Asymmetric Total Syntheses of Mitragynine, Speciogynine, and 7-Hydroxymitragynine

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A number of alkaloids found in Mitragyna species belonging to the Rubiaceae family have been shown to have potent biological activity such as analgesic properties. Here, we report the asymmetric total syntheses of mitragynine, speciogynine, and 7-hydroxymitragynine, which are classified as corynantheine-type monoterpenoid indole alkaloids, isolated from Mitragyna speciosa. These syntheses were accomplished within 12 steps and in >11% total yield from commercial 3-(trimethylsilyl)propanal using an organocatalytic anti-selective Michael reaction and bioinspired transformations.

Key words monoterpenoid indole alkaloid; mitragynine; speciogynine; 7-hydroxymitragynine; bioinspired reaction

Introduction

Mitragyna speciosa, which belongs to the Rubiaceae family, is endemic to the tropics of Southeast Asia, where it is called “Kratom” in Thailand and “Biak Biak” in Malaysia.1) Traditionally, the leaf of this plant has been used to alleviate the fatigue of workers laboring in the scorching heat and as a substitute for opium. Many chemists have been fascinated by its special biological activity, and isolation and structure elucidation studies of this plant have been conducted since the 1960s.2–6) As a result, several corynantheine-type monoterpenoid indole alkaloids have been found with a methoxy group attached to the C-9 position on the indole ring (Fig. 1).

Mitragynine (1) is the major component of a base fraction of Mitragyna speciosa leaves, and speciogynine (2) has been found as the stereoisomer at the C-20 position. Recently, the in vitro and in vivo activity of 2 at serotonin receptors (5-HTRs) was reported; speciogynine (2) exhibited a high affinity for 5-HT1ARs and 5-HT2BRs.7) 7-Hydroxymitragynine (3) was found as a minor component of the leaves; this molecule had a potent analgesic activity via opioidµ receptors (mitragynine (1) also showed mild analgesic activity).6,8–16) In addition, it was discovered that this alkaloid maintains potent activity through oral administration.19) This molecule is now widely recognized as a key component in folk medicine.

Because of their interesting biological activity, several total syntheses of these alkaloids have been reported.10,17–22) Very recently, our group also achieved the total syntheses of the same class of corynantheine-type monoterpenoid indole alkaloids, corynantheidine and dihydrocorynantheine.23) However, the efficiency of these total syntheses could be improved, specifically because the goal of previous total syntheses was to reproduce the biosynthetic transformations from strictosidine in the flask.

Here, we report the practical asymmetric total syntheses of mitragynine (1), speciogynine (2), and 7-hydroxymitragynine (3). These syntheses were achieved within 12 steps from commercially available materials with total yields of >11%.

Results and Discussion

Our retrosynthetic analysis of (−)-mitragynine (1) and (+)-speciogynine (2) is outlined in Chart 1. We envisioned that our previously developed bioinspired transformations toward the syntheses of corynantheine-type alkaloids could also reveal the syntheses of (−)-1 and its C-20 epimer (+)-2. Thus, (−)-1 and (+)-2 were retrosynthesized to 9-methoxystrictosidine derivative 5, via bioinspired skeletal transformations and stereoselective reduction of the common intermediate 4.

Preparation of key intermediate 5 was expected to be achieved by diastereoselective Pictet–Spengler cyclization using (R)-4-methoxy-a-cyanotryptamine (6) and secologanin derivative 7.24) Tryptamine derivative 6 was considered for the installation of a 4-methoxyindole unit to the known methyl (R)-N-benzylxycarbonyl (Cbz)-azirizine-2-carboxylate (8).25) For the concise synthesis of secologanin derivative 7, our discovered anti-selective organocatalytic Michael reaction was selected as a key step to install all carbons of 7.20) Thus, butyraldheyde (9) and conjugated ene-yne compound 10, prepared from commercially available 3-(trimethylsilyl)propanal (11), were assumed as optimal building blocks.

As shown in Chart 2, our synthesis commenced with the preparation of (R)-4-methoxy-a-cyanotryptamine (6). Synthesis of L-tryptophan derivative 13 was performed via a Lewis acid-mediated coupling reaction of 4-methoxyindole (12) with known chiral aziridine 8.27) After several trials, Yb(OTf)3 effectively promoted the coupling reaction and the desired 13 was obtained as a major product (1.5 equivalent (equiv.) of Yb(OTf)3; room temperature (r.t.)). Hydrolysis and subsequent

Fig. 1. Structures of Mitragynine, Speciogynine, and 7-Hydroxymitragynine

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amidation of the crude mixture of 13 gave primary amide 14 in gram quantities (39% yield over three steps). Then, amide 14 was converted to 6 via dehydration to construct a cyano group and deprotection of the Cbz group (74% yield over two steps).

As in our previous synthesis of monoterpenoid indole alkaloids, the preparation of secologanin derivative 7 commenced with the Knoevenagel condensation with aldehyde 11 and methyl 3-ethylthio-3-oxopropanoate (15) in the presence of trifluoroacetic acid (TFA), affording ene-yne compound 10 (81%, E:Z = 1:1) (Chart 3). To install the C-15 chiral center and C-20 ethyl group in (-)-1 and (+)-2, an anti-selective organocatalytic Michael reaction to form 16 was set up. Thus, when ene-yne compound 10 and butyraldehyde 9 were treated with 3 mol% diphenylprolinol trimethylsilyl ether catalyst in Et2O at 0 °C (40 h), the anti-adduct 16 was obtained with excellent diastereoselectivity (anti:syn = 11:1). Subsequent Fukuyama reduction to convert aldehyde from a thioester of 16 and spontaneous cyclization were carried out, affording optically active dihydropyran derivative 17 in 85% yield over two steps (4.5 equiv. Et3SiH, 15 mol% of Pd/C, r.t.). Subsequent silylation of the hemiacetal hydroxy group in 17 was performed. Thus, when 17 was treated with AgNO3 and tert-butylidimethylchlorosilane (TBSCI) in dry N,N-dimethylformamide (DMF), stereoselective silylation proceeded from the sterically less hindered site to afford α-oriented silyl ether 18 as a single isomer (87%). Enantiomeric excess was determined at this stage: >99% enantiomeric excess (ee) by chiral HPLC analysis. Finally, alkyne 18 was treated with hydroboration–oxidation conditions to afford secologanin derivative 7 in excellent yield (84%, 1.2 equiv. 9-borabicyclo[3.3.1]nonane (9-BBN), tetrahydrofuran (THF), r.t. then 5.0 equiv. H2O2, 1.0 equiv. NaOH, r.t.). All protocols in the synthesis of 7 were performed in gram-scale quantities.

With the desired synthons 6 and 7 in hand, we next attempted bioinspired transformations for the construction of a corynantheine-type scaffold (Chart 4). To prepare 9-methoxystrictosidine derivative 5, our developed diastereoselective
Pictet–Spengler cyclization/reductive decyanation sequences were examined. When a mixture of 6 and 7 was treated with 50 mol% TFA in CH₂Cl₂ at 0 °C (30 min), the desired 3S-isomer 19 was obtained as a single diastereomer in quantitative yield. Reductive removal of the cyanogroup in 19 was performed by treatment with NaBH₄CN in the presence of AcOH in MeOH, affording 9-methoxystrictosidine derivative 5 in excellent yield (78%).

Next, key bioinspired transformations triggered by removal of the silyl group in 5 were examined. Thus, 5 was exposed to a simple desilylation condition (2.0 equiv. tetrabutylammonium fluoride (TBAF), 2.0 equiv. AcOH, THF, −20 °C) to afford enamine 4 linked by N-4 and C-21. After confirming a full conversion to 4 from 5 by NMR spectroscopic analysis, the crude mixture of 4 was directly treated with 100 wt% PtO₂ under H₂ atmosphere. As a result, a kinetically reduced mixture of 4 was obtained as a separable mixture of (−)-mitragynine (1) and (+)-speciogynine (2) (−)-1/(+)−2 = 3.4:1, 55% yield over four steps].

Bioinspired transformations toward the selective synthesis of C-20R isomer (+)-speciogynine (2) were also demonstrated. After generating enamine 4 under the same conditions as for the synthesis of (−)-1, 2.0 equiv. NaBH₄(OAc)₂ was added in a one-pot protocol. In this case, thermodynamic controlled protonation at the C-20 position followed by reduction of a generated iminium ion afforded C-20R isomer 22 as a single diastereomer. Subsequent modification of the C-17 enol hydroxy group was carried out as in the synthesis of (−)-1, and the E1cB elimination reaction, following the formation of 23, afforded (+)-speciogynine (2) in 65% overall yield within four steps from 5.

In summary, practical total syntheses of (−)-mitragynine (1, total 16% over 11 steps from 11) and (+)-speciogynine (2, total 26% over 11 steps from 11) were accomplished.

Next, to prepare (+)-7-hydroxymitragynine (3), the direct C-7 oxidation of (−)-1 was investigated (Eq. 1). Following our previously reported method, when freshly purified (−)-1 was oxidized in aqueous acetonitrile by treatment with 1.0 equiv. [bis(trifluoroacetoxy)]iodobenzene (PIFA), (+)-3 was obtained in moderate yield (condition a in Eq. 1, 50%). After several trials toward further improvement of the chemical yield, it was determined that the addition of 2.0 equiv. TFA led to the effective production of (+)-3 (condition b in Eq. 1, 71%). We suppose that TFA masked the reactive lone pair of the N-4 nitrogen in (−)-1 as a salt, thereby suppressing undesired N-4 oxidation. As a result, the total synthesis of (+)-7-hydroxymitragynine (3) was accomplished with 11% overall yield within 12 steps from 11. 

Conclusion

In conclusion, we accomplished the total syntheses of three bioactive *Mitragyna* alkaloids: (−)-mitragynine (4), (+)-speciogynine (2), and (+)-7-hydroxymitragynine (3). The synthesis of secologanin derivative 7, a key fragment in this synthesis, was carried out via an anti-selective organocatalytic Michael reaction using ene-yne compound 10 and simple aldehyde 9, with excellent enantiomeric excess. Preparation of common intermediate 4 was achieved via bioinspired transformations of strictosidine derivative 5 triggered by the removal of a silyl group, which branched into (−)-1 and (+)-2 by stereoselective reduction. In addition, (+)-3 was obtained through direct oxidation of (−)-1 via a nitrogen-masking strategy. As a result, syntheses of (−)-mitragynine (1), (+)-speciogynine (2), and (+)-7-hydroxymitragynine (3) were realized within fewer than 12 steps and in >11% overall yield. Using the synthesized natural products and their derivatives, a study of their structure–activity relationships is currently under way in our laboratory.

Experimental

General Experimental Procedures All reactions were monitored by TLC using Merck 60 F254 precoated silica gel
plates (0.25 mm thick) and Fuji Silysia Chemical precoated amino-silica gel plates (0.25 mm thick). UV spectra were recorded in MeOH on a JASCO V-560 instrument. Specific optical rotations were measured using a JASCO P-2200 polarimeter. Circular dichromism spectra were recorded on a JASCO J-1100 spectrometer. Fourier transform (FT) IR spectra were recorded on a JASCO FT/IR-4700. 1H- and 13C-NMR spectra were recorded on a JEOL ECX 400 (400 MHz 1H-NMR, 100 MHz for 13C-NMR), ECS 400 (400 MHz 1H-NMR, 100 MHz for 13C-NMR), JEOL ECX 500 (500 MHz 1H-NMR, 125 MHz for 13C-NMR), and ECX 600 (600 MHz for 1H-NMR, 150 MHz for 13C-NMR) FT-NMR spectrometer instruments. Data for 1H-NMR are reported as chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration, and assignment. Data for 13C-NMR are reported as chemical shifts. The high-resolution mass spectra are recorded on a JEOL AcutoF LC-plus JMS-T100LP. Flash chromatography was performed using Kanto Chemical silica gel 60N and Fuji Silysia Chemical amino-silica gel (SiO2-NH, 125 MHz for 1H-NMR), and ECX 600 (600 MHz for 1H-NMR, 150 MHz for 13C-NMR) FT-NMR spectrometer instrument. To a solution of amide (608 mg, 1.65 mmol) in anhydrous pyridine (11 mL) was added phosphoryl chloride (355 µL, 3.80 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 50 min at 0 °C. MeOH was added at 0 °C to the resulting mixture and stirred for 10 min, followed by concentration under reduced pressure. The resulting mixture was dissolved in EtO and the organic layer was washed with 1 M aqueous NaOH three times, and with brine, dried over Na2SO4, and then concentrated under reduced pressure. Flash chromatography (SiO2, 1% MeOH/CHCl3) gave a dehydrated compound (510 mg, 88%). To a solution of the dehydrated compound (500 mg, 1.43 mmol) in degassed 1,4-dioxiane (10.4 mL) was added 10% Pd/C (152 mg, 0.143 mmol) at r.t. under Ar atmosphere. The resulting mixture was purged with a stream of hydrogen and the reaction mixture was stirred for 13 h at r.t. under H2 atmosphere. The resulting mixture was filtered with a Celite pad with CHCl3. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (SiO2, 60% AcOEt/n-hexane, then 5% MeOH/CHCl3) to afford (R)-4-methoxy-a-cyanotryptamine (6, 260.0 mg, 84%).

(R)-(4)-4-Methoxy-a-cyanotryptamine (6): Pale pink amorphous powder; [α]D2 15.0 (c 1.96, CHCl3); IR (ATR) νmax cm−1: 3363, 3194, 2914, 1741, 1587, 1547, 1510, 1431, 1356, 1257, 1167, 1132, 1086, 1053, 955, 895, 852, 814, 683, 623; HRMS (ESI) [M+Na]+ calcd. for [C14H13N2O2+Na]+: 244.0709; Found: 244.0698; UV (MeOH) λmax nm: 291, 281, 265, 220 nm; 1H-NMR (CD3)2SO) δ: 10.8 (bs, 1H), 7.34–7.19 (m, 5H), 7.03 (bs, 1H), 6.96–6.92 (m, 3H), 6.44 (d, J = 6.4 Hz, 1H), 4.95 (s, 2H), 4.23 (dt, J = 8.8, 4.4 Hz, 1H), 3.84 (s, 3H), 3.28 (dt, J = 14.4, 3.6 Hz, 1H), 2.98 (dd, J = 14.4, 10.0, 3.2 Hz, 1H); 13C-NMR (150 MHz, CD3)2SO): δ: 174.2, 155.8, 154.1, 137.8, 131.7, 128.4, 127.7, 127.4, 122.2, 121.8, 117.0, 110.6, 105.0, 98.9, 65.2, 56.2, 55.1, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.1, 29.3. Preparation of (R)-4-Methoxy-a-cyanotryptamine (6) To a solution of amide (608 mg, 1.65 mmol) in anhydrous pyridine (11 mL) was added phosphoryl chloride (355 µL, 3.80 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 50 min at 0 °C. MeOH was added at 0 °C to the resulting mixture and stirred for 10 min, followed by concentration under reduced pressure. The resulting mixture was dissolved in EtO and the organic layer was washed with 1 M aqueous NaOH three times, and with brine, dried over Na2SO4, and then concentrated under reduced pressure. Flash chromatography (SiO2, 1% MeOH/CHCl3) gave a dehydrated compound (510 mg, 88%). To a solution of the dehydrated compound (500 mg, 1.43 mmol) in degassed 1,4-dioxiane (10.4 mL) was added 10% Pd/C (152 mg, 0.143 mmol) at r.t. under Ar atmosphere. The resulting mixture was purged with a stream of hydrogen and the reaction mixture was stirred for 13 h at r.t. under H2 atmosphere. The resulting mixture was filtered with a Celite pad with CHCl3. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (SiO2, 60% AcOEt/n-hexane, then 5% MeOH/CHCl3) to afford (R)-4-methoxy-a-cyanotryptamine (6, 260.0 mg, 84%).
mixture was stirred for a further 18 h at r.t. before filtration with a Celite pad eluted with AcOEt, and partitioned between an AcOEt layer and an aqueous layer. The aqueous layer was extracted three times with AcOEt. The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 5%–20% AcOEt/n-hexane gradient) afforded two diastereomers of dihydropyran 17 (444.5 mg, 85% over two steps, d.r. = 4:1).

**Compound 17:** Yellow waxy solid; IR (ATR) νmax cm⁻¹ 3370, 2953, 1672, 1629, 1437, 1392, 1298, 1254, 1228, 1167, 1130, 1088, 1125, 1100, 1035, 981, 945, 908, 879, 835; HRMS (ESI) [M + Na]⁺ Calcd. for [C₇H₅Na₂O₅Si]⁺: 305.1185; Found: 305.1184. 1H-NMR (500 MHz, CDCl₃) δ: 7.53 (s, 1H), 7.46 (s, 1H), 5.36 (dd, J = 7.5 Hz, 1H), 4.85 (d, J = 7.5 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.58 (d, J = 5.0 Hz, 1H), 3.55 (d, J = 5.0 Hz, 1H), 2.07 (s, 3H), 1.85–1.71 (m, 3H), 1.64–1.53 (m, 3H), 1.05 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H), 0.14 (s, 9H), 0.12 (s, 9H); 13C-NMR (125 MHz, CDCl₃) δ: 169.9, 166.7, 153.3, 152.5, 107.2, 106.4, 104.0, 103.7, 97.1, 96.3, 90.1, 97.9, 51.7, 51.6, 42.2, 39.9, 26.8, 23.6, 21.6, 20.4, 11.0, 0.17 (3C), 0.12 (3C).

**Preparation of Compound 18** To a solution of two diastereomers of dihydropyran 17 (1.0 g, 3.54 mmol) in dry DMF (11.8 mL) were added AgNO₃ (782 mg, 4.60 mmol) and TBSCl (400 mg, 2.66 mmol) to a solution of two dia-stereomers of dihydropyran 17 (1.0 g, 3.54 mmol) in dry DMF (11.8 mL) were added AgNO₃ (782 mg, 4.60 mmol) and TBSCl (400 mg, 2.66 mmol) to a solution of two diastereomers of dihydropyran 17 (1.0 g, 3.54 mmol) in dry DMF (11.8 mL) were added AgNO₃ (782 mg, 4.60 mmol) and TBSCl (400 mg, 2.66 mmol) to a solution of two diastereomers of dihydropyran 17 (1.0 g, 3.54 mmol) in dry DMF (11.8 mL) were added AgNO₃ (782 mg, 4.60 mmol) and TBSCl (400 mg, 2.66 mmol) and sodium cyanoborohydride (582 mg, 9.26 mmol) and powdered HCl (104 mmol) in CH₂Cl₂ (18.7 mL) was added TFA (1.0 M in CH₂Cl₂, 467 μL, 0.467 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 0 °C. The resulting mixture was filtered through a short plug of silica gel eluted with 20% AcOEt/n-hexane and the filtrate was added to saturated NaHCO₃ solution at 0 °C. The aqueous layer was extracted three times with CHCl₃ and the combined organic layer was stirred for a further 36 h at r.t. The resulting mixture was quenched with HCl, and dried over MgSO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 5%–20% AcOEt/n-hexane gradient) afforded secologanin derivative 7 (887 mg, 84%).

Secologanin Derivative 7: Colorless oil; δD 231.0 (1.0 g, 0.934 mmol); (R)-4-methoxy-α-acynotryptamine (6, 201.1 mg, 0.934 mmol), and powdered MS 4 Å (1 g) in CH₃Cl (18.7 mL) was added TFA (1.0 M in CH₂Cl₂, 467 μL, 0.467 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 0 °C. The resulting mixture was filtered through a cotton plug with CHCl₃, and the filtrate was added to an excess amount of saturated aqueous NaHCO₃ solution at 0 °C. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was stirred for a further 36 h at r.t. The resulting mixture was quenched with HCl, and dried over MgSO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 5%–20% AcOEt/n-hexane gradient) afforded secologanin derivative 7 (887 mg, 84%).

**Preparation of Compound 19** To a solution of seco-loganin derivative 7 (320 mg, 0.934 mmol), (R)-4-methoxy-α-acynotryptamine (6, 201.1 mg, 0.934 mmol), and powdered MS 4 Å (1 g) in CH₃Cl (18.7 mL) was added TFA (1.0 M in CH₂Cl₂, 467 μL, 0.467 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 0 °C. The resulting mixture was filtered through a cotton plug with CHCl₃, and the filtrate was added to an excess amount of saturated aqueous NaHCO₃ solution at 0 °C. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was stirred for a further 36 h at r.t. The resulting mixture was quenched with HCl, and dried over MgSO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 5%–20% AcOEt/n-hexane gradient) afforded seco-loganin derivative 7 (887 mg, 84%).

**Preparation of Compound 18** To a solution of two diastereomers of dihydropyran 17 (1.0 g, 3.54 mmol) in dry DMF (11.8 mL) were added AgNO₃ (782 mg, 4.60 mmol) and TBSCl (400 mg, 2.66 mmol) and sodium cyanoborohydride (582 mg, 9.26 mmol) and powdered MS 4 Å (1 g) in CH₃Cl (18.7 mL) was added TFA (1.0 M in CH₂Cl₂, 467 μL, 0.467 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 0 °C. The resulting mixture was filtered through a short plug of silica gel eluted with 20% AcOEt/n-hexane and the filtrate was added to saturated NaHCO₃ solution at 0 °C. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was stirred for a further 36 h at r.t. The resulting mixture was quenched with HCl, and dried over MgSO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 5%–20% AcOEt/n-hexane gradient) afforded seco-loganin derivative 7 (887 mg, 84%).
saturated aqueous NaHCO₃ solution at 0 °C. The aqueous layer was extracted three times with AcOEt. The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude materials were filtered through a short plug of amino-silica gel (SiO₂-NH₂), eluted with 5% MeOH/CHCl₃, to remove an excess amount of sodium cyanoborohydride. Flash chromatography (SiO₂, 25% AcOEt/n-hexane then 20% MeOH/CHCl₃) afforded the 9-methoxystrictosidine derivative 5 (371.6 mg, 78%) with 80.5 mg of starting material 19.

9-Methoxystrictosidine Derivative 5

White amorphous powder; [α]²⁴D = −189.9 (c 0.93, CHCl₃); IR (ATR) νmax cm⁻¹ 2933, 2850, 1698, 1630, 1510, 1460, 1346, 1383, 1357, 1308, 1276, 1252, 1166, 1137, 1096, 1031, 1007, 975, 950, 927, 908, 872, 861, 836, 825; HRMS (ESI) [M + H]+ Calcd. for [C₂₇H₄₃N₂O₅Si₁]⁺: 515.2941, Found: 515.2955; UV (MeOH) λmax 292, 223 nm; ¹H-NMR (600 MHz, CDCl₃) δ: 8.33 (brs, 1H), 7.55 (s, 1H), 7.02 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 5.23 (d, J = 8.4 Hz, 1H), 4.01 (dd, J = 9.0, 3.0 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.29 (m, 1H), 3.05–2.95 (m, 4H), 1.92 (dd, J = 13.8, 10.8, 3.6 Hz, 1H), 1.71–1.61 (m, 2H), 1.52 (dd, J = 13.8, 10.2, 3.6 Hz, 1H), 1.27 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ: 169.3, 154.8, 154.6, 137.3, 133.6, 122.3, 117.5, 105.8, 108.6, 104.5, 99.9, 97.3, 55.4, 51.8, 50.5, 44.4, 42.1, 36.7, 28.0, 25.8, 24.2, 20.1, 18.1, 11.6, –4.0, –5.0.

Synthesis of (−)-Mitragynine (1)

To a solution of 9-methoxystrictosidine derivative 5 (150 mg, 0.291 mmol) in degassed anhydrous THF (2.9 mL) were added acetic acid (83.3 µL, 1.46 mmol) and tetrabutylammonium fluoride (1.0 M in THF solution, 117 µL, 0.291 mmol) in degassed anhydrous THF (2.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C under Ar atmosphere. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was washed with brine and the aqueous layer was extracted five times with CHCl₃. The resulting mixture was quenched with saturated aqueous NaHCO₃ solution and then concentrated under reduced pressure. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The crude materials of 23 were dissolved in dry degassed DMF (1.2 mL) to which was added t-BuOK (19.6 mg, 0.175 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 40 min at r.t. under Ar atmosphere. The resulting mixture was quenched with water and the aqueous layer was extracted five times with CHCl₃. The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 45% AcOEt/n-hexane) afforded (+)-speciogynine (2, 15.2 mg, 65% over four steps).

Synthesis of (+)-7-Hydroxymitragynine (3)

To a solution of freshly purified (−)-mitragynine (1, 30 mg, 0.0585 mmol) in degassed anhydrous THF (580 µL) were added acetic acid (167.6 µL, 0.291 mmol) and tetrabutylammonium fluoride (1.0 M in THF solution, 117 µL, 0.117 mmol) at –20 °C under Ar atmosphere. The reaction mixture was stirred for 5 h at –20 °C. To the resulting mixture was added sodium triacetoxoborohydride (24.7 mg, 0.117 mmol) at –20 °C under Ar atmosphere. The reaction mixture was quenched with water and the aqueous layer was extracted three times with AcOEt. The combined organic layer was washed with brine then dried over Na₂SO₄. The resulting residue of 22 was dissolved in degassed MeOH (2.9 mL), to which was added CH(OMe)₃ (10.5 µL, 0.0962 mmol) and p-TsOH H₂O (42.1 mg, 0.221 mmol), and then stirred at 70 °C for 12 h. The resulting mixture was quenched with saturated aqueous NaHCO₃ solution and then concentrated under reduced pressure. The aqueous layer was extracted three times with CHCl₃. The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The crude materials of 23 were dissolved in dry degassed DMF (1.2 mL) to which was added t-BuOK (19.6 mg, 0.175 mmol) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 45 min at r.t. under Ar atmosphere. The resulting mixture was quenched with water and the aqueous layer was extracted three times with CHCl₃. The combined organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (SiO₂, 45% AcOEt/n-hexane) afforded (+)-speciogynine (2, 15.2 mg, 65% over four steps).
concentrated under reduced pressure. Flash chromatography (SiO2-NH4, 40% AcOEt/hexane) afforded (+)-7-hydroxymitragynine (3), 22.0 mg, 71%). All spectral data of the obtained (+)-7-hydroxymitragynine (3) were identical to those of natural product.6,5,8

(+)-7-Hydroxymitragynine (3): Pale yellow amorphous powder; [α]D20 +62.5 (c 0.50, CHCl3) [lit. [α]D20 +47.9 (c 0.55, CHCl3)]; IR (ATR) νmax cm⁻¹ 3420, 2947, 2872, 2835, 2811, 2745, 1698, 1644, 1597, 1486, 1460, 1435, 1376, 1266, 1237, 1187, 1143, 1104, 1074, 1018, 899, 959, 935, 920, 870, 841; HRMS (ESI) [M + H]+ Calcd. for [C23H31N2O5]+: 415.2233, Found: 415.2256; CD (0.3 mM, MeOH, 23 °C) λnm (Δε): 344 (0), 305 (0.53), 282 (0), 258 (−0.55), 243 (0), 229 (−1.13), 214 (0); UV (MeOH) λmax 307, 245, 220 nm; 1H- and 13C-NMR see supplementary materials.

Acknowledgments We gratefully acknowledge financial support through a Grant-in-Aid for Scientific Research (B) (21H02608 to H. I. and 20H03395 to M. K.) from JSPS, and a JSFS Research Fellowships for Young Scientists (21J26966) to J. S.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.

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