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STEREOCHEMICAL REVISION AND ABSOLUTE CONFIGURATION OF CODONOPSININE

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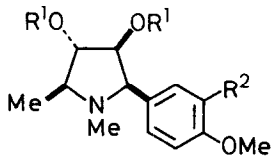
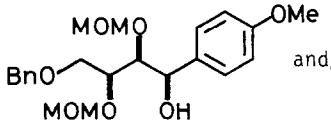
Abstract: The stereostructure of codonopsinine has been revised from 1 to 7 based on chemical correlation studies, NOE experiments, and X-ray crystallographic analysis. This establishes the absolute configuration of natural (-)-codonopsinine as 2R,3R,4R,5R.

Codonopsinine and codonopsine were isolated in 1969 from Codonopsis clematidea by a Russian group[1,2] and in 1972 their structures, lacking absolute stereochemistry, were reported as 1 and 2, respectively, by the same group.[3] We have recently reported[4] the first total synthesis of the (+)-enantiomer of natural codonopsinine, in which the less polar isomer (I), one of the epimeric products formed by Mitsunobu condensation of 3 and/or 4, was utilized as the key intermediate. The relative stereochemistry of I could not be determined at this stage but was tentatively assigned as syn 5 based on chemical correlation with the proposed structure 1 for codonopsinine by the Russian

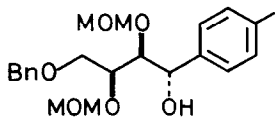


1 $R^1 = R^2 = H$
2 $R^1 = H$; $R^2 = OMe$
13 $R^1 = MOM$; $R^2 = H$



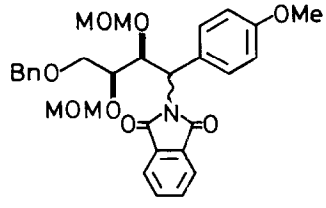
3

and/or

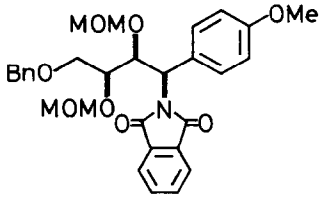


4

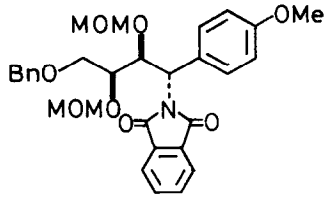
Mitsunobu



I (less polar)
II (more polar)

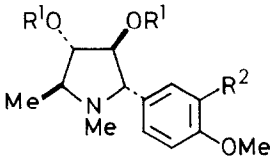


5 (syn)

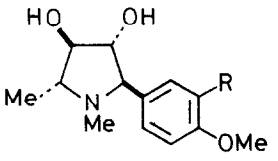


6 (anti)

group. Recently we found that hydride addition of chiral ketoximes gives diastereoselectivity favoring anti amines.[5] Prompted by this result, we have decided to reinvestigate the stereostructure of I. The present studies have provided results which show that the less polar epimer (I), previously identified as syn 5, is actually the anti isomer 6. This leads to stereochemical revision 7 for (+)-codonopsinine, thus establishing absolute structure 8 for the natural (-)-enantiomer.

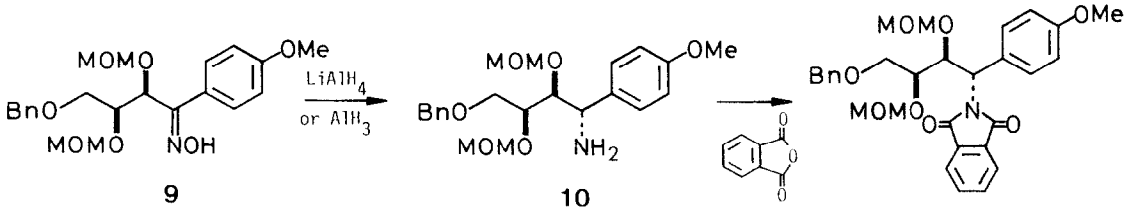


7 $R^1 = R^2 = H$
12 $R^1 = MOM$; $R^2 = H$
14 $R^1 = H$; $R^2 = OMe$



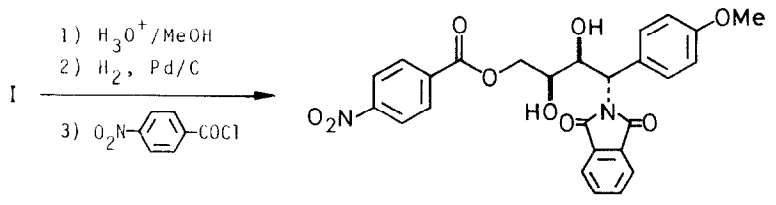
8 R = H
15 R = OMe

We set out to determine whether I or II corresponds to the anti amine 10, prepared by stereoselective hydride addition of the chiral ketoxime 9.[5] Accordingly, 10 was transformed by treatment with phthalic anhydride (toluene, reflux) into the anti phthalimide 6, which was found to be different from II and perfectly in accord with I. This correlation established that the less polar diastereomer I must have the relative and absolute configurations depicted by 6 and thus the more polar one II must have the configurations shown in 5.



9 **10** **6**

Unequivocal proof for the relative structure 6 assigned to I was obtained by X-ray crystallographic analysis[6] of the crystalline derivative of I, e.g., 11, mp 200-202 °C; $[\alpha]_D^{24}$ -20.5° (c 0.21, MeCN), prepared from I by sequential reaction involving cleavage of MOM ether (15% HCl/MeOH, reflux, 0.5 h), debenzylation (H_2, Pd/C, MeOH), and acylation (p-$NO_2C_6H_4COCl$ (1 equiv), Et_3N, CH_2Cl_2). The ORTEP drawing of 11 is shown in Figure 1.



11

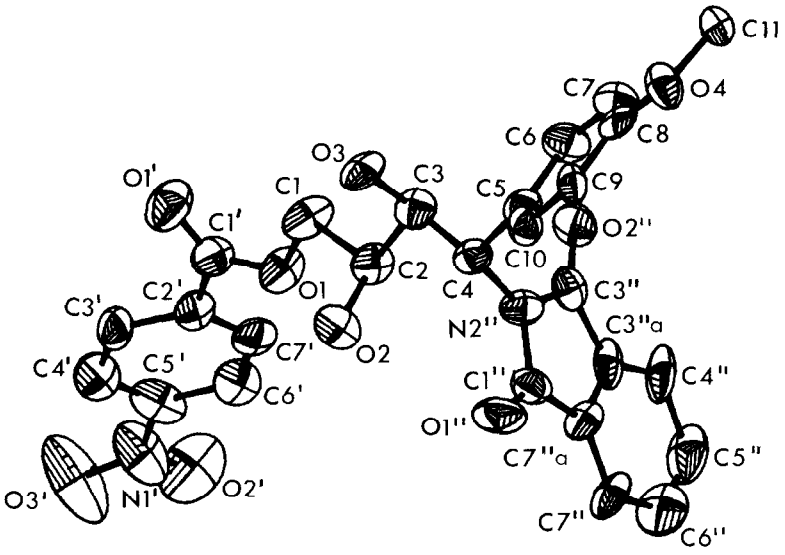
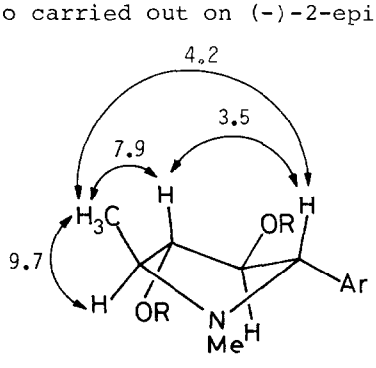


Figure 1. ORTEP drawing of the anti phthalimide derivative 11.

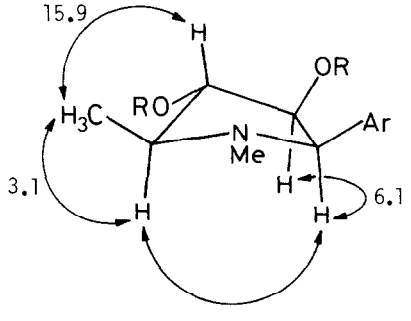
Since the less polar isomer I has been already correlated with the (+)-enantiomer of natural codonopsinine,[4] the new stereochemical assignment of I (from 5 to 6) indicated that the relative structure 1 for codonopsinine by the Russian workers[3] is in error, leading to the revised structure 7. More direct evidence for the newly assigned structure 7 was obtained from the study of NOE differences and 2D-NOE (NOESY) spectra performed with 12, the synthetic precursor[4] to (+)-codonopsinine. NOE enhancements observed among 2-H, 4-H, and 5-Me confirmed their cis relationship as shown in the formula (Figure 2).

In order to support above stereochemical arguments, NOE experiments were also carried out on (-)-2-epicodonopsinine bis(methoxymethyl) ether (13),



R = MOM; Ar = p-MeOC$_6$H$_4$

Figure 2. NOE enhancements (↷, %) of 12.



R = MOM; Ar = p-MeOC$_6$H$_4$

Figure 3. NOE enhancements (↷, %) of 13.

$[\alpha]_D^{21}$ -89.7° (c 1.19, MeOH), synthesized[5] from the more polar isomer II (5) in five steps in a manner similar to that for 12. NOE enhancements between 2-H and 3-H and between 2-H and 5-H indicated that these hydrogens are in cis relationship, being consistent with structure 13 (Figure 3). Furthermore, compound 13 was transformed into (-)-2-epicodonopsinine (1), $[\alpha]_D^{22}$ -33.0° (c 1.00, MeOH), by acid treatment (15% HCl/MeOH, reflux, 0.5 h). This material was found to be definitely different from natural codonopsinine by the ^{1}H NMR spectrum and physical properties,[5] although it possesses the relative structure corresponding to that originally assigned to codonopsinine. These findings lead to disproving the previous structure 1 for codonopsinine.

All our results indicate that the structure 1 previously assigned to (+)-codonopsinine[3,4] must be revised to 7 as shown. It establishes, therefore, that the naturally occurring (-)-enantiomer of codonopsinine possesses the 2R,3R,4R,-5R configuration as depicted in 8. This work should also lead to stereochemical revision for codonopsine from 2 to 14 and allow the absolute structure of the levorotatory natural product to be assigned as 15, since the stereostructure of codonopsine has been claimed to be identical with that of codonopsinine.[3]

References and Notes

(1) S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin, 1969, 5, 607 (C.A., 1970, 73, 25712d).

(2) S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin, 1969, 5, 30 (C.A., 1969, 71, 13245z).

(3) M. R. Yagudaev, S. F. Matkhalikova, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin, 1972, 8, 495 (C.A., 1972, 77, 164902m).

(4) H. Iida, N. Yamazaki, and C. Kibayashi, Tetrahedron Lett., 1985, 26, 3255.

(5) Details will be reported elsewhere.

(6) Crystal data: $C_{26}H_{22}N_2O_9$, M = 506.47, tetragonal, space group $p4_12_12$ or $p4_32_12$, a = 10.483 (3), c = 43.427 (8) Å, V = 4784 (1) Å^3, Z = 8, D_c = 1.41 g cm^{-3}. The crystal selected for X-ray studies had the dimensions 0.8 x 0.8 x 0.5 mm. Intensities of 2832 independent reflections within $2\theta \leq 52°$ were collected on a Rigaku AFC-5 FOS diffractometer using graphite-monochromated Mo-Kα radiation. The intensity data were corrected for Lorents- and polarization-effects, but not for absorption. A total of 2256 reflections with $F \geq 3\sigma(F)$ was used for the calculation of the structure. The structure was solved by MULTAN 80 and refined by the block-matrix technique to give an R value of 0.089 with all non hydrogen atoms treated anisotropically. Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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