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IMDAF Cascade Approach toward the Synthesis of the Alkaloid (±)-Minfiensine

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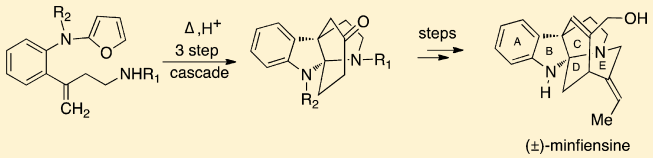
Supporting Information

ABSTRACT: The total synthesis of the *Strychnos* alkaloid (±)-minfiensine was achieved via an intramolecular amidofuran Diels–Alder cycloaddition/rearrangement followed by an iminium ion/cyclization cascade sequence. This domino process provides for a rapid access to the unique 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core structure found in the alkaloid minfiensine (**2**). In this paper, the full account of our synthetic study is described, highlighting the successful application of the cascade sequence to form the A/B/C/D rings of (±)-minfiensine (**2**) in high yield. A palladium-catalyzed enolate coupling reaction was then used to furnish the final E ring and complete the total synthesis of (±)-minfiensine (**2**).



INTRODUCTION

The *Strychnos* class of alkaloids, especially known for the presence of a vast array of interesting indole-based structures, have been isolated from a variety of natural sources and have been of long-standing interest to the synthetic community due to their interesting biological activities and challenging chemical complexity.[1] In 1989, Massiott and co-workers isolated minfiensine (**2**) from the African plant *Strychnos minfiensis*. The structure of this alkaloid was determined by NMR studies and was shown to contain the structurally unique 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole skeleton (**1**) (Figure 1).[2] While this tetracyclic structure is unprecedented in the *Strychnos* class, it is found to be more prevalent in the akuammiline skeleton of alkaloids, appearing in the structurally related alkaloids vincorine (**3**) and echitamine (**4**) (Figure 1). This type of molecular assemblage is recognized for its important role in traditional medicine.[3] Not surprisingly, due to the wide variety of biological properties they exhibit (i.e., anti-inflammatory, antibacterial, anticancer, and antimalarial activity),[3a] interest in the synthesis of the akuammiline alkaloids and related natural products containing the 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core structure has grown in recent years and provides the synthetic community with significant challenges due to their unique chemical complexity.[4]

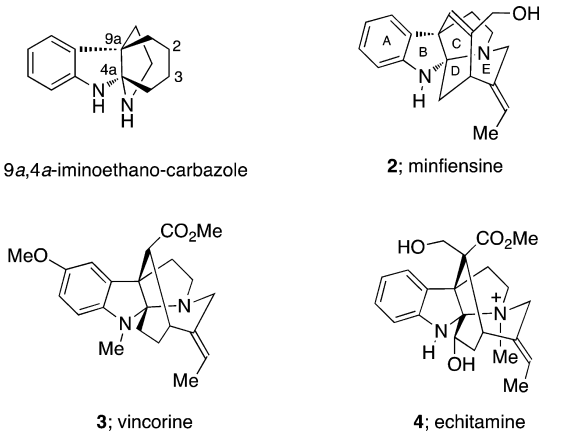


Figure 1. Core skeleton of Akuammiline alkaloids.

The first total synthesis of (+)-minfiensine (**2**) was reported by Overman and co-workers and utilized a sequential enantioselective intramolecular Heck/iminium ion addition sequence to generate the 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core.[5] The Overman group then demonstrated that two types of palladium-mediated routes can be used to prepare the natural product, one involving a Heck cyclization and the other a palladium-catalyzed enolate coupling to generate the pentacyclic framework. Soon thereafter, Qin and co-workers developed a three-step, one-pot cyclopropane-mediated route to the core of (±)-minfiensine (**2**).[6] Closure of the final E-ring was carried out via a palladium-catalyzed enolate coupling reaction similar to that used by Overman.[5] Wang and co-workers then reported on a transition-metal-catalyzed reaction as the key step in a formal synthesis of (±)-minfiensine (**2**).[7] This approach relied on a gold-catalyzed tandem cyclization to generate a key intermediate that had been employed in Overman's pioneering synthesis of (+)-minfiensine (**2**). Another route to (±)-minfiensine (**2**) was subsequently described by Qiu and co-workers and began with a Fischer indole reaction to generate the indolone skeleton.[8] This was followed by a palladium-catalyzed allylation sequence for installation of the quaternary stereocenter present in minfiensine (**2**). The Macmillan group also completed an efficient nine-step synthesis of (+)-minfiensine (**2**) which relied on a unique organocatalyzed route to generate the natural

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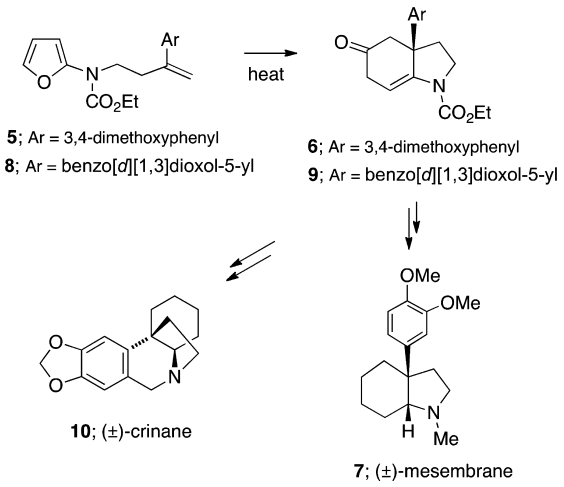
product. This was accomplished from a Boc-tryptamine intermediate via an organo-catalyzed Diels–Alder cycloaddition/amine cyclization.[9]

While a plethora of routes to minfiensine (**2**) exist,[10] we recognized that it would be desirable to develop a general and high-yielding method to prepare the important 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core **1** found in quite a number of different alkaloids. For some time, our research group has been utilizing the intramolecular furan Diels–Alder (IMDAF) reaction to prepare a wide assortment of complex natural products.[11] As a result of these studies, we envisioned a synthesis of minfiensine that would proceed via an IMDAF reaction of an appropriately substituted amidofuran[12] followed by an acid-catalyzed iminium-ion/addition sequence (vide infra) to generate the natural product. Herein we provide a full account of our studies toward a successful construction of (±)-minfiensine (**2**) that proceeds by use of the above protocol for its synthesis.[13]

RESULTS AND DISCUSSION

In a series of earlier papers from our research group, we demonstrated the utility of the intramolecular furan Diels–Alder (IMDAF) rearrangement cascade of amidofurans to prepare several alkaloids.[11] Thus, heating amidofurans **5** and **8** produced tetrahydroindolinone intermediates **6** and **9**, which in turn were employed to achieve the total syntheses of (±)-mesembrane **7** and (±)-crinane **10** (Scheme 1).[14]

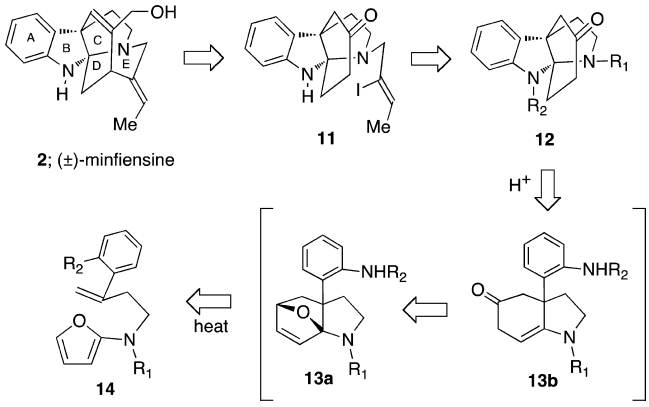
Scheme 1



We thought that by employing amidofuran **14** as the starting substrate (Scheme 2) we would be able to promote the formation of tetrahydroindolinone **13b**, which represents the C/D core portion of minfiensine (**2**). From this key intermediate, we believed that an acid-promoted addition of the tethered aryl amine **13b** onto a transient iminium ion would generate the B ring present in the 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core **12**. Installation of the final E ring could be induced to proceed by a palladium-catalyzed enolate cyclization of **11**[15] under conditions similar to those previously described in our synthesis of strychnine.[16]

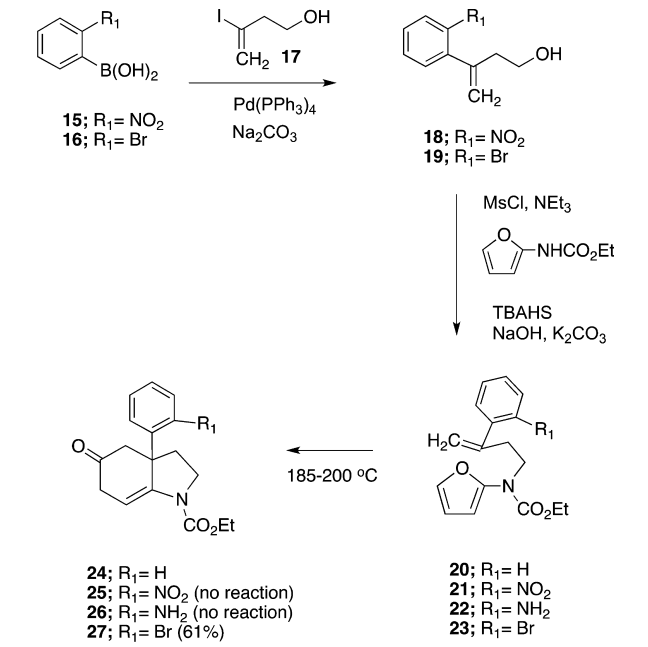
Previous results from our laboratory showed that the thermolysis of an amido furan such as **20** afforded tetrahydroindoline **24** in excellent yield.[14] On the basis of these earlier investigations, we decided to begin our studies

Scheme 2



toward minfiensine (**2**) by first making using of the *o*-nitroaryl substrate **21**,[17] which we believed could be readily reduced to the desired aniline after the key IMDAF cycloaddition reaction (Scheme 3). The desired amidofuran **21** was readily obtained

Scheme 3



by a Suzuki cross-coupling reaction of the commercially available boronic acid **15** with vinyl iodide **17**,[18] thereby generating compound **18** in good yield. From **18**, the alcohol moiety was converted into the corresponding mesylate, and a subsequent displacement with the amido anion derived from ethyl furan-2-yl carbamate led to the desired cycloaddition precursor **21**. Unfortunately, all of our attempts to induce the IMDAF cycloaddition of **21**, even at temperatures up to 200 °C, led to only recovered starting material. Using some conditions previously described by Heathcock ($Cu(acac)_2$, $NaBH_4$, EtOH),[19] reduction of the nitro group in **21** was cleanly achieved in near-quantitative yield. Once again, our efforts to induce an IMDAF cycloaddition of furan **22** also failed to produce any characterizable product. We also prepared the *o*-bromoaryl furan **23**, and in this case, a 61% yield of the desired tetrahydroindolinone intermediate **27** was obtained, but only by extensive heating for 6 days at 200 °C.

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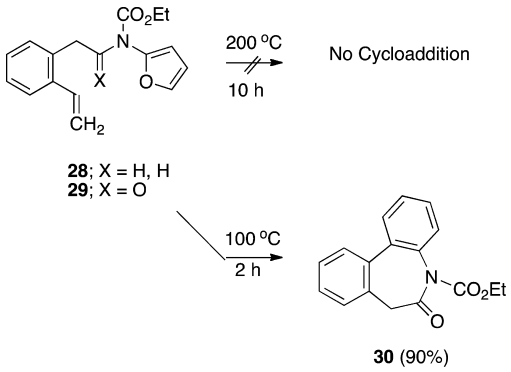
Considering our previous success with the IMDAF reactions of the related *meta*- and *para*-substituted systems (i.e., Scheme 1),[14] we suspected that the presence of a substituent in the *ortho*-position of the aromatic ring resulted in an unfavorable steric interaction in the required Diels–Alder transition state for the above cycloadditions, thereby diminishing the overall rate of the IMDAF reaction. Even though tetrahydroindolinone **27** could be obtained in somewhat reasonable yield, the required reaction conditions were certainly less than desirable for throughput of material in order to complete a total synthesis of (±)-minfiensine (**2**). At this point in time, we decided to make use of some information derived from some earlier work which showed that a significant enhancement of rate occurred when 2-iminofurans were used as substrates.[20] This substantial rate enhancement in the intramolecular 4 + 2 cycloaddition is most likely due to a conformational change which results by installation of a carbonyl group in the tether between the diene and dienophile. Our previous studies showed that the cycloaddition of enamido furan **28** did not occur even upon heating at 200 °C for 10 h. The incorporation of an additional carbonyl group in the tether as in imidofuran **29** led to a most facile cycloaddition reaction to provide **30** in 90% yield when heating **29** at 100 °C for only 2 h (Scheme 4).[20] We believe

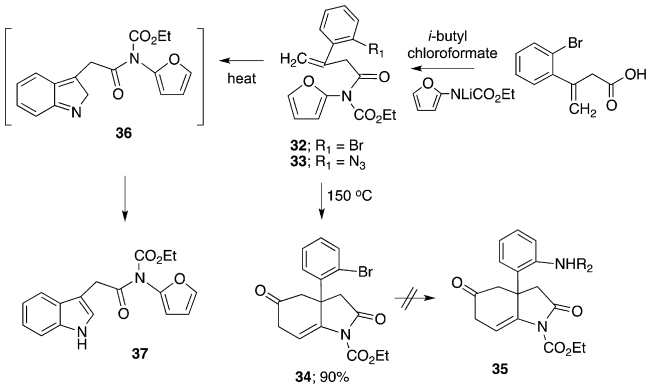
Scheme 4



that this remarkable rate enhancement is the result of the dienophile and furanyl ring being placed in closer proximity to each other for the cycloaddition as compared to those systems lacking the imido carbonyl group in the tether. With this in mind, we expected that the IMDAF reaction of imidofuran **32** would be much more facile than the corresponding amidofuran analogue **23**. Consequently, we prepared imidofuran **32** by a two-step sequence from 3-(2-bromophenyl)but-3-enoic acid (Scheme 5). To our delight, the Diels–Alder cycloaddition/rearrangement cascade of **32** to **34** occurred in 90% yield when heated at 150 °C for only 10 h.

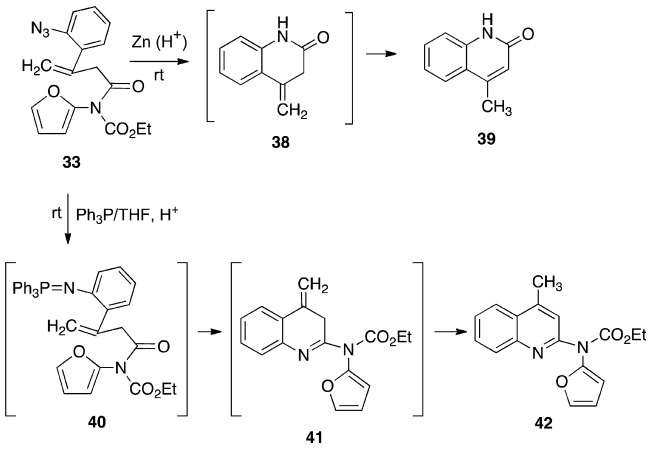
With a reasonable route now available for accessing the bromo-containing tetrahydroindolinone core **34**, we decided to pursue the installation of the anilino group which was necessary for our planned iminium ion cyclization. Unfortunately, all of the conditions we tried for the conversion of the bromo-substituted imidofuran **34** to the corresponding amino derivative **35** were unsuccessful.[21] As an alternative approach, we considered using the azido furan **33**, which we hoped would be readily converted to the desired aromatic amine through azide reduction after the IMDAF cycloaddition. However, the results were once again disappointing, as only 3-substituted indole **37** was observed upon heating rather than the desired Diels–Alder/rearrangement product (Scheme 5). Mechanistically indole **37** is thought to be formed via nitrogen extrusion, electrocyclization, and a subsequent 1,5-hydrogen shift.[22]

Scheme 5



We next examined the direct reduction of azido imidofuran **33** using traditional azide zinc-mediated or Staudinger[23] reduction conditions (Zn/acid or PPh_3/H_2O) (Scheme 6) so as to prepare the desired arylamine. However, when azide **33** was submitted to various Zn/acid conditions, azide reduction was rapidly followed by cyclization and displacement of the furanyl carbamate to provide lactam **38**. This transient species then underwent a further 1,3-hydrogen shift to eventually give 4-methylquinolin-2(1*H*)-one (**39**). Additional attempts to reduce azide **33** with PPh_3/THF did give the expected iminophosphorane **40**, but this transient intermediate rapidly reacted with the adjacent imido carbonyl group via an aza-Wittig[24] reaction to produce dihydroquinoline **41**, which rapidly isomerized with a trace of acid to the more stable quinoline **42** (Scheme 6).

Scheme 6



It became clear to us at this point in time that the presence of a substituent group in the ortho position of the aromatic ring of the amidofuranyl system significantly diminished the rate of the critical IMDAF cycloaddition in our first-generation approach toward minfiensine (**2**). To avoid this obstacle, a second-generation IMDAF approach was developed, and this involved a thermal IMDAF cycloaddition of the related aminofuran **43**. Our retrosynthetic plan for this new direction is outlined in Scheme 7. In this modified route, we believed that we could access the A/B/C tricyclic intermediate **44** via an IMDAF/rearrangement cascade of **43**. This proposed approach would

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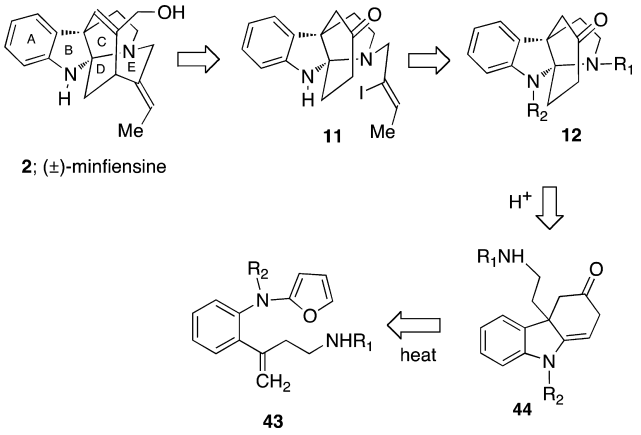
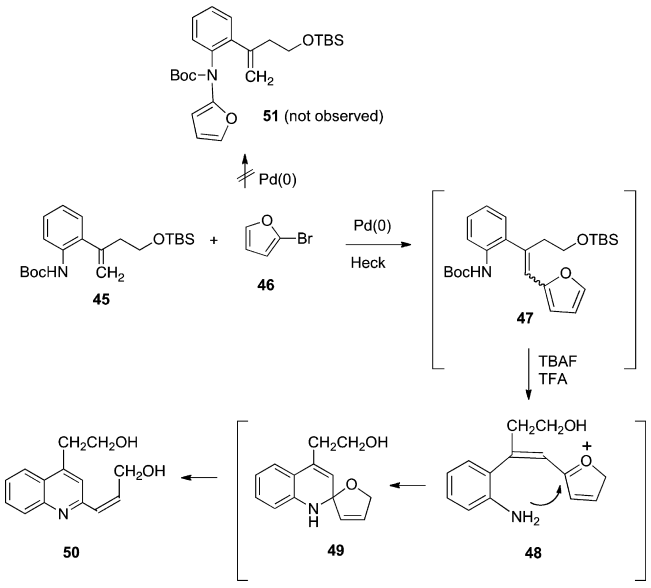
Scheme 7



alleviate the problematic pathways encountered in our first-generation route. Furthermore, we envisioned that this cascade sequence could be combined with a subsequent iminium ion cyclization to form the D ring present in intermediate **12**, thereby providing a rapid path toward the synthesis of (±)-minfiensine (**2**).

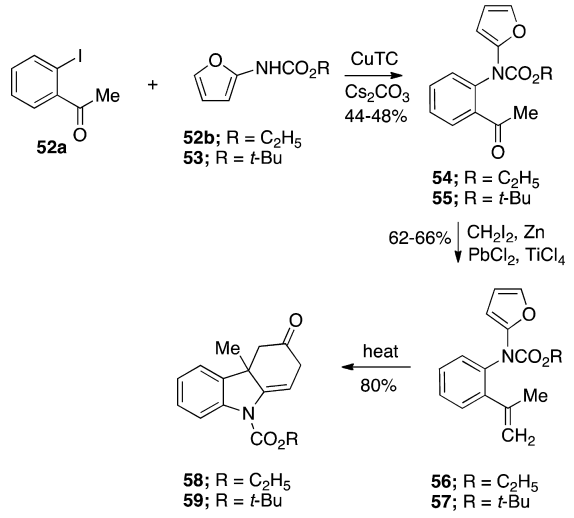
In order to ascertain the feasibility of this approach, we decided to first examine the cyclization of a model substrate (Scheme 8). Our initial attempts to prepare furan **51** by a

Scheme 8



palladium-catalyzed coupling of 2-bromofuran **46** with aryl amine **45** did not give the desired Buchwald–Hartwig coupling product **51**. Instead, we believe that a competitive Heck coupling reaction occurred across the vinyl group to produce intermediate **47**, which was eventually converted to quinoline **50** via the spirocyclic intermediate **49**. As a consequence of this competitive Heck reaction, we opted to prepare the desired model amidofuran system by reacting furanyl carbamates **52b** (and **53**) with aryl iodide **52a** (Scheme 9) in the presence of a transition-metal catalyst. We were pleased to note that amidofurans **54** and **55** were formed in good yield when the reaction was carried out employing Buchwald's copper-catalyzed amidation protocol using copper(I) thiophene-2-

Scheme 9



carboxylate (CuTC)/Cs_2CO_3 as the catalyst.[25] Submission of both of these substrates to standard olefination conditions[26] provided the model cycloaddition precursors **56** and **57**. Upon heating at 100 °C, these precursors underwent the desired IMDAF rearrangement cascade to give tetrahydroindolinone intermediates **58** and **59** in 80% yield.

With this positive result in hand from the model systems, we proceeded with our synthesis of minfiensine by preparing the necessary Diels–Alder cycloaddition precursor. Submission of commercially available boronate ester **60** to Suzuki–Miyaura cross-coupling conditions with vinyl iodide **17** resulted in the formation of the desired styrenyl alcohol intermediate **61** in good yield. Standard mesylation of **61** was followed by a subsequent displacement with allylamine to give **63** in 72% yield. Installation of the *t*-Boc from **63** proceeded in 74% yield to afford **64**. Once again, we found the Buchwald's (CuTC)/Cs_2CO_3 coupling conditions to be optimal, as smooth coupling of acyl amine **64** and 2-bromofuran **46** occurred at 90 °C. Under these conditions, the initially formed amidofuran spontaneously underwent the desired IMDAF cycloaddition giving rise to cycloadduct **66** which, in this case, was isolated in 82% yield. Additional heating of oxabicycle **66** at 120 °C triggered the expected ring-opening/rearrangement sequence, producing tetrahydroindolinone **68** in 31% yield. The unprotected amine **63** was also submitted to the CuTC coupling conditions and furnished the tandem coupling/Diels–Alder cycloaddition product **65** in 86% yield. To our delight, when oxabicycle **65** was heated at 120 °C in the presence of MgI_2, the required ring opening/rearrangement sequence took place which was then followed by a subsequent iminium ion cyclization cascade, all in one pot, to provide **69** from **63** in 60% overall yield (Scheme 10).

With the tetracyclic intermediate **69** in hand, we focused our efforts on completing the synthesis of (±)-minfiensine (**2**). This was accomplished by removal of the allyl group[27] in **69** followed by displacement of the mesylate functionality in **71**[28] with the secondary amino group in **70** to produce vinyl iodide **72**. Treatment of **72** under Pd-catalyzed enolate coupling conditions[15,16] ($PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3) led to the advanced intermediate **73** in good yield, thereby providing the structural framework of minfiensine. Enol triflate formation via the Comins reagent ($ArNTf_2$, NaHMDS) afforded **74**, which smoothly underwent a Stille cross-coupling reaction with

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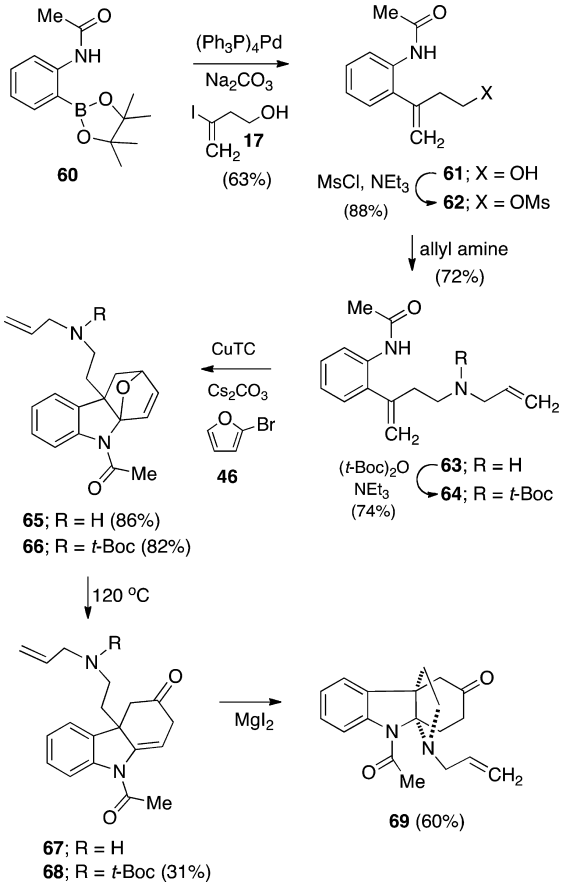
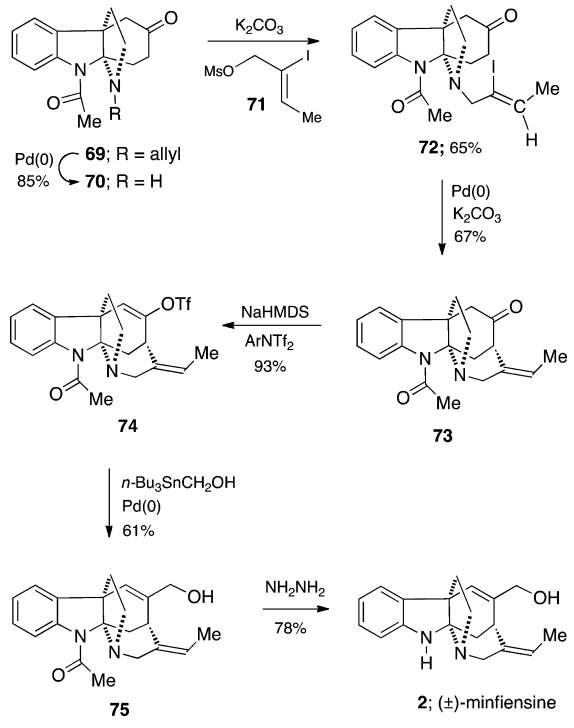
Scheme 10



Scheme 11



(tri-*n*-butylstannyl)methanol[29] to give the *N*-acylated minfiensine derivative **75**. Acyl group deprotection with hydrazine provided the natural product (±)-minfiensine (**2**) in 78% yield (Scheme 11).

In conclusion, in this paper, we have described our successful approach toward the total synthesis of the *Strychnos* alkaloid (±)-minfiensine by utilizing a one-pot intramolecular amidofuran [4 + 2]-cycloaddition (IMDAF) rearrangement/iminum ion cyclization cascade sequence as the key step to generate the A/B/C/D rings present in (±)-minfiensine. From this core structure, closure of the final E ring was accomplished by a palladium-catalyzed coupling of the tethered vinyl iodide and the keto−enolate. This work not only provides a versatile route to the complex and unique 1,2,3,4-tetrahydro-9a,4a-iminoethanocarbazole core structure present in minfiensine but also has the potential to provide access to other structurally related alkaloids.

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 measurements 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.

Ethyl Furan-2-yl-(3-(2-nitrophenyl)but-3-enyl)carbamate (21). To a stirred solution containing (2-nitrophenyl)boronic acid (0.6 g, 3.6 mmol), 3-iodobut-3-en-1-ol[18] (0.59 g, 3.0 mmol), benzene (30 mL), EtOH (15 mL), and 2 M aqueous Na_2CO_3 (15.2 mL) was added $Pd(PPh_3)_4$ (0.14 g, 0.06 mmol), and the reaction mixture was heated to 65 °C for 12 h. After being cooled to room temperature, the mixture was diluted with ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to provide 0.37 g (64%) of 3-(2-nitrophenyl)but-3-en-1-ol (**18**) as a yellow oil: IR (thin film) 3376, 2950, 2882, 1608, 1571, 1526, 1349, 048, 911, 787, 762, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.68−2.71 (m, 2H), 3.71 (t, 2H, J = 6.0 Hz), 5.07 (s, 1H), 5.29 (d, 1H, J = 0.8 Hz), 7.35 (dd, 1H, J = 7.6 and 1.2 Hz), 7.41−7.45 (m, 1H), 7.56 (dt, 1H, J = 7.6 and 1.2 Hz), 7.84−7.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.5, 60.6, 117.6, 124.5, 128.4, 130.8, 132.8, 137.4, 143.2, 149.1.

To a stirred solution of the above alcohol (0.16 g, 0.83 mmol) and methanesulfonyl chloride (0.07 mL, 0.91 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triethylamine (0.14 mL, 1.0 mmol), and the resulting mixture was stirred for 1 h at 0 °C. The mixture was then diluted with H_2O and extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel to provide 0.17 g (74%) of 3-(2-nitrophenyl)but-3-enyl methanesulfonate as a pale yellow oil: IR (thin film) 3031, 2941, 1638, 1608, 1571, 1526, 1352, 1175, 960, 913, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.86 (dt, 2H, J = 6.8 and 0.8 Hz), 2.97 (s, 3H), 4.31 (t, 2H, J = 6.8 Hz), 5.11 (s, 1H), 5.31 (d, 1H, J = 0.8 Hz), 7.34 (dd, 1H, J = 7.6 and 1.6 Hz), 7.44−7.48 (m, 1H), 7.59 (dt, 1H, J = 7.6 and 1.2 Hz), 7.92 (dd, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.5, 37.6, 67.7, 117.9, 124.6, 128.8, 131.4, 133.3, 137.0, 142.0, 148.3.

A solution of ethyl furan-2-ylcarbamate[30] (0.04 g, 0.24 mmol), K_2CO_3 (0.08 g, 0.48 mmol), tetrabutylammonium hydrogensulfate (0.015 g, 0.044 mmol), and freshly powdered NaOH (33 mg, 0.82 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture was cooled to room temperature, and a solution containing the above mesylate (0.08 g, 0.29 mmol) in benzene (3 mL) was added. The mixture was heated at 80 °C for 1 h and was then cooled to rt, diluted with Et_2O, and quenched with H_2O. The aqueous layer was extracted with Et_2O, and the organic layer was washed with a saturated

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aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography to provide 0.05 g (60%) of the titled compound **21** as a pale yellow oil: IR (thin film) 3085, 2983, 2935, 1717, 1610, 1527, 1350, 1297, 1378, 1195, 1145, 911, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, J = 6.8 Hz), 2.66 (t, 2H, J = 7.6 Hz), 3.70−3.74 (m, 2H), 4.15 (q, 2H, J = 14.0 and 6.8 Hz), 5.04 (s, 1H), 5.23 (d, 1H), 6.01 (brs, 1H), 6.34−6.36 (m, 1H), 7.19 (s, 1H), 7.30−7.32 (m, 1H), 7.40−7.44 (m, 1H), 7.53−7.57 (m, 1H), 7.88−7.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 35.8, 48.0, 62.4, 102.0, 111.2, 116.5, 124.4, 128.4, 131.3, 132.8, 138.0, 138.7, 144.2, 148.1, 148.8, 155.0.

All of our attempts to induce the IMDAF cycloaddition of **21**, even at temperatures up to 200 °C, led to only recovered starting material.

Ethyl 3-(2-Aminophenyl)but-3-enyl(furan-2-yl)carbamate (22). To a stirred solution of $Cu(acac)_2$ (22 mg, 0.085 mmol) in absolute EtOH (5.7 mL) was added $NaBH_4$ (0.1 g, 2.8 mmol). The reaction mixture changed color from purple to brown. The mixture was stirred at rt for 25 min, during which time the color turned clear and a brown precipitate formed. A solution of the above furanyl amide **21** (0.09 g, 0.28 mmol) in THF (5.7 mL) was added, and the resulting mixture was stirred for 1.25 h at rt. The mixture was then poured into a saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 0.08 g (93%) of the titled compound **22**: IR (thin film) 3447, 3369, 2980, 2931, 1713, 1615, 1495, 1409, 1379, 1298, 1194, 1155, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, J = 7.2 Hz), 2.65 (d, 1H, J = 6.8 Hz), 2.67 (d, 1H, J = 8.4 Hz), 3.68−3.72 (m, 2H), 4.15 (q, 2H, J = 7.2 Hz), 5.16 (d, 1H, J = 1.6 Hz), 5.32 (d, 1H, J = 1.6 Hz), 6.01 (brs, 1H), 6.35 (dd, 1H, J = 3.6 and 2.4 Hz), 6.68−6.74 (m, 2H), 6.97 (dd, 1H, J = 7.2 and 1.6 Hz), 7.06 (td, 1H, J = 7.6 and 1.6 Hz), 7.19−7.20 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 36.1, 48.0, 62.5, 111.2, 115.9, 116.7, 118.5, 127.6, 128.3, 128.7, 138.3, 138.8, 143.3, 144.4, 147.9, 155.2.

All of our attempts to induce the IMDAF cycloaddition of **22**, even at temperatures up to 200 °C, led to only recovered starting material.

Ethyl 3-(2-Bromophenyl)but-3-enyl(furan-2-yl)carbamate (23). To a stirred solution of 3-iodobut-3-en-1-ol (0.59 g, 3.0 mmol) in benzene (10 mL) was added $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), 2 M Na_2CO_3 (12 mL), and a solution of 2-bromophenylboronic acid (**16**) (0.71 g, 3.5 mmol) in EtOH (15 mL). The reaction mixture was heated to 65 °C for 14 h, cooled to rt, diluted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to yield 0.67 g (79%) of 3-(2-bromophenyl)but-3-en-1-ol (**19**) as a yellow oil: IR (thin film) 3339, 2944, 1638, 1468, 1427, 1042, 1024, 910, 761, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.70−2.73 (m, 2H), 3.64 (t, 2H, J = 6.0 Hz), 5.10−5.11 (m, 1H), 5.35−5.36 (m, 1H), 7.12−7.19 (m, 2H), 7.26−7.30 (dt, 1H, J = 8.0 and 1.2 Hz), 7.57 (dd, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.5, 60.4, 118.3, 122.2, 127.5, 128.9, 130.4, 133.0, 143.1, 146.3.

To a stirred solution of the above alcohol **19** (0.19 g, 0.82 mmol) and methanesulfonyl chloride (0.07 mL, 0.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (0.14 mL, 1.0 mmol), and the resulting mixture was stirred for 0.5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel chromatography to provide 0.27 g of 3-(2-bromophenyl)but-3-enyl methanesulfonate as a yellow oil: IR (thin film) 2937, 1719, 1468, 1427, 1353, 1173, 1028, 958, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.91−2.95 (m, 5H), 4.22−4.25 (m, 2H), 5.14 (s, 1H), 5.36−5.37 (m, 1H), 7.14−7.18 (m, 2H), 7.27−7.31 (m, 1H), 7.57 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.3, 37.7, 67.7, 119.1, 122.1, 127.7, 129.3, 130.8, 133.1, 142.3, 144.6.

A solution of ethyl furan-2-ylcarbamate (37 mg, 0.24 mmol), K_2CO_3 (0.09 g, 0.53 mmol), tetrabutylammonium hydrogen sulfate (16 mg, 0.05 mmol), and freshly powdered NaOH (33 mg, 0.82 mmol) in benzene (10 mL) was heated at reflux for 30 min. The mixture was cooled to rt, a solution containing the above mesylate (0.09 g, 0.29 mmol) in benzene (3 mL) was added, and the reaction mixture was then heated at 80 °C for 1 h. The mixture was cooled to rt, diluted with Et_2O, and quenched with H_2O. The aqueous layer was extracted with Et_2O, washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography to provide 12 mg (15%) of the titled compound **23** as a pale yellow oil: IR (thin film) 2984, 2929, 1718, 1614, 1407, 1467, 1295, 1194, 1025, 911, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, J = 7.2 Hz), 2.72 (t, 2H, J = 7.6 Hz), 3.67−3.70 (m, 2H), 4.15 (q, 2H, J = 14.4 and 7.2 Hz), 5.04 (s, 1H), 5.27 (d, 1H, J = 1.2 Hz), 6.02 (brs, 1H), 6.35 (m, 1H), 7.10−7.27 (m, 4H), 7.53−7.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 35.5, 47.7, 62.4, 102.5, 111.2, 117.4, 122.1, 127.4, 128.9, 130.6, 133.0, 138.8, 143.4, 146.8, 147.9, 155.1.

Ethyl 3a-(2-Bromophenyl)-5-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-1-carboxylate (27). A sample of *N*-furanyl carbamate **23** (12 mg, 0.03 mmol) in toluene (1.5 mL) was heated in a sealed tube at 200 °C for 6 days. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography to yield 7.5 mg (61%) of the titled compound **27** as a yellow oil: IR (thin film) 2984, 2927, 1715, 1672, 1408, 1326, 1175, 1140, 1024, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (brs, 3H), 2.00−2.09 (m, 1H), 2.62 (d, 1H, J = 15.2 Hz), 2.73 (dd, 1H, J = 22.4 and 2.4 Hz), 2.97 (dd, 1H, J = 22.4 and 5.6 Hz), 3.14 (m, 2H), 3.78 (t, 1H, J = 9.2 Hz), 3.98 (d, 1H, J = 15.2 Hz), 4.14−4.32 (m, 2H), 6.50 (brs, 1H), 7.11 (td, 1H, J = 7.6 and 1.6 Hz), 7.21 (td, 1H, J = 7.6 and 1.6 Hz), 7.33 (d, 1H, J = 7.6 Hz), 7.62 (dd, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 35.9, 37.6, 46.8, 50.0, 53.2, 61.8. 102.9, 122.4, 128.1, 129.7, 130.2, 136.5, 137.0, 142.5, 153.7, 209.0; HRMS calcd for $[(C_{17}H_{18}BrNO_3) + H^+]$ 364.0470, found 364.0546.

Ethyl 3-(2-Bromophenyl)but-3-enoyl(furan-2-yl)carbamate (32). To a stirred solution of 3-iodobut-3-en-1-ol (0.59 g, 3.0 mmol) in benzene (10 mL) were added $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol), a 2 M Na_2CO_3 solution (12 mL), and 2-bromophenylboronic acid (0.71 g, 3.5 mmol) in EtOH (15 mL). The reaction mixture was heated to 65 °C for 14 h, cooled to rt, diluted with ether, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to yield 0.67 g (79%) of 3-(2-bromophenyl)but-3-en-1-ol as a yellow oil: IR (thin film) 3339, 2944, 1638, 1468, 1427, 1024, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.70−2.73 (m, 2H), 3.64 (t, 2H, J = 6.0 Hz), 5.10−5.11 (m, 1H), 5.35−5.36 (m, 1H), 7.12−7.19 (m, 2H), 7.26−7.30 (dt, 1H, J = 8.0 and 1.2 Hz), 7.57 (dd, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.5, 60.4, 118.3, 122.2, 127.5, 128.9, 130.4, 133.0, 143.1, 146.3.

To a stirred solution of the above alcohol (0.15 g, 0.66 mmol) in acetone (27 mL) at 0 °C was added freshly prepared Jones' reagent (1.3 mL, 1.3 mmol, 1.0 M). The resulting solution was stirred at 0 °C for 1 h, warmed to rt, and stirred for an additional 1 h. The mixture was diluted with H_2O and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 0.16 g (91%) of 3-(2-bromophenyl)but-3-enoic acid as a pale yellow oil requiring no further purification: IR (thin film) 3088, 2920, 1709, 1295, 1025, and 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.55 (d, 2H, J = 0.8 Hz), 5.23 (s, 1H), 5.45 (d, 1H, J = 1.2 Hz), 7.13−7.15 (m, 1H), 7.25−7.29 (m, 2H), 7.54 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.1, 121.1, 122.2, 127.8, 129.6, 131.7, 133.2, 142.2, 142.6, 177.0.

To a stirred solution of ethyl furan-2-ylcarbamate (0.22 g, 1.4 mmol) in THF (7 mL) at −78 °C was added *n*-BuLi (0.6 mL, 1.5 mmol, 2.5 M in hexane) dropwise, and the reaction mixture was stirred at −78 °C for 45 min. In a separate flask, the above carboxylic acid (0.39 g, 1.6 mmol) was dissolved in THF (13 mL), and the mixture was cooled to 0 °C. 4-Methylmorpholine (0.18 mL, 1.6 mmol) and isobutyl chloroformate (0.2 mL, 1.6 mmol) were added dropwise, and the solution was stirred for 5 min. The mixture was filtered over Celite with THF (7 mL), the filtrate was cooled to 0 °C, and the preformed furanyl lithiate was added dropwise by cannula. The resulting reaction mixture was stirred for 30 min, quenched with H_2O, and extracted

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with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.29 g (55%) of the titled compound **32** as a yellow oil: IR (thin film) 3128, 2984, 1790, 1750, 1610, 1426, 1255, 1091, 840, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, J = 6.8 Hz), 4.10 (s, 2H), 4.21 (q, 2H, J = 6.8 Hz), 5.24 (d, 1H, J = 0.4 Hz), 5.42 (d, 1H, J = 1.2 Hz), 6.11 (dd, 1H, J = 3.2 and 1.2 Hz), 6.41 (dd, 1H, J = 3.2 and 2.0 Hz), 7.13 (td, 1H, J = 7.6 and 2.0 Hz), 7.27 (td, 1H, J = 7.2 and 1.2 Hz), 7.33 (dd, 1H, J = 2.0 and 1.2 Hz), 7.40 (dd, 1H, J = 7.6 and 2.0 Hz), 7.54 (dd, 1H, J = 8.0 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 44.5, 63.7, 106.5, 111.4, 120.7, 121.7, 127.3, 128.9, 131.6, 132.5, 140.9, 142.3, 142.4, 142.9, 152.8, 172.0; HRMS Calcd for $[(C_{17}H_{16}BrNO_4) + H^+]$ 378.0341, found 378.0344.

Ethyl 3a-(2-Bromophenyl)-2,5-dioxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-1-carboxylate (34). A solution of the above furanyl carbamate **32** (0.08 g, 0.2 mmol) in toluene (2.5 mL) was heated in a sealed tube at 150 °C for 10 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.07 g (90%) of the titled compound **34** as a yellow oil: IR (thin film) 2925, 2982, 1771, 1730, 1680, 1421, 1370, 1293, 1104, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, 3H, J = 7.6 Hz), 2.75 (d, 1H, J = 15.2 Hz), 2.84 (dd, 1H, J = 22.8 and 2.8 Hz), 2.98 (d, 1H, J = 18.0 Hz), 3.06 (dd, 1H, J = 22.8 and 5.6 Hz), 3.61 (d, 1H, J = 18.0 Hz), 3.99 (d, 1H, J = 15.2 Hz), 4.37−4.49 (m, 2H), 6.57 (dd, 1H, J = 5.6 and 2.8 Hz), 7.15 (td, 1H, J = 7.2 and 1.6 Hz), 7.25 (td, 1H, J = 7.6 and 1.6 Hz), 7.38 (dd, 1H, J = 7.6 and 1.6 Hz), 7.64 (dd, 1H, J = 7.6 and 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 38.0, 45.7, 47.9, 49.8, 64.0, 109.0, 122.6, 128.4, 128.9, 130.3, 136.7, 136.8, 139.7, 151.1, 171.2, 206.4; HRMS Calcd for $[(C_{17}H_{16}BrNO_4) + H^+]$ 378.0341, found 378.0338.

Ethyl 3-(2-Azidophenyl)but-3-enoyl(furan-2-yl)carbamate (33). To a stirred solution of 3-(2-bromophenyl)but-3-en-1-ol (0.73 g, 3.2 mmol) in dry DMF (24 mL) was added *tert*-butyldimethylsilyl chloride (1.07 g, 7.1 mmol) at rt under nitrogen followed by the addition of imidazole (0.66 g, 9.7 mmol) and DMAP (8 mg). The mixture was stirred for 2 h at 25 °C, poured into water, and extracted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was subjected to silica gel column chromatography to yield 1.0 g (91%) of (3-(2-bromophenyl)but-3-enyloxy)-*tert*-butyldimethylsilane as a clear oil: IR (neat) 2955, 2928, 2857, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 6H), 0.87 (s, 9H), 2.67 (t, 2H, J = 7.0 Hz), 3.65 (t, 2H, J = 7.0 Hz), 5.01 (d, 1H, J = 1.5 Hz), 5.26 (d, 1H, J = 1.5 Hz), 7.09−7.19 (m, 2H), 7.23−7.28 (m, 1H), 7.54 (dd, 1H, J = 7.9 and 1.2 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ −5.1, 18.5, 26.1, 40.3, 61.7, 117.1, 122.1, 127.2, 128.6, 130.8, 132.8, 143.9, 147.2.

A 0.17 g (0.48 mmol) sample of the above compound was dissolved in freshly distilled THF (5.5 mL) and cooled to −78 °C. To this mixture was added *n*-BuLi (27 mL, 1.9 M in hexane, 0.53 mmol) over a 5 min period, the reaction mixture was stirred for 30 min, and then tosyl azide (0.19 g, 0.97 mmol) was added in 400 mL of dry THF over 4 min. The solution was stirred at −78 °C for 1 h and then warmed to rt. After being stirred at this temperature for 45 min, 4 mL of H_2O was added, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was subjected to silica gel chromatography to provide 0.14 g (82%) of (3-(2-azidophenyl)but-3-enyloxy)-*tert*-butyldimethylsiline: IR (neat) 2955, 2929, 2857, 2128, 2095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.00 (s, 6H), 0.87 (s, 9H), 2.70 (dt, 2H, J = 7.0 and 0.6 Hz), 3.62 (t, 2H, J = 7.0 Hz), 5.04 (d, 1H, J = 1.8 Hz), 5.22−5.23 (m, 1H,), 7.07−7.19 (m, 3H), 7.29−7.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ −5.2, 18.5, 26.1, 40.2, 62.0, 117.1, 118.5, 124.9, 128.7, 130.8, 135.0, 137.0, 145.1.

To a stirred solution of the above silyl ether (0.41 g, 1.4 mmol) in dry THF (14 mL) was added tetra-*n*-butylammonium fluoride (1.8 mL, 1 M in THF, 1.8 mmol) at 25 °C. After stirring for 1 h, the solution was taken up in EtOAc, washed with water, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to provide 0.16 g (76%) of 3-(2-azidophenyl)but-3-en-1-ol as a clear oil: IR (neat) 3364, 2937, 2128, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (s, 1H), 2.70−2.73 (m, 2H), 3.61 (t, 2H, J = 6.0 Hz), 5.11 (d, 1H, J = 1.6 Hz), 5.32−5.33 (m, 1H), 7.11−7.20 (m, 3H), 7.32−7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 40.6, 60.4, 118.3, 118.4, 125.0, 128.8, 130.4, 134.2, 137.1, 144.0.

To a stirred solution of the above alcohol (0.22 g, 1.2 mmol) in acetone (24 mL) at 0 °C was added freshly prepared Jones' reagent (2.4 mL, 2.4 mmol, 1.0 M). The resulting solution was stirred at 0 °C for 1 h, and the mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.2 g (86%) of 3-(2-azidophenyl)but-3-enoic acid as a yellow solid: mp 73−74 °C; IR (CH_2Cl_2) 3080, 2926, 2130, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.58 (d, 2H, J = 0.6 Hz), 5.27 (d, 1H, J = 1.2 Hz), 5.38 (d, 1H, J = 1.2 Hz), 7.09−7.16 (m, 2H), 7.25−7.28 (m, 1H), 7.32−7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 41.9, 118.4, 120.7, 125.0, 129.2, 131.0, 133.2, 137.0, 139.9, 177.7.

To a stirred solution of ethyl furan-2-ylcarbamate (0.08 mg, 0.51 mmol) in dry THF (2.6 mL) cooled to −78 °C was added *n*-BuLi (224 mL, 0.56 mmol, 2.5 M in hexane) dropwise, and the reaction mixture was stirred at −78 °C for 45 min. In a separate flask, the above azido carboxylic acid (0.12 g, 0.6 mmol) was dissolved in dry THF (4.8 mL) and cooled to 0 °C. 4-Methylmorpholine (65 mL, 0.6 mmol) and isobutyl chloroformate (78 mL, 0.6 mmol) were added dropwise, and the solution was stirred for 10 min. The mixture was filtered over Celite with dry THF (1.5 mL). The filtrate was then cooled to 0 °C, and the preformed furanyl lithiate was added dropwise by cannula to the above mixture. The resulting solution was stirred for 30 min at 0 °C, diluted with ether, washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 0.11 g (66%) of the titled compound **33** as a yellow oil: IR (neat) 2959, 2934, 2130, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.0 Hz), 4.07 (d, 2H, J = 0.6 Hz), 4.22 (q, 2H, J = 7.0 Hz), 5.25 (d, 1H, J = 1.2 Hz), 5.33 (d,1H, J = 1.2 Hz), 6.09 (dd, 1H, J = 3.2 and 0.9 Hz), 6.41 (dd, 1H, J = 3.5 and 2.0), 7.08−7.14 (m, 2H), 7.29−7.35 (m, 3H).

Ethyl (2-(1*H*-Indol-3-yl)acetyl)(furan-2-yl)carbamate (37). A stirred solution of the above azido carbamate **33** (0.06 g, 0.17 mmol) in toluene (2.1 mL) was heated in a sealed tube at 150 °C for 12 h. The mixture was cooled to rt and then concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.03 g (57%) of **37** as a white solid: mp 124−126 °C; IR (neat) 3361, 2919, 1742, 1606, 1460 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz), 4.23 (q, 2H, J = 7.2 Hz), 4.32 (s, 2H), 6.14 (dd, 1H, J = 3.6 and 1.2 Hz), 6.43 (dd, 1H, J = 3.6 and 2.4 Hz), 7.12 (t, 1H, J = 7.2 Hz), 7.16−7.23 (m, 2H), 7.32−7.38 (m, 2H), 7.60 (d, 1H, J = 7.8 Hz), 8.10 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 34.1, 63.8, 106.7, 108.3, 111.3, 111.6, 119.2, 119.9, 122.4, 123.7, 127.6, 136.2, 141.0, 143.5, 153.2, 173.3; HRMS calcd for $[C_{17}H_{16}N_2O_4 + H^+]$ 313.1183, found 313.1182.

4-Methylquinolin-2(1*H*)-one (39). To a solution containing 0.008 g (0.024 mmol) of azido carbamate **33** in 0.6 mL of MeOH was added 0.0062 g (0.094 mmol) of zinc powder and 0.0044 g (0.070 mmol) of ammonium formate at 25 °C. The mixture was stirred at 25 °C for 1 h and was then filtered through a pad of Celite. The filtrate was diluted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.003 g (80%) of the known quinolinone **39** as a white solid[31]: mp 218−220 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 2.51 (s, 3H), 6.57 (s, 1H), 7.23−7.26 (m, 1H), 7.30 (d, 1H, J = 8.4 Hz), 7.51 (t, 1H, J = 7.8 Hz), 7.69 (d, 1H, J = 7.8 Hz), 10.75 (s, 1H).

Ethyl Furan-2-yl(4-methylquinolin-2-yl)carbamate (42). To a solution of azido carbamate **33** (0.07 g, 0.21 mmol) in THF (2.1 mL) was added triphenylphosphine (0.08 g, 0.3 mmol). The mixture was allowed to stir at rt for 2.5 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to

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afford 0.05 g (77%) of the titled compound **42** as a yellow oil: IR (neat) 2982, 2930, 1732, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3H, J = 7.03 Hz), 2.72 (d, 3H, J = 0.6 Hz), 4.30 (q, 2H, J = 7.0 Hz), 6.30 (dd, 1H, J = 3.2 and 0.9 Hz), 6.45 (dd, 1H, J = 3.2 and 2.1 Hz), 7.34 (dd, 1H, J = 2.1 and 0.9 Hz), 7.49 (s, 1H), 7.50−7.56 (m, 1H), 7.63−7.69 (m, 1H), 7.94−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.5,19.1, 63.1, 104.9, 111.4, 119.1, 123.7, 126.4, 127.0, 129.6, 129.8, 140.0, 140.6, 146.8, 147.0. 152.5, 154.5; HRMS calcd for [($C_{17}H_{16}N_2O_3$) + H^+] 297.1239, found 297.1236.

(*Z*)-3-(4-(2-Hydroxyethyl)quinolin-2-yl)prop-2-en-1-ol (50). A solution containing commercially available 2-(*N*-Boc-amino)-phenylboronic acid pinacol ester (1.5 g, 4.7 mmol) and the known (3-bromobut-3-enyloxy)(*tert*-butyl)dimethylsilane[32] (1.14 g, 4.27 mmol) in a mixture of benzene (100 mL), EtOH (25 mL), and 2 M aqueous Na_2CO_3 (10 mL) was deoxygenated by bubbling a stream of N_2 through the reaction mixture for 10 min. A sample of $Pd(PPh_3)_4$ (0.99 g, 0.85 mmol) was added, and the mixture was heated to 80 °C for 18 h and then cooled to rt. To this mixture was added Na_2SO_4, and the suspension was allowed to stand for 30 min. The mixture was then filtered and concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to provide 1.31 g (74%) of *tert*-butyl 2-(4-(*tert*-butyldimethylsilyloxy)but-1-en-2-yl)-phenylcarbamate (**45**) as a colorless oil: IR (film) 3409, 2959, 2933, 2858, 1731, 1518, 1452, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.50 (s, 9H), 2.55 (t, 2H, J = 6.1 Hz), 3.58 (t, 2H, J = 6.1 Hz), 5.08 (d, 1H, J = 1.6 Hz), 5.39 (d, 1H, J = 0.8 Hz), 6.95−7.10 (m, 3H), 7.23 (m, 1H, J = 8.0 and 2.0 Hz), 8.03 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1, 18.6, 26.2, 28.6, 41.7, 60.9, 80.3, 118.3, 120.2, 122.6, 127.9, 128.0, 131.7, 135.8, 143.7, 153.4; HRMS calcd for [($C_{21}H_{35}NO_3Si$) + H^+] 378.2464, found 378.2462.

To a 8 mL vial containing 0.046 g (0.12 mmol) of carbamate **45** were added 0.015 g (0.37 mmol) of *t*-BuONa and 0.012 g (0.02 mmol) of $Pd(dba)_2$. The vial was flushed with argon and to the above mixture were sequentially added 1 mL of toluene, 0.029 mL (0.31 mmol) of 2-bromofuran, and 0.005 mL (0.02 mmol) of *t*-Bu_3P. The mixture was placed in a sealed tube and was heated at 100 °C for 18 h. After being cooled to rt, the reaction mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.093 g of a crude oil which was allowed to react with TBAF and then treated with an excess of TFA to give 0.003 g (11%) of the titled compound **50** as a colorless oil: IR (neat) 3369, 2925, 2854, 1731, 1597 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.36 (t, 2H, J = 6.0 Hz), 4.06 (dd, 2H, J = 12.0 and 6.0 Hz), 4.44 (d, 2H, J = 6.0 Hz), 6.43 (dtd, 1H, J = 12.0, 6.0, and 0.6 Hz), 6.71 (dd, 1H, J = 12.0 and 0.6 Hz), 7.31 (s, 1H), 7.57 (td, 1H, J = 7.2 and 1.2 Hz), 7.73 (td, 1H, J = 7.8 and 1.2 Hz), 8.03 (d, 1H, J = 8.4 Hz), 8.08 (d, 1H, J = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 35.5, 59.5, 62.5, 123.5, 123.8, 126.3, 127.0, 129.7, 130.2, 131.3, 139.4; HRMS calcd for [$C_{14}H_{15}NO_2$ + H^+] 230.1176, found 230.1177.

Ethyl Furan-2-yl-2-(prop-1-en-2-yl)phenylcarbamate (56). To a vial containing 0.079 g (0.51 mmol) of ethyl furan-2-ylcarbamate (**52b**) was sequentially added 0.008 g (0.042 mmol) of CuI and 0.12 g (0.855 mmol) of K_2CO_3. The vial was flushed with argon, and to the above mixture was added 1 mL of toluene, 0.06 mL (0.43 mmol) of 1-(2-iodophenyl)ethanone (**52a**), and 0.009 mL (0.09 mmol) of *N*,*N*-dimethylethylenediamine (DMEDA). The mixture was placed in a sealed tube and heated at 110 °C for 44 h. After being cooled to rt, the reaction mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.026 g (22%) of ethyl (2-acetylphenyl)(furan-2-yl)carbamate (**54**) as a light yellow oil: IR (neat) 2983, 2933, 1727, 1692, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.2 Hz), 2.59 (s, 3H), 4.20 (q, 2H, J = 7.2 Hz), 6.27 (dd, 1H, J = 3.2 and 0.8 Hz), 6.37 (dd, 1H, J = 3.2 and 2.0 Hz), 7.21 (s, 1H), 7.31 (dd, 1H, J = 8.0 and 1.2 Hz), 7.36 (td, 1H, J = 8.0 and 1.2 Hz), 7.48 (td, 1H, J = 7.6 and 1.6 Hz), 7.64 (dd, 1H, J = 7.6 and 1.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 29.2, 63.1, 103.4, 111.4, 127.7, 128.8, 129.1, 132.4, 136.8, 138.3, 139.4, 147.6 154.5, 199.9; HRMS calcd for [$C_{15}H_{15}NO_4$ + H^+] 274.1074, found 274.1072.

To a solution containing 0.043 g (1 mmol) of zinc powder and a trace amount of Pb powder in 1 mL of THF was added 0.029 mL (0.26 mmol) of CH_2I_2 at 25 °C. The mixture was stirred at 25 °C for 30 min, and then 0.08 mL (0.051 mmol) of $TiCl_4$ (1 M) in CH_2Cl_2 was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 30 min, and then a solution of 0.016 g (0.073 mmol) of the above furanyl carbamate **54** in THF (1 mL) was added dropwise. After being stirred for 30 min at 25 °C, the mixture was diluted with ether (15 mL) and poured into a saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous phase was washed with ether. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.013 g (66%) of the titled compound **56** as a colorless oil: IR (neat) 2981, 1727, 1608, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.02 (s, 3H), 4.97 (brd, 1H, J = 0.8 Hz), 5.11−5.13 (m, 1H), 6.07 (brs, 1H), 6.31 (dd, 1H, J = 3.6 and 2.0 Hz), 7.10 (dd, 1H, J = 2.0 and 0.8 Hz), 7.23−7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 23.6, 62.7, 100.3, 111.2, 115.8, 128.0, 128.05, 129.0, 129.4, 137.2, 138.4, 142.1, 142.8, 148.3, 154.4; HRMS calcd for [$C_{16}H_{17}NO_3$ + H^+] 272.1281, found 272.1280.

Ethyl 2,3,4,4*a*-Tetrahydro-4a-methyl-3-oxocarbazole-9-carboxylate (58). A solution of 0.01 g (0.01 mmol) of the above carbamate **56** in 1 mL of toluene was heated in a sealed vial for 4 h at 100−110 °C. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and subjected to silica gel chromatography to give 0.008 g (80%) of the titled compound **58** as light yellow oil: IR (neat) 2925, 2854, 1716, 1482, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.46 (t, 3H, J = 7.6 Hz), 2.68 (d, 1H, J = 15.6 Hz), 2.89 (d, 1H, J = 15.6 Hz), 3.05 (dd, 1H, J = 22.8 and 6.0 Hz), 3.22 (dd, 1H, J = 22.8 and 2.4 Hz), 4.39−4.47 (m, 2H), 6.19 (brd, 1H, J = 3.2 Hz), 7.06−7.14 (m, 2H), 7.24−7.29 (m, 1H), 7.81 (brd, 1H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.7, 27.3, 38.2, 44.9, 49.4, 62.7, 103.1, 116.0, 122.1, 124.2, 128.6, 136.2, 141.1, 145.8, 152.9, 208.8; HRMS calcd for [$C_{16}H_{17}NO_3$ + H^+] 272.1281, found 272.1282.

***tert*-Butyl Furan-2-yl-2-(prop-1-en-2-yl)phenylcarbamate (57).** To a 8 mL vial containing 0.12 g (0.66 mmol) of *tert*-butyl furan-2-ylcarbamate[12] (**53**) were sequentially added 0.019 g (0.098 mmol) of copper(I) thiophene-2-carboxylate (CuTC) and 0.43 g (1.3 mmol) of Cs_2CO_3. The vial was flushed with argon, and to the above mixture were added 1 mL of toluene, 0.29 mL (2.0 mmol) of 1-(2-iodophenyl)ethanone, and 0.021 mL (0.2 mmol) of DMEDA. The mixture was placed in a sealed tube and heated for 40 h at 80−85 °C. After being cooled to rt, the reaction mixture was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.09 g (48%) of *tert*-butyl (2-acetylphenyl)-(furan-2-yl)carbamate (**55**) as a light yellow oil: IR (neat) 2980, 2933, 1724, 1694, 1610, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.59 (s, 3H), 6.23 (brd, 1H, J = 2.8 Hz), 6.36 (dd, 1H, J = 3.2 and 2.0 Hz), 7.20 (dd, 1H, J = 2.0 and 0.8 Hz), 7.28 (dd, 1H, J = 7.2 and 1.2 Hz), 7.32 (td, 1H, J = 7.6 and 1.2 Hz), 7.45 (td, 1H, J = 7.6 and 1.2 Hz), 7.64 (dd, 1H, J = 7.6 and 1.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.1, 29.2, 82.6, 102.7, 111.3, 127.4, 128.6, 128.9, 132.2, 137.2, 138.6, 139.1, 148.0, 200.0; HRMS calcd for [$C_{17}H_{19}NO_4$ + H^+] 302.1387, found 302.1385.

To a solution containing 0.045 g (0.7 mmol) of zinc powder and 0.002 g (0.0072 mmol) of $PbCl_2$ in 1 mL of THF was added 0.032 mL (0.4 mmol) of CH_2I_2 at 25 °C. The mixture was stirred at 25 °C for 30 min, and then 0.077 mL (0.077 mmol) of $TiCl_4$ in CH_2Cl_2 was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 30 min, and then a solution of 0.023 g (0.077 mmol) of carbamate **55** in THF (1 mL) was added dropwise. After being stirred for 30 min at 25 °C, the mixture was diluted with ether (20 mL) and poured into a saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous phase was washed with ether. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed

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under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.014 g (62%) of the titled compound **57** as a light yellow oil: IR (neat) 2979, 2930, 1725, 1608, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.02 (s, 3H), 4.97 (brd, 1H, J = 0.8 Hz), 5.11−5.13 (m, 1H), 6.07 (brs, 1H), 6.31 (dd, 1H, J = 3.6 and 2.0 Hz), 7.10 (dd, 1H, J = 2.0 and 0.8 Hz), 7.23−7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 28.3, 81.9, 100.6, 111.2, 115.7, 127.8, 127.9, 129.1, 129.3, 137.5, 138.0, 142.0, 143.1, 148.7, 153.2; HRMS calcd for $[C_{18}H_{21}NO_3 + H^+]$ 300.1594, found 300.1591.

***tert*-Butyl 2,3,4,4a-Tetrahydro-4a-methyl-3-oxocarbazole-9-carboxylate (59).** A solution of 0.03 g (0.01 mmol) of carbamate **57** in 2 mL of toluene was heated in a sealed vial for 3 h at 100−110 °C. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and subjected to silica gel chromatography to give 0.022 g (74%) of the titled compound **59** as a yellow oil: IR (neat) 2976, 2928, 1714, 1478, 1369 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.65 (s, 9H), 2.66 (d, 1H, J = 15.6 Hz), 2.87 (d, 1H, J = 15.6 Hz), 3.04 (dd, 1H, J = 22.2 and 6.0 Hz), 3.22 (dd, 1H, J = 22.2 and 1.2 Hz), 6.18 (brs, 1H), 7.06 (t, 1H, J = 7.2 Hz), 7.10 (d, 1H, J = 7.8 Hz), 7.23−7.26 (m, 1H), 7.76 (brd, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.2, 28.6, 38.2, 44.8, 49.5, 83.1, 102.6, 115.9, 122.1, 123.9, 128.5, 136.1, 141.4, 146.1, 151.7, 209.0; HRMS calcd for $[C_{18}H_{21}NO_3 + H^+]$ 300.1594, found 300.1592.

***N*-(2-(4-Hydroxybut-1-en-2-yl)phenyl)acetamide (61).** A solution containing 1.2 g (4.6 mmol) of commercially available *N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**60**) and 0.86 g (4.3 mmol) of 3-iodobut-3-en-1-ol[18] (**17**) in 5 mL of toluene, 20 mL of EtOH, and 17 mL of a 2 M aqueous Na_2CO_3 solution was purged with argon for 10 min. To this mixture was added 0.19 g of $Pd(Ph_3P)_4$, and the flask was recharged with argon. The above mixture was heated for 12 h at 65 °C and then cooled to rt. The reaction mixture was taken up in ether, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.8 g (63%) of the titled compound **61** as a light yellow oil: IR (neat) 3300, 2936, 1671, 1581, 1536 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.41 (s, 1H), 2.61 (t, 2H, J = 6.0 Hz), 3.66 (brs, 2H), 5.11 (s, 1H), 5.42 (s, 1H), 7.06−7.09 (m, 2H), 7.24−7.27 (m, 1H), 8.16 (d, 1H, J = 8.4 Hz), 8.29 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.6, 41.1, 59.9, 118.9, 121.7, 124.0, 128.1, 128.3, 132.8, 135.6, 143.8, 169.1; HRMS calcd for $[C_{12}H_{15}NO_2 + H^+]$ 206.1176, found 206.1177.

3-(2-Acetamidophenyl)but-3-enyl Methanesulfonate (62). To a stirred solution of the above alcohol **61** (0.053 g, 0.26 mmol) and Et_3N (0.053 mL, 0.39 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added methane sulfonyl chloride (0.033 mL, 0.39 mmol), and the resulting mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.064 g (88%) of mesylate **62** as a colorless oil: IR (neat) 3402, 2936, 1673, 1579, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.84 (t, 2H, J = 6.0 Hz), 2.92 (s, 3H), 4.21 (t, 2H, J = 6.0 Hz), 5.22 (s, 1H), 5.53 (s, 1H), 7.05−7.15 (m, 2H), 7.27−7.31 (m, 1H), 7.63 (s, 1H), 8.18 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 37.4, 37.8, 67.9, 120.0, 122.3, 124.3, 128.0, 128.6, 131.2, 135.0, 141.3, 168.8; HRMS calcd for $[C_{13}H_{17}NO_4S + H^+]$ 284.0951, found 284.0954.

***N*-(2-(4-(Allylamino)but-1-en-2-yl)phenyl)acetamide (63).** To a stirred solution of the above mesylate **62** (1.06 g, 3.8 mmol) in THF (3.5 mL) at rt was added prop-2-en-1-amine (2.7 mL, 38 mmol), and the resulting mixture was placed in a sealed vessel and heated at 70 °C for 22 h. The mixture was then diluted with EtOAc and washed with a 1 M HCl solution. The aqueous layer was treated with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue contained 0.7 g (72%) of the titled compound **63** as a yellow oil: IR (neat) 3292, 2926, 1683, 1582, 1547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.56−2.61 (m, 4H), 3.25 (d, 2H, J = 6.4 Hz), 4.98 (d, 1H, J = 2.0 Hz), 5.11−5.19 (m, 2H), 5.31 (d, 1H, J = 2.0 Hz), 5.87 (ddt, 1H, J = 16.8, 10.0, and 6.4 Hz), 7.04−7.08 (m, 2H), 7.23−7.28 (m, 1H), 8.08 (d, 1H, J = 8.0 Hz), 9.69 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.5, 39.2, 46.0, 52.1, 117.1, 117.8, 122.6, 123.8, 127.8, 128.0, 133.3, 135.9, 136.4, 145.0, 168.8; HRMS Calcd for $[C_{15}H_{20}N_2O + H^+]$ 245.1648, found 245.1647.

***tert*-Butyl 3-(2-Acetamidophenyl)but-3-enyl)allylcarbamate (64).** To a stirred solution of the above compound **63** (0.025 g, 0.1 mmol) and Et_3N (0.027 mL, 0.2 mmol) in CH_2Cl_2 (1.0 mL) was added di-*tert*-butyl dicarbonate (0.033 g, 0.15 mmol), and the resulting mixture was stirred at rt for 14 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.026 g (74%) of the titled compound **64** as a light yellow oil: IR (neat) 3294, 2977, 2931, 1694, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.17 (s, 3H), 2.59 (t, 2H, J = 6.8 Hz), 3.25 (brs, 2H), 3.77 (d, 2H, J = 5.2 Hz), 5.04−5.12 (m, 3H), 5.33 (s, 1H), 5.69−5.79 (m, 1H), 7.06−7.13 (m, 2H), 7.24−7.28 (m, 1H), 8.10 (brs, 1H), 8.46 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 28.6, 36.7, 45.7, 50.0, 80.0, 116.7, 117.7, 123.4, 124.3, 128.2, 128.3, 134.1, 135.0, 144.4, 156.0, 168.9; HRMS calcd for $[C_{20}H_{28}N_2O_3 + H^+]$ 345.2173, found 345.2176.

1-(4a-(2-(Allylamino)ethyl)-4,4a-dihydro-3,9a-epoxycarbazol-9(3*H*)-yl)ethanone (65). To a sealed tube containing 0.7 g (2.9 mmol) of compound **63** was sequentially added 0.17 g (0.86 mmol) of copper(I) thiophene-2-carboxylate (CuTC) and 1.88 g (5.8 mmol) of Cs_2CO_3. To the above mixture under an argon atmosphere were then added 2.9 mL of toluene, 0.38 mL (4.3 mmol) of 2-bromofuran (**46**), and 0.19 mL (1.7 mmol) of DMEDA. The tube was sealed and heated for 60 h at 90 °C. After being cooled to rt, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.42 g (82%) of the titled compound **65** as a yellow oil: IR (neat) 3074, 2942, 2853, 1681, 1458 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.50 (ddd, 1H, J = 12.6, 10.2, and 5.4 Hz), 1.56−1.61 (m, 2H), 2.28 (td, 1H, J = 11.4 and 5.4 Hz), 2.38 (s, 3H), 2.42−2.47 (m, 2H), 3.07 (d, 2H, J = 5.4 Hz), 4.93 (dd, 1H, J = 4.8 and 1.8 Hz), 5.03 (d, 1H, J = 10.2 Hz), 5.07 (dd, 1H, J = 17.4 and 1.2 Hz), 5.78 (ddt, 1H, J = 16.8, 10.8, and 6.0 Hz), 6.47 (dd, 1H, J = 6.0 and 1.8 Hz), 6.72 (d, 1H, J = 5.4 Hz), 7.09 (t, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 7.8 Hz), 7.24 (td, 1H, J = 7.8 and 1.2 Hz), 8.21 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 38.2, 40.7, 45.2, 52.5, 55.1, 75.7, 107.2, 116.0, 117.3, 124.4, 125.2, 128.1, 132.8, 134.9, 135.3, 136.7, 143.7, 171.0; HRMS calcd for $[C_{19}H_{22}N_2O_2 + H^+]$ 311.1754, found 311.1755.

(4b*R*,8a*S*)-9-Acetyl-10-allyl-7,8-dihydro-5*H*-8a,4b-(epiminoethano)carbazol-6(9*H*)-one (69). To the above compound **65** (0.022 g, 0.07 mmol) and MgI_2 (0.004 g, 0.014 mmol) was added toluene (1.2 mL) at rt, and the resulting mixture was sealed and stirred at 120 °C for 1 h. After being cooled to rt, the reaction mixture was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (triethylamine saturated silica gel) to give 0.013 g (60%) of **69** as a pale yellow solid: mp 120−122 °C; IR (neat) 2932, 2807, 1718, 1660, 1596 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.86 (td, 1H, J = 11.4 and 6.6 Hz), 1.94 (dd, 1H, J = 12.0 and 4.8 Hz), 2.21−2.33 (m, 3H), 2.46 (s, 3 H), 2.50 (ddd, 1H, J = 18.6, 11.4, and 4.2 Hz), 2.72 (d, 1H, J = 15.6 Hz), 2.80 (d, 1H, J = 15.6 Hz), 2.91 (dd, 1H, J = 9.0 and 6.0 Hz), 3.10 (dt, 1H, J = 14.4 and 4.8 Hz), 3.26 (dd, 1H, J = 15.0 and 7.8 Hz), 4.15 (dd, 1H, J = 15.0 and 4.2 Hz), 5.02 (d, 1H, J = 10.2 Hz), 5.11 (d, 1H, J = 17.4 Hz), 5.80 (dddd, 1H, J = 17.4, 10.8, 7.8, and 5.4 Hz), 7.07 (t, 1H, J = 7.8 Hz), 7.12−7.14 (m, 2H), 7.22 (t, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.4, 29.8, 35.4, 39.0, 48.2, 48.6, 51.5, 56.1, 92.9, 115.3, 116.0, 123.9, 124.2, 128.4, 136.8, 137.1, 142.9, 170.5, 211.1; HRMS calcd for $[C_{19}H_{22}N_2O_2 + H^+]$ 311.1754, found 311.1753.

***tert*-Butyl (2-(9-Acetyl-3-oxo-3,4,4a,9-tetrahydro-2*H*-carbazol-4a-yl)ethyl)-*N*-allylcarbamate (68).** To a sealed tube contain-

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ing 0.1 g (0.29 mmol) of the above compound **64** was sequentially added 0.017 g (0.09 mmol) of copper(I) thiophene-2-carboxylate (CuTC) and 0.19 g (0.58 mmol) of Cs_2CO_3. To this mixture under an argon atmoshpere was added 0.5 mL of toluene, 0.08 mL (0.87 mmol) of 2-bromofuran (**46**), and 0.018 mL (0.17 mmol) of DMEDA. The tube was sealed and heated at 90 °C for 48 h. After being cooled to rt, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give *tert*-butyl (2-(9-acetyl-3,4,4a,9-tetrahydro-3,9a-epoxycarbazol-4a-yl)ethyl)allylcarbamate (**66**) as the Diels–Alder cycloadduct, which was isolated as a pale yellow oil and was used immediately in the next step: IR (neat) 2976, 2943, 1689, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (brs, 9H), 1.49–1.65 (m, 3H), 2.39 (s, 3H), 2.45 (dd, 1H, J = 11.6 and 4.8 Hz), 2.70 (brt, 1H, J = 10.8 Hz), 3.03 (brs, 1H), 3.49 (brs, 1H), 3.63 (brs, 1H), 4.80–5.10 (m, 3H), 5.58 (brs, 1H), 6.50 (dd, 1H, J = 6.0 and 1.6 Hz), 6.72 (brs, 0.5H), 6.82 (brs, 0.5H), 7.10 (td, 1H, J = 7.2 and 0.8 Hz), 7.19 (brd, 1H, J = 7.2 Hz), 7.22–7.27 (m, 1H), 8.21 (brs, 1H); HRMS calcd for $[C_{24}H_{30}N_2O_4 + H^+]$ 411.2278, found 411.2280.

A solution of the above cycloadduct **66** in 2 mL of toluene was heated in a sealed tube at 120 °C for 4.5 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and subjected to silica gel chromatography to give 0.027 g (31% for two steps) of the titled compound **68** as a yellow oil: IR (neat) 2976, 2930, 1689, 1602 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, 60 °C) δ 1.29 (s, 9H), 1.55 (brt, 1H, J = 9.6H), 1.81 (brs, 1H), 2.01 (s, 3H), 2.08 (dd, 1H, J = 15.0 and 2.4 Hz), 2.48 (ddd, 1H, J = 21.2, 6.0, and 1.8 Hz), 2.63 (d, 1H, J = 15.6 Hz), 2.69 (brt, 1H, J = 11.4 Hz), 2.78 (d, 1H, J = 21.2 Hz), 3.01 (brs, 1H), 3.43 (brs, 1H), 4.71–4.76 (m, 2H), 5.10 (s, 1H), 5.42 (m, 1H), 6.67 (brs, 1H), 6.78 (td, 1H, J = 7.8 and 1.2 Hz), 6.98 (m, 1H), 8.15 (brs, 1H); HRMS calcd for $[C_{24}H_{30}N_2O_4 + H^+]$ 411.2278, found 411.2280.

(4b*R*,8a*R*)-9-Acetyl-7,8-dihydro-5*H*-8a,4b-(epiminoethano)-carbazol-6(9*H*)-one (70). To a vial containing 0.009 g (0.008 mmol) of (tetrakis(triphenyphosphine) palladium and 0.092 (0.59 mmol) g of *N*,*N*′-dimethylbarbituric acid[33] under an argon atmosphere was added a solution of compound **69** (0.06 g, 0.2 mmol) in dry degassed CH_2Cl_2 using a syringe. The resulting solution was washed with degassed CH_2Cl_2 (0.8 mL), and the mixture was stirred at 35 °C for 5.5 h. After being cooled to rt, the CH_2Cl_2 was removed under reduced pressure, and the residue was taken up in ether. The mixture was washed with a saturated aqueous Na_2CO_3 solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (triethylamine saturated silica gel) to give 0.045 g (85%) of the titled compound **70** as a light yellow oil: IR (neat) 3366, 2936, 1716, 1643, 1487 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.95–2.04 (m, 2H), 2.08 (ddd, 1H, J = 18.6, 6.6, and 4.8 Hz), 2.41–2.51 (m 4H), 2.54 (ddd, 1H, J = 13.8, 9.0, and 4.8 Hz), 2.61–2.70 (m, 1H), 2.71–2.84 (m, 3H), 3.02 (t, 1H, J = 7.2 Hz), 3.91 (brs, 1H), 7.05–7.12 (m, 2H), 7.17 (d, 1H, J = 7.2 Hz), 7.22 (t, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.8, 29.8, 35.2, 42.5, 43.2, 49.7, 53.3, 92.0, 113.6, 124.5, 124.7, 128.5, 137.2, 141.8, 169.5, 210.8; HRMS calcd for $[C_{16}H_{18}N_2O_2 + H^+]$ 271.1141, found 271.1140.

(4b*R*,8a*R*)-9-Acetyl-10-((*Z*)-2-iodobut-2-en-1-yl)-7,8-dihydro-5*H*-8a,4b-(epiminoethano)carbazol-6(9*H*)-one (72). To a mixture of the above compound **70** (0.021 g, 0.078 mmol), (*Z*)-2-iodo-2-butenyl mesylate[34] (**71**) (0.043 g, 0.16 mmol), KI (0.004 g, 0.024 mmol), and K_2CO_3 (0.04 g, 0.03 mmol) was added CH_3CN (1.3 mL).[35] The mixture was heated at 70 °C for 24 h, diluted with EtOAc and water, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.023 g (65%) of the titled compound **72** as a pale yellow oil: IR (neat) 2933, 2806, 1716, 1658, 1487 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.75 (d, 3H, J = 6.6 Hz), 1.86 (td, 1H, J = 11.4 and 6.6 Hz), 1.93 (dd, 1H, J = 12.0 and 4.2 Hz), 2.10–2.15 (m, 1H), 2.20 (ddd, 1H, J = 15.0, 12.0, and 3.0 Hz), 2.30 (dt, 1H, J = 19.2 and 4.2 Hz), 2.46 (s, 3H), 2.72 (d, 1H, J = 16.2 Hz), 2.79–2.86 (m, 3H), 3.25 (dt, 2H, J = 14.4 and 4.8 Hz), 4.52 (d, 1H, J = 13.8 Hz), 5.76 (q, 1H, J = 6.0 Hz), 7.06–7.11 (m, 2H), 7.14 (d, 1H, J = 7.2 Hz), 7.22 (t, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.9, 26.4, 29.7, 35.7, 39.0, 47.1, 48.5, 56.2, 60.3, 92.5, 111.8, 115.2, 124.0, 124.3, 128.4, 131.2, 136.8, 142.8, 170.5, 211.3; HRMS calcd for $[C_{20}H_{23}N_2O_2I + H^+]$ 451.0877, found 451.0876.

(2*S*,7a*R*,12a*R*)-(*E*)-12-Acetyl-3-ethylidene-2,3,4,6,7,12-hexahydro-1*H*-2,7a-ethanoindolizino[8a,1b]indol-14-one (73). To a vial containing compound **72** (0.018 g, 0.04 mmol) were added $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.004 mg, 0.005 mmol), K_2CO_3 (0.022 mg, 0.16 mmol), and dry MeOH (1.5 mL). The solution was degassed with argon for 10 min, and the sealed vial was wrapped with aluminum foil and heated at 70 °C for 1 h.[36] After being cooled to rt, the reaction mixture was diluted with Et_2O and water. The solution was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.0085 g (67%) of the titled compound **73** as a pale yellow oil: IR (neat) 2933, 2855, 1717, 1656, 1481 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.79 (brs, 3H), 1.90–2.10 (m, 2H), 2.22 (d, 1H, J = 13.8 Hz), 2.48 (s, 3H), 2.60–3.05 (m, 4H), 3.15–3.30 (m, 2H), 3.50 (brs, 1H), 4.04 (brs, 0.5H), 4.54 (brs, 0.5H), 5.59 (brs, 1H), 7.06 (t, 1H, J = 7.2 Hz), 7.14 (brd, 1H, J = 6.6 Hz), 7.24 (t, 1H, J = 7.8 Hz), 8.24 (brs, 1H); HRMS calcd for $[C_{20}H_{22}N_2O_2 + H^+]$ 323.1754, found 323.1752.

(2*S*,7a*R*,12a*R*)-(*E*)-(12-Acetyl-3-ethylidene-2,3,4,6,7,12-hexahydro-1*H*-2,7a-ethenoindolizino[8a,1b]indol-14-yl)-trifluoromethanesulfonate (74). To a solution of compound **73** (0.014 g, 0.044 mmol) in THF (2 mL) at −78 °C under an argon atmosphere was added 1.0 M NaHMDS in THF (0.05 mL, 0.05 mmol) dropwise. After the solution was stirred for 20 min, a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (0.021 g, 0.053 mmol) in THF (1.0 mL) was added to the mixture.[37] The resulting solution was stirred at −78 °C for another 20 min and then quenched with a saturated NH_4Cl solution (5 mL) at −78 °C. The above solution was allowed to warm to rt and was diluted with EtOAc (40 mL), washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give 0.0186 g (93%) of the titled compound **74** as a colorless oil: IR (neat) 2927, 2855, 1659, 1602, 1479 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, 60 °C) δ 1.40 (dd, 1H, J = 12.6 and 6.0 Hz), 1.50–1.63 (m, 4H), 1.69 (td, 1H, J = 12.0 and 7.8 Hz), 1.81 (brs, 0.5H), 2.02–2.20 (m, 3.5H), 2.36–2.46 (m,1H), 2.66 (d, 1H, J = 16.2 Hz), 2.80 (t, 1H, J = 7.8 Hz), 3.09 (s, 1H), 3.57 (brs, 1H), 5.12 (q, 1H, J = 6.6 Hz), 5.69 (s, 1H), 6.80–6.90 (m, 2H), 7.09 (t, 1H, J = 6.0 Hz), 8.36 (brs, 1H); ^{13}C NMR (150 MHz, C_6D_6, 60 °C) δ 14.3, 24.6, 29.2, 35.2, 37.9, 52.3, 53.7, 56.9, 91.8, 116.3, 118.5, 120.6, 122.6, 123.2, 123.8, 129.3, 132.4, 133.2, 141.4, 152.6, 169.4; HRMS Calcd for $[C_{21}H_{21}F_3N_2O_4S + H^+]$ 455.1247, found 455.1246.

1-((2*S*,7a*R*,12a*R*)-(*E*)-3-Ethylidene-14-(hydroxymethyl)-3,4,6,7-tetrahydro-1*H*-2,7a-ethenoindolizino[8a,1b]indol-12(2*H*)-yl)ethanone (75). To a 10 mL tube containing the above vinyl triflate **74** (0.03 g, 0.068 mmol), (tri-*n*-butylstannyl)methanol[29] (0.088 g, 0.27 mmol), LiCl (0.12 g, 2.8 mmol), and $Pd(PPh_3)_4$ (0.0078 g, 0.0067 mmol) was added dioxane (4 mL), and the resulting mixture was degassed for 10 min under an argon atmosphere. After being sealed with a microwave rubber cap, the tube was placed in the microwave reactor and irradiated at 200 W at 105 °C for 1 h. The mixture was cooled to rt, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography to give 0.014 g (61%) of the titled compound **75** as a clear oil: IR (neat) 3389, 2926, 2855, 1633, 1478 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, 60 °C) δ 1.50–1.59 (m, 4H), 1.63 (dd, 1H, J = 12.6 and 3.0 Hz), 1.79 (td, 1H, J = 12.0 and 7.8 Hz), 1.88 (brs, 1H), 2.29 (s, 3H), 2.42–2.50 (m,1H), 2.79 (d, 1H, J = 16.2 Hz), 2.90 (t, 1H, J = 7.8 Hz), 3.16 (s, 1H), 3.64 (brs, 1H), 3.88 (ABq, 2H, J_{AB} = 13.2 Hz), 5.07 (q, 1H, J = 6.6 Hz), 5.68 (s, 1H), 6.91 (t, 1H, J = 7.8 Hz), 7.05 (d, 1H, J = 7.2 Hz), 7.14 (t, 1H, J = 7.8 Hz), 8.64 (brs, 1H); ^{13}C NMR (150 MHz, C_6D_6, 30 °C) δ 14.7, 24.3, 29.5, 31.0, 38.3, 53.1, 54.3, 56.5, 65.4, 92.9, 119.4, 119.8, 121.7, 122.6, 123.7, 134.8, 136.5, 141.8, 143.5, 170.7; HRMS calcd for $[C_{21}H_{24}N_2O_2 + H^+]$ 337.1911, found 337.1910.

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((2*S*,7a*R*,12a*S*)-(*E*)-3-Ethylidene-2,3,4,6,7,12-hexahydro-1*H*-2,7*a*-ethenoindolizino[8a,1b]indol-14-yl)methanol (Minfiensine, 2). To a sealed tube containing the above compound **75** (0.006 g, 0.018 mmol) and hydrazine sulfate (0.007 g, 0.05 mmol) was added anhydrous NH_2NH_2 (0.7 mL). The tube was sealed and heated at 105 °C for 30 h under an argon atmosphere. After being cooled to rt, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and water (5 mL) and then washed with a saturated Na_2CO_3 solution. The aqueous layer was separated and extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (triethylamine saturated silica gel) to give 0.004 g (78%) of minfiensine (**2**) as a clear oil which did not solidify (see ref 9; minfiensine (**2**) was reported as a gum), but its spectral properties were identical to those reported by Qin[6] and MacMillan:[9] IR (neat) 3296, 2926, 1666, 1610, 1465 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.72 (d, 3H, J = 6.6 Hz), 1.93−1.97 (m, 2H), 1.97−2.03 (m, 1H), 2.03−2.10 (m, 1H), 2.65 (ddd, 1H, J = 9.6, 7.8, and 6.6 Hz), 3.15 (d, 1H, J = 15.0 Hz), 3.30 (ddd, 1H, J = 9.6, 6.0, and 4.2 Hz), 3.43 (brs, 1H), 3.69 (d, 1H, J = 15.0 Hz), 3.86 (brs, 1H), 4.11 (d, 2H, J = 1.2 Hz), 5.39 (q, 1H, J = 6.6 Hz), 6.04 (s, 1H), 6.56 (d, 1H, J = 7.2 Hz), 6.71 (t, 1H, J = 6.6 Hz), 7.02 (td, 1H, J = 7.2 and 1.2 Hz), 7.11 (d, 1H, J = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 31.4, 32.0, 38.3, 53.3, 53.8, 55.4, 65.6, 90.1, 109.8, 118.5, 119.4, 122.6, 124.6, 127.7, 133.5, 135.8, 140.9, 147.4; HRMS calcd for $[C_{19}H_{22}N_2O + H^+]$ 295.1805, found 295.1803.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00771.

^1H and ^{13}C NMR data of various key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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