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BISCHLER-NAPIERALSKI REACTION OF *N*-[2-(2-BROMO-4,5-DIALKYLOXYPHENYL)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.

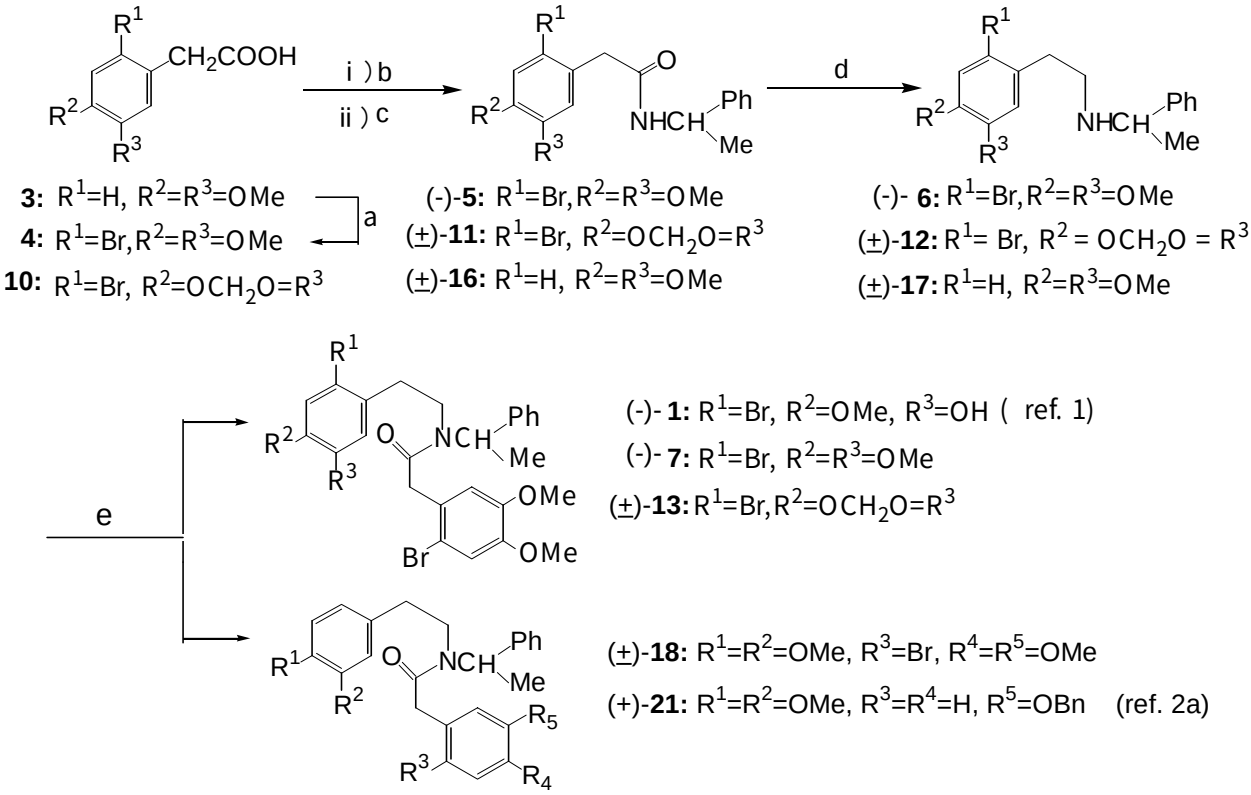
INTRODUCTION

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-dialkyloxyphenyl)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 BH_3-THF complex in the present of BF_3-Et_2O 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 $POCl_3$ 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-Et_2O / BH_3-THF e) 2-bromo-4,5-dimethoxyacetic acid chloride, Na_2CO_3

Scheme 1

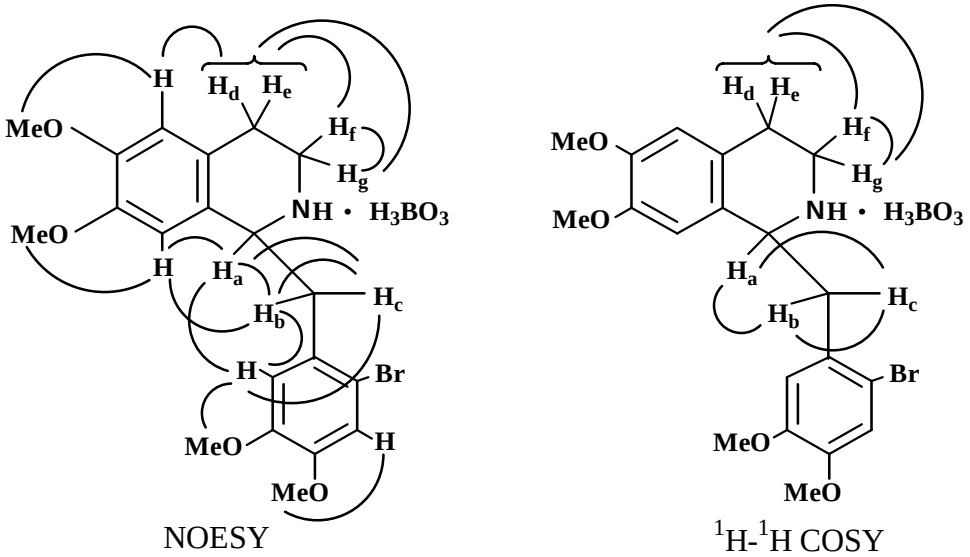
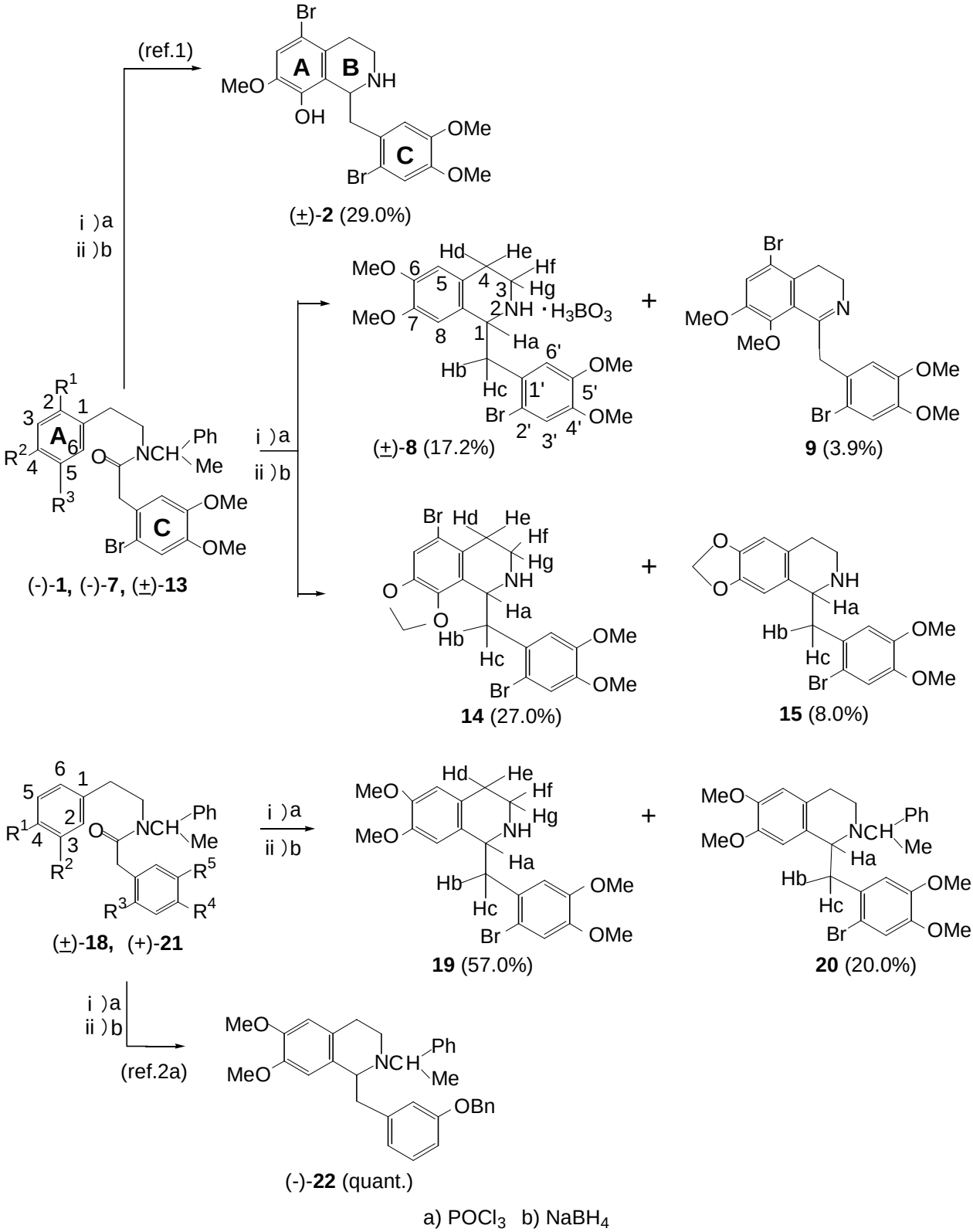


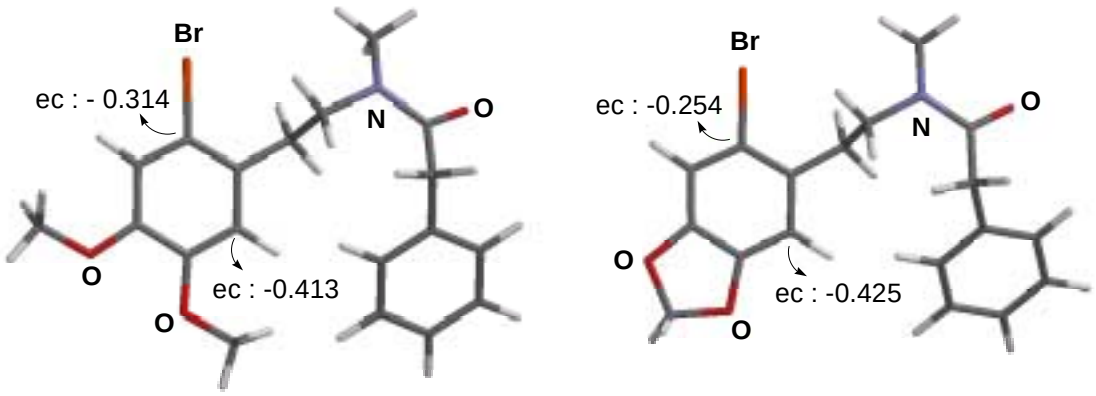
Figure 1 NOESY and ^1H-^1H COSY correlation of **8**



Scheme 2

The oily intermediate was treated without purification with $NaBH_4$ in MeOH at – 78℃ 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 ^{1}H-NMR (^{1}H-^{1}H 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 $NaBH_4$ 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 ^{1}H-NMR (^{1}H-^{1}H 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 cite 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).



ec : electrostatic charge

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 $NaBH_4$ to give two products, needles (**19**, 57.0 %) and a yellow oil (**20**, 20.0 %), structures of which were determined by their ^{1}H-NMR and MS spectra (Scheme 2). ^{1}H-NMR (HMBC, ^{1}H-^{1}H COSY and NOESY) and ^{13}C-NMR spectral data of **19** were shown in Figure 3. Styrene and 1-chloroethylbenzene were also detected in this reaction mixture.

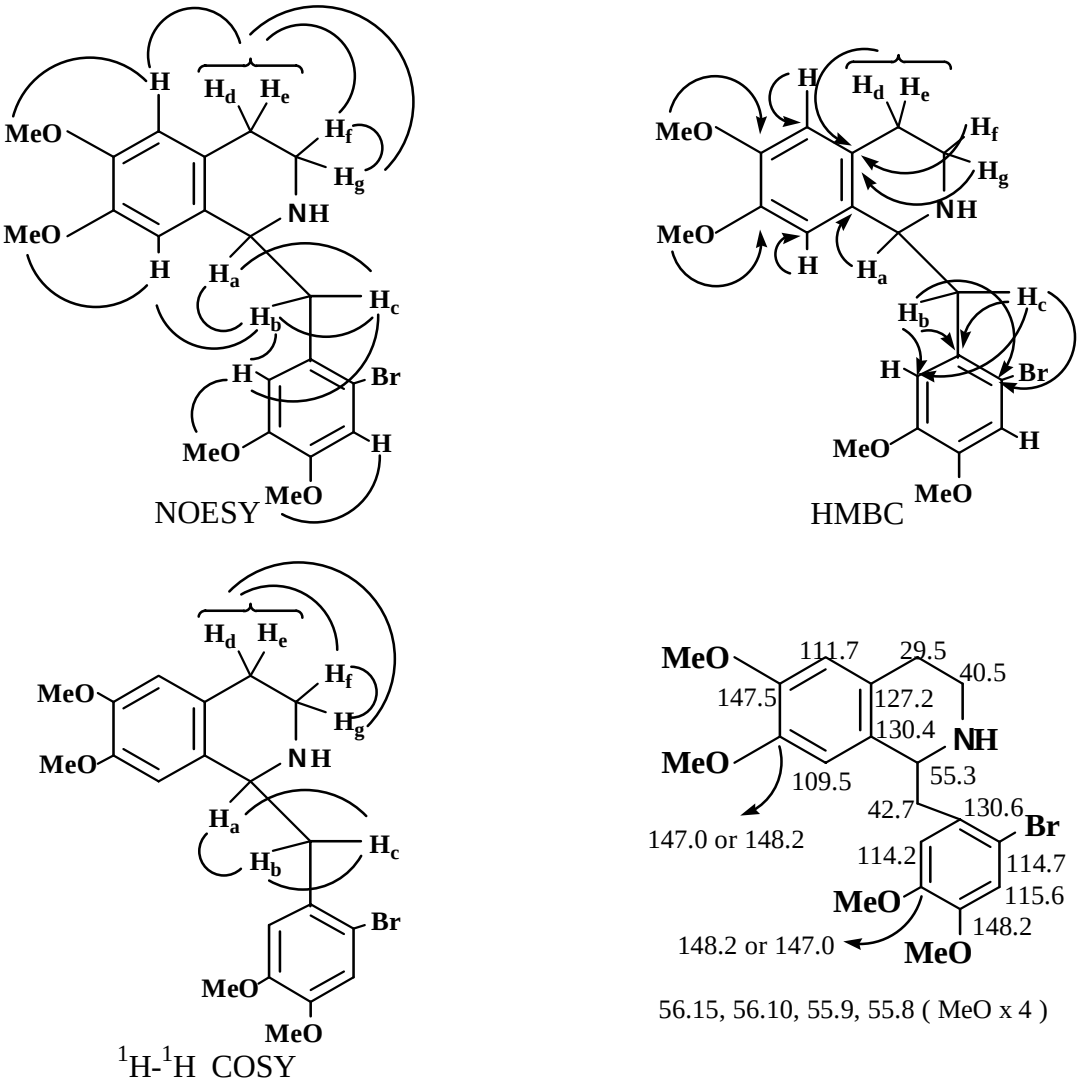


Figure 3 ^{1}H-NMR and ^{13}C-NMR Spectral Data of **19**

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. ^{1}H-NMR spectra were obtained on a JEOL PMX60 and JEOL GSX-500 spectrometers with tetramethyl-silane as an internal standard. ^{13}C-NMR and HMBC spectra were recorded on Varian UNITY IVOVA 400NB (^{1}H: 400 MHz, ^{13}C: 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 $CHCl_3$ 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). 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*)-(-)-α-phenylethylamine (7.66 mL, 0.059 mol) and 5 % aq. Na_2CO_3 solution (250 mL) in Et_2O (100 mL) was added dropwise the acid chloride of **4** (13.63 g, 0.050 mol) in dry Et_2O (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 %). $[\alpha]_D$: - 0.2 ° (c = 0.438, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.44 (3H, d, *J* = 6.8 Hz, -CHC<u>H</u>$_3$), 3.61 (1H, d, *J* = 15.8 Hz, one of -CH_2CO-), 3.65 (1H, d, *J* = 15.8 Hz, one of -CH_2CO-), 3.83 (3H, s, 4-OCH_3 or 5-OCH_3), 3.87 (3H, s, 4-OCH_3 or 5-OCH_3), 5.03 – 5.23 (1H, m, -C<u>H</u>CH_3), 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 $C_{20}H_{18}NO_3Br$, 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 BF_3-Et_2O complex (5.1 mL, 0.017 mol) and 1.0 M BH_3-THF complex (68 mL, 0.068 mol) under Ar atomosphere 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 CH_2Cl_2. The extract was washed with water, and solvent was evaporated off to give a oil, whose column chromatography on silica gel with $CHCl_3$ gave a pale yellow

oil (**6,** 9.6 g, 78.0 %), showing a single spot on TLC (Silica Gel 60 F_{254}), *Rf* = 0.25, $CHCl_3$–AcOEt（10 : 1）.[α]$_D$: -27.8 ° (c = 0.500, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.36 (3H, d, *J* = 6.8 Hz, -CHC<u>H</u>$_3$), 2.68-2.85 (4H, m, -CH_2CH_2N-), 3.81 (3H, s, 4-OCH_3 or 5-OCH_3), 3.83 (3H, s, 4-OCH_3 or 5-OCH_3), 3.83 (1H, q, -C<u>H</u>CH_3), 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 $C_{18}H_{22}NO_2Br$: 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-dimethoxy-pheny)acetamide (7)

To a mixture of **6** (12.26 g, 0.034 mol) and 5 % aq. Na_2CO_3 solution (250 mL) in Et_2O (100 mL) was added dropwise the acid chloride of **4** (10.29 g, 0.037 mol) in dry Et_2O (25 mL) with vigorous stirring at 10～15 ℃. After the reaction mixture was continuously stirred for 2 h at same temperature, the Et_2O 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 CH_2Cl_2-AcOEt [9 : 1 (v/v)] gave a pale yellow oil (**7**,12.6 g, 60.0 %), TLC (Silica Gel 60 F_{254}) *Rf* = 0.33, $CHCl_3$ - AcOEt [10 : 1 (v/v)]. [α]$_D$: -33.7 ° (c = 0.399, $CHCl_3$). The product (**7**) was estimated to constitute of two rotational isomers (1 : 1) with respect to the amide function on the basis of its ^{1}H-NMR.[4] ^{1}H-NMR ($CDCl_3$) δ : 1.62 (3H×0.55, d, *J* = 6.8 Hz, -CHC<u>H</u>$_3$), 1.63 (3H×0.45, d, *J* = 6.8 Hz, -CHC<u>H</u>$_3$), 2.32-3.47 (4H, m, -C<u>H</u>$_2$C<u>H</u>$_2$N-), 3.79 (3H, s, 4-OCH_3 or 5-OCH_3 or 4'-OCH_3 or 5'-OCH_3), 3.80 (3H, s, 4-OCH_3 or 5-OCH_3 or 4'-OCH_3 or 5'-OCH_3), 3.82 (1H×0.45, d, *J* = 16.7 Hz, one proton of -$COCH_2$-), 3.86 (3H, s, 4-OCH_3 or 5-OCH_3 or 4'-OCH_3 or 5'-OCH_3), 3.87 (3H, s, 4-OCH_3 or 5-OCH_3 or 4'-OCH_3 or 5'-OCH_3), 3.87 (1H×0.55, d, *J* = 15.8 Hz, one proton of -$COCH_2$-), 3.90 (1H×0.45, d, *J* = 16.7 Hz, one proton of -$COCH_2$-), 3.98 (1H×0.55, d, *J* = 15.8 Hz, one proton of -$COCH_2$-), 5.22 (1H×0.55, q, *J* = 6.8 Hz, -C<u>H</u>CH_3), 6.10 (1H×0.45, q, *J* = 6.8 Hz, -C<u>H</u>CH_3), 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 $C_{28}H_{31}NO_5Br_2$, 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 H_3BO_3 (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 $POCl_3$ (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 $NaBH_4$ (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 $NaBH_4$ was decomposed with 20 % AcOH solution, and most of solvent evaporated *in vacuo*. The residue was made

alkaline with 10 % NH_4OH and extracted with CH_2Cl_2. The extract was washed with water and dried. The CH_2Cl_2 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, $CHCl_3$). 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]. ^{1}H-NMR ($CDCl_3$) δ : 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'-OCH_3), 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-OCH_3 or 7-OCH_3 or 4'-OCH_3), 3.85 (3H, s, 6-OCH_3 or 7-OCH_3 or 4'-OCH_3), 3.86 (3H, s, 6-OCH_3 or 7-OCH_3 or 4'-OCH_3), 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 $C_{20}H_{23}O_4NBr$, 420.0811). *Anal.* Calcd for $C_{20}H_{24}NO_4Br \cdot 9/10\ H_3BO_3$: C, 50.26 ; H, 5.63 ; N, 2.93. Found : C, 50.22 ; H, 5.44 ; N, 2.91. IR ($CHCl_3$) cm^{-1} : 1507, 1462, 1255, 1160, 1110.

The mother liquor was dried up to give a residue whose column chromatography on silica gel with $CHCl_3$: AcOEt [5 : 2 (v/v)] to give **9** (58.9 mg, 3.9 %), as a yellow oily substance showing a single spot on TLC, *Rf* = 0.52, $CHCl_3$: AcOEt = 5 : 2. ^{1}H-NMR ($CDCl_3$) δ : 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, -C<u>H</u>$_2$C-), 3.31(1H, d, *J* = 2.4 Hz, -C<u>H</u>$_2$C-), 3.36-3.78 (1H, m, Hg), 3.80 (3H, s, -OCH_3), 3.86 (6H, s, -OCH_3×2), 3.91 (3H, s, -OCH_3), 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% Na_2CO_3 solution (150 mL, 0.071 mol) in Et_2O (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 %). ^{1}H-NMR ($CDCl_3$) δ : 1.45 (3H, d, *J*=6.8 Hz, -CHC<u>H</u>$_3$), 3.61 (2H, s, -CH_2CO-), 4.94-5.32 (1H, m, -C<u>H</u>CH_3), 5.70 (1H, br s, -NH-), 5.99 (2H, s, -OCH_2O-), 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 $C_{17}H_{16}NO_3Br$: 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 BH_3-Et_2O complex (2.25 mL, 7.5 mmol) and 1.0 M BH_3-THF solution (45 mL, 0.045 mol) under Ar atomosphere 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 CH_2Cl_2. The extract was washed with water, and solvent was evaporated off to give a residue which was recrystallized from MeOH - Et_2O (2 : 3) to give colorless prisms (**12**, 4.96 g, 86.0 %), mp 192.0～197.0°C. ^{1}H-NMR ($CDCl_3$) δ : 1.94 (3H, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 2.67-3.13 (2H, m, -C<u>H</u>$_2$CH$_2$N-), 3.08-3.48 (2H, m, -CH$_2$C<u>H</u>$_2$N-), 4.27 (1H, q, *J* = 7.0 Hz, -C<u>H</u>CH$_3$), 5.90 (2H, s, -OCH$_2$O-), 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 $C_{17}H_{18}NO_2Br$, 347.0521).

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

To a mixture of **12** (1.5 g, 3.8 mmol) and 5% Na_2CO_3 solution (50 mL, 0.024 mol) in Et_2O (50 mL) was added dropwise the acid chloride of 2-bromo-4,5-dimethoxyphenylacetic acid (1.2 g, 4.3 mmol) in dry Et_2O (20 mL) with vigorous stirring at 10～15°C. After the reaction mixture was continuously stirred for 2 h at 23～27°C, the Et_2O layer was separated. The Et_2O solution was washed with water and dried. Removal of the solvent gave a residue, which was recrystallized from Et_2O to give colorless needles (**13,** 1.7 g, 71.0 %), mp 115.0～118.5°C. ^{1}H-NMR ($CDCl_3$) δ : 1.58 (3H×0.5 ,d, *J*=7.0 Hz, -CHC<u>H</u>$_3$), 1.61 (3H×0.5, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 2.34-3.41 (4H, m, -CH$_2$CH$_2$N-), 3.84-3.88 (8H, m, -OCH$_3$×2 and -COCH$_2$-), 5.20 (1H×0.5, q, *J* = 7.0 Hz, -C<u>H</u>CH$_3$), 5.90 (2H, s, -OCH$_2$O-), 6.10 (1H×0.5, q, *J* = 7.0 Hz, -C<u>H</u>CH$_3$), 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 $C_{27}H_{27}NO_5Br_2$, 603.0256). IR ($CHCl_3$) 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 $POCl_3$ (1.05 mL, 11.4 mmol) in dry CH_3CN (30 mL) was stirred for 2 h at 80～83°C. 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 $NaBH_4$ (0.57 g, 15.2 mmol) at – 78°C with stirring. After the reaction mixture was continuously stirred for 2 h at same temperature, excess of $NaBH_4$ 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 % NH_4OH solution and extracted with $CHCl_3$. The solution was dried and evaporated to dryness leaving a powder, which was purified by column chromatography on silica gel with $CHCl_3$ to give prisms (**14**) and a powder (**15**). **14** — *Rf* = 0.75, CH_3Cl - MeOH (10 : 1), mp 85.0～88.0°C (recrystallized

from EtOH), 0.10 g, 27.0 %. ^{1}H-NMR ($CDCl_3$) δ : 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, -OCH_3), 3.86 (3H, s, -OCH_3), 4.38 (1H, dd, J_1 = 10.3 Hz, J_2 = 3.6 Hz, Ha), 5.96 (2H, s, -OCH_2O-), 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 (M^+ Br, 5.1), 322 (8.0), 254 (100), 229 (7.4), 175 (11.2). HREIMS *m/z* 482.9682 (Calcd for $C_{19}H_{19}NO_4Br_2$, 482.9681). IR ($CHCl_3$) cm^{-1} : 1500, 1450, 1260. **15** — Showing a single spot on TLC, *Rf* = 0.40, $CHCl_3$-MeOH (10 : 2). 24.6 mg, 8.0 %. ^{1}H-NMR ($CDCl_3$) δ : 2.71-3.31 (6H, m, NCH_2CH_2 and Hb, Hc), 3.84 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 4.26 (1H, m, Ha), 5.90 (2H, s, -OCH_2O-), 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 ($[M+1]^+$, 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℃. After stirring was continued for 2 h at 23～27℃, 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℃. ^{1}H-NMR ($CDCl_3$) δ : 1.40 (3H, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 3.52 (2H, s, -CH_2CO-), 3.83 (3H, s, -OCH_3), 3.88 (3H, s, -OCH_3), 5.13 (1H, m, *J* = 7.0 Hz, -C<u>H</u>CH_3), 5.62 (1H, d, *J*=7.0 Hz, -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 $C_{18}H_{21}NO_3$, 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 BF_3-Et_2O complex (47 %, 0.15 mL, 0.050 mol) and 1.0 M BH_3-THF complex (3 mL, 0.003 mol) under Ar atmosphere at 20～25℃ with stirring, and the mixture was further heated for 2.5 h at 68℃. 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}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 2.70 (4H, m, -CH_2CH_2N-), 3.75 (1H, q, *J* = 7.0 Hz, -C<u>H</u>CH_3), 3.82 (3H, s, -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 $C_{18}H_{23}NO_2$, 285.1729).

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

To a suspention 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℃. The reaction mixture was stirred at 80℃ 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, *Rf* = 0.64, AcOEt - MeOH (10 : 1). ^{1}H-NMR ($CDCl_3$) δ : 1.55 (3H×0.5, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 1.58 (3H ×0.5, d, *J* = 7.0 Hz, -CHC<u>H</u>$_3$), 2.19-3.31 (4H, m, -CH_2CH_2N-), 3.79-3.94 (14H, m, -$COCH_2$-, -OCH_3×4), 5.20 (1H×0.5, q, *J* = 7.0 Hz, -C<u>H</u>CH_3), 6.07 (1H×0.5, q, *J* = 7.0 Hz, -C<u>H</u>CH_3), 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 $C_{28}H_{32}NO_5Br$, 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 $POCl_3$ (2.01 mL, 21.90 mmol) in dry MeCN (40 mL) was stirred for 1 h at 80～82℃. 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 $NaBH_4$ (1.11 g, 29.2 mmol) at -78℃ with stirring. After the reaction mixture was continuously stirred for 30 min at same temperature, excess of $NaBH_4$ 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 CH_2Cl_2. The extract was evaporated to dryness leaving a colorless residue whose column chromatography on silica gel with $CHCl_3$ – 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, *Rf* = 0.40 [$CHCl_3$ – MeOH (10 : 1)], mp 113.3～114.5℃ (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ : 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-OCH_3), 3.84 (3H, s, 5'-OCH_3), 3.86 (3H, s, 6-OCH_3), 3.87 (3H, s, 4'-OCH_3), 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). ^{13}C-NMR (100 MHz, $CDCl_3$) : 148.24 (*C*OCH_3), 148.18 (*C*OCH_3), 147.5 (*C*OCH_3), 147.0 (*C*OCH_3), 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 (OCH_3), 56.10 (OCH_3), 55.9 (OCH_3), 55.8 (OCH_3), 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 $C_{20}H_{23}NO_4Br$, 420.0810). *Anal.* Calcd for $C_{20}H_{24}NO_4Br$: 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, *Rf* = 0.77 [$CHCl_3$ – MeOH (10 :

1)]. ^{1}H-NMR ($CDCl_3$) δ : 1.34 (3H, d, J = 6.6 Hz, -CHC<u>H</u>$_3$) 2.46 (1H, m, -NC<u>H</u>$_2$C<u>H</u>$_2$-), 2.87 (1H, dd, J_1 = 13.7 Hz, J_2 = 6.4 Hz, Hb), 2.93 (1H, m, -NC<u>H</u>$_2$C<u>H</u>$_2$-), 3.05 (1H, dd, J_1 = 13.7 Hz, J_2 = 8.2 Hz, Hc), 3.32 (1H, m, -NC<u>H</u>$_2$C<u>H</u>$_2$-), 3.42 (1H, m, -NC<u>H</u>$_2$C<u>H</u>$_2$-), 3.62 (3H, s, 5'-OCH$_3$), 3.72 (1H, q, J = 6.6 Hz, -C<u>H</u>CH$_3$), 3.72 (3H, s, 7-OCH$_3$), 3.80 (1H, undetectable, Ha), 3.85 (3H, s, 6-OCH$_3$), 3.86 (3H, s, 4'-OCH$_3$), 6.16 (1H, s, 6'-H), 6.43 (1H, s, 8-H), 6.60 (1H, s, 5-H), 6.91 (1H, s, 3'-H) 6.95-7.14 (5H, m, phenyl H). EIMS (70 eV) *m/z* (rel. int. %): 524 ([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 (M^+– CH = CH_2). 1-Chloroethylbenzene: GCMS (60～200℃, 3℃/min), t_R = 11.70 min, (70 eV) *m/z* : 140 (M^+), 105 (M^+– 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**).[2] The 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 –OR・$POCl_3$ complex in this conditions.