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Rhodium-Catalyzed Hydrocarbonylation of a Homoallylamine via N−H Activation and Application for Synthesis of Yohimbane Alkaloids

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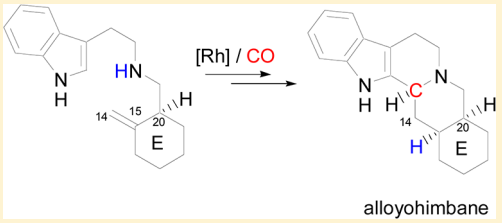
Supporting Information

ABSTRACT: We describe syntheses of *n*-yohimbane and alloyohimbane using Rh-catalyzed hydrocarbonylation, which provides a practical methodology to synthesize a δ-lactam from a secondary homoallyl amine. We have also observed an unexpected transformation where the amine proton served as a hydride to participate in hydrocarbonylation. The D-labeled experimental results and preliminary DFT-calculations suggest that the transformation can be rationalized by oxidative cleavage of the homoallyl amines to a metal hydride complex.



INTRODUCTION

The transition metal-catalyzed cyclization reaction of alkenes has played an important role in organic syntheses.[1] Among these catalytic cyclization reactions, Rh-catalyzed hydrocarbonylation and hydroformylation of functionalized alkenes provide powerful catalytic processes for the syntheses of heterocycles as well as carbocycles.[2] By means of reasonable design, the reactions also allow the formation of some complicated molecules in a *cascade* manner, which bring about advantages of novelty, elegance, and efficiency.[3] Since Knifton has reported synthesis of a γ-lactam by Rh-catalyzed cyclization of allyl amines, many valuable conditions have been developed for this useful transformation.[4] Krafft et al. have reported amine-directed regioselective Rh-catalyzed hydrocarboxylation of homoallylic amines in the presence of hydrogen chloride and trimethylphosphite, to yield δ-lactam derivatives in good yields.[5] Alper et al. have presented that employment of either a zwitterionic Rh complex or $HRh(CO)(PPh_3)_3$ in the presence of sodium borohydride and 2-propanol could be used for conversion of allyl amines to γ-lactams.[6] Ojima et al. have described the extensive investigation of the Rh-catalyzed hydrocarbonylation for syntheses of azabicycles.[7] These reported cyclization conditions are usually involved with the presence of hydrogen sources, such as syn gas, protic sources, and sodium borohydride.

During the course of our investigation on the syntheses of yohimbane-typed alkaloids, we have observed that treatment of a homoallylamine with Rh(I)/phosphite ligands under a neat CO atmosphere could yield a δ-lactam, also. Here we report our serendipitous findings and present a plausible mechanism for the formation of lactams through hydrogen-free Rh-catalyzed hydrocarbonylation. Preliminary studies including isotope experiments and DFT calculations suggest that the origin of the hydrogen for hydride addition could be best explained by oxidative cleavage of the homoallylamine to a metal hydride complex.

RESULTS AND DISCUSSION

Yohimbane alkaloids **1** (Figure 1), which are members of the *Rauwolfia* alkaloid family, possess a characteristic pentacyclic

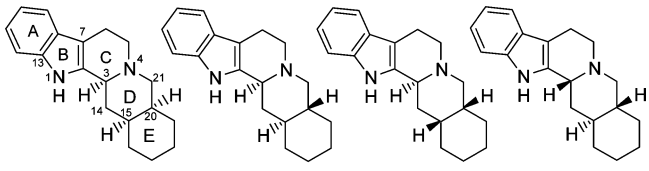


Figure 1. Structures of Yohimbane alkaloids.

indole ring framework in structure and exhibit a wide range of crucial pharmacological activities.[8] Various strategies have been developed for the syntheses of yohimbane-type alkaloids, briefly classified as follows: amino-Claisen rearrangement,[9] aziridine-allylsilane-mediated cyclization,[10] conjugate addition/condensation,[11] desymmetrized ring cleavage of carbobicyclics,[12] Diels−Alder cycloaddition,[13] dipolar cycloaddition,[14] Fry reaction of pyridium salts,[15] intramolecular Michael annulation,[16] nitrogen insertion,[17] organotin-aided three-compound coupling,[18] photocyclization of enamides,[19] radical-mediated cyclization,[20] sugar chiral auxiliary,[21] and Wolff rearrangement.[22]

We anticipate that yohimbane **1** can be obtained by intramolecular condensation/reduction (i.e., Bischler−Napieralski reaction) of lactam **2**, formed by Rh-catalyzed hydrocarbonylation or carbonylation of amine **3**. Alkenylamine **3** is easily synthesized by coupling 3-indoleacetic acid and alkenylamine **6** followed by reduction (Scheme 1).

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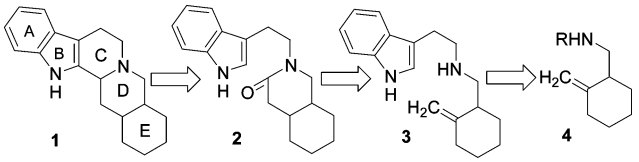
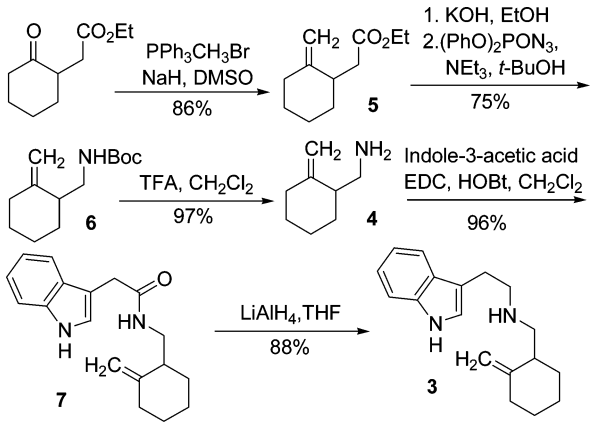
Scheme 1. Retrosynthetic Analysis



Our synthesis commenced with the preparation of 2-methylene-cyclohexaneacetate (**5**) (Scheme 2), readily available

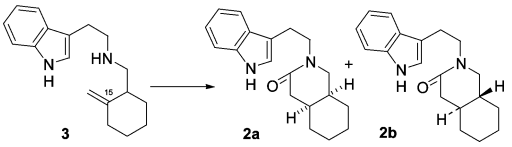
Scheme 2. Synthesis of Amine 3



by Wittig olefination of commercially available 2-cyclohexanoneacetate. Reaction of freshly distilled DMSO with NaH at 70 °C for 1 h produced methylsulfinyl carbanion, followed by addition of PPh_3MeBr salt to yield a Wittig reagent methylene triphenylphosphorane ($PPh_3{=}CH_2$). Subsequent addition of 2-cyclohexanoneacetate furnished alkene product **7** in 86% yield.[23] Treatment of ester **5** in basic hydrolysis conditions gave the corresponding acid, which was combined with diphenylphosphorazidate (DPPA) and triethylamine in the presence of *tert*-BuOH to afford BOC-protected amine **6** as a Curtius rearrangement product in 75% yield over two steps. Removal of the BOC protecting group was easily accomplished by treating protected amine **6** with TFA in dichloromethane at room temperature, yielding free amine **4** in 97% yield. Amine **4** was coupled with 3-indoleacetic acid using the EDC/HOBt activation protocol to produce indoleacetamide **7** in 96% yield. Subsequent reduction of indoleacetamide with $LiAlH_4$ produced amine **3** in 88% yield, as the substrate in the Rh-catalyzed hydrocarbonylation.

With alkenylamine **3** in hand, reaction of amine **3** was carried out in the cyclized conditions, i.e., $Rh(acac)(CO)_2$-$P(OPh)_3$ (2 mol %) catalyst at 65 °C under 80 atm of CO and H_2 (1:1) in toluene, to produce two separable lactam diastereomers, the major one, **2a**, in 61% and the minor one, **2b**, in 28% isolated yield, respectively (entry 1, Table 1). Reaction under CO (60 atm) and H_2 (20 atm) also produced the cyclized lactam product **2a** in 56% yield and product **2b** in 24% yield, which means reduction of the hydrogen partial pressure did not have a significant effect on product distribution (entry 2). However, to our surprise, the reaction could proceed smoothly in pure CO conditions (80 atm), to yield product **2a** in 53% yield and product **2b** in 25% yield (entry 3). The reaction with pure CO proceeded relatively slowly with respect to that with H_2 but was not complete within 48 h.

Table 1. Hydrocarbonylation of Amine 3

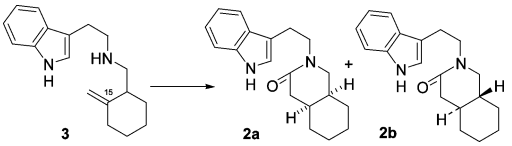


entry[a]	CO (atm)	H_2 (atm)	**2a**, %[b]	**2b**, %[b]
1	40	40	61	28
2	60	20	56	24
3	80	0	53	25

[a]All reactions were run with 1.0 mmol of amine **3**, $Rh(acac)(CO)_2$ (1 mol %), and $P(OPh)_3$ (2 mol %) in toluene at 65 °C. [b]Isolated yield.

Since the formation of the Rh−H complex is essential for triggering the subsequent corresponding reactions, it was unanticipated that the reaction proceeded without employment of hydrogen sources, compare to the reported methods such as exposure of a Rh(I) salt in CO/H_2 atmosphere at room temperature[24] and addition of hydrogen chloride[5] or sodium borohydride.[6] Therefore, the results brought about the question of how to form the Rh−H complex. In fact, the question did not attract too much attention in early reports,[25] but prompted us to explore more mechanistic insights especially in pure CO conditions. Therefore, we have performed isotope labeling experiments in the hydrocarbonylation reactions (Table 2).

Table 2. Hydrocarbonylation of Amine 3 with Different Additives



entry[a]	CO (atm)	additive	**2a**, %[b]	**2b**, %[b]
1	60	D_2[c]	40	14
2	60	CD_3OD[d]	17	14
3	60	d_2-dione[e]	36	19
4	60	d_2-dione[f]	25	14

[a]All reactions were run with 1.0 mmol of amine **9**, $Rh(acac)(CO)_2$ (1 mol %), and $P(OPh)_3$ (2 mol %) in toluene at 65 °C. [b]Isolated yield. [c]D_2 20 atm. [d]5% v/v CD_3OD in toluene. [e]2,2-Dideuteriocyclohexane-1,3-dione, 25 mol %. [f]50 mol %.

Reaction of amine **3** was carried out in CO (60 atm) and D_2 (20 atm) to yield the deuterated products **2a** in 40% yield and **2b** in 14% yield (entry 1, Table 2). On the basis of ^{13}C NMR studies, the ratio of deuterated product lactam D-**2b** to hydrogenated product lactam H-**2b** in lactam **2b** was about 2.8:1, while the ratio was 2.5:1 in lactam **2a** (Figure 2).[26] Reaction with CD_3OD additive as deuterium source reduced the yield, providing H-incorporated lactam **2a** in only 17% yield and **2b** in only 14% yield (entry 2). Employment of 2,2-dideuteriocyclohexane-1,3-dione[27] as additive (25 mol %, entry 3) did not afford any D-incorporated product either, but rather H-incorporated product **2a** in 36% yield and **2b** in 19% yield. More 2,2-dideuteriocyclohexane-1,3-dione (50 mol %, entry 4) could not provide any D-labeled product, but gave a lower yield (H-incorporated lactam **2a** in 25% yield and **2b** in 14% yield).

The presence of H-incorporated product in the reaction under D_2 indicates two different pathways are involved in hydrocarbonylation: one with the Rh−H complex and the

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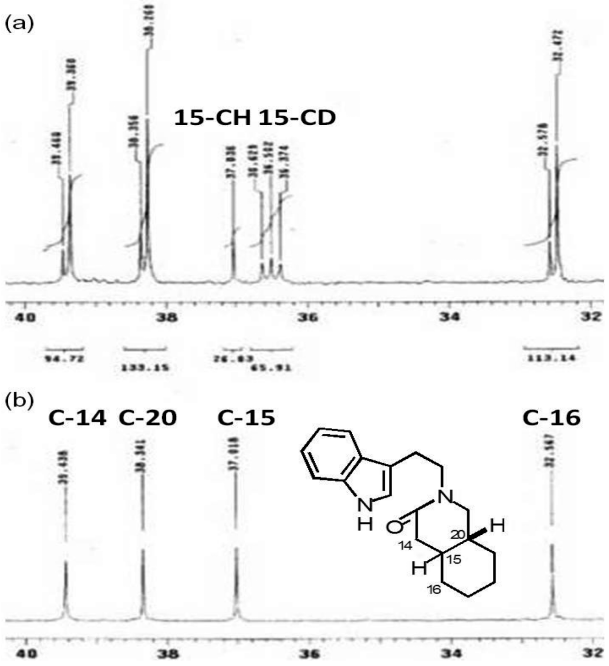


Figure 2. Expanded ^{13}C spectra of **2b** obtained from (a) CO/D_2 (Table 2, entry 1) and (b) CO/H_2 (Table 1, entry 2).

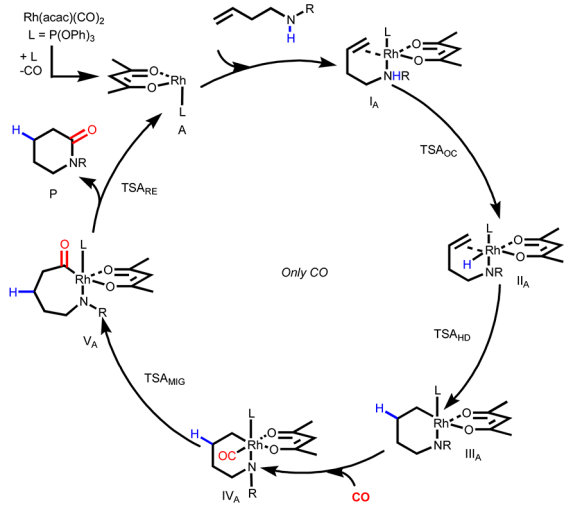
other with the Rh−D complex. Apparently, since the amino proton has appeared as the *only* proton source to give the Rh−H complex, the results suggest that the Rh−H complex should be subjected to an H−D exchange process to the Rh−D complex, probably through D_2 addition followed by H−D elimination. In addition, although deuterium sources such as CD_3OD and 2,2-dideuteriocyclohexane-1,3-dione (entries 2, 3, and 4, Table 2) are added in the system, there is only the H-incorporated product. The absence of D-incorporated product in reactions with deuterium additives excludes the possibility of proton movement from the amine through other molecules, finally to the metal. Therefore, based on these results, a Rh-mediated oxidative cleavage of N−H is required for the formation of the Rh−H complex, especially in the absence of a hydrogen atmosphere.[28]

Since Krafft has reported X-ray crystallographic investigations that disclose that a homoallylamine behaves as an N-ligand for complexation with Rh to give a rhodium amino-olefin complex,[29] and a subsequent acyl intermediate can adopt a *trans* configuration of the nitrogen with trimethylphosphite,[5] these results inspired us to consider that Rh(I) undergoes complexation with the homoallylamine and the phosphite ligand in a pure CO atmosphere to yield a *trans* complex and then transforms to an acyl-metal intermediate. Thus, taking into account the results observed above, we propose the catalytic cycle *in the absence of a hydrogen atmosphere* commences with complexation of the metal with the homoallylamine substrate and a ligand to a complex, which undergoes oxidative cleavage to give the Rh−H complex. Once the Rh−H complex appears, subsequent reactions including hydride addition, alkyl migration, and reductive elimination follow to furnish a lactam as the final product and regenerate the metal species for the next catalytic cycle. The Rh−H complex, derived from oxidative cleavage of the N−H bond, is also indispensable to explain the formation of the H-incorporated product *in the presence of a CO/D_2 atmosphere*. The formation of the mixture of the H- and D-incorporated products implies the H−D exchange is not complete so that the Rh−H and the Rh−D complexes are both present in the system.

To verify the hypotheses,[30] we try to locate the corresponding TSs by DFT calculations at the level of LanL2DZ, using *N*-methyl-3-butenamine as the aminoalkene substrate for minimizing calculation cost. Thus, two sets of transition-state geometries (TSA and TSB) have been obtained; one describes the processes *in the pure CO conditions* (TSA) and the other describes those *in the presence of a CO/D_2 atmosphere* (TSB). These geometries represent the transition-state structures in the processes including oxidative cleavage of the N−H bond (TS_{OC}), hydride addition to the olefin (TS_{HD}), alkyl migration to a CO ligand (TS_{MIG}), reductive elimination to the lactam product (TS_{RE}), and H−D exchange of the Rh−H complex to the Rh−D complex (TS_{D2}), described as follows.

In the pure CO conditions (Scheme 3), treatment of $Rh(acac)(CO)_2$ with $P(OPh)_3$ under pure CO conditions gives

Scheme 3. Proposed Mechanism for Rh-Catalyzed Hydrocarbonylation of *N*-Methyl-3-butenamine in a Pure CO Atmosphere



catalyst complex **A**. Complexation with *N*-methyl-3-butenamine affords rhodium amino-olefin complex $\mathbf{I_A}$, which undergoes oxidative cleavage to yield the key Rh−H complex $\mathbf{II_A}$. Hydride addition follows to give rhodazacycle $\mathbf{III_A}$ and then association with one CO molecule to form complex $\mathbf{IV_A}$. Next, alkyl migration of Rh complex $\mathbf{IV_A}$ generates acyl intermediate $\mathbf{V_A}$, followed by reductive elimination to yield lactam **P** as the final product, and regenerates the catalyst complex **A** to complete the whole catalytic cycle.

In the presence of a CO/D_2 atmosphere (Scheme 4), the Rh(I) salt is activated with the phosphite ligand to yield 3-deuterio-2,4-pentadione and the active catalyst Rh−D complex **B**, and then complexation with *N*-methyl-3-butenamine gives rhodium amino-olefin complex $\mathbf{I_B}$. Rh complex $\mathbf{I_B}$ can undergo hydride addition to give alkylrhodium complex $\mathbf{II_B}$, which is then subject to oxidative cleavage of the N−H bond to yield Rh−H complex $\mathbf{III_B}$. Formed by losing one CO molecule from metal complex $\mathbf{III_B}$, complex $\mathbf{III'_B}$ can undergo H−D exchange with D_2, to give Rh−D complex $\mathbf{III_B}$ and a H−D molecule.[31] Subsequent association with one CO molecule produces dicarbonyl complex $\mathbf{III_B}$ again, which continues the following alkyl migration and reductive elimination to give the lactam product and the metal species $\mathbf{V_B}$. Coordination with one CO

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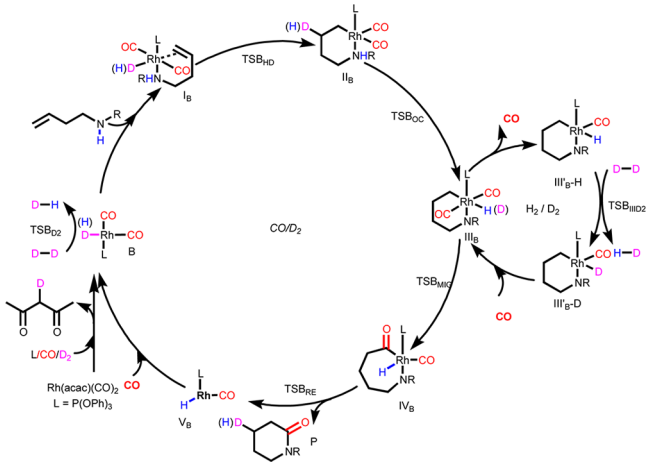
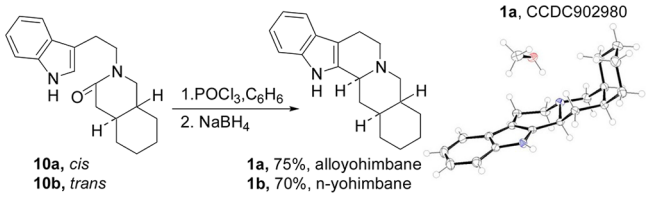
Scheme 4. Proposed Mechanism for Rh-Catalyzed Hydrocarbonylation of *N*-Methyl-3-butenamine in a CO/D_2 Atmosphere



molecule reproduces the original metal species **B**. It is worthy to note not only Rh−H complex $\mathbf{III_B}$ but also Rh−H complex **B** can undergo the "hydride washed out" process, i.e., H−D exchange, yielding Rh−D complex **B**. The models provide an explanation for the origin of hydride of the Rh-catalyzed carbonylation in the pure CO atmosphere, as well as the appearance of both H- and D-incorporated lactam products in the presence of D_2 gas.

To complete the syntheses of alloyohimbane and yohimbane, lactam **2a** was subjected to the Bischler−Napieralski reaction conditions, i.e., refluxing with $POCl_3$ in benzene followed by addition of $NaBH_4$, resulting solely in the formation of yellow solid **1a** in 75% yield (Scheme 5). The product could be

Scheme 5. Synthesis of Alloyohimbane and Yohimbane



recrystallized in methanol to give a single crystal for X-ray crystallography, which was determined as alloyohimbane (CCDC 902980). Thus, the major product lactam **2a** was assigned unambiguously as a *cis* conjunction. Similarly, treatment of lactam **2b** with the identical reaction conditions afforded *n*-yohimbane **1b** in 70% isolated yield, which displayed identical ^{13}C NMR data to that reported in the literature.[32]

CONCLUSION

We describe the syntheses of alloyohimbane and *n*-yohimbane featuring a Rh-catalyzed hydrocarbonylation strategy. This reaction proceeds under either a CO/H_2 or pure CO atmosphere. The results with deuterium additives under pure CO gas show the essential Rh−H complex *does not* result from the proton transfer of the NH through molecules to the metal in hydrocarbonylation of a homoallylamine, but suggest an intramolecular direct amino proton transfer from the nitrogen atom to the rhodium atom. This process can be viewed as an Rh-mediated oxidative cleavage of the N−H bond, which has not been reported yet. We have also proposed the mechanism in which the corresponding transition states have been supported by DFT calculations. Subsequent full calculations on this mechanism and extension of the methodology toward other natural products of interest are currently under way.

EXPERIMENTAL SECTION

General Materials and Methods. All reagents, solvents, and chemicals were purchased from commercial sources and used as soon as possible. All solvents were dried by using appropriate drying agents and distilled under argon before use. The reaction flasks were dried in a 110 °C oven, allowed to cool to room temperature in a desiccator, and assembled under an argon atmosphere. All reactions were carried out under argon except hydrocarbonylation. TLC analyses were carried out and visualized with 10% PMA solution or UV light. Purifications were performed by flash chromatography on commercially available silica gel. All NMR spectra, including ^1H, ^{13}C, DEPT, gHSQC, gCOSY, and gHMBC, were recorded on a 600 or 400 MHz NMR spectrometer.

Hydrocarbonylation. $Rh(acac)(CO)_2$ (2.7 mg, 10.0 μmol, 1 mol %) and $P(OPh)_3$ (6.0 μL, 20 μmol, 2 mol %) were dissolved in toluene (2 mL) under argon. The catalyst solution was degassed by a freeze−thaw procedure at least three times. Substrate amine **9** (1.0 mmol, 1.00 equiv) was placed in a 50 mL bottle. The catalyst solution was transferred to the reaction flask containing the substrate by a pipet, followed by addition of additives. The total volume was adjusted to 20 mL with toluene. The reaction flask was placed in a 300 mL stainless steel autoclave and then was pressurized up to the desired pressure with CO followed by H_2 or D_2. The reaction mixture was stirred at 65 °C for 16−20 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.

2a: yellow solid; mp 161−162 °C; R_f = 0.24; EtOAc/n-Hex = 1:2. ^1H NMR (600 MHz, 25 °C, $CDCl_3$, δ): 1.31−1.37 (m, 4H, H-16, H17, H-18, and H-19), 1.40−1.48 (m, 4H, H-16, H17, H-18, and H-19), 1.85−1.90 (m, 1H, H-15), 1.94−1.99 (m, 1H, H-20), 2.37 (dd, *J* = 6.0, 18.0 Hz, 1H, H-14), 2.42 (dd, *J* = 7.2, 18.0 Hz, 1H, H-14), 3.03−3.07 (m, 2H, H-6 × 2), 3.11 (dd, *J* = 6.6, 12.6 Hz, 1H, H-21), 3.17 (dd, *J* = 6.0, 12.6 Hz, 1H, H-21), 3.61 (ddd, *J* = 6.6, 6.6, 15.0 Hz, 1H, H-5), 3.74 (ddd, *J* = 4.8, 4.8, 15.0 Hz, 1H, H-5), 6.97 (s, 1H, H-2), 7.11 (t, *J* = 7.8 Hz, 1H, H-10), 7.17 (t, *J* = 7.8 Hz, 1H, H-11), 7.36 (d, *J* = 7.8 Hz, 1H, H-12), 7.68 (d, *J* = 7.8 Hz, 1H, H-9), 9.17 (brs, 1H, H-1). ^{13}C NMR (150 MHz, 25 °C, $CDCl_3$, δ): 22.4 (t, C-6), 22.8 (t, 2C, C-17 and C-18), 26.2 (t, C-19), 28.1 (t, C-16), 32.2 (d, C-15), 32.6 (d, C-20), 35.0 (t, C-14), 48.1 (t, C-5), 50.9 (t, C-21), 111.2 (d, C-12), 112.3 (s, C-7), 118.4 (d, C-9), 118.8 (d, C-10), 121.4 (d, C-11), 122.2 (d, C-2), 127.3 (s, C-8), 136.3 (s, C-13), 169.3 (s, C-3). EI-HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{24}N_2O^+$, 296.1889; found, 296.1885 (Δ = 1.4 ppm).

2b: yellow solid; mp 208−210 °C; R_f = 0.24; EtOAc/n-Hex = 1:2. ^1H NMR (600 MHz, 25 °C, $CDCl_3$, δ): 0.88−0.95 (m, 2H, H-16 and H-19), 1.18−1.29 (m, 2H, H-17 × 2*), 1.33−1.40 (m, 2H, H-15 and H-20), 1.62−1.66 (m, 1H, H-19), 1.70−1.76 (m, 3H, H-16 and H-18 × 2*), 2.01 (dd, *J* = 11.4, 17.4 Hz, 1H, H-14), 2.47 (dd, *J* = 3.6, 17.4 Hz, 1H, H-14), 2.89 (t, *J* = 11.4 Hz, 1H, H-21), 2.98−3.07 (m, 2H, H-6 × 2), 3.11 (dd, *J* = 4.8, 11.4 Hz, 1H, H-21), 3.60−3.70 (m, 2H, H-5 × 2), 7.03 (s, 1H, H-2), 7.12 (t, *J* = 7.8 Hz, 1H, H-10), 7.18 (t, *J* = 7.8 Hz, 1H, H-11), 7.36 (d, *J* = 7.8 Hz, 1H, H-12), 7.66 (d, *J* = 7.8 Hz, 1H, H-9), 8.28 (brs, 1H, H-1). ^{13}C NMR (150 MHz, 25 °C, $CDCl_3$, δ): 22.9 (t, C-6), 25.6 (t, 2C, C-17 and C-18), 29.7 (t, C-19), 32.6 (t, C-16), 37.0 (d, C-15), 38.3 (d, C-20), 39.4 (t, C-14), 47.9 (t, C-5), 54.4 (t, C-21), 111.1 (d, C-12), 113.2 (s, C-7), 118.7 (d, C-9), 119.2 (d, C-10), 121.89 (d, C-2), 121.91 (d, C-11), 127.5 (s, C-8), 136.3 (s, C-13), 169.7 (s, C-3). EI-HRMS (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{24}N_2O^+$, 296.1889; found, 296.1885 (Δ = 1.4 ppm).

Computational Details. All DFT calculations were performed at the level of LanL2DZ, using the Gaussian 09 package. All transition-

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state geometries were confirmed by vibration analyses at the same level. Thermal corrections were calculated at 1 atm and 298.15 K in the gas phase.

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **3**−**7**, the crystallographic data of **1a**, and calculated transition-state geometry figures. A text file of all Cartesian coordinates of computed transition states in .xyz format for convenient visualization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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