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A Short, Efficient, and Stereoselective Total Synthesis of a Pyrrolidine Alkaloid: (−)-Codonopsinine†

Jangari Santhosh Reddy and Batchu Venkateswara Rao*

Organic Division III, Indian Institute of Chemical Technology, Hyderabad 500007, India

venky@iict.res.in

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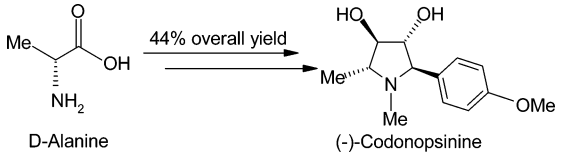


An efficient total synthesis of antibiotic (−)-codonopsinine **1** with an overall yield of 44% was achieved from D-alanine as a chiral template. The key steps in our strategy are modified Sharpless asymmetric dihydroxylation reaction and the highly stereoselective intramolecular acid-catalyzed amidocyclization.

The chiral polyhydroxy alkaloids (or iminosugars)[1] show remarkable biological properties and have attracted considerable attention in organic synthesis. Over the past two decades, many studies aimed at isolation and sterocontrolled syntheses of these alkaloids have been carried out.[1,2] Among these, pyrrolidine alkaloids carrying an aromatic substituent on the iminosugar ring are of a rare class found in nature. (−)-Codonopsinine **1** and (−)-codonopsine **2** are the first two examples in this unusual category (Figure 1), initially isolated in 1969 from *Codonopsis clematidea*.[3] These two compounds display antibiotic as well as hypotensive activities without affecting the central nervous system in animal tests.[4] After structural characterization,[3b,5] they were revealed to be a new class of simple pyrrolidine alkaloids possessing 1,2,3,4,5 penta-substituted pyrrolidine structures bearing four contiguous stereogenic centers, which are situated in all *trans* positions. The absolute configuration of the natural antibiotic **1** was determined as (2*R*,3*R*,4*R*,5*R*).[6] This was further confirmed by X-ray crystallographic studies of (−)-codonopsine **2**.[7]

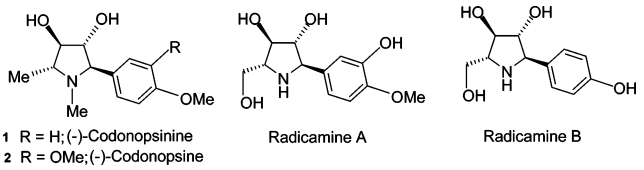
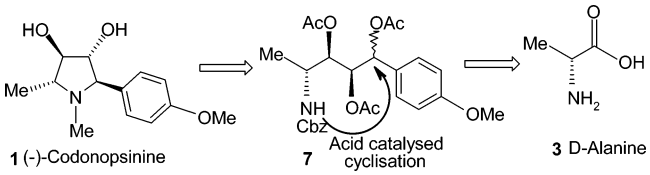


FIGURE 1. Structures of some important pyrrolidine iminosugar compounds carrying an aromatic substituent.

SCHEME 1. Retrosynthetic Analysis of (−)-Codonopsinine



Because of the interesting pharmacological activity and unique structural features, these iminosugar compounds have drawn considerable attention from many synthetic organic chemists. Although several synthetic approaches have been reported for (−)-codonopsinine **1**,[8] many of them involve long reaction sequences and also show poor stereoselectivity in key bond-forming reactions. Therefore the need for an efficient synthesis still remains. Consequently, development of new strategies and approaches to address the above challenges continue to be a worthwhile research goal.

Our interest in the development of new and efficient synthetic routes to some important chiral pyrrolidine compounds[9] prompted

* To whom correspondence should be addressed. Tel: + 91-040-27160123, Ext 2614. Fax: + 91-40-27193108.

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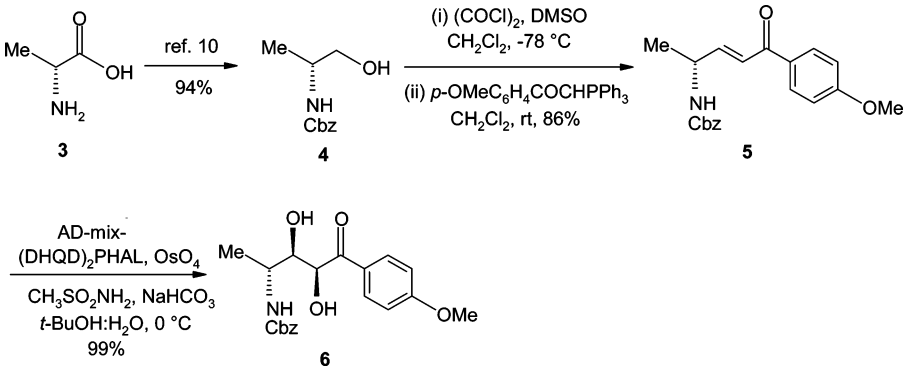
TABLE 1. Stereoselective Dihydroxylation Studies on Compound 5 under Various Conditions

entry	reagents	solvent (ratio)	conditions (time)	yield (%)[a]	dr
1	OsO_4 (1 mol %), NMO	acetone/water (5:1)	0 °C to rt (1 h)	92	54:46[b]
2	AD-mix-β (1.4 g/mmol)	*tert*-butanol/water (1:1)	0 °C (48 h) and 10 °C (48 h)	62	53:47[c]
3	AD-mix-β (1.4 g/mmol), OsO_4 (0.6 mol %), $CH_3SO_2NH_2$ (95 mg/mmol), $NaHCO_3$ (0.25 g/mmol)	*tert*-butanol/water (1:1)	0 °C (15 h)	96	89:11[b]
4	AD-mix-β (1.4 g/mmol), OsO_4 (0.6 mol %), $(DHQD)_2PHAL$ (4 mol %), $CH_3SO_2NH_2$ (95 mg/mmol), $NaHCO_3$ (0.25 g/mmol)	*tert*-butanol/water (1:1)	0 °C (15 h)	99	91:9[b]

[a] Yield represents the combined diastereomers after purfication. [b] Determined from HPLC. [c] Determined from ^{1}H NMR data.

SCHEME 2. Synthesis of the Basic Carbon Skelton of (−)-Codonopsinine



us to investigate the total synthesis of (−)-codonopsinine **1**, starting from simple and readily available amino acid D-alanine as a chiral template. Our retrosynthetic strategy is outlined in Scheme 1. The key transformations in the proposed strategy will involve (i) Sharpless asymmetric dihydroxylation reaction to install the hydroxy groups at C3 and C4 positions stereoselectively and (ii) an intramolecular acid-catalyzed amidocyclization protocol to construct the pivotal pyrrolidine core of the target molecule.

Using a literature procedure, D-alanine was readily converted to N-Cbz-protected alaninol derivative **4** (Scheme 2) in one pot (94%).[10] The alcohol functionality of the compound **4** was oxidized to aldehyde under Swern conditions. The resultant aldehyde on Wittig reaction with (4-methoxyphenacyl)triphenylphosphorane[11] yielded the *trans*-α,β-unsaturated ketone **5** (86%). Further, the compound **5** was subjected to dihydroxylation under various conditions; the results are summarized in Table 1. Using OsO_4 (entry 1) at room temperature for 1 h, the corresponding dihydroxylated compound **6** was obtained in 92% yield. Unfortunately this reaction gave poor stereoselectivity. Sharpless asymmetric dihydroxylation (SAD) using AD-mix-β [1.4 g contains $(DHQD)_2PHAL$ (7.73 mg, 1.0 mol %), $K_3Fe(CN)_6$ (980 mg, 3 mmol), $K_2OsO_2(OH)_4$ (1.46 mg, 0.004 mmol), K_2CO_3 (411 mg, 3 mmol)] at 0 °C for 48 h and another 48 h at 10 °C gave **6** in 62% yield also with poor stereoselectivity (entry 2). Treatment of compound **5** under modified SAD[12] (entry 3) condition at 0 °C for 15 h gave the desired diol derivative **6** in 96% yield (dr = 89:11). Finally, increasing the ligand concentration from 1 mol % to 5 mol % in the above modified SAD (entry 4) reaction at 0 °C for 15 h resulted in the formation of diol derivative **6** in 99% yield with increased diastereoselectivity (dr = 91:9). The product was carried to the next reaction without separating the diastereomers.

Reduction of compound **6** with $NaBH_4$ resulted in the formation of triol as a diastereomeric mixture (Scheme 3), which was utilized in the next reaction without purification. Treatment of the triol with the acetic anhydride in dichloromethane afforded the diastereomeric triacetate derivative **7** (∼1:1) in 90%. For the synthesis of the 2,5-*trans*-substituted pyrrolidine core, the diastereomeric mixture of **7**[13] was treated with trifluoroacetic acid in dichloromethane at 0 °C for 4 h to give the single isomer **8**[14] in 81% yield.

The stereoselective formation of pyrrolidine compound **8** from **7** can be explained through intramolecular S_N1 reaction via resonance-stabilized benzylic carbocation. The benzylic carbocation can be further stabilized by the neighboring acetoxy group to give a *trans* dioxolane carbocation (acetoxonium ion) intermediate, thereby further facilitating the approach of the N-nucleophile preferentially from the opposite face (Scheme 4) and giving stable 2,5-*trans*-substituted pyrrolidine **8**.[15] When compound **8** was treated with LAH in THF under reflux for 5 h, it smoothly led to the natural product (−)-codonopsinine **1** in 74% yield. In the above reaction concomitant convertion of N-Cbz to N-Me took place along with the deprotection of the

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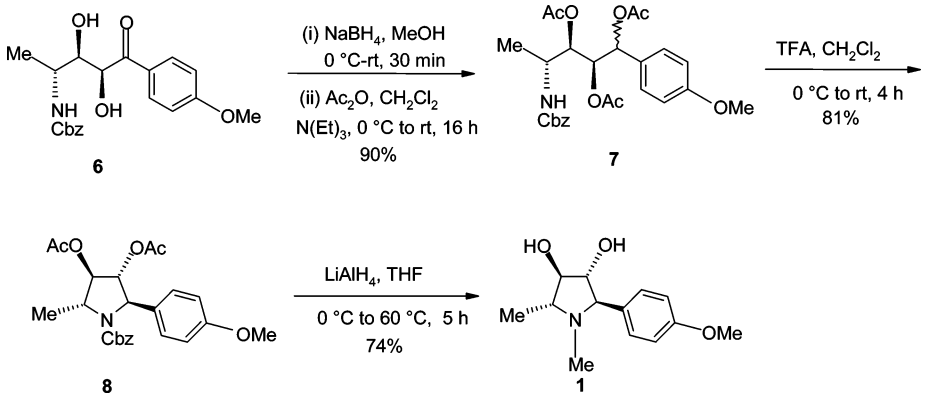
(12) Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605−606.

(13) Only for the sake of characterization, both diastereomers were separated and spectral data were taken.

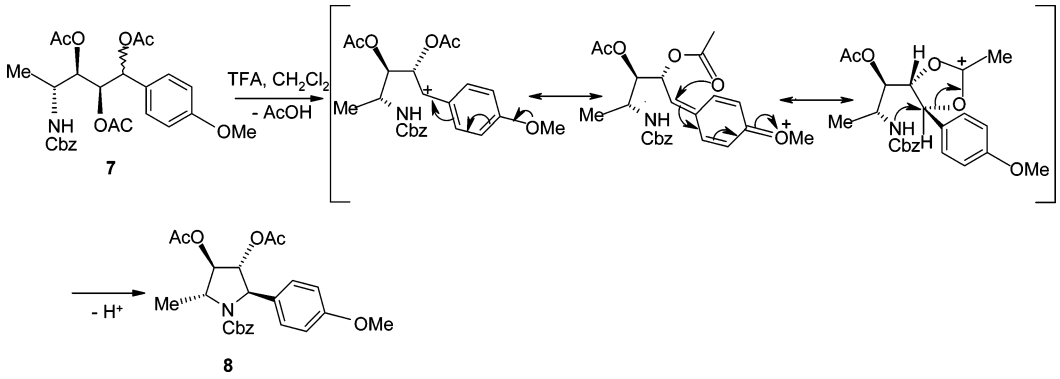
(14) Acid-mediated cyclization gave exclusive formation of compound **8**. We did not observe any other product, resulting from the minor diastereomer of compound **6**.

(15) Because of the existence of compound **8** in rotamers, we were unable to determine the isomeric purity at this stage. Therefore compound **8** was taken to the next reaction and treated with LAH, which gave only (−)-codonopsinine **1**. It denotes that the acid-catalysed cyclization gave exclusively *trans* isomer **8**.

SCHEME 3. Total Synthesis of (−)-Codonopsinine



SCHEME 4. Proposed Mechanism for the Stereoselective Cyclization



acetates. The spectral and analytical data of synthetic (−)-codonopsinine **1** were in excellent agreement with the reported values.[3a]

In summary, a novel, short, and efficient stereoselective synthesis of natural (−)-codonopsinine **1** was developed in good overall yield starting from D-alanine, utilizing highly stereoselective intramolecular amidocyclization protocol as the key step. The present synthesis compares well with the reported methods and offers an attractive alternate approach to the title compound. Application of the above strategy for the synthesis of some important pyrrolidine and piperidine molecules is in progress.

Experimental Section

(*R*,*E*)-Benzyl 5-(4-Methoxyphenyl)-5-oxopent-3-en-2-ylcarbamate (5). To a solution of DMSO (1.36 mL, 19.13 mmol) in dichloromethane (5 mL) was added oxalyl chloride (0.83 mL, 9.56 mmol) dropwise at −78 °C. After stirring for 30 min, a solution of the amido alcohol **4** (1 g, 4.78 mmol) in dichloromethane (15 mL) was added over a period of 10 min. After stirring for 30 min at −78 °C, the reaction mixture was quenched with diisopropyl ethylamine (4.16 mL, 23.92 mmol). The reaction mixture was slowly warmed to 0 °C, diluted with chloroform (30 mL), washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was dissolved in dichloromethane (20 mL), and (4-methoxyphenacyl)triphenylphosphorane (2.35 g, 5.74 mmol) was added and stirred for 4 h at room temperature. The reaction mixture was diluted with chloroform (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed over silica gel (hexane/ethyl acetate = 5:1) to afford the *trans* compound **5** (1.4 g, 86%) as colorless needles: mp 101−103 °C; $[\alpha]^{34}_D$ = +7.7 (*c* 0.3, $CHCl_3$); IR (KBr) 3301, 1683, 1568, 1535, 1457, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 6.8 Hz), 3.86 (3H, s), 4.49−4.58 (1H, br s), 4.85 (1H, d, J = 8.0 Hz), 5.09 (2H, s), 6.84 (1H, dd, J = 5.2, 15.2 Hz), 6.87 (2H, d, J = 8.0 Hz), 6.92 (1H, d, J = 15.2 Hz), 7.24−7.36 (5H, m), 7.87 (2H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 48.1, 55.4, 66.9, 113.8, 124.2, 128.1, 128.5, 130.5, 130.9, 136.3, 147.5, 155.5, 163.5, 188.7; LC-MS *m*/*z* 340 (M^+ + 1); HRMS calcd for $C_{20}H_{21}NO_4Na$ 362.1368, found 362.1380.

Benzyl (2*R*,3*R*,4*S*)-3,4-Dihydroxy-5-(4-methoxyphenyl)-5-oxopentan-2-ylcarbamate (6). To a stirred solution of AD-mix-β (3.3 g) in 1:1 *tert*-butanol/water (15 mL each) at room temperature were added toluene solutions of OsO_4 (2.83 mL, 0.05 M, 0.6 mol %), $(DHQD)_2PHAL$ (0.73 g, 4 mol %), $NaHCO_3$ (0.59 g, 7.05 mmol), and $MeSO_2NH_2$ (0.22 g, 2.35 mmol) sequentially. After 15 min, the clear solution was cooled to 0 °C ,and to it was added compound **5** (0.8 g, 2.35 mmol) at once. After 15 h of stirring at 0 °C, ethyl acetate (10 mL) was added followed by $Na_2S_2O_3$ (3.53 g), and the solution was warmed to room temperature with vigorous stirring for 1 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with the brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on silica gel (hexane/ethyl acetate = 2:1) to afford compound **6** (0.87 g, 99%) as a white powder: mp 144−146 °C; $[\alpha]^{34}_D$ = −55.7 (*c* 0.11, $CHCl_3$) [dr = 91:9 was determined from HPLC using C_{18} column (CH_3CN/H_2O = 34:66), flow rate = 1 mL/min]; IR (KBr) 3484, 3302, 1688, 1550, 1459, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, d, J = 6.4 Hz), 2.43 (1H, d, J = 9.4 Hz), 3.90 (3H, s), 3.94−4.11 (2H, m), 4.22 (1H, d, J = 4.9 Hz), 5.08−5.14 (2H, m), 5.16 (1H, d, J = 4.9 Hz), 5.47 (1H, d, J = 8.3 Hz), 6.97 (2H, d, J = 8.7 Hz), 7.30−7.39 (5H, m), 7.87 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 50.9, 55.6, 66.8, 72.8, 73.9, 114.2, 125.9, 128.1, 128.5, 130.9, 135.4, 136.4, 156.4, 164.3, 199.0; LC-MS *m*/*z* 374 (M^+ + 1); HRMS calcd for $C_{20}H_{23}NO_6Na$ 396.1423, found 396.1434.

(1*R*/S,2*R*,3*R*,4*R*)-4-(Benzyloxycarbonylamino)-1-(4-methoxyphenyl)pentane-1,2,3-triyl Triacetate (7). To a solution of keto diol **6** (0.62 g, 1.62 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (0.07 g, 1.99 mmol) in portions over a period of 10 min, and the mixture was stirred at the same temperature for 90 min. The mixture was neutralized by adding saturated aqueous NH_4Cl, and volatiles were removed under vacuum. The crude residue was subjected to flash column chromatography over silica gel (hexane/ethyl acetate = 1:1) to obtain a diastereomeric mixture of triol as a white solid. To the stirred diastereomeric mixture of triol in dichloromethane (10 mL) were added triethyl amine (1.39 mL, 9.97 mmol), acetic anhydride (0.47 mL, 4.98 mmol), and 4-dimethylamino pyridine (5 mg) at 0 °C. After completion of the addition, the reaction mixture was allowed to remain at room temperature and was stirred for 16 h. The reaction mixture was diluted with chloroform (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed over silica gel (hexane/ethyl acetate = 8.5:1.5) to afford the faster moving isomer of compound **7** (0.39 g, 47%) as a colorless oil: $[\alpha]^{33}_D = +10.6$ (*c* 1.55, $CHCl_3$); IR (neat) 3349, 1747, 1613, 1517, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, *J* = 6.8 Hz), 1.83 (3H, s), 1.98 (3H, s), 2.08 (3H, s), 3.76 (3H, s), 3.90−4.07 (1H, m), 4.85 (1H, d, *J* = 9.8 Hz), 5.00 (2H, dd, *J* = 12.1, 17.4 Hz), 5.15 (1H, dd, *J* = 2.3, 7.6 Hz), 5.53 (1H, dd, *J* = 2.3, 9.1 Hz), 5.63 (1H, d, *J* = 9.1 Hz), 6.7 (2H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz), 7.26−7.33(5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.5, 20.6, 20.9, 46.9, 55.1, 66.8, 71.4, 72.2, 72.5, 113.6, 128.0, 128.4, 128.8, 129.0, 129.4, 136.4, 155.4, 159.7, 169.2, 169.4, 170.4; LC-MS *m*/*z* 519 ($M^+ + H_2O$); HRMS calcd for $C_{26}H_{31}NO_9Na$ 524.1896, found 524.1903. The slower moving isomer of compound **7** (0.36 g, 43%) was eluted (hexane/ethyl acetate = 8.4:1.6) as a colorless oil: $[\alpha]^{32}_D = +72.9$ (*c* 0.4, $CHCl_3$); IR (neat) 3384, 1748, 1613, 1516, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.8 Hz), 2.02 (3H, s), 2.05 (3H, s), 2.1 (3H, s), 3.77 (3H, s), 3.89−4.03 (1H, m), 4.60 (2H, m), 5.03 (2H, dd, *J* = 12.5, 15.5 Hz), 5.48 (1H, dd, *J* = 3.2, 8.2 Hz), 5.72 (1H, d, *J* = 8.2 Hz), 6.8 (2H, d, *J* = 8.7 Hz), 7.19 (2H, d, *J* = 8.7 Hz), 7.23−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.7, 20.9, 47.2, 55.2, 66.8, 72.5, 73.0, 74.1, 114.3, 127.7, 128.0, 128.1, 128.5, 128.9, 136.5, 155.4, 160.1, 169.8, 170.0; LC-MS *m*/*z* 519 ($M^+ + H_2O$); HRMS calcd for $C_{26}H_{31}NO_9Na$ 524.1896, found 524.1919.

(2*R*,3*R*,4*R*,5*R*)-Benzyl 3,4-Diacetoxy-2-(4-methoxyphenyl)-5-methylpyrrolidine-1-carboxylate (8). To a stirred solution of the mixture of diastereomeric triacetate **7** (0.55 g, 1.09 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1.0 mL) in dichloromethane (2 mL) dropwise at 0 °C over a period of 5 min. After completion of the addition the reaction mixture was warmed to room temperature, and stirring was continued at the same temperature for 4 h. The reaction mixture was neutralized with $NaHCO_3$ at 0 °C, filtered through a celite pad, and washed with chloroform (2 × 20 mL). The chloroform layer was washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified through silica gel column chromatography (hexane/ethyl acetate = 6:1) to afford single desired pyrrolidine diacetate derivative **8** (0.39 g, 81%) as colorless oil: $[\alpha]^{34}_D = +20.2$ (*c* 0.11, $CHCl_3$); IR (neat) 1745, 1705, 1613, 1514, 1454, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* = 6.8 Hz), 1.81 (3H, s), 2.15 (3H, s), 3.80 (3H, s), 4.28 (1H, m), 4.76−5.2 (5H, m), 6.73−6.83 (3H, m), 7.06−7.39 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, *18.3, 20.7, 21.0, 55.2, *60.7, 61.4, 66.7, *67.2, 67.6, *68.0, 80.3, *81.3, *81.5, 82.4, 113.5, *113.6, 127.1, 127.3, 127.5, *127.6, 128.1, *128.2, *128.5, 131.6, 136.1, 154.2, 158.8, 169.5, 169.6. *rotamer; LC-MS *m*/*z* 442 ($M^+ + 1$); HRMS calcd for $C_{24}H_{27}NO_7Na$ 464.1685, found 464.1699.

(2*R*,3*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol [(-)-codonopsinine] (1). To a stirred suspension of $LiAlH_4$ (0.07 g, 1.9 mmol) in THF (3 mL) was added pyrrolidine derivative **8** (0.28 g, 0.63 mmol) in THF (5 mL) at 0 °C. After the completion of addition the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to 0 °C, and quenched with water (0.07 mL), 15% NaOH (0.07 mL), and water (0.20 mL) successively. After 15 min of stirring at room temperature, the reaction mixture was filtered through a celite pad, washed with chloroform (3 × 10 mL), and evaporated under vacuum. The residue was purified through silica gel column chromatography ($CHCl_3$/MeOH = 7:1) to afford the codonopsinine **1** (0.112 g, 74%) as a white powder: mp 168−170 °C, $[\alpha]^{34}_D = -8.7$ (*c* 0.3, MeOH) {lit.[3a] mp 169−170 °C, $[\alpha]^{20}_D = -8.8$ (*c* 0.1, MeOH)}; IR (KBr) 3378, 1580, 1515, 1054 cm^{-1}; ^1H NMR (300 MHz, pyridine-d_5) δ 1.31 (3H, d, *J* = 6.8 Hz), 2.20 (3H, s), 3.62−3.70 (4H, m), 4.00 (1H, d, *J* = 6.4 Hz), 4.36 (1H, dd, *J* = 3.8, 4.2 Hz), 4.60 (1H, dd, *J* = 4.2, 6.0 Hz), 6.96 (2H, d, *J* = 8.7 Hz), 7.58 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 34.8, 55.2, 65.2, 74.4, 85.0, 87.2, 114.2, 129.9, 134.9, 159.3; LC-MS *m*/*z* 238 ($M^+ + 1$); HRMS calcd for $C_{13}H_{20}NO_3$ 238.1443, found 238.1449.

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Supporting Information Available: Spectral (^1H and ^{13}C NMR) data for all synthetic intermediates (**1**, **5**−**8**) and HPLC diagram of compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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