A Simple Synthetic Route to Pterosin F and Other Pterosins

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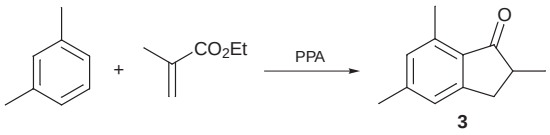
A simple method for the preparation of pterosin F is described in which the key step involves a tandem reaction of Friedel–Crafts acylation–cycloalkylation between 2,6-dimethylphenethyl chloride and ethyl methacrylate

A group of natural sesquiterpenes, which possess a structure of indan-1-one, named pterosins, were initially isolated from bracken fern, *Pteridium aquilinum*,[1] in Japan. These compounds are also present in other ferns[2] and in certain fungi of the class Basidiomycetes, in particular in *Cyathus* species.[3] Several pterosins have been shown to possess interesting biological properties, such as, cytotoxic effects on the ciliate *Paramecium caudatum*,[5] antibacterial activity[6] and smooth muscle relaxant activity.[7,8]

Because of their potential pharmacological activity, and since they are present only in minute amounts in ferns and their isolation is tedious, several routes of synthesis have been reported in the literature.[7]

In an attempt to find a new method to prepare pterosins, we resorted to a novel approach to the indanone skeleton from simple starting materials. As indicated in Scheme 1, tandem reaction of Friedel–Crafts acylation–cycloalkylation of *m*-xylene with ethyl methacrylate in the presence of polyphosphoric acid (PPA) at 100 °C for 4 h afforded 2,5,7-trimethylindan-1-one **3**[9] in 65% yield. The noteworthy feature of this reaction was the regiospecificity for pentagonal ring closure.

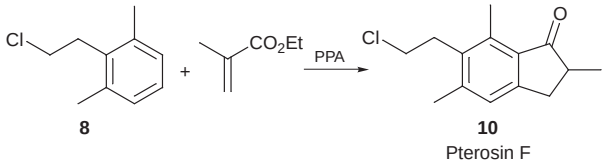


Scheme 1

Accordingly, we believed that this reaction could provide access to some pterosins. The results of our investigation using this approach are reported here.

The use of the PPA-mediated acylation–cycloalkylation reaction requires a suitable substituted aromatic ring. To this end, we used 2-methylphenethyl alcohol **4** as starting material (Scheme 2, see full text) which was converted to 5-methylisochroman **5** in 93% yield by cyclisation with paraformaldehyde in concentrated hydrochloric acid. To avoid oxidation, compound **5** was immediately treated with acetyl chloride using zinc chloride as catalytic to render 2-chloromethyl-6-methylphenethyl acetate **6** in 81% yield. Removal of the chloro substituent and reduction the ester group was achieved in one-pot reaction using lithium aluminium hydride to give 2,6-dimethylphenethyl alcohol **7** in 83% yield. Compound **7** was chlorinated and methoxylated to afford **8** and **9** respectively with a quantitative yield.

Tandem acylation–cycloalkylation of **8** with ethyl methacrylate rendered the racemic pterosin F **10** as single regioisomer in 15% yield (Scheme 3).



Scheme 3

Despite of the modest overall yield, the discovery of this route shows that pterosins may be synthesized in relatively few steps from cheap and readily available bulk starting materials, and that some reaction steps may be combined resulting in improved yield and lower cost.

Techniques used: ^{1}H and ^{13}C NMR, preparative TLC

Schemes: 3

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