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Asymmetric Total Syntheses of Rhynchophylline and Isorhynchophylline

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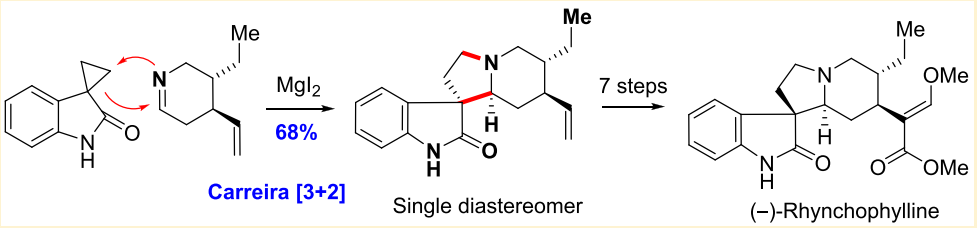
Supporting Information

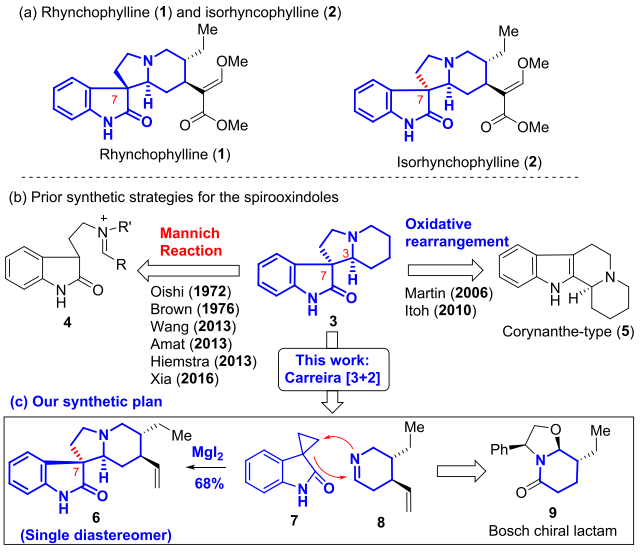


ABSTRACT: The asymmetric total syntheses of (−)-rhynchophylline and (+)-isorhynchophylline were achieved in 17 and 16 steps, respectively, from butanal and ethyl acrylate. Our synthesis features Carreira ring expansion to construct the tetracyclic spirooxindole core in high diastereoselectivity and the use of Bosch's chiral lactam for preparation of enantioenriched cyclic imine.

Rhynchophylline (Rhy, **1**, Scheme 1a)[1] is an active alkaloid isolated from *Uncaria rhynchophylla*, which has been widely used in traditional Chinese medicine for the treatment of stroke and hypertension. The antihypertensive and hypotensive activities of Rhy were linked to the inhibition of calcium ion entry in vascular smooth muscle, and therefore, Rhy is an effective Ca^{2+} channel antagonist.[2] A wide range of biochemical studies[3] have shown that Rhy exhibits a neuroprotective effect, for instance, reducing the ischemia-induced neuronal damage in the hippocampus[3a] and improving memory impairment in mice,[3b] through modulation/regulation of calcium/potassium ion channel activity and neurotransmission. Therefore, Rhy has been studied as a drug candidate for prevention and/or treatment of cardiovascular and central nervous system diseases.[3] Isorhynchophylline (iRhy, **2**), a C7 spiroisomer of Rhy (**1**), was also isolated from *Uncaria rhynchophylla* and possesses similar biological activities (neuroprotection and antihypertension).[3,4]

Rhy and iRhy are two representative members of a growing family of medicinally privileged bioactive tetracyclic 3-spirooxindole alkaloids[5] and therefore have attracted much synthetic interest. The prior synthetic efforts led to one semisynthesis (from dihydrosecologanin aglycone, Brown-1976),[6] two total syntheses (racemic, Oishi-1975[7a] and Hiemstra-2013[7b]), and five formal syntheses[8,9] (two racemic: Martin-2006[8a] and Xia-2016[8b] and three enantioselective: Amat-2013,[9a] Wang-2013,[9b] and Itoh-2010[9c]) (Scheme 1b). It was to our surprise that enantioenriched Rhy (**1**) and iRhy (**2**) have not been obtained by total synthesis. The key spirocyclization used in these synthetic endeavors was either intramolecular Mannich reaction[10] or biomimetic oxidative rearrangement[11] of tetrahydro-β-carbolines (corynanthe type) for the construction of a tetracyclic 3-spirooxindole core.[12] The major limitation of these two spirocyclization reactions was the poor diastereoselectivity at the spirocenter (C7), which might

Scheme 1. Rhynchophylline and Isorhynchophylline and Their Synthetic Strategies



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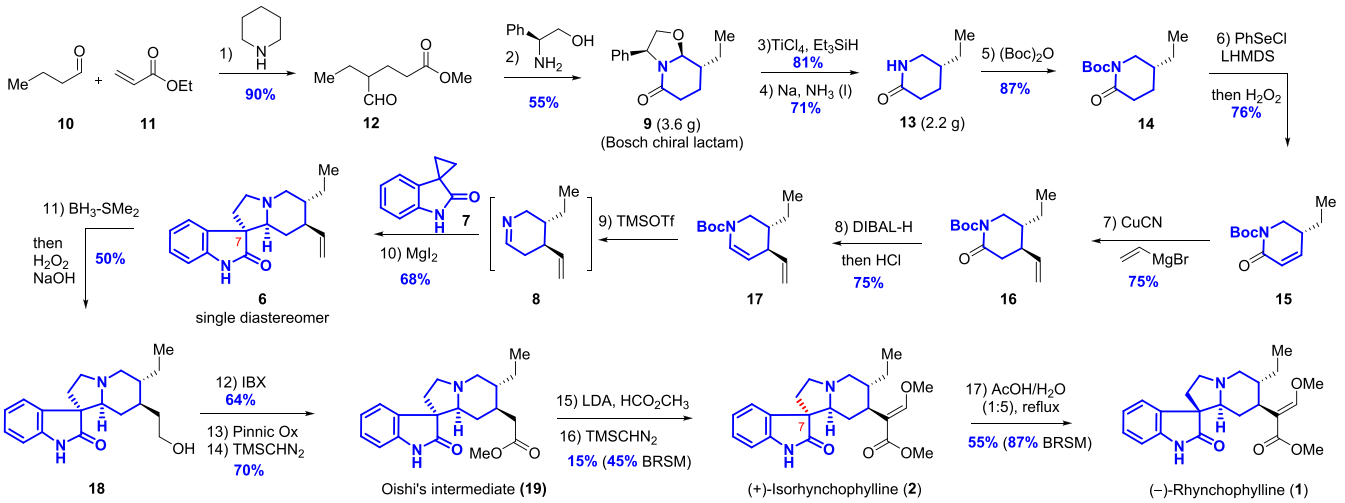
Scheme 2. Asymmetric Total Syntheses of Rhynchophylline and Isorhynchophylline[a]



[a]Conditions: (1) (a) K_2CO_3, neat, rt, 18 h; (b) CH_3CN, 80 °C, 12 h, then HOAc/H_2O, 80 °C, 2 h, 90%. (2) (a) Et_2O, 0 °C, 10 h, Na_2SO_4; (b) 90 °C, 15 Torr, 6 h, 55%. (3) Et_3SiH, $TiCl_4$, CH_2Cl_2, 40 °C, 48 h, 81%. (4) Na, NH_3 (liquid), THF, −33 °C, 5 min, 71%. (5) $(Boc)_2O$, Et_3N, DMAP, rt, 12 h, 87%; (6) (a) LiHMDS, PhSeCl, THF, −78 °C; (b) H_2O_2, EtOAc, rt, 76%. (7) CuCN, vinylMgBr, THF, −78 °C, 75%. (8) DIBAL-H, THF, −78 °C, then 1 N HCl, 75%. (9) TMSOTf, NEt_3, CH_2Cl_2, −20 °C. (10) MgI_2, THF, 80 °C, 68% (two steps). (11) (a) $BH_3{\cdot}Me_2S$, THF, rt, 10 h; (b) NaOH, H_2O_2, rt, 12 h, 50%. (12) IBX, DMSO, rt, 2 h, 64%. (13) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, CH_3CN/*t*-BuOH, rt, 2 h. (14) $TMSCHN_2$, MeOH/Et_2O, rt, 5 min, 70% (two steps). (15) LDA, HCO_2CH_3, THF, −78 °C. (16) $TMSCHN_2$, MeOH/Et_2O, rt, 5 h, 15% (two steps). (17) AcOH/H_2O, 110 °C, 24 h, 55%.

be attributed to a reversible Mannich-*retro*-Mannich process.[13] Herein, we report a new convergent strategy for the asymmetric total synthesis of Rhy and iRhy by exploiting Carreira's ring expansion[14] ([3 + 2]-cycloaddition) to efficiently construct the key tetracyclic spirooxindole (**6**) as a single C7 spiroisomer (Scheme 1c). The convergence and high spiro-diastereoselectivity were complementary to the previous linear syntheses with the thermodynamic control of the stereochemistry of spirocyclization.

Our recent study has shown that Rhy as a novel EphA4 inhibitor could effectively block the EphA4-dependent signaling in hippocampal neurons and reduce the EphA4 activity in the hippocampus of APP/PS1 transgenic mice.[15] To further study the bioactivity of Rhy, we initiated this program directed to developing a reliable and flexible chemical synthesis of enantioenriched Rhy and iRhy. Inspired by Carreira's elegant ring expansion strategy for the construction of a racemic spirooxindole core in the total synthesis of (±)-strychnofoline[14a−c] and (−)-spirotryprostatin B,[14d,e] we envisioned that using a chiral nonracemic cyclic imine **8** and cyclopropyl spirooxindole **7** as the annulation partners this ring expansion strategy might be exploited in an asymmetric fashion to provide the enantio-enriched tetracyclic spirooxindole **6** as a single spiroisomer (Scheme 1b). The chiral cyclic aldimine **8** could be derived from the known Bosch (*S*)-phenylglycinol-derived oxazolopiperidone lactam **9**.[16a]

As depicted in Scheme 2, our synthesis started with gram-scale preparation of enantiopure Bosch chiral lactam **9** (3.6 g/batch) from commercially available commodity butanal (**10**) and ethyl acrylate (**11**) through piperidine-mediated enamine Michael addition[17] and lactamization with (*S*)-phenylglycinol.[16b] Reductive removal of the chiral auxiliary with $TiCl_4$/Et_3SiH and Na/NH_3(liquid) provided enantiomerically pure *δ*-lactam **13** (2.2 g) in good overall yield. Protection of the *δ*-lactam with Boc permitted subsequent Sharpless[18] *α*,*β*-unsaturation with phenylselenyl chloride and hydrogen peroxide to afford *α*,*β*-unsaturated *δ*-lactam **15**. Michael addition of allyl Grignard reagent in the presence of stoichiometric copper (CuBr, CuI, CuBr−SMe_2, etc) was found to give poor diastereoselectivity (dr, 1:1 to 1:3) under various conditions.[19] Fortunately, the corresponding vinylcuprate generated *in situ* from vinyl Grignard reagent and CuCN underwent a highly diastereoselective conjugate addition to provide *trans*-substituted **16** as a single diastereomer in 60% yield. This finding was not surprising, since allylcuprate was a considerably harder nucleophile than vinylcuprate.[20] Next, we employed Carreira's method[14b] to partially reduce the *δ*-lactam with DIBAL-H as a hemiaminal, which upon treatment of 1 N HCl resulted in facile dehydration to cyclic enamine **17**. Notably, this enamine was stable for purification with column chromatography on silica gel. Tautomerization of enamine to aldimine was effected in the course of Boc deprotection with TMSOTf, and the resulting cyclic imine **8** was subjected to Carreira's [3 + 2] ring-expansion reaction with cyclopropyl spirooxindole **7**[21] in the presence of MgI_2.

To our delight, the cyclized spirooxindole **6** was isolated as a single diastereomer in 68% yield. This excellent diastereoselectivity was consistent with the observation of related annulation by Carreira and co-workers in the total synthesis of (±)-strychnofoline.[14] The C7 stereochemistry of spirooxindole **6** corresponded to iRhy, and it could be isomerized under acidic conditions via the *retro*-Mannich/Mannich process. We decided to isomerize this stereochemistry at a late stage for the synthesis of Rhy from iRhy. To obtain Oishi's intermediate **19**[7a] for Rhy and iRhy, we undertook a series of functional group manipulations[9b] (**6** → **18** → **19**): hydroboration/oxidation of the terminal alkene of **6**, IBX oxidation of the alcohol to the aldehyde, Pinnick oxidation of the resulting aldehyde to the corresponding carboxylic acid, and esterification of the carboxylic acid with $TMSCHN_2$. At this

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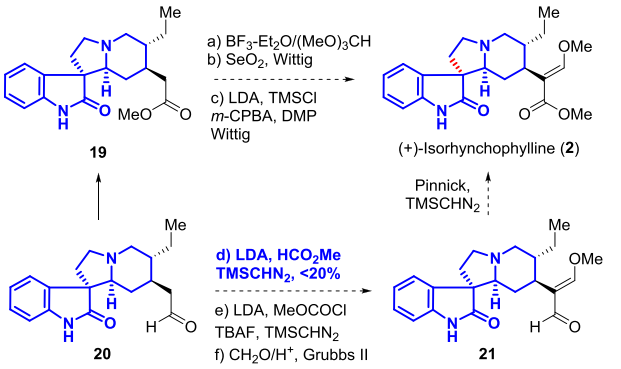
stage with Oishi's intermediate **19** in hand, we achieved the fourth enantioselective formal total synthesis of Rhy and iRhy.

Before trying to reproduce Oishi's last three steps (Claisen condensation, methyl esterification, C7 isomerization) for completing the total synthesis of Rhy, we realized that these three steps were low-yielding—13.7, 26.5, and 36.5%—and had not been reproduced by other research groups who arrived at the common intermediate **19**. Although we were able to reproduce these three steps and accomplished the first enantioselective total synthesis of Rhy and iRhy, the overall yield of these steps was consistently low. Claisen condensation of **19** with methyl formate using LDA as the base was identified to be responsible for the low yield (10−20%) because of low conversion (<20%) of **19** under various conditions attempted.

The low conversion of Claisen condensation prompted us to explore other methods for installation of the β-methoxyacrylate moiety (Scheme 3). Apparently, Lewis acid ($TiCl_4$ and BF_3−

Scheme 3. Other Attempted Sequence for Elaboration of Tetracyclic Spirooxindole 20 to Isorhynchophylline (2)



Et_2O) did not effect Claisen condensation of **19** with trimethyl orthoformate (method a). Inspired by Hiemstra's high-yielding synthesis of the β-methoxyacrylate moiety by Wittig olefination,[7b] we attempted various protocols for α-oxidation of the ester of **19** to the corresponding α-ketoester without success (methods b and c). We then hypothesized that the more reactive aldehyde (**20**) might be a better substrate for α-functionalization. Therefore, we attempted three methods (methods d−f) for the synthesis of β-methoxyacrolein **21**, which was expected to deliver iRhy through Pinnick oxidation and esterification. Unfortunately, only Claisen condensation of **20** with methyl formate (method d) gave the desired aldehyde **21** but in poor yield (<20%). The small amount of **21** could be converted by oxidation and esterification to iRhy in ∼70% yield. The other two methods (α-acylation and α-methylenation/cross-metathesis) did not generate any detectable aldehyde **21**. Despite that we could not improve the efficiency of installation of the β-methoxyacrylate moiety at the late stage of synthesis, our attempted methods would be instructive to invention of new synthetic techniques or strategies for the synthesis of a β-methoxyacrylate motif, which is ongoing in our laboratory.

We have achieved the first enantioselective total synthesis of rhynchophylline (**1**) and isorhynchophylline (**2**) in 17 and 16 steps, respectively, from commodity chemicals. Our synthesis features Carreira's highly diastereoselective [3 + 2] annulation of cyclopropyl oxindole and highly functionalized cyclic aldimine to construct the tetracyclic spirooxindole core as a single diastereomer. This remarkable diastereoselectivity addressed the unsolved problem of C7 spiroisomers by Mannich cyclization or oxidative rearrangement of corynanthe-type substrates in all previous syntheses of Rhy and iRhy. In addition, we successfully reproduced the reactions of the last three steps from Oishi's intermediate and explored alternative methods for the challenging synthesis of the β-methoxyacrylate motif that is also found in other spirooxindole natural products. Our synthetic study will allow us to further study the biological activity of Rhy and iRhy.

EXPERIMENTAL SECTION

General Information. Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as an indicator. Dichloromethane was freshly distilled before use from calcium hydride (CaH_2). All other solvents were dried over 3 or 4 Å molecular sieves. Solvents used in workup, extraction, and column chromatography were used as received from commercial suppliers without prior purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC, 0.25 mm) on Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040−0.062 mm) supplied by Grace. Infrared spectra were collected on a Bruker model TENSOR27 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR) or dimethylsulfoxide (2.5 ppm for ^1H NMR and 39.5 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured on a JASCO PerkinElmer model P-2000 polarimeter. High-resolution mass spectra were measured at the Hong Kong University of Science and Technology Mass Spectrometry Service Center on an Agilent GC/MS.

*Preparation of **12** (Methyl 4-Formylhexanoate).* Piperidine (24 mL, 0.225 mol) and anhydrous K_2CO_3 (7.5 g, 0.05 mol) were charged in a flask, and butanal (13.5 mL, 0.15 mol) was added dropwise to the reaction mixture at 0 °C. After stirring at this temperature for 2 h, the reaction mixture was warmed to room temperature and stirred for 36 h. The reaction mixture was filtered, and the filtrate cake was then rinsed with diethyl ether (50 mL). The combined filtrate was concentrated under reduced pressure to afford a crude. The crude product was dissolved in acetonitrile (60 mL), and then, ethyl acrylate (20.2 mL, 0.225 mol) was added dropwise at 0 °C and the mixture was stirred at reflux overnight. Aqueous acetic acid solution (10.5 mL of acetic acid in 60 mL of water) was added, and then, the resulting solution was heated to reflux for another 2 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with solid NaCl, the solution was extracted with Et_2O (60 mL × 3), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford compound **12** as a colorless oil (14.7 g, 62.1%). IR ν_{max} 2962, 1729, 1707, 1445, 1168, 854, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, J = 2.4 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 2.25 (td, J = 8.4, 6.8 Hz, 2H), 2.18 (ddt, J = 8.4, 7.4, 2.9 Hz, 1H), 1.95−1.83 (m, 1H), 1.76−1.67 (m, 1H), 1.67−1.57 (m, 1H), 1.53−1.41 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.2, 172.7, 60.2, 52.2, 31.3, 22.9, 21.5, 13.9, 11.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{17}O_3$, 173.1178; found, 173.1182.

*Preparation of **9** ((3S,8R,8aS)-8-Ethyl-3-phenylhexahydro-5H-oxazolo[3,2-a]pyridin-5-one).* A solution of compound **12** (4.8 g, 30 mmol), (*S*)-phenylglycinol (5 g, 38 mmol), and anhydrous Na_2SO_4 (17.2 g, 120 mmol) in Et_2O (50 mL) was stirred at 0 °C for 10 h. The resulting suspension was filtered, and the filtrate was concentrated

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under reduced pressure. The residue was then heated to 90 °C under *vacuo* (10−15 mmHg) for 1 h, and then, the residue was purified by column chromatography on silica gel (EtOAc/hexane/Et_3N 100:50:3) to afford compound **9** (4.0 g, 16.5 mmol, 55%). $[\alpha]_D^{25}$ = +88.2 (*c* 1.0, $CHCl_3$); IR ν_{max} 3062, 3031, 2959, 1656, 1458, 1413, 1383, 1090, 1032, 1002, 824, 760, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 2H), 7.32−7.23 (m, 3H), 5.27 (t, *J* = 7.9 Hz, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 4.50 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.77 (dd, *J* = 9.0, 7.8 Hz, 1H), 2.64−2.53 (m, 1H), 2.46−2.34 (m, 1H), 2.03−1.93 (m, 1H), 1.90−1.75 (m, 1H), 1.58−1.48 (m, 2H), 1.05 (t, *J* = 7.5 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1, 139.8, 129.0, 127.7, 126.3, 92.9, 72.6, 58.4, 41.5, 31.7, 24.9, 23.0, 11.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$, 246.1494; found, 246.1496.

Preparation of ***13*** *((R)-5-Ethylpiperidin-2-one).* To a solution of compound **9** (4.9 g, 20 mmol) in anhydrous CH_2Cl_2 (150 mL) were added triethylsilane (4.8 mL, 30 mmol) and $TiCl_4$ (4.8 mL, 44 mmol), and the mixture was stirred at 50 °C for 24 h. Then, additional triethylsilane (4.8 mL, 30 mmol) and $TiCl_4$ (4.8 mL, 44 mmol) were added, and stirring was continued at 50 °C for 24 h. The mixture was then cooled to 0 °C, and aqueous HCl (1 N) was added slowly to adjust the solution to be pH 1. The aqueous phase was separated and extracted with CH_2Cl_2 (150 mL × 3), and the combined organic phases were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/NH_4OH = 100:2) to afford the pure alcohol product (4.0 g, 16.2 mmol, 81.0%). A three-necked round-bottomed flask was equipped with a coldfinger condenser cooled with dry ice-acetone to collect the liquid NH_3 (∼40 mL) at −78 °C. A solution of the reduction product obtained above (4.0 g, 16.2 mmol) in dry THF (27 mL) was added slowly, and the reaction temperature was raised to −33 °C. Sodium metal (ca. 0.67 g) was added in a small portion until the blue color persisted. The reaction mixture was stirred at −33 °C for an additional 5 min and then quenched by addition of solid NH_4Cl until the blue color disappeared. The mixture was stirred at room temperature for 5 h and diluted with ethyl acetate (80 mL). The solid was removed by filtration, and the filtrate was collected and concentrated under reduced pressure to give the crude residue, which was purified by column chromatography on silica gel (EtOAc/NH_4OH = 100:1) to afford compound **13** (1.47 g, 11.5 mmol, 71.3%). $[\alpha]_D^{25}$ = +51.9 (*c* 1.0, $CHCl_3$); IR ν_{max} 3424, 2928, 2871, 1643, 1498, 1464, 1408, 1376, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (brs, 1H), 3.31−3.20 (m, 1H), 2.82 (dd, *J* = 11.9, 10.1 Hz, 1H), 2.31 (ddd, *J* = 17.9, 6.1, 3.3 Hz, 1H), 2.22 (ddd, *J* = 17.9, 11.1, 6.4 Hz, 1H), 1.81 (ddd, *J* = 11.8, 5.9, 2.8 Hz, 1H), 1.57 (tq, *J* = 10.9, 3.3 Hz, 1H), 1.41−1.31 (m, 1H), 1.27 (p, *J* = 7.5 Hz, 2H), 0.84 (t, *J* = 7.5 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 47.3, 34.8, 30.7, 26.7, 26.0, 11.5; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_7H_{14}NO$, 128.1075; found, 128.1076.

Preparation of ***14*** *(tert-Butyl (R)-5-Ethyl-2-oxopiperidine-1-carboxylate).* To a solution of lactam **13** (0.8 g, 6.3 mmol) in CH_3CN (20 mL) were added DMAP (77 mg, 0.63 mmol) and di-*tert*-butyl dicarbonate (2.1 g, 9.5 mmol) dropwise at 0 °C, and then, the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 95:5) to afford compound **14** (1.25 g, 5.5 mmol, 87.4%). $[\alpha]_D^{25}$ = +59.4 (*c* 1.0, $CHCl_3$); IR ν_{max} 3363, 2964, 2927, 1709, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (ddd, *J* = 12.7, 4.8, 1.8 Hz, 1H), 3.14 (dd, *J* = 12.7, 10.1 Hz, 1H), 2.54 (ddd, *J* = 17.3, 6.2, 4.2 Hz, 1H), 2.43 (ddd, *J* = 17.3, 10.6, 6.6 Hz, 1H), 1.91 (dqd, *J* = 12.9, 4.5, 2.2 Hz, 1H), 1.76−1.64 (m, 1H), 1.50 (s, 9H), 1.46−1.27 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.5, 152.7, 82.8, 50.9, 35.2, 34.1, 27.9, 26.2, 26.1, 11.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{22}NO_3$, 228.1600; found, 228.1606.

Preparation of ***15*** *(tert-Butyl (R)-3-Ethyl-6-oxo-3,6-dihydropyridine-1(2H)-carboxylate).* To a solution of **14** (520 mg, 2.3 mmol) in THF (11 mL) was added a solution of LiHMDS (6.9 mL, 6.9 mmol, 1 N in THF) dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Then, PhSeCl (669 mg, 3.5 mmol) in THF (2 mL) was added via cannula into the reaction mixture at −78 °C within 30 s. The reaction mixture was stirred at −78 °C for 1 h and then quenched at −78 °C by addition of saturated aqueous $NaHCO_3$. The reaction mixture was warmed to room temperature and diluted with water (20 mL) and EtOAc (20 mL). The organic layer was collected, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in EtOAc (11 mL), and then, H_2O_2 solution (2.5 mL, 35%) was added dropwise at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The organic layer was collected, washed with brine (10 mL × 2) and saturated aqueous $NaHCO_3$ (10 mL × 3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:10) to provide compound **15** (340 mg, 1.51 mmol, 75.5%). $[\alpha]_D^{25}$ = +9.4 (*c* 1.0, $CHCl_3$); IR ν_{max} 2969, 2930, 1761, 1714, 1310, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 9.8, 3.6 Hz, 1H), 5.90 (dd, *J* = 9.8, 1.9 Hz, 1H), 3.92 (ddd, *J* = 13.0, 5.0, 0.9 Hz, 1H), 3.55 (dd, *J* = 12.9, 8.3 Hz, 1H), 2.43−2.31 (m, 1H), 1.53 (s, 9H), 1.51−1.42 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6, 152.3, 147.9, 124.9, 82.6, 47.7, 36.0, 27.8, 27.7, 24.3, 11.0; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{20}NO_3$, 226.1443; found, 226.1446.

Preparation of ***16*** *(tert-Butyl (4R,5R)-5-Ethyl-2-oxo-4-vinylpiperidine-1-carboxylate).* To a suspension of CuCN (40.3 mg, 0.45 mmol) in THF (3 mL) was added a solution of vinylmagnesium bromide (0.9 mL, 0.9 mmol, 1 N in THF) at −78 °C. The reaction was warmed to 0 °C for 3 min and cooled to −78 °C. A solution of **15** (68 mg, 0.3 mmol) in THF (1 mL) was added, and the suspension was warmed to room temperature over 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl/NH_4OH (9:1, 3 mL) and H_2O (3 mL), and the resulting mixture was stirred for 20 min. A solution of TBAF (3 mL, 1 N in THF) was added to the reaction mixture. After stirring for 15 min, the organic layer was collected and the aqueous phase was extracted with EtOAc (6 mL × 2). The combined organic phases were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:9) to afford compound **16** (57 mg, 0.22 mmol, 75%). $[\alpha]_D^{25}$ = +25 (*c* 1.0, $CHCl_3$); IR ν_{max} 2971, 2928, 1770, 1713, 1290, 1246, 1152, 1094, 918, 852, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 20.5, 10.0, 8.0 Hz, 1H), 5.09−5.00 (m, 2H), 3.85−3.75 (m, 1H), 3.32 (dd, *J* = 13.2, 8.6 Hz, 1H), 2.56 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.36 (dd, *J* = 16.5, 10.0 Hz, 1H), 2.25 (q, *J* = 8.0 Hz, 1H), 1.63−1.56 (m, 2H), 1.51 (d, *J* = 1.8 Hz, 9H), 1.33−1.17 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.0, 152.7, 139.8, 115.9, 83.2, 48.8, 42.4, 40.1, 40.1, 28.2, 24.8, 11.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{23}NO_3$, 254.1756; found, 254.1763.

Preparation of ***17*** *(tert-Butyl (3R,4R)-3-Ethyl-4-vinyl-3,4-dihydropyridine-1(2H)-carboxylate).* To a solution of **16** (40 mg, 0.16 mmol) in THF (1.5 mL) at −78 °C was added DIBAL-H (0.32 mL, 0.32 mmol, 1 N in hexane) dropwise, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of saturated aqueous Rochelle salt (0.5 mL) and diluted with diethyl ether (6 mL). The reaction mixture was stirred vigorously overnight. The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude hemiaminal intermediate as an oil. To the hemiaminal in CH_2Cl_2 (2 mL) was added aqueous 1 N HCl (0.2 mL), and the reaction mixture was stirred vigorously for 5 min. The organic layer was collected, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:20) to provide compound **17** as a thick oil (28 mg, 0.12 mmol, 75%). $[\alpha]_D^{25}$ = +109 (*c* 1.0, $CHCl_3$); IR ν_{max} 2968, 2927, 2876, 1702, 1648, 1461, 1368, 1249, 1163, 1128, 913, 870, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 8.4 Hz, 1H, rotamer), 6.74 (d, *J* = 8.3 Hz, 2H), 5.76−5.58 (m, 1H), 5.10−4.94 (m, 2H), 4.72−4.60 (m, 1H), 3.73−3.43 (m, 1H, rotamer), 3.29−3.13 (m, 1H), 2.54−2.42 (m, 1H), 1.48

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(s, 9H), 1.46 (m, 2H), 1.28−1.12 (m, 1H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 152.9/152.4, 141.6/141.4, 125.3/125.1, 115.6, 107.0, 80.6/80.5, 43.1/42.9, 42.4, 41.9, 38.5/38.4, 28.4/28.3, 24.2/24.1, 11.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{24}NO_2$, 238.1807; found, 238.1812.

Preparation of ***6*** *(3S,6′R,7′R,8a′S)-6′-Ethyl-7′-vinyl-2′,3′,6′,7′,8′,8a′-hexahydro-5′H-spiro[indoline-3,1′-indolizin]-2-one).* To a solution of **17** (53 mg, 0.22 mmol) and Et_3N (0.62 mL, 4.4 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added dropwise trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.28 mL, 1.54 mmol). The reaction mixture was allowed to warm up to −20 °C and stirred at this temperature for 2 h. The reaction was quenched at −78 °C by addition of saturated aqueous $NaHCO_3$. After warming to room temperature, the organic layer was collected, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the cyclic aldimine. To a pressure tube charged with MgI_2 (61 mg, 0.22 mmol) and **7** (35 mg, 0.22 mmol) was added cyclic aldimine in THF (2 mL). The reaction mixture in the pressure tube was heated to reflux at 80 °C in an oil bath for 16 h. The reaction mixture was cooled to room temperature and diluted with diethyl ether (4 mL) and water (2 mL). The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to provide spirooxindole **6** as an oil (44 mg, 0.15 mmol, 67.6%). $[\alpha]_D^{25}$ = +19.3 (c 1.0, $CHCl_3$); IR ν_{max} 3074, 2927, 2800, 1708, 1618, 1469 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.17 (td, J = 7.7, 1.3 Hz, 1H), 7.02 (td, J = 7.5, 1.1 Hz, 1H), 6.94−6.87 (m, 1H), 5.44 (ddd, J = 16.9, 10.3, 8.8 Hz, 1H), 4.91−4.81 (m, 2H), 3.32 (dt, J = 9.9, 4.9 Hz, 2H), 2.56−2.33 (m, 3H), 2.05 (m, 1H), 1.78 (t, J = 10.9 Hz, 1H), 1.73−1.64 (m, 1H), 1.54 (ddd, J = 13.7, 7.5, 3.2 Hz, 1H), 1.29 (m, 1H), 1.15 (ddd, J = 12.6, 3.9, 2.5 Hz, 1H), 1.05−0.96 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 182.5, 142.2, 140.3, 127.5, 124.9, 122.3, 114.7, 109.6, 71.6, 57.5, 56.8, 54.1, 46.2, 41.1, 35.0, 32.9, 24.1, 11.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{25}N_2O$, 297.1967; found, 297.1966.

Preparation of ***18*** *((3S,6′R,7′R,8a′S)-6′-Ethyl-7′-(2-hydroxyethyl)-2′,3′,6′,7′,8′,8a′-hexahydro-5′H-spiro[indoline-3,1′-indolizin]-2-one).* To a solution of **6** (40 mg, 0.135 mmol) in dry THF (2 mL) was added $BH_3{\cdot}Me_2S$ (140 μL, 10 N in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 6 h. To the reaction mixture at 0 °C were added sequentially and slowly aqueous 3 N NaOH (0.4 mL) and H_2O_2 (0.4 mL, 35 wt %). The mixture was slowly warmed to room temperature and stirred overnight. After evaporation of the volatiles, H_2O (2 mL) was added and the solution was extracted with EtOAc (4 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc) to afford compound **18** as a colorless oil (21 mg, 0.067 mmol, 49.5%). $[\alpha]_D^{25}$ = +5.5 (c 1.0, $CHCl_3$); IR ν_{max} 2928, 2806, 1072, 1621, 1470, 1045, 743, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.18 (td, J = 7.7, 1.3 Hz, 1H), 7.01 (td, J = 7.6, 1.1 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 3.55−3.38 (m, 2H), 3.29 (q, J = 7.3, 4.3 Hz, 2H), 2.43 (m, 2H), 2.37 (ddd, J = 13.0, 9.1, 2.3 Hz, 1H), 2.08−2.00 (m, 1H), 1.86 (br, 1H), 1.85−1.74 (m, 2H), 1.60 (ddd, J = 13.8, 7.6, 2.6 Hz, 1H), 1.31−1.22 (m, 1H), 1.20−1.06 (m, 3H), 0.87 (t, J = 7.4 Hz, 3H), 0.67 (brs, 1H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 182.1, 140.2, 133.7, 127.5, 125.1, 122.4, 109.5, 71.9, 60.3, 57.9, 56.9, 54.0, 41.5, 36.4, 35.5, 35.2, 31.5, 23.4, 11.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2$, 315.2073; found, 315.2073.

Preparation of ***19*** *(Methyl 2-((3S,6′R,7′R,8a′S)-6′-Ethyl-2-oxo-2′,3′,6′,7′,8′,8a′-hexahydro-5′H-spiro[indoline-3,1′-indolizin]-7′-yl)acetate).* To a solution of compound **18** (29 mg, 92 umol) in dimethyl sulfoxide (2 mL) was added 2-iodoxybenzoic acid (39 mg, 0.14 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (6 mL), washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to afford the aldehyde as an amorphous white powder (18 mg, 59 μmol, 63.9%). To a solution of the aldehyde (18 mg, 57.7 umol) in acetonitrile (0.5 mL), *tert*-butyl alcohol (1.5 mL), and 2-methyl-2-butene (14 μL, 0.13 mmol) at 0 °C was added dropwise a solution of $NaClO_2$ (15.7 mg, 0.17 mmol) and NaH_2PO_4 (20.4 mg, 0.17 mmol) in H_2O (0.5 mL). The mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of aqueous sodium thiosulfate (1 N, 2 mL), and the pH of the resulting solution was adjusted with aqueous 1 N HCl to pH 2.0. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude carboxylic acid, which was used without further purification. To a solution of the obtained carboxylic acid in MeOH (0.5 mL) and Et_2O (0.5 mL) at 0 °C was added a solution of trimethylsilyl diazomethane ($TMSCHN_2$, ca. 0.1 mL, 2 N in hexane) until the yellow color persisted. The reaction mixture was stirred at 0 °C for 5 min before acetic acid (0.1 mL) was added to quench the excess $TMSCHN_2$ (the yellow color disappeared). The reaction mixture was then concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to afford compound **19** as a colorless oil (14 mg, 40.4 umol, 70%). $[\alpha]_D^{25}$ = +9.5 (c 1.0, $CHCl_3$); IR ν_{max} 3447, 2922, 2852, 1639, 1459, 1381, 1047, 751, 480 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 3.47 (s, 3H), 3.26−3.20 (m, 2H), 2.45 (dd, J = 15.5, 3.8 Hz, 1H), 2.31 (m, 1H), 2.25−2.16 (m, 2H), 1.93−1.80 (m, 2H), 1.70 (t, J = 10.4 Hz, 1H), 1.55−1.44 (m, 1H), 1.42−1.34 (m, 1H), 1.21−1.13 (m, 1H), 1.11−0.96 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H), 0.61 (q, J = 11.9 Hz, 1H). ^{13}C{1H} NMR (101 MHz, DMSO-d_6) δ 179.9, 172.6, 141.4, 133.5, 127.4, 124.4, 121.4, 109.2, 70.9, 57.0, 55.9, 53.3, 51.1, 40.5, 37.3, 36.6, 34.6, 31.5, 22.8, 10.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_3$, 343.2022; found, 343.2022.

*Preparation of (+)-Isorhynchophylline (****2****).* To a solution of **19** (42 mg, 0.12 mmol) in THF (2 mL) at −78 °C under a nitrogen atmosphere was added lithium diisopropylamine (LDA, 182 uL, 0.37 mmol, 2 N in THF). The reaction mixture was stirred at −78 °C for 1 h, and then, methyl formate (74 uL, 1.2 mmol) was added. The reaction mixture was allowed to warm up to room temperature and was stirred for an additional 12 h. The reaction solution was then poured into water (6 mL), and the solution was adjusted to pH 12 by addition of solid KOH. The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide the starting material **19** (12 mg), while the aqueous phase was acidified with aqueous 2 N citric acid solution to pH 3.0 and then extracted with CH_2Cl_2 (2 × 3 mL). The combined CH_2Cl_2 phases were dried over Na_2SO_4 and concentrated under reduced pressure to afford the Claisen condensation product, which was used for etherification without further purification. To a solution of Claisen condensation product obtained above in MeOH/Et_2O (1:1, 1 mL) was added trimethylsilyl diazomethane ($TMSCHN_2$, 0.2 mL, 2 N in hexane). After stirring at room temperature for 5 h, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:1) to afford isorhynchophylline (**2**, 7.0 mg, 18.4 umol, 15.3%, 44.8% based recovery of starting material). $[\alpha]_D^{25}$ = +11.2 (c 1.0, $CHCl_3$); IR ν_{max} 3253, 3013, 2954, 2800, 1700, 1625, 1468, 1239, 1103, 1017, 802, 748, 673, 624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (brs, 1H), 7.43 (brs, 1H), 7.20 (brs, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 3H), 3.33 (d, J = 12.5 Hz, 2H), 2.53−2.43 (m, 2H), 2.43−2.32 (m, 2H), 2.07 (brs, 2H), 1.77 (t, J = 11.1 Hz, 1H), 1.51 (brs, 1H), 1.35 (brs, 1H), 1.07 (brs, 1H), 0.97 (br, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 182.4, 167.9, 159.6, 140.3, 134.0, 127.4, 125.1, 122.3, 112.2, 109.4, 72.3, 61.2, 58.1, 56.8, 54.2, 50.6, 38.1, 37.5, 35.5, 30.2, 24.2, 11.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_4$, 385.2127; found, 385.2128.

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Preparation of (−)-Rhynchophylline (1). The solution of isorhynchophylline (13 mg, 34 umol) in acetic acid/H_2O (1:4, 3 mL) was heated to reflux overnight. The reaction mixture was cooled to room temperature and neutralized by addition of NH_4OH (1 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:1, then MeOH/CH_2Cl_2 1:10) to afford rhynchophylline (**1**, 7.1 mg, yield 54.6%, 86.9% BRSM) and isorhynchophylline (**2**, 4.2 mg, 32.3%). $[\alpha]_D^{25}$ = −15.4 (*c* 1.0, $CHCl_3$, $^{lit}[\alpha]_D^{22}$ = −6.2 (*c* 2.0, $CHCl_3$); IR ν_{max} 2958, 2788, 1702, 1627, 1470, 1441, 1234, 1183, 1090, 1020, 802, 748, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (brs, 1H), 7.25 (s, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.47−3.34 (m, 2H), 2.57−2.38 (m, 2H), 2.06−1.96 (m, 1H), 1.66 (t, *J* = 9.9 Hz, 1H), 1.36 (brs, 1H), 1.20 (brs, 1H), 0.95 (brs, 1H), 0.80 (t, *J* = 7.4 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 181.7, 169.3, (168.3), 159.7, 141.1, 133.8, 127.7, 123.1, 122.3, 111.8, 109.5, 75.5, 61.4, 58.2, 56.1, 55.0, 51.1, 39.6, 37.8, 34.8, 29.23, 24.1, 11.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_4$, 385.2127; found, 385.2126.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01977.

Tables of comparison of NMR data and copies of NMR spectra (PDF)

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Notes

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