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Synthesis of Podophyllotoxin A-Ring Pyridazine Analogue

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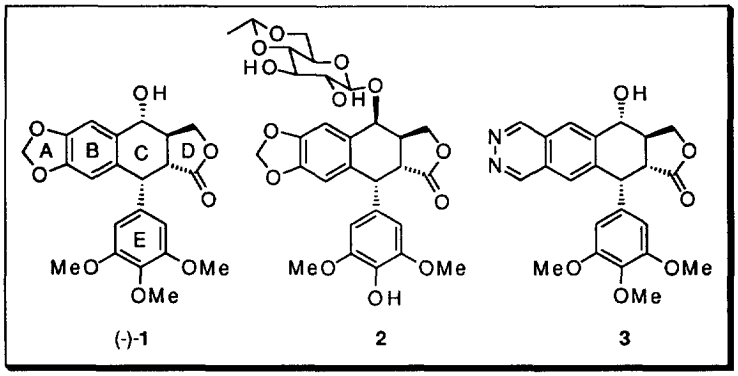
Abstract: Podophyllotoxin A-ring pyridazine analogue **3** has been constructed in nine steps from (-)-podophyllotoxin. The Stille reaction was exploited to generate the key intermediate **4**.

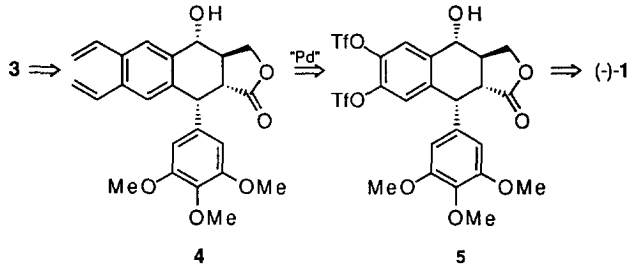
INTRODUCTION

(-)-Podophyllotoxin **1** is a naturally occurring aryltetralin lignan from *Podophyllum peltatum* and *P. Emodi*.[1] In the early 1950s, Hartwell and Schrecker[2] proposed its correct structure by a combination of chemical means. Interest in podophyllotoxin has been heightened by its potent antimitotic activity[3] and its challenging stereochemistry. Gensler and co-workers[4] did the pioneering work and published the first total synthesis in the 1960s. Several syntheses of racemic podophyllotoxin have been reported[5,6] in the past two decades. Additionally, asymmetric total syntheses have been accomplished by Vandewalle,[7] Meyers[8] and Jones.[9] (-)-Podophyllotoxin inhibits the assembly of tubulin protein,[10] a non-covalent heterodimer, into microtubules through tubulin binding at the colchicine site[11] and distinct from that occupied by the alkaloids[12] but failed to advance to human clinical trials due to toxic side-effects.[3] Podophyllotoxin has also stimulated intensive semi-synthetic activity performed at Sandoz, led by H. Stahelin,[13] which culminated in the development of etoposide **2** (VP-16-213, Vepesid®), a glucosidic derivative of podophyllotoxin, which started clinical evaluation in 1971. Etoposide has become an important anticancer drug used in the treatment of a wide range of neoplasms, including testicular teratoma, small-cell lung cancer, acute leukemia, lymphoma, and Kaposi's sarcoma[14] although it is not very effective against several other tumors, in particular non-small cell lung cancer.[15] In contrast with the activity of **1**, the mechanisms associated with the antitumor action of **2** involve the inhibition of topoisomerase II-mediated DNA ligation[16] by reversible cleavable complex stabilization resulting in tumor cell death and bioactivation[17] to its corresponding *ortho*-quinone *via* oxidative demethylation. Its current therapy is limited by myelosuppression, drug resistance, metabolic inactivation, and poor bioavailability.[18]



Studies on the structure-activity relationships (SAR) of podophyllotoxin **1** and etoposide **2** have disclosed the essential role of the *trans*-fused-γ-lactone ring (D-ring) for their strong anticancer activity. Indeed, under physiological conditions isomerization occurs at position C-2 leading to the corresponding thermodynamically stable *cis*-epimers which are devoid of antitumor activity.[19] Consequently, the antitumor properties of **2** as well as the deficiencies afore-mentioned have spurred a great deal of effort to synthesize podophyllotoxin[20] and etoposide[21] analogues that encompass a broad spectrum of antineoplastic activities and overcome any clinical limitation. Among recent examples in this field, is the synthesis of nonenolizable heterocyclic derivatives of podophyllotoxin such as 2-azapodophyllotoxins,[22] 2,4-diaza-4-deoxypodophyllotoxins,[23] 4-oxa-2-azapodophyllotoxin[24] and 4-thia-2-azapodophyllotoxin.[25] Interestingly, for the most part, these oxazolidinones retain antitumor activity. The study of congeners with N-heterocyclic A-ring appeared to be an unexplored area.[26] Furthermore, little was known about the SAR of the A-ring[27] of podophyllotoxin. As part of our ongoing research programme aimed at the synthesis and biological evaluation of new antitumor analogues, related to podophyllotoxin **1** and etoposide **2**, we have designed the A-ring pyridazine analogue **3** of podophyllotoxin that provides: (a) similar molecular shape for host molecular recognition, such as tubulin binding; (b) hydrogen bonding or basic sites, possibly increasing the interaction with tubulin; (c) potentially easier drug formulation *via* water-soluble salts.

Retrosynthetic analysis (Scheme 1) suggested that diazapodophyllotoxin analogue **3**, as well as various A-ring diaza analogues of **3**, should be available by a semi-synthetic strategy wherein the bisvinyl **4** is a key intermediate. We envisaged that the bisvinyl **4** could be derived from **5** *via* palladium-mediated σ-bond construction using the Stille reaction.[28] Introduction of the pyridazine ring would require oxidative functionalization of the double bond moities of **4**.

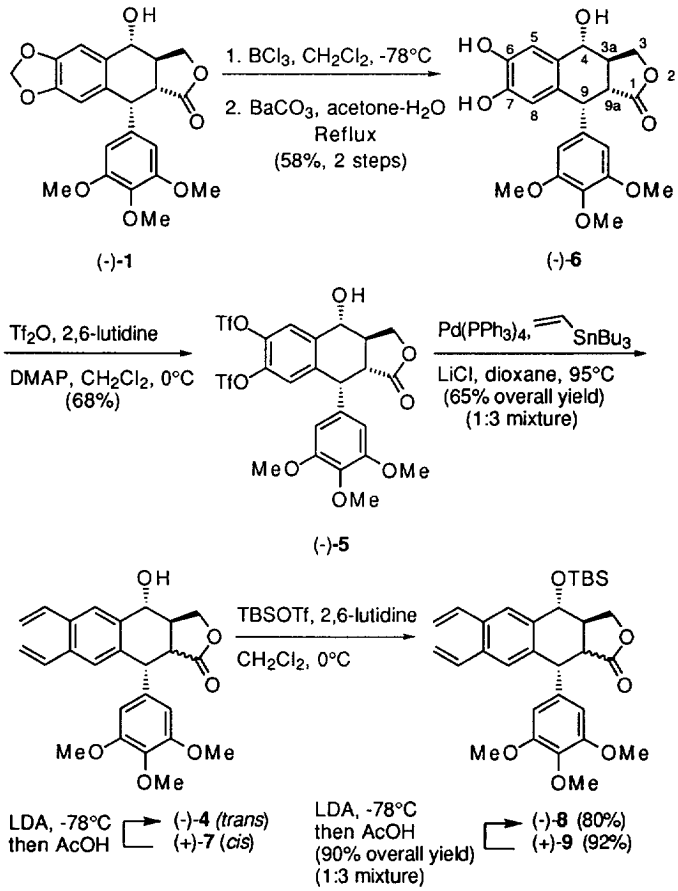


Scheme 1

Importantly, the application of reported synthetic transformations of aryl triflates[29] to **5** should provide access to other designed analogues of podophyllotoxin with either structural modification or destruction of the A-ring. In this full account, we report the synthesis of podophyllotoxin A-ring pyridazine analogue **3**.

RESULTS AND DISCUSSION

The preparation of A-ring diaza analogue **3** began with commercially available (-)-podophyllotoxin **1**, as shown in Scheme 2. As reported by Schreier[30] in 1964, and slightly modified by Lee and co-workers[27] in 1992, the known catechol (-)-**6** was prepared in 58% yield *via* treatment of podophyllotoxin **1** with boron trichloride in methylene chloride followed by exposure of the resultant boronate to $BaCO_3$ in acetone-water at reflux. In preliminary experiments, although we were pleased by the generation of (-)-**6** after following the literature work-up, the reaction led also to a significant quantity of the less polar epimer of **6** at C-4 [J = 3.4 Hz for H-4; 9a,3a-*trans* configuration[31] with J = 14.1, 5.3 Hz for H-9a], as determined by analysis of the ^1H NMR spectrum.



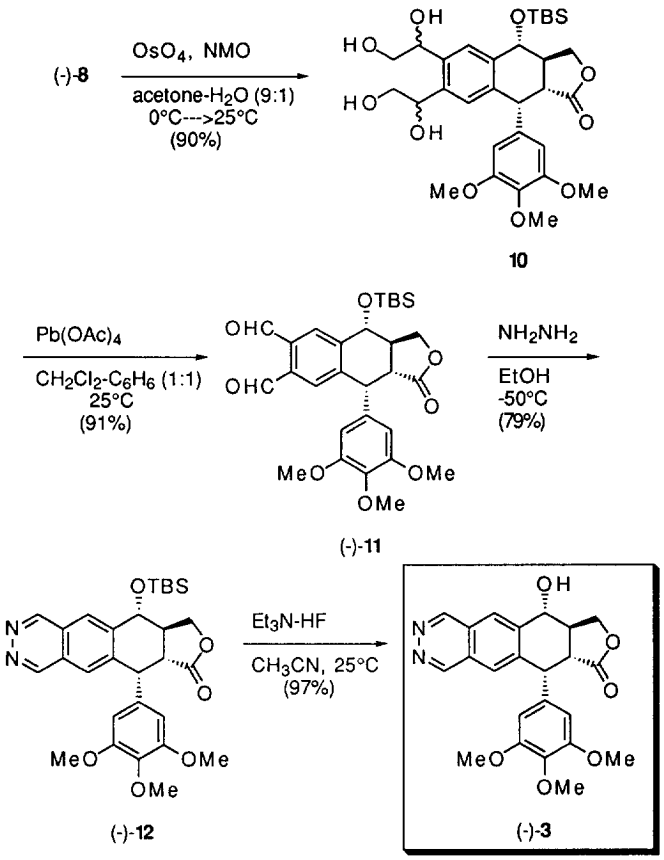
Scheme 2

Importantly, aware that the Terada group[32] had successfully obtained the cleavage of the methylenedioxy group of deoxypodophyllotoxin under these conditions, we completely suppressed the formation of the undesired isomer by mild basic hydrolysis of the reaction mixture followed by concentration *in vacuo* below 30 °C. Conversion of (-)-**6** to (-)-**5** (Tf_2O, 2,6-lutidine, DMAP) in 68% yield, then set the stage for an investigation of the critical Stille coupling[28] with tri-*n*-butylvinylstannane.

We originally thought that the bistriflate (-)-**5** would easily undergo palladium-catalyzed coupling with tri-*n*-butylvinylstannane to afford the desired bisvinyl intermediate **4**. However, several experiments revealed that the Stille reaction was very sensitive to catalyst and reaction time. The use of weakly ligated dibenzylideneacetonyl-Pd(0) catalyst Pd_2dba_3 (LiCl, PPh_3, NMP, 25 °C or 90 °C) according to Farina's finding[33] gave only destruction of the starting material. The coupling reaction with $PdCl_2(PPh_3)_2$ in the presence of LiCl in DMF at 90 °C resulted in low yield of **4** (13%) along with decomposition products. We then turned to the palladium-catalyzed cross-coupling under conventional conditions reported by Stille[28] $Pd(PPh_3)_4$, LiCl, dioxane, 90 °C). We were delighted to discover that it could be effected to afford a 1:3 mixture of the desired bisvinyl *trans* (-)-**4** and undesired bisvinyl *cis* (+)-**7** in 65 % overall yield with no recovered bistriflate, due to the excess of stannane (scale 1.48 mmol, 95 °C, 3.5 h)(Scheme 2). On a smaller scale (0.47 mmol, 95 °C, 75 min.), and in the presence of a stoichiometric quantity of stannane, bisvinyl *trans*(-)-**4** predominated, in a 3:2 mixture of (-)-**4** and (+)-**7** in 62% overall yield. Importantly, the epimers were separable by repeated flash chromatography on silica gel and the unambiguous determination of stereochemistry was obtained from ^1H NMR spectroscopy.[34] No explanation can be provided for this phenomenon. Such an epimerization at C-9a was not without precedent in the podophyllotoxin field. Indeed, Saulnier and co-workers[35] observed this concomitant epimerization of the *trans*-lactone to the thermodynamically preferred *cis*-lactone in the course of the synthesis of etoposide analogues by a Stille-based approach. Extended reaction time under these harsh conditions (scale : 0.93 mmol, overnight at 95 °C) led exclusively to bisvinyl *cis*(+)-**7** in only 25% yield along with drastic decomposition. Consequently, this reaction required repeated thin layer chromatography in order to obtain both the desired bisvinyl *trans* isomer in a not too unfavourable ratio and complete reaction of (-)-**5**. This coupling was also carried out overnight at room temperature but it was unsuccessful, and only decomposition of material was observed. In order to explore the extension of the Stille methodology in this area, we tried to investigate the coupling process with other stannanes. Surprisingly, the use of $Pd(PPh_3)_4$ as a catalyst (LiCl, dioxane, 95 °C) was fruitless with ethynyl-, phenylethynyl-, phenyl- and cyanostannanes ; only traces of the transfer of the allyl group were detected. Likewise, $PdCl_2(PPh_3)_2$, (PPh_3, LiCl, DMF, 145 °C)[36] led only to decomposition. However, the C-9a epimer product of allyl transfer was obtained in 17% yield. We next focused our attention on the conversion of (+)-**7** to (-)-**4**. Partial solution by kinetic deprotonation of (+)-**7** with bases such as LDA, LiHMDS, and KHMDS in THF at -78°C, followed by addition of glacial acetic acid, was examined. The best ratio was obtained with LDA, which furnished a 1:3 mixture of the *trans* (-)-**4** and the undesired (+)-**7** as determined by ^1H NMR spectroscopy of the crude product. But, as before, we confronted a fastidious separation of epimers at C-9a. We anticipated that the protection of the benzylic alcohol would facilitate the separation of epimers after kinetic protonation generating a suitable intermediate **8** for the oxidation phase of the synthesis. Consequently, we opted to convert the benzylic alcohols (-)-**4** and (+)-**7** independently to the *tert*-butyldimethylsilyl ethers (-)-**8** and (+)-**9** in 80% yield and 92% yield, respectively. Thus, kinetic deprotonation of (+)-**9** with LDA in THF at -78 °C and addition of glacial acetic acid then roughly afforded a

1:3 mixture of (-)-**8** and (+)-**9** in 90% overall yield accompanied by 10% decomposition. Indeed, chromatographic separation of these epimers was achieved without difficulty.

With the required bisvinyl *trans* (-)-**8** in hand, we turned to functionalization of the alkene moieties (Scheme 3).



Scheme 3

Reaction of (-)-**8** with catalytic OsO_4[37] in the presence of NMO gave an uncharacterized mixture of tetraols **10** in 90% yield. Oxidative cleavage of **10** with $Pb(OAc)_4$ provided the desired dialdehyde (-)-**11** in 91% yield. Attempts to obtain this latter compound directly from (-)-**8** using OsO_4-$NaIO_4$[38] failed. Construction of the pyridazine ring using the procedure of Hirsch[39] at -50 °C, in order to prevent the lactone-opening reaction with hydrazine reported by Kadow and co-workers,[40] gave the desired pyridazine (-)-**12** in 79% yield. All that remained to complete the synthesis of diazapodophyllotoxin **3** was desilylation of (-)-**12**. Attempts to cleave this *tert*-butyldimethylsilyl ether under acidic conditions with either pyridinium *p*-toluenesulfonate[41] in EtOH or trifluoroacetic acid-H_2O (9:1)[42] in methylene chloride gave the starting material or uncharacterized products, respectively. Deprotection under basic conditions[43] with TBAF resulted in the formation of the epimer of (-)-**3** at C-6a[31] (*cis*-lactone) as shown by analysis of the ^1H NMR spectrum which revealed characteristic coupling constants[34] (J) of 9.8 Hz for H-6a and H-9a, and 6.7 Hz, 1.5 Hz for H-9a and H-9. It is worth noting that, surprisingly, in the case of the synthesis of thymidine derivatives of

podophyllotoxin and 4'-demethylepipodophyllotoxin,[44] these conditions did not affect the C/D *trans* configuration. Finally, as previously reported by Kende[6] and Meyers[8] in the chemistry of podophyllotoxin, removal of this silyl ether using Et_3N-HF[45] in CH_3CN proceeded smoothly to afford the desired podophyllotoxin A-ring pyridazine analogue (-)-**3** in 97%.

Exploratory evaluations of the biological activity of some compounds were performed *in vitro* and *in vivo*.[46] Bisvinyl *trans*-lactone **4** appears to be the most interesting analogue by comparison with etoposide. Unfortunately, notwithstanding our design, pyridazine podophyllotoxin **3** displays no inhibition of tubulin polymerization ($IC_{50} > 10^{-5}$ M) and microtubule assembly[47] ($IC_{50} > 10^{-4}$ M). This result clearly indicates the importance of the methylenedioxy A ring,which is a common moiety in some antimitotic natural products, for the binding to tubulin.

In summary, we have developped a Stille approach to N-heterocyclic A-ring podophyllotoxin derivatives exemplified by a nine-step synthesis of A-ring pyridazine podophyllotoxin from (-)-podophyllotoxin. Efforts to extend this strategy from etoposide are presently underway.

EXPERIMENTAL SECTION

General Procedures. ^1H NMR spectra were recorded on a Bruker AM-250 or a Bruker AC-300 instrument. IR spectra were recorded on a Perkin-Elmer 1710 infrared spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were determined on either a Kofler hot-stage instrument or an Electrothermal digital melting point apparatus and are not corrected. Mass spectra (MS) were registered on a Nermag R10-10C mass spectrometer under chemical ionization (CI) conditions. Elemental analyses were performed by the " Service d'Analyse du CNRS, Vernaison, France ". All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% ethanolic phosphomolybdic acid-heat as developing agent. E Merck silica gel (particle size 0.040-0.063 mm) was used for flash column chromatography.[48] All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Podophyllotoxin, purified by flash chromatography before use, and 2M solution of lithium diisopropylamide in THF were obtained from Aldrich.

(3a*R*,4*R*,9*R*,9a*R*)-4-Hydroxy-3a,4,9,9a-tetrahydro-6,7-dihydroxy-9-(3,4,5-trimethoxy phenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (6). A solution of podophyllotoxin **1** (1.85 g, 4.46 mmol) in methylene chloride (50 mL) was added dropwise to a 1M solution of boron trichloride in methylene chloride (18 mL) at -78 °C. After 3 h at -78 °C, the resultant mixture was quenched with saturated aqueous $NaHCO_3$ (60 mL) and then warmed to room temperature. The mixture was extracted with ethyl acetate four times, and the combined extracts were washed with brine (pH 6-7), dried over $MgSO_4$, and concentrated *in vacuo* below 30 °C to give 2.07 g of a white solid. This crude product was dissolved in acetone (100 mL) and water (50 mL) and the resultant solution was treated with barium carbonate (3.45 g, 17.48 mmol) and refluxed for 3 h. The mixture was filtered, and the filtrate was neutralized to pH 2-3 with 1N HCl and extracted with ethyl acetate four times. The combined extracts were washed to pH 6-7 with brine, dried over $MgSO_4$, and concentrated *in vacuo* below 30 °C. Flash chromatography, with methylene chloride-acetone-methanol (100:10:5) as eluent, afforded 1.04 g (58% yield) of catechol **6**: spectroscopic data identical with those

reported by Lee and co-workers.[24] Selected data : ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.14 (s, 1H, H-5), 6.41 (s, 1H, H-8), 6.39 (s, 2H, H-2,6), 4.69 (d, *J* = 9.9 Hz, 1H, H-4), 4.43 (m, 2H, H-3,9), 4.06 (dd, *J* = 10.2, 8.7 Hz, 1H, H-3), 3.62 (s, 9H, OCH_3-3,4,5), 2.96 (dd, *J* = 14, 5.1 Hz, H-9a), 2.89 (bm, 3H, OH), 2.74 (m, 1H, H-3a). MS (DCI, NH_3) *m/e* 402 $[M]^+$, 420 $[M + 18]^+$.

(3a*R*,4*R*,9*R*,9a*R*)-4-Hydroxy-3a,4,9,9a-tetrahydro-6,7-di-*O*-trifluoromethylsulfonyl)-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (5). To a solution of catechol **6** (820 mg, 2.03 mmol) and DMAP (catalytic amount) in methylene chloride (55 mL) and 2,6-lutidine (10 mL) at 0 °C, triflic anhydride (685 μL, 4.06 mmol) was slowly added. The resultant mixture was stirred for 2 h at 0 °C, whereupon additional triflic anhydride (250 μL, 1.48 mmol) was added. After an additional 20 min at 0 °C, the mixture was diluted with ethyl acetate, washed with 10% aqueous HCl and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with methylene chloride-acetone 95:5 as eluent, furnished 920 mg (68% yield) of bistriflate **5** as a white solid: mp 198-200 °C. $[\alpha]_D^{22}$ -68.8° (*c* 0.75, $CHCl_3$). IR ($CDCl_3$) 3479, 3007, 2941, 2841, 1780, 1592, 1509, 1336, 1229, 1137 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H, H-5), 7.24 (s, 1H, H-8), 6.28 (s, 2H, H-2,6), 4.88 (t, *J* = 9.6 Hz, 1H, H-4), 4.82 (d, *J* = 4.6 Hz, 1H, H-9), 4.64 (dd, *J* = 8.8, 7 Hz, 1H, H-3), 4.10 (t, *J* = 9.4 Hz, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.75 (s, 6H, OCH_3), 2.97 (dd, *J* = 14, 4.6 Hz, 1H, H-9a), 2.85 (m, 1H, H-3a). MS (DCI, NH_3) *m/e* 684 $[M + NH_4]^+$. Anal. Calcd for $C_{23}H_{20}F_6O_{12}S_2$: C, 41.44; H, 3.02. Found: C, 41.79; H, 2.99.

(3a*R*,4*R*,9*R*,9a*R*)-4-Hydroxy-3a,4,9,9a-tetrahydro-6,7-diethenyl-9-(3,4,5-trimethoxy phenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (4) and **(3a*R*,4*R*,9*R*,9a*S*)-4-Hydroxy-3a,4,9,9a-tetrahydro-6,7-diethenyl-9-(3,4,5-trimethoxyphenyl) naphtho[2,3-*c*]furan-1(3*H*)-one (7).** To a solution of bistriflate **5** (990 mg, 1.48 mmol) in 1,4-dioxane (25 mL) LiCl (188 mg, 4.43 mmol), $Pd(PPh_3)_4$ (171 mg, 0.148 mmol), tri-*n*-butylvinylstannane (1.25 mL, 4.28 mmol) were added, and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol. The resultant mixture was heated to 95 °C and monitored closely by TLC (methylene chloride-acetone (10:0.5), three elutions) in order to limit epimerization at C-9a as much as possible. After 3 h, additional stannane (0.1 mL, 0.342 mmol) was added and the reaction was stirred for 30 min. The mixture was cooled to room temperature and treated with saturated aqueous KF (10 mL) for 30 min. After dilution with ethyl acetate and filtration, the filtrate was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Repeated flash chromatography with methylene chloride-acetone (10:0.5) as eluent gave -in order of elution- 313 mg (50% yield) of the *cis*-lactone **7** and 97 mg (15% yield) of the *trans*-lactone **4** (ca. 3/1 ratio of isomers), both as solids: Compound **4**: mp 88-90 °C. $[\alpha]_D^{22}$ -114.2° (*c* 1.04, $CHCl_3$). IR ($CDCl_3$) 3008, 2965, 2940, 2841, 1775, 1591, 1509, 1130 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-5), 7.25 (s, 1H, H-8), 7.03-6.86 (m, 2H, vinylic), 6.35 (s, 2H, H-2,6), 5.72-5.27 (m, 4H, vinylic), 4.82 (d, *J* = 9 Hz, 1H, H-4), 4.70 (d, *J* = 2.8 Hz, 1H, H-9), 4.58 (dd, *J* = 8.8, 6.6 Hz, 1H, H-3), 4.05 (m, 1H, H-3), 3.79 (s, 3H, OCH_3), 3.70 (s, 6H, OCH_3), 2.82 (m, 2H, H-3a, H-9a), 2.56 (bs, 1H, OH). MS (DCI, NH_3) *m/e* 423 $[M + H]^+$, 440 $[M + NH_4]^+$. Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 70.31; H,6.54. Compound **7**: mp 118-120 °C. $[\alpha]_D^{22}$ +38.6° (*c* 0.88, $CHCl_3$). IR ($CDCl_3$) 2940, 2841, 1772, 1594, 1509, 1131 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H, H-5), 7.04-6.86 (m, 2H, vinylic), 6.95 (s, 1H, H-8), 6.50 (s, 2H, H-2,6), 5.72-5.23 (m, 4H, vinylic), 4.59 (m, 2H, H-3,4), 4.43 (dd, *J* = 9.6, 6.3 Hz, 1H, H-3), 4.13 (d, *J* = 5.9 Hz, 1H, H-9), 3.87 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 3.26 (dd, J = 9.3, 5.9 Hz, 1H, H-9a), 2.75 (m, 1H, H-3a), 1.65 (bs, 1H, OH). MS (DCI, NH_3) *m/e* 423 $[M + H]^+$, 440 $[M + NH_4]^+$. Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 70.28; H, 6.47.

(3a*R*,4*R*,9*R*,9a*R*)-4-(*tert*-Butyldimethylsilyloxy)-3a,4,9,9a-tetrahydro-6,7-diethenyl-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (8). A solution of alcohol **4** (270 mg, 0.639 mmol) and 2,6-lutidine (126 µL, 1.08 mmol) in methylene chloride (10 mL) was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (173 µL, 0.756 mmol) was introduced dropwise. After 2 h at 0 °C, the reaction mixture was diluted with methylene chloride, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane-ethyl acetate (6:1) as eluent, gave 274 mg (80% yield) of silyl ether **8** as a solid: mp 212-214 °C. $[\alpha]_D^{22}$ -113.2° (*c* 1.08, $CHCl_3$). IR ($CDCl_3$) 2958, 2932, 2858, 1776, 1592, 1509, 1129 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H, H-5), 7.15 (s, 1H, H-8), 7.06-.6.88 (m, 2H, vinylic), 6.36 (s, 2H, H-2,6), 5.69-5.52 (m, 2H, vinylic), 5.38-5.28 (m, 2H, vinylic), 4.87 (d, *J* = 8.8 Hz, 1H, H-4), 4.70 (d, *J* = 4.3 Hz, 1H, H-9), 4.55 (dd, *J* = 8.3, 7 Hz, 1H, H-3), 4.02 (t, *J* = 9.2 Hz, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3), 2.90 (m, 1H, H-3a), 2.82 (dd, *J* = 14.3, 4.3 Hz, 1H, H-9a), 0.96 (s, 9H, $SiC(CH_3)_3$), 0.32 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$). MS (DCI, NH_3) *m/e* 536 $[M + H]^+$, 554 $[M + NH_4]^+$. Anal. Calcd for $C_{31}H_{40}O_6Si$: C, 69.37; H, 7.50. Found: C, 69.39; H, 7.94.

(3a*R*,4*R*,9*R*,9a*S*)-4-(*tert*-Butyldimethylsilyloxy)-3a,4,9,9a-tetrahydro-6,7-diethenyl-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (9). A solution of alcohol **7** (700 mg, 1.65 mmol) and 2,6-lutidine (328 µL, 2.81 mmol) in methylene chloride (10 mL) was cooled to 0 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (457 µL, 1.99 mmol) was added dropwise. After 1.5 h at 0 °C, the reaction mixture was diluted with methylene chloride, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane-ethyl acetate (4:1) as eluent, gave 822 mg (92% yield) of silyl ether **9** as a solid: mp 68-70 °C. $[\alpha]_D^{22}$ +109.8° (*c* 1.08, $CHCl_3$). IR ($CDCl_3$) 2932, 2858, 1773, 1594, 1509, 1131 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.64 (s, 1H, H-5), 7.06-6.84 (m, 2H, vinylic), 6.82 (s, 1H, H-8), 6.52 (s, 2H, H-2,6), 5.68-5.19 (m, 4H, vinylic), 4.55 (m, 2H, H-3,4), 4.36 (dd, *J* = 9.7, 6.2 Hz, 1H, H-3), 3.89 (dd, *J* = 7.6 Hz, 1H, H-9), 3.84 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 3.23 (dd, *J* = 9.3, 7.6 Hz, 1H, H-9a), 2.60 (m, 1H, H-3a), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.21 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$). MS (DCI, NH_3) *m/e* 554 $[M + NH_4]^+$. Anal. Calcd for $C_{31}H_{40}O_6Si$: C, 69.37; H, 7.50. Found: C, 69.32; H, 7.71.

Conversion of the *cis*-lactone (+)-9 into the *trans*-lactone (-)-8. A solution of *cis*-lactone **9** (522 mg, 0.972 mmol) in THF (5 mL) was cooled to -78°C, and 2M LDA in THF (530 µL, 1.06 mmol) was slowly added. The resultant solution was stirred for 15 min at -78 °C and quenched with glacial acetic acid (100 µL, 1.74 mmol). The mixture was warmed to room temperature, diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Following concentration *in vacuo*, the residue was purified by flash chromatography with cyclohexane-ethyl acetate (7:1) as eluent, to provide 110 mg (21% yield) of the less polar **8** and 360 mg (69% yield) of the more polar **9** as white solids.

(3a*R*,4*R*,9*R*,9a*R*)-4-(*tert*-Butyldimethylsilyloxy)-3a,4,9,9a-tetrahydro-6,7-(1,2-dihydroxy ethyl)-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (10). At 0 °C, a solution of bisvinyl **8** (290 mg, 0.54 mmol) and N-methylmorpholine-N-oxide (63.3 mg, 0.54 mmol) in acetone and H_2O (9:1, 20 mL) was treated with catalytic OsO_4 (700 µL of a 2.5 wt % solution in *t*.BuOH, 0.056 mmol). The ice bath was removed, and the reaction mixture was stirred for 5.5 h and then partitioned between 10% aqueous $NaHSO_3$ and ethyl acetate. The organic layer was washed with 10% aqueous $NaHSO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane-acetone (1:1), then

acetone as eluent, gave 293 mg (90% yield) of an uncharacterized mixture of tetrahydroxy lactones **10**: MS (DCI, NH_3) *m/e* 622 $[M + NH_4]^+$.

(3a*R*,4*R*,9*R*,9a*R*)-4-(*tert*-Butyldimethylsilyloxy)-3a,4,9,9a-tetrahydro-6,7-dicarboxyaldehyde-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (11). A solution of a mixture of these tetrahydroxy lactones **10** (293 mg, 0.484 mmol) in benzene (10 mL) and methylene chloride (10 mL) at room temperature was treated with lead tetraacetate (430 mg, 0.970 mmol). After 5 h, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. Flash chromatography, with methylene chloride, then methylene chloride-acetone 95:5 as eluent, gave 236 mg (91% yield) of **11** as a white solid: mp 102-104 °C. $[\alpha]_D^{22}$ -101.3° (*c* 0.76, $CHCl_3$). IR ($CDCl_3$) 2931, 2856, 1781, 1702, 1592, 1509, 1131 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H, CHO), 10.42 (s, 1H, CHO), 8.22 (s, 1H, H-5), 7.70 (s, 1H, H-8), 6.26 (s, 2H, H-2,6), 4.93 (d, *J* = 9.2 Hz, 1H, H-4), 4.83 (d, *J* = 4.6 Hz, 1H, H-9), 4.60 (dd, *J* = 8.7, 6.8 Hz, 1H, H-3), 4.06 (dd, *J* = 9.9, 8.7 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.72 (s, 6H, OCH_3), 3.03 (m, 1H, H-3a), 2.88 (dd, *J* =14.4, 4.6 Hz, 1H, H-9a), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.38 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$). MS (DCI, NH_3) *m/e* 541 $[M + H]^+$ 558 $[M + NH_4]^+$.

(6a*R*,6*R*,9a*R*,10*R*)-10-(*tert*-Butyldimethylsilyloxy)-6,6a,7,9,9a,10-hexahydro-6-(3,4,5-trimethoxyphenyl)-7-oxofuro[3,4-*i*]benzo[*g*]phthalazine (12). A solution of dialdehyde **11** (200 mg, 0.370 mmol) in ethanol (6 mL) and methylene chloride (3 mL) was cooled to -50 °C and hydrazine monohydrate (18 μL, 0.371 mmol) was added. After 45 min, the reaction mixture was diluted with methylene chloride, warmed to room temperature and then washed with water. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane-acetone(2:1, then 1:1) as eluent, afforded 157 mg (79% yield) of **12** as a white solid: mp 138-140 °C. $[\alpha]_D^{22}$ -58.7° (*c* 0.92, $CHCl_3$). IR ($CDCl_3$) 2931, 2853, 1780, 1592, 1510, 1130 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H, H-1), 9.43 (s, 1H, H-4), 8.18 (s, 1H, H-11), 7.78 (s, 1H, H-5), 6.21 (s, 2H, H-2,6), 5.07 (d, *J* = 8.9 Hz, 1H, H-10), 5.03 (d, *J* = 4.4 Hz, 1H, H-6), 4.62 (dd, *J* = 8.3, 6.9 Hz, 1H, H-9), 4.10 (t, *J* = 9.3 Hz, 1H, H-9a), 3.79 (s, 3H, OCH_3), 3.66 (s, 6H, OCH_3), 3.07 (m, 1H, H-9a), 2.96 (t, J = 14.2, 4.4 Hz, 1H, H-6a), 1.01 (s, 9H, $SiC(CH_3)_3$), 0.41 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$). MS (DCI, NH_3) *m/e* 537 $[M + H]^+$. Anal. Calcd for $C_{29}H_{36}N_2O_6Si$: C, 64.90; H, 6.76. Found: C, 64.31; H, 7.11.

(6a*R*,6*R*,9a*R*,10*R*)-10-Hydroxy-6,6a,7,9,9a,10-hexahydro-6-(3,4,5-trimethoxyphenyl)-7-oxofuro[3,4-*i*]benzo[g]phthalazine (3). Et_3N-HF (143 μL of a 9.3 M solution in acetonitrile, 1.33 mmol) was added to a solution of **12** (119 mg, 0.221 mmol) in acetonitrile (2 mL) at room temperature. The reaction mixture was stirred for 3 days and then concentrated *in vacuo*. Flash chromatography, with cyclohexane-acetone (1:1) then acetone as eluent, furnished 91 mg (97% yield) of pyridazine podophyllotoxin **3** as a white solid: mp 179-181 °C. $[\alpha]_D^{22}$ -57.5° (*c* 0.86, $CHCl_3$). IR (KBr) 1773, 1590, 1510, 1130 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 9.94 (s, 1H, H-1), 9.79 (s, 1H, H-4), 8.87 (s, 1H, H-11), 8.26 (s, 1H, H-5), 6.66 (s, 2H, H-2,6), 5.43 (d, *J* = 5.3 Hz, 1H, H-6), 5.39 (d, *J* = 10.9 Hz, 1H, H-10), 4.98 (dd, *J* = 8.5, 7.6 Hz, 1H, H-9), 4.57 (dd, *J* = 10.2, 8.9 Hz, 1H, H-9), 4.02 (s, 3H, OCH_3), 3.97 (s, 6H, OCH_3); 3.63 (dd, *J* =14, 5.3 Hz, 1H, H-6a), 3.30 (m, 1H, H-9a). MS (DCI, NH_3) *m/e* 423 $[M + H]^+$. Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.22; H, 5.28; N, 6.67.

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46. The biological activities of **4**, **5**, **8**, **10** and **11** were evaluated *in vitro* against L1210 leukemia and *in vivo* against the P388 leukemia. For L1210, IC_{50} values M are as follows : **4**, 1.2 x 10^{-7}; **5**, insoluble; **8**, > 10^{-6}; **10**, > 10^{-5}. **11**, > 10^{-5}; etoposide, 2 x 10^{-7}. For P388, EC_{50} values max effect mg. kg/days are roughly the same ≈ 40 inactive compounds. Only compounds **4** and **7** were tested *in vitro* against human non-small cell lung A549 and bladder T24 cancer cell lines. IC_{50} values M for **4** and **7** are as follows : A549 **4**, < 10^{-7}; **7**, 4.3 x 10^{-6}. T24 : **4**, < 10^{-7}; **7**, 8.7 x 10^{-6}.
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