Intramolecular cyclizations of *N*-acyliminium ions with pyridine rings

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Dedicated to Professor Charles W. Rees on the occasion of his 75th birthday

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Abstract

The reaction of *N*-Acyliminium ions with several activated pyridines resulted in an intramolecular cyclization to provide novel heterocycles. The reaction exhibited a regiochemical preference for cyclization *para* to the electron donating substitutent.

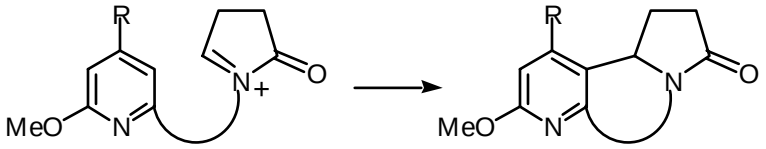
Keywords: N-Acyliminium ions, intramolecular cyclizations, pyridines, regiochemical

Introduction

The use of electron rich aromatic rings for cationic π-cyclizations[1] has emerged as a powerful method for the construction of novel heterocycles and natural products.[2] These cyclizations have been utilized as the key carbon-carbon bond forming reaction in the synthesis of several alkaloids, including the tetrahydroisoquinoline, β-carboline, and lycopodium classes.[3] From a synthetic standpoint, iminium and *N*-acyliminium ions have emerged as powerful electrophiles for these reactions, allowing for an overall α-imido alkylation.[4,5] The π-systems typically employed in these cyclizations are electron rich aromatics[6] as well as allyl[7] and vinyl silanes.[8] In contrast, the pyridine ring has received very little attention as a potential nucleophilic partner in cationic π-cyclizations despite its prevalence in a wide variety of biologically important heterocycles.[9] This is not so surprising as the electron-withdrawing effect of nitrogen in pyridine makes this heterocycle considerably less reactive than benzene toward electrophiles.[10]

Electrophilic attack at carbon is further complicated in that these reactions are often carried out in highly acidic conditions, which means that the reacting species is often the more electron-deficient conjugate acid. When electrophilic attack does occur, it is generally at the ring nitrogen. An obvious corollary of this ease of reaction of electrophilies with the ring nitrogen

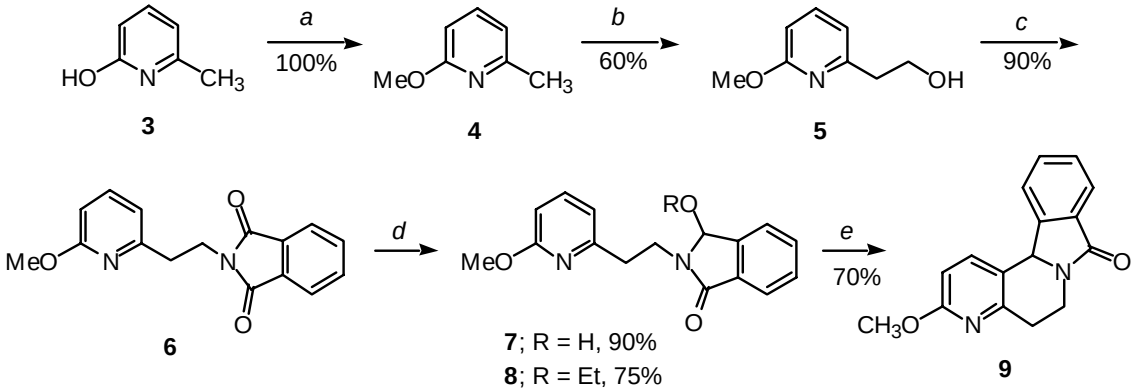
atom is that electrophilic heteroaromatic substitution of the π-deficient heterocycle is exceptionally difficult. Thus, nitration, sulfonation, and halogenation of pyridine requires drastic conditions and yields of the expected 3-substituted products are very low.[11] In this paper, the intramolecular cationic π-cyclization of pyridines of type **1** with tethered *N*-acyliminium ions is described.



1 **2**

Results and Discussion

Preparation of lactam **7** was accomplished in four steps in good overall yield starting from the appropriate hydroxy pyridine derivative (Scheme 1). Commercially available 2-hydroxy-6-methyl pyridine (**3**) was protected with MeI in the presence of Ag_2CO_3 to furnish 2-methoxy-6-methyl pyridine (**4**) in quantitative yield.[12]



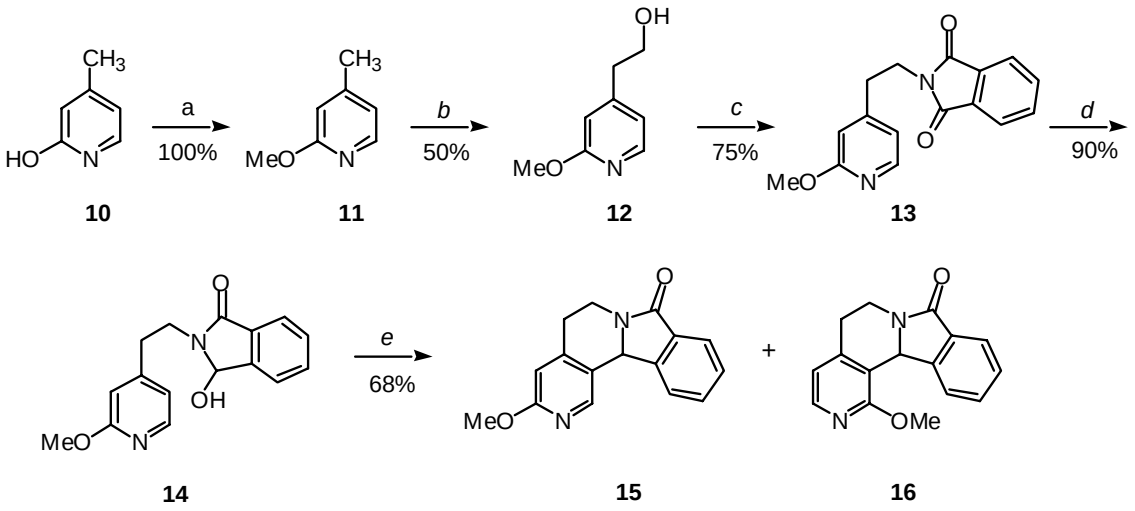
Conditions : (a) Ag_2CO_3, MeI, CH_2Cl_2; (b) *n*-BuLi, THF, 0 ^oC, $(CH_2O)_n$, rt; (c) PPh_3, DEAD, phthalimide, THF, rt; (d) $Li(Et)_3BH$, THF, -78 ^oC, HCl/H_2O (or HCl/EtOH); (e) *p*-TsOH, C_6H_6, Δ

Scheme 1

Deprotonation of **4** with *n*-BuLi at -78 ^oC followed by quenching with paraformaldehyde afforded the primary alcohol **5** in 60% yield. Incorporation of the phthalimide functionality was accomplished by nucleophilic substitution using Mitsunobu conditions to provide **6** in 90% yield.[13] Reduction of **6** to lactams **7** and **8** was carried out using super hydride ($Li(Et)_3BH$) at -78^oC.[14] Our initial attempts to cyclize lactam **7** or **8** using a variety of Lewis acid conditions

(BF_3**.**OEt_2, $TiCl_4$, $ZnCl_2$, $SnCl_4$, BF_3**.**2AcOH, *etc:*) were unsuccessful resulting only in recovered starting material or decomposition products. Cationic π-cyclization was ultimately successful when protic acids such as *p*-TsOH or CSA were used. For example, when lactam **7** was heated in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, the desired tetracyclic lactam **9** was obtained in 70 % yield. The same product was isolated in 55% yield when α-ethoxy amide **8** was treated under the above conditions.

In order to probe the regiochemical preference of the reaction, lactam **14** was synthesized in a manner similar to that described above (Scheme 2). 2-Hydroxy-4-methyl-pyridine (**10**) was converted to the methoxy derivative and then transformed into the phthalimide derivative **13** in 40 % overall yield. Reduction with super hydride provided lactam **14** in 90 % yield. Treatment of **14** with a catalytic amount of *p*-TsOH in benzene at reflux afforded a 3.5:1 mixture of regioisomers in 68 % isolated yield in addition to a dark polymer. Silica gel chromatography of the mixture furnished tetracyclic lactam **15** as the major product arising from electrophilic aromatic substitution *para* to the electron donating methoxy substituent.



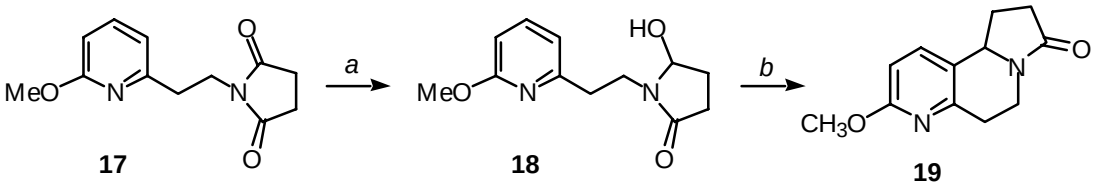
Conditions : (a) Ag_2CO_3, MeI, CH_2Cl_2; (b) *n*-BuLi, THF, 0 ^oC, $(CH_2O)_n$, rt; (c) PPh_3, DEAD, phthalimide, THF, rt; (d) $Li(Et)_3BH$, THF, -78 ^oC, HCl/H_2O; (e) *p*-TsOH, C_6H_6, Δ

Scheme 2

The minor product **16** arises from attack of the *N*-acyliminium ion *ortho* to the methoxy substituent on the pyridine ring.

Still another example involves the cyclization of lactam **18**. 2-(6-Methoxy-pyridin-2-yl)ethanol (**5**) was converted under Mitsunobu conditions to the succinimide derivative in 70 % yield (Scheme 3). Reduction of **17** to **18** followed by acid catalyzed cyclization led to the tricyclic lactam **19** in only 30% yield. All attempts to improve the yield of the cyclization were unsuccessful. The low yield of **19** is presumably related to proton loss from the *N*-acyliminium

ion followed by some alternate pathway. Clearly, the best results are obtained when a α-hydrogen is not present on the *N*-acyliminium ion precursor.

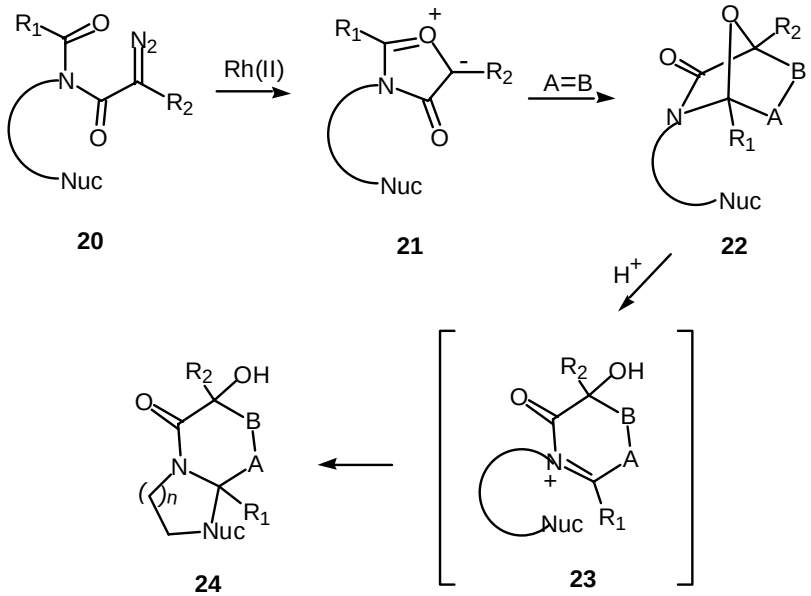


17 **18** **19**

Conditions: (a) $Li(Et)_3BH$, THF, -78 °C, HCl/H_2O; (b) *p*-TsOH, C_6H_6, Δ

Scheme 3

The next phase of our investigation involved an attempted cyclization of an electron rich pyridine ring with a *N*-acyliminium ion generated from an isomünchnone cycloadduct. Earlier studies in our laboratory showed that 1,3-oxazolium-4-oxides (isomünchnones) **21** can be generated by the rhodium(II)-catalyzed cyclization of a suitable diazo imide **20** (Scheme 4).[15] This type of mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [4+2]-cyclo-addition with suitable dipolarophiles.[16]



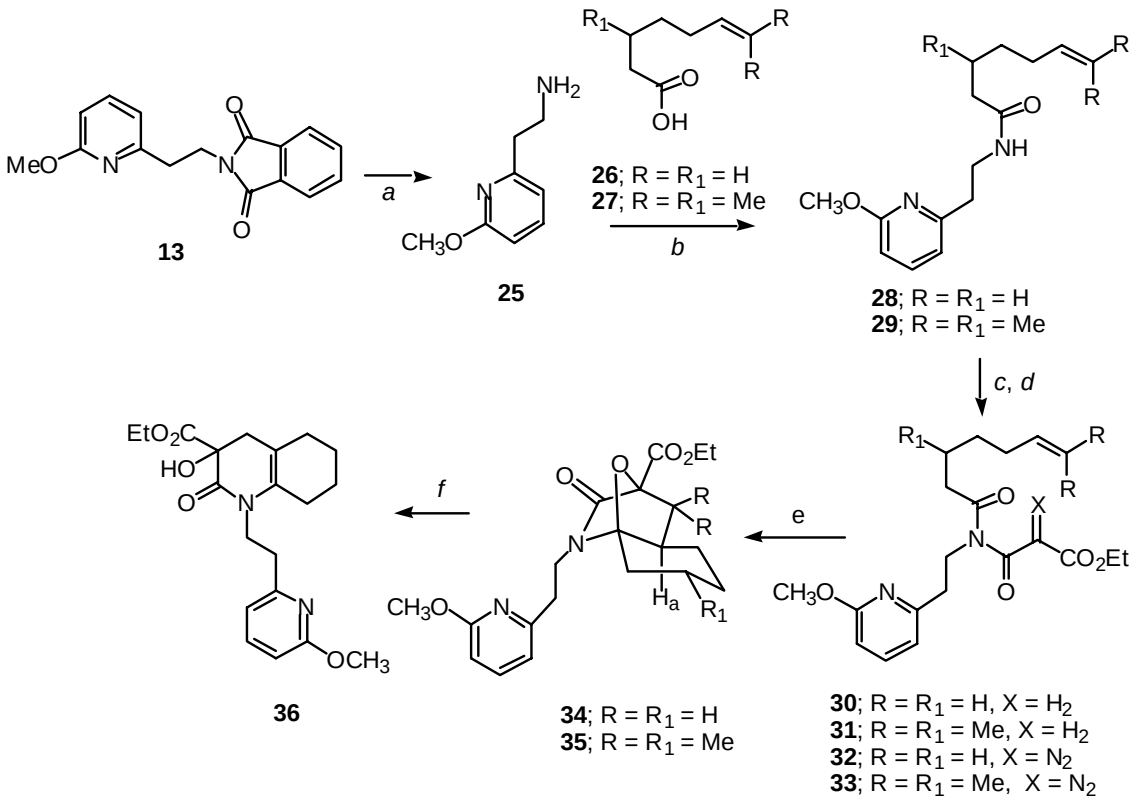
20 **21** **22** **24** **23**

Scheme 4

Formation of the isomünchnone cycloadduct proceeds by initial generation of a rhodium carbenoid species, followed by an intramole-cular cyclization onto the neighboring carbonyl oxygen to form the mesoionic ylide **21**.[16] The resultant isomünchnone may be trapped with electron rich or electron deficient dipolarophiles to give cycloadducts **22** in good yield.[17] These

uniquely functionalized cycloadducts contain a "*masked*" *N*-acyliminium ion which is generated by its treatment with a Lewis or protic acid.[18] By incorporating an internal nucleophile on the tether, annulation of the original cycloadduct **22** allows for the construction of a more complex nitrogen heterocyclic system.[19]

In order to test the above concept it was necessary to prepare a suitable isomünchnone cycloadduct (*i.e*. **34** or **35**) by first constructing the obligatory diazo imide. The synthesis began with commercially available hept-6-enoic acid (**26**) or citronellic (**27**) acid (Scheme 5). Treatment of these acids with 1,1-carbonyldiimidazole followed by reaction with 2-(6-methoxy-pyridin-2-yl)ethyl amine (**25**) afforded the corresponding amides **28** and **29** in good yield. Amine **25** was prepared by treating imide **13** with hydrazine hydrate in refluxing ethanol. The above amides were subjected to *N*-malonylacylation and the resulting imido esters **30** and **31** were then treated with mesyl azide in the presence of triethylamine to provide diazo imides **32** and **33**.[20]



Reagents: (a)NH_2NH_2, EtOH, 65 ^oC; (b) Im_2CO, CH_2Cl_2; (c) $ClCOCH_2CO_2Et$; (d) MsN_3, NEt_3 ; (e) $Rh_2(pfb)_4$, CH_2Cl_2, 65 ^oC; (f) *p*-TsOH, C_6H_6, Δ.

Scheme 5

Formation of the isomünchnone dipole proceeded smoothly when these diazo imides were

treated with rhodium(II) perfluorobutyrate in CH_2Cl_2 at 25 °C. After the initial generation of the rhodium carbenoid, intramolecular cyclization onto the substituted hex-7-enoic acyl carbonyl oxygen occurred to produce the mesoionic oxazolium ylide which underwent 1,3-dipolar cycloaddition across the pendant olefinic π-bond. In both cases, the reaction provided the expected cycloadducts **34** (92%) and **35** (82%) as single diastereomers resulting from *endo* cycloaddition with respect to the dipole. Assignment of the stereochemistry of the cycloadducts was based on a comparison of NMR signals with related substrates synthesized in this laboratory whose structures had been confirmed by X-ray crystallography.[18] In all cases, the *anti*-stereochemistry between the oxa-bridge and the angular proton (H_a) was obtained. Unfortunately, all of our attempts to trap the *N*-acyliminium ion derived from both cycloadducts **34** and **35** using the electron rich pyridine in a Pictet-Spengler type cyclization were unsuccessful. In the case of cycloadduct **34**, the 2-oxohexahydroquinolone **36** was isolated as the sole product in 92% yield.

In summary, we have shown that, in certain cases, the pyridine nucleus can be utilized as a suitable nucleophilic partner in cationic π-cyclizations. Although unactivated pyridine rings do not cyclize well, pyridines containing an electron donating substituent cyclize in good yield. The results presented herein demonstrate the potential of using such cyclizations for the synthesis of novel heterocycles and pyridine and pyridone containing natural products.

Experimental Section

General Procedures. Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

2-(6-Methoxy-pyridin-2-yl)ethanol (5). A solution containing 1.0 g (8.1 mmol) of 2-methoxy-5-methyl-pyridine[12] in 45 mL of dry THF at -78 °C was treated dropwise with 3.6 mL (9.0 mmol) of 2.5 M solution of *n*-BuLi in hexane. The mixture was stirred at -78 °C for 15 min and then 1.0 g (33 mmol) of paraformaldehyde was added and the resultant mixture was allowed to gradually warm to rt and stirred for an additional 5 h. The mixture was quenched with 10 mL of water and the aqueous phase was extracted with ether. The combined organic layers were washed with 10 mL of brine and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give 0.5 g (50%) of **5** as a colorless oil: IR (neat) 1599, 1578, 1465, and 1041 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.92 (t, 2H, *J* = 5.4 Hz), 3.89 (s, 3H), 3.97 (t, 2H, *J* = 5.4 Hz), 4.15 (brs, 1H), 6.61 (d, 1H, *J* = 8.1 Hz), 6.71 (d, 1H, *J* = 7.2 Hz), and 7.49 (dd, 1H, *J* =

8.1 and 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 38.5, 53.5, 62.2, 108.7, 115.9, 139.4, 158.4, and 163.7; HRMS Calcd for $C_8H_{11}NO_2$: 153.0790. Found: 153.0789.

2-[2-(6-Methoxy-pyridin-2-yl)ethyl]isoindole-1,3-dione (6). A solution of 1.0 g (6.0 mmol) of diethyl azodicarboxylate in 5 mL of THF was added to a solution of 0.9 g (6.0 mmol) of alcohol **5**, 0.9 g (6.0 mmol) of phthalimide, and 1.5 g (6.0 mmol) of triphenylphosphine in 50 mL THF at 0 °C. The mixture was allowed to warm to rt, stirred for 10 h and then concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 1.5 g (90%) of **6** as a white solid: mp 96-97 °C; IR (neat) 1769, 1705, 1581, 1393, and 1034 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.06 (t, 2H, *J* = 7.2 Hz), 3.76 (s, 3H), 4.09 (t, 2H, *J* = 7.2 Hz), 6.53 (d, 1H, *J* = 8.1 Hz), 6.70 (d, 1H, *J* = 7.2 Hz), 7.42 (dd, 1H, *J* = 7.5 and 7.5 Hz), 7.67-7.70 (m, 2H), and 7.79-7.82 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 36.1, 37.8, 53.2, 108.7, 115.9, 123.3, 132.4, 134.0, 139.0, 156.1, 163.8, and 168.4; Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; N, 9.92; H, 5.00. Found: C, 68.18; N, 9.88; H, 5.05.

3-Hydroxy-2-[2-(6-methoxy-pyridin-2-yl)ethyl]-2,3-dihydro-isoindol-1-one (7). To a solution of 0.2 g (0.7 mmol) of phthalimide **6** in 10 mL of THF at -78 °C was added 2.8 mL (3.0 mmol) of a 1.0 M lithium triethylborohydride solution. The reaction mixture was allowed to stir for 15 min and then quenched with 1 mL of 10% HCl, diluted with sodium carbonate, and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.18 g (90%) of **7** as a white solid: mp 98-99 °C; IR (neat) 1682, 1600, 1578, and 1280 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94-3.03 (m, 1H), 3.10-3.20 (m, 1H), 3.61 (s, 3H), 3.72-3.81 (m, 1H), 3.93-4.02 (m, 1H), 5.62 (s, 1H), 5.75 (s, 1H), 6.51 (d, 1H, *J* = 8.4 Hz), 6.75 (d, 1H, *J* = 7.2 Hz), and 7.36-7.57 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 36.1, 39.4, 53.5, 82.8, 108.5, 116.5, 123.2, 123.3, 129.6, 131.6, 132.2, 139.6, 144.5, 156.8, 163.7, and 167.5; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; N, 9.85; H, 5.67. Found: C, 67.47; N, 9.79; H, 5.74.

3-Ethoxy-2-[2-(6-methoxy-pyridin-2-yl)ethyl]-2,3-dihydro-isoindol-1-one (8). To a solution of 0.25 g (1.0 mmol) of phthalimide **6** in 25 mL of THF at -78 °C was added 3.5 mL (3.5 mmol) of a 1.0 M lithium triethylborohydride solution. The reaction mixture was allowed to stir for 15 min and then quenched with 5 mL of a 10% HCl/EtOH solution and stirred for an additional 2h. The reaction was neutralized with sodium carbonate and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.19 g (70 %) of **8** as a clear oil; IR (neat) 1704, 1600, 1578, 1467, and 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, 3H, *J* = 6.9 Hz), 2.96-3.19 (m, 4H), 3.70 (p, 1H, *J* = 7.0 Hz), 3.81 (s, 3H), 4.18 (p, 1H, *J* = 7.0 Hz), 5.74 (s, 1H), 6.54 (d, 1H, *J* = 8.1 Hz), 6.75 (d, 1H, *J* = 7.2 Hz), 7.41-7.57 (m, 4H), and 7.77-7.80 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.3, 36.2, 39.3, 53.3, 58.1, 86.5, 108.5, 115.9, 123.4, 123.5, 129.9, 132.0, 133.2, 139.1, 141.4, 156.8, 163.9, and 167.8; HRMS Calcd for $C_{18}H_{20}N_2O_3$: 312.1474. Found: 312.1474.

3-Methoxy-5,11*b*-dihydro-6*H*-4,6*a*-diazabenzo[*c*]fluoren-7-one (9). A solution of 0.1 g (0.4 mmol) of pyridine **7** in 15 mL of benzene was added 2 mg of *p*-toluenesulfonic acid. The

reaction was mixture was refluxed for 8 h and the solution was evaporated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.11 g (70%) of **9** as a white solid: mp 123-124 °C; IR (neat) 1681, 1601, 1575, 1482, and 1323 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.85-2.92 (m, 1H), 3.03-3.14 (m, 1H), 3.44 (ddd, 1H, *J* = 14.4, 9.9, and 4.8 Hz), 3.88 (s, 3H), 4.66 (ddd, 1H, *J* = 13.2, 6.5, and 2.4 Hz), 5.61 (s, 1H), 6.66 (d, 1H, *J* = 8.7 Hz), 7.46-7.51 (m, 1H), 7.56 (dt, 1H, *J* = 7.4 and 0.9 Hz), 7.76 (d, 1H, *J* = 7.5 Hz), and 7.85 (t, 2H, *J* = 9.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.6, 37.6, 53.7, 58.4, 109.3, 122.3, 123.1, 124.2, 128.8, 131.9, 132.7, 136.0, 144.5, 152.1, 162.9, and 168.0; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 70.17; N, 10.52; H, 5.30. Found: C, 70.85; N, 10.21; H, 5.49.

A solution of 0.17 g (0.6 mmol) of pyridine **8** in 15 mL of benzene was added 2 mg of *p*-toluenesulfonic acid. The reaction was mixture was refluxed for 8 h and the solution was evaporated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.14 g (55%) of 3-methoxy-5,11*b*-dihydro-6*H*-4,6*a*-diaza-benzo[*c*]fluoren-7-one (**9**) whose spectral properties were identical to a sample prepared by the cyclization of **7**.

2-(2-Methoxy-pyridin-4-yl)ethanol (12). A solution containing 1.0 g (8.0 mmol) of 2-methoxy-3-methyl-pyridine[21] in 40 mL of dry THF at -78 °C was treated dropwise with 3.6 mL (9.0 mmol) of 2.5 M solution of *n*-BuLi in hexane. The mixture was stirred at -78 °C for 15 min and then 1.0 g (33 mmol) of paraformaldehyde was added and the resultant mixture was allowed to gradually warm to rt and stirred for an additional 5h. The mixture was quenched with 10 mL of water and the aqueous phase was extracted with ether. The combined organic layers were washed with 10 mL of brine and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give 0.5 g (50%) of **12** as a colorless oil: IR (neat) 1613, 1560, and 1397 cm^{-1} H-NMR ($CDCl_3$, 300 MHz) δ 1.63 (brs, 1H), 2.81 (t, 2H, *J* = 6.6 Hz), 3.88 (t, 2H, *J* = 6.6 Hz), 3.92 (s, 3H), 6.62 (s, 1H), 6.76 (dd, 1H, *J* = 5.1 and 0.9 Hz), and 8.07 (d, 1H, *J* = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 38.5, 53.6, 62.5, 111.1, 118.0, 146.0, 151.1, and 164.6; HRMS Calcd for $C_8H_{11}NO_2$: 153.0790. Found: 155.0790.

2-[2-(2-Methoxy-pyridin-4-yl)ethyl]-isoindole-1,3-dione (13). A solution of 0.4 g (2.0 mmol) of diethyl azodicarboxylate in 5 mL of THF was added to a solution of 0.3 g (2.0 mmol) of alcohol **12**, 0.3 g (2.0 mmol) of phthalimide, and 0.5 g (2.0 mmol) of triphenylphosphine in 30 mL THF at 0 °C. The mixture was allowed to warm to rt, stirred for 10 h and then concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.44 g (75%) of **13** as a white solid: mp 147-148 °C; IR (neat) 1768, 1707, 1611, 1399, 1183, and 706 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94 (t, 2H, *J* = 7.6 Hz), 3.88 (s, 3H), 3.92 (t, 2H, *J* = 7.6 Hz), 6.61 (s, 1H), 6.77 (d, 1H, *J* = 4.8 Hz), 7.68-7.71 (m, 2H), 7.80-7.83 (m, 2H), and 8.05 (d, 1H, *J* = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.9, 38.2, 53.6, 111.0, 117.7, 123.5, 132.1, 134.2, 147.1, 149.8, 164.7, and 168.2; Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; N, 9.92; H, 5.00. Found: C, 68.17; N, 9.88; H, 4.96.

3-Hydroxy-2-[2-(2-methoxy-pyridin-4-yl)ethyl]-2,3-dihydro-isoindol-1-one (14). To a

solution of 0.8 g (3.0 mmol) of phthalimide **13** in 25 mL of THF at -78 °C was added 9 mL (9.0 mmol) of a 1.0 M lithium triethylborohydride solution. The reaction mixture was allowed to stir for 15 min and then quenched with 1 mL of 10% HCl, neutralized with sodium carbonate, and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.75 g (90%) of **14** as a white solid: mp 128-129 °C; IR (neat) 1699, 1673, 1615, 1450, and 1398 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.81-2.91 (m, 2H), 3.50-3.59 (m, 1H), 3.63-3.73 (m, 1H), 3.84 (s, 3H), 4.24 (d, 1H, *J* = 10.5 Hz), 5.60 (d, 1H, *J* = 10.0 Hz), 6.54 (s, 1H), 6.70 (d, 1H, *J* = 5.1 Hz), 7.38-7.43 (m, 1H), 7.50-7.60 (m, 3H), and 7.94 (d, 1H, *J* = 5.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 34.0, 39.7, 53.6, 82.3, 110.7, 117.7, 123.4, 123.6, 130.0, 131.5, 132.5, 144.1, 147.0, 150.8, 164.7, and 167.7; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; N, 9.85; H, 5.67. Found: C, 67.67; N, 9.85; H, 5.69.

3-Methoxy-5,11*b*-dihydro-6*H*-2,6*a*-diaza-benzo[*c*]fluoren-7-one (15). A solution of 0.2 g (0.7 mmol) of amide **14** in 15 mL of benzene was added 2 mg of *p*-toluenesulfonic acid. The reaction was mixture was refluxed for 8h and the solution was evaporated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.09 g (49 %) of **15** as a white solid: mp 168-169 °C; IR (neat) 1692, 1609, 1557, and 1401 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79-2.87 (m, 1H), 2.92, 3.03 (m, 1H), 3.42 (dd, 1H, *J* = 13.5, 9.2, and 5.1 Hz), 3.88 (s, 3H), 4.44 (dd, 1H, *J* = 13.1, 6.0, and 4.1 Hz), 5.64 (s, 1H), 6.56 (s, 1H), 7.49 (t, 1H, *J* = 7.4 Hz), 7.58-7.64 (m, 1H), 7.84 (t, 2H, *J* = 7.8 Hz), and 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.2, 37.5, 53.7, 57.3, 110.4, 123.6, 124.1, 124.2, 128.9, 132.0, 132.6, 143.8, 144.2, 146.8, 163.5, and 168.0; Anal. Calcd. $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found; C, 71.88; H, 5.37: N, 10.47.

The minor product isolated contained 0.04 g (19%) of 1-methoxy-5,11*b*-dihydro-6*H*-2,6*a*-diaza-benzo[*c*]fluoren-7-one (**16**) as a white solid: mp 93-94 °C; IR (neat) 1695, 1595, 1569, 1399, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62-2.70 (m, 1H), 2.85-2.96 (m, 1H), 3.12 (dt, 1H, *J* = 12.5 and 3.3 Hz), 4.16 (s, 3H), 4.69-4.77 (m, 1H), 5.92 (s, 1H), 6.68 (d, 1H, *J* = 5.1 Hz), 7.44-7.57 (m, 2H), 7.86 (d, 1H, *J* = 7.4 Hz), 7.95 (d, 1H, *J* = 5.1 Hz), and 8.13 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.4, 38.1, 53.5, 57.7, 117.7, 118.5, 123.7, 125.5, 128.8, 132.2, 132.7, 144.8, 145.6, 147.0, 161.7, and 169.5; Anal. Calcd. $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found; C, 71.88; H, 5.37: N, 10.47.

1-[2-(6-Methyoxy-pyridin-2-yl)ethyl]pyrrolidine-2,5-dione (17). A solution of 0.3 g (1.6 mmol) of diethyl azodicarboxylate in 5 mL of THF was added to a solution of 0.3 g (1.6 mmol) of alcohol **5**, 0.2 g (1.6 mmol) of phthalimide, and 0.4 g (1.6 mmol) of triphenylphosphine in 50 mL THF at 0 °C. The mixture was allowed to warm to rt, stirred for 10h and then concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.3 g (70%) of **17** as a clear oil; IR (neat) 1775, 1704, 1601, 1581, and 1465 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.64 (s, 4H), 2.94 (t, 2H, *J* = 7.8 Hz), 3.90 (t, 2H, *J* = 7.8 Hz), 3.89 (s, 3H), 6.54 (d, 1H, *J* = 8.4 Hz), 6.68 (d, 1H, *J* = 7.2 Hz), and 7.43 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.3, 35.2, 38.4, 53.4, 108.6, 115.8,

138.9, 155.9, 163.8, and 177.2; Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.51; N, 11.96; H, 6.03. Found: C, 61.44; N, 11.82; H, 5.91.

5-Hydroxy-1-[2-(6-methoxy-pyridin-2-yl)ethyl]pyrrolidin-2-one (18). To a solution of 0.8 g (3.0 mmol) of imide **17** in 100 mL of THF at -78 °C was added 13 mL (13 mmol) of a 1.0 M lithium triethylborohydride solution. The reaction mixture was allowed to stir for 15 min and then quenched with 5 mL of 10% HCl, neutralized with sodium carbonate, and extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.5g (70%) of **18** as a white solid: mp 79-80 °C; IR (neat) 1668, 1599, 1579, and 1466 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.86-1.95 (m, 1H), 2.16-2.29 (m, 2H), 2.45-2.56 (m, 1H), 2.93-3.02 (m, 1H), 3.04-3.12 (m, 1H), 3.52-3.61 (m, 1H), 3.90 (s, 3H), 3.92-3.96 (m, 1H), 5.19 (d, 1H, *J* = 4.8 Hz), 5.64 (brs, 1H), 6.60 (d, 1H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 7.2 Hz), and 7.53 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.5, 29.1, 36.2, 40.2, 54.1, 84.4, 108.2, 116.8, 140.0, 157.4, 164.1, and 175.0; Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; N, 11.86; H, 6.83. Found: C, 60.95; N, 11.82; H, 6.79.

3-Methoxy-5,9,10,10*a*-tetrahydro-6*H*-pyrrolo[2,1-*f*][1,6]naphthyridin-8-one (19). A solution of 0.1 g (0.4 mmol) of pyridine **18** in 25 mL of benzene was added 2 mg of *p*-toluenesulfonic acid. The reaction was mixture was refluxed for 12h and the solution was evaporated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.01 g (20%) of **19** as a clear oil; IR (neat) 1731, 1695, 1669, and 1597 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.68-1.85 (m, 2H), 2.43-2.66 (m, 2H), 2.79-2.96 (m, 2H), 2.99-3.09 (m, 1H), 3.70 (s, 3H), 4.38-4.44 (m, 1H), 4.70-4.75 (m, 1H), 6.63 (d, 1H, *J* = 8.4 Hz), and 7.30 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.6, 31.7, 31.9, 36.8, 53.6, 56.1, 109.5, 125.4, 135.7, 151.1, 162.7, and 173.3; Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.02; N, 12.84; H, 6.47. Found: C, 65.87; N, 12.73; H, 6.35.

2-(6-Methoxy-pyridin-2-yl)ethylamine (25). To a solution of imide **13** in 35 mL of absolute ethanol was added 0.4 g (13 mmol) of hydrazine hydrate and the solution was refluxed at 65 °C for 2 h. The precipitate was filtered and washed with 10 mL of ethanol and the solution was concentrated to provide 0.9 g (93%) of **25** as a clear oil: IR (neat) 1599, 1578, 1463, and 1291 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.70 (brs, 2H), 2.82 (t, 2H, *J* = 6.4 Hz), 3.10 (t, 2H, *J* = 6.4 Hz), 3.91 (s, 3H), 6.56 (d, 1H, *J* = 8.2 Hz), 6.72 (d, 1H, *J* = 7.2 Hz), and 7.47 (dd, 1H, *J* = 8.2 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 41.5, 41.7, 53.3, 107.9, 116.0, 138.9, 158.0, and 163.9; HRMS Calcd for $C_8H_{12}N_2O$: 152.0950. Found: 152.0948.

Hept-6-enoic acid [2-(6-methoxy-pyridin-2-yl)ethyl]amide (28). To a solution containing 0.8 g (7.0 mmol) of hept-6-enoic acid (**26**) in 100 mL of CH_2Cl_2 was added 1.0 g (7.0 mmol) of 1,1'-carbonyldiimidazole and the solution was stirred at rt for 2 h. To this mixture was added 1.0 g (6.6 mmol) of 5-methoxy-2-ethylamine-pyridine (**25**) at 0 °C, and the solution was allowed to warm to rt, stirred for 8 h, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.5 g (87%) of **28** as a colorless oil; IR (neat) 1644, 1600, 1579, and 1554 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.36 (p, 2H, *J* = 7.8 Hz), 1.60 (p, 2H,

J = 7.8 Hz), 2.01 (q, 2H, *J* = 7.2 Hz), 2.12 (t, 2H, *J* = 7.8 Hz), 2.85 (t, 2H, *J* = 6.3 Hz), 3.61 (q, 2H, *J* = 6.3 Hz), 3.89 (s, 3H), 4.89-4.98 (m, 2H), 5.67-5.81 (m, 1H), 6.48 (brs, 1H), 6.57 (d, 1H, *J* = 8.4 Hz), 6.68 (d, 1H, *J* = 7.2 Hz), and 7.46 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.4, 28.6, 33.6, 36.7, 36.9, 38.7, 53.3, 108.5, 114.8, 116.1, 138.6, 139.3, 157.5, 163.8, and 172.9; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.66; N, 10.68; H, 8.46. Found: C, 68.58; N, 10.73; H, 8.27.

3,7-Dimethyl-oct-6-enoic acid [2-(6-methoxy-pyridin-2-yl)ethyl]amide (29). To a solution containing 0.13 g (0.7 mmol) of citronellic acid (**27**) in 20 mL of CH_2Cl_2 was added 0.13 g (0.8 mmol) of 1,1'-carbonyldiimidazole and the solution was stirred at rt for 2 h. To this mixture was added 0.11 g (0.7 mmol) of 2-(6-methoxy-pyridin-2-yl)-ethylamine (**25**) at 0 °C, and the solution was allowed to warm to rt, stirred for 10 h, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.13 g (60%) of **29** as a colorless oil; IR (neat) 1643, 1598, 1579, and 1466 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, 3H, *J* = 8.4 Hz), 1.11-1.21 (m, 1H), 1.25-1.39 (m, 1H), 1.57 (s, 3H), 1.66 (s, 3H), 1.85-2.01 (m, 4H), 2.16 (m, 1H), 2.89 (t, 2H, *J* = 6.3 Hz), 3.66 (q, 2H, *J* = 8.0 Hz), 3.92 (s, 3H), 5.06 (t, 1H, *J* = 6.9 Hz), 6.39 (brs, 1H), 6.60 (d, 1H, *J* = 8.4 Hz), 6.72 (d, 1H, *J* = 7.2 Hz), and 7.49 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.9, 19.7, 25.7, 25.9, 30.7, 36.7, 37.2, 38.8, 45.1, 53.5, 108.6, 116.2, 124.6, 131.7, 139.4, 157.6, 163.9, and 172.5; HRMS Calcd for $C_{18}H_{28}N_2O_2$: 304.2151. Found: 304.2156.

***N*-Hept-6-enoyl-*N*-[2-(6-methoxy-pyridin-2-yl)ethyl]malonamic acid ethyl ester (30).** *N*-Malonylacylation was carried out on amide **28** in the normal manner to give 1.6 g (75%) of **30** as a colorless oil; IR (neat) 1741, 1698, 1598, and 1415 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, *J* = 7.2 Hz), 1.33 (p, 2H, *J* = 7.8 Hz), 1.56 (p, 2H, *J* = 7.5 Hz), 2.00 (q, 2H, *J* = 7.2 Hz), 2.51 (t, 2H, *J* = 7.5 Hz), 2.93 (t, 2H, *J* = 7.2 Hz), 3.79 (s, 2H), 3.99 (s, 3H), 4.05 (t, 2H, *J* = 7.8 Hz), 4.14 (q, 2H, *J* = 7.2 Hz), 4.89-4.99 (m, 2H), 5.67-5.80 (m, 1H), 6.55 (d, 1H, *J* = 8.1 Hz), 6.69 (d, 1H, *J* = 7.2 Hz), and 7.44 (dd, 1H, *J* = 8.1 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.2, 24.1, 28.3, 33.5, 36.5, 36.9, 44.3, 46.6, 53.2, 61.3, 108.8, 114.9, 116.3, 138.3, 139.2, 155.8, 163.9, 167.5, 168.9, and 176.0; Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.80; N, 7.44; H, 7.50. Found: C, 63.71; N, 7.38; H, 7.29.

***N*-(3,7-Dimethyl-oct-6-enoyl)-*N*-[2-(6-methoxy-pyridin-2-ylethyl]malonamic acid ethyl ester (31).** *N*-Malonylacylation was carried out on amide **29** in the normal manner to give 0.13 g (73%) of **31** as a colorless oil; IR (neat) 1741, 1696, 1599, and 1579 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3H, *J* = 6.6 Hz), 1.27 (t, 3H, *J* = 6.9 Hz), 1.20-1.55 (m, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.91-2.06 (m, 3H), 2.30-2.40 (m, 1H), 2.52 (dd, 1H, *J* = 16.2 and 5.4 Hz), 2.97 (t, 2H, *J* = 7.2 Hz), 3.84 (s, 2H), 3.91 (s, 3H), 4.06-4.12 (m, 1H), 4.19 (q, 2H, *J* = 6.9 Hz), 5.04-5.08 (m, 1H), 6.60 (d, 1H, *J* = 8.1 Hz), 6.74 (d, 1H, *J* = 7.2 Hz), and 7.48 (dd, 1H, *J* = 8.1 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 17.9, 19.8, 25.7, 25.9, 29.5, 37.0, 37.1, 44.0, 44.5, 46.7, 53.4, 61.4, 108.9, 116.4, 124.3, 131.8, 139.3, 155.8, 164.1, 167.7, 169.2, and 175.8; Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 65.99; N, 6.70; H, 8.19. Found: C, 65.76; N, 6.88; H, 8.29.

2-Diazo-*N*-hept-6-enoyl-*N*-[2-(6-methoxy-pyridin-2-yl)ethyl]malonamic acid ethyl ester

(32). Imide **30** was subjected to the standard diazo transfer conditions to give 1.4 g (95%) of **32** as a yellow oil: IR (neat) 2138, 1721, 1701, 1652, and 1577 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, *J* = 7.2 Hz), 1.37 (p, 2H, *J* = 7.8 Hz), 1.61 (p, 2H, *J* = 7.8 Hz), 2.02 (q, 2H, *J* = 7.2 Hz), 2.49 (t, 2H, *J* = 7.8 Hz), 2.98 (t, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 4.04 (t, 2H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 4.89-5.00 (m, 2H), 5.67-5.82 (m, 1H), 6.54 (d, 1H, *J* = 8.4 Hz), 6.68 (d, 1H, *J* = 7.2 Hz), and 7.44 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.4, 24.5, 28.5, 33.6, 35.8, 37.5, 46.2, 53.3, 61.9, 72.6, 108.5, 114.8, 116.5, 138.6, 139.1, 156.1, 160.6, 163.9, 166.6, and 175.5.

2-Diazo-*N*-(3,7-dimethyl-oct-6-eno-yl)-*N*-[2-(6-methoxy-pyridin-2-yl-ethyl]malo-namic acid ethyl ester (33). Imide **31** was subjected to the standard diazo transfer conditions to give 0.12 g (90%) of **33** as a yellow oil: IR (neat) 2137, 1722, 1701, and 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 3H, *J* = 6.6 Hz), 1.14-1.23 (m, 1H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.30-1.40 (m, 1H), 1.58 (s, 3H), 1.68 (s, 3H), 1.91-2.06 (m, 3H), 2.32 (dd, 1H, *J* = 15.8 and 7.8 Hz), 2.52 (dd, 1H, *J* = 15.8 and 5.7 Hz), 3.01 (t, 2H, *J* = 7.2 Hz), 3.90 (s, 3H), 4.06 (t, 2H, *J* = 7.2 Hz), 4.23 (q, 2H, *J* = 7.2 Hz), 5.07 (t, 1H, *J* = 9.0 Hz), 6.56 (d, 1H, *J* = 8.4 Hz), 6.71 (d, 1H, *J* = 7.2 Hz), and 7.46 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5, 17.9, 19.9, 25.7, 25.9, 30.1, 37.1, 37.5, 43.3, 46.3, 53.4, 62.0, 72.8, 108.6, 116.6, 124.5, 131.7, 139.2, 156.2, 160.6, 163.9, 166.9, and 174.9.

10-[2-(6-Methoxy-pyridin-2-yl)ethyl]-9-oxo-11-oxa-10-aza-tricyclo[6.2.1.0^{1,6}]un-decane-8-carboxylic acid ethyl ester (34). A solution containing 1.1 g (3.0 mmol) of diazoimide **32** in 50 mL of CH_2Cl_2 at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 1.0 g (92%) of **34** as a colorless oil; IR (neat) 1750, 1722, 1598, and 1464 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.07-1.17 (m, 2H), 1.32 (t, 3H, *J* = 6.9 Hz), 1.59-1.75 (m, 5H), 1.86-2.01 (m, 2H), 2.08-2.17 (m, 2H), 2.79-2.99 (m, 2H), 3.47-3.57 (m, 1H), 3.61-3.70 (m, 1H), 3.89 (s, 3H), 4.28-4.38 (m, 2H), 6.55 (d, 1H, *J* = 8.1 Hz), 6.70 (d, 1H, *J* = 7.2 Hz), and 7.45 (dd, 1H, *J* = 8.1 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 Hz) δ 14.4, 21.6, 24.6, 27.4, 32.7, 37.0, 37.2, 39.5, 42.1, 53.4, 62.2, 86.0, 96.9, 108.5, 116.2, 139.2, 156.2, 163.9, 166.3, and 171.4; Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.16; H, 7.00; N, 7.48. Found: C, 64.00; H, 6.91; N, 7.37.

10-[2-(6-Methoxy-pyridin-2-yl)ethyl]-3,7,7-trimethyl-9-oxo-11-oxa-10-aza-tricyclo-[6.2.1.0^{1,6}]undecane-8-carboxylic acid ethyl ester (35). A solution containing 0.05 g (0.1 mmol) of diazoimide **33** in 15 mL of CH_2Cl_2 at rt was treated with 2 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 0.04 g (82%) of **35** as a colorless oil; IR (neat) 1744, 1723, 1573, and 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.72-0.84 (m, 1H), 0.88 (d, 3H, *J* = 6.3 Hz), 1.00 (s, 3H), 1.15 (s, 3H), 1.22-1.29 (m, 2H), 1.34 (t, 3H, *J* = 7.2 Hz), 1.39-1.54 (m, 1H), 1.58-1.60 (m, 3H), 1.87-1.91 (m, 1H), 2.86-2.98 (m, 2H), 3.56-3.73 (m, 2H), 3.92 (s, 3H), 4.31-4.41 (m, 2H), 6.57 (d, 1H, *J* = 8.4 Hz), 6.72 (d, 1H, *J* = 7.2 Hz), and 7.46 (dd, 1H, *J* = 8.4 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$,

75 MHz) δ 14.6, 21.0, 22.2, 26.3, 26.5, 28.3, 33.0, 36.3, 37.5, 39.7, 44.7, 51.4, 53.5, 61.8, 92.0, 96.2, 108.5, 116.6, 139.2, 156.3, 163.9, 165.5, and 169.8; Anal. Calcd for $C_{23}H_{32}N_2O_5$: C, 66.31; N, 6.73; H, 7.75. Found: C, 66.25; N, 6.77; H, 7.66.

3-Hydroxy-1-[2-(6-methoxy-pyridin-2-yl)ethyl]-oxo-1,2,3,4,5,6,7,8-octahydroquino-line-3-carboxylic acid ethyl ester (36). A solution of 0.15 g (0.4 mmol) of cycloadduct **34** in 25 mL of benzene was added 2 mg of *p*-toluenesulfonic acid. The reaction was mixture was refluxed for 12h and the solution was evaporated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.14 g (93%) of **36** as a clear oil; IR (neat) 1738, 1667, 1598, and 1465 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, *J* = 7.2 Hz), 1.34-1.43 (m, 2H), 1.60-1.65 (m, 1H), 1.72-1.77 (m, 1H), 1.96-2.00 (m, 3H), 2.16-2.22 (m, 1H), 2.29-2.33 (m, 1H), 2.57 (d, 1H, *J* = 15.6 Hz), 2.83-2.99 (m, 2H), 3.75-3.82 (m, 1H), 3.91 (s, 3H), 4.14-4.22 (m, 2H), 4.59 (brs, 1H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.70 (d, 1H, *J* = 7.2 Hz), and 7.44 (dd, 1H, *J* = 8.0 and 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.3, 22.1, 22.8, 25.1, 29.2, 35.0, 36.6, 41.9, 53.4, 61.8, 73.7, 108.4, 114.6, 116.1, 131.3, 138.9, 156.3, 163.9, 168.6, and 170.1; Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.14; N, 7.48; H, 7.00. Found: C, 64.02; N, 7.53; H, 7.09.

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