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DIVERGENT TOTAL SYNTHESIS OF AZALAMELLARINS D AND N

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Abstract – Lamellarins are polycyclic marine alkaloids with potent cytotoxic activities against cancer cell lines. A divergent synthesis of azalamellarins D and N, lactam congeners of the marine natural products lamellarins D and N, has been achieved via the pentacyclic 14-bromo-8,9-dihydro-benzo[7,8]indolizino[3,2-*c*]-quinolin-6(5*H*)-one intermediate. The pentacyclic intermediate can be synthesized from methyl 1-(benzensulfonyl)-3-bromo-1*H*-pyrrole-2-carboxylate via the Suzuki–Miyaura cross-coupling and intramolecular direct arylation as key reactions.

INTRODUCTION

Lamellarins are polycyclic marine alkaloids with a unique polyaromatic structure. With some exceptions, these possess a 14-phenyl-6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one ring system (Figure 1).[1] Some lamellarins are of interest owing to their potent cytotoxic activities against cancer cell lines including the multi-drug-resistant (MDR) phenotype.[2] Among these, lamellarin D (**1**) shows a high therapeutic potential as an anticancer drug with multiple biological targets. In 2003, Bailly and coworkers identified that a major molecular target of lamellarin D (**1**) in cancer cells was topoisomerase I.[3] Lamellarin D (**1**) also induced apoptosis by acting directly on the mitochondria of the cancer cells.[4] Moreover, lamellarin D (**1**) induced cellular senescence in several cancer cells at sublethal doses via topoisomerase I inhibition and intracellular ROS production.[5] In recent years, lamellarin N (**2**), a structural isomer with the transposition of substituents at C13- and C14- positions of **1**, has also attracted significant attention owing to its potent inhibitory activity against several protein kinases related to cancer

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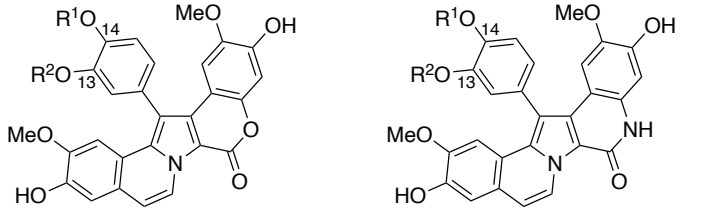
This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

and neurodegenerative diseases such as cyclin-dependent kinases (CDKs), glycogen synthase kinase-3 (GSK-3), Pim-1 proto-oncogene serine/threonine kinase (PIM1), and dual-specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A).[6] Although these have been selected as candidate compounds for the development of anticancer agents, pentacyclic lamellarins are insoluble in aqueous media. To overcome this issue, water-soluble derivatives possessing water-soluble substituents on the lamellarin scaffold have been developed.[2h,7] In contrast, Thasana and coworkers designed azalamellarins, in which the lactone ring (B-ring) of the lamellarins was substituted with a lactam ring to resolve this issue.[8] They synthesized azalamellarin D (**3**) and its derivatives utilizing a copper(I)-mediated and microwave-assisted C–N_{amide} bond formation reaction and evaluated their cytotoxic activities. Azalamellarin D (**3**) exhibited lower cytotoxicity than its parent compound, lamellarin D (**1**); however, it retained high activity at a low micromolar range against cancer cell lines such as HuCCA-1, A549, HepG2, and MOLT-3. Chittchang and coworkers improved the total synthesis to furnish both azalamellarins and parent lamellarins from the same pyrrole ester intermediates and synthesized lamellarins D (**1**) and N (**2**) as well as azalamellarins D (**3**) and N (**4**).[9] The evaluation of **1**–**4** revealed that both azalamellarins D (**3**) and N (**4**) showed cytotoxicities against several cancer cell lines. Interestingly, the replacement of lactone ring B with a lactam ring significantly increased the GSK-3β inhibitory activity; azalamellarin N (**4**) was more potent than azalamellarin D (**3**).



lamellarin D (**1**) (R^1 = H, R^2 = Me)
lamellarin N (**2**) (R^1 = Me, R^2 = H)
azalamellarin D (**3**) (R^1 = H, R^2 = Me)
azalamellarin N (**4**) (R^1 = Me, R^2 = H)

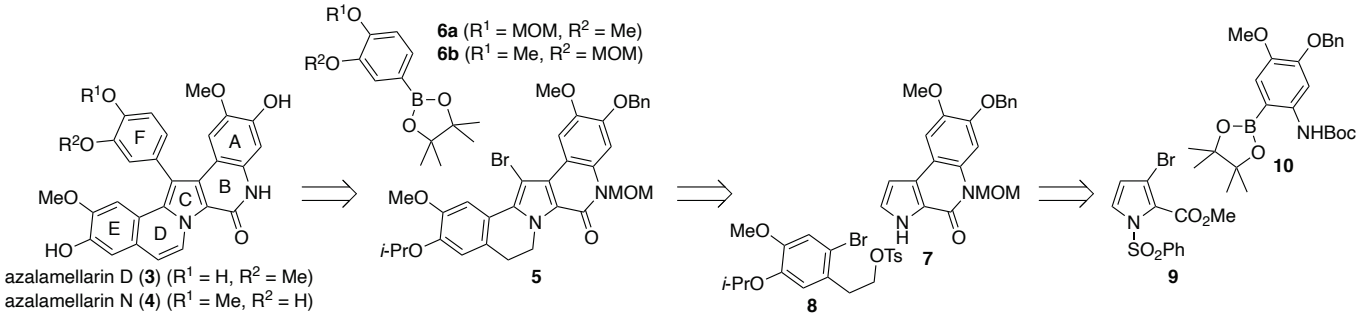
Figure 1

Considering the biological activities of azalamellarins D (**3**) and N (**4**), a new synthetic method is developed. Herein, a modular synthesis of azalamellarins D (**3**) and N (**4**) is accomplished via the Suzuki–Miyaura cross-coupling of the pentacyclic 14-bromo-8,9-dihydrobenzo[7,8]indolizino[3,2-*c*]-quinolin-6(5*H*)-one intermediate as a key reaction.

RESULTS AND DISCUSSION

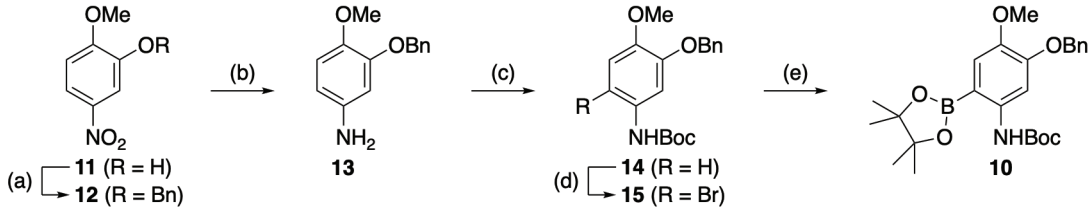
The target azalamellarins D (**3**) and N (**4**) possess the same substituent patterns except for the substituents at C13- and C14- positions on the F-ring. Therefore, the construction of pentacyclic (ABCDE-ring) scaffold, followed by the introduction of the F-ring module in the later stage of the synthesis was

considered an efficient strategy. As a similar strategy was previously used to synthesize 1-dearyllamellarin D and 1-substituted 1-dearyllamellarin D derivatives,[10] it was applied to synthesize the target azalamellarins. Accordingly, the retrosynthetic approach is shown in Scheme 1. The target compounds **3** and **4** can be obtained from pentacyclic intermediate **5** and pinacol borates **6** via the Suzuki–Miyaura cross-coupling reaction, followed by the dehydrogenation and subsequent deprotection of benzyl, isopropyl, and methoxymethyl (MOM) groups. Pentacyclic intermediate **5** can be obtained by the *N*-alkylation of **7** with tosylate **8**, followed by intramolecular direct arylation and subsequent regioselective bromination. Tricyclic compound **7** can be obtained from the known methyl 1-(benzenesulfonyl)-3-bromo-1*H*-pyrrole-2-carboxylate (**9**) and pinacol borate **10** by the Suzuki–Miyaura cross-coupling reaction and subsequent lactam ring formation/MOM-protection.



Scheme 1

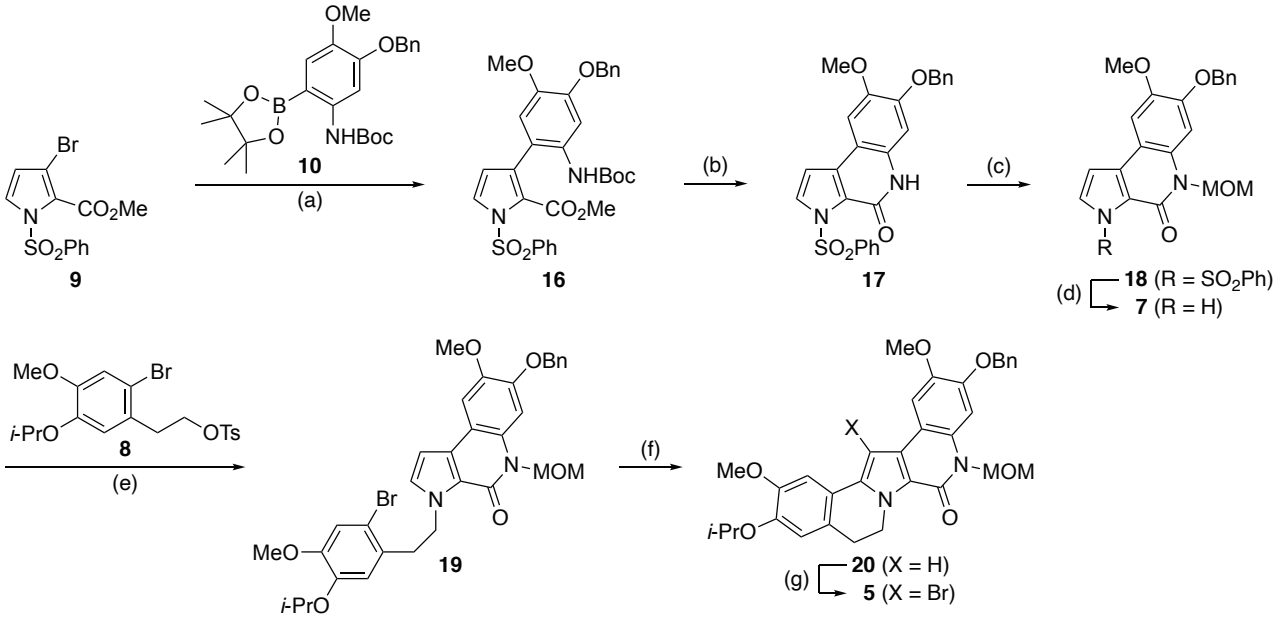
Based on this analysis, first, the synthesis of pinacol borate **10** was accomplished (Scheme 2). The benzylation of 5-nitroguaiacol (**11**) was performed to afford **12** in 82% yield. Compound **12** was treated with zinc powder in a mixed solvent system containing acetic acid and dichloromethane (DCM) to afford the reduced product **13**.[11] The amino group of **13** was protected with the *tert*-butoxycarbonyl (Boc) group to yield **14**. The reaction of **14** with *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF) afforded compound **15** in 92% yield. The conversion of **15** to **10** was performed using a modified procedure reported by Weiß and Podlech.[12] Thus, bromide **15** was treated with 1.1 equiv of bis(pinacolato)diboron



Scheme 2. *Reagents and conditions:* (a) BnBr (1.0 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, 7 h (82%); (b) zinc powder (8.0 equiv), AcOH, DCM, 0 °C, 10 min, then rt (89%); (c) Boc_2O (1.05 equiv), THF, reflux, 1.5 h (66%); (d) NBS (1.1 equiv), THF, −78 °C, 1 h to 0 °C, 17 h (92%); (e) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol%), B_2pin_2 (1.1 equiv), KOAc (3.0 equiv), 1,4-dioxane, 80 °C, 14 h (82%).

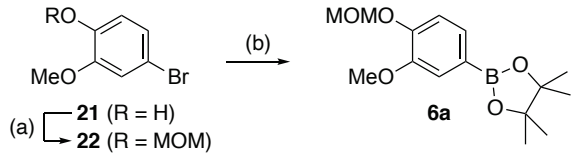
(B_2pin_2) in the presence of 5 mol% of Pd(dppf)Cl_2·CH_2Cl_2 and 3.0 equiv of potassium acetate in 1,4-dioxane at 80 °C for 14 h to provide pinacol borate **10** in 82% yield.

Next, pentacyclic intermediate **5** was synthesized (Scheme 3). The Suzuki–Miyaura cross-coupling of 3-bromopyrrole **9** with the pinacol borate **10** afforded **16** in 95% yield. The subsequent treatment of **16** with trifluoroacetic acid (TFA), followed by heating in acetic acid at 100 °C for 24 h afforded lactamized product **17** in 89% yield. The lactam NH of **17** was protected with the MOM group to provide **18** in 96% yield. The deprotection of the benzenesulfonyl group by treatment with tetrabutylammonium fluoride (TBAF) generated **7** in 93% yield.[13] Tricyclic lactam **7** was alkylated with tosylate **8** in the presence of cesium carbonate in dimethylformamide (DMF) to produce **19**.[6b] The intramolecular direct arylation of **19** in the presence of 5 mol% $Pd(PPh_3)_4$ and potassium carbonate in dimethylacetamide (DMA) at 125 °C afforded pentacyclic compound **20** in 90% yield. The treatment of **20** with 1.03 equiv of NBS produced regioselectively brominated product **5** in 92% yield.



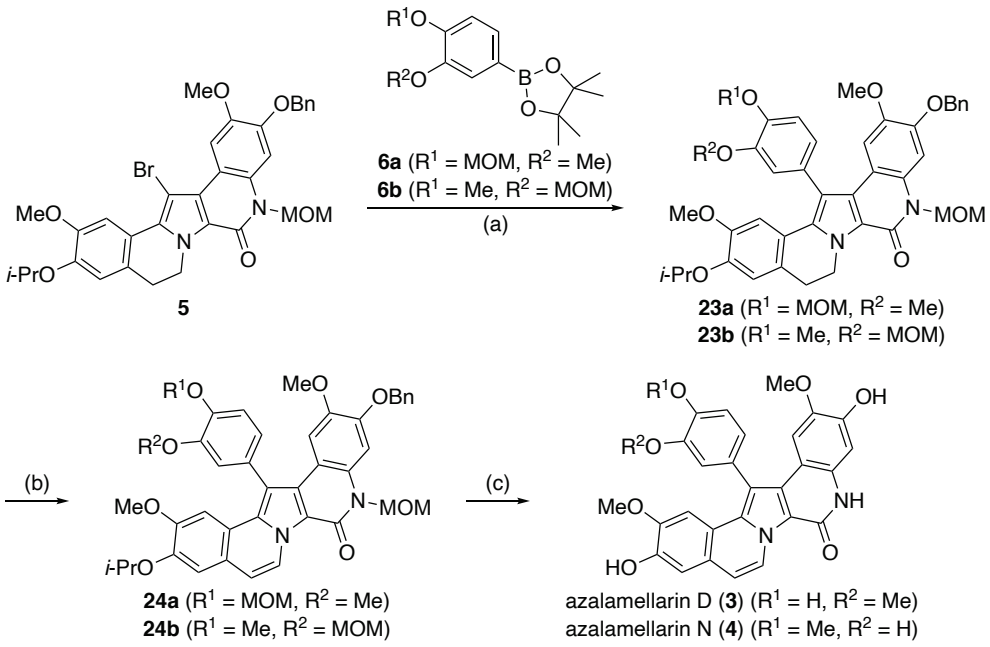
Scheme 3. *Reagents and conditions:* (a) Pd(dppf)Cl_2·CH_2Cl_2 (5 mol%), **9** (1.2 equiv), Na_2CO_3 (6.6 equiv), DME, water, 85 °C, 19 h (95%); (b) (1) TFA, DCM, rt, 1 h, (2) AcOH, 100 °C, 24 h (89%); (c) MOM-Cl (1.5 equiv), NaH (3.0 equiv), THF, 0 °C, 4 h (96%); (d) TBAF (1.5 equiv), THF, reflux, 2 h (93%); (e) **8** (1.5 equiv), Cs_2CO_3 (3.0 equiv), DMF, rt, 17 h (84%); (f) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2.2 equiv), DMA, 125 °C, 20 h (90%); (g) NBS (1.03 equiv), DMF, 0 °C, 24 h (92%).

The synthesis of pinacol borate **6a** is shown in Scheme 4. The protection of the hydroxy group of 4-bromo-2-methoxyphenol (**21**)[14] by the MOM group afforded **22** in 92% yield. The conversion of **22** to **6a** was performed using a modified procedure reported by Sen and Valiyaveettil.[15] Thus, bromide **22** was treated with 1.1 equiv of B_2pin_2 in the presence of 5 mol% Pd(dppf)Cl_2·CH_2Cl_2 and 3.0 equiv of potassium acetate in 1,4-dioxane at 80 °C for 14 h to provide pinacol borate **6a** in 84% yield.



Scheme 4. *Reagents and conditions:* (a) MOMCl (1.5 equiv), *i*-Pr_2NEt (2.0 equiv), DCM, 0 °C, 1 h, then rt, 18 h (92%); (b) Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (5 mol%), B_2pin_2 (1.1 equiv), KOAc (3.0 equiv), 1,4-dioxane, 80 °C, 14 h (84%).

With pentacyclic intermediate **5** and pinacol borate **6a** in hand, the next step involved their conversion to azalamellarin D (**3**) (Scheme 5). The Suzuki–Miyaura cross-coupling of **5** with pinacol borate **6a** under standard conditions [$Pd(PPh_3)_4$ (10 mol%), Na_2CO_3, water, 1,2-dimethoxyethane (DME), 85 °C] afforded **23a** in 59% yield. The subsequent dehydrogenation of **23a** using 1,2-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced **24a** in good yield.[14] Finally, the selective deprotection of the benzyl, isopropyl, and MOM groups of **24a** with 12 equiv of BCl_3 afforded azalamellarin D (**3**) in 77% yield.[14,16] Similarly, azalamellarin N (**4**) could also be obtained from **5** and **6b**.[16]



Scheme 5. *Reagents and conditions:* (a) $Pd(PPh_3)_4$ (10 mol%), **6** (1.5 equiv), Na_2CO_3 (6.6 equiv), DME, water, 85 °C, 21 h (**23a**: 59%, **23b**: 67%); (b) DDQ (1.5 equiv), toluene, 100 °C, 16 h (**24a**: 73%, **24b**: 70%); (c) BCl_3 (12 equiv), DCM, −78 °C, 0.5 h and then 0 °C, 3 h (**3**: 77%, **4**: 43%).

In conclusion, the synthesis of azalamellarins D (**3**) and N (**4**) is accomplished via the Suzuki–Miyaura cross-coupling of pentacyclic intermediate **5** as a key reaction. This strategy may allow the preparation of a wide range of F-ring-modified azalamellarins by simple structural modifications of the

14-bromo-8,9-dihydrobenzo[7,8]indolizino[3,2-*c*]quinolin-6(5*H*)-one intermediate and pinacol borate coupling partners. Further biological evaluations of **3** and **4** are currently in progress in our laboratories.

EXPERIMENTAL

The melting points were determined using a Yanagimoto micro melting point apparatus and were reported as obtained. The IR spectra were obtained using a Thermo Nicolet Nexus 670 NT FT-IR instrument (Thermo Fisher Scientific, Waltham, Massachusetts, USA) and reported in terms of the absorption frequency (cm^{-1}). The NMR spectra were recorded on a Varian NMR 500PS SN instrument (500 MHz for ^1H and 126 MHz for ^{13}C; Varian, Inc., Palo Alto, California, USA). The ^1H NMR chemical shifts are expressed in parts per million (ppm) relative to the $CDCl_3$ (tetramethylsilane, δ 0.0 ppm) and DMSO-d_6 (DMSO, δ 2.50 ppm) internal standards. The ^1H NMR data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, sep = septet, m = multiplet, br s = broad singlet), coupling constant (Hz), and integration. The ^{13}C NMR chemical shifts are expressed in ppm relative to the $CDCl_3$ (tetramethylsilane, δ 0.0 ppm) and DMSO-d_6 (DMSO-d_6, δ 39.52 ppm) internal standards. High-resolution mass spectra (HRMS) were recorded using a JEOL JMS-700N (JEOL, Ltd., Tokyo, Japan; fast atom bombardment mass spectrometry, FABMS) instrument. Column chromatography was performed using silica gel 60N, 63–210 μm (Kanto Chemical Co., Inc., Tokyo, Japan) or Chromatorex NH-DM1020 (Fuji Silysia Chemical Ltd., Kasugai, Japan).

2-Benzyloxy-1-methoxy-4-nitrobenzene (12). Under an argon atmosphere, a neat liquid of benzyl bromide (14.0 mL, 118 mmol) was added to a suspension of 5-nitroguaiacol (**11**) (20.0 g, 118 mmol) and potassium carbonate (24.5 g, 177 mmol) in acetone (500 mL) at room temperature and the mixture was refluxed for 7 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue was added water and the product was extracted with DCM. The extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was recrystallized from MeOH to give **12** as a pale yellow powder (25.0 g, 82%). Mp 92.5–93.5 °C (lit.[17] 97–98 °C). IR (KBr): 1514, 1340, 1262, 1226, 1091, 994 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 5.20 (s, 2H), 6.92 (d, J = 8.9 Hz, 1H), 7.32–7.36 (m, 1H), 7.37–7.42 (m, 2H), 7.45–7.48 (m, 2H), 7.80 (d, J = 2.6 Hz, 1H), 7.92 (dd, J = 2.6 and 8.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.4, 71.2, 108.6, 110.2, 118.1, 127.6, 128.4, 128.8, 135.7, 141.3, 147.9, 155.1. HRFABMS *m*/*z*. Calcd for $C_{14}H_{14}NO_4$ [$(M+H)^+$]: 260.0923. Found: 260.0923. These physical and spectroscopic data are in good agreement with those previously reported.[18]

3-Benzyloxy-4-methoxyaniline (13). Under an argon atmosphere, activated zinc powder[19] (20.2 g, 309 mmol) was added portionwise to a solution of **12** (10.0 g, 38.6 mmol) in DCM (390 mL) at room temperature. After cooling to 0 °C, acetic acid (57.9 mL) was added dropwise to the suspension. After

stirring for 10 min at 0 °C, the suspension was allowed to warm to room temperature and then passed through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was diluted with DCM. The product was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium suflate, and evaporated. The residue was purified by column chromatography over silica gel 60N (DCM–EtOAc= 100:1) to give **13** as a dark purple solid (7.86 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.33 (br s, 2H), 3.81 (s, 3H), 5.11 (s, 2H), 6.24 (dd, J = 2.6 and 8.4 Hz, 1H), 6.32 (d, J = 2.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.27–7.32 (m, 1H), 7.34–7.38 (m, 2H), 7.41–7.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 57.0, 70.9, 103.3, 107.2, 114.1, 127.2, 127.8, 128.5, 137.3, 140.6, 142.8, 149.2. HRFABMS *m/z* calcd for $C_{14}H_{16}NO_2$ [$(M+H)^+$]: 230.1181, found 230.1181. These physical and spectroscopic data are in good agreement with those previously reported.[18]

***tert*-Butyl *N*-[3-(benzyloxy)-4-methoxyphenyl]carbamate (14).** Under an argon atmosphere, di-*tert*-butyl dicarbonate (7.85 g, 36.0 mmol) was added as a neat liquid to a solution of **13** (7.86 g, 34.3 mmol) in THF (150 mL) at room temperature and the solution was refluxed for 1.5 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. After successive purification by column chromatography over Chromatorex NH-DM1020 (hexane–EtOAc = 3:1) and column chromatography over silica gel 60N (hexane−EtOAc = 3:1), **14** was obtained as a colorless solid (7.49 g, 66%). Recrystallization from Et_2O−hexane gave a colorless powder. Mp 100–101 °C. IR (KBr): 3362, 1697, 1517, 1407, 1267, 1238, 1169, 1134 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.84 (s, 3H), 5.12 (s, 2H), 6.35 (br s, 1H), 6.81 (s, 2H), 7.12 (br s, 1H), 7.27–7.32 (m, 1H), 7.34–7.39 (m, 2H), 7.43–7.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.4, 56.4, 71.0, 80.3, 106.1, 111.2, 112.4, 127.5, 127.8, 128.5, 131.9, 136.9, 145.7, 148.5, 153.0. HRFABMS *m/z* calcd for $C_{19}H_{23}NO_4$ (M^+): 329.1627, found 329.1627.

***tert*-Butyl *N*-[5-(benzyloxy)-2-bromo-4-methoxyphenyl]carbamate (15).** Under an argon atmosphere, NBS (4.45 g, 25.0 mmol) was added portionwise to a solution of **14** (7.49 g, 22.7 mmol) in THF (140 mL) at −78 °C. After stirring for 1 h at −78 °C, the mixture was allowed to warm to 0 °C and stirred for an additional 17 h at the same temperature. The reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The product was extracted with DCM and the extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 10:1) to give **15** as a colorless solid (8.50 g, 92%). Recrystallization from Et_2O–hexane gave a colorless powder. Mp 94–95 °C. IR (KBr): 3418, 1721, 1529, 1325, 1238, 1156 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 9H), 3.82 (s, 3H), 5.13 (s, 2H), 6.75 (br s, 1H), 6.99 (s, 1H), 7.28–7.33 (m, 1H), 7.34–7.39 (m, 2H), 7.46–7.49 (m, 2H), 7.90 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.3, 56.5, 71.0, 80.8, 102.4, 106.4, 115.4, 127.8, 128.0,

128.5, 129.9, 136.5, 145.6, 148.0, 152.6. HRFABMS *m*/*z*. Calcd for $C_{19}H_{22}BrNO_4$ (M^+): 407.0732. Found: 407.0746.

***tert*-Butyl *N*-[5-(benzyloxy)-4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-carbamate (10).** Under an argon atmosphere, a mixture of **15** (1.00 g, 2.45 mmol), bis(pinacolato)diboron (684 mg, 2.69 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (100 mg, 0.123 mmol), potassium acetate (721 mg, 7.35 mmol), and 1,4-dioxane (9.1 mL) was heated at 80 °C for 14 h. After cooling to room temperature, the mixture was diluted with water and concentrated under reduced pressure. The product was extracted with EtOAc and the extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 7:1) to give **10** as a colorless solid (916 mg, 82%). Recrystallization from Et_2O–hexane gave a colorless powder. Mp 128.5–129.5 °C. IR (KBr): 3367, 1725, 1613, 1529, 1365, 1311, 1237, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 12H), 1.52 (s, 9H), 3.86 (s, 3H), 5.19 (s, 2H), 7.18 (s, 1H), 7.27–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.47–7.51 (m, 2H), 8.03 (br s, 1H), 8.63 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.8, 28.4, 56.4, 70.4, 79.5, 84.0, 103.5, 118.3, 127.8, 127.9, 128.4, 136.7, 140.6, 143.9, 151.8, 153.2. HRFABMS *m*/*z*. Calcd for $C_{25}H_{34}BNO_6$ (M^+): 455.2479. Found: 455.2487.

Methyl 1-(benzenesulfonyl)-3-[4-(benzyloxy)-2-(*tert*-butoxycarbonylamino)-5-methoxyphenyl]-1*H*-pyrrole-2-carboxylate (16). Under an argon atmosphere, a mixture of **9**[10] (689 mg, 2.00 mmol), **10** (1.09 g, 2.40 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (81.7 mg, 0.107 mmol), sodium carbonate (1.40 g, 13.2 mmol), DME (21 mL), and degassed water (2.1 mL) was heated at 85 °C for 19 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the product was extracted with DCM. The extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give **16** as a pale yellow oil (1.13 g, 95%). IR (KBr): 1724, 1518, 1448, 1369, 1237, 1174 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.57 (s, 3H), 3.77 (s, 3H), 5.16 (s, 2H), 6.32 (d, J = 3.2 Hz, 1H), 6.36 (br s, 1H), 6.60 (s, 1H), 7.28–7.33 (m, 1H), 7.34–7.39 (m, 2H), 7.47–7.50 (m, 2H), 7.57–7.62 (m, 2H), 7.66 (d, J = 3.2 Hz, 1H), 7.66–7.70 (m, 1H), 8.03–8.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 28.3, 52.1, 56.4, 70.9, 80.3, 107.1, 113.7, 113.9, 116.5, 122.7, 126.9, 127.8, 127.9, 128.0, 128.5, 129.0, 129.7, 131.8, 134.1, 136.8, 138.9, 145.1, 148.4, 153.2, 160.5. HRFABMS *m/z* Calcd for $C_{31}H_{32}N_2O_8S$ (M^+): 592.1879. Found: 592.1882.

3-(Benzenesulfonyl)-7-(benzyloxy)-8-methoxy-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one (17). To a solution of **16** (1.13 g, 1.90 mmol) in DCM (6.0 mL) was added TFA (6.0 mL) at room temperature. After stirring for 1 h, the mixture was concentrated. The residue and acetic acid (15 mL) was heated in a sealed tube at 100 °C for 24 h under an argon atmosphere. After cooling to room temperature, the mixture was diluted with water. The precipitate thus formed was collected by filtration, washed with water, and

dried under reduced pressure to give **17** as a pale purple powder (776 mg, 89%). Recrystallization from DCM–hexane gave a colorless powder. Mp 268.5–270 °C. IR (KBr): 1654, 1449, 1383, 1178, 1136, 1086, 1017 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.85 (s, 3H), 5.08 (s, 2H), 7.00 (s, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.32–7.37 (m, 1H), 7.38–7.42 (m, 2H), 7.45–7.48 (m, 2H), 7.56 (s, 1H), 7.58–7.63 (m, 2H), 7.68–7.73 (m, 1H), 8.02–8.05 (m, 2H), 8.05 (d, J = 3.5 Hz, 1H), 11.28 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 56.1, 69.9, 99.9, 105.8, 105.9, 108.2, 120.5, 128.06, 128.10, 128.4, 129.1, 130.8, 131.4, 134.28, 134.35, 136.4, 138.4, 145.4, 149.3, 152.4. HRFABMS *m/z* Calcd for $C_{25}H_{21}N_2O_5S$ [$(M+H)^+$]: 461.1171. Found: 461.1171.

3-(Benzenesulfonyl)-7-(benzyloxy)-8-methoxy-5-(methoxymethyl)-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]-quinolin-4-one (18). Under an argon atmosphere, sodium hydride (60% dispersion in mineral oil, 200 mg, ca. 5.0 mmol) was added portionwise to a solution of **17** (776 mg, 1.68 mmol) in THF (60 mL) at 0 °C. After stirring for 0.5 h at 0 °C, chloromethyl methyl ether (192 μL, 2.55 mmol) was added to the mixture. After stirring for 4 h at 0 °C, the mixture was quenched with saturated aqueous ammonia. The product was extracted with DCM and the extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residual solid was washed with water and MeOH to give **18** as a pale purple solid (812 mg, 96%). Recrystallization from DCM–hexane gave a colorless powder. Mp 208–209 °C. IR (KBr): 1662, 1455, 1350, 1253, 1135, 1071 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.21 (s, 3H), 3.97 (s, 3H), 5.23 (s, 2H), 5.54 (br s, 2H), 6.83 (d, J = 3.5 Hz, 1H), 7.09 (s, 1H), 7.20 (s, 1H), 7.27–7.32 (m, 1H), 7.33–7.38 (m, 2H), 7.44–7.49 (m, 4H), 7.53–7.58 (m, 1H), 7.99 (d, J = 3.5 Hz, 1H), 8.03–8.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0, 56.4, 71.1, 73.3, 102.0, 104.2, 105.6, 109.9, 120.7, 127.6, 128.1, 128.4, 128.6, 128.7, 131.4, 131.9, 133.7, 133.9, 136.3, 138.9, 146.3, 149.4, 153.7. Anal. Calcd for $C_{27}H_{24}N_2O_6S$: C, 64.27; H, 4.79; N, 5.55. Found: C, 63.99; H, 4.52; N, 5.55.

7-(Benzyloxy)-8-methoxy-5-(methoxymethyl)-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one (7). Under an argon atmosphere, a THF solution of TBAF (1.0 M, 1.20 mL, 1.20 mmol) was added dropwise to a solution of **18** (406 mg, 0.804 mmol) in THF (44 mL) at room temperature. The mixture was refluxed for 2 h. After cooling to room temperature, the mixture was quenched with water, and concentrated under reduced pressure. The precipitate thus formed was collected by filtration, washed with water, and dried under reduced pressure to give **7** as a pale purple powder (273 mg, 93%). Recrystallization from DCM–hexane gave a colorless powder. Mp 243–245 °C. IR (KBr): 1652, 1536, 1436, 1361, 1252, 1076 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.39 (s, 3H), 4.01 (s, 3H), 5.27 (s, 2H), 5.75 (br s, 2H), 6.72 (t, J = 2.5 Hz, 1H), 7.25 (s, 1H), 7.29 (t, J = 2.7 Hz, 1H), 7.29–7.32 (m, 1H), 7.32 (s, 1H), 7.36–7.41 (m, 2H), 7.49–7.52 (m, 2H), 10.19 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0, 56.4, 71.3, 73.3, 102.0, 103.0, 105.6, 112.4, 121.2, 126.7, 127.7, 128.0, 128.0, 128.6, 130.2, 136.7, 146.4, 147.9, 156.1. HRFABMS *m/z* Calcd for $C_{21}H_{21}N_2O_4$ [$(M+H)^+$]: 365.1501. Found: 365.1502.

7-(Benzyloxy)-3-[2-(2-bromo-5-isopropoxy-4-methoxyphenyl)ethyl]-8-methoxy-5-(methoxymethyl)-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one (19). Under an argon atmosphere, a mixture of **7** (513 mg, 1.41 mmol), **8**[6b] (956 mg, 2.16 mmol), and cesium carbonate (1.39 g, 4.26 mmol) in DMF (20 mL) was stirred for 18 h at room temperature. The mixture was quenched with saturated aqueous ammonium chloride and diluted with water. The product was extracted with DCM, and the extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane−ethyl acetate = 2:1 to 1:1) to give **19** as a colorless solid (73.9 mg, 84%). Recrystallization from DCM–hexane gave a colorless powder. Mp 162.5–163.5 °C. IR (KBr): 1643, 1507, 1448, 1417, 1257, 1084 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.11 (d, J = 6.1 Hz, 6H), 3.20 (t, J = 6.6 Hz, 2H), 3.39 (s, 3H), 3.80 (s, 3H), 3.97 (s, 3H), 4.14 (sep, J = 6.1 Hz, 1H), 4.74 (t, J = 6.6 Hz, 2H), 5.26 (s, 2H), 5.70 (br s, 2H), 6.36 (s, 1H), 6.43 (d, J = 2.8 Hz, 1H), 6.73 (d, J = 2.8 Hz, 1H), 6.98 (s, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.29–7.33 (m, 1H), 7.36–7.40 (m, 2H), 7.48–7.52 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.8, 38.0, 48.8, 56.0, 56.1, 56.4, 71.3, 71.6, 73.1, 99.8, 102.8, 105.3, 112.1, 114.5, 115.9, 118.1, 119.3, 127.6, 128.0, 128.6, 129.4, 129.6, 130.4, 131.5, 136.8, 146.2, 146.5, 147.7, 149.7, 156.2. Anal. Calcd for $C_{33}H_{35}BrN_2O_6$: C, 62.36; H, 5.55; N, 4.41. Found: C, 62.25; H, 5.41; N, 4.29.

3-(Benzyloxy)-11-isopropoxy-2,12-dimethoxy-5-(methoxymethyl)-8,9-dihydrobenzo[7,8]indolizino-[3,2-*c*]quinolin-6(5*H*)-one (20). Under an argon atmosphere, a mixture of **19** (300 mg, 0.472 mmol), potassium carbonate (144 mg, 1.04 mmol) and $Pd(PPh_3)_4$ (27.9 mg, 24.1 μmol) in DMA (20 mL) was heated at 125 °C for 20 h. After cooling to room temperature, the mixture was diluted with water. The precipitate thus formed was collected by filtration, washed with water, and dried under reduced pressure. The crude product was purified by column chromatography over silica gel 60N (hexane–EtOAc = 2:1) to give **20** as a pale yellow solid (237 mg, 90%). Recrystallization from DCM–hexane gave a colorless powder. Mp 198.5–199.5 °C. IR (KBr): 1643, 1491, 1444, 1259, 1099 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.41 (d, J = 6.1 Hz, 6H), 3.07 (t, J = 6.8 Hz, 2H), 3.40 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H), 4.59 (sep, J = 6.1 Hz, 1H), 4.86 (t, J = 6.8 Hz, 2H), 5.25 (s, 2H), 5.68 (br s, 2H), 6.80 (s, 1H), 6.86 (s, 1H), 7.20 (s, 1H), 7.22 (s, 1H), 7.29–7.33 (m, 1H), 7.33 (s, 1H), 7.36–7.41 (m, 2H), 7.49–7.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 28.6, 42.3, 56.0, 56.3, 56.4, 71.3, 71.6, 73.1, 94.7, 102.7, 105.4, 108.1, 111.9, 115.1, 119.5, 120.7, 125.7, 127.7, 128.0, 128.6, 129.2, 130.5, 136.8, 138.5, 146.2, 147.7, 147.8, 149.6, 156.4. Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.34; H, 6.44; N, 4.88.

3-(Benzyloxy)-14-bromo-11-isopropoxy-2,12-dimethoxy-5-(methoxymethyl)-8,9-dihydrobenzo[7,8]-indolizino[3,2-*c*]quinolin-6(5*H*)-one (5). A solution of NBS (60.0 mg, 0.337 mmol) in DMF (2 mL) was added dropwise to a solution of **20** (180 mg, 0.325 mmol) in DMF (6 mL) at 0 °C. The mixture was stirred for 24 h at 0 °C. The solution was diluted with water and the product was extracted with DCM.

The extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 2:1 to EtOAc) to give **5** as a pale yellow solid (190 mg, 92%). Recrystallization from DCM–hexane gave a colorless powder. Mp 168.5–170.5 °C. IR (KBr): 1639, 1484, 1419, 1263, 1244, 1208 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.42 (d, J = 6.1 Hz, 6H), 3.01 (t, J = 6.5 Hz, 2H), 3.39 (s, 3H), 3.96 (s, 3H), 4.03 (s, 3H), 4.62 (sep, J = 6.1 Hz, 1H), 4.94 (t, J = 6.5 Hz, 2H), 5.27 (s, 2H), 5.66 (br s, 2H), 6.82 (s, 1H), 7.21 (s, 1H), 7.29–7.34 (m, 1H), 7.36–7.41 (m, 2H), 7.49–7.53 (m, 2H), 8.18 (s, 1H), 8.59 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 29.3, 42.6, 56.1, 56.3, 56.3, 71.1, 71.4, 73.3, 86.3, 102.4, 105.4, 109.9, 111.6, 114.7, 118.7, 119.9, 124.8, 127.6, 127.7, 128.0, 128.6, 130.7, 133.9, 136.7, 145.5, 147.6, 147.7, 148.8, 155.8. HRFABMS *m/z* Calcd for $C_{33}H_{33}BrN_2O_6$ (M^+): 632.1522. Found: 632.1522.

4-Bromo-2-methoxy-1-(methoxymethoxy)benzene (22). Under an argon atmosphere, chloromethyl methyl ether (8.42 mL, 111 mmol) was added dropwise to a solution of 4-bromo-2-methoxyphenol (**21**)[14] (15.0 g, 73.9 mmol) and *N*,*N*-diisopropylethylamine (25.7 mL, 148 mmol) in DCM (150 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 18 h. The mixture was quenched with saturated aqueous ammonia and the product was extract with DCM. The extract was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by distillation (77–85 °C/20 Pa) to give **22** as a pale yellow oil (16.8 g, 92%). IR (KBr): 1499, 1254, 1157, 1079, 993 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.50 (s, 3H), 3.87 (s, 3H), 5.20 (s, 2H), 7.00–7.03 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.1, 56.3, 95.6, 114.5, 115.2, 117.7, 123.6, 145.7, 150.5. HRFABMS *m/z* Calcd for $C_9H_{11}BrO_3$ (M^+): 245.9892. Found: 245.9891. These physical and spectroscopic data are in good agreement with those previously reported.[20]

2-[3-Methoxy-4-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6a). Under an argon atmosphere, a mixture of **22** (2.00 g, 8.09 mmol), bis(pinacolato)diboron (2.26 g, 8.90 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (331 mg, 0.405 mmol), potassium acetate (2.38 g, 24.3 mmol), and 1,4-dioxane (30 mL) was heated at 80 °C for 14 h. After cooling to room temperature, the mixture was diluted with water and concentrated under reduced pressure. The product was extracted with EtOAc and the extract was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed over silica gel 60N (hexane–EtOAc = 5:1). The crude product was purified by bulb-to-bulb distillation (125–135 °C/20 Pa) to give **6a** as a colorless oil (1.99 g, 84%). IR (KBr): 1388, 1356, 1325, 1144 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 12H), 3.51 (s, 3H), 3.93 (s, 3H), 5.27 (s, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 1.3 Hz, 1H), 7.39 (dd, J = 1.3 and 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.8, 55.9, 56.2, 83.7, 95.1, 115.1, 117.2, 128.4, 148.9, 149.2. HRFABMS *m/z* Calcd for $C_{15}H_{23}BO_5$ (M^+): 294.1639. Found: 294.1639.

3-(Benzyloxy)-11-isopropoxy-2,12-dimethoxy-14-[3-methoxy-4-(methoxymethoxy)phenyl]-5-(methoxymethyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-*c*]quinolin-6(5*H*)-one (23a). Under an argon atmosphere, a mixture of **5** (80.0 mg, 0.126 mmol), **6a** (55.7 mg, 0.189 mmol), $Pd(PPh_3)_4$ (14.6 mg, 12.6 μmol), sodium carbonate (88.3 mg, 0.833 mmol), DME (4.8 mL), and degassed water (480 μL) was heated at 85 °C for 21 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was extracted with DCM. The extract was washed successively with water and brine, dried over sodium sulfate, and evaporated. The crude product was purified by column chromatography over silica gel 60N (hexane–EtOAc = 1:1) to give **23a** as a colorless solid (53.6 mg, 59%). Recrystallization from DCM–hexane gave a colorless powder. Mp 196.5–197.5 °C. IR (KBr): 1640, 1420, 1243, 1213, 1186, 1151 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (d, J = 6.1 Hz, 6H), 3.03–3.14 (m, 2H), 3.34 (s, 3H), 3.41 (s, 3H), 3.43 (s, 3H), 3.53 (s, 3H), 3.84 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.85–4.93 (m, 1H), 4.99–5.08 (m, 1H), 5.22 (s, 2H), 5.28 (s, 2H), 5.69 (br s, 2H), 6.71 (s, 1H), 6.76 (s, 1H), 6.88 (s, 1H), 7.07 (d, J = 1.9 Hz, 1H), 7.11 (dd, J = 1.9 and 8.1 Hz, 1H), 7.17 (s, 1H), 7.27–7.31 (m, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.33–7.38 (m, 2H), 7.44–7.49 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 22.1, 29.0, 42.5, 55.1, 55.2, 56.0, 56.1, 56.1, 71.1, 71.3, 73.2, 95.6, 102.5, 105.6, 109.1, 112.3, 114.2, 114.7, 114.7, 117.8, 118.3, 120.7, 123.8, 126.2, 126.4, 127.6, 127.9, 128.5, 130.5, 131.3, 134.3, 136.8, 145.4, 145.7, 146.8, 147.0, 148.6, 150.8, 156.5. HRFABMS *m/z* Calcd for $C_{42}H_{44}N_2O_9$ (M^+): 720.3047. Found: 720.3048.

3-(Benzyloxy)-11-isopropoxy-2,12-dimethoxy-14-[4-methoxy-3-(methoxymethoxy)phenyl]-5-(methoxymethyl)-8,9-dihydrobenzo[7,8]indolizino[3,2-*c*]quinolin-6(5*H*)-one (23b). According to the procedure described for the preparation of **23a**, **5** (50.2 mg, 79.2 μmol), **6b**[16] (35.0 mg, 0.119 mmol), and $Pd(PPh_3)_4$ (9.7 mg, 8.4 μmol) were reacted. After chromatographic purification over silica gel 60N (toluene–EtOAc = 5:1), **23b** was obtained as a colorless solid (38.4 mg, 67%). IR (KBr): 1644, 1484, 1419, 1258, 1208, 1078 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 3H), 1.37 (d, J = 6.1 Hz, 3H), 3.01–3.13 (m, 2H), 3.34 (s, 3H), 3.41 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H), 3.95 (s, 3H), 4.54 (sep, J = 6.1 Hz, 1H), 4.84–4.91 (m, 1H), 4.99–5.06 (m, 1H), 5.20 (d, J = 6.8 Hz, 1H), 5.22 (s, 2H), 5.22 (d, J = 6.8 Hz, 1H), 5.69 (br s, 2H), 6.68 (s, 1H), 6.75 (s, 1H), 6.88 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.16 (dd, J = 2.0 and 8.3 Hz, 1H), 7.17 (s, 1H), 7.27–7.31 (m, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.33–7.38 (m, 2H), 7.45–7.49 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 29.0, 42.5, 55.0, 55.2, 56.0, 56.2, 56.3, 71.1, 71.3, 73.2, 95.6, 102.4, 105.7, 109.1, 112.4, 112.6, 114.1, 114.7, 118.2, 119.7, 120.8, 125.6, 126.3, 126.5, 127.6, 127.9, 128.5, 129.5, 130.5, 134.4, 136.8, 145.3, 146.8, 147.0, 147.2, 148.5, 149.6, 156.5. HRFABMS *m/z* Calcd for $C_{42}H_{44}N_2O_9$ (M^+): 720.3047. Found: 720.3047.

3-(Benzyloxy)-11-isopropoxy-2,12-dimethoxy-14-[3-methoxy-4-(methoxymethoxy)phenyl]-5-(methoxymethyl)benzo[7,8]indolizino[3,2-*c*]quinolin-6(5*H*)-one (24a). Under an argon atmosphere,

a solution of **23a** (40.0 mg, 55.5 μmol) and DDQ (18.9 mg, 83.2 μmol) in toluene (2.4 mL) was heated at 100 °C for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography over Chromatorex NH-DM1020 silica gel (hexane–EtOAc = 1:1) to give **24a** as a colorless solid (29.0 mg, 73%). Recrystallization from DCM–hexane gave a colorless powder. Mp 196.5–197.5 °C. IR (KBr): 1642, 1461, 1432, 1255, 1211, 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.43 (d, J = 6.1 Hz, 6H), 3.43 (s, 6H), 3.46 (s, 3H), 3.56 (s, 3H), 3.86 (s, 3H), 4.68 (sep, J = 6.1 Hz, 1H), 5.25 (s, 2H), 5.31 (s, 2H), 5.77 (br s, 2H), 6.93 (d, J = 7.4 Hz, 1H), 7.01 (s, 1H), 7.08 (s, 1H), 7.13 (s, 1H), 7.16 (d, J = 1.9 Hz, 1H), 7.21 (dd, J = 1.9 and 8.1 Hz, 1H), 7.23 (s, 1H), 7.27–7.32 (m, 1H), 7.34–7.39 (m, 2H), 7.41 (d, J = 8.1 Hz, 1H), 7.46–7.50 (m, 2H), 9.57 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 21.9, 55.1, 55.2, 56.0, 56.1, 56.2, 71.1, 71.1, 73.1, 95.6, 102.3, 105.8, 106.2, 110.2, 110.6, 111.1, 111.7, 112.4, 115.2, 118.0, 119.1, 123.6, 124.3, 124.4, 127.6, 127.6, 128.0, 128.6, 131.3, 131.5, 132.9, 136.6, 145.3, 145.9, 147.8, 147.9, 149.8, 151.0, 156.5. HRFABMS *m/z* Calcd for $C_{42}H_{42}N_2O_9$ (M^+): 718.2890. Found: 718.2891.

3-(Benzyloxy)-11-isopropoxy-2,12-dimethoxy-14-[4-methoxy-3-(methoxymethoxy)phenyl]-5-(methoxymethyl)benzo[7,8]indolizino[3,2-*c*]quinolin-6(5*H*)-one (24b). According to the procedure described for the preparation of **24a**, **23b** (33.2 mg, 46.1 μmol) and DDQ (15.8 mg, 69.6 μmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–EtOAc = 1:1), **24b** was obtained as a pale yellow solid (23.3 mg, 70%). IR (KBr): 1645, 1432, 1254, 1207, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.43 (d, J = 6.1 Hz, 6H), 3.43 (s, 3H), 3.44 (s, 3H), 3.46 (s, 3H), 3.47 (s, 3H), 3.99 (s, 3H), 4.68 (sep, J = 6.1 Hz, 1H), 5.24 (s, 2H), 5.25 (s, 2H), 5.76 (br s, 2H), 6.93 (d, J = 7.4 Hz, 1H), 6.98 (s, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 7.27 (dd, J = 1.9 and 8.2 Hz, 1H), 7.27–7.32 (m, 1H), 7.34–7.39 (m, 2H), 7.42 (d, J = 1.9 Hz, 1H), 7.46–7.50 (m, 2H), 9.57 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 55.0, 55.2, 56.0, 56.3, 56.4, 71.1, 71.1, 73.1, 95.6, 102.3, 105.8, 106.4, 110.1, 110.6, 111.1, 111.8, 112.4, 112.7, 119.2, 120.2, 123.6, 124.3, 126.1, 127.6, 127.8, 128.0, 128.6, 129.7, 131.3, 133.0, 136.6, 145.3, 147.4, 147.8, 147.9, 149.8, 149.8, 156.5. HRFABMS *m/z* Calcd for $C_{42}H_{42}N_2O_9$ (M^+): 718.2890. Found: 718.2888.

3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxybenzo[7,8]indolizino[3,2-*c*]-quinolin-6(5*H*)-one (azalamellarin D, 3). To a cooled (−78 °C) solution of **24a** (22.0 mg, 30.6 μmol) in DCM (3.3 mL), was added dropwise a solution of BCl_3 in heptane (1.0 M, 367 μL, 0.367 mmol) under an argon atmosphere. The mixture was stirred at −78 °C for 0.5 h and 0 °C for 3 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate and the mixture was concentrated under reduced pressure. The precipitated solid was filtered, washed with water, and dried under reduced pressure. After purification by column chromatography over silica gel 60N (EtOAc to acetone), **3** was obtained as a pale gray powder (11.7 mg, 77%). Recrystallization from DCM–cyclohexane gave a pale

gray powder. Mp >300 °C (sealed capillary) [lit.[9] Mp >295 °C]. IR (KBr): 3140, 1647, 1429, 1275, 1211 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.34 (s, 3H), 3.37 (s, 3H), 3.76 (s, 3H), 6.80 (s, 1H), 6.88 (s, 1H), 7.00 (dd, J = 1.9 and 7.9 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 7.12 (s, 1H), 7.12 (d, J = 1.9 Hz, 1H), 7.13 (s, 1H), 9.27 (s, 1H), 9.37 (d, J = 7.4 Hz, 1H), 9.49 (s, 1H), 9.71 (s, 1H), 11.27 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 54.5, 54.8, 56.0, 102.3, 105.5, 105.9, 108.6, 110.1, 110.4, 111.6, 112.0, 115.2, 116.4, 117.8, 122.6, 123.9, 124.0, 126.9, 127.9, 131.4, 131.4, 143.4, 146.5, 147.1, 147.4, 148.0, 148.7, 155.5. HRFABMS *m/z* Calcd for $C_{28}H_{22}N_2O_7$ (M^+): 498.1427. Found: 498.1427. These physical and spectroscopic data are in good agreement with those previously reported.[8,9]

3,11-Dihydroxy-14-(3-hydroxy-4-methoxyphenyl)-2,12-dimethoxybenzo[7,8]indolizino[3,2-*c*]-quinolin-6(5*H*)-one (azalamellarin N, 4). According to the procedure described for the preparation of **3**, **24b** (20.2 mg, 28.1 μmol) and a solution of BCl_3 in heptane (1.0 M, 340 μL, 0.340 mmol) were reacted. After purification by column chromatography over silica gel 60N (EtOAc to acetone), **4** was obtained as a pale yellow powder (6.0 mg, 43%). Mp >300 °C (sealed capillary) [lit.[9] Mp >290 °C]. IR (KBr): 3301, 1648, 1606, 1493, 1428, 1274, 1215 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.35 (s, 3H), 3.38 (s, 3H), 3.86 (s, 3H), 6.83 (s, 1H), 6.88 (s, 1H), 6.98 (d, J = 1.9 Hz, 1H), 7.00 (dd, J = 1.9 and 8.0 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 7.12 (s, 1H), 7.14 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 9.34 (s, 1H), 9.36 (d, J = 7.4 Hz, 1H), 9.50 (s, 1H), 9.72 (s, 1H), 11.27 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 54.5, 54.8, 56.2, 102.3, 105.4, 105.9, 108.4, 109.7, 110.5, 111.6, 112.1, 113.7, 117.7, 118.5, 122.3, 122.6, 123.9, 127.7, 128.8, 131.2, 131.4, 143.4, 147.1, 147.4, 147.7, 148.0, 155.4. HRFABMS *m/z* Calcd for $C_{28}H_{22}N_2O_7$ (M^+): 498.1427. Found: 498.1427. These physical and spectroscopic data are in good agreement with those previously reported.[9]

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