Isolation and Asymmetric Total Synthesis of a New *Mitragyna* Indole Alkaloid, (−)-Mitralactonine

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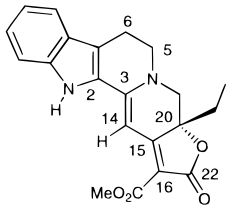
Mitragyna speciosa Korth. (Rubiaceae) is a tropical plant indigenous to Thailand and the Malay Peninsula. The leaves of this plant are known to produce narcotic-like actions when smoked or chewed and have been used traditionally as a stimulant like coca or as a substitute for opium. The unique properties of this medicinal plant have attracted many researchers over the last 50 years.[1] In our recent chemical[2] and pharmacological[3] studies on the *Mitragyna* alkaloids, potent analgesic activity due to the opioid agonistic property of mitragynine, a major indole alkaloid of *M. speciosa* in Thailand, and that of pseudoindoxyl derivatives[2g] has been demonstrated. This prompted us to investigate the constituents in the leaves of *M. speciosa* native to Malaysia.[2e] From the ethyl acetate extract of the young leaves of *M. speciosa* collected in Malaysia, a new alkaloid (**1**) could be isolated together with six known Corynanthe-type indole alkaloids. In this paper, we describe the structure elucidation of the novel monoterpenoid indole alkaloid **1** by means of spectroscopic analysis as well as racemic and asymmetric total syntheses.



(-)-mitralactonine (**1**)

The new compound **1**,[4] obtained as an orange amorphous powder, exhibited $[\alpha]^{18}_{D}$ −16.5 (*c* 0.17, $CHCl_3$). The ^1H and ^{13}C NMR spectra of **1** showed the presence of the fundamental structural units in the common Corynanthe-type monoterpenoid indole alkaloids, i.e., an indole nucleus, an ethane-bridge at C5−C6, an ethyl group at C-20, and a methoxycarbonyl group. The UV spectrum exhibited a long-wavelength absorption at 460 nm, indicating a high degree of unsaturation in the molecule. The ^{13}C NMR and HMBC spectra disclosed the presence of six conjugated sp^2 carbons including an ester and a lactone carbonyl carbon, besides the aromatic carbons due to the indole nucleus. The quite characteristic proton signal observed at δ 6.51 (1H, singlet) was unambiguously assigned to be the proton at C14 by the HMQC spectrum, and this signal has the HMBC connectivities between the C2, C3, C15, C16, and C20 carbons. The molecular formula ($C_{21}H_{20}N_2O_4$) obtained from a high-resolution mass spectrum as well as the fact that the carbon signal at C20 resonated at δ 77.4 ppm showed the presence of a lactone function constructed between the oxygen atom on C20 and the carbonyl group at the C22 position. All of the above findings as well as biogenetic consideration enabled us to compose the molecular structure of the new alkaloid, now named mitralactonine, to be the formula **1** having a highly conjugated pentacyclic Corynanthe skeleton. This is the first example of Corynanthe-type indole alkaloids carrying an oxygen function at the C20 position.

To establish the novel structure of mitralactonine, including the absolute configuration due to one chiral center at C20, we next planned the asymmetric total synthesis of **1**. Our synthesis started with the preparation of the chiral epoxy ketone **5**, which is an essential synthon for the construction of the functionalized tetracyclic compound **7** (Scheme 1). Attempts at the direct preparation of the highly optically active epoxide **5** from the known α,β-unsaturated ketone **2**[5] utilizing the known asymmetric oxidation procedures were unsuccessful. Thus, we synthesized the optically pure **5** in a stepwise manner as follows. By the reduction of the enone **2** using a chiral oxazaborolidine catalyst (0.7 equiv of BH_3, 0.2 equiv of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, −20 °C),[6] an optically active alcohol (+)-**3** [$[\alpha]^{23}_{D}$ +9.5 (*c* 0.35, $CHCl_3$)] was obtained in 93% ee. The enantiomeric excess of **3** was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivatives, and the absolute configuration was deduced to be *R* by the proposed reaction mechanism.[6b] Next, the allylic alcohol **3** (93% ee) was subjected to the Sharpless asymmetric epoxidation under the kinetic resolution conditions[7] (1.0 equiv of Ti(O-*i*-Pr)$_4$, 1.2 equiv of diisopropyl D-tartrate, *t*-BuOOH, −40 °C, 40.5 h) to give the (−)-epoxide **4** [$[\alpha]^{23}_{D}$ −12.4 (*c* 0.56, $CHCl_3$)]

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(4) Dark orange amorphous powder R_f value: 0.3 (SiO_2, solvent system: *n*-hexane/AcOEt = 1:2). $[\alpha]^{26}_{D}$: −16.5 (*c* 0.17, $CHCl_3$). UV λ_{max}^{MeOH} (log ϵ): 460 (4.49), 434 (sh, 4.37), 344 (3.78), 262 (sh, 3.79), 223 (4.24) nm. EI-MS *m/z*: 364 (M^+, 48), 335 (44), 320 (53), 289 (21), 262 (39), 261 (49), 220 (22), 219 (36), 97 (100). HR-FABMS: calcd for $C_{21}H_{21}O_4N_2$ (MH^+) 365.1501, found 365.1474. ^1H NMR (500 MHz, DMSO-d_6) δ: 11.91 (1H, s, Na-H), 7.61 (1H, d, *J* = 7.9 Hz, H-9), 7.43 (1H, d, *J* = 7.9 Hz, H-12), 7.28 (1H, dd, *J* = 7.9, 7.9 Hz, H-11), 7.09 (1H, dd, *J* = 7.9, 7.9 Hz, H-10), 6.51 (1H, s, H-14), 3.79 (1H, d, *J* = 12.8 Hz, H-21), 3.73 (3H, s, 22-OCH_3), 3.66 (1H, d, *J* = 12.8 Hz, H-21), 3.60−3.70 (2H, m, H-5), 3.08 (2H, m, H-6), 1.81 and 1.70 (2H, each m, H-19), 0.83 (3H, dd, *J* = 7.3, 7.3 Hz, H-18). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.87 (C-15), 168.56 (C-17), 163.08 (C-22), 149.27 (C-3), 138.67 (C-13), 126.89 (C-2), 125.19 (C-11), 124.90 (C-8), 120.00 and 119.95 (C-9 and C-10), 116.80 (C-7), 112.19 (C-12), 95.38 (C-16), 87.31 (C-14), 77.41 (C-20), 54.87 (C-21), 50.54 (22-OCH_3), 50.37 (C-5), 29.59 (C-19), 19.88 (C-6), 7.13 (C-18). It is interesting to note that the sp^2 carbons at C14 and C16 resonate at unusually higher field.

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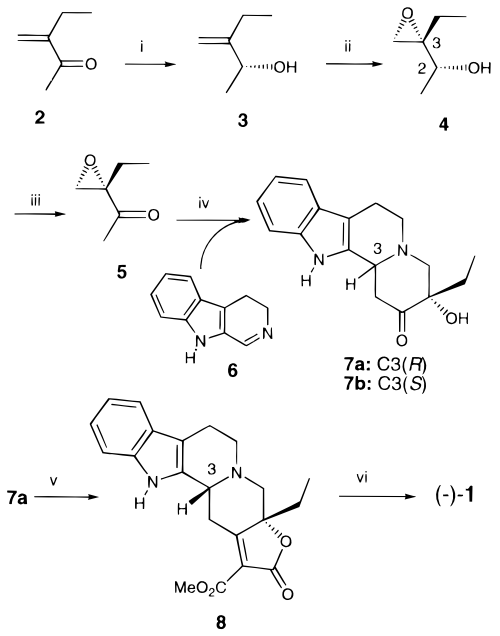
Scheme 1[a]



[a] Reagents and conditions: (i) 0.2 equiv of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, BH_3−THF complex, dry THF, −20 °C (65% after distillation); (ii) diisopropyl D-tartrate, Ti(*i*-PrO)$_4$, *t*-BuOOH, CH_2Cl_2, −40 °C (56% after distillation); (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (41% after distillation); (iv) MeOH, reflux (**7a** 36%. **7b** 9%); (v) dimethyl malonate, $AcONH_4$, AcOH, dry toluene, reflux (55%); (vi) (a) *t*-BuOCl, Et_3N, CH_2Cl_2, 0 °C, (b) 5 N ethanolic HCl, 0 °C, then alkaline workup (83%).

with >99% ee. The enantiomeric excess of **4** was determined by chiral HPLC analysis of the *p*-bromobenzoate derivatives, and the absolute configuration of the quaternary center was assigned as *S* by using the well-established enantioselectivity principle.[7b] The secondary carbinol in **4** was then converted to a ketone by Swern oxidation to give the (−)-epoxy ketone **5** [bp 44−81 °C (82−96 mmHg); $[\alpha]^{24}_D$ −57.7 (*c* 0.54, $CHCl_3$)].

The thus-obtained epoxide (−)-**5** and 3,4-dihydro-*β*-carboline (**6**)[8] were condensed[9] in heated MeOH to afford two diastereomeric tetracyclic compounds (**7a** and **7b**) in 36% and 9% yields, respectively. The C3 configurations of the major and minor products was deduced by comparison of their CD spectra.[10] The major isomer **7a** was subjected to Knoevenagel condensation with dimethyl malonate in refluxing toluene in the presence of $AcONH_4$ and AcOH to give directly the pentacyclic product **8** having a lactone residue in 55% yield. Finally, the double bond was introduced to the C3−14 position in **8** by a two-step operation ((i) *t*-BuOCl, Et_3N, (ii) ethanolic HCl then $NaHCO_3$). The synthetic compound was identified with the natural product by comparison of their chromatographic behavior, UV, ^1H and ^{13}C NMR, and mass spectra. The observed optical rotation of the synthetic compound was levorotatory as in the natural product; however, the specific rotation was very different [$[\alpha]^{24}_D$ −892 (*c* 0.63, $CHCl_3$)] from that of natural **1**. Then, we synthesized racemic mitralactonine starting from the achiral epoxy ketone **5** and analyzed the enantiomeric purity of both the synthetic (±)-**1** and (−)-**1** and of the natural product using chiral column chromatography. As a result, it was found that the natural mitralactonine contained the (−)-enantiomer slightly dominant over the (+)-enantiomer in a ratio of 54:46 (Figure 1).

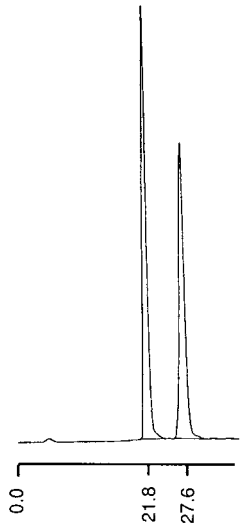


Figure 1. Chiral HPLC analysis of natural mitralactonine (conditions: Chiralcel OD; 20% EtOH/*n*-hexane; flow rate, 0.5 mL/min; column temperature, 30 °C).

In conclusion, a novel Corynanthe-type indole alkaloid, mitralactonine (**1**), having a highly conjugated pentacyclic skeleton was isolated from the Malaysian medicinal plant, *Mitragyna speciosa*, and the structure, including the absolute configuration, was elucidated by spectroscopic analysis and chiral total synthesis. It is interesting to note that natural mitralactonine comprises of a mixture slightly enriched with (−)-enantiomer. Further chemical investigation on the components in Malaysian *M. speciosa* and the pharmacological evaluation of these compounds are in progress in our laboratories.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds.

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