

Synthesis and Study of Naphthoquinones Derivatives

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Abstract. In this research, we reported the study and synthesis of naphthoquinones intermediate compounds lead to the target naphthoquinones derivatives product. Naphthoquinones derivatives have long been known to display anticancer and antimalarial activity in addition to a wide variety of other bioactivities. Moreover, it has been reported to possess antimalarial disease against *Plasmodium falciparum*. The naphthoquinones derivatives product (5) were synthesized by coupling with 2-(3-bromo-2,2-dimethylpropyl)-1-methoxynaphthalene (4) and methyl ketone fatty acid (3). The 2-(3-bromo-2,2-dimethylpropyl)-1-methoxynaphthalene (4) was constructed by 1-hydroxy-2-naphthoic acid (1) in 5 steps with good to excellent yield. The synthetic pathway was started with the methylation provided the methyl ester naphthoquinones compound in 93% yields. Then, the reduction of methyl ketone by using LiAlH_4 gave the alcohol compound in 90% yields. Methyl alcohol was changed to the alkyl bromide using PBr_3 in 75% yield. The alkylation reaction between compound and methyl isobutyl ketone by LDA as a catalyst provided the methyl ester compound followed by reduction using LiAlH_4 obtained the alcohol compound in 44% yield. The bromo-product core structure (2) was produced by using PBr_3 in 82%. Most of intermediate compounds were characterized by ^1H and ^{13}C NMR spectroscopy technique. The substitution reaction will be carried out by methyl ketone (3) as an efficient condensing agent leading to *gem*-dimethyl fatty acid naphthoquinones product (5) in Figures 1. Finally, the synthetic route utilizing hydroxy-1,4-naphthoquinones in 3 steps is being explored.

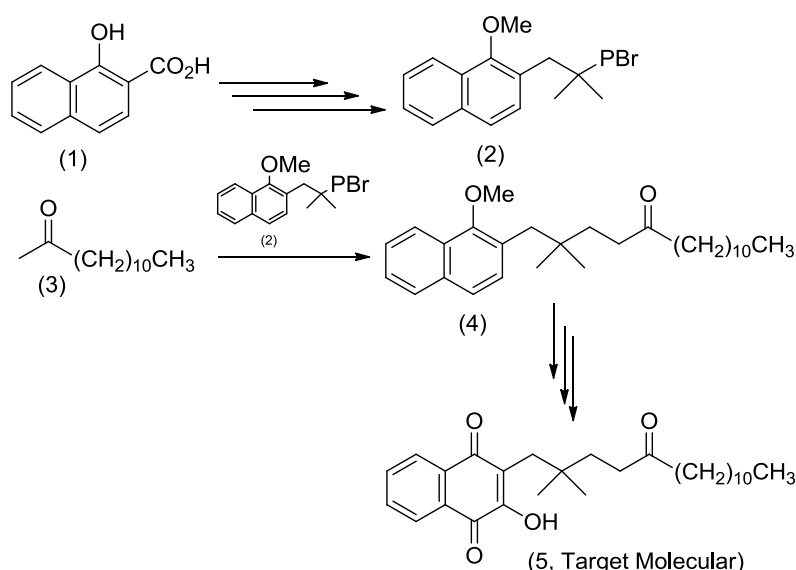


Fig. 1 The synthetic route of *gem*-dimethyl naphthoquinones fatty acid product

Introduction

Rhinacanthone was first isolated from the shrub, *Rhinacanthus nasutus*, which is used in Thai folk medicines. This herb has been used for treatment of ringworm, skin diseases, inflammation, and cancer. The major constituents in this plant are naphthoquinones which are rhinacanthone (1,2-naphthoquinone) (6), dehydro- α -lapachone (7), fifteen rhinacanthins (1,4-naphthoquinone) as shown in Figures 2. [1-5]. Naphthoquinone (NQs) are a group of highly reactive small molecules which have a diverse distribution in nature. They occur as the *para*- isomer 1,4-naphthoquinone and the *ortho*-isomer 1,2-naphthoquinone. These molecules are simple compounds having the C-6–C-4 skeleton. NQs having the 1,4-(1) and 1,2-(2) skeletons have been isolated from natural sources as monomers [6].

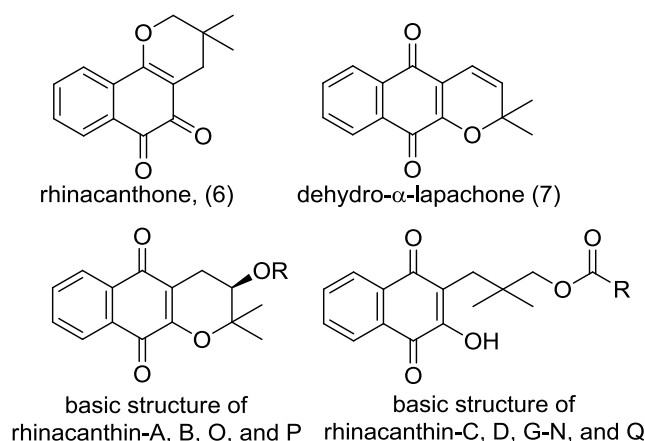


Fig. 2 Structures of the major components in *Rhinacanthus nasutus*

In 2003, Ngampong Kongkathip and co-worker have reported the successful synthesis and anticancer evaluation of rhinacanthone, 1,2-pyrano and -furanonaphthoquinones, 1,4-pyrano and -furanonaphthoquinones [7]. In Addition, rhinacanthins and fifty-one related 1,4-naphthoquinone aromatic esters with various C-2' substituents were reported and evaluated their anticancer activity in 2004 and 2010, also in Figures 3. [8,9]. Most of compound exhibited significant cytotoxicity against three cancer cell lines (KB (oral cavity cancer), HeLa (cervical cancer), and HepG2 (hepatocellular cancer)). They also reported the substituent at C-20 position played a crucial role by affecting the anticancer activity. Most naphthoquinone aromatic esters with 2',2'-dimethyl substituents exhibited the most potent cytotoxicity against KB, HeLa, and HepG2 cell lines than those of one methyl substituent, no methyl substituent, and also than with more rigid cyclopentyl and cyclohexyl substituents at C-2' position.

Thus in this research, we designed to synthesize the intermediate naphthoquinone derivatives leading to the novel naphthoquinone fatty acid derivatives and testing activity in the future.

Results and Discussion

A route for the synthesis of the intermediate naphthoquinones derivatives leading to novel gem-dimethyl naphthoquinones fatty acid derivatives were accomplished in six to twenty steps with good to excellent yield (Figures 4). Seven naphthoquinones derivatives were synthesized by a route starting from 1-hydroxy-2-naphthoic acid (1) in 6-steps with good to excellent yield. The synthetic pathway started with the methylation provided the methyl ester naphthoquinones compound (6) in 93% yields. Then, the reduction of (6) by using LiAlH_4 gave the alcohol compound (7) in 90% yields. Compound (7) was changed to the alkyl bromide (8) using PBr_3 in 75% yield. The alkylation reaction between compound (8) and methyl isobutyl ketone by LDA as a catalyst provided the methyl ester compound (9) followed by reduction using LiAlH_4 obtained the alcohol compound (10) in 44% yield. Finally, bromination of (10) gave bromo-naphthol product (2) in 82%. Most of intermediate compounds were characterized by ^1H and ^{13}C NMR spectroscopy technique.

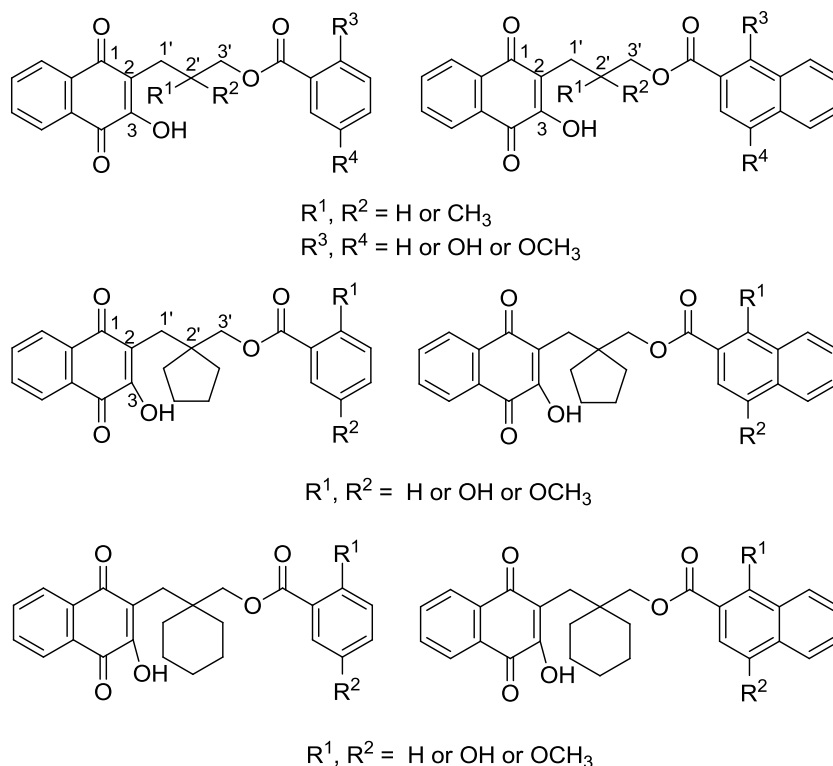


Fig. 3 Synthetic of 2'-substituted naphthoquinones aromatic ester

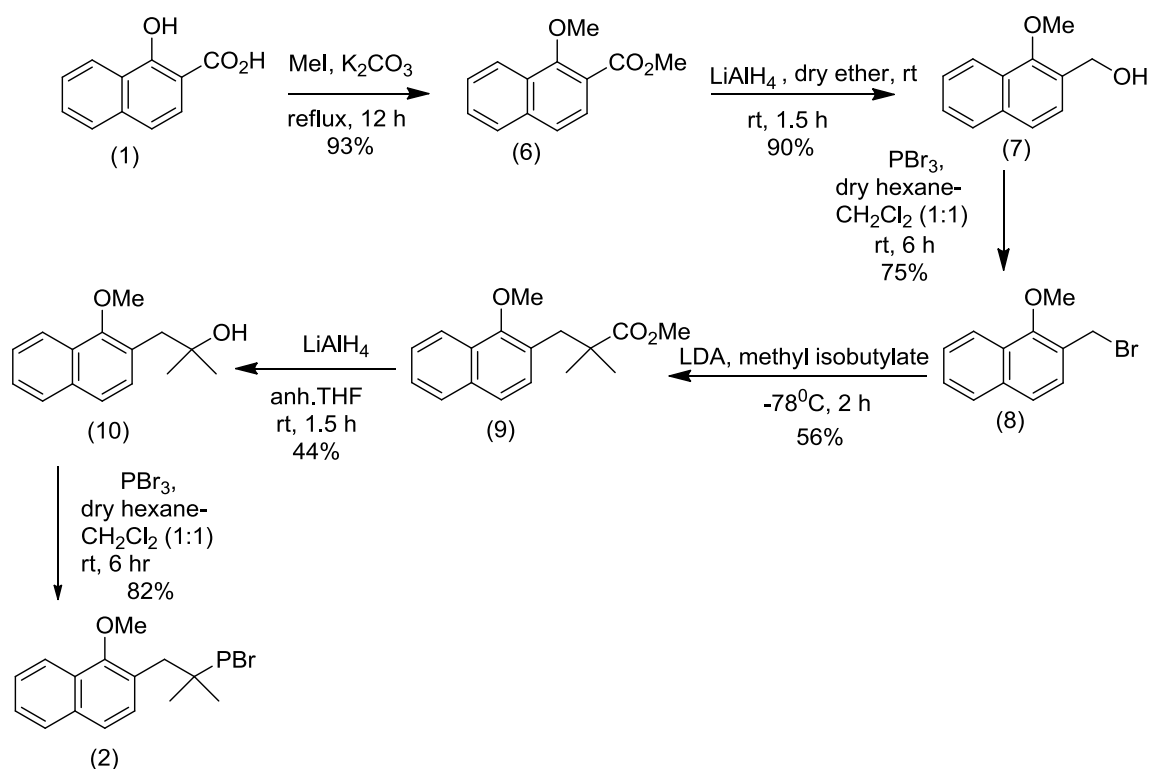


Fig. 4 The synthetic route to intermediate naphthoquinones derivatives

In this research, we attempts to couple bromide compounds (10) with methyl ketone fatty acid (13). So, we try to prepared methyl ketone fatty acid derivatives by selection from the bioactivity. From previous research in 2010 by Ngampong and co-worker [9] reported that the 1,4-naphthoquinone aliphatic were coupling with caprylic acid and myristic acid showed very good antimalarial activity. The original reaction involved two subsequent nucleophilic acyl substitutions.

The conversion of a fatty acid into an N,O-dimethylhydroxyamide gave a Weinreb–Amide and subsequent treatment of this species with an organometallic reagent such as a Grignard reagent or organolithium reagent to give methyl ketone fatty acid (13) in Figures 5.

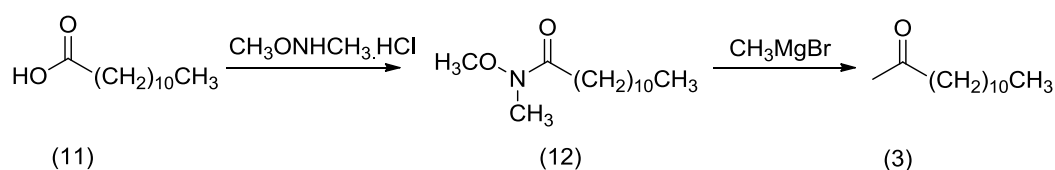


Fig. 5 Preparation of methyl ketone fatty acid compound

In our plan, we design to synthesize the target molecular (5) via coupling compound (3) with bromo-naphthoquinones compound (2) to give ketone fatty acid naphthoquinones compound (4). Afterthought, demethylation will be constructing to give compound (13). Fremy' salt is a key reagent for produce naphthoquinones fatty acid (14). Final step in the synthesis, the target product will be obtained via oxidation of compound (14) with DDQ in Figures 6.

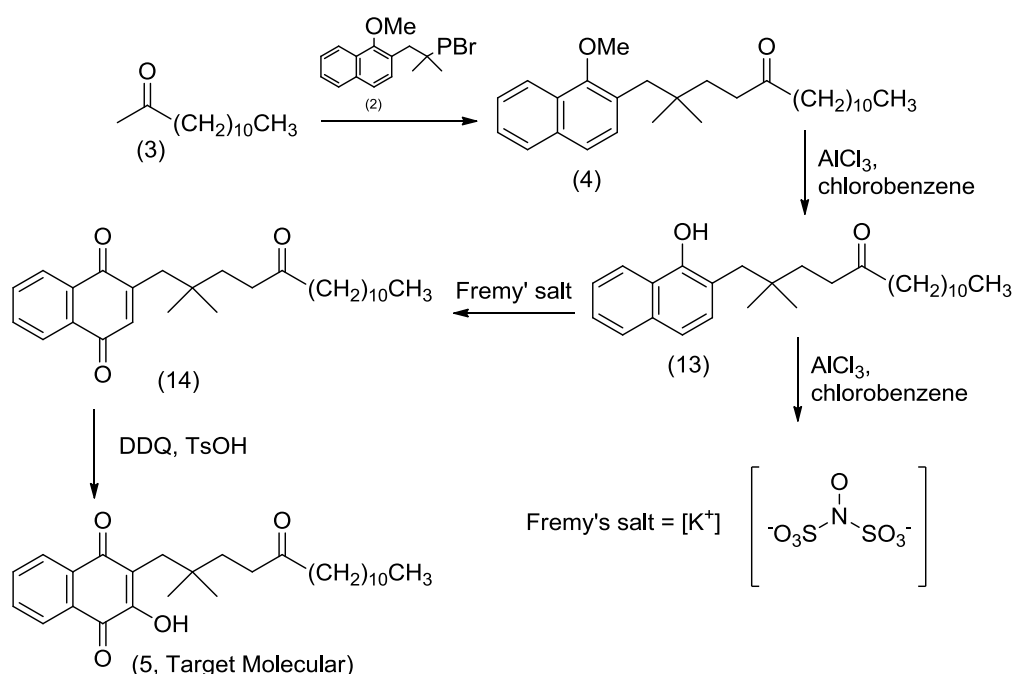


Fig. 6 The key synthetic route of *gem*-dimethyl naphthoquinone fatty acid product

Conclusion

In this report, 6-intermediate naphthoquinones derivatives were synthesized in an excellent yields. The key reaction is alkylation of resulting bromide (8) by methyl isobutylate gave compound (9). In this synthesis, we attempt to control the condition because the methyl isobutylate easy to decompose. The steric of *gem*-dimethyl group is hard to stay near aromatic ring. Furthermore, several step and studies are being carried out in our laboratory.

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