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# SYNTHESIS OF (+)-CODONOPSININE: DETERMINATION OF ABSOLUTE CONFIGURATION OF NATURAL (-)-CODONOPSININE

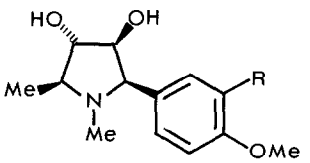
Hideo Iida, Naoki Yamazaki, and Chihiro Kibayashi*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Summary: (+)-Codonopsinine, the enantiomer of natural (-)-codonopsinine, was synthesized in an enantiomerically pure form from L-tartaric acid, which led to the establishment of the absolute configuration of the natural substance to be 2*S*,3*R*,4*R*,5*R*.

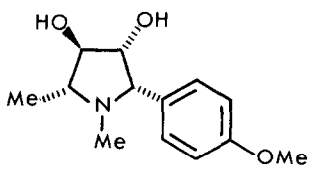
Codonopsine and codonopsinine isolated from *Codonopsis clematidea (Campanulaceae)*,[1,2] which after structural revision[3,4] have formulas 1 and 2, respectively, are a new type of the simple pyrrolidine alkaloids with 2,3,4,5-tetrasubstitution. In animal test the former possesses hypotensive pharmacological activity.[5] The relative stereochemistry for the four contiguous chiral centers in these alkaloids has been presented as 1 and 2 on the basis of $^1$H NMR analysis by Russian workers,[6] which, however, lacked the absolute stereochemistry.

We report here the first total synthesis of codonopsinine in an enantiomerically pure (+)-form (2) starting from L-tartaric acid which leads to the assignment of the absolute configuration as 3 (2*S*,3*R*,4*R*,5*R*) for natural (-)-codonopsinie.




**1** R = OMe

**2** R = H




**3**

Preparation of 2,3-bis-(methoxymethyl)-L-threitol (4), mp 62-63°; $[\alpha]_D^{23}$ -7.7° (*c* 3.37, MeOH), was carried out from L-tartaric acid by a three-step reaction sequence involving esterification (EtOH, TsOH), methoxymethylation (MOMCl, *i*-$Pr_2NEt$, $CHCl_3$, 60 °C, 36 h; 79%), and reduction ($LiAlH_4$, $Et_2O$/THF, rt, 14 h; 94%). Monobenzylation of 4 was effected by treatment with 1 equiv. of benzyl chloride (*n*-$Bu_4NBr$) to generate 5 (74%), $[\alpha]_D^{23}$ -2.1° (*c* 5.11, MeOH), which was then subjected to Swern oxidation[7] ($(COCl)_2$, DMSO, $Et_3N$) to give the aldehyde 6 (82%), $[\alpha]_D^{22}$ +10.3° (*c* 1.42, MeOH). This aldehyde was in turn treated with *p*-methoxyphenylmagnesium bromide (THF, -10° → rt) to produce a 3.3:1 mixture of two

diastereomeric alcohols (83%); *threo*-7a, $[\alpha]_D^{19}$ -26.0° (*c* 1.07, MeOH), and *erythro*-7b, $[\alpha]_D^{21}$ -61.3° (*c* 0.32, MeOH). The preponderance of the *threo* isomer in this Grignard addition is rationalized in terms of the chelate model[8] as shown in Fig. 1.[9] Interestingly, this finding is of opposite to stereochemical outcome in the addition of organometallics other than Grignard reagents to the 2,3-*O*-isopropylidene analog of 6 wherein the reaction does not follow the predictions of the cyclic model, but rather is consistent with the Felkin model.[10] The *R* configuration at the benzylic carbinol site of the major diastereomer 7a is not proper to that requested for the target 2 with the *R* configuration at C-2, since at the next stage it was necessary to introduce a nitrogen function onto the corresponding carbon atom which may involve $S_N2$ type inversion of the original configuration.

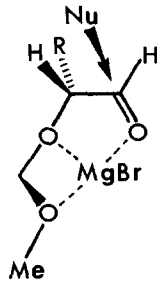
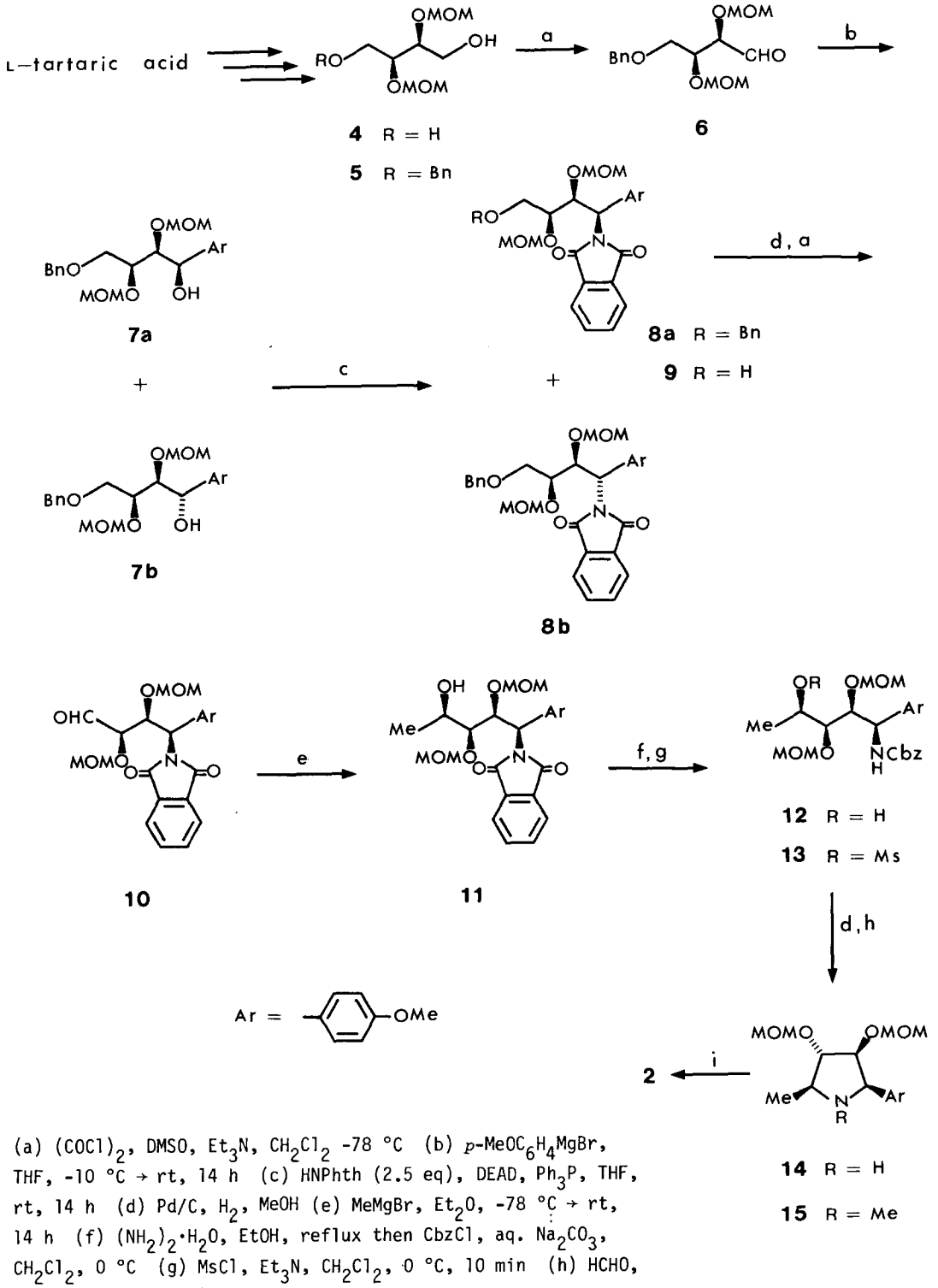


Fig. 1

However, this stereochemical problem was practically negligible sine either *threo* or *erythro* alcohols (7a or 7b) provided the same 1:1 epimeric mixture at C-2 (codonopsinine numbering) in the next step involving Mitsunobu reaction. Thus the threo/erythro mixture obtained was, without separation, treated with phthalimide, DEAD, and $Ph_3P$ (THF, 0 °C → rt) to give a 1:1 mixture of the chromatographically separable epimers, the *syn* isomer 8a, $[\alpha]_D^{20}$ -64.3° (*c* 4.20, MeOH), as the less polar component and the *anti* isomer 8b, $[\alpha]_D^{23}$ -61.9° (*c* 7.20, MeOH), as the more polar component in 64% total yield.

Debenzylation of 8a (Pd/C, $H_2$, MeOH) provided the alcohol 9 (70%), $[\alpha]_D^{20}$ -83.0° (*c* 22.47, MeOH), which was then converted to the aldehyde 10, $[\alpha]_D^{20}$ -85.7° (*c* 12.35, MeOH), by Swern oxidation in 83% yield. When treated with methylmagnesium bromide ($Et_2O$, -78 °C), the aldehyde 10 underwent highly stereoselective Grignard reaction involving the chelation controlled addition as described above (Fig. 1), and the desired *threo* alcohol 11, $[\alpha]_D^{20}$ -57.8° (*c* 3.25, MeOH), was obtained in 62% yield. Removal of the phthaloyl group ($H_2NNH_2 \cdot H_2O$, EtOH, reflux) followed by benzyloxycarbonylation (CbzCl, aq. $Na_2CO_3$) gave the carbamate 12, $[\alpha]_D^{20}$ +4.5° (*c* 2.43, MeOH), in quantitative overall yield from 11, which was then transformed to the mesylate 13, $[\alpha]_D^{20}$ +6.6° (*c* 4.81, MeOH), by standard procedure. Catalytic hydrogenolysis of 13 over Pd/C in methanol resulted in in situ cyclization to form stereospecifically 14 (75%), $[\alpha]_D^{20}$ -29.5° (*c* 2.51, MeOH), with the desired sense of chirality for the target.

Finally, N-methylation of 14 (HCHO, Pd/C, $H_2$ MeOH) affording 15, $[\alpha]_D^{20}$ +7.2° (*c* 2.92, MeOH), followed by deprotection (aq. HCl/MeOH, 50 °C) furnished (+)-codonopsinine (2), mp 172.5-173.5 °C (lit.[2] 169-170 °C for natural codonopsinine), in 58% overall yield from 14. The $^1H$ NMR and mass spectra of synthetic 2 was identical to those published[6,7] for natural codonopsinine. The synthetic material had $[\alpha]_D^{20}$ +12.5° (*c* 2.55, MeOH) while the natural product is reported[2]




(a) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$ -78 °C (b) *p*-$MeOC_6H_4MgBr$, THF, -10 °C → rt, 14 h (c) HNPhth (2.5 eq), DEAD, $Ph_3P$, THF, rt, 14 h (d) Pd/C, $H_2$, MeOH (e) MeMgBr, $Et_2O$, -78 °C → rt, 14 h (f) $(NH_2)_2 \cdot H_2O$, EtOH, reflux then CbzCl, aq. $Na_2CO_3$, $CH_2Cl_2$, 0 °C (g) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 10 min (h) HCHO, Pd/C, $H_2$, MeOH (i) aq. HCl/MeOH, 50 °C, 2.5 h

to have $[\alpha]_D^{20}$ -8.8° (*c* 0.1, MeOH). This leads to the conclusion that (+)-(2*R*,3*S*,4*S*,5*S*)-codonopsinine (2) is the enantiomer of the naturally occurring substance. Accordingly, this synthesis established the absolute configuration of natural codonopsinine to be 2*S*,3*R*,4*R*,5*R* as shown in 3.

The methodology presented herein promises to provide natural (-)-codonopsinine by using D-tartaric acid available as a starting material.

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