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# A Concise Synthesis of Taiwanin E Using a Michael Initiated Ring Closure Protocol

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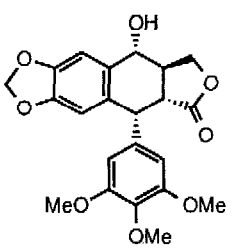
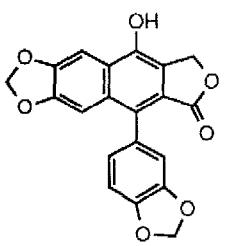
*Key Words:* Taiwanin E; *Podophyllum* lignans; Michael Initiated Ring Closure; arylnaphthalene lignans; Podophyllotoxin.

***Abstract:*** *A rapid entry towards the Podophyllum lignans is described exemplified by a concise regioselective total synthesis of taiwanin E (2). The synthesis features a Michael initiated ring closure sequence to access the key lignan intermediate (11) from the ketodithiolane (10) and the furanone (4).*

The *Podophyllum* lignans have attracted considerable pharmacological and synthetic interest due to their renowned antimitotic activity.[1] Indeed, etoposide and teniposide, two synthetically derived glycosidal derivatives of podophyllotoxin (1), are currently in clinical use as antitumor agents.[2] This *Letter* details a rapid synthetic entry into this class of compounds *via* type II Michael Initiated Ring Closure (MIRC) methodology.[3,4] The approach has lead to a new regioselective total synthesis of the cytotoxic arylnaphthalene lignan taiwanin E (2),[5] isolated from the heartwood of the Japanese tree *Taiwania cryptomerioides* Hayata (Taxodiaceae),[6] which possesses all the functionality of podophyllotoxin around a central aromatic ring.

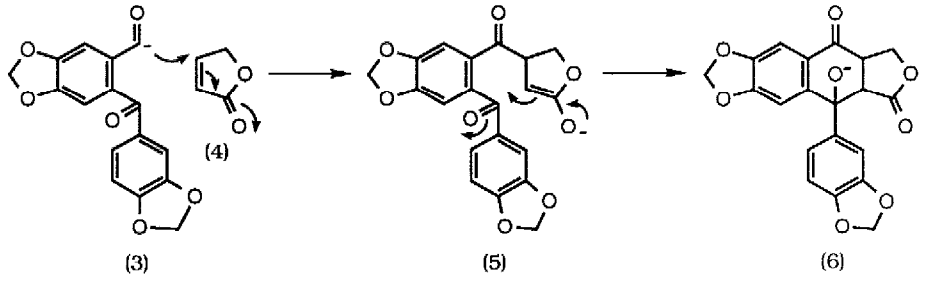



(1)




(2)

The key feature of our approach required the generation and intermolecular Michael addition of an acyl anion equivalent, *e.g.* (3), to 5(*H*)-2-furanone (4). The resulting ester enolate (5) could then undergo an intramolecular aldol condensation to effect closure of the central six-membered ring (Scheme 1).

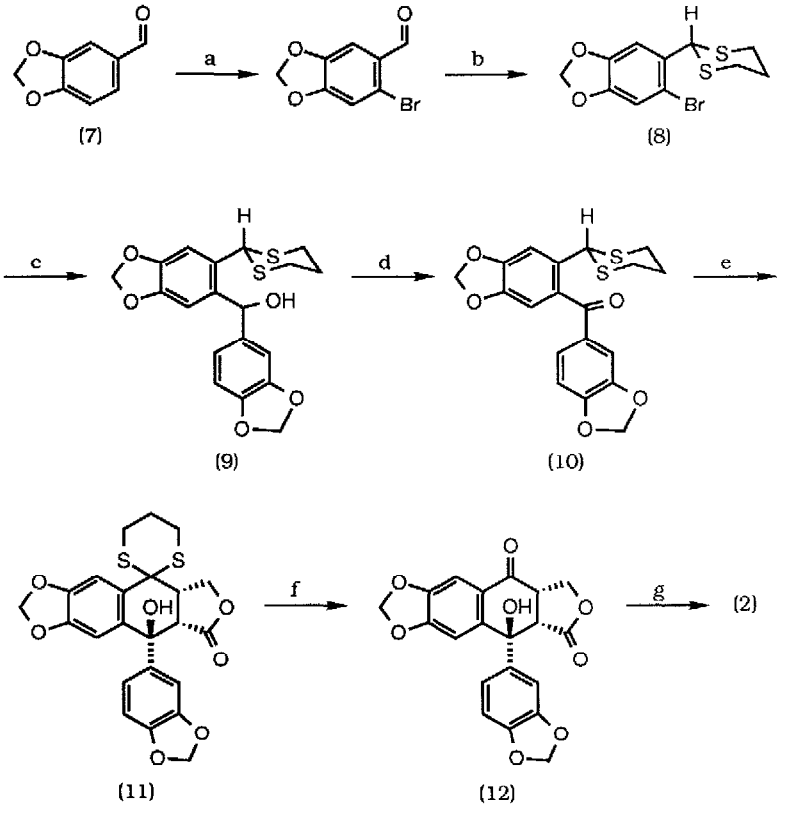



Scheme 1

Thus, piperonal (7) was treated sequentially with bromine[7] and with 1,3-propanedithiol, under acid catalysis, to give the dithiolane (8). Transmetallation of (8) to the corresponding aryllithium (*n*-BuLi) and subsequent treatment with piperonal (7) next gave the alcohol (9) with no observed formation of the lithiodithiolane. Benzylic oxidation of (9) using $MnO_2$ then yielded the desired intermediate (10) as a white crystalline solid.

Deprotonation of the dithiolane (10) with LiHMDS in THF at -78°C generated a purple anion. Addition of 5(*H*)-2-furanone gave, after work up, a single isomer of the desired lignan precursor (11) together with recovered starting material. Removal of the dithiolane residue next gave the stable hydroxyketone (12), whose relative stereochemistry was established by n.O.e. difference experiments.[8] The hydroxyketone (12) underwent smooth dehydration and aromatisation to taiwanin E (2)[9,10] by the action of either *p*-TsOH or Meerwein's salt (Scheme 2).

The role played by the lithiodithiolane in assisting ortho-transmetallation of the arylbromide (8),[11] effecting the Michael addition to the furanone (4)[12] and in acting as a masked acyl functionality was critical to this synthesis. Further application of this methodology towards the more demanding podophyllum lignans; *via* intermediates akin to (11) and (12), and the utility of ketodithiolanes, *e.g.* (10), as a precursor of such systems is currently under investigation.



***Reagents:*** **a**. $Br_2$, AcOH, 82%; **b**. 1,3-propanedithiol, *p*TsOH, PhH, 50°C, 2h, 95%; **c**. *n*-BuLi, THF, -78°C; (7), 92%; **d**. $MnO_2$, $CH_2Cl_2$, 95%; **e**. LiHMDS, THF, -78°C; (4) 50% and (10) 42%; **f**. $HgCl_2$, HgO, $CH_3CN_{(aq)}$, 62%; **g**. *p*TsOH, PhH, reflux, 12h, 98% or $Me_3O^+ BF_4^-$, $CH_2Cl_2$, 92%.

Scheme 2

***Acknowledgment:*** The author wishes to thank the University of Nottingham for a Teaching Fellowship and Professor G. Pattenden for his interest in this work.

### *References and Notes:*

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8. All new compounds gave satisfactory spectral and analytical data e.g. (12): **UV** ($CHCl_3$) $\mu_{max}$ 245.6, 285.3, 321.9, 325.7 nm; **FT-IR** ($CHCl_3$) $\lambda_{max}$ 3456br, 3079s, 2969m, 2912m, 1756s, 1673s, 1613s, 1504s, 1271vs and 732s, $cm^{-1}$; **$^1$H NMR** (250 MHz, $CHCl_3$) δ 7.43 (1H, s, Ar), 7.24 (1H, s, Ar), 6.85 (1H, d, J 1.9Hz, Ar), 6.65 (1H, d, J 8.2Hz, Ar), 6.42 (1H, dd, J 8.2, 1.9 Hz, Ar), 6.08 (2H, s, $OCH_2O$), 5.94 (2H, s, $OCH_2O$), 5.69 (1H, s, OH), 4.69 (1H, d, J 9.2Hz, C*H*HOCO), 4.31 (1H, dd, J 9.2, 5.6Hz, CH*H*OCO), 3.43 (1H, d, J 7.5Hz, $CHCO_2$) and 3.08 (1H, dd, J 7.5, 5.6Hz, C*H*$CH_2$) ppm; **n.O.e.** (270 MHz, $CHCl_3$) Irradiation of the signal at δ 5.69 ppm caused an n.O.e. enhancement at δ 3.43 ppm (13%); **$^{13}$C NMR** (67.8 MHz, $CHCl_3$) δ 192.6 (s), 176.7 (s), 154.3 (s), 148.7 (s), 148.1 (s), 147.5 (s), 143.6 (s), 138.0 (s), 127.1 (s), 119.9 (d), 107.8 (d), 107.0 (d), 106.8 (d), 105.7 (d), 102.3 (t), 101.3 (t), 73.0 (s), 70.7 (t), 50.1 (d) and 45.9 (d) ppm; **$^m/_z$** Found: $M^+$, 382.0646; $C_{20}H_{14}O_8$ requires 382.0689.
9. The synthetic sample exhibited : **m.p.** (acetone) 292-294°C with sublimation;[10] **UV** ($CHCl_3$) $\mu_{max}$ (ε) 243 (13600), 264 (21300), 286 (21450), 290 (6250), 310 (5690), 322 (5690), and 354 (2930); **FT-IR** ($CHCl_3$) $\lambda_{max}$ 3200br, 1712s and 1467s $cm^{-1}$; **$^1$H NMR** (400 MHz, acetone, 55°C) δ 8.85 (brs. OH), 7.65 (1H, s, Ar), 6.97 (1H, s, Ar), 6.92 (1H, d, J 7.8Hz, Ar), 6.78 (1H, d, J 1.4Hz, Ar), 6.74 (1H, dd, J 7.8, 1.4Hz, Ar), 6.12 (2H, s, $OCH_2O$), 6.05 (2H, s, $OCH_2O$) and 5.36 (2H, s, $CH_2OCO$); **$^m/_z$** Found: $M^+$, 364.0603 (70%); $C_{20}H_{12}O_7$ requires 364.0583.
10. Taiwanin E has been reported with a melting point of 263-267°C,[6] 292°C with sublimation,[5a] 298 - 300°C,[5c] 302-305°C[5b] and 340°C.[5d]
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