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Total Synthesis of Natural (-)-Codonopsinine Employing Stereoselective Reduction of Quaternary α-Hydroxypyrrolidine

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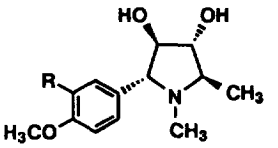
Abstract: A novel and efficient process is described for the total synthesis of a dihydroxypyrrolidine alkaloid, (-)-codonopsinine in 33% overall yield. The synthetic strategy is based on the stereoselective reduction of an α-hydroxypyrrolidine intermediate, elaborated through asymmetric deoxygenation of a homochiral quaternary α-hydroxylactam. Copyright © 1996 Elsevier Science Ltd

Codonopsinine (**1**) and codonopsine (**2**), antibiotics first isolated in 1969 from *Codonopsis clematidea* by a Russian group[1,2] exhibit hypotensive pharmacological activity with no effect on the central nervous system observed in animal tests.[3] After structural characterization,[4,5] these were revealed to be a new class of simple pyrrolidine alkaloids possessing 1,2,3,4,5-pentasubstituted structures. Further, in 1972 the relative stereochemistry of these alkaloids was elucidated by the same group[6] to be (2*R**,3*S**,4*S**,5*S**) without absolute configuration based on analyses of ^{1}H NMR coupling constants using the Karplus equation. It was not until the synthesis of **1** with stereochemistry different to the naturally occurring form was accomplished in 1987 by Kibayashi et al.[7] that the absolute stereochemistry of the natural antibiotic **1** was determined unambiguously to be (2*R*,3*R*,4*R*,5*R*). In addition, the structure of codonopsine (**2**) was recently confirmed by another group using X-ray crystallographic analysis of the chromatographically separated sample.[8] The four functional groups in the pyrrolidine ring of these compounds are situated in all *trans* positions.



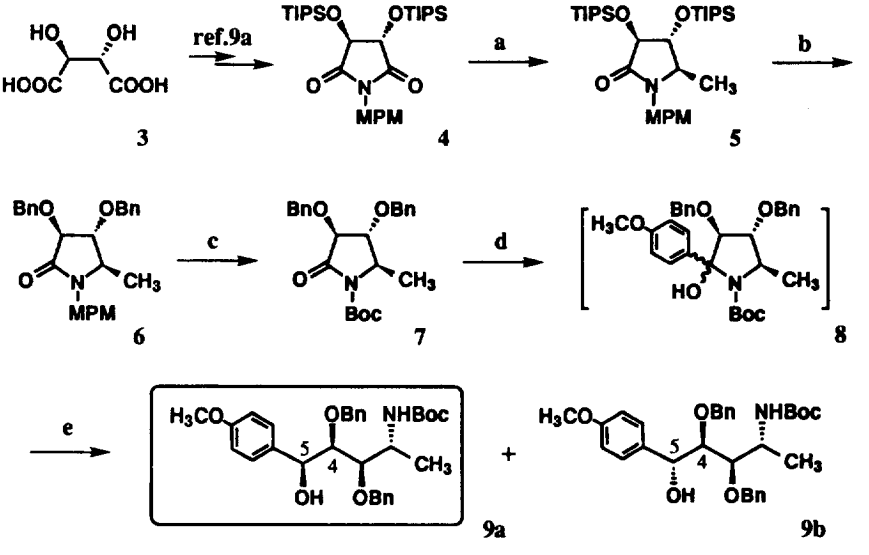
Codonopsinine (1): R = H
Codonopsine (2): R = CH_3

Thus, despite interesting pharmacological activity and unique structural features, to our knowledge, only two approaches (an enantiomer synthesis of **1**[7] and a nonstereoselective route with stereoisomer separation of **2**[8]) have been reported to date.

With these considerations in mind, we wish to describe herein a novel and short asymmetric synthesis of **1** by means of requisite stereoselective reduction of the quaternary α-hydroxypyrrolidine, which was obtained by Grignard addition to the homochiral lactam elaborated through Lewis-acid induced deoxygenation.

C_2-imide (**4**) with a *N*-*p*-methoxybenzyl (MPM) group, obtained from D-tartaric acid (**3**), was treated with methylmagnesium bromide to give the quaternary α-hydroxylactam intermediate. This readily underwent reductive deoxygenation with Et_3SiH in the presence of $BF_3 \cdot OEt_2$,[9] leading to the single stereoisomer of the homochiral lactam (**5**) (100% d.e. determined by HPLC using Daicel Chiralpak AS) in 89% yield. After exchange of the protecting groups in **5** to benzyl ethers to resist changes in pH, **6** thus obtained was transformed into the N-Boc lactam (**7**) by 2 steps. Nucleophilic addition of *p*-methoxyphenylmagnesium bromide to **7** easily afforded the labile quaternary α-hydroxypyrrolidine (**8**).

Since direct deoxygenation of **8** with Et_3SiH according to our recent communication[10] did not succeed in the preparation of the homochiral pentasubstituted pyrrolidine derivative (in this case the pyrrole-type elimination product was obtained in high yield), we examined stereoselective reduction leading to the corresponding alcohol (**9a**) with desired configuration. The details are summarized in Table 1. Whereas the reduction with $NaBH_4$ only gave the (5*R*)-stereoisomer **9b** as a major product (entry 1),[11] reaction in the presence of $CeCl_3$ or $SmCl_3$ predominantly afforded the desired (5*S*)-isomer **9a** (entries 7,8,10). The use of DIBALH[12] (entries 2,3) or $NaBH_4$ in the presence of other metal chlorides[13] (entries 4-6) brought about unsatisfactory stereoselectivities. After investigations under a variety of conditions employing $SmCl_3$ (entries 10-15), the best result (**95 : 5**) was observed under the conditions indicated in entry 14 in 88% yield.



Scheme 1. Reagents and conditions: (a) 1, CH_3MgBr, THF, -78 - -10 °C; 91%; 2, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 98%; (b) 1, aqHCl, MeOH; 99%; 2, BnBr, Ag_2O, EtOAc; 75%; (c) 1, $Ce(NH_4)_2(NO_3)_6$, CH_3CN-H_2O (9:1); 90%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 99%; (d) *p*-MeOPhMgBr, THF, -78 °C;(e)reducing agent (see Table 1).

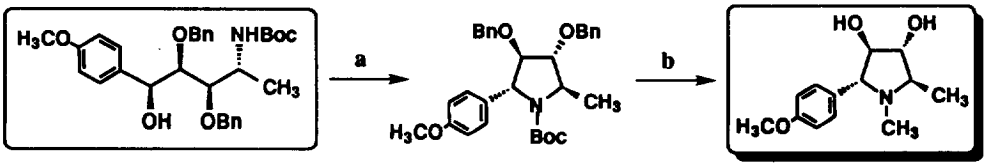
With the above stereochemical outcome in hand, mesylation and subsequent cyclization with *t*-BuOK of pure **9a** obtained after separation of the diastereomers were performed, smoothly leading to the optically pure pentasubstituted pyrrolidine derivative **10** in 92% yield. Finally, **10** was reduced with $LiAlH_4$ in refluxing

Table 1. Stereoselective reduction of the quaternary α-hydroxypyrrolidine (**8**) in the presence of metal halide.

Entry	Reagent	Additive [a] (equiv.)	Solvent	Temp. (°C)	Yield [b] (%)	Ratio of **9a** : **9b** [c]
1	$NaBH_4$	none	MeOH	18	86	17 : 83
2	DIBALH	$MgBr_2$ (2)	Et_2O	-78	69	61 : 39
3	DIBALH	$SmCl_3$ (2)	toluene	-78	90	73 : 37
4	$NaBH_4$	$MgCl_2$ (2)	MeOH	0	73	42 : 58
5	$NaBH_4$	$CaCl_2$ (2)	MeOH	0	82	67 : 33
6	$NaBH_4$	$MnCl_2$ (2)	MeOH	0	83	44 : 56
7	$NaBH_4$	$CeCl_3$ (2)	MeOH	0	87	80 : 20
8	**$NaBH_4$**	**$CeCl_3$ (2)**	**MeOH**	**-18**	**88**	**81 : 19**
9	$NaBH_4$	$CeCl_3$ (2)	MeOH	-78	90	68 : 32
10	**$NaBH_4$**	**$SmCl_3$ (2)**	**MeOH**	**0**	**90**	**92 : 8**
11	$NaBH_4$	$SmCl_3$(0.05)	MeOH	-18	90	68 : 32
12	$NaBH_4$	$SmCl_3$ (4)	MeOH	-18	89	82 : 18
13	$NaBH_4$	$SmCl_3$ (2)	*i*-PrOH	-18	72	86 : 14
14	**$NaBH_4$**	**$SmCl_3$ (2)**	**MeOH**	**-18**	**88**	**95 : 5**
15	$NaBH_4$	$SmCl_3$ (2)	MeOH	-78	89	80 : 20

a) Dried *in vacuo* at 140 °C. b) Isolated yield as a mixture of **9a** and **9b**. c) Determined by chiral HPLC (Daicel chiralpak AD).

THF after deprotection of the benzyl groups to complete the total synthesis of (-)-codonopsinine (**1**), $[\alpha]_D^{20}$-11.8° (c 0.69, MeOH) [natural **1**, $[\alpha]_D^{20}$-8.8° (c 0.1, MeOH)]. The spectral data of the synthetic white needles **1** were completely identical with those of the reported natural compound.[1]



9a **10** **Codonopsinine (1)**

Scheme 2. Reagents and conditions: (a) 1, MsCl, Et_3N, CH_2Cl_2; 2, t-BuOK, THF; 92% (2 steps); (b) 1, Pd (black), 4.4% HCOOH-MeOH; 99%; 2, $LiAlH_4$, THF, reflux; 69%.

In addition to the synthesis of **1**, we briefly investigated the mechanistic origin of the asymmetric reduction of **8**. As shown in Fig. 1, it was apparent that Cram's non-chelation or five-membered chelation model favors production of the undesirable (5***R***)-**9b**. Although the reasons why such an unusual stereoselective reduction was acomplished only by the use of $SmCl_3$ have not yet been clarified, under these

conditions it could proceed through the predominant attack of H^- on the carbonyl function from the top face of the six-membered metal-chelate rather than five-membered one due to the shielding effect of the three large functional groups.

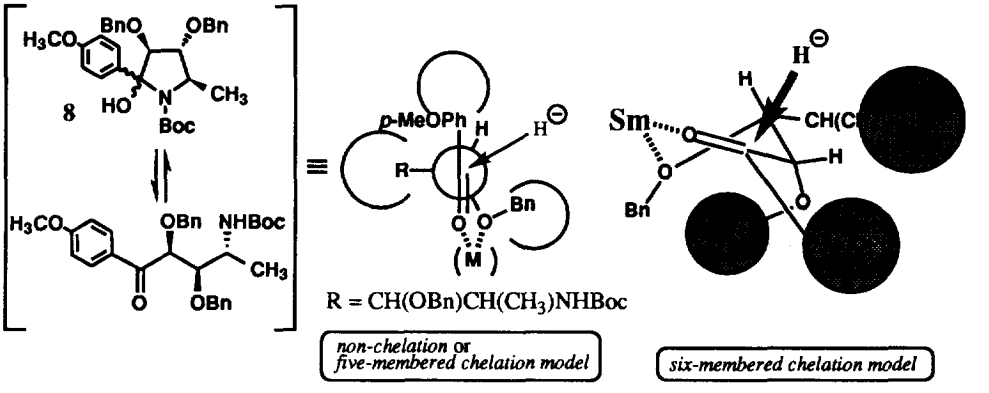


Fig. 1 Mechanistic origin of the stereoselective reduction.

In summary, a short and efficient method for the asymmetric synthesis of natural (-)-codonopsinine was established in 33% overall yield from C_2-imide based on the stereoselective reduction of the quaternary α-hydroxypyrrolidine intermediate, elaborated through asymmetric deoxygenation of a homochiral α-hydroxylactam. This is the first report of the synthesis of the natural product **1**.

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