An Approach toward Isoindolobenzazepines Using the Ammonium Ylide/Stevens [1,2]-Rearrangement Sequence

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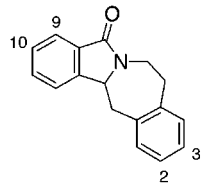
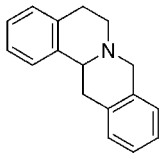
Ammonium ylides derived from the Cu(II)-catalyzed decomposition of α-diazo carbonyls tethered to tertiary amines underwent a benzylic Stevens [1,2]-rearrangement to give tetrahydroisoquinolines or benzazepines containing fused five-membered rings, a feature found in the cephalotaxus alkaloids. Model studies were also carried out toward the synthesis of lennoxamine, a member of the isoindolobenzazepine family of alkaloids. The approach utilized is based on the Rh(II)-catalyzed reaction of an α-diazo carbonyl compound containing an amido group in the γ-position. Treatment of several *N*,*N*-dialkyl-substituted amido diazo-esters with $Rh_2(OAc)_4$ in benzene at 80 °C in the presence of several dienophiles gave [4 + 2]-cycloadducts derived from the Diels−Alder reaction of a transient α-amino isobenzofuran intermediate. In the absence of an external trapping agent, no rearranged product derived from an ammonium ylide intermediate could be detected in the crude reaction mixture. In contrast to this result, reaction of the related diazo dihydroisoquinoline amide **46** with $Rh_2(OAc)_4$ afforded the isoindolobenzazepine ring system in high yield. Formation of the 5,7-fused skeleton was rationalized in terms of a spirocyclic ammonium ylide that underwent a preferential Stevens [1,2]-shift of the benzylic carbon atom. While we were ultimately thwarted in using the ammonium ylide/rearrangement cascade for a lennoxamine synthesis by an uncooperative diazo transfer reaction, the cascade sequence was shown to be useful for the preparation of various isoindolobenzazepines.

Polycyclic nitrogen containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active drugs.[1,2] Members of the botanical family *Berberidaceae* are known to be a rich source of alkaloids.[3] Recent studies of the Chilean Berberidaceae plant have provided the isoindolobenzazepine class of alkaloids isolated from Chilean barberries.[4] These plants were gathered in the vicinity of Ciudad Osorno, the southernmost region of Chile. The designation "*aporhoeadane*" has been applied to the family, connoting the close chemical kinship of the isoindolo[1,2-*b*][3]benzazepines (i.e., **1**) with the naturally occurring rhoeadine and papaverrubine alkaloids.[5] This ring system is biogenetically related to the highly oxidized protoberberine (**2**) alkaloids.[6] Typically, the isoindolobenzazepines bear oxygenated substituents on the benzene ring at positions 2, 3, 9, and 10 (usually two methoxy groups and a methylenedioxy group).[7] Such structures are interesting from both a synthetic and pharmacological point of view, since they incorporate the [3]benzazepine moiety, an important biological pharmacophore.[8]



1; isoindolobenzazepine ring system



2; Protoberberine ring system

Lennoxamine (**3**) and chilenine (**4**), isolated from the Chilean barberries species, represent the first examples of this interesting class of alkaloids.[6] Since their isolation in 1984, a number of related isoindolobenzazepine natural products have also been discovered.[4] Although members of this alkaloid family do not appear to possess any useful pharmacological activities, their unique structural features render them attractive synthetic targets. The ring system, which is accessible in vivo and in vitro by oxidation of berbine alkaloids,[6] has been the object of several synthetic approaches based on biomimetic pathways,[9] electrophilic alkylation,[10] photochemistry of enamides[11] or vinyl azide chemistry.[12]

* Corresponding author.

(1) (a) Szántay, C.; Blesko, G.; Hongy, K.; Dörnyei, G. In *The Alkaloids*; Academic: Orlando, 1986; Vol. 27, pp 131−268. (b) Szántay, C. *Pure Appl. Chem.* **1990**, *62*, 1299−1302.

(2) Cordell, G. A. In *Heterocyclic Compounds: The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, p 539.

(3) Shamma, M.; Rahimizadeh, M. *J. Nat. Prod.* **1986**, *49*, 398.

(4) (a) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39. (b) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599. (c) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M.; Urzúa, A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3957.

(5) Shamma, M.; Moniot, J. L. *Isoquinoline Alkaloid Research*; Plenum Press: New York, 1978.

(6) (a) Moniot, J. L.; Hindenlang, D. M.; Shamma, M. *J. Org. Chem.* **1979**, *44*, 4347. (b) Dorn, C. R.; Koszyk, F. J.; Lenz, G. R. *J. Org. Chem.* **1984**, *49*, 2642. (c) Teitel, S.; Klötzer, W.; Borgese, J.; Brossi, A. *Can. J. Chem.* **1972**, *50*, 2022.

(7) Napolitano, E.; Spinilli, G.; Fiaschi, R.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 785.

(8) (a) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645. (b) Csende, F.; Szabo, Z.; Stajer, G. *Heterocycles* **1993**, *36*, 1809.

(9) Epsztajn, J.; Grzebak, R.; Jozwiak, A. *Synthesis* **1996**, 1212.

(10) Kessar, S. V.; Singh, T.; Vohra, R. *Indian J. Chem.* **1991**, *30B*, 299.

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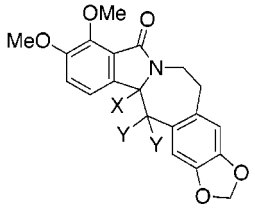
Published on Web 03/06/2001

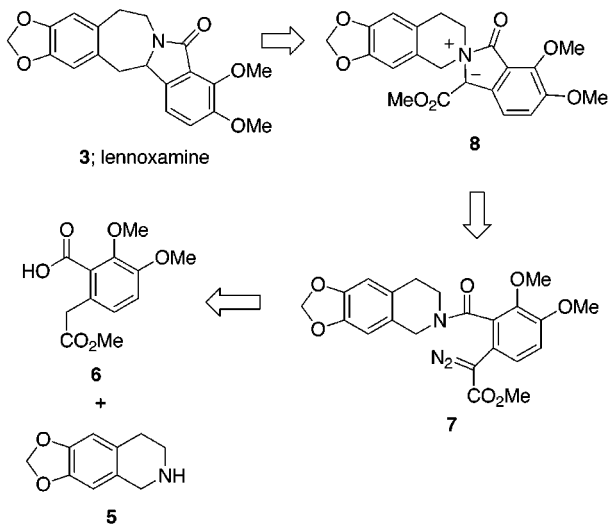


3; X = Y = H; lennoxamine
4; X = OH; Y-Y = O; chilenine

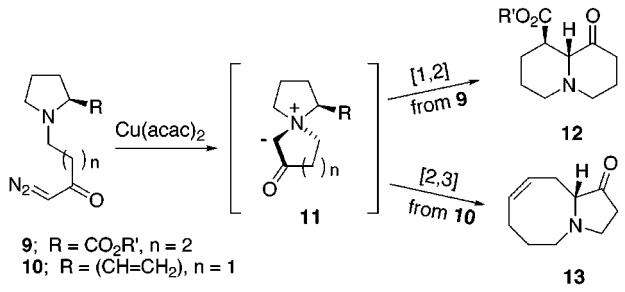
They are also accessible through (a) the cyclization of 2-arylbenzazepine derivatives *ortho*-substituted with carboxylate groups,[13] (b) the ring-expansion of isoindoloisoquinoline derivatives obtained by cyclization of acyliminium precursors,[14] (c) the regioselective 7-*endo*-*trig* radical cyclization of methylenephthalimidines,[15] (d) the Pummerer rearrangement of 3-phenylsulfanylisoindolinones followed by intramolecular electrophilic aromatic substitution and desulfurization,[16] and (e) the reduction/cyclization of 3-arylmethylene-lactams.[17]

Almost all of the synthetic approaches to lennoxamine **3** involve either the formation of the isoindolinone template or azepine ring system in the final step.[18] A strategy that we have found to be of some importance in the design of complex alkaloids is to make use of the tandem metallo-carbenoid generation/ylide rearrangement cascade.[19,20] The high efficiency and facility of this process suggested that this method might also serve as the basis for a new approach toward lennoxamine. Our strategy, which is depicted in retrosynthetic Scheme 1, is based on the Rh(II)-catalyzed reaction of diazoamide **7**. This compound could be obtained from the condensation of amine **5** with the benzoic acid derivative **6** followed by diazo transfer.[21−24] The notion of using **7** as the key starting material for lennoxamine was particularly attractive since the transition metal-catalyzed cyclization reaction was expected to produce the spirocyclic ammonium ylide **8**. A Stevens [1,2]-rearrangement would then provide the desired isoindolo[1,2-*b*][3]benzazepine ring system. In this paper we detail our observations dealing with the Rh(II)-catalyzed reaction of several α-diazo carbonyls tethered to both amino and amido

Scheme 1



Scheme 2



groups as well as the application of the method toward the synthesis of lennoxamine.

Results and Discussion

The tandem ammonium ylide generation/rearrangement sequence has been previously used in the preparation of various nitrogen-containing heterocycles.[25] A typical example involves the ring expansion reaction of spirocyclic ammonium ylides such as **11** which have been nicely exploited for the synthesis of a number of alkaloids. For example, the key step in West and Naidu's enantioselective synthesis of (−)-epilupinine[26] involved the ammonium ylide-Stevens [1,2]-rearrangement of the L-proline derivative **9** which furnished the advanced intermediate **12** in 84% yield and with 76% ee. Starting from a related L-proline derivative **10** (R = vinyl), Clark and Hodgson synthesized the partial CE ring system **13** in their approach to the Mazamine A ring skeleton[27] via an ammonium ylide-[2,3]-sigmatropic rearrangement (Scheme 2).[28]

Our own investigations of the ammonium ylide cascade sequence stemmed from an interest in using this strategy for the assemblage of the 5,7-fused ring framework found

(11) Bernhard, H. O.; Snieckus, V. *Tetrahedron Lett.* **1971**, 4867.
(12) Moody, C. J.; Warrellow, G. J. *Tetrahedron Lett.* **1987**, *28*, 6089.
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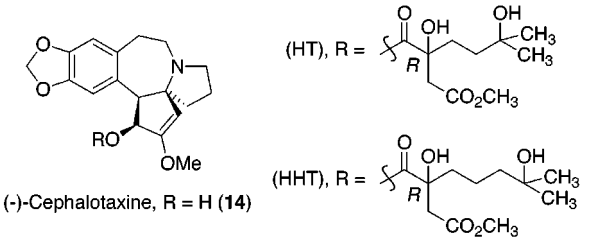
(15) Rodriguez, G.; Cid, M.; Saa, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1996**, *61*, 2780.
(16) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817.
(17) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491.
(18) For an exception, see: Rodriguez, G.; Casedo, L.; Dominguez, D.; Saa, C. *Tetrahedron Lett.* **1998**, *39*, 6551.
(19) (a) Curtis, E. A.; Worsencroft, K. J.; Padwa, A. *Tetrahedron Lett.* **1997**, *38*, 3319. (b) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78. (c) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.
(20) Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.
(21) (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. (b) Regitz, M.; Menz, F. *Chem. Ber.* **1968**, *101*, 2622. (c) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*; Academic Press: New York, 1986.
(22) (a) Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077. (b) Taber, D. F.; Gleeve, D. M.; Herr, R. J.; Moody, K.; Hennessy, M. J. *J. Org. Chem.* **1995**, *60*, 2283.
(23) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(24) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 4987.
(25) (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Ye, T.; McKervey, A. M. *Chem. Rev.* **1994**, *94*, 1901.
(26) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (b) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977. (c) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565.
(27) The Manzamine ring skeleton posseses a complex pentacyclic core containing 5-, 6-, 8-, and 13-membered rings. For ring notation, see ref 28.
(28) (a) Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2701. (b) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519. (c) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165.

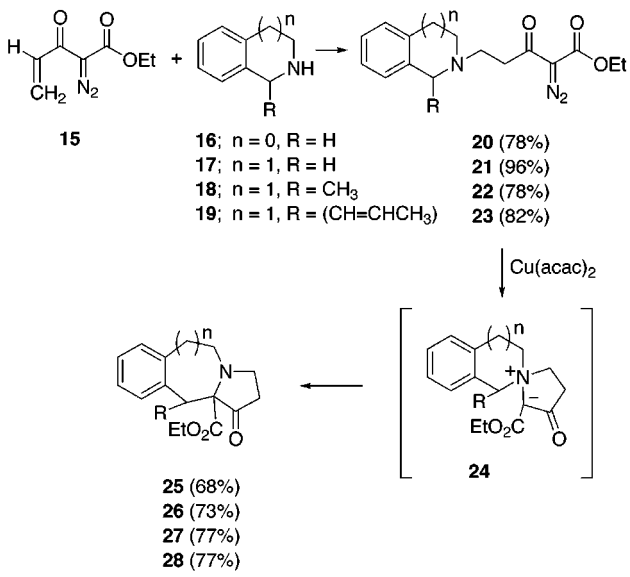
in cephalotaxine (**14**).[29] Cephalotaxine is the major alkaloid constituent isolated from *Cephalotaxus harringtonia*,[30] an evergreen tree native to Southern China. This alkaloid is of considerable interest due to the biological activity of its ester derivatives, harringtonine (HT) and homoharringtonine (HHT)[31] which have been used in the treatment of certain types of carcinomas.[32]



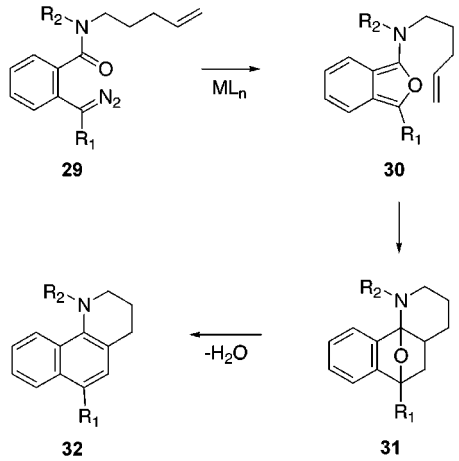
Our plan was to use the ammonium ylide/rearrangement sequence for the synthesis of the 5,7-fused ring system found in both cephalotaxine and lennoxamine. We first carried out some model studies in order to probe the likelihood of creating the desired skeleton by this method. Initial feasibility studies were conducted with amino keto esters **20**−**23**. We prepared diazo keto ester **15** using a diazo transfer reaction of the corresponding α,β-unsaturated keto ester.[33] Addition of **15** to a solution of the readily available amines **16**−**19** in CH_2Cl_2 at 25 °C afforded the desired amino keto esters **20**−**23** in 78−96% yield by conjugate addition. Early attempts at cyclizations using rhodium-based catalyst systems were observed to be sluggish, resulting in complex mixtures of products due to extended reaction times. Copper catalysis was found to be a superior alternative for effecting the desired rearrangement.[34] The $Cu(acac)_2$-catalyzed decomposition of the diazo compounds in toluene at reflux for 1 h furnished the rearranged 5,7-fused systems **25**−**28** in 68−77% yield as a 1:1-mixture of diastereomers. The formation of these ring-expanded products can be rationalized by the initial formation of ammonium ylide **24** followed by a preferential Stevens [1,2]-shift of the benzylic carbon atom.[35] Interestingly, in the case of **21**, it was possible to isolate ylide **24** (R = H) as a white crystalline solid. Further heating of the ylide in the absence of the Cu-catalyst cleanly afforded **26** in high yield. The reaction sequence worked well for both five (**16**) and six-membered (**17**−**19**) ring amine precursors leading to tetrahydroisoquinolines (**25**) or benzazepines (**26**−**28**) (Scheme 3), respectively, which contain the required fused 5,7-ring system present in many natural product systems.[36]

Unlike the cephalotaxine approach that required the presence of a γ-amino-substituted diazoester, the strategy

Scheme 3



Scheme 4



delineated in Scheme 1 for the synthesis of lennoxamine relies on a tandem ammonium ylide/Stevens rearrangement of an appropriately substituted amido diazoester (i.e., **7**). To pursue this approach, it was necessary to first probe whether the initially formed metallo-carbenoid would lead to an ammonium ylide or result in isobenzofuran formation via a carbonyl ylide intermediate. There are several reports in the literature where the metal-induced decomposition of *o*-(diazomethyl)benzamide derivatives preferentially gave benzannulated quinolines (Scheme 4).[37] Presumably, this reaction sequence involves the initial formation of an aminoisobenzofuran intermediate (i.e., **30**) that was trapped intramolecularly with subsequent elimination of water as shown in Scheme 4.

Recent results from our laboratory have shown that the Rh(II)-catalyzed reaction of α-diazoesters containing an amido group in the γ-position can lead to either five-membered ammonium or carbonyl ylides depending on the reaction conditions used.[20] The metallo-carbenoid

(29) Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4159.

(30) (a) Huang, L.; Xue, Z. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, Chapter 3. (b) Wickremesinhe, R. M.; Arteca, R. N. *J. Liq. Chrom., Relat. Technol.* **1996**, *19*, 889.

(31) Hudlicky, T.; Kwart, L. D.; Reed, J. W. In *Alkaloids. Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer-Verlag: New York, 1987; Vol. 5, Chapter 5.

(32) (a) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr. *J. Pharm. Sci.* **1972**, *61*, 1227. (b) Zhou, D. C.; Zittoun, R.; Marie, J. P. *Bull. Cancer* **1995**, *82*, 987.

(33) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.

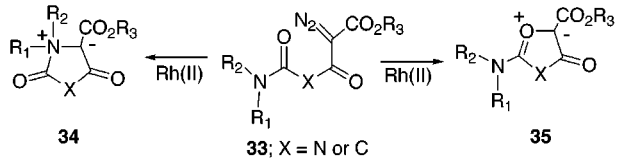
(34) For reports regarding the superiority of copper catalysts for generation of onium ylides, see: (a) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892. (b) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.

(35) For a similar reaction in the 6,6-system, see: Zaragoza, F. *Synlett* **1995**, 237.

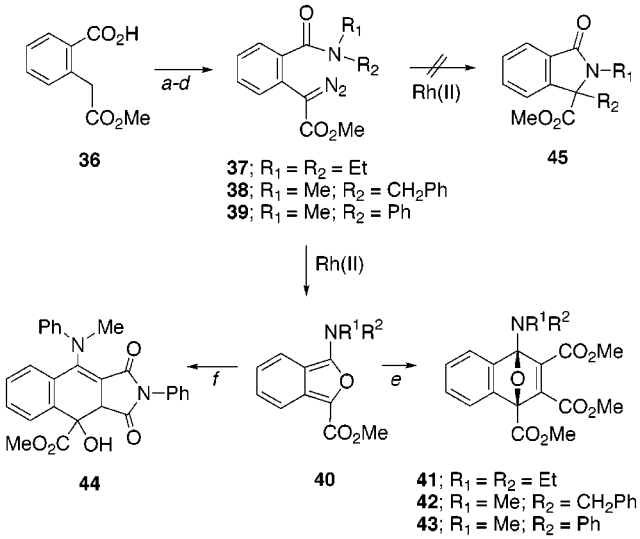
(36) Further studies are currently underway to determine the scope of the reaction with regard to ring size, ring substitution, catalytic effects, and its further application to the synthesis of cephalotaxine and related target molecules.

(37) (a) Peters, O.; Friedrichsen, W. *Tetrahedron Lett.* **1995**, *36*, 8581. (b) Bernabé, P.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1998**, *39*, 9785. (c) Sarkar, T. K.; Ghosh, S. K.; Nandy, S. K.; Chow, T. J. *Tetrahedron Lett.* **1999**, *40*, 397. (d) Sarkar, T. K.; Basak, S.; Ghosh, S. K. *Tetrahedron Lett.* **2000**, *41*, 759.

Scheme 5



Scheme 6[a]

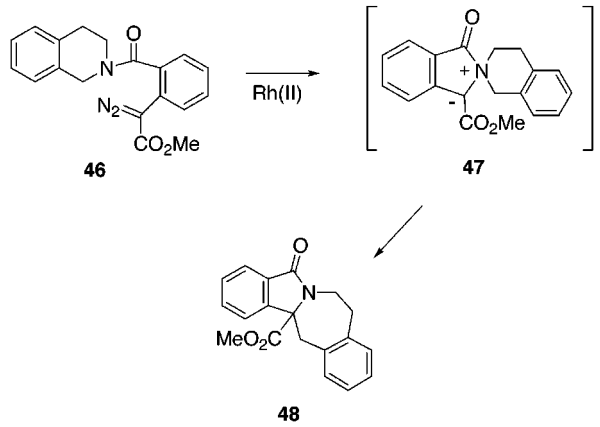


[a] Reagents: (a) $(COCl)_2$; (b) R_1NHR_2; (c) NaHMDS; (d) MsN_3; (e) DMAD; (f) *N*-phenylmaleimide.

intermediate generated in these reactions could either interact with the lone pair of electrons on the amide nitrogen (ammonium ylide formation) or the lone pair of electrons on the carbonyl oxygen (carbonyl ylide formation) (Scheme 5). The experimental observations reflect a catalyst-promoted system of equilibria with a thermodynamic bias for the ammonium ylide. This chemoselectivity issue is important because the key step in the planned lennoxamine synthesis requires selective ammonium ylide formation.

To sort out the factors influencing the regiochemistry of the cyclization, we opted to examine the Rh(II)-catalyzed behavior of several simple acyclic *o*-diazobenzamides. These *N*,*N*-dialkyl-substituted amido diazoesters (**37**−**39**) were easily prepared from the readily available carboxylic acid **36**[38] by the synthetic protocol shown in Scheme 6. When these substrates were treated with $Rh_2(OAc)_4$ at 80 °C in benzene with dimethyl acetylenedicarboxylate (DMAD), cycloadducts **41**−**43** were obtained in 85−97% yield. With *N*-phenylmaleimide as the trapping agent, the ring-opened cycloadduct **44** was isolated in 65% yield from the Rh(II)-catalyzed reaction of **39**. The formation of these products is easily rationalized in terms of a [4 + 2]-cycloaddition[39] of an initially formed amino isobenzofuran intermediate **40** with the added dienophile. Most importantly, in the absence of an external trapping agent, no rearranged product (i.e., **45**) derived from an ammonium ylide intermediate could be detected in the crude reaction mixture. The reaction mixture contained a significant amount of a dark tar which resisted characterization.

Scheme 7



The exclusive formation of isobenzofuran **40** from the Rh(II)-catalyzed reaction of α-diazo ketoamides **37**−**39**, while not unprecedented,[37] was disappointing for our planned lennoxamine synthesis. We decided at this point that the simplest adjustment to our model system would be to incorporate a tetrahydroisoquinoline skeleton within the amide moiety. This led us to study the Rh(II)-catalyzed behavior of the cyclic diazo ketoamide **46**, which is a more accurate model system for lennoxamine. In stark contrast to the acyclic *o*-(diazo)-benzamide series, and for reasons that still remain obscure, the reaction of **46** with $Rh_2(OAc)_4$ afforded the desired isoindolobenzazepine ring system in 83% yield. Formation of the 5,7-fused skeleton can be attributed to the initial formation of the spirocyclic ammonium ylide **47** followed by a preferential Stevens [1,2]-shift of the benzylic carbon atom to give **48** (Scheme 7).

With this encouraging result in hand, we proceeded to apply this strategy to the synthesis of lennoxamine. Amide **51** was readily prepared by conversion of the known carboxylic acid **49**[40] into the corresponding acid chloride followed by reaction with tetrahydro-1,2-dioxolo-[4,5-*g*]isoquinoline.[41] Unfortunately, all of our attempts to carry out the critical diazo transfer reaction using a wide variety of literature procedures did not give the desired diazo amide **52**. No tractable product was ever isolated from these reactions. Attempts to find alternative methods[42] for the diazo transfer were not successful. The failed diazo transfer of **51** to **52** may be attributed to the presence of the methoxy group in the 5-position of the aromatic ring that diminishes the acidity of the benzylic protons. Diazo transfer reactions are known to be extremely sensitive to the nature of the substrate. Indeed, conversion of the related amide **54** (R = H), which is devoid of the 5-methoxy group, to the corresponding amido diazoester **55** proceeded in 88% yield without any of the difficulties encountered with **51**. With amido diazoester **55** in hand, we carried out the Rh(II)-catalyzed

(38) Hutchings, M. G.; Chippendale, A. M.; Ferguson, I. *Tetrahedron* **1988**, *44*, 3727.

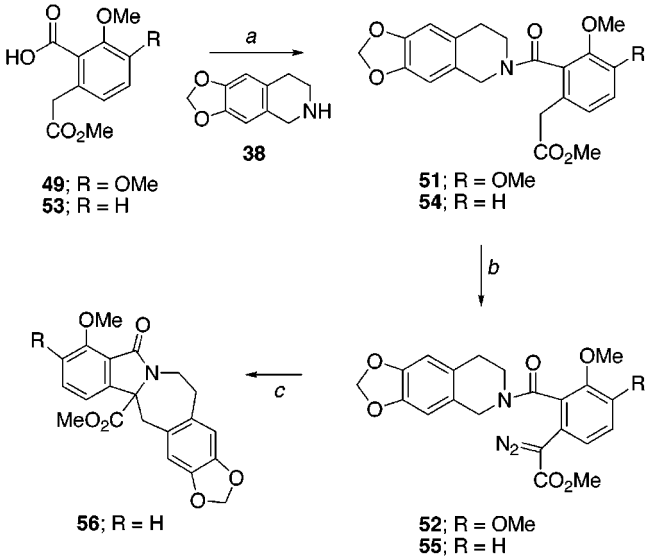
(39) (a) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1981**, *26*, 135. (b) Hildebrandt, K.; Friedrichsen, W. *Heterocycles* **1989**, *29*, 1243.

(40) Schöpf, C.; Jack-Tettweiler, I.; Perry-Fehrenbauch, P.; Winterhalder, L. *Justus Liebigs Ann. Chem.* **1940**, 77.

(41) Meyers, A. I.; Matulenko, M. A. *J. Org. Chem.* **1996**, *61*, 573.

(42) For reviews on diazo transfer reagents, see: (a) Bollinger, F. W.; Tuma, L. D. *Synlett* **1996**, 406. (b) Khare, A. B.; McKenna, C. E. *Synthesis* **1991**, 405. (c) Creary, X. *Org. Synth.* **1985**, *64*, 207. (d) Monteiro, H. *Synth. Commun.* **1987**, *17*, 983. (e) Hendrickson, J. B.; Wolff, W. A. *J. Org. Chem.* **1968**, *33*, 3610. (f) Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567. (g) Balli, H.; Low, R.; Muller, V.; Rempfler, H.; Sezen-Gezgin, G. *Helv. Chim. Acta* **1978**, *61*, 97. (h) Kokel, B.; Viehe, H. G. *Angew. Chem.* **1980**, *92*, 754. (i) Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *Synth. Commun.* **1981**, *11*, 947. (j) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

Scheme 8[a]



[a] Reagents: (a) $(COCl)_2$; (b) DBU, TsN_3; (c) $Rh_2(OAc)_4$.

reaction and were pleased to note that the desired ring expanded lactam **56** was formed in 75% yield. While we were ultimately thwarted in using the ammonium ylide/rearrangement cascade for a lennoxamine synthesis by an uncooperative diazo transfer reaction, there is no question that the method has shown its potential for the synthesis of 5,7-fused nitrogen heterocycles. In one operation, the isoindolo-benzazepine ring system was prepared in high yield from readily available starting materials. Application of this method to the synthesis of a number of related alkaloids is currently being explored and will be reported on at a later date.

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 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-Diazo-3-oxo-pent-4-enoic Acid Ethyl Ester (15). To a solution of 3.2 g (22 mmol) of 3-oxo-pent-4-enoic acid ethyl ester,[33] 2.7 g (22 mmol) of mesyl azide, and 100 mL of CH_2Cl_2 at 0 °C was added dropwise 6.3 mL (45 mmol) of Et_3N. After the addition was complete, the solution was allowed to warm to room temperature and was stirred for 2 h. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 2.3 g (61%) of **15** as a yellow oil: IR (neat) 2983, 2137, 1717, 1650, and 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, J = 7.0 Hz), 4.30 (q, 2H, J = 7.0 Hz), 5.73 (dd, 1H, J = 10.4 and 1.7 Hz), 6.44 (dd, 1H, J = 17.1 and 1.7 Hz), and 7.38−7.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 61.4, 128.1, 128.2, 131.4, 160.9, and 181.6. Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.79; H, 4.70; N, 16.36.

General Procedure for Conjugate Addition Reaction. To a 0.1 M solution of the appropriate amine in CH_2Cl_2 was added dropwise 0.9 equiv of 2-diazo-3-oxo-pent-4-enoic acid ethyl ester (**15**) as a solution in CH_2Cl_2. After the reaction was complete, the solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography.

2-Diazo-5-(1,3-dihydroisoindol-2-yl)-3-oxopentanoic Acid Ethyl Ester (20). Following the general procedure, the reaction of 0.23 g (2.0 mmol) of 1,3-dihydroisoindole (**16**) and diazoester **15** for 1 h gave 0.4 g (78%) of **20** as a pale yellow oil: IR (neat) 3029, 2933, 2769, 2136, 1717, and 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, J = 7.2 Hz), 3.08−3.19 (m, 4H), 3.97 (s, 4H), 4.31 (q, 2H, J = 7.2 Hz), and 7.17 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 39.1, 50.6, 58.9, 61.4, 76.3, 122.2, 126.6, 139.9, 161.2, and 191.4. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.69; H, 5.97; N, 14.63. Found: C, 62.58; H, 5.86; N, 14.41.

2-Diazo-5-(3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxopentanoic Acid Ethyl Ester (21). Following the general procedure, the reaction of 0.5 g (3.9 mmol) of tetrahydroisoquinoline (**17**) and diazoester **15** for 1 h gave 1.0 g (96%) of **21** as a pale yellow oil: IR (neat) 3065, 2919, 2136, 1717, and 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, 3H, J = 7.2 Hz), 2.77 (t, 2H, J = 6.1 Hz), 2.89−2.93 (m, 4H), 3.16 (t, 2H, J = 7.2 Hz), 3.67 (s, 2H), 4.28 (q, 2H, J = 7.2 Hz), and 6.99−7.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 28.9, 37.5, 50.6, 52.7, 55.7, 61.2, 76.1, 125.4, 125.9, 126.4, 128.4, 134.0, 134.5, 161.1, and 191.5. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.89; H, 6.38; N, 13.93.

2-Diazo-5-(1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxopentanoic Acid Ethyl Ester (22). Following the general procedure, the reaction of 0.35 g (2.3 mmol) of 1-methyltetrahydroisoquinoline (**18**) and diazoester **15** for 5 h gave 0.5 g (78%) of **22** as a pale yellow oil: IR (neat) 3049, 2971, 2821, 2135, 1712, and 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28−1.35 (m, 6H), 2.69−3.20 (m, 8H), 3.90 (q, 1H, J = 6.6 Hz), 4.30 (q, 2H, J = 7.1 Hz), and 7.05−7.13 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 19.6, 27.2, 29.2, 37.8, 38.4, 44.5, 49.2, 50.8, 53.0, 56.0, 56.6, 61.4, 76.3, 125.6, 125.7, 125.8, 126.1, 126.6, 127.3, 128.6, 128.8, 134.2, 134.3, 140.3, 161.3, and 192.0. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.47; H, 6.66; N, 13.26.

2-Diazo-3-oxo-5-(1-propenyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-pentanoic Acid Ethyl Ester (23). Following the general procedure, the reaction of 1.9 g (11 mmol) of 1-propenyltetrahydroisoquinoline (**19**) and diazoester **15** for 12 h gave 3.0 g (82%) of **23** as a pale yellow oil: IR (neat) 3018, 2911, 2805, 2129, 1716, and 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, 3H, J = 7.1 Hz), 1.75 (d, 1H, J = 6.2 Hz), 1.87 (d, 2H, J = 6.7 Hz), 2.55−3.25 (m, 8H), 4.05 (d, 0.67H, J = 8.6 Hz), 4.29 (q, 2H, J = 7.1 Hz), 4.45 (d, 0.33H, J = 9.8 Hz), 5.37−5.45 (m, 1H), 5.66−5.83 (m, 1H), and 7.01−7.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 14.5, 17.9, 29.2, 29.7, 37.7, 37.8, 46.8, 47.7, 49.5, 49.7, 59.6, 61.4, 65.6, 76.2, 125.5, 125.7, 126.1, 126.8, 127.7, 128.4, 128.7, 129.1, 132.2, 132.3, 134.6, 134.7, 137.3, 137.5, 161.4, and 192.1. Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.84; H, 6.84; N, 12.24.

1-Oxo-2,3,5,10-tetrahydro-1*H*-pyrrolo[1,2-*b*]isoquinoline-10a-carboxylic Acid Ethyl Ester (25). A 0.1 g (0.35 mmol) sample of 2-diazo-5-(1,3-dihydroisoindol-2-yl)-3-oxopentanoic acid ethyl ester (**20**) and 0.05 g of $Cu(acac)_2$ in 10 mL of xylene was heated at reflux for 15 min to give 0.06 g (68%) of **25** as a pale yellow solid after silica gel chromatography: mp 85−87 °C; IR (neat) 2980, 2927, 2851, 1761, and 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, 3H, J = 7.2 Hz), 2.50−2.70 (m, 2H), 2.87 (d, 1H, J = 15.9 Hz), 3.25 (dt, 1H, J = 10.6 and 4.1 Hz), 3.38−3.48 (m, 2H), 4.01 (d, 1H, J = 15.3 Hz), 4.11 (q, 2H, J = 7.2 Hz), 4.17 (d, 1H, J = 15.3 Hz), and 7.06−7.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 32.1, 35.8, 46.9, 50.2, 61.4, 70.1, 126.1, 126.4, 126.5, 129.2, 132.3, 133.4, 168.8, and 209.8. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.41; H, 6.58; N, 5.33.

1-Oxo-2,3,6,11-tetrahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine-11a-carboxylic Acid Ethyl Ester (26). A 0.3 g (1.0 mmol) sample of 2-diazo-5-(3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxopentanoic acid ethyl ester (**21**) and 0.07 g of $Cu(acac)_2$ in 10 mL of xylene was heated at reflux for 15 min to give 0.2 g (73%) of **26** as a pale yellow oil: IR (neat) 3023, 2933, 2856, 1764, and 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, 3H, J = 7.2 Hz), 2.43−2.58 (m, 2H), 2.75−2.81 (m, 1H), 3.00 (d, 1H, J = 14.3 Hz), 3.04−3.11 (m, 2H), 3.22−3.43 (m, 3H),

3.46 (d, 1H, J = 14.3 Hz), 3.94 (q, 2H, J = 7.2 Hz), and 7.07−7.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 34.9, 36.0, 40.6, 47.4, 48.5, 60.9, 73.3, 126.2, 126.9, 129.0, 130.9, 136.0, 141.3, 167.4, and 208.3. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.37; H, 7.01; N, 5.10.

11-Methyl-1-oxo-2,3,6,11-tetrahydro-1*H*,5*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepine-11a-carboxylic Acid Ethyl Ester (27). A 0.5 g (1.6 mmol) sample of 2-diazo-5-(1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxopentanoic acid ethyl ester (**22**) and 0.08 g of $Cu(acac)_2$ in 10 mL of xylene was heated at reflux for 1 h to give **27** as a 1:1-mixture of diastereomers. The two diastereomers were separated by silica gel chromatography. The first fraction contained 0.17 g (37%) of a white solid, mp 63−65 °C; IR (neat) 3060, 2977, 2934, 2856, 1762, and 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.0 (t, 3H, J = 7.2 Hz), 1.17 (d, 3H, J = 7.2 Hz), 2.45−2.50 (m, 2H), 2.61−2.67 (m, 1H), 3.04−3.11 (m, 1H), 3.28−3.49 (m, 4H), 3.76 (q, 1H, J = 7.2 Hz), 3.80−3.94 (m, 2H), and 7.00−7.21 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.8, 36.3, 36.8, 46.0, 48.7, 49.0, 60.9, 78.1, 126.4, 126.6, 130.9, 131.5, 139.9, 141.7, 167.8, and 210.3. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.22; H, 7.26; N, 4.75.

The other diastereomer was also isolated as a white solid, mp 65−67 °C; IR (neat) 3061, 2979, 2932, 2854, 1761, and 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, 3H, J = 7.1 Hz), 1.55 (d, 3H, J = 7.4 Hz), 2.50 (t, 2H, J = 6.7 Hz), 2.66 (dd, 1H, J = 13.7 and 5.4 Hz), 3.08−3.21 (m, 2H), 3.33−3.48 (m, 3H), 3.71 (q, 1H, J = 7.4 Hz), 3.86−4.03 (m, 2H), and 7.05−7.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 16.5, 33.4, 35.2, 39.5, 46.3, 48.7, 61.0, 75.2, 126.4, 126.8, 127.9, 128.8, 140.8, 141.1, 167.6, and 207.2. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.10; H, 7.35; N, 4.95.

1-Oxo-11-propenyl-2,3,6,11-tetrahydro-1*H*,5*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepine-11a-carboxylic Acid Ethyl Ester (28). A 3.0 g (8.8 mmol) sample of 2-diazo-3-oxo-5-(1-propenyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-pentanoic acid ethyl ester (**23**) and 0.1 g of $Cu(acac)_2$ in 10 mL of toluene was heated at reflux for 1 h to give 2.1 g (77%) of **28** as a yellow solid after silica gel chromatography: mp 69−71 °C; IR (neat) 3059, 2979, 2933, 2854, 1763, and 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98−1.27 (m, 3H), 1.58 (d, 1H, J = 6.5 Hz), 1.70 (dd, 1H, J = 6.8 and 1.6 Hz), 2.41−2.74 (m, 4H), 2.97−3.14 (m, 1H), 3.27−3.48 (m, 4H), 3.83−4.16 (m, 2H), 4.28 (d, 0.5H, J = 6.6 Hz), 4.59 (d, 0.5H, J = 9.5 Hz), 5.25−5.35 (m, 0.5H), 5.45−5.55 (m, 0.5H), 5.64−5.71 (m, 0.5H), 6.00−6.08 (m, 0.5H), and 7.00−7.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 13.9, 18.0, 35.8, 36.0, 36.6, 36.8, 48.6, 48.7, 48.9, 49.0, 54.5, 60.8, 77.5, 77.9, 126.0, 126.1, 126.2, 126.4, 126.5, 126.7, 127.7, 127.9, 130.6, 130.7, 131.6, 131.9, 139.3, 139.7, 139.9, 140.1, 167.3, 167.5, 208.9, and 209.3. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.71; H, 7.36; N, 4.40.

(2-Diethylcarbamoylphenyl)acetic Acid Methyl Ester. To a stirred solution of 5.0 g (26 mmol) of carboxylic acid **36**[20] in 125 mL of CH_2Cl_2 were added 4.5 mL (52 mmol) of oxalyl chloride and two drops of DMF. The mixture was stirred at room temperature for 2 h, and the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in 10 mL of CH_2Cl_2, and this was added to a solution of 6.7 mL (65 mmol) of diethylamine in 125 mL of CH_2Cl_2 at 0 °C. The reaction was allowed to warm to room temperature and was stirred for an additional 24 h. The mixture was quenched with 100 mL of water and the organic layer was separated and washed with 100 mL of a 10% HCl solution, 100 mL of a saturated $NaHCO_3$ solution, and 100 mL of a saturated NaCl solution. The solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude residue was chromatographed on silica gel to give 3.8 g (60%) of the title compound as a pale yellow oil; IR (neat) 3061, 2967, 1737, 1630, and 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, 3H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz), 3.13−3.18 (m, 2H), 3.67 (s, 3H), 3.72−3.88 (m, 4H), and 7.20−7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5, 13.8, 37.9, 38.6, 42.8, 51.9, 125.6, 126.9, 128.8, 130.8, 137.2, 170.1, and 171.6; HRMS Calcd for $C_{14}H_{19}NO_3$: 249.3124. Found: 249.3124.

Diazo-(2-diethylcarbamoylphenyl)acetic Acid Methyl Ester (37). To a stirred solution of 0.5 g (2.0 mmol) of the above amido ester in 5 mL of THF at −78 °C was added 2.4 mL (2.4 mmol) of a 1.0 M THF solution of lithium bis-(trimethylsilyl) amide dropwise over a 20 min period. The mixture was stirred at −78 °C for 1 h, and 0.5 g (2.2 mmol) of MsN_3 in 7 mL of THF was added in one portion. The solution was stirred at −78 °C for 1 h, warmed to room temperature, and stirred at room temperature for an additional 3 h. The mixture was quenched with 30 mL of a phosphate buffer solution (pH = 7.0) and extracted with CH_2Cl_2. The combined organic extracts were washed with 50 mL of a saturated NaCl solution, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford 0.18 g (40%) of **37** as a pale yellow oil which was used in the next step without further purification; IR (neat) 2096, 1744, 1704, 1631, and 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, 3H, J = 6.8 Hz), 1.25 (t, 3H, J = 6.8 Hz), 3.16−3.18 (m, 2H), 3.20−3.30 (m, 2H), 3.81 (s, 3H), 7.29 (dd, 1H, J = 7.6 and 1.2 Hz), 7.34 (td, 1H, J = 7.6 and 1.2 Hz), 7.42 (td, 1H, J = 7.6 and 1.6 Hz), and 7.51−7.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6, 13.7, 38.8, 42.8, 52.1, 52.9, 126.9, 128.2, 129.2, 130.6, 131.3, 136.6, 169.4 and 171.2.

8-Diethyl-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene-1,9,10-tricarboxylic Acid Trimethyl Ester (41). To a stirred solution of 0.05 g (0.18 mmol) of diazoester **37** in 10 mL of benzene were added 0.03 mL (0.27 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) acetate, and the mixture was heated at reflux for 2 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel gave 0.03 g (44%) of **41** as a yellow oil; IR (neat) 1740, 1734, 1703, 1235, 1155, and 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14−1.25 (m, 6H), 3.15−3.21 (m, 2H), 3.63 (s, 3H), 3.75 (s, 6H), 3.87 (d, 1H, J = 6.4 Hz), 3.93 (d, 1H, J = 6.4 Hz), and 7.43−8.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.1, 16.5, 29.6, 44.8, 45.8, 50.6, 52.8, 53.3, 82.8, 126.1, 126.2, 126.5, 127.2, 127.3, 130.1, 134.2, 153.7, 166.1, 166.8, and 168.3. Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.67; H, 5.96; N, 3.60. Found: C, 61.58; H, 5.79; N, 3.62.

[2-(Benzylmethylcarbamoyl)phenyl]acetic Acid Methyl Ester. To a stirred solution of 5.0 g (26 mmol) of carboxylic acid **36** in 125 mL of CH_2Cl_2 were added 6.8 mL (78 mmol) of oxalyl chloride and two drops of DMF. The mixture was stirred at room temperature for 2 h, and the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in 15 mL of CH_2Cl_2, and this was added to a solution of 5.2 mL (65 mmol) of *N*-benzylmethylamine in 125 mL of CH_2Cl_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 h. The mixture was quenched with 150 mL of water, the organic layer was separated, washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel gave 4.1 g (53%) of the title compound as a pale yellow oil; IR (neat) 1737, 1635, 1600, 1265, 1170, and 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.77 (s, 3H), 3.58 (s, 3H), 3.80 (s, 2H), 4.76 (s, 2H), and 7.17−7.37 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.4, 38.1, 50.3, 51.9, 126.4, 126.8, 127.1, 127.5, 128.3, 128.6, 128.8, 129.1, 129.3, 131.1, 136.6, 136.9, 170.8, and 171.6; HRMS Calcd for $C_{18}H_{19}NO_3$: 297.1364. Found: 297.1365.

[2-(Benzylmethylcarbamoyl)phenyl]diazoacetic Acid Methyl Ester (38). To a stirred solution of 0.5 g (1.6 mmol) of the above amido ester in 15 mL of THF at −78 °C was added 1.9 mL (1.9 mmol) of a 1.0 M THF solution of sodium bis(trimethylsilyl)amide dropwise over a 20 min period. The mixture was stirred at −78 °C for 1 h, and 0.2 mL (1.9 mmol) of mesyl azide in 1 mL of THF was added in one portion. The solution was stirred at −78 °C for 2 h, warmed to room temperature, and stirred for an additional 2 h. The mixture was quenched with 30 mL of a phosphate buffer solution (pH = 7.0) and extracted with CH_2Cl_2. The combined organic

extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 0.3 g (63%) of **38** as a pale yellow oil which was used in the next step without further purification; IR (neat) 2103, 1744, 1631, 1697, 1598, and 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.78 (s, 3H), 3.71 (s, 3H), 4.72 (d, 1H, $J = 14.8$ Hz), 4.85 (d, 1H, $J = 14.8$ Hz), and 7.18−7.49 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.5, 50.4, 52.9, 61.7, 126.8, 127.6, 127.7, 127.9, 128.3, 128.4, 128.7, 128.8, 128.9, 129.7, 136.3, 136.6, 169.4, and 169.8.

8-(Benzylmethylamino)-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene-1,9,10-tricarboxylic Acid Trimethyl Ester (42). To a stirred solution of 0.05 g (0.15 mmol) of diazo amido-ester **38** in 10 mL of benzene were added 0.03 mL (0.2 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) perfluorobutyrate, and the reaction mixture was heated at reflux for 24 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to provide 0.06 g (97%) of **42** as a clear oil; IR (neat) 1754, 1735, 1634, 1602, 1221, 1177, and 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.66 (s, 3H), 3.81 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 4.51 (d, 1H, $J = 14.4$ Hz), 4.76 (d, 1H, $J = 14.4$ Hz), and 7.01−7.57 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.9, 36.6, 50.4, 52.7, 53.5, 62.9, 126.1, 126.5, 126.9, 127.5, 128.2, 128.6, 129.3, 129.8, 130.0, 130.4, 135.9, 136.5, 139.6, 158.6, 160.2, 167.4, 169.5, and 170.2. Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.88; H, 5.30; N, 3.20. Found: C, 65.72; H, 5.29; N, 3.02.

[2-(Methylphenylcarbamoyl)phenyl]acetic Acid Methyl Ester. To a stirred solution of 5.0 g (26 mmol) of carboxylic acid **36** in 125 mL of CH_2Cl_2 were added 4.5 mL (52 mmol) of oxalyl chloride and two drops of DMF. The mixture was stirred at room temperature for 2 h, and the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in 15 mL of CH_2Cl_2, and this was added to a solution of 7.0 mL (65 mmol) of *N*-methylaniline in 125 mL of CH_2Cl_2 at 0 °C. The reaction was allowed to warm to room temperature and was stirred at room temperature for an additional 18 h. The mixture was quenched with 100 mL of water, the organic layer was separated and washed with 150 mL of a 10% HCl solution, 150 mL of a saturated $NaHCO_3$ solution, and 150 mL of a saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 3.8 g (51%) of the titled compound as a yellow oil; IR (neat) 1735, 1646, 1595, 1215, 1164, and 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.48 (brs, 3H), 3.73 (s, 3H), 3.88 (s, 2H), 6.96 (brs, 2H), and 7.06−7.21 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.6, 38.4, 51.9, 126.1, 126.3, 128.6, 128.8, 128.9, 130.8, 132.3, 135.5, 144.0, 169.9, and 171.7; HRMS Calcd for $C_{17}H_{17}NO_3$: 283.1208. Found: 283.1208.

Diazo-[2-(methylphenylcarbamoyl)phenyl]acetic Acid Methyl Ester (39). To a stirred solution of 2.0 g (7.1 mmol) of the above amido ester in 45 mL of THF at −78 °C was added 7.8 mL (7.8 mmol) of a 1.0 M THF solution of sodium bis(trimethyl-silyl)amide dropwise over a 30 min period. The mixture was stirred at −78 °C for 1 h, and 1.0 mL (7.8 mmol) of mesyl azide in 2 mL of THF was added in one portion. The solution was stirred at −78 °C for 2 h, warmed to room temperature, and stirred at room temperature for an additional 2 h. The mixture was quenched with 50 mL of a phosphate buffer solution (pH = 7.0) and extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford 1.0 g (47%) of **39** as a yellow oil which was used in the next step without further purification; IR (neat) 2108, 1743, 1635, 1594, 1203, 1115, and 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.53 (brs, 3H), 3.82 (s, 3H), and 6.96−7.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.6, 52.8, 61.6, 126.5, 126.7, 127.7, 127.9, 128.1, 129.0, 129.4, 132.7, 135.7, 143.8, 168.9, and 169.6.

8-(Methylphenylamino)-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene-1,9,10-tricarboxylic Acid Trimethyl Ester (43). To a stirred solution of 0.05 g (0.16 mmol) of diazo amido-ester **39** in 10 mL of benzene were added 0.03 mL (0.24 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) acetate, and the reaction was heated at reflux for 24 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel gave 0.06 g (94%) of **43** as a pale yellow solid; mp 185−186 °C; IR (neat) 1747, 1734, 1633, 1593, 1216, and 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.46 (brs, 3H), 3.84 (s, 3H), 3.97 (s, 3H), 4.03 (brs, 3H), 6.96−7.19 (m, 8H), and 7.43−7.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.8, 52.6, 53.4, 53.5, 62.6, 126.3, 126.7, 128.3, 129.1, 129.5, 130.2, 130.5, 131.0, 135.4, 139.3, 143.7, 158.9, 160.4, 167.5, and 168.8. Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31. Found: C, 65.16; H, 4.86; N, 3.35.

4-Hydroxy-9-(methylphenylamino)-1,3-dioxo-2-phenyl-2,3,3*a*,4-tetrahydro-1*H*-benzo[*f*]isoindole-4-carboxylic Acid Methyl Ester (44). To a stirred solution of 0.05 g (0.16 mmol) of diazo amido-ester **39** in 10 mL of benzene were added 0.04 g (0.24 mmol) of *N*-phenylmaleimide and 2 mg of rhodium(II) perfluorobutyrate, and the reaction was heated at reflux for 48 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Purification of the crude residue by flash chromatography on silica gel gave 0.05 g (65%) of the ring opened cycloadduct **44** as a pale yellow oil: IR (neat) 1709, 1649, 1595, and 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.55 (s, 3H), 3.85 (s, 3H), 5.31 (s, 1H), 5.74 (brs, 1H), and 6.84−7.52 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7, 38.2, 53.2, 57.8, 61.9, 87.9, 125.8, 126.2, 126.8, 127.2, 127.8, 128.7, 128.9, 129.2, 130.1, 131.2, 131.8, 133.6, 134.3, 139.0, 146.9, 166.2, 167.7, and 169.8. Anal. Calcd for $C_{27}H_{22}N_2O_5$: C, 71.34; H, 4.88; N, 6.17. Found: C, 71.25; H, 4.87; N, 6.09.

[2-(3,4-Dihydro-1*H*-isoquinoline-2-carbonyl)phenyl]-acetic Acid Methyl Ester. To a stirred solution of 10 g (52 mmol) of carboxylic acid **36** in 150 mL of THF was added 8.4 g (52 mmol) of carbonyl diimidazole. The reaction mixture was stirred at room temperature for 1 h, and 6.5 mL (52 mmol) of 1,2,3,4-tetrahydroisoquinoline was added. The mixture was stirred at room temperature for an additional 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in 200 mL of ether and consecutively washed with 100 mL of a 10% HCl solution, 100 mL of a saturated $NaHCO_3$, 100 mL of water, and a saturated NaCl solution. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 13 g (82%) of the titled compound as a yellow oil which consisted of a 1:1 mixture of rotomers; IR (neat) 1735, 1633, 1602, 1259, 1158, and 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.77 (brs, 2H), 2.90 (brs, 2H), 3.21 (s, 3H), 3.46−3.52 (m, 4H), 3.57 (s, 3H), 3.62−3.95 (m, 4H), 4.40 (s, 2H), 4.62−5.01 (m, 2H), 6.82 (d, 1H, $J = 7.6$ Hz), and 7.06−7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 29.2, 37.9, 38.0, 39.7, 44.2, 44.7, 49.0, 51.5, 51.8, 125.8, 125.9, 126.1, 126.2, 126.4, 126.5, 127.0, 128.4, 128.7, 129.1, 129.2, 131.0, 131.1, 131.4, 131.5, 132.6, 132.7, 133.8, 134.3, 136.2, 136.3, 169.4, 169.4, 171.2, and 171.6; HRMS Calcd for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1365.

Diazo-[2-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)phenyl]acetic Acid Methyl Ester (46). To a stirred solution of 0.5 g (1.6 mmol) of the above amido-ester **50** in 15 mL of acetonitrile was added 0.8 mL (5.3 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene followed by 0.9 mL (6.0 mmol) of *p*-toluenesulfonyl azide. After stirring for 48 h in the dark at room temperature, another 0.25 mL (1.6 mmol) of *p*-toluenesulfonyl azide was added. The reaction was stirred for an additional 24 h and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 0.44 g (85%) of **46** as a yellow oil that consisted of a 1:1 mixture of rotomers and which was used in the next step without further purification; IR (neat) 2106, 1740, 1633, 1606, 1260, 1206, and 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.77−

2.99 (m, 4H), 3.44−3.74 (m, 10H), 4.27−4.30 (m, 1H), 4.40 (s, 1H), 4.61−4.68 (m, 1H), 4.95−5.05 (m, 1H), 6.81−6.83 (m, 1H), and 7.09−7.53 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 29.0, 39.6, 44.2, 44.5, 48.8, 51.7, 51.8, 122.5, 122.8, 125.7, 125.9, 126.2, 126.3, 126.4, 126.5, 127.0, 127.4, 127.6, 127.9, 128.3, 128.7, 129.3, 129.4, 129.5, 129.8, 132.3, 132.3, 133.6, 134.1, 134.8, 165.2, 165.4, 168.2, and 169.2.

5-Oxo-8,13-dihydro-5*H*,7*H*-benzo[4,5]azepino[2,1-*a*]-isoindole-13*a*-carboxylic Acid Methyl Ester (48). To a refluxing solution of 0.01 g of rhodium(II) acetate in 200 mL of toluene was added 0.8 g (2.5 mmol) of diazoester **46** in 50 mL of toluene dropwise over a 30 min period. The mixture was heated at reflux for 1 h and cooled to room temperature. The solvent was removed under reduced pressure, and the crude residue was subjected to flash chromatography on silica gel to give 0.27 g (35%) of **48** as a yellow oil; IR (neat) 3024, 2951, 1740, and 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.84−3.03 (m, 2H), 3.07−3.10 (m, 1H), 3.25−3.32 (m, 1H), 3.55 (s, 3H), 3.75−3.79 (m, 1H), 4.81−4.87 (m, 1H), 7.15−7.30 (m, 4H), and 7.59−7.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.7, 39.5, 44.9, 52.6, 70.4, 122.3, 123.8, 126.7, 127.7, 129.3, 129.4, 130.9, 131.2, 132.0, 134.4, 141.3, 143.5, 167.2, and 169.2. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.24; H, 5.58; N, 4.56. Found: C, 74.13; H, 5.66; N, 4.31.

[2-(7,8-Dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isoquinoline-6-carbonyl)-3,4-dimethoxyphenyl]acetic Acid Methyl Ester (51). To a stirred solution of 0.5 g (1.9 mmol) of carboxylic acid **49**[40] in 5 mL of CH_2Cl_2 were added 0.3 mL (3.9 mmol) of oxalyl chloride and two drops of DMF. The mixture was stirred at room temperature for 2 h, and the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in 10 mL of CH_2Cl_2, and 0.5 g (3.9 mmol) of DMAP was added. The mixture was stirred at room temperature for 15 min, 0.4 g (1.9 mmol) of amine **50**[41] was added, and the solution was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, quenched with 35 mL of a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 0.45 g (60%) of **51** as a pale yellow solid which consisted of a 1:1 mixture of rotomers; mp 139−141 °C; IR (neat) 1745, 1650, 1556, 1272, 1252, 1029, and 1002 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58−2.66 (m, 1H), 2.80−2.87 (m, 3H), 3.32 (s, 2H), 3.35−3.52 (m, 2H), 3.62 (s, 2H), 3.64−3.72 (m, 2H), 3.77−3.81 (m, 6H), 3.88−3.90 (m, 6H), 3.97−4.06 (m, 6H), 4.12−4.35 (m, 2H), 4.69−4.71 (d, 1H, J = 17.4 Hz), 4.92−4.97 (d, 1H, J = 17.4 Hz), 5.87 (dd, 2H, J = 3.2 and 1.6 Hz), 5.92 (s, 2H), 6.37 (s, 1H), 6.56 (s, 1H), 6.61 (s, 1H), 6.65 (s, 1H), 6.89 (d, 1H, J = 2.4 Hz), 6.92 (d, 1H, J = 2.4 Hz), and 7.03 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 28.9, 37.3, 40.1, 44.2, 44.3, 48.3, 52.4, 52.6, 55.7, 56.3, 61.6, 100.9, 105.9, 106.4, 108.4, 108.5, 114.8, 119.7, 121.7, 124.8, 126.7, 127.2, 146.5, 151.0, 151.2, 153.7, 155.8, 161.1, 161.2, 164.1, and 164.3. Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found: C, 63.79; H, 5.68; N, 3.36.

[2-(7,8-Dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isoquinoline-6-carbonyl)-3-methoxyphenyl]acetic Acid Methyl Ester (54). To a stirred solution of 1.5 g (6.7 mmol) of carboxylic acid **53**[43] in 15 mL of CH_2Cl_2 were added 1.2 mL (13 mmol) of oxalyl chloride and two drops of DMF. The mixture was stirred at room temperature for 2 h, and the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride was dissolved in 15 mL of CH_2Cl_2, and 1.6 g (13 mmol) of DMAP was added. The mixture was stirred at room temperature for 15 min, 1.2 g (6.7 mmol) of amine **50** was added, and the solution was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, quenched with 40 mL of a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 1.2 g (50%) of **54** as a pale yellow oil which consisted of a 1:1 mixture of rotomers; IR (neat) 1729, 1649, 1596, 1268, and 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61−2.77 (m, 2H), 2.83 (t, 2H, J = 6.0 Hz), 3.36−3.80 (m, 20H), 4.21−4.32 (m, 2H), 4.68 (d, 1H, J = 17.2 Hz), 4.94 (d, 1H, J = 17.2 Hz), 5.88 (s, 2H), 5.92 (s, 2H), 6.37 (s, 1H), 6.57 (s, 1H), 6.62 (s, 1H), 6.65 (s, 1H), 6.82 (dd, 2H, J = 8.0 and 2.0 Hz), 6.93 (t, 2H, J = 8.0 Hz), and 7.31 (dt, 2H, J = 8.0 and 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 29.0, 37.7, 37.8, 39.4, 43.8, 47.6, 51.5, 51.7, 55.3, 100.5, 100.6, 105.6, 106.2, 107.9, 108.2, 109.2, 109.3, 122.7, 122.8, 125.3, 125.8, 126.9, 127.0, 127.4, 129.6, 129.7, 132.2, 132.4, 145.8, 145.9, 146.0, 146.1, 155.2, 155.3, 166.6, 167.1, 171.0, and 171.3. Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.64; H, 5.50; N, 3.47.

Diazo-[2-(7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isoquinoline-6-carbonyl)-3-methoxyphenyl]acetic Acid Methyl Ester (55). To a stirred solution of 0.5 g (1.2 mmol) of ester **54** in 15 mL of acetonitrile was added 0.6 mL (4.0 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene followed by 0.7 mL (4.6 mmol) of *p*-toluenesulfonyl azide. After stirring for 48 h in the dark at room temperature, another 0.2 mL (1.2 mmol) of *p*-toluenesulfonyl azide was added. The reaction mixture was stirred for an additional 24 h and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to give 0.4 g (88%) of **55** as a yellow oil that consisted of a 1:1 mixture of rotomers and which was used in the next step without further purification; IR (neat) 2087, 1705, 1638, 1591, 1255, and 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58−2.65 (m, 1H), 2.71−2.93 (m, 3H), 3.32−3.38 (m, 1H), 3.44−3.50 (m, 1H), 3.59 (s, 3H), 3.65−3.73 (m, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.19−4.31 (m, 2H), 4.62 (d, 1H, J = 17.2 Hz), 4.95 (d, 1H, J = 17.2 Hz), 5.88 (s, 2H), 5.92 (s, 2H), 6.34 (s, 1H), 6.56 (s, 1H), 6.63 (s, 1H), 6.65 (s, 1H), 6.89 (dd, 2H, J = 8.0 and 1.2 Hz), 7.13 (dd, 1H, J = 8.0 and 0.8 Hz), 7.18 (dd, 1H, J = 8.0 and 0.8 Hz), and 7.38 (dt, 2H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 29.2, 39.7, 43.9, 44.1, 47.9, 51.8, 51.9, 55.6, 55.7, 100.6, 100.7, 105.6, 106.4, 108.0, 108.5, 110.2, 110.5, 122.6, 122.9, 123.6, 123.9, 125.4, 125.7, 126.8, 127.1, 127.6, 129.5, 129.6, 130.0, 130.1, 145.9, 146.2, 155.7, 155.8, 165.5, 165.6, 165.7 and 166.1.

Methyl 11-Aza-8-methoxy-17,19-dioxa-10-oxopentacyclo-[12.7.0.0^{3,11}.0^{4,9}.0^{16,20}]henicosa-1(21),4(9),5,7,14(15),16(20)-hexaene-3-carboxylate (56). To a refluxing solution of 2 mg of rhodium(II) acetate in 30 mL of toluene was added 0.2 g (0.5 mmol) of diazoester **55** in 5 mL of toluene dropwise over a 1 h period. The mixture was heated at reflux for 15 min and cooled to room temperature. The solvent was removed under reduced pressure, and the crude residue was subjected to flash chromatography on silica gel to give 0.1 g (75%) of **56** as a clear oil; IR (neat) 1738, 1691, 1604, 1276, and 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.72−2.89 (m, 2H), 2.97 (d, 1H, J = 14.4 Hz), 3.11−3.17 (m, 1H), 3.59 (s, 3H), 3.97 (s, 3H), 4.72−4.77 (m, 2H), 5.91 (d, 1H, J = 10.0 Hz), 5.94 (d, 1H, J = 10.0 Hz), 6.64 (s, 1H), 6.74 (brs, 1H), 6.95 (d, 1H, J = 8.0 Hz), 7.31 (d, 1H, J = 7.6 Hz), and 7.35 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.6, 39.2, 44.8, 52.7, 55.9, 69.7, 100.9, 109.9, 111.6, 111.7, 114.2, 118.2, 127.7, 133.5, 135.0, 145.9, 146.0, 146.6, 157.3, 165.9, and 169.5. Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.12; H, 5.02; N, 3.67. Found: C, 66.08; H, 4.97; N, 3.53.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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