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Synthesis of Novel Quinone–Amino Acid Hybrids via Cross-Enyne Metathesis and Diels–Alder Reaction as Key Steps

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A "Building Block Approach" for the synthesis of various quinone-amino acid hybrids through ethylene cross-enyne metathesis and Diels–Alder reaction as key steps is described. A library of comformationally constrained quinone-based phenylalanine derivatives and dicarba analogs of cystine have been generated starting from a common precursor using Grubbs' catalysts. This methodology has also been extended for the synthesis of fullerene-based dicarba analogs of cystine.

Introduction

In recent years, synthesis of hybrid natural products has gained momentum. Generally, it is expected that combining features of more than one biologically active natural segments in a single molecule may result in pronounced pharmacological activity.[1] Quinones are an important class of natural compounds that show a wide range of applications in medicinal chemistry,[2] photochemistry, and redox systems.[3] They are present in several enzymes and is responsible for exhibiting various intricate biological properties.[4–6] The quinone component is also a useful tool for understanding the mechanism of various biological processes occurring in nature and can be successfully incorporated in hybrid molecules.[7–8] For example, enzymes containing quinone moiety play a critical role in oxidative deamination of biogenic amines.[9] Similarly, pyrrolo-quinoline quinone (PQQ, **1**), a hybrid of quinone and amino acid, serves as a redox cofactor for several bacterial dehydrogenases (Figure 1).[10] The extensive applications of quinone–amino acid hybrids in diverse fields make it worthwhile for the organic chemist to pursue their synthesis. However, limited reports are available describing quinone-containing amino acids.[11] Kotha et al. have reported a useful methodology for the synthesis of quinone-based amino acid derivatives by intramolecular alkylation of Schiff base with the *o*-xylylene dibromide derivative.[12] Similarly, Bittner and co-workers have synthesized various napthaquinoyl heterocyclic amino acids (such as **2**, Figure 1), some of which are crucial building blocks in cytotoxic peptide analogs.[13] To this end, the application of metathesis for the synthesis of novel quinone–amino acid hybrids has been envisaged.

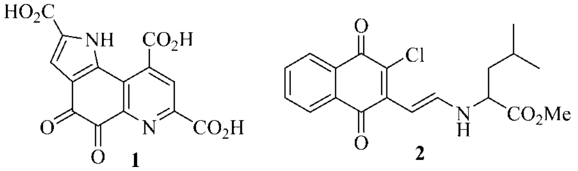

Figure 1. Biologically relevant quinone-based amino acid derivatives.

With the availability of well-defined and commercially available metal carbene complexes such as **3**[14a], **4**[14b] and **5**[14c] (Figure 2), the metathesis strategy has received a renewed interest and has opened up several new retrosynthetic pathways in organic synthesis.[15] Although RCM has

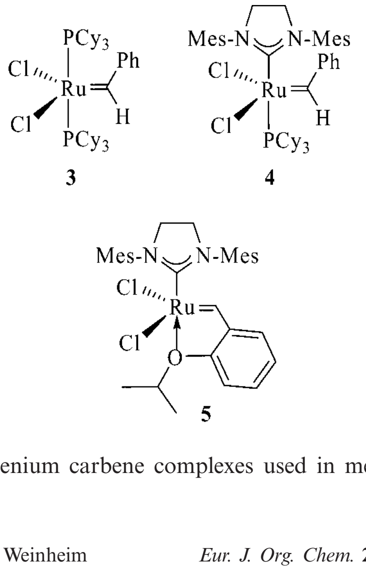

Figure 2. Ruthenium carbene complexes used in metathesis reactions.

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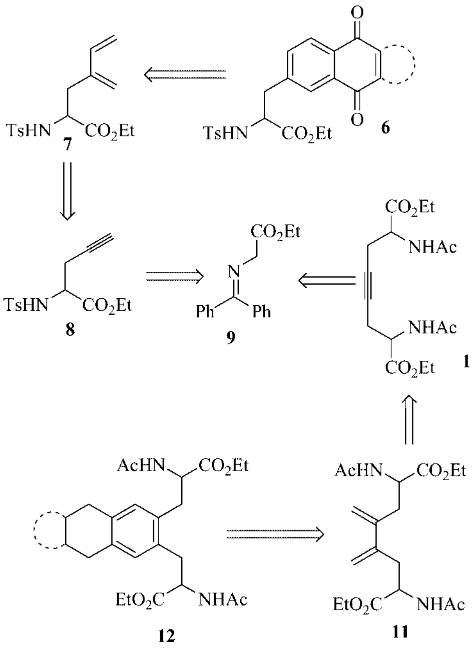
gained popularity, enyne metathesis, and more specifically, cross-enyne metathesis (CEM) with ethylene is less explored.[16–18]

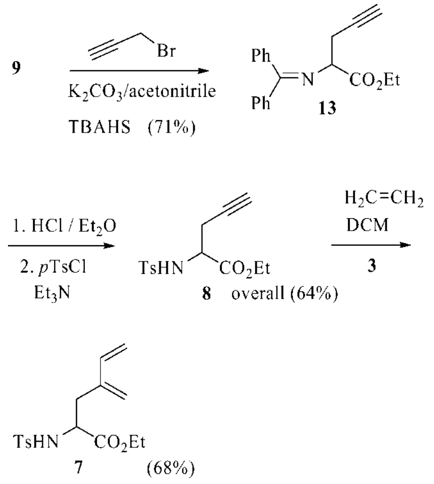
Towards the synthesis of novel quinone–amino acid hybrids the 'Building Block Approach' has been conceived for the generation of a diverse range of quinone-containing phenylalanine (Phe) derivatives and conformationally constrained dicarba analogs of cystine.[19] To this end, CEM and Diels–Alder (DA) reactions have been used as key steps. Here, the benzophenoneimine glycine ethyl ester **9** has been utilized as a glycine equivalent, which has been suitably modified by appending an acetylenic moiety.[20] The diene building blocks required here was prepared through Grubbs' catalyst induced CEM of alkynyl mono- and bis-(amino acid) derivatives with ethylene. DA reaction of the resulting dienes (e.g. **7** and **11**) with various dienophiles and the subsequent aromatization protocol delivered conformationally constrained quinones containing Phe and dicarba analogs of cystine derivatives **6** and **12**, respectively (Scheme 1).



Scheme 1. Strategy for the synthesis of quinone–amino acid hybrids.

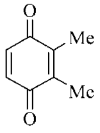
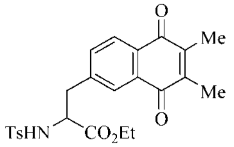
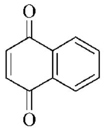
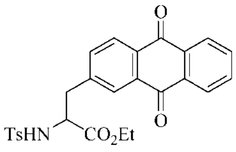
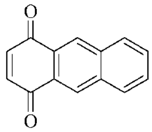
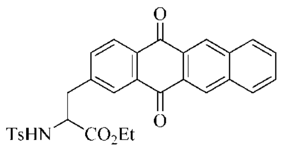
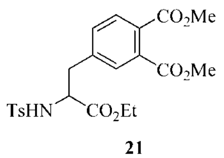
Results and Discussion

To begin with, the glycine equivalent, ethyl *N*-(diphenylmethylene)glycinate (**9**) was alkylated with propargyl bromide under phase-transfer catalysis (PTC) condition, using K_2CO_3 as a base to obtain the acetylene derivative **13** (Scheme 2).[20] Hydrolysis of the unsaturated amino acid derivative **13** with 1 M HCl delivered the expected hydrochloride salt, which was further neutralized with triethylamine and subsequently tosylated with *p*TsCl in one pot to obtain the requisite tosyl derivative **8**. The propargylated amino acid derivative **8** was then subjected to ethylene CEM reaction using Grubbs' first-generation catalyst **3** in DCM at room temp. to obtain the required diene building block **7**, which on reaction with suitable dienophiles containing the quinone moiety delivered the DA adducts. Subsequent aromatization of the DA adduct with MnO_2 gave the Phe derivatives in good yield (Table 1).



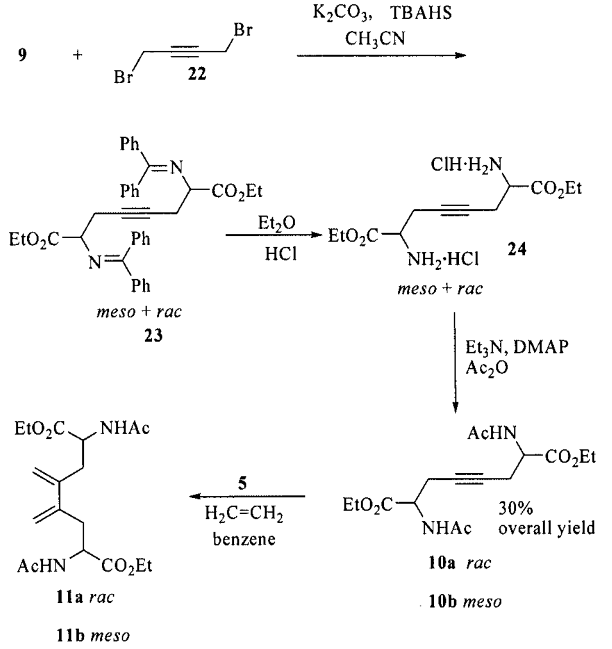
Scheme 2. Synthetic route to functionalized Phe derivatives based on CEM with ethylene.

Table 1. List of various quinone–phenylalanine hybrids prepared through DA strategy.

Entry	Dienophile	Product	Yield (%)[a,b]
1	 **14**	 **18**	81
2	 **15**	 **19**	77
3	 **16**	 **20**	93
4	 **17**	 **21**	67

[a] DA reaction was carried out by heating in toluene at 90 °C. [b] Isolated overall yield after DA and aromatization step.

Similar conditions were employed to prepare the diene building block **11** suitable for the synthesis of dicarba analogs of cystine derivatives such as **12**. Alkynylation of benzophenone imine **9** with 1,4-dibromo-2-butyne (**22**) was accomplished with potassium carbonate in refluxing acetonitrile in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) as a PTC (Scheme 3). Attempts to purify the bis(amino acid) derivative **23** were unsuccessful due to its rapid hydrolysis on a silica-gel or neutral alumina column. Therefore, compound **23** was hydrolyzed with 1 M HCl in diethyl ether to get the corresponding amino acid derivative as its hydrochloride salt (Scheme 3). Neutralization of **24** with aqueous ammonia to deliver the free amino acid was avoided due to high solubility of the free amine in water.



Scheme 3. Preparation of the diene building block **11**.

One-pot neutralization and acetyl protection of the amine groups present in **24** was achieved by using triethylamine and acetic anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Careful column chromatography afforded the two diastereomers **10a** and **10b** (1:1; *RR*/*SS* and *RS*/*SR*) in 30% overall yield after 3 steps (combined yields of **10a** and **10b**) (Scheme 3).[21] The stereochemistry of **10b** was assigned as *meso* based on its crystal structure, hence compound **10a** is racemic.

The bis(amino acid) derivatives **10a** and **10b** were then subjected to CEM in presence of ethylene with the aid of Ru catalysts **3**, **4** and **5**. When compounds **10a** and **10b** were subjected to CEM with Grubbs' first-generation catalyst **3** in presence of ethylene in DCM only minor amount (1.5%) of diene formation was observed. Even after prolonged stirring at room temp. (Table 2, entry 1–2), there was no improvement in conversion. Treatment with a more reactive Hoveyda–Grubbs' second-generation catalyst **5** afforded the desired CEM product **11** in good yield at room temp. under usual stirring conditions (Table 2, entry 3–6).

Surprisingly, with catalyst **5**, the racemic diastereomer **10a** was found to be less reactive as compared to the *meso* isomer **10b**. High catalyst loading (20 mol-%, DCM, room temp.) was necessary to deliver 80% conversion of the starting material in the case of racemic diastereomer (Table 2, entry 3). However, complete conversion with low catalyst loading was achieved by performing the reaction at elevated temperature (80 °C, benzene) in a sealed tube (Table 2, entry 5). On the other hand in the case of the *meso* diastereomer, room temp. stirring in DCM or benzene was found to be sufficient to achieve the complete conversion of the starting material by using Hoveyda–Grubbs catalyst (Table 2, entries 4, 6).[22]

With the requisite diene building blocks **11a** and **11b** in hand, the DA reaction with various dienophiles was performed to obtain a diverse collection of conformationally rigid dicarba analogs of cystine.[23] Both the racemic and the *meso* dienes were treated individually with different dienophiles at toluene reflux to afford the corresponding DA adducts. In some instances the DA adducts were contaminated with aromatized products. Hence, the crude DA adducts were aromatized with activated MnO_2 to obtain the dicarba analogs of cystine (Table 3).

The increasing number of chemical and biological studies of the carbon cluster C_{60} (fullerene) in the recent years has drawn our attention towards the synthesis of fullerene-based dicarba analogs of cystine by a DA approach (Scheme 4).[24]

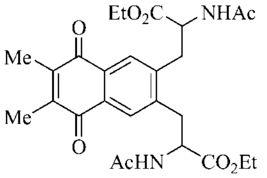
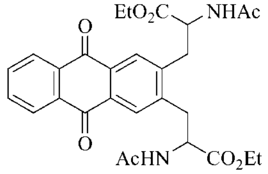
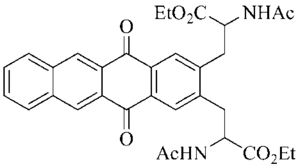
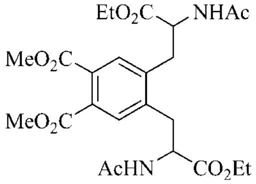
Treatment of dienes **11a** and **11b** with C_{60} fullerene (**25**) at toluene reflux temperature furnished stable cycloadducts **26a** and **26b**, respectively, in good yield (Scheme 4). The

Table 2. List of conditions for cross-enyne metathesis of **10** with ethylene mediated by a Ru catalyst.

Entry	Substrate	Ru catalyst	Conditions[a]	Conversion	Yield[b]
1	**10a**	**3** (10 mol-%)	DCM, room temp., 72 h	1.5%[c]	–
2	**10b**	**3** (10 mol-%)	DCM, room temp., 72 h	1.5%[c]	–
3	**10a**	**5** (20 mol-%)	DCM, room temp., 24 h	80%	68%, (85%)[d]
4	**10b**	**5** (10 mol-%)	DCM, room temp., 24 h	100	98%
5	**10a**	**5** (7 mol-%)	benzene, 80 °C, 24 h	100	96%
6	**10b**	**5** (7.5 mol-%)	benzene, room temp., 24 h	100	97%

[a] All reactions were carried out in ethylene atmosphere (p = 1 atm). [b] Isolated yield. [c] Percentage conversion indicated from the ^1H NMR analysis. [d] Yields mentioned in the parentheses refer to the yield based on starting material recovered.

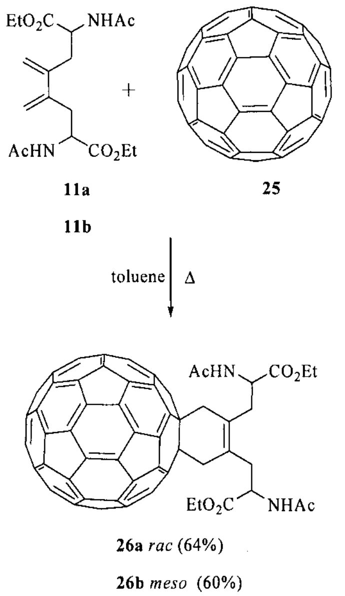
Table 3. List of various dicarba analogs of cystine synthesized from diene **11**.[a]

Entry	Diene		Dienophile	Product	Yield (%)[b]	
	rac	*meso*			*rac*	*meso*
1	**11a**	**11b**	**14**		**27a** (79)	**27b** (82)
2	**11a**	**11b**	**15**		**28a** (86)	**28b** (81)
3	**11a**	**11b**	**16**		**29a** (55)	**29b** (94)
4	**11a**	**11b**	**17**		**30a** (72)	**30b** (71)

[a] DA reaction was carried out in toluene reflux or heating in a sealed tube at 110 °C. [b] Isolated overall yield after DA reaction and aromatization.

structures of both of these compounds have been established unambiguously by complementary spectroscopic data. The molecular ion peak (*m*/*z*) observed at 1089 [M + H]$^+$ for both the isomers in QTof-MS confirmed the formation of 1:1 adduct. The appearance of the peak at 527 cm^{-1} characteristic of C_{60} core and peaks at 1739 cm^{-1} and 1652 cm^{-1} in IR absorption spectra of compound **26b** and 1736 cm^{-1} and 1656 cm^{-1} for compound **26a** indicated the presence of an ester and amide moiety in the molecule. Both the diastereomers showed a typical weak absorption band around 430 nm in the UV/Vis spectrum, similar to that of most dihydrofullerenes.[25]

The ^{1}H NMR spectra of the diastereomer *rac*-**26a** showed a broad singlet at $\delta \approx 4.4$ ppm corresponding to four protons (cyclohexene ring methylene protons), which could be attributed to a rapid boat-to-boat interconversion of the cyclohexene ring (Figure 3) indicating that the rate of the ring inversion is faster than the NMR time scale at room temp. (Figure 4).[25] The ^{13}C spectrum of **26a** showed the presence of 26 signals of which 17 correspond to sp^2 carbons, indicating that the molecule has an average C_{2v} symmetry resulting from the fast flipping motion of the cyclohexene ring connecting the C_{60} cage to the organic addend. In addition to the ester and amide carbonyl carbon atoms which appear at δ = 172.4 and 170.6 ppm, the signal at δ = 44.8 (cyclohexene ring CH_2 carbon) and a peak at δ = 65.9, characteristic of the quaternary sp^3-hybridized fullerene carbon atoms to which the substituents are attached, were also observed. However, broadened AB systems (centered at δ_A = 3.92 and δ_B = 4.12 ppm), corresponding to the methylene protons of cyclohexene ring were observed in the ^{1}H NMR spectra of the *meso* diastereomers **26b** at room temp., indicating the restricted boat-to-boat interconversion of the cyclohexene ring in the molecule (Figure 4). The ^{13}C



Scheme 4. Synthesis of fullerene-based dicarba analogs of cystine.

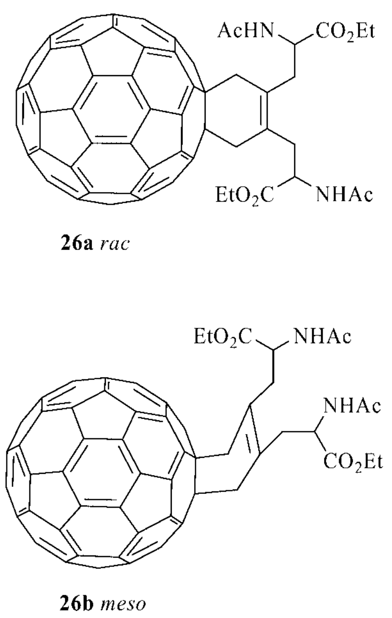


Figure 3. Boat-to-boat interconversion of the cyclohexene ring.

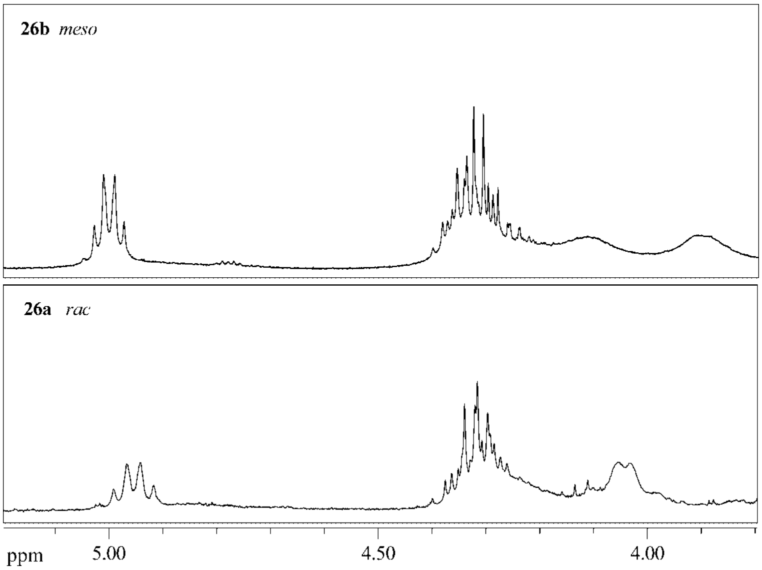


Figure 4. Expanded AB signals of **26a** and **26b** in 300-MHz ^{1}H-NMR spectra at room temp.

spectrum of **26b** exhibited signals for 32 C atoms (24 lines, 8 with double integral) for the fullerene sp^2-C atoms as well as a peak at δ = 65.9 ppm characteristic of those quaternary sp^3-hybridized C atom that constitute the 6–6 fusion point of attachment of the cyclohexenyl moiety which further confirmed the C_s symmetry of the molecule (Figure 3).[25]

Effect of Addition of Chiral Shift Reagent (CSR) on the Two Diastereomers

Determining the stereochemistry of the two diastereomers **10a** and **10b** (*rac* and *meso*) appeared to be a non-trivial task. Attempts to differentiate these two diastereomers by ^{1}H NMR and ^{13}C NMR spectroscopy were not successful due to a close similarity of their chemical shift values. It was considered that employment of a CSR might be helpful in assigning the stereochemistry of the two diastereomers where the chiral atoms are separated by four carbon units. As expected, it was observed that upon addition of Eu(tfc)$_3$ to a CDCl$_3$ solution of compound **10a** the signals were split into two sets of lines of equal intensity, for the racemic isomer (Figure 5, B), even the *meso* compound was also found to split into two set of lines with varying separation as shown in Table 4.[26] Literature reports also suggest that in the presence of CSR the *meso* isomer becomes "internally diastereotopic" and thus anisochronous.[27]

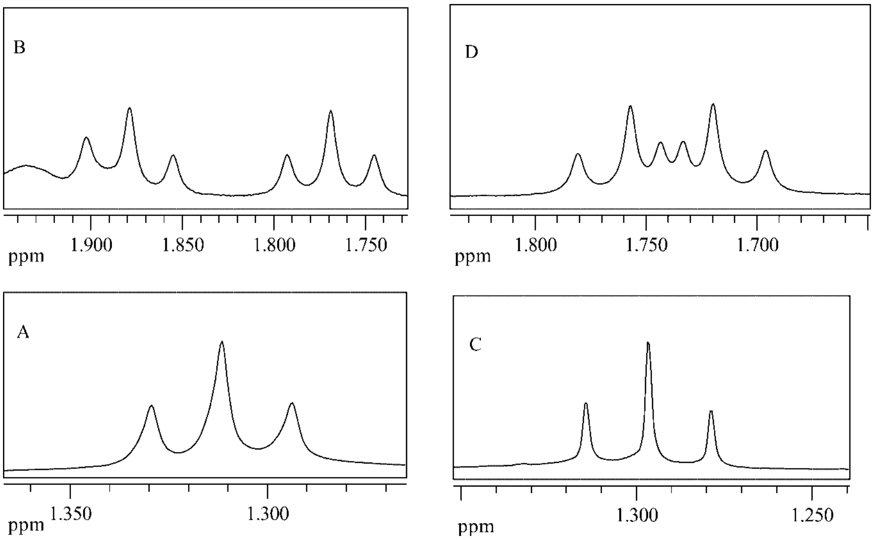


Figure 5. Splitting of the ester methyl proton triplet in the 300-MHz ^{1}H-NMR spectrum upon addition of the CSR; (A) **10a** in the absence of CSR, (B) **10a**: CSR (1:0.75), (C) **10b** in the absence of CSR, (D) **10b**: CSR (1:0.70).

Table 4. Effect of addition of CSR on ^{1}H NMR chemical shift.

CSR/substrate ratio	Change in chemical shift (in ppm) of **10a** $\Delta\delta = (\delta_{\mathrm{CSR+\mathbf{10a}}} - \delta_{\mathrm{CSR}})$[a]						
	$\mathrm{N}H\mathrm{Ac}$	$\mathrm{C}H\mathrm{NH}$	$\mathrm{OC}H_2\mathrm{CH}_3$	$\mathrm{CH^aH^bC{\equiv}C}$		$\mathrm{COC}H_3$	$\mathrm{OCH_2C}H_3$
				$\mathrm{H^a}$	$\mathrm{H^b}$		
0.24:1	1.06	1.5	0.24	0.32	0.51	1.04	0.10
							0.12
0.47:1	2.08	1.33	0.48	0.48	0.91	2.12	0.19
		2.72		0.63	1.2		0.22
0.75:1	3.26	–	0.74	0.69	1.43	3.15	0.29
				0.93	1.93	3.36	0.34
	Change in chemical shift (in ppm) of **10b** $\Delta\delta = (\delta_{\mathrm{CSR+\mathbf{10b}}} - \delta_{\mathrm{CSR}})$[a]						
0.22:1	0.89	1.2	0.19	0.27	0.66	0.93	0.075
							0.079
0.50:1	2.12	2.84	0.45	0.61	1.60	2.16	0.18
							0.19
0.70:1	3.48	4.65	0.75	0.94	2.41	3.54	0.29
				1.05	2.7	3.76	0.31

[a] ^{1}H NMR were recorded in $CDCl_3$ at room temp.

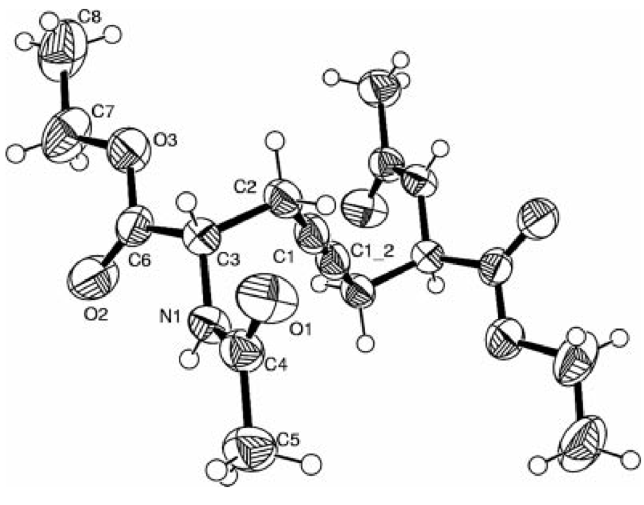


Figure 6. ORTEP diagram of compound **10b**.

Stereochemical Assignment of 10a and 10b

The stereochemistry of **10b** was assigned as *meso* based on its crystal structure as shown in Figure 6. Compound **10a** was obtained as racemic diastereomer.

Conclusions

We have prepared the new building blocks **7** and **11** suitable for the synthesis of quinone–amino acid hybrids. More specifically, various conformationally constrained quinone-containing dicarba analogs of cystine and Phe derivatives have been synthesized via ethylene cross-enyne metathesis using Grubbs' catalyst and DA reaction as key steps. Also, we have extended this methodology for the synthesis of fullerene-based dicarba analog of cystine. The stereochemistry of the *meso* diastereomer of the dicarba analog of cystine was assigned based on its crystal structure. We anticipate that these new advances for the preparation of quinone–amino acid hybrids might allow the synthesis of novel peptidomimetics and artificial proteins.

Experimental Section

General Remarks: All reactions were monitored by thin-layer chromatography (TLC) carried out on glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder). Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light. Flash chromatography was performed using Acme's silica gel (100–200 mesh). Petroleum ether refers to fraction with the boiling range 60–80 °C. Metathesis catalysts were purchased from Sigma–Aldrich (Milwaukee, USA). All the commercial-grade reagents were used without further purification. Infrared spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer in KBr/$CHCl_3$/CCl_4. ^1H NMR (300, 400 MHz) and ^{13}C NMR (75, 100 MHz) spectra were determined at room temp. on a Varian VXR 300 or AX 400 mercury plus in $CDCl_3$ solutions. Coupling constants (*J* values) are given in Hertz (Hz). Chemical shifts are expressed in δ values downfield from internal reference tetramethylsilane. High-resolution mass spectra were determined on Micromass Q-Tof spectrometer.

Ethyl 4-Methylene-2-[(4-methylphenyl)sulfonamido]hex-5-enoate (7): The amino ester **8** (41 mg, 0.13 mmol) in dichloromethane (10 mL) was degassed with nitrogen for 10 min and then degassed with ethylene for 10 min. Grubbs' first-generation catalyst **3** (6.2 mg, 0.008 mmol, 6 mol-%) was added and finally, the vessel was kept under pressure with ethylene (balloon pressure: 1 atm). The reaction mixture was then stirred at room temp. for 24 h. After completion of the reaction (TLC monitoring), the solvent was concentrated and the crude product was purified by flash silica-gel column chromatography (EtOAc/petroleum ether 20%) to afford a brownish liquid **7** (31 mg, 68%); R_f = 0.32 (silica gel, EtOAc/petroleum ether, 1:5). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.10 (t, J = 7.2 Hz, 3 H, -OCH_2CH_3), 2.41 (s, 3 H, Ar-CH_3) 2.58–2.62 (m, 2 H, $CHCH_2$), 3.90 (q, J = 7.2 Hz, 2 H, -OCH_2CH_3), 4.06–4.12 (m, 1 H, CH-CH_2), 5.02–5.22 [m, 5 H, $CH_2CHC(=CH_2)CH_2$, N*H*], 6.27 (dd, J = 14, 10.8 Hz, 1 H, -$CH=CH_2$), 7.28 (d, J = 8 Hz, 2 H, 2 ArH), 7.69 (d, J = 8.2 Hz, 2 H, 2 ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 21.7, 35.9, 54.8, 61.7, 114.5, 120.0, 127.5, 129.7, 136.9, 137.7, 140.3, 143.7, 171.4 ppm. IR (neat): ṽ = 1737 (ester C=O), 1645 cm^{-1} (ArC=O). HRMS (Q-Tof ES+): *m*/*z* calcd. for $C_{16}H_{21}NNaO_4S$ [M + Na] 346.1089, found 346.1105.

Ethyl 3-(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalen-2-yl)-2-[(4-methylphenyl)sulfonamido]propanoate (18): 2,3-Dimethylbenzoquinone (**14**) (15 mg, 0.11 mmol), was added to a solution of diene **7** (11 mg, 0.03 mmol), in toluene (5 mL) and the mixture was heated (90 °C, 24 h). Then, the solvent was concentrated under reduced pressure and the crude product obtained was purified by a flash column chromatography (silica gel, EtOAc/petroleum ether 25%) to afford the DA adduct as a semi solid. Subsequent oxidation of the DA adduct (15 mg, 0.03 mmol) was carried out with MnO_2 (100 mg, 1.15 mmol) in refluxing dioxane (14 mL) for 30 h. Then, the solvent was removed under reduced pressure and the crude product was purified by flash silica gel column chromatography (EtOAc/petroleum ether 25%) to afford the aromatized product **18** (12 mg, 81%) as a yellow solid. R_f = 0.41 (silica gel, EtOAc/petroleum ether, 1:4); m.p. 160–162 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.14 (t, J = 6.8 Hz, 3 H, -OCH_2CH_3), 2.17 (s, 6 H, 2 Me), 2.36 (s, 3 H, $ArCH_3$), 3.08 (d, 1/2 AB_q, J = 6.4, 14 Hz, 1 H, $CHCH^aH^b$), 3.18 (d, 1/2 AB_q, J = 5.6, 13.8 Hz, 1 H, $CHCH^aH^b$), 4.01 (q, J = 7.1 Hz, 2 H, -OCH_2CH_3), 4.19–4.21 (m, 1 H, $CHCH_2$), 5.18 (d, J = 8.8 Hz, 1 H, N-*H*), 7.20 (d, J = 8.0 Hz, 2 H, 2 ArH), 7.47 (d, J = 7.6 Hz, 1 H, ArH), 7.61 (d, J = 8.0 Hz, 2 H, 2 ArH), 7.75 (s, 1 H, ArH), 7.95 (d, J = 7.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.1, 14.1, 21.7, 39.6, 56.5, 62.4, 126.7, 127.2, 127.4, 129.8, 131.2, 132.2, 134.8, 136.6, 141.6, 143.5, 143.7, 143.9, 170.6, 184.7, 184.9 ppm. IR (neat): ṽ = 1738 (ester C=O), 1659 cm^{-1} (ArC=O). UV ($CHCl_3$): λ_{max} (ε) = 270 nm (12400 $mol^{-1}dm^3cm^{-1}$). HRMS (Q-Tof): *m*/*z* calcd. for $C_{24}H_{26}NO_6S$ [M + H] 456.1481, found 456.1487.

Ethyl 3-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-2-[(4-methylphenyl)sulfonamido]propanoate (19): 1,4-Naphthoquinone (**15**) (33 mg, 0.21 mmol) was added to a solution of diene **7** (27 mg, 0.08 mmol), in dry toluene (5 mL) was heated (90 °C, 24 h). Then, the solvent was concentrated under reduced pressure and the crude product obtained was purified by flash silica gel column chromatography (EtOAc/petroleum ether 25%) to afford DA adduct. Subsequent oxidation of the DA adduct (34 mg, 0.07 mmol) was carried out with MnO_2 (250 mg, 2.79 mmol) in refluxing dioxane (14 mL) for 30 h. Then, the solvent was removed under reduced pressure and the crude product was purified by flash silica-gel column chromatography (EtOAc/petroleum ether 25%) to afford the aromatized product **19** (30 mg, 77%) as a yellow solid; R_f = 0.48 (silica gel, EtOAc/petroleum ether, 1:3); m.p. 181–182 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.17 (t, J = 7.2 Hz, 3 H, -OCH_2CH_3), 2.26 (s, 3 H, Ar-CH_3), 3.10–3.28 (m, 2 H, $CHCH_2$), 4.07 (q, J = 6.4 Hz, 2 H, -OCH_2CH_3), 4.22–4.24 (m, 1 H, $CHCH_2$), 5.27 (d, J = 8.4 Hz, 1 H, N*H*), 7.17 (d, J = 8 Hz, 2 H, 2 ArH), 7.59–7.60 (m, 3 H, 3 ArH), 7.80–7.83 (m, 2 H, 2 ArH), 7.97 (s, 1 H, ArH), 8.18 (d, J = 8 Hz, 1 H, ArH), 8.31–8.36 (m, 2 H, 2 ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.2, 21.6, 39.6, 56.6, 62.5, 127.3, 128.0, 128.4, 129.79, 129.81, 130.33, 130.35, 133.5, 134.5, 135.3, 135.4, 135.7, 136.6, 142.7, 143.9, 170.7, 182.8, 182.9 ppm. IR (neat): ṽ = 1732 (ester C=O), 1660 cm^{-1} (ArC=O). UV ($CHCl_3$): λ_{max} (ε) = 258 nm (18916 $mol^{-1}dm^3cm^{-1}$). HRMS (Q-Tof): *m*/*z* calcd. for $C_{26}H_{23}NNaO_6S$ [M + Na] 500.1147, found 500.1144.

Ethyl 3-(5,12-Dioxo-5,12-dihydrotetracen-2-yl)-2-[(4-methylphenyl)sulfonamido]propanoate (20): 1,4-Anthraquinone (**16**) (26 mg, 0.13 mmol) was added to a solution of diene **7** (31, mg, 0.10 mmol), in dry toluene (5 mL) and was heated (90 °C, 24 h). Then, the solvent was concentrated under reduced pressure and the crude product obtained was purified by flash silica gel column chromatography (EtOAc/petroleum ether 30%) to afford the DA adduct. Subsequent oxidation of the DA adduct (47 mg, 0.09 mmol) was carried out with MnO_2 (150 mg, 1.72 mmol) in refluxing dioxane (14 mL) for 30 h. Then the solvent was removed under reduced pressure and the crude product was purified by flash silica-gel column chromatography (EtOAc/petroleum ether 30%) to afford the aromatized product **20** (46 mg, 93%) as a yellow solid; R_f = 0.39 (silica gel, EtOAc/petroleum ether, 1:3), m.p. 230 °C. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C, TMS): δ = 1.19 (t, J = 6.8 Hz, 3 H, -OCH_2CH_3), 2.25 (s, 3 H, $ArCH_3$), 3.13 (d, 1/2 AB_q, J = 13.6, 7.2 Hz, 1 H, $CHCH^aH^b$), 3.26 (d, 1/2 AB_q, J = 13.8, 5.4 Hz, 1 H, $CHCH^aH^b$), 4.05 (q, J = 5.6 Hz, 2 H, -OCH_2CH_3), 4.24–4.28 (m, 1 H, $CHCH_2$), 5.27 (d, J = 8.4 Hz, 1 H, N*H*), 7.17 (d, J = 8.4 Hz, 2 H, 2 ArH), 7.60–7.62 (m, 3 H, 3 ArH), 7.71 (dd, J = 6.6, 3.2 Hz, 2 H, 2 ArH), 8.05–8.12 (m, 3 H, 3 ArH), 8.25 (d, J = 8 Hz, 1 H, ArH), 8.84 (s, 1 H, ArH), 8.86 (s, 1 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.2, 21.5, 39.6, 56.6, 62.5, 127.32, 127.39, 127.4, 127.7, 128.1, 129.8, 132.5, 133.52, 133.56, 133.6, 134.3, 134.4, 135.6, 136.5, 142.6, 143.9, 170.6, 182.9, 183.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3409 (NH), 1736 (ester C=O), 1649 cm^{-1} (ArC=O). UV (CHCl$_3$): λ_{max} (ε) = 292 nm (18666 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof ES+): *m*/*z* calcd. for $C_{30}H_{26}NO_6S$ [M + H] 528.1481, found 528.1486.

Dimethyl 4-{3-Ethoxy-2-[(4-methylphenyl)sulfonamido]-3-oxopropyl}phthalate (21): Dimethyl acetylenedicarboxylate (**17**) (29 mg, 0.20 mmol) was added to a solution of diene **7** (30 mg, 0.09 mmol), in dry toluene (5 mL) was heated (90 °C, 18 h). Then the solvent was concentrated under reduced pressure and the crude product obtained was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether 40%) mixture to afford the Diels–Alder adduct. Subsequent oxidation of the DA adduct (31 mg, 0.06 mmol) was carried out with MnO$_2$ (232 mg, 2.6 mmol) in refluxing dioxane (dry) (14 mL) for 30 h. Then the solvent was removed under reduced pressure and the crude product was purified by flash silica-gel column chromatography (EtOAc/petroleum ether 40%) to afford the aromatized product **21** (29 mg, 67%) as a colorless liquid. R_f = 0.30 (silica gel, EtOAc/petroleum ether, 1:3). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.02 (t, *J* = 6.9 Hz, 3 H,-OCH$_2$C*H*$_3$), 2.36 (s, 3 H, Ar-CH$_3$), 3.05–3.11 (m, 2 H, CH-C*H*$_2$), 3.89 (s, 3 H, -CO$_2$C*H*$_3$), 3.90 (s, 3 H, -CO$_2$C*H*$_3$), 3.98 (q, *J* = 7.3 Hz, 2 H, -OC*H*$_2$CH$_3$), 4.12–4.19 (m, 1 H, C*H*-CH$_2$), 5.17 (d, *J* = 8.8 Hz, 1 H, N*H*), 7.22 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 7.28–7.31 (m, 1 H, ArH), 7.41 (d, *J* = 1.5 Hz, 1 H, ArH), 7.59–7.62 (m, 3 H, 3 ArH) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 14.0, 21.6, 39.0, 52.7, 52.8, 56.5, 62.3, 127.2, 129.26, 129.78, 130.01, 130.72, 132.30, 132.34, 136.4, 139.3, 143.9, 167.8, 167.9, 170.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1729 (ester C=O), 1435 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. for $C_{22}H_{25}NNaO_8S$ [M + Na] 486.1199, found 486.1186.

Diethyl 2,7-Bis(acetamido)oct-4-yne-1,8-dioate (10): To a solution of ethyl 2-[(diphenylmethylene)amino]acetate (**9**) (7.7 g, 29 mmol) in dry acetonitrile (30 mL) was added 1,4-dibromobut-2-yne (**22**) (2.8 g, 13.0 mmol), potassium carbonate (10 g, 72 mmol) and catalytic amount of TBHAS. The resulting heterogeneous mixture was then allowed to reflux. After completion of the reaction (20 h, TLC monitoring), the reaction mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure to give **23** as a brown color liquid which was directly used in the next step without further purification. A suspension of compound **23** (used as it is obtained from the earlier step) in diethyl ether (30 mL) was added 1 M HCl (40 mL). The reaction mixture was stirred at room temp. for 24 h. The ether layer was discarded and the aqueous layer was concentrated under reduced pressure by using a rotary evaporator and finally dried under high vacuum to give the bis(amino acid) hydrochloride salt **24**. This crude hydrochloride salt was directly used in the next step without further purification: To a suspension of crude **24** in dry dichloromethane (50 mL) was added triethylamine (3 g, 29.7 mmol), a catalytic amount of DMAP and acetic anhydride (4.9 g, 48.4 mmol); the temperature of the reaction mixture was kept at ice temperature. The resulting mixture was then allowed to warm up to room temp. and stirred for another 24 h. Then, the mixture was concentrated and the residue was directly (without any aqueous work up) charged on a silica gel column (length of the column: 25 cm, diameter: 5.5 cm, amount of silica gel: 430 g). Careful elution of the column with 80% EtOAc/petroleum ether afforded compounds **10a** and **10b** (1:1, 1.31 g, 30%, overall yield after three steps).

***rac*-Diethyl 2,7-Bis(acetamido)oct-4-yne-1,8-dioate (10a):** R_f = 0.32 (silica gel, EtOAc); m.p. 134 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.31 (t, *J* = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.14 (s, 6 H, 2 COC*H*$_3$), 2.59 (1/2 AB$_q$, *J* = 16.4 Hz, 2 H, 2 CHC*H*^{a}H^b), 2.67 (1/2 AB$_q$, *J* = 18.0 Hz, 2 H, 2 CHCH^a*H*^{b}) 4.26 (q, *J* = 7.2 Hz, 4 H, 2 OC*H*$_2$CH$_3$), 4.90 (dt, *J* = 8.8, 4.0 Hz, 2 H, 2 C*H*NHAc), 7.25 (d, *J* = 8.8 Hz, 2 H, 2 N*H*) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 14.2, 22.9, 23.6, 50.4, 62.0, 78.5, 170.5, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 3308 (NH), 1726 (ester C=O), 1650 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 208 nm (1698 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{16}H_{24}N_2NaO_6$ [M + Na]: 363.1532, found 363.1518.

***meso*-Diethyl 2,7-Bis(acetamido)oct-4-yne-1,8-dioate (10b):** R_f = 0.31 (silica gel, EtOAc); m.p. 134 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.30 (t, *J* = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.13 (s, 6 H, 2 COC*H*$_3$), 2.66 (d, 1/2 AB$_q$, *J* = 5.2, 2 Hz, 2 H, 2 CHC*H*^{a}H^b), 2.69 (d, 1/2 AB$_q$, *J* = 5.2, 2.8 Hz, 2 H, 2 CHCH^a*H*^{b}), 4.25 (q, *J* = 7.0 Hz, 4 H, 2 OC*H*$_2$CH$_3$), 4.78 (dt, *J* = 8.4, 4.4 Hz, 2 H, 2 C*H*NHAc), 6.56 (d, *J* = 8.4 Hz, 2 H, 2 N*H*) ppm. ^{13}C NMR (75.4 MHz, CDCl$_3$): δ = 14.2, 23.09, 23.14, 50.7, 61.9, 77.9, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 3332 (NH), 1734 (ester C=O), 1647 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 208 nm (1658 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{16}H_{24}N_2NaO_6$ [M + Na]: 363.1532, found 363.1543.

***rac*-Diethyl 2,7-Diacetamido-4,5-dimethyleneoctane-1,8-dioate (11a):** The amino ester **10a** (83 mg, 0.244 mmol) in dry benzene (7 mL) was degassed with nitrogen for 15 min and then with ethylene gas for 10 min in a sealed tube. Hoveyda's catalyst **5** (11 mg, 0.0175 mmol, 7.0 mol-%) was then added and finally, the vessel was kept under ethylene pressure (1 atm) and capped tightly. The reaction mixture was then heated to 80 °C. After completion of the reaction (24 h, TLC monitoring), the pressure was released and the resulting brown solution was concentrated under reduced pressure and the crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford *rac*-**11a** as a white crystalline solid (86 mg, 96%). R_f = 0.26 (silica gel, EtOAc); m.p. 136 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.32 (t, *J* = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.02 (s, 6 H, 2 COC*H*$_3$), 2.75 (d, 1/2 AB$_q$, *J* = 14.3, 5.9 Hz, 2 H, 2 CHC*H*^{a}H^b), 2.90 (d, 1/2 AB$_q$, *J* = 14.1, 5.1 Hz, 2 H, 2 CHCH^a*H*^{b}), 4.13 (q, 1/2 AB$_q$, *J* = 10.7, 7.2 Hz, 2 H, 2 OC*H*^{a}H^{b}CH$_3$), 4.25 (q, 1/2 AB$_q$, *J* = 10.7, 7.2 Hz, 2 H, 2 OCH^a*H*^{b}CH$_3$), 4.74 (dt, *J* = 8.7, 6.0 Hz, 2 H, 2 C*H*NHAc), 5.00 (s, 2 H, 2 C=C*H*^{a}H^b), 5.24 (s, 2 H, 2 C=CH^a*H*^{b}), 6.72 (d, *J* = 8.4 Hz, 2 H, 2 N*H*) ppm. ^{13}C NMR (75.4 MHz, CDCl$_3$): δ = 14.2, 23.0, 36.4, 51.2, 61.6, 117.1, 141.2, 170.0, 172.5 ppm. IR (neat): $\tilde{\nu}$ = 3414 (NH), 1732 (ester C=O), 1657 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 235 nm (6568 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{18}H_{28}N_2NaO_6$ [M + Na]: 391.1845, found 391.1839.

***meso*-Diethyl 2,7-Diacetamido-4,5-dimethyleneoctane-1,8-dioate (11b):** The amino ester **10b** (65 mg, 0.191 mmol) in dry benzene (10 mL) was degassed with nitrogen for 15 min and then with ethylene gas for 10 min. Hoveyda's catalyst **5** (9 mg, 0.014 mmol, 7.5 mol-%) was then added and finally, the vessel was kept under ethylene pressure (1 atm). The reaction mixture was stirred at room temp. After completion of the reaction (24 h, TLC monitoring), the pressure was released and the resulting brown solution was concentrated under reduced pressure and the crude product was purified by silica gel flash column chromatography. Elution of the column (EtOAc in petroleum ether 80%) to afford *meso*-**11b** as a white crystalline solid (68 mg, 97%). R_f = 0.28 (silica gel, EtOAc); m.p. 154 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.29 (t, *J* = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.02 (s, 6 H, 2 COC*H*$_3$), 2.52 (d, 1/2 AB$_q$, *J* = 14.7, 8.7 Hz, 2 H, 2 CHC*H*^{a}H^b), 2.88 (d, 1/2 AB$_q$, *J* = 14.7, 4.8 Hz, 2 H, 2 CHCH^a*H*^{b}), 4.14–4.25 (m, 4 H, 2 OC*H*$_2$CH$_3$), 4.73 (dt, *J* = 12.3, 4.2 Hz, 2 H, 2 C*H*NHAc), 5.05 (s, 2 H, 2 =C*H*^{a}H^b), 5.26 (s, 2 H, 2 = CH^a*H*^{b}), 6.45 (d, *J* = 7.5 Hz, 2 H, 2 N*H*) ppm. ^{13}C NMR (75.4 MHz, CDCl$_3$): δ = 14.2, 23.0, 36.8, 51.1, 61.5, 115.8, 141.6, 170.3, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 3326

(NH), 1749 (ester C=O), 1651 cm^{-1} (amide C=O). UV (CHCl$_3$): $\lambda_{\max}$ (ε) = 235 nm (5232 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m/z* calcd. for $C_{18}H_{28}N_2NaO_6$ [M + Na]: 391.1845, found 391.1855.

General Experimental Procedure for the DA Reaction and Aromatization: To a solution of the diene **11a**–**b** (1 equiv.) in dry toluene or 1,2-dichlorobenzene was added the dienophile (2–7 equiv.) and the reaction mixture was heated to reflux. After completion of the reaction (TLC monitoring), the solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane and activated MnO$_2$ (excess) was added. The reaction mixture was stirred at room temp. for 48 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent removed under reduced pressure. The crude product was purified by silica gel flash column chromatography. Elution of the column with appropriate mixture of EtOAc in petroleum ether afforded the desired aromatized cycloadduct.

***rac*-Diethyl 3,3′-(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-2,3-diyl)bis(2-acetamidopropanoate) (27a):** 2,3-Dimethylbenzoquinone (**14**) (26 mg, 0.19 mmol) was added to a solution of the diene **11a** (28 mg, 0.076 mmol) in dry toluene (3 mL) in a sealed tube and the reaction mixture was heated (110 °C, 48 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (7 mL) and activated MnO$_2$ (200 mg, 2.29 mmol) was added. The reaction mixture was stirred at room temp. for 48 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford compound **27a** (30 mg, overall yield 79%) as a light yellow crystalline solid. R_f = 0.30 (silica gel, EtOAc); m.p. 214–215 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.26 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$CH_3), 1.93 (s, 6 H, C^{2,3}-CH_3), 2.15 (s, 6 H, 2 COCH_3), 3.16 (d, 1/2 AB$_q$, J = 14.1, 8.4 Hz, 2 H, 2 CHCH^aH^b), 3.34 (d, 1/2 AB$_q$, J = 14.3, 5.9 Hz, 2 H, 2 CHCH^aH^b), 4.17–4.27 (m, 4 H, 2 OCH_2CH$_3$), 4.88 (dt, J = 7.1, 7.1 Hz, 2 H, 2 CHNHAc), 6.46 (d, J = 7.2 Hz, 2 H, 2 NH), 7.82 (s, 2 H, C^{5,8}-H) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 13.1, 14.3, 23.0, 35.4, 52.6, 62.1, 128.2, 130.8, 141.4, 143.7, 170.3, 171.6, 184.7 ppm. IR (KBr): $\tilde{\nu}$ = 3272 (NH), 1748 (ester C=O), 1726 (ArC=O), 1655 cm^{-1} (amide C=O). UV (CHCl$_3$): $\lambda_{\max}$ (ε) = 262 nm (11000 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m/z* calcd. for $C_{26}H_{33}N_2O_8$ [M + H]: 501.2237, found 501.2256.

***meso*-Diethyl 3,3′-(6,7-Dimethyl-5,8-dioxo-5,8-dihydronaphthalene-2,3-diyl)bis(2-acetamidopropanoate) (27b):** 2,3-Dimethylbenzoquinone (**14**) (33 mg, 0.24 mmol) was added to a solution of the diene **11b** (33 mg, 0.09 mmol) in dry toluene (3 mL) and the reaction mixture was heated (110 °C, 48 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (10 mL) and activated MnO$_2$ (200 mg, 2.29 mmol) was added. The reaction mixture was stirred at room temp. for 48 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford compound **27b** (37 mg, overall yield 82%) as a light yellow crystalline solid. R_f = 0.30 (silica gel, EtOAc); m.p. 219–220 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.24 (t, J = 7.2 Hz, 6 H, 2 OCH$_2$CH_3), 1.98 (s, 6 H, C^{2,3}-CH_3), 2.15 (s, 6 H, 2 COCH_3), 3.19 (d, 1/2 AB$_q$, J = 13.8, 6.6 Hz, 2 H, 2 CHCH^aH^b), 3.32 (d, 1/2 AB$_q$, J = 14.0, 6.5 Hz, 2 H, 2 CHCH^aH^b), 4.15–4.25 (m, 4 H, 2 OCH_2CH$_3$), 4.87 (dt, J = 8.1, 6.6 Hz, 2 H, 2 CHNHAc), 6.55 (d, J = 7.2 Hz, 2 H, 2 NH), 7.82 (s, 2 H, C^{5,8}-H) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 13.0, 14.2, 23.1, 35.3, 53.1, 62.1, 128.5, 130.7, 141.6, 143.6, 170.3, 171.5, 184.6 ppm. IR (KBr): $\tilde{\nu}$ = 3383 (NH), 1756 (ester C=O), 1725 (ArC=O), 1661 cm^{-1} (amide C=O). UV (CHCl$_3$): $\lambda_{\max}$ (ε) = 260 nm (16700 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m/z* calcd. for $C_{26}H_{33}N_2O_8$ [M + H]: 501.2237, found 501.2237.

***rac*-Diethyl 3,3′-(9,10-Dioxo-9,10-dihydroanthracene-2,3-diyl)bis(2-acetamidopropanoate) (28a):** 1,4-Napthoquinone (**15**) (30 mg, 0.19 mmol) was added to a solution of the diene **11a** (28 mg, 0.076 mmol) in dry toluene (7 mL) and the reaction mixture was heated (110 °C, 72 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (5 mL) and activated MnO$_2$ (100 mg, 1.15 mmol) was added. The reaction mixture was stirred at room temp. for 12 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford compound **28a** (34 mg, overall yield 86%) as a yellow crystalline solid. R_f = 0.23 (silica gel, EtOAc); m.p. 270–272 °C (dec.). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.27 (t, J = 7.2 Hz, 6 H, 2 OCH$_2$CH_3), 1.94 (s, 6 H, 2 COCH_3), 3.23 (d, 1/2 AB$_q$, J = 14.1, 8.1 Hz, 2 H, 2 CHCH^aH^b), 3.40 (d, 1/2 AB$_q$, J = 14.3, 5.9 Hz, 2 H, 2 CHCH^aH^b), 4.24 (q, 4 H, J = 7.1 Hz, 2 OCH_2CH$_3$), 4.92 (dt, J = 6.8, 6.8 Hz, 2 H, 2 CHNHAc), 6.47 (d, J = 7.2 Hz, 2 H, 2 NH), 7.79 (dd, J = 5.9, 3.2 Hz, 2 H, C^6-H, C^7-H), 7.80 (s, 2 H, C^1-H, C^4-H), 8.28 (dd, J = 5.9, 3.5 Hz, 2 H, C^5-H, C^8-H) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 14.3, 23.0, 35.5, 52.6, 62.2, 127.3, 129.2, 132.1, 133.6, 134.3, 142.6, 170.4, 171.6, 184.8 ppm. IR (neat): $\tilde{\nu}$ = 3272 (NH), 1736 (ester C=O), 1656 (amide C=O), 1674 cm^{-1} (ArC=O). UV (CHCl$_3$): $\lambda_{\max}$ (ε) = 266 nm (18085 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m/z* calcd. for $C_{28}H_{31}N_2O_8$ [M + H]: 523.2080, found 523.2073.

***meso*-Diethyl 3,3′-(9,10-Dioxo-9,10-dihydroanthracene-2,3-diyl)bis(2-acetamidopropanoate) (28b):** 1,4-Napthoquinone (**15**) (27 mg, 0.169 mmol) was added to a solution of the diene **11b** (25 mg, 0.068 mmol) in dry toluene (7 mL) and the reaction mixture was heated (110 °C, 48 h). The solution was concentrated under reduced pressure and the crude reaction mixture was then dissolved in dry dioxane (5 mL) and activated MnO$_2$ (96 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temp. for 12 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford compound **28b** (32 mg, overall yield 81%) as a yellow crystalline solid. R_f = 0.23 (silica gel, EtOAc); m.p. 246–248 °C (dec.). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.24 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$CH_3), 1.99 (s, 6 H, 2 COCH_3), 3.26 (d, 1/2 AB$_q$, J = 14.1, 6.9 Hz, 2 H, 2 CHCH^aH^b), 3.38 (d, 1/2 AB$_q$, J = 14.3, 5.9 Hz, 2 H, 2 CHCH^aH^b), 4.18–4.26 (m, 4 H, 2 OCH_2CH$_3$), 4.90 (dt, J = 7.8, 6.9 Hz, 2 H, 2 CHNHAc), 6.49 (d, J = 7.8 Hz, 2 H, 2 NH), 7.80 (dd, J = 5.9, 3.2 Hz, 2 H, C^6-H, C^7-H), 8.06 (s, 2 H, C^1-H, C^4-H), 8.29 (dd, J = 6.0, 3.3 Hz, 2 H, C^5-H, C^8-H) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 14.2, 23.2, 35.6, 53.2, 62.2, 127.4, 129.5, 132.1, 133.7, 134.3, 142.6, 170.3, 171.6, 182.9 ppm. IR (neat): $\tilde{\nu}$ = 3305 (NH), 1739 (ester C=O), 1671 (ArC=O); 1655 cm^{-1} (amide C=O). UV (CHCl$_3$): $\lambda_{\max}$ (ε) = 267 nm (16643 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m/z* calcd. for $C_{28}H_{31}N_2O_8$ [M + H]: 523.2080, found 523.2092.

***rac*-Diethyl 3,3′-(5,12-Dioxo-5,12-dihydrotetracene-2,3-diyl)bis(2-acetamidopropanoate) (29a):** 1,4-Anthraquinone (**16**) (27 mg, 0.132 mmol) was added to a solution of the diene **11a** (27 mg, 0.073 mmol) in dry toluene (7 mL) and the reaction mixture was heated (110 °C, 24 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (5 mL) and activated MnO$_2$ (188 mg, 2.16 mmol) was added. The reaction mixture was stirred at room temp. for 30 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) to afford compound **29a** (23 mg, overall yield 55%) as a yellow crystalline solid. R_f = 0.21 (silica gel, EtOAc); m.p. 292–294 °C (dec.). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 1.13 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 1.81 (s, 6 H, 2 COC*H*$_3$), 3.16 (d, 1/2 AB$_q$, J = 14.3, 8.9 Hz, 2 H, 2 CHC*H*^{a}H^b), 3.27–3.40 (m, 2 H, 2 CHCH^a*H*^{b}), 4.08 (q, J = 6.8 Hz, 4 H, 2 OC*H*$_2$CH$_3$), 4.56 (dt, J = 8.0, 7.1 Hz, 2 H, 2 C*H*NHAc), 7.80 (dd, J = 6.0, 3.2 Hz, 2 H, 2 ArH), 8.13 (s, 2 H, 2 ArH), 8.34 (dd, J = 6.0, 3.3 Hz, 2 H, 2 ArH), 8.52 (d, J = 7.8 Hz, 2 H, 2 N*H*), 8.87 (s, 2 H, 2 ArH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 14.0, 22.4, 33.8, 52.7, 61.1, 128.8, 129.3, 129.6, 130.1, 130.3, 132.4, 134.8, 143.6, 169.9, 171.4, 182.2 ppm. IR (KBr): ṽ = 3325 (NH), 1729 (ester C=O), 1678 (ArC=O); 1652 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 293 nm (29101 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{32}H_{33}N_2O_8$ [M + H]: 573.2237, found 573.2240.

***meso*-Diethyl 3,3′-(5,12-Dioxo-5,12-dihydrotetracene-2,3-diyl)bis(2-acetamidopropanoate) (29b):** 1,4-Anthraquinone (**16**) (23 mg, 0.1 mmol) was added to a solution of the diene **11b** (27 mg, 0.073 mmol) in dry toluene (10 mL) and the reaction mixture was heated (110 °C, 24 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (3 mL) and activated MnO$_2$ (100 mg, 1.15 mmol) was added. The reaction mixture was stirred at room temp. for 24 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether with 80%) to afford compound **29b** (39 mg, overall yield 94%) as a yellow crystalline solid. R_f = 0.21 (silica gel, EtOAc); m.p. 262–264 °C (dec.). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.26 (t, J = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.01 (s, 6 H, 2 COC*H*$_3$), 3.28 (d, 1/2 AB$_q$, J = 14.0, 6.8 Hz, 2 H, 2 CHC*H*^{a}H^b), 3.40 (d, 1/2 AB$_q$, J = 14.2, 7 Hz, 2 H, 2 CHCH^a*H*^{b}), 4.17–4.25 (m, 4 H, 2 OC*H*$_2$CH$_3$), 4.92 (dt, J = 7.6, 6.8 Hz, 2 H, 2 C*H*NHAc), 6.63 (d, J = 8.0 Hz, 2 H, 2 N*H*), 7.69 (dd, J = 6.4, 2.8 Hz, 2 H, 2 ArH), 8.08 (dd, J = 5.8, 3.6 Hz, 2 H, 2 ArH), 8.12 (s, 2 H, 2 ArH), 8.79 (s, 2 H, 2 ArH) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 14.0, 22.9, 35.2, 52.9, 62.0, 129.41, 129.46, 129.51, 129.54, 130.0, 132.7, 135.0, 142.5, 170.2, 171.4, 182.4 ppm. IR (KBr): ṽ = 3350 (NH), 1739 (ester C=O), 1673 (ArC=O); 1654 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 292 nm (22636 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{32}H_{33}N_2O_8$ [M + H]: 573.2237, found 573.2220.

***rac*-Dimethyl 4,5-Bis(2-acetamido-3-ethoxy-3-oxopropyl)phthalate (30a):** Dimethyl acetylenedicarboxylate (**17**) (50 mg, 0.352 mmol) was added to a solution of the diene **30a** (19 mg, 0.052 mmol) in 1,2-dichlorobenzene (5 mL) in a sealed tube and the reaction mixture was heated (170 °C, 24 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (7 mL) and activated MnO$_2$ (70 mg, 0.8 mmol) was added. The reaction mixture was stirred at room temp. for 12 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc/petroleum ether 80%) afforded compound **30a** (19 mg, overall yield 72%) as a colorless crystalline solid. R_f = 0.17 (silica gel, EtOAc); m.p. 225–226 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.24 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 1.95 (s, 6 H, 2 COC*H*$_3$), 3.12 (d, 1/2 AB$_q$, J = 14.1, 8.1 Hz, 2 H, 2 CHC*H*^{a}H^b), 3.25 (d, 1/2 AB$_q$, J = 14.1, 6.3 Hz, 2 H, 2 CHCH^a*H*^{b}), 3.89 (s, 6 H, 2 OC*H*$_3$), 4.13–4.24 (m, 4 H, 2 OC*H*$_2$CH$_3$), 4.84 (dt, J = 7.2, 7.2 Hz, 2 H, 2 C*H*NHAc), 6.41 (d, J = 8.4 Hz, 2 H, 2 N*H*), 7.48 (s, 2 H, C^{3,6}-*H*) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 14.0, 22.8, 34.8, 52.3, 52.6, 61.8, 130.4, 130.7, 138.8, 167.6, 170.2, 171.5 ppm. IR (neat): ṽ = 3256 (NH), 1742 (ester C=O), 1650 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 239 nm (8247 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{24}H_{32}N_2NaO_{10}$ [M + Na]: 531.1955, found 531.1956.

***meso*-Dimethyl 4,5-Bis(2-acetamido-3-ethoxy-3-oxopropyl)phthalate (30b):** Dimethyl acetylenedicarboxylate (**17**) (60 mg, 0.422 mmol) was added to a solution of the diene **11b** (42 mg, 0.114 mmol) in 1,2-dichlorobenzene (5 mL) in a sealed tube, and the reaction mixture was heated (170 °C, 24 h). The solution was concentrated under reduced pressure. The crude reaction mixture was then dissolved in dry dioxane (10 mL) and activated MnO$_2$ (60 mg, 0.69 mmol) was added. The reaction mixture was stirred at room temp. for 12 h and then filtered through a celite pad. The residue was washed with dioxane (3 × 5 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (EtOAc in petroleum ether 80%) to afford compound **30b** (41 mg, overall yield 71%) as a colorless crystalline solid. R_f = 0.24 (silica gel, EtOAc); m.p. 128–130 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.19 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.0 (s, 6 H, 2 COC*H*$_3$), 3.18 (s, 2 H, 2 CHC*H*^{a}H^b), 3.20 (s, 2 H, 2 CHCH^a*H*^{b}), 3.89 (s, 6 H, OC*H*$_3$), 4.10–4.21 (m, 4 H, 2 OC*H*$_2$CH$_3$), 4.80 (dt, J = 7.5, 6.9 Hz, 2 H, 2 C*H*NHAc), 6.48 (d, J = 7.5 Hz, 2 H, 2 N*H*), 7.49 (s, 2 H, C^{3,6}-*H*) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$, 25 °C, TMS): δ = 13.8, 22.8, 34.8, 52.6, 52.9, 61.8, 130.4, 131.0, 138.9, 167.5, 170.2, 171.4 ppm. IR (neat): ṽ = 3370 (NH), 1732 (ester C=O), 1661 cm^{-1} (amide C=O). UV (CHCl$_3$): λ_{max} (ε) = 248 nm (6593 mol^{-1}dm^{3}cm^{-1}). HRMS (Q-Tof): *m*/*z* calcd. for $C_{24}H_{32}N_2NaO_{10}$ [M + Na]: 531.1955, found 531.1965.

Fullerene Adduct 26a: Fullerene **25** (30 mg, 0.04 mmol) was added to a solution of the diene **11a** (7.5 mg, 0.02 mmol) in dry toluene (5 mL) in a sealed tube and the reaction mixture was heated (110 °C, 36 h). The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography (EtOAc in petroleum ether 75%) to afford compound **26a** (13 mg, 60%) as a brown solid. R_f = 0.30 (silica gel, EtOAc); m.p. >300 °C. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 1.38 (t, J = 7.2 Hz, 6 H, 2 OCH$_2$C*H*$_3$), 2.16 (s, 6 H, 2 COC*H*$_3$), 3.01 (br. s, 2 H, 2 CHC*H*^{a}H^b), 3.23 (br. s, 2 H, 2 CHCH^a*H*^{b}), 4.03 (s, 2 H, 2 C$_{60}$C*H*^{a}H^b), 4.05 (s, 2 H, 2 C$_{60}$CH^a*H*^{b}), 4.26–4.40 (m, 4 H, 2 OC*H*$_2$CH$_3$), 4.95 (dt, J = 7.5, 7.5 Hz, 2 H, 2 C*H*NHAc), 6.73 (br. s, 2 H, 2 N*H*) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 14.5, 23.3, 35.8, 44.8, 52.0, 62.2, 65.9, 135.4, 140.5, 141.9, 142.3, 142.4, 142.8, 143.3, 143.4, 144.9, 145.6, 145.7, 145.9, 146.5, 146.7, 147.9, 156.5, 170.6, 172.4 ppm. IR (KBr): ṽ = 3269 (NH), 1736 (ester C=O), 1656 (amide C=O), 527 cm^{-1} (C$_{60}$). UV (CHCl$_3$): λ_{max} (ε) = 276 nm (35377), 330 nm (32169 mol^{-1}dm^{3}cm^{-1}). MS (Q-Tof): 1089 [M + H].

Fullerene Adduct 26b: Fullerene **25** (30 mg, 0.04 mmol) was added to a solution of the diene **11b** (7.5 mg, 0.02 mmol) in dry toluene (7 mL) and the reaction mixture was heated (110 °C, 36 h). The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography (EtOAc in petroleum ether 75%) to afford compound **26b** (14 mg, 64%) as a brown solid. R_f = 0.30 (silica gel, EtOAc); m.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.38 (t, J = 7.2 Hz, 6 H, 2 OCH_2CH_3), 2.17 (s, 6 H, 2 $COCH_3$), 3.02 (br. s, 2 H, 2 $CHCH^aH^b$), 3.18 (br. s, 2 H, 2 $CHCH^aH^b$), 3.91 (s, 2 H, 2 $C_{60}CH^aH^b$), 4.12 (s, 2 H, 2 $C_{60}CH^aH^b$), 4.18–4.40 (m, 4 H, 2 OCH_2CH_3), 5.00 (dt, J = 7.6, 7.6 Hz, 2 H, 2 CHNHAc), 7.01 (d, J = 7.6 Hz, 2 H, 2 NH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.5, 23.4, 37.0, 45.4, 52.4, 62.3, 65.9, 135.8 (2 C), 140.35, 140.41 (2 C), 141.8 (2 C), 142.2, 142.3, 142.4 (2 C), 142.79 (2 C), 142.8, 143.26, 143.33, 144.9 (2 C), 145.5, 145.62, 145.65, 145.67, 145.7 (2 C), 145.9, 146.5 (2 C), 146.7 (2 C), 147.8, 156.4, 156.7, 170.6, 172.4 ppm. IR (neat): $\tilde{\nu}$ = 3404 (NH), 1739 (ester C=O), 1652 (amide C=O), 527 cm^{-1} (C_{60}). UV ($CHCl_3$): λ_{max} (ε) = 278 nm (35955), 704 nm (96 $mol^{-1}dm^3cm^{-1}$). MS (Q-Tof): 1089 [M + H].

X-ray Crystallographic Data of Compound 10b: The crystallographic data presented here is of the half molecule in a unit cell. $C_8H_{12}NO_3$, M = 170.19, triclinic, space group, $P\bar{1}$, a = 4.9555(6), b = 8.2940(19), c = 11.190(3) Å, β = 97.645(16)°, V = 449.98 (18) Å^3, T = 293(2) K, Z = 2, μ(Mo-K_α) = 0.096 mm^{-1}, 4519 reflections measured, 2045 unique (R_{int} = 0.0164), observed with $I > 2\sigma(I)$ which were used in all refinements; R_1 = 0.0874, wR_2 = 0.2358 for the observed data.

CCDC-621384 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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