Tandem Dipolar Cycloaddition−Mannich Cyclization as an Approach to Tricyclic Nitrogen Heterocycles†

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A series of 2-diazo-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-hept-6-enoylmalonamides were prepared and treated with a catalytic amount of rhodium(II) perfluorobutyrate. The resultant carbenoids undergo facile cyclization onto the neighboring amide carbonyl oxygen atom to generate isomünchnone-type intermediates. Subsequent 1,3-dipolar cycloaddition across the pendant olefin affords intramolecular cycloadducts in high yield. Exposure of these cycloadducts to boron trifluoride etherate results in a Lewis acid-induced ring opening to generate *N*-acyliminium ions which then undergo Mannich cyclization onto the neighboring π-framework attached to the amide nitrogen atom. The *cis* stereochemistry of the resulting A/B ring fusion is analogous to similar erythrinane products obtained *via* a Mondon-enamide-type cyclization. The stereochemical assignment of the final cyclized products was determined by X-ray crystallography. Molecular mechanics calculations show that the ground state energy of the *cis*-fused diastereomer is 4.6 kcal lower than that of the *trans* diastereomer, and presumably some of this thermodynamic energy difference is reflected in the transition state for cyclization. In certain cases, proton loss from the initially formed *N*-acyliminium ion occurs prior to cyclization to give acyl enamides which subsequently cyclize producing epimeric products.

Introduction

Tandem or cascade processes belong to a growing family of reactions which allow the regio- and stereocontrolled formation of several carbon−carbon bonds and/or ring systems in a single operation.[1−6] Important contributions to this area have been realized utilizing a combination of cationic,[7] anionic,[8] radical,[9] carbenoid,[10] and transition metal-catalyzed[11] processes. In recent years, consecutive pericyclic reactions[12] involving at least one cycloaddition have also been utilized for the synthesis of complex polycyclic ring systems.[13] In the realm of synthesis, in which a premium is put on the rapid construction of polyfunctional, highly bridged carbon and heteroatom networks, the 1,3-dipolar cycloaddition reaction has now emerged as a prominent synthetic method.[14−17] Carbon−carbon bond-forming reactions involving *N*-acyliminium ions also play an extremely

† This paper is dedicated to Rolf Huisgen on the occasion of his 75th birthday.

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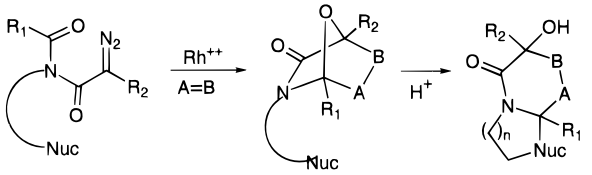
Scheme 1



1 **2** **3**

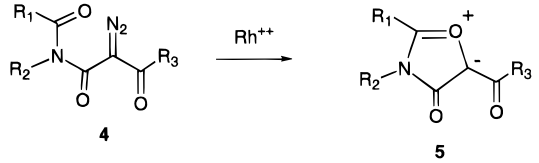
important role in the synthesis of nitrogen heterocycles.[18−20] The elaboration of ring-fused polyheterocycles, based on a sequential dipolar cycloaddition−*N*-acyliminium ion cyclization process,[21] would seem to offer a unique opportunity for a rapid stereocontrolled synthesis of a wide range of highly functionalized azapolycyclic natural products. With this aim in mind, we have investigated some of the general principles underlying the synthetic design presented in Scheme 1.

Our earlier studies of the 1,3-dipolar cycloaddition reactions of isomünchnones[22] derived from α-diazo imides **1** provided us with a uniquely functionalized cycloadduct **2** containing a "masked" *N*-acyliminium ion. By incorporating an internal nucleophile on the tether, annulation of the original dipolar cycloadduct **2** would allow for the construction of more complex nitrogen heterocyclic systems, particularly B-ring homologues of the erythrinane family of alkaloids.[23] By starting from simple acyclic diazo imides **1**, we have established a tandem carbenoid cyclization−dipolar cycloaddition−cationic π-cyclization protocol as a method for the construction of complex nitrogen polyheterocycles of type **3**. We are unaware of any previous examples in which the 1,3-dipolar cycloaddition and *N*-acyliminium ion cyclization are coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which, to our knowledge, is unprecedented. Herein the synthetic and mechanistic work are presented in full.

Results and Discussion

The synthesis of 1,3-oxazolium-4-oxides (isomünchnones) **5** (Scheme 2) is easily accomplished by the rhodium(II)-catalyzed cyclization of a suitable diazo imide

Scheme 2



4 **5**

4.[24] This type of mesoionic oxazolium ylide corresponds to the cyclic equivalent of a carbonyl ylide and readily undergoes 1,3-dipolar cycloaddition with suitable dipolarophiles.[25−28] Construction of the prerequisite diazo imides necessary for dipole generation was accomplished by the transformation of the corresponding carboxylic acids to their respective amides. Conversion to the diazo imides was straightforward using established malonylacylation[29] and diazotization procedures.[30] Formation of the isomünchnone ring proceeds by initial generation of a rhodium carbenoid species, followed by an intramolecular cyclization onto the neighboring carbonyl oxygen to form the dipole.[31] The resultant isomünchnone may be trapped with electron rich or electron deficient dipolarophiles to give the cycloadducts in high yield.[32]

Several years ago our laboratory became interested in using the intramolecular cycloaddition of isomünchnones for the construction of a variety of alkaloid systems.[22] Intramolecular dipolar cycloadditions have been particularly useful in natural product synthesis, as this reaction results in the formation of an additional ring and exhibits increased reactivity due to entropic factors.[33−35] The regiochemistry of the process is complicated by a complex interplay of factors such as the nature of the 1,3-dipole, alkene polarity, ring strain, and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between bridged and fused modes of cycloaddition.

We began our investigations of the sequential cycloaddition−Mannich cyclization protocol by first examining the Rh(II)-catalyzed reaction of diazo imide **6**. Treatment of **6** with a catalytic quantity of rhodium(II) perfluorobutyrate (Rh_2pfb_4) in CH_2Cl_2 at 25 °C provided cycloadduct **7** in 98% isolated yield. The assignment of the stereochemistry of **7** was based on the comparison of NMR signals of related substrates.[22] The formation of the *endo*-cycloadduct with respect to the carbonyl ylide dipole is in full accord with molecular mechanics calculations which show a large ground state energy difference between the two diastereomers. Exposure of **7** to $BF_3{\cdot}OEt_2$

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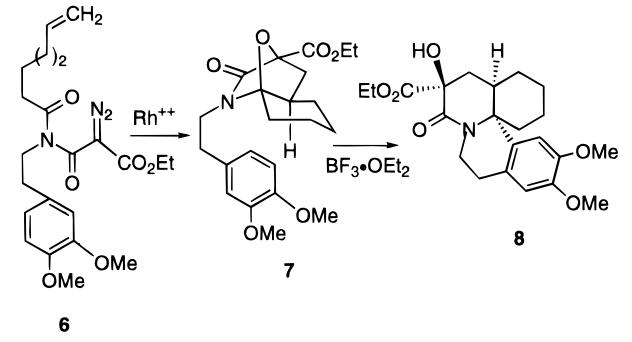
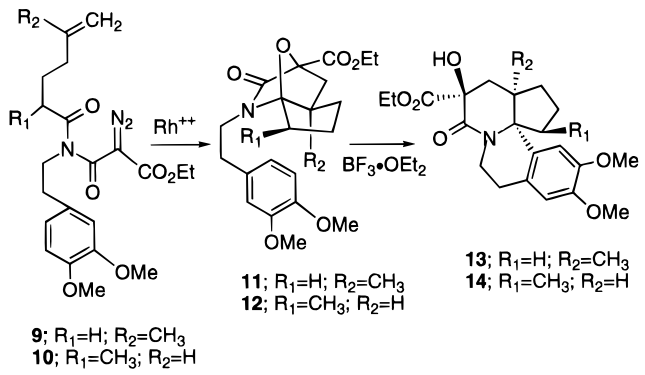


(2 equiv in CH_2Cl_2 at 0 °C) gave the cyclized product **8** (91%), isolated as a single diastereomer. The structural assignment was, in part, based, on the appearance of two aromatic CH protons observed as two individual singlets, each integrating for one proton. The proposed *cis* stereochemistry of the A/B ring junction for **8** was assigned by analogy to similar erythrinane products obtained *via* a Mondon-enamide-type cyclization.[36−38] The structure of **8** was unequivocally established by a single-crystal X-ray analysis.[39]

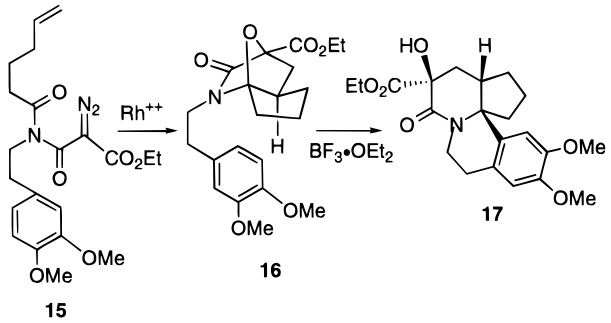
The formation of **8** is perfectly consistent with the sequence of events proposed in Scheme 1. The critical step in this transformation involves the Lewis acid-assisted generation of an *N*-acyliminium ion. In the initial studies, *p*-TsOH was utilized as the Lewis acid promoter for the unmasking of the *N*-acyliminium ion. Subsequent studies demonstrated that the cyclization reactions were capricious with variable yields of product being obtained. In order to overcome these difficulties, a survey of diverse Lewis acids was carried out. Among the many Lewis acids employed, $BF_3{\cdot}OEt_2$ routinely gave the highest yield of the cyclized product **8**.

The versatility of *N*-acyliminium ions for the synthesis of a wide variety of nitrogenous materials underscores the need to find new methods for their preparation.[18−20] *N*-Acyliminium ions are traditionally generated from the N-acylation of imines,[40] N-protonation[41] and oxidation[42] of amides, electrophilic additions to enamides,[43] and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[18] These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall α-amido alkylation. To further illustrate the scope and utility of *N*-acyliminium ion formation from the ring opening of an isomünchnone cycloadduct, we examined the tandem cycloaddition−cyclization reaction of α-diazo imides **9** and **10**. The Rh(II)-catalyzed reaction proceeded uneventfully to provide the expected isomünchnone cycloadducts **11** and **12** in 95% and 90% yield, respectively. As in the case of cycloadduct **7**, the $BF_3{\cdot}OEt_2$ induced cyclization afforded products **13** (95%) and **14** (85%) as



single diastereomers whose structures were unequivocally established by a single-crystal X-ray analysis.[39] It is noteworthy that in all three examples (*i.e.*, **8**, **13**, and **14**), the *anti* stereochemical relationship is still maintained between the hydroxyl stereocenter (from the oxygen bridge) and the bridgehead proton (R_2 = H) or methyl (R_2 = CH_3) group.

Interestingly, when the dipolar cycloadduct **16** derived from the unsubstituted alkenyl diazo imide **15** was exposed to $BF_3{\cdot}OEt_2$, the cyclized product **17** (90%) was identified as the all *syn*-tetracyclic lactam by a single-crystal X-ray analysis.[39] Thus, in contrast to the other three systems, the ring junction proton of **17** is *syn* to the newly formed hydroxyl group. We assume that the



intermediate *N*-acyliminium ions formed from the Lewis acid-assisted ring opening of the isomünchnone cycloadducts undergo rapid proton loss to produce tetrasubstituted enamides. Indeed, upon treatment of the isomünchnone cycloadduct **18** (containing one less methylene group on the nitrogen tether) with $BF_3{\cdot}OEt_2$, a 4:1 mixture of enamides **19** and **20** was formed in essentially quantitative yield. In this case, proton loss from the initially formed *N*-acyliminium ion occurs in preference to cyclization. We attribute this difference to the high strain associated with cyclization of **18** leading to a five membered ring.

In the case of **16**, this process is not operative as witnessed by the formation of compound **17**. Loss of the bridgehead proton H_A in **21** (dihedral angle 90° with respect to the *N*-acyliminium ion π-bond) is fast relative to π-cyclization. Intramolecular axial reprotonation of enamide **23** from the β-face generates the diastereomeric iminium ion **24** which then undergoes intramolecular cationic π-cyclization from the least sterically congested face to give the observed *all-syn* isomer **17**. Molecular mechanics calculations show that the ground state energy

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(39) The authors have deposited coordinates for structures **8**, **13**, **14**, and **17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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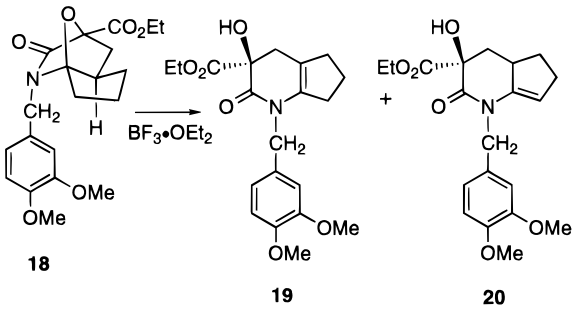
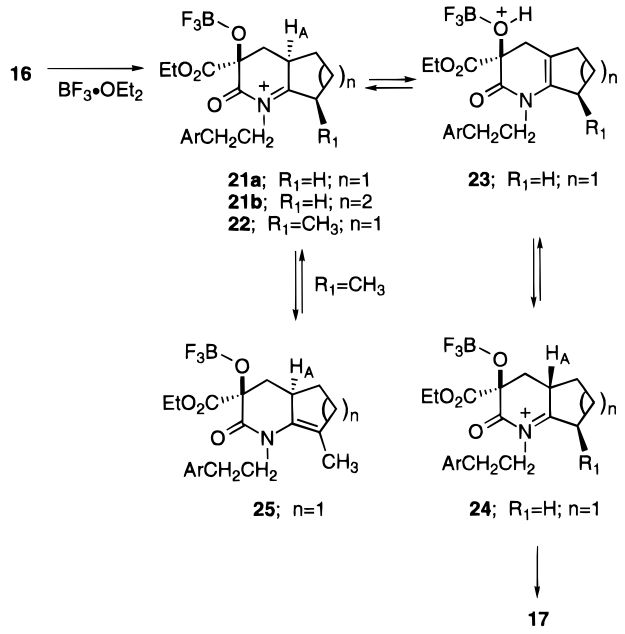


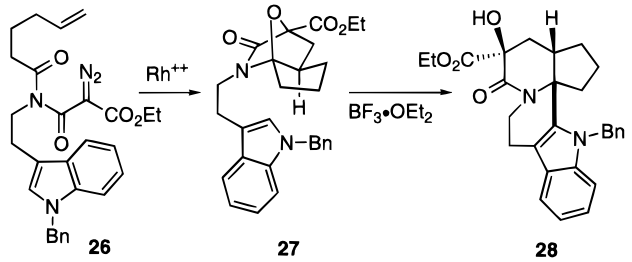
of the *cis*-fused diastereomer is 4.6 kcal lower than that of the *trans* diastereomer, and presumably some of this thermodynamic energy difference is reflected in the transition state for cyclization. The additional methyl group present in the related 6,5-fused cycloadduct **22** promotes loss of the proton adjacent to it, and this results in the formation of enamide **25**. Stereoselective reprotonation from the least congested α-face regenerates **22**, which is then trapped intramolecularly by the aromatic nucleus. Cyclization always occurs from the least hindered side of the molecule, as has already been established by Mondon and co-workers.[36] Cationic cyclizations



of this type are known to be governed by steric control.[44] Cycloadduct **11** does not possess a bridgehead proton, and therefore deprotonation can only occur from one direction. We believe that the initially formed iminium ion derived from **7** (*i.e.*, **21b**, $n = 2$) undergoes fast π-cyclization prior to proton loss. In this case, the deprotonation step is significantly slower than in the 6,5-system due to the larger dihedral angle (113°) between proton H_A and the π-system of the N-acyliminium ion. As before, the stereochemical outcome in **8** is the result of a stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion from the least hindered side.

So that a cross section of additional information could be obtained in regard to the tandem carbenoid cyclization−cycloaddition−cationic π-cyclization protocol, a series of α-diazo imides was needed representing a variety of different π-bonds. Compounds ranging from substituted aromatics to indoles to simple alkenyl tethered systems were considered. Ultimately, substrates **26**, **29**, **33**, and **36** were studied as they contain a range of synthetically interesting and easily attainable functionality. The synthesis of indoles bearing substituents at the 2- and 3-positions has been of interest for many years due to the large number of biologically active natural products having this substitution pattern.[45] Consequently, we decided to investigate the Rh(II)-catalyzed behavior of α-diazo imide **26** where an indolyl tether has been placed on the amide nitrogen as a method for generating highly functionalized indoles. Treatment of diazo imide **26** with $Rh_2(pfb)_4$ gave cycloadduct **27** (98%) which was readily converted into **28** in 60% isolated yield as a single diastereomer. The stereochemical assignment was based on analogy to the tetracyclic system **17**.

This sequential process provides a unique entry into 2,3-substituted indolo ring systems that would be extremely difficult to prepare by other methods. Two



additional systems involving *o*-allyl-substituted benzamides further illustrate the scope and variety of the π-systems that may be employed in this tandem process are outlined below. The Rh(II)-catalyzed reaction of diazo imide **29** gave rise to a 4:1 mixture of cycloadduct **30** and the conjugated indenyl enamide **31** in a combined yield of 75%. Treatment of either **30** or **31** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C afforded a 1:1 diastereomeric mixture of tetracyclic lactams **32** in 84% yield. The formation of a mixture of diastereomers is best understood in terms of the initial conversion of **30** to **31**. Nonstereoselective protonation of the enamide π-bond followed by a Pictet−Spengler cyclization then affords **32** as a mixture of diastereomers.

The reactions of iminium ions with tethered alkenes are among the most important methods for preparing N-heterocyclic compounds.[46] An antiperiplanar orientation of the developing nonbonded electron pair on nitrogen and the entering nucleophile is preferred, as are chair topologies in cyclizations that form piperidine rings.[46] Recent studies of this process have focused on the development of new procedures for initiating these cyclizations and for controlling the regiochemistry and product functionality of the cationic cyclization step.[47−49] Owing principally to efforts by the Overman group,[47] a variety of useful procedures have evolved for hydropyridine synthesis based on Mannich cyclization of iminium ions that contain tethered olefinic π-bonds. Since the earlier examples of our diazo imide cycloaddition reaction

(44) Dean, R. T.; Rapoport, H. A. *J. Org. Chem.* **1978**, *43*, 4183.

(45) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman: London, 1981.

(46) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming. I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.4.

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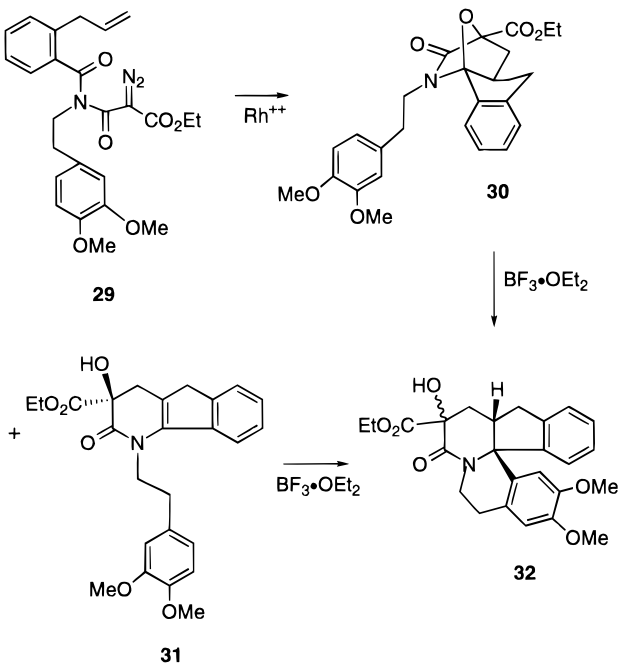
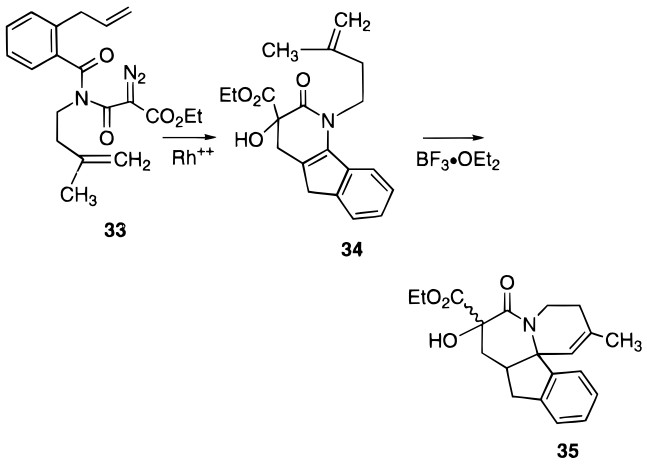
(48) Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067; *J. Chem. Soc., Chem. Commun.* **1987**, 185.

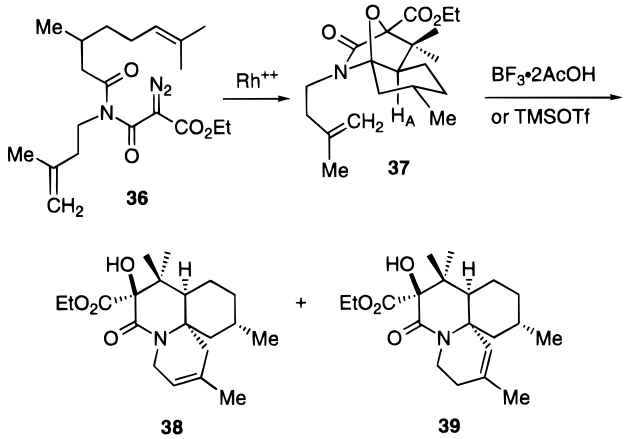
(49) Zhang, X.; Jung, Y. S.; Mariano, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239.



for promoting Mannich cyclization involve aromatic π-bonds, we decided to study several systems which possess a simple olefinic tether. Treatment of the acyclic substrate **33** with rhodium(II) perfluorobutyrate in CH_2Cl_2 at 25 °C gave a single product that corresponded to the indenyl enamide **34** in 85% yield. The anticipated product of 1,3-dipolar cycloaddition of the intermediate isomünchnone dipole was not observed. Exposure of **34** to $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 40 °C resulted in a 3:2 mixture of diastereomeric tetracyclic lactams **35** in 88% yield, thereby demonstrating that tethered alkenes can also be utilized in the third step of these cascade reactions.



In a further investigation of the sequential cycloaddition−π-cyclization process for the construction of nitrogen heterocycles, we examined the Rh(II)-catalyzed reaction of diazo imide **36**. The reaction afforded cycloadduct **37** as a single diastereomer in 94% yield. Formation of **37** is again the consequence of *endo*-cycloaddition with respect to the dipole. The resulting stereochemistry features the methyl substituent in a *syn* relationship to the angular hydrogen, in agreement with the previously studied systems.[22] Further exposure of cycloadduct **37** to a Lewis acid provided a mixture of the tetracyclic lactams **38** and **39** in good yield. In our earlier cationic cyclization studies, we determined that $BF_3{\cdot}OEt_2$ was the most effective Lewis acid to carry out this transformation. With diazo imide **36**, however, we found that $BF_3{\cdot}2AcOH$ was a particularly effective Lewis acid, probably as a consequence of its ability to serve in a dual capacity in this reaction. First, it acts as a typical Lewis acid, triggering the ring opening of the oxygen bridge of the isomünchnone cycloadduct. Second, once the Mannich



cyclization has occurred, $BF_3{\cdot}2AcOH$ functions as a protic acid allowing for the thermodynamic equilibration of the two regioisomers. Indeed, the same ratio of isomers (*i.e.*, **38**/**39** = 4:1) was obtained upon subjecting either product to the reaction conditions used to promote the cyclization. Interestingly, when the cyclization reaction was carried out using TMSOTf as the Lewis acid, the major regioisomer (80%) that formed corresponded to compound **39**. Under these conditions there was no interconversion of the two isomeric products, thereby suggesting kinetic control of the Mannich cyclization.

In conclusion, the results presented herein demonstrate the potential of the tandem carbenoid cyclization−dipolar cycloaddition−Mannich cyclization reaction of diazo imides for the construction of polyheterocyclic ring systems. This three-step protocol begins with the Rh(II)-catalyzed cyclization of an α-diazo imide to give rise to an isomünchnone 1,3-dipole. This is followed by an intramolecular 1,3-dipolar cycloaddition. *N*-Acyliminium ion formation is triggered by exposure of the cycloadduct to a Lewis acid. The annulation is completed by Mannich cyclization of a tethered π-bond onto the cationic intermediate. The overall transformation represents a highly effective means by which simple starting materials can be converted to relatively complex products by using the tandem chemistry of rhodium carbenoids. We have used this strategy to carry out a formal synthesis of (±)-lycopodine which is described in the following article.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. 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.

General Procedure for the Synthesis of Diazo Imides. A solution containing 5.0 mmol of the appropriate amide and 10.0 mmol of ethyl malonyl chloride in 15 mL of anhydrous benzene was heated at reflux for 1 h. After being cooled to rt, the reaction mixture was diluted with ether and washed with 10% aqueous NaOH and brine. The organic layer was dried

over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column. A variation of the procedure described by Taber and co-workers[50] was used to prepare the diazo imide system. To a solution containing 2 mmol of the appropriate imide and 2.2 mmol of mesyl azide in 5 mL of acetonitrile or CH_2Cl_2 was added 4.0 mmol of NEt_3 under N_2 at rt. After the solution was stirred for 3 h, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography on a silica gel column.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 2-Diazo-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-hept-6-enoylmalonamic Acid Ethyl Ester (6). To a solution containing 1.09 g (7.80 mmol) of 6-heptenoic acid[51] in 50 mL of CH_2Cl_2 was added 1.73 g (9.36 mmol) of 1,1′-carbonyldiimidazole and the solution was stirred at rt for 2 h. The reaction mixture was added to a solution of 2.02 g (8.97 mmol) of 3,4-dimethoxyphenethylamine in 100 mL of CH_2Cl_2 at 0 °C. The resulting solution was stirred at 25 °C for 10 h and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.01 g (89%) of hept-6-enoic acid [2-(3,4-dimethoxyphenyl)ethyl]amide as a white solid: mp 59−60 °C; IR (neat) 3302, 1639, 1514, 1233, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (quin, 2H, J = 7.2 Hz), 1.58 (quin, 2H, J = 7.2 Hz), 2.01 (q, 2H, J = 7.2 Hz), 2.09 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 6.9 Hz), 3.46 (q, 2H, J = 6.9 Hz), 3.83 (s, 6H), 4.89−4.98 (m, 2H), 5.46 (brs, 1H), 5.74 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), 6.68 (m, 2H), and 6.77 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.2, 28.4, 33.4, 35.3, 36.6, 40.6, 55.9, 111.3, 111.9, 114.6, 120.6, 131.4, 138.3, 147.6, 149.0, and 172.9.

N-Malonylacylation was carried out on the above amide in the normal manner to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-hept-6-enoylmalonamic acid ethyl ester as a clear oil (85%): IR (neat) 2936, 1738, 1696, 1515, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.2 Hz), 1.27 (m, 2H), 1.51 (quin, 2H, J = 7.5 Hz), 1.98 (m, 2H), 2.28 (t, 2H, J = 7.5 Hz), 2.81 (t, 2H, J = 7.5 Hz), 3.77 (s, 2H), 3.84 (m, 8H), 4.16 (q, 2H, J = 7.2 Hz), 4.93 (m, 2H), 5.73 (ddt, 1H, J = 17.1, 10.2, and 6.9 Hz), 6.71 (d, 1H, J = 8.7 Hz), 6.72 (s, 1H), and 6.77 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 23.8, 28.1, 33.3, 34.6, 36.2, 46.3, 46.4, 55.9, 61.1, 111.4, 112.3, 114.7, 120.7, 130.8, 138.2, 147.9, 149.1, 167.4, 168.7, and 175.8.

The above compound was subjected to the standard diazo transfer conditions to give 2-diazo-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-hept-6-enoylmalonamic acid ethyl ester (**6**) as a yellow oil (100%): IR (neat) 2938, 2136, 1718, 1647, 1512, and 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J = 7.2 Hz), 1.32 (quin, 2H, J = 7.2 Hz), 1.56 (quin, 2H, J = 7.2 Hz), 1.98 (q, 2H, J = 7.2 Hz), 2.38 (t, 2H, J = 7.2 Hz), 2.80 (t, 2H, J = 7.2), 3.78 (m, 8H), 4.17 (q, 2H, J = 7.2 Hz), 4.89 (m, 2H), 5.72 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), 6.65 (s, 1H), 6.67 (d, 1H, J = 8.7 Hz), and 6.73 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 24.4, 28.2, 33.3, 35.3, 35.8, 48.2, 55.8, 61.7, 72.4, 111.3, 112.3, 114.5, 120.9, 130.8, 138.3, 147.7, 148.9, 160.3, 166.3, and 175.2.

A solution of 0.99 g (2.23 mmol) of diazo imide **6** in 15 mL of CH_2Cl_2 at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred for 24 h at rt and was then concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 0.92 g (98%) of 10-[2-(2,3-dimethoxyphenyl)-ethyl]-9-oxo-11-oxa-10-azatricyclo[6.2.1.$0^{1,6}$]undecane-8-carboxylic acid ethyl ester (**7**) as a clear oil: IR (neat) 2937, 1749, 1720, 1516, and 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (m, 2H), 1.33 (t, 3H, J = 7.2 Hz), 1.57−1.84 (m, 7H), 2.15 (m, 2H), 2.75 (m, 2H), 3.25 (m, 1H), 3.42 (m, 1H), 3.83 (s, 6H), 4.34 (q, 2H, J = 7.2 Hz), 6.71 (m, 2H), and 6.77 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.4, 24.5, 27.4, 32.5, 35.2, 36.8, 41.5, 42.0, 55.9, 62.0, 85.8, 96.6, 111.3, 112.0, 120.6, 130.7, 147.7, 148.9, 166.0, and 171.1; HRMS calcd for $C_{22}H_{29}NO_6$ 403.1994, found 403.1981.

2-Hydroxy-6,7-dimethoxy-3-oxo-1,2,3,4,5,10,11,12,13,-13a-decahydro-3a-azabenzo[*d*]phenanthrene-2-carboxylic Acid Ethyl Ester (8). To a solution containing 0.20 g (0.47 mmol) of cycloadduct **7** in 2 mL of CH_2Cl_2 at 0 °C was added 0.11 g (0.95 mmol) of $BF_3{\cdot}Et_2O$. After the reaction mixture was stirredat rt for 3 h, the reaction was quenched with 2 mL of MeOH and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 183 mg (91%) of benzo[*d*]phenanthrene **8** as a white solid: mp 159−160 °C; IR (neat) 3420, 2935, 1750, 1643, and 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, J = 7.2 Hz), 1.28−1.47 (m, 4H), 1.61−1.76 (m, 3H), 1.97 (m, 1H), 2.27 (m, 2H), 2.52 (m, 2H), 3.02 (ddd, 1H, J = 16.5, 12.0, and 7.8 Hz), 3.30 (ddd, 1H, J = 19.5, 12.0, and 5.4 Hz), 3.74 (s, 3H), 3.78 (s, 3H), 3.85 (m, 2H), 3.94 (s, 1H), 4.64 (dd, 1H, J = 13.5 and 7.8 Hz), 6.49 (s, 1H), and 6.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 21.4, 25.9, 27.1, 27.3, 33.9, 35.4, 36.4, 41.0, 55.8, 56.2, 61.7, 61.8, 74.1, 106.3, 112.5, 127.0, 134.5, 147.2, 147.8, 170.9, and 172.9. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.26; N, 3.47. Found: C, 65.38; H, 7.29; N, 3.42.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 2-Diazo-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(5-methylhexenoyl)malonamic Acid Ethyl Ester (9). To a solution containing 1.09 g (8.50 mmol) of 5-methyl-5-hexenoic acid[52] in 50 mL of CH_2Cl_2 was added 1.65 mg (10.02 mmol) of 1,1′-carbonyldiimidazole, and the solution was stirred at rt for 2 h. The reaction mixture was added to a solution of 1.69 g (9.35 mmol) of 3,4-dimethoxyphenethylamine in 100 mL of CH_2Cl_2 at 0 °C. This mixture was stirred at 25 °C for 10 h and then concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 2.05 g (85%) of 5-methylhex-5-enoic acid [2-(3,4-dimethoxyphenyl)ethyl]amide as a white solid: mp 62-63 °C; IR (neat) 3305, 1641, 1515, and 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66 (s, 3H), 1.72 (quin, 2H, J = 7.5 Hz), 1.98 (t, 2H, J = 7.5 Hz), 2.08 (t, 2H, J = 7.5 Hz), 2.73 (t, 2H, J = 6.9 Hz), 3.47 (q, 2H, J = 6.9 Hz), 3.83 (s, 6H), 4.61 (s, 1H), 4.67 (s, 1H), 5.44 (brs, 1H), 6.69 (m, 2H), and 6.77 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 23.4, 35.2, 35.9, 37.0, 40.6, 55.8, 110.5, 111.3, 111.8, 120.5, 131.3, 144.8, 147.6, 148.9, and 172.8.

N-Malonylacylation was carried out on the above amide in the normal manner to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(5-methylhex-5-enoyl)malonamic acid ethyl ester as a clear oil (86%): IR (neat) 2932, 1737, 1695, 1515, and 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 6.9 Hz), 1.65 (m, 5H), 1.93 (t, 2H, J = 7.5 Hz), 2.29 (t, 2H, J = 7.5 Hz), 2.80 (t, 2H, J = 7.5 Hz), 3.78 (s, 2H), 3.83 (m, 8H), 4.17 (q, 2H, J = 6.9 Hz), 4.62 (s, 1H), 4.70 (s, 1H), 6.70 (d, 1H, J = 8.4 Hz), 6.71 (s, 1H), and 6.74 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 21.9, 22.0, 34.6, 35.6, 36.7, 46.3, 46.5, 55.8, 61.1, 110.7, 111.4, 112.2, 120.7, 130.7, 144.6, 147.9, 149.1, 167.4, 168.6, and 175.7.

The above compound was subjected to the standard diazo transfer conditions to give 2-diazo-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-(5-methylhexenoyl)malonamic acid ethyl ester (**9**) as a yellow oil (97%): IR (neat) 2936, 2137, 1718, and 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.2 Hz), 1.67 (s, 3H), 1.74 (quin, 2H, J = 7.5 Hz), 1.99 (t, 2H, J = 7.5 Hz), 2.41 (t, 2H, J = 7.5 Hz), 2.84 (t, 2H, J = 7.5 Hz), 3.83 (m, 8H), 4.21 (q, 2H, J = 7.2 Hz), 4.64 (s, 1H), 4.70 (s, 1H), 6.69 (s, 1H), 6.70 (d, 1H, J = 7.8 Hz), and 6.76 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.1, 22.6, 35.3, 35.4, 36.9, 48.2, 55.8, 61.7, 72.4, 110.6, 111.2, 112.2, 120.9, 130.7, 144.8, 147.7, 148.9, 160.3, 166.3, and 175.3.

To a mixture of 5 mg of rhodium(II) perfluorobutyrate in 10 mL of toluene at reflux was added a solution of 1.27 g (2.85 mmol) of diazo imide **9** in 5 mL of toluene. The reaction mixture was heated at reflux for 24 h, cooled to rt, and

(50) Taber, D. F.; Ruckle, R. E., Jr.; Hennesy, M. J. *J. Org. Chem.* **1986**, *51*, 1663. Regitz, M.; Hocker, J.; Leidhergener, A. *Organic Synthesis*; John Wiley: New York, 1973; Collect. Vol. 5, pp 179−183.

(51) Scarborough, R. M., Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1977**, *18*, 4361.

(52) Kappeler, H.; Stauffacher, D.; Eschenmoser, A.; Schinz, H. *Helv. Chim. Acta.* **1954**, *37*, 957.

concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.50 g (95%) of 9-[2-(3,4-dimethoxyphenyl)ethyl]-5-methyl-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**11**) as a clear oil: IR (neat) 2956, 1748, 1719, and 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3H), 1.32 (t, 3H, J = 7.2 Hz), 1.57−1.91 (m, 8H), 2.18 (d, 1H, J = 12.6 Hz), 2.76 (m, 2H), 2.97 (dt, 1H, J = 13.8 and 7.8 Hz), 3.82 (s, 3H), 3.86 (s, 3H), 4.33 (q, 2H, J = 7.2 Hz), 6.70 (m, 2H), and 6.77 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.3, 21.6, 23.3, 35.6, 37.5, 42.6, 43.9, 53.6, 55.8, 55.9, 62.0, 87.2, 107.8, 111.3, 112.3, 120.7, 130.9, 147.7, 148.9, 166.1, and 170.1; HRMS calcd for $C_{22}H_{29}NO_6$ 403.1994; found 403.1987.

2-Hydroxy-8,9-dimethoxy-13a-methyl-3-oxo-2,3,5,6,11,-12,13,13a-octahydro-1*H*-cyclopenta[2,3]pyrido[2,1-*a*]isoquinoline-2-carboxylic Acid Ethyl Ester (13). A solution containing 0.12 g (0.29 mmol) of cycloadduct **11** and 0.10 g (0.85 mmol) of $BF_3{\cdot}Et_2O$ in 4 mL of CH_2Cl_2 was heated at reflux for 24 h. The reaction mixture was cooled to rt, the reaction was quenched with 2 mL of MeOH, and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 75 mg (95%) of pyrido[2,1-*a*]isoquinoline **13** as a white solid: mp 207−208 °C; IR (neat) 3338, 2932, 1734, and 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz), 1.94−2.13 (m, 4H), 2.19 (d, 1H, J = 14.4 Hz), 2.31 (m, 1H), 2.34 (d, 1H, J = 14.4 Hz), 2.50 (m, 2H), 2.81 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.11 (m, 2H), 4.28 (s, 1H), 4.98 (m, 1H), 6.55 (s, 1H), and 6.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 20.6, 22.9, 30.0, 40.4, 41.7, 42.5, 42.9, 44.3, 55.7, 56.0, 61.9, 72.5, 74.8, 110.1, 111.5, 129.1, 132.2, 147.0, 147.3, 167.6, and 172.0. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.25; N, 3.47. Found: C, 65.24; H, 7.26; N, 3.48.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 2-Diazo-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(2-methylhex-5-enoyl)malonamic Acid Ethyl Ester (10). A solution containing 1.0 g (7.80 mmol) of 2-methyl-5-hexenoic acid[53] in 50 mL of CH_2Cl_2 at rt was stirred with 1.73 g (9.36 mmol) of 1,1′-carbonyldiimidazole at rt for 1 h. The mixture was added to a solution of 2.02 g (8.97 mmol) of 3,4-dimethoxyphenethylamine in 100 mL of CH_2Cl_2 at 0 °C. The solution was stirred at 25 °C for 10 h and then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.01 g (89%) of 2-methylhex-5-enoic acid [2-(3,4-dimethoxyphenyl)ethyl]amide as a white solid: mp 76−77 °C; IR (neat) 3299, 1659, 1028, and 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, 3H, J = 6.9 Hz), 1.39 (m, 1H), 1.68 (m, 1H), 1.89−2.14 (m, 3H), 2.72 (t, 2H, J = 6.9 Hz), 3.47 (m, 2H), 3.81 (s, 6H), 4.91 (m, 2H), 5.49 (brs, 1H), 5.70 (ddt, 1H, J = 17.1, 10.5, and 6.6 Hz), and 6.67−6.78 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.8, 31.4, 33.2, 35.3, 40.5, 40.6, 55.7, 55.8, 111.3, 111.8, 114.8, 120.6, 131.4, 138.0, 147.5, 148.9, and 176.2.

N-Malonylacylation was carried out on the above amide in the normal manner to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-(2-methylhex-5-enoyl)malonamic acid ethyl ester as a clear oil (70%): IR (neat) 2958, 1740, 1695, 1515, and 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (d, 3H, J = 6.9 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.39 (m, 1H), 1.70 (m, 1H), 1.96 (m, 2H), 2.68 (q, 1H, J = 6.9 Hz), 2.81 (m, 2H), 3.77 (s, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.88 (m, 2H), 4.17 (q, 2H, J = 7.2 Hz), 4.98 (m, 2H), 5.70 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), and 6.69−6.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 16.9, 30.9, 32.5, 34.8, 38.2, 46.0, 46.2, 55.7, 60.9, 111.4, 112.3, 115.3, 120.7, 130.5, 137.5, 147.8, 149.0, 167.2, 168.8, and 179.7.

The above compound was subjected to standard diazo transfer conditions to give 2-diazo-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-(2-methylhex-5-enoyl)malonamic acid ethyl ester (**10**) as a yellow oil (100%): IR (neat) 2939, 2135, 1719, 1693, and 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (d, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 7.2 Hz), 1.41 (m, 1H), 1.73 (m, 1H), 1.97 (m, 2H), 2.79 (m, 3H), 3.78 (m, 8H), 4.18 (q, 2H, J = 7.2 Hz), 4.87−4.96 (m, 2H), 5.66 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), and 6.37−6.65 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 17.1, 30.9, 33.1, 35.1, 38.5, 48.4, 55.6, 55.7, 61.6, 72.3, 111.2, 112.3, 114.9, 120.9, 130.7, 137, 147.6, 148.7, 159.8, 166.5, and 178.5.

A solution of 0.73 g (1.70 mmol) of diazo imide **10** in 15 mL of CH_2Cl_2 at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred at 25 °C for 24 h and was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 0.63 g (90%) of 9-[2-(2,3-dimethoxyphenyl)ethyl]-2-methyl-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**12**) as a clear oil: IR (neat) 2950, 1750, 1721, and 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (d, 3H, J = 6.9 Hz), 1.29 (t, 3H, J = 7.2 Hz), 1.35 (m, 1H), 1.63−2.31 (m, 7H), 2.76 (m, 2H), 3.25 (m, 1H), 3.36 (dt, 1H, J = 6.9 Hz), 3.80 (s, 6H), 4.29 (q, 2H, J = 7.2 Hz), and 6.67−6.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 14.1, 28.2, 32.0, 32.1, 34.7, 37.7, 41.9, 46.7, 55.9, 61.9, 87.7, 107.4, 111.4, 112.0, 120.5, 130.8, 147.8, 149.0, 166.0, and 171.7; HRMS calcd for $C_{22}H_{29}NO_6$ 403.1995; found 403.2000.

2-Hydroxy-7,8-dimethoxy-11-methyl-3-oxo-2,3,5,6,11,-12,13,13a-octahydro-1*H*-cyclopenta[2,3]pyrido[2,1-*a*]isoquinoline-2-carboxylic Acid Ethyl Ester (14). To a solution containing 40 mg (0.10 mmol) of cycloadduct **12** in 2 mL of CH_2Cl_2 at rt was added 29 mg (0.20 mmol) of $BF_3{\cdot}Et_2O$. After the reaction mixture was stirred at rt for 3 h, the reaction was quenched with 2 mL of MeOH and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 36 mg (90%) of pyrido[2,1-*a*]isoquinoline **14** as a white solid: mp 149−150 °C; IR (neat) 3401, 2951, 1743, 1640, and 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (t, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 7.2 Hz), 1.62 (m, 1H), 1.97 (m, 1H), 2.14 (m, 1H), 2.29−2.42 (m, 2H), 2.49−2.71 (m, 3H), 3.08 (m, 2H), 3.72 (m, 1H), 3.81 (s, 6H), 3.83 (m, 2H), 4.39 (s, 1H), 4.81 (m, 1H), and 6.53 (d, 2H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 17.2, 27.2, 29.8, 31.1, 39.0, 39.2, 39.6, 46.1, 55.8, 56.2, 61.6, 71.2, 73.4, 109.3, 111.5, 125.3, 136.3, 146.8, 147.8, 169.4, and 171.0. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.26; N, 3.47. Found: C, 65.41; H, 7.30; N, 3.45.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 2-Diazo-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-hex-5-enoylmalonamic Acid Ethyl Ester (15). To a solution of 1.06 g (9.28 mmol) of 5-hexenoic acid in 50 mL of CH_2Cl_2 was added 1.65 g (10.20 mmol) of 1,1′-carbonyldiimidazole, and the solution was stirred at rt for 2 h. The reaction mixture was added to a solution of 1.85 g (10.20 mmol) of 3,4-dimethoxyphenethylamine in 100 mL of CH_2Cl_2 at 0 °C. The resulting solution was warmed to 25 °C, stirred for 10 h, and then concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 2.01 g (83%) of hex-5-enoic acid [2-(3,4-dimethoxyphenyl)ethyl]amide as a crystalline solid: mp 39−40 °C; IR (neat) 3306, 2936, 1641, 1234, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (quin, 2H, J = 7.2 Hz), 1.95−2.12 (m, 4H), 2.69 (t, 2H, J = 7.2 Hz), 3.41 (q, 2H, J = 7.2 Hz), 3.78 (s, 6H), 4.87−4.94 (m, 2H), 5.71 (m, 2H), and 6.64−6.75 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 33.0, 35.2, 35.8, 40.6, 55.8, 111.3, 111.8, 115.1, 120.5, 131.4, 137.8, 147.6, 148.9, and 172.7.

N-Malonylacylation was carried out on the above amide in the normal manner to give *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-hex-5-enoylmalonamic acid ethyl ester as a clear oil (78%): IR (neat) 2950, 1738, 1697, 1516, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 6.9 Hz), 1.61 (quin, 2H, J = 7.2 Hz), 1.98 (q, 2H, J = 7.2 Hz), 2.30 (t, 2H, J = 7.2 Hz), 2.80 (t, 2H, J = 7.2 Hz), 3.78 (s, 2H), 3.83 (m, 8H), 4.17 (q, 2H, J = 6.9 Hz), 4.94−5.00 (m, 2H), 5.69 (ddt, 1H, J = 17.0, 10.2, and 7.0 Hz), and 6.69−6.79 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 23.3, 32.7, 34.6, 35.5, 46.2, 46.4, 55.8, 61.1, 111.5, 112.3, 115.4, 120.8, 130.8, 137.5, 147.9, 149.1, 167.4, 168.6, and 175.7.

The above compound was subjected to the standard diazo transfer conditions to give 2-diazo-*N*-[2-(3,4-dimethoxyphenyl)-

(53) Jellal, A.; Santelli, M. *Tetrahedron Lett.* **1980**, *21*, 4487.

ethyl]-*N*-hex-5-enoylmalonamic acid ethyl ester (**15**) as a yellow oil (95%): IR (neat) 2958, 2135, 1717, 1649, and 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, 3H, J = 6.9 Hz), 1.65 (quin, 2H, J = 7.2 Hz), 1.99 (q, 2H, J = 7.2 Hz), 2.38 (t, 2H, J = 7.2 Hz), 2.80 (t, 2H, J = 7.2 Hz), 3.78 (m, 8H), 4.16 (q, 2H, J = 6.9 Hz), 4.89−4.98 (m, 2H), 5.68 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), and 6.65−6.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 23.9, 32.9, 35.1, 35.4, 48.2, 55.8, 55.9, 61.7, 72.3, 111.3, 112.3, 115.2, 120.9, 130.7, 137.7, 147.7, 148.9, 160.3, 166.3, and 175.2.

A solution containing 0.99 g (2.26 mmol) of diazo imide **15** in 15 mL of CH_2Cl_2 at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred at 25 °C for 24 h and was then concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give 0.52 g (56%) of 9-[2-(2,3-dimethoxyphenyl)ethyl]-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**16**) as a clear oil: IR (neat) 2936, 1739, 1666, 1514, and 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, J = 7.2 Hz), 1.80−2.22 (m, 9H), 2.79 (m, 2H), 3.17 (m, 1H), 3.57 (m, 1H), 3.85 (s, 6H), 4.10 (m, 2H), and 6.71−6.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 24.6, 25.1, 30.2, 35.0, 35.6, 41.8, 47.9, 55.8, 62.0, 88.3, 106.9, 111.3, 112.0, 120.6, 130.8, 147.7, 148.9, 165.9, and 170.8; HRMS calcd for $C_{21}H_{27}NO_6$ 389.1838; found 389.1819.

2-Hydroxy-7,8-dimethoxy-3-oxo-2,3,5,6,11,12,13,13a-octahydro-1*H*-cyclopenta[2,3]pyrido[2,1-*a*]isoquinoline-2-carboxylic Acid Ethyl Ester (17). To a solution containing 0.15 g (130 mmol) of cycloadduct **16** in 2 mL of CH_2Cl_2 at rt was added 0.11 g (0.75 mmol) of $BF_3{\cdot}Et_2O$. After the reaction mixture was stirred at rt for 3 h, the mixture was quenched with 2 mL of MeOH and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.13 g (90%) of pyrido[2,1-*a*]isoquinoline **17** as a white solid: mp 142−143 °C; IR (neat) 3400, 1742, 1644, 1512, and 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.68 (t, 3H, J = 7.2 Hz), 1.69 (m, 4H), 2.12 (m, 2H), 2.32 (m, 2H), 2.60 (m, 2H), 2.99 (m, 1H), 3.22 (dt, 1H, J = 12.3 and 4.5 Hz), 3.78 (m, 8H), 4.34 (s, 1H), 4.71 (dd, 1H, J = 13.2 and 6.0 Hz), and 6.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 22.7, 27.5, 33.2, 36.4, 39.3, 40.3, 43.4, 55.8, 56.1, 61.6, 69.3, 73.5, 108.2, 111.7, 125.8, 135.0, 147.2, 147.8, 168.6, and 171.1. Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.75; H, 7.00; N, 3.59. Found: C, 64.47; H, 6.98; N, 3.49.

Lewis Acid Ring-Opening Reaction of 9-(3,4-Dimethoxybenzyl)-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic Acid Ethyl Ester (18). To a solution of 1.01 g (8.85 mmol) of 5-hexenoic acid in 50 mL of CH_2Cl_2 was added 1.70 g (10.48 mmol) of 1,1′-carbonyldiimidazole, and the mixture was stirred at rt for 2 h. This reaction mixture was added to a solution of 1.65 g (10.17 mmol) of 3,4-dimethoxybenzylamine in 100 mL of CH_2Cl_2 at 0 °C. This solution was warmed to rt and stirred for 10 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 1.91 g (82%) of hex-5-enoic acid (3,4-dimethoxybenzyl)amide as a crystalline solid: mp 65−66 °C; IR (neat) 3309, 1637, 1545, and 802 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.69 (quin, 2H, J = 7.5 Hz), 2.03 (q, 2H, J = 7.5 Hz), 2.14 (t, 2H, J = 7.5 Hz), 3.79 (s, 6H),4.28 (d, 2H, J = 5.7 Hz), 4.92 (m, 2H), 5.71 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), 5.97 (brs, 1H), 6.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 33.1, 35.8, 43.3, 55.8, 111.1, 115.2, 120.0, 131.0, 137.8, 148.3, 149.0, and 172.6.

N-Malonylation was carried out on the above amide in the normal manner to give 3-[(3,4-dimethoxybenzyl)hex-5-enoylamino]-3-oxopropionic acid ethyl ester as a clear oil (68%); IR (neat) 2935, 1737, 1701, 1519, and 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J = 7.2 Hz), 1.62 (quin, 2H, J = 7.2 Hz), 1.95 (m, 2H), 2.47 (t, 2H, J = 7.2 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 3.86 (s, 2H), 4.15 (q, 2H, J = 7.2 Hz), 4.85−4.91 (m, 4H), 5.62 (ddt, 1H, J = 17.1, 10.5, and 6.6 Hz), and 6.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 23.3, 32.6, 35.7, 46.3, 46.5, 55.9, 61.2, 109.6, 111.4, 115.3, 118.2, 129.0, 137.4, 148.3, 149.3, 167.4, 168.8, and 176.1.

The above compound was subjected to the standard diazo transfer conditions to give 2-diazo-3-[(3,4-dimethoxybenzyl)-hex-5-enoylamino]-3-oxopropionic acid ethyl ester as a yellow oil (100%): IR (neat) 2940, 2139, 1723, and 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H, J = 7.2 Hz), 1.64 (quin, 2H, J = 7.2 Hz), 1.96 (q, 2H, J = 7.2 Hz), 2.44 (t, 2H, J = 7.2 Hz), 3.77 (s, 6H), 4.18 (q, 2H, J = 7.2 Hz), 4.78 (s, 2H), 4.86−4.94 (m, 2H), 5.65 (ddt, 1H, J = 16.8, 10.2, and 6.6 Hz), and 6.71−6.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 23.8, 32.7, 35.1, 48.7, 55.7, 55.8, 61.7, 72.7, 110.5, 111.1, 115.2, 119.4, 129.5, 137.6, 148.3, 149.1, 160.4, 166.2, and 175.4.

To a mixture of 5 mg of rhodium(II) perfluorobutyrate in 15 mL of benzene at 80 °C was added a solution of 1.50 g (3.72 mmol) of the above diazo imide in 2 mL of benzene. The reaction was heated at reflux for 24 h and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 1.04 g (75%) of 9-(3,4-dimethoxybenzyl)-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**18**) as clear oil: IR (neat) 2944, 1750, 1719, 1515, and 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 3H, J = 7.2 Hz), 1.74 (m, 1H), 1.86 (m, 1H), 1.92−2.04 (m, 5H), 2.15−2.21 (m, 2H), 3.85 (s, 6H), 4.38 (m, 4H), and 6.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 24.6, 25.1, 30.1, 35.6, 43.4, 47.7, 55.8, 55.9, 62.0, 88.5, 106.9, 110.7, 111.0, 119.9, 128.9, 148.6, 149.2, 165.9, and 170.8; HRMS calcd for $C_{20}H_{25}NO_6$; 375.1681; found 375.1692.

1-(3,4-Dimethoxybenzyl)-3-hydroxy-2-oxo-2,3,4,5,6,7-hexahydro-1*H*-[1]pyrindine-3-carboxylic Acid Ethyl Ester (19). To a solution of 0.064 g (0.17 mmol) of cycloadduct **18** in 2.0 mL of CH_2Cl_2 at 0 °C was added 49 μL (0.34 mmol) of $BF_3{\cdot}Et_2O$. After the reaction mixture was warmed to rt and stirred for 2 h, the reaction was quenched with 1.0 mL of EtOH and the reaction mixture was diluted with 10 mL of CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 60 mg (95%) of **19** in 80% yield together with lesser quantities (20%) of the trisubstituted olefin **20** which could not be fully separated from **19**. The structure of **19** exhibited the following spectral properties: IR (neat) 3428 (br), 1738, 1668, 1515, and 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, 3H, J = 7.2 Hz), 1.84 (quin, 2H, J = 7.2 Hz), 2.34 (m, 4H), 2.42 (d, 1H, J = 15.4 Hz), 2.92 (d, 1H, J = 15.4 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.17 (q, 2H, J = 7.2 Hz), 4.58 (s, 1H), 4.67 (d, 1H, J = 15.6 Hz), 4.76 (d, 1H, J = 15.6 Hz), 6.75 (m, 2H), and 6.80 (m, 1H); HRMS (FAB/LSIMS) Calcd for $C_{20}H_{25}NO_6Li$: 375.1682; found 375.1684.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of *N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-2-diazo-*N*-hex-5-enoylmalonamic Acid Ethyl Ester (26). To a solution containing 1.40 g (12.30 mmol) of 5-hexenoic acid in 50 mL of CH_2Cl_2 was added 2.0 g (12.30 mmol) of 1,1′-carbonyldiimidazole, and the solution was stirred at rt for 1 h. To this reaction mixture was added a solution of 2.90 g (11.6 mmol) of 1-benzyltryptamine[54] in 25 mL of CH_2Cl_2, and the solution was allowed to stir for 1 h at rt. The solvent was removed under reduced pressure, and the residue was taken up in ether and washed with 10% aqueous HCl and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 1.22 g (30%) of hex-5-enoic acid [2-(1-benzyl-1*H*-indol-3-yl)ethyl]amide as a yellow oil: IR (neat) 3299, 1642, 1553, 1468, and 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67 (m, 2H), 2.05 (m, 4H), 2.96 (t, 2H, J = 6.8 Hz), 3.58 (q, 2H, J = 6.4 Hz), 4.95 (m, 2H), 5.26 (s, 2H), 5.52 (brs, 1H), 5.73 (m, 1H), 6.93 (s, 1H), and 7.05−7.65 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.3, 33.1, 36.0, 39.8, 49.9, 109.8, 112.3, 115.2, 119.0, 119.3, 122.0, 126.1, 126.9, 127.7, 128.0, 128.8, 136.8, 137.9, and 172.9.

N-Malonylacylation was carried out on the above amide in the normal manner to give *N*-[2-(1-benzyl-1*H*-indol-3-yl)ethyl]-2-diazo-*N*-hex-5-enoylmalonamic acid ethyl ester as a clear oil (68%): IR (neat) 2979, 1740, 1696, and 1333 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.1 Hz), 1.53 (m, 2H),

(54) Jahangir; Brook, M. A.; Maclean, D. B.; Holland, H. L. *Tetrahedron* **1987**, *43*, 5761.

1.84 (q, 2H, J = 7.0 Hz), 2.31 (t, 2H, J = 7.4 Hz), 3.04 (t, 2H, J = 7.3 Hz), 3.80 (s, 2H), 3.95 (t, 2H, J = 7.3 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.91 (m, 2H), 5.60 (m, 1H), 5.24 (s, 2H), 6.96 (s, 1H), and 7.05−7.70 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 23.4, 24.6, 32.7, 35.6, 45.2, 46.6, 50.0, 61.2, 109.9, 111.2, 115.4, 118.7, 119.3, 122.1, 126.9, 127.7, 127.9, 128.8, 136.6, 137.4, 137.6, 167.5, 168.8, and 175.9.

The above compound was subjected to the standard diazo transfer conditions to give *N*-[2-(1-benzyl-1*H*-indol-3-yl)ethyl]-2-diazo-*N*-hex-5-enoylmalonamic acid ethyl ester (**26**) as a bright yellow oil (98%): IR (neat) 3031, 2136, 1708, and 1370 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.69 (t, 3H, J = 7.2 Hz), 1.65 (m, 2H), 1.81 (q, 2H, J = 6.8 Hz), 2.31 (t, 2H, J = 7.3 Hz), 3.12 (t, 2H, J = 6.9 Hz), 3.67 (q, 2H, J = 7.2 Hz), 3.96 (t, 2H, J = 7.0 Hz), 4.58 (s, 2H), 4.88 (m, 2H), 5.54 (m, 1H), 6.48 (s, 1H), and 6.72−7.62 (m, 9H); ^{13}C NMR (C_6D_6, 75 MHz) δ 13.7, 24.0, 25.7, 32.9, 35.0, 46.9, 49.4, 60.9, 73.8, 109.8, 111.2, 114.9, 118.9, 119.3, 121.8, 126.6, 127.2, 128.2, 128.4, 136.8, 137.6, 137.9, 160.1, 166.0, and 174.9.

To a mixture of 3 mg of rhodium(II) perfluorobutyrate in 10 mL of benzene at 80 °C was added a solution of 0.27 g (0.56 mmol) of diazo imide **26** in 5 mL of benzene. After being heated at reflux for 30 min, the solution was cooled to rt and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.25 g (98%) of 9-[2-(1-benzyl-1*H*-indol-3-yl)ethyl]-8-oxo-10-oxa-9-azatricyclo-[5.2.1.0^{1,5}]decane-7-carboxylic acid ethyl ester (**27**) as a clear oil: IR (neat) 2942, 1753, 1718, 1468, and 847 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.87 (t, 3H, J = 7.1 Hz), 0.95 (m, 1H), 1.05−1.63 (m, 6H), 1.87 (ddd, 2H, J = 12.6, 7.9, and 3.5 Hz), 2.85 (m, 2H), 3.05 (m, 1H), 3.42 (m, 1H), 3.97 (q, 2H, J = 7.1 Hz), 4.60 (s, 2H), 6.56 (s, 1H), 6.70−7.20 (m, 8H), and 7.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 24.8, 25.1, 25.2, 30.4, 35.6, 40.9, 48.1, 50.0, 62.1, 88.4, 109.9, 111.6, 118.8, 119.3, 122.0, 126.3, 126.9, 127.6, 127.8, 128.8, 136.6, 137.5, 166.1, and 170.9; HRMS (FAB/LSIMS) Calcd for $C_{28}H_{30}N_2O_4Li$ 465.2366; found 465.2378.

11-*N*-Benzyl-2-carbethoxy-2-hydroxy-3-oxo-2,3,6,11,-12,13,14,14a-octahydro-1*H*,5*H*-cyclopent[*i*]indolo[2,3-*a*]-quinolizine (28). To a solution of 0.12 g (0.26 mmol) of cycloadduct **27** in 5.0 mL of CH_2Cl_2 at 0 °C was added 74 mg (0.52 mmol) of $BF_3{\cdot}Et_2O$. After the reaction mixture was warmed to rt and stirred for 6 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the reaction mixture was diluted with ether. The ether layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 61 mg (60%) of indolo[2,3-*a*]quinolizine **28** as a white solid: mp 72−73 °C; IR ($CHCl_3$) 3380, 1750, 1646, 1466, and 1346 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.64 (t, 3H, J = 7.0 Hz), 0.83 (t, 2H, J = 7.2 Hz), 1.38 (m, 1H), 1.45−1.85 (m, 1H), 1.90 (m, 1H), 2.04 (m, 1H), 2.23 (dd, 1H, J = 14.1 and 5.3 Hz), 2.35 (dd, 1H, J = 15.3 and 3.1 Hz), 2.68 (m, 1H), 2.80 (dt, 1H, J = 12.3 and 3.7 Hz), 3.00 (ddd, 1H, J = 15.1, 12.0, and 5.2 Hz), 3.75 (dq, 1H, J = 10.7 and 7.1 Hz), 3.80 (m, 2H), 4.52 (s, 1H), 4.84 (s, 2H), 4.98 (dd, 1H, J = 12.5 and 4.8 Hz), and 6.55−7.40 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 21.7, 23.6, 30.7, 31.3, 38.7, 39.5, 42.2, 48.1, 62.4, 70.2, 74.1, 110.6, 112.3, 118.2, 119.9, 122.4, 125.3, 126.5, 127.5, 129.0, 136.0, 137.5, 137.9, 169.1, and 172.5. Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.33; H, 6.60; N, 6.11. Found: C, 73.34; H, 6.60; N, 6.01.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 3-[(2-Allylbenzoyl)[2-(3,4-dimethoxyphenyl)ethyl]-amino]-2-diazo-3-oxopropionic Acid Ethyl Ester (29). To a solution of 0.68 g (3.80 mmol) of 2-allylbenzoic acid[55] in 25 mL of CH_2Cl_2 was added 0.75 g (4.60 mmol) of 1,1′-carbonyldiimidazole, and the solution was stirred at rt for 2 h. This mixture was added to a solution of 1.40 g (7.7 mmol) of 3,4-dimethoxyphenethylamine in 25 mL of CH_2Cl_2 at 0 °C. The solution was allowed to warm to rt, was stirred for 12 h at 25 °C, and was concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 1.10 g (88%) of 2-allyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-benzamide as a white solid: mp 98−99 °C; IR ($CDCl_3$) 3320, 1675, and 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (t, 2H, J = 6.8 Hz), 3.50 (d, 2H, J = 6.3 Hz), 3.68 (dd, 2H, J = 13.0 and 6.8 Hz), 3.86 (s, 6H), 4.90−5.05 (m, 2H), 5.85 (brs, 1H), 5.80−6.00 (m, 1H), 6.75−6.83 (m, 3H), and 7.20−7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.2, 37.4, 40.9, 55.8, 55.9, 111.4, 111.9, 115.9, 120.7, 126.3, 127.1, 130.0, 130.4, 131.3, 136.5, 137.5, 147.7, 149.1, and 169.8.

N-Malonylacylation was carried out on the above amide in the normal manner to give 3-[(2-allylbenzoyl)-[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-oxopropionic acid ethyl ester as a colorless oil (93%): IR (neat) 1738, 1687, 1510, and 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3H, J = 7.1 Hz), 2.74 (t, 2H, J = 7.6 Hz), 3.30 (d, 2H, J = 6.6 Hz), 3.60−3.72 (m, 4H), 3.79 (s, 3H), 3.87 (s, 3H), 4.18 (q, 2H, J = 7.1 Hz), 4.99−5.06 (m, 2H), 5.75−5.90 (m, 1H), 6.35−6.69 (m, 3H), and 7.06−7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 34.3, 37.1, 46.7, 48.5, 55.8, 55.9, 61.3, 111.3, 112.0, 117.0, 120.9, 126.4, 126.7, 130.2, 130.6, 135.0, 135.8, 137.2, 147.7, 148.9, 167.3, 168.8, and 173.6.

The above compound was subjected to the standard diazo transfer conditons to give 3-[(2-allylbenzoyl)-[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-diazo-3-oxopropionic acid ethyl ester (**29**) as a bright yellow oil (78%): IR (neat) 2129, 1716, 1687, and 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.19 (t, 3H, J = 7.1 Hz), 2.88 (t, 2H, J = 7.8 Hz), 3.49 (d, 2H, J = 6.4 Hz), 3.79 (s, 3H), 3.81 (s, 3H), 3.89 (t, 2H, J = 7.8 Hz), 4.14 (q, 2H, J = 7.1 Hz), 5.00−5.10 (m, 2H), 5.85−6.00 (m, 1H), 6.59−6.74 (m, 3H), and 7.19−7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 34.8, 37.2, 48.9, 55.8, 55.9, 61.6, 111.2, 112.1, 116.5, 120.9, 125.8, 128.1, 130.5, 130.7, 130.9, 134.3, 136.7, 139.9, 147.7, 148.9, 160.2, 166.4, and 172.0.

A mixture containing 0.25 g (0.54 mmol) of diazo imide **29** and 4 mg of rhodium(II) perfluorobutyrate in 3 mL of CH_2Cl_2 was allowed to stir at rt for 12 h. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography. The first fraction isolated (60%) was assigned as *N*-[(3,4-dimethoxyphenyl)ethyl]-3-carbethoxy-3,9b-epoxy-1,4,4a,5-tetrahydroindeno[1,2-b]pyridin-2-one (**30**) on the basis of its spectral properties: IR (neat) 1745, 1716, 1510, and 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, 3H, J = 7.1 Hz), 2.16 (dd, 1H, J = 12.6 and 4.1 Hz), 2.33 (dd, 1H, J = 12.6 and 7.6 Hz), 2.60−2.75 (m, 2H), 2.80−2.95 (m, 2H), 3.10 (dd, 1H, J = 14.7 and 7.2 Hz), 3.20−3.60 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.34 (q, 2H, J = 7.1 Hz), 6.60−6.76 (m, 3H), and 7.10−7.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 34.3, 35.1, 35.7, 43.5, 49.3, 55.8, 56.0, 62.1, 89.5, 107.2, 111.4, 112.1, 120.8, 125.3, 126.1, 127.1, 131.0, 131.2, 131.5, 147.2, 147.8, 149.0, 165.6, and 171.8; HRMS calcd for $C_{25}H_{27}NO_6$ 437.1838; found 437.1829.

The second fraction isolated (15%) from the column was assigned as *N*-[(3,4-dimethoxyphenyl)ethyl]-3-carbethoxy-3-hydroxy-4,5-dihydroindeno[1,2-b]pyridin-2-one (**31**) on the basis of its spectral properties: IR (neat) 3417, 1735, 1666, and 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, 3H, J = 7.1 Hz), 2.65 (d, 1H, J = 16.6 Hz), 2.80−3.40 (m, 5H), 3.80 (s, 3H), 3.83 (s, 3H), 4.07 (q, 2H, J = 7.1 Hz), 4.15−4.50 (m, 2H), 4.65, (s, 1H), 6.73−6.79 (m, 3H), and 7.20−7.50 (m, 4H); HRMS calcd for $C_{25}H_{27}NO_6$ 437.1838; found 437.1850.

2-Carbethoxy-8,9-dimethoxy-2-hydroxy-3-oxo-5,6,13,-13a-tetrahydro-1*H*-cyclopenta[2,3]pyrido[11,12]benzo-[2,1-*a*]isoquinoline (32). To a solution of 50 mg (0.11 mmol) of cycloadduct **30** in 5 mL of CH_2Cl_2 at 0 °C was added 30 mg (0.22 mmol) of $BF_3{\cdot}Et_2O$, and the mixture was stirred at 25 °C for 4 h. The reaction was quenched with brine, and the solution was diluted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 40 mg (80%) of benzo[2,1-*a*]isoquinoline **32** as a 1:1 mixture of diastereomers which could be separated by HPLC. Diastereomer **32a** exhibited the following spectral properties: IR (neat) 3400, 1720, 1630, 1510, and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, 3H, J = 7.1 Hz), 2.15 (dd, 1H, J = 14.8 and 3.5 Hz), 2.43 (dd, 1H, J = 14.8 and 3.5 Hz), 2.71 (dd, 1H, J =

(55) Padwa, A.; Ku, A. *J. Am. Chem. Soc.* **1978**, *100*, 2181.

16.1 and 3.5 Hz), 3.05−3.55 (m, 4H), 3.72 (s, 3H), 3.70−3.80 (m, 1H), 3.88 (s, 3H), 4.07 (s, 1H), 4.00−4.25 (m, 2H), 4.57 (dd, 1H, J = 13.1 and 5.8 Hz), 6.52 (s, 1H), 6.67 (s, 1H), 6.80 (d, 1H, J = 7.5 Hz), and 7.05−7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 28.5, 30.2, 34.5, 37.4, 42.8, 55.9, 56.0, 62.5, 72.5, 74.2, 107.9, 111.6, 124.9, 126.1, 126.2, 128.3, 128.6, 128.9, 143.0, 146.8, 147.5, 148.3, 167.4, and 172.9; HRMS calcd for $C_{25}H_{27}NO_6$ 437.1838; found 437.1854.

Diastereomer **32b** exhibited the following spectral properties: IR (neat) 3390, 1720, 1620, 1500, and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, 3H, J = 7.1 Hz), 2.02 (dd, 1H, J = 14.0 and 6.2 Hz), 2.65−2.75 (m, 2H), 3.00−3.60 (m, 4H), 3.62 (s, 3H), 3.70−3.80 (m, 1H), 3.84 (s, 3H), 3.98 (q, 1H, J = 7.1 Hz), 4.02 (q, 1H, J = 7.1 Hz), 4.53 (s, 1H), 4.81−4.85 (m, 1H), 6.28 (s, 1H), 6.61 (s, 1H), 7.05 (d, 1H, J = 7.6 Hz), and 7.11−7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 28.2, 33.6, 37.0, 39.8, 43.3, 55.8, 56.0, 62.0, 72.7, 73.0, 108.5, 111.4, 124.9, 125.4, 127.1, 128.7, 131.8, 141.6, 146.8, 148.0, 148.1, 169.8, and 170.6; HRMS calcd for $C_{25}H_{27}NO_6$ 437.1838; found 437.1854.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 3-[(2-Allylbenzoyl)(3-methylbut-3-enyl)amino]-2-diazo-3-oxopropionic Acid Ethyl Ester (33). To a solution of 0.63 g (3.8 mmol) of 2-allylbenzoic acid[55] in 50 mL of CH_2Cl_2 was added 0.75 g (4.6 mmol) of 1,1′-carbonyldiimidazole, and the solution was allowed to stir at rt for 2 h. This mixture was added to a solution of 0.58 g (5.8 mmol) of 1-amino-3-methyl-3-butene[56] in 25 mL of CH_2Cl_2 at 0 °C. The solution was allowed to stir at 25 °C for 12 h and was concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.25 g (28%) of 2-allyl-*N*-(3-methylbut-3-enyl)benzamide as a colorless oil: IR (neat) 3300, 1655, and 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 3H), 2.26 (t, 2H, J = 6.8 Hz), 3.40−3.60 (m, 4H), 4.73 (s, 1H), 4.79 (s, 1H), 4.90−5.10 (m, 2H), 5.90−6.00 (m, 2H), and 7.10−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9, 37.3, 37.4, 37.5, 112.4, 115.9, 126.2, 127.2, 129.9, 130.3, 136.6, 137.6, 142.5, and 169.8.

N-Malonylacylation was carried out on the above amide in the normal manner to give 3-[(2-allylbenzoyl)(3-methylbut-3-enyl)amino]-3-oxopropionic acid ethyl ester as a colorless oil (90%): IR (neat) 1760, 1710, 1670, and 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, 3H, J = 7.1 Hz), 1.48 (s, 3H), 2.18 (t, 2H, J = 7.7 Hz), 3.40 (d, 2H, J = 6.7 Hz), 3.63 (t, 2H, J = 7.7 Hz), 3.82 (s, 2H), 4.16 (q, 2H, J = 7.1 Hz), 4.52 (s, 1H), 4.65 (s, 1H), 5.00−5.10 (m, 2H), 5.80−6.00 (m, 1H), and 7.20−7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.1, 36.5, 37.1, 45.3, 46.0, 61.3, 112.5, 117.0, 126.4, 126.7, 130.4, 130.7, 134.9, 135.9, 137.4, 141.9, 167.3, 168.8, and 173.6.

The above compound was subjected to the standard diazo transfer conditions to give 3-[(2-allylbenzoyl)(3-methylbut-3-enyl)amino]-2-diazo-3-oxopropionic acid ethyl ester (**33**) as a bright yellow oil (90%): IR (neat) 2185, 1745, 1710, 1660, and 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, 3H, J = 7.2 Hz), 1.66 (s, 3H), 2.34 (t, 2H, J = 7.6 Hz), 3.50 (d, 2H, J = 6.5 Hz), 3.83 (t, 2H, J = 7.6 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.65 (s, 1H), 4.72 (s, 1H), 5.00−5.10 (m, 2H), 5.80−6.00 (m, 1H), and 7.20−7.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.2, 37.0, 37.2, 45.8, 61.5, 112.4, 116.4, 125.7, 128.2, 130.5, 131.0, 134.3, 136.8, 140.0, 142.2, 160.2, 166.4, and 171.8.

A mixture containing 0.14 g (0.38 mmol) of diazo imide **33** and 4 mg of rhodium(II) perfluorobutyrate in 5 mL of CH_2Cl_2 was allowed to stir at rt for 12 h. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.11 g (85%) of *N*-(3-methylbut-3-enyl)-3-carbethoxy-3-hydroxy-4,5-dihydroindeno-[1,2-b]pyridin-2-one (**34**) as a white solid: mp 83−84 °C; IR ($CDCl_3$) 3400, 1735, 1670, and 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, 3H, J = 7.0 Hz), 1.79 (s, 3H), 2.29−2.50 (m, 2H), 2.75 (d, 1H, J = 16.6 Hz), 3.32 (d, 1H, J = 16.6 Hz), 3.35−3.39 (m, 2H), 4.07 (q, 2H, J = 7.0 Hz), 4.10−4.40 (m, 2H), 4.70 (s, 2H), 4.82 (s, 1H), and 7.20−7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 22.5, 31.1, 36.4, 37.9, 42.3, 61.9, 74.3, 112.1, 118.7, 121.6, 124.5, 125.1, 126.6, 137.2, 137.9, 142.1, 143.1, 169.3, and 169.7; HRMS calcd for $C_{20}H_{23}NO_4$ 341.1627; found 341.1633.

6-Hydroxy-2-methyl-5-oxo-4,5,6,7,7a,8-hexahydro-1*H*-4a-azabenzo[*d*]fluorene-6-carboxylic Acid Ethyl Ester (35). To a solution containing 80 mg (0.23 mmol) of enamide **34** in 5 mL of CH_2Cl_2 at rt was added 65 mg (0.46 mmol) of $BF_3{\cdot}Et_2O$, and the mixture was heated at reflux for 12 h. After the reaction mixutre was cooled to rt, the reaction was quenched with brine and diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 70 mg (88%) of azabenzo[*d*]fluorene **35** as a 3:2 mixture of diastereomers. Recrystallization from CH_2Cl_2/hexane gave the major diastereomer as a white solid: mp 108−109 °C; IR ($CDCl_3$) 3389, 1741, 1634, and 1422 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, 3H, J = 7.1 Hz), 1.68 (s, 3H), 1.81 (dd, 1H, J = 13.6 and 4.6 Hz), 1.89 (dd, 1H, J = 17.1 and 3.6 Hz), 2.13−2.40 (m, 2H), 2.58 (d, 1H, J = 16.0 Hz), 2.70−2.80 (m, 1H), 3.35 (dd, 1H, J = 16.0 and 6.8 Hz), 3.37 (dt, 1H, J = 12.5 and 3.6 Hz), 4.08 (q, 2H, J = 7.1 Hz), 4.00−4.20 (m, 1H), 4.90−4.95 (m, 1H), 5.36 (s, 1H), and 7.18−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 23.1, 28.8, 33.5, 35.6, 39.2, 41.3, 62.4, 70.0, 74.3, 123.9, 124.2, 125.9, 127.2, 128.0, 131.7, 139.9, 144.8, 167.8, and 172.0; HRMS calcd for $C_{20}H_{23}NO_4$ 341.1627; found 341.1624.

Preparation and Rhodium(II)-Catalyzed Cycloaddition of 2-Diazo-*N*-(3,7-dimethyloct-6-enoyl)-*N*-(3-methylbut-3-enyl)malonamic Acid Ethyl Ester (36). To a solution containing 5.0 g (35.20 mmol) of citronellic acid in 125 mL of benzene were added 15.6 g (123.10 mmol) of oxalyl chloride and 0.14 mL (1.76 mmol) of DMF. The solution was stirred at rt for 2 h and concentrated under reduced pressure. The resulting oil was taken up in 20 mL of CH_2Cl_2 and was added to a solution of 3.59 g (42.2 mmol) of 1-amino-3-methyl-3-butene[56] in 150 mL of CH_2Cl_2 at 0 °C. The solution was stirred at 25 °C for 12 h and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.61 g (44%) of 3,7-dimethyloct-6-enoic acid (3-methylbut-3-enyl)amide as a clear oil: IR (neat) 3297, 1645, and 1551 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, 3H, J = 6.3 Hz), 1.17−1.24 (m, 1H), 1.30−1.41 (m, 1H), 1.59 (s, 3H), 1.68 (s, 3H), 1.74 (s, 3H), 1.86−2.03 (m, 4H), 2.15−2.02 (m, 1H), 2.21 (t, 2H, J = 6.8 Hz), 3.39 (t, 2H, J = 6.6 Hz), 4.74 (s, 1H), 4.82 (s, 1H), 5.06−5.11 (m, 1H), and 5.39 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 19.6, 22.1, 25.6, 30.5, 37.0, 37.1, 37.6, 44.6, 112.2, 124.5, 131.4, 142.7, and 172.7.

N-Malonylacylation was carried out on the above amide in the normal manner to give 2.16 g (73%) of *N*-(3,7-dimethyloct-6-enoyl)-*N*-(3-methylbut-3-enyl)-malonamic acid ethyl ester as a clear oil: IR (neat) 1743, 1699, and 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 3H, J = 6.6 Hz), 1.18−1.28 (m, 1H), 1.27 (t, 3H, J = 7.2 Hz), 1.32−1.39 (m, 1H), 1.60 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 1.97−2.10 (m, 3H), 2.27 (t, 2H, J = 7.7 Hz), 2.36 (dd, 1H, J = 16.2 and 8.1 Hz), 2.57 (dd, 1H, J = 16.2 and 5.4 Hz), 3.79 (t, 2H, J = 7.7 Hz), 3.81 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 4.74 (s, 1H), 4.82 (s, 1H), and 5.06−5.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 17.7, 19.8, 22.6, 25.5, 25.7, 29.5, 36.8, 36.9, 43.2, 43.9, 46.5, 61.2, 112.5, 124.2, 131.6, 142.1, 167.4, 168.7, and 175.3.

The above compound was subjected to the standard diazo transfer conditions to give 1.75 g (94%) of 2-diazo-*N*-(3,7-dimethyloct-6-enoyl)-*N*-(3-methylbut-3-enyl)malonamic acid ethyl ester (**36**) as a yellow oil: IR (neat) 3077, 2140, 1726, 1700, and 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, 3H, J = 6.6 Hz), 1.16−1.24 (m, 1H), 1.24−1.36 (m, 1H), 1.28 (t, 3H, J = 7.2 Hz), 1.57 (s, 3H), 1.65 (s, 3H), 1.73 (s, 3H), 1.94−2.04 (m, 3H), 2.31 (dd, 1H, J = 15.7 and 8.1 Hz), 2.30 (t, 2H, J = 8.0 Hz), 2.51 (dd, 1H, J = 15.7 and 5.4 Hz), 3.75 (t, 2H, J = 8.0 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.69 (s, 1H), 4.77 (s, 1H), and 5.06 (t, 1H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 17.8, 19.8, 22.5, 25.6, 25.8, 30.2, 37.0, 37.5, 43.4, 45.2, 61.9, 112.6, 124.4, 131.6, 142.4, 160.5, 166.7, and 174.6.

A solution of 1.70 g (4.50 mmol) of diazo imide **36** in 100 mL of CH_2Cl_2 at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred for 4 h

(56) Tietze, L. F.; Bratz, M.; Pretor, M. *Chem. Ber.* **1989**, *122*, 1955.

at rt and was then concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 1.49 g (94%) of 3,7,7-trimethyl-10-(3-methylbut-3-enyl)-9-oxo-11-oxa-10-azatricyclo[6.2.1.$0^{1,6}$]undecane-8-carboxylic acid ethyl ester (**37**) as a white solid; mp 90−91 °C; IR (neat) 1751, 1728, and 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89−0.92 (m, 1H), 0.97 (d, 3H, J = 6.6 Hz), 1.04 (s, 3H), 1.20 (s, 3H), 1.34 (t, 3H, J = 7.1 Hz), 1.30−1.38 (m, 1H), 1.43−1.47 (m, 1H), 1.51−1.57 (m, 1H), 1.68−1.74 (m, 3H), 1.77 (s, 3H), 2.17−2.26 (m, 3H), 3.23−3.41 (m, 2H), 4.36 (q, 2H, J = 7.1 Hz), 4.80 (s, 1H), and 4.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6, 21.1, 22.4, 22.6, 26.4, 26.6, 28.5, 33.2, 36.9, 37.8, 38.6, 44.7, 51.7, 61.8, 92.1, 96.0, 112.5, 142.5, 165.5, and 169.4. Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.64; H, 8.91; N, 3.98.

8-Hydroxy-3,9,9,13-tetramethyl-7-oxo-6-azatricyclo-[8.4.0.$0^{1,6}$]tetradec-3-ene-8-carboxylic Acid Ethyl Ester (38) and 8-Hydroxy-3,9,9,13-tetramethyl-7-oxo-6-azatricyclo[8.4.0.$0^{1,6}$]tetradec-2-ene-8-carboxylic Acid Ethyl Ester (39). To a solution of 0.30 g (0.86 mmol) of cycloadduct **37** in 20 mL of CH_2Cl_2 at rt was added 1.61 mL (8.56 mmol) of a BF_3·2AcOH complex. The reaction mixture was stirred at 25 °C for 10 h, and the reaction was then quenched with 2 mL of EtOH. The solution was taken up in 50 mL of CH_2Cl_2 and extracted with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.24 g (80%) of 8-hydroxy-3,9,9,13-tetramethyl-7-oxo-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecene-8-carboxylic acid ethyl ester as a 4:1 mixture of olefinic regioisomers. The major isomer was assigned as 8-hydroxy-3,9,9,13-tetramethyl-7,6-azatricyclo[8.4.0.$0^{1,6}$]tetradec-3-ene-8-carboxylic acid ethyl ester (**38**) on the basis of its spectral properties: mp 110−111 °C; IR (neat) 3424, 1746, 1720, 1629, and 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, 3H, J = 6.3 Hz), 0.97 (s, 3H), 0.99−1.09 (m, 2H), 1.00 (s, 3H), 1.30 (t, 3H, J = 7.2 Hz), 1.34−1.44 (m, 1H), 1.68 (s, 3H), 1.70−1.75 (m, 2H), 1.87−1.91 (m, 1H), 2.16−2.22 (d, 1H, J = 16.8 Hz), 2.23 (dd, 1H, J = 12.1 and 2.1 Hz), 2.28 (dd, 1H, J = 12.1 and 4.5 Hz), 2.54 (d, 1H, J = 17.7 Hz), 3.46 (d, 1H, J = 18.2 Hz), 4.23 (q, 2H, J = 7.2 Hz), 4.27 (s, 1H), 4.98 (d, 1H, J = 18.2 Hz), and 5.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 20.5, 21.0, 22.7, 23.8, 24.7, 29.2, 34.0, 35.6, 38.4, 39.2, 43.5, 46.3, 58.9, 62.2, 81.7, 117.6, 131.4, 168.1, and 172.1. Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.74; H, 8.90; N, 4.02.

When the reaction was carried out in the presence of 10 equiv of TMSOTf, a 1:6 mixture of the olefinic isomers **38**/**39** was isolated. Flash silica gel chromatography afforded 8-hydroxy-3,9,9,13-tetramethyl-7-oxo-6-azatricyclo[8.4.0.$0^{1,6}$]tetradec-2-ene-8-carboxylic acid ethyl ester (**39**) as a crystalline solid: mp 113−114 °C; IR (neat) 3434, 1744, 1633, 1457, and 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.92 (m, 6H), 0.95−1.07 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz), 1.61 (m, 6H), 1.86 (m, 2H), 2.13 (dd, 1H, J = 11.5 and 2.7 Hz), 2.30 (m, 1H), 2.46 (dd, 1H, J = 11.5 and 2.7 Hz), 3.32 (dt, 1H, J = 12.5 and 5.4 Hz), 4.21 (m, 2H), 4.35 (s, 1H), 4.50 (dd, 1H, J = 13.3 and 6.9 Hz), and 5.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 18.9, 20.7, 22.8, 23.6, 23.8, 28.8, 29.1, 35.4, 36.5, 38.9, 46.0, 50.0, 60.3, 62.0, 81.7, 125.8, 132.0, 169.7, and 171.8. Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.70; H, 8.92; N, 3.99.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds with high-resolution mass spectra together with ORTEP drawings for structures **8**, **13**, **14**, and **17** (16 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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