

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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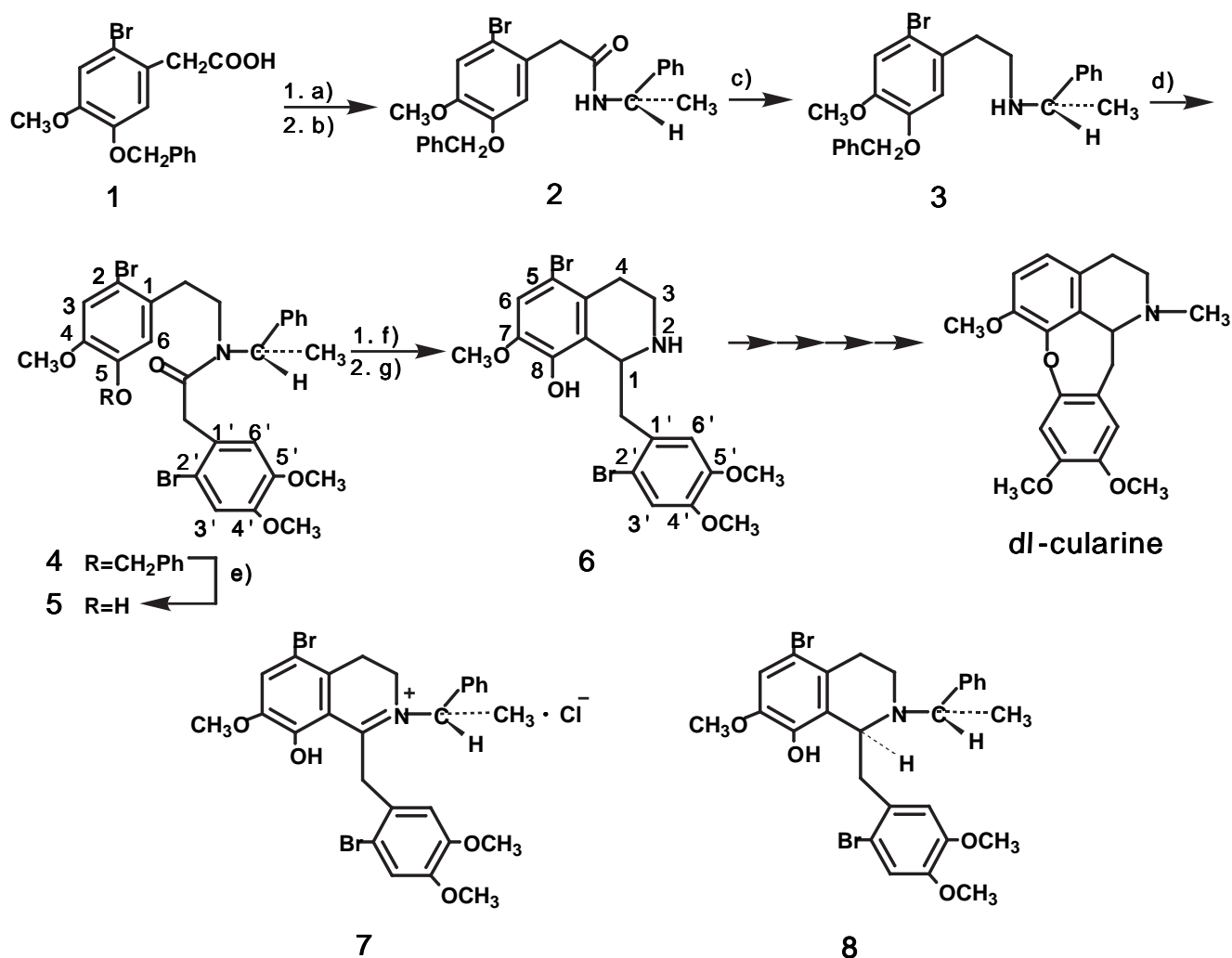
Abstract – *N*-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**5**) was cyclized under *N*-dealkylation at the 2-position to the racemic 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives (**6**) by the Bischler-Napieralski cyclization followed by NaBH₄ reduction (Polniaszek's method).

INTRODUCTION

We have reported total syntheses of several chiral 1-benzyltetrahydroisoquinoline alkaloids through the Bischler-Napieralski cyclization followed by stereoselective NaBH₄ 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*)-(-)-1-phenylethylamine afforded the optically active amide (**2**) in excellent yield. The amide (**2**) was reduced with BH₃-THF complex in the presence of BF₃-Et₂O complex to give the amine (**3**), which was



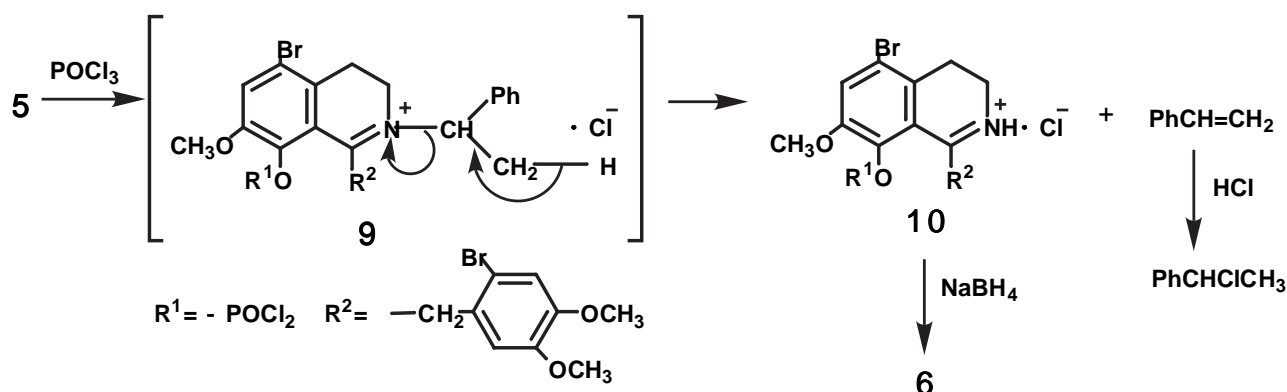
Scheme 1

condensed with the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid⁶ 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 ¹H-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°C according to the Polniaszek's method to afford colorless prisms, mp $99 \sim 101^\circ\text{C}$. 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 $^1\text{H-NMR}$ 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 cleaved 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. ¹H-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 CHCl₃ 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 MgSO₄. 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 ¹H-NMR spectra.

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

To a mixture of (*S*)-(-)-phenylethylamine (2.84 mL, 0.022 mol) and 5% Na₂CO₃ solution (100 mL, 0.050 mol) in Et₂O (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 Et₂O (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 %). [α]_D: -2.66 ° (c=0.432, CHCl₃). ¹H-NMR(CDCl₃) : 1.40 (3H, d, *J*=7.3 Hz, -CHCH₃), 3.58 (2H, s, -CH₂CO-), 3.87 (3H, s, -OCH₃), 5.07 (2H, s, -OCH₂Ph), 5.11 (1H, q, *J*=7.3 Hz, -CHCH₃), 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 C₂₄H₂₄NO₃Br : 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 BF₃- Et₂O complex (abt. 47 %, 1.5 mL, 0.050 mol) and 1.0 M BH₃- 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 CH₂Cl₂. The extract was washed with water, dried and solvent was evaporated off to give a residue, which was recrystallized from MeOH : Et₂O (1 : 1) to give colorless needles (**3**), mp 177.5 ~ 179.5 ° (4.03 g, 92.4 %). [α]_D: -31.03 ° (c=0.523, CHCl₃). ¹H-NMR (CDCl₃) : 1.91 (3H, d, *J*=6.6 Hz, -CHCH₃), 2.88 (2H, t, *J*=7.9 Hz, -CH₂CH₂N-), 3.27 (2H, m, -CH₂CH₂N-), 3.77 (3H, s, -OCH₃), 4.22 (1H, q, *J*=6.6 Hz, -CHCH₃), 5.00 (2H, s, -OCH₂Ph), 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 $\text{C}_{24}\text{H}_{27}\text{NO}_2\text{BrCl}$: 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, $R_f = 0.56$, CHCl_3 – acetone (5 : 1) (3.37g, 79.7%). $[\alpha]_D^{25}$: -25.40° ($c=0.668$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) : 1.36 (3H \times 0.55, d, $J=6.8$ Hz, $-\text{CHCH}_3$), 1.50 (3H \times 0.45, d, $J=7.3$ Hz, $-\text{CHCH}_3$), 2.08 (1H \times 0.45, m, $-\text{CH}_a\text{H}_b\text{CH}_2\text{N-}$), 2.27 (1H \times 0.55, m, $-\text{CH}_a\text{H}_b\text{CH}_2\text{N-}$), 2.50 (1H \times 0.45, m, $-\text{CH}_a\text{H}_b\text{CH}_2\text{N-}$), 2.68 (1H \times 0.55, m, $-\text{CH}_a\text{H}_b\text{CH}_2\text{N-}$), 3.16 (2H, m, $-\text{CH}_2\text{CH}_2\text{N-}$), 3.78 (3H, s, 4-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.79 (3H, s, 4-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.88 (3H, s, 4-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 4.96 ~ 5.04 (2H, m, $-\text{CH}_2\text{CO-}$), 5.06 (2H, s, $-\text{OCH}_2\text{Ph}$), 5.22 (1H \times 0.55, q, $J=6.8$ Hz, $-\text{CHCH}_3$), 6.04 (1H \times 0.45, q, $J=6.8$ Hz, $-\text{CHCH}_3$), 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 $\text{C}_{34}\text{H}_{35}\text{N}\text{O}_5\text{Br}_2$, 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 ° 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 %). $[\alpha]_D^{25}$: -47.15° ($c=0.545$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3) : 1.56 (3H \times 0.45, d, $J=6.8$ Hz, $-\text{CHCH}_3$), 1.62 (3H \times 0.55, d, $J=6.8$ Hz, $-\text{CHCH}_3$), 2.38 ~ 3.40 (4H, m, $-\text{CH}_2\text{CH}_2\text{N-}$), 3.82 ~ 3.88 (9H, s \times 6 signals, $-\text{OCH}_3 \times 3$), 3.82 ~ 3.99 (2H, m, $-\text{COCH}_2-$), 5.18 (1H \times 0.45, q, $J=6.8$ Hz, $-\text{CHCH}_3$), 6.10 (1H \times 0.55, q, $J=6.8$ Hz, $-\text{CHCH}_3$), 6.47 (1H \times 0.55, s, 6'-H), 6.75 (1H \times 0.45, s, 6'-H), 6.84 (1H \times 0.55, s, one of arom. H), 6.89 (1H \times 0.45, s, one of arom. H), 6.92 (1H \times 0.55, s, one of arom. H), 6.95 (1H \times 0.45, s, one of arom. H), 7.04 (1H \times 0.45, s, one of arom. H), 7.05 (1H \times 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 °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, $R_f = 0.32$, $CHCl_3 - acetone$ (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 °C 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 °C, (380 mg, 29.0 % from **4**). $[\alpha]_D^{25}$: -0.79°(c=0.277, $CHCl_3$). optical isomer ratio = 47.2 : 52.8 [CHIRALCEL OD column (4.6 mmI.D. × 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 ($CDCl_3$) : 2.67 (1H, m, $J_1=17.1$ Hz, $J_2=10.7$ Hz, $J_3=6.4$ Hz, $-CH_2CH_2N-$), 2.74 (1H, m, $J_1=17.1$ Hz, $J_2=4.7$ Hz, $J_3=2.1$ Hz, $-CH_2CH_2N-$), 3.04 (1H, m, $J_1=12.4$ Hz, $J_2=6.4$ Hz, $J_3=2.1$ Hz, $-CH_2CH_2N-$), 3.12 (1H, dd, $J_1=14.1$ Hz, $J_2=10.3$ Hz, $-CH_2CH-$), 3.23 (1H, dd, $J_1=14.1$ Hz, $J_2=3.0$ Hz, $-CH_2CH-$), 3.33 (1H, m, $J_1=12.4$ Hz, $J_2=10.7$ Hz, $J_3=4.7$ Hz, $-CH_2CH_2N-$), 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, $-CH_2CH-$), 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 °C, 3 °C/min), $t_R = 4.20$ min, (70 eV) m/z : 104 (M^+), 78 ($M^+ - CH=CH_2$).

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

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