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ORIGINAL ARTICLE

Total syntheses of codonopsinine and 4-*epi*-codonopsinine via gold-mediated tandem-catalyzed pyrrole synthesis

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The total syntheses of codonopsinine (1) and 4-*epi*-codonopsinine (2) were accomplished. The key substituted pyrrole intermediate was constructed via gold-catalyzed addition–cyclization cascade of an aminoacetaldehyde acetal derivative and a terminal alkyne. After diastereoselective reduction of the pyrrole intermediate to the corresponding 3-pyrroline derivative with zinc dust and sulfonic acid, the total synthesis of 4-*epi*-codonopsinine (2) was achieved via stereoselective construction of the diol by dihydroxylation. In addition, the total synthesis of codonopsinine (1) was completed through stereochemical inversion of the hydroxyl group via epoxide and subsequent ring cleavage under the acidic aqueous condition.
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INTRODUCTION

Codonopsinine, isolated from *Codonopsis clematidea* by Matkhalikova and colleagues in 1969,[1–5] has a 1,2,3,4,5-pentasubstituted pyrrolidine ring bearing a *p*-anisyl group at the C2 position. Two decades after its isolation, its structure was revised through a total synthesis of **1** by Kibayashi and colleagues.[6,7] Codonopsinine has garnered considerable attention from organic chemists because of its substantial biological activities, which include antibiotic activity and hypotensive pharmacological activity.[8] 4-*epi*-Codonopsinine, by contrast, exhibits inhibitory activity against α-fucosidase.[9] Furthermore, compound **1** and its synthetic analogs were recently demonstrated to possess anti-methicillin-resistant *Staphylococcus aureus* activity.[10] Because of these important biological activities, the development of new anti-infective agents through structure–activity relationships of these compounds is intriguing. However, the divergent synthesis of this class of compounds would be difficult because of the lack of an efficient and versatile synthetic route.[11–23]

Recently, we developed a method for the synthesis of substituted pyrroles via gold-catalyzed addition–cyclization cascade (Scheme 1).[24,25] This reaction proceeds via gold-mediated auto-tandem catalysis,[26] where the initially generated gold acetylide **5**[27] adds to oxonium ion **6** to give intermediate **7**, which cyclizes in 5-*endo-dig* manner by π-activation with the cationic gold catalyst. An advantage of this methodology is its versatility for the synthesis of substituted pyrroles **9**. Thus a variety of substituted pyrroles can be synthesized in a modular manner by changing two fragments. We envisioned that this methodology would be effective for constructing the pyrrolidine core of codonopsinine and its analogs. Herein we describe the total syntheses of codonopsinine (**1**) and 4-*epi*-codonopsinine (**2**) featuring our gold-mediated tandem-catalyzed pyrrole synthesis.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of codonopsinine (**1**) and 4-*epi*-codonopsinine (**2**) is shown in Scheme 2. Compounds **1** and **2** could be derived from the common 3-pyrroline intermediate **10** via dihydroxylation of the olefin. 3-Pyrroline derivative **10** would be obtained from the corresponding pyrrole **12** by diastereoselective reduction. We planned to synthesize 5-alkyl-2-*p*-anisyl pyrrole **12** via our gold-catalyzed addition–cyclization cascade using 4-methoxyphenylacetylene **13** and *N*-benzoyl 2-aminopropanal acetal **14**. The acetal segment **14** bearing a methyl group should be readily prepared from (L)-alanine (**15**). On the basis of our previous studies[24] on the scope of the substituted pyrrole synthesis by this cascade reaction, we selected diisopropyl acetal **14** as a suitable substrate for construction of the methyl-substituted pyrrole **12**.

First, we prepared *N*-benzoyl 2-aminopropanal diisopropyl acetal **14** according to the procedure established in our previous study[24] (Scheme 3). Our preliminary studies revealed that the benzoyl protected substrate provided better yield than that of the substrate with carbamate group. Therefore, after conversion of *N*-Cbz alaninal **16**[28] to the corresponding diisopropyl acetal by heating with pyridinium p-toluenesulfonate (PPTS) in *i*-PrOH, the Cbz group was replaced with a benzoyl group in a two-step sequence to give the requisite acetal segment **14** in good yield. Then we conducted an optimization study of the gold-catalyzed addition–cyclization cascade to maximize the yield of pyrrole **12** (Table 1). The previously established conditions of 10 mol% of RuphosAuCl[29] and AgOTf in

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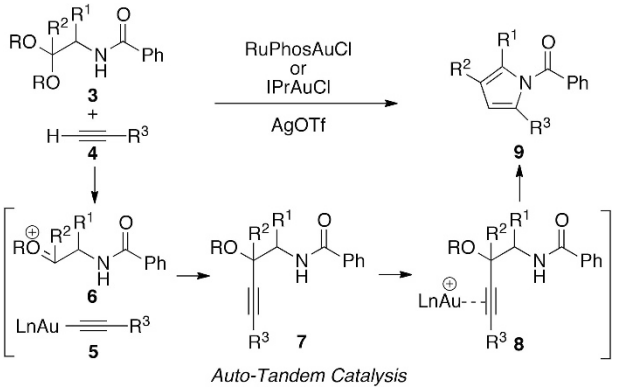
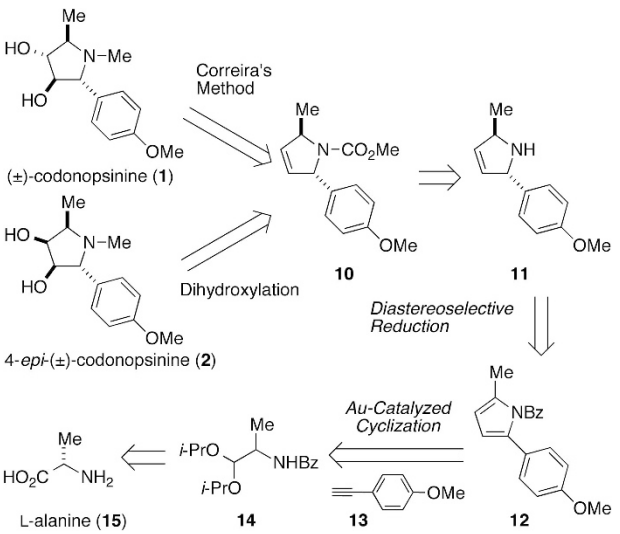
toluene at 110 °C provided the desired pyrrole **12** in 55% yield (entry 1). We observed that the choice of silver salt is important (entries 1–4) and that the yield of **12** was slightly improved when $AgBF_4$ was used (entry 4). Eventually, the desired pyrrole **12** was obtained in highest yield (84%) by treatment of a mixture of **13** and **14** with 10 mol% of RuphosAuCl and $AgBF_4$ in xylene (0.25 M) at 140 °C.

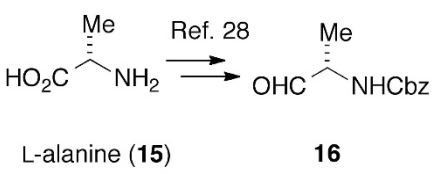
Having successfully constructed the 1,2,5-trisubstituted pyrrole intermediate **12**, we then focused on manipulating the pyrrole skeleton to complete the total syntheses of the target natural products. After removing the benzoyl group by heating **12** with aqueous KOH in a mixture of EtOH and CH_2Cl_2 (Scheme 4), we subjected the resulting pyrrole **17** to various reduction conditions to obtain the corresponding 2,5-*trans*-3,4-dehydropyrrolidine derivative **11** (Table 2). Initial trial by treatment of **17** with activated Zn dust[30] in a mixture of 6 M HCl and MeOH gave 3-pyrroline derivative **11** as a mixture of diastereomers (*trans*/*cis* = 5/4) in low yield associated with a mixture of 1-pyrroline and 5-pyrroline product (entry 1). Reaction using EtOH instead of MeOH gave 3-pyrroline derivative **11** in 27% yield (*trans*/*cis* = 2/1) (entry 2). When sulfonic acid was used instead of HCl, the ratio of diastereomers was improved to 5:1 (entry 3). After further examinations, we observed that the ratio of diastereomers dramatically improved (*trans*/*cis* = 33/1) when the solvent was switched from EtOH to MeCN (entry 4). Finally, we obtained the desired 3-pyrroline derivative **11** as a sole isomer by heating a MeCN solution of **17** in the



Scheme 1 Synthesis of pyrroles by gold-catalyzed addition–cyclization cascade.

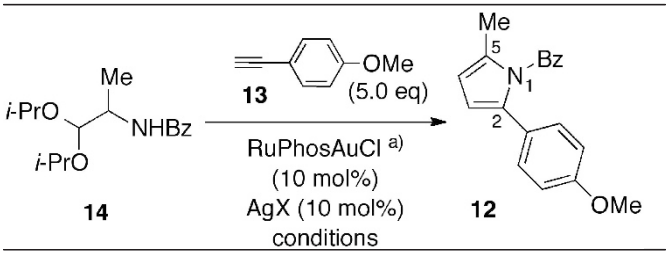


Scheme 2 Retrosynthetic analysis of codonopsinine (**1**) and its C-4 epimer (**2**).



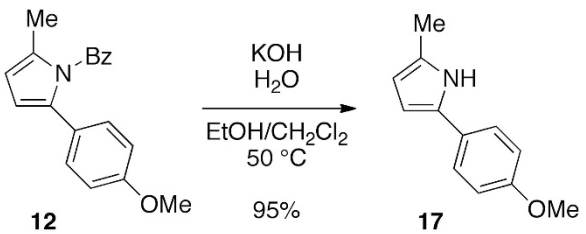
Scheme 3 Synthesis of key substrate **14**.

Table 1 Optimization of the pyrrole synthesis by gold-catalyzed addition–cyclization sequence



Entry	*AgX*	*Solvent (0.25 M)*	*Temp (°C)*	*Yield (%)*
1	AgOTf	Toluene	110	55
2	$AgSbF_6$	Toluene	110	34
3	$AgNTf_2$	Toluene	110	41
4	$AgBF_4$	Toluene	110	62
5	$AgBF_4$	Xylene	140	84

a) RuPhosAuCl



Scheme 4 Hydrolysis of benzoyl pyrrole **12**.

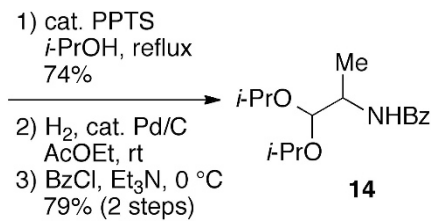
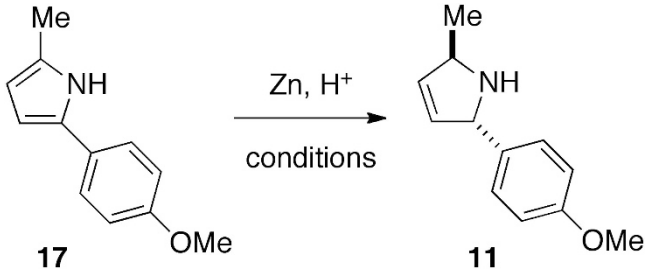
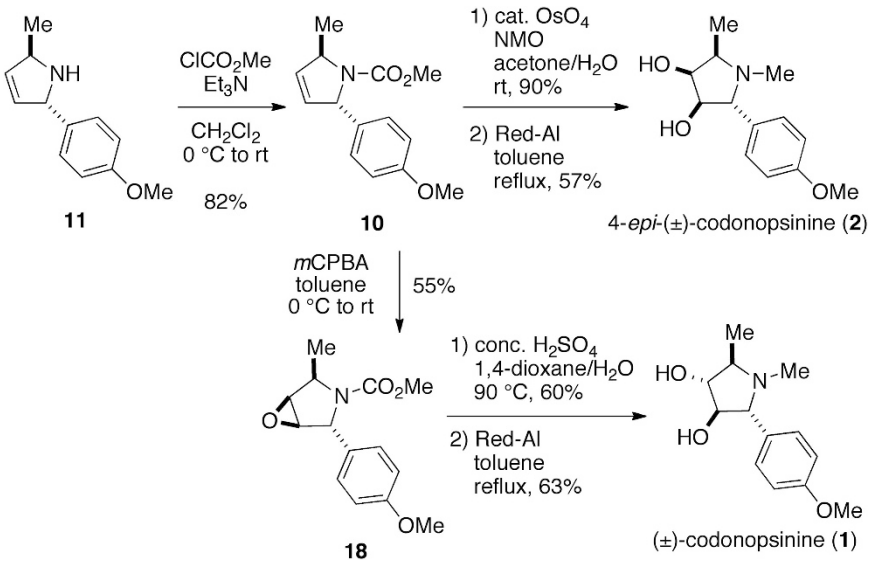


Table 2 Examination of the diastereoselective reduction of pyrrole ring



Entry	*Zn (equiv)*	*Acid*	*Solvent (0.1 M)*	*Temp (°C)*	*Yield (%)*	*dr*[a] *(trans:cis)*
1	8	HCl aq.	MeOH	–6 to RT	22	5:4
2	8	HCl aq.	EtOH	–6 to RT	27	2:1
3	9	Conc. H_2SO_4	EtOH	RT	34	5:1
4	9	Conc. H_2SO_4	MeCN	RT	45	33:1
5	9	Conc. H_2SO_4	MeCN	70	57	Sole isomer

Abbreviation: RT, room temperature.
[a]The ratio of diastereomers was determined by ^{1}H-NMR.



Scheme 5 Endgame of total syntheses of codonopsinine (**1**) and 4-*epi*-codonopsinine (**2**).

presence of Zn dust and sulfonic acid at 70 °C. The plausible mechanisms would be initiated by protonation of the pyrrole ring at the 5-position to give α,β-unsaturated iminium ion intermediate. Then the intermediate would be reduced by single-electron reduction with zinc dust to generate a stable 2,5-*trans* radical species, which would be further reduced by zinc reagent to provide the *trans* product after protonation.

The endgame sequence of the total synthesis of codonopsinine (**1**) and 4-*epi*-codonopsinine (**2**) is depicted in Scheme 5. First, methoxycarbonylation of secondary amine of **11** produced the pivotal intermediate **10**. The total synthesis of 4-*epi*-codonopsinine (**2**) was achieved by diastereoselective dihydroxylation of **10** and reductive transformation of methyl carbamate to the corresponding methyl amine. By contrast, conversion of **10** to codonopsinine (**1**) was executed by diastereoselective meta-3-chloroperoxybenzoic acid (*m*CPBA) epoxidation of the olefin, ring cleavage of the epoxide under acidic conditions and reduction with Red-Al according to the procedure[13] developed by Correira *et al*. All the properties of synthetic **1**[13] and **2**[9] were identical to the published data.

In conclusion, we accomplished the total syntheses of codonopsinine (**1**) and 4-*epi*-codonopsinine (**2**). For the construction of the pentasubstituted pyrrolidine core, we utilized our original multisubstituted pyrroles synthesis by gold-mediated auto-tandem catalysis and diastereoselective reduction of the pyrrole ring to the 3-pyrroline derivative. Taking advantage of our modular synthesis of substituted pyrroles, the synthetic strategy developed in this work should be applicable to the versatile synthesis of a wide range of codonopsinine congeners.

EXPERIMENTAL PROCEDURE

Gereral remarks

Unless otherwise noted, all reactions were performed using oven-dried glassware, sealed with a rubber septum under a slight positive pressure of argon. Anhydrous tetrahydrofuran, MeCN, 1,4-dioxane and dichloromethane

were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan) Anhydrous toluene, xylene, acetone and dimethylformamide were purchased from Wako Pure Industries (Osaka, Japan). Anhydrous EtOH, MeOH and Et_3N were dried and distilled according to the standard protocols. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Microwave irradiation experiments were performed on a CEM Discover Microwave Reactor (Discover-SP W/ACTIVENT, Tokyo, Japan). Reactions and chromatographical fractions were monitored by TLC analysis with precoated silica gel plates 60 F_{254} (Merck, Frankfurt, Germany). Flash column chromatography was carried out using Kanto silica gel 60N (spherical, neutral, 40–50 μm). Preparative TLC was performed on precoated silica gel plates 60 F_{254} (Merck). Gel permeation chromatography was carried out using a Japan Analytical Industry Co., Ltd., LC-9201 (Tokyo, Japan). IR spectra were measured on a Shimadzu FTIR-8300 spectrometer (Kyoto, Japan) or a JASCO FT/IR-4100 spectrometer (Tokyo, Japan). NMR spectra were measured on a JNM-AL400 spectrometer (JEOL Resonance Inc., Tokyo, Japan). For ^1H spectra, chemical shifts were expressed in p.p.m. downfield from internal tetramethylsilane (δ 0) or relative internal $CHCl_3$ (δ 7.26). For ^{13}C spectra, chemical shifts were expressed in p.p.m. downfield from relative internal $CHCl_3$ (δ 77.0). *J* values were expressed in Hertz. Elemental analyses were performed by a Yanaco CHN corder MT-6. Mass spectra (Kyoto, Japan) were recorded on a JEOL JMS-DX-303, a JMS-700, a JMS-T100GC (respectively, JEOL Ltd., Tokyo, Japan) and a Bruker micrOTOF spectrometer (MicrOTOF II-TH, Bruker Daltonics, Yokohama, Japan).

N-Carboxybenzylalaninal diisopropylacetal

To a solution of aldehyde **16** (1.23 g, 5.94 mmol) in *i*-PrOH (40 ml) was added PPTS (150 mg, 0.597 mmol). After stirring at reflux for 18 h with Dean–Stark trap containing MS4 Å, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/AcOEt = 9:1) to afford the titled compund (1.35 g, 4.37 mmol, 74%) as a colorless oil; R_f = 0.69 (silica gel, hexanes/AcOEt = 7:3); IR (neat) 3344, 2972, 1715, 1504, 1454, 1332, 1229, 1053, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 5.17–5.03 (m, 2H), 5.02–4.88 (m, 1H), 4.74 (s, 1H), 3.91–3.70 (m, 3H), 1.24–1.08 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.6, 128.5, 128.04, 128.01, 99.6, 69.5, 69.0, 66.5, 49.5, 23.00, 22.98, 22.4, 22.1, 14.6; LRMS (FAB) *m/z* 310.2 ($[M+H]^+$); HRMS Calcd for $C_{17}H_{28}NO_4$ ($[M+H]^+$) 310.2019, found 310.2008.

N-Benzoylalaninal diisopropylacetal (14)

A suspension of the above diisopropyl acetal (1.33 g, 4.29 mmol) and 10% Pd/C (457 mg, 0.429 mmol) in EtOH (42 ml) was stirred under a hydrogen atmosphere at room temperature for 1.5 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (13 ml), and Et_3N (1.69 ml, 12.1 mmol) and benzoyl chloride (510 μl, 4.40 mmol) were added at 0 °C. After stiring for 10 min, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/AcOEt = 8:2) to afford benzamide **14** (877 mg, 3.14 mmol, 73%) as a white solid; R_f = 0.33 (silica gel, hexanes/AcOEt = 7:3); Mp 89–90 °C; IR (KBr) 3292, 2970, 2361, 1636, 1558, 1377, 1339, 1159, 1047, 916, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.34 (br s, 1H), 4.59 (d, *J* = 2.4 Hz, 1H), 4.36–4.26 (m, 1H), 3.88 (sep, *J* = 6.0 Hz, 1H), 3.83 (sep, *J* = 6.0 Hz, 1H), 1.32–1.17 (m, 12H), 1.13 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 134.7, 131.3, 128.5, 126.8, 99.5, 69.6, 69.0, 48.0, 23.01, 22.99, 22.5, 22.2, 14.2; Anal Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.74; H, 9.26; N, 5.07.

1-Benzoyl-2-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole (12)

A two necked round-bottom flask equipped with a magnetic stirring bar was charged with $AgBF_4$ (18.1 mg, 92.8 μmol), RuPhosAuCl (64.9 mg, 92.8 μmol) and xylenes (3.7 ml, 0.25 M). To the solution were added benzamide **14** (260 mg, 0.928 mmol) and 1-ethynyl-4-methoxybenzene **13** (0.700 ml, 4.64 mmol) at room temperature. After stirring at 140 °C for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/toluene = 1:3) and preparative TLC on silica gel (hexanes/AcOEt = 9:1) to afford *N*-benzoyl pyrrole **12** (226 mg, 0.776 mmol, 84%) as a pale yellow solid; R_f = 0.40 (silica gel, hexanes/toluene = 1:3); Mp 103–104 °C (hexanes/CH_2Cl_2); IR (KBr) 1697, 1531, 1493, 1333, 1290, 1242, 1032, 833, 802, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33–7.20 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.21 (d, *J* = 3.6 Hz, 1H), 6.10 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 158.1, 135.1, 135.0, 133.2, 132.4, 130.4, 128.8, 128.2, 126.4, 113.6, 110.2, 110.0, 55.1, 14.0; Anal Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.07; H, 5.93; N, 4.78.

2-(4-Methoxyphenyl)-5-methyl-1*H*-pyrrole (17)

To a solution of *N*-benzoyl pyrrol **12** (225 mg, 0.774 mmol) in a mixture of EtOH (2.6 ml), CH_2Cl_2 (1.3 ml) and H_2O (0.7 ml) was added KOH (195 mg, 3.48 mmol). After stirring for 2 h at 50 °C, the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/AcOEt = 8:2) to afford pyrrol **17** (138 mg, 0.737 mmol, 95%) as a light yellow solid; Mp 129–131 °C; IR (neat) 3433, 3398, 2924, 1525, 1254, 824, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.27 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.93 (m, 1H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 130.8, 128.3, 126.1, 124.8, 114.3, 107.6, 105.0, 55.3, 13.1; ESI-MS *m/z* Calcd for $C_{12}H_{14}NO$ 188.1060 (M^++H), found 188.1070.

(2*S**,5*R**)-2-(4-Methoxyphenyl)-5-methyl-2,5-dihydro-1*H*-pyrrole (11)

To a suspension of pyrrole **17** (117 mg, 0.628 mmol) and zinc dust (activated, 367 mg, 5.61 mmol) in MeCN (6.3 ml) was added dropwise concentrated H_2SO_4 (0.402 ml). After stirring at 70 °C for 10 min, the mixture was filtered through a pad of Celite. The pH value of the filtrate was adjusted to 10 by addion of 2 M NaOH. The solution was saturated with NaCl and the mixture was extracted with AcOEt five times. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude product as a single isomer. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 10:1) to afford 3-pyrroline derivative **11** (67.2 mg, 0.355 mmol, 57%) as a pale yellow oil. R_f = 0.28 (Silica gel, MeOH/CH_2Cl_2 = 1:10); IR (neat) 2959, 2835, 1611, 1510, 1244, 1175, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.90 (d, *J* = 6.0 Hz, 1H), 5.80 (d, *J* = 6.0 Hz, 1H), 5.14 (br s, 1H), 4.37–4.26 (m, 1H), 3.79 (s, 3H), 2.47 (br s, 1H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 136.4, 134.2, 131.3, 127.9, 113.9, 68.2, 60.3, 55.2, 22.7; ESI-MS *m/z* Calcd for $C_{12}H_{16}NO$ 190.1226 (M^++H), found 190.1235.

(2*S**,5*R**)-2-(4-Methoxyphenyl)-5-methyl-2,5-dihydro-1*H*-pyrrole-1-carboxylic acid methyl ester (10)

To a solution of 3-pyrroline derivative **11** (40.2 mg, 0.212 mmol) and Et_3N (89 μl, 0.64 mmol) in CH_2Cl_2 (0.7 ml) was added methyl chloroformate (20 μl, 0.26 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexanes/AcOEt = 3:7) to afford methyl carbamate **10** (43.1 mg, 0.174 mmol, 82%) as a clear oil; its ^1H

NMR spectral data were identical with those reported[13]; ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers) δ 7.18 (d, J=8.8 Hz, 0.9H), 7.08 (d, J=8.8 Hz, 1.1H), 6.86 (d, J=8.8 Hz, 0.9H), 6.82 (d, J=8.8 Hz, 1.1H), 5.80–5.73 (m, 1H), 5.64 (ddd, J=6.4, 2.0, 0.5 Hz, 0.5H), 5.61 (ddd, J=6.4, 2.0, 0.5 Hz, 0.5H), 5.48 (m, 0.5H), 5.39 (m, 0.5H), 4.89–4.80 (m, 0.5H), 4.78–4.70 (m, 0.5H), 3.79 (s, 1.6H), 3.78 (s, 1.4H), 3.63 (s, 1.4H), 3.42 (s, 1.6H), 1.44 (d, J=6.0 Hz, 1.6H), 1.36 (d, J=6.0 Hz, 1.4H).

(2*R**,3*R**,4*S**,5*R**)-3,4-Dihydroxy-2-(4-methoxyphenyl)-5-methylpyrrolidine-1-carboxylic acid methyl ester

To a solution of 3-pyrroline derivative **10** (15.2 mg, 61.5 μmol) and N-methylmorpholine N-oxide (NMO) (10.8 ml, 92.3 μmol) in acetone (0.50 ml) and H_2O (0.12 ml) was added OsO_4 (1.0% in H_2O, 78 μl, 3.1 μmol). After stirring for 5 days at room temperature, the reaction was quenched with saturated aqueous $NaHSO_3$, and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexanes/AcOEt=1:1) to afford the titled *cis*-diol (15.6 mg, 55.5 μmol, 90%) as a colorless oil; R_f=0.20 (silica gel, hexanes/AcOEt=1:1); IR (neat) 3419, 3303, 2937, 1680, 1612, 1513, 1455, 1386, 1249 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN, 60 °C) δ 7.08–7.00 (m, 2H), 6.92–6.80 (m, 2H), 4.72 (br s, 1H), 4.29–4.18 (m, 1H), 4.17–4.09 (m, 1H), 3.86 (br s, 1H), 3.78–3.72 (m, 3H), 3.67–3.29 (m, 4H), 3.14 (br s, 1H), 1.35–1.33 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN, 60 °C) δ 160.1, 156.4, 130.3, 127.9, 115.1, 114.1, 70.9, 68.6, 64.3, 57.2, 56.2, 52.5; ESI-MS *m/z* Calcd for $C_{14}H_{19}NNaO_5$ 304.1155 (M^++Na), found 304.1157.

(2*R**,3*R**,4*S**,5*R**)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol; 4-*epi*-(±)-codonopsinine (2)

To a solution of the above *cis*-diol (12.1 mg, 43.0 μmol) in toluene (0.22 ml) was added Red-Al (65% w/v in toluene, 129 μl) at 0 °C. After heating at reflux for an hour, the reaction was quenched with saturated aqueous Rochell's salt at 0 °C. The resulting mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel ($CHCl_3$/MeOH=3:1) to afford 4-*epi*-(±)-codonopsinine (**2**) (5.8 mg, 24.4 μmol, 57%) as a white solid; its ^{1}H NMR spectral data were identical with those reported[9]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 4.28 (dd, J=6.4, 6.4 Hz, 1H), 4.06 (dd, J=6.4, 5.2 Hz, 1H), 3.81 (s, 3H), 3.66 (d, J=5.2 Hz, 1H), 3.53–3.45 (m, 1H), 2.64 (br s, 1H), 1.12 (s, 3H).

(1*S**,2*S**,4*S**,5*R**)-2-(4-Methoxyphenyl)-4-methyl-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid methyl ester (18)

To a solution of pyrroline **10** (14.7 mg, 59.4 μmol) in toluene (0.3 ml) was added *m*CPBA (51.0 mg, 0.297 mmol) at 0 °C. After stirring at room temperature for 28 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexanes/AcOEt=3:7) to afford epoxide **18** (8.6 mg, 33 μmol, 55%) as a clear oil; its ^{1}H NMR spectral data were identical with those reported[14]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J=8.4 Hz, 0.9H), 7.08 (d, J=8.8 Hz, 2.1H), 6.92–6.84 (m, 2H), 5.04 (br s, 0.3H), 4.96 (br s, 0.7H), 4.22–4.07 (m, 1H), 3.80 (s, 2.1H), 3.79 (m, 0.9H), 3.76–3.70 (m, 1H), 3.62 (s, 0.9H), 3.52–3.47 (m, 1H), 3.44 (s, 2.1H), 1.58 (d, J=6.0 Hz, 2.1H), 1.51 (d, J=6.0 Hz, 0.9H).

(2*R**,3*R**,4*R**,5*R**)-3,4-Dihydroxy-2-(4-methoxyphenyl)-5-methylpyrrolidine-1-carboxylic acid methyl ester

To a solution of epoxide **18** (8.6 mg, 33 μmol) in 1,4-dioxane (0.13 ml) and H_2O (90 μl) was added dropwise concentrated H_2SO_4 (9.0 μl). After stirring for 9 h at 90 °C, the reaction was quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexanes/AcOEt=2:1) to afford the titled *trans*-diol (5.5 mg, 20 μmol, 60%) as a clear oil; its ^{1}H NMR spectral data were identical with those reported[13]; ^{1}H NMR (400 MHz, C_5D_5N, a mixture of rotamers) δ 7.65 (d, J=7.6 Hz, 1H), 7.45 (br s, 1H), 6.93 (d, J=8.4 Hz, 2H), 4.66 (br s, 1H), 4.61–4.33 (m, 2H), 3.69 (br s, 1H), 3.60 and 3.59 (s, 3H), 3.48 (s, 3H), 1.93 (d, J=6.4 Hz, 1.8H), 1.75 (d, J=6.4 Hz, 1.8H).

(2*R**,3*R**,4*R**,5*R**)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol; codonopsinine (1)

To a solution of *trans*-diol compound (8.5 mg, 30.2 μmol) in toluene (0.15 ml) was added Red-Al (65% w/v in toluene, 233 μl) at 0 °C. After heating at reflux for 45 h, the reaction was quenched with saturated aqueous Rochell's salt at 0 °C, and the mixture was extracted with AcOEt three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel ($CHCl_3$/MeOH=4:1) to afford (±)-codonopsinine (**1**) (4.5 mg, 19 μmol, 63%) as a white solid; Mp 155–157 °C; IR (neat) 3365, 2919, 2837, 1611, 1514, 1459, 1249, 1180, 1035, 837 cm^{-1}; ^{1}H NMR (600 MHz, C_5D_5N) δ 7.58 (d, J=8.4 Hz, 2H), 6.97 (d, J=8.4 Hz, 2H), 4.60 (dd, J=6.0, 4.8 Hz, 1H), 4.36 (dd, J=6.0, 4.8 Hz, 1H), 4.02 (d, J=6.0 Hz, 1H), 3.67 (qd, J=6.4, 3.6 Hz, 1H), 3.66 (s, 3H), 2.20 (s, 3H), 1.31 (s, J=6.4 Hz, 3H); ^{13}C NMR (150 MHz, C_5D_5N) δ 159.0, 134.7, 129.5, 113.8, 86.9, 84.7, 74.0, 64.7, 54.8, 34.4, 13.6; ESI-MS *m/z* Calcd for $C_{13}H_{20}NO_3$ (M^++H) 238.1438, found 238.1435.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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