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Asymmetric synthesis of (−)-codonopsinine

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ABSTRACT

The asymmetric synthesis of (−)-codonopsinine was achieved in 7 steps (from commercially available *tert*-butyl crotonate) in 5% overall yield and >99:1 dr. The key step in this synthesis involved ring-closing iodoamination of a functionalised homoallylic amine, which occurred with concomitant *N*-debenzylation, to give a 3-iodopyrrolidine that was elaborated to (−)-codonopsinine.

Nitrogen-containing heterocycles are widespread in a multitude of natural and unnatural products.[1] Pyrrolidines (i.e., 5-membered azacyclic subunits) are one of the most prevalent core heterocyclic structures included within these series, and occur commonly in alkaloids as stand-alone polysubstituted pyrrolidines and more complex bicyclic systems such as tropanes, pyrrolizidines, and indolizidines.[2] Approximately 80 pyrrolidine alkaloids are known, found across a number of families such as solanaceae, convolvulaceae, and erythroxylaceae,[3] and many display potent biological activities ranging from antibacterial and neuroexcitatory agents to potent venoms, glycosidase inhibitors and fungicides.[4,5] Polysubstituted pyrrolidines have therefore been the subject of many total syntheses.[6,7] Pyrrolidine alkaloids with aromatic substituents, for example, (−)-codonopsinine **1**, (−)-codonopsine **2**, and radicamines A **3** and B **4**, occur fairly infrequently in nature (Fig. 1).[8] The dense functionality within these compounds, coupled with the presence of four contiguous stereogenic centres, makes them challenging synthetic targets.

(−)-Codonopsinine **1** was isolated in 1969 from *Codonopsis clematidea*, a flowering plant native to East Asia.[8a–d] Its structure was unambiguously assigned in 1986 by Kibayashi and co-workers via single crystal X-ray diffraction analysis of an intermediate in their total synthesis of the antipode (+)-codonopsinine **1**,[9] although a crystal structure of codonopsinine **1** itself is yet to be reported. Several syntheses of codonopsinine **1** have been reported: most of these approaches are enantiospecific, starting from either L-xylose,[4,10] D-alanine,[11,12] L-threonine,[13] D-tartaric acid,[14] L-tartaric acid,[15] L-pyroglutamic acid[16,17] or D-ribose.[18] In addition, one total

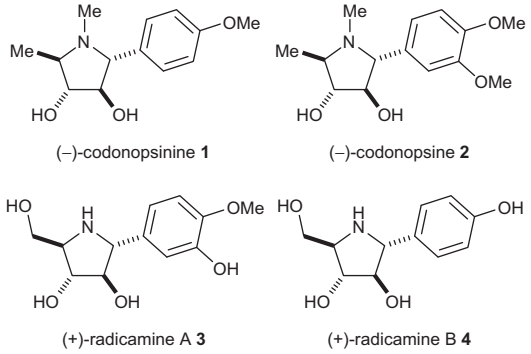

Figure 1. Examples of C(2)-aryl substituted pyrrolidines.

racemic synthesis[19] and one total asymmetric synthesis[20] of codonopsinine **1** are known. A diverse range of synthetic strategies have been adopted in these syntheses, including the diastereoselective addition of Grignard reagents to cyclic nitrones, the decarboxylative cyclisation of allylic carbamates, the Heck reaction of endocyclic enecarbamates, and intramolecular S_N2-type displacement reactions, amongst other approaches.

We have recently reported the total asymmetric syntheses of pyrrolidine,[21] piperidine[22], and pyrrolizidine[23] scaffolds using a ring-closing iodoamination protocol (which proceeds with concomitant *N*-debenzylation) as the key step. We envisaged that this strategy would also be applicable to the synthesis of C(2)-aryl substituted pyrrolidines and selected (−)-codonopsinine **1** as a target to probe the scope of this methodology. By analogy to our previous results, our strategy for the synthesis of a C(2)-aryl substituted pyrrolidine scaffold involved treatment of homoallylic amine **8** with iodine

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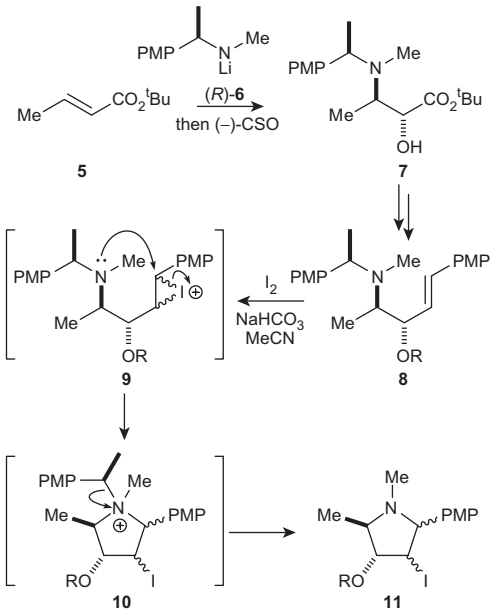
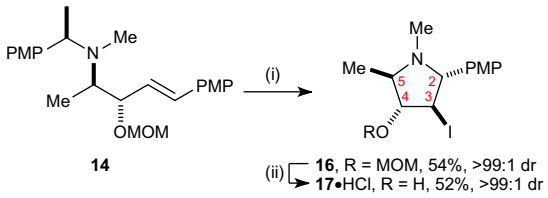


Scheme 1. Proposed synthetic strategy towards polysubstituted pyrrolidine scaffolds.



Scheme 3. Reagents and conditions: (i) $NaHCO_3$, I_2, MeCN, rt, 20 h; (ii) HCl, MeOH, rt, 48 h.

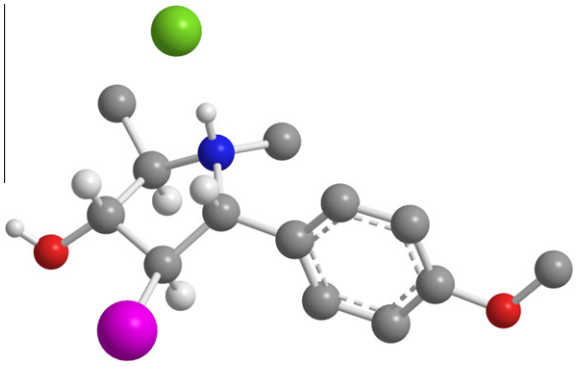
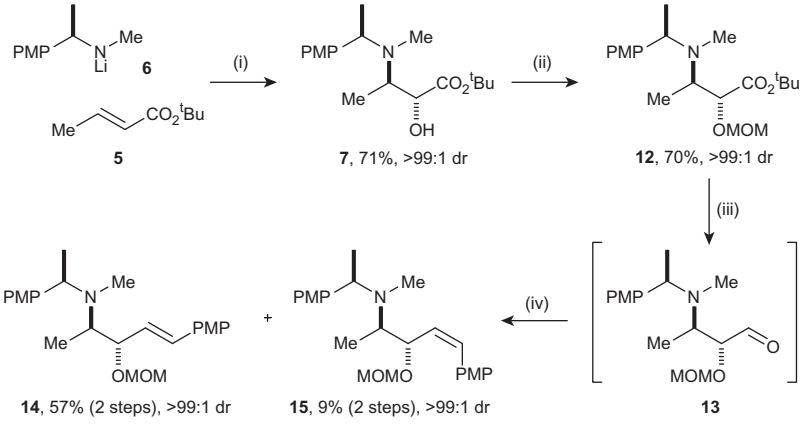


Figure 2. X-ray crystal structure of **17**·HCl (selected H-atoms are omitted for clarity).

leading to the formation of iodonium species **9**, which may undergo cyclisation to form ammonium ion **10**, followed by in situ S_N1-type loss of the *N*-α-methyl-*p*-methoxybenzyl protecting group (with ensuing Ritter reaction) to give 3-iodopyrrolidine **11**. Manipulation of the C(3)-iodide functionality within **11**, followed by deprotection would then give access to (−)-codonopsinine **1**. It was anticipated that homoallylic amine **8** could be easily synthesised from *tert*-butyl crotonate **5** using our asymmetric aminohydroxylation protocol[24,25] whereby conjugate addition of enantiopure lithium amide (*R*)-**6** to **5**, followed by in situ oxidation of the intermediate lithium β-amino enolate with (−)-camphorsulfonyloxaziridine [(−)-CSO], gives *anti*-α-hydroxy-β-amino ester **7** with high diastereoselectivity. Subsequent protection of the hydroxyl group within **7**, reduction of the *tert*-butyl ester moiety, and Wittig olefination of the resultant aldehyde was expected to give access to homoallylic amine **8** (Scheme 1).

Thus, the conjugate addition of enantiopure lithium amide **6** to *tert*-butyl crotonate **5** gave **7** as a single diastereoisomer (>99:1 dr) which was isolated in 71% yield after chromatographic purification. Subsequent protection of the C(2)-hydroxyl group within **7** as the corresponding *O*-MOM ether gave **12** in 70% yield and >99:1 dr. Reduction of the ester functionality within **12** with DIBAL-H, followed by Wittig olefination of the resultant aldehyde **13** gave a ~2:1 mixture of homoallylic amines (*E*)-**14** and (*Z*)-**15**, which were isolated in 57% and 9% yield (over 2 steps), respectively, and in >99:1 dr in each case (Scheme 2). The configurations of the newly formed double bonds within (*E*)-**14** and (*Z*)-**15** were assigned by ^{1}H NMR ^3J coupling constant analyses, with diagnostic *trans* [$J_{1,2}$ = 16.0 Hz for (*E*)-**14**] and *cis* [$J_{1,2}$ = 12.0 Hz for (*Z*)-**15**] olefinic coupling constants being observed.

Following our previously optimised procedure,[21a,24e] treatment of **14** with I_2 and $NaHCO_3$ in MeCN gave 3-iodopyrrolidine **16** as a single diastereoisomer (>99:1 dr), which was isolated in 54% yield and >99:1 dr after chromatographic purification. The relative configuration within **16** was unambiguously established by derivatisation to the corresponding alcohol **17** (which was achieved upon treatment with HCl in MeOH), followed by single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **17**·HCl (Scheme 3).[26] These crystallographic data allowed the relative configuration within **17**·HCl to be unambiguously assigned, with the



Scheme 2. Reagents and conditions: (i) THF, −78 °C, 2 h, then (−)-CSO, −78 °C to rt, 12 h; (ii) NaH, DMF, 0 °C, 30 min, then MOMCl, rt, 12 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iv) BuLi, $[4\text{-}MeOC_6H_4CH_2PPh_3]^+$ $[Cl]^-$, THF, −78 °C, 30 min, then rt, 12 h.

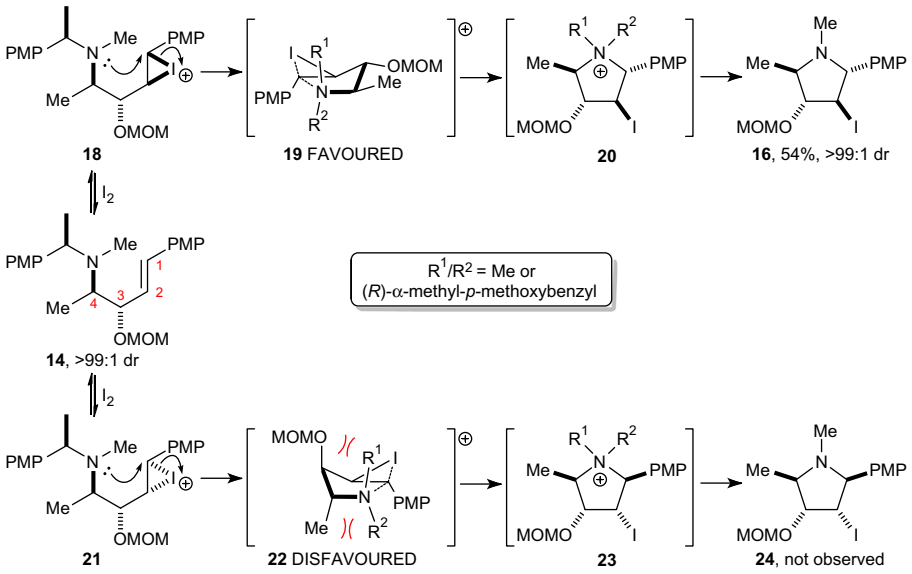
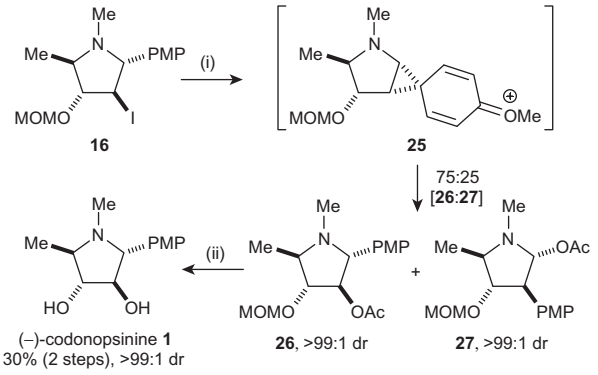


Figure 3. The origin of diastereoselectivity in the ring-closing iodoamination of **14**.



Scheme 4. Reagents and conditions: (i) AgOAc, AcOH, 40 °C, 24 h; (ii) HCl, MeOH, 50 °C, 48 h.

absolute (*R*,*R*,*R*,*R*)-configuration within **17** being assigned relative to the known configurations of the C(4) and C(5) stereocentres. Furthermore, the determination of a Flack *x* parameter[27,28] of −0.03(3) for the structure allowed the absolute (*R*,*R*,*R*,*R*)-configuration within **17**, and therefore also the absolute configurations within **7** and **12**–**16**, to be confirmed unambiguously (Fig. 2).

The formation of **16** as a single diastereoisomer in the ring-closing iodoamination step suggests that cyclisation occurs via the attack of an iodonium species (which is presumably formed reversibly from **14**), as cyclisation via the corresponding carbonium ion at C(1) would be expected to give rise to a mixture of diastereoisomeric pyrrolidines. The diastereoselectivity of this transformation can be rationalised by considering the two possible diastereoisomeric intermediate iodonium ions **18** and **21**: within transition state **22** for the cyclisation of iodonium **21**, both the C(3)-alkoxy and C(4)-methyl groups occupy pseudo-axial positions and experience unfavourable steric interactions with the nitrogen protecting groups (i.e., R^1 and R^2, one of which is α-branched). For cyclisation of iodonium **18**, however, the C(3)-alkoxy and C(4)-methyl groups occupy pseudo-equatorial positions and do not suffer unfavourable steric interactions with the nitrogen protecting groups in transition state **19**. If the *N*-α-methyl-*p*-methoxybenzyl group was to reside at position R^2 within the favoured transition state **19** it can minimise 1,2-strain with the C(1)-*p*-methoxyphenyl substituent by adopting a conformation with the aryl group oriented away from the site of reaction; this is not possible within disfavoured transition state **22** as, regardless of the conformation of the *N*-α-methyl-*p*-methoxybenzyl group (residing at either position R^1 or R^2), unfavourable steric interactions will be encountered (Fig. 3).

As (−)-codonopsinine **1** possesses the same 'all-*trans*' configuration as 3-iodopyrrolidine **16**, elaboration of **16** to enable the total synthesis of (−)-codonopsinine **1** required substitution of the iodide substituent at C(3) with retention of configuration. A double inversion strategy [e.g., S_N2 displacement with acetate, hydrolysis of the resultant 3-acetoxypyrrolidine then Mitsunobu reaction] was considered, but a strategy reliant on neighbouring group participation by the C(2)-*p*-methoxyphenyl group (i.e., an S_N1-type process) was envisaged to be more efficient in installing the oxygen functionality at C(3) with the correct configuration, with subsequent deprotection then providing access to (−)-codonopsinine **1**. In order to promote an S_N1-type reaction, **16** was treated with AgOAc in AcOH. Under these reaction conditions a mixture of **26** (>99:1 dr) and regioisomeric product **27** (>99:1 dr) was produced which, despite exhaustive efforts, proved to be inseparable by flash column chromatography and was therefore isolated as a 75:25 mixture; there was sufficient resonance dispersion in the ^{1}H NMR spectrum of this mixture (in $CDCl_3$) to allow the relative configurations within both **26** and **27** to be determined by ^{1}H

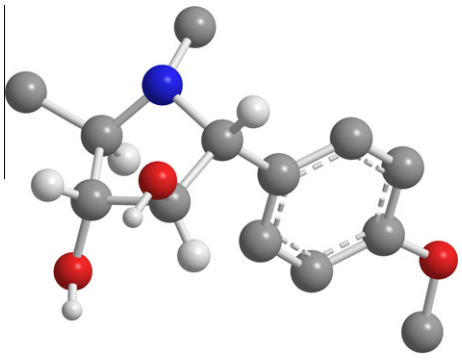


Figure 4. X-ray crystal structure of (−)-codonopsinine **1** (selected H-atoms are omitted for clarity).

NMR nOe analysis. The appearance of regioisomeric product **27** lends support to the original hypothesis that a mechanism involving neighbouring group participation via a phenonium ion intermediate **25** was occurring and also giving rise to retention of configuration upon attack of the acetate anion at C(3) to give **26**. Subsequently, treating the 75:25 mixture of **26** and **27** with methanolic HCl at 50 °C for 48 h was found to give (−)-codonopsinine **1** in 30% isolated yield (2 steps) and >99:1 dr, thus completing the total asymmetric synthesis of this pyrrolidine natural product (Scheme 4).

The spectroscopic data for the synthetic sample of (−)-codonopsinine **1**[29] were found to be in excellent agreement with those corresponding to the sample isolated from the natural source {$[\alpha]_D^{20}$ −9.1 (*c* 0.1 in MeOH); Lit.[8b] $[\alpha]_D^{20}$ −8.8 (*c* 0.1 in MeOH)} and other samples obtained by total synthesis.[30] Furthermore, recrystallisation of (−)-codonopsinine **1** from pyridine produced colourless plates which were subjected to X-ray diffraction analysis,[26] unambiguously confirming the relative configuration within codonopsinine (Fig. 4).

In summary, ring-closing iodoamination of a homoallylic amine, with concomitant *N*-debenzylation, was used to generate a 3-iodopyrrolidine in >99:1 dr. Subsequent elaboration upon treatment with AgOAc in AcOH, followed by global deprotection gave (−)-codonopsinine (in >99:1 dr) in 7 steps from commercially available *tert*-butyl crotonate in 5% overall yield. Furthermore, the single crystal X-ray diffraction structure of (−)-codonopsinine is, for the first time, disclosed herein.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.114.

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26. Crystallographic data (excluding structure factors) for compounds **17**·HCl and **1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 840035 and 840036, respectively. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif
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29. Data for (*R,R,R,R*)-*N*(1)-methyl-2-(4′-methoxyphenyl)-3-hydroxy-4-hydroxy-5-methylpyrrolidine [(−)-codonopsinine] **1**: mp 147–150 °C; $[\alpha]_D^{20}$ −9.1 (*c* 0.1 in MeOH); δ_H (400 MHz, pyridine-d_5) 1.34 (3H, d, *J* 6.8, C(5)*Me*), 2.23 (3H, s, N*Me*), 3.64 (3H, s, O*Me*), 3.67–3.72 (1H, m, C(5)*H*), 4.09 (1H, d, *J* 6.7, C(2)*H*), 4.39 (1H, dd, *J* 4.4, 3.8, C(4)*H*), 4.65 (1H, dd, *J* 6.7, 4.4, C(3)*H*), 5.25 (2H, br s, O*H*), 6.95 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.31 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, pyridine-d_5) 14.3 (C(5)*Me*), 35.2 (N*Me*), 55.5 (O*Me*), 65.7 (*C*(5)), 74.6 (*C*(2)), 85.6 (*C*(4)), 88.0 (*C*(3)), 114.7 (*C*(3′), *C*(5′)), 130.2 (*C*(2′), *C*(6′)), 135.4 (*C*(1′)), 160.1 (*C*(4′)); *m*/*z* (ESI$^+$) 238 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO_3^+$ ([M+H]$^+$) requires 238.1438; found 238.1437.
30. Ref. 4a: $[\alpha]_D^{28}$ −13.2 (*c* 0.3 in MeOH); Ref. 4b: $[\alpha]_D^{20}$ −8.8 (*c* 0.1 in MeOH); Ref. 10: $[\alpha]_D^{25}$ −12.4 (*c* 0.4 in MeOH); Ref. 11: $[\alpha]_D^{34}$ −8.7 (*c* 0.3 in MeOH); Ref. 13: $[\alpha]_D^{20}$ −10.5 (*c* 1.1 in MeOH); Ref. 15: $[\alpha]_D^{20}$ −7.2 (*c* 0.1 in MeOH); Ref. 17: mp 153–155 °C; $[\alpha]_D^{20}$ −7.3 (*c* 0.2 in MeOH); Ref. 20: $[\alpha]_D^{20}$ −13.1 (*c* 1.3 in MeOH).