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Cycloaddition Chemistry of 2-Vinyl-Substituted Indoles and Related Heteroaromatic Systems

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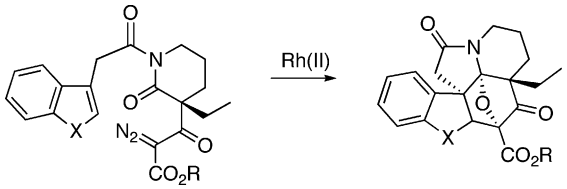
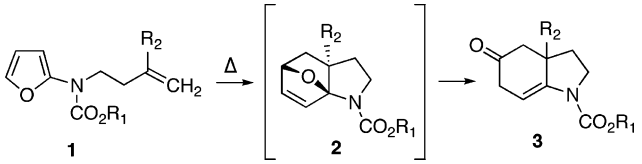


The intramolecular Diels−Alder cycloaddition reaction (IMDAF) of several *N*-phenylsulfonylindolyl-substituted furanyl carbamates containing a tethered π-bond on the indole ring were examined as an approach to the iboga alkaloid catharanthine. Only in the case where the tethered π-bond contained two carbomethoxy groups did the [4 + 2]-cycloaddition occur. Push−pull dipoles generated from the Rh(II)-catalyzed reaction of diazo imides, on the other hand, undergo successful intramolecular 1,3-dipolar cycloaddition across both alkenyl and heteroaromatic π-bonds to provide novel pentacyclic compounds in good yield and in a stereocontrolled fashion. The facility of the cycloaddition was found to be critically dependent on conformational factors in the transition state. Ligand substitution in the rhodium(II) catalyst markedly altered the product ratio between [3 + 2]-cycloaddition and intramolecular C−H insertion. The variation in reactivity reflects the difference in electrophilicity between the various rhodium carbenoid intermediates. Intramolecular C−H insertion is enhanced with the more electrophilic carbene generated using Rh(II) perfluorobutyrate.

Construction of azapolyheterocycles through cycloaddition chemistry has been a particularly fruitful area of investigation, and the synthesis of various types of alkaloids by this approach has been carried out by numerous investigators.[1−13] Several years ago, we began a synthetic program to provide general access to a variety of alkaloids by [4 + 2]-cycloaddition chemistry of furanyl carbamates.[14] This approach, demonstrated by the cyclization of **1** to the intermediate oxabicycle **2** (Scheme 1) was limited to systems containing an angular substituent in the resultant azabicycle **3** or else aromatic products were formed.[15] Our experience with this domino sequence prompted us to examine the method for an eventual synthesis of the iboga alkaloid catharanthine (**4**).[16] The dense, pentacyclic skeleton of catharanthine contains a tryptamine fragment substituted at the 2-position by a quaternary sp^3 carbon and thereby represents an attractive challenge for synthesis. (±)-Catharanthine (**4**) has been the target of numerous successful and formal total syntheses.[17] Despite the availability of many synthetic methods for the iboga alkaloids, there still exists a need to develop procedures more efficient and flexible than those currently in existence.

SCHEME 1



1 **2** **3**

Our synthetic plan for the synthesis of catharanthine (**4**) is shown in retrosynthetic format in Scheme 2 and is centered on the construction of the key benzo[2,3]azepino-[4,5-*b*]indole intermediate **8**, which, by analogy with previous work in our laboratory[14] should be available by the cycloaddition-nitrogen assisted ring opening cascade of indole **5** (R = Et).[18] In this paper, we give an account

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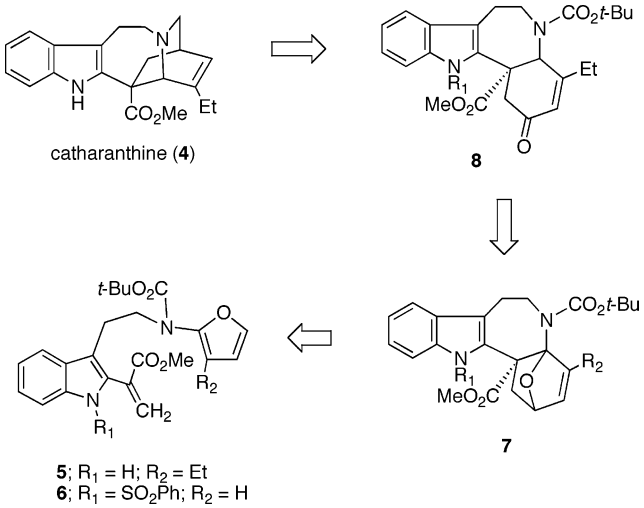
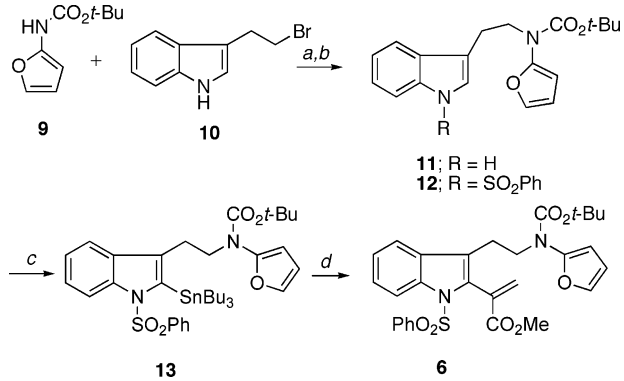
SCHEME 2



SCHEME 3[a]



[a] Reagents: (a) Cs_2CO_3, DMF/THF (4:1), 80 °C; (b) Bu_4NHSO_4, NaOH, $ClSO_2C_6H_5$, CH_2Cl_2, rt; (c) *t*-BuLi, pentane, −78 °C, *n*-Bu_3SnCl, pentane, −78 °C; (d) methyl α-bromoacrylate, DMF, $Pd(PPh_3)_4$, CuI, 25 °C.

of our efforts dealing with this unique cycloaddition approach to assemble the polycyclic array of catharanthine.

Results and Discussion

The potential of using this methodology for the synthesis of catharanthine and related iboga alkaloids prompted us to first carry out some model studies to prove the likelihood of the key intramolecular [4 + 2]-cycloaddition across the tethered acrylate π-bond. With this in mind, we reasoned that it would be easier to evaluate the IMDAF cycloaddition[2] using the *N*-phenylsulfonyl-indolyl furan **6** (R_2 = H) rather than the less activated ethyl substituted furan **5** for the initial model studies. After some experimentation, we found that the reaction of carbamate **9** with 3-(2-bromoethyl)indole (**10**) using Cs_2CO_3 as the base afforded the expected NH-indole **11** in 96% yield (Scheme 3). Subsequent *N*-sulfonylation under phase transfer conditions produced **12** in 86% yield. The presence of a *N*-benzenesulfonyl group on the indole nitrogen is known to facilitate regioselective metalation at the 2-position of the heteroaromatic ring via a chelate-stabilized lithiated intermediate.[19] Our intention was to exploit this lithiation reaction so as to eventually introduce the necessary acrylate π-bond required for the cycloaddition. Indeed, treatment of **12** with *t*-BuLi afforded the desired lithiate which, after quenching with Bu_3SnCl, afforded stannane **13** in 78% yield. This stannane derivative proved to be a versatile intermediate as it allowed the introduction of a variety of functional groups at the 2-position of the indole ring by making use of palladium cross-coupling chemistry.[20] Thus, the reaction of **13** with methyl α-bromoacrylate in the presence of catalytic $Pd(PPh_3)_4$ and CuI furnished the desired cycloaddition precursor **6** in 60% yield.

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(18) The conversion of **7** to **4** via **8** would require a number of additional steps including an oxabicyclic ring opening followed by double-bond isomerization as well as an eventual intramolecular nucleophilic N−C bond formation.

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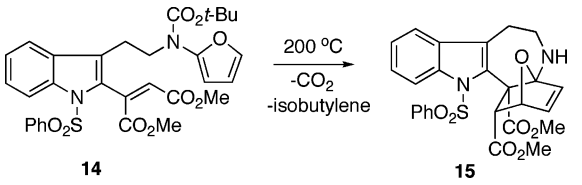
SCHEME 4

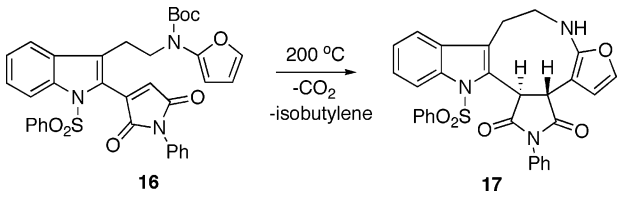


14 **15**

Unfortunately, all of our attempts to effect the [4 + 2]-cycloaddition of **6** resulted in the formation of dark tars and we were not able to isolate any characterizable product from the thermolysis reaction. In previous studies, structural features that facilitate the intramolecular Diels−Alder reaction of amidofurans were discovered.[21] On the basis of FMO considerations,[22] we anticipated that additional activation of the C=C double bond with another electron withdrawing group would facilitate the intramolecular [4 + 2]-cycloaddition.[23] With this in mind, the dicarbomethoxy substituted furanyl indole **14** was prepared in 64% yield by the Stille coupling of stannane **13** and 3-bromodimethyl maleate. Heating a sample of **14** at 200 °C for 7 h did furnish cycloadduct **15**, but only in 38% yield (Scheme 4). The isolation of azepine **15** was somewhat unexpected since related aza-substituted oxabicyclic compounds generally tend to undergo ring opening at elevated temperatures.[24] The presence of the oxabridge in **15** is especially striking and suggests that the loss of isobutylene and CO_2 from the *N*-Boc carbamate occurs first and that the transient NH-furan undergoes a subsequent cycloaddition across the diactivated π-bond. Examination of molecular models indicates that this particular seven-membered azepine adopts a severely twisted conformation in which the nitrogen atom lone pair resides nearly orthogonal to the oxygen bridge and consequently cannot participate in the ring-opening reaction.

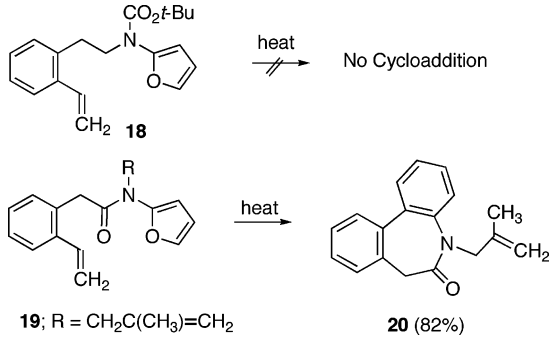
For comparison purposes, we have also investigated the thermal chemistry of the related *N*-phenylmaleimide substituted indole **16**. This compound was prepared in 76% yield by the Stille cross-coupling reaction[20] of stannane **13** with 3-bromo-1-phenylpyrrole-2,5-dione. As was the case with indole **14**, thermolysis of **16** at 200 °C (6 h) resulted in the loss of isobutylene and CO_2 and furnished the nine-membered azacycle **17** as the only detectable product in 45% yield. The structure of **17** was based on its spectroscopic properties and was further validated by single crystal X-ray analysis which clearly indicates the *trans*-substitution pattern present at the fused succinimide ring juncture (Scheme 5). This interesting product arises by conjugate addition of the furan on the activated maleimide ring. More than likely the steric bulk of the *N*-phenylmaleimide group interferes with the other substituents present in the two-plane orientation complex required for the Diels−Alder reaction and thereby prevents the cycloaddition from occurring. The bulky *N*-phenylmaleimide group apparently causes the molecule

SCHEME 5



16 **17**

SCHEME 6



19; R = $CH_2C(CH_3)=CH_2$ **20** (82%)

to adopt a conformation where conjugate addition by the furan onto the activated π-bond becomes the preferred pathway.

In earlier studies we had demonstrated that conformational effects can have a dramatic impact on the rate of the IMDAF reaction of amido-substituted furans.[25] Specifically, the incorporation of a carbonyl group such that an amide linkage joining the dienophile and furan moieties resulted in a conformation of the tether that brings the dienophile into closer proximity with the furan and facilitates the cycloaddition reaction relative to the simple amine tether. A recent example from our laboratory which illustrates this rate difference is seen in the thermal chemistry of carbamate **18** vs amidofuran **19** (Scheme 6). Heating a sample of **18** at 200 °C gave no sign of any product derived from a [4 + 2]-cycloaddition reaction. In sharp contrast, **19** gave **20** in 82% isolated yield when heated at 100 °C. In this case, the initially formed Diels−Alder cycloadduct underwent ring opening and subsequent loss of water to produce the aromatized product **20**.

In an attempt to exploit this conformational facilitating effect in the indole series, we examined the thermal behavior of indole **23** which could be formed by the base-induced alkylation of N−H furan **21** with 3-bromo-2-methyl-1-propene. In addition to the expected *N*-alkylated product **23**, a substantial amount of azepino[4,5-*b*]indole **22** was also isolated and is derived by conjugate addition of the amide anion onto the adjacent acrylate π-bond (Scheme 7). Unfortunately, all of our attempts to effect the IMDAF cycloaddition of **23** failed and only the starting furanyl indole was recovered. One possible explanation that might account for the lack of reactivity of **23** is that the presence of the amido group on the furan ring lowers the HOMO energy thereby widening the gap between the FMO levels and consequently diminishing the overall rate of the cycloaddition.[22]

Since the furanyl carbamate cycloaddition approach toward catharanthine proved not to be feasible, we

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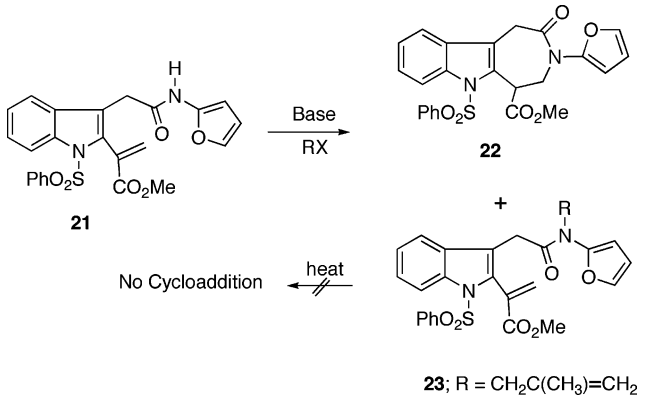
SCHEME 7



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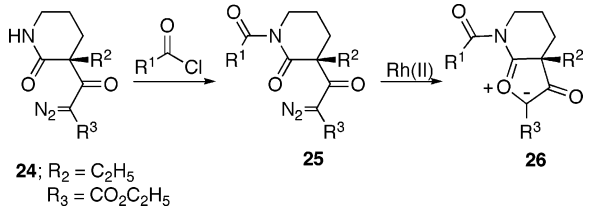
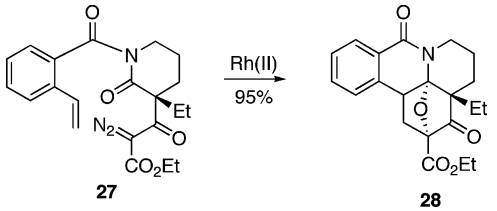


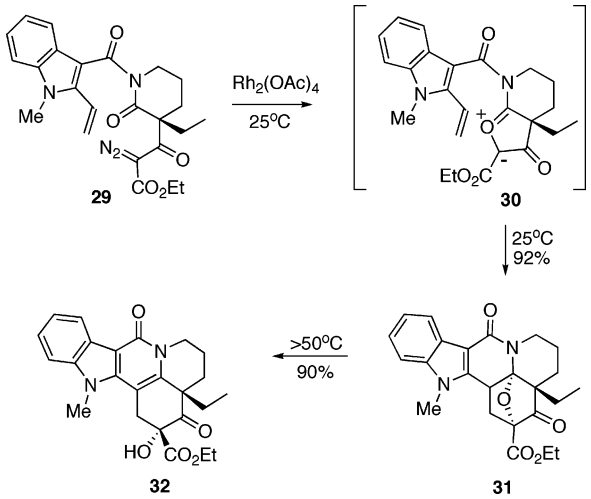
SCHEME 9



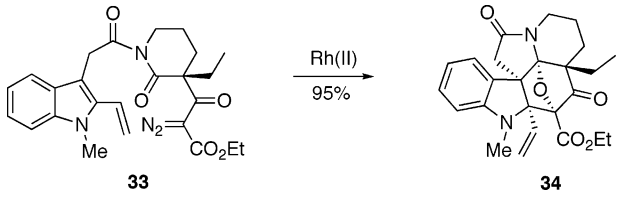
decided to explore the possibility of using the related amido-substituted carbonyl ylide dipole for the critical cycloaddition step. In earlier work, we had demonstrated that push−pull 1,3-dipoles of type **26** were highly reactive and synthetically useful intermediates for [3 + 2]-cycloaddition chemistry.[26] The potential of using carbonyl ylide dipoles such as **26** for the synthesis of catharanthine and related iboga alkaloids prompted us to first carry out some model studies to prove the likelihood of the key cycloaddition across a tethered vinyl group. The starting diazo imide substrates (i.e., **25**) were easily prepared by treating the stable N-H diazo amides **24** with an appropriate acid chloride in the presence of 4 Å molecular sieves (Scheme 8). Formation of the push−pull dipole **26** was achieved by reaction of **25** with $Rh_2(OAc)_4$, which afforded a rhodium carbenoid species that readily underwent cyclization onto the neighboring imido carbonyl to form the carbonyl ylide dipole.[27] Subsequent intramolecular cycloaddition across the tethered vinyl group in the model system **27** furnished cycloadduct **28** in 95% isolated yield, thereby demonstrating the facility of the cascade sequence (Scheme 9).

We were pleased to find that the analogous vinylindolyl-substituted diazoimide **29** underwent a related Rh-

SCHEME 10



SCHEME 11



(II)-catalyzed cyclization to give the azapolycyclic cycloadduct **31** in 92% yield. The cascade sequence was extremely facile and took place at room temperature. When the Rh(II)-catalyzed reaction was carried out at 50 °C or higher, the only product isolated corresponded to the ring-opened pyridone **32**. Control experiments demonstrated that heating a pure sample of **31** in ether provided **32** in 90% yield (Scheme 10).

Armed with these promising results, we set out to explore the cycloaddition chemistry of the homologous indolyl diazo imide **33**, which is a more suitable model for an eventual synthesis of catharanthine. Interestingly, subjection of **33** to Rh(II) catalysis led exclusively to cycloadduct **34** (95%) where cycloaddition of the 1,3-dipole occurred preferentially across the indole π-bond rather than with the tethered vinyl group (Scheme 11). Although there are examples in the literature where the 2,3-double bond of indole participates in [4 + 2]-cycloaddition chemistry,[28−30] the indole ring generally shows only a low tendency to act as a dienophile with electron-rich dienes.[31,32] In bimolecular Diels−Alder reactions that

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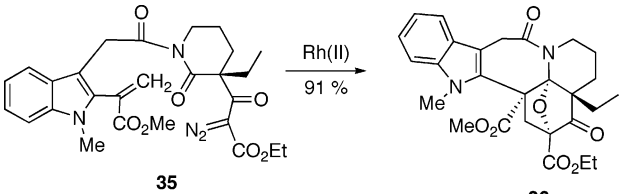
(32) Indole is quite a good dienophile in inverse electron-demand Diels−Alder cycloadditions; (a) Lee, L.; Snyder, J. K. *Advances in Cycloaddition Chemistry*; Harmata, M., Ed.; JAI Press: 1999; Vol. 6, p 119. (b) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.

SCHEME 12



occur with normal electron-demand, indole acts as a 2π-substrate only if electron-withdrawing groups are present in the 1 and 3-positions.[28] Intramolecular cycloaddition reactions, however, benefit from higher reactivity and greater control of stereoselectivity relative to their intermolecular counterparts. More than likely, the initially formed dipole derived from **33** resides in a conformation where the 4π-array of the carbonyl ylide dipole is able to better overlap in the traditional two-plane orientation approach with the indolyl π-bond than with the vinyl group, thereby controlling the periselectivity of the cycloaddition.

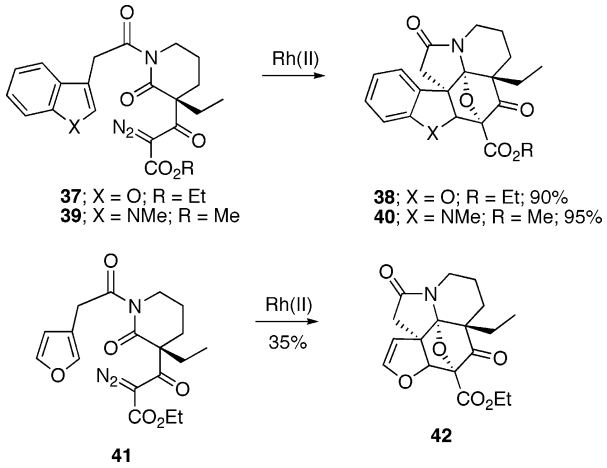
Most interestingly, the placement of a carbomethoxy group on the tethered vinyl group drastically altered the regioselectivity of the cycloaddition. Thus, exposure of the related diazo imide **35** to $Rh_2(OAc)_4$ at 90 °C furnished cycloadduct **36** in 91% yield as the only product formed. In this case, the initially generated carbonyl ylide dipole undergoes exclusive cycloaddition across the more activated acrylate π-bond to furnish cycloadduct **36** rather than undergoing addition across the indole system as was encountered with diazo imide **33**.

It would seem as though these indolyl substituted systems are markedly sensitive to both conformational and electronic factors in the key cycloaddition step (Scheme 12).

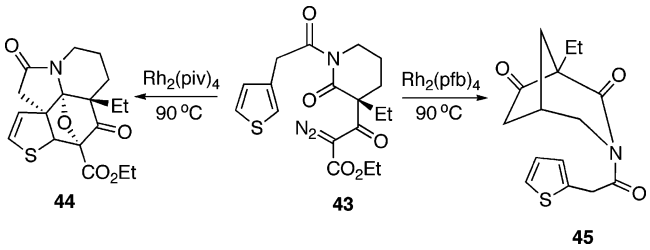
In the context of extending the above cycloaddition to other ring systems, we wondered whether the push−pull dipole found in **26** might also undergo intramolecular dipolar cycloaddition with different heteroaromatic π-bonds. Five-membered-ring heteroaromatics such as furan, thiophene and benzofurans have, despite their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[33] 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 function as 4_πs components,[34] but a study of their dipolarophilic reactivity has not been extensively examined to date.[32,35] Consequently, we initiated a study to determine whether push−pull dipoles of type **26** would undergo cycloaddition with several other heteroaromatic π-systems.

Our initial efforts focused on the Rh(II)-catalyzed reaction of the benzofuranyl-substituted diazo imide **37**. Gratifyingly, treatment of **37** with rhodium(II) pivalate at 100 °C in benzene using a microwave reactor afforded the polyheterocyclic adduct **38** in 90% yield and with

SCHEME 13



SCHEME 14



complete diastereospecificity. The regio- and relative stereochemistry of **38** was assigned by ^{1}H NMR and was confirmed by single-crystal X-ray analysis. A similar product (i.e., **40**) was obtained in 95% yield using the related indolyl-substituted diazo imide **39** (Scheme 13).[26]

Bolstered by these positive results, we next examined the Rh(II)-catalyzed behavior of the cyclic diazo imide containing a tethered furan ring. Treatment of **41** with rhodium(II) pivalate at 90 °C furnished cycloadduct **42** but only in 35% yield. The lower yield encountered with this system is probably related to its greater aromaticity relative to the benzo-fused systems. Thiophene has a lower lying HOMO level than does furan, which increases the energy gap between the interacting FMO's.[31] This is probably why so little is known about dipolar cycloadditions across thiophene rings. We found, however, that no significant difference in yield occurred when the related thiophenyl-substituted diazo imide **43** was treated with Rh(II) pivalate. The major product formed in 38% yield corresponded to cycloadduct **44** (Scheme 14). This result stands in contrast to other literature reports, where it is known that the greater aromatic character of thiophene considerably limits its ability to undergo cycloaddition chemistry.[28] This example also represents the first instance of an intramolecular [3 + 2]-cycloaddition of a 1,3-dipole across the thiophene 2,3-π-bond.

While searching for optimal reaction conditions to maximize the yield of cycloadduct **44**, we found that changing the ligand group on the rhodium catalyst resulted in a major difference in the overall reaction pathway.[36] Thus, the only compound that was isolated from the rhodium(II) perfluorobutyrate ($Rh_2(pfb)_4$) catalyzed decomposition of **43** (90 °C microwave) was lactam

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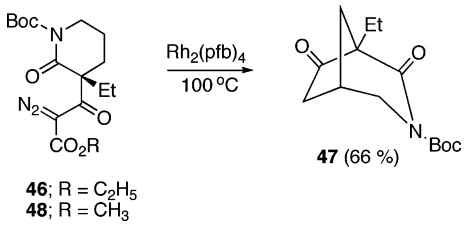
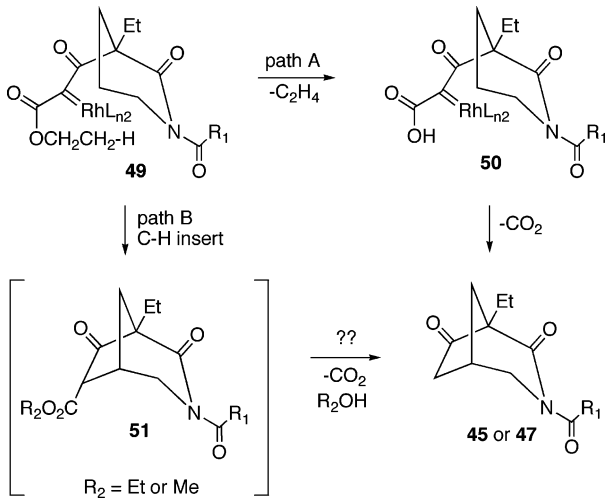
(34) (a) Sauer, J. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.
(35) For some related work, see: Oguri, H.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 47.
(36) Mejía-Oneto, J. M.; Padwa, A. *Tetrahedron Lett.* **2004**, *45*, 9115.

SCHEME 15



SCHEME 16



45 (51%), which arose from a formal insertion of the metal carbene into the C−H bond at the 5-position of the lactam ring[37] followed by an unusual ethoxy-decarboxylation reaction (vide infra). No signs of the previously isolated cycloadduct **44** were detected in the crude mixture. The structure of lactam **45** was assigned on the basis of its characteristic spectral data.

Formation of the 3-aza-bicyclo[3.2.1]octan-2,7-dione ring system was found to be a general reaction that also occurred with related α-diazo ketoamides just as long as $Rh_2(pfb)_4$ was used as the catalyst. Thus, the rhodium(II) perfluorobutyrate catalyzed decomposition of diazo ketoamide **46** at 100 °C in benzene afforded the analogous insertion product **47** in 66% isolated yield (Scheme 15). When the reaction of **46** was carried out using $Rh_2(OAc)_4$ as the catalyst, there were no detectable quantities of lactam **47** or any other characterizable product, thereby attesting to the sensitivity of the C−H insertion reaction to the nature of the ligand group attached to the rhodium metal (Scheme 15).

One conceivable route to account for aza-bicyclo lactam formation involves the production of ethylene from the initially formed rhodium carbenoid **49** followed by C−H insertion and eventual extrusion of CO_2 (Scheme 16, path A). To test this mechanistic possibility, we prepared the corresponding methyl ester (i.e., **48**) and noted no significant difference in the yield of product when **48** was treated with the $Rh_2(pfb)_4$ catalyst. It is for this reason that we propose the alternative mechanism (Scheme 16, path B), which involves initial C−H insertion into the 5-position of the lactam ring followed by a subsequent hydrolysis/decarboxylation reaction. Unfortunately, all of our efforts to detect the expected intermediate **51** failed to indicate its presence in the reaction mixture. Since it was necessary to carry out the catalyzed reaction at elevated temperatures (>90 °C) for the C−H insertion to proceed, we assume that **51** is simply too labile to be detected under the thermal conditions employed. Further work is clearly necessary before this pathway can be unequivocally established.

Earlier studies have shown that, despite their high reactivity, rhodium carbenoid intermediates are often highly chemoselective when two or more reaction pathways are open to them. Site selectivity has been found to depend not only on the type of α-diazocarbonyl utilized, but is also governed by steric,[39−42] conformational,[43] as well as electronic factors.[44−47] The earlier studies have revealed some interesting ligand effects,[38] and it is now established that carboxylate ligands can effectively control chemoselectivity in competitive carbenoid transformations of α-diazocarbonyl compounds.[48] To further investigate the chemoselectivity of the reaction as a function of the nature of the catalyst, we prepared the *N*-but-3-enoyl-substituted imide **52**, which possesses an unactivated terminal π-bond. The rhodium(II) pivalate catalyzed decomposition of **52** resulted in exclusive carbonyl ylide formation and subsequent intramolecular cycloaddition to give cycloadduct **53** in 98% yield (Scheme 17). No signs of any product derived from a C−H insertion could be detected in the crude reaction mixture. Virtually complete cycloaddition chemistry also occurred when rhodium(II) caprolactomate ($Rh_2(cap)_4$) was used as the catalyst. Although Rh(II) acetate ($Rh_2(OAc)_4$) and Rh(II) mandelate ($Rh_2(man)_4$) also afforded cycloadduct **53** as the major product, small amounts of the C−H

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(41) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *10*, 6, 5295.

(42) (a) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709. (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1508.

(43) (a) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384. (b) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.

(44) (a) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397. (b) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards. J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.

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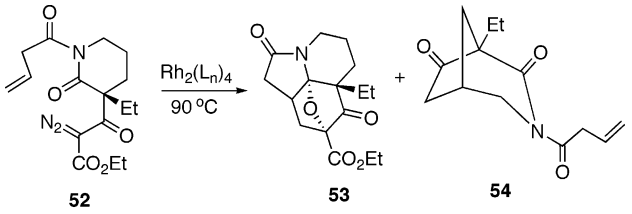
(46) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479.

(47) Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Ahmed-Schofield, R.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097.

(48) Padwa, A.; Austin, D. J. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

SCHEME 17



L_n = piv	98%	0%
L_n = cap	98%	0%
L_n = OAc	91%	4%
L_n = man	88%	6%
L_n = tfa	73%	22%
L_n = pfb	62%	32%

insertion product **54** could be detected in the crude reaction mixture. Catalysis by Rh(II) trifluoroacetate ($Rh_2(tfa)_4$) or $Rh_2(pfb)_4$, on the other hand, gave significant quantities of the insertion product **54** (22% and 32%). The variation in reactivity (yield) presumably reflects the differences in electrophilicity between the various rhodium carbenoid intermediates. Intramolecular C−H insertion is enhanced with the more electrophilic carbene generated using $Rh_2(pfb)_4$, as had been encountered earlier with allyl- and aryl-substituted 1-diazopentanediones.[38b] Either charge or HOMO/LUMO control or both may be operating in these Rh(II)-catalyzed transformations (Scheme 16).

In conclusion, several trends have surfaced from our investigations in this area. Furanyl carbamates possessing a vinyl group tethered to an indole ring undergo intramolecular [4 + 2]-cycloaddition only under forcing conditions and in low yield. Push−pull dipoles generated from the Rh(II)-catalyzed reaction of diazoimides, on the other hand, undergo successful intramolecular 1,3-dipolar cycloaddition across both alkenyl and heteroaromatic π-bonds to provide novel pentacyclic 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. In addition, ligand substitution in the rhodium(II) catalyst can markedly alter the product ratio between [3 + 2]-cycloaddition and intramolecular C−H insertion. We are currently investigating the scope and limitations of the intramolecular cycloaddition of these push−pull dipoles as a potential method for the synthesis of various alkaloid targets.

Experimental Section

[2-(1-Benzenesulfonyl-1*H*-indol-3-yl)ethyl]furan-2-ylcarbamic Acid *tert*-Butyl Ester (12). To a solution containing 1.4 g (4 mmol) of furan-2-yl-(2-(1*H*-indol-3-yl)ethyl)-carbamic acid *tert*-butyl ester (**11**)24 in 50 mL of benzene at rt was added 0.14 g (0.4 mmol) of tetrabutylammonium hydrogensulfate in 10 mL of 50% aqueous NaOH solution. The reaction mixture was stirred at rt for 10 min, and then 0.7 mL (5 mmol) of benzenesulfonyl chloride was added dropwise to the solution. The mixture was stirred at rt for 3 h and then diluted with H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (10% EtOAc in hexane) to afford 1.7 g (86%) of **12** as a colorless oil: IR (neat) 1705, 1613, 1449, 1367, and 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9H), 2.97 (t, 2H, J = 7.6 Hz), 3.86 (t, 2H, J = 7.6 Hz), 5.91 (brs, 1H), 6.32 (s, 1H), 7.17 (d, 1H, J = 1.2 Hz), 7.22−7.26 (m, 1H), 7.29−7.33 (m, 1H), 7.38 (s, 1H), 7.40−7.44 (m, 2H), 7.49−7.53 (m, 2H), 7.85−7.87 (m, 2H), and 7.98 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 28.3, 48.3, 81.6, 101.2, 111.2, 113.9, 119.7, 120.0, 123.4, 123.6, 125.0, 126.9, 129.4, 131.1, 133.9, 135.4, 138.2, 138.5, 148.6, and 153.7; HRMS calcd for $C_{25}H_{26}N_2O_5S$ 466.1562, found 466.1547.

[2-(1-Benzenesulfonyl-2-tributylstannanyl-1*H*-indol-3-yl)ethyl]furan-2-ylcarbamic Acid *tert*-Butyl Ester (13). To a solution containing 2.0 g (4.3 mmol) of the above indole **12** in 40 mL of THF at −78 °C was added 3.6 mL (4.7 mmol) of *t*-BuLi (1.3 M in pentane). The reaction mixture was stirred at −78 °C for 1 h, and then 1.4 g (4.3 mmol) of tributyltin chloride was added dropwise. The mixture was stirred at −78 °C for an additional 0.5 h and then quenched with saturated aqueous NH_4Cl and warmed to rt. The mixture was diluted with H_2O, extracted with EtOAc, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (8% EtOAc in hexane) to give 2.5 g (78%) of **13** as a colorless oil: IR (neat) 1716, 1618, 1449, 1362, and 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 9H, J = 7.2 Hz), 1.16−1.20 (m, 6H), 1.30−1.38 (m, 6H), 1.48 (s, 9H), 1.49−1.54 (m, 6H), 3.05−3.09 (m, 2H), 3.70−3.74 (m, 2H), 5.99 (brs, 1H), 6.38 (s, 1H), 7.18−7.20 (m, 2H), 7.24 (d, 1H, J = 1.2 Hz), 7.32 (t, 2H, J = 8.0 Hz), 7.42−7.46 (m, 1H), 7.53−7.55 (m, 2H), 7.62 (brs, 1H), and 7.83−7.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.1, 13.9, 26.2, 27.5, 28.4, 29.2, 49.9, 81.4, 101.7, 111.3, 114.7, 119.2, 123.4, 124.5, 126.4, 129.0, 132.7, 132.9, 133.4, 138.4, 138.8, 139.4, 140.8, 148.7, and 153.9; HRMS calcd for $C_{37}H_{52}N_2O_5SSnLi$ 763.2779, found 763.2764.

2-{1-Benzenesulfonyl-3-[2-(*tert*-butoxycarbonylfuran-2-ylamino)ethyl]-1*H*-indol-2-yl}but-2-enedioic Acid Dimethyl Ester (14). To a solution of 1.3 g (1.7 mmol) of stannane **13** in 2.0 mL of DMF under argon was added a solution of 0.44 g (2.0 mmol) of 3-bromodimethyl maleate in 1.0 mL of DMF followed by 0.09 g (0.08 mmol) of $Pd(PPh_3)_4$ and 0.06 g (0.33 mmol) of CuI. The reaction mixture was stirred at room temperature for 1 h, diluted with 30 mL of ether, and filtered over a pad of Celite. The filtrate was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (10% EtOAc in hexane) to provide 0.64 g (64%) of **14** as a pale yellow oil: IR (neat) 1736, 1710, 1613, 1449, 1367, and 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.98 (t, 2H, J = 7.6 Hz), 3.70 (brs, 2H), 3.77 (s, 3H), 3.89 (s, 3H), 5.87 (brs, 1H), 6.18 (brs, 1H), 6.28 (s, 1H), 7.09 (dd, 1H, J = 2.0 and 0.8 Hz), 7.27−7.31 (m, 1H), 7.37−7.41 (m, 3H), 7.51 (t, 1H, J = 7.6 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7.76 (d, 2H, J = 7.2 Hz), and 8.20 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 28.2, 48.3, 52.6, 52.9, 81.7, 100.1, 111.2, 115.3, 120.3, 124.3, 126.3, 127.1, 128.0, 129.3, 130.4, 131.5, 131.7, 132.9, 134.2, 136.7, 137.8, 138.1, 148.5, 153.3, 164.8 and 165.7; HRMS calcd for $C_{31}H_{32}N_2O_9S$ 608.1829, found 608.1830.

6-(Benzenesulfonyl[4,5-*b*]indole)-12-oxa-2-azatricyclo-[7.2.1.0^{1,7}]dodeca-5,10-diene-7,8-dicarboxylic Acid Dimethyl Ester (15). A solution of 0.005 g (0.08 mmol) of the above indole **14** in 2 mL of toluene was heated in a sealed pressure tube under argon at 200°C for 7 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography (8% EtOAc in hexane) to provide 0.002 g (38%) of **15** as a colorless oil: IR (neat) 3370, 1731, 1613, 1449, and 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.04−3.14 (m, 2H), 3.22−3.33 (m, 1H), 3.48−3.52 (m, 1H), 3.57 (s, 3H), 3.79 (s, 3H), 3.97−4.00 (m, 1H), 4.61 (d, 1H, J = 10.4 Hz), 5.50 (d, 1H, J = 10.4 Hz), 5.96 (d, 1H, J = 2.0 Hz), 6.55 (d, 1H, J = 2.0 Hz), 7.09−7.19 (m, 2H), 7.36−7.42 (m, 3H), 7.46−7.52 (m, 2H), and 7.64−7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.9, 45.1, 45.2, 47.1, 52.4, 53.0, 102.2,

112.7, 114.1, 118.9, 123.4, 123.5, 125.3, 126.8, 128.4, 129.3, 132.6, 133.6, 135.6, 136.3, 139.7, 154.4, 171.7, and 175.6. Anal. Calcd for $C_{26}H_{24}N_2O_7S$: C, 61.41; H, 4.76; N, 5.51. Found: C, 60.97; H, 4.83; N, 5.30.

{2-[1-Benzenesulfonyl-2-(2,5-dioxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indol-3-yl]ethyl}furan-2-ylcarbamic Acid *tert*-Butyl Ester (16). To a solution of 2.6 g (3.4 mmol) of stannane **13** in 4.0 mL of DMF under argon was added a solution of 0.9 g (3.7 mmol) of 3-bromo-1-phenylpyrrole-2,5-dione[49] in 3.0 mL of DMF followed by 0.2 g (0.2 mmol) of $Pd(PPh_3)_4$ and 0.13 g (0.7 mmol) of CuI. The reaction mixture was stirred at room temperature for 0.5 h, diluted with 60 mL of ether, and filtered over a pad of Celite. The filtrate was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (10% EtOAc in hexane) to provide 1.6 g (76%) of **16** as a pale yellow oil: IR (neat) 1721, 1603, 1393, 1367, and 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 3.04 (t, 2H, J = 7.8 Hz), 3.76 (brs, 2H), 5.90 (brs, 1H), 6.32 (s, 1H), 6.86 (brs, 1H), 7.13 (d, 1H, J = 1.2 Hz), 7.29 (t, 1H, J = 7.6 Hz), 7.35−7.41 (m, 5H), 7.46−7.51 (m, 4H), 7.57 (d, 1H, J = 8.0 Hz), 7.69−7.71 (m, 2H), and 8.04 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 28.3, 48.2, 82.0, 100.2, 111.5, 115.8, 120.4, 124.7, 125.5, 126.4, 127.0, 127.1, 128.0, 128.8, 129.3, 130.7, 130.9, 131.8, 134.2, 135.2, 137.2, 137.9, 138.7, 148.5, 153.5, 168.3 and 168.9; HRMS calcd for $C_{35}H_{31}N_3O_7SLi$ 644.2043, found 644.2048.

6,7-(1-Benzenesulfonyl-1*H*-indol-2,3-yl)-2,3-(furan-2,3-yl)-4,5-(1-phenylpyrrolidine-2,5-dion-3,4-yl)-1-azacyclononane (17). A solution of 0.5 g (0.8 mmol) of indole **16** in 4 mL of toluene was heated in a sealed pressure tube under argon at 200 °C for 6 h, and the tube was opened after cooling in dry ice. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography (10% EtOAc in hexane) to provide 0.18 g (45%) of **17** as a pale yellow solid: mp 187−189°C; IR (neat) 1715, 1385, 1359, and 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.69−2.77 (m, 1H), 2.85 (brs, 1H), 3.03−3.10 (m, 2H), 3.67−3.70 (m, 1H), 4.49 (d, 1H, J = 6.8 Hz), 4.98 (brs, 1H), 6.47 (d, 1H, J = 2.0 Hz), 7.16 (d, 1H, J = 2.0 Hz), 7.25−7.28 (m, 2H), 7.40−7.57 (m, 9H), 7.69−7.71 (m, 1H), and 7.97−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 45.2, 47.7, 48.7, 108.5, 110.8, 114.8, 119.1, 124.0, 124.2, 125.8, 127.3, 127.5, 128.9, 129.0, 129.4, 129.5, 131.8, 132.6, 134.2, 136.7, 137.9, 138.8, 151.6, 174.2, and 174.8; HRMS calcd for $C_{30}H_{23}N_3O_5S$ 537.1358, found 537.1359.

***N*-Furan-2-yl-2-(2-vinylphenyl)acetamide.** To a solution of 0.36 g (2.0 mmol) of furan-2-yl carbamic acid *tert*-butyl ester in 5 mL of THF at 0 °C was added dropwise 0.9 mL (2.2 mmol) of *n*-BuLi (2.5 M). The reaction mixture was stirred for 10 min at 0 °C. To a solution of 0.3 g (2.0 mmol) of (2-vinylphenyl)-acetic acid[50] in 5 mL of THF at 0 °C was added 0.3 mL (2.4 mmol) of *N*-methylmorpholine followed by the dropwise addition of 0.3 mL (2.2 mmol) of isobutyl chloroformate. After stirring for 5 min, the reaction mixture was filtered through a short path of Celite and washed with 2 mL of THF. The filtrate was cooled to 0 °, and the preformed 2-amidofuran lithiate was added dropwise via syringe. After stirring at 0 °C for an additional 10 min, the reaction was quenched with H_2O and extracted with EtOAc. The combined organic extracts were washed with H_2O, brine and dried over $MgSO_4$. After removing the solvent under reduced pressure, the resultant residue was dissolved into 5 mL of CH_3CN, and this was followed by the addition of 0.2 g (0.1 mmol) of magnesium perchlorate. The solution was heated to 50 °C for 2.5 h and then cooled to rt and quenched with H_2O. After extracting with EtOAc, the combined organic layer was washed with H_2O, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.25 g (40%) of the titled compound as a white solid: mp 115−116 °C; IR (neat) 3203, 1661, and 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 2H), 5.38 (dd, 1H, J = 10.8 and 0.8 Hz), 5.71 (dd, 1H, J = 17.2 and 0.8 Hz), 6.31 (m, 2H), 6.92 (dd, 1H, J = 17.2 and 10.8 Hz), 6.98 (dd, 1H, 2.0 and 1.2 Hz), 7.30 (m, 3H), and 7.58 (m, 2H); ^{13}C NMR (CDCl3, 100 MHz) δ 41.7, 95.7, 111.7, 117.9, 126.9, 128.7, 128.8, 131.1, 131.3, 133.7, 135.6, 137.9, 145.1, and 167.4; HRMS calcd for $[(C_{14}H_{13}NO_2) + Li]^+$ 234.1106, found 234.1098.

***N*-Furan-2-yl-*N*-(2-methylallyl)-2-(2-vinylphenyl)acetamide (19).** To a solution of 0.1 g (0.3 mmol) of the above furanyl amide in 2 mL of DMF at 0 °C was added 15 mg (0.36 mmol) of NaH (60% dispersion in mineral oil). After stirring for 10 min, the mixture was warmed to room temperature and stirred for an additional 30 min, and this was followed by the addition of 0.05 mL (0.45 mmol) of 2- bromo-2-methylpropene. The mixture was allowed to stir for 30 min, then quenched with H_2O and extracted with EtOAc. The organic layer was washed with H2O, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was subjected to flash silica gel chromatography (7% EtOAc in hexane) to give 0.09 g (80%) of **19** as a pale yellow oil: IR (neat) 2971, 2919, 1686, and 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 3H), 3.61 (s, 2H), 4.20 (s, 2H), 4.77 (s, 1H), 4.83 (s, 1H), 5.28 (dd, 1H, J = 11.2 and 1.2 Hz), 5.60 (dd, 1H, J = 17.6 and 1.2 Hz), 6.07 (dd, 1H, J = 3.2 and 0.8 Hz), 6.38 (dd, 1H, J = 3.2 and 2.0 Hz), 6.80 (dd, 1H, J = 17.6 and 11.2 Hz), 7.07 (dd, 1H, J = 6.8 and 1.6 Hz), 7.20 (m, 2H), 7.28 (dd, 1H, J = 2.0 and 0.8 Hz) and 7.47 (dd, 1H, 7.2 and 2.0 Hz); ^{13}C NMR (CDCl3, 100 MHz) δ 20.3, 38.7, 54.4, 105.1, 111.4, 113.3, 116.4, 126.2, 127.5, 127.9, 130.6, 132.8, 134.7, 137.5, 140.4, 140.8, 148.5, and 172.0; HRMS calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1418.

5-(2-Methylallyl)-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (20). A solution of 0.08 g (0.2 mmol) of acetamide **19** in 2 mL of toluene was heated at 200 °C in a sealed pressure vessel for 36 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and was subjected to flash silica gel chromato-graphy to give 0.066 g (82%) of **20** as a white solid: mp 82−83 °C; IR (neat) 2965, 1671, 1440, 1375, and 763 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.40 (s, 3H), 3.48 (d, 1H, J = 12.0 Hz), 3.60 (d, 1H, J = 12.0 Hz), 4.23 (d, 1H, J = 16.8 Hz), 4.54 (d, 1H, J = 16.8 Hz), 4.56 (d, 1H, J = 1.2 Hz), 4.70 (d, 1H, J = 1.2 Hz), 7.30 (dt, 1H, J = 7.8 and 1.8 Hz), 7.38−7.44 (m, 5H), and 7.57−7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.0, 42.4, 53.7, 111.9, 123.3, 125.7, 127.9, 128.0, 128.1, 128.5, 128.9, 130.3, 134.8, 135.7, 136.7, 140.6, 140.8, and 171.1; HRMS calcd for $C_{18}H_{17}ON$ 263.1310, found 263.1299.

2-Diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic Acid Ethyl Ester (24). To a 1.6 g (9.4 mmol) sample of 3-ethyl-2-oxopiperidine-3-carboxylic acid[26] in 20 mL of CH_2Cl_2 was added 1.8 g (11 mmol) of 1,1′-carbonyldiimidazole, and the solution was allowed to stir at rt under an argon atmosphere for 12 h. The resulting mixture was added dropwise to a solution of 1.8 g (14 mmol) of hydrogen ethyl malonate and 22 mL (44 mmol) of 2 M isopropylmagnesium chloride in 75 mL of THF at rt. The mixture was stirred at rt for 12 h, and then 30 mL of 1 N HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether. 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 (10% EtOAc in hexane) to give 1.3 g (61%) of 3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester as a yellow oil: IR (neat) 1742, 1701, 1655, and 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.26 (t, 3H, J = 7.2 Hz), 1.47−1.99 (m, 5H), 2.42−2.49 (m, 1H), 3.28−3.31 (m, 2H), 3.71 (d, 1H, J = 16.4 Hz), 3.88 (d, 1H, J = 16.4 Hz), 4.14−4.20 (m, 2H) and 6.09 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 14.3, 20.0, 26.7, 29.6, 42.8, 45.5, 60.7, 61.4, 168.0, 171.6, and 202.0.

To a 0.91 g (4 mmol) sample of the above ester in acetonitrile (35 mL) was added 0.49 g (4.8 mmol) of triethylamine, and the solution was vigorously stirred for 30 min. To this mixture was added 0.91 g (8 mmol) of mesyl azide and the solution

was stirred at 25 °C for 10 h. The solution was concentrated under reduced pressure and recrystallized from hexane/ether to give 0.77 g (76%) of the titled compound as a pale yellow solid: mp 100−101°C; IR (neat) 2134, 1720, 1669, 1480, 1318 and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.70 (m, 1H), 1.80 (m, 1H), 2.05 (s, 3H), 2.25 (dt, 1H, J = 13.0 and 4.4 Hz), 3.30 (m, 1H), 3.64 (dt, 1H, J = 11.7 and 4.5 Hz), 4.22 (q, 2H, J = 7.2 Hz), and 5.59 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 14.5, 18.9, 28.68, 28.71, 42.6, 57.6, 61.3, 76.6, 161.3, 173.0 and 191.5. Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.98; H, 6.45; N, 15.86.

2-Diazo-3-[3-ethyl-2-oxo-1-(2-vinylbenzoyl)piperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (27). A 0.25 g (3.4 mmol) sample of 2-vinylbenzoic acid[51] was dissolved in CH_2Cl_2 (10 mL), and 1.28 g (10.1 mmol) of oxalyl chloride was added dropwise. The mixture was stirred for 1 h, concentrated under reduced pressure, and dissolved in THF (10 mL). This solution was added dropwise over 1 h to a vigorously stirred mixture containing 0.45 g (3.4 mmol) of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and 3 g of 4 Å molecular sieves in THF (10 mL). After stirring for 8 h, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.94 g (70%) of **27** as a clear oil: IR (neat) 2136, 1711, 1680, 1327, 1260, 1178, and 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.75 (m, 1H), 2.05 (m, 4H), 2.29 (m, 1H), 3.90 (m, 1H), 4.20 (m, 3H), 5.26 (dd, 1H, J = 11.2 and 0.8 Hz), 5.70 (dd, 1H, J = 17.4 and 0.8 Hz), 7.76 (dd, 1H, J = 17.4 and 11.2 Hz), 7.11 (m, 1H), 7.20 (m, 1H), 7.32 (m, 1H), and 7.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.5, 19.4, 28.1, 30.7, 45.1, 59.7, 61.6, 76.0, 116.4, 125.2, 126.0, 127.2, 129.3, 134.4, 134.8, 161.6, 172.5, 174.1 and 190.3.

9-Aza-13-(ethoxycarbonyl)-16-oxa-8,14-dioxopentacyclo[13.2.1.0^{2,7}.0^{9,17}.0^{13,14}]-octadeca-2(3),4,5-triene-15-ethyl Ester (28). To an argon-filled round-bottom flask containing 0.08 g (0.2 mmol) of diazo amide **27** in benzene (10 mL) was added 4 mg (5 mol %) of dirhodium(II) tetraacetate. After stirring for 18 h, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.07 g (95%) of **28** as a white solid: mp 221−223 °C; IR (neat) 1767, 1742, 1700, and 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, 3H, J = 7.2 Hz), 1.31 (t, 3H, J = 7.2 Hz), 1.72 (m, 3H), 1.95 (m, 3H), 2.53 (dd, 1H, J = 13.6 and 4.8 Hz), 2.81 (dd, 1H, J = 13.6 and 9.2 Hz), 3.27 (dt, 1H, J = 13.2 and 4.0 Hz), 3.82 (m, 1H), 4.29 (m, 2H), 4.58 (m, 1H), 7.14 (m, 1H), 7.37 (m, 1H), 7.54 (m, 1H), and 8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 14.3, 18.5, 24.3, 37.0, 38.1, 40.5, 50.2, 62.4, 85.6, 96.6, 125.6, 127.1, 127.4, 128.9, 133.4, 139.6, 164.7, 165.2, and 207.6. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.07; H, 6.34; N, 3.64.

2-Diazo-3-[3-ethyl-1-(1-methyl-2-vinyl-1*H*-indole-3-carbonyl)-2-oxopiperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (29). A 0.4 g sample (2 mmol) of 1-methyl-2-vinylindole-3-carboxylic acid[52] was dissolved in CH_2Cl_2 (20 mL). To this solution was added oxalyl chloride (0.7 mL, 7 mmol) dropwise, and the solution was stirred for 30 min, concentrated under reduced pressure, and dissolved in THF (10 mL). This solution was added dropwise over 1 h to a vigorously stirred mixture of 0.56 g (3.4 mmol) of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and triethylamine (0.61 g, 0.84 mL) in THF (10 mL). After stirring for 8 h, the solvent was removed under reduced pressure and the residue was dissolved in ether, washed with sodium bicarbonate, basified to pH 10 with 10% NaOH, and washed with brine. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (25% EtOAc in hexane) to give 0.66 g (73%) of **29** as a white solid: mp 139−142 °C; IR (neat) 2130, 1716, 1700, 1680, and 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, 3H, J = 7.2 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.78 (m, 1H), 2.15 (m, 2H), 2.30 (dt, 1H, J = 5.4 and 4.4 Hz), 3.70 (s, 1H), 4.00 (m, 1H), 4.20 (m, 3H), 5.60 (dd, 1H, J = 13.8 and 1.2 Hz), 5.70 (dd, 1H, J = 11.6 and 1.2 Hz), 6.90 (dd, 1H, J = 13.8 and 11.6 Hz), 7.10 (m, 1H), 7.20 (m, 1H), 7.25 (m, 1H), and 7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.5, 19.6, 28.3, 30.3, 30.9, 46.3, 59.8, 61.5, 75.8, 109.7, 119.7, 121.2, 122.1, 122.9, 125.6, 137.1, 139.1, 161.4, 170.9, 172.2, and 190.8. Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 64.05; H, 5.88; N, 12.49.

3*a*-Ethyl-2,12*c*-epoxy-12*c*-methyl-3,7-dioxo-1,2,3a,4,5,6,-7,12,12b,12c-decahydro-3*H*-6a,12-diazaindeno[2,1-*a*]-phenalene-2-carboxylic Acid Ethyl Ester (31). A 0.07 g (0.15 mmol) sample of the above diazo amide **29** was dissolved in benzene (5 mL). Rhodium(II) acetate (6 mg) was added and the solution was stirred for 3 days at room temperature. The solution was filtered through a pad of Celite with ether (5 mL). The mixture was concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to give 0.06 g of **31** as a white solid in 92% yield: IR (neat) 1767, 1736, 1654, 1490, 1475, and 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.2 Hz), 1.70 (m, 3H), 1.90 (m, 3H), 2.40 (m, 1H), 2.75 (m, 1H), 3.20 (m, 1H), 3.65 (s, 1H), 3.90 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 4.50 (m, 1H), 7.20 (m, 3H), and 8.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2, 14.3, 18.7, 24.1, 24.5, 30.9, 34.2, 35.8, 39.7, 50.9, 62.5, 85.1, 99.0, 103.5, 109.3, 121.6, 122.4, 123.1, 125.3, 137.8, 143.0, 164.9, 165.2, and 208.0.

3*a*-Ethyl-2-hydroxy-12-methyl-3,7-dioxo-1,2,3*a*,4,5,6,7,-12-octahydro-3*H*-6*a*,12-diaza-indeno[2,1-*a*]phenalene-2-carboxylic Acid Ethyl Ester (32). A 0.06 g (0.14 mmol) sample of cycloadduct **31** was heated at reflux in ether for 5 min. The mixture was allowed to cool and was stored at 0 °C for 10 h. The solution was concentrated under reduced pressure, and the crude material was purified by flash column chromatography on silica gel (4% methanol in CH_2Cl_2) to give pyridone **32** in 90% yield: mp 252−255 °C; IR (neat) 1767, 1721, 1629, and 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz), 2.10 (m, 6H), 3.77 (d, 1H, J = 16.0 Hz), 3.85 (d, 1H, J = 16.0 Hz), 3.98 (m, 1H), 4.05 (s, 3H), 4.10−4.20 (m, 1H), 4.37 (dq, 1H, J = 10.8 and 7.2 Hz), 4.47 (dq, 1H, J = 10.8 and 7.2 Hz), 7.25 (m, 3H), and 8.40 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 14.3, 19.2, 28.2, 31.2, 32.1, 33.4, 42.0, 52.1, 63.4, 75.6, 100.2, 107.4, 108.7, 121.8, 122.1, 124.3, 124.6, 140.3, 140.9, 143.5, 160.2, 171.5, and 205.4. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.41; H, 6.50; N, 6.34.

(2-Bromo-1-methyl-1*H*-indol-3-yl)acetic Acid Ethyl Ester. A sample of (2-bromo-1*H*-indol-3-yl)-acetic acid ethyl ester[53] (1.7 g, 6 mmol) was taken up in acetonitrile (15 mL) and then 60% sodium hydride (0.24 g, 6 mmol) was added. The reaction mixture was stirred for 5 min and methyl iodide (1 g, 7.2 mmol) was added in one portion and the solution was stirred for 2 h. The mixture was diluted with water and the aqueous layer was taken up in EtOAc. The organic phase was collected and washed with sodium bicarbonate and brine. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10%

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EtOAc in hexane) to give 1.7 g (97%) of the titled compound as a white solid: mp 49−51 °C; IR (neat) 1731, 1470, 1373, 1337, and 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 3.77 (s, 3H), 3.79 (s, 1H), 4.18 (q, 4H, J = 7.2 Hz), 7.15 (m, 1H), 7.23 (m, 1H), 7.29 (m, 1H), and 7.57 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 31.7, 31.8, 61.0, 107.8, 109.5, 115.0, 118.6, 120.1, 122.2, 127.2, 137.0, and 171.2.

(1-Methyl-2-vinyl-1*H*-indol-3-yl)acetic Acid Ethyl Ester. A 2.5 g sample of the above indole (8.5 mmol) together with tributylvinyl tin (5 g, 15 mmol), tetrabutylammonium bromide (3.3 g, 10.2 mmol), bis(triphenylphosphine)palladium-(II) chloride (0.3 g, 0.42 mmol, 5 mol %) was taken up in DMF (30 mL) in a 60 mL microwave vessel. The solution was subjected to microwave irradiation at 100 W for 25 min. The resulting mixture was diluted with water and extracted with in EtOAc. The organic layer was collected and washed with sodium bicarbonate and brine. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 1.45 g (70%) of the titled compound as a clear oil: IR (neat) 1731, 1469, 1366, and 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 3.72 (s, 2H), 3.82 (s, 2H), 4.15 (q, 2H, J = 7.2 Hz), 5.60 (dd, 1H, J = 11.5 and 1.4 Hz), 5.75 (dd, 1H, J = 17.6 and 1.4 Hz), 6.79 (dd, 1H, J = 17.6 and 11.5 Hz), 7.11 (m, 1H), 7.23 (m, 2H), and 7.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 30.7, 31.6, 60.9, 106.2, 109.3, 119.3, 119.7, 120.2, 122.4, 125.7, 127.9, 136.3, 137.2, and 172.3.

2-Diazo-3-{3-ethyl-1-[2-(1-methyl-2-vinyl-1*H*-indol-3-yl)acetyl]-2-oxopiperidin-3-yl}-3-oxopropionic Acid Ethyl Ester (33). A 0.6 g (2.4 mmol) sample of the above 2-vinylindole-3-acetic acid ethyl ester and 85% potassium hydroxide pellets (12 mmol) in ethanol (50 mL) were stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in water. The solution was washed with ether and acidified to pH 2. The aqueous phase was extracted with EtOAc, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A 0.1 g (0.46 mmol) sample of the crude indole acetic acid and 0.1 g (0.48 mmol) of phosphorus pentachloride were combined in anhydrous ether (2.5 mL) at 0 °C under argon, and the mixture was stirred for 30 min until all the solid had dissolved. The solvent was concentrated under reduced pressure, and cold hexane (6 mL) was added. The solution was rapidly filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in THF (5 mL), and this solution was added dropwise over 1 h to a vigorously stirred mixture of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester (0.46 mmol) and 4 Å molecular sieves (2 g) in THF (10 mL). After stirring for 8 h, the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give 0.13 g (60%) of **33** as a white solid: mp 112−115 °C; IR (neat) 2131, 1711, 1682, 1311, and 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.29 (t, 3H, J = 7.2 Hz), 1.72 (m, 1H), 1.90 (m, 3H), 2.25 (m, 1H), 3.72 (s, 3H), 3.75 (m, 1H), 4.15 (m, 1H), 4.23 (m, 2H), 4.32 (s, 2H), 5.50 (m, 2H), 6.75 (dd, 1H, J = 18.2 and 11.4 Hz), 7.06 (m, 1H), 7.18 (m, 1H), 7.25 (m, 1H), and 7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 14.5, 19.6, 28.1, 30.0, 30.8, 35.9, 44.6, 60.1, 61.7, 76.0, 107.8, 109.3, 118.9, 119.3, 122.3, 126.2, 128.0, 136.1, 137.4, 161.5, 174.0, 176.8 and 190.8. Anal. Calcd for $C_{25}H_{28}N_4O_5$: C, 64.64; H, 6.08; N, 12.06. Found: C, 64.44; H, 5.88; N, 11.84.

3a-Ethyl-5,12b-epoxy-6-trimethyl-4,12-dioxo-5a-vinyl-2,3,3a,4,5,5a,6,11,12,12b-decahydro-1*H*-6,12a-diazaindeno-[7,1-*cd*]fluorene-5-carboxylic Acid Ethyl Ester (34). A 0.01 g (0.021 mmol) sample of diazo amide **33** was stirred with rhodium(II) acetate (1 mg) in toluene (4 mL) in a 10 mL microwave vessel. The mixture was heated at 100 °C (125 W) for 15 min. At the end of this time, the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography on silica gel (25% EtOAc in hexane) to give 0.009 g (95%) of **34** as a clear oil: IR (neat) 1775, 1726, 1598, 1496, 1358, and 1291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.49 (m, 1H), 0.76 (t, 3H, J = 7.2 Hz), 0.84 (m, 1H), 1.36 (t, 3H, J = 7.2 Hz), 1.59 (m, 2H), 1.77 (m, 1H), 1.95 (m, 2H), 2.44 (d, 1H, J = 17.5 Hz), 3.01 (s, 3H), 3.08 (dd, 1H, J = 17.5 and 0.4 Hz), 3.22 (dt, 1H, J = 13.0 and 4.8 Hz), 3.90 (dd, 1H, J = 5.6 and 1.6 Hz), 4.37 (dq, 2H, J = 7.2 and 1.6 Hz), 5.08 (d, 1H, J = 17.6 Hz), 5.41 (d, 1H, J = 11.6 Hz), 5.66 (dd, 1H, J = 17.6 and 11.6 Hz), 6.35 (d, 1H, J = 7.6 Hz), 6.61 (dt, 1H, J = 7.6 and 0.8 Hz), 6.89 (dd, 1H, J = 7.6 and 0.8 Hz), and 7.19 (dt, 1H, J = 7.6 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.28, 14.4, 17.9, 25.1, 30.1, 39.1, 41.7, 51.4, 62.5, 65.7, 85.0, 95.5, 103.1, 105.3, 117.2, 118.9, 124.0, 126.2, 130.6, 132.8, 151.6, 164.8, 176.8, and 205.1.

2-(1-Benzenesulfonyl-3-{2-[3-(2-diazo-2-ethoxycarbonylacetyl)-3-ethyl-2-oxopiperidin-1-yl]-2-oxoethyl}-1*H*-indol-2-yl)acrylic Acid Methyl Ester (35). To a solution of 0.34 g (0.87 mmol) of 2-[1-benzenesulfonyl-3-(2-hydroxyethyl)-1*H*-indol-2-yl]acrylic acid methyl ester in 7 mL of acetone at 0 °C was added dropwise 2.2 mL (2.2 mmol) of Jones' reagent (1.0 M). The reaction mixture was allowed to stir at rt for an additional 2 h. To this mixture was added isopropyl alcohol until the reaction mixture turned from a brown to a green color indicative of quenching the excess Jones' reagent. After filtering through a layer of Celite, the filtrate was concentrated and extracted with EtOAc. The combined organic layers were washed with H_2O and brine and dried over MgSO4. Removal of the solvent under reduced pressure left a solid residue which was dissolved in 20 mL of ether. To this solution was added 0.22 g (1.0 mmol) of phosphorus pentachloride at 0 °C. The reaction mixture was allowed to stir for 2 h at rt and was then filtered through a pad of Celite. After removing the solvent under reduced pressure, the residue was taken up in 15 mL of THF. This solution was added dropwise over 1 h to a vigorously stirred mixture of 0.26 g (0.96 mmol) of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and 4 Å molecular sieves (1 g) in 20 mL of THF. After stirring for 20 h, the mixture was filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give 0.35 g (62%) of **35** as a white solid: mp 134−136 °C; IR (neat) 2139, 1711, 1704, 1700, 1651, 1447, and 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.27 (t, 3H, J = 7.2 Hz), 1.72 (m, 1H), 1.84−2.08 (m, 4H), 2.21 (dt, 1H, J = 12.4 and 5.2 Hz), 3.60−3.74 (m, 1H), 3.77 (s, 1H), 3.82−4.38 (m, 3H), 4.20 (q, 2H, J = 7.2 Hz), 5.77 (br s, 1H), 6.66 (d, 1H, J = 1.6 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.24−7.38 (m, 4H), 7.45 (t, 1H, J = 7.6 Hz), 7.67 (d, 2H, J = 7.6 Hz), and 8.08 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 14.5, 19.4, 28.2, 29.7, 31.8, 44.5, 52.6, 60.0, 61.7, 76.0, 115.0, 118.9, 123.9, 125.6, 126.8, 129.2, 130.4, 130.9, 133.1, 133.9, 136.3, 138.5, 161.6, 166.2, 174.1, 174.6, and 190.3. Anal. Calcd for $C_{32}H_{32}N_4O_9S$: C, 59.25; H, 4.91; N, 8.64. Found: C, 59.18; H, 4.96; N, 8.64.

Rh(II)-Catalyzed Cycloaddition of 2-(1-Benzenesulfonyl-3-{2-[3-(2-diazo-2-ethoxycarbonylacetyl)-3-ethyl-2-oxopiperidin-1-yl]-2-oxoethyl}-1*H*-indol-2-yl)acrylic Acid Methyl Ester (36). A 10 mL microwave vessel was charged with 4 Å molecular sieves (1 g) and 2.7 mg of rhodium(II) acetate. The mixture was heated at 100 °C for 10 min and flushed with argon. A 0.04 g (0.062 mmol) sample of diazo amide **35** dissolved in 4 mL of benzene was syringed into the vessel, and the mixture was heated at 90 °C for 2 h (150 W) in a microwave reactor. At the end of this time, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was recrystallized from CH_2Cl_2−pentane to give 0.035 g (91%) of cycloadduct **36** as a white solid: mp 240−244 °C; IR (neat) 1768, 1732, 1718, 1702,

1367, and 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (d, 1H, J = 15.0 Hz), 0.83 (t, 3H, J = 7.2 Hz), 0.87−1.08 (m, 2H), 1.31 (t, 3H, J = 7.2 Hz), 1.46−1.57 (m, 1H), 1.63−1.76 (m, 1H), 1.80−1.92 (m, 2H), 2.72 (d, 1H, J = 15.0 Hz), 3.11 (dt, 1H, J = 12.8 and 2.8 Hz), 3.28 (d, 1H, J = 17.2 Hz), 3.44 (d, 1H, J = 17.2 Hz), 3.85−3.93 (m, 1H), 4.20−4.30 (m, 2H), 6.98−7.06 (m, 2H), 7.30−7.39 (m, 3H), 7.50−7.59 (m, 3H) and 7.78 (d, 1H, J = 5.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 8.2, 14.2, 18.0, 22.5, 24.5, 36.4, 38.5, 44.4, 50.0, 52.7, 61.9, 63.1, 83.7, 99.0, 119.1, 122.9, 123.7, 126.3, 127.9, 128.5, 129.3, 129.4, 134.6, 134.7, 137.1, 138.9, 143.0, 166.4, 169.1, 174.0, and 209.9; HRMS (FAB) calcd for $C_{32}H_{32}N_2O_9S$ (M + Li) 627.1989, found 627.1959. Anal. Calcd for $C_{32}H_{32}N_2O_9S$: C, 61.92; H, 5.20; N, 4.51. Found: C, 61.75; H, 5.19; N, 4.47.

3-[1-(2-Benzofuran-3-yl-acetyl)-3-ethyl-2-oxopiperidin-3-yl]-2-diazo-3-oxopropionic Acid Ethyl Ester (37). Benzofuran-3-acetic acid ethyl ester[54] (0.6 g, 2.4 mmol) and 85% potassium hydroxide pellets (12 mmol) in ethanol (50 mL) were stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in water. The solution was washed with ether and acidified to pH 2. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A 0.21 g (1 mmol) sample of benzofuran-3-yl-acetic acid was dissolved in CH_2Cl_2 (10 mL) and oxalyl chloride (0.3 mL, 3.5 mmol) was added followed by two drops of DMF. The solution was stirred for 1 h at rt, concentrated under reduced pressure, and dissolved in THF (5 mL). This solution was added dropwise over 1 h to 0.25 g (1 mmol) of a vigorously stirred mixture of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and 4 Å molecular sieves (3 g) in THF (10 mL). After stirring for 8 h, the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.37 g (86%) of **37** as a white solid: mp 102−104 °C; IR (neat) 2141, 1705, 1690, 1650, 1450, 1368, 1316 and 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.70−1.80 (m, 1H), 1.80−2.10 (m, 4H), 2.25 (dt, 1H, J = 12.8 and 4.8 Hz), 3.74 (dt, 1H, J = 12.8 and 4.8 Hz), 4.15−4.30 (m, 5H), 7.21−7.31 (m, 2H), 7.65 (d, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 8.0 Hz), and 7.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 14.5, 19.4, 28.2, 29.8, 34.5, 44.5, 60.1, 61.8, 76.0, 111.6, 114.1, 120.0, 122.7, 124.4, 128.3, 143.4, 155.2, 161.6, 174.0, 174.6, and 190.6. Anal. Calcd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.10; H, 5.54; N, 9.71.

3a-Ethyl-5,12b-epoxy-4,12-dioxo-2,3,3a,5,5a,11,12,12b-octahydro-1*H*,4*H*-6-oxa-12a-azaindeno[7, 1-*cd*]fluorene-5-carboxylic Acid Ethyl Ester (38). A 10 mL microwave reactor was charged with 4 Å molecular sieves (1 g) and 4 mg of rhodium(II) pivalate. The container was heated at 100 °C for 10 min and flushed with argon. A 0.05 g (0.117 mmol) sample of the above diazo amide **37** dissolved in benzene (4 mL) was syringed into the vessel and the mixture was heated in the microwave apparatus for 2 h at 70 °C (120 W). The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.045 g (90%) of cycloadduct **38** as a white solid: mp 185−187 °C; IR (neat) 1772, 1731, 1730, 1598, 1480, 1455, 1358, 1315, 1265 and 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24−0.34 (m, 1H), 0.78 (t, 3H, J = 7.2 Hz), 0.83−0.91 (m, 1H), 1.40 (t, 3H, J = 7.2 Hz), 1.52−2.12 (m, 4H), 2.86 (d, 1H, J = 17.6 Hz), 3.10 (d, 1H, J = 17.6 Hz), 3.22 (dt, 1H, J = 12.8 and 4.4 Hz), 3.91 (dt, 1H, J = 13.2 and 5.6 Hz), 4.36−4.50 (m, 2H), 5.39 (s, 1H), 6.86−6.96 (m, 2H), 7.04−7.08 (m, 1H), and 7.21−7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 14.4, 17.9, 20.4, 24.8, 39.3, 43.4, 52.1, 59.3, 63.0, 90.1, 92.3, 104.8, 111.6, 122.2, 124.4, 126.3, 131.0, 160.7, 165.0, 176.4, and 204.6. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.26; H, 5.64; N, 3.42.

2-Diazo-3-[3-ethyl-1-(2-furan-3-ylacetyl)-2-oxopiperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (41). To a 0.12 g (0.93 mmol) sample of furan-3-ylacetic acid[55] dissolved in CH_2Cl_2 (10 mL) was added 0.24 mL of oxalyl chloride followed by two drops of DMF. The solution was stirred for 2 h and was concentrated under reduced pressure and dissolved in THF (10 mL). This solution was added dropwise over 1 h to a vigorously stirred mixture of 0.23 g (0.85 mmol) of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and 4 Å molecular sieves (3 g) in THF (10 mL). After stirring for 8 h, the mixture was filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.21 g (60%) of **41** as a clear oil: IR (neat) 2140, 1702, 1689, 1649, 1468, 1371, 1317, and 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.70−1.78 (m, 1H), 1.83−1.98 (m, 2H), 2.02 (q, 4H, J = 7.2 Hz), 2.25 (dt, 1H, J = 12.0 and 5.3 Hz), 3.74 (dt, 1H, J = 12.0 and 4.9 Hz), 3.92 (d, 1H, J = 17.2 Hz), 4.02 (d, 1H, J = 17.2 Hz), 4.17−4.26 (m, 3H), 6.37 (m, 1H), and 7.36−7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 14.5, 19.5, 28.2, 29.9, 35.5, 44.4, 60.2, 61.8, 112.0, 118.5, 140.9, 142.8, 161.5, 173.9, 175.3, and 190.7.

Rh(II)-Catalyzed Cycloaddition of 2-Diazo-3-[3-ethyl-1-(2-furan-3-ylacetyl)-2-oxopiperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (42). A 10 mL microwave vessel was charged with 4 Å molecular sieves (0.5 g) and rhodium(II) pivalate (4 mg, 5 mol %). The container was placed in an oven at 100 °C for 10 min. The vessel was capped and flushed with argon and 0.05 g (0.13 mmol) of furanyl diazo amide **41** dissolved in benzene (2 mL) was syringed into the vessel, and the mixture was heated in the microwave reactor for 40 min at 90 °C (140 W). The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give cycloadduct **42** (0.015 g, 35%) as a clear oil: IR (neat) 1772, 1746, 1722, 1455, 1372, 1260, and 1022 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz), 1.81−1.85 (m, 1H), 1.90−2.04 (m, 1H), 2.12−2.22 (m, 3H), 2.56 (d, 1H, J = 17.7 Hz), 2.78 (d, 1H, J = 17.7 Hz), 3.18 (dt, 1H, J = 13.0 and 4.6 Hz), 3.86 (dd, 1H, J = 13.0 and 5.1 Hz), 4.34−4.40 (m, 2H), 4.90 (d, 1H, J = 2.7 Hz), 5.04 (s, 1H), and 6.32 (d, 1H, J = 2.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.2, 14.3, 18.0, 22.9, 24.7, 38.8, 42.5, 52.4, 60.7, 62.9, 92.1, 98.3, 104.2, 104.9, 148.5, 165.3, 176.0, and 197.2; HRMS (FAB) calcd for $C_{18}H_{21}NO_6$ (M + Li) 354.1529, found 354.1523.

2-Diazo-3-[3-ethyl-2-oxo-1-(2-thiophen-3-ylacetyl)piperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (43). To a 0.14 g (1 mmol) sample of thiophen-3-ylacetic acid dissolved in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.3 mL, 3.5 mmol) followed by two drops of DMF. The solution was stirred for 1 h, concentrated under reduced pressure, and dissolved in THF (5 mL). This solution was added dropwise over 1 h to a vigorously stirred mixture of 0.25 g (1 mmol) of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester and 4 Å molecular sieves (3 g) in THF (10 mL). After stirring for 8 h, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.38 g (97%) of **43** as a yellow oil: IR (neat) 2137, 1705, 1686, 1649, 1371, 1315, and 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.70−1.78 (m, 1H), 1.80−2.10 (m, 4H), 2.25 (dt, 1H, J = 12.4 and 5.5 Hz), 3.74 (dt, 1H, J = 12.8 and 4.8 Hz), 4.10−4.30 (m, 5H), 7.01 (dd, 1H, J = 4.8 and 1.2 Hz), 7.10 (dd, 1H, J = 2.8 and 1.2 Hz), and 7.25 (dd, 1H, J = 4.8 and 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 14.5, 19.4, 28.1, 29.9, 40.2, 44.4, 60.1, 61.7, 76.0, 123.1, 125.3, 129.1, 135.0, 161.5, 173.8, 175.3, and 190.7.

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Rh(II)-Catalyzed Cycloaddition of 2-Diazo-3-[3-ethyl-2-oxo-1-(2-thiophen-3-ylacetyl)piperidin-3-yl]-3-oxopropionic Acid Ethyl Ester (44). A 10 mL microwave vessel was charged with 4 Å molecular sieves (0.5 g) and 7 mg of rhodium(II) pivalate. The mixture was heated at 100 °C for 10 min and flushed with argon. A 0.05 g (0.12 mmol) sample of the above diazo amide **43** dissolved in benzene (1.6 mL) was syringed into the vessel and the mixture was heated at 90 °C for 40 min (140 W). At the end of this time, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give 0.017 g (38%) of **44** as a clear oil: IR (neat) 1772, 1746, 1727, 1462, 1402, 1360, and 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz), 1.70−1.76 (m, 1H), 1.80 (m, 1H), 2.00−2.14 (m, 3H), 2.59 (d, 1H, J = 17.2 Hz), 2.81 (d, 1H, J = 17.2 Hz), 3.17 (dt, 1H, J = 12.8 and 4.5 Hz), 3.86 (dd, 1H, J = 12.8 and 4.8 Hz), 4.36−4.50 (dq, 2H, J = 7.2 and 1.6 Hz), 4.48 (s, 1H), 5.35 (d, 1H, J = 6.0 Hz), and 6.08 (d, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 14.3, 18.0, 21.7, 24.9, 39.1, 45.0, 52.2, 60.8, 62.9, 67.45, 91.8, 105.5, 122.2, 128.9, 165.3, 176.0 and 205.2; HRMS (FAB) calcd for $C_{18}H_{21}NO_5S$ (M + Li: 370.1300, found 370.1302.

1-Ethyl-3-(2-thiophen-3-ylacetyl)-3-azabicyclo[3.2.1]-octane-2,7-dione (45). A 10 mL microwave vessel was loaded with 4 Å molecular sieves (0.7 g) and rhodium(II) perfluorobutyrate (0.01 g, 10 mol %). The container was placed in an oven at 100 °C for 10 min and was flushed with argon. Diazo amide **43** (0.037 g, 0.094 mmol) in 2 mL of benzene was added to the tube, and the solution was subjected to microwave radiation for 45 min at 90 °C (up to 120 W). The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to give **45** as a clear oil (0.014 g) in 51% yield: IR (neat) 1750, 1697, 1459, 1382, 1245, and 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, J = 7.2 Hz), 1.73 (dt, 1H, J = 14.8 and 7.2 Hz), 2.10−2.18 (m, 2H), 2.20 (ddd, 1H, J = 12.4, 3.2 and 1.2 Hz), 2.33 (dd, 1H, J = 19.0 and 2.8 Hz), 2.57 (ddd, 1H, J = 19.0, 7.2 and 1.2 Hz), 2.93−2.98 (m, 1H), 3.71 (ddd, 1H, J = 13.0. 1.8 and 1.6 Hz), 3.84 (ddd, 1H, J = 13.0, 4.4 and 1.2 Hz), 4.20 (d, 1H, J = 16.4 Hz), 4.27 (d, 1H, J = 16.4 Hz), 7.01 (dd, 1H, J = 4.8 and 1.2 Hz), 7.10 (dd, 1H, J = 2.8 and 1.2 Hz) and 7.25 (dd, 1H, J = 4.8 and 2.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.3, 21.9, 28.5, 33.5, 40.5, 43.8, 52.8, 63.6, 123.4, 125.6, 129.0, 134.2, 168.8, 175.4, and 209.2; HRMS calcd for $C_{15}H_{17}NO_3S$ 291.09292, found 291.09334.

3-(2-Diazo-2-ethoxycarbonylacetyl)-3-ethyl-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (46). A sample of di-*tert*-butyl dicarbonate (0.11 g, 0.51 mmol) was added to a solution of 2-diazo-3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester (0.1 g, 0.4 mmol) and 4-(dimethylamino)-pyridine (0.0024 g, 0.02 mmol) in 5 mL of acetonitrile. The mixture was stirred for 12 h at 25 °C and was concentrated under reduced pressure. The crude residue was purified by flash column chromato-graphy on silica gel (20% EtOAc in hexane) to give **46** as a clear oil (0.11 g, 75% yield): IR (neat) 2137, 1767, 1714, 1652, 1315, and 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.94 (s, 9H), 1.63−1.69 (m, 1H), 1.82−1.90 (m, 1H), 1.92−2.03 (m, 2H), 2.04−2.16 (m, 1H), 2.27 (dt, 1H, J = 13.2 and 4.8 Hz), 3.78−3.92 (m, 2H), and 4.16−4.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 14.4, 19.9, 28.1, 28.2, 30.8, 46.2, 60.3, 61.6, 82.6, 154.3, 161.4, 171.9, and 191.0.

1-Ethyl-2,7-dioxo-3-azabicyclo[3.2.1]octane-3-carboxylic Acid *tert*-Butyl Ester (47). A sample of the above diazo ketoamide **46** in 2 mL of benzene together with $Rh_2(pfb)_4$ as the catalyst (5 mol %) and 4 Å molecular sieves (0.7 g) was subjected to microwave radiation at 90 °C for 45 min. After the reaction was complete, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give **47** as a clear oil (0.024 g, 66% yield): IR (neat) 1772, 1751, 1717, 1282, 1253, and 1151 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.84 (t, 3H, J = 7.2 Hz), 1.50 (s, 9H), 1.72 (dt, 1H, J = 15.0 and 7.2 Hz), 2.06 (ddd, 1H, J = 12.0, 3.0 and 1.5 Hz), 2.10−2.14 (m, 1H), 2.19 (dd, 1H, J = 12.0 and 3.0 Hz), 2.39 (dd, 1H, J = 19.0 and 2.4 Hz), 2.55 (dd, 1H, J = 19.0 and 7.8 Hz), 2.87−2.90 (m, 1H), 3.59 (dd, 1H, J = 12.5 and 1.5 Hz) and 3.85 (dd, 1H, J = 12.5 and 3.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.3, 21.9, 28.2, 28.6, 33.3, 43.7, 53.7, 63.5, 83.7, 152.8, 166.3, and 209.5; HRMS (FAB) calcd for $C_{14}H_{21}NO_4$ (M + Li) 274.1631, found 274.1634.

2-Diazo-3-(3-ethyl-2-oxo-piperidin-3-yl)-3-oxopropionic Acid Methyl Ester. To a solution of 3-(3-ethyl-2-oxopiperidin-3-yl)-3-oxopropionic acid methyl ester[26] (0.55 g, 2.4 mmol) in 35 mL of acetonitrile was added triethylamine (0.41 g, 2.9 mmol), and the mixture was vigorously stirred for 30 min. To this mixture was added mesyl azide (0.37 g, 4.8 mmol), and the resulting mixture was stirred at rt for 10 h. The solution was concentrated under reduced pressure and the white solid that precipitated was recrystallized from hexanes−ether to give the titled compound in 76% yield: mp 103−105 °C; IR (neat) 2136, 1721, 1664, 1654, 1316, and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.2 Hz), 1.78−1.88 (m, 1H), 1.89−2.16 (m, 4H), 2.25 (dt, 1H, J = 13.0 and 4.4 Hz), 3.40 (m, 1H), 3.68 (dt, 1H, J = 11.7 and 4.5 Hz), 3.80 (s, 3H) and 5.44 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 18.8, 28.4, 42.4, 52.4, 65.2, 76.6, 161.9, 173.0, and 191.1. Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.01; H, 5.94; N, 16.51.

3-(2-Diazo-2-methoxycarbonylacetyl)-3-ethyl-2-oxopiperidine-1-carboxylic Acid *tert*-Butyl Ester (48). A sample of di-*tert*-butyl dicarbonate (0.57 g, 2.6 mmol) was added to a solution of the above diazo amide (0.5 g, 2.0 mmol) and 4-(dimethylamino)pyridine (0.012 g, 0.10 mmol) in 25 mL of acetonitrile. The solution was stirred for 12 h at 25 °C, and the mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give **48** as a clear oil (0.53 g, 75% yield): IR (neat) 2134, 1764, 1720, 1654, 1317, and 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.44 (s, 9H), 1.57−1.66 (m, 1H), 1.76−1.86 (m, 1H), 1.87−2.09 (m, 3H), 2.21 (dt, 1H, J = 13.2 and 4.8 Hz), 3.72 (s, 1H) and 3.74−3.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 19.7, 27.9, 28.1, 30.6, 46.0, 52.3, 60.2, 75.9, 82.5, 154.0, 161.7, 171.8, and 190.7.

3-(1-But-3-enoyl-3-ethyl-2-oxopiperidin-3-yl)-2-diazo-3-oxopropionic Acid Ethyl Ester (52). A sample of but-3-enoyl chloride[56] (0.3 g, 2.8 mmol) in THF (10 mL) was added dropwise over 1 h to a vigorously stirred mixture of diazo amide **10** (0.6 g, 2.4 mmol) and 4 Å molecular sieves (0.5 g) in 15 mL of THF. After stirring for 8 h, the solvent was removed under reduced pressure and the residue was dissolved in ether and filtered through a fritted glass tube. Removal of the solvent left a residue which was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give **52** (0.56 g, 71% yield) as a clear oil: IR (neat) 1711, 1689, 1650, 1316, and 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.69−1.77 (m, 1H), 1.82−1.95 (m, 2H), 1.98−2.15 (m, 2H), 2.20−2.30 (m, 1H), 3.44−3.55 (m, 1H), 3.64−3.74 (m, 2H), 4.15−4.28 (m, 3H), 5.09−5.18 (m, 2H) and 5.96−6.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 14.5, 19.5, 28.3, 30.0, 44.1, 44.2, 60.2, 61.7, 75.9, 118.2, 131.8, 161.5, 173.8, 175.7, and 190.7.

6a-Ethyl-8,9b-epoxy-2,7-dioxodecahydropyrrolo[3,2,1-*ij*]quinoline-8-carboxylic Acid Ethyl Ester (53). A 10 mL microwave vessel containing 4 Å molecular sieves (0.5 g) and rhodium(II) pivaloate (0.0025 g, 5 mol %) was flushed with argon. A solution of the above diazo compound **52** (0.027 g, 0.082 mmol) dissolved in 1 mL of benzene was added to the

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vessel, and the solution was subjected to microwave radiation for 30 min. at 80 °C (up to 120 W). The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give 0.023 g (91%) of **53** as a white solid: mp 103−106 °C; IR (neat) 1769, 1746, 1722, 1372, and 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, 3H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz), 1.43−1.62 (m, 3H), 1.76−1.83 (m, 1H), 1.97−2.03 (m, 2H), 2.15−2.21 (m, 1H), 2.34−2.47 (m, 2H), 2.60−2.72 (m, 2H), 3.11 (dt, 1H, J = 13.0 and 3.9 Hz), 3.83 (m, 1H), and 4.28−4.36 (dq, 2H, J = 7.2 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.65, 14.4, 18.4, 23.0, 23.5, 34.0, 36.5, 37.2, 38.2, 48.9, 62.4, 88.8, 102.6, 165.8, 176.1, and 206.6.

3-But-3-enoyl-1-ethyl-3-azabicyclo[3.2.1]octane-2,7-dione (54). A sample of diazo ketoamide **52** was subjected to microwave radiation as described above but using rhodium(II) perfluorobutyrate as the catalyst. The mixture was then filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give two products. The major product isolated was identified as cycloadduct **53** and was obtained in 62% yield (0.015 g). The minor product was obtained as a clear oil (0.0058 g, 30% yield) and was recrystallized from ether−pentane to give **54** as a white solid: mp 76−78 °C; IR (neat) 1752, 1697, 1175, and 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 1.74 (dt, 1H, J = 14.8 and 7.2 Hz), 2.10−2.18 (m, 2H), 2.23 (ddd, 1H, J = 12.4, 3.2 and 1.2 Hz), 2.37 (dd, 1H, J = 19.0 and 3.2 Hz), 2.59 (ddd, 1H, J = 19.0, 7.2 and 1.2 Hz), 2.87−2.90 (m, 1H), 3.58−3.74 (m, 2H), 3.85 (ddd, 1H, J = 13.2, 4.4 and 1.2 Hz), 5.10−5.18 (m, 2H), and 5.91−6.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 21.9, 28.5, 33.4, 43.9, 44.5, 52.5, 63.6, 118.6, 131.0, 168.7, 175.7, and 209.3. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.22; N, 5.82.

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Supporting Information Available: Spectroscopic and experimental procedures for compounds **6**, **18**, and **21**−**23**. ^1H and ^{13}C NMR spectra for new compounds lacking elemental analyses together with an ORTEP drawing for structures **17** and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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