An Improved Route to an Intermediate in Podophyllotoxin Synthesis

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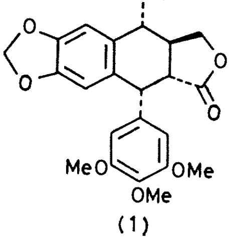
Summary Cyclopropanation of the chalcone (**3**) with dimethylsulphonium ethoxycarbonylmethylide affords a 1:1 mixture of the cyclopropanyl keto-ester epimers (**4**) and (**5**); both stannic chloride and boron trifluoride etherate in nitromethane catalyse the stereoselective cyclisation of this mixture to the tetralone (**2**), the known podophyllotoxin precursor, in 51% overall yield.

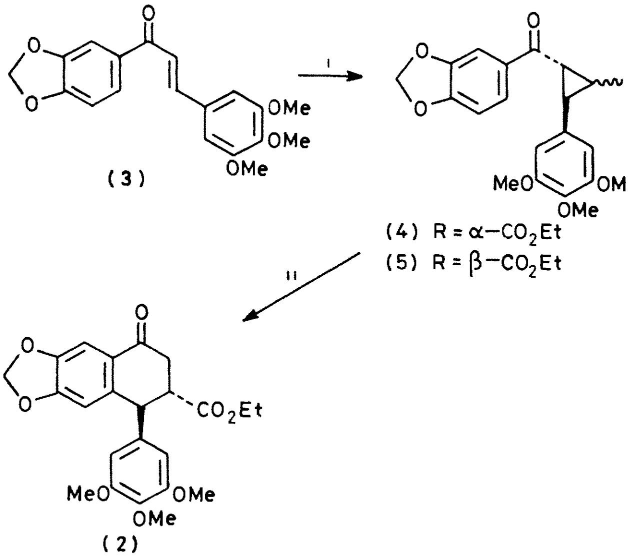
Podophyllotoxin (**1**) and other related lignan lactones have received considerable attention as cancer chemotherapeutic agents.[1] Accordingly much effort has been expended



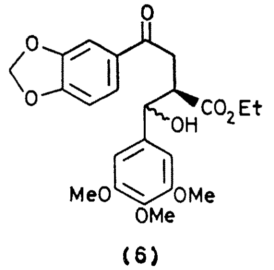
(1)

on new and improved syntheses of these lignans [2] Podophyllotoxin itself has been synthesised *via* the key intermediate, tetralone (**2**) [2b,c] One approach to (**2**), the Gensler[2b] classical[3] route, required separation of *E* and *Z* isomers of an intermediate Stobbe condensation product [2a] Most recently Kende and coworkers[2c] used a novel aryl benzyl coupling reaction but eight steps were involved in the synthesis of (**2**)

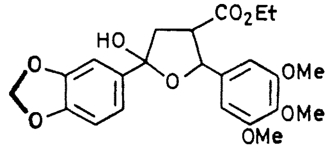
Further to our studies on phenol cyclisation,[4] the possibility arose that a one step tetralone synthesis could be effected by an acid catalysed reaction of aryl aroyl cyclopropanes The chalcone (**3**) was cyclopropanated using a modification of Trost's[5a] and Kondo's[5b] method The oily product (> 90%) was a separable (t l c) **1** : **1** mixture of (**4**) and (**5**) (see Scheme) The structure and stereochemistry of (**4**) and (**5**) were assigned by comparison (n m r) with known closely related aryl aroyl cyclopropanes [5a] Cyclisation of (**4**) or (**5**) separately or as a mixture with $SnCl_4$ in benzene[6] or in methylene chloride[7] under a variety of conditions failed, and (**2**) was not formed Varying yields of (**6**) and (**7**) as diastereomeric mixtures, were obtained following basic (dilute NaOH)[8] work-up However, when nitromethane[9] was used as solvent (**2**) was the main product (53%) Boron trifluoride etherate in nitromethane (15 d, N_2, room temp) was rather more effective and produced (**2**) (57%) and (**6**) (9%) but the diastereomer of (**2**) was not formed



SCHEME *Reagents* i, $Me_2S^+\bar{C}HCO_2Et$, ii, $SnCl_4$, $MeNO_2$



(**6**)



(**7**)

The epimers (**4**) and (**5**) either separately or as a mixture gave the same product Thus, (**4**) with stannic chloride in nitromethane produced (**2**) (43%) and (**6**) (31%), whereas (**5**) under the same conditions yielded (**2**) (53%) and (**6**) (40%) Close examination (t l c) of (**4**) and (**5**) in stannic chloride–nitromethane solution at 0 °C, under N_2, showed that (**5**) epimerised to (**4**) within 10 min, before cyclisation commenced, (**4**) did not rearrange to (**5**) [10]

Since the tetralone (**2**) has been converted by others[2b,c] into (**1**), this route to (**2**) constitutes a new total synthesis of podophyllotoxin

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