New Approach for the General Synthesis of Oxotetrahydroindoles via Intramolecular Cycloadditions of Azomethine Ylides with Tethered Alkynes†

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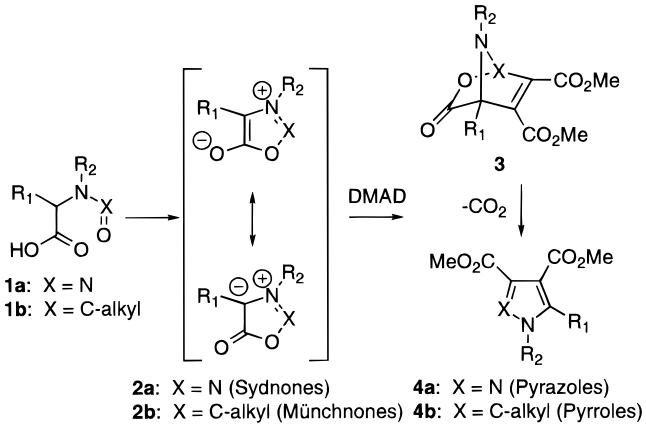
A new method for the synthesis of oxotetrahydroindoles has been achieved employing an intramolecular dipolar cycloaddition approach involving mesoionic species (münchnones) with electron-deficient alkynes. The methodology is quite general and convergent as shown by the synthesis of a variety of tri- and tetrasubstituted oxotetrahydroindoles **18**, **21**, **24**, **27**, **30**, and **34**. LiI-based ester cleavage in the presence of an electrophilic acetylenic ketone was critical for formation of the requisite cycloaddition substrates. The cycloaddition is virtually unaffected by the presence of *gem*-dimethyl groups in the side chain (cf. **38**). The presence of a substituted benzyl or a phenethyl moiety on nitrogen, a polarized acetylene, and an appropriate tether between dipole and dipolarophile are essential for obtaining optimal efficiency.

Introduction

The dehydration of *N*-imidoyl- or *N*-acylamino acids is known to afford mesoionic heterocycles,[1−3] which have been extensively utilized as substrates in 1,3-dipolar cycloadditions (Scheme 1). These mesoionic compounds (**2a,b**) can be readily prepared by cyclodehydration of *N*-nitroso-α-alkyl aminoacids **1a** or *N*-acylamino acids **1b** with reagents such as acetic anhydride. The former (sydnones, **2a**) behave like cyclic azomethine imines and undergo smooth cycloaddition with acetylenes to afford pyrazoles **4a** in high yields. Münchnones are mesoionic oxazolium 5-oxides[2] of type **2b** and show azomethine ylide characteristics. Such münchnones have generated considerable interest in our laboratories. The 1,3-dipolar cycloaddition reaction of münchnones with acetylenic dipolarophiles gives adducts **3**, followed by cycloreversion, eliminating carbon dioxide to furnish pyrrole derivatives **4b** in good yields, thus providing a very general pyrrole synthesis.[1−3] However, the intramolecular variant of the reaction has not been fully exploited.[3b,c] We describe herein our results on the synthesis of oxotetrahydroindoles via intramolecular cycloadditions of these azomethine ylides with tethered alkynes.

Extensive cycloaddition studies of münchnones **2b** with a large number of dipolarophiles have resulted in practical, unique syntheses of various natural and unnatural

Scheme 1



monocyclic and ring-annulated heterocycles.[3c] The development of new approaches for 4-substituted indoles[4,5] is important in view of the variety of biologically important alkaloids and quinones, e.g., **5**−**8**, which derive from this structural subunit (Figure 1).

The use of 4-oxo-4,5,6,7-tetrahydroindoles as intermediates for the syntheses of 4-substituted indoles has been well established.[6] One existing literature method consists of a sequence from cyclohexanedione enamines derived from amino acids based on the work of Franck[7] and represents a promising lead into substituted indoles that has yet to be fully exploited. Recently, Edstrom[8]

† Dedicated to Professor Yoshito Kishito on the occasion of his 60th birthday.

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(4) For a review, see: Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267.

(5) Teleocidins and indolactams: Fujiki, H.; Sugimura, T. *Adv. Cancer Res*. **1987**, *49*, 223. (b) Ergot alkaloids: Ninomiya, I.; Kiguchi, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 38, p 1.

(6) For oxidation to indoles see: (a) Remers, W. A.; Weiss, M. J. *J. Am. Chem. Soc*. **1965**, *87*, 5262. (b) Remers, W. A.; Roth, R. H.; Gibs, G. J.; Weiss, M. J. *J. Org. Chem*. **1971**, *36*, 1232. (c) Matsumoto, M.; Ishida, Y.; Watanabe, N. *Heterocycles* **1985**, *23*,165. (d) Hatanaka, N.; Ozaki, O.; Matsumoto, M. *Tetrahedron Lett*. **1986**, *27*, 3169. (e) Matsumoto, M.; Watanabe, Y. *Heterocycles* **1986**, *24*, 3149. (f) Ishibashi, H.; Tabata, T.; Hanaoka, K.; Iriyama, H.; Akamatsu, S.; Ikeda, M. *Tetrahedron Lett*. **1993**, *34*, 489. (g) For recent approaches to mitomycins see: Wang, Z.; Jimenez, L. S. *J. Am. Chem. Soc*. **1994**, *116*, 4977. Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1994**, *115*, 12305.

(7) Friary, R. J.; Gilligan, J. M.; Szaewski, R. P.; Falci, K. J.; Franck, R. W. *J. Org. Chem*. **1973**, *38*, 3487.

(8) (a) Edstrom, E. D. *Synlett* **1995**, 49. (b) Edstrom, E. D.;Yu, T.; Jones, J. *Tetrahedron Lett*. **1995**, *36*, 7035.

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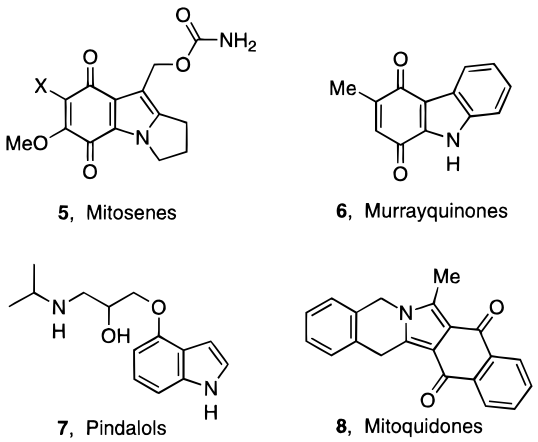
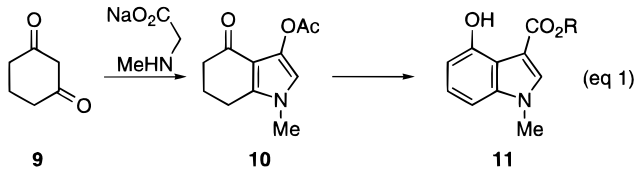
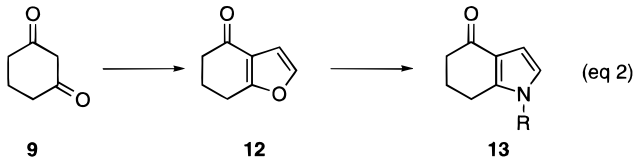


Figure 1.

employed this methodology to synthesize 4-hydroxyindoles **11** and indoloquinones (eq 1).



Other less efficient methods involve the condensation of 1,3-cyclohexanedione with aminoacetaldehyde diethyl acetal[9] or with oxoiminoglyoxal.[10] A more practical method is the transformation of the endocyclic oxygen atom to the nitrogen in a 4-oxo-4,5,6,7-tetrahydrobenzofuran skeleton such as **12**, but this ammonolysis requires furan activation, which limits the generality of this procedure (eq 2).[11]

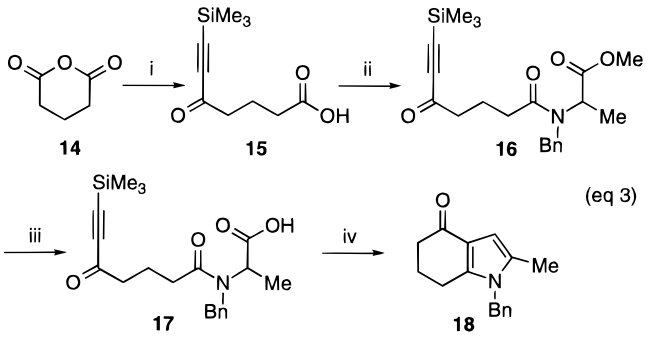


Stetter[12] and Torri[13] reported similar methodologies starting from 1,3-cyclohexanedione (**9**) with limited practical utility. We recently reported[14] a new general approach for the synthesis of oxotetrahydroindoles and detail herein a full account of our results of this intramolecular alkyne cycloaddition approach.

Results and Discussion

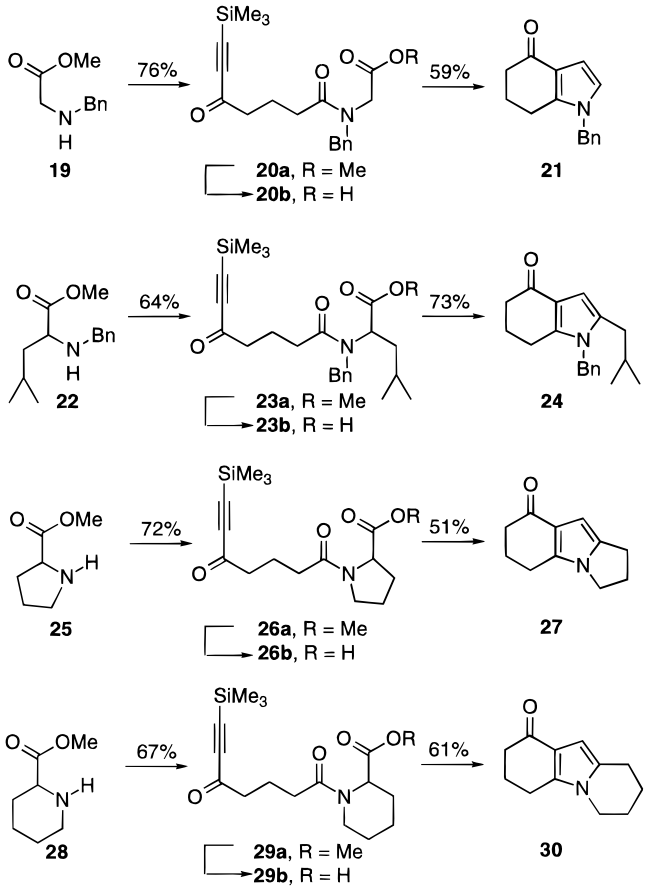
The requisite acetylenic amino acids, which are direct precursors for reactive münchnones, were prepared according to eq 3 (Scheme 2). Thus, a mixture of bis(trimethylsilyl)acetylene and glutaric anhydride (**14**) was treated with anhydrous $AlCl_3$ to afford acid **15** in 98%

Scheme 2



(i) $AlCl_3$, CH_2Cl_2, TMS—≡—TMS 98%
(ii) $BnNHCH(CH_3)CO_2Me$, CDMT, NMM, 83%
(iii) LiI, EtOAc, reflux, 75% (iv) Ac_2O, 70 °C (1 h) to 125 °C (3 h), 68%

Scheme 3



isolated yield.[15] The acetylenic keto acid **15** was then condensed with *N*-benzylalanine methyl ester hydrochloride in the presence of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)[16] to give **16** in 83% isolated yield. The initial attempts to convert ester **16** to the corresponding acid **17** using reagents such as NaOH, LiOH, Me_3SiCl, Me_3SiI, and $(Bu_3Sn)_2O$[17] gave incomplete reaction, extensive polymerization, or conjugate addition products across the triple bond. It was soon realized that the use of base for this transformation was detrimental to the sensitive acetylenic ketone moiety and trimethylsilyl group in **16**. The reaction of ester **16** with anhydrous

(9) Bobbitt, J. M.; Kulkarni, C. l.; Dutta, C. P.; Kofod, H.; NgChiong, K. *J. Org. Chem.* **1978**, *43*, 3541.
(10) Schoen, K. *Jpn. Tokkyo Koho* **1969**, *44*, 9904.
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(12) (a) Stetter, H.; Lauterbach, R. *Ann. Chem.* **1962**, *655*, 20. (b) Stetter, H.; Siehnhold, E. *Chem. Ber.* **1955**, *88*, 271.
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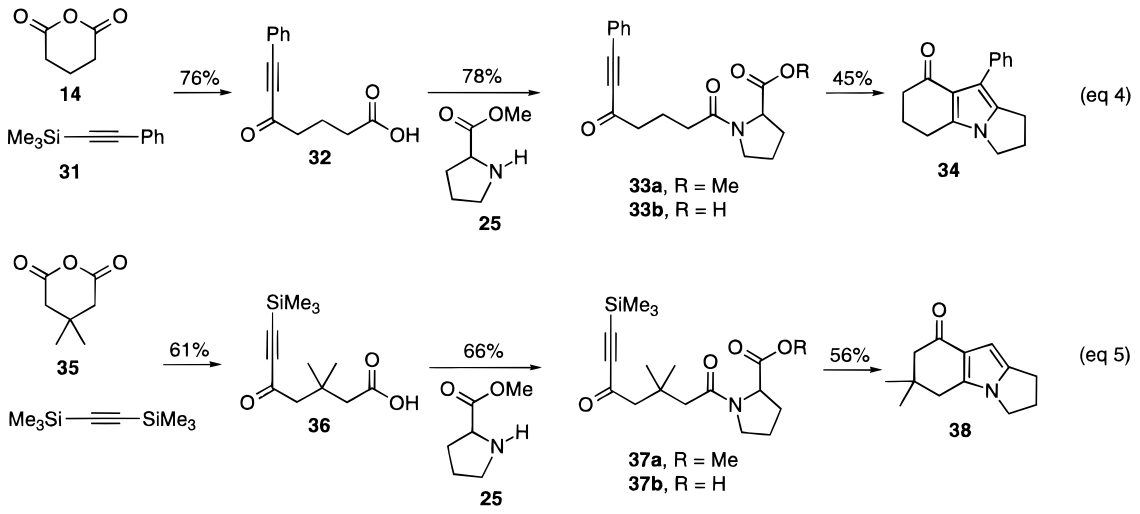
(14) Hutchison, D. R.; Nayyar, N. K.; Martinelli, M. J. *Tetrahedron Lett.* **1996**, *37*, 2887.
(15) Kundu, N. G.; Das, B.; Majumdar, A.; Choudhuri, L. N. *Tetrahedron Lett.* **1987**, *28*, 5543.
(16) Kaminski, Z. J. *Synthesis* **1987**, 917.
(17) For an excellent review see: Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691−3748.

Scheme 4



magnesium bromide in ether gave a comparatively clean but incomplete reaction, which suggested the use of a better nucleophilic reagent. One such reagent, lithium iodide,[18] is known in the literature to cause demethylation of esters in high boiling solvents, but in our hands heating ester **16** with LiI in solvents such as pyridine, DMF, or isobutyl acetate resulted only in decomposition. However, lithium iodide in THF, CH_2Cl_2, or EtOAc at reflux demethylates esters by a chelation-controlled push-pull mechanism.[19] Indeed, heating ester **16** in EtOAc with 3.0 equiv of lithium iodide for 10−18 h gave the cycloaddition precursor **17** in 85−90% crude yield and >90% purity. In solvents such as CH_2Cl_2 or THF, the cleavage was extremely slow. Purification of **17** by column chromatography gave the acid in 75% isolated yield. The other cycloaddition precursors were prepared in a similar manner from the corresponding esters **20a**, **23a**, **26a**, **29a** (Scheme 3), and **33a** (eq 4, Scheme 4) and were used without further purification.

With an effective preparation of precursors in hand, we then turned our attention to the cycloaddition reaction. The cycloaddition precursor **17** was heated in neat Ac_2O at 70−80 °C for 1 h and the temperature then slowly raised and maintained at 125 °C (evolution of CO_2 observed) for 2−3 h. The crude reaction profile showed a single product by NMR and TLC, which was purified by column chromatography to afford 4-oxo-2-methyl-4,5,6,7-tetrahydroindole (**18**) in 68% isolated yield. Alternatively, the reaction could also be carried out in one pot without purification of the intermediate acid, providing **18** in 52% overall isolated yield for the two steps.

It is noteworthy that final product **18** had entirely lost the TMS group at the 3-position. It is likely that silyl cleavage occurs after cyclization, since it was observed that the presence of silicon in substrate **17** facilitates cycloaddition (*vide infra*). At lower reaction temperatures, the reaction was incomplete but the 3-(trimethylsilyl) derivative of **18** was isolable. The above cycloaddition reaction is indeed a very general reaction as evidenced by the synthesis of a structural variety of oxotetrahydroindoles **21**, **24**, **27**, **30** (Scheme 3), and **34** (eq 4, Scheme 4) from the corresponding readily available amino ester substrates including glycine (**19**), leucine (**22**), proline (**25**), and pipecolinic acid (**28**).

This cycloaddition approach can also be employed for the synthesis of tetrasubstituted 4-oxotetrahydroindoles as exemplified by the synthesis of **34** (eq 4, Scheme 4). Thus, lithium phenylacetylide when treated with trimethylsilyl chloride in THF gave the corresponding trimethylsilyl acetylene **31**, which upon stirring with glutaric anhydride (**14**) in the presence of $AlCl_3$ gave acid **32** in 76% isolated yield. This acid was then condensed with proline methyl ester hydrochloride **25** using 2-chloro-4,6-dimethoxy-1,3,5-triazine to give ester **33a**. Cycloaddition precursor **33b** was generated by heating **33a** with LiI in EtOAc, which was then cyclized with Ac_2O to afford oxotetrahydroindole **34** in 45% isolated yield. The lower yield and longer reaction time (4 h relative to 2 h for **27**) further corroborates the supposition that silicon facilitates the cycloaddition reaction.

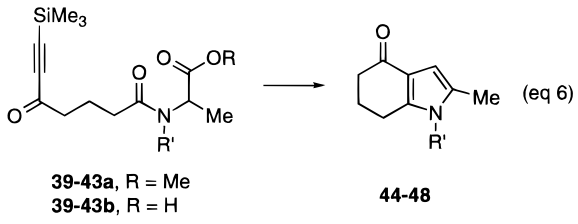
In order to elaborate the scope of this novel intramolecular cycloaddition reaction further, we investigated the effect of a *gem*-dimethyl group in the side chain. The substrate was readily prepared from commercially available 3,3-dimethylglutaric anhydride (**35**) and bis(trimethylsilyl)acetylene as before (eq 5, Scheme 4). Acid **36** was similarly coupled with proline ester **25** to afford **37a**. Heating the corresponding acid **37b**, prepared in the general manner, in Ac_2O furnished the corresponding oxotetrahydroindole **38** (56%) comparable to the 65% isolated yield for **18**.

To evaluate the effect of nitrogen substitution, the required precursors (**39**−**43**) were prepared by the methods described earlier (eq 6). It was found that small groups such as methyl gave a low overall yield (39%) of the oxotetrahydroindole, whereas benzylic substituents with or without electron-donating groups provided modest yields within the series. The 4-nitrophenethyl derivative afforded **46** in 67% isolated yield.

To better gauge the requisite electrophilicity of the acetylenic moiety, we prepared a substrate with an isolated triple bond based upon the analogy with intermolecular cycloaddition reactions of münchnones with phenyl acetylene.[3] We prepared **51** from commercially available acetylenic acid **49** (eq 7).[20] Heating **51** with

(18) (a) Meyer, W. L.; Levinson, A. S. *J. Org. Chem.* **1963**, *28*. 2184. (b) Wade, J. J.; Toso, C. B.; Hegel, R. F. *J. Org. Chem.* **1979**, *11*, 1811. (c) Dean, P. D. G. *J. Chem. Soc.* **1965**, 6655. (d) McMurry, J. E.; Wong, G. B. *Synth. Commun.* **1972**, *6*, 389.

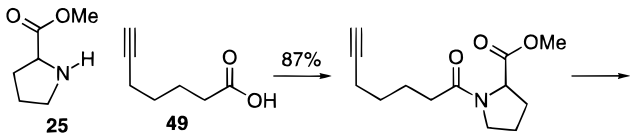
(19) Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505.



39-43a, R = Me
39-43b, R = H

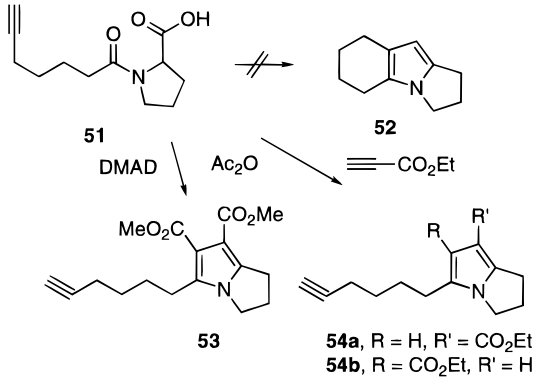
44-48

substrate	R'	product	yield
39	CH_3	44	39%
40	4-CH_3OPhCH_2	45	49%
41	4-$O_2NPhCH_2CH_2$	46	67%
42	3,4-$(MeO)_2PhCH_2$	47	45%
43	1-Naphthylmethyl	48	45%



25 **49** **50**

(eq 7)



51 **52** **53**

54a, R = H, R' = CO_2Et
54b, R = CO_2Et, R' = H

Ac_2O did not produce a trace of the expected cycloaddition product **52**; instead, only extensive decomposition was noted. However, heating **51** with Ac_2O in the presence of dimethyl acetylenedicarboxylate gave a 98% yield of **53**. Reaction of **51** with ethyl propiolate under the same conditions gave a 63% isolated yield of **54** as a 2:1 ratio of regioisomers. Thus, electron-deficient or perhaps just polarized acetylenes appear to undergo more facile cycloaddition than terminal alkylacetylenes.

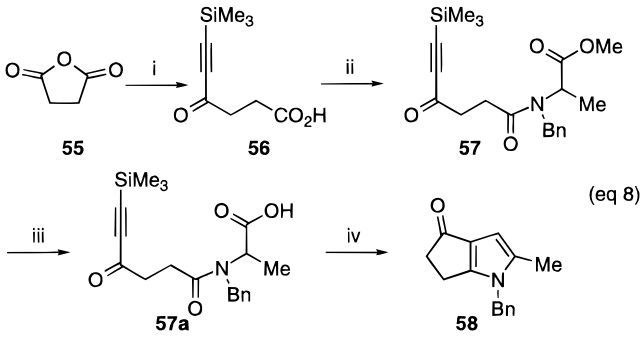
The tether length between dipole and dipolarophile was next evaluated. In parallel fashion, succinic anhydride was opened with bis(trimethylsilyl)acetylene and coupled with the appropriate amino ester to afford **57**. Ester cleavage furnished acid **57a**, which, when stirred in Ac_2O at 70−80 °C for 45 min with subsequent slow heating to 125 °C, furnished an unoptimized 20% isolated yield of **58** (eq 8, Scheme 5). The lower yield may reflect the geometric constraint associated with this type of ring closure. The shorter tether length requires the intervention of a tricyclic intermediate with a highly strained double bond (Figure 2).

Despite moderate overall yields, this new approach is a widely applicable methodology as shown by the following two applications, which provide quick entry into tri- and tetracyclic frameworks of biologically active natural products. The first application is the synthesis of the mitomycin analogue **62** (eq 9). The precursor was prepared from commercially available 3-methylglutaric anhydride (**59**) in the usual manner to give **60**, which was coupled with proline ester **25** to provide **61a**. This ester was cleaved as usual; ensuing münchnone generation was accompanied by rapid cycloaddition to furnish **62** in 62% overall yield from **61a**.

Similarly, **65** (eq 10) was ultimately derived from phenylalanine as follows. Pictet−Spengler adduct **63** was acylated with keto acid **15** in 80% yield. Ester cleavage and cycloaddition afforded the tetracyclic oxoindole **65** in 59% yield. The structural motif found in compound **65** represents the mitoquidone nucleus.

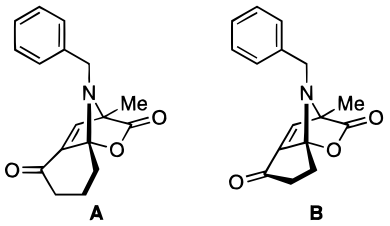
Summary. From these results, it is clear that the intramolecular cycloaddition approach described above is simple, convergent (two new C−C bonds are formed in one step), and widely applicable and can utilize not only natural but also unnatural amino acids including pipecolinic acid. It also provides quick entry into the mitomycin skeleton and other medicinally important polycyclic heterocyclic compounds. We have also shown that acetylenic precursors previously reported to be

Scheme 5



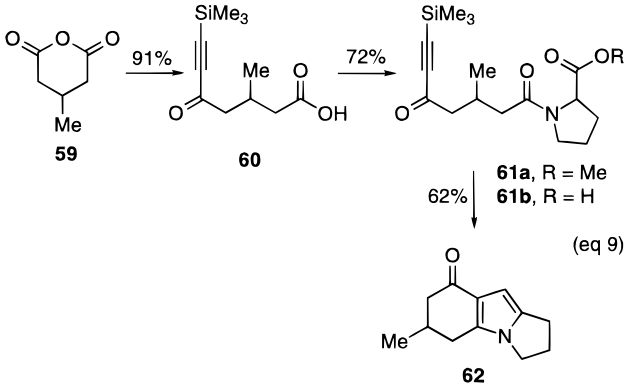
55 **56** **57** **57a** **58**

(i) $AlCl_3$, CH_2Cl_2, TMS—≡—TMS 91%
(ii) $BnNHCH(CH_3)CO_2Me$, CDMT, NMM, 79%
(iii) LiI, EtOAc, reflux, 60% (iv) Ac_2O, 70 °C (1 h) to 125 °C (3 h), 20%



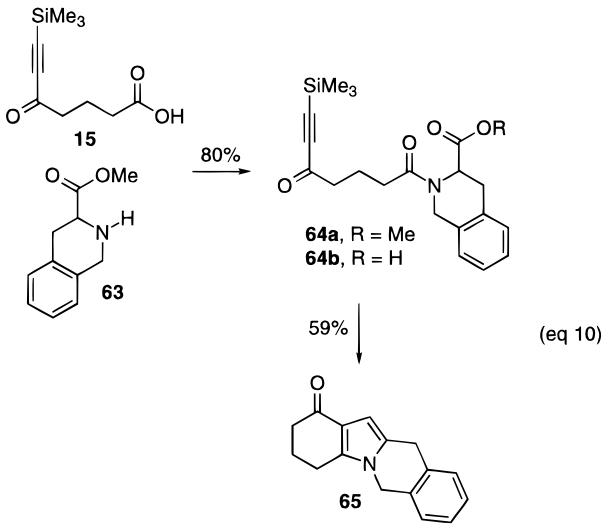
A **B**

Figure 2.



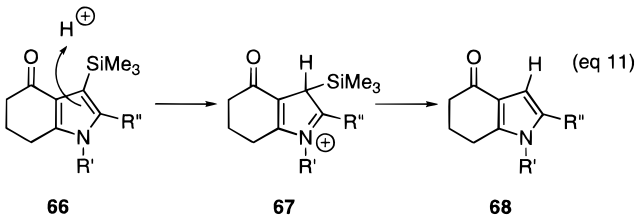
59 **60** **61a**, R = Me **61b**, R = H **62**

(20) 6-Heptynoic acid **46** was purchased from Farchan Laboratories, FL.



inaccessible[21] can readily be prepared from commercially available materials through use of lithium iodide for transformation of base-acid-sensitive methyl esters to substrates for the cycloaddition reaction. The intermediate anhydro-5-hydroxy-1,3-oxazolium hydroxides all possess a substituent in the 4-position necessitated by the use of acetic anhydride as the cyclodehydration agent. This is an apparent limitation of the method.

Although complete loss of silicon was observed, we have concluded based upon reaction times and yields of cycloaddition reactions that the presence of the TMS group facilitates the cycloaddition reaction but is not essential. The literature precedents for the TMS effect in Diels−Alder cycloadditions suggests the involvement of empty silicon d-orbitals.[22] Another interesting aspect is the loss of silicon in the process, presumably through initial protonation of **66** to form **67**, followed by loss of the trimethylsilyl moiety to provide **68** (eq 11).



The ability to incorporate virtually any amino acid into the ketopyrrole nucleus (and hence the indole nucleus) is a powerful synthetic methodology that will have broad applications. Efforts are currently underway to convert these ketopyrrole compounds to 4-hydroxyindoles and to synthesize interesting natural targets.

Experimental Section

Melting points were determined on a hot stage microscope and are uncorrected. All experiments were conducted under an inert atmosphere of nitrogen, unless otherwise noted, and monitored by thin-layer chromatography using Merck F254 silica gel plates. All solvents and reagents were used as obtained. ^{1}H and ^{13}C NMR and HETCOR spectra were obtained on either a GE QE-300 or a Bruker ACP-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Microanalyses were conducted by the Physical Chemistry Department of Lilly Research Laboratories. Glutaric anhydride, 3-methylglutaric anhydride, 3,3-dimethylglutaric anhydride, bis(trimethylsilyl)acetylene, lithium iodide, 2-chloro-4, 6-dimethoxy-1,3,5-triazine, 1-phenyl-2-(trimethylsilyl)acetylene, succinic anhydride, *p*-nitrophenethylamine hydrochloride, and 3,4-dimethoxybenzylamine were purchased from Aldrich and used as received. 1-Napthylmethylamine was purchased from Fluka and used as received. Methyl *N*-benzylglycinate and methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate were prepared according to known literature procedures.[23]

General Modified Procedure for Synthesis of *N*-Benzylglycine Methyl Ester,[24] *N*-Benzyl-L-alanine Methyl Ester,[25] and *N*-benzyl-L-leucine Methyl Ester.[26] A solution of benzaldehyde (1.05 mmol) in CH_2Cl_2 (1.5 mL) was added at once to a stirred solution of methyl amino ester hydrochloride (1.0 mmol) and triethylamine (1.0 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After 24 h at room temperature, the CH_2Cl_2 was evaporated, the residue was dissolved in diethyl ether (5.0 mL) and filtered, and the solids were washed with ether (2 × 5.0 mL). The ethereal layer was dried and concentrated to give an oil. The oil was dissolved in THF (1.0 mL) and transferred to a Parr bottle. PtO_2 (0.1 mmol) was added and the mixture hydrogenated at 50 psi for 18−20 h. The solution was filtered and washed with THF (2 × 5.0 mL), and the title *N*-benzyl derivatives were obtained in 95−98% crude yields and used without further purification.

***N*-(4-Nitrophenethyl)alanine Methyl Ester (General Procedure).** A suspension of 4-nitrophenethylamine hydrochloride (25.0 g, 123.4 mmol) in $CHCl_3$ (100 mL) was treated with NH_3 gas for 20 min. The precipitated NH_4Cl was filtered, and evaporation of filtrate afforded the free base, which was dissolved in THF (200 mL). The solution was treated with methyl (±)-2-bromopropionate (10.3 g, 61.7 mmol), and the resulting mixture was heated to reflux for 24 h. After cooling, the solid 4-nitrophenethylamine hydrobromide was removed by filtration. The filtrate was evaporated to give a light brown oil (14.94 g, 96%) that was used without purification: R_f 0.34 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 1.28 (d, J = 6.9 Hz, 3H, CH_3), 1.85 (bs, 1H, NH, exchangeable with D_2O), 2.91 (m, 4H, 2 × CH_2), 3.36 (q, J = 7.0 Hz, 1H, CH), 3.70 (s, 3H, OCH_3), 7.36 (d, J = 8.6 Hz, 2H, ArH), 8.14 (d, J = 8.7 Hz, 2H, ArH); ^{13}C NMR δ 18.6, 36.0, 48.1, 51.4, 56.1, 123.2, 129.1, 146.1, 147.5, 175.5; mass spectrum m/e 252 (M^+); IR ($CHCl_3$) 2955, 1734, 1606, 1521, 1340 cm^{-1}; HRMS calcd for $C_{12}H_{17}N_2O_4$ 253.1188, found 253.1183.

***N*-(3,4-Dimethoxybenzyl)alanine methyl ester** was prepared from 3,4-dimethoxybenzylamine (26.6 g, 155.8 mmol) and methyl (±)-2-bromopropionate (12.6 g, 75.44 mmol) as a yellow oil (17.15 g, 90%) after chromatography (hexanes/EtOAc, 4:6): R_f 0.41 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 1.32 (t, J = 7.0 Hz, 3H, CH_3), 1.80 (bs, 1H, NH, exchangeable with D_2O), 3.41 (q, J = 7.0 Hz, 1H, NCH), 3.60 (d, J = 12.6 Hz, 1H, CH), 3.74 (d, J = 12.4 Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.86 and 3.89 (two s, 6H, 2 × OCH_3), 6.79−6.89 (m, 3H, ArH); ^{13}C NMR δ 18.9, 51.6, 51.8, 55.6, 55.9, 59.5, 111.1, 111.6, 120.5, 148.3, 149.1, 153.5, 157.0, 175.9; mass spectrum m/e 253 (M^+); IR ($CHCl_3$) 3025, 2955, 1732, 1516, 1159 cm^{-1}; HRMS calcd for $C_{13}H_{20}NO_4$ 254.1392, found 254.1389. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.53; N, 5.53. Found: C, 61.25; H, 7.53; N, 5.89.

***N*-(1-Naphthylmethyl)alanine methyl ester** was prepared from 1-naphthylmethylamine (51.39 g, 326.9 mmol) and methyl (±)-2-bromopropionate (30.0 g, 179.6 mmol) as a yellow oil (36.18 g, 83%) after chromatography (hexanes/EtOAc, 4:6): R_f 0.43 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ 1.35 (d, J = 7.0 Hz, 3H, CH_3), 1.85 (bs, 1H, NH, exchangeable with D_2O), 3.51 (q, J = 7.0 Hz, 1H, NCH), 3.75 (s, 3H, OCH_3), 4.07 (d, J

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= 13.7 Hz, 1H, CH), 4.28 (d, J = 12.7 Hz, 1H, CH), 7.25−7.57 (m, 4H, ArH), 7.77 (d, J = 7.9 Hz, 1H, ArH), 7.85 (d, J = 8.1 Hz, 1H, ArH), 8.18 (d, J = 8.3 Hz, 1H, ArH); ^{13}C NMR δ 18.9, 49.5, 51.5, 56.1, 123.59, 125.1, 125.3, 125.8, 126.0, 127.6, 128.3, 131.6, 133.5, 135.0, 175.9; mass spectrum m/e 243 (M^+); IR ($CHCl_3$) 2954, 1732 cm^{-1}; HRMS calcd for $C_{15}H_{18}NO_2$ 244.1338, found 244.1343. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 7.04; N, 5.75. Found: C, 74.40; H, 7.04; N, 6.08.

General Procedure for Synthesis of 7-Alkyl-5-oxohept-6-ynoic Acids. Powdered anhydrous $AlCl_3$ (1.05 mmol) was added in portions to an ice-cold solution of the anhydride (1.0 mmol) and (trimethylsilyl)acetylene (1.0 mmol) in CH_2Cl_2 (8.5 mL). The mixture was stirred at 0 °C for 2 h and then at room temperature for 18 h. The dark brown viscous mixture was slowly quenched with 1 N HCl at 0 °C. The organic layer was separated, washed with 1 N HCl, water and brine, and dried over $MgSO_4$. On removal of solvent, the dark brown oil was purified by passing through a short pad of silica or recrystallization.

7-(Trimethylsilyl)-5-oxohept-6-ynoic acid (15) was prepared from glutaric anhydride (**14**) and bis(trimethylsilyl)acetylene in 98% yield as a colorless oil after chromatography (hexanes/EtOAc, 1:1): R_f 0.32 (SiO_2, 6:4 hexanes/EtOAc); ^{1}H NMR δ 0.25 (s, 9H, Me_3Si), 1.98 (p, J = 7.2 Hz, 2H, CH_2), 2.42 (t, J = 7.2 Hz, 2H, CH_2), 2.67 (t, J = 7.1 Hz, 2H, CH_2); ^{13}C NMR δ −0.9, 18.4, 32.6, 43.8, 98.2, 101.6, 179.3, 186.5; mass spectrum m/e 213 ($M^+ + 1$); IR (KBr) 2964, 2903, 2157, 1712, 1678 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_3Si$ 213.0947, found 213.0951.

7-Phenyl-5-oxohept-6-ynoic acid (32) was prepared from glutaric anhydride (**14**) and phenyl(trimethylsilyl)acetylene in 76% yield after crystallization (hexanes/CH_2Cl_2, 4:6): mp 110−112 °C: R_f 0.38 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ 2.02−2.11 (m, 2H, CH_2), 2.50 (t, J = 7.2 Hz, 2H, CH_2), 2.78 (t, J = 7.2 Hz, 2H, CH_2), 7.35−7.66 (m, 5H, ArH), 10.10 (bs, 1H, OH); ^{13}C NMR δ 18.7, 32.7, 44.0, 87.5, 91.1, 119.6, 123.0, 126.0, 128.5, 130.7, 133.0, 179.2, 186.7; mass spectrum m/e 216 (M^+); IR (KBr) 2972, 2200, 1704, 1661 cm^{-1}; HRMS calcd for $C_{13}H_{13}O_3$ 217.0865, found 217.0869.

7-(Trimethylsilyl)-5-oxo-3,3-dimethylhept-6-ynoic acid (36) was prepared from 3,3-dimethylglutaric anhydride (**35**) and bis(trimethylsilyl)acetylene in 61% yield as a colorless solid after chromatography (hexanes/EtOAc, 4:6): mp 42−43 °C: R_f 0.64 (SiO_2, 6:4 hexanes/EtOAc); ^{1}H NMR δ 0.18 (s, 9H, Me_3Si), 1.10 (s, 6H, 2 × CH_3), 2.46 (s, 2H, CH_2), 2.70 (s, 2H, CH_2), 11.72 (bs, 1H, OH); ^{13}C NMR δ −0.9, 27.6, 32.9, 44.6, 54.5, 97.2, 103.0, 178.3, 186.3; mass spectrum m/e 241 ($M^+ + 1$); IR ($CHCl_3$) 2964, 2149, 1710, 1676 cm^{-1}; HRMS calcd for $C_{12}H_{21}O_3Si$ 241.1260, found 241.1257.

6-(Trimethylsilyl)-4-oxohex-5-ynoic acid (56) was prepared from succinic anhydride (**55**) and bis(trimethylsilyl)acetylene in 91% yield as a colorless solid after crystallization from hexanes/CH_2Cl_2 (7:3): mp 66−67 °C: R_f 0.31 (SiO_2, 1:1 hexanes/EtOAc); ^{1}H NMR δ 0.24 (s, 9H, Me_3Si), 2.66 (t, J = 6.6 Hz, 2H, CH_2), 2.88 (t, J = 6.6 Hz, 2H, CH_2); ^{13}C NMR δ −0.89, 27.6, 39.4, 99.0, 101.2, 178.2, 184.8; IR (KBr) 2971, 2145, 1709, 1679 cm^{-1}; HRMS calcd for $C_9H_{15}O_3Si$ 199.0791, found 199.0793.

7-(Trimethylsilyl)-5-oxo-3-methylhept-6-ynoic acid (60) was prepared from 3-methylglutaric anhydride (**59**) and bis(trimethylsilyl)acetylene in 91% yield as a yellow oil after chromatography (hexanes/EtOAc, 4:6): R_f 0.37 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ 0.22 (s, 9H, Me_3Si), 1.03 (d, J = 6.3 Hz, 3H, CH_3), 2.22−2.68 (m, 5H, 2 × CH_2 and CH); ^{13}C NMR δ −0.9, 19.5, 26.1, 40.3, 51.2, 98.1, 101.8, 178.7, 186.2; mass spectrum m/e 227 ($M^+ + 1$); IR (film) 2964, 2150, 1711, 1677 cm^{-1}; HRMS calcd for $C_{11}H_{19}O_3Si$ 227.1104, found 227.1099.

General Procedure Synthesis of Methyl *N*-Alkyl-*N*-(7-alkyl-5-oxohept-6-yn-1-oyl)amino Acid Esters. To a stirred solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.05 mmol) and the 7-alkyl-5-oxohept-6-ynoic acids (1.0 mmol) in CH_2Cl_2 (2.5 mL) was added *N*-methylmorpholine (1.0 mmol) dropwise at a rate to keep the temperature at 0−5 °C, and stirring was continued at 0 °C until all 2-chloro-4,6-dimethoxy-1,3,5-triazine was consumed (ca. ∼2 h, monitored by TLC). To this crude suspension, was added a mixture of the appropriate amino acid ester hydrochloride (1.0−1.8 mmol) and *N*-methylmorpholine (1.0−1.8 mmol) in CH_2Cl_2 (1.0 mL) at −5 °C. Stirring was continued at 0 °C for 2 h and then at room temperature for 20−24 h. The solvent was evaporated, the residue was dissolved in EtOAc (10 mL), and the solids were filtered. The organic layer was washed successively with water, 1 N HCl, water, saturated $NaHCO_3$ solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash column chromatography to give the desired amide.

***N*-Benzyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-alanine methyl ester** (**16**) was prepared from methyl *N*-benzylalanine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 83% yield after chromatography (hexanes/EtOAc, 6:4): R_f 0.46 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ (rotamers) 0.21 and 0.22 (s, 9H, Me_3Si), 1.36 (d, J = 7.2 Hz, 3H, CH_3), 1.93−2.06 (m, 2H, CH_2), 2.25−2.47 (m, 2H, CH_2), 2.61−2.73 (m, 2H, CH_2), 3.58 and 3.68 (s, 3H, OCH_3), 4.48−4.80 (m, 3H, NCH_2 and NCH), 7.23−7.36 (m, 5H, ArH); ^{13}C NMR δ (rotamers) −0.6, −1.0, 14.58, 18.3, 18.9, 31.8, 43.9, 49.9, 51.8, 54.0, 97.4, 101.6, 126.0, 127.1, 127.3, 128.0, 128.5, 136.8, 171.39, 171.9, 172.6, 172.8, 186.8; mass spectrum m/e 387 (M^+); IR (film) 2955, 1744, 1675, 1653 cm^{-1}; HRMS calcd for $C_{21}H_{30}NO_4Si$ 388.1944, found 388.1961.

***N*-Benzyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-glycine methyl ester** (**20a**) was prepared from methyl *N*-benzylglycine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 76% yield after chromatography (hexanes/EtOAc, 7:3): R_f 0.5 (SiO_2, 1:1 hexanes/EtOAc); ^{1}H NMR δ (rotamers) 0.26 and 0.27 (two s, 9H, Me_3Si), 2.06 (t, J = 7.0 Hz, 2H, CH_2), 2.37 and 2.53 (t, J = 7.2 Hz, 2H, CH_2), 2.72 (t, J = 7.0 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.96 and 4.08 (s, 2H, CH_2), 4.64 and 4.67 (s, 2H, NCH_2), 7.19−7.39 (m, 5H, ArH); ^{13}C NMR δ (rotamers) −0.9, 18.7, 18.8, 31.3, 44.0, 47.2, 48.4, 49.8, 51.8, 51.9, 97.5, 101.7, 126.4, 127.8, 128.1, 128.4, 128.7, 136.4, 135.7, 169.3, 169.5, 172.3, 172.8, 186.8, 187.0; mass spectrum m/e 373 (M^+); IR ($CHCl_3$) 3019, 2958, 2150, 1749, 1661 cm^{-1}; HRMS calcd for $C_{20}H_{28}NO_4Si$ 374.1788, found 374.1780.

***N*-Benzyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-leucine methyl ester** (**23a**) was prepared from methyl *N*-benzylleucine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 64% yield after chromatography (hexanes/EtOAc): R_f 0.63 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ (rotamers) 0.22 and 0.23 (two s, 9H, Me_3Si), 0.69 (d, J = 6.6 Hz, 3H, CH_3), 0.77 (d, J = 6.3 Hz, 3H, CH_3), 0.88 (d, J = 6.3 Hz, 3H, CH_3), 1.47−2.47 (m, 9H, 4 × CH_2 and CH), 3.5 and 3.6 (s, 3H, OCH_3), 4.44−4.89 (m, 1H, NCH), 7.21−7.36 (m, 5H, ArH); ^{13}C NMR δ (rotamers) −1.0, 18.7, 18.9, 22.0, 22.2, 24.2, 24.9, 31.6, 31.9, 38.0, 38.1, 46.8, 49.7, 51.6, 51.9, 55.8, 57.8, 97.4, 101.6, 126.2, 127.2, 127.6, 127.9, 128.4, 136.7, 171.0, 171.8, 173.0, 173.2, 186.7; mass spectrum m/e 429 (M^+); IR (film) 2958, 1741, 1676, 1654 cm^{-1}; HRMS calcd for $C_{24}H_{36}NO_4Si$ 430.2414, found 430.2420.

Methyl *N*-1-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-pyrrolidine-2-carboxylate (**26a**) was prepared from L-proline methyl ester hydrochloride (**25**) and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 72% yield after chromatography (hexanes/EtOAc): R_f 0.44 (SiO_2, 1:1 hexanes/EtOAc); ^{1}H NMR δ (rotamers) 0.22 (s, 9H, Me_3Si), 1.94−2.39 (m, 8H, 4 × CH_2), 2.70 (t, J = 6.9 Hz, 2H, CH_2), 3.46 (m, 2H, NCH_2), 3.72 and 3.73 (two s, 3H, OCH_3), 4.45−4.49 (m, 1H, NCH); ^{13}C NMR δ (rotamers) −1.0, 18.3, 18.4, 22.2, 24.5, 28.9, 31.8, 32.6, 44.0, 46.2, 46.7, 51.9, 53.1, 58.3, 58.7, 97.5, 101.6, 170.7, 172.3, 172.5, 187.0; mass spectrum m/e 323 (M^+); IR (film) 2958, 2194, 1747, 1676, 1650 cm^{-1}; HRMS calcd for $C_{16}H_{26}NO_4Si$ 324.1631, found 324.1629.

Methyl *N*-1-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]piperidine-2-carboxylate (**29a**) was prepared from methyl pipecolinate hydrochloride (**28**) and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 67% yield after chromatography (hexanes/EtOAc): R_f 0.58 (SiO_2, 1:1 hexanes/EtOAc); ^{1}H NMR δ (rotamers) 1.28−2.71 (m, 12H, 6 × CH_2), 3.14−3.233 (m, 1H, NCH_2), 3.71 and 3.74 (two s, 4H, OCH_3 and NCH_2), 4.54 and 5.36 (two m, 1H, NCH); ^{13}C NMR δ (rotamers) −1.0, 18.7, 20.6,

24.2, 24.9, 26.2, 26.8, 31.2, 31.7, 39.6, 43.0, 44.1, 51.5, 51.8, 52.1, 55.9, 97.4, 101.6, 171.5, 171.6, 171.9, 186.9; mass spectrum *m*/*e* 337 (M^+); IR (film) 2953, 2194, 1742, 1676, 1650 cm^{-1}; HRMS calcd for $C_{17}H_{28}NO_4Si$ 338.1788, found 338.1783.

Methyl *N*-1-(7-phenyl-5-oxohept-6-yn-1-oyl)pyrrolidine-2-carboxylate (**33a**) was prepared from L-proline methyl ester hydrochloride (**25**) and 7-phenyl-5-oxohept-6-ynoic acid (**32**) in 78% yield after chromatography (hexanes/EtOAc, 2:8): R_f 0.45 (SiO_2, 1:1 hexanes:EtOAc); ^1H NMR δ (rotamers) 1.80−2.29 (m, 8H, 4 × CH_2), 2.68 (dt, J = 6.9, 7.0 Hz, 2H, CH_2), 3.31−3.52 (m, 2H, NCH_2), 3.59 and 3.63 (two s, 3H, OCH_3), 4.28−4.60 (m, 1H, NCH), 7.23−7.45 (, 5H, ArH); ^{13}C NMR δ (rotamers) 18.5, 18.7, 22.1, 24.4, 28.8, 31.0, 32.5, 44.1, 46.5, 46.6, 51.7, 52.2, 58.2, 59.0, 87.4, 90.3, 90.4, 119.4, 128.3, 130.4, 132.6, 170.5, 172.3, 172.5, 187.1; mass spectrum *m*/*e* 327 (M^+); IR ($CHCl_3$) 2956, 2202, 1743, 1644, 1438 cm^{-1}; HRMS calcd for $C_{19}H_{22}NO_4$ 328.1549, found 328.1555.

Methyl *N*-1-[7-(trimethylsilyl)-5-oxo-3, 3-dimethylhept-6-yn-1-oyl] pyrrolidine-2-carboxylate (**37a**) was prepared from L-proline methyl ester hydrochloride (**25**) and 7-(trimethylsilyl)-5-oxo-3,3-dimethylhept-6-ynoic acid (**36**) in 66% yield after chromatography (hexanes/EtOAc, 6:4): R_f 0.35 (SiO_2, 7:3 hexanes/EtOAc); ^1H NMR δ (rotamers) 0.21 and 0.22 (two s, 9H, Me_3Si), 1.13 and 1.16 (two s, 6H, 2 × CH_3), 1.90−2.96 (m, 8H, 4 × CH_2), 3.50−3.66 (m, 2H, NCH_2), 3.71 and 3.75 (two s, 3H, OCH_3), 4.42−4.48 (m, 1H, NCH); ^{13}C NMR δ (rotamers) −1.1, 21.8, 24.5, 27.6, 28.7, 28.8, 31.5, 33.2, 33.3, 42.8, 43.1, 45.6, 47.2, 51.6, 51.8, 54.4, 58.1, 59.3, 95.7, 102.9, 169.97, 172.4, 186.52; mass spectrum *m*/*e* 351 (M^+); IR ($CHCl_3$) 3021, 2958, 2148, 1742, 1672, 1638, 1192 cm^{-1}; HRMS calcd for $C_{18}H_{30}NO_4Si$ 352.1944, found 352.1950.

***N*-Methyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-alanine methyl ester** (**39a**) was prepared from methyl *N*-methylalanine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 72% yield after chromatography: R_f 0.43 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) ratio 0.23 (s, 9H, Me_3Si), 1.38 (d, J = 7.3 Hz, 3H, CH_3), 1.46 (d, J = 7.0 Hz, 3H, CH_3), 1.99 (m, 2H, CH_2), 2.37−2.42 (m, 2H, CH_2), 2.70 (t, J = 6.9 Hz, 2H, CH_2), 2.82 and 2.92 (s, 3H, NCH_3), 3.70 and 3.74 (s, 3H, OCH_3), 5.22 (q, J = 7.3 Hz, 1H, NCH); ^{13}C NMR δ (rotamers) −1.2, 14.0, 15.0, 18.4, 18.6, 31.0, 31.1, 31.3, 31.5, 31.6, 43.8, 44.0, 51.6, 52.0, 97.1, 97.2, 101.4, 101.5, 171.0, 171.6, 171.8, 171.9, 186.4, 186.6; mass spectrum *m*/*e* 311 (M^+); IR ($CHCl_3$) 2956, 2150, 1740, 1671, 1644 cm^{-1}; HRMS calcd for $C_{15}H_{26}NO_4Si$ 312.1631, found 312.1631.

***N*-(4-Methoxybenzyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine methyl ester** (**40a**) was prepared from methyl *N*-(4-methoxybenzyl)alanine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 84% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.55 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) 0.22 and 0.23 (two s, 9H, Me_3Si), 1.35 (d, J = 7.1 Hz, CH_3), 1.98−2.0 (m, 2H, CH_2), 2.35−2.50 (m, 2H, CH_2), 2.62−2.67 (m, 2H, CH_2), 3.53 and 3.67 (s, 3H, OCH_3), 3.76 and 3.80 (two s, 3H, OCH_3), 4.45−4.60 (m, 2H, NCH_2), 6.86−7.25 (m, 4H, ArH); ^{13}C NMR δ (rotamers) −1.0, −0.7, 14.4, 15.8, 18.7, 18.9, 31.7, 31.9, 43.9, 44.0, 45.6, 49.5, 49.6, 51.7, 51.9, 54.0, 54.6, 54.9, 97.3, 97.4, 101.6, 113.2, 113.8, 127.3, 127.4, 128.5, 128.6, 130.0, 158.2, 158.7, 171.3, 171.8, 172.4, 172.5, 186.7, 186.8; mass spectrum *m*/*e* 417 (M^+); IR ($CHCl_3$) 3012, 2958, 2150, 1740, 1670, 1646 cm^{-1}; HRMS calcd for $C_{22}H_{32}NO_5Si$ 418.2050, found 418.2047.

***N*-(4-Nitrophenethyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine methyl ester** (**41a**) was prepared from methyl *N*-4-(nitrophenethyl)alanine ester and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 91% yield after column chromatography (hexanes/EtOAc, 1:1): R_f 0.6 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) 0.23 (s, 9H, Me_3Si), 1.45 (d, J = 7.1 Hz, 3H, CH_3), 1.49 (d, J = 7.1 Hz, 3H, CH_3), 1.92−1.99 (m, 2H, CH_2), 2.01−2.42 (m, 2H, CH_2), 2.64−2.74 (m, 2H, CH_2), 2.89−3.00 (m, 2H, CH_2), 3.16−3.58 (m, 2H, NCH_2), 3.72 and 3.73 (two s, 3H, OCH_3), 4.44 and 4.56 (two q, J = 7.1 Hz, 1H, NCH), 7.40 (two d, J = 8.8 and 9.0 Hz, 2H, ArH), 8.18 (two d, J = 8.6 Hz, 2H, ArH); ^{13}C NMR δ (rotamers) −1.0, 14.7, 16.0, 18.7, 18.8, 31.4, 31.9, 34.7, 35.9, 43.8, 44.0, 44.9, 48.2, 52.0, 54.7, 54.8, 97.7, 101.6, 123.4, 123.7, 129.5, 129.6, 145.6, 146.6, 171.4, 171.7, 172.2, 186.9, 187.0; mass spectrum *m*/*e* 446 (M^+); IR (film) 2972, 2194, 1742, 1670, 1648 cm^{-1}; HRMS calcd for $C_{22}H_{31}N_2O_6Si$ 447.1951, found 447.1961.

***N*-(3,4-Dimethoxybenzyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine methyl ester** (**42a**) was prepared from methyl *N*-(3,4-dimethoxybenzyl) alanine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 84% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.42 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) 0.21 and 0.22 (two s, 9H, Me_3Si), 1.38 (d, J = 7.1 Hz, 3H, CH_3), 1.93−2.06 (m, 2H, CH_2), 2.26−2.47 (m, 2H, CH_2), 2.62−2.74 (m, 2H, CH_2), 3.53 and 3.68 (two s, 3H, OCH_3), 3.83, 3.84, 3.86, and 3.87 (four s, 6H, 2 × OCH_3), 4.4−4.65 (m, 3H, NCH_2 and NCH), 6.78−6.82 (m, 3H, ArH); ^{13}C NMR δ (rotamers) 14.4, 15.9, 18.7, 18.9, 31.7, 43.9, 44.0, 49.9, 50.0, 51.8, 52.1, 54.2, 55.6, 55.7, 97.4, 97.5, 101.6, 109.2, 10.4, 110.8, 111.0, 118.2, 119.6, 129.1, 130.6, 147.6, 148.1, 148.5, 149.0, 171.4, 171.8, 172.6, 186.8; mass spectrum *m*/*e* 447 (M^+); IR ($CHCl_3$) 3019, 2149, 1739, 1670, 1647 1516 cm^{-1}; HRMS calcd for $C_{23}H_{34}NO_6Si$ 448.2155, found 448.2148.

***N*-(1-Napthylmethyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine methyl ester** (**43a**) was prepared from methyl *N*-(1-napthylmethylamino)alanine ester hydrochloride and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 95% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.37 (SiO_2, 7:3 hexanes/EtOAc); ^1H NMR δ (rotamers) 1.31 (d, J = 7.2 Hz, 3H, CH_3), 1.88−2.06 (m, 2H, CH_2), 2.17−2.27 (m, 1H, CH_2), 2.34−2.44 (m, 1H, CH_2), 2.53−2.59 (m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 4.77−5.11 (m, 3H, NCH_2 and NCH), 7.40−7.54 (m, 4H, ArH), 7.73−7.77 (m, 2H, ArH), 7.85 (d, J = 7.1 Hz, 1H, ArH); ^{13}C NMR δ (rotamers) −1.0, 14.3, 14.5, 31.4, 32.0, 43.8, 44.0, 47.4, 51.8, 51.9, 53.9, 121.7, 122.9, 123.0, 125.1, 125.7, 126.2, 127.8, 128.7, 129.9, 131.9, 133.3172.0, 172.4, 173.3, 173.9, 186.6, 186.8; mass spectrum *m*/*e* 437 (M^+); IR ($CHCl_3$) 3010, 2143, 1739, 1669, 1650 cm^{-1}; HRMS calcd for $C_{25}H_{32}NO_4Si$ 438.2101, found 438.2095.

Methyl *N*-1-(hept-6-yn-1-oyl)pyrrolidine-2-carboxylate (**50a**) was prepared from L-proline methyl ester hydrochloride (**25**) and hept-6-ynoic acid (**49**) in 87% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.34 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) ^1H NMR δ 1.53−2.43 (m, 13H, 6 × CH_2 and CH), 3.48−3.68 (m, 2H, NCH_2), 3.72 and 3.76 (two s, 3H, OCH_3), 4.05 (m, 1H, NCH); ^{13}C NMR δ (rotamers) 17.6, 21.9, 23.0, 24.2, 24.4, 27.3, 28.6, 32.9, 33.1, 46.1, 46.4, 51.4, 51.6, 57.9, 58.0, 68.0, 83.5, 170.8, 172.2; mass spectrum *m*/*e* 237 (M^+); IR ($CHCl_3$) 3012, 2130, 1743, 1637, 1438 cm^{-1}; HRMS calcd for $C_{13}H_{20}NO_3$ 238.1443, found 238.1445.

***N*-[6-(Trimethylsilyl)-4-oxohex-5-yn-1-oyl]alanine methyl ester** (**57**) was prepared from methyl *N*-benzylalanine ester hydrochloride and 6-(trimethylsilyl)-4-oxohex-5-ynoic acid (**56**) in 79% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.42 (SiO_2, 7:3 hexanes:EtOAc); ^1H NMR δ (rotamers) 1.32 (d, J = 7.2 Hz, 3H, CH_3), 1.39 (d, J = 7.2 Hz, 3H, CH_3), 2.53−2.72 (m, 2H, CH_2), 2.94 (dd, J = 6.3, 6.5 Hz, 2H, CH_2), 3.65 and 3.66 (two s, 3H, OCH_3), 4.50−4.73 (m, 3H, NCH_2 and NCH), 7.24−7.37 (m, 5H, ArH); ^{13}C NMR δ (rotamers) 14.4, 15.7, 26.8, 39.7, 39.9, 46.2, 49.8, 49.9, 51.6, 51.9, 54.0, 54.6, 126.0, 126.4, 126.9, 127.1, 127.8, 128.4, 136.6, 137.8, 171.1, 171.3, 171.5, 171.7, 185.4, 185.8; mass spectrum *m*/*e* 373 (M^+); IR ($CHCl_3$) 3054, 1739, 1674, 1650 cm^{-1}; HRMS calcd for $C_{20}H_{28}NO_4Si$ 374.1788, found 374.1795.

Methyl *N*-1-[7-(Trimethylsilyl)-5-oxo-3-methylhept-6-yn-1-oyl]pyrrolidine-2-carboxylate (**61a**) was prepared from L-proline methyl ester hydrochloride (**25**) and 7-(trimethylsilyl)-5-oxo-3-methylhept-6-ynoic acid (**60**) in 72% yield after chromatography (hexanes/EtOAc, 4:6): R_f 0.45 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ (rotamers) 0.21 (s, 9H, Me_3Si), 1.01 and 1.02 (two d, J = 6.4, 6.5 Hz, 3H, CH_3), 1.90−2.79 (m, 9H, 4 × CH_2, CH), 3.48−3.74 (m, 2H, NCH_2), 3.70 (s, 3H, OCH_3), 4.44−4.48 (m, 1H, CH); ^{13}C NMR δ (rotamers) −1.1, −0.7, 19.4, 19.5, 22.0, 24.5, 25.9, 26.0, 28.7, 31.0, 39.8, 40.1, 40.2, 45.8, 46.7, 51.20, 58.2, 97.1, 101.8, 170.0, 172.2, 172.3, 172.4, 186.4, 186.5; mass spectrum *m*/*e* 337 (M^+); IR (film) 2960, 2149, 1747, 1675, 1649 cm^{-1}; HRMS calcd for $C_{17}H_{28}NO_4Si$ 338.1788, found 338.1789.

Methyl *N*-2-[7-(Trimethylsilyl)-5-oxohept-6-yn-1-oyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**64a**) was

prepared from methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**63**) and 7-(trimethylsilyl)-5-oxohept-6-ynoic acid (**15**) in 80% yield after chromatography (hexanes/EtOAc, 1:1): R_f 0.35 (SiO_2, 7:3 hexanes/EtOAc); ^{1}H NMR δ (rotamers) ratio 0.22 and 0.23 (two s, 9H, Me_3Si), 2.02−2.07 (m, 2H, CH_2), 2.50−2.52 (m, 2H, CH_2), 2.73 (t, J = 6.7 Hz, 2H, CH_2), 3.18−3.40 (m, 2H, NCH_2), 3.61 (s, 3H, CH_3), 4.67 (s, 2H, NCH_2), 5.44 (m, 1H, CH), 7.12−7.25 (m, 4H, ArH); ^{13}C NMR δ (rotamers) −1.1, 18.3, 18.5, 30.3, 31.3, 31.6, 31.9, 43.0, 43.8, 43.9, 45.0, 45.1, 51.0, 51.8, 52.1, 52.3, 54.2, 97.3, 101.5, 101.6, 125.6, 126.1, 126.3, 126.5, 126.6, 126.8, 127.7, 128.0, 128.1, 130.7, 131.6, 131.7, 132.0, 170.4, 170.9, 171.7, 171.8, 186.6; mass spectrum m/e 384 ($M^+ - 1$); IR ($CHCl_3$) 2959, 2162, 1740, 1669 cm^{-1}; HRMS calcd for $C_{21}H_{28}NO_4Si$ 386.1788, found 386.1779.

General Procedure for the Synthesis of *N*-Alkyl-*N*-(7-alkyl-5-oxohept-6-yn-1-oyl)amino Acids. A solution of methyl *N*-alkyl-*N*-(7-alkyl-5-oxohept-6-yn-1-oyl)amino acid esters (1.0 mmol) and lithium iodide (3.5−5.0 mmol) in EtOAc (1.3 mL) was heated at reflux for 10−24 h. The reaction mixture was diluted with water (5.0 mL), acidified with 1 N HCl, and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated, and used without purification (the crude product in most cases had purity >90% (as shown by ^{1}H NMR); hence, no attempt was made at purification, although it could be purified by chromatography without affectintg the overall yield).

***N*-Benzyl-*N*-(trimethylsilyl-5-oxohept-6-yn-1-oyl)alanine** (**17**) was prepared starting from methyl ester **16** in 80% crude yield: ^{1}H NMR δ (rotamers) 0.22 (s, 9H, Me_3Si), 1.39 (d, J = 7.2 Hz, 3H, CH_3), 1.99−2.09 (m, 2H, CH_2), 2.37 (m, 4H, 2 × CH_2), 4.48−4.70 (m, 3H, NCH_2 and NCH), 7.23−7.39 (m, 5H, ArH); ^{13}C NMR δ (rotamers) −0.11, 0.22, 14.4, 16.3, 18.8, 19.1, 31.9, 32.1, 44.1, 44.3, 47.4, 50.5, 54.6, 55.5, 78.9, 79.1, 81.1, 81.2, 126.2, 126.7, 127.0, 127.5, 128.2, 128.8, 136.6, 138.3, 173.5, 173.7, 175.0, 175.7, 186.7, 187.0; IR (film) 3298, 3020, 2097, 1718, 1682, 1646 cm^{-1}. The thermal instability of the acids precluded determination of elemental analysis.

***N*-Benzyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-glycine** (**20b**) was prepared starting from methyl ester **20a** in 80% crude yield: ^{1}H NMR δ (rotamers) 0.22 and 0.23 (s, 9H, Me_3Si), 2.03 9m, 2H, CH_2), 2.51−2.75 (m, 4H, 2 × CH_2), 3.96 and 4.07 (s, 2H, CH_2), 4.62 and 4.65 (s, 2H, NCH_2), 6.25 (bs, 1H, OH), 7.18−7.37 (m, 5H, ArH).

***N*-Benzyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-leucine** (**23b**) was prepared starting from the methyl ester **23a** in 82% crude yield: ^{1}H NMR δ (rotamers) 0.24 (s, 9H, Me_3Si), 0.75 (d, J = 6.2 Hz, 3H, CH_3), 0.86 (d, J = 6.8 Hz, 3H, CH_3), 1.44−1.62 (m, 2H, CH_2), 1.98−2.10 9 (m, 3H, CH_2 and CH), 2.32−2.78 (m, 4H, 2 × CH_2), 4.40−4.72 (m, 2H, NCH_2), 7.18−7.32 (m, 5H, ArH), 8.64 (bs, 1H, OH).

1-[7-(Trimethylsilyl)-5-oxohept-6-yn-1-oyl]pyrrolidine-2-carboxylic acid (**26b**) was prepared starting from the methyl ester **26a** in 86% crude yield: ^{1}H NMR δ (rotamers) 0.23 (s, 9H, Me_3Si), 1.98−2.08 (m, 6H, 3 × CH_2), 2.40 (t, J = 7.4 Hz, 2H, CH_2), 2.72 (t, J = 7.6 Hz, 2H, CH_2), 3.30−3.58 (m, 2H, NCH_2), 4.55 (m, 1H, NCH), 8.18 (bs, 1H, OH).

1-[7-(Trimethylsilyl)-5-oxohept-6-yn-1-oyl)pipecolinic acid (**29b**) was prepared starting from the methyl ester **29a** in 84% crude yield: ^{1}H NMR δ (rotamers) 1.34−2.75 (m, 12H, 6 × CH_2), 3.15 and 3.75 (m, 2H, NCH_2), 5.37 (m, 1H, NCH), 8.36 (bs, 1H, OH).

1-(7-Phenyl-5-oxohept-6-yn-1-oyl)pyrrolidine-2-carboxylic acid (**33b**) was prepared starting from the methyl ester **33a** in 88% crude yield: ^{1}H NMR δ (rotamers) 1.98−2.84 (m, 10H, 5 × CH_2), 3.42−3.63 (m, 2H, NCH_2), 4.58 (m, 1H, NCH), 7.25−7.58 (m, 5H, ArH).

1-[7-(Trimethylsilyl)-5-oxo-3, 3-dimethylhept-6-yn-1-oyl]pyrrolidine-2-carboxylic acid (**37b**) was prepared starting from the methyl ester **37a** in 84% crude yield: ^{1}H NMR δ (rotamers) 0.22 (s, 9H, Me_3Si), 1.15 (s, 6H, $(CH_3)_2$), 1.99−2.54 (m, 6H, 3 × CH_2), 2.74−2.94 (m, 2H, CH_2), 3.49−3.58 (m, 2H, NCH_2), 4.58 (d, J = 6.4 Hz, 1H, NCH).

***N*-Methyl-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]-alanine** (**39b**) was prepared starting from the methyl ester **39a** in 76% crude yield: ^{1}H NMR δ (rotamers) 0.23 (s, 9H, Me_3Si), 1.42 (d, J = 7.3 Hz, 3H, CH_3), 2.01−2.09 (m, 2H, CH_2), 2.39−2.43 (m, 2H, CH_2), 2.69−2.75 (m, 2H, CH_2), 2.95 (s, 3H, NCH_3), 5.13 (q, J = 7.4 Hz, 1H, NCH).

***N*-(4-Methoxybenzyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine** (**40b**) was prepared starting from the methyl ester **40a** in 83% crude yield: ^{1}H NMR δ (rotamers) 0.21 (s, 9H, Me_3Si), 1.36 (d, J = 7.2 Hz, 3H, CH_3), 1.96−2.07 (m, 2H, CH_2), 2.38−2.43 (m, 2H, CH_2), 2.61−2.66 (, 2H, CH_2), 3.79 (s, 4H, OCH_3 and NCH), 4.37−4.54 (m, 2H, NCH_2), 6.87 (d, J = 8.6 Hz, 2H, ArH), 7.15 (d, J = 8.5 Hz, 2H, ArH).

***N*-(4-Nitrophenethyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine** (**41b**) was prepared starting from the methyl ester **41a** in 90% crude yield: ^{1}H NMR δ (rotamers) 1.50 (m, 3H, CH_3), 1.91−2.00 (m, 2H, CH_2), 2.22−2.44 (m, 2H, CH_2), 2.62−2.75 (m, 2H, CH_2), 3.02−3.05 (m, 2H, CH_2), 3.24 and 3.26 (two s, 3H, OCH_3), 3.46−3.73 (m, 2H, NCH_2), 4.27 and 4.52 (m, 1H, NCH), 7.40 (two d, J = 8.5, 10.3 Hz, 2H, ArH), 8.12 and 8.15 (d, J = 8.3 Hz, 2H, ArH), 8.75 (bs, 1H, OH).

***N*-(3,4-Dimethoxybenzyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine** (**42b**) was prepared starting from the methyl ester **42a** in 82% crude yield: ^{1}H NMR δ (rotamers) 1.41 (d, J = 7.1 Hz, 3H, CH_3), 1.99−2.70 (m, 6H, 3 × CH_2), 3.87 (s, 6H, 2 × OCH_3), 4.34−4.64 (m, 3H, NCH_2 and CH), 6.77−6.86 (m, 3H, ArH).

***N*-(1-Naphthylmethyl)-*N*-[7-(trimethylsilyl)-5-oxohept-6-yn-1-oyl]alanine** (**43b**) was prepared starting from the methyl ester (**43a**) in 77% crude yield: ^{1}H NMR δ (rotamers) 0.2 (s, Me_3Si), 1.42 (d, J = 7.2 Hz, 3H, CH_3), 1.98−2.05 (m, 2H, CH_2), 2.31−2.68 (m, 4H, CH_2), 4.72−5.18 (m, 3H, NCH_2 and NCH), 7.26−7.59 (m, 4H, ArH), 7.76−7.83 9m, 2H, ArH), 7.91 (d, J = 7.3 Hz, 1H, ArH).

1-(Hept-6-yn-1-oyl)pyrrolidine-2-carboxylic acid (**51**) was prepared starting from the methyl ester **50** in 87% crude yield: ^{1}H NMR δ (rotamers) 1.50−2.42 (m, 13H, 6 × CH_2 and CH), 3.40−3.62 (m, 2H, 2 × CH_2), 4.33−4.62 (m, 1H, NCH); ^{13}C NMR δ 17.9, 22.3, 23.4, 23.8, 24.4, 27.3, 27.7, 27.9, 28.1, 31.2, 32.8, 33.5, 46.3, 47.359.1, 59.3, 68.3, 68.4, 74.9, 83.8, 84.0, 172.3, 173.4, 173.8, 174.8; mass spectrum m/e 224 ($M^+ + 1$); HRMS calcd for $C_{12}H_{18}NO_3$ 224.1287, found 224.1283.

***N*-Benzyl-*N*-[(trimethylsilyl)-4-oxohex-5-yn-1-oyl]alanine** (**57a**) was prepared starting from the corresponding methyl ester **57** in 60% crude yield: ^{1}H NMR δ (rotamers) 0.22 (s, 9H, Me_3Si), 1.38 (d, J = 7.2 Hz, 3H, CH_3), 2.61−2.86 (m, 2H, CH_2), 2.98−3.00 (m, 2H, CH_2), 4.53−4.75 (m, 3H, NCH_2 and NCH), 7.28−7.41 (m, 5H, ArH)

1-[7-(Trimethylsilyl)-5-oxo-3-methylhept-6-yn-1-oyl]-pyrrolidine-2-carboxylic acid (**61b**) was prepared starting from the methyl ester **61a** in 78% crude yield: ^{1}H NMR δ (rotamers) 0.22 (s, 9H, Me_3Si), 1.06 (d, J = 6.4 Hz, 3H, CH_3), 1.94−2.06 (m, 2H, CH_2), 2.40−2.85 (m, 7H, 3 × CH_2 and CH), 3.42−3.68 (m, 2H, NCH_2), 4.58 (s, 1H, NCH).

1-[7-(Trimethylsilyl)-5-oxohept-6-yn-1-oyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid (**64b**) was prepared starting from the corresponding methyl ester **64a** in 80% crude yield: ^{1}H NMR δ (rotamers) 1.98−2.10 (m, 2H, CH_2), 2.36−2.55 (m, 2H, CH_2), 2.70−2.78 (m, 2H, CH_2), 3.06−3.32 (m, 2H, CH_2), 4.60−4.70 (m, 2H, NCH_2), 5.32−5.38 (m, 1H, NCH), 7.08−7.28 (m, 5H, ArH).

General Procedure Synthesis of Oxotetrahydroindoles. A solution of this acid in Ac_2O (1.3 mL) was heated at 60−80 °C for 45 min and then slowly heated to 120−125 °C and maintained at that temperature for 2−3 h (evolution of CO_2 was observed). The Ac_2O was removed under vacuum to provide a dark brown oil that was purfied by flash column chromatography.

4-Oxo-1-benzyl-2-methyl-4,5,6,7-tetrahydroindole (**18**) was prepared starting from **17** in 68% yield as a yellow solid after chromatography (hexanes/EtOAc): mp 129−131 °C: R_f 0.38 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 2.08−2.14 (m, 2H, CH_2), 2.46 (dd, J = 5.9, 6.9 Hz, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.63 (t, J = 6.2 Hz, 2H, CH_2), 5.03 (s, 2H, NCH_2), 6.34 (d, J = 0.9 Hz, 1H, CH), 6.93 (dd, J = 1.5, 6.7 Hz, 2H, ArH), 7.26−7.33 (m, 3H, ArH); ^{13}C NMR δ 11.9, 21.8, 23.5, 37.5, 46.9, 103.4, 103.5, 119.7, 119.8, 125.4, 127.4, 128.8, 130.5, 136.5, 143.8,

193.9; mass spectrum *m*/*e* 240 ($M^+ + 1$); IR (KBr) 2942, 1642 cm^{-1}; HRMS calcd for $C_{16}H_{18}NO$ 240.1388, found 240.1383.

4-Oxo-1-benzyl-4,5,6,7-tetrahydroindole (**21**) was prepared starting from **20b** in 59% yield an off-white solid after chromatography: mp 76−78 °C (lit.[11] mp 80−81.3 °C): R_f 0.5 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 2.11 (dd, J = 6.2, 6.9 Hz, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.64 (dd, J = 6.1, 6.2 Hz, 2H, CH_2), 5.04 (s, 2H, NCH_2), 6.60 (m, 2H, CH), 6.98 (m, 2H, CH and ArH), 7.26−7.43 9 (m, 3H, ArH); mass spectrum *m*/*e* 225 (M^+); IR (neat) 2944, 1654 cm^{-1}.

4-Oxo-1-benzyl-2-(2-methylpropyl)-4,5,6,7-tetrahydroindole (**24**) was prepared starting from **23b** in 73% yield as a light brown oil after chromatography (hexanes/EtOAc, 1:1): R_f 0.4 (SiO_2, 7:3 hexanes/EtOAc); ^1H NMR δ 0.88 (d, J = 6.5 Hz, 6H, $(CH_3)_2$), 1.75−1.80 (m, 1H, CH), 2.06−2.10 (m, 2H, CH_2), 2.29 (d, J = 7.1 Hz, 2H, CH_2), 2.46 (dd, J = 6.1, 6.7 Hz, 2H, CH_2), 2.58 (t, J = 6.1 Hz, 2H, CH_2), 5.02 (s, 2H, NCH_2), 6.36 (s, 1H, CH), 6.87 (d, J = 7.1 Hz, 2H, ArH), 7.24−7.31 (m, 3H, ArH); ^{13}C NMR δ 21.8, 22.3, 23.5, 27.5, 35.2, 37.5, 46.8, 103.4, 119.8, 125.3, 127.3, 128.7, 134.3, 136.7, 143.7, 194.0; mass spectrum *m*/*e* 281 (M^+); IR ($CHCl_3$) 2958, 1644, 1476 cm^{-1}; HRMS calcd for $C_{19}H_{24}NO$ 282.1858, found 282.1865.

2,3,5,6,7,8-Hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole (**27**) was prepared starting from **26b** in 51% yield as a cream-colored solid after chromatography (hexanes/EtOAc): mp 77−79 °C: R_f 0.33 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 2.08−2.16 (m, 2H, CH_2), 2.43−2.55 (m, 4H, 2 × CH_2), 2.71 (t, J = 6.2 Hz, 2H, CH_2), 2.79−2.84 (m, 2H, CH_2), 3.83 (dd, J = 7.0, 7.1 Hz, 2H, NCH_2), 6.18 (dd, J = 1.1 Hz, 1H, CH); ^{13}C NMR δ 21.6, 23.2, 23.5, 27.4, 37.4, 43.7, 95.6, 95.7, 123.8, 137.4, 138.6, 193.8; mass spectrum *m*/*e* 175 (M^+); IR (KBr) 2920, 1646, 1468 cm^{-1}; HRMS calcd for $C_{11}H_{14}NO$ 176.1075, found 176.1072.

1,2,3,4,6,7,8,9-Octahydro-9-oxopyrido[1,2-*a*]indole (**30**) was prepared starting from **29b** in 61% yield as a colorless solid after chromatography (hexanes/EtOAc, 4:6): mp 100−102 °C: R_f 0.39 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 1.78−1.83 (m, 2H, CH_2), 1.92−1.98 (m, 2H, CH_2), 2.12 (p, J = 6.3 Hz, 2H, CH_2), 2.45 (dd, J = 6.1, 6.7 Hz, 2H, CH_2), 2.67 (t, J = 6.2 Hz, 2H, CH_2), 2.75 (t, J = 6.3 Hz, 2H, CH_2), 3.78 (dd, J = 6.2, 6.2 Hz, 2H, NCH_2), 6.20 (s, 1H, CH); ^{13}C NMR δ 20.3, 20.8, 22.7, 23.0, 23.2, 37.4, 42.7, 100.3, 100.4, 119.1, 130.4, 142.0, 193.6; mass spectrum *m*/*e* 189 (M^+); IR (KBr) 2938, 1651 cm^{-1}; HRMS calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1229.

2,3,5,6,7,8-Hexahydro-8-oxo-9-phenyl-1*H*-pyrrolo[1,2-*a*]indole (**34**) was prepared starting from **33b** in 45% yield as light yellow solid after chromatography (hexanes/EtOAc, 4:6): mp 158−159 °C: R_f 0.4 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ 2.10−2.19 (m, CH_2, 2H), 2.47−2.57 (m, 4H, 2 × CH_2), 2.77 (t, J = 6.2 Hz, 2H, CH_2), 2.95 (dd, J = 7.1, 7.5 Hz, 2H, CH_2), 3.89 (dd, J = 7.0, 7.1 Hz, 2H, NCH_2), 7.16−7.57 (m, 5H, ArH); ^{13}C NMR δ 22.2, 23.3, 23.8, 27.1, 38.8, 43.9, 114.6, 119.9, 125.3, 127.3, 128.5, 134.6, 135.5, 139.3, 193.2; mass spectrum *m*/*e* 251 (M^+); IR (KBr) 2929, 1637, 1604 cm^{-1}; HRMS calcd for $C_{17}H_{18}NO$ 252.1388, found 252.1393.

2,3,5,6,7,8-Hexahydro-6,6-dimethyl-8-oxo-1*H*-pyrrolo-[1,2-*a*]indole (**38**) was prepared starting from **37b** in 56% yield as a colorless solid after chromatography (hexanes/EtOAc,4:6): mp 125−126 °C: R_f 0.5 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ 0.92 (s, 6H, 2 × CH_3), 2.12 (s, 2H, CH_2), 2.36 (m, 2H, CH_2), 2.44 (s, 2H, CH_2), 2.64 (dd, J = 7.1, 7.3 Hz, 2H, CH_2), 3.68 (dd, J = 6.9, 7.1 Hz, 2H, NCH_2), 5.96 (s, 1H, CH); ^{13}C NMR δ 23.0, 27.2, 28.2, 35.0, 35.5, 43.5, 51.595.2, 95.3, 122.4, 137.1, 137.4, 192.8; mass spectrum *m*/*e* 203 (M^+); IR (KBr) 2958, 1638 cm^{-1}; HRMS calcd for $C_{13}H_{18}NO$ 204.1388, found 204.1392.

4-Oxo-1-methyl-2-methyl-4,5,6,7-tetrahydroindole (**44**) was prepared starting from **39b** in 39% yield as a light brown solid after chromatography (hexanes/EtOAc, 3:7): mp 80−82 °C: R_f 0.5 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 2.11−2.18 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.45 (dd, J = 6.2, 6.6 Hz, 2H, CH_2), 2.71 (t, J = 6.2 Hz, CH_2), 3.42 (s, 3H, NCH_3), 6.26 (s, 1H, CH); ^{13}C NMR δ 11.7, 21.6, 23.3, 30.1, 37.3, 102.4, 102.5, 118.9, 130.3, 143.5, 193.5; mass spectrum *m*/*e* 163 (M^+); IR (KBr) 2940, 1641 cm^{-1}; HRMS calcd for $C_{10}H_{14}NO$ 164.1075, found 164.1077.

4-Oxo-1-(4-methoxybenzyl)-2-methyl-4,5,6,7-tetrahydroindole (**45**) was prepared starting from **40b** in 49% yield as a colorless solid after chromatography: mp 96−98 °C: R_f 0.46 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ 2.07−2.13 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.45 (t, J = 6.9 Hz, 2H, CH_2), 2.63 (t, J = 6.2 Hz, CH_2), 3.77 (s, 3H, OCH_3), 4.95 (s, 2H, NCH_2), 6.23 (s, 1H, CH), 6.84 (s, 4H, ArH); ^{13}C NMR δ 11.8, 21.8, 23.5, 37.4, 46.4, 55.0, 103.2, 103.3, 114.0, 119.6, 126.7, 128.3, 130.4, 143.7, 158.7, 193.8; mass spectrum *m*/*e* 269 (M^+); IR (KBr) 2990, 1649, 1609, 1512 cm^{-1}; HRMS calcd for $C_{17}H_{20}NO_2$ 270.1494, found 270.1500.

4-Oxo-1-(4-nitrophenethyl)-2-methyl-4,5,6,7-tetrahydroindole (**46**) was prepared starting from **41b** in 67% yield as a yellow solid after chromatography (hexanes/EtOAc, 2:8): mp 137−139 °C: R_f 0.36 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 1.95 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.31−2.39 (m, 4H, 2 × CH_2), 3.04 (t, J = 6.8 Hz, 2H, CH_2), 4.03 (t, J = 6.8 Hz, 2H, NCH_2), 6.28 (s, 1H, CH), 7.11 (d, J = 9.5 Hz, 2H, ArH), 8.12 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR δ 11.7, 21.6, 23.3, 36.3, 37.3, 44.3, 103.5, 103.6, 119.3, 123.4, 129.6, 129.7, 143.1, 145.1, 146.5, 193.4; mass spectrum *m*/*e* 299 ($M^+ + 1$); IR (KBr) 2947, 1635, 1597, 1513, 1345 cm^{-1}; HRMS calcd for $C_{17}H_{19}N_2O_3$ 299.1396, found 299.1389.

4-Oxo-1-(3,4-dimethoxybenzyl)-2-methyl-4,5,6,7-tetrahydroindole (**47**) was prepared starting from **42b** in 45% yield as a yellow solid after chromatography (hexanes:EtOAc, 2:8): mp 107−109 °C: R_f 0.46 (SiO_2, 2:8 hexanes/EtOAc); ^1H NMR δ 2.09 (dd, J = 6.0, 6.5 Hz, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.45 (dd, J = 6.1, 6.7 Hz, 2H, CH_2), 2.63 (t, J = 6.1 Hz, 2H, CH_2), 3.79 and 3.84 (two s, 6H, 2 × OCH_3), 4.96 (s, 2H, CH_2Ph), 6.32 (s, 1H, CH), 6.38 (d, J = 8.1 Hz, 1H, ArH), 6.44 (s, 1H, ArH), 6.78 (d, J = 8.2 Hz, 1H, ArH); ^{13}C NMR δ 11.2, 21.2, 23.0, 36.9, 45.9, 55.0, 55.1, 102.6, 102.7, 108.2, 108.3, 110.7, 116.9, 118.9, 128.5, 129.9, 143.2, 147.5, 148.5, 193.0; mass spectrum *m*/*e* 299 ($M^+ + 1$); IR (KBr) 2938, 1647 cm^{-1}; HRMS calcd for $C_{18}H_{22}NO_3$ 300.1600, found 300.1604.

4-Oxo-1-(1-naphthylmethyl)-2-methyl-4,5,6,7-tetrahydroindole (**48**) was prepared starting from **43b** in 45% yield after chromatography (hexanes:EtOAc, 3:7): mp 158−160 °C: R_f 0.32 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ 2.05−2.11 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.48 (dist t, J = 5.7, 7.0 Hz, 2H, CH_2), 2.60 (dist t, J = 6.1 Hz, 2H, CH_2), 5.47 (s, 2H, NCH_2), 6.41 (d, J = 10.8 Hz, 1H, ArH), 6.43 (s, 1H, CH), 7.35 (dd, J = 6.4, 9.0 Hz, 1H, ArH), 7.55−7.65 (m, 2H, ArH), 7.78 (d, J = 8.2 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 7.98 (d, J = 8.1 Hz, 1H, ArH); ^{13}C NMR δ 11.6, 21.5, 23.5, 37.5, 44.7, 103.5, 119.8, 121.7, 125.5, 125.6, 127.9, 128.8, 129.7, 130.8, 131.8, 133.2, 144.2, 194.1; mass spectrum *m*/*e* 289 (M^+); IR (KBr) 2939, 1648 cm^{-1}; HRMS calcd for $C_{20}H_{20}NO$ 290.1545, found 290.1549.

Dimethyl 2,3-dihydro-5-(5-hexynyl)-1*H*-pyrrozoline-6,7-dicarboxylate (**53**) The crude acid **51** (1 mmol) was dissolved in Ac_2O (1.3 mL) and then heated at 60−80 °C for 30 min, dimethyl acetylenenedicarboxylate (1.6 mmol) was added, and the mixture was heated under reflux (120−125 °C bath temperature) for 6−8 h. The mixture was concentrated in vacuo, and the brown syrup was purified by column chromatography (hexanes:EtOAc, 6:4) to give **53** in 98% yield: R_f 0.53 (SiO_2, 1:1 hexanes/EtOAc); ^1H NMR δ 1.53−1.73 (m, 4H, 2 × CH_2), 1.93 (t, J = 2.6 Hz, 1H, CH), 2.21 (dt, J = 6.7, 6.9 Hz, 2H, CH_2), 2.45−2.55 (m, J = 7.1, 7.5 Hz, 2H, CH_2), 2.75 (dd, J = 7.2, 7.7 Hz, 2H, CH_2), 3.03 (dd, J = 7.3, 7.6 Hz, 2H, CH_2), 3.77 and 3.82 (two s, 6H, 2 × OCH_3), 3.90 (dd, J = 7.1, 7.2 Hz, 2H, NCH_2); ^{13}C NMR δ 18.3, 25.5, 25.9, 26.7, 28.0, 28.6, 45.7, 51.3, 51.5, 68.9, 84.3, 106.5, 115.9, 134.4, 143.4, 164.9, 165.9; mass spectrum *m*/*e* 303 (M^+); IR ($CHCl_3$) 3307, 3021, 2950, 2117, 1709 cm^{-1}; HRMS calcd for $C_{17}H_{22}NO_4$ 304.1549, found 304.1554.

Ethyl 2,3-dihydro-5-(5-hexynyl)-1*H*-pyrazolinecarboxylate (**54**) was prepared starting from the acid **51** (1.0 mmol) and ethyl propiolate (1.6 mmol) to give two regioisomers in 63% yield after chromatography (hexanes:EtOAc, 6:4): **major regioisomer** in 47% yield: R_f 0.52 (SiO_2, 85:15 hexanes/EtOAc); ^1H NMR δ 1.31 (t, J = 7.1 Hz, 3H, CH_3), 1.56−1.79 (m 4H, 2 × CH_2), 1.95 (t, J = 2.5 Hz, 1H, CH), 2.22 (m, 2H, CH_2), 2.51 (dd, J = 6.7, 6.9 Hz, 4H, 2 × CH_2), 3.05 (t, J = 7.5

Hz, 2H, CH_2), 3.85 (t, J = 7.1 Hz, 2H, NCH_2), 4.23 (q, J = 7.1Hz, 2H, OCH_2), 6.29 (s, 1H, CH); ^{13}C NMR δ 14.2, 17.7, 25.3, 25.5, 26.5, 27.3, 27.4, 44.7, 58.7, 68.2, 83.7, 105.8, 109, 109.1, 128.0, 142.2, 164.9; mass spectrum m/e 259 (M^+); IR ($CHCl_3$) 3307, 3012, 2942, 1686 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1656; **minor regioisomer** in 16% yield; R_f 0.38 (SiO_2, 85:15 hexanes/EtOAc); ^{1}H NMR δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 1.55−1.78 (m, 4H, 2 × CH_2), 1.93 (dd, J = 2.6 Hz, 1H, CH), 2.21 (ddd, J = 6.6, 6.8, 7.0, 7.3 Hz, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.80 (dd, J = 6.9, 7.5 Hz, 2H, CH_2), 2.89 (dd, J = 7.1, 7.7 Hz, 2H, CH_2), 3.85 (t, J = 7.0 Hz, 2H, NCH_2), 4.21 (q, J = 7.1 Hz, 2H, OCH_2), 6.18 (s, 1H, CH); ^{13}C NMR δ 14.2, 17.8, 23.5, 25.4, 27.1, 27.7, 28.2, 44.2, 58.6, 68.1, 83.9, 100.2, 100.3, 114.3, 134.24, 134.3, 165.2; mass spectrum m/e 259 (M^+); IR ($CHCl_3$) 3307, 3013, 1687, 1521 cm^{-1}; HRMS calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1646.

4-Oxo-1-benzyl-2-methyl-5,6-dihydropyrrolizine (**58**) was prepared starting from **57a** in 20% yield after chromatography (hexanes:EtOAc, 2:8): mp 142−144 °C: R_f 0.43 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 2.16 (s, 3H, CH_3), 2.75 (dd, J = 4.1, 5.3 Hz, 2H, CH_2), 2.85 (dd, J = 4.3, 5.3 Hz, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.11 (s, 1H, CH), 7.01 (d, J = 7.1 Hz, 2H, ArH), 7.26−7.37 (m, 3H, ArH); ^{13}C NMR δ 12.3, 20.2, 40.4, 47.7, 100.3, 100.4, 125.3, 125.9, 127.4, 128.6, 136.0, 137.0, 160.0, 196.0; mass spectrum m/e 225 (M^+); IR (KBr) 2918, 1668 cm^{-1}; HRMS calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1237.

2,3,5,6,7,8-Hexahydro-6-methyl-8-oxo-1*H*-pyrrolo[1,2-*a*]indole (**62**) was prepared starting from **61b** in 62% yield from **61a** as a yellow solid after chromatography (hexanes/EtOAc, 4:6): mp 99−101 °C: R_f 0.44 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 1.14 (d, J = 5.9 Hz, 3H, CH_3), 2.15−2.55 (m, 6H, 3 × CH_2), 2.75−2.83 (m, 3H, $COCH_3$ and CH), 3.82 (dt, J = 6.8, 7.1 Hz, 2H, NCH_2), 6.17 (s, 1H, CH); ^{13}C NMR δ 21.1, 23.3, 27.5, 30.0, 31.5, 43.7, 46.0, 95.7, 123.6, 137.7, 138.1, 193.5; mass spectrum m/e 189 (M^+); IR (KBr) 2941, 2864, 1641 cm^{-1}; HRMS calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1228.

1,2,3,4,5,10-Hexahydroindolo[1,2-*b*]isoquinoline (**65**) was prepared starting from **64b** in 59% yield after column chromatography (hexanes/EtOAc, 2:8): mp 141−143 °C: R_f 0.43 (SiO_2, 2:8 hexanes/EtOAc); ^{1}H NMR δ 2.16−2.22 (m, 2H, CH_2), 2.49 (dd, J = 5.7, 6.6 Hz, 2H, CH_2), 2.83 (t, J = 6.0 Hz, 2H, CH_2), 4.01 (s, 2H, CH_2), 4.94 (s, 2H, NCH_2), 6.39 (s, 1H, CH), 7.25−7.29 (m, 4H, ArH) ; ^{13}C NMR δ 20.9, 23.1, 27.7, 37.3, 44.9, 119.9, 125.8, 125.9, 127.1, 127.6, 128.4, 130.6, 132.4, 141.2, 193.5 ; mass spectrum m/e 237 (M^+); IR (KBr) 2937, 1639 cm^{-1}; HRMS calcd for $C_{16}H_{16}NO$ 238.1232, found 238.1226.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra (94 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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