Supplementary Information

A concise stereocontrolled formal total synthesis of podophyllotoxin using sulfoxide chemistry

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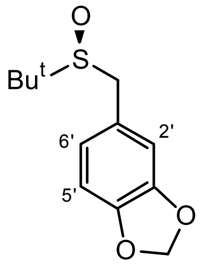
General

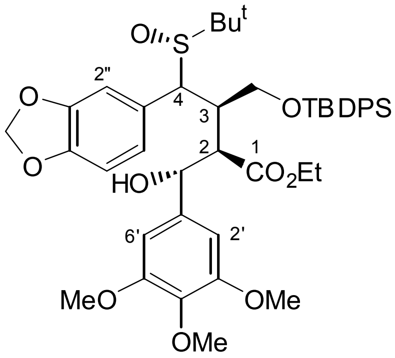
NMR spectra were recorded on Joel JNM-PMX-270, Varian Inova-300 and Varian Inova-5000 spectrometers. Tetramethylsilane was used as an internal reference (δ TMS = 0.0), and coupling constants are given in Hertz. IR spectra were recorded on Perkin-Elmer Paragon 1000 Fourier Transform spectrometer. Melting points were recorded on a Gallenkamp electrothermal melting point apparatus and are uncorrected. Elemental analyses were determined by the Microanalytical Laboratory, Department of Chemistry, University College Dublin. Flash column chromatography was preformed using flash silica 60 (230 – 400 mesh) 9385 supplied by Merck. Solvents were dried prior to use according to literature procedures. THF and diethyl ether was distilled from benzophenone ketyl immediately prior to use. Dichloromethane, toluene, diisopropylamine and triethylamine were distilled from calcium hydride immediately prior to use. *p*-Toluenesulfonyl chloride was extracted from a mixture of the acid and chloride by petroleum ether using a soxhlet apparatus. BuLi and TBAF were used as supplied by Aldrich Chemical Co.

(*R,S*)-*tert*-Butyl 3,4-methylenedioxybenzyl sulfoxide (2)



A mixture of piperonyl chloride (4.53 g, 27 mmol) and sodium *tert*-butanethiolate (2.33 g, 21 mmol) in absolute EtOH (90 mL) was heated at reflux for 2 days. The suspension was cooled and filtered, and the filtrate was diluted with water (90 mL). The solution was further cooled to 0 °C and sodium periodate (5.84 g, 27 mmol) was added. The reaction mixture was stirred at 0 °C for 45 min and was filtered through a sintered glass funnel to remove insoluble inorganic material. The filtrate was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude sulfoxide. Flash column chromatography (1:1 petrol: ethyl acetate) afforded the title compound as a white solid (3.25 g, 13.5 mmol, 65%), mp 115-116 °C, (Found: C 59.8; H 6.7; S 13.0. $C_{12}H_{16}O_3S$ requires: C 60.0; H 6.7; S 13.3%); ν_{max}(KBr)/cm^{-1}: 2939, 1503, 1498, 1252 and 1031; δ_H($CDCl_3$; 300 MHz; Me_4Si): 1.31 (9 H, s, Bu^t), 3.53 (1 H, d, *J* 12.7, CH_2Ar), 3.75 (1 H, d, *J* 12.7, CH_2Ar), 5.95 (2 H, s, OCH_2O) and 6.78–6.84 (3 H, m, H$^{2'}$, H$^{5'}$, H$^{6'}$); δ_C($CDCl_3$, 75.4 MHz): 23.3, 53.0, 53.9, 106.8, 108.8, 110.5, 123.7, 125.7, 147.8 and 148.4; m/z (EI) 240(M$^+$, 7), 135(100), 105(5), 77(21), 51(14), 41(13) and 28(19).

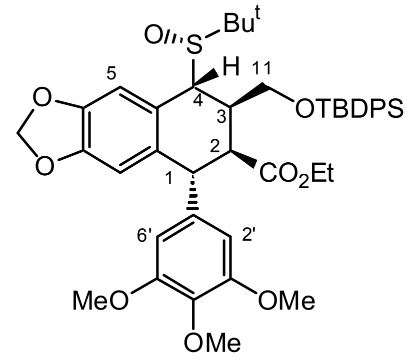
Ethyl (2*RS*,3*RS*,4*SR*,S*RS*)-3-(*tert*-butyldiphenylsilyloxymethyl)-4-*tert*-butylsulfinyl-2-[(*SR*)-hydroxy(3,4,5-trimethoxyphenyl)methyl]-4-(3,4-methylenedioxy)phenyl butanoate (4)



A solution of piperonyl *tert*-butyl sulfoxide **2** (760 mg, 3.17 mmol) in THF (6 mL) was deprotonated at –78 °C with LDA (preformed from DIPA (0.53 mL, 3.80 mmol) and BuLi (nominal 2.5 M solution in hexanes, 1.48 mL, 3.7 mmol) in THF (10 mL)). After 15 min a solution of ethyl γ-(*tert*-butyldiphenylsilyloxy)crotonate **3** (1.4 g, 3.8 mmol) in THF (5mL) was added dropwise. After 15 min a solution of 3,4,5-trimethoxybenzaldehyde (745 mg, 3.8 mmol) in THF (4 mL) was added at –78 °C and the resultant mixture was allowed to warm to –50 °C slowly before being poured into aqueous $NaHCO_3$. The aqueous was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified using column chromatography on silica (50:50 ethyl acetate: petrol) to yield the title compound as a yellow foam (1.63 g, 2.03 mmol, 64%), mp 77-78 °C (Found: C, 65.2; H, 7.1; S, 4.4. $C_{44}H_{56}O_{10}SSi$

requires: C, 65.7; H, 7.0; S 4.0%); ν_{max}(KBr)/cm^{-1}: 3481, 2958, 1728, 1592, 1504, 1252, 1127, 1035 and 707; δ_H(CDCl$_3$; 300 MHz; Me$_4$Si) (assignments supported by a COSY experiment): 0.97 (3 H, t, *J* 7.2, OCH$_2$C*H*$_3$), 0.99 (9 H, s, SiBu^t), 1.07 (9 H, s, SBu^t), 3.08–3.16 (1 H, m, 3-H), 3.43 (1 H, dd, *J* 3.7 and 9.4, 2-H), 3.79 (6 H, s, 2 x OMe), 3.80 (3 H, s, OMe), 3.92 (2 H, q, *J* 7.2, OC*H*$_2$CH$_3$), 3.98 (1 H, d, *J* 6.8, OH), 4.18 (1 H, dd, *J* 5.1 and 10.5, CHOSi), 4.24 (1 H, d, *J* 2.8, 4-H), 4.43 (1 H, dd, *J* 6.6 and 10.5, CHOSi), 4.88 (1 H, br dd, *J* 3.7 and 6.8, HOC*H*Ar), 5.94 (1 H, d, *J* 1.5, OCH$_2$O), 5.96 (1 H, d, *J* 1.5, OCH$_2$O), 6.43 (2 H, s, 2'-H and 6'-H), 6.67–6.70 (2 H, m, 5"-H and 6"-H), 6.78 (1 H, d, *J* 1.6, 2"-H) and 7.34–7.72 (10 H, m, Ar-H); δ_C(CDCl$_3$, 75.4 MHz): 14.0, 19.4, 23.8, 27.2, 46.0, 53.4, 56.3, 57.0, 60.0, 60.8, 61.0, 62.5, 71.7, 101.5, 103.0, 108.8, 110.0, 123.3, 128.0, 128.2, 130.0, 130.3, 130.3, 132.8, 132.9, 135.8, 135.9, 137.2, 138.0, 147.5, 148.2, 153.2 and 174.2; m/z (electrospray) 827 (M$^+$ + Na).

Ethyl (1*RS*, 2*SR*, 3*SR*,4*RS*, S*SR*)-3-(*tert*-butyldiphenylsilyloxymethyl)-4-*tert*-butylsulfinyl-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (5)



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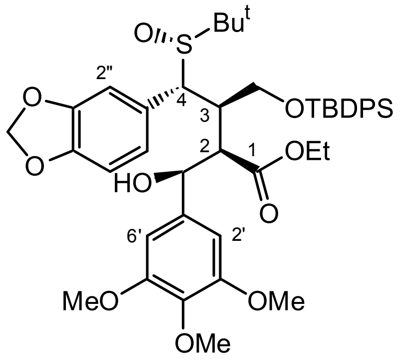


12

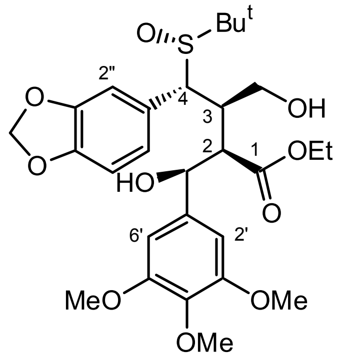
A solution of piperonyl *tert*-butyl sulfoxide **2** (251 mg, 1.04 mmol) in THF (4 mL) was reacted at –78 °C with LDA (preformed from DIPA (0.18 mL, 1.25 mmol) and BuLi (nominal 2.5 M solution in hexanes, 0.48 mL, 1.20 mmol) in THF (5 mL)). After 15 min a solution of ethyl γ-(*tert*-butyldiphenylsilyloxy)crotonate **3** (460mg, 1.25 mmol) in THF (4 mL) was added dropwise. After 15 min a solution of 3,4,5-trimethoxybenzaldehyde (247 mg, 1.25 mmol) in THF (3 mL) was added at –78 °C and the resultant mixture was allowed to warm to –50 °C slowly, before a solution of *p*-toluenesulfonyl chloride (257 mg, 1.3 mmol) in THF (3 mL) was added dropwise at –78 °C. The resultant mixture was allowed to warm to room temperature slowly before being poured into aqueous NaHCO$_3$, The aqueous was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude product was subjected to flash column chromatography on silica (30:70 ethyl acetate: petrol) to yield the title compound **5** (220 mg, 0.28

mmol, 27%) (Found: C, 66.9; H, 6.8; S, 4.4. $C_{44}H_{54}O_9SSi$ requires: C, 67.2; H, 6.85; S, 4.1%); ν_{max}(KBr)/cm^{-1}: 2974, 1722, 1593, 1500, 1250, 1129 and 1001; δ_H($CDCl_3$, 300 MHz; Me_4Si) (assignments supported by a COSY experiment): 1.01 (9 H, s, SiBu^t) 1.03 (3 H, t, *J* 7.1, $\mathrm{OCH_2C}\mathit{H_3}$), 1.56 (9 H, s, SBu^t), 3.26–3.29 (1 H, m, 3-H), 3.57 (1 H, apparent t, *J* 10.3, CHOSi), 3.77 (6 H, s, 2 x OMe), 3.80 (3 H, s, OMe), 3.76–3.81 (2 H, m, 2-H and CHOSi), 3.91–4.07 (3 H, m, 1-H/4-H and $\mathrm{OC}\mathit{H_2}\mathrm{CH_3}$), 4.39 (1 H, bd, *J* 1.4, 1-H/4-H), 5.92 (1 H, d, *J* 1.5, OCH_2O), 5.96 (1 H, d, *J* 1.5, OCH_2O), 6.32 (1 H, s, 5-H/8-H), 6.43 (2 H, s, 2'-H and 6'-H), 6.49 (1 H, s, 5-H/8-H) and 7.31–7.77 (10 H, m, Ar-H); δ_C($CDCl_3$, 75.4 MHz): 14.3 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 19.4, 24.0, 27.0, 37.4, 43.5, 46.7, 54.2, 56.2, 56.4, 60.7, 61.0, 62.0, 101.4, 106.8, 109.2, 110.1, 124.0, 127.9, 128.0, 130.0, 130.1, 132.7, 133.0, 134.3, 135.7, 136.0, 136.8, 140.6, 146.8, 147.8, 153.2 and 174.3; m/z (electrospray) 809 (M^+ + Na).

Crude aldol **12** (215 mg, 0.27 mmol, 26%) was also isolated, but was too unstable to be characterised: δ_H($CDCl_3$, 300 MHz; Me_4Si): 0.96 (9 H, s, SiBu^t), 1.10 (9 H, s, SBu^t), 1.19 (3 H, t, *J* 7.2, $\mathrm{OCH_2C}\mathit{H_3}$), 2.93–3.06 (1 H, m, 3-H), 3.62 (6 H, s, 2 x OMe), 3.78 (3 H, s, OMe), 3.80–4.30 (5 H, m, 2-H, $\mathrm{OC}\mathit{H_2}\mathrm{CH_3}$, CH_2OSi), 4.39 (1 H, d, *J* 4.1, 4-H), 5.13 (1 H, d, *J* 7.0, HOC*H*Ar), 5.93 (2 H, s, OCH_2O), 6.33 (2 H, s, 2'-H and 6'-H), 6.61–6.71 (3 H, m, 2"-H, 5"-H and 6"-H) and 7.32–7.70 (10 H, m, Ar-H).

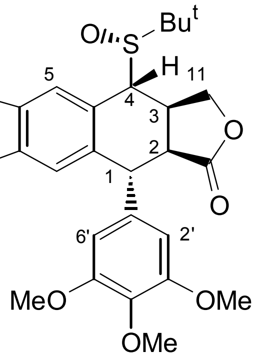
Ethyl (2*RS*,3*RS*,4*SR*,S*RS*)-4-*tert*-butylsulfinyl-3-hydroxymethyl-2-[(*RS)*-hydroxy-(3,4,5-trimethoxyphenyl)methyl]-4-(3,4-methylenedioxy)phenylbutanoate (15)

Treatment of crude **12** with TBAF in THF at room temperature gave the diol **15**, which had earlier been obtained as a side product in the conversion of the *tert*-butyldimethylsilyl analogue of adduct **4** into the *tert*-butyldimethylsilyl analogue of tetralin **5**.



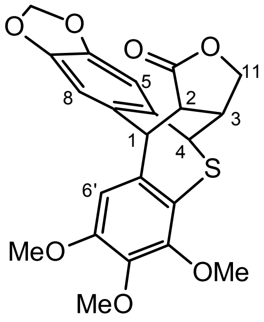
mp 95- 96 °C; ν_{max}(KBr)/cm^{-1}: 2921, 1721, 1592, 1508, 1467, 1259, 1130 and 1020; δ_H($CDCl_3$, 300 MHz; Me_4Si): 1.08 (3 H, t, *J* 7.2, $\mathrm{OCH_2C}\underline{\mathrm{H_3}}$), 1.22 (9 H, s, $\mathrm{C(C\underline{H_3)}_3)}$), 2.57 (1 H, apparent t, *J* 7.9, 2-H), 3.56–3.67 (1 H, m, 3-H), 3.84 (9 H, s, 3 x OMe), 3.76–3.96 (3 H, m, obscured by OMe, 4-H, OCH_2CH$_3$), 4.24 (1 H, dd, *J* 5.3 and 10.0, C$\underline{H}_2$OH), 4.42 (1 H, dd, *J* 7.8 and 10.0, C$\underline{H}_2$OH), 4.80 (1 H, d, *J* 8.0, HOC$\underline{H}$Ar), 5.94 (2 H, s, OC$\underline{H_2}$O), 6.50 (2 H, s, 2'-H, 6'-H), 6.60 (1 H, dd, *J* 1.6 and 7.9, 6''-H), 6.66 (1 H, d, *J* 1.6, 2''-H) and 6.71 (1 H, d, *J* 7.9, 5''-H); δ_C(CDCl$_3$, 75.4 MHz): 14.2, 24.1, 48.7, 56.3, 56.4, 57.7, 61.1, 61.2, 65.3, 73.0, 83.5, 101.6, 102.8, 108.8, 110.2, 123.9, 129.2, 135.8, 137.8, 147.9, 148.3, 153.5 and 172.33.

Tetralin (6)



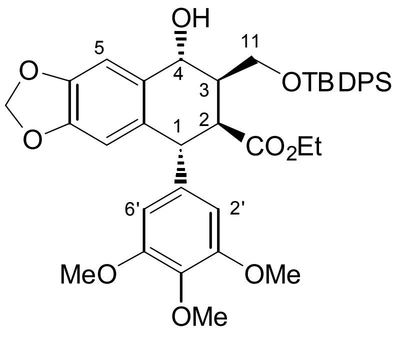
A solution of the sulfoxide **5** (100 mg, 0.13 mmol) in dry THF (4 mL) was stirred at room temperature while tetrabutylammonium fluoride (0.76 mL, nominal 1 M solution in Et$_2$O containing 1% water) was added dropwise. The resultant solution was stirred for 2 hours before being poured onto water, and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl, dried over MgSO$_4$ and concentrated *in vacuo* to yield, after flash column chromatography (90:10 ethyl acetate: petrol) the title compound **6** as a white powder (45 mg, 0.05 mmol, 71%), mp 86-88 °C; ν_{max}(KBr)/cm^{-1}: 2959, 1773, 1392, 1505, 1240 and 1125, 1039; δ_H(CDCl$_3$, 300 MHz; Me$_4$Si) (assignments supported by a COSY experiment): 1.31 (9 H, s, C(C$\underline{H_3}$)$_3$), 3.34 (1 H, dd, *J* 3.5 and 8.8, 2-H), 3.59–3.69 (1 H, m, 3-H), 3.81 (6 H, s, 2 x OMe), 3.82 (3 H, s, OCH$_3$), 3.87 (1 H, d, *J* 2.6, 4-H), 4.12 (1 H, dd, *J* 4.4 and 9.1, 11-H), 4.41 (1 H, d, *J* 3.5, 1-H), 4.44 (1 H, dd, *J* 6.8 and 9.1, 11-H), 5.96 (1 H, d, *J* 1.1, OC$\underline{H}_2$O), 5.97 (1 H, d, *J* 1.1, OC$\underline{H}_2$O), 6.36 (2 H, s, 2'-H, 6'-H),6.56 (1 H, s, 5-H/8-H) and 6.62 (1 H, s, 5-H/8-H); δ_C(CDCl$_3$, 75.4 MHz): 23.99, 29.6, 44.1, 45.2, 55.9, 56.5, 57.3, 61.1, 72.8, 101.8, 106.0, 109.2, 111.0, 124.7, 127.1, 137.3, 138.7*,* 147.8*,* 148.3*,* 153.5, 177.8.

Sulfide (7)



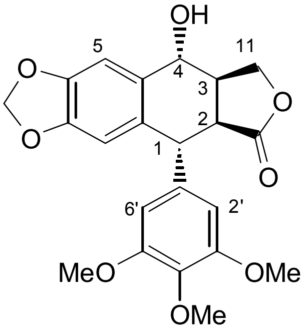
The sulfoxide **6** (20 mg, 0.04 mmol) in CH_2Cl_2 (2.4 mL) was stirred at –78 °C while collidine (11 µl, 0.08 mmol) and triflic anhydride (10 µl, 0.06 mmol) were added dropwise. The resultant solution was stirred at 0 °C for1 hour before water (2 µl) was added and then stirred for 3 hours before being diluted with CH_2Cl_2, washed with H_2O, dried over MgSO, and concentrated *in vacuo* The crude product was purified by preparative chromatography on silica (40:60 ethyl acetate: petrol), yielding the sulfide **7** as an oil (13 mg, 0.03 mmol, 76%); δ_H($CDCl_3$, 500 MHz; Me_4Si) (assignments supported by an HSQC experiment): 3.62 (1 H, dd, *J* 1.8, 10.8*,* 2-H), 3.77 (1 H, d, *J* 2.1*,* 4-H), 3.78 (1 H, dd, *J* 5.6 and 9.5*,* 11-H), 3.81 (3 H, s, OMe), 3.82 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.85–3.92 (1 H, m, 3-H), 4.13 (1 H, d, *J* 1.8*,* 1-H), 4.50 (1 H, apparent t, *J* 9.5*,* 11-H), 5.91 (1 H, d, *J* 1.6*,* OC$\underline{H_2}$O), 5.95 (1 H, d, *J* 1.6*,* OC$\underline{H_2}$O), 6.64 (1 H, s, 6'-H), 6.71 (1 H, s, 5-H/8H) and 6.76 (1 H, s, 5-H/8H); δ_C($CDCl_3$, 125 MHz) (assignments supported by an HSQC experiment): 43.3, 44.8, 47.50 (C-1), 48.8 (C-4), 56.1 (OCH_3), 60.6 (OCH_3), 61.0 (OCH_3), 72.0 (C-11), 101.4 (OCH_2O), 107.7 (C-6'), 108.3 (C-5/C-8), 109.8 (C-5/C-8), 126.8 (C-4'), 130.1*,* 131.9*,* 148.0*,* 148.1*,* 149.8*,* 151.0*,* 178.4 (C= O).

Ethyl (1*RS*,2*SR*,3*SR*,4*RS*)-3-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxy-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (8)



A solution of the sulfoxide **5** (39 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was stirred at –78 °C while collidine (14 µl, 0.11 mmol) and triflic anhydride (14 µl, 0.08 mmol) were added dropwise. The resultant solution was stirred at 0 °C for1 hour before water (2 µl) was added and then stirred for 3 hours before being diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product, an orange solid, was an extremely polar material, which was not purified (38 mg); δ_H($CDCl_3$; 300 MHz; Me_4Si): 1.32 (3 H, t, *J* 7.3, OCH_2CH_3), 2.60–2.78 (1 H, m, 3-H), 3.18–3.25 (1 H, dd, *J* 6 and 10, CHOSi), 3.58 (1 H, d, *J* 2.0, 1-H), 3.76 (6 H, s, 2 x OMe), 3.76–3.85 (2 H, m, 2-H and CHOSi), 3.89 (3 H, s, OMe), 4.25 (2 H, q, *J* 7.3, OCH_2CH_3), 4.60 (1 H, br s, 4-H), 5.94 (1 H, d, *J* 1.2, OCH_2O), 5.99 (1 H, d, *J* 1.2, OCH_2O), 6.05 (1 H, s, 5-H/8-H), 6.26 (1 H, s, 2'-H and 6'-H) and 6.59 (1 H, s, 5-H/8-H).

Picropodophyllin (9)



Tetrabutylammonium fluoride (nominal 1 M solution in Et_2O containing 1% water) (0.08 mL, 0.08 mmol) was added dropwise to a stirred solution of crude silyloxy ester **8** (35 mg assumed to contain approximately 20 mg of **8**, 0.027 mmol) in THF (3 mL) at room temperature. The resultant solution was stirred for a further 90 min and poured onto water. The mixture was extracted with EtOAc, and the combined extracts were washed with saturated $NaHCO_3$. The organic layer was dried and concentrated *in vacuo* to yield, after preparative thin layer chromatography (60:40 EtOAc : petrol) the title compound as a white solid (8 mg, 0.02 mmol, 38% from tetralin **5**). δ_H($CDCl_3$; 300 MHz; Me_4Si): 2.64-2.78 (1 H, m, 3-H), 3.23 (1 H, dd, *J* 4.4 and 8.2, 2-H), 3.81 (6 H, s, 2 x OMe), 3.85 (3 H, s, OMe), 4.09 (1 H, d, *J* 4.4, 1-H), 4.38–4.59 (3 H, m, 11-H_2 and 4-H), 5.91 (1 H, d, *J* 1.5, OCH_2O), 5.93 (1 H, d, *J* 1.5, OCH_2O), 6.35 (1 H, s, 5-H/8-H), 6.46 (1 H, s, 2'-H and 6'-H) and 7.07 (1 H, s, 5-H/8-H).