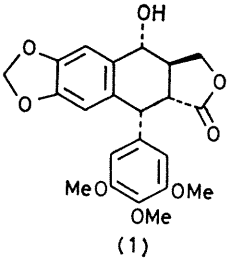
An Improved Route to an Intermediate in Podophyllotoxin Synthesis

By WILLIAM S. MURPHY* and SOMPONG WATTANASIN
(*Department of Chemistry, University College, Cork, Ireland*)

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.

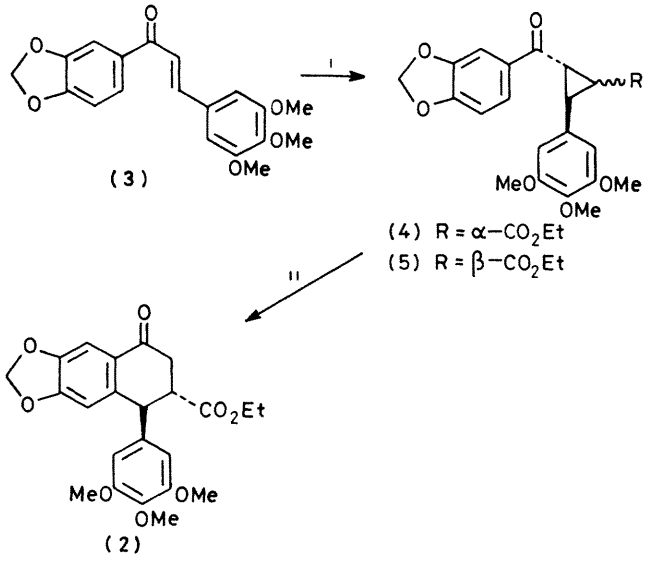
PODOPHYLLOTOXIN (**1**) and other related lignan lactones have received considerable attention as cancer chemotherapeutic agents.[1] Accordingly much effort has been expended



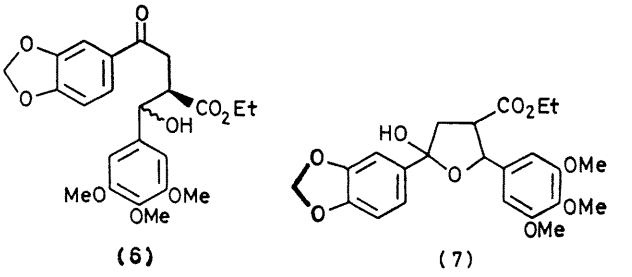
(1)

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, $SnCl_4$, $MeNO_2$



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

(*Received*, 19*th September* 1979, *Com* 1013)

[1] S M Kupchan, J C Hemingway, and J R Knox, *J Pharm Sci* , 1965 **54** 659, P Dombernowsky, N I Nissen, and V Larsen, *Cancer Chemother Rep* , 1972, **56**, 71, *Brit Med J* , 1972, **2**, 747
[2] (a) W J Gensler, C M Samour, S Y Wang, and F Johnson *J Amer Chem Soc* , 1960, **82**, 1714 (b) W J Gensler and C D Gatsonis, *J Org Chem* , 1966, **31**, 4004, (c) A S Kende, L S Liebeskind, J E Mills, P S Rutledge, and D P Curran, *J Amer Chem Soc* 1977, **99**, 7082, (d) E Brown, J -P Robin, and R Dhal, *J C S Chem Comm* , 1978, 556
[3] R D Haworth, T Richardson, and G Sheldrick, *J Chem Soc* , 1936, 1576
[4] W S Murphy and S Wattanasin, *J C S Perkin I*, in the press
[5] (a) J Adams, L Hoffman, Jr , and B M Trost, *J Org Chem* 1970 **35** 1600, (b) H Nozaki, D Tunemoto, S Maturaba, and K Kondo, *Tetrahedron*, 1967, **23**, 545
[6] G Stork and M Marx, *J Amer Chem Soc* , 1969, **91**, 2371, G Stork and M Gregson, *ibid* , p 2371, P A Grieco and R S Finkelhor, *Tetrahedron Letters*, 1974, 527
[7] F E Ziegler and J A Schwartz, *J Org Chem* , 1977, **43**, 983
[8] C U Pittman and S P McManus, *J Amer Chem Soc* , 1969, **91**, 5915
[9] W S Johnson, T-t Li, C A Harbert, W R Bartlett, T R Herrin, B Staskun, and D H Rich, *J Amer Chem Soc* , 1970, **92**, 4461
[10] O Itoh, N Yamamoto, H Fujimoto, and K Ichikawa, *J C S Chem Comm* , 1979, 101