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The First Total Synthesis of (-)-Mitragynine, An Analgesic Indole Alkaloid in *Mitragyna speciosa*

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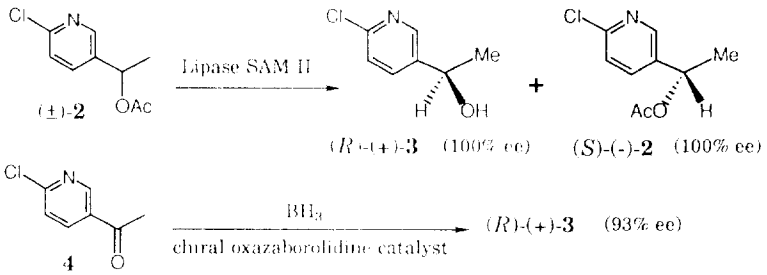
Abstract: Starting from an optically pure alcohol, (*R*)-(**3**), which was prepared by enzymatic hydrolysis of the racemic acetate (**2**) or enantioselective reduction of the ketone derivative (**4**), the chiral total synthesis of mitragynine (**1**), a major corynanthe-type indole alkaloid having an analgesic effect in *Mitragyna speciosa*, was accomplished.

The leaves of *Mitragyna speciosa* Korth. have been known as an opium substitute in traditional use by Thai and Malay natives. A number of pharmacological studies of this plant have been carried out, but the principle as well as the mechanism of the biological activities of this folk medicine have not been completely elucidated up to now.[1] In the course of our study of *Mitragyna speciosa*,[2] a major alkaloid, mitragynine (**1**), was found to exhibit a relative strong analgesia with different action mechanism from morphine.[1b] We embarked on the asymmetric total synthesis of this indole alkaloid having a 9-methoxylated corynanthe skeleton.

A vein of Ziegler-Winterfeldt-Lounasmaa's strategy[3] for the preparation of corynanthe-type alkaloids was applied to the synthesis of mitragynine. From the retrosynthetic analysis, two synthons, *i.e.*, the 4-methoxyindole derivative (**5**) and chiral pyridine derivative (**3**), were required. Furthermore, to construct the mitragynine having the natural absolute configuration, the alcohol (**3**) having the *R* configuration was required based on the mechanistic consideration of the Claisen rearrangement[3d, 4] of the allylic alcohol derivatives (**7** and **8**, *vide infra*).

We initiated the total synthesis from the preparation of the optically pure alcohol (*R*)-(**3**). The racemic acetate (**2**), which was prepared from the commercially available 6-chloronicotinic acid, was subjected to the enzymatic hydrolysis using Lipase SAM II[5] under phosphate buffer (pH 7.0) conditions to produce the secondary alcohol (+)-(**3**) {32% chemical yield, $[\alpha]_D^{25}$ +47.0 (*c* 1.44, $CHCl_3$), 100% ee} and the acetate (-)-(**2**) {38% chemical yield, $[\alpha]_D^{25}$ -103.4 (*c* 1.19, $CHCl_3$) 100% ee}.[6] From the reduction of the ketone derivative (**4**) using a chiral oxazaborolidine catalyst[7] (0.7 equiv of BH_3, 0.2 equiv of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine, THF, 30 °C), an optically active alcohol (+)-(**3**) {$[\alpha]_D^{25}$ +43.4 (*c* 1.58, $CHCl_3$), 93% ee} was obtained in 80% yield, which was then esterified with (*R*)-*O*-methylmandelic acid in order to prepare the optically pure alcohol (**3**). The resulting diasteromeric mixture was separated by column chromatography and then the diasteromeres were respectively hydrolyzed to give the

enantiomerically pure alcohols (+)-**3** and (-)-**3**. The absolute configuration of the alcohol (**3**) having a positive optical rotation was determined to be *R* by chemical correlation with the known (*R*)-(+)-3-pyridyl-1-ethanol.[8] The optically pure alcohol (-)-**3**, which was obtained by the hydrolysis of (-)-**2** and the chiral reduction route, could be converted to its enantiomer (+)-**3** using the sequential Mitsunobu reaction/alkaline hydrolysis.

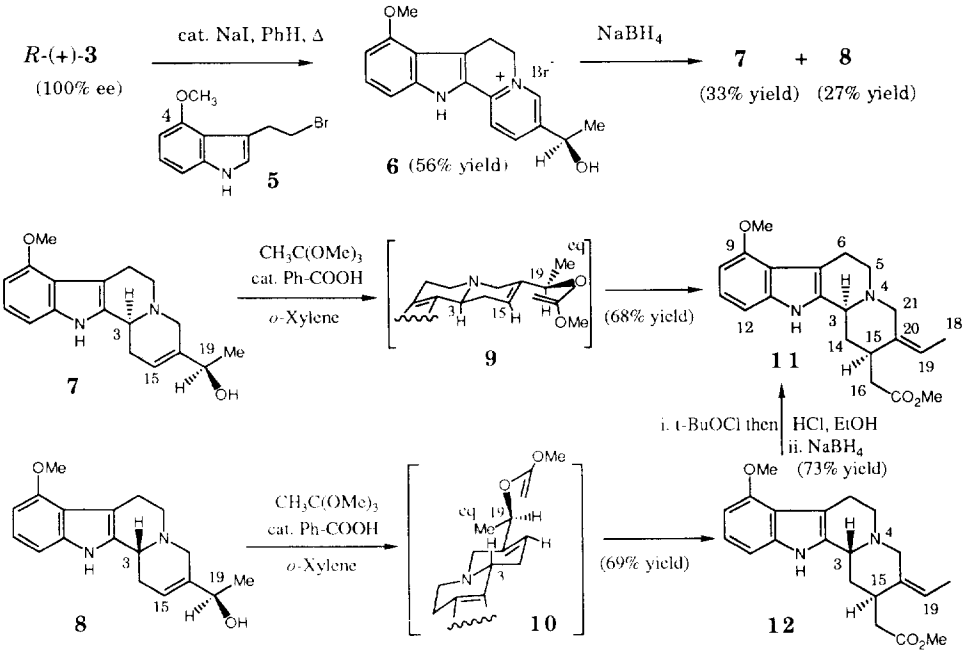


Scheme 1

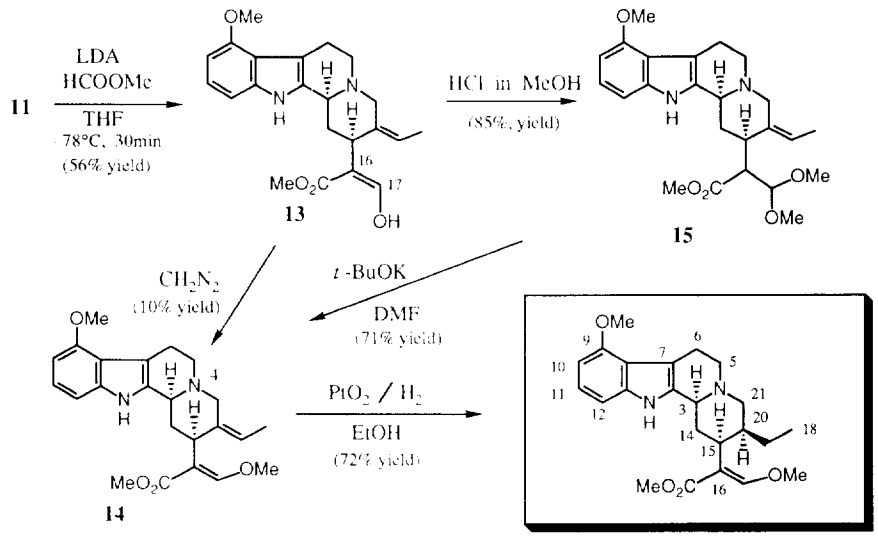
The other counterpart, 4-methoxytryptophylbromide (**5**), was prepared starting from 4-hydroxyindole via a five-step operation (i. *O*-methylation, ii. reaction with oxalyl chloride, iii. ethanolysis, iv. reduction with $LiAlH_4$, and v. bromination with PBr_3). The thus obtained bromide (**5**) and the optically pure pyridine derivative (*R*)-(**3**) was condensed in heated benzene in the presence of a catalytic amount of sodium iodide. The pyridinium salt (**6**) was then reduced with sodium borohydride to yield two diastereomers (**7** and **8**)[9] in 33% and 27% yield, respectively. The stereochemistry at C3[10] could be assumed by comparison of the chromatographic behaviors with those of analogous compounds in the literature[3c] and became clear from the CD and ^{13}C-NMR spectral data of the products (**11** and **12**) obtained by the next reaction. Although two isomers (**7** and **8**) have been formed in the reduction step, we anticipated that the new chiral center at C15, which would be generated in the next Claisen rearrangement via the chair-like transition states (**9** and **10**), could be controlled by the absolute stereochemistry at C19 and, furthermore, the configuration at C3 could be settled in the desired form during the subsequent reactions. Then, in order to install an acetic acid residue onto the C15 position, each allylic alcohol (**7** and **8**) was subjected to a Claisen rearrangement. By heating with trimethyl orthoacetate in the presence of a catalytic amount of benzoic acid in *o*-xylene, **7** and **8** produced the acetates (**11**) and (**12**),[11] respectively, as the sole product. The absolute configurations at C3 in **11** and **12** were clearly determined by the CD spectra.[12] Furthermore, the stereochemistry at C15 and C19 could be elucidated by the ^{1}H- and ^{13}C-NMR analyses.[11] Compound (**11**) has the appropriate absolute configuration at the C3 and C15 positions for further transformation to mitragynine, while the other isomer (**12**) has the opposite configuration at C3, which could be inverted to **11** by an oxidation-reduction sequence via a 3,4-dehydroimmonium salt. In this manner, we could convergently prepare the optically pure corynanthe-type compound (**11**).

Next, according to the conventional method (LDA, HCO_2Me), a formyl group was introduced onto C16 in **11**. Since the attempted *O*-methylation of the resulting enol system using a common reagent, CH_2N_2, afforded the N_4-methylated compound as a major product, the formyl group in **13** was first converted to the dimethyl acetal (**15**), which was then treated with KO^{t}Bu to give the desired methyl enol ether (**14**) in good yield. Finally, by stereoselective reduction of the double bond in **14** over PtO_2 under a H_2 atmosphere, the target compound, mitragynine (**1**) {$[\alpha]_D^{24}$ -125.2 (*c* 0.25, $CHCl_3$), natural product; $[\alpha]_D^{24}$ -125.8 (*c* 0.30, $CHCl_3$)} having the natural absolute configuration was obtained.

In conclusion, we succeeded in the first total synthesis of (-)-mitragynine in the optically pure form using an enantiomerically and stereochemically convergent route.



Scheme 2



Scheme 3

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5. Lipase SAM II from *Pseudomonas sp.* was obtained from AMANO Pharmaceutical Co.
6. Enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OB, *n*-hexane/ethanol = 95:5, flow rate 0.5 ml/min., retention time; (+)-(**3**): 26.6 min., (-)-(**3**): 20.9 min, (+)-(**2**): 28.1 min., (-)-(**2**): 25.6 min.
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9. Compound (**7**); mp. 208-212 °C (dec.), $[\alpha]_D^{26}$ -194.1 (*c* 0.48, MeOH). Compound (**8**); mp. 220-222 °C (dec.), $[\alpha]_D^{26}$ +211.5 (*c* 0.34, MeOH).
10. The numbering in compounds **7**-**15** conforms to the style for the common monoterpenoid indole alkaloids.
11. Compound (**11**); $[\alpha]_D^{18}$ -4.0 (*c* 1.42, $CHCl_3$), CD (c 0.34 mmol/l, MeOH), nm ($\Delta\varepsilon\lambda$) 301 (0), 291 (+3.22), 288 (+2.91), 268 (+5.10), 246 (+2.28), 233 (0), 222 (-25.96), 207 (0). ^{1}H-NMR (500 MHz, $CDCl_3$) δ; 5.24 (1H, q, *J*= 6.6 Hz, H-19), 3.74 (3H, s, CO_2Me), 3.60 (1H, br d, *J*=12.7 Hz, H-3), 1.71 (3H, d, *J*=6.6 Hz, H-18). ^{13}C-NMR (125 MHz, $CDCl_3$) δ; 132.3 (C2), 59.5 (C3), 52.9 (C5), 23.6 (C6), 108.0 (C7), 117.4 (C8), 154.5 (C9), 99.7 (C10), 122.0 (C11), 104.2 (C12), 137.4 (C13), 36.8 (C14)*, 38.0 (C15), 36.7 (C16)*, 13.1 (C18), 116.3 (C19), 136.0 (C20), 55.4 (C21), 173.5 (CO), 51.7 (O_2Me), 55.3 (9-OMe). Compound (**12**); $[\alpha]_D^{20}$ +32.8 (*c* 2.04, $CHCl_3$), CD (c 0.39 mmol/l, MeOH), nm ($\Delta\varepsilon\lambda$) 300 (0), 291 (-2.76), 287 (-2.03), 268 (-4.03), 245 (-1.88), 233 (0), 221 (+25.32), 207 (0). ^{1}H-NMR (500 MHz, $CDCl_3$) δ; 5.39 (1H, q, *J*= 6.8 Hz, H-19), 3.69 (3H, s, CO_2Me), 3.60 (1H, br d, *J*=12.9 Hz, H-3), 1.65 (3H, d, *J*=6.8 Hz, H-18). ^{13}C-NMR (125 MHz, $CDCl_3$) δ; 132.3 (C2), 54.7 (C3), 53.1 (C5), 23.1 (C6), 108.3 (C7), 117.5 (C8), 154.4 (C9), 99.8 (C10), 122.0 (C11), 104.3 (C12), 137.4 (C13), 34.7 (C14), 38.4 (C15), 37.9 (C16), 13.0 (C18), 120.3 (C19), 135.3 (C20), 50.9 (C21), 173.0 (CO), 51.6 (O_2Me), 55.3 (9-OMe).
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