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Intramolecular Cycloaddition Reactions of Furo[3,4-*b*]indoles for Alkaloid Synthesis

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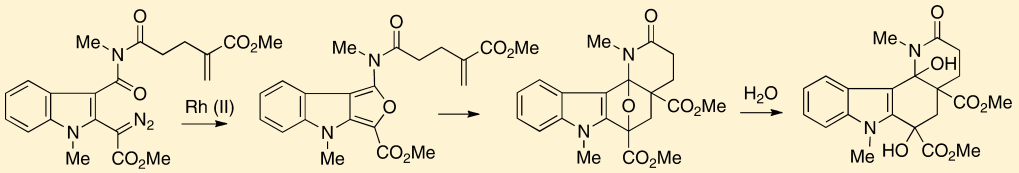
Supporting Information

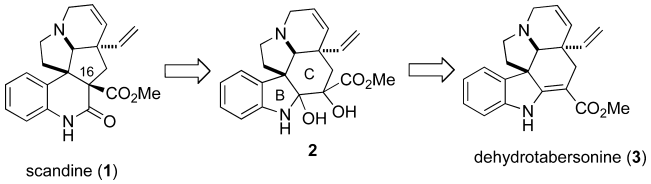


ABSTRACT: Model studies dealing with the Cu(II)- or Rh(II)-catalyzed carbenoid cyclization/cycloaddition cascade of several α-diazo indolo amido esters have been carried out as an approach to the alkaloid scandine. The Cu(II)-catalyzed reaction of an α-diazo indolo diester that contains a tethered oxa-pentenyl side chain was found to give rise to a reactive benzo[*c*]furan which undergoes a subsequent [4 + 2]-cycloaddition across the tethered π-bond. The reaction proceeds by the initial generation of a copper carbenoid intermediate which cyclizes onto the adjacent carbonyl group to give a reactive benzo[*c*]furan which in certain cases can be isolated. Disappointingly, the analogous reaction with the related amido indolo ester failed to take place, even when the tethered π-bond contained an electron-withdrawing carbomethoxy group. It would seem that the geometric requirements for the intramolecular cycloaddition of the furo[3,4-*b*]indole system with the tethered π-bond imposes distinct restrictions upon the bond angles of the reacting centers to prevent the cycloaddition reaction from occurring. However, the incorporation of another carbonyl group on the nitrogen atom of the tethered alkenyl diazo amido indolo ester seemingly provides better orbital overlap between the reacting π-systems and allows the desired cycloaddition reaction to occur.

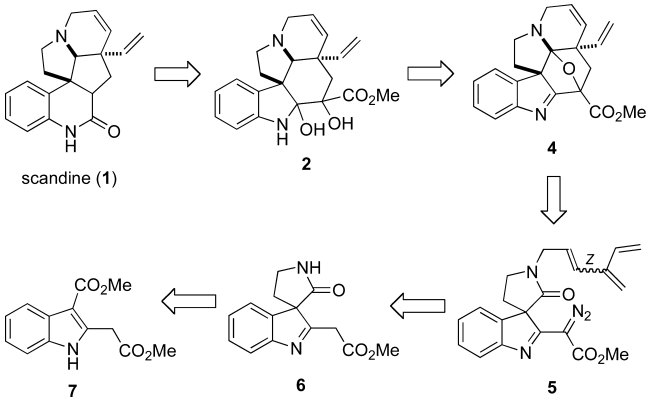
INTRODUCTION

Nitrogen-containing natural products are abundant in nature and exhibit diverse and important biological properties.[1] Accordingly, novel strategies for the stereoselective synthesis of azapolycyclic systems such the *Melodinus* alkaloids[2−4] continue to receive considerable attention in the field of synthetic organic chemistry. Although methods of preparing the melodinus alkaloids vary widely,[5−10] approaches that employ cycloaddition chemistry are particularly attractive given the rapid introduction of molecular complexity within a single chemical operation.[11] Scandine (**1**) is one of the key members of the *Melodinus* alkaloid family and was isolated from *Melodinus scandens* in 1969.[12] The highly functionalized C ring of scandine with its four stereocenters (three of which are quaternary) presents a significant synthetic challenge (Scheme 1).[5−10] The congested cyclopentane core of scandine (**1**) is thought to arise by means of a rearrangement of diol **2** by expansion of the B ring and contraction of the C ring.[12] Diol **2** is believed to be the result of an oxidative rearrangement of the aspidosperma alkaloid dehydrotabersonine (**3**).[12,13] Based on this biotransformation, we designed a total synthesis toward scandine (**1**) from diol **2** as outlined in Scheme 2. It is proposed that diol **2** could be prepared from the pentacyclic imine **4** by a reductive opening of its oxabicyclic ring followed by a hydroxylation reaction. An intramolecular metal-catalyzed carbenoid cyclization/cycloaddition reaction of pentacycle **5** should give

Scheme 1



Scheme 2



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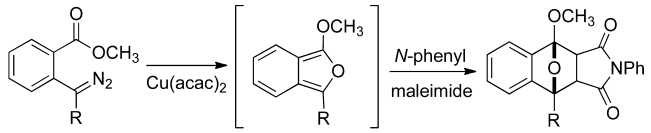
access to imine **4**. Spiro[indole-3,3′-pyrrolidin]-2′-one **6** was envisioned to arise from indole diester **7** via some standard alkylation chemistry.

In 1976, Hamaguchi and Ibata reported the first example of a related carbenoid cascade sequence (i.e., **5** to **4**).[14] These workers found that 1-methoxybenzo[*c*]furans (i.e., **9**) were generated as transient intermediates in the $Cu(acac)_2$-catalyzed decomposition of methyl diazomethylbenzoate derivatives (**8**). These highly reactive species were readily trapped with a variety of added dienophiles such as *N*-phenylmaleimide to afford bimolecular Diels–Alder cycloadducts of type **10** (Scheme 3).[15]

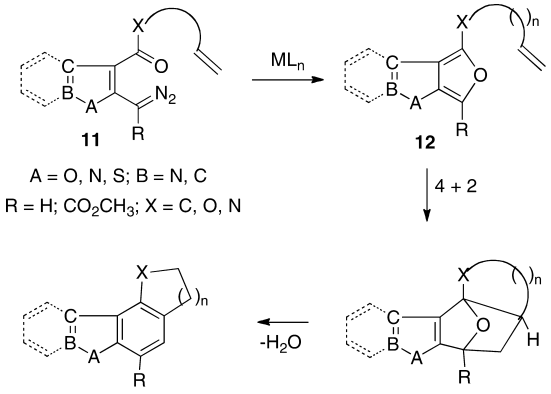
Scheme 3



8; R = H; CO_2CH_3 **9** **10**

Since the original report, quite a number of examples of this versatile reaction have been described in the literature.[16,17] In certain cases, the suspected benzo[*c*]furan **9** was isolated and characterized.[16b] In a series of publications, Friedrichsen and co-workers reported on the use of an intramolecular cycloaddition variant of the Hamaguchi–Ibata reaction as a method to prepare a number of annulated hydroquinolines.[17] His team found that the metal-catalyzed cyclization/cycloaddition reaction of α-diazo-esters of type **11** worked smoothly with thiopheno, isoxazolo, and indolo *c*-annulated furans to produce a variety of polycyclic ring systems (Scheme 4). The tethered X group

Scheme 4



11

A = O, N, S; B = N, C

R = H; CO_2CH_3; X = C, O, N

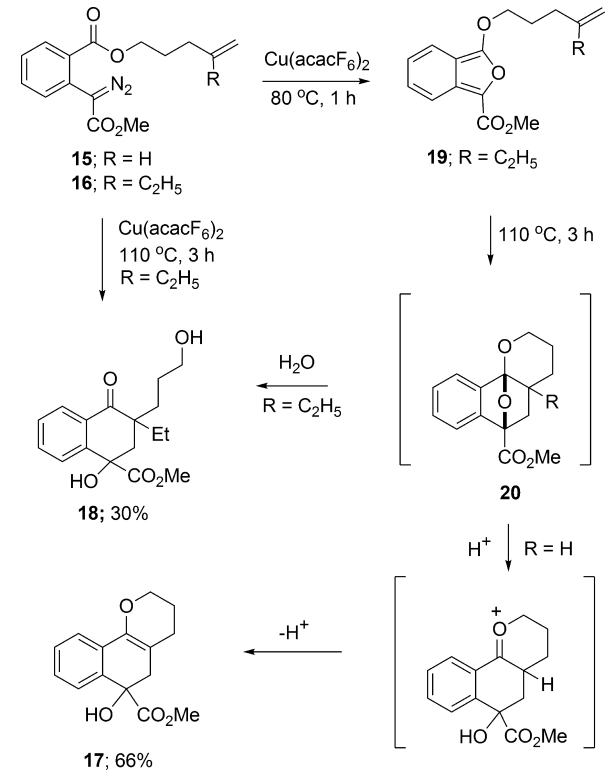
12 **13** **14**

corresponded to carbon, oxygen, or an amino-containing atom. Over a period of years, our research group has also made extensive use of the metal-catalyzed reaction of α-diazo carbonyl compounds to generate carbonyl ylide dipoles which underwent a smooth intramolecular [3 + 2]-cycloaddition reaction.[18,19] With our continuing interest in the total synthesis of pentacyclic alkaloids,[20] we wondered whether an intermediate related to **5** (Scheme 2) might undergo the Hamaguchi–Ibata reaction and thus be effectively employed for a scandine synthesis. With this in mind, we set out to examine a number of related model systems to probe whether this sequence of reactions could be employed for an eventual synthesis of scandine.

RESULTS AND DISCUSSION

For our initial investigations into the tandem process, we chose to examine the metallo-catalyzed behavior of α-diazo diester **15** which contains a tethered oxapentenyl side chain (i.e., R = H). Under a variety of experimental conditions and using several different Rh(II) catalysts with an assortment of ligand groups, we could not isolate any characterizable product. We were concerned that a competing C–H insertion of the rhodium carbenoid might be a problem with this system because of the propensity of C–H bonds proximate to ether oxygens to insert into rhodium carbenoids.[21a] Consequently, we turned our attention to the use of copper catalysts. The critical role played by the choice of the transition-metal catalyst used in carbene transfer processes is well-known.[21a] We found that when $Cu(acacF_6)_2$ hydrate[21b] was used as the catalyst (toluene reflux) with diazoester **15**, tetrahydrochromene **17** was obtained as the sole product in 66% yield (Scheme 5). The Cu(II)-catalyzed

Scheme 5



15; R = H
16; R = C_2H_5

19; R = C_2H_5

18; 30%

20

17; 66%

reaction (toluene reflux) of the closely related α-diazo diester **16** (R = C_2H_5) was also studied and found to afford dihydronaphthalen-1(2*H*)-one **18**, but in only 30% yield as the only identifiable product. When the Cu(II)-catalyzed reaction of **16** was carried out at a lower temperature (i.e., refluxing benzene), benzo[*c*]furan **19** could be isolated in modest yield. Obviously, the first step involves generation of a copper carbenoid intermediate which, after an intramolecular cyclization with the adjacent carbonyl group, yields the reactive benzo[*c*]furan **19** (R = C_2H_5). Further heating of **19** in toluene at 110 °C gave **18**. This reaction can be rationalized by a [4 + 2]-cycloaddition of **19** with the tethered alkenyl π-bond in refluxing toluene to give **21** as a transient intermediate which reacts further with some water derived perhaps from the $Cu(acacF_6)$ hydrate catalyst to produce **18**. We assume that a related cyclization reaction occurs with **15** to also afford a benzo[*c*]furan intermediate analogous to **19**,

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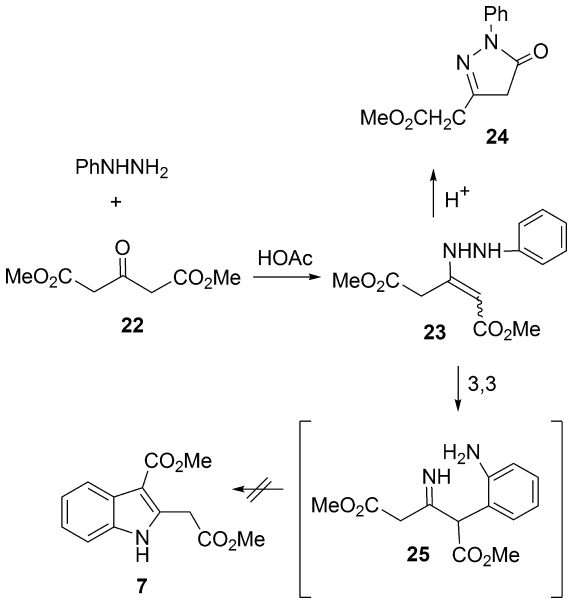
which then undergoes a subsequent Diels–Alder cycloaddition to produce **20** as a transient species. Loss of the now available bridgehead hydrogen from cycloadduct **20** leads to the formation of **17**.

Having established the facility with which the cyclization/cycloaddition cascade occurs with the simple aromatic systems of type **15**/**16**, we turned our attention to the indolo systems which would eventually be needed for a scandine synthesis. Our first efforts in this direction required the preparation of indole diester **7**. We envisioned that diester **7** could be readily synthesized from phenylhydrazine and dimethyl-1,3-acetone-dicarboxylate (**22**) via a Fischer indole reaction sequence (Scheme 6) as previously

Scheme 6

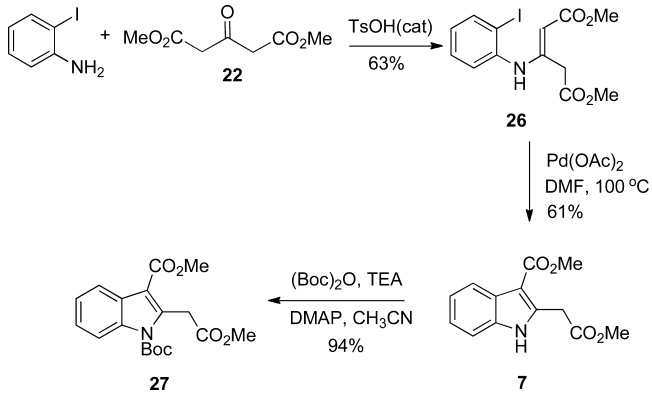


reported by Joule and co-workers for related 1,3-dicarbonyl phenylhydrazine derivatives.[22] We found, however, that only pyrazol-3-one **24** was formed under the conditions described by Joule. Thus, condensing phenylhydrazine and dimethyl-1,3-acetonedicarboxylate (**22**) in the presence of a catalytic amount of acetic acid in ether first gave the ene-hydrazone **23** which was subsequently transformed into pyrazol-3-one **24** by treatment with small quantities of acid. Although **23** could be isolated and purified, when it was subjected to various acidic conditions the desired indole diester **7** was not produced. Instead, only the formation of **24** was observed under these conditions.

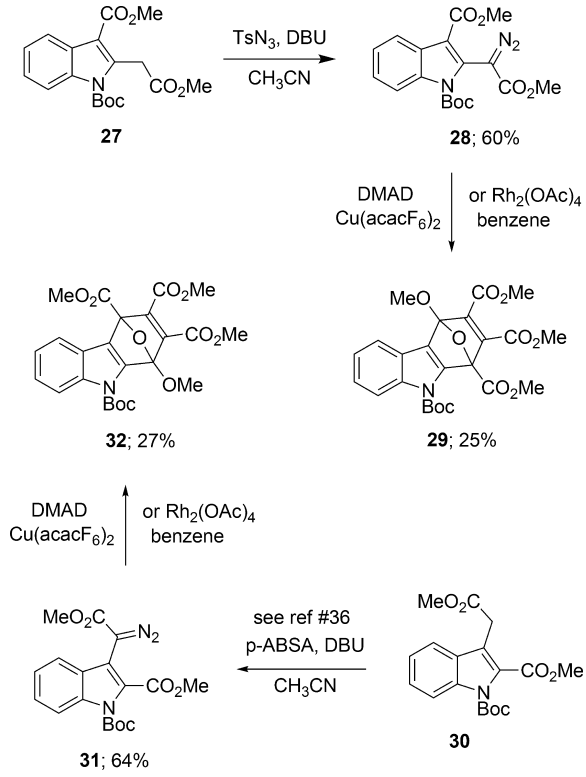
In a previous report, Yamanaka and co-workers described the formation of various 3-acyl-substituted indoles by a palladium-catalyzed cyclization of *β*-(2-halophenyl)amino substituted *α*,*β*-unsaturated ketones and esters.[23] Using this protocol, we found that the desired indole diester **7** could be prepared in a two-step procedure starting from the condensation of 2-iodoaniline and dimethyl-1,3-acetone-dicarboxylate (**22**). The resulting unsaturated ester **26** was subsequently cyclized to the required indole diester **7** by a palladium catalyzed reaction. The subsequent coupling of **7** with di-*tert*-butyl dicarbonate proceeded uneventfully to give amide **27** in 94% yield (Scheme 7).

The substituted diazoacetic ester **28** was then readily prepared from **27** using the Regitz diazo-transfer methodology.[24] In contrast with the results encountered with *α*-diazo diesters **15** and **16**, the carbenoid induced cyclization/cycloaddition reaction also worked reasonably well using either $Cu(acacF_6)$ or

Scheme 7



Scheme 8



rhodium(II) acetate as the catalyst. Thus, exposure of **28** to 5 mol % of $Rh_2(OAc)_4$ in benzene at 80 °C in the presence of an equivalent amount of DMAD afforded the expected Diels–Alder adduct **29** derived from a transient furo[3,4-*b*]indole intermediate (Scheme 8). A related sequence of reactions also occurred when the isomeric diazoacetic ester **31** was treated with either $Cu(acacF_6)$ or $Rh_2(OAc)_4$ and DMAD under similar experimental conditions to give cycloadduct **32**. The above findings are also consistent with the initial formation of a transient furo[3,4-*b*]indole intermediate which is subsequently trapped with the added dienophile.

In order to establish whether an intramolecular cycloaddition reaction will occur with the furo[3,4-*b*]indole system, we next investigated the metal-catalyzed reaction of diazoacetic ester **37**. Compound **37** was easily prepared from the known indole acid **33**[25] as outlined in Scheme 9. Most satisfactorily, the reaction of **37** with $Cu(acacF_6)_2$ in refluxing toluene gave dihydropyranocarbazole **38** in 64% yield (Scheme 9). The formation of **38**

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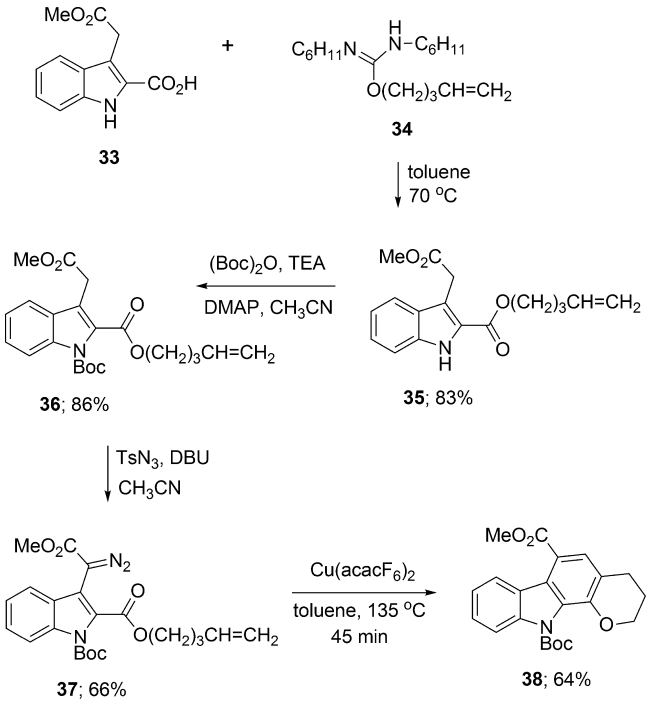
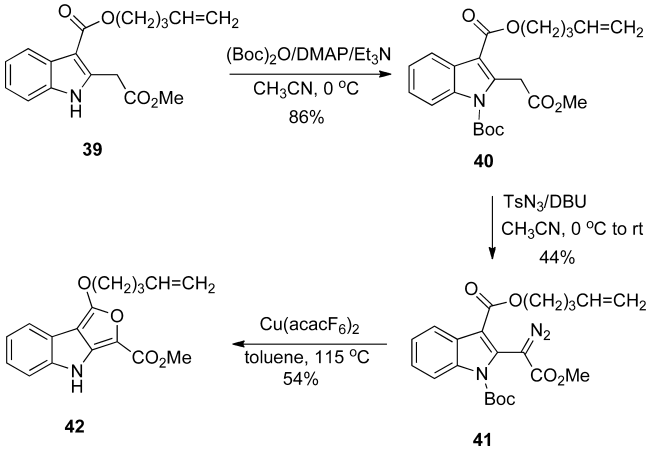
Scheme 9



Scheme 10

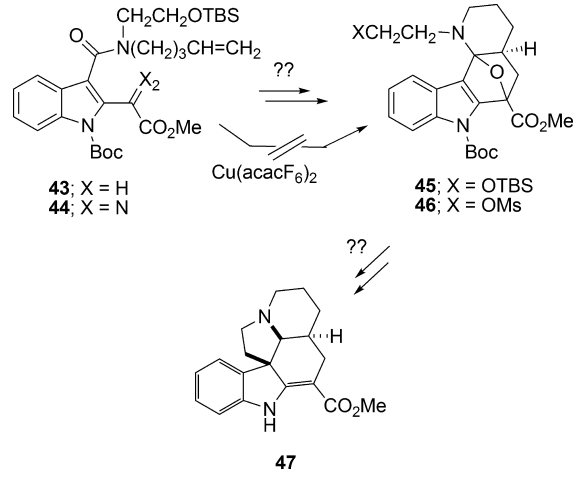


is perfectly consistent with the intramolecular trapping of a furo[3,4-*b*]indole intermediate with the tethered alkenyl group on the neighboring ester group. A subsequent ring-opening of the transient 1,4-oxido cycloadduct and elimination of water results in the observed product.

The exact role of the metal catalyst in these reactions is unclear, but increasing the reactivity of the metallo carbenoid could influence the reaction in several ways. Although carbonyl ylide formation will be more rapid when Rh(II) catalysts are employed, we believe that the higher yields of cyclized products from the Cu(II)-catalyzed reactions result from stabilization of the metal-bound ylide intermediates, which in turn suppress competitive reactions such as C−H insertions. With the knowledge that the Cu(II)-catalyzed reaction of **37** results in a facile intramolecular cyclization/cycloaddition cascade, we subsequently investigated the Cu(II)-catalyzed behavior of the isomeric diazoacetic ester **41** which represents a more appropriate model system for an eventual synthesis of scandine. In this case it was possible to actually isolate the initially formed furo[3,4-*b*]indole **42** in 54% yield (Scheme 10).

Since α-diazoacetic ester **41** underwent the desired cyclization when exposed to the copper catalyst producing an isolable benzo[*c*]furan derivative (i.e., **42**), we embarked on a further study of this type of reaction employing the closely related amide **44** as a key substrate. Our hope was to assemble the pentacyclic skeleton (i.e., **47**) of scandine should the intramolecular cyclization/cycloaddition cascade proceed in the desired manner (Scheme 11). Ideally, cycloadduct **45** would be formed from

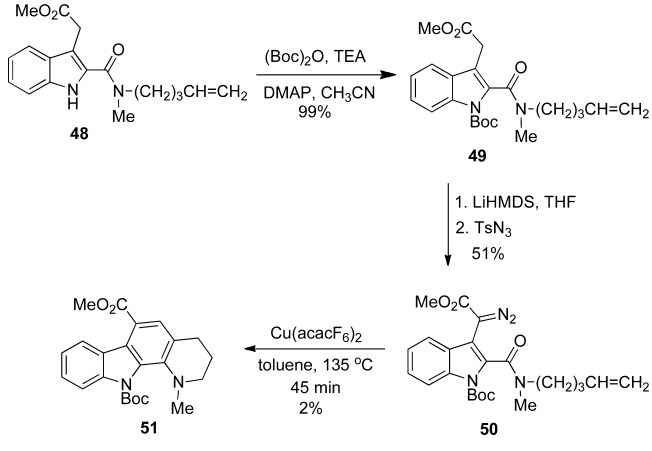
Scheme 11



diazo amido ester **44** and would then be used to prepare **47** via mesylate **46**. Unfortunately, the Cu(II) reaction of **44** was quite messy, and no signs of any cycloadduct could be detected in the crude reaction. Similar results were obtained using several Rh(II) catalysts or varying the nature of the solvent. Although the conformational approach of the tethered π-bond to the benzo[*c*]furan intermediate seemed quite feasible based on Dreiding molecular models, only decomposition of the starting material and unspecified side reactions were observed.[26].

This disappointing result led us to examine whether an intramolecular cyclization/cycloaddition cascade would occur with the isomeric diazo amido ester **50**. To this end, indole **49** was prepared from **48** as outlined in Scheme 12. Standard diazo

Scheme 12



transfer of **49** gave **50** which was then subjected to thermolysis with the Cu(II) catalyst in refluxing toluene. This reaction,

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however, gave rise to only a very poor yield (i.e., 2%) of the expected cyclic compound **51**. Several different Rh(II) catalysts were also employed but no improvement in the yield of **51** was seen.[26].

The negative results encountered with diazo-amido esters **44** and **50** stand in marked contrast with the cascade process that readily took place with diazoesters **15** and **16**. As was pointed out in a previous report by Friedrichsen,[27] furo[3,4-*b*]indoles are much less chemically reactive than the corresponding benzo[*c*]furans. This reactivity difference can be explained in terms of the thermodynamic parameters of the cycloaddition. By using quantum chemical methods, the data obtained showed that the [4 + 2]-cycloaddition of 4*H*-furo[3,4-*b*]indole with ethylene or acetylene is significantly less exothermic than the analogous reactions with benzo[*c*]furan. If the product from the benzo[*c*]-furan system (A) is more stable relative to the furo[3,4-*b*]indole product (B), the relative energy profiles are given qualitatively by Figure 1. We believe that this energy difference in the products

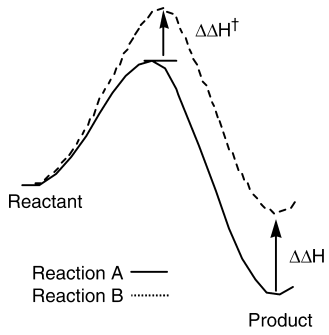
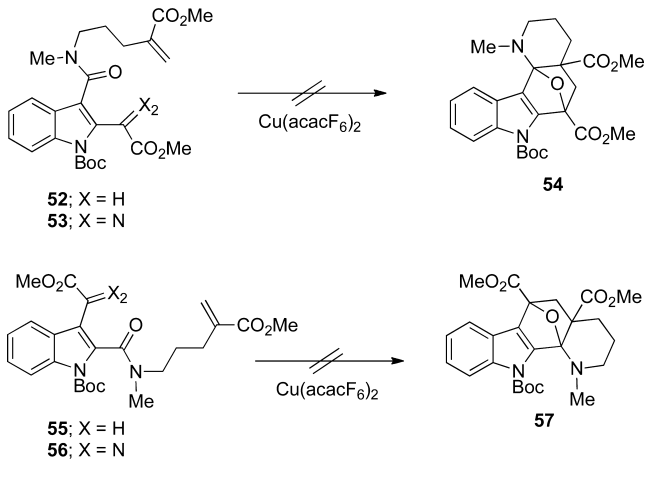


Figure 1. Possible reaction profiles.

mirrors an energy differential between the transition states thereby accounting for the reactivity difference between the two heterocyclic systems.

Since the furan ring generally shows low reactivity toward unactivated dienophiles as a consequence of a large HOMO–LUMO energy gap,[28] we thought that we might be able to promote the cycloaddition of the diazo-amido system by incorporating an electron-withdrawing group on the tethered π-bond. With this in mind, diazo-amido esters **53** and **56** were prepared and their behavior under the Cu(II)-catalyzed conditions was examined (Scheme 13). However, all of our attempts to

Scheme 13

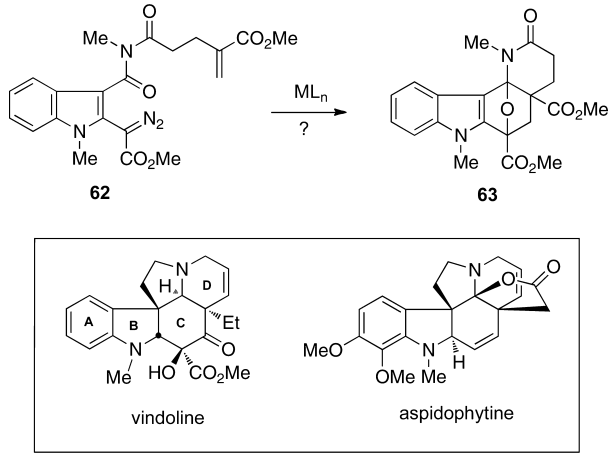


effect an intramolecular cycloaddition across the more activated π-bond were unsuccessful with both **53** and **56**. No signs of the expected cycloadducts **54** and **57** could be detected in the crude reaction mixture. Only decomposition of the starting materials and a rather messy mixture of uncharacterizable products was observed. The negative results obtained with diazo-amido esters **53** and **56** demonstrate that the attachment of an electron-withdrawing group on the tethered alkene is still insufficiently beneficial in promoting the intramolecular cascade reaction of these systems.

The lack of reactivity of the above diazoamido esters does not seem to be related to electronic factors associated with FMO considerations. Consequently, an alternative explanation was sought in terms of relative strain in the transition state. The geometric requirements for the intramolecular [4 + 2]-cycloaddition of the furo[3,4-*b*]indole system with the tethered π-bond imposes distinct restrictions upon the bond angles of the reacting centers. One possibility to provide a more favorable pathway for the cycloaddition would be to place another sp^2 center on the tethered side chain. We hoped that this would provide better overlap between the reacting π-systems and thus facilitate the internal cycloaddition. It should be noted that dramatic rate enhancing effects originating from placement of a carbonyl group on the tethered alkene for intramolecular [4 + 2]-cycloadditions have previously been reported in the literature.[29]

Should the key cyclization/cycloaddition cascade sequence work with an imido substituted diazo ester, we envisioned that this methodology could be used not only for a synthesis of scandine but also for the formation of the A–D rings of the pentacyclic aspidosperma family of alkaloids. The preparation of an appropriately functionalized indole **62** and its Rh(II)- or Cu(II)-catalyzed cyclization to give **63** would form the basis for further studies on the synthesis of aspidosperma alkaloids such as vindoline and aspidophytine (Scheme 14). Access to the starting

Scheme 14



material necessary to prepare this model system was straightforward. Indole **58** was prepared in large quantities via a four step literature procedure.[30] Conversion of **58** to amide **59** followed by acylation with **60**[31] afforded imide **61** in high overall yield. Diazo transfer using *p*-nitrobenzenesulfonyl azide (*p*NBSA)[32] and DBU as a base afforded diazoester **62** in 78% yield (Scheme 15).

Slow addition of **62** to a suspension of either $Cu(acacF_6)_2$ or $Rh_2(OAc)_4$ in benzene at 100 °C furnished the furo[3,4-*b*]indole intermediate **64**, which immediately underwent cycloaddition

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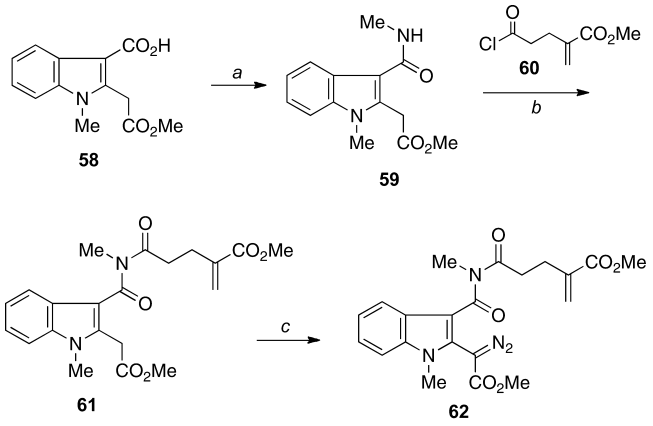
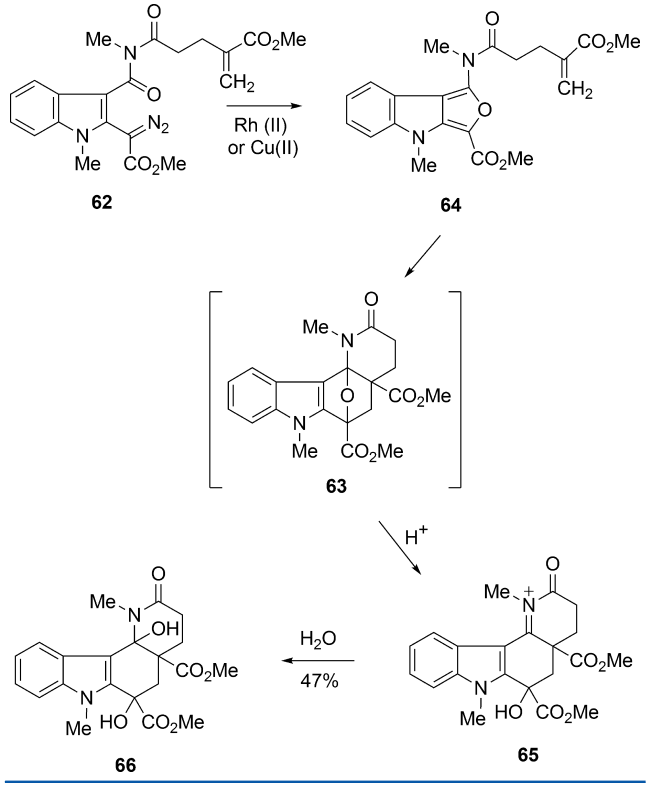
Scheme 15[a]



[a]Reagents: (a) $(COCl)_2$, $MeNH_2$, 81%; (b) PhH, Et_3N, 82%; (c) pNBSA, DBU, 78%.

with the tethered π-bond to form the oxobridged intermediate **63**. This compound could not be easily purified, but, rather, was taken up in wet ethyl acetate and heated briefly. When the solution was cooled, a pale yellow oil was isolated and the structure of this compound was assigned as diol **66** based on its spectroscopic properties and comparison to similar structures in the literature.[33] This product is the result of a nitrogen assisted opening of the oxobridge in cycloadduct **63** followed by addition of water to quench the iminium ion **65** (Scheme 16).

Scheme 16



In conclusion, an intramolecular tandem cyclization/cycloaddition reaction of an α-diazo indolo imido ester was used to assemble a heavily functionalized azapolycyclic ring system from easily available starting materials. The success with the model system provides a clue for an eventual synthesis of scandine and some related aspidosperma alkaloids. We are continuing to explore the scope, generality, and synthetic applications of the intramolecular cycloaddition of furo[3,4-*b*]indoles and will report additional findings at a later date.

EXPERIMENTAL SECTION

General Procedures. Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. The mass analyzer type used for the HRMS measurenments was TOF with electrospray as the ionization method. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of either dry nitrogen or argon. All solvents were distilled prior to use. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column (0.04−0.062 mm) using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data. Yields refer to isolated, spectroscopically pure compounds.

Pent-4-en-1-yl 2-(2-methoxy-2-oxoethyl)benzoate. A mixture of hex-5-en-1-ol (260 mg, 2.3 mmol), DCC (480 mg, 2.3 mmol), and CuCl (3 mg, 0. 03 mmol) was stirred at 0 °C under argon for 16 h. The solution was then diluted with hexane and filtered through a layer of Celite. The organic phase was collected and concentrated under reduced pressure to give 0.7 g of (*Z*)-pent-4-en-1-yl *N*,*N*′-dicyclohexylcarbamimidate as a pale yellow oil which was used directly in the next step without any purification.

A solution of 2-(2-methoxy-2-oxoethyl)benzoic acid[34] (187 mg, 0.96 mmol) and the above carbamimidate (310 mg, 1.06 mmol) in toluene (5 mL) was heated at 80 °C in a sealed tube for 18 h. After being cooled to rt, the mixture was filtered through a short pad of Celite with EtOAc. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 235 mg (93%) of the titled compound as a colorless oil: IR (thin film) 2951, 1739, 1714, 1262, 1165, 1079 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.85 (quint, 2H, J = 7.2 Hz), 2.20 (q, 2H, J = 7.2 Hz), 3.69 (s, 3H), 4.02 (s, 2H), 4.29 (t, 2H, J = 6.6 Hz), 5.03 (dd, 1H, J = 10.2 and 1.8 Hz), 5.07 (dd, 1H, J = 16.8 and 1.8 Hz), 5.81−5.87 (m, 1H), 7.26 (d, 1H, J = 7.8 Hz), 7.37 (td, 1H, J = 7.8 and 1.2 Hz), 7.49 (td, 1H, J = 7.8 and 1.2 Hz), 8.02 (dd, 1H, J = 7.8 and 1.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.6, 30.1, 40.4, 51.9, 64.4, 115.3, 127.4, 129.8, 130.9, 132.2, 132.3, 135.8, 137.4, 167.0, 171.9; HRMS calcd for $[C_{15}H_{18}O_4 + H^+]$ 263.1283, found 263.1277.

Pent-4-en-1-yl 2-(1-Diazo-2-methoxy-2-oxoethyl)benzoate (15). To a sample of the above diester (250 mg, 0.95 mmol) in CH_3CN (5 mL) at 0 °C under argon was added DBU (0.21 mL, 1.40 mmol). After the mixture was stirred for 10 min at 0 °C, TsN_3 (0.22 mL, 1.43 mmol) was added, and the solution was stirred for an additional 16 h at rt. The mixture was quenched with a phosphate buffer solution (10 mL, pH = 7.0) and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 210 mg (76%) of the titled compound **15** as a yellow oil: IR (thin film) 2092, 1705, 1435, 1292, 1246 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.85 (p, 2H, J = 6.6 Hz), 2.20 (q, 2H, J = 7.2 Hz), 3.80 (s, 3H), 4.30 (t, 2H, J = 6.6 Hz), 5.01 (d, 1H, J = 10.2 Hz), 5.07 (dd, 1H, J = 17.4 and 1.8 Hz), 5.80−5.87 (m, 1H), 7.39 (t, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.55 (td, 1H, J = 7.8 and 1.2 Hz), 7.99 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.8, 29.7, 30.1, 52.1, 64.8, 115.4, 126.0, 128.0, 129.5, 130.9, 131.1, 132.1, 137.3, 166.2, 166.5; HRMS calcd for $[C_{15}H_{16}N_2O_4 + Na^+]$ 311.1008, found 311.1002.

Methyl 6-Hydroxy-3,4,5,6-tetrahydro-2*H*-benzo[*h*]-chromene-6-carboxylate (17). A solution of the above compound **15** (45 mg, 0.16 mmol) in toluene (3 mL) was slowly added dropwise to a suspension of $Cu(acacF_6)$ hydrate (15 mg, 0.03 mmol) in toluene (3 mL) at reflux under argon. After the addition was complete, the mixture was heated for 3 h at 110 °C, cooled to rt, and filtered through a layer of Celite using EtOAc. The organic phase was concentrated under reduced pressure, and the residue was purified by flash chromatography to give 27 mg (66%) of the titled compound **17** as a colorless oil: IR

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(thin film) 3466, 2952, 2924, 1729, 1436, 1253, 1153, 1093 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.94−2.02 (m, 2H), 2.11−2.21 (m, 2H), 2.58 (d, 1H, J = 16.8 Hz), 2.93 (d, 1H, J = 16.8 Hz), 3.54 (s, 1H), 3.80 (s, 3H), 4.16 (t, 2H, J = 4.8 Hz), 7.14 (d, 1H, J = 7.8 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.32 (t, 1H, J = 7.8 Hz), 7.55 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.7, 25.2, 39.2, 53.2, 66.0, 74.7, 104.0, 121.4, 124.7, 127.4, 128.7, 131.0, 134.3, 143.4, 176.1; HRMS calcd for $[C_{15}H_{16}O_4 + H^+]$ 261.1127, found 261.1122.

4-Methylenehexyl 2-(2-Methoxy-2-oxoethyl)benzoate. A mixture of 4-methylene-1-hexanol (280 mg 2.45 mmol), DCC (506 mg, 2.45 mmol), and CuCl (3 mg, 0. 03 mmol) was stirred at 0 °C under argon for 16 h. The solution was then diluted with hexane and filtered through a layer of Celite. The organic phase was collected and concentrated under reduced pressure to give 0.66 g of (*Z*)-4-methylenehexyl *N*,*N*′-dicyclohexylcarbamimidate as a pale yellow oil which was used directly in the next step without any purification. A solution of 2-(2-methoxy-2-oxoethyl)benzoic acid (133 mg, 0.69 mmol) and the above imidate (220 mg, 0.69 mmol) in toluene (3 mL) was heated at 80 °C in a sealed tube for 18 h. After being cooled to rt, the mixture was filtered through a short pad of Celite with EtOAc. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give 165 mg (83%) of the titled compound as a colorless oil: IR (thin film) 2963, 1741, 1715, 1262, 1212, 1165, 1138, 1079 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.5 Hz), 1.89 (p, 2H, J = 7.2 Hz), 2.05 (q, 2H, J = 7.2 Hz), 2.16 (t, 2H, J = 7.2 Hz), 3.68 (s, 3H), 4.02 (s, 2H), 4.28 (t, 2H, J = 6.6 Hz), 4.75 (d, 2H, J = 9.6 Hz), 7.25 (d, 1H, J = 7.8 Hz), 7.36 (td, 1H, J = 7.8 and 1.2 Hz), 7.47 (td, 1H, J = 7.8 and 1.2 Hz) , 8.02 (dd, 1H, J = 7.8 and 1.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.2, 26.6, 28.6, 32.4, 40.3, 51.8, 64.6, 108.2, 127.3, 129.8, 130.8, 132.2, 132.2, 135.8, 149.9, 167.0, 171.8; HRMS calcd for $[C_{17}H_{22}O_4 + H^+]$ 291.1596, found 291.1592.

4-Methylenehexyl 2-(1-Diazo-2-methoxy-2-oxoethyl)-benzoate (16). To a solution of the above diester (87 mg, 0.30 mmol) in CH_3CN (3 mL) at 0 °C under argon was added DBU (0.13 mL, 0.87 mmol). After being stirred for 15 min at 0 °C, TsN_3 (0.13 mL, 0.85 mmol) was added, and the mixture was stirred for 20 min at 0 °C and then for 16 h at rt. The reaction mixture was quenched with a phosphate buffer solution (10 mL, pH = 7.0) and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 67 mg (71%) of the titled compound **16** as a yellow oil: IR (thin film) 2961, 2090, 1703, 1291, 1242, 1191 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.03 (t, 3H, J = 7.5 Hz), 1.89 (p, 2H, J = 7.2 Hz), 2.05 (q, 2H, J = 7.2 Hz), 2.16 (t, 2H, J = 7.8 Hz), 3.80 (s, 3H), 4.30 (t, 2H, J = 5.0 Hz), 4.75 (d, 2H, J = 11.4 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), 7.54 (t, 1H, J = 7.8 Hz), 7.99 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.2, 26.7, 28.6, 32.4, 52.1, 65.1, 108.2, 126.0, 128.0, 129.5, 129.7, 130.9, 131.1, 132.0, 150.0, 166.2, 166.4; HRMS calcd for $[C_{17}H_{20}N_2O_4 + H^+]$ 317.1501, found 317.1497.

Methyl 3-((4-Methylenehexyl)oxy)isobenzofuran-1-carboxylate (19). A solution of the above diazo compound **16** (20 mg, 0.06 mmol) in toluene (2 mL) was added dropwise to a suspension of $Cu(acacF_6)$ hydrate (6 mg, 0.012 mmol) in toluene (2 mL) at 80 °C under argon for 1 h. After being cooled to rt, the reaction mixture was filtered through a short silica pad with EtOAc. The organic phase was collected and concentrated under reduced pressure. The residue was purified by preparative chromatography to give 5 mg of the titled compound **19** (28%) as clear oil: IR (thin film) 2960, 2924, 1735, 1705, 1286, 1205 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.8 Hz), 1.89 (p, 2H, J = 7.2 Hz), 2.04 (q, 2H, J = 7.2 Hz), 2.14 (q, 2H, J = 7.8 Hz), 3.87 (s, 3H), 4.30 (t, 2H, J = 6.6 Hz), 4.74 (s, 1H), 4.77 (d, 1H, J = 0.6 Hz), 7.55 (dd, 1H, J = 7.2 and 1.2 Hz), 7.62 (td, 1H, J = 7.8 and 1.2 Hz), 7.67 (td, 1H, J = 7.8 and 1.2 Hz), 8.02 (dd, 1H, J = 7.8 and 1.2 Hz); HRMS calcd for $[C_{17}H_{20}O_4 + H^+]$ 289.1439, found 289.1436.

Methyl 3-Ethyl-1-hydroxy-3-(3-hydroxypropyl)-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (18). A solution of diazo compound **16** (37 mg, 0.12 mmol) in toluene (3 mL) was added dropwise to a suspension of $Cu(acacF_6)$ hydrate (11 mg, 0.02 mmol) in toluene (3 mL) at reflux for 3 h. After being cooled to rt, the reaction mixture was filtered through a short silica pad with EtOAc. The organic phase was collected and concentrated under reduced pressure. The residue was purified by preparative chromatography to give 10 mg (30%) of the titled compound **18** as a clear oil: IR (thin film) 3456, 2955, 1735, 1676, 1250, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 1.63−1.90 (m, 6H), 2.19 (d, 1H, J = 14.8 Hz), 2.65 (d, 1H, J = 14.8 Hz), 3.45−3.60 (m, 2H), 3.78 (s, 3H), 4.34 (s, 1H), 7.19 (d, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.8 Hz), 7.57 (td, 1H, J = 7.6 and 1.2 Hz), 8.03 (dd, 1H, J = 7.6 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 26.5, 27.3, 32.5, 39.1, 47.1, 53.8, 62.9, 73.6, 126.7, 127.7, 129.3, 131.0, 134.0, 140.3, 176.7, 201.1; HRMS calcd for $[C_{17}H_{22}O_5 + H^+]$ 307.1545, found 307.1542.

Compound **18** was also obtained in 30% yield by heating a sample of isobenzofuran **19** in toluene in the presence of $Cu(acacF_6)$ hydrate at reflux for 3 h.

(*E*)-Dimethyl 3-((2-Iodophenyl)amino)pent-2-enedioate (26). A solution of 2-iodoaniline (10.95 g, 50.0 mmol), dimethyl-1,3-acetonedicarboxylate (**22**) (8.7 g, 50.0 mmol), and $TsOH{\cdot}H_2O$ (0.95g, 5.0 mmol) in benzene (50 mL) was heated under reflux for 3 h using a Dean−Stark apparatus for the azeotropic removal of water. The solution was cooled to rt, and the mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 11.8 g (63%) of the titled compound **26** as a pale yellow oil: IR (thin film) 2949, 1738, 1660, 1610, 1579, 1256, 1159, 1047, 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.19 (s, 2H), 3.59 (s, 3H), 3.70 (s, 3H), 4.86 (s, 1 H), 6.93 (t, 1H, J = 7.8 Hz), 7.18 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.86 (d, 1H, J = 7.8 Hz), 10.1 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.3, 50.6, 52.3, 88.5, 98.3, 127.2, 127.8, 128.9, 139.5, 140.5, 153.6, 168.8, 170.3; HRMS calcd for $[C_{13}H_{14}INO_4 + H^+]$ 376.0046, found 376.0040.

Methyl 2-(2-Methoxy-2-oxoethyl)-1*H*-indole-3-carboxylate (7). A solution of the above compound **26** (3.66 g, 9.8 mmol), Et_3N (1.63 mL, 1.18 g, 11.7 mmol), and $Pd(OAc)_2$ (0.11 g, 0.5 mmol) in DMF (3 mL) was heated in a sealed tube at 100 °C for 3 h. The solution was cooled to rt, and the mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 1.47 g (61%) of the titled compound **7**:[22] IR (thin film) 3322, 1735, 1692, 1671, 1458, 1204, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.94 (s, 3H), 4.39 (s, 2H), 7.23−7.25 (m, 2H), 7.37−7.40 (m, 1H), 8.09−8.11 (m, 1H), 9.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.2, 50.9, 52.4, 105.0, 111.2, 121.3, 121.8, 122.8, 126.2, 134.7, 138.7, 166.1, 171.2; HRMS calcd for $[C_{13}H_{13}NO_4 + H^+]$ 248.0923, found 248.0919.

1-*tert*-Butyl 3-Methyl 2-(2-methoxy-2-oxoethyl)-1*H*-indole-1,3-dicarboxylate (27). The above NH-indole **7** (200 mg, 0.81 mmol), TEA (135 μL, 0.97 mmol), and DMAP (15 mg, 0.12 mmol) were dissolved in 10 mL of CH_3CN, and the solution was cooled to 0 °C. To this solution was added di-*tert*-butyl dicarbonate (424 mg, 1.94 mmol), and the reaction mixture was stirred at 0 °C for 1.5 h. The mixture was quenched with 5 mL of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 263 mg (94%) of the titled compound **27** as a white solid: mp 110−111 °C; IR (film) 2952, 1738, 1704, 1586, 1566, 1477, 1455, 1435, 1370, 1357, 1315, 1282, 1253, 1198, 1171, 1144, 1118, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.72 (s, 3H), 3.97 (s, 3H), 4.75 (s, 2H), 7.40−7.30 (m, 2H), 8.20−8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 52.3, 86.0, 112.0, 115.5,122.0 124.0, 125.1, 126.8, 135.8, 140.8, 150.1, 165.8, 170.5.

1-*tert*-Butyl 3-Methyl 2-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1,3-dicarboxylate (28). The above indole **27** (150 mg, 0.43 mmol) and TsN_3 (128 mg, 0.65 mmol) were dissolved in 3 mL of CH_3CN, and the solution was cooled to 0 °C. To this solution was added DBU (97 μL, 0.65 mmol) and the mixture was stirred at rt for 12 h. The solution was quenched with 3 mL of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced

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pressure, and the crude residue was subjected to silica gel chromatography to give 97 mg (60%) of the titled compound **28** as a yellow solid: mp 92−94 °C; IR (film) 2981, 2953, 2111, 1744, 1701, 1557, 1478, 1454, 1435, 1394, 1370, 1352, 1315, 1279, 1257, 1192, 1144, 1117, 1062, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 9H), 3.81 (d, 3H, J = 15.6 Hz), 4.00 (s, 3H), 7.48−7.32 (m, 2H), 8.18 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 52.1, 52.5, 85.8, 112.5, 115.3, 122.3, 124.2, 126.3, 126.0, 127.1, 129.0, 129.4, 137.0, 149.3, 164.4.

9-*tert*-Butyl 11,12,13-Trimethyl-(1*R*,11*R*)-1-methoxy-14-oxa-9-azatetracyclo[9.2.1.0^{2,10}.0^{3,8}]tetradeca-2(10),3,5,7,12-pentaene-9,11,12,13-tetracarboxylate (29). A sample of the above diazo compound **28** (31 mg, 0.083 mmol) and DMAD were taken up in 8 mL of benzene. To this solution was added $Rh_2(OAc)_4$ (1.8 mg, 0.0042 mmol), and the reaction mixture was heated at 80 °C for 100 min. After being cooled to rt, the mixture was concentrated under reduced pressure and the crude residue was subjected to silica gel chromatography to give 10 mg (25%) of the title compound **29** as a yellow solid: mp 176−178 °C; IR (film) 2953, 1741, 1690, 1602, 1533, 1434, 1410, 1369, 1350, 1312, 1283, 1241, 1214, 1150, 1093, 1047, 1020 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.67 (s, 9H), 3.86 (s, 6H), 3.89 (s, 3H), 4.07 (s, 3H), 7.38 (td, 1H, J = 7.2 and 1.2 Hz), 7.55 (td, 1H, J = 7.2 and 1.8 Hz), 8.13 (d, 1H, J = 8.4 Hz), 8.17 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 52.6, 53.9, 62.8, 72.8, 86.1, 114.1, 115.3, 123.5, 124.0, 124.9, 128.3, 130.0, 130.9, 140.4, 148.5, 159.8, 164.7, 165.7, 179.5; HRMS calcd for $[C_{24}H_{25}NO_{10} + H^+]$ 488.1557, found 488.1556.

1-*tert*-Butyl 2-Methyl-3-((methoxycarbonyl)diazomethyl)-1*H*-indole-1,2-dicarboxylate (31). To a solution containing 1-*tert*-butyl 2-methyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1,2-dicarboxylate (**30**)[35] (50 mg, 0.14 mmol) and 4-acetylamidobenzenesulfonyl azide (42 mg, 0.17 mmol) in 0.5 mL of CH_3CN under argon was added DBU (30 μL, 0.20 mmol). The reaction mixture was stirred at rt for 15 h, and then the mixture was quenched with 1 mL of H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 32 mg (64%) of the titled compound **31** as a yellow solid: mp 58−60 °C; IR (film) 2981, 2953, 2100, 1733, 1562, 1435, 1394, 1354, 1318, 1272, 1226, 1151, 1107, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 3.83 (s, 3H), 3.95 (s, 2H), 7.32 (ddd, 1H, J = 8.1, 7.2, and 1.0 Hz), 7.46 (ddd, 1H, J = 8.5, 7.2, and 1.3 Hz), 7.55 (ddd, 1H, J = 7.9, 1.1, and 0.6 Hz), 8.11 (dt, 1H, J = 8.5 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 52.5, 52.9, 85.4, 111.3, 115.2, 120.9, 121.4, 123.8, 127.3, 127.6, 127.8, 136.8, 149.1, 162.4.

9-*tert*-Butyl 1,12,13-Trimethyl (1*R*,11*R*)-11-Methoxy-14-oxa-9-azatetracyclo[9.2.1.0^{2,10}.0^{3,8}]tetradeca-2(10),3,5,7,12-pentaene-1,9,12,13-tetracarboxylate (32). The above diazo compound **31** (31 mg, 0.083 mmol) and 1.2 equiv of DMAD were dissolved in 8 mL of benzene. To this solution was added $Rh_2(OAc)_4$ (1.8 mg, 0.0042 mmol), and the mixture was heated at 80 °C for 100 min. After being cooled to rt, the reaction mixture was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 11 mg (27%) of the titled compound **32** as a yellow oil: IR (film) 2952, 1925, 2850, 1736, 1676, 1604, 1541, 1433, 1371, 1317, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 3.81 (s, 6H), 3.86 (s, 3H), 3.98 (s, 3H), 7.52−7.34 (m, 2H), 7.73 (dd, 1H, J = 8.1 and 0.9 Hz), 8.18 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 52.6, 54.0, 63.4, 86.7, 112.8, 115.9, 116.1, 122.5, 123.8, 125.3, 127.4, 138.3, 141.2, 148.9, 155.5, 164.5, 165.5, 182.9; HRMS calcd for $[C_{24}H_{25}NO_{10} + H^+]$ 488.1557, found 488.1554.

Pent-4-enyl 3-((Methoxycarbonyl)methyl)-1*H*-indole-2-carboxylate (35). A solution of 3-((methoxycarbonyl)methyl)-1*H*-indole-2-carboxylic acid (**33**)[25] (200 mg, 0.858 mmol) and 1,3-dicyclohexyl-2-(pent-4-enyl)isourea (**34**) (276 mg, 0.943 mmol) in toluene (6.6 mL) was heated under argon at 70 °C for 16 h. The reaction mixture was cooled to rt, filtered through a pad of Celite, and rinsed with EtOAc. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the titled compound **35** (213 mg, 83%) as a light yellow solid: mp 55−56 °C; IR (film) 3333, 1951, 1732, 1683, 1640, 1620, 1578, 1552, 1435, 1392, 1326, 1238, 1165, 1128, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (dq, 2H, J = 8.8 and 6.7 Hz), 2.30−2.19 (m, 2H), 3.71 (s, 3H), 4.20 (s, 2H), 4.37 (t, 2H, J = 6.6 Hz), 5.07−5.01 (m, 1H), 5.10 (dq, 1H, J = 17.2 and 1.7 Hz), 5.86 (ddt, 1H, J = 16.9, 10.2, and 6.6 Hz), 7.18 (t, 1H, J = 17.2 Hz), 7.34 (t, 1H, J = 17.2 Hz), 7.40 (dq, 1H, J = 8.3 and 0.9 Hz), 7.66 (d, 1H, J = 8.0 Hz), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 30.3, 30.7, 52.3, 64.7, 112.1, 115.7, 115.8, 120.7, 120.9, 124.55, 125.9, 128.1, 135.9, 137.5, 162.2, 171.9.

1-*tert*-Butyl-2-pent-4-enyl 3-((Methoxycarbonyl)methyl)-1*H*-indole-1,2-dicarboxylate (36). A solution of the above indole **35** (200 mg, 1 equiv), DMAP (0.15 mmol, 1 equiv), and TEA (1.2 equiv) in CH_3CN (8 mL) was cooled to 0 °C. To this mixture was added *t*-Boc_2O (2.4 equiv), and the reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with H_2O (5 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the titled compound **36** in 86% yield as a light yellow liquid: IR (film) 2025, 1736, 1641, 1592, 1568, 1451, 1405, 1356, 1332, 1277, 1240, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26−1.18 (m, 9H), 1.45 (dd, 2H, J = 9.7 and 5.0 Hz), 1.85−1.72 (m, 2H), 3.27 (dd, 3H, J = 2.9 and 1.3 Hz), 3.51 (d, 2H, J = 2.8 Hz), 3.94 (td, 2H, J = 6.9 and 2.8 Hz), 4.61 (d, 1H, J = 10.3 Hz), 4.73−4.63 (m, 1H), 5.42 (dd, 1H, J = 17.4 and 8.6 Hz), 6.92−6.87 (m, 1H), 7.07−6.97 (m, 1H), 7.18 (d, 1H, J = 8.3 Hz), 7.66 (dd, 1H, J = 8.6 and 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 28.1, 30.3, 30.4, 52.5, 65.2, 84.9, 115.3, 115.7, 119.3, 120.4, 123.5, 127.2, 128.5, 128.7, 136.8, 137.5, 149.4, 162.4, 170.8.

1-*tert*-Butyl-2-pent-4-enyl-3-((Methoxycarbonyl)-diazomethyl)-1*H*-indole-1,2-dicarboxylate (37). A sample of the above indole **36** (70 mg, 0.17 mmol) and TsN_3 (52 mg, 0.26 mmol) were dissolved in 1.1 mL of CH_3CN under argon, and the reaction mixture was cooled to 0 °C. To this mixture was added DBU (39 μL, 0.26 mmol), and the solution was stirred at 0 °C for 10 min and then at rt for 15 h. The mixture was quenched with 2 mL of H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 49 mg (66%) of the titled compound **37** as a yellow oil: IR (film) 2979, 2102, 1735, 1563, 1450, 1395, 1356, 1328, 1224, 1151, 1110 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.65 (s, 9H), 1.91−1.83 (m, 2H), 2.25−2.16 (m, 2H), 3.83 (s, 3H), 4.37 (td, 2H, J = 6.8 and 0.9 Hz), 5.02 (ddt, 1H, J = 10.2, 2.0, and 1.2 Hz), 5.08 (dq, 1H, J = 17.1 and 1.6 Hz), 5.83 (ddtd, 1H, J = 16.8, 10.2, 6.6, and 0.9 Hz), 7.32 (ddd, 1H, J = 8.1, 7.2, and 1.0 Hz), 7.46 (ddt, 1H, J = 8.4, 7.2, and 1.1 Hz), 7.58−7.53 (m, 1H), 8.09 (dd, 1H, J = 8.5 and 0.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.8, 28.0, 28.1, 30.1, 52.5, 65.6, 85.4, 110.9, 115.19, 115.7, 121.4, 123.7, 127.4, 127.5, 128.4, 136.7, 137.4, 149.1, 161.9.

11-*tert*-Butyl 6-Methyl 3,4-Dihydropyrano[2,3-*a*]carbazole-6,11(2*H*)-dicarboxylate (38). A 6.2 mg (0.013 mmol) sample of copper hexafluoroacetylacetonate hydrate was suspended in 2 mL of degassed toluene and heated to reflux. To this mixture was added a solution of the above diazo compound **37** (27 mg, 0.063 mmol) in 2 mL of degassed toluene over a period of 1 h, and the mixture was heated at reflux for 45 min. After cooling to rt, the mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 15 mg (64%) of the titled compound **38** as a light yellow solid: mp 120−122 °C; IR (film) 2928, 2184, 1719, 1615, 1563, 1502, 1453, 1433, 1393, 1355, 1324, 1298, 1274, 1231, 1203, 1157, 1136, 1094, 1059, 1043, 1022, 1002 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.63 (s, 9H), 2.15 (pent, 2H, J = 5.4 Hz), 2.99 (t, 3H, J = 6.4 Hz), 4.01 (s, 3H), 4.37 (t, 2H, J = 5.4 Hz), 7.34 (dt, 1H, J = 8.2 and 1.2 Hz), 7.49 (dt, 1H, J = 8.3 and 1.3 Hz), 7.76 (d, 1H, J = 1.2 Hz), 8.08 (d, 1H, J = 8.2 Hz), 8.82 (d, 1H, J = 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.4, 25.0, 28.1, 52.2, 67.0, 83.5, 113.4, 116.8, 119.4, 122.7, 124.5, 125.3, 125.9, 127.6, 128.9, 129.1, 141.0, 147.5, 150.8, 167.9; HRMS calcd for $[C_{22}H_{23}NO_5 + H^+]$ 382.1654, found 382.1649.

Pent-4-enyl 2-((Methoxycarbonyl)methyl)-1*H*-indole-3-carboxylate (39). A solution of 2-(2-methoxy-2-oxoethyl)-1*H*-indole-3-carboxylic acid[36] (21 mg, 0.09 mmol) and (*Z*)-pent-4-en-1-yl *N*,*N*′-dicyclohexylcarbamimidate (29 mg, 0.10 mmol) in toluene (1 mL) was

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heated at 80 °C in a sealed tube for 18 h. After being cooled to rt, the reaction mixture was filtered through a short pad of Celite with EtOAc. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give the titled compound **39** (21 mg, 78%) as a colorless oil: IR (thin film) 3323, 2852, 1736, 1689, 1668, 1457, 1201, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.93 (p, 2H, J = 7.2 Hz), 2.75 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 4.36 (s, 2H), 4.37 (t, 2H, J = 7.2 Hz), 5.03 (dd, 1H, J = 10.2 and 1.2 Hz), 5.10 (dt, 1H, J = 16.8 and 1.8 Hz), 5.85−5.92 (m, 1H), 7.21−7.26 (m, 2H), 7.35 (dd, 1H, J = 6.6 and 1.2 Hz), 8.11 (dd, 1H, J = 7.2 and 1.8 Hz), 9.80 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.10, 30.3, 32.2, 52.4, 63.2, 105.2, 111.2, 115.3, 121.4, 121.8, 122.8, 126.3, 134.7, 137.5, 138.6, 165.7, 171.2.

1-*tert*-Butyl 3-Pent-4-enyl 2-((Methoxycarbonyl)methyl)-1*H*-indole-1,3-dicarboxylate (40). To a solution of the above compound **39** (21 mg, 0.07 mmol) in CH_3CN (2 mL) at 0 °C were added DMAP (1.5 mg, 0.01 mmol), Et_3N (1.3 mL, 0.01 mmol), and *t*-Boc_2O (38 mg, 0.17 mmol). After being stirred for 1.5 h at 0 °C, the reaction mixture was quenched with a saturated NH_4Cl solution (2 mL). The mixture was then partitioned between CH_2Cl_2 and H_2O. The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 24 mg of the titled compound **40** (86%) as a colorless oil: IR (thin film) 2979, 1738, 1700, 1454, 1280, 1195, 1144, 1116 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.67 (s, 9H), 1.93 (p, 2H, J = 7.2 Hz), 2.25 (q, 2H, J = 7.2 Hz), 3.71 (s, 3H), 4.38 (t, 2H, J = 6.6 Hz), 4.75 (s, 2H), 5.03 (dd, 1H, J = 9.6 and 1.2 Hz), 5.10 (dd, 1H, J = 17.4 and 1.2 Hz), 5.83−5.90 (m, 1H), 7.30−7.36 (m, 2H), 8.11 (dd, 1H, J = 7.8 and 1.8 Hz), 8.14 (dd, 1H, J = 7.2 and 1.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.9, 28.0, 30.3, 33.7, 52.07, 63.9, 85.7, 111.9, 115.3, 115.5, 121.8, 123.8, 124.8, 126.7, 135.6, 137.4, 140.5, 149.8, 165.1, 170.2.

1-*tert*-Butyl 3-Pent-4-enyl 2-((Methoxycarbonyl)-diazomethyl)-1*H*-indole-1,3-dicarboxylate (41). A sample of DBU (42 mL, 0.28 mmol) was added to a solution of **40** (66 mg, 0.16 mmol) in CH_3CN (3 mL) at 0 °C under argon. After the mixture was stirred for 15 min at 0 °C, TsN_3 (101 mL, 0.66 mmol) was added to the solution, and the mixture was stirred for an additional 16 h at rt. The mixture was quenched with a phosphate buffer solution (10 mL, pH = 7.0) and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 31 mg (44%) of the titled compound **41** as a yellow oil: IR (thin film) 2111, 1744, 1701, 1478, 1317, 1280, 1257, 1192, 1146, 1117 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.65 (s, 9H), 1.93 (p, 2H, J = 7.2 Hz), 2.40 (q, 2H, J = 7.2 Hz), 3.71−3.86 (m, 3H), 4.40 (t, 2H, J = 6.6 Hz), 5.02 (dd, 2H, J = 10.2 and 1.2 Hz), 5.08 (dd, 2H, J = 16.8 and 1.2 Hz), 5.82−5.89 (m, 1H), 7.35 (t, 1H, J = 7.2 Hz), 7.40 (t, 1H, J = 7.2 Hz), 8.18 (d, 1H, J = 15.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.9, 28.0, 30.2, 52.1, 64.2, 85.4, 113.0, 115.1, 115.5, 122.1, 124.0. 125.8, 126.3, 127.8, 128.9, 129.8, 136.7, 137.3, 149.1, 163.7, 165.3.

Methyl 1-(Pent-4-en-1-yloxy)-1*H*,3*H*,4*H*-furo[3,4-*b*]indole-3-carboxylate (42). A solution of the above diazo compound **41** (29 mg, 0.068 mmol) in toluene (2 mL) was added dropwise to a suspension of $Cu(acacF_6)$ hydrate (6.5 mg, 0.014 mmol) in toluene (2 mL) at 135 °C under argon. The mixture was stirred for 1 h at 135 °C, cooled to rt, and filtered through a short pad of silica with EtOAc. The organic phase was collected and concentrated under reduced pressure, and the residue was purified by preparative chromatography to give 11 mg (54%) of **42** as a colorless oil: IR (thin film) 1813, 1760, 1719, 1454, 1354, 1217, 1178, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.89 (p, 2H, J = 7.2 Hz), 2.21 (q, 2H, J = 7.2 Hz), 3.86 (s, 3H), 4.35 (t, 2H, J = 6.6 Hz), 5.03 (dd, 1H, J = 10.2 and 1.2 Hz), 5.09 (dd, 1H, J = 17.4 and 1.2 Hz), 5.82−5.89 (m, 1H), 6.09 (s, 1H), 7.45−7.48 (m, 2H), 7.98 (t, 1H, J = 4.5 Hz), 8.15 (t, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 53.8, 64.4, 76.0, 106.5, 112.9, 115.6, 122.4, 125.6, 125.7, 130.1, 131.0, 137.2, 140.8, 148.2, 162.6, 164.3; HRMS calcd for $[C_{17}H_{17}NO_4 + H^+]$ 300.1236, found 300.1237.

***tert*-Butyl 3-((2-((*tert*-Butyldimethylsilyl)oxy)ethyl)(pent-4-en-1-yl)carbamoyl)-2-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (43).** To a solution of 2-(2-methoxy-2-oxoethyl)-1*H*-indole-3-carboxylic acid (19 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) at rt were added *N*,*N*-diisopropylethylamine (0.14 mL, 0.8 mmol), *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)pent-4-en-1-amine (29 mg, 0.12 mmol), hydroxybenzotriazole (18 mg, 0.13 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (23 mg, 0.12 mmol). After being stirred overnight for 18 h, the mixture was diluted with EtOAc, and the organic phase was washed with 1 M HCl, a saturated $NaHCO_3$ solution, and then brine. The organic layers were collected, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 35 mg (97%) of methyl 2-(3-((2-((*tert*-butyldimethyl-silyl)oxy)ethyl)(pent-4-en-1-yl)carbamoyl)-1*H*-indol-2-yl)acetate as a colorless oil which was immediately converted into the corresponding *t*-Boc indole derivative as outlined below.

To a solution of the above compound (35 mg, 0.08 mmol) in CH_3CN (3 mL) at 0 °C were added 4-(dimethylamino)pyridine (1.4 mg, 0.01 mmol), Et_3N (13 mL, 0.09 mmol), and *t*-Boc_2O (42 mg, 0.19 mmol). After being stirred for 1.5 h at 0 °C, the mixture was quenched with a saturated NH_4Cl solution and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 42 mg of the titled compound **43** (97%) as a colorless oil which consisted of a 3:2 mixture of rotamers: IR (thin film) 2952, 2930, 1739, 1631, 1456, 1371, 1357, 1328, 1171, 1120 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.09 (s, 2H), −0.08 (s, 2H), 0.10 (s, 3H), 0.11 (s, 3H), 0.81 (s, 6H), 0.93 (s, 9H), 1.48−1.58 (m, 2H), 1.65 (s, 15H), 1.74−1.68 (m, 3.7H), 2.15−2.19 (m, 1H), 3.34−3.57 (m, 6.7H), 3.67 (s, 3H), 3.69 (s, 2H), 3.83−3.97 (m, 3.3H), 4.03−4.18 (m, 3.3H), 4.83−4.87 (m, 2H), 5.01 (d, 0.67H, J = 9.6 Hz), 5.08 (d, 0.67H, J = 16.8 Hz), 5.56−5.63 (m, 1H), 5.84−5.91 (m, 0.67H), 7.23 (t, 1.7H, J = 7.2 Hz), 7.31 (t, 1.7H, J = 7.2 Hz), 7.37 (d, 0.7H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.8 Hz), 8.09−8.11 (m, 1.7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.1, 18.2, 27.0, 27.9, 28.0, 29.7, 30.5, 31.3, 34.0, 45.9, 47.1, 50.0, 50.8, 52.0, 61.3, 62.6, 84.9, 115.0, 115.2, 115.8, 115.9, 118.8, 118.9, 119.1, 119.5, 123.2, 123.3, 124.7, 124.8, 126.3, 126.5, 131.7, 131.9, 135.4, 137.3, 137.8, 150.1, 150.2, 166.2, 166.3, 170.1, 170.2.

Treatment of **43** with TsN_3 using the standard reaction conditions for the introduction of a diazo group followed by a subsequent thermolysis of the labile diazo ester **44** with $Cu(acacF_6)$ hydrate produced no characterizable products. There was no indication of the presence of an intramolecular cycloadduct in the crude reaction mixture which consisted of a multitude of products.

Methyl 2-(2-(*N*-Methyl-*N*-(pent-4-enyl)carbamoyl)-1*H*-indol-3-yl)acetate (48). A mixture of 3-(2-methoxy-2-oxoethyl)-1*H*-indole-2-carboxylic acid (200 mg, 1 equiv), *N*-methylpent-4-en-1-amine hydrochloride salt (1.5 equiv), EDCI (2 equiv), and BtOH (2.5 equiv) was taken up in 3.4 mL of THF. To the solution was added DIPEA (6 equiv) dropwise, and the resulting mixture was stirred at rt for 20 h. The solvent was removed under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the titled indole **48** as a pale yellow solid in 73% yield: mp 81−82 °C; IR (film) 3223, 3059, 2930, 1736, 1608, 1559, 1488, 1433, 1403, 1342, 1312, 1259, 1192, 1164, 1077, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (t, 2H, J = 7.6 Hz), 2.14−1.96 (m, 3H), 3.10 (s, 3H), 3.54 (t, 2H, J = 7.6 Hz), 3.69 (s, 3H), 3.85 (s, 2H), 4.98 (d, 1H, J = 10.4 Hz), 5.03 (d, 1H, J = 17.5 Hz), 5.90−5.70 (m, 1H), 7.17 (ddd, 1H, J = 8.0, 7.0, and 1.0 Hz), 7.30−7.26 (m, 1H), 7.35 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 7.6 Hz), 8.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 31.0, 52.3, 109.0, 111.8, 115.6, 120.0, 120.6, 124.0, 127.6, 129.1, 135.8, 137.6, 165.2, 171.8.

***tert*-Butyl 2-(*N*-Methyl-*N*-(pent-4-enyl)carbamoyl)-3-((methoxycarbonyl)methyl)-1*H*-indole-1-carboxylate (49).** The above indole **48** (200 mg, 1 equiv), DMAP (0.15 mmol, 1 equiv), and TEA (1.2 equiv) were dissolved in CH_3CN (8 mL), and the solution was cooled to 0 °C. To this mixture was added *t*-Boc_2O (2.4 equiv), and the mixture was stirred at 0 °C for 1 h. The reaction was then quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the corresponding *t*-Boc-protected indole **49** in 99% yield as a colorless liquid and was obtained as a 1.7:1-mixture of rotamers: IR (film) 2978, 2931, 1732, 1639, 1575, 1477, 1450, 1343, 1409, 1358, 1326, 1254, 1231, 1143, 1111, 1081,

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1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 1.89 (t, 1H, J = 7.5 Hz), 2.06 (m, 1H), 2.19 (q, 1H, J = 7.8 Hz), 2.88 (s, 3H), 3.06 (dt, 1H, J = 13.6 and 7.3 Hz), 3.13 (m, 1H), 3.19 (td, 1H, J = 9.3 and 6.1 Hz), 3.68 (s, 3H), 4.97−4.82 (m, 1H), 5.02−5.09 (m, 1H), 5.66 (m, 1H), 5.88 (m, 2H), 7.31−7.28 (m, 1H), 7.37 (m, 1H), 7.59−7.50 (m, 1H), 8.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.0, 28.1, 28.2, 30.1, 30.5, 30.8, 31.2, 32.3, 36.1, 46.9, 50.4, 52.3, 84.7, 84.8, 112.8, 113.2, 115.3, 115.5, 115.7, 119.1, 119.7, 123.4, 125.6, 129.1, 131.1, 131.8, 135.3, 135.6, 137.2, 140.0, 149.1, 149.2, 163.9, 164.0, 170.9, 171.0.

11-*tert*-Butyl 6-Methyl 1,2,3,4-Tetrahydro-1-methylpyrido-[2,3-*a*]carbazole-6,11-dicarboxylate (51). A 100 mg sample of the above *t*-Boc indole **49** and TsN_3 (2 equiv) were dissolved in 1.1 mL of CH_3CN under argon and the reaction mixture was cooled to 0 °C. To this mixture was added DBU (39 μL, 0.26 mmol), and the solution was stirred at 0 °C for 10 min and then at rt for 15 h. The mixture was quenched with 2 mL of H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give *tert*-butyl 2-(*N*-methyl-*N*-(pent-4-enyl)carbamoyl)-3-((methoxycarbonyl)-diazomethyl)-1*H*-indole-1-carboxylate (**50**) in 51% yield as a 1.4:1 mixture of rotamers and was used without further purification in the next step: ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 1.81−1.79 (m, 1H), 1.93−1.87 (m, 1H), 2.16 (q, 1H, J = 7.6 Hz), 2.89 (s, 1.8H), 3.11−3.02 (m, 1H), 3.12 (s, 1.2H), 3.19 (t, 1H, J = 7.8 Hz), 3.75−3.60 (m, 0.4H), 3.81 (s, 3H), 4.08−4.00 (m, 0.6H), 4.94−4.85 (m, 0.8H), 5.12−5.01 (m, 1.2H), 5.70−5.59 (m, 0.4H), 5.92−5.82 (m, 0.6H), 7.31 (t, 1H, J = 7.6 Hz), 7.42−7.37 (m, 1H), 7.49 (d, 1H, J = 8.4 Hz), 8.21−8.16 (m, 1H).

A sample of copper hexafluoroacetylacetonate hydrate (3.7 mg, 0.0075 mmol) was suspended in 1.3 mL of degassed toluene, and the mixture was heated at reflux. To this mixture was added a solution of diazo compound **50** (17 mg, 0.038 mmol) in 1.3 mL of degassed toluene over a period of 1 h, and heating was continued for 45 min. After being cooled to rt, the mixture was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give 0.3 mg (2%) of a light yellow foam whose structure was assigned as compound **51** on the basis of its NMR spectrum: ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 9H), 2.06 (br, 2H), 2.86 (t, 2H, J = 6.0 Hz), 2.97 (d, 3H, J = 0.8 Hz), 3.43 (br, 2H), 3.97 (d, 3H, J = 1.2 Hz), 7.32 (t, 1H, J = 8.0 Hz), 7.43 (t, 1H, J = 7.8 Hz), 7.68 (s, 1H), 8.12 (d, 1H, J = 8.0 Hz) and 8.86 (d, 1H, J = 8.4 Hz).

***tert*-Butyl 2-(2-Methoxy-2-oxoethyl)-3-[(5-methoxy-4-methylidene-5-oxopentyl)(methyl)carbamoyl]-1*H*-indole-1-carboxylate (52).** A 35 mg sample (0.28 mmol) of the known 1-methyl-3-methylenepiperidin-2-one[37] was suspended in 6 N HCl (1.7 mL), and the solution was heated at reflux for 48 h. After the mixture was cooled to rt, MeOH (2 mL) was added, and the mixture was saturated with HCl gas and then heated at reflux for 24 h. The solution was concentrated under reduced pressure to give 24 mg (44%) of methyl 5-(methylamino)-2-methylenepentanoate hydrochloride salt as a viscous yellow oil which was used in the next step without any purification: IR (film) 3418, 2950, 2778, 1716, 1632, 1695, 1455, 1440, 1298, 1168 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.94 (brs, 2H), 2.46 (brs, 2H), 2.74 (s, 3H), 3.50−3.79 (m, 5H), 5.78 (s, 1H), 6.24 (s, 1H), 7.10 (m, 2H), 7.25 (m, 1H), 7.40 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 26.4, 30.0, 34.8, 45.9, 52.9, 127.4, 140.1, 168.4.

A mixture of 2-(2-methoxy-2-oxoethyl)-1*H*-indole-3-carboxylic acid (200 mg, 1 equiv), the above amine salt (1.5 equiv), EDCI (2 equiv), and BtOH (2.5 equiv) was taken up in 3.4 mL of THF. To this solution was added DIPEA (6 equiv) dropwise, and the resulting mixture was stirred at rt for 20 h. The solvent was removed under reduced pressure, and the crude residue was subjected to silica gel chromatography to give methyl 5-[1-[2-(2-methoxy-2-oxoethyl)-1*H*-indol-3-yl]-*N*-methylformamido]-2-methylidenepentanoate as a yellow oil in 41% yield: IR (film) 3175, 2950, 2927, 1741, 1721, 1698, 1557, 1495, 1456, 1402, 1199, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62−1.82 (m, 2H), 1.95−2.20 (m, 3H), 3.04 (s, 3H), 3.55 (brs, 2H), 3.65−3.71 (m, 6H), 3.88 (d, 2H, J = 4.4 Hz), 5.57 (brs, 1H), 6.17 (brs, 1H), 7.09−7.14 (m, 2H), 7.24−7.25 (m, 1H), 7.38−7.42 (m, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 29.2, 31.9, 47.6, 52.0, 52.2, 52.4, 110.6, 111.6, 119.6, 120.8, 122.4, 125.5, 132.6, 135.0, 139.8, 167.6, 168.2, 171.0.

The above NH-indole (200 mg, 1 equiv), DMAP (0.15 mmol), and TEA (1.2 equiv) were dissolved in CH_3CN (8 mL), and the solution was cooled to 0 °C. To this mixture was added *t*-Boc_2O (2.4 equiv), and the mixture was stirred at 0 °C for 1 h. The reaction was then quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the corresponding *t*-Boc-protected indole **52** in 73% yield as a colorless liquid which was obtained as a 1.3:1 mixture of rotamers: IR (film) 2925, 2852, 1735, 1629, 1395, 1370, 1326, 1200, 1151, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 1.73−1.88 (m, 2H), 1.96−2.05 (m, 1H), 2.38−2.42 (m, 1H), 2.91 (s, 2H), 3.11 (s, 1H), 3.22−3.50 (m, 2H), 3.61−3.75 (m, 6H), 4.02−4.15 (m, 2H), 5.36 (s, 0.4H), 5.65 (s, 0.6H), 6.02 (s, 0.4H, 6.20 (s, 0.6H), 7.21−7.25 (m, 1H), 7.28−7.32 (m, 1H), 7.37 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.4, 28.2, 28.8, 29.6, 32.7, 34.1, 34.2, 36.8, 47.0, 50.8, 52.1, 52.3, 85.2, 116.1, 119.1, 119.5, 123.5, 125.0, 125.4, 125.8, 126.4, 126.6, 132.1, 132.4, 135.6, 139.6, 139.8, 150.3, 166.5, 166.6, 167.7, 170.6.

Treatment of **52** with TsN_3 using the standard reaction conditions for the introduction of a diazo group followed by a subsequent thermolysis of the labile diazo ester **53** with Cu(acacF_6) hydrate produced no characterizable products. There was no indication of the presence of an intramolecular cycloadduct such as **54** in the crude reaction mixture which consisted of a multitude of products.

***tert*-Butyl 3-(2-Methoxy-2-oxoethyl)-2-[(5-methoxy-4-methylidene-5-oxopentyl)(methyl)carbamoyl]-1*H*-indole-1-carboxylate (55).** A mixture of 3-((methoxycarbonyl)-methyl)-1*H*-indole-2-carboxylic acid (200 mg, 1 equiv), methyl 5-(methylamino)-2-methylenepentanoate hydrochloride salt (1.5 equiv), EDCI (2 equiv), and BtOH (2.5 equiv) was taken up in 3.4 mL of THF. To this solution was added DIPEA (6 equiv) dropwise, and the resulting mixture was stirred at rt for 20 h. The solvent was removed under reduced pressure, and the crude residue was subjected to silica gel chromatography to give methyl 5-[1-[3-(2-methoxy-2-oxoethyl)-1*H*-indol-2-yl]-*N*-methylformamido]-2-methylidenepentanoate as a yellow oil in 87% yield: IR (film) 3219, 2949, 1716, 1608, 1557, 1488, 1434, 1311, 1193, 1146, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (q, 2H, J = 7.4 Hz), 2.32 (s, 2H), 3.09 (s, 3H), 3.56 (t, 2H, J = 7.2 Hz), 3.69 (s, 3H), 3.77 (s, 3H), 3.87 (s, 2H), 5.59 (s, 1H), 6.15 (s, 1H), 7.16 (ddd, 1H, J = 7.8, 7.2, 1.0 Hz), 7.27 (d, 1H, J = 8.0, 1.2 Hz), 7.39 (dt, 1H, J = 8.0, 0.9 Hz), 7.60 (dt, 1H, J = 8.0, 0.9 Hz), 8.77 (s, 1H).

The above NH-indole (200 mg, 1 equiv), DMAP (0.15 mmol), and TEA (1.2 equiv) were dissolved in CH_3CN (8 mL), and the solution was cooled to 0 °C. To this mixture was added *t*-Boc_2O (2.4 equiv), and the mixture was stirred at 0 °C for 1 h. The reaction was then quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude residue was subjected to silica gel chromatography to give the corresponding *t*-Boc-protected indole **55** in 83% yield as a colorless liquid which was obtained as a 1.8:1-mixture of rotamers: IR (film) 2950, 1732, 1641, 1477, 1450, 1435, 1359, 1327, 1255, 1151, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56−1.63 (m, 9H), 1.65−1.75 (m, 1H), 1.80−1.91 (m, 1H), 2.06−2.16 (m, 0.4H), 2.43 (t, 1H, J = 7.6 Hz), 2.86 (s, 2H), 3.12 (s, 2H), 3.13−3.26 (m, 0.6H), 3.62−3.71 (m, 6H), 3.78 (s, 2H), 3.96−4.14 (m, 0.4H), 5.44 (s, 0.3H), 5.68 (s, 0.5H), 6.05 (s, 0.3H), 6.22 (s, 0.5H), 7.22−7.30 (m, 1H), 7.35−7.39 (m, 1H), 7.51 (t, 1H, J = 8.2 Hz), 8.12 (dd, 1H, J = 12.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.8, 28.3, 29.2, 29.5, 30.2, 30.4, 32.3, 36.1, 46.8, 50.5, 52.0, 52.3, 84.8, 84.9, 112.9, 113.3, 115.8, 115.9, 119.6, 119.8, 123.5, 125.5, 125.6, 129.1, 131.8, 135.4, 135.6, 139.5, 139.9, 149.2, 1634.0, 164.2, 167.7, 171.0, 171.1.

Treatment of **55** with TsN_3 using the standard reaction conditions for the introduction of a diazo group followed by a subsequent thermolysis of the labile diazo ester **56** with Cu(acacF_6) hydrate produced no characterizable products. There was no indication of the presence of an intramolecular cycloadduct such as **57** in the crude reaction mixture which consisted of a multitude of products.

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2-[3-[(1-Diazo-2-methoxycarbonylmethyl-1-methyl-1*H*-indole-3-carbonyl)methylamino]-3-oxo-propyl]acrylic Acid Methyl Ester (62). To a solution of 0.24 g (1.0 mmol) of 2-methoxycarbonylmethyl-1-methyl-1*H*-indole-3-carboxylic acid (**58**)[30] in 10 mL of dry CH_2Cl_2 containing 2 drops of dry DMF was added 0.13 g (1.1 mmol) of oxalyl chloride. The solution was stirred at rt for 30 min and concentrated under reduced pressure, and an additional 10 mL portion of CH_2Cl_2 was added followed by a 2.0 M solution of methyl amine in THF (3.3 mmol). The mixture was stirred at rt for 1 h, poured into water, and extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 0.2 g (81%) of (1-methyl-3-methyl-carbamoyl-1*H*-indol-2-yl)acetic acid methyl ester (**59**) as a white solid: mp 124−126 °C; IR (film) 1736, 1628, 1551, 1472, 1403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (m, 3H), 3.59 (s, 3H), 3.69 (s, 3H), 4.24 (s, 2H), 6.39 (brs, 1H), 7.13−7.28 (m, 3H), 7.74 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 29.8, 31.2, 52.5, 109.5, 109.7, 119.2, 121.1, 122.2, 124.7, 136.1, 136.5, 166.2, 170.3; HRMS calcd for $[C_{14}H_{16}N_2O_3 + H^+]$ 261.1239, found 261.1242.

A mixture of 0.98 g (3.8 mmol) of the above compound, 1.0 g (5.6 mmol) of 4-methoxycarbonylpent-4-enoyl chloride (**60**),[31] 3.5 g of powdered molecular sieves (4 Å, <5 μm), and 30 mL of CH_2Cl_2 was stirred for 18 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was washed with an aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting crude oil was subjected to silica gel chromatography to give 1.23 g (82%) of 2-[3-[(2-methoxycarbonylmethyl-1-methyl-1*H*-indole-3-carbonyl)methylamino]-3-oxopropyl]acrylic acid methyl ester (**61**) as a pale yellow oil: IR (neat) 1741, 1719, 1661, 1532, 1474, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.65 (t, 2H, J = 7.5 Hz), 2.82 (t, 2H, J = 7.5 Hz), 3.24 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 4.25 (s, 2H), 5.53 (d, 1H, J = 1.2 Hz), 6.14 (d, 1H, J = 1.2 Hz), 7.22−7.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 30.5, 31.5, 33.8, 35.7, 52.0, 52.8, 110.3, 110.4, 119.9, 122.7, 123.3, 124.7, 125.8, 136.7, 139.3, 140.6, 167.3, 169.3, 170.5, 175.1; HRMS calcd for $[C_{21}H_{24}N_2O_6 + H^+]$ 401.1713, found 401.1716.

To a solution containing 0.5 g (1.3 mmol) of the above compound **61** and 0.37 g (1.6 mmol) of 4-nitrobenzenesulfonyl azide[32] in 20 mL of CH_3CN at 0 °C under Ar was added 0.21 g (1.4 mmol) of DBU. The solution was stirred at 0 °C for 1 h, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.41 g (78%) of **62** as an orange oil which was used in the next step without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, 2H, J = 7.2 Hz), 2.81 (t, 2H, J = 7.2 Hz), 3.21 (s, 3H), 3.68 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 5.55 (d, 1H, J = 1.2 Hz), 6.15 (d, 1H, J = 1.2 Hz), 7.27−7.59 (m, 4H).

6,11*c*-Dihydroxy-1,7-dimethyl-2-oxo-1,2,3,4,5,6,7,11*c*-octahydropyrido[3,2-*c*]carbazole-4*a*,6-dicarboxylic Acid Dimethyl Ester (66). To a suspension of 10 mg of $Rh_2(OAc)_4$ in 10 mL of benzene at 100 °C was slowly added a solution of 0.21 g (0.49 mmol) of diazoindole **62** in 3 mL of benzene. The mixture was heated for 1.5 h, the solvent was removed under reduced pressure, and the residue was dissolved in 10 mL of EtOAc. The solution was allowed to cool to rt, and the resulting solid was filtered to give 0.09 g (47%) of **66** as a pale yellow oil: IR (Nujol) 1742, 1731, 1621, 1461, 1378 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 1.81−1.99 (m, 1H), 2.19 (d, 1H, J = 13.6 Hz), 2.25−2.36 (m, 2H), 2.64−2.70 (m, 1H), 2.78−2.81 (brd, 1H), 2.81 (s, 3H), 3.31 (s, 3H), 3.70 (s, 3H), 3.93 (s, 3H), 6.23 (s, 1H), 6.74 (s, 1H), 7.12 (t, 1H, J = 7.6 Hz), 7.23 (t, 1H, J = 7.6 Hz), 7.49 (d, 1H, J = 7.6 Hz), 7.60 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO) δ 25.1, 29.8, 32.4, 33.4, 41.6, 51.4, 52.5, 54.5, 72.0, 84.3, 109.8, 112.5, 119.4, 121.5, 121.8, 123.8, 136.9, 137.8, 171.2, 171.8, 172.1; HRMS calcd for $[C_{21}H_{24}N_2O_7 + H^+]$ 417.1662, found 417.1656.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR data of various key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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