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Total synthesis of (−)-codonopsinine via regioselective and diastereoselective amination using chlorosulfonyl isocyanate

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ABSTRACT

The total synthesis of (−)-codonopsinine (**1**) from the readily available (*S*)-3-chloropropan-1,2-diol is described. The key steps for the preparation of (−)-codonopsinine (**1**) involve the regioselective and diastereoselective amination of *anti*-1,2-dibenzyl ether **11** using chlorosulfonyl isocyanate and intramolecular amidomercuration to form the pyrrolidine ring. Notably, the reaction between *anti*-1,2-dibenzyl ether and chlorosulfonyl isocyanate in toluene at 0 °C produced the corresponding *anti*-1,2-amino alcohol **12a** as a major product with excellent diastereoselectivity (*anti*:*syn* = 29:1). This observation can be explained by the neighboring group participation leading to the retention of stereochemistry.

1. Introduction

Polyhydroxylated alkaloids are among the most notable achievements in the field of natural products[1] due to remarkable therapeutic potential for the treatment of viral infections, cancer, AIDS, diabetes, and etc.[2] With considerable progress in medicinal chemistry, a range of natural and unnatural polyhydroxylated alkaloids have been prepared and evaluated for clinical trial.[3] Indeed, miglitol (Glyset™) and *N*-butyldeoxynojirimycin (Zavesca™) are currently on the market as commercial drugs for the treatment of type II diabetes and Gaucher's disease.[4] In particular, polyhydroxylated pyrrolidine alkaloids are widely found to be biologically relevant scaffolds in natural products and pharmaceuticals.

Representative examples of polyhydroxylated pyrrolidine alkaloids, (−)-codonopsinine (**1**) and (−)-codonopsine (**2**) are first isolated from *Codonopsis clematidea*[5] in 1969 and their absolute stereochemistry was determined by the same group in 1972 (Fig. 1).[6] Notably, these compounds have attracted considerable attention due to the challenging *penta*-substituted pyrrolidine core containing four stereogenic centers with indiscrete *trans*-stereochemistry and diverse biological activities as antibiotic and antihypertensive effects without affecting the central nervous system.[7] Owing to interesting biological activity and unique structural feature, various synthetic routes for the preparation of (−)-codonopsinine (**1**) have been studied.[8] For example, Rao have been reported the total synthesis of (−)-codonopsinine (**1**) via the DDQ-promoted benzylic sp^3 C–H activation reaction[8a] and acid-catalyzed amidocyclization[8e] for the stereoselective intramolecular C–N bond formation. Davies described the ring-closing iodoamination reaction of homoallylic amines for the synthesis of polysubstituted pyrrolidines and its application to the asymmetric synthesis of **1**.[8b,c] Ooi demonstrated the efficient synthesis of **1** through the organocatalytic asymmetric Henry reaction between ynals and nitromethane leading to the formation of *anti*-vicinal amino alcohols.[8d] Goti and Merino disclosed the construction of (−)-codonopsinine (**1**) and its analog based on the iterative organometallic addition to chiral hydroxylated cyclic nitrones.[8g]

As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds via the stereoselective amination of chiral allylic and benzylic ethers using chlorosulfonyl isocyanate (CSI),[9] we herein describe an asymmetric total synthesis of (−)-codonopsinine (**1**) starting from commercially available (*S*)-3-chloropropan-1,2-diol via chelation-controlled Grignard reaction, diastereoselective amination of *anti*-vicinal dibenzyl ether and intramolecular cyclization by amidomercuration as the key steps.

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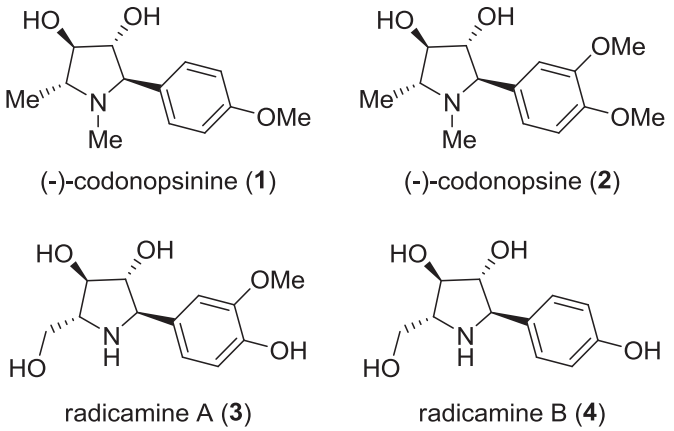


Fig. 1. Structure of representative polyhydroxylated pyrrolidines.

2. Results and discussion

Total synthesis of (−)-codonopsinine (**1**) was accomplished by using *anti*-vicinal dihydroxy ester **6** as a starting material, which can be readily prepared from (*S*)-3-chloropropan-1,2-diol (**5**) as reported in the literature (Scheme 1).[10] The diol **6** was easily converted into *anti*-1,2-dibenzyl ether **7** upon treatment with sodium hydride and benzyl bromide. The reduction of **7** and subsequent Swern oxidation afforded the corresponding aldehyde **9** in 77% yield for two steps. Next, we screened the Lewis acid-mediated Grignard-type addition reaction of **9** with vinylmagnesium bromide to yield 1,2-*syn*-allyl alcohol **10a**. The selected results are summarized in Table 1.[11]

As shown in entry 1, in the absence of Lewis acid, the addition of vinylmagnesium bromide to aldehyde **9** provided a mixture of **10a** and **10b** with 2:1 ratio in 58% yield. In addition, $MgBr_2 \cdot OEt_2$ as a Lewis acid in THF or CH_2Cl_2 solvents afforded our desired product **10a**, albeit resulting in low diastereoselectivity (Table 1, entries 2 and 3). After further evaluation of Lewis acids, we found that a combination of $ZnCl_2$ and THF solvent proved to be the most effective reaction condition furnishing **10a** as a major product with excellent diastereoselectivity of 13.9:1 (Table 1, entry 6). These results suggest that $ZnCl_2$ can initiate the formation of chelation

Table 1
Lewis acid-mediated addition of vinylmagnesium bromide to aldehyde **9**.[a]

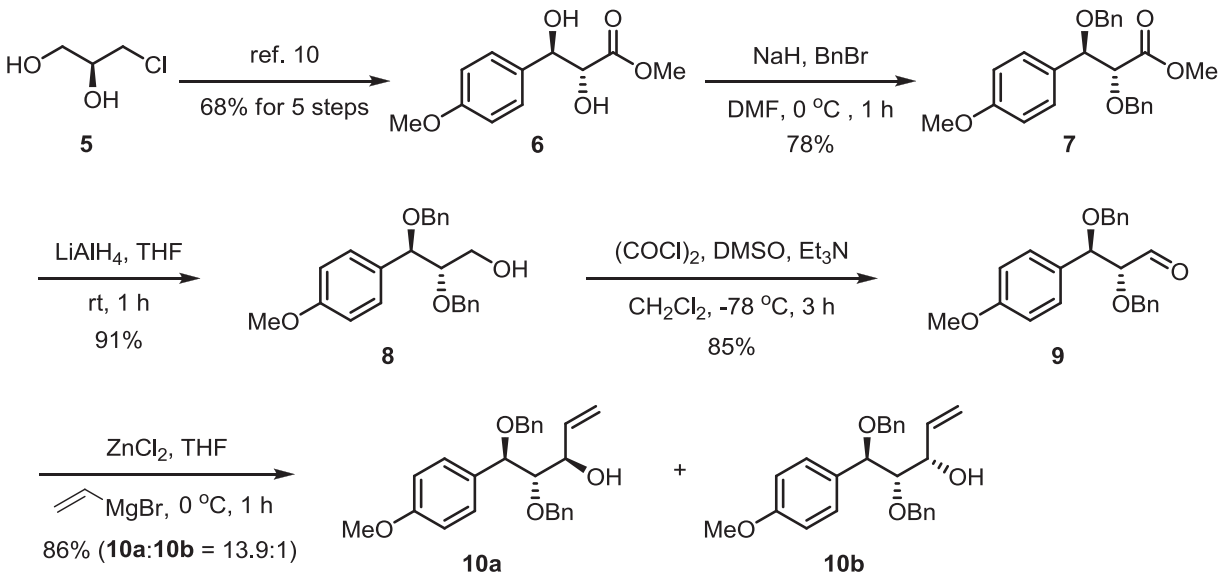
Entry	Lewis acid	Solvent	Ratio (10a:10b)[b]	Yield (%)[c]
1	–	THF	2.0:1	58
2	$MgBr_2 \cdot OEt_2$	THF	2.8:1	77
3	$MgBr_2 \cdot OEt_2$	CH_2Cl_2	4.9:1	62
4	$CeCl_3$	THF	3.1:1	73
5	$ZnCl_2$	CH_2Cl_2	15.7:1	63
6	$ZnCl_2$	THF	13.9:1	86

[a] *Reaction conditions*: **9** (1 equiv.), vinylmagnesium bromide (3 equiv.), Lewis acid (1.5 equiv.) at 0 °C for 3 h.
[b] Diastereomeric ratio was determined by HPLC analysis.
[c] Isolated combined yield of **10a** and **10b** by flash column chromatography.

complex between aldehyde group and α-OBn group, which smoothly participates in nucleophilic addition with vinylmagnesium bromide to deliver *syn*-isomer **10a** as a major diastereomer (Fig. 2). The stereochemistry of **10a** can be confirmed by the full agreement of spectral data between our synthesized (−)-codonopsinine (**1**) and reported literature.[8a,e]

As illustrated in Scheme 2, protection of the hydroxyl group of **10a** was subjected with Ac_2O to give the corresponding acetate **11** in 91% yield. Next, the reactivity and diastereoselectivity of **11** with chlorosulfonyl isocyanate were examined under various reaction conditions, and the selected results are summarized in Table 2. The reaction of **11** with CSI in CH_2Cl_2 at 0 °C gave the inseparable mixture of desired product **12a** and its diastereomer **12b** in 6:1 ratio in 84% yield (Table 2, entry 1). The screening of other solvents under identical reaction conditions showed that toluene was the most effective solvent for this reaction (Table 2, entry 4) to afford *anti*-vicinal amino alcohol **12a** in 73% yield with excellent diastereoselectivity (*anti*:*syn* = 29:1 as obtained by ^{1}H NMR and HPLC analysis), which was directly used in the next step. The diastereoselectivity of this reaction can be explained by the neighboring group effect, where the NHCbz group orientation retained its original configuration in benzyl ether via double inversion of the configuration (Fig. 3).[12]

Next, we focused on the synthesis of (−)-codonopsinine (**1**) from Cbz-protected amine **12a**, as illustrated in Scheme 3. The intramolecular amidomercurative cyclization[13] of **12a** with $Hg(CF_3SO_3)_2$, $NaHCO_3$ and KBr in nitromethane furnished the



Scheme 1. Synthesis of 1,2-*syn*-allyl alcohol **10a**.

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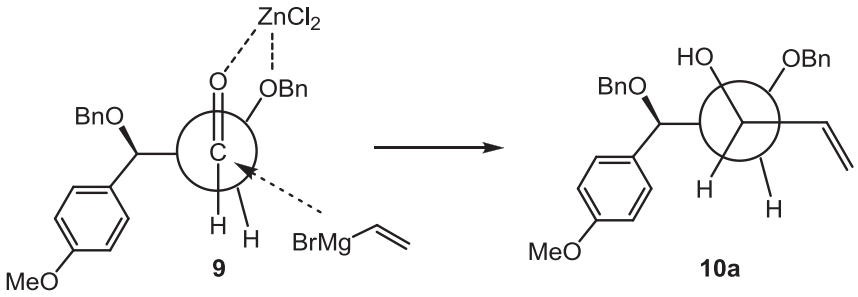
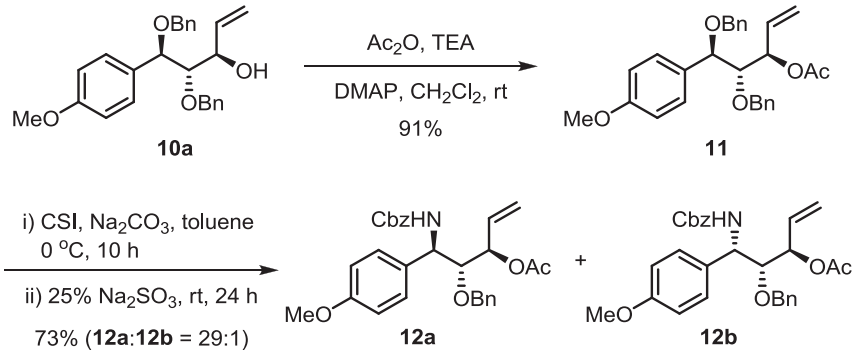


Fig. 2. Transition state model for the formation of **10a**.



Scheme 2. Synthesis of *anti*-vicinal amino alcohol **12a**.

corresponding organomercuric bromides **13a** and **13b** in 70% combined yield with diastereoselectivity of 3:1 between 2,5-*trans* and 2,5-*cis*.[14] The demercuration reaction of **13a** with $NaBH_4$ followed by reduction of a Cbz group led to the formation of compound **15**. Finally, the benzyl group was removed via hydrogenation to yield (−)-codonopsinine (**1**), which has spectral properties (^1H and ^{13}C NMR) and specific rotation in full agreement with previous reports.[8a,e]

3. Conclusions

In conclusion, we have developed a method for a highly regioselective and diastereoselective introduction of an NHCbz group to *anti*-vicinal dibenzyl ethers using chlorosulfonyl isocyanate (CSI). Moreover, we illustrated the application of this methodology to the total synthesis of (−)-codonopsinine (**1**). We believe that this synthetic strategy can be applied to the preparation of various polyhydroxylated alkaloids or other natural products containing a nitrogen atom in the ring.

4. Experimental section

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Varian Unit 400 (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) or Bruker Unit 400 (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) instrument with $CDCl_3$ or CD_3OD as solvent and residual $CHCl_3$ (δ 7.26 ppm) or CH_3OH (δ 3.31 ppm) as internal standard for ^1H NMR and $CDCl_3$ (δ 77.0 ppm) or CD_3OD (δ 49.0 ppm) as internal standard for ^{13}C NMR. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a JASCO FT/IR-4600 and reported as cm^{-1}. Optical rotations were measured with a JASCO P1020 polarimeter and are reported as [α]t D (concentration g/100 mL, solvent). Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-performance liquid chromatography (HPLC) was recorded on an Agilent 1200 series. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer.

4.2. Methyl-(2R,3R)-2,3-bis(benzyloxy)-3-(4-methoxyphenyl) propanoate (7)

To a suspension of NaH (3.6 g, 89.1 mmol, 60% in mineral oil) in DMF (150 mL) was added dropwise a solution of **6** (6.72 g, 29.7 mmol) in DMF (60 mL) at −20 °C. After stirring for 30 min at the same temperature, benzyl bromide (8.12 mL, 68.3 mmol) was added slowly over 10 min, and stirred further for 1 h at −20 °C. The temperature was slowly raised to 0 °C over 30 min, and the reaction mixture was further stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated solution of NH_4Cl (150 mL) and the solution was extracted with CH_2Cl_2 (200 mL × 2). The combined

Table 2
Diastereoselective amination of **11** with chlorosulfonyl isocyanate.[a]

Entry	Solvent	Time (h)	Ratio (12a:12b)[b]	Yield (%)[c]
1	CH_2Cl_2	6	6:1	84
2	Et_2O	8	19:1	71
3	*n*-hexane	24	20:1	52
4	toluene	10	29:1	73

[a] *Reaction conditions*: (i) **11** (1 equiv.), chlorosulfonyl isocyanate (4.5 equiv.), Na_2CO_3 (6.8 equiv.) at 0 °C, 10 h; (ii) aqueous solution of 25% Na_2SO_3 at room temperature for 24 h.
[b] Diastereomeric ratio was determined by HPLC analysis.
[c] Isolated yield by flash column chromatography.

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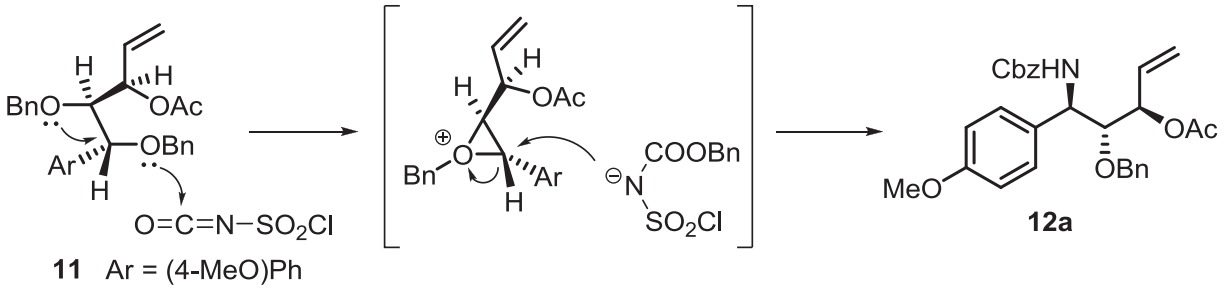


Fig. 3. Proposed reaction mechanism for the diasteroselective amination of **11** with CSI.

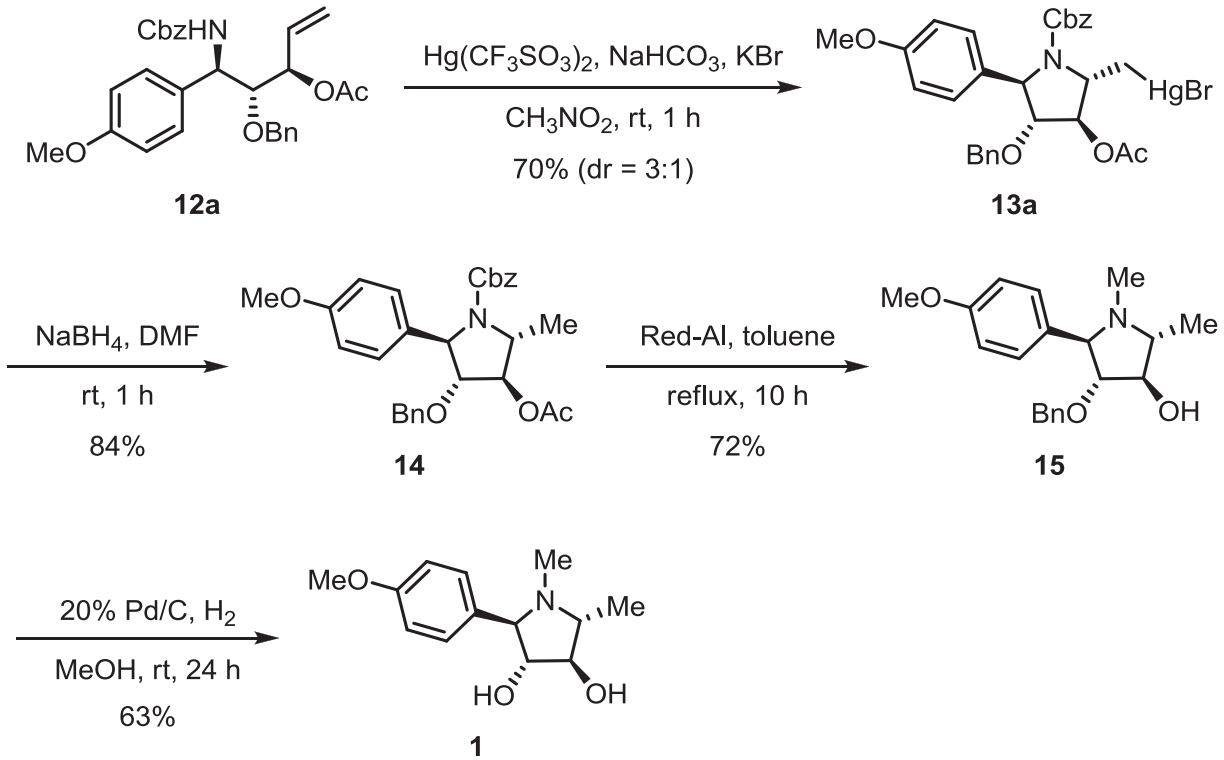
organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 5:1) to afford compound **7** (9.4 g, 78%) as a colorless oil; $[\alpha]_D^{20}$ −35.1 (*c* 1.0, $CHCl_3$); IR (neat) ν 3061, 3028, 2899, 1741, 1609, 1509, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.47 (m, 10H), 7.06–7.08 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.65 (d, *J* = 7.6 Hz, 1H), 4.51–4.57 (m, 2H), 4.29–4.35 (m, 2H), 4.11 (d, *J* = 7.6 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.7, 137.8, 136.9, 130.1, 129.2, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 113.7, 81.9, 80.5, 72.8, 70.5, 55.2, 51.9; HRMS (EI) calcd for $C_{25}H_{26}O_5$ $[M]^+$ 406.1780, found 406.1779.

4.3. (2S,3R)-2,3-Bis(benzyloxy)-3-(4-methoxyphenyl)propan-1-ol (**8**)

To a stirred solution of **7** (8.0 g, 19.7 mmol) in THF (80 mL) was added $LiAlH_4$ (1.12 g, 29.5 mmol) slowly at 0 °C. The mixture was stirred for 1 h at room temperature and quenched with 3 M HCl (15 mL). The resulting mixture was extracted with EtOAc (160 mL). The organic layer was washed with H_2O (2 × 60 mL), brine (60 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford **8** (6.8 g, 91%) as a colorless oil; $[\alpha]_D^{23}$ −48.8 (*c* 1.0, $CHCl_3$); IR (neat) ν 3493, 3026, 2907, 1609, 1587, 1509, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 10H), 7.10–7.08 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 7.6 Hz, 1H), 4.37–4.29 (m, 2H), 4.23 (d, *J* = 11.2 Hz, 1H), 3.89 (s, 3H), 3.87–3.84 (m, 2H), 3.66–3.62 (m, 1H), 2.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 138.0, 137.9, 131.2, 129.0, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 113.8, 82.4, 81.2, 72.9, 70.4, 62.5, 55.3; HRMS (EI) calcd for $C_{24}H_{26}O_4$ $[M]^+$ 378.1831, found 378.1827.

4.4. (2R,3R)-2,3-Bis(benzyloxy)-3-(4-methoxyphenyl)propanal (**9**)

To a stirred solution of oxalyl chloride (2.01 mL, 23.78 mmol) in CH_2Cl_2 (50 mL) was added dropwise DMSO (3.38 mL, 47.55 mmol) and CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and **8** (6.0 g, 15.85 mmol) in CH_2Cl_2 (100 mL) was added to resulting solution. After stirring for 1 h at same temperature, Et_3N (11.04 mL, 79.24 mmol) was added dropwise. The reaction mixture was further stirred for 0.5 h at −78 °C and carefully quenched with H_2O (100 mL). The organic layer was separated, washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography



Scheme 3. Synthesis of (−)-codonopsinine (**1**).

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(*n*-hexanes/EtOAc = 5:1) to afford **9** (5.07 g, 85%) as a colorless oil; $[\alpha]_D^{20}$ −37.8 (*c* 1.0, $CHCl_3$); IR (neat) *ν* 3020, 2730, 1730, 1620, 1575, 1509, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 9.67 (d, *J* = 2.4 Hz, 1H), 7.34–7.16 (m, 10H), 7.05–7.01 (m, 2H), 6.88–6.83 (m, 2H), 4.61–4.50 (m, 3H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 3.92 (dd, *J* = 2.8, 7.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.1, 159.7, 137.6, 137.0, 129.5, 129.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 113.9, 85.5, 79.8, 72.9, 70.3, 55.3; HRMS (FAB) calcd for $C_{24}H_{25}O_4$ $[M+H]^+$ 377.1753, found 377.1752.

4.5. (3R,4S,5R)-4,5-Bis(benzyloxy)-5-(4-methoxyphenyl)pent-1-en-3-ol (**10a**)

To a stirred solution of aldehyde **9** (5.97 g, 15.85 mmol) in THF (50 mL) was slowly added $ZnCl_2$ (3.24 g, 23.78 mmol) at 0 °C under N_2 atmosphere. Then, vinylmagnesium bromide solution (47.55 mL, 47.56 mmol, 1.0 M in THF) was added at 0 °C and stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated solution of NH_4Cl (100 mL) and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The organic layer was washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 8:1) to afford 5.14 g of **10a** (12.71 mmol, 80%) and 0.37 g of **10b** (0.91 mmol, 5.8%), respectively; colorless oil; $[\alpha]_D^{25}$ +16.2 (*c* 1.0, $CHCl_3$); IR (neat) *ν* 3472, 3029, 2894, 1735, 1609, 1541, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.37–7.22 (m, 10H), 6.99–6.92 (m, 4H), 6.09–6.00 (m, 1H), 5.43–5.22 (m, 2H), 4.49–4.45 (m, 3H), 4.26 (d, *J* = 10.8 Hz, 2H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.86 (s, 3H), 3.59 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.06 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.5, 139.2, 138.0, 137.6, 131.2, 130.2, 129.4, 129.0, 128.2, 128.1, 127.8, 127.7, 115.4, 113.7, 83.6, 80.9, 74.0, 71.9, 70.5, 55.3; HRMS (EI) calcd for $C_{26}H_{28}O_4$ $[M]^+$ 404.1988, found 404.1984; HPLC (Waters X-Bridge C18 column, MeCN:H_2O = 50:50 (0.1% TFA), 1.0 mL/min, 254 nm): t_{minor} = 20.6 min, t_{major} = 21.5 min; dr = 13.9:1.

4.6. (3S,4S,5R)-4,5-Bis(benzyloxy)-5-(4-methoxyphenyl)pent-1-en-3-ol (**10b**)

Colorless oil; $[\alpha]_D^{20}$ +9.2 (*c* 0.8, $CHCl_3$); IR (neat) *ν* 3471, 2894, 1733, 1609, 1540, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.31–7.21 (m, 10H), 6.99–6.93 (m, 4H), 6.07–5.98 (m, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 11.2 Hz, 1H), 4.45–4.35 (m, 3H), 4.22–4.18 (m, 2H), 3.86 (d, *J* = 11.2 Hz, 1H), 3.83 (s, 3H), 3.55 (dd, *J* = 8.2, 5.6 Hz, 1H), 3.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.5, 139.8, 138.6, 137.2, 131.24, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 116.5, 114.0, 113.8, 84.8, 82.4, 75.6, 74.6, 70.1, 55.3; HRMS (EI) calcd for $C_{26}H_{28}O_4$ $[M]^+$ 404.1988, found 404.1989.

4.7. (3R,4S,5R)-4,5-Bis(benzyloxy)-5-(4-methyoxyphenyl)pent-1-en-3-yl acetate (**11**)

To a stirred solution of **10a** (3.6 g, 8.90 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (2.5 mL, 17.8 mmol), 4-dimethylaminopyridine (0.22 g, 1.78 mmol) and acetic anhydride (1.36 g, 14.34 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and diluted with dichloromethane (20 mL). The resulting mixture was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 5:1) to afford 3.62 g of **11** (8.10 mmol, 91%) as a white solid; m.p. 83–85 °C; $[\alpha]_D^{25}$ −46.4 (*c* 0.9, $CHCl_3$); IR (neat) *ν* 3029, 2902, 1729, 1610, 1513, 1374, 1245, 1178, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.41–7.20 (m, 10H), 7.01–6.94 (m, 4H), 5.92–5.83 (m, 1H), 5.74–5.72 (m, 1H), 5.36 (d, *J* = 16.0 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 8.4 Hz, 1H), 4.19–4.14 (m, 2H), 3.38 (d, *J* = 9.6 Hz, 1H), 3.87 (s, 3H), 3.64 (dd, *J* = 8.8, 2.8 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.1, 159.6, 138.7, 137.4, 134.2, 131.1, 129.5, 128.5, 128.3, 128.0, 127.7, 127.6, 117.6, 113.8, 83.7, 78.6, 75.0, 74.0, 70.0, 55.3, 21.1; HRMS (EI) calcd for $C_{28}H_{30}O_5$ $[M]^+$ 446.2093, found 446.2097.

4.8. (3R,4R,5R)-4-(Benzyloxy)-5-(benzyloxycarbonylamino)-5-(4-methoxyphenyl)pent-1-en-3-ylacetate (**12a**)

To a stirred solution of **11** (3.40 g, 7.61 mmol) in anhydrous toluene (26 mL) was added Na_2CO_3 (5.48 g, 51.75 mmol) and chlorosulfonyl isocyanate (3.0 mL, 34.25 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 10 h at 0 °C and quenched with H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was added to a solution of 25% aqueous solution of Na_2SO_3 (150 mL), and the reaction mixture was further stirred for 24 h at room temperature. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford 2.72 g of **12a** (5.56 mmol, 73%) as a colorless syrup; $[\alpha]_D^{20}$ +33.9 (*c* 1.03, $CHCl_3$); IR (neat) *ν* 3353, 1732, 1683, 1530, 1454, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.35–7.21 (m, 12H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.81–5.72 (m, 1H), 5.44 (d, *J* = 9.2 Hz, 1H), 5.25–5.13 (m, 3H), 5.07–4.96 (m, 2H), 4.85–4.81 (m, 1H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 3.89 (br s, 1H), 3.78 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.7, 159.2, 155.4, 137.9, 136.4, 132.7, 13.3, 129.4, 128.6, 128.1, 128.1, 128.0, 127.9, 119.6, 113.9, 82.4, 75.4, 75.1, 66.7, 55.2, 21.2; HRMS (FAB) calcd for $C_{29}H_{32}NO_6$ $[M+H]^+$ 490.2230, found 490.2233; HPLC (Waters X-Bridge C18 column, MeCN:H_2O = 50:50 (0.1% TFA), 0.8 mL/min, 254 nm): t_{major} = 19.6 min, t_{minor} = 21.1 min, dr = 29:1.

4.9. (((2S,3R,4R,5R)-3-Acetoxy-4-(benzyloxy)-1-(benzyloxycarbonyl)-5-(4-methoxyphenyl)pyrrolidin-2-yl)methyl) mercury(II)bromide (**13a**)

A stirred solution of compound **12a** (2.70 g, 5.51 mmol) in nitromethane (30 mL) was added mercury triflate (4.13 g, 8.27 mmol) at room temperature. After the reaction mixture was stirred for 30 min and then saturated solution of KBr (13.7 mL) and NaHCO3 (13.7 mL) was added. The resulting mixture was further stirred for 30 min and the resulting solution was extracted with EtOAc (2 × 30 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1) to afford a separable mixture of **13a** and **13b** (2.97 g, 3.86 mmol, 70% combined yield of **13a** and **13b**) as a yellowish syrup. The diastereomer ratio of **13a** and **13b** was determined to be 3:1 by NMR spectra with the crude material before purified; $[\alpha]_D^{25}$ −17.3 (*c* 1.03, $CHCl_3$); IR (neat) *ν* 2924, 1733, 1690, 1669, 1510, 1401, 1346, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.39–7.30 (m, 6H), 7.22–7.13 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.81–6.74 (m, 3H), 5.24–5.09 (m, 1H), 5.07–5.03 (m, 2H), 4.92–4.65 (m, 4H), 3.85–3.72 (m, 1H), 3.78 (s, 3H), 2.59 (dd, *J* = 12.4, 5.6 Hz, 1H), 2.32 (dd, *J* = 12.4, 6.4 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.9, 158.6, 154.6, 136.7, 135.9, 132.0, 130.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.6, 127.5, 126.8, 113.7, 113.5, 87.3, 82.4, 68.1, 67.1, 66.5, 55.3, 35.2, 20.8; HRMS (FAB) calcd for $C_{29}H_{31}O_6NBrHg$ $[M+H]^+$ 770.1041, found 770.1047.

4.10. (((2R,3R,4R,5R)-3-Acetoxy-4-(benzyloxy)-1-(benzyloxycarbonyl)-5-(4-methoxyphenyl)pyrrolidin-2-yl)methyl) mercury(II) bromide (**13b**)

IR (neat) *ν* 2922, 2914, 1731, 1691, 1660, 1508, 1400, 1225, 1012,

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941 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.06 (m, 12H), 6.84 (d, J = 8.7 Hz, 2H), 5.16–4.97 (m, 2H), 4.90–4.66 (m, 2H), 4.55 (s, 2H), 4.06 (t, J = 4.8 Hz, 1H), 3.84–3.76 (m, 4H), 2.22–1.94 (m, 2H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.7, 155.8, 137.3, 135.8, 131.9, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.0, 113.9, 85.5, 77.1, 72.2, 67.3, 65.6, 58.4, 55.2, 20.7; HRMS (FAB) calcd for $C_{29}H_{31}O_6NBrHg$ $[M+H]^+$ 770.1041, found 770.1046.

4.11. Benzyl-(2R,3R,4R,5R)-3-acetoxy-4-(benzyloxy)-5-(4-methoxyphenyl)-2-methylpyrrolidine-1-carboxylate (**14**)

To a stirred solution of **13a** (1.0 g, 1.3 mmol) in DMF (4 mL) was added $NaBH_4$ (0.098 g, 2.6 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with H_2O (12 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexanes/EtOAc = 3:1) to afford 0.53 g of **14** (1.09 mmol, 84%) as a colorless oil; $[\alpha]_D^{23}$ +19.8 (c 1.0, $CHCl_3$); IR (neat) ν 2933, 1737, 1698, 1511, 1402, 1348, 1227, 1106, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7H), 7.23–7.05 (m, 4H), 6.82–6.76 (m, 3H), 5.20–4.94 (m, 3H), 4.84–4.63 (m, 3H), 4.36 (dq, J = 12.4, 6.8 Hz, 1H), 3.85 (d, J = 11.6 Hz, 1H), 3.79 (s, 3H), 1.83 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 169.9, 158.6, 154.5, 137.5, 136.6, 136.3, 133.1, 132.2, 128.5, 128.2, 127.9, 127.6, 127.5, 127.4, 127.2, 113.7, 113.5, 88.6, 87.9, 81.2, 80.1, 71.7, 67.9, 67.8, 67.1, 66.6, 61.0, 60.5, 55.3, 20.9, 18.4, 17.3; HRMS (FAB) calcd for $C_{29}H_{32}NO_6$ $[M+H]^+$ 490.2230, found 490.2235.

4.12. (2R,3R,4R,5R)-4-(Benzyloxy)-5-(4-methoxyphenyl)-1,2-dimethylpyrrolidine-3-ol (**15**)

To a stirred solution of **14** (0.40 g, 0.82 mmol) in dry toluene (15 mL) was added Red-Al (1.28 mL, 44.16 mmol, 3.5 M solution in toluene) at 0 °C. After addition was completed, the reaction mixture was heated to reflux for 10 h. The reaction mixture was cooled to 0 °C, and quenched with EtOAc (15 mL) and H_2O (5 mL). After stirring for 15 min, the reaction mixture was filtered through a celite pad and washed with ethyl acetate (3 × 10 mL). The filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 20:1) to afford 0.19 g of **15** (0.59 mmol, 72%) as a colorless oil; $[\alpha]_D^{23}$ −31.2 (c 1.0, MeOH); IR (neat) ν 3368, 3063, 3030, 2924, 2852, 1610, 1511, 1455, 1368, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 7H), 6.58 (d, J = 8.8 Hz, 2H), 4.49 (s, 2H) 3.93–3.89 (m, 2H), 3.82 (s, 3H), 3.70 (d, J = 5.2 Hz, 1H), 3.38 (dq, J = 7.6, 6.8 Hz, 1H), 2.15 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.0, 131.7, 129.3, 128.3, 127.6, 127.5, 113.9, 93.4, 80.6, 72.2, 72.1, 65.9, 55.2, 34.4, 29.7, 11.0; HRMS (FAB) calcd for $C_{20}H_{26}O_3N$ $[M+H]^+$ 328.1913, found 328.1915.

4.13. (−)-Codonopsinine (**1**)

To a stirred solution of **15** (0.19 g, 0.58 mmol) and 20% Pd/C (0.04 g, 20% w/w) in MeOH (6 mL) was shaken for 24 h under 60 psi hydrogen pressure by using hydrogenator. The reaction mixture was filtered through a celite pad and washed with MeOH (3 × 10 mL). The filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 9:1)[8a] to afford 0.09 g of **1** (0.38 mmol, 63%) as a white solid; m.p. 168–170 °C [Lit.[8e] m.p. 169–170 °C]; $[\alpha]_D^{23}$ −8.9 (c 0.1, MeOH); [Lit.[8e] $[\alpha]_D^{20}$ −8.8 (c 0.1, MeOH)]; IR (neat) ν 3361, 2938, 2361, 1834, 1742, 1698, 1514, 1460 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.62 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 4.64 (dt, J = 6.4, 6.8 Hz, 1H), 4.40 (dt, J = 6.4, 6.8 Hz, 1H), 4.04 (d, J = 6.0 Hz, 1H), 3.68 (m, 4H), 2.23 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.1, 135.0, 129.6, 113.8, 86.9, 84.8, 74.1, 64.8, 54.9, 34.5, 13.7; HRMS (EI) calcd for $C_{13}H_{19}NO_3$ $[M]^+$ 237.1365, found 237.1363.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.06.002.

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14. The stereochemistry of 13a was assumed by the full agreement of spectral data between our synthesized (−)-codonopsinine (1) and cited references 8a and 8e.