

ABSOLUTE STEREOCHEMISTRY OF THE PENTACYCLIC QUATERNARY INDOLE ALKALOID OPHIORRHIZINE: SYNTHETIC INCORPORATION OF CINCHOLOIPON ETHYL ESTER INTO (-)-OPHIORRHIZINE

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Abstract—The absolute stereochemistry of the *Ophiorrhiza* alkaloid ophiorrhizine has been defined as shown in formula [(−)-1] by a chemical correlation with the *Cinchona* alkaloid cinchonine through cincholoipon ethyl ester [(+)-3] and the lactim ether [(+)-2]. The correlation was achieved by the chiral synthesis of ophiorrhizine [(−)-1] from (+)-2 via the intermediates [(+)-5], [(+)-7], [(+)-6], (8), [(−)-9], [(−)-10], (11), [(−)-12], and [(−)-13].

In 1992, Arbain *et al.*¹ reported the isolation of a new C₁₉ pentacyclic quaternary indole alkaloid, ophiorrhizine, from the fresh aerial parts of *Ophiorrhiza major* Ridl. (Rubiaceae). They established the structure and relative stereochemistry of ophiorrhizine as 1 on the grounds of its spectral properties and X-ray molecular structure.¹ As regards its absolute stereochemistry, they proposed the stereoformula [(−)-1]² on the basis of the negative sign and magnitude of the specific rotation of the alkaloid.¹ The correctness of this proposal has now been confirmed as a result of the following chiral synthesis of the target compound with the candidate structure [(−)-1]. The synthesis features an adaptation of our favorite "cincholoipon-incorporating lactim ether route",³ which has been developed as the best available

$[\alpha]_D^{21} +64.3^\circ$ (*c* 0.307, EtOH)] in 58% yield. This two-step reduction of the carbonyl group to a methylene group through the oxazole derivative followed precedents^{3c-e} in similar systems. Bischler-Napieralski cyclization of the lactam [(+)-6] (POCl_3 , boiling toluene, 1.5 h) and catalytic hydrogenation of the resulting quaternary iminium salt (8) (Pt/H_2 , EtOH, 1 atm, room temp., 1.5 h) produced the tetracyclic ester [(-)-9] $[[\alpha]_D^{28} -22.0^\circ$ (*c* 0.750, EtOH); $\text{ir } \nu_{\text{max}}^{\text{CHCl}_3}$ 2811 and 2756 cm^{-1} (*trans*-quinolizidine ring¹¹)] in 56% overall yield [from (+)-6]. The hydrogen at C(3) was assigned the α configuration by analogy with catalytic hydrogenation of similar heterocyclic ring systems.^{3c-e,12}

On reduction with LiAlH_4 (tetrahydrofuran, room temp., 1.5 h), the tetracyclic ester [(-)-9] provided the alcohol [(-)-10] $[[\alpha]_D^{28} -30.0^\circ$ (*c* 0.813, EtOH)] in 94% yield. Treatment of the alcohol [(-)-10] with *p*-toluenesulfonyl chloride (pyridine, 4°C , 24 h) and heating of the resulting *O*-tosyl derivative (11) (boiling HCONMe_2 , 30 min) gave the quaternary tosylate [(-)-12] [mp $275\text{--}285^\circ\text{C}$ (decomp.); $[\alpha]_D^{32} -67.4^\circ$ (*c* 0.514, MeOH)] in 73% overall yield [from (-)-10]. Anion exchange of the tosylate [(-)-12] using Amberlyst A-26 (Cl^-) [$\text{MeOH-H}_2\text{O}$ (3 : 1, v/v)] afforded the quaternary chloride [(-)-13] [96% yield; mp $285\text{--}300^\circ\text{C}$ (decomp.); $[\alpha]_D^{29} -88.1^\circ$ (*c* 0.199, EtOH)].

Finally, catalytic hydrogenolysis of the chloride salt [(-)-13] (10% $\text{Pd-C}/\text{H}_2$, EtOH, 1 atm, room temp., 6 h) gave the target compound [(-)-1· H_2O] [93% yield; mp $282\text{--}285^\circ\text{C}$ (decomp.); $[\alpha]_D^{30} -102^\circ$ (*c* 0.209, MeOH); cd (*c* 2.56×10^{-4} M, MeOH) $[\theta]^{20}$ (nm): +1100 (302) (pos. max.), -230 (285) (neg. max.), +980 (270) (pos. max.), +570 (264) (neg. max.), +1020 (257) (pos. max.), -760 (245) (neg. max.)]. The uv (in MeOH), ir (KBr), and ^1H nmr (in CD_3OD) spectra and tlc mobility of the synthetic (-)-1· H_2O were virtually identical with those of natural (-)-ophiorrhizine, and the chiral identity of (-)-1· H_2O with the alkaloid [cd (*c* 2.77×10^{-4} M, MeOH) $[\theta]^{19}$ (nm): +1080 (302) (pos. max.), -180 (286) (neg. max.), +940 (270) (pos. max.), +540 (264) (neg. max.), +810 (257) (pos. max.), -1080 (245) (neg. max.)] was shown by the same sign of their specific rotations and by their virtually identical cd spectra.

In conclusion, the absolute configurations of the three asymmetric centers in the *Ophiorrhiza* alkaloid ophiorrhizine have now been defined as shown in formula [(-)-1] as a result of the above chiral synthesis. This synthesis is tantamount to a chemical correlation of ophiorrhizine with the *Cinchona* alkaloid cinchonine, since the lactim ether [(+)-2]⁵ employed as a starting material was prepared from cinchonine through cincholoipon ethyl ester [(+)-3].¹³ It also exemplifies the usefulness of our "cincholoipon-incorporating lactim ether route"³ for chiral syntheses of the *Corynanthe*-type indoloquinolizidine alkaloids.

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