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# Total synthesis of makaluvamine A/D, damirone B, batzelline C, makaluvone, and isobatzelline C featuring one-pot benzyne-mediated cyclization–functionalization

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ABSTRACT

Total synthesis of pyrroloquinoline alkaloids, such as makaluvamine A/D, damirone B, batzelline C, makaluvone, and isobatzelline C, was achieved featuring a one-pot benzyne-mediated cyclization–functionalization reaction. The synthetic utility was demonstrated by the construction of the common pyrrolo[4,3,2-*de*]quinoline skeleton.



## 1. Introduction

Marine alkaloids, such as makaluvamines,[1] damirones,[1c,2] batzellines,[3] makaluvone,[1a] and isobatzellines[3b,4] are of great importance owing to their potent pharmacological activities (Fig. 1). Makaluvamine A exhibits potent in vitro cytotoxicity with an $IC_{50}$ value of 1.3 μM against human colon tumor cell line HCT116 and inhibitory activity against topoisomerase II.[1a] Damirone A and B also displays in vitro antimalarial activity with $IC_{50}$ values of 0.36 μM and 3.8 μM against chloroquine-resistant (Dd2) *Plasmodium falciparum*, respectively.[5] Batzellines and isobatzellines, isolated from the marine sponge *Batzella* sp., show cytotoxic activity based on the inhibition of topoisomerase II and, in particular, the latter compound has been found to inhibit HIV-1 envelope-mediated cell fusion with an $IC_{50}$ value of 200 nM.[3b] In addition to the significant biological activities, these compounds commonly share a characteristic tricyclic pyrrolo[4,3,2-*de*]quinoline, which has attracted a great deal of attention in the synthetic community. While syntheses of these pyrroloquinolines have been extensively investigated,[6] development of a general and efficient synthetic methodology for these molecules is still needed. Recently we have developed total synthesis of batzelline C (**3c**) and isobatzelline C (**5c**)[7] featuring a facile construction of pyrrolo[4,3,2-*de*]quinolines via a benzyne-mediated cyclization that was developed during the total synthesis of dictyodendrins.[8] In this paper we describe full details of the sequential reaction and its application to the total synthesis of makaluvamine A (**1a**), D (**1c**), damirone B (**2b**), batzelline C (**3c**), makaluvone (**4**), and isobatzelline C (**5c**).

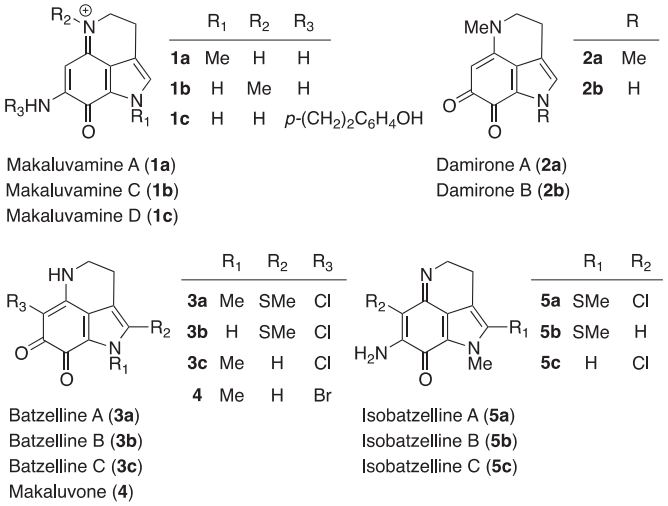


**Fig. 1.** Structure of pyrroloquinone alkaloids.

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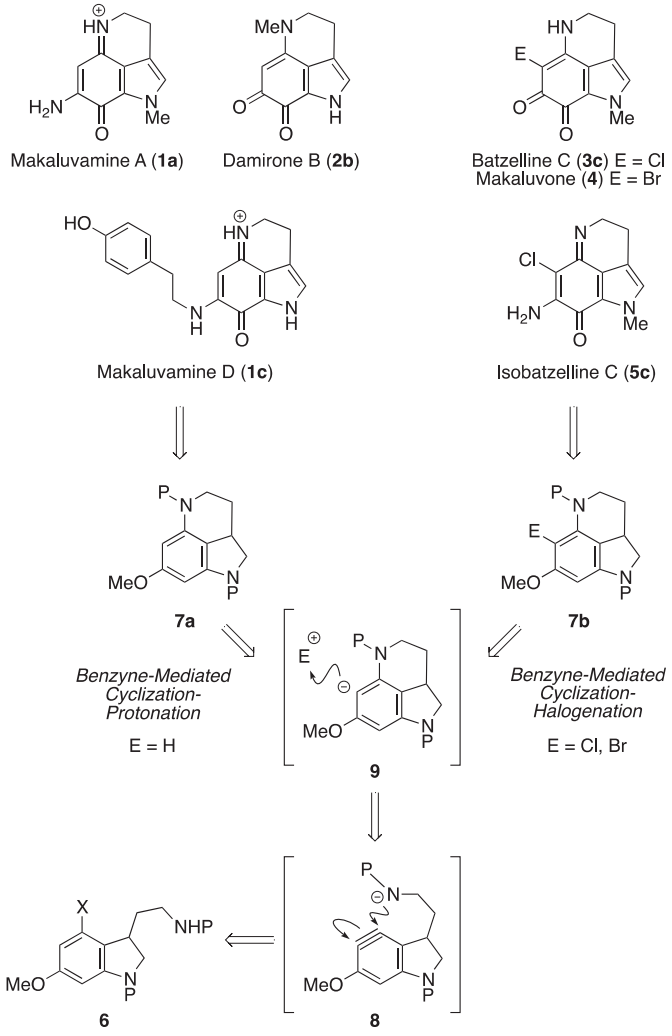
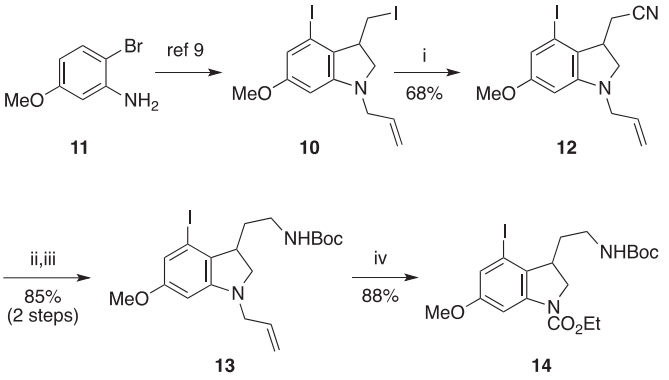
The retrosynthetic sequence in Scheme 1 demonstrates a divergent synthesis of pyrroloquinoline alkaloids using the pivotal intermediate **6**. Makaluvamine A (**1a**), D (**1c**), and damirone B (**2b**) would be synthesized from tricyclic compound **7a** via oxidation to *para*-iminoquinone/*ortho*-quinone and functional group manipulations. Key intermediate **7a** would be prepared by cyclization of benzyne **8** from the indoline **6** followed by subsequent protonation of the generated aryl anion species **9**. On the other hand, cyclization of benzyne **8** followed by trapping of the generated aryl anion species **9** with a chlorine/bromine atom should allow the regioselective halogenation to give **7b**, which is required for the synthesis of batzelline C (**3c**), makaluvone (**4**), and isobatzelline C (**5c**).




**Scheme 1.** Retrosynthetic analysis based on a benzyne-mediated reaction.

## 2. Results/discussion

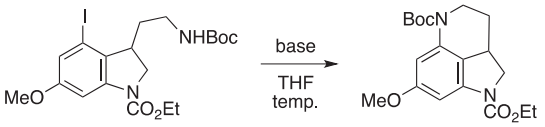
The synthesis commenced with the preparation of the known indoline **10** from *m*-anisidine derivative **11** according to the procedure by Buchwald and co-workers (Scheme 2).[9] The iodomethyl group at the 3-position of indoline **10** was homologated by treatment with potassium cyanide to provide **12**, which was then subjected to $AlH_3$ reduction followed by Boc protection to give carbamate **13**. The allyl group was then switched to the ethoxycarbonyl group by treatment with ethyl chloroformate and sodium iodide to provide the substrate **14** for the key reaction.




**Scheme 2.** Reagents and conditions; (i) KCN, $CH_3CN/H_2O$, reflux; (ii) LAH, $AlCl_3$, $Et_2O$, 0 °C; (iii) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, rt; (iv) $ClCO_2Et$, NaI, acetone, reflux.

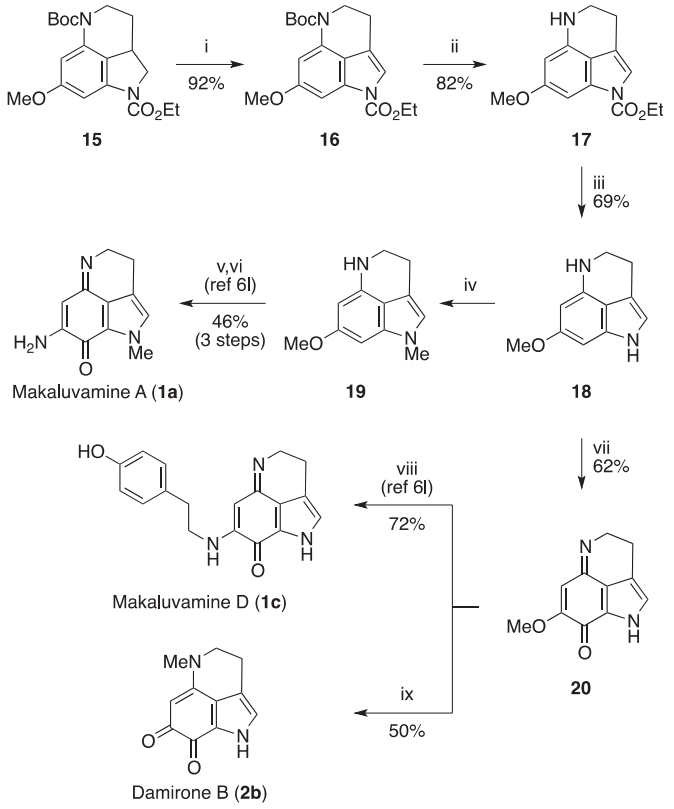
With 4-iodoindoline derivative **14** in hand, we then examined several amide bases for the benzyne-mediated construction of the pyrrolo[4,3,2-*de*]quinoline skeleton[10] (Table 1). Disappointingly, $Mg(TMP)_2\cdot 2LiBr$,[11] an optimal base in our synthesis of dictyodendrins, resulted in slow consumption of the starting material (entry 1). The use of $Mg(TMP)_2\cdot 2LiCl$,[12] also provided the desired compound **15** in low yield (entry 2). Best results were obtained when LiTMP[13] was added at −78 °C (entry 3). The use of *i*-$Bu_3Al(TMP)Li$[14] also provided **15** in moderate yield (entry 4). Related bases, such as $Me_2Zn(TMP)Li$[15] and $MeCu(TMP)CNLi_2$,[16] did not give the desired product at all with recovery of the starting material (entries 5 and 6).

**Table 1**
Exploration of bases for benzyne generation–cyclization cascade




| Entry | Base (5 equiv) | Temperature | Yield (%) |
|---|---|---|---|
| 1 | $Mg(TMP)_2\cdot 2LiBr$ | −78 °C to rt | 13 |
| 2 | $Mg(TMP)_2\cdot 2LiCl$ | −78 to 0 °C | 19 |
| 3 | LiTMP | −78 °C | 80 |
| 4 | *i*-$Bu_3Al(TMP)Li$ | −78 to 0 °C | 52 |
| 5 | $Me_2Zn(TMP)Li$ | −78 °C to rt | 0 |
| 6 | $MeCu(TMP)CNLi_2$ | −78 to 0 °C | 0 |

Having established the benzyne-mediated cyclization for the construction of the tricyclic pyrrolo[4,3,2-*de*]quinoline skeleton, we then pursued further transformations to synthesize makaluvamine A (**1a**), D (**1c**), and damirone B (**2b**) (Scheme 3). First, indoline **15** was smoothly converted to indole **16** using DDQ. Then, Boc and ethoxycarbonyl groups were removed in a stepwise manner to give known compound **18**.[6l] Selective methylation of the indole nitrogen of **18** provided **19**, which was converted to makaluvamine A (**1a**) in two steps according to Iwao's report.[6l] Makaluvamine D (**1c**) was also synthesized via oxidation of **18** using Fremy's salt.[6h] On the other hand, damirone B (**2b**) has the methyl group at the quinoline nitrogen, requiring an alternative method for the N-methylation. Considering that the imine nitrogen should have stronger nucleophilicity than pyrrole nitrogen under neutral conditions, we examined electrophilic methylating conditions. To this end, a combination of MeI and KI proved to be effective for the selective methylation of imine nitrogen and, gratifyingly, subsequent cleavage of the methyl ether smoothly took place to give damirone B (**2b**) in one pot.

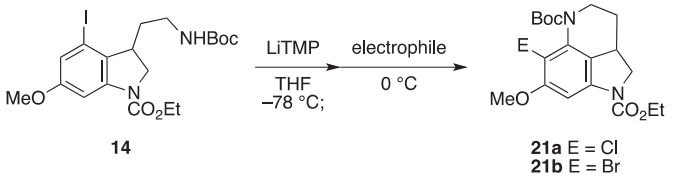



**Scheme 3.** Reagents and conditions; (i) DDQ, toluene, 0 °C; (ii) TMSOTf, $CH_2Cl_2$, 0 °C; (iii) NaOH aq, MeOH, reflux; (iv) MeI, NaH, DMF/THF, rt; (v) $O_2$, salcomine, DMF, rt; (vi) $NH_4Cl$, MeOH, rt; (vii) Fremy's salt, acetone/pH 6.86 buffer, 0 °C to rt; (viii) tyramine, MeOH, reflux; (ix) MeI, KI, acetone, reflux.

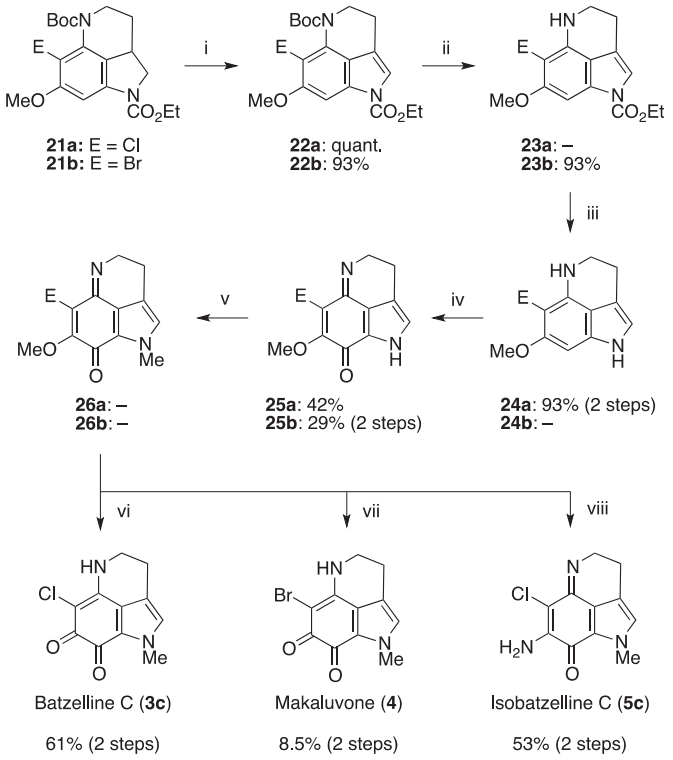
For the total synthesis of batzelline C (**3c**), makaluvone (**4**), and isobatzelline C (**5c**) having a chlorine/bromine atom on the aromatic ring, we then turned our efforts toward the one-pot cyclization–functionalization sequence, namely, construction of the piperidine ring followed by chlorination/bromination (Table 2). We found that the choice of chlorinating agent was important for the high-yielding process. Thus, the use of NCS or TfCl resulted in low yield of the desired product **21a**, and $Cl(CCl_2)_2Cl$ drastically improved the yield up to 64% (entries 1–3). Similarly, trapping of the generated aryl anion species with $Br(CCl_2)_2Br$ gave the corresponding bromide **21b** in 70% yield (entry 4).

With the chlorinated/brominated compounds **21a**/**21b** in hand, we focused on total synthesis of batzelline C (**3c**), makaluvone (**4**), and isobatzelline C (**5c**) (Scheme 4). Compounds **21a**/**21b** were converted to the unprotected dihydropyrroloquinoline **24a**/**24b** for the oxidation to construct iminoquinone. Thus, the Fremy's salt oxidation of indoles **22** or **23** resulted in slower conversion, associated with a substantial amount of unidentified side products, possibly due to the insufficient electron density of the aromatic rings. Methylation of the pyrrole nitrogen followed by acidic cleavage of the methyl ether and spontaneous isomerization led to batzelline C (**3c**) and makaluvone (**4**). We found that bromides **25b**/**26b** were quite unstable, which resulted in lower yields in the final stage of the synthesis. Total synthesis of isobatzelline C (**5c**) was achieved by treatment of iminoquinone **26a** with $NH_4Cl$/EtOH in 53% yield in over two steps.

**Table 2**
Benzyne-mediated double functionalization




| Entry | Electrophile (5 equiv) | E | Yield (%) |
|---|---|---|---|
| 1 | NCS | Cl | 5 |
| 2 | TfCl | Cl | Trace |
| 3 | $Cl(CCl_2)_2Cl$ | Cl | 64 |
| 4 | $Br(CCl_2)_2Br$ | Br | 70 |




**Scheme 4.** Reagents and conditions; (i) DDQ, toluene, rt; (ii) TMSOTf, $CH_2Cl_2$, 0 °C; (iii) NaOH aq, MeOH, reflux; (iv) Fremy's salt, acetone/pH 6.86 buffer, 0 °C; (v) MeI, $K_2CO_3$, DMF, rt; (vi) $BBr_3$, $CH_2Cl_2$, −40 °C; (vii) $BBr_3$, $CH_2Cl_2$, −78 °C; (viii) $NH_4Cl$, EtOH, reflux.

## 3. Conclusion

In summary, we have accomplished divergent synthesis of functionalized pyrrolo[4,3,2-*de*]quinolines by the benzyne-mediated cyclization–functionalization sequence. The presented synthetic strategy enabled us to access a variety of pyrroloquinolines from the common substrate. Thus, after construction of a piperidine ring, trapping the resulting aryl anion species with an electrophile rapidly provided substituted tricyclic compounds by simply switching an electrophile. The utility of this method is fully demonstrated by the total synthesis of a series of pyrroloquinoline natural products, makaluvamines A (**1a**), D (**1c**), damirone B (**2b**), batzelline C (**3c**), makaluvone (**4**), and isobatzelline C (**5c**). The one-pot cyclization–functionalization strategy developed in this work would be a powerful synthetic tool for highly substituted nitrogen-containing natural products, as well as polycyclic compounds found in drug candidates and functional molecules.

## 4. Experimental section

### 4.1. General remarks

All reactions were performed in oven-dried glassware, sealed with a rubber septum under a slight positive pressure of argon unless otherwise noted. Anhydrous THF, $Et_2O$, DMF, and dichloromethane were purchased from Kanto Chemical Co. Inc. 2,2,6,6-Tetramethylpiperidine was distilled from $CaH_2$. Unless otherwise mentioned, materials were obtained from commercial suppliers and were used without further purification. Chromatography was carried out using Kanto silica gel 60 (230–400 mesh) or Chromatorex® (FUJI SILYSIA, NH, 100–200 mesh). Preparative TLC was performed with precoated silica gel 60 $F_{254}$ plates (Merck). IR spectra were measured on a JASCO FTIR 4100 spectrometer. NMR spectra were measured on a JEOL AL 400 spectrometer and a JEOL ECA600 spectrometer. For $^1H$ NMR spectra, chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta$ 0) or relative internal $CHCl_3$ ($\delta$ 7.26), DMSO-$d_5$ ($\delta$ 2.49), or $CHD_2OD$ ($\delta$ 3.30). For $^{13}C$ NMR spectra, chemical shifts are expressed in ppm downfield from relative internal $CDCl_3$ ($\delta$ 77.0), DMSO-$d_6$ ($\delta$ 39.7), or $CD_3OD$ ($\delta$ 49.0). Coupling constants are in hertz. Mass spectra were recorded on a JEOL JMS–DX–303 or a JMS–700 spectrometer.

### 4.2. 2-(1-Allyl-4-iodo-6-methoxyindolin-3-yl)acetonitrile (12)

A 300-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **10** (11.2 g, 24.7 mmol), KCN (19.2 g, 296 mmol), $CH_3CN$ (90 mL), and $H_2O$ (30 mL). The resulting mixture was heated at reflux for 4 h, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **10**. The reaction mixture was treated with aqueous NaOH and was extracted with ethyl acetate three times. The organic extracts were washed with aqueous NaOH and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=9:1 to 5:1) to provide **12** (5.97 g, 16.9 mmol, 68%) as a pale yellow oil; $R_f$ (hexanes/ethyl acetate=3:1) 0.28; IR (neat, $cm^{-1}$) 3080, 3003, 2935, 2835, 2246, 1609, 1566, 1479, 1339, 1296, 1209, 1173, 1107, 1038, 927, 819; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.54 (d, 1H, $J$=2.0 Hz), 6.02 (d, 1H, $J$=2.0 Hz), 5.89–5.77 (m, 1H), 5.31–5.20 (m, 2H), 3.79–3.72 (m, 1H), 3.72 (s, 3H), 3.63–3.55 (m, 1H), 3.51 (d, 2H, $J$=4.4 Hz), 3.39–3.32 (m, 1H), 2.77 (dd, 1H, $J$=16.8, 3.4 Hz), 2.51 (dd, 1H, $J$=16.8, 10.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.5, 152.2, 132.4, 125.8, 118.3, 118.1, 111.2, 95.0, 92.1, 56.8, 55.5, 50.8, 40.7, 20.6; HRMS ($EI^+$) calcd for $C_{14}H_{15}IN_2O$ ($M^+$), 354.0229; found 354.0223.

### 4.3. *tert*-Butyl 2-(1-allyl-4-iodo-6-methoxyindolin-3-yl)ethylcarbamate (13)

A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with $AlCl_3$ (6.76 g, 16.9 mmol), and dry $Et_2O$ (160 mL). The solution was cooled to 0 °C. To the solution was added LAH (2.50 g, 65.9 mmol) at 0 °C and stirred for 10 min. To the mixture was added the solution of **12** (5.97 g, 16.9 mmol) in dry $Et_2O$ (40 mL) at 0 °C and the resulting mixture was stirred for 10 min, after which time TLC (dichloromethane/methanol=4:1) indicated complete consumption of **12**. The reaction was quenched with $H_2O$ followed by concd $H_2SO_4$. The mixture was basified with aqueous NaOH and extracted with $Et_2O$ three times. The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give amine as a pale yellow oil, which was used for the next reaction without further purification; IR (neat, $cm^{-1}$) 2931, 2834, 1607, 1565, 1476, 1337, 1292, 1207, 1174, 1106, 1038, 924, 817; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.51 (d, 1H, $J$=2.0 Hz), 5.97 (d, 1H, $J$=2.0 Hz), 5.87–5.76 (m, 1H), 5.26–5.15 (m, 2H), 3.75–3.67 (m, 1H), 3.70 (s, 3H), 3.53 (dd, 1H, $J$=15.4, 5.8 Hz), 3.38–3.28 (m, 2H), 3.11–3.03 (m, 1H), 2.79–2.73 (m, 2H), 1.85–1.69 (m, 2H), 1.16 (br, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.4, 152.2, 133.0, 129.5, 117.3, 110.4, 94.4, 91.8, 57.1, 55.3, 50.9, 40.9, 39.7, 36.4; HRMS ($EI^+$) calcd for $C_{14}H_{19}IN_2O$ ($M^+$), 358.0542; found 358.0533. A 300-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the crude amine, triethylamine (4.71 mL, 33.8 mmol), and dry dichloroethane (100 mL). To the solution was added $Boc_2O$ (7.38 g, 33.8 mmol). The reaction mixture was stirred for 10 h, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of starting material. The reaction mixture was treated with $H_2O$, and the mixture was extracted with dichloromethane three times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=9:1 to 5:1) to provide the title compound **13** (6.55 g, 14.3 mmol, 85%) as a colorless oil; $R_f$ (hexanes/ethyl acetate=3:1) 0.25; IR (neat, $cm^{-1}$) 3362, 2975, 2931, 2834, 1698, 1608, 1567, 1507, 1476, 1364, 1277, 1249, 1207; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.53 (d, 1H, $J$=2.0 Hz), 6.00 (d, 1H, $J$=2.0 Hz), 5.88–5.78 (m, 1H), 5.28–5.16 (m, 2H), 4.68 (br, 1H), 3.77–3.70 (m, 1H), 3.73 (s, 3H), 3.58–3.51 (m, 1H), 3.42–3.32 (m, 2H), 3.22–3.12 (m, 2H), 3.12–3.06 (m, 1H), 1.86–1.77 (m, 2H), 1.44 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.7, 155.9, 152.5, 133.0, 129.2, 117.7, 110.8, 94.8, 92.0, 78.9, 57.2, 55.5, 51.2, 40.9, 38.1, 32.7, 28.4; HRMS ($EI^+$) calcd for $C_{19}H_{27}IN_2O_3$ ($M^+$), 458.1066; found 458.1060.

### 4.4. Ethyl 3-(2-(*tert*-butoxycarbonylamino)ethyl)-4-iodo-6-methoxyindoline-1-carboxylate (14)

A 300-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with **13** (6.55 g, 14.3 mmol), ethyl chloroformate (6.84 mL, 71.5 mmol), NaI (10.7 g, 71.5 mmol), and acetone (70 mL). The resulting mixture was heated at reflux for 5 h, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **13**. The reaction mixture was treated with $H_2O$, and the mixture was extracted with ethyl acetate three times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=5:1 to 2:1) to provide the ethyl carbamate **14** (6.14 g, 12.5 mmol, 88%) as a colorless amorphous solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.19; IR (neat, $cm^{-1}$) 3370, 2977, 2933, 1707, 1601, 1571, 1519, 1474, 1446, 1312, 1220, 1173, 1141, 1053, 914; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (br, 1H), 6.90 (d, 1H, $J$=2.0 Hz), 4.56 (br, 1H), 4.27 (q, 2H, $J$=6.8 Hz), 3.97 (d, 2H, $J$=5.6 Hz), 3.77 (s, 3H), 3.27–3.06 (m, 3H), 2.01–1.90 (m, 1H), 1.72–1.59 (m, 1H), 1.45 (s, 9H) 1.36 (t, 3H, $J$=6.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.1, 155.9, 153.2, 143.2, 129.3, 117.9, 101.0, 91.6, 79.0, 61.6, 55.5, 52.8, 40.0, 37.9, 34.0, 28.3, 14.4; HRMS ($EI^+$) calcd for $C_{19}H_{27}IN_2O_5$ ($M^+$), 490.0965; found 490.0984.

### 4.5. 5-*tert*-Butyl 1-ethyl 7-methoxy-2,2a,3,4-tetrahydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (15)

A flame-dried 100-mL Schlenk tube equipped with a magnetic stirrer bar and an inlet adapter with three-way stopcock was charged with 2,2,6,6-tetramethylpiperidine (1.70 mL, 10.1 mmol) and dry THF (5 mL) under argon atmosphere. To the solution was added *n*-BuLi (1.60 M in *n*-hexane, 5.96 mL, 10.1 mmol) at −78 °C. The resulting solution was warmed to 0 °C over 25 min. The

resulting pale yellow solution was added to the solution of **14** (1.01 g, 2.01 mmol) in THF (15 mL) at −78 °C dropwise. The reaction mixture was stirred for 5 min, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **14**. The reaction mixture was treated with aqueous $NH_4Cl$, and the mixture was extracted with ethyl acetate three times. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=8:1) to provide the title compound **15** (582 mg, 1.61 mmol, 80%) as a pale yellow amorphous solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.28; IR (neat, $cm^{-1}$) 2978, 2935, 2879, 1708, 1613, 1496, 1472, 1450, 1410, 1379, 1339, 1300, 1201, 1160, 1132; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.20 (m, 1.5H), 7.20–7.00 (m, 0.3H), 6.82–6.64 (m, 0.2H), 4.40–4.21 (m, 3H), 4.10 (ddd, 1H, $J$=13.2, 4.8, 2.0 Hz), 3.79 (s, 3H), 3.51 (dd, 1H, $J$=10.8, 10.0 Hz), 3.42 (ddd, 1H, $J$=13.2, 13.2, 4.4 Hz), 3.28–3.17 (m, 1H), 2.31–2.23 (m, 1H), 1.70–1.58 (m, 1H), 1.57 (s, 9H), 1.58–1.28 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.7, 153.4, 153.0, 141.7, 135.7, 114.1, 101.0, 96.0, 81.1, 61.2, 55.5, 55.0, 45.6, 34.1, 28.2, 27.6, 14.5; HRMS ($EI^+$) calcd for $C_{19}H_{26}N_2O_5$ ($M^+$), 362.1842; found 362.1851.

### 4.6. 5-*tert*-Butyl 1-ethyl 7-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (16)

A 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **15** (212 mg, 591 μmol) and toluene (7 mL). To the solution was added DDQ (134 mg, 591 μmol) at 0 °C. The reaction mixture was stirred for 20 min, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **15**. The reaction mixture was treated with aqueous NaOH, and the mixture was extracted with ethyl acetate three times. The organic extracts were washed with aqueous $NaHCO_3$ and brine and dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=9:1 to 2:1) to provide the title compound **16** (196 mg, 544 μmol, 92%) as a white solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.34; IR (neat, $cm^{-1}$) 2977, 2939, 1735, 1700, 1377, 1357, 1260, 1239, 1134; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36–7.18 (m, 2H), 7.18–7.09 (m, 1H), 4.46 (q, 2H, $J$=7.2 Hz), 4.01 (t, 2H, $J$=5.6 Hz), 3.86 (s, 3H), 2.89 (t, 2H, $J$=5.6 Hz), 1.59 (s, 9H), 1.45 (t, 3H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 153.3, 151.2, 134.3, 133.4, 116.5, 116.1, 115.2, 103.2, 95.2, 81.3, 62.8, 55.8, 44.7, 28.2, 22.4, 14.2; HRMS ($EI^+$) calcd for $C_{19}H_{24}N_2O_5$ ($M^+$), 360.1685; found 360.1685.

### 4.7. Ethyl 7-methoxy-4,5-dihydropyrrolo[4,3,2-*de*]quinoline-1(3*H*)-carboxylate (17)

A 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **16** (195 mg, 541 μmol) and dichloromethane (10 mL) under argon atmosphere. To the solution was added TMSOTf (187 μL, 1.08 mmol) at 0 °C. The reaction mixture was stirred for 1 h, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of the **16**. The reaction mixture was treated with aqueous $NaHCO_3$, and the mixture was extracted with dichloromethane three times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude **17**, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=4:1 to 2:1) to provide the title compound **17** (115 mg, 441 μmol, 82%) as a white solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.16; IR (neat, $cm^{-1}$) 3381, 2938, 2837, 1730, 1624, 1415, 1309, 1253, 1165, 1128, 1029; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (br, 1H), 6.96 (br, 1H), 6.07 (d, 1H, $J$=1.6 Hz), 4.45 (q, 2H, $J$=7.2 Hz), 4.07 (br, 1H), 3.83 (s, 3H), 3.43 (t, 2H, $J$=5.6 Hz), 2.91 (t, 2H, $J$=5.6 Hz), 1.45 (t, 3H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.1, 151.5, 141.2, 134.8, 115.4, 114.7, 113.6, 94.0, 90.2, 62.6, 55.6, 42.7, 22.6, 14.3; HRMS ($EI^+$) calcd for $C_{14}H_{16}N_2O_3$ ($M^+$), 260.1161; found 260.1160.

### 4.8. 7-Methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (18)

A 20-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with **17** (105 mg, 405 μmol), 5 M aqueous NaOH (810 μL), and methanol (6 mL). The resulting mixture was heated at reflux for 30 min, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **17**. The solvent was removed under reduced pressure, and the residue was treated with aqueous $NH_4Cl$ and diluted with ethyl acetate, and filtered. The organic solvents were removed under reduced pressure to give **18** (52.6 mg, 279 μmol, 69%) as a pale yellow liquid, which was pure enough without further purification; $R_f$ (hexanes/ethyl acetate=3:1) 0.27; IR (neat, $cm^{-1}$) 3380, 2936, 2906, 2837, 1620, 1550, 1511, 1305, 1194, 1149, 1026, 806; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (br, 1H), 6.58 (s, 1H), 6.22 (s, 1H), 5.94 (s, 1H), 4.04 (br, 1H), 3.78 (s, 3H), 3.44 (t, 2H, $J$=5.8 Hz), 2.97 (t, 2H, $J$=5.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 141.4, 134.6, 113.8, 112.7, 110.3, 90.8, 85.0, 55.7, 43.5, 23.0; HRMS ($ESI^+$) calcd for $C_{11}H_{12}N_2O$ ($M^+$), 188.0950; found 188.0941.

### 4.9. Makaluvamine A (1a)

A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **18** (51.0 mg, 271 μmol) and THF/DMF (5:1, 2.4 mL) under argon atmosphere. To the solution were added NaH (13.0 mg, 325 μmol) and MeI (25.3 μL, 406 μmol) at 0 °C. The reaction mixture was stirred for 1 h, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **18**. The reaction mixture was treated with $H_2O$, and the mixture was extracted with ethyl acetate three times. The organic extracts were washed with $H_2O$ three times and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude **19**, which was used for the next reaction without further purification. A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with a crude **19**, salcomine (17.6 mg, 54.2 μmol), and DMF (0.5 mL). The reaction mixture was stirred for 1 h under oxygen atmosphere, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **19**. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (ethyl acetate, then dichloromethane/methanol=7:1) to provide the pyrroloiminoquinone compound. A 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the pyrroloiminoquinone compound, $NH_4Cl$ (145 mg, 2.71 mmol) and MeOH (7 mL) under argon atmosphere. The resulting mixture was stirred for 13 h, after which time TLC (dichloromethane/methanol=4:1) indicated complete consumption of starting material. The mixture was directly purified by column chromatography on silica gel (ethyl acetate, then dichloromethane/methanol=9:1 to 4:1) to provide makaluvamine A (**1a**) (24.9 mg, 124 μmol, 46% from **18**) as a brown solid; $R_f$ (dichloromethane/methanol=4:1) 0.42; IR (neat, $cm^{-1}$) 3233, 3033, 2925, 2854, 1698, 1610, 1541, 1522, 1436, 1393, 1354, 1323, 845; $^1H$ NMR (400 MHz, TFA salt, DMSO-$d_6$) $\delta$ 10.43 (br, 1H), 9.10 (br, 1H), 8.40 (br, 1H), 7.31 (s, 1H), 5.61 (s, 1H), 3.90 (s, 3H), 3.76 (td, 2H, $J$=7.6, 2.8 Hz), 2.84 (t, 2H, $J$=7.6 Hz); $^{13}C$ NMR (100 MHz, TFA salt, DMSO-$d_6$) $\delta$ 168.2, 156.8, 156.0, 131.0, 123.0, 122.4, 117.9, 86.5, 42.0, 35.8, 18.0; HRMS ($EI^+$) calcd for $C_{11}H_{12}N_3O$ ($M+H^+$), 202.0977; found 202.0980.

### 4.10. 7-Methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinolin-8(1*H*)-one (20)

A 200-mL round-bottomed flask equipped with a magnetic stirring bar was charged with Fremy's salt (1.25 g, 4.68 mmol) and pH 6.86 buffer solution (60 mL). To the solution was added **18** (22.0 mg, 117 μmol) in acetone (30 mL) dropwise over 10 min at 0 °C. The resulting solution was warmed to room temperature over 10 min. After which time TLC (ethyl acetate) indicated complete consumption of **18**. The reaction mixture was treated with brine, and the mixture was extracted with ethyl acetate eight times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate=1:1, then ethyl acetate/methanol=1:0 to 4:1) to afford **20** (14.6 mg, 72.2 μmol, 62%) as a yellow solid; $R_f$ (ethyl acetate/methanol=4:1) 0.24; IR (neat, $cm^{-1}$) 3065, 3011, 2927, 2837, 2752, 1654, 1624, 1566, 1395, 1238, 1074, 1008, 792, 733; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 9.69 (br, 1H), 6.90 (s, 1H), 6.14 (s, 1H), 4.20 (t, 2H, $J$=5.2 Hz), 3.86 (s, 3H), 2.80 (t, 2H, $J$=5.2 Hz); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 171.1, 158.4, 156.5, 123.9, 122.4, 121.3, 117.1, 106.6, 56.4, 51.0, 18.2; HRMS ($EI^+$) calcd for $C_{11}H_{10}N_2O_2$ ($M^+$), 202.0742; found 202.0738.

### 4.11. Makaluvamine D (1c)

A 10-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with **20** (7.8 mg, 39 μmol), tyramine (5.3 mg, 39 mmol) and MeOH (0.5 mL) under argon atmosphere. The resulting mixture was heated at reflux for 30 min. Then additional tyramine (1 mg) was added, and the resulting mixture was heated at reflux for 1 h, after which time TLC (ethyl acetate/methanol=4:1) indicated complete consumption of **20**. The reaction mixture was treated with $H_2O$, and the mixture was extracted with dichloromethane/MeOH ten times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude makaluvamine D, which was purified by preparative TLC (NH silica gel, acetone); to afford makaluvamine D (**1c**) (8.5 mg, 28 μmol, 72%) as a brown solid; $R_f$ (NH silica gel, acetone) 0.09; IR (neat, $cm^{-1}$) 2923, 2844, 1653, 1558, 1542, 1496, 1457, 1387, 1246, 1224, 1033, 1011, 826, 729; $^1H$ NMR (400 MHz, TFA salt, DMSO-$d_6$) $\delta$ 12.95 (br, 1H), 10.32 (br, 1H), 8.86 (t, 1H, $J$=6.2 Hz), 7.19 (d, 1H, $J$=2.0 Hz), 6.91 (d, 2H, $J$=8.4 Hz), 6.56 (d, 2H, $J$=8.4 Hz), 5.33 (s, 1H), 3.67 (td, 2H, $J$=7.6, 2.0 Hz), 3.39–3.28 (m, 2H), 2.74 (t, 2H, $J$=7.6 Hz), 2.66 (t, 2H, $J$=7.6 Hz); $^{13}C$ NMR (150 MHz, TFA salt, DMSO-$d_6$) $\delta$ 167.5, 157.1, 156.0, 153.1, 129.6, 128.2, 127.0, 123.8, 122.6, 118.7, 115.3, 84.1, 45.1, 42.5, 32.4, 18.2; HRMS ($FAB^+$) calcd for $C_{18}H_{18}N_3O_2$ ($M+H^+$), 308.1394; found 308.1397.

### 4.12. Damirone B (2b)

A sealed tube equipped with a magnetic stirring bar was charged with **20** (12.4 mg, 61.3 μmol), MeI (38.2 μL, 613 μmol) and acetone (4 mL). The resulting mixture was heated at 60 °C for 30 min. Then KI (102 mg, 613 μmol) was added, and the resulting mixture was heated at 70 °C for 7 h. The reaction mixture was passed through silica gel to remove salt. The organic solvents were removed under reduced pressure to give a crude damirone B, which was purified by preparative TLC (ethyl acetate/methanol=3:1) to afford damirone B (**2b**) (6.2 mg, 31 μmol, 50%) as a purple solid; $R_f$ (dichloromethane/methanol=4:1) 0.73; IR (neat, $cm^{-1}$) 3111, 2917, 2849, 1661, 1586, 1539, 1419, 1321; $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 12.44 (br, 1H), 7.08 (s, 1H), 5.11 (s, 1H), 3.59 (t, 2H, $J$=6.9 Hz), 3.03 (s, 3H), 2.81 (t, 2H, $J$=6.9 Hz); $^{13}C$ NMR (150 MHz, DMSO-$d_6$) $\delta$ 178.6, 170.4, 153.5, 124.9, 124.5, 124.1, 116.4, 92.4, 51.2, 37.7, 19.8; HRMS ($FAB^+$) calcd for $C_{11}H_{11}N_2O_2$ ($M+H^+$), 203.0821; found 203.0820.

### 4.13. 5-*tert*-Butyl 1-ethyl 6-chloro-7-methoxy-2,2a,3,4-tetrahydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (21a)

A flame-dried 50-mL Schlenk tube equipped with a magnetic stirrer bar and an inlet adapter with three-way stopcock was charged with 2,2,6,6-tetramethylpiperidine (1.70 mL, 10.0 mmol) and dry THF (20 mL) under argon atmosphere. To the solution was added *n*-BuLi (1.60 M in *n*-hexane, 6.14 mL, 10 mmol) at −78 °C. The resulting solution was warmed to 0 °C over 25 min. The resulting pale yellow solution was added to the solution of **14** (980 mg, 2.00 mmol) in THF (20 mL) at −78 °C dropwise over 5 min. The reaction mixture was stirred for 10 min, after which time TLC (hexanes/ethyl acetate=3:1) indicated complete consumption of **14**. To the reaction mixture was added 1,1,1,2,2,2-hexachloroethane (2.37 g, 10 mmol) at −78 °C. The resulting suspension was warmed to 0 °C for 30 min. The reaction mixture was treated with saturated aqueous $NH_4Cl$, and the mixture was extracted with ethyl acetate three times. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (hexanes/ethyl acetate=8:1 to 3:1) to provide the title compound **21a** (506 mg, 1.27 mmol, 64%) as a pale yellow amorphous solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.17; IR (neat, $cm^{-1}$) 2979, 2936, 1704, 1608, 1487, 1450, 1409, 1378, 1330, 1303, 1169, 1138, 760; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.25 (m, 0.8H), 7.06–6.87 (m, 0.2H), 4.38 (dd, 1H, $J$=1.0, 1.0 Hz), 4.35–4.18 (m, 2H), 4.07–3.92 (m, 1H), 3.91 (s, 3H), 3.60 (dd, 1H, $J$=11.2, 8.4 Hz), 3.45–3.28 (m, 1H), 3.26–3.14 (m, 1H), 2.54–2.40 (m, 1H), 1.56–1.44 (m, 1H), 1.49 (s, 9H), 1.44–1.26 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 156.3, 153.5, 152.9, 139.6, 134.5, 121.2, 111.3, 97.0, 81.2, 61.4, 56.7, 55.4, 44.3, 32.8, 31.2, 27.9, 14.5; HRMS ($EI^+$) calcd for $C_{19}H_{25}ClN_2O_5$ ($M^+$), 396.1452; found 396.1436.

### 4.14. 5-*tert*-Butyl 1-ethyl 6-bromo-7-methoxy-2,2a,3,4-tetrahydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (21b)

Compound **21b** was obtained starting from **14** by the same procedure for the preparation of **21a** in 70% yield as a pale yellow amorphous solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.27; IR (neat, $cm^{-1}$) 2979, 2935, 1704, 1605, 1450, 1407, 1329, 1301, 1167, 1139; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38–7.25 (m, 0.8H), 6.86–6.97 (m, 0.2H), 4.39 (t, 2H, $J$=1.0 Hz), 4.35–4.20 (m, 2H), 4.20–4.00 (m, 1H), 3.90 (s, 3H), 3.60 (dd, 1H, $J$=10.8, 8.4 Hz), 3.33–3.16 (m, 2H), 2.58–2.44 (m, 1H), 1.49 (s, 9H), 1.44–1.31 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.1, 153.3, 152.9, 140.6, 136.3, 121.9, 101.5, 97.0, 81.1, 61.4, 56.7, 55.6, 44.0, 32.6, 31.1, 27.9, 14.4; HRMS ($EI^+$) calcd for $C_{19}H_{25}BrN_2O_5$ ($M^+$), 440.0947; found 440.0961.

### 4.15. 5-*tert*-Butyl 1-ethyl 6-chloro-7-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (22a)

Compound **22a** was obtained from **21a** in quantitative yield as a white solid according to the same procedure for the preparation of **16**; $R_f$ (hexanes/ethyl acetate=3:1) 0.27; IR (neat, $cm^{-1}$) 3125, 2980, 2937, 1739, 1713, 1615, 1576, 1473, 1408, 1371, 1343, 1256, 1159, 1126, 887, 822, 761; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (br, 1H), 7.16 (br, 1H), 4.45 (q, 2H, $J$=6.8 Hz), 3.96 (s, 3H), 4.10–3.85 (m, 2H), 2.86–2.80 (m, 2H), 1.50 (s, 9H), 1.45 (t, 3H, $J$=6.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.6, 153.4, 151.1, 131.9, 131.8, 118.6, 117.9, 115.3, 112.8, 96.6, 81.6, 63.1, 56.9, 46.6, 28.0, 22.5, 14.3; HRMS ($EI^+$) calcd for $C_{19}H_{23}ClN_2O_5$ ($M^+$), 394.1295; found 394.1292.

### 4.16. 5-*tert*-Butyl 1-ethyl 6-bromo-7-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinoline-1,5-dicarboxylate (22b)

Compound **22b** was obtained from **21b** in 93% yield as a white solid according to the same procedure for the preparation of **16**; $R_f$ (hexanes/ethyl acetate=3:1) 0.42; IR (neat, $cm^{-1}$) 2979, 2938, 1737, 1706, 1471, 1440, 1408, 1370, 1342, 1314, 1254, 1157, 1125, 733; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.47 (br, 1H), 7.19 (br, 1H), 4.47 (q, 2H, $J$=6.8 Hz), 4.30–3.65 (m, 2H), 3.96 (s, 3H), 2.90–2.79 (m, 2H), 1.49 (s, 9H), 1.46 (t, 3H, $J$=6.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 155.1, 153.1, 150.9, 133.6, 132.6, 119.0, 117.7, 115.1, 103.3, 96.4, 81.4, 63.0, 56.9, 46.8, 27.9, 22.3, 14.2; HRMS ($EI^+$) calcd for $C_{19}H_{23}BrN_2O_5$ ($M^+$), 438.0790; found 438.0778.

### 4.17. Ethyl 6-chloro-7-methoxy-4,5-dihydropyrrolo[4,3,2-*de*]-quinoline-1(3*H*)-carboxylate (23a)

Compound **23a** was obtained from **22a** by the same procedure for the preparation of **17**, which was used for the next reaction without further purification; $R_f$ (hexanes/ethyl acetate=3:1) 0.29; IR (neat, $cm^{-1}$) 3410, 3388, 3119, 2973, 2938, 2908, 2844, 1735, 1627, 1575, 1475, 1412, 1312, 1252, 1217, 1128, 1085, 1021, 817, 759; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.10–7.00 (m, 2H), 4.46 (br, 1H), 4.45 (q, 2H, $J$=7.2 Hz), 3.93 (s, 3H), 3.50 (t, 2H, $J$=5.0 Hz), 2.93 (t, 2H, $J$=5.0 Hz), 1.45 (t, 3H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 151.4, 137.6, 132.5, 115.4, 114.8, 113.5, 99.7, 89.6, 62.9, 56.5, 42.6, 22.3, 14.3; HRMS ($EI^+$) calcd for $C_{14}H_{15}ClN_2O_3$ ($M^+$), 294.0771; found 294.0764.

### 4.18. Ethyl 6-bromo-7-methoxy-4,5-dihydropyrrolo[4,3,2-*de*]-quinoline-1(3*H*)-carboxylate (23b)

Compound **23b** was obtained from **22b** by the same procedure for the preparation of **17** in 93% yield as a white solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.46; IR (neat, $cm^{-1}$) 3381, 2978, 2940, 2838, 1731, 1626, 1469, 1439, 1410, 1311, 1249, 1218, 1145, 1121; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.16–6.96 (m, 2H), 4.51 (br, 1H), 4.45 (q, 2H, $J$=7.2 Hz), 3.93 (s, 3H), 3.50 (t, 2H, $J$=6.0 Hz), 2.92 (td, 2H, $J$=6.0, 1.6 Hz), 1.45 (t, 3H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 154.9, 151.1, 138.9, 133.0, 115.0, 114.6, 113.5, 89.4, 89.4, 62.7, 56.3, 42.6, 22.2, 14.2; HRMS ($EI^+$) calcd for $C_{14}H_{15}BrN_2O_3$ ($M^+$), 338.0266; found 338.0265.

### 4.19. 6-Chloro-7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-quinoline (24a)

Compound **24a** was obtained from **23a** by the same procedure for the preparation of **18** in 93% yield from **22a** as a white solid; $R_f$ (hexanes/ethyl acetate=3:1) 0.17; IR (neat, $cm^{-1}$) 3433, 3375, 3355, 2909, 2842, 1617, 1510, 1090, 763; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (br, 1H), 6.65 (s, 1H), 6.33 (s, 1H), 4.47 (br, 1H), 3.88 (s, 3H), 3.53 (t, 2H, $J$=5.8 Hz), 2.99 (t, 2H, $J$=5.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.3, 137.7, 132.1, 114.5, 112.5, 110.0, 96.3, 85.0, 56.5, 43.2, 22.6; HRMS ($EI^+$) calcd for $C_{11}H_{11}ClN_2O$ ($M^+$), 222.0555; found 222.0560.

### 4.20. 6-Bromo-7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-quinoline (24b)

Compound **24b** was obtained from **23b** by the same procedure for the preparation of **18**. **24b** was highly unstable and immediately used to the next step. $R_f$ (hexanes/ethyl acetate=3:1) 0.31.

### 4.21. 6-Chloro-7-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinolin-8(1*H*)-one (25a)

Compound **25a** was obtained from **24a** by the same procedure for the preparation of **20** in 42% yield as a yellow solid; $R_f$ (NH silica gel, hexanes/ethyl acetate=1:1) 0.19; IR (neat, $cm^{-1}$) 3065, 3002, 2926, 2908, 2841, 2767, 1738, 1657, 1615, 1260, 1067, 1006, 890, 801; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.31 (br, 1H), 7.08 (d, 1H, $J$=1.6 Hz), 4.13 (t, 2H, $J$=8.0 Hz), 3.89 (s, 3H), 2.69 (t, 2H, $J$=8.0 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 169.4, 154.9, 152.6, 127.8, 123.7, 122.9, 119.9, 116.6, 60.8, 50.9, 17.8; HRMS ($EI^+$) calcd for $C_{11}H_9ClN_2O_2$ ($M^+$), 236.0353; found 236.0358.

### 4.22. 6-Bromo-7-methoxy-3,4-dihydropyrrolo[4,3,2-*de*]quinolin-8(1*H*)-one (25b)

Compound **25b** was obtained from **24b** by the same procedure for the preparation of **20** in 29% yield from **23b** as a yellow solid; $R_f$ (NH silica gel, hexanes/ethyl acetate=1:1) 0.10; IR (neat, $cm^{-1}$) 3064, 2998, 2925, 2844, 1657, 1613, 1253; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.33 (br, 1H), 7.09 (s, 1H), 4.16 (t, 2H, $J$=7.8 Hz), 3.90 (s, 3H), 2.70 (t, 2H, $J$=7.8 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 169.0, 156.8, 152.9, 123.6, 123.1, 121.1, 120.3, 116.7, 60.6, 51.1, 17.7; HRMS ($FAB^+$) calcd for $C_{11}H_{10}BrN_2O_2$ ($M+H^+$), 280.9926; found 280.9916.

### 4.23. Batzelline C (3c)

A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **25a** (23.3 mg, 98.4 μmol), $K_2CO_3$ (27.2 mg, 197 μmol), and DMF (1 mL) under argon atmosphere. To the solution was added MeI (9.2 μL, 0.15 mmol). The reaction mixture was stirred for 10 min, after which time TLC (NH silica gel, hexanes/ethyl acetate=1:1) indicated complete consumption of **25a**. The reaction mixture was treated with $H_2O$, and the mixture was extracted with ethyl acetate three times. The organic extracts were washed with $H_2O$ three times and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude **26a**, which was used for the next reaction without further purification. A 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with a crude **26a** and dichloromethane (5 mL) under argon atmosphere. To the solution was added $BBr_3$ (1.0 M in dichloromethane, 246 μL, 0.25 mmol) at −40 °C. The reaction mixture was stirred for 10 min, after which time TLC (ethyl acetate) indicated complete consumption of **26a**. The reaction mixture was treated with methanol, and concentrated under reduced pressure to give a crude batzelline C, which was purified by column chromatography on silica gel (ethyl acetate/methanol=1:0 to 9:1, then dichloromethane/methanol=4:1) to afford batzelline C (**3c**) (14.1 mg, 59.6 μmol, 61% from **25a**) as a purple solid; $R_f$ (dichloromethane/methanol=9:1) 0.49; IR (neat, $cm^{-1}$) 3216, 3117, 2923, 2852, 1645, 1574, 1508, 1421, 1329, 833, 725; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.34 (s, 1H), 7.17 (s, 1H), 3.82 (s, 3H), 3.57 (td, 2H, $J$=7.2, 2.4 Hz), 2.74 (t, 2H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 171.4, 169.1, 149.0, 129.6, 123.4, 123.0, 116.8, 96.8, 41.7, 35.5, 18.9; HRMS ($EI^+$) calcd for $C_{11}H_9ClN_2O_2$ ($M^+$), 236.0353; found 236.0358.

### 4.24. Makaluvone (4)

A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **25b** (35.2 mg, 125 μmol), $K_2CO_3$ (34.5 mg, 250 μmol), and DMF (1 mL) under argon atmosphere. To the solution was added MeI (11.7 μL, 188 μmol). The reaction mixture was stirred for 15 min, after which time TLC (NH silica gel, hexanes/ethyl acetate=1:1) indicated complete consumption of **25b**. The reaction mixture was treated with $H_2O$, and the mixture

was extracted with ethyl acetate three times. The organic extracts were washed with $H_2O$ three times and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude **26b**, which was used for the next reaction without further purification. A 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with a crude **26b** and dichloromethane (10 mL) under argon atmosphere. To the solution was added $BBr_3$ (1.0 M in dichloromethane, 313 μL, 0.31 mmol) at −78 °C. The reaction mixture was stirred for 20 min, after which time TLC (NH silica gel, hexanes/ethyl acetate=1:1) indicated complete consumption of **26b**. The reaction mixture was treated with methanol, and concentrated under reduced pressure to give a crude makaluvone, which was purified by preparative TLC (ethyl acetate/methanol=4:1) to afford makaluvone (**4**) (3.0 mg, 11 μmol, 8.5% from **25b**) as a purple solid; $R_f$ (ethyl acetate/methanol=4:1) 0.17; IR (neat, $cm^{-1}$) 3332, 2921, 2851, 1655, 1636, 1588, 1561, 1533, 1417, 1403, 1351, 1201, 1123; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.15 (br, 1H), 7.16 (s, 1H), 3.83 (s, 3H), 3.58 (t, 2H, $J$=7.2 Hz), 2.74 (t, 2H, $J$=7.2 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 171.6, 168.8, 150.4, 129.4, 123.6, 123.6, 116.7, 87.5, 42.1, 35.5, 18.9; HRMS (EI$^+$) calcd for $C_{11}H_9BrN_2O_2$ ($M^+$), 279.9847; found 279.9851.

### 4.25. Isobatzelline C (5c)

A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **25a** (20.4 mg, 86.2 μmol), $K_2CO_3$ (23.8 mg, 172 μmol), and DMF (1 mL) under argon atmosphere. To the solution was added MeI (8.1 μL, 0.13 mmol). The reaction mixture was stirred for 10 min, after which time TLC (NH silica gel, hexanes/ethyl acetate=1:1) indicated complete consumption of **25a**. The reaction mixture was treated with $H_2O$, and the mixture was extracted with ethyl acetate three times. The organic extracts were washed with $H_2O$ three times and brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude **26a**, which was used for the next reaction without further purification. A 20-mL round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar was charged with a crude **26a**, $NH_4Cl$ (23.0 mg, 431 μmol) and EtOH (1 mL) under argon atmosphere. The resulting mixture was heated at reflux for 20 min, after which time TLC (ethyl acetate) indicated complete consumption of **26a**. The reaction mixture was concentrated under reduced pressure to give a crude isobatzelline C, which was purified by preparative TLC (ethyl acetate/methanol=1:0 to 20:1, then dichloromethane/methanol=4:1) to afford isobatzelline C (**5c**) (10.8 mg, 45.8 μmol, 53% from **25a**) as a brown solid; $R_f$ (dichloromethane/methanol=4:1) 0.22; IR (neat, $cm^{-1}$) 3010, 2919, 2851, 1670, 1604, 1520, 1406, 1348, 1324, 1256, 1204, 1144, 975; $^1H$ NMR (400 MHz, $CDCl_3/CD_3OD$=1:1) $\delta$ 7.10 (s, 1H), 3.98 (s, 3H), 3.94 (t, 2H, $J$=7.6 Hz), 2.99 (t, 2H, $J$=7.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3/CD_3OD$=1:1) $\delta$ 166.4, 154.6, 152.7, 131.9, 123.7, 122.6, 119.9, 94.0, 43.9, 36.6, 19.1; HRMS (EI$^+$) calcd for $C_{11}H_{10}ClN_3O$ ($M^+$), 235.0512; found 235.0518.

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