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

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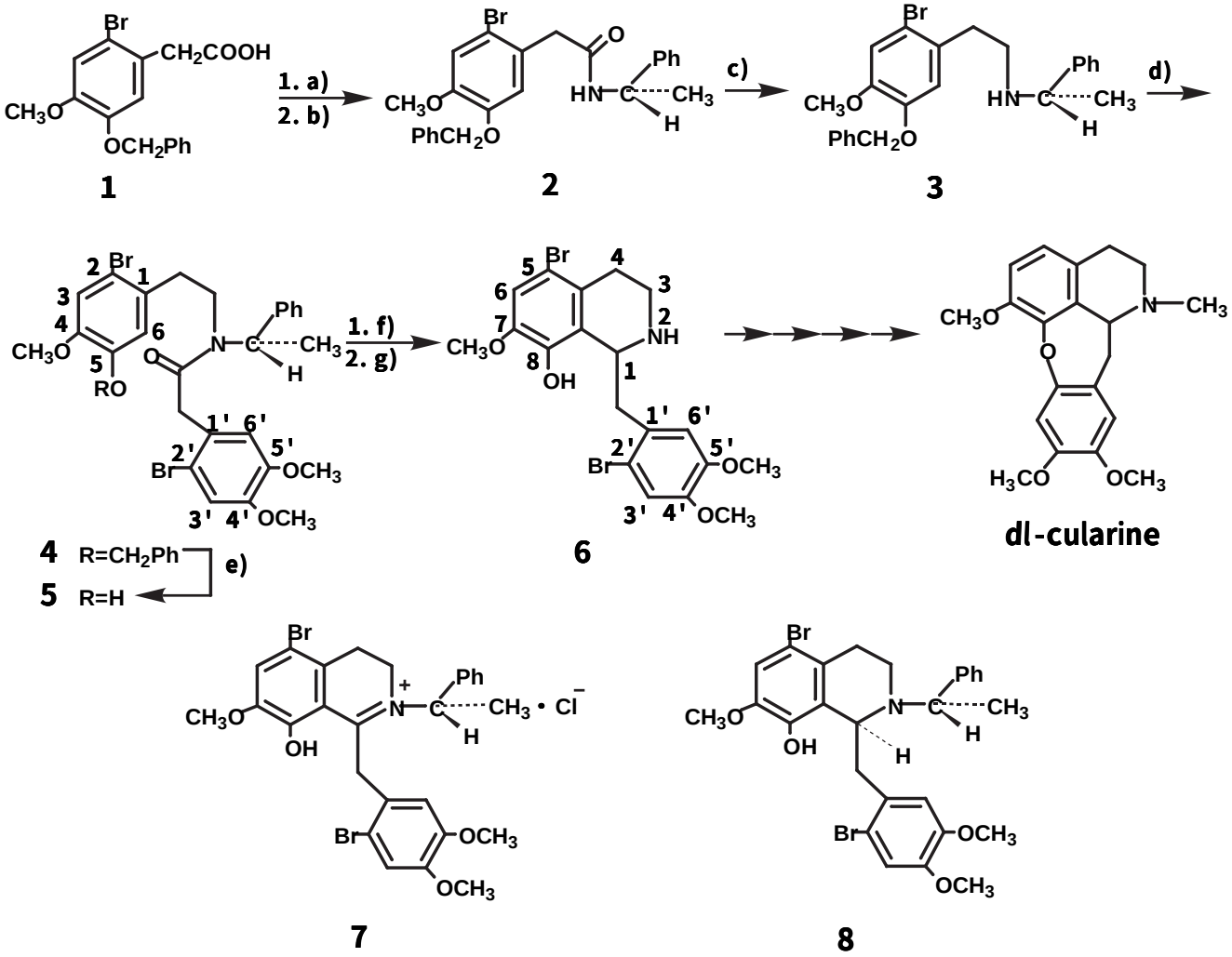
Abstract – *N*-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl] -*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**5**) was cyclized under *N*-dealkylation at the 2-position to the racemic 1-benzyl-1,2,3,4 -tetrahydroisoquinoline derivatives (**6**) by the Bischler-Napieralski cyclization followed by $NaBH_4$ reduction (Polniaszek's method).

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)[1] of the *N*-[2-(phenyl)ethyl]-2-phenylacetamides bearing an appropriate chiral auxiliary such as (*S*)-1-phenylethyl group on the nitrogen atom.[2] In the course of our studies, we have attempted a total synthesis of natural (*S*)-(+)-cularine[3,4] *via* *N*-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-*N*-[(*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 (*S*)-(+)- cularine from **5** by the Polniaszek's method and unexpected racemization during the reactions.

RESULTS AND DISCUSSION

The optically active key intermediate, *N*-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**5**), was prepared starting from 5-benzyloxy-2-bromo-4-methoxyphenylacetic acid (**1**)[5] as shown in Scheme 1. Treatment of the acid chloride of **1** with (*S*)-(–)- α -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- Et_2O complex to give the amine (**3**), which was



a) $SOCl_2$ b) (*S*)-(-)-α-phenylethylamine, Na_2CO_3 c) $BF_3 \cdot Et_2O$ / $BH_3 \cdot THF$
d) 2-bromo-4,5-dimethoxyphenylacetic acid chloride, Na_2CO_3 e) $SnCl_4$ f) $POCl_3$ g) $NaBH_4$

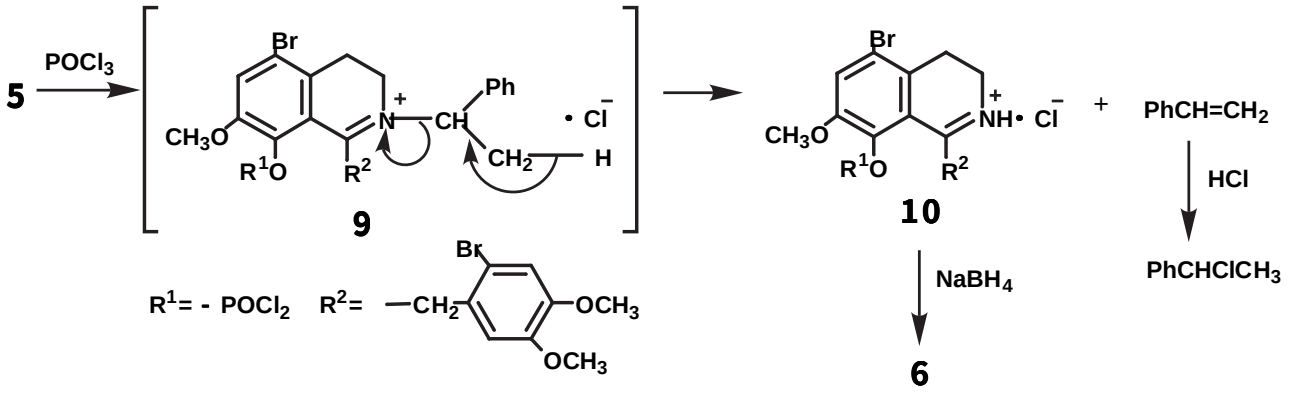
Scheme 1

condensed with the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid[6] to yield the acetamide (**4**).[4h] The optically active phenolic acetamide (**5**) for the cyclization was obtained by deprotection of the benzyloxy group of **4** with $SnCl_4$. 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 (1*S*)-1-benzyltetrahydroisoquinoline (**8**) *via* the iminium ion (**7**) through the Polniaszek's method.

Thus, treatment of the phenolic acetamide (**5**) with $POCl_3$ in dry CH_3CN under the Bischler-Napieralski cyclization conditions afforded a viscous substance.[9] The substance, without any purification, was treated with $NaBH_4$ in MeOH at –78 ℃ according to the Polniaszek's method to afford colorless prisms, mp 99 ～101℃. 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 ° 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.



Scheme 2 Proposed mechanism for the formation of the racemic tetrahydroisoquinoline (**6**)

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*)-1-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.

***N*-[(*S*)-1-Phenylethyl]-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)acetamide (2)**

To a mixture of (*S*)-(-)-α-phenylethylamine (2.84 mL, 0.022 mol) and 5% Na_2CO_3 solution (100 mL, 0.050 mol) in Et_2O (100 mL) was added dropwise the acid chloride of 5-benzyloxy-2-bromo-4-methoxyphenylacetic acid (**1**) (mp 147.5～149.5 ℃) (7.02 g, 0.020 mol) in dry Et_2O (25 mL) with vigorous stirring at 10～15℃. 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 ℃ (8.76 g, 96.7 %). $[\alpha]_D$: -2.66 ° (c=0.432, $CHCl_3$). ^{1}H-NMR($CDCl_3$) δ : 1.40 (3H, d, *J*=7.3 Hz, -CHC<u>H</u>$_3$), 3.58 (2H, s, -CH_2CO-), 3.87 (3H, s, -OCH_3), 5.07 (2H, s, -OC<u>H</u>$_2$Ph), 5.11 (1H, q, *J*=7.3 Hz, -C<u>H</u>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 $C_{24}H_{24}NO_3Br$: C, 63.44 ; H, 5.32 ; N, 3.08. Found : C, 63.40 ; H, 5.34 ; N, 3.08.

***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_2O 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 ℃ with stirring, and the mixture was further heated for 2.5 h at 70 ℃. After the reaction was complete, the excess reagent was decomposed with 5N HCl solution (95 mL) and organic solvent was evaporated off *in vacuo* to give acidic aqueous solution. The solution was made alkaline with 10% NaOH solution and extracted three times with CH_2Cl_2. The extract was washed with water, dried and solvent was evaporated off to give a residue, which was recrystallized from MeOH : Et_2O (1 : 1) to give colorless needles (**3**), mp 177.5～179.5 ℃ (4.03 g, 92.4 %). $[\alpha]_D$: -31.03 ° (c=0.523, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.91 (3H, d, *J*=6.6 Hz, -CHC<u>H</u>$_3$), 2.88 (2H, t, *J*=7.9 Hz, -C<u>H</u>$_2$$CH_2$N-), 3.27 (2H, m, -$CH_2$C<u>H</u>$_2$ N-), 3.77 (3H, s, -OCH_3), 4.22 (1H, q, *J*=6.6 Hz, -C<u>H</u>CH_3), 5.00 (2H, s, -OC<u>H</u>$_2$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 $C_{24}H_{27}NO_2BrCl$: C, 60.45 ; H, 5.71 ; N, 2.94. Found: C, 60.50 ; H, 5.76 ; N, 2.94.

***N*-[2-(5-Benzyloxy-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_2CO_3 solution (100 mL, 0,050 mol) in Et_2O (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 ℃. After stirring was continued for 2 h at same temperature, the Et_2O 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（v／v）］gave a colorless oil (**4**), showing a single spot on TLC, *Rf* = 0.56, $CHCl_3$ – acetone （5 : 1） (3.37g, 79.7%). ［α］$_D$: –25.40 ° (c=0.668, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.36 (3H×0.55, d, *J*=6.8 Hz, -CHC$\underline{H}_3$), 1.50 (3H×0.45, d, *J*=7.3 Hz, -CHC$\underline{H}_3$), 2.08 (1H×0.45, m, -C$\underline{H}_a$H$_b$CH$_2$N-), 2.27 (1H×0.55, m, -C$\underline{H}_a$H$_b$CH$_2$N-), 2.50 (1H×0.45, m, -CH$_a\underline{H}_b$CH$_2$N-), 2.6 8(1H×0.55, m, -CH$_a\underline{H}_b$CH$_2$N-), 3.16 (2H, m, -CH$_2$C$\underline{H}_2$N-), 3.78 (3H, s, 4-OCH$_3$ or 4'-OCH$_3$ or 5'-OCH$_3$), 3.79 (3H, s, 4-OCH$_3$ or 4'-OCH$_3$ or 5'-OCH$_3$), 3.88 (3H, s, 4-OCH$_3$ or 4'-OCH$_3$ or 5'-OCH$_3$), 4.96～5.04 (2H, m, -CH$_2$CO-), 5.06 (2H, s, -OC$\underline{H}_2$Ph), 5.22 (1H×0.55, q, *J*=6.8 Hz, -C$\underline{H}$CH$_3$), 6.04 (1H×0.45, q, *J*=6.8 Hz, -C$\underline{H}$CH$_3$), 6.26～7.09 (4H, m, arom. H), 7.22～7.40 (10H, m, arom. H). 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 $C_{34}H_{35}NO_5Br_2$, 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 ℃ 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_4OH 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_4Cl, extracted with CH_2Cl_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 ℃ (0.33 g, 11.35 %). ［α］$_D$: –47.15 ° (c=0.545, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.56 (3H×0.45, d, *J*=6.8 Hz, -CHC$\underline{H}_3$), 1.62 (3H×0.55, d, *J*=6.8 Hz, -CHC$\underline{H}_3$), 2.38～3.40 (4H, m, -C$\underline{H}_2$C$\underline{H}_2$N-), 3.82～3.88 (9H, s×6 signals, -OCH$_3$×3), 3.82～3.99 (2H, m, -COCH$_2$-), 5.18 (1H×0.45, q, *J*=6.8 Hz, -C$\underline{H}$CH$_3$), 6.10 (1H×0.55, q, *J*=6.8 Hz, -C$\underline{H}$CH$_3$), 6.47 (1H×0.55, s, 6'-H), 6.75 (1H×0.45, s, 6'-H), 6.84 (1H×0.55, s, one of arom. H), 6.89 (1H×0.45, s, one of arom. H), 6.92 (1H×0.55, s, one of arom. H), 6.95 (1H×0.45, s, one of arom. H), 7.04 (1H×0.45, s , one of arom. H), 7.05 (1H×0.55, s, one of arom. H), 7.20～7.44

(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 $C_{27}H_{29}NO_5Br_2$, 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 $POCl_3$ (5.0 mL, 5.40 mmol) in dry CH_3CN (41 mL) was stirred for 3.5 h at 75～80 ℃. 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, $CHCl_3$ – acetone（1 : 1）. To a solution of the residue (1.59 g) in MeOH (200 mL) was added gradually $NaBH_4$ (2.04 g, 0.054 mol) at –78 ℃ with stirring. The reaction mixture was continuously stirred for 2.5 h at the same temperature , excess of $NaBH_4$ 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% NH_4OH solution and extracted with CH_2Cl_2. 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 ℃, (380 mg, 29.0 % from **4**). $[\alpha]_D$: –0.79°(c=0.277, $CHCl_3$). optical isomer ratio ＝ 47.2 : 52.8 [CHIRALCEL OD column (4.6 mmI.D. × 250mml), mobile phase : *n*-hexane／isopropyl alcohol = 70／30（v／v）including 0.1 % diethylamine, flow rate : 0.5 ml／min , detection : 250 nm]. ^{1}H-NMR ($CDCl_3$) δ : 2.67 (1H, m, J_1=17.1 Hz, J_2=10.7 Hz, J_3=6.4 Hz, -C<u>H</u>$_2$CH$_2$N-), 2.74 (1H, m, J_1=17.1 Hz, J_2=4.7 Hz, J_3=2.1 Hz, -C<u>H</u>$_2$CH$_2$N-), 3.04 (1H, m, J_1=12.4 Hz, J_2=6.4 Hz, J_3=2.1 Hz, -CH$_2$C<u>H</u>$_2$N-), 3.12 (1H, dd, J_1=14.1 Hz, J_2=10.3 Hz, -C<u>H</u>$_2$CH-), 3.23 (1H, dd, J_1=14.1 Hz, J_2=3.0 Hz, -C<u>H</u>$_2$CH-), 3.33 (1H, m, J_1=12.4 Hz, J_2=10.7 Hz, J_3=4.7 Hz, -CH$_2$C<u>H</u>$_2$N-), 3.86 (3H, s, 5'-OCH_3), 3.86 (3H, s, 7-OCH_3 or 4'- OCH_3), 3.87 (3H, s, 7-OCH_3 or 4'-OCH_3), 4.47 (1H, dd, J_1=10.3 Hz, J_2=3.0 Hz, -CH$_2$C<u>H</u>-), 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 $C_{19}H_{21}NO_4Br_2$, 484.9837). IR (cm^{-1}): 2920,1478, 1250.

Detections of styrene and 1-chloroethylbenzene

The Bischler-Napieralski reaction mixture of **5** with $POCl_3$ in dry CH_3CN was checked with GCMS at the end of reaction. Styrene and 1-chloroethylbenzene were detected as follows.

Styrene: GCMS (60～200℃, 3℃/min), t_R =4.20 min, (70 eV) *m/z* : 104 (M^+), 78 (M^+– CH=CH$_2$).

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

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GCMS and elemental analyses measurements.

REFERENCES AND NOTES

1 a) R. P. Polniaszek and J. A. McKee, *Tetrahedron Lett*., 1987, **28**, 4511. b) R. P. Polniaszek, *J. Chem. Educ*., 1989, **66**, 970. c) T. Kametani and T .Okawara, *J. Chem. Soc. , Perkin Trans*. 1, 1977, 579.

2 a) K. Komori, K. Takaba, and J. Kunitomo, *Heterocycles*, 1996, **43**, 1681. b) K. Takaba, K. Komori, J. Kunitomo, and T. Ishida, *ibid.,* 1996, **43**, 1777. c) K. Takaba, J. Haginaka, J. Kunitomo, and T. Shingu, *ibid.,* 1997, **45**, 1111. d) K. Takaba and J. Kunitomo, *YAKUGAKU ZASSHI*, 1997, **117**, 555. e) A. Watanabe and J. Kunitomo, *Heterocycles*, 1998, **48**, 1623.

3 J. Kunitomo, K. Morimoto, K. Yamamoto, Y. Yoshikawa, K. Azuma, and K. Fujitani, *Chem. Pham. Bull*., 1971, **19**, 2197.

4 Syntheses of *dl*-cularine were reported. a) T. Kametani and K .Fukumoto, *J. Chem. Soc*., 1963, 4289. b) T. Kametani, S. Shibuya, and C. Kibayashi, *Tetrahedron Lett*., 1966, 3215. c) S. Ishiwatari, T. Fujii, N. Miyaji, Y. Satoh, and K. Itakura, *Chem. Pham. Bull*., 1970, **18**, 1850. d) A. H. Jackson and G. W. Stewart, *Chem. Comm*., 1971, 149. e) T. Kametani, K. Fukumoto, and M. Fujihara, *Bioorg. Chem*., 1971, **1**, 40. f) T. Kametani, K .Fukumoto, and M. Fujihara, *Chem. Commun*., 1971, 352. g) H. C. Hsu, T. Kikuchi, S. Aoyagi, and H. Iida., *YAKUGAKU ZASSHI*, 1972, **92**, 1030. h) H. Iida, H.- C. Hsu, and T. Kikuchi, *Chem. Pharm. Bull*., 1973, **21**, 1001. i) I. Noguchi and D. B. MacLean, *Can. J. Chem*.,1975, **53**, 125. j) A. H. Jackson, G. W. Stewart, G. A. Charnock, and J. A. Martin, *J. Chem. Soc. ,Perkin Trans*. 1, 1984, 2283.

5 A. H. Jackson and J. A. Martin, *J. Chem. Soc. C*, 1966, 2061.

6 T. Kametani, K. Fukumoto, S. Shibuya, and T. Nakano, *Chem. Pharm. Bull*., 1963, **11**,1299.

7 The acetamides (**4**, **5**) were constituted of two rotational isomers with respect to amide group. H. Ishii, T. Ishikawa, T. Watanabe, Y. Ichikawa, and E. Kawanabe, *J. Chem. Soc. , Perkin Trans*. 1, 1984, 2283.

8 L. Guerrier, J. Royer, D. S. Grierson, and H-P . Husson, *J. Am. Chem. Soc*., 1983, **105**, 7754. N. Magigrot, J-P. Mazaleyrat, and Z. Welvart, *J. Chem. Soc., Chem. Commun*., 1984, 40.

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 $NaBH_4$. (see reference 4h)