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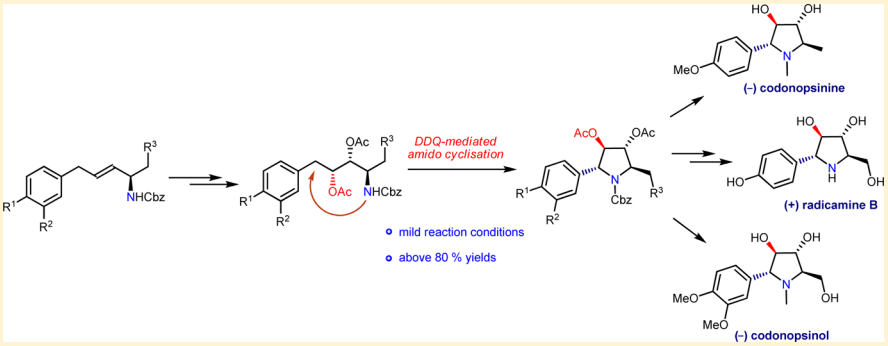
# DDQ-Promoted Benzylic/Allylic sp$^3$ C−H Activation for the Stereoselective Intramolecular C−N Bond Formation: Applications to the Total Synthesis of (−)-Codonopsinine, (+)-5-*epi*-Codonopsinine, (+)-Radicamine B, and (−)-Codonopsinol

Macha Lingamurthy, Yerri Jagadeesh, Katakam Ramakrishna, and Batchu Venkateswara Rao*

Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad, 500007 Telangana, India

Supporting Information




**ABSTRACT:** This is the first report on an intramolecular C−N bond formation of an amide-tethered benzylic/allylic system using DDQ under neutral conditions which has been successfully applied to the total synthesis of naturally occurring pyrolidine alkaloids. The key steps for the synthesis of corresponding precursors involve Julia−Kociensky olefination/cross-metathesis and dihydroxylation reactions, and this methodology is also extended to the $\omega$-unsaturated *N*-sulfanilamide to furnish piperidines.

## INTRODUCTION

Presently, oxidative functionalization of C−H bonds is an important strategy in organic synthesis. It provides an excellent approach to make complex molecules from readily accessible substrates.[1] Direct conversion of a C−H bond into a C−N bond is a useful method for the synthesis of valuable nitrogen-containing compounds, which are prevalent in pharmaceuticals, fine chemicals, and natural products. Several approaches have been developed for this purpose using metal catalysts and Hofmann−Loffler−Freytag reaction that involve activation of benzylic/allylic sp$^3$ C−H to form a C−N bond.[2] In general, the reaction onto nitrogen to give a C−N bond is more complicated, since it depends on the choice of protecting group, pH, etc., than the analogues reactions with O- and C-nucleophiles. Oxidation of benzylic and allylic C−H bonds with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) giving rise to carbenium ions and their reaction with carbon nucleophiles intramolecularly to give functionalized systems is a useful approach for making cyclic compounds.[3] Conversion of a benzylic/allylic C−H to a C−N bond in the presence of DDQ has not been exploited, and there are only a couple of reports known for its intermolecular formation.[4] To the best of our knowledge its intramolecular variant has not been studied. The development of such kind of strategy will provide an excellent opportunity to create nitrogen heterocyclics under metal-free conditions. Herein, we report the DDQ-mediated activation of a benzylic/allylic sp$^3$ C−H bond and its coupling with amide to get a C−N bond intramolecularly and application of this strategy for the synthesis of pyrrolidine alkaloids such as (−)-codonopsinine **1**,[5] (−)-codonopsinol **3**,[6] (+)-radicamine B **5**,[7] and (+)-5-*epi*-codonopsinine **6**.

(−)-Codonopsinine **1** and (−)-codonopsine **2** (Figure 1) were isolated in 1969 from *Codonopsis clematidea*. These two compounds have shown antibiotic and hypotensive activities without interfering the central nervous system in animal tests.[8] (−)-Codonopsinol **3** was isolated from *C. clematidea*, whose aerial parts are useful for treating liver diseases.[6a] (−)-Codonopsinol **3** was found to have an inhibitary activity against $\alpha$-glucosidase of yeast and *Bacillus stearothermophilus* lymph.[6c] Radicamine A **4** and radicamine B **5** were isolated from *Lobelia chinenis Lour*, an herb used in Chinese folk medicine.[9a,b] This herb is known for its diuretic, antidote, and hemostat activity. It also acts as a carcinostatic agent for stomach cancer and was found to exhibit inhibitory activity on $\alpha$-glucosidase.[9c,d] Recently, interest in the total synthesis of codonopsinine **1** and related structures originated because of their pharmacological activity and interesting structural features which

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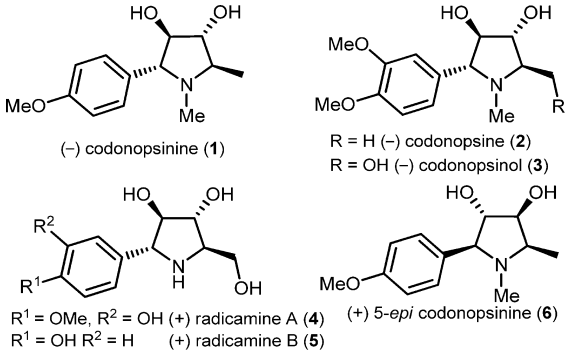



**Figure 1.** Pyrrolidine natural products.

constitute a 1,2,3,4-tetra-substituted pyrrolidine ring bearing four contiguous streogenic centers (2*R*, 3*R*, 4*R*, and 5*R*) in an all-trans arrangement (Figure 1).

## RESULTS AND DISCUSSION

The retrosynthetic plan was designed for the above natural products based on the envisaged DDQ-mediated C–N bond formation from **7** (Scheme 1).

Initially we planned to synthesize (−)-codonopsinine **1** starting from commercial available alcohol **8**. In the first step, compound **8** was converted to sulfone derivative **9** for conducting Julia–Kocienski olefination. Alcohol **8** was converted to sulfide by using Mitsunobu conditions in the presence of TPP, DIAD, and 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation with $H_2O_2$, and ammonium molybdate afforded the required sulfone **9**. Julia–Kocienski coupling[10] of the compound **9** with aldehyde **10** (obtained from D-alanine)[5c] in the presence of KHMDS at −78 °C afforded *E*-olefin **11** (Scheme 2).

The next step was to construct the diol **12** from **11** using dihydroxylation under various conditions (Table 1). For this purpose AD-mix-$\beta$ was chosen as a chiral reagent. When compound **11** was subjected to dihydroxylation with AD-mix-$\beta$ compounds **12** and **13** were formed in 50% yield (dr = 53:47, mismatched).[5c,11] To improve the yields and selectivity, compound **11** was subjected to modified SAD conditions (entries 2 and 3, Table 1); it gave a good yield of diols but without much improvement in diastereoselectivity. When dihydroxylation was carried with simple $OsO_4$ slightly better diastereoselectivity (dr = 70:30) with 90% yield was afforded (entry 4, Table 1). Treatment of compound **11** with AD-mix-$\alpha$ under modified SAD conditions afforded the diol **13** as a major product in 90% yield with good diastereoselectivity (dr = 5:95, matched) (entry 5, Table 1).

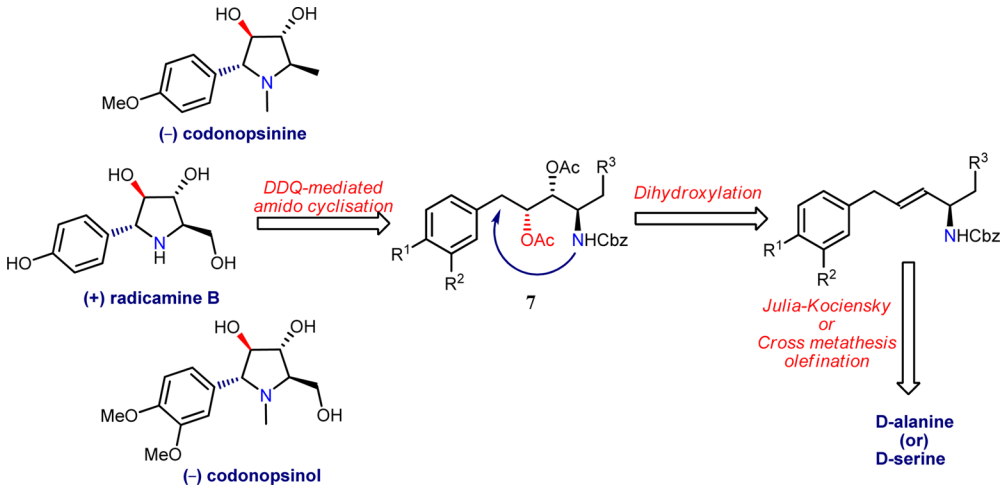
Acetylation of compounds **12** and **13** was carried out separately to furnish the corresponding diacetylated compounds **14** and **15**, respectively (Scheme 2). After having the acetate derivatives in hand, we proceeded further to study the DDQ-mediated amido cyclization on **14** to obtain the pyrrolidine core **16**.

Several explorations were carried out under various conditions in the presence of DDQ to get **16** from **14**, and the results are summarized in Table 2. The conversion was examined in the presence of various solvents. Chlorinated solvents gave poor yields (entries 1–3, Table 2), whereas in THF no reaction was observed (entry 4, Table 2). Dioxane and nitromethane gave moderate yields (entries 5 and 6, Table 2). In dry acetonitrile, the reaction was sluggish at room temperature, whereas at 85 °C for 4 h it gave the single diastereomer **16** in 90% yield. Generally, DDQ oxidation is conducted in aprotic polar solvents such as nitromethane, dioxane, acetonitrile, etc. In the conversion better yields were obtained in acetonitrile under reflux condition (entry 8, Table 2). In fact, there have been some studies reported earlier in support of acetonitrile as a better choice for DDQ oxidation.[3c,d]

Treatment of compound **16** with $LiAlH_4$ in dry THF under reflux condition for 6 h gave the (−)-codonopsinine **1** in 80% yield (Scheme 3). The spectral ($^1H$ and $^{13}C$) and analytical (optical rotation and melting point) data of synthetic (−)-codonopsinine **1** were in excellent agreement with the reported values.[5c] On the basis of these results we then proceeded to apply this methodology for the synthesis of other target molecules. A similar reaction sequence was carried on **15** to complete the total synthesis of (+)-5-*epi*-codonopsinine **6** in 80% yield (for 2 steps) (Scheme 3). The stereochemistry of compound **6** was confirmed with 1D nuclear overhauser enhancement (NOE) correlations (see Supporting Information).

The high stereoselectivity in this reaction can be explained as follows. The benzylic carbocation formed by DDQ oxidation was further stabilized by the neighboring acetoxy group to give

**Scheme 1. Retrosynthetic Analysis of (−)-Codonopsinine and Related Natural Products**



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**Scheme 2. Synthesis of the Basic Carbon Skeleton of (−)-Codonopsinine**

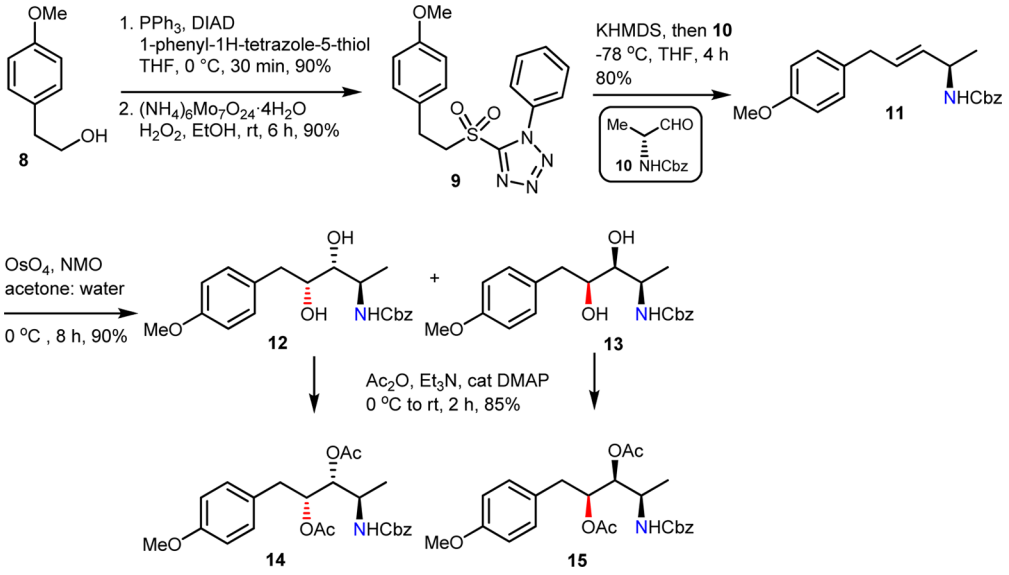
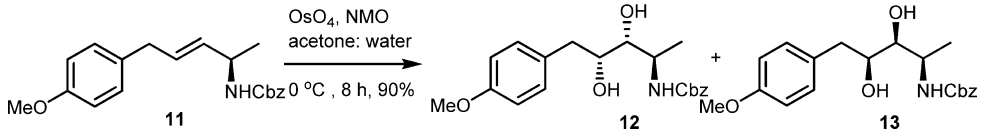



**Table 1. Asymmetric Dihydroxylation Studies on Compound 11 under Various Reaction Conditions**




| entry | reagents | solvents (ratio) | conditions | yield[a] | dr[b] (12 and 13) |
|---|---|---|---|---|---|
| 1 | AD-mix-$\beta$ (1.4 g/mmol) | *tert*-butanol:water (1:1) | 0 °C (24 h) to rt 24 h | 50 | 53:47 |
| 2 | AD-mix-$\beta$ (1.4 g/mmol)<br>$OsO_4$ (0.6 mol %)<br>$CH_3SO_2NH_2$ (95 mg/mmol)<br>$NaHCO_3$ (0.25 g/mmol | *tert*-butanol:water (1:1) | 0 °C (15 h) | 90 | 60:40 |
| 3 | AD-mix-$\beta$ (1.4 g/mmol)<br>$OsO_4$ (0.6 mol %)<br>$(DHQD)_2PHAL$ (4 mol %)<br>$CH_3SO_2NH_2$ (95 mg/mmol)<br>$NaHCO_3$ (0.25 g/mmol) | *tert*-butanol:water (1:1) | 0 °C (15 h) | 90 | 65:35 |
| 4 | $OsO_4$ (1 mol %), NMO | acetone:water (4:1) | 0 °C (8 h) | 90 | 70:30 |
| 5 | AD-mix-$\alpha$ (1.4 g/mmol)<br>$OsO_4$ (0.6 mol %)<br>$(DHQ)_2PHAL$ (4 mol %)<br>$CH_3SO_2NH_2$ (95 mg/mmol)<br>$NaHCO_3$ (0.25 g/mmol) | *tert*-butanol:water (1:1) | 0 °C (15 h) | 90 | 5:95 |

[a]Yield represents the separable diastereomers after purfication. [b]Diastereomers were separable.

a *trans*-dioxolane carbocation (acetoxonium ion) intermediate, thereby facilitating the approach of the *N*-nucleophile preferentially from the opposite face to yield the pyrrolidine core **16** with C-2 aryl and C-3 hydroxy groups in the trans position (Scheme 4).

For the synthesis of (+)-radicamine B **5**, the alcohol **17**[12] was converted into sulfone **18** by following the same procedure as described for compound **11**. 4-Benzyloxyethyl sulfone **18** on Julia−Kociensky olefination with aldehyde **19** (prepared from D-serine)[13] in dry THF at −78 °C gave *E*-olefin **20**. Further, compound **20** was subjected to dihydroxylation using $OsO_4$ in acetone and water at 0 °C for 8 h to afford the diol, which on treatment with $CuCl_2·2H_2O$ in $CH_3CN$ at 0 °C gave the triol. Subsequent acetylation afforded the separable triacetates **21** and **22** in a 70:30 ratio, respectively. Treatment of triacetate **21** with DDQ afforded **23** in 82% yield. The cyclic compound **23** on deacetylation with $K_2CO_3$ in MeOH yielded the carbamate **24** (84%). The spectral ($^1H$ and $^{13}C$) and analytical (optical rotation) data of **24** were in excellent agreement with the reported values (Scheme 5).[7d] Conversion of **24** to radicamine B **5** was reported earlier by our group.[7d]

For the synthesis of (−)-codonopsinol **3** we adopted a cross-metathesis approach for the synthesis of olefine unit **27**, since the starting material 3,4-dimethoxy allylbenzene **26** was commercially available. Cross-metathesis between **26** and olefin **25**[13] was carried out in the presence of Grubbs second-generation catalyst and CuI in dry $CH_2Cl_2$ at 45 °C to give exclusively the *E*-olefin **27** in 80% yield.[14] Compound **27** was converted into separable triacetates **28** and **29** (70:30 ratio) in good yields using the procedure described for **20**. Cyclization of major triacetate **28** with DDQ in dry $CH_3CN$ under reflux for 4 h afforded the *trans*-pyrrolidine compound **30** in 90% yield.



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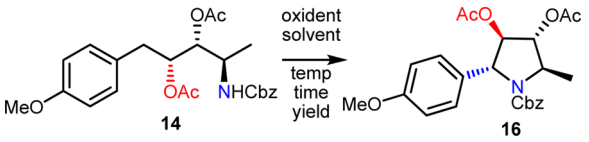
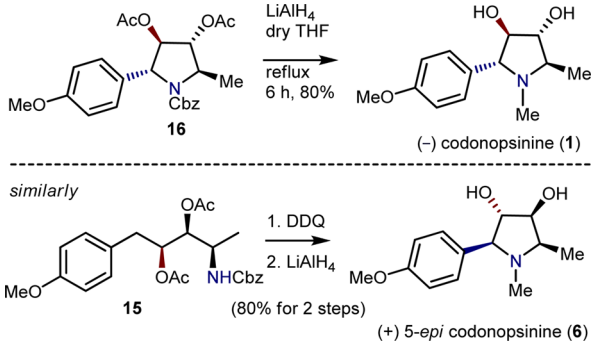
**Table 2. Optimization of Reaction Conditions**[a]




| entry | oxidant | solvent | temp (°C) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | DDQ | $CHCl_3$ | refux | 12 h | 10 |
| 2 | DDQ | $CH_2Cl_2$ | reflux | 12 h | 20 |
| 3 | DDQ | $ClCH_2CH_2Cl$ | reflux | 12 h | 30 |
| 4 | DDQ | THF | reflux | 12 h | no reaction[c] |
| 5 | DDQ | $CH_3NO_2$ | reflux | 6 h | 65 |
| 6 | DDQ | Dioxane | reflux | 6 h | 70 |
| 7 | DDQ | $CH_3CN$ | rt | 12 h | trace |
| 8 | DDQ | $CH_3CN$ | reflux | 4 h | 90 |

[a]**14** (1.0 mmol), DDQ (1.1 mmol), and indicated solvent temperature and time. [b]Isolated yield. [c]On the basis of TLC analysis.

**Scheme 3. Completion of Total Synthesis of (−)-Codonopsinine 1 and (+)-5-*epi*-Codonopsinine 6**




Treatment of **30** with $LiAlH_4$ in dry THF under reflux for 6 h afforded the (−)-codonopsinol **3** in 80% yield. The spectral ($^1H$ and $^{13}C$) and analytical (optical rotation and melting point) data of synthetic (−)-codonopsinol **3** were in excellent agreement with the reported values (Scheme 6).[6b]

Next, we turned our attention to study the DDQ-mediated intramolecular amido cyclization on allylic substrate. In 2012, Cossy et al. reported[2d] an elegant approach for allylic activation in the presence of Rh metal catalyst. In their approach, (*R*)-(+)-*β*-citronellol **31** was converted to *N*-sulfonylamines **32**. Intramolecular allylic amination of **32** in the presence of $[(MeCN)_3RhCp^*](SbF_6)_2/Cu(OAc)_2\cdot H_2O$ in refluxing dichloroethane for 16 h afforded the diastereomeric mixture of *cis*-piperidine **33** and *trans*-piperidine **34** in a 9:1 ratio in 27% yield.

We chose **32** to study the DDQ-mediated allylic amido cyclization. When compound **32** was treated with DDQ in dry $CH_3CN$, interestingly the reaction proceeded at 0 °C to rt to afford a diastereomeric mixture of compounds **33** and **34** in just 30 min with 90% yield. Here the *trans*-piperidine was formed as a major product (ratio 2:1). The spectral ($^1H$ and $^{13}C$) data of piperidine compounds were in excellent agreements with the reported values (Scheme 7).[2d] Thus, the DDQ is able to give metal-free condition to synthesize the above compounds.

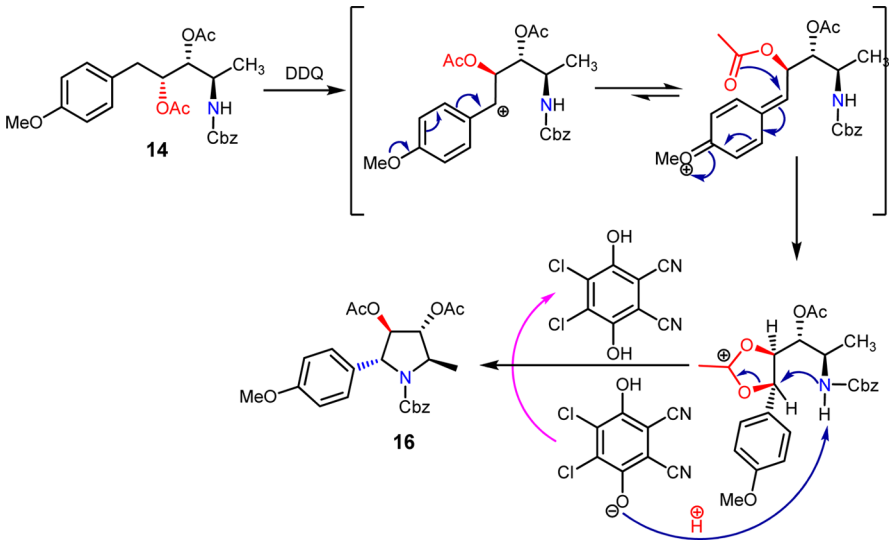
## CONCLUSIONS

In summary, we developed a novel reaction, i.e., DDQ-mediated stereoselective intramolecular dehydrogenative amido cyclization, which was successfully demonstrated for the synthesis of polyhydroxylated pyrrolidine alkaloids. We also extended this methodology to prepare piperidines by allylic C($sp^3$)−H activation. In most of the earlier approaches C−N bond formation requires prefunctionalization of substrates, whereas our strategy does not require any such kind of preactivation. Also, this method offers significant advantages such as mild reaction conditions, broad substrate scope, high conversions, metal-free conditions, and excellent diastereoselectivity, thus making it quite simple, more convenient, and practical. Further application of this methodology on different substrates is under progress.

## EXPERIMENTAL SECTION

**General Remarks.** All solvents were dried according to standard literature procedures. The reactions were performed in oven-dried round-bottom flasks, the flasks were fitted with rubber septa, and the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh.

**Scheme 4. Plausible Reaction Pathway**



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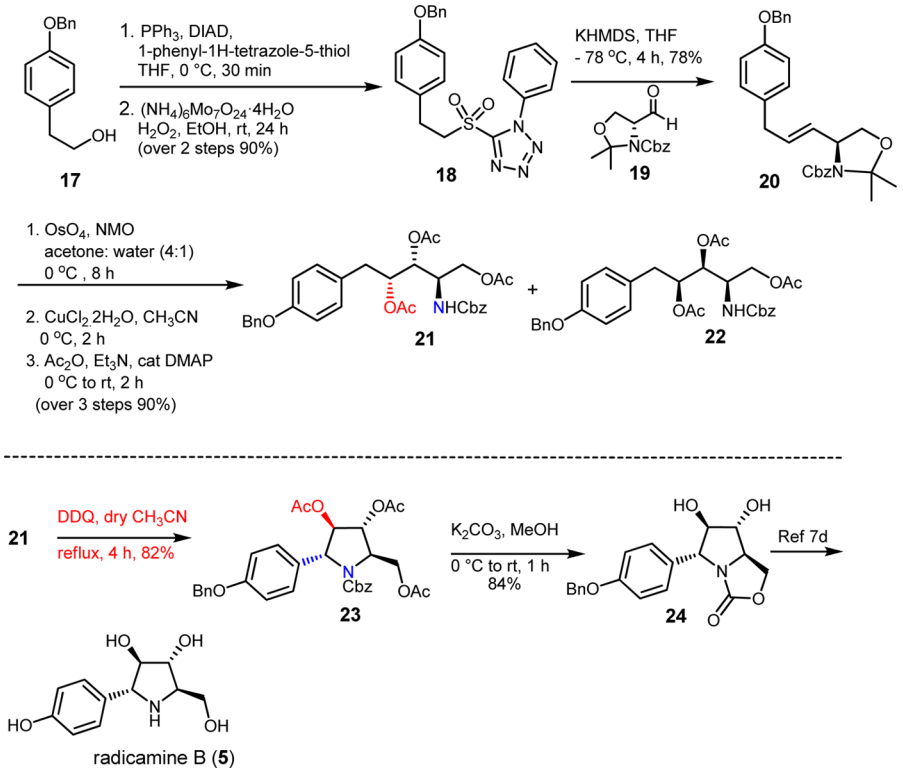
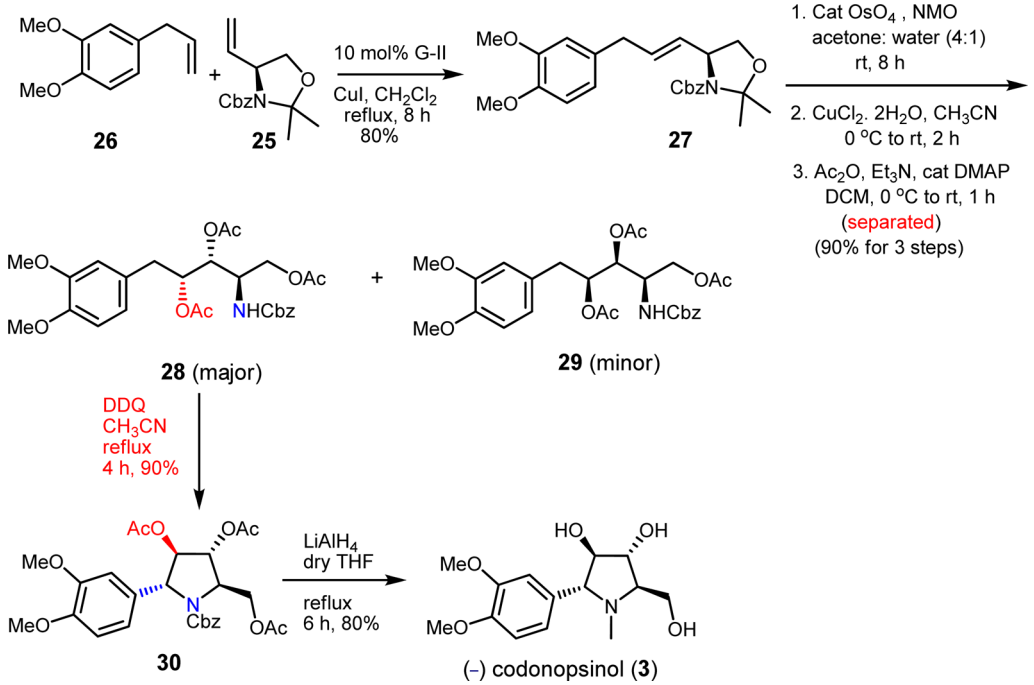
**Scheme 5. Total Synthesis of (+)-Radicamine B 5**




**Scheme 6. Total Synthesis of (−)-Codonopsinol 3**




Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. AD-mix-$\beta$ mixture contains $(DHQ)_2PHAL$ (0.0016 mol), potassium carbonate (0.4988 mol), potassium ferricyanide (0.4988 mol), and potassium osmate dihydrate (0.0007 mol). AD-mix-$\alpha$ mixture contains $(DHQ)_2PHAL$ (0.0016 mol), potassium carbonate (0.4988 mol), potassium ferricyanide (0.4988 mol), and potassium osmate dihydrate (0.0007 mol). IR spectra were recorded on an FT-IR spectrometer. $^1H$ and $^{13}C$ NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts ($\delta$) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants ($J$) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI)



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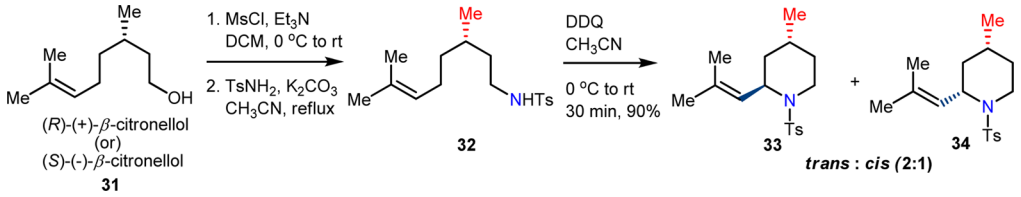
**Scheme 7. Synthesis of Cyclic Amines from $\omega$-Unsaturated *N*-Sulfonylamines**




technique and an orbitrap mass analyzer. Optical rotations were measured in a digital polarmeter.

*5-(4-Methoxyphenethylsulfonyl)-1-phenyl-1H-tetrazole (**9**).* To a solution of alcohol **8** (2.0 g, 13.1 mmol) in THF was added phenyltetrazole thiol (2.57 g, 14.4 mmol) and triphenylphosphine (3.79 g, 14.4 mmol), and the mixture was cooled to 0 °C. To the mixture was added dropwise a solution of DIAD (2.84 mL, 14.4 mmol). The cooling bath was removed, and the mixture was allowed to warm to ambient temperature and maintained for 1 h. The mixture was diluted with $CH_2Cl_2$, and silica gel was added. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (ethyl acetate/hexane 1:9) to furnish sulfide compound (3.69 g, 90%) as a colorless and very viscous oil. The sulfide compound (3.60 g, 1.5 mmol) was dissolved in EtOH (50 mL), and the solution was cooled to 0 °C. In a separate flask, aqueous $H_2O_2$ (30%, 7.84 mL, 69.2 mmol) was added to $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (2.85 g, 2.30 mmol), and the mixture was stirred vigorously until complete dissolution of the $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$. The $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/$H_2O_2$ solution was then added dropwise to the sulfide solution, and the cooling bath was removed. The mixture was allowed to warm to ambient temperature and maintained for 24 h. The mixture was diluted with water and $Et_2O$, and the layers were separated. The organic phase was washed twice with water and once with brine. The combined aqueous layers were extracted twice with $Et_2O$. The combined organic phases were dried with $NaSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane 1:9) furnished sulfone compound **9** (3.57 g, 90%) as a colorless and very viscous oil. IR (neat): 2923, 2851, 1725, 1508, 1338, 1244, 1148, 1030 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.72−7.57 (m, 5H), 7.16 (AA′ part of AA′BB′ (m), 2H), 6.85 (BB′ part of AA′BB′ (m), 2H), 4.00−3.93 (m, 2H), 3.80 (s, 3H), 3.23−3.17 (m, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.7, 153.2, 132.8, 131.3, 129.6, 129.4, 128.0, 124.9, 114.2, 57.3, 55.2, 27.5. ESIMS (*m/z*): 367 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{16}H_{16}O_3N_4NaS$: 367.08353. Found: 367.08523.

*(R,E)-Benzyl 5-(4-Methoxyphenyl)pent-3-en-2-ylcarbamate (**11**).* To a stirred solution of oxalyl chloride (1.83 mL, 21.0 mmol) in dry DCM (20 mL) under nitrogen atmosphere was added DMSO (3.12 mL, 44.0 mmol) slowly at −78 °C, and it was stirred further for 30 min at the same temperature. Then alcohol **10** (2.20 g, 10.5 mmol) in dry DCM (20 mL) was added slowly over 10 min and stirred further for 2 h at −78 °C, and then DIPEA (10.8 mL, 63.1 mmol) was added at −78 °C. The temperature was slowly raised to room temperature over 20 min, and the reaction mixture was diluted with DCM (50 mL). The organic layer was sequentially washed with saturated aq. $NH_4Cl$ solution and brine and dried over anhydrous $Na_2SO_4$. The solvent was removed on a rotary evaporator to give crude aldehyde, which was chromatographed on silica gel (ethyl acetate/hexane 1:9) to give aldehyde **10** (2.0 g, 90%) as a colorless oil.

To a stirred solution of sulfone **9** (3.0 g, 8.7 mmol) in THF (20 mL), KHMDS (32.8 mL of 0.5 M solution in toluene, 17.4 mmol) was added at −78 °C. After stirring for 1 h, aldehyde **10** (2.0 g, 9.6 mmol) was added (5 mL THF) at the same temperature and stirred for 1 h. The mixture was allowed to warm to room temperature over 1 h; by that time the reaction mixture turned into a white cloudy suspension, and the TLC analysis indicated complete consumption of the starting material. Solvents were removed under reduced pressure to give the crude product, which was chromatographed over silica gel (ethyl acetate/hexane 1:9) to give olefin **11** (2.20 g, 80%) as a colorless oil. $[\alpha]_D^{20}$ = +5.3 (*c* 0.47, $CHCl_3$). IR (neat): 3314, 2923, 2851, 2365, 1705, 1510, 1238, 1032 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.38−7.28 (m, 5H), 7.06 (AA′ part of AA′BB′ (m), 2H), 6.83 (BB′ part of AA′BB′ (m), 2H), 5.72 (m, 1H), 5.46 (dd, *J* = 5.0, 15.4 Hz), 5.09 (ABq, *J* = 12.3 Hz, 2H), 4.67 (br, 1H), 4.29 (br, 1H), 3.78 (s, 3H), 3.30−3.26 (m, 2H), 1.22 (d, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 157.9, 155.4, 136.5, 132.4, 131.9, 129.5, 129.3, 128.4, 127.9, 113.7, 66.5, 55.1, 48.0, 37.5, 21.0. ESIMS (*m/z*): 326 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{20}H_{24}O_3N$: 326.17507. Found: 326.17636.

*Benzyl (2R,3R,4R)-3,4-Dihydroxy-5-(4-methoxy phenyl)pentan-2-ylcarbamate (**12**).* To a stirred solution of olefin compound **11** (2.0 g, 6.15 mmol) and *N*-methyl morpholine-*N*-oxide (1.07 g, 9.23 mmol) in acetone and water at 0 °C was added a catalytic amount of $OsO_4$ solution in toluene (1.5 mL, 0.06 mmol). After stirring 8 h at room temperature, a saturated aqueous solution of $Na_2SO_3$ (4 mL) was added to the mixture and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over $Na_2SO_4$, and solvent was removed thoroughly under vacuum. The crude residue was chromatographed on silica gel (ethyl acetate/hexane 1:7) to afford dihydroxylated compounds **12** (1.40 g) and **13** (0.58 g) in 90% yield (dr = 70:30).

*Major Diol Compound **12**.* $[\alpha]_D^{20}$ = −0.4 (*c* 0.36, $CHCl_3$). IR (neat): 3393, 2922, 2852, 2364, 1693, 1513, 1459, 1247, 1036 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.41−7.32 (m, 5H), 7.12 (AA′ part of AA′BB′ (m), 2H), 6.84 (BB′ part of AA′BB′ (m), 2H), 5.10 (ABq, *J* = 12.0 Hz, 2H), 4.88 (d, *J* = 8.6 Hz), 3.84−3.66 (m, 2H), 3.79 (s, 3H), 3.29 (m, 1H, OH), 3.10 (m, 1H), 2.88−2.74 (m, 2H), 2.40 (d, *J* = 8.9 Hz, OH), 1.24 (d, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.2, 157.1, 136.1, 130.3, 130.1, 128.5, 128.3, 128.1, 113.9, 75.3, 71.1, 67.1, 55.2, 49.2, 38.4, 17.4. ESIMS (*m/z*): 360 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{20}H_{26}O_5N$: 360.18055. Found: 360.18242.

*Benzyl(2R,3S,4S)-3,4-dihydroxy-5-(4-methoxyphenyl)pentan-2-ylcarbamate (**13**).* $[\alpha]_D^{20}$ = +11.5 (*c* 0.27, $CHCl_3$). IR (neat): 3393, 2922, 2852, 2364, 1693, 1513, 1244, 1036 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.40−7.30 (m, 5H), 7.10 (AA′ part of AA′BB′ (m), 2H), 6.84 (BB′ part of AA′BB′ (m), 2H), 5.12 (ABq, *J* = 11.9 Hz, 2H), 5.02 (d, *J* = 8.9 Hz, 1H), 3.97 (m, 1H), 3.79 (s, 3H), 3.70 (m, 1H), 3.35 (m, 1H), 2.96 (m, 1H), 2.61 (dd, *J* = 8.9, 13.4 Hz, 1H), 1.25 (d, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.3, 156.5, 136.3, 130.4, 129.6, 128.5, 128.1, 128.0, 114.0, 76.3, 73.2, 66.8, 55.2, 48.2, 38.9, 18.8. ESIMS (*m/z*): 360 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{20}H_{26}O_5N$: 360.18055. Found: 360.18238.

*(2R,3R,4R)-4-(Benzyloxycarbonylamino)-1-(4-methoxyphenyl)-pentane-2,3-diyl Diacetate (**14**).* To a stirred solution of diol compound **12** (1.0 g, 2.78 mmol) in dichloromethane (10 mL) was added triethyl amine (1.36 mL, 9.74 mmol), acetic anhydride (0.78 mL, 8.3 mmol), and 4-dimethylamino pyridine (5 mg) at 0 °C under nitrogen atmosphere. After completion of the addition, the reaction mixture was kept at room temperature and stirred for 2 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 (ethyl acetate/hexane 1:8) to afford the diacetate compound **14** (1.0 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = +6.7 (*c* 0.53, $CHCl_3$). IR (neat): 2931, 2364, 2332, 1740, 1695, 1515, 1461, 1223, 1030 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.40−7.28 (m, 5H), 7.08 (AA′ part of AA′BB′ (m), 2H), 6.81 (BB′ part of AA′BB′ (m), 2H), 5.23 (m, 1H), 5.07 (brs, 2H), 4.89 (dd, *J* = 4.1, 5.2 Hz, 1H), 4.81 (d, *J* = 8.6 Hz, 1H), 4.08 (m, 1H), 3.77 (s, 3H), 2.89−2.67 (m, 2H), 2.14 (s, 3H), 2.01 (s, 3H), 1.11 (d, *J* = 6.8 Hz,



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3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 170.4, 170.0, 158.4, 155.4, 136.3, 130.2, 128.4, 128.0, 113.8, 74.6, 72.7, 66.7, 55.1, 46.9, 36.3, 20.9, 20.7, 16.6. ESIMS ($m/z$): 444 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{24}H_{30}O_7N$: 444.19939. Found: 444.19920.

*(2R,3R,4R,5R)-1-(Benzyloxycarbonyl)-2-(4-methoxy phenyl)-5-methylpyrrolidine-3,4-diyl Diacetate (**16**).* To a stirred solution of diacetate compound **14** (0.60 g, 1.35 mmol) in $CH_3CN$ (2 mL) was added DDQ (0.33 g, 1.48 mmol). The resulting mixture was heated at 80 °C for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to room temperature and quenched with $Et_3N$ and concentrated under reduced pressure to give crude residue, which was purified on silica gel column (ethyl acetate/hexane 1:8) to give cyclic compound **16** (0.53 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ = +19.1 ($c$ 0.20, $CHCl_3$){lit.,[5c] $[\alpha]_D^{34}$ = +20.2 ($c$ 0.11, $CHCl_3$)}. IR (neat): 2928, 2364, 1743, 1704, 1513, 1406, 1350, 1223, 1037 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.41−7.05 (m, 6H), 6.89−6.77 (m, 3H), 5.20−4.75 (m, 5H), 4.28 (qt, $J$ = 6.4, 12.4 Hz, 1H), 3.79 (s, 3H), 2.15 (s, 3H), 1.83 (s, 3H), 1.54 (d, $J$ = 6.7 Hz, 3H) (multiple peaks are due to rotameric mixture). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.5, 169.4, 158.7, 154.2, 136.1, 131.6, 130.5, 128.4, 128.2, 128.0, 127.5, 127.4, 127.3, 127.1, 113.6, 113.4, 82.4, 81.4, 81.2, 80.3, 68.0, 67.6, 67.2, 66.7, 61.3, 60.7, 55.2, 20.9, 20.6, 18.3, 17.1 (multiple peaks are due to rotameric mixture). ESIMS ($m/z$): 442 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{24}H_{28}O_7N$: 442.18338. Found: 442.18334.

*(2R,3R,4R,5R)-2-(4-Methoxyphenyl)-1,5-dimethylpyrrolidine-3,4-diol [(−)-Codonopsinine] (**1**).* To a stirred suspension of $LiAlH_4$ (0.103 g, 2.72 mmol) in THF (10 mL) was added pyrrolidine derivative **16** (0.2 g, 0.45 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 (0.1 mL), 15% NaOH (0.1 mL), and water (0.3 mL) successively. After 15 min stirring at room temperature, the reaction mixture was filtered through the Celite pad, washed with chloroform (3 × 10 mL), and evaporated under vacuum. The residue was purified through silica gel column ($CHCl_3$/MeOH = 7:1) to afford the codonopsinine 1 (0.1 g, 80%) as a white powder. The spectral ($^1$H and $^{13}$C) and analytical (optical rotation and melting point) data of synthetic (−)-codonopsinine **1** were in excellent agreement with the reported values.[5c] Mp 168−170 °C, $[\alpha]_D^{20}$ = −8.9 ($c$ 0.1, MeOH) {lit.[5c] mp 169−170 °C, $[\alpha]_D^{34}$ = −8.8 ($c$ 0.1, MeOH)}. IR (KBr): 3360, 2938, 2362, 1834, 1743, 1698, 1514, 1460, 1028 cm$^{-1}$. $^1$H NMR (300 MHz, pyridine-$d_5$): $\delta$ 7.58 (AA′ part of AA′BB′ (m), 2H), 6.96 (BB′ part of AA′BB′ (m), 2H), 4.60 (dd, $J$ = 4.5, 6.0 Hz, 1H), 4.36 (dd, $J$ = 3.7, 4.3 Hz, 1H), 4.00 (d, $J$ = 6.4 Hz, 1H), 3.66 (m, 1H), 3.65 (s, 3H), 2.20 (s, 3H), 1.31 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, pyridine-$d_5$): $\delta$ 159.3, 135.0, 129.8, 114.1, 87.2, 85.0, 74.3, 65.0, 55.1, 34.7, 13.9. ESIMS ($m/z$): 238 ($M^+$ + H). HRMS calcd for $C_{13}H_{20}NO_3$: 238.14377. Found: 238.14464.

*(2S,3S,4R)-4-(Benzyloxycarbonylamino)-1-(4-methoxy phenyl)-pentane-2,3-diyl Diacetate (**15**).* To the stirred solution of diol compound **13** (0.5 g, 1.39 mmol) in dichloromethane (6 mL) was added triethyl amine (0.77 mL, 5.57 mmol), acetic anhydride (0.39 mL, 4.17 mmol), and 4-dimethylamino pyridine (5 mg) at 0 °C under nitrogen atmosphere. After completion of the addition, the reaction mixture was kept at room temperature and stirred for 2 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 purified by column chromatography (ethyl acetate/hexane 1:8) to afford the compound **15** (0.5 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = +38.2 ($c$ 0.8, $CHCl_3$). IR (neat): 2925, 2363, 1740, 1708, 1515, 1461, 1224, 1030 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.40−7.30 (m, 5H), 7.05 (AA′ part of AA′BB′ (m), 2H), 6.79 (BB′ part of AA′BB′ (m), 2H), 5.23 (m, 1H), 5.12 ($AB_q$, $J$ = 12.1 Hz, 2H), 4.93−4.87 (m, 2H), 4.13 (m, 1H), 3.77 (s, 3H), 2.91 (dd, $J$ = 4.4, 13.8 Hz, 1H), 2.75 (dd, $J$ = 8.2, 13.8 Hz, 1H), 2.05 (s, 3H), 1.95 (s, 3H), 1.11 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 170.4, 170.0, 158.3, 155.7, 136.3, 130.3, 128.5, 128.1, 128.0, 113.8, 75.5, 73.0, 66.8, 55.1, 47.1, 36.1, 20.7, 20.6, 18.5. ESIMS (*m/zI*): 444 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{24}H_{30}O_7N$: 444.20168. Found: 444.20402.

*(2R,3S,4S,5R)-1-(Benzyloxycarbonyl)-2-(4-methoxy phenyl)-5-methylpyrrolidine-3,4-diyl Diacetate (**S1**).* To a stirred solution of diacetate compound **15** (0.4 g, 0.90 mmol) in $CH_3CN$ (2 mL) was added DDQ (0.23 g, 0.1 mmol). The resulting mixture was heated at 80 °C for 8 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to room temperature, quenched with $Et_3N$, and concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:8) to give cyclic compound **S1** (0.31 g, 80%) as colorless oil. $[\alpha]_D^{20}$ = −16.1 ($c$ 0.22, $CHCl_3$). IR (neat): 2930, 2363, 1743, 1705, 1513, 1222, 1032 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.30−7.10 (m, 7H), 6.86 (BB′ part of AA′BB′ (m), 2H), 5.24−4.86 (m, 5H), 4.42 (m, 1H), 3.81 (s, 3H), 2.08 (s, 3H), 1.83 (s, 3H), 1.44 (d, $J$ = 6.4 Hz, 3H) (multiple peaks are due to rotameric mixture). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 169.8, 169.7, 158.7, 155.4, 136.2, 131.0, 128.4, 128.3, 128.0, 127.8, 127.4, 127.0, 113.6, 80.2, 75.9, 74.1, 72.5, 66.9, 65.9, 55.5, 55.2, 20.9, 20.6, 20.4, 20.2, 14.8, 14.4 (multiple peaks are due to rotameric mixture). ESIMS ($m/z$): 442 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{24}H_{28}O_7N$: 442.18347. Found: 442.18341.

*(2S,3S,4S,5R)-2-(4-Methoxyphenyl)-1,5-dimethyl pyrrolidine-3,4-diol [(+)-5-epi-Codonopsinine] (**6**).* To a stirred suspension of $LiAlH_4$ (0.08 g, 2.26 mmol) in THF (3 mL) was added pyrrolidine derivative S1 (0.2 g, 0.45 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 (0.08 mL), 15% NaOH (0.08 mL), and water (0.24 mL) successively. After 15 min stirring at room temperature, the reaction mixture was filtered through the Celite pad, washed with chloroform (3 × 10 mL), and evaporated under vacuum. The residue was purified by column chromatography ($CHCl_3$/MeOH = 7:1) to afford the 5-*epi*-codonopsinine 6 (0.1 g, 80%) as a white powder. Mp 168−170 °C, $[\alpha]_D^{20}$ = +1.0 ($c$ 0.18, MeOH. IR (neat) 3360, 2938, 2362, 1743, 1698, 1514, 1028 cm$^{-1}$. $^1$H NMR (500 MHz, pyridine-$d_5$): $\delta$ 7.63 (AA′ part of AA′BB′ (m), 2H), 6.99 (BB′ part of AA′BB′ (m), 2H), 4.59 (dd, $J$ = 3.5, 6.8 Hz, 1H), 4.53 (dd, $J$ = 3.5, 6.8 Hz, 1H), 3.67 (s, 3H), 3.42 (d, $J$ = 7.0 Hz, 1H), 2.87 (m, 1H), 2.21 (s, 3H), 1.49 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR (125 MHz, pyridine-$d_5$): $\delta$ 159.8, 135.2, 130.1, 114.6, 87.4, 79.8, 78.6, 65.3, 55.6, 39.6, 14.7. ESIMS $m/z$ 238 $[M + H]^+$. HRMS calcd for $C_{13}H_{20}NO_3$: 238.14377. Found: 238.14454.

*2-(4-(Benzyloxy)phenyl)ethanol (**17**).* To a solution of (4-hydroxyphenyl)acetic acid (3.0 g, 19.7 mmol) in acetone (80 mL) were added benzyl bromide (7.03 mL, 59.2 mmol) and anhydrous $K_2CO_3$ (8.1 g, 59.2 mmol). The reaction mixture was refluxed for 10 h and then filtered over a Celite pad of silica gel and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane 1:20) to give dibenzylated compound (5.8 g, 90%) as a white solid. To a suspension of $LiAlH_4$ (2.28 g, 60.2 mmol) in THF (45 mL) at 0 °C under $N_2$ was added dropwise a solution of dibenzylated compound (4.98 g, 15 mmol) in THF. The mixture was refluxed for 4 h, and the reaction mixture was cooled to 0 °C and quenched with water (2.28 mL), 15% NaOH (2.28 mL), and water (6.84 mL) successively. After 30 min stirring at room temperature, the reaction mixture was filtered through the Celite pad, washed with EtOAc (3 × 50 mL), and evaporated under vacuum. The residue was purified by column chromatography (ethyl acetate/hexane 1:7) to afford **17** (2.91 g, 85%) as a white solid. IR (neat): 3271, 3032, 2924, 2862, 1610, 1511, 1246, 1217, 1013 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.45−7.29 (m, 5H), 7.14 (AA′ part of AA′BB′ (m), 2H), 6.93 (BB′ part of AA′BB′ (m), 2H), 5.04 (s, 2H), 3.81 (t, $J$ = 6.5 Hz, 2H), 2.80 (t, $J$ = 6.5 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 157.2, 136.9, 130.7, 129.7, 128.3, 127.7, 127.2, 114.7, 69.8, 63.4, 38.0. ESIMS ($m/z$): 246 $[M + NH_4]^+$. HRMS (ESI) $[M+NH_4]^+$ Anal. Calcd for $C_{15}H_{20}O_2N$: 246.14886. Found: 246.14859.

*5-(4-(Benzyloxy)phenethylsulfonyl)-1-phenyl-1H-tetrazole (**18**).* To a solution of alcohol **17** (2.5 g, 6.4 mmol) in THF (20 mL) was added phenyltetrazole thiol (1.26 g, 7.0 mmol) and triphenylphosphine (1.68 g, 7.0 mmol), and the mixture was cooled to 0 °C. To the



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mixture was added dropwise a solution of DIAD (1.39 mL, 7.0 mmol). The cooling bath was removed, and the mixture was allowed to warm to ambient temperature and maintained for 1 h. The mixture was diluted with $CH_2Cl_2$, and silica gel was added. The mixture was concentrated in vacuo, and residue was purified by column chromatography (ethyl acetate/hexane 1:8) to afford sulfide compound (3.82 g, 90%) as a colorless and viscous oil. The sulfide compound (3.5 g, 9.0 mmol) was dissolved in EtOH (80 mL), and the solution was cooled to 0 °C. In a separate flask, aqueous $H_2O_2$ (30%, 4.23 mL, 54.1 mmol) was added to $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (2.22 g, 1.80 mmol), and the mixture was stirred vigorously until complete dissolution of the $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$. The $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O/H_2O_2$ solution was then added dropwise to the sulfide solution, and the cooling bath was removed. The mixture was allowed to warm to ambient temperature and maintained for 24 h. The mixture was diluted with water and $Et_2O$, and the layers were separated. The organic phase was washed twice with water and once with brine. The combined aqueous layers were extracted twice with $Et_2O$. The combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (ethyl acetate/hexane 1:8) gave sulfone compound **18** (3.40 g, 90%) as a colorless and very viscous oil. IR (neat): 3019, 1728, 1511, 1215, 1154, 1016 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.71−7.58 (m, 5H), 7.45−7.29 (m, 5H), 7.16 (AA′ part of AA′BB′ (m), 2H), 6.93 (BB′ part of AA′BB′ (m), 2H), 5.06 (s, 2H), 3.96 (m, 2H), 3.21 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 157.9, 153.2, 136.7, 132.8, 131.3, 129.5, 129.49, 128.47, 128.42, 127.8, 127.3, 124.9, 115.2, 69.9, 57.3, 27.5. ESIMS (*m/z*): 421 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{22}H_{21}O_3N_4S$: 421.13071. Found: 421.13064.

*(S,E)-Benzyl 4-(3-(4-(Benzyloxy)phenyl)prop-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**20**).* To a stirred solution of oxalyl chloride (1.58 mL, 18.1 mmol) in dry DCM (20 mL) under nitrogen atmosphere was added DMSO (2.57 mL, 36.2 mmol) slowly at −78 °C and stirred further for 30 min at the same temperature. Then D-serine-derived alcohol (2.4 g, 9.0 mmol) in dry DCM (20 mL) was added slowly over 10 min and stirred further for 2 h at −78 °C, and then $Et_3N$ (7.57 mL, 54.3 mmol) was added at −78 °C. The temperature was slowly warmed to room temperature over 20 min, and the reaction mixture was diluted with DCM (50 mL). The organic layer was sequentially washed with saturated aq. $NH_4Cl$ solution and brine and dried over anhydrous $Na_2SO_4$. The solvent was removed on a rotary evaporator to give crude aldehyde, which was purified by column chromatography (ethyl acetate/hexane 1:9) to give aldehyde **19** (2.38 g, 90%) as a colorless oil.

To a stirred solution of sulfone **18** (3.0 g, 7.14 mmol) in THF (20 mL), KHMDS (28.5 mL of 0.5 M solution in toluene, 14.2 mmol) was added at −78 °C. After stirring for 1 h, aldehyde **19** (2.3 g, 7.14 mmol) was added (5 mL of THF) at the same temperature and stirred for 1 h. The mixture was allowed to warm to room temperature over 3 h, by which time the reaction mixture turned into awhite cloudy suspension and TLC analysis indicated complete consumption of the starting material. Solvents were removed under reduced pressure to give the crude product, which upon silica gel column chromatography (ethyl acetate/hexane 1:8) gave olefin **20** (2.58 g, 78%) as a colorless oil. $[\alpha]_D^{24}$ = −61.2 (*c* 0.65, $CHCl_3$). IR (neat): 2984, 2932, 1700, 1509, 1404, 1347, 1220, 1091, 1024 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.47−7.23 (m, 10H), 7.12−6.82 (m, 4H), 5.65 (m, 1H), 5.50 (dd, *J* = 7.3, 15.4 Hz, 1H), 5.22−4.5.01 (m, 4H), 4.38 (m, 1H), 4.04 (dd, *J* = 5.9, 8.8 Hz, 1H), 3.77 (dd, *J* = 1.9, 8.8 Hz, 1H), 3.38−3.20 (m, 2H), 1.65 (s, 3H), 1.55 (s, 3H) (multiple peaks are due to rotameric mixture). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 157.1, 157.0, 152.4, 137.0, 136.4, 132.4, 132.1, 132.0, 129.8, 129.6, 129.3, 129.0, 128.4, 128.3, 128.1, 127.9, 127.8, 127.3, 114.8, 94.2, 77.1, 69.9, 68.9, 68.6, 66.6, 66.4, 58.8, 54.8, 54.1, 37.5, 32.2, 27.3, 26.4, 23.7, 23.5 (multiple peaks are due to rotameric mixture). ESIMS (*m/z*): 480 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{29}H_{31}O_4NNa$: 480.21453. Found: 480.21382.

*(2R,3R,4R)-5-(4-(Benzyloxy)phenyl)-2-(benzyloxycarbonylamino)-pentane-1,3,4-triyl Triacetate (**21**).* To a stirred solution of olefin compound **20** (2.50 g, 5.47 mmol) and *N*-methyl morpholine-*N*-oxide (1.0 g, 8.20 mmol) in acetone and water at 0 °C was added a catalytic amount of $OsO_4$ solution in toluene (1.3 mL, 0.054 mmol). After stirring 8 h at room temperature, a saturated aqueous solution of $Na_2SO_3$ (4 mL) was added to the mixture and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over $Na_2SO_4$ and solvent removed thoroughly under vacuum. Purification by silica gel column chromatography (ethyl acetate/hexane 1:6) afforded dihydroxylated compound (2.41 g, 90%) as a colorless oil. To the dihydroxylated compound (2.41 g, 4.90 mmol) in $CH_3CN$ (5 mL) was added $CuCl_2{\cdot}2H_2O$ (0.97 g, 5.89 mmol), which was quenched with saturated $NaHCO_3$ and filtered through a Celite pad of silica gel, and solvents were removed under reduced pressure to give the crude product. To the crude triol compound in dichloromethane (10 mL) was added triethyl amine (2.73 mL, 19.6 mmol), acetic anhydride (1.38 mL, 14.7 mmol), and 4-dimethylaminopyridine (5 mg) at 0 °C under nitrogen atmosphere. After completion of the addition, the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with chloroform (50 mL), washed with water and brine, dried over $Na_2SO_4$, and concentrated under vacuum. Purification by silica gel column chromatography (ethyl acetate/hexane 1:8) afforded triacetate derivatives **21** (1.78 g) and **22** (0.76 g) in 90% yield (dr = 70:30).

*Major Triacetate Compound **21**.* $[\alpha]_D^{20}$ = −5.3 (*c* 0.25, $CHCl_3$). IR (neat): 2925, 2854, 1740, 1512, 1372, 1216, 1027 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.47−7.25 (m, 10H), 7.10 (AA′ part of AA′BB′ (m), 2H), 6.88 (BB′ part of AA′BB′ (m), 2H), 5.36−4.96 (m, 7H), 4.28 (m, 1H), 4.16 (dd, *J* = 4.5, 11.7 Hz, 1H), 3.99 (dd, *J* = 3.3, 11.7 Hz, 1H), 2.88−2.66 (m, 2H), 2.15 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 170.6, 170.1, 170.0, 157.6, 155.5, 136.9, 136.0, 130.4, 130.2, 128.5, 128.2, 128.1, 127.9, 127.4, 114.7, 114.6, 72.4, 70.9, 69.8, 67.1, 63.0, 49.5, 36.1, 20.9, 20.7, 20.6. ESIMS (*m/z*): 578 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{32}H_{36}O_9N$: 578.23555. Found: 578.23551.

*(2R,3S,4S)-5-(4-(Benzyloxy)phenyl)-2-(benzyloxycarbonylamino)-pentane-1,3,4-triyl Triacetate (**22**).* $[\alpha]_D^{20}$ = +6.7 (*c* 0.26, $CHCl_3$). IR (neat): 2924, 2853, 1742, 1512, 1371, 1219, 1027 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.47−7.30 (m, 10H), 7.05 (AA′ part of AA′BB′ (m), 2H), 6.87 (BB′ part of AA′BB′ (m), 2H), 5.29−5.01 (m, 7H), 4.30 (m, 1H), 4.07−3.98 (m, 2H), 2.89 (dd, *J* = 5.0, 13.9 Hz, 1H), 2.77 (dd, *J* = 8.0, 13.9 Hz, 1H), 2.04 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 170.4, 170.0, 169.9, 157.6, 155.9, 136.9, 136.1, 131.1, 130.3, 128.5, 128.2, 128.1, 127.9, 127.4, 127.0, 114.7, 72.7, 71.4, 69.9, 67.1, 63.1, 50.1, 36.0, 20.7, 20.5. ESIMS (*m/z*): 578 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{32}H_{36}O_9N$: 578.23544. Found: 578.23516.

*(2R,3R,4R,5R)-2-(Acetoxymethyl)-5-(4-(benzyloxy)phenyl)-1-(benzyloxycarbonyl)pyrrolidine-3,4-diyl Diacetate (**23**).* To a stirred solution of diacetate compound **21** (1.5 g, 2.5 mmol) in $CH_3CN$ (3 mL) was added DDQ (0.64 g, 2.85 mmol). The resulting mixture was heated at 80 °C for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to room temperature, quenched with $Et_3N$, and concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:8) to give cyclic compound **23** (1.22 g, 82%) as a colorless oil. $[\alpha]_D^{20}$ = −1.3 (*c* 0.89, $CHCl_3$) {lit.,[7d] $[\alpha]_D^{28}$ = −1.5 (*c* 2.83, $CHCl_3$)}. IR (neat): 2923, 2853, 1744, 1706, 1511, 1404, 1217, 1041 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.49−7.09 (m, 11H), 6.95−6.72 (m, 3H), 5.23−4.83 (m, 6H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.61 (dd, *J* = 4.1, 10.6 Hz, 1H), 4.48 (dd, *J* = 4.1, 9.7 Hz, 1H), 4.32 (t, *J* = 10.2 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 1.77 (s, 3H) (multiple peaks are due to rotameric mixture). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 170.6, 170.4, 170.2, 169.5, 169.2, 157.9, 154.3, 153.6, 136.8, 135.9, 135.8, 135.7, 131.2, 130.1, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 127.2, 126.9, 114.7, 82.1, 81.1, 76.4, 69.9, 68.1, 67.7, 67.6, 67.1, 63.6, 62.9, 61.7, 61.1, 20.9, 20.8, 20.6 (multiple peaks are due to rotameric mixture). ESIMS (*m/z*): 598 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{32}H_{33}NO_9Na$: 598.20475. Found: 598.20411.

*(5R,6R,7R,7αR)-5-(4-(Benzyloxy)phenyl)-6,7-dihydroxytetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (**24**).* To a



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stirred solution of cyclic compound **23** (1.0 g, 1.73 mmol) in dry MeOH (10 mL) was added $K_2CO_3$ (0.86 g, 6.26 mmol) under nitrogen atmosphere. After being stirred for 60 min at rt, the MeOH was evaporated under reduced pressure and the residue was extracted with chloroform (30 mL). The organic extract was washed with water (10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography using (ethyl acetate/hexane 1:3) as the eluant to afford a bicyclic carbamate **24** (0.49 g, 84%) as white solid. The spectral ($^1$H and $^{13}$C) and analytical (optical rotation and melting point) data of synthetic compound **24** were in excellent agreement with the reported values.[7d] Mp: 125−130 °C, $[\alpha]_D^{20}$ = −4.6 (*c* 0.68, MeOH) {lit.,[7d] mp 129−131 °C, $[\alpha]_D^{27}$ = −4.5 (*c* 1.4, MeOH)}. IR (neat): 3393, 3341, 2474, 2214, 2070, 1219, 1120, 1091 cm$^{-1}$. $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 7.49−7.25 (m, 7H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.09 (brs, 2H), 4.65 (dd, *J* = 8.3, 9.0 Hz, 1H), 4.49 (d, *J* = 6.3 Hz, 1H), 4.42 (dd, *J* = 4.1, 9.0 Hz, 1H), 4.08−3.97 (m, 2H), 3.85 (dd, *J* = 7.4, 15.1 Hz, 1H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 163.7, 159.6, 138.7, 134.0, 129.5, 128.8, 128.5, 128.1, 116.1, 86.7, 80.9, 71.0, 68.5, 67.7, 63.2. ESIMS (*m*/*z*): 364 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{19}H_{19}NO_5Na$: 364.11554. Found: 364.11592.

*(S)-Benzyl 2,2-Dimethyl-4-vinyloxazolidine-3-carboxylate (**25**).* To a solution of DMSO (2.14 mL, 30.18 mmol) in DCM (20 mL) was added oxalyl chloride (1.31 mL, 15.09 mmol) dropwise at −78 °C. After stirring for 30 min, a solution of D-serine-derived alcohol (2.0 g, 7.54 mmol) in DCM (30 mL) was added over a period of 10 min. After stirring for 2 h at −78 °C, the reaction mixture was quenched with triethylamine (6.32 mL, 45.28 mmol). The temperature was slowly raised to room temperature over 20 min, and the reaction mixture was diluted with chloroform (50 mL), washed with water and brine, dried over $Na_2SO_4$, and concentrated under vacuum. The crude residue was dissolved in THF (30 mL); a yellow solution of $Ph_3P{=}CH_2$ (4.26 g, 10.5 mmol) in THF (40 mL) was added at −10 °C. After stirring for 3 h, the reaction mixture was quenched with saturated aq $NH_4Cl$ at 0 °C, THF was removed under reduced pressure, and the residue was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with $H_2O$ (50 mL) and brine (40 mL), dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified by column chromatography (ethyl acetate/hexane 1:7) to afford compound **25** (1.37 g, 70%) as a colorless oil. The spectral ($^1$H and $^{13}$C) and analytical (optical rotation) data of synthetic compound **25** were in excellent agreement with the reported values.[13c] $[\alpha]_D^{20}$ = +19.1 (*c* 0.95, $CHCl_3$) {lit.,[13c] $[\alpha]_D^{24}$ = +19.6 (*c* 1.6, $CHCl_3$)}. IR (neat): 2984, 2937, 1696, 1413, 1403, 1345, 1251, 1208, 1089, 1058 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.43−7.23 (m, 5H), 5.84 (m, 1H), 5.32−5.06 (m, 4H), 4.40 (brs, 1H), 4.05 (dd, *J* = 6.0, 8.6 Hz, 1H), 3.79 (dd, *J* = 1.8, 8.6 Hz, 1H), 1.68−1.46 (3s, 6H) (multiple peaks are due to rotameric mixture). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 152.6, 152.3, 136.8, 136.4, 136.1, 128.4, 128.2, 127.9, 127.7, 127.6, 116.5, 116.1, 94.3, 93.7, 68.2, 67.9, 67.0, 66.4, 60.0, 59.2, 27.1, 26.2, 24.8, 23.4 (multiple peaks are due to rotameric mixture). ESIMS (*m*/*z*): 262 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{15}H_{20}NO_3$: 262.14377. Found: 262.14347.

*(S,E)-Benzyl 4-(3-(3,4-Dimethoxyphenyl)prop-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**27**).* To a solution of olefin compound **25** (1.2 g, 4.59 mmol) in dry DCM (10 mL) were added 4-allyl-1,2-dimethoxybenzene **26** (2.76 mL, 16.0 mmol), the Grubbs second-generation catalyst (0.39 g, 0.459 mmol), and CuI (0.07 g, 0.367 mmol) in one portion at room temperature and refluxed for 8 h under a $N_2$ atmosphere. Residue was concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane 1:8) to afford the olefin compound **27** (1.51 g, 80%) as a syrupy liquid. $[\alpha]_D^{20}$ = +5.0 (*c* 0.55, $CHCl_3$). IR (neat): 2984, 2936, 1701, 1590, 1514, 1406, 1348, 1260, 1236, 1140, 1092, 1028 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.45−7.23 (m, 5H), 6.83−6.61 (m, 3H), 5.67 (m, 1H), 5.52 (dd, *J* = 6.0, 15.1 Hz, 1H), 5.27−5.04 (m, 2H), 4.43 (m, 1H), 4.05 (dd, *J* = 6.0, 8.6 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (dd, *J* = 1.8, 8.6 Hz, 1H), 3.41−3.19 (m, 2H), 1.57 (3s, 6H) (multiple peaks are due to rotameric mixture). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 152.3, 148.7, 147.2, 136.4, 132.3, 131.7, 129.6, 128.2, 127.7, 120.2, 111.7, 111.1, 94.1, 68.5, 66.9, 66.3, 59.4, 58.7, 55.8, 55.6, 37.8, 27.2, 26.3, 24.7, 23.4 (multiple peaks are due to rotameric mixture). ESIMS (*m*/*z*): 412 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{24}H_{30}O_5N$: 412.20982. Found: 412.20985.

*(2R,3R,4R)-2-(Benzyloxycarbonylamino)-5-(3,4-dimethoxyphenyl)pentane-1,3,4-triyl Triacetate (**28**).* To a stirred solution of olefin compound **27** (1.0 g, 2.43 mmol) and *N*-methyl morpholine-*N*-oxide (0.43 g, 3.64 mmol) in acetone and water at 0 °C was added a catalytic amount of $OsO_4$ solution in toluene (0.61 mL, 0.0243 mmol). After stirring for 8 h at room temperature, a saturated aqueous solution of $Na_2SO_3$ (4 mL) was added to the mixture and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over $Na_2SO_4$, and solvent was removed thoroughly under vacuum. The crude residue was chromatographed on silica gel (hexane/ethyl acetate = 2/1) to afford dihydroxylated compound (0.97 g, 90%) as a colorless oil.

To a stirred solution of dihydroxylated compound in $CH_3CN$ (5 mL) was added $CuCl_2{\cdot}2H_2O$ (0.484 g, 2.91 mmol) at 0 °C, and the reaction mixture was warmed to room temperature under stirring for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ and filtered through a Celite pad of silica gel, and solvents were removed under reduced pressure to give the crude product. To the crude triol compound in dry DCM (10 mL) was added triethyl amine (2.03 mL, 14.59 mmol), acetic anhydride (0.92 mL, 9.73 mmol), and 4-dimethylamino pyridine (5 mg) at 0 °C under nitrogen atmosphere. After completion of the addition, the reaction mixture was kept at room temperature and stirred for 2 h. The reaction mixture was diluted with chloroform (50 mL), washed with water and brine, dried over $Na_2SO_4$, and concentrated under vacuum. Purification by column chromatography (ethyl acetate/hexane 1:8) afforded triacetate derivatives **28** (0.81 g) and **29** (0.34 g) in 90% yield (dr = 70:30).

*Major Triacetate Compound **28**.* $[\alpha]_D^{20}$ = +2.2 (*c* 0.32, $CHCl_3$). IR (neat): 3340, 2955, 2933, 1741, 1513, 1371, 1220, 1048, 1027 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.40−7.29 (m, 5H), 6.81−6.70 (m, 3H), 5.25 (m, 1H), 5.17−5.01 (m, 3H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.28 (m, 1H), 4.16 (dd, *J* = 4.5, 11.7 Hz, 1H), 4.01 (dd, *J* = 3.4, 11.7 Hz, 1H), 3.85 (s, 6H), 2.81 (dd, *J* = 6.2, 13.6 Hz, 1H), 2.70 (dd, *J* = 7.3, 13.6 Hz, 1H), 2.17 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 170.4, 170.1, 169.9, 155.8, 148.6, 147.8, 136.0, 128.5, 128.2, 128.1, 121.4, 112.3, 111.0, 72.7, 71.2, 67.1, 63.0, 55.7, 50.2, 36.4, 20.7, 20.5, 20.4. ESIMS (*m*/*z*): 554 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{27}H_{33}O_{10}NNa$ 554.19967. Found: 554.19876.

*(2R,3S,4S)-2-(Benzyloxycarbonylamino)-5-(3,4-dimethoxyphenyl)pentane-1,3,4-triyl Triacetate (**29**).* $[\alpha]_D^{20}$ = −0.6 (*c* 0.42, $CHCl_3$). IR (neat): 3339, 2934, 1742, 1702, 1605, 1515, 1451, 1371, 1218, 1148, 1048, 1024 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.40−7.28 (m, 5H), 6.79−6.67 (m, 3H), 5.26 (m, 1H), 5.16−5.10 (m, 3H), 5.07 (d, *J* = 10.1 Hz, 1H), 4.29 (m, 1H), 4.05−3.99 (m, 2H), 3.85 (s, 6H), 2.89 (dd, *J* = 5.3, 14.0 Hz, 1H), 2.79 (dd, *J* = 7.8, 14.0 Hz, 1H), 2.05 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 170.5, 170.1, 169.9, 155.5, 148.6, 147.7, 136.0, 128.4, 128.19, 128.15, 127.9, 121.5, 121.2, 112.4, 111.0, 72.5, 70.8, 67.1, 63.0, 55.7, 49.5, 36.5, 21.0, 20.7, 20.6. ESIMS (*m*/*z*): 532 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{27}H_{34}O_{10}N$: 532.21530. Found: 532.21527.

*(2R,3R,4R,5S)-2-(Acetoxymethyl)-1-(benzyloxycarbonyl)-5-(3,4-dimethoxyphenyl)pyrrolidine-3,4-diyl Diacetate (**30**).* To a stirred solution of triacetate compound **28** (0.6 g, 1.12 mmol) in $CH_3CN$ (3 mL) was added DDQ (0.28 g, 1.24 mmol). The resulting mixture was heated at 80 °C for 4 h under nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to room temperature, quenched with $Et_3N$, and concentrated under reduced pressure to give crude residue, which was purified by column chromatography (ethyl acetate/hexane 1:8) to afford cyclic compound **30** (0.50 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ = −9.8 (*c* 0.19, $CHCl_3$). IR (neat): 2924, 2852, 1743, 1705, 1515, 1404, 1219, 1141, 1029 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.46−7.12 (m, 5H), 6.88−6.73 (m, 3H), 5.28−4.91 (m, 4H), 4.85 (d, *J* = 12.4 Hz, 1H), 4.61 (m, 1H), 4.50 (m, 1H), 4.32 (m, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.17 (s, 3H),


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2.12 (s, 3H), 1.85 (s, 3H) (multiple peaks are due to rotameric mixture). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 170.6, 170.5, 169.6, 169.5, 169.2, 169.1, 154.3, 153.6, 148.77, 148.72, 148.1, 135.9, 135.6, 131.5, 130.3, 128.56, 128.51, 128.3, 128.1, 127.8, 127.7, 118.1, 117.9, 110.7, 110.6, 109.29, 109.24, 82.3, 81.2, 76.5, 68.3, 68.0, 67.6, 67.1, 63.6, 62.9, 61.7, 61.1, 55.9, 55.8, 55.6, 21.0, 20.8, 20.7 (multiple peaks are due to rotameric mixture). ESIMS ($m/z$): 552 $[M + Na]^+$. HRMS (ESI) $[M + Na]^+$ Anal. Calcd for $C_{27}H_{31}O_{10}NNa$: 552.18402. Found: 552.18300.

*(2R,3R,4R,5R)-2-(3,4-Dimethoxyphenyl)-5-(hydroxymethyl)-1-methylpyrrolidine-3,4-diol [(−)-Codonopsinol] (**3**).* To a stirred suspension of $LiAlH_4$ (0.13 g, 183 mmol) in THF (3 mL) was added pyrrolidine derivative **30** (0.3 g, 0.56 mmol) in THF (5 mL) at 0 °C. After completion of the addition the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to 0 °C and quenched with water (0.13 mL), 15% NaOH (0.13 mL), and water (0.4 mL) successively. After 15 min stirring at rt, the reaction mixture was filtered through the Celite pad and washed with ethyl acetate (3 × 10 mL), and the filtrate was evaporated under vacuum. The residue was purified through a silica gel column ($CHCl_3$/MeOH = 7:1) to afford the codonopsinol **3** (0.12 g, 80%) as a white solid. The spectral ($^1$H and $^{13}$C) and analytical data (optical rotation and melting point) of synthetic (−)-codonopsinol **3** were in excellent agreement with the reported values.[6b] Mp: 150−155 °C $[\alpha]_D^{20}$ = −13.8 (*c* 0.63, MeOH) {lit.,[6b] mp 150−152 °C $[\alpha]_D^{25}$ = −13.0 (*c* 1.37, MeOH)}. IR (neat): 3329, 2944, 2832, 2506, 2071, 1449, 1414, 1219, 1119, 1020 cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.03 (s, 1H), 6.90 (s, 2H), 4.03 (t, *J* = 4.4 Hz, 1H), 3.94 (dd, *J* = 5.0, 6.4 Hz, 1H), 3.78−3.87 (m, 8H), 3.66 (d,*J* = 6.6 Hz, 1H), 3.10 (m, 1H), 2.20 (s, 3H). $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ 150.5, 149.9, 134.7, 122.3, 112.6, 112.5, 85.8, 80.1, 75.8, 71.1, 60.8, 56.5, 56.4, 34.9. ESIMS ($m/z$): 284 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{14}H_{22}O_5N$: 284.14776. Found: 284.14777.

*(S)-N-(3,7-Dimethyloct-6-en-1-yl)-4-methylbenzenesulfonamide (**32**).* To a solution of (*S*)-3,7-dimethyloct-6-en-1-ol **31** (0.5 g, 3.20 mmol) and $Et_3N$ (1.34 mL, 9.61 mmol) in dry DCM (8 mL) at 0 °C was added MsCl (0.26 mL, 3.36 mmol). After 15 min the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with chloroform (20 mL), washed with water and brine, dried over $Na_2SO_4$, and concentrated under vacuum. The organic phase was washed with brine (20 mL), dried over $NaSO_4$, filtrated, and concentrated under vacuum to afford the compound as a colorless oil. To the crude compound (*S*)-3,7-dimethyloct-6-en-1-yl methanesulfonate (0.75 g, 3.20 mmol) in $CH_3CN$ (15 mL) were added $K_2CO_3$ (0.90 g, 6.41 mmol) and $TsNH_2$ (1.10 g, 6.41 mmol), and the reaction was heated to reflux. After 5 h, the reaction mixture was filtered through a Celite pad and evaporated under vacuum. Purification by silica gel column chromatography (ethyl acetate/hexane 1:9) afforded product **32** as a colorless oil (0.79 g, 80%). The spectral ($^1$H and $^{13}$C) data of synthetic compound **32** was in excellent agreement with the reported values.[2d] $[\alpha]_D^{20}$ = −5.6 (*c* 1.1, $CHCl_3$). IR (KBr): 3283, 2925, 2871, 1712, 1598, 1453, 1327, 1158, 1092 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.02 (dd, *J* = 7.0 Hz, 1H), 4.50 (m, 1H), 3.02−2.88 (m, 2H), 2.43 (s, 3H), 1.98−1.80 (m, 2H), 1.67 (s, 3H), 1.57 (s, 3H), 1.51−1.36 (m, 2H), 1.31−1.03 (m, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 143.0, 136.8, 131.1, 129.5, 126.9, 124.3, 41.1, 36.6, 36.3, 29.7, 25.5, 25.1, 21.3, 18.9, 17.4. ESIMS ($m/z$): 310 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{17}H_{28}NO_2S$: 310.18353. Found: 310.18295.

*4-Methyl-2-(2-methylprop-1-en-1-yl)-1-tosylpiperidine (**33**).* To a stirred solution of sulphonamide compound **32** (0.2 g, 0.64 mmol) in $CH_3CN$ (2 mL) was added DDQ (0.16 g, 0.71 mmol) at 0 °C. The resulting mixture was kept at room temperature for 30 min under a nitrogen atmosphere. After completion of the reaction as evidenced by TLC, the reaction mixture was cooled to room temperature, quenched with $Et_3N$, and concentrated under reduced pressure to give crude residue, which was purified by silica gel column chromatography (ethyl acetate/hexane 1:9) to give a mixture of cyclic compounds **33** and **34** (0.39 g, 90%) as colorless oils. The spectral ($^1$H and $^{13}$C) data of synthetic compounds **33** and **34** was in excellent agreement with the reported values.[2d]

*trans-(2R,4S)-4-Methyl-2-(2-methylprop-1-en-1-yl)-1-tosylpiperidine (**33**).* IR (KBr): 2921, 2867, 1597, 1449, 1338, 1306, 1261, 1160, 1088 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.56 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.29 (dqunit, *J* = 1.3, 9.3 Hz, 1H), 4.00 (dt, *J* = 4.1, 12.0 Hz, 1H), 3.36 (ddd, *J* = 2.8, 10.0, 12.3 Hz, 1H), 2.63 (ddd, *J* = 2.8, 11.2, 12.0 Hz, 1H), 2.41 (s, 3H), 1.74 (m, 1H), 1.62 (s, 3H), 1.55−1.40 (m, 2H), 1.48 (s, 3H), 1.25 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 142.7, 135.9, 130.9, 128.9, 127.7, 127.4, 126.0, 120.0, 57.1, 47.3, 41.3, 33.6, 30.0, 25.7, 21.3, 17.6. ESIMS ($m/z$): 308 $[M + H]^+$. HRMS (ESI) $[M + H]^+$ Anal. Calcd for $C_{17}H_{26}O_2NS$: 308.16788. Found: 308.16645.

*cis-(2S,4S)-4-Methyl-2-(2-methylprop-1-en-1-yl)-1-tosylpiperidine (**34**).* Only the following signals of the $^1$H NMR spectroscopic data were assigned unambiguously. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.57 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 5.02 (m, 1H), 4.84 (m, 1H), 3.73 (m, 1H), 2.83 (td, *J* = 2.6, 12.7 Hz, 1H), 2.40 (s, 3H), 1.66 (s, 3H), 1.49 (s, 3H), 0.85 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 142.6, 137.0, 133.8, 128.9, 51.5, 39.8, 33.6, 25.6, 25.1, 22.1, 17.9.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02275.

$^1$H and $^{13}$C NMR spectra (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: drb.venky@gmail.com, venky@iict.res.in


### Notes

The authors declare no competing financial interest.

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