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DDQ-Promoted benzylic/allylic sp3 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

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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

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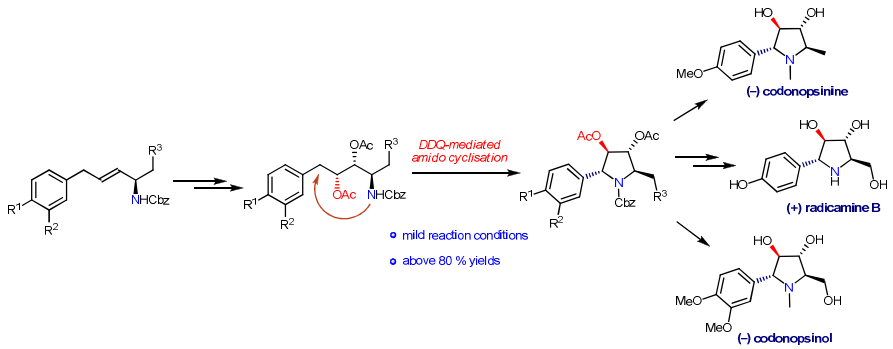


ABSTRACT: This is the first report on an intramolecular C–N bond formation of amide tethered benzylic / allylic system using DDQ under neutral conditions which has been successfully applied to the total synthesis of naturally occurring pyrolidine alkaloids. The key steps for the synthesis of corresponding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

INTRODUCTION

Presently, oxidative functionalisation of C–H bonds is an important strategy in organic synthesis. It provides excellent approach to make complex molecules from readily accessible substrates.[1] Direct conversion of C–H bond into 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 C–N bond.[2] In general, the reaction on to nitrogen to give 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 functionalised systems is a useful approach for making cyclic compounds.[3] Conversion of benzylic / allylic C–H to C–N bond in presence of DDQ has not been exploited and there are only couple of reports are 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 benzylic / allylic sp^3 C–H bond and its coupling with amide to get 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**.

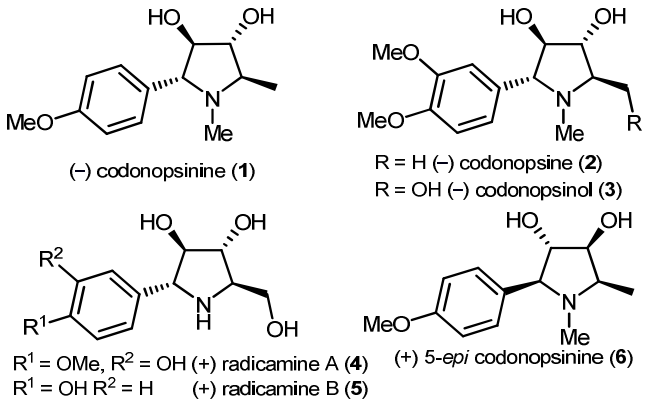


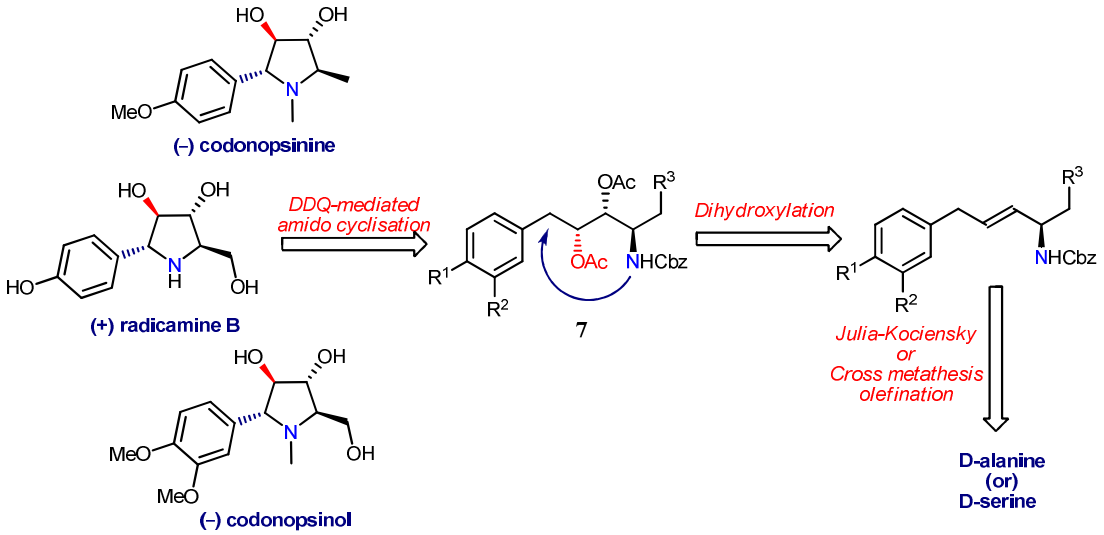
Figure 1: Pyrrolidine natural products

(–) Codonopsinine **1** and (–) codonopsine **2** (**Figure 1**) were isolated in 1969 from *Codonopsis clematidea*. These two compounds have shown antibiotic and hypotensive activi-

ties without interfering the central nervous system in animal tests.[8] (–) Codonopsinol **3** was isolated from the *C. clematidea*, whose aerial parts are useful for treating liver diseases.[6a] (–) Codonopsinol **3** was found to have an inhibitary activity against α-glucosidase of yeast and *Bacillus stearothermophilus* lymph.[6c] Radicamine A **4** and radicamine B **5** were isolated from *Lobelia chinenis Lour*, a 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 α-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 constitute 1,2,3,4-tetra substituted pyrrolidine ring bearing four contiguous streogenic centres (2*R*,3*R*,4*R*&5*R*) in all *trans* arrangement (**Figure 1**).

RESULTS AND DISCUSSION

Scheme 1: Retrosynthetic analysis of (–) codonopsinine and related natural products

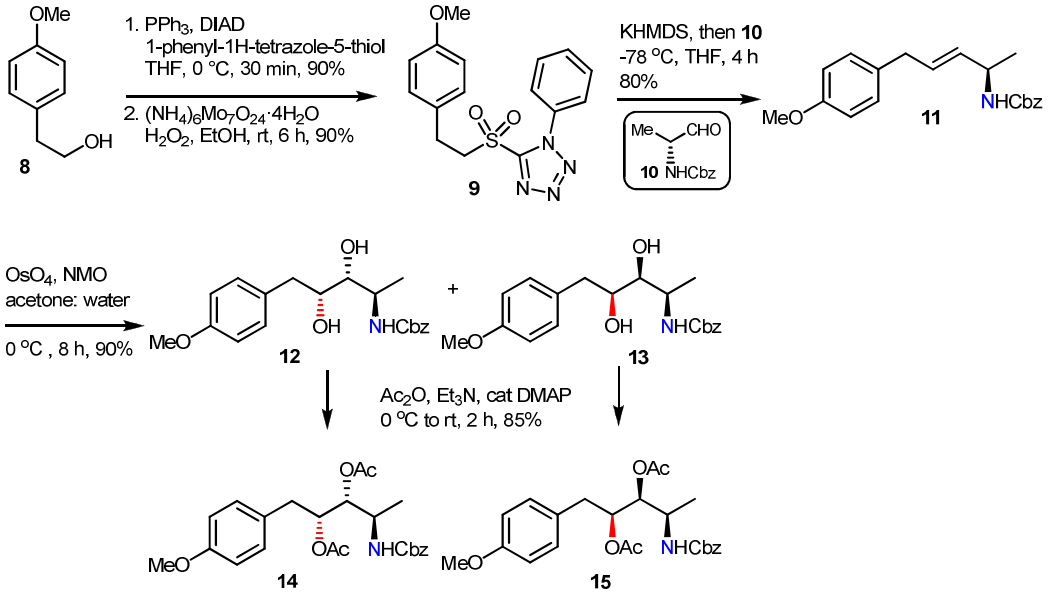


The retrosynthetic plan was designed for the above natural products based on the envisaged DDQ-mediated C–N bond formation from **7** (**Scheme 1**).

Initially we planned to synthesise, (–) 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 presence of TPP, DIAD and 1-phenyl-1H-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 presence of KHMDS at -78 °C afforded *E*-olefin **11** (**Scheme 2**).

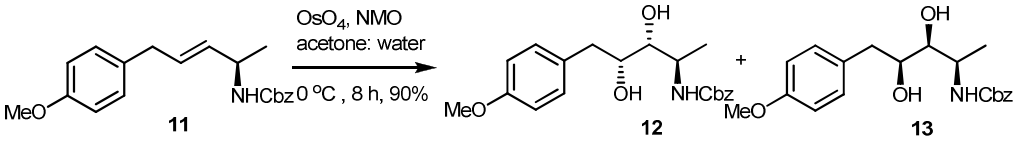
Scheme 2: Synthesis of the basic carbon skeleton of (–) codonopsinine



The next step was to construct the diol **12** from **11** using dihydroxylation under various conditions (Table 1). For this purpose AD-mix-β was choosen as a chiral reagent. When compound **11** was subjected to dihydroxylation with AD-mix-β gave the compounds **12** and **13** in 50% yield (*dr* = 53:47, mismatched).[5c,11] To improve the yields and selectivity, the compound **11** was subjected to modified SAD conditions (entries 2 and 3, Table 1), it gave good yield of diols but without much improvement in diastereoselectivity. When dihydroxylation was carried with simple OsO_4 afforded slightly better diastereoselectivity (*dr* = 70:30) with 90% yield (entry 4, Table 1). Treatment of compound **11** with AD-mix-α 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 cyclisation on **14** to obtain the pyrrolidine core **16**.

Table 1. Asymmetric dihydroxylation studies on compound 11 under various reaction conditions



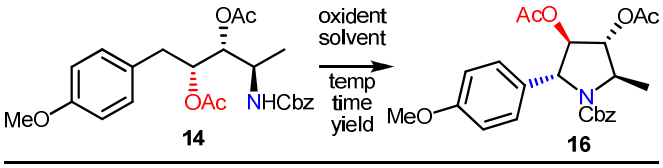
entry	reagents	solvents (ratio)	conditions	yield[a]	dr[b] (12 and13)
1	AD-mix-β (1.4 g/mmol)	*t*-butanol:water (1:1)	0 °C (24 h) to rt 24 h	50	53:47
2	AD-mix-β (1.4 g/mmol) OsO_4 (0.6 mol%) $CH_3SO_2NH_2$ (95 mg/mmol) $NaHCO_3$ (0.25 g/mmol	*t*-butanol:water (1:1)	0 °C (15 h)	90	60:40
3	AD-mix-β (1.4 g/mmol) OsO_4 (0.6 mol%) $(DHQD)_2PHAL$ (4 mol%) $CH_3SO_2NH_2$ (95 mg/mmol) $NaHCO_3$ (0.25 g/mmol)	*t*-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-α (1.4 g/mmol) OsO_4 (0.6 mol%) $(DHQ)_2PHAL$ (4 mol%) $CH_3SO_2NH_2$ (95 mg/mmol) $NaHCO_3$ (0.25 g/mmol)	*t*-butanol:water (1:1)	0 °C (15 h)	90	5:95

(a) yield represents the separable diastereomers after purfication;
(b) diastereomers were separable.

Several explorations were carried out under various conditions in presence of DDQ to get **16** from **14** and the results are summarized in Table 2. The conversion was examined in 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 below conversion better yields were obtained in acetonitrile under

reflux condition (entry 8, Table 2). In fact, there are some studies reported earlier in support of acetonitrile as a better choice for DDQ oxidation.[3c,d]

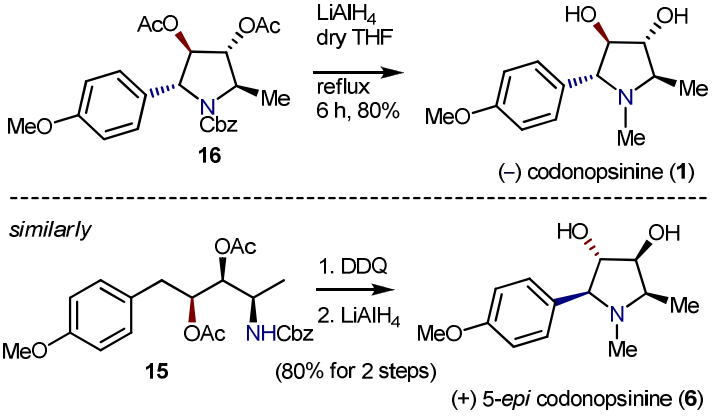
Table 2. Optimization of reaction conditions[a]



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] based on TLC analysis.

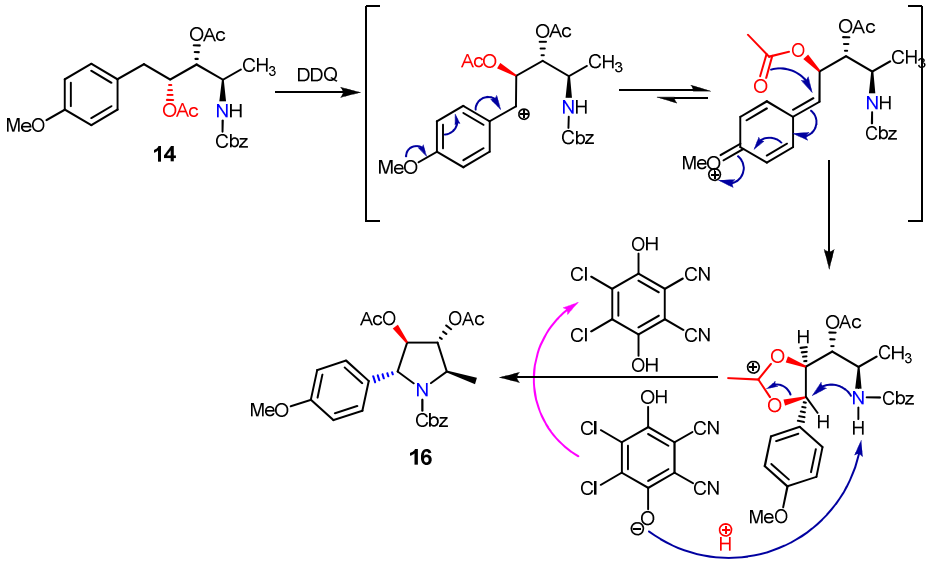
Scheme 3: Completion of total synthesis of (–) codonopsinine 1 and (+) 5-*epi*-codonopsinine 6



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] Based on these results, we then proceeded to apply this methodology for the synthesis of other target molecules. 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 over-hauser enhancement (*nOe*) correlations (see in supporting information).

Scheme 4: A plausible reaction pathway

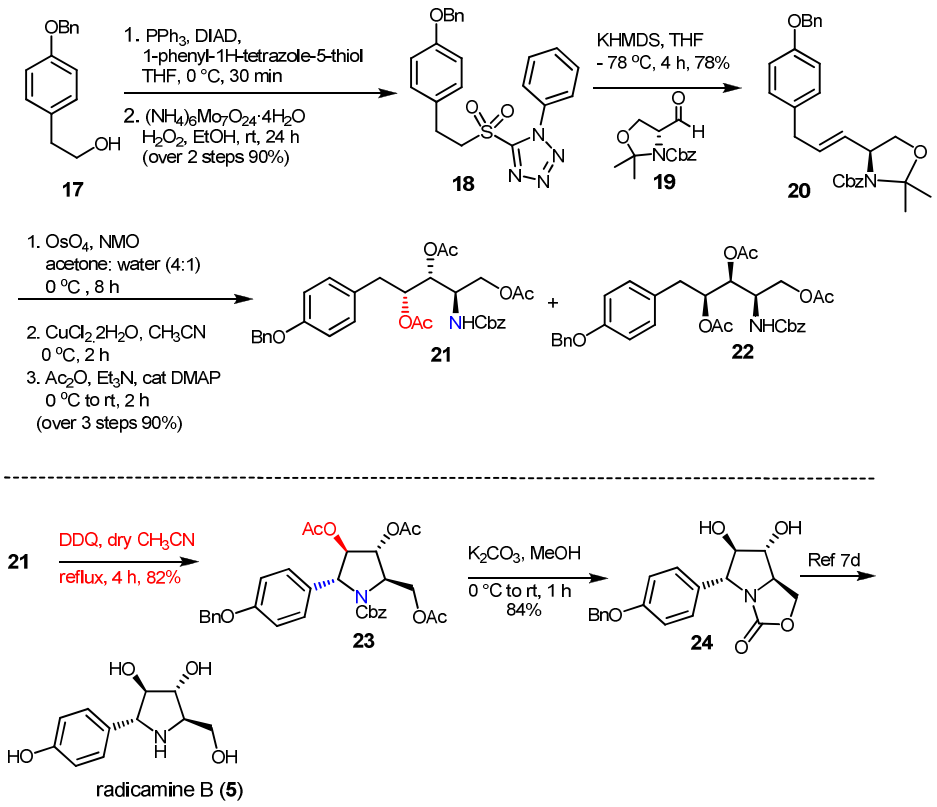


The high stereoselectivity in this reaction can be explained as follows. The benzylic carbocation formed by DDQ oxidation was further stabilized by the neighbouring acetoxy group to give a *trans*-dioxolane carbocation (acetoxonium ion) intermediate, thereby facilitating the approach of the *N*-nucleophile preferentially from the opposite face to yield the pyrrolidine core **16** with C-2 aryl and C-3 hydroxy groups in *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 the *E*-olefin **20**. Further, the 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 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]

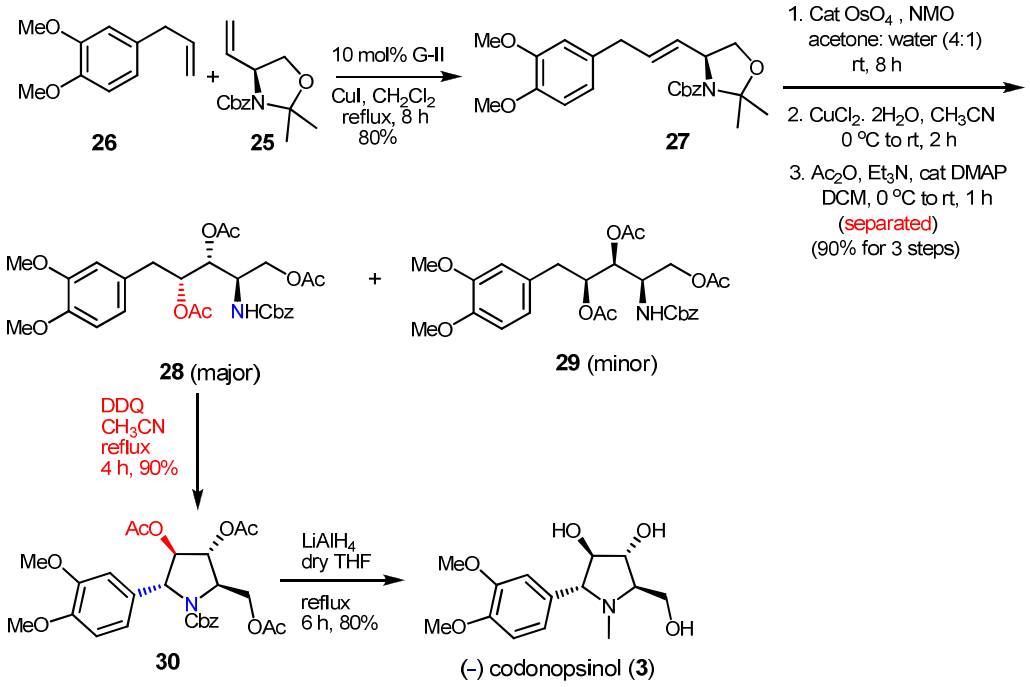
Scheme 5: Total synthesis of (+) radicamine B 5



For the synthesis of (–) codonopsinol **3**, we adopted 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 presence of Grubbs 2nd generation catalyst and CuI in dry CH_2Cl_2 at 45 °C to give exclusively the *E*-olefin **27** in 80% yield.[14] The compound **27** was converted into separable triacetates **28** and **29** (70:30 ratio) in good yields using the procedure which was described for **20**. Cyclisation

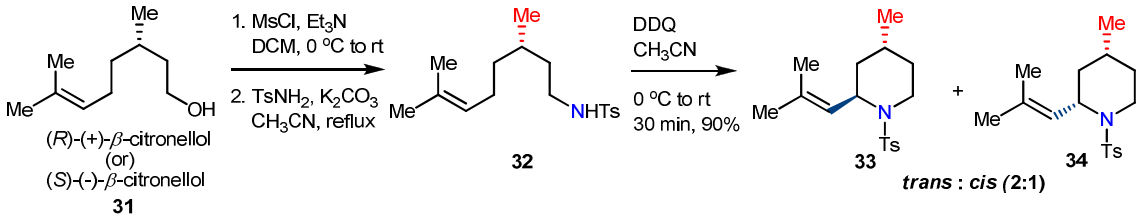
of major triacetate **28** with DDQ in dry CH_3CN under reflux for 4 h afforded the *trans*-pyrrolidine compound **30** in 90% yield. Treatment of **30** with $LiAH_4$ in dry THF under reflux for 6 h afforded the (–) codonopsinol **3** in 80% yield. The spectral (^1H and ^{13}C) and analytical (optical rotation and melting point) data of synthetic (–) codonopsinol **3** were in excellent agreement with the reported values (**Scheme 6**).[6b]

Scheme 6: Total synthesis of (–) codonopsinol 3



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

Scheme 7: Synthesis of cyclic amines from *ω*-unsaturated *N*-sulfonylamines



We have chosen **32** to study the DDQ-mediated allylic amido cyclisation. When the compound **32** was treated with DDQ in dry CH_3CN, interestingly the reaction proceeded at 0 ^oC to rt to afford the 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 synthesise the above compounds.

CONCLUSIONS

In summary, we have developed a novel reaction *i.e* DDQ mediated stereoselective intramolecular dehydrogenative amido cyclisation, which was successfully demonstrated for the synthesis of polyhydoxylated 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 prefunctionalisation 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 a 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. 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-β mixture contains $(DHQ)_2PHAL$ (0.0016 mole), potassium carbonate (0.4988 mole), potassium ferricyanide (0.4988 mole) and potassium osmate dihydrate (0.0007 mole). AD-mix-α mixture contains $(DHQ)_2PHAL$ (0.0016 mole), potassium carbonate (0.4988 mole), potassium ferricyanide (0.4988 mole) and potassium osmate dihydrate (0.0007 mole). 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 spectrometers. Chemical shifts (δ) 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) technique and orbitrap mass analyser. Optical rotations were measured in 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 was 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 1:9) to furnish sulphide compound (3.69 g, 90%) as colourless 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 was 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 colourless and very viscous oil. IR (neat): 2923, 2851, 1725, 1508, 1338, 1244, 1148, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 stirred further for 30 min at the same temp. 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 ^oC and then DIPEA (10.8 mL, 63.1 mmol) was added at -78 ^oC. 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, 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 colourless 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 white cloudy suspension and the TLC analysis indicated the 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 colourless 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 x 20 mL). The combined extracts were dried over Na_2SO_4 and solvent removed thoroughly un-

der *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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 colourless 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, $CDCl_3$): δ 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, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 ^oC 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, 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 colourless 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, 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 x 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 (^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] 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}; ^1H NMR (300 MHz, pyridine-d_5): δ 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): δ 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-diyldiacetate (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 chromatog-

raphy (ethyl acetate/hexane 1:8) to afford the compound **15** (0.5 g, 85%) as a colourless oil. $[\alpha]_D^{20}$ = +38.2 (*c* 0.8, $CHCl_3$); IR (neat): 2925, 2363, 1740, 1708, 1515, 1461, 1224, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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/z)*: 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 ^oC for 8 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, 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 colourless oil. $[\alpha]_D^{20}$ = -16.1 (*c* 0.22, $CHCl_3$); IR (neat): 2930, 2363, 1743, 1705, 1513, 1222, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, 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 x 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}; ^1H NMR (500 MHz, pyridine-d_5): δ 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): δ 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 ^oC 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, 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 x 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 ℃. To the 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 was 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 ℃. 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 was 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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)-Benzyl4-(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 ^oC and then Et_3N (7.57 mL, 54.3 mmol) was added at -78 ^oC. 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, 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 colourless 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 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 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 upon silica gel column chromatography (ethyl acetate/hexane 1:8) gave olefin

20 (2.58 g, 78%) as a colourless 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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-(benzyloxy carbonylamino)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 x 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 colourless oil. The dihydroxylated compound (2.41 g, 4.90 mmol) in CH_3CN (5 mL) was added $CuCl_2.2H_2O$ (0.97 g, 5.89 mmol) and quenched with saturated $NaHCO_3$ and filtered through 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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-(benzyloxy carbonylamino)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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 ^oC 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, 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 colourless 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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-dihydroxytetrahydropyr-rolo[1,2-c]ox-azol-3(1H)-one (24). To a 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), 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 (^1H and ^{13}C) and analytical (optical rotation and melting point) data of synthetic compund **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}; ^1H NMR (300 MHz, CD_3OD): δ 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): δ 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 ^{o}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 ^{o}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 the 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 ^{o}C. After stirring for 3 h, the reaction mixture was quenched with saturated aq NH_4Cl at 0 ^{o}C, THF was removed under reduced pressure and the residue was extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were washed with H_2O (50 mL) 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 colourless 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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)-Benzyl4-(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) and 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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 x 20 mL). The combined extracts were dried over Na_2SO_4 and

solvent 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 colourless oil.

To a stirred solution of dihydroxylated compound in CH_3CN (5 mL) was added $CuCl_2.2H_2O$ (0.484 g, 2.91 mmol) at 0 ^oC and the reaction mixture was warmed to room temperature under stirring for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$, filtered through 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}; ^1H NMR (400 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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}; ^1H NMR (400 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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-(benzyloxy carbonyl)-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 ^oC 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, 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 colourless oil. $[\alpha]_D^{20}$ = -9.8 (*c* 0.19, $CHCl_3$); IR (neat): 2924, 2852, 1743, 1705, 1515, 1404, 1219, 1141, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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), 2.12 (s, 3H), 1.85 (s, 3H) (multiple peaks are due to rotameric mixture); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 the completion of the addition the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to 0 °C, 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, washed with ethyl acetate (3 x 10 mL) and the filtrate was evaporated under *vacuum*. The residue was purified through silica gel column ($CHCl_3$/MeOH = 7:1) to afford the codonopsinol **3** (0.12 g, 80%) as white solid. The spectral (^1H 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}; ^1H NMR (400 MHz, CD_3OD): δ 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): δ 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-methylbenzene sulfonamide (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 colourless 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 celite pad and evaporated under *vacuum*. Purification by silica gel column chromatography (ethyl acetate/hexane 1:9) afforded product **32** as a colourless 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, $CDCl_3$): δ 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): δ 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 ^{o}C. The resulting mixture was allowed to room temperature for 30 min 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, concentrated under reduced pressure to give crude residue, which was purified by silica gel column chromatography (ethyl acetate/hexane 1:9) to give mixture of cyclic compounds **33** and **34** (0.39 g, 90%) as colourless oils. The spectral (^{1}H and ^{13}C) data of synthetic compound **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): δ 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, $CDCl_3$): δ 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): δ 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, $CDCl_3$): δ 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

Copies of ^{1}H and ^{13}C NMR spectra of this material is available free of charge via the internet at **http://pubs.acs.org**.

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