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A Late-Stage Functionalization Approach to Derivatives of the Pyrano[3,2-*a*]carbazole Natural Products

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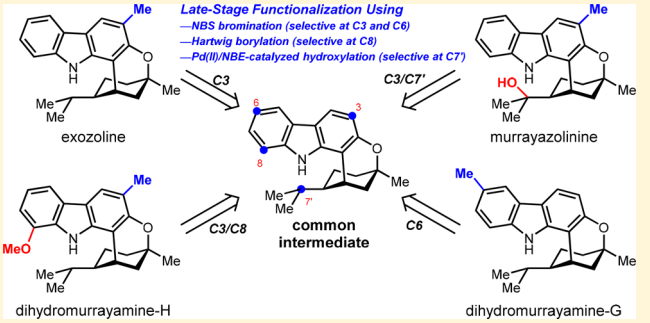
Supporting Information

ABSTRACT: Site-selective late-stage functionalizations of a pyrano[3,2-*a*]carbazole core related to the murrayamine natural products is reported. Specifically, selective C3 and C6 bromination has been achieved as well as C8 borylation. These functionalizations set the stage for access to a variety of natural products as well as their derivatives.



The pyrano[3,2-*a*]carbazole natural products are a well-known family of compounds that include the murrayamines, exozoline, mahanimbine, murrayazolinine, and murrayacinine (see Figure 1).[1−4] These molecules are characterized by a carbazole core and a chromene unit (e.g., as in murrayacinine, **6**) that may be further transformed into a bridged bicycle consisting of pyran and cyclohexane units (as in **1**−**5**).

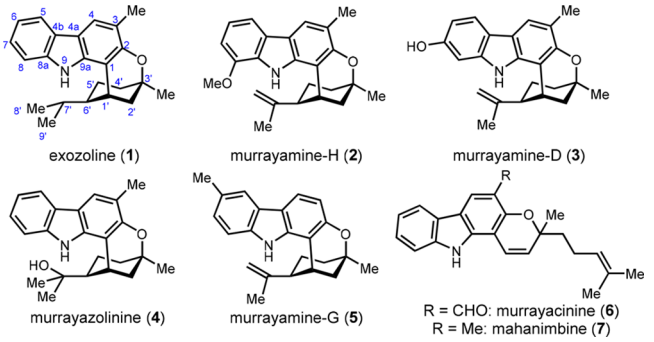


Figure 1. Selected natural products in the pyrano[3,2-*a*]carbazole family.

In addition to the carbazole and bridged rings that are found in these natural products, they also often possess a methyl group or an oxidized variant thereof (e.g., a formyl group) at C3 (see **1** for numbering). Methyl substituents are found in a wide range of bioactive molecules including natural products and can contribute significantly to their bioactivity.[5,6] The biological activity of pyrano[3,2-*a*]carbazole natural products includes anti-inflammatory, antimicrobial, antiulcer, antiplatelet aggregation, and antioxidant and anticancer activities.[7−10] This activity has primarily been explored only for molecules in this family that bear a methyl group at C3. It may be the case that the introduction of methyl groups or other substituents at other locations on these molecules could lead to novel or enhanced activity.

For example, the introduction of additional methyl groups on pharmaceutically active molecules can imbue them with conformations that enhance their activity, as well as increase their hydrophilicity and solubility. On the basis of the emerging importance of this "magic methyl" effect on biological activity as recently reviewed by Cernak et al.,[11] we wondered whether the bioactivity of the pyrano[3,2-*a*]-carbazole natural products could be varied or further enhanced by changing the group at C3. For example, an isotopically labeled variant of the methyl group as well as a range of heteroatoms, alkyl, aryl, alkenyl, and alkynyl groups could be introduced at a late stage.

We sought to test the importance of substitution to biological activity on the carbazole core of the exozoline-type natural products by designing a common intermediate that would enable late-stage installation of different groups at C3. We chose to focus on a subset of natural products for this study (**1**−**5**) that display the range of substituents found in the entire family (i.e., at C3, C6, C7, and C8). In addition to a late-stage functionalization at C3, an approach to all the targeted molecules from a common intermediate would require the identification of methods that also achieve C6−C8 functionalization.

To achieve these goals, we envisioned a series of site-selective functionalization reactions on common intermediate **8** (Figure 2). For example, bromination at C3 of **8** would set the stage for a variety of cross-coupling reactions including Suzuki, Sonogashira, Heck, Stille, and Kumada processes.

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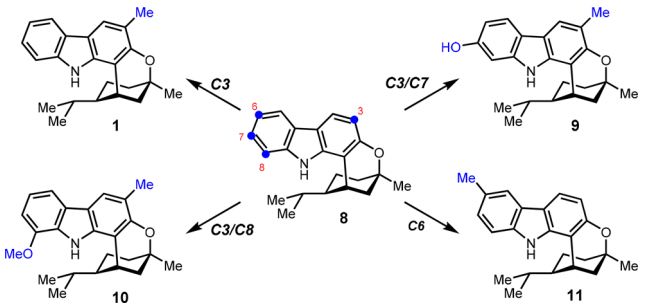


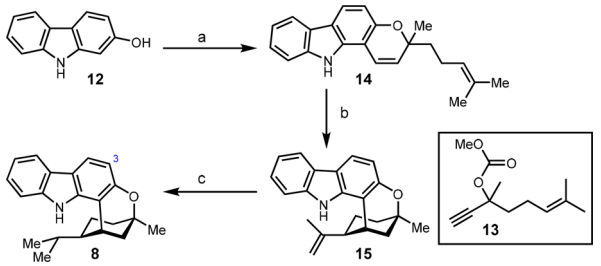
Figure 2. Potentially accessible exozoline derivatives from common intermediate **8**.

Alternatively, the ability to effect position-selective bromination at C6 of **8** would make possible a similar range of substitutions at this position as well. Borylation at C8 of **8** would set the stage for oxygenation at this position, which would lead to natural product derivatives such as dihydromurrayamine H (**10**). Finally, cine substitution of C8-borylated intermediates (e.g., using a borono-Catellani process)[12] could enable us to install substituents at C7.

■ PREPARATION OF COMMON INTERMEDIATE 8

Common intermediate **8** was readily prepared by adapting the known procedure for the preparation of exozoline reported by Knölker et al.[2,3,13] Commercially available 2-hydroxycarbazole (**12**, Scheme 1) was treated with carbonate **13**[14] in the

Scheme 1. Preparation of Common Intermediate 8 (All Compounds Are Racemic)[a]



[a](a) **13**, DBU, CuI, ACN, rt, o/n, then PhMe, 110 °C, o/n, 50% (97%); (b) (±)-CSA, PhMe, 40 °C, 41.5 h, 99%; (c) H_2, Pd/C, MeOH/DCM, 91%.

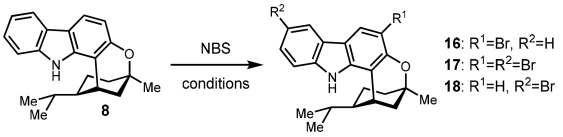
presence of CuI and DBU to form a phenol ether intermediate, which following a Claisen rearrangement provided **14**, bearing a chromene unit. Treatment of **14** with (±)-camphorsulfonic acid ((±)-CSA) effected an acid-mediated cyclization to afford **15**. Hydrogenation of the isopropenyl group of **15** using H_2 with Pd/C gave **8** in 45% yield over the three steps.

■ FUNCTIONALIZATION AT C3 AND C6 OF 8

Our plans to functionalize the carbazole core of **8** commenced with an attempted lithiation at C3 using *n*-BuLi, *s*-BuLi, or *t*-BuLi. It was anticipated that the ethereal oxygen atom at C2 of **8** would favor deprotonation at C3. However, the acidic carbazole N−H group necessitated the use of an excess of these bases. In all cases, only starting material was recovered upon quenching the presumed dianion intermediate with a range of electrophiles.

In the pursuit of milder conditions that would obviate the need for protection of the carbazole N−H group, we opted instead to investigate bromination, given the emerging successes of site-selective halogenations of carbazoles and the benzenoid portion of indoles.[15] Treating **8** with 1 equiv of NBS in acetonitrile at room temperature led smoothly to bromide **16** in 92% yield (entry 1, Table 1). Furthermore,

Table 1. Bromination of 8 Using *N*-Bromosuccinimide (NBS)



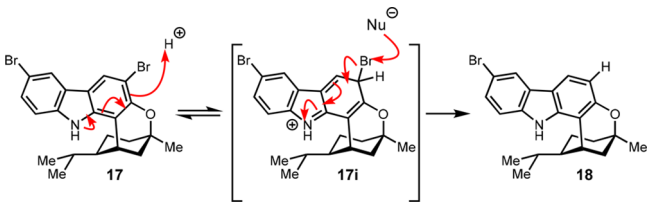
					yield[a] (%)		
entry	NBS (equiv)	solvent	temp	time	**16**	**17**	**18**
1	1	ACN	rt	<1 min	92	–	–
2	2	ACN	rt	<1 min	–	99	–
3	1	ACN	100 °C	o/n	–	32	11
4	2	ACN	100 °C	o/n	–	30	25

[a]Isolated yield.

upon treating **8** with 2 equiv of NBS, we observed the formation of the dibrominated product (**17**) in quantitative yield (entry 2). Interestingly, upon increasing the temperature of the bromination reaction to 100 °C, a mixture of **17** and **18** was obtained in moderate combined yield (entry 3). The use of a larger amount of NBS (2 equiv) under identical conditions led to a modest increase in the amount of **18** that was obtained (entry 4).

We hypothesize that C6-brominated **18** arises from C3, C6 dibrominated **17** by a protonation event at C3 (see Scheme 2). Addition of a nucleophile to the Br atom at C3 of the protonated intermediate (**17i**) would then restore the pyrano[3,2-*a*]carbazole nucleus.

Scheme 2. Possible Mechanism of C6 Bromination



On this basis, it was anticipated that introducing an acid during the bromination of **16** could increase the conversion to bromide **18**. Consistent with this hypothesis, when bromide **16** was treated with 1 equiv of NBS in AcOH at 100 °C for 5 min (Table 2, entry 2), it was completely converted to dibromide **17** (determined by TLC and subsequent ^{1}H NMR analysis). After 16 h at this temperature, a 1:1 ratio of C3 debrominated product **18** and dibromide **17** was observed (^{1}H NMR). Alternatively, adding 1 equiv of TMSCl during the bromination[16] of **16** (Table 2, entry 3) also led to some formation of **18**. On the other hand, the introduction of Ac_2O or HCl during the bromination of **16** only resulted in the formation of **17** (i.e., without the attendant debromination to give **18**; entries 4 and 5). Interestingly, **16** was recovered unchanged when subsequent bromination was attempted in HBr (entry 6). However, with HI as a mediator, we observed the C3 debromination to provide common intermediate **8**.

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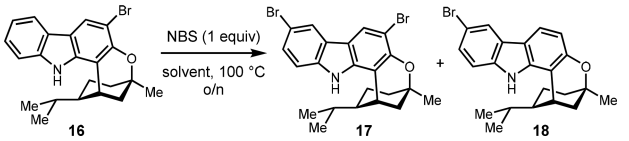
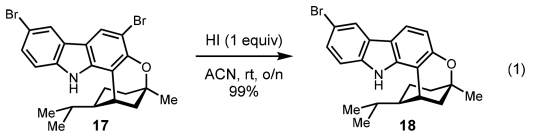
Table 2. Acid-Mediated Debromination Studies



entry	solvent[a]	conversion (%)	17:18[b]
1	ACN	100	1:0.2
2	AcOH	100	1:1
3[c]	ACN	100	1:1
4	Ac_2O	100	1:0
5	HCl	30	1:0
6	HBr	0	NA
7	HI	100	–[d]

[a][0.05 M]. [b]NMR ratio. [c]TMSCI (1 euqiv) was added. [d]only C3 debromination occurred.

Finally, treating **17** with 1 equiv of HI at 23 °C directly provided **18** in quantitative yield (eq 1). Overall, using a combination of NBS with acid additives, we are able to effect selective brominations at C3 and/or C6.

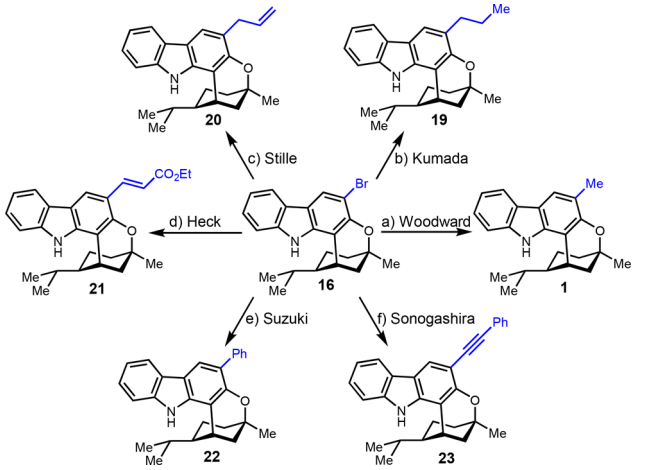


(1)

With bromide **16** in hand, we examined its conversion to exozoline (**1**) using several cross-coupling reactions to install the requisite methyl group. First, a Suzuki-type methyl coupling with trimethylboroxine (TMB)[17] using $Pd(PPh_3)_4$ and K_2CO_3 provided **1** in 41% yield (Table 3, entry 1). With Cs_2CO_3 as a base (entry 2), we observed only trace amounts of **1**. Surprisingly, with Cs_2CO_3 as the base but using Pd_2dba_3 and BF_3CH_3K as the cross-coupling partner, the desired product was obtained in 76% yield (entry 3). We have also explored the use of bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]-octane (DABAL-Me_3), which was reported by Woodward et al.,[18] as an effective cross-coupling partner for the introduction of methyl groups. While initial studies only yielded 43% of **1** (Pd_2dba_3 (1.5 mol %), DABAL-Me_3 (0.8 equiv), and XPhos (3 mol %) in THF; entry 4), increasing the amount of DABAL-Me_3 to 2 equiv gave **1** in quantitative yield (entry 5).

Cross-coupling of bromide **16** using a combination of Pd_2dba_3 (1.5 mol %) and XPhos (3.0 mol %) also worked well for Suzuki and Stille reactions to provide **22** and **20** in 99% and 62% yield, respectively (Scheme 3). However, for Kumada,

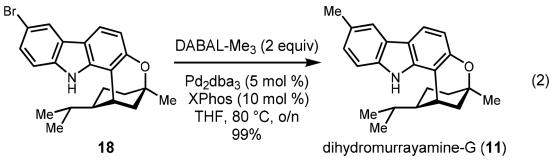
Scheme 3. Functionalization at C3[a]



[a](a) $Pd_2(dba)_3$, XPhos, DABAL-Me_3, THF, 80 °C, 4 h (99%); (b) $Pd_2(dba)_3$, XPhos, *i*-PrMgBr, THF, 80 °C, o/n, (78%); (c) $Pd_2(dba)_3$, XPhos, allyltributylstannane, THF, 80 °C, o/n, (62%); (d) $Pd_2(dba)_3$, XPhos, ethyl acrylate, THF, 80 °C, o/n, (99%); (e) $Pd_2(dba)_3$, XPhos, $PhB(OH)_2$ THF, 80 °C, o/n, (83%); (f) $Pd_2(dba)_3$, XPhos, phenylacetylene, THF, 80 °C, o/n (99%).

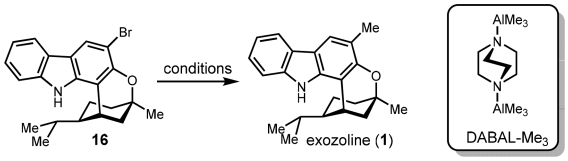
Heck, and Sonogashira-type cross-couplings, a higher loading of the catalyst (10 mol % Pd_2dba_3) and ligand (20 mol % XPhos) were necessary in order to obtain high yields of **19**, **21**, and **23**.

Using the conditions that provide **18** in high yield (i.e., **17** → **18**; eq 1), we have prepared reasonable amounts of **18** to investigate its cross-coupling. For example, in an initial study, using our optimal conditions for methyl cross-coupling (5 mol % Pd_2dba_3, 10 mol % XPhos) dihydromurrayamine G (**11**) was obtained from **18** in 99% yield (eq 2).



(2)

Table 3. Optimization of Methyl Cross-Coupling Reaction



entry	reagent (equiv)	catalyst	additive	solvent	temp	time	yield[a]
1	TMB (1.2)	$Pd(PPh_3)_4$	K_2CO_3	dioxane	reflux	o/n	41%
2	TMB (1.2)	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane	reflux	o/n	trace
3	$BF_3CH_3^-K^+$(1.0)	$Pd_2(dba)_3$	Cs_2CO_3	dioxane	reflux	6 h	76%
4	DABAL-Me_3 (0.8)	$Pd_2(dba)_3$	XPhos	THF	reflux	o/n	43%
5	DABAL-Me_3 (2.0)	$Pd_2(dba)_3$	XPhos	THF	reflux	4 h	99%

[a]Isolated yield.

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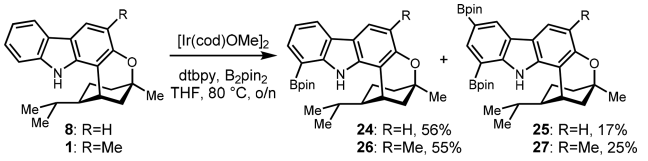
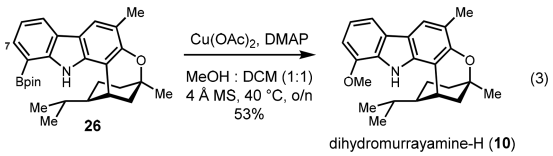
FUNCTIONALIZATION AT C8 OF 8

We successfully effected C8-selective late-stage functionalization of **8** using the Hartwig–Miyaura borylation[19] protocol (Scheme 4). Using $[Ir(OMe)COD]_2$ (5 mol %), dtbpy (10 mol %), and B_2pin_2 (2 equiv), **8** was borylated to give pinacolboronic ester **24** (56% yield) along with bis-boronic ester **25** (17% yield). We have also investigated the late-stage functionalization of exozoline (**1**), which bears a methyl group at C3. A selectivity trend for borylation similar to the case of **8** was observed here as well (see **26**/**27**). Borylation at the C8 position of the pyrano[3,2-*a*]carbazole system is likely directed by coordination to the nitrogen atom, consistent with observations on the indole system as reported by Maleczka, and Smith et al.[20] To improve the selectivity for C8 borylation, we attempted to install a directing group on the carbazole nitrogen. Unfortunately, we were unable to install a directing group due to pronounced steric hindrance presumably resulting from peri interactions as well as the isopropyl moiety. Regardless, the borylation yields that we obtain with **8** are comparable to those observed in silyl-directed iridium(III) borylations of typical carbazole systems reported by Hartwig et al.[21]

Scheme 4. Borylation at C6 and C8



Compound **26** was easily converted to dihydromurrayamine-H (**10**) in 53% yield using $Cu(OAc)_2$ and DMAP in $MeOH/H_2O$ in accord with the protocol of Sperry (eq 3).[22]

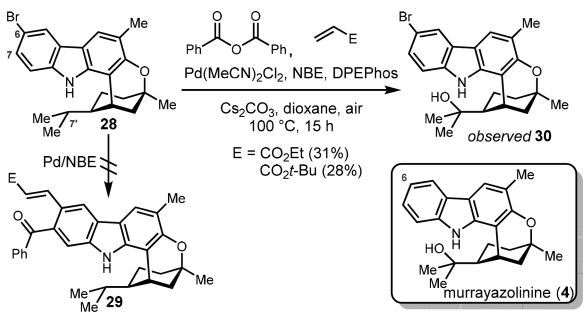


We then attempted to use **26** to functionalize at C7 using a borono-Catellani-type reaction ($Pd(OAc)_2$/NBE).[12] Unfortunately, **26** decomposed under the conditions attempted for cine functionalization at C7.

HYDROXYLATION AT C7′

In our attempts to functionalize **28**[23] at C7 (Scheme 5), we envisioned cine functionalization by exploiting the C6 bromine using a bromo-Catellani-type reaction on the basis of the precedent of Dong and co-workers.[24−26] In general, no reaction was observed using $Pd(OAc)_2$/NBE as catalyst. However, using $Pd(MeCN)_2Cl_2$/NBE with benzoyl anhydride and *tert*-butyl acrylate or ethyl acrylate,[25−27] we instead observed small amounts of hydroxylation at C7′ of isopropyl-containing **28** to furnish alcohol **30**, which is structurally related to the natural product murrayazolinine (**4**).[28] In addition, when exozoline (**1**) was treated under the same conditions, murrayazolinine (**4**) was isolated in 16% yield. Further studies to effect selective and high yielding hydroxylation at C7′ of related compounds are the subject of future studies in our laboratories.

Scheme 5. Synthesis of Alcohol 30



CONCLUSION

In conclusion, we report studies directed toward the late-stage functionalization of the pyrano[3,2-*a*]carbazole scaffold related to alkaloids in the murrayamine family using selective brominations (at C3 and C6) and borylations (at C8) from a common intermediate (**8**). The site-selective bromination and borylations have enabled the installation of many other functional groups at a late-stage, setting the stage for structure–activity relationship studies inspired by the "magic methyl" effect described for various pharmaceutically relevant scaffolds. Attempts to functionalize at C7 inadvertently identified conditions for hydroxylation at C7′ that pave the way to access murrayazolinine-type compounds bearing the characteristic isopropenyl group.

EXPERIMENTAL SECTION

General Experimental Methods. *i. Solvents and Reagents.* Commercial reagents were used without additional purification. Acetonitrile (ACN), tetrahydrofuran (THF), toluene (PhMe), methanol (MeOH), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns in a Glass Contour solvent purification system. *n*-BuLi solution, *s*-BuLi solution, *t*-BuLi solution, and Grignard solutions were purchased in Sure/Seal bottles and used directly. 1,4-Dioxane was purchased in an AcroSeal bottle (99.5%, anhydrous, stabilized, over 4 Å molecular sieves) and additionally sparged with N_2 prior to use.

ii. Reaction Setup, Monitoring, and Product Purification. Reactions were carried out in flame- or oven-dried glassware under a positive pressure of N_2 in anhydrous solvents using standard Schlenk techniques. Reactions run at room temperature (22–23 °C) were controlled by an IKA temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored using a combination of LC/MS analysis (Shimadzu LCMS-2020 (UFLC) equipped with the LC20AD solvent delivery system, a SPD-20AV prominence UV/vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 mm × 50 mm)) and thin layer chromatography (TLC) on EMD Millipore silica gel plates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). Visualization of the developed plates was performed under UV light (254 nm) irradiation, and subsequent gentle heating with *p*-anisaldehyde stain. Purification and isolation of products were performed using silica gel chromatography (both column and preparative thin layer chromatography). Flash column chromatography was performed with either glass columns using Silicycle silica gel (40–63 μm particle size) or with a Yamazen Smart S4 Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, Premium Universal columns using ACS grade solvents. Organic solutions were concentrated under reduced pressure on a Heidolph or Büchi temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser.

iii. Analytical Instrumentation. NMR spectral data were obtained using deuterated solvents obtained from Cambridge Isotope

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Laboratories, Inc. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AV-300, AVB-400, AVQ-400, AV-500, DRX-500, AV-600, or AV-700 MHz spectrometer using $CDCl_3$, CD_3OD, or C_6D_6, typically at 20−23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$).[29] Data for ^{1}H NMR spectroscopy are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, br d = broad doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets, ddt = doublet of doublets of triplets, dddd = doublet of doublets of doublets of doublets, td = triplet of doublets, tt = triplet of triplets, qd = quartet of doublets), coupling constant (Hz), integration. Data for ^{13}C NMR spectroscopy are reported in terms of chemical shift (δ ppm). IR spectroscopic data were recorded on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Samples are loaded onto the diamond surface as a solution in organic solvent, and the data acquired after the solvent had evaporated. Mass spectral data were obtained from the Catalysis Facility of Lawrence Berkeley National Laboratory (supported by US Department of Energy under contract no. DE-AC02-05CH11231), on a PerkinElmer AxION 2 UHPLC-TOF system (ESI). Data acquisition and processing were performed using the XcaliburTM software.

Synthesis of Common Intermediate 8 in Scheme 1. *3,7-Dimethyloct-6-en-1-yn-3-yl Methyl Carbonate (13).* 6-Methyl-5-hepten-2-one (5.0 g, 40 mmol) was dissolved in THF (40 mL, 1 M) in a round-bottomed flask equipped with a magnetic stir bar and cooled in an acetone/dry ice bath. Ethynylmagnesium bromide solution (0.5 M in THF, 0.10 L, 50 mmol) was added dropwise over 30 min. The reaction mixture was stirred in the bath for 30 min and then allowed to warm gradually to room temperature over 1 h. The resulting mixture was cooled in an acetone/dry ice bath again, and methyl chloroformate (6.1 mL, 79 mmol) was added dropwise over 15 min. The reaction mixture was stirred in the bath for 30 min and then allowed to warm gradually to room temperature over 2.5 h. The reaction mixture was quenched by the addition of NH_4Cl (saturated aqueous, 20 mL) and $NaHCO_3$ (saturated aqueous, 20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 1−5% EtOAc in hexanes) to provide **13** as a yellow oil (7.1 g, 34 mmol, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (dddd, J = 8.6, 5.8, 2.9, 1.4 Hz, 1H), 3.81 (s, 3H), 2.64 (d, J = 0.9 Hz, 1H), 2.34−2.13 (m, 2H), 2.08−1.96 (m, 1H), 1.96−1.82 (m, 1H), 1.76 (d, J = 1.1 Hz, 3H), 1.72 (s, 3H), 1.66 (s, 3H). Spectroscopic data for this compound were identical to those reported.[2,13]

3-Methyl-3-(4-methylpent-3-en-1-yl)-3,11-dihydropyrano[3,2-a]carbazole (14). 2-Hydroxycarbazole (**12**) (4.4 g, 24 mmol), carbonate **13** (9.3 mL, 48 mmol), and CuI (23 mg, 0.12 mmol) were dissolved in acetonitrile (0.80 L, 0.030 M) in a round-bottomed flask equipped with a magnetic stir bar. DBU (11 mL, 71 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 16 h, then concentrated in vacuo, and diluted with EtOAc (40 mL). The solution mixture was washed with HCl (1 M aqueous solution, 10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude extract was dissolved in toluene (0.40 L, 0.060 M) and then heated at reflux for 24 h. The reaction mixture was concentrated in vacuo to removed toluene. The residue was purified by column chromatography (eluting with 0−5% EtOAc in hexanes) to provide **14** as a yellow solid (3.8 g, 12 mmol, 50%); mp 82−84 °C; IR (thin film): 3459, 2925, 2866, 1069, 1457, 1305, 888, 738 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.96−7.93 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 9.4 Hz, 1H), 5.67 (d, J = 9.7 Hz, 1H), 5.14−5.09 (m, 1H), 2.20−2.15 (m, 2H), 1.84−1.77 (m, 1H), 1.78−1.71 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46 (s, 3H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 152.0, 139.6, 136.4, 131.9, 128.9, 124.6, 124.2, 124.1, 120.6, 119.9, 119.6, 117.6, 117.4, 110.6, 109.8, 104.7, 78.5, 41.0, 26.1, 25.8, 22.9, 17.8; HRMS (ESI/TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{24}NO$ 318.1852; found 318.1855.

(1R,2S,5R)-5-Methyl-2-(prop-1-en-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (15). Chromene **14** (1.3 g, 4.2 mmol) was dissolved in toluene (0.14 L, 0.030 M) in a round-bottomed flask equipped with a magnetic stir bar. (±)-CSA (0.10 g, 4.2 mmol) was added, and the solution was heated in an oil bath at 60 °C for 19 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to remove toluene. The residue was transferred to a separatory funnel using EtOAc as a solvent, then washed with $NaHCO_3$ (saturated aqueous, 15 mL), and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (eluting with 0−5% EtOAc in hexanes) to provide **15** as a light brown solid (1.3 g, 4.1 mmol, 99%); mp 141−142 °C; IR (thin film): 3416, 2967, 2918, 1457, 1081, 738 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 7.81 (br s, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 4.84 (s, 1H), 4.75 (s, 1H), 3.42 (s, 1H), 2.59 (br d, J = 12.2 Hz, 1H), 2.13 (br d, J = 10.4 Hz, 1H), 2.09−2.02 (m, 1H), 1.97−1.91 (m, 1H), 1.71−1.60 (m, 3H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 155.5, 149.9, 139.9, 139.5, 124.4, 124.0, 119.5, 119.33, 119.31, 115.6, 112.3, 110.4, 109.1, 105.9, 74.3, 48.7, 39.8, 37.6, 36.1, 29.0, 23.2, 21.7; HRMS (ESI/TOF) m/z: [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO$ 340.1672; found 340.1670.

(1R,2R,5R)-2-Isopropyl-5-methyl-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (8). A mixture of compound **15** (0.80 g, 2.5 mmol) and Pd/C (10 wt %, 0.27 g, 0.25 mmol) was suspended in MeOH/DCM (4:1, 0.10 L) in a round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was sparged with H_2 (balloon, 1 atm) for 15 min and then allowed to stir at room temperature for 16 h. The reaction mixture was filtered over a plug of Celite, which was rinsed with EtOAc (3 × 10 mL). The combined organic filtrates were concentrated in vacuo and purified by column chromatography (eluting with 5% EtOAc in hexanes) to provide **8** as an amorphous white solid (0.74 g, 2.3 mmol, 91%); IR (thin film): 3474, 2927, 2868, 1611, 1458, 1217, 738 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.93 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 3.46 (s, 1H), 2.09 (d, J = 13.7 Hz, 1H), 1.98−1.88 (m, 2H), 1.65 (d, J = 13.5 Hz, 1H), 1.60−1.53 (m, 1H), 1.49−1.42 (m, 2H), 1.42 (s, 3H), 1.30 (d, J = 6.1 Hz, 3H), 1.19 (qd, J = 13.1, 4.5 Hz, 1H), 0.68 (d, J = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.8, 139.7, 139.2, 124.3, 124.0, 119.6, 119.3, 119.2, 115.7, 110.3, 109.4, 106.1, 74.3, 49.9, 40.3, 37.3, 32.0, 29.7, 28.9, 22.8, 22.7, 20.1; HRMS (ESI/TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{26}NO$ 320.2009; found 320.2008.

Procedures for Bromination Reactions Using NBS. *C3-Monobromide (16).* Compound **8** (0.74 g, 2.3 mmol) was dissolved in acetonitrile (46 mL, 0.050 M) in a round-bottomed flask equipped with a magnetic stir bar. NBS (0.41 g, 2.3 mmol) was added to the clear yellow solution at room temperature. The reaction mixture was immediately quenched with H_2O (15 mL). The resulting milky mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 5% EtOAc in hexanes) to provide **16** as an amorphous white solid (0.90 g, 2.1 mmol, 92%); IR (thin film): 3460, 2949, 2869, 1610, 1447, 1380, 1221, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 3.45 (d, J = 3.4 Hz, 1H), 2.19−2.11 (m, 1H), 1.95 (dd, J = 13.0, 2.7 Hz, 1H), 1.89 (dt, J = 13.0, 3.3 Hz, 1H), 1.68−1.62 (m, 1H), 1.62−1.53 (m, 1H), 1.52−1.44 (m, 4H), 1.43−1.36 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 1.14 (qd, J = 13.2, 4.5 Hz, 1H), 0.68 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 151.5, 139.4, 138.8, 124.8, 123.4, 122.6, 120.0, 119.5, 116.6, 110.5, 107.6,

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102.9, 75.8, 50.0, 40.2, 37.3, 32.6, 29.8, 28.7, 22.9, 22.7, 20.1; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}{}^{79}BrNO$ 398.1114; found 398.1115.

*C3,C6-Dibromide (**17**).* Compound **8** (50 mg, 0.16 mmol) was dissolved in acetonitrile (3.0 mL, 0.050 M) in a round-bottomed flask equipped with a magnetic stir bar. NBS (56 mg, 0.31 mmol) was added to the clear yellow solution at room temperature. The solution mixture was immediately quenched with H_2O (1.0 mL). The resulting milky mixture was extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 5% EtOAc in hexanes) to provide **17** as an amorphous white solid (74 mg, 0.16 mmol, 99%); IR (thin film): 3468, 2926, 2868, 1618, 1439, 1078, 889 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.77 (br s, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 3.42 (br q, J = 3.1 Hz, 1H), 2.15 (br ddt, J = 14.0, 4.9, 2.4 Hz, 1H), 1.95 (dd, J = 13.0, 2.7 Hz, 1H), 1.87 (dt, J = 13.0, 3.2 Hz, 1H), 1.65 (br d, J = 13.7 Hz, 1H), 1.60−1.54 (m, 1H), 1.52−1.44 (m, 4H), 1.36 (ddt, J = 12.6, 8.7, 6.4 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.12 (qd, J = 13.2, 4.5 Hz, 1H), 0.67 (d, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 151.3, 138.5, 137.2, 126.6, 124.4, 122.0, 121.5, 114.8, 111.9, 111.1, 106.9, 102.7, 75.2, 49.1, 39.4, 36.4, 31.8, 29.1, 27.8, 22.1, 21.8, 19.3; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{24}{}^{79}Br_2NO$ 476.0219; found 476.0217.

*C6-Monobromide (**18**).* Compound **17** (39 mg, 0.083 mmol) was dissolved in acetonitrile (1.7 mL, 0.050 M) in a reaction tube equipped with a magnetic stir bar. HI solution (57 wt % in H_2O, 11 μL, 0.083 mmol) was added at room temperature. The reaction mixture was stirred at room temperature overnight, then quenched with $NaHCO_3$ (saturated aqueous, 1.0 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 5% EtOAc in hexanes) to provide **18** as a white solid (33 mg, 0.083 mmol, >99%); mp 169−170 °C; IR (thin film): 3449, 2947, 2925, 2866, 1619, 1557, 1217, 803 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.03 (d, J = 1.8 Hz, 1H), 7.78 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 8.4, 1.9 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 3.42 (br s, 1H), 2.09 (br d, J = 13.8 Hz, 1H), 1.95−1.88 (m, 2H), 1.65 (br d, J = 13.6 Hz, 1H), 1.60−1.52 (m, 1H), 1.49−1.43 (m, 1H), 1.41 (s, 3H), 1.41−1.36 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H), 1.17 (qd, J = 13.2, 4.6 Hz, 1H), 0.69 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 156.4, 140.1, 137.8, 126.6, 126.2, 122.0, 119.4, 114.8, 112.5, 111.7, 110.0, 106.2, 74.5, 49.9, 40.3, 37.3, 32.0, 29.8, 28.9, 22.9, 22.7, 20.2; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}{}^{79}BrNO$ 398.1114; found 398.1118.

*6-Bromoexozoline (**28**).* Exozoline (**1**) (48 mg, 0.14 mmol) was dissolved in acetonitrile (3.0 mL, 0.050 M) in a reaction tube equipped with a magnetic stir bar. NBS (26 mg, 0.14 mmol) and TMSCl (18 μL, 0.014 mmol) were added at room temperature. The reaction mixture was quenched with H_2O (1.0 mL). The resulting milky mixture was extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 5% EtOAc in hexanes) to provide **28** as a white solid (59 mg, 0.14 mmol, >99%); mp 218−220 °C; IR (thin film): 3465, 2926, 1625, 1460, 1211, 1055, 892, 797 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 1.9 Hz, 1H), 7.71 (br s, 1H), 7.60 (s, 1H), 7.35 (dd, J = 8.4, 1.9 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 3.42 (br d, J = 3.1 Hz, 1H), 2.31 (d, J = 0.9 Hz, 3H), 2.10−2.03 (m, 1H), 1.95−1.84 (m, 2H), 1.66−1.52 (m, 3H), 1.49−1.35 (m, 1H), 1.41 (s, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.14 (qd, J = 13.1, 4.5 Hz, 1H), 0.67 (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.8, 138.8, 137.8, 126.3, 126.2, 121.9, 119.7, 118.7, 114.0, 112.2, 111.6, 105.7, 74.3, 50.0, 40.6, 37.3, 32.3, 29.8, 29.0, 22.9, 22.8, 20.2, 17.0; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}{}^{79}BrNO$ 412.1271; found 412.1271.

Procedures for Cross-Coupling Reactions. *Exozoline (**1**).* To an oven-dried reaction tube bromide **16** (0.30 g, 0.75 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), XPhos (11 mg, 0.023 mmol), DABAL-Me_3 (0.39 g, 1.5 mmol), and a magnetic stir bar were added. The reaction tube was sealed with a PTFE lined cap. The solids were dissolved in THF (4.4 mL, 0.17 M) and allowed to stir at 80 °C in an oil bath for 4 h. The reaction mixture was carefully quenched by H_2O (2.0 mL) and extracted with EtOAc (3 × 2.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 10% EtOAc in hexanes) to provide **1** as an amorphous white solid (0.25 g, 0.75 mmol, 99%); ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.72 (br s, 1H), 7.68 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 3.45 (br s, 1H), 2.36 (s, 3H), 2.11−2.05 (m, 1H), 1.96−1.88 (m, 2H), 1.64 (br d, J = 11.2 Hz, 1H), 1.61−1.54 (m, 1H), 1.50−1.43 (m, 2H), 1.43 (s, 3H), 1.30 (d, J = 5.9 Hz, 3H), 1.18 (qd, J = 12.9, 4.5 Hz, 1H), 0.69 (d, J = 6.0 Hz, 3H). Spectroscopic data for this compound were identical to those reported.[2]

*(1R,2R,5R)-2-Isopropyl-5-methyl-7-propyl-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**19**).* To an oven-dried reaction tube bromide **16** (30 mg, 0.075 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), XPhos (7.4 mg, 0.016 mmol) and a magnetic stir bar were added. The reaction tube was sealed with a PTFE lined cap. The reaction mixture was dissolved in THF (0.44 mL, 0.17 M), and then isopropylmagnesium bromide solution (0.75 M in THF, 0.20 mL, 0.15 mmol) was added via syringe. The resulting mixture was stirred at 80 °C in an oil bath overnight, quenched with NH_4Cl (saturated aqueous, 0.20 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 2% EtOAc in hexanes) provided **19** as a colorless oil (21 mg, 0.059 mmol, 78%); IR (thin film): 3463, 2954, 2926, 2867, 1611, 1429, 1307, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 1H), 7.71 (br s, 1H), 7.64 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.30−7.25 (m, 1H), 7.15 (t, J = 7.4 Hz, 1H), 3.45 (br s, 1H), 2.70 (t, J = 7.5 Hz, 2H), 2.05 (br d, J = 13.1 Hz, 1H), 1.95−1.86 (m, 2H), 1.73−1.65 (m, 2H), 1.62 (br d, J = 14.5 Hz, 1H), 1.60−1.51 (m, 1H), 1.47−1.40 (m, 1H), 1.40 (s, 3H), 1.35−1.30 (m, 1H), 1.29 (d, J = 5.8 Hz, 3H), 1.15 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H), 0.67 (d, J = 5.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 153.9, 139.2, 138.3, 124.4, 123.7, 122.7, 119.4, 119.2, 119.0, 114.9, 110.2, 105.6, 74.0, 50.2, 40.6, 37.4, 33.2, 32.3, 29.7, 29.0, 23.6, 23.0, 22.9, 20.2, 14.3; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{32}NO$ 362.2478; found 362.2476.

*(1R,2R,5R)-7-Allyl-2-isopropyl-5-methyl-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**20**).* To an oven-dried reaction tube bromide **16** (30 mg, 0.075 mmol), $Pd_2(dba)_3$ (1.0 mg, 0.0011 mmol), XPhos (1.1 mg, 0.0023 mmol), and a magnetic stir bar were added. The reaction tube was sealed with a PTFE lined cap. The reaction mixture was dissolved in THF (0.44 mL, 0.17 M), and then allyltributylstannane (47 μL, 0.15 mmol) was added via syringe. The resulting mixture was stirred at 80 °C in an oil bath overnight, quenched with NH_4Cl (saturated aqueous, 0.20 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 2% EtOAc in hexanes) to provide **16** as a colorless oil (17 mg, 0.047 mmol, 62%); IR (thin film): 3319, 2929, 2830, 1452, 1216, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.8 Hz, 1H), 7.72 (br s, 1H), 7.66 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 6.11 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H), 5.12 (d, J = 16.2 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 3.49 (d, J = 6.7 Hz, 2H), 3.46 (br s, 1H), 2.09−2.02 (m, 1H), 1.95−1.89 (m, 2H), 1.63 (br d, J = 12.5 Hz, 1H), 1.60−1.48 (m, 1H), 1.48−1.40 (m, 2H), 1.41 (s, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.15 (qd, J = 12.9, 4.4 Hz, 1H), 0.67 (d, J = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 153.6, 139.2, 138.5, 138.2, 124.4, 123.8, 120.2, 119.4, 119.3, 118.9, 115.1, 114.8, 110.3, 105.8, 74.2, 50.1, 40.6, 37.3, 35.3, 32.3, 29.7, 29.0, 22.9, 22.9, 20.2; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}NO$ 360.2322; found 360.2312.

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*Ethyl (E)-3-((1R,2R,5R)-2-Isopropyl-5-methyl-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazol-7-yl)acrylate (**21**).* To an oven-dried reaction tube bromide **16** (30 mg, 0.075 mmol), $Pd_2(dba)_3$ (6.0 mg, 0.0075 mmol), XPhos (7.2 mg, 0.015 mmol), K_2CO_3 (31 mg, 0.23 mmol), and a magnetic stir bar were added. The reaction was sealed with a PTFE lined cap. The reaction mixture was dissolved in THF (0.44 mL, 0.17 M), and then ethyl acrylate (16 μL, 0.15 mmol) was added via syringe. The resulting mixture was stirred at 80 °C in an oil bath overnight, quenched with NH_4Cl (saturated aqueous, 0.20 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 2−10% EtOAc in hexanes) to provide **21** as an orange oil (31 mg, 0.075 mmol, 99%); IR (thin film): 3367, 2926, 2850, 1685, 1605, 1452, 1164, 1306, 1159, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, *J* = 16.0 Hz, 1H), 8.09 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.84 (br s, 1H), 7.38−7.31 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.45 (br s, 1H), 2.13 (br d, *J* = 13.8 Hz, 1H), 1.99−1.89 (m, 2H), 1.65 (d, *J* = 14.1 Hz, 1H), 1.61−1.56 (m, 1H), 1.50−1.44 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.28−1.22 (m, 1H), 1.14 (qd, *J* = 13.2, 4.5 Hz, 1H), 0.67 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.4, 155.1, 142.1, 141.3, 139.6, 124.9, 124.2, 120.3, 119.6, 119.3, 116.1, 115.6, 115.4, 110.5, 106.2, 75.5, 60.2, 49.9, 40.3, 37.1, 32.3, 29.8, 28.8, 22.9, 22.7, 20.1, 14.6; HRMS (ESI/TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{32}NO_3$ 418.2377; found 418.2384.

*(1R,2R,5R)-2-Isopropyl-5-methyl-7-phenyl-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**22**).* To an oven-dried reaction tube bromide **16** (30 mg, 0.075 mmol), $Pd_2(dba)_3$ (1.0 mg, 0.0011 mmol), XPhos (1.1 mg, 0.0023 mmol), phenylboronic acid (18 mg, 0.15 mmol), K_2CO_3 (31 mg, 0.23 mmol), and a magnetic stir bar were added. The reaction tube was sealed with a PTFE lined cap. The reaction mixture was dissolved in THF (0.44 mL, 0.17 M). The resulting mixture was stirred at 80 °C in an oil bath overnight, quenched with NH_4Cl (saturated aqueous, 0.20 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 2−10% EtOAc in hexanes) to provide **22** as a yellow oil (25 mg, 0.063 mmol, 83%); IR (thin film): 3460, 2926, 2867, 1611, 1429, 1307, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.86 (s, 1H), 7.80 (br s, 1H), 7.70−7.65 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.35−7.27 (m, 2H), 7.22−7.16 (m, 1H), 3.52 (br s, 1H), 2.11−2.05 (m, 1H), 2.02−1.92 (m, 2H), 1.68−1.62 (m, 1H), 1.58−1.51 (m, 1H), 1.50−1.44 (m, 2H), 1.37 (s, 3H), 1.32 (d, *J* = 5.9 Hz, 3H), 1.28−1.22 (m, 1H), 0.71 (d, *J* = 5.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 152.8, 140.2, 139.4, 139.3, 130.0, 127.8, 126.1, 124.5, 124.2, 122.6, 120.6, 119.7, 119.4, 115.6, 110.4, 106.2, 74.6, 50.2, 40.4, 37.3, 32.5, 29.8, 28.7, 23.0, 22.9, 20.2; HRMS (ESI/TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{30}NO$ 396.2322; found 396.2323.

*(1R,2R,5R)-2-Isopropyl-5-methyl-7-(phenylethynyl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**23**).* To an oven-dried reaction tube bromide **16** (30 mg, 0.075 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), XPhos (7.2 mg, 0.015 mmol), CuI (1.4 mg, 0.0075 mmol), and a magnetic stir bar were added. The reaction tube was sealed with a PTFE lined cap. The reaction mixture was sparged with N_2 for 15 min and then dissolved in Et_3N (0.50 mL, 0.17 M). Phenylacetylene (17 μL, 0.15 mmol) was added via syringe. The resulting mixture stirred at 80 °C in an oil bath overnight, quenched with NH_4Cl (saturated aqueous, 1.0 mL), and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 2−5% EtOAc in hexanes) to provide **23** as a yellow oil (32 mg, 0.075 mmol, 99%); IR (thin film): 3465, 2926, 2867, 2204, 1609, 1445, 1205, 741 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (br s, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.38−7.26 (m, 5H), 7.20 (t, *J* = 7.3 Hz, 1H), 3.46 (br s, 1H), 2.19 (br d, *J* = 13.9 Hz, 1H), 2.00−1.91 (m, 2H), 1.66 (br d, *J* = 14.2 Hz, 1H), 1.62−1.54 (m, 1H), 1.50 (s, 3H), 1.46−1.38 (m, 1H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.28−1.24 (m, 1H), 1.20 (qd, *J* = 13.1, 4.4 Hz, 1H), 0.69 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 156.6, 140.0, 139.5, 131.6, 128.3, 127.5, 124.8, 124.6, 124.0, 123.4, 120.1, 119.6, 115.7, 110.5, 106.1, 104.1, 91.7, 88.1, 75.2, 50.0, 40.3, 37.2, 32.3, 29.9, 28.8, 22.9, 22.8, 20.2; HRMS (ESI/TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{30}NO$ 420.2322; found 420.2320.

Procedures for Borylation Reactions. *(1R,2R,5R)-2-Isopropyl-5-methyl-12-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**24**) and (1R,2R,5R)-2-Isopropyl-5-methyl-10,12-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**25**).* To an oven-dried reaction tube **8** (10 mg, 0.031 mmol) and a magnetic stir bar were added. The reaction tube was transferred to a nitrogen-filled glovebox. $[Ir(cod)OMe]_2$ (0.60 mg, 0.94 μmol), dtbpy (0.50 mg, 1.9 μmol), and B_2pin_2 (16 mg, 0.063 mmol) were added. The reaction tube was sealed with a PTFE lined cap and transferred out of the glovebox. The reaction mixture was dissolved in THF (0.4 mL, 0.078 M) and allowed to stir at 80 °C in an oil bath overnight. The reaction mixture was concentrated in vacuo and purified by column chromatography (eluting with 2−5% EtOAc in hexanes) to provide **24** and **25** in 73% combined yield. *Compound **24***: a colorless oil (7.8 mg, 0.018 mmol, 56%); IR (thin film): 3452, 3053, 2971, 1620, 1431, 1396, 1130, 792, 680 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.76−7.71 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.54 (br s, 1H), 2.17 (s, 1H), 2.09 (br d, *J* = 13.8 Hz, 1H), 1.94 (s, 2H), 1.66 (br d, *J* = 14.2 Hz, 1H), 1.61−1.54 (m, 1H), 1.42 (s, 6H), 1.42 (s, 3H), 1.41 (s, 6H), 1.35 (d, *J* = 5.8 Hz, 3H), 1.20 (ddd, *J* = 25.0, 12.4, 3.6 Hz, 1H), 0.70 (d, *J* = 5.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 155.8, 144.8, 139.5, 131.0, 123.2, 122.6, 119.2, 118.8, 115.3, 109.0, 106.1, 84.1, 74.2, 50.1, 40.5, 37.4, 31.8, 29.5, 29.0, 25.3, 25.0, 23.6, 23.0, 20.5; HRMS (ESI/TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{37}BNO_3$ 446.2861; found 446.2858. *Compound **25***: a colorless oil (2.4 mg, 0.0050 mmol, 17%); IR (thin film): 3488, 2973, 2927, 1600, 1394, 1328, 1141, 1086, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 8.52 (s, 1H), 8.24 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.53 (br s, 1H), 2.08 (br d, *J* = 13.9 Hz, 1H), 1.93 (d, *J* = 3.0 Hz, 1H), 1.65 (br d, *J* = 13.7 Hz, 1H), 1.55 (d, *J* = 12.5 Hz, 3H), 1.50−1.43 (m, 1H), 1.41 (s, 9H), 1.40 (s, 6H), 1.38 (s, 12H), 1.34 (d, *J* = 5.8 Hz, 3H), 1.20 (ddd, *J* = 13.3, 12.6, 4.5 Hz, 1H), 0.70 (d, *J* = 5.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 155.9, 147.1, 139.6, 138.2, 129.7, 122.9, 119.5, 115.5, 109.3, 106.2, 84.0, 83.6, 74.2, 50.2, 40.5, 37.5, 31.9, 29.5, 29.0, 25.3, 25.1, 25.0, 23.6, 23.0, 20.5; HRMS (ESI/TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{48}B_2NO_5$ 572.3713; found 572.3715.

*(1R,2R,5R)-2-Isopropyl-5,7-dimethyl-12-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**26**) and (1R,2R,5R)-2-Isopropyl-5,7-dimethyl-10,12-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4,5,13-hexahydro-1,5-methanooxocino[3,2-a]carbazole (**27**).* To an oven-dried reaction tube exozoline (**1**) (32 mg, 0.096 mmol) and a magnetic stir bar were added. The reaction tube was transferred to a nitrogen-filled glovebox. $[Ir(cod)OMe]_2$ (3.2 mg, 0.0048 mmol), dtbpy (2.6 mg, 0.0096 mmol), and B_2pin_2 (49 mg, 0.19 mmol) were added. The reaction tube was sealed with a PTFE lined cap and then transferred out of the glovebox. The reaction mixture was dissolved in THF (1.2 mL, 0.078 M) and allowed to stir at 80 °C in an oil bath overnight. The reaction mixture was concentrated in vacuo and purified by column chromatography (eluting with 0−10% EtOAc in hexanes) to provide **26** and **27** in 80% combined yield. *Compound **26***: a colorless oil (24 mg, 0.053 mmol, 55%); IR (thin film): 3452, 2971, 2927, 1620, 1369, 1130 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.68 (s, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 3.55 (br s, 1H), 2.35 (s, 3H), 2.11−2.05 (m, 1H), 1.93 (d, *J* = 2.9 Hz, 2H), 1.68−1.62 (m, 1H), 1.58 (dt, *J* = 13.0, 7.0 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 6H), 1.36 (d, *J* = 5.2 Hz, 3H), 1.31−1.13 (m, 3H), 0.71 (d, *J* = 5.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 154.1, 144.8, 138.2, 130.7, 123.2, 122.4, 119.5, 118.5,

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117.5, 114.4, 105.5, 84.0, 74.0, 50.2, 40.8, 37.4, 32.0, 29.5, 29.1, 25.3, 25.0, 23.6, 23.1, 20.5, 17.0; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{39}BNO_3$ 460.3018; found 460.3022. *Compound* **27**: a colorless oil (14 mg, 0.024 mmol, 25%); IR (thin film): 3451, 2974, 1918, 1598, 1330, 1141 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 8.50 (s, 1H), 8.22 (s, 1H), 7.70 (s, 1H), 3.52 (br s, 1H), 2.31 (s, 3H), 2.06 (br d, J = 12.7 Hz, 1H), 1.91 (d, J = 2.9 Hz, 2H), 1.67−1.51 (m, 2H), 1.44−1.36 (m, 29H), 1.33 (d, J = 5.2 Hz, 3H), 1.22−1.11 (m, 1H), 0.69 (d, J = 5.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.0, 146.8, 138.0, 137.7, 129.4, 122.8, 119.8, 117.7, 114.4, 105.5, 83.8, 83.4, 73.9, 50.0, 40.6, 37.2, 31.9, 29.3, 28.9, 25.1, 24.9, 24.9, 23.5, 22.9, 20.4, 17.0; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{50}B_2NO_5$ 586.3870; found 586.3876.

Synthesis of Dihydromurrayamine-G (11). To an oven-dried reaction tube bromide **18** (21 mg, 0.053 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.0053 mmol), XPhos (5.0 mg, 0.011 mmol) and DABAL-Me_3 (27 mg, 0.11 mmol) were charged. The reaction tube was sealed with a PTFE lined cap. The mixture was dissolved in THF (0.30 mL, 0.17 M) and allowed to stir at 80 °C in an oil bath overnight. The reaction mixture was carefully quenched by H_2O (1.0 mL) and extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 5−10% EtOAc in hexanes) to provide **11** as a white solid (18 mg, 0.053 mmol, >99%); mp 180−181 °C; IR (thin film): 3445, 2924, 2867, 1613, 1401, 1217, 802 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 1H), 7.74 (br s, 1H), 7.70 (s, 1H), 7.29−7.25 (m, 1H), 7.13 (d, J = 8.1 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 3.45 (br s, 1H), 2.51 (s, 3H), 2.09 (br d, J = 13.7 Hz, 1H), 1.98−1.91 (m, 2H), 1.65 (br d, J = 13.9 Hz, 1H), 1.61−1.52 (m, 1H), 1.49−1.44 (m, 2H), 1.42 (s, 3H), 1.30 (d, J = 5.9 Hz, 3H), 1.20 (qd, J = 13.0, 4.4 Hz, 1H), 0.68 (d, J = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 155.8, 140.0, 137.5, 128.9, 125.3, 124.5, 119.4, 119.2, 115.7, 110.0, 109.2, 106.1, 74.3, 50.0, 40.4, 37.4, 32.1, 29.8, 29.0, 22.9, 22.8, 21.6, 20.2; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}NO$ 334.2165; found 334.2173.

Synthesis of Dihydromurrayamine-H (10). To an oven-dried reaction tube **26** (21 mg, 0.046 mmol), $Cu(OAc)_2$ (8.3 mg, 0.046 mmol), DMAP (11 mg, 0.092 mmol), molecular sieves (4 Å, 0.11 g), and a magnetic stir bar were added. The resultant was dissolved in MeOH/DCM (1:1, 2.0 mL, 0.020 M) and heated to 40 °C overnight. The reaction mixture was filtered through a plug of $MgSO_4$, which was rinsed with EtOAc (2.0 mL) and then H_2O (2.0 mL), and the aqueous filtrates were extracted with EtOAc (3 × 1.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude extract was purified by column chromatography (eluting with 0−10% EtOAc in hexanes) to provide **10** as a colorless oil (8.9 mg, 0.025 mmol, 53%); IR (thin film): 3483, 2927, 2867, 1626, 1147, 1258, 1091, 781, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.63 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.79 (dd, J = 7.8, 0.8 Hz, 1H), 4.00 (s, 3H), 3.49 (br s, 1H), 2.32 (d, J = 0.9 Hz, 3H), 2.06 (br d, J = 13.2 Hz, 1H), 1.96−1.87 (m, 2H), 1.63 (br d, J = 13.5 Hz, 1H), 1.60−1.52 (m, 1H), 1.49−1.41 (m, 2H), 1.41 (s, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.15 (qd, J = 13.1, 4.4 Hz, 1H), 0.67 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.1, 145.5, 138.1, 129.2, 125.3, 119.7, 119.6, 118.0, 115.3, 112.0, 105.8, 104.4, 74.1, 55.7, 50.1, 40.7, 37.3, 32.2, 29.7, 29.1, 22.9, 22.7, 20.3, 17.0; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}NO_2$ 364.2271; found 364.2276.

Synthesis of 7-Bromomurrayazolinine (30). To an oven-dried reaction tube bromide **28** (10 mg, 0.024 mmol), $Pd(MeCN)_2Cl_2$ (0.60 mg, 2.4 μmol), DPEPhos (1.3 mg, 2.4 μmol), 2-norbornene (4.6 mg, 0.049 mmol), *tert*-butyl acrylate (6.3 μL, 0.044 mmol), benzoic anhydride (9.9 mg, 0.044 mmol), Cs_2CO_3 (26 mg, 0.078 mmol), 1,4-dioxane (0.30 mL, 0.080 M), and a magnetic sir bar were added. The resultant mixture was heated at 100 °C in an oil bath overnight, then cooled to room temperature, and filtered through a plug of Celite, which was rinsed with EtOAc (5.0 mL). The combined organic filtrates were concentrated in vacuo and purified by preparative thin-layer chromatography (20% EtOAc in hexanes) to provide **30** as a yellow oil (2.9 mg, 0.0068 mmol, 28%); IR (thin film): 3466, 3302, 2928, 2866, 1626, 1211, 891 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.66 (br s, 1H), 7.99 (d, J = 1.9 Hz, 1H), 7.59 (s, 1H), 7.33 (dd, J = 8.5, 1.9 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 3.78 (s, 1H), 2.32 (s, 3H), 2.10 (br d, J = 13.7 Hz, 1H), 1.95−1.81 (m, 4H), 1.63 (td, J = 13.3, 5.3 Hz, 1H), 1.43 (s, 4H), 1.40 (dd, J = 13.0, 4.4 Hz, 1H), 1.33 (s, 3H), 0.53 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 154.4, 139.6, 138.4, 126.4, 126.0, 121.9, 119.7, 118.3, 114.0, 112.0, 111.7, 106.0, 74.6, 74.5, 52.9, 40.5, 38.3, 33.5, 29.3, 29.0, 23.3, 23.0, 17.0; HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}{}^{79}BrNO_2$ 428.1220; found 428.1224.

Synthesis of Murrayazolinine (4). To an oven-dried reaction tube exozoline (**1**) (10 mg, 0.030 mmol), $Pd(MeCN)_2Cl_2$ (0.80 mg, 3.0 μmol), DPEPhos (1.6 mg, 3.0 μmol), 2-norbornene (5.6 mg, 0.060 mmol), ethyl acrylate (0.60 mg, 6.0 μmol), benzoic anhydride (12 mg, 0.054 mmol), Cs_2CO_3 (29 mg, 0.090 mmol), 1,4-dioxane (0.30 mL, 0.10 M), and a magnetic sir bar were added. The resultant mixture was heated to 100 °C in an oil bath overnight, then cooled to room temperature, and filtered through a plug of Celite, which was rinsed with EtOAc (5.0 mL). The combined organic filtrates were concentrated in vacuo and purified by preparative thin-layer chromatography (20% EtOAc in hexanes) to provide **4** as a pale yellow solid (1.7 mg, 4.86 μmol,16%); IR (thin film): 3315, 2926, 2852, 1666, 1458, 1312, 1213, 1161, 1055, 745 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.66 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 15.3 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 3.81 (d, J = 3.2 Hz, 1H), 2.33 (s, 3H), 2.10 (d, J = 13.5 Hz, 1H), 2.01 (d, J = 6.6 Hz, 1H), 1.86 (dd, J = 8.2, 3.6 Hz, 2H), 1.71 (s, 1H), 1.65−1.59 (m, 1H), 1.46−1.42 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.31−1.28 (m, 1H), 0.55 (s, 3H); HRMS (ESI/TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2116. Spectroscopic data for this compound were identical to those reported.[2]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00631.

^1H and ^{13}CNMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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