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Paper

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Synthetic studies towards *N*-substituted 3-vinyl-4-piperidineacetic acid derivatives

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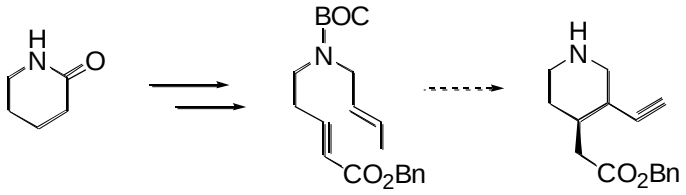
Abstract

The synthesis and full characterization of two new (*E*)-2-butenyl)-5-amino-2-pentenoates, (*Z*)-4-[*N*-(3-buten-1-yl)benzamido]-2-buten-1-ol, and (*Z*)-1-chloro-4-[*N*-(3-buten-l-yl)benzamido]-2-butene are reported. These were designed as substrates for a projected thermal ene cyclization leading to the *N*-substituted 3-vinyl-4-piperidineacetic acid scaffold. Although conditions for this ene-cyclization have not yet been uncovered, the ease of preparation of these ene-cyclization substrates gives promise for their future use.



Keywords: 2-Piperidone, 3-vinyl-4-piperidineacetic acid, 1,7-dienes, ene-cyclization

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Introduction

The intramolecular thermal ene reaction of 1,6-dienes in which the "enophile" is attached to an olefinic terminus ("ene") has been used extensively in the preparation of vinylcyclopentane derivatives, including natural products, in a regio- and stereoselective manner.[1-3] Although the formation of six-membered ring compounds by the analogous cyclization of 1,7-dienes (**1** to **2**) is less stereoselective and proceeds in lower yield,[1-3] good yields of cyclic products have been obtained from 1,7-dienes containing carbonyl-activated enophile or ene components.[4-7]

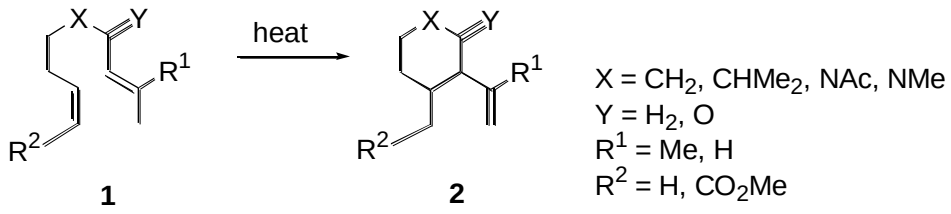

Figure 1. Formation of six-membered rings from 1,7-dienes.

Given the aforementioned precedent, we imagined that the thermal intramolecular ene cyclization of the carbonyl-activated indole diene **3** would be a viable synthetic route to highly substituted 2-(2-piperidinyl)-indoles **4**. These latter intermediates are of interest in a Friedel–Crafts-type cyclization approach to the *Corynanthe* and sarpagine alkaloid ring systems. Thus, in the cyclization step we envisioned formation of the piperidine C-4, C-5 bond with concomitant generation of the C-5 vinyl substituent. Assuming kinetic stereoselection, we presumed that the bulky *N*-protected 2-indolyl substituent would occupy a pseudo-equatorial position in the developing chair transition states thus providing the desired *cis*-diaxial disposition of C-2–H and C-4–H present in these alkaloids. Moreover, even though four diastereomeric piperidines are theoretically possible, only the two alternative chair-chair transition states giving rise to *cis* and *trans* esters **4a** and **4b**, might be expected to predominate. Also, a pseudoequatorial orientation of the *E*-enophile might favor formation of product **4b**.

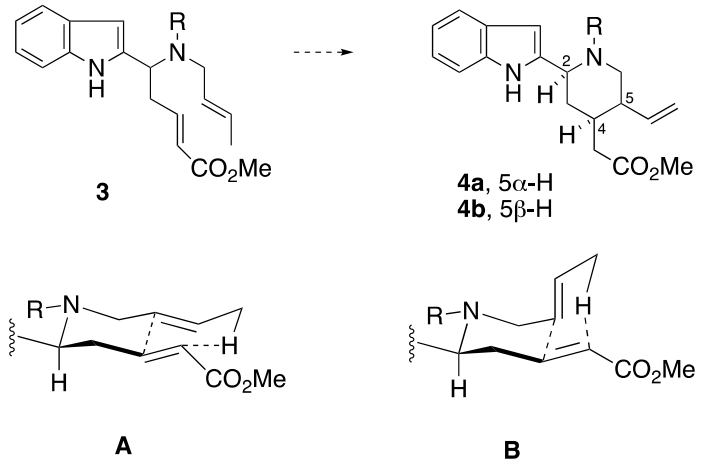

Figure 2. Ene cyclization of diene **3** forming 2-(2-indolyl)piperidines **4a,b.**

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Results and Discussion

Since the ene cyclization of activated 1,6- and 1,7-dienes that lack a methyl substituent at the terminus of the ene unit (e.g., **3**) can be capricious,[8-10] we examined the cyclization of a model 1,7-dienyl system first. Model diene **5** was particularly intriguing since deprotection of the product(s) would give meroquinene (**6a**, *cis*-3-ethenyl-4-piperidineacetic acid), a key intermediate in several total syntheses[11,12] of *Cinchona* alkaloids, and/or the unnatural *trans*-diastereomer **6b**, which was used to forge the D and E rings of the heteroyohimbe alkaloid ajmalicine.[13]

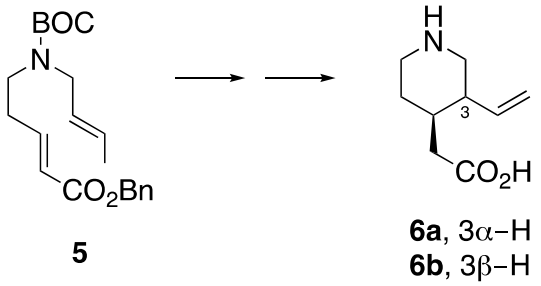

Figure 3. Proposed ene cyclization of diene **5** forming meroquinene (**6a**) and/or 3-*epi*-meroquinene (**6b**).

The synthesis of diene **5** was accomplished in five steps from 2-piperidone (**7**) (Scheme 1). Aqueous barium hydroxide hydrolysis[14] of **7** and liberation of the amino acid from its barium salt with carbon dioxide afforded 5-aminopentanoic acid (**8**) in 95% yield. Treatment of **8** in a 1,4-dioxane-water (1:1) mixture containing 2.5 equivalents of triethylamine with BOC-ON ([2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile][15] provided the crystalline *t*-BOC amino acid **9** in 75% yield. Esterification of acid **9** with benzyl bromide and triethylamine in refluxing chloroform[16] provided the benzyl ester **10** in 62% yield. Alkylation of **10** with *trans*-crotyl chloride[17] and sodium hydride in HMPA (0 °C to r.t., 8 h) furnished the monoolefin **11** but in only 25% yield. Since benzyl alcohol was also isolated from the reaction mixture (23% yield), the low yield of **11** can be attributed to the initially generated anion undergoing an intramolecular condensation to give the UV transparent imide **12** (not isolated). Deprotonation of ester **11** in THF at –78 °C with one equivalent of LDA followed by reaction of the enolate with phenylselenenyl chloride provided the selenide intermediate which was converted into the α,β-unsaturated ester **5** (40% yield) via selenoxide formation/elimination with sodium periodate in methanol/water at room temperature.[18] The *trans* (*E*)-stereochemistry of the newly formed double bond was readily apparent from inspection of the 300 MHz ^{1}H NMR spectrum of **5** in $CDCl_3$. The C-3 proton appears as a doublet of triplets centered at δ 6.96 which overlap to form a 1:2:2:2:1 pentet; the C-3 proton in **5** is *trans*-coupled to the C-2 proton (*J* 16 Hz) and is also split by the "geminal" C-4 methylene protons (*J* 7 Hz). The other vinyl proton of this ABX spin system, the C-2 proton, appeared as a sharp doublet (*J* 16 Hz) centered at δ 5.88. These coupling constants and chemical shifts are characteristic of an α,β-unsaturated ester with *trans*-geometry;[19] the calculated chemical shifts for the C-2 and C-3 protons are δ 5.86 (δ 5.88 observed) and δ 5.87 (δ 6.96 observed), respectively.[19,20]

We examined both the thermal ene reaction[3] as well as Lewis acid-induced cyclization[4-7,10] of the diene ester **5**. However, no reaction was observed in refluxing toluene (110 °C), and heating a 2% solution of **5** in *o*-xylene (145 °C) led to its slow decomposition as evidenced by the formation of benzyl alcohol by TLC. When neat **5** was heated under argon at 205 °C for several hours, complete decomposition was observed. Following Oppolzer's work[10] on the Lewis acid-promoted ene cyclization of 1,6-diene esters, we treated **5** with two

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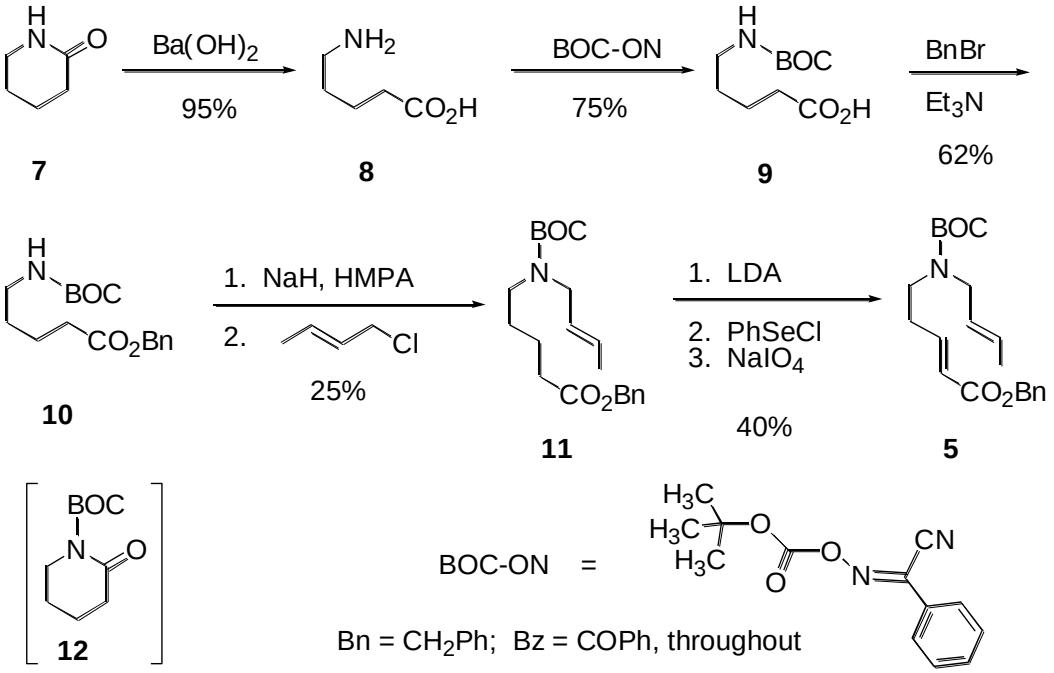
equivalents of diethylaluminum chloride in dry dichloromethane at –78 °C. Unfortunately, the anticipated ene-cyclization of **5** did not occur. When three quivalents of Et_2AlCl were employed (–78 °C, 3 h), cleavage of the benzyl ester group resulted.



Scheme 1. Preparation of the diene **5.**

We turned our attention to the synthesis of diene **13** by a route similar to that used in the preparation of **5**, reasoning that the methyl ester and *N*-benzoyl protective groups would be more stable to the projected cyclization conditions and, in the event of the successful ene cyclization, would provide known diastereomeric piperidines **14a** and **14b**[21] (Scheme 2). To circumvent the apparent intramolecular condensation reaction observed in the alkylation of **10**, we examined the alkylation of the dianion of acid amide **15**. *N*-Benzoyl 5-aminopentanoic acid (**15**) was commercially available and also could be conveniently prepared from **8** with benzoyl chloride in 1N aqueous sodium hydroxide at 0 °C (41%). Satisfyingly, treatment of a mixture of amino acid **15** and *trans*-crotyl chloride in dry DMF at –5 °C with excess sodium hydride furnished the desired amide **16** in 65% yield (~100% based on recovered starting material). Diazomethane methylation of **16** in ether at 0 °C gave the methyl ester **17** in 94% analytically pure yield. Unlike the colorless solution that was obtained by deprotonation of **11** with LDA, similar treatment of ester **17** with LDA at low temperature produced a dark purple solution which decolorized on quenching with phenyl-selenenyl chloride. Sodium periodate treatment of the crude reaction mixture led to a mixture of several very polar products, which were not identified. The known susceptibility of tertiary benzamides to nucleophilic attack[22] suggests that intramolecular condensation of the generated anion on the amide moiety had taken place. We anticipated that this difficulty could be circumvented by *N*-alkylation of the *trans*-α,β-unsaturated ester **18**. We would not have expected intramolecular attack on the ester carbonyl as this requires placing a *trans*-double bond in a six-membered ring transition state.

Although **18** has been prepared in several steps by two different routes from phthalimide,[23] we envisioned that it would be possible to introduce the double bond in one step from the dianion of ester **19** via successive selenation of the enolate, oxidation and selenoxide elimination. As anticipated, treatment of ester **19**, which

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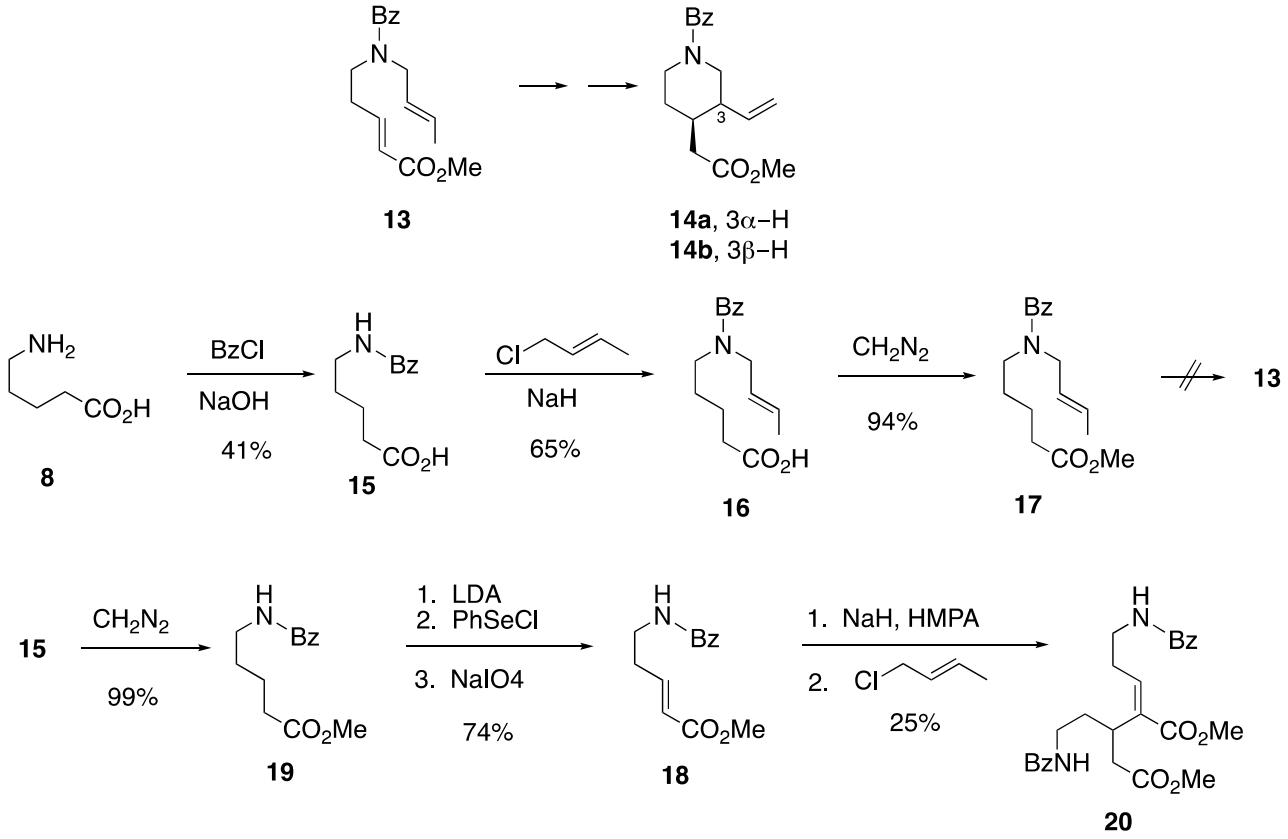
was readily prepared from **15** with diazomethane in ether-methanol (99% yield), with two equivalents of LDA at –78 °C in THF followed by the oxidative selenation protocol provided the desired enoate **18** in 74% yield. Because ester **18** was not easily separable from starting material **19** by chromatographic means, we found it convenient to isolate the intermediate α-phenylselenenyl derivative prior to oxidation and selenoxide elimination. In the 300 MHz ^{1}H NMR spectrum of **18** in $CDCl_3$, the C-1 vinyl protons appear as a doublet of narrow multiplets centered at δ 5.89, *trans*-coupled to the C-3 proton (*J* 16.5 Hz), and the C-2 vinyl proton appeared as a doublet of triplets centered at δ 6.93 split by C-3H and by the geminal methylene protons (J_{gem} 6.7 Hz). Unfortunately, alkylation of **18** with sodium hydride and crotyl chloride HMPA at 0 °C, irrespective of the order of addition of reactants or concentration, consistently gave one major product (25% isolated yield in one case) which was assigned the structure **20** on the basis of elemental analysis and spectroscopic data. The 300 MHz ^{1}H NMR spectrum of **20** in $CDCl_3$ exhibited very complex aromatic and aliphatic regions. A triplet centered at δ 6.85 was assigned to the single vinyl proton coupled to the geminal methylene protons (J_{gem} 6.9 Hz). The *E*-configuration depicted (vinyl proton *cis* to the ester group) follows from a comparison with the vinyl chemical shifts of *E*- and *Z*-methyl 2-methyl-2-butenoates[19] which resonate at δ 6.73 and δ 5.98, respectively (*vide supra*), and the C-3 vinyl proton of *E*-enoates **18** (δ 6.93) and **5** (δ 6.96). Broad exchangeable triplets centered at δ 7.55 and δ 7.13 were ascribed to the two amide protons in **20**. Other salient features included two methyl esters signals at δ 3.61 and δ 3.57 and two "haystack" multiples, each integrating for one proton, centered at δ 2.10 and δ 1.85. These latter signals, the only ones present above δ 2.5, were attributed to the methylene protons attached to the chiral center at C-3 of the heptenoate backbone. The ^{13}C NMR of **20** exhibited a total of 22 carbon signals: 4 in the range δ 174–166 (amide and ester carbonyl carbons), 10 aromatic/olefinic and 8 aliphatic signals. The MS and IR spectra are also consistent with structure **20**.



Scheme 2. Projected synthesis of diene **13**, and formation of dimer **20.**

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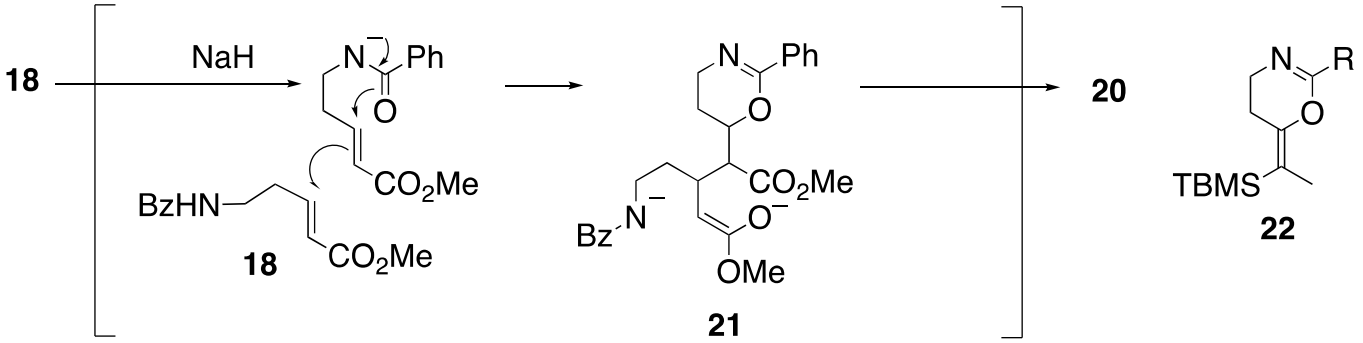
The dimeric by-product **20** may arise via intramolecular Michael attack of the generated amide anion from **18** on the enoate, followed by conjugate addition of the formed enolate on a second molecule of starting material to give intermediate dihydro-1,3-oxazine **21**. Base-catalyzed fragmentation of the oxazine ring or elimination on acidic work-up would give **20**. Danheiser[24] reported the formation of dihydro-1,3-oxazine by-products **22** from the titanium tetrachloride-catalyzed [2+3] cyclization of alicyclic *N*-acylimmonium ions and allenylsilanes, presumably via a related process involving amide capture of a vinyl cation intermediate.



Scheme 3. Suggested route to dimer **20** from **18.**

We examined the "hydrogen bond-assisted" *N*-alkylation[25] of **18** with crotyl chloride using potassium fluoride on alumina. Ando[26] has reported that secondary amides and lactams can be smoothly *N*-alkylated with benzyl chloride in acetonitrile in the presence of KF-alumina. However, in the case of **18** no reaction was observed. Similarly, attempts to *N*-alkylate **18** under S_N1 conditions[27] with silver trifluoroacetate at 100 °C produced no reaction. Therefore, we pursued a different synthetic route to the dienoate **13** (Scheme 4). Our plan was to construct the dienoate double bond in the last step from aldehyde **23** via a Horner–Wadsworth–Emmons reaction.[28] Accordingly, the commercially available bromide **24** was converted into the azide **25** with sodium azide under phase transfer conditions (PTC) and the crude azide was subjected to Staudinger conditions[29] to provide the amino acetal **26** in 65% overall yield from **24**. Acylation of **26** with benzoyl chloride and triethylamine in methylene chloride at 0 °C delivered the benzamide **27** (87% yield), which was alkylated with crotyl chloride and sodium hydride in DMF to provide amide acetal **28** in high yield. Acidic hydrolysis[30] of **28** in AcOH-THF-H_2O (2:2:1) at reflux provided the desired aldehyde **23** but in only 28% yield; also isolated were starting material **28** (14%) and elimination by-product **29** (25%). Treatment of **23** with the sodium salt of methyl diethylphosphonoacetate, generated with sodium hydride in dimethoxyethane (DME) at 0 °C,[31] provided the desired dienoate **13** in 78% yield. Inspection of the 300 MHz ^{1}H NMR of **13** (in $CDCl_3$) revealed, *inter alia*, the expected low field multiplet centered at δ 6.97 for the C-3 vinyl proton and a doublet centered at δ 5.91 for the *trans*-coupled C-1 vinyl protons (*J* 15.6 Hz), thus corresponding nicely to the ^{1}H NMR spectrum of diene **5**.

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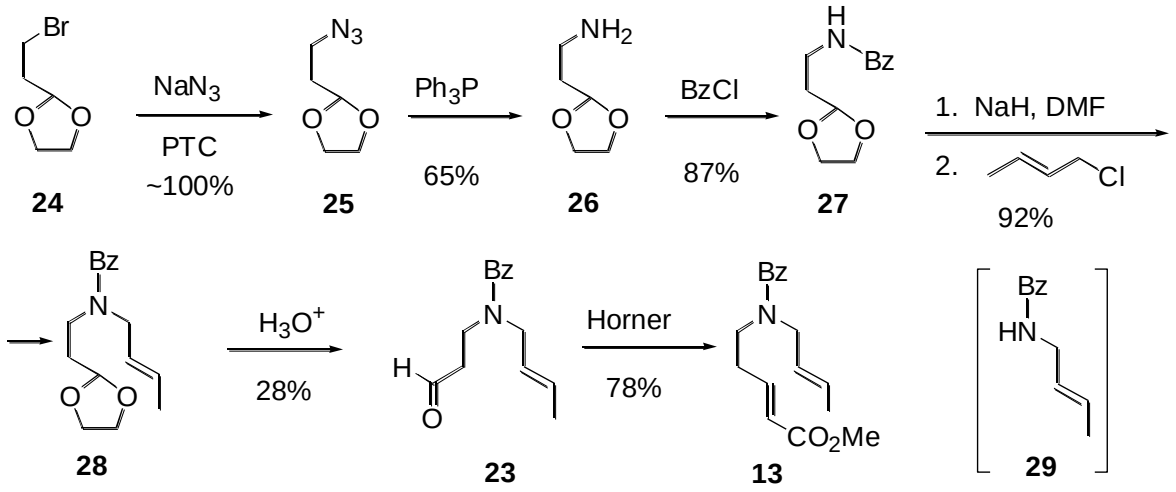

Scheme 4. Synthesis of diene **13.**

Thus far, our attempts to effect the ene cyclization of **13** to **14** under thermal and Lewis acid conditions analogous to those employed for **5** have been unsuccessful. Thermolysis of **13** under argon at 300 °C leads to extensive decomposition. Lower temperatures (220 °C, 250 °C) and longer reaction times produced very little reaction although the formation of several very minor products was observed by TLC. Similarly, attempts to cyclize **13** in methylene chloride, even at reflux, with excess diethylaluminum chloride, resulted in no reaction. Interestingly, treatment of **13** with excess Et_2AlCl in the absence of solvent at room temperature gave an unidentified substance, which does not appear by ^{1}H NMR and IR spectroscopy to be the desired ene product or the product of an intramolecular hetero-Diels–Alder reaction.[32] While our cyclization studies have been limited by the available supply of **13**, it is clear that the monoactivated 1,7-diene **13** is less reactive than anticipated.

In comparison to the intramolecular thermal ene reaction, intramolecular ene reactions involving the transfer of metal atoms have been effected under extraordinarily mild conditions (0°–80 °C, Et_2O) and in very good yield.[33-37] The formal ene addition of allylic Grignard reagents and allylic organolithium compounds to olefins and subsequent trapping of the cyclized organometallic intermediate with various electrophiles has led to the preparation of 1,3-disubstituted cyclopentane and cyclohexane derivatives in a regio- and stereoselective manner (*vide infra*).[38,39] We envisioned that the metallo-ene synthesis of the *N*-benzoyl derivative of meroquinene (**6a**) and its *trans* isomer **6b** could serve as a model study for the synthesis of the pivotal 2-(2-piperidinyl)indole intermediates that we required in our *Corynanthe*/sarpagine studies. We thought that the relative *cis* configuration about the C-3, C-4 bond of meroquinene (**6a**) might be achieved in a regioselective thermal cyclization of the *Z*-allylic Grignard (ene unit) **30** as shown retrosynthetically in Figure 4. Model considerations show that a chair-boat transition state results in the steric congestion of allylic and olefinic protons thus favoring formation of the *cis*-substituted piperidine **31** via the relatively unstrained chair-chair transition state **B**.

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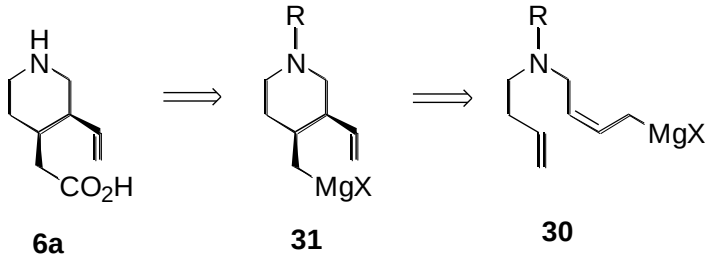
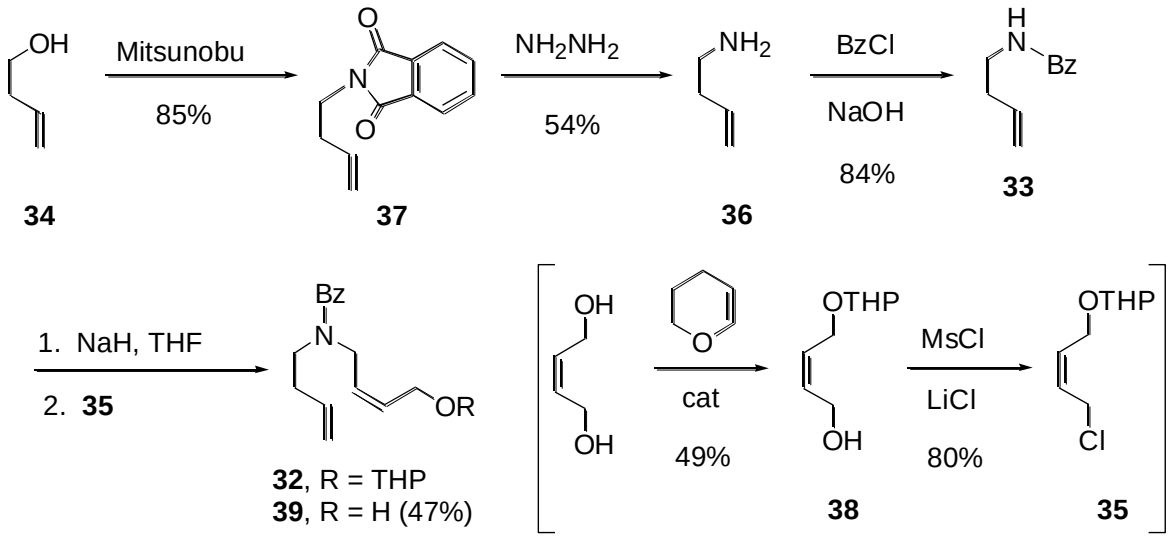


Figure 4. Possible route to meroquinene **6a** by intramolecular organometallic transfer reaction.

A suitable precursor to the *Z*-allylic Grignard **30** appeared to be the tetrahydropyranyl (THP) ether **32**, which was derivable from 4-benzamido-1-butene (**33**) and allylic chloride **35** (Scheme 5). Despite Brown's report[40] on the smooth reduction of allyl cyanide to 3-butenylamine (**36**) with aluminum hydride, we obtained very low yields (8–12%) of **36** by this procedure. Amine **36** could, however, be conveniently prepared from 3-butenyl alcohol in two steps. Thus, 3-butenyl alcohol (**34**) was converted into the *N*-alkylphthalimide **37** in 85% yield via a Mitsunobu reaction with triphenylphosphine and diethyl azodicarboxylate (DEAD). Imide **37** was subsequently treated with hydrazine hydrate in ethanol to give **36** in 54% distilled yield. 3-Butenylamine (**36**) was then converted to 4-benzamido-1-butene (**33**)[41] in 84% yield with benzoyl chloride in 10% aqueous sodium hydroxide. The synthesis of the requisite THP-protected chloride **35** was accomplished in two steps from 2-butene-1,4-diol. Following the report of Thuy and Maitte,[42] **38** was prepared in 49% yield by refluxing a benzene solution of 2-butene-1,4-diol and dihydropyran (DHP) in the presence of active montmorillonite. The alcohol **38** was readily transformed into allylic chloride (**35**) using methanesulfonyl chloride and a mixture of lithium chloride and *S*-collidine in DMF at 0 °C.[43,44] Reaction of amide **33** with 1.5 equivalents of sodium hydride in dry THF and alkylation of the resulting sodium salt with allylic chloride **35** at 55 °C for several hours furnished a mixture of amide product **32** and starting material **33** which appeared as one spot by TLC. Separation was achieved by THP-ether deprotection in AcOH-THF-H_2O (4:2:1) at 45–50 °C for four hours.[45] Flash chromatography of the resulting mixture afforded the desired dienol **39** in 47% yield (from **33**).



Scheme 5. Synthesis of the dienol **39.**

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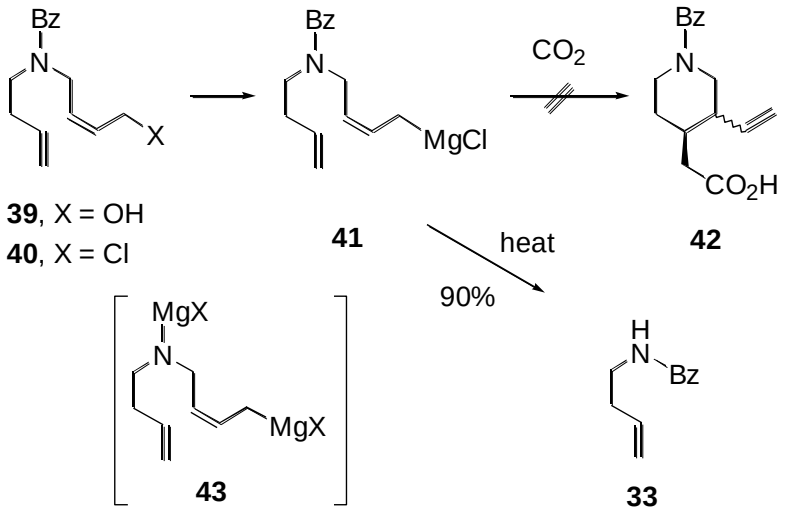
Compound **39** was transformed into the allylic chloride **40** using methanesulfonyl chloride and a mixture of lithium chloride and *S*-collidine in DMF at 0 °C (Scheme 6). The unstable allylic chloride **40** was purified by rapid filtration through silica gel to give analytically pure **40** in 73% yield. Conversion of **40** into the corresponding Grignard reagent **41** with magnesium turnings was accomplished by entrainment with 1,2-dibromoethane in THF at 60 °C. However, quenching the reaction at 0 °C with carbon dioxide led to the isolation of decomposition product **33** and not to the desired piperidine **42**. Presumably, the benzamide **33** arises from vinylogous β-elimination of Grignard **41** and concomitant formation of butadiene. In future work this latter complication may be circumvented by replacing the Grignard species **41** with a bis-metallo species such as **43.**



Scheme 6. Formation of the dienyl Grignard **41** and its fragmentation.

Conclusions

We have described the syntheses of several new dienes (*i.e*., **5**, **13**, **39** and **40**) preparatory for an ene cyclization leading to the *N*-substituted 3-vinyl-4-piperidineacetic acid scaffold, which is embedded in numerous alkaloids. Although conditions for the ene-cyclization have yet to be found, the relative ease of preparation of these cyclization diene substrates presages the opportunity for their future use.

Experimental Section

General. Melting points were determined in open capillaries (except for compound **25** which was determined in an evacuated capillary tube) with either a Mel-Temp Laboratory Devices apparatus or a Buchi 510 apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, or Micanal, Tucson, AZ. Infrared spectra were recorded on a Perkin-Elmer 599 instrument. ^{1}H NMR (60 MHz) spectra were obtained on a Perkin-Elmer R-24 or EM-360A spectrometer. ^{13}C NMR and 300 MHz ^{1}H NMR spectra were recorded on a Varian XL-300 multinuclear Fourier transform NMR. Mass spectra were obtained at the NSF regional instrumentation facility at Johns Hopkins University School of Medicine and on a Finnigan 4023 GC/MS system. UV spectra were recorded on a Unicam SP-800A spectrophotometer. Analytical and

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preparative TLC employed silica gel (Merck silica gel 60 F-254). TLC spots were visualized with 254 nm UV light and/or with an appropriate reagent: ketones, 2,4-dinitrophenylhydrazine (0.4% in 2 N HCl); acids, bromocresol green (0.3% in 80% methanol, 0.5% 30% NaOH); N-H indoles, ceric ammonium sulfate (3% in 10% H_2SO_4); aliphatic compounds, phosphomolybdic acid (5% in ethanol). Tetrahydrofuran (THF) was distilled from Na/benzophenone; other solvents were rigorously dried according to published procedures. Alkyllithium reagents were standardized by titration against 2,5-dimethoxybenzyl alcohol or diphenylacetic acid. All reagents were purchased from Aldrich Chemical Company unless otherwise indicated.

5-Aminopentanoic acid (**8**). A mixture of 2-piperidone (7) (5.0 g, 0.050 mol; Fluka) and barium hydroxide octahydrate (17.5 g, 0.055 mol) in H_2O (75 mL) was heated to reflux for 48 h. The cooled reaction mixture was treated with gaseous carbon dioxide until neutral to litmus. The precipitated barium carbonate was collected and triturated with hot H_2O (2 × 50 mL). The filtrate and triturates were combined and concentrated *in vacuo* to give 5.6 g (95%) of 8 as a colorless solid which was dried at 60 °C (0.5 mmHg): mp 152–154 °C. This material is also commercially available from Aldrich: mp 158–161 °C.

***N*-(*t*-Butoxycarbonyl)-5-aminopentanoic acid (9).** To a solution of 5-aminopentanoic acid (8, 2.17 g, 0.0185 mol) and triethylamine (4.7 g, 0.046 mol) in 1:1 dioxane-H_2O (50 mL) at 25 °C was added 2-(*t*-butoxycarbonyl-oxyimino)-2-phenylacetonitrile (BOC-ON; 5.0 g, 0.020 mol) over 5 min. The resulting reaction mixture was stirred at room temperature for 12 h, diluted with ethyl acetate (75 mL) and H_2O (75 mL) and the layers were separated. The aqueous phase was washed with ethyl acetate (15 mL), acidified to pH 2.85 with solid citric acid, and extracted with ethyl acetate (2 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give 3.0 g (75%) of 9 as a light yellow oil which crystallized on standing: mp 43–46 °C (lit.[46] mp 45–52 °C); ^{13}C NMR ($CDCl_3$) δ 178.5, 156.2, 78.7, 40.0, 33.5, 29.2, 28.3, 21.7.

Benzyl *N*-(*t*-butoxycarbonyl)-5-aminopentanoate (**10**). A solution of acid 9 (2.80 g, 0.0129 mol) in dry $CHCl_3$ (20 mL) at 0 °C was treated with triethylamine (1.30 g, 0.0129 mol), followed by benzyl bromide (2.27 g, 0.0129 mol), warmed to room temperature overnight and then treated with additional benzyl bromide (0.45 g, 2.6 mmol) along with triethylamine (0.26 g, 2.6 mmol). The resulting reaction mixture was heated at 35 °C for 8 h, diluted with $CHCl_3$ (50 mL) and washed twice with 20 mL portions of H_2O, 5% aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2.46 g (62%) of **10** as a light yellow oil which was pure by TLC: IR (neat) ν_{max} 3370 (m), 2980 (m), 2940 (m), 2870 (m), 1740 (s), 1720 (s), 1520 (m), 1460 (m), 1400 (m), 1375 (m), 1260 (m), 1170 (s), 1015 (w), 875 (w), 755 (m), 745 (m), 705 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.0 (br s, 1H), 7.33 (s, 5H), 5.12 (s, 2H), 3.11 (m, 2H), 2.38 (m, 2H), 1.78–1.12 (m, 4H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.9, 155.8, 128.2, 128.0, 127.8, 65.9, 53.3, 39.8, 33.6, 29.2, 28.2, 21.8; MS *m/e* (relative intensity) 251 (M^+-$(Me)_2C{=}CH_2$, 1), 236 (1), 206 (1), 146 (6), 116 (10), 115 (2), 100 (2), 92 (9), 91 (100), 89 (13), 77 (9), 78 (2), 76 (2), 65 (9), 57 (10), 51 (10), 50 (4).

Benzyl *N*-(*t*-butoxycarbonyl)-*N*-((*E*)-2-butenyl)-5-aminopentanoate (**11**). Dry sodium hydride (0.16 g, 0.0067 mol) was added to a solution of ester **10** (1.47 g, 0.00478 mol) and freshly distilled *trans*-crotyl chloride (0.56 g, 0.0062 mol) in HMPA (20 mL) at 0 °C, and the resulting gray suspension was stirred at 0 °C for 2 h and then allowed to warm slowly to 20 °C over 8 h. The reaction mixture was poured into ice cold brine (100 mL) and extracted with ether (3 x 75 mL). The combined ethereal layers were washed with brine (5 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Column chromatography over silica gel with 6:1 (v/v) hexanes-Et_2O afforded 0.43 g (25%) of **11** as a colorless oil. IR (neat) ν_{max} 2980 (m), 2940 (m), 1745 (s), 1700 (s), 1450 (m), 1420 (m), 1370 (m), 1245 (m), 1170 (s), 1095 (m), 975 (m), 880 (w), 740 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 3H), 5.65–4.85 (m, 2H), 5.08 (s, 2H), 3.70 (m, 2H), 3.15 (t, *J* 6.5 Hz, 2H), 2.38 (m, 2H), 1.8–1.5 (m, 7H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.1, 155.3, 135.9, 128.4, 128.3, 128.2, 128.1, 126.9, 79.1, 66.0, 48.8, 45.5, 33.8, 28.3, 22.1, 17.5; MS *m/e* (relative intensity) 305 ($M^+ - Me_2C{=}CH_2$, 2), 261 (18), 260 (13), 246 (6), 206 (7),

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170 (45), 91 (84), 84 (100), 70 (63), 57 (62), 55 (65), 41 (51). Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.95; H, 8.65; N, 3.86%.

Benzyl (*E*)-*N*-(*t*-butoxycarbonyl)-*N*-((*E*)-2-butenyl)-5-amino-2-pentenoate (**5**)**.** To a solution of diisopropylamine (0.11 g, 0.79 mmol) in THF (10 mL) under nitrogen at –78 °C was added dropwise over 10 min *n*-butyllithium (1.05 M in hexane, 0.72 mL, 0.76 mmol). After 20 min, the LDA was treated dropwise over 15 min with a solution of **11** (0.24 g, 0.66 mol) in THF (3 mL). The slightly turbid solution was stirred at –78 °C for 45 min and then treated dropwise with a solution of phenylselenenyl chloride (0.15 g, 0.76 mmol) in THF (2 mL) over 5 min. The resulting light yellow solution was allowed to warm to –15 °C over 5 h and then a solution of sodium periodate (0.43 g, 0.20 mmol) in 1:1 methanol-H_2O (10 mL) was added and the reaction was allowed to warm to room temperature overnight. The reaction mixture was partitioned between ether (50 mL) and cold saturated aqueous $NaHCO_3$ and the layers separated. The aqueous phase was extracted with Et_2O (25 mL) and the combined ethereal layers were washed with brine (2 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow oil. Column chromatography over silica gel (20 g) with 6.5:1 (v/v) ether-hexane afforded 0.095 g (40%) of **5** as a colorless oil; IR (neat) ν_{max} 2980 (m), 2930 (m), 1730 (s), 1700 (s), 1460 (m), 1420 (m), 1370 (m), 1270 (m), 1250 (m), 1170 (s), 1130 (m), 1095 (m), 1025 (w), 975 (w), 700 (m) cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ 7.36 (s, 5H), 6.96 (dt, *J* 16 Hz, *J* 7 Hz, 1H), 5.88 (d, *J* 16 Hz, 1H), 5.65–5.20 (m, 2H), 5.16 (s, 2H), 3.74 (m, 2H), 3.28 (m, 2H), 2.40 (m, 2H), 1.68 (d, *J* 7 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.0, 155.2, 146.6, 136.0, 128.5, 128.4, 128.4, 128.1, 126.8, 122.5, 79.6, 66.1, 49.0, 44.8, 28.4, 28.3, 17.6; MS *m/e* (relative intensity) 303 (M^+ – $Me_2C{=}CH_2$, 1), 261 (1), 260 (1), 218 (4), 184 (13), 128 (30), 91 (80), 84 (99), 57 (100). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.22; H, 8.16; N, 3.91%.

***N*-Benzoyl-5-aminopentanoic acid** (**15**)**.** Amide **15** was prepared in 41% yield from **8** and benzoyl chloride according to the procedure of Hurd[47]: mp 91.5–94 °C (lit.[47] mp 93–94 °C). This material is also commercially available from Sigma.

***N*-Benzyl-*N*-((*E*)-2-butenyl)-5-aminopentanoic acid** (**16**)**.** To a solution of **15** (2.45 g, 0.0111 mol) and *trans*-crotyl chloride (1.20 g, 0.0133 mol) in dry DMF (20 mL) at –5 °C was added sodium hydride powder (0.67 g, 0.028 mol) over 10 min. The resulting suspension was stirred at –5 °C for 40 min and then allowed to warm to room temperature overnight. The reaction mixture was heated to ~40 °C for 5 h, treated with additional crotyl chloride (0.20 g, 2.2 mmol) and heated at 40 °C for an additional 2.6 h. The reaction mixture was cooled to 0 °C, quenched carefully with H_2O (10 mL) and then poured into 5% aqueous HCl (100 mL) and extracted with ether (2 x 100 mL). The combined ethereal layers were washed with brine (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 2.6 g of crude **16** as a viscous light yellow oil. Attempts to crystallize **16** from ether-pentane instead provided 2.0 g (65%) of **16** as a colorless oil which was pure by TLC. Flash chromatography with hexane-EtOAc-AcOH (3:1:0.1) afforded the analytical sample: IR (neat) ν_{max} 3680–2380 (m), 2950 (s), 2870 (m), 1740 (s), 1605 (s), 1580 (s), 1510 (m), 1470 (s), 1440 (s), 1385 (m), 1220 (m), 1255 (m), 1185 (m), 1080 (m), 1035 (m), 975 (s), 795 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.91 (br s, 1H), 7.45 (s, 5H), 5.8–5.2 (m, 2H), 3.91 (m, 2H), 3.48 (m, 2H), 2.38 (m, 2H), 1.9–1.4 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 178.2, 171.9, 136.2, 129.3, 128.3, 128.2, 126.4, 125.7, 51.1, 43.9, 33.6, 26.4, 21.9, 17.6; MS: *m/e* (relative intensity) 275 (M^+, 3), 246 (4), 202 (2), 188 (3), 174 (3), 170 (24), 134 (4), 124 (4), 106 (11), 105 (100), 77 (37), 55 (11), 51 (6), 41 (3), 39 (3). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.62; H, 7.73; N, 5.03%.

Methyl *N*-benzoyl-*N*-((*E*)-2-butenyl)-5-aminopentanoate (**17**)**.** A –5 °C solution of diazomethane in ether (125 mL), generated from 1-methyl-3-nitro-1-nitrosoguanidine (2.2 g, 8.015 mol) and 5N NaOH (20 mL), was slowly poured into a solution of **16** (1.34 g, 4.87 mmol) in ether at 0 °C until a yellow color persisted. Acetic acid (1 mL) was added and the resulting colorless solution was washed with 5% aqueous NaOH (2 x 50 mL), brine (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 1.32 g (94%) of analytically pure **17** as a colorless oil:

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IR (neat) ν_{max} 2950 (m), 2865 (m), 1740 (s), 1635 (s), 1425 (3), 1380 (m), 1360 (m), 1315 (m), 1300 (m), 1250 (m), 1200 (m), 1175 (m), 1150 (m), 1110–1070 (m), 930 (m), 970 (s), 790 (m), 705 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (s, 5H), 5.8–5.2 (m, 2H), 3.90 (m, 2H), 3.70 (s, 3H), 3.45 (m, 2H), 2.33 (m, 2H), 1.9–1.3 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 173.6, 171.3, 136.6, 129.0, 128.9, 128.15, 128.1, 126.2, 125.9, 51.2, 50.8, 43.6, 33.4, 26.4, 22.0, 17.5; MS: *m/e* (relative intensity) 2890 (M^+, 2), 260 (2), 234 (1), 202 (1), 188 (2), 185 (3), 184 (23), 174 (2), 134 (2), 115 (2), 106 (8), 105 (100), 77 (25), 59 (2), 55 (9), 51 (4), 41 (2). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.48; H, 8.06; N, 4.80%.

Methyl *N*-benzoyl-5-aminopentanoate (**19**)**.** Application of the same diazomethane procedure that was used to prepare **17** (from **16**) to the preparation of ester **19** from **15** (1.00 g, 4.52 mmol) afforded 1.05 g (99%) of **19** as a colorless oil which crystallized on standing: mp 43–45.5 °C (lit.[48] mp 40–41 °C); IR (neat) ν_{max} 3300 (s), 2930 (s), 1740 (s), 1640 (s), 1585 (m), 1540 (s), 1495 (m), 1440 (m), 1310 (s), 1175 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03–7.73 (m, 2H), 7.60–7.30 (m, 2H), 7.05 (br s, 1H), 3.68 (s, 3H), 3.48 (m, 2H), 2.36 (m, 2H), 1.83–1.47 (m, 4H); ^{13}C NMR δ 173.7, 167.4, 134.4, 131.0, 128.2, 126.7, 51.4, 39.4, 33.4, 28.8, 22.0.

Methyl (*E*)-*N*-benzoyl-5-amino-2-pentanoate (**18**)**.** To a solution of LDA prepared from diisopropylamine (2.17 g, 0.0214 mmol) and *n*-butyllithium (0.99 M in hexane; 21.6 mL, 0.0214 mol) in THF (100 mL) at –78 °C was added dropwise over 15 min a solution of **19** (2.09 g, 8.91 mmol) in THF (25 mL). The solution was stirred at –78 °C for 45 min and the resulting densely turbid mixture was treated dropwise over 15 min with a solution of phenylselenenyl chloride (2.09 g, 0.0107 mol) in THF (20 mL). The resulting light yellow solution was stirred at –78 °C for 30 min, quenched with methanol (1 mL), and allowed to warm to room temperature overnight. The mixture was poured into saturated aqueous NH_4Cl (200 mL) and extracted with ether (3 x 75 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of selenide and starting material by TLC. Flash chromatography with EtOAc-hexane (1:2) furnished 2.62 g (75%) of the selenide as a colorless oil (MS *m/e* (relative intensity)) 391 (M+1, 1), 359 (6), 234 (6), 174 (5), 157 (6), 146 (5), 105 (100), 77 (46) followed by 0.31 g (15%) of recovered starting material **19**. A solution of the selenide (2.20 g, 5.64 mmol) in THF (100 mL) at –5 °C was treated dropwise over 30 min with a solution of sodium periodate (3.62 g, 0.17 mol) in MeOH-H_2O (1:1, 10 mL). The resulting mixture was allowed to warm to room temperature over 5 h and then was cooled to –5 °C and treated with pyridine (0.5 mL). After stirring 1 h at room temperature the resulting suspension was partitioned between ether (200 mL) and H_2O-brine (1:1, 200 mL) and the layers were separated. The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic layers were washed with 2% aqueous HCl (2 x 10 mL), H_2O (25 mL), brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 1.28 g (98%, 74% overall from **19**) of **18** as light yellow flakes: mp 84–88 °C (lit.[23] mp 86–87 °C); IR (KBr) ν_{max} 3270 (s), 1720 (s), 1655 (s), 1625 (s), 1530 (s), 1435 (m), 1325 (s), 1290 (s), 1270 (s), 1210 (s), 1170 (s), 975 (m), 870 (m), 800 (m), 710 (s), 690 (s) cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ 7.80–7.72 (m, 2H), 7.51–7.33 (m, 3H), 6.98 (br s, 1H), 6.93 (δ of t, *J* 15.9 Hz, *J* 6.8 Hz, 1H), 5.89 (δ of t, *J* 15.9 Hz, *J* 1.5 Hz, 1H), 3.55 (m, 2H), 2.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.7, 166.6, 145.6, 134.2, 131.3, 128.3, 126.8, 122.7, 51.4, 38.3, 32.1; MS: *m/e* (relative intensity) 233 (M^+, 1), 135 (2), 134 (23), 128 (2), 106 (8), 105 (100), 77 (28), 51 (3).

Attempted *N*-alkylation of 18: Self-condensation of 18 to give methyl (*E*)-*N*-benzoyl-3-benzamidoethyl-4-carbomethoxy-5-amino-3-heptenoate (**20**)**.** To a solution of **18** (0.307 g, 1.32 mmol) in HMPA (3 mL) at 0 °C under argon was added dropwise over 5 min a suspension of dry sodium hydride (0.035 g, 1.4 mmol) in HMPA (1 mL). The resulting reaction mixture was stirred at 0 °C for 15 min, and then treated dropwise with *trans*-crotyl chloride (0.15 g, 1.7 mmol). After stirring at 0 °C for 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl (75 mL) and extracted with ether (3 x 50 mL). The combined ethereal extracts were washed with brine (2 x 25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. Flash chromatography with EtOAc-hexane (3:2) afforded 0.155 g (25%) of **20** as a colorless oil. Crystallization from ether-pet ether

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furnished the analytical sample as extremely hygroscopic, fluffy crystals: mp 44–47 °C; IR (neat) ν_{max} 3300 (s), 3055 (m), 2940 (s), 2920 (s), 1730 (s), 1700 (s), 1660–1620 (s), 1600 (s), 1575 (s), 1555 (s), 1540 (s), 1530 (s), 1520 (s), 1490 (s), 1430 (s), 1360 (s), 1420–1230 (s), 1200 (s), 1155 (s), 1120 (s), 1080 (s), 1020 (m), 800 (m) cm^{-1}; 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.91–7.76 (m, 4H), 7.55 (br t, *J* 5.0 Hz, 1H), 7.49–7.29 (m, 6H), 7.13 (br t, *J* 5.5 Hz, 1H), 6.85 (t, *J* 6.9 Hz, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 3.47–3.22 (m, 4H), 2.85–2.53 (m, 5H), 2.19–2.02 (m, 1H), 1.93–1.77 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.3, 167.9, 167.7, 166.7, 143.0, 134.2, 134.15, 133.3, 131.3, 131.2, 128.3, 128.2, 127.1, 126.9, 51.5, 51.3, 39.3, 38.0, 37.8, 32.6, 32.2, 28.2; MS: *m/e* (relative intensity) 466 (M^+, 1), 393 (1), 333 (2), 313 (1), 301 (2), 252 (1), 240 (1), 210 (1), 197 (2), 180 (1), 165 (1), 150 (1), 149 (1), 136 (10), 122 (12), 106 (8), 105 (100), 103 (4), 77 (45), 51 (16). Anal. Calcd for $C_{26}H_{30}N_2O_6 \cdot 1/4\ H_2O$: C, 66.29; H, 6.53; N, 5.95. Found: C, 66.25; H, 6.56; N, 5.87%.

2-(2-Aminomethyl)-1,3-dioxolane (**26**)**.** Amine **26** was prepared in two steps in 65% overall yield from 2-(2-bromoethyl)-1,3-dioxolane (**24**) according to a known method:[49] bp 83–84 °C/25 mmHg (lit.[50] bp 70–75 °C/18 mmHg).

2-(2-Benzamidoethyl)-1,3-dioxolane (**27**)**.** To a solution of **26** (3.80 g, 0.0325 mol) and triethylamine (4.1 g, 0.041 mol) in dry CH_2Cl_2 (75 mL) at –10 °C was added dropwise over 45 min a solution of benzoyl chloride (5.5 g, 0.039 mol) in CH_2Cl_2 (20 mL). The resulting turbid solution was warmed to room temperature over 4 h and poured into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic phase was washed with 10% aqueous NaOH (3 x 50 mL), 2N aqueous HCl (2 x 50 mL), brine (2 x 100 mL), dried (K_2CO_3) and concentrated *in vacuo* to give a viscous oil. Flash chromatography with ether-hexane (1:1 to 2:1, gradient elution) furnished 6.23 g (87%) of analytically pure **27** as a colorless oil: IR (neat) ν_{max} 3330 (s), 2960 (m), 2885 (s), 1645 (s), 1585 (m), 1545 (s), 1495 (m), 1315 (m), 1300 (m), 1140 (s), 1090 (m), 1030 (m), 945 (m), 715 (s), 700 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.1–7.0 (m, 6H), 5.06 (t, *J* 4.5 Hz, 1H), 3.97 (m, 4H), 3.66 (m, 2H), 2.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.9, 134.2, 130.8, 128.0, 126.5, 103.2, 64.6, 35.0, 32.4; MS: *m/e* (relative intensity) 221 (M^+, 1), 178 (13), 149 (12), 148 (12), 134 (5), 116 (17), 106 (8), 105 (97), 104 (6), 99 (6), 87 (16), 77 (43), 73 (100), 51 (8), 45 (28). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.10; H, 6.83; N, 6.21%.

2-(*N*-Benzoyl-*N*-((*E*)-2-butenyl)-2-aminoethyl)-1,3-dioxolane (**28**)**.** To a solution of **27** (2.64 g, 0.0119 mol) in dry DMF (20 mL) at –5 °C was added sodium hydride powder (0.370 g, 0.0155 mol) over a 10 min period. The resulting solution was 28 at –5 °C for 45 min, treated dropwise over 10 min with the *trans*-crotyl chloride (1.29 g, 0.0143 mol) and allowed to warm to room temperature over 12 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with ether (3 x 75 mL). The combined ethereal extracts were washed with brine-H_2O (1:1, 4 x 100 mL), dried (K_2CO_3) and concentrated *in vacuo* to give 3.0 g (92%) of **28** as a light yellow oil which was pure by TLC. Kugelrohr distillation provided the analytical sample as a colorless oil: bp 250 °C (bath temp)/0.4 mmHg; IR (neat) ν_{max} 2940 (m), 2880 (m), 1635 (s), 1465 (m), 1445 (m), 1425 (m), 1375 (m), 1260 (m), 1245 (m), 1130 (m), 1085 (m), 1020 (m), 965 (m), 940 (m), 895 (m), 790 (m), 700 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 5H), 5.9–5.2 (m, 2H), 4.92 (m, 1H), 3.92 (m, 4H), 3.35 (m, 2H), 2.28–1.85 (m, 2H), 1.72 (d, *J* 5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 136.4, 129.0, 128.8, 128.0, 126.2, 102.6, 64.6, 51.1, 39.9, 31.5, 17.6; MS: *m/e* (relative intensity) 275 (M^+, 1), 232 (2), 202 (4), 188 (3), 174 (9), 170 (4), 106 (8), 105 (100), 99 (7), 87 (10), 82 (10), 77 (25), 73 (17), 55 (9), 45 (6). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.62; H, 7.73; N, 5.03%.

***N*-Benzoyl-*N*-(3-oxo-1-propyl)-(*E*)-1-amino-2-butene (23) and *N*-benzoyl-(*E*)-1-amino-2-butene (29).** A solution of **28** (2.20 g, 7.99 mmol) in a 2:2:1 (v/v) mixture of AcOH-THF-H_2O (30 mL) was heated at 70 °C for 12 h, then diluted with ether (200 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 50 mL). The ethereal layer was dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. Flash chromatography with EtOAc-hexane

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(1:4) afforded 0.35 g (25%) of by-product **29**, followed by 0.30 g (14%) of starting material **28** and 0.52 g (28%) of aldehyde **23** as a hygroscopic colorless oil which rapidly decomposed on standing.

Aldehyde **23**: IR (neat) ν_{max} 3410 (m), 2970 (m), 2920 (m), 2720 (w), 1730 (s), 1635 (s), 1470 (m), 1450 (m), 1430 (m), 1380 (m), 1070 (m), 975 (m), 795 (m), 710 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.95 (s, 1H), 7.48 (s, 5H), 5.8–5.2 (m, 2H), 3.80 (t, *J* 7 Hz, 2H), 2.85 (t of d, *J* 6 Hz, *J* 2 Hz, 2H), 1.75 (d, *J* 7 Hz, 3H); MS *m/e* (relative intensity) 231 (M^+, 1), 202 (3), 146 (3), 126 (12), 106 (8), 105 (100), 82 (4), 78 (3), 77 (42), 70 (5), 56 (4), 55 (8), 51 (5).

Amide **29**: colorless oil; IR (neat) ν_{max} 3300 (s), 3060 (m), 3020 (m), 2910 (m), 1640 (s), 1605 (m), 1540 (s), 1490 (m), 1450 (m), 1430 (m), 1310 (s), 970 (s), 805 (m), 715 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–7.7 (m, 2H), 7.65–7.30 (m, 2H), 6.7 (br s, 1H), 5.8–5.2 (m, 2H), 4.03 (t, *J* 6 Hz, 2H), 1.75 (d, *J* 4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.1, 134.2, 131.0, 128.1, 127.9, 126.8, 126.6, 41.8, 17.6; MS: *m/e* (relative intensity) 175 (M^+, 8), 146 (11), 106 (8), 105 (100), 104 (5), 78 (4), 77 (43), 70 (16), 55 (3), 51 (7).

Methyl (*E*)-*N*-benzoyl-*N*-((*E*)-2-butenyl)-5-amino-2-pentenoate (**13**)**.** To a slurry of sodium hydride powder (0.044 g, 1.8 mmol) in dry dimethoxyethane (DME) (4 mL) at 0 °C was added methyl diethyl phosphonoacetate (0.350 g, 1.66 mmol). After stirring for 1 h at room temperature, the resulting solution was cooled to –5 °C, treated dropwise with a solution of **23** (0.385 g, 1.66 mmol) in DME (4 mL), and allowed to warm slowly to room temperature over 6 h. The reaction mixture was poured into H_2O (50 mL) and extracted with ether (3 x 40 mL). The combined ethereal extracts were washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. Column chromatography over silica gel with hexane-EtOAc (5:1) afforded 0.195 g (78%) of **13** as an analytically pure colorless oil: IR (neat) ν_{max} 2950 (m), 2920 (m), 1730 (s), 1640 (s), 1610 (m), 1585 (m), 1505 (m), 1185 (m), 1150 (m), 1045 (m), 975 (m), 860 (m), 795 (m) cm^{-1}; 300 MHz ^1H NMR δ 7.37 (s, 5H), 7.06–6.87 (m, 1H), 5.91 (d, *J* 15.6 Hz, 1H), 5.85–5.25 (m, 2H), 3.72 (br s, 5H), 3.57 (br t, *J* 7 Hz, 2H), 2.57 (m, 2H), 1.72 (d, *J* 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 71.3, 166.3, 145.6, 136.1, 129.1, 128.1, 126.2, 126.6, 125.1, 122.4, 51.5, 51.3, 43.1, 30.1, 17.6; MS: *m/e* (relative intensity) 287 (M^+, 1), 286 (1), 272 (1), 256 (1), 228 (1), 189 (2), 188 (15), 182 (3), 174 (3), 134 (3), 106 (8), 105 (100), 77 (16), 55 (4). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.72; H, 7.57; N, 5.10%.

4-Benzamido-1-butene (33). Amide **33** was prepared in 84% yield from **36** according to the method of Davies:[41] IR (neat) ν_{max} 3330 (s), 3085 (m), 2990 (m), 2945 (m), 1650 (s), 1610 (m), 1585 (m), 1550 (s), 1500 (m), 1315 (s), 925 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.0 (m, 5H), 6.55 (broad s, 1H), 6.25–5.47 (m, 1H), 5.45–4.85 (m, 2H), 3.49 (q, $J_{H\text{-}N\text{-}C\text{-}H}$ $J_{H\text{-}C\text{-}C\text{-}H}$ 6 Hz, 2H), 2.60–2.10 (m, 2H); MS: *m/e* (relative intensity) 175 (M^+, 12), 134 (38), 105 (100), 77 (53), 51 (10), 39 (3).

(*Z*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)-2-butene-1-ol (**38**)[42]**..** A mixture of 2-butene-1,4-diol (17.6 g, 0.20 mol), dihydropyran (8.4 g, 0.10 mmol) and montmorillonite (0.2 g) in benzene (25 mL) was heated to 80 °C for 12 h. The reaction mixture was dried (Na_2CO_3) and concentrated *in vacuo* to give an oil which was distilled through a Vigreaux column (10 cm) to afford a colorless liquid (bp 104–106 °C, 10 mmHg; lit.,[42] bp 102–106 °C, 10 mmHg) which was a mixture of 2-butene-1,4-diol and THF-ether **38** by TLC and ^1H NMR analysis. Flash chromatography over silica gel with 1:2 (v/v) Et_2O-hexane furnished 7.3 g (42%) of **38** as a colorless oil: IR (neat) ν_{max} 3660–3080 (s), 3030 (m), 3000–2860 (s), 1470 (m), 1460 (m), 1455 (m), 1390 (m), 1355 (m), 1325 (m), 1265 (m), 1205 (s), 1185 (m), 1160 (m), 1150–930 (s), 905 (s), 870 (s), 815 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, 2H), 4.66 (m, 1H), 4.4–3.3 (m, 6H), 3.1 (t, 1H), 2.1–1.4 (m, 6H).

(*Z*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)-1-chloro-2-butene (**35**)**.**[43,44] To a mixture of alcohol **38** (0.5 g, 2.9 mmol) and s-collidine (0.39 g, 3.2 mmol) at 25 °C was added a solution of lithium chloride (0.123 g, 3.2 mmol) in dry DMF (1.5 mL). The resulting suspension was cooled to 0 °C and treated dropwise over 5 min with mesyl chloride (0.37 g, 3.2 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature over 2 h. The light yellow reaction mixture was then poured into ice-H_2O (25 mL) and extracted

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with cold pentane-Et_2O (1:1, v/v; 3 x 25 mL). The combined organic extracts were washed with saturated $Cu(NO_2)_2$ (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* at 25 °C bath temperature to afford 0.44 g (80%) of **35** as a light yellow oil (pure by TLC) that decomposed on standing: IR (neat) ν_{max} 3040 (w), 1950 (s), 2870 (m), 2860 (m), 1450 (m), 1440 (m), 1370 (s), 1025 (s), 965 (m), 900 (m), 865 (m), 810 (m), 750 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (m, 2H), 4.6 (m, 1H), 4.35–3.25 (m, 6H), 2.2–1.3 (m, 6H).

(*Z*)-4-[*N*-(3-buten-1-yl)benzamido]-2-buten-1-ol (**39**)**.** To a solution of amide **33** (0.32 g, 1.5 mmol) and allylic chloride **35** (0.37 g, 1.95 mmol) in THF (20 mL) at 0 °C under nitrogen was added dry sodium hydride (0.052 g, 2.1 mmol). The resulting suspension was stirred at –5 °C for 1 h and allowed to warm to ambient temperature overnight (10 h). The reaction mixture was then cooled to 0 °C and treated with additional sodium hydride (0.026 g, 1.05 mmol). The mixture was stirred at 0 °C for 1 h, allowed to warm to 25 °C over 1 h, and then heated to 50 °C for 20 h. The reaction mixture was poured over ice (50 g) and extracted with CH_2Cl_2 (4 x 50 mL). The combined CH_2Cl_2 extracts were washed with brine (2 x 25 mL), aqueous 5% Na_2CO_3 (2 x 25 mL), dried ($MgSO_4$-Na_2SO_4) and concentrated *in vacuo* to afford a light yellow oil. Flash chromatography over silica gel (25 g) with 1:1 (v/v) ether-hexane furnished a mixture (0.34 g) of starting material **33** and **32** (R_f 0.19 Et_2O-hexane, 1:1) by ^1H NMR and IR spectroscopy. A solution of this mixture (0.3 g) in AcOH-THF-H_2O (4:2:1, 10 mL) was heated at 45–50 °C for 6 h. The reaction mixture was diluted with Et_2O (100 mL) and extracted with saturated aqueous $NaHCO_3$ (2 x 25 mL). The base washes were extracted with Et_2O (2 x 25 mL) and the combined ethereal extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Flash chromatography over silica gel with EtOAc-hexane (2:1, v/v) afforded 0.15 g of **33** followed by 0.095 g (43%) of **39** as a colorless oil. Alcohol **39**: IR (neat) ν_{max} 3600–3020 (s), 3080 (w), 3030 (2), 2990 (2), 2940 (m), 1625 (s), 1585 (w), 1500 (w), 1470 (m), 1450 (m), 1430 (s), 1270 (m), 1030 (m), 920 (m), 790 (m), 735 (m), 705 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5H), 6.2–4.6 (m, 2H), 4.3–2.8 (m, 7H), 2.6–1.9 (m, 2H); MS: *m/e* (relative intensity) 204 (M^+-$CH_2C{=}CH_2$), 149 (40), 121 (12), 105 (100), 100 (30), 82 (21), 77 (46), 69 (16), 71 (15), 63 (8), 57 (22), 55 (24), 44 (14), 40 (24). Anal. Calcd for $C_{15}H_{19}NO_2 \cdot 1/8\ H_2O$: C, 72.77; H, 7.84; N, 5.66. Found: C, 72.73; H, 7.94; N, 5.64%.

(*Z*)-1-Chloro-4-[*N*-(3-buten-l-yl)benzamido]-2-butene (**40**)**.** To a solution of **39** (0.2 g, 0.82 mmol) in s-collidine (0.104 g, 0.86 mmol) at 25 °C was added a solution of lithium chloride (0035 g, 0.82 mmol) in dry DMF (0.75 mL). The resulting suspension was cooled to 0 °C and treated dropwise over 3 min with mesyl chloride (0.099 g, 0.86 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature over 1 h. The light yellow reaction mixture was poured into ice-H_2O (25 g) and extracted with cold pentane-ether (1:1, v/v; 3 x 25 mL). The combined organic extracts were washed with saturated $Cu(NO_2)_2$ (2 x 25 mL), brine (2 x 25 mL), dried ($MgSO_4$-$NaSO_4$) and concentrated *in vacuo* at 25 °C bath temperature to afford 0.22 g (100%) of **40** as a colorless oil that darkened on standing. Rapid, suction filtration through a pad of silica gel with cold Et_2O-pentane (7:3) provided 0.16 g (73%) of **40** as an analytically pure oil. IR (neat) ν_{max} 3070 (m), 3040 (m), 2970 (m), 2940 (s), 2880 (m), 1650 (s), 1500 (m), 1450 (s), 1425 (s), 1320 (m), 1300 (m), 1260 (m), 1080 (m), 1010 (m), 995 (m), 925 (m), 795 (m), 730 (m), 710 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (s, 5H), 6.2–4.8 (m, 2H), 4.5–3.1 (m, 7H), 2.6–1.8 (m, 2H); MS: *m/e* (relative intensity) 222 (M^+-$CH_2CH{=}CH_2$, 5), 149 (4), 105 (100), 77 (32). Anal. Calcd for $C_{25}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.21; H, 6.91; N, 5.26%.

Attempted synthesis of 1-benzoyl-3-vinyl-4-piperidine acetic acid (**42a,b**)**: Decomposition of 41 to 4-benzamido-1-butene** (**33**)**.** A solution of chloride **40** (0.10 g, 0.38 mmol) in THF (4 mL) was added dropwise over 1 h to magnesium turnings (0.020 g, 0.82 mmol) in THF (3 mL) under nitrogen at –70 °C. During the addition the internal reaction temperature rose to –20 °C. The cooling bath was removed and the mixture was allowed to warm to room temperature over 30 min. A few iodine crystals were then added and the resulting dark red mixture was heated at 45 °C for 15 h. Additional magnesium turnings (0.20 g, 0.82 mmol) and 1,2-

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dibromoethane (0.065 g, 0.35 mmol) were added and the reaction mixture was heated at 60 °C for 12 h. Excess carbon dioxide (g) was then introduced into the solution at 0 °C for 10 min and the mixture was poured into saturated aqueous ammonium chloride (20 mL) and extracted with ether (3 x 20 mL). The combined ethereal extracts were washed with water (20 mL), brine (20 mL) and dried (Na_2SO_4). Concentration *in vacuo* afforded 0.065 g (90%) of **33** as a light yellow oil which was identical by TLC, IR, and ^{1}H NMR to an authentic sample.

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