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Efficient Synthesis of Enynecarbamates and Their Ring-Closing Metathesis/[4 + 2] Diels−Alder Cycloaddition: Synthesis of Hexahydroisoquinolines

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Abstract: Enynes **5a**−**g** were prepared in moderate to good yields from 1-(triphenylphosphoranylideneaminoalkyl)benzotriazoles. Ring-closing metathesis of **5a**−**f** afforded functionalized dienes **6a**−**f**, respectively, which were used in a Diels−Alder cycloaddition reaction in the synthesis of the corresponding hexahydroisoquinoline derivatives **7a**−**f**.

Since its introduction by Tsuji[1a] and Villemin[1b] into organic synthesis, "ring-closing metathesis" (RCM) has become the cornerstone of new strategies for the preparation of diverse classes of compounds.[2] A significant breakthrough was achieved with the introduction of ruthenium catalysts[3] and its application to nitrogen-containing heterocycles.[4] This has driven olefin metathesis as a powerful method for C−C bond formation in the synthesis of both carbocyclic and heterocyclic ring systems with sizes varying from five to several dozens of atoms.[5]

Intramolecular enyne metathesis is attractive because carbon−carbon bond formation occurs between alkene and alkyne carbons to afford a cyclized product with the migration of the alkylidene portion of the alkene to the alkyne carbon. The resultant diene moiety can be used for subsequent synthetic transformations. Several researchers have established that intramolecular enyne metathesis can be used to construct ring structures. Katz and Sivavec first reported that pentacarbonyltungsten carbene catalyzes intramolecular enyne metathesis to generate substituted 1-vinylcycloolefins.[6] Subsequently, enyne metathesis using ruthenium catalyst was successfully applied to the synthesis of heterocycles, including natural products.[7] Sequential ring-closing metathesis/[4 + 2] cycloaddition have been used for the preparation of several carbocyclic and heterocyclic systems.[8] Spontaneous Diels−Alder dimerization of 2-vinylbutenolide prepared by enyne metathesis gives the perhydroisobenzofuranone *rac*-differolide.[9] Mori et al. has described the ring closing followed by Diels−Alder cycloaddition of a tosyl enyneamide during a study aimed at the effect of ethylene gas in the enyne metathesis and has reported the formation of an isoquinoline derivative.[10] Other reports on the enyne metathesis/Diels−Alder reaction include the preparation of tetrahydropyran and dihydrofuran derivatives,[11] heterocyclic boronic ester derivatives,[12] and perhydroindenes and perhydroisoindoles.[13]

The efficient application of this technique, however, relies on the ease of availability of corresponding enynes. Despite the many applications of eneyne metathesis, general methods for the synthesis of the starting eneynes are scarce. This was somewhat surprising given their versatile applications in the construction of heterocycles, particularly those containing fused ring systems. Earlier, we showed that 1-(triphenylphosphoranylideneaminoalkyl)benzotriazoles are excellent precursors for the preparation of bis alkenylamines and eneyneamines.[14] We now report on the synthesis of enynecarbamates and their ring-closing metathesis and the subsequent utilization of the resulting dienes in Diels−Alder cycloaddition reactions.

1-(Triphenylphosphoranilideaminomethyl)benzotriazole **1** was prepared following known methods. We have previously shown that aza-Wittig coupling of **1** and its derivatives with aldehydes occurs in THF at room temperature and the crude imines undergo facile bisallylation with 2.2 equiv of allylmagnesium bromide to afford bisbutenylamines in excellent yields.[14] Thus, the successive use of acetylenic and allyl Grignard reagents should lead to the formation of enynes. Thus, benzotriazole derivative **1** was treated in THF with 1 equiv of ethynylmagnesium bromide. The resulting intermediate **3a** was subjected to an aza-Wittig coupling with benzaldehyde. Imine **4a** was then treated with 1 equiv of allylmagnesium bromide. Upon quenching of the reaction with phenyl carbamate, the enyne carbamate **5a** was isolated in 47% overall yield after column chromatography. Advantageously, all of the above three steps were carried out without the isolation and purification of intermediates. Similarly other enynes **5b**−**g** were prepared following the above procedure in moderate to good

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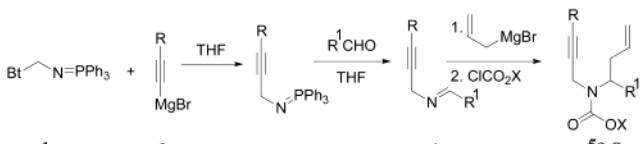
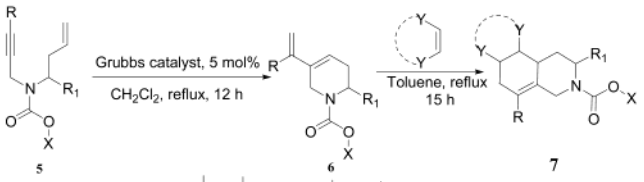
SCHEME 1



5	R	R^1	X	Yield (%)
a	H	Ph	Ph	47
b	H	2-thienyl	Me	52
c	H	cyclohexyl	Ph	68
d	CH3	2-furyl	Me	61
e	H	2-(5-methyl)furyl	Me	68
f	CH_3	Ph	Me	67
g	CH_3	Ph	Et	77

SCHEME 2



6	R	R_1	X	Yield(%)
a	H	Ph	Ph	96
b	H	2-thienyl	Me	87
c	CH_3	2-furyl	Me	61
d	CH_3	2-(5-methyl) furyl	Ph	88
e	H	cyclohexyl	Ph	81
f	CH_3	Ph	Me	52

yields (Scheme 1). NMR spectra of **5a**−**g** revealed that the enynecarbamates exist as a mixture of rotamers, as the ^{1}H and ^{13}C spectra were complicated by signals from both rotamers. Moreover, many signals in the ^{1}H NMR spectrum appeared as broad signals due to the rapid interconversion of these rotamers in solution and the ^{13}C NMR showed more signals than expected in accordance with the literature data for similar compounds.[16] Our literature search has revealed that this is the first report on the general synthesis of enynecarbamates, although Mori and co-workers[10] have studied the ring-closing metathesis of enyneamides.[15] Pearson et al. has reported a general synthesis of bisallylamines,[16] and other reports on similar systems include our own route to bisbutenylamines and enynamines.[14]

As shown in Scheme 2, enynes prepared were subjected to ring closure. When **5a** was refluxed in dichloromethane for 15 h in the presence of 5 mol % Grubbs catalyst, $(PCy_3)_2Cl_2Ru{=}CHPh$, the corresponding diene **6a**, was isolated in nearly quantitative yield. Enynes **5b**−**f** also reacted similarly, giving the corresponding piperidine carbamates **6b**−**f** in moderate to good yields. Since the products from ring closing have a diene moiety, we demonstrated the utility of **6a**−**f** in Diels−Alder cycloadditions.

In fact, tandem ring-closing/Diels−Alder reactions can be carried out in one pot. This methodology has been exhibited in two cases, **6a** and **6b**, where the crude piperidine carbamates were refluxed with maleic anhydride. We note that purification of the carbamates over silica gel significantly reduced the isolated yield, even though TLC analysis indicated a clean conversion of enynes to the piperidine derivative.

Subsequently, other piperidine carbamates **6a**−**f** were isolated in moderate to good yields and reacted with dienophiles, affording the respective isoquinolines **7a**−**f** in good yields. Table 1 summarizes these results. The NMR spectra of tetratrahydroisoquinolines **7a**−**f** showed the presence of rotamers, and the cis orientation of bridge protons H-2, H-4, H-9, and H-10 in these adducts was confirmed from the NOESY experiments.

In conclusion, we have demonstrated a general method for the preparation of enynecarbamates and applied the RCM/Diels−Alder strategy in the preparation of hexahydroisoquinolines, which are useful in the preparation of biologically active molecules. We expect that the method described here should offer a general synthetic method to enynes and thereby to the preparation of biologically important motifs such as piperidine carbamates and hexahydroisoquinolines.

Experimental Section

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in chloroform-*d* solution. Column chromatography was performed on silica gel. All of the Grignard reagents (as solutions in THF) were procured from commercially available sources. THF was distilled from sodium-benzophenone ketal prior to use. All the reactions were performed under a nitrogen and argon atmosphere and in flame-dried glassware. 1-(Triphenylphosphoranylideneaminoalkyl)benzotriazoles **1** were prepared following a literature method. All NMR spectra were recorded at room temperature unless mentioned otherwise.

General Procedure for the Preparation of 5a−**e.** 1-(Triphenylphosphoroylideneaminoalkyl)benzotriazole **1** (10 mmol) was taken in dry THF (50 mL), and the corresponding propargyl Grignard reagent (10.2 mmol) was added dropwise at room temperature. The mixture was allowed to stir at room temperature for 3 h, diluted with ether (200 mL), and filtered. The filtrate was dried over sodium sulfate and concentrated, and the oily residue was redissolved in THF (50 mL). The resulting solution was treated with the appropriate aldehyde (10 mmol) at room temperature for 5 h. After the TLC analysis indicated complete consumption of the aldehyde, allylmagnesium bromide (10 mmol, 1 M solution in THF) was added dropwise at room temperature. After the addition, the reaction mixture was stirred for 2 h at room temperature, poured into cold water, and extracted with ether (3 × 100 mL). The combined ethereal layer was washed with 2 N NaOH (2 × 50 mL) followed by water (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give the crude amine. To the amine in CH_2Cl_2 (50 mL) was added triethylamine (20 mmol), and the mixture was cooled in ice water followed by the addition of the corresponding chloroformate (20 mmol). The mixture was stirred overnight at room temperature, poured into water, and extracted with ethyl acetate (3 × 50 mL). The ethyl acetate layer was washed with water, brine, and dried over Na_2SO_4. The crude carbamate was purified by column chromatography over silica gel (200−400 mesh) using EtOAc/hexane (15:85) as the eluent. NMR spectra of **5a**−**f** were recorded at room temperature, and rotamers were present.

Phenyl *N*-(1-Phenyl-3-butenyl)-*N*-(2-propynyl)carbamate 5a: yellow oil (47%); ^{1}H NMR δ 2.16 (t, J = 2.4 Hz, 1H),

(15) Tosyl enyneamide is used for RCM. However, neither its preparative method nor any reference is provided (see ref 10).
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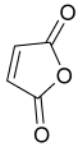
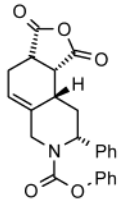
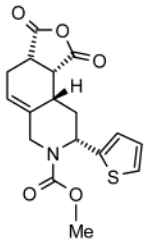
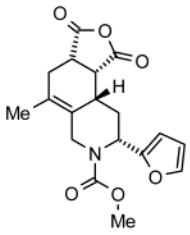
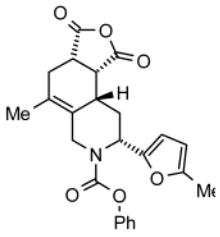
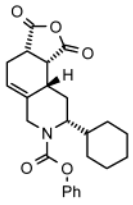
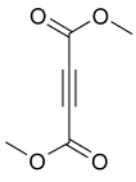
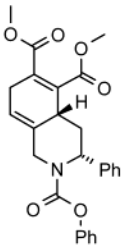
TABLE 1. Diels−Alder Reaction of Dienes 6a−f

7	Enyne	X	Diene	Dienophile	Product	Yield (%)
a	5a	Ph	6a			87
b	5b	Me	6b	″		82
c	5c	Ph	6c	″		58
d	5d	Me	6d	″		73
e	5e	Me	6e	″		68
f	5f	Et	6f			72

2.88−3.00 (m, 2H), 3.74 (dd, J = 1.8, 17.7 Hz, 1H), 4.06 (d, J = 18.0 Hz, 1H), 5.12−5.27 (m, 2H), 5.49 (br s, 1H), 5.95 (br s, 1H), 7.16−7.22 (m, 3H), 7.31−7.44 (m, 7H); ^{13}C NMR δ 35.4, 53.4, 59.3, 71.3, 80.1, 117.9, 121.7, 125.4, 127.9, 128.6, 129.2, 134.6, 138.6, 151.2, 154.5. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.27; N, 4.59. Found: C, 78.45; H, 6.58; N, 4.47.

Phenyl *N*-(2-Propynyl)-*N*-[1-(2-thienyl)-3-butenyl]carbamate 5b: yellow oil (52%); ^{1}H NMR δ 2.15 (t, J = 2.1 Hz.

1H), 2.85 (t, J = 7.2 Hz, 2H), 3.69 (dd, J = 1.8, 18 Hz, 1H), 3.79 (s, 3H), 4.00 (br s, 1H), 5.08−5.23 (m, 2H), 5.62 (br s, 1H), 5.81−5.91 (m, 1H); ^{13}C NMR δ 32.6, 37.1, 53.0, 55.2, 80.3, 117.9, 125.2, 125.7, 126.6, 134.1, 142.9, 156.2. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.91; H, 6.25; N, 6.14.

Phenyl *N*-(1-Cyclohexyl-3-butenyl)-*N*-(2-propynyl)carbamate 5c: yellow oil (68%); ^{1}H NMR δ 0.93−2.12 (m, 11H), 2.13−2.31 (m, 2H), 2.47−2.52 (m, 1H), 3.86−4.09 (m, 3H), 5.03−5.15 (m, 2H), 5.79−5.86 (m, 1H), 7.07−7.39 (m,5H); ^{13}C NMR (rotamers present) δ 25.7, 26.0, 26.2, 30.3, 34.1, 34.4, 39.9, 40.4, 62.1, 71.2, 80.01, 117.2, 120.8, 125.2, 126.2, 129.4, 135.4, 151.4. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.65; H, 8.15; N, 4.84.

Methyl *N*-(2-Butynyl)-*N*-[1-(2-furyl)-3-butenyl]-carbamate 5d: yellow oil (61%); ^{1}H NMR δ 1.73 (s, 3H), 2.77 (t, J = 7.28 Hz, 1H), 3.65 (br d, 1H), 3.76 (s, 3H), 3.89−4.00 (m, 1H), 5.10 (dd, J = 17.0, 14.8 Hz, 2H), 5.79 (m, 1H), 6.28−6.32 (m, 2H), 7.36(s, 1H); ^{13}C NMR δ 3.4, 31.2, 36.1, 39.0, 40.0, 54.1, 76.6, 78.9, 106.8, 109.7, 117.7, 134.6, 141.6, 155.2. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.23; H, 7.21; N, 6.00.

Phenyl *N*-(2-Butynyl)-*N*-[1-(5-methyl-2-furyl)-3-butenyl]-carbamate 5e: yellow oil (68%); ^{1}H NMR δ 1.76 (s, 3 H), 2.28 (s, 3H), 2.72 (br s, 2H), 3.75−3.83 (m, 1H), 4.09 (dd, J = 2.06, 17.8 Hz, 1H), 5.08−5.22 (m, 2H), 5.41 (t, J = 7.2 Hz, 1H), 5.92 (br s, 2H), 6.21 (d, J = 2.9 Hz, 1H), 7.12−7.22 (m, 3H),7.35 (t, J = 7.7 Hz, 2H); ^{13}C NMR δ 3.5, 13.5, 14.1, 33.1, 35.0, 41.7, 42.1, 105.9, 109.4, 117.5, 121.6, 124.8, 125.1, 129.0, 134.2, 150.3, 151.9, 154.01. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.45; H, 6.51; N, 4.58.

Ring-Closing Metathesis/Diels−Alder Reaction of Enynes 5a−e. To a solution of Grubbs catalyst (5 mol %) in CH_2Cl_2 (40 mL) was added enyne **5** (10 mmol), and the mixture was reflux under argon for 12 h. Methylene chloride was removed in vacuo, and the crude diene (in the cases of **6a** and **6b**) was refluxed with the respective dienophile (20 mmol) in toluene (25 mL) for 15 h. Other piperidine carbamates **6c−e** (10 mmol scale) were purified over silica gel and subsequently refluxed in toluene (25 mL) with the appropriate dienophile (20 mmol) for 15 h. After concentration, the residue was taken in ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. After concentration, the crude product was purified by column chromatography over silica gel (200−400 mesh) using hexane/EtOAc (70%) as the eluent. NMR spectra of **6a−f** and **7a−f** were recorded at room temperature, and rotamers were present.

Phenyl 1,3-Dioxo-8-phenyl-3,3a,4,6,8,9,9a,9b-octahydrofuro[3,4-*f*]isoquinoline-7(1*H*)-carboxylate 7a: brown oil (87%); ^{1}H NMR δ 1.90−2.16 (m, 3H), 2.64 (dd, J = 7.2, 8.4 Hz, 1H), 2.82−2.96 (m, 1H), 3.08 (dd, J = 6, 9.3 Hz, 1H), 3.20 (t, J = 8.7 Hz, 1H), 3.93 (d, J = 15.3, 0.63H), 4.13 (d, J = 14.4 Hz, 0.36H), 4.56−4.65 (m, 1H), 5.38−5.48 (br m, 1H), 5.94 (br s, 1H); ^{13}C NMR δ 24.2, 29.7, 29.8, 29.9, 30.0, 40.6, 43.4, 45.1, 45.7, 55.8, 56.0, 121.4, 122.0, 125.2, 126.9, 128.4, 128.9, 129.0, 137.1, 141.0, 141.9, 150.8, 154.0, 171.7, 173.8. Anal. Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47. Found: C, 71.67; H, 5.54; N, 3.12.

Methyl 1,3-Dioxo-8-(2-thienyl)-3,3a,4,6,8,9,9a,9b-octahydrofuro[3,4-*f*]isoquinoline-7(1*H*)-carboxylate 7b: yellow oil (82%); ^{1}H NMR δ 2.05−2.34 (m, 3), 2.61−2.75 (m, 2H), 3.22−3.33 (m, 2H), 3.57−3.65 (m, 2H), 3.91 (d, J = 15.3 Hz, 1H), 4.23 (t, J = 14.4 Hz, 1H), 5.45−5.60 (m, 1H), 5.85 (br s, 1H), 6.75 (br s, 1H), 6.90 (br s, 1H),7.15 (br s, 1H); ^{13}C NMR δ 24.1, 30.2, 30.9, 40.6, 43.5, 45.2, 51.9, 53.0, 121.7, 123.6, 123.9, 127.1, 156.2,-173.7, 171.6. Anal. Calcd for $C_{22}H_{19}NO_5$: C, 64.53; H, 4.68; N, 3.42. Found: C, 64.77; H, 4.54; N, 3.12.

Methyl 8-(2-Furyl)-4-methyl-1,3-dioxo-3,3a,4,6,8,9,9a,9b-octahydrofuro[3,4-f]isoquinoline-7(1*H*)-carboxylate 7c: white powder (58%), mp 165−167 °C; ^{1}H NMR (at 60 °C) δ 1.80 (s, 3H), 2.17 (s, 3H), 2.21 (br d, J = 15.5 Hz, 1H), 2.29−2.37 (m, 2H), 2.57 (dd, J = 15.5, 2.1 Hz, 1), 2.68 (ddd, J = 15.5, 4.6 Hz, 1H), 3.92 (app heptd, 1H), 3.23 (dd, J = 9.5, 5.9 Hz, 1H), 3.33 (ddd, J = 9.5, 6.9 Hz, 1H), 4.41 (d, J = 15.8 Hz, 1H), 5.39 (app t, 1H), 5.99 (dt, J = 3.24, 0.9 Hz, 1H), 6.26 (ddd, J = 3.24, 1.85 Hz, 1H), 7.29 (ddd, J = 1.85, 0.9 Hz, 1H); ^{13}C NMR (at 60 °C) δ 18.8, 28.7, 30.9, 31.7, 41.0, 41.4, 44.1, 49.5, 52.7, 106.1, 110.2, 128.0, 129.3, 141.6, 154.5, 171.5,173.5. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.11; H, 5.92; N, 3.98.

Phenyl 4-Methyl-8-(5-methyl-2-furyl)-1,3-dioxo-3,-3a,4,6,8,9,9a,9b-octahydrofuro[3,4-f]isoquinoline-7(1*H*)-carboxylate 7d: yellow oil (73%); ^{1}H NMR δ 1.82 (s, 3H), 2.26 (s, 3H), 2.28 (s, 1H), 2.36−2.39 (m, 2H), 2.71−2.88 (m, 1H), 3.30−3.38 (m, 2H), 3.90 (d, J = 14.8 Hz, 0.6 H), 4.12 (d, J = 14.8 Hz, 0.4 H), 4.62 (d, J = 15.8 Hz, 1H), 5.50 (br. s, 1H), 5.88−5.96 (m, 2H), 7.00 (d, J = 7.5 Hz, 1H), 7.10−7.19 (m, 2H), 7.26−7.34 (m, 2H); ^{13}C NMR δ 13.6, 19.1, 27.9, 30.8, 31.5, 40.9, 41.1, 44.0, 50.4, 76.5, 106.1, 106.8, 121.6, 121.7, 125.3, 127.6, 129.2, 129.9, 151.3, 152.1, 151.1,171.8. Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32. Found: C, 68.48; H, 5.18; N, 2.74.

Phenyl 8-Cyclohexyl-1,3-dioxo-3,3a,4,6,8,9,9a,9b-octahydrofuro[3,4-f]isoquinoline-7(1*H*)-carboxylate 7e: colorless oil (68%); ^{1}H NMR δ 1.02−1.26 (m, 5H), 1.60−1.82 (m, 4H), 2.17−2.20 (m, 4H), 2.28−2.33 (m, 1H), 2.71−2.85 (m, 2H), 3.41−3.43 (m, 2H), 3.74 (d, J = 16.4 Hz, 0.5 H), 4.01 (d, J = 16.4 Hz, 0.5 H), 4.14−4.23 (m, 1H), 4.45 (d, J = 15.6 Hz, 1H), 5.84 (br s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H); ^{13}C NMR δ 22.9, 26.0, 26.0, 29.7, 29.9, 37.2, 37.2, 39.9, 40.3, 43.2, 43.5, 45.0, 56.2, 120.5, 121.7, 125.2, 125.3, 129.1, 129.2, 134.8, 151.3,171.2. Anal. Calcd For $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.00; H, 6.89; N, 3.29.

8-Methyl-3-phenyl-3,4,4a,7-tetrahydro-1*H*-isoquinoline-2,5,6-tricarboxylicacid-trimethyl Ester 7f: colorless liquid (72%); ^{1}H NMR δ (at 60 °C) 1.76 (s, 3H), 1.80 (d, J = 5.4, 0.5 Hz, 0.5H), 1.85 (d, J = 5.4 Hz, 0.5 H), 2.64 (d, J = 13.3 Hz, 1H), 2.79 (d, J = 6.9 Hz, 0.5 H), 2.86 (d, J = 6.4 Hz, 0.5 H), 2.99 (d, J = 7.2 Hz, 0.5 H), 3.07 (d, J = 7.2 Hz, 0.5 H), 3.15 (d, J = 14.4 Hz, 1H), 3.74 (s, 3H), 3.24 (br s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 4.95 (d, J = 14.4 Hz, 1H), 5.57 (br s, 1H), 7.20−7.38 (m, 5 H); ^{13}C NMR δ (at 60 °C) 17.4, 33.7, 35.2, 41.6, 51.7, 51.8, 52.6, 53.9, 122.4, 124.9, 126.4, 126.9, 128.4, 128.7, 131.8, 135.9, 138.8, 156.3, 167.5, 167.7. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.10; H, 6.32; N, 3.28.

Supporting Information Available: Spectral data of **5f**,**g** and **6a−f**, ^{1}H NMR spectra of **6a** and **6b**, and NOESY spectrum of **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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