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New Procedure to Mask the 2,3-π Bond of the Indole Nucleus and Its Application to the Preparation of Potent Opioid Receptor Agonists with a Corynanthe Skeleton

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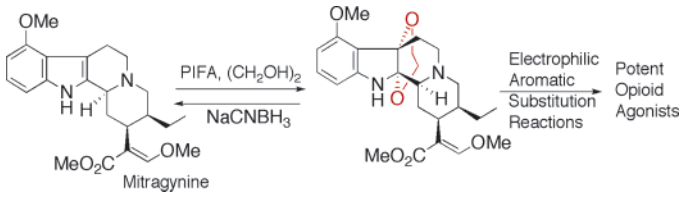
ABSTRACT



Treatment of indole alkaloids with hypervalent iodine in the presence of ethylene glycol provides 2,3-ethylene glycol bridged adducts that could be converted into the original indoles under mild reductive conditions. This procedure, which involves masking of the reactivity of the indole nucleus at the β-position, was utilized for the modification of the benzene ring of the indoline derivative and was applied to the preparation of potent opioid receptor agonists with the Corynanthe skeleton.

7-Hydroxy-7*H*-mitragynine (7-hydroxymitragynine, **1**)[1] is a minor constituent of a rubiaceous plant, *Mitragyna speciosa*,[2] that has long been used in Thailand for its opium-like effect. We have previously demonstrated in guinea pig ileum experiments that **1** inhibits electrically induced contraction through the opioid receptors, and its effect is approximately 13-fold more potent than that of morphine.[3] Further, **1** exhibits a potent antinociceptive effect in mouse tail-flick and hot-plate tests when administered subcutaneously or orally.[4] The antinociceptive effect of **1** is more potent than that of morphine in both tests and is induced mainly by

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(4) 7-Hydroxymitragynine (**1**) has an advantage over morphine when administered orally because morphine is not so effective when administered orally. Matsumoto, K.; Horie, S.; Ishikawa, H.; Takayama, H.; Aimi, N.; Ponglux, D.; Watanabe, K. *Life Sci.* **2004**, *74*, 2143−2155.

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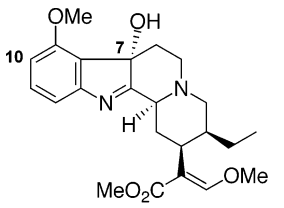
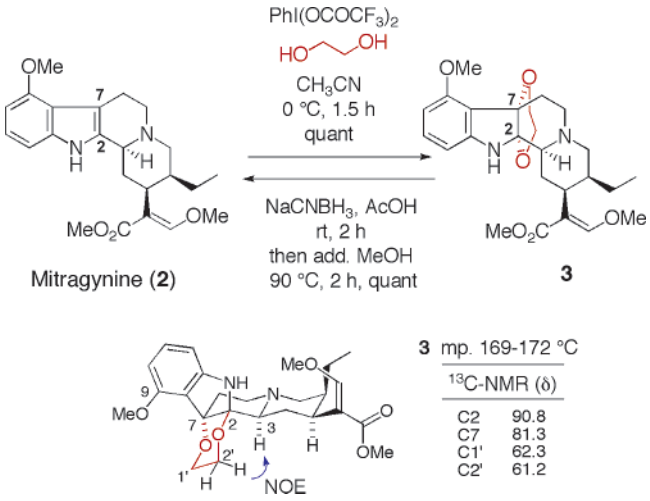
activating μ-opioid receptors. Development of tolerance to its antinociceptive effect and cross-tolerance to morphine antinociception were observed, indicating that **1** acts on μ-opioid receptors.[5] Furthermore, **1** induces constipation less potently than morphine at antinociceptive doses.[6] These interesting properties of **1**, which has a chemical structure different from that of morphine, have enabled us to pursue further investigations for the development of novel analgesics. To develop a more potent opioid receptor agonist based on **1**, we have initially planned the synthesis of compounds by modifying the benzene ring in **1** and the evaluation of their potency to opioid receptors. In the present study, we found a new method to protect the 2,3-π bond of indole alkaloids, which was applied to the preparation of derivatives having various substituents at the C-10 position in **1**. Among the synthetic derivatives, compound **11** showed the highest potency: 4-fold and 18-fold higher than that of **1** and morphine, respectively. In this communication, we report these chemical findings as well as the preliminary pharmacological results on the opioid agonistic effect of Corynanthe-type indole alkaloids.



7-Hydroxymitragynine (**1**)

Attempts at the direct introduction of electrophilic substituents on the benzene ring in **1** or in its parent compound, mitragynine (**2**),[7] were unsuccessful as expected. Then, we devised a method to protect the 2,3-π bond of indoles,[8] producing the aniline structure that should act as a reactive aromatic compound toward various electrophiles. When **2** was treated with 1 equiv of phenyliodine bis(trifluoroacetate) (PIFA)[9] in the presence of ethylene glycol (EG) in MeCN at 0 °C, a 2,3-ethylene glycol bridged indoline derivative (**3**) was obtained in quantitative yield. The structure of the adduct including the stereochemistry was determined from spectroscopic data, as shown in Scheme 1. Indoline **3** could be converted into starting indole **2** in almost quantitative yield upon reduction with $NaCNBH_3$ in AcOH at room temperature, followed by heating at 90 °C after addition of MeOH. Indoline **3** was put to practical use for the preparation of several benzene-substituted derivatives for the study of opioid receptor ligands, as described below.

Scheme 1



Using other indole alkaloids, we examined the generality of the newly developed method to mask the pyrrole moiety in the indole nucleus. Among the tested compounds, 2,3-dimethylindole, tetrahydrocarbazole, indoloquinolizidine, corynantheol, dihydrocorynantheol, and yohimbine, the corresponding EG adducts (**4**−**9**), were obtained in moderate yields. However, the best results (the yields are shown in Figure 1) were obtained when NH_4Cl was added to the reaction mixture (see Supporting Information).[10] In the case of reserpine, it was found that phenyliodine diacetate (PIDA) was a more suitable reagent than PIFA for the formation of the EG-bridged adduct (**10**), which was also useful as a starting material for the preparation of various kinds of A-ring-modified reserpine analogues.[11]

Using EG adduct **3** derived from mitragynine (**2**), various kinds of substituents were introduced onto the benzene ring, as shown in Scheme 2. Treatment of **3** with *N*-fluoro-2,6-dichloropyridinium triflate (FP-T800)[12] gave compound **11** fluorinated at the C-10 position in 53% yield. Exposure of **3** to NCS in AcOH afforded two chlorinated derivatives **12a** (10-Chloro) and **12b** (12-Chloro) in 88% and 11% yields, respectively. Using NBS in DMF, 10-bromo and 12-bromo derivatives (**13a** and **13b**) were obtained in 75% and 24% yields, respectively. To introduce the nitro group, a combination of CAN and concentrated H_2SO_4 in DCM[13] was used to give **14a** in 52% yield together with its 12-isomer (**14b**)

(5) Matsumoto, K.; Horie, S.; Takayama, H.; Ishikawa, H.; Aimi, N.; Ponglux, D.; Murayama, T.; Watanabe, K. *Life Sci.* **2005**, *78*, 2−7.

(6) Matsumoto, K.; Hatori, Y.; Murayama, T.; Tashima, K.; Wongseripipatana, S.; Misawa, K.; Kitajima, M.; Takayama, H.; Horie, S. *Eur. J. Pharmacol.* Available online 16 August 2006.

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(8) A method for protection−deprotection of the indole 2,3-bond using MTDA was reported. (a) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999−2001. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628−5629.

(9) (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893−2903. (c) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007−2010 and references cited therein.

(10) We found that treatment of 7-chloroindolenine derivatives, which were prepared by oxidation of indoles with *t*BuOCl, with ethylene glycol in the presence of TFA also afforded EG adducts, although the yields were inferior to those of the PIFA−EG-NH_4Cl method. The reaction mechanism for the formation of EG adducts with hypervalent iodines is still unclear.

(11) The preparation of various A-ring-modified reserpines will be published in due course.

(12) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563−8575.

(13) Mellor, J. M.; Mittoo, S.; Parkes, R.; Miller, R. W. *Tetrahedron* **2000**, *56*, 8019−8024.

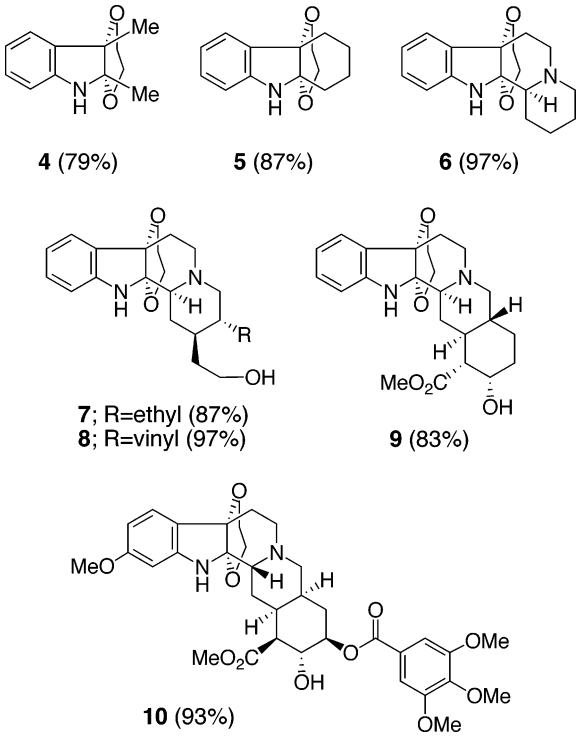
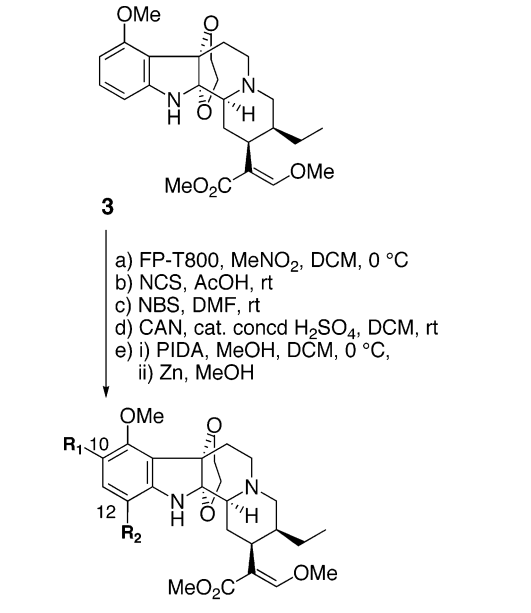


Figure 1. Ethylene glycol adducts of various indoles.

in 21% yield. 10-Methoxy derivative **15** was prepared in 64% yield by treatment of **3** with IBDA in MeOH, followed by the reduction of the resulting iminoquinone intermediate (see Supporting Information) with Zn in MeOH.[14]

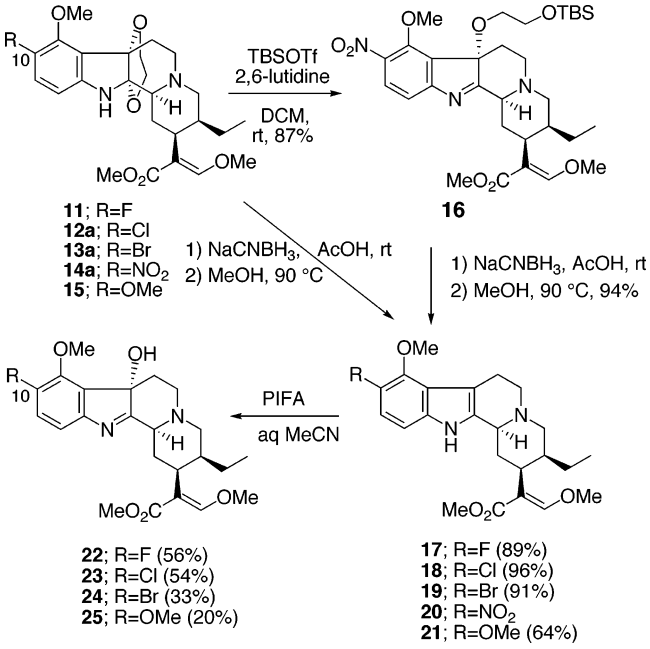
Scheme 2



a) **11**; R_1=F, R_2=H (53%)
b) **12a**; R_1=Cl, R_2=H (88%), **12b**; R_1=H, R_2=Cl (11%)
c) **13a**; R_1=Br, R_2=H (75%), **13b**; R_1=H, R_2=Br (24%)
d) **14a**; R_1=NO_2, R_2=H (52%), **14b**; R_1=H, R_2=NO_2 (21%)
e) **15**; R_1=OMe, R_2=H (64%, 2 steps)

The C10-substituted derivatives thus obtained as a major product of each electrophilic aromatic substitution reaction were converted into their indole derivatives in good yields by reduction with $NaCNBH_3$ in AcOH as described above (conversion from **3** into **2**). However, in the case of nitro derivative **14a**, a two-step procedure was needed; i.e., **14a** was treated with TBSOTf in the presence of 2,6-lutidine, and the resultant indolenine derivative **16** obtained in 87% yield was reduced with $NaCNBH_3$ to give the indole derivative **20** in 94% yield (Scheme 3). The thus obtained

Scheme 3



indole derivatives were, respectively, converted into 7-hydroxyindolenine derivatives (**22**−**25**) by oxidation with PIFA in aqueous MeCN.[15]

The series of C10-substituted mitragynine derivatives obtained by the above reactions was subjected to pharmacological evaluation. The opioid agonistic effect was evaluated in an experiment involving twitch contraction induced by electrical stimulation of guinea pig ileum. This experiment is generally used to study opioid analgesics. The results are shown in Table 1.

Among the EG-bridged derivatives (**3**, **11**, **12a**, **13a**, **14a**, and **15**) and the 7-hydroxyindolenine derivatives (**22**−**25**), C10-fluorinated derivatives (**11**, **22**) showed the highest potency. Derivatives having a chloro or bromo group at C10 showed lower potency than the corresponding fluorinated derivatives. These results suggest that the dimension or electronegativity of the functional group at the C10 position is important to elicit the opioid agonistic effect. None of the indole derivatives (**17**−**21**) showed any opioid agonistic

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Table 1. Opioid Effects of Mitragynine Derivatives on Twitch Contraction Induced by Electrical Stimulation in Guinea Pig Ileum[a]

compound	pD_2 value (−log M)	relative potency (%)	maximum inhibition (%)	inhibitory activity (%)
morphine	7.15 ± 0.05	100	87.2 ± 1.8	100
Ethylene Glycol Bridged Derivatives				
3	7.70 ± 0.10**	354	35.0 ± 11.0	40
11	8.40 ± 0.02**	1778	83.4 ± 3.2	96
12a	7.61 ± 0.17**	288	48.1 ± 9.3	55
14a	7.88 ± 0.18**	537	65.0 ± 4.3	75
Mitragynine Derivatives				
2	6.50 ± 0.06**	22	72.0 ± 5.0	83
7-Hydroxyindolenine Derivatives				
1	7.78 ± 0.10**	426	90.8 ± 3.4	104
22	7.87 ± 0.04**	524	82.5 ± 1.8	95
23	7.53 ± 0.08**	239	74.8 ± 3.0	86
24	7.45 ± 0.04**	199	61.7 ± 6.2	71

[a] Potency is expressed as a pD_2 value, which is the negative logarithm of the concentration required to produce 50% of the maximum response to each compound (EC_{50}). Relative potency is expressed as a percentage of the pD_2 value of each compound against that of morphine. Maximum inhibition (%), which is elicited by the compound when the response reaches a plateau, was calculated by regarding the twitch contraction as 100%. Relative inhibitory activity, which means intrinsic activity on opioid receptors, is expressed as a percentage of the maximum inhibition by each compound against that by morphine. Each value represents a mean ± the SEM of five or six animals. The asterisk (*) donates values that were significantly different from the morphine group by Student's t-test (**, $P < 0.01$). Compounds **13a**, **15**, **17**−**21**, and **25** did not show significant inhibition at 1 μM.

effect. Compound **22** showed potent agonistic effect, but its potency was nearly equal to that of 7-hydroxymitragynine (**1**). On the other hand, compound **11** showed the most potent opioid agonistic effect among the derivatives tested in the present study. Its potency was 18- and 4-fold higher than that of morphine and 7-hydroxymitragynine (**1**), respectively.

Next, we investigated the involvement of opioid receptor subtypes in the pharmacological effects of **11**. The μ-opioid receptor antagonist cyprodime (1 μM) and the κ-opioid receptor antagonist nor-binaltorphimine (30 nM) significantly reversed the inhibitory effect of **11** at 30 nM (data not shown), suggesting that **11** activates not only μ-opioid receptors but also κ-opioid receptors. Detailed results of the pharmacological and analgesic effects of **11** will be reported in due course.

In conclusion, we found a new method to mask the 2,3-π bond of indole alkaloids and to convert the protected compounds, i.e., 2,3-ethylene glycol adducts, back to the starting indoles. This procedure was utilized for the modification of the benzene ring of the indoline derivative and was applied to the preparation of potent opioid receptor agonists with the Corynanthe skeleton, one of which exhibited 18 times more potent opioid agonistic effect than morphine in in vitro experiments.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectral data for compounds **3**−**6**, **11**, **17**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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