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Practical and highly stereoselective approaches to the total synthesis of (−)-codonopsinine☆

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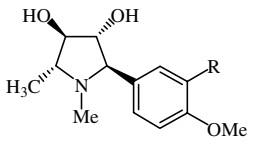
Abstract—The enantiopure total synthesis of (−)-codonopsinine is described using two effective chiron approaches starting either from commercially available L-xylose or from readily available Garner aldehyde. The key steps included Julia *trans*-olefination, highly diastereoselective alkylation and cascade epoxidation–cyclization strategies.

1. Introduction

(−)-Codonopsinine **1**, and (−)-codonopsine **2** are rather complex pyrrolidine alkaloids, isolated from *Codonopsis clematidea*[1] for the first time in 1969.[2] These compounds exhibit antibiotic activity and hypotensive activity without affecting the central nervous system.[3] The total synthesis of this class of compounds has always interested synthetic organic chemists, not only because many have significant biological activity, but also due to their complex structures and the synthetic challenges they pose. Interest in the synthesis of codonopsine and codonopsinine stems mainly from their pharmacological activity associated with the synthetic challenge they constitute in view of their 1,2,3,4,5-pentasubstituted pyrrolidine nucleus bearing four contiguous stereogenic centres (2*R*,3*R*,4*R*,5*R*) with substituents *trans* relative to each other. For the reasons described above, some elegant synthetic approaches for the synthesis of (−)-codonopsinine **1** have been described.[4] Most syntheses use chiral pool starting materials such as sugars and hydroxy acids.



1: R = H (-)-Codonopsinine
2: R = OMe (-)-Codonopsine

Over the course of our programme directed towards the synthesis of bioactive compounds,[5] we herein report in detail our synthetic endeavour towards the construction of (−)-codonopsinine **1** by two effective chiron approaches starting either from a pentose sugar namely L-xylose **6** or from D-serine derived Garner's aldehyde **9**[6] (Scheme 1).

2. Results and discussion

2.1. Synthesis of (−)-codonopsinine 1 starting from L-xylose 6

The synthesis of (−)-codonopsinine **1** starting from L-xylose **6** was begun with the transformation of L-(−)-xylose **6** in to 1,2-*O*-isopropylidine-α-L-xylofuranose **11** by a known route.[7] The primary alcohol in **11** was selectively tosylated by treating with *p*-tosyl chloride and triethylamine in dichloromethane to give **12** in 90% yield, which on reduction with lithium aluminium hydride in THF afforded **13** in 88% yield. Protection of the hydroxy group in **13** using *p*-methoxybenzyl bromide and NaH in THF gave **5** in 94% yield, which on hydrolysis of the 1,2-acetonide with catalytic H_2SO_4 and 60% aq AcOH furnished **14** in 87% yield. Oxidative cleavage of **14** with $NaIO_4$ in MeOH–H_2O (8:2) and subsequent Julia olefination of the unstable aldehyde **15** with sulfone **16** which was prepared from *p*-methoxybenzyl bromide and mercaptobenzothiazole,[8] gave **4** in 72% yield. The formyl group in compound

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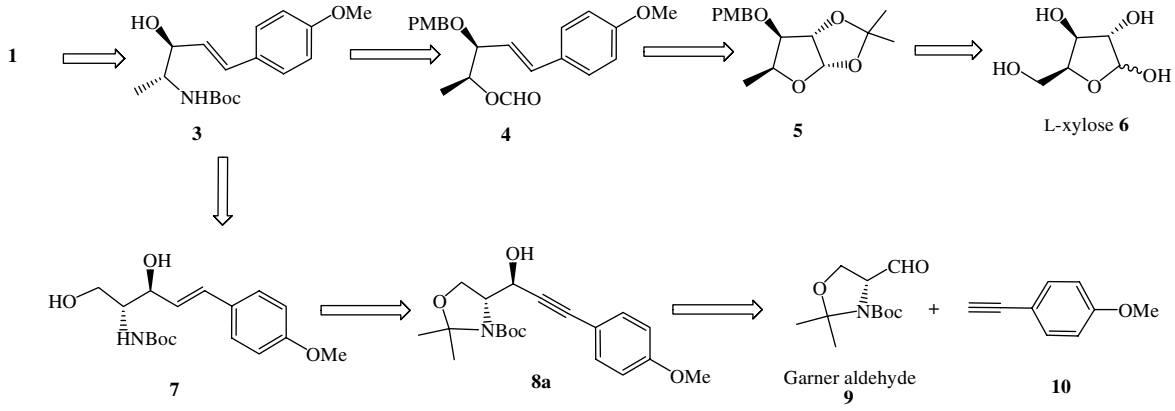
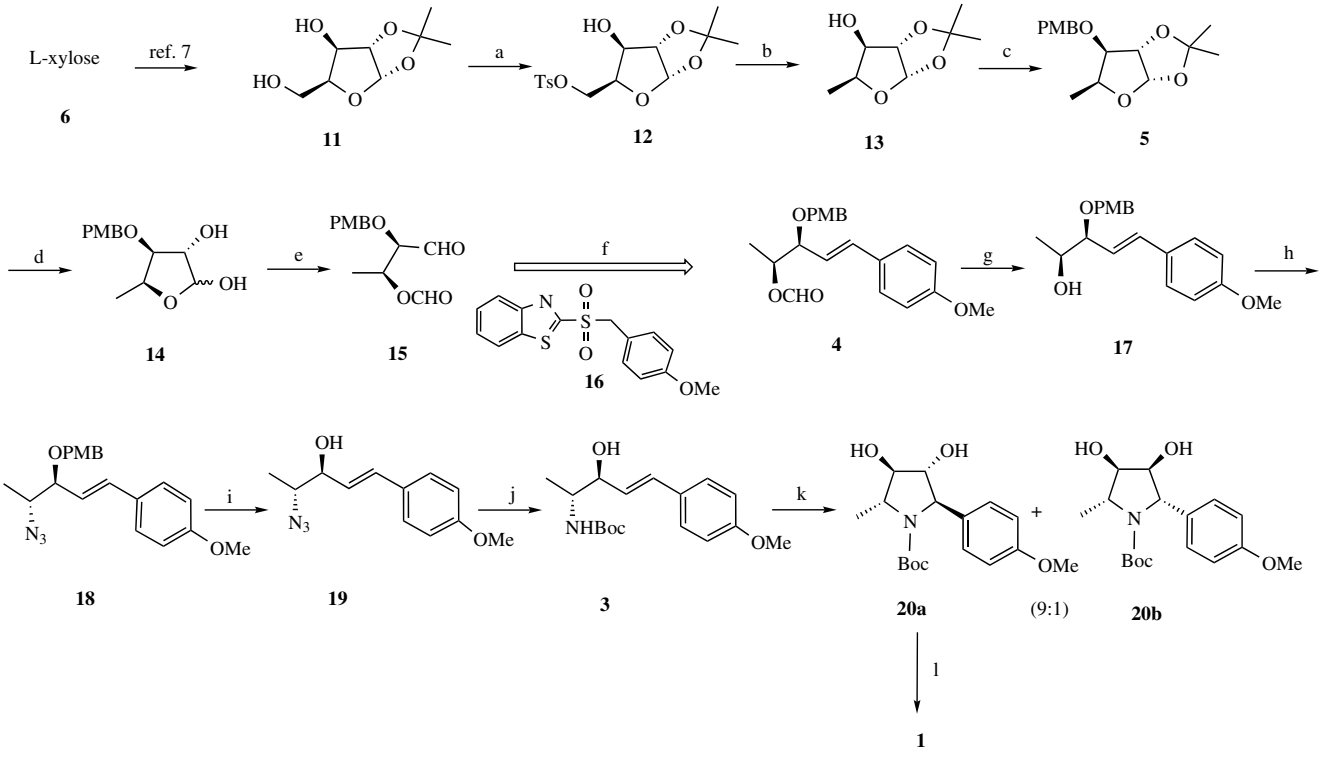


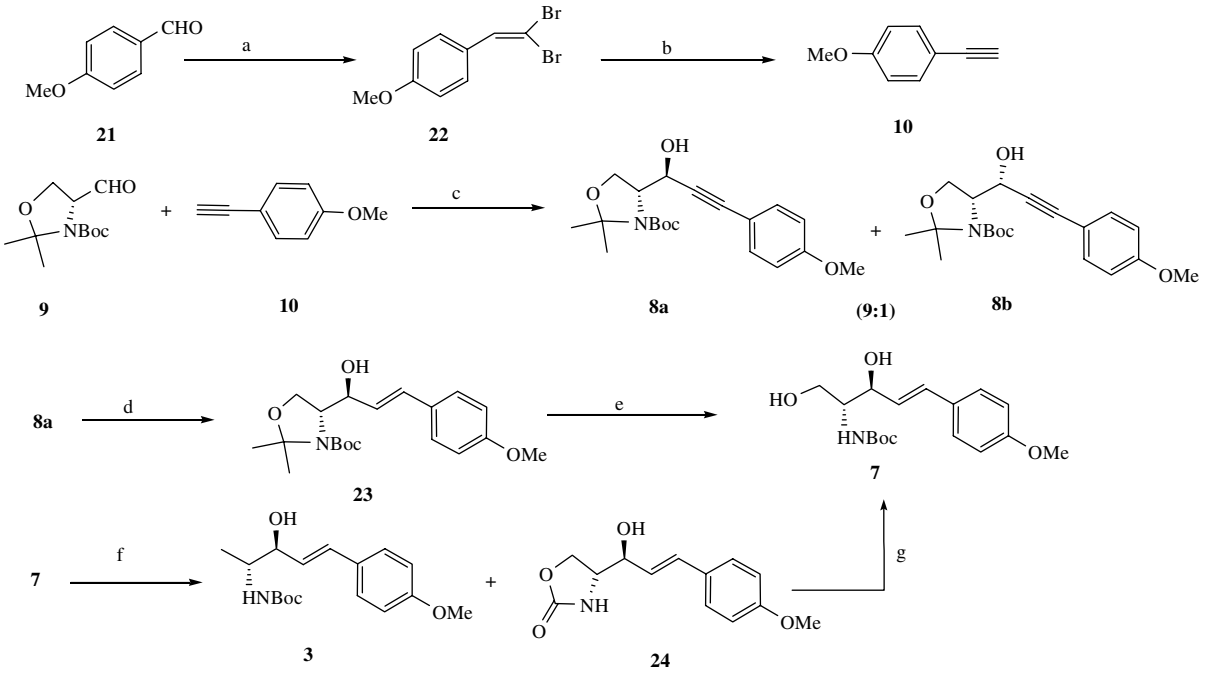
Scheme 1.

4 was subjected to de-O-formylation with $NaBH_4$ in MeOH to afford **17** in 97% yield. The hydroxy group in compound **17** was treated with mesyl chloride and triethylamine in dichloromethane and subsequent azidation with NaN_3 in hot DMF (70 °C) gave **18** in 89% overall yield. Removal of the PMB group in **18** with $ZrCl_4$ in CH_3CN gave allyl alcohol[9] **19** in 86% yield. The azide group in **19** was subjected to reduction and protection using PPh_3 in benzene and water at 45 °C followed by exposure to $(Boc)_2O$ to furnish **3** in 88% yield.

The allyl alcohol in **3** was epoxidized with *m*-CPBA in CH_2Cl_2 to furnish pyrrolidine diols, **20a** and **20b** in a ratio of 9:1 with a combined yield of 89% in a single pot transformation (Scheme 2). The absolute stereochemistry of the newly created diol was confirmed, based on the literature precedent[10] and from the spectral data of the final compound. The regioselective opening of epoxide with the internal nitrogen nucleophile in an *endo* fashion is facilitated by the 4-methoxy phenyl group which allows facile benzylic cleavage. The major isomer was easily isolated by flash column chromatography using 38% EtOAc in hexane. Finally, the Boc group in **20a** was converted to a methyl group using Red-Al in toluene at reflux[11] for 2 h to yield (−)-codonopsinine **1** in 83% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 90%; (b) $LiAlH_4$, THF, 0 °C to rt 88%; (c) PMBBr, NaH, THF, 94%; (d) 60% aq AcOH, cat. H_2SO_4, 87%; (e) $NaIO_4$, MeOH–H_2O; (f) NaHMDS, THF, −78 °C, 72% (for steps); (g) $NaBH_4$, MeOH, 97%; (h) (i) MsCl, Et_3N, 0 °C; (ii) NaN_3, DMF, 70 °C, 89% (for two steps); (i) $ZrCl_4$, acetonitrile, 86%; (j) (i) TPP, benzene, H_2O, 45 °C; (ii) $(Boc)_2O$, Et_3N, 88% (for two steps); (k) *m*-CPBA, CH_2Cl_2, 0 °C, 89%; (l) Red-Al, toluene, reflux, 83%.



Scheme 3. Reagents and conditions: (a) CBr_4–TPP, Et_3N, CH_2Cl_2, −30 °C to rt; (b) ^{n}BuLi, THF, −78 °C, 75% (for two steps); (c) ^{n}BuLi, THF, −78 °C, 90%; (d) Red-Al, ether, 0 °C, 89%; (e) 60% aq AcOH, 84%; (f) i. TsCl, Et_3N, Bu_2SnO, 0 °C; ii. $NaBH_4$, DMSO, 70 °C, 85% (for two steps); (g) $(Boc)_2O$, then Cs_2CO_3 0 °C to rt.

2.2. Synthesis of (−)-codonopsinine 1 starting from Garner's aldehyde 9

Initially, anisaldehyde **21** was subjected to the Corey–Fuchs protocol[12] using CBr_4 and TPP in dichloromethane to afford the dibromo olefine **22**, which was subsequently treated with ^{n}BuLi in THF at −78 °C to yield *p*-methoxyphenyl acetylene **10** in 75% yield for the two steps. Garner aldehyde **9**, derived from D-serine,[6] was reacted with lithiated *p*-methoxyphenyl acetylide in THF at −78 °C[13] to produce readily separable acetylene alcohols **8a** and **8b** in a 9:1 ratio, respectively (Scheme 3). Acetyleneic alcohol **8a** was reduced to allyl alcohol **23** using Red-Al in dry ether at 0 °C in 89% yield. The acetonide group of **23** was cleanly deprotected using 60% aq AcOH to afford amino protected diol **7**. The primary alcohol of diol **7** was selectively deoxygenated using *p*-toluene sulfonyl chloride, triethylamine and Bu_2SnO in dichloromethane[14] at 0 °C and subsequently treated with sodium borohydride in DMSO to afford amino protected alcohol **3** in 85% yield along with an oxazolidinone **24** as a side product in 10% yield which was converted to required diol **7** using $(Boc)_2O$ followed by treating with Cs_2CO_3[15] (Scheme 3).

The alcohol **3** was transformed to (−)-codonopsinine **1** as illustrated in Scheme 2.

3. Conclusion

In conclusion, two effective chiron approaches have been described for the synthesis of natural (−)-codonopsinine **1**. We have also shown the effect of a Julia olefination, highly diastereoselective alkylation and epoxidation–intramolecular cyclization cascade as an efficient sequence for the synthesis of polyhydroxylated pyrrolidines. The total synthesis of similar molecules using this strategy is currently being explored.

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ and deuterated pyridine solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as internal standard. Coupling constants (J) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separation was carried out using 230–400 mesh size silica gel. Mass spectra were obtained on Finnegan MAT 1020B or micromass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

4.1.1. 6-Hydroxy-2,2-dimethyl-5-(4-methylphenylsulfonyloxymethyl)-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxole 12. To a stirred solution of diol **11** (5.0 g, 26.3 mmol) was added triethylamine (9.25 mL, 65.7 mmol) at 0 °C under a nitrogen atmosphere in DCM was added *p*-toluenesulfonyl chloride (5.01 g, 26.3 mmol) very slowly and the reaction mixture allowed to stir at rt for 24 h. To the reaction

mixture water, was added and extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate and concentrated to yield a crude tosylated compound, which was purified by silica gel column chromatography using 20% of EA in hexane as an eluent to afford compound **12** (8.16 g, 90% yield) as a semi-solid. Compound **12** semi-solid: $[\alpha]_D^{20} = +13.8$ (*c* 1.0, CH_3OH); IR (neat): 3498, 2930, 1360, 1176, 1074 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, $J = 6.8$ Hz, 2H), 7.35 (d, $J = 6.8$ Hz, 2H), 5.80 (s, 1H), 4.47 (s, 1H), 4.34–4.25 (m, 3H), 4.10–3.98 (m, 1H), 2.45 (s, 3H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.2, 132.2, 129.9, 127.9, 112.0, 104.9, 84.9, 77.5, 74.1, 66.4, 26.7, 26.1, 21.6; HRMS calcd for $C_{15}H_{21}O_7S$ $[M+H]^+$ 345.1008, found 345.1012.

4.1.2. 2,2,5-Trimethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*]-[1,3]dioxol-6-ol 13. To a cooled mechanically stirred suspension of powdered LAH (1.76 g, 46.3 mmol) in anhydrous THF (80 mL) was added slowly a compound **12** (8 g, 23.1 mmol) in anhydrous THF (30 mL). After addition was completed the reaction mixture stirred for 4 h and then excess LAH was quenched by sequential addition of water, 15% NaOH solution and water. The mixture was filtered and the solids were extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to furnish methyl compound **13** (3.54 g, 88% yield). Purification on silica gel column chromatography using 22% of EA in hexane as an eluent afforded pure compound **13** as a colourless liquid. Compound **13** colourless liquid: $[\alpha]_D^{20} = +22.4$ (*c* 1.0, CH_3OH); IR (neat): 3445, 2989, 2938, 1385, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.85 (s, 1H), 4.45 (s, 1H), 4.30–4.21 (m, 1H), 3.88 (br s, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.6, 104.2, 81.9, 79.2, 72.8, 26.3, 26.1, 13.5; HRMS calcd for $C_8H_{14}O_5$ $[M]^+$ 174.0892, found 174.0894.

4.1.3. 6-(4-Methoxybenzyloxy)-2,2,5-trimethyl-(3a*S*,5*S*,-6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxole 5. To a stirred suspension of freshly activated NaH (1.24 g, 51 mmol) (60% w/v dispersion in mineral oil) in anhydrous THF (60 mL) was added alcohol **13** (3 g, 17.2 mmol) in dry THF (20 mL) at 0 °C. After 30 min, *p*-methoxybenzyl bromide (4.15 g, 20 mmol) was added and the reaction mixture brought to room temperature and stirred for 12 h. Ice pieces were then added to quench the reaction and then the THF was separated and the aq layer extracted with ether (3 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. After removing the volatiles under reduced pressure, crude *p*-methoxybenzyl ether was purified by silica gel column chromatography using 10% EA in hexane as an eluent to furnish **5** (4.75 g, 94% yield) as a colourless liquid. Compound **5** colourless liquid: $[\alpha]_D^{20} = +20.3$ (*c* 1, CH_3OH); IR (neat): 2989, 2936, 1613, 1514, 1249 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, $J = 6.8$ Hz, 2H), 6.82 (d, $J = 6.8$ Hz, 2H), 5.82 (s, 1H), 4.62–4.50 (m, 2H) 4.38 (d, $J = 6.2$ Hz, 1H), 4.30–4.20 (m, 1H), 3.78 (s, 3H), 3.65 (br s, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 129.5, 129.0, 113.6, 110.8, 104.5, 82.5, 82.1, 75.9, 71.1, 55.0, 26.4, 25.9, 13.1; HRMS calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ 317.1364, found 317.1361.

4.1.4. 4-(4-Methoxybenzyloxy)-5-methyl-(3*S*,4*R*,5*S*)-tetrahydro-2,3-furandiol 14. Compound **5** was hydrolyzed using 60% AcOH (40 mL) and catalytic amount of concentrated H_2SO_4. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction the reaction mixture was diluted with ethyl acetate and stirred for 30 min. after which it was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were neutralized with solid $NaHCO_3$ and stirred for one more hour, then filtered. The organic layer was separated and concentrated to afford a residue, which was purified by column chromatography on silica gel (EA/hexane in 4/6) to furnish pure compound **14** (3.38 g, 87% yield) as a colourless syrup. Compound **14** colourless syrup: ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (d, $J = 12.3$ Hz, 2H), 6.78 (d, $J = 12.3$ Hz, 2H), 5.36 (s, 1H), 4.55 (d, $J = 12.3$ Hz, 1H), 4.38–4.22 (m, 2H), 4.12–4.05 (m, 1H), 3.75 (s, 3H), 3.66 (s, 1H), 1.15 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 129.2, 127.9, 114.5, 99.4, 82.6, 78.2, 75.3, 71.2, 55.3, 13.2; HRMS calcd for $C_{13}H_{18}O_5Na$ $[M+Na]^+$ 277.1051, found 277.1047.

4.1.5. 2-(4-Methoxybenzyloxy)-4-(4-methoxyphenyl)-1-methyl-(1*S*,2*S*,3*E*)-3-butenyl formate 4. To a solution of compound **14** (3 g, 11 mmol) in methanol and water (8:2) was added $NaIO_4$ (6.31 g, 29 mmol) at 0 °C. The reaction mixture was brought to rt and allowed to stir for 4 h. The methanol was then removed under reduced pressure and the residue extracted with $CHCl_3$ (3 × 100 mL). Combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to yield the crude aldehyde, which was used for further reaction. To a stirred solution of the sulfone **16** (3.67 g, 11.5 mmol) in anhydrous THF at −78 °C under nitrogen atmosphere was added NaHDMS. The mixture was then stirred for 30 min before addition of the above crude aldehyde in anhydrous THF (5 mL). After stirring for a further 3 h at −78 °C the reaction mixture was allowed to warm to rt and stirred for 3 h where upon water and ether were added and the mixture was shaken well. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure, after which the crude residue was purified by silica gel column chromatography using EA/hexane (1:9) as an eluent to furnish compound **15** (2.94 g, 72% yield) as a colourless liquid. Compound **4** colourless liquid: $[\alpha]_D^{20} = +17.7$ (*c* 1.0, CH_3OH); IR (neat): 1706, 1607, 1510, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.39–7.20 (m, 4H), 6.86–6.82 (m, 4H), 6.58 (d, $J = 15.5$ Hz, 1H), 5.94 (dd, $J = 8.1$, 14.6 Hz, 1H), 5.18–5.02 (m, 1H), 4.62 (d, $J = 9.8$ Hz, 1H), 4.38 (d, $J = 9.8$ Hz, 1H), 3.86 (t, $J = 4.0$ Hz, 1H), 3.80 (s, 6H), 1.28 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.8, 159.7, 159.2, 130.2, 129.9, 129.4, 129.3, 127.8, 126.9, 113.8, 113.6, 81.0, 74.5, 72.4, 55.3, 55.2, 16.3; HRMS calcd for $C_{21}H_{24}O_5Na$ $[M+Na]^+$ 379.1521, found 379.1523.

4.1.6. 3-(4-Methoxybenzyloxy)-5-(4-methoxyphenyl)-(2*S*,3*S*,4*E*)-4-penten-2-ol 17. Compound **4** (2.8 g, 7.80 mmol) was taken in methanol (30 mL), and cooled to 0 °C at which point $NaBH_4$ (3.8 g, 11 mmol) was added in small portions under a nitrogen atmosphere. After complete addition, the reaction mixture was brought to room temperature and allowed to stir for 2 h. Methanol was removed under reduced pressure, and the residue was dissolved in water and extracted with $CHCl_3$. The combined organic layers were washed with aq $NaHCO_3$, water, brine, dried over anhydrous sodium sulfate and concentrated to give crude residue which was purified by column chromatography on silica gel using 20% of EA in hexane to afford alcohol **17** (2.4 g, 97% yield) as a colourless liquid. Compound **17** colourless liquid: $[\alpha]_D^{20} = +74.7$ (*c* 1.1, CH_3OH); IR (neat): 3559, 1608, 1510, 1249, 1034 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (d, $J = 10.8$ Hz, 2H), 7.28–7.20 (m, 3H), 6.78 (d, $J = 10.8$ Hz, 3H), 6.58 (d, $J = 16.8$ Hz, 1H), 5.90 (dd, $J = 12$, 18 Hz, 1H), 4.60 (d, $J = 12$ Hz, 1H), 4.32 (d, $J = 12$ Hz, 1H), 3.82 (s, 3H) 3.80 (s, 3H), 3.78–3.70 (m, 1H), 3.64 (t, $J = 10.8$ Hz, 1H), 1.14 (d, $J = 5.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.4, 159.1, 134.4, 130.0, 129.4, 128.8, 127.6, 124.0, 113.6, 113.5, 85.4, 69.8, 55.1, 55.0, 29.5, 18.3; HRMS calcd for $C_{20}H_{25}O_4$ $[M+H]^+$ 329.1752, found 329.1748.

4.1.7. 1-[4-Azido-3-(4-methoxybenzyloxy)-(*E*,3*S*,4*R*)-1-pentenyl]-4-methoxybenzene 18. To a stirred solution of alcohol **17** (2.3 g, 7 mmol) in dry DCM at −10 °C temperature, was added triethyl amine (1.47 mL, 10.5 mmol) under a nitrogen atmosphere. To this was added methanesulfonyl chloride (0.65 mL, 8.4 mmol) very slowly. The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was then poured into crushed ice and extracted with DCM. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to yield the mesylate (2.8 g) as a pale yellow liquid. It was used as such without any further purification for the following step.

A solution of mesylate (2.6 g, 6.4 mmol) in dry DMF (10 mL) was heated at 80 °C with NaN_3 (832 mg, 12.8 mmol) for 6 h. The reaction mixture was brought to room temperature and diluted with water and extracted with ether. The combined ether layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and on purification by silica gel column chromatography (EA/hexane in 1/9) yielded azide **18** (1.5 g, 89%) as a colourless liquid. Compound **18** colourless liquid: $[\alpha]_D^{25} = 70.2$ (*c* 0.5, MeOH); IR (neat) : 2103, 1608, 1512, 1034, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.18 (m, 4H), 6.88–6.79 (m, 4H), 6.48 (d, $J = 15.5$ Hz, 1H), 5.95 (dd, $J = 8.1$, 14.6 Hz, 1H), 4.58 (d, $J = 8.9$ Hz, 1H), 4.35 (d, $J = 8.9$ Hz, 1H), 3.88–3.77 (m, 7H), 3.58–3.49 (m, 1H), 1.22 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.5, 159.0, 134.5, 130.1, 129.2, 128.9, 127.8, 123.4, 114.0, 113.7, 82.7, 69.9, 60.7, 55.3, 55.2, 15.2; HRMS calcd for $C_{20}H_{24}N_3O_3$ $[M+H]^+$ 354.1817, found 354.1815.

4.1.8. 4-Azido-1-(4-methoxyphenyl)-(*E*,3*S*,4*R*)-1-penten-3-ol 19. To a stirred solution of PMB ether **18** (1.2 g, 3.3 mmol) in dry acetonitrile was added $ZrCl_4$ (0.67 mmol) and the mixture stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue treated with ethyl acetate (20 mL). This was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using EA/hexane (1:9) as an eluent to furnish the alcohol **19** (681 mg, 86% yield) as a viscous liquid. Compound **19** viscous liquid: $[\alpha]_D^{25} = +17.1$ (*c* 0.8, MeOH); IR (KBr): 2103, 3446 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, $J = 10.8$ Hz, 2H), 6.84–6.72 (m, 2H), 6.64 (d, $J = 15.5$ Hz, 1H), 6.31 (dd, $J = 8.1$, 15.5 Hz, 1H), 3.84–3.78 (m, 1H), 3.82 (s, 3H), 3.58–3.49 (m, 1H), 1.22 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.5, 131.8, 126.2, 120.9, 113.1, 112.8, 77.8, 60.6, 55.2, 14.5; HRMS calcd for $C_{12}H_{15}N_3O_2$ $[M+H]^+$ 234.1242, found 234.1245.

4.1.9. 2-[*tert*-Butoxy carbonylamino]-(2*R*,3*S*,4*E*)-5-(4-methoxyphenyl)-pent-4-en-3-ol 3. To a stirred solution of compound **19** (500 mg, 2.1 mmol) in benzene (10 mL) at 45 °C was added TPP (1.12 g, 4.2 mmol). After 30 min, water was added and stirring continued at 45 °C for 11 h. The mixture was cooled to room temperature and extracted with ethyl acetate, washed with saturated NH_4Cl, dried over anhydrous sodium sulfate, filtered and concentrated to give the amine product (350 mg) which was used without any for further purification for the subsequent reaction. To a solution of the above crude amine (300 mg, 1.6 mmol) in dry THF (20 mL) were added triethyl amine (0.35 mL, 2.5 mmol) and $(Boc)_2O$ (442 mg, 2.0 mmol) at 0 °C. The mixture was stirred at rt for 12 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (EA/hexane 2/8) to give compound **3** (0.45 g, 88% yield) as a semi-solid. Compound **19** semi-solid: $[\alpha]_D^{25} = -12.6$ (*c* 0.5, MeOH); IR (neat) : 3552, 1710, 1695, 1512, 1248 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (d, $J = 10.8$ Hz, 2H), 6.85 (d, $J = 10.8$ Hz, 2H), 6.55 (d, $J = 15.6$ Hz, 1H), 6.06 (dd, $J = 8.1$, 15.6 Hz, 1H), 4.65–4.55 (m, 1H), 4.30–4.10 (m, 1H), 3.80 (s, 3H), 1.40 (s, 9H), 1.15 (d, $J = 8.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.4, 149.2, 128.9, 125.1, 121.8, 112.1, 110.9, 77.2, 71.3, 62.1, 55.4, 20.5, 14.5; HRMS calcd for $C_{17}H_{26}NO_4$ $[M]^+$ 307.1783, found 307.1780.

4.1.10. *tert*-Butyl 3,4-dihydroxy-2-(4-methoxyphenyl)-5-methyl-(2*R*,3*R*,4*R*,5*R*)-tetrahydro-1*H*-1-pyrrolecarboxylate 20a. To a stirred solution of compound **3** (0.3 g, 0.97 mmol) in dry DCM (50 mL) was added *m*-CPBA (0.33 g, 1.9 mmol) in dry CH_2Cl_2 (10 mL) over a period of 10 min at 0 °C. The reaction mixture was brought to room temperature and allowed to stir for 4 h. After completion of the reaction saturated solution of $NaHCO_3$ was added and stirred for 30 min, then extracted in CH_2Cl_2 (3×100 mL) and the combined organic layers washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using 25% of EA in hexane to give cyclized compound **20a** (252 mg, 90% of 89 % yield) as a semi-solid. Compound **20a** semi-solid: $[\alpha]_D^{25} = -50.2$ (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, $J = 9.2$ Hz, 2H),

6.88 (d, $J = 9.2$ Hz, 2H), 4.55 (br s, 1H), 3.99 (m, 2H), 3.80 (m, 4H), 1.38 (d, $J = 6.0$ Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz): δ 158.7, 154.0, 134.6, 127.3, 113.8, 81.7, 79.6, 60.6, 59.3, 55.2, 28.0, 17.7; HRMS calcd for $C_{17}H_{25}NO_5Na$ $[M+Na]^+$ 332.1599, found 332.1603.

4.1.11. (−)-Codonopsinine 1. To a solution of compound **20a** (180 mg, 0.5 mmol) in dry toluene (20 mL) was added dropwise sodium bis-(2-methoxyethoxy)-aluminium hydride (70% in toluene) (563 g, 2.7 mmol) under an ice cold temperature. The reaction mixture was heated at reflux for 2 h and then treated with ethanol and water under ice cooling. The insoluble material was removed by filtration; the filtrate was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure the residue was purified by column chromatography on silica gel [MeOH/$CHCl_3$ (1:9)] to give compound **1** (109 mg, 83% yield) as a white solid. Compound **1**: white solid, mp 168–171 °C; $[\alpha]_D^{25} = -12.4$ (*c* 0.4, MeOH), lit.[1] mp 169–170 °C, $[\alpha]_D^{20} = -8.8$ (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, pyridine-d_5): δ 7.60 (d, $J = 8.4$ Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 4.63 (br t, $J = 3.0$, 7.2 Hz, 1H), 4.38 (br t, $J = 3.0$, 7.2 Hz, 1H), 4.08 (br d, $J = 6.0$ Hz, 1H), 3.70–3.60 (m, 4H), 2.22 (s, 3H), 1.30 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz pyridine-d_5): δ 159.5, 135.3, 130.0, 114.2, 86.7, 84.7, 74.2, 65.2, 55.1, 34.7, 13.9; HRMS calcd for $C_{13}H_{20}NO_3$ $[M+H]^+$ 238.1443, found 238.1439.

4.1.12. 1-(1-Ethynyl)-4-methoxybenzene 10. To a solution of CBr_4 (14.6 g, 44.0 mmol) in dry CH_2Cl_2 (100 mL) under nitrogen was dropwise added at −30 °C a solution of TPP (25.0 g, 88 mmol) over a period of 20 min. The mixture was allowed to stir for a further 30 min at −30 °C. Then a solution of aldehyde **21** (3.0 g, 22.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to the resultant red coloured solution. The reaction mixture was allowed to warm up to 30 °C over a period of 3 h. The resultant precipitate was filtered and the filtrate concentrated in vacuum to give the crude product, which was run through a filter column to give the dibromo olefin **22**. The dibromo olefin **22** (4.0 g, 13.69 mmol) was taken in anhydrous THF at −78 °C and to this was added *n*-BuLi (21 mL, 1.5 M solution in hexane, 34.24 mmol) dropwise over a period of 10 min. The reaction mixture was allowed to warm to 30 °C and quenched with saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), washed with water, brine, dried over sodium sulfate and concentrated. The crude product was purified to give the title compound **10** (1.45 g) as a liquid in 75% yield for two steps. Compound **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.42 (m, 2H), 6.80–6.90 (m, 2H), 3.85 (s, 3H), 2.85 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.5, 129.1, 126.3, 119.8, 88.7, 79.1, 55.4; HRMS calcd for C_9H_8O $[M]^+$ 132.0575, found 132.0577.

4.1.13. *tert*-Butyl 4-[1-hydroxy-3-(4-methoxyphenyl)-(1*S*)-2-propynyl]-2,2-dimethyl-(4*R*)-1,3-oxazolane-3-carboxylate 8a. To a solution of *p*-methoxy phenyl acetylene **10** (1.38 g, 10.4 mmol) in freshly distilled THF at −78 °C under nitrogen atmosphere was added *n*-BuLi (6.55 mL, 10.4 mmol, 1.6 M solution in hexane). The reaction mixture was allowed to warm at 30 °C and stirred for 30 min. The reaction mixture was again cooled to −78 °C and to this was added Garner aldehyde **9** (2 g, 8.7 mmol) in THF over a period of 15 min and stirred for 3 h at −78 °C and then quenched by the addition of saturated NH_4Cl. The organic layers were extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (EA/hexane 2/8) to afford compound **8a** (2.74 g, 87% yield) as a colourless liquid. Compound **8a** colourless liquid: $[\alpha]_D^{25} = +26.8$ (*c* 1.4, MeOH); IR (KBr): 3443, 2979, 2936, 2225, 1694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, $J = 8.3$ Hz, 2H), 6.83 (d, $J = 8.3$ Hz, 2H), 4.75–4.65 (m, 1H), 4.30–4.10 (m, 2H), 4.00–3.90 (m, 1H), 3.80 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5, 149.0, 128.0, 109.5, 108.5, 90.0, 80.5, 76.2, 60.5, 59.5, 57.5, 50.2, 23.5, 20.8, 20.5; HRMS calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$ 362.1967, found 332.1973.

4.1.14. *tert*-Butyl 4-[1-hydroxy-3-(4-methoxyphenyl)-(1*S*,2*E*)-2-propenyl]-2,2-dimethyl-(4*R*)-1,3-oxazolane-3-carboxylate 23. To a solution of sodium bis (2-methoxyethoxy) aluminium hydride (9.99 mL, 34.6 mmol, 70% in toluene) in dry ether (30 mL) at 0 °C under a nitrogen atmosphere was added compound **8a** (2.5 g, 6.9 mmol) in ether (10 mL) and the reaction mixture allowed to stir for 1 h at 0 °C. The reaction was quenched by the addition of ethanol (two drops) and a saturated solution of potassium sodium tartarate, then extracted in ether (3 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography (EA–hexane 1:4) to afford compound **23** (2.2 g, 89% yield). Compound **23**: $[\alpha]_D^{25} = -15.1$ (*c* 1.9, MeOH); IR (KBr) : 3445, 2978, 1691, 1381, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.24 (m, 2H), 6.80 (d, $J = 8.3$ Hz, 2H), 6.58 (d, $J = 15.6$ Hz, 1H), 6.08–5.98 (m, 1H), 4.41–3.88 (m, 4H), 3.80 (s, 3H), 1.48 (br s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 131.0, 127.8, 126.5, 114.2, 108.5, 94.5, 81.2, 74.5, 65.0, 62.2, 55.3, 28.5, 26.7, 24.5; HRMS calcd for $C_{20}H_{29}NO_5Na$ $[M+Na]^+$ 386.1943, found 386.1949.

4.1.15. 2-[*tert*-Butylcarbonylamino]-(2*R*,3*S*,4*E*)-5-(4-methoxyphenyl)-pent-4-ene-1,3-diol 7. Compound **23** was hydrolyzed using 60% aq AcOH (30 mL) and the reaction mixture stirred at room temperature for 12 h. After completion of the reaction, ethyl acetate was added and stirred for 30 min then extracted with ethyl acetate. The combined organic layers were neutralized with solid $NaHCO_3$ and stirred for a further hour, then filtered and concentrated to afford the residue, which was purified by column chromatography on silica gel (EA–hexane 1:2) to give compound **7** (1.5 g, 84% yield) as a semi-solid. Compound **7** semi-solid: $[\alpha]_D^{25} = -20.2$ (*c* 1.4, CH_3OH); IR (KBr): 3424, 2925, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, $J = 8.3$ Hz, 2H), 6.87 (d, $J = 8.3$ Hz, 2H), 6.65 (d, $J = 15.8$ Hz, 1H), 6.20–6.00 (m, 1H), 5.40–5.32 (m, 1H), 4.60–4.50 (m, 1H), 4.10–4.00 (m, 1H), 3.85 (s, 3H),

3.80–3.70 (m, 1H), 1.42 (br s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.1, 147.2, 129.6, 127.1, 123.4, 112.1, 109.8, 78.9, 72.1, 65.2, 63.7, 55.1, 22.1; HRMS calcd for $C_{17}H_{25}NO_5Na$ $[M+Na]^+$ 346.3789, found 346.3782.

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