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# Total synthesis of (−)-codonopsinol and (+)-2-*epi* codonopsinol via acid catalyzed amido cyclisation

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ABSTRACT

A short and stereoselective synthesis of (−)-codonopsinol **5** and its C-2 epimer **6** were accomplished from commercially available starting material D-1,5-gluconolactone, using acid mediated amido cyclisation as the key step. The inhibitory activitiy of these compounds against glucosidase and galactosidase has been studied.



## 1. Introduction

Synthesis of natural and synthetic polyhydroxylated pyrrolidines is gaining more and more importance because of their highly active and efficient glycosidase inhibitory activity.[1] Polyhydroxylated pyrrolidine alkaloids containing an aromatic substituent on the iminosugar ring are of a rare class found in nature (Fig. 1). (−)-Codonopsinine **1** and (−)-codonopsine **2** are the first two examples in this unusual category, initially isolated in 1969 from *Codonopsis clematidea*.[2,3] These two compounds display antibiotic as well as hypotensive activities without affecting the central nervous system in animal tests.[4] Radicamine A **3** and radicamine B **4** are another examples for this category, isolated from *Lobelia chinensis* LOUR (Campanulaceae) by Kusano et al. and exhibited glycosidase inhibitory activity.[5,6] Recently, Ishida and co-workers reported another new codonopsine related alkaloid (−)- codonopsinol **5** from the aerial parts of *C. clematidea*.[7a] The aerial parts of *C. clematidea* are well known for their medicinal properties in treating liver diseases. The (−)-codonopsinol **5** is also known for its inhibitory activity against the α-glucosidase of yeast and bacillus stearothermophilus lymph.[7b] Ishida et al. established the relative stereochemistry of the molecule **5** by nuclear Overhauser enhancement (NOE) correlations.[7a] These correlations were found to be same as those of codonopsine **2**,[3b,d,f,8] where all the four contiguous stereogenic centers are situated in all *trans* positions. Later Tsou et al.[7b] synthesized (2*R*,3*R*,4*R*,5*R*) isomer of codonopsinol **5**, whose spectral data was very much in agreement with the reported values. The specific rotation of synthetic sample is found to be $[\alpha]_D$ −15, where as the natural product rotation is $[\alpha]_D$ −3.5. Therefore the absolute configuration of the molecule **5** can be considered as (2*R*,3*R*,4*R*,5*R*) at the four stereogenic centers as per the synthesis.

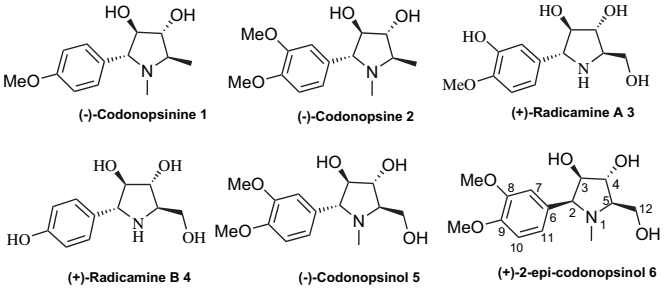


**Figure 1.**

In continuation of our efforts in the synthesis of polyhydroxylated pyrrolidine alkaloids and azasugars,[9] here in we wish to report the total synthesis of (−)-codonopsinol **5** and 2-*epi*-codonopsinol **6** and their inhibitory activity against glucosidases and galactosidases. So far only one synthesis for **5** is reported.[7b] Recently we developed a strategy for the synthesis of phenyl substituted polyhydroxylated pyrrolidines[3a] and its application to codonopsinine **1** using acid catalyzed amido cyclisation, taking advantage of the stability of the benzylic carbocation.[10] Based on this protocol we envisaged the following retro synthesis for (−)-codonopsinol **5** (Scheme 1). The pyrrolidine core skeleton can be obtained from protected amino alcohol **7** by means of acid catalyzed cyclisation through intramolecular $S_N1$ reaction based on our earlier observation for the synthesis of codonopsinine **1**. The compound **7** can be obtained from commercially available D-1,5-gluconolactone **8**.

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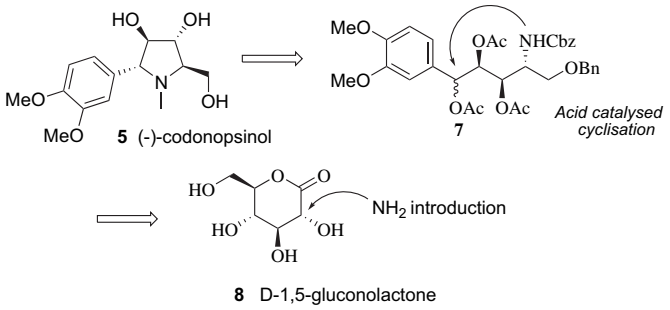
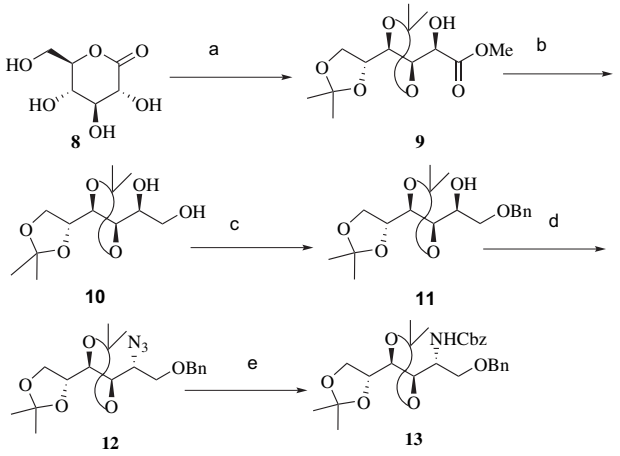



**Scheme 1.**

## 2. Results and discussions

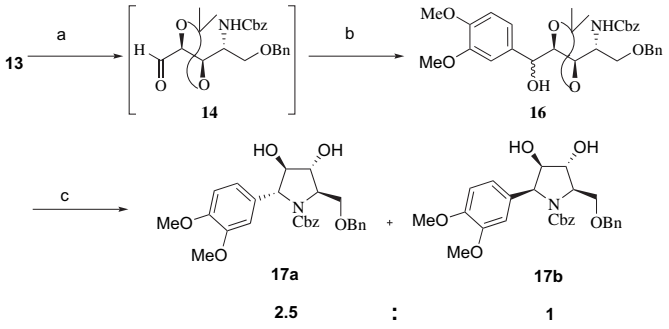
D-Gluconolactone **8** on treatment with 2,2-DMP in presence of catalytic amount of PTSA in acetone, methanol gave α-hydroxy ester **9** in 76% yield.[11] Reduction of the ester functionality of **9** with LAH afforded diol **10**. Regioselective benzylation of diol **10** with dibutyl tin oxide in toluene followed by the addition of benzyl bromide in presence of catalytic TBAI gave compound **11** in 89% yield. Compound **11** on treatment with $MsCl/Et_3N$ gave corresponding mesylate derivative, which up on treatment with $NaN_3$/DMF yielded corresponding azido derivative **12** in 80% yield. Reduction of the azido functionality with $LiAlH_4$/THF gave amine, which was immediately treated with $CbzCl/Na_2CO_3$ in $CH_2Cl_2$ affording the fully protected compound **13**[12] (Scheme 2).



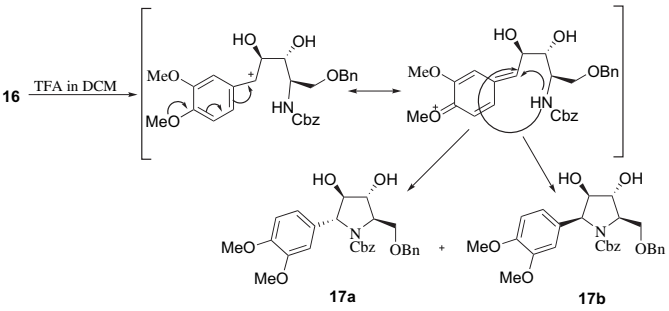
**Scheme 2.** Reagents and conditions: (a) 2,2-DMP, PTSA, Acetone, MeOH, 0 °C-rt, 50 h, 76%; (b) $LiAlH_4$, THF, 0 °C-rt, 4 h, 93%; (c) (i) $Bu_2SnO$, Toluene, reflux, 8 h; (ii) BnBr, TBAI, reflux, 16 h, 89%; (d) (i) MsCl, $N(Et)_3$, $CH_2Cl_2$, 0 °C-rt, 3 h; (ii) $NaN_3$, DMF, 80 °C, 24 h, 80%; (e) (i) $LiAlH_4$, THF, 0 °C-rt, 5 h; (ii) CbzCl, $Na_2CO_3$, $CH_2Cl_2$, 0 °C-rt, 8 h, 87%.

Selective deprotection of the terminal acetonide of **13** and in situ oxidative cleavage[13] of the resulting diol with periodic acid in ether gave aldehyde **14**. The aldehyde **14** was treated with the freshly prepared Grignard reagent from 3,4-dimethoxybromobenzene and Mg in THF to give diastereomeric mixture **16** in 65% yield (**~3:1** ratio based on $^1H$ NMR signals). Initially it was planned to deprotect the acetonide of **16** and convert the hydroxyls to acetate groups to conduct amido cyclisation in presence of TFA.

Basically the presence of acetate helps in fixing the stereochemistry exclusively on benzylic carbon during cyclisation by its participation as neighboring group.[3a] Interestingly when the alcoholic mixture was treated with $TFA/CH_2Cl_2$ (1:1) for 4 h gave directly *trans* pyrroilidine compound **17a** as a major isomer along with *cis* isomer **17b** (2.5:1) in 80% isolated yield.[14] The formation of mixture of products (**17**) further confirmed our earlier proposed mechanism[3a] where acetate presence directs the nucleophile to under go cyclisation to give single isomer (Scheme 3). The mechanism of formation of cyclic compounds **17a** and **17b** from **16** can be explained as shown in Scheme 4.

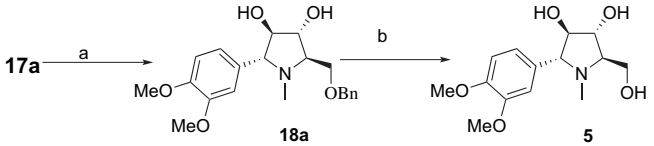



**Scheme 3.** Reagents and conditions: (a) $H_5IO_6$, Ether, 0 °C-rt, 6 h; (b) 3,4-dimethoxy phenyl magnesium bromide (**15**), THF, 0 °C-rt, 16 h, 65%; (c) $TFA,CH_2Cl_2$, 0 °C-rt, 4 h, 80%.



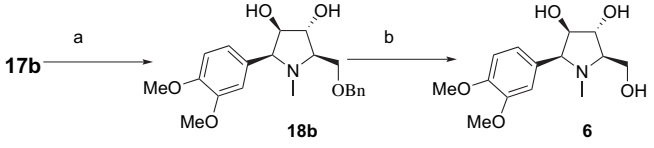

**Scheme 4.**

The major isomer **17a** was treated with LAH in THF under reflux for 5 h, to give *N*-methyl derivative **18a** in 82%. Compound **18a** on catalytic hydrogenation with $PdCl_2/H_2$ in methanol gave (−)-codonopsinol **5** in 85% isolated yield. The spectral and analytical data of synthetic (−)-codonopsinol **5** were in excellent agreement with the reported values[7b] (Scheme 5). Our synthesis further confirms the absolute stereochemistry of the molecule **5**.




**Scheme 5.** Reagents and conditions: (a) $LiAlH_4$, THF, 0–60 °C, 5 h, 82%; (b) $PdCl_2/H_2$, MeOH, 12 h, 70%.

The minor isomer **17b** was transferred to (+)-2-*epi*-codonopsinol **6** following similar reaction pathway used for the preparation of **5** in 65% yield for two steps (Scheme 6). The stereochemistry of compound **6** was confirmed with 1D nuclear Overhauser enhancement (NOE) correlations.[15]




**Scheme 6.** Reagents and conditions: (a) $LiAlH_4$, THF, 0–60 °C, 5 h, 82%; (b) $PdCl_2/H_2$ MeOH, 12 h, 70%.

## 3. Assay of enzyme inhibition

Glucosidase and galactosidase inhibitory activities of **5** and **6** were determined by measuring the enzyme activity in presence of the compounds on a Perkin–Elmer Lambda 2 UV-visible spectrophotometer equipped with temperature control and PECSS software. All enzyme assays were performed at 25 °C. All experiments were repeated three times and were reproducible within ±5%. The enzymes and corresponding substrates used for assay were as follows: α-glucosidase from yeast (4-nitrophenyl-α-D-glucopyranoside), β-glucosidase from almonds (2-nitrophenyl-β-D-glucopyranoside), α-galactosidase from green coffee beans (4-nitrophenyl-α-D-galactopyranoside), and β-galactosidase from *Kluyveromyces lactis* (*p*-nitrophenyl-β-D-galactopyranoside).

### 3.1. Enzyme assay

The *p*-nitrophenyl derivative of the substrate (1.6 mM) in phosphate buffer (0.25 M, pH 6.8, 2.0 mL) was placed in a cuvette, and the enzyme solution (1 mg/mL, 100 μL) was added. Change in absorbance due to release of *p*-nitrophenol was monitored at 410 nm (molar extinction coefficient at 410 nm, $\Delta\varepsilon$ 8800 $M^{-1}$ $cm^{-1}$) for 3–5 min. Similar experiments were performed in presence of the compounds **5** and **6** at concentrations varying from 1 μM to 2 mM. The values of $IC_{50}$ were calculated using non-linear regression analysis of GraphPad Prism Version 5. The values are given in Table 1. The compound **5** has better activity than **6** against glucosidases. Probably the all *trans* configuration as in **5** may be an essential feature for the activity. This fact further requires to be established by making and scanning more analogues. Both the compounds have not shown inhibition against galactosidases at 1 mM.

**Table 1**
$IC_{50}$ values in μm

| Compound | $IC_{50}$ (μm) | | | |
|---|---|---|---|---|
| | α-glucosidase | β-glucosidase | α-galactosidase | β-galactosidase |
| **5** | 54 | 53.8 | NI[a] | NI[a] |
| **6** | 457 | 137 | NI[a] | NI[a] |

[a] No inhibition at 1 mm.

## 4. Conclusion

In summary, we developed a novel synthetic approach for the natural (−)-codonopsinol **5** and its epimer, (+)-2-*epi*-codonopsinol **6** from D-1,5-gluconolactone, using stereoselective intramolecular $S_N1$ cyclisation protocol as the key step.

## 5. Experimental section

### 5.1. General

Moisture- and oxygen- sensitive reactions were carried out under nitrogen gas atmosphere. All solvents and reagents were purified by standard techniques. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 and 100–200 mesh) using ethyl acetate, hexane and chloroform, methanol as eluents. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FTIR system. $^1$H NMR (400, 300 and 200 MHz) and $^{13}$C NMR (75 and 100 MHz) spectra were recorded on corresponding MHz. Chemical shifts were reported in parts per million with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in Hertz. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

*5.1.1. (R)-Methyl 2-hydroxy-2-((4R,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl) acetate* ***9***. To a stirred suspension of D-glucono-1,5-lactone **8** (10.0 g, 56.0 mmol) in a mixture of 2, 2-dimethoxypropane (20 mL), acetone (6 mL) and methanol (2 mL) was added catalytic amount of *p*-toluenesulfonic acid (150 mg) at 0 °C under nitrogen atmosphere. Then the reaction mixture was allowed to stir for 50 h at room temperature. TLC indicated complete conversion of the starting material to a major product. Sodium hydrogen carbonate (1.5 g) was added for neutralization and the reaction mixture was stirred for 1 h and filtered through Celite. The filtrate was evaporated under reduced pressure; the residue was dissolved in dichloromethane (100 mL) and washed with water (20 mL). The aqueous phase was extracted with dichloromethane (40 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexane=1:3) to afford **9** (12.38 g, 76%) as a colorless oil. $R_f$ (30% ethyl acetate/hexane) 0.6; $[\alpha]_D^{28}$ +2.4 (*c* 0.8, $CHCl_3$) {lit.[11], $[\alpha]_D^{20}$ 1.7 (*c* 1.18, $CHCl_3$)}; IR (neat) $\nu_{max}$ 3498, 2988, 2936, 1748, 1377, 1252, 1215, 1133, 1072, 846 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.33 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$), 1.38 (s, 3H, $CH_3$), 2.88 (d, 1H, *J*=9.06 Hz, OH), 3.84 (s, 3H, OMe), 3.91–4.19 (m, 5H, $CH_2$OH and 3C*H*O–), 4.26 (dd, 1H, *J*=1.17, 8.59 Hz, C*H*OH); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.9, 26.2, 26.4, 26.9, 52.4, 67.6, 69.2, 76.2, 77, 80.6, 109.6, 109.8, 172.7; ESI/MS (*m*/*z*) 313 ($M^+$+Na); HRMS calcd for $C_{13}H_{22}O_7Na$ 313.126, found 313.1258.

*5.1.2. (S)-1-((4R,4′R,5R)-2,2,2′,2′-Tetramethyl-4,4′-bi-(1,3-dioxolan)-5-yl)ethane-1,2-diol* ***10***. To a suspension of $LiAlH_4$ (2.04 g, 53.79 mmol) in anhydrous THF (50 mL) at 0 °C was added methyl ester **9** (12.0 g, 41.38 mmol) in THF (30 mL) drop wise over a period of 20 min. After being stirred for 4 h at room temperature, the reaction mixture was quenched with water (2.0 mL), 15% NaOH (2.0 mL), and water (6.0 mL) drop wise sequentially at 0 °C. After completion of the addition, the reaction mixture was allowed to stir at room temperature for 2 h, filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:1.5) to give **10** (10.1 g, 93%) as white solid. $R_f$ (40% ethyl acetate/hexane) 0.16; mp 50–52 °C; $[\alpha]_D^{28}$ −34.14 (*c* 0.3, $CHCl_3$); IR (neat) $\nu_{max}$ 3445, 2987, 2927, 1376, 1251, 1216, 1156, 1069, 847 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.32 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$), 1.40 (s, 3H, $CH_3$), 1.41 (s, 3H, $CH_3$), 2.53 (br s, 1H, OH), 2.68 (d, 1H, *J*=7.93 Hz, OH), 3.63–3.80 (m, 3H, $CH_2$OH and C*H*O–), 3.92–4.07 (m, 4H, $CH_2$O– and 2C*H*O–), 4.09–4.18 (m, 1H, C*H*O–); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 25.1, 26.4, 26.7, 26.9, 64.6, 67.7, 70.5, 77.1, 77.2, 81.1, 109.6, 109.8; ESI/MS (*m*/*z*) 285 ($M^+$+Na); HRMS calcd for $C_{12}H_{22}O_6Na$ 285.1314, found 285.1302.

*5.1.3. (S)-2-(Benzyloxy)-1-((4R,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)ethanol* ***11***. To a stirred solution of compound **10** (8 g, 30.53 mmol) in dry toluene (60 mL) was added dibutyl tin oxide (9.87 g, 39.69 mmol) at room temperature. The reaction was slowly heated to 80 °C, after being stirred for 8 h, the reaction mixture was allowed to room temperature. Benzyl bromide (4 mL) and catalytic amount of TBAI was added to the cooled reaction mixture and stirred for 16 h at 80 °C. The reaction mixture was cooled to room temperature and evaporated the solvent under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:7) to give benzyl derivative **11** (9.6 g, 89%) as thick syrup. $R_f$ (30% ethyl acetate/hexane) 0.8; $[\alpha]_D^{28}$ +4.60 (*c* 1.55, $CHCl_3$)IR (neat) $\nu_{max}$ 3479, 2986, 2928, 1627,

1455, 1375, 1247, 1214, 1151, 1070, 846 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.30 (s, 3H, $CH_3$), 1.34 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$), 1.38 (s, 3H, $CH_3$), 2.22 (d, 1H, $J$=7.74 Hz, OH), 3.53 (d, 2H, $J$=6.04 Hz, $CH_2$OBn), 3.85–4.02 (m, 5H, $CH_2$OH, 2CHO–and CHOH), 4.05–4.12 (m, 1H, CHO–), 4.55 (dd, 2H, $J$=12.08, 18.50 Hz, PhC$H_2$O), 7.20–7.34 (m, 5H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 25.2, 26.5, 26.8, 27.1, 67.7, 68.9, 71.9, 73.2, 77, 77.1, 80.1, 109.4, 109.6, 127.6, 127.6, 128.2, 137.9; ESI/MS ($m/z$) 375 ($M^+$+Na); HRMS calcd for $C_{19}H_{28}O_6Na$ 375.1783, found 375.1797.

*5.1.4. (4S,4′R,5R)-5-((R)-1-Azido-2-(benzyloxy)ethyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane)* ***12****.* To a stirred solution of **11** (6 g, 17.04 mmol) in dry $CH_2Cl_2$ (35 mL) was added $N(Et)_3$ (7.1 mL, 51.13 mmol) at 0 °C under nitrogen atmosphere. After 5 min. stirring, methane sulfonylchloride (1.6 mL, 20.45 mmol) was added drop wise to the reaction mixture and allowed to stir at room temperature for 3 h, the reaction mixture was diluted with $CHCl_3$ (80 mL). The organic solution was washed with water (30 mL), brine (10 mL), dried over $Na_2SO_4$ and evaporation of the solvent under reduced pressure afforded corresponding mesyl derivative as yellow oil, which was carried to the next step without any purification.

To a stirred solution of above mesylate derivative in dry DMF (20 mL) was added $NaN_3$ (3.32 g, 51.13 mmol) under nitrogen atmosphere at room temperature, the reaction was slowly heated to 80 °C, after being stirred for 24 h, the reaction mixture was allowed to room temperature, poured in to ice cold water (20 mL), and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane=1:19) to afford **12** (5.14 g, 80%) as yellowish oil. $R_f$ (20% ethyl acetate/hexane) 0.85; $[\alpha]_D^{28}$ +9.09 (*c* 2.02, $CHCl_3$); IR (neat) $\nu_{max}$ 2987, 2932, 2101, 1455, 1375, 1253, 1214, 1154, 1067, 847 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.30 (s, 3H, $CH_3$), 1.34 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$), 1.38 (s, 3H, $CH_3$), 3.56 (dd, 1H, $J$=7.55, 9.82 Hz, CHHOBn), 3.66–3.79 (m, 2H, CHHOBn and CHN$_3$), 3.89 (m, 2H, CHHO and CHO–), 4.01 (m, 2H, CHHO and CHO–), 4.07 (dd, 1H, $J$=6.23, 8.42 Hz, CHO–) 4.55 (s, 2H, PhC$H_2$O), 7.23–7.34 (m, 5H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 25.2, 26.3, 27.1, 27.3, 62.6, 67.2, 69.6, 73.3, 76.8, 78.7, 79.4, 109.7, 110.0, 127.5, 127.7, 128.3, 137.6; ESI/MS ($m/z$) 400 ($M^+$+Na); HRMS calcd for $C_{19}H_{27}N_3O_5Na$ 400.1848, found 400.1834.

*5.1.5. Benzyl (R)-2-(benzyloxy)-1-((4S,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl) ethylcarbamate* ***13****.* To a suspension of $LiAlH_4$ (523 mg, 13.79 mmol) in dry THF (15 mL) was added compound **12** (4 g, 10.61 mmol) in dry THF (20 mL) drop wise at 0 °C under nitrogen atmosphere. After being stirred for 5 h at room temperature, the reaction mixture was quenched with water (0.5 mL), 15% aq NaOH (0.5 mL), water (1.5 mL) successively at 0 °C. After 1 h stirring at room temperature, the reaction mixture filtered through a pad of Celite and filtrate was evaporated under reduced pressure. The crude residue dissolved in $CH_2Cl_2$ (20 mL), to it was added $Na_2CO_3$ (1.12 g, 10.61 mmol) and CbzCl (3.55 mL, 21.22 mmol) drop wise at 0 °C. After being stirred for 8 h at room temperature, the reaction mixture was diluted with $CHCl_3$ (50 mL). The organic solution was washed with water (20 mL), brine (10 mL), dried over $Na_2SO_4$, evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (ethyl acetate/hexane=1:6) afforded **13** (4.46 g, 87%) as crystalline solid. $R_f$ (30% ethyl acetate/hexane) 0.52; mp 53–55 °C; $[\alpha]_D^{28}$ −56 (*c* 1.90, $CHCl_3$); IR (neat) $\nu_{max}$ 3424, 2986, 2927, 1721, 1517, 1374, 1215, 1061, 754 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.26 (s, 3H, $CH_3$), 1.29 (s, 3H, $CH_3$), 1.35 (s, 6H, 2-C$H_3$'s), 3.68 (br s, 2H, $CH_2$OBn), 3.83 (dd, 2H, $J$=5.28, 8.12 Hz, CHO– and CHNH), 3.92 (m, 2H, CHHO and CHO–), 4.10 (m, 2H, CHHO and CHO–), 4.53 (s, 2H, PhC$H_2$O), 5.05 (dd, 2H, $J$=12.27, 15.01 Hz, PhC$H_2$O), 5.32 (d, 1H, $J$=8.12 Hz, NH), 7.19–7.34 (m, 10H, Ph); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 25.2, 26.2, 27.2, 27.5, 53.6, 66.6, 67.5, 68.6, 73.1, 76.9, 78.5, 79.9, 109.6, 109.9, 127.4, 127.9, 128, 128.2, 128.3, 136.3, 138.0, 155.9; ESI/MS ($m/z$) 508 ($M^+$+Na); HRMS calcd for $C_{27}H_{35}NO_7Na$ 508.2311, found 508.2328.

*5.1.6. Benzyl(R)-2-(benzyloxy)-1-((4R,5R)-5-((3,4-dimethoxy-phenyl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxol-an-4-yl)ethylcarbamate* ***16****.* To a solution of **13** (1 g, 2.06 mmol) in dry ether (20 mL) was added periodic acid (704 mg, 3.09 mmol) portion wise at 0 °C under nitrogen atmosphere. After being stirred for 6 h at room temperature, the reaction mixture was neutralized with $NaHCO_3$, filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give crude aldehyde derivative **14**, which was carried to the next step without any purification.

To a stirred solution of 3,4-dimethoxy phenyl magnesium bromide **15**{freshly prepared with Mg (465 mg, 19.4 mmol) and 3,4-dimethoxybromobenzene (1.4 ml, 9.69 mmol) in dry THF (15 mL) at 80 °C for 2 h under stirring} was added aldehyde 14 in dry THF (20 mL) drop wise at 0 °C under nitrogen atmosphere. After being stirred for 12 h at room temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ at 0 °C, THF was removed under reduced pressure and the residue was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane=1:5) to afford diastereomeric mixture **16** (0.7 g, 65%) as pale brown oil. $R_f$ (40% ethyl acetate/hexane) 0.43; IR (neat) $\nu_{max}$ 3436, 2934, 1714, 1514, 1457, 1260, 1030, 748 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.45 (s, 3H), 1.51 (s, 3H), 2.68(d, 1H, OH), 3.45–3.61(m, 1H), 3.62–3.97 (m, 8H), 4.07and 4.26 (2 m, 2H), 4.4–4.81 (m, 4H), 5 (m, 2H), 6.58–6.93 (m, 3H) 7.14–7.38 (m, 10H); ESI/MS ($m/z$) 574 ($M^+$+Na); HRMS calcd for $C_{31}H_{37}NO_8Na$ 574.2416, found 574.2397.

*5.1.7. (2R,3R,4R,5R/S)-Benzyl 2-(benzyloxymethyl)-5-(3,4-dimethoxyphenyl)-3,4-dihydroxypyrrolidine-1-car-boxylate* ***17a****/****17b****.* To a stirred solution of diastereomeric mixture **16** (800 mg, 1.45 mmol) in $CH_2Cl_2$ (5 mL) was added TFA (5 mL) drop wise at 0 °C. After completion of the addition, the reaction mixture was warmed to room temperature and stirring was continued at the same temperature for 12 h. The reaction mixture was neutralized with $NaHCO_3$ at 0 °C and filtered through the Celite pad and washed with the chloroform (2×20 mL). The chloroform layer was washed with water and brine, dried over $Na_2SO_4$ and concentrated under vacuum. The crude residue was purified through silica gel column chromatography.

The faster moving *trans* cyclised compound **17a** (400 mg, 59%) was eluted in the column (ethyl acetate/hexane=2:3) as a major isomer and as a white solid. $R_f$ (50% ethyl acetate/hexane) 0.28; mp 152–154 °C; $[\alpha]_D^{25}$ −43.5 (*c* 0.86, $CHCl_3$); IR (neat) $\nu_{max}$ 3420, 2924, 1694, 1514, 1455, 1411, 1349, 1260, 1025, 751 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.67 (OH, 1H), 3.57–3.93 (m, 8H, include 2-OMe's), 4.06–4.34 (2s, 2H), 4.31 (dd, 1H, $J$=2.93, 9.89 Hz), 4.42–4.72 (m, 2H), 4.74–4.95 (m, 2H), 5.05 (d, 1H), 6.67–6.88 (m, 3H), 7.10–7.42 (m, 10H) (Because of the rotameric nature of compound, NMR is not resolved clearly); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ *55.7, 55.8, *66.7, *67.4, *67.9, *71.8, *73.9, *80.8, *83.3, *109.4, *110.9, *117.5, 127.4, *127.6, *127.9, *128.1, *128.3, *128.6, *133.9, *136.1, *136.5, *147.8, *148.9, *154.7; (*rotamer); ESI/MS ($m/z$) 516 ($M^+$+Na); HRMS calcd for $C_{28}H_{31}NO_7Na$ 516.1998, found 516.1992.

The slower moving diastereomeric compound **17b** (150 mg, 21%) was eluted in the column (ethyl acetate/hexane=2:3) as a thick syrup. $R_f$ (50% ethyl acetate/hexane) 0.25; $[\alpha]_D^{25}$ +3 (*c* 1.6, $CHCl_3$); IR (neat) $\nu_{max}$ 3421, 2929, 1694, 1515, 1457, 1411, 1347, 1260, 1136, 1028, 751, 698 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.40 (OH,

1H), 3.5–4.31 (m, 12H, include 2-OMe's), 4.48–4.75 (m, 2H), 4.8–5.20 (m, 3H), 6.61–6.92 (m, 3H), 6.97–7.52 (m, 10H); (Because of the rotameric nature of compound, NMR is not resolved clearly). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.6, 55.8, 65.7, 66.9, 69.7, 73.8, 77.9, 110.5, 110.9, 119.4, 127.9, 128.1, 128.6, 137, 148.2, 148.8; ESI/MS (*m*/*z*) 516 ($M^+$+Na); HRMS calcd for $C_{28}H_{31}NO_7Na$ 516.1998, found 516.1989.

*5.1.8. (2R,3R,4R,5R)-2-(Benzyloxymethyl)-5-(3,4-dimethoxyphenyl)-1-methylpyrrolidine-3,4-diol* ***18a****.* To a stirred suspension of $LiAlH_4$ (0.07 g, 183 mmol) in THF (3 mL) was added pyrrolidine derivative **17a** (0.3 g, 0.6 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 (0.07 mL), 15% NaOH (0.07 mL) and water (0.20 mL) successively. After 15 min stirring at room temperature, the reaction mixture was filtered through the Celite pad, washed with ethyl acetate (3×10 mL) and the filtrate was evaporated under vacuum. The residue was purified through silica gel column chromatography ($CHCl_3$/MeOH=7:1) to afford the *N*-methyl derivative **18a** (0.112 g, 74%) as white solid. $R_f$ (ethyl acetate) 0.1; mp 65–67 °C; $[\alpha]_D^{25}$ −25.1(c 2.58, $CDCl_3$); IR (KBr) 3414, 2931, 1514, 1456, 1261, 1136, 1026, 754 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.20 (s, 3H, NMe), 3.01–3.41 (m, 3H, 2-OH's and $H_5$), 3.53–3.69 (m, 2H, $H_2$and $H_3$), 3.75–3.95 (m, 8H, $H_{12}$and 2-OMe's), 4.10 (br s,1H, $H_4$), 4.55 (s,2H, PhC$H_2$O), 6.74–6.95 (m, 3H, Ph), 7.22–7.49(m, 5H, Ph); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 34.3, 55.8, 62.5, 68.4, 68.7, 73.6, 75.7, 80.5, 85.5, 110.2, 110.8, 119.9, 127.8, 127.9, 128.5, 133.5, 137.4, 148.3, 149.1; ESI/MS (*m*/*z*) 374 ($M^+$+H); HRMS calcd for $C_{21}H_{28}NO_5$ 374.1967, found 374.1967.

*5.1.9. (2R,3R,4R,5R)-2-(3,4-Dimethoxyphenyl)-5-(hydroxymethyl)-1-methylpyrrolidine-3,4-diol [(−)-codonopsinol] (****5****).* An ethanolic solution of **18a** (100 mg, 0.27 mmol) in 6 mL was stirred at room temperature in the presence of $PdCl_2$ (catalytic amount) under hydrogen atmosphere for 12 h. The catalyst was removed by filtration and the reaction mixture was concentrated. Further evaporation under high vacuum gave codonopsinol **5** (65 mg, yield, 85%) as a white powder. $R_f$ (20% MeOH/$CHCl_3$) 0.25; mp 150–152 °C; $[\alpha]_D^{25}$ −13 (c 1.37, MeOH) {lit.[6] $[\alpha]_D^{20}$ −15 (*c* 0.22, MeOH)}; IR (KBr) 3356, 2933, 1593, 1515, 1261, 1142, 1026 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 2.20 (s, 3H, NMe), 3.10 (m, 1H *J*=7.78, 4.09 Hz, $H_5$), 3.66 (d, 1H, *J*=6.6 Hz, $H_2$), 3.78–3.87 (m, 8H, $H_{12}$and 2-OMe's), 3.94 (dd, 1H, *J*=5.0, 6.4 Hz, $H_3$), 4.03 (t, 1H, *J*=4.4, 4.4 Hz, $H_4$), 6.90 (s, 2H, $H_{10}$and $H_{11}$), 7.03 (s, 1H, $H_7$); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 35.1, 56.5, 56.6, 60.9, 71.2, 75.9, 80.1, 85.8, 112.5, 112.6, 122.4, 134.6, 149.9, 150.5; ESI/MS (*m*/*z*) 284 ($M^+$+H); HRMS calcd for $C_{14}H_{22}NO_5$ 284.1497, found 284.1503.

*5.1.10. (2R,3R,4R,5S)-2-(Benzyloxymethyl)-5-(3,4-dimethoxy-ph-enyl)-1-methylpyrrolidine-3,4-diol* ***18b****.* To a stirred suspension of $LiAlH_4$ (0.023 g, 0.6 mmol) in THF (2 mL) was added pyrrolidine derivative **17b** (0.1 g, 0.2 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 (0.023 mL), 15% NaOH (0.023 mL) and water (0.7 mL) successively. After 15 min stirring at room temperature, the reaction mixture was filtered through the Celite pad, washed with ethyl acetate (3×5 mL) and evaporated under vacuum. The residue was purified through silica gel column chromatography ($CHCl_3$/MeOH=7:1) to afford the *N*-methyl derivative **18b** (0.06 g, 79%) as a thick syrup. $R_f$ (ethyl acetate) 0.08; $[\alpha]_D^{25}$ +87.9 (*c* 0.79, $CHCl_3$); IR (KBr) 3420, 2929, 1513, 1456, 1262, 1026, 754 cm$^{-1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.22 (3H, s, NMe), 2.63 (br s, 2H, OH and $H_5$), 3.59–3.91 (m, 10H, $H_2$,$H_3$,$H_{12}$and 2-OMe's), 4.10 (br s, 1H, $H_4$), 4.61 (s,2H, PhC$H_2$O), 6.81–6.98 (m, 3H, Ph), 7.28–7.42 (m, 5H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 39.7, 55.7, 55.8, 70.6, 72.4, 73.1, 73.5, 79.2, 79.8, 110.9, 111.6, 120.6, 127.5, 127.7, 128.4, 129.7, 137.7, 148.3, 148.8; ESI/MS (*m*/*z*) 374 ($M^+$+H); HRMS calcd for $C_{21}H_{28}NO_5$ 374.1967, found 374.1960.

*5.1.11. (2S,3R,4R,5R)-2-(3,4-Dimethoxyphenyl)-5-(hydroxymethyl)-1-methylpyrrolidine-3,4-diol [(+)-2-epi codonopsinol]* ***6****.* An ethanolic solution of **18b** (40 mg, 0.1 mmol) in 6 mL was stirred at rt in the presence of $PdCl_2$ (catalytic amount) under hydrogen atmosphere for 12 h. The catalyst was removed by filtration and the reaction mixture was concentrated. Further evaporation under high vacuum gave (2)-*epi* codonopsinol **6** (25 mg, yield, 80%) as a thick syrup. $R_f$ (20% MeOH/$CHCl_3$) 0.23; $[\alpha]_D^{25}$ +103.9 (*c* 1.81, MeOH); IR (KBr) 3376, 2939, 1514, 1460, 1262, 1137, 1026 cm$^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 2.20 (3H, s, NMe), 2.43 (td, 1H, *J*=3.7, 4.1 Hz, $H_5$), 3.65 (d, 1H, *J*=4.5 Hz, $H_2$), 3.72–3.86 (m, 9H, $H_3$,$H_{12}$and 2-OMe's), 3.98 (dd, 1H, *J*=3.7, 1.2 Hz, $H_4$), 6.88–6.97 (m, 2H, $H_{10}$and $H_{11}$), 7.10 (s, 1H, $H_7$); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 40.23, 56.4, 56.5, 62.3, 75.2, 75.8, 80.2, 80.5, 112.5, 114.1, 122.7, 131.9, 149.7, 150.2; ESI/MS (*m*/*z*) 284 ($M^+$+H); HRMS calcd for $C_{14}H_{22}NO_5$ 284.1497, found 284.1488.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.12.035.

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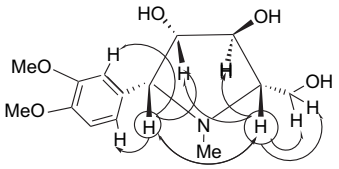
14. As per the suggestion of referee to see the influence of the newly generated chiral center (on benzylic carbon) on the stereochemical out come of the cyclisation, the mixture **16** was separated by preperative TLC (by running the plate in solvent system 20% EtOAc/hexane for ten times). The major and minor isomers were separated and they were subjected to TFA conditions independently. Both gave the cyclised product **17a** and **17b** again in 2.5:1 ratio. $^1$H NMR data for major isomer (300 MHz, $CDCl_3$) $\delta$ 1.38 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 2.65(d, 1H, *J*=5.4 Hz, OH), 3.50 (dd, 1H, *J*=3.6, 9.3 Hz, C*H*HO), 3.63–3.93 (m, 8H, C*H*NH, CH*H*O and 2-OMe's), 4.08 (dd, 1H, *J*=6.4, 8.7 Hz, C*H*O–), 4.28 (br t, 1H, *J*=6.4, C*H*O–), 4.47 (m, 3H, C*H*OHand PhC*H*$_2$O), 4.74 (m, 1H, *J*=9.3 Hz, NH), 5.02 (m, 2H, PhC*H*$_2$O), 6.68 (d, 1H, *J*=8.2, Ph), 6.78 (br d, 1H, *J*=8.2, Ph), 6.86 (br s, 1H, Ph), 7.19–7.38 (m, 10H, Ph); $^1$H NMR data for minor isomer (300 MHz, $CDCl_3$) $\delta$ 1.36 (s, 3H, C*H*$_3$), 1.42 (s, 3H, C*H*$_3$), 2.41 (br s, 1H, OH), 3.52 (dd, 1H, *J*=3.8, 9.3 Hz, C*H*HOBn), 3.68–3.88 (m, 8H, C*H*NH, CH*H*OBn and 2-OMe's), 4.20 (m, 2H, 2C*H*O–), 4.46 (dd, 2H, *J*=5.1, 17.3 Hz, PhC*H*$_2$O), 4.60 (d, 1H, *J*=9.3 Hz, NH), 4.68 (br s, 1H, C*H*OH), 5.0 (dd, 2H, *J*=12.4, 16.5 Hz, PhC*H*$_2$O), 6.64 (d, 1H, *J*=8.2, Ph), 6.74 (dd, 1H, *J*=1.5, 8.2, Ph), 6.84 (d, 1H, *J*=1.6, Ph), 7.19–7.38 (m, 10H, Ph).
15. The structure of 2-*epi*-codonopsinol **6** can be established thorough 1D nuclear Overhause enhancement (NOE) correlations.


**(+)-epi codonopsinol 6**