Synthesis of 4-thia-2-azapodophyllotoxin, a new analogue of the antitumour lignan podophyllotoxin

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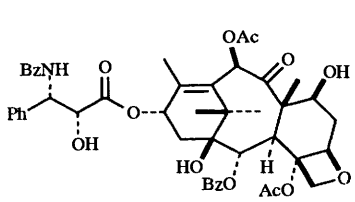
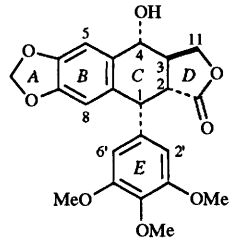
An efficient synthesis of 4-thia-2-azapodophyllotoxin **6**, a new analogue of podophyllotoxin, is described. The hydantoin **11**, prepared from the benzenethiol **10**, was condensed with 3,4,5-trimethoxybenzaldehyde in the presence of trifluoromethanesulfonic acid to produce the pentacyclic fused imidazolidinedione **12** stereospecifically. Compound **12** was protected and reductively converted into the alcohol **16**. Dehydration of **16** under Mitsunobu conditions allowed for the predominant formation of the *N*-trityl cyclic isourea **17**, which was converted into the oxazolone **6** in two steps. Cytotoxicity (KB cells) testing revealed that **6** is less toxic than podophyllotoxin **2** or the known analogue **4**.

Since the advent of taxol **1**, which has recently been approved for the treatment of metastatic carcinoma of the ovary, microtubules are considered to be an important target for antitumour drugs.[1] Podophyllotoxin **2** has been known to inhibit the assembly of tubulin into microtubules through tubulin binding, but the high toxicity of podophyllotoxin has limited its application as a drug in cancer chemotherapy.†[,2] It is well established that the configuration at position 2 of podophyllotoxin **2** is important for its activity and that picropodophyllin **3**, the 2-*epi*-analogue of **2**, has weak inhibitory activity.[2a] For this reason, although much effort has been devoted thus far to identifying a less toxic alternative to **2**, the stereogenic centre was unchanged in all of the analogues. Recently, the 2-azapodophyllotoxin analogues (*e.g.* **4**[3b,c] and **5**[3a,d]) have been synthesised by several groups[3] and have attracted much attention because they retain antitumour activities,[3b] in spite of the tetrahedral C-2 centre being replaced with the trigonal amide-like nitrogen. To better understand these modifications, we have designed 4-thia-2-azapodophyllotoxin **6**. We suggest that further substitution of the methylene group at position 4 of **4** by a sulfur atom would modify the geometry of the molecule, because of a much longer C–S bond,‡ and would also modify the electric field potential of the molecule.[5] These influences on the biological activity are a matter of extreme interest. We report here on the efficient synthesis of the new analogue **6**.



1



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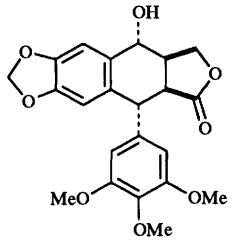

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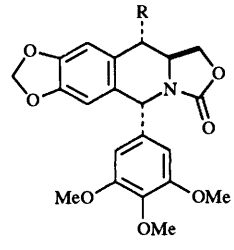
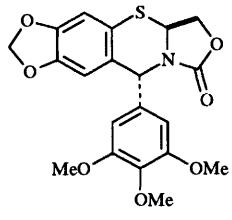
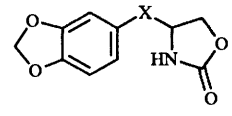


4; R = H
5; R = OH



6



7; X = CH_2
8; X = S

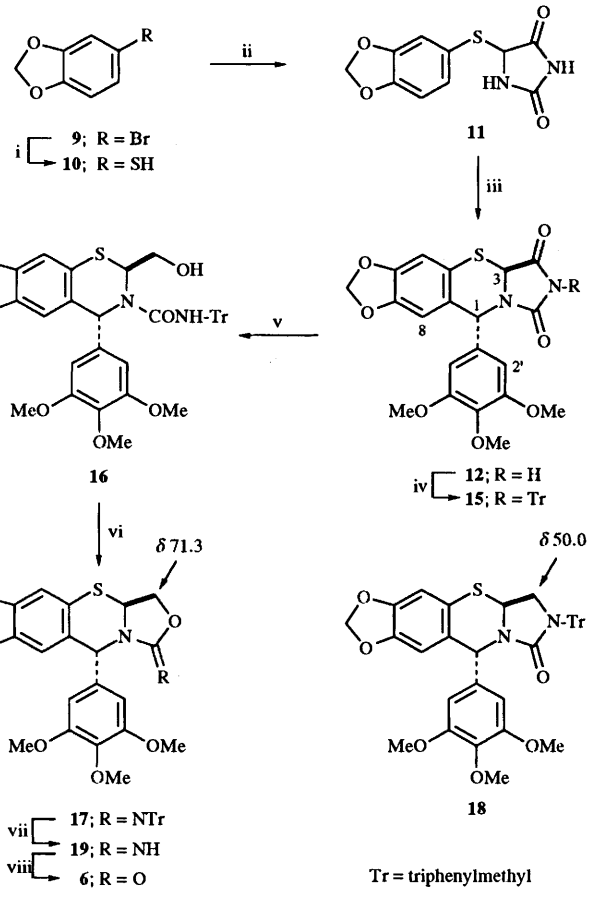
Results and discussion

It has been established that 4-(arylmethyl)oxazolidones (*e.g.* **7**) are condensed with 3,4,5-trimethoxybenzaldehyde under acidic conditions to produce oxazoloisoquinoline analogues (*e.g.* **4**) in good to excellent yields.[3b,d,f] Although the application of this methodology for the synthesis of the analogue **6** appeared to be successful, the possible precursor **8**§ was unstable under the condensation conditions (H_2SO_4 or trifluoromethanesulfonic acid in CH_2Cl_2, trifluoroacetic acid, polyphosphate ester in $CHCl_3$, *etc.*). To circumvent this problem, we proposed using 5-(3,4-methylenedioxyphenyl)-sulfanylimidazolidine-2,4-dione **11** as an alternative to **8** because **11** appeared to be more chemically stable than **8** owing to its partial aromaticity. Although 5-(arylsulfanyl)hydantoins are unknown, **11** proved to be readily synthesised in 86% yield by heating a mixture of 1,3-benzodioxole-5-thiol **10**, which was prepared by the thionation of the Grignard reagent generated from 5-bromo-1,3-benzodioxole **9**, urea, and glyoxylic acid monohydrate in dioxane and 6 mol dm^{-3} HCl (Scheme 1). Condensation of the hydantoin **11** with 3,4,5-trimethoxybenzaldehyde was examined under various conditions. The best

† It is important to note that the clinically used etoposide has the same podophyllotoxin core, but its mechanism of action is not the inhibition of the microtubule assembly but the inhibition of DNA topoisomerase II.[2b]

‡ The C–S bond length of dimethyl sulfide and the C–C bond length of propane have been determined to be 1.807(2)[4a] and 1.532(3)[4b] Å, respectively.

§ The oxazolidone **8** was synthesised by the addition of 1,3-benzodioxole-5-thiol **9** to oxazol-2(3*H*)-one in trifluoroacetic acid at room temperature for 48 h in 70% yield; mp 136–138 °C.



Scheme 1 *Reagents:* i, Mg, THF; S (71%); ii, $CO(NH_2)_2$, $OHCCO_2H{\cdot}H_2O$, dioxane–6 mol dm^{-3} HCl, (86%); iii, 3,4,5-trimethoxybenzaldehyde, CF_3SO_3H, CF_3CH_2OH (88%); iv, TrCl, K_2CO_3, acetone–CH_2Cl_2; v, $NaBH_4$, dioxane–H_2O (97% from **12**); vi, diethyl azodicarboxylate, triphenylphosphine, benzene (**17**, 85%; **18**, 12%); vii, CF_3CO_2H, EtOH (97%); viii, $NaNO_2$, AcOH (91%)

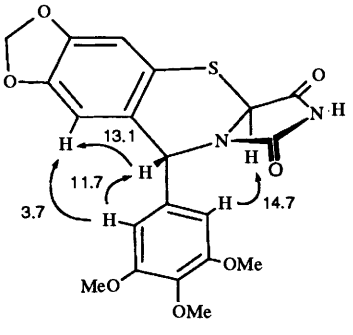
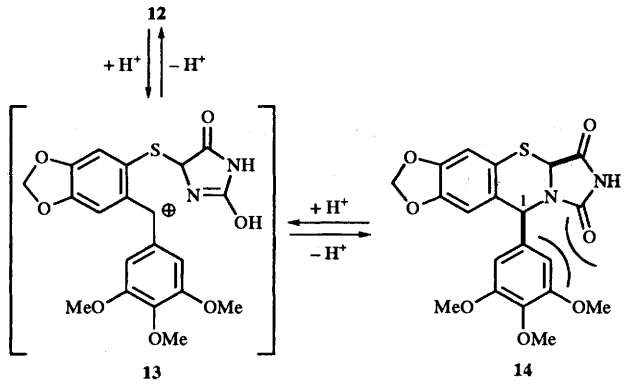


Fig. 1 Selected NOE (%) for **12**

result (88% yield) was obtained when 2,2,2-trifluoroethanol was used as the solvent and trifluoromethanesulfonic acid (1 equiv.) was used as the acid catalyst. The reaction proceeded in a stereospecific manner, and only one cyclised product **12** was obtained. The stereochemistry of **12** was established to be a *trans* relation by the observation of the strong NOE (14.7%) between 3-H and 2′(6′)-H (podophyllotoxin numbering, Fig. 1). The NOE experiments also suggested the orientation of the C-1 substituents. This strong NOE is possible when the trimethoxyphenyl group adopts a quasi-axial position. Another strong NOE (13.1%) between 1-H and 8-H shows 1-H being in a quasi-equatorial position. This stereochemical outcome could be explained by assuming the possible carbocation intermediate **13**, which after the cyclisation, could be generated under the given reaction conditions (Scheme 2). The *trans* compound **12**



Scheme 2

is more thermodynamically stable than the *cis* compound **14** which suffers allylic strain [6] between the carbonyl oxygen atom of the oxazolidone and the quasi-equatorially orientated trimethoxyphenyl group at C-1. A similar stereochemical argument has been documented for the condensation of **7**.[3b]

The conversion of the hydantoin moiety of **12** into an oxazolidone ring was a rather difficult problem. All attempts to hydrolyse the hydantoin moiety under various acidic or basic conditions failed. However, the hydantoin ring proved to be reductively cleaved by the following procedures. Treatment of **12** with triphenylmethyl chloride and K_2CO_3 in acetone–CH_2Cl_2 (10:1) produced the *N*-trityl derivative **15** that, without purification, was reduced with an excess of sodium borohydride in dioxane–H_2O (2:1) to produce the alcohol **16** in 97% yield. This *N*-tritylation was necessary to avoid the imidazolidone formation during the reduction process. Recyclisation of the alcohol **16** under Mitsunobu conditions,[7] which utilized diethyl azodicarboxylate (1.3 equiv.) and triphenylphosphine (1.3 equiv.) in benzene at room temperature, afforded the cyclic isourea **17** and the cyclic urea **18** in yields of 85 and 12%, respectively. Their structures were distinguished by comparing the chemical shifts of the ring-D methylene carbon resonances (δ 71.3 for **17** and δ 50.0 for **18**) in the ^{13}C NMR spectra. The **17**:**18** ratio was greatly influenced by the solvent. When CH_2Cl_2 or THF was used as the solvent, the **17**:**18** percentage yields were 50:47 or 72:24, respectively. The *N*-trityl group of **17** was removed using EtOH–trifluoroacetic acid (1:2) which produced **19** in 97% yield. Treatment of **19** with sodium nitrite in acetic acid effectively converted the cyclic isourea into the oxazolidone **6** in 91% yield.

The analogue **6** showed cytotoxicity against human epidermoid carcinoma of nasopharynx (KB) cells (IC_{50} 0.30 μg cm^{-3}), but was much weaker than podophyllotoxin **2** (0.0033 μg cm^{-3}) or the analogue **4** (0.0041 μg cm^{-3}).

Experimental

Organic solutions, dried over $MgSO_4$, were evaporated under an aspirator vacuum with a rotary evaporator. Benzene was distilled from calcium hydride, and THF was distilled from sodium. Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. NMR spectra were measured on a Bruker AM 400 spectrometer or on a Varian Gemini 300 spectrometer. ^1H Chemical shifts are referenced in $CDCl_3$ and [$^2H_6$]DMSO to residual $CHCl_3$ (7.26 ppm) and [$^2H_5$]DMSO (2.50 ppm); ^{13}C chemical shifts are referenced to the solvent ($CDCl_3$, 77.03; [$^2H_6$]DMSO 39.5 ppm). *J* Values are given in Hz. IR spectra were recorded on a JASCO A-302 spectrophotometer. MS were taken using a VG AutoSpecE spectrometer.

1,3-Benzodioxole-5-thiol 10

To a suspension of magnesium turnings (1.17 g, 48 mmol) in THF (20 cm^3) was added dropwise 5-bromo-1,3-benzodioxole **9** (4.8 cm^3, 40 mmol) over 1 h under an atmosphere of argon. After being heated under reflux for 30 min, the mixture was cooled to −45 °C and powdered sulfur (1.28 g, 40 mmol) was added to it. The mixture was stirred at −45 °C for 1.5 h and then at room temperature for 1.5 h, at which time water (2 cm^3) and 6 mol dm^{-3} HCl (12 cm^3) were added to it. The mixture was extracted with ether (3 × 20 cm^3), and the combined organic layers were washed with brine (5 cm^3), dried ($MgSO_4$) and concentrated. Purification of the residue by distillation gave **10** as a colourless oil (4.38 g, 71%): bp 125–128 °C/17 mmHg (Found: C, 54.7; H, 3.9. $C_7H_6O_2S$ requires C, 54.53; H, 3.92%); δ_H(400 MHz; $CDCl_3$) 6.84–6.78 (2 H, m), 6.69 (1 H, d, *J* 8.5), 5.93 (2 H, s) and 3.42 (1 H, s); δ_C(100 MHz, $CDCl_3$) 148.0 (s), 146.6 (s), 124.1 (d), 121.3 (s), 111.6 (d), 108.8 (d) and 101.2 (t).

5-(3,4-Methylenedioxyphenylsulfanyl)imidazolidine-2,4-dione 11

A mixture of compound **10** (1.0 g, 6.5 mmol), urea (0.78 g, 13 mmol), glyoxylic acid monohydrate (0.717 g, 7.8 mmol), dioxane (3 cm^3) and 6 mol dm^{-3} HCl (3 cm^3) was stirred at room temperature for 1 h. The mixture was warmed to 50 °C and stirred at this temperature for 2 h, and then at 90 °C for 15 h. The mixture was concentrated, and water (30 cm^3) was added to the residue. The precipitate was filtered off and recrystallized from EtOH to give **11** as colourless prisms (1.41 g, 86%): mp 191–192 °C (Found: C, 47.6; H, 3.2; N, 11.2. $C_{10}H_8N_2O_4S$ requires C, 47.62; H, 3.20; N, 11.10%); ν_{max}(KBr)/cm^{-1} 3300, 3250, 1770, 1715 and 1240; δ_H(300 MHz; [$^2H_6$]DMSO) 10.57 (1 H, s), 8.55 (1 H, s), 7.01–6.91 (3 H, m), 6.07 (2 H, s) and 5.35 (1 H, s); δ_C(100 MHz; [$^2H_6$]DMSO) 171.9 (s), 156.1 (s), 148.8 (s), 147.3 (s), 130.3 (d), 119.7 (s), 115.3 (d), 108.7 (d), 101.6 (t) and 62.6 (d); *m*/*z* 252 (M^+, 10%), 154 (100), 153 (53), 95 (42) and 69 (42).

6,7-Methylenedioxy-9-(3,4,5-trimethoxyphenyl)-1,3,3a,10-tetrahydro-9*H*-imidazo[4,3-*b*][1,3]benzothiazine-1,3-dione 12

To a suspension of compound **11** (1.01 g, 4.0 mmol) and 3,4,5-trimethoxybenzaldehyde (1.02 g, 5.2 mmol) in 2,2,2-trifluoroethanol (6 cm^3) under an atmosphere of argon was added trifluoromethanesulfonic acid (0.35 cm^3, 4.0 mmol). The mixture was stirred at room temperature for 15 h and then at 50 °C for 2 h, at which time it was diluted with $CHCl_3$–MeOH (10:1; 150 cm^3), washed with saturated aqueous $NaHCO_3$ (20 cm^3), dried ($MgSO_4$) and concentrated. Purification of the residue by SiO_2 column chromatography (5:1, CH_2Cl_2–EtOAc) followed by recrystallization from diisopropyl ether–EtOAc gave **12** as colourless fine needles (1.51 g, 88%): mp 206–207 °C (Found: C, 55.9; H, 4.2; N, 6.6. $C_{20}H_{18}N_2O_7S$ requires C, 55.81; H, 4.21; N, 6.51%); ν_{max}(KBr)/cm^{-1} 1780, 1710 and 1130; δ_H(300 MHz; [$^2H_6$]DMSO)¶ 11.47 (1 H, s, NH), 6.95 (1 H, s, 5-H), 6.87 (1 H, s, 8-H), 6.50 (2 H, s, 2′- and 6′-H), 6.10 (1 H, s, 1-H), 6.04 (1 H, d, *J* 0.9, OCH_2O), 6.03 (1 H, d, *J* 0.9, OCH_2O), 5.59 (1 H, s, 3-H), 3.72 (6 H, s, 3′- and 5′-OMe) and 3.65 (3 H, s, 4′-OMe); δ_C(100 MHz; [$^2H_6$]DMSO) 171.2 (s), 155.4, (s), 152.9 (s), 147.2 (s), 145.9 (s), 137.2 (s), 134.6 (s), 125.9 (s), 120.6 (s), 109.8 (d), 107.7 (d), 105.2 (d), 101.5 (t), 59.9 (q), 55.9 (q), 54.7 (d) and 54.3 (d); *m*/*z* 430 (M^+, 100%) and 301 (76). Selected NOE data:¶ 1-H→8-H 13.1%), 1-H→2′(6′)-H (8.2%), 3-H→2′(6′)-H (4.7%), 8-H→1-H (11.5%), 2′(6′)-H→1-H (11.7%), 2′(6′)-H→3-H (14.7%) and 2′(6′)-H→8-H (3.7%).

¶ The chemical shifts assignments and the NOE data are given based on the podophyllotoxin numbering.

2-Hydroxyethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-*N*-trityl-3,4-dihydro-2*H*-1,3-benzothiazine-3-carboxamide 16

To a mixture of compound **12** (2.58 g, 6.0 mmol) and K_2CO_3 (1.66 g, 12 mmol) in acetone (100 cm^3) and CH_2Cl_2 (10 cm^3) was added triphenylmethyl chloride (2.01 g, 7.2 mmol). The mixture was stirred at room temperature for 5 h, after which it was filtered and the residue was washed with CH_2Cl_2. The combined filtrate and washings were evaporated under reduced pressure to leave a residue, which was dissolved in dioxane (120 cm^3) and water (60 cm^3). $NaBH_4$ (2.27 g, 60 mmol) was added to the solution which was then stirred at 50 °C for 18 h and finally evaporated. The residue was dissolved in CH_2Cl_2 (150 cm^3) and the solution washed with water (15 cm^3), dried ($MgSO_4$) and concentrated. Purification of the residue by SiO_2 column chromatography (5:1, CH_2Cl_2–EtOAc) followed by recrystallization from diisopropyl ether gave **16** as colourless crystals (3.94 g, 97%): mp 190–193 °C (Found: C, 69.3; H, 5.3; N, 4.15. $C_{39}H_{36}N_2O_7S$ requires C, 69.21; H, 5.36; N, 4.14%); ν_{max}(KBr)/cm^{-1} 3450, 3410 and 1650; δ_H(400 MHz; $CDCl_3$) 7.24–6.98 (15 H, m), 6.85 (2 H, s), 6.80 (1 H, s), 6.70 (1 H, s), 5.95 (1 H, d, *J* 1.3), 5.93 (1 H, s), 5.90 (1 H, d, *J* 1.3), 5.77 (1 H, dd, *J* 8.9, 6.3), 5.61 (1 H, s), 3.74 (6 H, s), 3.73 (3 H, s), 3.63 (1 H, dd, *J* 11.0, 6.3), 3.43 (1 H, br m) and 2.69 (1 H, br s); δ_C(100 MHz; $CDCl_3$) 156.8 (s), 153.9 (s), 147.4 (s), 146.9 (s), 144.7 (s), 138.5 (s), 138.0 (s), 129.9 (s), 128.5 (d), 127.7 (d), 126.8 (d), 120.6 (s), 110.8 (d), 108.8 (d), 103.0 (d), 101.6 (t), 70.3 (s), 65.2 (t), 62.4 (d), 60.8 (q), 56.8 (d) and 56.1 (q); *m*/*z* 676 (M^+, 4%), 598 (46), 463 (59), 352 (62), 300 (100), 243 (51) and 208 (50).

Cyclisation of 16 under Mitsunobu conditions

To a solution of compound **16** (2.03 g, 3.0 mmol) and triphenylphosphine (1.02 g, 3.9 mmol) in benzene (35 cm^3) was added diethyl azodicarboxylate (0.62 cm^3, 3.9 mmol) over a period of 45 min at room temperature. The mixture was stirred for 2.5 h and concentrated. Purification of the residue by SiO_2 column chromatography (40–20:1, CH_2Cl_2–EtOAc) gave the isourea **17** (1.68 g, 85%) and the urea **18** (0.23 g, 12%). Compound **17**: colourless fine needles; mp 213–214 °C (from EtOH) (Found: C, 70.2; H, 5.2; N, 4.2. $C_{39}H_{34}N_2O_6S{\cdot}0.5H_2O$ requires C, 70.15; H, 5.28; N, 4.20%); ν_{max}(KBr)/cm^{-1} 1700; δ_H(400 MHz; $CDCl_3$) 7.26–7.10 (15 H, m), 6.79 (1 H, s), 6.73 (1 H, s), 6.55 (2 H, s), 6.26 (1 H, s), 5.96 (1 H, d, *J* 1.3), 5.90 (1 H, d, *J* 1.3), 4.97 (1 H, d, *J* 5.4), 4.15 (1 H, dd, *J* 9.3, 5.4), 4.01 (1 H, d, *J* 9.3), 3.84 (3 H, s) and 3.73 (6 H, s); δ_C(100 MHz; $CDCl_3$) 153.4 (s), 149.8 (s), 148.1 (s), 147.5 (s), 145.9 (s), 137.7 (s), 135.3 (s), 128.9 (d), 127.2 (d), 125.8 (d), 124.8 (s), 123.8 (s), 110.5 (d), 107.9 (d), 105.9 (d), 101.3 (t), 71.8 (s), 71.3 (t), 60.8 (q), 58.9 (d), 56.3 (q) and 56.1 (d); *m*/*z* 415 (100%), 372 (18), 243 (41) and 165 (40). Compound **18**: colourless fine needles; mp 218 °C (from EtOAc) (Found: C, 71.3; H, 5.2; N, 4.3. $C_{39}H_{34}N_2O_6S$ requires C, 71.11; H, 5.20; N, 4.25%); ν_{max}(KBr)/cm^{-1} 1700; δ_H(400 MHz; $CDCl_3$) 7.42–7.18 (15 H, m), 6.71 (1 H, s), 6.58 (1 H, s), 6.35 (2 H, s), 5.96 (1 H, d, *J* 1.2), 5.95 (1 H, d, *J* 1.2), 5.90 (1 H, s), 4.95 (1 H, d, *J* 6.3), 3.82 (3 H, s), 3.73 (6 H, s), 3.57 (1 H, d, *J* 10.5) and 3.45 (1 H, dd, *J* 10.5, 6.3); δ_C(100 MHz; $CDCl_3$) 157.7 (s), 153.2 (2), 147.4 (s), 145.6 (s), 142.6 (s), 137.5 (s), 136.3 (s), 129.3 (d), 127.6 (d), 126.8 (d), 123.8 (s), 123.3 (s), 110.3 (d), 107.4 (d), 105.7 (d), 101.2 (t), 73.2 (d), 60.8 (q), 56.2 (q), 55.9 (d), 52.1 (d) and 50.0 (t); *m*/*z* 415 (77%), 331 (24), 301 (41), 243 (100) and 165 (81).

1-Imino-6,7-methylenedioxy-9-(3,4,5-trimethoxyphenyl)-1,3,3a,10-tetrahydro-9*H*-oxazolo[4,3-*b*][1,3]benzothiazine 19

To a suspension of compound **17** (283 mg, 0.43 mmol) in EtOH (5 cm^3) was slowly added trifluoroacetic acid (10 cm^3). The mixture was stirred at room temperature for 48 h, after which it was evaporated under reduced pressure to leave a residue. This

was dissolved in CH_2Cl_2 (50 cm^3) and the solution washed with saturated aqueous $NaHCO_3$ (10 cm^3), dried ($MgSO_4$) and concentrated. Purification of the residue by SiO_2 column chromatography (20:1, CH_2Cl_2–MeOH) gave **19** as colourless fine needles (173 mg, 97%): mp 182–184 °C (from EtOH) (Found: C, 57.8; H, 4.8; N, 6.8. $C_{20}H_{20}N_2O_6S$ requires C, 57.68; H, 4.84; N, 6.73%); ν_{max}(KBr)/cm^{-1} 3375, 1680, 1670 and 1125; δ_H(400 MHz; $CDCl_3$) 6.63 (1 H, s), 6.62 (1 H, s), 6.48 (2 H, s), 5.95 (1 H, br s), 5.95 (1 H, d, *J* 1.3), 5.92 (1 H, d, *J* 1.3), 5.14 (1 H, dd, *J* 5.6, 0.9), 4.48 (1 H, dd, *J* 9.2, 5.6), 4.23 (1 H, dd, *J* 9.2, 0.9), 3.84 (3 H, s) and 3.80 (6 H, s); δ_C(100 MHz; $CDCl_3$) 158.6 (s), 153.5 (s), 147.6 (s), 145.9 (s), 138.0 (s), 135.5 (s), 123.1 (s), 122.8 (s), 110.0 (d), 107.4 (d), 105.9 (d), 101.3 (t), 70.2 (t), 60.8 (q), 58.0 (d), 56.3 (q) and 55.9 (d); *m/z* 417 (M + 1, 94), 358 (100), 341 (35), 332 (39), 302 (77) and 86 (47).

4-Thia-2-azapodophyllotoxin 6

To a solution of compound **19** (713 mg, 1.71 mmol) in AcOH (50 cm^3) was added $NaNO_2$ (708 mg, 10.3 mmol) over a period of 5 h at room temperature. The mixture was stirred for 1 h and concentrated. The residue was dissolved in CH_2Cl_2 (100 cm^3) and the solution washed successively with 1 mol dm^{-3} KOH (20 cm^3) and water (20 cm^3), dried ($MgSO_4$) and concentrated. Purification of the residue by SiO_2 column chromatography (20–5:1, CH_2Cl_2–EtOAc) followed by recrystallization from MeOH gave **6** as colourless needles (648 mg, 91%): mp 202–204 °C (Found: C, 57.4; H, 4.6; N, 3.5. $C_{20}H_{19}NO_7S$ requires C, 57.54; H, 4.59; N, 3.36%); ν_{max}(KBr)/cm^{-1} 1760, 1750, 1220 and 1130; δ_H(400 MHz; $CDCl_3$)¶ 6.64 (s, 1 H, 5-H), 6.56 (s, 1 H, 8-H), 6.44 (s, 2 H, 2′- and 6′-H), 5.96 (1 H, d, *J* 1.3, OCH_2O), 5.93 (1 H, d, *J* 1.3, OCH_2O), 5.91 (1 H, s, 1-H), 5.18 (1 H, dd, *J* 6.7, 1.9, 3-H), 4.55 (1 H, dd, *J* 9.6, 6.7, 11_α-H), 4.30 (1 H, dd, *J* 9.6, 1.9, 11_β-H), 3.84 (3 H, s, 4′-OMe) and 3.80 (6 H, s, 3′- and 5′-OMe); δ_C(100 MHz; $CDCl_3$) 156.0 (s), 153.6 (s), 147.7 (s), 146.3 (s), 138.2 (s), 135.5 (s), 122.7 (s), 122.5 (s), 109.8 (d), 107.4 (d), 105.7 (d), 101.5 (t), 68.2 (t), 60.8 (q), 57.0 (d), 56.3 (q) and 53.3 (d); *m/z* 417 (M^+, 35%), 332 (22) and 301 (100). Selected NOE data:¶ 1-H→8-H (10.2%), 1-H→2′(6′)-H (6.4%), 3-H→11_α-H (6.4%), 3-H→2′(6′)-H (2.4%), 8-H→1-H (7.5%), 2′(6′)-H→1-H (13.0%), 2′(6′)-H→3-H (4.7%), 2′(6′)-H→3′(5′)-OMe (3.1%), 3′(5′)-OMe→3-H (2.3%) and 3′(5′)-OMe→2′(6′)-H (16.9%).

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