Radical-Mediated Synthesis of Racemic Deoxypodophyllotoxin and Related Lignans

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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 aryl-lithium 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. This class includes several closely related chemical structures such as podophyllotoxin (1), deoxypodophyllotoxin (2), and isodeoxypodophyllotoxin (iso-2) (Figure 1). They also include some semi-synthetic compounds such as etoposide and teniposide, which are used in cancer therapy. Podophyllotoxin itself serves as the starting material for the synthesis of both compounds as well as for the treatment of angogenital warts. Podophyllotoxin causes inhibition of tubulin polymerization. The binding sites on tubulin for colchicine and podophyllotoxin were found to overlap significantly. Deoxypodophyllotoxin is a cytotoxic and antineoplastic agent. 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. Here, we report the total synthesis of racemic deoxypodophyllotoxin (2), isodeoxypodophyllotoxin (iso-2), and dehydrodeoxy-podophyllotoxin (15). A mixture of diastereomeric polygamain (3) and 1β-polygamain (1β-3) 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) followed by a radical aromatic substitution.

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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 substituents at C-8 and C-8'. Moreover, a related cascade process involving a radical aromatic substitution was recently used by Zard in an elegant synthesis of lycorane. 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-
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 1

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 from 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 from the corresponding bromide by treatment with n-BuLi) affords the desired alcohol 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 LiCl41 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, CS2, MeI; ii. Bu3SnH, 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.
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. Conversion of deoxypodophyllotoxin (2) into podophyllotoxin (1) and epipodophyllotoxin via microbial oxidation has been reported. 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 PhSeCH2Cl/KH furnished the deoxygenated product 20 as a 1:1 mixture of diastereomers. The mixture of 20 and 1\(\beta\)-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 1\(\beta\)-polygamain (1\(\beta\)-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 stereocent 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.

THF, Et2O, CH2Cl2, benzene and toluene were dried by filtration under argon through dried Al2O3 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, Et2O, CH2Cl2, and hexane as eluents. TLC: Merck silica gel 60 F254 analytical plates; detection either with UV or by spraying with a solution of vanillin or a solution of phosphomolybdenum.
dic acid (25 g), Ce(SO4)2·4H2O (10 g), concd H2SO4 (60 mL) and H2O (940 mL) with subsequent heating. FT-IR: Mattson Unicam 5000 and Perkin-Elmer 1600. NMR: Varian Gemini 200 (1H = 200 MHz, 13C = 50.3 MHz), Bruker AM 360 (1H = 360 MHz, 13C = 90.5 MHz).

1H NMR (360 MHz, CDCl3): δ = 7.31 (dd, J = 8.1, 1.8 Hz, 1H, Hס), 7.22 (d, J = 1.8 Hz, 1H, Hמש), 6.82 (d, J = 8.1 Hz, 1H, Hחומכ), 6.01 (s, 2 H, CH2), 3.57 (s, 3 H, CH3), 3.34 (s, 3 H, CH3).

13C NMR (360 MHz, CDCl3): 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), 63.1 (q), 34.3 (q).

IR (KBr): 3361, 3060, 2921, 1590, 1480, 1460, 1360, 1300, 1230, 1192, 1110, 1090, 1040, 1020, 920, 810, 720 cm–1.

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 C17H19O5 + Na (M+ + Na+): 455.0323; found: 455.0324.

Radical Cascade Reaction (Scheme 3)
To a suspension of 9 (1.0 g, 2.3 mmol) and NaHCO3 (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–CH2Cl2, 1:2) gave the tetracyclic compounds 10 (225 mg, 32%) and 11 (126 mg, 18%) together with 12 (338 mg, 34%).

Benzonitrile-1-benzo[1,3]dioxol-5-yl-3-tet-butoxy-2-isopropyl-1-one (9)
To a solution of the crude enol ether (Z)-8 (3.0 g, 12.1 mmol), allyl alcohol (12 mL) and Et3N (0.17 mL) in CH2Cl2 (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 Na2S2O3, H2O and brine, dried (MgSO4) and the solvent evaporated in vacuo. FC (EtOAc–hexane, 1:20) gave 9 (4.2 g, 81%).

IR (CHCl3): 3007, 2981, 2904, 1674, 1604, 1504, 1371, 1352, 1298, 1248, 1090, 1041, 911 cm–1.

1H NMR (360 MHz, CDCl3): δ = 7.55 (dd, J = 8.2, 1.8 Hz, 1H, Hמש), 7.42 (d, J = 1.4 Hz, 1H, Hחומכ), 6.86 (d, J = 8.2 Hz, 1H, Hחומכ), 6.06 (s, 2 H, OCH3), 6.06–5.95 (m, 1 H, CH=CH2), 5.39 (d, J = 8.6 Hz, 1H, CH2CH=), 5.34 (d, J = 8.6 Hz, 1H, CHCH2CH3), 4.31 (dd, J = 11.8, 5.0 Hz, 1H, CH=CH2), 4.07 (dd, J = 11.8, 5.5 Hz, 1H, CH2OH), 4.15 (1.15 s, 9 H, r-C3H9).

13C NMR (100.6 MHz, CDCl3): 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 (%) = 343 (M* + 1, 0.9), 149 (100), 374 (11), 290 (17), 121 (15), 91 (6), 58 (34).


Radical Cascade Reaction (Scheme 3)
To a suspension of 9 (1.0 g, 2.3 mmol) and NaHCO3 (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–CH2Cl2, 1:2) gave the tetracyclic compounds 10 (225 mg, 32%) and 11 (126 mg, 18%) together with 12 (338 mg, 34%).

Benzonitrile-1-benzo[1,3]dioxol-5-yl-(3t,2?,3r,4?,4r)-2-tet-butoxy-4-isopropyltetrahydrofuran-3-yl)methanone (12) (Scheme 3)
To a suspension of 9 (5.59 g, 12.9 mmol) and NaHCO3 (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–CH2Cl2).

(Z)-1-Benzonitrile-1-benzo[1,3]dioxol-5-yl-3-tet-butoxypropenone [(Z)-8]
To a solution of (Z)-1-bromo-2-tet-butoxyethene[(2.56 g, 14.3 mmol) in anhyd THF (72 mL) was added r-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. NH4Cl was added and the mixture was allowed to warm up to r.t. After extraction with Et2O, the organic layers were dried (MgSO4), and the solvent was evaporated to give (Z)-8 (3.52 g, >95%) that was used without further purification. Purification by FC (EtOAc–hexane, 1:5) was possible and afforded the desired enol ether 8 as a ZIE (11:1 mixture of isomers).

3-Allylxy-1-benzo[1,3]dioxol-5-yl-3-tet-butoxy-2-isopropyl-1-one (9)
To a solution of the crude enol ether (Z)-8 (3.0 g, 12.1 mmol), allyl alcohol (12 mL) and Et3N (0.17 mL) in CH2Cl2 (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 Na2S2O3, H2O and brine, dried (MgSO4) and the solvent evaporated in vacuo. FC (EtOAc–hexane, 1:20) gave 9 (4.2 g, 81%).
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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 (CHCl₃): 2978, 1673, 1604, 1489, 1448, 1360, 1254, 1040, 1004, 938 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.69 (dd, J = 8.2, 1.7 Hz, 1 H), 7.53 (d, J = 1.7 Hz, 1 H, H₃m(3)), 6.88 (d, J = 8.2 Hz, 1 H, H₃m(1)), 6.07 (d, J = 1.4 Hz, 1 H, OCH₃OH), 5.48 (d, J = 3.2 Hz, 1 H, OCHO-Bu), 4.15 (dd, J = 8.6, 7.2 Hz, 1 H, CH₂OH), 3.38 (t, J = 8.3 Hz, 1 H, CH₂CH₂O), 3.63 (dd, J = 6.8, 3.2 Hz, 1 H, CHCHO-Bu), 3.31 (dd, J = 9.7, 6.4 Hz, 1 H, CH₂H), 3.25 (dd, J = 9.6, 7.9 Hz, 1 H, CHH₂O), 2.32–2.35 (m, 15 H, CH₃CH₂CH₂O), 1.19 (s, 9 H, t-CH₃).

13C NMR (125.8 MHz, CDCl₃): 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 (t), 65 (t).

NOE Difference Spectra (500 MHz, δ): 3.95–4.05 (CH₂O) → 3.33–3.42 (4.2%); 3.27–3.15 (CH₂CH₂O) → 5.38 (1.8%).

EI-MS: m/z (%) = 431 (M⁺ – 1, 5), 420 (100), 374 (99), 360 (25), 423 (203), 190 (40), 144 (79), 121 (55), 65 (82), 57 (95).

HRMS (ESI-MS in MeOH): m/z for C₁₁H₂₀O₅ + Na⁺ (M⁺ + Na⁺): 455.0331; found: 455.0349.

(r-6J,5a-c,6a-a)-6-tert-Butoxy-5,6a,8a,9-tetrahydro-6H-furo[3',4',5':6,7]naptho[2,3-d][1,3]dioxol-5-one (13) To 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. H₂O was added and the mixture was extracted with EtO. The organic phase was washed with sat. NaHCO₃ and brine, dried (MgSO₄), 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 (CHCl₃): 3009, 2977, 2939, 1589, 1504, 1482, 1412, 1367, 1321, 1213, 1104, 992, 940 cm⁻¹.

1H NMR (500 MHz, CDCl₃): 10% ethylbenzene: δ = 6.75 (s, 1 H₃m(3)), 6.58 (s, 1 H₃m(1)), 6.48 (s, 2 H, 2 CH₂COMe), 5.91 (d, J = 1.3 Hz, 1 H, 1H, OCHOH), 5.90 (d, J = 1.3 Hz, 1 H, OCHOH), 5.69 (d, J = 1.3 Hz, 1 H, 1H, OCHOH), 5.69 (d, J = 7.9, 6.2 Hz, 1 H, CHCH₂O), 3.86 (dd, J = 10.7, 7.9 Hz, 1 H, CHCH₂O, 3.01 (d, J = 15.8, 4.2 Hz, 1 H, C₃m(4,5)CH₂O, 2.98 (dd, J = 15.7, 11.7, 1.0 Hz, 1 H, C₃m(4,5)CH₂O), 2.76 (dd, J = 14.1, 6.1 Hz, 1 H, 1H, OCHO-Bu), 2.56–2.46 (m, 1 H, CH₃CH₂CH₂O), 1.26 (s, 9 H, t-CH₃).

13C NMR (125.8 MHz, CDCl₃): δ = 193.3 (s), 152.1 (s), 147.2 (s), 139.8 (s), 128.4 (d), 106.2 (d), 106.1 (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 (C₃m(4,5)CH₂O) → 2.76 (5.8%); 2.89 (C₃m(4,5)CH₂O) → 5.69 (1.2%); 2.56–2.46 (CH₃CH₂O) → 5.69 (2.5%).


11 IR (CHCl₃): 2979, 1694, 1631, 1592, 1467, 1358, 1260, 1107, 1010, 977 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.67 (d, J = 8.2 Hz, 1 H₃m(3)), 6.80 (dd, J = 8.2, 0.4 Hz, 1 H₃m(1)), 6.064 (d, J = 9.9 Hz, 1 H, OCHOH), 6.061 (d, J = 9.9 Hz, 1 H, OCHOH), 5.72 (d, J = 6.1 Hz, 1 H, OCHO-Bu), 4.06 (dd, J = 7.9, 6.2 Hz, 1 H, CH₃CH₂O), 3.89 (dd, J = 10.6, 8.0 Hz, 1 H, CH₃CH₂O), 3.13 (dd, J = 16.1, 4.2 Hz, 1 H, C₃m(4,5)CH₂H), 2.80 (dd, J = 14.0, 6.1 Hz, 1 H, 1H, OCHOH-Bu), 2.69 (dd, J = 16.1, 12.0, 0.7 Hz, 1 H, C₃m(4,5)CH₂H), 2.56–2.47 (m, 1 H, CH₃CH₂CH₂O), 1.34 (s, 9 H, t-CH₃).

13C NMR (125.8 MHz, CDCl₃): δ = 193.2 (s), 151.2 (s), 145.1 (s), 128.7 (s), 123.9 (s), 120.7 (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 (C₃m(4,5)CH₂O) → 2.56–2.47 (6.6%); 2.68 (C₃m(4,5)CH₂O) → 2.80 (6.3%), 2.56–2.47 (CH₃CH₂CH₂O) → 5.72 (2.7%).

FAB-MS: m/z (%) = 304 (M⁺, 30), 231 (100), 249 (58), 202 (12), 163 (21), 154 (96), 136 (66), 107 (22).


6-tert-Butoxy-5-(3,4,5-trimethoxyphenyl)-5a,6,8a,9-tetrahydrodifu[3',4',5':6,7]naptho[2,3-d][1,3]dioxol-5-one (13)
CH₂(C₆H₄)O, 2.80 (dd, J = 15.3, 6.3 Hz, 1 H, CH₃CH₂OCH₃), 1.26 (s, 9 H, CH₃CH₂OCH₃).

1°C NMR (100.6 MHz, CDCl₃): 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 calc'd for C₁₃H₁₈O₄Na + Na (M⁺ + Na): 327.1208; found: 327.1187.

(±)-Dehydrodeoxypodophyllotoxin (15) (16 mg, 99%).

To a solution of 13 (4 mg, 0.0423 mmol) in CDCl₃ (4 mL) were added 0 °C, Et₂SiH (9 mg, 0.08 mmol) and TFA (149 mg, 1.3 mL, 13 mmol). The solution was stirred at r.t. for 30 min before diluting with Et₂O. The organic phase was washed with aq sat. NaHCO₃, brine and H₂O, dried (MgSO₄) 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, CDCl₃): δ = 6.72 (d, J = 1.0 Hz, 1Hₐ), 6.45 (s, 1Hₐ), 6.41 (s, 2H, 2CHCOMe), 5.91 (d, J = 1.5 Hz, 1H, OCH₃CO), 5.90 (d, J = 1.5 Hz, 1H, OCH₃CO), 4.68 (dd, J = 1.46 Hz, 1H, CH₂OCH₃), 4.38 (t, J = 8.0 Hz, 1H, CH₂CH₂O), 4.23 (dd, J = 14.7, 2.7 Hz, 1H, CH₂OH), 3.89 (s, 3H, OCH₃), 3.83 (s, 6H, 2OCH₃), 3.56 (dd, J = 9.3, 8.3 Hz, 1H, CH₂CH₂O), 3.17–3.08 (m, 1H, CH₂CH₂OCH₃), 2.82 (dd, J = 14.7, 6.5 Hz, 1H, C₆H₅CH₂O), 2.66 (t, J = 1.7 Hz, 1H, C₆H₅OCH₃).

13C NMR (125.8 MHz, CDCl₃): 146.4 (s), 146.3 (s), 137.9 (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), 109.9 (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 dimethoxethane (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 5h. H₂O was added to hydrolyze the excess of KH and the solution was then extracted with Et₂O. The combined organic phases were washed with aq sat. NaHCO₃, brine, dried (MgSO₄) and concentrated in vacuo. FC (hexane-EtOAc) afforded intermediates Lactol from iso-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).

1H NMR (400 MHz, CDCl₃): δ = 6.61 (s, 1 H), 6.42 (s, 1 H), 6.22 (s, 2H), 5.89 (2d, J = 1.5 Hz, 2H, AB), 4.81 (d, J = 6.5 Hz, 1H, 4.22 (d, J = 6.0 Hz, 1H), 3.99 (t, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.65 (dd, J = 10.0, 7.8 Hz, 1H, 2.95 (dd, J = 15.8, 5.0 Hz, 1H, 2.62 (dd, J = 15.6, 11.6 Hz, 1H, 2.48–2.32 (m, 1H), 2.21 (dd, J = 6.3 Hz, 1H, 1.25 (s, 9 H).

iso-16

1H NMR (300 MHz, CDCl₃): δ = 6.58 (s, 1H), 6.38 (s, 2H), 6.29 (s, 1H), 5.86 (s, 2H), 5.12 (d, J = 5.5 Hz, 1H), 4.05 (dd, J = 7.7, 5.9 Hz, 1H), 3.89 (s, 3H), 3.85–3.70 (m, 2H), 3.81 (s, 6H), 2.90–2.70 (m, 2H), 2.35–2.12 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H).

Mixture of 16 and iso-16

EI-MS: m/z (%) = 456 (M⁺, 27), 350 (50), 341 (23), 321 (20), 181 (35), 41 (42).

HRMS (ESI-MS): m/z calc'd for C₂₁H₂₃O₇ + Na (M⁺ + Na): 479.2045; found: 479.2099.

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iso-2

1H NMR (400 MHz, CDCl3): 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, OCH3), 5.89 (d, J = 1.4 Hz, 1 H, OCH3), 4.52 (dd, J = 8.6, 6.2 Hz, 1 H, CH2O), 4.06 (d, J = 10.4 Hz, 1 H, benzyl CH), 3.99 (dd, d, 1 H, J = 10.0, 8.7 Hz, 1 H, CH2O), 3.85 (s, 3 H, OCH3), 3.82 (s, 6 H, OCH3), 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-butyloxy-5,6,5a,6,8,8a,9-hexahydrofurao[3,4,6:7]naptho[2,3-d][1,3]dioxol-5-ol (19)

To a solution of BuLi (1.2 mL, 2.87 mmol) in hexane (20), 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. H2O was added and the mixture was extracted with Et2O. The organic phase was washed with aq sat. NaHCO3 and brine, dried (MgSO4), and concentrated in vacuo. FC (hexane–EtOAc, 8:2) afforded 437 mg (47%) as a 1:1 mixture of two diastereomers.

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