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Michael Initiated Ring Closure Reactions in Natural Product Synthesis: A Concise Entry to the Podophyllins.

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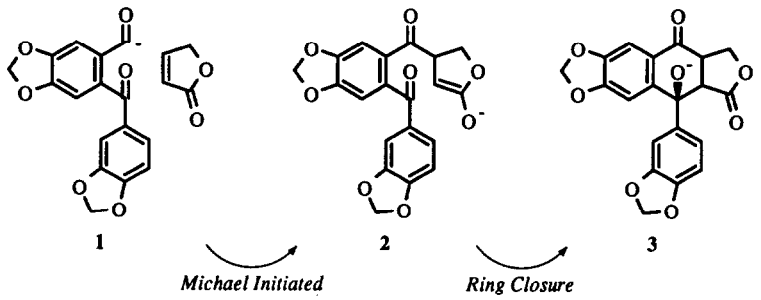
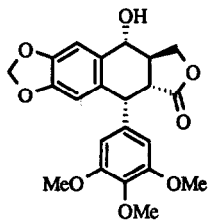
Abstract : *A rapid entry towards the Podophyllum lignans is described exemplified by a concise regioselective total synthesis of taiwanin E* **5** *and chinensinaphthol* **6**. *The approach features a Michael Initiated Ring Closure (MIRC type II) sequence to access the key lignan intermediates* **11a** *&* **b** *from the ketodithianes* **10a** *&* **b** *and 2-(5H)-furanone.*

Illustrations of the explosive power and diverse application of tandem and cascade reaction sequences in organic synthesis abound in the contemporary literature.[1] Whilst considerable attention has recently been focused on radical[2] and cationic[3] intermediates as triggers for multiple bond construction, the use of anionic species has not been overlooked.[4] Indeed, cyclisations initiated by Michael addition reactions have found extensive use in the synthesis of both simple and complex substrates.[5]



Scheme 1

This paper outlines in detail our recently disclosed entry to the podophyllins based on a type II Michael initiated ring closure (MIRC) protocol.[5a,d] The versatility of this approach is highlighted through the synthesis of taiwanin E **5**[6,7] and chinensinaphthol **6**,[8,9] naturally occurring arylnaphthalene lignans which possess all the functionality of podophyllotoxin **4** around a central aromatic ring.



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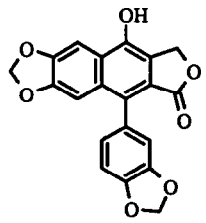

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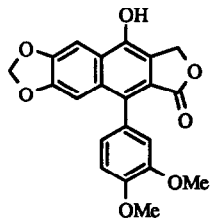
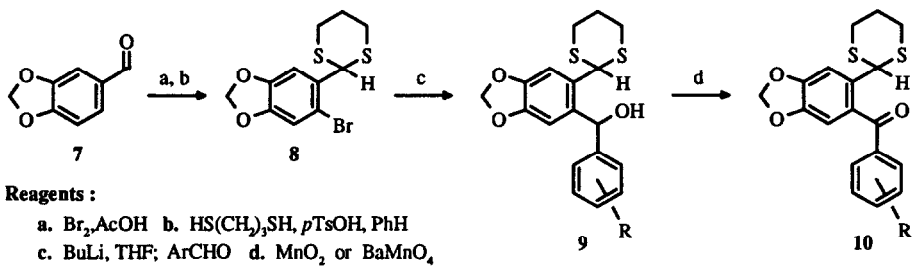


6

The key feature of our approach required the generation and intermolecular Michael addition of an acyl anion equivalent, *e.g.* **1** to 5(*H*)-furan-2-one. The resulting ester enolate **2** could then undergo an intramolecular aldol condensation to effect closure of the central six-membered ring (Scheme 1). We therefore chose to prepare the 1,3-dithianes **10a,b** since lithiated dithianes of this type are known to undergo vinylogous addition to α,β-unsaturated lactones.

Thus, piperonal **7** was treated sequentially with bromine and with 1,3-propanedithiol, under acid catalysis, to give the dithiane **8**. Transmetallation of **8** to the corresponding aryllithium and subsequent treatment with either piperonal **7** or 3,4-dimethoxybenzaldehyde furnished the alcohols **9a** or **9b** respectively. Benzylic oxidation of these alcohols **9a,b**, using either manganese(IV)oxide or barium manganate, then yielded the desired precursors **10a,b** (Scheme 2).



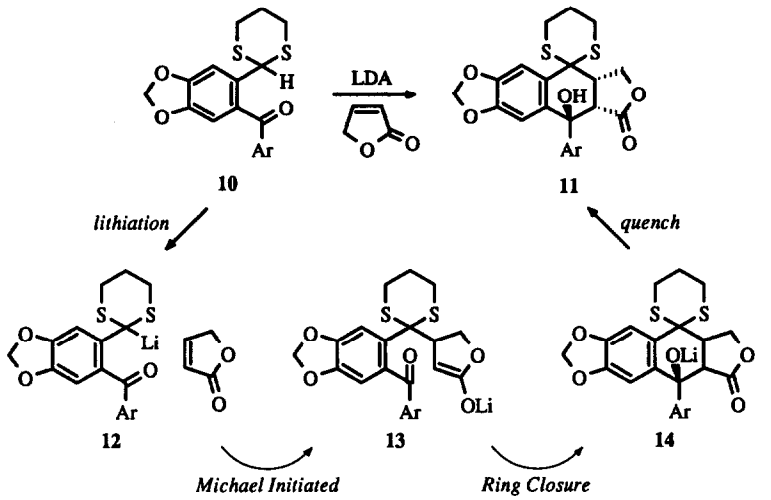
Reagents :

a. Br_2,AcOH b. $HS(CH_2)_3SH$, *p*TsOH, PhH
c. BuLi, THF; ArCHO d. MnO_2 or $BaMnO_4$

a : R = 3,4-methylenedioxy
b : R = 3,4-dimethoxy

Scheme 2

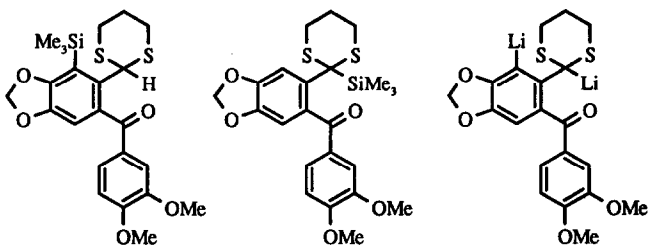
Deprotonation of dithiane **10a**, by adding it to a THF solution of LDA maintained at -78°C, resulted in the generation of a purple solution. Quenching this with 5(*H*)-furan-2-one, followed by the usual aqueous work up, gave a single diastereoisomer[10] of the desired lignan precursor **11a** (46%) together with recovered starting material (50%) (Scheme 3). Our initial attempts to optimise this procedure met with limited success; the use of LiHMDS gave a marginal improvement in yield (50%) but significant quantities of the dithiane **10a** remained (42%).



10 11 12 13 14

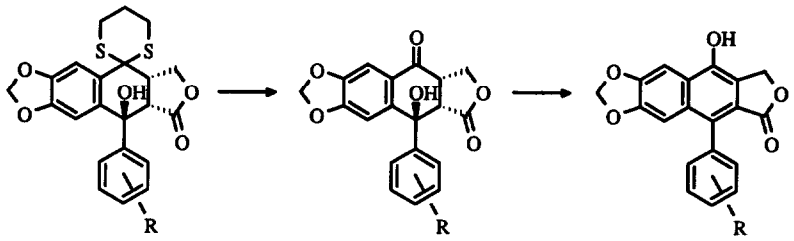
Scheme 3

To investigate this process in more detail we decided to quench the anion derived from **10b** with chlorotrimethylsilane. To our suprise this furnished the aryl silane **15**, not the anticipated silyldithiane **16**. We therefore concluded that the anion **10b** was either ambident in character or, more likely, under the deprotonation conditions adopted we had generated the dilithiated intermediate **17**. To circumvent this we decided to effect the lithiation by adding a THF solution of LDA to **10a**, hoping that this would facilitate monolithiation to **12a**. Indeed, when 5(*H*)-furan-2-one was added to the resulting solution the lignan precursor **11a** was produced in a more satisfactory 79% yield and only traces of 'unreacted' ketone **10a** (9%) remained.



15 16 17

To complete the synthesis of taiwanin E **5** the dithiane **11a** was next subjected to standard hydrolysis conditions ($HgCl_2$, HgO, aq.CH_3CN). The resulting hydroxyketone **18a** underwent smooth dehydration - aromatisation to taiwanin E **5** on exposure to tosic acid. This overall strategy was similarly employed in a synthesis of the related lignan chinensinaphthol **6** *via* the ketodithiane **10b**. Details of this synthesis are presented in the experimental section of this article.



11 18 4, 5

It is perhaps noteworthy that lignans of this type have been shown to exhibit both cytotoxic[11] and piscicidal activity.[12] Moreover, their use as hypolipidemic agents has attracted much recent attention.[13] Further application of this methodology towards the more demanding podophyllum lignans, *e.g.* podophyllotoxin **4**, *via* intermediates akin to **11** and **18**, is currently under investigation together with a range of other applications of the MIRC protocol in target orientated synthesis.

Experimental

5-Bromo-6-(1,3-dithian-2-yl)-1,3-benzodioxole **8**

A benzene solution (350ml) of 6-bromopiperonal[14] (43g, 188mmol), 1,3-propanedithiol (18.8ml, 20.26g, 187mmol) and *p*-toluenesulfonic acid (1.8g, 9.5mmol) were stirred at reflux for 2h then ambient temperature for 2 days. The solution was partitioned between ether (250ml) and 2M NaOH (250ml), washed with 2M NaOH (250ml) and separated. The organics were dried ($MgSO_4$) then concentrated *in vacuo* to yield a pale yellow solid (59g, 98%). This material was suficiently pure to be used directly in the next stage but could be further purified by recrystallisation from ethanol (first crop 39g, from 59g of crude) to give **8** as colourless needles: m.p. 102-106°C; (Found: C, 41.9; H 3.3. $C_{11}H_{11}BrO_2S_2$ requires C, 41.4; H 3.5); υ_{max} ($CHCl_3$) 2905m, 2830m, 1865w, 1685m, 1620m, 1485s, 1465s and 1115s cm^{-1}; λ_{max} ($CHCl_3$) 250 (2700), 254 (2900) and 297 (2100) nm; δ_H (80MHz, $CDCl_3$) 7.18 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 5.96 (2H, s, OCH_2O), 5.53 (1H, s, SC*H*S), 3.3 to 2.7 (4H, m, 2xSCH_2) and 2.3 to 1.7 (2H, m, $CH_2CH_2CH_2$) p.p.m.; m/z (EI) 320 (M^+ (^{81}Br), 32%), 318 (M^+ (^{79}Br), 34), 246 (M-$S(CH_2)_3^+$, 48), 244 (M-$S(CH_2)_3^+$, 48), 240 (M-Br^+, 18), 239 (M-HBr^+, 21) and 165 (M-Br-$S(CH_2)_3^+$, 100).

α-1,3-Benzodioxol-5-yl-6-(1,3-dithian-2-yl)-1,3-benzodioxole-5-methanol **9a**

was prepared by the method of Takano *et al.*[15] and exhibited: υ_{max} ($CHCl_3$) 3420br, 2900m, 1860w, 1620m, 1505m, 1485m, 1240m and 1040m cm^{-1}; λ_{max} ($CHCl_3$) 252 (10100) and 293 (8950) nm; δ_H (270MHz, $CDCl_3$) 7.14 (1H, s, Ar*H*), 6.87 (1H, d, J 0.6Hz, Ar*H*), 6.85 (1H, app. ddd, J 7.6, 1.7 and 0.6Hz, Ar*H*), 6.78 (1H, dd, J 7.6 and 1.0Hz, Ar*H*), 6.42 (1H, s, Ar*H*), 6.11 (1H, brs, C*H*OH), 5.95 (2H, s, OCH_2O), 5.93 (2H, abq, OCH_2O), 5.42 (1H, s, SC*H*S), 2.98 (2H, app. ddd, J 14.0, 11.9 and 4.0Hz, 2 x SC*H*H), 2.84 (2H, app. dt, J 14.0 and 3.5Hz, 2 x SCH*H*), 2.77 (1H, brs, O*H*), 2.13 (1H, app. dtt, J 14.0, 4.0 and 3.5Hz, CH_2CHHCH_2) and 1.87 (1H, app. dtt, J 14.0, 11.9 and 3.5Hz, CH_2CHHCH_2) p.p.m.; δ_C (67.8MHz, $CDCl_3$) 147.7(s), 147.6 (s), 147.4 (s), 146.7 (s), 136.8 (s), 135.0 (s), 130.3 (s), 119.7 (d),

108.7 (d), 108.2 (d), 107.9 (d), 107.2 (d), 101.4 (t), 101.0 (t), 71.7 (d), 47.8 (d), 32.4(t), 32.3 (t) and 24.9 (t); m/z (EI) Found: M-H_2O^+, 372.0506 (15%); $C_{19}H_{16}O_4S_2$ requires 372.0489; 325 (29), 298 (25), 284 (100), 283 (99), 282 (50), 267 (40), 254 (22), 151 (89), 139 (33) and 93 (58).

α-3.4-Dimethoxyphenyl-6-(1.3-dithian-2-yl)-1.3-benzodioxole-5-methanol **9b**
was prepared by the method of Takano *et al.*[15] and exhibited: white needles, m.p. (ether) 195-196°C (lit.[14] 185-187°C); (Found: C, 59.5; H 5.6. $C_{20}H_{22}O_5S_2$ requires C, 59.1; H 5.5); δ_H (80MHz, $CDCl_3$) 7.14 (1H, s, Ar*H*), 6.90 (2H, m, Ar*H*), 6.86 (1H, s, Ar*H*), 6.71 (1H, s, Ar*H*), 6.12 (1H, brs, C*H*OH), 5.90 (2H, s, OCH_2O), 5.44 (1H, s, SC*H*S), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.1-2.7 (5H, m, O*H* & 2xSCH_2), 2.3-1.7 (2H, m, $CH_2CH_2CH_2$) p.p.m.

1.3-Benzodioxol-5-yl[6-(1.3-dithian-2-yl)-1.3-benzodioxole-5-yllmethanone **10a**
Either : the alcohol **9a** (4.4g, 113mmol) was stirred with activated manganese dioxide (20g, 230mmol) in CH_2Cl_2 (200ml) at ambient temperature under nitrogen for 16h. The whole was then filtered through a plug of celite, the residual solids washed with copious quantities of $CHCl_3$ (300ml) then evaporated to dryness to give **10a** as a white solid (4.2g, 108mmol, 96%).
Or : the alcohol **9a** (3.77g, 9.7mmol) was stirred with barium manganate(VII) (12.5g, 48.8mmol) in CH_2Cl_2 (75ml) at ambient temperature under nitrogen for 16h. A further portion of barium manganate (5.0g, 19.5mmol) was added and stirred for 1h. The whole was then filtered through a plug of silica, the residual solids were washed with copious quantities of CH_2Cl_2 (200ml) and the organics evaporated to dryness *in vacuo* to yield **10a** as a white solid (3.31g, 8.5mmol, 88%): m.p. 232 - 236°C; (Found: C, 58.6; H 4.2. $C_{19}H_{16}O_5S_2$ requires C, 58.8; H 4.2); υ_{max} ($CHCl_3$) 2905m, 1650s, 1605s, 1485m, 1370m, 1285m, 1100m and 940m cm^{-1}; λ_{max} ($CHCl_3$) 250 (12800), 282 (7900), 318 (12000) and 323 (11500) nm; δ_H (250MHz, $CDCl_3$) 7.37 (1H, d, J 2.0Hz, Ar*H*), 7.34 (1H, dd, J 7.9 and 2.0Hz, Ar*H*), 7.32 (1H, s, Ar*H*), 6.84 (1H, d, J 7.9, Ar*H*), 6.75 (1H, s, Ar*H*), 6.07 (2H, s, OCH_2O), 6.04 (2H, s, OCH_2O), 5.42 (1H, s, SC*H*S), 2.94 (2H, dm, J 14.2Hz and others, 2 x SC*H*H), 2.84 (2H, app. dt, J 14.2 and 3.6Hz, 2 x SCH*H*), 2.10 (1H, dm, J 14.0Hz and others, CH_2CHHCH_2) and 1.87 (1H, dm, J 14.0Hz and others, CH_2CHHCH_2) p.p.m.; δ_C (67.8MHz, $CDCl_3$) 194.5 (s), 152.1 (s), 149.6 (s), 148.0 (s), 146.7 (s), 133.1 (s), 132.3 (s), 131.3 (s), 127.5 (d), 109.6 (d), 109.5 (d), 109.0 (d), 107.7 (d), 101.9 (t), 101.9 (t), 47.5 (d), 32.1 (2xt) and 24.9 (t); m/z (EI) Found: M^+, 388.0433 (10%); $C_{19}H_{16}O_5S_2$ requires 388.0439; 296 (22), 282 (100), 239 (30) and 180 (42).

3.4-Dimethoxyphenyl[6-(1.3-dithian-2-yl)-1.3-benzodioxole-5-yllmethanone **10b**
was prepared by the method outlined above using **9b** (6.2g, 15.3mmol) and activated manganese dioxide (20g, 230mmol) in CH_2Cl_2 (200ml); purification by column chromatography (silica, 1:2 petrol : ether) to give **10b** as a white crystalline solid (5.5g, 13.6mmol, 89%) : m.p. 160-162°C; (Found: C, 59.7; H 5.0. $C_{20}H_{20}O_5S_2$ requires C, 59.4; H 5.0); υ_{max} ($CHCl_3$) 2905m, 2840m, 1650s, 1595s, 1485m, 1370m, 1295m, 1275m, 1130m, 1020w and 940w cm^{-1}; λ_{max} ($CHCl_3$) 248 (15000), 285 (11500) and 320 (11800) nm; δ_H (250MHz, $CDCl_3$) 7.51 (1H, d, J 2.0Hz, Ar*H*), 7.34 (1H, dd, J 8.4 and 2.0Hz, Ar*H*), 7.32 (1H, s, Ar*H*), 6.87 (1H, d, J 8.4, Ar*H*), 6.78 (1H, s, Ar*H*), 6.04 (2H, s, OCH_2O), 5.38 (1H, s, SC*H*S), 3.96 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 2.89 (2H, dm, J 14.2Hz and others, 2 x SC*H*H), 2.79 (2H, app. dt, J 14.2 and 3.6Hz, 2 x SCH*H*), 2.10 (1H, dm, J 14.0Hz and others, CH_2CHHCH_2) and 1.87 (1H, dm, J 14.0Hz

and others, $CH_2CH\mathit{H}CH_2$) p.p.m.; δ_C (67.8MHz, $CDCl_3$) 195.0 (s), 153.5 (s), 149.5 (s), 148.9 (s), 146.8 (s), 132.9 (s), 131.4 (s), 130.5 (s), 125.9 (d), 111.5 (d), 109.8 (d), 109.5 (d), 108.9 (d), 101.8 (t), 56.1 (q), 56.0 (q), 47.6 (d), 32.1 (2xt) and 24.9 (t).

(5'aα,8'aα,9'α)-9'-(1,3-Benzodioxol-5-yl)-5'a,6',8'a,9'-tetrahydro-9'-hydroxy-spiro[1,3-dithiane-2,5'(8*H*)-furo[3',4':6,7]naphtho[2,3-d][1,3]dioxol]-8'-one **11a**

n-Butyllithium (1.6M solution in hexanes, 4ml, 6.0mmol) was added dropwise over 5 min to a cooled (-78°C) solution of diisopropylamine (840μl, 607mg, 6.0mmol) in THF (20ml) under nitrogen. The solution was warmed to ambient temperature over 30 min and 13ml added, dropwise *via* syringe over 3 min, to a cooled (-78°C), THF solution (100ml) of the dithiane **10a** (1.23g, 3.17mmol). After 20min 2(5*H*)-furanone (293mg, 3.5mmol), as a solution in THF (4ml), was added over 1 min. The whole was warmed to ambient temperature (1h) then partitioned between $CHCl_3$ (150ml) and water (150ml). The organics were separated, dried ($MgSO_4$) and purified by column chromatography (silica, gradient ellution, 2:1 petrol:ether to neat ether) to give firstly recovered starting material (90mg, 7%), then 2(5*H*)-furanone (trace), and finally the MIRC adduct **11a** (1.17g, 2.50mmol, 79%) as a sparingly soluble white solid; υ_{max} ($CHCl_3$) 3470br, 2855m, 1785s, 1770s, 1485m and 1110s cm^{-1}; λ_{max} ($CHCl_3$) 254 (9300), 290 (7900) and 293 (8100) nm; δ_H (250MHz, $CDCl_3$) 7.61 (1H, s, Ar*H*), 6.97 (1H, dd, J 8.2 and 1.7Hz, Ar*H*), 6.84 (1H, d, J 1.7Hz, Ar*H*), 6.78 (1H, d, J 8.2Hz, Ar*H*), 6.40 (1H, s, Ar*H*), 5.97 (2H, s, OCH_2O), 5.96 (2H, s, OCH_2O), 4.41 (1H, dd, J 8.8 and 7.8Hz, C*H*HOCO), 4.22 (1H, dd, J 11.6 and 8.8Hz, CH*H*OCO), 3.86 (1H, ddd, J 11.6, 7.8 and 7.2Hz, $CHCHCH_2$), 3.39 (1H, d, J 7.2Hz, C*H*CO), 3.22 (1H, ddd, J 14.7, 12.8 and 3.3Hz, SC*H*H), 3.13 (1H, ddd, J 14.7, 12.8 and 3.4Hz, SC*H*H), 2.90 (1H, app. dt, J 14.7 and 3.3Hz, SCH*H*), 2.79 (1H, app. dt, J 14.7 and 3.3Hz, SCH*H*), 2.24 (1H, dm, J 12.8Hz and others, CH_2CHCH_2) and 1.98 (1H, app. dt, J 12.8 and 3.4Hz, $CH_2CH\mathit{H}CH_2$) p.p.m.; δ_C (100MHz, $CDCl_3$) 174.5 (s), 148.7 (s), 148.5 (s), 147.7 (s), 146.9 (s), 141.5 (s), 134.9 (s), 128.0 (s), 119.4 (d), 108.2 (d), 107.8 (d), 107.7 (d), 107.2 (d), 101.8 (t), 101.2 (t), 71.7 (s), 69.2 (t), 50.5 (d), 49.3 (s), 42.5 (d), 29.4 (t), 27.3 (t) and 23.9 (t); m/z (EI) Found: M^+, 472.0661 (25%); $C_{23}H_{20}O_7S_2$ requires 472.0650; 454 (100), 407 (31), 398 (43), 380 (24), 365 (46), 348 (29), 324 (39), 314 (79) and 149 (50).

(5'aα,8'aα,9'α)-9'-(3,4-Dimethoxyphenyl)-5'a,6',8'a,9'-tetrahydro-9'-hydroxy-spiro[1,3-dithiane-2,5'(8*H*)-furo[3',4':6,7]naphtho[2,3-d][1,3]dioxol]-8'-one **11b**

n-Butyllithium (1.6M solution in hexanes, 1.6ml, 2.56mmol) was added dropwise over 3min to a stirred solution of diisopropylamine (360μl, 259mg, 2.56mmol) in THF (50ml) maintained at -78°C under nitrogen. After 20min the dithiane **10b** (868mg, 2.0mmol), as a solution in THF (12ml), was added dropwise over 5min. After a further 15min 2(5*H*)-furanone (215mg, 2.56mmol), as a solution in THF (4ml), was added dropwise over 3min. The whole was warmed to -50°C over 25min, then to ambient temperature over a further 30min, concentrated *in vacuo* and partitioned between $CHCl_3$ (200ml) and water (200ml). The organics were separated, dried ($MgSO_4$) and purified by column chromatography (silica, gradient ellution, 1:1 ether:petrol to neat ether) to give firstly recovered starting material (347mg, 40%), then 2(5*H*)-furanone, and finally the MIRC adduct **11b** (513mg, 1.05mmol, 53%) as a sparingly soluble white solid m.p. 238-241°C (ether - petrol); υ_{max} ($CHCl_3$) 3400br, 2910m, 2835m, 1780vs, 1605m, 1485m and 1140s cm^{-1}; δ_H (250MHz, $CDCl_3$) 7.58 (1H, s, Ar*H*), 6.92 (2H, m, Ar*H*), 6.80 (1H, d, J 8.9Hz, Ar*H*), 6.40 (1H, s, Ar*H*), 5.93 (4H, m, $2xOCH_2O$), 4.39 (1H, dd, J 8.6 and 7.5Hz, C*H*HOCO), 4.18 (1H, dd, J 11.5 and 8.6Hz, CH*H*OCO), 3.86 (1H, ddd, J 11.5, 7.5 and 7.2Hz, $CHCHCH_2$), 3.85 (3H,

OC*H*$_3$), 3.79 (3H, OC*H*$_3$), 3.41 (1H, d, J 7.2Hz, C*H*CO), 3.21 (1H, ddd, J 12.6, 12.4 and 2.3Hz, SC*H*H), 3.12 (1H, ddd, J 12.6, 12.4 and 2.3Hz, SC*H*H), 2.87 (1H, app. dt, J 14.5 and 3.3Hz, SCH*H*), 2.75 (1H, app. dt, J 14.5 and 3.3Hz, SCH*H*), 2.28 (1H, app. dm, J 14.5Hz and others, CH_2CHHCH_2) and 1.98 (1H, m, CH_2CHHCH_2) p.p.m.; δ_C (100MHz, $CDCl_3$) 174.7 (s), 148.7 (s), 148.5 (s), 148.3 (s), 148.1 (s), 140.1 (s), 134.9 (s), 127.8 (s), 117.9 (d), 110.5 (d), 109.7 (d), 108.3 (d), 107.4 (d), 101.7 (t), 71.4 (t), 69.1 (s), 55.8 (q), 55.8 (q), 50.6 (d), 49.2 (s), 42.3 (d), 29.2 (t), 27.1 (t) and 23.8 (t); m/z (EI) Found: M^+, 488.0960 (22%); $C_{24}H_{24}O_7S_2$ requires 488.0963; 470 (85), 444 (7), 426 (37), 414 (67), 396 (25), 381 (50), 364 (29), 352 (21), 330 (66), 113 (50) and 100 (100).

3,4-Dimethoxyphenyl[6-(1,3-dithian-2-yl)-1,3-benzodioxole-5-yl]methanone **15**

n-Butyllithium (1.6M solution in hexanes, 1.6ml, 2.56mmol) was added dropwise over 2min to a stirred solution of diisopropylamine (360µl, 259mg, 2.56mmol) in THF (50ml) maintained at -78°C under nitrogen. After 10min chlorotrimethylsilane (310µl, 270mg, 2.5mmol) was added followed by the dithiane **10b** (770mg, 1.9mmol), added dropwise over 3min as a solution in THF (20ml). The whole was warmed to -50°C over 30min, to ambient temperature over a further 30min, then the whole was concentrated *in vacuo* and partitioned between $CHCl_3$ (200ml) and water (200ml). The organics were separated, dried ($MgSO_4$) and purified by column chromatography (silica, gradient ellution, 1:1 ether:petrol to neat ether) to give firstly the arylsilane **15** (524mg, 1.10mmol, 58%) which exhibited the following n.m.r. characteristics : δ_H (270MHz, $CDCl_3$) 7.51 (1H, brs, Ar*H*), 7.30 (1H, brd, J 8.5Hz, Ar*H*), 7.23 (1H, s, Ar*H*), 6.83 (1H, d, J 8.5, Ar*H*), 5.97 (2H, s, OC*H*$_2$O), 4.79 (1H, s, SC*H*S), 3.94 (3H, s, OC*H*$_3$), 3.93 (3H, s, OC*H*$_3$), 2.68 (4H, m, 2 x SC*H*$_2$), 2.02 (1H, m, CH_2CHHCH_2), 1.84 (1H, m, CH_2CHHCH_2) and 0.06 (9H, s, Si(C*H*$_3$)$_3$) p.p.m.; δ_C (67.8MHz, $CDCl_3$) 196.8 (s), 153.7 (s), 152.8 (s), 148.8 (s), 146.7 (s), 136.6 (s), 131.1 (s), 129.4 (s), 126.2 (brd), 117.1 (s), 110.8 (brd), 109.7 (d), 109.3 (d), 100.6 (t), 55.9 (q), 55.9 (q), 48.3 (d), 32.0 (2xt), 24.7 (t) and 0.06 (3xq); then recovered starting material **10b** (231mg, 30%).

(5aα,8aα,9α)-9-(1,3-Benzodioxol-5-yl)-5a,6,8a,9-tetrahydro-9-hydroxyfuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxole-5,8-dione **18a**

A solution of the MIRC adduct **11a** (100mg, 0.21mmol), HgO (50mg, 0.23mmol) and $HgCl_2$ (130mg, 0.48mmol) in aqueous (1.5ml) acetonitrile (8ml) was heated to reflux for 40min. The whole was then partitioned between $CHCl_3$ (50ml) and sat. ammonium carbonate (50ml), the organics were washed with brine (50ml), dried ($MgSO_4$), concentrated *in vacuo*, then purified by column chromatography (silica, 1:1 ether : petrol (having introduced the crude material as a solution in $CHCl_3$)) to yield the ketone **18a** as a white solid (50mg, 0.13mmol, 62%); υ_{max} ($CHCl_3$) 3455br, 3080w, 2970m, 2910m, 1755s, 1675s, 1615s, 1505s, 1270vs and 730s cm^{-1}; λ_{max} ($CHCl_3$) 285 (3000), 322 (2300) and 326 (2300) nm; δ_H (250MHz, $CDCl_3$) 7.43 (1H, s, Ar*H*), 7.24 (1H, s, Ar*H*), 6.85 (1H, d, J 1.9Hz, Ar*H*), 6.65 (1H, d, J 8.2Hz, Ar*H*), 6.42 (1H, dd, J 8.2 and 1.9Hz, Ar*H*), 6.08 (2H, s, OC*H*$_2$O), 5.94 (2H, s, OC*H*$_2$O), 5.69 (1H, s, O*H*), 4.69 (1H, d, J 9.2Hz, C*H*HOCO), 4.31 (1H, dd, J 9.2 and 5.6Hz, CH*H*OCO), 3.43 (1H, d, J 7.5Hz, C*H*CO$_2$) and 3.08 (1H, dd, J 7.5 and 5.6Hz, C*H*CH$_2$) p.p.m.; n.O.e. (270MHz, $CDCl_3$) Irradiation of the signal at δ_H 5.69 p.p.m. caused an n.O.e. enhancement at δ_H 3.43 p.p.m. (13%); δ_C (67.8MHz, $CDCl_3$) 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); m/z (EI) Found: M^+, 382.0646 (30%); $C_{20}H_{14}O_8$ requires 382.0689; 364 (M-H_2O, 8), 298 (M-$C_4H_4O_2^+$, 100), 240 (19) and 149 (25).

(5aα,8aα,9α)-9-(3,4-Dimethoxyphenyl)-5a,6,8a,9-tetrahydro-9-hydroxyfuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxole-5,8-dione **18b**

MIRC adduct **11b** (230mg, 0.47mmol) was treated in a similar fashion: HgO (110mg, 0.46mmol), $HgCl_2$ (260mg, 0.96mmol), aqueous (10ml) acetonitrile (25ml), reflux 3h, to give **18b** as a white solid (79mg, 0.20mmol, 42%): υ_{max} ($CHCl_3$) 3450br, 3020m, 2960m, 2915m, 2840m, 1755s, 1670s, 1615s, 1265s, 1025s and 755s cm^{-1}; λ_{max} ($CHCl_3$) 286 (3300) and 324 (2900) nm; δ_H (270MHz, $CDCl_3$) 7.45 (1H, s, Ar*H*), 7.26 (1H, s, Ar*H*), 7.10 (1H, d, J 2.3Hz, Ar*H*), 6.66 (1H, d, J 8.3Hz, Ar*H*), 6.30 (1H, dd, J 8.3 and 2.3Hz, Ar*H*), 6.08 (2H, s, OCH_2O), 5.73 (1H, s, O*H*), 4.70 (1H, d, J 9.2Hz, C*H*HOCO), 4.30 (1H, dd, J 8.3 and 5.6Hz, CH*H*OCO), 3.87 (3H, s, CH_3), 3.82 (3H, s, CH_3), 3.45 (1H, d, J 7.5Hz, $CHCO_2$) and 3.08 (1H, dd, J 7.5 and 5.6Hz, $CHCH_2$) p.p.m.; δ_C (67.8MHz, $CDCl_3$) 192.8(s), 176.8 (s), 154.3 (s), 149.2 (s), 148.9 (s), 148.7 (s), 143.6 (s), 136.5 (s), 127.2 (s), 118.7 (d), 110.3 (d), 109.0 (d), 107.0 (d), 105.6 (d), 102.3 (t), 73.0 (s), 70.7 (t), 55.9 (2xq), 50.2 (d) and 45.9 (d); m/z (EI) Found: M^+, 398.1008 (36%); $C_{21}H_{18}O_8$ requires 398.1001; 314 ($M-C_4H_4O_2^+$, 100), 283 (40) and 149 (11).

5-(1,3-Benzodioxol-5-yl)-9-hydroxyfuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6-(8*H*)-one (taiwanin E) **5**

The ketone **18a** (74mg, 0.19mmol) and *p*-toluenesulfonic acid (21mg, 0.11mmol) were heated to reflux in benzene (12ml) for 16h. The whole was evaporated on to silica (0.5g) then purified by column chromatography (silica, acetone) to yield a sparingly soluble white solid **5** (70mg, 0.19mmol, 99%) ; m.p. (acetone) 292-294°C with sublimation; υ_{max} ($CHCl_3$) 3200br, 1712s and 1467s cm^{-1}; λ_{max} ($CHCl_3$) 243 (13600), 264 (21300), 286 (21450), 290 (6250), 310 (5690), 322 (5690) and 354 (2930) nm; δ_H (400MHz, d_6-acetone at 55°C) 8.85 (1H, brs, O*H*), 7.65 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 6.92 (1H, d, J 7.8Hz, Ar*H*), 6.78 (1H, d, J 1.4Hz, Ar*H*), 6.74 (1H, dd, J 7.8 and 1.4Hz, Ar*H*), 6.12 (2H, s, OCH_2O), 6.05 (2H, s, OCH_2O) and 5.36 (2H, s CH_2OCO) p.p.m.; m/z (EI) Found: M^+, 364.0603 (70%); $C_{20}H_{12}O_7$ requires 364.0583; 277 (13), 163 (12) and 46 (100).

5-(3,4-Dimethoxyphenyl)-9-hydroxyfuro[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6-(8*H*)-one (chinensinaphthol) **6**

The ketone **18b** (34mg, 0.089mmol) and p-toluene sulfonic acid (3.0mg, 0.016mmol) were in heated to reflux in benzene (20ml) for 12h. The whole was evaporated on to silica (0.5g) then purified by column chromatography (silica, ether then ethyl acetate) to yield a sparingly soluble white solid (30mg, 0.082mmol, 92%); m.p. (EtOAc) 265-270°C dec., but the sample appears, in part, to sublime above *c.a.* 255°C; υ_{max} ($CHCl_3$) 3210br, 1725s, 1710s, 1460m, 1360m, 1140m and 1000m cm^{-1}; λ_{max} ($CHCl_3$) 265 (32000), 313 (7800), 322 (8100) and 357 (4200) nm; δ_H (270MHz, d_6-DMSO) 8.39 (1H, brs, O*H*), 7.68 (1H, s, Ar*H*), 7.12 (1H, d, J 8.2Hz, Ar*H*), 6.93 (1H, s, Ar*H*), 6.91 (1H, d, J 2.0Hz, Ar*H*), 6.85 (1H, dd, J 8.2 and 2.0Hz, Ar*H*), 6.23 (2H, s, OCH_2O), 5.43 (2H, s CH_2OCO), 3.92 (3H, s, CH_3) and 3.79 (3H, s, CH_3) p.p.m.; δ_C (67.8MHz, d_6-DMSO) 169.6 (s), 148.8 (s), 148.4 (s), 148.3 (s), 148.1 (s), 145.3 (s), 131.2 (s), 130.4 (s), 127.6 (s), 124.7 (s), 122.6 (d), 122.4 (s), 119.2 (s), 114.3 (d), 111.2 (d), 102.6 (d), 102.1 (t), 98.1 (d), 66.6 (t), 55.5 (q) and 55.5 (q); m/z (EI) Found: M^+, 380.0912 (100%); $C_{21}H_{16}O_7$ requires 380.0896; 204 (25), 162 (33), 151 (64) and 113 (66).

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References and Notes:

1. For our recent studies involving the use of tandem and cascade reaction sequences see: **a.** Harrowven, D.C.; Dennison, S.T.; *Tetrahedron Letters*, **1993**, *34*, 3323; **b.** Harrowven, D.C.; *Tetrahedron Letters*, **1992**, *32*, 2879; **c.** Ali, A.; Harrowven, D.C.; Pattenden, G.; *Tetrahedron Letters*, **1992**, *33*, 2851; **d.** Harrowven, D.C.; *Tetrahedron Letters*, **1991**, *32*, 3735; **e.** Harrowven, D.C.; Pattenden, G.; *Tetrahedron Letters*, **1991**, *32*, 243.
2. For a selection of review articles and papers see: **a.** Hitchcock, S.A.; Pattenden, G.; *Tetrahedron Lett.*, **1992**, *33*, 4843; **b.** Jasperse, C.P.; Curran, D.P.; Fevig, T.L.; *Chem. Rev.*, **1991**, *91*, 1237; **c.** Schwartz, C.E.; Curran, D.P.; *J. Am. Chem. Soc.*, **1990**, *112*, 9272; **d.** Curran, D.P.; Fevig, T.L.; Totleben, M.J.; *Synlett*, **1990**, 773; **e.** Parsons, P.J.; Willis, P.A.; Eyley, S.C.; *J. Chem. Soc., Chem. Commun.*, **1988**, 283; **f.** Stork, G.; Sher, P.M.; *J. Am. Chem. Soc.*, **1986**, *108*, 303.
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5. For recent examples see **a.** Chem, C.; Huang, Y.-Z.; Shen, Y.; *Tetrahedron Lett.*, **1988**, *29*, 1033; **b.** Hudlicky, T.; Radesca-Kwart, L.; Li, L.; Bryant, T.; *Tetrahedron Lett.*, **1988**, *29*, 3283; **c.** Kurihara, T.; Santo, K.; Harusawa, S.; Yoneda, R.; *Chem. Pharm. Bull.* **1987**, *29*, 4777.
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