CHAPTER V

CONCLUSION

As previously reported, 5-naphthyl-1,2,3,4-tetrahydroisoquinoline alkaloids isolated from Ancistrocladaceae, known as moderately to highly active against *Plasmodium falciparum*, were used to be the lead compounds in order to explore the antimalarial activity (Saxena, Jain and Bhakuni, 2003). Various 5-aryl-1,2,3,4-tetrahydroisoquinoline derivatives were designed to investigate the essential pharmacophore of them. The target compounds were synthesized through the *N*-benzyl-2-(3′,5′-dimethoxyphenyl)-1-methylethylamine along with *O,N*-acetal intermediate cyclization to generate 1,2,3,4-tetrahydroisoquinoline derivatives. Consequently, these derivatives were prepared the various target compounds through Suzuki cross-coupling reaction.

This investigation could successfully synthesize 5-aryl-3-methyl-tetrahydro-isoquinoline and its derivatives with various substituents on 1-position and 5-position of the 1,2,3,4-tetrahydroisoquinoline nucleus which the synthetic routes were divided into five major steps as followed.

I. Procedures for the synthesis of *N*-benzyl-2-(3′,5′-dimthoxyphenyl)-1-methylethylamine, the starting material.

The *N*-benzyl-2-(3′,5′-dimthoxyphenyl)-1-methylethylamine intermediate could be prepared through several steps. The condensation between 3,5-dimethoxy benzaldehyde and nitroethane was introduced to generate the corresponding nitrostyrene compound. Next step, the reduction of unsaturated double bond and the catalytic hydrogenation were employed to afford the 2-(3′,5′-dimethoxyphenyl)-1-methylethylamine. Finally, Schiff base intermediate was prepared and continuously

reduced to give *N*-benzyl-2-(3′,5′-dimthoxyphenyl)-1-methylethylamine as the starting material for the 1,2,3,4-tetrahydroisoquinoline cyclization.

Unfortunately, If Schiff base intermediate is incompletely reduced, the by-product, 1-phenyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline, will be presented in synthetic process. This related compound could be isolated from the target compound with the chromatographic technique as the purification process.

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

For this experiment, the *O,N*-acetal cyclization was chosen being the synthetic strategy because this procedure is operationally simple and gives moderately pure products under mild conditions for preparing the diastereospecific THIQ derivatives. The cyclization product could be prepared via two consequent steps. Firstly, the amine derivative reacted with paraformaldehyde in presence of potassium carbonate to afford the *O,N*-acetal intermediate. And then, the intermediate was treated with one equivalent of 0.5 M TFA in CH_2Cl_2 at 0 °C to immediately induce the cyclization process becoming the corresponding tetrahydroisoquinoline compound in good yield.

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

Cyclization through the *O,N*-acetal intermediate with the butyl glyoxal reagent to proceed the preceding condition can also generate the corresponding tetrahydroisoquinoline compound with two asymmetric carbon including position 1 and 3. Diastereospecific synthesis strategy was essentially employed to prepare the pure diastereomer. Sterically hindered benzylic group was used to control the configuration of the target compound. *O,N*-acetal cyclization, one of the various synthetic procedure, was introduced in this experiment because it represents the mild and convenient condition.

The cyclization product could be prepared through two consequent steps. Firstly, the amine derivative reacted with butyl glyoxal in presence of potassium carbonate to afford the *O,N*-acetal intermediate. And then, the intermediate was treated with 1 equivalent of 0.5 M TFA in CH_2Cl_2 at 0 $^{\circ}C$ to immediately induce the cyclization process becoming the corresponding tetrahydroisoquinoline compound in high yield.

IV. The procedure for halogenation of 1,2,3,4-tetrahydroisoquinoline derivatives.

In synthetic procedure, various halogens can be introduced in the tetraydroisoqinoline nucleus. In addition, regiospecific-controlled by sterically hindered of the both 6- and 8-methoxy group on the position 7 occurred in the halogenation reaction to enhance only 5-position substituted on benzene ring. Although iodine is the least reactive of the various halogens in aromatic substitution and reversibility is important enough so that iodination is seldom feasible, the highest relative reactivity on Suzuki cross-coupling of these derivatives is essential to access the reasonable yield and high purity. Furthermore, iodine was chosen to prepare the halogenated-1,2,3,4-THIQ derivatives in this experiment due to easy handle and mild condition. It was introduced to generate the electrophile with silver nitrate as the catalyst.

V. The corresponding 5-aryl-3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives synthesis via Suzuki Coupling reaction.

The cross-coupling reaction between 1,2,3,4-THIQ derivatives and the various aryl boronic acids were introduced to generate the corresponding 5-aryl-1,2,3,4-THIQ derivatives. The reason for the successful introduction of the Suzuki reaction in synthetic procedure are that it is very versatile, tolerates numerous functional groups and usually works under gentle conditions. The reaction mechanism of this catalytic cycle consists of three major steps. Firstly, oxidative addition of the halogen compounds onto the palladium(0) catalyst, subsequent transmetallation of the radical by the boron compound with formation of an organopalladium(II) compound. Finally, reductive

elimination of the coupling product. The rate-determining step is the oxidative addition of the aryl halide (Miyaura and Suzuki, 1995). Therefore, the good leaving group on the aromatic nucleus as well as iodine is the highest reactivity in this reaction. Electron withdrawing substituted on aryl boronic acid nucleus also increase the reactivity.

Asymmetrical biaryl compound including CU-21-05 and CU-21-10 can show rotational isomer phenomenon in the solution. This phenomenon can be proved by the NMR spectroscopy techniques in low temperature condition. Atropisomerism, a type of stereoisomerism that steric congestion between the substituents restricts free rotation about the sp^2-sp^2 carbon-carbon bond, is eradicated in these analogues because it is not manifested typically in *ortho*-substituted biphenyls. Suzuki reaction is successful for aryl triflates and iodo- and bromoarenes. Chlorobenzene derivatives are generally quite inert to oxidative addition. The reaction is proceeded in heterogeneous conditions with moderate reactivity. Although steric hindrance of aryl halides not a major factor for the biaryls, low yield are resulted in when using *ortho*-disubstituted arylboronic acids. The addition of strong bases, e.g., aqueous NaOH or $Ba(OH)_2$, both in benzene and DME exerts a remarkable effect on the acceleration of the coupling rate but weak bases give better results of less hindered arylboronic acids. Even if there is no great steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive hydrolytic deboronation as contaminant. This problem can be improved by using the corresponding ester of boronic acid instead of the aryl boronic acid. In the other case, aryl-aryl exchange between the palladium center and phosphine ligands in palladium (II) complexes can be enhanced by the electron-donating type of aryl boronic acid results in contamination of the coupling product with the aryl group on phosphine ligand. Tris(2-methoxyphenyl) phosphine is effective in reducing the formation of the contaminant and maintaining a high yield of the target product. Thus, the experiment condition was designed to be the reaction between the corresponding 1,2,3,4-tetrahydroisoquinoline derivatives and various aryl boronic acids in the present of tetrakis(triphenylphosphine) palladium as catalyst and saturated sodium bicarbonate in toluene as solvent at 110 °C.