# CHAPTER IV

RESULTS AND DISCUSSION

These synthetic procedures in this study can be divided into five major steps as follows.

I.   The synthesis of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methyl- ethylamine.

II. The procedures for cyclization of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methylethylamine to the tetrahydroisoquinoline with paraformaldehyde.

III. The procedures for cyclization of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methylethylamine to the tetrahydroisoquinoline with butyl glyoxalate.

IV. The procedures for iodination of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives.

V.   The synthesis of 5-aryl-1,2,3,4-tetrahydroisoquinoline via Suzuki coupling reaction.

I. The synthesis of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methyl-ethylamine

CU-19-01   **CU-19-02**

CU-19-03

CU-19-04
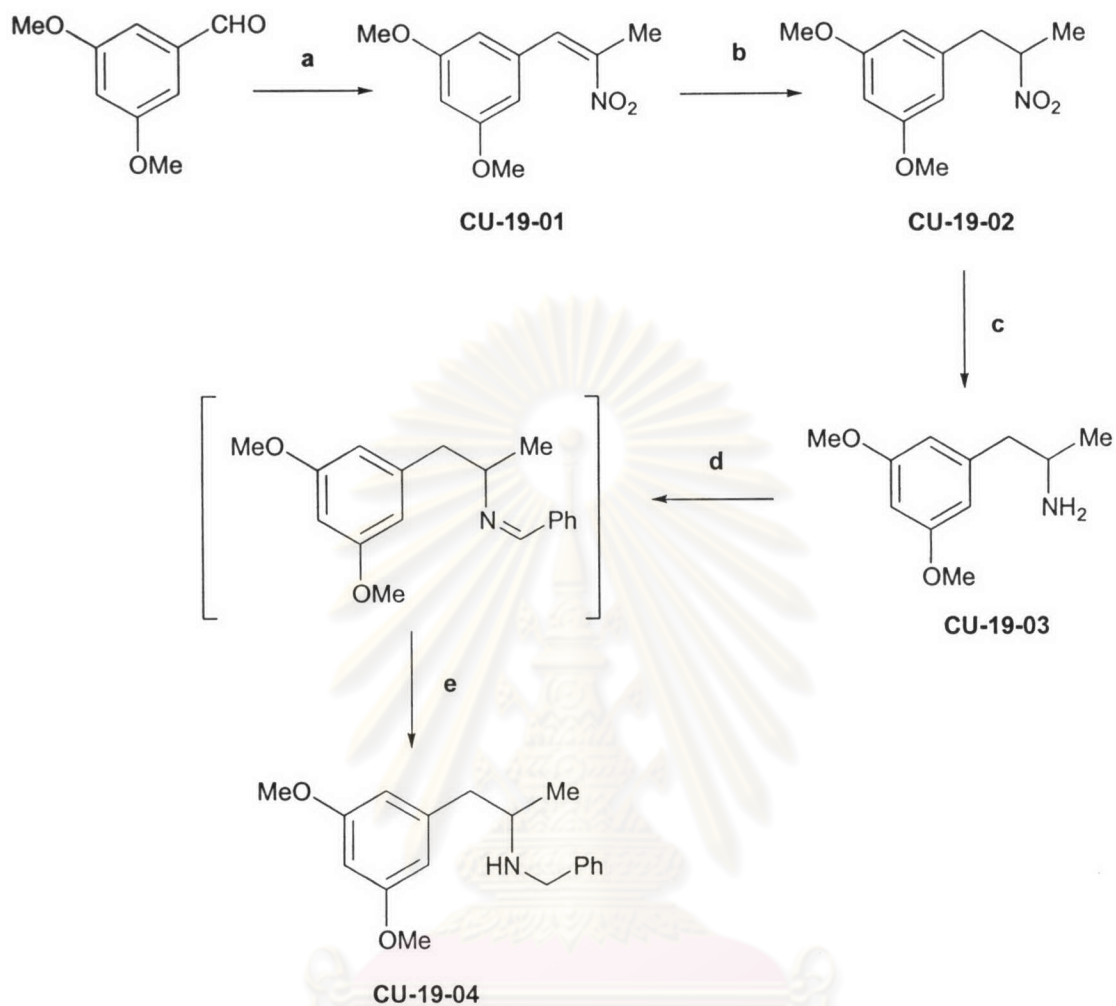
Scheme 6 The synthesis of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methylethylamine; a) $CH_3CH_2NO_2$, NH_4OAc, reflux; b) $NaBH_4$, IPA/CH_2Cl_2, SiO_2, room temperature; c) 10 % Pd/C , H_2, EtOH; d) benzaldehyde, bezene, reflux ; e) $NaBH_4$, EtOH, room temperature.

2-(3′,5′-Dimethyoxyphenyl)-1-methyl-1-nitroethene (CU-19-01)

The 2-(3′,5′-dimethyoxyphenyl)-1-methyl-1-nitroethene(CU-19-01) was prepared by the condensation between 3′,5′-dimethoxybenzaldehyde and nitroethane under refluxing condition in the presence of ammonium acetate. The primary and secondary nitroalkanes are called pseudo acids (false acids) because of the slowness with which they react with base, where true acids instantaneously react with base. The

carbanion can be generated by the acetate anion which acts as base. Nitro group on the molecule can provide the stabilization through the delocalization of negative charge. The carbanion exhibits the nucleophilic character which attacks to the carbonyl carbon of aldehyde to a C-C bond formation. Moreover, the dehydration process can consequently occurred which can be smoothly activated by glacial acetic acid. Finally, the yellow-colored crude products can be recrystallized from the methanol to give an excellent yield (> 90 %) of the 2-(3′,5′-dimethyoxyphenyl)-1-methyl-1-nitroethene. The mechanism of reaction is showed in Figure 186.
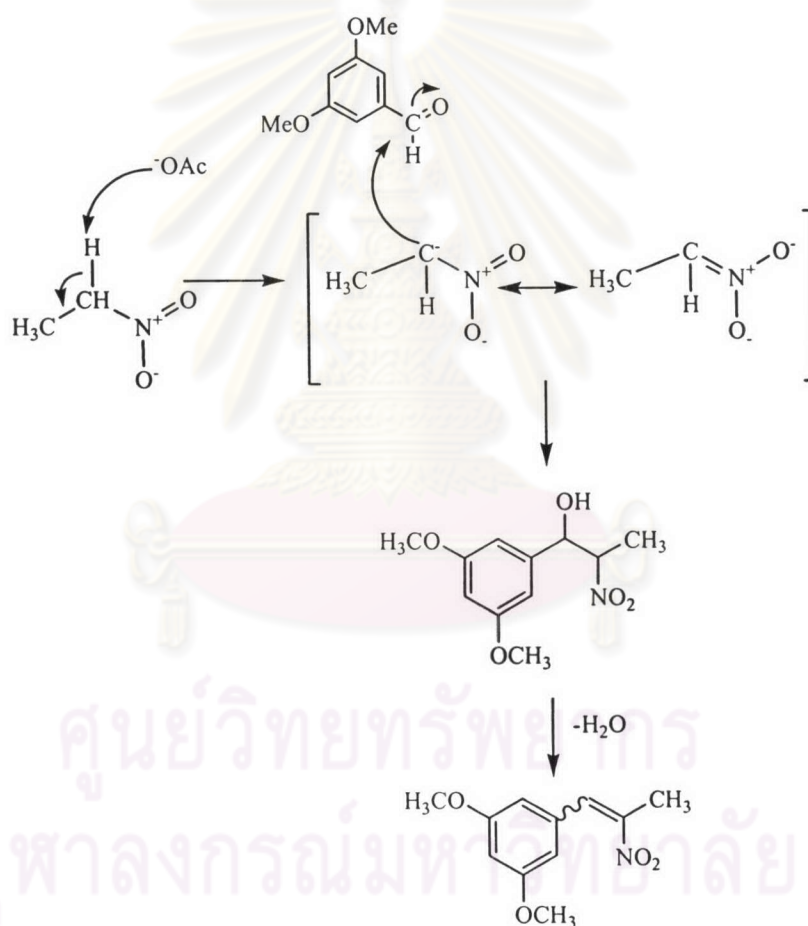

Figure 186 The reaction mechanism of the condensation between 3,5-dimethoxy benzaldehyde and nitroethane

The IR spectrum of product is shown in Figure 16. The nitrostyrene exhibits the specific signal such as the symmetric C=C (aliphatic) stretching vibration at 1649 cm^{-1}, the

asymmetric NO_2 stretching vibration at 1519 cm^{-1} and the symmetric NO_2 stretching vibration at 1321 cm^{-1}, respectively. The region of 1210-1157 cm^{-1} is the result of the asymmetric C-O-C stretching vibration.

The 300 MHz ^{1}H-NMR spectrum of the product in CDCl$_3$ is shown in Figure 17. The olefinic proton signal at δ 8.02 and the methyl proton signal at δ 2.54 confirm the propylene side chain. Moreover, the proton signals exhibit the correlation of all. The proton data are summarized in Table 4.

2-(3$^/$,5$^/$-Dimethoxyphenyl)-1-methyl-1-nitroethane (CU-19-02)

The reduction of nitroalkenes to produce a nitroalkane can be achieved by several distinct methods. Reagents such as sodium borohydride, sodium cyanoborohydride, various complex metal hydrides, and catalytic hydrogenation have been employed for this purpose. Of these, perhaps the most widely used method is the reduction using sodium borohydride. This experiment used sodium borohydride changing the nitrostyrene to nitroalkane in good yield. Unfortunately, in some cases, dimeric products are produced during the borohydride reduction. Mechanistically, these arise from Michael addition of the nitronate intermediate with starting nitroalkene which is shown in Figure 187. Usually with aliphatic nitroalkenes, the formation of these by-products may be suppressed by reaction at reduced pH. In contrast, sodium borohydride reductions of β-nitrostyrenes often result in significant dimerization even when the reaction is run at pH 3. It has recently been reported that the use of silica gel in mixed chloroform-propanol solvent system assists the sodium borohydride reductions of nitroalkenes (Sinhababu and Borchardt, 1983). The products are obtained in high yield and purity and are largely free of dimeric contaminants. Moreover, the yields are generally superior to the silica method which increases the surface of reaction. In this experiment, the method is operationally simple and gives pure products under mild conditions. Conclusively, the solvent mixture prevented the production of dimeric products since the nitronate intermediates were poorly soluble in this medium. The solvent mixture ratio, which reduced the dimeric by-product in this experiment, is 50 % isopropanol in dichloromethane. The

reaction smoothly occurred at room temperature overnight. After that, the glacial acetic acid was used to neutralize the alkaline and eliminate the excess borohydride reagent. The reaction mixture was filtrated and washed the silica gel with dichloromethane in order to minimize the silica gel absorption of the product. Then, the concentrated solution was extracted by 5% sodium bicarbonate solution to neutralize the excess acid in previous step and washed the solution by water, respectively.
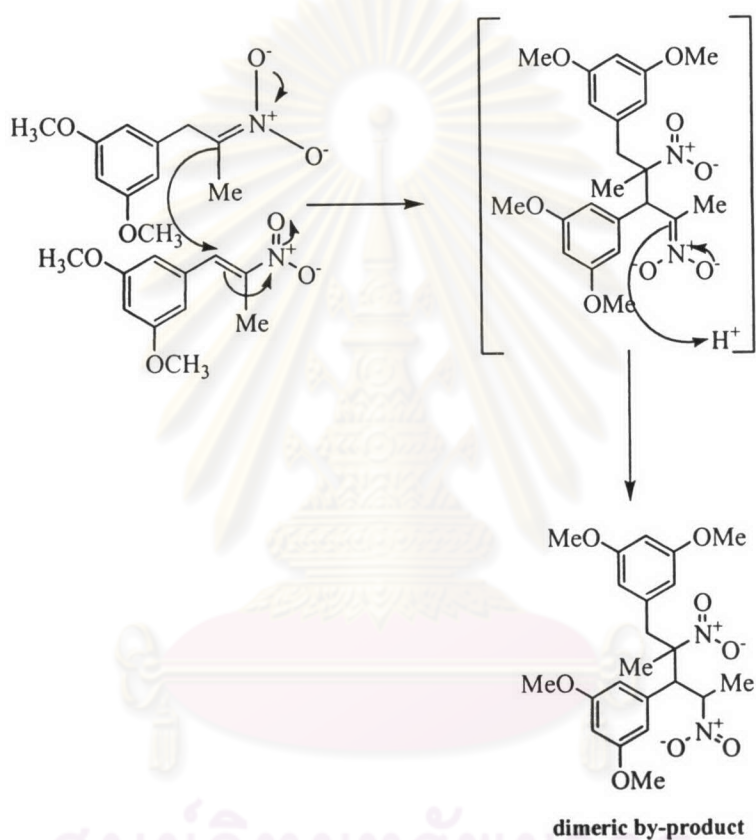

Figure 187 The reaction mechanism of the dimerization of nitrostyrene

The IR spectrum of the reduced product is illustrated in Figure 19. It has not the absorption signal of C=C stretching vibration at 1649 cm^{-1}.

The 300 MHz ^{1}H-NMR of the reduced product is illustrated in Figure 20 and the data are summarized in Table 4.

2-(3′,5′-Dimethoxyphenyl)-1-methylethylamine (CH-19-03)

Functional groups with multiple bonds to nitrogen are also readily reduced by catalytic hydrogenation. Nitro compounds are smoothly converted into primary amines. Thus β-phenylethylamines, useful for the synthetic of isoquinolines, are conveniently obtained by catalytic hydrogenation of α,β -unsaturated nitro compounds. Anhydrous inorganic acids are often used as the catalyst in the catalytic hydrogenation. Sulfuric acid, the choice in the hydrogenation, is responsible to remove and to stabilize the phenylethylamine product. Unfortunately, sulfonation on the aromatic ring containing electron donating group are the competitive side reaction. Thus, glacial acetic acid, anhydrous organic acids, is recommended in this condition. In this experiment, 10 % Pd/C including 5 % glacial acetic acid in ethanol solution was used. Then, the reaction mixture was shaken under pressure of hydrogen atmosphere in a Parr hydrogenation apparatus.

In the process, the amine salt can be separated from the nitro starting compound by partition in acidic aqueous solution. The acidic aqueous solution was basified to convert the salt form to the free amine base.

IR spectrum of product is shown in Figure 24 which has N-H stretching vibration at 3200 cm^{-1}.

The 300 MHz ^{1}H-NMR of product is shown in Figure 25, and the data are summarized in Table 4.

N-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methylethylamine (CU-19-04)

The purpose of the benzyl group addition on the nitrogen of the phenylethylamine is responsible for the control of stereochemistry in the next ring closure step. Formation of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine is prepared through two consequent steps. First step, the imine intermediate is occurred by reacting between benzaldehyde and phenylethylamine in benzene solution. The reaction smoothly generated the Schiff base after dehydration process in the Dean-Stark apparatus. The imine is unstable in the air and high

moisture condition. Therefore, the next reduction was continuously proceeded by using sodium borohydride. The reaction mechanism is illustrated in Figure 188.
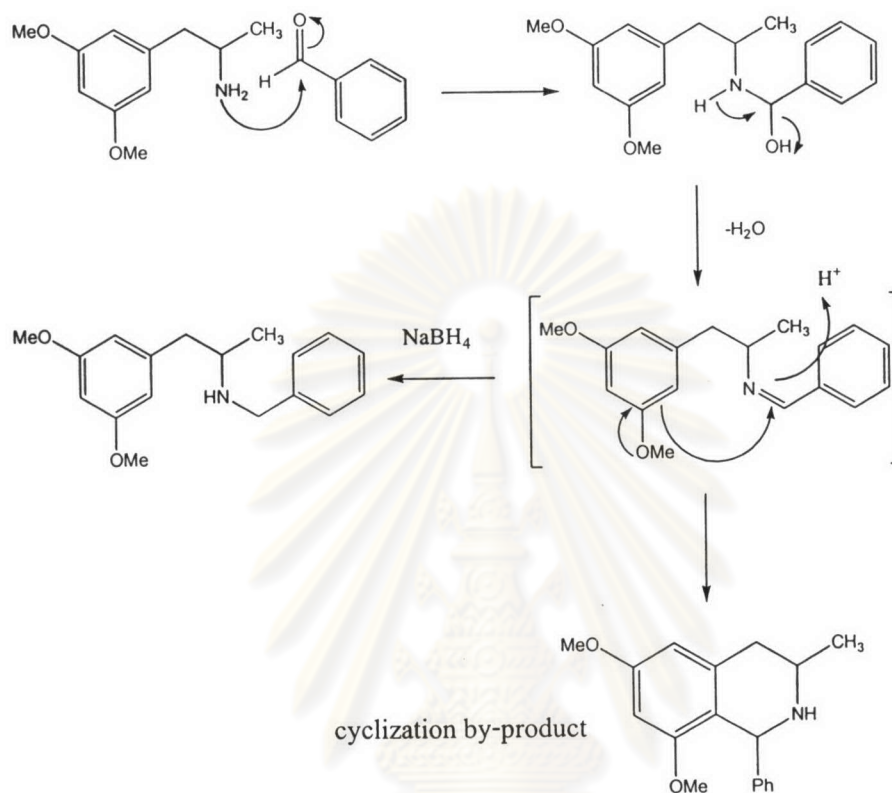

Figure 188 The reaction mechanism to synthesis of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine and 1-phenyl-1,2,3,4-THIQ.

The IR spectrum of the target product is shown in Figure 29. Its spectrum shows N-H stretching vibration of secondary amine at 3250 cm^{-1}

The 300 MHz H^1-NMR of the target product is shown in Figure 30, and the data are summarized in Table 4.

In this experiment, excess benzaldehyde is used to promote the complete Schiff base formation. However, the excessive benzaldehyde can also react with sodium borohydride in the next step to form benzyl alcohol as the impurity which can be separated by the column chromatography. When less than 3 equivalents of the sodium borohydride was added, the Schiff base intermediate may be incompletely reduced and can be cyclized to the 1-phenyl

THIQ (proved by ^{1}H NMR and ^{13}C-NMR) by glacial acetic acid addition in the workup process. Therefore, accurately adding 3-5 equivalents of sodium borohydride of the starting material may be also essential to obtain the highest yield and the lowest 1,2,3,4-tetrahydro-isoquinoline (THIQ) by-product (CU-22-01) in this step.

Moreover, this byproduct (CU-22-01), the *trans*-diastereoisomer compound, can be proved by various NMR techniques. As for the coupling constants in ^{1}H-NMR, the coupling constant value between H_{ax} or H_{eq} of 4-position and H of 3 position have been very useful to show the configuration of 3-H. Coupling constants were shown in two values as previous reported two different values (11.0 Hz. and 4.0 Hz) which they imply the axial-axial vicinal coupling and the axial-equatorial vicinal coupling of them, respectively. In addition, a strong Nuclear Overhauser effect (NOE) between H (aromatic system) and H_{ax} at the position 3 that is present in CU-22-01 can proved the *trans*-directional orientation between 1-phenyl ring and 3-methyl group. Finally, the three dimensional structure can be elucidated and illustrated in Figure 189.
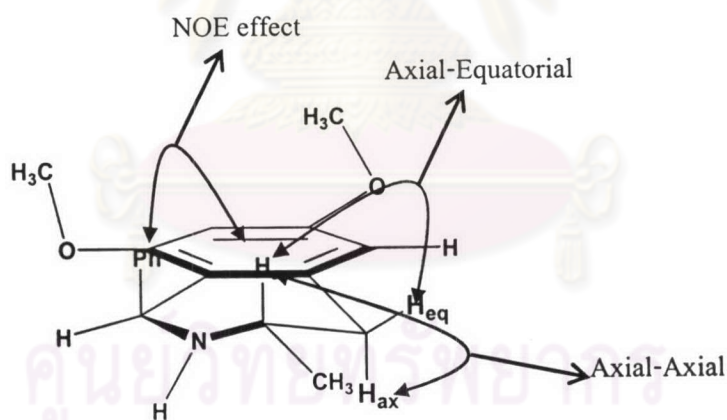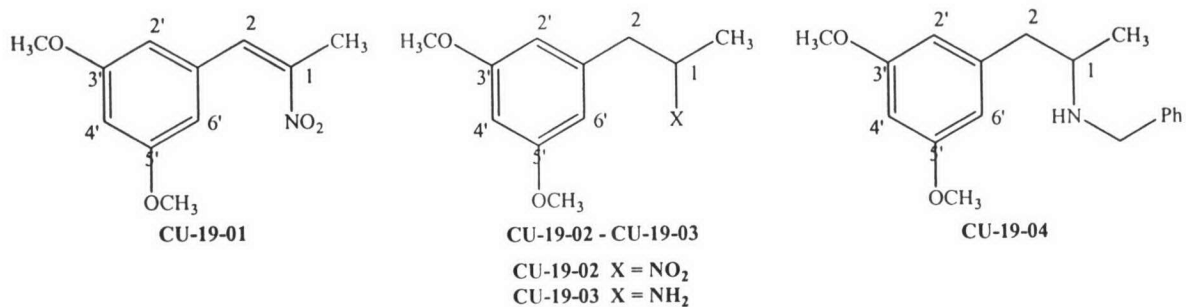

Figure 189 Structure of 1-phenyl-3-methyl-6,8-dimethoxy-1,2,3,4-THIQ in three dimensions

The IR spectrum of the cyclizing THIQ by-product is shown in Figure 176.

The 300 MHz H^1-NMR of the target product is shown in Figure 177 and 178. The proton chemical shift of proton at C-1 exhibited at 5.34 ppm, and the data are summarized in Table 5.

Table 4 The ^{1}H-NMR spectral data of CU-19-01, CU-19-02, CU-19-03, and CU-19-04

CU-19-01

CU-19-02 - CU-19-03
CU-19-02 X = NO$_2$
CU-19-03 X = NH$_2$

CU-19-04

positions	δ_H(ppm) , mult (J in Hz)			
	CU-19-01	CU-19-02	CU-19-03	CU-19-04
1-CH$_3$	2.45, s	1.55, d (6.5)	1.12, d (6.3)	1.11, d (6.2)
1	-	4.77, m	3.16, m	2.93, m
2	8.01, s	2.91, dd (13.7,6.7)	2.44, dd (13.1,8.3)	2.60, dd (13.2, 6.2)
		3.29, dd (13.7,7.3)	2.66, dd (13.1,5.1)	2.70, dd (13.2, 7.4)
2$'$	6.55, d (2.1)	6.31, s	6.34, m	6.32, s
3$'$-OCH$_3$	3.82, s	3.77, s	3.77, s	3.75, s
4$'$	6.52, d (2.1)	6.39, s	6.34, m	6.32, s
5$'$-OCH$_3$	3.82, s	3.77, s	3.77, s	3.75, s
6$'$	6.55, d (2.1)	6.31, s	6.34, m	6.32, s
NH	-	-	1.52, s	1.80, s
N-CH$_2$-Ph	-	-	-	3.70, d (13.2)
				3.88, d (13.2)
Aromatic -H	-	-	-	7.18-7.34

Table 5 The ^{1}H-NMR spectral data of CU-22-01
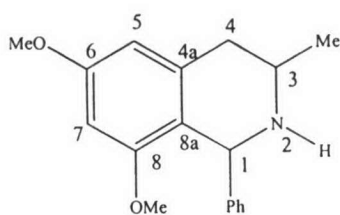
positions	δ_H(ppm) , mult (J in Hz)
	CU-22-01
1-CH$_3$	1.10, d (6.2)
1	5.30, s
2	2.00, s
3	3.00, m
4	2.58, dd (11.0, 16.5)
	2.79, dd (4.0, 16.5)
6-OCH$_3$	3.55 or 3.82, s
5	6.30, s
7	6.25, s
8-OCH$_3$	3.85 or 3.55, s
Aromatic -H	7.09-7.28

II. The procedures for cyclization of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methyl-ethylamine to the tetrahydroisoquinoline with paraformaldehyde.
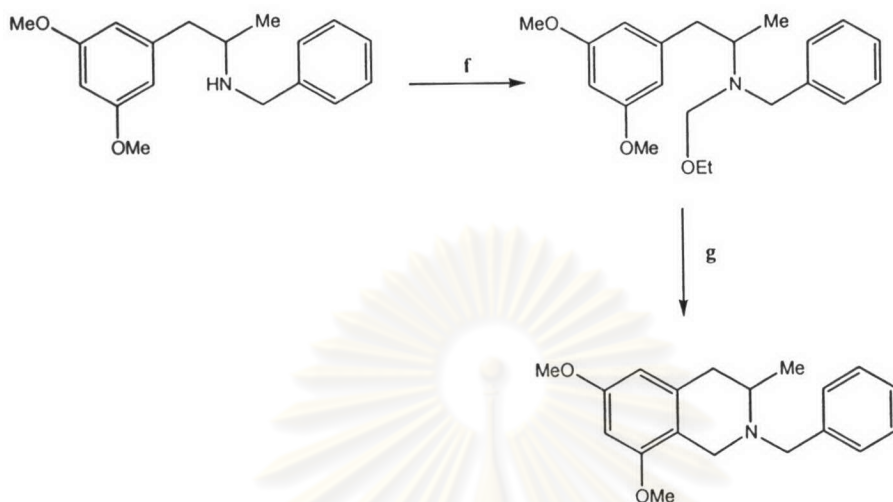
Scheme 7 The synthetic routes of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydro-isoquinoline; f) HCHO, K_2CO_3, EtOH, room temperature; g) 0.5 M TFA in CH_2Cl_2, 0 $^\circ$C

2-Benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline(CU-19-05)

Cyclization of the phenethylamine to tetrahydroisoquinoline can be carried out by various methods. *O,N* -acetal cyclization is the mild and convenient reaction that is chosen in this experiment. Moreover, *trans*-diastereospecific of variable substitutes at the first position of 1,2,3,4-tetrahydroisoquinoline derivative can be easily prepared by the corresponding various aldehyde which will be discussed later. In this experiment, paraformaldehyde in the presence of suitable base as potassium carbonate was used to generate the *O,N* -acetal intermediate, which on subsequence ring closure in presence the efficient trifluoroacetic acid to give the corresponding 1,2,3,4-THIQ compound. The cyclization reaction mechanism is illustrated in Figure 190 (Kubo *et al.*, 1987).
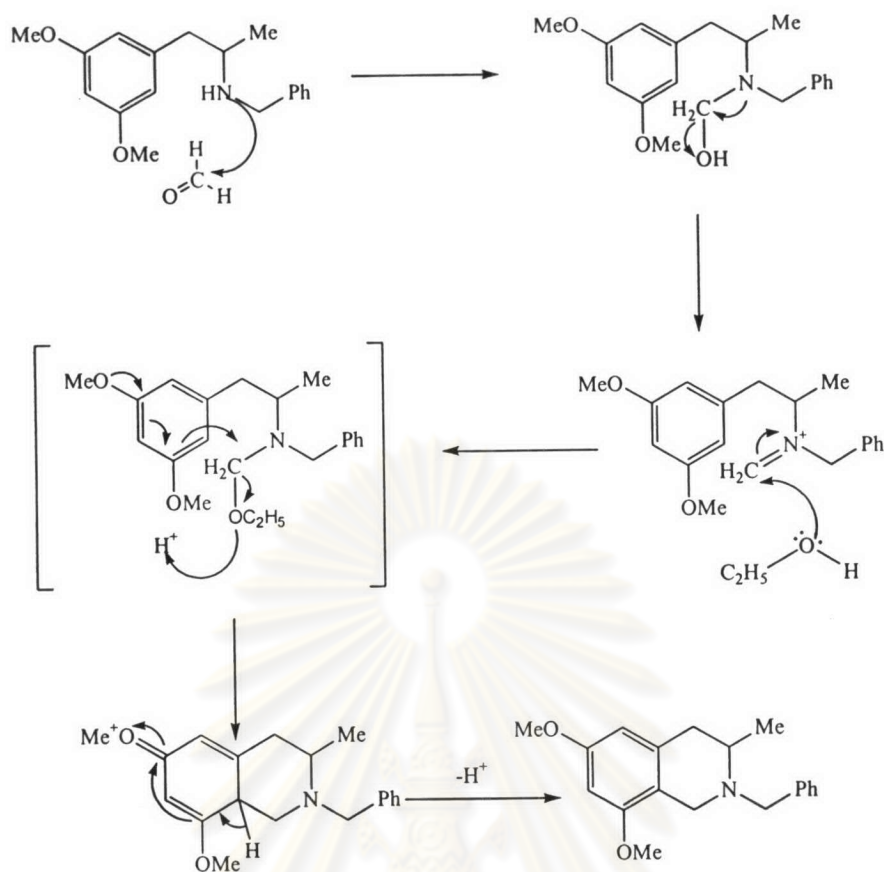
Figure 190 The reaction mechanism of ring cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine to generate the 1,2,3,4-tetraydroisoquinoline with paraformaldehyde.

The IR spectrum of the THIQ derivative is shown in Figure 34.

The 300 MHz H^1-NMR of the target product is exhibited in Figure 35 and 36 and the data are summarized in Table 6.

III. The procedures for cyclization of *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methyl-ethylamine to the tetrahydroisoquinoline with butyl glyoxal.
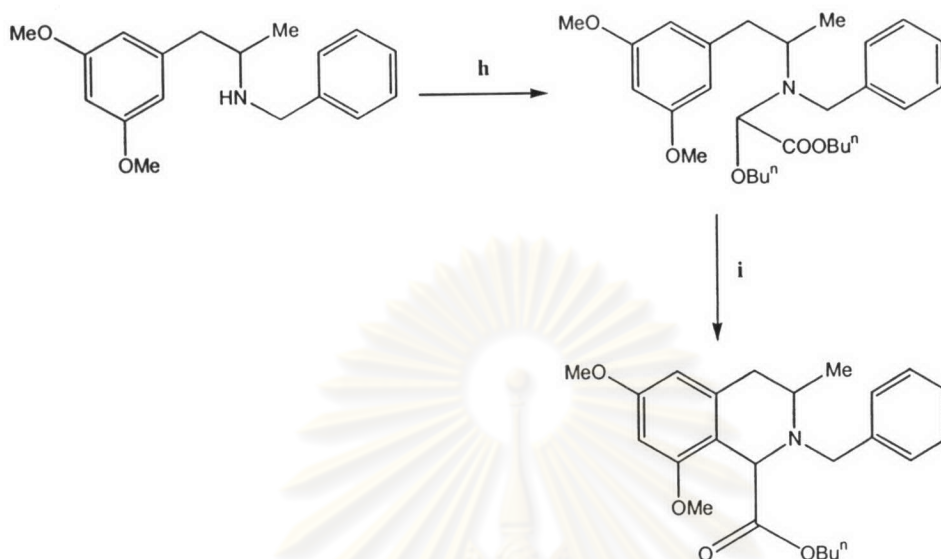
Scheme 8 The synthetic routes of butyl-2-benzyl-6,8-dimethoxy-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate; h) $Bu^nOCOCHO$, K_2CO_3, Bu^nOH, room temperature; i) 0.5 M TFA in CH_2Cl_2, 0 °C.

Butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate(CU-19-10)

Reaction between *N*-benzyl-2-(3,5-dimethoxyl)-1-methylethylamine and butyl glyoxal generated through the *O,N*-acetal intermediate (Kubo *et al.*, 1987). As for the starting aldehyde, butyl glyoxal was prepared by dibutyl L-(+)-tartate through the oxidization of periodic acid. The reaction was carried out in ether at ambient temperature. The vigorous stirring is necessary to generate the completely oxidized product.

The reaction can be prepared in n-butanol as solvent in the presence of suitable base as potassium carbonate to generate the *O,N*-acetal intermediate. It will be smoothly cyclized to the corresponding tetrahydroisoquinoline with 1 equivalent of 0.5 M trifluoacetic acid in CH_2Cl_2 at 0 °C (scheme 8). The cyclization reaction mechanism is illustrated in Figure 192 (Kubo *et al.*, 1987).

Moreover, *trans*-diasteriospecific controlled by sterically hindered benzyl group occurred in the cyclization procedure. Based on assumption of various possible conformations of the six-member ring, two possible chair-like conformations, Ia or Ib, may be adopted. Of these, Ia, which should lead to the *trans*-diastereomer, has its methyl group at the stereogenic center in an axial position, and should be more favorable than Ib, where the equatorial methyl group is likely to be destabilized by the steric effect of benzene. The mechanistically controlled ring-closure of benzyl group is shown in Figure 191.
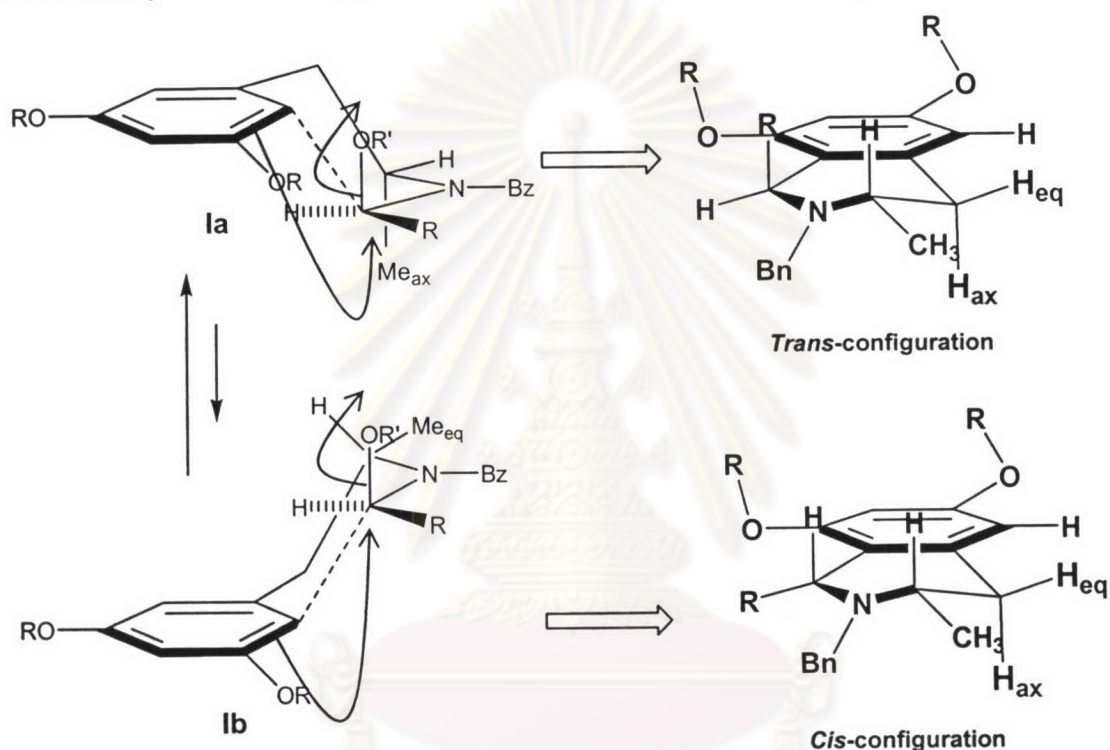

Figure 191 Sterically hindered "benzyl group" controlling *trans*-diasterioselective through *O,N*-acetal cyclization.

In addition, the coupling constant values between both protons at position 4 and the chiral proton at position 3 are 4.4 Hz (J_{eq}) and 9.3 (J_{ax}) Hz, respectively. It shows the 3-methyl group to be the equatorial configuration due to the difference of vicinal coupling constant values between non-equivalent protons at position 4 and the chiral proton at position 3.
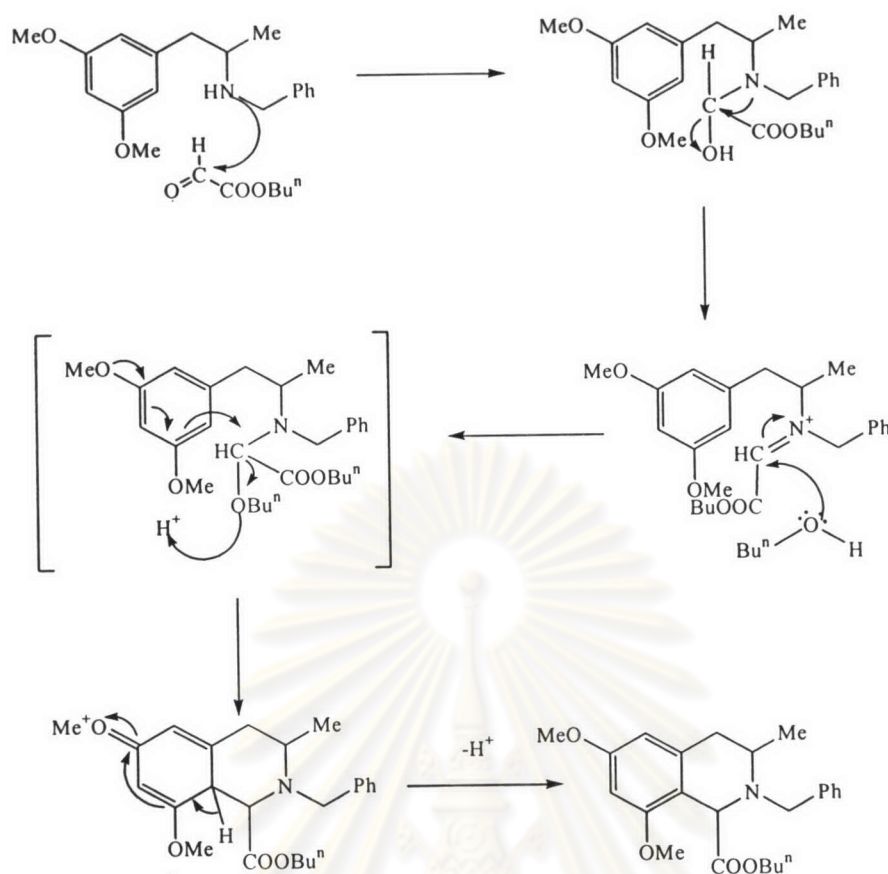
Figure 192 The reaction mechanism of ring cyclization of *N*-benzyl-2-(3,5-dimethoxyphenyl)-1-methylethylamine to generate the 1,2,3,4-tetrahydroisoquinoline with butyl glyoxal

The IR spectrum of target compound is shown in Figure 44 which it is expressed the C=O (ester) stretching vibration at 1735 cm^{-1} and overtone absorption at 3330 cm^{-1}.

The 300 MHz ^{1}H-NMR of product is exhibited in Figure 45 and 46 and the data are summarized in Table 6.

IV. The procedures for iodination of 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives.

CU-20-01 R = H
CU-20-02 R = COOBu^n
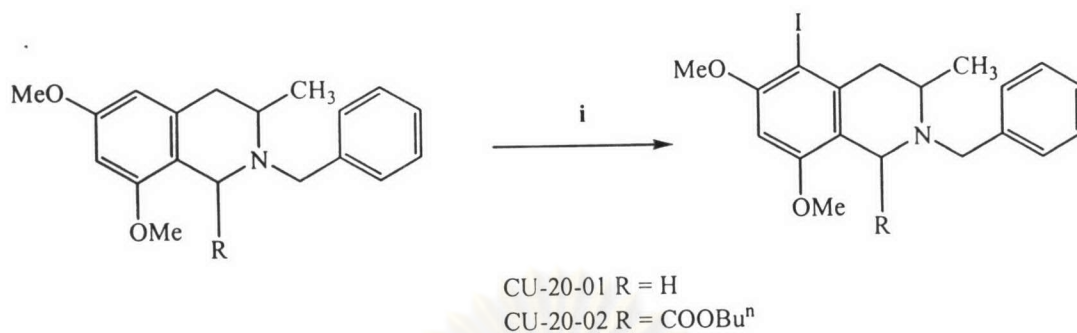
Scheme 9 The synthetic routes of 5-iodo-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetra-hydroisoquinoline derivatives; i) I_2, $AgNO_3$, $EtOH/CH_2Cl_2$, room temperature.

5-Iodo-2-benzyl-6,8-dimethoxy -3-methyl-1,2,3,4-tetrahydroiso-quinoline (CU-20-01)

Iodination of 1,2,3,4-Tetrahydroisoquinoline can be generated in the mild condition. Iodine is slowly added and vigorous stirred in the reaction that composed between 1,2,3,4-THIQ and silver nitrate as the catalyst in ethanol/CH_2Cl_2. Regiospecifically, only 5-position substituted on benzene system was efficiently enhanced with the sterically hindered of the both 6- and 8-methoxy group that protect position 7 from iodide cation attack. Moreover, electron shield of iodide was expelled from negative-charged lone pair electron on the oxygen of the methoxy group. The mechanistically regiospecific-controlled reaction of methoxy group is shown in Figure 194. The deshielded 5-carbon position that is present in the starting material is lost in the iodinated-1,2,3,4-THIQ derivative. The 5-carbon position chemical shift shown in Figure 57 will be changed from 104.27 ppm to 82.96 ppm in the 300 MHz ^{13}C-NMR (Figure 193). Furthermore, the 5-iodo THIQ was confirmed with the 300 MHz HMBC experiment that is shown in Figure 64.
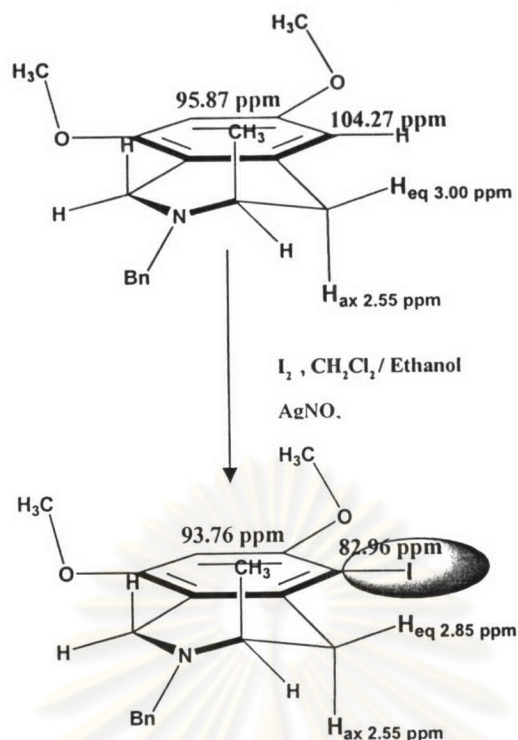
Figure 193 ^{1}H and ^{13}C NMR chemical shift to prove 5-position substitution of iodination.

The IR spectrum of the target compound is shown in Figure 54.

The 300 MHz ^{1}H-NMR of product is exhibited in Figure 55 and 56 and the data are summarized in Table 6.

5-Iodo-butyl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-20-02)

The halogenated derivative can be carried out by various halogens. Iodo-1,2,3,4-THIQ derivatives is the highest relative reactivity in the Suzuki cross-coupling reaction as previous mentioned. Thus, iodine is chosen to prepare the halogenated-1,2,3,4-THIQ derivative in this work. Iodine is slowly added and vigorous stirred in the reaction that contains 1,2,3,4-THIQ and silver nitrate as the catalyst in ethanol/CH$_2$Cl$_2$. Regiospecifically, only 5-position substituted on benzene system was efficiently enhanced with the sterically hindered of the both 6- and 8- methoxy group (Hoye *et al.*, 1999; Sasaki *et al.*, 2003). The mechanistically regiospecific-controlled reaction of the methoxy group is shown in Figure 194. The deshielded 5-carbon position that is present in the starting material is lost in the

iodinated-1,2,3,4-THIQ derivative. The 5-carbon position chemical shift shown in Figure 68 will be changed from 104.76 ppm to 83.17 ppm in the 300 MHz ^{13}C-NMR. Furthermore, the 5-iodo THIQ was confirmed with the 300 MHz HMBC experiment that is shown in Figure 75.
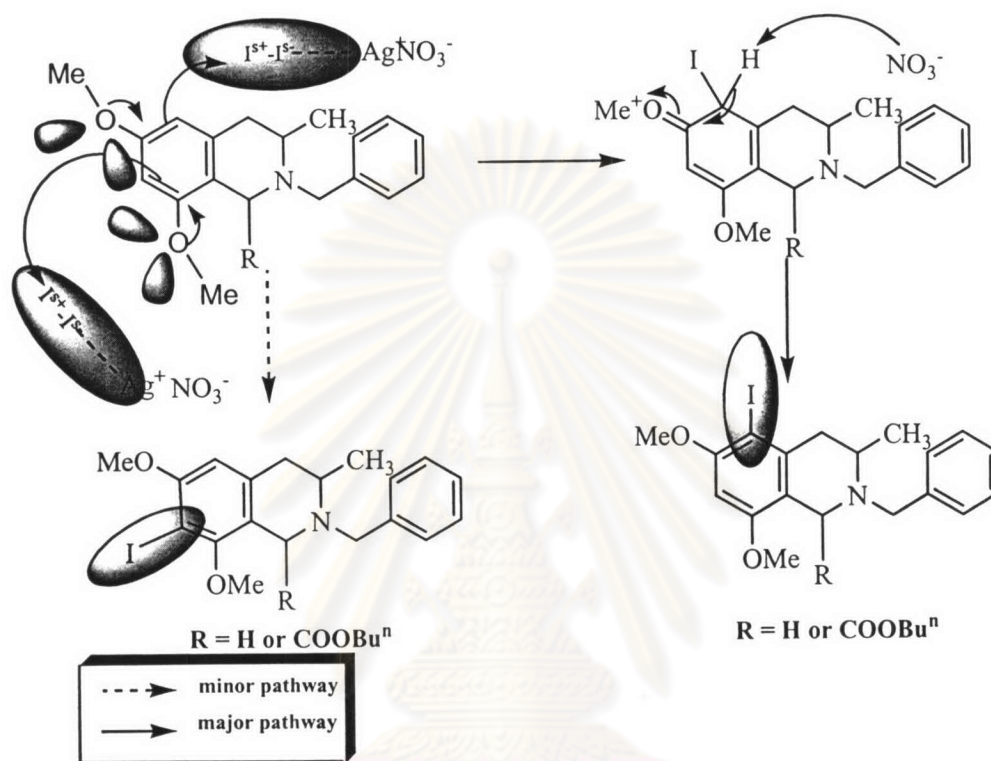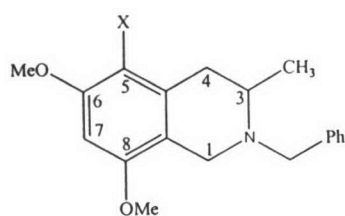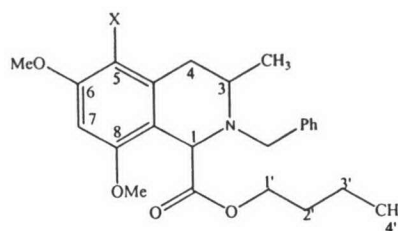

Figure 194 The reaction mechanism of iodination of the 2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives.

The IR spectrum of the target compound is shown in Figure 65.

The 300 MHz ^{1}H-NMR of product is exhibited in Figure 66 and 67 and the data are summarized in Table 6.

Table 6 The ^{1}H-NMR spectral data of CU-19-05, CU-19-10, CU-20-01, and CU-20-02

CU-19-05, CU-20-01   **CU-19-10, CU-20-02**

positions	δ_H (ppm), mult (J in Hz)			
	CU-19-05 X = H	CU-19-10 X = H	CU-20-01 X = I	CU-20-02 X = I
1	3.57, d	4.41, s	3.51, d (16.2) 3.60, d (16.5)	4.40, s
3	3.10, m	3.46, m	3.10, m	3.42, m
3-CH$_3$	1.09, d (6.4)	1.17, d (6.6)	1.15, d (6.5)	1.28, d (6.6)
4	2.55, dd (16.4, 4.7) 3.00, dd (16.4, 4.8)	2.62, dd (16.6, 9.3) 2.74, dd (16.6, 4.4)	2.55, dd (16.9, 5.6) 2.85, dd (16.9, 4.9)	2.49, dd (17.2, 10.5) 2.70, dd (17.2, 4.1)
5	6.25 or 6.27, s	6.26, s	-	-
6-OCH$_3$	3.74 or 3.79, s	3.65 or 3.78, s	3.78 or 3.89, s	3.70 or 3.85, s
7	6.25 or 6.27, s	6.26, s	6.30, s	6.35, s
8-OCH$_3$	3.79 or 3.74, s	3.65 or 3.78, s	3.89 or 3.78, s	3.70 or 3.85, s
N-CH$_2$-Ph	3.65, d (13.4) 3.85, d (13.4)	3.59, d (14.5) 3.90, d (14.5)	3.59, d (13.4) 3.82, d (13.4)	3.41, d (14.5) 3.90, d (14.5)
Aromatic-H	7.20-7.41	7.20-7.42	7.20-7.39	7.20-7.48
1$^/$	-	4.08, m	-	4.10, m
2$^/$	-	1.57, m	-	1.65, m
3$^/$	-	1.35, m	-	1.35, m
4$^/$	-	0.91, t (7.3)	-	0.95, t (7.3)

VI. The synthesis of 5-aryl-1,2,3,4-tetrahydroisoquinoline via Suzuki coupling reaction.

R = H or COOBu^n

Ar =
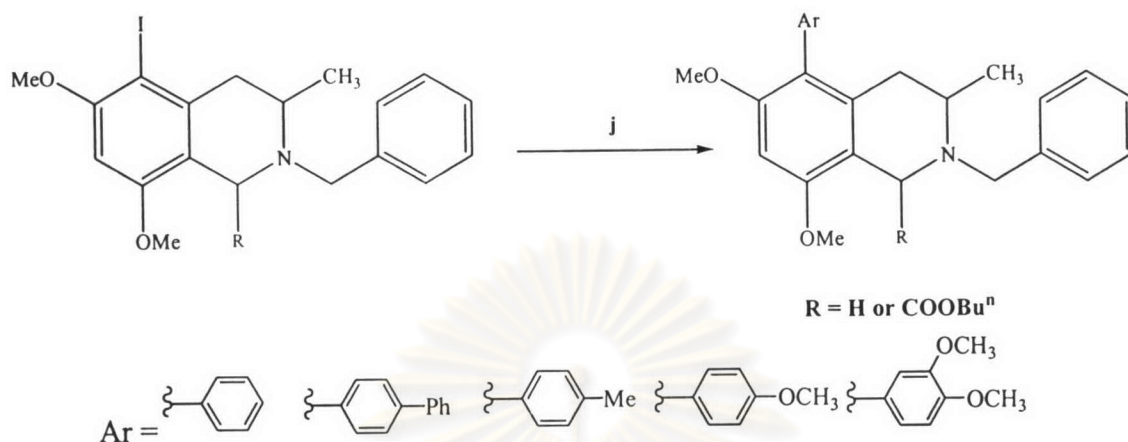
Scheme 10 The synthetic routes of 5-aryl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives ; j) ArB(OH)$_2$, Pd(PPh$_3$)$_4$,toluene, sat. NaHCO$_3$, 110 ^{o}C.

5-Aryl-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (CU-21-01-CU-21-05)

The Suzuki reaction is one of the most common cross-coupling methods in modern organic synthesis and allows C-C bonds to be formed between aryl or alkenyl halides and aryl, alkenyl or alkyl borates in the presence of a palladium(0) catalyst and, if necessary, a suitable base (Miyaura and Suzuki, 1995). The reaction between iodo-1,2,3,4-THIQ and the various aryl boronic acids were introduced to generate the corresponding 5-aryl-1,2,3,4-THIQ derivatives. The reaction condition was proceeded in the presence of the tetrakis(triphenylphosphine) palladium as the catalyst and a suitable base in the refluxed toluene at 110 ^{o}C. A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition, transmetalation and reductive elimination sequences, is illustrated in Figure 193. The reaction mechanism of the catalytic cycle consists of oxidative addition of the halide R-X (R = aryl) onto the palladium(0) catalyst, subsequent transmetallation of the radical R$'$ (R$'$= aryl, alkenyl, alkyl) by the boron compound with formation of an organopalladium(II) compound, and finally reductive

elimination of the coupling product R-R'. The rate-determining step is the oxidative addition of the aryl. The reactivity deceases in the sequence I > OTf > Br >> Cl. Electron-withdrawing substituents on the aryl boronic acid increase the reactivity. Therefore, the preparation of the starting material though the iodinated aromatic compound in the previous step can increase the reaction yield and lessen the reaction time. In many cases, a combination of $Pd(PPh_3)_4$ and aqueous sodium carbonate solution in dimethoxyethane (DME) or toluene are the most suitable. However, other bases, such as Et_3N, $NaHCO_3$ and K_3PO_4, have also successfully been employed. In the case of sterically hindered boronic acids, strong bases, for example aqueous $Ba(OH)_2$ or NaOH, reaction, while weak bases are more favorable in the case of sterically unhindered boronic acids since hydrolytic deboronation is suppressed. The coupling reaction is catalyzed by many palladium(0) complexes. Although phosphine-stabilized palladium complexes are generally more thermally stable, $Pd(PPh_3)_4$, for example, is, however, air- and light-sensitive and has to be used in amounts of up to 10 mol% owing to its limited reactivity. Phosphine-free complexes, for example $Pd(OAc)_2$, are significantly more active. They are reduced to palladium(0) compounds under the reaction conditions. These catalysts are also easier to handle than $Pd(PPh_3)_4$ in air. As previously mentioned, an aryl-aryl exchange between the palladium center and phosphine ligands in palladium(II) complexes is enhanced by electron donating substituents. The synthesis of biaryls substituted with electron-donating groups results in contamination of the coupling product with the aryl group on phosphine ligand. The impurities can be reduced by using Tris(2-methoxyphenyl) phosphine while maintaining a high yield of the desired product (Miyaura and Suzuki ,1995). The condition and the corresponding yield of cross-coupling reaction were summarized in Table 7.

The IR spectra of the target compounds (CU-21-01 to CU-21-05) are shown in Figure 76, 82, 92, 102 and 112, respectively.

The ^{1}H-NMR spectra of products are exhibited in Figure 77, 83, 93, 103 and 113, respectively and the data are summarized in Table 8.

Butyl-(5-aryl)-2-benzyl-6,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (CU-21-06 – CU-21-10)

The cross-coupling reaction between butyl iodo-1,2,3,4-THIQ carboxylate and the various aryl boronic acids were introduced to generate the corresponding butyl 5-aryl-1,2,3,4-THIQ derivatives. The reaction condition was proceeded in the presence of the tetrakis(triphenylphosphine) palladium as the catalyst and a suitable base in the refluxed toluene at 110 °C. However, the reaction reactivity upon the substituents on aryl boronic acid can be showed in the variety of reaction time. The electron-donating substituted aryl boronic acid such as 4-methoxy phenyl boronic acid and 3,4-dimethoxy phenyl boronic acid, decrease the reactivity while the aryl-aryl exchange by-product proved with H^1-NMR technique can be found in this condition. The side-reaction can be minimized by using Tris (2-methoxyphenyl) phosphine in place of tetrakis(triphenylphosphine) palladium while maintaining a high yield of the desired product (Miyaura and Suzuki ,1995). The condition and corresponding yield of cross-coupling reaction are summarized in Table 7.
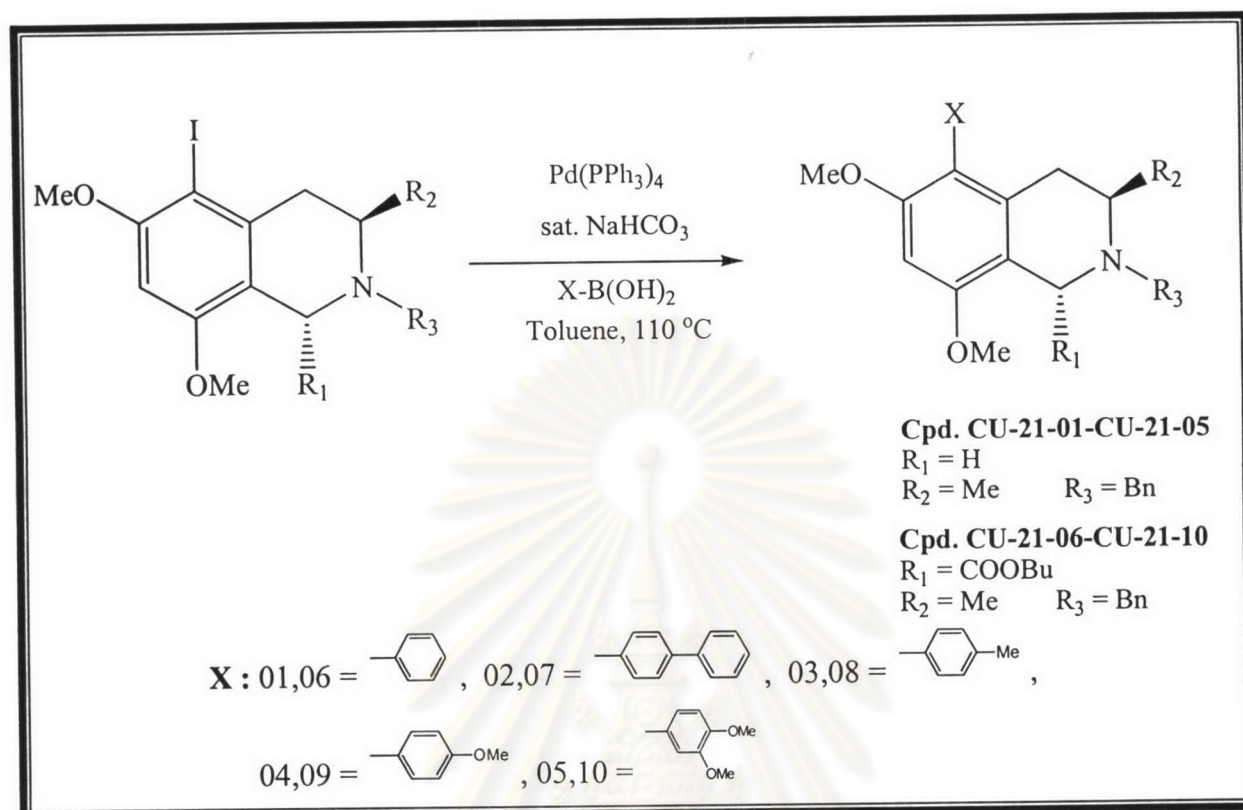
The IR spectra of the target compounds (CU-21-06 to CU-21-10) are shown in Figure 130, 136, 146, 156 and 166, respectively.

The ^{1}H-NMR spectra of products are exhibited in Figure 131, 137, 147, 157 and 167, respectively and the data are summarized in Table 9.

The mechanistically catalytic cycle for cross-coupling is illustrated in Figure 195.

Table 7 Conditions and yield of Suzuki cross-coupling reaction.

Cpd. **CU-21-01-CU-21-05**
R_1 = H
R_2 = Me R_3 = Bn

Cpd. **CU-21-06-CU-21-10**
R_1 = COOBu
R_2 = Me R_3 = Bn

X : 01,06 = , 02,07 = , 03,08 = ,

04,09 = , 05,10 =

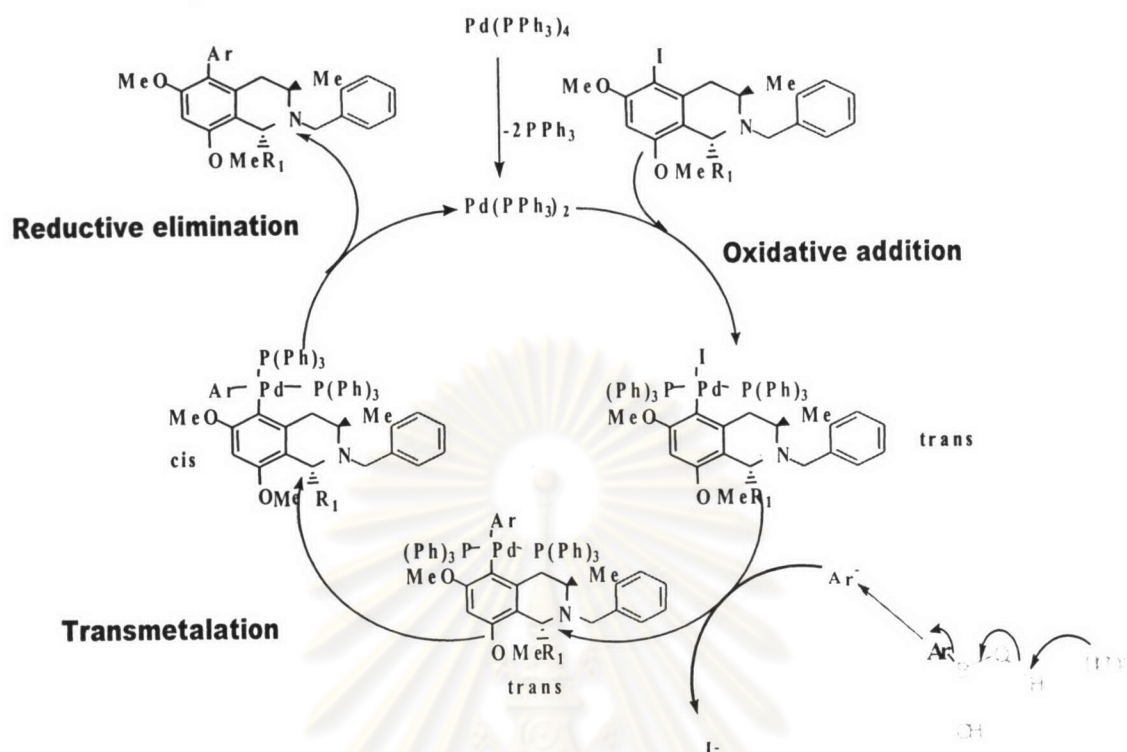| Product	X	Catalyst (eq.)	Reaction Time (h.)	Yield (%)
CU-21-	01	0.24	12	85
CU-21-	02	0.24	5	100
CU-21-	03	0.24	17	95
CU-21-	04	0.24	30	78
CU-21-	05	0.24	48	72
CU-21-	06	0.24	15	96
CU-21-	07	0.24	5	100
CU-21-	08	0.24	20	96
CU-21-	09	0.24	24	86
CU-21-	10	0.24	48	72

Figure 195 A mechanistically catalytic cycle for cross-coupling of 5-iodo-2-benzyl-(6,8-dimethoxy)-3-methyl-1,2,3,4-THIQ derivatives.

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Table 8 The ^{1}H-NMR spectral data of CU-21-01, CU-21-02, CU-21-03, CU-21-04 and CU-21-05
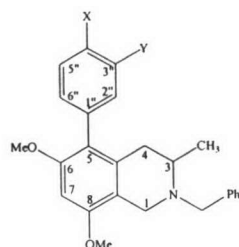
CU-21-01 – CU-21-05

positions	δ_H (ppm), mult (J in Hz)				
	CU-21-01 X = H, Y = H	CU-21-02 X = Ph, Y = H	CU-21-03 X= Me, Y = H	CU-21-04 X = MeO, Y = H	CU-21-05 X, Y= MeO
1	3.65, s	3.65, s	3.62, s	3.62, d	3.62, m
3	2.98, m	3.00, m	2.96, m	2.96, m	2.95, m
3-CH$_3$	1.03, d (6.3)	1.03, d (6.2)	1.04, d (6.4)	1.04, d (6.4)	1.03, d (6.4)
4	2.23, dd (16.9,5.4) 2.65, dd (16.9, 4.6)	2.31, dd (16.8,5.3) 2.71, dd (16.8,4.5)	2.27, dd (16.8,5.4) 2.40, dd (16.8,4.7)	2.28, dd (16.9,5.5) 2.64, dd (16.9,4.6)	2.26, dd (16.8,5.5) 2.67, dd (16.8,5.2)
6-OCH$_3$	3.70 or 3.84, s	3.74 or 3.86, s	3.71 or 3.84, s	3.71 or 3.85, s	3.71 or 3.85, s
7	6.42, s	6.45, s	6.42, s	6.41, s	6.41, s
8-OCH$_3$	3.84 or 3.70, s	3.86 or 3.74, s	3.84 or 3.71, s	3.85 or 3.71, s	3.85 or 3.71, s
N-CH$_2$-Ph	3.60, d (13.6) 3.86, d (13.6)	3.63, d (13.7) 3.88, d (13.7)	3.61, d (13.5) 3.86, d (13.5)	3.59, d (13.3) 3.86, d (13.3)	3.61, m 3.82, m
Aromatic-H	7.10-7.40	7.23-7.74	7.25-7.40	7.22-7.40	7.24-7.39
2$''$	-	-	7.21, d (8.0)	7.13, d (8.6)	6.73, d (1.8)
3$''$	-	-	7.09, d (8.0)	6.95, d (8.5)	-
3$''$-OCH$_3$	-	-	-	-	3.81 or 3.91, s
4$''$	-	-	-	-	-
4$''$-OCH$_3$	-	-	-	3.81, s	3.91 or 3.81, s
4$''$-CH$_3$	-	-	2.40, s	-	-
5$''$	-	-	7.09, d (8.0)	6.95, d (8.5)	6.92, d (7.9)
6$''$	-	-	7.21, d (8.0)	7.13, d (8.6)	6.75, dd (1.8, 7.9)

Table 9 The ^{1}H-NMR spectral data of CU-21-06, CU-21-07, CU-21-08, CU-21-09 and CU-21-10
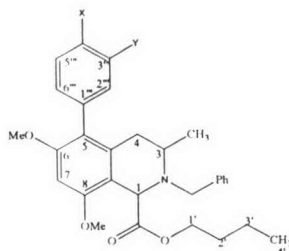
CU-21-06 – CU-21-10

positions	δ_H (ppm), mult (J in Hz)				
	CU-21-06 X = H, Y = H	CU-21-07 X = Ph, Y = H	CU-21-08 X = Me, Y = H	CU-21-09 X = MeO, Y = H	CU-21-10 X, Y = MeO
1	4.53, s	4.56, s	4.50, s	4.51, s	4.52, s
3	3.37, m	3.39, m	3.40, m	3.37, m	3.35, m
3-CH$_3$	1.07, d (6.6)	1.13, d (6.5)	1.07, d (6.6)	1.07, d (6.6)	1.07, d (6.5)
4	2.33, m	2.39, m	2.34, m	2.32, m	2.35, m
6-OCH$_3$	3.73 or 3.78, s	3.76 or 3.79, s	3.72 or 3.77, s	3.72 or 3.76, s	3.73 or 3.77, s
7	6.43, s	6.45, s	6.42, s	6.41, s	6.42, s
8-OCH$_3$	3.78 or 3.73, s	3.79 or 3.76, s	3.77 or 3.72, s	3.76 or 3.72, s	3.77 or 3.73, s
N-CH$_2$-Ph	3.60, d (14.6) 3.89, d (14.6)	3.64, d (14.4) 3.93, d (14.4)	3.60, d (14.5) 3.90, d (14.5)	3.60, d (14.5) 3.90, d (14.5)	3.62, m 3.92, d
Aromatic-H	7.25-7.41	7.20-7.80	7.24-7.47	7.13-7.45	7.22-7.47
1$'$	4.12, m	4.13, m	4.13, m	4.13, m	4.11, m
2$'$	1.65, m	1.63, m	1.63, m	1.63, m	1.63, m
3$'$	1.42, m	1.47, m	1.41, m	1.42, m	1.41, m
4$'$	0.96, t (7.3)	0.95, t (7.3)	0.95, t (7.3)	0.95, t (7.3)	0.90, t (7.3)
2$'''$	-	-	7.13, m	7.17, m	6.75, s
3$'''$	-	-	7.22, d (8.0)	6.96, d (8.5)	-
3$'''$-OCH$_3$	-	-	-	-	3.89 or 3.93, s
4$'''$-CH$_3$	-	-	2.41, s	-	-
4$'''$-OCH$_3$	-	-	-	3.86, s	3.93 or 3.89,s
5$'''$	-	-	7.22, d (8.0)	6.96, d (8.5)	6.93, d (7.9)
6$'''$	-	-	7.13, m	7.17, m	6.79, d (7.9)