Supporting information for
Enantioselective Sequential Conjugate Addition-Allylation reactions: A Concise Total Synthesis of (+)-Podophyllotoxin

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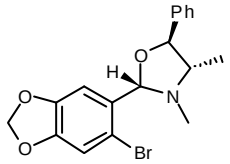
General Experimental: Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was recorded on Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low-resolution Mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High Resolution Mass spectra were taken on AB QSTAR Pulsar mass spectrometer. Chiral HPLC analyses were performed on Agilent 1100 series with a tunable UV detector at wavelength λ = 254 nm. Optical rotations were obtained on a UV-210A spectrometer. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

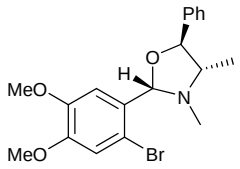


8 (2*S*,4*S*,5*S*)-2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3,4-dimethyl-5-phenyloxazolidine

$C_{18}H_{18}BrNO_3$ Mol. Wt.: 376.24

To a solution of 6-bromopiperonal (10 g, 43.6 mmol) in toluene (50 mL), (1*S*,2*S*)-(+)-pseudoephedrine (8.6 g, 52.3 mmol, 1.2 eq.) was added, followed by 1 drop of acetic acid. The resulting mixture was then stirred at reflux with a Dean-Stark trap for 20 hours. The reaction mixture was cooled to room temperature then treated with Et_3N (2 mL) for 1 hour. The solvent was then removed under reduced pressure and the residue was chromatographed on Aluminum oxide (100-200 mesh, Petroleum ether 60-90°C : Et_3N = 30: 1) to afford the product (15.6g , 95%) as a white powder.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.42-7.27 (5H, *m*), 7.25 (1H, *s*), 6.97 (1H, *s*), 5.92(2H, *d*, *J* = 1.8 Hz), 5.41 (1H, *s*), 4.68 (1H, *d*, *J*= 8.7 Hz), 2.54 (1H, *dq*, *J* = 6.0, 8.7 Hz), 2.23 (3H, *s*), 1.20 (3H, *d*, *J*= 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.83, 147.83, 140.36, 131.60, 128.45, 127.98, 126.59, 115.26, 112.29, 109.48, 101.86, 96.81, 86.40, 68.59, 35.22, 14.49. EIMS *m*/*z* (%) : 377 (M^+, 1%), 376 (4), 375 (M^+, 1%), 374 (4), 320 (5), 318 (5), 291 (12), 289 (14), 271 (94), 269 (100), 268 (67), 239 (56), 227 (24), 210 (9), 190 (59), 175 (13), 148 (27), 146 (28), 133 (34), 117 (38). HRMS *m*/*z* Found: 376.0545, Calcd. for $C_{18}H_{19}NO_3Br$ $(M+1)^+$: 376.0548.

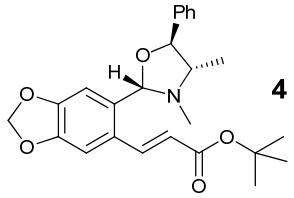


(2*S*,4*S*,5*S*)-2-(2-bromo-4,5-dimethoxyphenyl)-3,4-dimethyl-5-phenyloxazolidine

$C_{19}H_{22}BrNO_3$ Mol. Wt.: 392.29

To a solution of 2-bromo-4,5-dimethoxybenzaldehyde (3 g, 20.4 mmol) in toluene (30 mL), (1*S*,2*S*)-(+)-pseudoephedrine (4.1 g, 24.5 mmol, 1.2 eq.) was added, followed by 1 drop of acetic acid. The resulting mixture was then stirred at reflux with a Dean-Stark trap for 20 hours. The reaction mixture was cooled to room temperature then treated with Et_3N (1 mL) for 1 hour. The solvent was then removed under reduced pressure and the residue was chromatographed on Aluminum oxide (100-200 mesh, Petroleum ether 60-90°C : Et_3N = 30: 1) to afford the product (7.45g , 93%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.45-7.29 (5H, *m*), 7.25 (1H, *s*), 6.99 (1H, *s*), 5.41 (1H, *s*), 4.74 (1H, *d*, *J* = 8.7 Hz), 3.92 (3H, *s*), 3.87 (3H, *s*), 2.55 (1H, *dq*, *J* = 6.0, 8.7 Hz), 2.25 (3H, *s*), 1.24 (3H, *d*, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.02, 148.90, 140.53, 129.85, 128.50, 128.01, 126.59, 114.96, 114.80, 111.83, 97.00, 86.42, 68.84, 56.24, 56.09, 35.33, 14.50. EIMS *m*/*z* (%) : 393 (M^+, 0.5%), 392 (2), 391 (M^+, 0.5%), 390 (2), 336 (7), 334 (7), 307 (11), 305 (11), 287 (45), 285 (49), 272 (28), 270 (30), 255 (52), 245 (24), 243 (25), 224 (11), 206 (100), 191 (14), 176 (12), 149 (28), 148 (45), 147 (32), 132 (18), 117 (37). HRMS *m*/*z* Found: 392.0868, Calcd. for $C_{19}H_{23}NO_3Br$ $(M+1)^+$: 392.0861.



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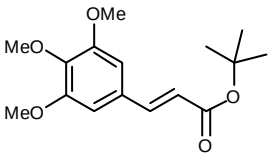
(*E*)-*tert*-butyl 3-(6-((2*S*,4*S*,5*S*)-3,4-dimethyl-5-phenyloxazolidin-2-yl)benzo[*d*][1,3]dioxol-5-yl)acrylate

$C_{25}H_{29}NO_5$ Mol. Wt.: 423.50

To a solution of Aldehyde 23 (300 mg, 1.09 mmol) in toluene (10 mL), (1*S*,2*S*)-(+)-pseudoephedrine (358.8 g, 2.18 mmol, 2 eq.) was added, followed by 1 drop of acetic acid. The resulting mixture was then stirred at reflux with a Dean-Stark trap for 20 hours. The reaction mixture was cooled to room temperature then treated with Et_3N (1 ml) for 1 hour. The solvent was then removed under reduced pressure and the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate: Et_3N = 40: 1:1) to afford the product (430 mg , 93%) as a white powder.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 8.25 (1H, *d*, *J* = 15.7 Hz), 7.42-7.29 (5H, *m*), 7.20 (1H, *s*), 7.05 (1H, *s*), 6.18 (1H, *d*, *J* = 15.7 Hz), 5.98 (2H, *s*), 5.27 (1H, *s*), 4.74 (1H, *d*, *J* = 8.7 Hz), 2.53 (1H, *dq*, *J* = 6.0, 8.7 Hz), 2.18 (3H, *s*), 1.55 (9H, *s*), 1.24 (3H, *d*, *J* = 6.0 Hz). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 166.52, 149.26, 148.45, 140.40, 133.10, 129.22, 128.53, 128.05, 126.71, 120.44, 109.01, 106.25, 101.65, 96.05, 86.31, 80.41, 68.90, 35.36, 28.43, 14.55. EIMS *m*/*z* (%) : 423 (M^+, 10%), 366 (100), 350 (18), 322 (87), 290 (14), 261 (13), 246 (17), 234 (10), 216 (91), 204

(47), 188 (17), 175 (54), 162 (27), 159 (21), 148 (28), 146 (32), 132 (13), 117 (41). HRMS *m/z* Found: 424.2130, Calcd. for $C_{25}H_{30}NO_5$ $(M+1)^+$: 424.2123.



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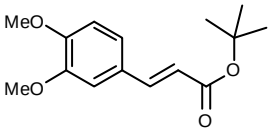
(*E*)-*tert*-butyl 3-(3,4,5-trimethoxyphenyl)acrylate

$C_{16}H_{22}O_5$ Mol. Wt.: 294.34

To a mixture of 3,4,5-trimethoxy cinnamic acid (3g, 12.6 mmol,), DCC (3.9g, 18.9 mmol, 1.5 eq.) and DMAP (1.85g, 15.1 mmol, 1.2 eq.) in anhydrous DCM (25 mL), 2-methylpropan-2-ol (1.87g, 25.2 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen overnight. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 20:1) to afford the product (3.2g, 86%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.47 (1H, *d*, *J* = 15.8 Hz), 6.71 (2H, *s*), 6.25 (1H, *d*, *J* = 15.8 Hz), 3.86 (3H, *s*), 3.85 (6H, *s*), 1.52 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 169.78, 166.32, 153.50, 143.60, 130.30, 119.58, 105.25, 80.57, 61.01, 56.23, 28.31.

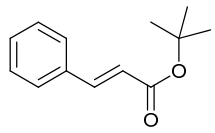


(*E*)-*tert*-butyl 3-(3,4-dimethoxyphenyl)acrylate

$C_{15}H_{20}O_4$ Mol. Wt.: 264.32

To a mixture of 3,4-dimethoxy cinnamic acid (3g, 14.4 mmol,), DCC (4.5g, 21.6 mmol, 1.5 eq.) and DMAP (2.1g, 17.3 mmol, 1.2 eq.) in anhydrous DCM (25 mL), 2-methylpropan-2-ol (2.2g, 28.8 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen overnight. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 10:1) to afford the product (3.3g, 87%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.52 (1H, *d*, *J* = 15.8 Hz), 7.06 (1H, *dd*, *J* = 1.9, 8.2 Hz), 7.02 (1H, *d*, *J* = 1.9Hz), 6.83 (1H, *d*, *J* = 8.2 Hz), 6.22 (1H, *d*, *J* = 15.8 Hz), 3.89 (6H, *s*), 1.52 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 166.20, 150.63, 148.92, 143.22, 127.36, 122.17, 117.61, 110.78, 109.28, 79.87, 55.59, 55.53, 27.98.

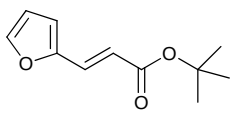


(*E*)-*tert*-butyl cinnamate

$C_{13}H_{16}O_2$ Mol. Wt.: 204.26

To a mixture of cinnamic acid (5g, 33.8 mmol,), DCC (10.45g, 50.6 mmol, 1.5 eq.) and DMAP (4.95g, 40.5 mmol, 1.2 eq.) in anhydrous DCM (30 mL), 2-methylpropan-2-ol (5g, 67.5 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen overnight. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C) to afford the product (5.5g, 80%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.59 (1H, *d*, *J* = 16.0 Hz), 7.51-7.48 (2H, *m*), 7.37-7.34 (3H, *m*), 6.36 (1H, *d*, *J* = 16.0 Hz), 1.54 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 166.27, 143.52, 134.69, 129.93, 128.80, 127.93, 120.22, 80.43, 28.20.

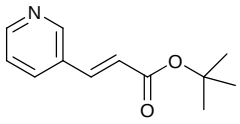


(*E*)-*tert*-butyl 3-(furan-2-yl)acrylate

$C_{11}H_{14}O_3$ Mol. Wt.: 194.23

To a mixture of (*E*)-3-(furan-2-yl)acrylic acid (3g, 21.7 mmol,), DCC (6.72g, 32.6 mmol, 1.5 eq.) and DMAP (3.1g, 26.0 mmol, 1.2 eq.) in anhydrous DCM (25 mL), 2-methylpropan-2-ol (3.3g, 43.4 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen overnight. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 8:1) to afford the product (3.5g, 83%) as a yellow solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.44 (1H, *d*, *J* = 1.0 Hz), 7.32 (1H, *d*, *J* = 15.7 Hz), 6.55 (1H, *d*, *J* = 3.3 Hz), 6.43 (1H, *dd*, *J* = 1.0, 3.3 Hz), 6.24 (1H, *d*, *J* = 15.7 Hz), 1.51(9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 166.41, 151.23, 144.49, 130.15, 118.09, 114.09, 112.22, 80.44, 28.27.

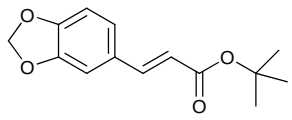


(*E*)-*tert*-butyl 3-(pyridin-3-yl)acrylate

$C_{12}H_{15}NO_2$ Mol. Wt.: 205.25

To a mixture of (*E*)-3-(pyridin-3-yl)acrylic acid (2g, 13.4 mmol,), DCC (4.2g, 20.1 mmol, 1.5 eq.) and DMAP (2.0g, 16.1 mmol, 1.2 eq.) in anhydrous DCM (30 mL), 2-methylpropan-2-ol (2.0g, 26.8 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen for 48 hours. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 12:1) to afford the product (2.4g, 87%) as a white powder.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 8.73 (1H, *d, J* = 1.7 Hz), 8.58 (1H, *dd, J* = 1.7, 4.8 Hz), 7.82 (1H, *dt, J* = 1.7, 8.0 Hz), 7.57 (1H, *d*, *J* = 16.1 Hz), 7.32 (1H, *dd*, *J* = 4.8, 8.0 Hz), 6.45 (1H, *d*, *J* = 16.1 Hz), 1.54 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 165.57, 150.72, 149.60, 139.79, 134.13, 130.41, 123.71, 122.39, 80.97, 28.15.



(*E*)-*tert*-butyl 3-(benzo[*d*][1,3]dioxol-5-yl)acrylate

$C_{14}H_{16}O_4$ Mol. Wt.: 248.27

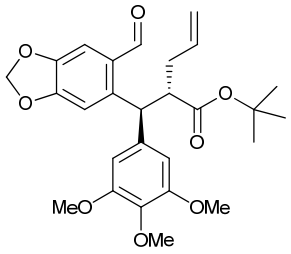
To a mixture of (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylic acid (5g, 26.0 mmol,), DCC (8.0g, 39.0 mmol, 1.5 eq.) and DMAP (3.8g, 31.2 mmol, 1.2 eq.) in anhydrous DCM (30 mL), 2-methylpropan-2-ol (4.0g, 52.0 mmol, 2.0 eq.) was added. The resulting solution was degassed and purged with nitrogen. The reaction was then stirred at reflux under nitrogen overnight. After filtration through Celite, the solvent was removed under reduced pressure and the residue was directly chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 40:1) to afford the product (5.5g, 85%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.48 (1H, *d*, *J* = 15.8 Hz), 7.0 (1H, *s*), 6.97 (1H, *d*, *J* = 8.0 Hz), 6.78 (1H, *d*, *J* = 8.0 Hz), 6.18 (1H, *d*, *J* = 15.8 Hz), 5.98 (2H, *s*), 1.52 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 166.64, 149.47, 148.43, 143.37, 129.29, 124.22, 118.37, 108.63, 106.63, 101.60, 80.48, 28.37.

General Procedure for Sequential Conjugate addition-Allylations:

To a solution of 2-(2-bromoaryl)-3,4-dimethyl-5-phenyloxazolidine (6.80 mmol, 2.0 eq.) in anhydrous THF (8 mL) was added *n*-BuLi (2.5M in hexane, 2.72 mL, 6.80 mmol, 2.0 eq.) under nitrogen atmosphere at –78ºC. The resulting solution was stirred at –78ºC for 30 minutes. To this solution, TMEDA (*N,N,N',N'*-tetramethylethylenediamine, 1.03 mL, 6.80mmol) was added dropwise. After stirring at –78ºC for 10 minutes, a solution of *t*-butyl ester (3.40 mmol) in anhydrous THF (10 mL) was added dropwise. After addition, the resulting mixture was stirred under nitrogen at –78ºC for 1.5 hours. Allyl bromide (2.08 g, 17.19 mmol, 5.0 eq.) or other alkyl bromide (17.19 mmol, 5.0 eq.) was added at –78ºC and the reaction mixture was gradually warmed to room temperature and stirred for another 2 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and diluted with water (30 mL). The mixture was extracted with ethyl acetate (5X 10 mL). The

organic phases were combined and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were re-dissolved in THF (20 mL) and treated with aqueous acetic acid (HOAc : H_2O = 1:1, 8 mL) at room temperature for 12 hours. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (5X 10 mL). The combined organic phases were dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were chromatographed on silica gel (Petroleum ether 60-90°C: ethyl acetate = 8:1) to provide olefin **7** (55-68%) as colorless oil. The aqueous phases were treated with sodium bicarbonate (PH = 8) then extracted with ethyl acetate (5X 10 mL). After removal of solvent, the residue were subjected to recrylstallization with ethyl acetate/ hexane to afford (1*S*,2*S*)-(+)-pseudoephedrine (890 mg, 79%) as a white solid.



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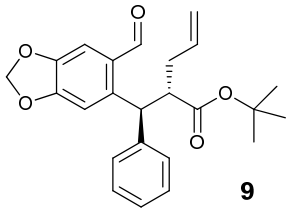
(*S*)-*tert*-butyl 2-((*S*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(3,4,5-trimethoxyphenyl)methyl)pent-4-enoate

$C_{27}H_{32}O_8$ Mol. Wt.: 484.54

Yield: (1.07g), 65%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 9.1 min; major isomer: 16.1 min. $[\alpha]^{27}_D$ -26.37° (c 4.55, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.37 (1H, *s*), 7.26 (1H, *s*), 7.09 (1H, *s*), 6.52 (2H, *s*), 6.02 (1H, *s*), 6.00 (1H, *s*), 5.83-5.70 (1H, *m*), 5.11 (1H, *d*, *J* = 11.7 Hz), 5.05 (1H, *d*, *J* = 3.6 Hz), 5.03 (1H, *d*, *J* = 11.7 Hz), 3.84 (6H, *s*), 3.80 (3H, *s*), 3.18-3.08 (1H, *m*), 2.29 (1H, *t*, *J* = 7.1Hz), 1.19 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.43, 172.52, 153.42, 152.30, 146.72, 142.47, 136.98, 136.72, 134.65, 128.27, 117.08, 109.38, 107.73, 105.20 (X2), 102.01, 80.84, 60.71, 56.18 (X2), 51.47, 45.84, 35.97, 27.72 (X3). EIMS *m*/*z* (%) : 484 (M^+, 12%), 427 (39), 409 (11), 386 (6), 368 (10), 340 (17), 327 (100), 312 (26), 297 (54), 282 (6), 266 (4), 254 (7), 233 (3), 224 (3), 195 (7). HRMS *m*/*z* Found: 507.1989, Calcd. for $C_{27}H_{32}O_8Na$ $(M+Na)^+$: 507.1994.



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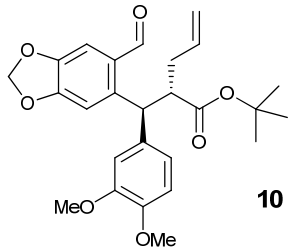
(*S*)-*tert*-butyl 2-((*S*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(phenyl)methyl)pent-4-enoate

$C_{24}H_{26}O_5$ Mol. Wt.: 394.46

Yield: (926 mg) 69%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 9.0 min; major isomer: 15.4 min. $[\alpha]^{27}_D$ -18.12° (c 5.52, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.41 (1H, *s*), 7.31-7.26 (5H, *m*), 7.24-7.18 (1H, *m*), 7.09 (1H, *s*), 6.00(1H, *s*), 5.97 (1H, *s*), 5.73-5.70 (1H, *m*), 5.14 (1H, *d*, *J* = 11.6 Hz), 5.03 -4.97 (2H, *m*), 3.22-3.18 (1H, *m*), 2.25 (2H, *t*, *J* =

7.1 Hz), 1.19(9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 188.94, 172.37, 152.14, 146.52, 142.49, 140.98, 134.49, 128.72, 128.14, 127.98, 126.76, 116.85, 108.56, 107.79, 101.79, 80.47, 51.09, 45.60, 35.78, 27.53. EIMS *m*/*z* (%) : 394 (M^+, 6%), 338 (70), 320 (16), 293 (8), 279 (18), 251 (100), 239 (63), 221 (7), 211 (8), 193 (3), 181 (11), 165 (7), 152 (24). HRMS *m*/*z* Found: 417.1668, Calcd. for $C_{24}H_{26}O_5Na$ $(M+Na)^+$: 417.1677.



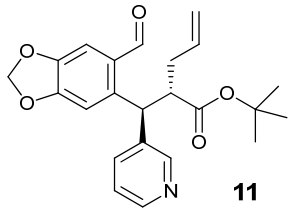
10

(*S*)-*tert*-butyl 2-((*S*)-(3,4-dimethoxyphenyl)(6-formylbenzo[*d*][1,3]dioxol-5-yl)methyl)pent-4-enoate

$C_{26}H_{30}O_7$ Mol. Wt.: 454.51

Yield: (942 mg), 61%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 10.3 min; major isomer: 25.6 min. $[\alpha]^{27}_D$ -21.17° (c 4.96, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.36 (1H, *s*), 7.22 (1H, *s*), 7.06 (1H, *s*) , 6.85 (1H, *dd*, *J* = 1.8, 8.3 Hz), 6.79 (1H, *d*, *J* = 1.8 Hz), 6.77 (1H, *d*, *J* = 8.3 Hz), 5.98 (1H, *s*), 5.94 (1H, *s*), 5.77-5.68 (1H, *m*), 5.08 (1H, *d*, *J* = 11.5 Hz), 5.00 (1H, *d*, *J* = 2.9 Hz), 4.98 (1H, *d*, *J* = 11.5 Hz), 3.82 (3H, *s*), 3.80 (3H, *s*), 3.16-3.08 (1H, *m*), 2.25 (2H, *t*, *J* = 7.1 Hz), 1.16 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.27, 172.55, 152.25, 149.09, 147.91, 146.59, 142.89, 134.69, 133.65, 128.15, 119.92, 116.94, 111.57, 111.48, 108.97, 107.73, 101.92, 80.61, 55.83, 55.69, 51.42, 45.27, 35.94, 27.66. EIMS *m*/*z* (%) : 454 (M^+, 7%), 398 (31), 381 (8), 339 (13), 311 (35), 299 (100), 298 (41), 297 (39), 268 (20), 253 (6), 241 (6), 225 (7), 207 (3), 197 (4). HRMS *m*/*z* Found: 477.1878, Calcd. for $C_{26}H_{30}O_7Na$ $(M+Na)^+$: 477.1889.



11

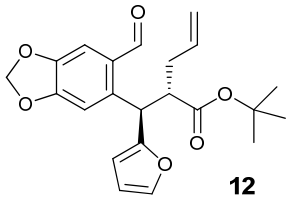
(*S*)-*tert*-butyl 2-((*R*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(pyridin-3-yl)methyl)pent-4-enoate

$C_{23}H_{25}NO_5$ Mol. Wt.: 395.45

Yield: (901 mg) 67%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 11.9 min; major isomer: 21.5 min. $[\alpha]^{27}_D$ -8.87° (c 9.58, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.24 (1H, *s*), 8.64 (1H, *d*, *J* = 1.8 Hz), 8.46 (1H, *d*, *J* = 4.6 Hz), 7.67 (1H, *d*, *J* = 7.9 Hz), 7.23 (2H, *m*), 7.13 (1H, *s*), 6.04 (1H, *s*), 6.00 (1H, *s*), 5.77-5.68 (1H, *m*), 5.32 (1H, *d*, *J* = 11.6 Hz), 5.04-4.98 (2H, *m*), 3.25-3.17 (1H, *m*), 2.31-2.18 (2H, *m*), 1.20 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.49, 172.19, 152.40, 149.97, 148.38, 146.96, 141.27, 136.82, 135.83, 134.16, 128.31, 123.69, 117.54, 110.76, 108.07,

102.22, 81.11, 51.10, 43.61, 35.88, 27.81. EIMS *m*/*z* (%) : 396 (M^++1, 4%), 395 (M^+, 2%), 354 (3), 339 (45), 321 (13), 298 (41), 294 (15), 280 (9), 252 (100), 240 (71), 224 (7), 212 (21), 195 (4), 182 (7), 166 (4), 154 (13). HRMS *m*/*z* Found: 396.1803, Calcd. for $C_{23}H_{26}NO_5$ $(M+1)^+$: 396.1810.



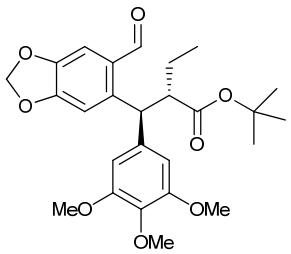
12

(*S*)-*tert*-butyl 2-((*R*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(furan-2-yl)methyl)pent-4-enoate

$C_{22}H_{24}O_6$ Mol. Wt.: 384.42

Yield: (810 mg) 62%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase : hexane / *iso*-propanol 95 / 5; flow rate: 1.50 mL/min; detection, UV 254 nm; *t*R for minor isomer: 10.4 min; major isomer: 21.8 min. $[\alpha]^{27}_D$ -75.40° (c 3.78, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.33 (1H, *s*), 7.33 (1H, *s*), 7.26 (1H, *s*), 7.14 (1H, *s*), 6.27(1H, *m*), 6.21 (1H, *d*, *J* = 3.1 Hz), 6.00 (1H, *s*), 5.96 (1H, *s*), 5.79-5.70 (1H, *m*), 5.26 (1H, *d*, *J* = 11.3 Hz), 5.06-5.00 (2H, *m*), 3.25-3.19 (1H, *m*), 2.29 (2H, *t*, *J* = 7.6 Hz), 1.16 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.16, 172.01, 153.54, 152.23, 147.03, 142.06, 139.91, 134.48, 128.30, 117.16, 110.32, 108.89, 108.60, 107.43, 101.97, 80.87, 50.81, 39.70, 35.95, 27.72. EIMS *m*/*z* (%) : 384 (M^+, 2%), 328 (81), 311 (4), 287 (20), 282 (10), 269 (9), 241 (100), 229 (52), 213 (9), 201 (17). HRMS *m*/*z* Found: 407.1474, Calcd. for $C_{22}H_{24}O_6Na$ $(M+Na)^+$: 407.1470.



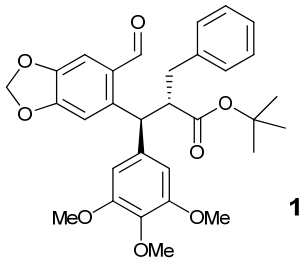
13

(*S*)-*tert*-butyl 2-((*S*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(3,4,5-trimethoxyphenyl)methyl)butanoate

$C_{26}H_{32}O_8$ Mol. Wt.: 472.53

Yield: (1.03 g) 64%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 8.8 min; major isomer: 13.3 min. $[\alpha]^{24}_D$ -27.78° (c 0.264, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.36 (1H, *s*), 7.23 (1H, *s*), 7.08 (1H, *s*), 6.48 (1H, *s*), 6.00 (1H, *s*), 5.97 (1H, *s*), 5.03 (1H, *d, J* = 11.6 Hz), 3.81 (6H, *s*), 3.76 (3H, *s*), 2.99-2.91 (1H, *m*), 1.59-1.50 (2H, *m*), 1.19 (9H, *s*), 0.91 (3H, *t, J* = 7.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.53, 173.34, 153.50, 152.42, 146.79, 142.99, 137.23, 137.11, 128.44, 109.33, 107.87, 105.37, 102.07, 80.76, 60.87, 56.34, 53.59, 46.39, 27.85, 24.99, 11.84. EIMS *m*/*z* (%) : 473 (M^++1, 5%), 472 (M^+, 16%), 416 (40), 398 (17), 329 (87), 328 (100), 298 (56), 283 (16), 267 (10), 255 (16), 225 (7), 222 (9), 209 (6), 185 (7), 181 (12). HRMS *m*/*z* Found: 495.2009, Calcd. for $C_{26}H_{32}O_8Na$ $(M+Na)^+$: 495.1994.



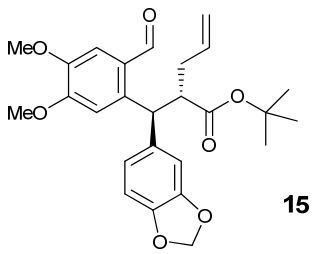
14

(2*S*,3*S*)-*tert*-butyl 2-benzyl-3-(6-formylbenzo[*d*][1,3]dioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)propanoate

$C_{31}H_{34}O_8$ Mol. Wt.: 534.60

Yield: (1.05 g) 58%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 9.3 min; major isomer: 20.4 min. $[\alpha]^{24}_D$ -16.28° (c 0.215, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.40 (1H, *s*), 7.27-7.10 (7H, *m*), 6.63 (2H, *s*), 6.00 (1H, *d*, *J* = 1.1 Hz), 5.97 (1H, *d*, *J* = 1.1 Hz), 5.22 (1H, *d*, *J* = 11.6 Hz), 3.88 (6H, *s*), 3.81 (3H, *s*), 3.39-3.32 (1H, *m*), 2.85-2.80 (2H, *m*), 1.02 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.54, 172.69, 153.62, 152.29, 146.84, 142.25, 138.89, 137.16, 136.90, 128.94, 128.33, 126.52, 109.50, 108.06, 105.34, 102.07, 80.80, 60.88, 56.33, 53.96, 46.60, 38.14, 27.59. EIMS *m*/*z* (%) : 535 (M^++1, 9%), 534 (M^+, 35%), 478 (45), 461 (8), 415 (4), 387 (27), 369 (21), 329 (93), 328 (100), 298 (64), 283 (23), 267 (16), 255 (20), 239 (8), 225 (7), 195 (18), 181 (9), 153 (8), 139 (5), 115 (4), 91 (53). HRMS *m*/*z* Found: 557.2143, Calcd. for $C_{31}H_{34}O_8Na$ $(M+Na)^+$: 557.2151.



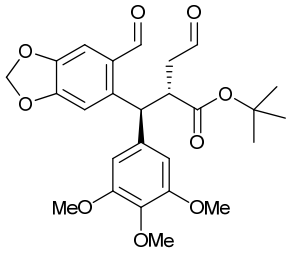
15

(*S*)-*tert*-butyl 2-((*S*)-benzo[*d*][1,3]dioxol-5-yl(2-formyl-4,5-dimethoxyphenyl)methyl)pent-4-enoate

$C_{26}H_{30}O_7$ Mol. Wt.: 454.51

Yield: (850 mg) 55%; Chiral HPLC analysis: 25°C; column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol 80 / 20; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for minor isomer: 7.5 min; major isomer: 8.9 min. $[\alpha]^{27}_D$ -16.88° (c 6.22, $CHCl_3$).

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.38 (1H, *s*), 7.30 (1H, *s*), 7.07 (1H, *s*), 6.80-6.71 (3H, *m*), 5.91(1H, *s*), 5.90 (1H, *s*), 5.76-5.70 (1H, *m*), 5.07-5.00 (3H, *m*), 4.01 (3H, *s*), 3.88 (3H, *s*), 3.16-3.12 (1H, *m*), 2.27 (2H, *t*, *J* = 7.1 Hz), 1.14 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 189.51, 172.64, 153.38, 147.90, 147.50, 146.27, 140.25, 135.09, 134.57, 126.47, 121.37, 117.02, 111.73, 109.89, 108.32, 108.07, 100.95, 80.58, 56.03, 55.79, 51.51, 45.47, 36.01, 27.58. EIMS *m*/*z* (%) : 455 (M^++1, 1%), 454 (M^+, 4%), 398 (40), 380 (5), 353 (4), 339 (8), 311 (57), 299 (100), 268 (18), 267 (16), 253 (6), 241 (10), 225 (7), 209 (3), 197 (6), 165 (3). HRMS *m*/*z* Found: 477.1882, Calcd. for $C_{26}H_{30}O_7Na$ $(M+Na)^+$: 477.1889.



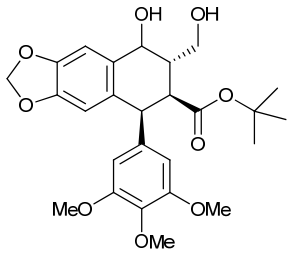
16

(*S*)-*tert*-butyl 2-((*S*)-(6-formylbenzo[*d*][1,3]dioxol-5-yl)(3,4,5-trimethoxyphenyl)methyl)-4-oxobutanoate

$C_{26}H_{30}O_9$ Mol. Wt.: 486.51

To a mixture of olefin **5** (1.80 g, 3.71 mmol) in THF-*t*-BuOH-H_2O (19 mL, 10:8:1) was added *N*-methylmorpholine *N*-oxide (869.3 mg, 7.42 mmol, 2.0 eq.) followed by osmium tetroxide (94.4 mg, 0.37 mmol, 0.1 eq.). The resulting mixture was stirred at room temperature. The reaction progress was monitored by thin layer chromatography. Aqueous saturated sodium sulfite (10 mL) was added. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (5X20 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dissolved in DCM (40 mL) and subjected to oxidative cleavage with silica gel supported sodium periodate (7.4 g, $NaIO_4/SiO_2$ = 1 mmol/2 g, 1.0 eq.).*[$NaIO_4$ (2.57 g, 12.0 mmol) was dissolved in 5 mL of hot water (~70°C) in a 25 mL round-bottomed flask. To the hot solution was added silica gel (230-400 mesh, 10 g) with vigorous swirling and shaking. The resultant silica gel coated with $NaIO_4$ was in a powder form. Y.-L. Zhong, T. K. M. Shing, *J. Org. Chem*. **1997**, *62*, 2622.] The resulting mixture was stirred at room temperature for 2-3 hours. The reaction progress was monitored by thin layer chromatography. After filtration and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 4:1) to afford the product (1.71 g, 94% yield). The dialdehyde **16** is unstable and the crude product could be used directly in next step without further purification.

$[\alpha]^{27}_D$ -95.38° (c 1.66, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 10.24 (1H, *s*), 9.66 (1H, *s*), 7.23 (1H, *s*), 7.13 (1H, *s*), 6.54 (2H, *s*), 6.05 (1H, *s*), 6.01 (1H, *s*), 5.23 (1H, *d*, *J* = 11.7 Hz), 3.82 (6H, *s*), 3.78 (3H, *s*), 3.65-3.57 (1H, *m*), 2.87 (1H, *dd*, *J* = 9.9, 18.2 Hz), 2.60 (1H, *dd*, *J* = 3.2, 18.2 Hz), 1.17 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 199.42, 189.59, 172.19, 153.63, 152.21, 146.95, 141.27, 137.33, 136.12, 128.35, 110.33, 108.37, 105.24, 102.10, 81.39, 60.79, 56.28, 45.63, 45.57, 45.03, 27.59. EIMS *m*/*z* (%) : 486 (M^+, 12%), 468 (4), 429 (11), 411 (37), 394 (13), 367 (32), 349 (47), 338 (41), 327 (100), 313 (37), 296 (35), 282 (16), 266 (7), 255 (11), 238 (7), 225 (5), 210 (22), 195 (19), 181 (9), 168 (12), 153 (7). HRMS *m*/*z* Found: 509.1790, Calcd. for $C_{26}H_{30}O_9Na$ $(M+Na)^+$: 509.1787.



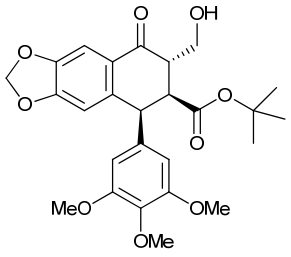
17

(5*S*,6*S*,7*S*)-*tert*-butyl 8-hydroxy-7-(hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxole-6-carboxylate

$C_{26}H_{32}O_9$ Mol. Wt.: 488.53

To a solution of dialdehyde **16** (500 mg, 1.02 mmol) in dichloromethane (20 mL) was added L-Proline (11.8 mg, 0.10 mmol, 0.1 eq.). The resulting mixture was stirred at 25ºC for 3-4 hours. The reaction progress was monitored frequently (ca 10 minutes interval) by thin layer chromatography. The reaction mixture was cooled to 0ºC in an ice-water bath and a powder of sodium borohydride (46.3 mg, 1.22 mmol, 1.2 eq.) was added. Methanol (1.0 mL) was added dropwise over a period of 5 minutes. After stirring at 0ºC for 30 minutes, silica gel was added and the resulting mixture was stirred at room temperature for 30 minutes. After filtration and removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 4:1) to afford a mixture of diols (400 mg, 80%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.05 (1H, *s*, C4α-isomer), 6.81 (1H, *s*, C4β-isomer), 6.41 (1H, *s*, C4β-isomer), 6.39 (1H, *s*, C4α-isomer), 6.33 (2H, *s*, C4α-isomer), 6.16 (2H, *s*, C4β-isomer), 5.92 (2H, *s*, C4β-isomer), 5.90 (2H, *s*, C4α-isomer), 4.99 (1H, *brs*, C4β-isomer), 4.87 (1H, *m*, C4α-isomer), 4.38 (1H, *d*, *J* = 6.4Hz, C4β-isomer), 4.23 (1H, *d*, *J* = 5.7Hz, C4α-isomer), 4.12-3.92 (2H, *m*, C4β-isomer), 3.90-3.60 (4H, *m*), 3.84 (3H, *s*, C4α-isomer), 3.83 (3H, *s*, C4β-isomer), 3.80 (6H, *s*, C4α-isomer), 3.76 (6H, *s*, C4β-isomer), 3.37 (1H, *dd*, *J* = 6.4, 12.4Hz, C4β-isomer), 2.86 (1H, *dd*, *J* = 5.7, 12.3Hz, C4α-isomer), 2.70 (1H, *m*), 2.55-2.43 (1H, *m*), 2.26 (1H, *brs*), 1.29 (9H, *s*), 1.28 (9H, *s*).



18

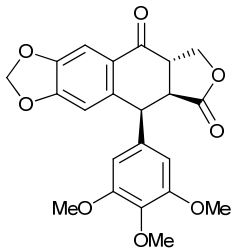
(5*S*,6*S*,7*S*)-*tert*-butyl 7-(hydroxymethyl)-8-oxo-5-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxole-6-carboxylate

$C_{26}H_{30}O_9$ Mol. Wt.: 486.51

To a solution of diol mixture **17** ((130 mg, 0.27 mmol) in acetonitrile (10 ml) was added a powder of activated MnO_2 (235 mg, 2.70 mmol, 10 eq.).* [The activated MnO_2 was freshly prepared by addition of an aqueous solution of $MnSO_4$•H_2O (14.24 g in 33 mL of water) and an aqueous solution of NaOH (11.33g in 17 mL of water) simutaneously to a solution of $KMnO_4$ (16.25 g in 100 mL of water) at 90°C over a period of 1 hour. After addition, the resulting mixture was stirred at 90°C for 1.5 hours. The suspension was filtered and washed with water (4 X 10 mL) then washed with 5% aqueous solution of acetic acid (2 X 10 mL) and dried under reduced pressure for 5-10 minutes.] The resulting mixture was stirred at room temperature for 2-3 days. The reaction progress was monitored by thin layer chromatography. After filtration and removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 2:1) to afford the product (105 mg, 81 %) as a colorless syrups.

$[\alpha]^{27}_D$ +226.12° (c 12.98, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.43 (1H, *d, J* = 1.8 Hz), 6.54 (1H, *s*), 6.17 (2H, *s*), 5.97 (1H, *s*), 5.95 (1H, *s*), 4.47 (1H, *d*, *J* = 5.4 Hz), 4.21-4.10 (1H, *m*), 3.85-3.70 (1H, *m*), 3.74 (3H, *s*), 3.70 (6H, *s*), 3.42 (1H, *dd*, *J* = 5.4, 12.8 Hz), 3.13-3.00 (1H, *m*), 2.97 (1H, *brs*), 1.28 (9H, *s*). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 198.16, 170.22, 153.17, 153.07, 147.86, 141.35, 137.53, 134.39, 126.67, 108.42, 106.69, 105.80, 102.04, 81.61, 62.18, 60.78, 56.15, 47.27, 45.85, 27.94. EIMS *m*/*z* (%) : 486 (M^+, 40%), 467 (16), 456 (87), 455 (85), 429

(11), 411 (55), 399 (80), 383 (20), 366 (100), 354 (93), 338 (36), 324 (38), 308 (18), 296 (30), 265 (11), 253 (13), 237 (7), 225 (12), 215 (15), 199 (13), 195 (21), 187 (44), 181 (31), 168 (35), 153 (20). HRMS *m/z* Found: 509.1775, Calcd. for $C_{26}H_{30}O_9Na$ $(M+Na)^+$: 509.1787.



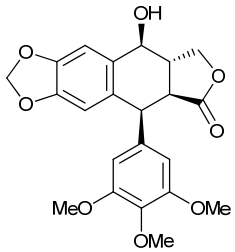
***ent*-2**

(+)-Podophyllotoxone

$C_{22}H_{20}O_8$ Mol. Wt.: 412.39

To a solution of alcohol **18** (70 mg, 0.144 mmol) in acetonitrile (3 mL) was added a solution of aqueous HCl in acetonitrile (3 mL) *[prepared by addition of 37% aqueous HCl (4 g) to acetonitrile (7.48 g) at 0ºC]. The resulting mixture was stirred at room temperature for 4 hours. The reaction progress was monitored by thin layer chromatography. The reaction mixture was cooled to 0ºC and an aqueous solution of saturated $NaHCO_3$ was added until PH = 6. The resulting mixture was extracted with ethyl acetate (5X10 mL) and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was dissolved in DCM (5mL) and treated with DCC (30mg, 0.144mmol). The resulting mixture was stirred at room temperature for 10 minutes. After removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 2:1) to afford the product (57 mg, 90%) as a white solid.

$[\alpha]^{27}_D$ +92.92° (c 1.13, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.53 (1H, *s*), 6.69 (1H, *s*), 6.37 (2H, *s*), 6.09 (1H, *s*), 6.07 (1H, *s*), 4.83 (1H, *d*, *J* = 4.1 Hz), 4.55 (1H, *t*, *J* = 8.7 Hz), 4.34 (1H, *t*, *J* = 10.0 Hz), 3.80 (3H, *s*), 3.74 (6H, *s*), 3.56-3.45 (1H, *m*), 3.27 (1H, *dd*, *J* = 4.2, 15.5 Hz). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 192.39, 173.00, 153.18, 153.10, 148.13, 141.53, 137.83, 132.10, 128.23, 109.64, 107.79, 106.09, 102.38, 66.96, 60.74, 56.30, 46.69, 44.67, 43.46. EIMS *m/z* (%) : 412 (M^+, 100%), 397 (4), 367 (27), 353 (12), 336 (18), 321 (5), 306 (6), 297 (3), 267 (4), 254 (5), 244 (8), 225 (9), 216 (10), 200 (13), 188 (7), 168 (23), 153 (22). HRMS *m/z* Found: 435.1050, Calcd. for $C_{22}H_{20}O_8Na$ $(M+Na)^+$: 435.1055. ^{1}H-NMR spectra agreed with those published (P. M. Dewick, D. E. Jackson, *Phytochemistry*, **1981**, *20*, 2277).



***ent*-1**

(+)-Podophyllotoxin

$C_{22}H_{22}O_8$ Mol. Wt.: 414.41

To a solution of podophyllotoxone **2** (30 mg, 0.07 mmol) in anhydrous THF (5 mL) was added a solution of L-Selectride (0.09 mL, 1M in THF, 0.09 mmol, 1.3 eq.) at –78ºC under nitrogen. The resulting mixture was stirred at –

78ºC for 2 hours then treated with aqueous solution of saturated NH_4Cl (5 mL). The mixture was stirred at room temperature for 30 minutes then diluted with water (10 mL). The mixture was extracted with ether (5X5mL) and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (Petroleum ether 60-90°C : ethyl acetate = 2:1) to afford the product (29.5 mg, 98%) as a white solid.

HPLC analysis of Racemic sample: (made by our previous total synthesis) column: DAICEL Chiralpak OD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for (+)-enanitiomer, 13.3 min; (-)-enanitiomer, 18.5 min.
HPLC analysis of authentic sample: column: DAICEL Chiralpak OD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for podophyllotoxin (natural product): 18.6 min.
HPLC analysis of asymmetric synthetic sample: column: DAICEL Chiralpak OD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for asymmetric total synthesis of podophyllotoxin: major enantiomer, 13.6 min (Area %: 99.6128); minor enantiomer, 18.9 min (Area %: 0.3872). ee% = 99.2

HPLC analysis of Racemic sample: (made by our previous total synthesis) column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for (-)-enanitiomer, 8.2 min; (+)-enanitiomer, 14.0 min.
HPLC analysis authentic sample: column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for podophyllotoxin (natural product): 8.1 min.
HPLC analysis of asymmetric synthetic sample: column: DAICEL Chiralpak AD-H; mobile phase: hexane / *iso*-propanol = 70 / 30; flow rate: 1.00 mL/min; detection, UV 254 nm; *t*R for asymmetric total synthesis of podophyllotoxin: minor enantiomer, 8.1 min (Area %: 0.9024); major enantiomer, 14.2 min (Area %: 99.0976). ee% = 98.2

$[\alpha]^{27}_D$ +91.81° (c 7.08, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$), δ (ppm): 7.10 (1H, *s*), 6.49 (1H, *s*), 6.36 (2H, *s*), 5.97 (1H, *s*), 5.95 (1H, *s*), 4.74 (1H, *t*, *J* = 7.9 Hz), 4.64-4.53 (2H, *m*), 4.05 (1H, *t*, *J* = 9.3 Hz), 3.79 (3H, *s*), 3.73 (6H, *s*), 2.84-2.70 (2H, *m*), 2.12 (1H, *d*, *J* = 7.0 Hz, OH). ^{13}C-NMR (75MHz, $CDCl_3$), δ (ppm): 174.73, 152.67, 147.82, 147.75, 137.32, 135.65, 133.42, 131.19, 109.82, 108.60, 106.47, 101.51, 72.73, 71.52, 60.85, 56.37, 45.40, 44.21, 40.80. EIMS *m*/*z* (%) : 414 (M^+, 100%), 413 (91), 398 (5), 380 (2), 364 (4), 354 (5), 336 (6), 321 (6), 297 (4), 282 (4), 267 (4), 229 (3), 207 (4), 201 (12), 181 (13), 168 (22), 153 (17). HRMS *m*/*z* Found: 437.1224, Calcd. for $C_{22}H_{22}O_8Na$ $(M+Na)^+$: 437.1212. ^{1}H-NMR spectra agreed with authentic sample and those published (C. F. Brewer, J. D. Loike, S. B. Horwitz, H. Sternlicht, W. J. Gensler, *J. Med. Chem.* **1979**, *22*, 215; A. J. Reynolds, A. J. Scott, C. I. Turner, M. S. Sherburn, *J. Am. Chem. Soc.*. **2003**, *125*, 12108).