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Intramolecular Heck cyclization to the galanthamine-type alkaloids: total synthesis of (±)-lycoramine

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Abstract—A novel approach towards the construction of the galanthamine skeleton was demonstrated by the total synthesis of (±)-lycoramine. The key steps include a Pd-catalyzed intramolecular cyclization to form the seven-membered azepane ring and a spontaneous intramolecular Michael addition to afford the five-membered furan ring. This synthetic route has also been demonstrated to be useful for the preparation of novel derivatives with simplified galanthamine skeletons.

1. Introduction

Galanthamine ((−)-**1**),[1] an alkaloid isolated from the *Amaryllidaceae* species, has been shown to be a potent acetylcholinesterase (AChE) inhibitor and significantly enhances cognitive functions in patients who suffered from Alzheimer's disease (AD).[2–4] Galanthamine was first approved in Austria and most recently in the rest of Europe and in the United States for the treatment of AD.

Galanthamine is produced by isolation from botanical sources (e.g., *Galanthus nivalis*, *G. narcissus*, *G. leucojum*, or *G. crinium*) and these sources are limited.[5] Thus, synthetic approaches to the large-scale production of galanthamine have been sought and a number of total syntheses of galanthamine have appeared in the literatures.[6–26] Most of them utilized a biomimetic oxidative bisphenol coupling to create the critical spiroquarternary carbon of galanthamine.[6–19] Lycoramine ((−)-**2**, 1,2-dihydrogalanthamine), another galanthamine-type alkaloid, has been claimed to have significant activities in inhibiting the formation of peptide bond in protein synthesis.[20] In a formal synthesis of **2**, the intramolecular Heck reaction was used to construct the quaternary carbon center via a 6-*exo* cyclization.[21] From then on, several groups have utilized palladium-catalyzed cyclization to build the quaternary center of galanthamine-type alkaloids.[22–26]

Galanthamine is structurally related to morphine in topology (Chart 1). Morphine and its simplified analogs morphinan, benzomorphan, and 4-phenylpiperidine derivatives, remain the most widely used analgesics for the treatment of severe pain. Therefore, derivatives containing simplified galanthamine skeleton may be potential candidates for the development of novel AChE inhibitors. Prior research in this laboratory has focused on the development of novel synthetic strategies for the efficient preparation of compounds

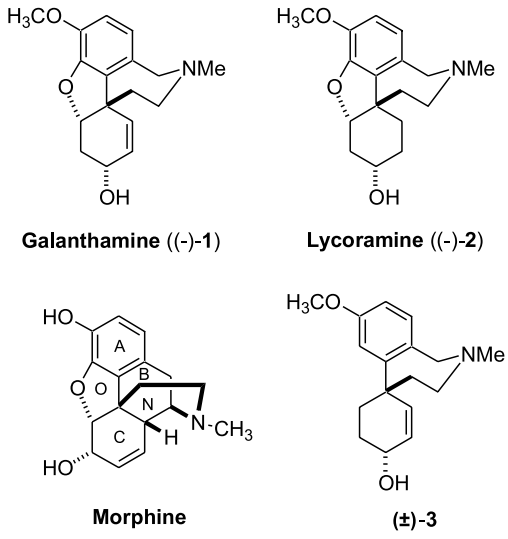

Chart 1.

Keywords: Galanthamine; Lycoramine; Intramolecular cyclization; Heck reaction.

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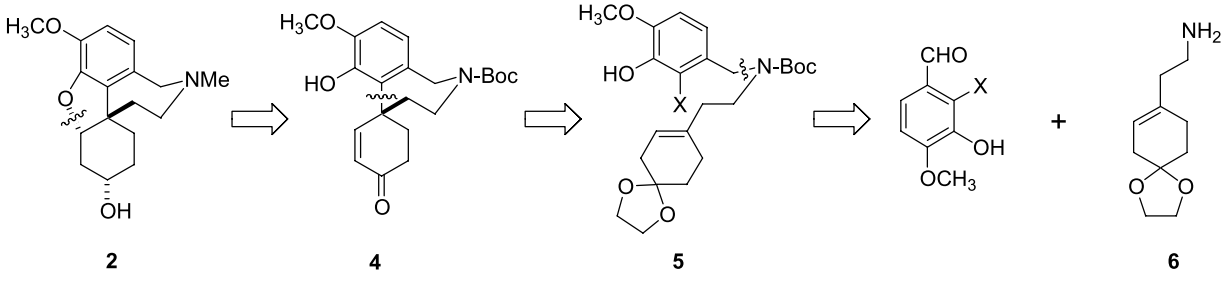
possessing morphine partial structures.[27–32] The Heck reaction was one of the key reactions used for construction of the O ring in the ANO and ACNO ring systems of morphine.[28] This experience has prompted us to extend our methodology to the synthesis of structurally simplified galanthamine analogs, including the 12-aza-benzo[*h*]spiro [5.6]dodecane (±)-**3**, which retains most of the rigidity of galanthamine and demonstrated the desired, albeit weak AChE inhibition.[33] To further explore the utilities of our methodology, we have achieved the total synthesis of the galanthamine-type alkaloid lycoramine ((±)-**2**). Here, we report in detail the novel synthetic strategy for the preparation of (±)-**2**.

2. Results and discussion

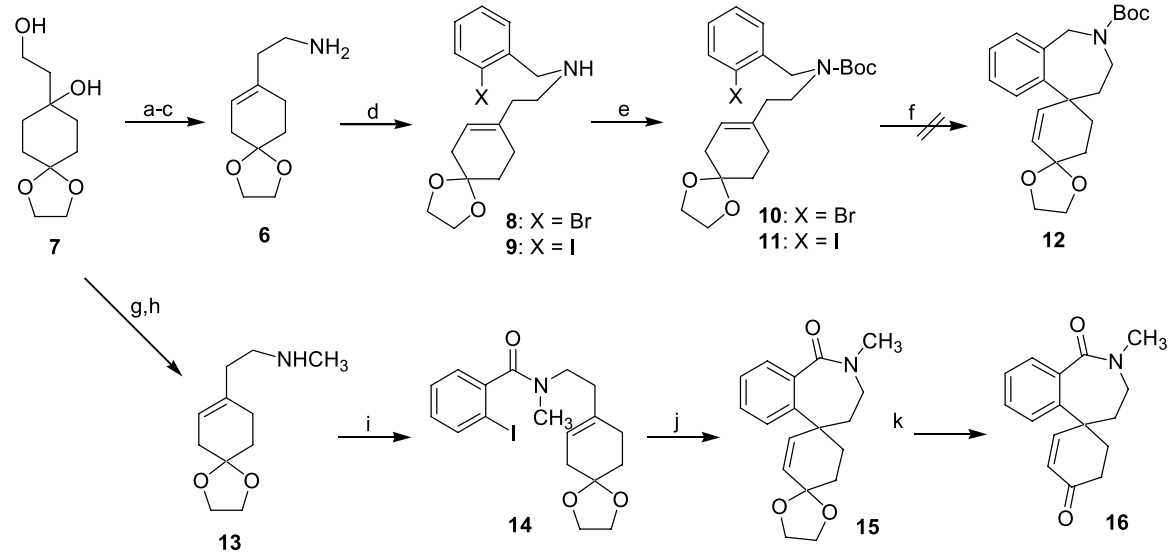
Retrosynthetic consideration led us to propose the route as shown in Scheme 1. The dihydrofuran ring in **2** could be generated by an intramolecular Michael addition of the phenol group to the enone functionality of **4**. The seven-membered tetrahydroazepine ring in compound **4** could be formed via a Pd-catalyzed 7-*exo-trig* cyclization of the key intermediate **5**. Compound **5** can be synthesized from the coupling of a 2-haloisovanillin and 2-(1,4-dioxa-spiro[4,5] dec-7-en-8-yl)ethylamine (**6**) via a reductive amination reaction.

The starting amine **6** was prepared from diol **7** via a reaction sequence of Mitsunobu reaction with phthalimide, dehydration, and deprotection. Diol **7** was obtained from cyclohexane-1,4-dione monoethylene ketal, as previously described.[33] Reductive amination of 2-halobenzaldehydes with amine **6**, followed by protection of the secondary amine intermediates with $(Boc)_2O$ afforded compounds **10** and **11**, respectively (Scheme 2). However, all attempts to effect the intramolecular Heck reaction to prepare the desired cyclized product **12** failed, resulting primarily in dehalogenated products. Earlier reports suggested that compounds with an *endo*-amide group may favor the intramolecular Heck reaction due to the added conformational restriction.[34,35] Therefore, we turned our attention to the use of *endo*-amide intermediates, such as compound **14**.

Treatment of compound **7** with MsCl, followed by methylamine, resulted in nucleophilic substitution and dehydration to afford the secondary amine **13**. The advantage of this alternative process for the preparation of the said amines was to avoid the use of very toxic reagents, DEAD and hydrazine, for the Mitsunobu and the subsequent deprotection steps, respectively. Compound **14** was prepared by the coupling of 2-iodobenzoic acid with amine **13**. To our delight, compound **14** underwent the desired intramolecular Pd-catalyzed cyclization smoothly to provide spiro-amide **15** in 67% yield. However, the desired cyclization was not observed when the bromo-analog of



Scheme 1. Retrosynthetic analysis of galanthamine-type alkaloids (X=Br or I).



Scheme 2. Reagents and conditions: (a) phthalimide, DEAD, PPh_3, THF, rt; (b) *p*-TsOH, toluene, reflux; (c) $N_2H_4 \cdot H_2O$, ethanol, reflux; (d) 2-bromobenzaldehyde or 2-iodobenzaldehyde, CH_2Cl_2, rt; then $NaBH_4$, MeOH, rt; (e) $(Boc)_2O$, $NaHCO_3$, MeOH, rt; (f) Heck reaction conditions; (g) MsCl, CH_2Cl_2, −23 °C to rt; (h) 40% CH_3NH_2, reflux; (i) 2-iodobenzoic acid, $SOCl_2$, THF, −23 °C to rt; (j) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, 130 °C; (k) 1 N HCl, rt.

compound **14** was subjected to the same Heck reaction condition. Hydrolysis of the ketal function in **15** with HCl afforded enone **16** in 63% yield.

With the success in the synthesis of compound **16**, we then turned our efforts to the construction of the complete tetracyclic skeleton of galanthamine. Thus, 2-iodoisovanillin (**18**) was prepared from isovanillin in four steps according to the literature.[36] The aldehyde and phenol groups of isovanillin were protected by reacting with trimethyl orthoformate and chloromethyl methyl ether, respectively, to afford compound **17**. Treatment of **17** with *n*-butyl lithium and I_2, followed by acidic work-up furnished compound **18**. Direct oxidation of **18** to the corresponding acid failed due to the sensitivity of its phenol group. Therefore, the phenol group of **18** was first protected as a benzyl ether, and then the protected aldehyde was oxidized with $KMnO_4$ to give acid **19**. Coupling of compound **19** with amine **13** afforded amide **20** in 73% yield (Scheme 3).

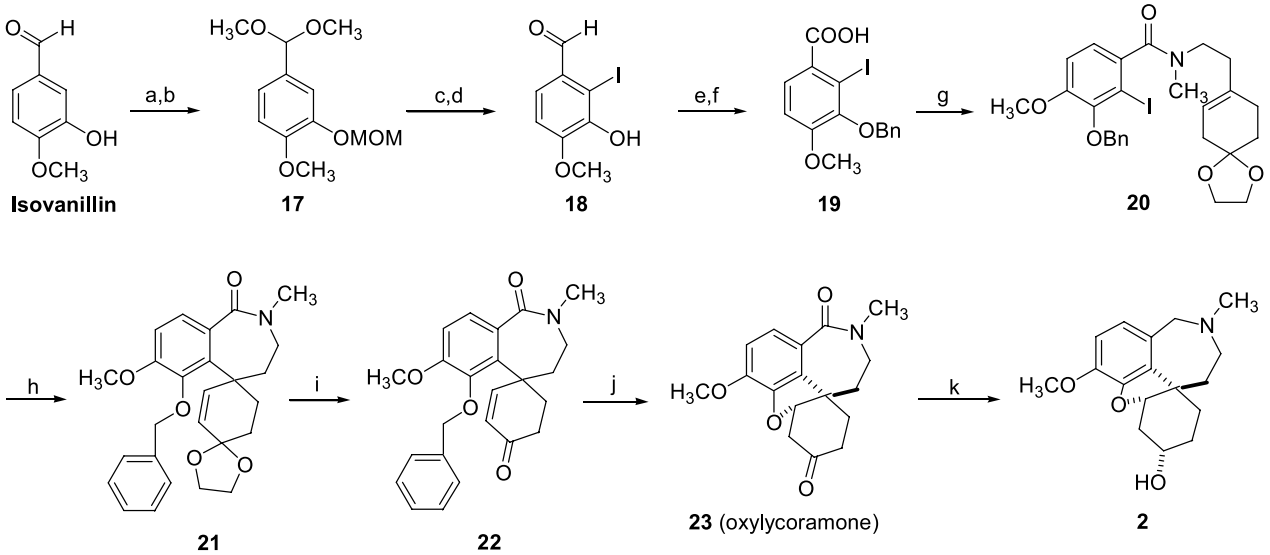
When compound **20** was subjected to Heck reaction condition using $Pd(OAc)_2$, Ph_3P, and K_2CO_3 in CH_3CN, the desired intramolecular cyclization was achieved to provide dispiro-compound **21**. Other reaction conditions, with different phosphine ligands (Ph_3As, BINAP), bases (NEt_3, Ag_2CO_3, proton sponge), and solvents (THF, DMF), resulted in the formation of **21** from **20** in lower yields. Longer reaction time or higher reaction temperature resulted in significant decomposition of the starting compound **20**. The ethylene ketal group of **21** was removed easily when put in contact with silical gel in methanol to give ketone **22** in 95% yield. Subsequent removal of the benzyl group in **22** with $SnCl_4$ was accompanied by a spontaneous intramolecular Michael addition to afford the tetracyclic oxolycoraminone (**23**)[37] in 75% yield. Simultaneous reduction of both the ketone and amide groups of **23** with $LiAlH_4$ afforded (±)-**2**[37,38] with excellent diastereoselectivity (de >95%). The hydroxyl group of (±)-**2** was assigned to be *cis* to the oxide ring based on analysis of its ^1H NMR spectrum, which is identical to that of an authentic sample of lycoramine.

In summary, we have demonstrated a novel synthetic route to the galanthamine skeleton and its simplified analogs, such as **16**. To our knowledge, the direct construction of the seven-membered ring of galanthamine-type alkaloids via an intramolecular Heck reaction as exemplified by the total synthesis of (±)-**2** has not been documented yet. The total synthesis starts from simple cyclohexane-1,4-dione monoethylene ketal and isovanillin, and completes in eight steps with an overall yield of 3%. Notable features of this synthetic route include a Pd-catalyzed intramolecular cyclization and a spontaneous intramolecular Michael addition to form the seven-membered azepane ring and the five-membered furan ring, respectively. This synthetic strategy may be developed into an alternative process for galanthamine production, and provide derivatives possessing simplified galanthamine skeleton as potential drug candidates. Further work towards the synthesis of novel galanthamine-related compounds and their pharmacological studies are in progress.

3. Experimental

3.1. General procedures

Melting points were taken in capillary tubes on a MEL-TEMP II apparatus by Laboratory Devices and are uncorrected. NMR spectra were recorded on Bruker DPX-200 and AMX-400 FT-NMR spectrometers; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded on a Jeol JMS-D300 mass spectrometer; HRMS was obtained with a Jeol-HX110 mass spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400-CHN instrument. TLC was performed on Merck (art. 5715) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor or upon heating after treatment with 5%



Scheme 3. Reagents and conditions: (a) trimethy orthoformate, CH_2Cl_2, rt; (b) LDA, MOMCl, THF, −78 °C; (c) *n*-butyllithium, I_2, −78 °C; (d) 3 N HCl, rt; (e) benzyl bromide, K_2CO_3, acetone, rt; (f) $KMnO_4$, acetone–H_2O, rt; (g) $SOCl_2$, THF, −23 °C; then **13**, NEt_3, THF, −23 °C to rt; (h) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, 130 °C; (i) silical gel, MeOH, rt; (j) $SnCl_4$, CH_2Cl_2, rt; (k) LAH, THF, reflux.

phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (art. 9385) 40–63 μm silical gel 60. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone prior to use.

3.1.1. (2-Bromobenzyl)-[2-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)ethyl]carbamic acid *tert*-butyl ester (10). A mixture of **6**[33] (355 mg, 1.94 mmol) and 2-bromobenzaldehyde (390 mg, 2.13 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 30 min. The mixture was evaporated and was added MeOH (20 mL) and $NaBH_4$ (232 mg, 5.82 mmol). The resulting mixture was stirred at rt for 1 h. The solution was evaporated and the residue was partitioned with EtOAc (3×15 mL) and H_2O (10 mL). The combined extract was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silical gel; EtOAc) to afford **8** (442 mg, 65%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24–1.78 (m, 4H), 1.92–2.02 (m, 4H), 2.67 (t, J=6.5 Hz, 2H), 3.83 (s, 2H), 3.94 (s, 4H), 5.04 (s, 1H), 7.08 (t, J=7.0 Hz, 1H), 7.24 (t, J=7.0 Hz, 1H), 7.35 (d, J=6.5 Hz, 1H), 7.50 (d, J=7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7, 31.5, 36.0, 37.7, 47.0, 54.1, 64.7, 108.4, 109.9, 120.4, 124.3, 127.8, 128.9, 130.7, 133.1, 135.4. To a solution of **8** (442 mg, 1.26 mmol) in MeOH (30 mL) was added $(Boc)_2O$ (330 mg, 1.51 mmol) and $NaHCO_3$ (260 mg, 3.05 mmol) and stirred at rt for 2 h. The mixture was evaporated and the residue was partitioned with EtOAc (2×20 mL) and H_2O (10 mL). The combined extract was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silical gel; EtOAc/*n*-hexane 2:3) to afford **10** (368 mg, 64%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36–1.47 (m, 9H), 1.75 (t, J=6.4 Hz, 2H), 2.16–2.22 (m, 6H), 3.23–3.27 (m, 2H), 3.93 (s, 4H), 4.45–4.49 (m, 2H), 5.30 (s, 1H), 7.04–7.29 (m, 3H) 7.49 (d, J=7.8 Hz, 1H); MS (EI, 70 eV) *m*/*z* 451 (M^+), 298, 168; HRMS calcd for $C_{22}H_{30}BrNO_4^+$: 451.1358, found 451.1356.

3.1.2. [2-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)ethyl]-(2-iodobenzyl)carbamic acid *tert*-butyl ester (11). [2-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)ethyl]-(2-iodobenzyl)amine (**9**) was synthesized using compound **6** and 2-iodobenzaldehyde as described above to afford **9** in 55% yield as a yellow oil. Compound **11** was then synthesized from compound **9** as described above to afford **11** in 53% yield as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36–1.49 (m, 9H), 1.90–1.94 (m, 2H), 2.10–2.16 (m, 6H), 3.20–3.21 (m, 2H), 3.93 (s, 4H), 4.35–4.44 (m, 2H), 5.30 (s, 1H), 6.91 (t, J=7.4 Hz, 1H), 7.11 (d, J=7.4 Hz, 1H), 7.27 (t, J=7.4 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H); MS (EI, 70 eV) *m*/*z* 499 (M^+), 398, 216; HRMS calcd for $C_{22}H_{30}INO_4^+$: 499.1220, found 499.1233.

3.1.3. [2-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)ethyl]-methylamine (13). To a stirred solution of diol **7**[33] (3.44 g, 17 mmol) and Et_3N (12 mL) in CH_2Cl_2 (125 mL) was added MsCl (2.64 mL, 34 mmol). The resulting mixture was stirred at rt under N_2 for 1 h. The solvent was evaporated and then water (100 mL) was added to the residue. The solution was extracted with CH_2Cl_2 (100 mL ×2) and the combined extract was dried over $MgSO_4$, filtered, and evaporated to afford methanesulfonic acid 2-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)ethyl ester (2.37 g, 53%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71–1.77 (t, J=8.6 Hz, 2H), 2.15–2.22 (m, 4H), 2.37–2.43 (t, J=8.6 Hz, 2H), 2.97 (s, 3H), 3.91–3.96 (m, 4H), 4.23–4.30 (m, 2H), 5.40–5.41 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.6, 30.9, 35.6, 36.4, 37.4, 64.3, 68.3, 107.6, 121.8, 132.1. To a stirred mixture of the mesylate (1.29 g, 4.92 mmol) and Et_3N (1 mL) in THF (10 mL) was added methylamine (40% in water, 2.55 mL). The reaction mixture was heated at reflux overnight and the solvent was evaporated. The residue was treated with water (15 mL) and then extracted with a solution of IPA/$CHCl_3$ (1:4; 3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to afford **13** (870 mg, 90%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70–1.75 (m, 3H), 2.15–2.20 (m, 5H), 2.40 (s, 3H), 2.63 (t, J=7.4 Hz, 2H), 3.94 (s, 4H), 5.33 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 31.0, 33.5, 35.6, 41.4, 55.5, 64.3, 107.8, 119.8, 134.7; MS (EI, 70 eV) *m*/*z* 198 (M^++1), 157 (base); HRMS calcd for $C_{11}H_{19}NO_2^+$: 197.1416, found 197.1432.

3.1.4. *N*-[2-(1,4-Dioxa-spiro[4.5]dec-7-en-8-yl)-ethyl]-2-iodo-*N*-methyl-benzamide (14). To a solution of 2-iodobenzoic acid (1.50 g, 6.04 mmol) in THF (50 mL) was added $SOCl_2$ (0.7 mL, 6.64 mmol) at −78 °C and stirred for 30 min. The temperature was allowed to raise to −20 °C, and then a solution of **13** (1.20 g, 6.56 mmol) and Et_3N (2.3 mL, 18.1 mmol) in THF (15 mL) was added. The mixture was stirred for 6 h and the reaction temperature was slowly raised to rt. The solvent was evaporated and the residue was partitioned with CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica gel; EtOAc/*n*-hexane 3:2) to afford **14** (1.62 g, 63%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60 (t, J=6.0 Hz, 1H), 1.72 (t, J=6.0 Hz, 1H), 1.84–1.88 (m, 1H), 2.0–2.3 (m, 5H), 2.72 and 3.04 (s, 3H), 3.06–3.11 (m 1H), 3.51–3.65 (m, 1H), 3.87 and 3.90 (s, 4H), 5.16 and 5.38 (s, 1H), 6.91–7.05 (m, 1H), 7.12–7.17 (m, 1H), 7.27–7.31 (m, 1H), 7.71–7.77 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.3, (30.9, 32.4), 34.0, (35.6, 36.3), 45.3, 49.4, 64.2, (92.1, 92.6), (107.4, 107.7), (120.2, 120.8), (126.8, 127.2), (128.0, 128.2), (129.8, 129.9), (133.3, 134.4), 138.9, (142.4, 142.8), (170. 170.6); IR (neat) cm^{-1} 3450, 2926, 1636, 1488; MS (EI, 70 eV) *m*/*z* 427 (M^+), 166; HRMS calcd for $C_{18}H_{22}INO_3^+$: 427.0644, found 427.0621. (Since the amide group in **14** could adopt either a *cis* or *trans* configuration, some of the ^{1}H and ^{13}C signals appear as pairs.)

3.1.5. 12-Methyl-12-aza-benzo[*h*]spiro[5.6]dodec-1-en-3,11-dione (16). A solution of **14** (950 mg, 2.22 mmol), $Pd(OAc)_2$ (54 mg, 0.22 mmol), triphenylphosphine (233 mg, 0.89 mmol), and K_2CO_3 (618 mg, 4.44 mmol) in acetonitrile (150 mL) was heated in a sealed round bottle at 130 °C for 36 h. The mixture was cooled, filtered, and evaporated to afford crude 14-methyl-1,4-dioxa-14-aza-benzo[*j*]dispiro[4.2.6.2]hexadec-6-en-13-one (**15**). The crude **15** was treated with 1 N HCl for 30 min. The resulting mixture was evaporated and partitioned with CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography (silica gel; EtOAc/*n*-hexane 3:2) to afford **16** (349 mg, 63%). Compound **16** was recrystallized from EtOAc as colorless crystals: ^{1}H NMR

(200 MHz, $CDCl_3$) δ 2.11–2.39 (m, 6H), 3.15 (s, 3H), 3.18–3.38 (m, 1H), 3.38–3.50 (m, 1H), 6.06 (d, $J=10.6$ Hz, 1H), 6.91 (dd, $J=10.4$, 1.0 Hz, 1H), 7.21–7.25 (m, 1H), 7.35–7.40 (m, 2H), 7.71–7.75 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.3, 34.4, 38.0, 42.4, 43.7, 48.2, 126.5, 127.9, 129.0, 130.4, 130.7, 135.6, 138.9, 156.5, 170.6, 198.8; IR (KBr) cm^{-1} 3478, 1680, 1639; MS (EI, 70 eV) *m/z* 255 (M^+, base). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.21; H, 6.65; N, 5.26.

3.1.6. 3-Benzyloxy-2-iodo-4-methoxybenoic acid (19). A solution of 2-iodo-isovanillin (**18**)[36] (1.50 g, 5.39 mmol), benzyl bromide (2.0 mL, 7.54 mmol), and K_2CO_3 (3.75 g, 27.1 mmol) in acetone (60 mL) was heated at reflux for 2 h. The solvent was evaporated and the crude was purified by recrystallization from EtOAc to give 3-benzyloxy-2-iodo-4-methoxy-benaldehyde (1.97 g, 99%) as a light yellow solid. To a solution of 3-benzyloxy-2-iodo-4-methoxy-benaldehyde (1.30 g, 3.53 mmol) in acetone (60 mL) was added $KMnO_4$ (19.5 g, 12.3 mmol) in water (30 mL) and stirred for 24 h. The mixture was filtered to remove MnO_2 and the filtrate was partitioned with 1 N NaOH (20 mL) and CH_2Cl_2 (100 mL). The organic layer was collected to recover the starting material. The aqueous layer was separated, acidified with 3 N HCl (20 mL), and extracted with a solution of IPA/$CHCl_3$ (1:4; 80 mL $\times$2). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to afford **19** (1.55 g, 75%) as a yellow solid. This solid was recrystallized from CH_2Cl_2 to give colorless crystals: mp 176–178 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 5.0 (s, 3H), 6.93 (d, $J=8.7$ Hz, 1H), 7.33–7.41 (m, 3H), 7.58–7.60 (m, 2H), 7.87 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 74.2, 95.8, 111.2, 125.9, 128.1, 128.3, 128.5, 129.5, 136.8, 148.6, 156.1, 171.0; IR (neat) cm^{-1} 1687, 1577, 1274; MS (EI, 70 eV) *m/z* 384 (M^+), 91 (base); HRMS calcd for $C_{15}H_{13}IO_4^+$: 383.9859, found 383.9847.

3.1.7. 3-Benzyloxy-*N*-[2-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)-ethyl]-2-iodo-4-methoxy-*N*-methyl-benzamide (20). A mixture of **19** (355 mg, 0.93 mmol), $SOCl_2$ (0.11 mL, 1.02 mmol), and DMF (three drops) in THF (30 mL) was stirred at −78 °C for 30 min. The reaction temperature was raised to −40 °C and then a solution of **13** (240 mg, 1.21 mmol) and Et_3N (0.36 mL, 2.77 mmol) in THF (10 mL) was added. The resulting mixture was stirred and the temperature was slowly raised to rt. The solution was evaporated and the residue was partitioned with EtOAc (3$\times$15 mL) and H_2O (10 mL). The combined extract was dried over $MgSO_4$, filtered, and evaporated to afford **20** (382 mg, 73%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–1.68 (m, 1H), 1.73–1.77 (m, 1H), 1.80–1.93 (m, 1H), 2.16–2.34 (m, 5H), 2.72 and 3.05 (s, 3H), 3.12–3.20 (m, 1H), 3.60–3.62 (m, 1H), 3.83 (s, 3H), 3.90–3.93 (m, 4H), 4.91–4.97 (m, 2H), 5.19 and 5.40 (s, 1H), 6.90–6.92 (m, 2H), 7.30–7.35 (m, 3H), 7.49–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 31.0, (32.6, 32.4), (35.5, 36.5), 45.6, 49.7, 64.3, 74.4, (92.1, 92.5), (107.6, 107.9), (112.7, 112.9), (120.2, 120.8), (122.8, 123.2), (128.1, 128.3), (128.5, 128.6), 131.9, (132.1, 132.6), (135.9, 136.3), 136.9, 147.8, 152.4, (170.2, 170.6); IR (neat) cm^{-1} 2927, 1633, 1261; MS (EI, 70 eV) *m/z* 563 (M^+), 367 (base); HRMS calcd for $C_{26}H_{30}INO_5^+$: 563.1169, found 563.1143. (Since the amide group in **20** could adopt either a *cis* or *trans* configuration, some of the ^1H and ^{13}C signals appear as pairs.)

3.1.8. 9-Benzyloxy-10-methoxy-14-methyl-1,4-dioxa-14-aza-benzo[*j*]dispiro[4.2.6.2]hexadec-6-en-13-one (21). A mixture of **20** (250 mg, 0.44 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), triphenylphosphine (23 mg, 0.088 mmol), and K_2CO_3 (123 mg, 0.86 mmol) in CH_3CN (40 mL) was heated in a sealed round bottle at 130 °C for 5 days. The resulting mixture was filtered, evaporated, and partitioned with CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated. The residue was purified with prepared TLC (silica gel; EtOAc/*n*-hexane/$NH_{3(conc)}$ 3:2:0.005) to afford compound **21** (53 mg, 28%) as an oil with recovered starting material **20** (21%) and de-iodinated by-product (15%). Compound **21**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.58–1.95 (m, 4H), 2.12–2.29 (m, 2H), 2.96–3.03 (m, 1H), 3.09 (s, 3H), 3.29–3.43 (m, 1H), 3.87 (s, 3H), 3.92–4.00 (m, 4H), 4.68 (d, $J=10.3$ Hz, 1H), 4.87 (d, $J=10.3$ Hz, 1H), 5.32 (d, $J=10.6$ Hz, 1H), 6.30 (d, $J=10.1$ Hz, 1H), 6.88 (d, $J=8.4$ Hz, 1H), 7.24–7.38 (m, 3H), 7.42–7.50 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.9, 34.2, 38.5, 43.3, 44.0, 48.1, 55.6, 64.2, 64.4, 74.0, 105.7, 110.1, 121.9, 126.3, 127.9, 128.1, 132.0, 135.3, 138.1, 141.6, 146.2, 155.3, 171.1; MS (EI, 70 eV) *m/z* 435 (M^+), 91 (base); HRMS calcd for $C_{26}H_{29}NO_5^+$: 435.2046, found 435.2030.

3.1.9. 7-Benzyloxy-8-methoxy-12-methyl-12-aza-benzo[*h*]spiro[5.6]dodec-1-en-3,11-dione (22). To a solution of **21** (53 mg, 0.12 mmol) in methanol (10 mL) was added silical gel (20 mg) and stirred at rt for 1 h. The mixture was filtered and evaporated. The residue was partitioned with CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford compound **22** (45 mg, 95%) as a light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (dd, $J=14.4$, 1.4 Hz, 1H), 2.09 (ddd, $J=12.0$, 9.6, 2.8 Hz, 1H), 2.19–2.23 (m, 1H), 2.24–2.32 (m, 2H), 2.41–2.44 (m, 1H), 3.05–3.11 (m, 1H), 3.11 (s, 3H), 3.39–3.48 (m, 1H), 3.90 (s, 3H), 4.40 (d, $J=10.8$ Hz, 1H), 4.98 (d, $J=10.8$ Hz, 1H), 5.69 (d, $J=10.0$ Hz, 1H), 6.94 (d, $J=10.0$ Hz, 1H), 7.23 (d, $J=8.4$ Hz, 1H), 7.25–7.34 (m, 5H), 7.50 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3, 34.7, 39.7, 42.2, 44.0, 48.0, 55.7, 74.1, 110.9, 123.4, 126.8, 127.7, 127.9, 128.5, 129.2, 133.4, 136.8, 145.5, 155.0, 158.5, 170.5, 200.0; IR (neat) cm^{-1} 3428, 2938, 1672, 1635; MS (EI, 70 eV) *m/z* 391 (M^+), 91 (base); HRMS calcd for $C_{24}H_{25}NO_4^+$: 391.1784, found 391.1773.

3.1.10. Oxylycoramone (23).[37] To s solution of compound **22** (29 mg, 0.074 mmol) was added $SnCl_4$ (72 mg, 0.27 mmol) in CH_2Cl_2 (5 mL). After 30 min, the mixture was evaporated and partitioned with CH_2Cl_2 (20 mL) and $NH_{3(conc)}$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford compound **23** (16.7 mg, 75%) as a light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.80–1.88 (m, 1H), 1.92–1.99 (m, 1H), 2.01–2.08 (m, 2H), 2.17–2.22 (m, 1H), 2.45 (td, $J=7.0$, 2.2 Hz, 1H), 2.76 (dd, $J=8.6$, 1.4 Hz, 1H), 2.99 (dd, $J=8.6$, 1.4 Hz, 1H), 3.13 (s, 3H), 3.15–3.20 (m, 1H), 3.67–3.78 (m, 1H), 3.88 (s, 3H), 4.91 (s, 1H), 6.87 (d, $J=8.4$ Hz, 1H), 7.39 (d, $J=$

8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8, 35.8, 36.7, 40.7, 43.0, 48.0, 49.5, 56.0, 91.0, 112.3, 123.8, 123.9, 130.7, 146.1, 146.6, 168.9, 207.8; IR (neat) cm^{-1} 2928, 1719, 1636; MS (EI, 70 eV) *m/z* 301 (M^+, base); HRMS calcd for $C_{17}H_{19}NO_4^+$: 301.1314, found 301.1301.

3.1.11. Lycoramine (2).[37,38] To a solution of **23** (20 mg, 0.066 mmol) in THF (15 mL) was added LAH (5 mg, 0.13 mmol) and heated at reflux for 24 h. The mixture was evaporated and the residue was chromatographed (silica gel; CH_2Cl_2/MeOH 8:1) to afford **2** (10 mg, 53%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51–1.56 (m, 1H), 1.63–1.71 (m, 1H), 1.73–1.80 (m, 2H), 1.83–1.89 (m, 1H), 1.91–1.98 (m, 1H), 2.36 (s, 3H), 2.34–2.49 (m, 2H), 3.04 (d, J=14.4 Hz, 1H), 3.21 (t, J=12.8 Hz, 1H), 3.62 (d, J=14.8 Hz, 1H), 3.81 (s, 3H), 4.01 (d, J=14.8 Hz, 1H), 3.99–4.05 (m, 1H), 4.34 (s, 1H), 6.57 (d, J=8.4 Hz, 1H), 6.63 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 27.7, 31.0, 31.6, 41.5, 46.7, 54.0, 55.9, 60.3, 65.4, 90.0, 110.8, 122.0, 128.1, 136.2, 144.3, 146.0; IR (neat) cm^{-1} 3365, 2932, 1506; MS (EI, 70 eV) *m/z* 289 (M^+, base); HRMS calcd for $C_{17}H_{23}NO_3^+$: 289.1678, found 289.1678.

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