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Synthesis of podophyllotoxin analogues: δ-lactone-containing picropodophyllin, podophyllotoxin and 4′-demethyl-epipodophyllotoxin derivatives

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Abstract—Non-epimerizable *cis* and *trans* δ-lactone analogues of podophyllotoxin have been prepared. Thus the synthesis of the *cis* isomer **4** has been achieved in 8 steps and 4% overall yield from podophyllotoxin **1** via the reduction of the γ lactone ring into the *trans* diol, selective protection of the 4-OH and 11-OH as a benzylidene acetal, and Wittig elongation at C-13 with inversion of configuration at C-2. Same elongation at C-13 but via the formation of a mesylate and introduction of a cyano group, led to the *trans* δ-lactone **5** (7 steps from **1** and 6% overall yied) with a small amount of its C-4 epimer **6**. The synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8** are also reported. The synthesis of **7** and **8** was based upon the reduction of the γ-lactone ring of 4′-demethyl-4-epipodophyllotoxin followed by selective protection at C-11 and elongation at C-13. (8–15% and 4% overall yields). Compounds **4**, **5** and **7** did not display relevant cytotoxicity in vitro against L1210 murine leukemia.

1. Introduction

(−)-Podophyllotoxin **1** is a naturally occurring aryltetralin from *Podophyllum peltatum* and *P. emodi*.[1] Interest in podophyllotoxin has been heightened by its potent antimitotic activity.[2] Podophyllotoxin inhibits the assembly of tubulin protein into microtubules through tubulin binding at the colchicin site[3] but failed to advance in human clinical trials because of toxic side-effects. Extensive structure modifications have been performed since the 1950s, principally at Sandoz Laboratories[4] which led to the semi-synthetic etoposide (VP-16, **2**) and teniposide (VM-26, **3**). Both derivatives demonstrated significant activity and low toxicity in clinical trials (Fig. 1).

Despite the fact that they derived from podophyllotoxin, there was early evidence that these drugs did not share the same mechanism. In 1976, Loike and Horwitz made relevant observations[5] which ultimately led to the identification of DNA topoisomerase II as the intracellular target for the action of these drugs. Although etoposide has been used successfully in the clinic for many years in the treatment of small-cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma,[6,7] several problems still exist. Besides the poor solubility of etoposide and the development of drug resistance, the metabolism of etoposide results in inactivation by epimerisation of the *trans* lactone ring giving the *cis* isomer, the picropodophyllin analogue which is 100-fold less toxic.[8] A second metabolite

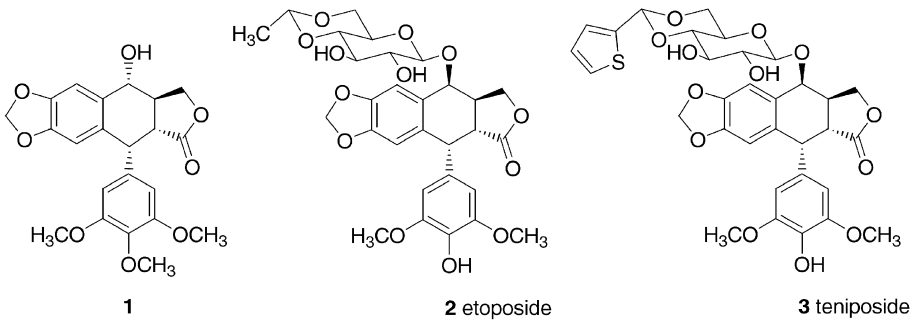

Figure 1.

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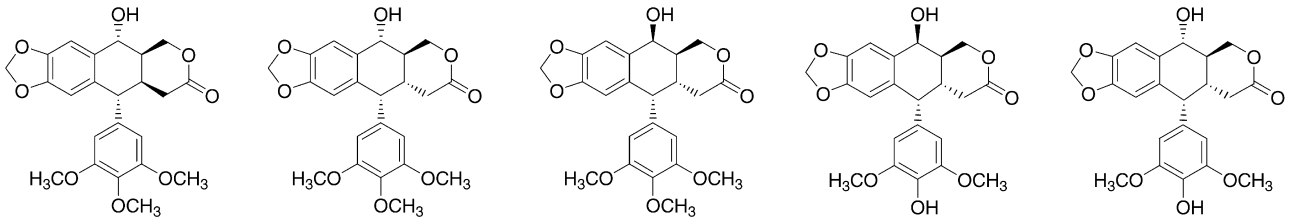


Figure 2.

is the *cis*-hydroxy acid which results from the opening of the lactone ring with subsequent epimerisation and which is 500-fold less cytotoxic than etoposide. In order to avoid or minimize the C-2 epimerization and/or the lactone ring opening, two main alternatives have been proposed. The first included the replacement of the γ-lactone with furan, thiolane, cyclopentane rings[9] whereas the second took advantage of the preparation of derivatives substituted at the 2-position such as methyl, halogeno, hydroxy[10,11] or nitrogen derivatives.[12] On the other hand, a few years ago, the groups of Gordaliza[13] and Subrahmanyam[14] have reported that podophyllotoxin analogues lacking the lactone ring are still endowed with relevant cytotoxic effects towards colon cancer cell lines. However, as no in vivo evaluation were reported in both cases, it remains to ascertain whether they present a relevant anti-tumour activity and lack of general toxicity.

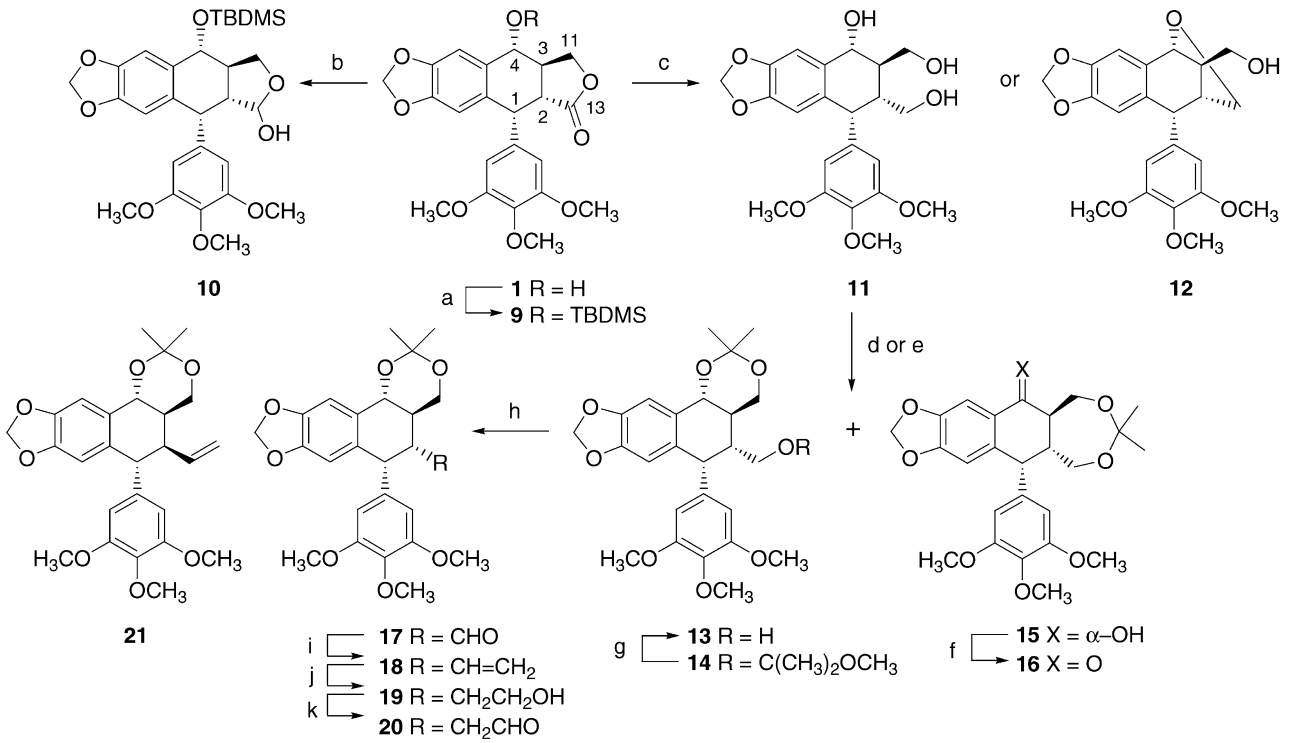
As part of our ongoing research program aimed at the synthesis and biological evaluation of new anti-tumour analogues[15–18] related to podophyllotoxin and etoposide, we have already been engaged in the synthesis of analogues including six-membered lactone ring since enhancement of the lactone ring may give access to more stable isomers. Thus we recently reported the synthesis of the δ-*cis*-lactone analogue of picropodophyllin[17] in which the carbonyl group was adjacent to the epimerizable C-2 as in natural lignans. Herein we describe the synthesis of non-epimerizable δ-lactone analogues of picropodophyllin **4** and of podophyllotoxin **5** and **6**, and the synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8**, possessing the carbonyl in β-position of the C/D ring junction. Exploratory evaluation of the biological activity of **4**, **5** and **7** is also presented (Fig. 2).

2. Results and discussion

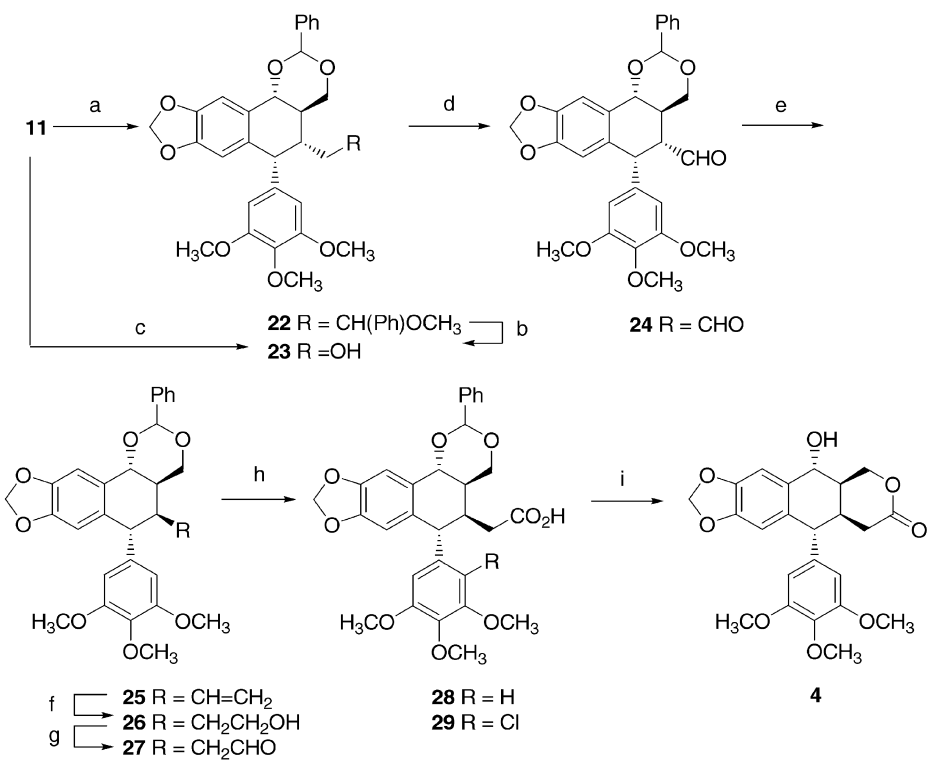
Our point of departure for the synthesis of **4**–**6** was the reduction of podophyllotoxin **1**: two different ways have been successively followed which consist in partial or total reduction of the lactone ring with retention of configuration at C-2 (Scheme 1). First, podophyllotoxin **1** was converted into silyl ether **9**[17] which was next reduced according to Lee et al.[19] in the presence of DIBAL-H to afford **10** in 87% yield. Unfortunately, subsequent attempts to introduce a side-chain via a Wittig reaction, using for example the ylide obtained from methoxymethyltriphenylphosphonium bromide,[20] did not succeed, even in the case of the free lactol at C-4. The same lack of reactivity of the lactol was observed when treated with 1,3-dithianyl anions prepared from 1,3-dithiane-2-yl-triphenylphosphonium chloride,[21] diethyl(1,3-dithian-2-yl)phosphonate,[22] or 2-trimethylsilyl-1,3-dithiane[23] for Wittig, Horner–Emmons and Peterson olefinations, respectively. Interestingly, the unprotected lactol reacted with methyl(triphenylphosphoranylidene)-acetate and pyridine in toluene at 90 °C to produce the expected α,β-unsaturated ester.[14b]

The alternative way involved the reductive cleavage of the lactone moiety into triol **11** by LAH. Indeed such a reductive method[24] is one among the few methods which allow the reductive opening of the lactone ring of podophyllotoxin with preservation of the 2,3-*trans* relationship[25] However, the crucial and immediate problem which is attached to this transformation is due to the fact that triol **11** is prone to dehydration during the work-up to readily afford the neoanhydropodophyllol **12**.[26]

Formation of this side-product has been contradictorily attributed to an acidic medium[24] and later to a basic medium[26] involved during the different work-up. In our laboratory, we observed that **12** is ineluctably formed upon addition of EtOAc and HCl, we decided to carefully remove the excess of hydride with successive addition of water and NaOH at low temperature.[27] Interestingly, under these conditions, triol **11** was obtained in 60% yield without any traces of **12**. The following step consisted in selectively protection of the C-11 hydroxyl by taking into account its vicinal situation with the C-4 hydroxyl to form a cyclic acetal. Moreover it was expected that treatment of **11** with α,α-dimethoxypropane would selectively afford a 6-membered isopropylidene. This acetonide protection have been previously used for the 1,3-diol system of the tetraline intermediate in the synthesis of (±)-podophyllotoxin.[28] In fact, such a treatment led to a mixture of three products which contained the expected isopropylidene acetal **13** along with the hemiketal derivative **14** and with the 7-membered acetal **15**, in 7, 62 and 28% yields, respectively. Additional amount of **13** could be obtained by selective deprotection at C-13 (AcOH, H_2O, MeOH, 88%) of **14**. Alternatively, addition of Et_3N (10 equiv.) to the crude reaction mixture, followed by concentration in vacuo and heating at 60 °C for 8 h in aqueous methanolic solution, afforded compounds **13** (54%) and **15** (15%) without any traces of the hemiketal **14**, allowing an easier purification of **13**. The structure of **15** was determined by ^1H NMR and by chemical means upon periodinane oxidation[29] of **15** leading to the corresponding keto-derivative **16** (74%). A compound having a similar skeleton had been already obtained by Pelter et al.[30]



Scheme 1. Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.3 h, 92%; (b) DIBALH, toluene, −78 °C, 40 min, 87%; (c) LAH, THF, 0 °C, 4 h, then basic work up according Ref. 27 gave **11** (60%), or work up according Refs. 24 or 26 gave **12**; (d) α,α-DMP, PTSA, rt, 7 h, **13** (7%), **14** (62%) and **15** (28%); (e) α,α-DMP, PTSA, rt, 3.5 h, then Et_3N, MeOH/H_2O (10/1), 8 h, 60 °C, **13** (54%) and **15** (15%); (f) Dess–Martin periodinane, CH_2Cl_2, rt, 40 min, 74%; (g) AcOH/H_2O (1/1), MeOH, rt, 3.5 h, 88%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, 87%; (i) Ph_3PCH_3,Br, *n*-BuLi, THF, −78 °C, 45 min, 86%; (j) 9-BBN, THF, rt, 3.5 h, then H_2O_2 (30%), MeOH, pH 7.2 phosphate buffer, 74% (two steps); (k) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 92%.



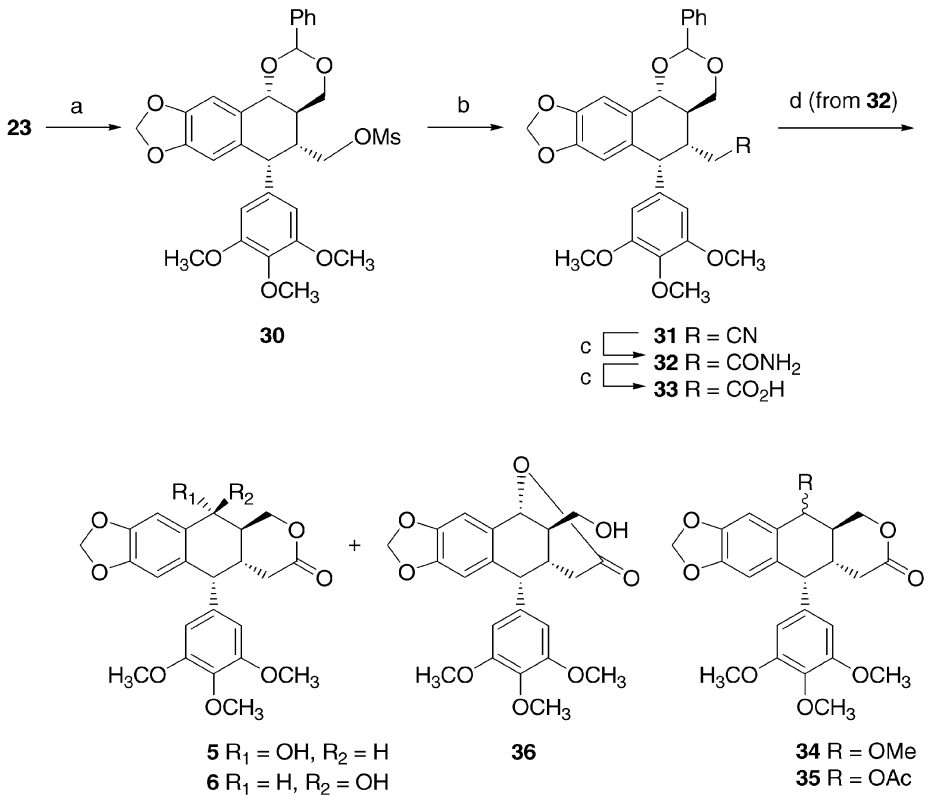
Scheme 2. Reagents and conditions: (a) α,α-dimethoxytoluene, PTSA, rt, 40 min, 73%; (b) AcOH/H_2O (1/1), MeOH, CH_2Cl_2, rt 5 days, 66%; (c) α,α-dimethoxytoluene, PTSA, CH_2Cl_2, rt, 10 min, **23** (37%), **22** (8%) and **12** (32%) (d) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, 87%; (e) Ph_3PCH_3,Br, K_2CO_3, 18-crown-6, THF, reflux, 19 h, 92%; (f) 9-BBN, THF, rt, 1.75 h, then H_2O_2 (30%), MeOH, pH 7.2 phosphate buffer, rt, 3 h, 80%; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 65%; (h) $NaClO_2$, NH_2SO_3H, *t*-BuOH/H_2O (2/1), rt, 25 min, 76%; (i) CSA, THF/H_2O (10/1), 80 °C, 6 h, 66%.

Once isolated, isopropylidene acetal **13** was oxidized in the presence of Dess–Martin reagent (87%) and the aldehyde derivative **17** (80 mg scale) was submitted to Wittig reagent to give **18**. The stereochemical assignment of **18** was based on $J_{3,4}$=(10.1 Hz) and $J_{1,2}$=(6.4 Hz) coupling constants, respectively consistent with 3,4-*trans* and 1,2-*cis* relationships, and a comparison with similar compounds.[28,31] Hydroboration followed by a second Dess–Martin oxidation of alcohol **19**, afforded **20** in 68% overall yield from **18**. On 500 mg scale for the synthesis of **13**, we noted the preponderant formation of the seven-membered during the first step (**13**:**15**=13:86 instead of 78:22). In addition, Wittig olefination of **17** (300 mg scale) provided an inseparable mixture of **18** and **21** which was attributed to the pronounced basic character of the ylide. This led us to consider the benzylidene protection for **11** (Scheme 2). This protective group was exploited in an exploratory approach towards podophyllotoxin[32] and epipodophyllotoxin.

Treatment of **11** with α,α-dimethoxytoluene, both as reagent and solvent, and PTSA exclusively afforded the six-membered benzylidene acetal **22** (73%) which was next converted into **23** by aqueous acidic hydrolysis (48% overall yield) (Scheme 3). Removal of α,α-dimethoxytoluene proved more troublesome than expected on larger scale. Alternatively, the use a stoichiometric amount of the reagent in dichloromethane led to a separable mixture of the desired acetal **23**, **22** and neoanhydropodophyllol **12**. Upon periodinane oxidation of **23**, the resulting aldehyde **24** was treated with the required ylide prepared in situ by deprotonation of methyl triphenylphosphonium bromide with potassium carbonate and 18-crown-6[33] to afford the *cis*-vinyl derivative **25** (92% yield). The assignment of the relative stereochemistry was based upon $J_{1,2}$ and $J_{2,3}$=(2.9 and 8.9 Hz). Note that the reaction of **24** with methylenetriphenylphosphorane (Ph_3PCH_3,Br, *n*-BuLi, THF, −78 °C, 1 h 30) furnished an inseparable stereoisomeric mixture of **25** and of the 2,3-*trans* isomer (30:70 ratio) in 81% yield. The same result was observed under various conditions of time, temperature, or in the presence of various ratios of the reagents versus the starting material. Furthermore, subsequent hydroboration of this mixture led to the separation problem again. Hydroboration of **25** gave alcohol **26** in 80% yield. Periodinane oxidation followed by sodium chlorite oxidation of aldehyde **27** led to the expected carboxylic acid **28** (76%) along with a small amount of **29** (8%) resulting from the chloration of the aromatic ring. Unfortunately, direct oxidation of the aformentioned vinyl or alcohol mixture at C-2 into the corresponding acids failed.[34] Acid hydrolysis of the benzylidene moiety of **28** took place without inversion[35] at C-4 ($J_{3,4}$=8.2 Hz) to provide the δ-lactone-containing picropodophyllin derivative **4** in 66% yield (e.g., 8 steps from **1** and 4% overall yield).

To obtain the corresponding *trans* isomer **5** of podophyllotoxin configuration (Scheme 3), compound **23** was first mesylated (99%) and mesylate **30** readily afforded the cyano derivative **31** (95%).

Next, hydrolysis of nitrile **31** was carried out in the presence of a large excess of NaOH (40 equiv.) in EtOH under reflux giving amide **32** in 83% yield. Carboxylic acid **33** could be obtained as a mixture with **32** by prolonging the reaction time to 16 h. Exposure of **32** to PTSA in MeOH led

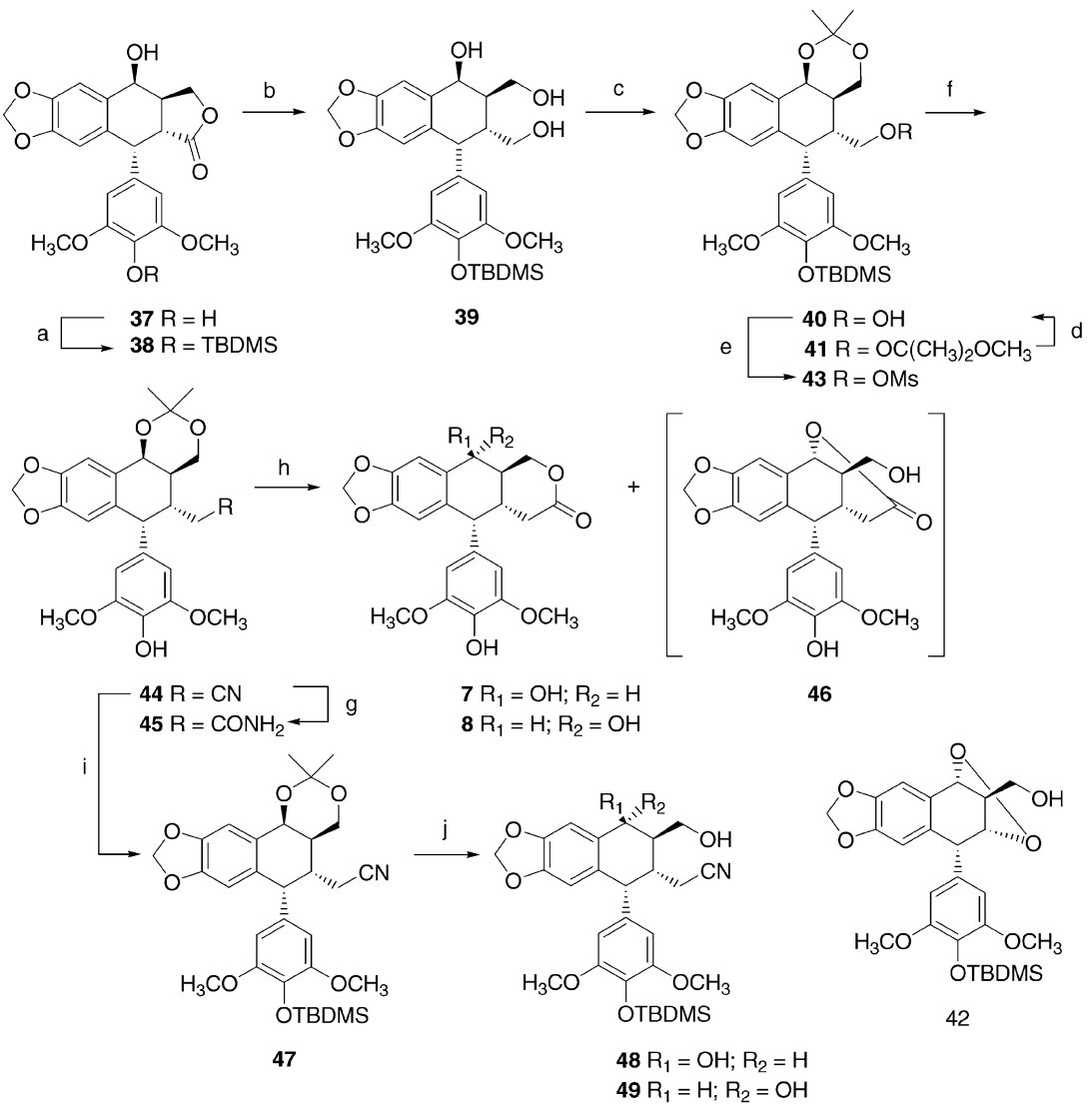


Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 99%; (b) NaCN, DMF, 85 °C, 6 h, 95%; (c) NaOH (25%), EtOH, reflux, 7 h, **32** (83%)/reflux 16 h, mixture of **32** (24%) and **33** (47%); (d) CSA, THF/H_2O (1/1), 85 °C, 17 h, **5** (28%), **6** (7%) and **36** (13%).

exclusively to **34** as an epimeric mixture at C-4 whereas 80% aqueous AcOH gave **5**, **35** as an epimeric mixture, and **36**. To circumvent the problem of substitution at C-4, the reaction was carried out with CSA in THF/H_2O (1/1). Under these conditions, **32** was converted to the δ-lactone-containing podophyllotoxin derivative **5** (28%), along with a small amount of **6** (7%) and **36** (13%). Homolactone **5** showed a broad triplet at 4.51 ($J_{3,4}$=$J_{4,OH}$=7.6 Hz) and homolactone **6** showed a broad singlet at 4.76 due to H-4, respectively, indicating 3,4-*trans* and 3,4-*cis* relationships. The synthesis of **5** proceeds in 7 steps from **1** and in 6% overall yield.

The chemistry developed in the podophyllotoxin series was extended to 4′-demethyl-4-epipodophyllotoxin **37**. Protection of this latter as the *tert*-butyldimethylsilyl ether **38**, followed by treatment with LAH, afforded triol **39** (Scheme 4). Treatment of **39** with α,α-dimethoxypropane led to a mixture of three compounds which contained the expected isopropylidene acetal **40**, along with the hemiketal derivative **41** and with the 4′-demethyl-neoanhydropodophyllol derivative **42**. The 7-membered acetal was not detected. Prior to chromatographic isolation of **40**, the crude mixture was then treated in acidic medium to carry out selective deprotection at C-13. Under these conditions, **40** was more easily isolated (41%, 3 steps from **38**).

Mesylation of **40**, and cyanation with concomitant loss of the TBDMS group, gave **44** in 53% overall yield. Hydrolysis of nitrile **44** furnished amide **45** in acceptable (44%) albeit lower yield than in the podophyllotoxin series. One-pot deketalization and lactonization of **45** by a two-fold acidic treatment led to a mixture of three compounds: the expected δ-lactone **7** (31%), and an inseparable mixture of two other δ-lactone derivatives postulated from our previous results as being the epimer at C-4 **8** and the regioisomeric lactone **46**. Homolactone **7** showed a large singulet at 4.75 due to H-4 indicating a 3,4-*cis* relationship.



Scheme 4. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, 1.5 h, 89%; (b) LAH, THF, 0 °C, 1.5 h, 51%; (c) α,α-DMP, PTSA, rt, 35 min, (d) AcOH/H_2O (1/1), MeOH, rt, 6 h, **40** (41%, 3 steps from **38**); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 50 min; (f) NaCN, DMF, 85 °C, 5 h, **44** (53%, 2 steps); (g) NaOH (25%), EtOH, 75 °C, 28 h, 44%; (h) (a) APTS, THF: H_2O (10/1), 45 °C, 7 h; (b) CSA, CH_2Cl_2, rt, 30 min, **7** (31%); (i) TBDMSCl, imidazole, DMF, rt, 2.5 h; (j) APTS, THF/H_2O (10/1), 70 °C, 25 h, **48** (29%) and **49** (36%).

The structure of **8** was confirmed from ^{1}H NMR comparison with **8** prepared otherwise (vide infra). Epimerization at C-4 occurred before the cyclization step as shown in the case of the cyano-derivative **47** which, under these reaction conditions, led to a mixture of **48** (29%) and **49** (36%). The conversion of methyl epipodophyllate into methyl podophyllate was obtained in a similar fashion during the asymmetric total synthesis of (−)-podophyllotoxin.[36] Hydrolysis of each cyano-derivative failed to furnish the corresponding amide.

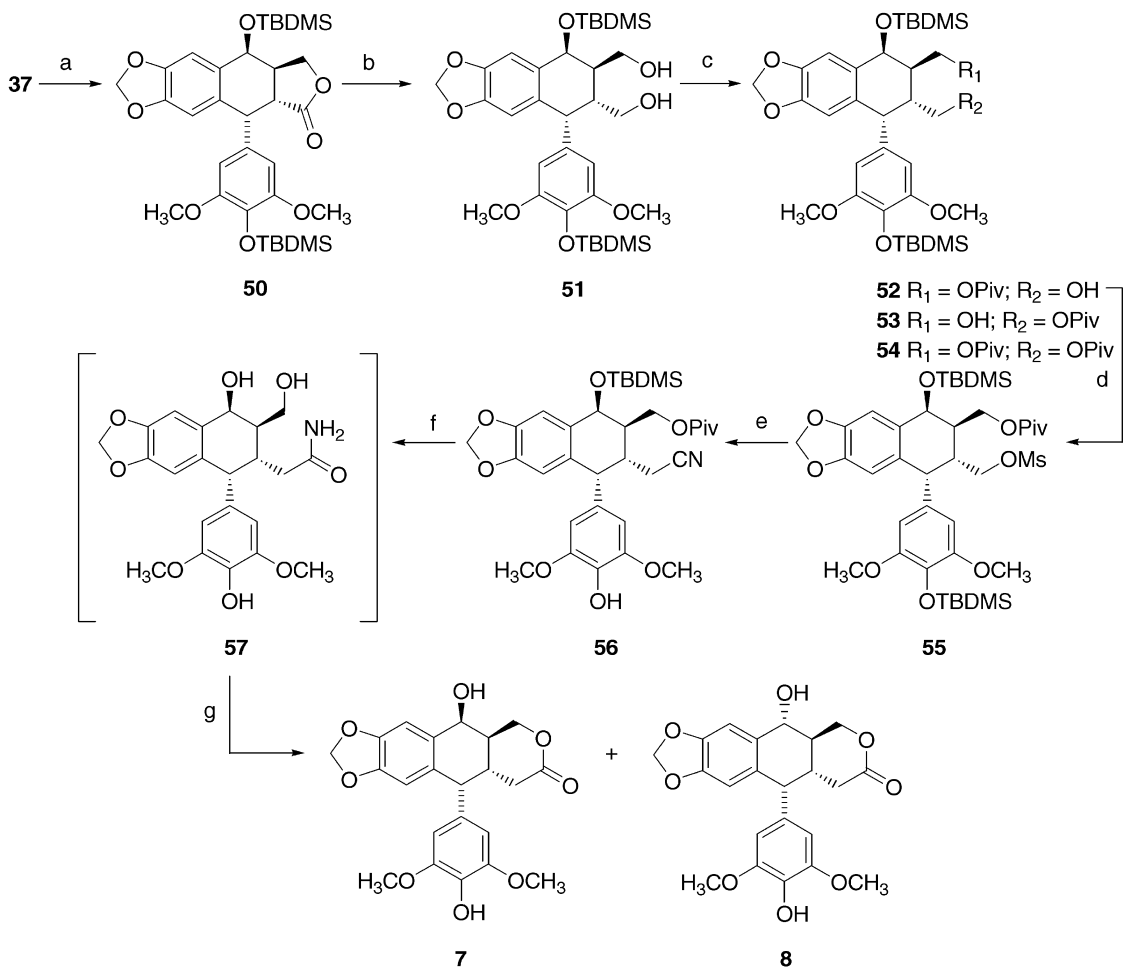
Our alternative synthesis of **7** involved the differential protection of the hydroxyl groups at C-4 and C-11.

As shown in Scheme 5, bis-silylation of **37** generated **50**[37] which was reduced as the diol **51**. Selective acylation with 2.5 equiv. of PivCl (Et_3N, cat. 4-DMAP) afforded a separable mixture of **52** (65%), **53** (27%) and **54** (8%). Mesylation of **52** and cyanation provided **56** (54%, 2 steps). Basic hydrolysis of the nitrile led to a polar compound—as judged by TLC—which was presumably **57** according to our knowledge in the podophyllotoxin series, and subsequent neutralization gave **7** (32–60%) and **8** (15%). The large coupling constant of **8** ($J_{3,4}$=8.4 Hz) is indicative of a 3,4-*trans* relationship. The syntheses of **7** and **8** proceeded in 8–15% and 4% overall yields from 4′-demethyl-epipodophyllotoxin **37**, respectively.

Exploratory evaluation of the biological activity of the six-membered lactone derivatives **4**, **5** and **7** were performed in vitro. None of these compounds exhibited relevant cytotoxicity against L1210 murine leukemia since the values of their IC_{50} were 73.9, 38 μM and>100 μM, respectively (**1**, IC_{50}=0.008 μM). The lack of cytotoxic effect may be due to the D-ring enhancement of the podophyllotoxin framework or more probably it means that the position of the carbonyl group on the lactone ring is important for activity.[17]

3. Conclusion

The synthesis of non-epimerizable δ-lactone analogues of picropodophyllin **4** and of podophyllotoxin **5** and **6** has been achieved. Analogues **4** and **5** did not display significant cytotoxicity in vitro against L1210. We have also completed the synthesis of non-epimerizable δ-lactone analogues of 4′-demethyl-epipodophyllotoxin **7** and of 4-demethyl podophyllotoxin **8**. Work toward the preparation of δ-lactone



Scheme 5. Reagents and conditions: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 81%; (b) LAH, THF, 0 °C to rt, 30 min, 92%; (c) PivCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 40 min, **52** 65%), **53** (27%) and **54** (8%); (d) MsCl, Et_3N, CH_2Cl_2, rt, 2 h; (e) NaCN, DMF, 85 °C, 24 h (54%, 2 steps); (f) NaOH (25%), EtOH, 85 °C, 7 h; (g) 1 N HCl (→pH 2–3), then work-up and stirring overnight of the combined organic phases. **7** (32–60%) and **8** (15%).

analogues having the carbonyl in α-position of the C/D ring junction is under investigation.

4. Experimental

4.1. Materials and methods

^{1}H NMR spectra were recorded on a Bruker AM-250 or a Brucker 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 ionisation (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 a developing agent. E Merck silica gel (particle size 0.040–0.063 mm) was used for flash column chromatography. All reactions were carried out using heat gun-dried glassware 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 was purified by flash chromatography before use.

4.1.1. 4-*O*-(*tert*-Butyldimethylsilyl)-13-hydroxypodophyllotoxin (10). Compound **10** was prepared according to Lee et al.[19]

4.1.2. Podophyllol 11. To a suspension of LAH (18.44 g, 486 mmol) in THF (315 mL) at 0 °C was added podophyllotoxin **1** (24.26 g, 58.54 mmol) in THF (250 mL) over a period of 1.5 h. The mixture was stirred for an additional 2.5 h at the same temperature and under argon atmosphere prior to successive additions of water (18.5 mL), 15% aqueous solution of NaOH (18.5 mL) and water (56 mL). The crude mixture was filtered, washed with THF (4×100 mL) and the filtrate was concentrated under reduced pressure to c.a. 150 mL. The aqueous residue was extracted thrice with EtOAc (250 mL and then 2×150 mL) and the combined organic layers were washed with brine (2×250 mL), dried ($MgSO_4$) and concentrated in vacuo. The yellow solid residue was triturated with MeOH (75 mL) and the crystals were separated by precipitation to give podophyllol **11** (14.82 g, 60%) as a white powder, pure enough for the next step. Mp 178–179 °C (MeOH); $[\alpha]_D^{20}=-234.5$ (*c* 0.25, EtOH). [Lit.[25]: mp 179–181 °C; $[\alpha]_D^{18.5}=-179$ (*c* 0.27, $CHCl_3$); Lit.[26]: mp 186–188 °C (EtOAc); $[\alpha]_D^{19}=-203$ (*c* 0.25, EtOH)].

4.1.3. 4,11-*O*-Isopropylidene podophyllol (13), 11,13-*O*-isopropylidene podophyllol (15) and 4,11-*O*-isopropylidene-9-(2-methoxyisopropylether) podophyllol (14). *Procedure 1*. To a suspension of podophyllol **11** (224 mg, 0.53 mmol) in 2,2-dimethoxypropane (13 mL), *p*-toluenesulfonic acid monohydrate (10.2 mg, 53.5 μmol) was added. The reaction mixture was stirred at rt for 7 h, diluted with methylene chloride (20 mL) and with an aqueous saturated solution of sodium hydrogenocarbonate (15 mL). The aqueous layer was separated and washed with methylene chloride (15 mL). The combined organic layers were dried ($MgSO_4$), and.concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1, then 2:1 and 1:1) successively gave **13** (17.2 mg, 7%) as a white solid, **15** (68.8 mg, 28%) as a white solid, and **14** (176 mg, 62%) as an amorphous solid.

Procedure 2. Podophyllol **11** (52.5 mg, 0.125 mmol) was treated as above but, after 3.5 h, as a tlc control indicated disappearance of **11** and appearance of **13**, **14** and **15**, Et_3N (20 μL, 0.143 mmol) was added to the mixture and, 15 min later, the reaction mixture was concentrated under reduced pressure. The solid was dissolved in MeOH (1.8 mL) and water (0.2 mL), and the solution was heated at 60 °C for 8 h. Work-up and flash chromatography as above led to isolation of **13** (31.1 mg, 54%), and **15** (8.7 mg, 15%).

Compound **13**. Mp 169–170 °C (CH_2Cl_2); $[\alpha]_D^{20}=-133$ (*c* 0.62, $CHCl_3$); IR ($CDCl_3$) 3620 (OH), 2939, 1590, 1505, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.35 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.88 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.71 (d, 1H, *J*=9.2 Hz, H-4), 4.18 (d, 1H, *J*=5.4 Hz, H-1), 3.94 (dd, 1H, *J*=11.1, 4.2 Hz, H-11), 3.85 (m, 1H, H-11), 3.83 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 3.51 (m, 1H, H-13), 3.41 (m, 1H, H-13), 2.24–2.05 (m, 2H, H-2, H-3), 1.60 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 458 $[M]^+$, 476 $[M+NH_4]^+$.

Compound **14**. $[\alpha]_D^{20}=-139.5$ (*c* 0.63, $CHCl_3$); IR ($CDCl_3$) 2940, 1590, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.33 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.88 (d, 1H, *J*=1.4 Hz, OCH_2O), 4.69 (d, 1H, *J*=9.1 Hz, H-4), 4.20 (d, 1H, *J*=5.6 Hz, H-1), 3.83 (m, 1H, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.77 (m, 1H, H-11), 3.17 (s, 3H, OCH_3), 3.05 (m, 2H, H-13), 2.16 (m, 2H, H-2, H-3), 1.61 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 530 $[M-H_2O+NH_4]^+$.

Compound **15**. Mp 150–152 °C (CH_2Cl_2); $[\alpha]_D^{20}=-199.5$ (*c* 0.75, $CHCl_3$); IR ($CDCl_3$) 3594 (OH), 2938, 1590, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, H-5), 6.37 (s, 1H, H-8), 6.18 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 4.31 (t, 1H, *J*=8.4 Hz, H-4), 4.10 (dd, 1H, *J*=11.6, 2.7 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 3.70 (m, 1H, H-11), 3.63 (m, 1H, H-13), 3.24 (m, 1H, H-13), 2.03 (m, 2H, H-2, H-3), 1.73 (d, 1H exch. D_2O, *J*=8.4 Hz, OH), 1.33 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); MS (DCI, NH_3) *m*/*z* 458 $[M-H_2O+NH_4]^+$.

4.1.4. Ketone 16. Dess–Martin periodinane (26 mg, 61.5 μmol) was added to a solution of **15** (23.5 mg, 51 μmol) in methylene chloride (2 mL) at rt. After 40 min, the mixture was diluted with methylene chloride (3 mL), then a 10% aqueous $NaHSO_3$ solution (2 mL) and a saturated aqueous saturated $NaHCO_3$ solution (2 mL) were added. The aqueous layer was extracted with methylene chloride, and the combined organic layers were dried

($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) led to ketone **16** (17.3 g, 74%) as a syrup; IR ($CDCl_3$) 2941, 1669, 1590, 1505, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H, H-5), 6.52 (s, 1H, H-8), 6.15 (s, 2H, H-2′, H-6′), 6.02 (s, 2H, OCH_2O), 4.42 (dd, 1H, J=12.6, 3.7 Hz, H-11), 4.20 (d, 1H, J=4.6 Hz, H-1), 3.84 (dd, 1H, J=12.6, 9.8 Hz, H-11), 3.83 (s, H, OCH_3-4′), 3.76 (s, 6H, OCH_3-3′,5′), 3.72 (dd, 1H, J=11.9, 3 Hz, H-13), 3.40 (dd, 1H, J=11.9, 10.4 Hz, H-13), 2.88 (m, 1H, H-3), 2.52 (m, 1H, H-2), 1.32 (s, 3H, CH_3), 1.22 (s, 3H, CH_3).

4.1.5. Aldehyde 17. Periodinane (374 mg, 0.885 mmol) was added to a solution of **13** (338 mg, 0.737 mmol) in methylene chloride (35 mL) at rt. After stirring for 30 min, the reaction mixture was poured into a 10% aqueous $NaHSO_3$ solution (25 mL) and a saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous layer was extracted with methylene chloride (25 mL), and the combined organic layers were washed with water (2×30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to aldehyde **17** (293 mg, 87%) as an amorphous solid; $[\alpha]_D^{20}=-116$ (c 0.05, $CHCl_3$); IR ($CDCl_3$) 2936, 1719, 1592, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, 1H, J=3.9 Hz, CHO), 7.01 (s, 1H, H-5), 6.37 (s, 1H, H-8), 6.23 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O),4.68 (d,1H, J=10 Hz, H-4), 4.40 (d, 1H, J=6.8 Hz, H-1), 3.94 (dd, 1H, J=11.5, 4.1 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.78 (s, 7H, OCH_3-3′,5′, H-11), 2.71 (m, 1H, H-2), 2.55 (m, 1H, H-3), 1.60 (s, 3H, CH_3), 1.55 (s, 3H, CH_3); MS (DCI, NH_3) m/z 457 $[M+H]^+$, 4.74 $[M+NH_4]^+$.

4.1.6. Vinyl 18. To a suspension of methyltriphenylphosphonium bromide (315 mg, 0.883 mmol) in tetrahydrofuran (4 mL) at −78 °C was added n-butyl lithium (2.5 M in hexane, 0.32 mL, 0.795 mol). After 5 min, a solution of **17** (80.6 mg, 0.177 mmol) in tetrahydrofuran (2 mL) was added and the resulting mixture was stirred at −78 °C for 45 min, quenched by addition of acetone (0.5 mL) and allowed to reach rt. Upon addition of methylene chloride (10 mL) and H_2O (10 mL), the aqueous layer was extracted with methylene chloride (10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:1) gave **18** (68.7 mg, 86%) as a syrup; $[\alpha]_D^{20}=-195.5$ (c 0.07, $CHCl_3$); IR ($CDCl_3$) 2926, 1592, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H, H-5), 6.36 (s, 1H, H-8), 6.19 (s, 2H, H-2′, 6′), 5.91 (d, 1H, J=1.4 Hz, OCH_2O), 5.89 (d, 1H, J=1.4 Hz, OCH_2O), 5.11–4.99 (m, 3H, 3H-vinyl), 4.67 (d, 1H, J=10.1 Hz, H-4), 4.03 (d, 1H, J=6.4 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.76 (s, 6H, OCH_3-3′,5′), 3.69–3.54 (m, 2H, H-11), 2.56 (m, 1H, H-2), 2.13 (m, 1H, H-3), 1.59 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) m/z 455 $[M+H]^+$, 4.72 $[M+NH_4]^+$.

4.1.7. Alcohol 19. A solution of 9-BBN (0.5 M in THF, 1.2 mL, 0.6 mmol) was added to a solution of **18** (53.1 mg, 0.117 mmol) in anhydrous THF (3 mL) and the reaction mixture was stirred for 3.5 h at rt prior to addition of pH 7.2 phosphate buffer (1.5 mL), methanol (4.5 mL) and a 35% (weight) aqueous solution of hydrogen peroxide (3 mL). After further stirring for 2.5 h, the mixture was diluted with methylene chloride (15 mL) and poured into water (10 mL). The aqueous layer was extracted with methylene chloride (15 mL), and the combined organic layers were washed with water (2×20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1, then 2:1) gave compound **19** (41 mg, 74%) as a syrup; $[\alpha]_D^{20}=-161.5$ (c 0.13, $CHCl_3$); IR ($CDCl_3$) 3690, 3629 (OH), 2934, 1590, 1505, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1H, H-5), 6.34 (s, 1H, H-8), 6.28 (s, 2H, H-2′, 6′), 5.88 (s, 1H, OCH_2O), 5.86 (s, 1H, OCH_2O), 4.67 (d, 1H, J=8.8 Hz, H-4), 3.90 (dd, 1H, J=11.3, 3.7 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.80–3.70 (m, 3H, H-11, H-14), 2.22–2.10 (m, 2H, H-2, H-3), 1.59 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.31 (m, 3H, H-13, OH); MS (DCI, NH_3) m/z 490 $[M+NH_4]^+$.

4.1.8. Aldehyde 20. Dess–Martin periodinane (34 mg, 81 μmol) was added to a solution of **19** (31.5 mg, 66.7 μmol) in methylene chloride (5 mL) at rt. After 1 h, a 10% aqueous $NaHSO_3$ solution (2.5 mL) and a saturated aqueous $NaHCO_3$ solution (2.5 mL) were added. The aqueous layer was extracted with methylene chloride (5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) provided **20** (28.9 mg, 92%) as a syrup; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 6.98 (s, 1H, H-5), 6.32 (s, 1H, H-8), 6.16 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, J=1.3 Hz, OCH_2O), 5.88 (d, 1H, J=1.3 Hz, OCH_2O), 4.72 (d, 1H, J=9.9 Hz, H-4), 4.16 (d, 1H, J=6.2 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 3.75–3.65 (m, 2H, H-11), 2.66 (m, 1H, H-2), 2.18 (d, 2H, J=6.8 Hz, H-13), 2.10 (m, 1H, H-3), 1.60 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); MS (DCI, NH_3) m/z 488 $[M+NH_4]^+$.

4.1.9. Hemiacetal 22. p-Toluene sulfonic acid monohydrate (8.7 mg, 0.046 mmol) was added to a suspension of podophyllol **11** (191 mg, 0.456 mmol) in benzaldehyde dimethylacetal (5 mL) at rt. After 40 min, the mixture was diluted with methylene chloride (20 mL) and poured into a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with methylene chloride (10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane then cyclohexane/EtOAc 95:5 then 90:10) gave **22** (210 mg, 73%) as a mixture of diastereoisomers at C-13 (ratio 60:40 from ^1H NMR data). Such a mixture was not purified further but, after MS control (DCI, NH_3 m/z 644 $[M+NH_4]^+$), engaged into the following step.

4.1.10. Alcohol 23. *From podophyllol* **11**. Benzaldehyde dimethylacetal (0.23 mL, 1.43 mmol) and p-toluenesulfonic acid monohydrate (22.7 mg, 0.12 mmol) were successively added to a suspension of podophyllol (500 mg, 1.19 mmol) in methylene chloride (30 mL). The reaction mixture was stirred for 10 min at rt, and then treated with a saturated aqueous $NaHCO_3$ solution (30 mL). After 30 min, the aqueous layer was extracted with methylene chloride (20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1 then 1:1 then 1:2)

successively afforded **22** (62 mg, 8%), **23** (224 mg, 37%) and **12** (153 mg, 32%).

From hemiacetal **22**. A solution of **22** (71 mg, 0.113 mmol) in a mixture of methylene chloride (6 mL), H_2O (0.6 mL) and acetic acid (0.6 mL) was stirred for 4 days at rt. After dilution with methylene chloride (10 mL), the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (15 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1) furnished **23** (37.7 mg, 66%) as a white solid. Mp 159–160 °C; $[\alpha]_D^{20}=-95.5$ (*c* 0.56, $CHCl_3$); IR ($CDCl_3$) 3621, 1590, 1505, 1484 cm^{-1}; ^1H NMR, (300 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2H, Ar–H), 7.44–7.38 (m, 3H, Ar–H), 7.10 (s, 1H, H-5), 6.38 (s, 3H, H-8, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 5.81 (s, 1H, CHPh), 4.69 (d, 1H, *J*=9.8 Hz, H-4), 4.37 (dd, 1H, *J*=10.8, 4.1 Hz, H-11), 4.22 (d, 1H, *J*=6 Hz, H-1), 3.87 (t, 1H, *J*=10.8 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 3.54 (m, 1H, H-13), 3.46 (m, 1H, H-13), 2.41 (m, 1H, H-3), 2.19 (m, 1H, H-2); MS (DCI, NH_3) *m/z* 524 $[M+NH_4]^+$; Anal. Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97. Found: C, 68.49; H, 6.01.

4.1.11. Aldehyde 24. Dess–Martin periodinane (2.9 g, 6.84 mmol) was added to a solution of **23** (2.31 g, 4.56 mmol) in methylene chloride (350 mL) at rt. After 20 min, a 10% aqueous $NaHSO_3$ solution (220 mL) and a saturated aqueous $NaHCO_3$ solution (220 mL) were added to the reaction mixture. After stirring for 30 min, the organic layer was washed with water (2×450 mL) and brine (450 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to **24** (1.95 g, 87%) as an amorphous solid; IR ($CDCl_3$) 2935, 1720, 1592, 1505, 1484 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.19 (d, 1H, *J*=3.3 Hz, CHO, 7.62–7.55 (m, 2H, Ar–H), 7.46–7.36 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.39 (s, 1H, H-8), 6.24 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.81 (s, 1H, CHPh), 4.65 (d, 1H, *J*=8.5 Hz, H-4), 4.45 (d, 1H, *J*=5.7 Hz, H-1), 4.40 (dd, 1H, *J*=11, 3.5 Hz, H-11), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′, 5′), 3.73 (t, 1H, *J*=11 Hz, H-11), 2.79–2.72 (m, 2H, H-2, H-3); MS (DCI, NH_3) *m/z* 505 $[M+H]^+$, 5.22 $[M+NH_4]^+$; Anal. Calcd for $C_{29}H_{28}O_8$: C, 69.04; H, 5.59. Found: C, 68.85; H, 5.62.

4.1.12. Vinyl 25. To a solution of methyltriphenylphosphonium bromide (1.03 g, 2.88 mmol) and anhydrous potassium carbonate (349.4 mg, 2.53 mmol) in tetrahydrofuran (20 mL) was added a solution of **24** (1.037 g, 2.055 mmol) in tetrahydrofuran (20 mL). The reaction mixture was refluxed for 19 h and, after cooling to rt, diluted with ethyl acetate (150 mL). The mixture was washed successively with 1 N HCl (50 mL), water (2×150 mL) and brine (150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:1 then 5:1) afforded **25** as a white crystalline solid (0.95 g, 92%). Mp 162–163 °C; $[\alpha]_D^{20}=-37.5$ (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) 2939, 1591, 1505, 1485 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H, Ar–H), 7.43–7.35 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.23 (s, 2H, H-2′, 6′), 5.93 (s, 2H, OCH_2O), 5.92 (m, 1H, H-vinyl), 5.72 (s, 1H, CHPh), 5.30 (br s, 1H, H-vinyl), 5.15 (br d, 1H, *J*=10.3 Hz, H-vinyl), 4.73 (d, 1H, *J*=10.6 Hz, H-4), 4.06–4.00 (m, 2H, H-1, H-11), 3.95 (t, 1H, *J*=10.4 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.53 (dd, 1H, *J*=8.9, 2.9 Hz, H-2), 2.39 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 520 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{30}O_7$: C, 71.70; H, 6.02. Found: C, 71.66; H, 6.07.

4.1.13. Alcohol 26. A solution of 9-BBN in THF (0.5 M, 10.8 mL, 5.4 mmol) was added to a solution of **25** (270 mg, 0.537 mmol) in anhydrous THF (25 mL) at rt. After stirring for 1.75 h, an aqueous solution of pH 7.2 phosphate buffer (8 mL), methanol (22 mL) and a 30% aqueous H_2O_2 solution (13.2 mL) were successively added to the reaction mixture. Further stirring was maintained for 3 h at rt, then the reaction mixture was diluted with ethyl acetate (40 mL). The aqueous layer was extracted with ethyl acetate (2×30 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) afforded **26** (223.6 g, 80%) as a syrup; IR ($CDCl_3$) 3614, 2933, 1590, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.56 (m, 2H, Ar–H), 7.42–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.23 (s, 2H, H-2′, 6′), 5.94 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.92 (m, 1H, *J*=1.3 Hz, OCH_2O), 5.76 (s, 1H, CHPh), 4.77 (d, 1H, *J*=10.6 Hz, H-4), 4.09–3.90 (m, 5H, H-1, H-11, H-14), 3.83 (s, 3H, OCH_3-4′), 3.78 (s, 6H, OCH_3-3′,5′), 2.47–2.33 (m, 1H, H-2), 2.05 (m, 1H, OH), 1.90–1.80 (m, 1H, H-3), 1.68–1.50 (m, 2H, H-13).

4.1.14. Aldehyde 27. Dess–Martin periodinane (810 mg, 1.91 mmol) was added to a solution of derivative **26** (506 mg, 0.972 mmol) in methylene chloride (150 mL) at rt. After 1 h, a 10% aqueous $NaHSO_3$ solution (50 mL) and a saturated aqueous $NaHCO_3$ solution (50 mL) were successively added to the reaction mixture. After further stirring for 15 min, the organic layer was washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) led to **27** (327.6 g, 65%) as a white foam; $[\alpha]_D^{20}=-10$ (*c* 0.25, $CHCl_3$); IR ($CDCl_3$) 2939, 1724, 1591, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H, CHO), 7.58–7.55 (m, 2H, Ar–H), 7.42–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.37 (s, 2H, H-2′, H-6′), 5.94 (s, 1H, OCH_2O), 5.93 (s, 1H, OCH_2O), 5.76 (s, 1H, CHPh), 4.69 (d, 1H, *J*=10.7 Hz, H-4), 4.03 (dd, 1H, H-1, *J*=10.9, 4 Hz, H-11), 3.93 (ls, 1H, H-1), 3.87 (t, 1H, *J*=10.9 Hz, H-11), 3.84 (s, 3H, OCH_3-4′), 3.84 (s, 6H, OCH_3-3′,5′), 3.81 (m, 1H, H-13), 2.72–2.60 (m, 2H, H-2, H-13), 2.46 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 536 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{30}O_8$: C, 69.49; H, 5.83. Found: C, 69.23; H, 5.86.

4.1.15. Carboxylic acid 28. Sulfamic acid (53.8 mg, 0.554 mmol) and sodium chlorite (49.2 mg, 0.435 mmol) were added to a suspension of **27** (205.3 mg, 0.396 mmol) in *tert*-butanol (16 mL) and H_2O (8 mL). The reaction mixture was stirred for 30 min at rt, at which point the reaction was poured into water (15 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc/AcOH 2:1:0.1) successively gave **28**

(161 mg, 76%) as a syrup and **29** (18 mg, 8%) as a white solid.

Compound **28**. $[\alpha]_D^{20}=0$ (*c* 0.5, $CHCl_3$); IR ($CDCl_3$) 3679, 2929, 1709, 1591, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2H, Ar–H), 7.42–7.36 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.33 (s, 2H, H-2′, H-6′), 5.95 (s, 1H, OCH_2O), 5.94 (s, 1H, OCH_2O), 5.76 (s, 1H, CHPh), 4.69 (d, 1H, *J*=10.5 Hz, H-4), 4.05 (m, 1H, H-11), 4.05 (br s, 1H, H-1), 3.92 (t, 1H, *J*=10.9 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.66–2.43 (m, 4H, H-2, H-3, H-13); MS (DCI, NH_3) *m/z* 552 $[M+NH_4]^+$.

Compound **29**. Mp 131–133 °C; $[\alpha]_D^{20}=0$ (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) 3680, 2939, 1709, 1573, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H, Ar–H), 7.41–7.37 (m, 3H, Ar–H), 7.11 (s, 1H, H-5), 6.41 (s, 1H, H-8), 5.99 (s, 1H, H-6′), 5.95 (s, 1H, OCH_2O), 5.94 (s, 1H, OCH_2O), 5.77 (s, 1H, CHPh), 4.76 (d, 1H, *J*=10.5 Hz, H-4), 4.44 (br s, 1H, H-1), 4.08 (dd, 1H, *J*=10.9, 3.8 Hz, H-11), 3.97 (s and partially overlapped m, 4H, OCH_3, H-11), 3.86 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3) 2.73–2.41 (m, 4H, H-2, H-3, H-13); MS (DCI, NH_3) *m/z* 569 $[M+H]^+$, 586 $[M+NH_4]^+$.

4.1.16. Homolactone 4. CSA (34 mg, 0.146 mmol) was added to a solution of acid **28** (71.1 mg, 0.133 mmol) in THF (4 mL) and water (0.4 mL) at rt. The reaction mixture was heated at 80 °C for 6 h, then allowed to cool to rt. After dilution with ethyl acetate (10 mL) and water (5 mL), the aqueous layer was extracted with ethyl acetate (5 mL), and the organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 1:1) furnished **4** (37.5 mg, 66%) as a white solid. Mp 171–172 °C; $[\alpha]_D^{20}=+9.5$ (*c* 0.27, $CHCl_3$); IR ($CDCl_3$) 3624, 2939, 1739, 1592, 1504, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H, H-5), 6.36 (s, 2H, H-2′, H-6′), 6.29 (s, 1H, H-8), 5.93 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.92 (s, 1H, *J*=1.3 Hz, OCH_2O), 4.65 (d, 1H exch. with D_2O, *J*=8.2 Hz, H-4), 4.49 (m, 2H, H-11), 3.87 (s, 3H, OCH_3-4′), 3.83 (s, 6H, OCH_3-3′,5′), 3.52 (d, 1H, *J*=9.3 Hz, H-1), 2.67 (m, 1H, H-2), 2.58 (dd, 1H, *J*=16.2, 6.1 Hz, H-13), 2.41 (dd, 1H, *J*=16.2, 6.1 Hz, H-13), 2.39 (m, 1H, H-3); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$; Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.27; H, 5.69.

4.1.17. Mesylate 30. To a cooled 0 °C solution of **23** (530 mg, 1.046 mmol) in methylene chloride (50 mL), were added successively triethylamine (1.45 mL, 10.46 mmol) and methanesulfonyl chloride (0.410 mL, 5.27 mmol). After stirring for 30 min at 0 °C, the reaction mixture was quenched with water (50 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 2:1) gave **30** (604 mg, 99%) as a white foam; $[\alpha]_D^{20}=-114$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 2937, 1590, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H, Ar–H), 7.46–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.38 (s, 1H, H-8), 6.32 (s, 2H, H-2′, H-6′), 5.92 (s, 1H, OCH_2O), 5.91 (s, 1H, OCH_2O), 5.81 (s, 1H, CHPh), 4.70 (d, 1H, *J*=8.7 Hz, H-4), 4.28–4.24 (m, 1H, H-11), 4.03–3.88 (m, 3H, H-11, H-13), 3.84 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 2.97 (s, 3H, SO_2CH_3), 2.46 (m, 2H, H-2, H-3); MS (ES) *m/z* 607 $[M+Na]^+$.

4.1.18. Cyanide 31. A solution of sodium cyanide (25.8 mg, 0.526 mmol) in anhydrous dimethylformamide (15 mL) was added to a solution of mesylate **30** (153.7 mg, 0.263 mmol) ar rt. The reaction medium was heated at 85 °C for 6 h and, after cooling to rt, poured into water (75 mL). The mixture was extracted with ether (4×40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) gave **31** (129 mg, 95%) as a white solid; $[\alpha]_D^{20}=-175$ (*c* 0.88, $CHCl_3$); IR ($CDCl_3$) 2933, 1591, 1506, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H, Ar–H), 7.46–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.41 (br s, 3H, H-8, H-2′, H-6′), 5.93 (s, 1H, OCH_2O), 5.92 (s, 1H, OCH_2O), 5.79 (s, 1H, CHPh), 4.67 (d, 1H, *J*=9.1 Hz, H-4), 4.31 (d, 1H, *J*=5.3 Hz, H-1), 4.21 (dd, 1H, *J*=10.6, 3.8 Hz, H-11), 3.84 (s and overlapped m, 4H, OCH_3-4′, H-11), 3.81 (s, 6H, OCH_3-3′,5′), 2.40 (m, 2H, H-2, H-3), 2.22 (dd, 1H, *J*=16.5, 3.9 Hz, H-13), 1.88 (dd, 1H, *J*=16.5, 10.6 Hz, H-13); MS (DCI) *m/z* 533 $[M+NH_4]^+$; Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.67; N, 2.72. Found: C, 69.77; H, 5.71; N, 2.70.

4.1.19. Amide 32 and carboxylic acid 33. A solution of aqueous sodium hydroxide (6.25 M, 1.86 mL, 11.6 mmol) was added to a solution of **31** (143 mg, 0.277 mmol) in 95% ethanol (11 mL) at rt. The reaction mixture was heated at 80 °C for 7 h and then allowed to cool to rt. After quenching with 1 N HCl (11 mL), the reaction mixture was diluted with ethyl acetate (30 mL) and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 97:3) afforded **32** (123 mg, 83%) as a white solid. Prolonged reaction time (16 h) gave a mixture of **32** (24%) and **33** (47%).

Compound **32**. Mp 140–142 °C; $[\alpha]_D^{20}=-118$ (*c* 1.02, $CHCl_3$); IR ($CDCl_3$) 3523, 3408 (NH_2), 2939, 1683, 1595, 1590, 1595, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H, Ar–H), 7.45–7.27 (m, 3H, Ar–H), 7.08 (s, 1H, H-5), 6.34 (s, 2H, H-8), 6.28 (s, 2H, H-2′, H-6′), 5.90 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.89 (d, 1H, *J*=1.4 Hz, OCH_2O), 5.78 (s, 1H, CHPh), 5.38 and 5.33 (2 br s, 2H exch. D_2O, NH_2), 4.71 (d, 1H, *J*=9.7 Hz, H-4), 4.28 (d, 1H, *J*=6.1 Hz, H-1), 4.20 (dd, 1H, *J*=10.9, 4.2 Hz, H-11), 3.83 (s, 3H, OCH_3-4′), 3.77 (s and overlapped m, 7H, OCH_3-3′,5′, H-11), 2.71 (m, 1H, H-2), 2.32 (m, 1H, H-3), 2.01 (dd, 1H, *J*=16.3, 4.9 Hz, H-13), 1.82 (dd, 1H, *J*=16.3, 9.6 Hz, H-13); MS (DCI) *m/z* 551 $[M+NH_4]^+$.

Compound **33**. $[\alpha]_D^{20}=-130.5$ (*c* 0.78, $CHCl_3$); IR ($CDCl_3$) 3522, 3400–2500, 2939, 1708, 1590, 1505, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.621–7.57 (m, 2H, Ar–H), 7.44–7.39 (m, 3H, Ar–H), 7.09 (s, 1H, H-5), 6.35 (s, 2H, H-8), 6.23 (br s, 2H, H-2′, H-6′), 5.90 (br s, 2H, OCH_2O), 5.78 (s, 1H, CHPh), 4.69 (d, 1H, *J*=9.7 Hz, H-4), 4.22 (m, 2H, H-1, H-11), 3.83 (s, 3H, OCH_3-4′), 3.76 (s and overlapped m, 7H, OCH_3-3′,5′, H-11), 2.58 (m, 1H, H-2), 2.33 (m, 1H, H-3), 2.13 (m, 2H, H-13); MS (DCI, NH_3) *m/z* 552 $[M+NH_4]^+$.

4.1.20. Homolactones 5, 6 and 36. CSA (161 mg, 0.693 mmol) was added to a solution of amide **32** (246 mg, 0.462 mmol) in THF (15 mL) and water (15 mL) at rt. The reaction mixture was heated at 85 °C for 17 h, then allowed to cool to rt. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 6:4 then 1:1) gave **5** (55.4 mg, 28%), **6** (14 mg, 7%) and **36** (26 mg, 13%) as amorphous solids.

Compound **5**. $[\alpha]_D^{20}=118$ (*c* 0.77, $CHCl_3$); IR ($CDCl_3$) 3610, 2927, 1733, 1590, 1505, 1595, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H, H-5), 6.43 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.95 (s, 2H, OCH_2O), 4.79 (dd, 1H, *J*=11.3, 5.3 Hz, H-11), 4.51 (br t, 1H, *J*=7.6 Hz, H-4), 4.18 (dd, 1H, *J*=11.3, 10.1 Hz, H-11), 3.92 (d, 1H, *J*=5.4 Hz, H-1), 3.83 (s, 3H, OCH_3-4′), 3.79 (s, 6H, OCH_3-3′,5′), 2.62 (dd, 1H, *J*=17.4, 12, 5.6 Hz, H-13), 2.51–2.39 (m, 1H, H-2), 2.37–2.25 (m, 1H, H-3), 2.19 (d, 1H exch. with D_2O, *J*=7.6 Hz, OH), 2.09 (dd, 1H, *J*=17.4, 11.7 Hz, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$; Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.36; H, 5.67.

Compound **6**. IR ($CDCl_3$) 3597, 2927, 1733, 1506, 1595, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.06 (s, 2H, H-2′, H-6′), 5.96 (s, 1H, OCH_2O), 5.95 (s, 1H, OCH_2O), 4.76 (br s, 1H, H-4), 4.58–4.50 (m, 2H, H-11), 4.03 (d, 1H, *J*=6.2 Hz, H-10), 3.82 (s, 3H, OCH_3-4′), 3.77 (s, 6H, OCH_3-3′,5′), 2.90–2.80 (m, 1H, H-2), 2.67 (dd, 1H, *J*=17.8, 6.4 Hz, H-13), 2.40–2.30 (m, 1H, H-3), 2.08 (dd, 1H, *J*=17.8, 11.6 Hz, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$.

Compound **36**. $[\alpha]_D^{20}=-11.5$ (*c* 0.65, $CHCl_3$); IR ($CDCl_3$) 3608, 2927, 1735, 1590, 1504, 1485, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.48–6.10 (m, 2H, H-2′, H-6′), 5.97 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.95 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.24 (t, 1H, *J*=2.4 Hz, H-4), 4.28 (d, 1H, *J*=5.8 Hz, H-l), 3.86 (s, 3H, OCH_3-4′), 3.83–3.73 (m, 8H, OCH_3-3′,5′, H-11), 2.83 (m, 1H, H-3), 2.65–2.59 (m, 1H, H-2), 2.50–2.45 (m, 2H, H-13); MS (DCI, NH_3) *m/z* 446 $[M+NH_4]^+$.

4.1.21. 4′-*tert*-Butyldimethylsilanyloxy-podophyllol 39. To a suspension of $LiAlH_4$ (134 mg, 3.53 mmol) in THF (12 mL) cooled to 0 °C was added alcohol **38** (227 mg, 0.441 mmol) in solution in THF (7 mL). After 1.5 h at 0 °C, water (0.140 mL), a 25% NaOH aqueous solution (0.140 mL), and water (0.420 mL) were successively added to the reaction mixture. The precipitate was eliminated by filtration, and the filtrate was diluted with ethyl acetate (25 mL) and washed with Rochelle's salt saturated water (25 mL). The organic layer was washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue, often directly used for the following reactions, could also be purified by flash chromatography (cyclohexane/EtOAc 1:2, 1:4), leading to **39** (117.4 mg, 51%) as a white solid. Mp 180–181 °C; $[\alpha]_D^{20}=-98.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3600–3200, 2936, 1587, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H, H-5), 6.41 (s, 1H, H-8), 6.12 (s, 2H, H-2′, H-6′), 5.93 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.91 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.96 (d, 1H, *J*=3.1 Hz, H-4), 4.18 (d, 1H, *J*=5.5 Hz, H-1), 4.05 (dd, 1H, *J*=12, 1.9 Hz, H-11), 3.93 (dd, 1H, *J*=12, 4.1 Hz, H-11), 3.77 (dd, 1H, *J*=11, 4 Hz, H-13), 3.68 (s, 6H, OCH_3-3′,5′), 3.64 (m, 1H exch. with D_2O, OH), 3.46 (dd, 1H, *J*=11, 6.8 Hz, H-13), 3.08 (m, 1H exch. with D_2O, OH), 2.10 (m, 1H, H-3), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.10 (s, 6H, $(CH_3)_2Si$); MS (ES) *m/z* (%) 541 $[M+Na]^+$.

4.1.22. (1α,2α,3β,4β)-4,11-*O*-Isopropylidene-4′-*tert*-butyldimethylsilanyloxy)-podophyllol 40. Monohydrated *p*-toluenesulfonic acid (51.1 mg, 0.269 mmol) was added to a solution of crude **39** (1.39 g, 2.68 mmol) in 2,2-dimethoxypropane (125 mL). After 35 min at rt, the reaction mixture was concentrated under reduced pressure until it reached a volume of 50 mL. A saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (100 mL) were then added. The organic layer was washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure, affording a crude residue (1.65 g) as a beige foam, which was poured into methanol (85 mL). Water (1.2 mL) and acetic acid (1.2 mL) were then added. Stirring was maintained for 6 h at rt before addition of a saturated aqueous $NaHCO_3$ solution (35 mL) and ethyl acetate (100 mL). In order to obtain decantation, brine (100 mL) was added. The aqueous layer was extracted with ethyl acetate (80 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 4:1) afforded acetonide **40** (901 mg, 60%) as a white foam; $[\alpha]_D^{20}=-50$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3564, 2931, 1586, 1506, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H, H-5), 6.43 (s, 1H, H-8), 6.22 (s, 2H, H-2′, H-6′), 5.92 (d, 1H, *J*=1.3 Hz, OCH_2O), 5.87 (d, 1H, *J*=1.3 Hz, OCH_2O), 4.94 (d, 1H, *J*=3.6 Hz, H-4), 4.20 (d, 1H, *J*=5.4 Hz, H-l), 4.07 (dd, 1H, *J*=12.3, 4.3 Hz, H-11), 3.89 (dd, 1H, *J*=12.3, 3.5 Hz, H-11), 3.82 (dt, 1H, $J_{gem}=11.7$ Hz, $J_{13,2}=J_{13,OH}=3$ Hz, H-13), 3.70 (s, 6H, OCH_3-3′,5′), 3.63 (m, 1H, H-13), 2.76 (m, 1H, H-2), 2.06 (m, 1H, H-3), 1.63 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.90 (dd, 1H exch. with D_2O, *J*=3, 9 Hz, OH), 0.10 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 559 $[M+H]^+$; Anal. Calcd for $C_{30}H_{42}O_7Si$: C, 64.49; H, 7.58. Found: C, 64.28; H, 7.59.

4.1.23. Cyanide 44. Triethylamine (4 mL, 28.62 mmol) and methanesulfonyl chloride (0.57 mL, 7.182 mmol) were added to a solution of **40** (800 mg, 1.431 mmol) in methylene chloride (60 mL), cooled to 0 °C. After 50 min at 0 °C, water (60 mL) and methylene chloride (100 mL) were poured into the reaction mixture. The organic layer was washed with brine, acidified with 1 N HCl until pH 2, neutralized with water, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude mesylate **43** (939.6 mg). The latter was dissolved into anhydrous DMF (80 mL), and sodium cyanide (143.1 mg, 2.916 mmol) was added. The mixture was heated at 85 °C for 5 h, then allowed to reach rt. The reaction mixture was then poured into water (300 mL), the aqueous layer was extracted with ethyl acetate (3×150 mL) [Bad decantation can be remedied by addition of brine into the emulsion]. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining DMF traces were

eliminated by evaporation under high vacuum. Flash chromatography (cyclohexane/EtOAc 2:1) gave cyanide **44** (345.6 mg, 53% for the two steps) as a syrup; IR ($CDCl_3$) 3540, 2940, 1619, 1519, 1505, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H, H-5), 6.46 (s, 1H, H-8), 6.31 (br s, 2H, H-2′, H-6′), 5.94 (d, 1H, J=1.3 Hz, OCH_2O), 5.90 (d, 1H, J=1.3 Hz, OCH_2O), 5.44 (s, 1H exch. with D_2O, OH), 4.93 (d, 1H, J=3.6 Hz, H-4), 4.34 (d, 1H, J=5.1 Hz, H-1), 4.06 (dd, 1H, J=12.6, 4.1 Hz, H-11), 3.81 (s, 6H, OCH_3-3′, 5′), 3.68 (dd 1H, J=12.6, 3.4 Hz H-11), 3.04 (m, 1H, H-2), 2.56 (dd, 1H, J=16.5, 3.5 Hz, H-13), 1.94 (m, 1H, H-3), 1.87 (dd, 1H, J=16.5, 12 Hz, H-13), 1.62 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); MS (DCI, NH_3) m/z 471 $[M+NH_4]^+$.

4.1.24. Amide 45. A 6.25 M sodium aqueous solution (0.181 mL, 1.13 mmol was added to a solution of **44** (12.2 mg, 26.9 mmol) in ethanol. The reaction mixture was heated at 75 °C for 28 h. After cooling, the mixture was neutralized with 1 N HCl. The aqueous layer was extracted with ethyl acetate (2×8 mL), and the combined organic layers were washed with brine (2×10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 97:3) gave **45** (5.8 mg, 44%) as a syrup; IR ($CDCl_3$) 3694, 3527, 3409, 2926, 1681, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.91 (d, 1H, J=1.3 Hz, OCH_2O), 5.87 (d, 1H, J=1.3 Hz, OCH_2O), 5.55 (br s, 1H exch. with D_2O, NH), 5.39 (s, 1H (d, 1H exch. with D_2O, OH), 5.35 (br s, 1H exch. with D_2O, NH), 4.92 (d, 1H, J=3.9 Hz, H-4), 4.34 (d, 1H, J=5 Hz, H-1), 4.01 (dd, 1H, J=12.3, 4.9 Hz, H-11), 3.80 (s, 6H, OCH_3-3′,5′), 3.74 (dd, 1H, J=12.3, 4.5 Hz, H-11), 3.03 (m, 1H, H-2), 2.30 (dd, 1H, J=15.7, 3.8 Hz, H-13), 2.01 (m, 1H, H-3), 1.86 (dd, 1H, J=15.7, 10.9 Hz, H-13), 1.62 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); MS (DCI, NH_3) m/z (%) 489 $[M+NH_4]^+$.

4.1.25. Homolactones 7 and 8. *From cyanide* **44**. A solution of nitrile **44** (105 mg, 0.172 mmol) in 95% ethanol (14 mL) containing a 25% aqueous NaOH solution (1.15 mL, 7.2 mmol) was heated at 85 °C for 7 h. After cooling to rt, the reaction mixture was neutralized with 1 N HCl (7.2 mL) (the bright yellow color disappeared). A small excess of 1 N HCl (0.5 mL) was added to obtain pH 3–4, and after 10 min the mixture was poured into ethyl acetate (30 mL) and water (10 mL). The aqueous layer was extracted twice with ethyl acetate (2×10 mL), and the combined organic layers were stirred for 15 h, then washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:2 then 97:3) afforded **7** (36.2 mg, 51%) as a white powder and **8** (8.5 mg, 12%) as a syrup.

From amide **45**. *p*.Toluenesulfonic acid (23 mg, 0.12 mmol) was added to a solution of **45** (48.6 mg, 0.1 mmol) in THF (5 mL) and water (0.5 mL). The reaction mixture was heated at 45 °C for 7 h and subsequently poured into brine (3 mL) and ethyl acetate (5 mL). The aquous layer was extracted twice with ethyl acetate (2×10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue (56.1 mg) in anhydrous methylene chloride (3 mL) was treated with camphorsulfonic acid (3.7 mg, 0.016 mmol). After 30 min (TLC control showed the disappearance of polar compounds), the reaction was diluted with methylene chloride (8 mL), washed with brine (8 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative chromatography on silica gel (methylene chloride/MeOH 95:5) led to **7** (12.8 mg, 31%) and to an inseparable mixture (7.2 mg) containing its 4-epimer **8** and the postulated bridged δ-lactone **46**.

Homolactone **7**. Mp 135–137 °C; $[\alpha]_D^{20}=-126$ (c 0.29, $CHCl_3$); IR ($CDCl_3$) 3544, 2917, 1734, 1619, 1519, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.07 (s, 2H, H-2′, H-6′), 5.95 (s, 2H, OCH_2O), 5.45 (s, 1H, exch. with D_2O, OH-4′), 4.75 (br s, 1H, H-4), 4.60–4.50 (m, 2H, H-11), 4.02 (d, 1H, J=6.1 Hz, H-1), 3.80 (s, 6H, OCH_3-3′,5′), 2.89–2.77 (m, 1H, H-2), 2.65 (dd, J=17.7, 6.3 Hz, H-13), 2.39–2.27 (m, 1H, H-3), 2.06 (dd, 1H, J=17.7, 11.3 Hz, H-13); HRMS (DCI, NH_3) m/z (%) Calcd: 415.1393 $[M+H]^+$. Found: 415.1384 $[M+H]^+$; Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.53; H, 5.31.

Homolactone **8**. IR ($CDCl_3$) 3541, 2898, 1729, 1620, 1517, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.22 (s, 2H, H-2′, H-6′), 5.94 (s, 2H, OCH_2O), 5.46 (s, 1H, exch. with D_2O, H-4′), 4.78 (dd, 1H, J=11.3, 5.3 Hz, H-11), 4.50 (br d, 1H, J=8.3 Hz, H-4), 4.18 (dd, 1H, J=11.3, 9.7 Hz, H-11), 3.91 (d, 1H, J=5.4 Hz, H-1), 3.83 (s, 6H, OCH_3-3′,5′), 2.60 (dd, 1H, J=17.5, 5.6 Hz, H-13), 2.49–2.37 (m, 1H, H-2), 2.34–2.24 (m, 1H, H-3), 2.07 (dd, 1H, J=17.5, 11.7 Hz, H-13); HRMS (DCI, NH_3) m/z (%) Calcd: 415.1393 $[M+H]^+$. Found 415.1386 $[M+H]^+$.

4.1.26. Cyanide 17. Imidazole (1.22 g, 8.94 mmol) and *tert*-butyldimethylsilyl chloride (1.35 g, 8.94 mmol) were added at rt to a solution of cyanide **44** (700 mg, 1.54 mmol) in anhydrous DMF (25 mL). After 2.5 h the reaction mixture was poured into water (100 mL) and ethyl acetate (50 mL) was added. The aqueous layer was extracted thrice (3×50 mL), and the combined organic layers were washed with brine (2×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) gave cyanide **47** (537 mg, 61%) as a white foam. IR ($CDCl_3$) 2932, 1587, 1506, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H, H-5), 6.47 (s, 1H, H-8), 6.25 (s, 2H, H-2′, H-6′), 5.94 (d, 1H, J=1.3 Hz, OCH_2O), 5.89 (d, 1H, J=1.3 Hz, OCH_2O), 4.92 (d, 1H, J=3.4 Hz, H-4), 4.31 (d, 1H, J=5.1 Hz, H-1), 4.05 (dd, 1H, J=12.5, 4.1 Hz, H-11), 3.72 (s, 6H, OCH_3-3′,5′), 3.68 (dd, 1H, J=12.5, 3.5 Hz, H-11), 3.02 (m, 1H, H-2), 2.53 (dd, 1H, J=16.4, 3.5 Hz, H-13), 1.95 (m, 1H, H-3), 1.84 (dd, 1H, J=16.4, 11.9 Hz, H-13), 1.62 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.11 (s, 6H, CH_3Si); MS (DCI, NH_3) m/z (%) 585 $[M+NH_4]^+$.

4.1.27. Cyanides 48 and 49. Monohydrated *p*-toluenesulfonic acid (3.4 mg, 0.0176 mmol) was added to a solution of **47** (100 mg, 0.176 mmol) in a mixture of THF (10 mL) and water (1 mL), and the reaction mixture was heated at 70 °C for 25 h. The mixture was then diluted with water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate (2×10 mL) and the combined organic layers

were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:1) furnished a mixture of **48** (27 mg, 29%) and **49** (33.8 mg, 36%).

Compound **48**. Mp 144–145 °C; $[\alpha]_D^{20}=-182$ (*c* 0.59, $CHCl_3$); IR ($CDCl_3$): 3616, 2932, 1587, 1505, 1485 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.49 (s, 1H, H-8), 6.24 (s, 2H, H-2′, H-6′), 5.96 (d, 1H, *J*=1.1 Hz, OCH_2O), 5.95 (d, 1H, *J*=1.1 Hz, OCH_2O), 4.97 (t, 1H, *J*=3.7 Hz, H-4), 4.38 (d, 1H, *J*=5.3 Hz, H-1), 4.05 (br d, 1H, *J*=12 Hz, H-11), 3.71 (s, 6H, OCH_3-3′,5′), 3.67 (m, 1H, H-11), 3.05–2.90 (m, 2H, H-2, H-3), 2.79 (dd, 1H, *J*=16.3, 3.6 Hz, H-13), 2.09 (d, 1H exch. with D_2O, *J*=3.7 Hz, OH-4), 2.06 (m, 1H exch. with D_2O, OH-11), 1.85 (dd, 1H, *J*=16.3, 11.8 Hz, H-13), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.10 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 545 $[M+NH_4]^+$.

Compound **49**. Mp 100–102 °C; $[\alpha]_D^{20}=-215.5$ (*c* 0.66, $CHCl_3$); IR ($CDCl_3$): 3628, 2932, 1588, 1503, 1485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H, H-5), 6.45 (s, 1H, H-8), 6.39 (s, 2H, H-2′, H-6′), 5.93 (s, 2H, OCH_2O), 4.80 (br d, 1H, *J*=8.4 Hz, H-4), 4.21 (d, 1H, *J*=4.6 Hz, H-1), 4.00 (br dd, *J*=10.6, 3.4 Hz, H-11), 3.73 (s, 6H, OCH_3-3′, 5′), 3.70 (m, 1H, H-11), 2.85 (br s, 1H exch. with D_2O, OH), 2.52 (dd, 1H, *J*=16.2, 4.3 Hz, H-13), 2.41 (m, 1H, H-2), 2.06 (m, 1H, H-3), 1.91 (dd, 1H, *J*=16.2, 10.7 Hz, H-13), 1.88 (m, 1H exch. with D_2O, OH), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.13 (s, 6H, $(CH_3)_2Si$); MS (DCI, NH_3) *m/z* (%) 545 $[M+NH_4]^+$.

4.1.28. Alcohol 51. A solution of **50**[41] (6.7 g, 10.65 mmol) in THF (200 mL) was cooled to 0 °C, and lithium aluminium hydride (0.61 g, 16 mmol) was slowly added. After 15 min at 0 °C, the reaction mixture was warmed to rt for 15 min. The reaction was quenched by successive additions of water (0.6 mL), a 15% NaOH aqueous solution (0.6 mL) and water (1.8 mL). The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) furnished diol **51** (6.22 g, 92%) as a white solid. Mp 156–158 °C (Lit.[37]: mp 160–162 °C); $[\alpha]_D^{20}=-50.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3688, 3573, 2938, 1586, 1505, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H, H-5), 6.40 (s, 1H, H-8), 6.21 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.01 (d, 1H, *J*=3.2 Hz, H-4), 4.16 (d, 1H, *J*=6.3 Hz, H-1), 3.85 (m, 2H, H-11), 3.70 (s, 6H, OCH_3-3′,5′), 3.67 (m, 2H, H-13), 2.66 (m, 1H, H-2), 2.32 (m, 1H, H-3), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.20 (s, 3H, CH_3Si), 0.11 (s, 6H, $(CH_3)_2Si$), −0.02 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 650 $[M+NH_4]^+$; Anal. Calcd for $C_{33}H_{52}O_8Si_2$: C, 62.62; H, 8.28. Found: C, 62.38, H, 8.25.

4.1.29. Pivaloyls 52 and 53, and bis-pivaloyl 54. To a solution of **51** (5.71 g, 9.02 mmol) in methylene chloride (325 mL) were added, at rt, triethylamine (6.3 mL, 435.3 mmol), 4-DMAP (110 mg, 0.9 mmol) and pivaloyl chloride (2.8 mL, 22.5 mmol). After 25 min, the reaction mixture was poured into water (300 mL) and acidified with 1 N HCl until pH 2–3. The aqueous layer was extracted twice with methylene chloride (2×100 mL), and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 9:1 then 8:2) successively gave **52** (4.2 g, 65%), **53** (1.75 g, 27%) and **54** (0.5 g, 8%) as foams.

Compound **52**. $[\alpha]_D^{20}=-30.5$ (*c* 1, $CHCl_3$); IR ($CDCl_3$) 3630, 2931, 1719, 1587, 1507, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.27 (s, 2H, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 4.93 (d, 1H, *J*=3.4 Hz, H-4), 4.32–4.25 (m, 2H, H-1, H-11), 4.15 (dd, 1H, *J*=11, 7.5 Hz, H-11), 3.70 (s, 6H, OCH_3-3′,5′), 3.60 (dd, 1H, *J*=11.3, 5 Hz, H-13), 3.42 (dd, 1H, *J*=11.3, 7.2 Hz, H-13), 2.59 (m, 1H, H-2), 2.49 (m, 1H, H-3), 1.20 (s, 9H, $(CH_3)_3CCO$), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.18 (s, 3H, CH_3Si), 0.12 (s, 6H, $(CH_3)_2Si$), 0.02 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 734 $[M+NH_4]^+$.

Compound **53**. IR ($CDCl_3$) 3629, 2930, 1718, 1603, 1507, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H, H-5), 6.46 (s, 1H, H-8), 6.18 (s, 2H, H-2′, H-6′), 5.92 (s, 2H, OCH_2O), 5.08 (d, 1H, *J*=4 Hz, H-4), 4.23 (d, 1H, *J*=6.1 Hz, H-1), 4.00–3.85 (m, 3H, H-11, H-13), 3.74 (m, 1H, H-13), 3.69 (s, 6H, OCH_3-3′,5′), 2.64 (m, 1H, H-2), 2.29 (m, 1H, H-3), 1.17 (s, 9H, $(CH_3)_3CCO$), 1.00 (s, 9H, $(CH_3)_3CSi$), 0.92 (s, 9H, $(CH_3)_3CSi$), 0.19 (s, 3H, CH_3Si), 0.13 (s, 6H, $(CH_3)_2Si$), 0.05 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 734 $[M+NH_4]^+$.

Compound **54**. IR ($CDCl_3$) 2932, 1722, 1587, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H, H-5), 6.42 (s, 1H, H-8), 6.15 (s, 2H, H-2′, H-6′), 5.91 (s, 2H, OCH_2O), 4.94 (d, 1H, *J*=3.3 Hz, H-4), 4.34 (dd, 1H, *J*=11.2, 6.6 Hz, H-11), 4.25 (d, 1H, *J*=5.8 Hz, H-1), 4.11 (dd, 1H, *J*=11.2, 7.6 Hz, H-11), 3.94 (dd, 1H, *J*=11.4, 6.3 Hz, H-13), 3.83 (dd, 1H, *J*=11.4, 7.6 Hz, H-13), 3.68 (s, 6H, OCH_3-3′,5′), 2.74 (m, 1H, H-2), 2.42 (m, 1H, H-3), 1.19 (s, 9H, $(CH_3)_3CCO$), 1.16 (s, 9H, $(CH_3)_3CCO$), 0.99 (s, 9H, $(CH_3)_3CSi$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.17 (s, 3H, CH_3Si), 0.11 (s, 6H, $(CH_3)_2Si$), 0.00 (s, 3H, CH_3Si); MS (DCI, NH_3) *m/z* 818 $[M+NH_4]^+$.

4.1.30. Cyanide 56. To a solution of **52** (4.2 g, 5.86 mmol) in methylene chloride (300 mL) were added, at rt, triethylamine (4.1 mL, 29.3 mmol) and methanesulfonyl chloride (1.14 mL, 14.64 mmol). After 2 h, the reaction was poured into water (250 mL) and acidified with 1 N HCl until pH 2–3. The aqueous layer was extracted twice with methylene chloride (2×100 mL), and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Sodium cyanide (860 mg, 17.54 mmol) was added to a solution of the crude mesylate **55** (4.65 g) in anhydrous DMF (300 mL) at rt, and the mixture was heated to 85 °C for 24 h. After cooling to rt, the mixture was concentrated under reduced pressure until to obtain a residual volume of 20 mL. Addition of water (100 mL) to this residue was followed by extraction with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 3:1) led to **56** (1.95 g, 54%) as a foam. Mp 83–85 °C; $[\alpha]_D^{20}=-88$ (*c* 1.01, $CHCl_3$); IR ($CDCl_3$) 3540, 2931, 1724, 1519, 1505, 1485 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H, H-5), 6.44 (s, 1H, H-8), 6.29 (s, 2H, H-2′, H-6′), 5.93 (s, 2H, OCH_2O), 5.46 (s, 1H exch. with D_2O, OH), 4.93 (d, 1H, J=3.2 Hz, H-4), 4.39–4.34 (m, 2H, H-1, H-11), 4.03 (dd, 1H, J=11.2, 8 Hz, H-11), 3.82 (s, 6H, OCH_3-3′,5′), 2.89 (m, 1H, H-2), 2.45 (m, 1H, H-3), 2.38 (dd, 1H, J=16.7, 6 Hz, H-13), 1.87 (dd, 1H, J=16.7, 10.3 Hz, H-13), 1.16 (s, 9H, $(CH_3)_3CCO$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.22 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); MS (DCI, NH_3) m/z 629 $[M+NH_4]^+$.

4.1.31. Homolactones 7 and 8 from 56. A 25% aqueous NaOH solution (1.15 mL, 7.2 mL) was added to a solution of nitrile **56** (105 mg, 0.172 mmol) in 95% ethanol (14 mL). The reaction mixture was heated at 85 °C for 7 h. Ater cooling to rt, the mixture was neutralized with 1 N HCl (7.2 mL) until the bright yellow color disappeared. A small amount of 1 N HCl (0.5 mL) was added until pH 3–4. After stirring for 10 min at rt, the mixture was poured into ethyl acetate (30 mL) and water (10 mL). The aqueous layer was extracted twice (2×15 mL), and the combined organic layer was stirred for 15 h. The latter was then washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (methylene chloride/MeOH 98:2 then 97:3) led to **7** (36.2 mg, 51%) as a white powder and **8** (8.5 mg, 12%) as a syrup.

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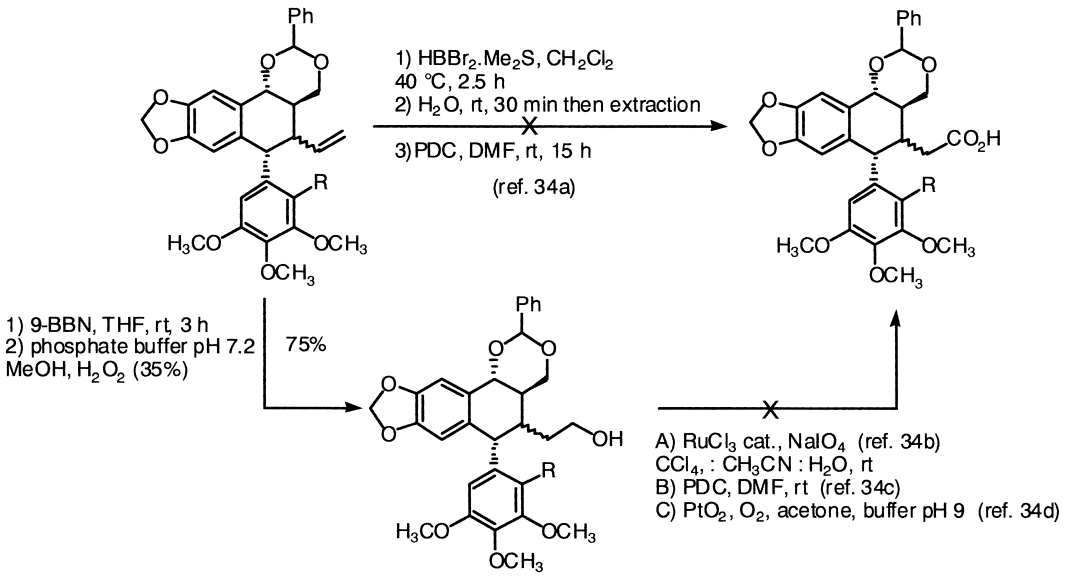

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