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Total Synthesis of Dactylicapnosines A and B

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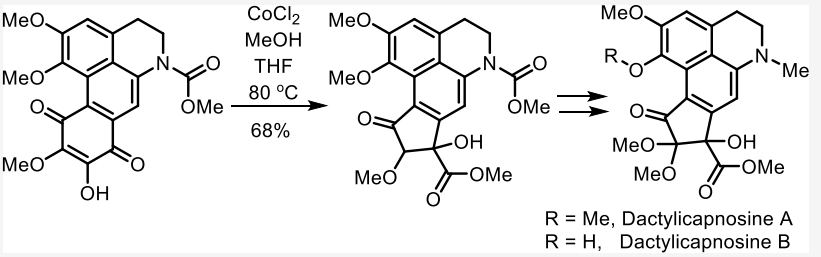

ABSTRACT: Dactylicapnosines A and B, two natural products from *Dactylicapnos scandens*, exhibited potent anti-inflammatory and analgesic activities both in vitro and in vivo. In this paper, we report our second-generation synthesis of dactylicapnosine A and the first total synthesis of dactylicapnosine B. Our synthetic route features acid-induced isomerization of *o*-quinone (**16**), Co-mediated regioselective ring contraction of *p*-quinone (**8b**), and oxidative methoxylation of enone (**18**). This modified sequence provides dactylicapnosine A in 14 steps with an overall yield of 12% from a known compound (**14a**) and also offers opportunities to synthesize dactylicapnosine-like analogues for biological investigations.

INTRODUCTION

Dactylicapnosines A and B are two racemic natural products isolated from *Dactylicapnos scandens* (Papaveraceae), a traditional Chinese medicinal herb used widely for treatment of various pains in the southwest of China.[1] The structures of these two compounds are 9,10-seco-7-dehydroaporphines with unprecedented highly oxygenated five-membered D-rings (Figure 1). Biosynthetically, dactylicapnosines A and B might derive from oxidative D-ring contractions of isocorydione and demethylsonodione, two known aporphine alkaloids present also in *Dactylicapnos scandens*, respectively.[2]

Dactylicapnosine A exhibited significant anti-inflammatory activity in vitro by inhibition of the expression of TNF-α, IL-1β, and PGE2. In our previous studies,[1] the in vivo anti-inflammatory and analgesic activities of dactylicapnosine A were also evaluated using samples provided by our bioinspired total synthesis. Although the total synthesis of dactylicapnosine A, with the key steps being oxidative aromatization of the aporphinoid derivative (Scheme 1, **7**) and oxidative rearrangement of *p*-quinone (**8**), was completed in 10 steps with 5% overall yield, the shortcoming associated with our first generation synthetic route is the unbiased oxidative ring contraction of *p*-quinone **8**, which provided the desired cyclopentanone (**9**) in only 32% yield (Scheme 1). The undesired regioisomer (**10**) was also produced in similar yield.

To access the sample of dactylicapnosine A as well as its analogues more for further biological evaluation, it is of our interest to develop a regioselective strategy with better overall yield. In this full paper, we report the first total synthesis of dactylicapnosine B and our second-generation synthesis of dactylicapnosine A through regioselective oxidative ring contraction of the isocorydione derivative.

RESULTS AND DISCUSSION

Our retrosynthetic analysis for dactylicapnosine A and dactylicapnosine B is indicated in Scheme 2. Dactylicapnosine B could be prepared by regioselective demethylation of dactylicapnosine A with the assistance of the neighboring carbonyl group. The isocorydione derivative (**8a**) could be obtained by oxidative formation of the *p*-quinone moiety and oxidative aromatization of the B-ring. The aporphinoid intermediate (**11**) can be synthesized by a palladium-mediated coupling reaction of compound **12**. Pictet–Spengler cyclization of aldehyde **14** (X = O) with commercially available amine derivative **13** would lead to tetrahydroisoquinoline **12**. The highly oxy-substituted benzene derivative **14** (X = CH_2) could be accessed by Claisen rearrangement of intermediate **15c** followed by a number of functional group manipulations. Compound **15c** could be obtained from commercially available 2,3,4-trimethoxybenzaldehyde.

We began our investigations by preparing intermediate 7 (Scheme 3) according to our previous procedure.[1] Starting from 2,3,4-trimethoxybenzaldehyde (**15a**), Baeyer–Villiger

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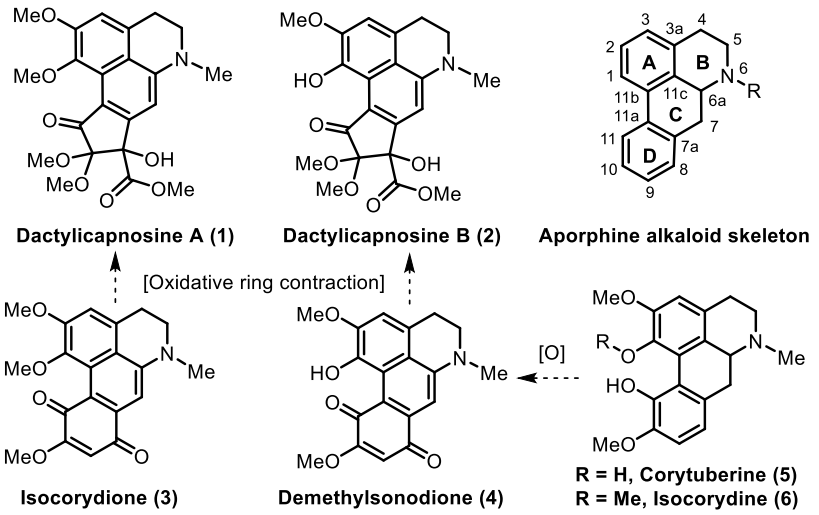
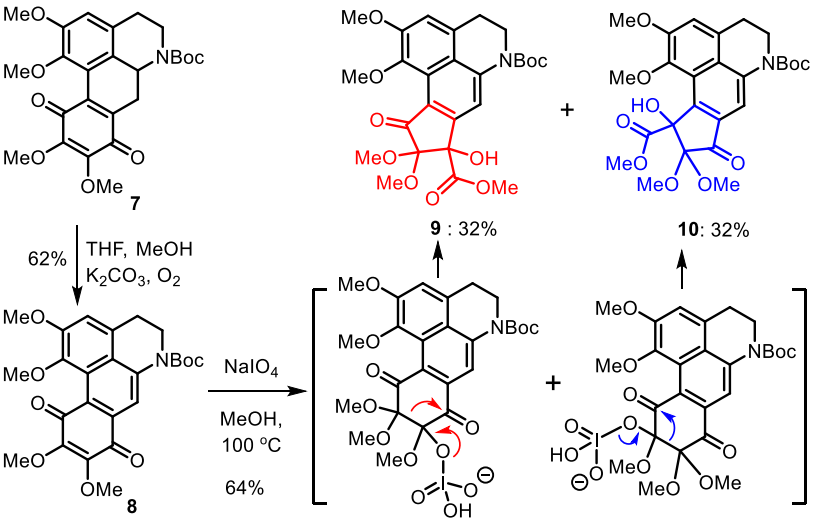


Figure 1. Alkaloids from *Dactylicapnos scandens* and a possible biosynthetic relationship.

Scheme 1. Bio-inspired synthesis of dactylicapnosine A



oxidation followed by allyl ether formation (to **15b**) and Claisen rearrangement afforded 14a in 89% overall yield in 3 steps.[3] Treatment of phenol 14a with benzyl bromide in the presence of potassium carbonate provided **14b** in 99% yield. After oxidative cleavage of the double bond, the resulting aldehyde (**14c**) was then converted to its bromide 14d using standard NBS conditions,[4] with 74% yields in two steps. Treatment of 14d with amine **13a** in the presence of trifluoroacetic acid afforded tetrahydroisoquinoline **12a** in yields of 86%.[5] With intermediate **12a** in hand, we next conducted the coupling reaction with palladium acetate and triphenylphosphine[6] under microwave conditions and the aporphinoid derivative 11a was obtained in 78% yield (Scheme 3). After removal of the benzyl-protecting group, oxidation of the resulting phenol with iodobenzene diacetate (IBD) in hexafluoroisopropanol (HFIP) gave quinone **7** in 86% yield over two steps.

In our previous synthesis,[1] compound 8 was obtained by oxidative aromatization and used in the following sodium periodate-mediated ring contraction (Schemes 3 and 1). In this study, further attempts were made toward oxidative ring contraction of quinones **7** and **8** using a range of oxidants (Oxone, $KMnO_4$, $NaBO_3{\cdot}4H_2O$, $NaIO_4$, and H_2O_2); however, only epoxide **7a**, the structure being established by X-ray crystallography (see the Supporting Information), was isolated when hydrogen peroxide was used in the presence of sodium carbonate (Scheme 4).[7] Other reaction conditions resulted in decomposition of substrate **7**. Although sodium perborate tetrahydrate ($NaBO_3{\cdot}4H_2O$) and hydrogen peroxide (H_2O_2) could promote the oxidative ring-contraction of quinone **8** to compounds **9**, **9a**, and **10** (structures of **9a** and **10** were confirmed by X-ray crystallography analysis, see the Supporting Information) under mild reaction conditions, no improved yields or regioselectivities were observed (Scheme 4).

Having failed to improve the regioselectivity, we decided to explore alternative ring contraction mediated by cobaltous chloride.[8] After removal of the Boc-protecting group under acidic conditions, amine **11b** was converted to intermediate **11c** by treating with *N*-chlorosuccinimide, potassium *tert*-butoxide,[9] and methyl chloroformate (Scheme 5). Next, palladium-catalyzed hydrogenolysis followed by oxidation with IBX (*o*-iodoxybenzoic acid) afforded *o*-quinone **16** in 77% yield.[10] To our delight, *o*-quinone **16** could be readily isomerized to *p*-quinone **8b** in the presence of sulfuric acid in high yield (Scheme 5).

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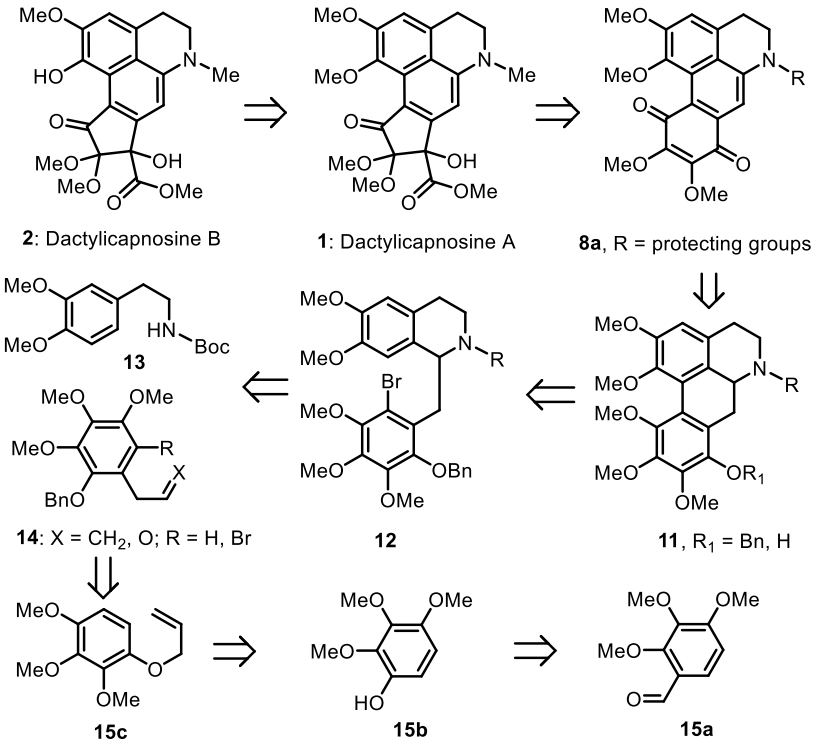
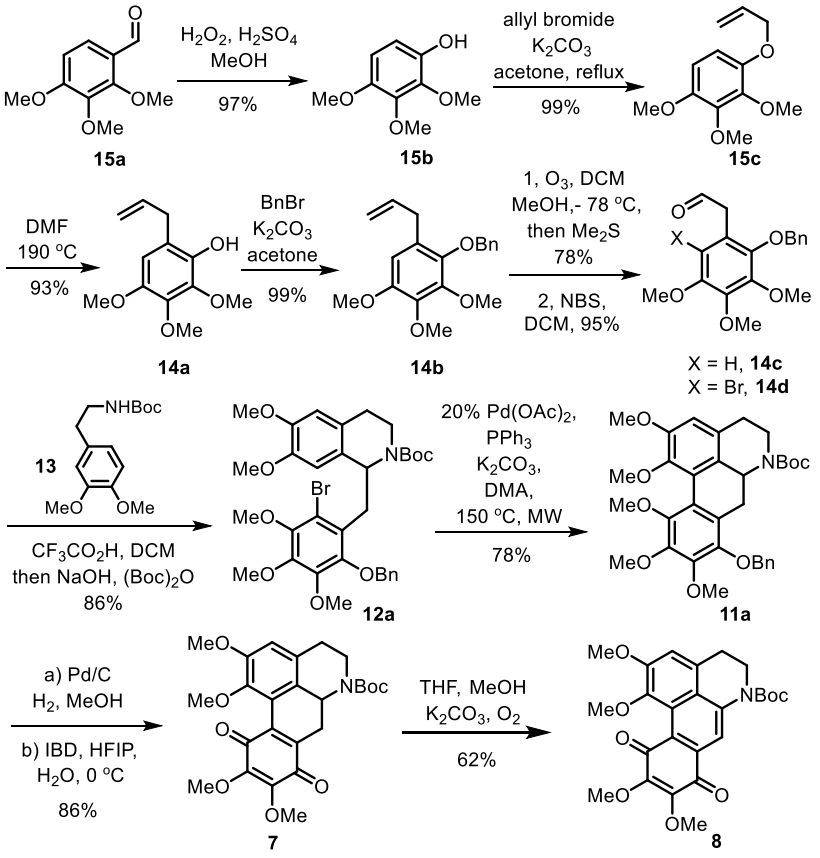
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Retrosynthetic Analysis of Dactylicapnosines A and B



Scheme 3. Synthesis of Intermediates 7 and 8



With intermediate **8b** in hand, we next conducted a cobalt-mediated ring contraction reaction.[8] Treating *p*-quinone **8b** with cobaltous chloride in methanol and tetrahydrofuran (THF) afforded cyclopentenone **17** in 68% yield. Dehydration with trifluoroacetic anhydride in the presence of triethylamine[11] provided intermediate **18**. Oxidation of the enone

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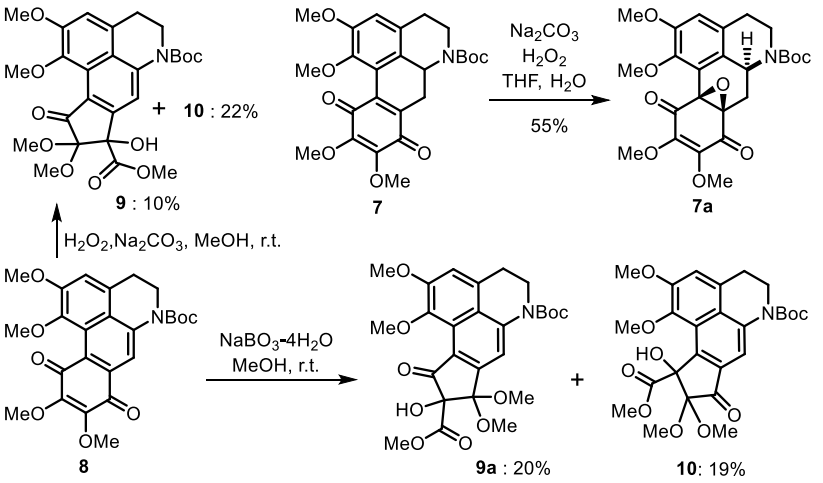
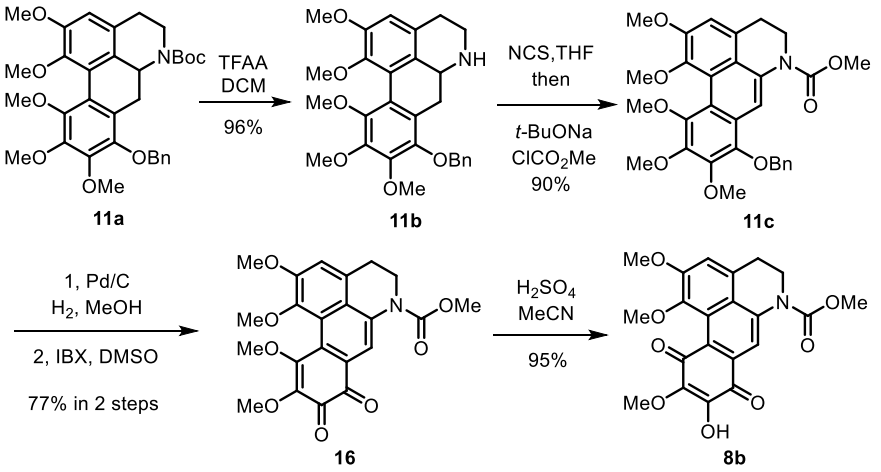
J. Org. Chem. XXXX, XXX, XXX−XXX

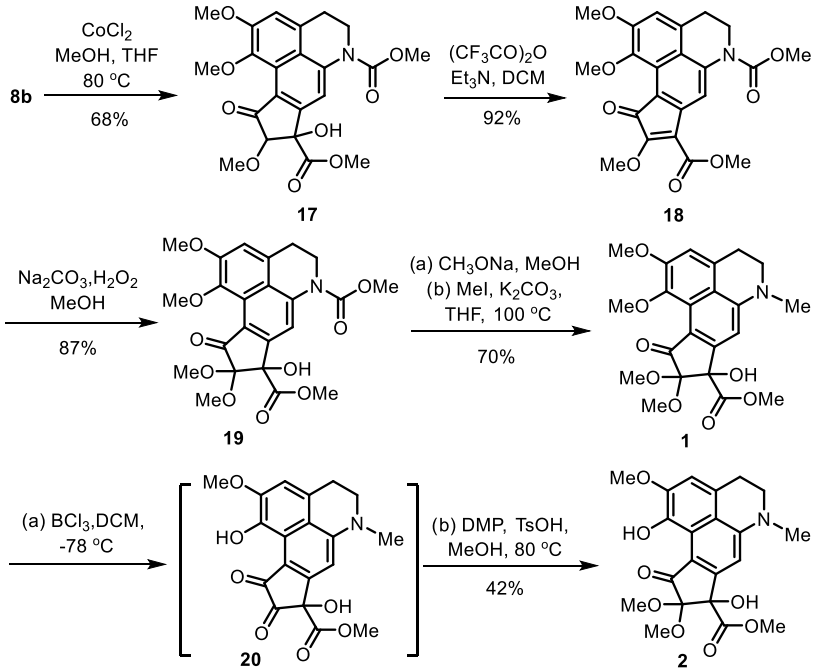
Scheme 4. Further Studies on Oxidative Ring Contraction



Scheme 5. Transformation of 11a to *p*-Quinone 8b



Scheme 6. Final Stage toward the Synthesis of Dactylicapnosines A and B



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system with hydrogen peroxide in the presence of potassium carbonate led to the precursor of dactylicapnosine A in 87% yield. After deprotection with sodium methoxide and methylation with methyl iodide, dactylicapnosine A was obtained in 70% yield. Finally, treatment of dactylicapnosine A with boron trichloride,[12] leading to an unstable diketone intermediate (**20**, NMR spectra shown in the Supporting Information), followed by methoxylation with 2,2-dimethoxypropane completed the first total synthesis of dactylicapnosine B (Scheme 6). The NMR spectra as well as physical data, including X-ray analysis (of compounds **19** and **1**), of our synthetic dactylicapnosine A and dactylicapnosine B were consistent with those of natural products.[1]

CONCLUSIONS

In summary, we have completed the total synthesis of two bioactive natural alkaloids bearing a 9,10-seco-7-dehydroaporphinoid skeleton. Our second-generation synthetic route toward dactylicapnosines A and B features acid-induced isomerisation of *o*-quinone, a Co-mediated regioselective ring contraction reaction of *p*-quinone, and oxidative methoxylation of the enone system. This modified sequence led to the target (dactylicapnosine A) in 12% overall yields from a known compound (**14a**), much better than our previous synthesis. This new synthetic route should be useful in the future for the synthesis of medicinally interesting dactylicapnosine-like analogues.

EXPERIMENTAL SECTION

General Experiments. All reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Anhydrous THF was dried by distillation over metallic sodium and benzophenone; dichloromethane and methanol were distilled from calcium hydride. Starting materials and reagents used in reactions were obtained commercially from Adamas-β, Aldrich, and Accela ChemBio and were used without purification, unless otherwise indicated. Nuclear magnetic resonances (^{1}H NMR and ^{13}C NMR) spectra were recorded on either Bruker Avance 300 or 400 spectrometers. High-resolution mass spectra (HRMS) were recorded on an Agilent G6230 TOF MS spectrometer. Melting points were measured with a capillary melting point instrument and are uncorrected.

*8-(Benzyloxy)-1,2,9,10,11-pentamethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline (**11b**).* To a solution of compound **11a** (2 g, 3.466 mmol) in dichloromethane (20 mL), trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The mixture was quenched carefully by addition of water (60 mL) and a 10% aqueous solution of sodium hydroxide, until pH 13−14. The resulting mixture was then extracted with dichloromethane (4 × 20 mL), and the combined organic phases were dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 → DCM/MeOH = 5:1) to afford amine **11b** (1.58 g, 96%) as a pale yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.46−7.34 (m, 5H), 6.66 (s, 1H), 5.02 (s, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H), 3.44−3.40 (m, 1H), 3.31−3.30 (m, 1H), 3.14−3.08 (m, 1H), 2.95−2.93 (m, 2H), 2.68−2.64 (m, 1H), 2.05−1.86 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ: 151.6, 148.8, 146.4, 145.5, 145.4, 143.7, 137.4, 130.1, 128.5, 128.3, 128.0, 127.6, 126.4, 124.2, 120.6, 111.9, 75.5, 61.3, 61.1, 60.9, 60.8, 56.0, 53.9, 43.0, 31.2, 28.7; IR (KBr, thin film, cm^{-1}): 2940, 2839, 1661, 1596, 1563, 1515, 1462, 1409, 1379, 1354, 1328, 1296, 1261, 1195, 1119, 1104, 1082, 1065, 1039, 1023, 972, 755, 734, 700; HRMS (electrospray ionization (ESI$^+$)) m/z [M + H]$^+$: calcd for $C_{28}H_{32}NO_6$: 478.2224, found: 478.2223.

*Methyl-8-(benzyloxy)-1,2,9,10,11-pentamethoxy-4,5-dihydro-6H-dibenzo[de,g]quinoline-6- carboxylate (**11c**).* Amine **11b** (1.346 g, 2.82 mmol) was dissolved in THF (40 mL). To this solution, *N*-chlorosuccinimide (NCS, 450 mg, 3.39 mmol) was added in a nitrogen-filled glovebox. After being stirred at room temperature for 2 h, sodium *tert*-butoxide (2.710 g, 28.2 mmol) was introduced. The reaction mixture was then stirred for 12 h before addition of methyl chloroformate (2.664 g, 28.2 mmol). The resulting mixture was allowed to stir at ambient temperature for 24 h. After thin-layer chromatography (TLC) analysis, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford carbomate **11c** (1.5 g, 90%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.02 (s, 1H), 7.62−7.60 (m, 2H), 7.43−7.32 (m, 3H), 7.05 (s, 1H), 5.16 (s, 2H), 4.07−4.05 (m, 8H), 3.97 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 3.16 (t, J = 4.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ: 155.2, 150.8, 149.2, 145.9, 145.1, 141.7, 137.8, 132.1, 128.5, 128.2, 127.9, 127.1, 124.5, 123.6, 120.3, 116.1, 112.8, 111.1, 76.1, 61.6, 60.9, 60.8, 56.7, 53.0, 43.5, 30.3; IR (KBr, thin film, cm^{-1}): 3030, 2993, 2940, 2844, 1704, 1619, 1584, 1496, 1456, 1447, 1390, 1361, 1334, 1323, 1280, 1255, 1235, 1219, 1201, 1142, 1120, 1097, 1078, 1051, 1023, 988, 762, 735, 700; HRMS (ESI$^+$) m/z [M + H]$^+$: calcd for $C_{30}H_{32}NO_8$: 534.2122, found: 534.2121.

*Methyl-1,2,10,11-tetramethoxy-8,9-dioxo-4,5,8,9-tetrahydro-6H-dibenzo[de,g]quinoline-6- carboxylate (**16**).* To a solution of carbamate **11c** (1.33 g, 2.495 mmol) in methanol (20 mL), palladium on carbon (10% Pd/C, 270 mg, 2.495 mmol) was added. The resulting mixture was stirred at room temperature in an autoclave under a hydrogen atmosphere (0.4 MPa H_2) for 12 h. The mixture was filtered through a short column of silica gel and washed with ethyl acetate (ca. 50 mL). The filtrate was concentrated under reduced pressure to give crude phenol, which was used for the next step without further purification. The crude phenol was dissolved in dimethyl sulfoxide (DMSO) (20 mL), and then, 2-iodoxybenzoic acid (0.838 g, 2.994 mmol) was added. The resulting mixture was allowed to stir at room temperature for 24 h. After TLC analysis, silica gel (ca. 2g) was added. The mixture was stirred at ambient temperature for 24 h, and at this time, the color of the mixture turned dark blue. The mixture was filtered and washed with ethyl acetate. The filtrate was diluted with water (100 mL) and extracted with ethyl acetate. (4 × 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1 → 1:1) to yield *o*-quinone **16** (unstable, used as soon as possible, 0.820 g, 77%) as a dark blue plate. Mp: 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.05 (s, 1H), 7.16 (s, 1H), 4.21 (s, 3H), 4.09 (t, J = 5.6 Hz, 2H), 4.02 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.17 (t, J = 5.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ: 179.7, 177.4, 163.5, 154.6, 150.4, 144.3, 137.8, 137.3, 129.0, 127.9, 127.2, 126.1, 124.1, 116.7, 113.4, 62.0, 61.2, 56.9, 53.8, 43.7, 30.2; IR (KBr, thin film, cm^{-1}): 2995, 2948, 2847, 1712, 1661, 1622, 1604, 1538, 1508, 1456, 1441, 1405, 1380, 1349, 1308, 1216, 1204, 1141, 1119, 1090, 1034, 1001, 906, 764; HRMS (ESI$^+$) m/z [M + H]$^+$: calcd for $C_{22}H_{22}NO_8$: 428.1340, found: 428.1340.

*Methyl-9-hydroxy-1,2,10-trimethoxy-8,11-dioxo-4,5,8,11-tetrahydro-6H- dibenzo[de,g]quinoline-6-carboxylate (**8b**).* To a solution of *o*-quinone **16** (427 mg, 1 mmol) in acetonitrile (CH_3CN, 10 mL), concentrated sulphuric acid (H_2SO_4, 10 drops) was added, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with water (50 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1 → DCM/MeOH = 5:1) to afford *p*-quinone **8b** (392 mg, 95%) as a red solid. Mp: 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.17 (s, 1H), 7.14 (s, 1H), 6.64 (br s, 1H), 4.23 (s, 3H), 4.09 (t, J = 5.6 Hz, 2H), 4.00 (s, 3H),

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J. Org. Chem. XXXX, XXX, XXX−XXX

3.98 (s, 3H), 3.89 (s, 3H), 3.17 (t, J = 5.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ: 182.2, 181.9, 154.7, 151.2, 143.6, 142.2, 140.1, 138.9, 129.9, 128.7, 127.9, 126.1, 123.2, 116.3, 111.9, 61.2, 60.3, 56.7, 53.7, 43.9, 30.1; IR (KBr, thin film, cm^{-1}): 3383, 2949, 1713, 1683, 1658, 1603, 1584, 1510, 1443, 1405, 1380, 1346, 1310, 1254, 1229, 1214, 1205, 1141, 1120, 1097, 1084, 1030, 1012, 996, 963, 908, 764; HRMS (ESI^+) m/z $[M + H]^+$: calcd for $C_{21}H_{20}NO_8$: 414.1183, found: 414.1182.

*Dimethyl -8-hydroxy-1,2,9-trimethoxy-10-oxo-4,8,9,10-tetrahydrobenzo[de]cyclopenta[g]quinoline-6,8(5H)-dicarboxylate (**17**).* To a sealable tube (Teflon cap), *p*-quinone **8b** (207 mg, 0.5 mmol), anhydrous methanol (10 mL), THF (1 mL), and cobaltous chloride ($CoCl_2$, 649 mg, 5 mmol) were added. The resulting mixture was sealed and was allowed to stir at 80 °C (oil bath) for 24 h. The reaction mixture was cooled to room temperature. After TLC analysis, the mixture was filtered through a short column of silica gel and washed with ethyl acetate (ca. 40 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to yield the ring contraction product **17** (152 mg, 68%) as a pale yellow solid. Mp: 202−203 °C; ^1H NMR (400 MHz, $CDCl_3$): δ: 7.75 (s, 1H), 7.12 (s, 1H), 4.66 (s, 1H), 4.46 (s, 1H), 4.22−4.16 (m, 1H), 4.07−4.00 (m, 7H), 3.87 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.22−3.17 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ: 192.4, 172.8, 154.7, 151.8, 149.9, 143.9, 142.9, 129.6, 125.7, 120.9, 114.5, 110.9, 92.3, 80.2, 61.7, 60.7, 56.7, 54.1, 53.7, 43.9, 30.6; IR (KBr, thin film, cm^{-1}): 3594, 3469, 1727, 1604, 1516, 1465, 1440, 1404, 1345, 1312, 1276, 1253, 1228, 1209, 1147, 1105, 1092, 1040, 1008, 989, 960, 765; HRMS (ESI^+) m/z $[M + H]^+$: calcd for $C_{22}H_{24}NO_9$: 446.1446, found: 446.1447.

*Dimethyl-1,2,9-trimethoxy-10-oxo-4,10-dihydrobenzo[de]-cyclopenta[g]quinoline- 6,8(5H)-dicarboxylate (**18**).* Compound **17** (143 mg, 0.32 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (1.5 mL). The solution was cooled to 0 °C before addition of trifluoroacetic anhydride (0.5 mL). The resulting mixture was then stirred for 2 h. After TLC analysis, the reaction mixture was quenched with water (15 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to afford enone **18** (125 mg, 92%) as a brown solid. Mp: 170−171 °C; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.15 (s, 1H), 6.86 (s, 1H), 4.30 (s, 3H), 4.07 (t, J = 5.4 Hz, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.10 (t, J = 5.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ: 187.1, 164.1, 155.7, 154.7, 151,9, 149.7, 143.9, 142.0, 130.1, 127.7, 119.7, 113.2, 112.8, 112.0, 111.8, 61.5, 60.5, 56.7, 53.6, 51.8, 44.2, 30.5; IR (KBr, thin film, cm^{-1}): 3400, 1704, 1622, 1608, 1574, 1523, 1464, 1439, 1405, 1338, 1307, 1275, 1261, 1205, 1160, 764, 750; HRMS (ESI^+) m/z $[M + H]^+$: calcd for $C_{22}H_{22}NO_8$: 428.1340, found: 428.1340.

*Dimethyl-8-hydroxy-1,2,9,9-tetramethoxy-10-oxo-4,8,9,10-tetrahydrobenzo[de]cyclopenta[g]quinoline-6,8(5H)-dicarboxylate (**19**).* To a solution of compound **18** (43 mg, 0.1 mmol) in methanol (2 mL), hydrogen peroxide (30%, 2 drops) was added followed by sodium carbonate (16 mg, 0.15 mmol). The resulting mixture was then stirred at room temperature for 1 h. The mixture was filtered through a short column of silica gel and washed with ethyl acetate (ca. 20 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to provide product **19** (41 mg, 87%) as a pale yellow syrup. ^1H NMR (300 MHz, $CDCl_3$): δ: 7.75 (s, 1H), 7.11 (s, 1H), 4.26−4.18 (m, 1H), 4.08 (s, 3H), 3.99−3.94 (m, 4H), 3.84 (s, 3H), 3.67 (s, 3H), 3.56 (s, 3H), 3.47 (s, 3H), 3.20−3.15 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ: 189.0, 170.9, 154.6, 152.1, 151.8, 143.6, 143.1, 129.8, 125.9, 125.5, 120.8, 114.2, 111.2, 102.7, 80.9, 61.6, 56.6, 53.7, 52.2, 51.9, 44.0, 30.5; IR (KBr, thin film, cm^{-1}): 3484, 2951, 2844, 1733, 1604, 1515, 1464, 1440, 1404, 1348, 1312, 1253, 1228, 1212, 1164, 1107, 1075, 1043, 1011, 991, 895, 763, 733; HRMS (ESI^+) m/z $[M + H]^+$: calcd for $C_{23}H_{26}NO_{10}$: 476.1551, found: 476.1551.

*Dactylicapnosine A (**1**).* To a solution of compound **19** (48 mg, 0.1 mmol) in methanol (2 mL), sodium methoxide (6 mg, 0.11 mmol) was added. After being stirred at room temperature for 2 h, the mixture was filtered through a short column of silica gel and washed with a solution of triethylamine in ethyl acetate (v/v = 1:100, ca. 20 mL). The filtrate was concentrated under reduced pressure to give crude amine, which was used for the next step without further purification. The crude amine product was transferred to a sealable tube (Teflon cap) together with potassium carbonate (138 mg, 1 mmol), methyl iodide (142 mg, 1 mmol), and anhydrous THF (2 mL). The sealed reaction mixture was allowed to stir at 100 °C (oil bath) for 30 h. After TLC analysis, the mixture was filtered through a short column of silica gel and washed with a solution of triethylamine in ethyl acetate (v/v = 1: 100, ca. 30 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/acetone = 2:1 → 1:1) to yield dactylicapnosine A (30 mg, 70%) as a pale yellow plate. Mp: 179−180 °C; ^1H NMR (300 MHz, $CDCl_3$): δ: 6.91 (s, 1H), 6.39 (s, 1H), 3.99−3.94 (m, 7H), 3.65 (s, 3H), 3.52−3.45 (m, 8H), 3.15 (t, J = 6.3 Hz, 2H), 3.10 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ: 187.6, 171.4, 155.4, 152.5, 152.0, 143.7, 129.5, 126.6, 117.9, 117.4, 111.7, 102.0, 95.8, 81.2, 61.6, 56.5, 53.5, 52.0, 51.7, 50.2, 40.4, 29.8; IR (KBr, thin film, cm^{-1}): 3442, 2925, 1735, 1583, 1525, 1459, 1411, 1344, 1303, 1165, 1104, 1069; HRMS (ESI^+) m/z $[M + Na]^+$: calcd for $C_{22}H_{25}NNaO_8$: 454.1472, found: 454.1472.

*Dactylicapnosine B (**2**).* Dactylicapnosine A (**1**, 19 mg, 0.044 mmol) was dissolved in anhydrous dichloromethane (2 mL), and this solution was cooled to −78 °C. Boron trichloride in dichloromethane (1M, 0.5 mL, 0.5 mmol) was then added, and the resulting mixture was allowed to stir at −78 °C for 3 h. After TLC analysis, the mixture was diluted with water (5 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (6 × 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was obtained (17 mg) as a red solid. This crude product was added to a sealable tube (Teflon cap) together with anhydrous methanol (1 mL), 2,2-dimethoxypropane (1 mL), and *p*-toluenesulfonic acid (17 mg). The resulting mixture was then sealed and was allowed to stir at 80 °C (oil bath) for 16 h. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/acetone = 2:1) to afford dactylicapnosine B (**2**, 8 mg, 42%) as a yellow syrup. ^1H NMR (300 MHz, $CDCl_3$): δ: 12.55 (s, 1H), 6.90 (s, 1H), 6.38 (s, 1H), 4.05(s, 1H), 3.98 (s, 3H), 3.70 (s, 3H), 3.58 (t, J = 6.6 Hz, 2H), 3.52 (s, 3H), 3.50 (s, 3H), 3.14 (dd, J = 6.3, 10.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ: 192.2, 170.9, 157.5, 154.2, 147.5, 143.0, 124.0, 121.5, 116.8, 115.9, 111.6, 101.0, 96.0, 82.5, 56.4, 53.7, 52.2, 51.7, 50.5, 40.6, 28.8; IR (KBr, thin film, cm^{-1}): 3410, 2962, 2924, 2853, 1739, 1630, 1573, 1528, 1460, 1425, 1584, 1316, 1243, 1179, 1072, 1046; HRMS (ESI^+) m/z $[M + H]^+$: calcd for $C_{21}H_{24}NO_8$: 418.1496, found: 418.1495.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01900.

^1H and ^{13}C NMR spectra of new compounds; X-ray crystallographic data of **7a** (CCDC2018119), **9a** (CCDC2018120), **10** (CCDC2018122), **19** (CCDC2018123), and **1** (CCDC2018121 for synthetic dactylicapnosine A) (PDF)

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Notes

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