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

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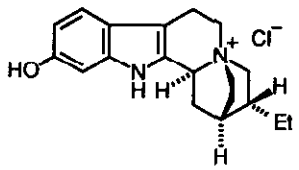
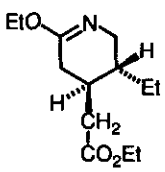
Abstract——The absolute stereochemistry of the *Ophiorrhiza* alkaloid ophiorrhizine has been defined as shown in formula [(–)-**1**] by a chemical correlation with the *Cinchona* alkaloid cinchonine through cincholoipon ethyl ester [(+)-**3**] and the lactim ether [(+)-**2**]. The correlation was achieved 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 C_{19} 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

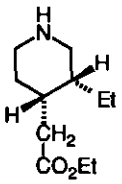
vehicle for unified chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids and *Corynanthe*-type indoloquinolizidine alkaloids.



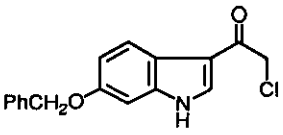
(–)-**1**



(+)-**2**



(+)-**3**



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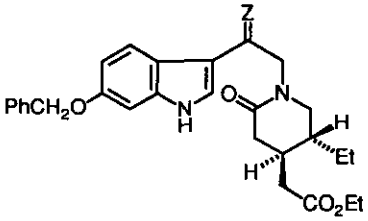
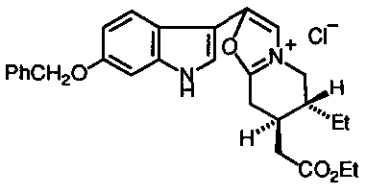
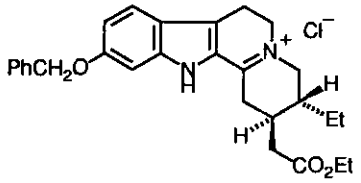


(+)-**5**: Z = O

(+)-**6**: Z = H_2



(+)-**7**



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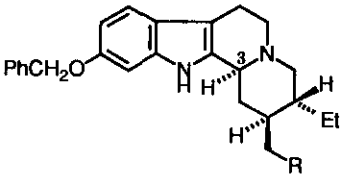
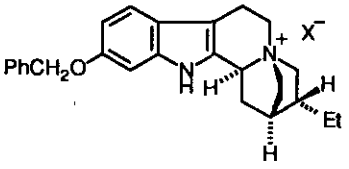


(–)-**9**: R = CO_2Et

(–)-**10**: R = CH_2OH

11: R = CH_2OTs



(–)-**12**: X = OTs

(–)-**13**: X = Cl

At the outset of the present synthesis, we needed two starting materials. One of them was the lactim ether [(+)-**2**],[4,5] readily available from cincholoipon ethyl ester [(+)-**3**] according to our previously reported procedure;[5] and the other, 6-benzyloxy-3-chloroacetylindole (**4**), was prepared from 6-benzyloxyindole[6] and chloroacetyl chloride (pyridine/dioxane, 55–60°C, 30 min)[7,8] according to a general 3-chloroacetylation procedure.[9] Coupling of the lactim ether [(+)-**2**] with the chloroacetylindole (**4**) (KBr/$HCONMe_2$, 60°C, 48 h) gave the lactam ketone [(+)-**5**] [mp 146–147°C; $[\alpha]_D^{19}$ +25.2° (*c* 0.479, EtOH)][10] in 62% yield. Treatment of the lactam ketone [(+)-**5**] with $POCl_3$ (boiling toluene, 1 h) furnished the oxazolium salt [(+)-**7**] [95% yield; mp 239–243°C (decomp.); $[\alpha]_D^{20}$ +54.2° (*c* 0.306, MeOH)], which was then subjected to catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temp., 3 h), giving the lactam [(+)-**6**] [mp 125.5–126°C;

$[\alpha]_D^{21}$ +64.3° (*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° (*c* 0.750, EtOH); ir $\nu_{max}^{CHCl_3}$ 2811 and 2756 cm^{-1} (*trans*-quinolizidine ring[11])] 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° (*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 275–285°C (decomp.); $[\alpha]_D^{32}$ –67.4° (*c* 0.514, MeOH)] in 73% overall yield [from (–)-**10**]. Anion exchange of the tosylate [(–)-**12**] using Amberlyst A-26 (Cl^-) [MeOH–H_2O (3 : 1, v/v)] afforded the quaternary chloride [(–)-**13**] [96% yield; mp 285–300°C (decomp.); $[\alpha]_D^{29}$ –88.1° (*c* 0.199, EtOH)].

Finally, catalytic hydrogenolysis of the chloride salt [(–)-**13**] (10% Pd–C/H_2, EtOH, 1 atm, room temp., 6 h) gave the target compound [(–)-**1**·H_2O] [93% yield; mp 282–285°C (decomp.); $[\alpha]_D^{30}$ –102° (*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.

ACKNOWLEDGMENT

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