BISCHLER-NAPIERALSKI CYCLIZATION OF N-[2-(2-BROMO-5-HYDROXY-4-METHOXYPHENYL)ETHYL]-N-[\(\text{S}\)-1-PHENYLETHYL]-2-(2-BROMO-4,5-DIMETHOXYPHENYL)ACETAMIDE ACCOMPANIED BY ELIMINATION OF CHIRAL AUXILIARY

Kumiko Miyatani\textsuperscript{a}, Mariko Ohno\textsuperscript{a}, Kazuyo Tatsumi\textsuperscript{a}, Yoshitaka Ohishi*\textsuperscript{a}, Jun-ichi Kunitomo\textsuperscript{a}, Ikuo Kawasaki\textsuperscript{b}, Masayuki Yamashita\textsuperscript{b}, and Shunsaku Ohta\textsuperscript{b}

\textsuperscript{a}Faculty of Pharmaceutical Science, Mukogawa-Women’s University, 11-68 Koushien Kyuban-cho, Nishinomiya 663-8179, Japan, \textsuperscript{b}Kyoto Pharmaceutical University, Misasagi Yamashinaku, Kyoto 607-8171, Japan

\textbf{Abstract} – \(N\)-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-\(N\)-[\(\text{S}\)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (5) was cyclized under \(N\)-dealkylation at the 2-position to the racemic 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives (6) by the Bischler-Napieralski cyclization followed by NaBH\(_4\) reduction (Polniaszek’s method).

\textbf{INTRODUCTION}

We have reported total syntheses of several chiral 1-benzyltetrahydroisoquinoline alkaloids through the Bischler-Napieralski cyclization followed by stereoselective NaBH\(_4\) reduction (Polniaszek’s method)\textsuperscript{1} of the \(N\)-[2-(phenyl)ethyl]-2-phenylacetamides bearing an appropriate chiral auxiliary such as \(\text{S}\)-1-phenylethyl group on the nitrogen atom.\textsuperscript{2} In the course of our studies, we have attempted a total synthesis of natural \(\text{S}\)-(+)\textsuperscript{3,4} cularine via \(N\)-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-\(N\)-[\(\text{S}\)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (5), as a key intermediate. In this paper, we would like to describe attempts for the preparation of \(\text{S}\)-(+) cularine from 5 by the Polniaszek’s method and unexpected racemization during the reactions.

\textbf{RESULTS AND DISCUSSION}

The optically active key intermediate, \(N\)-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-\(N\)-[\(\text{S}\)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (5), was prepared starting from 5-benzyloxy-2-bromo-4-methoxyphenylacetic acid (1)\textsuperscript{5} as shown in Scheme 1. Treatment of the acid chloride of 1 with \(\text{S}\)-(\(\text{S}\)-D)-phenylethylamine afforded the optically active amide (2) in excellent yield. The amide (2) was reduced with BH\(_3\)-THF complex in the presence of BF\(_3\)-\(\text{Et}_2\)O complex to give the amine (3), which was
condensed with the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid \(^6\) to yield the acetamide \((4)\). \(^4\)h The optically active phenolic acetamide \((5)\) for the cyclization was obtained by deprotection of the benzyloxy group of \(4\) with \(\text{SnCl}_4\). The racemization of such optically active acetamide derivatives has not been found in our previous work. \(^2\) The phenolic acetamide \((5)\) was estimated to constitute of two rotational isomers \((45:55)\) \(^7\) with respect to the amide function on the basis of its \(^1\)H-NMR. Based on our previous works, \(^2\) it was rationally expected that the chiral auxiliary of \(5\) would result in 1,3-asymmetric induction \(^1a,8\) to produce the chiral \((1S)-1\)-benzyltetrahydroisoquinoline \((8)\) via the iminium ion \((7)\) through the Polniaszek’s method.

Thus, treatment of the phenolic acetamide \((5)\) with \(\text{POCl}_3\) in dry \(\text{CH}_3\text{CN}\) under the Bischler-Napieralski cyclization conditions afforded a viscous substance. \(^9\) The substance, without any purification, was treated with \(\text{NaBH}_4\) in \(\text{MeOH}\) at \(-78\) \(\square\) according to the Polniaszek’s method to afford colorless prisms, \(\text{mp} \ 99 \sim 101\) \(\square\). The structure of the product was assigned as \(N\)-unsubstituted 5-bromo-1-(2-bromo-4,5-
dimethoxybenzyl)-8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (6) on the basis of \(^1\)H-NMR and MS. (Chart 1) However, specific rotation ([\(\alpha\)]\(_D\)) of 6 was only –0.79 \(\alpha\) and the enantiomer ratio was observed 47.2 : 52.8 by HPLC with a chiral stationary phase, namely, it was clarified that the product (6) was almost racemic compound. The phenolic acetamide (5) resulted in the formation of a major product and several minor products under the Bischler-Napieralski cyclization conditions. The mixture of these products was examined with MS and no isoquinoline derivatives bearing the chiral auxiliary such as 7 were detected. The racemic tetrahydroisoquinoline (6) had been converted successfully to dl-cularine according to the reported procedure.\(^{4g}\)

Next, we examined mechanism for the formation of unexpected racemic (6). Styrene and 1-chloroethylbenzene were detected in the reaction mixture of the Bischler-Napieralski cyclization of 5 by GCMS. This suggested that the chiral phenethyl group on nitrogen atom of 5 was cleavaged somewhere in the cyclization to give styrene which was partially converted to 1-chloroethylbenzene by HCl during the reaction. A plausible mechanism for the formation of 6 can be postulated as shown in Scheme 2.

The acetamide (5) would afford the intermediate iminium ion (9) by the treatment with POCl\(_3\). The intermediate (9) with the steric repulsion among the four serial and relatively large substituents at the 1-, 2-, 7- and 8-positions on the isoquinoline ring would be converted to the more stable iminium ion (10) accompanying elimination of styrene. The reduction of the iminium ion (10) with NaBH\(_4\) would give the racemic tetrahydroisoquinolinol (6).

In conclusion, it was clarified that \(N\)-(2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl)-\(N\)-(S)-phenylethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (5) possessing a hydroxy group at 5-position afforded racemic 5-bromo-1-(2-bromo-4,5-dimethoxybenzyl)-8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (6) by the Polniaszek’s method because of the elimination of the chiral auxiliary in the Bischler-Napieralski cyclization prior to 1,3-asymmetric reduction with NaBH\(_4\).
EXPERIMENTAL

All melting points were determined using a Yanako microscopic hotstage apparatus and are uncorrected. \( ^1 \)H-NMR spectra were obtained on a JEOL PMX60 and JEOL GSX-500 spectrometers with tetramethylsilane as an internal standard. MS spectra (MS, HRMS) were obtained using a JEOL JMS DX-303 EIMS spectrometer. IR spectra were taken on a Shimadzu IR-435 spectrophotometer in CHCl\(_3\) solution. Optical rotations were measured on a JASCO DIP-360 polarimeter. GCMS spectra were obtained on a JEOL MS-BU20 (GC mate) [carrier gas He, flow 1.0 mL/min on a HP-5 column (crosslinked 5% PH ME Siloxane, length 30 m, I.D. 0.32 mm with film of 0.25 mm)] Elemental analyses were performed on a CHN CORDER MT-3 (Yanako). All organic extracts were dried over anhydrous MgSO\(_4\). Column chromatography was carried out on Wakogel C-200 (100 ~ 200). Thin layer chromatography was performed on a E. Merck silica gel plate (0.5 mm, 60F-254). The numbering for the compounds (4, 5, 6) shown in Scheme 1 was applied to the assignments of \( ^1 \)H-NMR spectra.

\( \textit{N-[(S)-1-Phenylethyl]-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)acetamide (2)} \)

To a mixture of \( (S)\)-( -) - \( \text{-phenylethylamine (2.84 mL, 0.022 mol) and 5% Na}_2\text{CO}_3 \) solution (100 mL, 0.050 mol) in Et\(_2\)O (100 mL) was added dropwise the acid chloride of 5-benzyloxy-2-bromo-4-methoxyphenylacetic acid (1) (mp 147.5 ~ 149.5 \( \degree \)C) (7.02 g, 0.020 mol) in dry Et\(_2\)O (25 mL) with vigorous stirring at 10 ~ 15 \( \degree \). After stirring was continued for 2 h at same temperature, a resulting precipitate was collected by filtration. The precipitate was recrystallized from EtOH : hexane (2 : 1) to give colorless prisms (2), mp 145.0 ~ 147.5 \( \degree \)C (8.76 g, 96.7 %). \( \left[ \alpha \right]_D^2 = -2.66 \degree \) (c=0.432, CHCl\(_3\)). \( ^1 \)H-NMR(CDCl\(_3\)) : 1.40 (3H, d, \( J = 7.3 \) Hz, -CHCH\(_3\)), 3.58 (2H, s, -CH\(_2\)CO -), 3.87 (3H, s, -OCH\(_3\)), 5.07 (2H, s, -OCH\(_2\)Ph), 5.11 (1H, q, \( J = 7.3 \) Hz, -CH\(_3\)), 5.61 (1H, d, \( J = 7.7 \) Hz, -NH-), 6.87 (1H, s, 3-H or 6-H), 7.06 (1H, s, 3-H or 6-H), 7.21 ~ 7.40 (10H, m, arom. H). EIMS (70 eV) m/z (rel. int. %): 453 (M\(^+\), 15.0), 374 (84.9), 270 (55.9), 105 (72.0), 91 (100). IR (cm\(^{-1}\)) : 3420, 1660 (C=O), 1500. Anal. Calcd for C\(_{24}\)H\(_{24}\)NO\(_3\)Br : C, 63.44 ; H, 5.32 ; N, 3.08. Found : C, 63.40 ; H, 5.34 ; N, 3.08.

\( \textit{N-[(S)-1-Phenylethyl]-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)ethylamine (3)} \)

To a solution of 2 (4.5g, 0.010 mol) in abs. THF (200 mL) was carefully added dropwise BF\(_3\)- Et\(_2\)O complex (abt. 47 %, 1.5 mL, 0.050 mol) and 1.0 M BH\(_3\)- THF complex (30 mL, 0.030 mol) under argon at 20 ~ 25 \( \degree \) with stirring, and the mixture was further heated for 2.5 h at 70 \( \degree \). After the reaction was complete, the excess reagent was decomposed with 5N HCl solution (95 mL) and organic solvent was evaporated off \textit{in vacuo} to give acidic aqueous solution. The solution was made alkaline with 10% NaOH solution and extracted three times with CH\(_2\)Cl\(_2\). The extract was washed with water, dried and solvent was evaporated off to give a residue, which was recrystallized from MeOH : Et\(_2\)O (1 : 1) to give colorless needles (3), mp 177.5 ~ 179.5 \( \degree \)C (4.03 g, 92.4 %). \( \left[ \alpha \right]_D^2 = 1.03 \degree \) (c=0.523, CHCl\(_3\)). \( ^1 \)H-NMR (CDCl\(_3\)) : 1.91 (3H, d, \( J = 6.6 \) Hz, -CHCH\(_3\)), 2.88 (2H, t, \( J = 7.9 \) Hz, -CH\(_2\)CH\(_3\)N-), 3.27 (2H, m, -CH\(_2\)CH\(_3\)N-), 3.77 (3H, s, -OCH\(_3\)) 4.22 (1H, q, \( J = 6.6 \) Hz, -CHCH\(_3\)), 5.00 (2H, s, -OCH\(_2\)Ph), 6.82 (1H, s, 3-H or 6-H), 6.89
(1H, s, 3-H or 6-H), 7.23-7.62 (10H, m, arom. H). EIMS (70 eV) m/z (rel. int. %): 440 ([M+1]^+ , 0.5), 360 (27.0), 306 (5.1), 228 (6.1), 134 (64.0), 105 (100), 91 (52.7). IR (cm\(^{-1}\)): 3010, 1613, 1503, 1244.

Anal. Calcd for C\(_{24}\)H\(_{27}\)NO\(_2\)BrCl: C, 60.45; H, 5.71; N, 2.94. Found: C, 60.50; H, 5.76; N, 2.94.

N-[2-(5-Benzoyloxy-2-bromo-4-methoxyphenyl)ethyl]-N-[\((S)-1\)-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (4)

To a mixture of 3 (2.47 g, 5.60 mmol) and 5% Na\(_2\)CO\(_3\) solution (100 mL, 0.050 mol) in Et\(_2\)O (100 mL) was added dropwise the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid (2.0 g, 7.28 mmol) in dry ether (25 mL) with vigorous stirring at 10-15 ºC. After stirring was continued for 2 h at same temperature, the Et\(_2\)O layer was separated. The organic layer was washed with water, dried, and evaporated to dryness leaving a colorless oil, whose column chromatography on silica gel with CHCl\(_3\) – acetone (10 : 1) gave a colorless oil (4), showing a single spot on TLC, \(R_f\) = 0.56, CHCl\(_3\) – acetone (5 : 1) (3.37g, 79.7%). EIMS (20 eV) \(m/z\) (rel. int. %): 695 (M^+ , 2.8), 616 (94.7), 537 (6.7), 319 (4.6), 240 (15.7), 105 (10.3), 91 (14.0). HREIMS \(m/z\) 695.0880 (Calcd for C\(_{34}\)H\(_{35}\)N\(_2\)O\(_5\)Br\(_2\), 695.0882). IR (cm\(^{-1}\)): 3000, 1630 (C=O), 1495, 1250.

N-[2-(2-Bromo-5-hydroxy-4-methoxyphenyl)ethyl]-N-[\((S)-1\)-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (5)

To a solution of 4 (3.37 g, 4.83 mmol) in dry benzene (38 mL) was added dropwise SnCl\(_4\) (2.0 g, 7.73 mmol) in dry benzene (10 mL) at 5-8 ºC with stirring. After the reaction mixture was continuously stirred for 4 h at rt, ice water was poured into the reaction mixture carefully. The mixture was made alkaline with 10% NH\(_4\)OH solution and a resulting precipitation was removed by filtration. The filtrate was extracted with ether. The ether solution was extracted with 25% KOH solution. After the KOH solution was treated with NH\(_4\)Cl, extracted with CH\(_2\)Cl\(_2\). The extract was treated by the usual method and gave a powder. The powder was recrystallized from EtOH to give colorless prisms (5), mp 82.0-84.0 ºC (0.33 g, 11.35 %). EIMS (20 eV) m/z (rel. int. %): 695 (M\(^+\), 15.6), 616 (94.7), 537 (6.7), 319 (4.6), 240 (15.7), 105 (10.3), 91 (14.0). HREIMS \(m/z\) 695.0880 (Calcd for C\(_{34}\)H\(_{35}\)NO\(_3\)Br, 695.0882). IR (cm\(^{-1}\)): 3000, 1630 (C=O), 1495, 1250.
(5H, m, phenyl H, arom.H=3 or 6 or 3’-H). EIMS (20 eV) m/z (rel. int. %) : 605 (M⁺, 0.8), 528 (100), 448 (11.5), 231 (4.5), 105 (5.4). HREIMS m/z 605.0413 (Calcd for C₂₇H₂₉NO₅Br₂, 605.0413). IR (cm⁻¹) : 3510, 1625 (C=O), 1255.

5-Bromo-1-(2-bromo-4,5-dimethoxybenzyl)-8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (6)
The mixture of 5 (1.64 g, 2.70 mmol) and POCl₃ (5.0 mL, 5.40 mmol) in dry CH₃CN (41 mL) was stirred for 3.5 h at 75~80 °C. Evaporation of excess reagent and solvent left a yellow viscous residue, which was thoroughly washed with hexane. The residue (1.59 g) was used for the following reaction without purification. The residue showed a major spot on TLC, Rf = 0.32, CHCl₃ – acetone (1 : 1). To a solution of the residue (1.59 g) in MeOH (200 mL) was added gradually NaBH₄ (2.04 g, 0.054 mol) at –78 °C with stirring. The reaction mixture was continuously stirred for 2.5 h at the same temperature, excess of NaBH₄ was decomposed with 20% AcOH solution, and most of solvent was evaporated to dryness in vacuo leaving a residue. The residue was made alkaline with 10% NH₄OH solution and extracted with CH₂Cl₂. The extract was evaporated to dryness leaving a powder. The powder was recrystallized from MeOH to give colorless prisms (6), mp 99.0~101.0 °C, (380 mg, 29.0 % from 4).

\[ \text{[d]D} = -0.79°(c=0.277, \text{CHCl}_3) \], optical isomer ratio = 47.2 : 52.8 [CHIRALCEL OD column (4.6 mm.ID. × 250mm), mobile phase : n-hexane / isopropyl alcohol = 70 / 30 (v/v) including 0.1 % diethylamine, flow rate : 0.5 ml/min, detection : 250 nm]. ¹H-NMR (CDCl₃) \[ \delta \] : 2.67 (1H, m, \( J_1 =17.1 \) Hz, \( J_2 =10.7 \) Hz, \( J_3 =6.4 \) Hz), 2.74 (1H, m, \( J_1 =17.1 \) Hz, \( J_2 =10.7 \) Hz, \( J_3 =4.7 \) Hz), 3.04 (1H, m, \( J_1 =12.4 \) Hz, \( J_2 =6.4 \) Hz, \( J_3 =2.1 \) Hz), 3.12 (1H, dd, \( J_1 =14.1 \) Hz, \( J_2 =10.3 \) Hz), 3.23 (1H, dd, \( J_1 =14.1 \) Hz, \( J_2 =3.0 \) Hz), 3.33 (1H, m, \( J_1 =12.4 \) Hz, \( J_2 =10.7 \) Hz, \( J_3 =4.7 \) Hz), 3.86 (3H, s, 5’-OCH₃), 3.86 (3H, s, 7-OCH₃ or 4’-OCH₃), 3.87 (3H, s, 7-OCH₃ or 4’-OCH₃), 4.47 (1H, dd, \( J_1 =10.3 \) Hz, \( J_2 =3.0 \) Hz), 6.93 (1H, s, 6’-H), 7.00 (1H, s, 6-H or 3’-H), 7.02 (1H, s, 6-H or 3’-H). EIMS (70 eV) m/z (rel. int. %): 485 (M⁺, 0.1), 406 (1.3), 390 (0.6), 376 (0.4), 256 (100), 177 (6.4). HREIMS m/z 484.9821 (Calcd for C₁₉H₂₁NO₄Br₂, 484.9837). IR (cm⁻³): 2920,1478,1250.

Detections of styrene and 1-chloroethylbenzene
The Bischler-Napieralski reaction mixture of 5 with POCl₃ in dry CH₃CN was checked with GCMS at the end of reaction. Styrene and 1-chloroethylbenzene were detected as follows.

Styrene: GCMS (60~200 °C, 3 °C/min), \( t_R =4.20 \) min, (70 eV) m/z : 104 (M⁺), 78 (M⁺–CH=CH₂).

1-Chloroethylbenzene: GCMS (60~200 °C, 3 °C/min), \( t_R =11.70 \) min, (70 eV) m/z : 140 (M⁺), 105 (M⁺–Cl).

ACKNOWLEDGMENT
We are grateful to the staff of the instrumental analysis center of our Universities for ¹H-NMR, MS,
GCMS and elemental analyses measurements.

REFERENCES AND NOTES
9 A phenolic acetamide derivative was subjected to the Bischler-Napieralski cyclization to give corresponding the 3,4-dihydroisoquinoline derivative which was converted into 1,2,3,4-tetrahydroisoquinoline derivative by treatment with NaBH₄. (see reference 4h)