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PREPARATION OF ETHYLENE GLYCOL ADDUCTS AT 2,3-POSITIONS OF INDOLES WITH HYPERVALENT IODINE†

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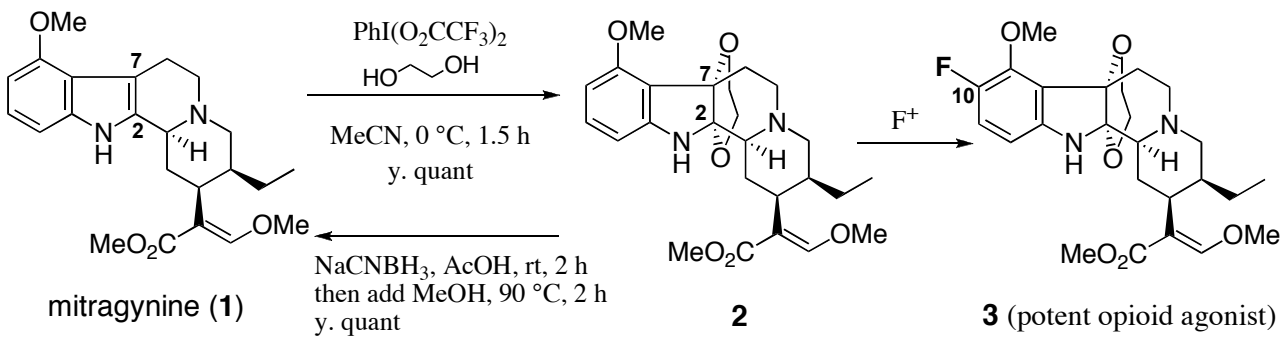
Abstract – An efficient method for protection–deprotection of the 2,3-bond of indoles was developed. Treatment of various indole derivatives with hypervalent iodine–ethylene glycol in the presence of ammonium chloride provided 2,3-ethylene glycol bridged adducts in excellent yields. The adducts, which possessed a masked form of pyrrole moiety in the indole nucleus, could be converted back to the mother indoles under mild reductive conditions.

†Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

INTRODUCTION

In the course of our studies of potent opioid ligands having the Corynanthe skeleton,[1] we recently found a new reaction to mask the 2,3-π bond of an indole alkaloid,[2] mitragynine (**1**),[3] a major constituent of *Mitragyna speciosa*,[4] a rubiaceous plant that has long been used in Thailand and Malaysia for its opium-like effect. Further, utilizing ethylene glycol (EG) adduct **2** that acted as a reactive aromatic compound toward various electrophiles on the benzene ring, we succeeded in the preparation of highly potent opioid agonist (**3**) having a fluorine function at C-10 (Scheme 1). Its potency was approximately

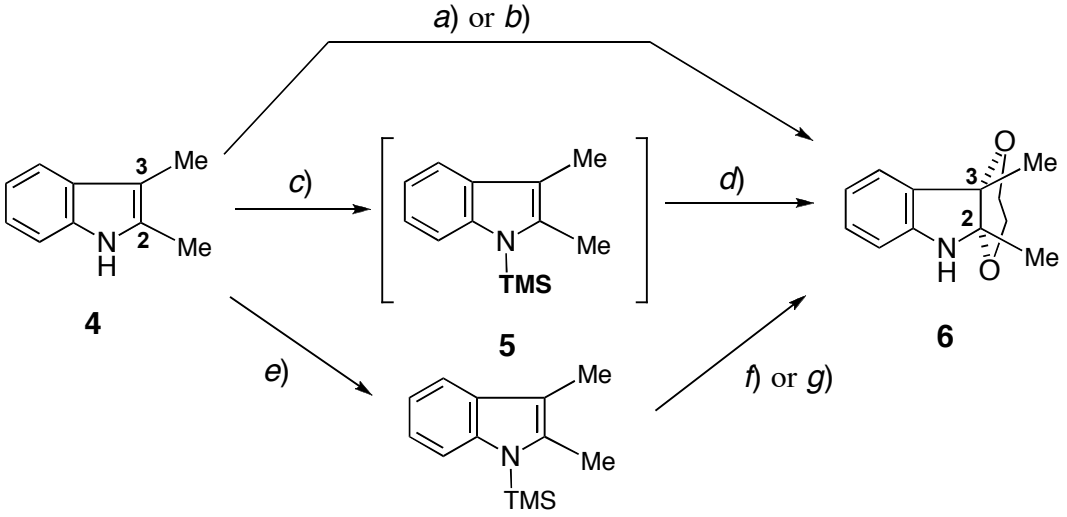


Scheme 1

18-fold higher than that of morphine.[2] Here we describe the results of further examination of the generality of the newly developed method, using various indole derivatives to construct the EG adduct.

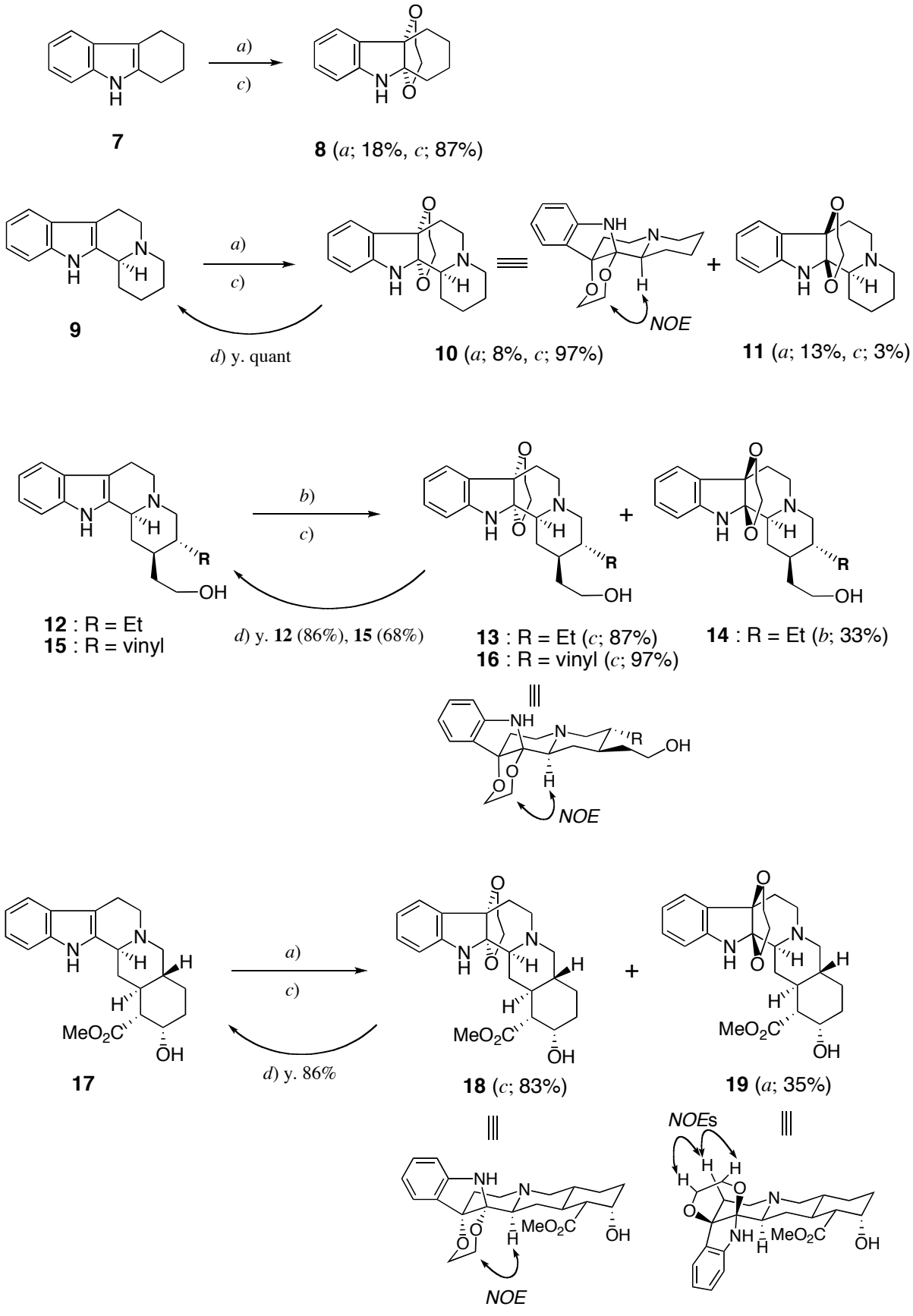
RESULTS AND DISCUSSION

To inspect the scope and limitations of the reaction of indoles with a combination of hypervalent iodine, such as phenyliodine bis(trifluoroacetate) (PIFA), and EG, which gives a 2,3-EG bridged adduct, we initially applied this reaction to 2,3-dimethylindole (**4**), tetrahydrocarbazole (**7**), indoloquinolizidine (**9**), dihydrocorynantheol (**12**), and yohimbine (**17**). Using the reaction conditions employed for mitragynine (**1**), the corresponding EG adducts were obtained in low yields, as shown in Scheme 2 [from **4** to **6**, condition *a*: PIFA, EG, MeCN, 0 °C, y. 49%] and in Scheme 3 [from **7** to **8**, condition *a*: 18%; from **9** to **10** and **11**, condition *a*: **10** (8%), **11** (13%); from **12** to **14**, condition *b*: 33%; from **17** to **19**, condition *a*: 35%]. Based on these results, it was apparent that the primarily found reaction conditions were not suitable to indoles in general. Then, we attempted to improve the reaction conditions.



Scheme 2. Reagents and conditions; *a*) phenyliodine bis(trifluoroacetate) (PIFA), ethylene glycol (EG), MeCN, 0 °C, 49%; *b*) PIFA, EG, NH_4Cl (5 equiv), MeCN, 0 °C, 79%; *c*)NaH, MeCN, 0 °C, then TMSCl, rt; *d*) PIFA, EG, 0 °C, 1.5 h, 68%; *e*) n-BuLi, THF, -78 °C, then TMSCl, -40 °C, 4 h, 77%; *f*) PIFA, EG, MeCN, 0 °C, 2 h, 38%; *g*) PIFA, EG, NaCl (2.5 equiv), MeCN, 0 °C, 3 h, 68%.

We deduced that the presence of an electron-donating group, such as a methoxy function on the indole nucleus in **1**, would facilitate this oxidative reaction. Then, we employed an N_1-silyl derivative of indoles with the expectation that the reactivity toward oxidation would be increased due to the electropositive nature of silicon. When **4** was treated successively with NaH and TMSCl and then with PIFA and EG (conditions *c* and *d* in Scheme 2), adduct (**6**) was obtained in 68% yield, which was somewhat higher than

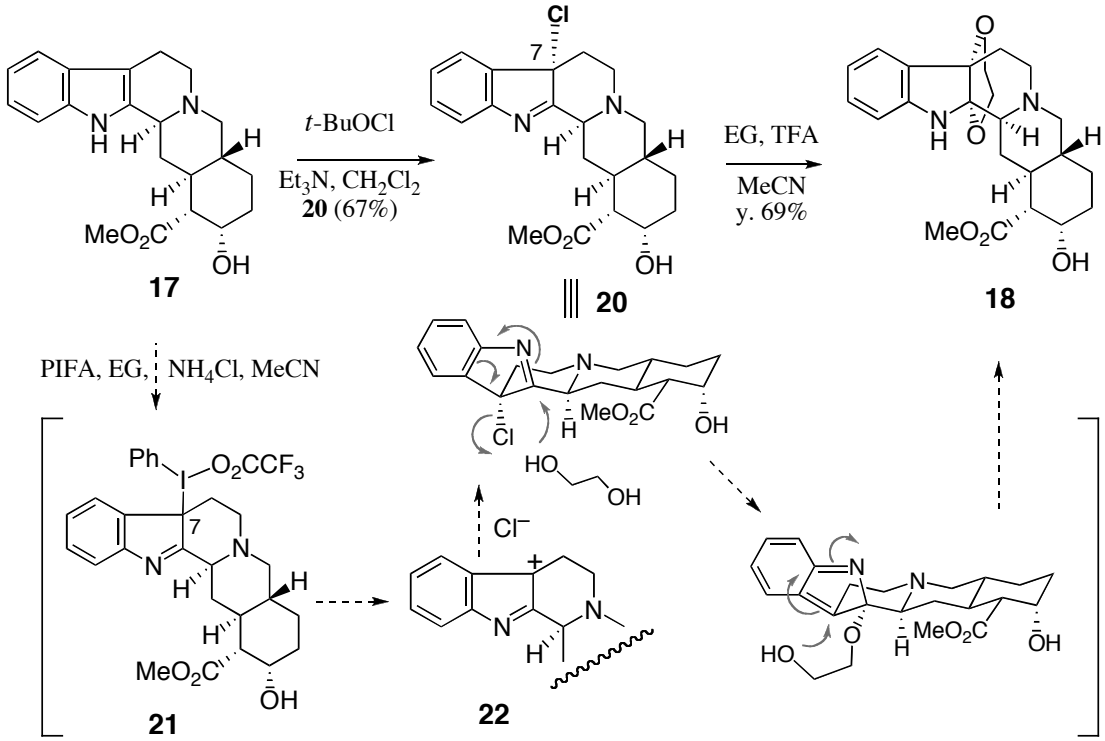


Scheme 3 Reagents and conditions; *a*) phenyliodine bis(trifluoroacetate) (PIFA), ethylene glycol (EG), MeCN, 0 °C; *b*) phenyliodine diacetate (PIDA), EG, MeCN, 0 °C; *c*) PIFA, EG, NH_4Cl (1.3–5.0 equiv), MeCN; *d*) $NaCNBH_3$, AcOH, rt, then add MeOH, 90 °C.

that obtained by initial condition *a* (49% yield). To examine the effect of the N_1-silyl function, we isolated N_1-silyl derivative (**5**)[5] and treated it with PIFA and EG (condition *f* in Scheme 2), but this resulted in a decrease of the yield (38%). Comparing the reaction conditions, i.e., one-pot experiment vs. stepwise procedure, we found that the difference lies in the presence or absence of NaCl when I(III)/EG reacted with indoles. Then, we reacted TMS derivative (**5**) with PIFA and EG in the presence of NaCl (condition *g* in Scheme 2), and this oxidative reaction afforded adduct (**6**) in 68% yield. Encouraged by this result, we next investigated the additive to the reaction mixture. Several inorganic or organic salts, such as NH_4Cl, LiCl, n-Bu_4NCl, NaBr, or NaI, were examined and the use of NH_4Cl in MeCN (condition *b* in Scheme 2) was found to afford the best result (79% yield). Then, this condition was employed to other indole substrates (**7**, **9**, **12**, **15** and **17**). As shown in Scheme 3, the yields were dramatically improved (**8**: 87%, **10**: 97%, **13**: 87%, **16**: 97%, and **18**: 83%) when NH_4Cl was added to the reaction mixture (condition *c*).

Quite interestingly, under the reaction conditions in the presence of NH_4Cl, adducts (**10**, **13**, **16**, and **18**) having the *syn* structure, i.e., H-3 and EG bridge positioned on the same face were obtained. Their stereochemistry was elucidated by nOe observation, as shown in Scheme 3. On the other hand, in the absence of NH_4Cl, adducts (**11**, **14**, and **19**) with the *anti* structure were obtained as the main product, and the chemical yields were low. To understand the reaction mechanisms and the role of chloride ion in the reaction, we next attempted the preparation of EG adducts via chloroindolenine derivatives, which are a candidate for the reaction intermediate in the presence of NH_4Cl.

We employed the well-studied chloroindolenine derivative of yohimbine (**17**).[6] According to the literature, yohimbine was treated with ^{t}BuOCl in the presence of triethylamine to give 7α-chloroindolenine (**20**) and its β-isomer in 67% and 28% yields, respectively. When **20** was treated with EG at rt to 40 °C in the presence of trifluoroacetic acid, desired adduct **18** was obtained in 69% yield (Scheme 4). This result indicated that unstable cationic intermediate (**22**) generated from 7-iodo-indolenine (**21**) was once trapped as stable 7α-chloroindolenine derivative (**20**), which reacted gradually with EG to afford adduct (**18**). In the transformation from **20** to **18**, EG would attack the imine function from the α side, as described by Borschberg and co-workers[7] in their mechanistic studies of the rearrangement of 7-chloroyohimbine derivatives, and successive Cl^- elimination–addition at the other terminal of EG would give adduct (**18**) with *syn* stereochemistry. The present results, i.e., indole alkaloids **9**, **12**, **15**, and **17** giving α-oriented EG adducts, are in accordance with previously reported observations that indole alkaloids having a *trans*-quinolizidine structure gave mainly 7α-substituted indolenine derivatives under various oxidative conditions, such as ^{t}BuOCl,[6d] lead tetraacetate,[8] or IBDA/alcohol,[9] which respectively afforded 7α-chloroindolenine, 7α-acetoxyindolenine, or 7α-alkoxyindolenine. However, the mechanism for the production of β-adducts when the reaction was conducted in the absence of NH_4Cl is still unclear.



Scheme 4

Next, we attempted the conversion of EG adducts back to the starting indoles. As has been proven using mitragynine (**1**),[2] a series of reactions, i.e., indole → EG adduct → regeneration of indole,[10] enabled us to modify the benzene ring of the indole nucleus in **1**. According to the method discovered in **1**, adducts **10**, **13**, **16**, and **18** could be converted respectively into their starting indoles (**9**, **12**, **15**, and **17**) in good yields upon reduction with $NaCNBH_3$ in AcOH at rt, followed by heating at 90 °C after the addition of MeOH (Scheme 3). In the case of compounds **6** and **8**, the desired indoles could not be isolated in good yields, probably due to the instability of compounds **4** and **7** under the present conditions. The developed protocol, i.e., preparation of 2,3-EG adducts of indole derivatives to mask the pyrrole moiety in the indole nucleus and conversion back to the mother indoles, would offer a new and general method to synthesize various A-ring-modified indole derivatives. The application of this methodology to other indoles is under way.

EXPERIMENTAL

UV: recorded in MeOH on a JASCO V-560 instrument. IR: recorded on a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra: recorded on a JEOL JNM A-400, JNM A-500, JNM ECP-400 or JNM ECP-600 spectrometer, *J* values are given in Hz. EI-MS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. FAB-MS: recorded on a JEOL JMS-AX500 or JMS-HX110 mass spectrometer. Optical rotation: measured with a JASCO P-1020 polarimeter. Melting

Point: Yanagimoto Micro Melting Point Apparatus 1631A. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column chromatography: Kieselgel 60 [Merck, 70-230 mesh (for open chromatography) and 230-400 mesh (for flash chromatography)], Chromatorex NH [Fuji Silysia Chemical, 100-200 mesh (for amino-silica gel column chromatography)]. Medium pressure liquid chromatography (MPLC): C. I. G. prepacked column CPS-HS-221-05 (Kusano Kagakukikai, SiO_2).

Preparation of EG adduct 6

To a stirred solution of 2,3-dimethylindole (**4**, 74.3 mg, 0.51 mmol) in dry MeCN (2.6 mL) and dry EG (2.6 mL) were successively added NH_4Cl (132.2 mg, 2.45 mmol) and PIFA (251.5 mg, 0.61 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by pre-packed silica gel column chromatography (EtOAc/*n*-hexane = 30:70) to give 83.1 mg (79%) of **6** as a yellowish amorphous powder, a portion of which was recrystallized from *n*-hexane to give pale yellowish prisms (mp 79–81 °C). Compound **6**: UV (MeOH) λ_{max} nm: 290, 269, 241, 233, 220, 218, 104. IR (KBr) ν_{max} cm^{-1}: 3329, 2979, 2960, 2864, 1612, 1468. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.21 (1H, d, *J*=7.3 Hz, H-5), 7.15 (1H, ddd, *J*=7.7, 7.7, 1.3 Hz, H-7), 6.86 (1H, ddd, *J*=7.4, 7.4, 0.9 Hz, H-6), 6.71 (1H, d, *J*=7.9 Hz, H-8), 4.11 (1H, br s, N_a-H), 3.72 (2H, m, H-1' and H-2'), 3.65 (1H, m, H-2'), 3.58 (1H, m, H-1'), 1.56 (3H, s, 2-CH_3), 1.38 (3H, s, 3-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.6 (C-9), 131.1 (C-4), 129.0 (C-7), 123.1 (C-5), 119.8 (C-6), 110.5 (C-8), 93.2 (C-2), 81.5 (C-3), 61.3 (C-2'), 61.1 (C-1'), 23.3 (2-CH_3), 18.0 (3-CH_3). FAB-MS (NBA) *m/z*: 206 $[M+H]^+$. HR-FAB-MS (NBA/PEG): calcd. for $C_{12}H_{16}NO_2$: 206.1181, found: 206.1180.

Preparation of EG adduct 8

To a stirred solution of tetrahydrocarbazole (**8**, 110.9 mg, 0.65 mmol) in dry MeCN (3.3 mL) and dry EG (3.3 mL) were added NH_4Cl (167.8 mg, 2.60 mmol) and PIFA (335.6 mg, 0.78 mmol) at 0 °C and the mixture was stirred for 30 min at 0 °C under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel (EtOAc/*n*-hexane = 0:100 – 50:50) to give 129.5 mg (87%) of **8** as a colorless amorphous powder, a portion of which was recrystallized from EtOAc to give colorless prisms (mp 156–157 °C). **Compound 8**: UV (MeOH) λ_{max} nm: 295, 275, 247, 223, 205. IR (KBr) ν_{max} cm^{-1}: 3311, 3035, 2958, 2933, 2864, 1616. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.18 (1H, d, *J*=7.3Hz, H-9), 7.14 (1H, ddd, *J*=7.6, 7.6, 1.2Hz, H-11), 6.85 (1H, dd, *J*=7.4, 7.4Hz, H-10), 6.71 (1H, d, *J*=7.6Hz, H-12), 4.01 (1H, br s, N_a-H), 3.81 (1H,

m, H-1', overlapped with H-2'), 3.65 (2H, m, H-1', overlapped with H-2'), 2.12 (1H, ddd, *J*=10.4, 10.4, 2.7), 2.00 (1H, m), 1.70 (2H, m), 1.52 (3H, m), 1.42 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.4 (C-13), 131.6 (C-8), 128.8 (C-11), 122.4 (C-9), 119.7 (C-10), 111.1 (C-12), 92.3 (C-2), 80.6 (C-7), 61.4 (C-1'), 61.0 (C-2'), 36.4, 29.4, 22.9, 20.6. FAB-MS (NBA) *m/z*: 231 $[M]^+$. HR-FAB-MS (NBA/PEG): calcd. for $C_{14}H_{17}NO_2$: 231.1259, found: 231.1269.

Preparation of EG adducts 10 and 11

To a stirred solution of indoloquinolizidine (70.4 mg, 0.31 mmol) in dry MeCN (1.6 mL) and dry EG (1.6 mL) were added NH_4Cl (83.2 mg, 1.55 mmol) and PIFA (157.8 mg, 0.37 mmol) at rt and the mixture was stirred for 2 h at 50 °C under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by pre-packed silica gel column chromatography (5% MeOH in $CHCl_3$) to give 86.0 mg (97%) of **10** as a colorless amorphous powder, a portion of which was recrystallized from acetone and *n*-hexane to give colorless prisms (mp 142–143 °C). **Compound 10**: UV (MeOH) λ_{max} nm: 290, 262, 238, 221, 206. IR (ATR) ν_{max} cm^{-1}: 3313, 3033, 2964, 2939, 2924, 2910, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.18 (1H, dd, *J*=7.2, 0.6 Hz, H-9), 7.14 (1H, ddd, *J*=7.6, 7.6, 1.3 Hz, H-11), 6.86 (1H, ddd, *J*=7.4, 7.4, 0.9 Hz, H-10), 6.71 (1H, d, *J*=7.7 Hz, H-12), 4.20 (1H, br s, N_a-H), 3.90 (2H, m, H-1', overlapped with H-2'), 3.61 (1H, m, H-1' or H-2'), 3.44 (1H, m, H-1' or H-2'), 2.99 (1H, d, *J*=11.0 Hz), 2.57 (1H, m), 2.50 (1H, dd, *J*=10.9, 2.1 Hz, H-3), 2.41 (1H, ddd, *J*=12.3, 12.3, 2.5 Hz), 2.16 (1H, ddd, *J*=11.1, 11.1, 4.3 Hz), 2.05 (1H, d, *J*=10.3 Hz), 1.91 (2H, m), 1.80 (1H, ddd, *J*=13.8, 13.8, 4.5 Hz), 1.68 (2H, m), 1.43 (1H, m), 1.33 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.8 (C-13), 130.8 (C-8), 128.6 (C-11), 122.0 (C-9), 119.9 (C-10), 111.8 (C-12), 91.1 (C-2), 80.4 (C-7), 62.0 (C-1'), 61.2 (C-2'), 59.5, 56.5, 50.6, 37.4, 25.5, 24.8, 24.6. FAB-MS (NBA) *m/z*: 287 $[M+H]^+$. HR-FAB-MS (NBA/PEG): calcd. for $C_{17}H_{23}N_2O_2$: 287.1760, found: 287.1762.

Under the reaction conditions above without the addition of NH_4Cl, compounds **10** and **11** were obtained in 13% and 8% yields, respectively. **Compound 11**: UV (MeOH) λ_{max} nm: 298, 243, 205. IR (ATR) ν_{max} cm^{-1}: 3310, 2922, 1613, 1466. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (2H, m), 6.83 (1H, dd, *J*=7.4, 7.4 Hz), 6.74 (1H, d, *J*=7.5 Hz), 4.36 (1H, ddd, *J*=11.6, 11.6, 2.8 Hz, H-1' or H-2'), 4.10 (1H, br s, N_a-H), 4.05 (1H, ddd, *J*=11.8, 11.8, 2.7 Hz, H-1' or H-2'), 3.65 (1H, dd, *J*=11.4, 2.4 Hz, H-1' or H-2'), 3.49 (1H, dd, *J*=11.9, 2.7 Hz, H-1' or H-2'), 2.92 (1H, d, *J*=11.0 Hz), 2.83 (1H, d, *J*=12.1 Hz), 2.69 (1H, ddd, *J*=13.4, 13.4, 4.6 Hz), 2.12 (1H, ddd, *J*=13.5, 2.6, 2.6 Hz), 1.97 (1H, dd, *J*=11.2, 11.2 Hz), 1.82-1.56 (7H, overlapped), 1.11 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.7, 130.1, 129.5, 123.1, 119.5, 110.8, 92.2 (C-2), 75.6 (C-7), 68.3 (C-3), 60.6 (C-1' or C-2'), 58.2 (C-1' or C-2'), 56.4, 53.7, 25.2, 24.3, 23.9, 23.8. FAB-MS (NBA) *m/z*: 287 $[M+H]^+$. HR-EI-MS: calcd. for $C_{17}H_{22}N_2O_2$: 286.1681, found: 286.1683.

Preparation of EG adducts 13 and 14

To a stirred solution of dihydrocorynantheol (229 mg, 0.77 mmol) in dry MeCN (4.0 mL) and dry EG (4.0 mL) was added NH_4Cl (55.4 mg, 1.04 mmol), and then PIFA was added portionwise to the stirred mixture at rt under argon atmosphere in the following manner: 0 min, 157.6 mg (0.37 mmol); 1 h, 175.7 mg (0.41 mmol); 4 h, 37.5 mg (0.08 mmol). The reaction mixture was stirred at the same temperature for further 3 h under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on amino-silica gel (EtOAc/$CHCl_3$ = 30:70) to give 238.7 mg (87%) of **13** as a colorless amorphous powder, a portion of which was recrystallized from EtOAc and *n*-hexane to give colorless prisms (mp 108-111 °C). **Compound 13**: UV (MeOH) λ_{max} nm: 292, 264, 239, 221, 205. IR (ATR) ν_{max} cm^{-1}: 3313, 2958, 2866, 1614, 1466. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.17 (1H, d, *J*=7.0 Hz, H-9), 7.13 (1H, ddd, *J*=7.6, 7.6, 1.2 Hz, H-11), 6.86 (1H, ddd, *J*=7.3, 7.3, 0.9 Hz, H-10), 6.71 (1H, d, *J*=7.6 Hz, H-12), 4.23 (1H, br s, N_a-H), 3.89 (2H, m, H-1', overlapped with H-2'), 3.75 (2H, m, H_2-17), 3.61 (1H, m, H-1'), 3.44 (1H, m, H-2'), 3.05 (1H, dd, *J*=11.3, 3.6 Hz, H-21), 2.60 (1H, dddd, *J*=11.6, 2.2, 2.2, 2.2 Hz, H-5), 2.51 (1H, dd, *J*=11.1, 1.9 Hz, H-3), 2.39 (1H, ddd, *J*=12.4, 12.4, 2.4 Hz, H-5), 2.15 (1H, ddd, *J*=12.0, 2.8, 2.8 Hz, H-14), 1.96 (2H, m, H-6, overlapped with H-16), 1.88 (1H, dd, *J*=11.3, 11.3 Hz, H-21), 1.80 (1H, ddd, *J*=13.8, 13.8, 4.4 Hz, H-6), 1.67 (1H, m, H-19), 1.38 (3H, m, H-15, overlapped with H-16 and H-20), 1.24 (1H, ddd, *J*=11.6, 11.6, 11.6 Hz, H-14), 1.11 (1H, m, H-19), 0.89 (3H, dd, *J*=7.5, 7.5 Hz, H_3-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.7 (C-13), 130.8 (C-8), 128.7 (C-11), 122.0 (C-9), 119.9 (C-10), 111.8 (C-12), 91.1 (C-2), 80.3 (C-7), 62.0 (C-1'), 61.3 (C-2'), 61.0 (C-21), 60.5 (C-17), 59.1 (C-3), 50.3 (C-5), 41.5 (C-20), 37.4 (C-6), 37.0 (C-15), 35.8 (C-16), 30.5 (C-14), 23.3 (C-19), 11.0 (C-18). $[\alpha]_D^{25}$ -72 (*c* 1.1, $CHCl_3$). EI-MS *m/z* (%): 358 (100, M^+), 313 (20), 169 (95), 156 (41). HR-FAB-MS (NBA/PEG): calcd. for $C_{21}H_{31}N_2O_3$: 359.2335, found: 359.2344.

To a stirred solution of dihydrocorynantheol (**12**, 11 mg, 0.04 mmol) in dry MeCN (0.3 mL) and dry EG (0.3 mL) was added PIDA (12.7 mg, 0.04 mmol) to the stirred mixture at 0 °C under argon atmosphere. The reaction mixture was stirred at the same temperature for further 12 h under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by pre-packed silica gel column chromatography (7% MeOH in $CHCl_3$) to give 4.4 mg (33%) of **14** as a colorless amorphous powder together with 5.5 mg of the starting material (**12**). **Compound 14**: UV (MeOH) λ_{max} nm: 298, 242, 227, 204. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.22-7.18 (2H, overlapped), 6.83 (1H, ddd, *J*=7.5, 7.5, 1.1 Hz), 6.76 (1H, d, *J*=7.5 Hz), 4.35 (1H, ddd, *J*=11.6, 11.6, 2.7 Hz, H-1' or H-2'), 4.04 (1H, ddd, *J*=11.9, 11.9, 2.8 Hz, H-1' or H-2'), 3.79-3.70 (3H, overlapped), 3.64 (1H, dd, *J*=11.4, 2.4 Hz, H-1' or H-2'), 3.49 (1H, dd, *J*=11.9, 2.6 Hz, H-1' or H-2'), 2.96 (1H, dd, *J*=11.4,

3.7 Hz), 2.85 (1H, m), 2.69 (1H, ddd, *J*=13.4, 13.4, 4.8 Hz), 2.13 (1H, ddd, *J*=14.1, 2.5, 2.5 Hz), 2.00-1.88 (3H, overlapped), 1.73-1.52 (4H, overlapped), 1.40-1.32 (3H, overlapped), 1.31 (1H, m), 1.00 (1H, m), 0.82 (3H, dd, *J*=7.4, 7.4 Hz). EI-MS *m/z* (%): 358 (M^+, 100), 313 (20), 169 (95). HR-EI-MS: calcd. for $C_{21}H_{30}N_2O_3$: 358.2256, found: 358.2261.

Preparation of EG adduct 16

To a stirred solution of corynantheol (**15**, 302 mg, 1.02 mmol) in dry MeCN (15.0 mL) and dry EG (15.0 mL) was added NH_4Cl (107.4 mg, 2.01 mmol), and then PIFA was added portionwise to the stirred mixture at 0 °C under argon atmosphere in the following manner: 0 min, 139.1 mg (0.32 mmol); 10 min , 142.3 mg (0.33 mmol); 20 min, 175.5 mg (0.41 mmol); 30 min, 100.5 mg (0.23 mmol). The reaction mixture was stirred at rt for further 15 h under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on amino-silica gel (EtOAc/$CHCl_3$ = 30:70) to give 352.9 mg (97%) of **16** as an yellowish amorphous powder, a portion of which was recrystallized from EtOAc and *n*-hexane to give colorless prisms (mp 105–110 °C). **Compound 16**: UV (MeOH) λ_{max} nm: 291, 265, 239, 222, 205. IR (KBr) ν_{max} cm^{-1}: 3315, 2924, 2866, 2821, 1614, 1466. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.18 (1H, d, *J*=7.3 Hz, H-9), 7.14 (1H, ddd, *J*=7.6, 7.6, 1.3 Hz, H-11), 6.87 (1H, dd, *J*=7.3, 7.3 Hz, H-10), 6.72 (1H, d, *J*=7.6 Hz, H-12), 5.58 (1H, ddd, *J*=17.2, 10.2, 8.9 Hz, H-19), 5.12 (1H, dd, *J*=17.2, 1.7 Hz, H-18), 5.09 (1H, dd, *J*=10.2, 1.7 Hz, H-18), 4.23 (1H, br s, N_a-H), 3.89 (2H, m, H-1', overlapped with H-2'), 3.75 (2H, m, H_2-17), 3.61 (1H, m, H-1'), 3.44 (1H, m, H-2'), 2.89 (1H, dd, *J*=11.1, 3.7 Hz, H-21), 2.57 (2H, m, H-3, overlapped with H-5), 2.40 (1H, ddd, *J*=12.4, 12.4, 2.4 Hz, H-5), 2.19 (2H, m, H-14, overlapped with H-20), 2.07 (1H, dd, *J*=11.1, 11.1 Hz, H-21), 1.92 (2H, m, H-6, overlapped with H-16), 1.79 (1H, ddd, *J*=13.9, 13.9, 4.6 Hz, H-6), 1.46 (1H, m, H-15), 1.35 (1H, m, H-16), 1.24 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H-14). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.7 (C-13), 139.5 (C-19), 130.7 (C-8), 128.7 (C-11), 122.1 (C-9), 120.0 (C-10), 116.9 (C-18), 111.8 (C-12), 91.0 (C-2), 80.3 (C-7), 61.9 (C-1'), 61.7 (C-21), 61.3 (C-2'), 60.4 (C-17), 58.9 (C-3), 50.0 (C-5), 46.8 (C-20), 37.3 (C-6), 36.8 (C-16), 36.7 (C-15), 30.1 (C-14). $[\alpha]_D^{24}$ -81 (*c* 1.0, $CHCl_3$). EI-MS *m/z* (%): 356 (100, M^+), 166 (76), 154 (37). HR-FAB-MS (NBA/PEG): calcd. for $C_{25}H_{35}N_2O_6$: 459.2495, found: 459.2515.

Preparation of EG adducts 18 and 19

To a stirred solution of yohimbine (**17**, 117.4 mg, 0.33 mmol) in dry MeCN (1.7 mL) and dry EG (1.7 mL) were added NH_4Cl (69.8 mg, 1.29 mmol) and PIFA (157.0 mg, 0.36 mmol) at rt and the mixture was stirred for 3h at 40 °C under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the

mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel (10% MeOH in $CHCl_3$) to give 113.2 mg (83%) of **18** as a pale yellowish amorphous powder, a portion of which was recrystallized from acetone and *n*-hexane to give colorless prisms (mp 231–234 °C). **Compound 18**: UV (MeOH) λ_{max} nm: 292, 265, 239, 222, 205. IR (KBr) ν_{max} cm^{-1}: 3381, 2924, 1726, 1616, 1468. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.17 (1H, d, *J*=6.8 Hz, H-9), 7.13 (1H, ddd, *J*=7.6, 7.6, 1.3 Hz, H-11), 6.87 (1H, dd, *J*=7.3, 7.3 Hz, H-10), 6.72 (1H, d, *J*=7.8 Hz, H-12), 4.19 (1H, br s, N_a-H), 4.18 (1H, m, H-17), 3.87 (2H, m, H-1', overlapped with H-2'), 3.76 (3H, s, 22-OCH_3), 3.60 (1H, d, *J*=9.3 Hz, H-1'), 3.42 (1H, d, *J*=9.5 Hz, H-2'), 3.27 (1H, br s, 17-OH), 2.88 (1H, dd, *J*=11.1, 3.1 Hz, H-21), 2.61 (1H, d, *J*=11.5 Hz, H-3), 2.57 (1H, m, H-5), 2.42 (1H, ddd, *J*=12.3, 12.3, 2.4 Hz, H-5), 2.31 (1H, dd, *J*=11.1, 1.8 Hz, H-16), 2.02 (1H, dd, *J*=10.9, 10.9 Hz, H-21), 1.99 (1H, m, H-18), 1.90 (3H, m, H-6, overlapped with H-14 and H-15), 1.77 (1H, ddd, *J*=13.8, 13.8, 4.4 Hz, H-6), 1.50 (3H, m, H-18, overlapped with H-19 and H-20), 1.39 (1H, m, H-19), 1.24 (1H, ddd, *J*=12.1, 12.1, 12.1 Hz, H-14). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 176.1 (C-22), 146.6 (C-13), 130.7 (C-8), 128.7 (C-11), 122.1 (C-9), 120.1 (C-10), 111.8 (C-12), 90.9 (C-2), 80.2 (C-7), 66.6 (C-17), 61.9 (C-1'), 61.8 (C-21), 61.3 (C-2'), 59.2 (C-3), 52.3 (C-16), 51.9 (22-OCH_3), 50.1 (C-5), 40.3 (C-20), 37.4 (C-6), 36.8 (C-15), 31.1 (C-18), 29.3 (C-14), 23.2 (C-19). $[\alpha]_D^{25}$ -44 (*c* 0.98, $CHCl_3$). FAB-MS (NBA) *m/z*: 415 $[M+H]^+$. HR-FAB-MS (NBA/PEG): calcd. for $C_{23}H_{31}N_2O_5$: 415.2233, found: 415.2202.

Under the reaction conditions above without the addition of NH_4Cl, compound **19** was obtained in 35% yields. **Compound 19**: UV (MeOH) λ_{max} nm: 297, 242, 206. IR (KBr) ν_{max} cm^{-1}: 3399, 2927, 1727, 1615. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.20 (1H, ddd, *J*=7.4, 7.4, 1.2 Hz, H-9), 7.19 (1H, d, *J*=7.6 Hz, H-11), 6.83 (1H, ddd, *J*=7.5, 7.5, 0.8 Hz, H-10), 6.76 (1H, dd, *J*=8.4, 1.1 Hz, H-12), 4.34 (1H, ddd, *J*=11.6, 11.6, 2.8 Hz, H-2'), 4.16 (1H, m, H-17), 4.07 (1H, br s, N_a-H), 4.02 (1H, ddd, *J*=11.9, 11.9, 2.8 Hz, H-1'), 3.78 (3H, s, 16-CO_2CH_3), 3.63 (1H, dd, *J*=11.4, 2.4 Hz, H-2'), 3.49 (1H, dd, *J*=11.9, 2.4 Hz, H-1'), 2.83 (1H, m, H-5), 2.80 (1H, dd, *J*=11.8, 2.6 Hz, H-21), 2.66 (1H, ddd, *J*=13.4, 13.4, 4.8 Hz, H-6), 2.28 (1H, dd, *J*=11.3, 2.1 Hz, H-16), 2.12 (1H, ddd, *J*=13.7, 2.4, 2.4 Hz, H-6), 1.98 (1H, ddd, *J*=12.5, 12.5, 2.6 Hz, H-5), 1.91 (1H, dd, *J*=13.7, 3.1 Hz, H-18), 1.83 (1H, dd, *J*=10.8, 2.6 Hz, H-3), 1.66 (2H, overlapped, H-15, and H-21), 1.58 (1H, m, H-14), 1.50 (1H, m, H-18), 1.46 (1H, ddd, *J*=12.7, 2.7, 2.7 Hz, H-14), 1.38-1.34 (2H, overlapped, H-19, and H-20), 1.31-1.26 (1H, m, H-19). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 175.6 (16-$\underline{C}O_2CH_3$), 148.4 (C-13), 130.2 (C-9), 129.1 (C-8), 123.0 (C-11), 119.6 (C-10), 111.1 (C-12), 92.0 (C-2), 75.6 (C-7), 68.0 (C-3), 66.8 (C-17), 61.7 (C-21), 60.6 (C-2'), 58.1 (C-1'), 53.1 (C-5), 52.4 (C-16), 51.9 (16-$CO_2\underline{C}H_3$), 39.7 (C-20), 35.7 (C-15), 31.3 (C-18), 28.7 (C-14), 23.7 (C-6), 23.0 (C-19). EI-MS *m/z* (%): 414 (M^+, 67), 225 (100). HR-EI-MS: calcd. for $C_{23}H_{30}N_2O_5$: 414.2154, found: 414.2142.

Preparation of EG adduct 18 from 7-chloroindolenine 20

To a stirred solution of **20** (34.7 mg, 0.0 mmol) in dry MeCN (0.5 mL) and dry EG (0.5 mL) was added trifluoroacetic acid (0.1 mL) at 0 °C and the mixture was stirred at rt for 3 h and then at 40 °C for 6 h under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution, the mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel (10% MeOH in $CHCl_3$) to give 25.5 mg (69%) of **18** as a pale yellowish amorphous powder, which was identical with the product prepared directly from **17**.

Conversion of EG adduct 10 into indoloquinolizidine 9

To a stirred solution of **10** (21.4 mg, 0.08 mmol) in dry AcOH (0.8 mL) was added $NaCNBH_3$ (24.8 mg, 0.50 mmol) at rt and the mixture was stirred for 4 h at rt under argon atmosphere. MeOH (100 μL) was added to the reaction mixture, which was then heated under reflux at 90 °C for 4 h. The reaction mixture was poured into cold aqueous NH_4OH solution, and this mixture was extracted three times with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated to give a residue that was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give 19.9 mg (quantitative) of indoloquinolizidine (**9**), which was completely identical with the authentic sample.

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