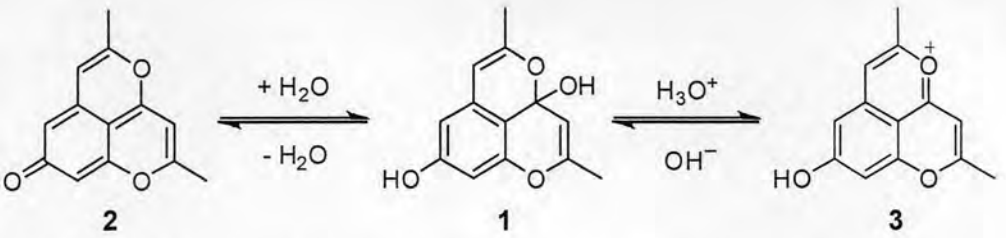
CHAPTER I

INTRODUCTIONS

Cassia siamea or Thai name called "Khi Lek" is a small to medium sized tree with a short bole, low branching and high crown. Leaves are the pinnate and alternated leaves with a marked furrow 8 to 13 pairs of leaflets in different size. Flowers are yellow color, which are dense racemes at the end of the shoots (Figure 1). *Cassia siamea* is a plant belonging to the family *Caesalpiniaceae* which is a distributed plant in the Southeast Asia including Thailand. In Thailand, the different parts of this plant have been known as Thai traditional medicines for, such as, fever, diabetes, hypertension, asthma, constipation, diuresis and insomia [1]. From the previous researches, the chemical constituents of *Cassia siamea* are known such as antraquinones [2,3], isoquinolone alkaloids [4], chromones and chromone alkaloids [5,6] and dioxanphenalenes [7]. Especially, barakol (**1**, Scheme 1-1) is a major natural compound of dioxaphenalene or chromone hemiacetal which is a major natural product in fresh young leaves and flowers of this plant.

Figure 1-1. *Cassia siamea*; (a) trunk of *C. siamea*, (b) flowers of *C. siamea* and (c) leaves of *C. siamea*.



Scheme 1-1. Chemical conversion of barakol (**1**), anhydrobarakol (**2**) and anhydrobarakol salt (**3**).

1.1 Chemical and Biological Properties of Barakol

Compound **1** as pale yellow needle crystals is stable in hydroxylic solvents or in a moist atmosphere. Therefore, barakol is easily dehydrated even *in vacuo* or dissolved in non-hydroxylic solvents such as chloroform, acetone or acetonitrile to convert an anhydrobarakol (**2**) as a green solid which is unstable and decompose at high temperature (Scheme 1-1). However, barakol can be recovered by dissolving **2** in aqueous hydroxylic solvents. In addition, reaction of alcoholic solutions of barakol, for example the solution in methanol and ethanol, with concentrated hydrochloric acid or hydrobromic acid produce an anhydronium salt of an anhydrobarakol chloride or bromide (**3**) which are more stable than **2** [8].

Moreover, barakol has been known for its various effects in the biological activities such as reduction of spontaneous locomotor activity [9], stimulation of ions secretion [10] and suppression of norepinephrine-induced inhibition [11].

1.2 Discovery of Cassiarins A and B

In 2007, Morita and co-workers [12] discovered two new natural products which were isolated from leaves of *Cassia siamea*, called cassiarin A (**4**) and cassiarin B (**5**) (Chart 1). **4** and **5** are alkaloids with an unprecedented tricyclic skeleton structure similar to the anhydronium salt **3** and to the neutral **2**, respectively.

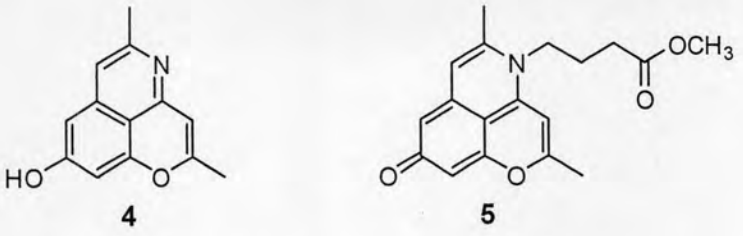
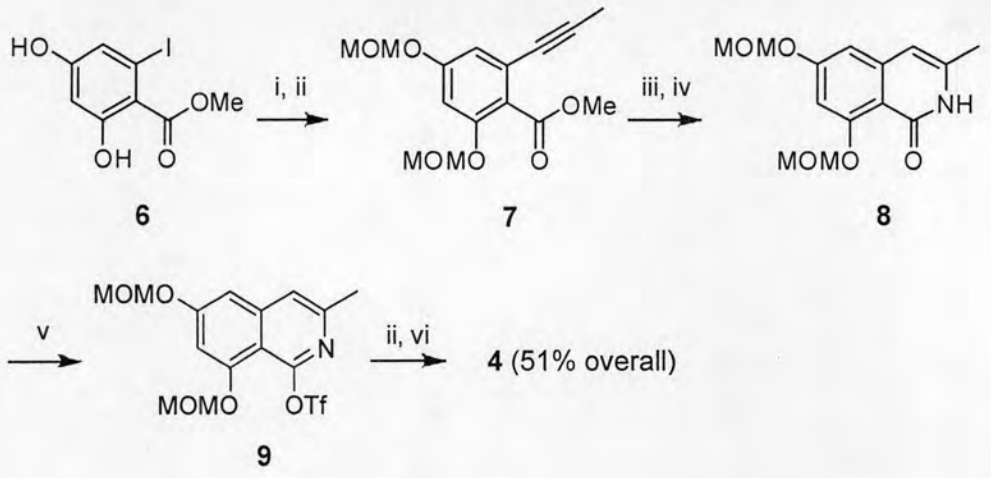


Chart 1-1. Structure of **4** and **5**.

Furthermore, these two cassiarins exhibit the potent antiplasmodial activity against *Plasmodium falciparum* [12] and, hence, become very attractive target molecules in organic synthesis.

1.3 Total Synthesis of Cassiarins A and B

The first total synthesis of **4** was reported by Rudyanta and co-workers [13]. The synthesis was started with MOM-protection of methyl-6-iodo-2,4-dihydroxybenzoate (**6**) followed by Sonogashira coupling of the resulting protected intermediate with *in situ* generated propyne to provide compound **7** (Scheme 1-2). Hydrolysis of **7** with an aqueous basic solution and then condensation with ammonium hydroxide produced isoquinolone **8**. Treatment of the latter with *N*-phenyl-bis(trifluoromethanesulfomide) in the presence of sodium hydride afforded triflate compound **9**. Finally, Sonogashira coupling of **9** with *in situ* another portion of generated propyne and upon the subsequent 6-endo-dig acid-catalyzed cyclization was performed to give **4** in 51% overall yield.



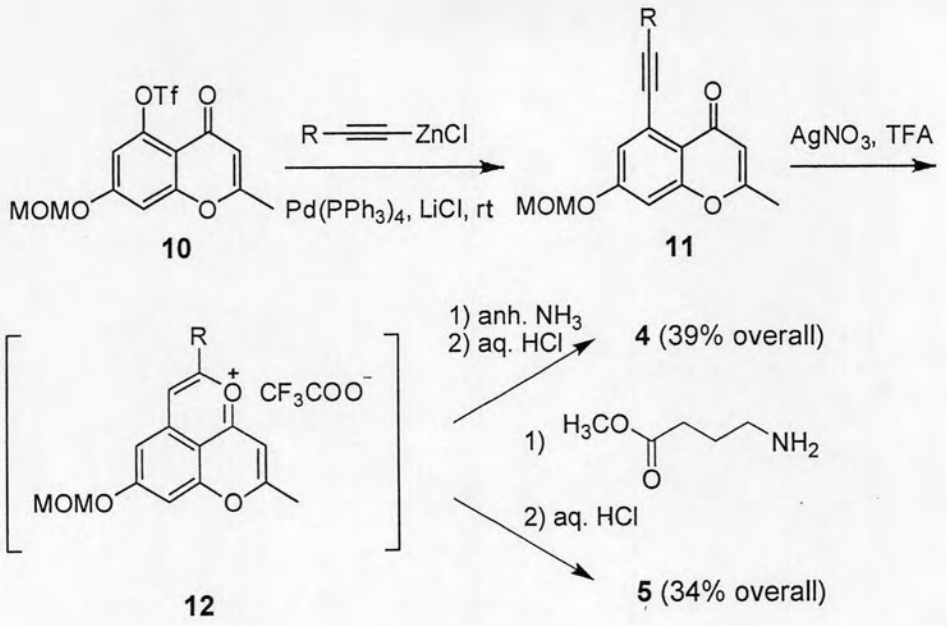
6 7 8 9

conditions: i) MOMCl, *i*-Pr_2NEt, rt; ii) propyne, $Pd(PPh_3)_2Cl$, CuI, rt; iii) 10% NaOH, 40 °C then HCl, rt; iv) 28% NH_4OH, rt then 80 °C; v) NaH, $PhN(Tf)_2$, rt; vi) 10% aq. HCl.

Scheme 1-2. Total synthesis of **4**.

However, according to the reported data, effort to perform direct *N*-alkylation of **4** with methyl bromo- or iodobutyrate at nitrogen atom under various reaction conditions failed to give desirable compound **5**.

In the same year, Yao and Yao [14] successfully performed total syntheses of both **4** and **5**. Firstly, compound **10** was reacted with 1-propynylzinc chloride under Sonogashira-type condition to afford alkyne **11** (Scheme 1-3). Then, Negishi-type coupling of **11** was conducted to generate intermediate **12**, which was condensed further with ammonia or methyl-4-aminobutyrate to give **4** or **5** in 39% or 34% overall yield, respectively. Furthermore, three new analogues of cassiarins bearing different substituents at the C-11 position were prepared under the same procedure.



Scheme 1-3. Total synthesis of **4** and **5**.

In this work, the alternative efficient syntheses of **4**, **5** and their derivatives bearing different *N*-substituents from the naturally occurring barakol are investigated to offer a practical approach of the use of inexpensive natural resource in the preparation of the valuable bioactive compounds. Furthermore, effects of the *N*-substituents in the cassiarin structures on the antiplasmodial activity and other possible bioactive properties of the compounds are studied.