Constrained Phenylalanine Derivatives by Enyne Metathesis and Diels–Alder Reaction

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Keywords: Amino acids / Cycloadditions / Drug research / Metathesis / Peptidomimetics

A conceptually new approach for the synthesis of indane-based α-amino acid derivatives is reported. In this regard, the synthesis of five-membered exocyclic and five-membered inner-outer ring diene building blocks (**7** and **15**) containing α-amino acid moieties is described. Diene **15** is prepared by an enyne metathesis reaction as a key step. In this paper, a full account of our work regarding the Diels–Alder reaction of these dienes with various dienophiles, and the subsequent oxidation of the cycloadducts to give various indane-based α-amino acid derivatives is reported.

Introduction

Incorporation of constrained α-amino acids (AAAs) in a given peptide chain limits the number of possible confirmations.[1] For example, indanylglycine (Ind, R = H) **1** is a constrained analogue of phenylalanine (Phe) in which the rotational freedom of the aromatic ring is restrained due to an additional methylene bridge. Indane-based amino acids have been used in the design of chemotactic peptides[2] and also for analyzing the binding pockets of substance P.[3]

Among the unusual AAAs, α,α-dialkylated and cyclic AAAs have attracted increased attention because they stiffen the backbone of peptides through the formation of helices and β-turns.[4] Only the simplest members of cyclic AAAs are ordinarily used because general methods for the synthesis of complex AAAs are not available. In this context, the development of novel AAAs with a strong preference for well-defined regions of backbone conformational space would increase the tools available to the protein chemist.[5] Traditionally, the Bucherer–Berg method has been used to prepare indane-based AAAs.[6] However, this method doesn't tolerate sensitive functional groups in the aromatic ring.[7] In this regard, a comprehensive approach to indane-based AAAs based on our "building block approach" is useful for the synthesis of complex derivatives with varying steric and electronic properties.[8,9] The cycloaddition approach to AAAs is conceptually different from the other known routes. This approach involves generation of the benzene ring with a [4+2] cycloaddition reaction as the key step, while the other methods rely on manipulation of preformed benzene derivatives.[10] Since the Diels–Alder strategy can create considerable functionality in the final target by appropriate selection of the reacting partners, this strategy is useful for the introduction of diverse functionality in indane-based AAAs.

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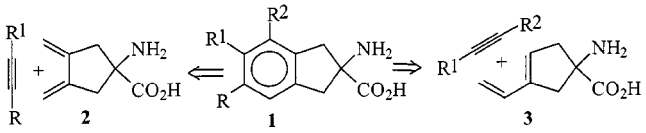
With this in mind, it was of interest to prepare dienes containing an AAA moiety which might be useful for the preparation of indane-based AAAs. A few examples of unsaturated AAAs have been reported in the literature.[11] Unfortunately, some of these derivatives are very delicate compounds, and, consequently, very limited work about the utility of these unsaturated systems in the synthesis of complex AAAs has been reported. In the present paper, as a continuation of our interest in the preparation of various constrained Phe analogs, such as indane systems with extended appendages,[8] we would like to report the full details of our efforts using the enyne metathesis and a Diels–Alder reaction as key steps.

The possibility of utilizing cycloaddition reactions for the synthesis of cyclic AAAs appears to be an attractive option. In this regard, the dienes **2** and **3** containing α,α-dialkylated amino acid moieties were identified as possible building blocks for the synthesis of various Ind derivatives using a Diels–Alder reaction as the key step. Thus, the [4+2] cycloaddition reaction of exocyclic diene **2** with a suitable dienophile, followed by oxidation, is expected to provide the linearly substituted Ind derivatives. Similarly, the inner-outer ring diene **3** delivers the angularly substituted Ind derivatives (Scheme 1).



Scheme 1

Results and Discussion

For the synthesis of **2**, our attention focused on the preparation of 2,3-bis(iodomethyl)-1,3-butadiene **(5a)** as a key precursor, and in this regard tetrabromide **4** was prepared according to the literature procedure (Scheme 2).[12] Thus, addition of bromine to 2,3-dimethyl-1,3-butadiene at 0 °C followed by reaction with *N*-bromosuccinimide gave tetrabromide **4**, which was converted into 2,3-bis(bromomethyl)-

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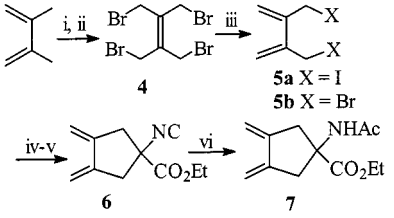
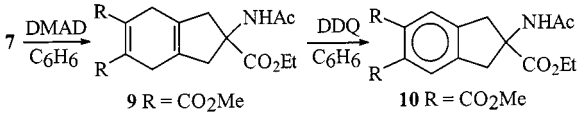
1,3-butadiene **(5b)** by a Zn/Cu-mediated reductive debromination reaction.[13] Since the dibromide **5b** is known to be highly unstable and difficult to handle, the corresponding diiodide **5a**, which is more stable than the dibromide, was chosen. Although diene **5a** polymerizes readily in the solid state, it can be stored at 0 °C as an ethereal solution (0.1 M) for several months.



Scheme 2. Reagents: (i) Br_2, CCl_4, 0 °C; (ii) NBS, AIBN, CCl_4, Δ; (iii) KI, $Na_2S_2O_3{\cdot}5H_2O$, acetone, 45 °C; (iv) $CNCH_2CO_2Et$, **8**, NaH, DMSO/ether, 10 °C; (v) HCl, EtOH; (vi) Ac_2O, DMAP

The dialkylation of ethyl isocyanoacetate **8** with **5a** under mild reaction conditions using NaH/DMSO-ether gave the coupling product **6**.[14] Attempts to purify the isonitrile **6** by silica gel or alumina column chromatography resulted in extensive decomposition. So, in the subsequent attempts **6** was hydrolyzed to the amino ester by simply stirring with 1 N HCl in ethanol. This amino ester was converted into the *N*-acetyl derivative **7** as shown in Scheme 2. The structure of **7** was deduced based on spectral data. In the ^1H NMR spectrum, compound **7** shows a triplet at δ = 1.25 (J = 7.1 Hz) and a quadruplet at δ = 4.19 (J = 7.1 Hz) due to the presence of the ethyl ester. It also displays two singlets at δ = 1.97 and 5.82 due to the acetyl and amide protons, respectively. The ^{13}C NMR spectrum of **7** shows nine signals at δ = 14.0 (q), 23.1(q), 43.3 (t), 61.5 (t), 62.7 (s), 106.3 (t), 144.2 (s), 170.1 (s) and 172. 2 (s) supporting the presence of C_2 symmetry in the molecule.

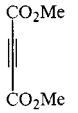
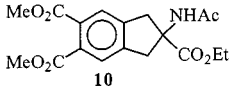
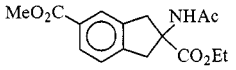
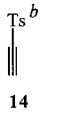
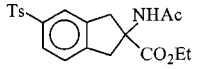
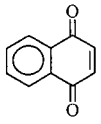
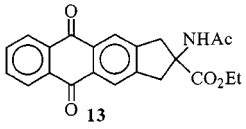
The Diels–Alder reaction of diene **7** with dimethyl acetylenedicarboxylate (DMAD) at room temperature gave the adduct **9** in good yield (Scheme 3). The dehydrogenation of the cycloadduct **9** in the presence of DDQ gave the 5,6-bis(methoxycarbonyl) Ind derivative **10** (93% overall yield for two steps).



Scheme 3

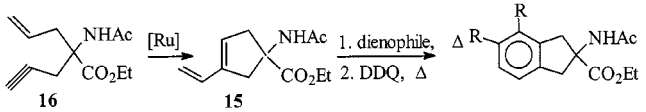
The other dienophiles such as methyl propiolate, ethynyl *p*-tolylsulfone **(14)**,[15] and naphthoquinone underwent a similar [4+2] cycloaddition reaction, and subsequent oxidation of the adducts with DDQ[16] gave the corresponding Ind derivatives **11–13**, respectively; these results are summarized in Table 1.

Table 1. Synthesis of indane-based α-amino acid derivatives by a [4+2] cycloaddition strategy from diene **7**

S. No	Dienophile	Aromatized Product	Yield %[a]
1		 **10**	97
2		 **11**	81
3	 **14**	 **12**	96
4		 **13**	89

[a] Yields refers to combined isolated yields for both the Diels–Alder and DDQ products. – [b] Ts = *p*-toluenesulfonyl.

In order to prepare the angularly substituted Ind derivatives by a Diels–Alder approach, the key inner-outer ring diene building block **15** was identified (Scheme 4). In this regard, a ring-closing enyne-metathesis reaction is known to provide access to 1-vinylcycloalkene derivatives from acyclic enyne derivatives. Towards this objective the synthesis of the required enyne derivative **16** was conceived by two independent routes. Initially the enyne **16** was synthesized using ethyl isocyanoacetate as a glycine equivalent.[14] Sequential allylation and propargylation of ethyl isocyanoacetate **8** under phase transfer catalysis (PTC) conditions gave **17**, which on hydrolysis with 1 N HCl, followed by acetylation, gave the enyne building block **16** in 6% overall yield.

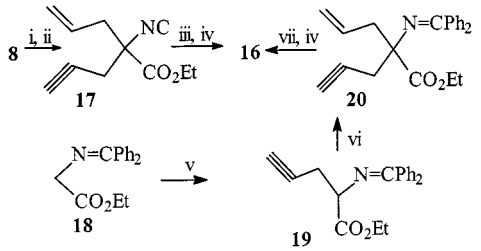


Scheme 4

The major problem here was that the required mono allyl compound was formed as the minor product and the undesired dialkylated product was formed as the major product. In addition, the mono allyl derivative was found to be highly volatile. In order to improve the yield of the building block **16**, a propargylation and allylation sequence was also attempted, although to little effect.

Since the benzophenone Schiff base **18** is known to undergo stepwise alkylation under PTC conditions[17] the two-step alkylation of **18** with propargyl bromide in the presence of K_2CO_3 gave **19** (Scheme 5). Subsequent allylation under

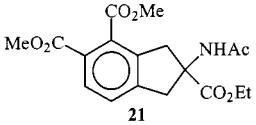
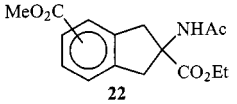
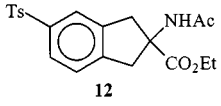
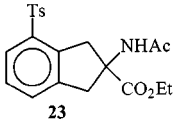
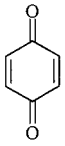
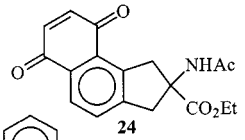
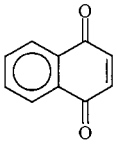
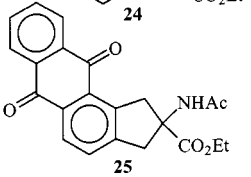
solid-liquid PTC conditions gave the enyne derivative **20**. Hydrolysis of **20**, followed by acetylation, gave the enyne building block **16**.



Scheme 5. (i) Allyl bromide, nBu$_4$NHSO$_4$, K$_2$CO$_3$; (ii) propargyl bromide, nBu$_4$NHSO$_4$, K$_2$CO$_3$; (iii) HCl, EtOH; (iv) Ac$_2$O, DMAP, CH$_2$Cl$_2$; (v) propargyl bromide, K$_2$CO$_3$; (vi) allyl bromide, KOH, nBu$_4$NBr; (vii) 1 N HCl, ether

The enyne derivative **16** was subjected to the RCM reaction in the presence of Grubbs′ ruthenium catalyst [Cl$_2$(PCy$_3$)$_2$Ru=CHPh][18] to give the inner-outer ring diene **15** in 75% isolated yield (Scheme 4). The ^{13}C NMR spectral data [75.4 MHz, CDCl$_3$: δ = 14.0, 23.0, 42.6, 44.3, 61.5, 64.1, 115.1, 126.6, 132.5, 140.2, 170.0, 173.5] of **15** confirmed its structure. The treatment of diene **15** with various dienophiles in refluxing benzene (or toluene) gave the cyclo adducts and dehydrogenation with DDQ gave the angularly substituted Ind derivatives (**21**−**25**, Table 2). In entry no. 2, a regioisomeric mixture of products was obtained and attempts to isolate these compounds were not successful. However, in entry no. 3, after considerable efforts, only compound **12** was isolated, and its spectral data confirmed that it was identical to that of the material obtained from diene **7**. Compound **23** was obtained in an impure form. Since most of the Diels−Alder adducts were found to be contaminated with a small amount of aromatized products, as indicated by NMR spectroscopic data, no special attempts were made to isolate and characterize these adducts.

Table 2. Synthesis of angularly substituted indane-based AAA derivatives by a [4+2] cycloaddition strategy from the inner-outer ring diene **15**

S. No	Dienophile	Oxidation Product	Yields % [a]
1		 **21**	88
2		 **22**	67
3	 **14**	 **12**  **23**	82[b]
4		 **24**	67
5		 **25**	87

[a] Isolated combined yields for two steps. − [b] Overall yield for both isomers

Conclusions

To conclude, a new and general methodology has been developed for the synthesis of linear and angularly substituted indane-based α,α-AA derivatives by a [4+2] cycloaddition strategy. The angularly substituted diene **15** is prepared using enyne metathesis reaction as a key step. Since the Diels−Alder reaction[19] is useful for the preparation of various polycyclic frames, the methodology described here is of immense potential in the preparation of various constrained Phe analogues. The α,α-AA derivatives prepared here are not accessible by other conventional methods, such as the Buchrer−Burg method.

Experimental Section

Diethyl ether, tetrahydrofuran, benzene and toluene were dried by distilling over benzophenone ketyl. Chloroform, dichloromethane, carbon tetrachloride and acetonitrile were distilled over phosphorus pentoxide. *p*-Toluenesulfonyl chloride (TsCl) was purified by dissolving in ether and washing with 20% aq. NaOH solution and water and then crystallized from ether. Aluminum chloride was sublimed before use. Ethyl isocyanoacetate and DDQ were purchased from Aldrich Chemical Co. LiAlH$_4$, KHCO$_3$ were obtained from Fluka. Methyl propiolate and bis(trimethylsilyl)acetylene were purchased from Lancaster Synthesis. The dienes **7** and **15** are unstable: they can only be stored at 0 °C for a few days and it was difficult to get the elemental analyses.

Precaution: *Ethyl isocyanoacetate and the electrophiles used in this study are lachrymators and irritants and must be handled with proper care. Some of them are also potent mutagens.*

Ethyl 3,4-Dimethylene-1-isocyanocyclopentane-1-carboxylate (6): To a stirred solution of ethyl isocyanoacetate **8** (100 mg, 0.86 mmol) and **5a** (319 mg, 0.95 mmol) in dry DMSO/ether (4 mL, 1:1) was added a suspension of NaH (63 mg, 2.65 mmol; 60% in mineral oil, used after washing with dry hexane) in dry ether at 0 °C. The brown reaction mixture was stirred for 15 min at 10 °C. Then, the reaction mixture was quenched with ice-cold water and extracted with ether (3 × 20 mL). The combined organic phase was filtered to remove the yellow polymeric material and the filtrate was washed with water, brine and dried over MgSO$_4$. Evaporation of the solvent gave the crude product **6** (120 mg, 71%) as a brown liquid, which was used in the subsequent reaction without further purification. Attempts to purify compound **6** by a silica gel column

resulted in extensive decomposition of the product. IR (neat): $\tilde{\nu}$ = 2140, 1740 cm^{-1}.

Ethyl 1-Acetamido-3,4-dimethylenecyclopentane-1-carboxylate (7): To the crude isonitrile derivative **6** (120 mg, 0.63 mmol) in absolute ethanol (4 mL) was added conc. HCl (4 drops) at 0 °C and the reaction mixture was stirred at 20−25 °C for 30 min. Then, the solvent was evaporated under reduced pressure. The residue obtained was dissolved in water, basified with ammonia solution (pH = 10) and then extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water and brine, and then dried. Evaporation of the solvent gave the amino ester (61 mg, 54%) as a brown liquid which was used in the next step without any further purification. IR (neat): $\tilde{\nu}$ = 3445, 1740 cm^{-1}.

To a solution of the above amino ester (60 mg, 0.38 mmol) and 4-(dimethylamino)pyridine (DMAP) (5 mg) in dry CH_2Cl_2 (2 mL) was added a solution of acetic anhydride (84.5 mg, 0.82 mmol) in CH_2Cl_2 (2 mL) at room temp. The mixture was stirred for 1 h and then diluted with CH_2Cl_2 (10 mL), washed with water and brine, and dried. Evaporation of the solvent and purification of the crude product by a silica gel column with ethyl acetate/hexane (1:2) as eluent gave **7** (43 mg, 60%) as a white crystalline solid. M.p. 93−95 °C. − IR (KBr): $\tilde{\nu}$ = 3270, 1740, 1645 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.97 (s, 3 H), 2.80 (1/2 ABq, *J* = 16.3 Hz, 2 H), 3.07 (t 1/2 ABq, *J* = 16.6, 2.7 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.97 (d, *J* = 1.3 Hz, 2 H), 5.46 (d, *J* = 1.6 Hz, 2 H), 5.82 (br s, 1 H). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.0 (q), 23.1 (q), 43.3 (t), 61.5 (t), 62.7 (s), 106.3 (t), 144.2 (s), 170.1 (s), 172.2 (s). − MS: *m*/*z* = 223 [M^+].

General Procedure for the Diels−Alder Reaction of Dienes: A solution of the diene (1 mmol), dienophile (1 mmol) and a catalytic amount of hydroquinone in toluene (or benzene) was refluxed until completion of the reaction (TLC monitoring). Subsequently, the Diels−Alder adduct was treated with DDQ in refluxing benzene (or toluene) to give the aromatized product. Evaporation of the solvent and purification of the crude product on a silica gel column with ethyl acetate/hexane (1:1) as eluent gave the aromatized product.

Ethyl 2-Acetamido-5,6-bis(methoxycarbonyl)-4,7-dihydroindanecarboxylate (9): A solution of diene **7** (10 mg, 0.04 mmol) and DMAD (9.5 mg, 0.06 mmol) in dry benzene (3 mL) containing a pinch of hydroquinone was reacted according to the general procedure for 24 h at room temp. Evaporation of the solvent and purification of the crude product on a silica gel column with ethyl acetate/hexane (1:1) as eluent gave **9** (15 mg, 98%) as a colorless sticky solid. IR (KBr): $\tilde{\nu}$ = 3245, 1745, 1635 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.9 Hz, 3 H), 1.99 (s, 3 H), 2.61 (1/2 ABq, *J* = 15.9 Hz, 2 H), 2.99 (s, 4 H), 3.02 (1/2 ABq, *J* = 17.4 Hz, 2 H), 3.78 (s, 6 H), 4.20 (q, *J* = 7.14 Hz, 2 H), 6.07 (s, 1 H). − MS: *m*/*z* = 365 [M^+].

Ethyl 2-Acetamido-5,6-dicarbomethoxyindane-2-carboxylate (10): A mixture of compound **9** (16.4 mg, 0.04 mmol) and DDQ (10.2 mg, 0.04 mmol) in dry benzene was refluxed under N_2 for 10 h. Evaporation of the solvent and purification of the crude product on a neutral alumina column with ethyl acetate/hexane (1:1) as eluent gave the aromatized product **10** (15.5 mg, 95%) as a white crystalline solid. M.p. 145−146 °C. − UV ($CHCl_3$): λ_{max} (ε, M^{-1} cm^{-1}) = 248 (2096) nm. − IR (KBr): $\tilde{\nu}$ = 3326, 1750, 1629cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H), 1.96 (s, 3 H), 3.36 (1/2 ABq, *J* = 17.2 Hz, 2 H), 3.62 (1/2 ABq, *J* = 17.0 Hz, 2 H), 3.89 (s, 6 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.14 (s, 1 H), 7.54 (s, 2 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 23.2, 43.1, 52.6, 62.0, 65.7, 125.0, 131.2, 143.8, 168.1, 170.1, 172.5. − MS: *m*/*z* = 363 [M^+]. − $C_{18}H_{21}NO_7$ (363.36): calcd. C 58.99, H 5.78, N 3.82; found C 59.33, H 5.64, N 3.73.

Ethyl 2-Acetamido-6-bis(methoxycarbonyl-2-carboxylate (11): A mixture of diene **7** (8 mg, 0.03 mmol), methyl propiolate (5.65 mg, 0.06 mmol) and a pinch of hydroquinone in dry toluene (4 mL) was heated at 100−110 °C for 24 h. Evaporation of the solvent and purification of the crude product by silica gel column chromatography with ethyl acetate/hexane (1:1) as eluent gave the Diels−Alder adduct as a colorless liquid (9 mg, 93%). IR (neat): $\tilde{\nu}$ = 3245 (NH), 1745, 1635 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.98 (s, 3 H), 2.58 (d, *J* = 16.3 Hz, 2 H), 2.86 (s, 4 H), 3.05 (dd, *J* = 10.9, 8.2 Hz, 2 H), 3.76 (s, 3 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 6.06 (s, 1 H), 7.01−7.25 (m, 1 H). − MS: *m*/*z* = 307 [M^+].

The cycloadduct (9 mg, 0.03 mmol) obtained in the above reaction and DDQ (7.98 mg, 0.35 mmol) in dry benzene were refluxed under a N_2 atmosphere for 3 h. Evaporation of the solvent and purification of the product by silica gel column chromatography with ethyl acetate/hexane (1:1) as eluent gave **11** (8 mg, 87%) as a colorless liquid. UV ($CHCl_3$): λ_{max} (ε, M^{-1} cm^{-1}) = 245 (2654) nm. − IR (KBr): $\tilde{\nu}$ = 3328, 1745, 1636 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.96 (s, 3 H), 3.31 (d 1/2 Abq, *J* = 16.8, 13.7 Hz, 2 H), 3.64 (d 1/2 ABq, *J* = 18.2, 18.5 Hz, 2 H), 3.90 (s, 3 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.07 (s, 1 H), 7.25 (1/2 ABq, *J* = 7.7 Hz, 1 H), 7.86 (1/2 ABq, *J* = 3.6 Hz, 1 H), 7.90 (s, 1 H). − MS: *m*/*z* = 305 [M^+]. − EI-HRMS ($C_{16}H_{19}NO_5$): calcd. 305.1263; found 305.1251.

Ethyl 2-Acetamido-6-(*p*-toluenesulfonyl)indane-2-carboxylate (12): A solution of diene **7** (14 mg, 0.06 mmol), tosyl acetylene **14** (7.2 mg, 0.07 mmol) and a pinch of hydroquinone in dry benzene was refluxed under N_2 for 24 h. Evaporation of the solvent and purification of the crude product on a silica gel column with ethyl acetate/hexane (1:3) as eluent gave the cycloadduct as a white crystalline solid (19 mg, 99%, Mp, 84−86 °C).

The adduct (16 mg, 0.05 mmol) obtained in the above reaction was refluxed in the presence of DDQ (15 mg, 0.06 mmol) in dry benzene under N_2 for 24 h. Evaporation of the solvent and purification of the residue on a neutral alumina column eluting with ethyl acetate/hexane (1:1) gave the aromatized product **12** (15.4 mg, 97%) as a sticky solid. IR (neat): $\tilde{\nu}$ = 3340, 1743, 1638 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3 H), 1.94 (s, 3 H), 2.41 (s, 3 H), 3.34 (d 1/2 Abq, *J* = 17.0, 11.7 Hz, 2 H), 3.58 (d 1/2 ABq, *J* = 17.2, 17.1 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 6.16 (s, 1 H), 7.30 (1/2 ABq, *J* = 8.4 Hz, 2 H), 7.72 (s, 1 H), 7.75−7.82 (m, 2 H), 7.81 (1/2 ABq, *J* = 7.8 Hz, 2 H). − EI-HRMS ($C_{20}H_{21}NO_3S$ [M − CH_2O_2]): calcd. 355.0878; found 355.0905.

Ethyl 2-*N*-(Diphenylmethylene)propargylglycinate (19): To a solution of ethyl *N*-(Diphenylmethylene)glycinate (**18;**3.0 g, 11.2 mmol) in dry acetonitrile (55 mL) were added propargyl bromide (2 g, 16.8 mmol) and potassium carbonate (7.7 g, 56 mmol). The resulting heterogeneous mixture was refluxed for 30 h. The reaction mixture was cooled, filtered and concentrated under reduced pressure. The residue was taken up in ether (200 mL) and washed with water, brine and dried over $MgSO_4$. The evaporation of solvent gave the product, which was purified by flash column chromatography (neutral alumina, 1:20 ethyl acetate/hexane) to give **19** (2.8 g 86%) as a brown colored liquid. IR (neat): $\tilde{\nu}$ = 3295, 2124, 1738 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (t, *J* = 7.2 Hz, 3 H,), 1.95 (t, *J* = 3.0 Hz, 1 H), 2.7−2.9 (m, 2 H), 4.18 (q, *J* = 6 Hz, 2 H), 4.28 (t, *J* = 5.1 Hz, 1 H), 7.2−7.8 (m, 10 H).

Ethyl 2-Allyl-*N*-(diphenylmethylene)-2-propargylglycinate (20): A stirred solution of *n*-tetrabutylammonium bromide (143 mg, 0.44 mmol) and KOH (750 mg, 13.4 mmol) in dry acetonitrile (15 mL) was added to a solution of **19** (1.365 g, 4.47 mmol) and allyl bromide (812 mg, 6.71 mmol) in acetonitrile (10 mL) at 0 °C over a period of 5 min. The reaction mixture was then stirred for 6 h at 0−10 °C. At the conclusion of the reaction (TLC monitoring), the reaction mixture was filtered and concentrated, the residue was taken up in ether (150 mL), and washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified on a flash alumina column (1:20, ethyl acetate/hexane) to give **20** (1.2 g, 77%) as a colorless liquid. IR (neat): $\tilde{\nu}$ = 3300, 1731cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.9 (t, *J* = 2.4 Hz, 1 H) 2.8−2.9 (m, 4 H), 3.75 (q, *J* = 7.2 Hz, 2 H), 5.1−5.2 (m, 2 H), 5.7−5.9 (m, 1 H), 7.1−7.8 (m, 10 H).

Hydrolysis of the Enyne Building Block (20): To a solution of glycinate **20** (700 mg, 2.02 mmol) in diethyl ether (15 mL) was added 1 N HCl (3 mL). The reaction mixture was stirred at room temp. for 24 h. The ether layer was then discarded and the aqueous layer basified with ammonia solution to pH ≈ 10. The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to give the amino ester as a light yellow oil (347 mg, 95%). IR (neat): $\tilde{\nu}$ = 3371, 2119, 1733 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 6.0 Hz, 3 H), 1.88 (br s, 2 H), 2.06 (t, *J* = 2.7 Hz, 1 H), 2.31−2.70 (m, 4 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.01−5.23 (m, 2 H), 5.61−5.82 (m, 1 H).

Ethyl *N*-acetamido-(±)2-allyl-4-pentynoate (16): To a solution of the above amino ester (346 mg, 1.9 mmol) in dichloromethane (20 mL) was added a catalytic amount of DMAP and acetic anhydride (520 mg, 5.0 mmol). The resulting reaction mixture was stirred at room temp. for 8 h. Then, the reaction mixture was concentrated and the residue was chromatographed on a silica gel column (1:5 ethyl acetate/hexane) to give crystalline product **16** (300 mg, 70%). M.p. 90−91 °C. − IR (neat): $\tilde{\nu}$ = 3419 1735, 2121, 1647cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H), 1.96 (t, *J* = 2.4 Hz, 1 H), 2.09 (s, 3 H), 2.49 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.79 (d 1/2 ABq, *J* = 2.7, 16.8 Hz, 1 H), 3.12 (dd, *J* = 7.5, 13.5 Hz, 1 H), 3.34 (d 1/2 ABq, *J* = 3.0, 17.1 Hz, 1 H), 4.26 (dq, *J* = 1.8, 5.4 Hz, 2 H), 5.07−5.15 (m, 2 H), 5.53 (m, 1 H), 6.35 (s, 1 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.2, 23.8, 25.0, 39.0, 62.2, 62.7, 70.8, 79.3, 119.6, 131.5, 169.5, 171.8. − MS: *m*/*z* = 223 [M$^+$]. − $C_{12}H_{17}NO_3$ (223.27): calcd. C 64.53, H 7.67, N 6.27; found C 64.31, H 7.41, N 6.01.

Ethyl (±)-1-Acetamido-3-cyclopentene-3-vinyl-1-carboxylate (15): To a solution of the enyne building block **16** (200 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) was added Grubbs′ catalyst [$Cl_2(PCy_3)_2Ru$=CHPh] (73 mg 0.086 mmol) (10 mol%) and the reaction mixture was stirred at room temp. for 24 h under an argon atmosphere. The reaction mixture was then concentrated under vacuum and purified on a silica gel column by eluting with petroleum ether/ethyl acetate (5:1) to give **15** (150 mg, 75%) as a crystalline product. M.p. 85−86 °C. − IR (neat): $\tilde{\nu}$ = 3296, 1732, 1663 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.98 (s, 3 H), 2.74 (dd, *J* = 16.2, 16.7 Hz, 2 H), 3.17 (dd, *J* = 16.5, 15.9 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.04−5.12 (m, 2 H), 5.62 (s, 1 H) 6.10 (s, 1 H), 6.51 (dd, *J* = 10.8, 17.4 Hz, 1 H). − ^{13}C NMR (75.43 MHz, $CDCl_3$): δ = 14.0, 22.9, 42.5, 44.3, 61.5, 64.1, 115.1, 126.5, 132.5, 140.1, 170.0, 173.4. − MS: *m*/*z* = 223 [M$^+$]. − EI-HRMS ($C_{10}H_{12}NO_3$ [M − C_2H_5]): calcd. 194.0817; found 194.0815.

Ethyl 8-Acetamido-3,4-dihydro-5*H*-cyclopenta[*e*]-1,4-naphthoquinone-8-carboxylate (24): A solution of the diene **15** (25 mg, 0.11 mmol), benzoquinone (12.1 mg, 0.11 mmol) and a catalytic amount of hydroquinone (1 mg) in dry toluene (3 mL) was refluxed for 2 days. The solvent was concentrated under reduced pressure and the crude product was purified on a silica gel column with ethyl acetate/hexane (2:3) as eluent to give the cycloadduct (34.4 mg, 93%) as a thick liquid. Subsequently, this adduct (20 mg, 0.06 mmol) and DDQ (13.4 mg, 0.05 mmol) were refluxed in toluene (3 mL) for 24 h. The solvent was then evaporated and the residue was purified by flash column chromatography (silica gel, 1:5 ethyl acetate/hexane) to give **24** as a dark brown liquid (13.1 mg, 67%). IR (neat): $\tilde{\nu}$ = 3296, 1732 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.98 (s, 3 H), 3.53 (1/2 ABq, *J* = 17.7 Hz, 1 H) 3.74 (1/2 ABq, *J* = 17.7 Hz, 1 H), 3.82 (d, *J* = 2.7 Hz, 2 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 6.30 (s, 1 H), 6.92 (ABq, *J* = 10.5 Hz, 2 H), 7.56 (d, *J* = 7.8 Hz,1 H) 8.01 (d, *J* = 7.8 Hz, 1 H). − UV ($CHCl_3$): λ_{max} (ε, M^{-1} cm^{-1}) = 250 (8.6 × 10^3), 358 (2.06 × 10^3). − EI-HRMS ($C_{18}H_{17}NO_5$): calcd. 327.1106; found 327.1104.

Acknowledgments

We are thankful to DST, New Delhi for the financial support. N. S and E. B thank CSIR, New Delhi for the award of Fellowships. We also thank RSIC-Mumbai, TIFR & Dr. M. S. Nair for recording the spectral data.

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Received July 27, 2000
[O00393]