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 Ca2+ channel antagonist.2 A wide range of biochemical studies3 have shown that Rhy exhibits a neuroprotective effect, for instance, reducing the ischemia-induced neuronal damage in the hippocampus and improving memory impairment in mice, 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 alkaloids5 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-19757a and Hiemstra-20137b), and five formal syntheses (two racemic: Martin-20068a and Xia-20168b and three enantioselective: Amat-20139a, Wang-20139b, and Itoh-20109c) (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 reaction10 or biomimetic oxidative rearrangement11 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...
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 expansion14 ([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 efficacious chemical synthesis of Rhy and iRhy. Inspired by Carreira and co-workers in the total synthesis of (+)-strychnofoline,14 we envisioned that using a chiral nonracemic cyclic imine 8 and cyclopropyl spiroindole 7 as the annulation partners this ring expansion strategy might be exploited in an asymmetric fashion to provide the enantioenriched tetracyclic spirooxindole 6 as a single spiroisomer (Scheme 1b). The chiral cyclic aldime 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 addition17 and lactamization with (S)-phenylglycinol.16b Reductive removal of the chiral auxiliary with TiCl4/Et3SiH and Na/NH3(liquid) provided enantiomerically pure δ-lactam 13 (2.2 g) in good overall yield. Protection of the δ-lactam with Boc permitted subsequent Sharpless α,β-unsaturation with phenylethynyl chloride and hydrogen peroxide to afford α,β-unsaturated δ-lactam 15. Michael addition of allyl Grignard reagent (CuBr, Cul, CuBr–SMe2, 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 method14b 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 aldime 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 spiroindole 721 in the presence of Mg2+

To our delight, the cyclized spiroindoxole 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 late stage for the synthesis of Rhy from iRhy. To obtain Oishi’s intermediate19 for Rhy and iRhy, we undertook a series of functional group manipulations20 (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 TMSCHN2. At this
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 (TiCl4 and BF3−Et2O) 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,76 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-methylation/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 explore other 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.

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

![Scheme 3](image)

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 (CaH2). 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 0.040–0.063 mm) supplied by Grace. Infrared spectra were collected on a Bruker model TENSOR27 spectrophotometer. 1H and 13C NMR spectra were recorded on a Bruker model AV-400 spectrometer (400 MHz for 1H, 100 MHz for 13C). 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 13C NMR) or dimethylsulfoxide (2.5 ppm for 1H NMR and 39.5 ppm for 13C 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 K2CO3 (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 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 Et2O (60 mL × 3), and the combined organic phases were dried over Na2SO4, 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 (KBr): 3392, 2958, 1721, 1445, 1168, 845, 777 cm−1; 1H NMR (400 MHz, CDCl3) δ 9.53 (d, J = 2.4 Hz, 1H), 4.05 (s, 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); 13C NMR (101 MHz, CDCl3) 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 C9H17O3, 173.1178; found, 173.1182.

Preparation of 9 (35,45,Br5Ra5s5 & Ethyl 3-phenylpyridinehydroxaoxazolo[3,2-lypyrindin-2-one). A solution of compound 12 (4.8 g, 30 mmol), (S)-phenylglycinol (5 g, 38 mmol), and anhydrous Na2SO4 (17.2 g, 120 mmol) in Et2O (50 mL) was stirred at 0 °C for 10 h. The resulting suspension was filtered, and the filtrate was concentrated.
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,N 100:50:3) to afford compound 9 (4.4 g, 16.5 mmol, 55%). [α]D25 = +88.2 (c 1.0, CHCl3); IR νmax 3062, 3031, 2959, 1656, 1548, 1413, 1383, 1090, 1032, 1002, 824, 760, 699 cm−1; 1H NMR (400 MHz, CDCl3) 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); 13C{1H} NMR (100 MHz, CDCl3) δ 169.1, 139.8, 129.0, 127.7, 126.9, 92.9, 72.6, 58.4, 41.5, 31.7, 24.9, 23.0, 11.2; HRMS (ESI-TOF) m/z: [M + H]+ calcld for C7H14NO, 128.1075; found, 128.1076.

Preparation of 13 (R)-3-Ethylidene-5,7-dihydropyridine-1(2H)-carboxylate. To a solution of compound 9 (4.9 g, 20 mmol) in anhydrous CH2Cl2 (150 mL) were added triethylsilane (4.8 mL, 30 mmol) and TiCl4 (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 TiCl4 (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 washed with saturated NH4Cl solution and brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 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 NH3 (~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 disappeared. The reaction mixture was stirred at −33 °C for an additional 5 min and then quenched by addition of solid NH4Cl 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/hexane = 100:1) to afford compound 13 (1.47 g, 11.5 mmol, 71.3%). [α]D25 = +51.9 (c 1.0, CHCl3); IR νmax 3424, 2928, 2871, 1643, 1498, 1464, 1408, 1376, 698 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.29 (brs, 1H), 3.31 (m, 1H), 2.25 (q, J = 12.9, 4.5 Hz, 2H), 1.33 (d, J = 6.9 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); 13C{1H} NMR (100 MHz, CDCl3) 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]+ calcld for C12H20NO3, 226.1443; found, 226.1446.

Preparation of 16 (tert-Butyl (4R,5R)-5-Ethyl-2-oxo-4-vinyl-piperidine-1-carboxylate). To a suspension of CuCN (0.34 g, 5.0 mmol, 81% in hexane) 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 NH4Cl/NH4OH (9:1, 3 mL) and H2O (3 mL), and the resulting mixture was stirred for 20 min. A solution of TBAP (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%). [α]D25 = +25 (c 1.0, CHCl3); IR νmax 2971, 2928, 1770, 1713, 1290, 1246, 1152, 1094, 918, 852 cm−1; 1H NMR (400 MHz, CDCl3) δ 6.53 (s, J = 6.0, 9.0 Hz, 1H), 5.00−5.05 (m, 2H), 4.35−4.37 (m, 1H), 3.56−3.58 (m, 2H), 2.54−2.56 (m, 1H), 1.98−1.99 (m, 1H), 1.70−1.76 (m, 1H), 1.51−1.53 (m, 1H), 1.21−1.23 (m, 1H), 0.84 (t, J = 7.5 Hz, 3H); 13C{1H} NMR (100 MHz, CDCl3) δ 173.2, 172.3, 134.8, 30.7, 26.7, 26.0, 11.5; HRMS (ESI-TOF) m/z: [M + H]+ calcld for C12H20NO3, 226.1475; found, 226.1476.
Preparation of 18 (35,6′R,7′R,8a′S)-6′-Ethyl-7′-2-oxo-6,7′,8′,9′-tetrahydro-5′-H-spiro[indoline-3,1′-indolin-2′-one]. To a solution of 17 (35 mg, 0.02 mmol) and Et3N (0.62 mL, 4.4 mmol) in CH2Cl2 (4 mL) at −78 °C was added dropwise trimethylsilylethynitrifluoromethanesulfonate (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 NaHCO3. After warming to room temperature, the organic layer was collected, washed with saturated aqueous NaHCO3 and brine, dried over Na2SO4 and concentrated under reduced pressure to afford the cyclic aldimine. To a pressure tube charged with MgI2 (61 mg, 0.22 mmol) and Et3N (0.62 mL, 4.4 mmol) in CH2Cl2 (4 mL) at −20 °C and 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 Na2SO4 and concentrated under reduced pressure to afford a colorless oil (21 mg, 0.067 mmol, 49.5%).

Preparation of (+)-Isorhynchophylline (2). To a solution of compound 19 (42 mg, 0.12 mmol) in THF (2 mL) at −78 °C under a nitrogen atmosphere was added lithium disopropylamide (LDA, 182 µL, 0.37 mmol, 2 N in THF). The reaction mixture was stirred at −78 °C for 1 h, and then methyl formate (74 µL, 1.2 mmol) was added. The reaction mixture was allowed to warm up to room temperature and 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 washed, with brine, dried over Na2SO4 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 CH2Cl2 (2 × 3 mL). The combined CH2Cl2 phases were dried over Na2SO4 and concentrated under reduced pressure to afford the Claissen condensation product, which was used for etherification without further purification. To a solution of Claissen condensation product obtained above in MeOH/ EtO (1:1, 1 mL) was added trimethylsilylethynitrifluoromethanesulfonate (TMSCH2N, 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 a colorless oil (21 mg, 0.0667 mmol, 49.5%).

1H NMR (400 MHz, CDCl3) δ 8.97 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.7, 1.3 Hz, 1H), 7.01 (d, 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 = 13.6, 9.1, 2.3 Hz, 1H), 2.08–2.00 (m, 1H), 1.86 (brs, 1H), 1.85–1.74 (m, 2H), 1.60 (dd, 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 (bs, 1H), 1H NMR (101 MHz, CDCl3) δ 182.1, 140.2, 133.7, 127.5, 121.5, 122.4, 109.5, 71.9, 60.3, 57.9, 56.9, 54.0, 41.5, 36.4, 35.5, 32.5, 31.2, 23.4, 11.0; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C20H27N2O3, 343.2022; found, 343.2022.

Preparation of 19 (Methyl 2-((3S,6′R,7′R,8a′S)-6′-Ethyl-2-oxo-6,7′,8′,9′-tetrahydro-5′-H-spiro[indoline-3,1′-indolin-2′-one]). To a mixture of compound 18 (29 mg, 0.09 mmol) 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 H2O and brine, dried over anhydrous Na2SO4 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 µmol) in acetonitrile (0.5 mL), tert-butyl alcohol (1.5 mL), and 2-methyl-2-buten-14 Li (0.13 mmol) at 0 °C was added dropwise a solution of NaHCO3 (15.7 mg, 0.17 mmol) and NaH2PO4 (20.4 mg, 0.17 mmol) in H2O (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 Na2SO4 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 Et3O (0.5 mL) at 0 °C was added a solution of trimethylsilyldiazomethane (TMSCH2N, 0.1 mL 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 TMSCH2N, (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 (14 mg, 40.4 µmol, 70%). [α]D20 = +11.2 (c 1.0, CHCl3); IR νmax 3447, 2922, 2852, 1639, 1459, 1381, 1047, 751, 480 cm−1; 1H NMR (400 MHz, DMSO-d6) 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 (s, 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), 1H NMR (101 MHz, DMSO-d6) δ 179.9, 172.6, 141.4, 133.5, 127.4, 124.4, 109.2, 70.9, 57.0, 55.9, 53.3, 51.1, 40.5, 37.3, 36.6, 34.1, 31.5, 22.8, 10.8; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C22H29N2O4, 385.2127; found, 385.2128.
Preparation of (−)-Rhynchophylline (I). The solution of isorhynchophylline (13 mg, 34 umol) in acetic acid/H2O (1:4, 3 mL) was heated to reflux overnight. The reaction mixture was cooled to room temperature and neutralized by addition of NH4OH (1 mL). The mixture was extracted with CH2Cl2 (2 × 10 mL). The combined organic layers were washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:1, then of oxindole alkaloids from the hooks of Uncaria rhynchophylla (Miquel). Naunyn-Schmiedeberg’s Arch. Pharmacol. 2004, 369, 232–238.


(19) Carreira and co-workers also found the low diastereoselectivity (5:1) of this conjugate addition with CuBr to allylMgCl and the diastereomers were inseparable; see ref 14b.
