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Synthesis of highly functionalized phenylalanine derivatives via cross-enyne metathesis reactions

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Abstract—A new method for the synthesis of constrained phenylalanine derivatives is described. In this regard, the simple synthesis of acyclic diene building blocks embodying an α-amino acid moiety has been achieved. The diene building blocks have been prepared by cross enyne-metathesis reaction as a key step. The Diels–Alder reaction of the dienes with a dienophile such as dimethyl acetylenedicarboxilate (DMAD) followed by oxidation of the resulting cycloadduct gave highly substituted phenylalanine derivatives.

1. Introduction

Unusual α-amino acids (AAA) are useful in modulating the stability and activity of therapeutically useful peptides.[1] In this respect the development of synthetic methods that can generate a series of unusual AAA derivatives is useful for structure–activity relationship. Towards this goal, we conceived 'building block approach' that can deliver a series of AAA derivatives with varing steric and electronic properties.[2–4] In this regard, we have synthesized dienes **1**–**3** (Fig. 1) in our laboratory which are useful precursors for the synthesis of highly functionalized 2-indanyl glycine and Tic derivatives, which are the constrained analogs of phenylalanine (Phe).[3] Dienes **2** and **3** were prepared using the enyne metathesis reaction as a key step. Also, in connection with our interest to prepare cyclic amino acid derivatives and peptides we have utilized ring-closing metathesis as a key reaction.[4] Here we describe the full details for the preparation of various Phe derivatives using the cross-enyne metathesis reaction as a key step.

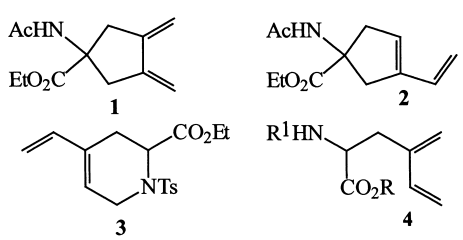
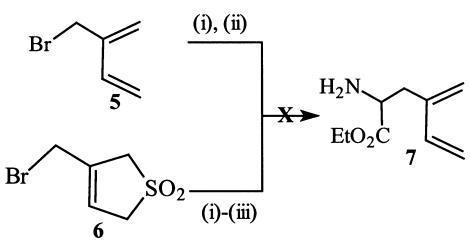


Figure 1.

To explore our building block approach to unusual AAA syntheses we were interested in preparing dienes such as **4**, that can deliver highly substituted Phe derivatives via the Diels–Alder strategy. Compounds of type **4** have been prepared via the palladium-catalyzed coupling reaction between γ-iodo allylglycine derivatives and alkenes. However, the Diels–Alder chemistry of these dienes was not explored.[5] In this connection, we were interested in developing an alternative strategy. Towards this goal, initially we attempted alkylation of ethyl isocyanoacetate with 2-bromomethyl-1,3-butadiene **5**[6] and sulfolene bromide **6**[7] to prepare the diene **7** under several reaction conditions and were unsuccessful (Scheme 1).[8]

To overcome these problems we considered a cross-enyne metathesis reaction where 1,3-dienes can be generated from alkyne and alkene moieties (Scheme 2). Grubbs catalyst [bis(tricyclohexylphosphine)benzylidine ruthenium(lV) dichloride] was used for the metathesis reactions in the present study.

To prepare highly functionalized Phe derivative **9** by the building block approach, it was considered that the diene containing amino acid moiety can deliver the highly



Scheme 1. (i) Base (ii) $CNCH_2CO_2Et$, HCl (iii) Δ.

Keywords: amino acids and derivatives; metathesis; dienes; Diels–Alder reaction.

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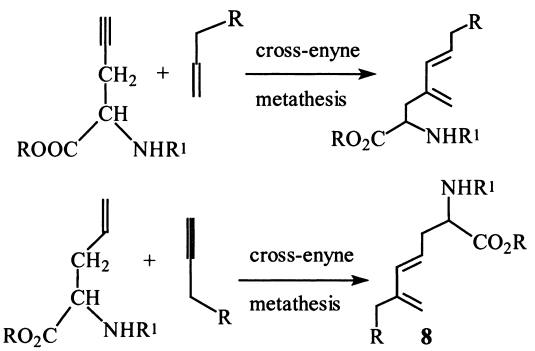


Scheme 2.

functionalized Phe derivative after Diels–Alder reaction with a suitable dienophile (Scheme 3).[9]

2. Results and discussion

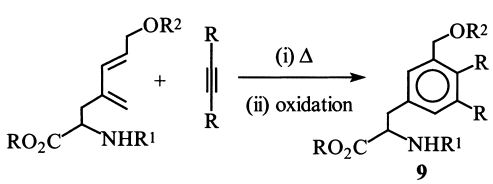
Towards the synthesis of dienes such as **4**, various acetylene building blocks containing an amino acid moiety were prepared from Schiff-base *N*-(diphenyl-methyelene)glycine ester **10** or **11**.[10]

Alkylation of **10** (R=Me) with propargyl bromide in the presence of K_2CO_3/acetonitrile reflux gave the propargylated derivative. Since propargylated Schiff-base was unstable it was hydrolyzed with 1N HCl and the resulting amino ester **12** was protected with acetic anhydride and trimethylacetyl chloride in dry DCM at RT to obtain acetyl derivative **14** (mp 78–79°C) and trimethylacetyl derivative **15** (as a semi solid), respectively. Reaction of **11** (R=Et) with propargyl bromide and subsequent hydrolysis to the amino ester **13** followed by protection with acetic anhydride and trimethylacetyl chloride gave the acetyl derivative **16** (mp 69–70°C) and trimethylacetyl derivative **17** (as a liquid), respectively (Scheme 4).

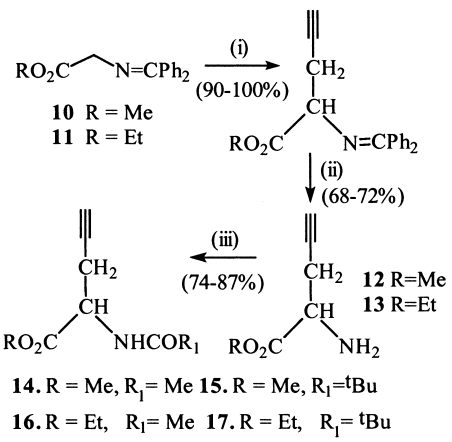
Having prepared several acetylene building blocks, the cross-enyne metathesis reaction of **14** with allyl acetate using Grubbs catalyst[11] in refluxing benzene gave the diene **18** as a 1:1 *cis*/*trans* mixture (Scheme 5). Attempts to separate the *cis*/*trans* isomers were not successful. Moreover, the stereochemistry of the diene is of no consequence in the final target molecule.

To generalize the metathesis reaction, various other dienes **19**–**21** were prepared under cross-metathesis reaction conditions as outlined in Table 1. All the products were characterized with appropriate spectral data and the details are described in Section 4.

When the cross metathesis reaction was tried with different alkenes such as allyl alcohol and allyl silane to obtain



Scheme 3.



Scheme 4. (i) Propargyl bromide, K_2CO_3, CH_3CN (ii) 1N HCl, RT (iii) ^tBuCOCl, Et_3N, or Ac_2O, CH_2Cl_2, RT.

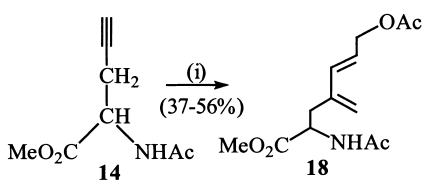
different functionalized dienes, no metathesis product was obtained. The metathesis reaction was successful only with allyl acetate and allyl phenyl ether. Towards the synthesis of diene **8**, the allyl building block embodying an amino acid moiety was prepared and found to be inert towards cross metathesis reaction with various alkynes.[12]

Having several dienes in hand, we next studied the Diels–Alder (DA) chemistry with dienophiles such as DMAD and subsequent oxidation of the Diels–Alder adduct with DDQ to give highly functionalized Phe derivatives. Thus, the Diels–Alder reaction[13] of diene **18** with DMAD in dry toluene in the presence of a pinch of hydroquinone (to avoid polymerization) in a sealed tube at 120°C gave the Diels–Alder adduct which was directly aromatized by DDQ oxidation to give highly functionalized derivatives of Phe **22** (Scheme 6).

The structure of **22** was in full agreement with its spectral data. The ^1H NMR spectrum showed singlets at δ 2.02 and 2.08 due to *O*-acetyl and *N*-acetyl functional group, respectively. In ^1H NMR spectrum a doublet of part of AB system at δ 3.17 (J_1=5.3 Hz, J_2=13.8 Hz) and another doublet of part of AB system at δ 3.26 (J_1=5.8 Hz, J_2=13.8 Hz) showed the presence of diastereotopic CH_2 protons.

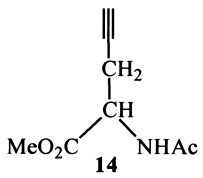
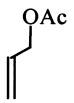
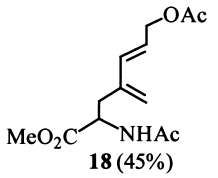
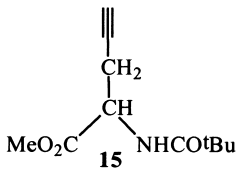
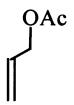
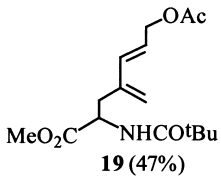
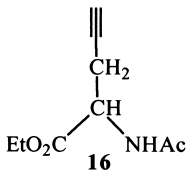
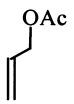
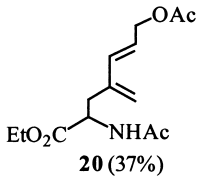
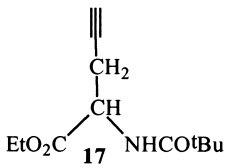
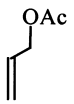
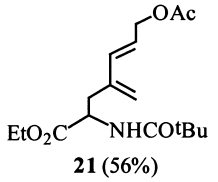
Various other Phe derivatives (**23**–**25**) prepared by this route are shown in Table 2. All the products were fully characterized by their spectral data and the details are presented in Section 4. The yield of the Diels–Alder step is moderate (40–62%) and in entry 3 (Table 2) unreacted starting diene was isolated from the reaction mixture.

To improve the yield of the Diels–Alder step we have tried several reaction conditions such as microwave assisted



Scheme 5. CH_2=$CHCH_2OAc$, Grubbs catalyst.

Table 1. List of dienes prepared by cross-enyne metathesis

Entry	AAA building block	Olefin	Diene (yield)
1	 **14**		 **18** (45%)
2	 **15**		 **19** (47%)
3	 **16**		 **20** (37%)
4	 **17**		 **21** (56%)

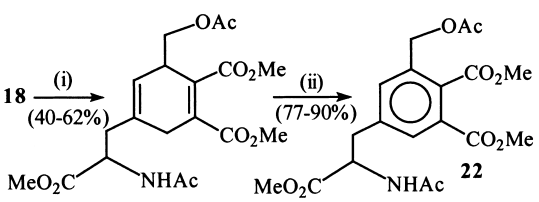
Diels–Alder reaction and Lewis acid ($ZnCl_2$, $AlCl_3$ and BF_3OEt_2) catalyzed DA reaction. However, we found, there was no improvement in the yield of the products.

3. Conclusions

The cross-enyne metathesis reaction and Diels–Alder strategy has been found to be a useful method for the synthesis of various highly functionalized Phe derivatives. The diene building blocks prepared here are useful for the creation of combinatorial libraries.

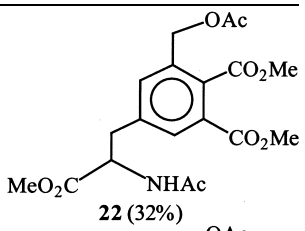
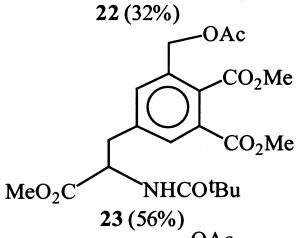
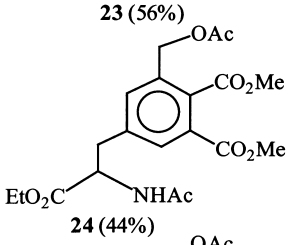
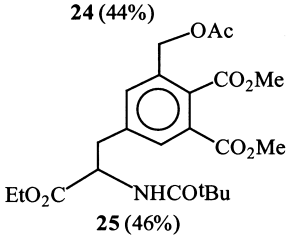
4. Experimental

Diethyl ether, tetrahydrofuran, benzene and toluene were dried by distilling benzophenone ketyl. Chloroform, dichloromethane and acetonitrile were distilled over phosphorus pentoxide. Allylacetate was purchased from E. Merck (India) limited. Grubbs catalyst was purchased from Strem Chemicals, Newburyport, MA, USA. Mps were obtained on a Labhosp or Veego melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker 300 or 500 MHz instrument. High resolution mass



Scheme 6. (i) DMAD, toluene, Δ (ii) DDQ, C_6H_6, Δ.

Table 2. List of Phe derivatives

Entry	Diene	Product (yield)[a]
1	**18**	 **22** (32%)
2	**19**	 **23** (56%)
3	**20**	 **24** (44%)
4	**21**	 **25** (46%)

[a] Yields refer to combined yields for both Diels–Alder and oxidation reactions.

spectra were obtained on JEOL JMS-DX 303 GC-MS instrument. The FAB mass spectra were obtained on JEOL SX 102/DA-6000 Mass spectrometer. UV spectra were obtained on Shimadzu UV-2100 or UV-260 instrument. Room temperature IR spectra were obtained on Nicolet Impact-400 FT IR spectrometer.

4.1. General procedure for the preparation of acetylene building blocks

A solution of Schiff-base (1 equiv.) in dry acetonitrile was added propargyl bromide (1.5 equiv.) and potassium carbonate (5 equiv.). The resulting heterogeneous mixture was refluxed for 20–30 h (TLC monitoring). The reaction mixture was cooled, filtered, and the filtrate was concentrated at reduced pressure. The residue was taken in diethyl ether and washed with water, brine and dried over $MgSO_4$. The evaporation of solvent gave the crude product, which was dissolved in diethyl ether and 1N HCl was added at RT and stirred for 10–15 h. Then, the aqueous layer was separated and washed with excess diethyl ether to remove unwanted organic residues. The aqueous layer was basified with ammonia solution to pH ~10 and then extracted with ethyl acetate. The combined ethyl acetate layer was washed with water, brine and dried over $MgSO_4$. Evaporation of the solvent gave amino ester.

A solution of amino ester (1 equiv.) in dry dichloromethane was added acetic anhydride or trimethylacetyl chloride

(3 equiv.) and a pinch of DMAP or triethylamine. The reaction mixture was stirred at RT for 24 h. Then, the solvent was removed and the residue was taken in ethyl acetate and washed with water, brine and dried over $MgSO_4$. The evaporation of solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with ethyl acetate petroleum ether mixture gave the product.

4.1.1. Methyl-2-acetylamino-4-pentynoate (14). Methyl *N*-(diphenylmethylene)glycinate (**10**) (1.7 g, 6.71 mmol), propargyl bromide (1.2 g, 10.08 mmol) and potassium carbonate (4.6 g, 33.6 mmol) in dry acetonitrile (25 mL) was refluxed for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure and was extracted with diethyl ether (100 mL), washed with water (20 mL), brine (15 mL) and dried over $MgSO_4$. Evaporation of solvent gave the crude alkylated Schiff-base product (1.76 g, 90%). The crude alkylated product (3.1 g, 10.65 mmol) was hydrolyzed in diethyl ether (25 mL) and 1N HCl (10 mL) stirred at RT for 24 h. Work up according to the general procedure gave amino ester **12** (975 mg, 72%) as a light yellow oil.

A solution of amino ester **12** (735 mg, 5.78 mmol) in dry dichloromethane (15 mL) was added acetic anhydride (1.77 g, 17.35 mmol) and a pinch of DMAP. The reaction mixture was stirred at RT for 24 h. Then, the solvent was removed and the residue was taken in ethyl acetate (100 mL) and washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent under reduced pressure gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 17% ethyl acetate/petroleum ether mixture gave **14** (783 mg, 80%) as a white solid. Mp: 78–79°C. IR (KBr): ν 3308, 2120, 1736, 1642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.04 (t, J=2.6 Hz, 1H, C≡C*H*), 2.07 (s, 3H, NHCOCH_3), 2.78 (dd, J_1=2.6 Hz, J_2=4.7 Hz, 2H, CHCH_2), 3.80 (s, 3H, CO_2Me), 4.76 (td, J_1=4.7 Hz, J_2=7.7 Hz, 1H, C*H*CH_2), 6.34 (br s, 1H, N*H*). Mass: *m*/*z* 169 (M^+). Anal: for $C_8H_{11}NO_3$; calcd 56.80 (C), 6.55 (H), 8.28 (N); found: 56.47 (C), 6.49 (H), 8.19 (N).

4.1.2. Methyl-2-trimethylacetylamino-4-pentynoate (15). A solution of amino ester **12** (320 mg, 2.51 mmol) in dry dichloromethane (20 mL) was added trimethylacetyl chloride (1.2 g, 9.95 mmol) and triethylamine (1.01 g, 10.0 mmol). The reaction mixture was stirred at RT for 3 h. Then, the solvent was removed and the residue was taken in ethyl acetate (100 mL) and washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified by silica gel flash column chromatography. Elution of the column with 15% ethyl acetate/petroleum ether mixture gave **15** (463 mg, 87%) as a pure semi solid product. IR (neat): ν 3361, 1754, 2121, 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H, CMe_3), 2.03 (t, J=2.6 Hz, 1H, C≡C*H*), 2.73–2.80 (m, 2H, CHCH_2), 3.80 (s, 3H, CO_2Me), 4.73 (td, J_1=4.7 Hz, J_2=7.7 Hz, 1H, C*H*CH_2), 6.5 (br s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.4, 27.5, 38.9, 50.5, 52.9, 71.6, 78.5, 171.3, 178.4. Mass: *m*/*z* 211 (M^+). HRMS: *m*/*z* (positive ion FAB) for (M+H) $C_{11}H_{18}NO_3$; calcd 212.1287; found: 212.1282.

4.1.3. Ethyl-2-acetylamino-4-pentynoate (16). A solution of ethyl *N*-(diphenylmethylene)glycinate **11** (3 g, 11.2 mmol), propargyl bromide (2 g, 16.8 mmol) and potassium carbonate (7.7 g, 56 mmol) in dry acetonitrile (55 mL) was reflux for 20 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure and was extracted with diethyl ether (150 mL). Evaporation of solvent gave the crude product (3.42 g, 100%), The crude alkylated product (2.1 g, 6.88 mmol) was hydrolyzed in diethyl ether (15 mL) and 1N HCl (9 mL), at RT for 12 h, work up according to the general procedure gave amino ester **13** (660 mg, 68%) as a yellow oil.

The amino ester **13** (660 mg, 4.68 mmol), acetic anhydride (1.43 g, 14.0 mmol) and a pinch of DMAP in dry dichloromethane (18 mL) was stirred for 24 h at RT, then the solvent was removed and work up according to the general procedure. The crude product was purified by silica gel flash column chromatography. Elution of the column with 20% ethyl acetate petroleum ether mixture gave **16** as a white solid (634 mg, 74%). Mp: 69–70°C. IR (KBr): ν 3319, 1731, 2123, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J=7.3 Hz, 3H, CO_2CH_2Me), 2.03 (t, J=2.6 Hz, 1H, C≡C*H*), 2.06 (s, 3H, NHCO*Me*), 2.77–2.79 (m, 2H, CHCH_2), 4.20–4.31 (m, 2H, CO_2CH_2Me), 4.73 (td, J_1=4.4 Hz, J_2=8.0 Hz, 1H, C*H*CH_2), 6.35 (br s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.3, 22.7, 23.4, 50.8, 62.2, 71.7, 78.7, 169.9, 170.6. Mass: *m*/*z* 183 (M^+). HRMS: *m*/*z* (positive ion FAB) for (M+H) $C_9H_{14}NO_3$; calcd 184.0973; found: 184.0976.

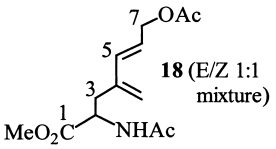
4.1.4. Ethyl-2-trimethylacetylamino-4-pentynoate (17). Amino ester **13** (587 mg, 4.16 mmol), trimethylacetyl chloride (2 g, 16.6 mmol) and triethylamine (1.68 g, 16.64 mmol), in dichloromethane (dry) (35 mL) was stirred at RT for 3 h, then the solvent was removed and work up according to the general procedure. The crude product was purified by silica gel flash column chromatography. Elution of the column with 7.5% ethyl acetate/petroleum ether mixture gave **17** as a thick liquid (703 mg, 75%). IR (neat): ν 3375, 2121, 1741, 1657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 9H, CMe_3), 1.30 (t, J=7.5 Hz, 3H, CO_2CH_2Me), 2.00 (t, J=2.7 Hz, 1H, C≡C*H*), 2.71–2.86 (m, 2H, CH_2CH), 4.17–4.33 (m, 2H, CO_2CH_2Me), 4.67 (td, J_1=4.5 Hz, J_2=7.5 Hz, 1H, CH_2C*H*), 6.49 (br s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 22.2, 27.3, 38.7, 50.3, 61.8, 71.3, 78.4, 170.6, 178.2. HRMS: *m*/*z* (EI) for $C_{12}H_{19}NO_3$; calcd 225.1365; found: 225.1366.

4.2. General procedure for cross-enyne metathesis reaction

A solution of alkyne building block (1 equiv.), alkene (allylacetate) (5 equiv.) in dry benzene (10 mL) was degased by passing nitrogen for 30 min. Then, Grubbs catalyst $RuCl_2(CHC_6H_5)PCy_3$ (10–12 mol%) was added and refluxed for 40–50 h under nitrogen. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography. Elution with ethyl acetate/petroleum ether mixture gave the dienes.

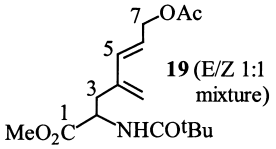
4.2.1. (*E*/*Z*) 7-Acetoxy-2-acetylamino-4-methylene-hept-5-enoic acid methyl ester (18). Alkyne building block **14**

(150 mg, 0.88 mmol), benzene (dry) (10 mL), allyl acetate (477 mg, 4.76 mmol) and Grubbs catalyst (10 mol%), refluxed for 48 h. The column was eluted with 25% ethyl acetate/petroleum ether mixture to give **18** (107 mg, 45%) as a brown liquid. IR (neat): ν 3273, 1742, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H, OCO*Me*), 2.01 (s, 3H, OCO*Me*), 2.08 (s, 3H, NHCO*Me*), 2.09 (s, 3H, NHCO*Me*), 2.60–2.80 (m, 4H, H-3), 3.72 (s, 3H, CO_2*Me*), 3.73 (s, 3H, CO_2*Me*), 4.61–4.71 (m, 2H, H-2), 4.73–4.77 (m, 4H, H-7), 4.85–6.32 (m, 8H, alkene-*H*), 6.47 (d, J=6.6 Hz, 2H, N*H*). Mass: *m/z* 269 (M^+). HRMS: *m/z* (EI) for $C_9H_{15}NO_3$ ($M-C_4H_4O_2$); calcd 185.1052; found: 185.1055.



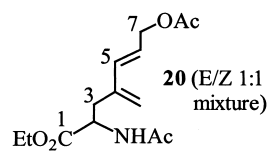
18 (E/Z 1:1 mixture)

4.2.2. (*E*/*Z*) 7-Acetoxy-2-(2,2-dimethyl-propionyl amino)-4-methylene-hept-5-enoic acid methyl ester (19). Alkyne building block **15** (100 mg, 0.47 mmol), benzene (dry) (8 mL), allyl acetate (210 mg, 2.1 mmol) and Grubbs catalyst (8 mol%), refluxed for 60 h. The column was eluted with 17% ethyl acetate/petroleum ether mixture to give **19** (49 mg, 47%, based on starting material recovered 30 mg) as a brown liquid. IR (neat): ν 3381, 1749, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19, (s, 9H, C*Me*$_3$), 1.20 (s, 9H, C*Me*$_3$), 2.07 (s, 3H, OCO*Me*), 2.08 (s, 3H, OCO*Me*), 2.60–2.79 (m, 4H, H-3), 3.72 (s, 3H, CO_2*Me*), 3.73 (s, 3H, CO_2*Me*), 4.58–4.68 (m, 2H, H-2), 4.70–4.75 (m, 4H, H-7), 4.88–6.01 (m, 8H, alkene-*H*), 6.12 (d, J=7.6 Hz, 2H, N*H*). HRMS: *m/z* (EI) for $C_{16}H_{25}NO_5$; calcd 311.1732; found: 311.1730.



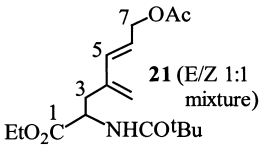
19 (E/Z 1:1 mixture)

4.2.3. (*E*/*Z*) 7-Acetoxy-2-acetylamino-4-methylene-hept-5-enoic acid ethyl ester (20). Alkyne building block **16** (150 mg, 0.82 mmol), benzene (dry) (12 mL), allyl acetate (410 mg, 4.1 mmol), Grubbs catalyst (6 mol%), refluxed for 48 h. The column was eluted with 30% ethyl acetate/petroleum ether mixture to give **20** (86 mg, 37%) as a brown liquid. IR (neat): ν 3301, 1741, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J=7.3 Hz, 6H, CO_2CH_2*Me*), 1.99 (s, 6H, OCO*Me*), 2.08 (s, 6H, NHCO*Me*), 2.57–2.73 (m, 4H, H-3), 4.20 (m, 4H, CO_2CH_2Me), 4.62–4.69 (m, 2H, H-2), 4.73–4.77 (m, 4H, H-7), 4.85–5.99 (m, 8H, alkene-*H*), 6.44 (d, J=7.3 Hz, 2H, N*H*). HRMS: *m/z* (EI) for $C_{12}H_{17}NO_3$ ($M-CH_3CO_2H$); calcd 223.1208; found: 223.1217.



20 (E/Z 1:1 mixture)

4.2.4. (*E*/*Z*) 7-Acetoxy 2-(2,2-dimethyl-propionyl amino)-4-methylene-hept-5-enoic acid ethyl ester (21). Alkyne building block **17** (100 mg, 0.44 mmol), benzene (dry) (10 mL), allyl acetate (223 mg, 2.23 mmol) and Grubbs catalyst (12 mol%), refluxed for 50 h. The column was eluted with 8% ethyl acetate/petroleum ether mixture to give **21** (81 mg, 56%) as a brown liquid. IR (neat): ν 3369, 1742, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H, C*Me*$_3$), 1.21 (s, 9H, C*Me*$_3$), 1.28 (t, 6H, J=6.9 Hz, CO_2CH_2*Me*), 2.06 (s, 3H, OCO*Me*), 2.09 (s, 3H, OCO*Me*), 2.55–2.78 (m, 4H, H-3), 4.13–4.23 (m, 4H, CO_2CH_2Me), 4.50–4.63 (m, 4H, H-7), 4.68–4.79 (m, 2H, H-2), 4.86–5.99 (m, 8H, alkene-*H*), 6.3 (d, J=6.6 Hz, 2H, N*H*). HRMS: *m/z* (EI) for $C_{17}H_{27}NO_5$; calcd 325.1889; found: 325.1877.



21 (E/Z 1:1 mixture)

4.3. General procedure for the Diels–Alder reaction and DDQ oxidation

In a sealed tube, a solution of diene (1 equiv.), DMAD (3 equiv.) and catalytic amount of hydroquinone in dry toluene was heated at 110–140°C under nitrogen for 40–50 h. Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography. Elution of the column with ethyl acetate/petroleum ether mixture to give Diels–Alder adduct. Subsequently the Diels–Alder adduct (1 equiv.) was oxidized with DDQ (2–3 equiv.) in refluxing benzene (dry) for 48 h, which was purified by passing through silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether mixture to give the aromatized product.

4.3.1. 3-Acetoxymethyl-5-(2-acetylamino-2-methoxy carbonyl-ethyl)-phthalic acid dimethyl ester (22). Diene **18** (60 mg, 0.22 mmol), DMAD (100 mg, 0.70 mmol) and dry toluene (3 mL), heated at 120°C for 36 h. The column was eluted with 70% ethyl acetate/petroleum ether mixture to give the Diels–Alder adduct (37 mg, 40%). Subsequently the Diels–Alder adduct (22 mg, 0.05 mmol) was oxidized with DDQ (23 mg, 0.10 mmol) in refluxing benzene (dry) (4 mL) for 48 h. The column was eluted with 60% ethyl acetate/petroleum ether mixture to give the aromatized product **22** (17.5 mg, 80%) as a semi-solid. UV ($CHCl_3$): λ_{max} nm (ε, $M^{-1}\,cm^{-1}$), 282.5 (1.41×10^3), 246.0 (3.47×10^3). IR (KBr): ν 3366, 1738, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H, OCO*Me*), 2.08 (s, 3H, NHCO*Me*), 3.17 (doublet of part of AB system, J_1=5.3 Hz, J_2=13.8 Hz, 1H, diastereotopic proton CH_aCH$_b$), 3.26 (doublet of part of AB system, J_1=5.8 Hz, J_2=13.8 Hz, 1H, diastereotopic proton CH$_a$CH_b), 3.76 (s, 3H, CO_2*Me*), 3.89 (s, 3H, CO_2*Me*), 3.93 (s, 3H, CO_2*Me*), 4.87–4.93 (m, 1H, C*H*NHCOMe), 5.12 (s, 2H, CH_2OCOMe), 5.95 (d, J=7.5 Hz, 1H, N*H*), 7.35 (d, J=1.6 Hz, 1H, Ar–*H*), 7.67 (d, J=1.6 Hz, 1H, Ar–*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 22.9, 37.0, 52.4, 52.5, 52.6, 52.7, 63.0, 128.9, 130.4, 133.0, 133.8, 134.2, 137.8, 165.7, 168.3, 169.5, 170.2, 171.3. Mass: *m/z* 410 (M+1). HRMS: *m/z* (EI) for $C_{18}H_{19}NO_8$ ($M-CH_3OH$); calcd 377.1110; found: 377.1101.

4.3.2. 3-Acetoxymethyl-5-[2-(2,2-dimethyl-propionyl-amino)-2-methoxycarbonyl-ethyl]-phthalic acid dimethyl ester (23). Diene **19** (10 mg, 0.03 mmol), DMAD (15 mg, 0.10 mmol) and dry toluene (3 mL) was heated at 110°C for 42 h. The column was eluted with 80% ethyl acetate/petroleum ether mixture to give the Diels–Alder adduct (9 mg, 62%). Subsequently the Diels–Alder adduct (7 mg, 0.015 mmol) was oxidized with DDQ (7 mg, 0.03 mmol) in refluxing benzene (dry) (3 mL) for 16 h. The column was eluted with 80% ethyl acetate/petroleum ether mixture to give aromatized product **23** (6.3 mg, 90%). UV ($CHCl_3$): λ_{max} nm (ε, $M^{-1}cm^{-1}$), 247.0 (3.85×10^3). IR (KBr): ν_{max} 3414, 1742, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 9H, C*Me*$_3$), 2.07 (s, 3H, OCO*Me*), 3.18 (doublet of part of AB system, J_1=8.1 Hz, J_2=13.8 Hz, 1H, diastereotopic proton C*H*$_a$CH$_b$), 3.29 (doublet of part of AB system, J_1=8.7 Hz, J_2=13.8 Hz, 1H, diastereotopic proton CH$_a$C*H*$_b$), 3.70 (s, 3H, CO_2*Me*), 3.87 (s, 3H, CO_2*Me*), 3.92 (s, 3H, CO_2*Me*), 4.85–4.87 (m, 1H, C*H*NHCOCMe$_3$), 5.10 (s, 2H, C*H*$_2$OCOMe), 6.13 (d, *J*=7.1 Hz, 1H, N*H*), 7.30 (s, 1H, Ar–*H*), 7.60 (s, 1H, Ar–*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.7, 27.3, 37.0, 38.7, 52.5, 52.6, 52.7, 63.1, 128.9, 130.8, 133.2, 133.9, 134.2, 138.1, 165.7, 168.5, 170.3, 171.5, 178.0. HRMS: *m*/*z* (EI) for $C_{22}H_{29}NO_9$; calcd 451.1842; found: 451.1838.

4.3.3. 3-Acetoxymethyl-5-(2-acetylamino-2-ethoxycarbonyl-ethyl)-phthalic acid dimethyl ester (24). Diene **20** (105 mg, 0.37 mmol), DMAD (151 mg, 1.06 mmol) and toluene (dry) (3 mL), heated at 140°C for 5 days. The column was eluted with 50% ethyl acetate/petroleum ether mixture to give the Diels–Alder adduct (55 mg, 53% based on starting material recovered 36 mg). Subsequently the Diels–Alder adduct (34 mg, 0.08 mmol) was oxidized with DDQ (32 mg, 0.14 mmol) in refluxing benzene (dry) (5 mL) for 48 h. The column was eluted with 50% ethyl acetate/petroleum ether mixture to give the aromatized product **24** (28 mg, 83%) as a semi solid. UV ($CHCl_3$): λ_{max} nm (ε, $M^{-1}cm^{-1}$), 246.0 (3.90×10^3), 282.0 (1.65×10^3). IR (KBr): ν_{max} 3369, 1740, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.2 Hz, 3H, CO_2CH_2*Me*), 1.95 (s, 3H, OCO*Me*), 2.01 (s, 3H, NHCO*Me*), 3.17 (doublet of part of AB system, J_1=4.2 Hz, J_2=13.8 Hz, 1H, diastereotopic proton C*H*$_a$CH$_b$), 3.17 (doublet of part of AB system, J_1=4.8 Hz, J_2=13.8 Hz, 1H, diastereotopic proton CH$_a$C*H*$_b$), 3.80 (s, 3H, CO_2*Me*), 3.86 (s, 3H, CO_2*Me*), 4.09–4.16 (m, 2H, CO_2CH_2Me), 4.77–4.83 (m, 1H, C*H*NHCOMe), 5.05 (s, 2H, C*H*$_2$OCOMe), 5.92 (d, *J*=7.8 Hz, 1H, N*H*), 7.29 (d, *J*=1.5 Hz, 1H, Ar–*H*), 7.62 (d, *J*=1.5 Hz, 1H, Ar–*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 20.6, 22.9, 37.1, 52.5, 52.6, 52.8, 61.7, 63.1, 129.0, 130.6, 133.1, 133.9, 134.2, 138.0, 165.6, 168.2, 169.5, 170.0, 170.9. HRMS: *m*/*z* (EI) for $C_{19}H_{21}NO_8$ (M−CH_3OH); calcd 391.1267; found: 391.1248.

4.3.4. 3-Acetoxymethyl-5-[2-(2,2-dimethyl-propionyl-amino)-2-ethoxycarbonyl-ethyl]-phthalic acid dimethyl ester (25). Diene **21** (39 mg, 0.11 mmol), DMAD (50 mg, 0.35 mmol) and dry toluene (2 mL), heated at 140°C for 24 h. The column was eluted with 20% ethyl acetate/petroleum ether mixture to give the Diels–Alder adduct (33.5 mg, 60%). Subsequently the Diels–Alder adduct (30 mg, 0.06 mmol) was oxidized with DDQ (24 mg, 0.10 mmol) in refluxing benzene (dry) (3 mL) for 48 h. The column was eluted with 85% ethyl acetate/petroleum ether mixture to give aromatized product **25** (23 mg, 77%) as a semi-solid. UV ($CHCl_3$): λ_{max} nm (ε, $M^{-1}cm^{-1}$), 245.5 (2.58×10^3), 282.0 (8.40×10^2). IR (KBr): ν_{max} 3414, 1742, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 9H, C*Me*$_3$), 1.30 (t, *J*=7.1 Hz, 3H, CO_2CH_2*Me*), 2.08 (s, 3H, OCO*Me*), 3.19 (doublet of part of AB system, J_1=4.9 Hz, J_2=13.8 Hz, 1H, diastereotopic proton C*H*$_a$CH$_b$), 3.29 (doublet of part of AB system, J_1=5.8 Hz, J_2=13.8 Hz, 1H, diastereotopic proton CH$_a$C*H*$_b$), 3.87 (s, 3H, CO_2*Me*), 3.93 (s, 3H, CO_2*Me*), 4.17–4.25 (m, 2H, CO_2CH_2Me), 4.80–4.86 (m, 1H, C*H*NHCOCMe$_3$), 5.11 (s, 2H, C*H*$_2$OCOMe), 6.17 (d, *J*=6.8 Hz, 1H, N*H*), 7.35 (d, *J*=1.6 Hz, 1H, Ar–*H*), 7.68 (d, *J*=1.6 Hz, 1H, Ar–*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 20.5, 27.2, 29.3, 36.8, 38.6, 52.4 (2C?), 52.6, 61.7, 63.0, 128.7, 130.7, 133.1, 133.8, 134.0, 138.0, 165.4, 165.6, 168.3, 171.0, 177.8. HRMS: *m*/*z* (EI) for $C_{23}H_{31}NO_9$; calcd 465.1998; found: 465.1977.

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