Rhodium(II)-Catalyzed Cyclization of Amido Diazo Carbonyl Compounds

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A series of acyclic diazo ketoamides were prepared from *N*-benzoyl-*N*-alkylaminopropanoic acids and were treated with a catalytic amount of rhodium(II) acetate. The resultant carbenoids underwent facile cyclization onto the neighboring amide carbonyl oxygen atom to generate seven-membered carbonyl ylide dipoles. Subsequent collapse of the dipoles with charge dissipation produce bicyclic epoxides which undergo further reorganization to give substituted 5-hydroxydihydropyridones in good yield. Depending on the nature of the substituent groups, it was possible to trap some of the initially formed carbonyl ylide dipoles with a reactive dipolarophile such as DMAD. In other cases, cyclization of the dipole to the epoxide is much faster than bimolecular trapping. A related cyclization/rearrangement sequence occurred when diazo ketoamides derived from the cyclic pyrrolidone and piperidone ring systems were subjected to catalytic quantities of Rh(II) acetate. With these systems, exclusive *O*-cyclization of the amido group onto the carbenoid center occurs to generate a seven-ring carbonyl ylide dipole. Starting materials are easily prepared, and the cascade sequence proceeds in good yield and does not require special precautions. The overall procedure represents an efficient one-pot approach toward the synthesis of various indolizidine and quinolizidine ring systems.

The cyclization of cationic species containing internal nitrogen nucleophiles represents a very useful method for obtaining a wide range of substituted aza heterocycles.[1,2] A variety of alkenylamine derivatives, such as amides,[3] carbamates,[4] hydroxamic acids,[5] imidates,[6] imines,[7] isoureas,[8] oximes,[9] and ureas[10] have been employed to effect ring closure by treatment with different electrophilic reagents. Competitive reactions are often observed when the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms, as in the case of amides. For example, in the halocyclization reaction of olefinic compounds possessing a tethered amido group, O-cyclized products are generally obtained in preference to N-cyclized products[11] (Scheme 1). The O-selective cyclization in these reactions is understandable on the basis of HSAB theory;[12] that is, an oxygen atom, more electronegative than a nitrogen atom, should preferentially attack the iodine−olefin π-complex characterized as a hard electrophile. To obtain N-cyclized products, it was necessary to carry out the reaction in the presence of a basic metallic reagent such as *n*-BuLi. This crossover in selectivity was attributed to the formation of a metal imidate intermediate which enhances the reactivity at the nitrogen atom.[13]

For the past several years, our group has been interested in a related cyclization process involving the interaction of an amido group onto an electrophilic metallocarbene complex generated from the reaction of α-diazo carbonyls with Rh(II) carboxylates.[14] In our early studies dealing with the *tandem cyclization−cycloaddition* reaction of diazo ketoamides of type **4**, the carbonyl ylide dipole **5** was generated by cyclization of the amido oxygen atom onto the electrophilic rhodium carbenoid center.[15] The resulting dipole underwent intramolecular

* Corresponding author.

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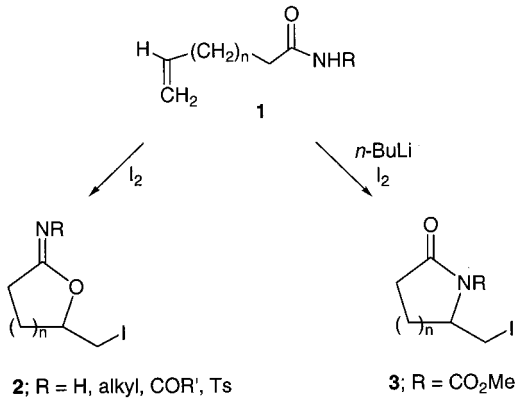
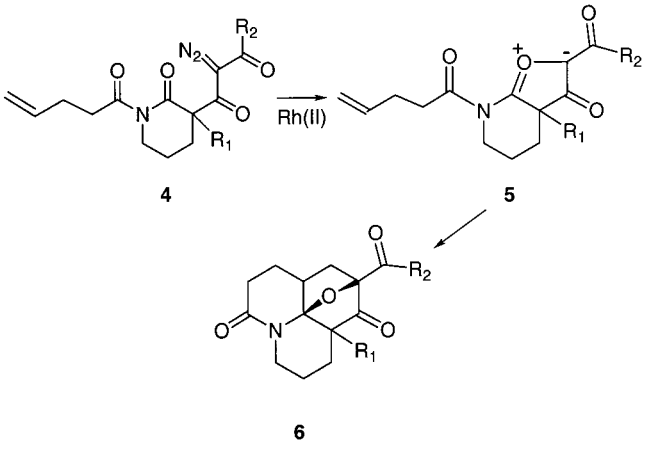
Scheme 1



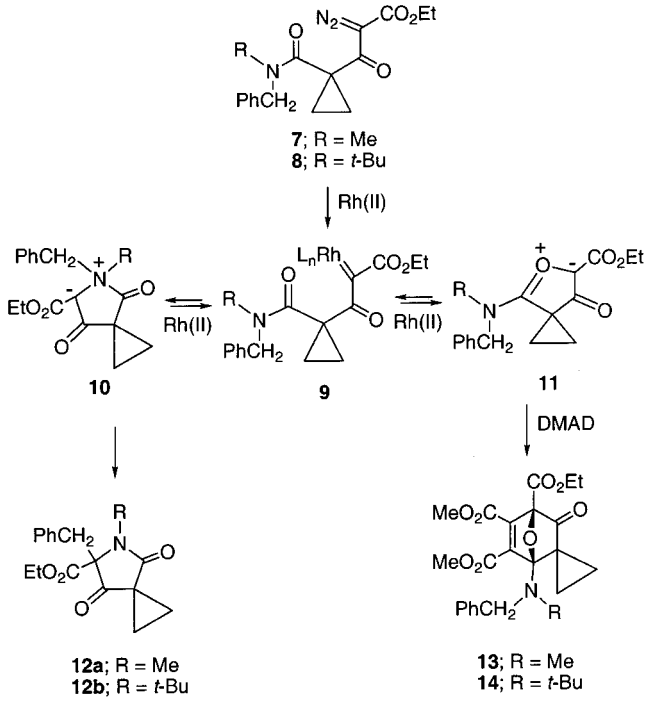
Scheme 2



cycloaddition across the tethered π-bond to give cycloadduct **6** in near-quantitative yield (Scheme 2). In this case, geometric factors prevent the amido nitrogen atom from attacking the carbenoid center.

In contrast to this result, treatment of acyclic diazoamides such as **7** with $Rh_2(OAc)_4$ afforded five-membered ammonium (**10**) and carbonyl ylides (**11**) depending on the reaction conditions.[16] Thus, when the reaction was carried out in the presence of a typical dipolarophile such as DMAD, cycloadduct **13** derived from a cyclic carbonyl ylide was formed as the major product (57%) together with lesser quantities of the rearranged lactam **12** (23%). When the reaction of **7** was carried out in the absence of DMAD, lactam **12** could be isolated in very high yield. The formation of **12** can be attributed to the initial formation of ammonium ylide **10** followed by a 1,2-benzyl shift[17] (Scheme 3). It would appear as though the highly electrophilic carbenoid center[15] present in **9** can be attacked by the lone pair of electrons on the amide nitrogen[18] (ammonium ylide formation) or by the lone pair of electrons on the carbonyl oxygen (carbonyl ylide formation). The experimental observations reflect a catalyst-promoted system of equilibria with a clear-cut thermodynamic bias in favor of the more stable ammonium ylide **10**.[19] The ambident properties of the rhodium carbenoid **9** flanked by reversible equilibria

Scheme 3



permits both the interconversion of uncomplexed ylides **10** and **11** and their subsequent isolation or capture as cycloadducts. More recently (see Experimental Section), we noted that the cyclization reaction can be influenced by the nature of the substituent group on the nitrogen atom as well as by the experimental conditions employed. Thus, the Rh(II)-catalyzed reaction of *N*-benzyl-*N*-*tert*-butyl diazo amide **8** afforded only products derived from a carbonyl ylide dipole (i.e., **14**; R = *t*-Bu). There was no indication of any rearranged lactam (i.e., **12b**; R = *t*-Bu) in the crude reaction mixture, even in the absence of a trapping dipolarophile. Indeed, no characterizable products could be obtained when DMAD was absent from the reaction mixture. With both diazo amides **7** and **8**, the bimolecular trapping of carbonyl ylide **11** is faster than the rearrangement of ammonium ylide **10**. The presence of the bulky *tert*-butyl group on the nitrogen atom, however, seems to significantly retard the 1,2-benzylic shift; perhaps the consequence of a steric effect.

α-Diazo carbonyls which possess an interacting γ-amido group were found to afford products derived from a six-ring carbonyl ylide intermediate.[20,21] A particularly interesting example involves the Rh(II)-catalyzed reaction of *N*-acetyl-2-(1-diazoacetyl)pyrrolidine (**15**)[20] (Scheme 4) which gave the novel rearranged cycloadduct **19** when treated with DMAD in the presence of a Rh(II) catalyst. The mechanism proposed to rationalize the formation of this unusual product involves generation of the expected carbonyl ylide dipole **16** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group.[20] Isomerization of **16** to the thermodynamically

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(18) For a related example, see: Kappe, C. O. *Tetrahedron Lett.* **1997**, *38*, 3323.

(19) Density functional theory (DFT) calculations show that ammonium ylide 10 is ca. 7 kcal/mol lower in energy than carbonyl ylide **11**: Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.

(20) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593. Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451. Padwa, A.; Price, A. T.; Zhi, L. *J. Org. Chem.* **1996**, *61*, 2283.

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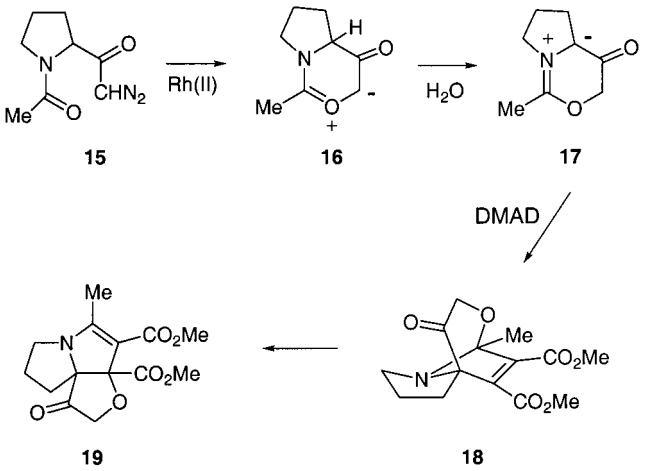
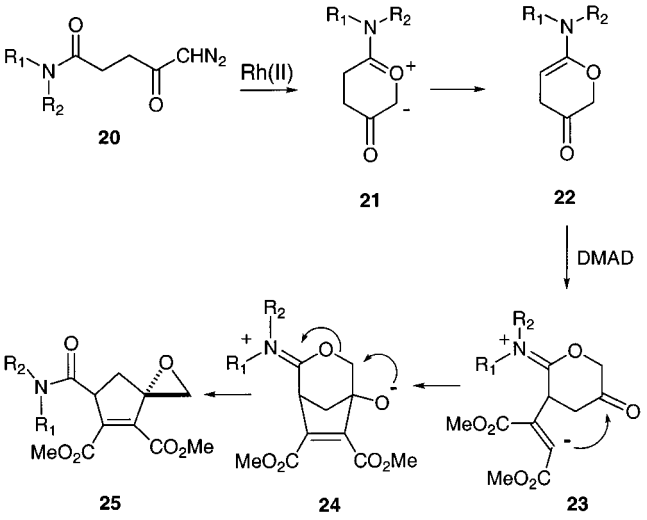
Scheme 4



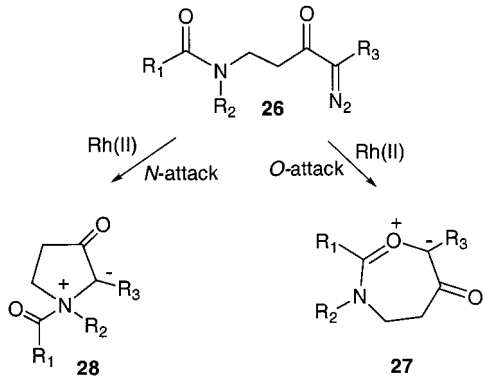
Scheme 5



more stable azomethine ylide **17** occurs via a proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with DMAD provided cycloadduct **18** which underwent a subsequent 1,3-alkoxy shift to afford the tricyclic dihydropyrrolizine **19**. Ammonium ylide formation requires a more highly strained four-membered ring, and consequently, this reactive intermediate is not produced.

Experiments with this particular diazoamide were followed soon thereafter by a study of systems derived from acyclic precursors.[20] In the case of α-diazo ketoamide **20**, the Rh(II)-catalyzed reaction in the presence of DMAD furnished the novel epoxy-cycloadduct **25**. Once again, the initial cyclization involved generation of a six-ring carbonyl ylide **21** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group (Scheme 5). This highly stabilized dipole does not readily undergo 1,3-dipolar cycloaddition but rather isomerizes to the cyclic ketene *N*,*O*-acetal **22** by proton exchange.[22] Structure **22** reacts further with the activated π-bond of DMAD to produce zwitterion **23**. The anionic portion of **23** then undergoes addition to the adjacent carbonyl group, affording a new zwitterionic intermediate **24**. Under the anhydrous conditions, epoxide formation occurred with charge dissipation to give the observed cycloadduct **25**.

Scheme 6



Because of the vast array of pathways available to keto carbenoids possessing tethered amido groups and the demonstrated susceptibility of the transient dipoles to undergo unexpected rearrangement, we felt that a systematic study of the related 4-(*N*-acyl)amino-1-diazobutan-2-one (**26**) system was warranted. In this case, O-cyclization of the amido group on the carbenoid center would lead to a seven-ring carbonyl ylide dipole (**27**) whereas N-cyclization should ultimately afford products derived from a transient five-ring ammonium ylide of type **28** (Scheme 6). We therefore initiated a study to probe the above competition and now wish to report results emanating from this investigation.

Results and Discussion

The tandem ammonium ylide generation/rearrangement sequence represents a very effective method for the preparation of nitrogen-containing heterocycles.[23] A typical example involves the ring expansion reaction of a spirocyclic ammonium ylide such as **31,** which has been nicely exploited for the synthesis of a number of alkaloids. Thus, the key step in West and Naidu's enantioselective synthesis of (−)-epilupinine[24] involved the ammonium ylide-Stevens [1,2]-rearrangement of the (L)-proline derivative **29** which furnished the advanced intermediate **32** in 84% yield and with 76% ee (Scheme 7). In this case, the starting diazo carbonyl compound has the dialkylamino center six atoms away from the carbenoid site. Starting from a related (L)-proline derivative **30** (R = vinyl), Clark and Hodgson synthesized the CE ring system **33** in their approach to the Mazamine A ring skeleton via an ammonium ylide-[2,3]-sigmatropic rearrangement (Scheme 7).[25,26]

To further document the scope and generality of five-ring ammonium ylide formation of diazo carbonyl compounds bearing a nitrogen substituent in the β−position, we first opted to study the Rh(II)-catalyzed behavior of 4-(1-pyrrolidino)-1-diazo-2-butanone (**34**). A Stevens [1,2]-shift of one of the methylene groups of the anticipated

(22) For a related proton exchange of a carbonyl ylide derived from the Rh(II)-catalyzed reaction of an amide with diazoacetic ester, see: Busch-Petersen, J.; Corey, E. J. *Org. Lett.* 2000, *2*, 1641.

(23) Padwa, A.; Beall, L. S. *Advances in Nitrogen Heterocycles*; JAI Press: Stamford, CT, 1998; Vol. 3, pp 117−158.

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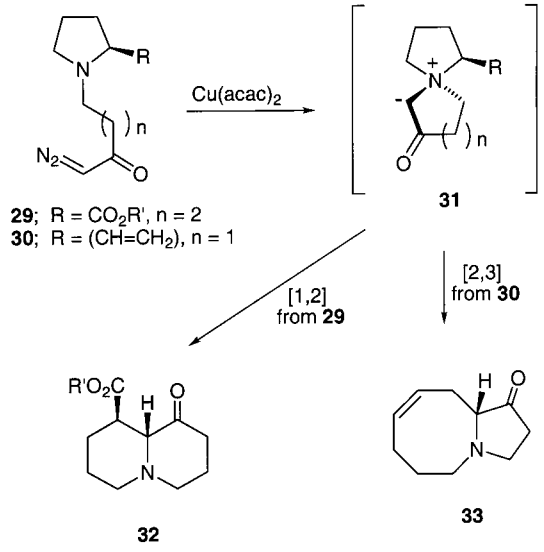
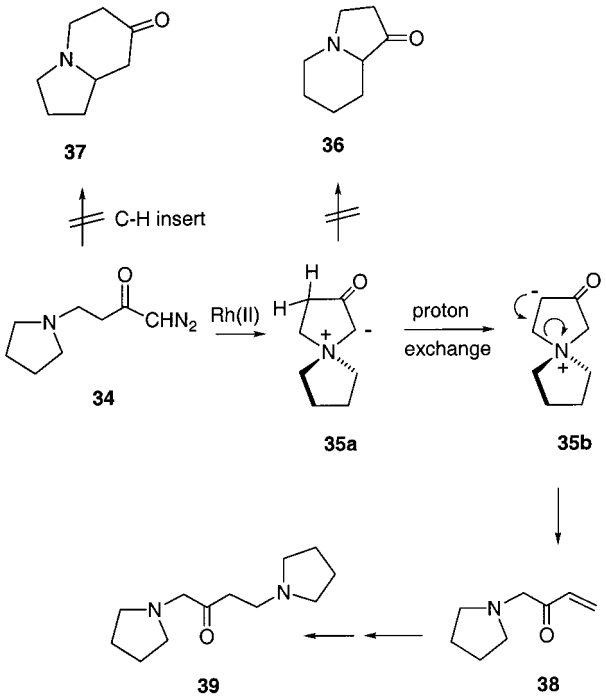
(25) Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2701. Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519.

(26) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165.

Scheme 7

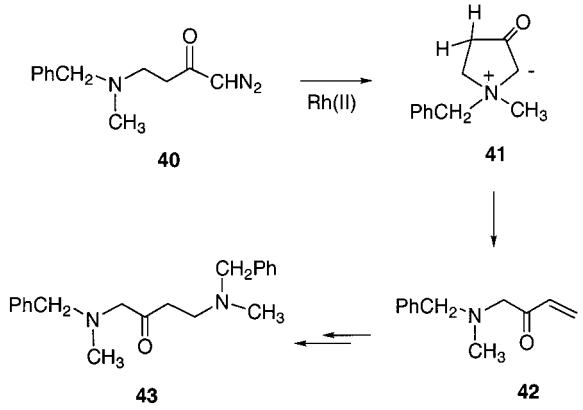


Scheme 8

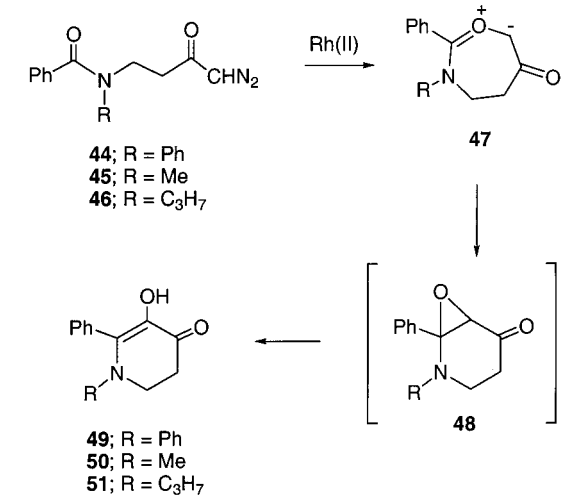


ammonium ylide **35** was expected to give rise to indolizidone **36** (Scheme 8). A competing C−H insertion of the initially formed rhodium carbenoid might also produce the isomeric indolizidone **37**. In the event, diazo ketoamide furnished a 3:1-mixture of the unexpected pyrrolidino butanones **38** and **39** in 58% yield. No detectable quantities of either indolizidones **36** or **37** were found in the crude reaction mixture. Both of these products can be rationalized in terms of the initial formation of ammonium ylide **35a** which seemingly undergoes proton exchange with an adjacent α-hydrogen to give **35b.** A subsequent C−N bond cleavage then occurs so as to dissipate the charges. This process would have to occur at a faster rate than either insertion into a C−H bond or the Stevens 1,2-shift in order to account for the exclusive formation of **38** and **39**. We assume that **39** is derived from the Michael reaction of enone **38** with either pyrrolidine or perhaps the starting diazo carbonyl substrate. A similar transformation also occurred with *N*-benzyl-*N*-methyl-4-amino-1-diazobutanone (**40**), which furnished a 1:1-mixture of butanones **42** and **43** by a similar mechanism (Scheme 9).

Scheme 9



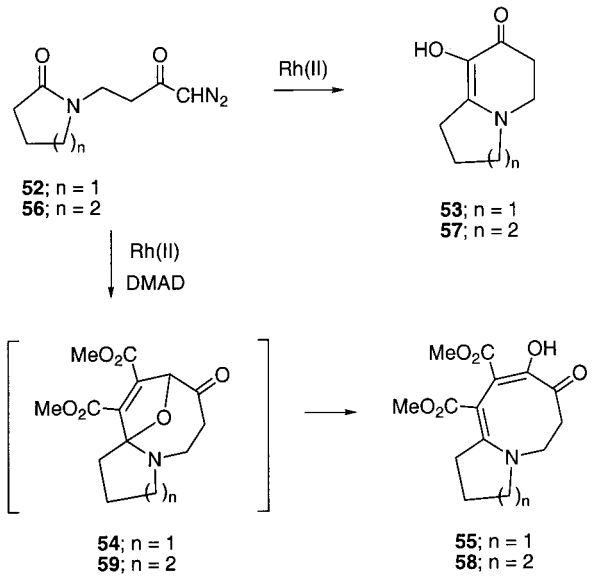
Scheme 10



In contrast to these results, the Rh(II)-catalyzed reaction of *N*-benzoyl-*N*-phenyl-4-amino-1-diazobutan-2-one (**44**) proceeded by way of a seven-ring dipole derived from O-cyclization of the amido group onto the carbenoid center. Thus, treatment of **44** with $Rh_2(OAc)_4$ afforded 5-hydroxydihydropyridone **49** as the exclusive product in 71% isolated yield. This same compound was isolated in essentially identical yield when the reaction was carried out in the presence of a trapping agent such as DMAD. No signs of any product derived from a five-ring ammonium ylide could be detected in the crude reaction mixture. A similar reaction using diazo ketoamides **45** and **46** afforded the related rearranged products **50** and **51** in 75% and 82% yield, respectively. The formation of these compounds can best be rationalized in terms of an initially formed carbonyl ylide dipole (i.e., **47**) which collapses to produce epoxide **48** as a transient intermediate (Scheme 10). A subsequent isomerization of **48** affords the thermodynamically more stable dihydropyridone tautomer **49**. It would appear as though cyclization of carbonyl ylide **47** to epoxide **48** is much faster than bimolecular trapping with DMAD. The overall pathway is somewhat related to that encountered by Danishefsky and co-workers in the diazo thioamide coupling reaction used in the synthesis of the angiotensin converting enzyme inhibitor A58365A.[27]

The facility with which diazo ketoamides **44**−**46** underwent cyclization led us to study the related cyclic diazo pyrrolidone and piperidone ring systems (i.e., **52** and **56**). A Rh(II)-catalyzed reorganization similar to that described in Scheme 10 would result in the ready formation of the indolizidine and quinolizidine skeletons.[28] Alkaloids containing these 5,6- and 6,6-ring systems have been popular targets for total synthesis due to their interesting biological activity.[29] Annulation of cyclic lactams with closure of the ring at the lactam carbonyl group represents an attractive method to construct these izidine skeletons due to the easy availability of the lactam unit. This annulation strategy has been realized by using such processes as cyclodehydration,[30] metal-induced zipper reaction,[31] titanium-mediated cyclization of *ω*-vinyl imides,[32] and intramolecular nucleophilic addition of allyl silane to imides,[33] as well as intramolecular 1,4-dipolar cycloaddition.[34] Annulation of thiolactams has also been carried out by a Rh(II)-mediated diazo thioamide coupling[35] and thioisomünchnone cycloaddition.[36] Our investigations along these lines began with a study of the Rh(II)-catalyzed behavior of diazo pyrrolidone **52** which is an appropriate starting material for the construction of the indolizidine skeleton. We found that the treatment of **52** with a catalytic quantity of $Rh_2(OAc)_4$ in chloroform at 25 °C gave 8-hydroxyhexahydroindolizinone **53** in 86% yield. Interestingly, when the reaction was carried out in the presence of 1.2 equiv of DMAD, hexahydropyrrolo-[1,2-*a*]azocinone **55** (40%) was obtained in addition to indolizinone **53** (32%) (Scheme 11). We assume that **55** is derived by a rapid rearrangement of a transient dipolar cycloadduct (i.e. **54**). Apparently, the rate of ring closure of the carbonyl ylide dipole to a bicyclic epoxide is sufficiently slow to allow a competitive dipolar cycloaddition to occur. More than likely, the slower rate of ring closure is probably a consequence of the more highly strained nature of the epoxide intermediate (i.e., **48**). In a like manner, the Rh(II)-catalyzed reaction of the related diazo piperidone system **56** afforded hydroxy quinolizinone **57** in 65% yield. Capture of the transient carbonyl ylide dipole with DMAD proceeded uneventfully to produce azocinone **58** in 67% yield.

Scheme 11



For comparison purposes, we have also carried out a study of the Rh(II)-catalyzed reaction of the closely related amido diazo ketoesters **60** and **61**. Incorporation of a carbomethoxy substituent on a diazo carbonyl group generally facilitates carbonyl ylide formation since the initially formed rhodium carbenoid is highly electrophilic and prone to interact with a neighboring Lewis base.[37] In the case of diazo amidoester **60** (or **61**), the initially formed dipole was expected to cyclize in a manner analogous to that encountered earlier (i.e., **47** → **48**) thereby generating amino epoxide **62** as a transient species. Since this epoxide does not possess an α-hydrogen, deprotonation cannot take place. Although several possible pathways are available, we found that the reaction of **60** with $Rh_2(OAc)_4$ cleanly afforded the rearranged indolizidone **64** in 80% yield.[38] A similar transformation occurred with the homologous piperidinyl system **61** producing pyrroloazepine **65** in 72% yield (Scheme 12). When the Rh(II)-catalyzed reaction of **61** was carried out in the presence of 1 equiv of DMAD, the expected dipolar cycloadduct **66** was obtained in 38% yield together with lesser quantities of **65** (22%).

The most plausible mechanism for the conversion of **60** to **64** involves the intermediacy of aminoepoxide **62**.

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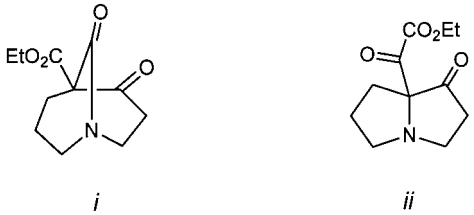
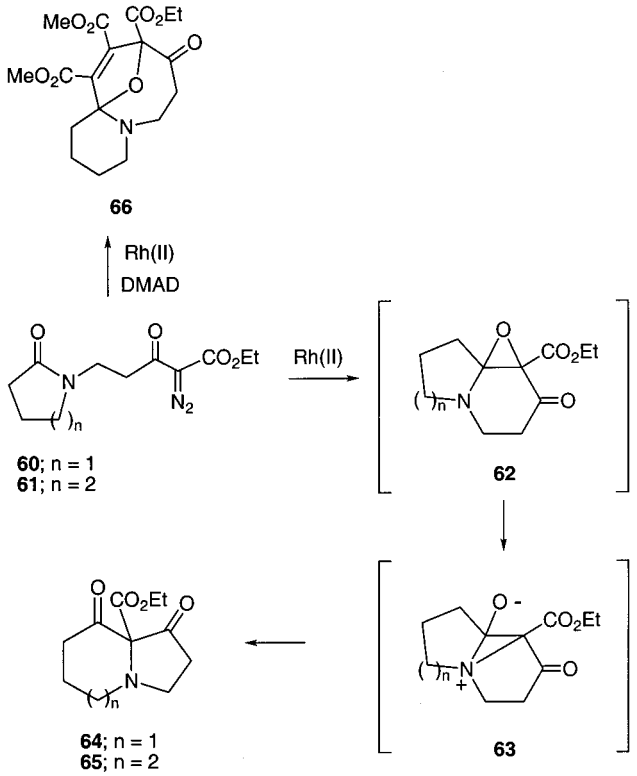


i *ii*

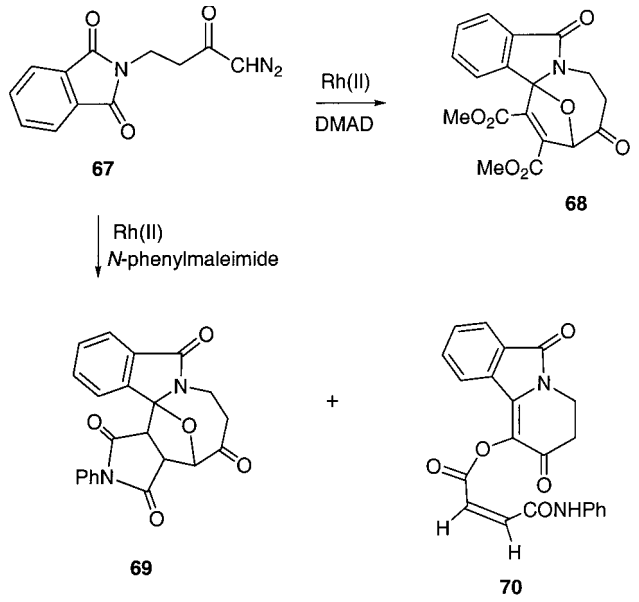
Scheme 12



α-Amino epoxides have been invoked as intermediates in the oxidation of enamines[40−44] and in the rearrangement of α-halo ketones and amines to α-amino ketones.[45] These highly reactive three-ring heterocycles undergo facile rearrangement and the specific product isolated has been found to be dependent on the nature of the substituents on both the epoxide and nitrogen atom.[46] The isolation of diketo indolizidone **64** strongly suggests that the reorganization of epoxide **62** to **64** may involve the intermediacy of aziridinium ion **63** (Scheme 12).

Seven-ring carbonyl ylides derived from the cyclization of an imido group on the carbenoid center can also participate in these tandem cyclization−cycloaddition reactions. Thus, the $Rh_2(OAc)_4$ catalyzed reaction of 1-diazo-4-phthalimidobutanone (**67**) proceeded quite smoothly with DMAD and *N*-phenylmaleimide. With DMAD, cycloadduct **68** was formed in 63% yield. When *N*-phenylmaleimide was used as the trapping agent, cycloadduct **69** (45%) together with dihydropyridone **70** (26%) were isolated as the two major products. Compound **70** is derived by a cyclization−rearrangement reaction of the initially formed carbonyl ylide followed by attack of the hydroxyl group of the dihydropyridone on to one of the carbonyl groups of *N*-phenylmaleimide (Scheme 13).

Scheme 13



In summary, we have demonstrated that the overall sequence of rhodium(II)-catalyzed carbenoid generation/carbonyl ylide formation/rearrangement utilizing a series of cyclic diazo ketoamides can be utilized for the synthesis of the indolizidine and quinolizidine ring skeletons. Starting materials are easily prepared and the cascade sequence proceeds in good yield and does not require special precautions. With these systems, exclusive O-cyclization of the amido group onto the carbenoid center occurs to generate a seven-ring carbonyl ylide dipole. The use of this tandem sequence for the synthesis of alkaloid targets is currently being investigated, and further details will be reported in due course.

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.

1-(Benzyl-*tert*-butylcarbamoyl)cyclopropanecarboxylic Acid. To a solution containing 10.0 g (63 mmol) of 1,1-cyclopropanecarboxylic acid monoethyl ester in 50 mL of CH_2Cl_2 was slowly added 12.6 mL (146 mmol) of oxalyl chloride and two drops of DMF. After the solution was stirred for 6 h, the solvent was removed under reduced pressure, and the crude acid chloride was dissolved in 5 mL of CH_2Cl_2. The mixture was added to a solution of 29 mL (158 mmol) of *tert*-butylbenzylamine in 50 mL of dry CH_2Cl_2 and was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in a 10% HCl solution, extracted with ether, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 18.1 g (95%) of 1-(benzyl-*tert*-butylcarbamoyl)cyclopropane carboxylic acid ethyl ester as a clear oil: IR (neat) 3062, 1723, 1651, 1605, and 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25−1.34 (m, 7H), 1.41 (s, 9H), 4.10 (q, 2H, J = 7.2 Hz), 4.68 (s, 2H), and 7.16−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 15.7, 28.0, 28.4, 31.6, 49.9, 58.4, 61.4, 125.8, 126.8, 126.9, 128.3, 128.5, 139.6, 169.5, and 171.9.

To a stirred solution of 18.0 g (59 mmol) of the above ester in 200 mL of a 2:1 ethanol−water mixture was added 7.1 g

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(126 mmol) of KOH dissolved in 20 mL of water, and the mixture was stirred at room temperature for 24 h. The solution was washed with ether, and the aqueous layer was acidified with a 50% HCl solution to a pH of 2, extracted with ether, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 11.5 g (71%) of the title compound as a white solid: mp 164−165 °C; IR ($CHCl_3$) 3403, 1709, 1595, and 1388 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.30−1.51 (m, 4H), 1.45 (s, 9H), 4.75 (s, 2H), 7.20−7.41 (m, 5H) and 11.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 29.0, 29.5, 32.6, 50.2, 59.9, 126.3, 127.0, 129.5, 140.0, 169.7, and 178.4. Anal.Calcd for $C_{16}H_{21}NO_3$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.65; H, 7.52; N, 4.97.

3-[1-(Benzyl-*tert*-butylcarbamoyl)cyclopropyl]-3-oxopropionic Acid Ethyl Ester. To a solution containing 1.1 g (8.0 mmol) of 2-(carboethoxy)acetic acid in 50 mL of CH_2Cl_2 at 0 °C was slowly added 8.0 mL (16 mmol) of isopropylmagnesium chloride. The mixture was stirred at 0 °C for 30 min, heated to 40 °C, and stirred for an additional 30 min. In a separate flask, 1.0 mL (11 mmol) of oxalyl chloride and two drops of DMF were slowly added to a solution of 2.0 g (7.3 mmol) of 1-(benzyl-*tert*-butylcarbamoyl)cyclopropanecarboxylic acid in 50 mL of CH_2Cl_2. The solution was allowed to stir for 2 h at room temperature and was concentrated under reduced pressure. The residue was dissolved in 5 mL of CH_2Cl_2, and this solution was added to the above magnesium dianion solution. The reaction mixture was stirred at 0 °C for 1 h and quenched with 50 mL of a 50% HCl solution. The mixture was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude oil by flash chromatography on silica gel gave 1.2 g (48%) of the title compound as a clear oil: IR (neat) 1737, 1694, 1637, and 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.1 Hz), 1.30−1.51 (m, 4H), 1.43 (s, 9H), 3.60 (s, 2H), 4.20 (q, 2H, J = 7.1 Hz), 4.78 (s, 2H), and 7.20−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.4, 17.2, 28.6, 40.8, 46.2, 50.3, 59.1, 61.7, 126.5, 127.4, 128.8, 139.3, 167.1, 170.2, and 199.2. Anal.Calcd for $C_{20}H_{27}NO_4$: C, 69.53; H, 7.88; N, 4.06. Found: C, 69.41; H, 7.62; N, 3.97.

3-[1-(Benzyl-*tert*-butylcarbamoyl)cyclopropyl]-2-diazo-3-oxopropionic Acid Ethyl Ester (8). To a stirred solution of 1.2 g (3.5 mmol) of the above compound in 10 mL of acetonitrile at 0 °C was added 1.2 g (8.4 mmol) of triethylamine. The mixture was stirred at 0 °C for 30 min, and 0.8 g (4.2 mmol) of tosyl azide was added in one portion. The reaction mixture was stirred for 24 h at room temperature, the solvent was removed under reduced pressure, and the crude oil was purified by silica gel chromatography to give 1.0 g (80%) of **8** as a yellow oil which was used in the next step without further purification: IR (neat) 2128, 1723, 1687, 1645, and 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 1.20−1.31 (m, 4H), 1.36 (s, 9H), 4.25 (q, 2H, J = 7.1 Hz), 4.71 (s, 2H), and 7.10−7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.5, 28.1, 38.1, 49.1, 58.5, 61.6, 125.8, 126.7, 128.0, 139.3, 160.5, 169.7, and 186.1.

Dimethyl 5-Carboethoxy-5,8-epoxy-8-(benzyl-*tert*-butylcarbamoyl)-4-oxo-6-spiro[2.5]octene-6,7-dicarboxylate (14). To a solution containing 0.17 mL (1.4 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) acetate in 5 mL of refluxing benzene was added dropwise 0.06 g (0.17 mmol) of diazo amide **8**. The reaction mixture was heated at reflux for 30 min, and the solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.06 g (69%) of **14** as a clear oil: IR (neat) 1737, 1694, and 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.30−1.41 (m, 4H), 1.42 (s, 9H), 3.74 (s, 3H), 3.77 (s, 3H), 4.01−4.22 (m, 4H), and 7.10−7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 13.9, 15.6, 29.5, 32.4, 51.5, 51.7, 52.5, 60.4, 62.3, 76.9, 77.2, 117.4, 117.5, 127.4, 128.1, 128.9, 129.3, 129.6, 158.6, 161.5, 164.7, 165.7, and 170.9. Anal.Calcd for $C_{26}H_{31}NO_8$: C, 64.30; H, 6.44; N, 2.89. Found: C, 64.18; H, 6.22; N, 2.71.

4-(1-Pyrrolidino)-1-diazo-2-butanone (34). A sample of 4-bromo-1-diazo-2-butanone was prepared according to a literature procedure[47] and was obtained as a yellow liquid: IR (neat) 2107, 1638 and 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90 (t, 2H, J = 6.6 Hz), 3.60 (t, 2H, J = 6.6 Hz), and 5.37 (s, 1H). To a 0.18 g (1 mmol) sample of this diazoketone in 10 mL of ether was added dropwise a solution of 0.14 g (2 mmol) of pyrrolidine in 5 mL of ether under an argon atmosphere. After being stirred for 4 h at room temperature, the mixture was passed through a short silica gel column. Elution with ethyl acetate gave 0.098 g (59%) of pyrrolidinodiazobutanone **34** as a yellow oil which was immediately used in the next step: IR (neat) 2102, 1638, and 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65−1.77 (m, 4H), 2.39−2.48 (m, 2H), 2.47 (t, 2H, J = 7.2 Hz), 2.70 (t, 2H, J = 7.2 Hz), 3.50 (s, 2H), and 5.37 (s, 1H).

1,4-Bis(1-pyrrolidino)-2-butanone (39). To a solution containing 0.099 g (0.6 mmol) diazopyrrolidinone **34** in 10 mL of dry CH_2Cl_2 was added 2 mg of rhodium(II) acetate under an argon atmosphere. After the solution was stirred overnight at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on a short silica gel column. Elution with ethyl acetate gave 0.026 g (43%) of **39** as a labile yellow oil which gradually decomposed on standing: IR (neat) 2963, 2791, 1716, 1459, 1352 and 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70−1.86 (m, 8H), 2.46−2.61 (m, 4H), 2.61−2.72 (m, 4H), 2.64−2.80 (m, 4H), and 3.38 (s, 2H). In addition to compound **39**, 1-(1-pyrrolidino)-3-buten-2-one (**38**) (16%) was also formed but its high lability prevented isolation of a pure sample. Its structure was determined by its characteristic NMR spectrum: ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−1.78 (m, 4H), 2.38−2.56 (m, 4H), 3.47 (s, 2H), 5.72 (dd, 1H, J = 10.4 and 1.7 Hz), 6.29 (dd, 1H, J = 17.4 and 1.7 Hz), and 6.45 (dd, 1H, J = 17.4 and 10.4 Hz).

4-(Benzylmethylamino)-1-diazo-2-butanone (40). To a 1.59 g (9 mmol) sample of 4-bromo-1-diazo-2-butanone in 50 mL of ethyl acetate was added dropwise 2.2 g (18 mmol) of *N*-benzyl-*N*-methylamine under an argon atmoshere. The mixture was heated at 65 °C for 12 h, and the solid that formed was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give 1.72 g (88%) of diazobutanone **40** as a reddish yellow oil which was immediately used in the next step: IR (neat) 2103, 1639, 1453, and 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.51 (t, 2H, J = 6.9 Hz), 2.73 (t, 2H, J = 6.9 Hz), 3.50 (s, 2H), 5.33 (s, 1H) and 7.25−7.35 (m, 5H).

1,4-Bis(benzylmethylamino)-2-butanone (43). To a solution containing 0.6 g (2.8 mmol) of diazobutanone **40** in 10 mL of dry CH_2Cl_2 was added 2 mg of rhodium(II) acetate under an argon atmosphere. After the solution was stirred overnight at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give 0.22 g (51%) of **43** as a labile yellow oil which decomposed on standing: IR (neat) 3027, 2944, 2789, 1717, and 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.27 (s, 3H), 2.61−2.72 (m, 4H), 3.16 (s, 2H), 3.46 (s, 2H), 3.55 (s, 2H), and 7.18−7.39 (m, 10 H). In addition to compound **43**, 1-(benzylmethylamino)-3-buten-2-one (**42**) was also formed (50% yield) but its high lability prevented isolation of a pure sample. Its structure was determined by its characteristic NMR spectrum: ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.32 (s, 2H), 3.59 (s, 2H), 5.76 (dd, 1H, J = 10.7 and 1.4 Hz), 6.30 (dd, 1H, J = 17.6 and 1.4 Hz), 6.60 (dd, 1H, J = 17.6 and 10.7 Hz), and 7.18−7.39 (m, 5 H).

4-(Benzoylphenylamino)-1-diazo-butan-2-one (44). *N*-benzoyl-*N*-phenylaminopropanoic acid was prepared according to literature procedures[48] and was obtained as a yellow solid; mp 74−75 °C. Treatment of 5.4 g (19 mmol) of the acid with 1.6 mL (20 mmol) of methyl chloroformate, 2.8 mL (20 mmol) of triethylamine, and 45 mmol of ethereal diazomethane afforded diazo ketoamide **44** in 82% yield as a yellow solid: mp 74−75 °C; IR (neat) 2110, 1640, 1497, 1380, and 708 cm^{-1};

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^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (t, 2H, J = 7.5 Hz), 4.21 (t, 2H, J = 7.5 Hz), 5.36 (s, 1H), and 6.98−7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 46.3, 54.5, 126.2, 127.1, 128.1, 128.6, 129.2, 135.0, 142.6, 170.0, and 191.9. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.65; H, 5.19; N, 14.28.

2,3-Dihydro-1,6-diphenyl-5-hydroxy-4(1*H*)-pyridinone (49). Treatment of 0.85 g (2.9 mmol) of diazo ketoamide **44** in 10 mL of chloroform with 2 mg of rhodium(II) acetate gave dihydropyridinone **49** in 71% yield as a pale yellow solid after silica gel chromatography: mp 174−175 °C; IR (neat) 3380, 1640, 1587, 1283, and 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (t, 2H, J = 6.9 Hz), 4.16 (t, 2H, J = 6.9 Hz), 5.83 (s, 1H), and 6.88−7.54 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 51.9, 122.9, 123.7, 127.4, 128.3, 128.5, 129.6, 132.0, 134.6, 140.2, 145.5, and 188.2. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.14; H, 5.75; N, 5.20.

4-(Benzoylmethylamino)-1-diazo-butan-2-one (45). A sample of diazo ketoamide **45** was prepared from 3.0 g (22 mmol) of *N*-methylbenzamide and 2 mL (22 mmol) of methyl acrylate using a procedure similar to that described above: IR (neat) 2110, 1630, 1385, and 1353 cm^{-1}. The high-field NMR showed that diazo ketoamide **45** exists as a 3:1 mixture of nitrogen rotamers: ^{1}H NMR (300 MHz, $CDCl_3$; major) δ 2.72 (brs, 2H), 2.97 (s, 3H), 3.78 (brs, 2H), 5.49 (s, 1H) and 7.83 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.7, 38.4, 43.3, 54.4, 126.2, 127.7, 128.9, 135.6, 170.8, and 192.3; ^{1}H NMR (300 MHz, $CDCl_3$; minor) δ 2.49 (brs, 2H), 3.03 (s, 3H), 3.57 (brs, 2H), 5.31 (s, 1H), and 7.83 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 38.4, 46.3, 54.7, 125.8, 127.7, 128.9, 135.6, 170.9, and 192.2. This compound was used in the next step without further purification

2,3-Dihydro-5-hydroxy-1-methyl-6-phenyl-4(1*H*)-pyridone (50). Treatment of a 0.26 g (1.1 mmol) sample of diazo ketoamide **45** in 5 mL of $CHCl_3$ with 2 mg of rhodium(II) acetate afforded dihydropyridone **50** in 75% yield: mp 136−137 °C; IR (neat) 3385, 1643, 1275, 1203, and 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, 2H, J = 7.7 Hz), 2.70 (s, 3H), 3.47 (t, 2H, J = 7.7 Hz), 5.22 (brs, 1H), and 7.35−7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 40.2, 49.9, 127.9, 128.1, 128.6, 130.5, 131.7, 148.3, and 184.6. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.08; H, 6.48; N, 6.80.

4-(Benzoylpropylamino)-1-diazobutan-2-one (46). A solution containing 3.1 g (36 mmol) of methyl acrylate and 3.4 g (57 mmol) of propylamine in 25 mL of chloroform was stirred at 40 °C for 12 h. The solvent was removed under reduced pressure to give 5.0 g (95%) of methyl 3-(propylamino)-propanoate as a colorless liquid: IR (neat) 3430, 2970, 1750, 1460, 1200, and 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.35−1.60 (m, 3H), 2.48 (t, 2H, J = 6.6 Hz), 2.54 (d, 2H, J = 7.2 Hz), 2.84 (t, 2H, J = 6.6 Hz), and 3.60 (s, 3H).

The above compound was dissolved in 15 mL of chloroform, and then 5.8 mL (50 mmol) of benzoyl chloride was added. The resulting mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel to give 8.9 g (90%) of methyl 3-(benzoylpropylamino)pentanoate as a colorless oil: IR (neat) 2957, 1734, 1631, 1419, 1254, 1146, 784, and 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (brs, 3H), 1.61 (brs, 2H), 2.78 (brs, 2H), 3.23 (brs, 2H), 3.72 (brs, 5H), and 7.35−7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 21.9, 32.3, 41.3, 51.5, 51.6, 126.4, 128.3, 129.2, 136.6, 167.6, and 171.9; HRMS (*m*/*e*) calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1363.

A mixture containing 5.0 g (20 mmol) of the above compound and 5.1 g (40 mmol) of potassium trimethylsilanolate in 150 mL of tetrahydrofuran was heated at reflux for 5 h, and then 3.1 mL (40 mmol) of methyl chloroformate was added. The mixture was allowed to stir for 3 h at room temperature, and the solid that formed was filtered. To the filtrate was added 80 mmol of ethereal diazomethane at 0 °C, and the resulting solution was stirred overnight. The solvent was removed under reduced pressure, and the crude residue was chromatographed on silica gel to give 3.2 g (52%) of diazo ketoamide 46 as a yellow solid which was immediately used in the next step: mp 40−41 °C; IR (neat) 2110, 1660, 1390, 1105, and 710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (brs, 3H), 1.43 (brs, 2H), 2.75 (brs, 2H), 3.19 (brs, 2H), 3.73 (brs, 2H), 5.38 (s, 1H), and 7.23−7.40 (m, 5H).

2,3-Dihydro-5-hydroxy-1-propyl-6-phenyl-4-(1*H*)-pyridinone (51). To a solution containing 0.35 g (1.36 mmol) of α-diazo ketoamide **46** in 10 mL of dichloromethane was added 2 mg of rhodium(II) acetate, and the mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel chromatography to give dihydropyridinone **51** as a yellow solid in 82% yield: mp 97−98 °C; IR (neat) 3380, 1660, 1550, 1290, 770, and 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (t, 3H, J = 7.2 Hz), 1.50 (m, 2H), 2.60 (t, 2H, J = 7.5 Hz), 2.94 (t, 2H, J = 7.2 Hz), 3.54 (t, 2H, J = 7.5 Hz), 5.24 (s, 1H), and 7.25−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 22.3, 33.5, 47.1, 53.5, 128.3, 128.7, 129.1, 130.4, 132.0, 148.6, and 184.5. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.43; H, 7.55; N, 5.87.

1-(4-Diazo-3-oxobutyl)-2-pyrrolidone (52). To a solution containing 4.1 g (26 mmol) of 3-(2-oxopyrrolidin-1-yl)propionic acid[49] and 3.9 mL (26 mL) of hexachloroacetone in 40 mL of dry THF at −78 °C was added dropwise a solution of 6.7 g (26 mmol) of triphenylphosphine in 20 mL of dry THF. After the addition was complete, the mixture was stirred at −78 °C for 1 h and was allowed to warm to room temperature for 30 min. The crude acid chloride solution was cannulated into 100 mmol of a diazomethane ethereal solution, and the resulting mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 2.3 g (41%) of diazopyrrolidone **52** as a yellow solid: mp 60−62 °C; IR (neat) 2105, 1680, 1645, 1380, and 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (q, 2H, J = 7.5 Hz), 2.33 (t, 2H, J = 7.5 Hz), 2.58 (brs, 2H), 3.40 (t, 2H, J = 6.6 Hz), 3.54 (t, 2H, J = 6.6 Hz), and 5.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 30.2, 37.8, 38.0, 47.3, 54.3, 174.5, and 191.9. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.13; H, 6.16; N, 23.23.

8-Hydroxy-2,3,5,6-tetrahydro-1*H*-indolizin-7-one (53). Treatment of 0.2 g of diazopyrrolidone **52** in 5 mL of chloroform with 2 mg of rhodium(II) acetate at room temperature for 12 h afforded hydroxyindolizinone **53** in 86% yield: mp 154−155 °C; IR (neat) 3320, 1670, 1547, 1500, 1270, and 1205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (tt, 2H, J = 7.6 and 7.0 Hz), 2.56 (t, 2H, J = 7.8 Hz), 2.82 (t, 2H, J = 7.6 Hz), 3.26 (t, 2H, J = 7.0 Hz), 3.29 (t, 2H, J = 7.8 Hz), and 5.24 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 27.7, 33.6, 45.9, 53.4, 126.9, 154.4, and 182.1. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.68; H, 7.18; N, 9.06.

9,10-Dicarbomethoxy-1,2,3,5,6,7-hexahydro-8-hydroxypyrrolo[1,2*a*]-azocin -7-one (55).Treatment of a 0.2 g sample of diazo ketoamide **52** in 5 mL of chloroform with 2 mg of rhodium(II) acetate at 25 °C for 12 h in the presence of 1.2 equiv of dimethyl acetylenedicarboxylate afforded a mixture of two major products. The minor fraction isolated (32%) from the silica gel column corresponded to hydroxyindolizinone **53.** The major fraction (40%) isolated from the column was assigned as pyrrolo[1,2-*a*]azocinone **55** on the basis of its spectral data: mp 159−160 °C; IR (neat) 1730, 1655, 1540, 1445, 1405, 1270, and 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00−2.14 (m, 2H), 2.21−2.52 (m, 4H), 3.80 (s, 3H), 3.98 (s, 3H), 3.98−4.17 (m, 2H), 4.21 (ddd, 1H, J = 10.7, 10.2, and 7.6 Hz), 4.52 (dd, 1H, J = 10.2 and 7.6 Hz), and 6.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 31.1, 32.2, 52.4, 53.8, 62.0, 63.2, 113.6, 124.9, 141.7, 161.3, 162.3, 178.7, and 181.2. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.85; H, 5.79; N, 4.74.

1-(4-Diazo-3-oxo-butyl)piperidin-2-one (56). To a solution containing 1.0 g (5.8 mmol) of 3-(2-oxopiperidin-1-yl)-

(49) Morosawa, S.; Yokoo, A. *Bull. Soc. Chem. Jpn.* **1963**, *36*, 179.

propionic acid[50] and 1.6 g (5.8 mmol) of hexachloroacetone in 20 mL of dry THF was added dropwise a solution of 1.5 g (5.8 mmol) of triphenylphosphine in 10 mL of THF at −78 °C. The resulting mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature. The resulting acid chloride solution was cannulated into 25 mmol of a diazomethane ethereal solution. The resultant solution was stirred at room temperature overnight, and the mixture was then concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.46 g (41%) of **56** as a pale yellow solid: mp 54−56 °C; IR (neat) 2945, 2100, 1726, 1624, and 1358 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72−1.79 (m, 4H), 2.32 (t, 2H, J = 5.6 Hz), 2.60 (m, 2H), 3.31 (t, 2H, J = 5.6 Hz,), 3.57 (t, 2H, J = 7.2 Hz), and 5.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 23.5, 32.5, 38.8, 44.0, 49.2, 55.3, 170.4, and 193.4. Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.25; H, 6.69; N, 21.42.

1-Hydroxy-3,4,6,7,8,9-hexahydroquinolizin-2-one (57). To a suspension containing 10 mg of $Rh_2(OAc)_4$ in 50 mL of CH_2Cl_2 was added dropwise a solution of 0.9 g (4.6 mmol) of diazo ketone **56** in 50 mL of CH_2Cl_2 at room temperature under an argon atmosphere. After the addition was complete, the mixture was allowed to stir at room temperature for 3 h and was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.5 g (65%) of **57** as a yellow solid: mp 115−117 °C; IR (neat) 3342, 2941, 1622, 1563, and 1288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63−1.71 (m, 2H), 1.78−1.85 (m, 2H), 2.48 (t, 2H, J = 7.8 Hz), 2.64 (t, 2H, J = 6.6 Hz), 3.10 (t, 2H, J = 6.6 Hz), 3.23 (t, 2H, J = 7.8 Hz), and 5.28 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 23.4, 23.5, 33.6, 50.4, 51.3, 129.6, 149.2, and 182.0. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.63; H, 7.84; N, 8.37.

9-Hydroxy-8-oxo-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2*a*]-azocine-10, 11-dicarboxylic Acid Dimethyl Ester (58). To a suspension containing 5 mg of $Rh_2(OAc)_4$ and 0.078 g (0.55 mmol) of DMAD in 4 mL of CH_2Cl_2 was added dropwise a solution of 0.07 g (0.36 mmol) of diazo ketone **56** in 6 mL of CH_2Cl_2 at room temperature under an argon atmosphere. The mixture was allowed to stir at room temperature for 4 h and was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.074 g (67%) of cycloadduct **58** as a yellow solid: mp 141−143 °C: IR (neat) 3483, 2954, 1738, 1437, and 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54−1.78 (m, 5H), 2.11−2.41 (m, 3H), 2.71 (dt, 1H, J = 10.5 and 2.7 Hz), 2.83−2.94 (m, 3H), 3.28 (s, 1H), 3.84 (s, 3H), and 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 24.7, 28.3, 38.6, 49.2, 52.1, 52.9, 53.2, 76.2, 90.3, 130.8, 160.9, 165.3, 173.6, and 200.9. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.47; H, 6.15; N, 4.52.

3-Oxo-5-(2-oxopyrrolidin-1-yl)pentanoic Acid Ethyl Ester. A mixture containing 5.0 g (32 mmol) of 3-(2-oxopyrrolidin-1-yl)propionic acid and 5.2 g (32 mmol) of carbonyldiimidazole (CDI) in 80 mL of dry THF was stirred at room temperature for 6 h. The resulting acylimidazole solution was used directly in the next step reaction. To a solution of 4.2 g (32 mmol) of ethyl hydrogen malonate in 35 mL of dry THF was added dropwise 32 mL (64 mmol) of a 2 M isopropylmagnesium chloride/THF solution at 0 °C. The mixture was stirred at room temperature for 2 h, and the above acyl imidazole solution was cannulated into this suspension. The resulting mixture was maintained at room temperature for 16 h, quenched with a 2 M HCl solution, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 4.1 g (56%) of the titled compound as a colorless oil: IR (neat) 3457, 2980, 1737, 1710, 1680, and 1291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.99 (p, 2H, J = 7.2 Hz), 2.34 (t, 2H, J = 7.2 Hz), 2.85 (t, 2H, J = 6.8 Hz), 3.42 (t, 2H, J = 7.2 Hz), 3.46 (s, 2H), 3.54 (t, 2H, J = 6.8 Hz), and 4.18 (q, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 18.3, 31.1, 37.6, 41.1, 48.4, 49.3, 61.7, 167.2, 175.6, and 201.6. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.39; H, 7.78; N, 6.09.

2-Diazo-3-oxo-5-(2-oxopyrrolidin-1-yl)pentanoic Acid Ethyl Ester (60). A mixture containing 2.0 g (8.8 mmol) of the above keto ester, 2.4 g (11 mmol) of *p*-nitrobenzenesulfonyl azide, and 3.7 mL (26 mmol) of triethylamine in 50 mL of CH_2Cl_2 was stirred at room temperature for 20 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 1.8 g (83%) of diazo amido ester **60** as a yellow oil: IR (neat) 2981, 2138, 1714, 1690, and 1297 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.98 (p, 2H, J = 7.2 Hz), 2.33 (t, 2H, J = 7.2 Hz), 3.08 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 7.2 Hz), 3.59 (t, 2H, J = 7.2 Hz), and 4.27 (q, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 18.2, 31.1, 38.2, 38.4, 47.8, 61.8, 161.4, 175.3, and 190.9. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.33; H, 6.04; N, 16.39.

1,8-Dioxohexahydroindolizine-8*a*-carboxylic Acid Ethyl Ester (64). To a solution containing 0.76 g (3.0 mmol) of diazo amido ester **60** in 100 mL of CH_2Cl_2 was added 10 mg of $Rh_2(OAc)_4$ under an argon atmosphere. After the solution was stirred at room temperature for 2 h, the mixture was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography to give 0.54 g (80%) of **64** as a pale yellow oil: IR (neat) 2940, 1773, 1744, 1720, and 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.03−2.09 (m, 1H), 2.41−2.63 (m, 5H), 3.02−3.07 (m, 1H), 3.16−3.22 (m, 1H), 3.30−3.35 (m, 1H), 3.38−3.45 (m, 1H), and 4.31 (dq, 2H, J = 7.2 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 25.6, 36.2, 39.4, 45.4, 45.5, 62.9, 81.3, 165.6, 201.3, and 202.6; HRMS (*m/e*) calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.1004.

3-Oxo-5-(2-oxopiperidin-1-yl)pentanoic Acid Ethyl Ester. A mixture containing 5.0 g (29 mmol) of 3-(2-oxopiperidin-1-yl)propionic acid and 4.7 g (29 mmol) of carbonyldiimidazole in 80 mL of dry THF was stirred at room temperature for 6 h. The resulting acylimidazole solution was used directly in the next step. To a solution of 3.8 g (29 mmol) of ethyl hydrogen malonate in 30 mL of dry THF was added dropwise 29 mL (58 mmol) of 2 M isopropylmagnesium chloride/THF solution at 0 °C. The mixture was stirred at room temperature for 2 h, and the above acyl imidazole solution was cannulated into this suspension. The resulting mixture was maintained at room temperature for 16 h, quenched with 2 M HCl solution, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 4.1 g (59%) of the titled compound as a white solid: mp 50−52 °C; IR (neat) 3442, 2934, 1742, 1711, 1630, and 1332 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.75−1.78 (m, 4H), 2.34 (t, 2H, J = 7.2 Hz), 2.89 (t, 2H, J = 6.8 Hz), 3.34 (t, 2H, J = 7.2 Hz), 3.47 (s. 2H), 3.57 (t, 2H, J = 6.8 Hz), and 4.18 (q, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.4, 23.5, 32.5, 41.1, 43.0, 49.3, 49.5, 61.6, 167.3, 170.4, and 202.1. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.49; H, 7.93; N, 5.65.

2-Diazo-3-oxo-5-(2-oxopiperidin-1-yl)pentanoic Acid Ethyl Ester (61). A mixture containing 2.9 g (12 mmol) of the above keto ester, 3.2 g (14 mmol) of *p*-nitrobenzenesulfonyl azide, and 4.8 mL (35 mmol) of triethylamine in 80 mL of CH_2Cl_2 was stirred at room temperature for 20 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give 2.5 g (80%) of **61** as a yellow oil: IR (neat) 2947, 2135, 1717, 1643, and 1299 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 1.76−1.77 (m, 4H), 2.32 (t, 2H, J = 6.8 Hz), 3.12 (t, 2H, J = 6.8 Hz), 3.32 (t, 2H, J = 6.8 Hz), 3.64 (t, 2H, J = 7.2 Hz), and 4.28 (q, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 21.5, 23.4, 32.5, 38.3, 43.2, 48.7, 61.6, 161.4, 170.0, and 191.3. Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.76; H, 6.65; N, 15.72.

1,9-Dioxohexahydropyrrolo[1,2-*a*]azepine-9*a*-carboxylic Acid Ethyl Ester (65). A mixture containing 8 mg of $Rh_2(OAc)_4$ and 0.5 g (1.9 mmol) of diazo amido ester **61** in 80

(50) Adams, R.; Jones, V. V. *J. Am. Chem. Soc.* **1949**, *71*, 3826.

mL of CH_2Cl_2 was stirred at room temperature for 2 h under an argon atmosphere. The mixture was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.31 g (72%) of **65** as a pale yellow oil: IR (neat) 2940, 1768, 1727, 1706, and 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.59−1.65 (m, 1H), 1.76−1.90 (m, 3H), 2.54−2.61 (m, 3H), 2.73−2.81 (m, 1H), 3.02−3.20 (m, 3H), 3.32−3.37 (m, 1H), and 4.27 (dq, 2H, J = 7.2 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 22.3, 28.5, 36.8, 42.2, 48.5, 50.7, 62.1, 82.6, 166.1, 202.6, and 203.2. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.05; H, 7.25; N, 5.84.

9-Oxo-13-oxa-6-azatricyclo[8.2.1.0^{1,6}]tridec-11-ene-10,11,12-tricarboxylic Acid 10-Ethyl Ester 11,12-Dimethyl Ester (66). A mixture containing 10 mg of $Rh_2(OAc)_4$, 0.27 g (1.0 mmol) of diazo amido ester **61**, and 0.14 g (1.0 mmol) of DMAD in 10 mL of CH_2Cl_2 was stirred at room temperature for 4 h under an argon atmosphere. The mixture was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography to give 0.053 g (22%) of **65** and 0.14 g (38%) of cycloadduct **66** as a pale yellow solid: mp 105−106 °C; IR (neat) 2950, 1721, 1649, 1434, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.59−1.70 (m, 1H), 1.75−1.96 (m, 2H), 2.05−2.14 (m, 1H), 2.59−2.71 (m, 2H), 2.75−2.81 (m, 1H), 2.99−3.02 (m, 2H), 3.12−3.20 (m, 1H), 3.72 (s, 3H), 3.76−3.80 (m, 1H), 3.82 (s, 3H), 4.24 (q, 2H, J = 7.2 Hz), and 4.37 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 20.0, 20.4, 38.2, 43.2, 47.7, 51.1, 52.2, 52.3, 62.3, 71.7, 80.9, 139.5, 150.8, 161.7, 162.2, 168.7, and 204.0. Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.58; H, 6.12; N, 3.54.

1-Diazo-4-phthalimido-2-butanone (67). A solution containing 4.5 g (19 mmol) of *N*-phthalyl-β-alanine in 20 mL of thionyl chloride was allowed to stir at room temperature for 4 h. Removal of the excess thionyl chloride under reduced pressure afforded the acid chloride as a white solid which was immediately used in the next step. To a freshly prepared diazomethane (45 mmol) ether solution at 0 °C was slowly added a tetrahydrofuran solution containing the above acid chloride. The reaction mixture was stirred for several hours at 25 °C, and the resulting solid was filtered and washed with ether to give 4.8 g (98%) of diazoimide **67** as a yellow solid: mp 129−130 °C; IR ($CHCl_3$) 2108, 1769, 1641, 1364, 1317, 1143, and 995 cm^{-1}; ^1H NMR (90 MHz, $CDCI_3$) δ 2.77 (t, 2H, J = 7.5 Hz), 4.01 (t, 2H, J = 7.5 Hz), 5.32 (s, 1H), and 7.66−7.93 (m, 4H). Anal. Calcd for $C_{12}H_9N_3O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.00; H, 3.69; N, 17.12.

11,12-Dicarbomethoxy-5,9-dioxo-10,12*a*-epoxy-5,7,8,9,10,12*a*-hexahydroaz ocino[2,1*a*]isoindole (68). To a solution containing 0.5 g (2.0 mmol) of diazoimide **67** and 0.4 g (2.8 mmol) of dimethyl acetylenedicarboxylate in 15 mL of dichloromethane was added 2 mg of rhodium(II) acetate. The resulting solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the crude product was subjected to flash chromatography on silica gel to give 0.45 g (63%) of cycloadduct **68** as a white solid: mp 142−143 °C; IR (KBr) 1727, 1717, 1395, 1328, and 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.62−2.71 (m, 1H), 2.97−3.14 (m, 2H), 3.55 (s, 3H), 3.90 (s, 3H), 4.52−4.60 (m, 1H), 5.42 (s, 1H), 7.55−7.68 (m, 3H), 7.89 (dd, 1H, J = 6.3 and 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 42.8, 52.7, 53.1, 87.8, 102.9, 123.2, 123.7, 131.0, 132.1, 132.7, 135.4, 139.6, 139.8, 160.5, 160.7, 164.8, and 205.2. Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.41; H, 4.27; N, 3.85.

Rhodium(II)-Catalyzed Cycloaddition Reaction of 1-Diazo-4-phthalimido-2-butanone (67) with *N*-Phenylmaleimide. A mixture containing 0.5 g (2 mmol) of diazoimide **67**, 2 mg of rhodium(II) octanoate, and 0.35 g (2.0 mmol) of *N*-phenyl-maleimide in 15 mL of dichloromethane was allowed to stir for 10 h at 25 °C. Standard workup followed by silica gel chromatography afforded cycloadduct **69** in 45% yield: mp 230−232 °C; IR ($CHCl_3$) 1723, 1396, 1182, and 1054 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.73 (dd, 1H, J = 13.3 and 5.0 Hz), 3.00−3.20 (m, 2H), 3.70 (d, 1H, J = 8.0 Hz), 3.91 (d, 1H, J = 8.0 Hz), 4.70−4.85 (m, 1H), 5.22 (s, 1H), and 7.20−7.90 (m, 9H); ^{13}C NMR (75 MHz, DMSO) δ 32.3, 43.2, 51.5, 52.0, 85.7, 100.1, 123.0, 124.1, 127.0, 128.9, 129.2, 130.8, 131.1, 131.9, 132.3, 139.8, 163.7, 172.8, 175.1, and 210.3. Anal. Calcd for $C_{22}H_{16}N_2O_5$: C, 68.04; H, 4.15; N, 7.21. Found: C, 68.04; H, 4.06; N, 7.06.

The second product isolated from the silica gel column in 26% yield was assigned as the rearrangement product 70: mp 163−164 °C; IR (neat) 1773, 1717, 1397, 1187, 1073, and 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (t, 2H, J = 6.7 Hz), 3.59 (dt, 1H, J = 14.1 and 6.7 Hz), 3.82 (dt, 1H, J = 14.1 and 6.7 Hz), 6.14 (s, 1H), 6.27 (d, 1H, J = 6.0 Hz), 6.57 (d, 1H, J = 6.0 Hz), 7.20−7.36 (m, 5H), and 7.71−7.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 34.8, 119.8, 123.2, 123.9, 127.5, 127.7, 128.0, 128.8, 131.7, 133.4, 134.0, 137.4, 140.8, 167.6, and 167.8. Anal. Calcd for $C_{22}H_{16}N_2O_5$ C, 68.04; H, 4.15; N, 7.21. Found: C, 68.00; H, 4.17; N, 7.16.

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Supporting Information Available: ^{13}C NMR spectrum for compound **64**. This material is available free of charge via the Internet at http://pubs.acs.org.

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