Intramolecular Cycloaddition of Isomünchnone Dipoles to Heteroaromatic π-Systems

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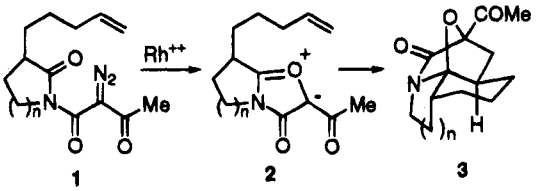
A series of furanyl-, thienyl-, and indolo-substituted diazo imides were prepared by treating the appropriate amides with diketene to give the N-acetoacylated imides. Exposure of the imides to standard diazo transfer conditions afforded the desired diazo imides. Treatment of these diazo imides bearing tethered heterocyclic rings with rhodium(II) acetate affords transient isomünchnone dipoles. The mesoionic dipoles are formed by cyclization of the rhodium carbenoid onto the neighboring amide carbonyl oxygen atom. The scope and limitations of the intramolecular 1,3-dipolar cycloaddition of the isomünchnones across a tethered furan and thiophene ring were studied. The facility of the internal cycloaddition is influenced by the length and nature of the tether connecting the dipole and dipolarophile functionalities. The reaction is critically dependent on conformational factors in the transition state. In addition, the first examples of intramolecular cycloaddition of isomünchnones to indole dipolarophiles are reported. Cycloadditions of this type generate highly functionalized polyheterocyclic systems with complete relative stereocontrol at the newly formed stereocenters.

Mesoionic compounds have proven to be valuable intermediates in organic chemistry from both physical and synthetic perspectives.[1-7] These substances contain a masked 1,3-dipole within their framework and are therefore willing participants in 1,3-dipolar cycloadditions.[8-16] The cycloaddition chemistry of mesoionic systems with various dipolarophiles has also proven to be quite valuable for natural product synthesis.[17] When an olefin is employed as the dipolarophile, this methodology represents a powerful tool for the construction of novel heterocyclic systems because it creates two new carbon–carbon bonds in a single operation and the reaction often allows for high regio- and stereochemical control of the remote substituents.[1]

Our interest in the chemistry of mesoionic dipoles stems from studies in our laboratory dealing with the rhodium(II)-catalyzed reactions of α-diazo carbonyl compounds in the presence of various heteroatoms.[18] In earlier reports, we showed that the isomünchnone[19] class of mesoionics can be easily generated from the Rh(II)-catalyzed reaction of α-diazo imides.[20] This mesoionic dipole was found to undergo cycloaddition with both electron-rich and electron-deficient dipolarophiles.[21,22] We were able to show that the dipolar cycloaddition of isomünchnones with alkenes also occurred intramolecularly and that the overall reaction represents an efficient way to synthesize complex polyheterocyclic ring systems.[23] The complexity of the resultant cycloadducts was



significantly increased by generation of isomünchnones

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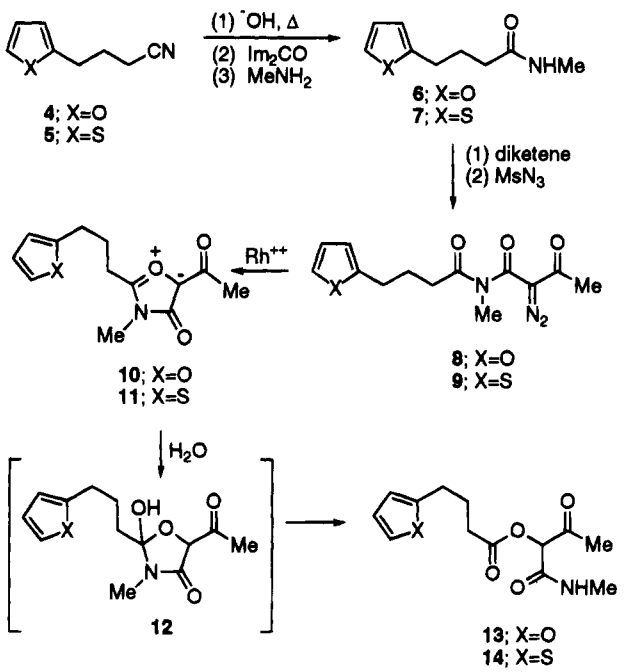
where the peripheral substituents were part of a cyclic system containing a tethered alkene.[24]

In the context of extending such transformations to more highly substituted substrates, we wondered whether the isomünchnone class of mesoionics might also undergo intramolecular dipolar cycloaddition with heteroaromatic π-bonds. Five-membered-ring heteroaromatics such as furan, thiophene, and indole have, in spite of their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[25] The reactivity of these heteroaromatic dipolarophiles is, however, sharply decreased because of the loss of aromaticity in the cycloaddition transition states. A vast amount of information is available concerning the reactivity of heteroaromatics in cycloadditions where the heteroaromatics enter as 4_πs components,[26] but a study of their dipolarophilic activities has not been extensively examined to date.[27-38] We therefore initiated an investigation to determine whether cycloaddition of isomünchnones to heteroaromatic π-systems would occur. In this paper we report results emerging from this inquiry.

Results and Discussion

Three key questions emerged at the outset of these investigations: (1) What types of heteroaromatic systems work best, (2) what effect will a variation in the spatial proximity between the isomünchnone center and the heteroaromatic ring have on the course of the reaction, and (3) how will the point of attachment of the dipole to the heteroaromatic ring affect the facility of the cycloaddition. To address the first question, the Rh(II)-catalyzed reaction of several furanyl-, thienyl- and indolo-substituted α-diazo imides were examined. Construction of the prerequisite diazo imides necessary for dipole generation was accomplished by initial conversion of nitriles **4** and **5** to the corresponding carboxylic acids by basic hydrolysis in refluxing aqueous ethanol. Reaction with 1,1'-carbonyldiimidazole generated a transient acylimidizolide which, when treated with methylamine, gave the primary amides **6** and **7**. The desired α-diazo imides **8** and **9** were prepared by reaction with diketene[39] followed by diazo transfer of the resulting imide with mesyl azide and triethylamine.[40,41]

The Rh(II)-catalyzed decomposition of α-diazo imide **8** (or **9**) results first in the formation of a rhodium carbenoid which then cyclizes onto the neighboring amide carbonyl oxygen to generate the intermediate isomünchnone **10** (or **11**).[19-24] Unfortunately, no products resulting from intramolecular dipolar cycloaddition across the heteroaromatic ring could be detected in the crude reaction mixture. The only isolable material proved to be the



carbamoyl-2-oxopropyl-substituted ester **13** (or **14**) which is formed by the addition of adventitious water to the isomünchnone dipole followed by ring opening of the transient hemiaminal **12**. When water was deliberately added to the reaction mixture, a high yield of compound **13** (or **14**) was obtained.

Whereas the reaction of the furanyl-substituted diazo imide **8** with rhodium(II) acetate under the standard conditions failed to produce a cycloadduct, reaction in the presence of dimethyl acetylenedicarboxylate (DMAD) proved fruitful. The initially formed isomünchnone **10** underwent bimolecular 1,3-dipolar cycloaddition with DMAD to provide **15**, which spontaneously underwent an intramolecular Diels–Alder reaction to give **16** in 56% overall yield. Noteworthy in this tandem cycloaddition is the creation of six stereogenic centers in one synthetic operation with complete diastereospecificity. The stereo-

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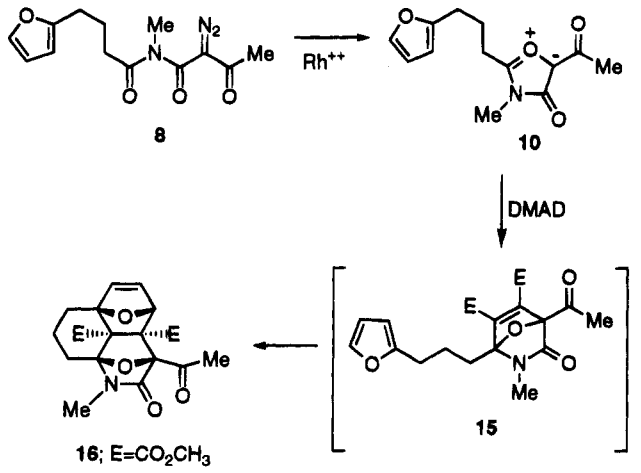
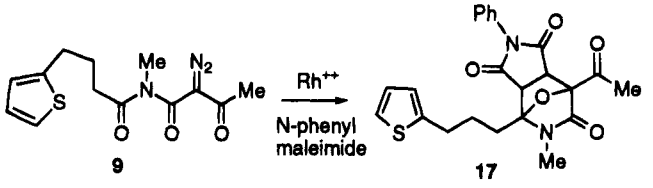
chemical assignment of **16** is based upon its spectroscopic properties as well as molecular mechanics calculations[42] which show that *endo* isomer **16** is 14.9 kcal/mol more



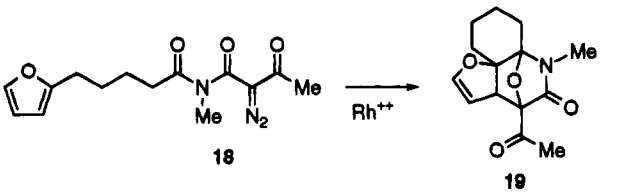
stable than the corresponding *exo* isomer. The order of cycloaddition was determined by a control experiment in which an isomünchnone dipole was shown to react at a significantly faster rate with DMAD than did a substituted 2-alkylfuran. Even though the isomünchnone dipole derived from the thienyl-substituted diazo imide **9** did not undergo internal cycloaddition, it did cycloadd with *N*-phenylmaleimide, producing the expected dipolar cycloadduct **17** as a 2:1 mixture of *endo* and *exo* isomers in 92% yield.



Isomünchnones contain a carbonyl ylide dipole within their framework and are therefore willing participants in 1,3-dipolar cycloaddition.[3] Of the three categories described by Sustmann,[43] type II is particularly common for carbonyl ylides, since they possess one of the smallest HOMO–LUMO energy gaps of all the common 1,3-dipoles.[44] The HOMO of the dipole is dominant in reactions with electron-deficient dipolarophiles whereas the LUMO of the dipole is the controlling molecular orbital in reactions with electron-rich dipolarophiles. Earlier studies in our laboratory demonstrated that the bimolecular cycloaddition of isomünchnones with electron-rich π-systems such as diethylketene acetal was a remarkably efficient process.[21] Thus, we were somewhat puzzled by the absence of internal cycloaddition with the furanyl-substituted diazo imide **8**, especially since molecular orbital calculations revealed a small energy gap (8.12 eV) between the LUMO of the isomünchnone and the HOMO of the 2-alkyl-substituted furan. The MNDO calculations indicated that the energy gap between the FMOs with the furanyl system is, in fact, smaller than when diethylketene acetal (ΔE = 8.69 eV) was used as the dipolarophile. The lower dipolarophilic reactivity of the furan ring, in comparison with other vinyl ethers, must be related to its aromatic structure. Nevertheless, there are many examples in the literature where the furan ring readily undergoes cycloaddition with a variety of 1,3-dipoles.[28–38] This led us to consider the possibility that the absence of internal cycloaddition with diazo imide **8** may be related to conformational rather than electronic factors.

The interaction of two reactive groups within the same molecule has always been of paramount concern to organic chemists.[45] The geometric requirements for interaction are generally evaluated through systems that have the reacting centers connected together by a few intervening atoms. This linkage provides a cyclic transition state, which imposes distinct restrictions upon the bond angles at the reacting centers.[46] The primary spatial requirement for intramolecular cycloaddition of an isomünchnone with some neighboring π-bond is that the distance between the two reactive centers be sufficiently close so that effective overlap of the dipole array with the π-bond can occur. Good yields of cycloadducts are generally obtained with tethers leading to five- and six-membered ring formation.[24] Although the entropy of activation associated with the more flexible four methylene group tether (*i.e.*, six-membered ring formation) is more negative than that with five-ring formation, the activation energy for cycloaddition will be somewhat dependent on ring size[47] and this may influence the facility of the internal cycloaddition. The success of the intramolecular dipolar cycloaddition will also be critically dependent on the relative rates of cycloaddition as compared to unproductive decomposition pathways (*i.e.*, reaction with H_2O). With this in mind, we felt that it would be worthwhile to extend our studies to the homologous furanyl diazo imide **18** to determine if this extension of chain length would facilitate the internal cycloaddition reaction.

Gratifyingly, treatment of diazo imide **18** with a catalytic quantity of rhodium(II) acetate in benzene (80 °C) gave the polyheterocyclic adduct **19** in 74% yield and with complete diastereospecificity. When the related



thienyl-substituted diazo imide **20** was allowed to react under the same experimental conditions, the crude reaction mixture showed only the presence of the carbamoyl-2-oxopropyl-substituted ester **21**, which is derived from hydrolysis of the initially generated isomünchnone. Supporting evidence for initial formation of the isomünchnone dipole derived from **20** was obtained by carrying out the reaction in the presence of *N*-phenyl-

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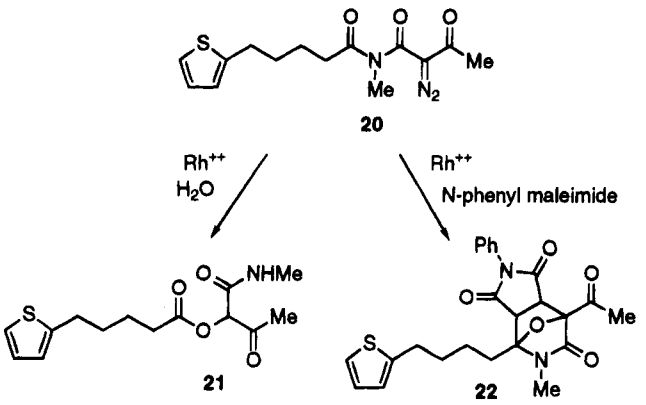
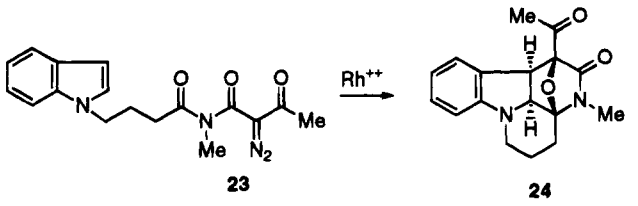
maleimide and isolating the bimolecular cycloadduct **22** in 78% yield.

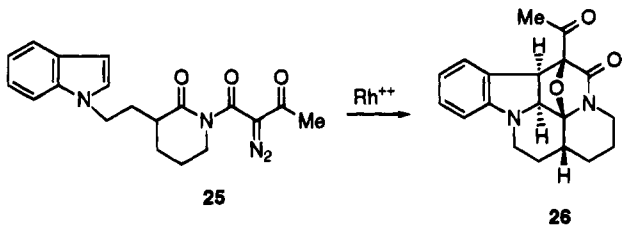


The rate of an intramolecular cycloaddition reaction will depend on the energy level of the open-chain initial state, compared to the transition state resembling the cyclic product. Clearly, the facility of the process will be influenced by the length and nature of the tether connecting the dipole and dipolarophile functionalities. The activation energy of the process will also reflect the strain energy of the ring to be formed and the stereoelectronic interactions in the transition state. The fact that intramolecular cycloaddition across the furan ring occurs with diazo imide **18** but not with **8** implies that the additional methylene group allows for better overlap of π-orbitals in the transition state. The absence of internal cycloaddition with the related thienyl-substituted diazo imide **20** is presumably related to electronic factors. Thiophene has a lower lying HOMO level than does furan, which increases the energy gap between the interacting FMOs, thereby diminishing the cycloaddition rate. Indeed, this is probably why so little is known about dipolar cycloaddition across thiophene rings.

To further illustrate the scope and synthetic utility of the intramolecular isomünchnone cycloaddition reaction, we became interested in knowing whether such a process would also take place with nitrogen-containing heterocycles. Although bimolecular dipolar cycloadditions involving pyrroles or indoles are known,[28] very little has been reported about the intramolecular counterpart.[36] Our interest in such reactions was further stimulated by the possibility of using these intramolecular cycloadditions to generate the skeleton found in the alkaloid vallesamidine (*vide infra*).[48,49] First, we decided to examine the Rh(II)-catalyzed behavior of indolyl-substituted diazo imide **23**. In marked contrast to the furanyl system **8**, diazo imide **23** underwent smooth intramolecular cycloaddition upon treatment with rhodium(II) acetate to produce cycloadduct **24** in 75% yield as a single diastereomer. Its spectroscopic properties support the stereochemical assignment of **24** as being the result of an *endo* cycloaddition, and this was confirmed by X-ray crystallography.[50] In the presence of *N*-phenylmaleimide, the intramolecular process was completely shut down, and the only product isolated was the bimolecular cycloadduct derived from trapping the isomünchnone dipole.



Bolstered by this positive result, we next examined the Rh(II)-catalyzed behavior of a cyclic diazo imide containing an indolyl group. Treatment of diazo imide **25** with a catalytic quantity of rhodium(II) acetate in refluxing benzene gave the polyheterocyclic system **26** in 67% yield. Compound **26** is produced with complete diastereoselectivity and is also the result of *endo* cycloaddition with regard to the dipole. The structural assignment of compound **26** was unequivocally established by an X-ray crystal analysis.[50] These two cases represent the first examples of intramolecular dipolar cycloaddition of an isomünchnone dipole across an indolyl π-bond.



Two additional systems we chose to study corresponded to α-diazo imides **27** and **28** which contain a smaller and larger tether unit between the dipole and indolyl ring. The consequence of removing one of the methylene groups in the tether of the diazo imide (*i.e.*, **27**) was that no internal cycloaddition occurred across the indolyl π-bond. The only product that could be isolated corresponded to the carbamoyl ester **29** (68%). We assume that the length of the tether only influences the entropy of cycloaddition without affecting the rate of isomünchnone formation. Apparently, the ring strain of the resulting tricyclic adduct is sufficiently reflected in the transition state of cycloaddition so that a substantial kinetic barrier to this process exists. However, the isomünchnone derived from **27** is indeed formed, as smooth bimolecular cycloaddition occurred when the reaction was carried out in the presence of *N*-phenylmaleimide (*i.e.*, **30**, 70%). Expansion of the tether with a fourth methylene group gave no detectable quantities of an intramolecular cycloadduct, affording only carbamoyl ester **31** (69%). In order to confirm that the isomünchnone was being formed from **28**, the reaction was repeated in the presence of *N*-phenylmaleimide. This reaction afforded the bimolecular cycloadduct **32** as a 5:3 mixture of diastereomers in 80% overall yield. Thus, a four-carbon tether (leading conceptually to a seven-membered ring) is ineffective at directing intramolecular cycloaddition. Evidently the additional entropy introduced by the longer tether was sufficient to slow down intramolecular dipolar cycloaddition, thereby allowing hydrolysis of the dipole to occur.

The ability to intramolecularly cycloadd an isomünchnone dipole across an indolyl π-bond opens up a new

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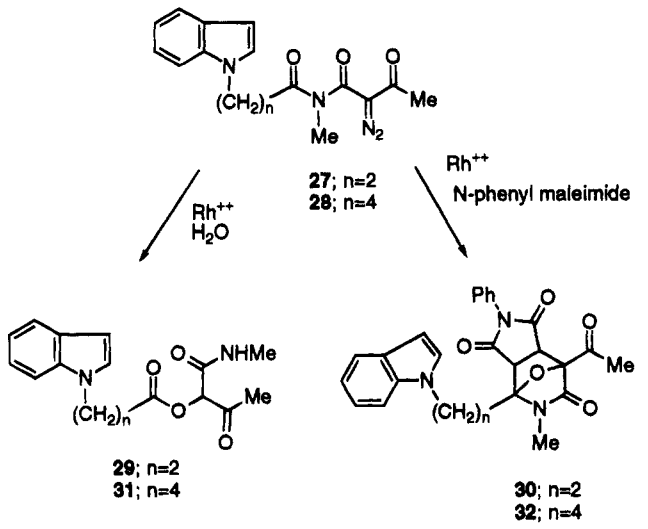
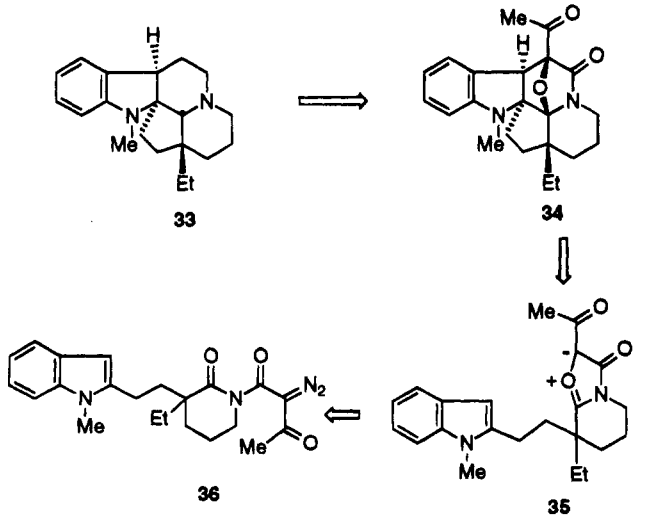
(50) The authors have deposited atomic coordinates for structures **24** and **26** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

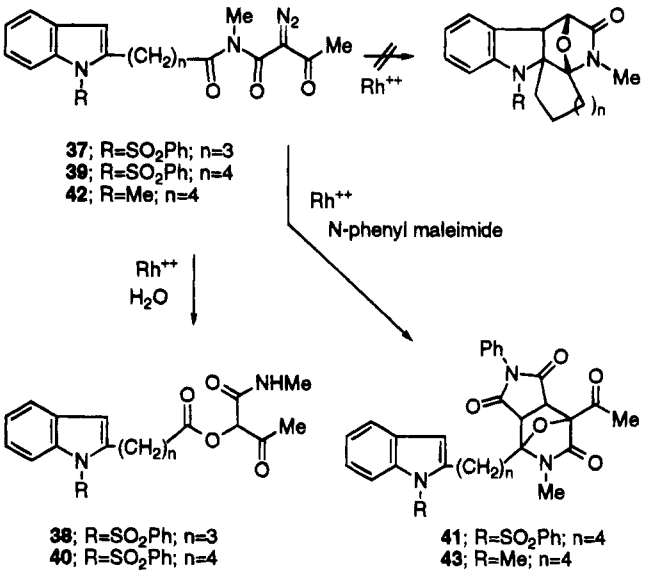


strategy for alkaloid synthesis. In connection with a project aimed at the synthesis of 3*H*-indoline alkaloids, we have investigated the isomünchnone cycloaddition as a possible approach for the synthesis of vallesamidine.[48,49] Vallesamidine is a structurally unique member of the 2,2,3-trialkylindoline class of alkaloids and has been independently synthesized by two different groups.[49,51] Analysis of the challenges posed by the synthesis of the aspidospermine skeleton present in vallesamidine suggested a convergent approach that involves intramolecular dipolar cycloaddition of isomünchnone **35** derived from diazo imide **36**.

Our initial efforts focused on the synthesis of the *N*-(phenylsulfonyl)-substituted diazo imide **37** to test the feasibility of our approach to vallesamidine. The preparation of **37** was achieved in six steps starting from 3-(1*H*-indol-2-yl)propan-1-ol. With the isomünchnone dipole precursor in hand, we examined its Rh(II)-catalyzed



behavior. Unfortunately, all attempts to effect the intramolecular 1,3-dipolar cycloaddition across the indolyl π-bond proved fruitless. The only characterizable product isolated in 50% yield corresponded to addition of water across the dipole center, giving rise to the carbamoyl oxopropyl ester **38**. We also attempted to induce intramolecular cycloaddition by extending the tether length by one carbon atom. Once again, the only isolable product corresponded to carbamoyl ester **40**. The isomünchnone dipole was formed in good yield with this system since smooth bimolecular addition occurred when the reaction was carried out in the presence of *N*-phenylmaleimide.



One conceivable rationale to explain why these two indolyl-substituted diazo imides do not undergo internal cycloaddition is that the phenylsulfonyl group adversely influences the electronic nature of the indolyl π-bond toward the isomünchnone dipole. In order to probe this point, we investigated the cycloaddition behavior of the closely related *N*-methyl-substituted indole **42**. Although the isomünchnone dipole derived from **42** is formed in high yield, as is evidenced by the isolation of bimolecular cycloadduct **43**, no trace of an intramolecular cycloadduct was detected in the crude reaction mixture by NMR spectroscopy. Thus, it would appear as though the facility of internal cycloaddition of an isomünchnone across an indolyl π-bond is critically related to the point at which the tether is connected to the heteroaromatic ring. Undoubtedly, conformational factors in the transition state for cycloaddition play an important role.

In conclusion, we have demonstrated that isomünchnone dipoles generated from the Rh(II)-catalyzed reaction of diazo imides undergo successful 1,3-dipolar cycloaddition across heteroaromatic π-bonds to provide novel tricyclic compounds in good to excellent yield and in a stereocontrolled fashion. The facility of the cycloaddition is critically dependent on conformational factors in the transition state. We are currently investigating the scope and limitations of the intramolecular dipolar cycloaddition of isomünchnones derived from indolyl-substituted cyclic diazo imides as a potential method for the synthesis of vallesamidine. The results of this investigation 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 oven-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the

(51) Dickman, D. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1528. Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798.

residue was chromatographed on a silica gel column using an ethyl acetate–hexane mixture as the eluent unless specified otherwise.

General Procedure for N-Acetoacetylation of Indole Amides. A procedure similar to that described by Doyle and co-workers[52] was used to prepare the desired *N*-acetoacetyl amides. To a solution containing 4.7 mmol of the appropriate amide in 100 mL of dry THF at −78 °C under N_2 was added 4.9 mmol of *n*-butyllithium in hexane dropwise. After the addition was complete, the solution was allowed to stir at −78 °C for an additional 60 min. To the resulting mixture was added 5.6 mmol of freshly distilled diketene, and the solution was allowed to warm to rt over a 60 min period and then mixed with 50 mL of a saturated NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude residue was subjected to silica gel chromatography.

General Procedure for Synthesis of Diazo Imides. A procedure similar to that described by Taber and co-workers[40] was used to prepare the desired diazo imide. To a solution containing 2 mmol of the appropriate imide and 2.2 mmol of mesyl azide in 5 mL of acetonitrile was added 4.0 mmol of triethylamine at rt. After the solution was stirred for 3–12 h, the solvent was removed under reduced pressure, and the residue was taken up in 25 mL of CH_2Cl_2, washed with 10% NaOH and brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-[4-(furan-2-yl)butyryl]-*N*-methyl-3-oxobutyramide (8). To a stirred solution containing 15 g (0.22 mol) of furan in 250 mL in THF at 0 °C was added 138 mL (0.22 mol) of a 1.6 M solution of *n*-butyllithium in hexane. The mixture was stirred at 0 °C for 1 h, and then a solution containing 55 g (0.28 mol) of 1,3-dibromopropane in 50 mL of dry THF was rapidly added. The mixture was allowed to warm to rt over a 12 h period and was then quenched with a saturated NH_4Cl solution. The solution was extracted with ether, and the combined ether layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was distilled at 100–103 °C (20 mm) to give 20.97 g (50%) of 2-(3-bromopropyl)furan as a colorless oil: IR (neat) 1590, 1500, and 1430 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.10 (quin, 2H, J = 7.2 Hz), 2.76 (t, 2H, J = 7.2 Hz), 3.38 (t, 2H, J = 7.2 Hz), 5.90–6.10 (m, 1H), 6.20–6.35 (m, 1H), and 7.22–7.38 (m, 1H).

A solution contanining 21.0 g of the above bromofuran and 7.07 g (0.144 mol) of NaCN in 100 mL of DMSO was stirred at 70 °C under N_2 for 12 h. At the end of this time the solution was poured into 200 mL of water and extracted with ether. The combined organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 13.6 g (91%) of 4-(furan-2-yl)-butanenitrile (**4**) as a pale yellow oil: IR (neat) 2270, 1610, and 1520 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.80 (quin, 2H, J = 7.5 Hz), 2.68 (t, 2H, J = 7.5 Hz), 3.64 (t, 2H, J = 7.5 Hz), 5.86–6.03 (m, 1H), 6.15–6.30 (m, 1H), and 7.18–7.31 (m, 1H).

A solution containing 13.6 g (0.101 mol) of the above nitrile and 56 g (1 mol) of KOH in 200 mL of a 50% ethanol–water mixture was heated at reflux for 30 h. At the end of this time the solution was allowed to cool to rt, and the mixture was concentrated under reduced pressure. The aqueous solution was diluted with 200 mL of water, extracted with ether, and then acidified with 6 N HCl. The solution was extracted again with ether, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 12.6 g (93%) of 4-(furan-2-yl)butyric acid as a yellow oil: IR (neat) 2800–2400, 1708, 1598, and 1414 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.87 (quin, 2H, J = 7 Hz), 2.40 (t, 2H, J = 7 Hz), 2.70 (t, 2H, J = 7 Hz), 6.00 (d, 1H, J = 3 Hz), 6.25 (t, 1H, J = 3 Hz), 7.28 (d, 1H, J = 3 Hz), and 11.20 (brs, 1H).

To a solution containing 12.4 g (80.1 mmol) of the above acid in 100 mL of CH_2Cl_2 was added 15.6 g (96.1 mmol) of 1,1′-carbonyldiimidazole over a period of 20 min. After being stirred for 2 h, the solution was poured into a 40% aqueous methylamine solution at 0 °C. The solution was allowed to warm to rt overnight and was then acidified with 6 N HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 11.9 g (89%) of 4-(furan-2-yl)-*N*-methylbutyramide (**6**) as a pale yellow oil: IR (neat) 3114, 1654, and 1559 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.86–1.98 (m, 2H), 2.16 (t, 2H, J = 7.5 Hz), 2.61 (t, 2H, J = 7.3 Hz), 2.72 and 2.74 (s, 3H) (1:1 mixture of rotamers), 5.95 (dd, 1H, J = 3.0 and 0.7 Hz), 6.04 (brs, 1H), 6.22 (dd, 1H, J = 3.0 and 1.9 Hz), and 7.20–7.28 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.0, 26.1, 27.1, 35.4, 105.1, 110.0, 140.8, 155.1, and 173.2.

N-Acetoaceylation of the above amide gave *N*-[4-(furan-2-yl)butyryl]-*N*-methyl-3-oxobutyramide (57%) as a white solid: mp 61–62 °C; IR (KBr) 1702, 1654, 1559, and 1297 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.75–2.10 (m, 2H), 2.22 (s, 3H), 2.55 (t, 2H, J = 7 Hz), 2.68 (t, 2H, J = 7 Hz), 3.20 (s, 3H), 3.95 (s, 2H), 6.00 (d, 1H, J = 3 Hz), 6.25 (t, 1H, J = 3 Hz), and 7.30 (d, 1H, J = 2 Hz).

Diazo transfer of the above compound gave 2-diazo-*N*-[4-(furan-2-yl)butyryl]-*N*-methyl-3-oxobutyramide (**8**) (75%) as a yellow oil: IR (neat) 2133, 1670, and 1260 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.90 (quin, 2H, J = 7.2 Hz), 2.33 (s, 3H), 2.47 (t, 2H, J = 7.2 Hz), 2.60 (t, 2H, J = 7.3 Hz), 3.08 (s, 3H), 5.92 (d, 1H, J = 2.7 Hz), 6.18 (dd, 1H, J = 2.7 and 1.6 Hz), and 7.20 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.8, 26.7, 28.2, 32.9, 34.7, 81.3, 105.3, 110.0, 140.9, 154.7, 164.8, 174.2, and 189.0. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.07; H, 5.43; N, 15.02.

A mixture containing 51 mg (0.18 mmol) of **8** in 4 mL of benzene and 2 mg of rhodium(II) acetate was heated at reflux for 70 min and then cooled to rt. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 26 mg (56%) of 4-(furan-2-yl)-butyric acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**13**) as a clear oil: IR (neat) 1735, 1700, 1670, and 1525 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.95–2.08 (m, 2H), 2.42 (s, 3H), 2.51 (dt, 2H, J = 7.3 and 3.1 Hz), 2.72 (t, 2H, J = 7.2 Hz), 5.50 (s, 1H), 6.02 (d, 1H, J = 2.9 Hz), 6.25–6.31 (m, 1H), 6.37 (brs, 1H), and 7.30 (d, 1H, J = 1.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.1, 26.1, 26.9, 27.8, 32.7, 78.9, 105.6, 110.1, 141.1, 154.6, 163.5, 170.9, and 199.6. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.53; H, 6.44; N, 5.25.

To a solution containing 97 mg (0.35 mmol) of **8** and 150 mg (1.0 mmol) of DMAD in 1.5 mL of benzene was added 2 mg of rhodium(II) acetate. The solution was placed in an oil bath preheated to 95 °C, and the mixture was heated at reflux for 12 h. The solution was cooled to rt, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 76 mg (56%) of 3-acetyl-3a,9b-dicarbomethoxy-9a,3:6a,4-diepoxy-2,3,3a,4,-6a,7,8,9,9a,9b-decahydro-1-methyl-2-oxo-1*H*-benzo[*de*]quinoline (**16**) as a white solid: mp 158–159 °C; IR (KBr) 1733, 1719, 1382, and 1274 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.77–2.20 (m, 5H), 2.29 (s, 3H), 2.55–2.72 (m, 1H), 2.89 (s, 3H), 3.56 (s, 3H), 3.63 (s, 3H), 5.02 (d, 1H, J = 1.6 Hz), 6.13 (d, 1H, J = 5.5 Hz), and 6.77 (dd, J = 5.5 and 1.6 Hz); ^{13}C-NMR (CDCl3, 75 MHz) δ 16.6, 24.5, 24.7, 26.5, 27.7, 52.0, 52.2, 67.8, 70.4, 82.2, 90.1, 93.8, 96.7, 138.1, 140.5, 168.1, 168.7, 170.5, and 201.1. Anal. Calcd for $C_{19}H_{21}NO_8$: C, 58.31; H, 5.41; N, 3.58. Found: C, 58.15; H, 5.45; N, 3.57.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-[(4-(thiophene-2-yl)-butyryl]-*N*-methyl-3-oxobutryamide (9). To a solution containing 10.0 g (0.12 mol) of thiophene in 75 mL of THF under N_2 was added 70.5 mL (0.11 mol) of a 1.6 M solution of *n*-butyllithium in hexane at 0 °C. The solution was stirred at 0 °C for 1 h, and then a solution containing 22.8 mL (0.11 mol) of 1,3-dibromopropane

(52) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1986**, *51*, 4077.

in 20 mL of THF was added. The mixture was allowed to warm to rt over a 12 h period and was then quenched with 100 mL of a saturated NH_4Cl solution. The solution was extracted with ether, and the combined organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was distilled at 103–107 °C (3 mm) to give 13.4 g (58%) of 2-(3-bromopropyl)thiophene as a colorless oil: IR (neat) 1684, 1535, and 1438 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.20 (quin, 2H, J = 6.8 Hz), 3.01 (t, 2H, J = 7.2 Hz), 3.42 (t, 2H, J = 6.4 Hz), 6.84 (d, 1H, J = 3.1 Hz), 6.93 (dd, 1H, J = 5.0 and 3.5 Hz), and 7.14 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.0, 32.7, 34.3, 123.4, 124.9, 126.8, 142.9.

A solution containing 13.4 g (65.3 mmol) of the above bromothiophene and 4.8 g (98.0 mmol) of NaCN in 50 mL of DMSO under N_2 was heated at 70 °C for 3 h and then poured into 150 mL of water. The mixture was extracted with ether, and the combined organic layer was washed with a saturated NaCl solution. The solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 9.3 g (94%) of 4-(thiophene-2-yl)butanenitrile (**5**) as a yellow oil: IR (neat) 2248, 1536, and 1441 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.96 (quin, 2H, J = 7.2 Hz), 2.30 (t, 2H, J = 7.2 Hz), 2.94 (t, 2H, J = 7.2 Hz), 6.80 (d, 1H, J = 3.3 Hz), 6.90 (dd, 1H, J = 5.1 and 3.3 Hz), and 7.11 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.1, 26.2, 28.4, 119.3, 123.8, 125.2, 127.0, and 142.1.

A solution containing 9.29 g (61.43 mmol) of the above nitrile and 20 g of KOH in 150 mL of a 50% ethanol–water mixture was heated at reflux for 24 h. At the end of this time the solution was allowed to cool to rt and the ethanol was removed under reduced pressure. The aqueous layer was extracted with ether and then acidified with 6 N HCl at 0 °C. The solution was extracted again with ether, the combined organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 9.6 g (92%) of 4-(thiophene-2-yl)butyric acid as a yellow oil: IR (neat) 3523–2385, 1703, 1432, and 1412 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.99 (quin, 2H, J = 7.4 Hz), 2.40 (t, 2H, J = 7.4 Hz), 2.88 (t, 2H, J = 7.4 Hz), 6.78 (d, 1H, J = 7.4 Hz), 6.78 (d, 1H, J = 3.3 Hz), 6.90 (dd, 1H, J = 5.0 and 3.5 Hz), 7.10 (d, 1H, J = 5.0 Hz), and 10.75 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.4, 28.9, 33.0, 123.2, 124.6, 126.7, 143.7, and 179.9.

To a solution containing 3.67 g (21.56 mmol) of the above acid in 30 mL of CH_2Cl_2 at 0 °C was added 4.19 g (25.9 mmol) of 1,1′-carbonyldiimidazole over a 20 min period. The solution was allowed to warm to rt over a 90 min period and was then poured into 100 mL of a 40% aqueous solution of methylamine. The mixture was allowed to stir overnight and was then acidified with 6 N HCl at 0 °C and extracted with CH_2Cl_2. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 3.77 g (97%) of *N*-methyl-4-(thiophene-2-yl)-butyramide (**7**) as a pale yellow oil: IR (neat) 1636, 1441, and 1410 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.91 (quin, 2H, J = 7.5 Hz), 2.14 (t, 2H, J = 7.5 Hz), 2.67 and 2.68 (s, 3H) (1:1 mixture of rotamers), 2.77 (t, 2H, J = 7.4 Hz), 6.36 (brs, 1H), 6.69 (d, 1H, J = 2.3 Hz), 6.80–6.83 (m, 1H), and 7.01 (d, 1H, J = 4.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.1, 27.5, 29.2, 35.3, 123.0, 124.3, 126.7, 144.2, and 173.4.

To a solution containing 263 mg (1.5 mmol) of the above amide and 0.76 mL (4.4 mmol) of HMPA in 3 mL of THF cooled to −78 °C under N_2 was added 1.00 mL (1.5 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. The solution was allowed to stir for 10 min, and then 135 mg (1.6 mmol) of freshly distilled diketene in 1 mL of THF was rapidly added *via* syringe. The reaction mixture was allowed to warm to rt over a 3 h period and was then quenched with a saturated 10% HCl solution. The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 156 mg (40%) of *N*-[(4-thiophene-2-yl)butyryl]-*N*-methyl-3-oxobutyramide as a pale yellow oil: IR (neat) 2927, 1692, and 1165 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.80–2.20 (m, 2H), 2.20 (s, 3H), 2.55 (t, 2H, J = 7 Hz), 2.87 (t, 2H, J = 7 Hz), 3.20 (s, 3H), 3.95 (s, 2H), 6.70–7.00 (m, 2H), and 7.13 (d, 1H, J = 4 Hz).

Diazo transfer of the above compound gave 2-diazo-*N*-[(4-thiophene-2-yl)butyryl]-*N*-methyl-3-oxobutyramide (**9**) (68%) as a yellow oil: IR (neat) 2136, 1661, 1536, and 1536 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.92–2.05 (m, 2H), 2.38 (s, 3H), 2.52 (t, 2H, J = 7.3 Hz), 2.85 (t, 2H, J = 7.3 Hz), 3.11 (s, 3H), 6.74 (d, 1H, J = 3.2 Hz), 6.86 (dd, 1H, J = 4.9 and 3.6 Hz), and 7.07 (dd, 1H, J = 5.1 and 0.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.2, 28.3, 28.7, 33.0, 34.6, 81.3, 123.2, 124.5, 126.7, 143.7, 164.8, 174.2, and 189.0.

A solution containing 39 mg of **9** and 2 mg of rhodium(II) acetate in 10 mL of benzene was placed in an oil bath preheated to 95 °C. The solution was heated at reflux for 6 h and then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 22 mg (51%) of 4-(thiophene-2-yl)-butyric acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**14**) as a colorless oil: IR ($CHCl_3$) 3430, 1725, 1670, 1410, and 1530 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.98–1.22 (m, 2H), 2.43 (s, 3H), 2.47–2.58 (m, 2H), 2.82 and 2.84 (s, 3H) (1:1 mixture of rotamers), 2.92 (t, 2H, J = 7.3 Hz), 5.50 (s, 1H), 6.32 (bs, 1H), 6.82 (d, 1H, J = 3.3 Hz), 6.92 (dd, 1H, J = 4.9 and 3.6 Hz), and 7.13 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 26.1, 26.4, 27.8, 28.7, 32.5, 79.0, 123.3, 124.7, 126.8, 143.5, 163.5, 170.9, 199.6. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.95. Found: C, 55.02; H, 6.26; N, 4.71.

To a solution containing 250 mg of *N*-phenylmaleimide and 2 mg of rhodium(II) acetate in 3.5 mL of benzene at 80 °C was added 106 mg (0.36 mmol) of **9** in 1 mL of benzene over a 7 min period *via* syringe. The mixture was heated at reflux for 1.5 h and then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give a 2:1 mixture of the *endo:exo* isomers of 7-acetyl-4,7-epoxy-5-methyl-2,3,3a,4,5,6,7,7a-octahydro-1,3,6-trioxo-4-[3-(thiophene-2-yl)propyl]-1*H*-pyrrolo-[3,4-*c*]pyridine (**17**). The minor fraction contained 48 mg (30%) of the *exo* isomer of **17** as a white crystalline solid: mp 196–197 °C; IR (KBr) 1787, 1730, 1381, and 1190 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.78–1.94 (m, 1H), 1.96–2.12 (m, 1H), 2.20–2.42 (m, 2H), 2.65 (s, 3H), 2.75 (s, 3H), 2.96 (q, 2H, J = 7.0 Hz), 3.70 (d, 1H, J = 8.3 Hz), 3.79 (d, 1H, J = 8.3 Hz), 6.82 (d, 1H, J = 3.2 Hz), 6.91 (dd, 1H, J = 5.0 and 3.5 Hz), 7.10–7.20 (m, 3H), and 7.35–7.52 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.8, 26.8, 27.9, 29.2, 29.3, 48.7, 54.5, 90.8, 97.4, 123.4, 124.7, 126.4, 126.4, 124.7, 126.4, 126.8, 129.1, 129.3, 130.8, 143.2, 167.0, 170.0, 170.4, and 197.3. Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39; S, 7.31. Found: C, 62.93; H, 5.11; N, 6.35; S, 7.24.

The major fraction contained 99 mg (62%) of the *endo* isomer of **17** as a white solid: mp 166–167 °C; IR (KBr) 1780, 1609, 1389, and 1203 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.64–1.75 (m, 1H), 1.95–2.13 (m, 1H), 2.14–2.30 (m, 2H), 2.56 (s, 3H), 2.72 (s, 3H), 2.77–2.89 (m, 1H), 2.90–3.15 (m, 1H), 3.33 (d, 1H, J = 6.9 Hz), 3.69 (d, 1H, J = 6.9 Hz), 6.79 (d, 1H, J = 3.0 Hz), 6.90 (dd, 1H, J = 5.0 and 3.4 Hz), 7.12 (dd, 1H, J = 5.0 and 3.4 Hz), 7.19 (dd, 2H, J = 7.6 and 1.5 Hz), and 7.34–7.55 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.0, 25.8, 27.1, 28.1, 29.2, 49.4, 52.6, 91.0, 98.2, 123.3, 124.8, 126.2, 126.8, 129.0, 129.1, 130.9, 143.5, 169.0, 171.3, 171.4, and 196.4. Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39; S, 7.31. Found: C, 62.92; H, 5.05; N, 6.38; S, 7.40.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-[5-(furan-2-yl)pentanoyl]-*N*-methyl-3-oxobutyramide (18). To a solution containing 6.0 mg (40.3 mmol) of 2-(4-cyanobutyl)furan[53] in 80 mL of 95% ethanol was added 22.5 mg (403 mmol) of KOH in 60 mL of water, and the mixture was heated at reflux for 12 h. The solution was cooled to rt and poured into 160 mL of 6 N HCl at 0 °C. The mixture was extracted with ether, and the combined ethereal layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 5.62 g (83%) of the corresponding

(53) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Nguyen, D.; Lipshutz, B. *Tetrahedron Lett.* **1988**, *29*, 3045.

carboxylic acid which was used in the next step without further purification. The crude acid (29.8 mmol) was taken up in 50 mL of dry THF and treated with 5.06 g (31.3 mmol) of 1,1'-carbonyldiimidazole, and the solution was stirred at rt for 6 h. The mixture was treated with 100 mL of a 40% solution of aqueous methylamine and was stirred overnight. The organic solvent was removed under reduced pressure, and the aqueous residue was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography to give 5.0 g (93%) of 5-(furan-2-yl)-pentanamide as a clear oil; IR (neat) 1709, 1645, and 1410 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.52–1.70 (m, 4H), 2.13 (t, 2H, J = 6.6 Hz), 2.55 (t, 2H, J = 6.6 Hz), 2.68 and 2.69 (s, 3H) (1:1 mixture of rotamers), 5.87–5.93 (m, 1H), 6.05–6.23 (m, 1H), 6.58 (s, 1H), and 7.18–7.23 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.0, 25.9, 27.4, 35.8, 104.6, 109.8, 140.4, 155.5, and 173.7.

N-Acetoacetylation of the above amide in the standard manner gave *N*-[5-(furan-2-yl)pentanoyl]-*N*-methyl-3-oxobutyramide in 60% yield as a white solid: mp 52–53 °C; IR (neat) 1696, 1370, and 1105 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.59–1.70 (m, 4H), 2.19 (s, 3H), 2.49 (t, 2H, J = 6.9 Hz), 2.59 (t, 2H, J = 6.9 Hz), 3.16 (s, 3H), 3.89 (s, 2H), 5.91–5.98 (m, 1H), 6.19–6.22 (m, 1H), and 7.20–7.25 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.5, 27.0, 27.4, 29.8, 30.8, 36.3, 54.2, 104.7, 109.8, 140.6, 155.3, 169.0, 175.2, and 201.3. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.25; H, 7.23; N, 5.25.

Diazo transfer of the above imide in the standard manner gave 2-diazo-*N*-[5-(furan-2-yl)pentanoyl]-*N*-methyl-3-oxobutyramide (**18**) in 68% yield as a bright yellow oil: IR (neat) 2136, 1700, and 1360 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.64–1.78 (m, 4H), 2.46 (s, 3H), 2.54 (t, 2H, J = 6.7 Hz), 2.66 (t, 2H, J = 6.7 Hz), 3.19 (s, 3H), 5.97–6.02 (m, 1H), 6.25–6.29 (m, 1H), and 7.28–7.30 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.0, 27.4, 27.6, 28.3, 33.1, 35.6, 81.4, 104.9, 110.1, 140.8, 155.5, 165.0, 174.6, and 189.2.

To a solution containing 0.22 g (0.77 mmol) of **18** in 10 mL of benzene was added 2 mg of rhodium(II) acetate under N_2, and the mixture was heated at reflux for 2 h. The solution was cooled to rt and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 152 mg (74%) of 4-acetyl-4,6a-epoxy-6-methyl-3a,4,6,-6a,7,8,9,10-octahydro-5-oxofuro[2,3-*d*]quinoline (**19**) as a colorless solid: mp 148–149 °C; IR ($CHCl_3$) 1723, 1710, and 1602 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.50–1.78 (m, 4H), 1.80–1.91 (m, 1H), 2.02–2.23 (m, 3H), 2.37 (s, 3H), 2.81 (s, 3H), 3.17–3.24 (m, 1H), 4.96 (t, 1H, J = 2.5 Hz), and 6.27 (dd, 1H, J = 2.5 and 1.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.0, 21.7, 25.5, 26.9, 27.4, 35.8, 57.2, 92.9, 95.4, 95.7, 99.5, 148.8, 168.9, and 200.4. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.51; N, 5.34.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-methyl-3-oxo-*N*-[5-(thiophene-2-yl)pentanoyl]-butyramide (20). A solution containing 10 g (119 mmol) of thiophene in 120 mL of dry THF at −78 °C was treated with 74 mL (119 mmol) of 1.6 M n-BuLi in hexane, and the mixture was stirred at −78 °C for 1 h. The resulting solution was treated with 17.7 mL (149 mmol) of 1,4-dibromobutane at −78 °C in 15 mL of dry THF, and the solution was allowed to warm to rt and stirred overnight. The solution was quenched with a saturated NH_4Cl solution and extracted with ether. The combined ether extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was distilled at 95 °C (0.6 mm) to give 19.15 g (74%) of 2-(4-bromobutyl)thiophene as a clear oil: IR (neat) 1431 and 1254 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.80–2.00 (m, 4H), 2.90 (t, 2H, J = 6.7 Hz), 3.45 (t, 2H, J = 6.7 Hz), 6.83 (d, 1H, J = 3.5 Hz), 6.96 (dd, 1H, J = 5.0 and 3.5 Hz), and 7.16 (d, 1H, J = 5.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.8, 30.0, 31.8, 33.2, 123.0, 124.1, 126.6, and 144.4.

The above bromide was converted to 2-(4-cyanobutyl)-thiophene in 98% yield by reaction with NaCN in DMSO: IR (neat) 2243, 1453, and 1232 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.67–1.89 (m, 4H), 2.34 (t, 2H, J = 7.1 Hz), 2.88 (t, 2H, J = 7.1 Hz), 6.80 (d, 1H, J = 3.6 Hz), 6.93 (dd, 1H, J = 5.0 and 3.6 Hz), and 7.13 (d, 1H, J = 5.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.7, 24.5, 28.8, 30.4, 119.3, 123.1, 124.8, 126.7, and 143.7.

The above nitrile was converted into 5-(thiophene-2-yl)-pentanoic acid, methylamide in 81% yield by hydrolysis to the acid and conversion to the amide using 1,1'-carbonyldiimidazole and aqueous methylamine: mp 36–37 °C; IR ($CHCl_3$) 3358, 1670, 1430, and 1159 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.60–1.69 (m, 4H), 2.15 (t, 2H, J = 6.6 Hz), 2.69 and 2.70 (s, 3H), 2.77 (t, 2H, J = 6.6 Hz), 6.67 (s, 1H), 6.71 (d, 1H, J = 3.6 Hz), 6.83 (dd, 1H, J = 5.1 and 3.6 Hz), and 7.02 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.9, 25.8, 29.2, 31.0, 35.7, 122.6, 123.8, 126.4, 144.6, and 173.5. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.73; H, 7.70; N, 7.14; S, 16.19.

To a solution containing 2.0 g (10.1 mmol) of the above amide in 10 mL of xylene was added 1.46 mL (11.2 mmol) of 2,2,6-trimethyl-1,3-dioxin-4-one,[54] and the mixture was heated at reflux for 3 h. The solution was cooled to rt and concentrated under reduced pressure. The orange residue was subjected to flash silica gel chromatography to give 0.92 g (32%) of *N*-methyl-3-oxo-*N*-[5-(thiophene-2-yl)pentanoyl]butyramide as a yellow oil: IR (neat) 1724, 1695, and 1353 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.62–1.73 (m, 4H), 2.22 (s, 3H), 2.53 (t, 2H, J = 6.7 Hz), 6.88 (dd, 1H, J = 5.1 and 3.4 Hz), and 7.07 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.6 29.5, 30.0, 30.8, 30.9, 36.5, 54.3, 122.9, 124.1, 126.6, 144.6, 169.1, 175.4, and 201.3.

Diazo transfer of the above imide in the normal manner gave 2-diazo-*N*-methyl-3-oxo-*N*-[5-(thiophene-2-yl)pentanoyl]butyramide (**20**) in 75% yield: mp 46–47 °C; IR (neat) 2129, 1659, and 1097 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.67–1.77 (m, 4H), 2.41 (s, 3H), 2.52 (t, 2H, J = 6.6 Hz), 2.82 (t, 2H, J = 6.6 Hz), and 7.06 (d, 1H, J = 5.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.8, 28.1, 29.4, 30.8, 32.9, 35.5, 81.1, 122.8, 124.0, 126.5, 144.5, 164.8, 174.3, and 188.9.

A solution containing 0.10 mg (0.33 mmol) of **20** in 10 mL of dry CH_2Cl_2 under N_2 was treated with 2 mg of rhodium(II) perfluorobutyrate, and the mixture was stirred for 2 h at rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 72 mg (75%) of 5-(thiophene-2-yl)pentanoic acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**21**) as a colorless oil: IR (neat) 1730, 1674, 1410, and 1353 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.65–1.80 (m, 4H), 2.38 (s, 3H), 2.40–2.50 (m, 2H), 2.78–2.90 (m, 5H), 5.47 (s, 1H), 6.38 (brs, 1H), 6.76 (d, 1H, J = 2.6 Hz), 6.88 (dd, 1H, J = 5.1 and 2.6 Hz), and 7.07 (d, 1H, J = 5.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.9, 26.1, 27.7, 29.3, 30.8, 33.3, 78.9, 123.9, 124.2, 126.6, 144.5, 163.6, 171.1, and 199.6; HRMS calcd for $C_{14}H_{19}NO_4S$ 297.1030, found 297.1035.

A solution containing 0.20 g (0.65 mmol) of **20** and 0.23 g (1.3 mmol) of *N*-phenylmaleimide in 15 mL of dry benzene under N_2 was treated with 2 mg of rhodium(II) acetate, and the mixture was heated at reflux for 1 h. The solution was cooled to rt, and the solvent was removed under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.22 g (78%) of 7-acetyl-4,7-epoxy-2,3a,4,5,7,7a-hexahydro-5-methyl-2-phenyl-1,3,6-trioxo-4-[4-(thiophene-2-yl)butyl]-1*H*-pyrrolo[3,4-*c*]pyridine (**22**) as a white solid: mp 137–138 °C; IR ($CHCl_3$) 1724, 1520, 1400, and 1210 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.39–1.52 (m, 1H), 1.60–1.82 (m, 3H), 2.08–2.21 (m, 2H), 2.53 (s, 3H), 2.72 (s, 3H), 2.81 (t, 2H, J = 6.8 Hz), 3.12 (d, 1H, J = 6.9 Hz), 3.67 (d, 1H, J = 6.9 Hz), 6.74 (d, 1H, J = 3.0 Hz), 6.86 (dd, 1H, J = 5.1 and 3.0 Hz), 7.06 (d, 1H, J = 5.1 Hz), 7.16–7.19 (m, 2H), and 7.34–7.42 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.0, 25.7, 27.7, 28.0, 29.4, 31.1, 49.4, 52.6, 89.9, 98.2, 122.9, 124.1, 126.1, 126.6, 128.9, 129.0, 131.0, 144.3, 168.9, 171.6, and 196.4. Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19; S, 7.09. Found: C, 63.67; H, 5.31; N, 6.10; S, 7.15.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-(4-(indol-1-yl)butyryl)-*N*-methyl-3-oxobutyramide (23). To a solution containing 4.76 g of 4-(indol-1-yl)-

(54) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315.

butyric acid[55] in 100 mL of dry THF under N_2 was added 4.64 g of 1,1'-carbonyldiimidazole, and the mixture was stirred for 4 h. The solution was poured into 200 mL of a 40% aqueous methylamine solution at 0 °C. The mixture was allowed to warm to rt and was stirred overnight. The resulting solution was extracted with CH_2Cl_2, and the combined organic layer was washed with sodium bicarbonate and brine and dried over anhydrous Na_2SO_4. The organic phase was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 5.0 g (99%) of 4-(indol-1-yl)butyric acid, methylamide as a yellow oil: IR (neat) 1653 and 1559 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.98 (t, 2H, J = 6.8 Hz), 2.10 (quin, 2H, J = 6.8 Hz), 2.65 and 2.67 (s, 3H) (1:1 rotamer mixture), 4.12 (t, 2H, J = 6.8 Hz), 5.66 (brs, 1H), 6.48 (d, 1H, J = 3.5 Hz), 7.04 (d, 1H, J = 3.5 Hz), 7.07–7.33 (m, 3H), and 7.61–7.63 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.8, 26.1, 32.6, 45.2, 101.1, 109.3, 119.0, 120.8, 121.4, 127.7, 128.4, 135.9, and 172.4.

N-Acetoacetylation was carried out on the above amide to give *N*-(4-(indol-1-yl)butyryl)-*N*-methyl-3-oxobutyramide (57%) as a yellow oil: IR (neat) 1701 and 1512 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.09 (quin, 2H, J = 6.6 Hz), 2.23 (s, 3H), 2.32 (t, 2H, J = 6.6 Hz), 2.98 (s, 3H), 3.87 (s, 2H), 4.11 (t, 2H, J = 6.6 Hz), 6.49 (d, 1H, J = 3.0 Hz), 7.05 (d, 1H, J = 3.0 Hz), 7.06–7.34 (m, 3H), and 7.61–7.63 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.4, 29.8, 30.5, 33.0, 44.6, 54.1, 101.1, 109.0, 119.1, 120.7, 121.3, 127.6, 128.3, 135.6, 168.7, 174.7, and 201.3.

Diazo transfer on the above compound gave 2-diazo-*N*-(4-(indol-1-yl)butyryl)-*N*-methyl-3-oxobutyramide (**23**) (71%) as a yellow oil: IR (neat) 2122 and 1717 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.14 (quin, 2H, J = 6.8 Hz), 2.36 (t, 2H, J = 6.8 Hz), 2.40 (s, 3H), 3.01 (s, 3H), 4.15 (t, 2H, J = 6.8 Hz), 6.50 (d, 1H, J = 3.0 Hz), 7.06 (d, 1H, J = 3.0 Hz), 7.09–7.35 (m, 3H), and 7.62–7.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.7, 28.0, 32.2, 32.7, 44.7, 80.9, 101.1, 109.1, 119.1, 120.7, 121.3, 127.5, 128.3, 135.7, 164.5, 173.6, and 188.6.

To a solution containing 380 mg (1.17 mmol) of **23** in 35 mL of dry benzene under N_2 was added a catalytic amount of rhodium(II) acetate. The solution was placed in an oil bath preheated at 90 °C. The mixture was heated at reflux for 90 min and then cooled to rt. The solvent was removed under reduced pressure, and the resulting residue was recrystallized from CH_2Cl_2 and diispropyl ether to give 264 mg (75%) of 1-acetyl-1,13a-epoxy-2,3,3a,4,5,6,11b,11c-octahydro-3-methyl-2-oxo-1*H*-indolo[3,2,1-*de*][1,5]naphthyridine (**24**) as colorless crystals: mp 174–175 °C; IR ($CHCl_3$) 1742, 1484, and 1071 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.64–1.70 (m, 1H), 1.93 (m, 1H), 2.15 (dt, 1H, J = 13.5 and 4.4 Hz), 2.36–2.42 (m, 1H), 3.11 (dt, 1H, J = 13.6 and 2.4 Hz), 3.70–3.75 (m, 1H), 3.94 (d, 1H, J = 7.4 Hz), 4.08 (d, 1H, J = 7.4 Hz), 6.40–6.58 (m, 2H), and 6.94–7.11 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.9, 25.7, 25.8, 28.6, 42.8, 50.5, 65.9, 93.7, 94.4, 106.7, 117.5, 124.0, 125.5, 129.4, 152.0, 169.5, and 200.1. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.36; H, 6.12; N, 9.34.

To a solution containing 0.35 mmol of diazo imide **23** and 0.42 mmol of *N*-phenylmaleimide in 5 mL of dry benzene under N_2 was added a catalytic amount of rhodium(II) acetate. The solution was placed in an oil bath preheated at 90 °C, and the mixture was heated at reflux for 2 h. The solution was cooled to rt, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 7-acetyl-4,7-epoxy-2,3a,4,5,7,7a-hexahydro-4-(4-indolylpropyl)-5-methyl-2-phenyl-1,3,6-trioxo-1*H*-pyrrolo[3,4-*c*]pyridine (65%) as a white solid: mp 249–250 °C; IR ($CHCl_3$) 1716 and 1211 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.93–2.31 (m, 4H), 2.48 (s, 3H), 2.61 (s, 3H), 3.24 (d, 1H, J = 7.0 Hz), 3.65 (d, 1H, J = 7.0 Hz), 4.06–4.17 (m, 1H), 4.28–4.37 (m, 1H), 6.48 (d, 1H, J = 3.0 Hz), 7.09 (d, 1H, J = 3.0 Hz), 7.06–7.49 (m, 8H), and 7.60–7.63 (m, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 24.0, 24.6, 25.9, 28.4, 45.0, 52.8, 91.1, 98.0, 101.0, 110.1, 119.2, 120.7, 121.3, 127.0, 128.4, 128.8, 129.1, 131.8, 136.0, 169.1, 172.3, 172.7, and 197.1; HRMS calcd for $C_{27}H_{25}N_3O_5$ 471.1794, found 471.1792.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-1-[3-(2-(Indol-1-yl)ethyl)-2-oxopiperidin-1-yl]butane-1,3-dione (25). A solution containing 20.0 g of tetrahydro-2-(2-bromoethoxy)-2*H*-pyran[56] in 50 mL of benzene was added to 1.1 g of n-Bu_4NHSO_4 and 25 mL of a 50% NaOH solution. To this two-phase solution was added 7.47 g of indole, and the resulting mixture was stirred at rt for 72 h. The solution was diluted with 250 mL of water, and the organic phase was separated and washed with 10% HCl and water and dried over anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure to give 15.6 g (100%) of 1-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indole as a yellow oil which was used in the next step without further purification: IR (neat) 1613, 1512, and 1464 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.43–1.83 (m, 6H), 3.36–3.43 (m, 1H), 3.56–3.63 (m, 1H), 3.65–3.79 (m, 1H), 4.02–4.10 (m, 1H), 4.34 (t, 2H, J = 5.3 Hz), 4.50 (t, 1H, J = 3.2 Hz), 6.52 (d, 1H, J = 3.1 Hz), 7.10–7.15 (m, 1H), 7.22 (d, 1H, J = 3.1 Hz), 7.23–7.25 (m, 1H), 7.39–7.42 (m, 1H), and 7.64–7.67 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 19.0, 25.2, 30.3, 46.2, 61.7, 66.2, 98.6, 101.1, 109.3, 119.2, 120.7, 121.3, 128.3, 128.5, and 136.0.

To a solution containing 15.6 g of the above compound in 500 mL of a 90% aqueous methanol solution was added 0.61 g of *p*-toluenesulfonic acid monohydrate, and the resulting solution was stirred for 14 h at rt and then the solvent was removed under reduced pressure. The residue was taken up in 250 mL of CH_2Cl_2 and was washed with saturated $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 9.0 g (88%) of 2-(indol-1-yl)ethanol as a light yellow oil: IR (neat) 3385 and 1512 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 1H), 3.69 (t, 2H, J = 5.3 Hz), 4.08 (t, 2H, J = 5.3 Hz), 6.55 (d, 1H, J = 3.1 Hz), 7.09 (d, 1H, J = 3.1 Hz), 7.18–7.37 (m, 3H), and 7.69–7.72 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 48.3, 61.3, 101.0, 109.2, 119.3, 120.8, 121.4, 128.2, 128.4, and 135.8.

To a solution containing 1.0 g of the above alcohol in 15 mL of pyridine was added 2.36 g of *p*-toluenesulfonyl chloride at 0 °C. After the addition was complete, the flask was kept at 0 °C for 12 h. The resulting solution was then poured onto 100 g of ice water and extracted with ether. The combined ether layer was washed with 50 mL of 6 N HCl and 50 mL of water and dried over anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure to give 1.56 g (100%) of *p*-toluenesulfonic acid, 2-(indol-1-yl)-ethyl ester as a yellow oil which was used in the next step without further purification: IR (neat) 1599, 1464, 1360, and 1175 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H), 4.23 (s, 4H), 6.47 (d, 1H, J = 3.1 Hz), 7.01 (d, 1H, J = 3.1 Hz), 7.02–7.05 (m, 1H), 7.12–7.15 (m, 1H), 7.44–7.47 (m, 1H), and 7.61–7.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.2, 44.6, 67.8, 101.5, 108.6, 119.2, 120.6, 121.3, 127.1, 127.9, 128.4, 129.3, 131.4, 135.3, and 144.5.

To a solution containing 15.7 g of the above compound in 150 mL of acetone under N_2 was added 15.0 g of NaI, and the solution was heated at reflux for 14 h. The mixture was cooled to rt, and most of the solvent was removed under reduced pressure. The residue was taken up in 125 mL of water and extracted with pentane. The combined organic layer was washed with 50 mL of an aqueous 10% sodium thiosulfate solution and dried over anhydrous $MgSO_4$. The organic layer was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1-(2-iodoethyl)-1*H*-indole as a light yellow oil: IR (neat) 1887, 1512, 1312, and 1227 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.46, (t, 2H, J = 7.5 Hz), 4.50 (t, 2H, J = 7.5 Hz), 6.69 (d, 1H, J = 3.2 Hz), 7.17 (d, 1H, J = 3.2 Hz), 7.30–7.41 (m, 3H), and 7.82–7.84 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 2.3, 48.5, 101.7, 108.7, 119.7, 121.0, 121.7, 127.4, 128.5, and 135.2.

To a solution containing 2.0 g of 2-piperidone in 250 mL of dry THF under N_2 at 0 °C was added 26.5 mL of a 1.6 M

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(56) Anantanarayan, A.; Dutton, P. J.; Fyles, T. M.; Pitre, M. J. *J. Org. Chem.* **1986**, *51*, 752.

solution of *n*-butyllithium in hexane, and the mixture was stirred for 1 h at 0 °C. To the resulting mixture was added 5.71 g of *N*-(2-iodoethyl)indole in 15 mL of dry THF. The solution was allowed to warm to rt and was stirred overnight at rt. The solution was poured into 200 mL of a saturated NH_4Cl solution, and the organic solvent was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, the combined organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3-(2-(indol-1-yl)ethyl)piperidin-2-one as a clear oil: IR (neat) 1667, 1489, and 1314 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.41–1.52 (m, 1H), 1.59–2.01 (m, 4H), 2.21–2.43 (m, 2H), 3.23–3.30 (m, 2H), 4.34 (t, 2H, J = 7.3 Hz), 6.51 (d, 1H, J = 3.1 Hz), 7.00 (s, 1H), 7.10–7.25 (m, 2H), 7.18 (d, 1H, J = 3.1 Hz), 7.43–7.45 (m, 1H), and 7.64–7.67 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.3, 26.9, 32.4, 38.1, 41.9, 44.3, 100.9, 109.4, 119.0, 120.7, 121.2, 127.7, 128.4, 135.8, and 174.5.

N-Acetoacetylation of the above amide in the standard manner gave 1-[3-(2-(indol-1-yl)ethyl)-2-oxopiperidin-1-yl]butane-1,3-dione (51%) as a clear oil: IR (neat) 1699, 1512, 1464, and 1315 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40–1.52 (m, 1H), 1.64–2.00 (m, 4H), 2.25–2.30 (m, 5H), 3.45–3.55 (m, 1H), 3.88–4.04 (m, 3H), 4.22 (t, 2H, J = 6.8 Hz), 6.49 (d, 1H, J = 3.1 Hz), 7.10 (d, 1H, J = 3.1 Hz), 7.10–7.39 (m, 3H), and 7.61–7.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.8, 25.7, 30.0, 31.5, 40.3, 42.4, 43.9, 54.3, 101.2, 109.1, 119.1, 120.8, 121.4, 127.5, 128.4, 135.7, 168.6, 175.6, and 201.4.

Diazo transfer of the above compound gave 2-diazo-1-[3-(2-(indol-1-yl)ethyl)-2-oxopiperidin-1-yl]butane-1,3-dione (**25**) (61%) as a yellow oil: IR (neat) 2137, 1684, 1464, and 1315 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40–1.50 (m, 1H), 1.65–1.90 (m, 4H), 2.20–2.40 (m, 2H), 2.46 (s, 3H), 3.44–3.53 (m, 1H), 3.62–3.72 (m, 1H), 4.20–4.30 (m, 2H), 6.50 (d, 1H, J = 3.1 Hz), 7.08–7.38 (m, 3H), 7.11 (d, 1H, J = 3.1 Hz), and 7.63–7.65 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.1, 26.5, 28.1, 31.3, 39.8, 43.7, 45.3, 81.7, 100.9, 118.9, 120.5, 121.1, 127.4, 128.1, 135.5, 164.0, 174.5, and 188.7.

To a solution containing 212 mg (0.60 mmol) of **25** in 10 mL of dry benzene under N_2 was added 2 mg of rhodium(II) acetate. The solution was placed in an oil bath preheated at 90 °C, and the mixture was heated at reflux for 2.5 h. The solution was cooled to rt, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 130 mg (67%) of 6-acetyl-6,13b-epoxy-2,3,5,6,6a,12,13,13a,13b,13c-decahydro-5-oxo-1*H*-indolo-[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine (**26**) as a colorless solid: mp 176–177 °C; IR ($CHCl_3$) 1740, 1607, 1404, and 1273 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.38–1.45 (m, 1H), 1.60–2.00 (m, 3H), 2.08–2.20 (m, 2H), 2.24 (s, 3H), 2.35–2.42 (m, 1H), 2.78 (dt, 1H, J = 13.1 and 3.5 Hz), 3.28 (dt, 1H, J = 14.1 and 2.5 Hz), 3.50–3.57 (m, 1H), 3.84 (dd, 1H, J = 13.6 and 4.4 Hz), 4.04 (d, 1H, J = 7.5 Hz), 4.10 (d, 1H, J = 7.5 Hz), 6.39–6.41 (m, 1H), 6.52–6.57 (m, 1H), 6.93–6.95 (m, 1H), and 7.05–7.11 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.9, 23.9, 24.7, 28.5, 33.0, 37.8, 39.5, 49.6, 62.7, 91.6, 94.0, 106.2, 117.3, 123.9, 125.3, 129.1, 151.9, 168.5, and 199.9. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.13; H, 6.22; N, 8.69.

Preparation and Rhodium(II)-Catalyzed Decomposition of 2-Diazo-*N*-(3-(indol-1-yl)propionyl)-*N*-methyl-3-oxobutyramide (27). To a solution containing 1.05 g of 3-(indol-1-yl)propanoic acid[57] in 25 mL of dry THF under N_2 was added 1.10 g of 1,1′-carbonyldiimidazole, and the mixture was stirred for 4 h at rt. The solution was poured into 60 mL of a 40% aqueous methylamine solution at 0 °C. The mixture was allowed to warm to rt and was stirred overnight. The resulting solution was extracted with CH_2Cl_2, and the combined organic layer was washed with $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The organic layer was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.95 g (85%) of 3-(indol-1-yl)propanoic acid methylamide as a clear oil: IR (neat) 1734, 1653, and 1047 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.43 (t, 2H, J = 6.5 Hz), 2.53 (s, 3H), 4.34 (t, 2H, J = 6.5 Hz), 5.75 (brs, 1H), 6.44 (d, 1H, J = 3.1 Hz), 7.04 (d, 1H, J = 3.1 Hz), 7.07–7.30 (m, 3H), and 7.60–7.62 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.1, 36.6, 42.3, 101.2, 109.1, 119.4, 120.9, 121.4, 128.1, 128.5, 135.4, and 170.9.

N-Acetoacetylation of the above amide gave *N*-(3-(indol-1-yl)propionyl)-*N*-methyl-3-oxobutyramide (49%) as a yellow oil: IR (neat) 1728, 1512, 1105, and 912 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.99 (t, 2H, J = 6.7 Hz), 3.03 (s, 3H), 3.87 (s, 2H), 4.43 (t, 2H, J = 6.7 Hz), 6.50 (d, 1H, J = 3.2 Hz), 7.13 (d, 1H, J = 3.2 Hz), 7.09–7.34 (m, 3H), and 7.62–7.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.1, 30.7, 37.2, 41.1, 54.1, 101.5, 108.9, 119.4, 120.9, 121.5, 128.0, 128.5, 135.4, 168.8, 173.3, and 201.3.

Diazo transfer of the above compound gave 2-diazo-*N*-(3-(indol-1-yl)propionyl)-*N*-methyl-3-oxobutyramide (**27**) (55%) as a yellow oil: IR (neat) 2134, 1698, 1512, and 1464 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 3.01–3.05 (m, 5H), 4.49 (t, 2H, J = 6.6 Hz), 6.46 (d, 1H, J = 2.9 Hz), 7.12 (d, 1H, J = 2.9 Hz), 7.07–7.34 (m, 3H), and 7.59–7.62 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.2, 33.0, 36.4, 41.7, 80.7, 101.5, 108.9, 119.5, 121.0, 128.2, 135.3, 164.6, 172.5, and 188.8.

To a solution containing 220 mg (0.71 mmol) of **27** in 10 mL of dry benzene under N_2 was added 2 mg of rhodium(II) acetate. The solution was placed in an oil bath preheated to 90 °C. The mixture was heated at reflux for 90 min and then cooled to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 144 mg (68%) of 3-(indol-1-yl)pentanoic acid, 1-(methylcarbamoyl-2-oxopropyl ester (**29**) as a yellow oil: IR (neat) 3397, 1761, and 912 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.63 and 2.64 (s, 3H), 2.96 (t, 2H, J = 6.5 Hz), 4.46 (t, 2H, J = 6.5 Hz), 5.37 (s, 1H), 5.93 (s, 1H), 6.48 (d, 1H, J = 3.1 Hz), 7.08–7.34 (m, 4H), and 7.60–7.63 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.9, 27.6, 34.4, 41.6, 79.0, 101.6, 109.0, 119.7, 121.1, 121.8, 127.9, 128.5, 135.3, 163.1, 169.2, and 199.1; HRMS calcd for $C_{16}H_{18}N_2O_4$ 302.1260, found 302.1262.

Cycloaddition of **27** with *N*-phenylmaleimide as above gave 7-acetyl-4,7-epoxy-2,3a,4,5,7,7a-hexahydro-4-(3-indolylethyl)-5-methyl-2-phenyl-1,3,6-trioxo-1*H*-pyrrolo[3,4-*c*]pyridine (**30**) (70%) as a white solid: mp 229–230 °C; IR ($CHCl_3$) 1735, 1712, and 1648 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 2.66 (s, 3H), 2.73 (m, 2H), 3.34 (d, 1H, J = 6.7 Hz), 3.71 (d, 1H, J = 6.7 Hz), 4.43 (t, 2H, J = 6.9 Hz), 6.49 (d, 1H, J = 3.1 Hz), 7.05 (d, 1H, J = 3.1 Hz), 7.10–7.47 (m, 8H), and 7.60–7.62 (m, 1H): ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 23.1, 26.3, 28.4, 49.6, 53.1, 55.2, 91.2, 96.8, 101.3, 109.9, 119.3, 120.8, 121.5, 127.0, 128.5, 129.1, 129.4, 131.8, 135.7, 168.9, 172.4, 172.4, 172.7, and 197.0; HRMS calcd for $C_{26}H_{23}N_3O_5$ 457.1629, found 457.1628.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Diazo-*N*-(5-(indol-1-yl)pentanoyl)-*N*-methyl-3-oxobutyramide (28). To a slurry containing 2.90 g of 5-(indol-1-yl)pentanoic acid[55] in 125 mL of dry THF under N_2 was added 2.65 g of 1,1′-carbonyldiimidazole, and the mixture was stirred at rt for 2 h. The solution was poured into 150 mL of a 40% aqueous methylamine solution at 0 °C and was stirred overnight at rt. The resulting solution was extracted with CH_2Cl_2, and the combined organic layer was washed with saturated $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The organic layer was filtered, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.35 g (77%) of 5-(indol-1-yl)pentanoic acid methylamide as an oil: IR (neat) 1647, 1559, 1512, 1464, and 1315 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.57 (quin, 2H, J = 7.2 Hz), 1.78 (quin, 2H, J = 7.2 Hz), 2.0 (t, 2H, J = 7.2 Hz), 2.63 and 2.64 (s, 3H) (1:1 rotamer mixture), 4.07 (t, 2H, J = 7.2 Hz), 5.80 (s, 1H), 6.48 (d, 1H, J = 3.0 Hz), 7.05 (d, 1H, J = 3.0 Hz), 7.07–7.32 (m, 3H), and 7.62–7.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.9, 25.9, 29.5, 35.5, 45.9, 100.8, 109.2, 119.1, 120.8, 121.2, 127.7, 128.4, 135.7, and 173.0.

N-Acetoacetylation of the above amide gave *N*-(5-(indol-1-yl)pentanoyl)-*N*-methyl-3-oxobutyramide (73%) as a yellow

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oil: IR (neat) 1692, 1512, 1464, and 1360 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.55 (quin, 2H, J = 7.2 Hz), 1.79 (quin, 2H, J = 7.2 Hz), 2.19 (s, 3H), 2.32 (t, 2H, J = 7.2 Hz), 3.02 (s, 3H), 3.85 (s, 2H), 4.06 (t, 2H, J = 7.2 Hz), 6.46 (d, 1H, J = 3.0 Hz), 7.06 (d, 1H, J = 3.0 Hz), 7.06–7.32 (m, 3H), and 7.59–7.62 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.3, 28.9, 29.8, 30.5, 35.8, 45.8, 54.1, 100.8, 109.1, 119.0, 120.6, 121.1, 127.5, 128.3, 135.5, 168.8, 174.8, and 201.2.

Diazo transfer of the above compound gave 2-diazo-*N*-(5-(indol-1-yl)pentanoyl)-*N*-methyl-3-oxobutyramide (**28**) (78%) as a yellow oil: IR (neat) 2132, 1701, 1464, and 1107 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.62 (quin, 2H, J = 7.3 Hz), 1.83 (quin, 2H, J = 7.3 Hz), 2.36 (t, 2H, J = 7.3 Hz), 2.41 (s, 3H), 3.03 (s, 3H), 4.09 (t, 2H, J = 7.3 Hz), 6.47 (d, 1H, J = 3.2 Hz), 7.06 (d, 1H, J = 3.2 Hz), 7.06–7.32 (m, 3H), and 7.60–7.62 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.7, 28.1, 29.1, 32.8, 34.9, 45.8, 81.0, 100.8, 109.0, 119.0, 120.6, 121.1, 127.5, 128.3, 135.5, 164.6, 174.0, and 188.8.

To a solution containing 194 mg (0.54 mmol) of **28** in 5 mL of dry benzene under N_2 was added 2 mg of rhodium(II) acetate. The solution was placed in an oil bath preheated to 90 °C. The mixture was heated at reflux for 2 h and then cooled to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 130 mg (69%) of 3-(indol-1-yl)propanoic acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**31**) as a yellow oil: IR (neat) 3392, 1753, and 1464 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.66 (quin, 2H, J = 7.2 Hz), 1.91 (quin, 2H, J = 7.2 Hz), 2.39–2.49 (m, 5H), 2.79 and 2.80 (s, 3H) (1:1 rotamer mixture), 4.15 (t, 2H, J = 7.2 Hz), 5.45 (s, 1H), 6.28 (s, 1H), 6.48 (d, 1H, J = 2.5 Hz), 7.05–7.22 (m, 2H), 7.09 (d, 1H, J = 2.5 Hz), 7.32–7.35 (m, 1H), and 7.61–7.63 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.1, 26.1, 27.7, 29.3, 33.0, 45.8, 78.9, 101.0, 109.2, 119.2, 120.9, 121.3, 127.7, 128.5, 135.8, 163.4, 170.8, and 199.6; HRMS calcd for $C_{18}H_{22}N_2O_4$ 330.1572, found 330.1568.

Cycloaddition of **28** with *N*-phenylmaleimide as above gave *exo*-7-acetyl-4,7-epoxy-2,3a,4,5,7,7a-hexahydro-4-(4-indolylpropyl)-5-methyl-2-phenyl-1,3,6-trioxo-1*H*-pyrrolo[3,4-*c*]pyridine (**32a**) (29%): IR (neat) 1785, 1728, and 1238 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.47–1.67 (m, 2H), 1.95 (t, 2H, J = 6.7 Hz), 2.23 (dt, 2H, J = 10.1 and 6.7 Hz), 2.63 (s, 3H), 2.67 (s, 3H), 3.59 (d, 1H, J = 8.3 Hz), 3.70 (d, 1H, J = 8.3 Hz), 4.16 (t, 2H, J = 6.7 Hz), 6.49 (d, 1H, J = 3.0 Hz), 7.10 (d, 1H, J = 3.0 Hz), and 7.06–7.63 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.1, 26.7, 27.9, 29.5, 29.7, 45.7, 48.6, 54.1, 90.8, 97.3, 101.3, 109.2, 119.3, 121.0, 121.5, 126.4, 127.7, 128.6, 129.1, 129.3, 130.9, 135.8, 167.0, 170.1, 170.4, and 197.3; HRMS calcd for $C_{28}H_{27}N_3O_5$ 485.1941, found 485.1951.

The second fraction contained *endo*-7-acetyl-4,7-epoxy-2,-3a,4,5,7,7a-hexahydro-4-(4-indolylpropyl)-5-methyl-2-phenyl-1,3,6-trioxo-1*H*-pyrrolo[3,4-*c*]pyridine (**32b**) (51%) as a yellow solid: mp 164–166 °C; IR (neat) 1714, 1494, and 1195 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.35–1.43 (m, 1H), 1.65–1.74 (m, 2H), 1.85–1.99 (m, 2H), 2.07–2.22 (m, 2H), 2.60 (s, 3H), 2.64 (s, 3H), 3.25 (d, 1H, J = 6.9 Hz), 3.63 (d, 1H, J = 6.9 Hz), 4.07–4.20 (m, 2H), 6.49 (d, 1H, J = 3.0 Hz), 7.08 (d, 1H, J = 3.0 Hz), and 7.08–7.64 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.2, 25.8, 27.7, 28.1, 29.8, 45.7, 49.3, 52.6, 91.1, 98.1, 101.3, 109.1, 119.3, 121.0, 121.4, 126.1, 127.5, 128.3, 129.1, 129.14, 130.9, 135.8, 169.0, 171.1, 171.3, and 198.1. Anal. Calcd for $C_{28}H_{27}N_3O_5$: C, 69.26; H, 5.60; N, 8.65. Found: C, 68.99; H, 5.64; N, 8.52.

Preparation and Rhodium(II)-Catalyzed Reaction of *N*-[4-(1-Benzenesulfonyl-1*H*-indol-2-yl)butyroyl]-2-diazo-*N*-methyl-3-oxobutyramide (37). To a solution containing 1.31 g (7.48 mmol) of 3-(1H-indol-2-yl)propan-1-ol[58] in 25 mL of pyridine at 0 °C was added 2.14 g (11.21 mmol) of *p*-toluenesulfonic acid in portions. The solution was kept at 10 °C for 16 h and was then poured into 25 mL of ice water. The solution was extracted with ether and the combined organic extracts were washed with 6 N HCl at 0 °C followed by brine. The ethereal solution was dried over $MgSO_4$ and concentrated under reduced pressure to give 2.23 g (91%) of *p*-toluenesulfonic acid, 3-(indol-2-yl)propyl ester as a red-brown oil: IR (neat) 1595, 1454, 1348, and 1171 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.97 (quin, 2H, J = 7.5 Hz), 2.38 (s, 3H), 2.75 (t, 2H, J = 7.5 Hz), 4.05 (t, 2H, J = 7.5 Hz), 6.09 (s, 1H), 6.95–7.60 (m, 4H), 7.27 (d, 2H, J = 9.0 Hz) 7.75 (d, 2H, J = 9.0 Hz), and 7.98 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.6, 23.8, 28.6, 69.4, 99.8, 110.5, 119.6, 119.7, 121.1, 127.8, 128.6, 129.9, 132.7, 135.9, 137.5, and 144.9.

A solution containing 2.23 g (6.77 mmol) of the above indole and 0.50 g (10.16 mmol) of NaCN in 25 mL of DMSO was stirred overnight at rt. At the end of this time the reaction mixture was poured into 75 mL of water and the solution was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 1.25 g (100%) of 4-(1*H*-indol-2-yl)butanenitrile as a red-brown oil: IR (neat) 2249, 1457, 1351, and 1171 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.03 (quin, 2H, J = 7.1 Hz), 2.41 (t, 2H, J = 7.0 Hz), 2.95 (t, 2H, J = 7.2 Hz), 6.29 (d, 1H, J = 1.1 Hz), 7.00–7.60 (m, 4H), and 7.94 (brs, 1H).

A solution containing 1.25 g (6.78 mmol) of the above nitrile and 3.80 g (67.8 mmol) of KOH in a 50% ethanol–water mixture was heated at reflux for 24 h. At the end of this time the solution was allowed to cool to rt and was then poured into 25 mL of water. The solution was extracted with ether and acidified with 6 N HCl at 0 °C. The ether extracts were washed with a saturated NaCl solution and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 1.22 g (88%) of 4-(1*H*-indol-2-yl)butyric acid as a brown oil: IR (neat) 3500–2500, 2945, 1702, 1449, and 1409 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.97 (quin, 2H, J = 7.5 Hz), 2.38 (t, 2H, J = 7.5 Hz), 2.78 (t, 2H, J = 7.5 Hz), 6.22 (s, 1H), 6.85–7.38 (m, 3H), 7.40–7.65 (m, 1H), 7.95 (brs, 1H), and 9.55 (brs, 1H).

To a solution containing 314 mg (1.55 mmol) of the above acid in 5 mL of CH_2Cl_2 was added dropwise a solution containing 313 mg (1.93 mmol) of 1,1′-carbonyldiimidazole in 3 mL of CH_2Cl_2. The solution was stirred for 1 h at rt and was then poured into 50 mL of a 40% solution of methylamine in water at 0 °C. After being stirred overnight, the solution was extracted with CH_2Cl_2 and the combined organic extracts were washed with 10% HCl and a saturated NaCl solution. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 332 mg (92%) of 4-(1*H*-indol-2-yl)butyric acid methylamide as a red oil: IR (neat) 1643, 1536, and 1408 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.01 (quin, 2H, J = 6.7 Hz), 2.18 (t, 2H, J = 7.1 Hz), 2.76 and 2.78 (s, 3H) (1:1 rotamer mixture), 2.79 (t, 2H, J = 7.0 Hz), 5.48 (brs, 1H), 6.22 (s, 1H), 7.00–7.16 (m, 2H), 7.28 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 7.4 Hz), and 8.69 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.2, 26.2, 27.1, 35.0, 99.4, 110.6, 119.3, 119.5, 120.8, 128.5, 136.0, 139.0, and 173.6.

To a solution containing 308 mg (1.42 mmol) of the above amide in 4.5 mL of benzene was added 1.5 mL of a 50% aqueous NaOH solution containing 50 mg (0.142 mmol) of tetrabutylammonium hydrogen sulfate. The reaction mixture was stirred for 45 min at rt, and then a solution containing 380 mg (2.13 mmol) of benzenesulfonyl chloride in 1.5 mL of benzene was added. After being stirred for 3 h, the solution was poured into 10 mL of water and acidified with 10% HCl. The solution was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography to give 164 mg (32%) of 4-(1-benzenesulfonyl-1*H*-indol-2-yl)butyroyl]-*N*-methyl-3-oxobutyramide as a red oil: IR (neat) 3310, 1654, and 1376 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.09 (quin, 2H, J = 7.4 Hz), 2.17 (t, 2H, J = 7.4 Hz), 2.79 and 2.81 (s, 3H) (1:1 rotamer mixture), 3.12 (t, 2H, J = 7.4 Hz), 5.58 (brs, 1H), 7.26–7.56 (m, 7H), 7.69 (dd, 2H, J = 4.0 and 1.0 Hz), and 8.18 (dd, 1H, J = 7.3 and 0.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.5, 25.6, 26.1, 35.5, 114.5, 115.0, 118.2, 124.2, 125.4, 126.1, 127.7, 129.2, 133.9, 135.3, 135.8, 137.9, and 172.9.

A solution containing 366 mg (1.03 mmol) of the above compound in 2 mL of THF was cooled to −78 °C under N_2. To this solution was added 0.84 mL (1.13 mmol) of a 1.35 M

(58) Smith, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957.

solution of *n*-butyllithium in hexane. The reaction mixture was kept at −78 °C for 30 min and then warmed to 0 °C for 30 min. The solution was recooled to −78 °C, and a solution containing 108 mg (1.28 mmol) of diketene in 1 mL of THF was added dropwise. The solution was stirred at −78 °C for 1 h and was then allowed to warm to rt over 1 h. The reaction was quenched with 3 mL of a saturated solution of NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 100 mg (22%) of 4-(1-benzenesulfonyl-1*H*-indol-2-yl)-butyroyl]-*N*-methyl-3-oxobutyramide as a pale yellow oil: IR (neat) 1696, 1627, and 1449 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.10 (quin, 2H, J = 7.0 Hz), 2.23 (s, 3H), 2.62 (t, 2H, J = 7.0 Hz), 3.15 (t, 2H, J = 6.8 Hz), 3.21 (s, 3H), 3.88 (s, 2H), 7.25−7.57 (m, 7H), 7.69 (d, 2H, J = 7.9 Hz), and 8.18 (d, 1H, J = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.1, 25.1, 30.1, 31.1, 35.6, 54.5, 114.7, 115.2, 118.3, 124.4, 125.6, 126.3, 127.7, 129.3, 134.0, 135.5, 135.7, 138.2, 169.2, 175.0, and 201.4.

To a solution containing 100 mg (0.23 mmol) of the above indole and 55 mg (0.452 mmol) of mesyl azide in 1.3 mL of acetonitrile was added a solution of 46 mg (0.452 mmol) of triethylamine in 0.25 mL of acetonitrile under N_2. The solution was stirred at rt overnight, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 83 mg (79%) of 4-(1-benzenesulfonyl-1*H*-indol-2-yl)butyroyl]-2-diazo-*N*-methyl-3-oxobutyramide (**60**) as a yellow oil: IR ($CHCl_3$) 1710, 1605, 1445, 1180, and 1090 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.14 (quin, 2H, J = 7.0 Hz), 2.45 (s, 3H), 2.62 (t, 2H, J = 7.0 Hz), 3.16 (2H, J = 7.0 Hz), 3.19 (s, 3H), 7.26−7.58 (m, 7H), 7.68 (d, 2H, J = 7.5 Hz), and 8.17 (dd, 1H, J = 8.0 and 0.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.2, 25.0, 28.4, 33.1, 34.8, 81.4, 114.6, 115.1, 118.2, 124.3, 125.6, 126.2, 127.7, 129.3, 134.0, 135.4, 135.6, 138.1, 164.8, 174.0, and 189.5.

To a refluxing solution containing 2 mg of rhodium(II) perfluorobutyrate in 7 mL of benzene was added dropwise a solution containing 31 mg (0.07 mmol) of diazo amide **37** in 3 mL of benzene *via* syringe over a 15 min period. The solution was heated at reflux for an additional 15 min and was then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 15 mg (50%) of 4-(1-benzenesulfonyl-1*H*-indol-2-yl)butyric acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**38**) as a colorless oil: IR ($CHCl_3$) 1733, 1679, 1448, and 1367 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.05−2.30 (m, 2H), 2.43 (s, 3H), 2.61 (t, 2H, J = 7.2 Hz), 2.83 and 2.85 (s, 3H), 3.10−3.30 (m, 2H), 5.50 (s, 1H), 6.52 (brs, 1H), 7.23−7.58 (m, 7H), 7.71 (d, 2H, J = 8.0 Hz), and 8.18 (dd, 1H, J = 7.5 and 0.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.5, 25.3, 26.0, 27.8, 32.9, 79.0, 114.7, 115.0, 118.3, 124.3, 125.6, 126.1, 127.7, 129.3, 134.0, 135.3, 135.4, 137.9, 163.6, 170.6, and 199.5.

Preparation and Rhodium(II)-Catalyzed Reaction of 1-Benzenesulfonyl-1*H*-indolyl-*N*-(2-diazo-1,3-dioxobutyl)-*N*-methyl-2-pentanamide (39). To a solution containing 3.0 g (11.7 mmol) of *N*-benzenesulfonyl-1*H*-indole[59] in 50 mL of dry THF under N_2 at 0 °C was added 7.3 mL (11.7 mmol) of *n*-butyllithium. The solution was allowed to stir at 0 °C for 1 h, and then 1.74 mL (14.6 mmol) of 1,4-dibromobutane was added and the solution was allowed to stir at rt overnight. The resulting solution was treated with 25 mL of a saturated NH_4-Cl solution and extracted with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting yellow solid was recrystallized from ethyl acetate and hexane to give 3.48 g (76%) of 1-benzenesulfonyl-2-(4-bromobutanyl)-1*H*-indole as a white solid: mp 132−133 °C; IR ($CHCl_3$) 1460, 1379, and 1183 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.83−2.03 (m, 4H), 3.04 (t, 2H, J = 6.6 Hz), 3.45 (t, 2H, J = 6.6 Hz), 7.19−7.33 (m, 2H), 7.36−7.45 (m, 3H), 7.45−7.57 (m, 1H), 7.70−7.80 (m, 2H), 8.17−8.22 (m, 1H), and 8.43 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.4, 28.1, 32.2, 33.4, 109.2, 114.7, 120.2, 123.6, 124.0, 126.1, 129.2, 129.6, 133.6, 137.1, 138.9, and 141.3. Anal. Calcd for $C_{18}H_{18}BrNO_2S$: C, 55.11; H, 4.62; Br, 20.37; N, 3.57; S, 8.17. Found: C, 55.21; H, 4.67; Br, 20.45; N, 3.62; S, 8.07.

A solution containing 5.74 g (14.6 mmol) of the above indole in 40 mL of DMSO was treated with 1.08 g (22 mmol) of NaCN, and the mixture was heated at 80 °C for 12 h. The solution was cooled to rt and diluted with 80 mL of water, and the precipitated solid was recrystallized from CH_2Cl_2−hexane to give 4.93 g (100%) of 5-(1-benzenesulfonyl-1*H*-indol-2-yl)-pentanenitrile as a white solid: mp 119−120 °C; IR ($CHCl_3$) 2260, 1455, 1374, and 1182 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.77 (quin, 2H, J = 7.2 Hz), 1.92 (quin, 2H, J = 7.2 Hz), 2.38 (t, 2H, J = 7.2 Hz), 3.05 (t, 2H, J = 7.2 HZ), 6.42 (s, 1H), 7.19−7.58 (m, 2H), 7.62−7.79 (m, H), and 8.14−8.19 (m 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.0, 25.0, 28.2, 28.3, 110.6, 114.9, 119.6, 120.3, 123.7, 124.2, 126.1, 129.2, 129.6, 133.7, 137.3, 138.9, and 140.8. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.24; H, 5.31; N, 8.29; S, 9.54.

A solution containing 1.28 g (3.79 mmol) of the above indole in 20 mL of 95% ethanol was treated with 2.12 g (37.9 mmol) of KOH dissolved in 6 mL of water, and the mixture was heated at reflux for 12 h. The solution was cooled to rt and poured into 40 mL of ice-cold 6 N HCl and then extracted with ether. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was taken up in 40 mL of THF and was treated with 0.64 g (3.98 mmol) of 1,1'-carbonyldiimidazole under N_2. The solution was stirred for 4 h and then poured in 40% aqueous methylamine and stirred for an additional 4 h. The solution was concentrated under reduced pressure, and the remaining aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The yellow solid was recrystallized from CH_2Cl_2−hexane to give 0.70 g (80%) of 5-(1*H*-indol-2-yl)pentanoic acid methylamide as a white solid: mp 119−120 °C; IR ($CHCl_3$) 3480, 1675, and 1465 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.63−1.82 (m, 4H), 2.12−2.28 (m, 2H), 2.70−2.80 (m, 2H), 2.74 and 2.76 (s, 3H) (1:1 rotamer mixture), 5.60 (s, 1H), 6.21 (s, 1H), 7.02−7.20 (m, 2H), 7.26−7.35 (m, 1H), 7.50−7.54 (m, 1H), and 8.54 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) 25.1, 24.3, 27.8, 28.9, 36.1, 99.3, 110.5, 119.4, 119.6, 120.8, 128.7, 135.9, 139.6, and 173.7. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.91; H, 7.86; N, 12.11.

To a solution containing 2.0 g (8.7 mmol) of the above indole in 45 mL of benzene were added 9 mL of 50% NaOH and 0.29 g (0.87 mmol) of n-Bu_4NHSO_4. The mixture was stirred for 30 min, and then 1.66 mL (13.0 mmol) of benzenesulfonyl chloride was added. The solution was stirred vigorously for 8 h, and an additional 1.66 mL (13.0 mmol) of benzenesulfonyl chloride was added. After being stirred overnight, the solution was poured into 45 mL of water and the solvent was removed under reduced pressure. The remaining aqueous layer was acidified with 6 N HCl and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was subjected to flash silica gel chromatography to give 1.70 g (53%) of 5-(1-benzenesulfonyl-1*H*-indol-2-yl)pentanoic acid methylamide as a white fluffy solid: mp 99−100 °C; IR ($CHCl_3$) 3470, 1675, 1380, and 1183 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.70−1.81 (m, 4H), 2.21 (t, 2H, J = 6.9 Hz), 2.75 and 2.76 (s, 3H) (1:1 rotamer mixture), 3.07 (t, 2H, J = 6.9 Hz), 5.93 (s, 1H), 7.22−7.52 (m, 7H), 7.65−7.69 (m, 2H), and 8.13−8.17 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.2, 25.9, 26.2, 29.2, 36.1, 114.1, 115.0, 118.2, 124.2, 125.4, 126.1, 127.8, 129.2, 133.9, 135.4, 136.4, 138.1, and 173.4.

N-Acetoacetylation of the above amide gave *N*-[5-(1-benzenesulfonyl-1*H*-indol-2-yl)pentanoyl]-*N*-methyl-3-oxobutyramide (54%) as a yellow oil: IR (neat) 1723, 1705, 1445, and 1175 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.66−1.82 (m, 4H), 2.22 (s, 3H), 2.56 (t, 2H, J = 7.1 Hz), 3.08 (t, 2H, J = 7.1 Hz), 3.19 (s, 3H), 3.93 (s, 2H), 7.20−7.50 (m, 7H), 7.65−7.68 (m, 2H), and 8.13−8.17 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.0, 25.8,

(59) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

28.7, 29.9, 30.8, 36.2, 54.3, 114.0, 114.9, 118.0, 124.1, 125.3, 126.0, 127.6, 129.1, 133.8, 135.2, 136.2, 138.0, 169.0, 175.3, and 201.3.

Diazo transfer of the above compound in the normal manner gave *N*-[5-(1-benzenesulfonyl-1*H*-indol-2-yl)pentanoyl]-2-diazo-*N*-methyl-3-oxobutyramide (**39**) (85%) as a bright yellow oil: IR (neat) 2129, 1700, and 1648 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.75–1.85 (m, 4H), 2.46 (s, 3H), 2.61 (t, 2H, J = 6.7 Hz), 3.10 (t, 2H, J = 6.7 Hz), 3.21 (s, 3H), 7.26–7.55 (m, 7H), 7.67–7.71 (m, 2H), and 8.15–8.19 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.9, 25.9, 28.3, 28.9, 33.0, 35.4, 81.4, 114.1, 115.0, 18.2, 124.2, 125.4, 126.1, 127.7, 129.2, 133.9, 135.3, 136.2, 138.1, 164.9, 174.5, and 189.3.

To a solution containing 30 mg (0.06 mmol) of **39** in 5 mL of benzene under N_2 was added 2 mg of rhodium(II) perfluorobutyrate, and the mixture was stirred at rt for 4 h. The solution was concentrated under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to give 22 mg (78%) of 4-(1-benzenesulfonyl-1*H*-indol-2-yl)pentanoic acid, 1-(methylcarbamoyl)-2-oxopropyl ester (**40**) as a yellow oil: IR (neat) 1732, 1677, and 1174 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.75–1.88 (m, 4H), 2.41 (s, 3H), 2.54 (t, 2H, J = 6.9 Hz), 2.81 and 2.83 (s, 3H), 3.09 (t, 2H, J = 6.9 Hz), 5.62 (s, 1H), 6.42 (s, 1H), and 7.22–8.20 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.2, 25.9, 26.1, 27.9, 29.0, 33.4, 79.0, 115.1, 118.3, 124.3, 124.4, 124.5, 126.2, 127.9, 129.4, 133.9, 134.0, 135.5, 136.2, 163.7, 171.2, and 199.6.

Cycloaddition of **39** with *N*-phenylmaleimide in the normal fashion gave 1-acetyl-7-[4-(1-benzenesulfonyl-1*H*-indol-2-yl)-butyl]-4,8-diaza-8-methyl-4-phenyl-10-oxotricyclo[5.2.1.$0^{2,6}$]-decane-3,5,9-trione (**41**) (62%) as a white solid: mp 204–205 °C: IR ($CHCl_3$) 1716, 1374, and 1211 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.51–1.85 (m, 4H), 2.15–2.33 (m, 2H), 2.61 (s, 3H), 2.85 (s, 3H), 3.00–3.12 (m, 2H), 3.34 (d, 1H, J = 6.8 Hz), 3.71 (d, 1H, J = 6.8 Hz), 7.21–7.68 (m, 14H), and 8.15–8.18 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.6, 26.0, 26.1, 27.8, 28.2, 29.4, 45.5, 52.8, 91.3, 98.4, 114.1, 115.1, 118.3, 124.3, 125.5, 126.2, 126.3, 127.8, 129.1, 129.2, 129.3, 131.0, 133.9, 135.5, 136.2, 169.2, 171.2, 171.2, and 196.2; HRMS calcd for $C_{34}H_{31}N_3O_7S$ 625.1883, found 625.1880.

Preparation and Rhodium(II)-Catalyzed Reaction of *N*-Methyl-[5-(1-methyl-1*H*-indol-2-yl)pentanoyl]-2-diazo-3-oxobutyramide (42). A variation of the procedure of Barco and co-workers was used to prepare the starting amide.[60] To a solution containing 0.30 mL (4.8 mmol) of methyl iodide, 5 mL of 50% NaOH, 1.09 g (3.2 mmol) of n-Bu_4NHSO_4, and 10 mL of benzene was added 0.74 g (3.2 mmol) of 5-(1*H*-indol-2-yl)pentanoic acid methylamide, and the mixture was heated at 33 °C for 12 h. The solution was diluted with water, and the mixture was extracted with benzene. The combined organic layer was dried over $MgSO_4$ and filtered, and the solution was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.58 g (74%) of 5-(1-methyl-1*H*-indol-2-yl)pentanoic acid methylamide as a yellow oil: IR ($CHCl_3$) 3460, 1661, and 1446 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.65–1.80 (m, 4H), 2.19 (t, 2H, J = 6.8 Hz), 2.67–2.77 (m, 2H), 2.72 and 2.73 (s, 3H), 3.61 (s, 3H), 5.86 (s, 1H), 6.21 (s, 1H), and 7.00–7.52 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.4, 26.1, 26.5, 28.1, 29.3, 36.2, 98.7, 108.7, 119.1, 119.6, 120.4, 127.7, 137.2, 140.8, and 173.3.

N-Acetoacetylation of the above amide gave *N*-methyl-[5-(1-methyl-1*H*-indol-2-yl)pentanoyl]-3-oxobutyramide (20%) as a colorless solid: mp 110–111 °C; IR ($CHCl_3$) 1716, 1688, and 1460 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.72–1.82 (m, 4H), 2.24 (s, 3H), 2.54 (t, 2H, J = 6.7 Hz), 2.75 (t, 2H, J = 6.7 Hz), 3.18 (s, 3H), 3.63 (s, 3H), 3.93 (s, 2H), 6.26 (s, 1H), and 7.03–7.55 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.0, 26.7, 27.8, 29.4, 30.1, 31.1, 39.7, 54.5, 98.9, 108.8, 119.3, 119.8, 120.6, 127.9, 137.4, 140.5, 169.2, 175.5, and 201.5.

Diazo transfer of the above compound in the normal manner gave *N*-methyl-[5-(1-methyl-1*H*-indol-2-yl)pentanoyl]-2-diazo-3-oxobutyramide (**42**) (63%) as a yellow solid: mp 98–99 °C; IR ($CHCl_3$) 2129, 1666, and 1317 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.72–1.88 (m, 4H), 2.45 (s, 3H), 2.57 (t, 2H, J = 6.7 Hz), 2.77 (t, 2H, J = 6.7 Hz), 3.16 (s, 3H), 3.64 (s, 3H), 6.25 (s, 1H), and 7.03–7.54 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.2, 26.6, 27.9, 28.3, 29.3, 33.1, 35.7, 98.8, 108.7, 119.2, 119.7, 120.5, 127.7, 137.3, 140.4, 165.0, 174.5, and 189.1.

To a solution containing 25 mg (0.07 mmol) of **42** and 24 mg (0.14 mmol) of *N*-phenylmaleimide in 5 mL of benzene under N_2 was added a catalytic amount of rhodium(II) acetate, and the resulting solution was heated at reflux for 1.5 h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 27 mg (77%) of 1-acetyl-4,8-diaza-8-methyl-7-[4-(1-methyl-1*H*-indol-2-yl)butyl]-4-phenyl-10-oxotricyclo[5.2.1.0^{26}]decane-3,5,9-trione (**43**) as a white solid: mp 226–227 °C; IR ($CHCl_3$) 1716, 1386, and 1207 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.50–1.85 (m, 4H), 2.18–2.26 (m, 2H), 2.61 (s, 3H), 2.75 (t, 2H, J = 7.0 Hz), 2.81 (s, 3H), 3.30 (d, 1H, J = 6.7 Hz), 3.63 (s, 3H), 3.66 (d, 1H, J = 6.7 Hz), 6.22 (s, 1H), and 7.00–7.52 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.6, 26.0, 26.5, 28.0, 28.2, 29.4, 49.4, 52.7, 91.2, 98.3, 98.9, 108.7, 119.3, 119.7, 120.7, 126.2, 127.7, 129.17, 129.20, 131.0, 137.3, 140.2, 169.2, 171.2, 171.3, and 196.1; HRMS calcd for $C_{29}H_{29}N_3O_5$ 499.2108, found 499.2113.

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Supplementary Material Available: Copies of ^{13}C-NMR spectra (75 MHz) of compounds lacking analyses (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(60) Barco, A.; Benetti, G. P.; Pollini, G. P. *Synthesis* **1976**, 124.