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Synthesis of (±)-Aphanorphine Using Rh-Catalyzed Cyclohydrocarbonylation

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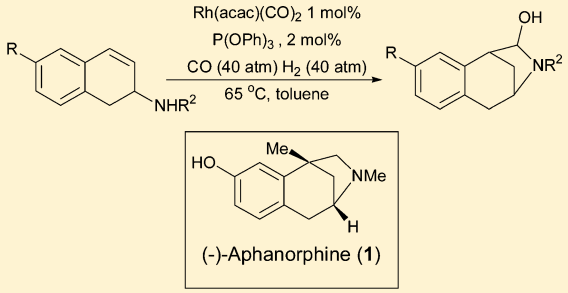
Supporting Information

ABSTRACT: A facile formal synthesis to aphanorphine and its analogue is described, featuring Rh-catalyzed cyclohydrocarbonylation of 2-aminodihydronaphthalene to the bridged benzazepine core. Subsequent introduction of the methyl group and functional group transformation complete the synthesis of aphanorphine and its analogue over eight steps.



In 1989, Shimizu and Clardy reported a tricyclic alkaloid, aphanorphine (**1**), isolated from the freshwater blue-green algae *Aphanizomenon flos-aquae*.[1] Aphanorphine is a bridged benzazepine alkaloid whose framework resembles that of the analgesic benzomorphane alkaloids such as metazocine, eptazocine, and morphine (Figure 1).

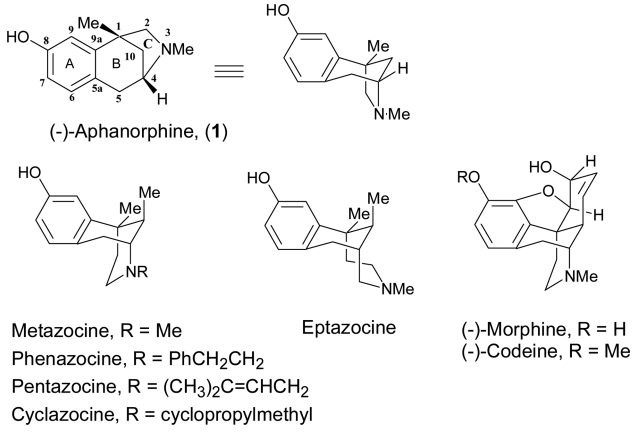
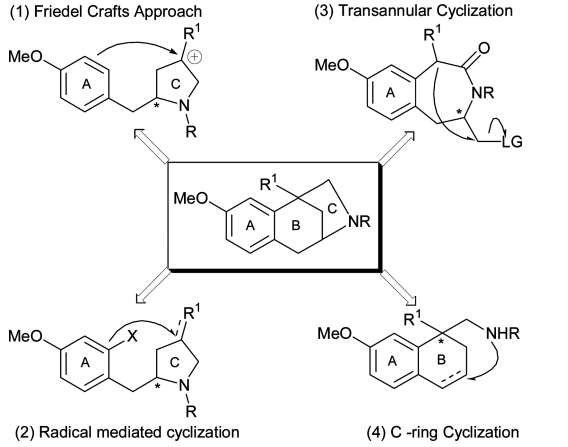


Figure 1. Aphanorphine and its analogues.

As a possible candidate for bioactivity investigation and an intriguing structure for methodology development, aphanorphine has attracted synthetic chemists' interest to develop various approaches to its synthesis. These approaches can be generally classified as follows (Scheme 1): (1) Friedel–Crafts alkylation of a tertiary carbocation at the C ring with an electron-rich aromatic A ring contributes the largest portion among these approaches.[2−11] (2) Similar strategies include radical-initiated coupling or Pd-catalyzed Heck reaction of an aryl halide with an olefin or enol at the C ring.[12−17] (3) Transannular substitution in the benzazepine moiety can produce the B and C ring in one step. With suitable arrangements, intramolecular substitution allows formation of a bicyclo[3.2.1] system from a 7-membered ring intermediate.[18−22] (4) Preparation of suitable tetraline or dihydronaphthalene derivatives followed by construction of the C ring.[23−39] In addition, Grainger et al. reported a dithiacarbamate initiated radical cyclization to build the B and C ring followed by construction of the aromatic A ring, which does not belong to those shown above.[40] These creative and elegant works have provided valuable routes not only to the alkaloid but also to the critical intermediates, which can be used for development of other analogues or asymmetric synthesis.

Scheme 1. Classification of Strategies for Syntheses of Aphanorphine



As part of our interest in synthesis of medicinal active alkaloids for medicinally purposes, our group has utilized the

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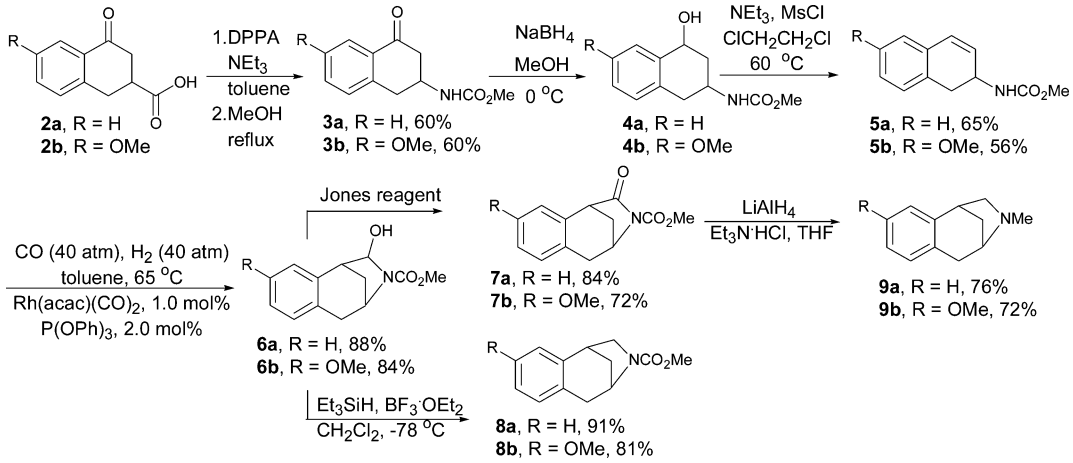
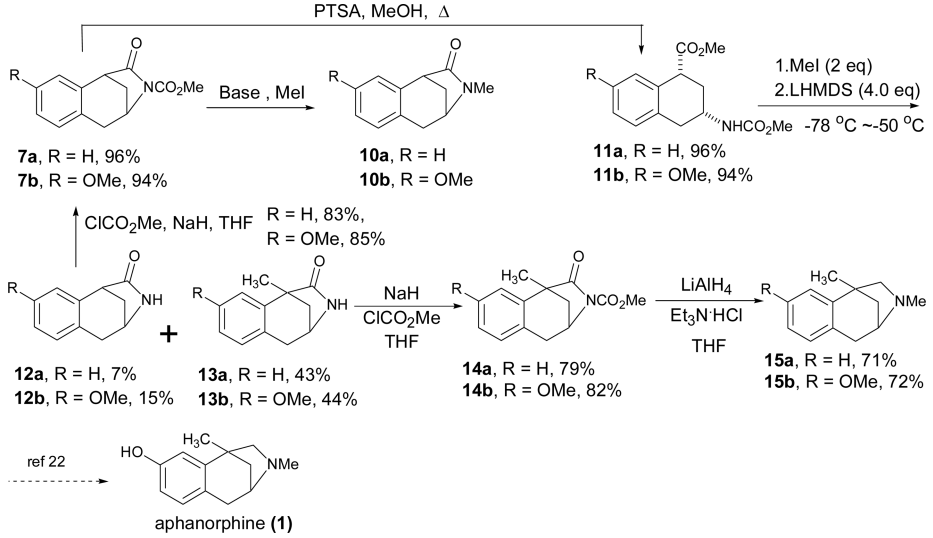
Scheme 2. Syntheses of Tricyclic Benzazepine s 7−9



Scheme 3. Synthesis of Aphanorphine



Rh-catalyzed cyclohydrocarbonylation[41−43] strategy as a practical route to construct the piperidines, pyrrolidinoindoline and tetrahydrofuranoindoline alkaloids.[44,45] Here we report our progress in using this methodology to construct bridged benzazepine skeleton and its application to the formal syntheses of aphanorphine and its analogue.

Our syntheses commenced with the preparation of tetralone-3-carboxylic acid derivative **2a**, which was readily available according to Ravina's procedure.[46] Treatment of acid **2a** with diphenyl phosphorazidate (DPPA) and triethylamine in the presence of methanol afforded carbamate **3a** as a Curtius rearrangement product in 60% yield. The use of two equivalents of triethylamine was crucial in the reaction, because an insufficient amount of the base would result in the formation of the corresponding isonitrile, as did a prolonged heating time and higher temperature. The ketone group of **3a** was reduced to a secondary alcohol in quantitative yield using standard sodium borohydride reduction conditions (dr ∼4.4). Heating alcohol **4a** at reflux with 5 mol % of PTSA in toluene gave a mixture of the desired dihydronaphthalene carbamate **5a** in 24% yield and twice eliminated product naphthalene in 70% yield. We considered that acidic conditions were likely to have caused the undesired second elimination. Thus, we changed to using MsCl and triethylamine in dichloroethane at 60 °C and successfully obtained product **5a** in 65% yield in two steps from ketone **3a** (Scheme 2).

With the crucial intermediate dihydronaphthalenes **5a** and **5b** in hand, we were pleased to find that treatment under hydroformylation conditions, i.e., 1 mol % of $Rh(acac)(CO)_2$ and 2 mol % of $P(OPh)_3$ catalyst under 80 atm of CO and H_2 (1:1) at 65 °C, resulted cleanly in formation of tricyclic amidal **6a** in 88% yield and amidal **6b** in 84% yield (dr ∼1.5), respectively. The results suggested that no matter which side hydroformylation proceeded at the substrate to give either *syn*- or *anti*- aldehyde, the cyclization eventually proceed probably due to epimerization on the benzylic position or directing effect by coordination of the Rh metal atom with the carbamate group.[47] As a versatile intermediate, amidal **6** could be either oxidized by Jones reagent to lactam **7** or reduced to bridged benzazepine **8** by Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ in excellent yield. An X-ray analysis result of **7a** was obtained to confirm the bridged benzazepine structure (see the Supporting Information, CCDC no. 1016796). Reduction with the alane−triethylamine complex of either **7** or **8** furnished the bridged benzazepine structure **9**.

To complete the synthesis, our efforts were focused on introduction of a functional group on the C-1 position. We conducted a screening for radical-mediated benzylic bromina-

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tion on norbenzomorphanes **7**, **8**, and **9** using the NBS or 1,3-dibromo-5,5-dimethylhydantoin/AIBN protocol. However, we only received the undesired secondary benzylic bromides in the reaction of lactam **7** and carbamate **8** in moderate yield and decomposed product from tertiary amine **9**. We next turned to direct methylation methods using various strong bases (e.g., LDA, LiHMDS, NaHMDS) followed by addition of iodomethane, but this transformation appeared to be difficult to effect. These conditions generally brought formation of either decomposed residue or starting material recovery. Although the Simpkins' protocol[48,49] using LDA/LiCl or LTMP/LiCl complex followed by alkylating reagents was known as a practical route to alkylate the bridge methine in a bicyclo system, the conditions only afforded an undesired *N*-methyl lactam **10**. Formation of *N*-methylated product **10** could be attributed to the fact that the strong base reacted first with the N-carbamate group to yield the resulting anion, rather than abstracted a proton from the methine position. Thus, we switched to a stepwise strategy to install the methyl substituent at the 1 position.

Treatment of imide **7a** in methanol in the presence of PTSA resulted in methyl ester **11a** in 96% yield (Scheme 3). With the substrate ester **11** in hand, we examined various bases for methylation. Reaction with *t*-BuOK or K_2CO_3 led to intact starting material recovery, while reactions with LDA, NaH, and NaHMDS yielded *N*-methyl lactam **10** or carbamate-free lactam **12**. To our delight, the desired methylated lactam **13a** was successfully obtained in 43% yield by treatment with 4 equiv of LiHMDS in the presence of 2 equiv of iodomethane, accompanied by carbamate-free secondary lactam **12a** in 7% yield. It was noteworthy that removal of the carbamate protecting group and formation of the lactam moiety occurred in this transformation.[50] Thus, the exact amount of the base and iodomethane were critical because incorrect ratio or base would lead either to *N*-methylated product **10** or starting material recovery. Reaction of lactam **12a** and **13a** with methyl chloroformate and sodium hydride in THF afforded *N*-methyl imide **14a** in 79% yield and imide **7a** in 83% yield, which could be reused in the next cycle. Applied to the synthesis shown above, *O*-methyl aphanorphine derivative **14b** can be obtained and recrystallized from ethyl acetate and hexane solution to give single crystals for X-ray diffraction analysis to confirm the structure (see the Supporting Information, CCDC no. 1016795).

Global reduction with alane−triethylamine complex afforded the desired methylated norbenzomorphane product **15a** in 71% yield as well as product **15b** in 72% yield. The NMR data of **15b** were in agreement with those reported in the literature.[10] *O*-Methyl product **15b** could be further converted to aphanorphine according to the known boron tribromide mediated demethylation protocol,[22] thus completing the synthesis of aphanorphine.

In conclusion, we have completed the syntheses of potentially analgesic bridged benzazepine alkaloid **15a** and its methoxy analogue **15b** from readily available starting materials in eight steps, featuring Rh-catalyzed hydroformylation. This methodology provides a readily feasible route to construct the norbenzomorphane structure. In addition, we have developed a method for the introduction of the methyl group at the angular position in the norbenzomorphane structure via a stepwise alkylation strategy. Subsequent investigation and application of the methodology toward other interesting targets is currently underway.

EXPERIMENTAL SECTION

All reactions were performed under an argon atmosphere and in anhydrous solvent, unless otherwise stated. The solvents and reagents were dried or refined according to the literature procedures. The reaction flasks were dried in a 110 °C oven and allowed to cool to room temperature in a desiccator with drying agents and assembled under an argon atmosphere. TLC analyses were visualized with UV light, iodine chamber, 10% sulfuric acid or 10% PMA solution. The crude products were purified by flash column chromatography on silica gel to give isolated yield. Melting points were recorded on a melting apparatus. The results of the X-ray crystal structure determination have been checked to obtain the corresponding CCDC number. All NMR spectra, e.g., ^{1}H, ^{13}C, DEPT, gCOSY, gHSQC, and gHMBC, were recorded on a 400 or 600 MHz NMR spectrometer, which provided all necessary data for the full assignment of each compound. Chemical shifts (δ) are reported in ppm using residual undeuterated solvent as an internal standard. Coupling constants are described in hertz. Mass spectra were recorded on a mass spectrometer with a magnetic sector using the electrospray ionization (ESI) or fast atom bombardment (FAB).

Preparation of 3-Methoxycarbonylamino-1-tetralone (3). A mixture of 1-tetralone-3-carboxylic acid[46] (6.66 g, 35.0 mmol, 1.0 equiv), Et_3N (7.08 g, 70 mmol, 2.0 equiv), and DPPA (10.6 g, 38.5 mmol, 1.1 equiv) in toluene (175 mL) was allowed to be heated at 65 °C under argon. It took around 30 min until gas evolution had ceased. After gas evolution has ceased, MeOH (5.61 g, 175 mmol, 5.0 equiv) was added via a syringe, and the reaction mixture was heated at 65 °C for 5 h. Upon completion of the reaction monitored by TLC analysis, the solution was cooled to room temperature and concentrated under reduced pressure to remove excess volatile substances to yield a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/*n*-Hex as the eluant afforded the titled product.

*3-Methoxycarbonylamino-1-tetralone (**3a**).* Light brown solid (4.59 g, 20.9 mmol, 60%). Mp: 112−114 °C. R_f = 0.29; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 2.62 (dd, J = 9.6, 16.8 Hz, 1H, H-2), 2.85 (dd, J = 3.6, 16.8 Hz, 1H, H-2), 2.93 (dd, J = 8.8, 16.0 Hz, 1H, H-4), 3.38 (d, J = 15.6 Hz, 1H, H-4), 3.54 (s, 3H, $-NHCO_2CH_3$), 4.24 (brs, 1H, H-3), 5.47 (brs, 1H, N*H*), 7.19 (t, J = 7.6 Hz, 1H, H-5), 7.28 (t, J = 7.2 Hz, 1H, H-7), 7.43 (t, J = 7.2 Hz, 1H, H-6), 7.91 (d, J = 7.6 Hz, 1H, H-8). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 35.8 (t, C-4), 44.7 (t, C-2), 46.9 (d, C-3), 51.9 (q, $-NHCO_2CH_3$), 126.8 (d, C-8), 127.0 (d, C-7), 129.3 (d, C-5), 131.8 (s, C-8a), 133.9 (d, C-6), 140.7 (s, C-4a), 156.1 (s, $-NHCO_2CH_3$), 195.9 (s, C-1). EI-HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{13}NO_3^+$ 219.0895, found 219.0890 (Δ = 2.3 ppm).

*7-Methoxy-3-methoxycarbonylamino-1-tetralone (**3b**).* Light brown solid (359 mg, 1.44 mmol, 60%). Mp: 96−98 °C. R_f = 0.26; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 2.67 (dd, J = 9.2, 16.8 Hz, 1H, H-2), 2.87−2.93 (m, 2H, H-2 and H-4), 3.22 (d, J = 15.6 Hz, 1H, H-4), 3.64 (s, 3H, $-NHCO_2CH_3$), 3.81 (s, 3H, $-OCH_3$ at C-7), 4.32 (brs, 1H, H-3), 5.02 (brs, 1H, N*H*), 7.08 (dd, J = 2.8, 8.4 Hz, 1H, H-6), 7.17 (d, J = 8.4 Hz, 1H, H-5), 7.48 (d, J = 2.0 Hz, 1H, H-8). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 35.1 (t, C-4), 44.6 (t, C-2), 47.2 (d, C-3), 52.0 (q, $-NHCO_2CH_3$), 55.3 (q, $-OCH_3$ at C-7), 109.0 (d, C-8), 122.2 (d, C-6), 130.5 (d, C-5), 132.7 (s, C-8a), 133.1 (s, C-4a), 156.2 (s, $-NHCO_2CH_3$), 158.6 (s, C-7), 195.9 (s, C-1). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NO_4^+$, 249.1001, found 249.0995 (Δ = 2.4 ppm).

Preparation of 2-Methoxycarbonylamino-1,2-dihydronaphthalene (5). To a solution of tetralone (**3a**, 3.87 g, 17.7 mmol, 1.0 equiv) in MeOH (44 mL) in an ice bath was added $NaBH_4$ (1.00 g, 26.6 mmol, 1.5 equiv) in portions. During the course of addition, substantial gas evolution was observed. The reaction mixture was allowed to stir for 3 h in an ice bath. Upon completion of the reaction monitored by TLC analysis, 10% of the HCl solution was added until the pH value was smaller than 7. The reaction mixture was concentrated under reduced pressure to remove excess volatile substances and then extracted with EtOAc (30 mL × 4). The combined organic layers were washed with brine (30 mL), dried over

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anhydrous $MgSO_4$, and then concentrated under reduced pressure to give a crude product. The crude alcohol product was used directly without further purification.

To a solution of the crude alcohol product and Et_3N (14.3 g, 142 mmol, 8.0 equiv) in 1,2-dichloroethane (44 mL) which was allowed to stir in an ice bath for 10 min was added $MeSO_2Cl$ (8.08 g, 70.8 mmol, 4.0 equiv) over 30 min. The reaction mixture was allowed to be heated at 60 °C for 18 h. Upon completion of the reaction monitored by TLC analysis, water (30 mL) was added, and then the reaction mixture was partitioned with CH_2Cl_2 (30 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel using EtOAc/n-Hex as the eluant afforded the titled product.

*2-Methoxycarbonylamino-1,2-dihydronaphthalene (**5a**).* Light brown solid (2.34 g, 11.5 mmol, 65%). Mp: 69−71 °C. R_f = 0.57; EtOAc/n-Hex = 1:1. ^{1}H NMR[51] (400 MHz, 25 °C, $CDCl_3$, δ): 2.93 (dd, J = 6.0, 16 Hz, 1H, H-4), 3.06 (dd, J = 6.4, 16 Hz, 1H, H-4), 3.64 (s, 3H, $-NCO_2CH_3$), 4.54 (t, J = 6.4 Hz, 1H, H-3), 4.81 (s, 1H, NH), 5.99 (dd, J = 4.8, 9.6 Hz, 1H, H-2), 6.56 (d, J = 9.6 Hz, 1H, H-1), 7.07−7.09 (m, 1H, H-8), 7.13−7.20 (m, 3H, H-5, H-6 and H-7). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 34.5 (t, C-4), 44.9 (d, C-3), 52.0 (q,-NCO_2CH_3), 126.5 (d, C-8), 126.9 (d, C-7), 127.6 (d, C-6), 127.7 (d, C-2), 128.6 (d, C-5), 129.6 (d, C-1), 132.5 (s, C-8a), 132.7 (s, C-4a), 156.2 (s, $-NCO_2Me$). EI-HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{13}NO_2^+$ 203.0946, found 203.0943 (Δ = 1.5 ppm).

*6-Methoxy-2-methoxycarbonylamino-1,2-dihydronaphthalene (**5b**).* Light brown solid (189 mg, 0.810 mmol, 56%). Mp: 94−96 °C. R_f = 0.52; EtOAc/n-Hex = 1:1. ^{1}H NMR[51] (400 MHz, 25 °C, $CDCl_3$, δ): 2.83 (dd, J = 6.4, 16 Hz, 1H, H-4), 2.97 (dd, J = 6.4, 16.0 Hz, 1H, H-4), 3.61 (s, 3H, $-NCO_2CH_3$), 3.76 (s, 3H, $PhOCH_3$), 4.49 (m, 1H, H-3), 4.97 (s, 1H, NH), 5.97 (dd, J = 4.8, 9.6 Hz, 1H, H-2), 6.48 (d, J = 9.6 Hz, 1H, H-1), 6.63 (d, J = 2.8 Hz, 1H, H-8), 6.70 (dd, J = 2.4, 8.0 Hz, 1H, H-6), 7.02 (d, J = 8.4 Hz, 1H, H-5). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 33.6 (t, C-4), 45.2 (d, C-3), 51.9 (q, $-NCO_2CH_3$), 55.2 (q, $PhOCH_3$), 112.1 (d, C-8), 112.7 (d, C-6), 124.7 (s, C-4a), 128.4 (d, C-2), 129.2 (d, C-5), 129.5 (d, C-1), 133.5 (s, C-8a), 156.2 (s, $-NCO_2Me$), 158.6 (s, C-7). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NO_3^+$ 233.1052, found 233.1047 (Δ = 2.1 ppm).

Cyclohydrocarbonylation. $Rh(acac)(CO)_2$ (11.0 mg, 40 μmol, 1 mol %) and $P(OPh)_3$ (21 μL, 80 μmol, 2 mol %) were dissolved in toluene (1 mL) under an argon atmosphere. The catalyst solution was degassed by a frozen−thawed procedure at least three times. In a 50 mL flask were placed substrate carbamate **5** (**5a**, 813 mg, 4.00 mmol, 1.00 equiv) followed by transfer of the catalyst solution to the substrate flask by a pipet, and the total volume was adjusted to 20 mL with the solvent. The reaction flask was placed in a 300 mL stainless steel autoclave and then was pressurized with CO (40 atm) followed by H_2 (40 atm.) The reaction mixture was heated at 65 °C for 18 h. Upon completion of the reaction, the gas was carefully released in a good ventilated hood, and the reaction mixture was concentrated under reduced pressure to give a crude residue. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant to give the product.

*3-Methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-ol (**6a**).* Light brown oil (820 mg, 3.52 mmol, 88%). R_f = 0.33; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.79−1.83 (m, 1H), 2.55−2.61 (m, 1H), 2.82−2.88 (m, 1H), 2.98−3.19 (m, 2H), 3.71 (s, 1.1H), 3.72 (s, 1.9H), 4.39 (t, J = 2.8 Hz, 0.6H), 4.48, (t, J = 2.8 Hz, 0.4H), 5.16 (s, 0.4H), 5.25 (s, 0.6H), 7.04−7.19 (m, 4H). ^{13}C NMR[52] (100 MHz, 25 °C, $CDCl_3$, δ): 30.2 (t), 31.1 (t), 34.2 (t), 35.1 (t), 46.1 (d), 47.1 (d), 52.0 (q), 52.3 (q), 53.8 (d), 54.0 (d), 86.5 (d), 87.2 (d), 125.6 (d), 125.8 (d), 127.1 (d), 127.2 (d), 127.6 (d), 127.7 (d), 129.4 (d), 129.6 (d), 133.5 (s), 133.9 (s), 137.8 (s), 137.9 (s), 154.4 (s), 155.6 (s). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NO_3^+$, 233.1052, found 233.1047 (Δ = 2.1 ppm).

*8-Methoxy-3-methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-ol (**6b**).* Yellow oil (220 mg, 0.836 mmol, 84%). R_f = 0.31; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.79−1.81 (m, 1H), 2.54−2.56 (m, 1H), 2.75−2.80 (m, 1H), 2.90−2.94 (m, 0.6H), 3.06−3.09 (m, 1.4H), 3.64 (s, 1.4H), 3.71 (s, 1.6H), 3.76 (s, 3H), 4.38−4.46 (m, 1H), 5.15−5.23, (m, 1H), 6.68 (s, 1H), 6.72−6.74 (m, 1H), 6.94−6.99 (m, 1H). ^{13}C NMR[52] (100 MHz, 25 °C, $CDCl_3$, δ): 30.5 (t), 31.4 (t), 33.5 (t), 34.5 (t), 46.4 (d), 47.4 (d), 52.2 (q), 52.4 (q), 54.2 (d), 54.4 (d), 55.2 × 2 (q), 86.7 (d), 87.4 (d), 112.9 (d), 113.0 (d), 113.1 (d), 113.2 (d), 125.4 (s), 125.8 (s), 130.4 (d), 130.7 (d), 139.0 (s), 139.1 (s), 154.4 (s), 155.7 (s), 157.56 (s), 157.65 (s). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{17}NO_4^+$ 263.1158, found 263.1159 (Δ = 0.38 ppm).

Jones Oxidation. To a solution of amidal (**6a**, 385 mg, 1.65 mmol, 1.0 equiv) in acetone (20 mL) and water (5 mL) in an ice bath was slowly added Jones reagent[53] (1.34 M, 2.46 mL, 3.30 mmol, 2.0 equiv) via a syringe. The reaction mixture was allowed to stir for 3 h in an ice bath. Upon completion of the reaction as monitored by TLC analysis, 2-propanol (3 mL) was added to quench the reaction. The reaction mixture was allowed to stir for 10 min and turned blue-green. The mixture was concentrated under reduced pressure to remove excess volatile substances. The residue was partitioned with water (10 mL) and CH_2Cl_2 (10 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (10 mL × 4) again. The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant to give the titled product.

*3-Methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**7a**).* Light brown solid (322 mg, 1.39 mmol, 84%). Mp: 116−118 °C. R_f = 0.36; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.92 (d, J = 11.2 Hz, 1H, H-10), 2.42 (ddd, J = 4.8, 4.8, and 11.2 Hz, 1H, H-10), 3.04 (dd, J = 2.8 and 18.0 Hz, 1H, H-5), 3.15 (d, J = 17.6 Hz, 1H, H-5), 3.44 (d, J = 4.4 Hz, 1H, H-1), 3.78 (s, 3H, $-NCO_2CH_3$), 4.66−4.71 (m, 1H, H-4), 7.08 (d, J = 7.6 Hz, 1H, H-6), 7.11−7.21 (m, 3H, H-7, H-8 and H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 31.1 (t, C-10), 32.4 (t, C-5), 47.8 (d, C-1), 53.3 (q, $-NCO_2CH_3$), 54.7 (d, C-4), 126.5 (d, C-8), 127.6 (d, C-9), 128.1 (d, C-7), 129.8 (d, C-6), 132.2 (s, C-5a), 134.3 (s, C-9a), 151.9 (s, $-NCO_2CH_3$), 173.2 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{13}NO_3^+$ 231.0895, found 231.0890 (Δ = 2.2 ppm).

*8-Methoxy-3-methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**7b**).* Brown oil (157 mg, 0.601 mmol, 72%). R_f = 0.33; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.88 (d, J = 11.2 Hz, 1H, H-10), 2.38 (ddd, J = 4.0, 4.0, and 11.2 Hz, 1H, H-10), 2.95 (dd, J = 2.4 and 17.2 Hz, 1H, H-5), 3.05 (d, J = 17.6 Hz, 1H, H-5), 3.36 (d, J = 4.0 Hz, 1H, H-1), 3.71 (s, 3H, $-OCH_3$ at C-8), 3.78 (s, 3H, $-NCO_2CH_3$), 4.65 (m, 1H, H-4), 6.68 (d, J = 2.4 Hz, 1H, H-9), 6.72 (dd, J = 2.4, 8.4 Hz, 1H, H-7), 6.96 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 31.1 (t, C-10), 31.6 (t, C-5), 48.1 (d, C-1), 53.2 (q, $-NCO_2CH_3$), 54.8 (d, C-4), 55.1 (q, $-OCH_3$ at C-8), 112.2 (d, C-9), 114.4 (d, C-7), 123.8 (s, C-5a), 130.7 (d, C-6), 135.2 (s, C-9a), 151.8 (s, $-NCO_2CH_3$), 157.9 (s, C-8), 173.0 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{15}NO_4^+$ 261.1001, found 261.0995 (Δ = 2.3 ppm).

Silane Reduction. To a solution of amidal (**6a**, 1.42 g, 6.09 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at −78 °C was added Et_3SiH (1.42 g, 12.2 mmol, 2.0 equiv) via a syringe. The reaction mixture was allowed to stir at −78 °C for 30 min, followed by slow addition of a $BF_3{\cdot}OEt_2$ (1.73 g, 12.2 mmol, 2.0 equiv) solution in CH_2Cl_2 (11 mL) via a syringe. The reaction mixture was allowed to stir at −78 °C for 2 h. Upon completion of the reaction monitored by TLC analysis, chilled satd $NaHCO_3$ solution (20 mL) was added, and then the reaction mixture was warmed to room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (30 mL × 4). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant to give the titled product.

*3-Methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**8a**).* White solid (1.20 g, 5.52 mmol, 91%). Mp: 64−66 °C. R_f = 0.43; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.90−1.94 (m, 1H), 2.07−2.14 (m, 1H), 2.91−2.95 (m, 1H),

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3.04−3.08 (m, 0.5H), 3.18−3.23(m, 1.5H), 3.39−3.59 (m, 2H), 3.62 (s, 1.65H), 3.71 (s, 1.35H), 4.37 (ddd, J = 2.8, 2.8, and 5.6 Hz, 0.45H), 4.48 (ddd, J = 2.4, 2.4, and 5.2 Hz, 0.55H), 7.05−7.18 (m, 4H). ^{13}C NMR[52] (100 MHz, 25 °C, $CDCl_3$, δ): 33.6 (t), 34.2 (t), 35.6 (t), 36.3 (t), 39.0 (d), 39.9 (d), 51.8 (q), 52.1 (q), 53.4 (d), 53.6 (d), 55.5 (t), 56.0 (t), 125.6 (d), 125.7 (d), 126.73 (d), 126.78 (d), 126.82 (d), 126.89 (d), 129.3 (d), 129.6 (d), 133.0 (s), 133.4 (s), 141.4 (s), 141.5 (s), 150.0 (s), 155.2 (s). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NO_2^+$ 217.1103, found 217.1109 (Δ = 2.8 ppm).

*8-Methoxy-3-methoxycarbonyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**8b**).* Light brown oil (118 mg, 0.477 mmol, 84%). R_f = 0.40; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.87−1.91 (m, 1H), 2.02−2.09 (m, 1H), 2.82−2.86 (m, 1H), 2.95−2.99 (m, 0.45H), 3.09−3.16(m, 1.55H), 3.38−3.57 (m, 2H), 3.61 (s, 1.65H), 3.69 (s, 1.35H), 3.75 (s, 3H), 4.40 (ddd, J = 2.4, 2.4, 5.6 Hz, 0.45H), 4.48 (ddd, J = 2.4, 2.4, 5.6 Hz, 0.55H), 6.60−6.61 (m, 1H), 6.68−6.72 (m, 1H), 6.94−6.99 (m, 1H). ^{13}C NMR[52] (100 MHz, 25 °C, $CDCl_3$, δ): 33.6 (t), 34.2 (t), 34.8 (t), 35.5 (t), 39.3 (d), 40.2 (d), 51.9 (q), 52.1 (q), 53.5 (d), 53.8 (d), 55.05 (q), 55.07 (q), 55.4 (t), 55.9 (t), 112.24 (d), 112.29 (d), 112.32 (d), 112.4 (d), 124.8 (s), 125.1 (s), 130.2 (d), 130.4 (d), 142.56 (s), 142.62 (s), 155.0 (s), 155.2 (s), 157.4 (s), 157.5 (s). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{17}NO_3^+$ 247.1208, found 247.1204 (Δ = 1.6 ppm).

Methanolysis. A solution of lactam (**7a**, 1.43 g, 6.18 mmol, 1.0 equiv) and *p*-toluenesulfonic acid (236 mg, 1.24 mmol, 20 mol %) in MeOH (124 mL) was allowed to be refluxed for 4 days under argon. Upon completion of the reaction monitored by TLC analysis, the solution was concentrated under reduced pressure to remove excess volatile substances to yield a crude product. Purification of the crude product by flash chromatography on silica gel using EtOAc/n-Hex as the eluant afforded the titled product.

*1-Methoxycarbonyl-3-methoxycarbonylaminonaphthalene (**11a**).* Light yellow oil (1.57 g, 5.96 mmol, 96%). R_f = 0.45; EtOAc/n-Hex = 1:1. ^{1}H NMR[51] (400 MHz, 25 °C, $CDCl_3$, δ): 2.03−2.13 (m, 1H, H-10), 2.26−2.34 (m, 1H, H-10), 2.76 (dd, J = 8.4 and 16.0 Hz, 1H, H-5), 3.02 (dd, J = 4.8 and 16.0 Hz, 1H, H-5), 3.63 (s, 3H, $-NHCO_2CH_3$), 3.73 (s, 3H, $-CO_2CH_3$), 3.94−4.05 (m, 2H, H-1 and H-4), 5.56 (brs, 1H, −N*H*), 7.07 (d, J = 7.2 Hz, 1H, H-6), 7.13−7.19 (m, 3H, H-7, H-8 and H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 31.6 (t, C-10), 35.6 (t, C-5), 44.1 (d, C-1), 45.3 (d, C-4), 51.8 (q, $-NHCO_2CH_3$), 52.2 (q, $-CO_2CH_3$), 126.4* (d, C-7), 127.1* (d, C-8), 128.1 (d, C-9), 129.6 (d, C-6), 131.8 (s, C-9a), 134.4 (s, C-5a), 156.3 (s, $-NHCO_2CH_3$), 175.1 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{17}NO_4^+$ 263.1158, found 263.1163 (Δ = 1.9 ppm).

*1-Methoxycarbonyl-7-methoxy-3-methoxycarbonylaminonaphthalene (**11b**).* Light yellow oil (414 mg, 1.41 mmol, 94%). R_f = 0.43; EtOAc/n-Hex = 1:1. ^{1}H NMR[48] (400 MHz, 25 °C, $CDCl_3$, δ): 2.00−2.10 (m, 1H, H-10), 2.26 (dddd, J = 1.6, 3.6, 6.8, and 13.2 Hz, 1H, H-10), 2.67 (dd, J = 8.4 and 15.6 Hz, 1H, H-5), 2.94 (dd, J = 4.8 and 15.6 Hz, 1H, H-5), 3.62 (s, 3H, $-NHCO_2CH_3$), 3.72 (s, 3H, $-CO_2CH_3$), 3.73 (s, 3H, $-OCH_3$ at C-8), 3.90−4.02 (m, 2H, H-1 and H-4), 5.54 (brs, 1H, −N*H*), 6.69 (d, J = 2.4 Hz, 1H, H-9), 6.73 (dd, J = 2.8 and 8.4 Hz, 1H, H-7), 6.97 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 31.8 (t, C-10), 34.9 (t, C-5), 44.2 (d, C-1), 45.5 (d, C-4), 51.8 (q, $-NHCO_2CH_3$), 52.3 (q, $-CO_2CH_3$), 55.2 (q, $-OCH_3$ at C-8), 113.1 (d, C-9), 113.3 (d, C-7), 126.4 (s, C-5a), 130.6 (d, C-6), 132.8 (s, C-9a), 156.3 (s, $-NHCO_2CH_3$), 158.0 (s, C-8), 175.0 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{19}NO_5^+$, 293.1263, found 293.1270 (Δ = 2.4 ppm).

Methylation. To a solution of hexamethyldisilazane (710 mg, 4.40 mmol, 4.4 equiv) in THF (10 mL) at −78 °C was added BuLi (1.6 M, 2.5 mL, 4.0 mmol, 4.0 equiv) via a syringe. The reaction mixture was warmed to room temperature, stirred at 0 °C for 1 h, transferred to an additional funnel, and then cooled to −78 °C. The cool base solution was slowly added to a solution of ester (**11a**, 263 mg, 1.00 mmol, 1.0 equiv) and iodomethane (284 mg, 2.00 mmol, 2.0 equiv) in THF (10 mL) at −78 °C over 40 min. The reaction mixture was allowed to stir at −78 to −50 °C for 3 h. Upon completion of the reaction monitored by TLC analysis, chilled satd NH_4Cl solution (5 mL) was added, and then the reaction mixture was warmed to room temperature. The reaction mixture was extracted with EtOAc (10 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant.

*1,3,4,5-Tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**12a**).* Colorless oil (19 mg, 0.0680 mmol, 7%). R_f = 0.40; pure EtOAc. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.90 (d, J = 10.8 Hz, 1H, H-10), 2.46 (ddd, J = 5.2, 5.2, 10.4 Hz, 1H, H-10), 2.79 (d, J = 17.2 Hz, 1H, H-5), 3.00 (dd, J = 2.8, 17.6 Hz, 1H, H-10), 3.23 (d, J = 4.4 Hz, 1H, H-1), 4.00 (s, 1H, H-4), 6.83 (s, 1H, NH), 7.08 (d, J = 7.2 Hz, 1H, H-6), 7.11−7.22 (m, 3H, H-7 and H-8 and H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 34.0 (t, C-5), 34.7 (t, C-10), 45.9 (d, C-1), 50.6 (d, C-4), 126.3 (d, C-8), 127.2 (d, C-9), 127.5 (d, C-7), 130.2 (d, C-6), 132.6 (s, C-5a), 136.7 (s, C-9a), 179.4 (s, −CON−). EI-HRMS (m/z): $[M]^+$ calcd for $C_{11}H_{11}NO^+$ 173.0841, found 173.0843 (Δ = 1.2 ppm).

*1-Methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**13a**).* White solid (80 mg, 0.427 mmol, 43%). Mp: 168−170 °C, R_f = 0.49. EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.54 (s, 3H, CH_3 at C-1), 2.00 (d, J = 10.8 Hz, 1H, H-10), 2.23 (ddd, J = 1.2, 5.6, and 10.8 Hz, 1H, H-10), 2.85 (d, J = 17.2 Hz, 1H, H-5), 3.05 (dd, J = 3.2 and 17.2 Hz, 1H, H-5), 3.94 (brs, 1H, H-4), 6.73 (brs, 1H, N*H*), 7.03−7.09 (m, 1H, H-6), 7.15−7.21 (m, 2H, H-7 and H-8), 7.23−7.28 (m, 1H, H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 17.0 (q, CH_3 at C-1), 35.1 (t, C-5), 41.9 (t, C-10), 44.4 (s, C-1), 48.5 (d, C-4), 124.0 (d, C-9), 126.3* (d, C-8), 127.3* (d, C-7), 130.0 (d, C-6), 133.0 (s, C-5a), 140.1 (s, C-9a), 180.5 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{13}NO^+$ 187.0997, found 187.1000 (Δ = 1.6 ppm).

*8-Methoxy-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**12b**).* Colorless oil (40 mg,0.197 mmol, 15%). R_f = 0.35; pure EtOAc. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.91 (d, J = 10.8 Hz, 1H, H-10), 2.48 (ddd, J = 5.2, 5.2, 10.8 Hz, 1H, H-10), 2.76 (d, J = 17.2 Hz, 1H, H-5), 2.97 (dd, J = 3.2, 17.2 Hz, 1H, H-10), 3.20 (d, J = 4.8 Hz, 1H, H-1), 3.77 (s, 3H, PhO*Me*), 4.04 (d, J = 2.4 Hz, 1H, H-4), 6.27 (s, 1H, NH), 6.76−6.78 (m, 2H, H-7 and H-9), 7.00 (d, J = 8.0 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 33.4 (t, C-5), 34.8 (t, C-10), 46.2 (d, C-1), 50.8 (d, C-4), 55.3 (q, PhO*Me*), 112.2 (d, C-9), 113.9 (d, C-7), 124.2 (s, C-5a), 131.1 (d, C-6), 137.5 (s, C-9a), 158.0 (s, C-8), 179.0 (s, −CON−). EI-HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{13}NO_2^+$ 203.0946, found 203.0950 (Δ = 2.0 ppm).

*8-Methoxy-1-methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**13b**).* White solid (128 mg, 0.589 mmol, 44%). Mp: 202−204 °C. R_f = 0.47; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.52 (s, 3H, CH_3 at C-1), 1.98 (d, J = 10.4 Hz, 1H, H-10), 2.21 (ddd, J = 1.2, 5.6, and 10.8 Hz, 1H, H-10), 2.78 (d, J = 16.8 Hz, 1H, H-5), 2.99 (dd, J = 3.2 and 16.8 Hz, 1H, H-5), 3.76 (s, 3H, $-OCH_3$ at C-8), 3.92−3.96 (m, 1H, H-4), 6.49 (brs, 1H, N*H*), 6.73 (dd, J = 2.4 and 8,4 Hz, 1H, H-7), 6.82 (d, J = 2.8 Hz, 1H, H-9), 6.97 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 17.0 (q, CH_3 at C-1), 34.4 (t, C-5), 41.8 (t, C-10), 44.5 (s, C-1), 48.5 (d, C-4), 55.2 (q, $-OCH_3$), 109.9 (d, C-7), 112.9 (d, C-9), 124.8 (s, C-5a), 130.8 (d, C-6), 141.3 (s, C-9a), 158.1 (s, C-8), 180.5 (s, C-2),. EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NO_2^+$, 217.1103, found 217.1107 (Δ = 1.6 ppm).

Preparation of Imide 14. To a solution of lactam (**12a**, 81 mg, 0.47 mmol, 1.0 equiv) in THF (4.7 mL) in an ice bath was added NaH (60%, 38 mg, 0.94 mmol, 2.0 equiv) in portions. The reaction mixture was allowed to stir for an additional 10 min. Methyl chloroformate (73 μL, 0.94 mmol, 2.0 equiv) was added to the solution via a syringe. The reaction mixture was allowed to stir at room temperature for 3 h. Upon completion of the reaction monitored by TLC analysis, satd $NaHCO_3$ solution (3 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant.

*3-Methoxycarbonyl-1-methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**14a**).* Colorless oil (29 mg, 0.118 mmol,

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79%). R_f = 0.40; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.58 (s, 3H, CH_3 at C-1), 2.06 (d, J = 11.2 Hz, 1H, H-10), 2.20 (ddd, J = 1.2, 6.0, and 11.2 Hz, 1H, H-10), 3.11 (dd, J = 2.8 and 17.6 Hz, 1H, H-5), 3.20 (d, J = 17.6 Hz, 1H, H-5), 3.81 (s, 3H, $-NCO_2CH_3$), 4.66 (ddd, J = 2.8, 2.8, and 6.0 Hz, 1H, H-4), 7.07−7.11 (m, 1H, H-6), 7.16−7.22 (m, 2H, H-7 and H-8), 7.24−7.29 (m, 1H, H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 17.6 (q, CH_3 at C-1), 33.5 (t, C-5), 38.7 (t, C-10), 46.8 (s, C-1), 52.8 (d, C-4), 53.4 (q, $-NCO_2CH_3$), 124.5 (d, C-9), 126.7* (d, C-8), 127.9* (d, C-7), 129.8 (d, C-6), 132.8 (s, C-5a), 138.1 (s, C-9a), 152.2 (s, $-NCO_2CH_3$), 174.9 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{15}NO_3^+$ 245.1052, found 245.1046 (Δ = 2.5 ppm).

*8-Methoxy-3-methoxycarbonyl-1-methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepin-2-one (**14b**).* White solid (24 mg, 0.087 mmol, 76%). Mp: 136−138 °C.R_f = 0.40; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.56 (s, 3H, CH_3 at C-1), 2.04 (d, J = 11.2 Hz, 1H, H-10), 2.18 (ddd, J = 1.2, 6.0, and 11.2 Hz, 1H, H-10), 3.04 (dd, J = 3.2 and 17.2 Hz, 1H, H-5), 3.13 (d, J = 17.2 Hz, 1H, H-5), 3.76 (s, 3H, $-OCH_3$ at C-8), 3.81 (s, 3H, $-NCO_2CH_3$), 4.64 (ddd, J = 2.8, 2.8, and 5.6 Hz, 1H, H-4), 6.76 (dd, J = 2.8 and 8.4 Hz, 1H, H-7), 6.81 (d, J = 2.8 Hz, 1H, H-9), 7.01 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 17.6 (q, CH_3 at C-1), 32.7 (t, C-5), 38.7 (t, C-10), 46.9 (s, C-1), 52.9 (d, C-4), 53.4 (q, $-NCO_2CH_3$), 55.3 (q, $-OCH_3$ at C-8), 110.3 (d, C-9), 113.5 (d, C-7), 124.6 (s, C-5a), 130.7 (d, C-6), 139.2 (s, C-9a), 152.2 (s, $-NCO_2CH_3$), 158.4 (s, C-8), 174.7 (s, C-2). EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{17}NO_4^+$ 275.1158, found 275.1154 (Δ = 1.5 ppm).

$LiAlH_4$ Reduction. To a mixture of $LiAlH_4$ (82 mg, 2.16 mmol, 5.0 equiv) and Et_3NHCl (297 mg, 2.16 mmol, 5.0 equiv) in an ice bath under argon was slowly added THF (3 mL) via a syringe. Substantial gas evolution was observed during addition. The reaction mixture was allowed to stir in an ice bath until evolution had ceased. To the alane solution in an ice bath was slowly cannulated a solution of the imide substrate (**7a**, 100 mg, 0.432 mmol, 1.0 equiv) in THF (1.3 mL). The reaction mixture was allowed to stir at room temperature for 2 h. Upon completion of the reaction monitored by TLC analysis, the reaction mixture was cooled in an ice bath. Addition of water (0.4 mL), NaOH (15%, 0.4 mL), and water (0.4 mL) in sequence resulted in the formation of white solid precipitates, which were filtered off to give a filtrate. The filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using EtOAc/n-Hex as the eluant to give the titled product.

*3-Methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**9a**).* Colorless oil (57 mg, 0.329 mmol, 76%). R_f = 0.52; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.83 (d, J = 11.2 Hz, 1H, H-10), 2.11 (ddd, J = 4.4, 4.4, and 10.8 Hz, 1H, H-10), 2.48 (s, 3H, $-NCH_3$), 2.82−2.88 (m, 2H, H-2 and H-5), 2.95−3.03 (m, 2H, H-2 and H-5), 3.10 (t, J = 4.4 Hz, 1H, H-1), 3.35−3.38 (m, 1H, H-4), 6.97 (d, J = 7.2 Hz, 1H, H-9), 7.01−7.12 (m, 3H, H-6, H-7 and H-8). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 33.0 (t, C-10), 35.8 (t, C-5), 41.6 (d, C-1), 41.8 (q, $-NCH_3$), 60.1 (d, C-4), 65.0 (t, C-2), 125.3* (d, C-8), 126.2 (d, C-9), 126.3* (d, C-7), 129.3 (d, C-6), 133.6 (s, C-5a), 143.7 (s, C-9a). EI-HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{15}N^+$ 173.1204, found 173.1195 (Δ = 5.2 ppm).

*8-Methoxy-3-methyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**9b**).* Colorless oil (88 mg, 0.433 mmol, 72%). R_f = 0.50; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.81 (d, J = 10.8 Hz, 1H, H-10), 2.09 (ddd, J = 4.4, 4.4, and 10.8 Hz, 1H, H-10), 2.46 (s, 3H, $-NCH_3$), 2.76 (dd, J = 3.2, 16.8 Hz, 1H, H-5), 2.83 (dd, J = 1.2, 9.2 Hz, 1H, H-2), 2.93 (d, J = 17.6 Hz, 1H, H-5), 2.98 (dd, J = 3.6, 9.2 Hz, 1H, H-2), 3.04 (t, J = 4.4 Hz, 1H, H-1), 3.33−3.37 (m, 1H, H-4), 3.73 (s, 3H, $-OCH_3$ at C-8), 6.53 (d, J = 2.4 Hz, 1H, H-9), 6.65 (dd, J = 2.8, 8.4 Hz, 1H, H-7), 6.96 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 33.2 (t, C-10), 35.0 (t, C-5), 41.8 (q, $-NCH_3$), 42.0 (d, C-1), 55.1 (q, $-OCH_3$ at C-8), 60.3 (d, C-4), 65.0 (t, C-2), 111.7 (d, C-7), 111.8 (d, C-9), 125.5 (s, C-5a), 130.2 (d, C-6), 145.1 (s, C-9a), 157.3 (s, C-8). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{17}NO^+$ 203.1310, found 203.1314 (Δ = 3.0 ppm).

*1,3-Dimethyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**15a**).* Colorless oil (16 mg, 0.0854 mmol, 73%). R_f = 0.47; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.48 (s, 3H, CH_3 at C-1), 1.85 (d, J = 11.2 Hz, 1H, H-10), 2.01 (ddd, J = 1.6, 6.0, and 11.2 Hz, 1H, H-10), 2.46 (s, 3H, $-NCH_3$), 2.73 (d, J = 9.2 Hz, 1H, H-2), 2.82 (dd, J = 1.2 and 9.2 Hz, 1H, H-2), 2.90 (dd, J = 3.2 and 16.8 Hz, 1H, H-5), 3.06 (d, J = 17.2 Hz, 1H, H-5), 3.39−3.43 (m, 1H, H-4), 7.06−7.13 (m, 3H, H-6, H-7 and H-8), 7.17−7.22 (m, 1H, H-9). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 21.4 (q, CH_3 at C-1), 36.5 (t, C-5), 41.5 (t, C-10), 41.7 (q, $-NCH_3$), 43.0 (s, C-1), 60.3 (d, C-4), 71.4 (t, C-2), 122.8 (d, C-9), 125.7* (d, C-8), 126.2* (d, C-7), 129.4 (d, C-6), 134.0 (s, C-5a), 146.5 (s, C-9a). EI-HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{17}N^+$ 187.1361, found 187.1357 (Δ = 2.1 ppm).

*8-Methoxy-1,3-dimethyl-1,3,4,5-tetrahydro-2H-1,4-methano-3-benzazepine (**15b**).* Colorless oil (14 mg, 0.0644 mmol, 74%). R_f = 0.44; EtOAc/n-Hex = 1:1. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$, δ): 1.45 (s, 3H, CH_3 at C-1), 1.83 (d, J = 10.8 Hz, 1H, H-10), 1.99 (ddd, J = 2.0, 6.0, and 10.8 Hz, 1H, H-10), 2.44 (s, 3H, $-NCH_3$), 2.72 (d, J = 9.2 Hz, 1H, H-2), 2.81 (dd, J = 1.2 and 9.2 Hz, 1H, H-2), 2.83 (dd, J = 3.2 and 17.2 Hz, 1H, H-5), 3.00 (d, J = 16.8 Hz, 1H, H-5), 3.39 (ddd, J = 3.2, 3.2, and 5.6 Hz, 1H, H-4), 3.76 (s, 3H, $-OCH_3$ at C-8), 6.66 (dd, J = 2.8, 8.4 Hz, 1H, H-7), 6.76 (d, J = 2.8 Hz, 1H, H-9), 7.00 (d, J = 8.4 Hz, 1H, H-6). ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 21.4 (q, CH_3 at C-1), 35.6 (t, C-5), 41.5 (t, C-10), 41.6 (q, $-NCH_3$), 43.2 (s, C-1), 55.2 (q, $-OCH_3$ at C-8), 61.2 (d, C-4), 71.2 (t, C-2), 109.4 (d, C-9), 110.9 (d, C-7), 126.0 (s, C-5a), 130.2 (d, C-6), 148.0 (s, C-9a), 157.7 (s, C-8). EI-HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{19}NO^+$ 217.1467, found 217.1466 (Δ = 0.5 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00923.

^{1}H and ^{13}C NMR spectra of all compounds (PDF)

X-ray crystallographic data of **7a** (CIF)

X-ray crystallographic data of **14b** (CIF)

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Notes

The authors declare no competing financial interest.

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(50) The alkylation may proceed as follows: The two acidic protons were removed by treatment with the strong base to yield the corresponding dianion species. The benzylic anion was reacted with iodomethane to yield the alkylated product, while the carbamate anion may undergo the cyclization to form the C ring again. The methoxycarbonylamino group is vulnerable to possible nucleophile attack, which produces the protecting-group-free lactam anion. Hence, tricyclic secondary lactams were obtained as the products after workup.
(51) The ^{1}H and ^{13}C assignments follow the numbering pattern in the parent compound for easy comparison.
(52) Two sets of signal values have been reported since a strong rotamer effect has been observed.
(53) Preparation of Jones reagent: Dissolve chromium oxide (CrO_3) (23.5 g) in concd sulfuric acid (21 mL) with cooling and then dilute with distilled water to give a total volume of 175 mL. See: *Organic Syntheses*; Wiley, 1998; Vol. *9*, p 432.

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