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The Enantioselective Synthesis of (−)-Lycoramine with the Birch−Cope Sequence

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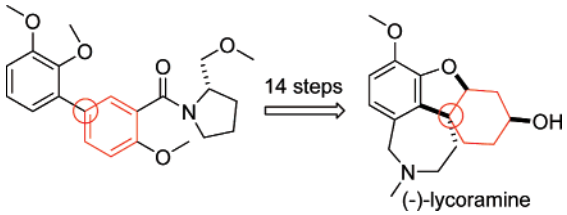

The first enantioselective synthesis of (−)-lycoramine has been achieved in 14 steps and 5% overall yield from the biaryl derivative **1**. The synthesis applies the previously developed Birch−Cope sequence to create the key arylic quaternary stereocenter of (−)-lycoramine with excellent enantioselective control. The product of the Birch−Cope sequence, a versatile 4,4-disubstituted-2-carboxamide-2-cyclohexen-1-one, was elaborated through an intramolecular conjugate addition of a phenol to create the dihydrofuran ring. Chemoselective elaboration of the allyl group into an amide followed by a modified Pictet-Spengler reaction generated the azepine ring.

Introduction

Alzheimer's disease is a neurodegenerative disorder that primarily strikes elderly individuals. There is currently no cure, and with the general population aging, the incidence of the disease will increase rapidly over the next decades.[1] An important advance in the treatment of Alzheimer's disease was recently realized with the development of (−)-galanthamine (Figure 1). The unique mechanism of action as both an acetylcholinesterase inhibitor and an allosteric potentiating ligand of the nicotine acetylcholine receptor distinguishes (−)-galanthamine from most of the currently marketed drugs.[2,3] The therapeutic value of (−)-galanthamine combined with its complex structure has prompted several enantioselective synthetic efforts.[4−9]

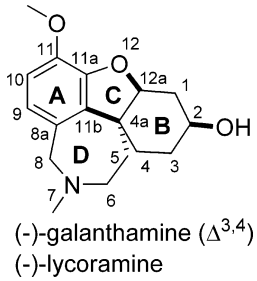

FIGURE 1. (−)-Galanthamine and (−)-lycoramine.

(−)-Lycoramine (Figure 1) is a member of the galanthamine-type alkaloid family and is the close saturated relative of the parent galanthamine. The complexity of lycoramine's structure has likewise attracted a range of synthetic efforts,[10−12] although none has culminated in an asymmetric synthesis. Lycoramine has similar, albeit less potent, activity as an acetylcholinesterase inhibitor[13] and an allosteric potentiating ligand. Indeed, the

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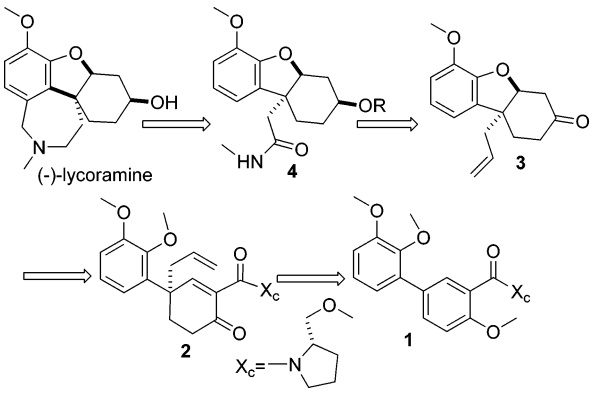
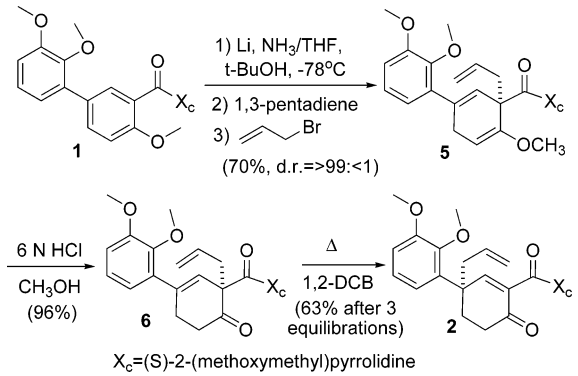
SCHEME 1. Retrosynthetic Analysis of (−)-Lycoramine



SCHEME 2. Birch−Cope Sequence in (−)-Lycoramine Synthesis



proven therapeutic activity of (−)-galanthamine and its structural similarity with (−)-lycoramine has resulted in several patents for these two compounds and their derivatives.[14]

Central to any enantioselective construction of galanthamine-type alkaloids is an asymmetric method for assembling the chiral arylic quaternary stereocenter. We recently described a new reaction sequence, the Birch−Cope sequence,[15,16] that efficiently and enantioselectively generates quaternary stereocenters on carbocyclic rings through the combination of three reactions: an enantioselective Birch reduction-allylation,[17] an enol ether hydrolysis reaction, and a Cope rearrangement.[18] Furthermore, the sequence transforms inexpensive, readily available aromatic starting materials into a chiral 4,4-disubstituted-2-carboxamide-2-cyclohexen-1-one, which is a versatile intermediate in natural product synthesis.[19] Application of the Birch−Cope sequence to the synthesis of (−)-lycoramine would further illustrate the potential of the sequence to address challenges in natural product synthesis.

For the synthesis of (−)-lycoramine, a biaryl derivative such as **1** (Scheme 1) would be subjected to the Birch−Cope sequence to afford **2**. Deprotection of the ortho methyl ether followed by conjugate addition to the enone system would generate **3** with the dihydrofuran ring of (−)-lycoramine. Oxidation of the allyl group to an amide (**4**) would precede the formation of the azepine ring by a modified Pictet-Spengler reaction.[10,11]

Results and Discussion

Application of the Birch−Cope Sequence. The asymmetric synthesis of the key 2-cyclohexen-1-one **2** occurred by subjecting **1** to the Birch−Cope sequence (Scheme 2).[15,16] Multigram scale enantioselective Birch reduction-allylations afforded 70% yield of the 1,4-cyclohexadiene **5**. Hydrolysis of the enol ether afforded one 1,5-diene system in **6**, which was immediately subjected to Cope equilibrium in refluxing 1,2-dichlorobenzene. Although the sterically congested arylic center of **2** makes this particular Cope equilibrium less thermodynamically favorable, most of the starting material can be recovered and resubjected to equilibration to afford a good yield of the key intermediate **2**.

A variety of reagents (e.g., $AlCl_3$, BCl_3, BBr_3, $SnCl_4$, and TMS−I) were tried to deprotect the aryl methyl ether of **2** and effect the conjugate addition of the resulting phenol on the enone system. However, most conditions failed to efficiently deprotect the methyl ether or afforded complex product mixtures. Nevertheless, if the classic BBr_3 conditions were applied with careful attention to maintaining the reaction temperature between −35 and −40 °C, a crude product that contained primarily **7a** was obtained (Scheme 3). The crude product was a mixture of epimers at the 2-cyclohexanone position and contained some phenol side product (**7b**), which was generated with the excess BBr_3 used in the reaction. To continue with the synthesis, it was easiest to carry this crude material forward, cleave the chiral auxiliary and form the 5-isoxazolinone, a mixture of **8a** and the phenol **8b**. Methylation of **8b** occurred by subjecting the mixture **8a**/**8b** to dimethyl sulfate and K_2CO_3. As seen in our previous work,[16] the use of $Mo(CO)_6$ was again the most effective reagent to reduce the N−O bond of the isoxazolinone. Under the refluxing aqueous conditions, the resulting acid spontaneously decarboxylates and the imine is hydrolyzed to afford cyclohexanone **3**.

A comparison of literature precedents[11,20] in the racemic synthesis of lycoramine indicated higher stereoselectivity in ketone reductions with L-selectride and before the azepine ring

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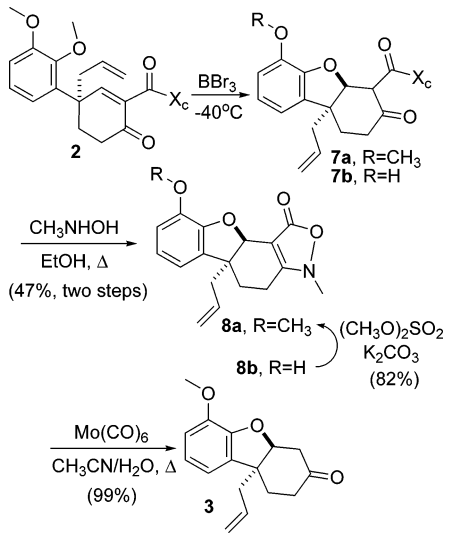
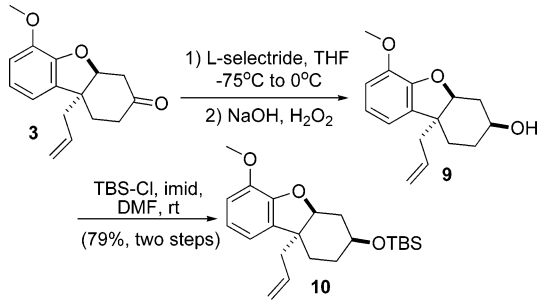
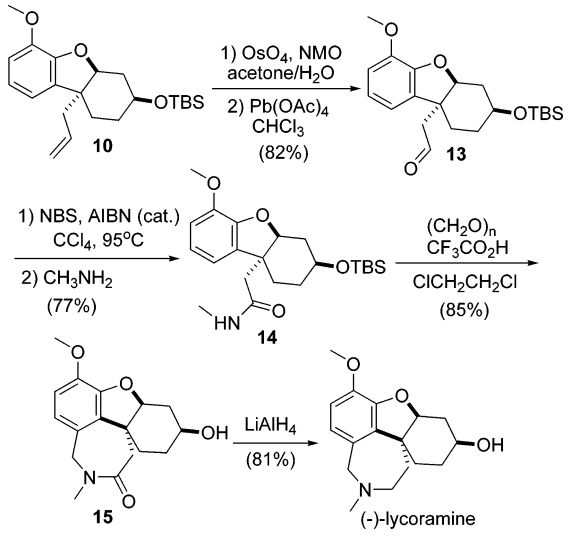
SCHEME 3. Synthesis of Dihyrofuran Ring



SCHEME 4. Stereoselective Formation of Alcohol



SCHEME 5. Formation of Azepine Ring



was formed. Consequently, we chose to reduce the ketone of **3** at this stage and found the reaction with L-selectride afforded complete stereocontrol (Scheme 4). The axial alcohol **9** was immediately protected as the tert-butyldimethylsilyl (TBS) ether **10**. In the reduction and TBS protection, there was a minor side product that was identified as **11 (**Figure 2**)**, presumably the result of elimination of the beta-phenoxy group during the reduction process. Careful control of the reaction temperature minimized the formation of **11**. With the cyclohexane ring of

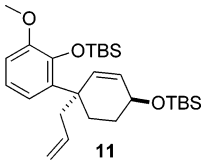


FIGURE 2. Side product from L-selectride reduction/TBS protection of **3**.

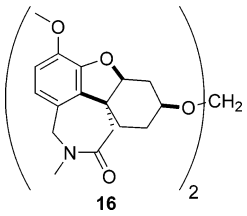


FIGURE 3. Acetal dimer side product formed in modified Pictet−Spengler reaction.

(−)-lycoramine set, attention turned to assembling the azepine ring.

Although ozonolysis was successfully employed to oxidatively cleave the alkene of the allyl group in our synthesis of (+)-mesembrine,[16] the oxidative cleavage of the weakly nucleophilic terminal alkene in the presence of an electron rich aromatic ring can be difficult. Indeed, the use of ozonolysis or Lemieux-Johnson conditions[21] resulted in the oxidation of the aromatic ring and was generally inefficient. Instead, the oxidative cleavage of the terminal alkene in **10** to the aldehyde **13** (Scheme 5) was best accomplished through a two step process, which was previously applied with a similarly complex substrate by Fuchs and co-workers in their synthesis of morphine.[22] Therefore, OsO_4-catalyzed oxidation of the alkene in **10** to a diol **12** (not shown) followed by $Pb(OAc)_4$ cleavage provided aldehyde **13**.

Aldehyde **13** was the same intermediate used by Tu et al. in a recently reported racemic synthesis of lycoramine;[10] consequently, their work guided the final steps in our synthesis (Scheme 5). The neutral, radical-mediated oxidation procedure of Marko[23] selectively transformed the aldehyde **13** to an acid bromide, which was reacted *in situ* with methyl amine to generate amide **14**. A modified Pictet−Spengler reaction, which was originally used by Hoshino in a racemic lycoramine synthesis,[11] was successful in forming the azepine ring of **15**. However, in our hands, the reaction provided a crude product **15** contaminated with approximately 25−30% of the acetal dimer **16 (**Figure 3**)**. Stirring the crude product with wet silica gel[24] prior to column chromatography efficiently hydrolyzed **16** to **15**. Reduction of the amide in **15** with lithium aluminum hydride completed the synthesis and provided pure (−)-lycoramine. Gratifyingly, the synthetic (−)-lycoramine matched the spectral information (IR, MS, ^{1}H and ^{13}C NMR) for previously synthetized racemic material[10−12] and had spectral information (^{1}H and MS), melting point and an optical rotation,

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$[\alpha]_D = -100$ ($c = 0.35$, EtOH), lit.[25] $[\alpha]_D = -100$ ($c = 0.05$, EtOH), matching natural (−)-lycoramine.

Conclusion

The first enantioselective synthesis of (−)-lycoramine has been achieved in 14 steps and 5% overall yield from the biaryl compound **1**. The synthesis features the application of the Birch−Cope sequence to efficiently generate the arylic quaternary chiral center with exceptionally high enantioselectivity. Furthermore, the synthesis highlights the utility of the Birch−Cope sequence products, chiral 4,4-disubstituted-2-cyclohexen-1-ones, in addressing challenges in natural product synthesis.

Experimental Section

(R)-10b-Allyl-7-methoxy-[(3,4-c)-2-methyl-isoxazolin-5-one]-1,2,(R)-5b,10b-tetrahydrodibenzofuran (8a) and (R)-10b-Allyl-7-hydroxy-[(3,4-c)-2-methyl-isoxazolin-5-one]-1,2,(R)-5b,10b-tetrahydrodibenzofuran (8b). 2-Cyclohexenen-1-one **2**[15] (520 mg, 1.26 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to −40 °C. Boron tribromide (12.6 mL, 1 M in CH_2Cl_2) was added dropwise over 10 min. The temperature (temp.) was maintained between −35 and −40 °C for 2 h, and then the reaction mixture was poured into saturated (satd.) $NaHCO_3$ (100 mL) at 0 °C. The organic layer was separated, washed with H_2O (2×) and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded **7a**/**7b** as a yellow oil, 550 mg. This crude product was dissolved in EtOH (10 mL) and treated with $CH_3NHOH{\cdot}HCl$ (210 mg, 2.52 mmol) and heated at reflux temp. overnight. After the removal of EtOH *in vacuo*, the product was extracted with EtOAc (3×). The organic layer was washed consecutively with satd. $NaHCO_3$, H_2O, and finally with half satd. brine. The organic layer was dried over Na_2SO_4 and evaporated to furnish a yellow oil. Column chromatography (2:1 EtOAc/hexanes) afforded a colorless foam that was approximately a 1/1 mixture of **8a** and **8b** (180 mg, 47%). The mixture precluded complete characterization and the material was used immediately in the next step, the methylation reaction to convert **8b** to **8a**. TLC of **8a**/**8b** mixture $R_f = 0.22$ (2:1 EtOAc/hexanes). ^{1}H NMR of **8a**/**8b** mixture ($CDCl_3$) δ 6.87−6.63 (m, 3H), 5.75−5.65 (m, 1H), 5.34 (d, 1H, $J = 7.7$ Hz), 5.12−5.05 (m, 2H), 3.83 (s, 1.7H), 3.32 (s, 1.7H), 3.28 (s, 1.3H), 2.42−2.36 (m, 3H), 2.31−2.17 (m, 1.5H), 2.06−1.91 (m, 1.5H). IR ($CDCl_3$) 3551, 1739, 1622 cm^{-1}.

(R)-10b-Allyl-7-methoxy-[(3,4-c)-2-methyl-isoxazolin-5-one]-1,2,(R)-5b,10b-tetrahydrodibenzofuran (8a). A mixture of **8a** and **8b** (428 mg, ∼1.40 mmol) was dissolved in acetone (20 mL), and K_2CO_3 (390 mg 2.8 mmol) and $(CH_3O)_2SO_2$ (0.22 mL, 2.3 mmol) were added sequentially. After heating the reaction mixture for 18 h at reflux, the reaction was concentrated and the residue was partitioned between EtOAc and satd. $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (2×). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to a yellow, opaque oil. The crude product was purified by column chromatography (7:3 EtOAc/hexanes) to afford 358 mg (82%) of **8a** as a pure white foam. TLC $R_f = 0.26$ (7:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ 6.88−6.71 (m, 3H), 5.77−5.68 (m, 1H), 5.34 (s, 1H), 5.12−5.06 (m, 2H), 3.84 (s, 3H), 3.29 (s, 3H), 2.44−2.37 (m, 4H), 2.25−2.17 (m, 1H), 2.05−1.95 (m, 1H). ^{13}C NMR ($CDCl_3$)δ_u 132.8, 121.2, 114.9, 112.5, 79.3, 56.0, 36.9; δ_d 168.9, 164.6, 147.2, 145.3, 132.3, 119.1, 96.4, 48.2, 43.1, 29.9, 22.6. IR ($CDCl_3$) 1740, 1641 cm^{-1}. GC $t_R = 18.63$ min. EI-MS *m*/*z* (%): 314 ($M^+ + 1$, 13), 313 (M^+, 62), 273 (17), 272 (100), 254 (15), 244 (22), 228 (15), 213 (23).

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(R)-9b-Allyl-6-methoxy-1,2,3,4,(S)-4a,9b-hexahydrodibenzofuran-3-one (3). Isoxazolinone **8a** (483 mg, 1.54 mmol) was dissolved in a mixture of CH_3CN (40 mL) and H_2O (3 mL), and the reaction was degassed by bubbling an Ar stream through the solution for approximately 45 min. $Mo(CO)_6$ (489 mg, 1.85 mmol) was added, and the reaction was placed in an oil bath at 55 °C. After 20 h, the reaction was concentrated and the product purified by separation on a silica gel column (4:1 hexanes/EtOAc). Ketone **3** was isolated as a light brown oil, 393 mg (99%). TLC $R_f = 0.24$ (4:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 6.92−6.87 (m, 1H), 6.78−6.74 (m, 2H), 5.77−5.66 (m, 1H), 5.17 (d, 1H, $J = 1.1$ Hz), 5.13 (dd, 1H, $J = 2.8$, 1.1 Hz), 4.96 (t, 1H, $J = 3.4$ Hz), 3.85 (s, 3H), 2.95 (dd, 1H, $J = 17.2$, 3.2 Hz), 2.65−2.57 (m, 2H), 2.50 (dd, 1H, $J = 14.0$, 8.1 Hz), 2.29−2.23 (m, 1H), 2.09−1.93 (m, 3H). ^{13}C NMR ($CDCl_3$)δ_u 132.7, 121.9, 115.4, 111.6, 85.1, 55.9; δ_d 208.9, 144.4, 133.1, 119.6, 47.7, 44.2, 41.6, 35.8, 32.2. IR ($CDCl_3$) 1719 cm^{-1}. GC $t_R = 13.05$ min. EI-MS *m*/*z* (%): 259 ($M^+ + 1$, 6), 258 (M^+, 32), 218 (17), 217 (100), 161 (45).

(R)-9b-Allyl-(S)-3-hydroxy-6-methoxy-1,2,3,4,(S)-4a,9b-hexahydrodibenzofuran (9). To a stirred solution of L-Selectride (1.0 mL, 1 M in THF) in anhydrous THF (10 mL) at −78 °C was added dropwise a pre-cooled −78 °C solution of ketone **3** (159 mg, 0.616 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C for 2 h and then slowly warmed to 0 °C over 1.5 h. After 2 h at 0 °C, the reaction was cooled to −30 °C and quenched by the addition of 1 N NaOH (0.75 mL) and 30% H_2O_2 (0.45 mL). The reaction mixture was stirred for 4 h while warming to r.t. and then diluted with water and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated to furnish a pale yellow oil (152 mg, 95%). TLC $R_f = 0.29$ (2:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 6.89−6.80 (m, 1H), 6.78−6.70 (m, 2H), 5.77−5.63 (m, 1H), 5.06−4.98 (m, 2H), 4.59 (t, 1H, $J = 5.2$ Hz), 3.86 (s, 3H), 3.84−3.75 (m, 1H), 2.34 (d, 1H, $J = 7.4$ Hz), 2.16−2.08 (m, 2H), 2.01−1.76 (m, 3H), 1.59−1.47 (m, 1H), 1.39−1.26 (m, 1H). ^{13}C NMR ($CDCl_3$)δ_u 133.6, 121.4, 115.1, 111.4, 86.5, 66.1, 55.8; δ_d 146.3, 145.2, 135.4, 118.3, 43.0, 35.2, 29.8, 28.8. IR ($CDCl_3$) 3606 cm^{-1}. GC $t_R = 12.94$ min. EI-MS *m*/*z* (%): 261 ($M^+ + 1$, 5), 260 (M^+, 24), 219 (72), 201 (45), 175 (100).

(R)-9b-Allyl-(S)-3-*tert*-butyldimethylsiloxy-6-methoxy-1,2,3,4,-(S)-4a,9b-hexahydrodibenzofuran (10). Alcohol **9** (152 mg, 0.585 mmol) was dissolved in DMF (2.5 mL), and imidazole (0.17 g, 2.5 mmol) and TBS−Cl (0.18 g, 1.2 mmol) were added sequentially. After 5 h, the reaction was diluted with satd. NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with H_2O (3X) and brine, dried with Na_2SO_4, filtered, and concentrated. The pure TBS ether **10** was obtained after column chromatography (1:1 hexanes/CH_2Cl_2) as a pale yellow oil, 181 mg (83%). TLC $R_f = 0.33$ (1:1 hexanes/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.86−6.66 (m, 3H), 5.71−5.62 (m, 1H), 5.05−4.93 (m, 2H), 4.60−4.54 (m, 1H), 3.86 (s, 3H), 3.59−3.52 (m, 1H), 2.32−2.11 (m, 2H), 1.74−1.23 (m, 6H), 0.84 (s, 9H), 0.28 (s, 6H). ^{13}C NMR ($CDCl_3$)δ_u 133.7, 120.9, 115.2, 111.6, 86.8, 67.6, 55.9, 25.7, −4.8; δ_d 146.6, 145.8, 134.4, 118.2, 47.8, 45.7, 38.6, 31.4, 28.0, 17.9. IR ($CDCl_3$) 2957, 1489 cm^{-1}. GC $t_R = 15.28$ min. EI-MS *m*/*z* (%): 374 (M^+, 3), 317 (31), 299 (76), 284 (20), 201 (100).

(S)-3-*tert*-Butyldimethylsiloxy-(R)-9b-[(R/S)-2′,3′-dihydroxypropane]-6-methoxy-1,2,3,4,(S)-4a,9b-hexahydrodibenzofuran (12). To a solution of the alkene **10** (97 mg, 0.26 mmol) in acetone (6 mL) and H_2O (4 mL) was added NMO (34 mg, 0.29 mmol) and an OsO_4 solution (0.10 mL, 0.05 M in THF). After stirring for 20 h, another aliquot of NMO (19 mg, 0.16 mmol) and OsO_4 solution (0.08 mL) was added. After 2 d, an aqueous slurry of florisil (160 mg) and $Na_2S_2O_4$ (40 mg) was added. The heterogeneous mixture was gravity filtered through a cotton plug and the filtrate was adjusted to pH 7 with 1 M $KHSO_4$. The resulting solution was saturated with solid NaCl and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification by column

chromatography (1:1 hexanes/EtOAc) afforded 93 mg (88%) of diol **12** as a colorless oil. TLC $R_f = 0.19$ (1:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 6.92−6.66 (m, 3H), 4.81, 4.63 (two dd, 1H, J = 9.8, 6.8 Hz), 3.85 (s, 3H), 3.67, 2.99 (two br s, 1H), 3.60−3.52 (m, 1H), 3.30−3.21 (m, 2H), 2.47−2.21 (m, 2H), 1.73−1.22 (m, 8H), 0.82 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$)δ_u 122.4, 121.4, 115.4, 114.5, 111.9, 111.7, 88.2, 87.3, 69.2, 69.0, 67.5, 55.9, 25.7, −4.8; δ_d 146.5, 145.8, 133.8, 133.4, 67.4, 67.0, 47.4, 47.3, 46.2, 44.0, 38.7, 31.5, 30.4, 28.9, 18.0. IR ($CDCl_3$) 3582 cm^{-1}.

(S)-3-*tert*-Butyldimethylsiloxy-6-methoxy-(R)-9b-(2′-oxoethyl)-1,2,3,4,(S)-4a,9b-hexahydrodibenzofuran (13). Diol **12** (135 mg, 0.330 mmol) was dissolved in $CHCl_3$ (7 mL) and treated with a solution of $Pb(OAc)_4$ (165 mg, 0.372 mmol) in $CHCl_3$ (5 mL). After 10 min, satd. $NaHCO_3$ was added, and the resulting mixture was extracted with CH_2Cl_2 (3×), dried with Na_2SO_4, filtered, and concentrated. Purification with column chromatography (7:1 hexanes/EtOAc) afforded aldehyde **13** (115 mg, 93%) as white crystals. mp = 58.5−60 °C. TLC $R_f = 0.16$ (7:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 9.58 (t, 1H, J = 2.3 Hz), 6.92−6.87 (m, 1H), 6.82−6.75 (m, 2H), 4.69 (dd, 1H, J = 9.6, 6.7 Hz), 3.87 (s, 3H), 3.66−3.59 (m, 1H), 2.65 (dd, 1H, J = 15.5, 2.2 Hz), 2.46 (dd, 1H, J = 15.5, 2.6 Hz), 2.36−2.22 (m, 2H), 1.79−1.68 (m, 2H), 1.52−1.26 (m, 2H), 0.84 (s, 9H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$)δ_u 201.2, 121.8, 115.0, 112.3, 86.9, 67.2, 56.0, 25.7, −4.8; δ_d 146.5, 146.1, 132.8, 53.8, 46.7, 38.3, 31.3, 28.5, 18.0. IR ($CDCl_3$) 1718 cm^{-1}. GC t_R = 16.29 min. EI-MS *m*/*z* (%): 376 (M^+, 2), 319 (7), 302 (23), 301 (100), 275 (30), 209 (37).

(S)-3-*tert*-Butyldimethylsiloxy-6-methoxy-(R)-9b-[2′-(N-methyl)-methylcarboxamido]-1,2,3,4,(S)-4a,9b-hexahydrodibenzofuran (14). AIBN (3.0 mg, 0.018 mmol) and NBS (71 mg, 0.397 mmol) were added to a solution of the aldehyde **13** (115 mg, 0.305 mmol) in CCl_4 (8 mL), and the mixture was placed in a pre-heated oil bath at 95 °C. After 25 min, the reaction mixture was removed from the oil bath and cooled to 0 °C. A stream of $MeNH_2$ was bubbled through the reaction mixture; the $MeNH_2$ stream was generated by adding ∼10 M NaOH to $MeNH_2$·HCl in a separate flask and passing the gas through a KOH drying tube. After 25 min of the $MeNH_2$ stream, the reaction mixture was diluted with CH_2Cl_2, washed with 1 M NaOH (3×) and brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (3:2 EtOAc/hexanes) to afford 96 mg (77%) of the amide as white crystals. mp = 114−115.5 °C. TLC $R_f = 0.21$ (3:2 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ 6.88−6.83 (m, 1H), 6.79−6.76 (m, 1H), 6.72−6.69 (m, 1H), 5.08 (br s, 1H), 4.86 (dd, 1H, J = 9.7, 6.8 Hz), 3.87 (s, 3H), 3.64−3.57 (m, 1H), 2.68 (d, 3H, J = 4.8 Hz), 2.39−2.22 (m, 4H), 1.93 (dt, 1H, J = 14.0, 3.9 Hz), 1.76−1.70 (m, 1H), 1.46−1.24 (m, 2H), 0.83 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$)δ_u 121.4, 115.0, 112.1, 86.7, 67.4, 56.0, 26.1, 25.7, −4.8; δ_d 170.7, 146.5, 146.0, 133.9, 47.5, 47.0, 38.6, 31.5, 27.5, 18.0. IR ($CDCl_3$) 3455, 1669 cm^{-1}. GC t_R = 18.71 min. EI-MS *m*/*z* (%): 405 (M^+, 2), 372 (4), 348 (16), 331 (27), 330 (100), 275 (62).

6-Oxo-lycoramine (15). To a solution of amide **14** (31.2 mg, 0.0769 mmol) in 1,2-dichloroethane (3.5 mL) was added paraformaldehyde (9.2 mg, 0.308 mmol) and CF_3CO_2H (0.077 mL, 1.0 mmol). The reaction mixture was stirred at ambient temperature for 1 h and then diluted with H_2O and quenched with satd. $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product (31.8 mg) was dissolved in CH_2Cl_2 (5 mL) and treated with silica gel (100 mg) and 15% H_2SO_4 (1 drop). The mixture was stirred for 1 h at r.t. and then concentrated *in vacuo*. The resulting powder was purified by column chromatography (CH_2Cl_2, then 2% MeOH/CH_2Cl_2) to afford **15** (19.9 mg, 85%) as a white crystalline solid. mp = 159−161 °C. TLC $R_f = 0.47$ (10% MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.69, 6.65 (ABq, 2H, J = 8.3 Hz), 4.41, 4.32 (ABq, 2H, J = 16.1 Hz), 4.39 (br s, 1H), 4.12 (br s, 1H), 3.87 (s, 3H), 3.03 (s, 3H), 2.87, 2.81 (ABq, 2H, J = 13.9 Hz), 2.72−2.50 (br s, 1H), 2.56 (dd, 1H, J = 2.3 Hz), 2.01−1.55 (m, 6H). ^{13}C NMR ($CDCl_3$)δ_u 119.7, 111.6, 89.2, 64.7, 56.2, 36.2; δ_d 171.9, 146.4, 144.9, 137.0, 124.6, 52.0, 41.7, 39.9, 30.9, 27.7, 27.6. IR ($CDCl_3$) 3578, 1635 cm^{-1}. GC t_R = 17.89 min. EI-MS *m*/*z* (%): 304 (M^+ + 1, 20), 303 (M^+, 100), 244 (24), 231 (55), 188 (35).

(−)-Lycoramine. To a suspension of $LiAlH_4$ (36.0 mg, 0.949 mmol) in THF (3 mL) at −78 °C, was added a pre-cooled (−78 °C) solution of lactam **15** (35.0 mg, 0.115 mmol) in THF (3 mL). After the complete addition, the reaction mixture was warmed to r.t. and then heated at reflux for 2.5 h. The reaction was cooled to r.t. and quenched with 10% NaOH (4 mL). The reaction mixture was extracted with EtOAc (5×) and CH_2Cl_2 (2×). The combined organic layers were dried with K_2CO_3, filtered, and concentrated. The product was purified by column chromatography (gradient elution: CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to afford (−)-lycoramine as a yellowish-white oil (27.2 mg, 81%). Trituration with hot Et_2O provided a cluster of white crystals, mp = 117−118 °C (lit:[25] 122−124 °C, lit:[26] 120−122 °C, lit:[13] 110−112 °C, lit:[27] 106−107 °C). $[\alpha]^{20}_D$ −100 (*c* = 0.35, EtOH) (lit:[25] $[\alpha]^{22}_D$ −100.0 (*c* = 0.05, EtOH), lit:[26] $[\alpha]^{22}_D$ −96.0 (*c* = 0.71, EtOH), lit:[28] $[\alpha]^{25}_D$ −97.4 (*c* = 1.252, 90% EtOH)). TLC $R_f = 0.18$ (15% MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.65, 6.60 (ABq, 2H, J = 8.2 Hz), 4.37 (t, 1H, J = 3.0 Hz), 4.09−4.03 (m, 1H), 4.01 (d, 1H, J = 15.0 Hz), 3.86 (s, 3H), 3.63 (d, 1H, J = 15.0 Hz), 3.21 (t, 1H, J = 12.5 Hz), 3.08−3.01 (m, 1H), 2.50 (dd, 1H, J = 15.9, 1.5 Hz), 2.40−2.10 (br s, 1H), 2.38 (s, 3H), 2.02−1.53 (m, 7H). ^{13}C NMR ($CDCl_3$)δ_u 121.8, 110.7, 90.0, 65.5, 55.9, 41.8; δ_d 146.0, 144.1, 136.3, 128.8, 60.5, 54.1, 46.7, 31.6, 31.2, 27.7, 23.7. IR (CH_2Cl_2) 3576, 2927, 1624 cm^{-1}. GC t_R = 15.99 min. EI-MS *m*/*z* (%): 290 (M^+ + 1, 10), 289 (M^+, 60), 288 (100).

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Supporting Information Available: General experimental details; copies of ^{1}H and ^{13}C NMR spectra, gas chromatographs and mass spectra for compounds **3**, **8a/8b** mix, **8a**, **9**, **10**, **12**−**15**, and (−)-lycoramine; COSY for (−)-lycoramine. This material is available free of charge via the Internet at http://pubs.acs.org.

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