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From biomass to natural flavonoids: Studies for total synthesis of Podocarflavone A

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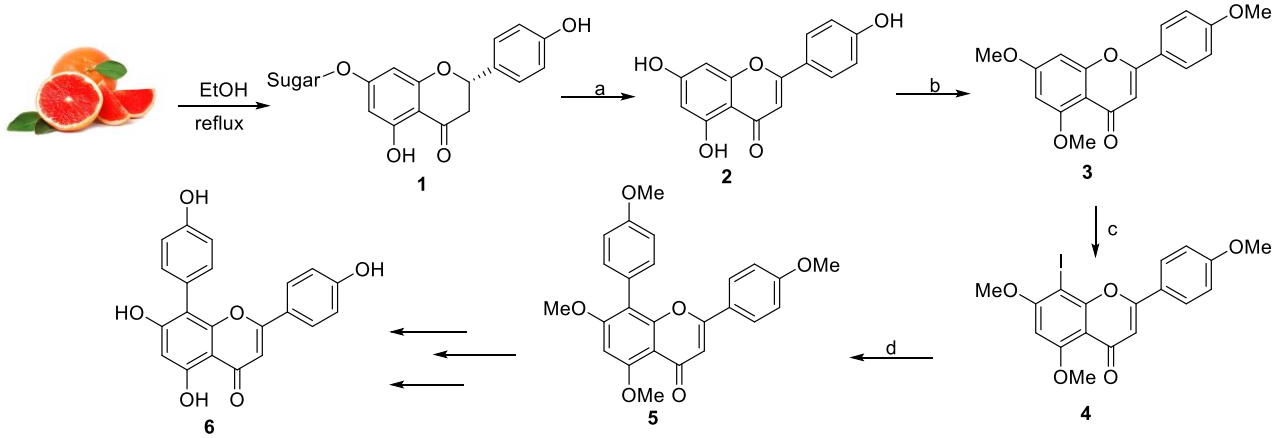
ABSTRACT

Natural products are secondary metabolites produced by plants for various functions.[1] Flavonoids, a class of these metabolites, are polyphenolic compounds vital for plant metabolism, defense, and cellular signaling.[2] Podocarflavone A (**6**), a natural flavonoid, was first isolated from *Podocarpus macrophyllus* in 2014.[3] Few studies have evaluated its biological activities due to its recent isolation. Only one total synthesis has been reported, by Puranik and coworkers[4] in 2022, using a linear route from commercial materials. Our aim is to synthesize Podocarflavone A from grapefruit (*Citrus paradisi*) biomass wastes using an environmentally friendly extraction method.[5] The synthetic route developed includes five steps after extracting the O-glycosylated flavone: oxidation of natural flavonoid naringin **1**, followed by hydrolysis, full protection of apigenin **2**, regioselective halogenation, and a not-optimized microwave-mediated Suzuki-Miyaura coupling to compound 5. We will apply a demethylation protocol to obtain Podocarflavone A (**6**).



Scheme 1: Synthetic route to synthesize Podocarflavone A **6**.(a) i) I_2, pyridine, 100 °C, 16h, ii) H_2SO_4, glycerol, 120 °C, 1h, **74%** (over 2 steps); (b) $(CH_3)_2SO_4$, K_2CO_3, acetone, 16h, **70%**; (c) NIS, DMF, 70 °C, **65%**; (d) 4-methoxyphenylboronic acid, $Pd(OAc)_2$, K_3PO_4, toluene, MW, 150 °C, 2h, **26%**.

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