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Total syntheses of justicidin B and retrojusticidin B using a tandem Horner–Emmons–Claisen condensation sequence

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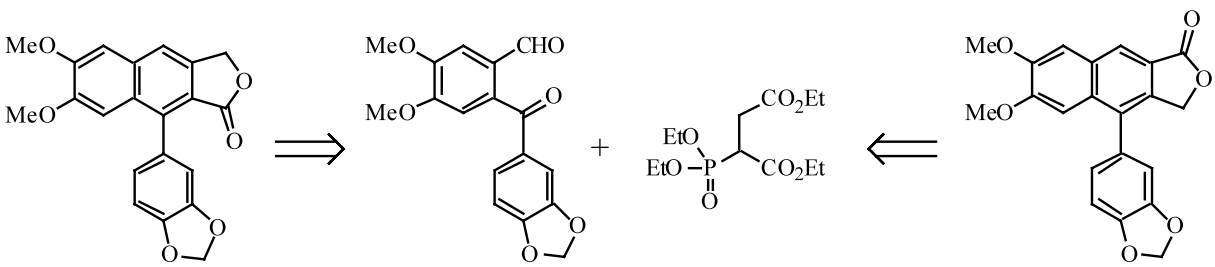
Abstract—Short syntheses of justicidin B **1** and retrojusticidin B **4** are reported. The key feature is a new annulation reaction, involving a base induced union of ketoaldehyde **2** and phosphonate **3**, that is used to construct the highly substituted naphthalene core. © 2001 Elsevier Science Ltd. All rights reserved.

The arylnaphthalene lignans have attracted considerable attention in recent years with biological studies uncovering a host of potentially exploitable activities.[1] These include the inhibition of leukotriene biosynthesis by human leukocytes,[2] as well as antitumour,[3] antifungal,[4] hypolipidemic,[5] antiviral and anti-PAF activity.[6,7] Unsurprisingly, many synthetic entries to this family of natural products have been developed.[1] In this Letter we report a new approach that has culminated in short syntheses of justicidin B **1** and retrojusticidin B **4**, a recently identified natural product and inhibitor of HIV-1 reverse transcriptase.[8,9] A key feature is the base induced union of ketoaldehyde **2** and phosphonate **3** by sequential Horner–Emmons and Claisen condensations, used to construct the highly substituted naphthalene core (Scheme 1).[10]

Each synthesis began with the known conversion of veratraldehyde **5** into 6-bromoveratryl alcohol **7**.[11] Sequential treatment of **7** with sodium hydride and butyllithium next facilitated union with piperonal to give diol **8** which was oxidized with PCC on alumina to give ketoaldehyde **2**.[12] Simultaneous addition of this material **2** and phosphonate **3** to a cooled (0°C) solution of sodium ethoxide in THF–ethanol then effected the desired annulation, giving a 14:1 ratio of diester **9** and acid **10** in 73% yield (Scheme 2).

To complete the total syntheses of justicidin B and retrojusticidin B was straightforward from this juncture.[6,13] Thus, diester **9** was first hydrolyzed to acid **10** with potassium trimethylsilanolate.[13] Reduction of **10** with borane dimethylsulfide complex then gave justicidin B **1** after an acidic work-up while reduction of the sodium salt of **10** with lithium borohydride gave retrojusticidin B **4** as the major product, together with some justicidin B **1** (Scheme 3).



Justicidin B **1** **2** **3** Retrojusticidin B **4**

Scheme 1.

Keywords: natural products; annulation; lignans; Horner–Emmons; Claisen condensation.
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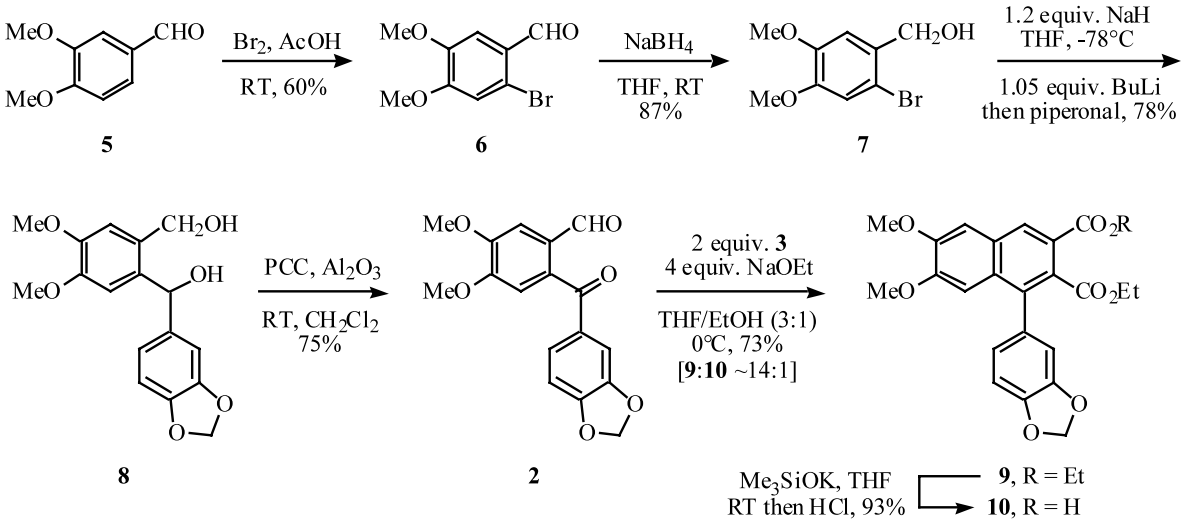
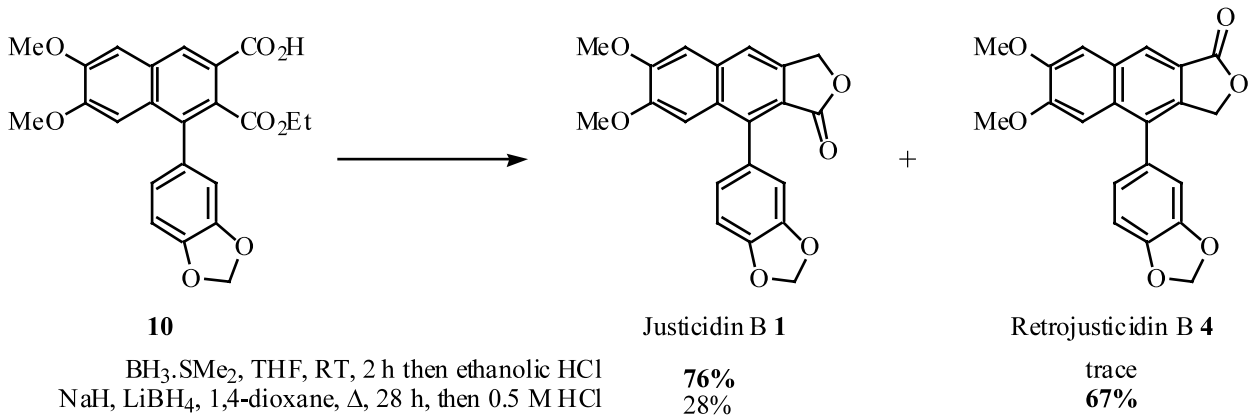


Scheme 2.



Scheme 3.

In conclusion, we have developed a new annulation reaction based on the union of a ketoaldehyde and phosphonate **3** by sequential Horner–Emmons and Claisen condensation reactions.[14] The utility of the method has been demonstrated through the total synthesis of two arylnaphthalene lignans, justicidin B **1** and retrojusticidin B **4**. We are presently seeking to extend the scope of this method to other ring systems and to exploit it in combinatorial library synthesis.

Acknowledgements

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