

BISCHLER-NAPIERALSKI REACTION OF *N*-[2-(2-BROMO-4,5-DIALKOXYPHENYL)ETHYL]-*N*-(1-PHENYLETHYL)-2-(2-BROMO-4,5-DIMETHOXYPHENYL)ACETAMIDES

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Abstract – Direction of Bischler-Napieralski reaction of *N*-[2-(2-bromo- or 2-unsubstituted 4,5-dialkoxyphenyl)ethyl]-*N*-(1-phenylethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamides is discussed.

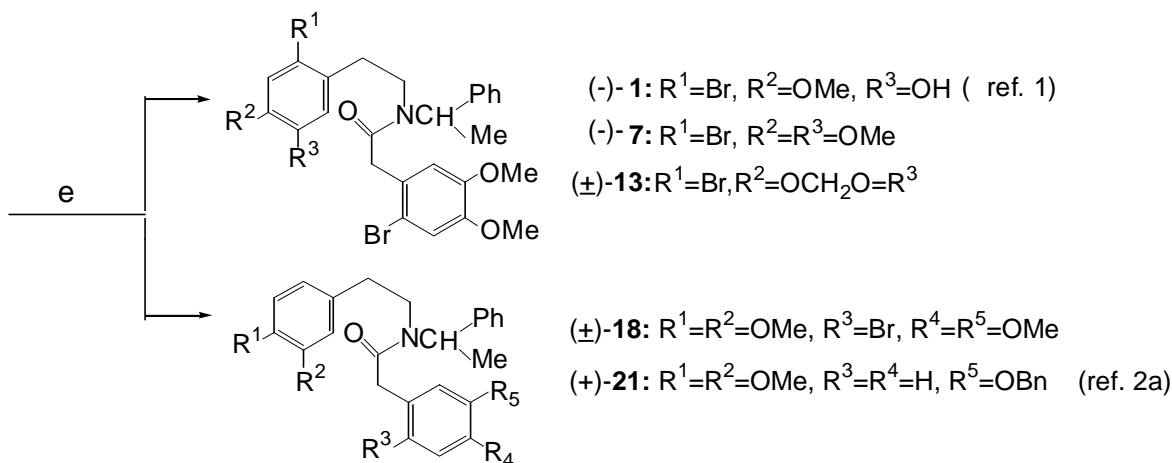
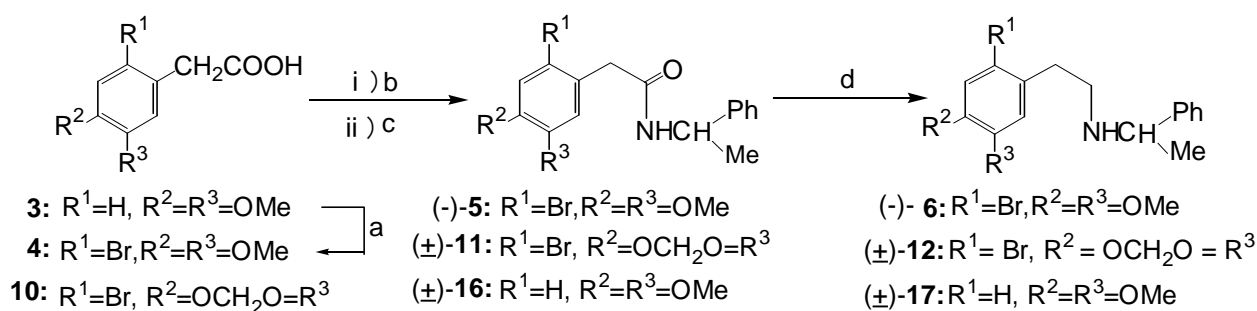
INTRODUCTION

We have reported that *N*-[2-(2-bromo-5-hydroxy-4-methoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**1**) afforded 5-bromo-1-(2-bromo-4,5-dimethoxybenzyl)-8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**2**) accompanied by cleavage of the chiral auxiliary under the Bischler-Napieralski (BN) reaction (Polniaszek's method)¹ (Schemes 1, 2). We have applied the BN reaction to several *N*-[2-(substituted phenyl)ethyl]-*N*-(1-phenylethyl)-2-(substituted phenyl)acetamide analogs in the course of our studies,² and found an unusual BN reaction on the carbon at 2-position of the A ring, where bears a bromine atom. In this paper, we mainly describe direction of the BN cyclization of several *N*-[2-(2-bromo- or 2-unsubstituted 4,5-dialkoxyphenyl)ethyl]-*N*-(1-phenylethyl)-2-(substituted phenyl)acetamides.

RESULTS AND DISCUSSION

N-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**7**) was prepared starting from 3,4-dimethoxyphenylacetic acid (**3**) as shown in Scheme 1. Bromination of the phenylacetic acid (**3**) gave selectively 2-bromo-4,5-dimethoxyphenyl acetic acid (**4**),³ and the acid chloride of **4** was treated with (*S*)-(-)-1-phenylethylamine to afford the amide (**5**), which was reduced with BH₃-THF complex in the present of BF₃-Et₂O complex to give the amine (**6**). The amine (**6**) was condensed with the acid chloride of **4** to afford the acetamide (**7**). Treatment of the acetamide (**7**) with POCl₃ in dry MeCN (BN reaction conditions) afforded an oily residue, which contained several products

to be detectable on thin layer chromatography (TLC). Styrene and 1-chloroethylbenzene in this reaction mixture were detected by gas liquid layer chromatographical (GLC) analysis. This suggested that the chiral auxiliary of the acetamide (**7**) was cleaved during the cyclization process as reported as previous papers.¹



a) Br_2 b) $SOCl_2$ c) *(S)*-(-)-1-phenylethylamine or *(±)*-1-phenylethylamine, Na_2CO_3 ;
 d) $BF_3 \cdot Et_2O$ / $BH_3 \cdot THF$ e) 2-bromo-4,5-dimethoxyacetic acid chloride, Na_2CO_3

Scheme 1

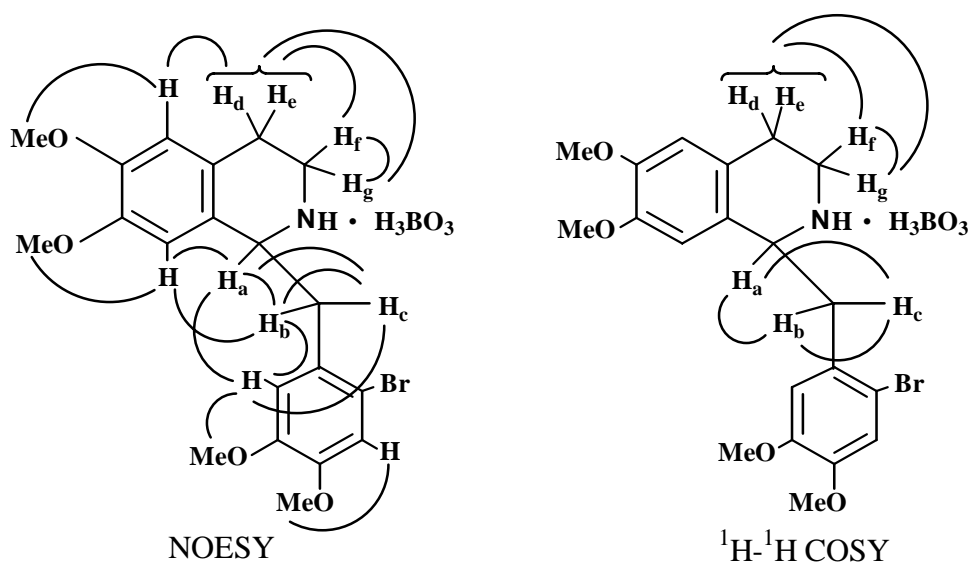
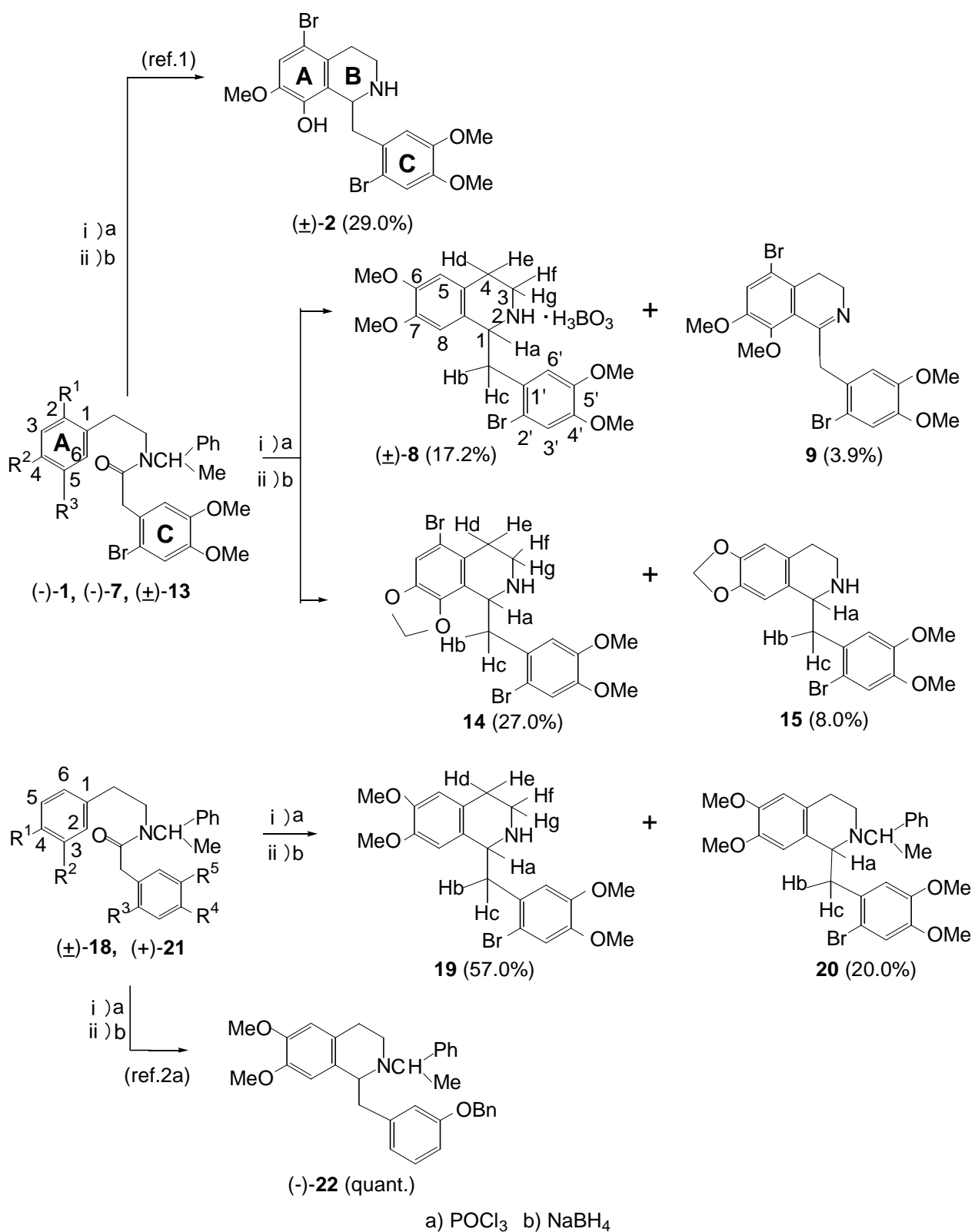


Figure 1 NOESY and $^1H-^1H$ COSY correlation of **8**



Scheme 2

The oily intermediate was treated without purification with NaBH₄ in MeOH at -78 °C to give two products, colorless needles ((±)-**8**, 17.2 %) and a pale yellow oil (**9**, 3.9 %), the structures of which were determined on the basis of ¹H-NMR (¹H-¹H COSY and NOESY) and MS spectrometries (Figure 1 and

Scheme 2).^{4,5} This result suggested that substituent groups at 2- and 5-position of **7** might be responsible for the unusual BN reaction. Further, we examined the unusual reaction using optically inactive acetamides (**13**, **18**). *N*-[2-(2-bromo-4,5-methylenedioxyphenyl)ethyl]-*N*-(1-phenylethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**13**) having a methylenedioxy group at 4,5-position was prepared starting from 2-bromo-4,5-methylenedioxyphenyl acetic acid (**10**)⁶ through **11** and **12** in the usual manner (Scheme 1). BN reaction of **13** proceeded faster than that of the acetamide (**7**) to afford a pale yellow oily product,⁷ which was treated with NaBH₄ to give two products, prisms (**14**, 27.0 %) and a colorless powder (**15**, 8.0 %). The structures of **14** and **15** were determined on the basis of ¹H-NMR (¹H-¹H COSY) and MS spectrometries (Scheme 2). Styrene and 1-chloroethylbenzene in this reaction mixture were also detected by GLC analysis. In the BN reaction of the acetamide (**13**) having a bromine atom at 2-position and a methylenedioxy group at 4,5-position of the A ring, the amide carbonyl carbon could mainly attack the carbon at 6-position to give the bromotetrahydroisoquinoline (**14**). These results indicate that steric hindrance of the alkoxy substituents at 5-position of the A ring may influence on the cyclization site and elimination of the chiral auxiliary. Stable conformation and negative electrostatic charge of the model compounds of **7** and **13** were calculated by the semi-empirical molecular orbital method (PM3)^{8,9} to examine difference of the reaction site of **7** and **13** (Figure 2).

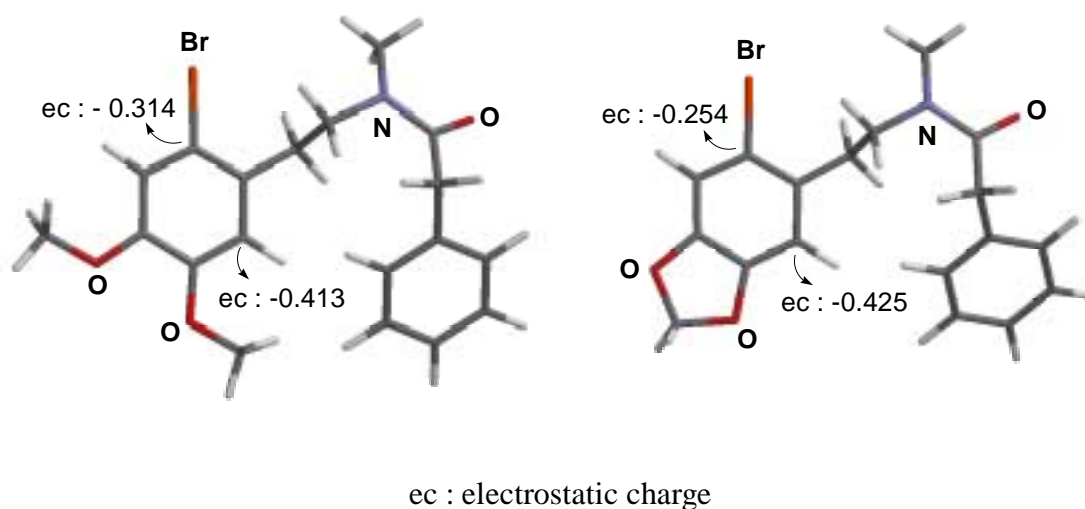


Figure 2 The Most Stable Structure for the Model Compound of **7** and **13**

In the case of **7**, approach of the amido carbonyl to the carbon at 2-position of the A ring might be favored rather than that of the 6-position because of steric hindrance by the 5-methoxy group in spite of more negative charge on carbon at 6-position (Figure 2). In the case of **13**, the amide carbonyl might attack to the carbon at 6-position easily because of no significant steric hindrance of the 4,5-methylenedioxy group as well as more electron richness (Figure 2). The acetamide (**18**) was prepared in the above-mentioned manner starting from 3,4-dimethoxyphenylacetic acid (**3**) through **16** and **17** in order to examine its

reactivity for BN reaction (Scheme 1). A crude product mixture obtained from the BN reaction of **18** was treated with NaBH₄ to give two products, needles (**19**, 57.0 %) and a yellow oil (**20**, 20.0 %), structures of which were determined by their ¹H-NMR and MS spectra (Scheme 2). ¹H-NMR (HMBC, ¹H-¹H COSY and NOESY) and ¹³C-NMR spectral data of **19** were shown in Figure 3. Styrene and 1-chloroethylbenzene were also detected in this reaction mixture.

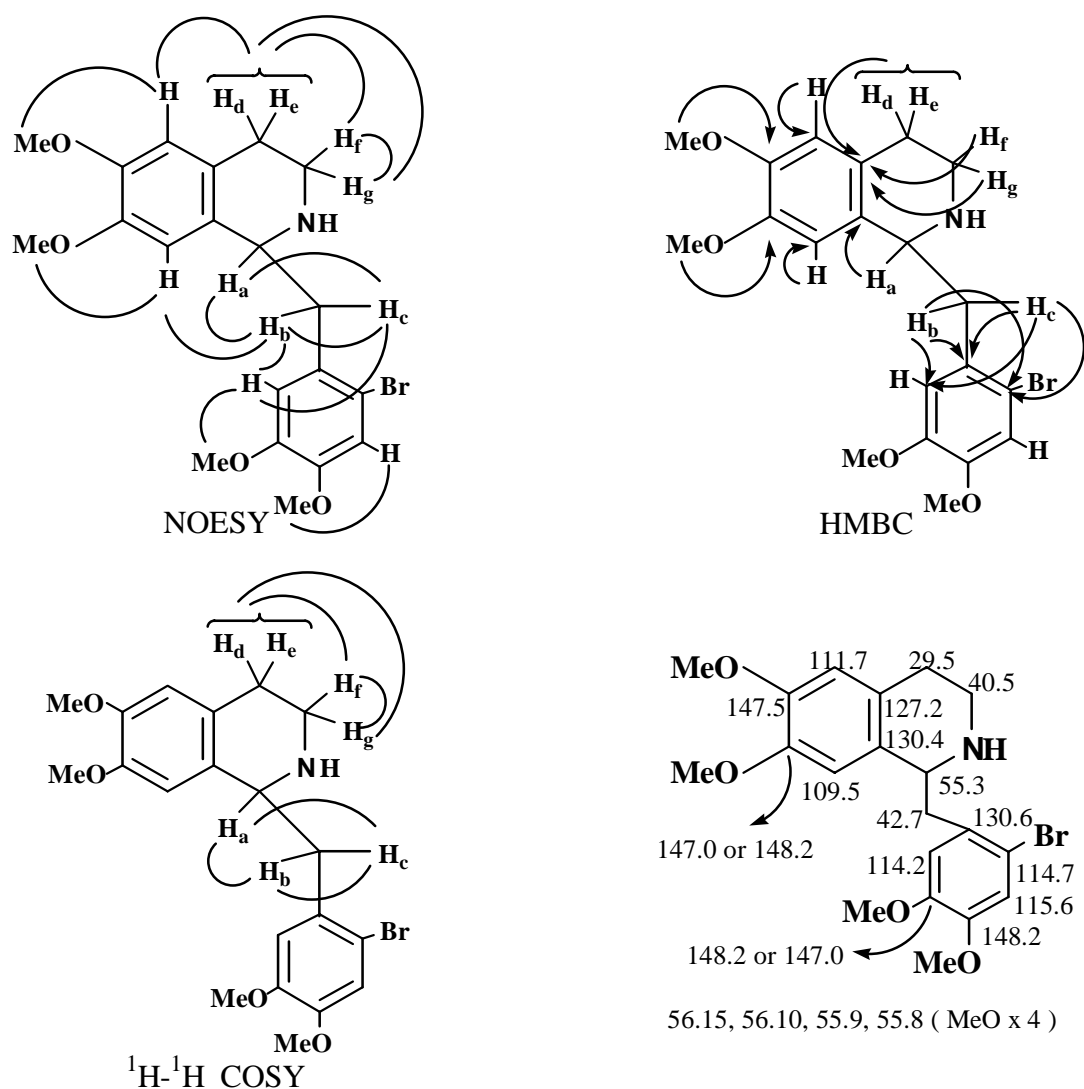


Figure 3 ¹H-NMR and ¹³C-NMR Spectral Data of **19**

This indicates that ring closure of the acetamide (**18**) proceeds smoothly on the carbon at 6-position where was unsubstituted with bromine atom than the cases of **7** and **13** but with some loss of the chiral auxiliary.¹⁰ In conclusion, it can be stated that direction (which 2- or 6-position of the A ring) of the BN reaction of *N*-[2-(2-bromo-4,5-dialkyloxyphenyl)ethyl]-*N*-(1-phenylethyl)-2-phenylacetamides may depend on the steric hindrance of substituent group at the 5-position. Ring closure at the 6-position is favored than that of the 2-position in the case of the acetamides without the significant steric hindrance.

While, bulky alkoxy group at the 5-position interferes the reaction at 6-position to force the cyclization at the 2-position accompanied by elimination of the bromine atom.¹¹

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. ¹³C-NMR and HMBC spectra were recorded on Varian UNITY IVOVA 400NB (¹H: 400 MHz, ¹³C: 100 MHz). 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). TLC was performed on a E. Merck silica gel plate (0.5 mm, 60F-254).

N-[(*S*)-1-Phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**5**)

To a mixture of (*S*)-(-)-phenylethylamine (7.66 mL, 0.059 mol) and 5 % aq. Na₂CO₃ solution (250 mL) in Et₂O (100 mL) was added dropwise the acid chloride of **4** (13.63 g, 0.050 mol) in dry Et₂O (25 mL) with vigorous stirring at 10 ~ 15 °. After stirring was continued for 3.5 h at same temperature, a result precipitate was collected by filtration. The precipitate was recrystallized from EtOH to give colorless needles (**5**), mp 141.0 ~ 142.0 ° (12.92 g, 68.9 %). [α]_D: - 0.2 ° (c = 0.438, CHCl₃). ¹H-NMR (CDCl₃) : 1.44 (3H, d, *J* = 6.8 Hz, -CHCH₃), 3.61 (1H, d, *J* = 15.8 Hz, one of -CH₂CO-), 3.65 (1H, d, *J* = 15.8 Hz, one of -CH₂CO-), 3.83 (3H, s, 4-OCH₃ or 5-OCH₃), 3.87 (3H, s, 4-OCH₃ or 5-OCH₃), 5.03 – 5.23 (1H, m, -CHCH₃), 5.70 (1H, d, *J* = 13.7 Hz, -NH-), 6.82 (1H, s, 3-H or 6-H), 7.03 (1H, s, 3-H or 6-H), 7.10 - 7.44 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %): 377 (M⁺, 7.0), 298 (100), 229 (44.9), 194 (93.2). IR (cm⁻¹) : 3400 (NH), 1660 (C=O), 1500. HREIMS *m/z* 377.0623 (Calcd for C₂₀H₁₈NO₃Br, 377.0627).

N-[(*S*)-1-Phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)ethylamine (**6**)

To a solution of **5** (12.73 g, 0.034 mol) in dry THF (160 mL) was carefully added dropwise BF₃-Et₂O complex (5.1 mL, 0.017 mol) and 1.0 M BH₃-THF complex (68 mL, 0.068 mol) under Ar atmosphere at 20 ~ 25 ° with stirring, and the mixture was further stirred for 2 h at 70 °. After the reaction was completed, the excess reagents were decomposed with 5 N HCl solution (120 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 with CH₂Cl₂. The extract was washed with water, and solvent was evaporated off to give a oil, whose column chromatography on silica gel with CHCl₃ gave a pale yellow

oil (**6**, 9.6 g, 78.0 %), showing a single spot on TLC (Silica Gel 60 F₂₅₄), *R_f* = 0.25, CHCl₃-AcOEt (10 : 1). [α]_D: -27.8° (c = 0.500, CHCl₃). ¹H-NMR (CDCl₃) : 1.36 (3H, d, *J* = 6.8 Hz, -CHCH₃), 2.68-2.85 (4H, m, -CH₂CH₂N-), 3.81 (3H, s, 4-OCH₃ or 5-OCH₃), 3.83 (3H, s, 4-OCH₃ or 5-OCH₃), 3.83 (1H, q, -CHCH₃), 6.70 (1H, s, 3-H or 6-H), 6.98 (1H, s, 3-H or 6-H), 7.21-7.32 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %) : 362 ([M-1]⁺, 0.4), 284 (57.0), 148 (5.2), 134 (97.3), 105 (100). IR (cm⁻¹): 2920, 1600, 1495, 1250. *Anal.* Calcd for C₁₈H₂₂NO₂Br : C, 59.35; H, 6.09; N, 3.85. Found : C, 59.39 ; H, 6.11 ; N 3.83.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-*N*-[(*S*)-1-phenylethyl]-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (7)**

To a mixture of **6** (12.26 g, 0.034 mol) and 5 % aq. Na₂CO₃ solution (250 mL) in Et₂O (100 mL) was added dropwise the acid chloride of **4** (10.29 g, 0.037 mol) in dry Et₂O (25 mL) with vigorous stirring at 10 ~ 15 °. After the reaction mixture was continuously stirred for 2 h at same temperature, the Et₂O layer was separated. It was washed with 10 % HCl solution and water and then dried. Removal of the solvent gave the residue, whose column chromatography on silica gel with CH₂Cl₂-AcOEt [9 : 1 (v/v)] gave a pale yellow oil (**7**, 12.6 g, 60.0 %), TLC (Silica Gel 60 F₂₅₄) *R_f* = 0.33, CHCl₃-AcOEt [10 : 1 (v/v)]. [α]_D: -33.7° (c = 0.399, CHCl₃). The product (**7**) was estimated to constitute of two rotational isomers (1 : 1) with respect to the amide function on the basis of its ¹H-NMR. ¹H-NMR (CDCl₃) : 1.62 (3H × 0.55, d, *J* = 6.8 Hz, -CHCH₃), 1.63 (3H × 0.45, d, *J* = 6.8 Hz, -CHCH₃), 2.32-3.47 (4H, m, -CH₂CH₂N-), 3.79 (3H, s, 4-OCH₃ or 5-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.80 (3H, s, 4-OCH₃ or 5-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.82 (1H × 0.45, d, *J* = 16.7 Hz, one proton of -COCH₂-), 3.86 (3H, s, 4-OCH₃ or 5-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.87 (3H, s, 4-OCH₃ or 5-OCH₃ or 4'-OCH₃ or 5'-OCH₃), 3.87 (1H × 0.55, d, *J* = 15.8 Hz, one proton of -COCH₂-), 3.90 (1H × 0.45, d, *J* = 16.7 Hz, one proton of -COCH₂-), 3.98 (1H × 0.55, d, *J* = 15.8 Hz, one proton of -COCH₂-), 5.22 (1H × 0.55, q, *J* = 6.8 Hz, -CHCH₃), 6.10 (1H × 0.45, q, *J* = 6.8 Hz, -CHCH₃), 6.24 (1H × 0.45, s, 6'-H), 6.69 (1H × 0.55, s, 6'-H), 6.84 (1H × 0.45, s, one of arom.H), 6.90 (1H × 0.55, s, one of arom.H), 6.92 (1H × 0.45, s, one of arom.H), 6.93 (1H × 0.55, 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), 7.23-7.47 (5H, m, phenyl.H). EIMS (70 eV) *m/z* (rel. int. %) : 619 (M⁺, 1.3), 540 (71.4), 229 (40.6), 164 (22.0), 105 (100). HREIMS *m/z* 619.0558 (Calcd for C₂₈H₃₁NO₅Br₂, 619.0569). IR (cm⁻¹) : 3040-2830, 1640 (C=O), 1250.

(±)-1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline · 9/10 H₃BO₃ (8) and 5-Bromo-1-(2-bromo-4,5-dimethoxybenzyl)-7,8-dimethoxy-3,4-dihydroisoquinoline (9)

The mixture of **7** (1.89 g, 3.04 mmol) and POCl₃ (5.6 mL, 6.20 mmol) in dry MeCN (54 mL) was stirred for 5 h at 80 ~ 83 °. Evaporation of excess reagent and solvent left a residue, which was washed with hexane. The residue (1.84 g) was used for the following reaction without purification. To a solution of the residue in MeOH (200 mL) was added gradually NaBH₄ (2.3 g, 0.061 mol) at -78 ° with stirring. After the reaction mixture was continuously stirred for 1.5 h at same temperature, excess of NaBH₄ was decomposed with 20 % AcOH solution, and most of solvent evaporated *in vacuo*. The residue was made

alkaline with 10 % NH₄OH and extracted with CH₂Cl₂. The extract was washed with water and dried. The CH₂Cl₂ solution was evaporated leaving a powder. The powder was recrystallized from EtOH to give colorless needles (**8**, 0.244 g, 17.2 %), mp 202.0 ~ 203.0 °. [α]_D: +1.67 ° (c = 0.343, CHCl₃). optical isomer ratio = 48.6 : 51.4 [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]. ¹H-NMR (CDCl₃) : 3.08-3.21 (2H, m, Hd and He), 3.34 (1H, dd, *J*₁ = 13.7 Hz, *J*₂ = 8.6 Hz, Hb), 3.28-3.58 (1H, m, Hf), 3.55 (3H, s, 5'-OCH₃), 3.58 (1H, dd, *J*₁ = 13.7 Hz, *J*₂ = 6.0 Hz, Hc), 3.46-3.70 (1H, m, Hg), 3.84 (3H, s, 6-OCH₃ or 7-OCH₃ or 4'-OCH₃), 3.85 (3H, s, 6-OCH₃ or 7-OCH₃ or 4'-OCH₃), 3.86 (3H, s, 6-OCH₃ or 7-OCH₃ or 4'-OCH₃), 4.79 (1H, dd, *J*₁ = 8.6 Hz, *J*₂ = 6.0 Hz, Ha), 6.05 (1H, s, 8-H), 6.60 (1H, s, 5-H), 6.96 (1H, s, 6'-H), 7.02 (1H, s, 3'-H). EIMS (70 eV) *m/z* (rel. int. %): 420 ([M - H]⁺, 0.2), 340 (6.7), 338 (3.3), 229 (2.0), 192 (100), 176 (8.5). HREIMS *m/z* 420.0815 (Calcd for C₂₀H₂₃O₄NBr, 420.0811). *Anal.* Calcd for C₂₀H₂₄NO₄Br · 9 / 10 H₃BO₃: C, 50.26 ; H, 5.63 ; N, 2.93. Found : C, 50.22 ; H, 5.44 ; N, 2.91. IR (CHCl₃) cm⁻¹ : 1507, 1462, 1255, 1160, 1110.

The mother liquor was dried up to give a residue whose column chromatography on silica gel with CHCl₃ : AcOEt [5 : 2 (v/v)] to give **9** (58.9 mg, 3.9 %), as a yellow oily substance showing a single spot on TLC, *R*_f = 0.52, CHCl₃ : AcOEt = 5 : 2. ¹H-NMR (CDCl₃) : 2.26-2.70 (1H, m, Hd), 2.78-3.04 (1H, m, He), 2.87-3.09 (1H, m, Hf), 3.26(1H, d, *J* = 2.4 Hz, -CH₂C-), 3.31(1H, d, *J* = 2.4 Hz, -CH₂C-), 3.36-3.78 (1H, m, Hg), 3.80 (3H, s, -OCH₃), 3.86 (6H, s, -OCH₃ × 2), 3.91 (3H, s, -OCH₃), 6.99 (1H, s, arom. H), 7.05 (1H, s, arom.H), 7.06 (1H, s, arom. H). EIMS (70 eV) *m/z* (rel. int. %): 497 (M⁺, 60.3), 418 (M⁺ - Br, 77.6), 388 (18.3), 229 (35.9), 201 (20.7), 151 (20.7).

***N*-(1-Phenylethyl)-2-(2-bromo-4,5-methylenedioxyphenyl)acetamide (11)**

To a mixture of (±)-1-phenylethylamine (3.86 mL, 0.030 mol) and 5% Na₂CO₃ solution (150 mL, 0.071 mol) in Et₂O (150 mL) was added dropwise the acid chloride of 2-bromo-4,5-methylenedioxyphenylacetic acid (**10**) (6.48 g, 0.025 mol) in dry benzene (50 mL) with stirring at 0 ~ 5 °. After stirring was continued for 1 h at same temperature, a resulting precipitate was collected by filtration. The precipitate was recrystallized from EtOH-hexane (1 : 1) to give colorless prisms (**11**), mp 135.0 ~ 136.0 ° (8.12 g, 89.7 %). ¹H-NMR (CDCl₃) : 1.45 (3H, d, *J* = 6.8 Hz, -CHCH₃), 3.61 (2H, s, -CH₂CO-), 4.94-5.32 (1H, m, -CHCH₃), 5.70 (1H, br s, -NH-), 5.99 (2H, s, -OCH₂O-), 6.82 (1H, s, 6-H), 7.03 (1H, s, 3-H), 7.23-7.32 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %): 361 (M⁺, 2.0), 282 (M⁺ - Br, 100), 213 (45.4), 178 (68.6), 105 (86.5). *Anal.* Calcd for C₁₇H₁₆NO₃Br : C, 56.73 ; H, 4.45 ; N, 3.87. Found : C, 56.28 ; H, 4.38 ; N, 3.90.

***N*-(1-Phenylethyl)-2-(2-bromo-4,5-methylenedioxyphenyl)ethylamine · HCl (12)**

To a solution of **11** (5.43 g, 0.015 mol) in dry THF (90 mL) was carefully added dropwise BH₃-Et₂O complex (2.25 mL, 7.5 mmol) and 1.0 M BH₃-THF solution (45 mL, 0.045 mol) under Ar atmosphere at 20 ~ 25 ° with stirring, and the mixture was further stirred for 2.5 h at 70 ~ 80 °. After the reaction was

completed, the excess reagents were decomposed with 5 N HCl solution (135 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 with CH₂Cl₂. The extract was washed with water, and solvent was evaporated off to give a residue which was recrystallized from MeOH - Et₂O (2 : 3) to give colorless prisms (**12**, 4.96 g, 86.0 %), mp 192.0 ~ 197.0 . ¹H-NMR (CDCl₃) : 1.94 (3H, d, *J* = 7.0 Hz, -CHCH₃), 2.67-3.13 (2H, m, -CH₂CH₂N-), 3.08-3.48 (2H, m, -CH₂CH₂N-), 4.27 (1H, q, *J* = 7.0 Hz, -CHCH₃), 5.90 (2H, s, -OCH₂O-), 6.71 (1H, s, 3-H or 6-H), 6.89 (1H, s, 3-H or 6-H), 7.34-7.45 (5H, m, phenyl H). EIMS (20 eV) *m/z* (rel. int. %): 347 (M⁺, 0.3), 268 (60.8), 134 (100), 105 (9.6). HREIMS *m/z* 347.0512 (Calcd for C₁₇H₁₈NO₂Br, 347.0521).

***N*-[2-(2-Bromo-4,5-methylenedioxyphenyl)ethyl]-*N*-(1-phenylethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (**13**)**

To a mixture of **12** (1.5 g, 3.8 mmol) and 5% Na₂CO₃ solution (50 mL, 0.024 mol) in Et₂O (50 mL) was added dropwise the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid (1.2 g, 4.3 mmol) in dry Et₂O (20 mL) with vigorous stirring at 10 ~ 15 . After the reaction mixture was continuously stirred for 2 h at 23 ~ 27 , the Et₂O layer was separated. The Et₂O solution was washed with water and dried. Removal of the solvent gave a residue, which was recrystallized from Et₂O to give colorless needles (**13**, 1.7 g, 71.0 %), mp 115.0 ~ 118.5 . ¹H-NMR (CDCl₃) : 1.58 (3H × 0.5, d, *J* = 7.0 Hz, -CHCH₃), 1.61 (3H × 0.5, d, *J* = 7.0 Hz, -CHCH₃), 2.34-3.41 (4H, m, -CH₂CH₂N-), 3.84-3.88 (8H, m, -OCH₃ × 2 and -COCH₂-), 5.20 (1H × 0.5, q, *J* = 7.0 Hz, -CHCH₃), 5.90 (2H, s, -OCH₂O-), 6.10 (1H × 0.5, q, *J* = 7.0 Hz, -CHCH₃), 6.30 (1H × 0.5, s, arom. H), 6.68 (1H × 0.5, s, arom. H), 6.85 (1H × 0.5, s, arom. H), 6.88 (1H × 0.5, s, arom. H), 6.91 (1H × 0.5, s, arom. H), 6.93 (1H × 0.5, s, arom. H), 7.04 (1H, s, arom. H), 7.21-7.44 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %): 603 (M⁺, 1.2), 526 (68.0), 229 (39.8), 134 (55.1), 105 (100). HREIMS *m/z* 603.0261 (Calcd for C₂₇H₂₇NO₅Br₂, 603.0256). IR (CHCl₃) cm⁻¹: 1630 (C=O), 1500, 1255, 1480.

5-Bromo-1-(2-bromo-4,5-dimethoxybenzyl)-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (14**) and 1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**15**)**

The mixture of **13** (0.46 g, 0.76 mmol) and POCl₃ (1.05 mL, 11.4 mmol) in dry CH₃CN (30 mL) was stirred for 2 h at 80 ~ 83 . Evaporation of excess reagent and solvent left a residue. The residue (0.76 g) was used for the following reaction without purification. To a solution of the residue in MeOH (50 mL) was added gradually NaBH₄ (0.57 g, 15.2 mmol) at - 78 with stirring. After the reaction mixture was continuously stirred for 2 h at same temperature, excess of NaBH₄ was decomposed with 20 % AcOH solution, and most of solvent evaporated to dryness *in vacuo* leaving a residue. The residue was made alkaline with 10 % NH₄OH solution and extracted with CHCl₃. The solution was dried and evaporated to dryness leaving a powder, which was purified by column chromatography on silica gel with CHCl₃ to give prisms (**14**) and a powder (**15**). **14** *R*_f = 0.75, CH₃Cl - MeOH (10 : 1), mp 85.0 ~ 88.0 (recrystallized

from EtOH), 0.10 g, 27.0 %. $^1\text{H-NMR}$ (CDCl_3) : 2.60-2.75 (2H, m, Hd and He), 2.98 (1H, m, Hf), 3.02 (1H, dd, $J_1 = 13.9$ Hz, $J_2 = 10.3$ Hz, Hb), 3.25 (1H, m, Hg), 3.36 (1H, dd, $J_1 = 13.9$ Hz, $J_2 = 3.6$ Hz, Hc), 3.84 (3H, s, $-\text{OCH}_3$), 3.86 (3H, s, $-\text{OCH}_3$), 4.38 (1H, dd, $J_1 = 10.3$ Hz, $J_2 = 3.6$ Hz, Ha), 5.96 (2H, s, $-\text{OCH}_2\text{O}-$), 6.78 (1H, s, arom. H), 6.97 (1H, s, arom. H), 7.03 (1H, s, arom. H). EIMS (70 eV) m/z (rel. int. %): 483 (M^+ , 0.8), 404 ($\text{M}^+ - \text{Br}$, 5.1), 322 (8.0), 254 (100), 229 (7.4), 175 (11.2). HREIMS m/z 482.9682 (Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{Br}_2$, 482.9681). IR (CHCl_3) cm^{-1} : 1500, 1450, 1260. **15** Showing a single spot on TLC, $R_f = 0.40$, CHCl_3 -MeOH (10 : 2). 24.6 mg, 8.0 %. $^1\text{H-NMR}$ (CDCl_3) : 2.71-3.31 (6H, m, NCH_2CH_2 and Hb, Hc), 3.84 (3H, s, $-\text{OCH}_3$), 3.86 (3H, s, $-\text{OCH}_3$), 4.26 (1H, m, Ha), 5.90 (2H, s, $-\text{OCH}_2\text{O}-$), 6.57 (1H, s, arom. H), 6.75 (1H, s, arom. H), 6.79 (1H, s, arom. H), 7.05 (1H, s, arom. H). EIMS (70 eV) m/z (rel.int.%): 406 ($[\text{M}+1]^+$, 7.2), 324 (6.0), 272 (12.1), 256 (15.3), 229 (10.0), 176 (100), 148 (6.0).

***N*-(1-Phenylethyl)-2-(3,4-dimethoxyphenyl)acetamide (16)**

To a mixture of 1-phenylethylamine (5.76 g, 0.046 mol) and 5% Na_2CO_3 solution (60 mL, 0.028 mol) in Et_2O (60 mL) was added dropwise the acid chloride of 3,4-dimethoxyphenylacetic acid (**3**) (5.00 g, 0.026 mol) in dry Et_2O (40 mL) with vigorous stirring at 10 ~ 15 °C. After stirring was continued for 2 h at 23 ~ 27 °C, a resulting precipitate was collected by filtration. The precipitate was recrystallized from EtOH to give colorless prisms (**16**, 5.98 g, 78.4 %), mp 119.5 ~ 201.1 °C. $^1\text{H-NMR}$ (CDCl_3) : 1.40 (3H, d, $J = 7.0$ Hz, $-\text{CHCH}_3$), 3.52 (2H, s, $-\text{CH}_2\text{CO}-$), 3.83 (3H, s, $-\text{OCH}_3$), 3.88 (3H, s, $-\text{OCH}_3$), 5.13 (1H, m, $J = 7.0$ Hz, $-\text{CHCH}_3$), 5.62 (1H, d, $J=7.0$ Hz, $-\text{NH}-$), 6.75-7.31 (8H, m, arom. H and phenyl H). EIMS (70 eV) m/z (rel. int. %): 229 (M^+ , 82.2), 151 (100), 105 (33.6). HREIMS m/z 229.1522 (Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$, 299.1522).

***N*-(1-Phenylethyl)-2-(3,4-dimethoxyphenyl)ethylamine (17)**

To a solution of **16** (0.3 g, 0.001 mol) in dry THF (12 ml) was carefully added dropwise $\text{BF}_3\text{-Et}_2\text{O}$ complex (47 %, 0.15 mL, 0.050 mol) and 1.0 M $\text{BH}_3\text{-THF}$ complex (3 mL, 0.003 mol) under Ar atmosphere at 20 ~ 25 °C with stirring, and the mixture was further heated for 2.5 h at 68 °C. After the reaction was complete, the excess reagent was decomposed with 10 % HCl solution (10 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 and dried. Removal of the solvent by evaporation left a residue, which was chromatographed with hexane-AcOEt [5 : 3 (v/v)] to give the amide (**17**, 0.18 g, 62.9 %) as a yellow oily substance. $^1\text{H-NMR}$ (CDCl_3) : 1.30 (3H, d, $J = 7.0$ Hz, $-\text{CHCH}_3$), 2.70 (4H, m, $-\text{CH}_2\text{CH}_2\text{N}-$), 3.75 (1H, q, $J = 7.0$ Hz, $-\text{CHCH}_3$), 3.82 (3H, s, $-\text{OCH}_3$), 6.61-7.44 (8H, m, arom. H and phenyl H). EIMS (70 eV) m/z (rel. int. %): 285 (M^+ , 9.8), 152 (50.3), 134 (64.8), 105 (100). HREIMS m/z 285.1730 (Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_2$, 285.1729).

***N*-[2-(3,4-Dimethoxyphenylethyl)]-*N*-(1-phenylethyl)-2-(2-bromo-4,5-dimethoxyphenyl)acetamide (18)**

To a suspension of **17** (1.00 g, 3.51 mmol) and Na_2CO_3 (1.76 g, 11.6 mmol) in benzene (30 mL) was

added dropwise the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid (1.06 g, 3.86 mmol) in dry benzene (30 mL) with vigorous stirring at 23 °C. The reaction mixture was stirred at 80 °C for 1 h. The mixture was evaporated to dryness leaving a colorless oil, whose column chromatography on silica gel with Hexane-AcOEt [7 : 3 (v/v)] gave **18** (colorless oil, 1.3 g, 66.5 %). Showing a single spot on TLC, *R_f* = 0.64, AcOEt - MeOH (10 : 1). ¹H-NMR (CDCl₃) : 1.55 (3H × 0.5, d, *J* = 7.0 Hz, -CHCH₃), 1.58 (3H × 0.5, d, *J* = 7.0 Hz, -CHCH₃), 2.19-3.31 (4H, m, -CH₂CH₂N-), 3.79-3.94 (14H, m, -COCH₂-, -OCH₃ × 4), 5.20 (1H × 0.5, q, *J* = 7.0 Hz, -CHCH₃), 6.07 (1H × 0.5, q, *J* = 7.0 Hz, -CHCH₃), 6.69 (1H × 0.5, s, arom. H), 6.71 (1H × 0.5, s, arom. H), 6.72 (1H × 0.5, s, arom. H), 6.74 (1H × 0.5, s, arom. H), 6.89 (1H × 0.5, s, arom. H), 6.90 (1H × 0.5, s, arom. H), 6.95 (1H × 0.5, s, arom. H), 7.02 (1H × 0.5, s, arom. H), 7.05 (1H × 0.5, s, arom. H), 7.20 (1H × 0.5, s, arom. H), 7.22 (1H × 0.5, s, arom. H), 7.21-7.43 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %): 541 (M⁺, 4.2), 462 (M⁺-Br, 41.5), 164 (100), 105 (54.5). HREIMS *m/z* 541.1468 (Calcd for C₂₈H₃₂NO₅Br, 541.1464). IR (cm⁻¹) : 1630 (C=O), 1500, 1260.

1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19) and 1-(2-Bromo-4,5-dimethoxybenzyl)-2-(1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20)

The mixture of **18** (0.79 g, 1.46 mmol) and POCl₃ (2.01 mL, 21.90 mmol) in dry MeCN (40 mL) was stirred for 1 h at 80 ~ 82 °C. Evaporation of excess reagent and solvent left a residue, which was washed with hexane. The residue (0.77 g) was used for the following reaction without purification. To a solution of the residue in MeOH (180 mL) was added gradually NaBH₄ (1.11 g, 29.2 mmol) at -78 °C with stirring. After the reaction mixture was continuously stirred for 30 min at same temperature, excess of NaBH₄ was decomposed with 20 % AcOH solution, and most of solvent was evaporated leaving a residue. The residue was made alkaline with 10 % NaOH solution and extracted with CH₂Cl₂. The extract was evaporated to dryness leaving a colorless residue whose column chromatography on silica gel with CHCl₃ - MeOH [10 : 1(v/v)] gave pale yellow needles (**19**, 0.48 g, 57.0 %) and an yellow oil (**20**, 0.21 g, 20.0 %).

19 : Pale yellow needles, *R_f* = 0.40 [CHCl₃ - MeOH (10 : 1)], mp 113.3 ~ 114.5 °C (recrystallized from AcOEt). ¹H-NMR (CDCl₃) : 2.68-2.81 (2H, m, Hd and He), 2.92 (1H, dd, *J*₁ = 13.9 Hz, *J*₂ = 9.7 Hz, Hb), 2.96 (1H, m, Hf), 3.25 (1H, m, Hg), 3.31 (1H, dd, *J*₁ = 13.9 Hz, *J*₂ = 4.0 Hz, Hc), 3.83 (3H, s, 7-OCH₃), 3.84 (3H, s, 5'-OCH₃), 3.86 (3H, s, 6-OCH₃), 3.87 (3H, s, 4'-OCH₃), 4.24 (1H, dd, *J* = 9.7 Hz, *J*₂ = 4.0 Hz, Ha), 6.60 (1H, s, 5-H), 6.73 (1H, s, 8-H), 6.77 (1H, s, 6'-H), 7.06 (1H, s, 3'-H). ¹³C-NMR (100 MHz, CDCl₃) : 148.24 (COCH₃), 148.18 (COCH₃), 147.5 (COCH₃), 147.0 (COCH₃), 130.6 (C-9), 130.4 (C-7), 127.2 (C-4), 115.6 (C-11), 114.7 (C-10), 114.2 (C-12), 111.7 (C-5), 109.5 (C-6), 56.15 (OCH₃), 56.10 (OCH₃), 55.9 (OCH₃), 55.8 (OCH₃), 55.3 (C-1), 42.7 (C-8), 40.5 (C-2), 29.5 (C-3). EIMS (70 eV) *m/z* (rel. int. %): 420 ([M-1]⁺, 1.1), 340 (13.9), 229 (4.9), 192 (100), 176 (20.0). HREIMS *m/z* 420.0811 (Calcd for C₂₀H₂₃NO₄Br, 420.0810). *Anal.* Calcd for C₂₀H₂₄NO₄Br : C, 56.88; H, 5.73 ; N, 3.32. Found : C, 56.49; H, 5.81; N, 3.28. IR (cm⁻¹) : 1507, 1462, 1255, 1160, 1110. **20** : Yellow oil, *R_f* = 0.77 [CHCl₃ - MeOH (10 :

1)]. $^1\text{H-NMR}$ (CDCl_3) : 1.34 (3H, d, $J = 6.6$ Hz, $-\text{CHCH}_3$) 2.46 (1H, m, $-\text{NCH}_2\text{CH}_2-$), 2.87 (1H, dd, $J_1 = 13.7$ Hz, $J_2 = 6.4$ Hz, Hb), 2.93 (1H, m, $-\text{NCH}_2\text{CH}_2-$), 3.05 (1H, dd, $J_1 = 13.7$ Hz, $J_2 = 8.2$ Hz, Hc), 3.32 (1H, m, $-\text{NCH}_2\text{CH}_2-$), 3.42 (1H, m, $-\text{NCH}_2\text{CH}_2-$), 3.62 (3H, s, $5'-\text{OCH}_3$), 3.72 (1H, q, $J = 6.6$ Hz, $-\text{CHCH}_3$), 3.72 (3H, s, $7-\text{OCH}_3$), 3.80 (1H, undetectable, Ha), 3.85 (3H, s, $6-\text{OCH}_3$), 3.86 (3H, s, $4'-\text{OCH}_3$), 6.16 (1H, s, $6'-\text{H}$), 6.43 (1H, s, $8-\text{H}$), 6.60 (1H, s, $5-\text{H}$), 6.91 (1H, s, $3'-\text{H}$) 6.95-7.14 (5H, m, phenyl H). EIMS (70 eV) m/z (rel. int. %): 524 ($[\text{M} - 1]^+$, 0.7), 296 (100), 192 (74.5), 105 (53.8). IR (cm^{-1}): 1500, 1260.

Detection of styrene and 1-chloroethylbenzene

The Bischler-Napieralski reaction mixture of **7**, **13** and **18** with POCl_3 in dry MeCN was checked with GCMS at the middle and end points during the reaction. Styrene and 1-chloroethylbenzene were detected in all of the reaction mixtures. Styrene: GCMS (60 ~ 200 , 3 /min), $t_R = 4.20$ min, (70 eV) m/z : 104 (M^+), 78 ($\text{M}^+ - \text{CH} = \text{CH}_2$). 1-Chloroethylbenzene: GCMS (60 ~ 200 , 3 /min), $t_R = 11.70$ min, (70 eV) m/z : 140 (M^+), 105 ($\text{M}^+ - \text{Cl}$).

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7. The Bischler-Napieralski reaction of the similar acetamides having no substituent groups at both of the 2- and 6-positions of the A ring proceeded faster than that of the acetamide (**13**).²The almost reactions were completed in 1 h.
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9. The calculation was carried out using the software "PC SPARTAN Pro, version 1", Wavefunction, Inc.
10. BN reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-[(*R*)-1-phenylethyl]-2-(3-benzyloxyphenyl)-acetamide (**21**) having no bromine atom at 2-position of the C ring afforded only the (1*R*)-tetrahydroisoquinoline (**22**) in almost quantitative yield in contrast to the BN reaction of the acetamide (**18**) (Scheme 2).^{2a} This suggests that the bromine atom on the C ring also may somewhat

interfere the BN reaction.

11. The alkoxy group may form more bulky $\text{-OR} \cdot \text{POCl}_3$ complex in this conditions.