Radical-Mediated Synthesis of Racemic Deoxypodophyllotoxin and Related Lignans

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Dedicated with admiration to Professor Bernd Giese for his essential contribution to the development of radical chemistry

Abstract: An approach for the synthesis of lignans related to the podophyllotoxin family is reported. The key reaction is a highly diastereoselective iodoacetal cyclization under iodine atom transfer conditions followed by a homolytic aromatic substitution. The second aromatic ring is introduced at a later stage via addition of aryllithium to an aryl ketone. A novel and very mild method for the deoxygenation of the intermediate tertiary benzylic alcohols is described.

Key words: radicals, iodoacetals, lignans, podophyllotoxin, deoxygenation, benzylic alcohols

Podophyllotoxins are naturally occurring lignans that are found in plants of the genus podophyllum.[1,2] This class includes several closely related chemical structures such as podophyllotoxin (**1**),[3–5] deoxypodophyllotoxin (**2**)[6] and isodeoxypodophyllotoxin (iso-**2**) (Figure 1).[7] They also include some semi-synthetic compounds such as etoposide and teniposide, which are used in cancer therapy.[8–11] Podophyllotoxin itself serves as the starting material for the synthesis of both compounds as well as for the treatment of angogenital warts.[12] Podophyllotoxin causes inhibition of tubulin polymerization.[13] The binding sites on tubulin for colchicine and podophylloxin were found to overlap significantly. Deoxypodophyllotoxin is a cytotoxic and antineoplastic agent.[14,15] Finally, polygamain (**3**) and 1β-polygamain (1β-**3**) (Figure 1), two structurally closely related lignans isolated from *Polygala polygama* were found to have interesting antibacterial effect on *Staphylococcus aureus* and *E. coli*.[16–19] Here, we report the total synthesis of racemic deoxypodophyllotoxin (**2**),[20–22] isodeoxypodophyllotoxin (iso-**2**)[23–31] and dehydrodeoxypodophyllotoxin (**15**).[32] A mixture of diastereomeric polygamain (**3**) and 1β-polygamain (1β-**3**)[33] has also been prepared according to the same synthetic strategy to illustrate its flexibility.

The retrosynthetic analysis is described in Scheme 1. The aromatic substituent at C-7′ will be introduced by nucleophilic addition to the ketone **4** followed by deoxygenation of the benzylic alcohol. We plan to prepare the keto lactone **4** via a 5-*exo-trig* radical cyclization of the iodoacetal **5** under iodine atom transfer conditions (Ueno–Stork cyclization)[34] followed by a radical aromatic substitution[35,36]

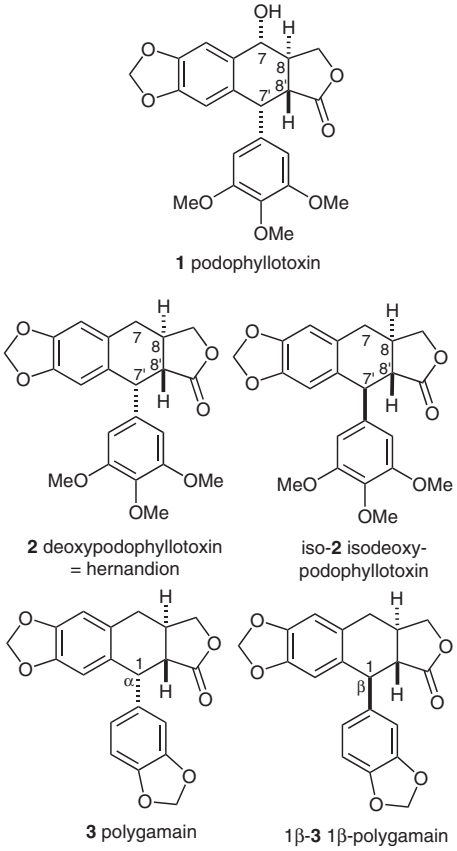

Figure 1 Naturally occurring podophyllotoxin and related lignans

and oxidation of the acetal to the corresponding lactone. The formation of the five- and six-membered rings in a single radical cascade process will be investigated. Based on previous studies with related systems, we expect that the 5-*exo-trig* cyclization should deliver the desired isomer having a *trans* relationship between the substitutents at C-8 and C-8′.[37,38] Moreover, a related cascade process involving a radical aromatic substitution was recently used by Zard in an elegant synthesis of lycorane.[39] The iodoacetal **5** should be easily prepared from commercially available piperonyloyl chloride (**6**).

Conversion of piperonyloyl chloride (**6**) into the desired iodide **9** is achieved according to standard procedures (Scheme 2) by first converting the acyl chloride **6** into the Weinreb amide **7**, followed by its reaction with the *Z*-lithiated enol ether [prepared from *t*-BuLi and the (*Z*)-(2-bro-

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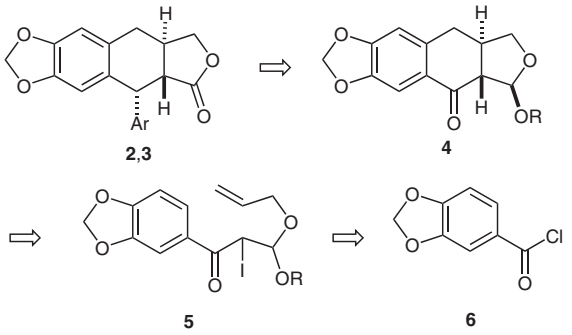
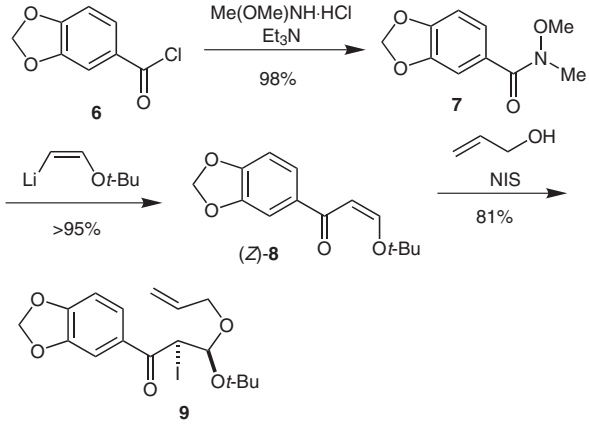


Scheme 1

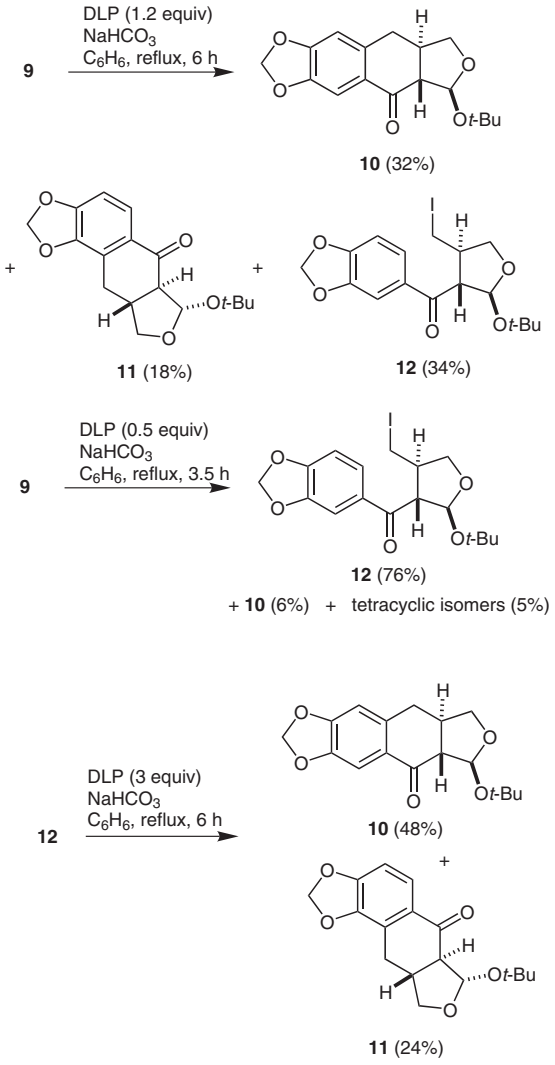
movinyl) *tert*-butyl ether]. The enol ether (*Z*)-**8** gives the iodoacetal **9** as a single diastereomer upon treatment with allyl alcohol and *N*-iodosuccinimide (NIS).[40]



Scheme 2

The cyclization cascade was then investigated (Scheme 3). Under treatment with a stoichiometric amount of dilauroyl peroxide (DLP), the desired tetracyclic compound **10** is isolated in 32% yield together with the regioisomer **11** (18%) and the product of monoyclization **12** (34%). It is, however, difficult to isolate **10** from the reaction mixture due to the presence of isomeric side products (presumably 8,8′-*cis* isomers). Interestingly, this problem is solved by running the two cyclizations separately. Treatment of **10** with 0.5 equivalent of DLP affords the monocyclic iodide **12** in 76% yield as a single diastereomer together with **10** (6%) and a small amount of isomeric tetracyclic products.[36] The monocyclized product **12** is easily separated for the other tetracyclic isomers by flash chromatography. Upon treatment of **12** with 3 equivalents of DLP in refluxing benzene, a clean conversion to **10** (48%) and **11** (24%) is obtained. As predicted, the cyclization process is highly stereoselective for the formation of all *trans* tetrahydrofuran moiety. The aromatic substitution is only moderately regioselective.

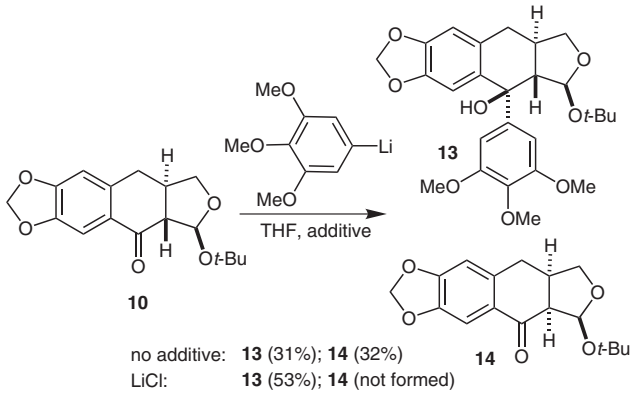
Introduction of the 3,4,5-trimethoxyphenyl group was investigated next (Scheme 4). Addition of 3,4,5-trimethoxyphenyllithium (prepared form the corresponding bromide by treatment with *n*-BuLi) affords the desired al-



Scheme 3

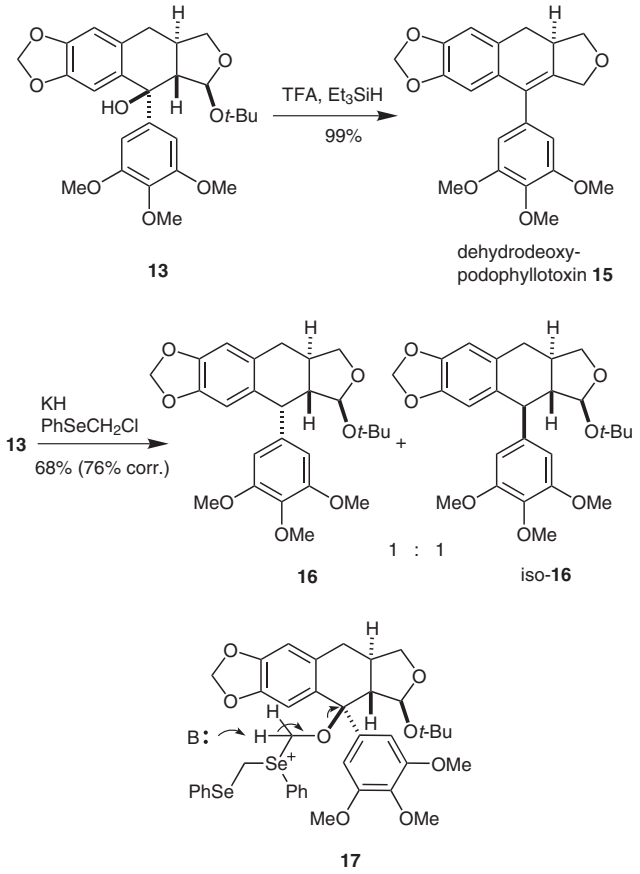
cohol **13** in low yield (31%) together with the epimerized 8,8-*cis* derivative **14** (32%). Attempt to use an organocerium(III) derivative did not lead to any improvement of the yield. Finally, it was found that running the reaction in the presence of LiCl[41] as an additive eliminates completely the isomerization process and affords the alcohol **13** as a single diastereomer in 53%.

A first attempt to deoxygenate the benzylic alcohol **13** with triethylsilane in the presence of trifluoroacetic acid afforded the cyclic ether dehydrodeoxypodophyllotoxin (**15**) in nearly quantitative yield. Dehydrodeoxypodophyllotoxin is a known compound showing similar cytotoxic effects on cancer cells as podophyllotoxin (**1**) itself.[32] All attempts to deoxygenate **13** to **16** failed with the exception of the Barton deoxygenation process[42] (i. KH, CS_2, MeI; ii. Bu_3SnH, AIBN) that gave traces of the desired reduced product **16**. Unexpectedly, we discovered that treatment of the alcohol **13** with KH and chloromethyl phenyl selenide affords the desired deoxygenated product **16** in 68% isolated yield (76% based on recovered starting material) as a 1:1 mixture of diastereomers. The scope and limitations of this new process is still under investigation



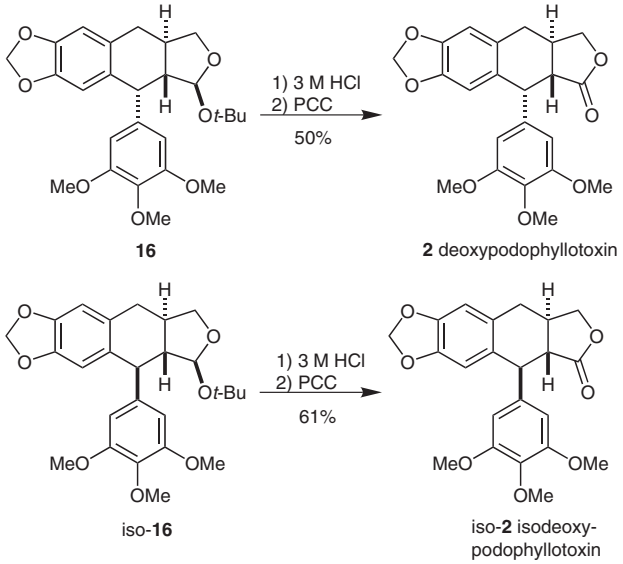
Scheme 4

and will be published elsewhere. The mechanism involves most probably a base promoted decomposition of the selenonium salt **17** (Scheme 5). The two diastereomers, **16** and iso-**16** were separated by flash chromatography and used for the synthesis of deoxypodophyllotoxin (**2**) and isodeoxypodophyllotoxin (iso-**2**), respectively.



Scheme 5

The final steps of the synthesis of deoxypodophyllotoxin (**2**) and isodeoxypodophyllotoxin (iso-**2**) are presented in Scheme 6. Direct Jones oxidation of the acetals **16** and iso-**16** leads to degradation products. Therefore, a two-step procedure involving hydrolysis with 3 M HCl of the cyclic acetal to a lactol followed by oxidation with pyridinium chlorochromate (PCC) gives deoxypodophyllotoxin (**2**) and isodeoxypodophyllotoxin (iso-**2**) in 50 and 61% yield, respectively.[31] Conversion of deoxypodophyllotoxin (**2**) into podophyllotoxin (**1**) and epipodophyllotoxin via microbial oxidation has been reported.[43] Therefore, the synthesis of **2** represents also a formal synthesis of podophyllotoxin (**1**).

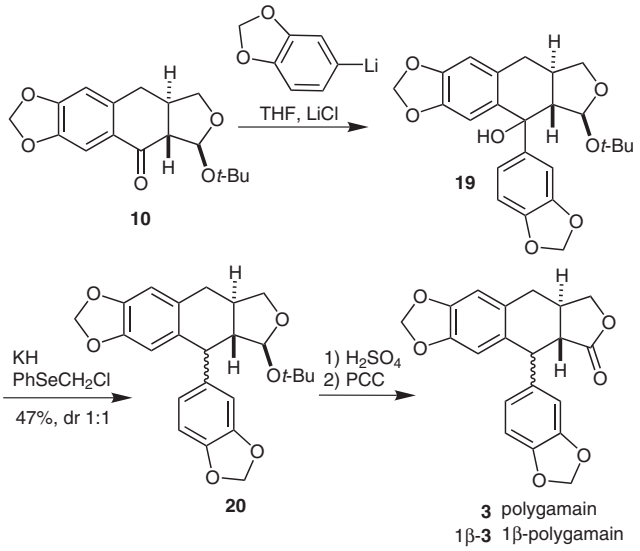


Scheme 6

The synthesis of polygamain (**3**) from the ketone intermediate **10** is described in Scheme 7. Treatment of the ketone with 3,4-methylenedioxyphenyllithium/LiCl gives the tertiary alcohol **19** in 74% yield. Reaction of **19** with $PhSeCH_2Cl/KH$ furnished the deoxygenated product **20** as a 1:1 mixture of diastereomers. The mixture of **20** and 1β-**20** was treated with H_2SO_4 in THF) to hydrolyze the acetal. Oxidation of the lactol with PCC afforded a mixture of polygamain (**3**) and 1β-polygamain (1β-**3**) respectively.

In conclusion, we have developed a versatile method for the synthesis of polycyclic lignans of the podophyllotoxin family. The reaction sequence is short and the second aromatic ring is introduced at the end of the synthesis allowing the easy preparation of analogues. An excellent stereocontrol for the formation of the *trans* lactone is observed and no epimerization was noticed during the reaction sequence. Extension of the procedure for the preparation of optically pure material should be possible by using a chiral auxiliary control of the acetal center.[37,44–46]

THF, Et_2O, CH_2Cl_2, benzene and toluene were dried by filtration under argon through dried Al_2O_3 columns. Other reagents were obtained from commercial sources and used as received. Flash column chromatography (FC) and filtration: Baker silica gel (0.063–0.200 mm); EtOAc, Et_2O, CH_2Cl_2 and hexane as eluents. TLC: Merck silica gel 60 F_{254} analytical plates; detection either with UV or by spraying with a solution of vanillin or a solution of phosphomolyb-



Scheme 7

dic acid (25 g), $Ce(SO_4)_2{\cdot}4H_2O$ (10 g), concd H_2SO_4 (60 mL) and H_2O (940 mL) with subsequent heating. FT-IR: Mattson Unicam 5000 and Perkin-Elmer 1600. NMR: Varian Gemini 200 (^1H = 200 MHz, ^{13}C = 50.3 MHz), Bruker AM 360 (^1H = 360 MHz, ^{13}C = 90.5 M), Bruker Avance DRX 500 (^1H = 500.13 MHz, ^{13}C = 125.8 MHz); Bruker DRX 400 (^1H = 400 MHz, ^{13}C = 100.6 MHz), Bruker Avance DRX 300 (^1H = 300 MHz); chemical shift in ppm relative to tetramethylsilane (0 ppm) or $CHCl_3$ (7.26 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. MS: Vacuum Generators Micromass VG 70/70E, DS 11-250 and VG Autospec; CI (CH_4), EI (70 eV); *m*/*z* (%). High resolution mass spectra (HRMS) were recorded on a FTICR mass spectrometer Bruker 4.7 BioApex II and VG Autospec.

Benzo[1,3]dioxole-5-carboxylic Acid Methoxymethylamide (7)

To a solution of piperonyloyl chloride (**6**; 25 g, 135 mmol) in CH_2Cl_2 (1.35 L) was added *N*,*O*-dimethylhydroxylamine hydrochloride (14.5 g, 149 mmol) under N_2. The mixture was cooled to 0 °C and Et_3N (41.5 mL, 297 mmol) was added dropwise. After complete addition of Et_3N, the reaction mixture was stirred for 2 h at 0 °C and 1 h at r.t., and the solvent was removed under reduced pressure. The residue was partitioned between brine and a 1:1 mixture of Et_2O and CH_2Cl_2. The aqueous layer was extracted twice with a 1:1 mixture of Et_2O and CH_2Cl_2 (2 ×). The combined organic phases were washed with 1 M HCl, aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo to afford 28 g (98%) of **7** as a colorless liquid.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 8.1, 1.8 Hz, 1 H_{arom}), 7.22 (d, *J* = 1.8 Hz, 1 H_{arom}), 6.82 (d, *J* = 8.1 Hz, 1 H_{arom}), 6.01 (s, 2 H, CH_2), 3.57 (s, 3 H, CH_3), 3.34 (s, 3 H, CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4 (s), 150.0 (s), 147.5 (s), 127.9 (s), 124.0 (d), 109.5 (d), 108.2 (d), 101.8 (t), 61.3 (q), 34.3 (q).

EI–MS: *m*/*z* (%) = 209 (M^+, 11), 149 (100), 121 (28), 91 (12), 65 (33), 63 (29).

HRMS (EI-MS): *m*/*z* calcd for $C_{10}H_{11}NO_4$ (M^+): 209.0688; found: 209.0688.

(*Z*)-1-Benzo[1,3]dioxol-5-yl-3-*tert*-butoxypropenone [(*Z*)-8]

To a solution of (*Z*)-1-bromo-2-*tert*-butoxyethene[47] (2.56 g, 14.3 mmol) in anhyd THF (72 mL) was added *t*-BuLi (1.5 M solution in pentane, 19 mL, 28.6 mmol) at –78 °C and then the Weinreb amide **7** (1.00 g, 4.78 mmol) dissolved in THF (18 mL) was added dropwise. The solution was stirred for 30 min. Aq sat. NH_4Cl was added and the mixture was allowed to warm up to r.t. After extraction with Et_2O, the organic layers were dried ($MgSO_4$), and the solvent was evaporated to give (*Z*)-**8** (3.52 g, >95%) that was used further without purification. Purification by FC (EtOAc–hexane, 1:5) was possible and afforded the desired enol ether **8** as a *Z*/*E* (11:1) mixture of isomers.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.1 Hz, 1 H_{arom}), 7.42 (s, 1 H_{arom}), 6.88 (d, *J* = 7.2 Hz, 1 H, COCH=C*H*O*t*-Bu), 6.81 (d, *J* = 8.1 Hz, 1 H_{arom}), 6.01 (s, 2 H, CH_2), 5.80 (d, *J* = 7.2 Hz, 1 H, COC*H*=CHO*t*-Bu), 1.41 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 188.6, 159.4, 151.1, 148.0, 133.6, 123.7, 108.0, 107.7, 103.6, 101.6, 80.5, 79.1, 28.2.

EI-MS: *m*/*z* (%) = 248 (M^+, 35), 192 (100), 162 (25), 149 (58), 123 (58), 57 (85), 42 (62).

HRMS (ESI-MS): *m*/*z* calcd for $C_{14}H_{17}O_4$ (M^+ + H): 249.1126; found: 249.1122.

3-Allyloxy-1-benzo[1,3]dioxol-5-yl-3-*tert*-butoxy-2-iodopropan-1-one (9)

To a solution of the crude enol ether (*Z*)-**8** (3.0 g, 12.1 mmol), allyl alcohol (12 mL) and Et_3N (0.17 mL) in CH_2Cl_2 (50 mL) was added NIS (1.4 g, 6.2 mmol) in two portions at –60 °C. The mixture was allowed to slowly warm up to 0 °C. TLC indicated that the reaction was complete. The mixture was allowed to warm up to r.t., hexane was added and the precipitate was filtered off. The filtrate was washed with aq sat. solution of $Na_2S_2O_3$, H_2O and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. FC (EtOAc–hexane, 1:20) gave **9** (4.2 g, 81%).

IR ($CHCl_3$): 3007, 2981, 2904, 1674, 1604, 1504, 1371, 1352, 1298, 1248, 1090, 1041, 911 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 8.2, 1.8 Hz, 1 H_{arom}), 7.42 (d, *J* = 1.4 Hz, 1 H_{arom}), 6.86 (d, *J* = 8.2 Hz, 1 H_{arom}), 6.06 (s, 2 H, OCH_2O), 6.06–5.95 (m, 1 H, CH_2=C*H*CH_2), 5.50 (d, *J* = 8.6 Hz, 1 H, C*H*ICH), 5.39–5.30 (m, 1 H, CH*H*=CH), 5.34 (d, *J* = 8.6 Hz, 1 H, CHIC*H*O*t*-Bu (overlaps with CH*H*=CH)), 5.20 (dd, *J* = 10.4, 0.9 Hz, 1 H, C*H*H=CH), 4.31 (dd, *J* = 11.8, 5.0 Hz, 1 H, C*H*HO), 4.07 (dd, *J* = 11.8, 5.5 Hz, 1 H, CH*H*O), 1.15 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 192.0 (s), 152.1 (s), 148.3 (s), 134.1 (d), 129.5 (s), 124.9 (d), 116.8 (t), 108.4 (d), 108.0 (d), 102.0 (t), 96.4 (d), 76.3 (s), 62.8 (t), 28.4 (q), 25.4 (d).

EI-MS: *m*/*z* (%) = 433 (M^+ + 1, 0.9), 149 (100), 374 (11), 290 (17), 121 (15), 91 (6), 58 (34).

HRMS (ESI-MS in MeOH): *m*/*z* calcd for $C_{17}H_{21}IO_5$ + Na (M^+ + Na): 455.0326; found: 455.0324.

Radical Cascade Reaction (Scheme 3)

To a suspension of **9** (1.0 g, 2.3 mmol) and $NaHCO_3$ (194 mg, 2.3 mmol) in benzene (115 mL) heated at reflux, were added DLP (1.1 g, 2.8 mmol) by portions (183 mg every 1 h) during 6 h. Then the reaction mixture was cooled to r.t. and filtered through silica gel. Evaporation of the solvent and purification by FC (hexane–CH_2Cl_2, 10:1; then hexane–EtOAc, 10:1) gave the tetracyclic compounds **10** (225 mg, 32%) and **11** (126 mg, 18%) together with **12** (338 mg, 34%).

Benzo[1,3]dioxol-5-yl-[(*r*-2,*t*-3,*c*-4)-2-*tert*-butoxy-4-iodomethyltetrahydrofuran-3-yl]methanone (12) (Scheme 3)

To a suspension of **9** (5.59 g, 12.9 mmol) and $NaHCO_3$ (1.2 g, 14.3 mmol) in benzene (325 mL) heated at reflux, was added DLP (2.5 g, 6.2 mmol) in portions during 6 h. The reaction mixture was cooled to r.t., filtered through a short pad of silica gel and concentrated. Purification of the crude product by FC (hexane–CH_2Cl_2,

10:1; then hexane–EtOAc, 10:1) afforded **12** (4.46 g, 76%) and **10** (235 mg, 6%), and other tetracyclic isomers (200 mg, 5%).

IR ($CHCl_3$): 2978, 1673, 1604, 1504, 1489, 1448, 1360, 1254, 1040, 1004, 938 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 8.2, 1.7 Hz, 1 H_{arom}), 7.53 (d, *J* = 1.7 Hz, 1 H_{arom}), 6.88 (d, *J* = 8.2 Hz, 1 H_{arom}), 6.07 (d, *J* = 1.4 Hz, 1 H, OCH*H*O), 6.06 (d, *J* = 1.4 Hz, 1 H, OC*H*HO), 5.38 (d, *J* = 3.2 Hz, 1 H, OC*H*O*t*-Bu), 4.15 (dd, *J* = 8.6, 7.2 Hz, 1 H, C*H*HO), 3.82 (t, *J* = 8.3 Hz, 1 H, CH*H*O), 3.63 (dd, *J* = 6.8, 3.2 Hz, 1 H, C*H*CHO*t*-Bu), 3.31 (dd, *J* = 9.7, 6.4 Hz, 1 H, C*H*HI), 3.25 (dd, *J* = 9.6, 7.9 Hz, 1 H, CH*H*I), 3.22–3.15 (m, 1 H, ICH_2CHCH_2O), 1.19 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 195.1 (s), 152.3 (s), 148.3 (s), 131.3 (s), 125.7(d), 108.6 (d), 107.9 (d), 102.1 (d), 101.98 (t), 75.3 (s), 72.5 (t), 61.5 (d), 43.3 (d), 28.8 (q), 6.5 (t).

NOE Difference Spectra (500 MHz, δ): 3.64–3.62 (C*H*CHO*t*-Bu) → 3.33–3.24 (4.2%); 3.27–3.15 (ICH_2CHCH_2O) → 5.38 (1.8%).

EI-MS: *m*/*z* (%) = 431 (M^+ – 1, 5), 42 (100), 374 (99), 360 (65), 246 (42), 203 (70), 190 (42), 149 (75), 121 (55), 65 (82), 57 (95).

HRMS (ESI-MS in MeOH): *m*/*z* for $C_{17}H_{21}IO_5$ + Na (M^+ + Na): 455.0331; found: 455.0349.

(*r*-6,*t*-5a,*c*-8a)-6-*tert*-Butoxy-5a,6,8a,9-tetrahydro-8*H*-furo[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-5-one (10) and (*r*-7,*c*-6a,*t*-9a)-7-*tert*-Butoxy-6a,7,9a,10-tetrahydro-9*H*-furo[3′,4′:6,7]naphtho[1,2-*d*][1,3]dioxol-6-one (11) (Scheme 3)

To a solution of **12** (7.19 g, 16.6 mmol) and $NaHCO_3$ (1.53 g, 18.3 mmol) in benzene (1.2 L) heated at reflux was added DLP (19.8 g, 49.8 mmol) by portions (3.3 g every 1 h) during 6 h. The reaction mixture was cooled to r.t., filtered through a short pad of silica gel. Evaporation of the solvent and purification by FC (hexane–EtOAc, 10:1) gave **10** (2.44 g, 48%) and **11** (1.22 g, 24%).

10

IR ($CHCl_3$): 2980, 1690, 1618, 1504, 1479, 1436, 1403, 1368, 1328, 1286, 1242, 1024, 973, 940, 886 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (s, 1 H_{arom}), 6.68 (s, 1 H_{arom}), 6.021 (d, *J* = 1.3 Hz, 1 H, OCH*H*O), 6.018 (d, *J* = 1.3 Hz, 1 H, OC*H*HO), 5.69 (d, *J* = 6.1 Hz, 1 H, OC*H*O*t*-Bu), 4.03 (dd, *J* = 7.9, 6.2 Hz, 1 H, CHC*H*HO), 3.86 (dd, *J* = 10.7, 7.9 Hz, 1 H, CHCH*H*O), 3.01 (dd, *J* = 15.8, 4.2 Hz, 1 H, $C_{arom}CH$*H*), 2.89 (ddd, *J* = 15.7, 11.7, 1.0 Hz, 1 H, $C_{arom}CH$*H*), 2.76 (dd, *J* = 14.1, 6.1 Hz, 1 H, C*H*CHO*t*-Bu), 2.56–2.46 (m, 1 H, CH_2CHCH_2O), 1.26 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 193.3 (s), 152.1 (s), 147.2 (s), 139.8 (s), 128.4 (s), 108.5 (d), 106.2 (d), 101.9 (t), 97.5 (d), 75.4 (s), 70.4 (t), 59.9 (d), 43.2 (d), 33.0 (t), 28.9 (q).

NOE Difference Spectra (500 MHz, δ): 3.01 ($C_{arom}CH$HO) → 2.76 (5.8%); 2.89 ($C_{arom}CH$*H*O) → 5.69 (1.2%), 2.56–2.46 (5.8%); 2.56–2.46 (CH_2CHCH_2O) → 5.69 (2.5%).

FAB-MS: *m*/*z* (%) = 304 (M^+, 24), 231 (100), 249 (44), 202 (16), 189 (36), 154 (29), 115 (11).

Anal. Calcd for $C_{17}H_{20}O_5$ (304.34): C, 67.09; H, 6.62. Found: C, 67.00; H, 6.62.

11

IR ($CHCl_3$): 2979, 1694, 1631, 1592, 1467, 1358, 1260, 1107, 1010, 977 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 1 H_{arom}), 6.80 (dd, *J* = 8.2, 0.4 Hz, 1 H_{arom}), 6.064 (d, *J* = 9.9 Hz, 1 H, OCH*H*O), 6.061 (d, *J* = 9.9 Hz, 1 H, OC*H*HO), 5.72 (d, *J* = 6.1 Hz, 1 H, OC*H*O*t*-Bu), 4.06 (dd, *J* = 7.9, 6.2 Hz, 1 H, CHC*H*HO), 3.89 (dd, *J* = 10.6, 8.0 Hz, 1 H, CHCH*H*O), 3.13 (dd, *J* = 16.1, 4.2 Hz, 1 H, $C_{arom}CH$*H*), 2.80 (dd, *J* = 14.0, 6.1 Hz, 1 H, C*H*CHO*t*-Bu), 2.69 (ddd, *J* = 16.1, 12.0, 0.7 Hz, 1 H, $C_{arom}CH$*H*), 2.56–2.47 (m, 1 H, CH_2CHCH_2O), 1.34 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 193.2 (s), 151.2 (s), 145.1 (s), 128.7 (s), 123.9 (s), 123.0 (d), 107.2 (d), 102.0 (t), 97.4 (d), 75.4 (s), 70.5 (t), 60.1 (d), 42.4 (d), 29.0 (q), 26.2 (t).

NOE Difference Spectra (500 MHz, δ): 3.13 ($C_{arom}CH$HO) → 2.56–2.47 (6.6%); 2.68 ($C_{arom}CH$*H*O) → 2.80 (6.3%), 2.56–2.47 (CH_2CHCH_2O) → 5.72 (2.7%).

FAB-MS: *m*/*z* (%) = 304 (M^+, 30), 231 (100), 249 (58), 201 (12), 163 (21), 154 (96), 136 (66), 107 (22).

Anal. Calcd for $C_{17}H_{20}O_5$ (304.34): C, 67.09; H, 6.62. Found: C, 67.00; H, 6.63.

6-*tert*-Butoxy-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxo-5-ol (13)

To a solution of *n*-BuLi (2.2 mL, 5.34 mmol, 2.4 M in hexane) in THF (15 mL) was slowly added 3,4,5-trimethoxyphenyl bromide (1.32 g, 5.34 mmol) dissolved in THF (15 mL) at –78 °C. The mixture was kept at this temperature for 30 min and LiCl (424 mg, 10 mmol) was added. A solution of **12** (813 mg, 2.67 mmol) in THF (15 mL) was then slowly added and the mixture was kept at –78 °C for 2 h. The mixture was allowed to warm up to r.t. overnight. H_2O was added and the mixture was extracted with Et_2O. The organic phase was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. FC (hexane–EtOAc, 7:3) afforded compound **13** (664 mg) in 53% yield. When the reaction was run in the absence of LiCl (same reaction conditions), the alcohol **13** was isolated in 31% yield together with the isomerized ketone **14**.

IR ($CHCl_3$): 3009, 2977, 2939, 1589, 1504, 1482, 1412, 1367, 1321, 1234, 1130, 1041, 992, 940 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, 10% ethylbenzene): δ = 6.75 (s, 1 H_{arom}), 6.58 (s, 1 H_{arom}), 6.48 (s, 2 H, 2 C*H*COMe), 5.91(d, *J* = 1.3 Hz, 1 H, OCH*H*O), 5.90 (d, *J* = 1.3 Hz, 1 H, OC*H*HO), 5.01 (d, *J* = 6.6 Hz, 1 H, OC*H*O*t*-Bu), 3.94 (dd, *J* = 7.7, 6.3 Hz, 1 H, CHC*H*HO), 3.83 (s, 3 H, OCH_3), 3.76 (s, 6 H, 2 OCH_3), 3.67 (dd, *J* = 9.9, 7.9 Hz, 1 H, CHCH*H*O), 2.96 (dd, *J* = 16.1, 5.4 Hz, 1 H, $C_{arom}CH$*H*), 2.91 (s, 1 H, OH), 2.73 (dd, *J* = 15.9, 11.4 Hz, 1 H, $C_{arom}CH$*H*), 2.49–2.39 (m, 1 H, CH_2CHCH_2O), 2.31 (dd, *J* = 13.2, 6.5 Hz, 1 H, C*H*CHO*t*-Bu), 1.29 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 152.3 (s), 147.2 (s), 146.9 (s), 139.8 (s), 137.3 (s), 136.9 (s), 128.8 (s), 107.6 (d), 107.4 (d), 105.9 (d), 101.9 (t), 99.3 (d), 76.7 (s), 75.2 (s), 71.2 (t), 60.9 (q), 60.8 (q), 56.1 (d), 37.3 (d), 32.3 (t), 29.4 (q).

NOE difference spectra (500 MHz, δ): 6.48 (2 C*H*COMe) → 2.49–2.39 (5.0%), 5.01 (3.0%); 5.01 (OC*H*O*t*-Bu) → 2.49–2.39 (2.8%); 3.94 (CHC*H*HO) → 2.49–2.39 (7.9%); 3.67 (CHCH*H*O) → 2.31 (5.1%).

EI-MS: *m*/*z* (%) = 472 (M^+, 4), 59 (100), 397 (44), 364 (27), 352 (35), 334 (53), 319 (47), 43 (90).

HRMS (EI-MS): *m*/*z* calcd for $C_{22}H_{32}O_8$ (M^+): 472.2097; found: 472.2114.

14

IR ($CHCl_3$): 2978, 1666, 1618, 1504, 1481, 1382, 1305, 1252, 1099, 1042, 1005 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (s, 1 H_{arom}), 6.63 (s, 1 H_{arom}), 6.10 (d, *J* = 1.3 Hz, 1 H, OCH*H*O), 5.99 (d, *J* = 1.3 Hz, 1 H, OC*H*HO), 5.64 (d, *J* = 5.8 Hz, 1 H, C*H*O*t*-Bu), 4.10 (dd, *J* = 8.5, 6.3 Hz, 1 H, CHC*H*HO), 3.97 (dd, *J* = 8.5, 2.3 Hz, 1 H, CHCH*H*O), 3.31 (dd, *J* = 15.8, 12.05 Hz, 1 H, $C_{arom}CH$*H*CH), 3.06 (dd, *J* = 15.3, 12.1 Hz, 1 H, C*H*CHO*t*-Bu), 2.96–2.87 (m, 1 H,

CH_2CHCH_2O), 2.80 (dd, J = 15.3, 6.3 Hz, 1 H, $C_{arom}CHHCH$), 1.26 (s, 9 H, t-C_4H_9).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 193.3 (s), 152.1 (s), 146.9 (s), 140.4 (s), 128.2 (s), 107.8 (d), 106.1 (d), 101.5 (t), 99.7 (d), 74.5 (s), 73.6 (t), 54.0 (d), 37.1 (d), 33.2 (t), 28.9 (q).

ESI-MS: m/z = 305 (M^+ + 1, 0.3%).

HRMS (ESI-MS): m/z calcd for $C_{17}H_{20}O_5$ + Na (M^+ + Na): 327.1208; found: 327.1187.

(±)-Dehydrodeoxypodophyllotoxin (15)

To a solution of **13** (20 mg, 0.0423 mmol) in CH_2Cl_2 (4 mL) were added at 0 °C, Et_3SiH (9 mg, 0.08 mmol) and TFA (149 mg, 0.1 mL, 1.3 mmol). The solution was stirred at r.t. for 30 min before diluting with Et_2O. The organic phase was washed with aq sat. $NaHCO_3$, brine and H_2O, dried ($MgSO_4$) and the solvent was evaporated. Purification by FC (hexane–EtOAc, 10:1) afforded the cyclic ether (±)-dehydrodeoxypodophyllotoxin (**15**) (16 mg, 99%).

^1H NMR (500 MHz, $CDCl_3$): δ = 6.72 (d, J = 1.0 Hz, 1 H_{arom}), 6.45 (s, 1 H_{arom}), 6.41 (s, 2 H, 2 CHCOMe), 5.91(d, J = 1.5 Hz, 1 H, OCHHO), 5.90 (d, J = 1.5 Hz, 1 H, OCHHO), 4.68 (dd, J = 14.6, 1.9 Hz, 1 H, CCHHO), 4.38 (t, J = 8.0 Hz, 1 H, CHCHHO), 4.23 (dd, J = 14.7, 2.7 Hz, 1 H, CCHHO), 3.89 (s, 3 H, OCH_3), 3.83 (s, 6 H, 2 OCH_3), 3.56 (dd, J = 9.3, 8.3 Hz, 1 H, CHCHHO), 3.17–3.08 (m, 1 H, CH_2CHCH_2O), 2.82 (dd, J = 14.7, 6.5 Hz, 1 H, $C_{arom}CHH$), 2.66 (t, J = 14.7 Hz, 1 H, $C_{arom}CHH$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 153.1 (s), 146.2 (s), 146.0 (s), 139.5 (s), 137.2 (s), 134.0 (s), 130.5 (s), 129.7 (s), 128.6 (s), 108.6 (d), 106.7 (d), 106.1 (d), 100.9 (t), 77.2 (d), 74.6 (t), 69.5 (t), 60.9 (q), 56.1 (q), 40.5 (d), 32.2 (t).

Spectral and physical data were in agreement with the literature data.[32]

6-*tert*-Butoxy-5-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole (16 and iso-16)

KH (386 mg, 9.6 mmol) was added to **13** (312 mg, 0.66 mmol) in dimethoxyethane (15 mL) and the solution was refluxed for 30 min. Chloromethyl phenyl selenide (515 mg, 2.5 mmol) was added at r.t. and the solution was stirred for 5 h. H_2O was added to hydrolyze the excess of KH and the solution was then extracted with Et_2O. The combined organic phases were washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. FC (hexane–EtOAc, 8:2) afforded **16** (205 mg, 68%) as a 1:1 mixture of diastereomers. Unreacted starting material **13** (33 mg, 0.07 mmol) was recovered. Diastereomers **16** and iso-**16** were separated by FC (hexane–EtOAc, 9:1).

16

^1H NMR (400 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 6.42 (s, 1 H), 6.22 (s, 2 H), 5.89 (2 d, J = 1.5 Hz, 2 H, AB), 4.81 (d, J = 6.5 Hz, 1 H), 4.22 (d, J = 6.0 Hz, 1 H), 3.99 (t, J = 7.8 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 6 H), 3.65 (dd, J = 10.0, 7.8 Hz, 1 H), 2.95 (dd, J = 15.8, 5.0 Hz, 1 H), 2.62 (dd, J = 15.6, 11.6 Hz, 1 H), 2.48–2.32 (m, 1 H), 2.21 (q, J = 6.3 Hz, 1 H), 1.25 (s, 9 H).

iso-16

^1H NMR (300 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 6.38 (s, 2 H), 6.29 (s, 1 H), 5.86 (s, 2 H), 5.12 (d, J = 5.5 Hz, 1 H), 4.05 (dd, J = 7.7, 5.9 Hz, 1 H), 3.89 (s, 3 H), 3.85–3.70 (m, 2 H), 3.81 (s, 6 H), 2.90–2.70 (m, 2 H), 2.35–2.12 (m, 2 H), 0.90 (s, 9 H).

Mixture of 16 and iso-16

EI-MS: m/z (%) = 456 (M^+, 27), 57 (100), 382 (39), 351 (50), 341 (23), 321 (20), 181 (35), 41 (42).

HRMS (ESI-MS): m/z calcd for $C_{26}H_{32}O_7$ + Na (M^+ + Na): 479.2045; found: 479.2059.

(±)-Deoxypodophyllotoxin (2)

A solution of **16** (53 mg, 0.116 mmol) in THF (1.5 mL) and 3 M HCl (0.7 mL) was kept at r.t. for 30 min. After extraction with Et_2O, the combined organic phases were washed with aq sat. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by FC (EtOAc–hexane, 1:1) to afford the corresponding lactol (35 mg, 75%).

Intermediate Lactol from 16

^1H NMR (400 MHz, $CDCl_3$): δ = 6.63 (s, 1 H_{arom}), 6.46 (s, 1 H_{arom}), 6.20 (s, 2 H_{arom}), 5.91 (d, J = 1.2 Hz, OCHHO), 5.89 (d, J = 1.3 Hz, OCHHO), 4.84 (d, J = 7.03 Hz, 1 H, HOCHO), 4.34 (d, J = 6.3 Hz, 1 H, benzyl CH), 4.04 (t, J = 7.3 Hz, 1 H, CHHO), 3.81 (s, 3 H, OCH_3), 3.76 (s, 6 H, 2 OCH_3), 3.71 (dd, J = 10.3, 7.8 Hz, 1 H, CHHO), 2.95 (dd, J = 15.8, 5.3 Hz, 1 H, benzyl CHH), 2.63 (dd, J = 15.8, 11.8 Hz, 1 H, benzyl CHH), 2.47–2.34 (m, 1 H, CH_2CHCH_2O), 2.17–2.10 (m, 1 H, CHCHOH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.8 (s), 146.6 (s), 146.4 (s), 137.7 (s), 136.9 (s), 131.2 (s), 128.9 (s), 110.5 (d), 108.3 (d), 107.3 (d), 100.9 (t), 100.5 (d), 71.9 (t), 60.8 (q), 56.1 (q), 53.1 (d), 44.8 (d), 35.0 (d), 32.3 (t).

To a solution of the above lactol (21 mg, 0.053 mmol) and molecular sieves (4Å) in CH_2Cl_2 (0.5 mL) was added PCC (57 mg, 0.265 mmol) at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h at r.t., filtered through a short pad of Celite and silica gel, and concentrated. FC (hexane–EtOAc, 7:3) gave deoxypodophyllotoxin (**2**) (14 mg, 66%).

2

IR ($CHCl_3$): 2964, 1778, 1711, 1590, 1504, 1484, 1375, 1332, 1226, 1129, 1042, 1002 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.52 (s, 1 H), 6.34 (s, 2 H), 5.94 (d, J = 1.3 Hz, 2 H, AB), 4.60 (br s, 1 H), 4.47–4.44 (m, 1 H), 3.94–3.89 (m, 1 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.11–2.96 (m, 1 H), 2.83–2.67 (m, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.9 (s), 152.5 (s), 147.0 (s), 146.7 (s), 137.0 (s), 128.3 (s), 110.5 (d), 108.5 (d), 108.2 (d), 101.2 (t), 72.1 (t), 60.7 (q), 56.2 (q), 47.5 (d), 43.7 (d), 33.1 (t), 32.7 (d).

EI-MS: m/z (%) = 398 (M^+, 100), 383 (6), 339 (7), 283 (6), 230 (8), 181 (12), 173 (10), 131 (16), 119 (11), 91 (10), 69 (41).

HRMS (EI-MS): m/z calcd for $C_{22}H_{22}O_7$ (M^+): 398.1365; found: 398.1365.

Spectral data were in agreement with the literature.[20]

(±)-Isodeoxypodophyllotoxin (iso-2)

Starting from iso-**16** (35 mg, 0.077 mmol) and following the same procedure used for the preparation of **2** from **16** gave first the corresponding lactol (19 mg, 63%).

Intermediate Lactol from iso-16

^1H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 1 H_{arom}), 6.41 (s, 2 H_{arom}), 6.35 (s, 1 H_{arom}), 5.89 (d, J = 1.3 Hz, 2 H, OCH_2O), 5.87 (d, J = 1.3 Hz, 2 H, OCH_2O), 5.14 (d, J = 4.2 Hz, 1 H, HOCHO), 4.35 (dd, J = 7.8, 7.7 Hz, 1 H, CHHO), 4.06 (d, J = 11.6 Hz, 1 H, benzyl CH), 3.90 (s, 3 H, OCH_3), 3.80 (s, 6 H, 2 OCH_3), 3.59 (dd, J = 9.8, 8.1 Hz, 1 H, CHHO), 3.00 (dd, J = 15.2, 4.6 Hz, 1 H, benzyl CHH), 2.73–2.57 (m, 2 H, benzyl CHH, benzyl $CHCH_2$), 1.99 (dd, J = 11.9, 4.2 Hz, 1 H, CHCHOH).

Spectral data were in agreement with the literature data.[31]

PCC oxidation of the lactol was done according to the procedure used for compound **16**. Isodeoxypodophyllotoxin (iso-**2**) obtained was purified by FC (hexane–EtOAc, 7:3) to give an amorphous solid (81%).

iso-2

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1 H_{arom}), 6.41 (s, 2 H_{arom}), 6.35 (s, 1 H_{arom}), 5.90 (d, *J* = 1.4 Hz, 1 H, OC*H*HO), 5.89 (d, *J* = 1.4 Hz, 1 H, OCH*H*O), 4.52 (dd, *J* = 8.6, 6.2 Hz, 1 H, C*H*HO), 4.06 (d, *J* = 10.4 Hz, 1 H, benzyl C*H*), 3.99 (dd, 1 H, *J* = 10.0, 8.7 Hz, 1 H, CH*H*O), 3.85 (s, 3 H, OCH_3), 3.82 (s, 6 H, OCH_3), 3.01–2.91 (m, 2 H), 2.68–2.47 (m, 2 H).

EI-MS: *m*/*z* (%) = 398 (M^+, 100), 230 (16), 181 (68), 173 (76), 168 (27), 128 (22), 115 (24).

Spectral data were in agreement with the literature.[31]

5-Benzo[1,3]dioxol-5-yl-6-*tert*-butoxy-5,5a,6,8,8a,9-hexahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-5-ol (19)

To a solution *n*-BuLi (1.2 mL, 2.87 mmol, 2.4 M in hexane) in THF (7.5 mL) was slowly added 3,4-methylenedioxyphenyl bromide (577 mg, 2.87 mmol) dissolved in THF (7.5 mL) at –78 °C. The solution was kept at this temperature for 30 min. LiCl (250 mg, 6 mmol) was added and a solution of ketone **10** (437 mg, 1.44 mmol) in THF (7.5 mL) was then slowly added and the mixture was kept at –78 °C for 2 h. The solution was allowed to warm up to r.t. during overnight. H_2O was added and the mixture was extracted with Et_2O. The organic phase was washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid, which was purified partially by FC (hexane–EtOAc, 4:1) and by recrystallization (Et_2O–hexane) to give **19** (454 mg, 74%) as one diastereomer.

IR ($CHCl_3$): 2978, 1503, 1482, 1436, 1396, 1368, 1098, 1041, 984, 940 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74–6.71 (m, 4 H), 6.57 (s, 1 H), 5.93 (s, 2 H), 5.90 (s, 2 H), 4.97 (d, *J* = 6.02 Hz, 1 H), 3.91 (dd, *J* = 7.8, 6.3 Hz, 1 H), 3.67 (dd, *J* = 8.9, 7.0 Hz, 1 H), 2.97–2.91 (m, 2 H), 2.71 (dd, *J* = 15.8, 10.3 Hz, 1 H), 2.42–2.26 (m, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 147.2 (s), 147.0 (s), 146.9 (s), 146.6 (s), 138.2 (s), 136.9 (s), 128.9 (s), 121.5 (d), 108.9 (d), 107.5 (d), 107.3 (d), 107.1 (d), 101.1 (t), 101.2 (t), 99.4 (d), 75.4 (s), 71.1 (t), 60.4 (d), 37.0 (d), 32.3 (t), 29.3 (q).

EI-MS: *m*/*z* (%) = 426 (M^+, 7), 351 (100), 335 (21), 247 (25), 189 (20), 149 (27), 135 (23), 57 (45), 41 (28).

HRMS (EI-MS): calcd for $C_{24}H_{26}O_7$ (M^+): 426.16785; found: 426.16971.

5-Benzo[1,3]dioxol-5-yl-6-*tert*-butoxy-5,5a,6,8,8a,9-hexahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole (20)

KH (300 mg, 7.5 mmol) was added to a solution of **19** (205 mg, 0.50 mmol) in dimethoxyethane (15 mL) and the solution was refluxed for 30 min. Chloromethyl phenyl selenide (500 mg, 2.4 mmol) was added at r.t. and the mixture was stirred overnight. H_2O was slowly added and the solution was then extracted with Et_2O. The organic phases were washed with aq sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. FC (hexane–EtOAc, 8:2) afforded compound **20** (96 mg, 47%) as a 1:1 mixture of two diastereomers.

IR ($CHCl_3$): 1978, 1600, 1503, 1484, 1225, 1101, 1041, 986 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 8.3 Hz, 1 H), 6.59 (s, 1 H), 6.53 (dd, *J* = 8.0, 1.8 Hz, 1 H), 6.43 (d, *J* = 1.8 Hz, 1 H), 6.40 (s, 1 H), 5.91 (d, *J* = 1.5 Hz, 2 H, AB), 5.88 (d, *J* = 1.5 Hz, 1 H), 5.87 (d, *J* = 1.5 Hz, 1 H), 4.78 (d, *J* = 6.8 Hz, 1 H), 4.23 (d, *J* = 5.8 Hz, 1 H), 3.97 (t, *J* = 7.5 Hz, 1 H), 3.63 (dd, *J* = 10.0, 7.8 Hz, 1 H), 2.92 (dd, *J* = 15.9, 5.0 Hz, 1 H), 2.60 (dd, *J* = 14.8, 11.5 Hz, 1 H), 2.39–2.28 (m, 1 H), 2.21–2.15 (m, 1 H), 1.25 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 147.4 (s), 146.4 (s), 146.3 (s), 146.2 (s), 136.4(s), 132.1 (s), 129.1 (s), 123.3 (d), 110.4 (d), 110.3 (d), 108.4 (d), 107.6 (d), 100.9 (t), 100.8 (t), 100.4 (d), 74.7 (s), 71.3 (t), 52.9 (d), 44.6 (d), 34.16 (d), 32.3 (t), 29.3 (q).

EI-MS: *m*/*z* (%) = 409 (M^+ – 1, 5), 231 (100), 352 (14), 187 (52), 173 (33), 149 (35), 135 (49), 57 (77), 42 (61).

HRMS (EI-MS): *m*/*z* calcd for $C_{24}H_{26}O_6$ + Na (M^+ + Na): 433.1627; found: 433.1615.

(±)-Polygamain (3) and (±)-1β-Polygamain (1β-3)

To a solution of **20** (1:1 mixture of diastereomers, 40 mg, 0.097 mmol) in anhyd THF (4 mL) was added conc. H_2SO_4 (0.5 mL) and the solution was kept at r.t. for 30 min. Et_2O was added and the solution was washed with aq sat. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by FC (hexane–EtOAc, 7:3) to afford the lactol (19 mg). PCC oxidation of the lactol (17 mg, 0.048 mmol) was done according to the procedure reported for **2**. FC (hexane–EtOAc, 7:3) gave a mixture of polygamain (**3**) and 1β-polygamain (1β-**3**) (5 mg, 30%).

Polygamain (3)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (s, 1 H_{arom}), 5.92 (s, 2 H, OCH_2O), 5.90 (2 d, *J* = 1.5 Hz, 2 H, OCH_2O), 4.57 (d, *J* = 4.3 Hz, 1 H, C*H*–Aryl), 4.45 (m, 1 H, C*H*HO), 3.91 (t, *J* = 8.5 Hz, 1 H, CH*H*O), 3.05 (t, *J* = 10.6, 1 H, C_{arom}C*H*H), 2.81–2.70 (m, 3 H, CHC=O, CH*H*C*H*CH_2O).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.7, 147.2, 147.0, 146.8, 146.5, 134.5, 131.0, 128.2, 124.1, 111.1, 110.3, 108.4, 107.6, 101.1, 101.0, 72.0, 47.3, 43.2, 33.0, 32.6.

EI–MS: *m*/*z* (%) = 352 (M^+, 100), 307 (20), 267 (23), 185 (50), 152 (32), 135 (53), 115 (31).

Spectroscopic data were in accordance with the literature data.[18]

1β-Polygamain (1β-3)

^{1}H NMR ($CDCl_3$): δ = 6.77 (s, 2 H_{arom}), 6.58 (s, 2 H_{arom}), 5.93 (2 d, *J* = 0.8 Hz, 2 H, OC*HH*O), 5.89 (s, 2 H, OC*HH*O), 4.51 (dd, *J* = 8.5, 6.5 Hz, 1 H, C*H*HO), 4.04 (d, *J* = 11.0 Hz, 1 H, C*H*–Aryl), 3.97 (dd, *J* = 10.3, 8.5 Hz, 1 H, CH*H*O), 2.97 (dd, *J* = 15.3, 4.8 Hz, 1 H, C_{arom}C*H*H), 2.88 (dd, *J* = 15.3, 10.8 Hz, 1 H, C_{arom}CH*H*), 2.66–2.51 (m, 1 H, CH_2C*H*CH_2O), 2.48 (dd, *J* = 13.6, 11.0 Hz, 1 H, CHC=O).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.4, 147.8, 146.7, 146.5, 146.4, 136.9, 132.6, 127.8, 123.0, 109.9, 109.1, 108.4, 108.2, 101.1, 101.0, 70.9, 48.8, 46.1, 39.9, 33.0.

EI-MS: *m*/*z* (%) = 352 (M^+, 100), 292 (8), 280 (17), 267 (20), 230 (7), 176 (17), 152 (25), 135 (28), 115 (21), 76 (21)

Spectral data of **3** and 1β-**3** were in agreement with the literature data.[19,33,48]

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