg (19%); HPLC, 1 mL min^{-1}: t_R 3.98 min; ν_{max}(ATR IR) 2974, 2925, 2852, 1729, 1455, 1429, 1368, 1216, 1152, 834, 754, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, d, *J* 3.5 Hz, Ar), 7.36–7.34 (1H, dd, *J* 0.9, 5.2, Ar), 7.07–7.05 (1H, dd, *J* 3.4, 4.9, Ar), 6.81 (1H, s, C*H*Ar), 5.65 (1H, s, C*H*COO), 1.55 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 945 (37, M^-), 720 (100, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 890 (5, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+); HRMS (ESI): MH^+, found 946.0899. $C_{71}H_{16}NO_2S$ requires 946.0902.

3.4. Synthesis of 3,4-fulleroproline esters 4a,b

A mixture of C_{60} (100 mg, 0.14 mmol), glycine ester (0.17 mmol), paraformaldehyde (5 mg, 0.17 mmol), lithium perchlorate (18 mg, 0.17 mmol), and triethylamine (23 μL, 0.17 mmol) in toluene (120 mL) was heated under reflux for 2 h. Purification by flash column chromatography (toluene, subsequently ethyl acetate–toluene (v/v) 17/83) gave brown solid esters **4a** and **4b**.

*3.4.1. 3,4-Fulleroproline tert-butyl ester (**4a**).* Yield 76 mg (63%); HPLC, 2 mL min^{-1}: t_R 3.05 min; ν_{max}(ATR IR) 2965, 2924, 2865, 1726, 1452, 1425, 1366, 1248, 1211, 1150, 751, 574 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.40 (1H, s, C*H*COO); 5.08 (1H, d, *J* 12.2 Hz, *H*CH); 4.76 (1H, d, *J* 12.2 Hz, *H*CH); 1,51 (9H, s, *t-Bu*); *m*/*z* (MALDI-TOF MS NI) 877 (11, $\{M+O\}^-$), 863 (100, M^-), 720 (21, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 863 (17, M^+), 808 (80, $\{M-C_4H_7\}^+$), 720 (100, C_{60}^+).

*3.4.2. 3,4-Fulleroproline ethyl ester (**4b**).* Yield 94 mg (81%); HPLC, 2 mL min^{-1}: t_R 2.59 min; ν_{max}(ATR IR) 2974, 2954, 2925, 2876, 2844, 2785, 1742, 1462, 1428, 1265, 1189, 1094, 752, 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.66 (1H, s, C*H*COO), 5.26 (1H, d, *J* 12.2 Hz, *H*CH),

4.92 (1H, d, *J* 12.2 Hz, *H*CH), 4.49–4.36 (2H, m, CH_2O), 1.30–1.26 (3H, t, *J* 7.31, CH_3); *m*/*z* (MALDI-TOF MS NI) 835 (100, M^-), 720 (15, C_{60}^-); *m*/*z* (MALDI-TOF MS PI) 836 (41, $\{M+H\}^+$), 835 (27, M^+), 720 (100, C_{60}^+).

References and notes

1. Guldi, D. M. *Chem. Soc. Rev.* **2002**, *31*, 22.
2. Nielsen, G.; Roursgaard, M.; Jensen, K.; Poulsen, S.; Larsen, S. *Basic Clin. Pharmacol. Toxicol.* **2008**, *103*, 197.
3. Bakry, R.; Vallant, R.; Najam-ul-Haq, M.; Rainer, M.; Szabo, Z.; Huck, C.; Bonn, G. *Int. J. Nanomed.* **2007**, *2*, 639.
4. Maggini, M.; Scorrano, G.; Prato, M. *J. Am. Chem. Soc.* **1993**, *115*, 9798.
5. Prato, M.; Maggini, M.; Scorrano, G. *Synth. Met.* **1996**, *77*, 89.
6. Wilson, S. R.; Wang, Y.; Cao, J.; Tan, X. *Tetrahedron Lett.* **1996**, *37*, 775.
7. Wang, G. W.; Tian, Z. G. *Tetrahedron Lett.* **2009**, *50*, 3860.
8. Bianco, A.; Maggini, M.; Scorrano, G.; Toniolo, C.; Marconi, G.; Villani, C.; Prato, M. *J. Am. Chem. Soc.* **1996**, *118*, 4072.
9. Wu, S.; Sun, W.; Zhang, D.; Shu, L.; Wu, H.; Xu, J.; Lao, X. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1733.
10. Maggini, M.; Scorrano, G.; Bianco, A.; Toniolo, C.; Sijbesma, R. P.; Wudl, F.; Prato, M. *J. Chem. Soc., Chem. Commun.* **1994**, 305.
11. Zhang, X.; Willems, M.; Foote, C. *Tetrahedron Lett.* **1993**, *34*, 8187.
12. Thayumanavan, R.; Hawkins, B. C.; Keller, P. A.; Pyne, S. G.; Ball, G. E. *Org. Lett.* **2008**, *10*, 1315.
13. Lawson, G.; Kitaygorodskiy, A.; Sun, Y.-P. *J. Org. Chem.* **1999**, *64*, 5913.
14. Pellisier, H. *Tetrahedron* **2007**, *63*, 3259.
15. Ruano, J. L. G.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981.
16. Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.
17. Grigg, R.; Cooper, D. M.; Holloway, S.; McDonald, S.; Millington, E.; Sarker, M. A. B. *Tetrahedron* **2005**, *61*, 8677.
18. Filipone, S.; Maroto, E. E.; Martin-Domenech, A.; Suarez, M.; Martin, N. *Nat. Chem.* **2009**, *1*, 578.
19. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.
20. Rickborn, B.; Gerkin, R. *J. Am. Chem. Soc.* **1971**, *93*, 1693.
21. Markov, V. Y.; Ioutsi, V. A.; Lanskih, M. A.; Apenova, M. G.; Ovchinnikova, N. S.; Ioffe, I. N.; Sidorov, L. N. *Mass-Spectrometry* **2009**, *6*, 121 (in russian).
22. Grigg, R.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1669.
23. Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.