Supporting Information

Kinase Inhibition by Deoxy Analogs of the Resorcylic Lactone L-783277

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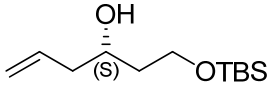
1. General Methods

All manipulations were conducted under an argon atmosphere using flame-dried glassware and standard syringe/septa techniques. Absolute solvents were purchased from Fluka (absolute over molecular sieves). Commercial chemicals were used without further purification. Aldehyde **4** was prepared according to literature procedures in two steps from commercially available 1,3-propanediol.
Solvents for extractions, flash column chromatography (FC) and thin layer chromatography (TLC) were purchased as commercial grade and distilled prior to use. TLC was performed on Merck TLC aluminum sheets (silica gel 60 F_{254}). Spots were visualized with UV light (λ = 254 nm) or through staining with $Ce_2(SO_4)_3$/phosphomolybdic acid/H_2SO_4 (CPS), vanillin/H_2SO_4 or $KMnO_4/K_2CO_3$. Chromatographic purification of products (FC) was performed using Fluka silica gel 60 for preparative column chromatography (particle size 40-63 µm).
NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer at 300 K. Chemical shifts (δ) are reported in ppm and are either referenced to the solvent signal as an internal standard (chloroform δ 7.26 ppm for ^{1}H and δ 77.00 ppm for ^{13}C spectra; DMSO-d_6 δ 2.50 ppm for ^{1}H and δ 39.43 ppm for ^{13}C spectra) or to TMS for benzene-d_6. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, m_c = centered multiplet, br = broad signal, *J* = coupling constant in Hz. All ^{13}C-NMR spectra were measured with complete proton decoupling. ^{1}H- and ^{13}C-signals were assigned using DEPT135 experiments and two-dimensional correlation experiments (COSY, HMQC, HMBC, NOESY). IR spectra were recorded on a Jasco FT/IR-6200 instrument as thin film. Optical rotations were measured on a Jasco P-1020 polarimeter operating at the sodium D line (λ = 589 nm) and are reported as follows: $[\alpha]_D^T$, concentration (*c* in g/100 mL) and solvent. Melting points were obtained in open capillary tubes using a Büchi melting point apparatus B-540 and are uncorrected. Mass spectra were recorded by the ETH Zürich MS service; HRMS (ESI) spectra were measured on a Bruker Daltonics maxis (UHR-TOF) and HRMS (EI) on a Waters Micromass AutoSpec Ultima instrument.

2. Synthesis of 5-deoxy L-783277 (1)

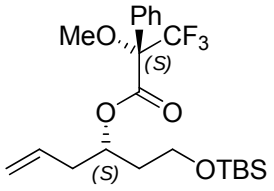


5

Homoallylic alcohol 5: A mixture of (*S*)-BINOL (73.7 mg, 0.26 mmol, 5 mol%) and oven-dried powdered molecular sieves (160 mg) in anhydrous toluene (9.7 mL) was treated with Ti(O*i*Pr)$_4$ (38.5 µl, 0.13 mmol, 2.5 mol%) and stirred for 2.5 h at rt.

Aldehyde **4**[1] (0.97 g, 5.15 mmol, 1.0 equiv) was then added at rt and the reaction mixture was stirred for 5 min. After cooling to –78 °C allylbutyltin (2.40 ml, 7.73 mmol, 1.5 equiv) was added and the mixture was stirred for –78 °C for 10 min followed by 139 h at –20 °C. Sat. aq $NaHCO_3$ was then added and the resulting mixture was extracted with hexane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by FC (hexane/Et_2O, 5:1) to give **5** as a yellowish oil (1.07 g, 90%, 98% *ee*).

R_f = 0.24 (hexane/Et_2O 5:1).
$[\alpha]_D^{24}$ = −7.8° (*c* = 0.843, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 5.85 (tdd, *J* = 7.1, 10.2, 17.3 Hz, 1H, CH_2CH=CH_2), 5.14-5.06 (m, 2H, CH_2CH=CH_2), 3.93-3.86 (m, 2H, C*H*OH and C*H*HOSi), 3.81 (m_c, 1H, CH*H*OSi), 3.30 (d, *J* = 1.5 Hz, 1H, OH), 2.25 (m_c, 2H, CH_2CH=CH_2), 1.67 (m_c, 2H, CH_2CH_2OSi), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 6H, Si(CH_3)$_2$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 135.0 (CH_2*C*H=CH_2), 117.3 (CH_2CH=*C*H_2), 71.2 (CHOH), 62.6 (CH_2OSi), 42.0 (*C*H_2CH=CH_2), 37.8 (CH_2CH_2OSi), 25.9 (SiC(*C*H_3)$_3$), 18.1 (Si*C*(CH_3)$_3$), -5.5 (Si(*C*H_3)(CH_3)),
-5.6 (Si(CH_3)(*C*H_3)).
IR (neat, ν/cm^{-1}): 3435w, 3078w, 2955m, 2929m, 2958m, 1642w, 1471m, 1389w, 1362w, 1255m, 1085s, 1005m, 913m, 835s, 776s, 729w, 663w.
HRMS (ESI): *m/z* calcd for $C_{12}H_{27}O_2Si$ $[M + H]^+$: 231.1775, found: 231.1764.



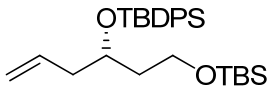
5a

Mosher ester 5a: To a solution of **5** (16.0 mg, 69.4 µmol, 1.0 equiv) in 0.1 mL DCM was added pyridine (0.1 ml, 1.24 mmol, 18 equiv), DMAP (30.0 mg, 246 µmol, 3.5 equiv) and (*R*)-(–)-MTPA-Cl (37.0 µL, 198 µmol, 2.9 equiv). The reaction mixture was stirred for 16 h at rt and the reaction was then quenched with 1 mL of water. The aqueous phase was extracted with Et_2O (3 x 4 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by FC (hexane/Et_2O 1:0 → 30:1 → 10:1) to afford *Mosher* ester **5a** as a colorless oil (30.0 mg, 97%, 98% *de*). The diastereoisomeric excess was determined by ^{1}H-NMR and chiral HPLC.

R_f = 0.43 (hexane/ Et_2O 10:1).
$[\alpha]_D^{24}$ = +1.0° (*c* = 0.855, $CHCl_3$).

[1] Mortensen, M. S.; Osbourn, J. M.; O'Doherty, G. A. *Org. Lett.* **2007**, *9*, 3105-3108.

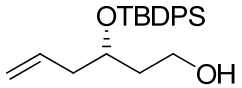
^{1}H-NMR (400.1 MHz, $CDCl_3$: δ 7.54 (m_c, 2H, Ph-*o*-CH), 7.42-7.37 (m, 3H, Ph-*m*-CH and Ph-*p*-CH), 5.66 (m_c, 1H, CH_2CH=CH_2), 5.31 (m_c, 1H, C*H*OH), 5.07-5.00 (m, 2H, CH_2CH=CH_2), 3.65 (m_c, 2H, CH_2OSi), 3.54 (d, *J* = 1.18 Hz, 3H, OCH_3), 2.41 (m_c, 2H, CH_2CH=CH_2), 1.86 (m_c, 2H, CH_2CH_2OSi), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 166.0 (C=O), 132.7 (CH_2*C*H=CH_2), 132.3 (Ph-*i*-C), 129.5 (Ph-*p*-C), 128.3 (Ph-*m*-C), 127.5 (Ph-*o*-C), 123.4 (q, *J* = 288 Hz, CF_3), 118.4 (CH_2CH=*C*H_2), 84.6 (q, *J* = 27.6 Hz, *C*OCH_3), 73.8 (CHOH), 59.0 (CH_2OSi), 55.3 (OCH_3), 38.3 (*C*H_2CH=CH_2), 36.2 (CH_2CH_2OSi), 25.8 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.4 ($Si(CH_3)_2$).
IR (neat, ν/cm^{-1}): 3078w, 2954m, 2930m, 2858m, 1746s, 1644w, 1472w, 1389w, 1254s, 1168s, 1099s, 1018s, 993m, 964w, 919w, 836s, 776s, 717m, 664w.
HRMS (ESI): *m/z* calcd for $C_{22}H_{34}F_3O_4Si$ $[M + H]^+$: 447.2173, found: 447.2167.
HPLC (Daicel Chiracel OD, hexane, 100%, 25 °C, 0.5 mL/min, UV): t_R/min = 12.0 (*RS*), 20.1 (*SS*).



6

Protected diol 6: A stirred solution of **5** (2.10 g, 9.11 mmol, 1.0 equiv) in dry DMF (4.6 mL) was treated at rt with imidazole (1.86 g, 27.3 mmol, 3.0 equiv) followed by TBDPSCl (3.31 mL, 12.8 mmol, 1.4 equiv). After stirring for 21 h the reaction mixture was diluted with EtOAc (30 mL). The resulting mixture was washed with brine (6 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residiue was purified by FC (hexane/Et_2O, 1:0 → 100:1) to give **6** (3.86 g, 90%) as a colorless oil.

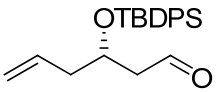
R_f = 0.30 (hexane/ Et_2O 100:1).
$[\alpha]_D^{24}$ = +14.5° (*c* = 0.763, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 7.70 (m_c, 4H, Ph-*o*-CH), 7.46-7.35 (m, 6H, Ph-*m*-CH and Ph-*p*-CH), 5.74 (tdd, *J* = 7.1, 10.2, 17.3 Hz, 1H, CH_2CH=CH_2), 4.95 (m_c, 2H, CH_2CH=CH_2), 3.97 (m_c, 1H, CHOSi), 3.64 (m_c, 2H, CH_2OSi), 2.20 (m_c, 2H, CH_2CH=CH_2), 1.73 (m_c, 2H, CH_2CH_2OSi), 1.08 (s, 9H, $Ph_2SiC(CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 135.9 (Ph-*o*-C), 134.7 (CH_2*C*H=CH_2), 134.5 (Ph-*i*-C), 134.3 (Ph-*i*-C'), 129.5 (Ph-*p*-C), 127.5 (Ph-*m*-C), 127.4 (Ph-*m*-C'), 116.9 (CH_2CH=*C*H_2), 70.4 (CHOSi), 60.0 (CH_2OSi), 41.4 (*C*H_2CH=CH_2), 39.2 (CH_2CH_2OSi), 27.0 ($Ph_2SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 19.4 ($Ph_2SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.3 ($Si(CH_3)_2$).
IR (neat, ν/cm^{-1}): 3072w, 3051w, 2954m, 2930m, 2857m, 1471m, 1428m, 1389w, 1361w, 1255m, 1105s, 1006m, 912m, 835s, 775m, 739m, 701s, 611m, 507m.
HRMS (ESI): *m/z* calcd for $C_{28}H_{45}O_2Si_2$ $[M + H]^+$: 469.2953, found: 469.2945.



7

Monoprotected diol 7: To a solution of **6** (3.68 g, 7.86 mmol, 1.0 equiv) in 20:1 THF/water (39.5 mL) was added *p*-TsOH monohydrate (150 mg, 0.79 mmol, 0.1 equiv) and the resulting solution was stirred at rt for 10 h. Sat. $NaHCO_3$ was then added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by FC (hexane/Et_2O 10:1 → 5:1 → 2:1) to give **7** as a colorless oil (2.55 g, 92%).

R_f = 0.23 (hexane/Et_2O 2:1).
$[\alpha]_D^{24}$ = +26.5° (*c* = 0.755, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 7.71 (m_c, 4H, Ph-*o*-CH), 7.48-7.37 (m, 6H, Ph-*m*-CH and Ph-*p*-CH), 5.61 (ddt, *J* = 7.2, 10.2, 17.3 Hz, 1H, CH_2CH=CH_2), 4.91 (m_c, 2H, CH_2CH=CH_2), 3.99 (m_c, 1H, CHOSi), 3.77 (ddd, *J* = 4.9, 8.3, 11.0 Hz, 1H, C*H*HOH), 3.67 (dt, *J* = 5.5, 11.0 Hz, 1H, CH*H*OH), 2.30 (dt, *J* = 7.7, 14.1 Hz, 1H, C*H*HCH=CH_2), 2.19 (m_c, 1H, CH*H*CH=CH_2), 1.88-1.78 (m, 2H, CH_2O*H* and C*H*HCH_2OH), 1.67 (ddd, *J* = 5.5, 11.2, 14.3 Hz, 1H, CH*H*CH_2OH), 1.08 (s, 9H, $Ph_2SiC(CH_3)_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 135.9 (Ph-*o*-C), 134.2 (CH_2CH=CH_2), 133.9 (Ph-*i*-C), 133.6 (Ph-*i*-C'), 129.8 (Ph-*p*-C), 129.7 (Ph-*p*-C'), 127.7 (Ph-*m*-C), 127.6 (Ph-*m*-C'), 117.3 (CH_2CH=CH_2), 71.7 (CHOSi), 59.7 (CH_2OH), 41.1 (CH_2CH=CH_2), 37.5 (CH_2CH_2OH), 27.0 ($Ph_2SiC(CH_3)_3$), 19.3 ($Ph_2SiC(CH_3)_3$).
IR (neat, v/cm^{-1}): 3370w, 3072w, 2931m, 2889w, 2858m, 1640w, 1590w, 1472m, 1428m, 1390w, 1362w, 1105s, 1169m, 1106m, 915m, 822m, 739m, 701s, 611m, 506s.
HRMS (ESI): *m/z* calcd for $C_{22}H_{31}O_2Si$ $[M + H]^+$: 355.2088, found: 355.2085.

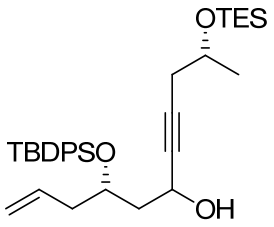


8

Aldehyde 8: To a solution of oxalylchloride (0.89 ml, 10.6 mmol, 1.5 equiv) in DCM (62 mL) at –78 °C was added dropwise DMSO (1.50 ml, 21.2 mmol, 3.0 equiv) in 39 mL DCM. After stirring at –78 °C for 10 min a solution of **7** (2.50 g, 7.05 mmol, 1.0 equiv) in DCM (23 mL) was added dropwise. The resultant cloudy mixture was stirred at –78 °C for 60 min, TEA (3.93 mL, 28.2 mmol, 4.0 equiv) was added slowly and the reaction mixture was allowed to warm to room temperature (60 min). The reaction was quenched with water (125 mL) and the layers were separated. The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic

phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (hexane/Et_2O 5:1) to give **8** (2.34 g, 94%) as a yellowish oil.

R_f = 0.41 (hexane/ Et_2O 5:1).
$[\alpha]_D^{24}$ = +17.7° (*c* = 1.08, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 9.70 (t, *J* = 2.4 Hz, 1H, CHO), 7.69 (m_c, 4H, Ph-*o*-CH), 7.48-7.37 (m, 6H, Ph-*m*-CH and Ph-*p*-CH), 5.68 (tdd, *J* = 7.2, 10.2, 17.3 Hz, 1H, CH_2CH=CH_2), 5.03 (m_c, 1H, CH_2CH=C*H*H), 4.96 (ddd, *J* = 1.4, 3.3, 17.1 Hz, 1H, CH_2CH=CH*H*), 4.28 (m_c, 1H, CHOSi), 2.52 (ddd, *J* = 1.4, 2.3, 5.9 Hz, 2H, CH_2CHO), 2.29 (m_c, 2H, CH_2CH=CH_2), 1.07 (s, 9H, $Ph_2SiC(CH_3)_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 201.7 (CHO), 135.8 (Ph-*o*-C), 133.7 (Ph-*i*-C), 133.5 (CH_2CH=CH_2), 133.4 (Ph-*i*-C'), 129.9 (Ph-*p*-C), 129.8 (Ph-*p*-C'), 127.7 (Ph-*m*-C), 127.6 (Ph-*m*-C'), 118.3 (CH_2CH=CH_2), 68.8 (CHOSi), 49.8 (CH_2CHO), 41.8 (CH_2CH=CH_2), 26.9 ($Ph_2SiC(CH_3)_3$), 19.2 ($Ph_2SiC(CH_3)_3$).
IR (neat, ν/cm^{-1}): 3072w, 2958w, 2931m, 2893w, 2858m, 1725s, 1472m, 1428m, 1391w, 1362w, 1105s, 998m, 919m, 822m, 741m, 701s, 612m, 507s, 489s.
HRMS (ESI): *m/z* calcd for $C_{12}H_{32}NO_2Si$ $[M + NH_4]^+$: 370.2197, found: 370.2203.

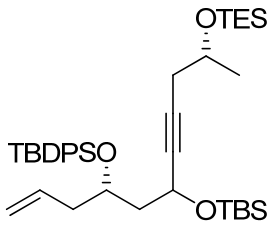


10

Acetylene 10: To a solution of **9** (1.53 g, 7.73 mmol, 1.2 equiv) in 41 mL abs. THF was added dropwise *n*-BuLi (4.83 mL, 7.73 mmol, 1.2 equiv) at –78 °C over a period of 10 min and the mixture was then stirred for 30 min at –10 °C. After re-cooling to –78 °C and a pre-cooled solution (–78 °C) of **8** (2.27 g, 6.44 mmol 1.0 equiv) in 31 mL abs. THF was added dropwise over a period of 20 min. After stirring for 45 min at –78 °C, the solution was allowed to warm to rt (1.5 h) and the reaction was quenched by adding sat. NH_4Cl to give a yellow solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 90 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by FC (hexane/Et_2O 6:1 → 4:1) to give a diastereoisomeric mixture of **10** as a yellow oil (3.29 g, 93%, dr 1:1).

R_f = 0.38 (dia1), 0.33 (dia2) (hexane/Et_2O 4:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 7.75-7.68 (m, 8H, Ph-*o*-CH), 7.48-7.35 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 5.58 (tdt, *J* = 7.2, 10.2, 17.4 Hz, 2H, CH_2CH=CH_2), 4.93 (ddd, *J* = 1.0, 1.9, 10.2 Hz, 2H, CH_2CH=C*H*H), 4.84 (dddd, *J* = 1.3, 3.3, 4.6, 17.1 Hz, 2H, CH_2CH=CH*H*), 4.58 (m_c, 2H, C*H*OH), 4.05 (m_c, 2H, C*H*CH_2CHOH), 3.90 (m_c, 2H,

C*H*CH_3), 2.60 (d, *J* = 0.5 Hz, 1H, OH), 2.42-2.31 (m, 2H, CCC*H*H), 2.30-2.08 (m, 7H, CCCH*H*, OH' and C*H*$_2$CH=CH_2), 1.98-1.79 (m, 4H, C*H*$_2$CHOH), 1.21 (dd, *J* = 6.1, 7.7 Hz, 6H, CHC*H*$_3$), 1.06 (d, *J* = 5.6 Hz, 18H, SiC(CH_3)$_3$), 0.96 (dt, *J* = 1.1, 7.9 Hz, 18H, Si(CH_2C*H*$_3$)$_3$), 0.60 (dq, *J* = 2.5, 8.0 Hz, 12H, Si(C*H*$_2$$CH_3$)$_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 135.9 (Ph-*o*-C), 134.1 (Ph-*i*-C), 134.0 (CH_2*C*H=CH_2), 133.9 (Ph-*i*-C'), 133.8 (CH_2*C*H=CH_2'), 133.6 (Ph-*i*-C''), 133.3 (Ph-*i*-C'''), 129.8 (Ph-*p*-C), 129.7 (Ph-*p*-C'), 129.6 (Ph-*p*-C''), 127.7 (Ph-*m*-C), 127.6 (Ph-*m*-C'), 127.5 (Ph-*m*-C''), 117.6 (CH_2CH=*C*H_2), 117.5 (CH_2CH=*C*H_2'), 82.7 (CC), 82.6 (CC'), 82.5 (CC''), 82.2 (CC'''), 71.6 (*C*HCH_2CHOH), 70.9 (*C*HCH_2CHOH'), 67.5 (*C*HCH_3), 67.4 (*C*HCH_3'), 61.0 (CHOH), 59.5 (CHOH'), 44.2 (*C*H$_2$CHOH), 43.0 (*C*H$_2$CHOH'), 41.7 (*C*H$_2$CH=CH_2), 41.1 (*C*H$_2$CH=CH_2'), 29.7 (CC*C*H$_2$), 27.0 (SiC(*C*H$_3$)$_3$), 23.4 (CH*C*H$_3$), 23.3 (CH*C*H$_3$'), 19.3 (Si*C*(CH_3)$_3$), 6.8 (Si(CH_2*C*H$_3$)$_3$), 4.8 (Si(*C*H$_2$$CH_3$)$_3$).
IR (neat, ν/cm^{-1}): 3431w, 3072w, 2955m, 2932w, 2877w, 1472w, 1428m, 1377w, 1238w, 1105s, 1078m, 998s, 912m, 853w, 822m, 736s, 701s, 611m, 505s.
HRMS (ESI): *m/z* calcd for $C_{33}H_{51}O_3Si_2$ [M + H]$^+$: 551.3371, found: 551.3360.

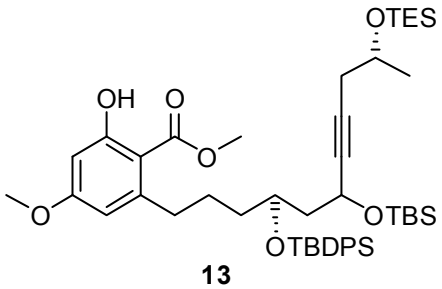


11

Protected triol 11: To a stirred solution of **10** (3.23 g, 5.86 mmol, 1.0 equiv) in dry DMF (3 mL) was added imidazole (1.20 g, 17.6 mmol, 3.0 equiv) at rt followed by TBSCl (1.24 g, 8.21 mmol, 1.4 equiv). After stirring for 15 h at rt the reaction mixture was diluted with EtOAc (60 mL). The resulting mixture was washed with brine (3 x 40 mL) and the combined aqueous extracts were re-extracted once with EtOAc (90 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by FC (hexane/Et_2O 50:1) to give **11** (3.74 g, 96%) as a yellowish oil.

R_f = 0.19 (hexane/ Et_2O 50:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 7.72-7.66 (m, 8H, Ph-*o*-CH), 7.45-7.33 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 5.68 (tdt, *J* = 7.1, 10.2, 17.4 Hz, 2H, CH_2C*H*=CH_2), 4.99-4.82 (m, 4H, CH_2CH=C*H*$_2$), 4.56 (m_c, 1H, CCC*H*OSi), 4.44 (m_c, 1H, CCC*H*OSi'), 4.01 (m_c, 2H, C*H*CH_2CH=CH_2), 3.86 (m_c, 2H, C*H*CH_3), 2.38-2.29 (m, 2H, CCC*H*H), 2.24-2.07 (m, 6H, CCCH*H*, and C*H*$_2$CH=CH_2), 1.97-1.79 (m, 4H, C*H*$_2$CHCC), 1.19 (dd, *J* = 1.9, 6.0 Hz, 6H, CHC*H*$_3$), 1.06 (d, *J* = 1.3 Hz, 18H, Ph_2SiC(CH_3)$_3$), 0.96 (dt, *J* = 0.5, 7.8 Hz, 18H, Si(CH_2C*H*$_3$)$_3$), 0.85 (d, *J* = 13.1 Hz, 18H, (CH_3)$_2$SiC(C*H*$_3$)$_3$), 0.60 (dq, *J* = 1.4, 7.9 Hz, 12H, Si(C*H*$_2$$CH_3$)$_3$), 0.10-0.01 (m, 12 H, (C*H*$_3$)$_2$SiC(CH_3)$_3$).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 135.9 (Ph-*o*-C), 134.6 (Ph-*i*-C), 134.5 (Ph-*i*-C'), 134.4 ($CH_2CH=CH_2$), 134.3 ($CH_2CH=CH_2$'), 134.2 (Ph-*i*-C''), 134.0 (Ph-*i*-C'''), 129.5 (Ph-*p*-C), 129.4 (Ph-*p*-C'), 127.5 (Ph-*m*-C), 127.4 (Ph-*m*-C'), 117.2 ($CH_2CH=CH_2$), 117.1 ($CH_2CH=CH_2$'), 83.3 (CHCC), 83.1 (CHCC'), 82.0 (CHCC), 70.3 ($CHCH_2CH=CH_2$), 70.2 ($CHCH_2CH=CH_2$'), 67.5 ($CHCH_3$), 67.4 ($CHCH_3$'), 61.0 (CCCHOSi), 60.0 (CCCHOSi'), 45.8 (CH_2CHCC), 45.4 (CH_2CHCC'), 41.4 ($CH_2CH=CH_2$), 29.8 ($CCCH_2$), 27.0 ($Ph_2SiC(CH_3)_3$), 25.8 ($(CH_3)_2SiC(CH_3)_3$), 23.3 ($CHCH_3$), 23.2 ($CHCH_3$'), 19.4 ($Ph_2SiC(CH_3)_3$), 18.2 ($(CH_3)_2SiC(CH_3)_3$), 6.8 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$), -4.2 ($(CH_3)_2SiC(CH_3)_3$), -4.5 ($(CH_3)_2SiC(CH_3)_3$'), -4.8 ($(CH_3)_2SiC(CH_3)_3$''), -5.0 ($(CH_3)_2SiC(CH_3)_3$''').
IR (neat, ν/cm^{-1}): 3073w, 2955m, 2930m, 2878m, 2858m, 1472w, 1428m, 1376w, 1361w, 1251m, 1080s, 999s, 914w, 836s, 776s, 737s, 701s, 611m, 506s, 487m.
HRMS (ESI): *m/z* calcd for $C_{39}H_{68}NO_3Si_3$ $[M + NH_4]^+$: 682.4502, found: 682.4498.

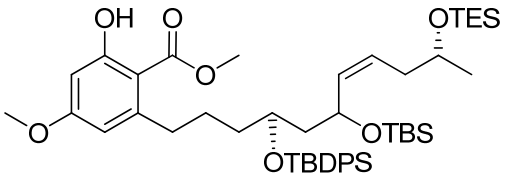


13

Ester 13: To a solution of **11** (1.12 g, 1.69 mmol, 1.10 equiv) in 4.5 mL THF was added a 0.5 M solution of 9-BBN (5.10 mL, 2.55 mmol, 1.67 equiv) in THF and the mixture was stirred at rt for 5 h. Then a 2 M solution of K_3PO_4 (1.53 mL, 3.06 mmol, 2.00 equiv) was added to the mixture (solution A). In a separate flask aryl bromide **12** (400 mg, 1.53 mmol, 1.00 equiv), trifurylphosphine (285 mg, 1.23 mmol, 0.80 equiv) and [$Pd(OAc)_2$] (68.8 mg, 0.31 mmol, 0.20 equiv) were dissolved in 1.5 mL degassed abs. DME (solution B) and stirred for 5 min to give an orange suspension. Solution A was added to solution B at rt (1.5 mL THF washing) and the reaction mixture was refluxed for 19 h. Sat. NH_4Cl was then added, the phases were separated, and the aqueous solution was extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/EtOAc 100:1 → 90:1 → 80:1 → 70:1, then 10:1) to give **13** as a colorless oil (2.03 g, 68%).

R_f = 0.46 (hexane/EtOAc 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 11.75 (d, *J* = 3.8 Hz, 2H, -OH), 7.69-7.62 (m, 8H, Ph-*o*-CH), 7.44-7.30 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 6.31 (dd, *J* = 0.6, 2.6 Hz, 1H, $CH_{Ar}COH$), 6.12 (t, *J* = 2.5 Hz, 2H, $CH_{Ar}COCH_3$), 4.56 (m_c, 1H, CHOTBS), 4.45 (m_c, 1H, CHOTBS'), 4.02-3.93 (m, 2H, CHOTBDPS), 3.93-3.80 (m, 2H, CHOTES), 3.77 (s, 6H, $C_{Ar}OCH_3$), 3.77 (d, *J* = 0.9 Hz, 6H, $COOCH_3$), 2.70-2.46 (m, 4H, $C_{Ar}CH_2$), 2.39-2.29 (m, 2H, $CHHCHCH_3$), 2.20 (m_c, 2H, $CHHCHCH_3$), 1.96-1.68 (m, 4H,

CH_2CHOTBS), 1.42-1.35 (m, 8H, CH_2CH_2CHOTBDPS and CH_2CH_2CHOTBDPS), 1.20 (dd, *J* = 4.8, 5.9 Hz, 6H, CHCH_3), 1.03 (d, *J* = 2.7 Hz, 18H, $Ph_2SiC(CH_3)_3$), 0.95 (dt, *J* = 6.2, 7.9 Hz, 18H, $Si(CH_2CH_3)_3$), 0.85 (d, *J* = 16.8 Hz, 18H, $(CH_3)_2SiC(CH_3)_3$), 0.59 (quint, *J* = 7.7 Hz, 12H, $Si(CH_2CH_3)_3$), 0.10-0.00 (m, 12H, $(CH_3)_2SiC(CH_3)_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.8 (C=O), 165.6 ($C_{Ar}OH$), 163.9 ($C_{Ar}OCH_3$), 147.4 ($C_{Ar}CH_2$), 135.9 (Ph-*o*-C), 135.8 (Ph-*o*-C'), 134.7 (Ph-*i*-C), 134.6 (Ph-*i*-C'), 134.3 (Ph-*i*-C''), 134.0 (Ph-*i*-C'''), 129.5 (Ph-*p*-C), 129.4 (Ph-*p*-C'), 127.5 (Ph-*m*-C), 127.4 (Ph-*m*-C'), 110.6 ($CH_{Ar}C_{Ar}CH_2$), 104.5 ($C_{Ar}COOCH_3$), 98.9 ($CH_{Ar}COH$), 98.8 ($CH_{Ar}COH$'), 83.5 (CHCC), 83.2 (CHCC'), 82.1 (CHCC), 81.9 (CHCC'), 70.6 (CHOTBDPS), 70.5 (CHOTBDPS'), 67.4 (CHOTES), 61.2 (CHOTBS), 60.2 (CHOTBS'), 55.2 ($C_{Ar}OCH_3$), 51.8 ($COOCH_3$), 46.3 (CH_2CHOTBS), 45.6 (CH_2CHOTBS'), 37.1 (CH_2CHOTBDPS), 36.9 (CH_2CHOTBDPS'), 36.6 ($C_{Ar}CH_2$), 29.8 (CH_2CHCH_3), 27.0 ($Ph_2SiC(CH_3)_3$), 26.8 (CH_2CH_2CHOTBDPS), 26.7 (CH_2CH_2CHOTBDPS'), 25.8 ($(CH_3)_2SiC(CH_3)_3$), 23.3(CHCH_3), 23.2 (CHCH_3'), 19.4 ($Ph_2SiC(CH_3)_3$), 18.2 ($(CH_3)_2SiC(CH_3)_3$), 18.1 ($(CH_3)_2SiC(CH_3)_3$'), 6.8 ($Si(CH_2CH_3)_3$), 4.8 ($Si(CH_2CH_3)_3$), -4.1 ($(CH_3)_2SiC(CH_3)_3$), -4.5 ($(CH_3)_2SiC(CH_3)_3$'), -4.9 ($(CH_3)_2SiC(CH_3)_3$''), -5.1 ($(CH_3)_2SiC(CH_3)_3$''').
IR (neat, ν/cm^{-1}): 3071w, 2954m, 2931m, 2878w, 2857w, 1653m, 1616m, 1577w, 1462w, 1435m, 1377w, 1326m, 1255s, 1215m, 1158m, 1104m, 1000m, 957w, 836m, 756s, 738s, 701s, 611m, 506m.
HRMS (ESI): *m/z* calcd for $C_{48}H_{78}NO_7Si_3$ $[M + NH_4]^+$: 864.5081, found: 864.5080.

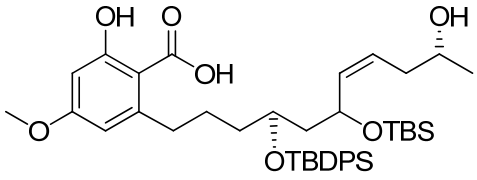


14

Ester 14: To a solution of **13** (831 mg, 981 µmol, 1.00 equiv) in EtOAc (7.6 mL) was added *Lindlar* catalyst (105 mg, 49.3 µmol, 5 mol%). The mixture was stirred under a hydrogen atmosphere (7.5 bar) and the progress of the reaction was monitored by MS. After 50 min the suspension was filtered through celite, the solvent was removed under reduced pressure and the residue was purified by FC (hexane/Et_2O 100:0 → 50:1 → 10:1) to give **14** as a colorless oil (812 mg, 97%).

R_f = 0.41 (hexane/Et_2O, 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 11.76 (d, *J* = 4.9 Hz, 2H, -OH), 7.69-7.60 (m, 8H, Ph-*o*-CH), 7.44-7.29 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 6.32 (dd, *J* = 2.6, 6.6 Hz, 2H, CH_{Ar}COH), 6.19 (d, *J* = 2.6 Hz, 1H, C$H_{Ar}COCH_3$), 6.12 (d, *J* = 2.6 Hz, 1H, C$H_{Ar}COCH_3$'), 5.35-5.21 (m, 4H, CH=CH), 4.52 (dt, *J* = 4.6, 8.1 Hz 1H, CHOTBS), 4.38 (m_c, 1H, CHOTBS'), 3.97 (m_c, 1H, CHOTBDPS), 3.89 (m_c, 1H, CHOTBDPS'), 3.86-3.76 (m, 2H, CHOTES), 3.79 (d, *J* = 13.8 Hz, 6H, $COOCH_3$), 3.78 (d, *J* = 4.9 Hz, 6H, $C_{Ar}OCH_3$), 2.81-2.52 (m, 4H, $C_{Ar}CH_2$), 2.22-1.99 (m, 4H, CH_2CHCH_3), 1.84-1.37

(m, 12H, CH_2CHOTBS, CH_2CH$_2$CHOTBDPS and CH$_2$CH_2CHOTBDPS), 1.09 (dd, *J* = 2.1, 6.1 Hz, 6H, CHCH_3), 1.03 (d, *J* = 0.7 Hz, 18H, Ph$_2$SiC(CH$_3$)$_3$), 0.96 (t, *J* = 7.9 Hz, 18H, Si(CH$_2$CH_3)$_3$), 0.78 (d, *J* = 20.3 Hz, 18H, (CH$_3$)$_2$SiC(CH_3)$_3$), 0.59 (m_c, 12H, Si(CH_2CH$_3$)$_3$), -0.07 (dd, *J* = 11.5, 14.0 Hz, 12H, (CH_3)$_2$SiC(CH$_3$)$_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.9 (C=O), 171.8 (C=O'), 165.6 (C_{Ar}OH), 165.5 (C_{Ar}OH'), 163.9 (C_{Ar}OCH$_3$), 147.6 (C_{Ar}CH$_2$), 147.5 (C_{Ar}CH$_2$'), 135.8 (Ph-*o*-C), 135.4 (*C*HCH$_2$CHCH$_3$), 135.2 (*C*HCH$_2$CHCH$_3$'), 134.9 (Ph-*i*-C), 134.7 (Ph-*i*-C'), 134.6 (Ph-*i*-C''), 134.4 (Ph-*i*-C'''), 129.4 (Ph-*p*-C), 129.3 (Ph-*p*-C'), 127.5 (Ph-*m*-C), 127.4 (Ph-*m*-C'), 125.5 (*C*HCHOTBS), 125.0 (*C*HCHOTBS'), 110.7 ($CH_{Ar}C_{Ar}CH_2$), 110.6 ($CH_{Ar}C_{Ar}CH_2$'), 104.5 (C_{Ar}COOCH$_3$), 98.9 (CH_{Ar}COH), 98.8 (CH_{Ar}COH'), 70.8 (CHOTBDPS), 70.5 (CHOTBDPS'), 68.1 (CHOTES), 66.4 (CHOTBS), 66.3 (CHOTBS'), 55.2 (C_{Ar}OCH$_3$), 51.8 (COO*C*H$_3$), 45.9 (*C*H$_2$CHOTBS), 44.9 (*C*H$_2$CHOTBS'), 37.9 (*C*H$_2$CHCH$_3$), 37.6 (*C*H$_2$CHOTBDPS), 36.8 (C_{Ar}*C*H$_2$), 36.7 (C_{Ar}*C*H$_2$'), 35.7 (C*H*$_2$CHOTBDPS'), 27.1 (Ph$_2$SiC(*C*H$_3$)$_3$), 26.9 (*C*H$_2$CH$_2$CHOTBDPS), 26.8 (*C*H$_2$CH$_2$CHOTBDPS'), 25.9 ((CH$_3$)$_2$SiC(*C*H$_3$)$_3$), 25.7 ((CH$_3$)$_2$SiC(*C*H$_3$)$_3$'), 23.8 (CH*C*H$_3$), 23.2 (CH*C*H$_3$'), 19.4 (Ph$_2$Si*C*(CH$_3$)$_3$), 19.3 (Ph$_2$Si*C*(CH$_3$)$_3$'), 18.0 ((CH$_3$)$_2$Si*C*(CH$_3$)$_3$), 17.9 ((CH$_3$)$_2$Si*C*(CH$_3$)$_3$'), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 4.9 (Si(*C*H$_2$CH$_3$)$_3$), -3.8 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$), -4.1 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$'), -4.7 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''), -5.0 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''').
IR (neat, ν/cm^{-1}): 3071w, 3049w, 3014w, 2954m, 2933m, 2878w, 2857w, 1653m, 1615m, 1577m, 1462w, 1429m, 1376w, 1326m, 1305w, 1255s, 1204m, 1158m, 1108m, 1081s, 1004m, 958w, 834m, 755s, 734s, 701s, 610m, 509m, 487m.
HRMS (ESI): *m/z* calcd for $C_{48}H_{76}NaO_7Si_3$ $[M + Na]^+$: 874.4791, found: 871.4797.

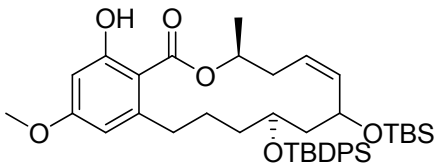


15

Seco acid 15: To a solution of **14** (80.1 mg, 94.3 µmol, 1.0 equiv) in MeOH (4.2 mL) was added 1 M NaOH (1.4 mL, 1400 µmol, 15 equiv) and the reaction mixture was refluxed at 87 °C for 21 h. It was then diluted with 0.2 M NaH_2PO_4 solution and EtOAc (5 mL), the pH was adjusted to 5 through addition of solid NaH_2PO_4, and the phases were separated. The aqueous solution was extracted with EtOAc (3 x 15 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/EtOAc 5:1 → 3:1 → 2:1, then DCM/MeOH, 100:1 → 50:1 → 30:1 → 10:1 → 5:1) to give **15** (40.5 mg, 60%) as a yellowish solid.

R_f = 0.42 (DCM/MeOH 10:1).
m.p. 108-110 °C.

^{1}H-NMR (400.1 MHz, DMSO-d_6): δ 7.64-7.54 (m, 8H, Ph-*o*-CH), 7.47-7.33 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 6.17 (t, *J* = 2.4 Hz, 2H, C*H*$_{Ar}$COH), 6.00 (d, *J* = 2.5 Hz, 1H, C*H*$_{Ar}$COCH$_3$), 5.93 (d, *J* = 2.5 Hz, 1H, C*H*$_{Ar}$COCH$_3$'), 5.31 (m_c, 2H, CH=C*H*CH$_2$), 5.17 (m_c, 2H, C*H*=CHCH$_2$), 4.51 (dt, *J* = 4.6, 8.5 Hz, 1H, CHOTBS), 4.34 (dt, *J* = 3.8, 8.8 Hz, 1H, CHOTBS'), 3.95 (m_c, 1H, CHOTBDPS), 3.83 (m_c, 1H, CHOTBDPS'), 3.67 (d, *J* = 4.0 Hz, 6H, C$_{Ar}$OCH$_3$), 3.59 (tdd, *J* = 6.2, 12.3 Hz, 2H, C*H*CH$_3$), 2.94-2.82 (m, 1H, C*H*HCH$_2$CHOTBDPS), 2.80-2.59 (m, 3H, CH*H*CH$_2$CHOTBDPS and C*H*$_2$CH$_2$CHOTBDPS), 2.12-1.94 (m, 4H, C*H*$_2$CHOH), 1.71-1.31 (m, 12H, C$_{Ar}$CH$_2$, C*H*$_2$CHOTBDPS and C*H*$_2$CHOTBS), 1.22 (br s, 2H, OH), 1.00-0.96 (m, 6H, CHC*H*$_3$), 0.98 (s, 18H, Ph$_2$SiC(CH$_3$)$_3$), 0.72 (d, *J* = 20.9 Hz, 18H, (CH$_3$)$_2$SiC(C*H*$_3$)$_3$), -0.12 (dd, *J* = 12.6, 13.3 Hz, 12H, (C*H*$_3$)$_2$SiC(CH$_3$)$_3$).
^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 173.1 (C=O), 172.9 (C=O'), 164.9 (C$_{Ar}$OH), 164.8 (C$_{Ar}$OH'), 161.5 (*C*$_{Ar}$OCH$_3$), 161.4 (*C*$_{Ar}$OCH$_3$'), 146.6 (*C*$_{Ar}$CH$_2$), 146.5 (*C*$_{Ar}$CH$_2$'), 135.2 (Ph-*o*-C), 134.4 (*C*H=CHCH$_2$), 134.3 (*C*H=CHCH$_2$'), 134.0 (Ph-*i*-C), 133.9 (Ph-*i*-C'), 133.8 (Ph-*i*-C''), 133.7 (Ph-*i*-C'''), 129.6 (Ph-*p*-C), 129.5 (Ph-*p*-C'), 127.5 (Ph-*m*-C), 125.9 (CH=*C*HCH$_2$), 125.7 (CH=*C*HCH$_2$'), 108.7 (*C*$_{Ar}$COOH), 108.4 (*C*$_{Ar}$COOH'), 107.4 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 98.5 (*C*H$_{Ar}$COH), 70.5 (CHOTBDPS), 69.9 (CHOTBDPS'), 65.8 (CHOTBS and CHCH$_3$), 65.7 (CHOTBS and CHCH$_3$), 65.6 (CHOTBS and CHCH$_3$), 54.7 (C$_{Ar}$O*C*H$_3$), 45.6 (*C*H$_2$CHOTBS), 44.1 (*C*H$_2$CHOTBS'), 37.1 (*C*H$_2$CHOTBDPS and *C*H$_2$CHOH), 37.0 (*C*H$_2$CHOTBDPS and *C*H$_2$CHOH), 35.1 (C$_{Ar}$*C*H$_2$ and *C*H$_2$CH$_2$CHOTBDPS) , 34.8 (C$_{Ar}$*C*H$_2$ and *C*H$_2$CH$_2$CHOTBDPS) , 34.6 (C$_{Ar}$*C*H$_2$ and *C*H$_2$CH$_2$CHOTBDPS) , 26.8 (Ph$_2$SiC(*C*H$_3$)$_3$), 26.7 (Ph$_2$SiC(*C*H$_3$)$_3$'), 25.6 ((CH$_3$)$_2$SiC(*C*H$_3$)$_3$), 25.5 ((CH$_3$)$_2$SiC(*C*H$_3$)$_3$'), 23.2 (CH$_3$), 23.0 (CH$_3$'), 18.8 (Ph$_2$Si*C*(CH$_3$)$_3$), 17.5 ((CH$_3$)$_2$Si*C*(CH$_3$)$_3$), -4.0 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$), -4.2 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$'), -5.0 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''), -5.3 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''').
IR (neat, ν/cm^{-1}) : 3415w, 3071w, 3049w, 3012w, 2929m, 2856m, 1584m, 1462w, 1428m, 1372m, 1253m, 1202m, 1159m, 1106s, 1079s, 1005m, 939w, 834s, 775s, 739m, 701s, 612m, 509m, 485m.
HRMS (ESI): *m/z* calcd for $C_{41}H_{60}NaO_7Si_2$ [M + Na]$^+$: 743.3770, found: 743.3767.

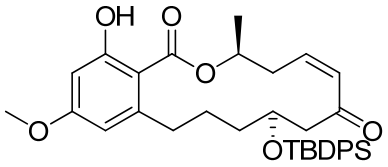


16

Protected macrolactone 16: To a solution of Ph_3P (1.67 g, 6.37 mmol, 12.0 equiv) in 128 mL toluene was added DEAD (1.00 mL, 6.37 mmol, 12.0 equiv) dropwise at rt. The solution was stirred at rt for 40 min. To this solution was added a solution of **15** (383 mg, 531 µmol, 1.0 equiv) in toluene (168 mL + 10 mL washing) at 0 °C over a period of 1.5 h. The resulting mixture was stirred for 1 h at 0 °C and then allowed to warm to rt over 1.5 h. After quenching with water (170 mL) the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with

brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/Et_2O 100:1 → 20:1, then hexane/EtOAc 10:1) to give **16** as a colorless oil (181.2 mg, 49%).

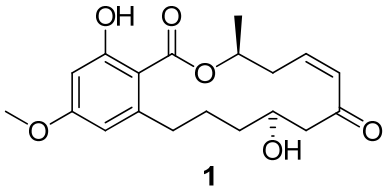
R_f = 0.23 (hexane/ Et_2O 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 12.09 (s, 1H, -OH), 11.76 (s, 1H, -OH'), 7.69-7.60 (m, 8H, Ph-*o*-CH), 7.42-7.25 (m, 12H, Ph-*m*-CH and Ph-*p*-CH), 6.32 (d, *J* = 2.6, 1H, CH_{Ar}COH), 6.16 (d, *J* = 2.6 Hz, 1H, CH_{Ar}COCH$_3$), 6.10 (d, *J* = 2.6 Hz, 1H, CH_{Ar}COCH$_3$'), 5.47-5.38 (m, 1H, C*H*=CHCH), 5.35-5.14 (m, 4H, C*H*CH$_3$, C*H*=CHCH', CH=C*H*CH), 5.10-5.02 (m, 1H, CH=C*H*CH'), 4.47-4.38 (m, 1H, CHOTBS), 4.33-4.25 (m, 1H, CHOTBS'), 3.78 (d, *J* = 3.5 Hz, 6H, C_{Ar}OCH$_3$), 3.70-3.63 (m, 1H, CHOTBDPS), 3.58-3.50 (m, 1H, CHOTBDPS'), 2.79-2.60 (m, 4H, C_{Ar}C*H*H, C_{Ar}C*H*H', C*H*HCH=CH and C*H*HCH=CH'), 2.42-2.16 (m, 4H, C_{Ar}CH*H*, C_{Ar}CH*H*', CH*H*CH=CH and CH*H*CH=CH'), 2.03-1.82 (m, 3H, CH_2CHOTBS and C*H*HCHOTBS'), 1.78-1.54 (m, 5H, CH*H*CHOTBS', C*H*HCH$_2$CHOTBDPS, CH$_2$CHOTBDPS and C*H*HCHOTBDPS'), 1.45-1.28 (m, 4H, CH*H*CHOTBDPS', CH*H*CH$_2$CHOTBDPS and CH_2CH$_2$CHOTBDPS'), 1.38 (s, *J* = 6.2 Hz, 6H, CHCH_3), 1.05 (d, *J* = 3.0 Hz, 18H, Ph$_2$SiC(CH$_3$)$_3$), 0.84 (d, *J* = 5.9 Hz, 18H, (CH$_3$)$_2$SiC(CH_3)$_3$'), 0.03 (d, *J* = 11.6 Hz, 6H, (CH_3)$_2$SiC(CH$_3$)$_3$), -0.04 (d, *J* = 7.4 Hz, 6H, (CH_3)$_2$SiC(CH$_3$)$_3$').
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.6 (C=O), 165.9 (C_{Ar}OH), 165.0 (C_{Ar}OH'), 164.0 (C_{Ar}OCH$_3$), 163.8 (C_{Ar}OCH$_3$'), 147.8 (C_{Ar}CH$_2$), 135.9 (Ph-*o*-C), 135.2 (CH=*C*HCHOTBS), 134.6 (CH=*C*HCHOTBS'), 134.3 (Ph-*i*-C), 134.2 (Ph-*i*-C'), 134.1 (Ph-*i*-C''), 129.6 (Ph-*p*-C), 129.5 (Ph-*p*-C'), 129.4 (Ph-*p*-C''), 127.5 (Ph-*m*-C), 127.4 (Ph-*m*-C'), 126.7 (*C*H=CHCHOTBS), 126.2 (*C*H=CHCHOTBS'), 109.1 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 108.8 (*C*H$_{Ar}$C$_{Ar}$CH$_2$'), 105.7 (C_{Ar}COOCH), 104.8 (C_{Ar}COOCH'), 98.7 (*C*H$_{Ar}$COH), 98.6 (*C*H$_{Ar}$COH'), 72.7 (*C*HCH$_3$), 72.6 (*C*HCH$_3$'), 71.0 (CHOTBDPS), 69.9 (CHOTBDPS'), 67.0 (CHOTBS), 65.1 (CHOTBS'), 55.2 (C_{Ar}O*C*H$_3$), 45.7 (*C*H$_2$CHOTBS), 45.3 (*C*H$_2$CHOTBS'), 36.8 (*C*H$_2$CHOTBDPS), 36.2 (C_{Ar}*C*H$_2$), 35.0 (*C*H$_2$CH=CH), 34.5 (*C*H$_2$CH=CH'), 34.2 (C_{Ar}*C*H$_2$'), 27.7 (*C*H$_2$CH$_2$CHOTBDPS'), 27.1 (Ph$_2$SiC(*C*H$_3$)$_3$), 25.8 ((CH$_3$)$_2$SiC(*C*H$_3$)$_3$), 21.1 (CH*C*H$_3$), 19.3 (CH*C*H$_3$' and Ph$_2$Si*C*(CH$_3$)$_3$), 18.1 ((CH$_3$)$_2$Si*C*(CH$_3$)$_3$), 18.0 ((CH$_3$)$_2$Si*C*(CH$_3$)$_3$'), -4.1 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$), -4.4 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$'), -4.6 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''), -4.9 ((*C*H$_3$)$_2$SiC(CH$_3$)$_3$''').
IR (neat, ν/cm^{-1}) : 2957m, 2927s, 2858m, 1726s, 1644w, 1614w, 1579w, 1462m, 1380w, 1269s, 1159w, 1120s, 1071s, 1040m, 962m, 834w, 774m, 741s, 703s, 651w, 611w, 510w.
HRMS (ESI): *m/z* calcd for $C_{41}H_{58}NaO_6Si_2$ $[M + Na]^+$: 725.3664, found: 725.3665.



17

Enone 17: *Jones* reagent (8 N) was prepared by dissolving pure chromium trioxide (266.8 mg) in distilled water, adding conc. H_2SO_4 (0.213 mL) and then diluting the mixture with water to 1 mL.
To a solution of **16** (83 mg, 118 µmol, 1.0 equiv) in 2.2 mL acetone at –15 °C were added KF (15.7 mg, 270 µmol, 2.3 equiv) and freshly prepared 8 N *Jones* reagent (177 µL; CrO_3: 473 µmol, 4.0 equiv; H_2SO_4: 708 mmol, 6.0 equiv). The reaction mixture was stirred at –10 °C for 2 h and diluted with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified FC (hexane/EtOAc 50:1 → 20:1 → 15:1 → 10:1 → 8:1) to give **17** as a white foam (44.0 mg, 64%).

R_f = 0.25 (hexane/EtOAc 8:1).
$[\alpha]_D^{24}$ = +46.5° (*c* = 0.882, $CHCl_3$).
^{1}H-NMR (400.1 MHz, C_6D_6): δ12.75 (s, 1H, -OH), 7.75-7.69 (m, 4H, Ph-*o*-CH), 7.23-7.13 (m, 6H, Ph-*m*-CH and Ph-*p*-CH), 6.44 (d, *J* = 2.6, 1H, C*H*$_{Ar}$COH), 6.25 (d, *J* = 2.6 Hz, 1H, C*H*$_{Ar}$COCH$_3$), 5.45 (dd, *J* = 2.3, 11.5 Hz, 1H, CH=C*H*CCH$_2$), 5.24 (dt, *J* = 3.2, 11.1 Hz, 1H, C*H*=CHCCH$_2$), 4.95 (m$_c$, 1H, C*H*CH$_3$), 3.98 (m$_c$, 1H, CHOTBDPS), 3.24-3.12 (m, 1H, C*H*HCH=CH), 3.18 (s, 3H, C$_{Ar}$OCH$_3$), 2.79 (m$_c$, 1H, C$_{Ar}$C*H*H), 2.61-2.51 (m, 2H, C*H*$_2$CCH), 2.28 (ddd, *J* = 5.7, 11.0, 14.6 Hz, 1H, C$_{Ar}$CH*H*), 1.93 (ddd, *J* = 3.0, 5.2, 16.9 Hz, 1H, CH*H*CH=CH), 1.85 (m$_c$, 1H, C*H*HCHOTBDPS), 1.63-1.52 (m, 1H, CH*H*CHOTBDPS), 1.52-1.29 (m, 2H, C*H*$_2$CH$_2$CHOTBDPS), 1.16 (s, 9H, Ph$_2$SiC(CH$_3$)$_3$), 0.90 (d, J = 6.2 Hz, 3H, CHC*H*$_3$).
^{13}C-NMR (100.6 MHz, C_6D_6): δ 198.8 (CH*C*=O), 171.9 (C=O), 167.4 (C$_{Ar}$OH), 164.7 (*C*$_{Ar}$OCH$_3$), 147.5 (*C*$_{Ar}$CH$_2$), 141.2 (*C*H=CHCCH$_2$), 136.2 (Ph-*o*-C), 134.4 (Ph-*i*-C), 134.0 (Ph-*i*-C'), 130.6 (CH=*C*HCCH$_2$), 130.1 (Ph-*p*-C), 128.0 (Ph-*m*-C), 110.1 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 105.0 (*C*$_{Ar}$COOCH), 99.2 (*C*H$_{Ar}$COH), 73.0 (*C*HCH$_3$), 71.2 (CHOTBDPS), 54.7 (C$_{Ar}$O*C*H$_3$), 52.8 (*C*H$_2$CCH), 37.3 (*C*H$_2$CHOTBDPS), 36.3 (CH$_2$), 36.2 (CH$_2$), 27.8 (*C*H$_2$CH$_2$CHOTBDPS), 27.1 (Ph$_2$SiC(*C*H$_3$)$_3$), 20.2 (CH*C*H$_3$), 19.4 (Ph$_2$Si*C*(CH$_3$)$_3$).
IR (neat, ν/cm^{-1}): 3070w, 2932m, 2857w, 1690m, 1640m, 1612s, 1577m, 1463w, 1427m, 1379w, 1351m, 1305m, 1251s, 1215m, 1159s, 1106s, 1047s, 1004m, 957w, 823m, 755s, 701s, 612m, 509s, 488m.
HRMS (ESI): *m/z* calcd for $C_{35}H_{46}NO_6Si$ $[M + NH_4]^+$: 604.3089, found: 604.3088.

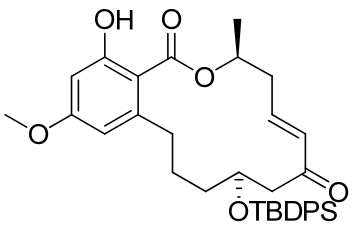


1

5'-Deoxy L-783277 (1): To a solution of **17** (64.4 mg, 0.11 mmol, 1.0 equiv) in 4.9 mL THF was added HF•pyridine (1.23 mL, 47.4 mmol, 431 equiv) at –10 °C. The reaction mixture was stirred at rt for 9 h; it was then added to a mixture of sat. $NaHCO_3$ (150 mL) and EtOAc (100 mL) under vigorous stirring. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with sat. $CuSO_4$ (2 x 50 mL) and brine (70 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/EtOAc 5:1 → 3:1 → 1:1 → 1:2) to give **1** as a white solid (33.7 mg, 88%). HPLC purity >95% (Waters Symmetry C_{18} column, 3.5 µm, 4.6×100 mm, rt, 1.0 mL/min, 10 µL injected: H_2O/MeCN 80/20 → 50/50 in 5 min, → 30/70 in 5 min, → 10/90 in 5 min, 10:90, 5 min), detection at λ = 254 nm, t_R = 8.6 min).

R_f = 0.64 (EtOAc).
m.p. 115-116 °C.
$[\alpha]_D^{24}$ = −46.4° (*c* = 0.822, $CHCl_3$).
^{1}H-NMR (400.1 MHz, C_6D_6): δ 12.75 (s, 1H, -OH), 6.47 (d, *J* = 2.7, 1H, C*H*$_{Ar}$COH), 6.30 (d, *J* = 2.6 Hz, 1H, C*H*$_{Ar}$COCH$_3$), 5.55 (dd, *J* = 3.0, 11.6 Hz, 1H, CH=C*H*CCH$_2$), 5.27 (dt, *J* = 2.8, 11.6 Hz, 1H, C*H*=CHCCH$_2$), 5.13 (m$_c$, 1H, C*H*CH$_3$), 3.66 (m$_c$, 1H, C*H*OH), 3.33 (d, *J* = 10.4 Hz, 1H, OH), 3.16 (s, 3H, C$_{Ar}$OCH$_3$), 3.14-2.97 (m, 2H, C*H*HCH=CH and C$_{Ar}$C*H*H), 2.29-2.09 (m, 3H, C*H*$_2$CCH and C$_{Ar}$CH*H*), 1.85-1.66 (m, 2H, CH*H*CH=CH and C*H*HCOH), 1.56-1.44 (m, 1H, CH*H*COH), 1.33-1.20 (m, 1H, C*H*HCH$_2$CH), 1.15-1.01 (m, 1H, CH*H*CH$_2$CH), 0.88 (d, J = 6.2 Hz, 3H, CHC*H*$_3$).
^{13}C-NMR (100.6 MHz, C_6D_6): δ 204.8 (CH*C*=O), 171.9 (C=O), 167.4 (C$_{Ar}$OH), 164.7 (*C*$_{Ar}$OCH$_3$), 147.7 (*C*$_{Ar}$CH$_2$), 139.1 (*C*H=CHCCH$_2$), 132.4 (CH=*C*HCCH$_2$), 111.2 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 104.9 (*C*$_{Ar}$COOCH), 99.4 (*C*H$_{Ar}$COH), 72.2 (*C*HCH$_3$), 70.4 (CHOH), 54.8 (C$_{Ar}$O*C*H$_3$), 45.7 (*C*H$_2$CCH), 37.3 (C$_{Ar}$*C*H$_2$), 37.2 (*C*H$_2$CHOH), 36.3 (*C*H$_2$CH=CH), 29.5 (*C*H$_2$CH$_2$CHOH), 20.6 (CH*C*H$_3$).
IR (neat, ν/cm^{-1}): 3505w, 2931w, 2859w, 1684w, 1639s, 1611s, 1576m, 1421w, 1380w, 1350m, 1304m, 1250s, 1203s, 1159s, 1138m, 1101m, 1045s, 1016m, 957w, 828m, 750s, 714m, 622w, 601w, 539w.
HRMS (ESI): *m/z* calcd for $C_{19}H_{25}O_6$ $[M + H]^+$: 349.1646, found: 349.1638.

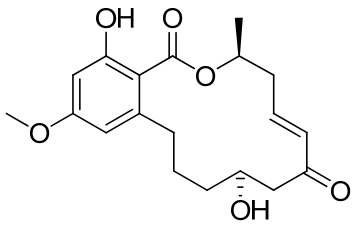
3. Synthesis of *E*-5-deoxy L-783277 (2)



18

***E*-Enone 18**: **17** (12.6 mg, 21.5 µmol, 1.0 equiv) was dissolved in $CDCl_3$ (0.7 mL). The progress of the isomerization was followed by ^{1}H-NMR. After 4 days (96% conversion), the solvent was removed under reduced pressure and the residue was purified by FC (hexane/EtOAc 50:1 → 20:1 → 15:1 → 10:1 → 8:1) to give **18** as a colorless oil (10.4 mg, 83%).

R_f = 0.13 (hexane/EtOAc, 8:1).
$[\alpha]_D^{24}$ = –13.7° (*c* = 0.520, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 11.64 (s, 1H, -OH), 7.71-7.65 (m, 4H, Ph-*o*-CH), 7.45-7.32 (m, 6H, Ph-*m*-CH and Ph-*p*-CH), 6.74 (dd, *J* = 6.2, 8.5, 15.8 Hz, 1H, C*H*=CHCCH$_2$), 6.32 (d, *J* = 2.6, 1H, CH_{Ar}COH), 6.16 (d, *J* = 2.7 Hz, 1H, CH_{Ar}COCH$_3$), 5.98 (d, *J* = 16.0 Hz, 1H, CH=C*H*CCH$_2$), 5.47 (m_c, 1H, C*H*CH$_3$), 4.02-3.93 (m, 1H, CHOTBDPS), 3.79 (s, 3H, C_{Ar}OCH$_3$), 2.83-2.68 (m, 3H, C_{Ar}C*H*H, C*H*HCCH and C*H*HCH=CH), 2.64 (dd, *J* = 3.8, 12.0 Hz, 1H, CH*H*CCH), 2.50-2.32 (m, 2H, C_{Ar}CH*H* and CH*H*CH=CH), 1.65-1.44 (m, 3H, CH_2CHOTBDPS and C*H*HCH$_2$CHOTBDPS), 1.46 (d, *J* = 6.5 Hz, 1H, CHCH_3), 1.37-1.24 (m, 1H, CH*H*CH$_2$CHOTBDPS), 1.08 (s, 9H, Ph$_2$SiC(CH$_3$)$_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 198.6 (CH*C*=O), 170.5 (C=O), 165.6 (C_{Ar}OH), 164.1 (C_{Ar}OCH$_3$), 147.3 (C_{Ar}CH$_2$), 141.0 (*C*H=CHCCH$_2$), 135.9 (Ph-*o*-C), 135.6 (CH=*C*HCCH$_2$), 134.0 (Ph-*i*-C), 133.9 (Ph-*i*-C'), 129.7 (Ph-*p*-C), 127.6 (Ph-*m*-C), 110.0 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 104.6 (*C*$_{Ar}$COOCH), 99.0 (*C*H$_{Ar}$COH), 70.8 (CHOTBDPS), 70.6 (*C*HCH$_3$), 55.3 (C_{Ar}O*C*H$_3$), 46.7 (*C*H$_2$CCH), 37.4 (*C*H$_2$CH=CH), 37.1 (*C*H$_2$CHOTBDPS), 35.8 (C_{Ar}*C*H$_2$), 27.1 (*C*H$_2$CH$_2$CHOTBDPS), 27.0 (Ph$_2$SiC(*C*H$_3$)$_3$), 19.3 (CH*C*H$_3$), 19.2 (Ph$_2$Si*C*(CH$_3$)$_3$).
IR (neat, ν/cm^{-1}): 3070w, 3045w, 2933m, 2894w, 2857m, 1645s, 1614s, 1577m, 1463m, 1428m, 1387w, 1359m, 1303m, 1255s, 1205m, 1159m, 1110s, 1041m, 1007w, 981w, 823m, 759m, 740m, 704s, 611w, 506m, 460m, 429m, 409m.
HRMS (ESI): *m/z* calcd for $C_{35}H_{42}NaO_6Si$ [M + Na]$^+$: 609.2643, found: 609.2642.

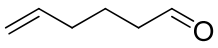


2

***E*-5'-Deoxy L-783277 (2)**: To a solution of **18** (10.4 mg, 17.7 µmol, 1.0 equiv) in 0.8 mL THF was added HF•pyridine (0.20 mL, 7.70 mmol, 434 equiv) at –10 °C. The reaction mixture was stirred at rt for 10 h; it was then added to a mixture of sat. $NaHCO_3$ (15 mL) and EtOAc (15 mL) under vigorous stirring, the phases were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with sat. $CuSO_4$ (2 x 7 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by FC (hexane/EtOAc 10:1 → 3:1 → 1:1) to give **2** as a white solid (5.0 mg, 81%, 94% pure NMR and HPLC). After purification by preparative HPLC **2** was isolated as a white solid (4.06 mg, 66%). HPLC purity >99% (Waters Symmetry C_{18} column, 3.5 µm, 4.6×100 mm, rt, 1.0 mL/min, 10 µL injected): H_2O/MeCN 80/20 → 50/50 in 5 min, → 30/70 in 5 min, → 10:90 in 5 min, 10/90, 5 min, detection at λ = 254 nm, t_R = 7.2 min).

R_f = 0.20 (hexane/EtOAc 1:1).
m.p. 137-142 °C.
$[\alpha]_D^{24}$ = −90.9° (*c* = 0.249, $CHCl_3$).
^{1}H-NMR (400.1 MHz, C_6D_6): δ 12.45 (s, 1H, -OH), 6.51 (d, *J* = 2.7, 1H, C*H*$_{Ar}$COH), 6.30 (d, *J* = 2.7 Hz, 1H, C*H*$_{Ar}$COCH$_3$), 6.24 (m$_c$, 1H, C*H*=CHCCH$_2$), 5.84 (d, *J* = 16.2 Hz, 1H, CH=C*H*CCH$_2$), 5.06 (m$_c$, 1H, C*H*CH$_3$), 3.68 (m$_c$, 1H, C*H*OH), 3.19 (s, 3H, C$_{Ar}$OCH$_3$), 2.94 (dt, J = 3.8, 12.3 Hz, 1H, C$_{Ar}$C*H*H), 2.63 (dd, J = 2.7, 12.7 Hz, 1H, C*H*HCCH), 2.32 (m$_c$, 1H, C*H*HCH=CH), 2.25-2.11 (m, 2H, C$_{Ar}$CH*H* and CH*H*CCH), 1.65 (m$_c$, 1H, C*H*HCOH), 1.55 (m$_c$, 1H, CH*H*CH=CH), 1.27-1.00 (m, 3H, C*H*$_2$CH$_2$CH and CH*H*COH), 0.75 (d, J = 6.6 Hz, 3H, CHC*H*$_3$).
^{13}C-NMR (100.6 MHz, C_6D_6): δ 200.8 (CH*C*=O), 171.2 (C=O), 167.1 (C$_{Ar}$OH), 164.9 (*C*$_{Ar}$OCH$_3$), 147.9 (*C*$_{Ar}$CH$_2$), 142.4 (*C*H=CHCCH$_2$), 137.0 (CH=*C*HCCH$_2$), 111.6 (*C*H$_{Ar}$C$_{Ar}$CH$_2$), 104.8 (*C*$_{Ar}$COOCH), 99.5 (*C*H$_{Ar}$COH), 70.6 (*C*HCH$_3$), 70.0 (CHOH), 54.8 (C$_{Ar}$O*C*H$_3$), 41.7 (*C*H$_2$CCH), 37.2 (*C*H$_2$CHOH), 36.9 (C$_{Ar}$*C*H$_2$), 36.2 (*C*H$_2$CH=CH), 29.9 (*C*H$_2$CH$_2$CHOH), 18.5 (CH*C*H$_3$).
IR (neat, ν/cm^{-1}): 3431w, 2979m, 2937m, 2858w, 1717w, 1646s, 1614s, 1577m, 1441m, 1385m, 1353m, 1318m, 1302m, 1255s, 1204s, 1160s, 1109m, 1036m, 982m, 957w, 848w, 810w, 759m, 715w, 476w, 419w.
HRMS (ESI): *m/z* calcd for $C_{19}H_{25}O_6$ $[M + H]^+$: 349.1646, found: 349.1653.

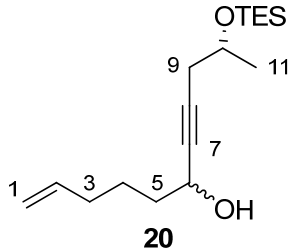
4. Synthesis of dideoxy L-783277 (3)



19

Aldehyde 19: To a solution of oxalylchloride (2.90 ml, 30.31 mmol, 1.5 equiv) in DCM (50 ml) was added DMSO (4.70 ml, 66.61 mmol, 3 equiv) dropwise within 5 minutes at -78 °C. The mixture was stirred at -78 °C for 10 min and a solution of 5-hexen-1-ol (2.50 ml, 20.82 mmol, 1 equiv) in DCM (7.5 ml) was added dropwise within 10 min. After stirring for 1 h at -78 °C TEA (9.20 ml, 66.19 mmol, 3 equiv) was added within 10 minutes and the reaction mixture was allowed to warmed to 0 °C. Water (60 ml) and DCM (60 ml) were then added and the phases were separated. The aqueous solution was extracted with DCM (2 x 60 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* (up to 700 mbar). The crude product was purified by FC (pentane/Et_2O 10:1) to give **19** (2.0 g, quant.) as a colorless oil.

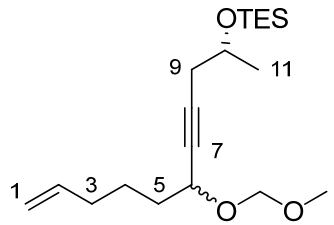
R_f = 0.53 (hexane/EtOAc 5:1); 0.44 (pentane/Et_2O 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 9.77 (t, *J* = 1.6 Hz , 1H, H-6); 5.81-5.71 (m, 2H, H-2); 5.05-4.93 (m, 2H, H-1); 2.46-2.42 (m, 2H, H-5); 2.14-2.04 (q, *J* = 7.4 Hz, 2H, H-3); 1.77-1.63 (m, 2H, H-4).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 202.5 (C-6); 137.7 (C-2); 115.7 (C-1); 43.3 (C-5); 33.1 (C-3); 21.3 (C-4).
IR (neat, ν/cm^{-1}): 3075, 2939, 2863, 1727, 1640, 1443, 1356, 1137, 993, 910.
HRMS (EI): *m/z* calcd for $C_6H_{10}O$ $[M-H]^+$: 98.0726, found: 98.0724.



20

Acetylene 20: To a solution of **19** (100 mg, 0.50 mmol, 1 equiv) in abs. THF (5 ml) was added *n*-BuLi (1.6 M in hexane; 380 µl, 0.61 mmol, 1.2 equiv) at -10 °C and the mixture was stirred for 20 min. After cooling to -78 °C a precooled solution of **19** (60 mg, 0.61 mmol, 1.2 equiv) in abs. THF (3.5 ml) was added dropwise. The reaction mixture was stirred at -78 °C for 1.5 h and then allowed to warm to -18 °C. The reaction was quenched at this temperature by addition of sat aqu NH_4Cl (10 ml). The mixture was extracted with Et_2O (1 x 10 ml) and the extract was dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by FC (hexane/Et_2O 4:1 → 2:1) to give **20** (76 mg, 51%) as a pale yellow oil.

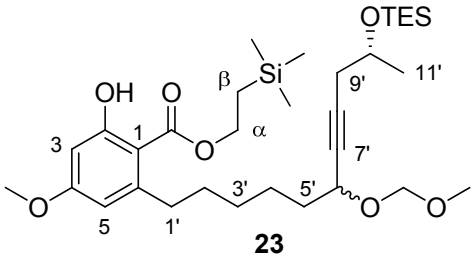
R_f = 0.51 (hexane/Et_2O 4:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 0.58-0.63 (q, *J* = 7.9 Hz, 6H, SiC*H*$_2$CH$_3$); 0.94-0.99 (t, *J* = 7.9 Hz, 9H, SiCH$_2$C*H*$_3$); 1.22-1.24 (d, *J* = 6.0 Hz, 3H, H-11); 1.52-1.58 (m, 2H, H-4'); 1.65-1.72 (m, 2H, H-5); 2.06-2.11 (q, *J* = 7.6 Hz, 2H, H-3); 2.24-2.42 (m, 2H, H-9); 3.90-3.95 (m, 1H, H-10); 4.35-4.36 (m, 1H, H-6); 4.94-5.04 (m, 2H, H-1); 5.77-5.84 (m, 1H, H-2).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 5.0 (Si*C*H$_2$CH$_3$); 7.0 (SiCH$_2$*C*H$_3$); 23.5 (C-11); 24.6 (C-4); 29.8 (C-9); 33.5 (C-3); 37.6 (C-5); 62.7 (C-6); 67.6 (C-10); 82.9 (C-7/C-8); 114.9 (C-1); 138.6 (C-2).
IR (neat, ν/cm^{-1}): 3379, 3077, 2955, 2912, 2876, 1813, 1641, 1459, 1377, 1239, 1125, 1096, 1000, 909, 724.
HRMS (EI): *m/z* calcd for $C_{15}H_{27}O_2Si$ $[M-C_2H_5]^+$: 267.1775, found: 267.1777.



21

MOM-Ether 21: To a solution of **20** (587 mg, 1.98 mmol, 1 equiv) in DMF (60 ml) were added sequentially TBAI (3.7 mg, 0.01 mmol, 0.005 equiv), DIEA (2.76 ml, 15.85 mmol, 8 equiv) und MOM-Cl (1.20 ml, 15.85 mmol, 8 equiv) and the mixture was stirred for 17 h. EtOAc (50 ml) and diluted $NaHCO_3$ solution (50 ml) were then added to the mixture, the pH was adjusted 7 by addition of sat aqu NH_4Cl and the phases were separated. The aqueous solution was extracted with EtOAc (3 x 50 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by FC (hexane/EtOAc 20:1) to give **21** (614 mg, 91%) as a colorless oil.

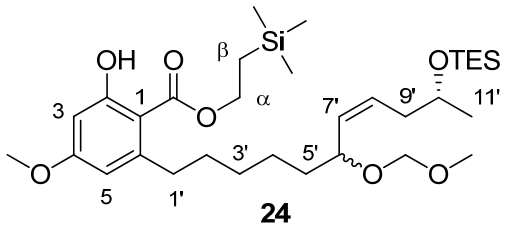
R_f = 0.50 (hexane/EtOAc 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 5.84-5.76 (m, 1H, H-2); 5.04-4.97 (m, 2H, H-1); 0.60 (q, *J* = 8.2 Hz, 6H, Si*C*H$_2$CH$_3$); 4.75 (dd, 2H, MOM-CH$_2$); 4.33-4.30 (m, 1H, H-6); 3.95-3.90 (m, 1H, H-10); 3.36 (s, 3H, MOM-CH$_3$); 2.43-2.24 (m, 2H, H-9); 2.12-2.06 (q, *J* = 7.3 Hz, 2H, H-3); 1.75-1.68 (m, 2H, H-5); 1.61-1.54 (m, 2H, H-4); 1.23 (d, *J* = 6.3 Hz, 3H, H-11); 0.95 (t, *J* = 8.2 Hz, 9H, SiCH$_2$*C*H$_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 138.7 (C-2); 5.0 (Si*C*H$_2$CH$_3$); 114.8 (C-1); 94.0 (MOM-CH$_2$); 83.5 (C-8); 80.3 (C-7); 67.6 (C-10); 65.8 (C-6'), 55.7 (MOM-CH$_3$); 35.5 (C-5); 33.5 (C-3); 29.9 (C-9); 24.8 (C-4); 23.5 (C-11); 7.0 (SiCH$_2$*C*H$_3$).
IR (neat, ν/cm^{-1}): 3077, 2954, 2877, 1641, 1461, 1239, 1097, 1034, 1000,741, 735, 725.
HRMS (EI): m/z calcd for $C_{15}H_{27}O_2Si$ $[M-C_2H_5]^+$: 311.2050, found: 311.2050.



23

Ester 23: To a solution of **21** (100 mg, 0.30 mmol, 1.1 equiv) in 0.65 ml abs. THF was added dropwise a 0.5 M solution of 9-BBN in THF (0.75 ml, 0.37 mmol, 1.2 equiv), and the mixture was stirred at rt for 1 h. A 2 M solution of K_3PO_4 (267 μl, 0.53 mmol, 2 equiv) was added to the mixture (solution A). In a separate flask, 2-(trimethylsilyl)ethyl 2-bromo-6-hydroxy-4-methoxybenzoate (**22**) (92 mg, 0.26 mmol, 1 equiv) was added to a mixture of trifurylphosphine (37 mg, 0.16 mmol, 0.6 equiv) and $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.15 equiv) in 1 ml of degassed abs. DME (solution B). Solution B was stirred for 5 min (with the color changing from red to yellow) and solution A was added dropwise at rt. The reaction mixture was refluxed for 1.5 h and then adsorbed on Celite and purified by FC (hexane/Et_2O 20:1 → 10:1) to give **23** (133 mg, 83%) as a colorless oil.

R_f = 0.28 (hexane/Et_2O 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 11.83 (s, 1H, 2-OH); 6.32-6.33 (d, *J* = 2.9 Hz , 1H, H-3); 6.27 (d, *J* = 2.9 Hz, 1H, H-5); 4.71 (dd, 2H, MOM-C*H*$_2$); 4.39-4.44 (m, 2H, H-α); 4.32-4.30 (m, 1H, H-6'); 3.94-3.91 (m, 1H, H-10'); 3.79 (s, 3H, 4-C*H*$_3$); 3.36 (s, 3H, MOM-C*H*$_3$); 2.88 (t, *J* = 7.7 Hz, 2H, H-1'); 2.42-2.27 (m, 2H, H-9'); 1.72-1.68 (m, 2H, H-5'); 1.59-1.51 (m, 2H, H-2'); 1.50-1.48 (m, 2H, H-4'); 1.42-1.36 (m, 2H, H-3'); 1.23 (d, *J* = 7.1 Hz, 3H, H-11'); 1.13-1.17 (m, 2H, H-β); 0.95 (t, *J* = 8.2 Hz, 9H, $SiCH_2CH_3$); 0.59 (q, *J* = 8.2 Hz, 6H, $SiCH_2CH_3$); 0.09 (s, 9H, $SiCH_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.8 (C=O); 165.7 (C-2); 163.9 (C-4); 147.9 (C-6); 110.8 (C-5); 105.1 (C-1); 99.0 (C-3); 94.0 (MOM-CH_2); 83.4 (C-8'); 80.4 (C-7'); 67.6 (C-10'); 65.9 (C-6'); 63.8 (C-α); 55.7 (MOM-CH_3); 55.4 (4-O-CH_3); 36.9 (C-1'); 36.1 (C-5'); 32.0 (C-2'); 29.9 (C-9'); 29.6 (C-3'); 25.5 (C-4'); 23.5 (C-11'); 17.7 (C-β); 6.9 ($SiCH_2CH_3$); 5.0 ($SiCH_2CH_3$); -1.4 ($Si-CH_3$).
IR (neat, ν/cm^{-1}) 950, 2875, 1646, 1613, 1576, 1251, 1157, 1038, 837, 743, 732, 726.
HRMS (EI): *m/z* calcd for $C_{32}H_{56}NaO_7Si_2$ $[M-Na]^+$: 631.3457, found: 631.3457.

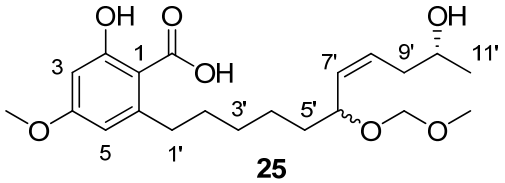


24

Ester 24: To a solution of **23** (924 mg, 1.52 mmol, 1 equiv) in 40 ml EtOAc was added *Lindlar* catalyst (162 mg, 0.08 mmol, 0.05 equiv) and the suspension was

vigorously stirred under a hydrogen atmosphre (baloon); after every 30 min the flask was flushed with argon and the progress of the reaction was assessed by MS and TLC. After 3 h the reaction was complete. The mixture was filtered through Celite, the solvent was evaporated and the residue was purified by FC (hexane/EtOAc 50:1 → 20:1 → 10:1) to give **24** (853 mg, 92%) as a colorless oil.

R_f = 0.35 (hexane/EtOAc 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 11.83 (s, 1H, 2-OH); 6.33 (d, 1H, *J* = 2.6 Hz, H-3); 6.27 (d, 1H, *J* = 2.6 Hz, H-5); 5.67-5.60 (m, 1H, H-8'); 5.29 (t, 1H, *J* = 9.8 Hz, H-7'); 4.46-4.67 (m, 2H, MOM-C*H*$_2$); 4.44-4.39 (m, 2H, H-α); 4.36-4.30 (m, 1H, H-6'); 3.88-3.81 (m, 1H, H-10'); 3.79 (s, 3H, 4-O-C*H*$_3$); 3.34 (s, 3H, MOM-C*H*$_3$); 2.88 (t, 2H, *J* = 8.0 Hz, H-1'); 2.31-2.22 (m, 2H, H-9'); 1.65-1.52 (m, 3H, H-2', H-5'); 1.44-1.26 (m, 5H, H-3', H-4', H-5'); 1.26 (d, 3H, *J* = 2.1 Hz, H-11); 1.26-1.09 (m, 5H, H-β (2H), 0.95 (t, 9H, *J* = 8.0 Hz, Si(CH_2C*H*$_3$)$_3$); 0.59 (q, 6H, *J* = 8.0 Hz, Si(C*H*$_2$$CH_3$)$_3$); 0.09 (s, 9H, Si(C*H*$_3$)$_3$).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.8 (C=O);165.7 (C-2); 163.9 (C-4); 148.0 (C-6); 131.6 (C-7'); 130.1 (C-8'); 110.8 (C-5); 105.1 (C-1); 99.0 (C-3); 93.5 (MOM-*C*H_2); 71.0/71.1 (C-6'); 68.3/68.4 (C-10'); 63.8 (C-α); 55.4 (4-O-*C*H_3/MOM-*C*H_3); 37.9/38.0 (C-9'); 37.0 (C-1'); 35.8/35.9 (C-5'); 32.1 (C-2'); 30.0 (C-3'); 25.6/25.8 (C-4'); 23.6/23.7 (C-11'); 17.7 (C-β); 7.0 (Si(*C*$H_2$$CH_3$)$_3$); 5.0/5.1 (Si($CH_2$*C*$H_3$)$_3$); -1.4 (Si(*C*$H_3$)$_3$).
IR (neat, ν/cm^{-1}): 2950, 2875, 1646, 1613, 1577, 1320, 1251, 1204, 1157, 1096, 1037, 837, 743, 725.
HRMS (ESI): *m/z* calcd for $C_{32}H_{58}NaO_7Si_2$ $[M-Na]^+$: 633.3613, found: 633.3616.

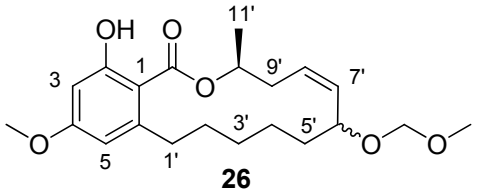


25

Seco acid 25: To a solution of **24** (746 mg, 1.22 mmol, 1 equiv) in THF (45 ml) was added TBAF (1 M in THF; 2.4 ml, 2.44 mmol, 2 equiv) and the reaction mixture was stirred for 2 h. Sat aqu NH_4Cl was then added and the mixture was extracted with EtOAc (3 x 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by FC (EtOAc/MeOH 100:0 → 10:1 → 2:1) to give **25** (436 mg, 90%) as a light-brown resin.

R_f = 0.43 (EtOAc/MeOH 10:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 6.25 (s, 1H, H-3/H-5); 5.17 (s, 1H, H-3/H-5); 5.58-5.45 (m, 1H, H-8'); 5.30-5.22 (m, 1H, H-7'); 4.71-4.43 (m, 2H, MOM-C*H*$_2$); 4.33-4.28 (m, 1H, H-6'); 3.89-3.81 (m, 1H, H-10'); 3.73 (s, 3H, 4-O-C*H*$_3$); 3.32 (s, 3H, MOM-C*H*$_3$); 2.35-2.12 (m, 2H, H-9'); 3.13-2.94 (m, 2H, H-1'); 1.79-1.15 (m, 11H, H-2', H-3', H-4', H-5', H-11').

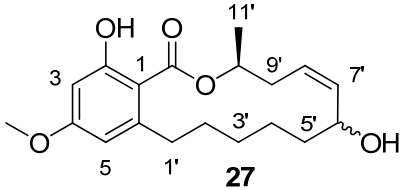
IR (neat, ν/cm^{-1}): 3367, 2933, 2877, 1610, 1582, 1430, 1375, 1157, 1034, 843.
HRMS (ESI): *m/z* calcd for $C_{21}H_{32}NaO_7$ $[M\text{-}Na]^+$: 419.2040, found: 419.2040.



26

Protected macrolactone 26: To solution of **25** (427 mg, 1.08 mmol, 1 equiv) in toluene (150 ml, 0.007 M) and THF (4 ml) were added PPh_3 (565 mg, 2.16 mmol, 2 equiv) und DEAD (350 µl, 2.16 mmol, 2 equiv) and the reaction mixture was stirred for at rt for 1 h. The whole mixture was then adsorbed on Celite and purified by FC (hexane/EtOAc 10:1 → 5:1 → 3:1) to give **26** (261 mg, 64%) as an off-white solid.

R_f = 0.80 (hexane/EtOAc 1:1).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 12.14 (s, 1H, 2-O*H*); 6.32-6.31 (m, 1H, H-3); 6.29-6.27 (m, 1H, H-5); 5.60-5.92 (m, 1H, H-8'); 5.51-5.46 (m, 0.4H, H-7'); 5.44-5.37 (m, 1H, H-10'); 5.34-5.28 (m, 0.6H, H-7'); 5.10-5.03 (m, 0.5H, H-10'); 4.53-4.70 (m, 2H, MOM-C*H$_2$*); 4.40-4.56 (m, 1H, H-6'); 3.79 (s, 3H, 4-O-C*H$_3$*); 3.37 (s, 3H, MOM-C*H$_3$*); 3.21-3.07 (m, 1H, H-1'); 2.98-2.88 (m, 1H, H-9'); 2.73-2.51 (m, 1H, H-1'); 2.247-2.27 (m, 1H, H-9'); 1.78-1.72 (m, 1H, H-5'); 1.62-1.22 (m, 10H, H-2', H-3', H-4', H-5', H-11'(d, 3H, *J* = 6.7 Hz)).
^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.0 (C=O); 166.3 (C-2); 165.4 (C-2); 164.1 (C-4); 164.0 (C-4); 148.2 (C-6); 148.1 (C-6); 133.1 (C-7'); 132.1 (C-7'); 130.7 (C-8'); 127.6 (C-8'); 109.5 (C-5); 109.2 (C-5); 105.8 (C-1); 105.1 (C-1); 98.8 (C-3); 98.7 (C-3); 93.6 (MOM-*C*H$_2$); 93.5 (MOM-*C*H$_2$); 72.7 (C-10'); 71.9 (C-10'); 70.6 (C-6'); 69.1 (C-6'); 55.3/55.4 (MOM-*C*H$_3$/4-O-*C*H$_3$); 36.1 (C-1'); 35.1 (C-9'); 34.4 (C-1'); 33.4/33.5 (C-5'/C-9'); 30.9 (C-2'); 29.3 (C-2'); 27.4 (C-3'); 27.1 (C-3'); 24.6 (C-4'); 22.8 (C-4'); 21.4 (C-11'); 18.5 (C-11').
IR (neat, ν/cm^{-1}): 2932, 2860, 1736, 1640, 1612, 1576, 1249, 1204, 1158, 1033, 829.
HRMS (ESI): *m/z* calcd for $C_{21}H_{30}NaO_6$ $[M\text{-}Na]^+$: 401.19346, found: 401.1935.

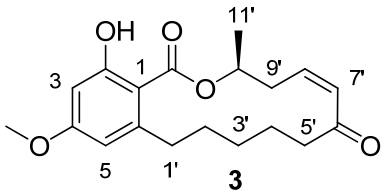


27

Macrolactone 27: To a solution of **26** (235 mg, 0.62 mmol) in MeOH (21 ml) was added sulfonic acid resin (3.1 mmol/g; 220 mg, 0.68 mmol) and the mixture was refluxed for 3 h. The resin was then removed by filtration and washed with MeOH.

The filtrate was evaporated *in vacuo* and the residue was purified by FC (hexane/EtOAc 4:1 → 2:1 → 1:1) to give **27** (152 mg, 73%) as colorless crystals.

R_f = 0.47 (hexane/EtOAc 1:1).
M.p: 66 °C.
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 12.09 (s, 0.45H, 2-O*H*); 11.78 (s, 0.4H, 2-O*H*); 6.32 (d, *J* = 2.6 Hz, 1H, H-3); 6.29 (d, *J* = 2.6 Hz, 1H, H-5); 5.82-5.76 (m, 0.45H, H-8'); 5.65-5.60 (m, 0.5H, H-7'); 5.56-5.50 (m, 0.54H, H-8'); 5.48-5.38 (m, 1.5H, H-10' (1H), H-7' (0.5H)); 4.61-4.56 (m, 0.55H, H-6'); 4.48-4.53 (m, 0.45H, H-6'); 3.22-3.06 (m, 1H, H-1'); 2.97-2.84 (m, 1H, H-9'); 2.73-2.53 (m, 1H, H-1'); 2.49-2.42 (m, 0.5H, H-9'); 2.35-2.29 (m, 0.5H, H-9'); 1.79-1.68 (m, 1H, H-5'); 1.67-1.30 (m, 9.45H, H-2', H-3', H-4', H-5', H-11 (d, *J* = 6.6 Hz)); 1.22-1.17 (m, 0.55H, H-4').
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.8 (C=O); 171.3 (C=O); 166.1 (C-2); 165.5 (C-2); 164.1 (C-4); 164.1 (C-4); 148.1 (C-6); 135.7 (C-7'); 134.9 (C-7'); 129.1 (C-8'); 126.0 (C-8'); 109.3 (C-5); 109.3 (C-5); 105.7 (C-1); 105.2 (C-1); 98.8 (C-3); 98.8 (C-3); 72.6 (C-10'); 71.8 (C-10'); 67.8 (C-6'); 66.5 (C-6'); 55.4 (4-O-*C*H_3); 36.1 (C-5'); 35.7 (C-5'); 35.4 (C-1'); 35.2 (C-9'); 34.4 (C-1'); 33.3 (C-9'); 30.5 (C-2'); 29.4 (C-2'); 27.4 (C-3'); 27.2 (C-3'); 24.4(C-4'); 22.7 (C-4'); 21.4 (C-11'); 18.4 (C-11').
IR (neat, ν/cm^{-1}): 3440, 2932, 2856, 1739, 1637, 1611, 1575, 1248, 1201, 1158, 1040, 826.
HRMS (ESI): *m/z* calcd for $C_{19}H_{26}NaO_5$ $[M-Na]^+$ 357.16725, found: 357.1672.



3

Dideoxy L-783277 (3): To a solution of **27** (91 mg, 0.27 mmol, 1 equiv) in CH_2Cl_2 (5 ml) was added DMP (15% in CH_2Cl_2; 400 µl, 0.19 mmol, 0,7 equiv). The mixture was stirred for 30 minutes and a second portion of DMP (400 µl, 0.19 mmol, 0,7 equiv) was added. After 1 h a third portion of DMP (330 µl, 0.16 mmol, 0,6 equiv) was added. After 3 h the mixture was directly put on a column and purified by FC (hexane/EtOAc 5:1) to give **3** (65 mg, 72%) as a colorless crystals.

R_f = 0.18 (hexane/EtOAc 10:1).
M.p.: 100 °C.
$[\alpha]_D^{20}$ = -24.5° (*c* = 0.89, $CHCl_3$).
^{1}H-NMR (400.1 MHz, $CDCl_3$): δ 6.35-6.32 (m, 1H, H-3); 6.30-6.29 (m, 1H, H-7'); 6.24-6.23 (m, 1H, H-5); 5.92-5.86 (m, 1H, H-8'); 5.52-5.44 (m, 1H, H-10'); 3.79 (s, 3H, 4-OC*H*$_3$); 3.29-3.20 (m, 1H, H-9'); 3.15-3.09 (m, 1H, H-1'); 2.64-2.57 (m, 1H, H-5'); 2.46-2.41 (m, 1H, H-9'); 2.40-2.32 (m, 1H, H-1'); 2.27-2.21 (m, 1H, H-5'); 2.09-2.02 (m, 1H, H-4'); 1.53-1.43 (m, 3H, H-3', H-2', H-4'); 1.40 (d, *J* = 5.7 Hz, 3H, H-11'); 1.36-1.23 (m, 2H, H-3' und H-2').

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 204.7 (C=O); 171.6 (C-6'); 166.3 (C-2); 164.1 (C-4); 147.8 (C-6); 138.9 (C-8'); 132.7 (C-7'); 110.5 (C-5); 104.8 (C-1); 99.1 (C-3); 72.4 (C-10'); 40.3 (C-5'); 55.4 (4-O-*C*H_3); 37.3 (C-1'); 36.3 (C-9'); 31.4 (C-2'); 27.2 (C-3'); 24.0 (C-4'); 21.2 (C-11').
IR (near, ν/cm^{-1}): 3060, 2928, 2854, 1728, 1685, 1642, 1616, 1575, 1319, 1254, 1205, 1162, 1039, 826.
HRMS (ESI): *m/z* calcd for $C_{19}H_{24}NaO_5$ $[M\text{-}Na]^+$ 355.15159, found: 355.1516.

5. Individual IC_{50} values for kinase inhibition by L-783277 and 1

Table 1A: Inhibition of protein kinases by RL **L-783277**, **1**, **2**, and **3**[a,b]

Kinase[c]	IC_{50} [nM]			
	L-783277	**1**	**2**	**3**
ALK	810/740/740	850/730/710	> 10000	3500/4400
ERK2	950/1300	6600/6400	> 10000	> 10000
EPHB4	>10000	7400/7500	> 10000	> 10000
cKIT	150/360/400	540/770/710	7600/8500	> 10000
LCK	6200/7000	4800/4700	> 10000	> 10000
MEK2[d]	15[e]	N. D.	N. D.	6840[e]
MK5	640[e]	N. D.	N. D.	> 10000
MNK2	N. D.	150[e]	N. D.	> 10000
PDGFRα[f]	2.1/0.64/4.4	6.0/7.4/8.3	180/220	95/100
RET	>10000	9900/7200	>10000	> 10000
TYK2	4100/5600	4400/5700	> 10000	> 10000
VEGFR2	2.0/3.4/0.6	4.7/5/3/5/6	230/190	170/190