SUPPORTING INFORMATION

Synthesis and antiproliferative actvity of new Tonantzitlolone-derived diterpene derivatives

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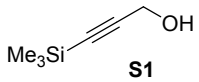
1. General Remarks

General information: All reactions were performed in oven dried glassware under an atmosphere of nitrogen gas unless otherwise stated. ^{1}H-NMR spectra were recorded at 400 MHz with a BRUKER Avance-400 or at 500 MHz with a Bruker DRX-500 at room temperature. ^{13}C-NMR spectra were recorded at 100 MHz with a Bruker Avance-400 and at 125 MHz with a BRUKER DRX-500. Chemical shift values of ^{1}H and ^{13}C NMR spectra are reported as values in ppm relative to (residual undeuterated) solvent signal as internal standard.[S1] Multiplicities for ^{1}H NMR signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; where appropriate with the addition of *br* = broad or *p* = pseudo. Coupling constants (*J*) are stated in Hertz (Hz) and were determined after Gaussian multiplication. Multiplicities for ^{13}C NMR signals refer to the resonances as they would appear in the non-proton-decoupled spectra and were elucidated using phase-sensitive HSQC experiments. Multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbo), d = doublet (methine), t = triplet (methylene), q = quartet (methyl). High resolution mass spectra are obtained with a Micromass LCT via loop-mode injection from a Waters (Alliance 2695) HPLC system. Alternatively a Micromass Q-TOF in combination with a Waters Aquity Ultraperformance LC system was employed. Ionization was achieved by ESI. Modes of ionization, calculated and found mass are given. Analytical thin-layer chromatography was performed using precoated ALUGRAM SIL G/UV254 plates (Macherey-Nagel) and the spots were visualized with UV light at 254 nm or alternatively by staining with permanganate or 4-methoxybenzaldehyde solutions.[S2] Tetrahydrofuran (THF) was distilled under nitrogen from sodium/benzophenone. Commercially available reagents were used as supplied. Flash chromatography was performed with J.T. Baker brand silica gel (40 -60 μm, 60 Å pores). Eluents used for flash chromatography were destilled prior to use. Isolation of selected substrates was achieved by preparative high performance liquid chromatography using a Merck Hitachi LaChrom system (pump L-7150, interface D-7000, diode array detector L-7450 (λ = 220-400 nm, preferred monitoring at λ = 230 nm)) with column (abbreviation referred to in the experimental part given in parentheses): Trentec Reprosil-Pur 120 C18 AQ 5

µm, 250 × 8 mm, with guard column, 40 × 8 mm (C18-SP). Operating conditions and retention times (*t*R) are reported in the experimental part. Melting points were measured using a SRS OptiMelt apparatus. Optical rotations [α] were measured on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. (*R*)-Alkene **13** was prepared according to the procedure reported for the (*S*)-enantiomer.[S3] (*R*)-Aldehyde **14** was prepared according to the procedure reported for the (*S*)-enantiomer.[S3] The syntheses of oxazaborolidin-4-one **11**[S4] and *O*,*O*-ketene acetal **12**[S5] have been reported before.[S4,S5] Carboxylic acid **39** was prepared according to ref. S6. Carboxylic acid **43** was prepared from 2-methylthiazole-4-carbaldehyde after Wittig olefination with ethyl 2-(triphenyl-λ5-phosphanylidene) propanoate followed by saponification with LiOH.[S7] β-Lactam **47** was synthesized following the report by Lee et al. S8.

2. **Synthesis of building blocks**

3-Trimethylsilyl-2-propyne-1-ol (**S1**)[S9]



S1

A preheated 1L three neck flask was equipped with a mechanical stirrer and filled with propargylic alcohol (11.2 mL, 192.4 mmol) and dry THF (500 mL) under nitrogen atmosphere and cooled to -78°C. n-Butyl lithium (250 mL, 1.6 M in hexane, 400 mmol, 2.1 eq) was added dropwise so that the reaction temperature did not rise above -60 °C. After 30 min trimethylchlorosilane (51 mL, 403 mmol, 2.1 eq) was added and the solution was slowly warmed up to rt. After 12 h aqueous HCl (3N, 240 ml) was added and the mixture was stirred vigorously for 1 h. Water and diethyl ether were added and the combined organic extracts were washed with an aqueous bicarbonate solution and with brine, dried ($MgSO_4$) filtered and distilled (32 mbar, 83-85 °C) to yield the title compound **S1** (24.0 g, 187.1 mmol; 97 %) as a yellowish liquid which was stored at -20°C.

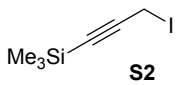
IR: ν = 3345 (br m), 2960 (m), 2901 (w), 2865 (w), 2177 (m), 1410 (w), 1351 (w), 1250 (s), 1038 (s), 982 (m), 838 (s), 759 (m), 699 (w), 646 (w) cm^{-1};

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 4.25 (s, 2 H, C*H*$_2$), 2.06 (br s, 1 H, O*H*), 0.16 (s, 9 H, Si(C*H*$_3$)$_3$) ppm;

^{13}C-NMR (50 MHz, $CDCl_3$ = 77.16 ppm): 104.0 (CH_2*C*C), 90.8 (CH_2C*C*), 51.7 (HO*C*H$_2$), -0.1 (Si(*C*H$_3$)$_3$) ppm.

The spectroscopic data of compound **S1** were reported in ref. S9 before.

(3-Iodo-1-propynyl)-trimethylsilane (**S2**)[S10]



S2

Alcohol **S1** (1.52 g, 11.9 mmol) was dissolved in diethyl ether/acetonitrile (3:1, 60 mL) and at 0°C, triphenyl phosphine (4.76 g, 18.1 mmol, 1.5 eq), imidazole (1.24 g, 18.2 mmol, 1.5 eq) and iodine (4.75 g, 18.0 mmol, 1.5 eq) were added and the reaction mixture was stirred for 1.5 h in the dark. Then, an aqueous bicarbonate solution was added and stirring was continued for 5 min. The phases were separated and the aqueous phase was extracted with diethyl ether. The

combined organic phases were washed with an aqueous $Na_2S_2O_3$-solution, dried ($MgSO_4$), filtered and carefully concentrated under reduced pressure (p > 250 mbar) to provide the title compound **S2** (2.86) as a colorless liquid which turns to red under light. As some solvent was still present, the yield was only estimated (75-85 %) by ^{1}H-NMR spectroscopy.

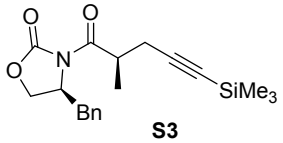
IR: ν = 3797 (w), 3746 (w), 3658 (w), 2959 (m), 2899 (w), 2289 (w), 2172 (m), 2067 (w), 1949 (w), 1887 (w), 1789 (w), 1707 (w), 1410 (w), 1250 (s), 1149 (s), 1042 (s), 838 (s), 759 (s), 700 (m), 638 (m) cm^{-1};

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 3.71 (s, 2 H, CH_2), 0.16 (s, 9 H, Si(CH_3)$_3$) ppm;

^{13}C-NMR (50 MHz, $CDCl_3$= 77.16 ppm): 102.1 (CH_2*C*C), 90.9 (CH_2C*C*), -0.2 (Si(*C*H$_3$)$_3$), 18.1 (I*C*H$_2$) ppm. [S10]

The spectroscopic data of compound **S2** were reported in ref. S10 before.

Alkyne **S3**



S3

Lithium-bis-(trimethylsilyl)-amide (1 M solution in THF, 1.7 mL, 1.7 mmol, 1.1 eq) was diluted in dry THF (2 mL) under nitrogen atmosphere and cooled to -78°C. A solution of benzylpropionyloxazolidinone (350 mg, 1.5 mmol) in dry THF (3 ml) was added dropwise and the solution was stirred for 1h at rt. Iodide **S3** (1.43 g, ca. 80%, ca. 4.8 mmol, ca. 3.2 eq) was added dropwise in the dark and stirring was continued for 1h. The temperature was increased to -10°C and after 2 h, an aqueous saturated ammonium chloride solution was added. The temperature was lowered to -10 °C and after 2 h, a solution of an aqueous saturated ammonium chloride solution was added. The layers were separated and the aqueous phase was extracted with MTBE. The combined, organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (silica; petroleum ether / ethyl acetate= 15:1 → 1:1) yielded the title compound (333 mg as a 4:1 mixture with starting oxazolidinone; ca. 0.83 mmol, approx. . 49 %). In addition the diastereomeric alkylation product was collected (15.4 mg, 0.045 mmol, 3 %).

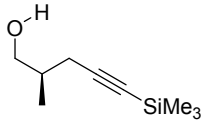
IR: ν = 2961 (w), 2178 (m), 1780 (s), 1705 (s), 1495 (w), 1477 (w), 1455 (w), 1395 (m), 1371 (m), 1354 (m), 1290 (m), 1235 (w), 1212 (m), 1126 (m), 1100 (m), 1079 (w), 1026 (m), 970 (m), 834 (s), 748 (m), 719 (w), 696 (m), 635 (w) cm^{-1};

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 7.39-7.20 (m, 5 H, Ph), 4.71 (dddd, *J* = 9.4, 6.9, 4.0, 3.3 Hz, 1 H, NC*H*), 4.22 (ddd, *J* = 9.1, 6.9, 0.4 Hz, 1 H, OCH_2), 4.16 (dd, *J* = 9.1, 4.0 Hz, 1 H, OCH_2), 3.94 (sext, *J* = 6.8 Hz, 1 H, CH_3C*H*), 3.30 (dd, *J* = 13.4, 3.3 Hz, 1 H, PhCH_2), 2.76 (dd, *J* = 13.4, 9.4 Hz, 1 H, PhCH_2), 2.64 (dd, *J* = 16.9, 6.7 Hz, 1 H, CH_2CC), 2.53 (dd, *J*= 16.9, 6.8 Hz, 1 H, CH_2CC), 1.27 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.12 (s, 9 H, Si(CH_3)$_3$) ppm;

^{13}C-NMR (50 MHz, $CDCl_3$= 77.16 ppm): 175.3 (N*C*(O)CH), 153.2 (O*C*(O)N), 135.4 (Ph, q), 129.6, 129.1 (*o*-Ph, *m*-Ph), 127.5 (*p*-Ph), 103.9 (CH_2*C*C), 86.7 (CH_2C*C*), 66.3 (O*C*H$_2$), 55.4 (N*C*H), 38.2 (Ph*C*H$_2$), 37.6 (CH_3*C*H), 24.2 (*C*H$_2$CC), 16.7 (*C*H$_3$), 0.2 (Si(*C*H$_3$)$_3$) ppm;

HRMS-ESI ($C_{19}H_{24}NO_3Si$): calculated 344.1682 [M+H]+, found 344.1682.

(*R*)-2-Methyl-5-(trimethylsilyl)pent-4-yn-1-ol (**S4**)



S4

Oxazolidinone **S3** (3.65 g, 10.2 mmol, 94 % purity) was dissolved in diethylether (200 mL) at 0 °C and treated with $LiBH_4$ (293 mg, 13.5 mmol, 1.3 eq) and water (0.23 mL, 12.8 mmol, 1.3 eq). The reaction mixture was stirred for 2 h and a second portion of $LiBH_4$ (100 mg, 4.6 mmol) was added and stirring was continued for 1 h. Then, the reaction was terminated by addition of an aqueous phosphate buffer (pH 7). The mixture was extracted with diethylether and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate= 5:1) to yield the title compound **S4** (1.92 g, 9.6 mmol; 90 %) as a colorless oil.

$[\alpha]^D_{20}$ = + 6.6° (*c*= 0.92 in $CHCl_3$);

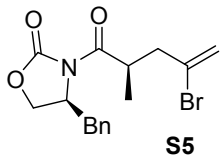
IR: ν = 3325 (br, w), 2959 (m), 2901 (w), 2173 (m), 1459 (m), 1409 (m), 1378 (m), 1330 (m), 1248 (s), 1078 (w), 1035 (s), 995 (m), 926 (w), 836 (s), 758 (s), 697 (m), 646 (m) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 3.61 (dd, *J* = 10.9, 6.4 Hz, 1 H, HOCH_2), 3.58 (dd, *J* = 10.9, 5.7 Hz, 1 H, HOCH_2), 2.31 (dd, *J* = 17.0, 6.6 Hz, 1 H, CH_2CC), 2.26 (dd, *J* = 17.0, 6.2 Hz, 1 H, CH_2CC), 1.89 (oct, *J* = 6.4 Hz, 1 H, CH_3C*H*), 1.72 (br s, 1 H, O*H*), 0.99 (d, *J* = 6.9 Hz, 3 H, C*H*3), 0.17 (s, 9 H, Si(CH_3)$_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 105.6 (CH_2*C*C), 86.3 (CH_2C*C*), 67.4 (HO*C*H_2), 35.2 (CH_3*C*H), 24.0 (*C*H_2CC), 16.4 (*C*H_3), 0.2 (Si(*C*H_3)$_3$) ppm.

HRMS-ESI ($C_9H_{19}OSi$): calculated 171.1205 [M+H]+, found 171.1210.

Vinyl bromide **S5**

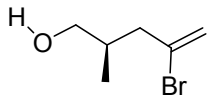


S5

Lithium-bis-(trimethylsilyl)-amide (1 M in THF, 4.4 ml, 4.4 mmol, 1.1 eq) was cooled under nitrogen atmosphere to -78 °C and benzylpropionyloxazolidinone (933 mg, 4 mmol) dissolved in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h and 2,3-dibromopropene (1.5 mL, 3.2 g, 16.0 mmol, 4 eq) was added. Within the next hour the temperature was slowly raised to -35 °C and stirring was continued for 17.5 h at this temperature followed by 1h at -15°C. Then, the reaction mixture was terminated by addition of a saturated aqueous solution of ammonium chloride. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined, organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified

by flash chromatography (silica; petroleum ether/ ethyl actetate= 10:1 → 3:1) to furnish the title compound **S5** (1.1 g, 3.1 mmol; 78 %).
^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): 7.39-7.18 (m, 5 H, Ph), 5.69 (ddd, *J* = 1.7, 1.1, 0.9 Hz, 1 H, H_2C=C), 5.50 (d, *J* = 1.7 Hz, 1 H, H_2C=C), 4.69 (dddd, *J* = 9.5, 7.0, 3.7, 3.4 Hz, 1 H, NC*H*), 4.29-4.10 (m, 3 H, OCH_2, CH_3CH), 3.28 (dd, *J* = 13.4, 3.4 Hz, 1 H, PhCH_2), 3.01 (ddd, *J* = 14.5, 7.6, 0.9 Hz, 1 H, *H*2CC=CH_2), 2.75 (dd, *J* = 13.4, 9.5 Hz, 1 H, PhCH_2), 2.52 (ddd, *J* = 14.5, 6.6, 1.1 Hz, 1 H, H_2CC=CH_2), 1.22 (d, *J* = 6.9 Hz, 3 H, CH_3) ppm.
HRMS-ESI ($C_{16}H_{19}BrNO_3$): calculated 352.0548 [M+H]+, found 352.0553.

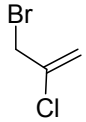
(*R*)-2-Methyl-4-bromo-4-penten-1-ol (**S6**)



S6

Oxazolidinone **S5** (285 mg, 0.81 mmol) was dissolved in diethylether (15 mL) cooled to 0 °C and treated with $LiBH_4$ (30 mg, 1.38 mmol, 1.7 eq) and water (20 µl, 1.1 mmol, 1.4 eq). The reaction mixture was stirred for 30 min and then a phosphate buffer solution (pH 7) was added. The mixture was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica; petroleum ether/ ethyl acetate= 3:1) to furnish the title compound **S6** (140.8 mg, 0.79 mmol; 98 %) as a colorless oil.
^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.61-5.59 (m, 1 H, H_2C=C), 5.45 (dd, *J*= 1.5, 0.3 Hz, 1 H, H_2C=C), 3.54 (d, *J* = 5.5 Hz, 2 H, HOCH_2), 2.59 (ddd, *J* = 14.0, 6.0, 1.1 Hz, 1 H, H_2CC=CH_2), 2.23 (ddd, *J* = 14.0, 8.1, 0.9 Hz, 1 H, H_2CC=CH_2), 2.15-1.97 (m, 1 H, CH_3CH), 1.6-1.3 (br s, 1 H, O*H*), 0.95 (d, *J* = 6.7 Hz, 3 H, CH_3) ppm.
HRMS-ESI ($C_6H_{12}BrO$): calculated 179.0072 [M+H]+, found 179.0067.

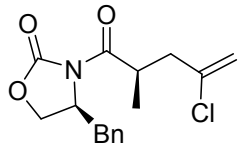
3-Bromo-2-chloropropene (**S7**)[S11]



S7

2,3-Dichloropropene (6 ml, 7.2 g, 65 mmol) was dissolved in dry DMF (125 ml) and NaBr (16.6 g, 161 mmol, 2.5 eq) was added. The mixture was heated to 90°C for 16 h. After cooling to rt water and pentane were added. The phases were separated and the aqueous phase was extracted with *n*-pentane and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was distilled to yield the title compound **S7** (3.57 g, 23 mmol; 35 %) as a colorless oil.
^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.61-5.57 (m, 1 H, H_2C=C), 5.40 (d, *J* = 1.8 Hz, 1 H, H_2C=C), 4.09 (d, *J* = 0.6 Hz, 2 H, BrCH_2) ppm.
The spectroscopic data of compound **S7** were reported in ref. S11 before.

Vinyl chloride (**S8**)



S8

Lithium-bis-(trimethylsilyl)-amid (1 ml 1 M solution in THF, 1.0 mmol, 1.1 eq) was cooled under a nitrogen atmosphere at -78 °C. Benzylpropionyloxazolidinone (215 mg, 0.92 mmol) dissolved in dry THF (1 mL) was added dropwise. The solution was stirred for 1 h and 2-chloro-3-bromopropene (0.35 ml, 0.56 g, 3.6 mmol, 3.9 eq) was added dropwise. The temperature was slowly raised to -50°C within 3 h and stirring was continued at this temperature for 4 h. Then, the solution was stirred at -60°C overnight before addition of an aqueous solution of ammonium chloride terminated the reaction. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (silica; petroleum ether/ ethyl acetate= 8:1) yielded the title compound **S8** (110.6 mg, 0.36 mmol; 39 %) as a yellowish oil.

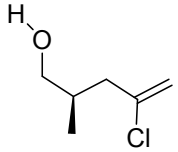
$[\alpha]^{D}_{20}$ = + 33.8 ° (*c*= 1.0 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): 7.38-7.21 (m, 5 H, Ph), 5.27 (s, 2 H, H_2C=C), 4.69 (dtd, *J* = 7.5, 6.4, 3.2 Hz, 1 H, NC*H*), 4.25-4.16 (m, 3 H, OCH_2, CH_3C*H*), 3.27 (dd, *J* = 13.5, 3.4 Hz, 1 H, H_2CC=CH_2), 2.91 (dd, *J* = 14.3, 7.5 Hz, 1 H, PhCH_2), 2.74 (dd, *J* = 13.5, 9.6 Hz, 1 H, H_2CC=CH_2), 2.45 (dd, *J* = 14.3, 6.4 Hz, 1 H, PhCH_2), 1.22 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 175.8 (N*C*(O)CH), 153.0 (O*C*(O)N), 139.9 (*C*Cl), 135.2, 129.4, 129.0, 127.4 (Ph), 114.6 (H_2*C*=C), 66.0 (O*C*H_2), 55.3 (N*C*H), 42.5 (Ph*C*H_2), 37.9 (H_2*C*C=CH_2), 36.0 (CH_3*C*H), 17.0 (*C*H_3) ppm.

HRMS-ESI ($C_{16}H_{19}ClNO_3$): calculated 308.1053 [M+H]+, found 308.1049.

(*R*)-2-Methyl-4-chloro-4-penten-1-ol (**S9**)



S9

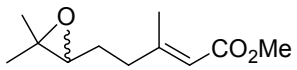
Oxazolidinone **S8** (ca. 300 mg, containing ca. 200 mg benzylpropionyloxazolidinone, in total 1.8 mmol) was dissolved in diethylether (30 mL), cooled to 0 °C and treated with $LiBH_4$ (60 mg, 2.75 mmol, 1.5 eq) and distilled water (40 µL, 2.2 mmol, 1.2 eq) was added. The reaction mixture was stirred for 70 min and a buffer solution (pH 7) was added. After extraction with CH_2Cl_2 the organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified (silica; petroleum ether/diethylether= 4:1) to furnish the title compound **S9** (130 mg, 0.97 mmol; 90 %) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.20 (d, *J* = 1.0 Hz, 1 H, H_2C=C), 5.19-5.18 (m, 1H, H_2C=C), 3.57 (d, *J* = 10.9, 5.6 Hz, 1 H, HOCH_2), 3.55 (d, *J* = 10.9, 5.6 Hz, 1 H, HOCH_2), 2.50 (ddd, *J* = 14.1, 6.1, 0.8 Hz, 1 H, H_2CC=CH_2), 2.16 (ddd, *J* = 14.1, 8.2, 0.7 Hz, 1 H, H_2CC=CH_2), 2.14-2.02 (m, 1 H, CH_3C*H*), 1.38 (br. s, 1 H, O*H*), 0.96 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 141.5 (*C*Cl), 113.8 (H2*C*=C), 67.3 (HO*C*H_2), 43.1 (H_2*C*C=CH_2), 33.6 (CH_3*C*H), 16.0 (*C*H_3) ppm.
HRMS-ESI ($C_6H_{12}ClO$): calculated 135.0577 [M+H]+, found 135.0581.

3. **Synthesis of tonantzitlolone**

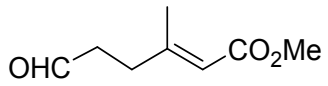
Methyl (*E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enoate (**S10**)



S10

Methyl geranoate (1.01 g, 5.54 mmol, *E/Z* ≅ 7/3) was dissolved in CH_2Cl_2 (2 mL) and while stirring at 0°C *m*CPBA (70% assay, 1.35 g, 5.48 mmol, 0.99 eq) dissolved in CH_2Cl_2 (10.5 mL) was added. Stirring was continued for 1.5 h at 0°C and for 1 h at rt. Then, an aqueous solution of Na_2SO_3 was added and stirring was continued until an homogeneous, biphasic solution was obtained. The phases were separated and the organic phase was washed twice with an aqueous bicarbonate solution. The combined aqueous phases were extracted with CH_2Cl_2 (2x), the organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure. The colorless oil obtained **S10** (1.08 g, 5.45 mmol; 98 %) was directly used in the next step without further purification. For analytical purposes 200 mg of the crude oil were purified by column chromatography (silica; petroleum ether/ethyl acetate= 6:1).
IR: ν = 2952 (m), 2927 (w), 1717 (s), 1650 (s), 1435 (m), 1378 (m), 1361 (w), 1323 (w), 1281 (w), 1248 (w), 1224 (s), 1176 (w), 1148 (s), 1099 (w), 1068 (w), 1025 (m), 919 (w), 903 (w), 867 (m), 796 (w), 738 (w), 680 (w) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.69 (m, 1 H, H-2), 3.66 (s, 3 H, OMe), 2.69 (dd, *J* = 6.8, 5.7 Hz, 1 H, H-6), 2.32 (dddd, *J* = 14.5, 8.7, 6.5, 1.0 Hz, 1 H, H-4), 2.24 (dddd, *J* = 14.5, 8.8, 6.9, 1.2 Hz, 1 H, H-4'), 2.16 (d, *J* = 1.4 Hz, 3 H, 3-Me), 1.76 – 1.63 (m, 2 H, H-5, H-5'), 1.28 (s, 3 H, H-8), 1.24 (s, 3 H, H-8') ppm;
^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 167.1 (C-1), 159.0 (C-3), 115.8 (C-2), 63.6 (C-6), 58.5 (C-7), 50.9 (OMe), 37.7 (C-4), 27.1 (C-5), 24.9 (C-8), 18.9 (3-Me), 18.8 (C-8') ppm.
The spectroscopic data of compound **S10** were reported in ref. S3 before.

Methyl (*E*)-3-methyl-6-oxohex-2-enoate (**6**)

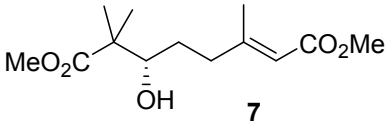


6

The crude oil **S10** (obtained from 28.2g, 155 mmol methyl geranoate) was dissolved in diethylether (240 mL) and cooled to 0 °C. Over a period of 10 min H_5IO_6 (42.4 g, 186 mmol, 1.2 eq) dissolved in THF (60 mL) was added. The solution was stirred for 15 min at 0 °C before ice-cold water was added to terminate the reaction. The phases were separated and the aqueous layer was extracted with diethylether (6x). The combined organic phases were washed with water, a saturated, aqueous bicarbonate solution, a $Na_2S_2O_3$ solution, brine, and water, were dried ($MgSO_4$ and a little bit $Na_2S_2O_3$), filtered and concentrated under reduced pressure. Flash column chromatography (silica; petroleum ether/ ethyl acetate= 7:1) yielded two aldehydes **6** (*Z*-aldehyde: 5.54 g, 35.5 mmol; 23 % for two steps and *E*-aldehyde: 18.05 g, 106.8 mmol; 69 %, 92 % purity).

IR: ν = 2951 (m), 2842 (w), 2725 (w), 1713(s), 1648 (m), 1435 (m), 1387 (m), 1361 (m), 1281 (m), 1221 (s), 1148 (s), 1080 (m), 1021 (m), 924 (w), 871 (m), 744 (m), 677 (w) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 9.68 (td, *J* = 1.3, 0.5 Hz, 1 H, H-6), 5.57 (qd, *J* = 1.3, 0.4 Hz, 1 H, H-2), 3.57 (d, *J* = 0.6 Hz, 3 H, OMe), 2.57 – 2.53 (m, 2 H, H-5), 2.37 (t, *J* =7.3 Hz, 2 H, H-4), 2.07 (s, 3 H, 3-Me) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 200.5 (C-6), 166.7 (C-1), 157.5 (C-3), 115.8 (C-2), 50.8 (OMe), 41.3 (C-5), 32.6 (C-4), 18.7 (3-Me) ppm;
HRMS-ESI ($C_{10}H_{15}NaNO_3$): calculated 220.0950 [M+Na^++MeCN], found 220.0950.

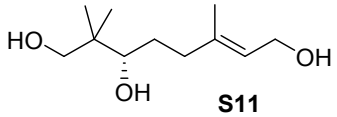
Dimethyl (*S,E*)-6-hydroxy-3,7,7-trimethyloct-2-enedioate (**7**)



7

N-para-Toluenesulfonyl-*D*-phenylalanine (10 g, 31.3 mmol, 1.2 eq) was dissolved in dry CH_2Cl_2 (280 mL) and a solution of borane-THF-complex (30 mL, 1 M in THF, 30 mmol, 1.19 eq) was added dropwise. The reaction mixture was stirred at rt for 20 min and then cooled to -85 °C. Then, aldehyde **6** (3.94 g, 25.2 mmol, 1 eq) dissolved in dry CH_2Cl_2 (25 mL) and keteneacetal **12** (4.9g, 28.1 mmol, 1.12 eq) dissolved in dry 30 ml abs. CH_2Cl_2 (30 mL) were added slowly. After 30 min the cooling was stopped and the reaction mixture was warmed up to -40°C. Then, phosphate buffer (90 mL, pH 7) was added and the mixture was stirred for 20 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (6x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was taken up with petroleum ether and the precipitate (*N-para*-toluenelsulfonyl-*D*-phenylalanine was sufficiently pure for reuse) was filtered and thoroughly washed with petroleum ether. The combined organic phases were concentrated under reduced pressure and treated with methanol and a few drops of acetyl chloride. After removal of the solvent a crude yellowish oil **7** was collected (5.9 g, 22.8 mmol, 90 %, 98.5-99 % *ee*; determined using $Eu(hfc)_3$ as NMR shift reagent).
$[\alpha]^D_{20}$ = - 22.48° (*c*= 1.17 in $CHCl_3$) (for enaniomer + 20.3°)[S3];
IR: ν = 3508 (br, w), 2951 (m), 1715 (s), 1648 (m), 1435 (m), 1387 (w), 1359 (w), 1271 (w), 1223 (s), 1146 (s), 1076 (m), 1022 (w), 926 (w), 860 (w), 772 (w), 733 (m), 681 (w) cm^{-1};
^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.71 (sext., *J* = 1.3 Hz, 1 H, H-2), 3.70 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.57 (ddd, *J* = 10.6, 6.9, 2.2 Hz, 1 H, H-6), 2.59 (d, *J* = 6.9 Hz, 1H, OH), 2.48 (dddd, *J* = 14.5, 9.6, 5.1, 1.2 Hz, 1 H, H-4), 2.21 (dddd, *J* = 14.5, 9.5, 6.6, 1.0 Hz, 1 H, H-4'), 2.16 (d, *J* = 2.2 Hz, 3 H, 3-Me), 1.63 (ddddd, *J* = 13.6, 9.6, 6.6, 2.2, 0.6 Hz, 1H, H-5), 1.44 (dddd, *J* = 13.6, 10.6, 9.5, 5.1 Hz, 1 H, H-5'), 1.20 (s, 3 H, 7-Me), 1.17 (s, 3 H,7-Me') ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 178.1 (C-8), 167.2 (C-1), 160.0 (C-3), 115.5 (C-2), 76.0 (C-6), 52.1 (OMe), 50.9 (OMe), 47.2 (C-7), 37.9 (C-4), 29.4 (C-5), 22.3 (7-Me), 20.5 (7-Me'), 18.9 (3-Me) ppm;
The spectroscopic data of compound **7** were reported in ref. S3 before.

(*E*,*S*)-2,2,6-Trimethyl-6-octene-1,3,8-triol (**S11**)



S11

Lithiumaluminium hydride (1.76 g, 46.4 mmol, 5 eq) was suspended in dry diethylether (92 mL) and cooled to 0°C. Diester **7** (2.4 g, 9.29 mmol) dissolved in dry diethylether (9 mL) was added and the suspension was stirred overnight at rt. Water (7 mL) and NaOH (4 M, 1.75 mL) were added and stirring was continued for 30 min. After addition of $MgSO_4$ the suspension was stirred for another 30 min and filtered. The solid was washed with diethyl ether and the combined organic extracts were concentrated under reduced pressure to yield a crude yellowish oil **S11** (1.94 g, 9.6 mmol; 103 %). For analytical purposes, a small sample was purified by flash column chromatography (silica; ethyl acetate).

$[\alpha]^{D}_{20}$= - 24.6 (*c*= 1.17 in $CHCl_3$) (+ 23.6° for the enantiomer)[S3];

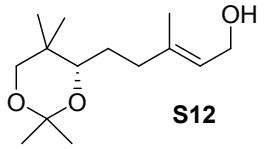
IR: ν = 3313 (br, s), 2954 (m), 2926 (m), 2873 (m), 1703 (w), 1668 (w), 1436 (m), 1382 (m), 1232 (w), 1178 (w), 1151 (w), 1034 (s), 994 (s), 930 (m), 732 (m) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.42 (tt, *J* = 6.9, 1.3 Hz, 1 H, H-2), 4.13 - 4.10 (m, 2 H, H-1, H-1'), 3.54 (d, *J* = 10.7 Hz, 1 H, H-8), 3.41 (dd, *J* = 10.2, 1.3 Hz, 1 H, H-6), 3.36 (d, *J* = 10.7 Hz, 1 H, H-8'), 2.24 (ddd, *J* = 13.9, 8.5, 5.2 Hz, 1 H, H-4), 2.11 – 2.04 (m, 1 H, H-4'), 1.65 (s, 3 H, 3-Me), 1.63 – 1.58 (m, 1 H, H-5), 1.49 – 1.39 (m, 1 H, H-5'), 0.86 (s, 3 H, 7-Me), 0.82 (s, 3 H, 7'-Me) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 139.3 (C-3), 124.0 (C-2), 78.0 (C-6), 71.9 (C-8), 59.2 (C-1), 38.6 (C-7), 36.6 (C-4), 29.3 (C-5), 22.7 (7-Me), 19.0 (7'-Me), 16.2 (3-Me) ppm

HRMS-ESI ($C_{11}H_{22}NaO_3$): calculated 225.1467 [M+Na]+, found 225.1469.

(*E*,*S*)-3-Methyl-5-(2,2,5,5-tetramethyl-[1,3]dioxan-4-yl)-2-penten-1-ol (**S12**)



S12

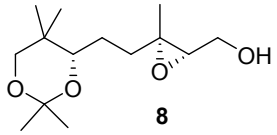
Triol **S11** (1.93 g, 9.5 mmol) was dissolved in dry DMF (19 mL) and treated with 2,2-dimethoxypropane (6 mL, 48.4 mmol, 5.1 eq) and *p*TsOH (17.2 mg, 0.1 mmol, 0.01 eq) and the reaction mixture was stirred at rt for 2.5 h. For work-up dist. water was added and after 35 min the acid was neutralized by addition of K_2CO_3. The solution was extracted with MTBE (4x) and the combined organic phases were washed with dist. water and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (silica; petroleum ether/ethyl acetate = 3:1) yielded the title product **S12** (1.87 g, 7.7 mmol, 81 %) as a colorless oil.

IR: ~ν = 3401 (br, m), 2929 (m), 2856 (m), 2243 (w), 1723 (w), 1668 (w), 1463 (m), 1392 (w), 1378 (m), 1360 (w), 1263 (m), 1228 (w), 1199 (m), 1171 (w), 1156 (m), 1103 (m), 1072 (m), 1051 (w), 1005 (m), 919 (m), 906 (m), 849 (w), 776 (w), 732 (s), 674 (w) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.39 (t sext., *J* = 6.9, 1.3 Hz, 1 H, H-2), 4.13 (ddq, *J* = 6.9, 2.4, 0.8 Hz, 2 H, H-1, H-1'), 3.56 (dd, *J* = 11.4, 0.6 Hz, 1 H, H-8), 3.42 (dd, *J* = 10.2, 2.0 Hz, 1 H, H-6), 3.25 (d, *J* =11.4 Hz, 1 H, H-8'), 2.18 (dddd, *J* = 14.2, 9.3, 4.2, 0.5 Hz, 1 H, H-4), 1.95 (dddd, *J* = 14.2, 8.9, 7.2, 0.9 Hz, 1 H, H-4'), 1.77 (br s, 1 H, OH), 1.65 (dd, *J* = 1.4, 0.5 Hz, 3 H, 3-Me), 1.51 (dddd, *J* = 13.7, 9.3, 7.2, 2.0 Hz, 1 H, H-5), 1.38 (dddd, *J* =

13.7, 10.2, 8.9, 5.0 Hz, 1 H, H-5'), 1.38 (s, 3 H, 9-Me), 1.37 (s, 3 H, 9'-Me), 0.99 (d, *J* = 0.4 Hz, 3 H, 7-Me), 0.69 (s, 3 H, 7'-Me) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 139.5 (C-3), 123.9 (C-2), 98.7 (C-9), 76.6 (C-6), 72.2 (C-8), 59.4 (C-1), 36.0 (C-7); 32.9 (C-4), 29.8 (3-Me), 27.1 (C-5), 21.9, 19.1, 18.3, 16.3 (all Me) ppm;
The spectroscopic data of compound **S12** were reported in ref. S3 before.

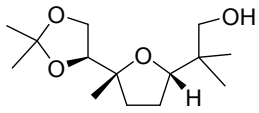
(*E*,*S*)-{3-Methyl-3-[2-(2,2,5,5-tetramethyl-[1,3]dioxan-4-yl)-ethyl]-oxiranyl}-methanol (**8**)



8

Molecular sieves 4Å (850 mg) were suspended in dry CH_2Cl_2 (36 mL)under an atmosphere of nitrogen and cooled to -15 °C. Then, Ti(O*i*-Pr)$_4$ (150 µl, 0.5 mmol, 5.9 mol%), L-(+)-diethyl tartrate (100 µl, 0.68 mmol, 7.4 mol%) and *tert*-butylhydroperoxide (5.5 M in decane, 4.25 ml, 23.4 mmol, 2.8 eq) were added dropwise and the reaction mixture was stirred for 30 min. After cooling to -25 °C allyl alcohol **S12** (2.43 g, approx. 85% assay, 8.5 mmol), dissolved in dry CH_2Cl_2 (60 mL), was added dropwise. The solution was stirred for 20 h and terminated by addition of water (2.9 ml) and aq. NaOH (30%, 0.6 ml, saturated with NaCl). After stirring for 1 h at rt the mixture was filtered through diatomaceous earth which was washed with water and with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$) and after filtration the solution was concentrated under reduced pressure. These reaction was carried out four times (same scale) and the combined crude products were purified by flash chromatography (silica, petroleum ether/ethyl acetate = 3:1, doped with 1% of triethyl amine) to yield the title compound **8** (8.55 g, 33.1 mmol; 97 %) as a colorless oil.
$[\alpha]^D_{20}$= - 26.67 (*c*= 0.96 in $CHCl_3$) (+ 22.9° for enantiomer)[S3];
IR: ~ν = 3434 (br, m), 2990 (w), 2958 (m), 2864 (m), 1463 (m), 1378 (s), 1360 (m), 1263 (m), 1227 (m), 1198 (s), 1157 (m), 1106 (s), 1078 (m), 1041 (s), 1010 (m), 972 (w), 921 (m), 900 (m), 855 (m), 796 (w), 734 (w), 674 (w) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 3.74 (dd, *J* = 12.1, 4.2 Hz, 1 H, H-1), 3.61 (dd, *J* = 12.1, 6.7 Hz, 1 H, H-1'), 3.53 (d, *J* = 11.4 Hz, 1 H, H-8), 3.39 (dd, *J* = 10.0, 2.0 Hz, 1 H, H-6), 3.21 (d, *J* = 11.4 Hz, 1 H, H-8'), 2.94 (dd, *J* = 6.7, 4.2 Hz, 1 H, H-2), 1.91-1.86 (m, 1 H, H-4), 1.42-1.36 (m, 1 H, H-5), 1.35-1.30 (m, 1 H, H-5'), 1.33 (s, 3 H, Me acetonide), 1.32 (s, 3 H, 9-Me, acetonide), 1.30-1.25 (m, 1 H, H-4'), 1.23 (s, 3 H, 3-Me), 0.94 (s, 3 H, 7-Me), 0.66 (s, 3 H, 7-Me') ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 98.7 (C-9), 76.8 (C-6), 72.0 (C-8), 62.5 (C-2), 61.3 (C-1), 61.0 (C-3), 34.6 (C-4), 32.9 (C-7), 29.7 (9-Me), 24.4 (C-5), 21.8 (7-Me), 18.9 (9-Me'), 18.1 (7-Me'), 17.4 (3-Me) ppm.
The spectroscopic data of compound **8** were reported in ref. S3 before.

Alcohol **9**



9

Oxirane **8** (8.55 g, 33.1 mmol) was dissolved under nitrogen in dry CH_2Cl_2 (330 ml) and treated with ethylene glycol (2.2 ml, 39.4 mmol, 1.2 eq) dissolved in a dry solvent mixture of CH_2Cl_2/THF (6.5:1, 415 mL). Then, *p*TsOH (1.1 g, 6.4 mmol, 0.2 eq) was added. The reaction was monitored by tlc and after 55 min 2,2-dimethoxypropane (55 mL, 444 mmol, 13.4 eq) was added. Stirring was continued overnight after which time water was added and the mixture was neutralized by addition of sodium bicarbonate. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with brine. Drying ($MgSO_4$), filtration and concentration under reduced pressure yielded a crude material which was purified by flash column chromatography (silica; petroleum ether/ ethyl acetate= 3:1) to yield the title compound **9** (6.64 g, 25.7 mmol; 78 % and 1.5 g of mixture) as a colourless oil.

$[\alpha]^{D}_{20}$= + 4.1 (*c*= 1 in $CHCl_3$) (- 4.5° for enantiomer)[S3];

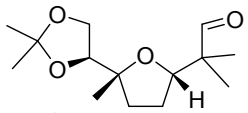
IR: ν = 3471 (br, w), 2976 (m), 2936 (w), 2874 (m), 1474 (m), 1458 (m), 1371 (m), 1263 (m), 1211 (m), 1156 (m), 1130 (w), 1098 (w), 1064 (s), 959 (w), 906 (w), 855 (m), 798 (w), 734 (m), 647 (w) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 3.98-3.91 (m, 2 H, H-9, H-10), 3.78 (dd, *J* = 9.4, 6.1 Hz, 1 H, H-14), 3.73-3.67 (m, 1 H, H-9), 3.40 (d, *J* = 10.9 Hz, 1 H, H-1), 3.33 (d, *J* = 10.9 Hz, 1 H, H-1), 3.16 (br s, 1 H, OH), 1.94 (ddd, *J* = 12.3, 8.6, 3.7 Hz, 1 H, H-12), 1.78 (dddd, *J* = 12.2, 8.6, 6.1, 3.7 Hz, 1 H, H-13), 1.73 (dddd, *J* = 12.2, 8.7, 9.4, 8.6 Hz, 1 H, H-13), 1.57 (ddd, *J* = 12.3, 8.7, 8.6 Hz, 1 H, H-12), 1.37 (s, 3 H, O2C(CH_3)$_2$), 1.27 (s, 3 H, O2C(CH_3)$_2$), 1.10 (s, 3 H, H-18), 0.84 (s, 3 H, H-16), 0.79 (s, 3 H, H-17) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 109.4 ($O_2C(CH_3)_2$), 86.4 (C-14), 83.3 (C-11), 80.2 (C-10), 71.6 (C-1), 65.7 (C-9), 37.3 (C-15), 33.9 (C-12), 27.1 (C-13), 26.2 ($O_2C(CH_3)_2$), 24.9 ($O_2C(CH_3)_2$), 22.9 (C-16), 22.1 (C-18), 19.3 (C-17) ppm;

HRMS-ESI ($C_{14}H_{26}NaO_4$): calculated 281.1729 $[M+Na]^+$, found 281.1803.

Aldehyde **S13**



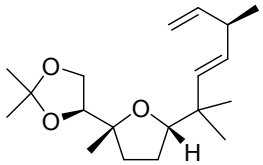
S13

Alcohol **9** (205 mg, 0.79 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under nitrogen and in the following molecular sieves 4Å (120 mg) , *N*-methylmorpholine-*N*-oxide (138.5 mg, 1.18 mmol, 1.5 eq) and tetra-*n*-propylammonium perruthenate (15.3 mg, 0.04 mmol, 5.1 mol%) were added and the reaction mixture was stirred at rt for 2.5 h. The deep dark solution was filtered through a pad of diatomaceous earth (5 g) using petroleum ether/ethyl acetate= 8:1 as eluent. The filtrate was concentrated under reduced pressure to yield the title compound **S13** (184.1 mg, 0.72 mmol; 91 %) as a colorless oil.

IR: ν = 2979 (m), 2878 (w), 1725 (s), 1458 (m), 1370 (m), 1211 (m), 1155 (m), 1068 (s), 854 (s) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 9.56 (s, 1 H, H-1), 3.97-3.89 (m, 3 H, H-9, H-10, H-14), 3.76-3.71 (m, 1 H, H-9), 2.01-1.93 (m, 1 H, H-12), 1.90-1.81 (m, 1 H, H-13), 1.74-1.59 (m, 2 H, H-12, H-13), 1.36 (s, 3 H, $O_2C(CH_3)_2$), 1.27 (s, 3 H, $O_2C(CH_3)_2$), 1.11 (s, 3 H, H-18), 1.01 (s, 3 H, H-16), 0.97 (s, 3 H, H-17) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 206.3 (C-1), 109.4 (O2*C*(CH3)2), 83.4 (C-11), 82.7 (C-14), 80.3 (C-10), 65.8 (C-9), 48.8 (C-15), 34.9 (C-12), 27.1 (C-13), 26.3 ($O_2C(CH_3)_2$), 25.0 ($O_2C(CH_3)_2$), 21.6, 19.6, 17.1 (C-16, C-17, C-18) ppm;
HRMS-ESI ($C_{14}H_{25}O_4$): calculated 257.1753 $[M+H]^+$, found 257.1753.

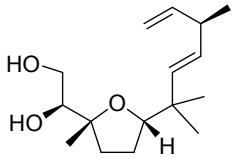
Diene **S14**



S14

Diisopropylamine (0.55 mL, 3.9 mmol, 1.4 eq) was dissolved in dry THF (2.5 mL) under nitrogen and cooled to -78 °C. Then, n-butyl lithium (1.56 mL, 2.5 M in hexane, 3.9 mmol, 1.4 eq) was added dropwise and stirring was continued for 55 min. This solution was added dropwise to sulfone **13** (0.96 g, 3.4 mmol, 1.2 eq) dissolved in dry THF (15 mL) at -78 °C and the solution was stirred for 70 min. Then, aldehyde **S3** (0.725 g, 2.8 mmol) dissolved in dry THF (2.5 mL) was added and the solution was slowly warmed up to rt, stirred for 39 h at rt and heated for 4.5 h under refluxing conditions. After cooling to rt the reaction was terminated by addition of an aqueous ammonium chloride solution, the phases were separated and the aqueous phase was extracted with MTBE. The combined organic phase was dried ($MgSO_4$) filtered and concentrated under reduced pressure. The brownish crude material was purified by flash column chromatography (silica; petroleum ether/ ethyl acetate= 10:1) and the product **S14** (671 mg, 2.2 mmol; 79%) as a yellow oil.
IR: ν = 2966 (m), 2872 (m), 1636 (w), 1455 (m), 1380 (m), 1369 (m), 1262 (m), 1210 (m), 1156 (m), 1069 (s), 1018 (w), 995 (w), 911 (m), 855 (s), 798 (w), 680 (w), 620 (w) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.81 (ddd, *J* = 17.1, 10.3, 6.7 Hz, 1 H, H-4), 5.45 (dd, *J* = 15.9, 1.1 Hz, 1 H, H-1), 5.33 (dd, *J* = 15.9, 6.7 Hz, 1 H, H-2), 5.00 (ddd, *J* = 17.1, 1.7, 1.5 Hz, 1 H, H-5), 4.96 (ddd, *J* = 10.3, 1.7, 1.2 Hz, 1 H, H-5), 4.01 (dd, *J* = 5.8, 4.6 Hz, 1H, H-9), 3.95-3.88 (m, 2 H, H-9, H-10), 3.69-3.65 (m, 1 H, H-14), 2.84 (sext. q, *J* = 6.8, 1.3 Hz, 1 H, H-3), 1.92-1.89 (m, 1 H, H-12), 1.78-1.72 (m, 1 H, H-13), 1.67-1.59 (m, 2 H, H-13, H-12), 1.41 (d, *J* = 0.6 Hz, 3 H, $O_2C(CH_3)_2$), 1.32 (d, *J* = 0.6 Hz, 3 H, $O_2C(CH_3)_2$), 1.16 (s, 3 H, H-18), 1.10 (d, *J* = 6.8 Hz, 3 H, H-20), 0.99 (s, 3 H, H-16), 0.93 (s, 3 H, H-17) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 143.4 (C-4), 135.2 (C-1), 131.7 (C-2), 112.7 (C-5), 109.2 (O2*C*$(CH_3)_2$), 86.5 (C-14), 82.7 (C-11), 80.1 (C-10), 65.7 (C-9), 40.6 (C-3), 39.1 (C-15), 36.0 (C-12), 27.1 (C-13), 26.4 ($O_2C(CH_3)_2$), 25.1 ($O_2C(CH_3)_2$), 24.7 (C-16), 24.4 (C-17'), 21.2 (C-18), 20.2 (C-20) ppm;
HRMS-ESI ($C_{19}H_{32}NaO_3$): calculated 331.2249 $[M+Na]^+$, found 331.2455.

Diol **S15**



S15

Acetonide **S14** (1 g, 3.24 mmol) was dissolved in methanol/water (1:1, 100 mL) and treated with *p*-toluenesulfonic acid (140 mg, 0.81 mmol, 0.25 2q) and stirred for 6.5 h at 50 °C. A saturated bicarbonate solution was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the diol **S15** (931.8, mg; > 99 %) as a colorless oil.

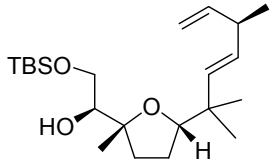
IR: ν = 3374 (br m), 2964 (s), 2871 (m), 1636 (w), 1454 (m), 1370 (m), 1306 (w), 1082 (s), 1014 (s), 910 (s) cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): 5.76 (ddd, *J* = 17.3, 10.4, 6.7 Hz, 1 H, H-4), 5.41 (d, *J* = 16.0 Hz, 1 H, H-1), 5.35 (dd, *J* = 16.0, 5.8 Hz, 1 H, H-2), 4.95 (ddd, *J* = 17.3, 1.7, 1.4 Hz, 1 H, H-5), 4.92 (ddd, *J* = 10.4, 1.7, 1.2 Hz, 1 H, H-5), 3.68 (dd, *J* = 10.9, 3.4 Hz, 1 H, H-9), 3.67 (dd, *J* = 8.1, 6.7 Hz, 1 H, H-14), 3.61 (dd, *J* = 7.2, 3.4 Hz, 1 H, H-10), 3.53 (dd, *J* = 10.9, 7.2 Hz, 1 H, H-9), 2.9-2.7 (br s, 2 H, OH), 2.81 (qdddd, *J* = 6.9, 6.8, 5.8, 1.4, 1.2 Hz, 1H, H-3), 1.89 (ddd, *J* = 11.9, 9.5, 5.7 Hz, 1 H, H-12), 1.81 (dddd, *J* = 12.4, 8.3, 6.7, 5.7 Hz, 1 H, H-13), 1.62 (dddd, *J* = 12.4, 9.5, 8.1, 6.5 Hz, 1 H, H-13), 1.48 (ddd, *J* = 11.9, 8.3, 6.5 Hz, 1 H, H-12), 1.12 (s, 3 H, H-18), 1.06 (d, *J* = 6.9 Hz, 3 H, H-20), 1.01 (s, 3 H, H-16), 0.93 (s, 3H, H-17) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 143.2 (C-4), 134.6 (C-1), 132.8 (C-2), 112.8 (C-5), 85.1 (C-14), 84.2 (C-11), 76.7 (C-10), 63.3 (C-9), 40.5 (C-3), 39.0 (C-15), 32.7 (C-12),27.0 (C-13), 24.7 (C-16), 24.6 (C-17), 22.1 (C-18), 20.1 (C-20) ppm;

HRMS-ESI ($C_{16}H_{28}NaO_3$): calculated 291.1936 $[M+Na]^+$, found 291.1949.

Silyl ether **S16**

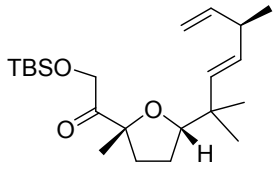


S16

Diol **S15** (81 mg, 0.3 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under nitrogen and treated with imidazole (43 mg, 0.63 mmol, 2.1 eq), TBSCl (71 mg, 0.47 mmol, 1.6 eq) and 4-DMAP (3.5 mg, 0.029 mmol, 0.1 eq). After stirring at rt for 2 h additional portions of imidazole (23 mg, 0.34 mmol, 1.1 eq) and TBSCl (30 mg, 0.2 mmol, 0.7 eq) were added. After 1 h the reaction was terminated by addition of a saturated solution of ammonium chloride solution. The phases were separated and the aqueous phase was washed with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) filtered and concentrated under reduced pressure. Flash column chromatography (silica; petroleum ether / ethyl acetate= 10:1) yielded the title compound **S16** (110.4 mg, 0.29 mmol; 97 %) as a colorless oil.

IR: ν = 3573 (w), 3081(w), 2957 (m), 2930 (m), 2857 (m), 1637 (w), 1463 (m), 1385 (w), 1362 (w), 1327 (w), 1253 (m), 1061 (s), 1024 (m), 994 (m), 938 (w), 910 (m), 835 (s), 776 (s), 679 (m) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.77 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1 H, H-4), 5.42 (dd, *J* = 15.9, 1.1 Hz, 1 H, H-1), 5.32 (dd, *J* = 15.9, 6.6 Hz, 1 H, H-2), 4.96 (ddd, *J* = 17.2, 1.6, 1.4 Hz, 1 H, H-5), 4.92 (ddd, *J* = 10.4, 1.6, 1.3 Hz, 1 H, H-5), 3.76 (dd, *J* = 10.3, 3.8 Hz, 1 H, H-9), 3.68 (dd, *J* = 8.2, 6.5 Hz, 1 H, H-14), 3.62 (dd, *J* = 10.3, 7.0 Hz, 1 H, H-9), 3.50 (ddd, *J* = 7.0, 3.8, 2.3 Hz, 1 H, H-10), 2.81 (sext q, *J* = 6.7, 1.2 Hz, 1 H, H-3), 2.64 (d, *J* = 2.3 Hz, 1 H, OH), 2.00-1.95 (m, 1 H, H-12), 1.82-1.75 (m, 1 H, H-13), 1.65-1.50 (m, 2 H, H-12, H-13), 1.14 (s, 3 H, H-18), 1.07 (d, *J* = 6.8 Hz, 3 H, H-20), 1.01 (s, 3 H, H-16), 0.94 (s, 3 H, H-17), 0.90 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2C(CH_3)_3$) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 143.4 (C-4), 135.1 (C-1), 132.2 (C-2), 112.7 (C-5), 85.7 (C-14), 83.8 (C-11), 76.7 (C-10), 63.8 (C-9), 40.6 (C-3), 39.1 (C-15), 34.3, (C-12), 27.0 (C-13), 26.0 ($Si(CH_3)_2C(CH_3)_3$), 24.6 (C-16), 24.5 (C-17), 21.9, 20.2 (C-18, C-20), 18.4 ($Si(CH_3)_2C(CH_3)_3$), -5.2, -5.2 ($Si(CH_3)_2C(CH_3)_3$) ppm;
HRMS-ESI ($C_{22}H_{42}NaO_3Si$): calculated 405.2801 $[M+Na]^+$, found 405.2814.

Siloxyketone **10**

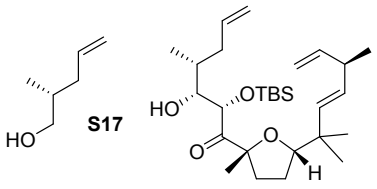


10

Alcohol **S16** (1.29, 3.5 mmol) was dissolved in CH_2Cl_2 (30 mL) at 0 °C and the Dess-Martinreagent (2.2 g, 5.2 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt for 6.5 h and treated with a saturated mixture of an aqueous $NaHCO_3/Na_2S_2O_3$ solution for 30 min. After phase separation, the aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica; petroleum ether / ethyl acetate= 40:1) to afford the title compound **10** (1.25 g, 3.3 mmol; 94 %) as a colorless oil.
$[\alpha]^{D}_{20}$= + 12.0° (*c*= 1.13 in $CHCl_3$) (- 12.3° for enantiomer[S3]);
IR: ν = 2958 (m), 2929 (m), 2857 (m), 1735 (s), 1636 (w), 1463 (m), 1420 (w), 1387 (w), 1363 (m), 1253 (m), 1159 (m), 1099 (m), 1047 (m), 1001 (s), 938 (w), 912 (m), 835 (s), 776 (s), 681 (w) cm^{-1};
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.76 (ddd, *J* = 17.2, 10.3, 6.5 Hz, 1 H, H-4), 5.42 (dd, *J* = 15.9, 0.7 Hz, 1 H, H-1), 5.34 (dd, *J* = 15.9, 6.5 Hz, 1 H, H-2), 4.96 (ddd, *J* = 17.2, 1.7, 1.6 Hz, 1 H, H-5), 4.93 (ddd, *J* = 10.3, 1.7, 1.3 Hz, 1 H, H-5), 4.70-4.68 (m, 2 H, 2xH-9), 3.74 (dd, *J* = 8.3, 6.0 Hz, 1 H, H-14), 2.81 (sext td, *J* = 6.7, 1.2, 0.7 Hz, 1 H, H-3), 2.03-2.00 (m, 1 H, H-12), 1.82-1.70 (m, 2 H, 2xH-13), 1.57-1.50 (m, 1 H, H-12), 1.29 (s, 3 H, H-18), 1.06 (d, *J* = 6.9 Hz, 3 H, H-20), 1.03 (s, 3 H, H-16), 0.98 (s, 3 H, H-17), 0.91 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$), 0.07 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$) ppm;
^{13}C-NMR (50 MHz, $CDCl_3$= 77.16 ppm): 211.7 (C-10), 143.2 (C-4), 134.9 (C-1), 132.4 (C-2), 112.8 (C-5), 88.0 (C-11), 86.9 (C-14), 66.7 (C-9), 40.6 (C-3), 38.9, 36.0 (C-12, C-15),

26.5 (C-13), 26.0 ($Si(CH_3)_2C(CH_3)_3$), 24.5, 24.4, 24.0 (C-16, C-17, C-18), 20.2 (C-20), 18.7 ($Si(CH_3)_2C(CH_3)_3$), -5.2, -5.3 ($Si(CH_3)_2C(CH_3)_3$) ppm;
HRMS-ESI ($C_{22}H_{40}NaO_3Si$): calculated 403.2644 [M+Na]+, found 403.2681.

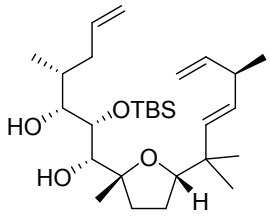
Aldol product **18**



18

Oxalyl chloride (3.6 mL, 42 mmol, 2 eq) was dissolved in CH_2Cl_2 (200 mL) and DMSO (6 ml, 84.5 mmol, 4.0 eq) was added at -78°C and the solution was stirred for 15 min. Then, alcohol **S17** (2.1 g, 21 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and added dropwise. Stirring was continued for 70 min. After addition of E_3N (22 ml, 156.5 mmol, 7.5 eq) the temperature was slowly raised to -25°C within 2 h. Addition of water terminated the reaction. After separation of the phases, the aqueous layer was extracted with n-pentane and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure (p > 550 mbar) to yield crude aldehyde **14**.
Ketone **10** (1.84 g, 4.8 mmol) was dissolved in dry THF (100 mL) cooled to -78 °C and treated with KHMDS (10.6 mL, 0.5 M in THF 5.3 mmol, 1.1 eq). After 30 min the freshly prepared aldehyde **14**, dissolved in dry THF (10 mL) was added dropwise and the reaction mixture was stirred for 70 min. Then, methanol and an aqueous solution of ammonium chloride were added. After warming up to rt, the mixture was extracted with MTB-ether and the combined organic phases were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica; petroleum ether / ethyl acetate= 40:1≪20:1) to yield the title compound **18** (2.1 mg, 4.4 mmol; 92 %) as a colorless oil which was utilized for the next reaction due to lack of stability (e.g. retro aldol reaction).
^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.92-5.66 (m, 1 H, H-5'), 5.77 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-4), 5.46 (d, *J* = 15.8 Hz, 1 H, H-1), 5.34 (dd, *J* = 15.8, 5.9 Hz, 1 H, H-2), 5.16-4.90 (m, 5 H, H-5, H-4', H-9), 3.94-3.76 (m, 2 H, H-8, H-14), 2.80 (ps sext. *J* = 6.6 Hz, 1 H, H-3), 2.63-2.51 (m, 1 H, H-6), 2.00-1.66 (m, 6 H, H-12, H12′, H-13H-6, H-7, 8-OH), 1.56-1.45 (m, 1 H, H-13), 1.34 (s, 3 H, H-18), 1.07 (d, *J* = 6.9 Hz, 3 H, H-20), 1.03, 1.01 (2s, 6 H, H-16, H-17), 0.96 (d, *J* = 6.8 Hz, 3 H, H-19), 0.93 (s, 9 H, $Si(Me)_2$*t-Bu*), 0.11 (s, 3 H, $Si(CH_3)_2$*t*-Bu), -0.02 (s, 3 H, $Si(CH_3)_2$*t*-Bu) ppm.
HRMS-ESI ($C_{28}H_{51}O_4Si$): calculated 479.4445 [$M+H^+$], found 479.4448.

Diol **22**



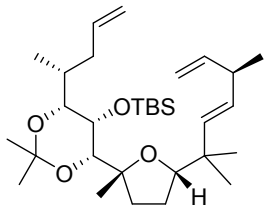
22

Aldol product **18** (2.1 g, 4.4 mmol) was dissolved in dry CH_2Cl_2 (100 mL) cooled to -78 °C and treated with Dibal-H (22 mL, 1 M in hexane, 22 mmol, 5 eq) versetzt. After 2.5 h a second portion of Dibal-H (15 mL, 15 mmol, 3.4 eq) was added and after 5 h of stirring the reaction mixture was warmed up to –30 °C and terminated by addition of water (3.5 ml). Then, a saturated potassium-sodium tartrate solution was added and stirring at rt was continued overnight. The phases were seprated and the aqueous phase was extracted with CH_2Cl_2.The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica; petroleum ether / ethyl acetate= 20:1✂10:1) to afford the title compound **22** as well as the starting material **18**. The procedure was repeated (25 ml CH_2Cl_2 and 9 ml Dibal-H) with the recovered starting material the title compound **22** (1.37 g, 2.9 mmol; 66 %) was obtained as colorless oil.

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.91-5.68 (m, 1 H, H-5'), 5.68 (ddd, *J* = 17.3, 10.2, 6.7 Hz, 1 H, H-4), 5.45 (d, *J* = 15.7 Hz, 1 H, H-1), 5.34 (dd, *J* = 15.7, 5.9 Hz, 1 H, H-2), 5.10-4.98 (m, 2 H, 2xH-4'), 4.97 (ps td, *J* = 17.3, 1.8 Hz, 1 H, H-5), 4.94 (ddd, *J* = 10.2, 1.8, 1.2 Hz, 1 H, H-5), 3.78 (dd, *J* = 6.4, 1.0 Hz, 1 H, H-9), 3.71 (dd, *J* = 8.5, 6.3 Hz, 1 H, H-14), 3.46 (dd, *J* = 6.4, 4.5 Hz, 1 H, H-10), 3.18 (ps t, *J* = 8.4 Hz, 1 H, 8), 2.86 (d, *J* = 8.4 Hz, 1 H, 8-OH), 2.84 (ps sext. *J* = 6.3 Hz, 1 H, H-3), 2.73 (d, *J* = 4.5 Hz, 1 H, 10-OH), 2.56-2.43 (m, 1 H, H-6), 2.18-2.08 (m, 1 H, H-7), 2.05-1.55 (m, 5 H, H-12,H-12`,H13,H-13`, H-6), 1.21 (s, 3 H, H-18), 1.08 (d, *J* = 6.9 Hz, 3 H, H-20), 1.04, 0.96 (2s, 6 H, H-16, H-17), 0.91 (s, 9 H, Si(Me)$_2$*t-Bu*), 0.84 (d, *J* = 6.7 Hz, 3 H, H-19), 0.16 (s, 3 H, Si(C*H*$_3$)$_2$*t*-Bu), 0.12 (s, 3 H, Si(C*H*$_3$)$_2$*t*-Bu) ppm.

HRMS-ESI ($C_{28}H_{52}NaO_4Si$): calculated 518.3767 [M+Na$^+$], found 518.3770.

Acetonide **23**



23

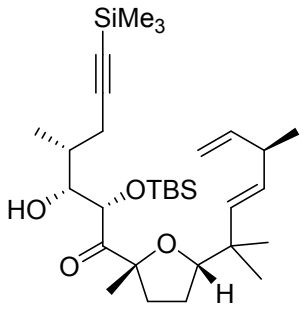
1,3-Diol **22** (91.8 mg, 191 µmol) was dissolved in 2,2-dimethoxypropane (5 mL), treated with a few crystals *p*TsOH and stirred at rt for 13 h. After addition of an aqueous saturated solution of $NaHCO_3$ the mixture was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered concentrated under reduced pressure to yield a crude product **23**

(101.2 mg) as a colorless oil which was already very pure for determining the relative stereochemistry of the triol stereotriade.

^{1}H-NMR (200 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.87-5.65 (m, 1 H, H-5'), 5.78 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1 H, H-4), 5.42 (d, *J* = 15.9 Hz, 1 H, H-1), 5.29 (dd, *J* = 15.9, 6.0 Hz, 1 H, H-2), 5.07-4.89 (m, 4 H, 2xH-4', 2xH-5), 3.78 (dd, *J* = 7.8, 4.1 Hz, 1 H, H-14), 3.75 (s, 1 H, H-9), 3.52 (s, 1 H, H-10), 3.18 (d, *J* = 9.5 Hz, 1 H, H-8), 2.81 (sext , *J* = 6.6 Hz, 1 H, H-3), 2.40-2.26 (m, 1 H, H-6), 2.01-1.80 (m, 3 H, 13-H, H-6, H-7), 1.73-1.52 (m, 3 H,12-H, 12-H`, 13-H), 1.46 (s, 3 H, $O_2C(CH_3)_2$), 1.39 (s, 3 H, $O_2C(CH_3)_2$), 1.22 (s, 3 H, H-18), 1.07 (d, *J* = 6.8 Hz, 3 H, H-20), 0.99 (s, 3 H, H-16), 0.94 (s, 3 H, H-17), 0.91 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.81 (d, *J* = 6.5 Hz, 3 H, H-19), 0.10 (s, 6 H, $Si(CH_3)_2C(CH_3)_3$) ppm.

HRMS-ESI ($C_{31}H_{56}NaO_4Si$): calculated 543.3846 [M+Na$^+$], found 543.3842

Aldol product **19**



19

Ketone **10** (41 mg, 0.11 mmol) was taken up in dry THF (2.6 ml) and cooled to -78 °C. Then, KHMDS (0.2 mL solution in toluene, 15 %, 0.66 mol/l, 0.13 mmol, 1.2 eq) were added and stirring was continued for 30 min. The freshly prepared aldehyde **15** (obtained by oxidation of **S4**), dissolved in dry THF (0.3 mL) was added dropwise and the reaction mixture was stirred for 35 min. Then, methanol and an aqueous solution of ammonium chloride were added. After warming up to rt, the mixture was extracted with MTB-ether and the combined organic phases were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate 40:1) to yield the title compound **19** (37 mg, 0.067 mmol; 61 %) as a colorless oil.

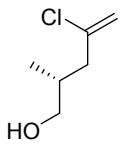
[α**]**$^D_{20}$= + 53.9 ° (*c*= 0.88 in $CHCl_3$);

IR: ν = 3566 (w), 2959 (m), 2931 (m), 2859 (m), 2174 (m), 1728 (m), 1463 (m), 1387 (m), 1364 (w), 1333 (w), 1249 (s), 1154 (m), 1090 (m), 1042 (m), 995 (m), 917 (w), 839 (s), 808 (w), 779 (m), 760 (m), 698 (w), 646 (w) cm^{-1}.

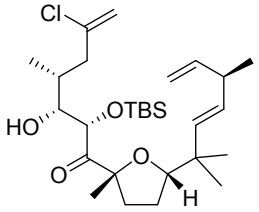
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.76 (ddd, *J* = 17.2, 10.3, 6.4 Hz, 1 H, H-4), 5.44 (dd, *J* = 15.8, 0.7 Hz, 1 H, H-1), 5.35 (dd, *J* = 15.8, 6.7 Hz, 1 H, H-2), 5.09 (d, *J* = 1.1 Hz, 1 H, H-9), 4.96 (dt, *J* = 17.2, 1.6 Hz, 1 H, H-5), 4.93 (ddd, *J* = 10.3, 1.6, 1.4 Hz, 1 H, H-5), 4.03 (br t, *J* = 10.5 Hz, 1 H, H-8), 3.79 (dd, *J* = 8.1, 6.7 Hz, 1 H, H-14), 2.81 (sext ddd, *J* = 6.7, 1.6, 1.4, 0.7 Hz, 1 H, H-3), 2.50 (dd, *J* = 16.9, 4.0 Hz, 1 H, H-6), 2.41 (dd, *J* = 16.9, 6.9 Hz, 1 H, H-6), 2.00 (br d, *J* = 11.9 Hz, 1 H, OH), 1.97-1.87 (m, 3 H, H-7, 2xH-12), 1.80 (ddt, *J* = 12.3, 7.4, 6.9 Hz, 1 H, H-13), 1.49 (dddd, *J* = 12.3, 9.5, 8.1, 6.8 Hz, 1 H, H-13'), 1.34 (s, 3 H, H-18), 1.12 (d, *J* = 6.8 Hz, 3 H, H-19), 1.07 (d, *J* = 6.9 Hz, 3 H, H-20), 1.05 (s, 3 H, H-16),

1.02 (s, 3 H, H-17), 0.93 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.14 (s, 9 H, $Si(CH_3)_3$), 0.11 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$), -0.02 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 212.8 (C-10), 143.2 (C-4), 134.7 (C-1), 132.5 (C-2), 112.9 (C-5), 105.7 (C-5'), 88.8 (C-11), 86.5 (C-14), 86.2 (C-4'), 76.1 (C-9), 74.3 (C-8), 40.7 (C-3), 39.1 (C-15), 37.5 (C-12), 35.9 (C-7), 26.0 ($Si(CH_3)_2C(CH_3)_3$), 25.9 (C-13), 24.9 (C-16), 24.3 (C-18), 24.1 (C-17), 24.0 (C-6), 20.3 (C-20), 18.6 ($Si(CH_3)_2C(CH_3)_3$), 16.3 (C-19), 0.3 ($Si(CH_3)_3$), -4.1, -5.2 ($Si(CH_3)_2C(CH_3)_3$) ppm;
HRMS-ESI ($C_{31}H_{57}O_4Si_2$): calculated 549.3795 [M+H]+, found 549.3800.

Aldol product **20**



S9

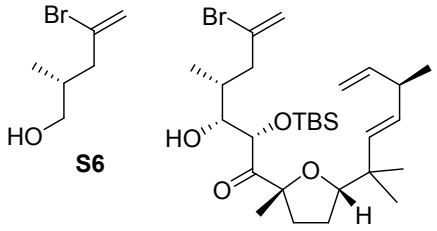


20

Oxalyl chloride (0.12 mL, 0.18 g, 1.4 mmol, 1.6 eq) was dissolved in CH_2Cl_2 (7 mL) and DMSO (0.2 ml, 0.22 g, 2.8 mmol, 3.1 eq)) was added at -78°C and the solution was stirred for 15 min. Then, alcohol **S9** (120 mg, 0.89 mmol) dissolved in dry CH_2Cl_2 (3.5 mL) was added dropwise and stirring was continued for 25 min. After addition of E_3N (0.6 ml, 0.44 g, 4.3 mmol, 4.8 eq) the temperature was slowly raised to -20°C within 2 h. Addition of water terminated the reaction. After separation of the phases, the aqueous layer was extracted with n-pentane and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure (p > 550 mbar) to yield crude aldehyde **16**.
Ketone **10** (156 mg, 0.41 mmol) was dissolved in dry THF (8 mL) cooled to -78 °C and treated with KHMDS (0.68 ml, solution in toluene, 15 %, 0.66 mol/L, 0.45 mmol, 1.1 eq). After 35 min the freshly prepared aldehyde **16**, dissolved in dry THF (3 mL) was added dropwise and the reaction mixture was stirred for 70 min. Then, methanol und an aqueous solution of ammonium chloride were added. After warming up to rt, the mixture was extracted with MTB-ether and the combined organic phases were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate 20:1) to yield the title compound **20** (85 mg, 0.17 mmol; 41 %) as a colorless oil.
$[\alpha]^D_{20}$= + 46.5 ° (*c* = 0.94 in $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.76 (ddd, *J* = 17.3, 10.3, 6.7 Hz, 1 H, H-4), 5.44 (d, *J* = 15.9 Hz, 1 H, H-1), 5.35 (dd, *J* = 15.9, 6.5 Hz, 1 H, H-2), 5.19 (s, 1 H, H-4'), 5.14 (s, 1 H, H-4'), 5.10 (d, *J* = 0.7 Hz, 1 H, H-9), 4.95 (dt, *J* = 17.3, 1.6 Hz, 1 H, H-5), 4.93 (dt, *J* = 10.3, 1.5 Hz, 1 H, H-5), 3.88 (dd, *J* = 11.6, 9.9 Hz, 1 H, H-8), 3.80 (dd, *J* = 7.9, 6.8 Hz, 1 H, H-14), 2.95 (br. d, *J* = 12.3 Hz, 1 H, H-6), 2.80 (sext. m, *J* = 6.6 Hz, 1 H, H-3), 2.19-2.03 (m, 2 H, H-6, H-7), 2.04 (d, *J* = 11.6 Hz, 1 H, 8-OH), 1.92-1.87 (m, 2 H, 2xH-12), 1.85-1.76 (m, 1 H, H-13), 1.56-1.46 (m, 1 H, H-13), 1.34 (s, 3 H, H-18), 1.07 (d, *J* = 6.8 Hz, 3 H, H-20), 1.03 (s, 3 H, H-16), 1.01 (s, 3 H, H-17), 0.97 (d, *J* = 6.5 Hz, 3 H, H-19), 0.93 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.12 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$), -0.02 (s, 3 H, $Si(CH_3)_2C(CH_3)_3$) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 212.5 (C-10), 143.2 (C-4), 142.4 (C-5'), 134.9 (C-1), 132.4 (C-2), 113.6 (C-4'), 112.9 (C-5), 88.8 (C-11), 86.5 (C-14), 76.2 (C-9), 75.2 (C-8), 42.8 (C-6), 40.7 (C-3), 39.0 (C-15), 37.4 (C-12), 34.5 (C-7), 26.0 ($Si(CH_3)_2C(\mathit{C}H_3)_3$), 25.8 (C-13), 24.4, 24.3, 24.2 (C-16, C-17, C-18), 20.3 (C-20), 18.6 ($Si(CH_3)_2\mathit{C}(CH_3)_3$), 15.7 (C-19), -4.1, -5.3 ($Si(\mathit{C}H_3)_2C(CH_3)_3$) ppm;
HRMS-ESI ($C_{30}H_{52}NaNO_4SiCl$): calculated 576.3252 $[M+Na+MeCN]^+$, found 576.3262.

Aldol product **21**

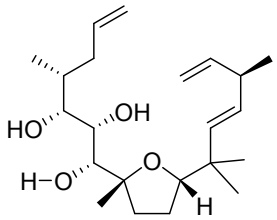


S6 **21**

Oxalyl chloride (0.2 mL, 0.3 g, 2.4 mmol, 2 eq) dissolved in CH_2Cl_2 (12 mL) and DMSO (0.35 ml, 0.39 g, 4.9 mmol, 4.1 eq)) was added at -78°C and the solution was stirred for 30 min. Then, alcohol **S6** (215.5 mg, 1.2 mmol) dissolved in dry CH_2Cl_2 (4 mL) was added dropwise and stirring was continued for 50 min. After addition of E_3N (1.25 ml, 0.91 g, 9.0 mmol, 7.5 eq) the temperature was slowly raised to -10°C within 2 h. Addition of water terminated the reaction. After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure (p > 550 mbar).
Ketone **10** (151.7 mg, 0.4 mmol) was dissolved in dry THF (8 mL) cooled to -78 °C and treated with KHMDS (0.67 ml, solution in toluene, 15 %, 0.66 mol/L, 0.44 mmol, 1.1 eq). After 35 min the freshly prepared aldehyde **17**, dissolved in dry THF (2 mL) was added dropwise and the reaction mixture was stirred for 70 min. Then, methanol and an aqueous solution of ammonium chloride were added. After warming up to rt, the mixture was extracted with MTB-ether and the combined organic phases were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica, petroleum ether / ethyl acetate 40:1) to yield the title compound **21** (150.5 mg, 0.27 mmol; 68 %) as a colorless oil.
$[\alpha]^D_{20}$ = + 44.4 ° (*c*= 0.95 in $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.79 (ddd, *J* = 17.1, 10.3, 6.5 Hz, 1 H, H-4), 5.61 (t, *J* = 1.4 Hz, 1 H, H-4'), 5.47 (t, *J* = 1.1 Hz, 1 H, H-4'), 5.46 (d, *J* = 16.1 Hz, 1 H, H-1), 5.38 (dd, *J* = 16.1, 6.6 Hz, 1 H, H-2), 5.13 (d, *J* = 0.9 Hz, 1 H, H-9), 4.98 (dt, *J* = 17.1, 1.6 Hz, 1 H, H-5), 4.96 (dt, *J* = 10.3, 1.6 Hz, 1 H, H-5), 3.93 (ddd, *J* = 11.8, 9.2, 0.9 Hz, 1 H, H-8), 3.82 (dd, *J* = 7.9, 6.8 Hz, 1 H, H-14), 3.10-3.07 (m, 1 H, H-6), 2.82 (sext. m, *J* = 6.7 Hz, 1 H, H-3), 2.23-2.11 (m, 2 H, H-6, H-7), 2.08 (d, *J* = 11.8 Hz, 1 H, 8-OH), 1.95-1.90 (m, 2 H, 2xH-12), 1.88-1.79 (m, 1 H, H-13), 1.59-1.49 (m, 1 H, H-13), 1.36 (s, 3 H, H-18), 1.09 (d, *J* = 6.9 Hz, 3 H, H-20), 1.06 (s, 3 H, H-16), 1.04 (s, 3 H, H-17), 0.99 (d, *J* = 6.4 Hz, 3 H, H-19), 0.97 (s, 9 H, $Si(CH_3)_2C(C\mathit{H}_3)_3$), 0.14 (s, 3 H, $Si(C\mathit{H}_3)_2C(CH_3)_3$), 0.02 (s, 3 H, $Si(C\mathit{H}_3)_2C(CH_3)_3$) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 212.6 (C-10), 143.2 (C-4), 134.9 (C-1), 134.4 (C-

5'), 132.4 (C-2), 118.0 (C-4'), 112.9 (C-5), 88.8 (C-11), 86.5 (C-14), 76.2 (C-9), 75.1 (C-8), 44.9 (C-6), 40.7 (C-3), 39.0 (C-15), 37.4 (C-12), 35.1 (C-7), 26.0 ($Si(CH_3)_2C(CH_3)_3$), 25.8 (C-13), 24.4, 24.3, 24.2 (C-16, C-17, C-18), 20.3 (C-20), 18.6 ($Si(CH_3)_2C(CH_3)_3$), 15.6 (C-19), -4.1, -5.3 ($Si(CH_3)_2C(CH_3)_3$) ppm;
HRMS-ESI ($C_{28}H_{49}NaO_4SiBr$): calculated 579.2481 [M+Na^+], found 579.2482.

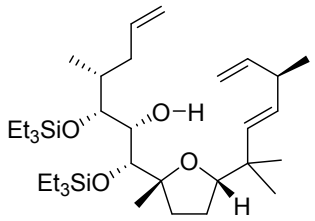
Triol **S18**



S18

Silylether **22** (1.37 g, 2.9 mmol) was dissolved in dry THF (50 mL) and TBAF·$3H_2O$ (2.2 g, 7.0 mmol, 2.4 eq) was added. The reaction mixture was stirred for 45 min at rt. The solution was filtered through a pad of silica which was washed with MTBE. After concentration under reduced pressure the title compound **S18** (1.05 g, 2.9 mmol; 100 %) was obtained as a colorless oil.
$[\alpha]^{D}_{20}$= - 17.3 ° (*c*= 1.0 in $CHCl_3$) (+ 14.4° for the enantiomer)[S3];
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.80 (dddd, *J* = 16.8, 10.1, 7.8, 6.6 Hz, 1 H, H-5'), 5.78 (ddd, J = 17.3, 10.5, 6.7 Hz, 1 H, H-4), 5.45 (d, *J* = 16.0 Hz, 1 H, H-1), 5.38 (dd, *J* = 16.0, 6.1 Hz, 1 H, H-2), 5.07-4.98 (m, 2 H, 2xH-4'), 4.97 (d ps t, *J* = 17.3, 1.5 Hz, 1 H, H-5), 4.94 (d ps t, *J* = 10.5, 1.5 Hz, 1 H, H-5), 3.99-3.97 (m, 1 H, H-9), 3.74 (dd, *J* = 8.7, 6.3 Hz, 1 H, H-14), 3.66 (d, *J* = 2.4 Hz, 1 H, OH), 3.47-3.40 (m, 2 H, H-8, H-10), 3.12 (d, *J* = 4.4 Hz, 1H, OH), 3.07 (d, *J* = 7.5 Hz, 1 H, OH), 2.83 (ps sext., *J* = 6.6 Hz, 1 H, H-3), 2.41-2.34 (m, 1 H, H-6), 2.18 (ddd, *J* = 12.1, 9.4, 4.8 Hz, 1 H, H-12), 2.02-1.94 (m, 1 H, H-6), 1.88-1.67 (m, 3 H, H-7, 2xH-13), 1.62-1.55 (m, 1 H, H-12), 1.23 (s, 3 H, H-18), 1.08 (d, *J* = 6.8 Hz, 3 H, H-20), 1.03, 0.96 (2s, 6 H, H-16, H-17), 0.95 (d, *J* = 6.9 Hz, 3 H, H-19) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 143.2 (C-4), 137.5 (C-5'), 134.5 (C-1), 133.0 (C-2), 116.2 (C-4'), 112.9 (C-5), 86.8 (C-14), 86.2 (C-11), 77.9 (C-8), 77.0 (C-10), 69.3 (C-9), 40.7 (C-3), 39.0 (C-15), 36.4 (C-6), 35.5 (C-7), 35.0 (C-12), 27.1 (C-13), 24.7, 24.5 (C-16, C-17), 23.7 (C-18), 20.2 (C-20), 16.2 (C-19) ppm.
HRMS-ESI ($C_{22}H_{38}NaO_4$): calculated 367.2848 [M+Na+], found 367.2853.

Bis-triethylsilyl ether **S19**

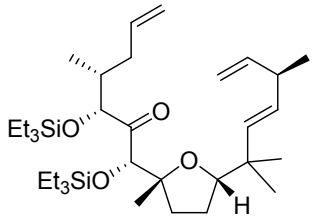


S19

Triol **S18** (132.1 mg, 0.36 mmol) was dissloved in dry DMF (20 ml) and treated with imidazole (160 mg, 2.4 mmol, 6.7 eq) and TESCl (300 µl, 1.8 mmol, 5 eq). The reaction

mixture was stirred at rt for 5 h after which time additional imidazole (40 mg, 0.6 mmol, 1.7 eq) und TESCl (60 µl, 0.35 mmol, 1 eq) were added. Additional amounts were added after another 21 h. After 24 h of stirring at 50°C the reaction was terminated by addition of an aqueous ammonium chloride solution and a mixture of petroleum ether /ethyl acetate= 10:1.
The aqueous phase was extracted with petroleum ether /ethyl acetate= 10:1 and the combined organic phases were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (silica; petroleum ether /ethyl acetate= 40:1) to furnish the title compound **S19** (189.9 mg, 0.32 mmol; 89 %) as a colorless oil.
[α]$^{D}_{20}$= - 8.7 ° (*c*= 0.95 in $CHCl_3$) (+ 9.3° for other enantiomer)[S3];
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.77 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H-4), 5.75 (dddd, J = 16.8, 10.3, 7.9, 6.5 Hz, 1 H, H-5'), 5.46 (dd, *J* = 15.9, 1.1 Hz, 1 H, H-1), 5.33 (dd, *J* = 15.9, 6.5 Hz, 1 H, H-2), 5.01-4.91 (m, 4 H, H-4', H-5), 3.74 (dd, *J* = 8.6, 5.7 Hz, 1 H, H-14), 3.65 (s, 1 H, H-10), 3.45 (dd, *J* = 8.9, 1.8 Hz, 1 H, H-8), 3.38 (ps t, *J* = 8.8 Hz, 1 H, H-9), 2.80 (ps sext q, *J* = 6.8, 1.3 Hz, 1 H, H-3), 2.64 (d, *J* = 8.7 Hz, 1 H, OH), 2.18-2.10 (m, 1 H, H-6), 1.96-1.81 (m, 2 H, H-6, H-13), 1.70-1.57 (m, 3 H, H-7, H-12, H-13), 1.35-1.26 (m, 1 H, H-12), 1.16 (s, 3 H, H-18), 1.07 (d, *J* = 6.7 Hz, 3 H, H-20), 1.00-0.94 (m, 27 H, H-16, H-17, H-19, $Si(CH_2C\mathit{H}_3)_3$), 0.80-0.60 (m, 12 H, $Si(C\mathit{H}_2CH_3)_3$) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$= 77.16 ppm): 143.5 (C-4), 138.2 (C-5'), 135.5 (C-1), 131.7 (C-2), 115.7 (C-4'), 112.7 (C-5), 86.2 (C-11), 84.7 (C-14), 79.1 (C-8), 77.3 (C-10), 72.9 (C-9), 40.5 (C-3), 39.4 (C-15), 35.0 (C-13), 34.9 (C-7), 34.4 (C-6), 26.1 (C-13), 24.4, 24.2 (C-16, C-17), 20.2 (C-20), 18.5 (C-18), 18.2 (C-19), 7.3, 7.2 ($Si(CH_2\mathit{C}H_3)_3$), 5.7, 5.3 ($Si(\mathit{C}H_2CH_3)_3$) ppm.
HRMS-ESI ($C_{34}H_{67}O_4Si_2$): calculated 595.4578 [M+H$^+$] found 595.4572.

Ketone **S20**

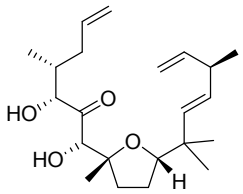


S20

Alcohol **S19** (169 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (22 ml) cooled to 0 °C and treated with Dess-Martin periodinane (500 mg, 1.18 mmol, 4.2 eq). The reaction mixture was warmed up to rt and stirred for 3 h. Then, an aqueous saturated solution of $NaHCO_3$/$Na_2S_2O_3$- was added and the mixture was stirred for 1 h. After phase separation, the aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (silica; petroleum ether /ethyl acetate= 40:1) to furnish the title compound **S20** (152.1 mg, 0.26 mmol; 93 %) as a colorless oil.
[α]$^{D}_{20}$= - 42.5 ° (*c*= 0.67 in $CHCl_3$) (+ 40.1° for other enantiomer)[S3];
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.76 (ddd, *J* = 17.2, 10.3, 6.6 Hz, 1 H, H-4), 5.70 (dddd, *J* = 16.8, 10.4, 7.8, 6.4 Hz, 1 H, H-5'), 5.44 (dd, *J* = 15.9, 1.1 Hz, 1 H, H-1), 5.32 (dd, *J* = 15.9, 6.6 Hz, 1 H, H-2), 4.99-4.90 (m, 4 H, H-4', H-5), 4.65 (d, *J* = 2.8 Hz, 1 H, H-8),

4.20 (s, 1 H, H-10), 3.68 (dd, *J* = 8.0, 6.2 Hz, 1 H, H-14), 2.80 (ps sext q, *J* = 6.7, 1.1 Hz, 1 H, H-3), 2.11-2.02 (m, 1 H, H-7), 2.02-1.94 (m, 1 H, H-6), 1.92-1.78 (m, 3 H, H-6, H-12, H-13), 1.62-1.54 (m, 1 H, H-13), 1.47-1.39 (m, 1 H, H-12), 1.08 (s, 3 H, H-18), 1.06 (d, *J* = 6.9 Hz, 3 H, H-20), 1.02-0.93 (m, 27 H, H-16, H-17, H-19, $Si(CH_2C\mathit{H}_3)_3$), 0.79-0.72 (m, 6 H, $Si(C\mathit{H}_2CH_3)_3$), 0.62-0.56 (m, 6 H, $Si(C\mathit{H}_2CH_3)_3$) ppm;
^{13}C-NMR (100 MHz, CDCl3 = 77.16 ppm): 209.5 (C-9), 143.5 (C-4), 137.5 (C-5'), 135.6 (C-1), 131.7 (C-2), 116.1 (C-4'), 112.7 (C-5), 84.9 (C-11), 84.2 (C-14), 81.7 (C-10), 79.5 (C-8), 40.6 (C-3), 39.3 (C-15), 36.4 (C-7), 34.7 (C-6), 34.7 (C-12), 26.3 (C-13), 24.5, 24.2 (C-16, C-17), 20.2 (C-20), 18.2 (C-18), 17.1 (C-19), 7.1, 7.0 ($Si(CH_2\mathit{C}H_3)_3$), 5.1, 5.0 ($Si(\mathit{C}H_2CH_3)_3$) ppm.
HRMS-ESI ($C_{34}H_{64}NaO_4Si_2$): calculated 615.4241 [M+Na^+] found 615.4248.

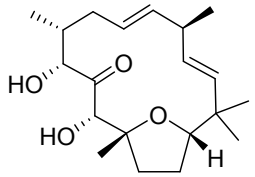
Dihydroxyketone **S21**



S21

Ketone **S20** (15 mg, 25 μmol) was dissolved in dry THF (1 mL), cooled to 0°C and treated with TBAF·$3H_2O$ (22 mg, 70 μmol, 2.8 eq) dissolved in dry THF (1 mL). After 20 min stirring at rt the solution was passed through a pad of silica which was washed with petroleum ether/ethyl acetate= 10:1. After concentration under reduced pressure the title compound **S21** (8.4 mg, 23 μmol; 92 %) was obtained as a colorless oil.
$[\alpha]^D_{20}$= + 70.3 ° (*c*= 1.02 in $CHCl_3$) (- 64.1° for other enantiomer)[S3];
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): 5.75 (ddd, *J* = 17.0, 10.3, 6.6 Hz, 1 H, H-4), 5.68 (dddd, J = 17.3, 10.0, 7.4, 7.3 Hz, 1 H, H-5'), 5.36 (dd, *J* = 16.0, 5.6 Hz, 1 H, H-2), 5.30 (d, *J* = 16.0 Hz, 1 H, H-1), 5.03-4.91 (m, 4 H, H-4', H-5), 4.47 (d, *J* = 6.8 Hz, 1 H, H-10), 4.29 (d, *J*= 3.4 Hz, 1 H, 8-OH), 4.14 (ps t, *J* = 3.4 Hz, 1 H, H-8), 3.82-3.78 (m, 1 H, H-14), 3.20 (d, *J* =6.8 Hz, 1 H, 10-OH), 2.80 (ps sext m, *J* = 6.6 Hz, 1 H, H-3), 2.20-2.11 (m, 1 H, H-7), 2.10-2.02 (m, 1 H, H-6), 2.00-1.92 (m, 1 H, H-6), 1.86-1.77 (m, 2 H, H-12, H-13), 1.67-1.51 (m, 2 H, H-12, H-13), 1.29 (s, 3 H, H-18), 1.06 (d, *J* = 6.8 Hz, 3 H, H-20), 1.01 (d, *J* = 7.2 Hz, 3 H, H-19), 0.97, 0.91 (2s, 6 H, H-16, H-17) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 216.2 (C-9), 143.0 (C-4), 137.0 (C-5'), 134.3 (C-1), 133.0 (C-2), 116.6 (C-4'), 113.0 (C-5), 86.5 (C-14), 85.7 (C-11), 79.9 (C-8), 78.5 (C-10), 40.5 (C-3), 38.9 (C-15), 37.3 (C-7), 35.4 (C-6), 32.1 (C-12), 25.4 (C-13), 24.9, 23.7 (C-16, C-17), 23.4 (C-18), 20.0 (C-20), 16.6 (C-19) ppm;
HRMS-ESI ($C_{22}H_{36}NaO_4$): calculated 387.2511 [M+Na^+], found 387.2506.

Olefin **24**



24

Ketone **S21** (310 mg, 0.85 mmol) was dissolved in dry CH_2Cl_2 (500 mL) and the Grubbs II catalyst (75 mg, 88.2 µmol, 0.1 eq) was added. The reaction mixture was heated for 1.5 h under refluxing conditions. The solution was cooled to rt, saturated with air and concentrated under reduced pressure. The crude material was purified by column chromatography (silica; petroleum ether / ethyl acetate= 10:1) to yield the title compound **24** as two fractions (70.7 mg, 0.21 mmol; 25%, only *E*-isomer as acolorless solid and 194 mg, 0.58 mmol; 68 % as mixture of *E/Z*-isomers). The *E/Z*-ratio was determined to be 4:1 as judged from analysis of the ^{1}H-NMR spectrum

Mp: 95-96 °C (*E*-isomer)

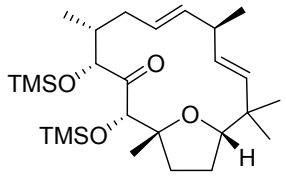
$[\alpha]^{D}_{20}$= - 54.0 ° (*c*= 0.70 in $CHCl_3$) (+ 48.2° for other enantiomer)[S3];

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 5.40 (dd, *J* = 15.5, 8.7 Hz, 1 H, H-4), 5.33 (d, J = 15.4 Hz, 1 H, H-1), 5.27 (dd, *J* = 15.4, 7.7 Hz, 1 H, H-2), 5.25-5.16 (m, 1 H, H-5), 4.56 (s, 1 H, H-10), 4.35 (br s, 1 H, H-8), 3.80 (dd, *J* = 8.2, 3.1 Hz, 1 H, H-14), 3.55 (d, *J* = 4.4 Hz, 1 H, 10-OH), 2.8 (br s, 1 H, 8-OH), 2.80 (ps sext m, *J* = 7.4 Hz, 1 H, H-3), 2.57-2.48 (m, 1 H, H-7), 2.08-1.96 (m, 2 H, H-6, H-13), 1.95-1.77 (m, 4 H, H-6, H-12, H-13), 1.16 (d, *J* = 7.2 Hz, 3 H, H-19), 1.09 (s, 3 H, H-18), 1.03 (d, *J* = 6.8 Hz, 3 H, H-20), 1.05, 0.88 (2s, 6 H, H-16, H-17) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 212.6 (C-9), 137.4 (C-4), 134.0 (C-1), 132.9 (C-5), 128.0 (C-2), 88.3 (C-14), 85.6 (C-11), 82.0 (C-10), 78.0 (C-8), 42.2 (C-3), 40.4 (C-7), 39.8 (C-15), 34.8 (C-6), 32.5 (C-12), 26.9 (C-13), 25.8, 24.4 (C-16, C-17), 21.5 (C-20), 21.2 (C-18), 20.5 (C-19) ppm;

HRMS-ESI ($C_{20}H_{32}NaO_4$): calculated 359.2198 [M+Na^+], found 359.2204.

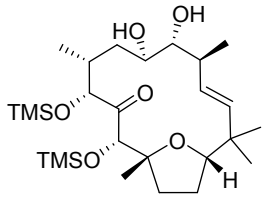
Bis-trimethylsilyl ether **S22**



S22

Ketone **24** (187 mg, 0.56 mmol) was dissolved in dry DMF (70 mL), cooled to 0°C and treated with Et_3N (530 µl, 3.8 mmol, 6.8 eq) and TMSCl (340 µl, 2.7 mmol, 4.8 eq). The reaction mixture was stirred for 2 h. The reaction mixture was terminated by addition of an aqueous ammonium chloride solution and petroleum ether / ethyl acetate= 10:1. After phase separation, the aqueous layer was extracted with petroleum ether / ethyl acetate= 10:1 and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash filtration (petroleum ether / ethyl acetate= 10:1) through a pad of silica provided the title compound **S22** (250 mg, 0.52 mmol; 93 %) as a colorless oil which was directly subjected for the next step.

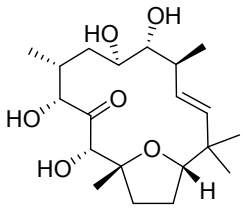
Diol **S23**



S23

Alkene **S22** (140 mg, 0.29 mmol) was dissolved in *tert*-butanol/water (18 mL, 1:1) and treated with DHQD-CLB (50 mg, 0.11 mmol, 0.38 eq), $K_3Fe(CN)_6$ (290 mg, 0.88 mmol, 3.0 eq), K_2CO_3 (125 mg, 0.90 mmol, 3.1 eq) and methylsulfonamide (85 mg, 0.89 mmol, 3.1 eq). The solution was cooled to 0°C and while rigorously stirring osmium tetroxide (2.5% in *tert*-butanol, 0.36 ml, 29 µmol, 10 mol%) was added. After 3 h the reaction was terminated by addition of a saturated aqueous $Na_2S_2O_3$-solution which followed by extraction with CH_2Cl_2. The organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Due to chemical lability further purification of the crude product **S23** (155 mg) was conducted after the next step.

Tetraol **25**



25

The crude product **S23** (155 mg) collected after the dihydroxylation was dissolved in dry THF (9 ml) and cooled to 0°C. TBAF·$3H_2O$ (120 mg, 0.38 mmol, 1.3 eq) dissolved in dry THF (5 m) was added and after 15 min stirring the solution was filtered through a pad of silica using MTBE→MTBE/methanol as eluents. After concentration under reduced pressure the title compound **25** (103 mg, 0.28 mmol; 97 % for two steps) as an inseparable mixture (~4:1) of two diastereomers was obtained

Analytical data of main diastereoisomer:

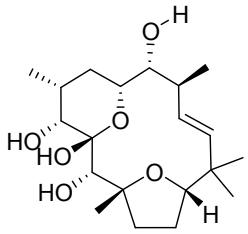
R_f = 0.18 (petroleum ether / ethyl acetate = 2:1); $[\alpha]^D_{20}$ = - 2.7° (*c* = 0.66 in CH_2Cl_2);

^{1}H-NMR ($CDCl_3$, 400 MHz, $CDCl_3$ = 7.26 ppm): δ_H = 5.55 (d, *J* = 15.4 Hz, 1 H, 1-H), 5.28 (dd, *J* = 15.4, 9.3 Hz, 1 H, 2-H), 4.19 (dd, *J* = 2.4, 1.0 Hz, 1 H, 8-H), 4.12 (d, *J* = 2.4 Hz, 1 H, 10-H), 3.88 (pdt, *J* = 11.5, 1.9 Hz, 1 H, 5-H), 3.70 (dd, *J* = 8.2, 7.1 Hz, 1 H, 14-H), 3.39 (dd, *J* = 6.1, 1.9 Hz, 1 H, 4-H), 2.62-2.52 (m, 1 H, 7-H), 2.38-2.27 (m, 2 H, 3-H, OH), 2.23-2.11 (m, 2 H, 6-H, 12-H), 2.06 (ddd, *J* = 13.4, 7.0, 2.3 Hz, 1 H, 6-H), 1.95-1.77 (m, 2 H, 13-H), 1.56 (pdt, *J* = 11.9, 7.7 Hz, 1 H, 12-H), 1.78 (d, *J* = 6.7 Hz, 3 H, 19-H), 1.14 (d, *J* = 6.8 Hz, 3 H, 20-H), 1.10 (s, 3 H, 18-H), 1.15 u. 0.92 (2 x s, 6 H, 16-H, 17-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 208.9 (q, 9-C), 135.8 (t, 1-C), 129.7 (t, 2-C), 86.6 (t, 14-C), 84.2 (q, 11-C), 81.0 (t, 8-C), 78.6, 77.4 (2 x t, 4-C, 5-C), 72.5 (t, 10-C), 44.9 (t, 3-C), 43.0 (t, 7-C), 38.7 (q, 15-C), 37.6 (s, 6-C), 34.1 (s, 12-C), 27.1 (s, 13-C), 26.2, 25.9, 25.5 (3 x p, 16-C, 17-C, 18-C), 20.0 (p, 19-C), 15.1 (p, 20-C) ppm;

HRMS-ESI ($C_{20}H_{34}NaO_6$): calculated 393.2253 $[M+Na]^+$, found 393.2259.

Semiacetal **26**



26

Tetraol **25** (17.6 mg, 47.5 µmol) was dissolved in CH_2Cl_2 (10 mL), treated with PPTS (35 mg, 139 µmol, 2.9 eq) and the reaction mixture was stirred for 20 min at rt. The reaction was terminated by the addition of solid $NaHCO_3$ and the mixture was purified by chromatography (silica, ethyl acetate → ethyl acetate/methanol 5:1) to yield the title compound **26** (8.9 mg, 24.0 µmol; 51 %) and a diastereomeric mixture of starting tetraols **25** (6.3 mg, 17.0 µmol; 36 %).

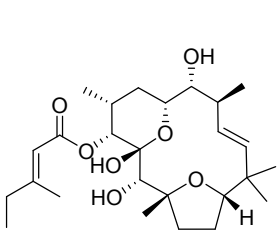
$[\alpha]^D_{20}$ = - 34.7 ° (c = 0.89 in $CHCl_3$) + 30.6° for other enantiomer)[S3];

^{1}H-NMR (400 MHz, CD_3OD, CD_2HOD= 3.31 ppm): 5.50 (d, *J* = 15.4 Hz, 1 H, H-1), 5.36 (dd, *J* = 15.4, 9.2 Hz, 1 H, H-2), 4.15-4.09 (m, 1 H, H-5), 3.86 (dd, *J* = 7.9, 6.1 Hz, 1 H, H-14), 3.72 (s, 1 H, H-10), 3.34 (d, *J* = 2.4 Hz, 1 H, H-8), 3.28 (dd, *J* = 6.3, 2.2 Hz, 1 H, H-4), 2.38-2.17 (m, 3 H, H-3, H-7, H-13), 2.08-1.90 (m, 2 H, H-12, H-13), 1.74 (q, *J* = 12.7 Hz, 1 H, H-6), 1.61 (ddd, *J*= 12.3, 7.2, 5.1 Hz, 1 H, H-12), 1.31 (s, 3 H, H-18), 1.09 (d, *J* = 6.8 Hz, 3 H, H-20), 1.12-1.03 (m, 1 H, H-6), 0.94 (d, *J* = 6.8 Hz, 3 H, H-19), 1.08, 0.92 (2s, 6 H, H-16, H-17) ppm;

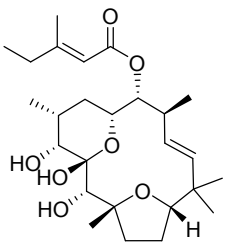
^{13}C-NMR (100 MHz, CD_3OD = 49.0 ppm): 136.0 (C-1), 131.6 (C-2), 98.5 (C-9), 89.5, 89.4 C-14, C-11), 81.4 (C-10), 79.5 (C-4), 76.1 (C-8), 70.5 (C-5), 46.7 (C-3), 39.8 (C-15), 35.6 (C-7), 30.9 (C-12), 30.2 (C-6), 27.9 (C-18), 26.8 (C-13), 26.6, 24.7 (C-16, C-17), 21.5 (C-20), 17.8 (C-19) ppm.

HRMS-ESI ($C_{20}H_{35}O_6$): calculated 371.2434 $[M+H]^+$, found 371.2440.

Ester **27** and **28**



27



28

Semiacetal **26** (7.5 mg, 20 µmol) and (*E*)-Et(Me)C=$CHCO_2H$ (34 mg, 298 µmol, 14.9 eq) were dissolved in dry CH_2Cl_2 (1.6 mL) and treated with DIC (45 µl, 289 µmol, 14.5 eq). The reaction mixture was stirred at rt for 1 h and then DMAP (2.9 mg, 24 µmol, 1.2 eq) was added. Stirring was continued for 18 h and then passed through a pad of silica with petroleum

ether / ethyl acetate= 1:1. After concentration under reduced pressure the crude product was purified by column chromatography (silica; petroleum ether / ethyl acetate= 10:1 ⪡5:1 ⪡3:1 ⪡1:1) to yield a mixture of esters **27**/**28** (ester at C4 and C8) and **27** (4.2 mg, 9.0 μmol; 45 %) which was directly used in the next step.

Tonantzitlolone (**1**)

The mixture of esters **27** and **28** (4.2 mg, 9.0 μmol) was dissolved in dry CH_2Cl_2 (1 mL) and treated with molecular sieves 4Å (13 mg), NMO (2.5 mg, 21 μmol, 2.3 eq) and TPAP (1 mg, 2.8 μmol, 0.3 eq). The reaction mixture was stirred for 40 min. The solvent was removed by passing a stream of nitrogen gas through the flask. The crude material obtained was purified by column chromatography (silica; petroleum ether / ethyl acetate= 10:1) to yield tonantzitlolone **1** (0.9 mg, 1.9 μmol, 21 %) and the regioisomer **29** (0.9 mg, 1.9 μmol, 21 %). Alternatively, purification was also achieved by HPLC (reversed phase C18, 250 x 8 mm, methanol/water= 9:1).

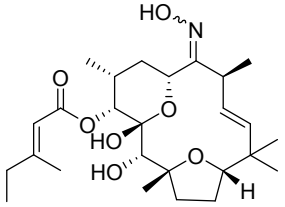
$[\alpha]^{D}_{20}$ = +116° (*c* 0.5 in $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): 5.86 (d, *J* = 15.3 Hz, 1 H, H-1), 5.70 (sext., *J* = 1.3 Hz, 1 H, H-2'), 5.66 (s, 1 H, 9-OH), 5.24 (dd, J = 15.3, 9.7 Hz, 1 H, H-2), 4.90 (d, *J* = 2.7 Hz, 1 H, H-8), 4.62 (dd, *J* = 11.9, 2.9 Hz, 1 H, H-5), 3.77 (dd, *J* = 11.3, 5.2 Hz, 1 H, H-14), 3.43 (d, *J* = 6.3 Hz, 1 H, H-10), 3.33 (dq, *J* = 9.7, 6.8 Hz, 1 H, H-3), 3.10 (d, *J* = 6.3 Hz, 1 H, 10-OH), 2.44 (dd, *J* = 12.5, 7.3 Hz, 1 H, H-12), 2.38-2.28 (m, 1 H, H-7), 2.17 (q, *J* = 7.5 Hz, 2 H, 2xH-4'), 2.16 (d, *J* = 1.3 Hz, 3 H, H-6'), 2.08-1.98 (m, 1 H, H-13), 1.85 (ddd, *J* = 13.3, 3.8, 2.9 Hz, 1 H, H-6), 1.80-1.73 (m, 1 H, H-13), 1.43-1.35 (m, 1 H, H-6), 1.38 (s, 3 H, H-18), 1.12 (d, *J* = 6.8 Hz, 3 H, H-20), 1.07 (t, *J* = 7.3 Hz, 3 H, H-5'), 1.14, 0.91 (2s, 6 H, H-16, H-17), 0.84 (d, *J* = 6.8 Hz, 3 H, H-19) ppm;

HRMS-ESI ($C_{26}H_{40}NaO_7$): calculated 487.2672 [M+Na^+], found 487.2671.

4. Synthesis of new Tonantzitlolone derivatives

Oximes **30a,b**



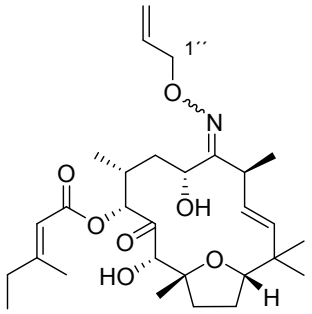
30a,**b**

Tonantzitlolone (**1**) (21.9 mg, 0.05 mmol) was dissolved in dry pyridine (9 mL, 0.129 mmol, 2.6 eq) under nitrogen and was treated with hydroxylamine hydrochloride (9 mg, 0.129 mmol, 2.6 eq). The reaction mixture was stirred overnight at rt. After removal of the solvent under reduced pressure the crude material was taken up with toluene (3x) and concentrated under reduced pressure in order to remove traces of pyridine. The crude material was purified by column chromatography (silica; petroleum ether/ ethyl acetate= 10:1) to provide the two oximes **30a** (2.9 mg, 0.027 mmol; 54%) and **30b** (6.3 mg, 0.013 mmol; 26%).

Analytic data of *E*-isomer **30a**:

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 6.22 (s, 1 H, 9-OH), 5.72 (q, *J* = 1.5 Hz, 1 H, 2′-H), 5.45 (d, *J* = 15.7 Hz, 1 H, 1-H), 5.35 (dd, *J* = 15.7, 8.5 Hz, 1 H, 2-H), 4.98 (d, *J* = 2.4 Hz, 1 H, 8-H), 4.73 (dd, *J* = 12.1, 2.2 Hz, 1 H, 5-H), 3.88-3.78 (dq, *J* = 8.8, 7.0 Hz, 1 H, 3-H), 3.70 (dd, *J* = 7.7, 6.7 Hz, 1 H, 14-H), 3.52 (d, *J* = 6.5 Hz, 1 H, 10-H), 2.78 (d, *J* = 7.9 Hz, 1 H, 10-OH), 2.44-2.34 (m, 1 H, 7-H), 2.32 (ddd, *J* = 11.9, 7.9, 6.1 Hz, 1 H, 12-H), 2.16 (d, *J* = 1.4 Hz, 3 H, 6′-H), 2.16 (q, *J* = 8.0 Hz, 2 H, 4′-H), 1.96-1.85 (m, 1 H, 6-H), 1.85-1.76 (m, 1 H, 13-H), 1.73-1.60 (m, 1 H, 13-H), 1.52-1.42 (m, 1 H, 12-H), 1.32-1.26 (m, 1 H, 6-H), 1.29 (s, 3 H, 18-H), 1.18 (d, *J* = 7.2 Hz, 3 H, 20-H), 1.06 (t, *J* = 7.5 Hz, 3 H, 5′-H), 1.13, 0.92 (2s, 6 H, 16-H, 17-H), 0.86 (d, *J* = 6.8 Hz, 3 H, 19-H) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.8 (q, 4-C), 162.5, 162.2 (2 x q, 1′-C, 3′-C), 135.8, 130.5 (2 x t, 1-C, 2-C), 114.4, 97.8, 88.2, 87.9, 78.4, 72.8, 66.8 (5-C, 8 -C, 9-C, 10-C, 11-C, 14-C, 2′-C), 38.7, 35.4, 35.0, 34.0, 29.7, 29.4, 27.8, 27.1, 26.7, 25.3 (3-C, 6-C, 7-C, 12-C, 13-C, 15-C, 16-C, 17-C, 18-C, 4′-C), 19.2, 18.2, 17.2, 12.0 (19-C, 20-C, 5′-C, 6′-C) ppm.
Analytic data of *Z*-isomer **30b**:
^{1}H-NMR (400 MHz, , $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 5.72 (q, *J* = 1.5 Hz, 1 H, 2′-H), 5.58 (d, *J* = 15.7 Hz, 1 H, 1-H), 5.14 (dd, *J* = 15.9, 6.7 Hz, 1 H, 2-H), 5.11 (dd, *J* = 11.6, 2.0 Hz, 1 H, 5-H), 4.95 (d, *J* = 2.7 Hz, 1 H, 8-H), 4.84 (s, 1 H, 9-OH), 3.75 (dd, *J* = 10.4, 5.6 H, 1 H, 14-H), 3.43 (d, *J* = 5.1 Hz, 1 H, 10-H), 3.37-3.29 (m, 1 H, 3-H), 2.91 (bd, *J* = 6.8 Hz, 1 H, 10-OH), 2.44-2.34 (m, 2 H, 7-H, 12-H), 2.15 (q, *J* = 6.8 Hz, 2 H, 4′-H), 2.17 (d, *J* = 1.0 Hz, 3 H, 6′-H), 2.09 (ddd, *J* = 13.1, 3.7, 2.3 Hz, 1 H, 6-H), 1.96-1.85 (m, 1 H, 13-H), 1.73-1.64 (m, 1 H, 13-H), 1.64-1.41 (m, 2 H, 6-H, 12-H), 1.35 (s, 3 H, 18-H), 1.18 (d, *J* = 7.2 Hz, 3 H, 20-H), 1.06 (t, *J* = 7.5 Hz, 3 H, 5′-H), 1.12 u. 0.86 (2 x s, 6 H, 16-H, 17-H), 0.83 (d, *J* = 6.8 Hz, 3 H, 19-H) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.8 (t, 4-C), 162.8, 162.7 (2 x q, 1′-C, 3′-C), 137.7, 130.1 (2 x t, 1-C, 2-C), 114.3, 97.1, 89.6, 87.7, 78.9, 72.8, 68.0 (5-C, 8 -C, 9-C, 10-C, 11-C, 14-C, 2′-C), 40.0, 38.6, 37.1, 34.1, 30.3, 29.4, 28.4, 28.2, 27.0, 25.0 (3-C, 6-C, 7-C, 12-C, 13-C, 15-C, 16-C, 17-C, 18-C, 4′-C), 19.1, 17.9, 17.1, 12.0 (19-C, 20-C, 5′-C, 6′-C) ppm;
HRMS-ESI ($C_{26}H_{41}NaNO_7$): calculated 502.2781 $[M+Na]^+$, found 502.2786.

Allyl-oxime **37**



37

Tonantzitlolone (**1**) (15 mg, 32.3 µmol) was dissolved in pyridine (2.5 mL), treated with *O*-allylhydroxylamine hydrochloride (35.4 mg, 322.8 µmol, 10 eq.) and stirred for 12 h at rt. After removal of the solvent under reduced pressure and removal of water by azeotropic distillation with toluene under reduced pressure the crude material was purified by HPLC

(reversed phase; H_2O : MeOH = 20 : 80 (5 min), 20 : 80 → 0 : 100 (in 30 min), 0 : 100 (10 min), **31a**,**b** after 21 min) to afford the title compound **37** (6.4 mg, 12.3 µmol; 38 %) as a mixture of *E/Z*-diastereoisomers (6:1 judged by ^{1}H NMR spectroscopy).

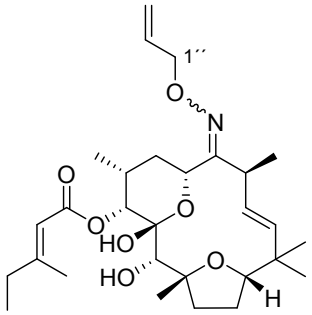
Analytical data:

R_f = 0.24 (petroleum ether / ethyl acetate = 5:1); $[\alpha]^{20}_D$= + 11.9 (*c* = 0.16 in CH_2Cl_2); ^{1}H-NMR (400 MHz, , $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 5.96 (ddt, *J* = 16.9, 10.8, 5.4 Hz, 1 H, 2´´-H), 5.78 (q, *J* = 1.3 Hz, 1 H, 2´-H), 5.55-5.52 (m, 2 H, 1-H, 2-H), 5.34 (d, *J* = 2.7 Hz, 1 H, 8-H), 5.28 (ddt, *J* = 16.9, 1.5, 1.5 Hz, 1 H, 3´´-H), 5.19 (ddt, 10.8, 1.5, 1.5 Hz, 1 H, 3´´-H), 4.82 (pdt, 2.5, 12.0 Hz, 1 H, 5-H), 4.52 (pddd, *J* = 5.4, 3.3, 1.5 Hz, 2 H, 1´´-H), 4.32 (d, *J* = 6.8 Hz, 1 H, 10-H), 3.78 (dd, *J* = 9.2, 6.5 Hz, 1 H, 14-H), 3.26 (br d, *J* = 6.8 Hz, 1 H, 10-OH), 3.17 (dq, *J* = 7.2, 3.0 Hz, 1 H, 3-H), 2.83-2.72 (m, 1 H, 7-H), 2.65-2.52 (m, 1 H, 12-H), 2.55 (d, *J* = 12.0 Hz, 5-OH), 2.19 (dq, *J* = 1.4, 7.4 Hz, 2 H, 4´-H), 2.13 (d, *J* = 1.0 Hz, 3 H, 6´-H), 1.92-1-72 (m, 3 H, 6-H, 13-H), 1.83-1.72 (m, 1 H, 6-H), 1.67-1.60 (m, 1 H, 12-H), 1.53-1.47 (m, 1 H, 6-H), 1.44 (d, *J* = 7.2 Hz, 3 H, 20-H), 1.44 (s, 3 H, 18-H), 1.13 (d, *J* = 6.8 Hz, 3 H, 19-H), 1.08 (t, *J* = 7.4 Hz, 3 H, 5´-H), 0.95 u. 0.89 (2 x s, 6 H, 16-H, 17-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 205.8 (q, 9-C), 166.6 (q, 1´-C), 165.6 (q, 4-C), 164.0 (q, 3´-C), 139.9 (t, 1-C), 134.4 (t, 2-C), 127.4 (t, 2´´-C), 116.9 (s, 3´´-C), 113.5 (t, 2´-C), 87.0 (t, 14-C), 85.5 (q, 11-C), 80.6 (t, 8-C), 79.1 (t, 10-C), 74.6 (s, 1´´-C), 68.9 (t, 5-C), 40.6 (t, 3-C), 39.7 (q, 15-C), 36.0 (s, 12-C), 35.9 (s, 6-C), 34.1 (s, 4´-C), 28.9 (t, 7-C), 29.8, 26.5, 26.3, 26.3, 19.2, 17.2, 16.1, 12.0 (13-C, 16-C, 17-C, 18-C, 19-C, 20-C, 5´-C, 6´-C) ppm;

HRMS-ESI ($C_{29}H_{45}NaNO_7$)**:** calculated 542.3094 $[M+Na]^+$, found 542.3084.

Allyl-oxime **31a,b**



31a,b

Allyloxime **37** (6.4 mg, 12.3 µmol) was dissolved in CH_2Cl_2 (1 mL) and PPTS (3 mg, 12.3 µmol, 1 eq.) was added and the reaction mixture was stirred for 6 h at rt. Addition of solid $NaHCO_3$ terminates the reacton. Addition of ethyl acetate was followed by filtration over a pad of silica and concentration under reduced pressure. Column chromatography (petroleum ether / ethyl acetate = 10:1 → petroleum ether / ethyl acetate = 2:1) yielded the title compound **31a**,**b** (2.2 mg, 4.2 µmol; 34 %) as a mixture of *E/Z*- diastereoisomers (6:1, judged by ^{1}H NMR spectroscopy) along with the starting material **37** (3.5 mg, 6.7 µmol; 55 %).

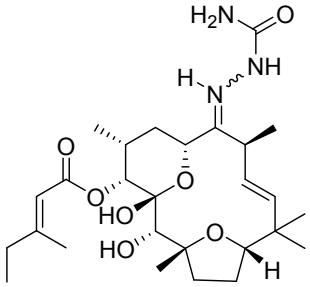
Analytic data of major isomer **31a**:

R_f = 0.70 (petroleum ether / ethyl acetate = 5:1); $[\alpha]^{20}_D$= + 100.9 (*c* = 0.12 in CH_2Cl_2);

^{1}H-NMR (400 MHz, , $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 5.99 (ddt, *J* = 10.6, 17.3, 5.4 Hz, 1 H, 2´´-H), 5.70 (q, *J* = 1.3 Hz, 1 H, 2´-H), 5.56 (dd, *J* = 15.8, 1.1 Hz, 1 H, 1-H), 5.30 (ddt, *J* = 17.3, 1.7, 1.7 Hz, 1 H, 3´´-H), 5.19 (ddt, *J* = 10.6, 1.7, 1.7 Hz, 1 H, 3´´-H), 5.14 (dd, *J* = 15.8, 6.2 Hz, 1 H, 2-H), 5.00 (s, 1 H, 9-OH), 4.98 (dd, *J* = 11.5, 2.1 Hz, 1 H, 5-H), 4.97 (d, *J* = 2.7

Hz, 1 H, 8-H), 4.56 (dddd, *J* = 5.4, 1.7, 1.7, 0.5 Hz, 2 H, 1´´-H), 3.75 (dd, *J* = 9.8, 5.8 Hz, 1 H, 14-H), 3.43 (d, *J* = 7.5 Hz, 1 H, 10-H), 3.31-3.24 (m, 1 H, 3-H), 2.87 (d, *J* = 7.5 Hz, 1 H, 10-OH), 2.41-2.30 (m, 2 H, 7-H, 12-H), 2.17 (q, *J* = 7.6 Hz, 2 H, 4´-H), 2.17 (d, *J* = 1.1 Hz, 3 H, 6´-H), 1.95-1.84 (m, 2 H, 6-H, 13-H), 1.77-1.65 (m, 2 H, 6-H, 13-H), 1.51-1.42 (m, 1 H, 12-H), 1.33 (s, 3 H, 18-H), 1.17 (d, *J* = 7.1 Hz, 3 H, 20-H), 1.08 (t, *J* = 7.6 Hz, 3 H, 5´-H), 1.11 u. 0.86 (2 x s, 6 H, 16-H, 17-H), 0.82 (d, *J* = 6.7 Hz, 3 H, 19-H) ppm;
^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.8 (q, 1´-C), 162.6 (q, 3´-C), 161.6 (q, 4-C), 137.6 (t, 1-C), 134.6 (t, 2´´-C), 130.2 (t, 2-C), 116.9 (s, 3´´-C), 114.3 (t, 2´-C), 97.1 (q, 9-C), 89.5 (t, 14-C), 87.9 (q, 11-C), 78.8 (t, 10-C), 74.9 (s, 1´´-C), 72.7 (t, 8-C), 67.9 (t, 5-C), 40.0 (t, 3-C), 38.7 (q, 15-C), 36.7 (s, 12-C), 34.1 (s, 4´-C), 30.2 (t, 7-C), 29.6 (s, 6-C), 28.3 (p, 18-C), 27.9 (s, 13-C), 26.8, 25.2 (2 x p, 16-C, 17-C), 19.2 (p, 6´-C), 18.0 (p, 20-C), 17.2 (p, 19-C), 12.0 (p, 5´-C) ppm.
HRMS-ESI ($C_{29}H_{45}NaNO_7$): calculated 519.3196 [M+Na$^+$], found 519.3203.

Semicarbazones **32a,b**

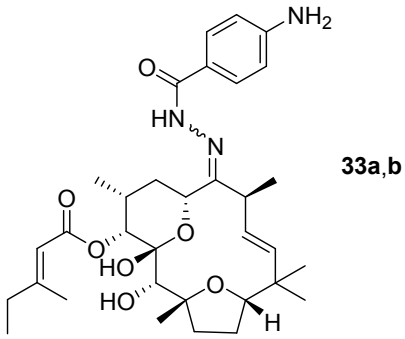


32a,b

Tonantzitlolone (**1**) (5 mg, 10.8 µmol) was dissolved in pyridine (1 mL), treated with semicarbazide hydrochloride (12 mg, 107.7 µmol, 10 eq.) and was stirred for 12 h at rt. After removal of the solvent under reduced pressure and removal of water by azeotropic distillation with toluene under reduced pressure the crude material was purified by column chromatography (petroleum ether / ethyl acetate= 1:1 → ethyl acetate) to yield the title compound **32a**,**b** (5.1 mg, 9.8 µmol; 91 %) as a mixture of *E/Z*-diastereoisomers (10:1). A second chromatographic separation (petroleum ether / ethyl acetate = 1:1) provided the *E*-isomer (3.2 mg, 6.1 µmol; 56 %) and a mixture of *E/Z*- isomers (1.4 mg, 2.7 µmol; 25 %). The *E/Z*-ratio was determined by HPLC.
Analytical data of *E*-isomer **32a**:
R_f = 0.60 (petroleum ether / ethyl acetate = 5:1); $[\alpha]^{20}_D$= - 4.1 (*c* = 0.22 in CH_2Cl_2);
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 7.76 (br s, 1H, N*H*), 6.22 (s, 1 H, 9-OH), 5.69 (q, *J* = 1.3 Hz, 1 H, 2´-H), 5.44 (d, *J* = 15.5 Hz, 1 H, 1-H), 5.37 (dd, *J* = 15.5, 7.3 Hz, 1 H, 2-H), 4.99 (d, *J* = 2.6 Hz, 1 H, 8-H), 4.74 (dd, *J* = 11.9, 2.3 Hz, 1 H, 5-H), 3.70 (dd, *J* = 8.0, 6.4 Hz, 1 H, 14-H), 3.52 (d, *J* = 8.0 Hz, 1 H, 10-H), 3.22 (dq, *J* = 7.0, 7.3 Hz, 1 H, 3-H), 2.76 (d, *J* = 8.0 Hz, 1 H, 10-OH), 2.45-2.36 (m, 1 H, 7–H), 2.30 (ddd, *J* = 11.9, 7.8, 5.8 Hz, 1 H, 12-H), 2.17 (dq, *J* = 1.4, 7.5 Hz, 1 H, 4´-H), 2.16 (d, *J* = 1.3 Hz, 3 H, 6´-H), 1.98-1.87 (m, 1 H, 6-H), 1.86-1.77 (m, 1 H, 13-H), 1.68-1.60 (m, 1 H, 13-H), 1.51-1.42 (m, 12-H), 1.29 (s, 1 H, 18-H), 1.29-1.22 (m, 1 H, 6-H), 1.15 (d, *J* = 7.0 Hz, 3 H, 20-H), 1.07 (t, *J* = 7.5 Hz, 3 H, 5´-H), 1.14, 0.94 (2 x s, 6 H, 16-H, 17-H), 0.87 (d, *J* = 6.9 Hz, 3 H, 19-H) ppm;
^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.7 (q, 1´-C), 162.6 (q, 3´-C), 157.0 (q, -NH-*C*O-NH_2), 152.4 (q, 4-C), 136.2 (t, C-1), 129.9 (t, C-2), 114.4 (t, 2´-C), 97.9 (q,

9-C), 88.1 (q, 11-C), 87.7 (t, 14-C), 78.3 (t, 10-C), 72.9 (t, 8-C), 67.7 (t, 5-C), 38.7 (q, 15-C), 36.7 (t, 3-C), 35.1 (s, 12-C), 34.1 (s, 4′-C), 29.5, 29.4, 27.8, 27.0, 26.8, 25.3 (6-C, 7-C, 13-C, 16-C, 17-C, 18-C), 19.2 (p, 6′-C), 17.4, 17.3 (p, 19-C, 20-C), 12.0 (p, 5′-C) ppm;
HRMS-ESI ($C_{27}H_{44}O_7N_3$): calculated 522.3179 $[M+H]^+$, found 522.3184.

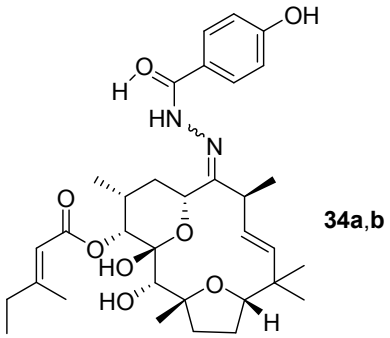
Hydrazones **33a,b**



33a,**b**

Tonantzitlolone (**1**) (7 mg, 15.1 µmol) was dissolved in pyridine (2 mL), treated with *p*-aminobenzhydrazide (11.3 mg, 75.3 µmol, 5 eq.) and 1 N HCl (15 µL) and stirred for 24 h at rt. After that time, another portion of 1 N HCl (10 µL) and *p*-aminobenzhydrazide (3.5 mg, 7.5 µL, 2.5 eq.) were added and stirring was continued for another 12h at rt. After removal of the solvent under reduced pressure and removal of water by azeotropic distillation with toluene under reduced pressure the crude material was purified by column chromatography (petroleum ether / ethyl acetate = 2:1 → petroleum ether / ethyl acetate 1:1) to yield the title compound **33a**,**b** (6.9 mg, 11.5 µmol; 76 %) as a mixture of *E/Z*-diastereoisomers (10:1). A second chromatographic separation was carried out by HPLC (reversed phase; H_2O : MeOH = 50 : 50 (5 min), 50 : 50 → 10 : 90 (80 min), 10 : 90 → 0 : 100 (15 min), 0 : 100 (10 min), **33a**,**b** after 31 min) to yield **33a**,**b** as a mixture of *E/Z*- isomers (1:5 as determined ^{1}H-NMR-spectroscopically).
Analytical data of the *Z*-isomer **33b**:
R_f = 0.30 (petroleum ether / ethyl acetate = 1:2); $[\alpha]^{20}_D$= + 48.7 (*c* = 0.23 in CH_2Cl_2);
^{1}H-NMR ($CDCl_3$, 400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 10.89 (s, 1 H, N*H*), 7.90 (d, *J* = 8.4 Hz, 2 H, *o*-Ar-*H*), 6.59 (d, *J* = 8.4 Hz, 2 H, *m*-Ar-*H*), 6.31 (s, 1 H, 9-OH), 5.77 (dd, *J* = 16.3, 2.1 Hz, 1 H, 1-H), 5.37 (dd, *J* = 16.3, 3.0 Hz, 1 H, 2-H), 5.24 (s, 1 H, 2′-H), 4.97 (d, *J* = 2.0 Hz, 1 H, 8-H), 4.84 (dd, *J* = 13.0, 2.5 Hz, 1 H, 5-H), 3.98 (d, *J* = 5.3 Hz, 1 H, 10-H), 3.97 (dd, *J* = 9.8, 4.3 Hz, 1 H, 14-H), 3.99-3.85 (br s, 2 H, NH_2), 3.59-3.51 (m, 1 H, 3-H), 2.75 (d, *J* = 5.3 Hz, 1 H, 10-OH), 2.56-2.47 (m, 1 H, 7-H), 2.49-2.41 (m, 1 H, 12-H), 2.21-2.14 (m, 2 H, 4′-H), 2.16 (d, *J* = 1.0 Hz, 3 H, 6′-H), 2.14-2.06 (m, 1 H, 6-H), 2.01-1.89 (m, 2 H, 13-H), 1.71-1.63 (m, 1 H, 12-H), 1.32 (s, 3 H, 18-H), 1.26 (t, *J* = 7.6 Hz, 3 H, 5′-H), 1.25 (d, *J* = 7.5 Hz, 3 H, 20-H), 1.18, 0.92 (2 x s, 6 H, 16-H, 17-H), 0.82 (d, *J* = 6.6 Hz, 3 H, 19-H) ppm;
^{13}C-NMR ($CDCl_3$, 125 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 167.6 (q, 1′-C), 165.4 (q, 3′-C), 164.1 (q, NH-*C*O-Ar), 158.6 (q, 4-C), 149.9 (q, *p*-Ar-*C),* 139.5 (t, 1-C), 130.1, 129.9 (2 x t, *o*-Ar-*C*), 123.1 (q, *ipso*-Ar-*C*), 114.3 (2 x q, *m*-Ar-*C*), 113.8 (t, 2′-C), 97.9 (q, 9-C), 88.7, 88.4 (11-C, 14-C), 79.4 (t, 10-C), 73.2 (t, 8-C), 67.8 (t, 5-C), 42.1 (t, 3-C), 39.9 (q, 15-C), 34.0 (s, 4′-C), 33.0 (s, 12-C), 29.9 (s, 6-C), 28.4 (t, 7-C), 27.1, 26.3, 25.7 (3 x p, 16-C, 17-C, 18-C), 24.4 (s, 13-C), 19.0 (p, 6′-C), 17.4, 17.1 (2 x p, 19-C, 20-C), 12.0 (p, 5′-C) ppm;
HRMS-ESI ($C_{33}H_{47}O_7N_3$): calculated 620.3312 $[M+Na]^+$, found 620.3318.

Hydrazones **34a,b**



Tonantzitlolone (**1**) (10 mg, 21.5 µmol) was dissolved in pyridine (2 mL), treated with *p*-hydroxybenzhydrazide (16.7 mg, 107.6 µmol, 5 eq.) and 1 N HCl (110 µL) and stirred for 24 h at rt. After that time, another portion of 1 N HCl (110 µL) was added and stirring was continued for another 24 h at rt. Within the next 48 h two additional portions of 1 N HCl (2 x 100 µL) were added. After removal of the solvent under reduced pressure and removal of water by azeotropic distillation with toluene under reduced pressure the crude material was purified by column chromatography (petroleum ether / ethyl acetate = 2:1 → ethyl acetate) to yield the title compound **34a**,**b** (10.1 mg, 16.9 µmol, 79 %) as a mixture of *E/Z*-diastereoisomers. A second chromatographic separation was carried out by HPLC (reversed phase; H_2O : MeOH = 50 : 50 (5 min), 50 : 50 → 10 : 90 (in 80 min), 10 : 90 → 0 : 100 (in 15 min), 0 : 100 (10 min), **34a**,**b** after 58 min) to yield **34a**,**b** as a mixture of *E/Z*- isomers (1:9 as determined ^{1}H-NMR spectroscopically).

Analytical data of *Z*-isomer **34b**:

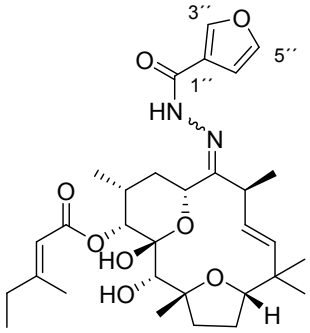
R_f = 0.43 (petroleum ether / ethyl acetate = 1:2); $[\alpha]^{20}_D$= + 60.3 (*c* = 0.3 in CH_2Cl_2);

^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): δ_H = 10.96 (s, 1 H, N*H*), 7.95 (d, *J* = 8.6 Hz, 2 H, *o*-Ar-*H*), 6.77 (d, *J* = 8.6 Hz, 2 H, *m*-Ar-*H*), 6.29 (s, 1 H, 9-OH), 5.87 (br s, 1 H, Ar-O*H*), 5.74 (dd, *J* = 16.3, 2.0 Hz, 1 H, 1-H), 5.34 (dd, *J* = 16.3, 3.1 Hz, 1 H, 2-H), 5.12 (d, *J* = 1.3 Hz, 1 H, 2´-H), 4.92 (d, *J* = 2.3 Hz, 1 H, 8-H), 4.82 (dd, *J* = 12.9, 2.6 Hz, 1 H, 5-H), 3.96 (d, *J* = 5.3 Hz, 1 H, 10-H), 3.94 (dd, *J* = 9.5, 4.3 Hz, 1 H, 14-H), 3.56-3.46 (m, 1 H, 3-H), 2.73 (d, *J* = 5.3 Hz, 1 H, 10-OH), 2.55-2.36 (m, 2 H, 7-H, 12-H), 2.12 (d, *J* = 1.3 Hz, 3 H, 6´-H), 2.09-2.03 (m, 1 H, 6-H), 2.02-1.92 (m, 3 H, 4´-H, 13-H), 1.92-1.81 (m, 1 H, 13-H), 1.69-1.62 (m, 1 H, 12-H), 1.33-1.26 (m, 1 H, 6-H), 1.30 (s, 3 H, 18-H), 1.22 (d, *J* = 7.4 Hz, 20-H), 1.16, 0.90 (2 s, 6 H, 16-H, 17-H), 0.87 (t, *J* = 7.4 Hz, 3 H, 5´-H), 0.80 (d, *J* = 6.9 Hz, 3 H, 19-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 167.7, 165.7, 164.0, 159.5, 159.2 (4-C, 1´-C, 3´-C, *ipso*-Ar-*C, p*-Ar-*C*), 139.6, 130.2, 130.0, 125.6, 115.7, 113.6 (1-C, 2-C, 2´-C, *o*-Ar-*C, m*-Ar-*C*), 97.9 (q, 9-C), 88.7, 88.4 (11-C, 14-C), 79.3 (t, 10-C), 73.2 (t, 8-C), 67.8 (t, 5-C), 42.1 (t, 3-C), 39.9 (q, 15-C), 34.0 (s, 4´-C), 33.0 (s, 12-C), 29.8 (t, 7-C), 28.4 (s, 6-C), 27.1, 26.3, 25.6 (3 x p,16-C, 17-C, 18-C), 24.4 (s, 13-C), 19.0 (p, 6´-C), 17.3, 17.1 (2 x p, 19-C, 20-C), 11.9 (p, 5´-C) ppm;

HRMS-ESI ($C_{33}H_{47}O_8N_2$): calculated 599.3332 $[M+H]^+$, found 599.3326.

Hydrazones **35a,b**



35a,**b**

Tonantzitlolone (**1**) (8 mg, 17.2 µmol) was dissolved in dichloromethane (2 mL), treated with 3-furan-carbohydrazide (12 mg, 86.1 µmol, 5 eq.), PTSA (2 mg, 10.5 µmol, 0.6 eq.) and molecular sieves 4 Å (3 mg) and then stirred for 24 h at 40 °C. After that time, Et_3N (5 µL, 5.7 µmol, 2 eq.) was added for neutralization and the reaction mixture was filtered over a pad of silica with ethyl acetate as eluent. After removal of the solvent under reduced pressure the crude material was purified by column chromatography (petroleum ether / ethyl acetate = 2:1) to yield the title compound **35a**,**b** (6.6 mg, 11.5 µmol; 67 %) as a mixture of *E/Z*-diastereoisomers (1:9 as determined ^{1}H-NMR spectroscopically) and the starting material **1** (1.5 mg, 3.2 µmol; 19 %).

Analytical data of *Z*-isomer:

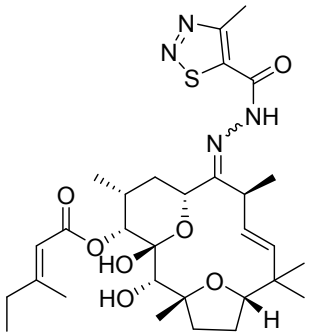
R_f = 0.13 (petroleum ether / ethyl acetate = 2:1); $[\alpha]^{20}_D$= + 63.8 (*c* = 0.66 in CH_2Cl_2);

^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): δ_H = 11.05 (s, 1 H, 1´´-H), 7.37-7.33 (m, 2 H, 3´´-H, 5´´-H), 6.49 (dd, *J* = 3.2, 1.9 Hz, 1 H, 4´´-H), 6.38 (s, 1 H, 9-OH), 5.71 (dd, *J* = 16.4, 2.1 Hz, 1 H, 1-H), 5.37 (q, *J* = 1.2 Hz, 1 H, 2´-H), 5.37 (dd, *J* = 16.4, 3.1 Hz, 1 H, 2-H), 5.10 (d, *J* = 2.6 Hz, 1 H, 8-H), 4.85 (dd, *J* = 12.9, 2.5 Hz, 1 H, 5-H), 3.94 (dd, *J* = 9.5, 4.4 Hz, 1 H, 14-H), 3.87 (d, *J* = 9.4 Hz, 1 H, 10-H), 3.55-3.48 (m, 1 H, 3-H), 2.59 (d, *J* = 9.4 Hz, 1 H, 10-OH), 2.50-2.42 (m, 1 H, 7-H), 2.26-2.16 (m, 1 H, 12-H), 2.19 (d, *J* = 1.3 Hz, 3 H, 6´-H), 2.02 (q, *J* = 7.5 Hz, 2 H, 4´-H), 2.12-2.01 (m, 1 H, 6-H), 1.99-1.91 (m, 1 H, 13-H), 1.88-1.80 (m, 1 H, 13-H), 1.59-1.51 (m, 1 H, 12-H), 1.34-1.28 (m, 1 H, 6-H), 1.30 (s, 3 H, 18-H), 1.26 (d, *J* = 7.5 Hz, 3 H, 20-H), 0.98 (t, *J* = 7.5 Hz, 3 H, 5´-H), 1.18, 0.91 (2 x s, 6 H, 16-H, 17-H), 0.85 (d, *J* = 6.8 Hz, 19-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.5, 164.2 (2 x q, 3´-C, 1´-C), 160.5 (q, 4-C), 155.1 (q, 1´´-C), 147.6 (q, 2´´-C), 144.7 (t, 3´´-C), 139.6 (t, 1-C), 130.0 (t, 2-C), 115.9 (t, 5´´-C), 114.0 (t, 2´-C), 112.4 (t, 4´´-C), 98.3 (q, 9-C), 88.9, 88.8 (11-C, 14-C), 79.5 (t, 10-C), 71.8 (t, 8-C), 68.1 (t, 5-C), 42.1 (t, 3-C), 40.0 (q, 15-C), 34.1 (s, 4´-C), 32.9 (s, 12-C), 29.8, 28.6 (6-C, 7-C), 27.1, 26.3, 25.5 (3 x p, 16-C, 17-C, 18-C), 24.3 (s, 13-C), 18.8 (p, 6´-C), 17.2, 17.0 (2 x p, 19-C, 20-C), 12.0 (p, 5´-C) ppm;

HRMS-ESI ($C_{31}H_{44}NaN_2O_8$): calculated 595.2995 $[M+Na]^+$, found 595.3019.

Hydrazones **36a,b**



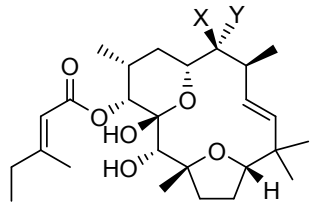
36a,**b**

Tonantzitlolone (**1**) (10 mg, 21.5 µmol) was dissolved in pyridine (2 mL), treated with 4-methyl-1,2,3-thiadiazol-5-carbohydrazide (17.0 mg, 107.6 µmol, 5 eq.) and 1 N HCl (110 µL) and then stirred for 24 h at rt. After that time, a second portion of 4-methyl-1,2,3-thiadiazol-5-carbohydrazide (17.0 mg, 107.6 µmol, 5 eq.) and 1 N HCl (110 µL) were added and stirring was continued for another 24 h at rt. Within the next 48 h two additional portions of 1 N HCl (2 x 100 µL) were added. Within the next nine days four portions of 1 N HCl (4 x 110 µL) were added. After removal of the solvent under reduced pressure and removal of water by azeotropic distillation with toluene under reduced pressure the crude material was purified by HPLC (reversed phase; H_2O : MeOH = 50 : 50 (5 min), 50 : 50 → 10 : 90 (80 min), 10 : 90 → 0 : 100 (15 min), 0 : 100 (10 min), **36a**,**b** at 58 min) to furnish **36a**,**b** (1.5 mg, 2.5 µmol; 12 %) as a mixture of *E/Z*-diastereoisomers (1:7 as determined ^{1}H-NMR spectroscopically) and the starting material **1** (1.5 mg, 3.2 µmol; 19 %).

Analytic data of *Z*-isomer:

R_f = 0.68 (petroleum ether / ethyl acetate = 1:1); $[\alpha]^{20}_D$= + 22.7 (*c* = 0.15 in CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 400 MHz, $CDCl_3$ = 7.26 ppm): δ_H = 9.23 (s, N*H*), 6.30 (s, 1 H, 9-OH), 5.88 (q, *J* = 1.3 Hz, 1 H, 2´-H), 5.51 (d, *J* = 15.6 Hz, 1 H, 1-H), 5.39 (dd, *J* = 15.6, 7.0 Hz, 1 H, 2-H), 5.05 (d, *J* = 2.5 Hz, 1 H, 8-H), 4.85 (dd, *J* = 12.0, 2.4 Hz, 1 H, 5-H), 3.74 (pt, *J* = 7.2 Hz, 1 H, 14-H), 3.59 (d, *J* = 7.9 Hz, 1 H, 10-OH), 3.56-3.48 (m, 1 H, 3-H), 3.09 (s, 3 H, Ar-C*H*$_3$), 2.65 (d, *J* = 7.9 Hz, 10-OH), 2.52-2.41 (m, 1 H, 7-H), 2.33-2.19 (m, 3 H, 12-H, 4´-H), 2.19 (d, *J* = 1.3 Hz, 3 H, 6´-H), 2.14-1.59 (m, 4 H, 6-H, 12-H, 13-H), 1.52-1.34 (m, 1 H, 6-H), 1.29 (s, 3 H, 18-H), 1.25 (d, *J* = 6.9 Hz, 3 H, 20-H), 1.08 (t, *J* = 7.4 Hz, 3 H, 5´-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 19-H), 1.16 u. 0.94 (2 x s, 6 H, 16-H, 17-H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.7, 164.8, 163.6, 161.5, 158.3, 138.2, 135.0, 128.4 (1-C, 2-C, 4-C, 1´-C, 3´-C, 2 x Ar-*C*, NH-*C*O-Ar), 114.2 (t, 2´-C), 98.0 (q, 9-C), 88.4, 87.8 (11-C, 14-C), 78.5, 72.6, 68.0 (5-C, 8-C, 10-C), 39.1, 36.6, 34.8, 34.1, 30.8, 29.6, 27.8, 26.9, 26.5, 25.1, 19.2, 17.6, 17.5, 15.7, 12.1 (3-C, 6-C, 7-C, 12-C, 13-C, 15-C, 16-C, 17-C, 18-C, 19-C, 20-C, 4´-C, 5´-C, 6´-C, Ar-*C*H$_3$) ppm; HRMS-ESI ($C_{30}H_{44}NaN_4O_7S$): calculated 627.2828 $[M+Na]^+$, found 627.2829.

Synthesis of carbinols **27** and **38** from tonantzitlolone

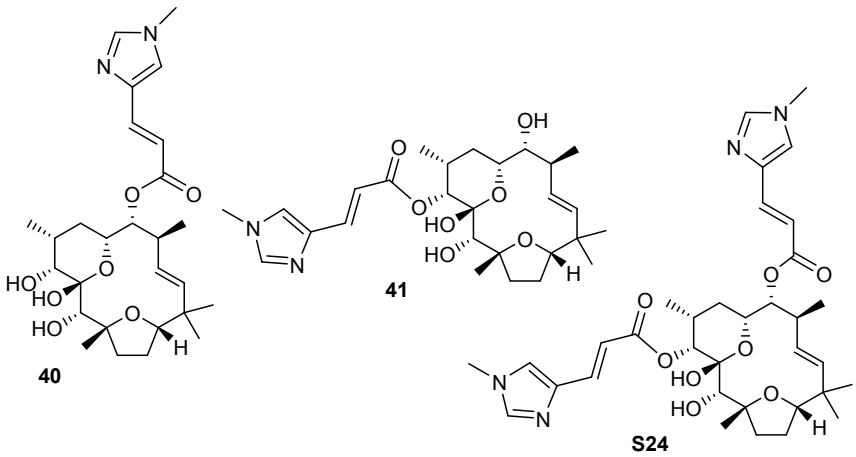


27 X= H, Y= OH, **38** X= OH, Y= H

Tonantzitlolone (**1**) (21.6 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (1 mL) under inert gas. The solution was cooled to -78°C and DIBAL-H was added (41.5 µL, 1M in toluene, 1 eq). After 1 h the reaction was terminated by addition of an aqueous solution of Na/K-tartrate. The mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by chromatography (silica, petroleum ether / ethyl acetate= 20:1) to yield the two diastereomeric alcohols **38** (6.3 mg, 0.013 mmol; 26%) and **27** (12.9 mg, 0.027 mmol; 54%).
Alternatively, tonantzitlolone (**1**) (15 mg, 0.034 mmol) was dissolved in dry MeOH (2 mL) under inert gas and borohydride resin (254 mg) was added. The mixture was shaken for 2 h after which time a second portion of borohydride resin (130.6 mg) was added. After 5 h the polymer was filtered and washed with MeOH (50 mL). The combined organic phases were concentrated under reduced pressure and the crude material was purified by chromatography (silica, petroleum ether/ ethyl acetate= 60:1≪30:1≪5:1) to yield the two diastereomeric alcohols **38** (8.8 mg, 0.019 mmol; 56%) and **27** (5.7 mg, 0.012 mmol; 35%).
38: ^{1}H-NMR (400 MHz, $CDCl_3$, TMS= 0.0 ppm): 6.21 (s, 1H, 9-OH), 5.7 (q, *J*=1.6 Hz, 1H, 2′-H), 5.49 (d, *J*=15.6 Hz, 1H, 1-H), 5.27 (dd, *J*=15.6, 9.4 Hz, 1H, 2-H), 4.9 (d, *J*=2.6 Hz, 1H, 8-H), 4.19 (ddd, *J*=12.4, 6.4, 2.4 Hz, 1H, 5-H), 3.68 (dd, *J*=10.0, 6.0 Hz, 1H, 14-H), 3.45 (bd, *J*=6.4, 1H, 10-H), 3.36 (bddd, *J*=6.4, 6.4, 2.4 Hz, 1H, 4-H), 3.07 (bd, *J*=6.5 Hz, 1H, 10-OH), 2.41 (dddq, *J*=12.8, 7.0, 4.2, 2.6 Hz, 1H, 7-H), 2.34 (ddd, 2*J*=12.4, *J*=7.8, 3.4 Hz, 1H, 12-H), 2.24 (ddq, *J*=9.4, 6.4 und 7.2 Hz, 1H, 3-H), 2.15 (dq, *J*=7.2, J= 1 Hz, 2H, 4′-H), 2.15 (d, *J*=1.6 Hz, 3H, 6′-H), 1.94-1.83 (m, 1H, 13-H), 1.80-1.70 (m, 1H, 13-H), 1.74 (ddd, 2*J*=13.4, *J*=12.8 und 12.4 Hz, 1H, 6-H), 1.48 (ddd, 2*J*=12.4 Hz, *J*=10.0, 7.2 Hz, 1H, 12-H), 1.31 (s, 3H, 18-H), 1.18 (ddd, *J*=13.4 Hz, *J*=4.3, 2.4 Hz, 1H, 6-H), 0.88 (s, 3H. 16-H), 0.82 (d, *J*=7.0 Hz, 3H, 19-H), 1.1 (d, *J*=7.2 Hz, 3H, 20-H), 1.08 (s, 3H, 17-H), 1.06 (t, *J*=7.2 Hz, 3H, 5′-H) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$, TMS=0.0 ppm): 12.81 (p, 5′-C), 18.18 (p, 19-C), 19.96 (p, 6′-C), 21.81 (p, 20-C), 26.12 (p, 17-C),28.18 (p, 16-C), 28.92 (s, 13-C), 29.95 (p, 18-C), 30.81 (t, 7-C), 34.84 (s, 6-C), 37.12 (s, 4′-C), 39.28 (s, 12-C), 46.46 (q, 15-C), 69.37 (t, 3-C), 74.33 (t, 5-C), 77.62 (t, 8-C), 78.99 (t, 4-C), 79.18 (t, 10-C), 88.83 (q, 11-C), 88.93 (t, 14-C), 97.67 (q, 9-C), 115.0 (t, 2′-C), 131.24 (t, 2-C), 135.95 (t, 1-C), 163.69 (q, 3′-C), 167.55 (q, 1′-C) ppm.
27: ^{1}H-NMR (400 MHz, $CDCl_3$, TMS=0.0 ppm): 5.93 (s, 1H, 9-OH), 5.7 (q, *J*=1.2 Hz, 1H, 2′-H), 5.58 (d, *J*=15.6 Hz, 1H, 1-H), 5.44 (dd, *J*=15.6, 9.6 Hz, 1H, 2-H), 4.88 (d, *J*=2.8 Hz, 1H, 8-H), 3.97 (ddd, *J*=11.6, 8.4, 2.4 Hz, 1H, 5-H), 3.36 (d, *J*=7.2 Hz, 1H, 10-H), 3.69 (dd,

J=11.2 und 5.6 Hz, 1H, 14-H), 3.62 (bddd, *J*=8.4, 5.6, 4.0 Hz, 1H, 4-H), 3.25 (d, *J*=7.0 Hz, 1H, 10-OH), 2.55 (ddq, *J*=9.6, 7.2, 4.0 Hz, 1H, 3-H), 2.38 (dddq, *J*=12.0, 7.0, 3.2, 2.8 Hz, 1H, 7-H), 2.37 (ddd, *J*=12.8 Hz, *J*=8.0, 6.8 Hz, 1H, 12-H), 2.15 (q, *J*=7.6 Hz, 2H, 4′-H), 2.14 (d, *J*=1.2 Hz, 1H, 6′-H), 1.98 (dddd, 2*J*=12.4 Hz, *J*=12.0, 11.2, 8.0 Hz, 1H, 13-H), 1.76-1.71 (m, 1H, 6-H), 1.54 (bd, *J*=5.6 Hz, 1H, 4-OH), 1.72 (dddd, *J*=12.4 Hz, 7.6, 6.8, 5.6 Hz, 1H, 13-H), 1.47 (ddd, 2*J*=12.8 Hz, *J*=12.0, 7.6 Hz, 1H, 12), 1.32 (s, 3H, 18-H), 1.10 (s, 3H, 17-H), 1.30-1.21 (m, 1H, 6-H), 1.06 (t, *J*=7.6 Hz, 3H, 5′-H), 1.04 (d, *J*=7.2 Hz, 3H, 20-H), 0.85 (s, 3H, 16-H), 0.81 (d, *J*=7.0 Hz, 3H, 19-H);
^{13}C-NMR (100 MHz, $CDCl_3$, TMS=0.0 ppm) : 11.86 (p, 5′-C) 17.17 (p, 19-C), 17.73 (p, 20-C), 18.95 (t, 6′-C), 24.93 (p, 17-C), 25.42 (p, 16-C), 27.73 (s, 13-C), 28.05 (p, 18-C), 29.04 (t, 7-C), 33.20 (s, 6-C), 33.89 (s, 4′-C), 37.05 (s, 12-C), 38.40 (p, 15-C), 41.33 (t, 3-C), 70.69 (t, 5-C), 73.46 (t, 8-C), 78.03 (t, 4-C), 78.03 (t, 10-C), 87.96 (t, 14-C), 88.22 (q, 11-C), 96.22 (q, 9-C), 114.17 (t, 2′-C), 127.74 (t, 2-C), 136.49 (t, 1-C). 162.43 (q, 3′-C), 166.80 (q, 1′-C) ppm.
HRMS-ESI ($C_{26}H_{43}O_7$): calculated 467.3009 [M+H$^+$], found 467.3002.

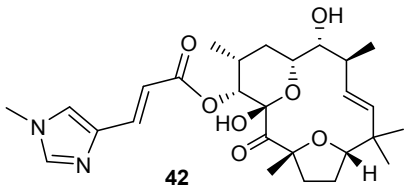
Ester **40**-**42**



Alcohol **26** (17 mg, 46 µmol) and carboxylic acid **39** (21 mg, 138 µmol, 3 eq) were dissolved in dry CH_2Cl_2 (3.5 mL) and treated with DIC (18 µL, 116 µmol, 2.5 eq) and the reaction mixture was stirred at rt for 1 h. Then DMAP (6 mg, 49 µmol, 1.1 eq) was added. After 19 h a second portion of carboxylic acid **39** (7 mg, 46 µmol, 1 eq) and DIC (6 µL, 39 µmol, 0.8 eq) were added and the reaction mixture was stirred for additional 5 h at rt. The solution was passed through a pad of silica with CH_2Cl_2/methanol (100:1→ 50:1→ 10:1) to yield a mixture of the esters **40** and **41** (16.8 mg, ~2:1, 33.3 mmol, 72 %) as well as diester **S24** (4.8 mg, 7.5 µmol, 16 %) as colorless oils.
40 (data collected when isolated after oxidation to follow): $[\alpha]^D_{20}$ = - 37.5° (c = 0.4 in $CHCl_3$);
^{1}H-NMR (400 MHz, CD_3OD; CHD_2OD= 3.31 ppm): 7.70 (s, 1 H, H-6'), 7.63 (d, *J* = 15.7 Hz, 1 H, H-3'), 7.43 (d, *J* = 1.1 Hz, 1 H, H-5'), 6.49 (d, *J* = 15.7 Hz, 1 H, H-2'), 5.63 (d, *J* = 15.3 Hz, 1 H, H-1), 5.42 (dd, J = 15.3, 9.3 Hz, 1 H, H-2), 4.98 (dd, *J* = 7.8, 3.0 Hz, 1 H, H-4), 4.35 (ddd, *J* = 11.9, 3.0, 2.3 Hz, 1 H, H-5), 3.88 (dd, *J* = 7.6, 6.3 Hz, 1 H, H-14), 3.75 (s, 3 H, H-7'), 3.74 (s, 1 H, H-10), 3.35-3.32 (m, 1 H, H-8), 2.61-2.51 (m, 1 H, H-3), 2.40 (dt, *J* = 12.3, 8.0 Hz, 1 H, H-12), 2.24-2.15 (m, 1 H, H-7), 2.11-2.02 (m, 1 H, H-13), 2.01-1.91 (m, 1 H, H-13), 1.63 (ddd, *J* = 12.3, 7.2, 5.3 Hz, 1 H, H-12), 1.46 (q, *J* = 12.4 Hz, 1 H, H-6), 1.32 (s, 3 H,

H-18), 1.11 (s, 3 H, H-16), 1.11-1.06 (m, 1 H, H-6), 1.01 (d, *J* = 6.9 Hz, 3 H, H-20), 0.93 (s, 3 H, H-17), 0.88 (d, *J* = 7.0 Hz, 3 H, H-19) ppm;
^{13}C-NMR (100 MHz, CD_3OD = 49.00 ppm): 169.3 (C-1'), 141.2 (C-6'), 138.6 (C-4'), 137.9 (C-3'), 137.4 (C-1), 130.3 (C-2), 125.2 (C-5'), 116.3 (C-2'), 98.7 (C-9), 89.53 (C-11), 89.47 (C-14), 81.3 (C-10), 80.2 (C-4), 75.9 (C-8), 70.1 (C-5), 43.3 (C-3), 39.8 (C-15), 35.7 (C-12), 33.9 (C-7'), 31.1 (C-7), 30.1 (C-6), 27.8 (C-18), 27.0 (C-13), 26.4 (C-16), 24.5 (C-17), 20.8 (C-20), 17.7 (C-19) ppm;
HRMS-ESI ($C_{27}H_{41}N_2O_7$): calculated 505.2914 [M+H$^+$], found 505.2917.
S24: $[\alpha]^D_{20}$ = + 26.5° (c = 0.48 in $CHCl_3$);
^{1}H-NMR (400 MHz, CD_3OD CHD_2OD = 3.31 ppm): 7.72 (s, 1 H, H-6'), 7.66 (s, 1 H, H-6'), 7.70-7.65 (m, 1 H, H-3'), 7.53 (d, *J* = 15.7 Hz, 1 H, H-3'), 7.45 (s, 1 H, H-5'), 7.33 (s, 1 H, H-5'), 6.56 (d, *J* = 15.7 Hz, 1 H, H-2'), 6.44 (d, *J* = 15.7 Hz, 1 H, H-2'), 5.68 (d, *J* = 15.3 Hz, 1 H, H-1), 5.42 (dd, J = 15.3, 9.5 Hz, 1 H, H-2), 5.06 (dd, *J* = 8.1, 3.2 Hz, 1 H, H-4), 4.85-4.84 (m, 1 H, H-8), 4.46 (ddd, *J* = 11.8, 3.0, 2.5 Hz, 1 H, H-5), 3.79 (dd, *J* = 9.3, 6.1 Hz, 1 H, H-14), 3.73 (s, 3 H, H-7'), 3.70 (s, 3 H, H-7'), 3.46 (s, 1 H, H-10), 2.67-2.59 (m, 1 H, H-3), 2.50-2.42 (m, 1 H, H-7), 2.37 (ddd, *J* = 12.2, 8.0, 3.6 Hz, 1 H, H-12), 2.08-1.97 (m, 1 H, H-13), 1.89-1.80 (m, 1 H, H-13), 1.60-1.55 (m, 1 H, H-16), 1.51 (m, 1 H, H-12), 1.48-1.40 (m, 1 H, H-6), 1.32 (s, 3 H, H-18), 1.28-1.23 (m, 1 H, H-6), 1.14 (s, 3 H, H -9), 1.03 (d, *J* = 6.9 Hz, 3 H, H-20), 0.92 (s, 3 H, H-17), 0.79 (d, *J* = 6.9 Hz, 3 H, H-19) ppm;
^{13}C-NMR (100 MHz, CD_3OD= 49.00 ppm): 169.1 (C-1'), 168.9 (C-1'), 141.2, 141.14, 141.11 (2xC-6', C-4'), 138.6, 138.2, 137.7 (2x C-3', C-4'), 137.8 (C-1), 130.2 (C-2), 125.6 (C-5'), 125.2 (C-5'), 116.4 (C-2'), 116.0 (C-2'), 98.0 (C5), 89.7 (C-14), 89.5 (C-11), 80.0 (C-4), 79.6 (C-10), 75.6 (C-8), 70.0 (C-5), 43.6 (C-3), 39.5 (C-15), 37.2 (C-12), 33.94 (C-7'), 33.92 (C-7'), 30.6 (C-6), 30.2 (C-7), 28.3 (C-18), 28.2 (C-13), 26.1 (C-16), 25.1 (C-17), 21.0 (C-20), 17.6 (C-19) ppm;
HRMS-ESI ($C_{34}H_{47}N_4O_8$): calculated 639.3394 [M+H$^+$], found 639.3395.

Ketone **42**

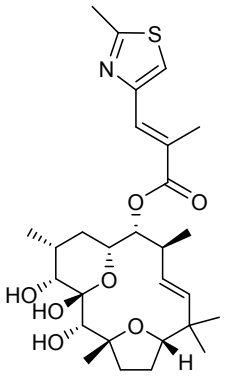


42

The mixture of ester **40**/**41** (~2:1, 8.4 mg, 16.7 µmol) was dissolved in dry CH_2Cl_2 (2.5 mL), and molecular sieves 4Å (25 mg), NMO (3 mg, 26 µmol, 1.7 eq) and TPAP (1 mg, 2.8 µmol, 0.2 eq) were added. The mixture was stirred for 80 min. and the solution was filtered through a pad of silica using CH_2Cl_2/methanol (100:1→ 10:1) as eluent. The target ketone **42** (1.0 mg, 2 µmol, 36 %) and ester **40** (2.6 mg, 4.8 µmol) were isolated as colorless oils.
42: $[\alpha]^D_{20}$ = - 11.6° (c = 0.37 in $CHCl_3$);
^{1}H-NMR (400 MHz, CD_3OD, CHD_2OD= 3.31 ppm): 7.69 (s, 1 H, H-6'), 7.62 (d, *J* = 15.7 Hz, 1 H, H-3'), 7.42 (d, *J* = 0.8 Hz, 1 H, H-5'), 6.48 (d, *J* = 15.7 Hz, 1 H, H-2'), 5.59 (dd, *J* = 15.5, 9.2 Hz, 1 H, H-2), 5.49 (s, 1 H, 9-OH), 5.48 (d, J = 15.5 Hz, 1 H, H-2), 4.91-4.88 (m, 1 H, H-4), 4.38 (dt, *J* = 12.0, 2.3 Hz, 1 H, H-5), 3.95 (t, *J* = 7.5 Hz, 1 H, H-14), 3.75 (s, 3 H, H-7'), 3.53 (br d, *J* = 2.5 Hz, 1 H, H-8), 2.64-2.57 (m, 1 H, H-12), 2.54-2.45 (m, 1 H, H-3), 2.23-

2.15 (m, 1 H, H-7), 2.08-2.00 (m, 2 H, 2xH-13), 1.76 (ddd, *J* = 12.3, 7.8, 6.1 Hz, 1 H, H-12), 1.63-1.52 (m, 1 H, H-6), 1.37 (s, 3 H, H-18), 1.19 (s, 3 H, H-16), 1.13-1.05 (m, 1 H, H-6), 1.04 (d, *J* = 6.9 Hz, 3 H, H-20), 0.96 (s, 3 H, H-17), 0.92 (d, *J* = 6.9 Hz, 3 H, H-19) ppm;
^{13}C-NMR (100 MHz, CD_3OD = 49.00 ppm): 209.3 (C-10), 169.1 (C-1'), 141.2 (C-6'), 138.6 (C-4'), 137.9 (C-3'), 136.1 (C-1), 132.3 (C-2), 125.2 (C-5'), 116.3 (C-2'), 99.4 (C-9), 91.0 (C-11), 90.4 (C-14), 79.8 (C-4), 71.9 (C-8), 69.4 (C-5), 42.5 (C-3), 39.3 (C-15), 36.2 (C-12), 33.9 (C-7'), 30.5 (C-7), 30.4 (C-6), 27.0 (C-16), 26.5 (C-13), 25.6 (C-17), 23.9 (C-18), 19.8 (C-20), 17.8 (C-19) ppm;
HRMS-ESI ($C_{27}H_{39}N_2O_7$): calculated 503.2757 [M+H$^+$], found 503.2753.

Ester **44**

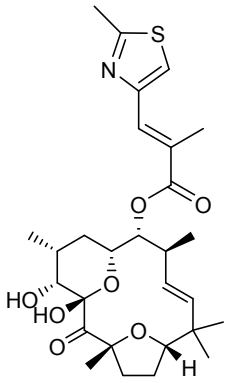


44

Alcohol **26** (8.1 mg, 21.9 µmol) and carboxylic acid **43** (12 mg, 65.5 µmol, 3 eq) were dissolved in dry CH_2Cl_2 (3.5 mL) and treated with DIC (5 µL, 32.2 µmol, 1.5 eq). The reaction mixture was stirred for 4 h at rt. Then, carboxylic acid **43** (65.5 µmol, 3 eq) and DIC (10 µL, 64.4 µmol, 3 eq) were added. After 16 h DMAP (3 mg, 24.6 µmol, 1.1 eq) was added. After stirring for 24 h at rt another portion of carboxylic acid **43** (12 mg, 65.5 µmol, 3 eq) and DIC (10 µL, 64.4 µmol, 3 eq) were added and stirring was continued for additional 5 h. The solution was passed through a pad of silica with n-pentane/ ethyl acetate. The solution was concentrated under reduced pressure. The crude material was subjected to a second chromatographic purification step (silica, n-pentane/ethyl acetate= 10:1→ 4:1) to yield the title product **44** (27.5 mg) which was contaminated with DIC-carboxylic acid adducts. The yield was determined from the ^{1}H- NMR-spectrum (about 6.2 mg, 11.5 µmol; 53 %). In addition about 3 mg of the starting alcohol **26** was reisolated.
44: $[\alpha]^D_{20}$ = - 54.5° (c = 0.62 in $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 7.67 (d, *J* = 1.4 Hz, 1 H, H-3'), 7.30 (s, 1 H, H-5'), 6.04 (s, 1 H, OH), 5.55 (d, *J* = 15.3 Hz, 1 H, H-1), 5.35 (dd, J = 15.3, 9.3 Hz, 1 H, H-2), 4.98 (dd, *J* = 7.1, 3.1 Hz, 1 H, H-4), 4.36-4.30 (m, 1 H, H-5), 3.75 (dd, *J* = 9.0, 6.3 Hz, 1 H, H-14), 3.67 (s, 1 H, H-10), 3.33 (d, *J* = 2.4 Hz, 1 H, H-8), 2.73 (s, 3 H, H-7'), 2.55 (ddq, *J* = 9.3, 7.1, 6.8 Hz, 1 H, H-3), 2.47 (ddd, *J* = 12.2, 7.9, 4.1 Hz, 1 H, H-12), 2.35 (d, *J* = 1.4 Hz, 3 H, H-8'), 2.32 (d, 1.7 Hz, 1 H, OH), 2.24-2.17 (m, 1 H, H-7), 1.95-1.89 (m, 1 H, H-13), 1.88-1.80 (m, 1H, H-13), 1.56 (ddd, *J* = 12.2, 9.3, 7.4 Hz, 1 H, H-12), 1.37-1.28 (m, 1 H, H-6), 1.33 (s, 3 H, H-18), 1.25-1.17 (m, 1 H, H-6), 1.11 (s, 3 H, H-16), 1.02 (d, *J* = 6.8 Hz, 3 H, H-20), 0.91 (d, *J*= 7.2 Hz, 3 H, H-19), 0.91 (s, 3 H, H-17) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 168.9 (C-1'), ca. 165.6 (C-6'), 151.7 (C-4'), 135.6 (C-1), 131.2 (C-3'), 129.9 (C-2), 128.6 (C-2'), 121.8 (C-5'), 97.3 (C-9), 88.2 (C-14), 87.9 (C-11), 79.3 (C-10), 79.2 (C-4), 74.9 (C-8), 68.4 (C-5), 42.1 (C-3), 38.6 (C-15), 35.9 (C-12), 29.6 (C-7), 28.8 (C-6), 27.9 (C-18), 27.4 (C-13), 26.0 (C-17), 25.1 (C-16), 20.6 (C-20), ca. 19.4 C-7'), 17.4 (C-19), 14.7 (C-8') ppm;
HRMS-ESI ($C_{28}H_{41}NNaO_7S$): calculated 558.2501 [M+Na$^+$], found 558.2501.

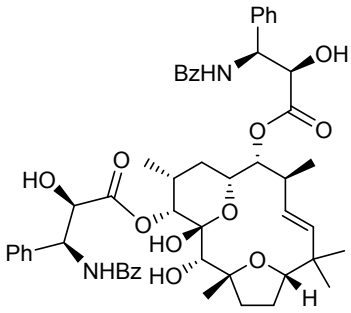
Ketone **45**



45

The impure ester **44** (containing about 2.2 mg, 4.1 μmol) was dissolved in dry CH_2Cl_2 (2 mL) and molecular sieves 4Å (15 mg), NMO (2.5 mg, 21 μmol, 5.1 eq) and TPAP (1 mg, 2.8 μmol, 0.7 eq) were added. The reaction mixture was stirred for 3.5 h and the solvent was removed by passing a stream of nitrogen through the flask. The residue was purified over a pad of silica using pentane/ethyl acetate (10:1→ 4:1) to furnish the target ketone **45** (1.7 mg, 3.2 μmol; 78 %) as a colorless oil.
45: ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$= 7.26 ppm): 7.70 (q, *J* = 1.4 Hz, 1 H, H-3'), 7.27 (s, 1 H, H-5'), 6.11 (s, 1 H, OH), 5.50 (d, *J* = 15.3 Hz, 1 H, H-1), 5.42 (dd, *J* = 15.3, 8.8 Hz, 1 H, H-2), 4.97 (dd, *J* = 7.1, 2.8 Hz, 1 H, H-4), 4.34 (dt, *J* = 12.0, 2.6 Hz, 1 H, H-5), 3.95 (t, *J* = 7.4 Hz, 1 H, H-14), 3.54 (d, *J* = 2.5 Hz, 1 H, H-8), 2.74 (s, 3 H, H-7'), 2.57 (d quin, *J* = 8.8, 7.0 Hz, 1 H, H-3), 2.44-2.35 (m, 1 H, H-12), 2.35 (d, *J* = 1.4 Hz, 3 H, H-8'), 2.23-2.15 (m, 1 H, H-7), 2.05-1.95 (m, 2 H, 2xH-13), 1.83 (ddd, *J* = 12.4, 7.7, 6.2 Hz, 1 H, H-12), 1.70-1.60 (m, 1 H, H-6), 1.43 (s, 3 H, H-18), 1.19 (s, 3 H, H-16), 1.12 (ddd, *J* = 13.1, 4.1, 2.3 Hz, 1 H, H-6), 1.03 (d, *J*= 6.9 Hz, 3 H, H-20), 0.95 (d, *J* = 7.0 Hz, 3 H, H-19), 0.94 (s, 3 H, H-17) ppm;
^{13}C-NMR (100 MHz, $CDCl_3$ = 77.16 ppm): 208.9 (C-10), 169.0 (C-1'), 135.2 (C-1), 131.2 (C-3'), 130.3 (C-2), 128.8 (C-2'), 121.5 (C-5'), 97.2 (C-9), 91.0 (C-11), 89.4 (C-14), 78.9 (C-4), 70.8 (C-8), 68.7 (C-5), 41.6 (C-3), 38.8 (C-15), 36.3 (C-12), 29.5 (C-7), 29.0 (C-6), 26.3 (C-16), 25.4 (C-13), 24.8 (C-17), 24.5 (C-18), 20.4 (C-20), 19.5 (C-7'), 17.5 (C-19), 14.7 (C-8') ppm (the carbon atoms at C-6' and C-4' could not be detected due to the small amount of material available).
HRMS-ESI ($C_{28}H_{40}NO_7S$): calculated 534.2525 [M+H$^+$], found 534.2524.

Diester **48**



48

Alcohol **26** (25.6 mg, 69.1 µmol) and lactam **47** (80 mg, 210 µmol, 3 eq) were dissolved in dry THF (6 ml) and cooled to 0°C. NaHMDS (2 M in THF, 38 µL, 76 µmol, 1.1 eq) was added portionwise. After 30 min the reaction was terminate by addition of an aqueous solution of ammonium chloride. The phases were separated and the aqueous phase was extracted with MTBE. The combined organic layers were dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica, n-pentane/ethyl acetate= 10:1→8:1→ 7:1) to yield four fractions. Fraction 3 (25.4 mg) was dissolved taken up in dry THF (6 ml) and TBAF 3 H_2O (15 mg, 47.5 µmol) was added. The reaction mixture was stirred at rt for 20 min. The solution was filtered through a pad of silica using n-pentane/ethyl acetate (1:1→1:3→ ethyl acetate). Further purification was carried out by HPLC (RP C18, methanol/water) to yield the diester **48** (4.7 mg, 5.1 µmol, 7 %).

48: $[\alpha]^{D}_{20}$ = + 84.3° (c = 0.47 in $CHCl_3$);

^{1}H-NMR (400 MHz, CDCl3 = 7.26 ppm): 7.94-7.91 (m, 2 H, Ph), 7.76-7.73 (m, 2 H, Ph), 7.54-7.27 (m, 17 H, Ph, NH), 7.06 (d, 1 H, *J* = 8.9 Hz, NH), 5.88 (dd, 1 H, *J* = 9.0, 2.1 Hz, H-3'), 5.74 (dd, 1 H, *J* = 8.8, 2.2 Hz, H-3'), 5.51 (s, 1 H; H-10), 5.18 (dd, 1 H, *J* = 15.7, 9.7 Hz, H-2), 5.05-4.92 (m, 2 H, H-1, H-8), 4.79 (br. s, 1 H, H-2'), 4.63 (br. s, 1 H, H-2'), 3.60 (br. s, 1 H, H-5), 3.42 (t, 1 H, *J* = 7.6 Hz, H-14), 3.41 (br. s, 1 H, OH), 3.34 (dd, 1 H, *J* = 10.0, 2.6 Hz, H-4), 2.45-2.33 (m, 1 H, H-7), 2.08-1.98 (m, 1 H, H-3), 1.65-1.46 (m, 4 H, 2xH-6, 2xH-13), 1.07 (d, 3 H, *J* = 6.8 Hz, H-19), 1.00 (d, 3 H, *J* = 6.4 Hz, H-20), 1.04, 0.92, 0.70 (3 s, 9 H, H-16, H-17, H-18): H-12, H-13 and 2x OH could not be unequivocally be determined;
HRMS-ESI ($C_{52}H_{61}N_2O_{12}$): calculated 905.4225 [M+H$^+$], found 905.4221.

Cell proliferation assay

Cell lines were obtained from DMSZ (L-929, MCF-7) and ATCC (PtK2). Growth inhibition was measured in microtiter plates. 60 µL of serial dilutions of the test compounds were added to 120 µL aliquots of a cell suspension (50.000/mL) in 96-well plates and incubated at 37 °C and 10% CO_2 for 5 days. MTT [3(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide] was used to measure growth and viability of cells which are capable of reducing it to a violet formazan product. 20 µL MTT in phosphate buffered saline (PBS) were added to a final concentration of 0.5 mg/mL. After 2 h the precipitate of formazan crystals was centrifuged, and the supernatant discarded. The precipitate was washed with 100 µL PBS and dissolved in 100 µL isopropanol containing 0.4% hydrochloric acid. The microplates were measured at 595 nm using an ELISA plate reader. All experiments were carried out in two parallel

experiments. The percentage of viable cells was calculated as the mean with respect to the controls set to 100%.

Fluorescence staining

PtK2 cells (from ATCC) were grown on round glass coverslips (13 mm diameter) in four-well plates. Exponentially growing cells were incubated with the compounds for 18 hours. Cells were fixed with cold (–20 °C) acetone-methanol (1:1) for 10 minutes. For labelling the microtubules, cells were first incubated with a mouse antibody against α-tubulin (1:500; Sigma), then with a secondary goat anti-mouse IgG antibody conjugated with Alexa Fluor 488 (1:200; Molecular Probes) at 37°C for 45 minutes. The nuclei and chromosomes were stained with DAPI (1 µg/ml). The cells were washed with PBS between different incubations. The coverslips were mounted using Prolong Antifade (Molecular Probes), and viewed with a Zeiss Axiophot fluorescence microscope using appropriate filter sets.

5. References supporting information

S1 H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.

S2 J. Leonard, B. Lygo, G. Procter, *Praxis in der organischen Chemie*, VCH, Weinheim, **1996**.

S3 C. Jasper, R. Wittenberg, M. Quitschalle, J. Jakupovics, A. Kirschning, *Org. Lett.* **2005**, *7*, 479-482.

S4 R. I. Storer, T. Takemoto, P. S. Jackson, D. S. Brown, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2004**, *10*, 2529-2547.

S5 S. Kiyooka, M. A. Hena, *J. Org. Chem.* **1999**, *64*, 5511-5523.

S6 From the methyl ester of urocanic acid by *N*-methylation followed by saponification according to: N. Shih, A. T. Lupo, Jr., R. Aslanian, S. Orlando, J. J. Piwinski, M. J. Green, A. K. Ganguly, M. A. Clark, S. Tozzi, W. Kreutner, J. A. Hey, *J. Med. Chem.* **1995**, *38*, 1593-1599.

S7 K. C. Nicolaou, N. Winssinger, D. Vourloumis, T. Oshima, S. Kim, J. Pfefferkorn, J. Xu, T. Li, *J. Am. Chem. Soc.* **1998**, *120*, 10814-10826

S8 C. E. Song, S. W. Lee, E. J. Roh, S. Lee, W. Lee, *Tetrahedron Asymm.* **1998**, *9*, 983-992.

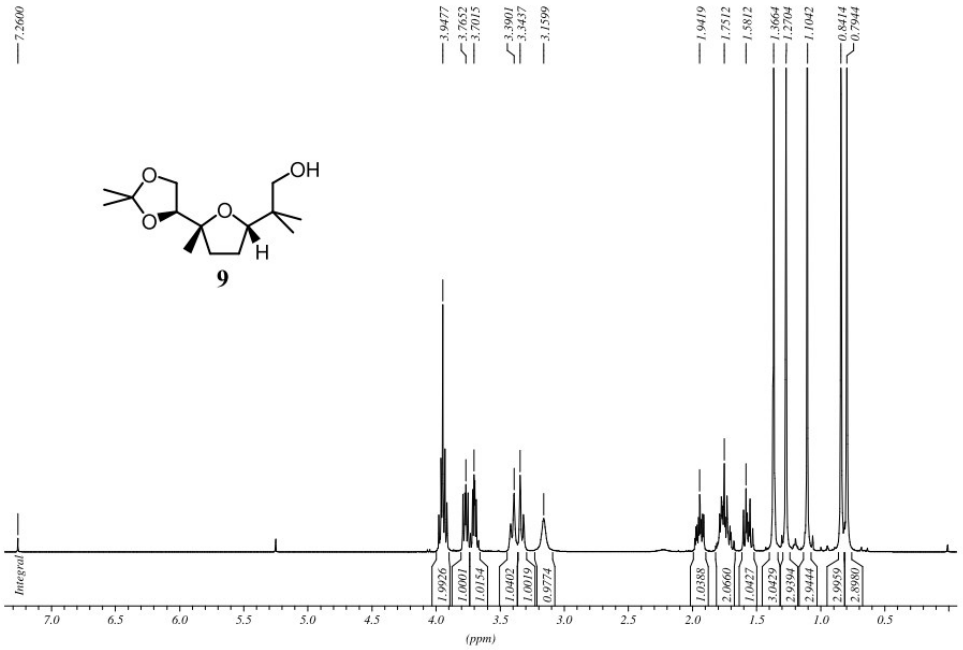
S9 R. Wu, J. S. Schumm, D. L. Pearson, J. M. Tour, *J. Org. Chem.* **1996**, *61*, 6906-6921.

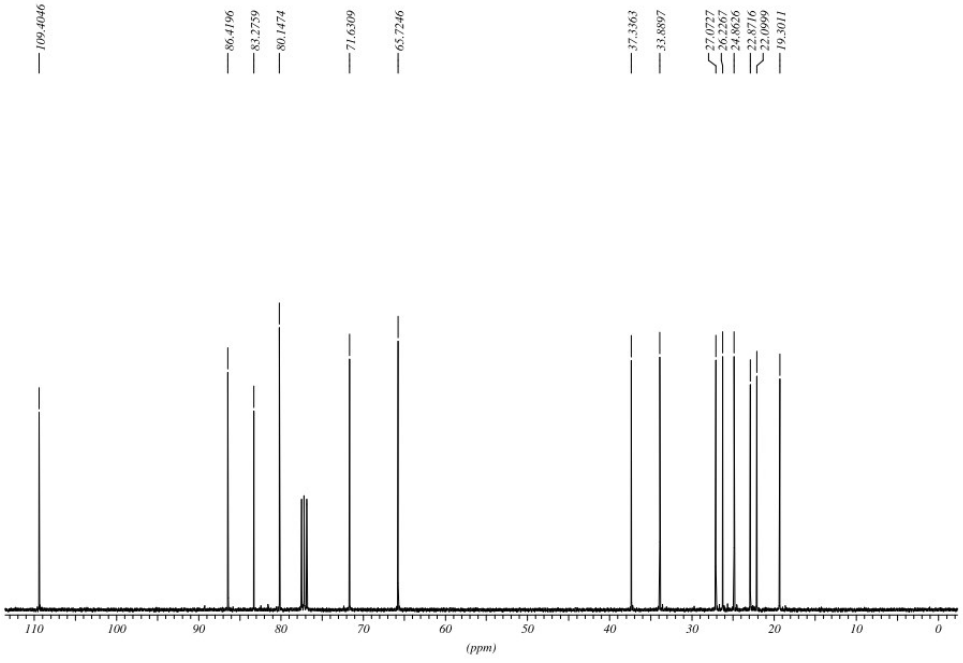
S10 J. H. Rigby, S. V. Cuisiat, *J. Org. Chem.* **1993**, *58*, 6286-6291.

S11 M. Kurosu, M. Lin, Y. Kishi, *J. Am. Chem. Soc.* **2004**, *126*, 12248- 12249.

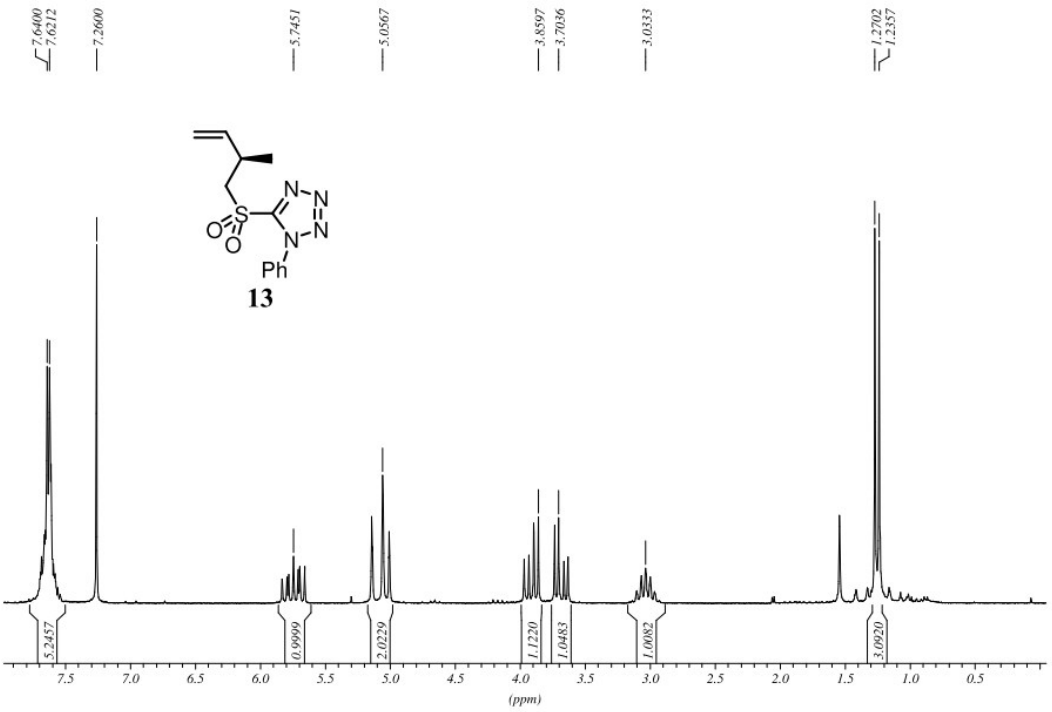
6. Attachments (Copies of ^{1}H-and ^{13}C-NMR spectra)

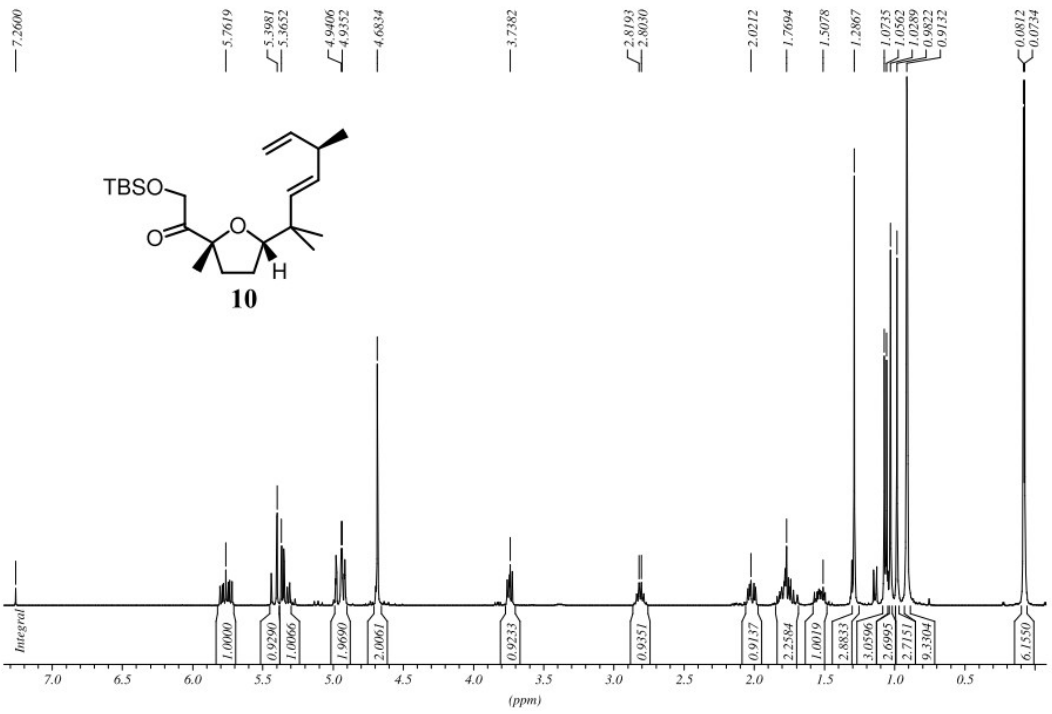
NMR spectra of compound **9**



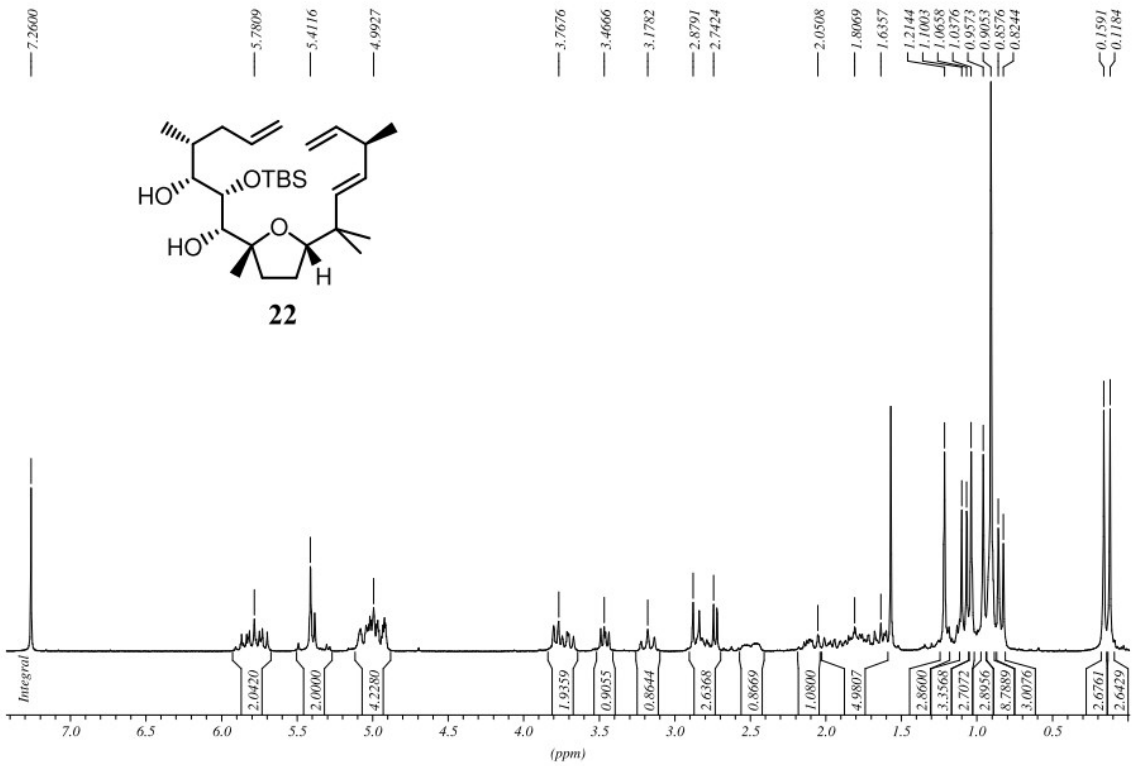


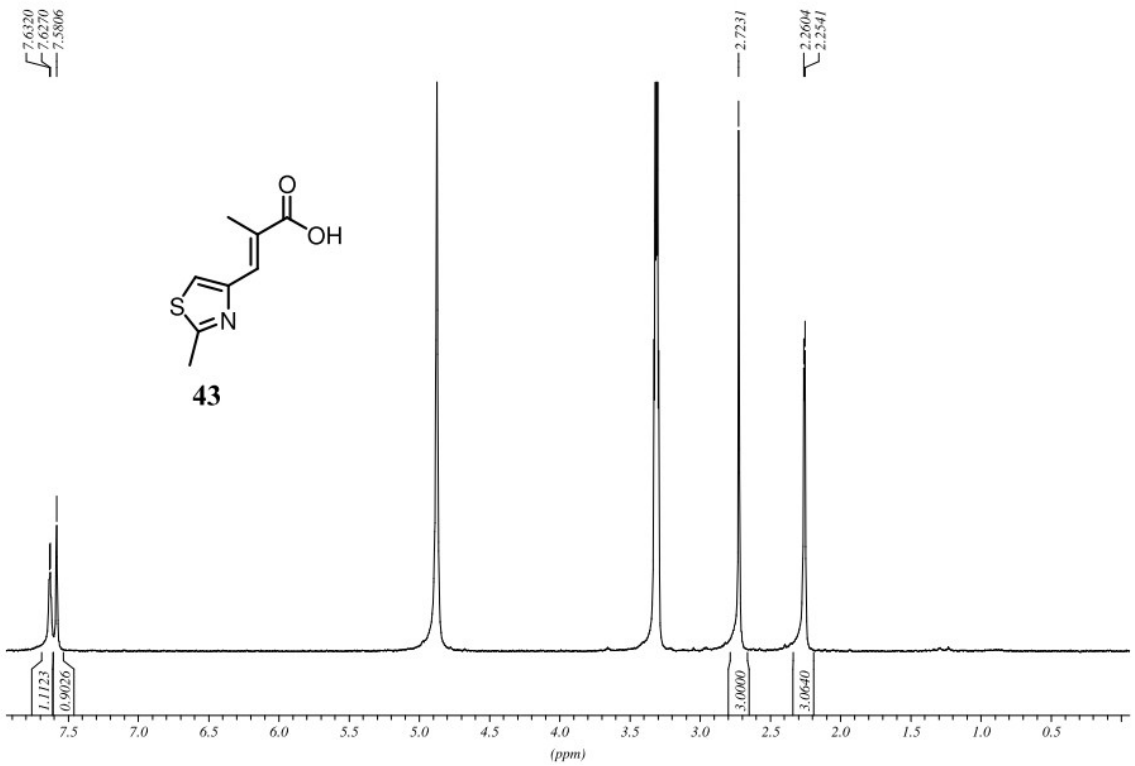
NMR spectra of compounds **13** and **10**



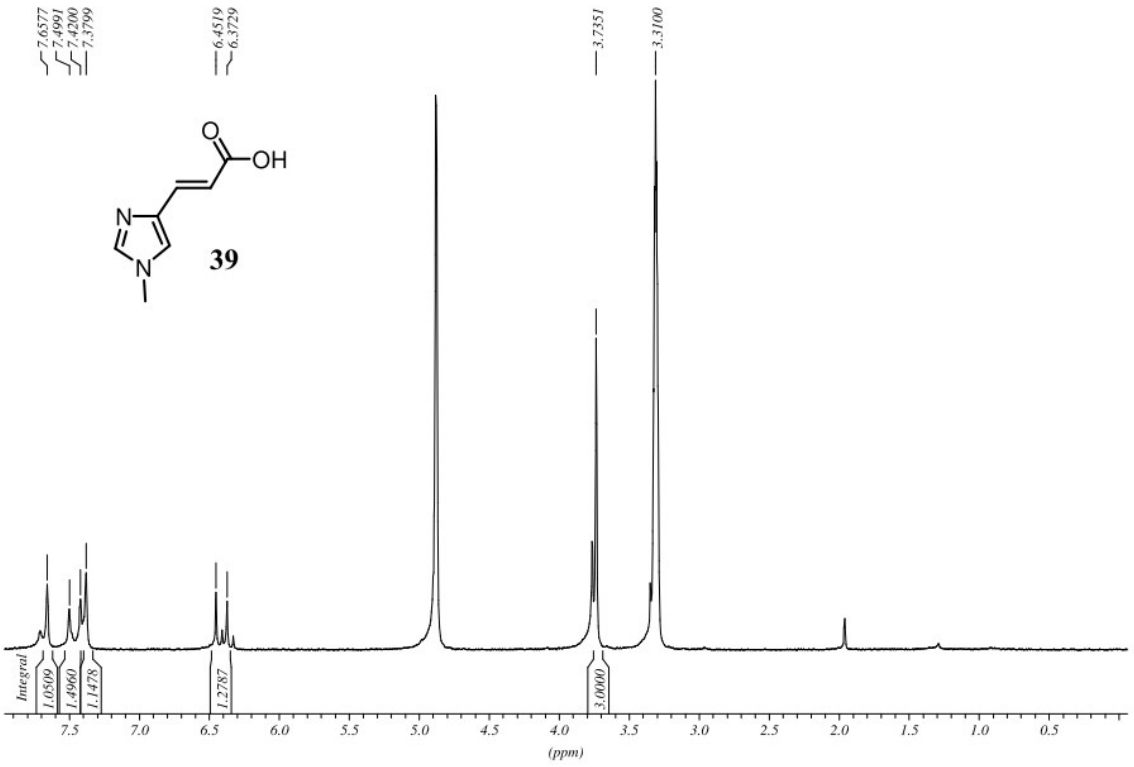


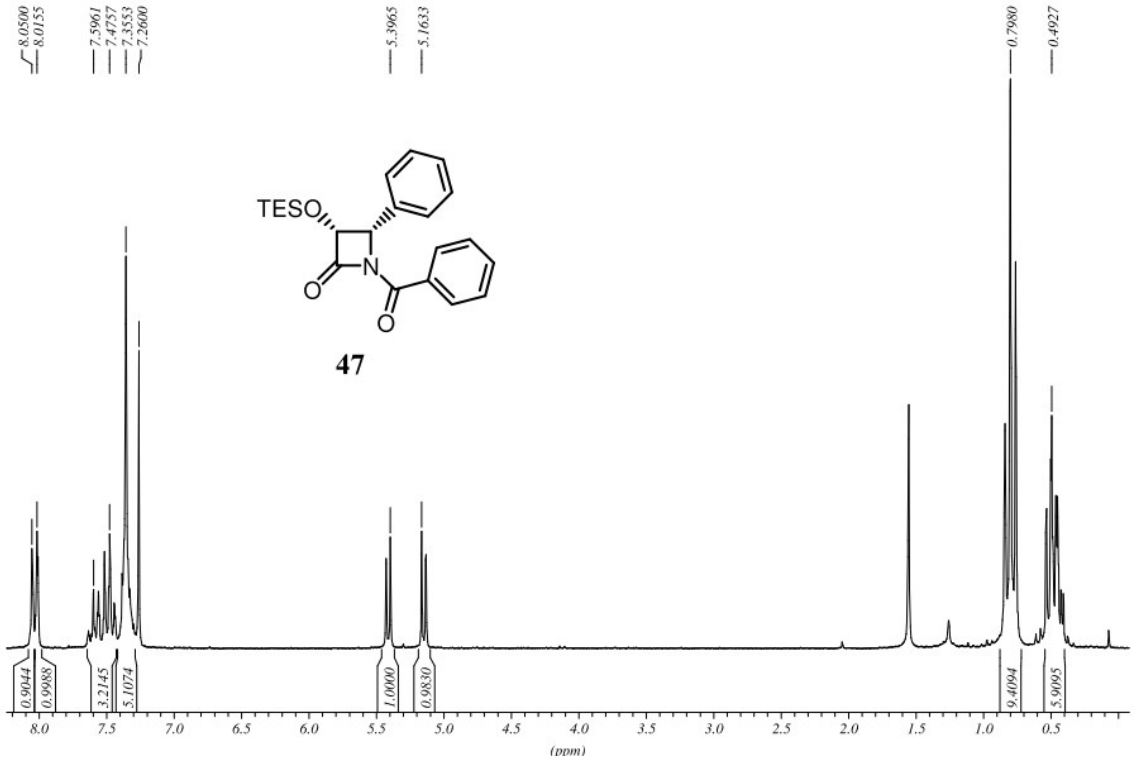
NMR spectra of compound **22** and **43**



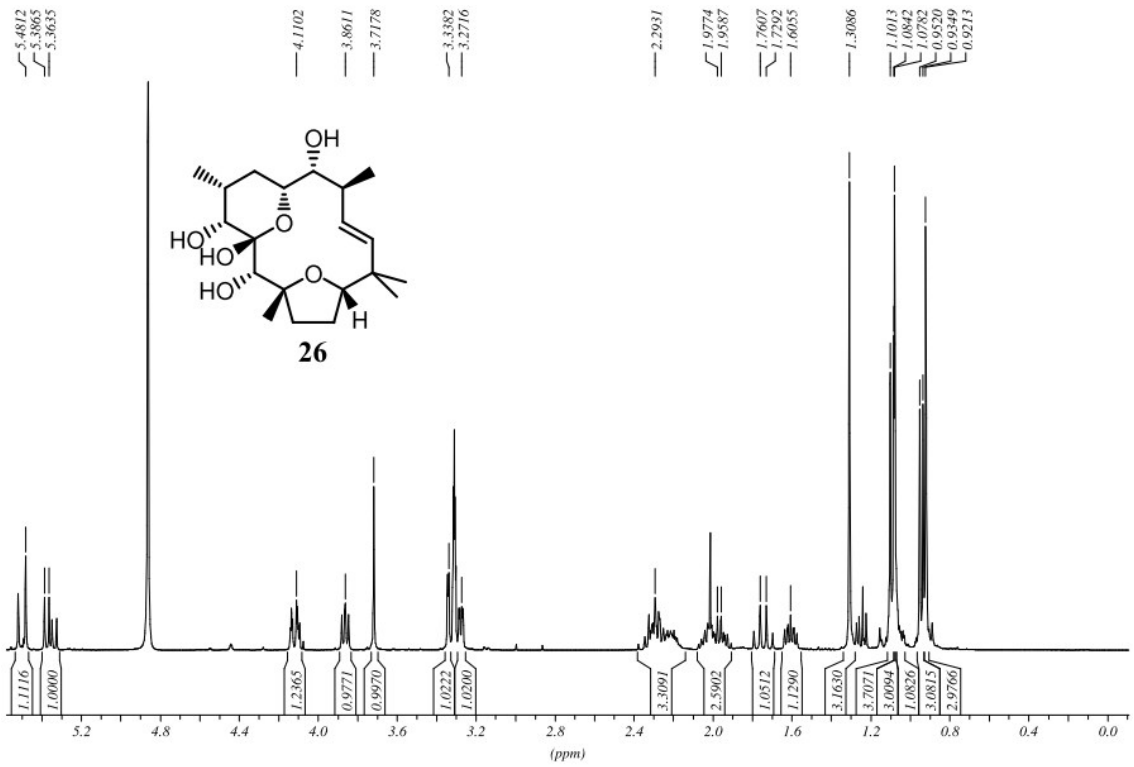


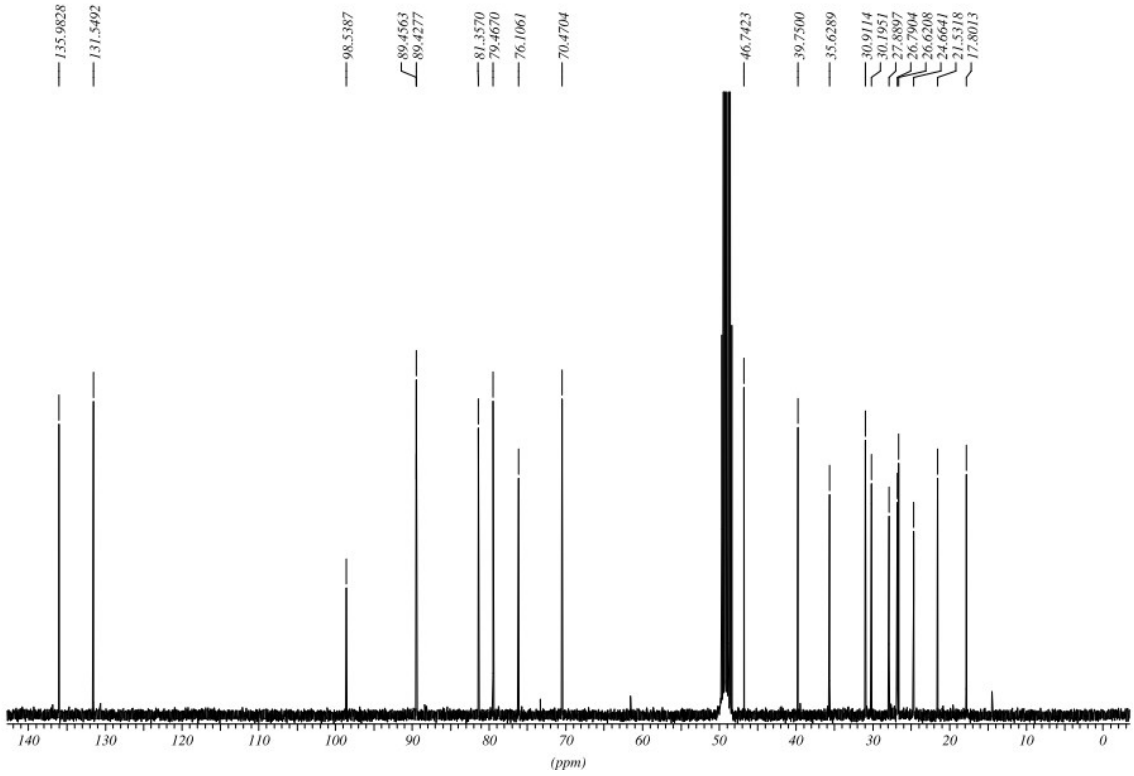
NMR spectra of compound **39** and **47**



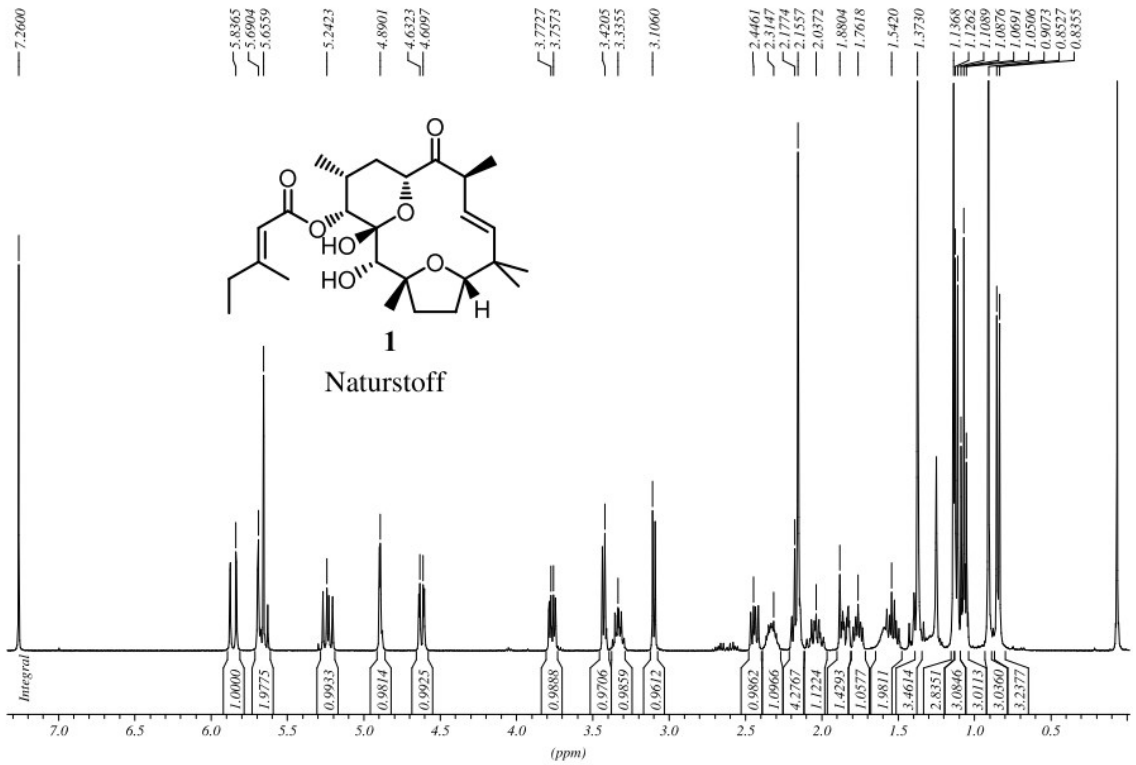


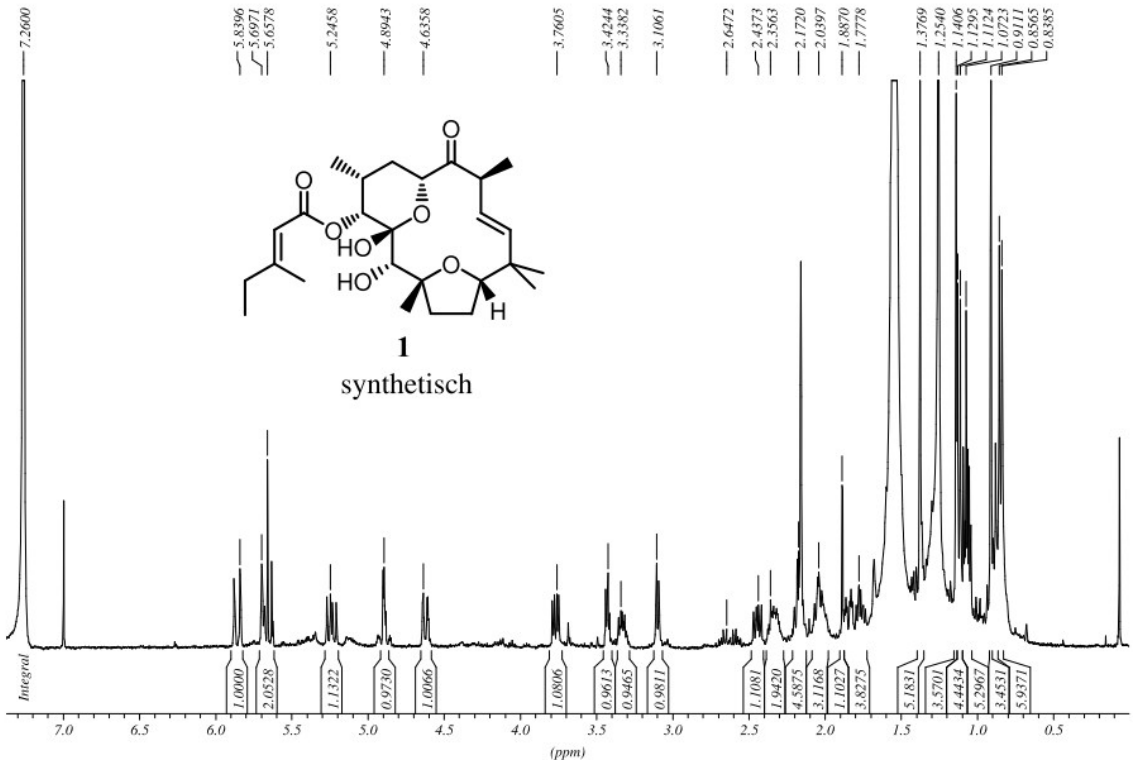
NMR spectra of compound **26**



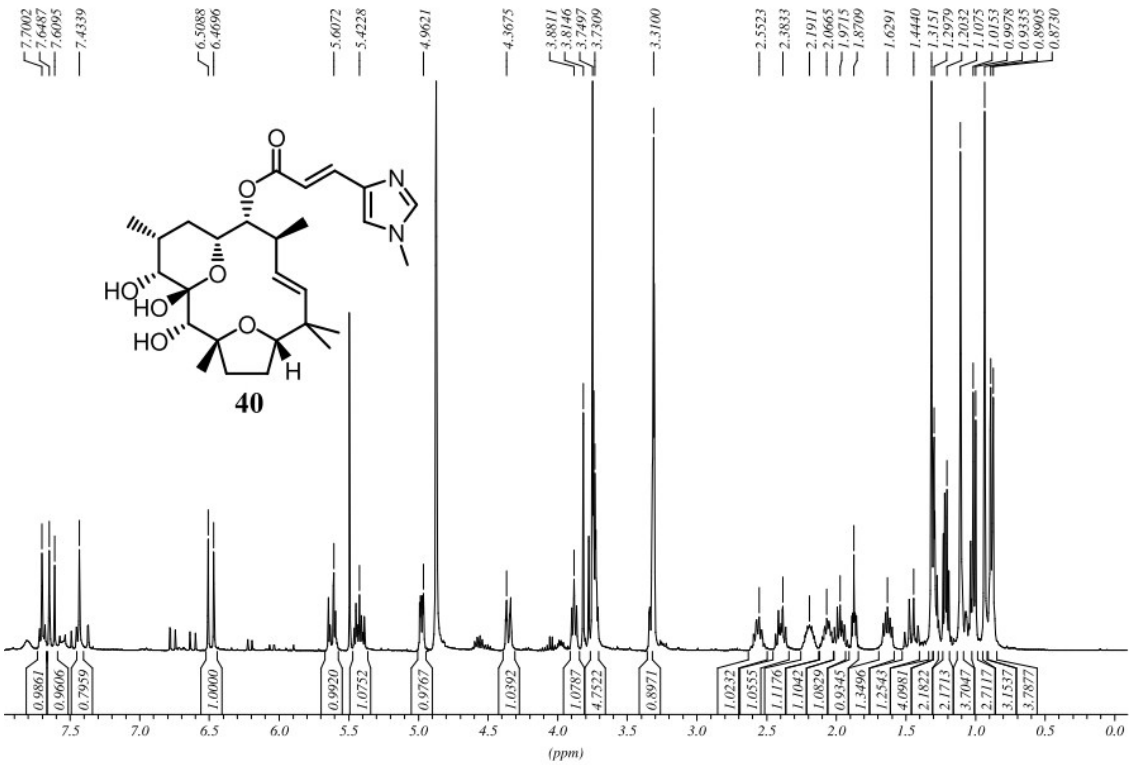


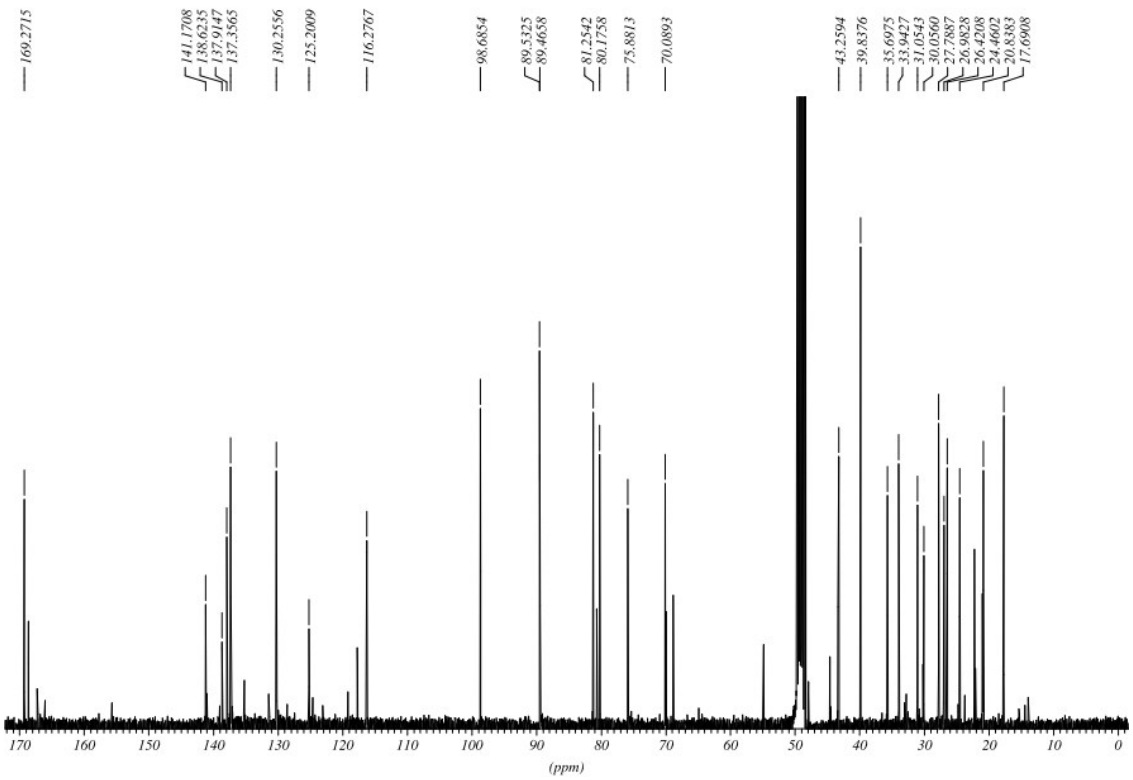
NMR spectra of compound **1** (natural source and synthetic sample)



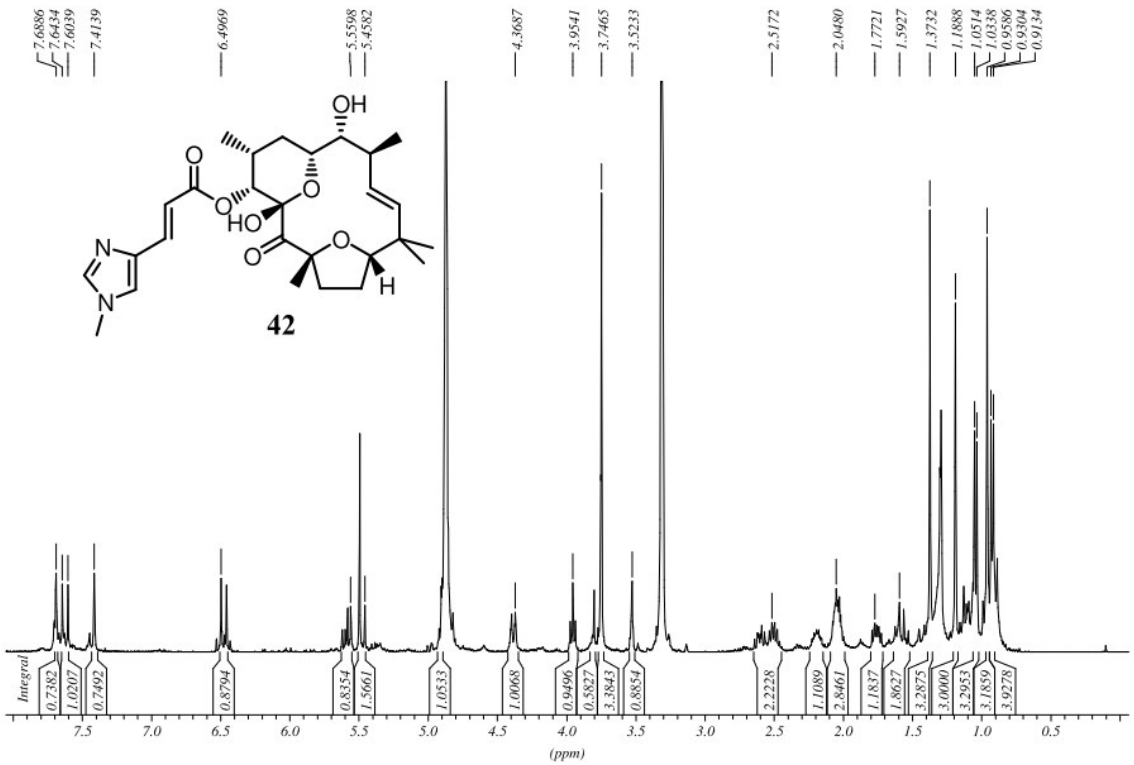


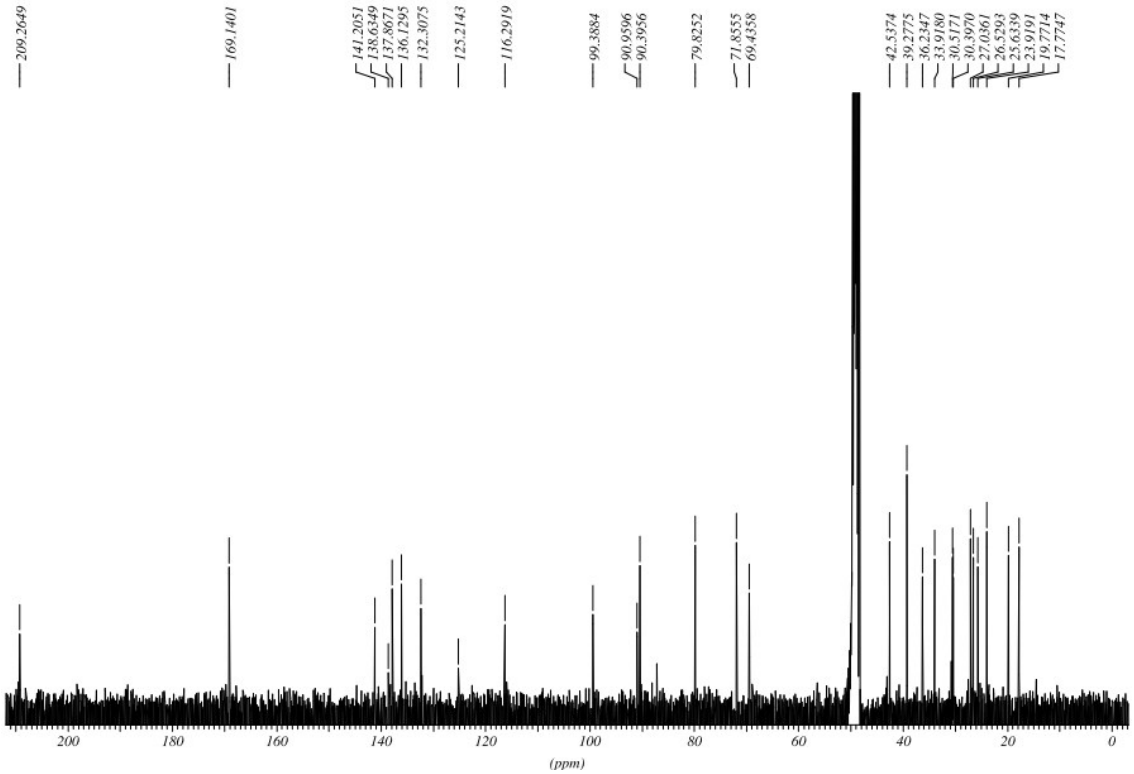
NMR spectra of compound **40**



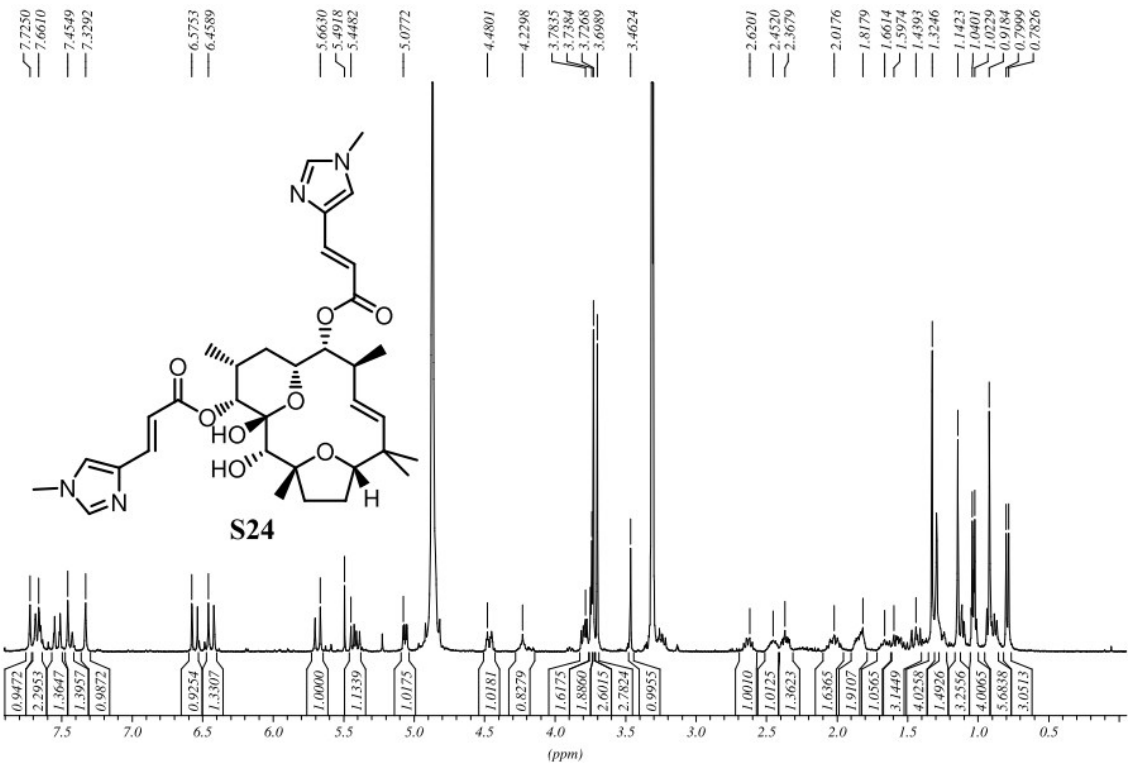


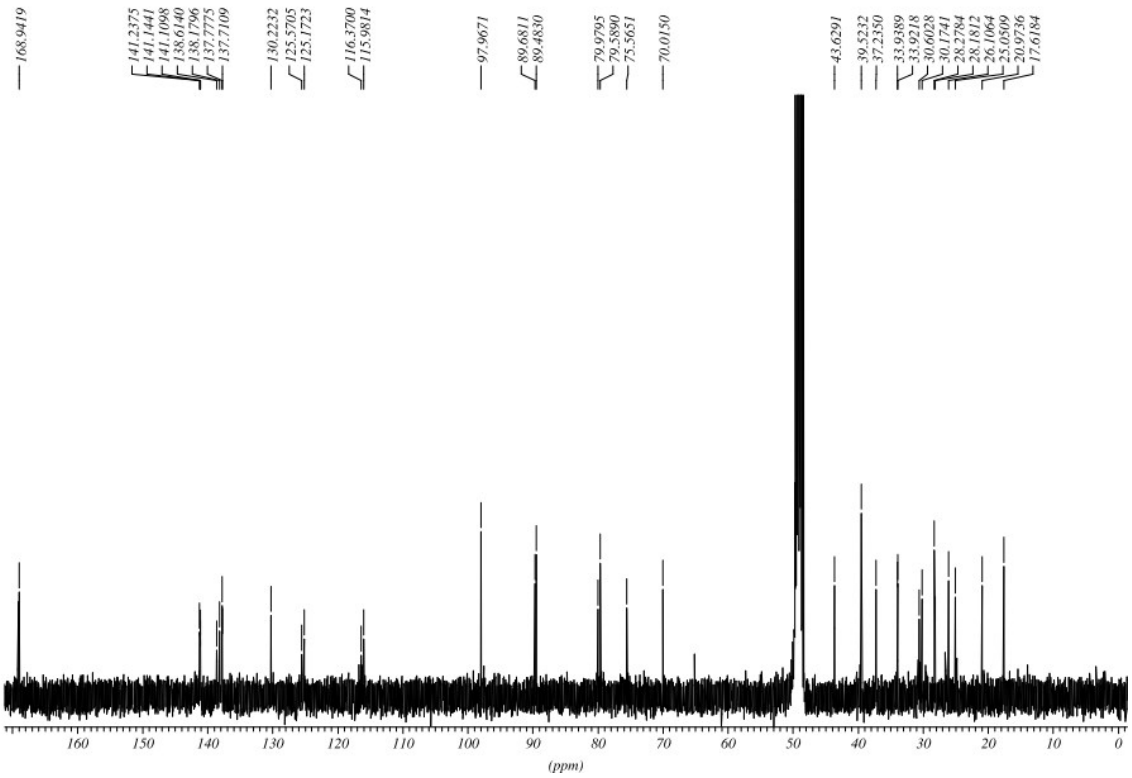
NMR spectra of compound **42**



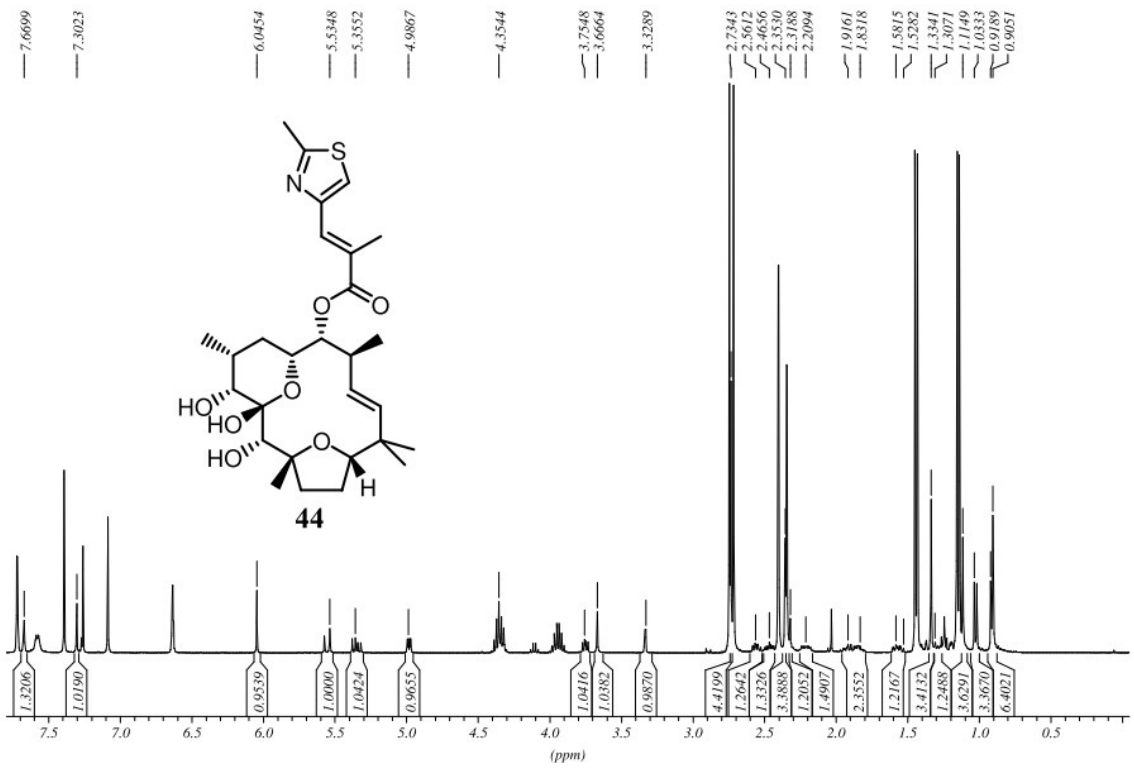


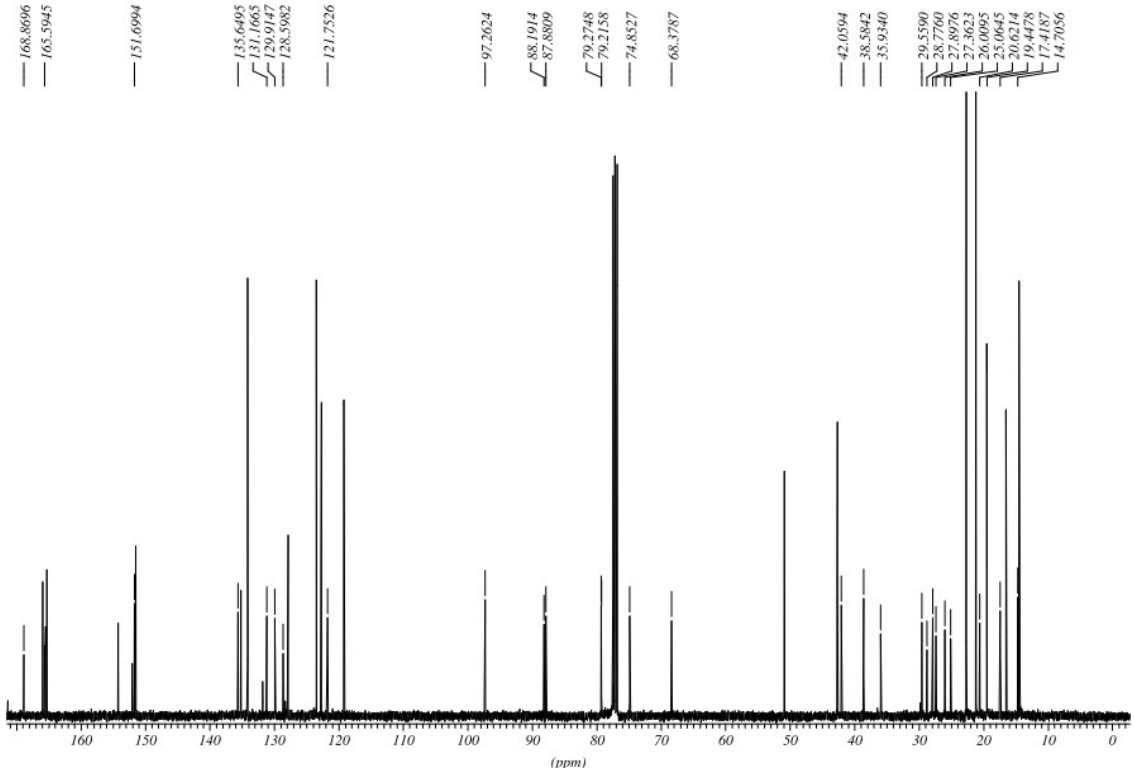
NMR spectra of compound **S24**



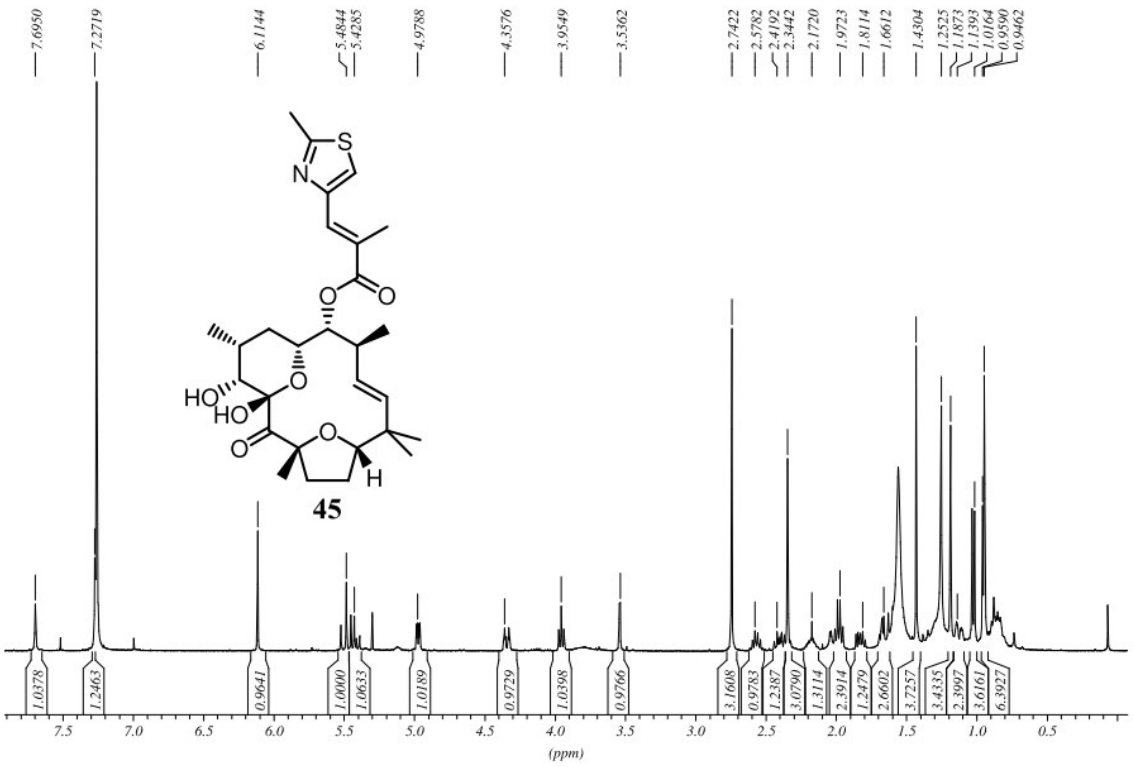


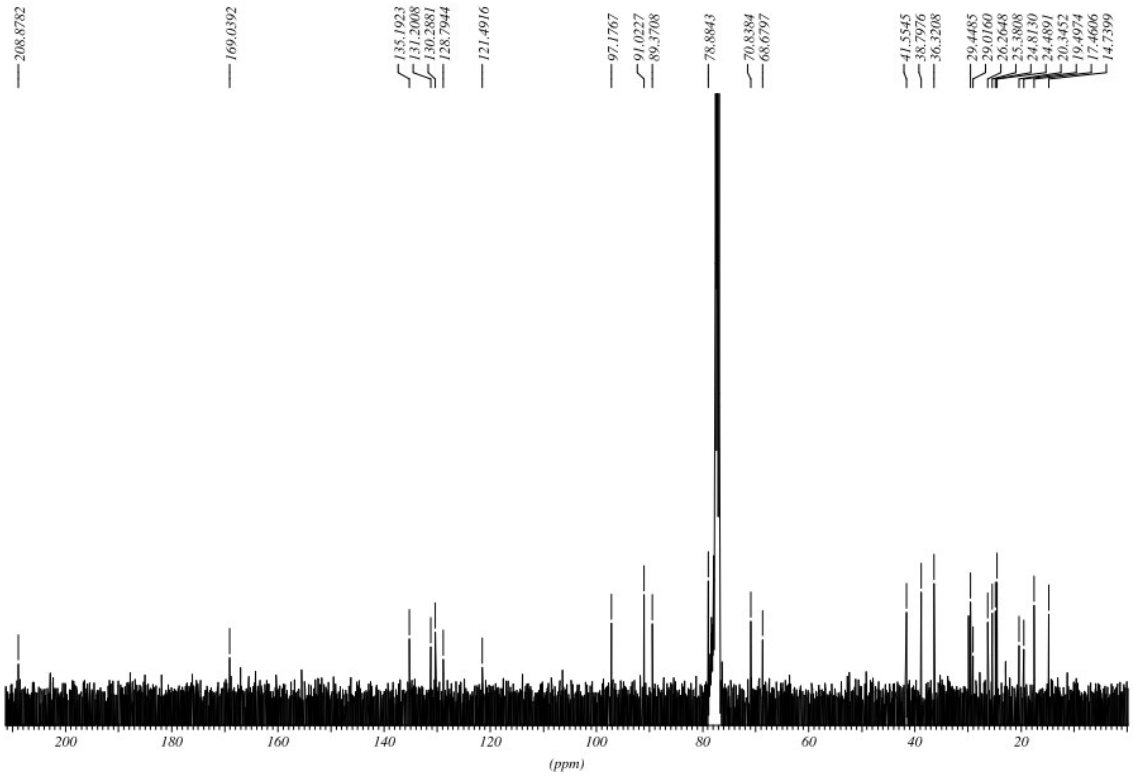
NMR spectra of compound **44**



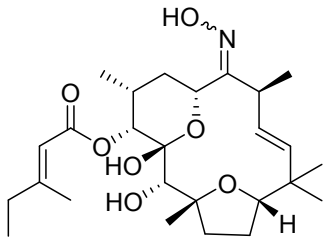


NMR spectra of compound **45**

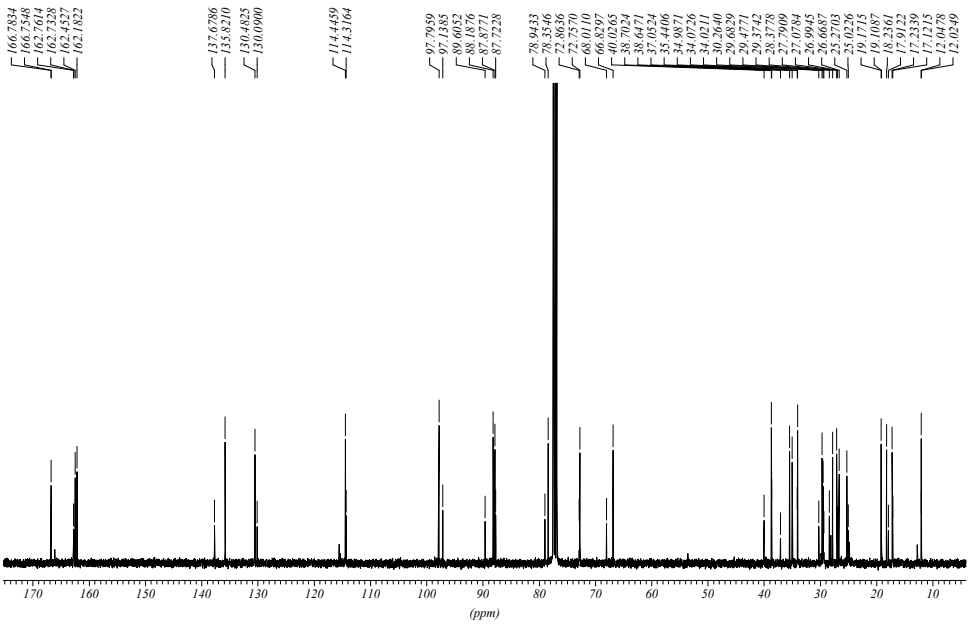




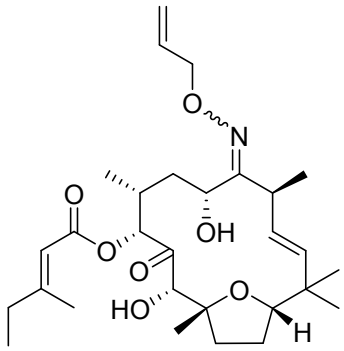
NMR spectra of compound **30a**,**b**



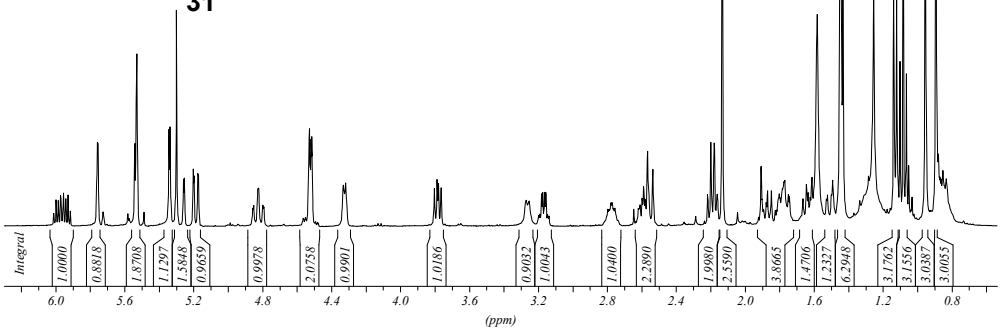
30a,b

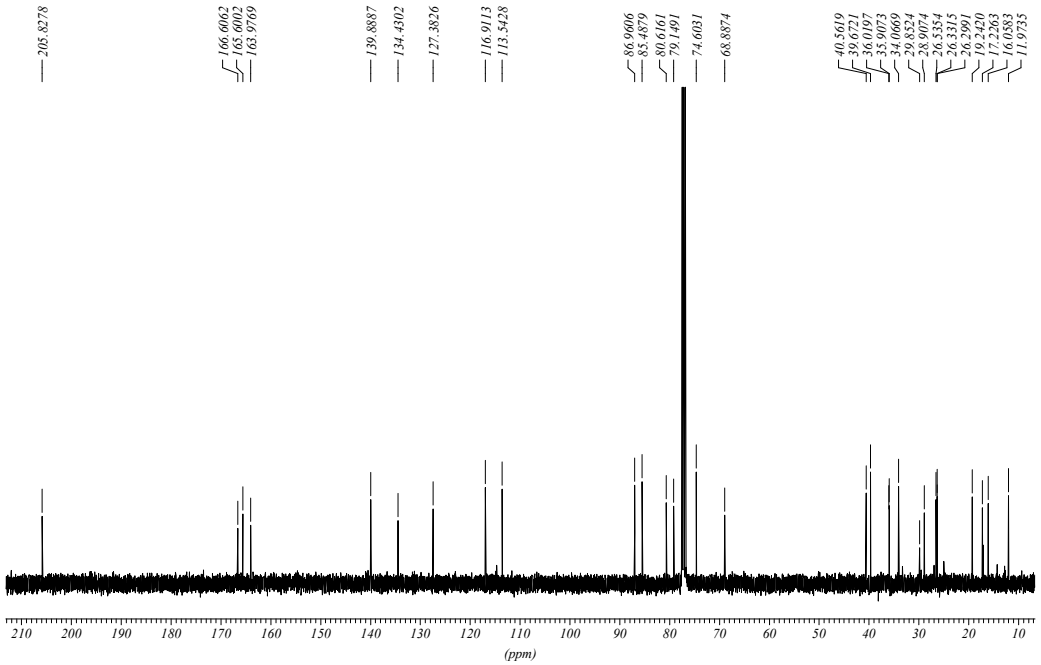


NMR spectra of compound **31**

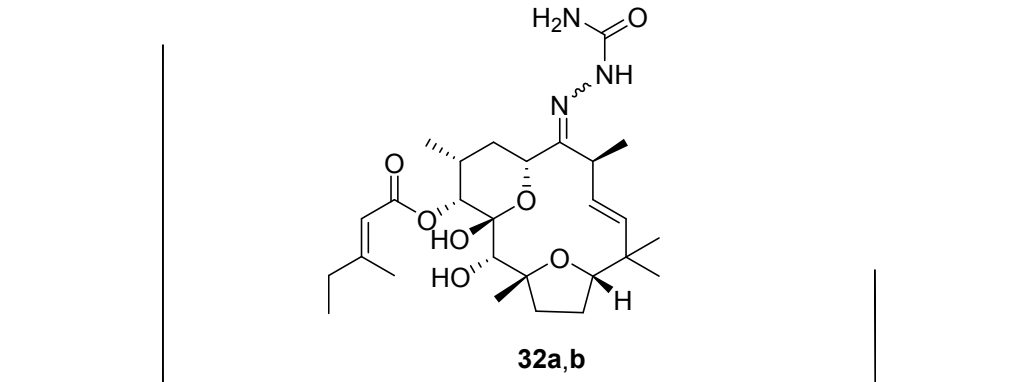


31

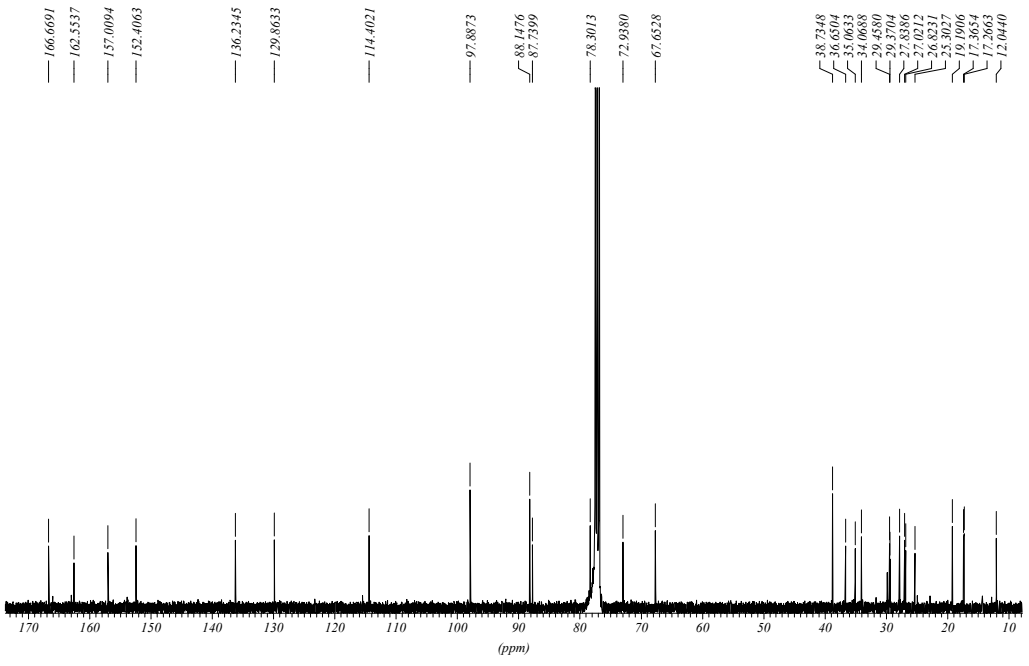




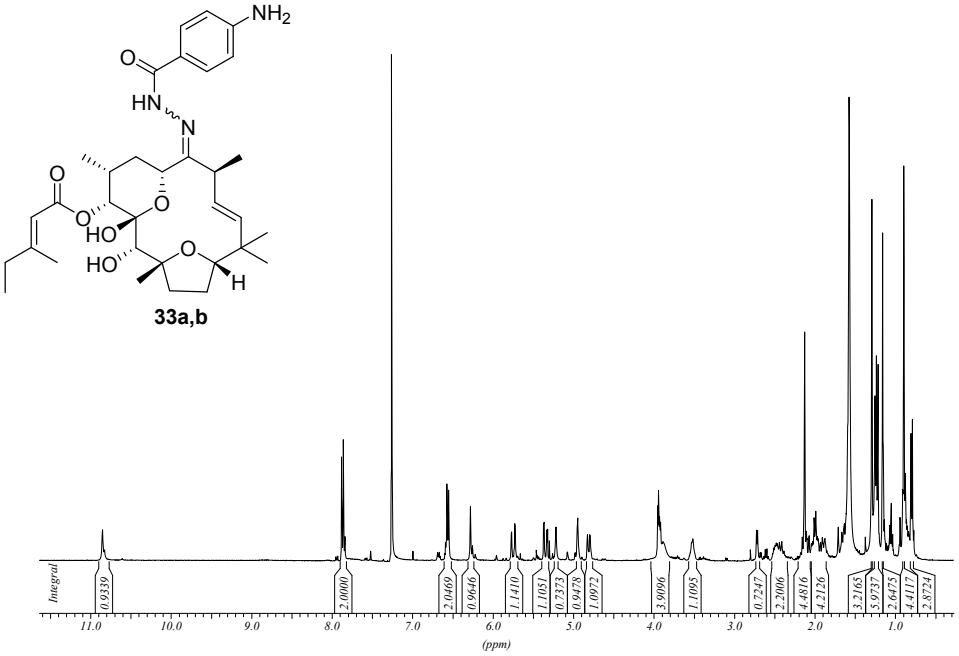
NMR spectra of compound **32a**,**b**

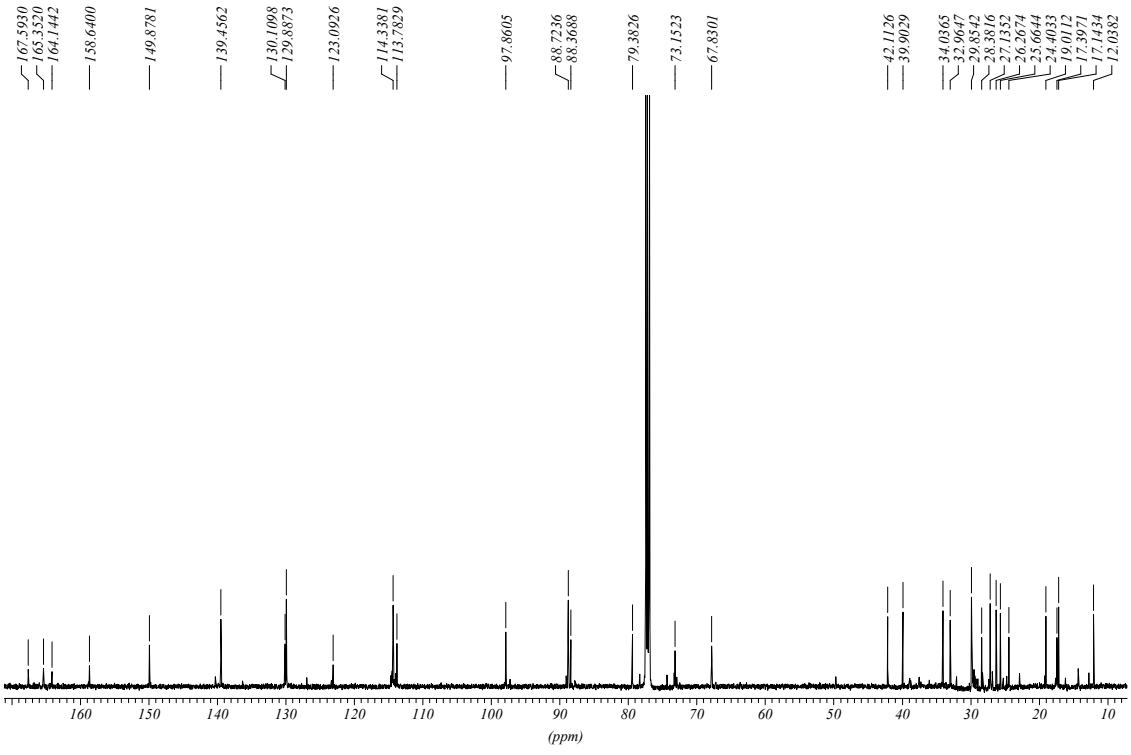


32a,**b**

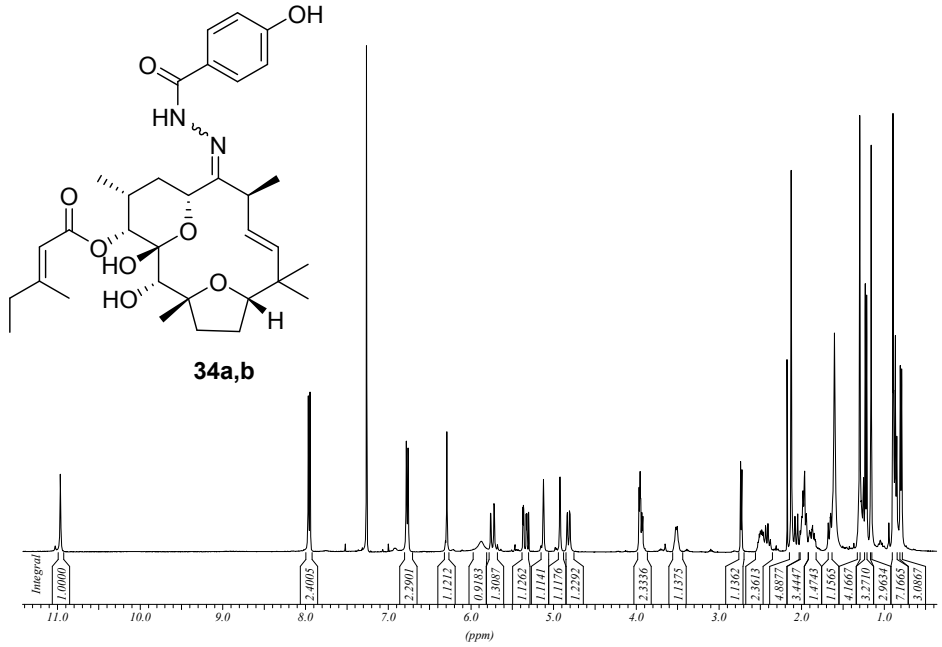


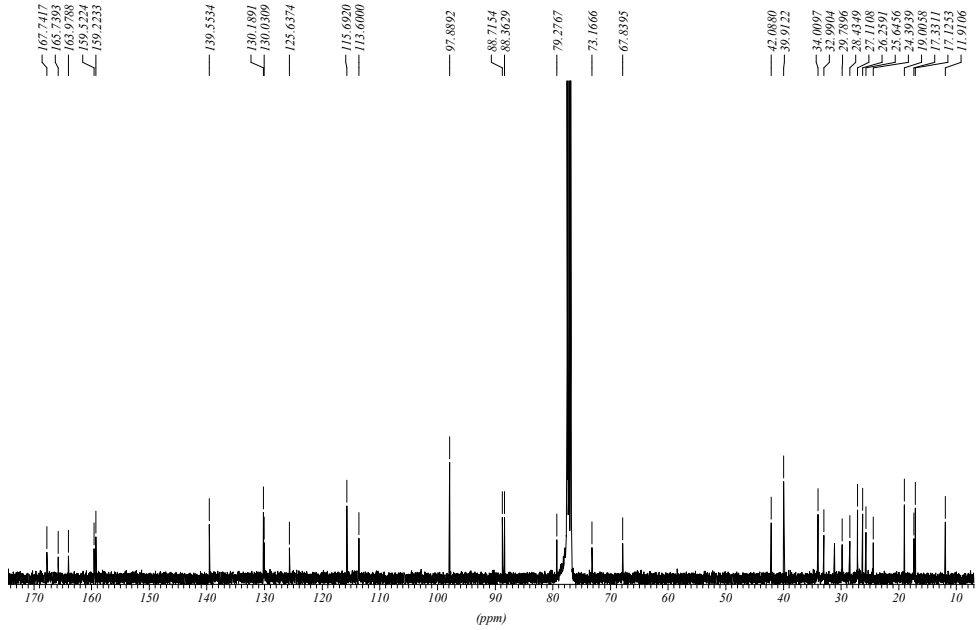
NMR spectra of compound **33a**,**b**



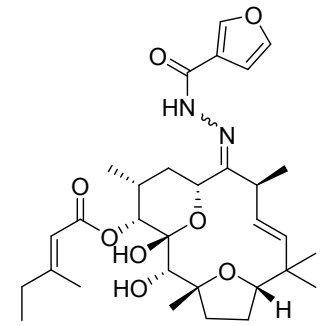


NMR spectra of compound **34a**,**b**

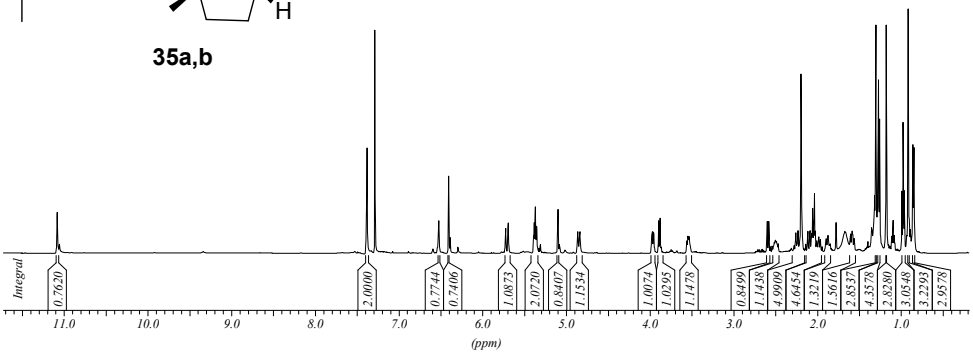


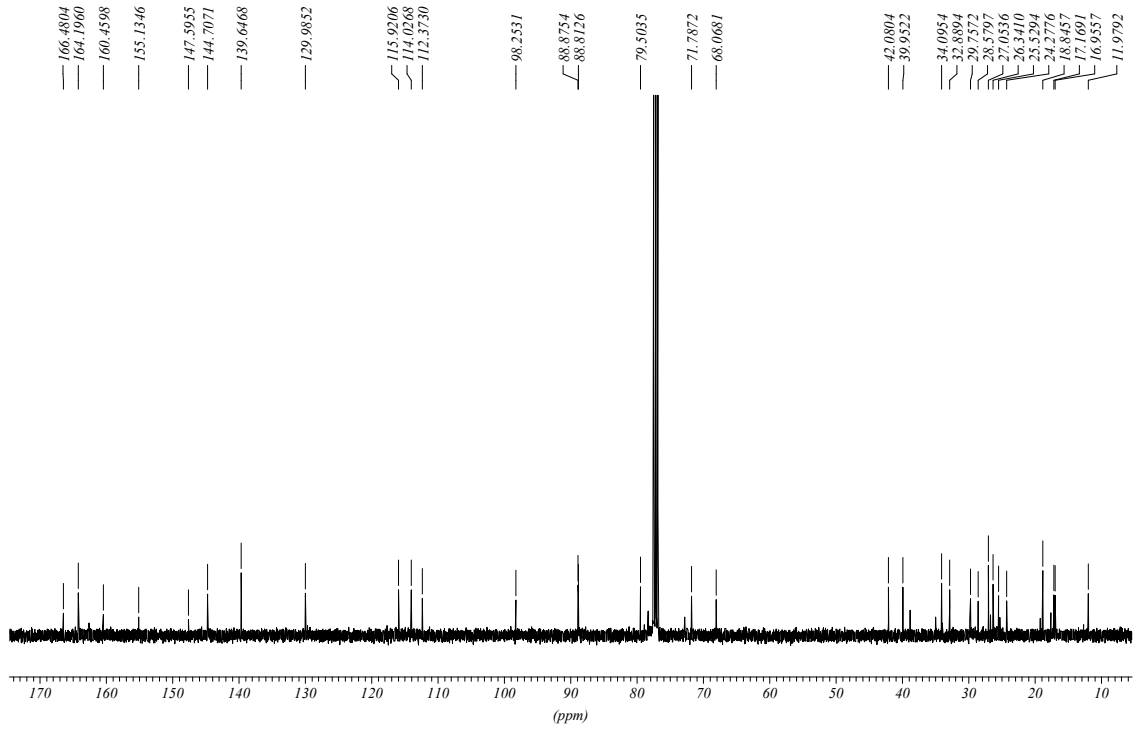


NMR spectra of compound **35a**,**b**

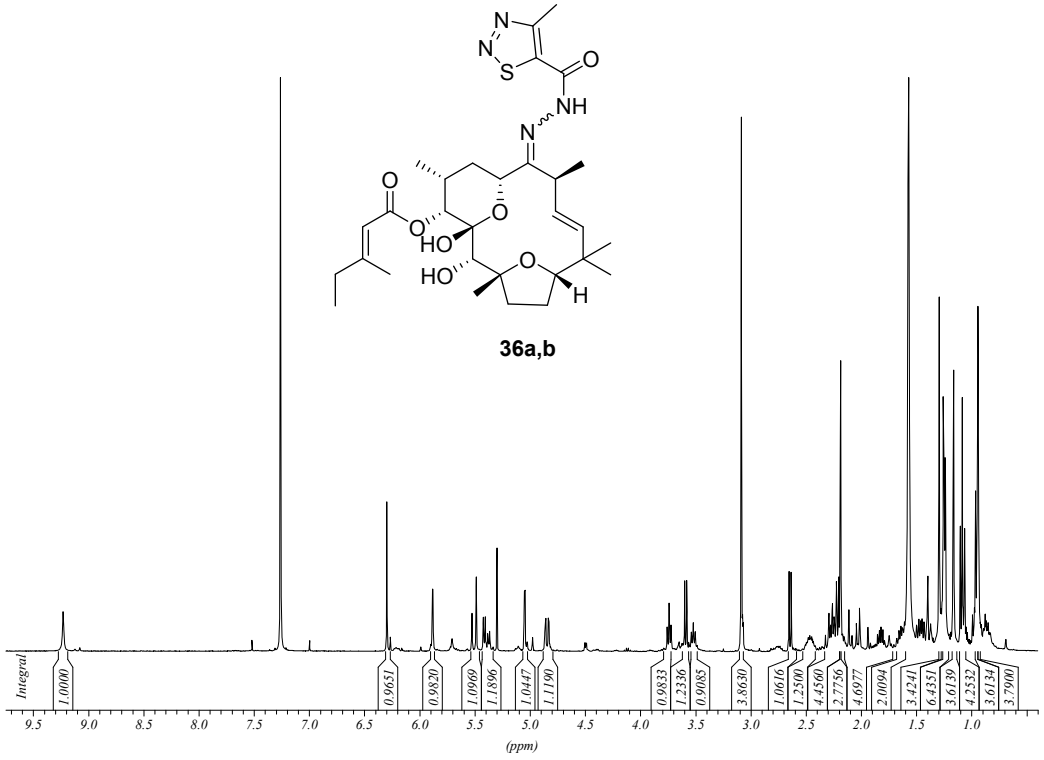


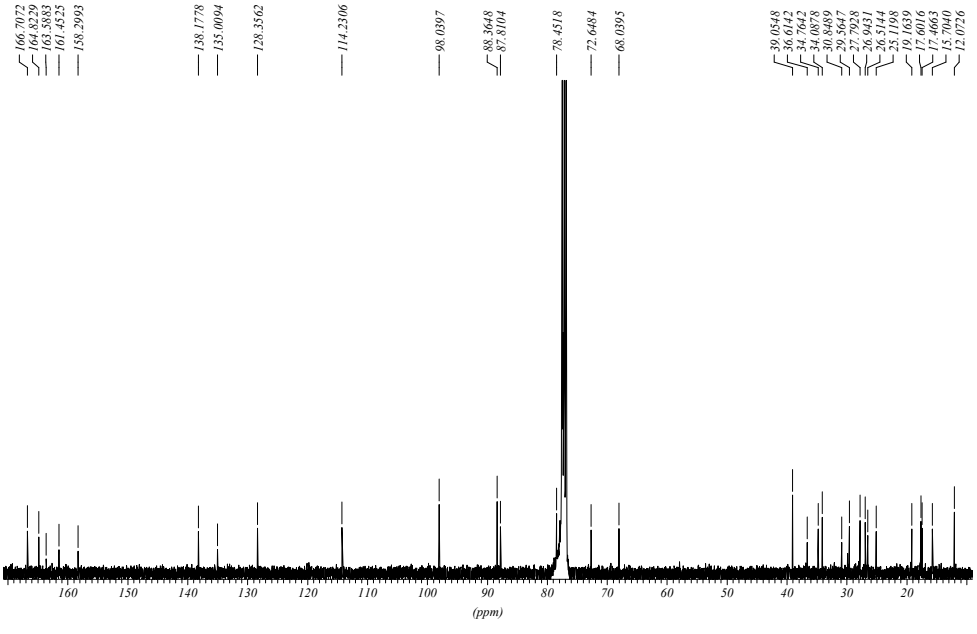
35a,b



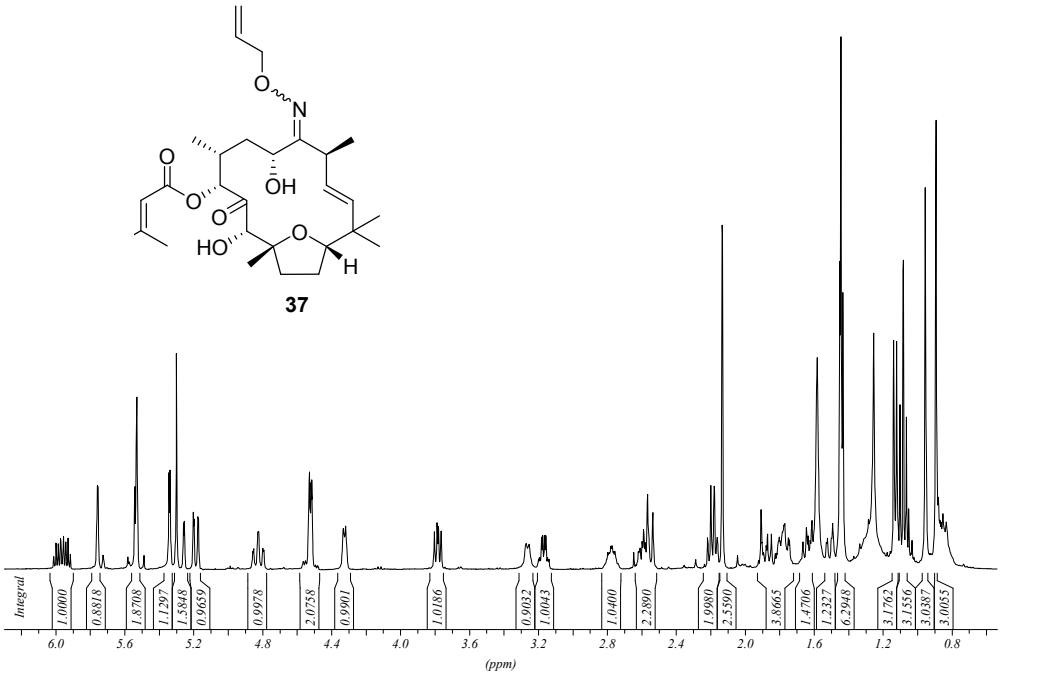


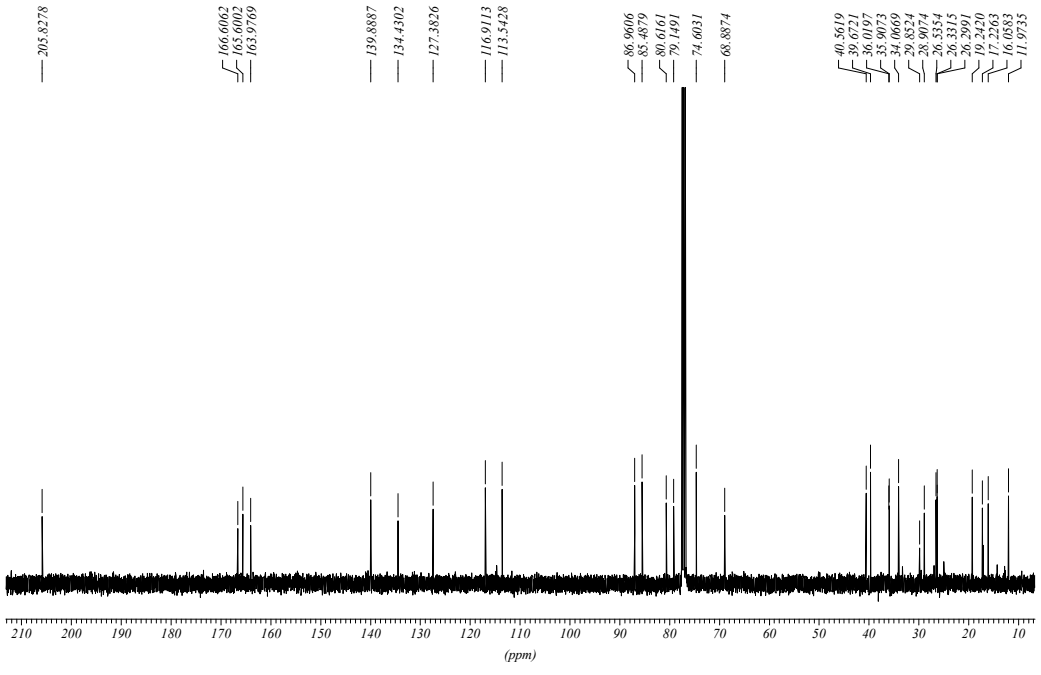
NMR spectra of compound **36a**,**b**



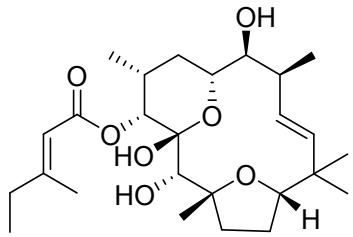


NMR spectra of compound **37**

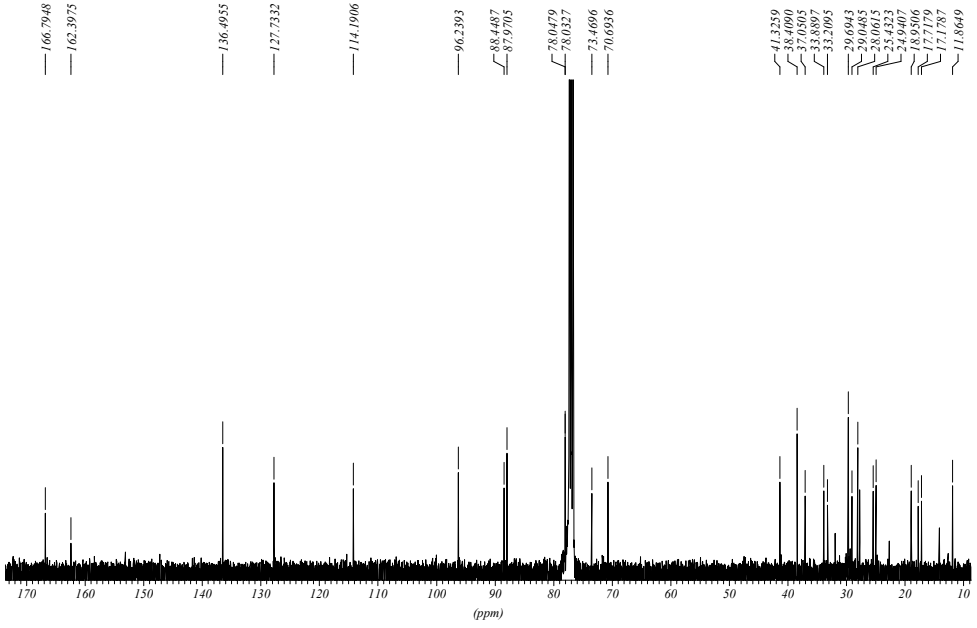




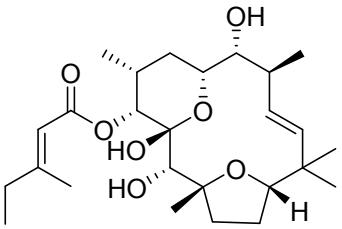
NMR spectra of compound **38**



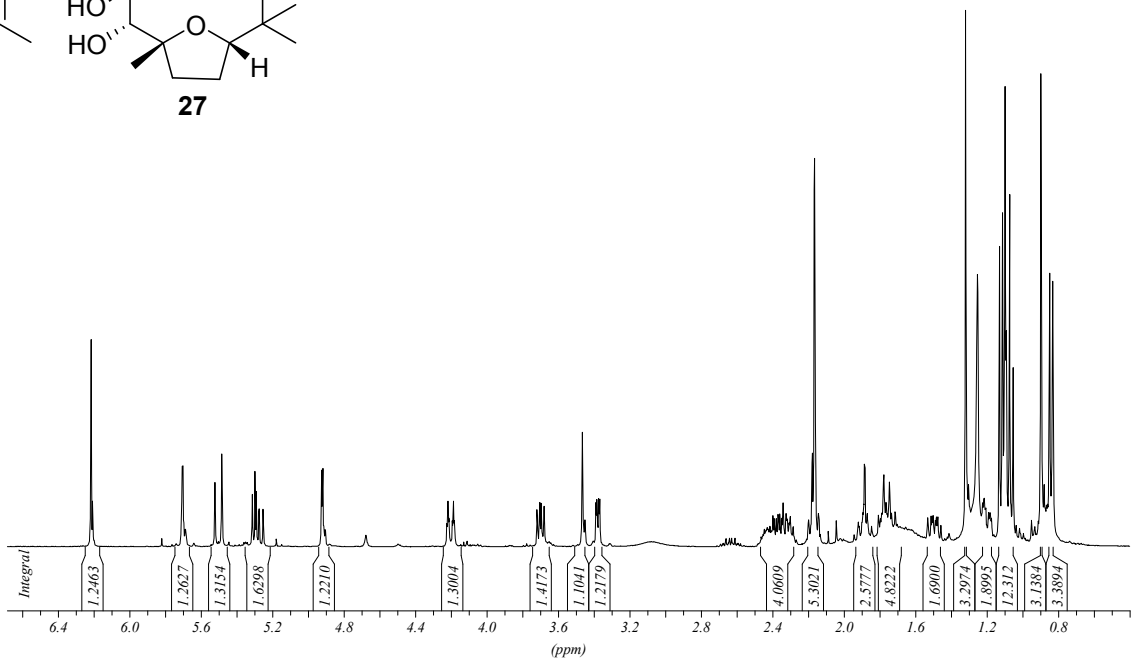
38

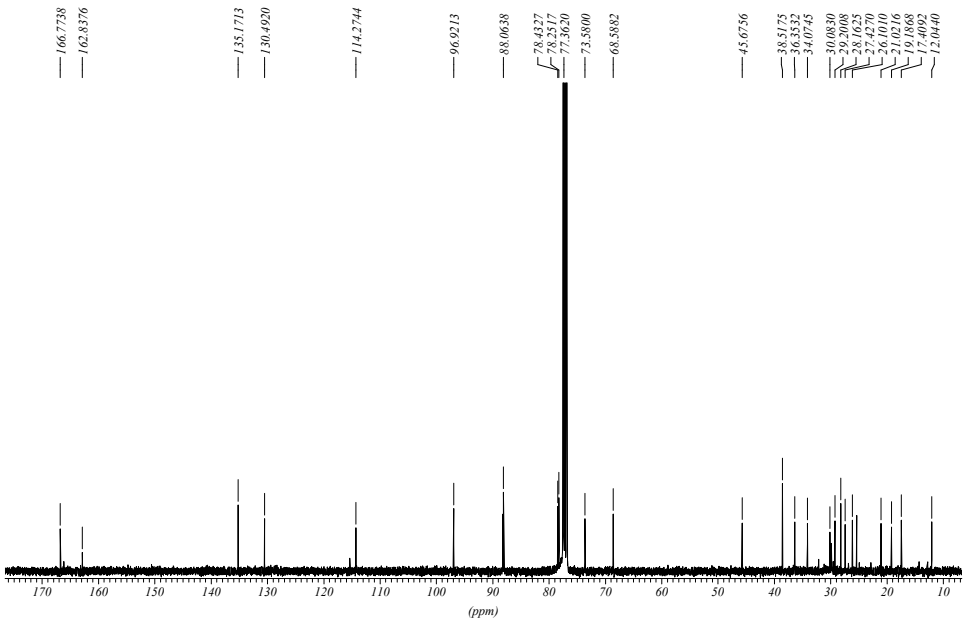


NMR spectra of compound **27**

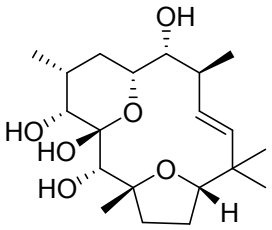


27

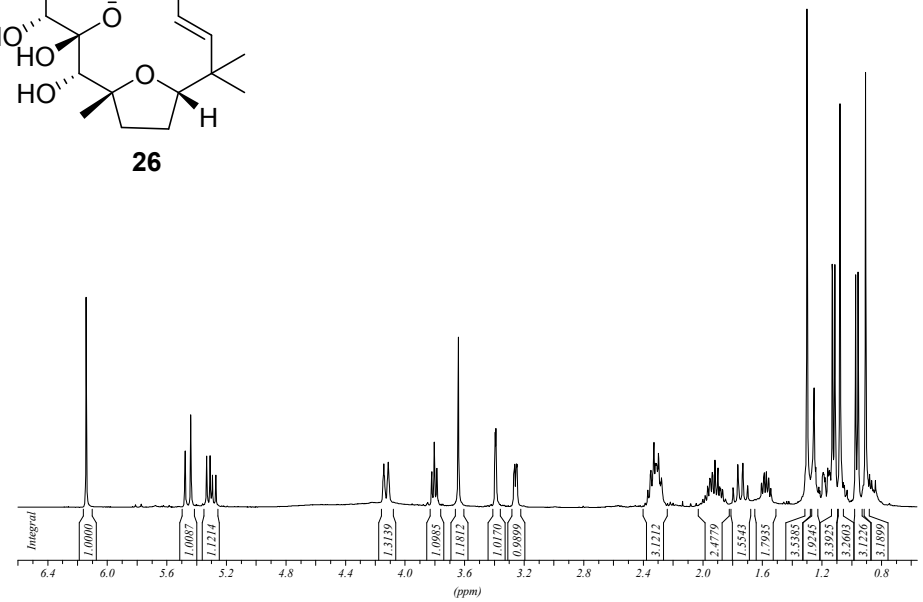


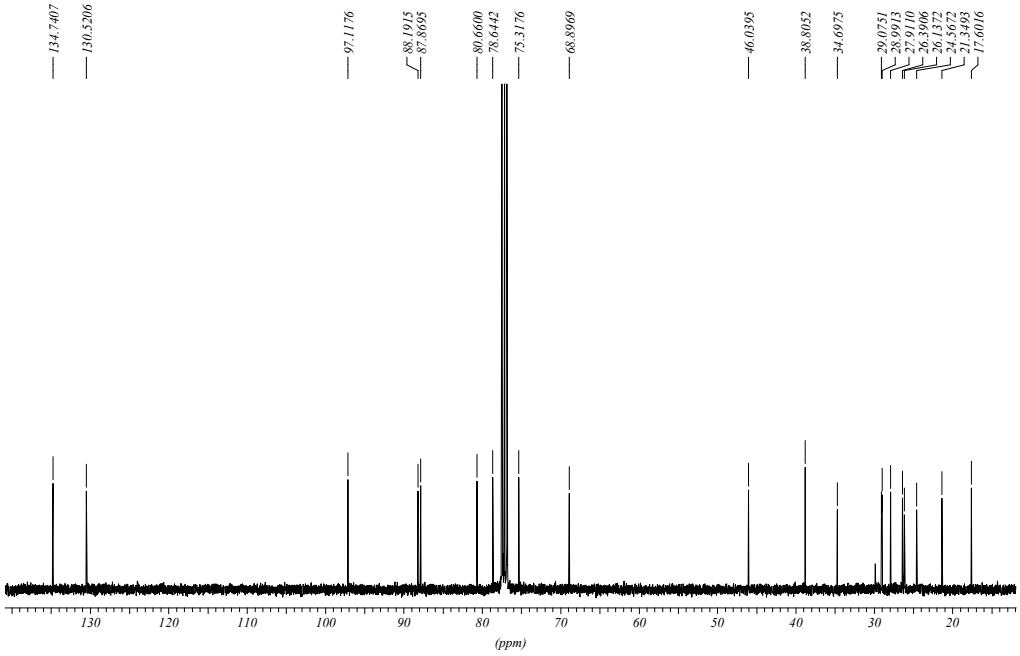


NMR spectra of compound **26**

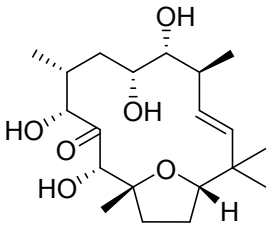


26





NMR spectra of compound **25**



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