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An IMDAF Cycloaddition Approach toward the Synthesis of the Lycopodium Alkaloid (±)-Fawcettidine

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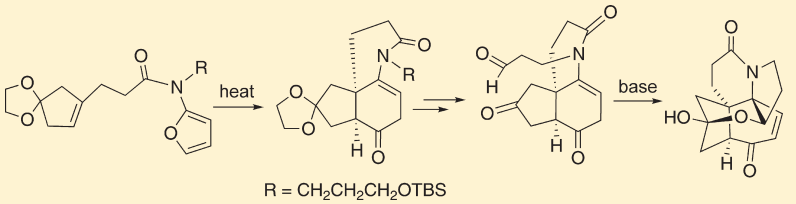
Supporting Information

ABSTRACT:



Using an intramolecular [4 + 2] cycloaddition/rearrangement cascade of 3-(1,4-dioxaspiro[4.4]non-7-en-7-yl)-*N*-furan-2-ylpropionamide (**23**) as the key step, the BCD core of the lycopodium alkaloid fawcettidine was constructed. Heating the initially formed Diels−Alder cycloadduct at 180 °C results in a nitrogen-assisted ring opening followed by a deprotonation/reprotonation of the ensuing zwitterion to give a rearranged hexahydroindolinone. Our attempts to induce a related intramolecular furan Diels−Alder reaction (IMDAF) from the corresponding ketone of **23** failed to give any cycloaddition product. Instead, the only product obtained corresponded to a cyclopentenone derivative derived by isomerization of the double bond into the thermodynamically more stable α,β-position. Efforts toward construction of the final skeleton of fawcettidine by ring A closure of the rearranged cycloadduct derived from furanyl amide **23** are discussed.

INTRODUCTION

The genus *Lycopodium* consists of a large group of species that are commonly known as club mosses.[1] These plants comprise over 500 species that are distributed around the world. To date, a subset of 53 species has been investigated and which have resulted in the isolation of over 200 natural products.[2] This list can be divided into four topographically related classes, including lycopodine **1**, lycodine **2**, fawcettimine **3**, and various miscellaneous classes **4**, as shown in Figure 1.[3] Many of the *Lycopodium* species have a long history of use in Chinese folk medicine for the treatment of contusions, strains, swelling, and schizophrenia. Pharmacological studies also show that the *Lycopodium* alkaloids can be used in the treatment of diseases that affect the cardiovascular or neuromuscular system.[4] The intriguing structure of fawcettimine **3**, which possesses a dense stereochemical array of functional groups, renders this alkaloid a challenging synthetic target.[5] A notable feature of fawcettimine **3** is that it contains a single quaternary carbon center[6] and has been proposed to be biosynthetically derived from the lycopodane core by means of an oxidative rearrangement reaction.[3] Methodologies for assembling fawcettimine **3** have been described by Inubushi and co-workers,[7] who made use of a stereoselective Diels−Alder reaction followed by an intramolecular aldol condensation, and by the Heathcock group,[8] who employed a direct closure of a 9-membered heterocyclic ring as a key step in their 13-step synthesis. The Toste team[9] implemented a sequence of conjugate propargylation, acetylene iodination, and gold(I)-catalyzed cyclization reactions

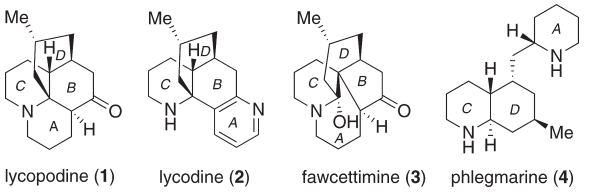


Figure 1. Four related classes of *Lycopodium* alkaloids.

to provide a key vinyl iodide intermediate that subsequently underwent a palladium-catalyzed cross-coupling reaction to eventually allow for an intramolecular alkylation of a tethered amine to complete the synthesis. Later, Mukai and co-workers[10] reported a total synthesis of (+)-fawcettimine **3** starting from an oxatricyclo[7.3.0.0^{1,5}]dodecane dione derivative utilizing an intramolecular Mitsunobu reaction to construct the azanonane framework of the alkaloid. More recently, Jung and Chang reported on a formal total synthesis of (+)-fawcettimine **3** by making use of a stepwise Mukaiyama−Michael addition of the silyl enol ether of acetylcyclopropane-1,1-dicarboxylate.[11]

Despite these earlier efforts, new and efficient approaches toward the fawcettimine class of alkaloids are still important, as they would allow the synthesis of not only other members of this

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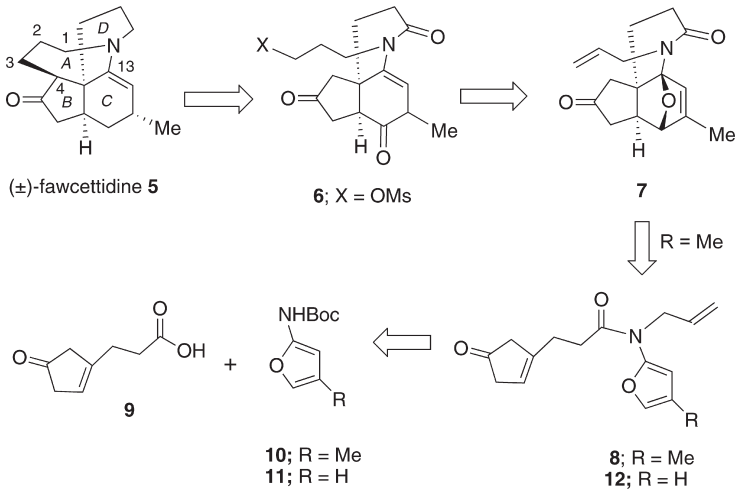
Scheme 1



family of alkaloids (such as (±)-fawcettidine **5**) but also related non-natural analogues possessing biological activity. Along these lines, we have recently become involved in the development and optimization of a new cycloaddition procedure for the construction of the azacyclic framework present in various alkaloids.[12] In this paper we report on an IMDAF cycloaddition approach for the synthesis of the ABC core structure of the *Lycopodium* alkaloid (±)-fawcettidine **5**.

Fawcettidine **5** was isolated from a Jamaican *Lycopodium* plant in 1950,[5] and its structure was established on the basis of its semisynthesis from other members of the *Lycopodium* family.[13] Despite its close similarity to fawcettimine **3**, the synthesis of fawcettidine **5** has only recently been reported by Dake and Kozak.[14] Key features of their approach include a platinum (II)-catalyzed annulation of a highly functionalized enamide[15] and a one-pot Ramberg−Bäcklund reaction[16] to form the seven-membered ring. Our synthetic approach to the core ABC ring of fawcettidine **5** was guided by a longstanding interest in developing new applications of the *intramolecular [4 + 2] cycloaddition/rearrangement cascade* of 2-amidofurans toward the synthesis of complex natural products.[12] Our recently completed syntheses of (±)-erysotramidine,[17] (±)-lycoricidine,[18] and (±)-strychnine[19] nicely demonstrate the utility of this process for the construction of various alkaloids. An abbreviated retrosynthetic plan that features this key step for the synthesis of (±)-fawcettidine **5** is outlined in Scheme 1.

The previous syntheses of the closely related alkaloid fawcettimine **3** left the formation of the $N-C_{13}$ bond until the last step.[7−10] Our strategy differs markedly from the earlier approaches to this class of alkaloids in that a C−C bond disconnection would be employed to produce the seven-membered ring of fawcettidine **5** and this step would occur at a late stage of the synthetic sequence. We hoped that the enolate anion derived from ketone **6** would allow for an intramolecular alkylation reaction so as to create the C_3-C_4 bond. A critical component of our synthetic plan relies upon the efficient construction of the tetrahydro-1*H*-inden-2(6*H*)-one structure found in **6** by an intramolecular [4 + 2] cycloaddition/rearrangement cascade of 2-amidofuran **8**. Intermediate **8** should be available by a well-precedented acylation of furanyl carbamate **10** with the mixed anhydride derived from carboxylic acid **9**.[12]

RESULTS AND DISCUSSION

To quickly validate this general plan, we decided to first prepare the simpler 2-amidofuran **12** (Scheme 2). Although furan **12** lacks the methyl substituent necessary for the synthesis of fawcettidine **5**, a successful IMDAF cycloaddition reaction of **12** would provide good support for the viability of the synthetic strategy outlined in Scheme 1. Our model studies commenced by reaction of the lithiate anion of cyclopentadiene with methyl 3-iodopropanoate,[20] and this was followed by hydroboration of the resulting isomeric mixture with disiamylborane to give methyl 3-(4-hydroxycyclopent-1-enyl)propanoate (**13**) in 69% yield. Alcohol **13** was protected as the TBS ether and then hydrolyzed to furnish the corresponding carboxylic acid.

Formation of the mixed anhydride followed by reaction with the lithiated Boc-protected aminofuran afforded amide **14** in 72% overall yield (Scheme 2). Removal of the carbamate moiety from **14** proceeded smoothly when **14** was treated with $Mg(ClO_4)_2$ in CH_3CN. Reaction of the corresponding sodium salt with allyl iodide followed by desilylation and subsequent oxidation of the resulting alcohol **16** with IBX delivered the desired β,δ-unsaturated ketone **12** containing the tethered furanyl ring in 51% yield for the four-step sequence. Unfortunately, all of our attempts to induce the desired IMDAF reaction by heating **12** at 180 °C in toluene failed to give any cycloaddition product. Instead, the only product obtained corresponded to cyclopentenone **15**, derived by a prior isomerization of the double bond into the thermodynamically more stable α,β-position. Interestingly, thermolysis of the related cyclopentenyl alcohol **16** at 180 °C did proceed in the expected manner and gave rise to the desired cycloadduct **17**, but as an inseparable mixture of diastereomers in 67% yield (Scheme 3).

As a consequence of the facile thermal isomerization of the double bond that occurred with ketone **12**, we decided to protect the keto group so as to avoid the competitive 1,3-hydrogen shift. We found that the easiest way to prepare amidofuran **21** involved an initial oxidation of alcohol **13** to give ketone **18**. This was followed by the reaction of **18** with 1,2-bis(trimethylsiloxy)ethane in the presence of a catalytic amount of TMSOTf at 0 °C. A subsequent base-promoted saponification produced the expected

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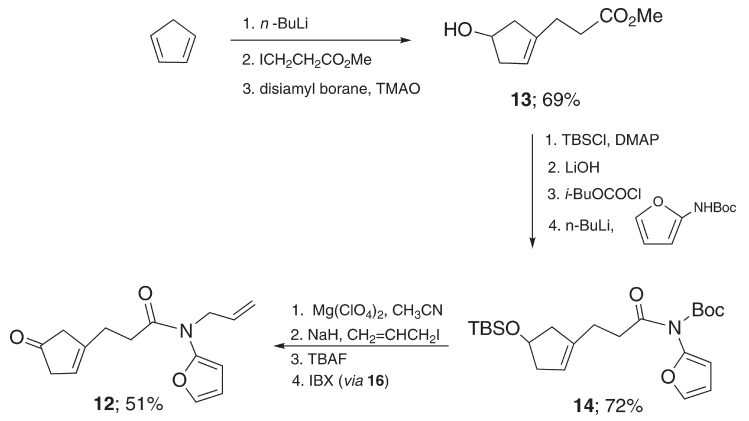
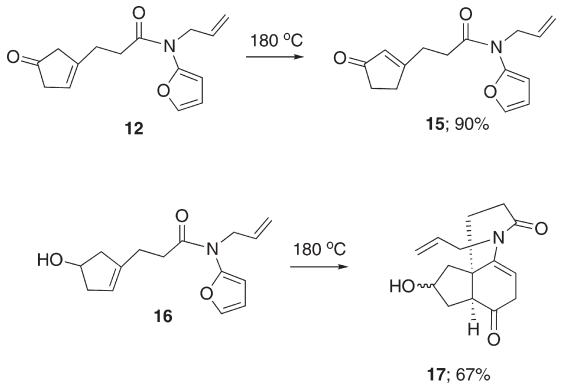
Scheme 2



Scheme 3



carboxylic acid, which was smoothly converted to the corresponding furanyl amide **20** according to the reactions outlined in Scheme 4. Further N-allylation of **20** using sodium hydride and allyl iodide afforded aminofuran **21** in high yield. Gratifyingly, thermolysis of a sample of **21** at 180 °C gave the desired rearranged cycloadduct **22** in 67% yield.

At this point we intended to subject cycloadduct **22** to a hydroboration reaction in order to prepare the related azatricycle **24**, whose primary hydroxyl group would be subsequently converted into the correponding mesylate for the desired internal alkylation reaction (see Scheme 1). Unfortunately, all of our attempts to hydroborate **22**, or for that matter the corresponding amidofuran **21**, led to a complex mixture of products. Instead, we decided to synthesize furanyl amide **23**, which already contains the TBS-protected propanyl side chain directly from **20** and thereby avoid the problematic hydroboration step. Thus, exposure of **20** to sodium hydride followed by alkylation with *tert*-butyl(3-iodopropoxy)dimethylsilane resulted in a high yield of the N-alkylamide **23**. We were pleased to find that the thermolysis of **23** furnished the desired rearranged cycloadduct **24** in 88% yield (Scheme 4). When this compound was allowed to stand under an open atmosphere for several days, it was slowly oxidized to 2,3-dihydroindenone **25** in 75% yield. The structure of **25** was unequivocally established from a single-crystal X-ray analysis.

In order to generate the requisite intermediate **30** needed for the key cyclization step, both the TBS and acetal protecting groups of **24** need to be removed and this is best accomplished under an inert nitrogen atmosphere. After several reagents were screened, it was discovered that brief treatment of **24** with $PdCl_2(MeCN)_2$[21] afforded the free alcohol **26** in 84% yield (Scheme 5). Longer reaction times resulted in the hydrolysis of the ketal functionality and formation of tetracycle **28**. This compound probably arises by the generation of a transient iminium ion (i.e., **27**), which subsequently reacts with the free hydroxyl group present on the side chain. This same compound was also formed in 68% yield by subjecting **24** to a 5% HCl solution in THF. We found, however, that the hydrolysis of **24** under mild basic conditions using a catalytic amount of CAN as a Lewis acid[22] afforded the fully deprotected alcohol **29** in 61% yield.

We next investigated the key A ring closure step by making use of alcohol **29**. For these feasibility studies, we converted alcohol **29** into the corresponding mesylate **30** using NEt_3 and mesyl chloride. Unfortunately, all of our efforts to induce ring A closure with various bases and under different experimental conditions so as to form the desired tetracycle **31** were unsuccessful. Presumably this failure to cyclize is related to unfavorable conformational issues and suggests that the mesylate group is not sufficiently reactive enough to undergo reaction with the enolate anion resulting from deprotonation of the cyclopentanone portion of the molecule. Consequently, we turned our attention to replacing the mesylate group with the more reactive aldehyde functionality on the side chain. To this end, the oxidation of alcohol **29** was carried out using IBX[23] and the resulting aldehyde **32** was then heated with a small amount of *p*-TsOH in an attempt to form the cyclized enone **33**. However, rather than affording **33**, the aldehydic group present in **32** underwent cyclization with the enamide π bond to eventually produce dihydropyridine **34** in 60% overall yield (Scheme 6).

Since the primary difficulty with the reaction of **32** under acidic conditions involved reaction of the aldehyde with the enamide π bond, we decided to investigate its behavior under basic conditions, hoping to induce an aldol reaction with formation of tetracycle **33**. Various bases at different temperatures were examined but generally resulted in a complex mixture of products that could not be separated by silica gel chromatography. However, when aldehyde**32** was treated with NaH in THF, a rather unique product was isolated in 35% yield, whose structure was assigned as hemiketal **37** on the basis of its spectral properties. The ^{1}H NMR of **37** showed the absence of both the enamide (δ 5.19) and aldehyde (δ 9.89) hydrogens but the

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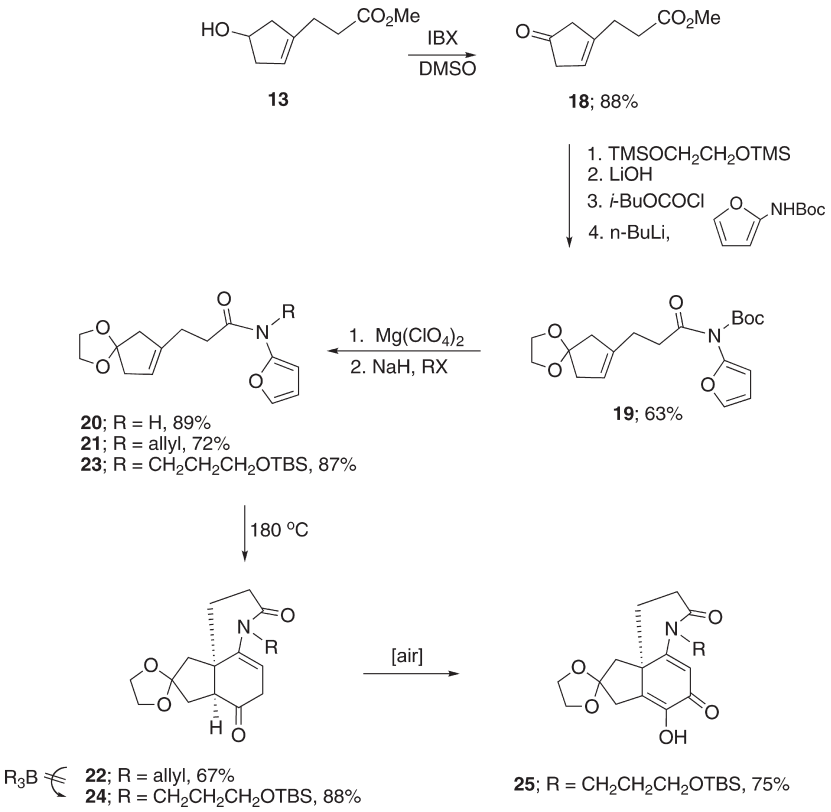
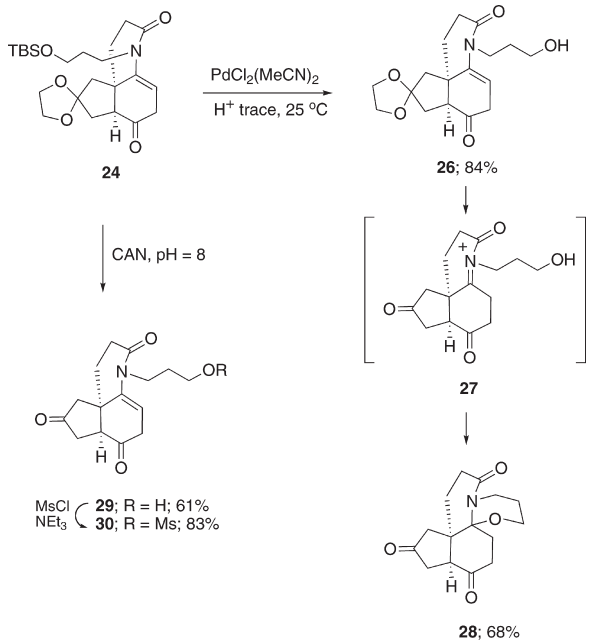
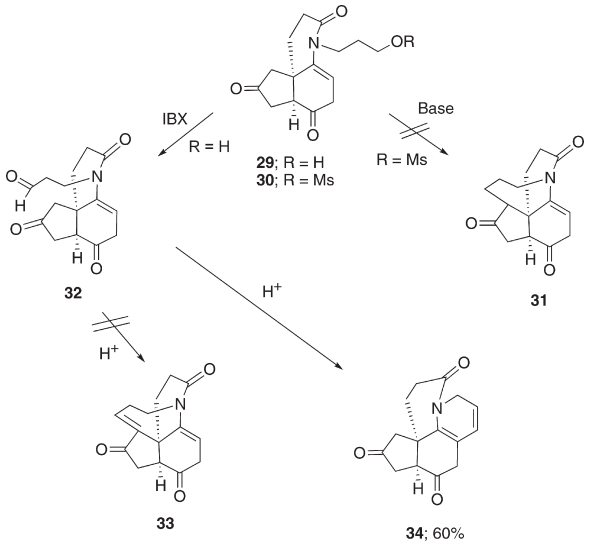
Scheme 4



Scheme 5



Scheme 6



presence of two protons for the enone π -system at 6.02 and 6.76 (doublets, $J = 9.6$ Hz) as well as an exchangeable OH singlet at 3.15 ppm. The ^{13}C NMR exhibited the presence of two carbonyl groups at 196.6 and 169.8 ppm. The structure of **37** was unequivocally established on the basis of a single-crystal X-ray analysis. This unusual reorganization can be rationalized by the cascade pathway proposed in Scheme 7. We assume that the first step proceeds by deprotonation on the six-membered ring followed by attack of the resulting enolate onto the tethered aldehyde. The ensuing alkoxide anion present in intermediate **36** then undergoes addition onto the proximal carbonyl group and ultimately affords the observed product **37** after protonation.

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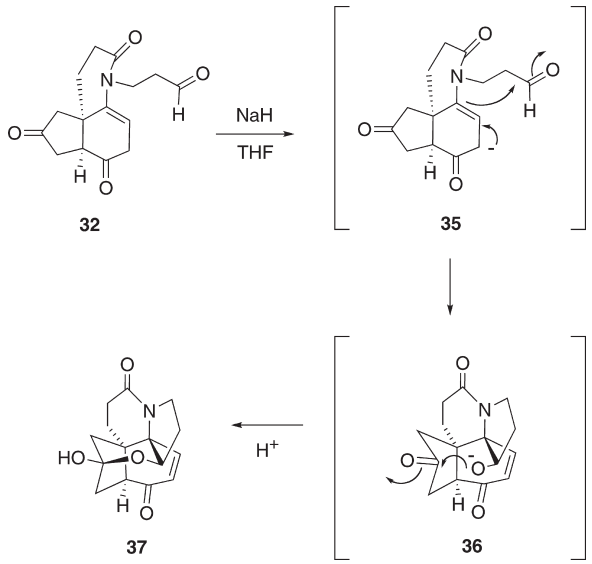
Scheme 7



In summary, the preparation of the BCD core skeleton of the lycopodium alkaloid fawcettidine (**5**) highlights the value of the *[4 + 2] cycloaddition/rearrangement cascade* of *N*-furanyl amides for increasing molecular complexity in a single operation. This IMDAF cascade sequence has produced a compound that might serve as a viable intermediate for an eventual fawcettidine synthesis. Key objectives that would need to be performed include the incorporation of a methyl group on the furanyl ring for the cycloaddition reaction as well as working out conditions for A ring closure. Preliminary investigations to achieve this latter goal produced some unexpected results. Further efforts to resolve A ring formation of the rearranged cycloadduct as well as to apply the IMDAF cycloaddition in the synthesis of related lycopodium alkaloids are ongoing and will be reported at a later date.

EXPERIMENTAL SECTION

{3-[4-((*tert*-Butyldimethylsilanyl)oxy)cyclopent-1-enyl]-propionyl}furan-2-ylcarbamic Acid *tert*-Butyl Ester (14). To 330 mL of THF stirred at 0 °C was added 83 mL (83 mmol) of borane−THF complex (1.0 M solution in THF) followed by the addition of 17.5 mL (165 mmol) of 2-methylbut-2-ene. The resulting solution was stirred at 0 °C for 2 h. A solution containing 10.5 g (69 mmol) of methyl 3-(cyclopenta-1,3-dienyl)propanoate[19] in 275 mL of THF was added to the above solution of disiamylborane via cannula. The reaction mixture was stirred at 0 °C for 1 h, followed by stirring for an additional 2 h at room temperature. The reaction mixture was then diluted with 275 mL of toluene, and the THF was removed under reduced pressure. To the resulting solution was added 46.0 g (414 mmol) of trimethylamine *N*-oxide (TMAO) at room temperature, and the mixture was vigorously stirred at reflux for 1 h. After the mixture was cooled to room temperature, Et_2O was added and the precipitate that formed was removed by filtration and was further washed with Et_2O. A saturated aqueous NH_4Cl solution was added to the filtrate, and the mixture was stirred for 1 h at room temperature. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 8.1 g (69%) of methyl 3-(4-hydroxycyclopent-1-enyl)propanoate (**13**) as a pale yellow oil: IR (neat) 3391, 2950, 2917, 2840, 1728, 1650, 1434, and 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (br s, 1H), 2.16−2.26 (m, 2H), 2.32−2.38 (m, 2H), 2.44 (dd, 1H, J = 6.8 and 2.0 Hz), 2.46 (dd, 1H, J = 6.8 and 2.0 Hz), 2.53−2.64 (m, 2H), 3.63 (s, 3H), 4.45 (tt, 1H, J = 6.4 and 2.0 Hz), and 5.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 32.3, 42.6, 45.0, 51.6, 71.9, 121.3, 140.4, and 173.8.

To a stirred solution containing 0.2 g (1.18 mmol) of the above alcohol in 0.6 mL of DMF was added 0.2 g (2.94 mmol) of imidazole and a crystal of 4-(dimethylamino)pyridine (DMAP). The resulting mixture was cooled to 0 °C for 15 min, and then 0.27 g (1.76 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) was added in one portion. The reaction mixture was warmed to room temperature and was stirred for 2 h and then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.3 g (90%) of 3-{4-[(*tert*-butyldimethylsilanyl)oxy]cyclopent-1-enyl}propionic acid methyl ester as a clear oil: IR (neat) 2955, 2930, 2848, and 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 2.15−2.60 (m, 8H), 3.62 (s, 3H), 4.47−4.53 (m, 1H), and 5.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 18.2, 25.9, 26.5, 32.3, 42.6, 45.1, 51.5, 72.7, 121.4, 140.3, and 173.7.

To a stirred solution of the above ester in a 4:1:3 mixture containing 4.0 mL of THF, water, and MeOH at room temperature was added 0.049 g (1.16 mmol) of $LiOH \cdot H_2O$ in one portion. The reaction mixture was stirred at room temperature overnight and was then quenched with an aqueous solution containing 0.16 g (1.16 mmol) of $NaHSO_4$ in 2 mL of water. The mixture was extracted with EtOAc, the combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure to provide 0.26 g (90%) of 3-{4-[(*tert*-butyldimethylsilanyl)oxy]cyclopent-1-enyl}propionic acid as a pale yellow oil: IR (thin film) 2950, 2925, 2852, 1706, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 1H), 0.88 (s, 9H), 2.16−2.30 (m, 2H), 2.32−2.40 (m, 2H), 2.45−2.62 (m, 4H), 4.52 (m, 1H), and 5.28 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 18.2, 25.9, 26.2, 32.3, 42.6, 45.1, 72.7, 121.5, 140.1, and 179.4.

To a stirred solution containing 0.07 g (0.37 mmol) of furan-2-ylcarbamic acid *tert*-butyl ester in 1.5 mL of THF at 0 °C was added 0.18 mL (0.41 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred at 0 °C for 20 min. In a separate flask, 0.1 g (0.37 mmol) of the above carboxylic acid was dissolved in 1.5 mL of THF at 0 °C and 0.04 mL (0.37 mmol) of 4-methylmorpholine and 0.048 mL (0.37 mmol) of isobutyl chloroformate were added dropwise. After the mixture was stirred for 1 h, the white precipitate that formed was removed by filtration and was washed with 0.5 mL of THF. The filtrate was cooled to 0 °C and the preformed lithiate was transferred to the above solution via cannula. The reaction mixture was warmed to room temperature and then quenched with water and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine and then dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash column chromatography to provide 0.14 g (90%) of the title compound **14** as a pale yellow oil: IR (thin film) 2955, 2925, 2853, 1741, and 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.88 (s, 9H), 1.43 (s, 9H), 2.16−2.28 (m, 2H), 2.34−2.42 (m, 2H), 2.46−2.61 (m, 2H), 2.86−2.92 (m, 2H), 4.46−4.55 (m, 1H), 5.27 (br s, 1H), 6.14 (d, 1H, J = 3.2 Hz), 6.41 (dd, 1H, J = 2.3 and 2.4 Hz), and 7.32−7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 18.3, 25.9, 26.2, 27.8, 35.5, 42.6, 45.2, 72.8, 83.8, 105.9, 111.2, 121.4, 140.4, 140.5, 143.9, 151.4, and 174.6.

3-{4-[(*tert*-Butyldimethylsilanyl)oxy]cyclopent-1-enyl}-*N*-furan-2-ylpropionamide. To a stirred solution containing 0.5 g (1.15 mmol) of the above Boc-amide **14** in 5 mL of CH_3CN was added 0.51 g (0.23 mmol) of magnesium perchlorate. The reaction mixture was stirred at 50 °C for 4 h and was cooled to room temperature. The solvent

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was removed under reduced pressure, and the crude residue was purified by flash silica gel column chromatography to provide 0.29 g (80%) of the title compound as a pale yellow oil: IR (thin film) 3252, 3057, 2955, 2930, 2848, 1665, and 1557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 2.18−2.62 (m, 8H), 4,.47−4.56 (m, 1H), 5.36 (s, 1H), 6.28 (d, 1H, J = 3.2 Hz), 6.35 (t, 1H, J = 3.2 Hz), 7.02 (s, 1H), and 7.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, 18.1, 25.8, 26.8, 34.3, 42.6, 44.9, 72.7, 95.3, 111.2, 121.8, 135.1, 140.3, 145.3, and 169.8.

***N*-Allyl-3-{4-[(*tert*-butyldimethylsilanyl)oxy]cyclopent-1-enyl}-*N*-furan-2-ylpropionamide.** To a stirred solution containing 0.08 g (0.238 mmol) of the above furanyl amide in 1 mL of THF was added 0.011 g (0.011 mmol) of NaH (60% in mineral oil) at 0 °C. The solution was warmed to room temperature and was stirred at this temperature for 1 h. The reaction mixture was recooled to 0 °C, and 0.026 mL (0.29 mmol) of allyl iodide was added dropwise. After it was warmed to room temperature, the mixture was stirred for 2 h and was then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.06 g (70%) of the title compound as a pale yellow oil: IR (thin film) 3252, 3057, 2955, 2953, 2848, 1665, and 1557 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 2.07−2.36 (m, 6H), 2.42 (dd, 1H, J = 16.4 and 6.8 Hz), 2.52 (dd, 1H, J = 16.4 and 6.8 Hz), 4.19 (d, 1H, J = 6.0 Hz), 4.30−4.51 (m, 1H), 5.09−5.16 (m, 3H), 5.75−5.86 (m, 1H), 6.70 (d, 1H, J = 3.2 Hz), 6.34−6.38 (m, 1H), and 7.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 18.2, 25.9, 26.6, 32.0, 42.6, 45.0, 50.8, 72.7, 104.7, 111.1, 117.6, 121.1, 132.8, 140.1, 140.7, 148.4, and 173.4.

***N*-Allyl-*N*-furan-2-yl-3-(4-hydroxycyclopent-1-enyl)propionamide (16).** To a stirred solution containing 0.17 g (0.45 mmol) of the above silyl-protected alcohol in 1.8 mL of THF was added 0.54 mL (0.54 mmol) of tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.11 g (98%) of the title compound **16** as a pale yellow oil: IR (thin film) 3432, 2919, 2843, 1680, 1608, and 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08−2.38 (m, 7H), 2.45−2.62 (m, 2H), 4.16 (d, 2H, J = 6.4 Hz), 4.39−4.45 (m, 1H), 5.07- 5.14 (m, 2H), 5.20 (s, 1H), 5.72−5.84 (m, 1H), 6.05 (d, 1H, J = 3.2 Hz), 6.36 (dd, 1H, J = 3.2 and 1.6 Hz), and 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 32.0, 42.6, 45.0, 50.8, 71.8, 104.7, 111.1, 117.7, 121.1, 132.7, 140.1, 140.8, 148.2, and 173.3. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.88; H, 7.41; N, 5.21.

***N*-Allyl-*N*-furan-2-yl-3-(4-oxocyclopent-1-enyl)propionamide (12).** To a stirred solution containing 0.08 g (0.32 mmol) of the above alcohol **16** in 0.7 mL of DMSO was added 0.10 g (0.35 mmol) of *o*-iodoxybenzoic acid (IBX) at room temperature. The reaction mixture was stirred for 3 h and was then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.08 g (91%) of the title compound **12** as a pale yellow oil: IR (thin film) 2919, 1742, 1675, and 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (d, 1H, J = 6.4 Hz), 2.32 (d, 1H, J = 8.0 Hz), 2.45 (br t, 2H, J = 7.0 Hz), 2.75 (s, 2H), 2.86 (d, 2H, J = 2.0 Hz), 4.20 (d, 2H, J = 6.0 Hz), 5.09−5.18 (m, 2H), 5.62 (br t, 1H, J = 1.6 Hz), 5.75−5.87 (m, 1H), 6.09 (d, 1H, J = 3.2 Hz), 6.39 (dd, 1H, J = 3.2 and 2.4 Hz), and 7.29 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 31.3, 43.6, 45.2, 50.9, 104.8, 111.2, 117.9, 121.2, 132.6, 140.2, 140.9, 148.2, 172.8, and 216.8; HRMS m/z calcd for $[C_{15}H_{17}NO_3 + H^+]$ 260.1287, found 260.1274.

***N*-Allyl-*N*-furan-2-yl-3-(3-oxocyclopent-1-enyl)propionamide (15).** A solution containing 0.05 g (0.26 mmol) of the above furanyl ketone **12** in 0.8 mL of toluene in a sealed tube was heated at 180 °C for 12 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.045 g (90%) of the title compound **15** as a pale yellow oil: IR (thin film) 2919, 1711, 1675, and 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35−2.40 (m, 2H), 2.42 (d, 1H, J = 6.8 Hz), 2.44 (d, 1H, J = 7.2 Hz), 2.53−2.59 (m, 2H), 2.70 (t, 2H, J = 7.2 Hz), 4.20 (d, 2H, J = 6.4 Hz), 5.08−5.18 (m, 2H), 5.74−5.86 (m, 2H), 6.11 (d, 1H, J = 3.2 Hz), 6.40 (dd, 1H, J = 3.2 and 2.0 Hz), and 7.29 (d, 1H, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 31.1, 31.7, 35.2, 51.0, 105.0, 111.3, 118.1, 129.1, 132.5, 140.4, 147.9, 172.1, 181.3, and 209.8; HRMS m/z calcd for $[C_{15}H_{17}NO_3 + H^+]$ 260.1287, found 260.1281.

7-Allyl-2-hydroxy-1,2,3,3*a*,5,7,9,10-octahydro-7-azacyclopenta[*d*]naphthalene-4,8-dione (17). A solution containing 0.06 g (0.23 mmol) of amidofuran **16** in 1 mL of toluene in a sealed tube was heated at 180 °C for 24 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.04 g (67%) of an inseparable 1.3:1 mixture of diastereomers of **17** as a pale yellow oil: IR (thin film) 3441, 2935, 2868, 1706, 1624, and 1199 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 29.2, 31.7, 35.0, 37.1, 43.2, 46.8, 48.8, 56.7, 71.2, 100.2, 116.4, 132.7, 141.3, 168.4, and 208.1.

[3-(1,4-Dioxaspiro[4.4]non-7-en-7-yl)propionyl]furan-2-ylcarbamic Acid *tert*-Butyl Ester (19). To a stirred solution containing 1.5 g (8.81 mmol) of cyclopentenyl alcohol **13** in 35 mL of DMSO was added 2.7 g (9.7 mmol) of 2-iodoxybenzoic acid (IBX) at room temperature. The mixture was stirred at room temperature for 4 h and was then quenched with water. The white precipitate that formed was removed by filtration and washed with EtOAc. The filtrate was further extracted with EtOAc, and the combined organic layer was washed several times with water followed by brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by flash silica gel column chromatography to provide 1.3 g (88%) of 3-(4-oxocyclopent-1-enyl)propionic acid methyl ester (**18**) as a pale yellow solid: mp 31−33 °C; IR (thin film) 2911, 1747, 1435, 1265, and 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40−2.50 (m, 4H), 2.78 (s, 2H), 2.83 (d, 2H, J = 1.6 Hz), 3.62 (s, 3H), and 5.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 31.5, 43.6, 45.1, 51.6, 121.4, 140.4, 173.2, and 216.4.

To a stirred solution containing 11.7 g (69.6 mmol) of the above ketone **18** in 278 mL of CH_2Cl_2 at −78 °C was added 61.4 mL (250 mmol) of 1,2-bis(trimethylsiloxy)ethane. After this mixture was stirred for 15 min at −78 °C, a 1.3 mL (7.0 mmol) sample of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added dropwise. The resulting solution was stirred at −78 °C for 15 min followed by stirring for an additional 3 h at 0 °C. The reaction mixture was quenched using 0.56 mL (7.0 mmol) of pyridine, and the mixture was warmed to room temperature. The solution was poured into an aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 10.5 g (71%) of 3-(1,4-dioxaspiro[4.4]non-7-en-7-yl)propionic acid methyl ester as a yellow oil: IR (thin film) 2907, 1739, 1438, 1337, 1018, and 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35−2.37 (m, 2H), 2.45 (d, 1H, J = 8.0 Hz), 2.49 (dd, 1H, J = 8.0 and 1.6 Hz), 2.52 (s, 2H), 2.56 (s, 2H), 3.66 (s, 3H), 3.93 (s, 4H), and 5.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 32.0, 43.3, 45.5, 51.6, 64.2, 117.0, 120.9, 139.9, and 173.6.

To a stirred solution containing 9.8 g (46 mmol) of the above cyclic acetal in 184 mL of a 4:1:3 mixture of MeOH, THF, and water was added 2.3 g (55 mmol) of $LiOH \cdot H_2O$ at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then a 7.7 g (55 mmol) sample of sodium hydrogen sulfate ($NaHSO_4$) was slowly added

to the reaction mixture. The mixture was stirred for 30 min, and the organic solvent was removed under reduced pressure. The aqueous layer was extracted with a 4:1 mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 9.0 g (98%) of 3-(1,4-dioxaspiro[4.4]non-7-en-7-yl)propionic acid as a pale yellow oil: IR (thin film) 3492, 2906, 1707, 1651, 1424, 1342, 1016, and 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34−2.40 (m, 2H), 2.48−2.53 (m, 4H), 2.57 (br s, 2H), 3.95 (s, 4H), and 5.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 31.9, 43.3, 45.6, 64.1, 117.0, 121.1, 139.7, and 179.0.

To a stirred solution containing 0.6 g (3.3 mmol) of furan-2-ylcarbamic acid *tert*-butyl ester in 13 mL of THF at −78 °C was added 1.3 mL (3.3 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred at −78 °C for 1 h. In a separate flask a sample of 0.65 g (3.3 mmol) of the above carboxylic acid was dissolved in 13 mL of THF at 0 °C and 0.36 mL (3.3 mmol) of 4-methylmorpholine and 0.42 mL (3.3 mmol) of isobutyl chloroformate were added consecutively. After the mixture was stirred for 5 min, the white precipitate that formed was removed by filtration and was washed with 0.5 mL of THF. The filtrate was cooled to 0 °C and the preformed lithiate was added rapidly via cannula to the above solution. After it was stirred at 0 °C for 30 min and then for an additional 2 h at room temperature, the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to provide 1.1 g (89%) of the title compound **19** as a pale yellow solid: mp 96−98 °C; IR (thin film) 2911, 1749, 1723, 1650, 1262, and 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42q (s, 9H), 2.40 (t, 2H, J = 7.6 Hz), 2.52 (s, 2H), 2.55−2.58 (m, 2H), 2.86−2.92 (m, 2H), 3.92 (s, 4H), 5.34 (quin, 1H, J = 2.0 Hz), 6.14 (dd, 1H, J = 2.8 and 0.8 Hz), 6.41 (dd, 1H, J = 2.8 and 2.0 Hz), and 7.32 (dd, 1H, J = 2.0 and 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 27.7, 35.2, 43.4, 45.7, 64.1, 83.8, 105.9, 111.2, 117.1, 121.0, 140.0, 140.5, 143.8, 151.3, and 174.4. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.78; H, 6.94; N, 3.86. Found: C, 62.90; H, 7.03; N, 3.82.

3-(1,4-Dioxaspiro[4.4]non-7-en-7-yl)-*N*-furan-2-ylpropionamide (20). To a stirred solution containing 0.7 g (1.9 mmol) of the above Boc-amide **19** in 1.1 mL of CH_3CN was added 0.04 g (0.19 mmol) of magnesium perchlorate. The reaction mixture was stirred at 50 °C for 2 h, and then the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.45 g (89%) of the title compound **20** as a white solid: mp 93−94 °C; IR (thin film) 3200, 3047, 2897, 1654, 1557, 1334, and 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40−2.60 (m, 8H), 3.92 (s, 4H), 5.34 (br t, 1H, J = 1.6 Hz), 6.26 (d, 1H, J = 2.8 Hz), 6.32 (dd, 1H, J = 2.8 and 2.0 Hz), 6.98−7.01 (m, 1H), and 8.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 34.1, 43.2, 45.4, 64.1, 95.2, 111.3, 117.0, 121.3, 135.1, 140.0, 145.2, and 169.2. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.42; N, 5.09.

***N*-Allyl-3-(1,4-dioxaspiro[4.4]non-7-en-7-yl)-*N*-furan-2-ylpropionamide (21).** To a stirred solution containing 0.42 g (1.6 mmol) of the above primary amide **20** in 6 mL of DMF at 0 °C was added 0.064 g (1.6 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to room temperature and was stirred for an additional 1 h. The mixture was then recooled to 0 °C, and 0.15 mL (1.6 mmol) of allyl iodide was added dropwise. After it was warmed to room temperature, the mixture was stirred for 2 h, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.4 g (80%) of the title compound **21** as a pale yellow oil: IR (thin film) 2905, 1683, 1609, 1504, 1015, 854, and 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24−2.27 (m, 2H), 2.31−2.36 (m, 2H), 2.43 (s, 2H), 2.51 (s, 2H), 3.90 (s, 4H), 4.18 (d, 2H, J = 6.8 Hz), 5.09 (s, 1H), 5.12 (dd, 1H, J = 6.8 and 1.6 Hz), 5.22 (t, 1H, J = 1.6 Hz), 5.73−5.84 (m, 1H), 6.07 (dd, 1H, J = 3.2 and 0.8 Hz), 6.36 (dd, 1H, J = 3.2 and 2.0 Hz), and 7.25−7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 31.7, 43.3, 45.5, 50.8, 64.0, 104.7, 111.1, 117.0, 117.7, 120.6, 132.7, 140.1, and 140.3; HRMS m/z calcd for $[C_{17}H_{21}NO_4 + H^+]$: 304.1549, found 304.1556.

1-Allyl-3,4,7,7a-tetrahydro-1*H*-spiro[cyclopenta[*e*]quinoline-6,2′-[1,3]dioxolane]-2,8(5*H*,9*H*)-dione (22). A mixture containing 0.06 g (0.2 mmol) of the above furanyl carbamate **21** in 1 mL of toluene was heated at 180 °C in a sealed tube for 7 days. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.042 g (67%) of the title compound **22** as a pale yellow oil: IR (thin film) 3441, 2935, 2868, 1706, 1624, and 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (d, 2H, J = 14.0 Hz), 1.83−1.93 (m, 2H,), 2.06−2.20 (m, 3H), 2.60−2.74 (m. 4H), 3.03 (dd, 1H, J = 20.8 and 4.0 Hz), 3.11 (dd, 1H, J = 20.8 and 4.0 Hz), 3.75−3.90 (m, 3H), 4.05 (dd, 1H, J = 16.4 and 5.2 Hz), 4.57 (dd, 1H, J = 16.4 and 5.2 Hz), 5.08 (t, 1H, J = 4.0 Hz), 5.10 (d, 1H, J = 10.4 Hz), 5.16 (d, 1H, J = 10.4 Hz), 5.70−5.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 31.7, 35.0, 37.1, 43.2, 46.8, 48.8, 56.7, 71.2, 100.2, 116.4, 132.7, 141.3, 168.4, and 208.1; HRMS m/z calcd for $[C_{17}H_{21}NO_4 + H^+]$ 304.1549, found 304.1547.

***N*-{3-[(*tert*-Butyldimethylsilanyl)oxy]propyl}-3-(1,4-dioxaspiro[4.4]non-7-en-7-yl)-*N*-furan-2-ylpropionamide (23).** To a stirred solution containing 3.2 g (12 mmol) of primary amide **20** in 24 mL of DMF at 0 °C was added 0.51 g (12.8 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to room temperature and was stirred for an additional 1 h. The mixture was recooled to 0 °C, and 3.8 mL (12.8 mmol) of *tert*-butyl(3-iodopropoxy)dimethylsilane in 24 mL of DMF was added dropwise. After it was warmed to room temperature, the mixture was stirred for 2 h, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 4.6 g (87%) of the title compound **23** as a pale yellow oil: IR (thin film) 3122, 2860, 1685, 1608, and 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.03, (s, 6H), 0.80 (s, 9H), 1.68−1.74 (m, 2H), 2.17−2.21 (m, 2H), 2.27−2.32 (m, 2H), 2.41 (s, 2H), 2.50 (s, 2H), 3.59 (t, 2H, J = 6.0 Hz), 3.63 (t, 2H, J = 6.8 Hz), 3.88 (s, 4H), 5.19 (s, 1H), 6.05 (d, 1H, J = 3.2 Hz), 6.35 (dd, 1H, J = 2.0 and 3.2 Hz), and 7.24 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.2, 25.8, 26.9, 31.3, 31.8, 43.3, 45.5, 45.6, 60.6, 64.1, 104.5, 111.1, 117.0, 120.6, 140.0, 140.4, 148.6, and 173.3; HRMS m/z calcd for $[C_{23}H_{37}NO_5Si + H^+]$ 436.2519, found 436.2508.

1-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-3,4,7,7*a*-tetrahydro-1*H*-spiro[cyclopenta[*e*]quinoline-6,2′-[1,3]dioxolane]-2,8(5*H*,9*H*)-dione (24). A solution containing 4.6 g (11 mmol) of furanyl carbamate **23** in 110 mL of toluene was heated at 200 °C in a sealed tube for 10 days. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 3.2 g (88%) of the title compound **24** as a pale yellow oil: IR (thin film) 2928, 1743, 1720, 1652, 1602, 1378, and 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.65−1.90 (m, 3H), 1.72 (d, 1H, J = 13.6 Hz), 2.05−2.15 (m, 3H), 2.56−2.62 (m, 2H), 2.68 (s, 1H), 2.69 (dd, 1H, J = 24.0 and 3.2 Hz), 3.07 (dd, 1H, J = 21.0 and 4.0 Hz), 3.13 (dd, 1H, J = 21.0 and 4.0 Hz), 3.58−3.96 (m, 8H), and 5.25 (t, 1H, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 25.8, 29.0, 30.0, 30.7, 36.0, 37.1, 41.0, 43.9, 46.5, 55.3, 60.5, 64.2, 64.5, 99.7, 115.4, 140.5, 168.0, and 207.3; HRMS m/z calcd for $[C_{23}H_{37}NO_5Si + H^+]$ 436.2519, found 436.2521.

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1-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-8-hydroxy-3,4-dihydro-1*H*-spiro[cyclopenta[*e*]quinoline-6,2′-[1,3]dioxolane]-2,9(5*H*,7*H*)-dione (25). After it stood in an open flask for several days, compound **24** was transformed into the new compound (75%) **25**, the structure of which was assigned on the basis of a single-crystal X-ray analysis: mp 119−121 °C; IR (thin film) 3355, 2952, 2933, 2887, 2859, 1734, 1686, 1629, 1586, 1386, 1182, 1104, 838, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, H, J = 4.0 Hz), 0.90 (s, 9H), 1.75 (dd, 1H, J = 13.2 and 1.2 Hz), 1.68−1.85 (m, 5H), 2.31 (d, 1H, J = 13.2 Hz), 2.48−2.56 (m, 1H), 2.78 (dd, 1H, J = 8.0 and 2.0 Hz), 2.76 (dd, 1H, J = 12.0 and 7.2 Hz), 2.84 (d, 1H, J = 17.6 Hz), 3.10 (d, 1H, J = 17.6 Hz), 3.57−3.67 (m, 2H), 3.80−3.94 (m, 6H), 4.00−4.06 (m, 1H), 6.00 (s, 1H), and 6.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) −5.5, 18.2, 25.8, 26.5, 28.8, 30.1, 37.6, 41.4, 44.3, 46.5, 60.3, 64.3, 64.8, 105.4, 114.9, 129.9, 141.8, 161.9, 168.4, and 181.1; HRMS m/z calcd for $[C_{23}H_{35}NO_6Si + H^+]$ 450.2312, found 450.2324.

1-(3-Hydroxypropyl)-3,4,7,7*a*-tetrahydro-1*H*-spiro[cyclopenta[*e*]quinoline-6,2′-[1,3]dioxolane]-2,8(5*H*,9*H*)-dione (26). To a solution containing 0.027 g (0.062 mmol) of the silyl-protected alcohol **24** in 2 mL of aqueous acetone (1%) at room temperature under a nitrogen atmosphere was added 6 mg of $PdCl_2(CH_3CN)_2$ in one portion.[21] The solution was sonicated at 25 °C for 4 h. The solvent was removed under reduced pressure, and the crude residue was filtered and purified by flash silica gel column chromatography to provide 0.016 g (84%) of the title compound **26** as a clear oil: IR (thin film) 3420, 2952, 1717, 1669, and 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −1.66 (d, 1H, J = 14 Hz), 1.69−1.80 (m, 2H), 1.80−1.90 (m, 1H), 2.06−2.16 (m, 3H), 2.58−2.74 (m, 4H), 3.05 (dd, 1H, J = 21.2 and 4.4 Hz), 3.13 (dd, 1H, J = 21.2 and 4.4 Hz), 3.38−3.54 (m, 3H), 3.78−3.96 (m, 6H), and 5.16 (t, 1H, J = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 29.6, 30.3, 36.0, 37.2, 39.4, 44.0, 46.5, 55.3, 58.4, 64.3, 64.6, 100.4, 115.3, 140.0, 169.8, and 206.8. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.52; H, 7.22; N, 4.36. Found: C, 63.58; H, 7.29; N, 4.43.

Octahydro-1*H*-cyclopenta[*e*][1,3]oxazino[3,2-*j*]quinoline-7,9,13(10*H*)-trione (28). To a solution containing compound **24** in 1 mL of THF at 0 °C under a nitrogen atmosphere was added 0.5 mL of a 5% solution of HCl in THF dropwise. The reaction was warmed to room temperature and was stirred for an additional 12 h. The mixture was then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to give 0.013 g (68%) of the title compound **28** as a white solid: mp 168−171 °C; IR (thin film) 2963, 2880, 1753, 1710, 1643, and 1404 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (br d, 1H, J = 13.6 Hz), 1.72 (ddd, 1H, J = 14.0, 6.4, and 1.2 Hz), 1.83 (qt, 1H, J = 13.0, 5.6 Hz), 1.98 (d, 1H, J = 17.6 Hz), 2.04 (td, 1H, J = 14.0 and 4.8 Hz), 2.15 (ddd, 1H, J = 14.0, 12.4, and 6.4 Hz), 2.35 (br d, 1H, J = 15.6 Hz), 2.45 (t, 1H, J = 18.4 Hz), 2.46 (dt, 1H, J = 18.4 and 2.4 Hz), 2.50 (dd, 1H, J = 7.2 and 1.2 Hz), 2.63−2.73 (m, 2H), 2.86 (td, 1H, J = 11.6 and 1.2 Hz), 2.90 (td, 1H, J = 11.6 and 1.2 Hz), 2.90 (td, 1H, J = 14.0 and 3.2 Hz), 2.99 (d, 1H, J = 17.6 Hz), 3.01 (ddd, 1H, J = 14.4, 6.4, and 2.4 Hz), 3.83 (qd, 1H, J = 11.6 and 2.4 Hz), 3.88 (dd, 1H, J = 11.6 and 5.6 Hz), and 4.68 (ddt, 1H, J = 14.4, 3.2, and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 25.8, 29.4, 30.7, 33.2, 34.9, 40.6, 45.6, 48.6, 55.7, 59.9, 88.1, 167.3, 207.9 and 212.7; HRMS m/z calcd for $[C_{15}H_{19}NO_4 + H^+]$ 278.1392, found 278.1384.

7-(3-Hydroxypropyl)-3,3*a*,5,7,9,10-hexahydro-7-azacyclopenta[*d*]naphthalene-2,4,8-trione (29). To a stirred solution containing 0.12 g (0.28 mmol) of tricycle **24** in 1.4 mL of CH_3CN and 1.4 mL of a borate pH 8 buffer (prepared by the addition of 41 mL of an aqueous 0.1 M HCl solution to 100 mL of an aqueous 0.025 M solution of $Na_2B_4O_7 \cdot 10H_2O$ (borax)) was added 0.015 g (0.028 mmol) of ammonium cerium nitrate (CAN) in one portion. The resulting mixture was heated at 75 °C for 7 h and was then diluted with $CHCl_3$ and extracted with a 4:1 mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.07 g (61%) of the title compound **29** as a light yellow oil: IR (thin film) 3423, 2929, 1745, 1718, 1635, 1403, and 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (quin, 3H, J = 6.0 Hz), 2.86 (dd, 1H, J = 14.0 and 6.8 Hz), 2.04 (d, 1H, J = 18.0 Hz) 2.06−2.18 (m, 1H), 2.35 (dd, 1H, J = 19.2 and 8.4 Hz), 2.50 (d, 1H, J = 18.0 Hz), 2.60 (ddd, 1H, J = 19.2, 12.4, and 6.8 Hz), 2.75 (dd, 1H, J = 19.2 and 6.8 Hz), 3.10 (br d, 1H, J = 8.4 Hz), 3.11 (dd, 1H, J = 21.0 and 4.8 Hz), 3.23 (d, 1H, J = 19.2 Hz), 3.31 (dd, 1H, J = 21.0 and 3.2 Hz), 3.44−3.58 (m, 2H), 3.84−4.00 (m, 2H), and 5.31 (dd, 1H, J = 4.8 and 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.7, 30.3, 34.7, 37.8, 40.1, 45.5, 45.9, 53.1, 58.5, 101.5, 139.1, 168.7, 205.1, and 212.2; HRMS m/z calcd for $[C_{15}H_{19}NO_4 + H^+]$ 278.1392, found 278.1391.

Methanesulfonic Acid 3-(2,4,8-Trioxo-1,2,3,3*a*,4,5,9,10-octahydro-8*H*-7-azacyclopenta[*d*]naphthalen-7-yl) Propyl Ester (30). To a stirred solution containing 0.015 g (0.054 mmol) of alcohol **24** in 0.5 mL of CH_2Cl_2 under a nitrogen atmosphere was added 0.009 mL (0.065 mmol) of triethylamine followed by 0.005 mL (0.065 mmol) of methanesulfonyl chloride. The resulting solution was stirred at 0 °C for 1 h and was then quenched with water and extracted with a 4:1 mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.016 g (83%) of the title compound **30** as a light yellow oil: IR (thin film) 2932, 1744, 1720, 1639, 1405, 1346, and 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (dd, 1H, J = 13.8 and 6.6 Hz), 1.97−2.15 (m, 3H), 2.07 (d, 1H, J = 18.6 Hz), 2.35 (dd, 1H, J = 19.2 and 9.0 Hz), 2.51 (d, 1H, J = 18.6 Hz), 2.56 (ddd, 1H, J = 19.2, 12.6, and 6.6 Hz), 2.70 (dd, 1H, J = 19.2 and 6.6 Hz), 3.04 (s, 3H), 3.10 (d, 1H, J = 9.0 Hz), 3.11 (dd, 1H, J = 21.0 and 4.8 Hz), 3.22 (d, 1H, J = 19.2 Hz), 3.30 (dd, 1H, J = 21.0 and 3.0 Hz), 3.82 (ddd, H, J = 14.0, 8.4, and 6.0 Hz), 3.94 (ddd, 1H, J = 14.0, 8.4, and 6.0 Hz), 4.22−4.30 (m, 2H), and 5.23 (dd, 1H, J = 4.8 and 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 28.4, 30.5, 34.8, 37.4, 37.8, 40.6, 45.6, 46.0, 53.1, 68.0, 101.0, 139.3, 167.5, 205.2, and 212.3.

Hexahydrocyclopenta[*e*]quinoline-2,6,8(1*H*,5*H*,9*H*)-trione (34). To a solution containing 0.015 g (0.054 mmol) of alcohol **29** in a sealed tube was added 0.045 (0.16 mmol) of iodoxybenzoic acid (IBX)[23] in one portion at room temperature. The reaction vessel was sealed and heated at 80 °C for 1 h and then cooled to 0 °C. The white precipitate that formed was removed by filtration and washed with CH_2Cl_2. The solvent was removed under reduced pressure to provide aldehyde **32** as a pale yellow oil: IR (thin film) 2931, 2736, 1744, 1639, 1403, 1178, 915, and 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, 1H, J = 13.6, 7.2, and 1.2 Hz), 2.05 (d, 1H, J = 17.6 Hz), 2.05−2.15 (m, 1H), 2.34 (ddd, 1H, J = 19.2, 8.4, and 1.2 Hz), 2.47 (d, 1H, J = 17.6 Hz), 2.60 (dd, 1H, J = 12.8 and 7.2 Hz), 2.65−2.83 (m, 3H), 3.04−3.12 (m, 2H), 3.20 (d, 1H, J = 19.2 Hz), 3.28 (dd, 1H, J = 20.4 and 3.2 Hz), 3.97−4.14 (m, 2H), 5.18 (dd, 1H, J = 4.8 and 3.2 Hz), 9.78 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 30.9, 35.0, 38.0, 38.1, 41.9, 45.7, 46.2, 53.3, 101.3, 139.5, 167.8, 200.1, 205.4, and 212.6.

To a stirred solution containing the above aldehyde **32** in 0.5 mL of THF was added 0.001 g (0.005 mmol) of *p*-TsOH·H_2O. The resulting solution was heated at 65 °C for 2 h. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel chromatography to give 0.008 g (60%) of the title compound **34** as a light yellow oil: IR (thin film) 2928, 1743, 1720, 1652, 1602, 1378, and 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, 1H, J = 13.0, 6.8, and 1.2 Hz), 2.10 (ddd, 1H, J = 13.0, 6.8, and 1.2 Hz), 2.16 (d, 1H, J = 19.0 Hz), 2.33 (ddd, 1H, J = 19.0, 8.8, and 1.2 Hz), 2.52 (d, 1H, J = 19.0

Hz), 2.60 (ddd, 1H, J = 19.0, 6.8, and 1.2 Hz), 2.75 (ddd, 1H, J = 19.0, 6.8, and 1.2 Hz), 3.03 (d, 1H, J = 20.0 Hz), 3.08 (d, 1H, J = 8.8 Hz), 3.22 (dd, 1H, J = 19.0 and 2.2 Hz), 3.32 (d, 1H, J = 20.0 Hz), 3.76 (dd, 1H, J = 18.0 and 2.4 Hz), 5.12 (dd, 1H, J = 18.0 and 5.2 Hz), 5.70 (dd, 1H, J = 9.6 and 2.4 Hz), and 5.7 (ddd, 1H, J = 9.6, 5.3, and 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 30.2, 34.6, 40.3, 41.8, 45.4, 46.0, 53.5, 109.1, 121.9, 124.0, 132.6, 166.3, 204.8, and 121.6; HRMS m/z calcd for $[C_{15}H_{15}NO_3 + H^+]$ 258.1130, found 258.1136.

Hemiketal of (3′*R*,10*R*,10′*R*,13a*S*)-10-hydroxy-4,5,9,10-tetrahydro-1*H*-cyclopenta[*e*]pyrrolo[1,2-*j*]quinoline-2,6,13-(3*H*,8*H*,13a*H*)-trione (37). To a solution containing 0.03 g (0.11 mmol) of alcohol **29** in a sealed tube was added 0.091 (0.33 mmol) of iodoxybenzoic acid (IBX)[23] in one portion at room temperature. The reaction vessel was sealed and heated at 80 °C for 1 h and then cooled to 0 °C. The white precipitate that formed was removed by filtration and washed with CH_2Cl_2. The solution was concentrated under reduced pressure to provide 3-(2,6,8-trioxo-3,4,5,6,7,7a,8,9-octahydrocyclopenta[*e*]quinolin-1(2*H*)-yl)propanal (**32**), which was used in the next step without further purification.

To a solution containing the above aldehyde **32** in 0.5 mL of THF was added 0.009 g (0.23 mmol) of NaH (60% in mineral oil). The resulting solution was stirred at 0 °C for 2 h, after which time small pieces of ice were added. The reaction mixture was warmed to room temperature and extracted with a 4:1 mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.01 g (35%) of the title compound **37** as a white solid: IR (thin film) 3375, 2924, 1739, 1667, 1618, 1457, and 1321 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55−1.65 (m, 1H), 1.75−1.85 (m, 1H), 2.00−2.05 (m, 1H), 2.10−2.25 (m, 2H), 2.35−2.43 (m, 2H), 2.53 ; (t, 1H, J = 14.0 Hz), 2.78 (dd, 1H, J = 13.6 and 6.8 Hz), 3.15 (br s, 1H), 3.74−3.85 (m, 2H), 4.23 (t, 1H, J = 2.0 Hz), 6.02 (dd, 1H, J = 9.6 and 2.0 Hz), and 6.60 (d, 1H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 27.9, 29.2, 37.0, 42.9, 45.7, 49.5, 50.8, 66.3, 85.0, 104.8, 129.4, 152.7, 169.8, and 196.6; HRMS m/z calcd for $[C_{15}H_{17}NO_4 + H^+]$ 276.1236, found 276.1231.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving ^{1}H and ^{13}C NMR data of various key compounds lacking CHN analyses together with ORTEP drawings, CIF files, and tables giving crystallographic data for compounds **25** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org. Atomic coordinates for compounds **25** and **37** will also be deposited with the Cambridge Crystallographic Data Centre.

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