Expanding the antibacterial selectivity of polyether ionophore antibiotics through diversity focused semi-synthesis

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Supplementary Information

Supplementary Figures

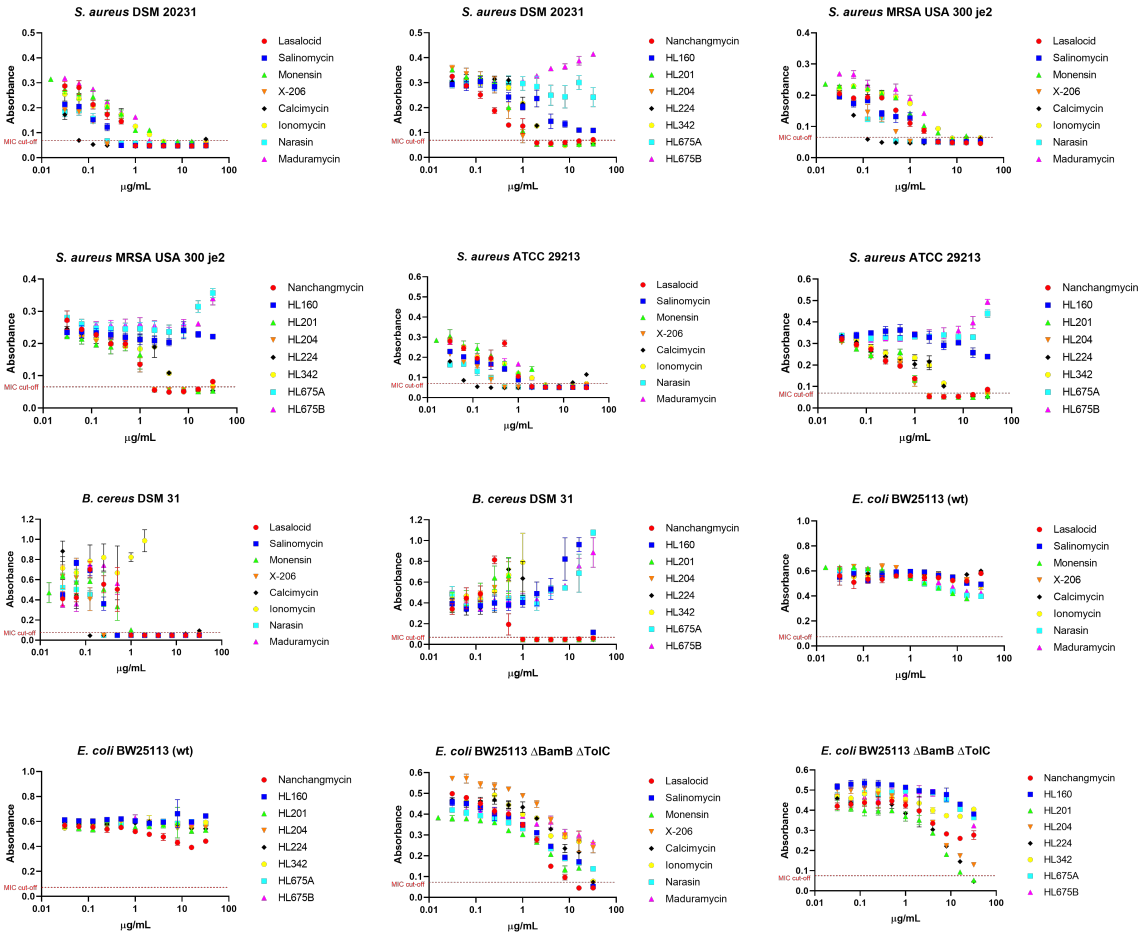


Fig. 1. Representative response curves for MIC determination in *S. aureus* DSM 20231, *S. aureus* MRSA USA 300 je2, *S. aureus* ATCC 29213, and *B. cereus* DSM 31. Bacteria with the density $5x10^5$ CFU/mL were treated with serial dilutions of compounds in DMSO in 96-well microtiter plates for 20-24 hours at 37 °C. The MIC values were determined from absorbance measurements at 600 nm where absorbances below 0.07 indicates complete inhibition of bacterial growth. For *B. cereus* DSM 31, pellicle formation was observed resulting in the large standard deviations and high absorbance values for concentrations with growth. The control, vancomycin, is omitted from the plots. Individual data points are mean ± s.d. (N = 3, independent wells). Error bars smaller than the symbol size are not drawn. For the complete MIC data set, see Supplementary Table 1.

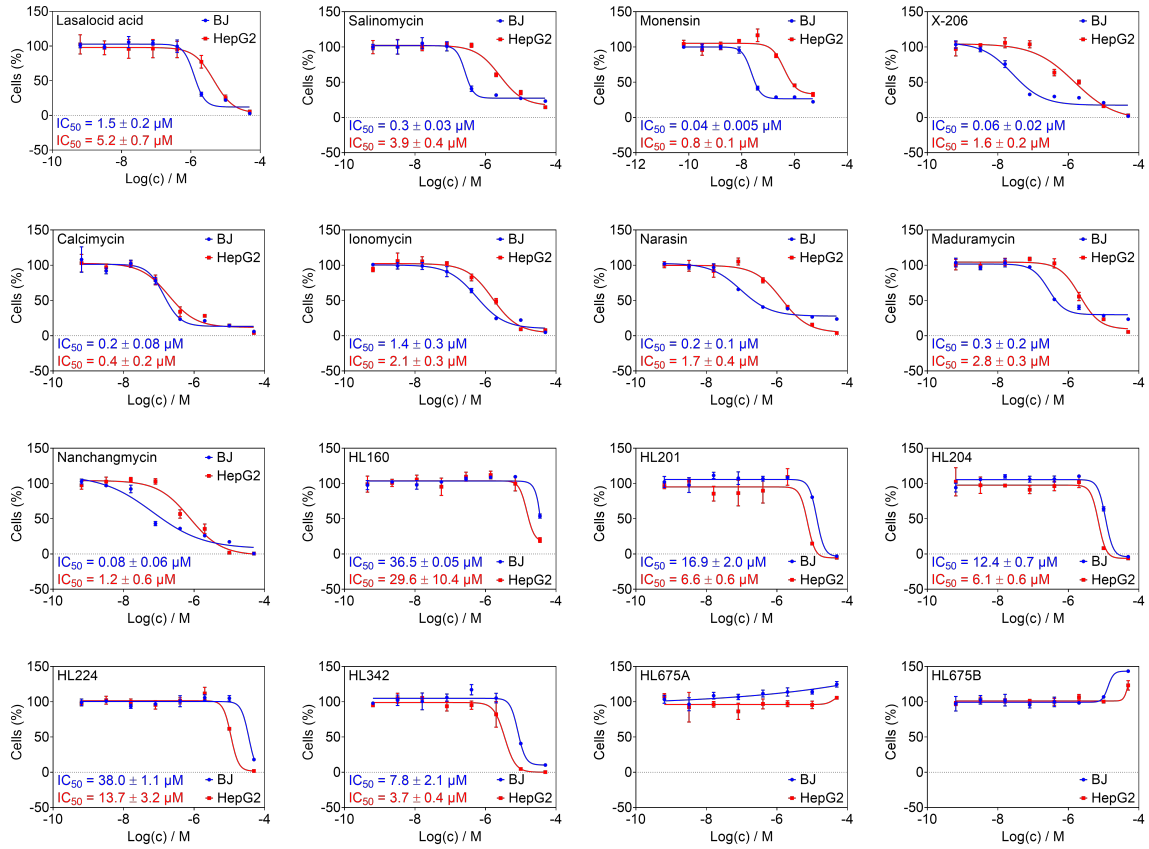


Fig. 2. Representative dose response curves in HepG2 and BJ cells after 48 h of treatment. Cells were seeded in 96-well plates (HepG2: 2000 cells/well and BJ: 1500 cells/well). Twenty-four hours after seeding cells were treated with serial dilutions of compounds in DMSO for 48 hours. The viability was determined by adding CellTiter Blue (20 µL/well, Promega, Cat#: G8081) to each well in the final 1.5 hours of incubation and ultimately quantifying viability as a measure of fluorescence in a Tecan SPARK 10M plate reader (552 ± 10 nm excitation; 598 ± 10 nm emission). Individual data points on the plots are mean ± s.d. (N = 3, independent wells). Error bars smaller than the symbol size are not drawn. The IC_{50} values listed on the graphs are mean ± s.d of two independent biological determinations for all compounds except ionomycin, which are mean ± s.d of three independent biological determinations. For the complete cell viability data in mammalian cell lines, see Supplementary Table 1.

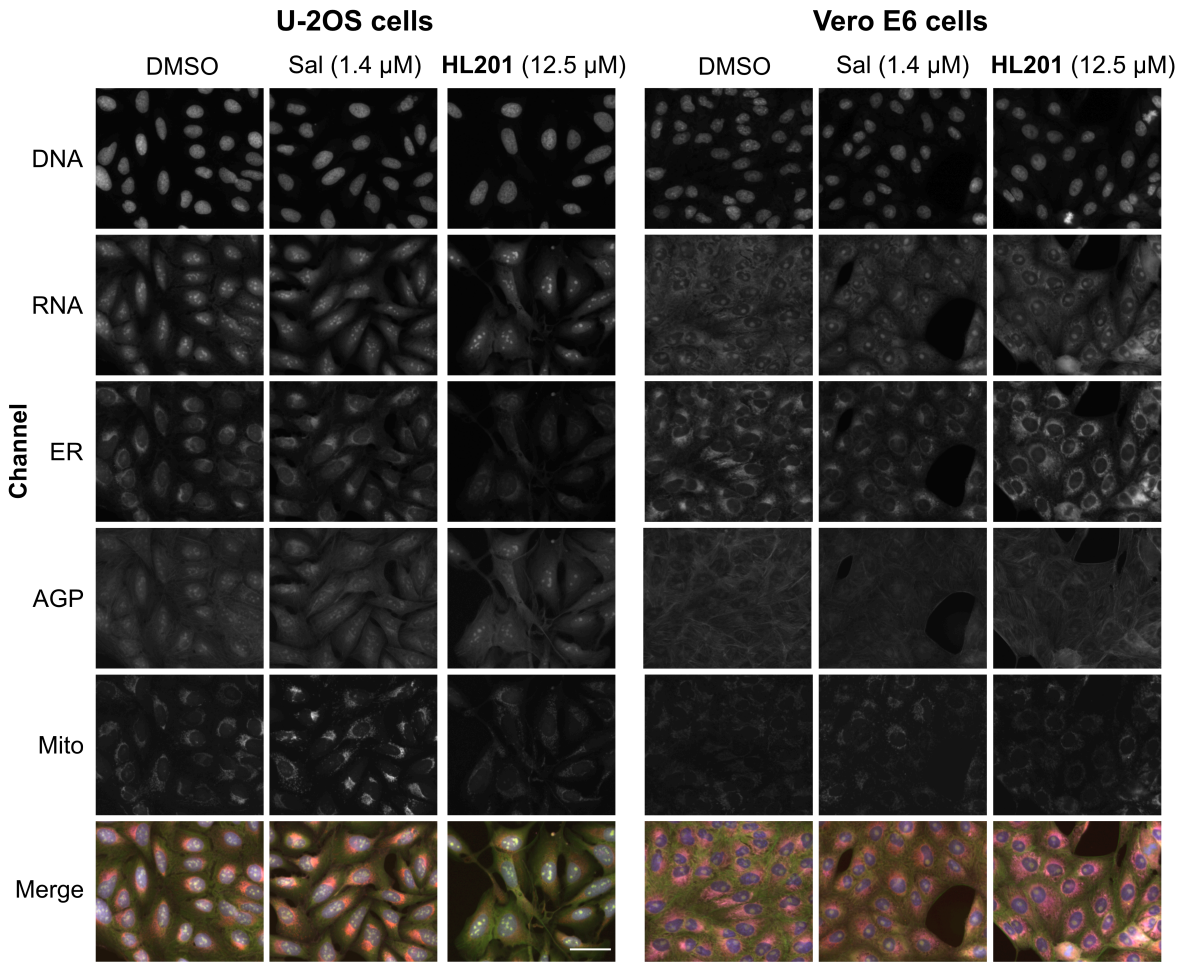


Fig. 3 Representative crops of images from the morphological profiling. Images are shown for DMSO treatment, 1.4 µM Salinomycin and 12.5 µM **HL201** treatment. Scalebar: 50 µM. See the methods section for description of fluorophores in the different channels. Merge: DNA (blue), RNA (yellow), ER (magenta), AGP (green), Mito (red). Images were acquired at 9 sites in each of four distinct wells for each biological replicate (36 images per treatment). Images are shown in the full dynamic range.

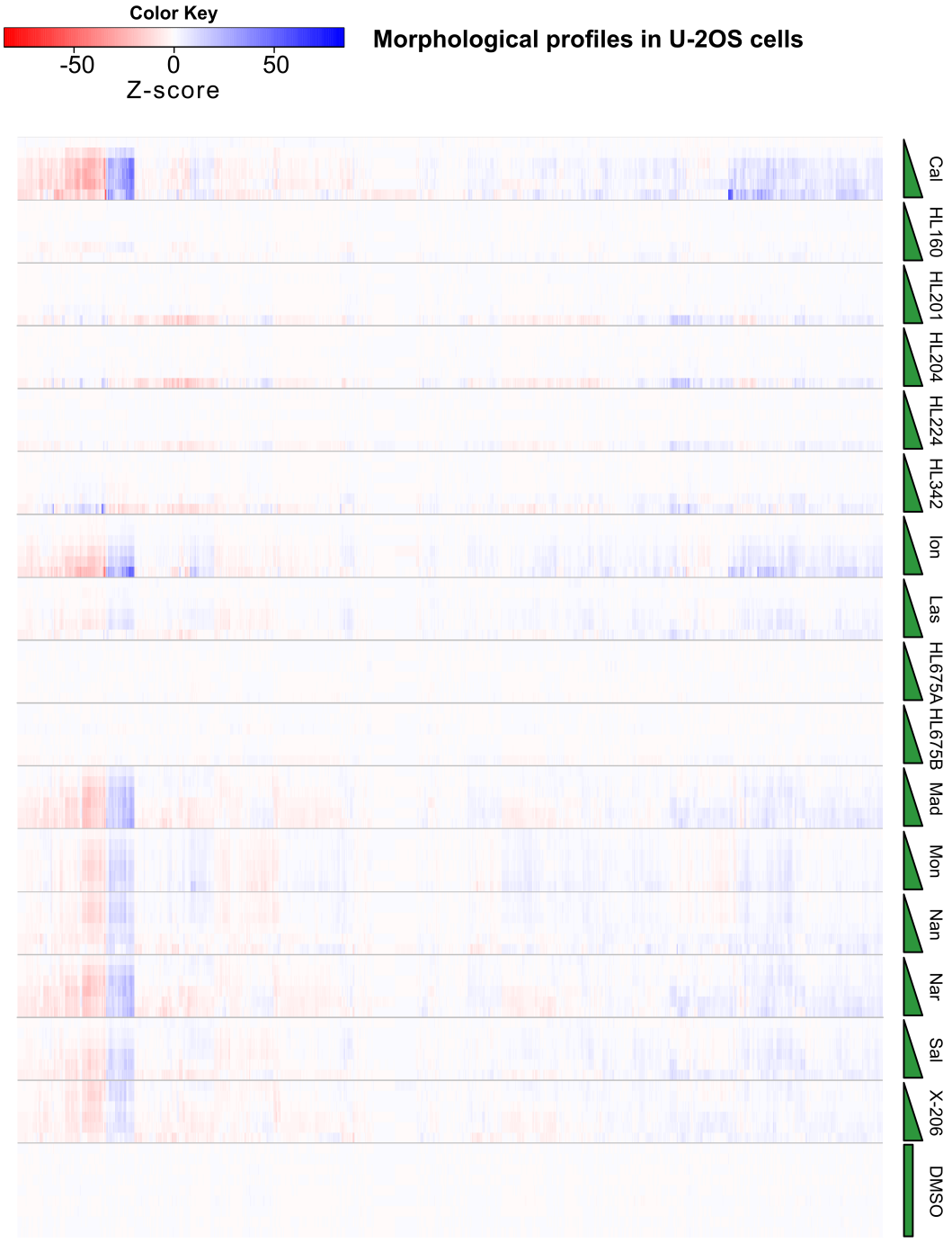


Fig. 4 Heatmap of morphological profiles in U-2OS cells. Compounds are dosed as a 6-point 3-fold dilution series starting from 12.5 µM, except monensin (Mon) which starts at 4.2 µM.

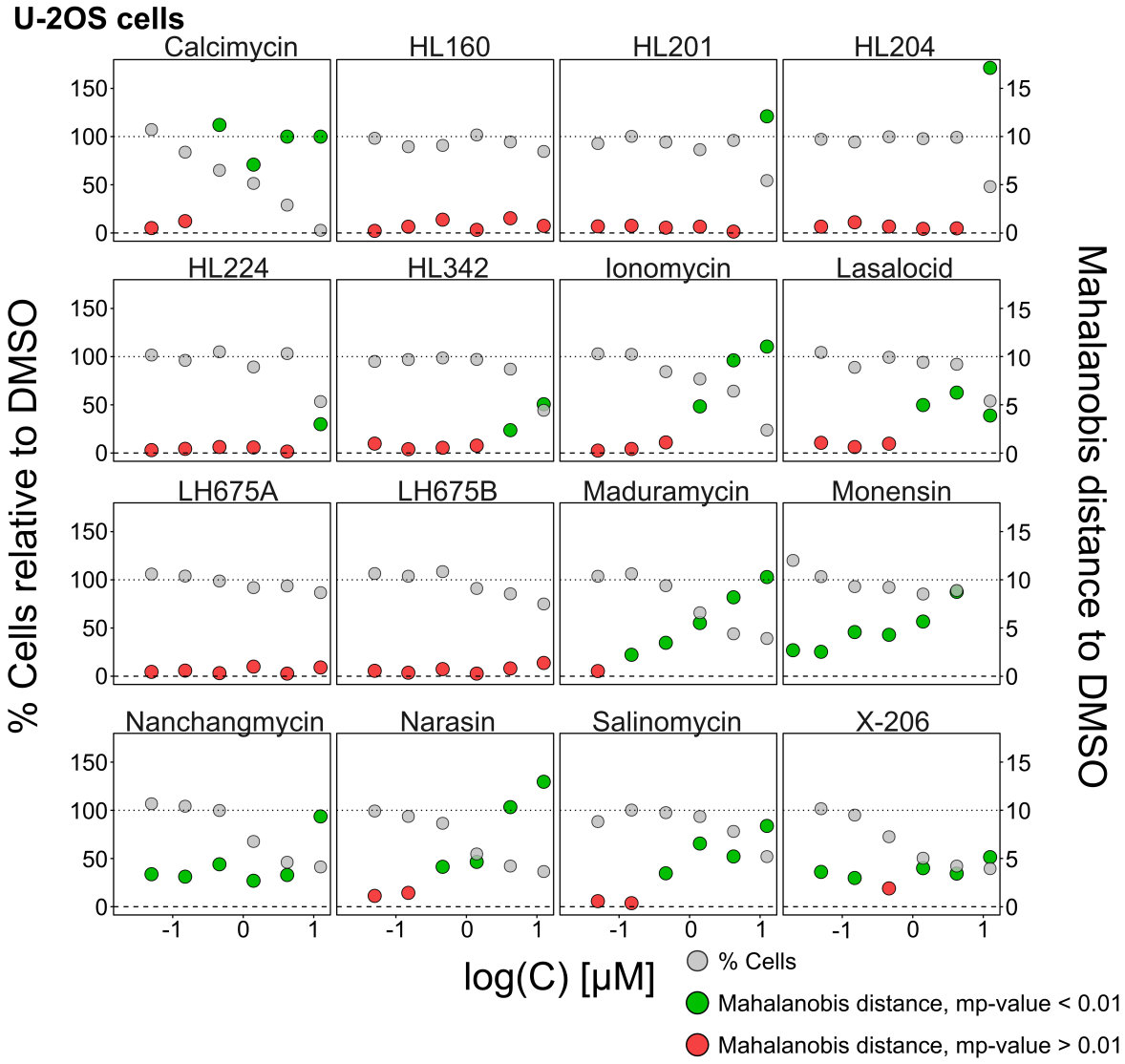


Fig. 5 Cell counts and Mahalanobis distances from morphological profiling in U-2OS cells. The points for the Mahalanobis distance are coloured based on the mp-value. Active profiles are observed for most ionophores before a significant drop in cell viability is observed while activities for synthetic ionophores are accompanied with a decrease in viability. Note that X-206 at 0.46 µM falls below the activity threshold, but the profile is still contained in the "high concentration" cluster in Supplementary Fig. 6.

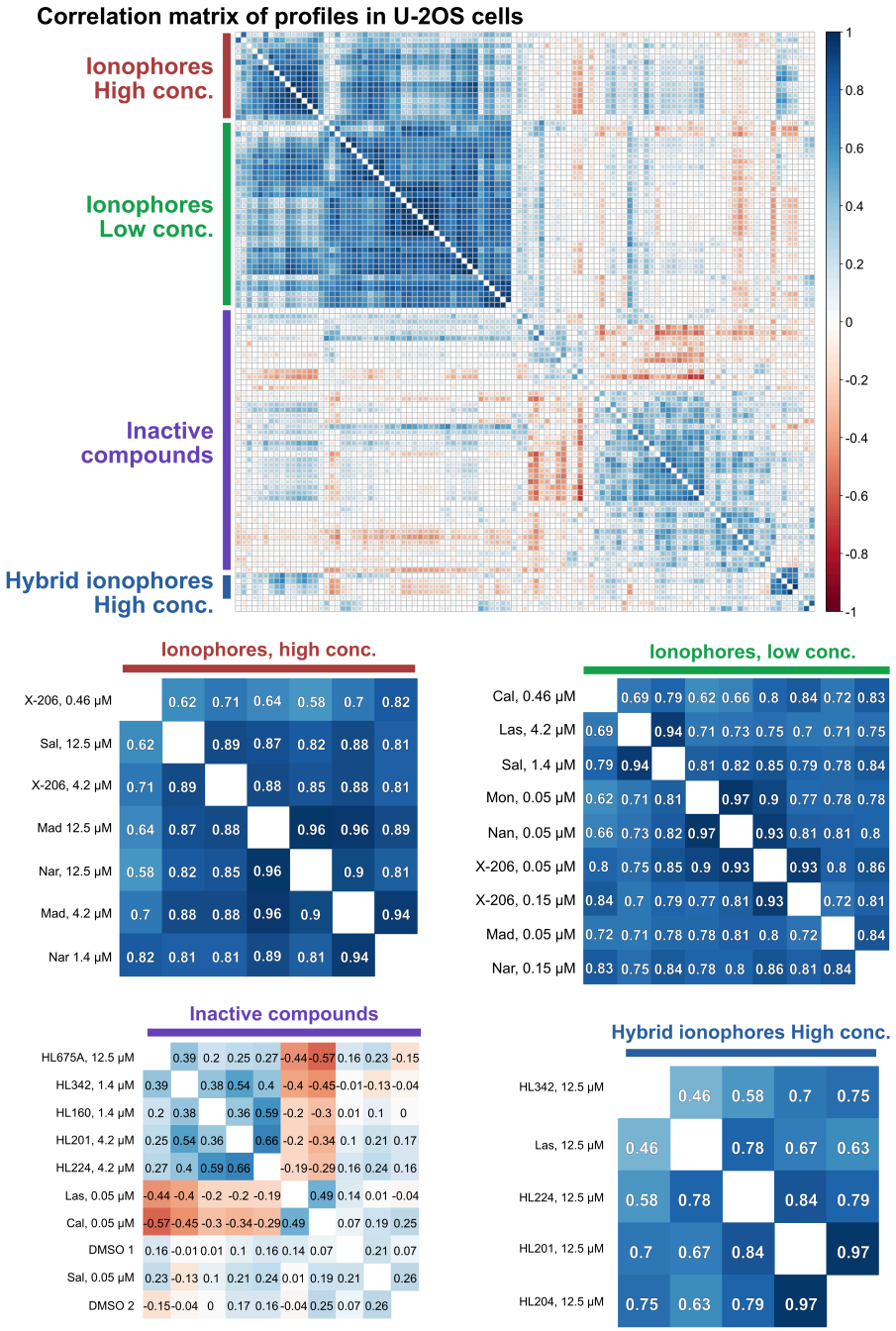


Fig. 6. Top: Correlation matrix (pearson correlations) for all morphological profiles in U-2OS cells. In general, four clusters are observed which contains: High concentrations of ionophores, generally related to loss of cells; low concentrations of ionophores, before loss of cells is observed; inactive profiles with mp-value > 0.01; high concentrations of hybrid ionophores associated with low cell viability. Interestingly Lasalocid at 12.5 µM is also contained in last cluster, but this is probably related to cell death. The full correlation matrix with compound annotations is available on Mendeley Data. Bottom: Selected correlations for some of the clusters observed in the full correlation matrix.

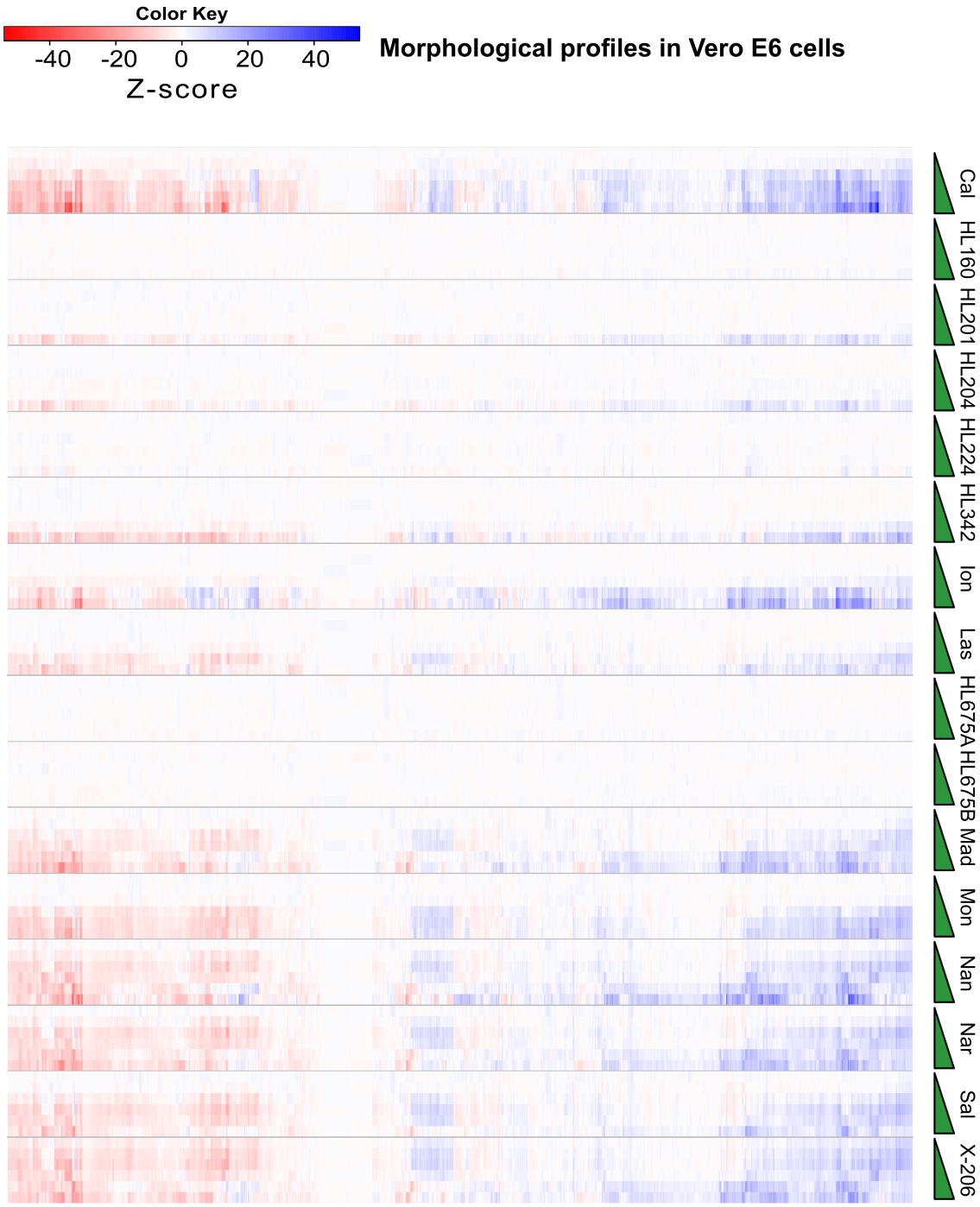


Fig. 7 Heatmap of morphological profiles in Vero E6 cells. Compounds are dosed as a 6-point 3-fold dilutions series starting from 12.5 µM, except monensin (Mon) which starts at 4.2 µM.

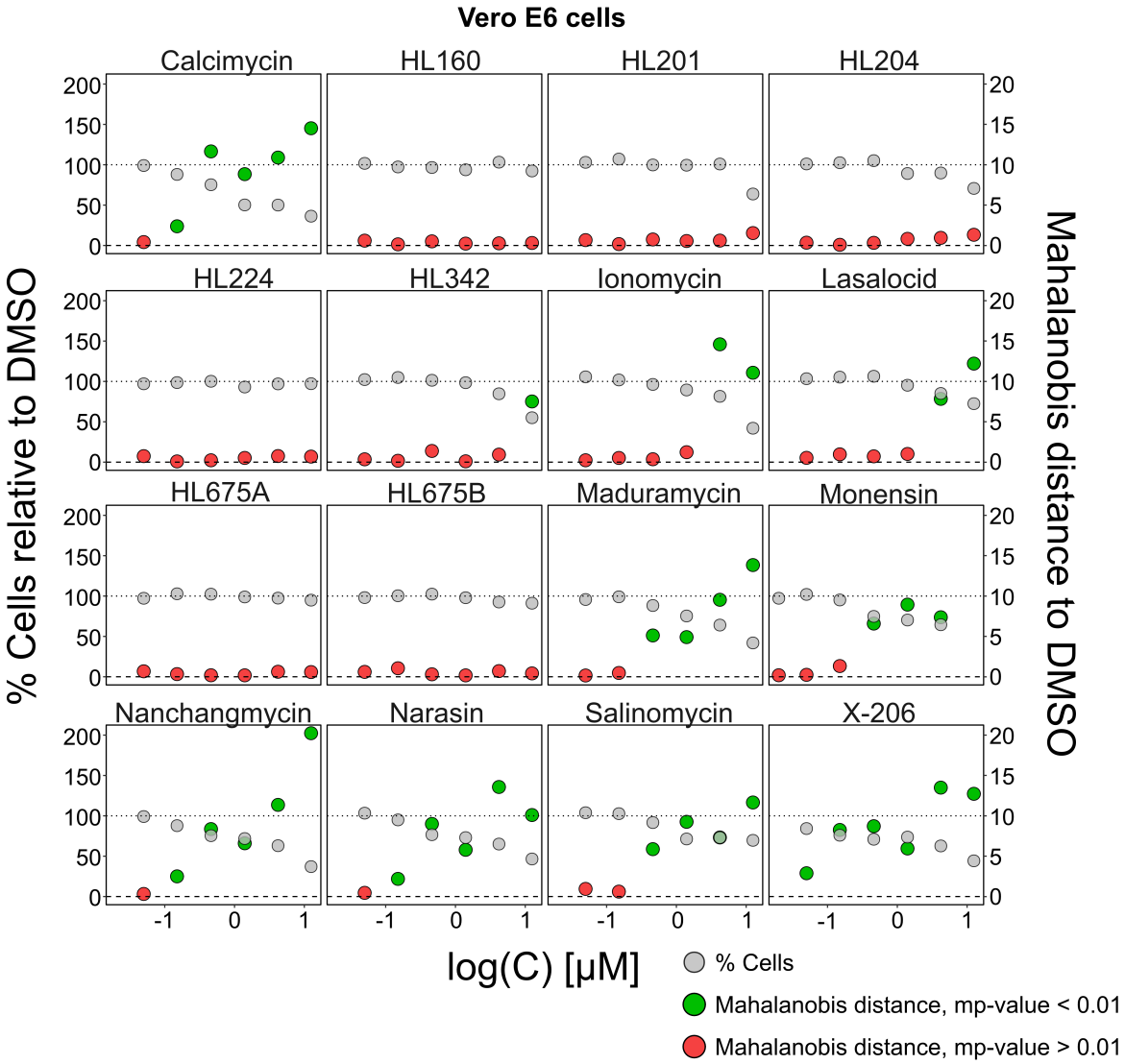


Fig. 8 Cell counts and Mahalanobis distances from morphological profiling in Vero E6 cells. The points for the Mahalanobis distance are coloured based on the mp-value. Active profiles are observed for most ionophores before a significant drop in cell viability is observed. Only the profile for 12.5 µM HL342 reaches mp-value < 0.01 while the highest concentration for HL201 and HL204 are close to reaching significance (mp-value 0.02 and 0.06 respectively).

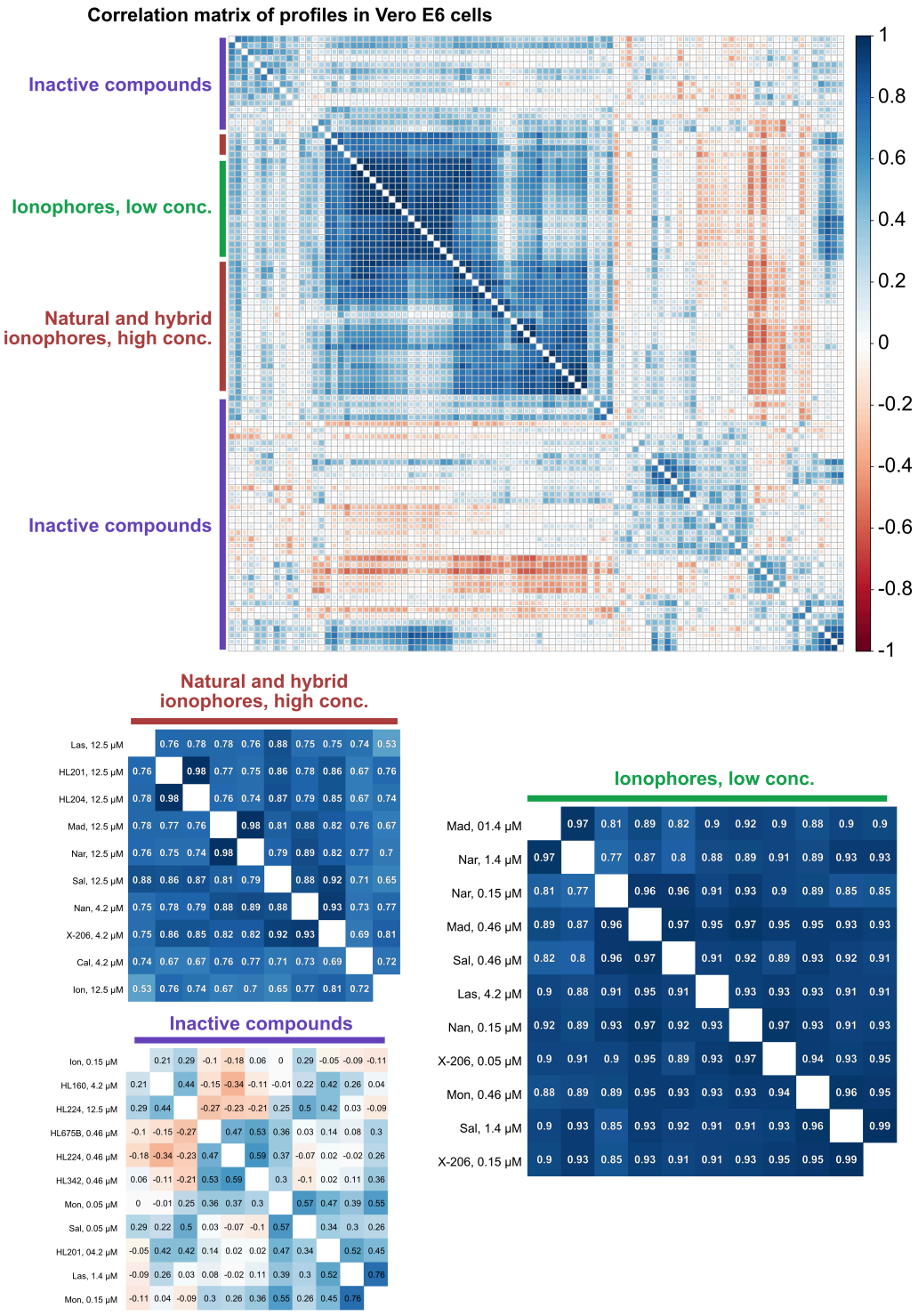


Fig. 9 Top: Correlation matrix (pearson correlations) for all morphological profiles in Vero E6 cells. In general, the same clusters as in U-2OS cells (Supplementary Fig. 6) are found, however the high concentrations of both natural and hybrid ionophores are contained in the same cluster, most likely due to toxic effects. Bottom: Selected correlations for some of the clusters observed in the full correlation matrix.

X-ray crystallography

Crystal structure **6-Na**, **14**, **24** and **31-Na**

Crystallographic single crystal X-ray data for three structures were collected on a Bruker Kappa *Apex2* diffractometer equipped with a Ag source (**6-Na**, **14** and **31-Na**). The crystals were cooled to 100(1) K using an Oxford Cryosystems liquid nitrogen Cryostream device. Crystallographic single crystal X-ray data for **24** was collected on a different Bruker Kappa *Apex2* diffractometer equipped with a Mo source at room temperature. Absorption correction for all four structures were done with SADABS. Cell refinement and data reduction were done in SAINT-plus.[1] The structures were solved and refined with SHELXT and SHELXL, respectively, in Olex2.[2–4]

Crystal structure **29-Na**

Crystallographic single crystal X-ray data was collected using an Oxford Diffraction Supernova instrument equipped with a Mo micro-focus X-ray source, an Atlas charge-coupled device detector, and a four-circle goniometer. The crystal was cooled to 100(1) K using an Oxford Cryosystems liquid nitrogen Cryostream device. The intensities were empirically corrected for absorption using SCALE3 ABSPACK implemented in CrysAlisPRO.[5] The unit cell parameters were determined, and the Bragg intensities were integrated using CrysAlisPRO. The structure was solved and refined with SHELXT and SHELXL, respectively, in Olex2.[2–4]

The X-ray crystallography data have been deposited in the Cambridge Crystallographic Data Centre (CCDC) using the following identifiers (www.ccdc.cam.ac.uk/structures/): 1920656 (compound 6-Na), 1920657 (compound 14), 1920658 (compound 24), 1920659 (compound 29-Na) and 1920660 (compound 31-Na).

Crystallographic details:

	6-Na	**14**	**24**	**29-Na**	**31-Na**
Molecular formula	C38 H58 Cl Na O10	C14 H24 O3	C34 H60 O8	C38 H58 Br Na O10	C38 H58 Cl Na O10, 2(C2 H3 N), H2O
Formula weight	733.28	240.33	596.82	777.74	833.4
Crystal system	orthorhombic	monoclinic	monoclinic	orthorhombic	orthorhombic
Space Group	P 21 21 21	P 1 21 1	P 1 21 1	P 21 21 21	P 21 21 21
a (Å)	17.3673	8.5919	8.8767	17.5111	11.9272
b (Å)	18.6159	9.104	10.3495	18.5108	13.616
c (Å)	53.386	9.673	19.4472	53.5509	27.774
α (°)	90	90	90	90	90
β (°)	90	114.391	91.299	90	90
γ (°)	90	90	90	90	90
Volume ($Å^3$)	17260	689.1	1786.14	17358.2	4510.7
Z	16	2	2	16	4
T (K)	100	100	296	100	100
ρ ($g\ cm^{-1}$)	1.129	1.158	1.11	1.19	1.227
λ (Å)	0.56086	0.56086	0.71073	0.71073	0.56086
μ (mm^{-1})	0.084	0.05	0.077	1.006	0.087
# measured refl	110795	11684	28112	35203	25547
# unique refl	19216	2616	6640	17560	6250
R_{int}	0.0694	0.0486	0.0273	0.0443	0.0474
# parameters	1834	158	391	1759	532
$R(F^2)$, all refl	0.0925	0.0511	0.0584	0.0977	0.0538
$R_w(F^2)$, all refl	0.2365	0.103	0.1278	0.2421	0.121
Goodness of fit	1.007	1.048	1.047	1.04	1.045
CCDC no.	1920656	1920657	1920658	1920659	1920660

Comments for crystal structure **6-Na**

The crystallographic structure refinement gave rise to one A-alert and two B-alerts. The alerts are commented in the cif file and reproduced here:

start Validation Reply Form

_vrf_THETM01_20181203_shao_0m

;

PROBLEM: The value of sine(theta_max)/wavelength is less than 0.550

RESPONSE: The long-range order of crystal was the not good enough to give scattering out to more than 0.5113 sin(theta)/lambda.

It is likely due to the disorder of solvent (acetonitrile), which do not affect the absolute structure determination.

;

_vrf_PLAT241_20181203_shao_0m

;

PROBLEM: High 'MainMol' Ueq as Compared to Neighbors of C1 Check

RESPONSE: Data quality low, and the structure has both rigid and flexible units.

;

_vrf_PLAT340_20181203_shao_0m

;

PROBLEM: Low Bond Precision on C-C Bonds ..... 0.01749 Ang.

RESPONSE: The data quality does not allow refinement of disorder due to displacement of the atoms.

;

end Validation Reply Form

Comments for crystal structure **29-Na**

The crystallographic structure refinement gave rise to two A-alerts and two B-alerts. The alerts are commented in the cif file and reproduced here:

start Validation Reply Form

_vrf_THETM01_exp_64

;

PROBLEM: The value of sine(theta_max)/wavelength is less than 0.550

RESPONSE: The long-range order of crystal was the not good enough to give scattering out to more than 0.5001 sin(theta)/lambda.
It is likely due to the disorder of solvent(acetonitrile) and large number of degrees of freedom in the fragments that are around the sodium atoms. However, the absolute configuration is not affected by this disorder. Furthermore, it was observed that the crystals decomposes when taken out of the mother liqour.
;
_vrf_PLAT027_exp_64
;
PROBLEM: _diffrn_reflns_theta_full value (too) Low ..... 20.82 Degree
RESPONSE: The crystals decomposes when taken out of the mother liqour.
Hence, the crystal quality is poor and the crystals do not scatter to high q.
;
_vrf_PLAT090_exp_64
;
PROBLEM: Poor Data / Parameter Ratio (Zmax > 18) ..... 5.65 Note
RESPONSE: The crystal quality and the size of the unit cell give rise to this poor ratio.
;
_vrf_PLAT341_exp_64
;
PROBLEM: Low Bond Precision on C-C Bonds ..... 0.02374 Ang.
RESPONSE: The poor crystal quality gives a high degree of disorder in the crystal structure. Hence, precise determination of bonds is not possible.
;
end Validation Reply Form

Comments for crystal structure **31-Na**

The crystallographic structure refinement gave rise to one B-alert. The alerts are commented in the cif file and reproduced here:

start Validation Reply Form
_vrf_THETM01_20181024_shao_0m

;

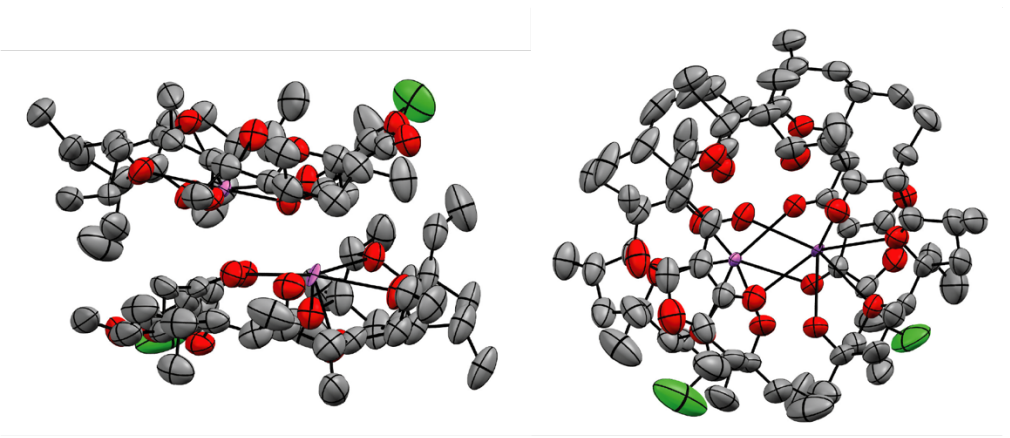
PROBLEM: The value of sine(theta_max)/wavelength is less than 0.575

RESPONSE: The long-range order of crystal was the not good enough to give scattering out to more than 0.5568 sin(theta)/lambda. It is likely due to large number of degrees of freedom in the fragments that are around the sodium atoms. Hence, bond distances might be affected. However, the absolute positions of the atoms are not affected by this kind of disorder.

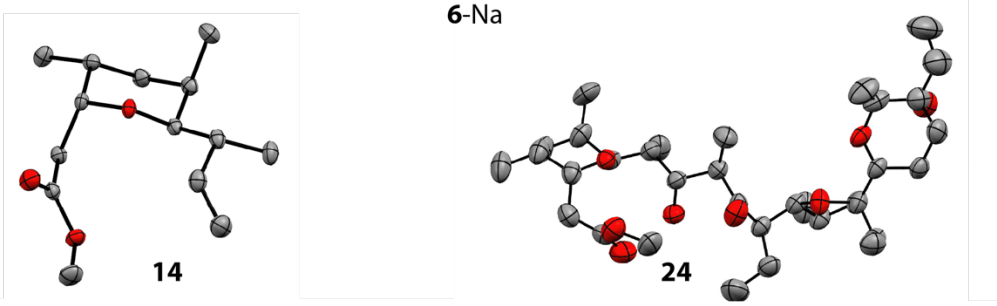
;

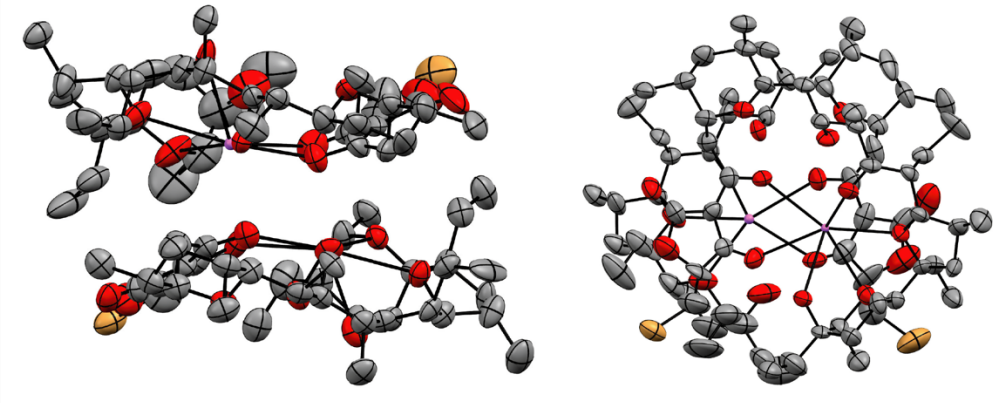
end Validation Reply Form

Ellipsoid structures:

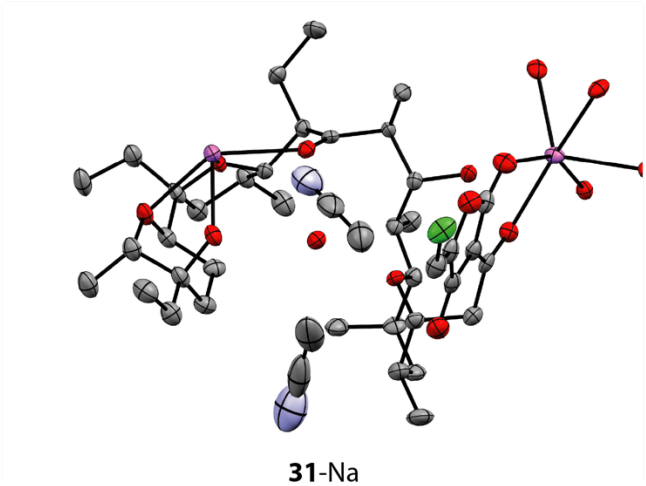


6-Na





29-Na



31-Na

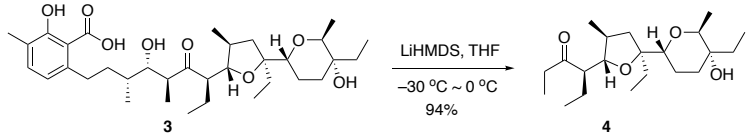
Morphological profiling imaging settings

The following imaging settings were used on a Zeiss Celldiscoverer 7 microscope:

Channel	Dyes	Excitation LED	Beamsplitter	Emission filter
DNA	Hoechst 33342	385 nm	RTBS 405 + 493 + 610	TBP 425/30 + 524/50 + 688/154
ER	Concanavalin-AF488	470 nm	RTBS 405 + 493 + 610	TBP425/30 + 524/50 + 688/145
RNA	SYTO 14 green fluorescent nucleic acid stain	511 nm	RTBS 450 + 538 + 610	TBP 467/24 + 555/25 + 687/145
AGP	Phalloidin-AF568 + Wheat-germ agglutinin-AF555	567 nm	RQBS 405 + 493 + 575 + 653	QBP 425/30 + 514/30 + 592/25 + 709/100
Mito	MitoTracker Deep Red	625 nm	RQBS 405 + 493 + 575 + 653	QBP 425/30 + 514/30 + 592/25 + 709/100

Synthesis protocols and characterization data

(*R*)-4-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)hexan-3-one (4):



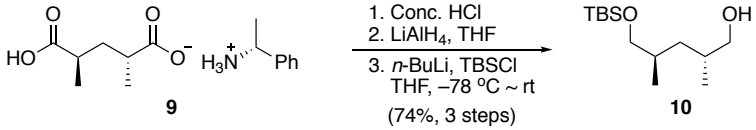
Lasalocid acid **3** was extracted from the commercial product Bovatec. To a solution of the Lasalocid acid (11.8 g, 20 mmol, 1 eq.) in 200 mL of THF was added LiHMDS (120 mL, 1.0 M in THF, 6 eq.) slowly at -30 °C under Ar. The resulting mixture was slowly warmed to 0 °C and stirred for 6 d. It was quenched with sat. NH_4Cl and extracted with ether. The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product **4** as a pale yellow oil (6.64 g, 94%).

R_f: 0.22 (EtOAc/pentane 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (q, *J* = 6.9 Hz, 1H), 3.57 – 3.54 (m, 1H), 3.49 – 3.46 (m, 1H), 2.63 – 2.53 (m, 3H), 2.44 (dq, *J* = 18.4, 7.2 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.83 (dd, *J* = 12.5, 8.1 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.66 – 1.25 (m, 10H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.89 (m, 6H), 0.81 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.1, 86.0, 84.4, 77.0, 73.0, 71.1, 57.6, 40.8, 37.4, 37.0, 30.5, 29.4, 28.7, 21.4, 21.2, 16.8, 14.2, 12.6, 8.2, 7.5, 6.6.

(2*R*,4*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (10):



The optically active salt **9** (5.39 g, 19.2 mmol, 1.0 eq.) was dissolved in conc. HCl (50 mL), and the resulting clear solution was stirred for 5 mins before solvent was removed. The residue was extracted with ether. The combined organic layers were dried with Na_2SO_4, and then solvent was removed. The crude product was used directly in the next step.

The crude product was dissolved in 120 mL dry THF under Ar and cooled to 0 °C, $LiAlH_4$ (2.91 g, 76.8 mmol, 4 eq.) was added in small portions. Then the mixture was warmed to

room temperature and stirred overnight. It was quenched with water (2.91 g), 10% NaOH (2.91 g), and water (8.73 g). The white precipitate was filtered off and washed with EtOAc. The crude product was used directly in the next step.

To a solution of crude diol in dry THF (35 mL) at -78 °C under Ar, *n*-BuLi (7.3 mL, 2.5 N, 0.95 eq.) was added dropwise and the resulting solution was stirred for 1 h at -78 °C. Then, a solution of TBSCl (2.75 g, 18.2 mmol, 0.95 eq.) in THF (5 mL) was added rapidly, and the resulting mixture was stirred at -78 °C for 10 min before it was warmed to room temperature and stirred for another 3 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ether. The combined organic layers were washed with brine and dried with Na_2SO_4. Then the solvent was removed and the crude product was purified by flash column chromatography to yield the product **10** as a clear oil (3.48 g, 74%).

R_f: 0.25 (EtOAc/pentane= 1/9).

$[\alpha]_D^{296.6\ K}$ +18.6 (c = 1, $CHCl_3$).

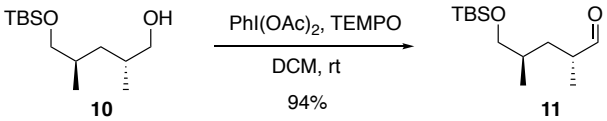
IR ν_{max} (cm^{-1}): 3308 (br), 2955, 2928, 2857, 1472, 1388, 1254, 1095, 1036.

^1H NMR (400 MHz, $CDCl_3$): δ 3.50 –3.39 (m, 4H), 1.79 – 1.68 (m, 2H), 1.47 (s, 1H), 1.25 – 1.10 (m, 2H), 0.92 – 0.85 (m, 15H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 69.2, 69.1, 37.0, 33.2, 33.1, 26.1, 18.5, 16.8, 16.6, -5.2.

HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{13}H_{31}O_2Si$: 247.2088; found 247.2092.

(2*R*,4*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentanal (11):



To a solution of mono-TBS protected diol **10** (3.48 g, 14.1 mmol, 1 eq.) in dry DCM (70 mL) under Ar, $PhI(OAc)_2$ (6.81 g, 21.2 mmol, 1.5 eq.) and TEMPO (443 mg, 2.82 mmol, 0.2 eq.) were added. The mixture was stirred until SM disappeared (6 h) at room temperature under Ar. Then, the reaction was quenched with aq. $Na_2S_2O_3$ and extracted with DCM. The combined organic phases were washed with sat. aq. $NaHCO_3$, brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to yield the aldehyde **11** as a clear oil (3.24 g, 94%).

R_f: 0.50 (EtOAc/pentane = 1/19).

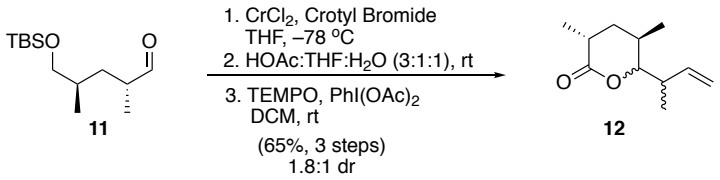
IR ν_{max} (cm^{-1}): 2956, 2929, 2857, 1728, 1462, 1252, 1093, 836, 765.

^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (d, *J* = 2.0 Hz, 1H), 3.47 – 3.40 (m, 2H), 2.48 – 2.39 (m, 1H), 1.75 – 1.66 (m, 1H), 1.53 – 1.38 (m, 2H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.89 – 0.87 (m, 12H), 0.04 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.5, 68.3, 44.3, 34.1, 33.4, 26.1, 18.5, 16.6, 13.6, -5.3.

HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{13}H_{29}O_2Si$: 245.1931; found 245.1929.

(3*R*,5*R*)-6-(But-3-en-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (12):



To $CrCl_2$ (3.613 g, 29.4 mmol, 4 eq.) at 0 °C under Ar was added dry THF (40 mL) with vigorous stirring. After 30 min, aldehyde **11** (1.796 g, 7.35 mmol, 1 eq.) in THF (4.0 mL) and 1-bromo-2-butene (2.27 mL, 22.1 mmol, 3 eq.) in THF (2 mL) were added dropwise. The mixture was stirred at 0 °C for 20 h after which it was poured into ice-cold water (150 mL) and extracted with ether. Then, the solvent was removed, and the crude mixture was used in the next step without further purification.

The crude mixture was dissolved in 10 mL of HOAc-THF-H_2O (3:1:1) and was stirred until SM disappeared (overnight). The reaction mixture was diluted with water and quenched with solid $NaHCO_3$. The mixture was extracted with ether and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude mixture that was used without further purification.

To a solution of the crude mixture in DCM (45 mL) at room temperature under Ar, TEMPO (230 mg, 1.47 mmol, 0.2 eq.) and $PhI(OAc)_2$ (4.735 g, 14.7 mmol, 2.0 eq) were added. After 12 h, the reaction mixture was partitioned between aq. $Na_2S_2O_3$ and DCM. The combined organic phases were washed with sat. aq. $NaHCO_3$, brine and dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product mixture was purified by flash column

chromatography to obtain the product **12** as a clear oil (867 mg, 65%, *dr*: 1.8:1). NMR data are reported for the major diastereomer.

R_f: 0.26 (EtOAc/pentane 1:9).

$[\alpha]_D^{296.6\ K}$ +69.4 (c = 1, $CHCl_3$).

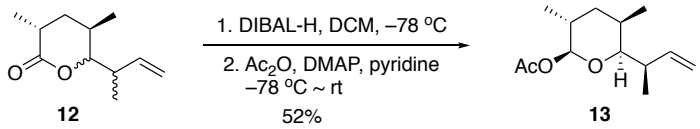
IR ν_{max} (cm^{-1}): 3090, 2968, 2934, 2850, 1734, 1460, 1378, 1199, 1101, 989, 737.

^1H NMR (400 MHz, $CDCl_3$): δ 5.94 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.15 – 5.05 (m, 2H), 4.02 (dd, *J* = 9.7, 2.6 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.46 – 2.37 (m, 1H), 2.19 – 2.12 (m, 1H), 1.94 (ddd, *J* = 13.6, 7.2, 3.4 Hz, 1H), 1.68 (td, *J* = 12.8, 3.9 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 140.4, 115.1, 87.1, 39.5, 36.4, 31.3, 28.1, 18.0, 15.5, 10.8.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{11}H_{18}O_2Na$: 205.1199; found 205.1209.

(2*S*,3*R*,5*R*,6*S*)-6-((*R*)-But-3-en-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl acetate (13):



12 **13**

To a solution of lactone **12** (403 mg, 2.21 mmol, 1 eq.) in DCM (22 mL) under Ar was cooled to -78 °C, DIBAL-H (2.87 mL, 1.0 M in cyclohexane, 1.3 eq.) was added dropwise. After 5 h, acetic anhydride (2.07 mL, 22.1 mmol, 10 eq.), pyridine (1.43 mL, 17.7 mmol, 8 eq.), and DMAP (351 mg, 3.87 mmol, 1.3 eq.) were added. The reaction mixture was slowly warm to room temperature and stirred for overnight. Sat. aq. NH_4Cl was added and the DCM was removed. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with sat. aq. Na_2HPO_4 twice, NaH_2PO_4 twice, and sat. aq. $CuSO_4$ twice. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography to afford the major product **13** as a clear solid (259 mg, 52%).

R_f: 0.42 (EtOAc/pentane 1:15).

$[\alpha]_D^{296.8\ K}$ –27.4 (c = 1, $CHCl_3$).

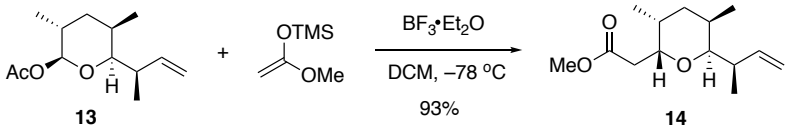
IR ν_{max} (cm^{-1}): 3081, 2968, 2921,1757, 1462, 1228, 1105, 1044, 902.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (ddd, *J* = 17.1, 10.4, 6.3 Hz, 1H), 5.22 (d, *J* = 9.2 Hz, 1H), 5.07 – 4.96 (m, 2H), 3.27 (dd, *J* = 10.0, 2.2 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.11 (s, 3H), 1.88 – 1.83 (m, 2H), 1.74 – 1.69 (m, 1H), 1.45 (td, *J* = 13.2, 5.2 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 141.9, 113.7, 99.7, 83.1, 39.0, 38.5, 29.6, 29.0, 21.3, 16.2, 15.5, 12.1.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{13}H_{22}O_3Na$: 249.1461; found 249.1464.

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-6-((*R*)-but-3-en-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetate (14):



To a solution of acetal **13** (326 mg, 1.44 mmol, 1 eq.) in DCM (14 mL) under Ar at -78 °C, ((1-methoxyvinyl)oxy)trimethylsilane (2.46 mL, 14.4 mmol, 10 eq.) was added. Then $BF_3{\cdot}OEt_2$ (274 µL, 2.16 mmol, 1.5 eq.) was added dropwise. The resulting mixture was stirred at -78 °C for 22 h. Then, sat. aq. $NaHCO_3$ was added at -78 °C and the mixture was allowed to warmed to room temperature. The mixture was extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford the product **14** as a clear solid (323 mg, 93%). The single crystal sample for XRD analysis was obtained via the single-tube method using acetone/MeOH as solvent.

R_f: 0.31 (EtOAc/pentane 1:15).

$[\alpha]_D^{296.6\ K}$ +71.0 (c = 1, $CHCl_3$).

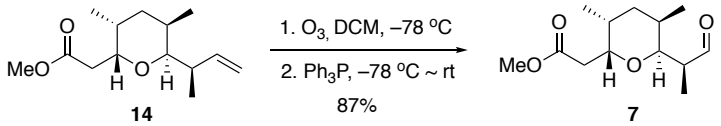
IR ν_{max} (cm^{-1}): 3092, 2961, 2913, 1741, 1436, 1378, 1288, 1213, 1070, 966, 906.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (ddd, *J* = 17.7, 10.4, 7.8 Hz, 1H), 5.00 – 4.89 (m, 2H), 4.35 (dt, *J* = 10.8, 5.1 Hz, 1H), 3.68 (s, 3H), 3.30 (dd, *J* = 9.8, 2.5 Hz, 1H), 2.79 (dd, *J* = 14.3, 11.4 Hz, 1H), 2.30 (dd, *J* = 14.3, 4.5 Hz, 1H), 2.27 – 2.13 (m, 2H), 1.90 – 1.84 (m, 1H), 1.56 – 1.42 (m, 2H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 143.3, 113.1, 75.1, 75.0, 51.8, 39.9, 34.9, 31.9, 29.0, 26.8, 17.6, 16.1, 11.8.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{14}H_{24}O_3Na$: 263.1618; found 263.1633.

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-3,5-dimethyl-6-((*S*)-1-oxopropan-2-yl)tetrahydro-2*H*-pyran-2-yl)acetate (7):



A stream of ozone was bubbled through a solution of alkene **14** (305 mg, 1.27 mmol, 1.0 eq.) in DCM (30 mL) at -78 °C until the blue color persisted. Excess ozone was removed with a stream of oxygen (until solution becomes colorless) and then a stream of nitrogen (30 min) at -78 °C. Ph_3P (1.666 g, 6.35 mmol, 5.0 eq.) was added and the reaction mixture was stirred for 2 h at -78 °C. Then, it was allowed to warm to room temperature and stirred for 18 h. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product **7** as a white solid (269 mg, 87%).

R_f: 0.42 (EtOAc/pentane 1:9).

$[\alpha]_D^{296.6\ K}$ +106 (c = 1, $CHCl_3$).

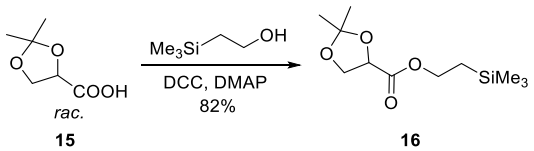
IR ν_{max} (cm^{-1}): 2960, 2917, 2879, 2857, 2726, 1736, 1462, 1438, 1261, 1289, 1176, 1077, 968, 856.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 3.5 Hz, 1H), 4.31 (dt, *J* = 10.9, 5.0 Hz, 1H), 3.81 (dd, *J* = 10.3, 2.6 Hz, 1H), 3.67 (s, 3H), 2.81 (dd, *J* = 14.0, 11.6 Hz, 1H), 2.39 – 2.23 (m, 3H), 1.88 – 1.84 (m, 1H), 1.61 – 1.46 (m, 2H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3, 172.4, 75.3, 72.0, 52.0, 48.3, 34.4, 31.8, 28.6, 26.8, 17.5, 11.9, 9.8.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{13}H_{22}O_4Na$: 265.1410; found 265.1415.

2-(Trimethylsilyl)ethyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (16):



15 **16**

To the solution of racemic acid **15** (2.294 g, 15.7 mmol, 1.0 equiv) in anhydrous DCM (20 mL), 2-trimethylsilylethanol (2.93 mL, 20.4 mmol, 1.3 equiv) was added. The mixture was cooled to 0 °C, then the solution of DCC (4.21 g, 20.4 mmol, 1.3 equiv) in DCM (10 mL) was added, followed by DMAP (96 mg, 0.78 mmol, 0.05 equiv). The white precipitate DCU was generated immediately. After 5 h reaction, the mixture was diluted with pentane and filtered through celite to remove DCU. The filtrate was concentrated and the residue was purified by silica gel column chromatography using pentane/ethyl acetate 50:1 *v*/*v* as eluent. The product **16** was obtained as colorless oil (3.179 g, 82%).

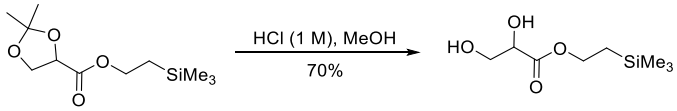
R_f: 0.34 (Pentane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.32 – 4.22 (m, 3H), 4.10 (dd, *J* = 8.8, 5.2 Hz, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.04 (t, *J* = 8.8 Hz, 2H), 0.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 111.4, 74.4, 67.4, 63.9, 26.0, 25.7, 17.5, -1.4.

The synthetic compound showed identical spectroscopic data to the reported one.[6]

2-(Trimethylsilyl)ethyl 2,3-dihydroxypropanoate (SI-1):



16 **SI-1**

To the solution of acetonide protected ester **16** (6.93 g, 28.1 mmol, 1.0 equiv) in MeOH (24 mL), the solution of 1 M HCl (aq, 35.1 mL, 35.1 mmol, 1.25 equiv) was added. The mixture was stirred at r.t. for 12 h. After full conversion, the reaction was quenched by Et_3N (6 mL) and concentrated under vacuum. The residue was then purified by silica gel column chromatography using pentane/ethyl acetate 3:1 to 2:1 as eluent. The product **SI-1** was obtained as colorless oil (4.027 g, 70%).

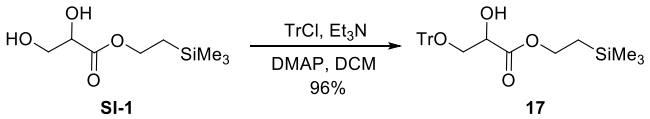
R_f: 0.60 (Pentane/EtOAc 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 – 4.30 (m, 2H), 4.24 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.93 – 3.81 (m, 2H), 3.19 (d, *J* = 4.4 Hz, 1H), 2.17 (dd, *J* = 8.0, 5.2 Hz, 1H), 1.08 – 1.04 (m, 2H), 0.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 71.7, 64.8, 64.2, 17.5, -1.4.

The synthetic compound showed identical spectroscopic data to the reported one.[6]

2-(Trimethylsilyl)ethyl 2-hydroxy-3-(trityloxy)propanoate (17):



To as stirred solution of **SI-1** (1.50 g, 7.27 mmol, 1.0 equiv) in anhydrous DCM (15 mL) were added Et_3N (1.52 mL, 10.9 mmol, 1.5 equiv) and DMAP (45 mg, 0.36 mmol, 0.05 equiv). The mixture was cooled to 0 °C, then the solution of trityl chloride (3.04 g, 7.27 mmol, 1.0 equiv) in anhydrous DCM (5 mL) was added dropwise. After addition, the mixture was stirred at 0 °C to r.t. for 20 h. When full conversion was achieved, the mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography using pentane/ethyl acetate 40:1 *v*/*v* as eluent. The trityl protection product **17** was obtained as colorless oil (3.14 g, 96%).

R_f: 0.30 (Pentane/EtOAc 15:1).

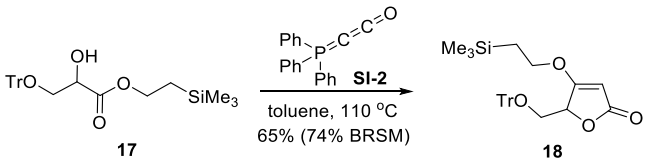
IR ν_{max} (cm^{-1}): 3059, 2952, 2897, 1733, 1597, 1490, 1449, 1249, 1231, 1118, 1095, 1029, 933, 858, 835.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.44 (m, 6H), 7.33 – 7.29 (m, 6H), 7.27 – 7.23 (m, 3H), 4.32 – 4.24 (m, 3H), 3.51 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.38 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.27 (d, *J* = 7.6 Hz, 1H), 0.96–1.00 (m, 2H), 0.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 143.7, 128.7, 127.9, 127.2, 86.4, 70.9, 65.4, 64.2, 17.6, -1.4.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{27}H_{32}NaO_4Si$: 471.1962; found 471.1983.

4-(2-(Trimethylsilyl)ethoxy)-5-((trityloxy)methyl)furan-2(5*H*)-one (18):



To a stirred solution of **17** (1.46 g, 3.24 mmol, 1.0 equiv) in anhydrous toluene (35 mL) was added Bestmann reagent (**SI-2**) (1.76 g, 5.83 mmol, 1.8 equiv, prepared according to published procedure). The mixture was heated under argon to 110 °C for 24 h. After being cooled to r.t., the mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography. The recovered starting material **17** was eluted by pentane/ethyl acetate 40:1 *v*/*v* (192 mg, 13%), then the product **18** was eluted by pentane/ethyl acetate 6:1 and obtained as white solid (989 mg, 64%, 74% BRSM).

R_f: 0.44 (Pentane/EtOAc 6:1).

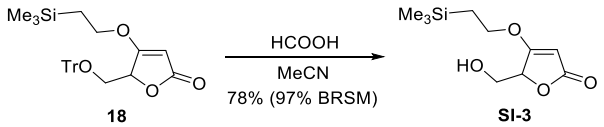
IR ν_{max} (cm^{-1}): 3058, 2951, 1760, 1628, 1490, 1448, 1350, 1292, 1248, 1232, 1151, 1115, 1077, 1033, 930, 836.

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.43 (m, 6H), 7.33 – 7.29 (m, 6H), 7.28 – 7.23 (m, 3H), 5.14 (s, 1H), 4.84 – 4.82 (m, 1H), 4.16 – 4.05 (m, 2H), 3.59 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.28 (dd, *J* = 10.4, 4.4 Hz, 1H), 1.10 – 1.06 (m, 2H), 0.03 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.0, 173.2, 143.5, 128.7, 128.0, 127.2, 89.6, 86.6, 78.7, 71.2, 62.0, 17.3, -1.3.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{29}H_{32}NaO_4Si$: 495.1962; found 495.1971.

5-(Hydroxymethyl)-4-(2-(trimethylsilyl)ethoxy)furan-2(5*H*)-one (SI-3):



The solid **18** (941 mg, 1.99 mmol, 1.0 equiv) was dissolved in MeCN (18 mL) and then formic acid (6.0 mL, excess amount) was added. The mixture was stirred at r.t. for 5 h, then was diluted by ethyl acetate (300 mL). The organic phase was thoroughly washed with sat. $NaHCO_3$ (aq) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography. The recovered starting material was eluted by pentane/ethyl acetate *v*/*v* 6:1 (184 mg, 20%), then the deprotection product **SI-3**

was eluted by pentane/ethyl acetate 1:1 *v*/*v* and obtained as white solid (356 mg, 78%, 97% BRSM).

R_f: 0.16 (Pentane/EtOAc 2:1).

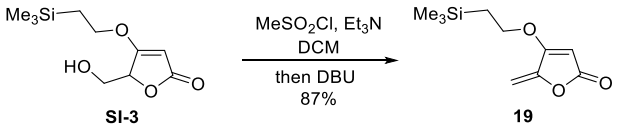
IR ν_{max} (cm^{-1}): 3428 (br), 3122, 2954, 2892, 1738, 1678, 1620, 1463, 1449, 1403, 1379, 1354, 1313, 1246, 1196, 1161, 1100, 1058, 1031, 946, 923, 836.

^1H NMR (400 MHz, $CDCl_3$): δ 5.08 (s, 1H), 4.80 – 4.79 (m, 1H), 4.14 (dd, *J* = 9.6, 7.6 Hz, 2H), 4.04 (ddd, *J* = 12.4, 6.0, 2.8 Hz, 1H), 3.80 (ddd, *J* = 12.4, 8.0, 4.0 Hz, 1H), 2.59 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.19 – 1.13 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8, 173.3, 89.8, 79.9, 71.5, 61.2, 17.4, -1.4.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{10}H_{18}NaO_4Si$: 253.0867; found 253.0874.

5-Methylene-4-(2-(trimethylsilyl)ethoxy)furan-2(5*H*)-one (19):



To a stirred solution of **SI-3** (357 mg, 1.55 mmol, 1.0 equiv) in anhydrous DCM (18 mL) was added Et_3N (0.54 mL, 3.88 mmol, 2.5 equiv). The mixture was cooled to 0 °C, then $MeSO_2Cl$ (0.18 mL, 2.33 mmol, 1.5 equiv) was added dropwise. The mixture was stirred at 0 °C to r.t. for 2 h, and full mesylation of **SI-3** was achieved. However, the elimination of the mesylate was incomplete (> 20% mesylate left). To facilitate complete elimination, DBU (0.046 mL, 0.31 mmol, 0.2 equiv) was added. The mixture was further stirred at r.t. for 2 h, then was diluted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography using pentane/ethyl acetate 20:1 *v*/*v* as eluent. The product **19** was obtained as white solid (287 mg, 87%).

R_f: 0.36 (Pentane/EtOAc 15:1).

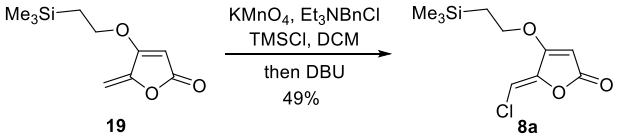
IR ν_{max} (cm^{-1}): 3128, 2953, 2897, 1783, 1669, 1603, 1466, 1415, 1372, 1348, 1260, 1229, 1176, 1097, 1065, 1038, 969, 935, 857, 838, 797.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (d, *J* = 1.2 Hz, 1H), 5.04 – 5.02 (m, 2H), 4.17 (t, *J* = 8.4 Hz, 2H), 1.18 (t, *J* = 8.4 Hz, 2H), 0.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 168.7, 150.2, 92.3, 89.8, 71.1, 17.3, -1.3.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{10}H_{16}NaO_3Si$: 235.0761; found 235.0763.

(*Z*)-5-(Chloromethylene)-4-(2-(trimethylsilyl)ethoxy)furan-2(5*H*)-one (8a):



To a flame dried Schlenk flask were added $KMnO_4$ (174 mg, 1.10 mmol, 1.0 equiv), triethylbenzylammonium chloride (251 mg, 1.10 mmol, 1.0 equiv) and anhydrous DCM (20 mL). The mixture was stirred at r.t. for 40 min to generate a homogeneous solution. Then the mixture was cooled to 0 °C and TMSCl (0.56 mL, 4.40 mmol, 4.0 equiv) was added. The mixture was stirred at 0 °C for 20 min to generate a dark green colored solution. To this mixture, the solution of **19** (234 mg, 1.10 mmol, 1.0 equiv) in anhydrous DCM (5 mL) was added at 0 °C dropwise. After addition, the mixture was stirred at 0 °C to r.t. overnight to achieve full conversion. To this mixture, DBU (0.82 mL, 5.50 mmol, 5.0 equiv) was added to facilitate elimination of the dichloride intermediate. After full conversion of the intermediate (ca. 5 h), the mixture was quenched with sat. $NaHCO_3$ (aq) and filtered through celite to remove precipitate. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography using pentane/ethyl acetate 20:1 *v/v* as eluent. The product **8a** was obtained as white solid (132 mg, 49%).

R_f: 0.38 (Pentane/EtOAc 15:1).

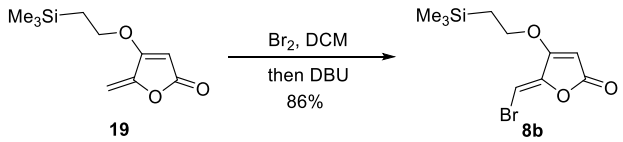
IR ν_{max} (cm^{-1}): 3098, 2954, 2901, 1769, 1588, 1461, 1432, 1401, 1356, 1295, 1248, 1236, 1172, 1067, 942, 922, 882, 836.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (s, 1H), 5.20 (s, 1H), 4.18 (t, *J* = 8.4 Hz, 2H), 1.17 (t, *J* = 8.4 Hz, 2H), 0.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 167.3, 145.4, 100.0, 89.3, 71.6, 17.4, -1.3.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{10}H_{15}ClNaO_3Si$: 269.0371; found 269.0371.

(*Z*)-5-(Bromomethylene)-4-(2-(trimethylsilyl)ethoxy)furan-2(5*H*)-one (8b):



To a flame dried Schlenk flask were added **19** (110 mg, 0.516 mmol, 1.0 equiv) and anhydrous DCM (8 mL). To this solution, Br_2 (0.026 mL, 0.516 mmol, 1.0 equiv) was added dropwise. The mixture was stirred at r.t. overnight, and full conversion of **19** was achieved accompanied by the disappearance of the color of Br_2. To this mixture, DBU (0.085, 0.568 mmol, 1.1 equiv) was added to facilitate elimination of the dibromide intermediate. After 2 h, the mixture was diluted with ethyl acetate, and successively washed with $Na_2S_2O_3$ (aq), water and brine. The organIc phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography using pentane/ethyl acetate 20:1 *v*/*v* as eluent. The product **8b** was obtained as white solid (129 mg, 86%).

R_f: 0.32 (Pentane/EtOAc 15:1).

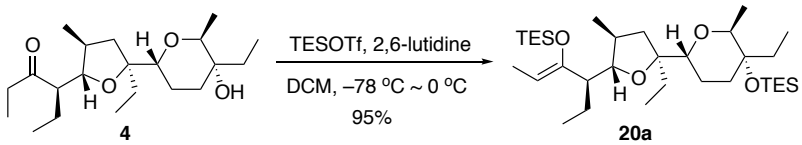
IR ν_{max} (cm^{-1}): 3097, 2954, 2901, 1764, 1725, 1589, 1460, 1432, 1398, 1353, 1248, 1233, 1161, 1068, 941, 916, 860, 836.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.23 (s, 1H), 4.18 (t, J = 8.4 Hz, 2H), 1.17 (t, J = 8.4 Hz, 2H), 0.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 167.3, 147.4, 89.6, 87.8, 71.6, 17.4, -1.3.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{10}H_{15}BrNaO_3Si$: 312.9866; found 312.9870.

Triethyl(((*R*,*Z*)-4-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)hex-2-en-3-yl)oxy)silane (20a):



To a solution of alcohol **4** (3.02 g, 8.52 mmol, 1 eq.) in 35 ml dry DCM cooled to -78 °C, 2,6-lutidine (9.9 mL, 85.2 mmol, 10 eq.) was added under Ar. Then TESOTf (4.8 mL, 21.3

mmol, 2.5 eq.) was added dropwise. The obtained mixture was warmed to 0 °C and stirred overnight. The mixture was diluted with ether and then was washed with water, brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product **20a** as colorless oil (4.73 g, 95%). The *Z* and *E* configurations are determined by NOE.

R_f: 0.90 (EtOAc/pentane 1:9).

$[\alpha]_D^{299.2\ K}$ +7.8 (c = 1, $CHCl_3$).

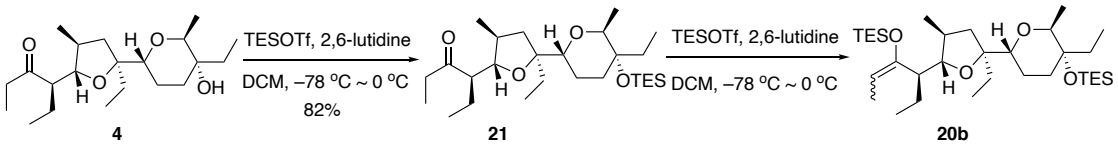
IR ν_{max} (cm^{-1}): 2954, 2912, 2876, 1669, 1458, 1240, 1096, 1064, 1046, 1007, 723.

^1H NMR (400 MHz, $CDCl_3$): δ 4.53 (q, *J* = 6.6 Hz, 1H), 3.79 (q, *J* = 6.9 Hz, 1H), 3.41 (d, *J* = 9.3 Hz, 1H), 3.35 (t, *J* = 7.8 Hz, 1H), 1.93 – 1.84 (m, 2H), 1.81 – 1.73 (m, 2H), 1.70 – 1.63 (m, 2H), 1.60 – 1.28 (m, 10H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.01 – 0.84 (m, 31H), 0.71 – 0.59 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 101.9, 87.7, 84.4, 76.7, 75.2, 74.9, 53.5, 41.9, 38.6, 31.0, 30.9, 28.4, 22.8, 21.8, 17.6, 15.5, 12.5, 11.0, 8.3, 7.5, 7.13, 7.08, 7.0, 6.1.

HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{33}H_{67}O_4Si_2$: 583.4572; found 583.4587.

Triethyl(((*R*,*E*)-4-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)hex-2-en-3-yl)oxy)silane (20b):



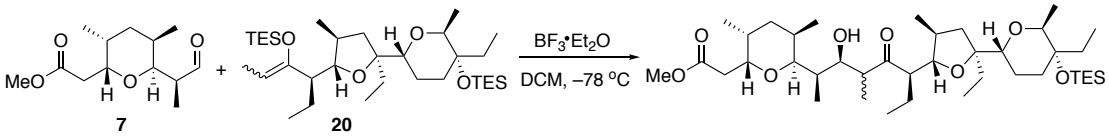
To a solution of alcohol **4** (520 mg, 1.468 mmol, 1 eq.) in 15 ml DCM (0.1 M) cooled to -78 °C under Ar, 2,6-lutidine (850 uL, 7.34 mmol, 5 eq.) was added. Then TESOTf (400 uL, 1.76 mmol, 1.2 eq.) was added slowly. The resulting mixture was slowly warmed to -10 °C and stirred overnight. The mixture was diluted with ether and then was washed with 2 N HCl, sat. aq. $NaHCO_3$, brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product **21** as colorless oil (562 mg, 82%).

To a solution of mono-TES protected ketone **21** (1.0 eq.) in DCM (0.1 M) was added TESOTf (10 eq.) slowly at -78 °C under Ar. The mixture was stirred at -78 °C for another 2 h before pyridine (10 eq.) was added dropwise. The resulting mixture was warmed to 0 °C and stirred until the ketone disappeared. The mixture was diluted with ether and then was washed with cold sat. aq. $NaHCO_3$, brine and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product (**20a**/**20b** ratio 1:2.3) as colorless oil (Note: the *Z*/*E* isomers are very difficult to be separated by flash column chromatography. To get acceptable amount of enolate, a mixture of **20a**/**20b** (ratio range from 1:1.7 to 1:3.0) was collected). The total yield is more than 90%.

Only the ^{1}H NMR characteristic peaks were reported here, **20a/20b** (*Z*/*E*) ratio 1:2.3:

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61 (q, *J* = 6.7 Hz, 2.3H) (*E* enolate), 4.53 (q, *J* = 6.7 Hz, 1.0H) (Z enolate), 2.33 (ddd, *J* = 11.1, 8.5, 3.1 Hz, 2.4H) (*E* enolate).

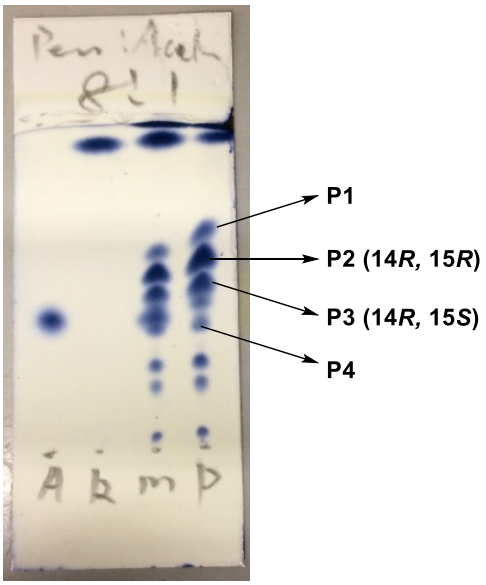
General protocol for the Mukaiyama-aldol reaction:



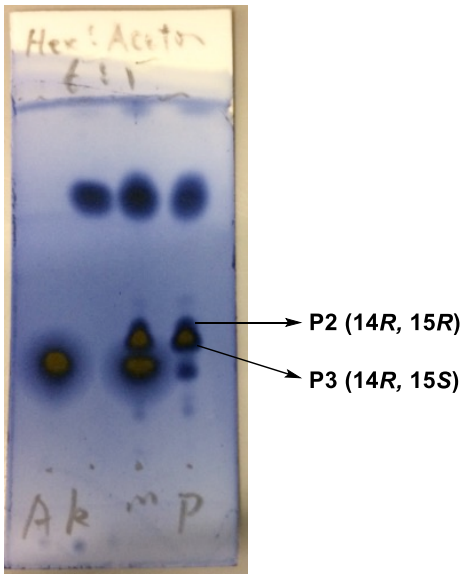
To a solution of aldehyde **7** (1.0 eq) and enolate **20** (2.0-3.0 eq.) in DCM (0.05 M) at -78 °C, $BF_3{\cdot}OEt_2$ (1.5 eq.) was added slowly. The obtained mixture was stirred at -78 °C until the enolate disappeared. The reaction was quenched with sat. aq. $NaHCO_3$ at -78 °C and the mixture was extracted with DCM and dried with Na_2SO_4. The solvent was removed and the crude mixture was purified by flash column chromatography to afford the aldol products (P1, P2, P3, and P4). P2 (**22**) and P3 (**23**) were unambiguously assigned by x-ray crystallography of derivatives. P1 and P4 were tentatively assigned as aldol diastereomers based on ^{1}H and ^{13}C NMR (NMR spectra are attached), but full stereochemical assignment of those compounds have not been done.

Using pure *Z*-enolate **20a** (3.0 eq.), 60 h: P2 (442.5 mg, 56%), P3 (232.7 mg, 30%)

Using a mixture of *Z*/*E*-enolate **20a/22b** (*Z*/*E*=1/2.3, 2.0 eq.), 36 h: P2 (41.2 mg, 7%), P3 (457.2 mg, 81%)

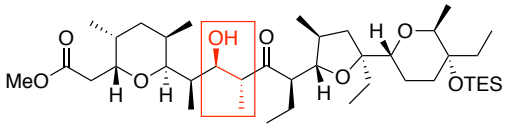


Using pure *Z*-enolate



Using a mixture of *Z*/*E*-enolate (*Z*/*E*=1/2.3)

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetate (22):



22

22: P2 (14*R*, 15*R*)

R_f: 0.58 (Pentane/Acetone= 8/1).

$[\alpha]_D^{296.8\ K}$ –12.8 (c = 1, $CHCl_3$).

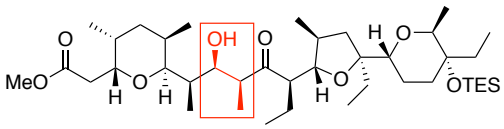
IR ν_{max} (cm^{-1}): 3533 (br), 2957, 2876, 1723, 1458, 1377, 1291, 1132, 1072, 1047, 1010, 985, 957.

^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (dt, *J* = 12.2, 4.7 Hz, 1H), 3.95 (ddd, *J* = 10.3, 5.9, 1.5 Hz, 1H), 3.83 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.77 – 3.71 (m, 4H), 3.52 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.45 (dd, *J* = 11.3, 2.5 Hz, 1H), 3.19 (d, *J* = 5.9 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.81 (t, *J* = 12.7 Hz, 1H), 2.70 (dt, *J* = 9.8, 3.3 Hz, 1H), 2.30 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.24 (dt, *J* = 12.1, 6.0 Hz, 1H), 2.02 – 1.71 (m, 5H), 1.63 – 1.35 (m, 9H), 1.32 – 1.25 (m, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 – 0.82 (m, 27H), 0.76 (d, *J* = 6.9 Hz, 6H), 0.66 – 0.52 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.8, 174.7, 84.6, 83.8, 76.7, 75.4, 75.0, 74.0, 72.0, 70.4, 57.8, 52.7, 47.2, 40.1, 37.0, 36.3, 35.0, 32.3, 31.8, 30.3, 29.1, 28.9, 27.0, 22.2, 17.8, 17.6, 16.1, 15.5, 13.6, 12.5, 11.7, 8.0, 7.5, 7.2, 7.1, 7.0, 6.7, 6.4, 5.9.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{40}H_{74}NaO_8Si$: 733.5045; found 733.5088.

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*S*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-6-methyl-5-((triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetate (23):



23

23: P3 (14*R*, 15*S*)

R_f: 0.50 (Pentane/Acetone= 8/1).

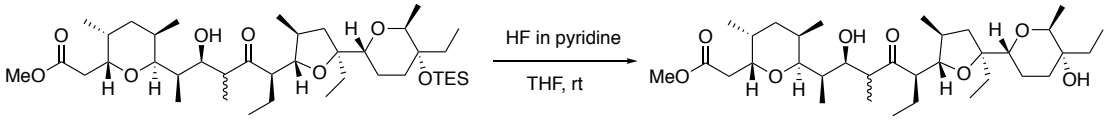
$[\alpha]_D^{296.8\ K}$ −1.0 (c = 1, $CHCl_3$).

IR ν_{max} (cm^{-1}): 3542 (br), 2959, 2935, 2876, 1726, 1458, 1378, 1290, 1132, 1062, 984. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (ddd, *J* = 9.2, 6.0, 3.1 Hz, 1H), 4.02 – 3.96 (m, 1H), 3.75 – 3.65 (m, 5H), 3.51 – 3.47 (m, 1H), 3.45 – 3.39 (m, 2H), 2.94 – 2.89 (m, 1H), 2.81 (td, *J* = 12.7, 2.5 Hz, 1H), 2.58 (dq, *J* = 9.5, 3.4 Hz, 1H), 2.27 – 2.14 (m, 2H), 1.91 – 1.77 (m, 4H), 1.71 – 1.68 (m, 1H), 1.65 – 1.55 (m, 2H), 1.52 – 1.36 (m, 4H), 1.34 – 1.25 (m, 3H), 1.22–1.18 (m, 3H), 1.12 (dd, *J* = 6.9, 2.5 Hz, 3H), 0.96 – 0.71 (m, 33H), 0.63 – 0.50 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.1, 174.5, 84.9, 83.9, 76.7, 75.2, 75.0, 73.9, 71.3, 69.4, 55.7, 52.2, 48.2, 40.9, 37.9, 37.6, 35.0, 31.61, 31.59, 30.4, 28.9, 28.5, 27.0, 21.8, 18.9, 17.7, 16.8, 15.5, 15.4, 12.3, 11.8, 8.6, 8.1, 7.4, 7.0, 6.9.

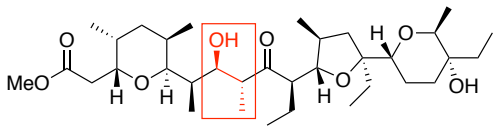
HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{40}H_{74}NaO_8Si$: 733.5045; found 733.5089.

General protocol for the TES deprotection:



To a solution of the ester (1.0 eq.) in dry THF (0.1 M) in a plastic vial under Ar at room temperature, hydrogen fluoride in pyridine (1.0 mL per 1.0 mmol) was added dropwise. The resulting mixture was stirred until SM disappeared (~24 h). The mixture was diluted with water and extracted with ether. The combined organic layers were washed with 1N HCl and dried with Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product.

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetate (24):



24

24: 81%. The single crystal sample for XRD analysis was obtained via the single-tube method using EtOAc/Pentane as solvent.

R_f: 0.13 (Pentane/EtOAc 4:1).

$[\alpha]_D^{296.7\ K}$ –4.2 (c = 1, $CHCl_3$).

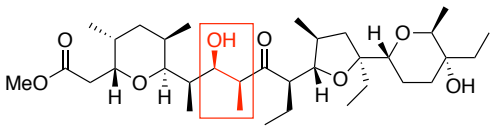
IR ν_{max} (cm^{-1}): 3530 (br), 2961, 2936, 2877, 1720, 1458, 1378, 1291, 1215, 1179, 1131, 1072, 1050, 984, 956.

^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (dt, *J* = 11.9, 4.8 Hz, 1H), 3.95 (ddd, *J* = 10.3, 6.5, 1.5 Hz, 1H), 3.83 – 3.72 (m, 5H), 3.54 – 3.48 (m, 2H), 3.26 (d, *J* = 6.0 Hz, 1H), 2.93 (dq, *J* = 10.2, 6.8 Hz, 1H), 2.81 (t, *J* = 12.7 Hz, 1H), 2.70 – 2.66 (m, 2H), 2.31 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.24 (dt, *J* = 11.8, 6.0 Hz, 1H), 2.06 – 1.78 (m, 4H), 1.66 – 1.25 (m, 13H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.92 – 0.88 (m, 9H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.77 – 0.75 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.6, 174.7, 84.5, 84.0, 76.9, 75.4, 73.0, 72.0, 71.0, 70.4, 57.7, 52.7, 47.1, 40.1, 36.8, 36.3, 35.0, 32.3, 30.5, 29.5, 29.2, 28.9, 27.0, 21.8, 17.7, 17.6, 16.3, 14.2, 13.8, 12.4, 11.7, 8.1, 7.3, 6.6.

HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{34}H_{60}NaO_8$: 619.4180; found 619.4181.

Methyl 2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*S*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetate (25):



25

25: 93%

R_f: 0.13 (Pentane/EtOAc 4:1).

$[\alpha]_D^{296.4\ K}$ +4.0 (c = 1, $CHCl_3$).

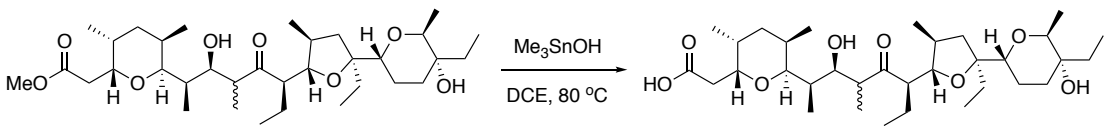
IR ν_{max} (cm^{-1}): 3539 (br), 2961, 2935, 2876, 1725, 1457, 1379, 1290, 1214, 1177, 1132, 1050, 985, 956.

^1H NMR (400 MHz, $CDCl_3$): δ 4.25 (dt, *J* = 12.4, 4.2 Hz, 1H), 3.99 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.77 – 3.65 (m, 5H), 3.52 – 3.45 (m, 3H), 2.95 – 2.88 (m, 1H), 2.82 (t, *J* = 12.6 Hz, 1H), 2.62 – 2.56 (m, 2H), 2.27 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.24 – 2.16 (m, 1H), 1.93 – 1.84 (m, 3H), 1.82 – 1.76 (m, 1H), 1.62 – 1.40 (m, 11H), 1.38 – 1.26 (m, 2H), 1.21 – 1.18 (m, 6H), 0.95 (d, *J* = 5.7 Hz, 3H), 0.92 – 0.79 (m, 12H), 0.77 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 214.9, 174.5, 84.6, 84.0, 77.1, 75.3, 73.1, 71.3, 71.1, 69.6, 55.7, 52.3, 48.2, 41.1, 37.9, 37.6, 35.0, 31.6, 30.5, 29.4, 28.9, 28.3, 27.0, 21.4, 18.9, 17.7, 17.0, 15.5, 14.2, 12.2, 11.8, 8.7, 8.2, 6.6.

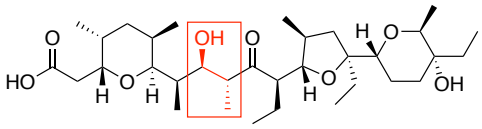
HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{34}H_{60}NaO_8$: 619.4180; found 619.4198.

General protocol for the methyl ester hydrolysis:



To a solution of the ester (1 eq.) and Me_3SnOH (5 eq.) in DCE (0.025 M) was heated to 80 °C until TLC analysis indicated a complete reaction (48 h). Then solvent was removed and the residue was taken up in EtOAc. The organic layer was then washed with aq. HCl (5%), brine and dried over Na_2SO_4. The solvent was removed, and the crude mixture was purified by flash column chromatography to afford the product.

2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-Ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetic acid (SL415, 26):



26

SL415 **(26)**: quantitative yield.

R_f: 0.40 (DCM/MeOH/AcOH 20:1:0.01).

$[\alpha]_D^{296.2\ K}$ −10.8 (c = 1, MeOH).

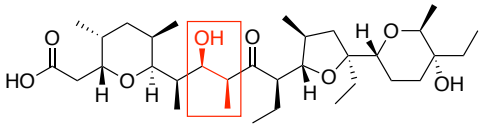
IR ν_{max} (cm^{-1}): 3484 (br), 2961, 2935, 2879, 1711, 1598 (br), 1458, 1379, 1288, 1130, 1108, 1071, 1053, 988, 956.

^1H NMR (400 MHz, CD_3OD): δ 4.27 (dt, *J* = 10.5, 4.3 Hz, 1H), 4.03 (dd, *J* = 10.4, 1.7 Hz, 1H), 3.88 (dd, *J* = 10.0, 2.7 Hz, 1H), 3.77 (q, *J* = 6.9 Hz, 1H), 3.62 – 3.54 (m, 2H), 3.02 (dq, *J* = 10.4, 7.1 Hz, 1H), 2.79 – 2.73 (m, 2H), 2.34 (dd, *J* = 13.1, 3.8 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.07 – 2.00 (m, 1H), 1.93 – 1.83 (m, 3H), 1.78 (dd, *J* = 12.3, 8.0 Hz, 1H), 1.65 – 1.28 (m, 12H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.92 – 0.85 (m, 12H), 0.80 – 0.77 (m, 6H).

^{13}C NMR (101 MHz, CD_3OD): δ 218.5, 177.7, 86.5, 85.6, 77.2, 74.0, 73.6, 72.2, 71.5, 58.9, 48.0, 40.3, 37.6, 37.4, 35.9, 32.6, 32.4, 30.7, 30.6, 30.2, 28.5, 22.7, 18.2, 17.8, 16.0, 14.9, 14.1, 13.2, 12.0, 8.4, 7.6, 6.7.

HRMS (ESI) *m/z* $[M-H]^-$ calc. for $C_{33}H_{57}O_8$: 581.4059; found 581.4064.

2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*S*,6*R*)-6-((2*S*,3*S*,5*S*)-5-Ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetic acid (SL382, 27):



27

SL382 **(27)**: 89%

R_f: 0.24 (DCM/MeOH/AcOH 20:1:0.01).

$[\alpha]_D^{296.2\ K}$ +6.0 (c = 1, MeOH).

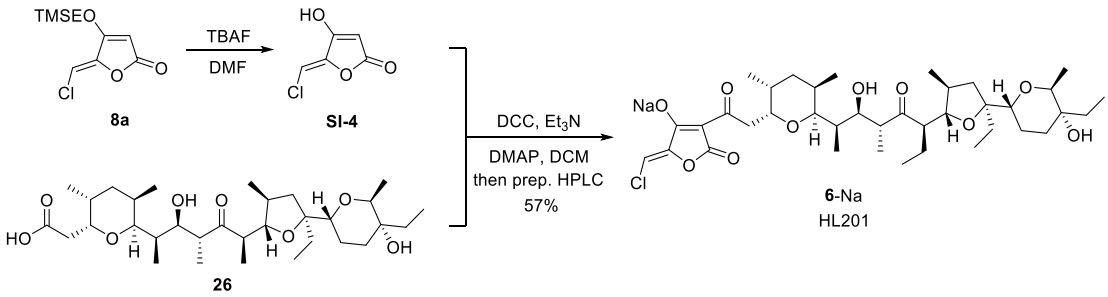
IR ν_{max} (cm^{-1}): 3474 (br), 2963, 2937, 2879, 1710, 1618 (br), 1458, 1379, 1284, 1215, 1176, 1132, 1095, 1077, 1050, 986, 954.

^{1}H NMR (400 MHz, CD_3OD): δ 4.31 – 4.26 (m, 1H), 4.10 (d, *J* = 9.4 Hz, 1H), 3.80 – 3.71 (m, 2H), 3.60 – 3.46 (m, 3H), 2.99 – 2.91 (m, 1H), 2.72 (t, *J* = 12.3 Hz, 1H), 2.69 (dq, *J* = 12.3 Hz, 1H), 2.37 (d, *J* = 13.6 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.04 – 1.95 (m, 1H), 1.90 – 1.83 (m, 3H), 1.74 – 1.40 (m, 12H), 1.36 – 1.29 (m, 3H), 1.21 – 1.16 (m, 6H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.92 – 0.83 (m, 12H), 0.80 – 0.78 (m, 6H).

^{13}C NMR (101 MHz, CD_3OD): δ 216.5, 178.0 (br), 86.5, 85.0, 77.4, 76.9, 74.2, 72.5, 72.2, 71.0, 66.9, 64.2, 56.8, 49.5, 41.4, 39.0, 38.6, 36.0, 32.8 (br), 32.4, 30.7, 30.2, 29.7, 28.5, 22.3, 19.6, 17.9, 17.1, 15.9, 15.5, 15.0, 12.4, 12.3, 8.9, 8.6, 6.8.

HRMS (ESI) *m/z* $[M-H]^-$ calc. for $C_{33}H_{57}O_8$: 581.4059; found 581.4068.

Sodium (*Z*)-2-(chloromethylene)-4-(2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetyl)-5-oxo-2,5-dihydrofuran-3-olate (HL201, 6-Na):



To a stirred solution of TMSE protected tetronate **8a** (49 mg, 0.20 mmol, 2.0 equiv) in DMF (3.6 mL) was added TBAF (1 M solution in THF, 0.40 mL, 0.40 mmol, 4.0 equiv). The mixture was stirred at r.t. for 4 h, then was acidified with 1 M HCl (aq) and diluted with ethyl acetate. The organic phase was thoroughly washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude tetronic acid **SI-4** was obtained as white solid almost quantitatively and directly used in the next coupling reaction without further purification.

To a flame dried Schlenk tube were added tetronic acid **SI-4** (crude solid, 0.20 mmol, 2.0 equiv) and acid **26** (58 mg, 0.10 mmol, 1.0 equiv). To this mixture, anhydrous DCM (4 mL) was added, followed by Et_3N (0.028 mL, 0.20 mmol, 2.0 equiv) to give a clear solution. To this solution, DCC (41 mg, 0.20 mmol, 2.0 equiv) was added, followed by DMAP (4.0 mg, 0.033 mmol, 0.33 equiv). After 1 h, DCU started to precipitate. The mixture was stirred at r.t. for 24 h, till the full conversion of the acid **26**. The mixture was then diluted with ethyl acetate, and the organic phase was washed with 1 M HCl (aq) to remove DMAP and Et_3N. Then the organic phase was washed with sat. $NaHCO_3$ (aq) to removed excess amount of tetronic acid **SI-4**, and the product **6** with ionophore property was transformed to its sodium salt **6**-Na and retained in the organic phase. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was treated with MeCN, and the insoluble DCU was removed by filtration. The filtrate was concentrated again, and the residue was dissolved into MeCN/10 mM $NaHCO_3$ (aq) 1:1 *v*/*v* (10 mL in total) and filtered through PTFE membrane to give the sample solution for preparative HPLC separation (concentration of product ~ 10 mM). The sample was then separated on C18 preparative HPLC column using MeCN/10 mM NH_4HCO_3 (aq) as eluent (40% to 50% MeCN gradient, multiple injections). The peak with strong UV absorption was eluted at 14 min and was collected. The collected solutions from all injections were combined and concentrated under vacuum to remove most of the MeCN, and the water phase was thoroughly extracted with DCM (5 × 100 mL). The combined or-

ganic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product **6**-Na (in sodium salt form as shown in the XRD structure), also named as HL201, was obtained as colorless solid (42.1 mg, 57%). The single crystal sample for XRD analysis was obtained via the single-tube method using MeCN as solvent.

R_f: 0.52 (pentane/EtOAc 1:1).

$[\alpha]_D^{296.7\ K}$ +114.3 (c = 0.46, CH_2Cl_2).

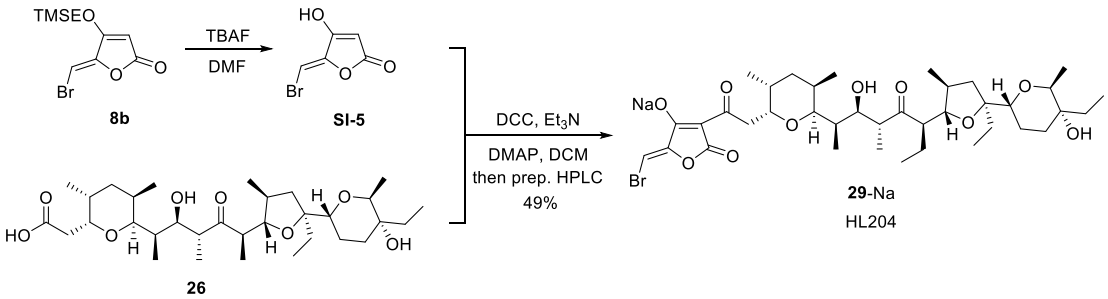
IR ν_{max} (cm^{-1}): 3409 (br), 2964, 2909, 2880, 1760, 1705, 1663, 1626, 1555, 1454, 1424, 1379, 1308, 1055, 988, 964, 949, 834.

^{1}H NMR (500 MHz, d_6-DMSO): δ 6.04 (s, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.12 (m, 1H), 3.91 (s, 1H), 3.79 – 3.75 (m, 2H), 3.66 (q, *J* = 7.0 Hz, 1H), 3.50 (d, *J* = 9.5 Hz, 1H), 3.40 (d, *J* = 11.0 Hz, 1H), 3.35 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.88 – 2.81 (m, 1H), 2.63 – 2.61 (m, 1H), 2.47 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.06 – 2.03 (m, 1H), 1.95 – 1.89 (m, 1H), 1.78 – 1.67 (m, 4H), 1.59 – 1.52 (m, 2H), 1.50 – 1.26 (m, 8H), 1.21 – 1.16 (m, 2H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.80 – 0.77 (m, 6H), 0.74 (d, *J* = 6.5 Hz, 6H), 0.66 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, d_6-DMSO): δ 214.5, 193.1, 178.4, 167.9, 148.9, 94.2, 94.1, 84.1, 83.7, 75.4, 74.7, 72.5, 70.8, 69.6, 69.5, 56.3, 46.1, 35.9, 35.7, 35.4, 34.9, 31.4, 29.3, 28.9, 28.4, 27.5, 21.2, 17.4, 16.9, 15.7, 14.6, 13.3, 12.8, 11.9, 7.8, 7.3, 6.4.

HRMS (ESI) *m/z* $[M-Na]^-$ calc. for $C_{38}H_{58}ClO_{10}$: 709.3724; found 709.3765.

Sodium (*Z*)-2-(bromomethylene)-4-(2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetyl)-5-oxo-2,5-dihydrofuran-3-olate (HL204, 29-Na):



To a stirred solution of TMSE protected tetronate **8b** (23 mg, 0.080 mmol, 2.0 equiv) in DMF (1.6 mL) was added TBAF (1 M solution in THF, 0.16 mL, 0.16 mmol, 4.0 equiv). The mixture was stirred at r.t. for 4 h, then was acidified with 1 M HCl (aq) and diluted with ethyl acetate. The organic phase was thoroughly washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude tetronic acid **SI-5** was obtained as white solid almost quantitatively and directly used in the next coupling reaction without further purification.

To a flame dried Schlenk tube were added tetronic acid **SI-5** (crude solid, 0.080 mmol, 2.0 equiv) and acid **26** (23 mg, 0.040 mmol, 1.0 equiv). To this mixture, anhydrous DCM (2 mL) was added, followed by Et_3N (0.011 mL, 0.080 mmol, 2.0 equiv) to give a clear solution. To this solution, DCC (16 mg, 0.080 mmol, 2.0 equiv) was added, followed by DMAP (1.6 mg, 0.013 mmol, 0.33 equiv). After 1 h, DCU started to precipitate. The mixture was stirred at r.t. for 24 h, till the full conversion of the acid **26**. The mixture was then diluted with ethyl acetate, and the organic phase was washed with 1 M HCl (aq) to removed DMAP and Et_3N. Then the organic phase was washed with sat. $NaHCO_3$ (aq) to removed excess amount of tetronic acid **SI-5**, and the product **29** with ionophore property was transformed to its sodium salt **29**-Na and retained in the organic phase. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was treated with MeCN, and the insoluble DCU was removed by filtration. The filtrate was concentrated again, and the residue was dissolved into MeCN/10 mM $NaHCO_3$ (aq) 1:1 *v*/*v* (10 mL in total) and filtered through PTFE membrane to give the sample solution for preparative HPLC separation (concentration of product ~ 10 mM). The sample was then separated on C18 preparative HPLC column using MeCN/10 mM NH_4HCO_3 (aq) as eluent (30% to 50% MeCN gradient, multiple injections). The peak with strong UV absorption was eluted at 18 min and was collected. The collected solutions from all injections were combined and concentrated under vacuum to remove most of the MeCN, and the water phase was thoroughly extracted with DCM (5 × 100 mL). The com-

bined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product **29**-Na (in sodium salt form as shown in the XRD structure), also named as HL204, was obtained as colorless solid (15.2 mg, 49%). The single crystal sample for XRD analysis was obtained via the single-tube method using MeCN as solvent.

R_f: 0.55 (pentane/EtOAc 1:1).

$[\alpha]_D^{296.7\ K}$ +137.8 (c = 0.50, DCM).

IR ν_{max} (cm^{-1}): 3418 (br), 2962, 2933, 2876, 1761, 1705, 1683, 1625, 1555, 1450, 1424, 1381, 1298, 1091, 988, 964, 949.

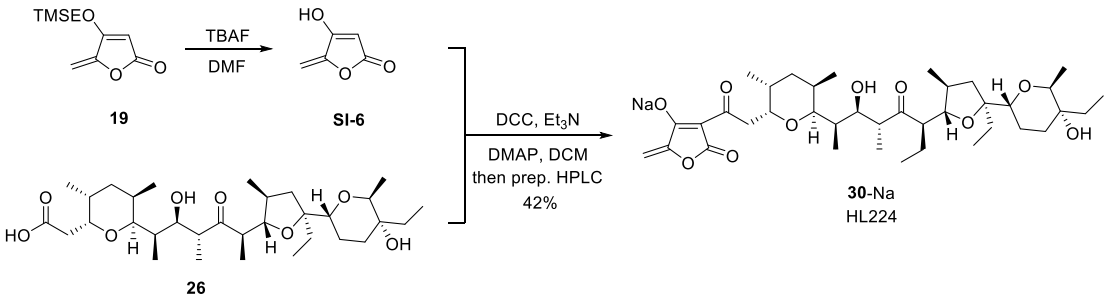
^{1}H NMR (500 MHz, d_6-DMSO): δ 6.06 (s, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.12 (m, 1H), 3.90 (s, 1H), 3.78 – 3.75 (m, 2H), 3.65 (q, *J* = 7.0 Hz, 1H), 3.50 (d, *J* = 9.0 Hz, 1H), 3.40 (d, *J* = 11.0 Hz, 1H), 3.36 – 3.32 (m, 1H), 2.88 – 2.81 (m, 1H), 2.64 – 2.61 (m, 1H), 2.46 (dd, *J* = 13.0, 8.5 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.95 – 1.88 (m, 1H), 1.78 – 1.67 (m, 4H), 1.58 – 1.50 (m, 2H), 1.47 – 1.26 (m, 8H), 1.21 – 1.16 (m, 2H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H), 0.81 – 0.77 (m, 6H), 0.74 (d, *J* = 6.5 Hz, 6H), 0.66 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, d_6-DMSO): δ 214.7, 193.4, 178.0, 168.0, 151.0, 94.3, 84.2, 83.7, 82.8, 75.4, 74.7, 72.4, 70.7, 69.6, 69.5, 56.2, 46.1, 35.8, 35.7, 35.4, 34.9, 31.4, 29.3, 28.9, 28.4, 27.5, 21.1, 17.3, 16.7, 15.7, 14.5, 13.3, 12.9, 11.9, 7.9, 7.3, 6.4.

HRMS (ESI) m/z [M-Na]$^-$: calcd. for $C_{38}H_{58}BrO_{10}$: 753.3219; found: 753.3261.

Sodium

4-(2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*R*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetyl)-2-methylene-5-oxo-2,5-dihydrofuran-3-olate (HL224, 30-Na):



To a stirred solution of TMSE protected tetronate **19** (29 mg, 0.14 mmol, 3.0 equiv) in DMF (2.7 mL) was added TBAF (1 M solution in THF, 0.28 mL, 0.28 mmol, 6.0 equiv). The mixture was stirred at r.t. for 4 h, then was acidified with 1 M HCl (aq) and diluted with ethyl acetate. The organic phase was thoroughly washed with water and brine, and dried over anhydrous Na_2SO_4. During the workup process, some white precipitate was observed, which was attributed to the partial dimerization of the tetronic acid **SI-6** via hetero-Diels-Alder reaction. The amount of **SI-6** consumed in the side reaction was lower than 1/3, so the amount of **SI-6** obtained should be around 0.092 mmol (2.0 equiv). The precipitate was removed via filtration, and the filtrate was concentrated under vacuum. The crude tetronic acid **SI-6** was obtained as white solid and directly used in the next coupling reaction without further purification.

To a flame dried Schlenk tube were added tetronic acid **SI-6** (crude solid, 0.092 mmol, 2.0 equiv) and acid **26** (27 mg, 0.046 mmol, 1.0 equiv). To this mixture, anhydrous DCM (3 mL) was added, followed by Et_3N (0.013 mL, 0.092 mmol, 2.0 equiv) to give a clear solution. To this solution, DCC (19 mg, 0.092 mmol, 2.0 equiv) was added, followed by DMAP (1.8 mg, 0.015 mmol, 0.33 equiv). After 1 h, DCU started to precipitate. The mixture was stirred at r.t. for 24 h, till the full conversion of the acid **26**. The mixture was then diluted with ethyl acetate, and the organic phase was washed with 1 M HCl (aq) to remove DMAP and Et_3N. Then the organic phase was washed with sat. $NaHCO_3$ (aq) to remove excess amount of tetronic acid **SI-6**, and the product **30** with ionophore property was transformed to its sodium salt **30**-Na and retained in the organic phase. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was treated with MeCN, and the insoluble DCU was removed by filtration. The filtrate was concentrated again, and the residue was dissolved into MeCN/10 mM $NaHCO_3$ (aq) 1:1 *v*/*v* (10 mL in total) and filtered through PTFE membrane to give the sample solution for preparative HPLC separation (concentration of product ~ 10 mM). The sample was then separated on C18 preparative HPLC column using MeCN/10

mM NH_4HCO_3 (aq) as eluent (40% to 50% MeCN gradient, multiple injections). The peak with strong UV absorption was eluted at 14 min and was collected. The collected solutions from all injections were combined and concentrated under vacuum to remove most of the MeCN, and the water phase was thoroughly extracted with DCM (5 × 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product **30**-Na (in sodium salt form), also named as HL224, was obtained as colorless solid (15.2 mg, 42%).

R_f: 0.34 (pentane/EtOAc 1:1).
$[\alpha]_D^{296.7\ K}$ +107.0 (c = 0.34, DCM).

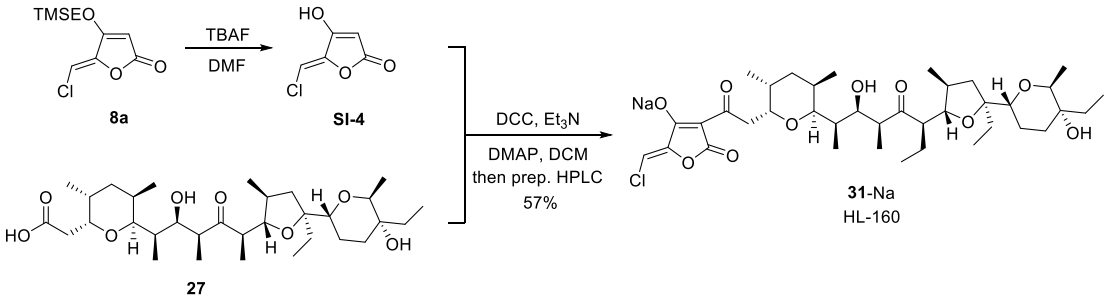
IR ν_{max} (cm^{-1}): 3411 (br), 2964, 2935, 2911, 2878, 1752, 1705, 1679, 1633, 1557, 1453, 1426, 1379, 1292, 1053, 988, 972, 949.

^{1}H NMR (400 MHz, d_6-DMSO): δ 4.74 (s, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 4.48 (s, 1H), 4.16 – 4.12 (m, 1H), 3.92 (s, 1H), 3.81 – 3.75 (m, 2H), 3.66 (q, *J* = 6.8 Hz, 1H), 3.50 (d, *J* = 10.0 Hz, 1H), 3.43 – 3.39 (m, 2H), 2.89 – 2.81 (m, 1H), 2.63 – 2.59 (m, 1H), 2.44 (dd, *J* = 12.8, 8.8 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.96 – 1.88 (m, 1H), 1.79 – 1.70 (m, 4H), 1.62 – 1.52 (m, 2H), 1.48 – 1.16 (m, 10H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.87 – 0.74 (m, 18H), 0.66 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, d_6-DMSO): δ 214.7, 193.3, 180.0, 169.3, 154.2, 94.7, 85.5, 84.2, 83.7, 75.5, 74.8, 72.5, 70.7, 69.6, 69.5, 56.2, 46.1, 35.8, 35.7, 35.2, 35.0, 31.4, 29.3, 28.9, 28.4, 27.5, 21.1, 17.4, 16.7, 15.7, 14.5, 13.3, 13.0, 11.9, 7.9, 7.3, 6.4.

HRMS (ESI) m/z [M-Na]$^-$: calcd. for $C_{38}H_{59}O_{10}$: 675.4114; found: 675.4149.

Sodium (*Z*)-2-(chloromethylene)-4-(2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*R*,4*S*,6*R*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3-hydroxy-4-methyl-5-oxooctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetyl)-5-oxo-2,5-dihydrofuran-3-olate (HL160, 31-Na):



The product **31** was synthesized following the same procedure as product **6**, using acid **27** (undesired epimer of **26**) as the coupling partner. After workup, the crude mixture was dissolved into MeCN/10 mM $NaHCO_3$ (aq) 1:1 *v*/*v* (10 mL in total) and filtered through PTFE membrane to give the sample solution for preparative HPLC separation (concentration of product ~ 10 mM). The sample was then separated on C18 preparative HPLC column using MeCN/10 mM NH_4HCO_3 (aq) as eluent (35% to 45% MeCN gradient, multiple injections). The peak with strong UV absorption was eluted at 13 min and was collected. The collected solutions from all injections were combined and concentrated under vacuum to remove most of the MeCN, and the water phase was thoroughly extracted with DCM (5 × 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product **31**-Na (in sodium salt form as shown in the XRD structure), also named as HL160, was obtained as colorless solid (42.2 mg, 57%). The single crystal sample for XRD analysis was obtained via single-tube method using MeCN as solvent.

R_f: 0.69 (ethyl acetate).

$[\alpha]_D^{296.7\ K}$ −1.4 (c = 0.71, DCM).

IR ν_{max} (cm^{-1}): 3408 (br), 2962, 2933, 2876, 1755, 1694, 1662, 1623, 1563, 1454, 1379, 1310, 1222, 1105, 1051, 1029, 989, 948, 833.

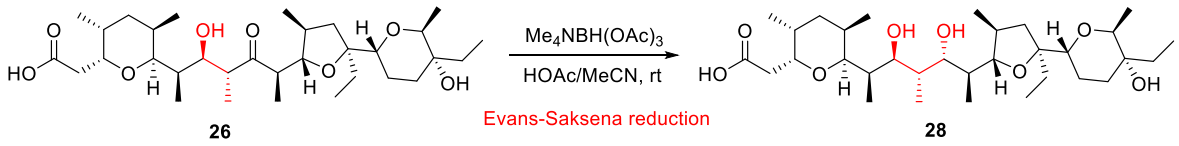
^{1}H NMR (500 MHz, d_6-DMSO): δ 6.08 (s, 1H), 4.63 (s, 1H), 4.16 (s, 1H), 3.87 (s, 1H), 3.76 (t, *J* = 8.0 Hz, 1H), 3.65 – 3.59 (m, 2H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.38 – 3.33 (m, 1H), 2.80 – 2.74 (m, 1H), 2.54 – 2.50 (m, 1H), 2.44 – 2.36 (m, 1H), 2.06 – 2.00 (m, 1H), 1.89 – 1.82 (m, 1H), 1.80 – 1.70 (m, 3H), 1.63 – 1.51 (m, 3H), 1.47 – 1.32 (m, 6H), 1.24 – 1.16 (m, 5H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.60 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.81 – 0.71 (m, 15H), 0.65 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, d_6-DMSO): δ 213.4, 94.2, 84.2, 82.5, 75.6, 74.4, 73.1, 70.4, 69.5, 68.5, 54.8, 47.5, 40.6, 37.2, 37.0, 36.2, 34.9, 31.4, 29.4, 28.3, 27.7, 27.3, 20.9, 17.7, 17.2, 16.7, 15.9,

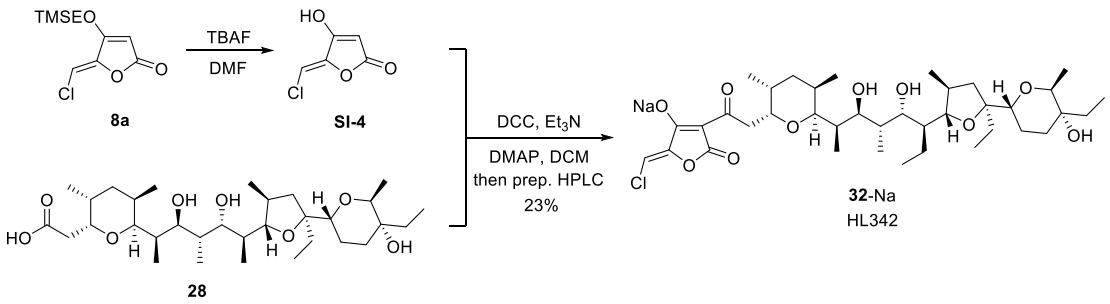
14.6, 11.6(2), 11.5(6), 8.1, 7.9, 6.4. (The absence of four peaks from the 3-acyl tetronic acid unit and some broaden peaks were observed after > 20000 scans for 20 mg sample, due to the conformational flexibility.)

HRMS (ESI) m/z [M-Na]$^-$: calcd. for $C_{38}H_{58}ClO_{10}$: 709.3724; found: 709.3773.

Sodium (*Z*)-2-(chloromethylene)-4-(2-((2*R*,3*R*,5*R*,6*S*)-6-((2*R*,3*S*,4*R*,5*S*,6*S*)-6-((2*S*,3*S*,5*S*)-5-ethyl-5-((2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)-3-methyltetrahydrofuran-2-yl)-3,5-dihydroxy-4-methyloctan-2-yl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)acetyl)-5-oxo-2,5-dihydrofuran-3-olate (HL342, 32-Na):



To a solution of $Me_4NBH(OAc)_3$ (132 mg, 0.5 mmol, 10 eq.) in MeCN (1.0 mL) was added HOAc (1.0 mL). The solution was stirred for 30 min at rt and then cooled to 0 °C before the ketone **26** (29.1 mg, 0.05 mmol, 1.0 eq.) in MeCN/AcOH (1:1) (1.0 mL) was added dropwise. The obtained mixture was warmed to rt and stirred for 72 h at rt. The reaction mixture was diluted with EtOAc and poured into sat. $NaHCO_3$. Solid $NaHCO_3$ was added until pH>7. Then Rochelles salt solution was added and the mixture was stirred for another 2 h. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$, aq. 0.1 N HCl, brine and dried over Na_2SO_4, filtered, and concentrated to give the crude product **28** which was used directly in the next step.



The product **32** was synthesized following the same procedure as product **6**, using crude acid **28** (obtained via 1,3-*anti* reduction of acid **26** on 0.05 mmol scale) as the coupling partner. After workup, the crude mixture was dissolved into MeCN/10 mM $NaHCO_3$ (aq) 1:1 *v*/*v* (10

mL in total) and filtered through PTFE membrane to give the sample solution for preparative HPLC separation (concentration of product ~ 10 mM). The sample was then separated on a C18 preparative HPLC column using MeCN/10 mM NH_4HCO_3 (aq) as eluent (40% to 50% MeCN gradient, multiple injections). The peak with strong UV absorption was eluted at 18 min and was collected. The collected solutions from all injections were combined and concentrated under vacuum to remove most of the MeCN, and the water phase was thoroughly extracted with DCM (5 × 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product **32**-Na (in sodium salt form), also named as HL342, was obtained as colorless solid (8.4 mg, 23%).

R_f: 0.67 (pentane/EtOAc 1:1).

$[\alpha]_D^{296.7\ K}$ +83.8 (c = 0.42, DCM).

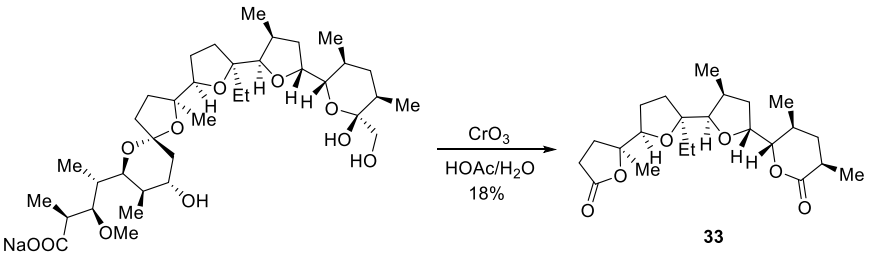
IR ν_{max} (cm^{-1}): 3435 (br), 2961, 2935, 2878, 1741, 1661, 1626, 1557, 1453, 1422, 1380, 1310, 1221, 1091, 1083, 990, 964, 947, 834.

^{1}H NMR (400 MHz, d_6-DMSO): δ 6.06 (s, 1H), 4.18 – 4.16 (m, 1H), 4.12 (d, *J* = 6.4 Hz, 1H), 3.86 (s, 1H), 3.90 – 3.83 (m, 1H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.66 (q, *J* = 6.8 Hz, 1H), 3.56 – 3.48 (m, 2H), 3.44 – 3.35 (m, 2H), 2.46 – 2.40 (m, 1H), 2.08 – 2.00 (m, 1H), 1.96 – 1.88 (m, 1H), 1.86 (dd, *J* = 12.4, 8.0 Hz, 1H), 1.73 (br, 1H), 1.66 – 1.33 (m, 13H), 1.26 – 1.17 (m, 4H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.78 (m, 15H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 6.8 Hz, 3H), 0.58 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, d_6-DMSO): δ 194.0, 178.4, 168.7, 148.8, 94.5, 94.4, 84.2, 83.7, 75.7, 74.1, 72.8, 70.3, 69.8, 69.6, 67.7, 42.6, 37.6, 37.0, 36.0, 34.90, 34.86, 31.2, 29.5, 28.3, 28.0, 27.2, 20.7, 17.8, 17.2, 15.8, 14.6, 13.9, 11.7, 9.6, 8.2, 7.3, 6.4.

HRMS (ESI) m/z [M-Na]$^-$: calcd. for $C_{38}H_{60}ClO_{10}$: 711.3880; found: 711.3919.

(2*S*,2'*R*,2''*R*,3''*S*,5'*S*,5''*R*)-5''-((2*S*,3*S*,5*R*)-3,5-Dimethyl-6-oxotetrahydro-2H-pyran-2-yl)-5'-ethyl-2,3''-dimethyldecahydro-[2,2':5',2''-terfuran]-5(2*H*)-one (33):



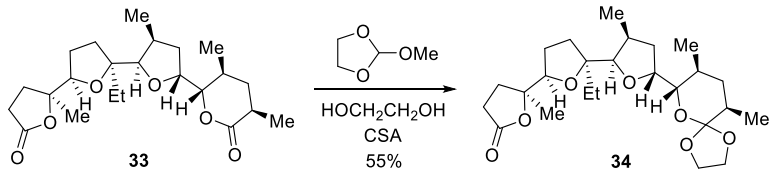
To a 250 mL round bottom flask, HOAc (36 mL) and H_2O (9 mL) were added, followed by CrO_3 (4.08 g, 40.8 mmol, 9.4 equiv). The mixture was cooled to 0 °C, then the solution of monensin sodium salt (3.00 g, 4.33 mmol, 1.0 equiv) in HOAc (42 mL) was added. The mixture was stirred at 0 °C to r.t. overnight. The mixture was then diluted with sat. NaCl solution (100 mL) and was extracted with $CHCl_3$ (5 × 100 mL). The combined organic phase was concentrated under vacuum, and the residue was co-evaporated with heptane to remove HOAc. The residue was then dissolved in water and extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography using heptane/EtOAc 3:1 to 2:1 *v*/*v* as eluent. The pure dilactone product **33** was obtained after two rounds of column chromatography separation as colorless syrup (311 mg, 18%). The product show identical spectroscopic data as the reported.[7,8]

R_f: 0.31 (heptane/EtOAc 1:1).

^{1}H NMR (400 MHz, in $CDCl_3$): δ 4.24 – 4.29 (m, 1H), 4.07 (dd, J_1 = 9.6 Hz, J_2 = 4.0 Hz, 1H), 4.02 (d, J = 4.0 Hz, 1H), 3.90 (dd, J_1 = 10.0 Hz, J_2 = 6.4 Hz, 1H), 2.84 (ddd, J_1 = 18.0 Hz, J_2 = 10.8 Hz, J_3 = 8.4 Hz, 1H), 2.63 (ddd, J_1 = 12.4 Hz, J_2 = 10.4 Hz, J_3 = 4.0 Hz, 1H), 2.39–2.48 (m, 2H), 2.24 – 2.32 (m, 1H), 2.09 – 2.15 (m, 1H), 2.05 (ddd, J_1 = 12.0 Hz, J_2 = 9.6 Hz, J_3 = 6.4 Hz, 1H), 1.90 (ddd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, J_3 = 4.0 Hz, 1H), 1.46 – 1.84 (m, 8H), 1.38 (q, J = 12.4 Hz, 1H), 1.31 (s, 3H), 1.26 (d, J = 7.2 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, in $CDCl_3$): δ 178.0, 174.0, 88.3, 88.1, 87.5, 86.8, 82.7, 77.4, 37.5, 36.2, 35.0, 34.9, 31.7, 30.4, 30.3, 30.0, 29.2, 28.3, 23.8, 18.4, 17.3, 15.7, 8.0.

(2*S*,2'*R*,2''*R*,3''*S*,5'*S*,5''*R*)-5''-((7*S*,8*S*,10*R*)-8,10-Dimethyl-1,4,6-trioxaspiro[4.5]decan-7-yl)-5'-ethyl-2,3''-dimethyldecahydro-[2,2':5',2''-terfuran]-5(2H)-one (34):



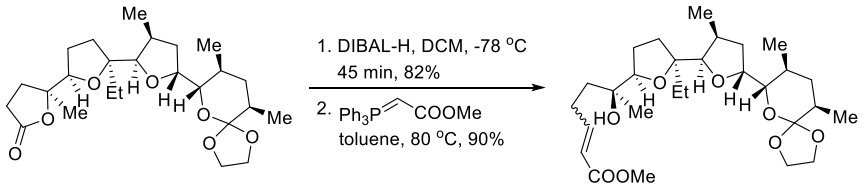
To a round bottom flask containing the dilactone **33** (152 mg, 0.372 mmol, 1.0 equiv), ethylene glycol (0.042 mL, 0.744 mmol, 2.0 equiv) and 2-methoxy-1,3-dioxolane (1.78 mL, 18.6 mmol, 50 equiv) were added, followed by camphorsulfonic acid (17 mg, 0.074 mmol, 0.20 equiv). The mixture was stirred at r.t. overnight. The reaction was then quenched by sat. $NaHCO_3$ solution, and the mixture was diluted with EtOAc. The organic phase was washed sequentially with sat. $NaHCO_3$ solution and brine, dired over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (buffered with Et_3N) using heptane/EtOAc 6:1 *v*/*v* as eluent. The product **34** was obtained as colorless liquid (92 mg, 55%). The product show identical spectroscopic data as the reported.[9,10]

R_f: 0.62 (heptane/EtOAc 1:1).

^{1}H NMR (400 MHz, in C_6D_6): δ 4.17 – 4.23 (m, 2H), 4.13 (d, J = 4.4 Hz, 1H), 4.07 (q, J = 6.8 Hz, 1H), 3.71 – 3.77 (m, 3H), 3.65 – 3.70 (m, 1H), 2.89 (ddd, J_1 = 17.6 Hz, J_2 = 10.4 Hz, J_3 = 8.4 Hz, 1H), 2.26 – 2.37 (m, 2H), 2.19 (ddd, J_1 = 17.2 Hz, J_2 = 10.4 Hz, J_3 = 4.4 Hz, 1H), 1.94 – 2.10 (m, 3H), 1.47 – 1.56 (m, 1H), 1.14 – 1.43 (m, 9H), 1.03 (d, J = 6.8 Hz, 3H), 1.02 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, in C_6D_6): δ 176.4, 121.4, 87.7, 87.0, 84.7, 81.8, 81.5, 77.2, 65.1, 64.8, 39.6, 36.7, 35.0, 34.1, 33.3, 30.2, 30.1, 29.8, 28.5, 28.4, 23.7, 17.3, 16.4, 15.5, 8.2.

Methyl (*S,Z/E*)-6-((2*S*,2'*R*,3'*S*,5*R*,5'*R*)-5'-((7*S*,8*S*,10*R*)-8,10-dimethyl-1,4,6-trioxaspiro[4.5]decan-7-yl)-2-ethyl-3'-methyloctahydro-[2,2'-bifuran]-5-yl)-6-hydroxyhept-2-enoate (36):



34 **36**

To a round bottom flask containing mono-protected dilactone **34** (92 mg, 0.202 mmol, 1.0 equiv), anhydrous DCM (5 mL) was added. The solution was cooled to -78 °C, then DIBAL-H (1.0 M solution in heptane, 0.283 mL, 0.283 mmol, 2.0 equiv) was added dropwise. The mixture was then stirred at -78 °C for 45 min. The reaction was quenched by MeOH, then water was added and the mixture was further stirred at r.t. for 30 min. The mixture was ex-

tracted with DCM, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (buffered with Et_3N) using heptane/EtOAc 2:1 *v*/*v* as eluent. The hemiacetal product **35** (mixture of two diastereomers) was obtained as colorless oil (76 mg, 82%), which was directly used in the next step.

To the round bottom flask containing the hemiacetal **35** (61 mg, 0.133 mmol, 1.0 equiv), anhydrous toluene (3 mL) was added, followed by ylide reagent (67 mg, 0.200 mmol, 1.5 equiv). The mixture was stirred at 80 ºC overnight. After cooled down to r.t., the mixture was directly purified by silica gel column chromatography (buffered with Et_3N) using heptane/EtOAc 6:1 *v*/*v* as eluent. The product **36** was obtained as colorless oil (*E*/*Z* > 10:1, 62 mg, 90%). The pure *E* product was obtained in pure form for characterization.

R_f: 0.43 (heptane/EtOAc 3:1).

$[\alpha]_D^{296.6\ K}$: +63.3 (*c* = 1.1, DCM).

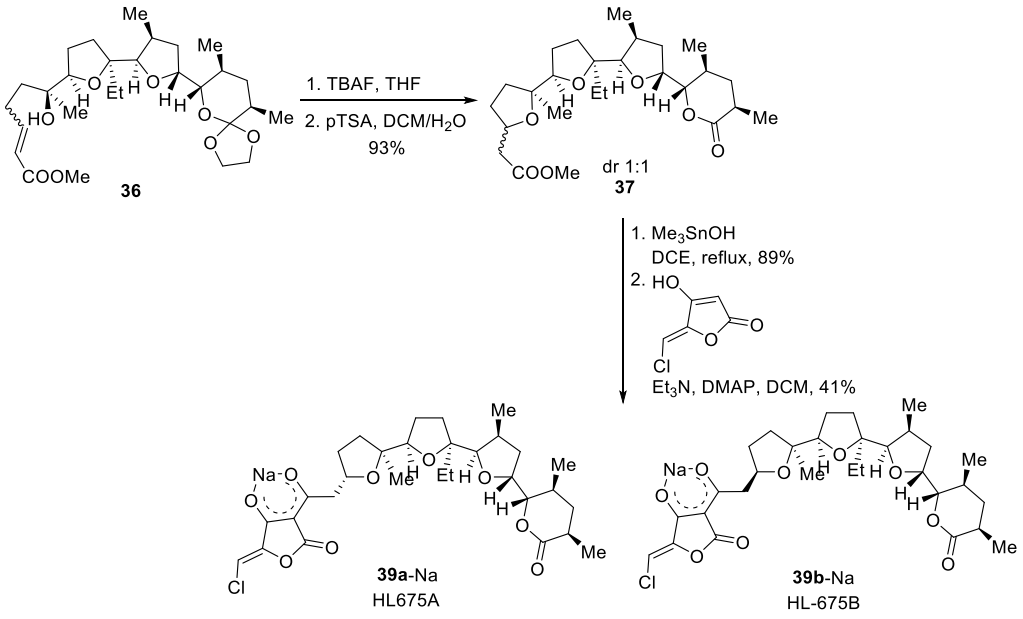
IR ν_{max} (cm^{-1}): 3439, 2965, 2923, 2880, 1725, 1656, 1462, 1271, 1094, 1039, 949.

^1H NMR (400 MHz, in C_6D_6, pure *E* isomer): δ 7.16 (dt, J_1 = 15.6 Hz, J_2 = 7.2 Hz, 1H), 5.93 (dt, J_1 = 15.6 Hz, J_2 = 1.6 Hz, 1H), 4.33 – 4.38 (m, 1H), 4.22 (d, *J* = 4.0 Hz, 1H), 4.13 – 4.19 (m, 3H), 3.85 (dd, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1H), 3.62 – 3.71 (m, 3H), 3.43 (s, 3H), 2.31 – 2.48 (m, 2H), 2.16 – 2.28 (m, 2H), 2.01 – 2.15 (m, 2H), 1.90 – 1.98 (m, 1H), 1.62 – 1.71 (m, 1H), 1.55 (ddd, J_1 = 13.2 Hz, J_2 = 12.0 Hz, J_3 = 4.8 Hz, 1H), 1.29 (s, 3H), 1.24 – 1.41 (m, 5H), 1.11 – 1.21 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.52 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, in C_6D_6, pure *E* isomer): δ 166.7, 150.3, 121.4, 121.1, 87.6, 87.5, 85.1, 80.3, 76.4, 73.0, 64.9, 64.1, 50.9, 39.4, 37.0, 36.5, 34.9, 32.9, 32.5, 31.3, 30.0, 27.7, 26.8, 24.8, 16.7, 15.9, 15.5, 8.1.

HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{28}H_{47}O_8$: 511.3265; found: 511.3280.

Sodium (*Z*)-2-(Chloromethylene)-4-(2-((2*S*,2'*R*,2''*R*,3''*S*,5*S*/*R*,5'*S*,5''*R*)-5''-((2*S*,3*S*,5*R*)-3,5-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)-5'-ethyl-2,3''-dimethyldodecahydro-[2,2':5',2''-terfuran]-5-yl)acetyl)-5-oxo-2,5-dihydrofuran-3-olate (HL675A, 39a-Na/HL675B, 39b-Na):



According to Fürstner's procedure[11], to a round bottom flask containing the enoate **36** (64 mg, 0.125 mmol, 1.0 equiv), anhydrous THF (6.2 mL, 50 mL/mmol substrate) was added. The mixture was cooled to 0 ºC, then TBAF (1 M solution in THF, 0.188 mL, 0.188 mmol, 1.5 equiv) was added. The mixture was stirred at 0 ºC for 3 h, then full conversion of the enoate was observed. The mixture was diluted with EtOAc and washed thoroughly with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was dissolved in DCM (5 mL). To this mixture, water (0.05 mL) was added, followed by *p*-toluenesulfonic acid monohydrate (24 mg, 0.125 mmol, 1.0 equiv). The mixture was stirred at r.t. for 2 h. After full conversion of the orthoester, the mixture was diluted with DCM. The organic phase was washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography using heptane/EtOAc 5:1 to 3:1 *v*/*v* as eluent. The product **37** was obtained as colorless oil (1:1 mixture of diastereomers, 54 mg, 93%).

To a round bottom flask containing the methyl ester **37** (49 mg, 0.105 mmol, 1.0 equiv), Me_3SnOH (95 mg, 0.525 mmol, 5.0 equiv) was added, followed by anhydrous 1,2-dichloroethane (DCE, 5 mL). The mixture was heated to reflux and stirred under argon for 48 h. After full conversion of the methyl ester, the mixture was cooled to r.t., and acidified with 1 M HCl solution. The organic phase was washed with 1 M HCl solution and water, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography using heptane/EtOAc 2:1 to 1:1 *v*/*v* (with 0.1% *v*/*v* HOAc

added) as eluent. The acid product **38** (HL749) was obtained as colorless oil (1:1 mixture of diastereomers, 42 mg, 89%).

To a flame dried Schlenk tube containing tetronic acid (crude solid prepared from **8a** as mentioned before, 0.080 mmol, 2.0 equiv), the acid (1:1 mixture of diatereomers, 18 mg, 0.040 mmol, 1.0 equiv) was added, followed by anhydrous DCM (2 mL). To this mixture, Et_3N (0.011 mL, 0.080 mmol, 2.0 equiv) was added, followed by DCC (17 mg, 0.080 mmol, 2.0 equiv) and DMAP (1.6 mg, 0.013 mmol, 0.33 equiv). The mixture was stirred at r.t. under argon overnight, and the formation of white precipitate DCU was observed. The mixture was then diluted with ethyl acetate, and the organic phase was washed with 1 M HCl (aq) to removed DMAP and Et_3N. Then the organic phase was washed with sat. $NaHCO_3$ (aq) to removed excess amount of tetronic acid, and the product with ionophore property was transformed to its sodium salt and retained in the organic phase. The organic phase was dired over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was treated with MeCN, and the insoluble DCU was removed by filtration. The filtrate was concentrated again, and the residue was separated by preparative TLC using EtOAc as eluent to separate the two diastereomers. The upper spot A and lower spot B were further purified respectively by preparative HPLC on C18 column using MeCN/10 mM NH_4HCO_3 (aq) as eluent (45% to 60% MeCN gradient, multiple injections). Both spots A and B were eluted at the same retention time (8.3 min). For each spot, the collected fractions were combined and concentrated under vacuum to remove MeCN. Then the water solution was extracted repeatedly with DCM (5 × 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The spot A (sodium salt) **39a**-Na, also named as HL675A, was obtained as white solid (5.8 mg), and the spot B (sodium salt) **39b**-Na, also named as HL675B, was obtained as white solid (4.0 mg). The combined yield for the two diastereomers was 41%. The configuration of the new chiral center in **39a**-Na and **39b**-Na was assigned ambiguously, based on the comparison of the structures with the reported XRD structure of monensin-Na complex. The structure of **39a**-Na bearing *S* configuration at the new chiral center overlaps well with monensin-Na, which leads to sharp ^{13}C signals for the tetronate group. Meanwhile, the structure of **39b**-Na bearing *R* configuration at the new chiral center shows much inferior overlap with monsin-Na, which leads to flexible complex structure in solution phase and broaden (even disappearing) ^{13}C signals of the tetronate group.

Compound HL675A (39a-Na):

R_f: 0.40 (EtOAc).

$[\alpha]_D^{296.6\ K}$: –35.6 (*c* = 0.32, DCM).

IR ν_{max} (cm^{-1}): 2965, 2917, 1754, 1713, 1664, 1624, 1454, 1377, 1220, 1087, 935, 735.

^1H NMR (500 MHz, in d_6-DMSO): δ 6.03 (s, 1H), 4.18 – 4.23 (m, 2H), 4.05 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 3.90 (d, *J* = 4.5 Hz, 1H), 3.62 (dd, J_1 = 9.0 Hz, J_2 = 6.5 Hz, 1H), 2.93 (dd, J_1 = 14.5 Hz, J_2 = 6.0 Hz, 1H), 2.74 (dd, J_1 = 14.5 Hz, J_2 = 7.5 Hz, 1H), 2.46 – 2.49 (m, 1H), 2.23 – 2.27 (m, 1H), 1.91 – 2.04 (m, 4H), 1.74 – 1.81 (m, 3H), 1.56 – 1.64 (m, 2H), 1.43 – 1.54 (m, 5H), 1.36 (q, *J* = 12.5 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, in d_6-DMSO): δ 190.7, 178.3, 173.7, 168.6, 148.9, 94.4, 94.1, 87.3, 86.1, 84.9, 83.4, 82.8, 77.2, 76.1, 47.1, 36.3, 35.1, 35.0, 34.4, 33.7, 31.5, 30.8, 30.3, 28.8, 28.1, 23.4, 18.2, 16.8, 15.5, 8.0.

HRMS (ESI) *m/z* $[M-H]^-$ calc. for $C_{30}H_{40}ClO_9$: 579.2366; found: 579.2392.

Compound HL675B (39b-Na):

R_f: 0.28 (EtOAc).

$[\alpha]_D^{296.6\ K}$: +55.4 (*c* = 0.27, DCM).

IR ν_{max} (cm^{-1}): 2968, 2915, 1754, 1732, 1626, 1448, 1085, 943, 736.

^1H NMR (500 MHz, in d_6-DMSO): δ 6.01 (s, 1H), 4.18 – 4.23 (m, 2H), 4.05 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 3.92 (d, *J* = 4.5 Hz, 1H), 3.59 (dd, J_1 = 9.0 Hz, J_2 = 6.5 Hz, 1H), 2.95 (dd, J_1 = 14.5 Hz, J_2 = 6.0 Hz, 1H), 2.69 (dd, J_1 = 14.5 Hz, J_2 = 7.5 Hz, 1H), 2.47 – 2.52 (m, 1H), 2.23 – 2.27 (m, 1H), 1.89 – 2.02 (m, 4H), 1.74 – 1.82 (m, 3H), 1.59 – 1.67 (m, 2H), 1.44 – 1.55 (m, 5H), 1.34 (q, *J* = 12.5 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, in d_6-DMSO): δ 178.3, 173.7, 168.5, 94.3, 93.9, 87.3, 86.0, 84.7, 83.3, 82.5, 77.2, 74.9, 46.7, 36.3, 35.1, 35.0, 34.8, 34.4, 31.4, 30.8, 30.5, 28.8, 27.6, 21.7, 18.2, 16.8, 15.6, 8.0. (The absence of two peaks from the 3-acyl tetronic acid unit and some broaden peaks were observed after > 20000 scans due to the conformational flexibility.)

HRMS (ESI) *m/z* $[M-H]^-$ calc. for $C_{30}H_{40}ClO_9$: 579.2366; found: 579.2387.

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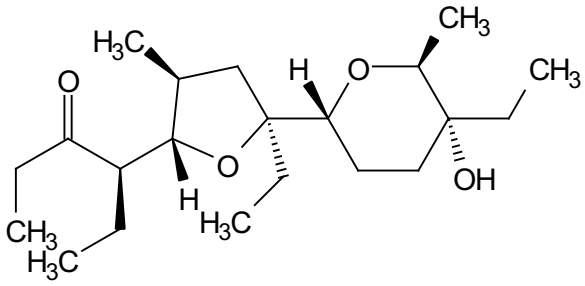
11. Valot, G. *et al.* Total Synthesis of Amphidinolide F. *Angew. Chemie Int. Ed.* **52**, 9534–9538 (2013).

Compound 4



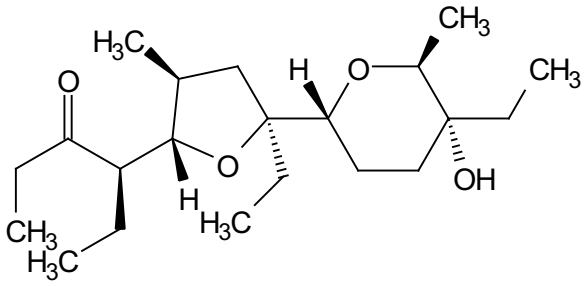
3.7642 3.7471 3.5672 3.5539 3.5431 3.4890 3.4668 2.6251 2.6132 2.5997 2.5953 2.5902 2.5857 2.5771 2.5736 2.5668 2.5603 2.5495 2.4689 2.4509 2.4229 1.8547 1.8343 1.8234 1.8032 1.7538 1.7358 1.7277 1.6243 1.6141 1.6108 1.6071 1.5972 1.5897 1.5735 1.5676 1.5588 1.5450 1.5407 1.5325 1.5275 1.5153 1.5084 1.5007 1.4938 1.4901 1.4740 1.4693 1.4623 1.4552 1.4463 1.4356 1.4151 1.3968 1.3837 1.3797 1.3662 1.3623 1.3484 1.3404 1.3296 1.3217 1.3109 1.3036 1.2858 1.1970 1.1797 1.0207 1.0027 0.9847 0.9088 0.8984 0.8902 0.8824 0.8715 0.8327 0.8143 0.7957

1.00 1.05 0.96 3.17 1.14 1.22 1.04 1.28 11.54 3.03 3.19 6.34 6.08

.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

f1 (ppm)

Compound 4

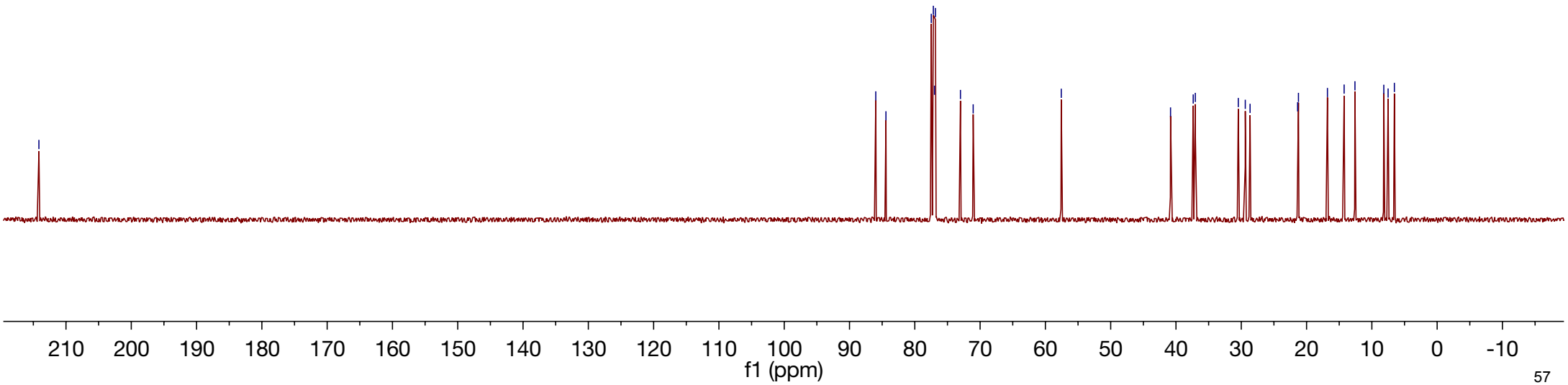


214.1463

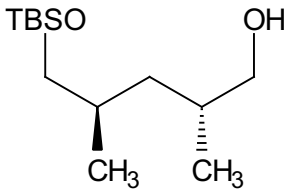
85.9790
84.4197
77.4780
77.1600
76.9802
76.8416
73.0083
71.0595

57.5702

40.8321
37.3610
37.0394
30.4575
29.3856
28.6525
21.3692
21.2420
16.8021
14.2465
12.5901
8.1714
7.5124
6.5505

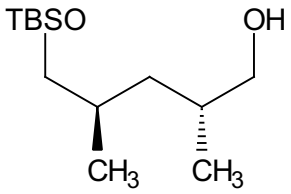


Compound 10

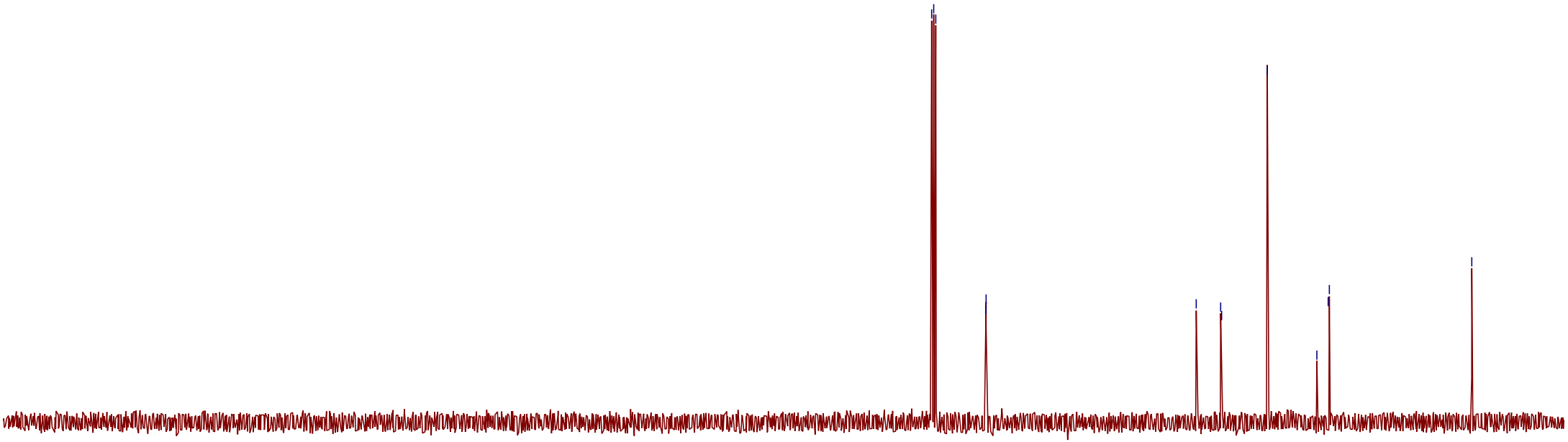

TBSO
OH
CH3
CH3

3.5017
3.4863
3.4756
3.4599
3.4524
3.4368
3.4253
3.4154
3.4110
3.3995
3.3954
3.3864
1.7916
1.7753
1.7627
1.7580
1.7525
1.7474
1.7410
1.7363
1.7308
1.7249
1.7203
1.7143
1.7092
1.6977
1.6819
1.5428
1.4726
1.2494
1.2375
1.2155
1.2039
1.1933
1.1813
1.1652
1.1528
1.1424
1.1307
1.1089
0.9022
0.8960
0.8855
0.8671
0.8505
4.30
2.13
1.00
2.19
16.41
6.48
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

Compound 10



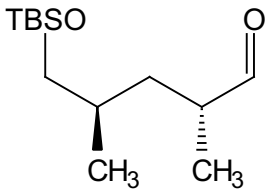
77.4779
77.1604
76.8429
69.1760
69.1416
36.9753
33.2353
33.0867
26.1006
18.5076
16.7764
16.5982
-5.2078



210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

Compound 11

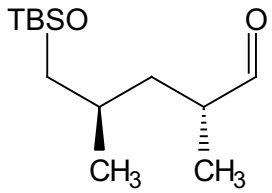


9.6255
9.6206
7.2600
3.4707
3.4561
3.4461
3.4354
3.4315
3.4204
3.4110
3.3958
2.4833
2.4815
2.4676
2.4633
2.4470
2.4303
2.4141
2.4096
2.3971
2.3941
1.7453
1.7301
1.7139
1.7090
1.6990
1.6940
1.6779
1.6629
1.5498
1.5309
1.5160
1.5096
1.4963
1.4818
1.4754
1.4604
1.4494
1.4357
1.4284
1.4149
1.4014
1.3942
1.3804
1.0848
1.0674
0.8948
0.8875
0.8802
0.8728
0.0350

0.90
2.09
1.00
0.99
2.05
3.07
12.15
6.00

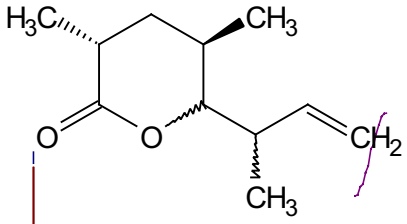
f1 (ppm)

Compound 11


TBSO
O
CH3
CH3

205.5086
77.4786
77.1611
76.8438
68.2843
44.2959
34.1069
33.3817
26.0664
18.4647
16.6352
13.6062
-5.2546
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 12



7.2598

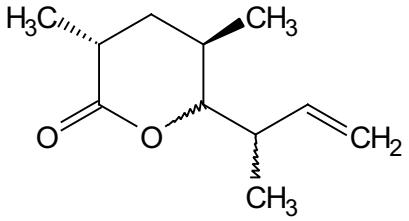
5.9840 5.9661 5.9580 5.9405 5.9231 5.9148 5.8970 5.1386 5.1351 5.1316 5.1036 5.1010 5.0970 5.0919 5.0885 5.0775 5.0748 5.0714 4.0398 4.0334 4.0154 4.0090 2.6574 2.6395 2.6273 2.6217 2.6093 2.5915 2.5736 2.4424 2.4237 2.4024 2.3832 2.1775 2.1685 2.1600 2.1512 2.1427 2.1339 2.1252 2.1179 1.9687 1.9604 1.9507 1.9425 1.9347 1.9263 1.9170 1.9085 1.7143 1.7045 1.6829 1.6731 1.6502 1.6404 1.5495 1.3006 1.2828 1.0366 1.0189 1.0126 0.9853

0.99 2.08 1.00 1.00 1.05 1.04 1.02 1.04 3.25 2.68 3.28

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

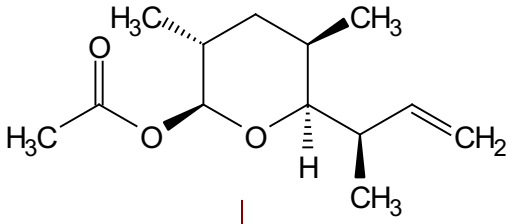
f1 (ppm)

Compound 12


H3C
CH3
O
O
CH2
CH3

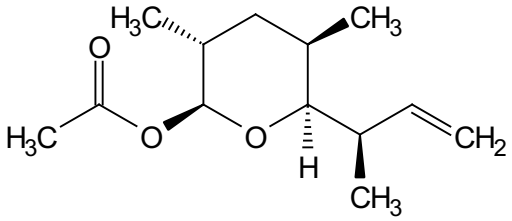
174.2021
140.3642
115.1480
87.1455
77.4775
77.1595
76.8412
39.5137
36.4427
31.2932
28.0722
17.9847
15.5138
10.8444
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 13


H3C
CH3
O
H3C
O
O
H
CH2
CH3

5.9609
5.9451
5.9346
5.9180
5.9015
5.8912
5.8753
5.2345
5.2117
5.0599
5.0559
5.0521
5.0167
5.0128
5.0090
5.0021
4.9985
4.9948
4.9758
4.9716
3.2887
3.2833
3.2636
3.2582
2.3310
2.3135
2.2905
2.2721
2.1127
1.8776
1.8724
1.8551
1.8484
1.8324
1.8251
1.7403
1.7335
1.7236
1.7063
1.6996
1.6899
1.5453
1.4927
1.4811
1.4598
1.4484
1.4302
1.4155
1.0096
0.9922
0.9375
0.9204
0.8359
0.8197
0.0669
1.02
1.00
2.09
1.03
1.02
3.16
2.05
1.09
1.27
3.10
3.13
3.14
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

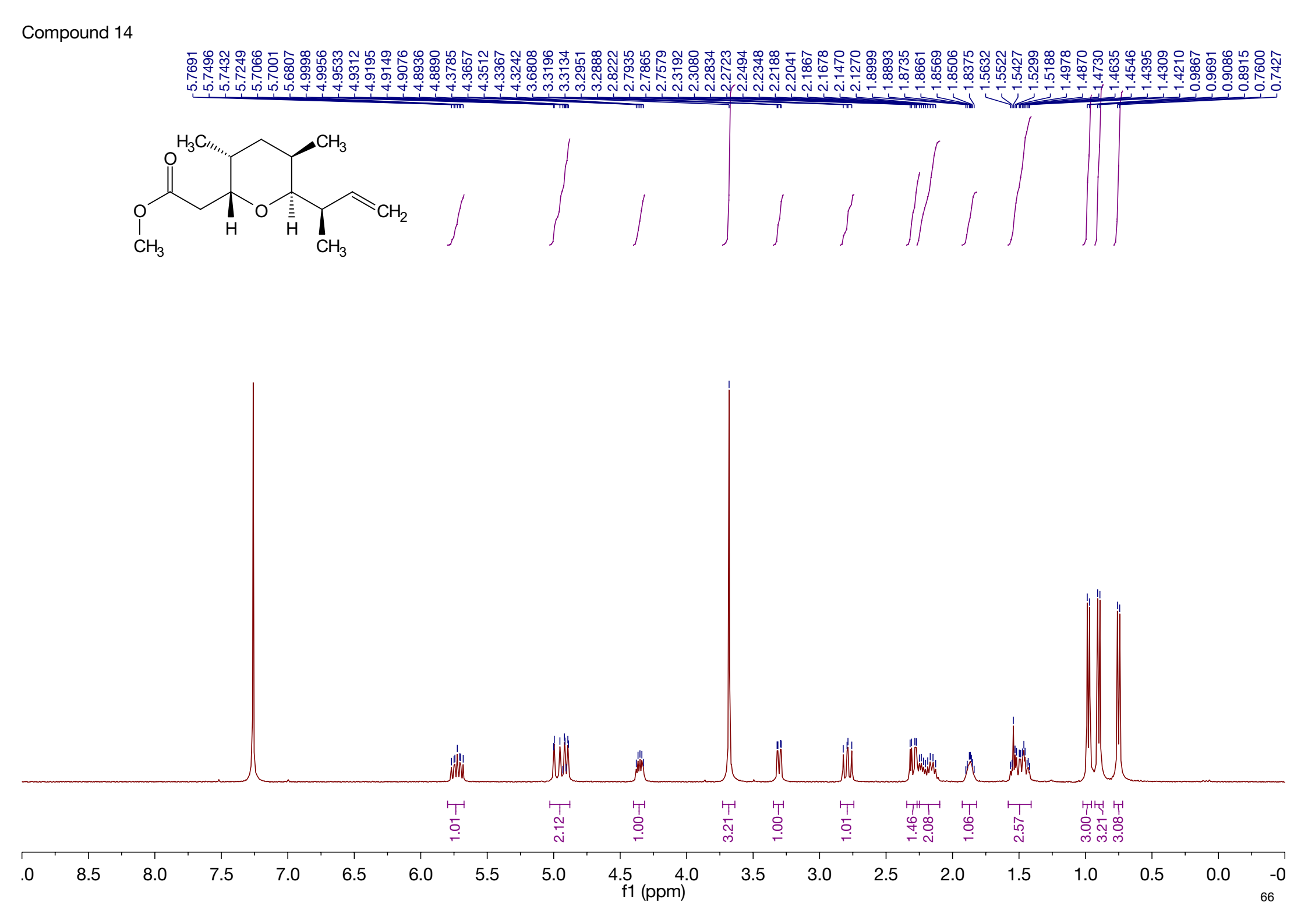
Compound 13



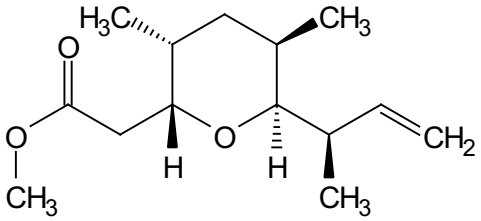
169.9535
141.8777
113.6680
99.6772
83.1048
77.4806
77.1629
76.8450
39.0442
38.5232
29.6018
28.9855
21.3302
16.2024
15.4799
12.0853

f1 (ppm)

Compound 14

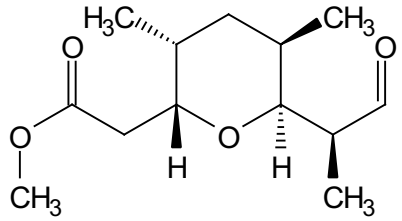

5.7691
5.7496
5.7432
5.7249
5.7066
5.7001
5.6807
4.9998
4.9956
4.9533
4.9312
4.9195
4.9149
4.9076
4.8936
4.8890
4.3785
4.3657
4.3512
4.3367
4.3242
3.6808
3.3196
3.3134
3.2951
3.2888
2.8222
2.7935
2.7865
2.7579
2.3192
2.3080
2.2834
2.2723
2.2494
2.2348
2.2188
2.2041
2.1867
2.1678
2.1470
2.1270
1.8999
1.8893
1.8735
1.8661
1.8569
1.8506
1.8375
1.5632
1.5522
1.5427
1.5299
1.5188
1.4978
1.4870
1.4730
1.4635
1.4546
1.4395
1.4309
1.4210
0.9867
0.9691
0.9086
0.8915
0.7600
0.7427
H3C
CH3
O
O
CH3
H
O
H
CH2
CH3
1.01
2.12
1.00
3.21
1.00
1.01
1.46
2.08
1.06
2.57
3.00
3.21
3.08
f1 (ppm)

Compound 14


H3C
CH3
O
O
O
CH3
H
H
CH3
CH2

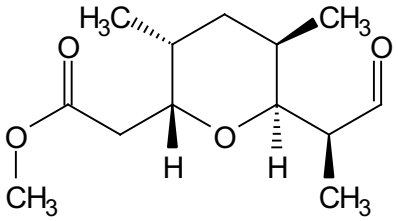
172.4625
143.3232
113.1055
77.4776
77.1604
76.8422
75.1439
74.9580
51.7955
39.9454
34.9390
31.9034
29.0077
26.8324
17.5850
16.1116
11.8257
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 7


H3C
CH3
O
O
O
O
H
H
CH3
CH3

9.5392
9.5304
7.2593
4.3405
4.3280
4.3135
4.2987
4.2862
3.8248
3.8185
3.7991
3.7927
3.6890
3.6810
3.6699
3.6601
2.8378
2.8090
2.8029
2.7738
2.3898
2.3729
2.3644
2.3556
2.3471
2.3388
2.3324
2.3220
2.3119
2.3041
2.2982
2.2873
2.2727
2.2583
2.2427
2.2272
1.8822
1.8741
1.8646
1.8561
1.8468
1.8388
1.6093
1.5982
1.5791
1.5752
1.5646
1.5434
1.5326
1.5160
1.5067
1.4979
1.4822
1.4734
1.4637
0.9977
0.9802
0.9567
0.9393
0.7801
0.7627
0.95
1.00
1.01
3.01
1.03
3.14
1.04
2.41
2.97
3.16
3.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

Compound 7

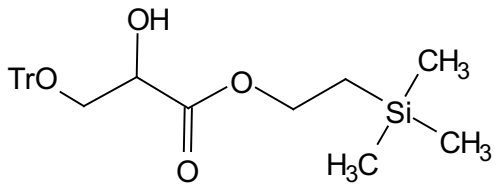


205.3160
172.4413
77.4778
77.1599
76.8420
75.3122
71.9929
51.9986
48.3274
34.3802
31.7709
28.5813
26.8057
17.5395
11.8764
9.7613

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

f1 (ppm)

Compound 17



7.462 7.458 7.441 7.331 7.314 7.309 7.294 7.273 7.270 7.266 7.258 7.252 7.245 7.234

4.321 4.315 4.298 4.294 4.277 4.272 4.266 4.266 4.258 4.255 4.247 4.240 3.525 3.517 3.501 3.494 3.396 3.388 3.373 3.365 3.277 3.258

1.005 0.999 0.989 0.982 0.978 0.972 0.962 0.956

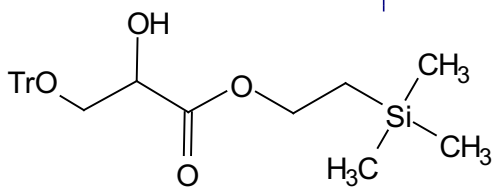
0.046

6.22 6.16 3.07 3.07 1.03 1.05 1.00 2.00 8.06

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0

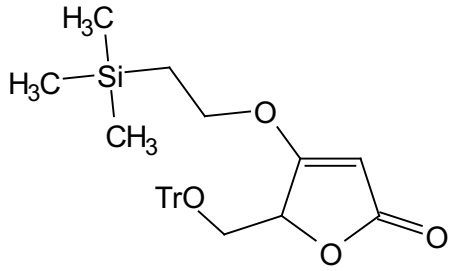
f1 (ppm)

Compound 17


OH
TrO
O
O
Si
CH3
CH3
H3C

173.339
143.689
128.737
127.928
127.195
86.419
77.479
77.161
76.843
70.868
65.420
64.228
17.583
1.418
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 18



7.448 7.444 7.427 7.334 7.330 7.325 7.313 7.294 7.276 7.274 7.270 7.267 7.259 7.253 7.251 7.246 7.238 7.234 7.231

5.145 4.837 4.833 4.830 4.826 4.822 4.820 4.163 4.145 4.138 4.118 4.096 4.076 4.069 4.051 3.609 3.602 3.583 3.576 3.294 3.283 3.268 3.257

1.103 1.098 1.083 1.079 1.076 1.061 1.056

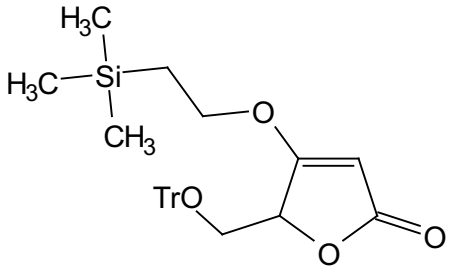
0.032

5.97 5.93 3.32 0.99 1.00 2.03 1.00 1.00 2.03 8.99

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

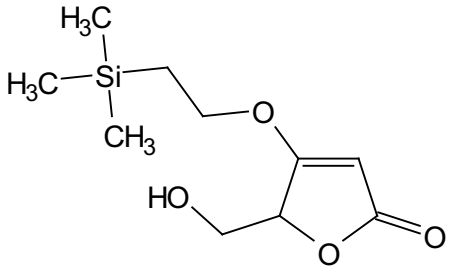
f1 (ppm)

Compound 18

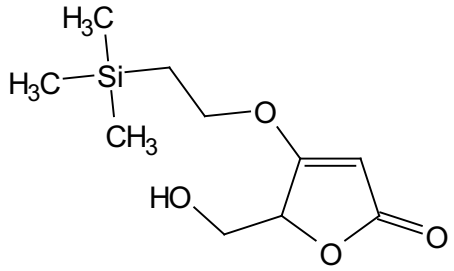

H3C
H3C
Si
CH3
O
TrO
O
O

179.036
173.173
143.515
128.722
127.988
127.248
89.617
86.620
78.677
77.477
77.158
76.840
71.242
61.987
17.343
1.344
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

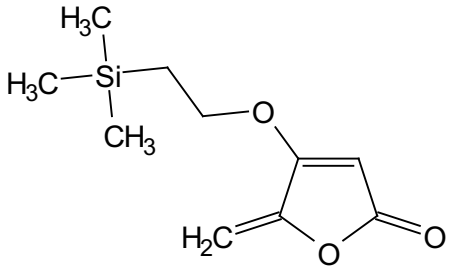
Compound SI-3



Compound SI-3

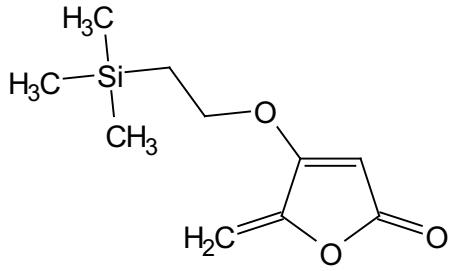


Compound 19


H3C
H3C
Si
CH3
O
H2C
O
O

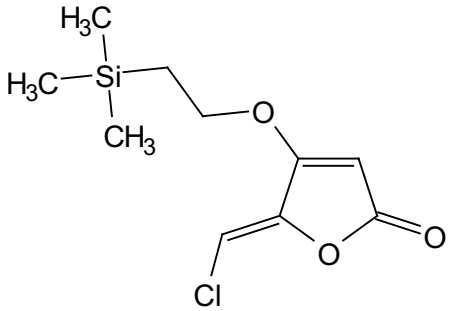
7.270
5.190
5.187
5.042
5.036
5.032
5.025
5.023
5.018
5.017
4.195
4.174
4.153
1.201
1.180
1.160
0.086
1.00
2.10
2.11
2.09
9.34
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

Compound 19


H3C
H3C
Si
CH3
O
H2C
O
O

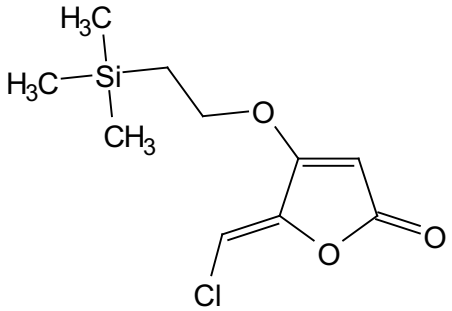
168.802
168.745
150.217
92.295
89.844
77.479
77.161
76.843
71.105
17.301
1.319
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 8a


H3C
H3C
Si
CH3
O
O
O
Cl

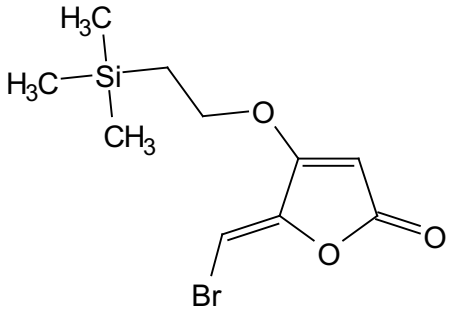
7.270
6.063
5.205
4.205
4.184
4.163
1.191
1.171
1.150
0.087
1.00
1.03
2.14
2.17
9.31
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

Compound 8a


H3C
H3C
Si
CH3
O
O
O
Cl

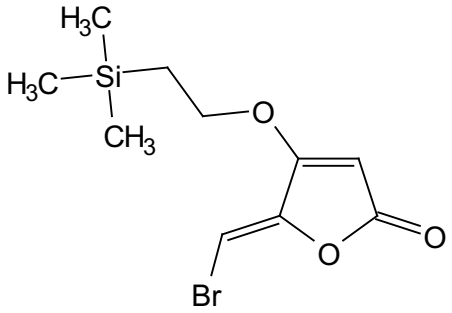
168.045
167.265
145.391
99.951
89.325
77.479
77.160
76.842
71.560
17.368
-1.319
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 8b


H3C
H3C
Si
CH3
O
O
O
Br

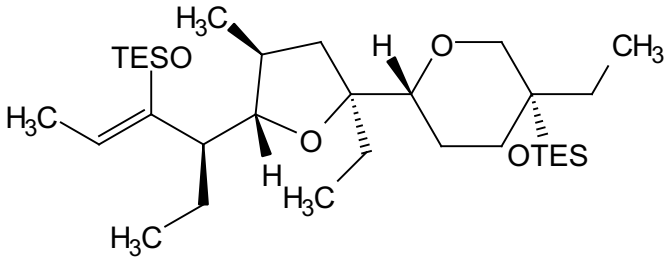
7.270
6.165
5.234
4.199
4.179
4.157
1.192
1.171
1.151
0.088
1.00
1.03
2.11
2.10
9.38
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

Compound 8b

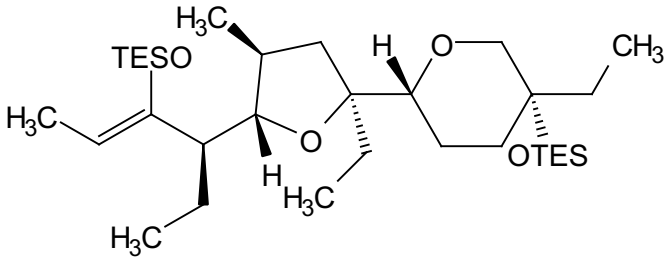

H3C
H3C
Si
CH3
O
O
O
Br

167.690
167.301
147.400
89.558
87.767
77.477
77.161
76.841
71.576
17.362
-1.315
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 20a

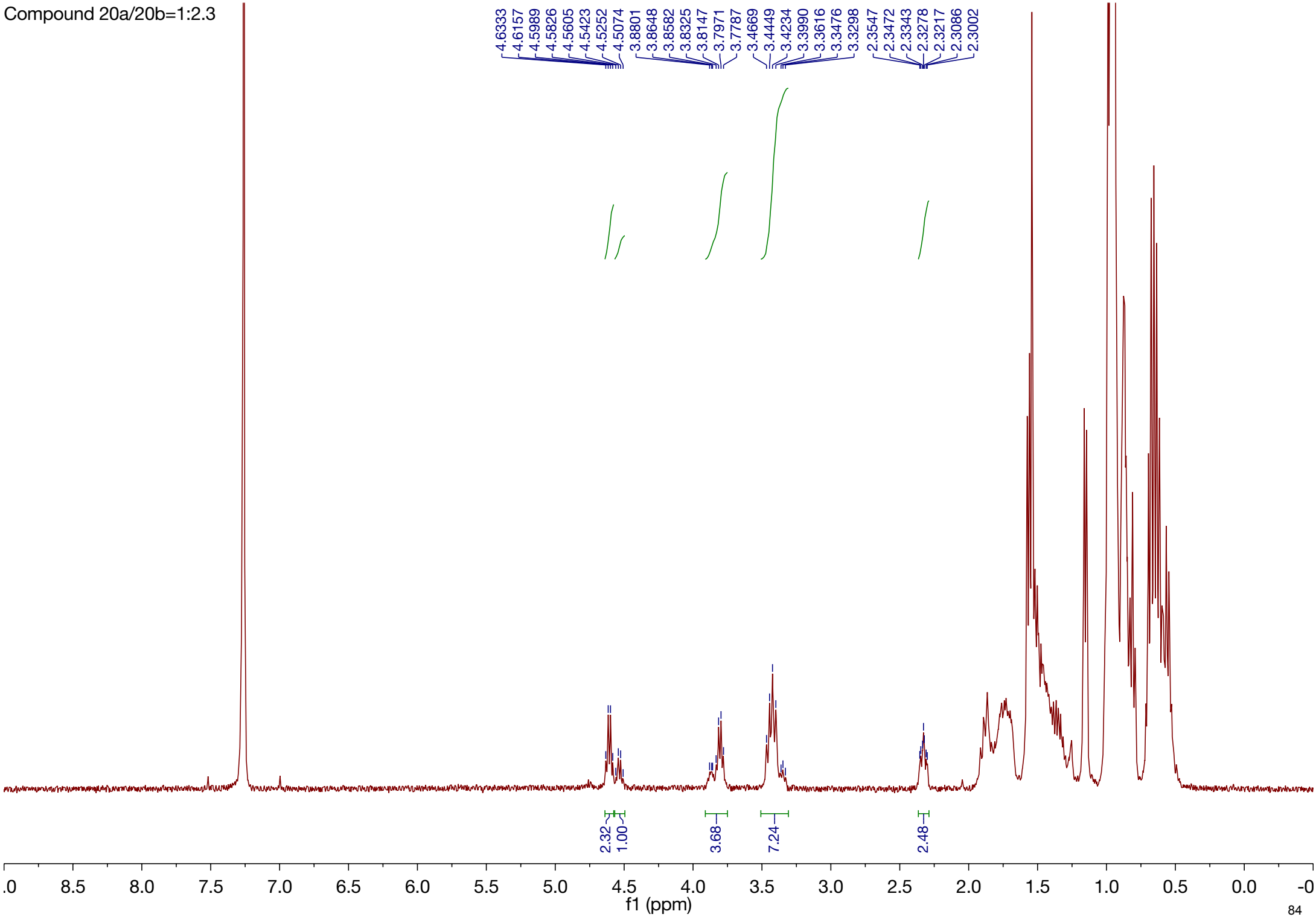


Compound 20a

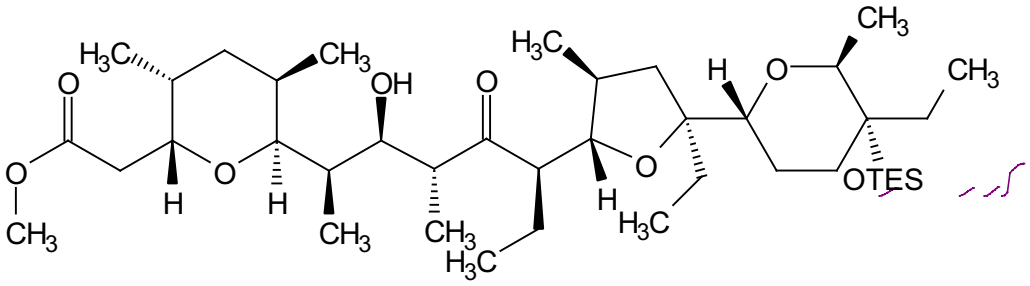


151.1084
101.9469
87.7450
84.4323
77.4781
77.1602
76.8429
76.6731
75.1538
74.9340
53.5193
41.9384
38.6458
30.9956
30.8817
28.3631
22.8474
21.7859
17.6149
15.5228
12.5248
11.0218
8.3052
7.4661
7.1357
7.0804
7.0006
6.1180

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

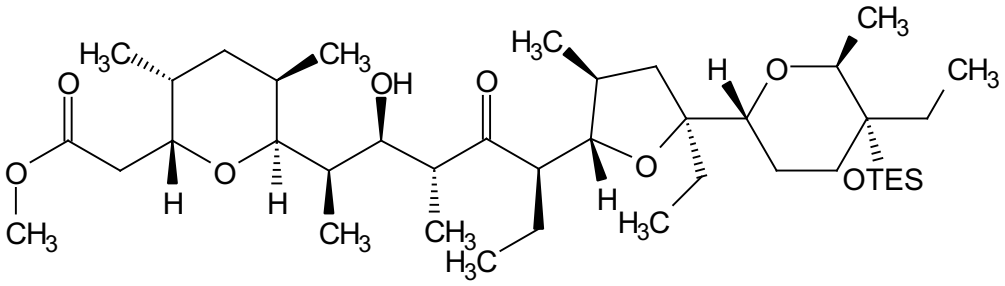

Compound 20a/20b=1:2.3
4.6333
4.6157
4.5989
4.5826
4.5605
4.5423
4.5252
4.5074
3.8801
3.8648
3.8582
3.8325
3.8147
3.7971
3.7787
3.4669
3.4449
3.4234
3.3990
3.3616
3.3476
3.3298
2.3547
2.3472
2.3343
2.3278
2.3217
2.3086
2.3002
2.32
1.00
3.68
7.24
2.48
f1 (ppm)

Compound 22


H3C
CH3
OH
O
O
O
O
CH3
H
H
CH3
CH3
H3C
H3C
H
O
CH3
CH3
OTES
H
H3C

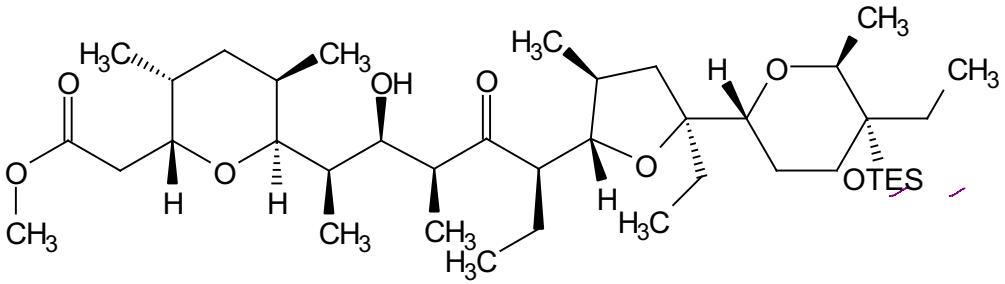
3.8507 3.8424 3.8262 3.7667 3.7480 3.7305 3.5308 3.5252 3.5058 3.5002 3.4660 3.4382 3.1962 3.1815 2.8066 2.3215 2.3114 2.2885 2.2784 1.8574 1.8272 1.8000 1.7650 1.7446 1.6314 1.5997 1.5386 1.5264 1.5115 1.5053 1.4944 1.4868 1.4830 1.4717 1.4631 1.4492 1.4308 1.4204 1.4123 1.3940 1.3841 1.3008 1.2962 1.2822 1.2789 1.2621 1.1247 1.1076 0.9887 0.9782 0.9744 0.9681 0.9586 0.9483 0.9439 0.9386 0.9132 0.8955 0.8772 0.8673 0.8543 0.8492 0.8357 0.8308 0.8170 0.7677 0.7505 0.6558 0.6362 0.6220 0.6184 0.6155 0.6018 0.5942 0.5820 0.5728 0.5610 0.5388
1.00 1.00 1.12 4.02 0.99 1.01 1.00 1.00 0.99 0.97 1.03 0.98 5.28 10.35 3.15 2.85 34.21 6.06 9.96
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

Compound 22



215.7639
174.6516
84.5870
83.8220
77.4775
77.1597
76.8431
76.6599
75.3654
74.9973
73.9576
71.9766
70.4209
57.7517
52.7321
47.1887
37.0274
36.3358
34.9926
32.3083
31.8014
28.9208
26.9763
17.7747
17.6466
16.1123
15.5470
13.6468
12.4959
11.7018
7.9687
7.4649
7.2460
7.0551
6.9543
6.7495

Compound 23



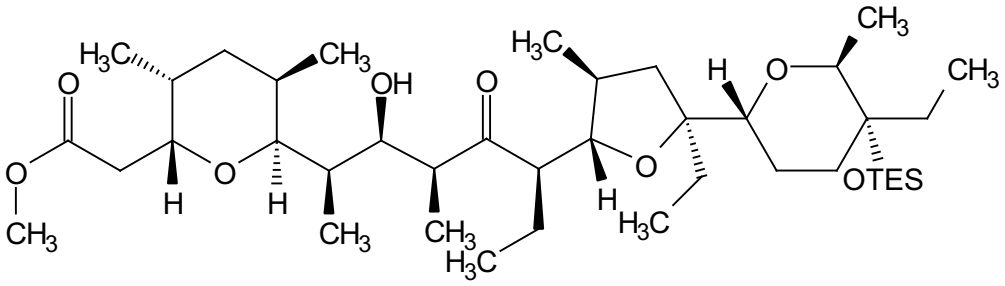
3.7006 3.6939 3.6822 3.5035 3.4794 3.4370 3.4309 3.4233 3.4176 2.2304 1.7946 1.7865 1.7741 1.7659 1.6803 1.6154 1.5889 1.5818 1.4824 1.4674 1.4471 1.4362 1.4290 1.4227 1.4185 1.4115 1.3136 1.3070 1.2960 1.2895 1.2825 1.2714 1.2648 1.2030 1.1966 1.1855 1.1790 1.1279 1.1218 1.1107 1.1045 0.9556 0.9449 0.9385 0.9247 0.9180 0.9049 0.8986 0.8844 0.8784 0.8672 0.8612 0.8483 0.8422 0.8297 0.8235 0.8172 0.8048 0.7986 0.7860 0.7806 0.7732 0.7668 0.7560 0.7498 0.7337 0.7275 0.7164 0.7100 0.6219 0.6156 0.6022 0.5961 0.5822 0.5768 0.5654 0.5596 0.5535

1.03 0.95 5.32 1.00 2.16 1.05 1.01 1.01 2.31 4.43 0.93 2.38 7.88 3.52 3.52 3.27 34.68 7.18

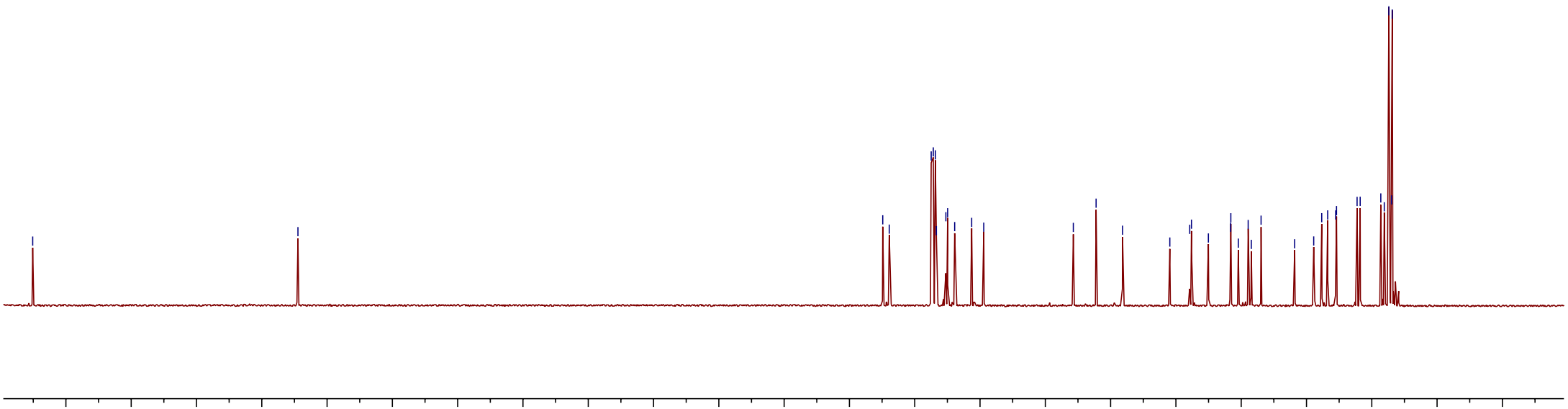
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

f1 (ppm)

Compound 23

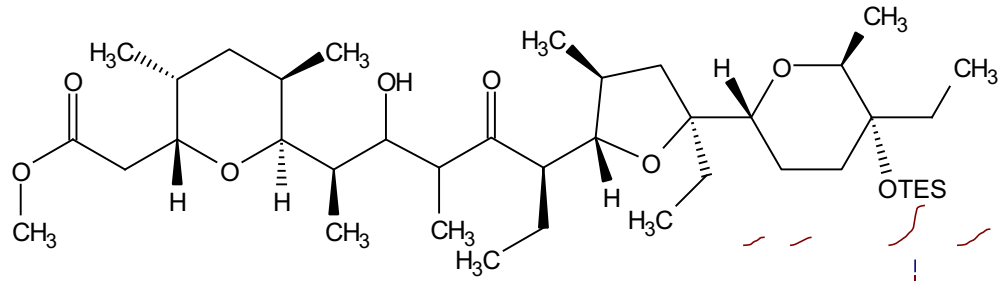


215.0843
174.4631
84.8977
83.9030
77.4793
77.1600
76.8420
76.6815
75.2290
74.9599
73.8825
71.2776
69.4293
55.7100
52.2223
48.1714
40.9319
37.8829
37.6167
35.0249
31.6105
31.5877
30.4429
28.9318
26.9562
18.8938
17.6677
16.7527
15.5302
15.4030
12.2511
11.7770
8.6186
8.0872
7.3884
6.9821

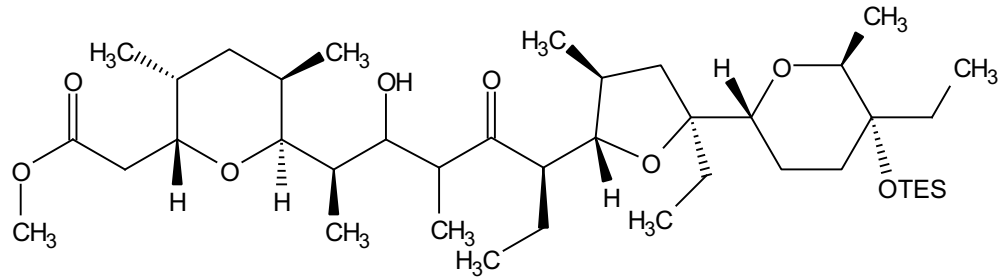


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

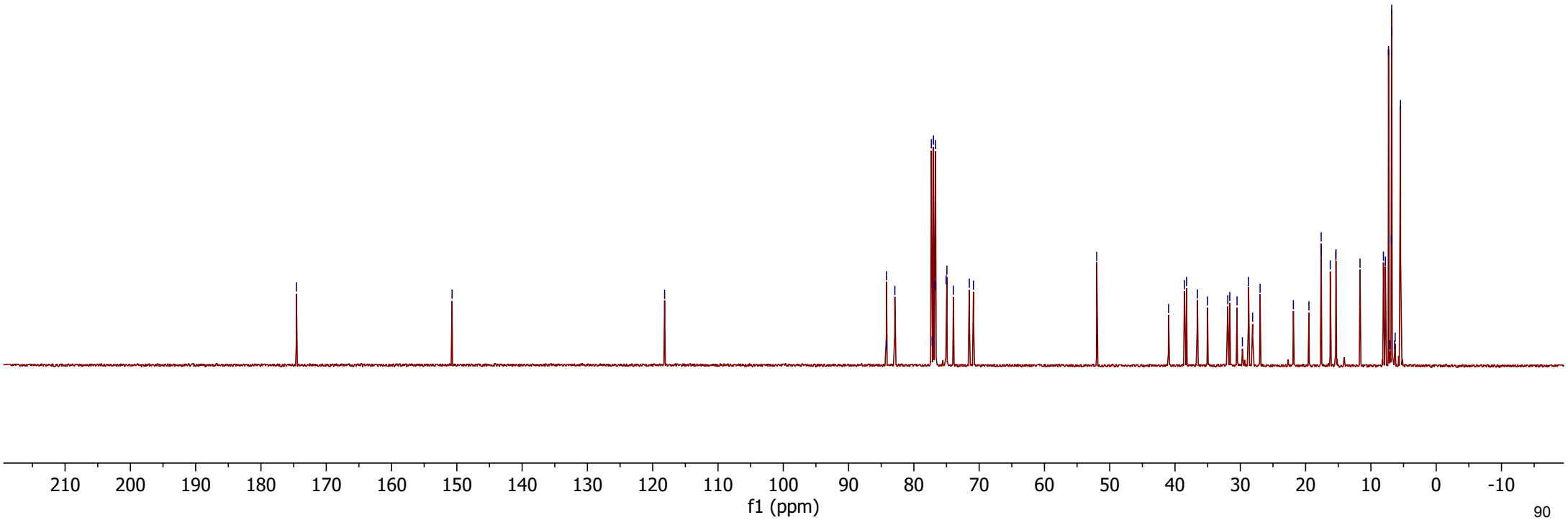
f1 (ppm)

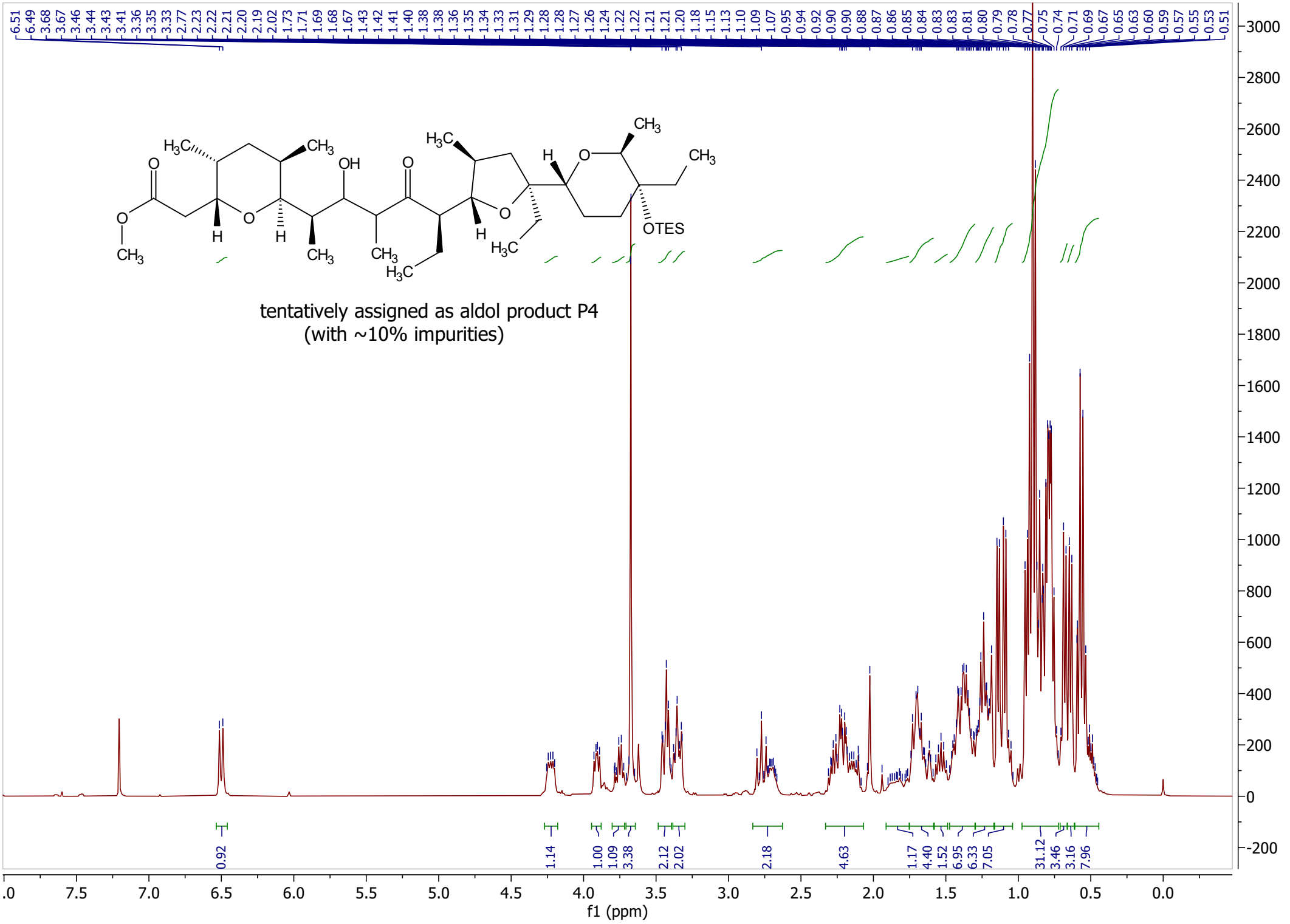


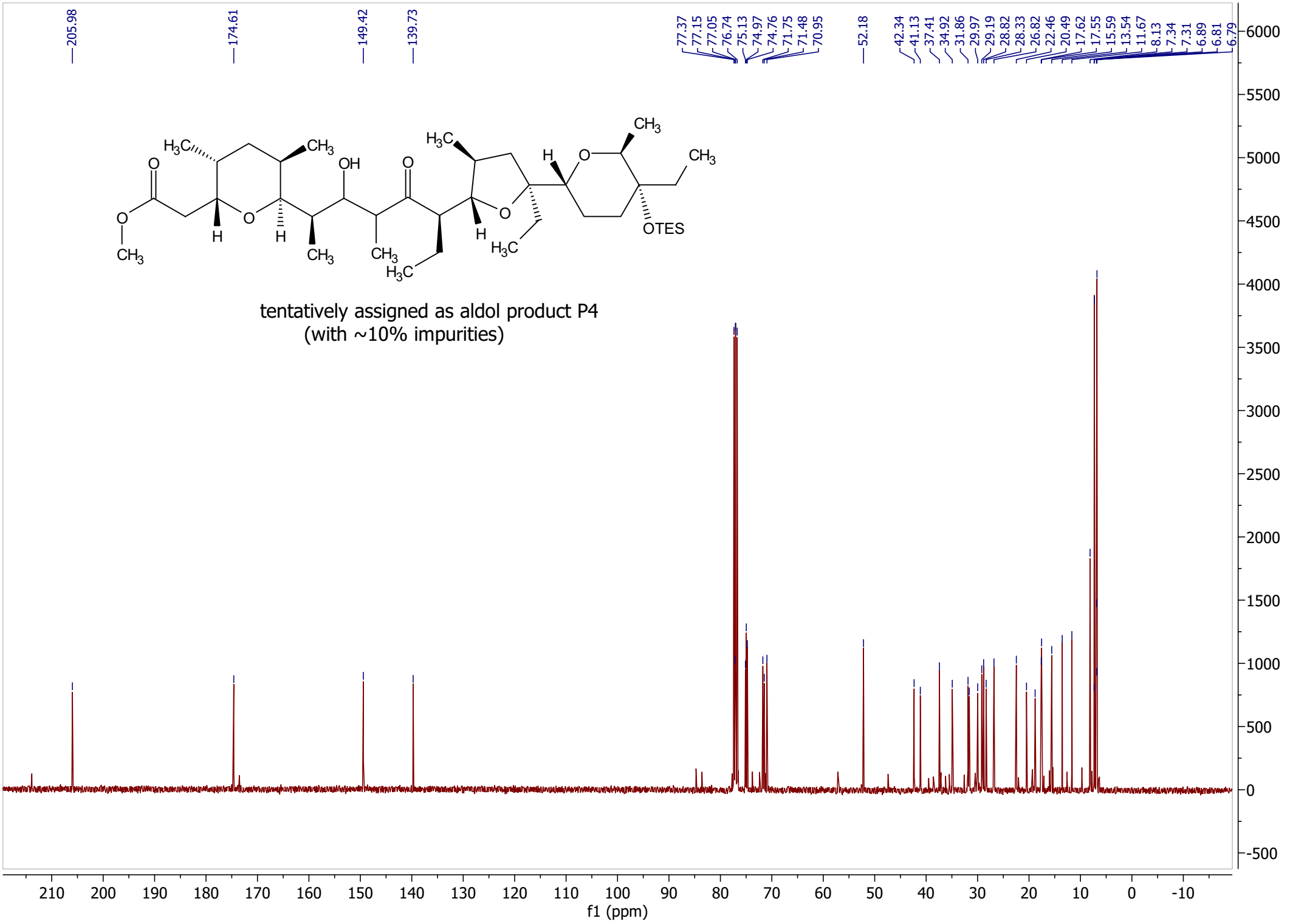
tentatively assigned as aldol product P1



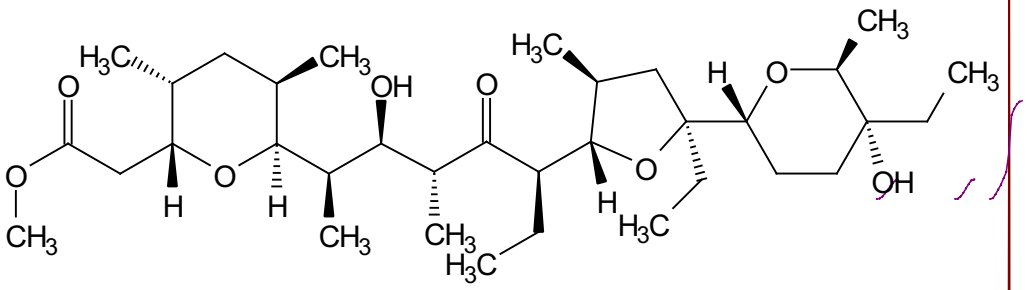
tentatively assigned as aldol product P1



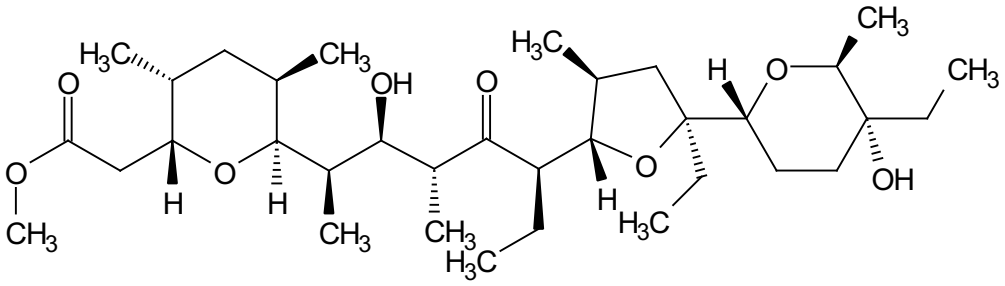

tentatively assigned as aldol product P4
(with ~10% impurities)
f1 (ppm)

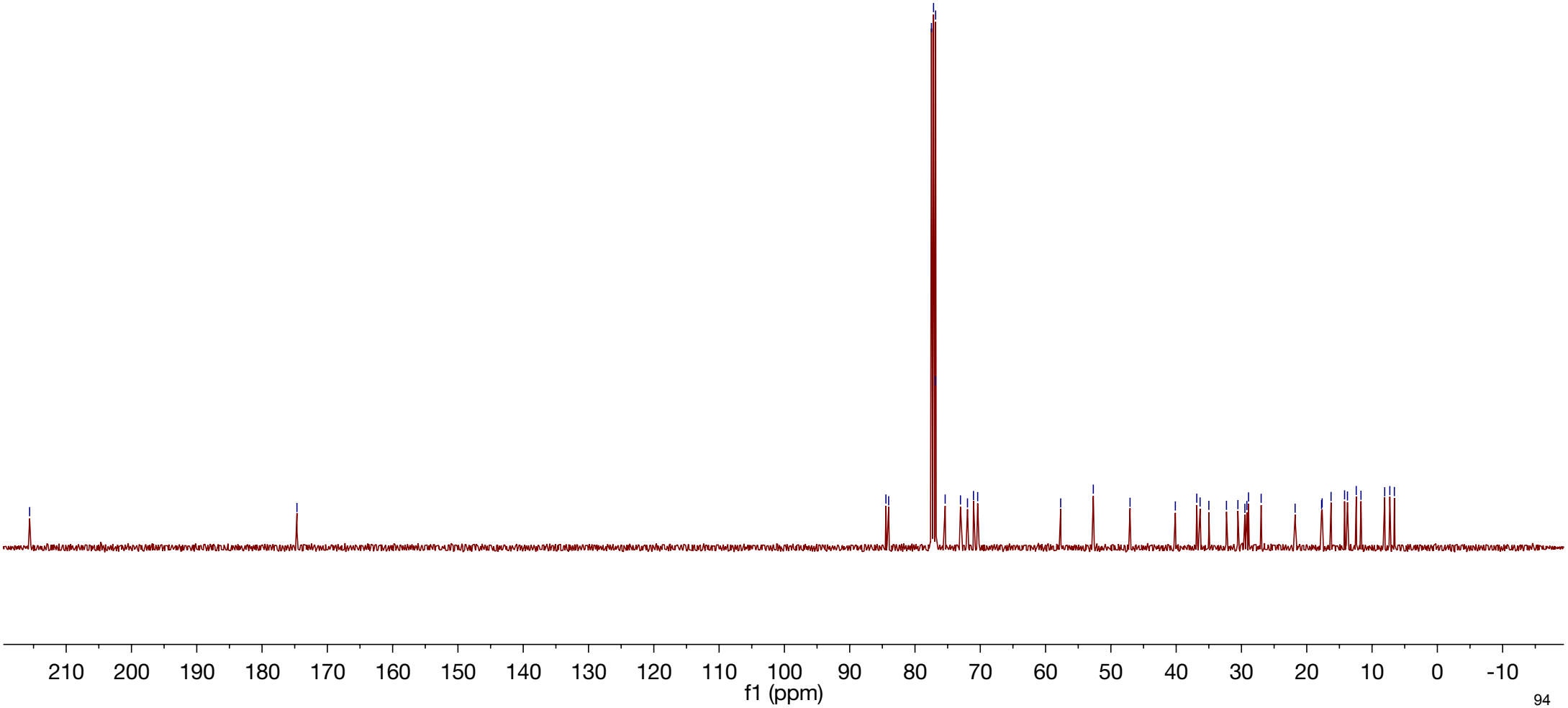

205.98
174.61
149.42
139.73
77.37
77.15
77.05
76.74
75.13
74.97
74.76
71.75
71.48
70.95
52.18
42.34
41.13
37.41
34.92
31.86
29.97
29.19
28.82
28.33
26.82
22.46
20.49
17.62
17.55
15.59
13.54
11.67
8.13
7.34
7.31
6.89
6.81
6.79
OTES
tentatively assigned as aldol product P4
(with ~10% impurities)
f1 (ppm)

Compound 24

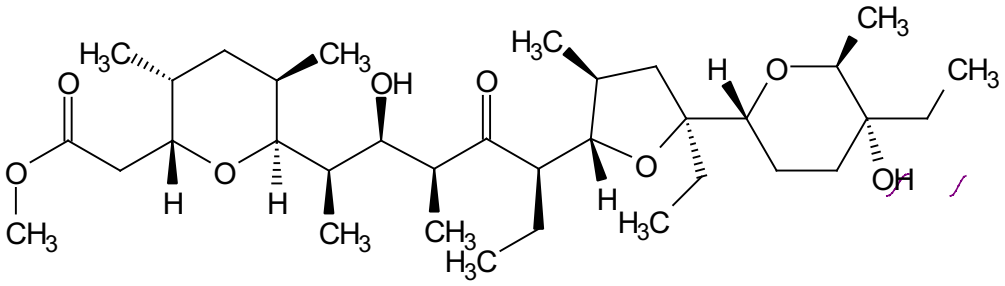


Compound 24



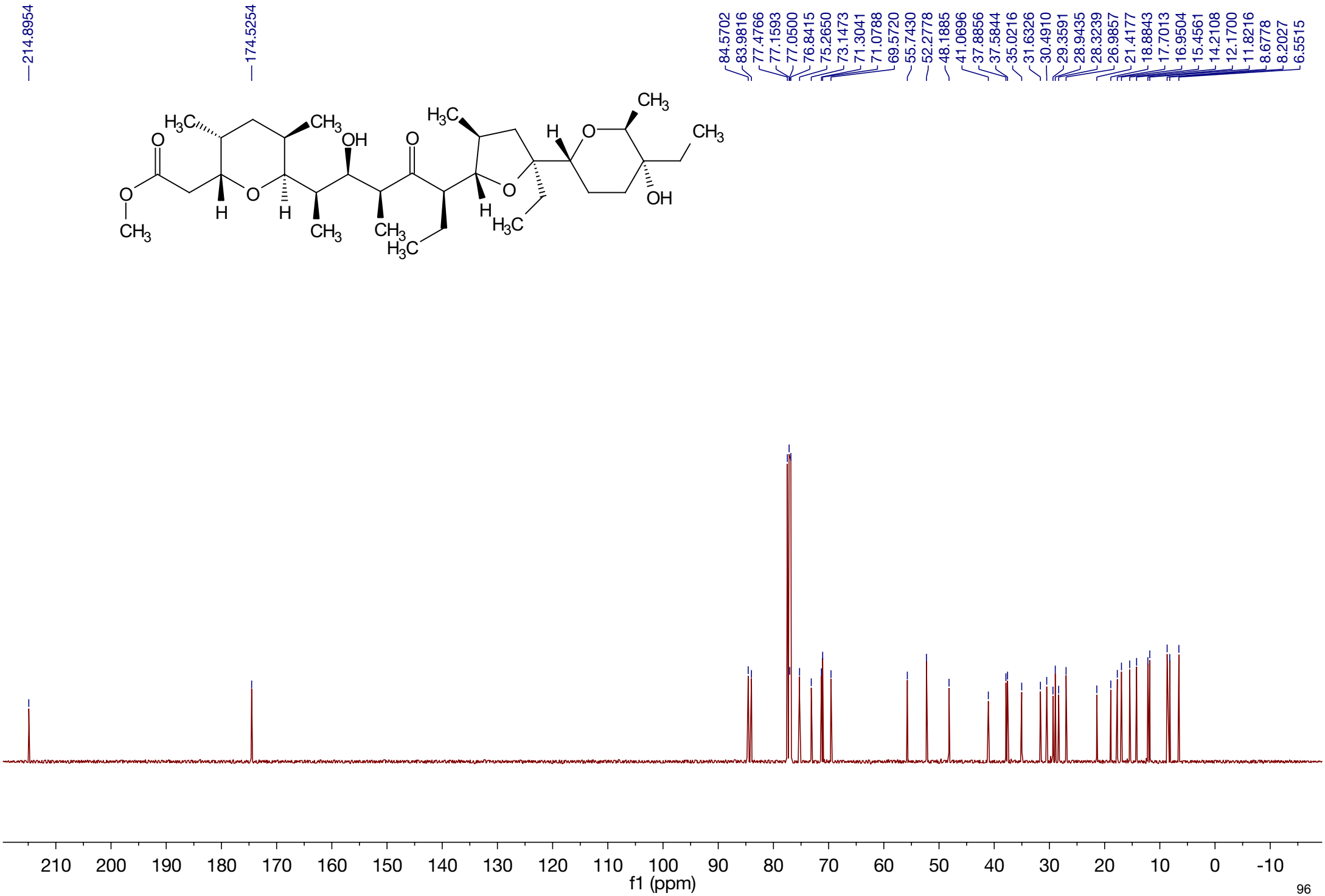

215.5996
174.6547
84.4536
84.0352
77.4778
77.1594
76.8749
76.8421
75.3796
73.0345
71.9614
71.0407
70.4010
57.6856
52.6910
47.0653
40.1268
36.8444
36.3373
34.9953
32.2980
30.5469
29.4759
29.1746
28.9182
26.9863
21.7849
17.7300
17.6447
16.2804
14.2099
13.7662
12.4217
11.6943
8.0633
7.2788
6.5831
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 25

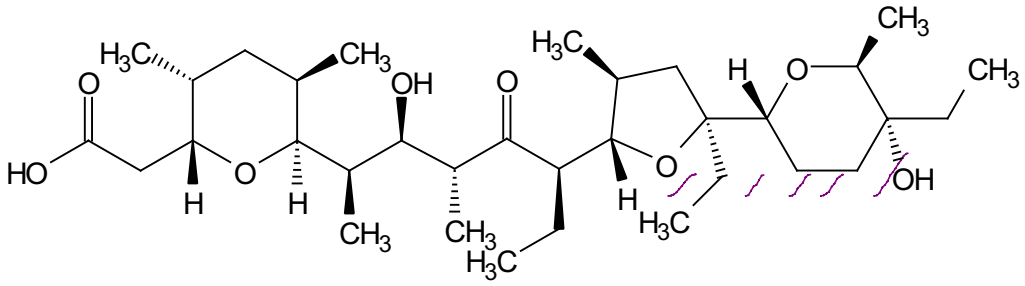


3.9916 3.9814 3.7480 3.7309 3.7106 3.6876 3.6776 3.6643 3.6541 3.5164 3.5107 3.4919 3.4862 3.4708 3.4563 3.4460 2.9160 2.9112 2.8188 2.7875 2.6020 2.5930 2.5847 2.5805 2.5704 2.2863 2.2770 2.2536 2.2442 1.9144 1.8970 1.8912 1.8813 1.8738 1.8618 1.8416 1.7978 1.7892 1.6024 1.5954 1.5788 1.5684 1.5585 1.5447 1.5398 1.5226 1.5116 1.4896 1.4835 1.4697 1.4516 1.4420 1.4324 1.4249 1.4072 1.3980 1.3422 1.3237 1.3173 1.2997 1.2815 1.2109 1.1937 1.1763 0.9616 0.9472 0.9060 0.8894 0.8736 0.8686 0.8537 0.8349 0.8160 0.7974 0.7835 0.7664 0.7445 0.7272
1.00 0.91 5.07 3.02 1.00 1.00 1.80 1.09 1.00 2.90 1.15 11.57 2.29 6.45 2.95 12.58 2.99 3.06
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

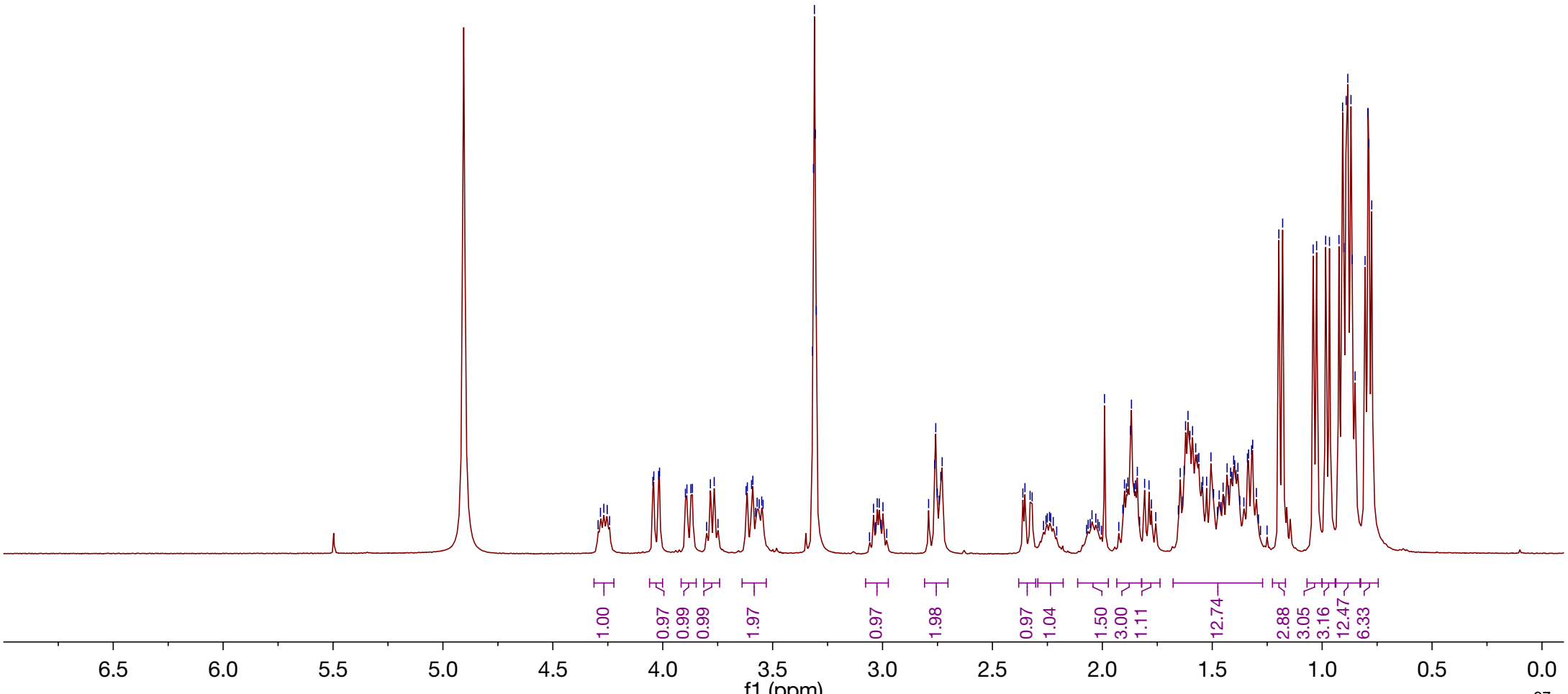
Compound 25


214.8954
174.5254
84.5702
83.9816
77.4766
77.1593
77.0500
76.8415
75.2650
73.1473
71.3041
71.0788
69.5720
55.7430
52.2778
48.1885
41.0696
37.8856
37.5844
35.0216
31.6326
30.4910
29.3591
28.9435
28.3239
26.9857
21.4177
18.8843
17.7013
16.9504
15.4561
14.2108
12.1700
11.8216
8.6778
8.2027
6.5515
f1 (ppm)

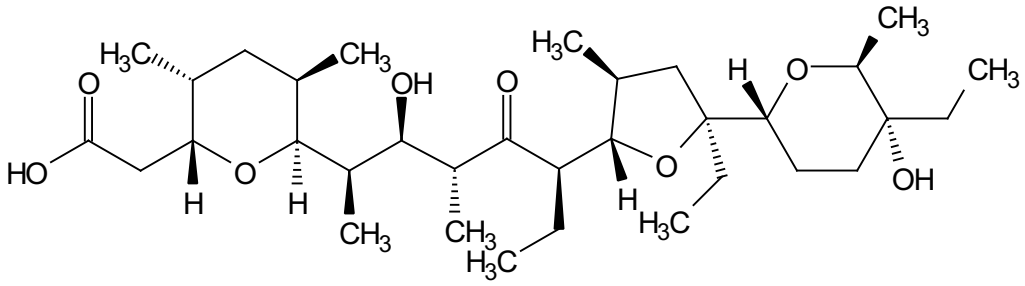
Compound 26



4.0448 4.0406 4.0188 4.0145 3.8900 3.8718 3.8650 3.7832 3.7658 3.6208 3.6151 3.5958 3.5900 3.3183 3.3142 3.3099 3.3056 3.3014 2.7629 2.7579 2.7350 2.7287 2.3521 1.9902 1.8993 1.8904 1.8837 1.8720 1.8676 1.8551 1.8489 1.8408 1.8076 1.7877 1.6456 1.6278 1.6215 1.6103 1.6016 1.5895 1.5753 1.5676 1.5609 1.5481 1.5429 1.5255 1.5058 1.4507 1.4324 1.4262 1.4164 1.4107 1.4025 1.3977 1.3918 1.3833 1.3398 1.3346 1.3209 1.3161 1.1970 1.1797 1.0409 1.0252 0.9841 0.9666 0.9235 0.9070 0.9010 0.8907 0.8833 0.8688 0.8637 0.8501 0.8047 0.7917 0.7874 0.7744

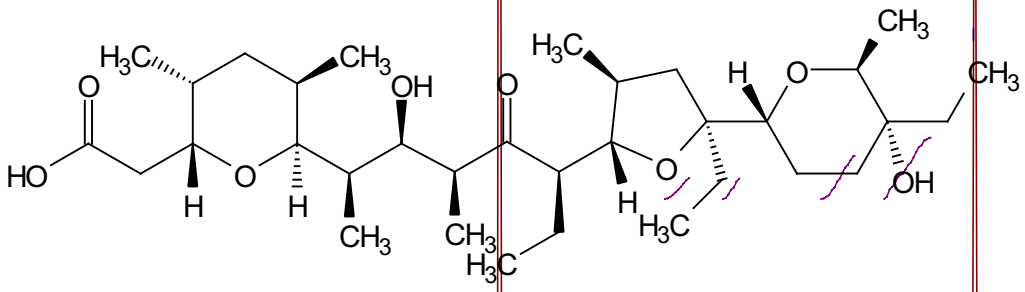


Compound 26



218.4693
177.6942
86.4622
85.5507
77.2372
73.9560
73.6315
72.1508
71.5366
58.8961
49.6393
49.2129
48.9995
48.7875
48.5746
48.3608
47.9854
37.6368
37.3559
30.6898
30.6067
30.2274
28.5273
18.1886
17.8476
16.0362
14.9156
14.1421
13.1777
12.0248
8.3652
7.5821
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 27



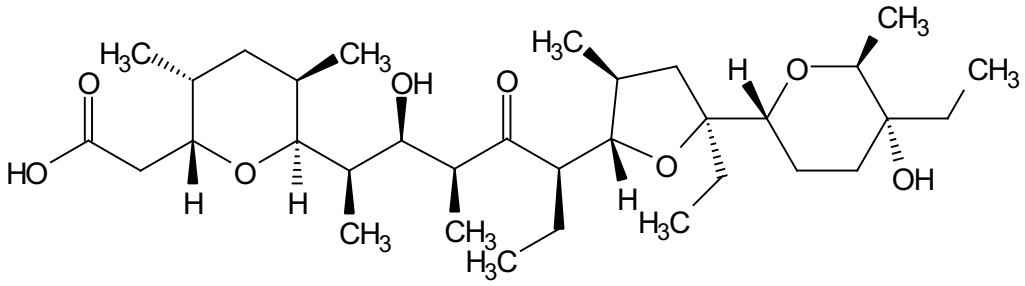
4.1156 4.0921 3.7809 3.7637 3.7472 3.7383 3.7234 3.7143 3.5954 3.5897 3.5708 3.5651 3.5363 3.5158 3.5072 3.4990 3.4815 3.3184 3.3143 3.3100 3.3057 3.3015 2.9540 2.9474 2.6965 2.6736 1.9888 1.9032 1.8850 1.8710 1.8515 1.8328 1.7387 1.7117 1.7066 1.6793 1.6503 1.6239 1.6135 1.6081 1.5989 1.5884 1.5740 1.5661 1.5547 1.5094 1.4891 1.4719 1.4531 1.4375 1.4072 1.4013 1.3424 1.3235 1.3045 1.2905 1.2145 1.2020 1.1973 1.1847 1.1799 1.1623 1.0173 1.0015 0.9363 0.9188 0.9136 0.8993 0.8953 0.8807 0.8765 0.8639 0.8469 0.8284 0.8019 0.7940 0.7847 0.7765

1.03 1.00 2.12 3.02 1.04 0.94 1.08 0.94 1.09 1.44 3.10 12.32 2.94 7.48 3.14 13.55 6.69

6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

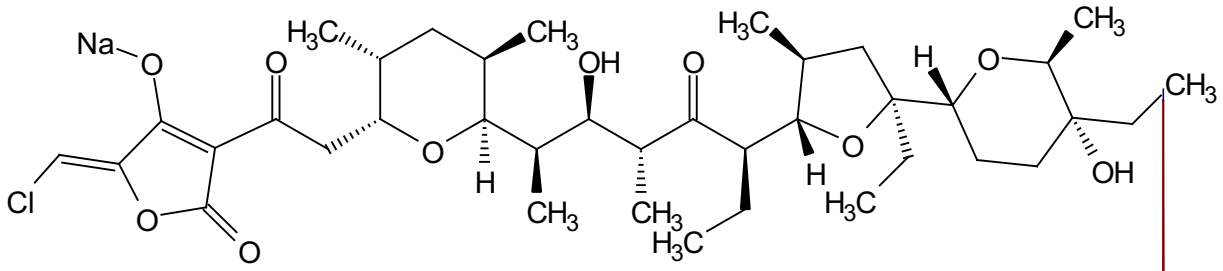
f1 (ppm)

Compound 27



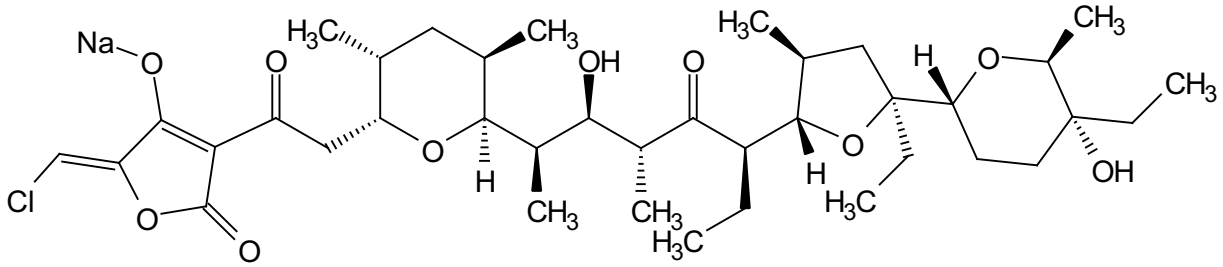
216.5420
178.0131
86.5465
84.9501
77.4492
76.8874
74.1669
72.4694
72.1510
71.0192
66.8637
64.2498
56.8100
49.6399
49.4915
49.4261
49.2132
49.0012
48.7880
48.5750
48.3615
38.9503
38.5637
32.4293
30.1638
28.4685
19.5915
17.8482
17.0896
15.9262
14.9558
12.4242
12.2969
8.9420
8.6026
f1 (ppm)
100

Compound 6



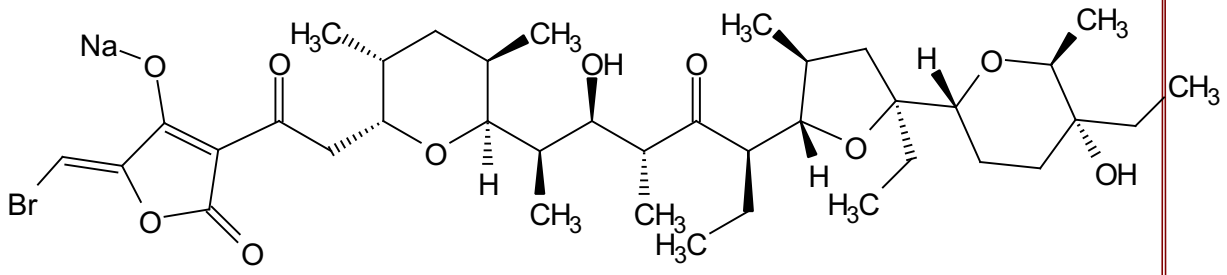
6.043 4.466 4.454 4.151 4.142 4.133 3.908 3.789 3.775 3.769 3.755 3.749 3.663 3.649 3.505 3.486 3.415 3.393 3.369 3.360 3.342 3.331 2.861 2.848 2.841 2.828 2.629 2.611 2.471 2.463 2.445 2.049 2.041 1.923 1.916 1.752 1.729 1.716 1.699 1.584 1.565 1.563 1.538 1.475 1.443 1.422 1.409 1.394 1.350 1.325 1.297 1.256 1.232 1.207 1.194 1.190 1.179 1.173 1.160 1.076 1.063 0.955 0.943 0.868 0.854 0.841 0.826 0.811 0.802 0.796 0.788 0.782 0.774 0.768 0.750 0.737 0.668 0.655

Compound 6



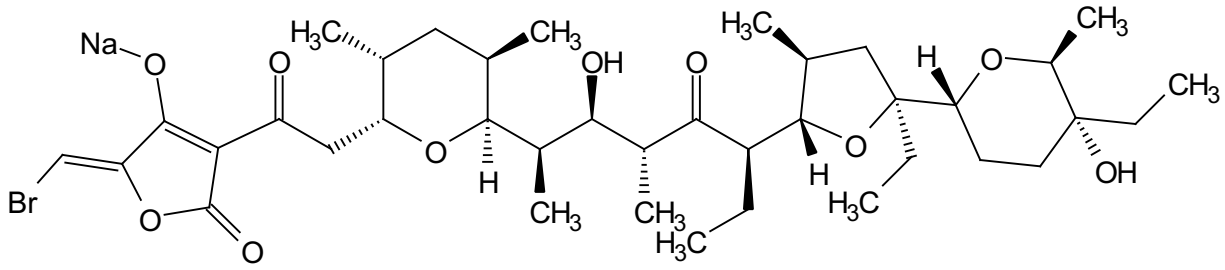
214.498
193.148
178.426
167.880
148.895
94.162
94.135
84.134
83.696
75.434
74.692
72.519
70.793
69.618
69.483
56.318
46.106
40.147
39.939
39.730
39.522
39.313
39.104
38.896
35.881
35.729
31.421
28.879
28.402
27.494
17.364
15.744
14.559
13.284
12.838
11.929
7.821
7.334

Compound 29


Na
O
O
Br
O
O
H3C
CH3
OH
O
O
H
CH3
CH3
H3C
H3C
O
H
H3C
H
O
CH3
CH3
OH

6.057 4.461 4.449 4.148 4.139 3.904 3.779 3.772 3.759 3.752 3.660 3.646 3.504 3.486 3.412 3.390 3.365 3.356 2.636 2.631 2.625 2.618 2.612 2.507 2.503 2.500 2.496 2.492 2.482 2.466 2.457 1.760 1.734 1.714 1.697 1.567 1.557 1.541 1.531 1.472 1.441 1.415 1.402 1.387 1.348 1.342 1.327 1.327 1.324 1.314 1.299 1.295 1.255 1.232 1.206 1.192 1.185 1.177 1.170 1.075 1.062 0.956 0.943 0.867 0.853 0.837 0.823 0.807 0.801 0.797 0.787 0.782 0.771 0.767 0.748 0.735 0.667 0.654
0.58 0.83 0.87 0.88 1.80 0.90 1.03 0.97 0.64 0.86 1.01 0.77 0.94 1.01 3.77 2.08 8.48 2.20 3.00 2.98 2.94 3.11 5.81 5.46 2.79
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

Compound 29

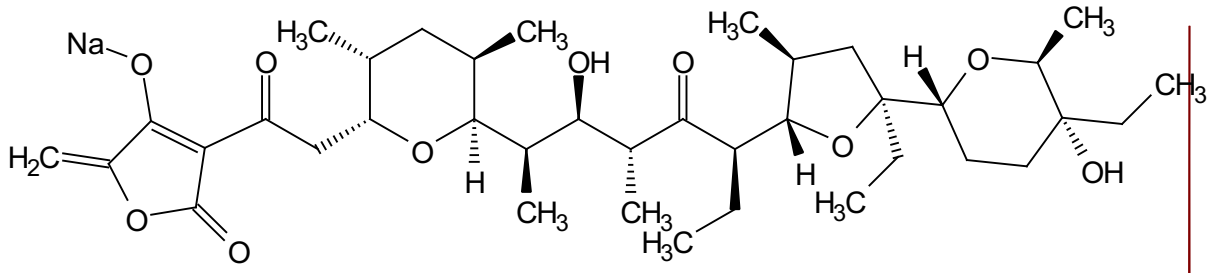


214.666 193.374 178.021 167.996 151.007 94.277 84.187 83.689 82.786 75.435 74.693 72.423 70.729 69.638 69.490 56.184 46.141 40.146 39.937 39.729 39.520 39.312 39.104 38.894 35.823 35.700 31.405 28.390 27.482 17.340 15.717 14.514 13.288 12.894 11.893 7.858 7.319

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

Compound 30



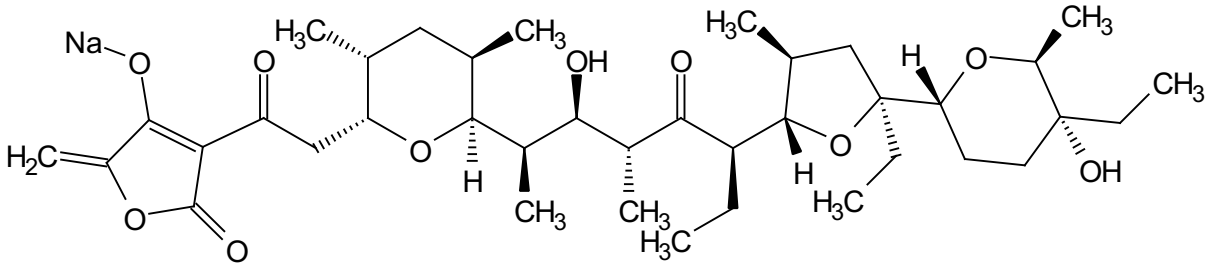
4.737 4.578 4.563 4.485 4.152 4.140 4.129 3.921 3.795 3.785 3.778 3.770 3.752 3.746 3.667 3.650 3.515 3.490 3.431 3.419 3.397 3.388 2.856 2.847 2.623 2.616 2.609 2.602 2.500 2.464 2.441 2.431 2.409 1.772 1.757 1.751 1.737 1.720 1.697 1.593 1.579 1.570 1.560 1.550 1.537 1.525 1.478 1.470 1.439 1.420 1.402 1.386 1.360 1.348 1.343 1.324 1.307 1.289 1.231 1.198 1.194 1.177 1.159 1.080 1.063 0.955 0.940 0.872 0.854 0.834 0.790 0.781 0.766 0.755 0.749 0.738 0.673 0.656

1.01 1.04 0.99 0.91 1.02 1.97 1.02 1.06 1.81 0.98 0.96 1.42 1.07 1.11 3.76 2.27 10.90 3.15 3.00 17.24 3.44

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

Compound 30

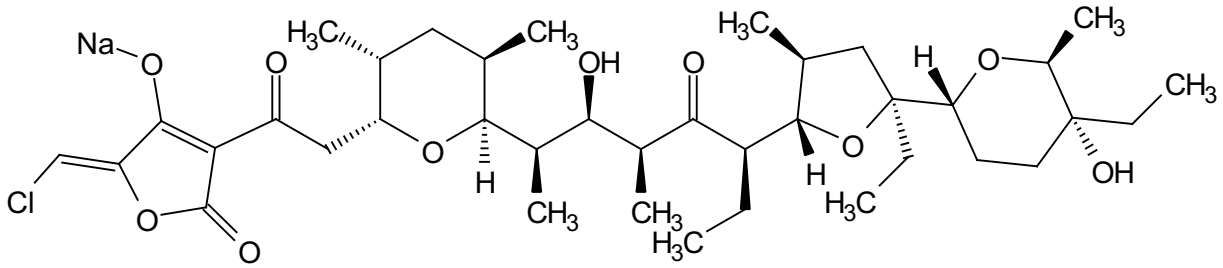


214.704
193.333
180.028
169.281
154.184
94.719
85.482
84.173
83.680
75.471
74.845
72.454
70.713
69.607
69.495
56.198
40.146
39.937
39.728
39.520
39.311
39.104
38.894
35.834
35.696
31.420
28.893
28.413
27.547
17.395
15.728
14.542
13.301
12.961
11.924
7.865
7.338
6.408

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

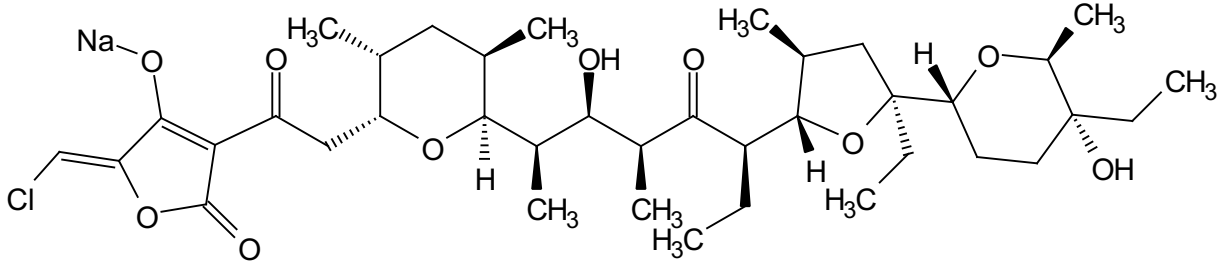
f1 (ppm)

Compound 31


Na
O
O
Cl
O
O
H3C
CH3
OH
O
O
H
CH3
CH3
H3C
H3C
O
H
O
H3C
CH3
CH3
OH

4.629 3.874 3.773 3.758 3.741 3.639 3.625 3.614 3.607 3.596 3.589 3.488 3.468 3.377 3.364 3.332 3.326 2.785 2.772 2.765 2.752 2.538 2.525 2.521 2.500 2.036 2.024 1.843 1.829 1.804 1.779 1.764 1.753 1.739 1.724 1.709 1.697 1.607 1.607 1.585 1.584 1.565 1.549 1.540 1.522 1.434 1.419 1.405 1.376 1.361 1.347 1.319 1.238 1.230 1.221 1.209 1.194 1.186 1.179 1.171 1.158 1.085 1.071 1.063 1.050 0.914 0.902 0.806 0.800 0.791 0.785 0.776 0.771 0.738 0.724 0.709 0.659 0.645
0.41 0.71 0.78 0.94 0.90 1.93 1.01 0.88 0.92 0.57 0.75 0.92 0.84 3.08 3.04 5.91 4.55 5.81 3.00 14.30 3.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

Compound 31



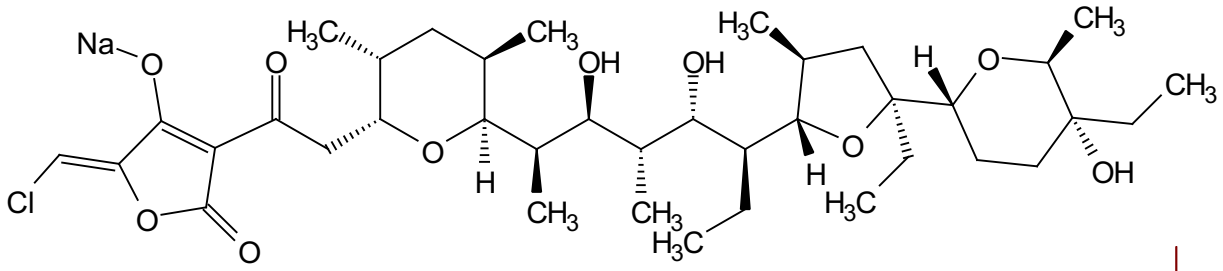
213.371

94.168
84.188
82.548
75.585
74.391
73.090
70.444
69.528
68.458
54.774
47.488
40.553
40.146
39.937
39.728
39.521
39.311
39.103
38.894
37.191
37.017
36.213
34.873
31.385
29.420
28.279
27.739
27.331
20.917
17.707
17.251
16.655
15.905
14.601
11.623
11.556
8.064
7.862
6.438

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

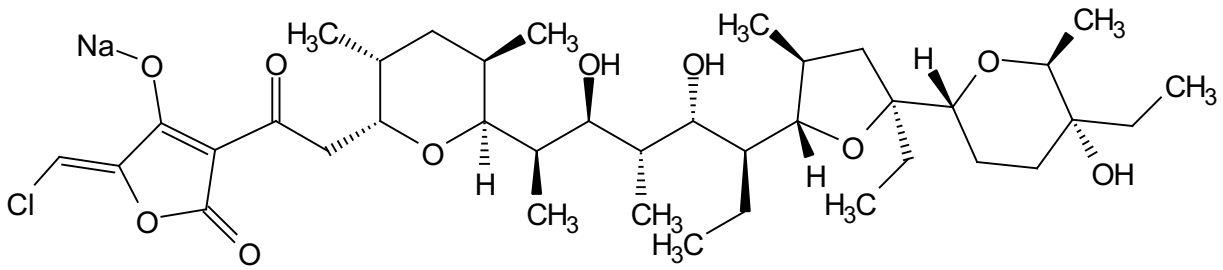
f1 (ppm)

Compound 32


Na
O
O
Cl
O
O
H3C
CH3
O
H
CH3
CH3
H3C
OH
OH
H3C
O
H
H3C
H
O
CH3
CH3
OH

6.064
4.183
4.169
4.168
4.157
4.132
4.116
3.898
3.880
3.856
3.856
3.793
3.768
3.666
3.649
3.560
3.544
3.535
3.511
3.487
3.438
3.412
3.407
3.370
3.353
3.329
2.499
2.461
2.432
2.038
2.034
1.941
1.923
1.905
1.830
1.810
1.799
1.779
1.736
1.682
1.665
1.655
1.639
1.619
1.609
1.586
1.575
1.555
1.518
1.499
1.484
1.435
1.415
1.399
1.360
1.332
1.233
1.211
1.192
1.173
1.120
1.103
0.912
0.897
0.879
0.861
0.850
0.843
0.833
0.816
0.799
0.780
0.732
0.715
0.621
0.604
0.592
0.575
0.70
1.83
1.83
0.88
0.99
2.01
1.27
1.21
0.74
0.92
0.98
1.11
1.13
13.41
3.97
2.93
15.00
2.99
5.43
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

Compound 32



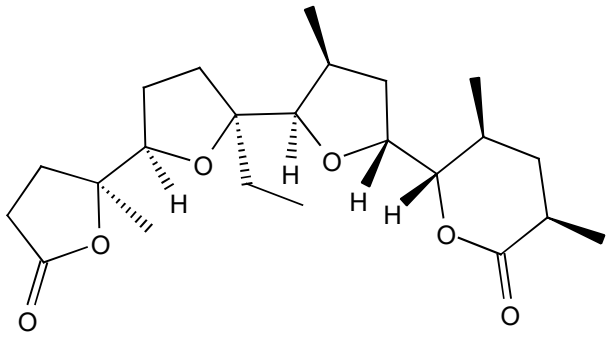
194.027
178.368
168.749
148.833

94.520
94.389
84.163
83.687
75.741
74.141
72.770
70.315
69.841
69.601
67.659
42.551
40.146
39.937
39.729
39.520
39.313
39.103
38.894
37.593
36.954
35.984
34.904
34.858
31.191
29.536
28.335
28.027
27.226
20.658
17.819
17.172
15.801
14.568
13.940
11.738
9.613
8.158
7.343
6.423

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

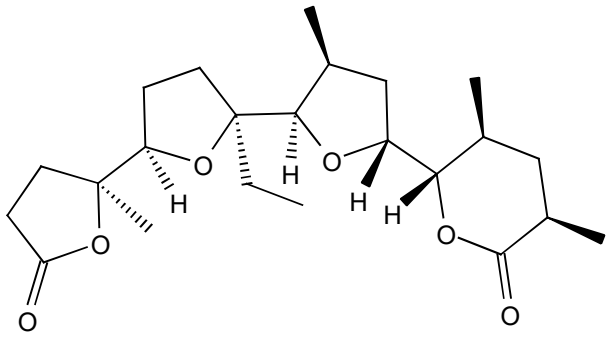
f1 (ppm)

Compound 33



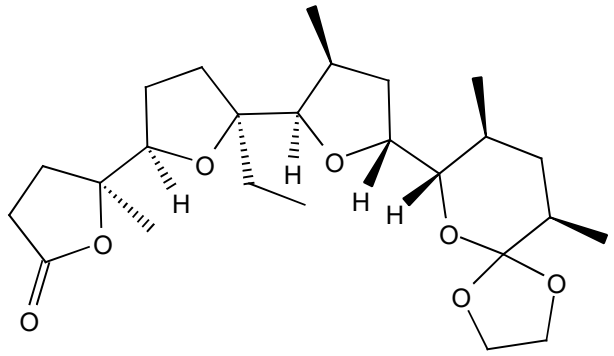
f1 (ppm)

Compound 33



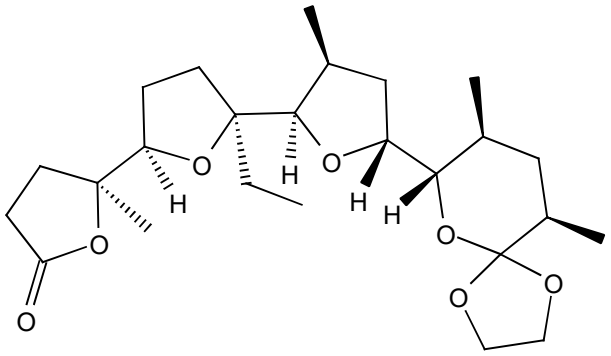
177.982
174.048
88.345
88.125
87.468
86.779
82.722
77.479
77.450
77.160
76.842
37.498
36.166
35.019
34.941
31.658
30.393
30.301
29.988
29.172
28.334
23.805
18.414
17.301
15.732
8.045
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 34



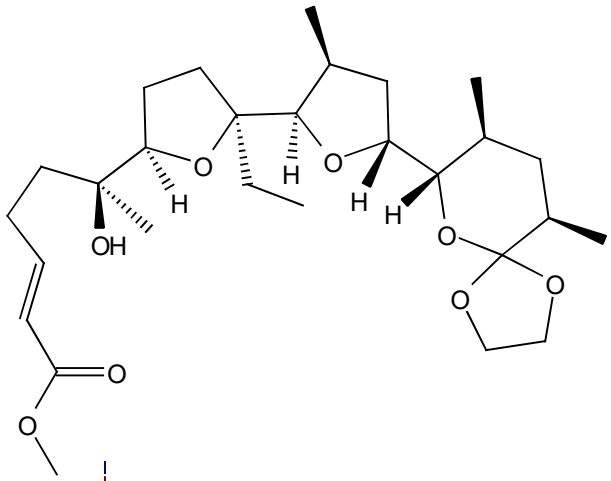
f1 (ppm)

Compound 34

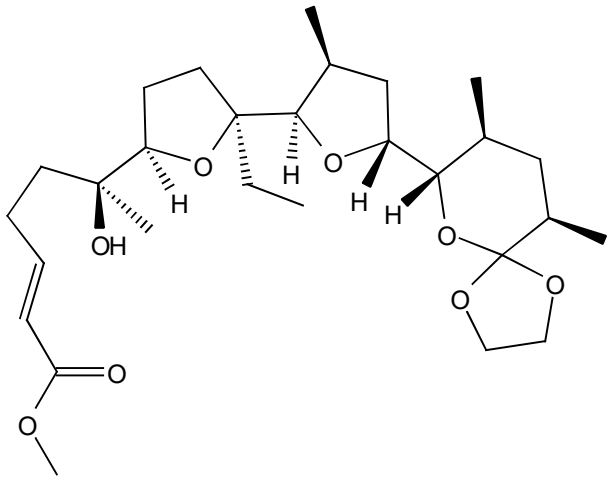


176.417
128.302
127.820
121.444
87.738
86.961
84.723
81.829
81.513
77.196
65.134
64.794
39.590
36.697
35.038
34.086
33.269
30.168
30.130
29.822
28.509
28.386
23.728
17.284
16.407
15.485
8.164
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound 36



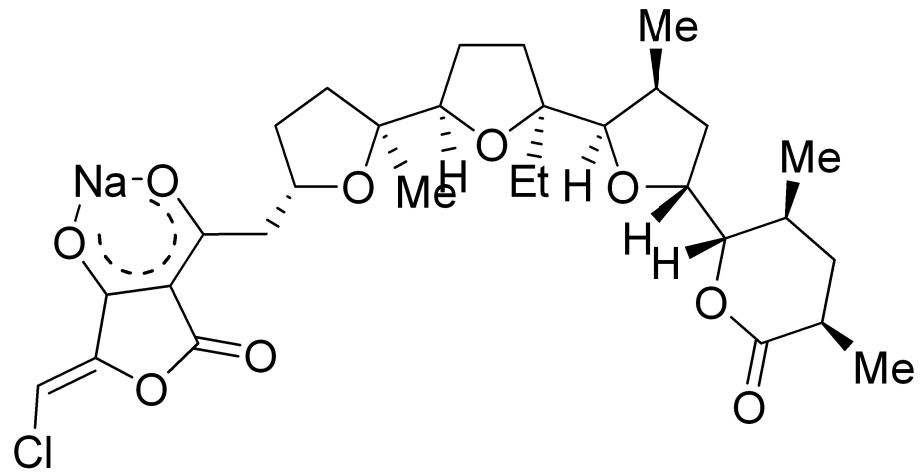
Compound 36



166.733
150.328
128.301
128.060
127.820
121.367
121.100
87.620
87.474
85.135
80.288
76.403
73.001
64.918
64.134
50.922
39.365
36.997
36.510
34.946
32.918
32.468
31.264
29.999
27.721
26.848
24.824
16.694
15.896
15.499
8.052

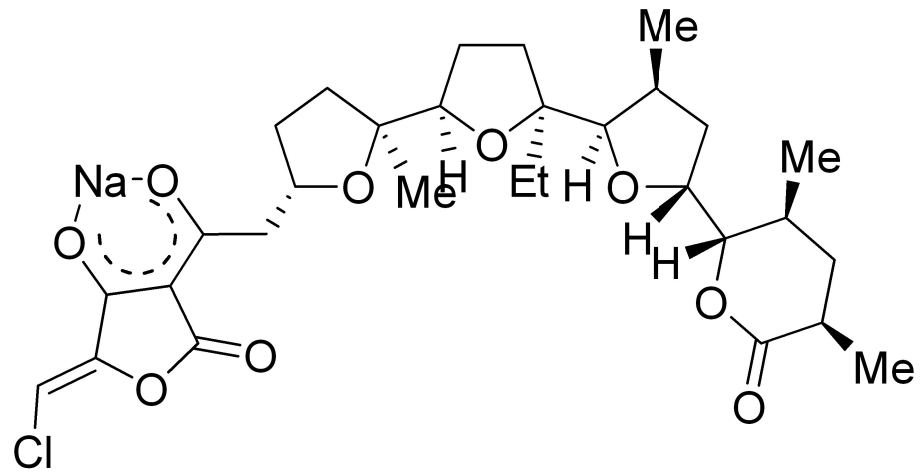
f1 (ppm)

Compound 39a

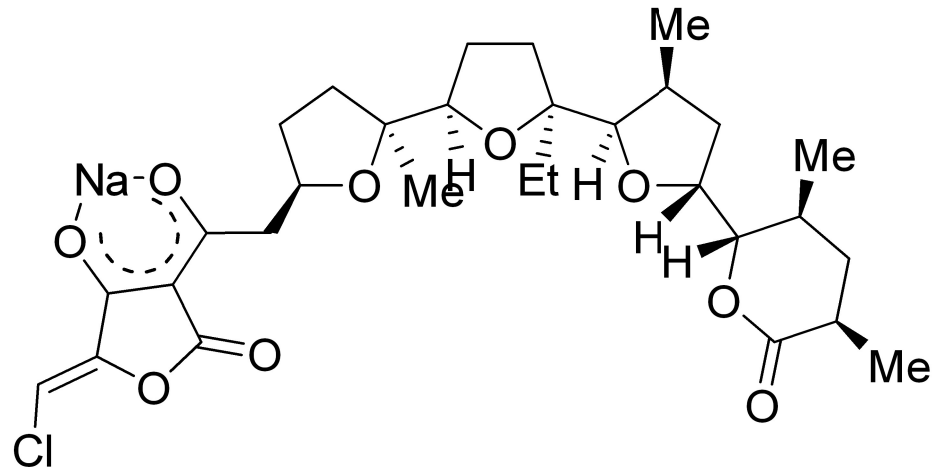


f1 (ppm)

Compound 39a

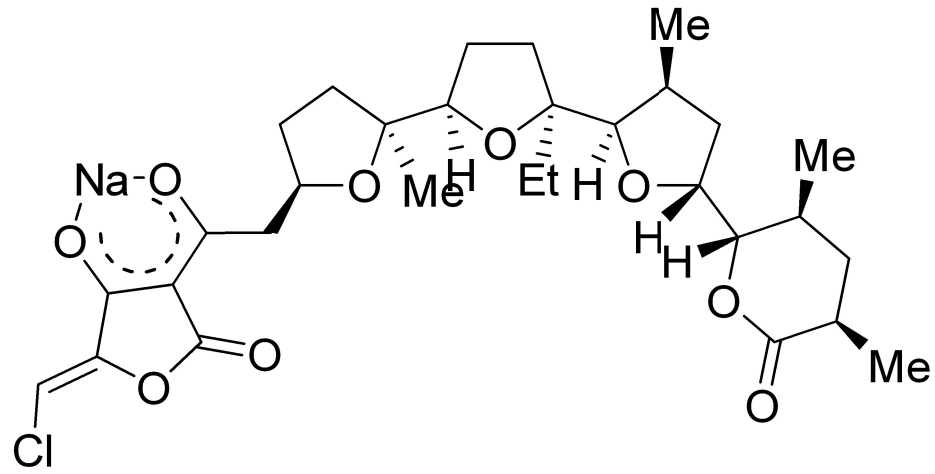


Compound 39b



f1 (ppm)

Compound 39b



178.279
173.687
168.492
94.311
93.947
87.316
85.966
84.748
83.309
82.539
77.238
74.930
46.669
40.022
39.856
39.689
39.521
39.355
39.188
39.021
36.281
35.090
34.982
34.440
31.426
30.782
30.471
28.790
27.623
21.719
18.227
16.750
15.562
8.038

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)