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Synthesis and biological evaluation of isoflavone analogues from *Dalbergia oliveri*

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Abstract—Mucronulatol **1** and violanone **2** isolated from *Dalbergia oliveri* Gamble, and the corresponding isoflavone **3** were prepared by ligand coupling reactions involving organolead reagent. Biological studies have shown a significant cytotoxic effect against an HBL100 leukemia cell line only for isoflavan **1** with an IC_{50} value amounting to 5.7 μM. All the drugs modestly inhibit the in vitro microtubule assembly, independently of the cytotoxic ability. Natural compounds **1** and **2** have no antibacterial activity, but are potent inhibitors of the *Fusarium oxysporum* phytopathogenic fungal growth.

1. Introduction

Dalbergia oliveri Gamble belongs to the family of Leguminosae-Papilionoideae and grows in Thailand and Burma. This plant has been used in traditional Thai medicine for the treatment of chronic ulcer. Some preliminary activity screening showed that crude extracts of *D. oliveri* exhibit significant biological activities, such as antibacterial and anti-inflammatory effects. In previous investigations, many isoflavonoids and neoflavonoids have been isolated by extraction and fully characterized.[1,2] Flavonoid derivatives, either naturally occurring or from synthetic origin, are well known to exhibit a wide range of biological activities.[3] Some of them, belonging to the structural groups of flavones,[4–6] neoflavones,[7,8] isoflavone, and open-chain analogue chalcones[9,10] possess cytotoxicity against cancer cell lines, acting as tubulin polymerization inhibitors. This activity on the protein stabilization is frequently associated with the antimitotic properties.[11]

Due to the presence of mucronulatol **1** and violanone **2** in *D. oliveri* extracts, respectively, an isoflavan compound and an isoflavanone compound, we decided to synthesize these natural products as well as the isoflavone analogue **3** to investigate their activity as potential mitosis inhibitor agents (Fig. 1).

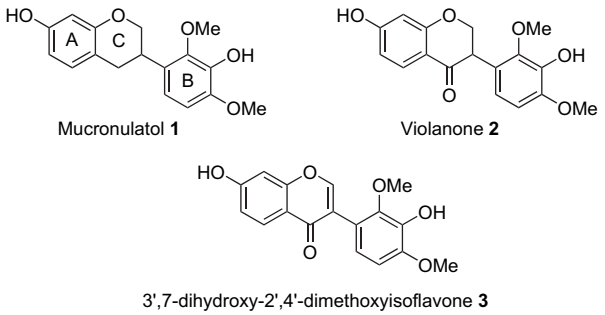

Figure 1. Structures of compounds **1–3**.

2. Chemistry

Because of their remarkably rich spectrum of biological activities,[12] isoflavones have been the topic of a number of studies toward their synthesis. Almost all published synthetic methods used the cyclization of 2-hydroxyarylalkylketones under acidic or basic condition as the key step.[13] However, in recent years, convergent approaches were developed taking advantage of the ligand coupling concept[14] via a Suzuki reaction[15,16] or using organolead chemistry.[17]

Keywords: Isoflavone; Ligand coupling; Cytotoxicity; Antimitotic; Antimicrobial.
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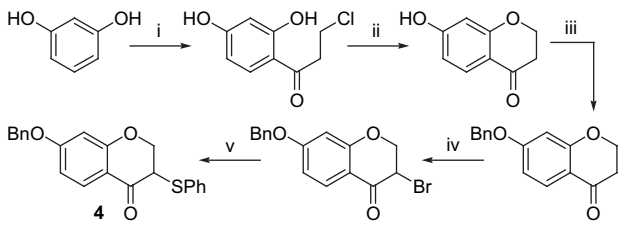
The synthesis of natural compounds **1** and **2** have previously been addressed by the oxidative rearrangement of 2′-hydroxychalcone with TTN in MeOH followed by cyclization to give isoflavone derivative. Finally, deprotection and subsequently catalytic hydrogenation in the presence of AcOH yielded mucronulatol **1** or hydrogenation in acetone on Pd–C catalyst furnished violanone **2**.[18] However, this method was unsatisfactory since the reactions proceeded in very poor yield with these chalcones. In addition, this method suffered from requiring the use of stoichiometric quantities of highly toxic thallium salts.

The method utilizing aryllead (IV) chemistry for the synthesis of isoflavones, isoflavanones, and neoflavonoids including naturally occurring products has been reported by Donnelly and colleagues,[19–22] the coupling reactions proceeding smoothly to give 7,4′-dimethoxyisoflavone, 2′,4′-dimethoxyisoflavone, 5,7,4′-trimethoxyisoflavone, 2′,4′-dimethoxyisoflavanone, 5,7-dimethoxyisoflavanone, and 3-hydroxy-8-methoxycoumarin in high yields, and by others for the synthesis of 3-arylflavanones.[23] Thus, aryllead-mediated route offered a direct, efficient, and selective entry into the synthesis of isoflavanones and isoflavones and their derivatives.

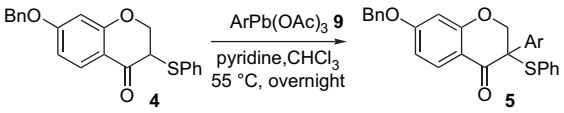
Here, we describe the synthesis of **1**–**3** via an aryllead-mediated coupling reaction using 3-phenylthio-chroman-4-one **4** as the common intermediate. The required 3-phenylthio-chroman-4-one **4** was prepared in five steps from resorcinol as outlined in Scheme 1.



Scheme 1. Synthesis of the chromanone intermediates. Reagents and conditions: (i) 3-chloropropionyl chloride, $AlCl_3$, Et_2O, 0 °C, 1 h; (ii) aq NaOH, rt, 2 h; (iii) BnBr, K_2CO_3, acetone, reflux, overnight; (iv) $CuBr_2$, EtOAc–$CHCl_3$, reflux, overnight; (v) PhSH, NaH, THF, 0 °C, 1 h.

The chromanone ring was prepared efficiently by the method of Naylor et al.[24] As the selective monoarylation of ketonic substrates with aryllead reagents requires activation to the enol form, the phenylthio group was introduced by reaction of sodium phenylthiolate with the required α-bromo-ketone.[20]

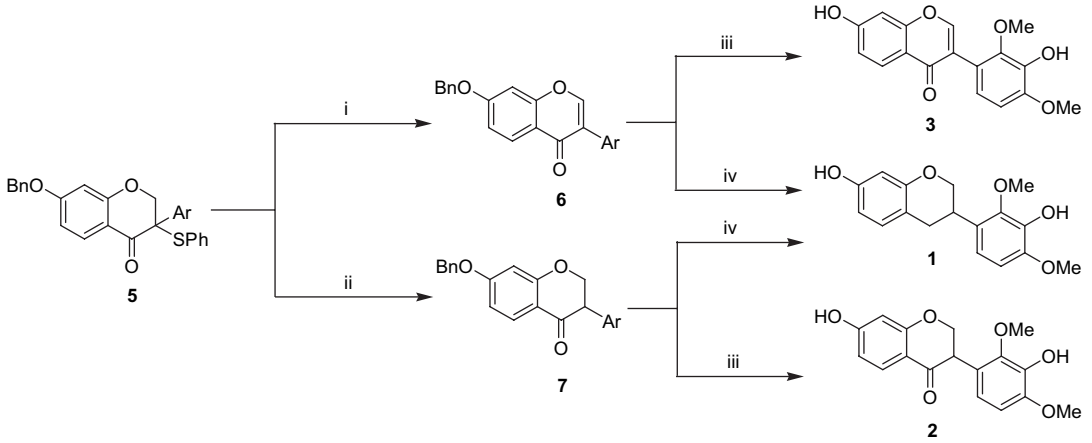
The aryllead triacetate **9**, prepared in good yield by tin–lead exchange,[25] was used in the coupling reaction to afford the protected 3-aryl-3-phenylthiochroman-4-one **5** in 51% yield (Scheme 2).



Scheme 2. Ligand coupling reaction with activated chroman-4-one.

Removal of the phenylthio group by mild oxidation of **5** with *m*-chloroperbenzoic acid (MCPBA) followed by thermal elimination led to isoflavone **6** in 86% yield (Scheme 3). Reduction of **5** with an excess of in situ generated nickel boride led to the corresponding isoflavanone **7** in 59% yield. Mucronulatol **1** was prepared from either **6** or **7** by hydrogenation in ethanol in the presence of catalytic amounts of palladium on charcoal. Violanone **2** and 3′,7-dihydroxy-2′,4′-dimethoxyisoflavone **3** were obtained in excellent yields by hydrolysis of the benzyloxy protecting group using a 47% HBr aqueous solution.

The molecular structures of mucronulatol **1** and the corresponding isoflavone **3** have been determined by single-crystal X-ray crystallography. The ORTEP diagrams of **1** and **3** are presented in Figures 2 and 4, while selected parameters are listed in Table 1.



Scheme 3. Synthesis of isoflavonoid derivatives. Reagents and conditions: (i) MCPBA, EtOAc, 0 °C, then toluene, reflux; (ii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, EtOH–H_2O, reflux, 4 h; (iii) 47% aq HBr, 50 °C, overnight; (iv) H_2, Pd–C, EtOH, rt.