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Access to 6a-Alkyl Aporphines: Synthesis of (±)-*N*-Methylguattescidine

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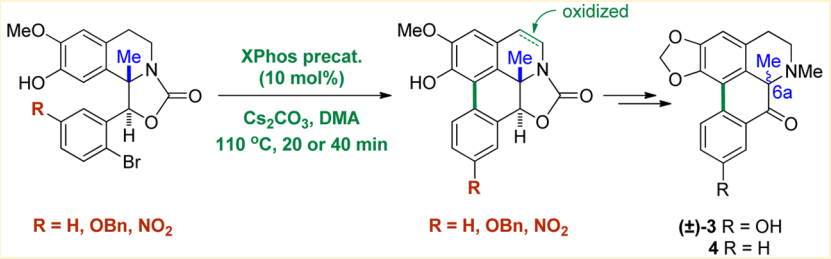
Supporting Information



ABSTRACT: (−)-*N*-Methylguattescidine (**3**) is an alkaloid recently isolated from *Fissistigma latifolium* and assigned as a rare example of a 6a-alkyl aporphine. Herein, we report the synthesis of (±)-**3** and the des-hydroxyl derivative **4** using our previously reported *ortho*-phenol arylation methodology mediated by the XPhos precatalyst as a key synthetic step. In addition, substituents on the aryl halide portion of the *ortho*-phenol arylation substrates significantly influenced the formation of an oxidized side product.

Aporphine alkaloids are natural products possessing a 1,2,3,4-tetrahydroisoquinoline tetracyclic ring system. Various aporphine alkaloids have been identified from natural sources,[1] with many of these compounds displaying interesting biological properties, such as antimicrobial,[2a] anticancer,[2b,c] and central nervous system (CNS) related activities.[2d−f] However, aporphines with a substituent at the 6a-position have rarely been reported (Figure 1). In two cases, the 6a-alkyl aporphines, i.e., guattescine (**1a**) and guattescidine (**2a**),[3] were subsequently revised to non-6a-alkyl structures **1b** and **2b**, respectively.[4] Recently, the aporphine (−)-*N*-methylguattescidine (**3**) was isolated from the bark of the shrub *Fissistigma latifolium* (Annonaceae) and assigned with a methyl at the 6a-position.[5] In addition, this compound was predicted by molecular docking simulation to be a human DEK oncoprotein ligand,[6] suggesting potential anticancer activity. Therefore, we set out to establish a synthetic methodology to provide access to 6a-alkyl aporphines in order to confirm the structure of **3** and to generate other 6a-alkyl aporphines for pharmacological evaluation.

Our laboratory previously reported syntheses of several 7-hydroxyaporphine alkaloids characterized with an *anti*-configuration between protons 6a and 7, such as (−)-oliveroline and (−)-noroliveroline, from enantiopure mandelic acids.[7] With a designated stereocenter at C-7, a diastereoselective one-pot cyclization favoring *anti*-isomers, followed by an *ortho*-phenol arylation mediated with the XPhos precatalyst, resulted in enantiopure intermediates that were readily converted to a series of aporphines. We also found that *ortho*-phenol arylations were feasible with both *syn*- and *anti*-isomers, whereas *ortho*-ether arylations only occurred with *syn*-isomers.[7] Herein, we report the expansion of this methodology to the syntheses of (±)-**3** and des-hydroxyl derivative **4** via *anti*-isomer **6** using the strategy outlined in Figure 2.

The feasibility of the strategy was first examined by targeting des-hydroxyl derivative **4**. As illustrated in Scheme 1, the synthesis commenced with Grignard addition of methyl magnesium chloride to *N*-acylcarbamate **7**, which was prepared from 2-bromomandelic acid.[7] In this reaction, the methyl group was selectively introduced to the more electron deficient amide at −30 °C.[8] Furthermore, addition occurred to the less sterically hindered face, furnishing diastereomer **8** in 80% yield as the only product. The relative configuration was confirmed based on strong correlations in the 2D-NOESY spectra between the proton on the carbon atom in the cyclic carbamate and the adjacent methyl group. Acid-mediated cyclization of **8** in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ generated only the *anti*-isomer **9** in 99% isolated yield. The diastereoselectivity observed with this substrate may be enhanced due to allylic strain between the methyl and the *N*-phenethyl groups in the iminium intermediate since lower diastereoselectivity (*dr* 87:13) was obtained for a similar substrate that had a proton in place of the methyl.[7] Treatment of **9** with 10 mol % XPhos precatalyst in the presence of Cs_2CO_3 at 110 °C for 40 min furnished intermediate **6** in 77% yield. The predicted *anti*-configuration of the methyl group at C-6a and the proton at C-7 in **6** (atoms C-9 and C-10, respectively, in Figure S1) was

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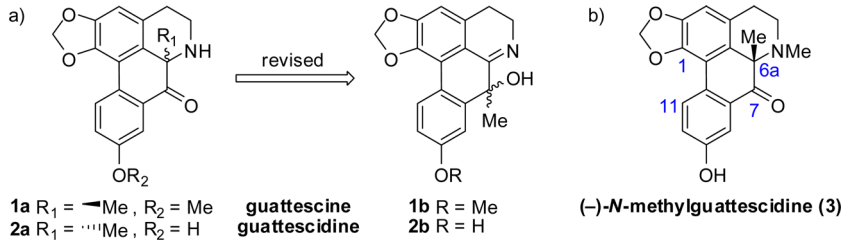


Figure 1. (a) Structure revisions of guattescine and guattescidine.[4] (b) Reported structure of (−)-*N*-methylguattescidine (**3**)[5] with ring system atoms numbered.

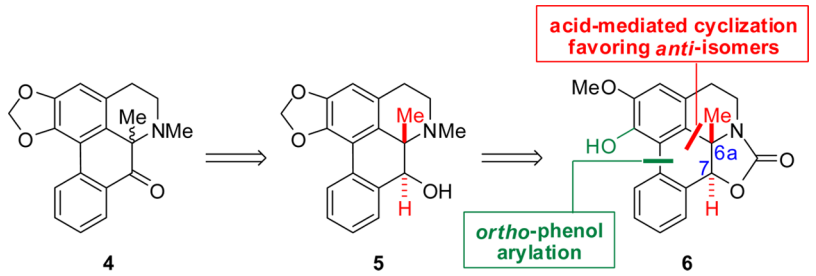
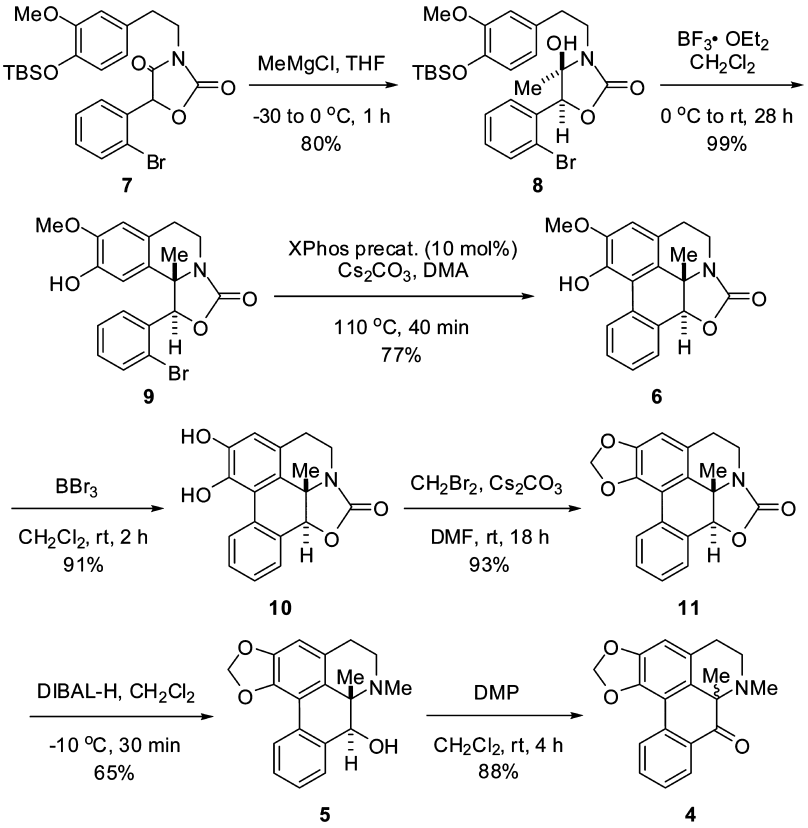


Figure 2. Retrosynthetic analysis of **4**.

Scheme 1. Synthesis of Des-hydroxyl Derivative 4



confirmed by X-ray crystallography. Following demethylation of **6** with BBr_3 and treatment of **10** with CH_2Br_2, oxazoloaporphine **11** was formed in 85% yield over two steps. Reduction of **11** with DIBAL-H gave *N*-methyl 7-hydroxyaporphine **5** in 65% yield. Finally, the desired product **4** was obtained in 88% yield by oxidation of **5** with Dess−Martin periodinane (DMP).

In order to prepare (±)-**3**, a slightly different strategy was used in the initial stage of the synthesis. As illustrated in Scheme 2, the α-hydroxyketone **14a** was prepared using an irregular Wittig reaction.[9] (1-Methoxyethyl)triphenylphosphonium ylide was generated *in situ* from Wittig salt **12**[9,10] and *n*-BuLi at −40 °C. Then, addition of this ylide to benzaldehyde **13a**[11] at −78 °C, followed by quenching at −78 °C with saturated aqueous NH_4Cl, afforded **14a** in 82% yield. Coupling **14a** with isocyanate **15** furnished **16a**, as a mixture of diastereomers (*dr* 1:1), in 90% yield. This mixture was then treated with $BF_3{\cdot}OEt_2$ at −78 °C to induce cyclization, followed

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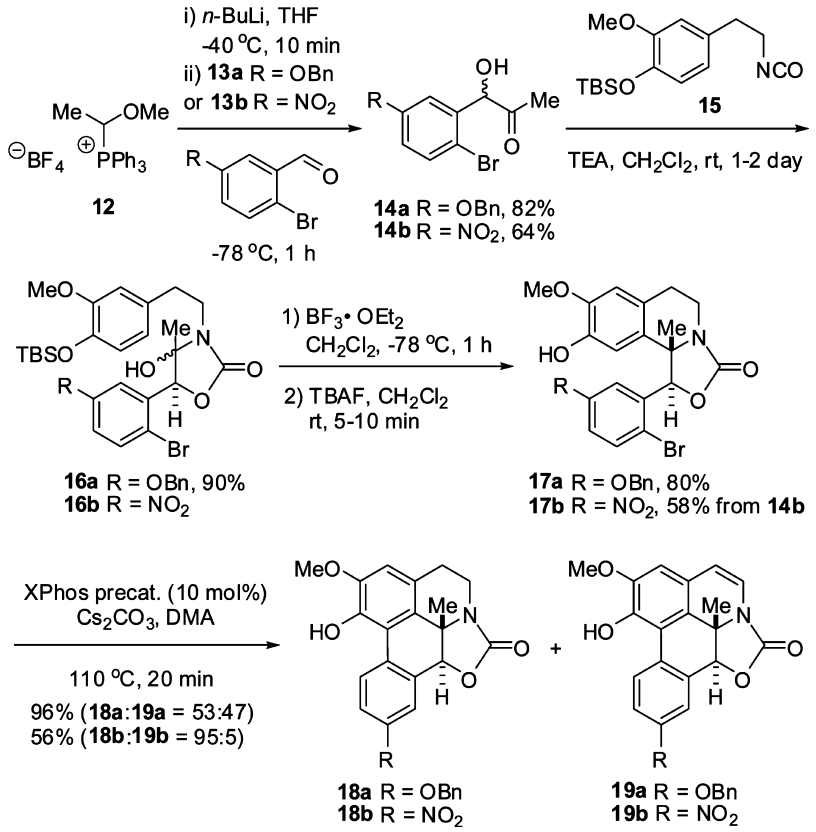
Scheme 2. Synthesis of 6a-Methyl Aporphines 18a and 18b



by silyl deprotection with TBAF, which gave *anti*-isomer **17a** in 80% yield. Intermediate **17a** was then subjected to *ortho*-phenol arylation with the XPhos precatalyst at 110 °C for 20 min. Surprisingly, this substrate furnished not only the desired arylated products **18a** but also the oxidized derivative **19a** in a ratio of 53:47 and a combined yield of 96%. Heating the reaction for a longer time favored formation of **19a**. For instance, 1 h of heating generated **18a** and **19a** in a ratio of 23:77. The electron donating benzyloxy (OBn) group appeared to have facilitated oxidation of the tetrahydroisoquinoline ring since this type of product was not observed during the *ortho*-phenol arylation of **9**.

To evaluate this structure−reactivity relationship in more detail, the OBn substituent was replaced with nitro (NO_2), a strong electron withdrawing group that could be subsequently converted to a hydroxy present in natural product **3**. Following a similar procedure from commercially available aldehyde **13b**, *anti*-isomer **17b** was obtained in 37% yield over three steps. As anticipated, *ortho*-phenol arylation of **17b** favored formation of the desired product **18b** with only trace amounts of oxidized product **19b** (**18b**:**19b** = 95:5 and combined yield of 56%) being observed.

As shown in Scheme 3, demethylation of **18b** with BBr_3 furnished catechol **20** in 98% yield. Treatment of this material with CH_2I_2, followed by reduction of the nitro with iron, generated **22** in 76% yield over two steps. A Sandmeyer reaction of the aniline in the presence of sulfuric acid gave **24**,[12] which is a precursor to (±)-**3**, in 89% yield.

The benzyloxy derivative **18a** was also converted to precursor **24**. Dealkylation of both the methyl and benzyl groups in **18a** with BBr_3 at room temperature for 30 min generated catechol **23** in 87% yield. In addition, **23** was obtained from **19a** in 79% yield after dealkylation of the methyl and benzyl groups and hydrogenation of the alkene. Intermediate **23** was converted to **24** in 69% yield upon treatment with CH_2I_2. However, intermediate **24** had very poor solubility, making subsequent reactions difficult. Consequently, the phenol was reprotected as **25** and reduced with DIBAL-H to give 7-hydroxyaporphine **26**. Oxidation of **26** with DMP generated 7-oxoaporphine **27** in 94% yield, which, upon hydrogenolysis, furnished (±)-**3** in 96% yield.[13]

In summary, the strategy of utilizing an acid-mediated cyclization, followed by palladium-catalyzed *ortho*-phenol arylation as key steps, has been successfully extended to the synthesis of (±)-**3** and derivative **4**. This study has also confirmed the structure of **3** as a rarely encountered 6a-alkyl aporphine alkaloid. Finally, the electronic property of substituents on the aryl halide portion of the *ortho*-phenol arylation substrates (e.g., OBn vs NO_2) was shown to significantly influence the formation of an oxidized side product. This methodology should allow for the synthesis of additional 6a-alkyl aporphines and exploration of their pharmacology.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions involving air-sensitive reagents were carried out with magnetic stirring and in oven-dried glassware with rubber septa under argon unless otherwise stated. All commercially available chemicals and reagent grade solvents were used directly without further purification unless otherwise specified. XPhos precatalyst was used as received from commercial suppliers without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agents (e.g., ninhydrin or phosphomolybdic acid stain). Flash chromatography was conducted

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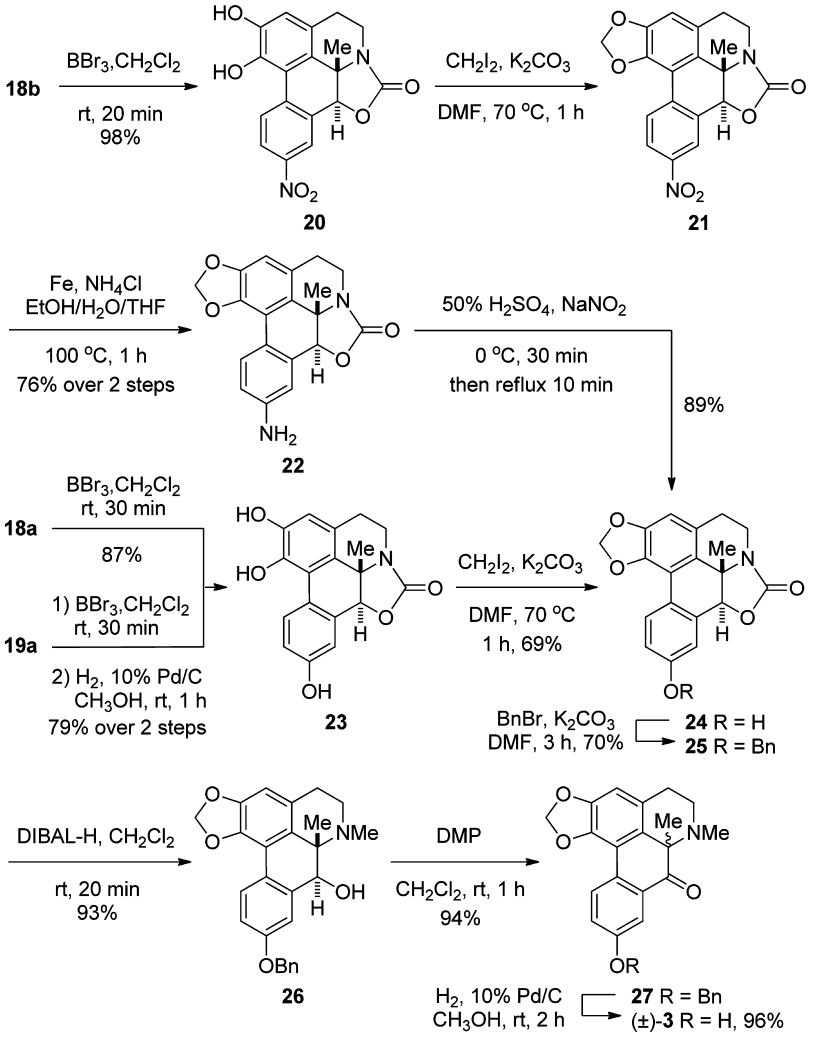
Scheme 3. Synthesis of (±)-3



on a silica gel (40−60 μm). Melting points were measured using a capillary melting point apparatus. NMR spectra were recorded at room temperature (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), DMSO-d_6 (2.50 ppm); ^{13}C NMR: $CDCl_3$ (77.0 ppm), CD_3OD (49.15 ppm), DMSO-d_6 (39.51 ppm)]. Signal patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are given in Hz. Nuclear Overhauser enhancement spectroscopy (NOESY) spectra were obtained to observe correlations between proton signals. High-resolution mass spectra (HRMS) were measured using TOF-MS with a DART ionization source and reported as m/z (relative intensity) for the molecular ion [M].

5-(2-Bromophenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenethyl)oxazolidine-2,4-dione (7). 7 was prepared according to the previously reported method.[7]

***rel*-(4*R*,5*S*)-5-(2-Bromophenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenethyl)-4-hydroxy-4-methyloxazolidin-2-one (8).** To a solution of MeMgCl (3.0 M in anhydrous THF, 2 mL, 5.9 mmol) was added a solution of 7 (1.5 g, 2.9 mmol) in anhydrous THF (5 mL) at −30 °C under argon, and the temperature was slowly allowed to rise from −30 to 0 °C over 1 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl, evaporated *in vacuo* to remove THF, and partitioned between H_2O and CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 20:80) to afford **8** (1.26 g, 80%) as a white solid; mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.57 (1 H, dd, J = 8.0, 1.2 Hz), 7.41 (1 H, dd, J = 8.0, 1.7 Hz), 7.36 (1 H, td, J = 8.0, 1.2 Hz), 7.22 (1 H, td, J = 8.0, 1.7 Hz), 6.71−6.69 (2 H, m), 6.62 (1 H, dd, J = 8.0, 1.7 Hz), 5.70 (1 H, s), 3.78 (3 H, s), 3.52−3.40 (2 H, m), 3.02−2.96 (1 H, m), 2.92−2.87 (1 H, m), 1.55 (3 H, s), 0.98 (9 H, s), 0.10 (3 H, s), 0.09 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.3, 151.0, 143.7, 133.1, 133.0, 132.1, 130.5, 128.6, 127.7, 123.1, 121.1, 120.8, 112.9, 88.3, 82.9, 55.5, 41.9, 34.3, 25.7 (3 ×), 25.2, 18.4, −4.7 (2 ×); HRMS (DART-TOF) m/z calculated for $C_{25}H_{35}BrNO_5Si$ $[M + H]^+$: 536.1468; found: 536.1481.

***rel*-(1*S*,10b*S*)-1-(2-Bromophenyl)-9-hydroxy-8-methoxy-10b-methyl-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (9).** To a solution of **8** (480 mg, 0.9 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (330 μL, 2.7 mmol) at 0 °C under argon, and the mixture was stirred at room temperature for 28 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **9** (360 mg, 99%) as a white solid; mp 174−175 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.64 (1 H, d, J = 8.0 Hz), 7.45−7.39 (2 H, m), 7.29−7.25 (2 H, m), 6.57 (1 H, s), 6.03 (1 H, s), 5.74 (1 H, s, OH), 4.09−4.06 (1 H, m), 3.88 (3 H, s), 3.27−3.19 (2 H, m), 2.58−2.56 (1 H, m), 1.21 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.7, 146.0, 144.4, 135.9, 133.1, 132.9, 130.3, 128.6, 127.8, 124.8, 123.0, 111.7, 111.1, 84.4, 64.0, 55.9, 37.0, 25.9,

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24.9; HRMS (DART-TOF) m/z calculated for $C_{19}H_{19}BrNO_4$ $[M + H]^+$: 404.0497; found: 404.0509.

***rel*-(3^1*S*,12b*S*)-8-Hydroxy-7-methoxy-3^1-methyl-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de*,*g*]oxazolo[5,4,3-*ij*]quinolin-2-one (6).** To a mixture of **9** (176 mg, 0.44 mmol), Cs_2CO_3 (424 mg, 1.3 mmol), and XPhos precatalyst (30 mg, 0.04 mmol) was added anhydrous DMA (1 mL) under argon. The reaction was stirred at room temperature for 5 min and then put into a preheated oil bath (110 °C) for another 40 min. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 50 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 30:70) to afford **6** (109 mg, 77%) as a pale yellow solid; mp 180−182 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.36 (1 H, d, J = 8.0 Hz), 7.41 (2 H, t, J = 8.0 Hz), 7.34 (1 H, t, J = 8.0 Hz), 6.67 (1 H, s), 6.33 (1 H, s, OH), 5.04 (1 H, s), 3.93 (3 H, s), 3.90−3.85 (1 H, m), 3.63−3.57 (1 H, m), 2.97 (2 H, t, J = 6.3 Hz), 0.98 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.2, 147.0, 143.0, 132.2, 130.9, 129.4, 128.3, 127.6 (2 ×), 121.8, 119.6, 115.5, 109.5, 84.4, 56.4, 56.3, 36.2, 26.4, 16.7; HRMS (DART-TOF) m/z calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$: 324.1236; found: 324.1236.

***rel*-(3^1*S*,12b*S*)-7,8-Dihydroxy-3^1-methyl-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de*,*g*]oxazolo[5,4,3-*ij*]quinolin-2-one (10).** To a solution of **6** (79 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (5 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 590 μL, 0.59 mmol) under argon, and the mixture was stirred at room temperature for 2 h. After being quenched with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60 to 50:50) to afford **10** (69 mg, 91%) as a white solid; mp 245−247 °C; ^{1}H NMR (CD_3OD, 500 MHz) 8.44 (1 H, d, J = 8.0 Hz), 7.40−7.37 (1 H, m), 7.34−7.30 (2 H, m), 6.66 (1 H, s), 5.07 (1 H, s),3.78−3.73 (1 H, m), 3.63−3.58 (1 H, m), 2.98−2.86 (2 H, m), 0.93 (3 H, s); ^{13}C NMR (CD_3OD, 125 MHz) 159.8, 147.1, 144.9, 133.6, 133.4, 131.0, 128.7, 128.3, 128.1, 122.4, 120.9, 117.2, 114.8, 86.6, 58.1, 37.8, 27.1, 17.1; HRMS (DART-TOF) m/z calculated for $C_{18}H_{16}NO_4$ $[M + H]^+$: 310.1079; found: 310.1060.

***rel*-(4b*S*,4b^1*S*)-4b^1-Methyl-4b,4b^1,8,9-tetrahydro-6*H*-[1,3]-dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]oxazolo[5,4,3-*ij*]-quinolin-6-one (11).** To a solution of **10** (125 mg, 0.4 mmol) and Cs_2CO_3 (260 mg, 0.8 mmol) in anhydrous DMF (1 mL) was added CH_2Br_2 (42 μL, 0.6 mmol) under argon, and the mixture was stirred at room temperature for 18 h. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to afford **11** (120 mg, 93%) as a white solid; mp 213−215 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.01 (1 H, d, J = 7.5 Hz), 7.44 (1 H, d, J = 6.9 Hz), 7.42−7.35 (2 H, m), 6.63 (1 H, s), 6.10 (1 H, d, J = 1.2 Hz), 5.99 (1 H, d, J = 1.2 Hz), 5.07 (1 H, s), 3.89−3.84 (1 H, m), 3.62−3.57 (1 H, m), 2.95 (2 H, t, J = 6.3 Hz), 1.02 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.0, 148.2, 143.5, 132.0, 129.7, 128.3, 128.2, 128.0, 127.8, 122.4, 122.1, 112.8, 107.7, 101.2, 84.2, 56.4, 36.3, 26.6, 17.1; HRMS (DART-TOF) m/z calculated for $C_{19}H_{16}NO_4$ $[M + H]^+$: 322.1079; found: 322.1052.

***rel*-(7a*S*,8*S*)-7,7a-Dimethyl-6,7,7a,8-tetrahydro-5*H*-[1,3]-dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]quinolin-8-ol (5).** To a solution of **11** (80 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 320 μL, 0.48 mmol) at −10 °C under argon. The mixture was stirred at −10 °C for 30 min and then quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90 to 15:85) to afford **5** (48 mg, 65%) as a white solid; mp 201−202 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.08−8.07 (1 H, m), 7.69 (1 H, d, J = 6.9 Hz), 7.37−7.32 (2 H, m), 6.56 (1 H, s), 6.08 (1 H, d, J = 1.7 Hz), 5.95 (1 H, d, J = 1.7 Hz), 5.06 (1 H, s), 3.56−3.51 (1 H, m), 3.09−2.99 (2 H, m), 2.53 (3 H, s), 2.50−2.45 (1 H, m), 1.16 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 146.8, 142.7, 137.8, 128.6, 127.9, 127.8, 127.0, 126.5, 125.6, 124.1, 116.0, 108.2, 100.7, 71.2, 59.9, 46.1, 36.2, 22.3, 19.5; HRMS (DART-TOF) m/z calculated for $C_{19}H_{20}NO_3$ $[M + H]^+$: 310.1443; found: 310.1458.

7,7a-Dimethyl-5,6,7,7a-tetrahydro-8*H*-[1,3]dioxolo-[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]quinolin-8-one (4). To a mixture of **5** (15 mg, 0.048 mmol) and Dess−Martin periodinane (47 mg, 0.11 mmol) was added anhydrous CH_2Cl_2 (2 mL) under argon. The reaction was stirred at room temperature for 4 h. After being quenched by the addition of 1 M $Na_2S_2O_{3(aq)}$, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:99 to 2:98) to afford **4** (13 mg, 88%) as a pale yellow solid; mp 167−169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.35 (1 H, d, J = 8.0 Hz), 8.06 (1 H, d, J = 7.5 Hz), 7.63 (1 H, t, J = 8.0 Hz), 7.40 (1 H, t, J = 7.5 Hz), 6.61 (1 H, s), 6.11 (1 H, d, J = 1.2 Hz), 6.02 (1 H, d, J = 1.2 Hz), 3.52−3.46 (1 H, m), 3.13−3.01 (2 H, m), 2.58 (1 H, dd, J = 15.5, 6.9 Hz), 2.40 (3 H, s), 1.54 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 199.8, 147.0, 143.5, 134.2, 134.0, 129.3, 128.6, 127.9, 127.7, 127.3, 127.2, 114.1, 109.0, 100.9, 66.5, 45.7, 38.5, 27.6, 24.1; HRMS (DART-TOF) m/z calculated for $C_{19}H_{18}NO_3$ $[M + H]^+$: 308.1287; found: 308.1294.

(1-Methoxyethyl)triphenylphosphonium Tetrafluoroborate (12). To a solution of acetaldehyde dimethyl acetal (9.6 mL, 90 mmol) and PPh_3 (15.8 g, 60 mmol) in toluene (100 mL) was added $BF_3{\cdot}OEt_2$ (10 mL, 81 mmol) at 0 °C under argon, and the mixture was stirred at room temperature for 16 h. The residue was filtered and washed with toluene and dried under reduced pressure to afford **12** (25 g, 98%) as a white solid. The spectral data of the Wittig salt correspond with the literature data.[9,10] The crude product was used in the next step without further purification.

5-Benzyloxy-2-bromobenzaldehyde (13a).[11] To a solution of 2-bromo-5-hydroxybenzaldehyde (2.05 g, 10 mmol) and K_2CO_3 (1.66 g, 12 mmol) in anhydrous DMF (5 mL) was added BnBr (1.4 mL, 12 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 0:100 to 5:95) to afford **13a** (2.82 g, 96%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 10.31 (1 H, s), 7.53 (1 H, d, J = 8.5 Hz), 7.51 (1 H, d, J = 2.5 Hz), 7.44−7.35 (5 H, m), 7.10 (1 H, d, J = 2.5 Hz), 5.09 (2 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 191.6, 158.2, 135.8, 134.6, 133.9, 128.6 (2 ×), 128.2, 127.5 (2 ×), 123.6, 118.1, 113.7, 70.3; HRMS (DART-TOF) m/z calculated for $C_{14}H_{12}BrO_2$ $[M + H]^+$: 291.0021; found: 290.9988.

1-(5-(Benzyloxy)-2-bromophenyl)-1-hydroxypropan-2-one (14a). To a solution of **12** (1.23 g, 3 mmol) in anhydrous THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 1.2 mL, 3 mmol) at −40 °C under argon. After being stirred at −40 °C for 10 min, **13a** (587 mg, 2 mmol) in anhydrous THF (2 mL) was added to the dark red ylide solution at −78 °C, and the resulting mixture was stirred at −78 °C for 1 h. The reaction was then quenched at −78 °C by the addition of saturated aqueous NH_4Cl and evaporated *in vacuo* to remove the THF. The remaining aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 10:90) to afford **14a** (550 mg, 82%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.49 (1 H, d, J = 8.5 Hz), 7.40−7.33 (5 H, m), 6.87−6.83 (2 H, m), 5.56 (1 H, d, J = 4.0 Hz), 5.04−4.98 (2 H, m), 4.41 (1 H, d, J = 4.0 Hz), 2.14 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz)

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J. Org. Chem. 2016, 81, 10062−10070

206.2, 158.5, 138.2, 136.1, 133.9, 128.6 (2 ×), 128.1, 127.5 (2 ×), 117.3, 114.7, 114.1, 78.5, 70.2, 25.4; HRMS (DART-TOF) m/z calculated for $C_{16}H_{16}BrO_3$ $[M + H]^+$: 335.0283; found: 335.0258.

***tert*-Butyl(4-(2-isocyanatoethyl)-2-methoxyphenoxy)-dimethylsilane (15).**[7] A suspension of 4-hydroxy-3-methoxyphenethylamine hydrochloride (2.1 g, 10.3 mmol) and imidazole (2.4 g, 40 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 min, and then TBSCl (1.7 g, 11 mmol) was added under argon. The resulting mixture was stirred at room temperature for 3 h and then quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). After neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:99 to 5:95) to afford the *O*-silylated phenethylamine product (2.8 g, 97%) as a colorless oil, and the spectral data correspond with the literature data.[7] To a solution of triphosgene (1.1 g, 3.75 mmol) in anhydrous toluene (10 mL) was added a solution of the *O*-silylated phenethylamine (1.5 g, 5.33 mmol) in anhydrous toluene (5 mL) under argon. The mixture was stirred at room temperature for 30 min and heated to 100 °C for another 1 h. After being quenched by the addition of saturated aqueous NH_4Cl, the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford **15** (1.6 g, 98%) as a light yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 6.81 (1 H, d, J = 8.0 Hz), 6.70 (1 H, d, J = 2.0 Hz), 6.67 (1 H, dd, J = 8.0, 2.0 Hz), 3.81 (3 H, s), 3.48 (2 H, t, J = 7.0 Hz), 2.84 (2 H, t, J = 7.0 Hz), 1.00 (9 H, s), 0.16 (6 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 150.9, 144.0, 131.1, 122.6, 121.0, 120.9, 112.8, 55.4, 44.4, 37.4, 25.7 (3 ×), 18.4, −4.7 (2 ×). The isocyanate product was freshly prepared and used in the next step.

5-(5-(Benzyloxy)-2-bromophenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenethyl)-4-hydroxy-4-methyloxazolidin-2-one (16a): A Mixture of *rel*-(4*R*,5*S*)-16a and *rel*-(4*S*,5*S*)-16a. A suspension of **14a** (330 mg, 0.98 mmol) and triethylamine (270 μL, 1.9 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 min, and then **15** (600 mg, 1.95 mmol) was added under argon. After being stirred at room temperature for 2 days, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, extracted with EtOAc (2 × 30 mL), and neutralized with saturated aqueous $NaHCO_3$. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to afford diastereomers *rel*-(4*R*,5*S*)-**16a** and *rel*-(4*S*,5*S*)-**16a** (570 mg, *dr* 1:1) in a combined yield of 90%. Analytical samples were obtained by additional column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85), and relative configurations of these two diastereomers were confirmed by 2D-NOESY.

***rel*-(4*R*,5*S*)-16a.** White solid; mp 165−166 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.44 (1 H, d, J = 9.5 Hz), 7.38−7.31 (6 H, m), 6.86 (1 H, dd, J = 9.5, 3.0 Hz), 6.74 (1 H, d, J = 8.0 Hz), 6.69 (1 H, d, J = 2.0 Hz), 6.63 (1 H, dd, J = 8.0, 2.0 Hz), 5.65 (1 H, s), 5.04 (1 H, d, J = 12.0 Hz), 4.96 (1 H, d, J = 12.0 Hz), 3.75 (3 H, s), 3.54−3.48 (1 H, m), 3.45−3.39 (1 H, m), 2.92−2.89 (2 H, m), 1.47 (3 H, s), 0.99 (9 H, s), 0.12 (3 H, s), 0.12 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.3, 156.9, 150.9, 143.7, 136.2, 133.7, 133.5, 132.1, 128.6 (2 ×), 128.1, 127.6 (2 ×), 121.1, 120.8, 118.0, 115.1, 113.3, 112.8, 88.8, 83.2, 70.4, 55.4, 42.2, 34.6, 25.7 (3 ×), 24.6, 18.4, −4.7 (2 ×); HRMS (DART-TOF) m/z calculated for $C_{32}H_{41}BrNO_6Si$ $[M + H]^+$: 642.1887; found: 642.1879.

***rel*-(4*S*,5*S*)-16a.** Light yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.44−7.29 (6 H, m), 6.85−6.81 (6 H, m), 6.44 (1 H, s), 6.71 (1 H, d, J = 8.0 Hz), 6.69 (1 H, d, J = 2.0 Hz), 6.63 (1 H, dd, J = 8.0, 2.0 Hz), 5.76 (1 H, s), 5.07−5.01 (2 H, m), 4.33 (1 H, s, br, OH), 3.74 (3 H, s), 3.44 (2 H, t, J = 8.0 Hz), 2.96−2.82 (2 H, m), 0.97 (9 H, s), 0.93 (3 H, s), 0.09 (3 H, s), 0.09 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.3, 157.2, 150.9, 143.6, 136.5, 136.1, 133.7, 132.1, 128.6 (2 ×), 128.2, 127.5 (2 ×), 121.1, 120.8, 116.7, 113.5, 113.1, 112.8, 90.0, 85.7, 70.2, 55.5, 42.2, 34.8, 25.7 (3 ×), 22.0, 18.4, −4.7 (2 ×); HRMS (DART-TOF) m/z calculated for $C_{32}H_{41}BrNO_6Si$ $[M + H]^+$: 642.1887; found: 642.1878.

***rel*-(1*S*,10b*S*)-1-(5-(Benzyloxy)-2-bromophenyl)-9-hydroxy-8-methoxy-10b-methyl-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (17a).** To a solution of **16a** (106 mg, 0.165 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (60 μL, 0.49 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. After being quenched with saturated aqueous $NaHCO_3$ (10 mL) at −78 °C, the mixture was slowly allowed to warm to room temperature and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to afford cyclized intermediate **TBS-17a** (85 mg, 82%). To a solution of **TBS-17a** (85 mg, 0.136 mmol) in anhydrous CH_2Cl_2 (3 mL) was added TBAF (1.0 M in THF, 140 μL, 0.14 mmol) under argon. The resulting mixture was stirred at room temperature for 5 min and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 35:65) to afford **17a** (67 mg, 98%).

***TBS-17a*.** Pale yellow solid; mp 150−151 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.49 (1 H, d, J = 9.0 Hz), 7.43−7.30 (5 H, m), 7.21 (1 H, s), 6.98 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 9.0, 2.5 Hz), 6.52 (1 H, s), 5.93 (1 H, s), 5.12−5.05 (2 H, m), 4.05−3.99 (1 H, m), 3.78 (3 H, s), 3.24−3.14 (2 H, m), 2.57−2.50 (1 H, m), 1.10 (3 H, s), 1.00 (9 H, s), 0.16 (3 H, s), 0.15 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.6, 158.2, 150.4, 143.7, 136.9, 136.1, 133.7, 132.4, 128.6 (2 ×), 128.1, 127.5 (2 ×), 126.3, 118.2, 117.5, 114.8, 113.3, 112.3, 84.3, 70.2, 63.9, 55.4, 37.1, 25.7 (4 ×), 24.8, 18.4, −4.6, −4.7; HRMS (DART-TOF) m/z calculated for $C_{32}H_{39}BrNO_5Si$ $[M + H]^+$: 624.1781; found: 624.1779.

***17a*.** White solid; mp 212−213 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.49 (1 H, d, J = 9.0 Hz), 7.42−7.30 (5 H, m), 7.24 (1 H, s), 6.99 (1 H, d, J = 2.5 Hz), 6.89 (1 H, dd, J = 9.0, 2.5 Hz), 6.54 (1 H, s), 5.94 (1 H, s), 5.74 (1 H, s, OH), 5.12−5.05 (2 H, m), 4.06−3.99 (1 H, m), 3.86 (3 H, s), 3.24−3.14 (2 H, m), 2.57−2.52 (1 H, m), 1.12 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.5, 158.1, 146.0, 144.4, 136.7, 136.1, 133.7, 132.8, 128.6 (2 ×), 128.0, 127.5 (2 ×), 124.7, 117.5, 114.8, 113.4, 111.7, 111.1, 84.3, 70.2, 63.9, 55.9, 37.0, 25.8, 24.7; HRMS (DART-TOF) m/z calculated for $C_{26}H_{25}BrNO_5$ $[M + H]^+$: 510.0916; found: 510.0907.

Preparation of 18a and 19a. To a mixture of **17a** (52 mg, 0.1 mmol), Cs_2CO_3 (98 mg, 0.3 mmol), and XPhos precatalyst (8 mg, 0.01 mmol) was added anhydrous DMA (500 μL) under argon. The reaction was stirred at room temperature for 5 min and then put into a preheated oil bath (110 °C) for another 20 min. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 10 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70 to 40:60) to afford **18a** (22 mg, 51%) and **19a** (19 mg, 45%).

***rel*-(3^1*S*,12b*S*)-11-(Benzyloxy)-8-hydroxy-7-methoxy-3^1-methyl-3^1,4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (18a).** White solid; mp 225−226 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.29 (1 H, d, J = 8.5 Hz), 7.48−7.33 (5 H, m), 7.09 (1 H, d, J = 2.0 Hz), 6.98 (1 H, dd, J = 8.5, 2.0 Hz), 6.63 (1 H, s), 6.27 (1 H, s, OH), 5.13 (2 H, s), 5.00 (1 H, s), 3.92 (3 H, s), 3.89−3.84 (1 H, m), 3.62−3.57 (1 H, m), 2.96 (2 H, t, J = 7.0 Hz), 1.00 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.1, 157.1, 147.0, 142.3, 136.5, 134.0, 130.8, 128.6 (2 ×), 128.0, 127.6, 127.5 (2 ×), 123.4, 119.6, 115.6, 113.2, 109.1, 108.7, 84.2, 70.0, 56.4, 56.3, 36.3, 26.4, 16.6; HRMS (DART-TOF) m/z calculated for $C_{26}H_{24}NO_5$ $[M + H]^+$: 430.1654; found: 430.1632.

***rel*-(3^1*S*,12b*S*)-11-(Benzyloxy)-8-hydroxy-7-methoxy-3^1-methyl-3^1,12b-dihydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (19a).** Light yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.33 (1 H, d, J = 9.0 Hz), 7.47−7.33 (5 H, m), 7.09 (1 H, d, J = 3.0 Hz), 6.98 (1 H, dd,

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J = 9.0, 3.0 Hz), 6.64 (1 H, d, J = 7.5 Hz), 6.60 (1 H, s), 6.39 (1 H, s, OH), 5.82 (1 H, d, J = 7.5 Hz), 5.50 (1 H, s), 5.13 (2 H, s), 3.93 (3 H, s), 1.02 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.3, 154.7, 147.2, 143.6, 136.4, 133.7, 130.9, 128.6 (2 ×), 128.1, 127.5 (2 ×), 124.3, 123.1, 119.1, 118.3, 115.6, 113.2, 109.6, 109.3, 106.2, 85.3, 70.0, 57.5, 56.5, 16.1; HRMS (DART-TOF) m/z calculated for $C_{26}H_{22}NO_5$ [M + H]$^+$: 428.1497; found: 428.1508.

1-(2-Bromo-5-nitrophenyl)-1-hydroxypropan-2-one (14b). The same procedure as **14a** was used to synthesize **14b** starting from 2-bromo-5-nitrobenzaldehyde (**13b**) to afford **14b** in 64% yield. Pale yellow solid; mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.14 (1 H, d, J = 3.0 Hz), 8.06 (1 H, dd, J = 8.5, 3.0 Hz), 7.82 (1 H, d, J = 8.5 Hz), 5.63 (1 H, d, J = 3.0 Hz), 4.55 (1 H, d, J = 3.0 Hz, OH), 2.20 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 204.6, 147.7, 139.5, 134.4, 130.4, 124.5, 124.0, 78.2, 25.6; HRMS (DART-TOF) m/z calculated for $C_9H_9BrNO_4$ [M + H]$^+$: 275.9695; found: 275.9689.

5-(2-Bromo-5-nitrophenyl)-3-(4-((*tert*-butyldimethylsilyl)-oxy)-3-methoxyphenethyl)-4-hydroxy-4-methyloxazolidin-2-one (16b). A suspension of **14b** (400 mg, 1.46 mmol) and triethylamine (420 μL, 3 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature for 15 min, and then **15** (820 mg, 3 mmol) was added under argon. After being stirred at room temperature for 16 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (2 × 20 mL), and neutralized with saturated aqueous $NaHCO_3$. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture was used directly for the next step. One diastereomer was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) and determined to be ***rel*-(4*R*,5*S*)-16b** by 2D-NOESY.

***rel*-(4*R*,5*S*)-16b**. White solid; mp 207−208 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) 8.28 (1 H, d, J = 3.0 Hz), 8.14 (1 H, dd, J = 9.0, 3.0 Hz), 7.98 (1 H, d, J = 9.0 Hz), 6.88 (1 H, d, J = 2.0 Hz), 6.76 (1 H, d, J = 8.0 Hz), 6.69 (1 H, dd, J = 8.0, 2.0 Hz), 6.20 (1 H, s, OH), 5.70 (1 H, s), 3.76 (3 H, s), 3.44−3.39 (1 H, m), 3.30−3.24 (1 H, m), 2.82 (2 H, t, J = 7.5 Hz), 1.40 (3 H, s), 0.95 (9 H, s), 0.10 (6 H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) 155.9, 150.4, 146.7, 142.7, 135.8, 134.2, 132.7, 129.7, 124.9, 124.8, 121.0, 120.3, 113.1, 87.9, 81.9, 55.4, 41.7, 34.3, 25.6 (3 ×), 24.6, 18.2, −4.7 (2 ×); HRMS (DART-TOF) m/z calculated for $C_{25}H_{34}BrN_2O_7Si$ [M + H]$^+$: 583.1302; found: 583.1317.

***rel*-(1*S*,10b*S*)-1-(2-Bromo-5-nitrophenyl)-9-hydroxy-8-methoxy-10b-methyl-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (17b).** To a solution of crude **16b** in anhydrous CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (660 μL, 5.4 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. After being quenched with saturated aqueous $NaHCO_3$ (10 mL) at −78 °C, the mixture was slowly allowed to warm to room temperature and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 10:90) to afford cyclized intermediate **TBS-17b** (488 mg, 59% over 2 steps). To a solution of **TBS-17b** (143 mg, 0.254 mmol) in anhydrous CH_2Cl_2 (5 mL) was added TBAF (1.0 M in THF, 250 μL, 0.25 mmol) under argon. The resulting mixture was stirred at room temperature for 10 min and then concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 2:98 to 5:95) to afford **17b** (114 mg, 99%).

TBS-17b. Pale yellow solid; mp 167−168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.26 (1 H, d, J = 3.0 Hz), 8.12 (1 H, dd, J = 8.5, 3.0 Hz), 7.85 (1 H, d, J = 8.5 Hz), 7.10 (1 H, s), 6.55 (1 H, s), 6.01 (1 H, s), 4.12−4.05 (1 H, m), 3.79 (3 H, s), 3.27−3.18 (2 H, m), 2.61−2.55 (1 H, m), 1.20 (3 H, s), 0.99 (9 H, s), 0.16 (3 H, s), 0.15 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.8, 150.6, 147.6, 143.8, 138.4, 134.3, 131.4, 129.6, 126.5, 124.8, 123.7, 117.9, 112.4, 83.7, 63.8, 55.4, 37.2, 25.8, 25.7 (3 ×), 25.0, 18.4, −4.6, −4.7; HRMS (DART-TOF) m/z calculated for $C_{25}H_{32}BrN_2O_6Si$ [M + H]$^+$: 565.1197; found: 565.1171.

17b. White solid; mp > 250 °C (decomposed); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.27 (1 H, d, J = 3.0 Hz), 8.13 (1 H, dd, J = 9.0, 3.0 Hz), 7.86 (1 H, d, J = 9.0 Hz), 7.13 (1 H, s), 6.58 (1 H, s), 6.04 (1 H, s), 5.63 (1 H, s, OH), 4.13−4.06 (1 H, m), 3.89 (3 H, s), 3.27−3.19 (2 H, m), 2.62−2.55 (1 H, m), 1.24 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.7, 147.6, 146.2, 144.5, 138.2, 134.4, 132.0, 129.9, 125.0, 124.8, 123.8, 111.4, 111.3, 83.6, 63.8, 56.0, 37.2, 25.9, 24.9; HRMS (DART-TOF) m/z calculated for $C_{19}H_{18}BrN_2O_6$ [M + H]$^+$: 451.0330; found: 451.0362.

Preparation of 18b and 19b. To a mixture of **17b** (209 mg, 0.465 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), and XPhos precatalyst (34 mg, 0.046 mmol) was added anhydrous DMA (5 mL) under argon. The reaction was stirred at room temperature for 5 min and then put into a preheated oil bath (110 °C) for another 20 min. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 20 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **18b** (91 mg, 53%) and **19b** (5 mg, 3%).

rel-(3^{1}S,12bS)-8-Hydroxy-7-methoxy-3^1-methyl-11-nitro-3^1,4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (18b). Yellow solid; mp > 250 °C (decomposed); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.57−8.55 (1 H, m), 8.29−8.27 (2 H, m), 6.76 (1 H, s), 6.49 (1 H, s, OH), 5.05 (1 H, s), 3.97 (3 H, s), 3.93−3.88 (1 H, m), 3.65−3.59 (1 H, m), 3.00 (2 H, t, J = 7.0 Hz), 1.01 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.5, 147.2, 146.3, 143.9, 137.6, 133.8, 130.1, 128.3, 123.2, 120.1, 117.3, 113.8, 111.1, 83.2, 56.6, 55.9, 36.2, 26.3, 17.1; HRMS (DART-TOF) m/z calculated for $C_{19}H_{17}N_2O_6$ [M + H]$^+$: 369.1087; found: 369.1105.

rel-(3^{1}S,12bS)-8-Hydroxy-7-methoxy-3^1-methyl-11-nitro-3^1,12b-dihydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (19b). Yellow solid; mp > 250 °C (decomposed); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.62−8.60 (1 H, m), 8.31−8.29 (2 H, m), 6.73 (1 H, s), 6.68 (1 H, d, J = 7.5 Hz), 6.58 (1 H, s, OH), 5.86 (1 H, d, J = 7.5 Hz), 5.59 (1 H, s), 3.98 (3 H, s), 1.04 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.0, 147.4, 146.5, 145.0, 137.3, 133.5, 130.2, 124.9, 123.4, 119.7, 118.7, 117.3, 113.7, 109.3, 108.5, 84.3, 57.2, 56.7, 16.6; HRMS (DART-TOF) m/z calculated for $C_{19}H_{15}N_2O_6$ [M + H]$^+$: 367.0930; found: 367.0946.

***rel*-(3^1*S*,12b*S*)-7,8-Dihydroxy-3^1-methyl-11-nitro-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de*,*g*]oxazolo[5,4,3-*ij*]quinolin-2-one (20).** To a solution of **18b** (90 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (20 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 490 μL, 0.49 mmol) under argon, and the reaction was stirred at room temperature for 20 min. After being quenched by the addition of CH_3OH (1 mL) and $NaHCO_{3(s)}$ (10 mg), the mixture was stirred for another 5 min. Then, the solid was separated by filtration, and the combined filtrates were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 0:100 to 5:95) to afford **20** (85 mg, 98%) as a yellow solid; mp > 250 °C (decomposed); ^{1}H NMR (DMSO-d_6, 500 MHz) 8.61 (1 H, d, J = 9.0 Hz), 8.33 (1 H, dd, J = 9.0, 2.0 Hz), 8.00 (1 H, d, J = 2.0 Hz), 6.77 (1 H, s), 5.19 (1 H, s), 3.69−3.64 (1 H, m), 3.58−3.53 (1 H, m), 2.92−2.84 (2 H, m), 0.88 (3 H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) 156.0, 145.8, 145.3, 144.2, 138.8, 133.8, 130.1, 126.5, 123.0, 119.6, 116.0, 115.6, 114.0, 82.5, 55.3, 36.3, 25.3, 17.3; HRMS (DART-TOF) m/z calculated for $C_{18}H_{15}N_2O_6$ [M + H]$^+$: 355.0930; found: 355.0938.

***rel*-(4b*S*,4b^1*S*)-4b^1-Methyl-3-nitro-4b,4b^1,8,9-tetrahydro-6*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]oxazolo[5,4,3-*ij*]-quinolin-6-one (21).** To a solution of **20** (50 mg, 0.14 mmol) and K_2CO_3 (40 mg, 0.28 mmol) in anhydrous DMF (1 mL) was added CH_2I_2 (20 μL, 0.25 mmol) under argon, and the mixture was stirred at 70 °C for 1 h. After being quenched with H_2O (5 mL), the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mixture containing **21** was used directly for the next step. A sample for characterization was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **21** as a yellow solid; mp > 250 °C (decomposed); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.32−8.27 (2 H, m), 8.20 (1 H, d, J = 8.5 Hz),

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6.74 (1 H, s), 6.17 (1 H, d, J = 1.0 Hz), 6.06 (1 H, d, J = 1.0 Hz), 5.10 (1 H, s), 3.92−3.87 (1 H, m), 3.65−3.59 (1 H, m), 2.99 (2 H, t, J = 7.0 Hz), 1.05 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.3, 148.6, 146.9, 144.6, 136.3, 133.6, 128.7, 128.3, 123.4, 122.6, 117.9, 110.9, 109.5, 101.8, 83.1, 56.1, 36.2, 26.6, 17.5; HRMS (DART-TOF) m/z calculated for $C_{19}H_{15}N_2O_6$ $[M + H]^+$: 367.0930; found: 367.0951.

***rel*-(4b*S*,4b^1*S*)-3-Amino-4b^1-methyl-4b,4b^1,8,9-tetrahydro-6*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]oxazolo-[5,4,3-*ij*]quinolin-6-one (22).** To a solution of crude **21** and NH_4Cl (40 mg, 0.28 mmol) in a mixture of EtOH/H_2O/THF (2:1:1, 2 mL) was added Fe powder (80 mg), and the mixture was vigorously stirred at 100 °C for 1 h. After the mixture was allowed to cool to room temperature, the solid was removed by filtration through a Celite pad and the filtrate was concentrated. The residue was purified by column chromatography (CH_3OH/CH_2Cl_2, 1:99 to 5:95) to afford **22** (36 mg, 76% over 2 steps) as a white solid; mp > 250 °C (decomposed); ^{1}H NMR (DMSO-d_6, 500 MHz) 7.62 (1 H, d, J = 8.0 Hz), 6.68 (1 H, s), 6.59 (1 H, s), 6.54 (1 H, dd, J = 8.0, 2.0 Hz), 6.08 (1 H, s), 6.01 (1 H, s), 5.70 (2 H, s, NH_2), 5.01 (1 H, s), 3.67−3.62 (1 H, m), 3.56−3.51 (1 H, m), 2.91−2.85 (2 H, m), 0.92 (3 H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) 156.4, 149.2, 147.5, 141.4, 133.3, 129.0, 126.8, 122.6, 115.8, 113.3, 111.5, 107.7, 105.7, 100.8, 83.4, 55.9, 36.3, 26.1, 16.9; HRMS (DART-TOF) m/z calculated for $C_{19}H_{17}N_2O_4$ $[M + H]^+$: 337.1188; found: 337.1204.

Preparation of 23. Method A. To a solution of **18a** (150 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (5 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 1.75 mL, 1.75 mmol) under argon, and the reaction was stirred at room temperature for 30 min. After being quenched by the addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined filtrates were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:99 to 5:95) to afford **23** (99 mg, 87%).

Preparation of 23. Method B. To a solution of **19a** (25 mg, 0.058 mmol) in anhydrous CH_2Cl_2 (1 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 300 μL, 0.3 mmol) under argon, and the reaction was stirred at room temperature for 30 min. After being quenched by the addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined filtrates were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude intermediate. To a solution of the intermediate in CH_3OH (10 mL) was added 10% Pd/C (5 mg), and the mixture was vigorously stirred under an atmosphere of H_2 at room temperature for 1 h. The solid was removed by filtration through a Celite pad, and the filtrate was concentrated. The residue was purified by column chromatography (CH_3OH/CH_2Cl_2, 1:99 to 5:95) to give **23** (15 mg, 79%) over two steps.

rel-(3^1*S*,12b*S*)-7,8,11-Trihydroxy-3^1-methyl-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (**23**). Pale yellow solid; mp > 250 °C (decomposed); NMR data were collected from material prepared by Method A: ^{1}H NMR (CD_3OD, 500 MHz) 8.27 (1 H, d, J = 8.5 Hz), 6.81−6.76 (2 H, m), 6.60 (1 H, s), 5.02 (1 H, s), 3.77−3.72 (1 H, m), 3.63−3.58 (1 H, m), 2.96−2.87 (2 H, m), 0.95 (3 H, s); ^{13}C NMR (CD_3OD, 125 MHz) 159.8, 158.1, 146.9, 144.0, 135.3, 132.5, 127.4, 124.4, 120.8, 117.7, 114.5, 113.7, 110.2, 86.6, 58.1, 37.9, 27.1, 17.0; HRMS (DART-TOF) m/z calculated for $C_{18}H_{16}NO_5$ $[M + H]^+$: 326.1028; found: 326.1018.

Preparation of 24. Method A. To a solution of **22** (10 mg, 0.03 mmol) in 50% H_2SO_4 (0.5 mL) was added a cool solution of $NaNO_2$ (4 mg, 0.06 mmol) in H_2O (0.5 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then, the resulting mixture was poured into boiling water (20 mL) and refluxed for 10 min. After being quenched by slow addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 0:100 to 1:99) to afford **24** (9 mg, 89%).

Preparation of 24. Method B. To a solution of **23** (91 mg, 0.28 mmol) and K_2CO_3 (116 mg, 0.84 mmol) in anhydrous DMF (1 mL) was added CH_2I_2 (25 μL, 0.31 mmol) under argon, and the mixture was stirred at 70 °C for 1 h. After being quenched with H_2O (5 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:99 to 2:98) to afford **24** (65 mg, 69%).

rel-(4b*S*,4b^1*S*)-3-Hydroxy-4b^1-methyl-4b,4b^1,8,9-tetrahydro-6*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-de]benzo[g]oxazolo[5,4,3-ij]-quinolin-6-one (**24**). Pale yellow solid; mp > 250 °C (decomposed); NMR data were collected from material prepared by Method A: ^{1}H NMR (DMSO-d_6, 500 MHz) 10.07 (1 H, s, OH), 7.78 (1 H, d, J = 8.5 Hz), 6.81−6.76 (3 H, m), 6.12 (1 H, s), 6.03 (1 H, s), 5.08 (1 H, s), 3.68−3.63 (1 H, m), 3.57−3.52 (1 H, m), 2.94−2.86 (2 H, m), 0.91 (3 H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) 157.7, 156.2, 147.6, 142.0, 133.9, 129.4, 127.1, 122.7, 119.8, 113.9, 112.4, 109.8, 106.7, 101.0, 83.1, 55.8, 36.3, 26.0, 17.0; HRMS (DART-TOF) m/z calculated for $C_{19}H_{16}NO_5$ $[M + H]^+$: 338.1028; found: 338.1047.

***rel*-(4b*S*,4b^1*S*)-3-(Benzyloxy)-4b^1-methyl-4b,4b^1,8,9-tetrahydro-6*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]-oxazolo[5,4,3-*ij*]quinolin-6-one (25).** To a solution of **24** (58 mg, 0.17 mmol) and K_2CO_3 (29 mg, 0.2 mmol) in anhydrous DMF (0.5 mL) was added BnBr (24 μL, 0.2 mmol) under argon, and the mixture was stirred at room temperature for 3 h. After being quenched by the addition of 1 M $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to afford **25** (51 mg, 70%) as a white solid; mp 197−198 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.93 (1 H, d, J = 8.5 Hz), 7.46−7.33 (5 H, m), 7.10−7.09 (1 H, m), 6.96 (1 H, dd, J = 8.5, 2.0 Hz), 6.59 (1 H, s), 6.07 (1 H, d, J = 2.0 Hz), 5.97 (1 H, d, J = 2.0 Hz), 5.12 (2 H, s), 5.01 (1 H, s), 3.87−3.83 (1 H, m), 3.61−3.56 (1 H, m), 2.94 (2 H, t, J = 6.0 Hz), 1.03 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.7, 156.9, 148.1, 142.8, 136.3, 133.8, 129.4, 128.6 (2 ×), 128.1, 127.5 (2 ×), 122.1, 122.0 (2 ×), 113.5, 112.8, 109.5, 106.8, 101.1, 84.0, 70.0, 56.4, 36.3, 26.6, 16.9; HRMS (DART-TOF) m/z calculated for $C_{26}H_{22}NO_5$ $[M + H]^+$: 428.1498; found: 428.1521.

***rel*-(7a*S*,8*S*)-10-(Benzyloxy)-7,7a-dimethyl-6,7,7a,8-tetrahydro-5*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]-quinolin-8-ol (26).** To a solution of **25** (42 mg, 0.098 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 200 μL, 0.3 mmol) under argon. The mixture was stirred at room temperature for 20 min and then quenched by the addition of saturated aqueous potassium sodium tartrate (Rochelle's salt) (5 mL). The mixture was stirred for another 1 h until two layers separated; then the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **26** (38 mg, 93%) as a white solid; mp 159−160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.01 (1 H, d, J = 8.5 Hz), 7.48−7.32 (6 H, m), 6.93 (1 H, dd, J = 8.5, 3.0 Hz), 6.52 (1 H, s), 6.06 (1 H, d, J = 2.0 Hz), 5.93 (1 H, d, J = 2.0 Hz), 5.17−5.11 (2 H, m), 5.03 (1 H, s), 3.58−3.51 (1 H, m), 3.09−2.99 (2 H, m), 2.53 (3 H, s), 2.48−2.45 (1 H, m), 1.18 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.8, 146.8, 142.0, 139.9, 136.9, 128.5 (2 ×), 128.0, 127.9, 127.6 (2 ×), 127.0, 125.5, 121.5, 115.9, 113.3, 110.5, 107.3, 100.6, 71.2, 69.9, 60.1, 46.2, 36.1, 22.3, 19.4; HRMS (DART-TOF) m/z calculated for $C_{26}H_{26}NO_4$ $[M + H]^+$: 416.1862; found: 416.1834.

10-(Benzyloxy)-7,7a-dimethyl-5,6,7,7a-tetrahydro-8*H*-[1,3]-dioxolo[4′,5′:4,5]benzo[1,2,3-*de*]benzo[*g*]quinolin-8-one (27). To a solution of **26** (32 mg, 0.077 mmol) and Dess−Martin periodinane (68 mg, 0.16 mmol) was added anhydrous CH_2Cl_2 (3 mL) under argon. The reaction was stirred at room temperature for 1 h. After being quenched by the addition of 1 M $Na_2S_2O_{3(aq)}$, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 1:99 to 2:98) to

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afford **27** (30 mg, 94%) as a pale yellow solid; mp 170−171 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.31 (1 H, d, J = 8.5 Hz), 7.68 (1 H, d, J = 3.0 Hz), 7.47−7.33 (5 H, m), 7.26 (1 H, dd, J = 8.5, 3.0 Hz), 6.57 (1 H, s), 6.08 (1 H, d, J = 1.0 Hz), 6.01 (1 H, d, J = 1.0 Hz), 5.15 (2 H, s), 3.55−3.50 (1 H, m), 3.11−3.02 (2 H, m), 2.59−2.54 (1 H, m), 2.39 (3 H, s), 1.55 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 199.6, 158.3, 146.9, 142.8, 136.3, 130.6, 128.9, 128.6 (2 ×), 128.1, 127.9, 127.6 (2 ×), 127.5, 127.1, 122.2, 114.0, 111.1, 108.2, 100.8, 70.2, 66.6, 45.6, 38.3, 28.0, 23.8; HRMS (DART-TOF) m/z calculated for $C_{26}H_{24}NO_4$ $[M + H]^+$: 414.1705; found: 414.1687.

(±)-*N*-Methylguattescidine (3).[5,13] To a solution of **27** (20 mg, 0.048 mmol) in CH_3OH (10 mL) was added 10% Pd/C (4 mg), and the mixture was vigorously stirred under an atmosphere of H_2 at room temperature for 2 h. The solid was removed by filtration through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (CH_3OH/CH_2Cl_2, 2:98 to 5:95) to give (±)-**3** (15 mg, 96%) as a pale yellow solid; mp > 250 °C (decomposed); ^{1}H NMR (CD_3OD, 500 MHz) 8.27 (1 H, d, J = 8.5 Hz), 7.36 (1 H, d, J = 3.0 Hz), 7.12 (1 H, dd, J = 8.5, 3.0 Hz), 6.62 (1 H, s), 6.09 (1 H, d, J = 1.0 Hz), 6.02 (1 H, d, J = 1.0 Hz), 3.54−3.47 (1 H, m), 3.12−3.04 (1 H, m), 2.99−2.95 (1 H, m), 2.67−2.62 (1 H, m), 2.36 (3 H, s), 1.51 (3 H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) 199.5, 157.3, 146.6, 142.1, 131.0, 128.7, 127.5, 127.4, 124.7, 121.4, 113.6, 112.6, 107.7, 100.9, 66.1, 45.4, 38.3, 26.2, 24.3; HRMS (DART-TOF) m/z calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$: 324.1236; found: 324.1232.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02024.

Copies of ^{1}H and ^{13}C spectra for reaction products and 2D NMR spectra for **8**, *rel*-(4*R*,5*S*)-**16a**, *rel*-(4*S*,5*S*)-**16a**, *rel*-(4*R*,5*S*)-**16b**, and **17a** (PDF)

X-ray crystallographic data of **6** (CCDC 1495290) (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The ^{1}H NMR data of (±)-**3** corresponded with the reported natural product given a correction of two protons in the range of 3.12−2.95 ppm instead of three protons as previously reported (Dr. Nor Hadiani Ismail, personal communication).

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