

THE ABSOLUTE CONFIGURATIONS OF (+)-THALICTRIFOLINE
AND (+)-CORYDALIC ACID METHYL ESTER.
TOTAL SYNTHESIS OF (+)-THALICTRIFOLINE.

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Abstract. (+)-Thalictrifoline (3) has been synthesized from an optically resolved (+)-8-oxo-13-carboxytetrahydroprotoberberine (13) whose absolute configuration was established by correlation with (+)-18. This determines the absolute configurations of (+)-thalictrifoline (3) as 13R, 14R and (+)-corydalic acid methyl ester (9) as 3R, 4R.

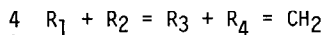
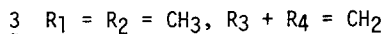
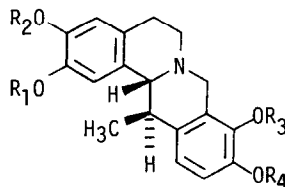
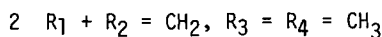
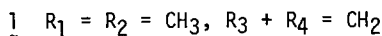
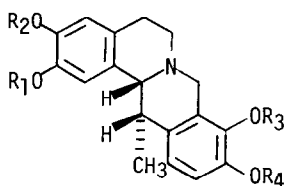
Both cis- and trans-13-methyltetrahydroprotoberberine alkaloids have been isolated from various species of Corydalis, as exemplified by (+)-cavidine (1), also known as Base II) and (+)-thalictrifoline (3).¹ Certain metabolites of both classes have been shown to be converted to benzophenanthridine alkaloids [e.g. (+)-corynoline (5) and (+)-14-epicorynoline (6)] via the protopines [e.g. (+)-corycavine (7)] in the plant and the callus cells.² The determination of the absolute configurations of the cis- and trans-13-methyltetrahydroprotoberberines is important in understanding the biosynthetic mechanisms of these interconversions. In a recent communication,³ we reported the synthesis of (+)-thalictricavine (2) and (+)-canadine (8) of known absolute configuration from an optically resolved common intermediate, (+)-12. This established the configuration of (+)-thalictricavine (2) as 13S, 14R. The same absolute configuration was also assigned to (+)-cavidine (1) since these changes in the aromatic substitution pattern have a negligible effect on the conformation and the specific rotation. We now report the elucidation of the absolute configurations of the trans isomer (+)-thalictrifoline (3) and (+)-corydalic acid methyl ester (9). A modified form of the latter compound is probably an intermediate between certain tetrahydroprotoberberine and benzophenanthridine alkaloids.⁴

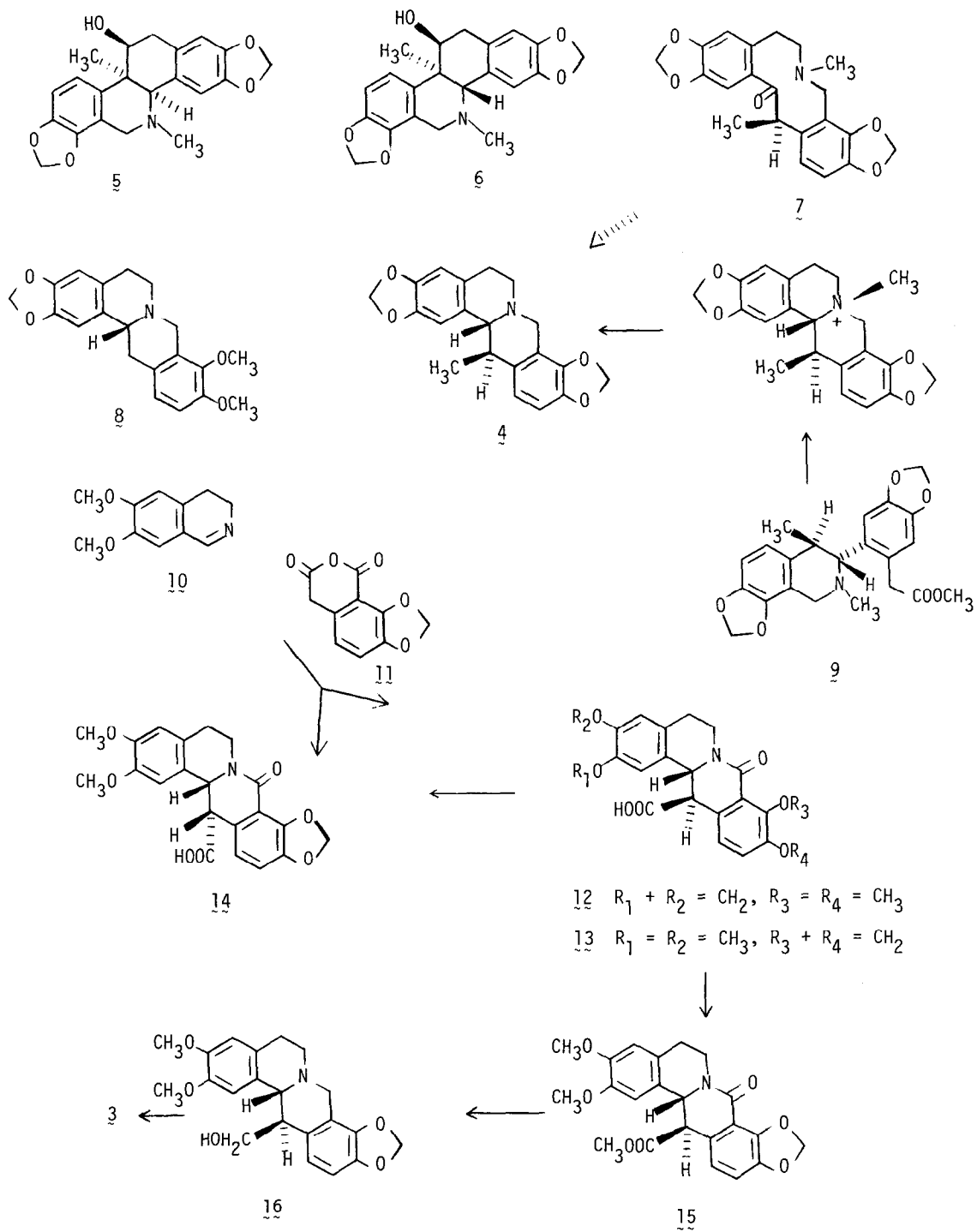
Condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline (10) with 3,4-methylenedioxyhomophthalic anhydride (11)⁵ in chloroform at room temperature proceeded exothermally to yield a diastereomeric mixture of trans- and cis-2,3-dimethoxy-8-oxo-9,10-methylenedioxy-13-carboxytetrahydroprotoberberines from which the major (±)-trans isomer 13 (mp 252-254°C, Anal Found: C, 63.51; H, 5.06; N, 3.40) crystallized in 80% yield.⁶ Heating this product in refluxing acetic acid resulted in epimerization to the thermodynamically more stable (±)-cis

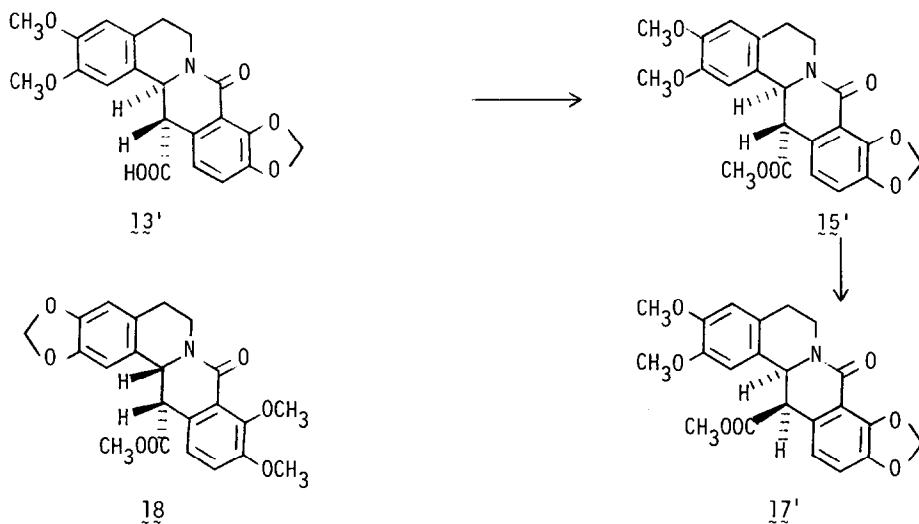
isomer 14 (mp 259-261°C, Anal Found: C, 63.47; N, 3.24). The (±)-trans acid 13 afforded a crystalline salt [mp 230-233°C dec, $[\alpha]_D - 100^\circ$ (c = 0.14, CHCl₃)] when treated with (-)-strychnine in ethyl acetate followed by recrystallization from chloroform-ethyl acetate. This salt gave the free (-)-trans acid 13' [mp 235-240°C dec, $[\alpha]_D - 228^\circ$ (c = 0.116, CHCl₃-MeOH 3:1)] on decomposition. The (+)-trans isomer 13 [mp 233-235°C dec, $[\alpha]_D + 231^\circ$ (c = 0.13, CHCl₃-MeOH 3:1)] was obtained by decomposition followed by recrystallization of the mother liquors. The (-)- and (+)-trans acids 13' and 13 gave the (-)-trans ester 15' [mp 182-183°C, $[\alpha]_D - 273^\circ$ (c = 0.096, CHCl₃)] and (+)-trans ester 15 [mp 182-183°C, $[\alpha]_D + 258^\circ$ (c = 0.102, CHCl₃)], respectively, by treatment with diazomethane. Lithium aluminum hydride reduction of the (+)-trans ester 15 provided the (+)-amino alcohol 16 [mp 147-148°C, $[\alpha]_D + 4.8^\circ$ (c = 0.146, CHCl₃)]. This radical alteration of the optical rotation relative to (+)-15 and (+)-3 results from a change in conformation of the amino alcohol due to hydrogen bonding.⁶ Reduction of the mesylate of the (+)-trans amino alcohol 16 with lithium aluminum hydride gave (+)-thalictrifoline [3, mp 149-151°C, $[\alpha]_D + 199^\circ$ (c = 0.136, CHCl₃), lit⁷ mp 155°C]. The IR spectra of the synthetic compound and an authentic sample are identical. This is the first total synthesis of (+)-thalictrifoline.

In order to determine the absolute configurations of the (-)-trans and (+)-trans esters 15' and 15 a methanolic solution of the (-)-trans ester 15' containing sodium methoxide was stirred at room temperature. This afforded the (-)-cis ester 17 [mp 229-230°C, $[\alpha]_D - 462^\circ$ (c = 0.08, CHCl₃)] whose absolute configuration must be opposite to that of the (+)-cis ester 18 since the conformations of both of these esters are identical as indicated by their pmr spectra and the optical rotations are opposite and almost of the same magnitude. Since the absolute configuration of 18 has already been established as 13S, 14R,^{3,10} the absolute configuration of (+)-thalictrifoline 3 is 13R, 14R.

(+)-Corydalic acid methyl ester (9) has also been isolated from *Corydalis incisa*.⁸ Since this alkaloid has been converted to (+)-mesotetrahydrocorysamine (4),⁸ its absolute configuration may now be assigned as 3R, 4R. This work should also allow the determination of the absolute configuration of (+)-corycavine (7)² because (±)-corycavine has also been converted to (±)-mesotetrahydrocorysamine.⁹







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References

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10. The absolute configuration of 18 was determined by correlation with (+)-canadine of known absolute configuration.

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