JOC*Note*

Total Synthesis of (+)-Hygrine via Asymmetric Phase-Transfer Catalytic Alkylation

Jeong-Hee Lee, Byeong-Seon Jeong, Jin-Mo Ku, Sang-sup Jew,* and Hyeung-geun Park*

Research Institute of Pharmaceutical Science and College of Pharmacy, Seoul National University, Seoul 151-742, Korea

hgpk@plaza.snu.ac.kr

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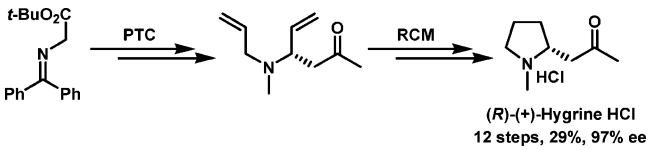
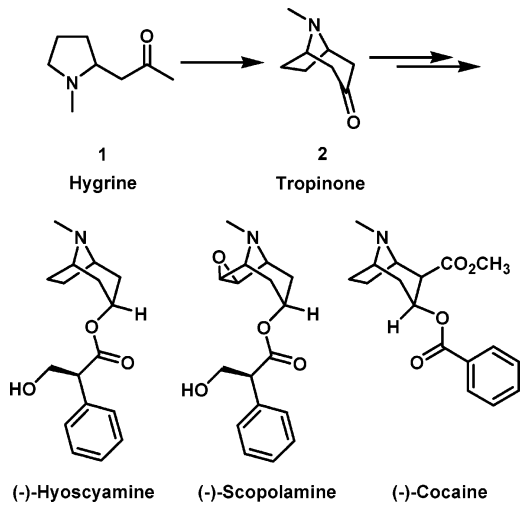


The first enantioselective synthesis of (+)-hygrine (**1**) is reported. **1** was obtained in 12 steps with 29% overall yield and 97% ee via asymmetric phase-transfer catalytic alkylation and ring-closing metathesis as key steps. The absolute configuration of (+)-hygrine could be directly confirmed as *R*.

Over the last few decades, the biosynthesis of the tropane alkaloids, such as (−)-hyoscyamine, (−)-scopolamine, and (−)-cocaine, has been extensively studied.[1] As a main skeleton, tropinone (**2**) is a key intermediate in the biosynthesis of tropane alkaloids, which is transformed from hygrine (**1**).[2] The incorporation studies of radio-labeled hygrines[^{14}C] into the tropane alkaloids showed that only (+)-hygrine serves as a precursor for the tropane ring.[3] Since hygrine is known to racemize readily in neutral or basic conditions,[3] the enantioselective synthesis of optically pure hygrine has been quite challenging.



So far there have been only two synthetic methods for (±)-hygrine, but no chiral version has been reported.[3,4] The incorporation studies were performed with the diastereomeric salts prepared from the resolution of the (±)-hygrine with D-(+)-tartrate, but the diastereomeric purity could not be higher than 80% even through several recrystallizations.[3,5] Also, the absolute configurations of (+)-hygrine and (−)-hygrine are determined by the relative correlation with those of D-proline and L-proline, respectively.[3,6] In this note, we report the first enantioselective synthesis of (+)-hygrine (**1**) via asymmetric phase-transfer catalytic alkylation and ring-closing metathesis (RCM) and confirm the absolute configuration of (+)-hygrine directly as *R*.

Recently, the asymmetric phase-transfer alkylation of the *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) in the presence of *cinchona*-derived ammonium salts was developed and successfully applied to the enantioselective synthesis of natural and non-natural α-amino acids.[7] As shown in Scheme 1, the enantioselective phase-transfer catalytic alkylation[8] was employed as the key step of the introduction of the chirality of (+)-hygrine, and the construction of the pyrrolidine ring system was planned by RCM.[9]

First, the phase-transfer catalytic alkylation was performed with *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) along with 1 mol % of the 2,7-bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]naphthalene dibromide (**6**),[8f] methallyl bromide, and 50% aqueous KOH in toluene/chloroform (volume ratio = 7:3) at −20 °C (7 h) to give **7** in 95% yield. The enantioselectivity was determined by chiral HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol = 500:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times; *S* (major) 9.6 min, *R* (minor) 17.4 min, 97% ee). The absolute configuration of **7** {$[\alpha]^{23}_D$ = −134.2° (*c* 1.0, CH_2Cl_2)} was determined as *S* by comparison of the optical rotation with the reported value {$[\alpha]^{23}_D$ = −127.8° (*c* 1.0, CH_2Cl_2)[8c]}.

The hydrolysis of the benzophenone imine group of **7** with 1 N HCl, followed by the protection of amine using ethyl

* To whom correspondence should be addressed. Tel: 82-2-880-7871. Fax: 82-2-872-9129.

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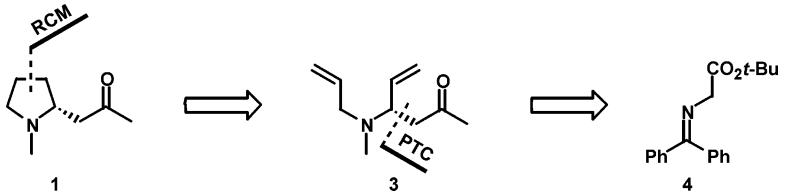
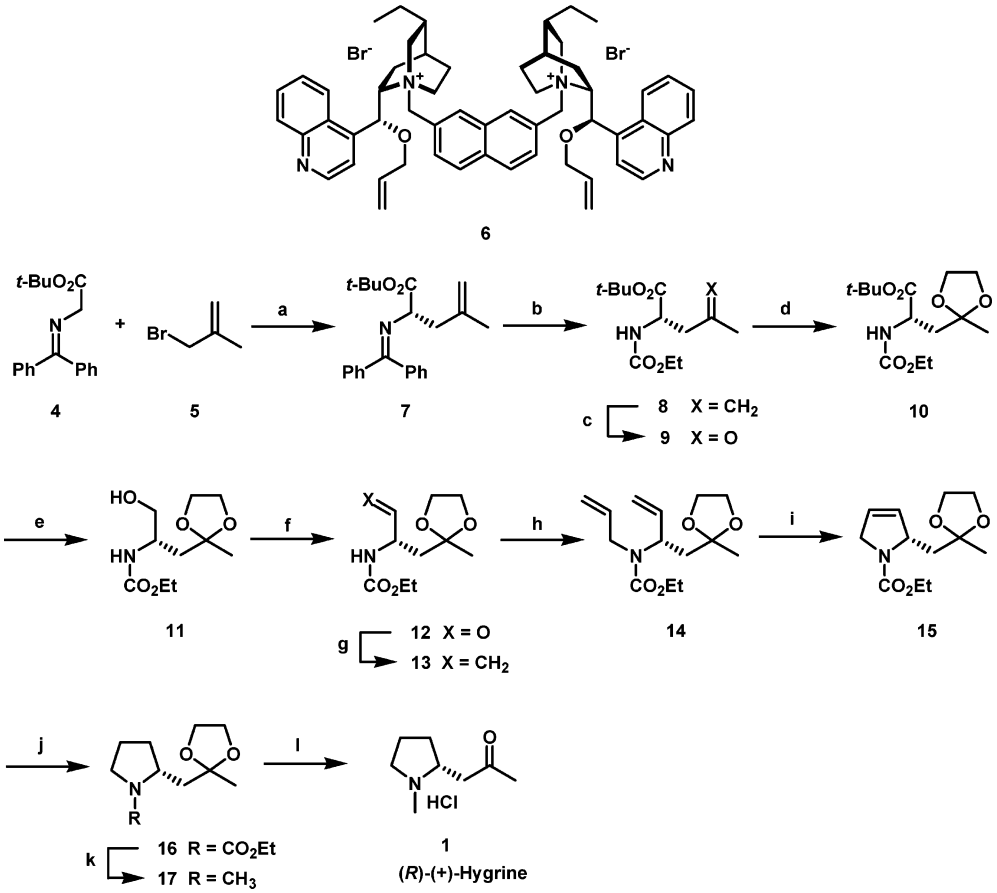
SCHEME 1



SCHEME 2 [a]



[a] Reagents and conditions: (a) **6**, methallyl bromide, 50% KOH, $PhCH_3-CHCl_3$ (7/3), −20 °C, 7 h, 95%; (b) (i) 1 N HCl, THF, rt, 2 h, (ii) $ClCO_2Et$, Et_3N, CH_2Cl_2, rt, 1 h, 85%; (c) O_3, EtOAc, 85%; (d) $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, reflux, 4 h, 85%; (e) $LiAlH_4$, THF, rt, 2 h, 96%; (f) Dess−Martin periodinane, CH_2Cl_2, rt, 6 h, 92%; (g) Tebbe reagent, THF, rt, 0.5 h, 82%; (h) KOH, allyl bromide, DMF, rt, 3 h, 94%; (i) Grubbs' second-generation catalyst, CH_2Cl_2, rt, 3 h, 99%; (j) H_2, Pd/C, THF, rt, 2 h, 93%; (k) $LiAlH_4$, THF, reflux, 5 min, 95%; (l) 6 N HCl, THF, rt, 2 h, 85%.

chloroformate in basic conditions, afforded the ethyl carbamate **8** (85%). After the ozonolysis of **8**, which gave the methyl ketone **9** (85%), the protection of the ketone of **9** using ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid provided the ketal **10** (85%). For the RCM, the conversion of the *tert*-butyl ester of **10** to the terminal olefin was carried out in three steps. The $LiAlH_4$ reduction of the *tert*-butyl ester, followed by oxidation of the resulting alcohol **11** using Dess−Martin periodinane, gave the aldehyde **12** in high yield (88% from **10**). Next, we adapted the Wittig reaction for the formation of the terminal olefin, but the poor chemical yield (52%) and the potential possibility of partial racemization in basic conditions led us find more mild reaction conditions. Finally, we employed Tebbe reagents in THF solvent at room temperature to obtain **13** in 82% yield. We could confirm that there was no racemization during the olefination step by the chiral HPLC analysis of the *N*-α-naphthylmethyl derivative of **13** (Chiralcel OD column, hexanes:2-propanol = 99:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times; *S* (major) 29 min, *R* (minor) 31 min, 97% ee). *N*-Allylation of **13** by KOH base in DMF solvent afforded **14** (94%). The RCM of **14**, the second key step, could be accomplished with very high chemical yield using Grubbs' second-generation catalyst to give **15** (99%). After the catalytic hydrogenation of the olefin in **15** generated during the RCM, the *N*-methyl group of **17** was introduced by the $LiAlH_4$ reduction of the *N*-carboethoxy group in **16**. Finally, deprotection of the ketal with 6 N HCl in THF provided (+)-hygrine·HCl (**1**) {$[\alpha]^{23}_D$ = +34.5° (*c* 0.5, H_2O)} (81% from **15**).

In conclusion, we could synthesize (+)-hygrine·HCl (**1**) in 12 steps with 29% overall yield and 97% ee by enantioselective phase-transfer catalytic alkylation and ring-closing metathesis as key steps from *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) and also directly confirm the absolute configuration of (+)-

hygrine as *R*. We believe the efficient synthetic method of (+)-hygrine would facilitate the studies on the biosynthesis of tropane alkaloids.

Experimental Section

Enantioselective Phase-Transfer Catalytic Alkylation (7): To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **4** (1.0 g, 3.39 mmol) and the chiral catalyst **6** (167.5 mg, 0.34 mmol) in toluene/$CHCl_3$ (v/v = 7:3, 15 mL) was added methallyl bromide **5** (1.8 mL, 16.93 mmol). The reaction mixture was then cooled (−20 °C), 50% aqueous KOH (5.0 mL, 44.01 mmol) was added, and the reaction mixture was stirred at −20 °C until the starting material had been consumed (7 h). The suspension was diluted with ether (400 mL), washed with water (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes:EtOAc = 50:1) afforded the desired product **7** (1.13 g, 95%) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol = 500:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm; retention times = 9.6 min (major, *S* isomer), 17.4 min (minor, *R* isomer), 97% ee). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.[8c]

Ring-Closing Metathesis (15): To a solution of **14** (688 mg, 2.55 mmol) in anhydrous dichloromethane (69 mL) was added Grubbs' second-generation catalyst (174 mg, 0.20 mmol). The reaction mixture was stirred for 6 h at room temperature. After addition of DMSO, the reaction mixture was concentrated in reduced pressure. Purification of the residue by column chromatography on silica gel (hexanes:EtOAc = 6:1) afforded **15** (609 mg, 99%) as a colorless caramel: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01−5.95 (m, 1H), 5.69−5.67 (m, 1H), 4.65−4.57 (m, 1H), 4.22−3.85 (m, 8H), 1.70−1.63 (m, 2H), 1.38 (s, 3H), 1.26−1.20 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.5, 132.0, 123.8, 109.1, 64.6, 64.1, 61.9, 60.7, 52.9, 43.1, 24.3, 14.9; IR (KBr) ν 2982, 1701, 1417, 1380, 1325, 1112, 1042, 773, 713 cm^{-1}; $[\alpha]^{20}_D$ = +128.09° (*c* 1.0, $CHCl_3$); MS (EI) 241 $[M]^+$; HRMS (EI) calcd for $C_{12}H_{19}NO_4$ $[M]^+$ 241.1314, found 241.1288.

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Supporting Information Available: Spectroscopic characterizations of **1** and **7**−**17** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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