Supporting Information

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF DIMUNITIVE FORMS OF (+)-SPONGISTATIN 1: LESSONS LEARNED

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Table of Contents

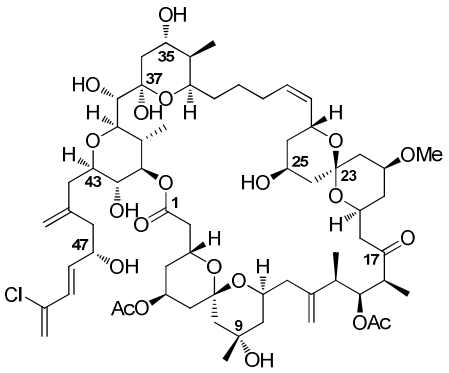
A. General Methods and Experimental Procedures

1) Materials and Methods

Except as otherwise indicated, all reactions were run under an argon atmosphere in flame- or oven-dried glassware, and solvents were freshly distilled. The argon was deoxygenated and dried by passage through an OXICLEAR^{TM} filter from Aldrich and Drierite tube, respectively. Diethyl ether (Et_2O), tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Aldrich (HPLC purity) and further purified by using the Pure Solve^{TM} PS-400. All other reagents were purchased from Aldrich or Acros and used as received. Reactions were monitored by thin layer chromatography (TLC) either with 0.25-mm Silicycle or 0.25-mm E. Merck (Kieselgel $60F_{254}$, Merck) pre-coated silica gel plates. Silica gel for flash chromatography (particle size 0.040–0.063 mm) was supplied by Silicycle or Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^{1}H and ^{13}C spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26), acetonitrile (δ 1.94) or benzene (δ 7.15) for ^{1}H and either chloroform (δ 77.0), acetonitrile (δ 1.4, 118.7) or benzene (δ 128.0) for ^{13}C. Infrared spectra were recorded JASCO FTIR-480plus spectrometer. Optical rotations were measured on a JASCO P-2000 polarimeter in the solvent indicated. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center by Dr. Rakesh Kohli on either a VG Micromass 70/70H or VG ZAB-E spectrometer.

2) Experimental Details

I. NMR Experiments



(+)-Spongistatin 1 (**1**)

A . $^{1}H/^{13}C$ signals of (+)Spongistatin 1 in MeCN

From published NMR spectra of Kitagawa, Pettit , Paterson and Smith

$^{1}H/^{13}C$	Natural	Synthetic	Natural	Synthetic
Atom No	^{13}C (100 MHz)	^{13}C (125 MHz)	^{1}H (400 MHz) ($^{3}J_{H-H}$ in Hz)	^{1}H (500 MHz) ($^{3}J_{H-H}$ in Hz)
1	173.07	173.07		
2	40.86	40.86	2.44 dd (10, 18)	2.45 dd (10.5, 16.2)
			2.53 dd (2, 18)	2.52 dd (1.8, 16.2)
3	63.59	63.59	4.25 brt (10)	4.24 brt (10.7)
4	34.65	34.65	1.55*, 1.68*	1.55*, 1.68*
5	67.06	67.06	4.92 brs	4.92 brs
6	38.17	38.16	1.67 dd (5, 14); 1.78 brd (14)	1.66 dd (4.4, 15.2); 1.78 d (15.1)
7	99.26	99.25		
8	46.76	46.75	1.47 d (14), 1.60*	1.46 d (14.0), 1.60*
9	69.64	69.63		
9a	30.21	30.21	1.06 s	1.06 s
10	44.96	44.95	1.28*, 1.55*	1.28*, 1.55*

11	64.701	64.70	4.25 brt (10)	4.24 brt (10.7)
12	44.24	44.24	1.99*; 2.27 brd (14)	1.99*; 2.26 brd (14.0)
13	148.03	148.03		
13a	114.86	114.86	4.83 brs; 4.83 brs	4.83 brs; 4.83 brs
14	36.60	36.59	2.78*	2.78*
14a	12.09	12.09	1.04 d (6.9)	1.04 d (6.9)
15	75.34	75.34	5.12 dd (1.7, 11)	5.11 dd (1.8, 10.7)
16	47.62	47.61	3.04 dq (7, 11)	3.04 dq (6.9, 10.7)
16a	13.73	13.73	1.15 d (7)	1.15 d (6.9)
17	213.52	213.52		
18	51.94	51.95	2.62 brd (18); 2.86 dd (11, 18)	2.61 brd (18.2); 2.86 dd (10.1, 19.4)
19	66.16	66.15	4.00 brt (11)	3.99 brt (11.1)
20	37.70	37.70	0.97 ddd (12, 12, 12); 1.98*	0.96 ddd (12, 12, 12); 1.98*
21	73.98	73.98	3.46 tt (4, 4, 12, 12)	3.46 tt (4.2, 4.2, 11.6, 11.6)
22	44.18	44.18	1.08 t (12); 1.99*	1.08 t (12.1), 1.99*
23	99.91	99.91		
24	34.91	34.90	1.55*; 2.28*	1.55*; 2.27*
25	64.41	64.41	3.93 brm	3.94 brm
26	39.11	39.11	1.57*; 1.57*	1.57*; 1.57*
27	61.22	61.21	5.00 ddd (4.3, 10, 10)	5.00 ddd (3.8, 9.9, 9.9)
28	131.22	131.21	15.32 brd (10)	5.32 brd (10.8)
29	133.42	133.41	5.48 ddd (10, 10, 10)	5.48 ddd (9.9, 9.9, 10.6)
30	28.07	28.08	2.00*; 2.19*	2.00*;2.18*
31	27.04	27.04	1.23*;1.60*	1.23*;1.60*

32	32.82	32.83	1.30 m; 1.42 m	1.30m; 1.42 m
33	67.15	67.15	4.13 dt (3.4, 3.4, 8)	4.12 dt (3.0, 3.0, 9.0)
34	39.32	39.32	1.57 m	1.57 m
34a	11.55	11.55	0.81 d (7)	0.81 d (7.2)
35	71.47	71.47	3.65 brs	3.65 m
36	33.79	33.78	1.61*;1.89*	1.61*;1.89*
37	99.41	99.41		
38	73.11	73.09	3.34 brs	3.34 d (10.7)
39	81.30	81.30	3.72 brd (10)	3.72 brd (10.2)
40	37.26	37.26	1.91*	1.91*
40a	12.69	12.69	0.74 d(7)	0.74 d(6.6)
41	80.60	80.60	4.75 dd (9,11)	4.75 dd (9.2,11)
42	73.11	73.09	3.12t (9)	3.11 dt (5.4, 9.1)
43	78.72	78.70	3.39 brt (9)	3.38 dt (2.2, 8.6)
44	40.24	40.23	2.08*; 2.76 brd (13)	2.08*; 2.75 brd (13.9)
45	144.00	143.98		
45a	116.61	116.63	4.86 brs; 4.89 brs	4.86 brs; 4.89 brs
46	43.93	43.92	2.33 brdd (7, 14); 2.19*	2.33 brdd (6.3, 13.6); 2.18*
47	70.13	70.12	4.36 ddd (6, 7, 11)	4.36*
48	139.21	139.20	6.11 dd (6, 15)	6.11 dd (5.7, 15.0)
49	126.99	126.98	6.41 brd (15)	6.41 dd (1.1, 15.0)
50	139.21	139.20		
51	116.48	116.49	5.35 brs; 5.45 brs	5.35 brs; 5.45 brs
OMe	55.72	55.71	3.24s	3.24s

OAc	21.78	27.78	1.94s	1.94s
	171.61	171.61		
OAc	21.00	21.00	1.84s	1.84s
	170.21	170.19		
OH(C9)			4.32 brs	4.31 brs
OH(C25)			4.39 d (9.9)	4.39d (10.0)
OH(C35)			3.83 brm	3.82 d (9.4)
OH(C37)			4.73 d (2)	4.72 d (2.5)
OH(C38)				2.86 brd (10.1)
OH(C42)				4.35 brd (5.3)
OH(C47)				3.51 brd (2.5)

* Coupling constants for these signals were not measured due to overlapping.

B. ^{1}H signals of (+)-Spongistatin 1 in DMSO

* Coupling constants for these signals were not measured due to overlapping.

Proton	^{1}H (500 MHz) ($^{3}J_{H\text{-}H}$ in Hz)
H2	2.47*, 2.70*
H3	4.15 brt (11.3)
H4	1.52*, 1.65*
H5	4.88 brs
H6	1.65*, 1.76*
H8	1.63* , 1.65*
H9a	1.00 s
H10	1.23*, 1.54*
H11	4.13 bd (10.7)
H12	2,01*; 2.28*
H13a	4.71 brs; 4.73 brs
H14	2.82dq (6.8, 1.5)

H14a	0.9 (6.7)
H15	5.17 dd (1.5, 10.8)
H16	3.04 dq (6.9, 10.4)
H16a	1.07 d (6.9)
H18	2.61 brd (18.2); 2.86 dd (10.1, 19.4)
H19	3.99 brt (11.1)
H20	0.96*; 1.98*
H21	3.46 tt (4.2, 4.2, 11.6, 11.6)
H22	1.23*, 1.99*
H24	1.52*; 2.24*
H25	3.84 brm
H26	1.55*; 1.55*
H27	4.88*
H28	5.33 brd (10.1)
H29	5.35 ddd (9.7, 9.7, 10.2)
H30	2.00*;2.10*
H31	1.11 m;1.24 m
H32	1.11 m;1.24 m
H33	3.58 dt (3.3, 2.9, 9.3)
H34	1.40 m
H34a	0.79 d (7.1)
H35	3.58 m
H36	1.52*;2.24*
H38	3.27 d (10.2)
H39	3.65 brd (10.0)
H40	1.83*
H40a	0.71 d(6.5)
H41	4.67 dd (9.7,11)
H42	3.11 dt (6.4, 9.7)
H43	3.36 dt (1.9, 9.1)
H44	2.05*; 2.71*

H45a	4.80 brs; 4.83 brs
H46	2.05*, 2.23*
H47	4.24 brd (5.9)
H48	6.11 dd (5.4, 15.1)
H49	6.40 dd (1.1, 15.1)
H51	5.36 brs; 5.55 brs
OMe	3.19s
OAc	1.93s
OAc	1.80s
OH(C9)	3.91 brs
OH(C25)	4.32d (10.0)
OH(C35)	4.56 d (9.3)
OH(C37)	4.78 brs
OH(C38)	4.02 d (9.7)
OH(C42)	4.15 brd (5.1)
OH(C47)	5.05 brd (2.5)

* overlapping protons

C. Buildup curves for determination optimum mixing time for NOESY experiments

NOESY integrations between two protons at different mixing time

Mixing time (ms)	**H43/H40Me**	**H39/H40Me**	**H38/H40Me**	**H15/H16Me**	**H19/H21**
30	45.05	44.27	51.48	38.09	135.37
50	101.78	95.41	53.64	118.06	285.69
80	132.23	110.96	146.02	136.13	299.68
100	250.47	187.12	202.06	234.05	550.54
200	264.12	246.6	336.07	299.77	565.96
400	359.33	358.44	456.23	395.16	713.12
600	390.44	384.42	466.57	422.19	657.55
800	369.56	360.21	425.01	385.5	536.64

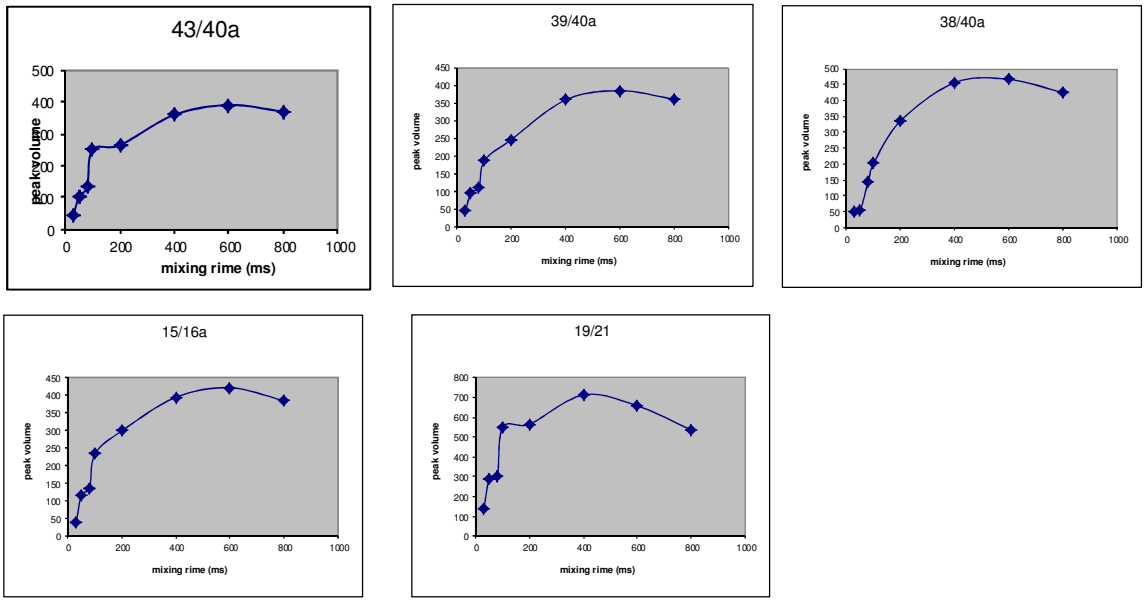


Figure SI-1: NOESY Buildup curves at various mixing times

D. NOESY derived inter-proton distances of (+)-spongistatin 1 used in DISCO calculations

H1	H2	NOE distance in Angstroms
40Me	38	2.82
40Me	42	4.8
40Me	16	4.08
40Me	14	4.94
40Me	16Me	4.06
34Me	21	5.11
34Me	38	5.56
14Me	35OH	4.23
9Me	21	3.82
9Me	21OMe	6.08
16Me	39	3.46
16Me	43	4.75
16Me	38	6.3
16Me	41	3.25
34Me	21OMe	6.79

E. ^{1}H NMR Coupling constants of (+)-spongistatin 1 used in DISCO calculations

H1	H2	$^{3}J_{H\text{-}H}$ (Hz)
2proR	3	1.8
5	6proS	4.4
15	14	1.8
15	16	10.7
27	28	9.9
29	30proR	9.9
29	30proS	9.9
33	32proR	9.0
33	33proS	3.0
38	39	10.2
43	44proS	2.2

F. Distinctive long range NOESY constraints that are used in DISCO calculations

H1	H2	NOE peak integrals
H3	H4b	1.00 (ref)
H11	H14a	2.31
H51a	H115	0.21
H49	H115	0.11
H47	H44b	1.29
H92	H46b	0.48

G. ^{1}H NMR Coupling constants of the ABEF analog used in DISCO calculations

H1	H2	$^{3}J_{H\text{-}H}$ (Hz)
H47	H48	5.4
H43	H42	8.5
H43	H44a	10.1
H43	H44b	1.1

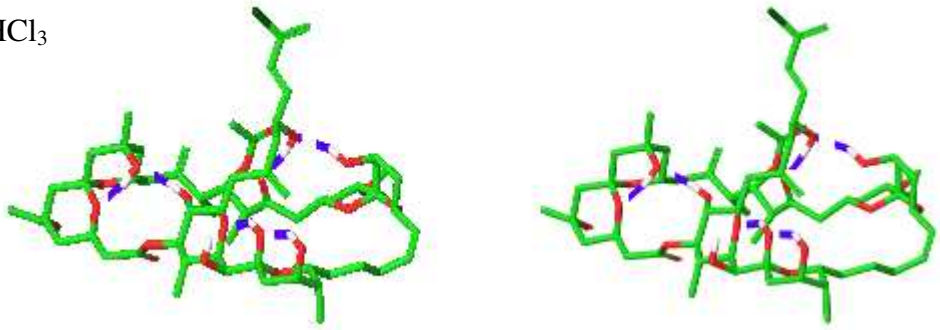
H42	H41	7.5
H38	129 H129	7.4
H38	H39	0.9
H33	94 H94	1.1
H33	93 H93	10.4
H3	H2b	1.1
H3	H2a	10.5
H11	H12	7.8
H13	H14b	1.7
H13	H14a	7.7
H28	85 H85	5.2
H28	86 H86	6.6
H29	90 H90	2.3
H29	89 H89	8.1

II. Computational Studies

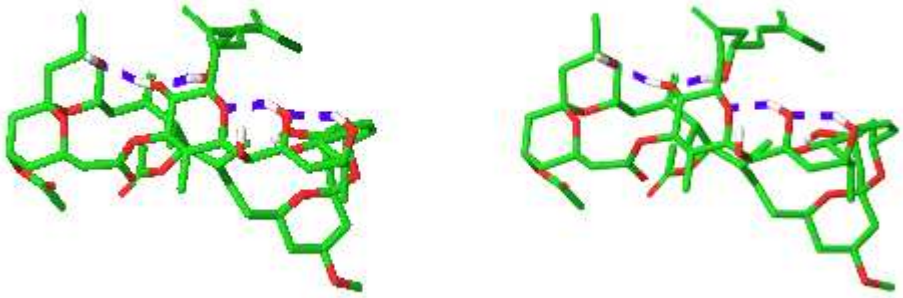
A. Conformational Searches

Energy calculations were performed with MMFF94 force field in Macromodel 7.2 by utilizing the GB/SA solvation in water, chloroform, DMSO or acetonitrile with constant dielectric constant. For the later the dielectric constants were adjusted to the experimental value. MMFF was chosen as the force field as it is better parameterized for our system (185 high, 1 medium quality stretch parameters; 351 high, 1 medium quality bending parameters; 533 high, 10 low quality torsion parameters). In calculations constant dielectric constants with extended cutoffs were utilized. Custom choice of longer VDW, electrostatic and H-bond cutoffs did not alter the energy ordering of the lowest energy conformers. (Our observations revealed extended VDW and electrostatic cutoffs may change energy ordering of conformations in older

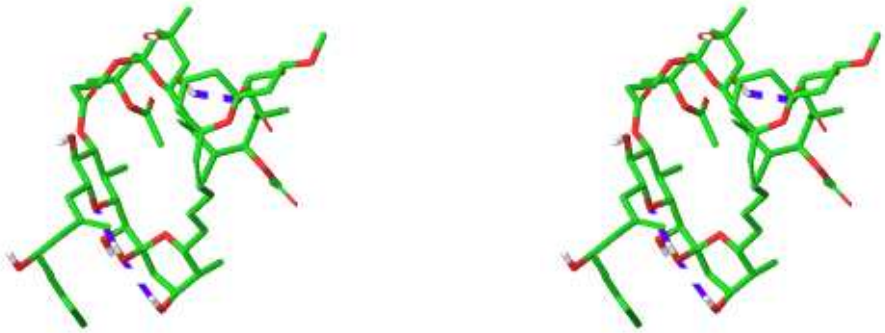
In $CHCl_3$



In H_2O



In DMSO



Kitagawa

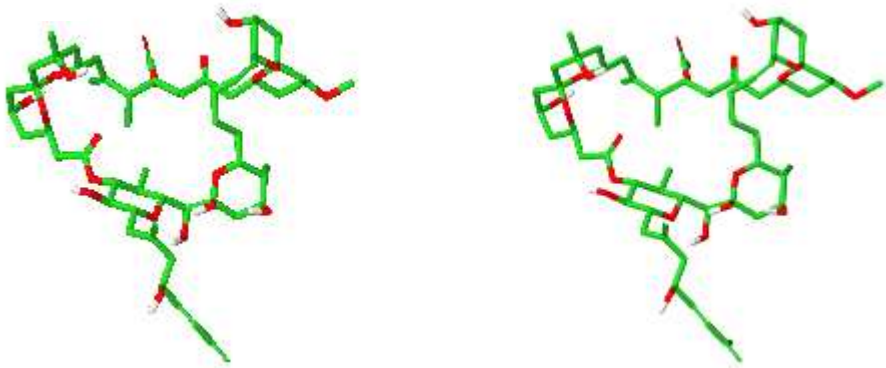


Figure SI-2: Calculated (MM) minimum energy conformations of (+)-spongistatin in different solvents.

versions of Macromodel). Atomic charges were calculated by Gaussian software package with CHELPG keyword. The MMFF values found to be in acceptable limits with the extracted atomic charges so they are utilized for all calculations.

Conformational searches were performed without any constraints. MCMM torsional sampling was employed where intermediate torsional sampling options were chosen. A 100 kJ/mol energy window was chosen for keeping the conformations. Consecutive conformational searches of 30,000 steps were utilized. Final conformers were saved and minimized for complete convergence (with Polak-Ribiere conjugate gradient algorithm) with the default gradient convergence threshold (0.05). The final compounds were clustered according to their backbone dihedral angles with XCluster software as implemented in Macromodel 7.2. These calculations were repeated initating from different geometries (obtained from a simulated annealing calculation) until not new low energy families were detected after clustering.

Solvation energies of conformations in water vary −30 to −90 kJ/mol where the total energy is in the order of ~430 kJ/mol. PM3 level relative energies of the conformers minimized in gas phase are shown below.

	$CHCl_3$	**water**	**DMSO**	**Kitagawa structure**
PM3 energy (kcal/mol)	0	0.2	6.6	50.4

B. MD Simulations

MD simulations in water were performed with Macromodel 7.2 with the same options for the force field and solvation. SHAKE algorithm was used for bonds to hydrogen. Structures at every 150 fs were extracted from 100 nanosecond simulation

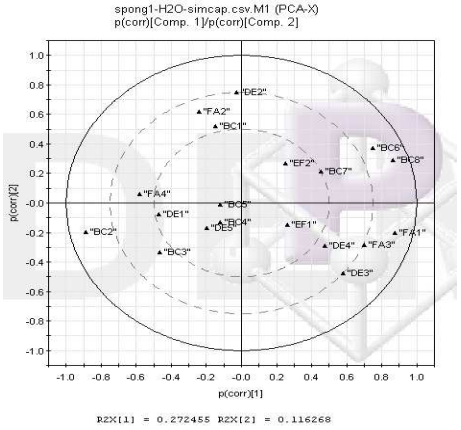
(1.5 fs timestep, 300 K). The structures were minimized first and clustered by XCluster based on their backbone torsional angles. Elimination of redundant structures yielded 2921 distinct structures. The dihedral angles extracted from these were given into PCA. During the simulation western perimeter was observed to have a preferred conformation where the **CD** ring made twisting and bending movements within the macrocyclic ring corresponding to a variety of conformers. The potential energy surface was flat allowing the molecule to have large amount of conformations.

C. Principal Component Analysis

Principal component analysis (PCA) is utilized to identify the correlated separated torsional angles responsible for the twisting and bending movements of the macrocycles during the molecular dynamics simulations. Identification of these "flexible" torsions not only reveals how the molecule is adopting different geometries but elucidate the macromolecular movements of the macrocycle. To this end backbone dihedral angles of the conformations obtained in water were converted to a 0–360 º scale and given into PCA analysis utilizing SIMCA-P software[1] using the default settings. Only 40% of the variation could be expressed by 2 principal components while the 4 principal components generated 60% of the variation.

[1] Simca-P, Umetrics http://www.umetrics.com

a.



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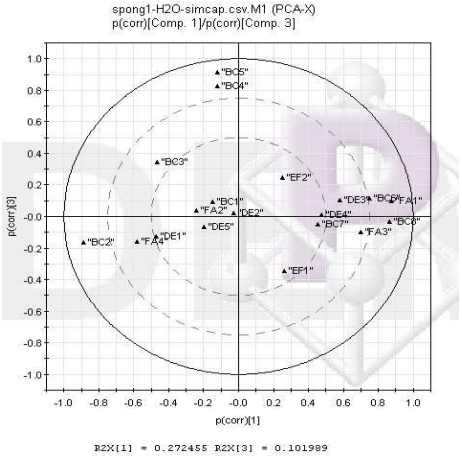

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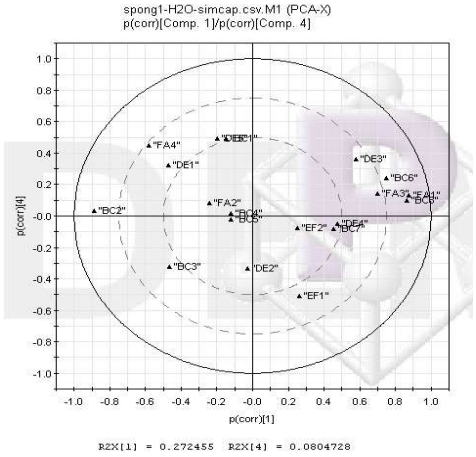


d.

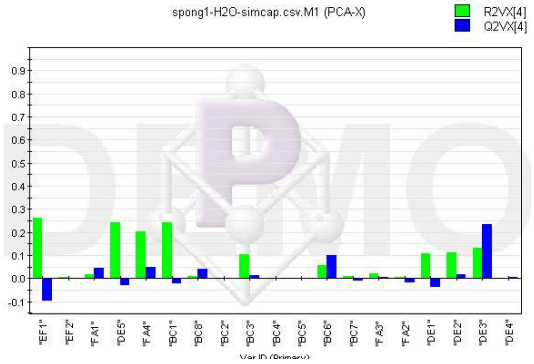


Figure SI-3 (a) Loadings PCA 1 *vs.* 2 (38%) (**b)** Loadings PCA 1 *vs.* 3 (37%) (**c)** Loadings PCA 1 *vs.* 4 (35%) (**d)** Component contributions

The most important correlations among long range (non-adjacent) torsional angles are as following (see Figure SI-4 for the torsion names)

1. **DE3** and **BC8**

2. **DE4** and **BC7**

3. **DE2** and **BC1**

Rest of the long range changes seen in torsional angles are not found to be correlated. Changes around **EF1**, **DE5**, **FA4**, **BC1** have the highest component contributions in the PCA model.

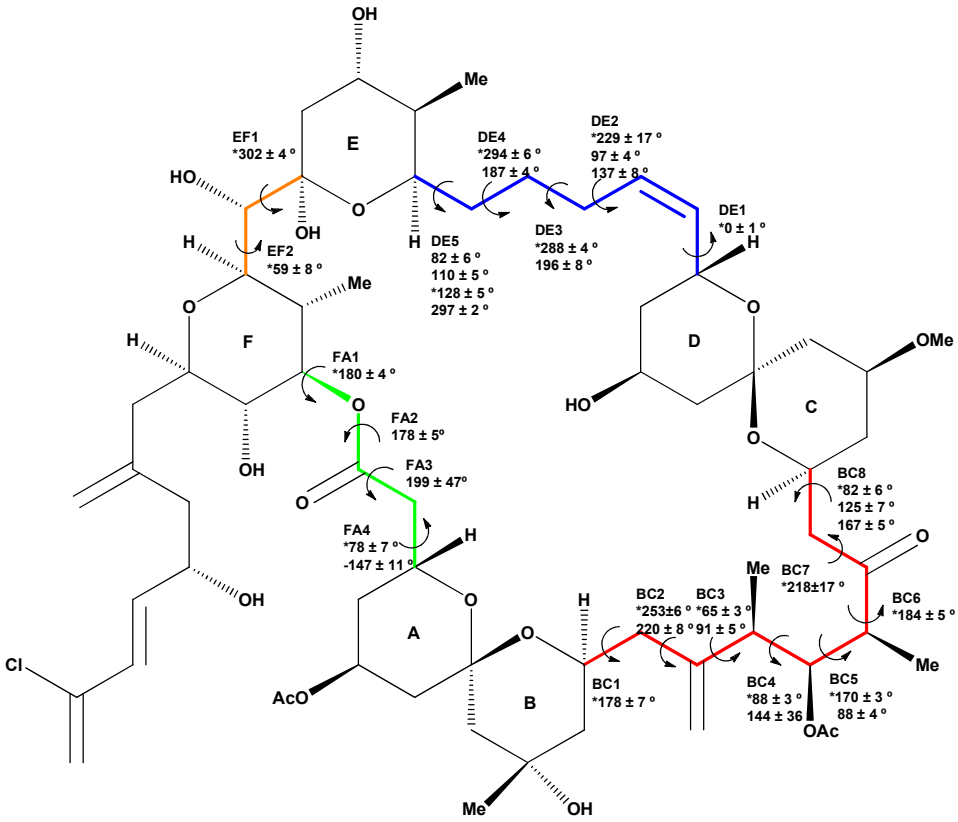


Figure SI-4: Summary of preferred angles for each backbone torsional angle. Most accessed values are indicated with a * sign. See Figure SI-5 for details.

This analysis provides the "fulcrum" or "hinge" points within the macrocyclic ring. Although from a design point of view it is not viable to manipulate these torsions individually for restricting a conformation, they are informative for understanding the flexible points of the molecule.

D. Polar Maps

Backbone dihedral angles of the conformations obtained in water were converted into 0–360 ° scale and plotted onto polar coordinate graphs by using OriginPro 7.5[2] software. Conformations within 20 kJ/mol energy to the global minimum were taken.

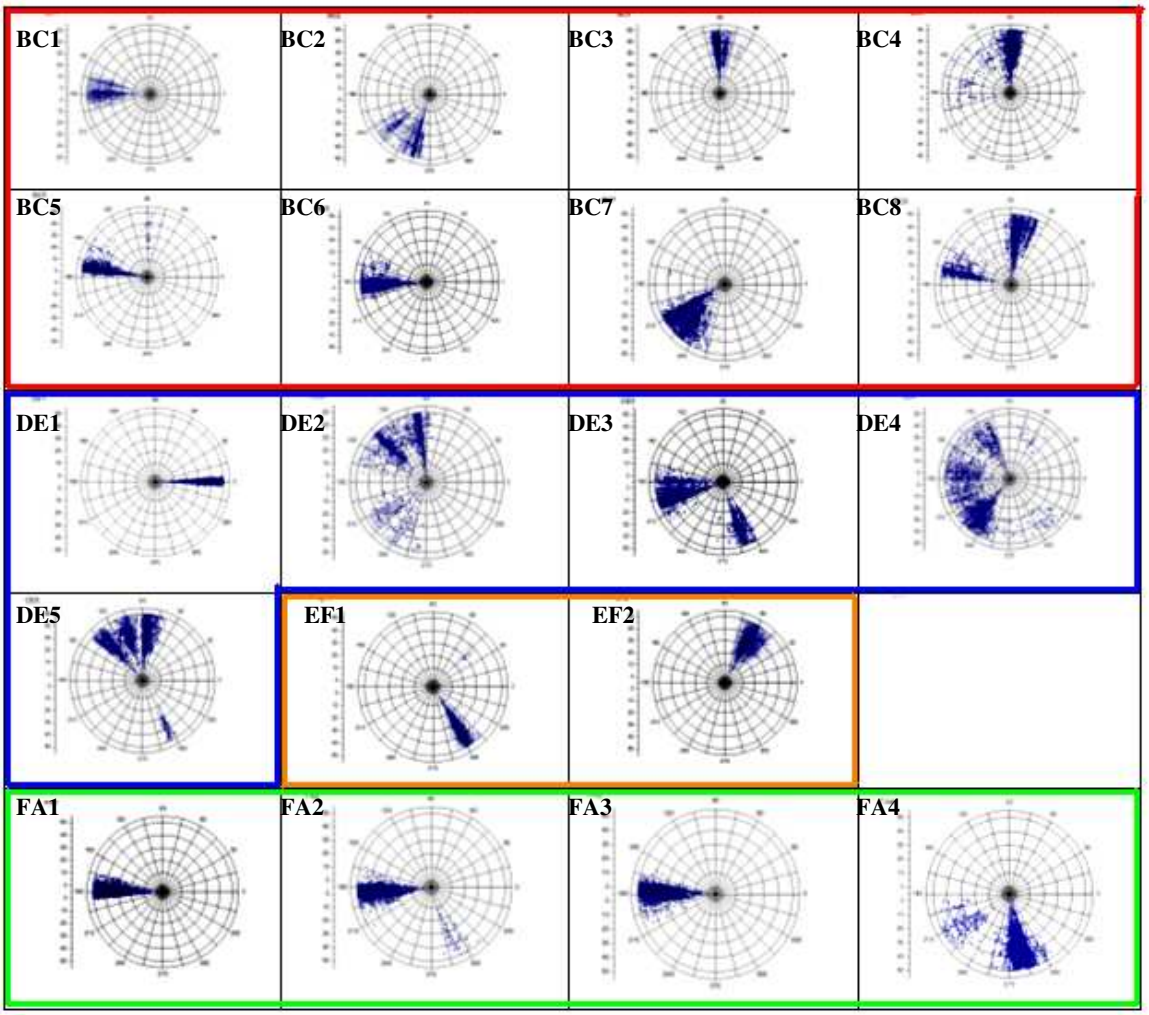


Figure SI-5: Polar map of each backbone dihedral angle is given. Each dot represents a conformer. Center in each map represents the lowest energy. **Raw 1** BC1–BC4; **Raw 2** BC5–BC8; **Raw 3** DE1–DE4 **Raw 4** DE5, EF1, EF2 **Raw 5** FA1–FA4 (For names of the dihedral angles and color codes see Figure SI-4).

[2] OriginLab http://www.originlab.com/

E. DISCO (Distribution of Conformations)

DISCO (Distribution of conformations) is an in-house implemented application for calculation of the solution conformation distributions of organic molecules from NOEs, coupling constants and a set of pre-calculated conformations. DISCO utilizes deconvolution methods similar to the ones developed earlier[3] with two main differences **1**) A clustering routine clusters conformations according to the given NOEs and coupling constants prior to deconvolution at the desired level. **2**) A general genetic algorithm solver is utilized for deconvolution which is advantageous for finding the global minimum.

i. DISCO Calculations of (+)-Spongistatin 1

Spongistatin conformers obtained from conformational searches with different solvent models were combined and subjected to DISCO where NMR observables were extracted from spectra taken in DMSO. Hierarchical clustering followed by selection of representative structures from the clusters gradually decreased to a set of 220 conformers. The clustering level than gradually lowered to 25 where RMS deviation of 3.08 was observed (Discrimination and clustering analysis were repeated to lower the number of independent variables). The separate calculation with NOE and torsional constraints are calculated and similar results were obtained. Overall the consistency of the distributions for two independent observations shows the success of the current distribution. RMS deviations calculated for NOE constrained calculations were is 3.1 angstroms where in *J* constrained calculations it was 0.7 Hz.

[3] Cicero, D.O.; Barbato, G.; Bazzo R. *J. Am. Chem. Soc.*, **1995**, 117 , 1027.

Calculated distribution of conformations under NOE and/or *J* coupling constraints obtained from NMR studies

	NOE+*J*	**NOE**	**J**
Conformation 1 %	57	66	53
Conformation 2 %	13	7	11
Conformation 3 %	8	10	9
Conformation 4 %	4	6	4

ii. DISCO Calculations of ABEF Analog

DISCO calculations revealed the important coupling and NOE constraints. As seen from the program clustering output of the NMR observables (Figure SI-6), the side-

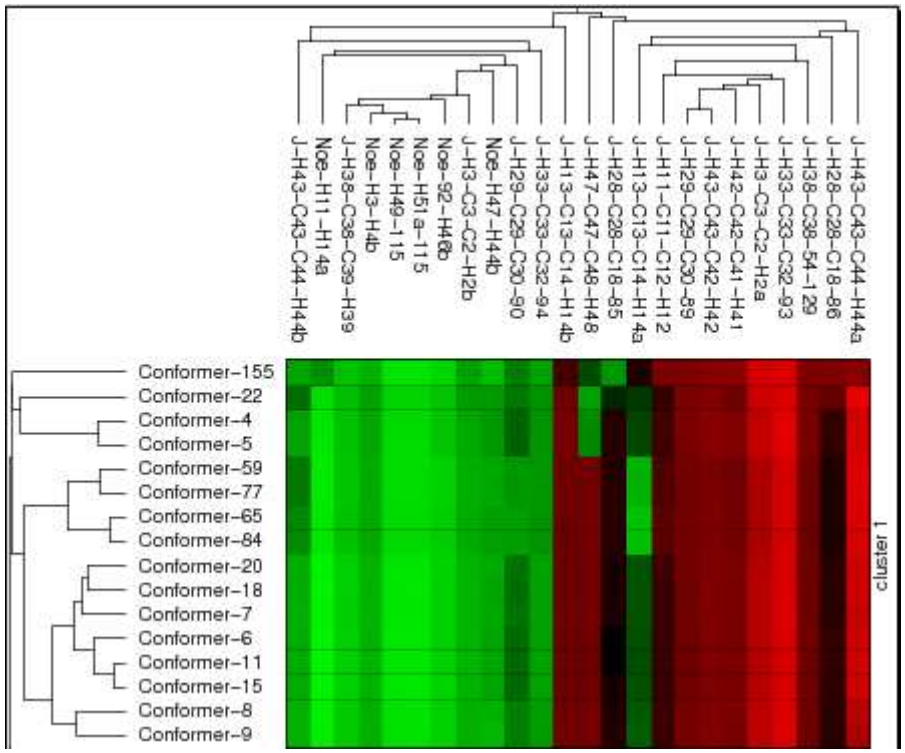


Figure SI-6. DISCO clustering output (partial) for the **ABEF** analog

chain torsions around the C(43)-C(44) and C(47)-C(48) bonds as well as the macrolide torsions around the C(28)-C(18) and C(13)-C(14) bonds are distinctive in the partitioning the conformers. When the representative structures of conformational families were investigated (A–C, Figure SI-7), these torsions correspond to the observed differences in the H-bond network due the side-chain and the lactone carbonyl orientations.

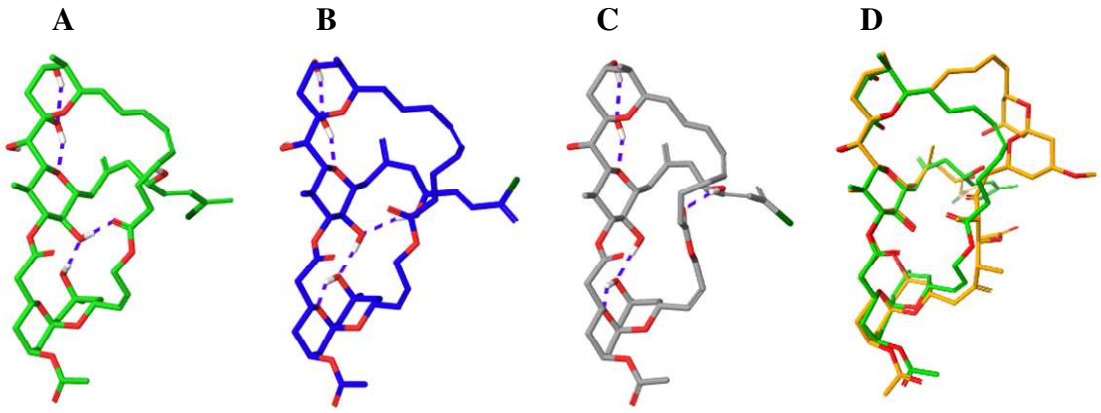


Figure SI-7: Calculated solution conformations of the **ABEF** analog (**A-C**). Overlay of the major conformer **A** with the "flat" conformer of (+)-spongistatin 1. H-bonds are represented as blue dashed lines.

DISCO calculations revealed the carbonyl group on introduced linker involves in H-bonds with the hydroxyl groups of the **F** ring as well as the side-chain. When the characteristics of these conformers were investigated the main backbone torsional differences are identified in the methylene linkers around the ester linkage. Orientation of the **ABEF** perimeter was conserved in all conformers. Side-chain was found to be less mobile.

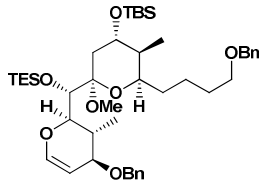
	Conformation A	**Conformation B**	**Conformation C**
NOE+*J*	59	33	8

In Silico Screening of Potential Linkers

A library of possible methylene linkers differing in length and various ester, olefin and alcohol substitutions was prepared *in silico* by an in house written script in SMILES notations. These later converted to 3D chemical representations via Balloon software package.[4] Each member of the library was attached manually to the minimum energy conformation in chloroform and subjected to a preliminary conformational step of 1000 steps. The non-suitable linkers were identified by the comparison of the **EF**-ring conformation. Successful linkers were than given to longer conformational searches. This procedure was later repeated for water GB/SA solvation model starting from the "twist" conformation. As stated earlier, conformations those cannot preserve the required **EF**-ring orientation were eliminated. Successful linkers than given to MD simulations and the "flexibility" (*vide infra*) of the molecules were examined. In addition the hydrogen bond networking was investigated to see if the introduced H-bonds are feasible in rigidification of the geometry. In contrast to our earlier design strategy, which involves enforcing the molecule to a rigid conformational state, utilization of the softer H-bonds was envisioned to mimic the parent molecule in case of a conformational change is required for the activity. As explained in the text, the strain energies were also calculated to circumvent the issues of increased macrocyclic strain. For the isodesmic calculations the acyclic congeners were prepared via cleaving the macrocyclic ester linkages and the **E**-ring followed by minimization of the "open" conformers to the closest local minima. Strain energies were than extracted from the single point energy calculations via MMFF94 as implemented in Macromodel 7.2.

[4] Puranen, J. S., Mikko J. V., Johnson M. S. *J. Comp. Chem*. **2010**, *31*, 1722-1732.

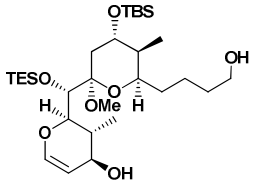
III. Synthetic Procedures



(+)-**22**

A solution of pyran (+)-**21** (150 mg, 0.19 mmol) and pyridine (0.155 mL, 1.9 mmol) in CH_2Cl_2 (4.3 mL) was cooled to 0 °C and treated with trifluoromethanesulfonic anhydride (50 mL, 0.31 mmol). The reaction was stirred for 2 h and quenched with water. The aqueous layer was extracted with one time CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was placed under high vacuum for 0.2 h, taken up in THF (4.4 mL) and HMPA (0.25 mL), and cooled to −78 °C. The solution was treated with NaHMDS (0.38 mL, 1.0 M in THF, 0.38 mmol), warmed to −30 °C, stirred for 74 h, quenched with saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted three times with diethyl ether, and the pooled organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography [on silica gel neutralized by stirring with triethylamine-hexanes (5:95) for 0.5 h] using ethyl acetate-hexanes (1:99) as elutant afforded dihydropyran (+)-**22** (105 mg, 72%) as a yellow oil. $[\alpha]_D^{20}$ +46.0 (*c* 0.15, CH_2Cl_2); IR (thin film) 2949 (s), 2876 (s), 1653 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32 (m, 3H), 7.16 (m, 5H), 7.10 (m, 2H), 6.39 (dd, *J* = 6.1, 0.8 Hz, 1H), 4.76 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.36 (s, 2H), 4.31–4.26 (m, 2H), 4.03–3.99 (m, 2H), 3.88 (dd, *J* =6.1, 2.8 Hz, 1H), 3.64 (ddd, *J* = 8.7, 1.6, 1.6 Hz, 1H), 3.38 (t, *J* = 6.2 Hz, 2H), 3.10 (s, 3H), 2.43 (dd, *J* = 15.2, 3.9 Hz, 1H), 2.30 (m, 1H), 1.96 (dd, *J* = 15.2, 1.5 Hz, 1H), 1.71–1.64 (m, 4H), 1.57 (m, 1H),

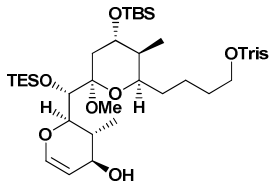
1.47 (m, 1H), 1.36 (m, 1H), 1.12–1.05 (m, 21H), 0.95 (d, J = 7.2 Hz, 3H), 0.83–0.76 (m, 6H), 0.18 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.9, 139.3, 139.2, 128.5, 128.4, 127.6, 127.5, 127.4, 127.3, 101.3, 100.6, 78.0, 76.0, 72.7, 70.9, 70.6, 70.1, 69.1, 67.0, 46.7, 38.5, 33.9, 32.8, 30.4, 30.1, 25.9, 23.2, 18.0, 14.9, 7.3, 7.1, 5.9, −4.5, −5.0; high resolution mass spectrum (ESI$^+$) *m/z* 791.4739 [(M+Na)$^+$; calcd for $C_{44}H_{72}O_7Si_2Na$: 791.4714].



(+)-**24**

A solution of (+)-**22** (44 mg, 0.057 mmol) in THF (5.25 mL) was cooled to −78 °C and treated with LDBB [0.5 M in THF, 2.1 mL, 1.05 mmol; freshly prepared by sonication of Li metal (110 mg, 15.8 mmol) and 4,4'-di-*tert*-butylbiphenyl (3.83 g, 14.9 mmol) in THF (28 mL) at 0 °C for 3.5 h)]. The dark green solution was stirred for 3.5 h, quenched with saturated aqueous NH_4Cl, and warmed to room temperature. The aqueous layer was extracted three times with diethyl ether and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography [on silica gel neutralized by stirring with triethylamine-hexanes (5:95) for 0.5 h] using a gradient of ethyl acetate-hexanes (0:1 to 1:4) as elutant afforded diol (+)-**24** (29 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +29.2 (*c* 0.20, CH_2Cl_2); IR (thin film) 3343 (s), 2935 (s), 2876 (s), 1654 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 6.26 (d, J = 6.2 Hz, 1H), 4.6 (dd, J =6.2, 2.1 Hz, 1H), 4.28 (m, 1H), 4.01 (s, 1H), 3.96 (d, J = 6.2 Hz, 2H), 3.12 (s, 3H). 2.30 (dd, J = 15.3, 3.6 Hz, 1H), 2.04–1.99 (m, 2H), 1.68–1.58

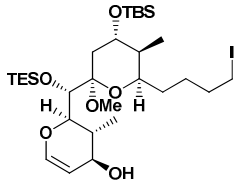
(m, 2H), 1.54–1.49 (m, 1H), 1.48–1.38 (m, 2H), 1.36–1.21 (m, 4H), 1.10 (t, J = 7.9 Hz, 9H), 1.03–1.01 (m, 12H), 0.91 (d, J = 7.1 Hz, 3H), 0.83–0.74 (m, 6H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.9, 104.4, 101.4, 78.1, 71.7, 71.1, 68.6, 67.3, 62.1, 47.5, 38.5, 36.9, 33.6, 33.0, 30.2, 25.8, 22.6, 18.0, 15.2, 10.4, 7.1, 5.8, –4.7, –5.1; high resolution mass spectrum (ESI$^+$) m/z 611.3775 [(M+Na)$^+$; calcd for $C_{30}H_{60}O_7Si_2Na$: 611.3775].



(+)-**25**

A solution of diol (+)-**24** (60 mg, 0.102 mmol) in CH_2Cl_2 (6.6 mL) was cooled to 0 °C and treated sequentially with triethylamine (0.36 mL, 2.58 mmol), 2,4,6-tri-*iso*-propylbenzenesulfonyl chloride (153 mg, 0.54 mmol) and N,N-4-dimethylaminopyridine (12 mg, 0.103 mmol). The reaction was stirred for 6 h, quenched with saturated aqueous NH_4Cl and extracted two times with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography [on silica gel neutralized by stirring with triethylamine-hexanes (5:95) for 0.5 h] using a gradient of ethyl acetate-hexanes (0:1 to 3:7) as elutant afforded trisylate (+)-**25** (67 mg, 76%) as a colorless oil. $[\alpha]_D^{20}$ +15.0 (*c* 0.12, CH_2Cl_2); IR (thin film) 2955 (s), 2875 (m), 1653 (m), 1606 (w) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 7.31 (s, 2H), 6.27 (dd, J = 6.2, 1.1 Hz, 1H), 4.6 (sept, J = 6.8 Hz, 2H), 4.52 (dd, J = 6.4, 2.0 Hz, 1H), 4.17 (m, 1H), 3.99–3.93 (m, 3H), 3.83 (dd, J = 5.9, 2.8 Hz, 1H), 3.67 (t, J = 7.5 Hz, 1H), 3.08 (s, 3H), 2.63 (sept, J = 6.8 Hz, 1H), 1.55–1.44 (m, 6H), 1.32 (d, J = 6.8 Hz, 18H), 1.29–1.11 (m, 2H), 1.19–1.07 (m, 9H), 1.05 (s, 9H),

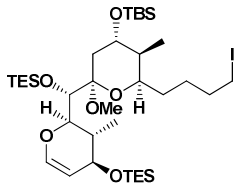
1.02 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 7.2 Hz, 3H), 0.82–0.73 (m, 6H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.4, 151.0, 144.0, 128.8, 123.7, 104.5, 101.4, 78.1, 71.1, 70.9, 68.9, 67.0, 59.7, 47.1, 38.9, 37.1, 34.2, 32.3, 30.3, 29.7, 29.3, 25.8, 24.6, 23.2, 22.3, 20.2, 18.0, 15.0, 13.4, 10.3, 7.1, 5.8, −4.6, −5.1; high resolution mass spectrum (ESI$^+$) *m/z* 877.5081 [(M+Na)$^+$; calcd. for $C_{45}H_{82}O_9SSi_2Na$: 877.5115].



(+)-**26**

A solution of trisylate (+)-**25** (5 mg, 0.006 mmol) in acetonitrile (0.54 mL) was treated sequentially with 2,6-lutidine (0.015 mL, 0.13 mmol) and LiI (9 mg, 0.068 mmol). The reaction was heated to 70 °C for 2 h, cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was extracted three times with ethyl acetate and the combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography [on silica gel neutralized by stirring with triethylamine-hexanes (5:95) for 0.5 h] using ethyl acetate-hexanes (1:9) as elutant afforded iodide (+)-**26** (5 mg, 99%) as a yellow oil. $[\alpha]_D^{20}$ +15.0 (*c* 0.12, CH_2Cl_2); IR (thin film) 3392 (s), 2932 (s), 2875 (m), 1652 (m), 1588 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 6.27 (dd, J = 6.1, 1.3 Hz, 1H), 4.5 (dd, J = 6.1, 2.1 Hz, 1H), 4.21 (m, 1H), 4.01 (s, 1H), 4.00 (d, J = 10 Hz, 1H), 3.80 (dd, J = 6.3, 2.9 Hz, 1H), 3.68 (m, 1H), 3.10 (s, 3H), 2.77 (m, 2H), 2.33 (dd, J = 15.2, 3.8 Hz, 1H), 2.00–1.92 (m, 2H), 1.60–1.48 (m, 6H), 1.29–1.11 (m, 2H), 1.10 (t, J = 8.0 Hz, 9H), 1.05 (s, 9H), 1.03 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 7.2 Hz, 3H), 0.83–0.79 (m, 6H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.9, 104.5, 101.4, 78.0, 71.1, 70.9, 68.7, 67.0,

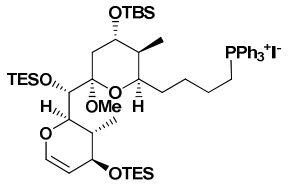
47.2, 38.4, 37.0, 33.6, 30.3, 27.2, 25.8, 24.3, 18.1, 15.0, 10.3, 7.2, 7.7, 5.9, 5.8, –4.6, –5.4; high resolution mass spectrum (ESI$^+$) *m/z* 721.2762 [(M+Na)$^+$; calcd for $C_{30}H_{59}IO_6Si_2Na$: 721.2792].



(+)-**27**

Triethylsilyl trifluoromethanesulfonate (0.011 mL, 0.048 mmol) was added to a flame dried flask containing 2,6-lutidine (0.01 mL, 0.09 mmol). The mixture was stirred for 0.5 h and then transferred via cannula into a solution of (+)-**26** (5 mg, 0.007 mmol) and 2,6-lutidine (0.21 mL, 0.18 mmol) in THF (1.2 mL) at −78 °C under argon. The reaction was warmed to 0 °C, stirred for 1.75 h, then warmed to room temperature, stirred for an additional 0.5 h and quenched with saturated aqueous $NaHCO_3$. The reaction was extracted three times with ethyl acetate and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Flash chromatography [on silica gel neutralized by stirring with triethylamine-hexanes (5:95) for 0.5 h] using a gradient of ethyl acetate-hexanes (0:1 to 1:99) as elutant afforded TES ether (+)-**27** (5.7 mg, 99%) as a clear oil. $[\alpha]_D^{20}$ +43.9 (*c* 0.28, CH_2Cl_2); IR (thin film) 2953 (s), 2876 (s), 1652 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 6.33 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.65 (dd**,** *J* = 6.2, 1.7 Hz, 1H), 4.21 (m, 1H), 4.06–4.04 (m, 2H), 3.94 (ddd, *J* = 8.5, 1.7, 1.7 Hz, 1H), 3.87 (dd, *J* = 6.2, 3.3 Hz, 1H), 3.15 (s, 3H), 2.78 (m, 2H), 2.43 (dd, *J* = 15.2, 3.9 Hz, 1H), 1.97 (dd, *J* = 15.3, 1.5, 1H), 1.6–1.5 (m, 6H), 1.23–1.13 (m, 2H), 1.1 (d**,** *J* = 6.5 Hz, 3H), 1.09 (t, *J* = 7.9 Hz, 9H), 1.07 (s, 9H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.93 (d, *J* =*7.9* Hz, 3H), 0.83–0.75 (m, 6H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.10 (s, 3H);

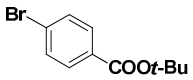
^{13}C NMR (125 MHz, C_6D_6) δ143.7, 104.9, 101.5, 77.9, 70.9, 70.7, 67.0, 46.7, 38.5, 37.0, 38.6, 31.7, 30.5, 27.3, 25.8, 18.1, 14.9, 10.4, 7.1, 6.9, 5.9, 5.9, 5.8, 5.7, 5.3, –4.6, –5.1; high resolution mass spectrum (ESI$^+$) *m/z* 835.3654 [(M+Na)$^+$; calcd for $C_{36}H_{73}IO_6Si_3Na$: 835.3657].



(+)-**18**

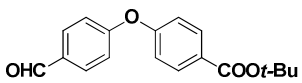
To a solution of TES ether (+)-**27** (33.1 mg, 0.041 mmol) in acetonitrile (2.8 mL) was added Ph_3P (112 mg, 0.42 mmol). The reaction was heated to 73 °C for 50 h, cooled to room temperature and concentrated *in vacuo.* Flash chromatography using a gradient of acetonitrile-ethyl acetate (0:1 to 3:7) as elutant afforded Wittig salt (+)-**18** as a yellow film. Trace amounts of water were removed by freeze-drying the film with benzene to give a pale yellow powder (43.8 mg, 99%). $[\alpha]_D^{20}$ +39.9 (c 0.07, CH_2Cl_2); IR (thin film) 2945 (s), 2867 (s), 1716 (s), 1645 (m), 1607 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 7.76–7.68 (m, 6H), 7.07 (s, 9H), 6.36 (d, *J* = 6.2 Hz, 1H), 4.65 (dd, *J* =6.2, 1.7 Hz, 1H), 4.38–4.22 (m, 4H), 4.13 (d, *J* = 11.4 Hz, 1H), 3.95 (ddd, *J* = 8.6, 1.6, 1.6 Hz, 1H), 3.92 (m, 1H), 3.33 (s, 3H), 2.48 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.27 (m, 2H), 2.02 (d, *J* = 14.7 Hz, 1H), 1.91 (m, 1H), 1.71–1.63 (m, 2H), 1.49 (m, 2H), 1.33 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.12 (t, *J* = 7.9 Hz, 9H), 1.06 (s, 9H), 1.05–1.00 (m, 12 H), 0.90–0.83 (m, 6H), 0.72, (q, *J* = 7.9 Hz, 6H), 0.19 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.7, 134.2, 134.1, 134.0, 132.2, 132.1, 130.0, 129.9, 119.2, 118.5, 105.0, 101.6, 78.1, 71.2, 70.9, 70.4, 66.8, 47.9, 38.8, 37.0, 33.0, 30.6, 27.4, 27.2, 26.0, 23.0,

18.2, 15.2, 10.8, 7.4, 7.0, 6.9, 5.9, 5.3. 5.2, –4.5, –4.7; high resolution mass spectrum (ESI^+) *m/z* 947.5622 [$(M–I+Na)^+$; calcd for $C_{54}H_{88}O_6PSi_3Na$: 947.5636].



29

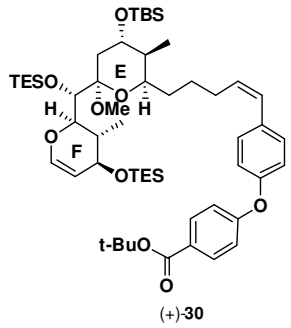
A solution of 4-bromobenzoic acid (2.02 g, 10 mmol) and carbonyldiimidazole (2.43 g, 15 mmol) in DMF (6 mL) was heated to 43 °C for 3 h. The mixture was then treated with *t*-BuOH (2.85 mL, 30 mmol) and DBU (1.5 mL, 10 mmol), stirred for 48 h and diluted with diethyl ether (150 mL). The organic phase was washed with 1M HCI, water and saturated aqueous K_2CO_3, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (1:4) as elutant afforded ester **29** (2.15 g, 83%) as a colorless oil. IR (thin film) 2977 (m), 1716 (s), 1589 (m) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 131.5, 130.5, 130.3, 127.4, 81.4, 28.1, 27.9; high resolution mass spectrum (+CI) *m/z* 256.0099 [$(M)^+$; calcd for $C_{11}H_{13}O_2Br$: 256.0098].



20

Ester **29** (557 mg, 2.15 mmol), 4-hydroxybenzaldehyde (460 mg, 1.77 mmol) and K_2CO_3 (596 mg, 4.34 mmol) were suspended in 2.6 mL pyridine and heated to 90 °C. The resulting solution was treated with Cu_2O (771 mg, 5.4 mmol) and heated to reflux. After 7 d at reflux, the reaction was cooled to room temperature, diluted with CH_2Cl_2 (40 mL) and filtered through Celite. The filtrate was washed with 1N aqueous $NaHSO_4$

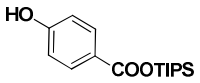
and a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography using ethyl acetate-hexanes (1:9) as elutant afforded aldehyde **20** (196 mg, 37%) as a colorless oil. IR (thin film) 2976 (w), 1706 (s), 1591 (s), 1498 (m) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 158.9, 131.9, 131.7, 128.2, 119.1, 118.5, 81.2, 28.14; high resolution mass spectrum (+CI) *m/z* 289.1199 [$(M)^+$; calcd for $C_{18}H_{18}O_4$: 298.1204].



(+)-**30**

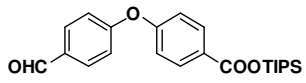
A solution of **EF** phosphonium salt (+)-**18** (9.3 mg, 8.6 μmol) in THF (0.05 mL) was cooled to −78 °C and treated with LHMDS [0.5 M, 0.018 mL, 9.0 μmol; prepared by diluting LHMDS (1.0M, 1 mL) in THF (0.66 mL) and HMPA (0.33 mL)]. The reaction was stirred for 25 min and then treated with a solution of aldehyde **20** (1.7 mg, 5.7 μmol) in THF (0.04 mL), stirred at −78 °C for 10 min and warmed to 0 °C. After 2 h the reaction was quenched with saturated aqueous NH_4Cl and saturated aqueous $Na_2S_2O_3$, and diluted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Flash chromatography using ethyl acetate-hexanes (1:49) as elutant afforded Wittig product (+)-**30** (0.7 mg, 13%) as a thin film, $[\alpha]_D^{20}$ +33.3 (*c* 0.05, CH_2Cl_2); IR (thin

film) 2927 (s), 1713 (m), 1595 (w), 1499 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 8.15–8.07 (m, 2H), 7.20–7.18 (m, 2H), 6.93–6.88 (m, 4H), 6.50 (d, *J* = 11.6 Hz, 1H), 6.33 (d, *J* = 6.2 Hz, 1H), 5.71 (ddd, *J* = 11.5, 7.1, 7.1 Hz, 1H), 4.65 (dd, *J* = 6.2, 1.7 Hz, 1H), 4.27 (m, 1H), 4.08–4.04 (m, 2H), 3.93 (m, 1H), 3.88 (m, 1H), 3.12 (s, 3H), 2.53 (dd, *J* = 15.3, 3.8 Hz, 1H), 2.39 (m, 2H), 2.16 (m, 1H), 1.97 (d, *J* = 15.1 Hz), 1.78–1.66 (m, 4H), 1.46 (s, 9H), 1.32 (m, 2H), 1.20–1.15 (m, 12H), 1.05 (s, 9H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.84–0.72 (m, 6H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (s, 3H); high resolution mass spectrum (ESI^+) *m/z* 989.5789 [$(M+Na)^+$; calcd for $C_{54}H_{90}O_9NaSi_2$: 989.5790].



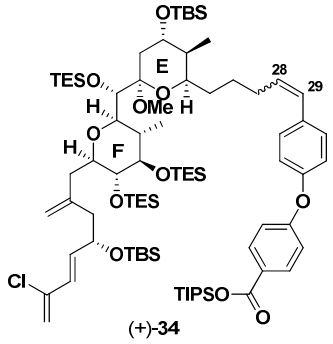
33

A solution of 4-hydroxybenzoic acid (1.0 g, 7.2 mmol) in THF (240 mL) was treated with triethylamine (4.0 mL, 29 mmol) and chlorotri-*iso*-propylsilane (2.3 mL, 10.8 mmol). The reaction was stirred for 15 min, diluted with diethyl ether (200 mL), filtered through celite and concentrated *in vacuo.* Flash chromatography using ethyl acetate-hexanes (1:4) as elutant afforded ester **33** (1.66 g, 78%) as an amorphous solid. IR (thin film) 3366 (s), 2946 (s), 2868 (s) 1695 (m), 1661 (s), 1607 (s), 1512 (m) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J*= 8.8 Hz, 2H), 6.87 (d, J= 8.8 Hz, 2H), 5.94 (s, 1H), 1.42 (septet, *J* = 7.5 Hz, 3H), 1.14 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 160.4, 132.5, 123.4, 115.3, 17.9, 12.0. High resolution mass spectrum (+CI) *m/z* 295.1719 [$(M)^+$; calcd for $C_{16}H_{27}O_3Si$: 295.1729].



32

Ester **32a** (149 mg, 0.5 mmol), 4-formylphenylboronic acid (132 mg, 0.88 mmol), $Cu(OAc)_2$ (93 mg, 0.5 mmol), 4 Å molecular sieves (200 mg) and CH_2Cl_2 (5 mL) were placed in a flame dried flask fitted with a drying tube and treated with triethylamine (0.36 mL, 2.5 mmol). The resulting suspension was stirred for 2.5 h, filtered through celite and concentrated *in vacuo.* Flash chromatography using a gradient of ethyl acetate-hexanes (1:9 to 1:4) afforded aldehyde **32** (89 mg, 44%) as a colorless oil. IR (thin film) 2946 (m), 2869 (m), 1700 (s), 1589 (s), 1500 (m) cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 9.66 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 1.41 (m, 3H), 1.16 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 189.4, 165.1, 161.1, 159.4, 132.6, 132.5, 131.6, 129.0, 118.9, 118.7, 17.8, 12.1; high resolution mass spectrum (+CI) *m/z* 398.1916 [$(M)^+$; calcd for $C_{23}H_{30}O_4Si$: 615.3540].

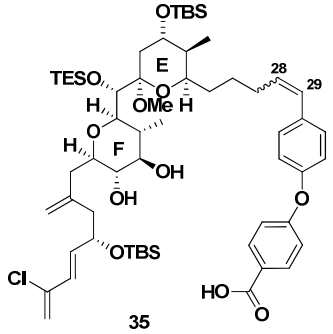


(+)-34

To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**4** (94%, 143.7 mg, 0.096 mmol), which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (1.5 mL), cooled to –78 °C. MeLi·LiBr complex (1.22 M in ether, 87 μL, 0.11 mmol) was added dropwise, and the resulting

orange solution was allowed to stir for 30 min. Aldehyde (+)-**31** (78 mg, 0.20 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (1 mL) and added dropwise, via cannula, to the ylide solution. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to room temperature over 2 h. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl-saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (5:95) as an elutant afforded Wittig product **34** (66 mg, 49%) as a mixture of olefin isomers, (*Z*:*E* = 4:1). (* indicates data for the minor isomer): IR (neat) 2952 (s), 2876 (s), 1701 (m), 1595 (m), 1500 (m), 1464 (m), 1290 (m), 1244 (m), 834 (m), 739 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.18–8.14 (m, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.86–6.82* (m, 4H), 6.73* (d, *J* = 8.9 Hz, 2H), 6.50 (dd, *J* = 14.9, 4.8 Hz, 1H), 6.45 (d, *J* = 14.9 Hz, 1H), 6.41 (d, *J* = 11.5 Hz, 1H), 6.12* (ddd, *J* = 15.8, 7.1, 7.1 Hz, 1H), 5.67 (ddd, *J* = 11.5, 7.2, 7.2 Hz, 1H), 5.17 (s, 1H), 5.14 (s, 1H), 5.13 (s, 1H), 5.06 (s, 1H), 4.54–4.49 (m, 1H), 4.36–4.32* (m, 1H), 4.27 (ddd, *J* = 8.6, 4.7, 2.0 Hz, 1H), 3.97–3.86 (m, 2H), 3.61–3.48 (m, 4H), 3.19* (s, 3H), 3.14 (s, 3H), 2.76–2.67 (m, 2H), 2.56 (dd, *J* = 13.0, 7.4 Hz, 1H), 2.42–2.30 (m, 4H), 2.25–2.19* (m), 1.97 (ddd, *J* = 10.7, 7.0, 7.0 Hz, 1H), 1.82–1.70 (m, 3H), 1.58–1.27 (m, 6H), 1.19–1.07 (m, 57H), 1.04 (s, 9H), 0.97 (d, 3H), 0.84–0.77 (m, 18H), 0.29* (s, 3H), 0.25* (s, 3H), 0.24 (s, 3H), 0.17 (s, 3H), 0.15* (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 162.6, 155.3, 144.7, 139.2, 134.8, 133.2, 133.1, 131.1, 127.0, 126.9, 126.2,

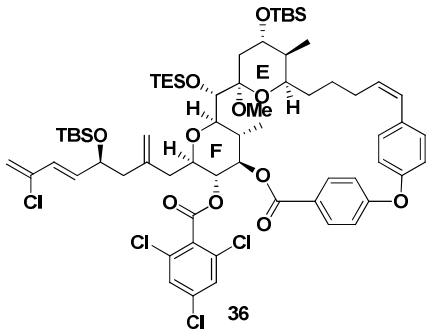
120.9, 120.4, 119.4, 118.2, 118.0, 115.9, 115.4, 102.0, 82.1, 81.1, 78.1, 77.7, 72.2, 72.0, 71.6, 67.8, 47.5, 47.3, 40.7 (2), 39.4, 39.3, 33.4, 30.8, 30.6, 30.6, 29.6, 27.5, 26.5 (2), 18.9, 18.7, 18.5, 16.5, 12.8, 11.0, 7.9, 7.8, 7.8, 6.5, 6.5, –3.7, –3.9, –4.1, –4.2; high resolution mass spectrum (ESI$^+$) *m/z* 1505.8826 [(M+Na)$^+$; calcd for $C_{80}H_{143}ClO_{11}Si_6Na$: 1505.8832].



35

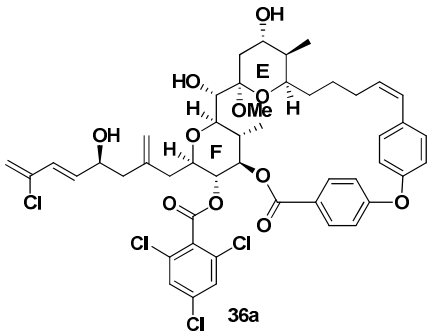
To a solution of Wittig product **34** (80 mg, 0.054 mmol) in THF (10.8 mL) at 0 °C was added TBAF (1M in THF, 0.16 mL, 0.16 mmol) over 1 hour via syringe pump. After an additional 2 h at 0 °C, the reaction mixture was diluted with ether and washed with 1M $KHSO_4$ and brine. The combined aqueous phases were then back extracted with ether (2X). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (20:80–40:60) with 0.5 % AcOH as an elutant afforded *seco*-acid **35** (40 mg, 67%) as a mixture of olefin isomers. Note: toluene was added to the collection flask before concentrating to avoid the *seco*-acid being exposed to neat AcOH (* Indicates data for the minor isomer): IR (neat) 3391 (br s), 2924 (s), 1692 (m), 1245 (m), 1097 (m), 835 (w) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 8.11–8.03 (m, 2H), 7.22–7.18 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.79* (d, *J* = 8.9 Hz, 2H), 6.48–6.36 (m, 3H), 6.13* (ddd, *J* = 15.4, 7.5, 7.5 Hz, 1H), 5.68 (ddd, *J* = 11.4, 7.0, 7.0 Hz, 1H), 5.18 (s, 1H), 5.10

(s, 1H), 5.06 (s, 1H), 5.05 (s, 1H), 4.48–4.42 (m, 1H), 4.34–4.30* (m, 1H), 4.28–4.23 (m, 1H), 3.98–3.96* (m, 1H), 3.96–3.92 (m, 1H), 3.88* (s, 1H), 3.85 (s, 1H), 3.35–3.26 (m, 2H), 3.18–3.12 (m, 1H), 3.08 (s, 3H), 2.95 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.71 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.59–2.48 (m, 2H), 2.44–2.28 (m, 4H), 2.25–2.19* (m, 1H), 1.85–1.66 (m, 5H), 1.63–1.20 (m, 5H), 1.12 (t, *J* = 8.0 Hz, 9H), 1.09 (s, 9H), 1.03 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.84–0.71 (m, 6H), 0.26* (s, 3H), 0.24 (s, 3H), 0.16* (s, 3H), 0.15 (s, 6H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 163.2, 155.0, 144.2, 139.3, 139.2, 135.0, 133.3, 133.2, 131.2, 131.1, 130.1, 126.8, 124.6, 121.0, 120.6, 118.1, 117.8, 116.1, 115.5, 102.0, 79.6, 79.2, 79.1, 76.1, 72.6, 71.6, 71.5, 67.7, 67.6, 47.3, 46.7, 40.0, 39.4, 33.4, 30.9, 30.6, 29.5, 27.5, 26.5, 26.5, 18.9, 18.7, 4.1, 11.0, 7.9, 6.5, –3.7, –3.9, –4.1, –4.2; high resolution mass spectrum (ESI$^+$) *m*/*z* 1121.5763 [(M+Na)$^+$; calcd for $C_{59}H_{95}ClO_{11}Si_3Na$: 1121.5768].



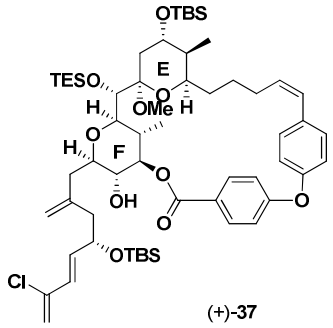
To *seco*-acid (+)-**35** (10.1 mg, 0.009 mmol) dissolved in toluene (2.8 mL) was added a solution of *i*-Pr_2NEt (0.4 M in toluene, 1.4 mL, 0.55 mmol, 60 equiv) followed by a solution of 2,4,6-TBCCl (0.4 M in toluene, 0.46 mL, 0.18 mmol, 20 equiv). The reaction mixture was allowed to stir at room temperature for 4 h before being further diluted with toluene (3.5 mL) and than added dropwise, via syringe pump over 24 h to a second flask containing DMAP (56 mg, 0.46 mmol, 50 equiv) and toluene (13.5 mL)

heated to 90 °C. After the addition, the flask containing seco-acid residue was rinsed with toluene (0.9 mL) and transferred over 12 h to the reaction mixture via a syringe pump, followed by a third time rinsing with toluene (0.6 mL) and adding over 2 h. After the third rinse, the reaction mixture was allowed to cool to room temperature and stirred for an additional 18 h. The reaction mixture was diluted with ether and then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the organic layer rinsed with brine. The combined aqueous layers were then back extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:99 to 9:91) as an elutant afforded lactone **36** (8.4 mg) with a minor impurity. ^{1}H NMR (500 MHz, C_6D_6) δ 8.20 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 2H), 6.44–6.32 (m, 2H), 5.61–5.53 (m, 3H), 5.19 (s, 1H), 5.09 (s, 1H), 5.05 (s, 1H), 4.53 (ddd, *J* = 4.2, 6.4, 9.1 Hz, 1H), 4.23–4.18 (br m, 1H), 3.99 (d, *J* = 4.5 Hz, 1H) 3.81 (m, 1H), 3.74 (br s, 1H), 3.42 (apparent dd, , *J* = 4.4, 15.3 Hz, 2H), 3.15 (s, 3H), 2.97–2.87 (m, 2H), 2.61 (dd, *J* = 9.8, 7.5 Hz, 1H), 2.54–2.43 (m, 2H), 2.31 (dd, *J* = 15.2, 3.6 Hz, 1H), 2.16–2.06 (m, 2H), 1.61–1.46 (m, 2H), 1.45–1.17 (m, 14 H), 1.02 (s, 9H), 1.01 (s, 9H), 1.02 (m, 11H), 1.01 (s, 9H), 0.89 (d, *J* = 7.4 Hz, 2H); 0.72 (d, *J* = 7.4 Hz, 3H); 0.13 (s, 6H), 0.11 (d, *J* = 7.8 Hz, 9H), 0.06 (s, 6H).



36a

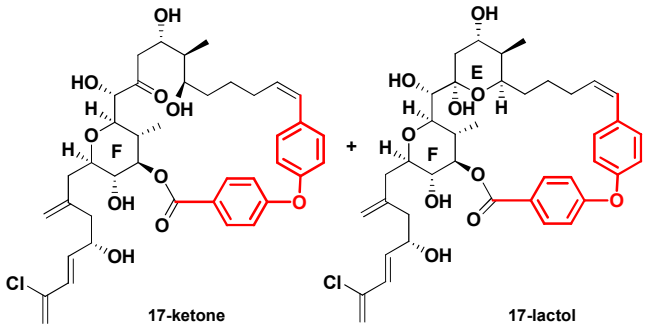
To macrolactone (+)-**36** (8.2 mg) in acetonitrile (1.6 mL) at –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (1.6 mL) via syringe pump over 2 hours. Note: The HF solution was prepared by the dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL). After the addition was complete, the reaction mixture was allowed to stir for an additional 17 h at –20 °C, before being quenched by the dropwise addition of Et_3N (2.0 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a mixture of ethyl acetate and methylene chloride (2:1) and washed with saturated $NaHCO_3$ and brine. The aqueous layers were back extracted with ethyl acetate and methylene chloride (2:1 X2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using methanol-methylene chloride (2:98 to 3:97) as an elutant afforded **36a**. High resolution mass spectrum (ESI^+) *m/z* 953.2015 [$(M+Na)^+$; calcd for $C_{47}H_{50}Cl_4O_{11}Na$: 953.2005].



(+)-37

To *seco*-acid (+)-**35** (30.3 mg, 0.028 mmol) dissolved in toluene (2.8 mL) was added a solution of *i*-Pr_2NEt (0.4 M in toluene, 1.05 mL, 0.42 mmol) followed by a solution of 2,4,6-TBCCl (0.4 M in toluene, 0.63 mL, 0.25 mmol). The reaction mixture was allowed to stir at room temperature for 5.5 h before being further diluted with toluene (8.0 mL) and than added dropwise, via syringe pump over 24 h to a second flask containing DMAP (68 mg, 0.56 mmol) and toluene (40.5 mL) heated to 90 °C. After the addition, the flask containing seco-acid residue was rinsed with toluene (2.8 mL) and transferred over 12 h to the reaction mixture via a syringe pump, followed by a third time rinsing with toluene (1.9 mL) and adding over 2 h. After the third rinse, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ether and then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the organic layer rinsed with brine. The combined aqueous layers were then back extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:99 to 9:91) as an elutant afforded lactone (+)-**37** (18.2 mg, 62%) with a minor impurity. $[\alpha]_D^{20}$ +12.17 (*c* 0.03, C_6H_6); IR (neat); ^{1}H NMR (500 MHz, C_6D_6) δ 8.12 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.52–6.35 (m*, 4H), 5.70 (ddd, *J* = 8.1, 1.3, , 8.5 Hz, 1H), 5.17 (s, 1H), 5.07 (s, 1H), 5.05 (s, 1H), 4.97 (s, 1H), 4.80 (apparent t, *J* = 7.1 Hz, 1H), 4.47 (m, 1H), 4.27 (br s, 1H), 4.23 (apparent t, *J* = 6.4 Hz, 1H), 3.98 (d, *J* = 4.3 Hz, 1H) 3.81 (m, 1H), 3.54 (dd, *J* = 6.4, 9.2 Hz), 3.42–3.33 (m, 2H), 3.27 (s, 3H), 2.90–2.74 (m, 2H), 2.90–2.74 (m, 2H), 2.47–2.30 (m, 3H), 2.26 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.15–2.01 (m, 2H), 1.65–1.46 (m, 4H), 1.18 (d, *J* = 6.4 Hz, 2H), 1.15 (d, *J* = 6.4 Hz,

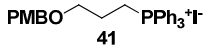
2H), 1.02 (m, 11H), 1.01 (s, 9H), 0.86 (d, J = 7.5 Hz, 3H); 0.82 (d, J = 6.5 Hz, 3H); 0.12 (s, 6H), 0.10 (d, J = 7.4 Hz, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, C_6D_6) δ 166.1, 165.6, 157.3, 142.8, 138.7, 138.5, 135.2, 133.3, 131.9, 130.5, 128.6, 126.3, 122.6, 121.9, 118.4, 117.4, 115.0, 114.8, 100.5, 83.4, 78.4, 77.6, 73.6, 71.2, 70.8, 67.3, 49.9, 45.8, 39.3, 37.3, 33.3, 30.7, 29.9, 29.5, 25.9, 19.8, 18.2, 10.3, 7.1, 5.4, 4.8, –4.4, –4.7, –4.8, –5.1; high resolution mass spectrum (ESI$^+$) m/z 1103.5706 [(M+Na)$^+$; calcd for $C_{59}H_{93}ClO_{10}Si_3Na$: 1103.5663].



To macrolactone (+)-**37** (24.3 mg, 0.022 mmol) in acetonitrile (1.6 mL) at –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (1.6 mL) via syringe pump over 2 hours. Note: The HF solution was prepared by the dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL). After the addition was complete, the reaction mixture was allowed to stir for an additional 17 h at –20 °C, before being quenched by the dropwise addition of Et_3N (2.0 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a mixture of ethyl acetate and methylene chloride (2:1) and washed with saturated $NaHCO_3$ and brine. The aqueous layers were back extracted with ethyl acetate and methylene chloride (2:1 X2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

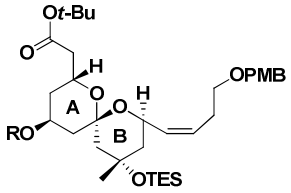
Column chromatography using methanol-methylene chloride (2:98 to 3:97) as an elutant afforded **EF** analog **17-lactol** and **17-ketone** as a mixture (1:11) (9.6 mg, 42%). $[\alpha]_D^{20}$ +8.57 (*c* 0.035, C_6H_6); IR (neat) 3420 (br s), 2929 (s), 1708 (s), 1594 (m), 1498 (s), 1234 (s), 1097 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 11.3 Hz, 1H), 6.37 (dd, *J* = 14.9, 1.2 Hz, 1H), 6.27 (dd, *J* = 15.0, 4.7 Hz, 1H), 5.70 (ddd, *J* = 11.3, 7.5, 7.5 Hz, 1H), 5.16 (s, 1H), 5.01 (s, 1H), 4.99 (s, 1H), 4.91 (s, 1H), 4.67 (dd, *J* = 7.4, 6.8 Hz, 1H), 4.30–4.25 (m, 3H), 3.54–3.47 (m, 2H), 3.45–3.41 (m, 1H), 3.29 (ddd, *J* = 8.2, 8.2, 3.5 Hz, 1H), 3.22 (dd, *J* = 17.2, 9.5 Hz, 1H), 2.87–2.72 (m, 1H), 2.64 (dd, *J* = 14.8, 3.1 Hz, 1H), 2.32–2.13 (m, 6H), 1.74 (dd, *J* = 17.2, 3.2 Hz, 1H), 1.41–1.19 (m, 5H), 1.05–0.80 (m, 7H), 0.74 (d, *J* = 7.4 Hz, 3H); ^1H NMR (500 MHz, CD_3CN) δ 7.93 (d, *J* = 8.9 Hz, 2H), 8.52 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 11.3 Hz, 1H), 6.41 (dd, *J* = 15.0, 1.1 Hz, 1H), 6.15 (dd, *J* = 15.0, 5.3 Hz, 1H), 5.79 (ddd, *J* = 11.3, 7.4, 7.4 Hz, 1H), 5.45 (s, 1H), 5.36 (s, 1H), 4.95 (s, 1H), 4.91 (s, 1H), 4.66 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.42–4.36 (m, 2H), 4.26–4.24 (m, 1H), 4.30 (d, *J* = 4.3 Hz, 1H), 3.66–3.61 (m, 1H), 3.59 (d, *J* =3.7 Hz, 1H), 3.54–3.45 (m, 3H), 3.42–3.36 (m, 2H), 3.21 (dd, *J* = 17.4, 9.0 Hz, 1H), 3.09–3.05 (m, 1H), 2.99 (d, *J* = 4.5 Hz, 1H), 2.63 (dd, *J* = 15.0, 2.2 Hz, 1H), 2.39–2.18 (m, 4H), 1.50–1.28 (m, 4H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.4, 167.1, 165.3, 155.4, 143.1, 139.2, 138.2, 136.1, 134.1, 132.8, 133.1, 129.6, 126.9, 124.7, 122.2, 117.4, 116.2, 115.8, 82.1, 81.8, 80.3, 79.3, 76.6, 74.0, 72.3, 70.2, 45.7, 45.1, 42.3, 39.4, 37.2, 34.6, 28.9, 27.2, 15.6, 6.2; ^{13}C NMR (125 MHz, CD_3CN) δ 211.7, 166.6, 165.2, 155.7, 144.3, 139.3, 139.2, 136.8, 135.0, 132.8,

131.6, 129.4, 129.3, 126.8, 125.7, 122.4, 117.7, 116.4, 115.5, 82.3, 81.5, 80.4, 79.4, 76.1, 73.6, 71.2, 70.0, 45.7, 45.6, 43.3, 39.3, 38.5, 35.2, 29.2, 27.4, 14.7, 7.1; high resolution mass spectrum (ESI^+) *m/z* 747.2923 [$(M\text{-}H_2O+Na)^+$; calcd for $C_{40}H_{47}ClO_9Na$: 747.2912].



41

To a flame dried flask containing PMB protected 3-iodopropanol (3.52 g, 11.5 mmol) was added anhydrous acetonitrile (115 mL) followed by PPh_3 (30.2 g., 115 mmol) and *i*-Pr_2NEt (6.0 mL, 35 mmol) and the reaction mixture was then heated to 83°C. After 18 h, the mixture was cooled to room temperature, concentrated *in vacuo*, and purified by column chromatography using methanol-methylene chloride (1:99 to 5:95) as an elutant to afford Wittig salt **41** (6.0 g, 92%). IR (neat) 3423 (br w), 3052 (w), 3006 (w), 2932 (w), 2863 (m), 1513 (s), 1437 (s), 1247 (s), 1113 (s), 722 (s), 689 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.70 (m, 8H), 7.67–7.60 (m, 7H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.38 (s, 2H), 3.75–3.66 (m, 7H), 1.96–1.88 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 134.9 (d, *J* = 2.8 Hz), 133.4 (d, *J* = 9.9 Hz), 130.3 (d, *J* = 12.7 Hz), 129.9, 129.3, 117.8 (d, *J* = 86.3 Hz), 113.6, 72.7, 68.4 (d, *J* = 16.1 Hz), 55.1, 23.1, 19.8 (d, *J* = 52.6 Hz); high resolution mass spectrum (ESI^+) *m/z* 441.1967 [$(M–I)^+$; calcd for $C_{29}H_{30}O_2P$: 441.1983].



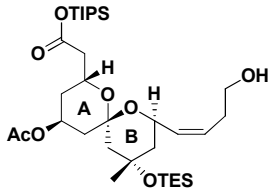
(–)-**42** R = Ac
(–)-**42a** R = H

To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**41** (816.7 mg, 1.44 mmol) which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (29 mL), cooled to –78 °C. MeLi LiBr complex (1.22 M in ether, 1.2 mL, 1.44 mmol) was added dropwise, and the resulting orange solution was allowed to stir for 30 min. Aldehyde (+)-**40** (376 mg, 0.79 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (10 mL) and added dropwise, via cannula, to the ylide solution. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to 10 C over 90 min. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl and saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (1:10 to 1:4) as an elutant afforded Wittig product (–)-**42** (344 mg, 66%) and C(5) deacetylated (–)-**42a** (74 mg, 15%).

Wittig Product (–)-**42**: $[\alpha]_D^{20}$ –115.0 (*c* 0.26, C_6H_6); IR (neat) 2953 (s), 2875 (m), 1734 (s), 1514 (w), 1367 (w), 1248 (m), 1150 (m), 1098 (w), 1020 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.74–5.66 (m, 2H), 5.19 (ddd, *J* = 11.1, 7.3, 1.9 Hz, 1H), 5.00–4.97 (m, 1H), 4.75–4.69 (m, 1H), 4.42 (s, 2H), 3.58 (dt, *J* = 9.0, 6.5 Hz, 1H), 3.53 (dt, *J* = 9.0, 6.7 Hz, 1H), 3.31 (s, 3H), 2.80 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.78–2.66 (m, 2H), 2.37 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.12 (ddd, *J* = 14.8, 2.2, 2.2 Hz, 1H), 1.89–1.83 (m, 4H), 1.68–1.63 (m, 1H), 1.62 (ddd, *J* = 13.2,

1.8, 1.8 Hz, 1H), 1.37 (s, 9H), 1.35–1.22 (m, 4H), 1.05 (t, *J* = 7.8 Hz, 9H), 1.02 (s, 3H), 0.70–0.63 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.6, 170.4, 160.0, 133.3, 131.8, 129.6, 128.7, 114.4, 97.7, 80.3, 73.0, 70.9, 70.5, 67.8, 63.0, 62.3, 55.1, 47.7, 45.9, 42.4, 38.8, 34.8, 32.5, 29.4, 28.5, 21.5, 8.0, 7.7; high resolution mass spectrum (ESI$^+$) *m*/*z* 685.3715 [(M+Na)$^+$; calcd for $C_{36}H_{58}O_9SiNa$: 685.3748].

(–)-**42a**: $[\alpha]_D^{20}$ –115.4 (*c* 2.16, C_6H_6); IR (neat) 3521 (br w), 2953 (s), 2875 (s), 1733 (s), 1514 (m), 1367 (m), 1248 (s), 1148 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.61 (dt, *J* = 10.8, 7.4 Hz, 1H), 5.53–5.47 (m, 1H), 5.22–5.15 (m, 1H), 4.66 (dddd, *J* = 12.4, 7.3, 5.0, 2.2 Hz, 1H), 4.40 (s, 2H), 4.24 (d, *J* = 10.4 Hz, 1H), 4.06–4.00 (m, 1H), 3.52 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.46 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.34 (s, 3H), 2.79 (dd, *J* = 15.4, 5.0 Hz, 1H), 2.74–2.67 (m, 1H), 2.66–2.58 (m, 1H), 2.40 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.99–1.93 (m, 1H), 1.72 (ddd, *J* = 14.1, 2.2, 2.2, 1H), 1.68 (dd, *J* = 14.3, 2.0 Hz, 1H), 1.54 (ddd, *J* = 13.4, 2.0, 2.0 Hz, 1H), 1.40–1.32 (m, 10H), 1.23 (d, *J* = 11.2 Hz, 1H), 1.20 (d, *J* = 11.2 Hz, 1H), 1.09 (d, *J* = 14.5 Hz, 1H), 1.03 (t, *J* = 7.8 Hz, 9H), 1.00 (s, 3H), 0.65–0.59 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.4, 160.0, 131.9, 131.8, 130.2, 129.7, 114.4, 99.7, 80.4, 73.1, 70.5, 70.3, 65.4, 63.5, 62.3, 55.1, 47.5, 45.8, 42.7, 41.8, 38.4, 32.4, 29.4, 28.5, 7.9, 7.6; high resolution mass spectrum (ESI$^+$) *m*/*z* 643.3648 [(M+Na)$^+$; calcd for $C_{34}H_{56}O_8SiNa$: 643.3642].



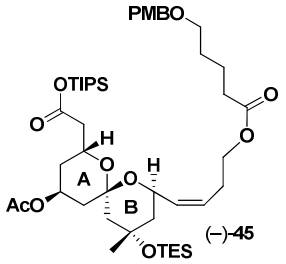
(–)-**43**

Step a. To a flask containing *t*-butyl ester (–)-**42** (45 mg, 0.068 mmol) in CH_2Cl_2 (1.1 mL) at room temperature was added 2,6-lutidine (0.12 mL, 1.0 mmol) followed by TMSOTf (59 μL, 0.31 mmol). After stirring for 1 h, the reaction mixture was diluted with ether and quenched with 1M $KHSO_4$. The organic layer was washed with water then brine. dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Step b. The resulting crude mixture was dissolved in MeOH (6.8 mL) and THF (1.7 mL) and treated with KF (119 mg, 2.04 mmol). After stirring 30 min at room temperature, the reaction mixture was quenched by the addition of brine. The resulting salts were dissolved in water and the aqueous layer was extracted with ethyl acetate (3X) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the desired hydroxy acid which was used without further purification.

Step c. To a flask containing the hydroxy acid in CH_2Cl_2 (0.68 mL) at 0 °C was added Et_3N (94 μL, 0.67 mmol) followed by TIPSCl (70μL, 0.33 mmol). The resulting mixture was allowed to stir for an additional 1h 0 °C, before it was diluted with ether and quenched by the addition of saturated $NaHCO_3$. The aqueous phase was extracted with ether (3X), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (20:80) as an elutant afforded TIPS-ester (–)-**43** (42 mg, 96% over 3 steps). $[\alpha]_D^{20}$ –95.1 (*c* 1.03, C_6H_6); IR (neat) 3502 (br w), 2950 (s), 2871 (s), 1736 (s), 1369 (w), 1247 (s), 1184 (s), 1065 (m), 1019 (s), 728 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.60 (dd, *J* = 10.4, 9.3 Hz, 1H), 5.48 (dt, *J* = 10.0, 6.2 Hz, 1H), 5.10–5.04 (m, 1H), 5.00–4.96 (m, 1H), 4.73 (dddd, *J* = 9.5, 9.5, 3.8, 1.9 Hz, 1H), 3.72–3.65 (m, 2H), 3.01 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.73–2.64 (m, 1H), 2.53

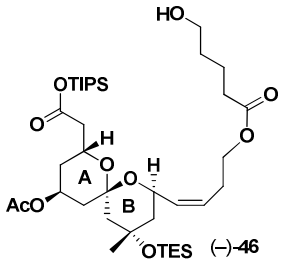
(dd, *J* = 16.1, 9.5, 1H), 2.41–2.33 (m, 1H), 2.24–2.18 (m, 1H), 2.12 (ddd, *J* = 14.8, 1.9, 1.9 Hz, 1H), 2.00–1.95 (m, 1H), 1.89 (s, 3H), 1.64 (dd, *J* = 14.2, 2.0 Hz, 1H), 1.57 (ddd, *J* = 13.3, 1.8, 1.8 Hz, 1H), 1.30–1.19 (m, 7H), 1.11–1.01 (m, 30H), 0.70–0.57 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.1, 170.7, 133.5, 129.3, 97.8, 70.8, 67.6, 62.7, 62.4, 62.4, 47.6, 45.7, 43.1, 38.7, 35.1, 32.9, 32.4, 21.5, 18.3, 12.6, 7.9, 7.7; high resolution mass spectrum (ESI$^+$) *m/z* 665.3892 [(M+Na)$^+$; calcd for $C_{33}H_{62}O_8Si_2Na$: 665.3881].



(–)-45

To alcohol (–)-**43** (238 mg, 0.37 mmol) in CH_2Cl_2 (3 ml) was added acid **44** (108 mg, 0.48 mmol) and DMAP (4.5 mg, 0.037 mmol). The resulting mixture was cooled to 0 °C and a solution of DCC (1M in CH_2Cl_2, 0.56 mL, 0.56 mmol) was added. The reaction mixture was then allowed to warm to room temperature and stir for 18 h. Column chromatography directly on the reaction mixture using ethyl acetate-hexanes (1:9 to 1:3) as an elutant afforded PMB ether (–)-**45** (280 mg, 88%). $[\alpha]_D^{20}$ –0.858 (*c* 0.99, C_6H_6); IR (neat) 2949 (s), 1735 (s), 1514 (w), 1248 (s), 1182 (m), 1019 (m), 734 (w) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.65 (dd, *J* = 10.8, 8.6 Hz, 1H), 5.46 (dt, *J* = 10.9, 7.4 Hz, 1H), 5.12–5.05 (m, 1H), 4.99–4.96 (m, 1H), 4.67 (dddd, *J* = 11.4, 9.3, 4.1, 2.0 Hz, 1H), 4.31 (s, 2H), 4.22 (dt, *J* = 10.7, 6.6 Hz, 1H), 4.16 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.33 (s, 3H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.99 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.64–2.57 (m, 2H), 2.53 (dd, *J* = 16.2, 9.4 Hz,

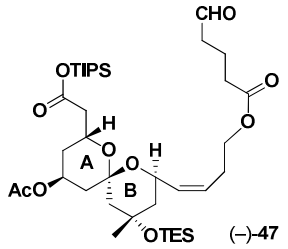
1H), 2.23 (t, *J* = 7.8 Hz, 2H), 2.15–2.09 (m, 1H), 2.03–1.96 (m, 1H), 1.87 (s, 3H), 1.80–1.72 (m, 2H), 1.67–1.52 (m, 4H), 1.38–1.20 (m, 7H), 1.12 (d, *J* = 7.4 Hz, 18 H), 1.07 (t, *J* = 7.9 Hz, 9H), 1.02 (s, 3H), 0.73–0.59 (m, 6H) ; ^{13}C NMR (125 MHz, C_6D_6) δ 173.2, 170.9, 170.5, 160.0, 134.3, 131.7, 129.6, 126.8, 114.4, 97.7, 73.1, 70.8, 70.0, 67.7, 64.1, 63.0, 62.3, 55.1, 47.6, 45.8, 43.0, 38.7, 35.0, 34.4, 32.4, 30.0, 28.3, 22.6, 21.5, 18.4, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI$^+$) *m/z* 885.4999 [(M+Na)$^+$; calcd for $C_{46}H_{78}O_{11}Si_2Na$: 885.4980].



(–)-46

To a flask containing PMB ether (–)-**45** (280 mg, 0.32 mmol) was added CH_2Cl_2 (5.8 mL) and a solution of pH 7 phosphate buffer solution (0.58 mL). The solution was cooled to 0 °C and DDQ (147 mg, 0.65 mmol) was added in a single portion. After 90 min, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with ethyl acetate (3X). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:4 to 1:1) as an elutant afforded the alcohol (–)-**46** (213 mg, 89%). $[\alpha]_D^{20}$ –0.664 (*c* 0.69, C_6H_6); IR (neat) 3429 (br w), 2949 (s), 2871 (m), 1736 (s), 1379 (w), 1248 (m), 1183 (m), 1018 (m), 884 (w), 737 (w) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.68–5.62 (m, 1H), 5.46 (dt, *J* = 11.0, 7.4 Hz, 1H), 5.11–5.05 (m, 1H), 5.00–4.96 (m, 1H), 4.70–4.63 (m, 1H), 4.22 (dt, *J* = 10.6, 6.7 Hz, 1H), 4.16 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.31 (t, *J* = 6.3 Hz, 2H), 2.99 (dd, *J* = 16.1, 4.2 Hz, 1H), 2.66–2.50 (m, 3H), 2.19 (t, *J* =

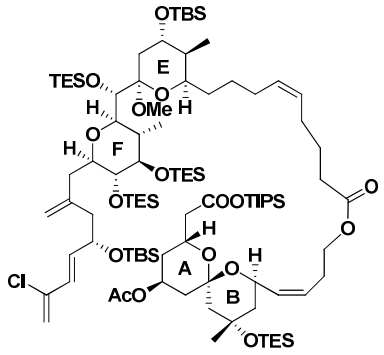
7.4 Hz, 2H), 2.15–2.10 (m, 1H), 2.03–1.97 (m, 1H), 1.88 (s, 3H), 1.67–1.60 (m, 3H), 1.57–1.53 (m, 1H), 1.39–1.20 (m, 9H), 1.12 (d, J = 7.4 Hz, 18H), 1.08 (t, J = 8.0 Hz, 9H), 1.05–1.01 (m, 4H), 0.73–0.60 (m, 6H) ; ^{13}C NMR (125 MHz, C_6D_6) δ 173.4, 171.0, 170.6, 134.3, 126.8, 97.7, 70.8, 67.7, 64.2, 63.0, 62.4, 62.3, 47.6, 45.8, 43.0, 38.7, 35.0, 34.3, 32.8, 32.4, 28.3, 21.9, 21.5, 18.4, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI$^+$) *m/z* 765.4439 [(M+Na)$^+$; calcd for $C_{38}H_{70}O_{10}Si_2Na$: 765.4405].



(–)-47

To a flask containing alcohol (–)-**46** (88 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added anhydrous DMSO (43 μL, 0.60 mmol) and *i*-Pr_2NEt (62 μL, 0.36 mmol). The flask was cooled to –5 °C and SO_3·Py (57 mg, 0.36 mmol) was added in a single portion. After 30 min, the reaction mixture was diluted with ether and then quenched with water. The organic phase was washed with 1M $KHSO_4$, water and brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*, to afford aldehyde (–)-**47** (87 mg, 99%) was azeotroped with benzene (3X) and used in the next step without further purification. $[\alpha]_D^{20}$ –105.67 (*c* 0.6, C_6H_6); IR (neat) 2950 (m), 2871 (m), 1735 (s), 1247 (m), 1183 (m), 1019 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.23 (t, J = 1.2 Hz, 1H), 5.65 (dddd, J = 11.1, 8.4, 1.5, 1.5 Hz, 1H), 5.41 (dddd, J = 11.0, 7.4, 7.4, 0.9 Hz, 1H), 5.09–5.04 (m, 1H), 4.99–4.95 (m, 1H), 4.66 (dddd, J = 11.3, 9.2, 4.2, 2.0 Hz, 1H), 4.18 (dt, J = 10.7, 6.7 Hz, 1H), 4.13 (dt, J = 10.7, 7.0 Hz, 1H), 2.98 (dd, J = 16.1, 4.3 Hz, 1H), 2.64–2.50 (m, 3H), 2.12 (ddd, J = 15.0, 2.2, 2.2 Hz, 1H), 2.07 (t, J = 7.2 Hz, 2H),

2.01–1.96 (m, 1H), 1.89–1.84 (m, 5H), 1.68 (p, J = 7.0 Hz, 2H), 1.64 (dd, J = 14.2, 2.0 Hz, 1H), 1.54 (ddd, J = 13.1, 1.9, 1.9 Hz, 1H), 1.34–1.21 (m, 6H), 1.12 (d, J = 7.9 Hz, 18H), 1.07 (t, J = 7.9 Hz, 9H), 1.04–1.01 (m, 4H), 0.72–0.59 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.1, 172.7, 171.0, 170.5, 134.4, 126.7, 97.7, 70.8, 67.6, 64.3, 63.0, 62.3, 47.6, 45.8, 43.2, 43.0, 38.7, 35.0, 33.5, 32.4, 28.3, 21.5, 18.4, 17.9, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI$^+$) m/z 763.4274 [(M+Na)$^+$; calcd for $C_{38}H_{68}O_{10}Si_2Na$: 763.4249].

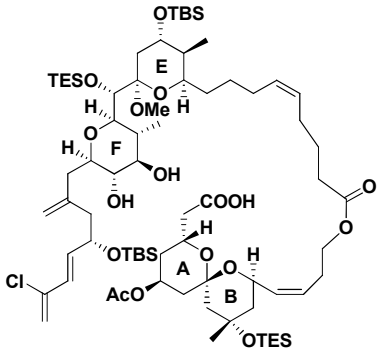


(–)-48

To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**31** (94%, 170 mg, 0.107 mmol), which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (1.1 mL), cooled to –78 °C. MeLi·LiBr complex (0.8 M in ether, 0.14 mL, 0.11 mmol) was added dropwise, and the resulting orange solution was allowed to stir for 30 min. Aldehyde (–)-**47** (102 mg, 0.137 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (1.1 mL) and added dropwise, via cannula, to the ylide solution. The flask which contained the aldehyde was then rinsed with THF (0.55 mL) and the solution

was transferred to the reaction flask dropwise via cannula. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to room temperature over 2 h. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl-saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (1:9 to 2:3) as an elutant afforded *Z* olefin (–)-**48** (124 mg, 64%. $[\alpha]_D^{20}$ –15.51 (*c* 0.56, C_6H_6); IR (neat) 2953 (s), 2875 (s), 1738 (m), 1462 (w), 1368 (w), 1248 (m), 1113 (m), 1006 (m), 738 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.50 (dd, *J* = 14.9, 5.0 Hz, 1H), 6.44 (d, *J* = 15.0 Hz, 1H), 5.67–5.61 (m, 1H), 5.53–5.36 (m, 3H), 5.17 (s, 1H), 5.13 (s, 1H), 5.12 (s, 1H), 5.11–5.04 (m, 2H), 4.98–4.95 (m, 1H), 4.69–4.63 (m, 1H), 4.53–4.48 (m, 1H), 4.32–4.26 (m, 1H), 4.23 (ddd, *J* = 10.7, 6.7, 6.7 Hz, 1H), 4.17 (ddd, *J* = 10.7, 7.1, 7.1 Hz, 1H), 3.96–3.93 (m, 1H), 3.89 (s, 1H), 3.60–3.47 (m, 4H), 3.17 (s, 3H), 2.98 (dd, *J* = 16.0, 4.2 Hz, 1H), 2.76–2.66 (m, 2H), 2.63–2.48 (m, 4H), 2.39–2.30 (m, 2H), 2.29–2.21 (m, 2H), 2.14–2.05 (m, 5H), 2.03–1.92 (m, 2H), 1.87 (s, 3H), 1.79–1.68 (m, 5H), 1.64 (dd, *J* = 14.2, 1.8 Hz, 1H), 1.62–1.52 (m, 2H), 1.48–1.21 (m, 14H), 1.20–0.99 (m, 76H), 0.86–0.76 (m, 18H), 0.71–0.61 (m, 6H), 0.24 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.1, 170.9, 170.5, 144.7, 139.2, 139.2, 134.3, 131.3, 129.6, 126.8, 126.8, 115.9, 115.4, 101.9, 97.7, 82.1,81.1, 78.1, 77.8, 72.1, 71.9, 71.6, 70.8, 67.8, 67.6, 64.2, 63.0, 62.3, 47.6, 47.4, 45.9, 43.0, 40.8, 40.7, 39.4, 38.7, 35.0, 34.2, 33.3, 32.4, 30.8, 30.6, 30.6, 28.4, 28.2, 27.4, 27.2, 26.5, 25.7, 21.5, 18.9, 18.7, 18.4, 16.5, 12.6, 11.1,

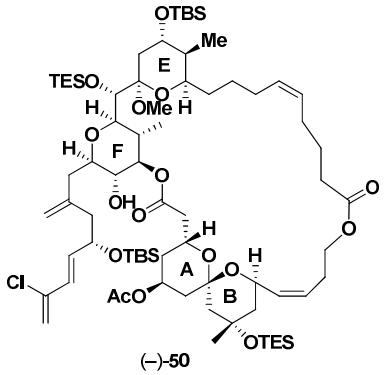
8.0, 7.9, 7.8, 7.8, 7.7, 6.5, 6.5, –3.7, –3.9, –4.1, –4.2; high resolution mass spectrum (ESI$^+$) *m*/*z* 1848.1361 [(M+Na)$^+$; calcd for $C_{95}H_{181}ClO_{17}Si_7Na$: 1848.1270].



(–)-**49**

To a solution of Wittig product (–)-**48** (70 mg, 0.038 mmol) in THF (7.6 mL) at 0 °C was added TBAF (1M in THF, 0.12 mL, 0.115 mmol) over 1 hour via syringe pump. After stirring for an additional 2 h at 0 °C, the reaction mixture was diluted with ether and quenched with 1M $KHSO_4$, and washed with brine. The combined aqueous phases were then back extracted with ether (2X). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:4-1:1) with 0.5% AcOH as an elutant afforded *seco*-acid (–)-**49** (30.5 mg, 56%). Note: toluene was added the collection before concentrating to avoid the *seco*-acid being exposed to neat AcOH. $[\alpha]_D^{20}$ –18.06 (*c* 1.5, C_6H_6); IR (neat) 3441 (br s), 2952 (s), 1737 (s), 1461 (w), 1383 (w), 1250 (m), 1111 (s), 1019 (m), 836 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.45 (dd, *J* = 14.8, 5.0 Hz, 1H), 6.39 (d, *J* = 14.9 Hz, 1H), 5.67 (dd, *J* = 10.8, 8.4 Hz, 1H), 5.53–5.36 (m, 3H), 5.18 (s, 1H), 5.18–5.11 (m, 2H), 5.08 (s, 1H), 5.06 (s, 1H), 4.94–4.90 (m, 1H), 4.68–4.62 (m, 1H), 4.49–4.44 (m, 1H), 4.36–4.26 (m, 2H), 4.10 (ddd, *J* = 10.7, 7.3, 7.3 Hz, 1H), 3.97–3.94 (m, 1H), 3.90 (s, 1H), 3.39–3.31 (m, 2H), 3.23 (dd, *J* = 8.9, 8.8 Hz, 1H), 3.17 (s, 3H), 3.04 (dd, *J*

= 9.8, 9.0 Hz, 1H), 2.79–2.70 (m, 2H), 2.62 (dd, *J* = 16.4, 7.3 Hz, 1H), 2.59–2.45 (m, 3H), 2.38–2.20 (m, 5H), 2.15–2.03 (m, 6H), 1.88 (s, 3H), 1.87–1.53 (m, 10H), 1.47–1.20 (m, 7H), 1.20–0.97 (m, 46H), 0.86–0.76 (m, 6H), 0.75–0.64 (m, 6H), 0.26 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.9, 173.7, 170.8, 144.2, 139.3, 139.2, 134.5, 131.3, 129.5, 126.7, 126.4, 116.1, 115.5, 102.1, 97.7, 79.7, 79.2, 79.1, 76.1, 72.6, 71.6, 71.6, 70.8, 67.7, 67.5, 64.5, 63.1, 62.1, 47.6, 47.4, 46.8, 45.8, 40.8, 39.9, 39.4, 39.4, 38.7, 34.7, 34.3, 33.2, 32.5, 30.8, 28.4, 28.1, 27.4, 27.1, 26.5 (2), 25.7, 21.5, 18.9, 18.8, 14.1, 11.0, 8.0, 7.9, 7.6, 6.5, –3.7, –3.9, –4.1, –4.3; high resolution mass spectrum (ESI$^+$) *m*/*z* 1463.8246 [(M+Na)$^+$; calcd for $C_{74}H_{133}ClO_{17}Si_4Na$: 1463.8206].

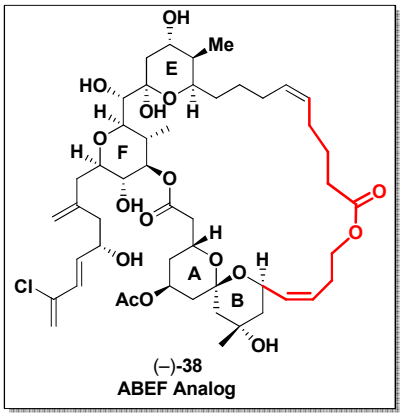


(–)-50

To a flask containing *seco*-acid (–)-**49** (15 mg, 0.010 mmol) dissolved in toluene (1 mL) was added a solution of *i*-Pr_2NEt (0.4 M in toluene, 0.39 mL, 0.156 mmol) followed by a solution of 2,4,6-TBCCl (0.4 M in toluene, 0.23 mL, 0.090 mmol). The reaction mixture was allowed to stir at room temperature for 5.5 h before being further diluted with toluene (2.9 mL) and then added dropwise, via syringe pump, over 24 h to a second flask containing DMAP (24 mg, 0.2 mmol) and toluene (14.3 mL) heated to 90 °C. After the addition, the flask containing seco-acid residue was rinsed with toluene (1 mL) and this solution was transferred over 12 hours via syringe pump, to the

reaction mixture, followed by rinsing a third time of the first flask with toluene (0.67 mL) and adding over 2 h. After the third rinse, the reaction mixture was allowed to cool to room temperature, before being diluted with ether and then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the organic layer was rinsed with saturated NaCl and the combined aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:19-1:9-1:4) as an elutant afforded the desired lactone (–)-**50** with a minor impurity. $[\alpha]_D^{20}$ – 38.4 (*c* 1.15, C_6H_6); IR (neat) 3480 (br w), 2952 (s), 2932 (s), 2876 (m), 2856 (m), 1737 (s), 1251 (s), 1168 (m), 1147 (m), 1115 (s), 1077 (m), 1019 (m), 835 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.45 (dd, *J* = 15.0, 5.1 Hz, 1H), 6.38 (d, *J* = 15.1 Hz, 1H), 5.68–5.60 (m, 2H), 5.60–5.24 (m, 1H), 5.41–5.33 (m, 1H), 5.16 (s, 1H), 5.13–5.05 (m, 3H), 5.04 (s, 1H), 4.91–4.88 (m, 1H), 4.71(dd, *J* = 10.1, 9.1 Hz, 1H), 4.67–4.60 (m, 1H), 4.48–4.43 (m, 1H), 4.30–4.22 (m, 2H), 4.10 (ddd, *J* = 10.7, 7.7, 5.0 Hz, 1H), 3.94–3.88 (m, 2H), 3.45–3.31 (m, 3H), 3.26 (s, 3H), 2.94 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.91–2.85 (m, 1H), 2.61–2.45 (m, 4H), 2.37 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.30–2.08 (m, 6H), 2.03–1.91 (m, 6H), 1.89–1.83 (m, 2H), 1.73–1.58 (m, 5H), 1.56–1.43 (m, 3H), 1.25–1.17 (m, 2H), 1.17–0.94 (m, 50H), 0.85–0.73 (m, 6H), 0.71–0.59 (m, 6H), 0.24 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.3, 172.4, 170.5, 143.8, 139.4, 139.2, 133.8, 131.2, 129.7, 127.3, 126.7, 116.2, 115.4, 101.6, 97.8, 82.3, 80.1, 78.3, 74.1, 73.1, 72.6, 71.7, 70.8, 68.5, 67.8, 64.7, 63.0, 62.0, 48.6, 47.5, 46.9, 45.7, 42.1, 40.4, 39.4, 38.6, 38.4, 35.2, 34.3, 34.0, 32.4, 30.6, 30.4, 29.3, 28.8, 28.1, 27.6, 26.5, 26.5, 26.2, 21.6, 18.8, 18.7, 14.7, 11.2, 8.0, 7.9, 7.7, 6.5, –3.8, –3.9, –

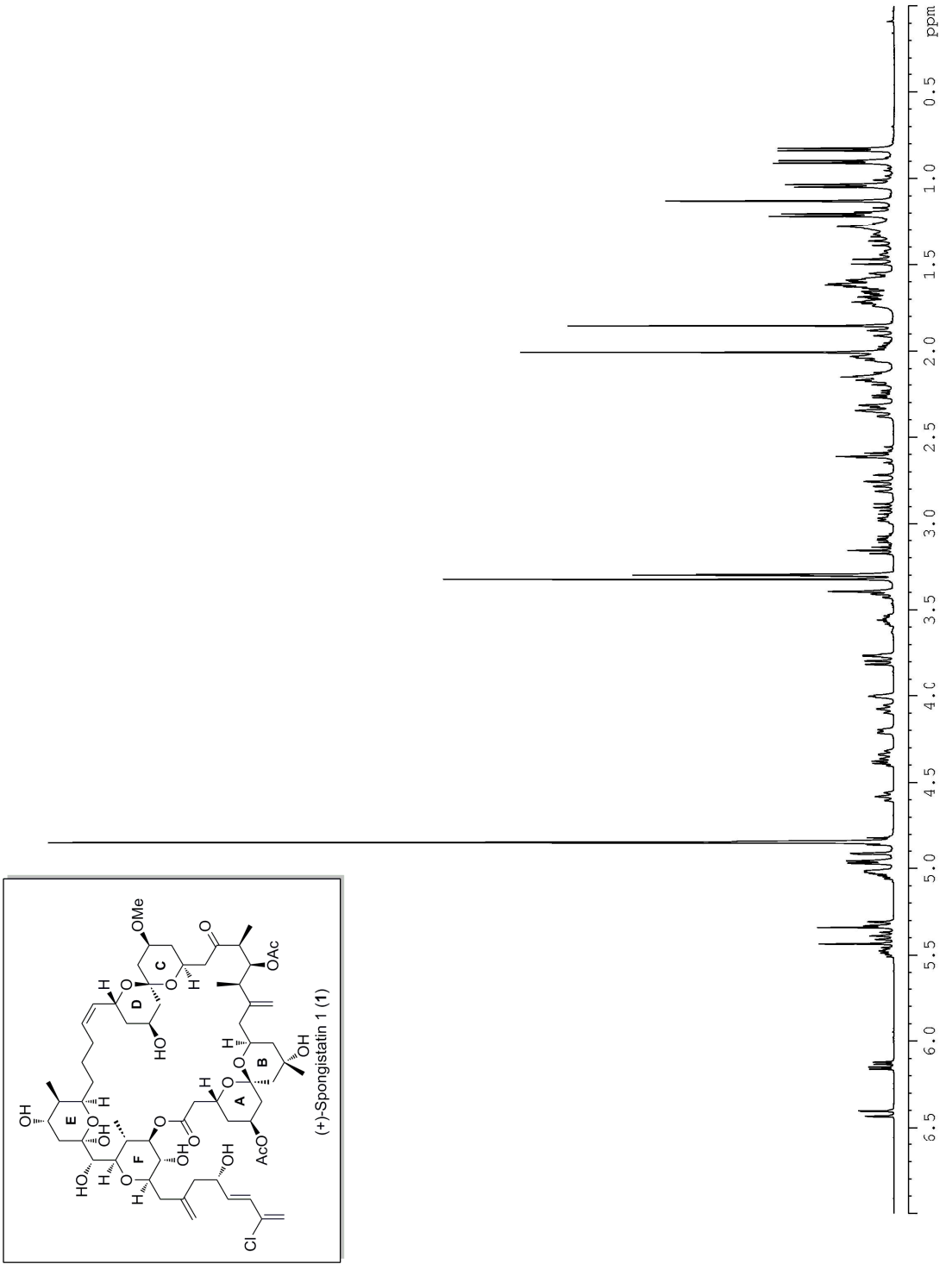
4.1, –4.3; high resolution mass spectrum (ESI$^+$) *m/z* 1445.8168 [(M+Na)$^+$; calcd for $C_{74}H_{131}ClO_{16}Si_4Na$: 1445.8101].



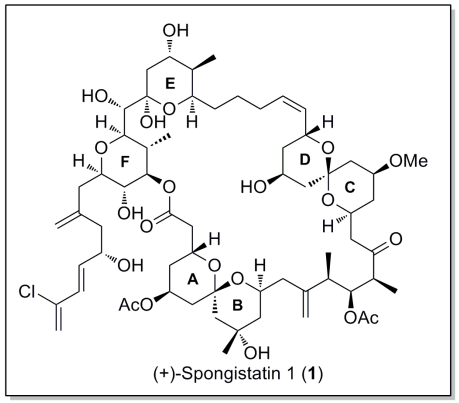
To flask macrolactone (–)-**50** (23 mg, 0.016 mmol) in acetonitrile (1.2 mL) at –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (1.2 mL) via syringe pump over 2 h. [HF solution prepared by dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL)] Following the addition, the reaction mixture was allowed to stir for an additional 14 h at –20 °C before being quenched by the dropwise addition of Et_3N (1.5 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a mixture of ethyl acetate and methylene chloride (2:1) and washed with saturated $NaHCO_3$ then brine. The aqueous layers were back extracted with ethyl acetate and methylene chloride (2:1 X2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using methanol-methylene chloride (2:98 to 3:97) as an elutant afforded the desired **ABEF** analog (–)-**38** (9.2 mg, 48% over 2 steps). $[\alpha]_D^{20}$ –20.0 (*c* 0.2, C_6H_6); IR (neat) 3419 (br s), 2939 (br s), 1735 (s), 1402 (w), 1383 (w), 1325 (w), 1252 (m), 1207 (w), 1175 (s), 1090 (m), 1064 (m), 1024 (w), 991 (w) cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 6.42 (d, *J* = 15.0 Hz, 1H), 6.16 (dd, *J* = 15.0, 5.4 Hz, 1H), 5.53–

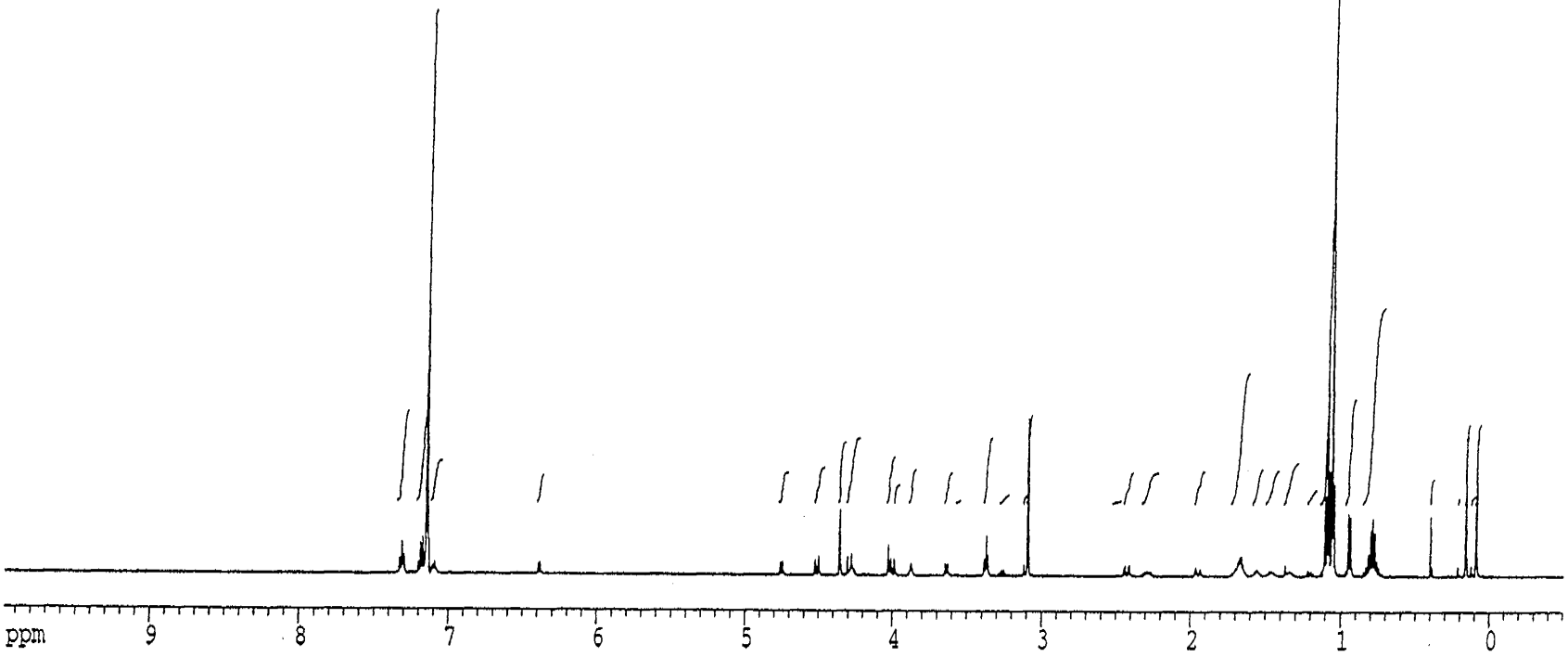
5.42 (m, 4H), 5.39–5.32 (m, 2H), 5.00–4.94 (m, 2H), 4.94–4.90 (m, 1H), 4.89 (s, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 4.80 (dd, *J* = 10.2, 9.4 Hz, 1H), 4.49–4.42 (m, 1H), 4.39 (s, 1H), 4.37–4.31 (m, 1H), 4.31–4.22 (m, 2H), 4.22–4.17 (m, 1H), 3.92–3.84 (m, 2H), 3.80 (d, *J* = 10.4 Hz, 1H), 3.70–3.64 (m, 1H), 3.43–3.37 (m, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 3.16–3.11 (m, 2H), 2.85 (d, *J* = 10.7 Hz, 1H), 2.77 (d, *J* = 14.6 Hz, 1H), 2.69–2.57 (m, 2H), 2.52 (dd, *J* = 16.2, 10.6 Hz, 1H), 2.44–2.23 (m, 6H), 2.14 (s, 3H), 2.13–1.97 (m, 5H), 1.93–1.88 (m, 1H), 1.79–1.73 (m, 1H), 1.70–1.57 (m, 7H), 1.54–1.41 (m, 4H), 1.41–1.30 (m, 4H), 1.08 (s, 3H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.41 (d, *J* = 15.3 Hz, 1H), 6.08 (dd, *J* = 15.2, 5.3 Hz, 1H), 5.56 (s, 1H), 5.49 (dd, *J* = 10.2, 8.6 Hz, 1H), 5.45–5.36 (m, 3H), 5.34–5.26 (m, 2H), 5.18–5.12 (m, 2H), 5.02 (d, *J* = 5.2 Hz, 1H), 4.88–4.84 (m, 2H), 4.81 (s, 1H), 4.73 (d, *J* = 8.3 Hz, 1H), 4.65 (dd, *J* = 10.8, 9.0 Hz, 1H), 4.41 (d, *J* = 6.9 Hz, 1H), 4.37–4.30 (m, 1H), 4.29–4.23 (m, 1H), 4.23–4.14 (m, 2H), 4.13 (s, 1H), 3.79 (ddd, *J* = 10.4, 7.9, 7.9 Hz, 1H), 3.66–3.61 (m, 2H), 3.31–3.26 (m, 1H), 3.21 (d, *J* = 8.1 Hz, 1H), 3.02 (ddd, *J* = 9.1, 9.1, 5.5, 1H), 2.74–2.64 (m, 2H), 2.59–2.51 (m, 2H), 2.42–2.34 (m, 2H), 2.31–2.24 (m, 1H), 2.23–2.17 (m, 1H), 2.15–2.04 (m, 2H), 2.04–1.81 (m, 11H), 1.74–1.69 (m, 1H), 1.64–1.28 (m, 13H) 1.03 (s, 3H), 0.74 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 174.5, 173.0, 171.4, 144.5, 139.2, 134.5, 131.6, 130.2, 129.4, 127.8, 126.9, 116.5, 115.9, 99.9, 99.4, 80.9, 80.9, 78.4, 73.4, 73.1, 71.5, 71.1, 69.3, 67.9, 67.6, 64.0, 63.8, 63.8, 46.1, 44.2 (2), 40.8, 40.6, 39.1, 37.7, 37.4, 34.6, 34.6, 33.8, 33.3, 30.3, 28.5, 28.4, 28.0, 27.3, 26.2, 21.6, 12.7, 11.0; high resolution mass spectrum (ESI$^+$) *m/z* 975.4518 [(M+Na)$^+$; calcd for $C_{49}H_{73}O_{16}NaCl$: 975.4485

B. ^{1}H and ^{13}C NMR Spectra

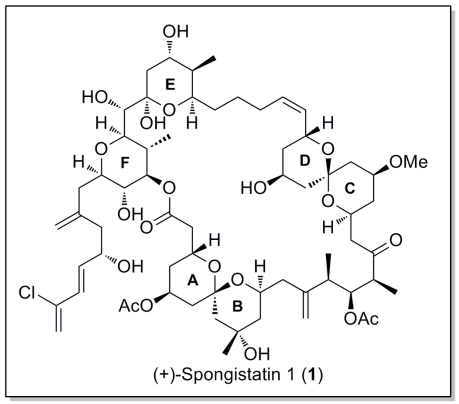


^{1}H NMR spectrum of (+)-Spongistatin 1 in methanol-d_4



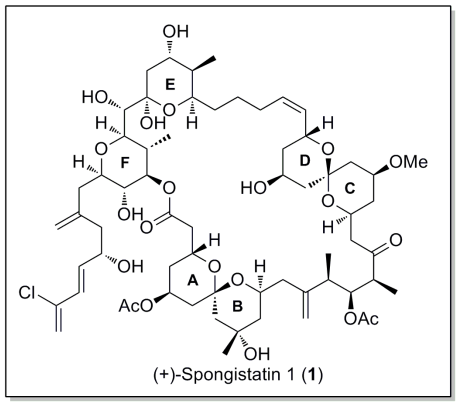


^{1}H NMR spectrum of (+)-Spongistatin 1 in benzene-d_6

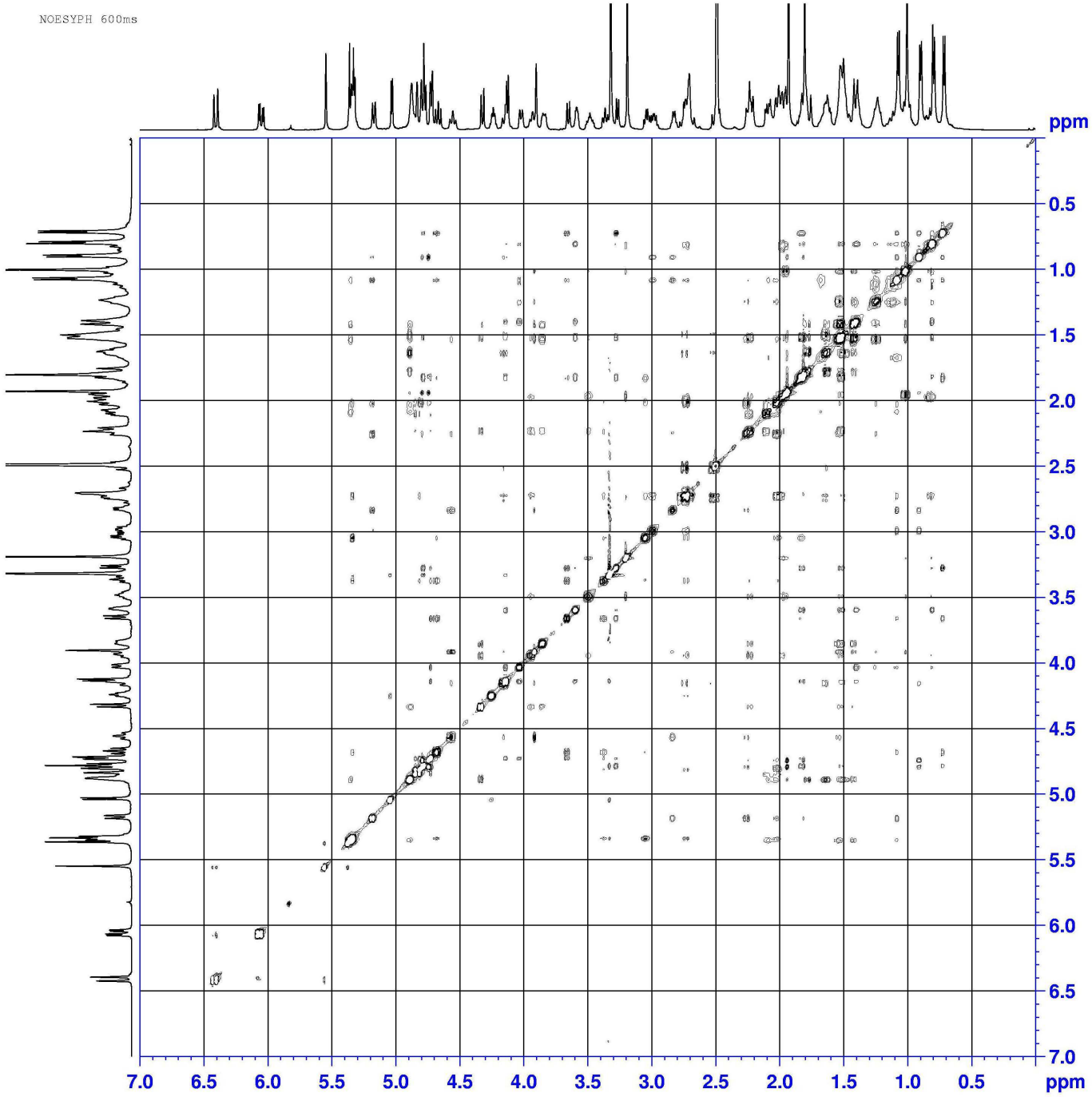


(+)-Spongistatin 1 (**1**)

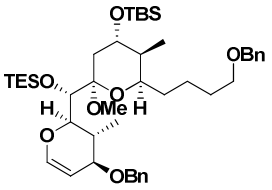
^{1}H NMR spectrum of (+)-Spongistatin 1 in acetonitrile-d_3



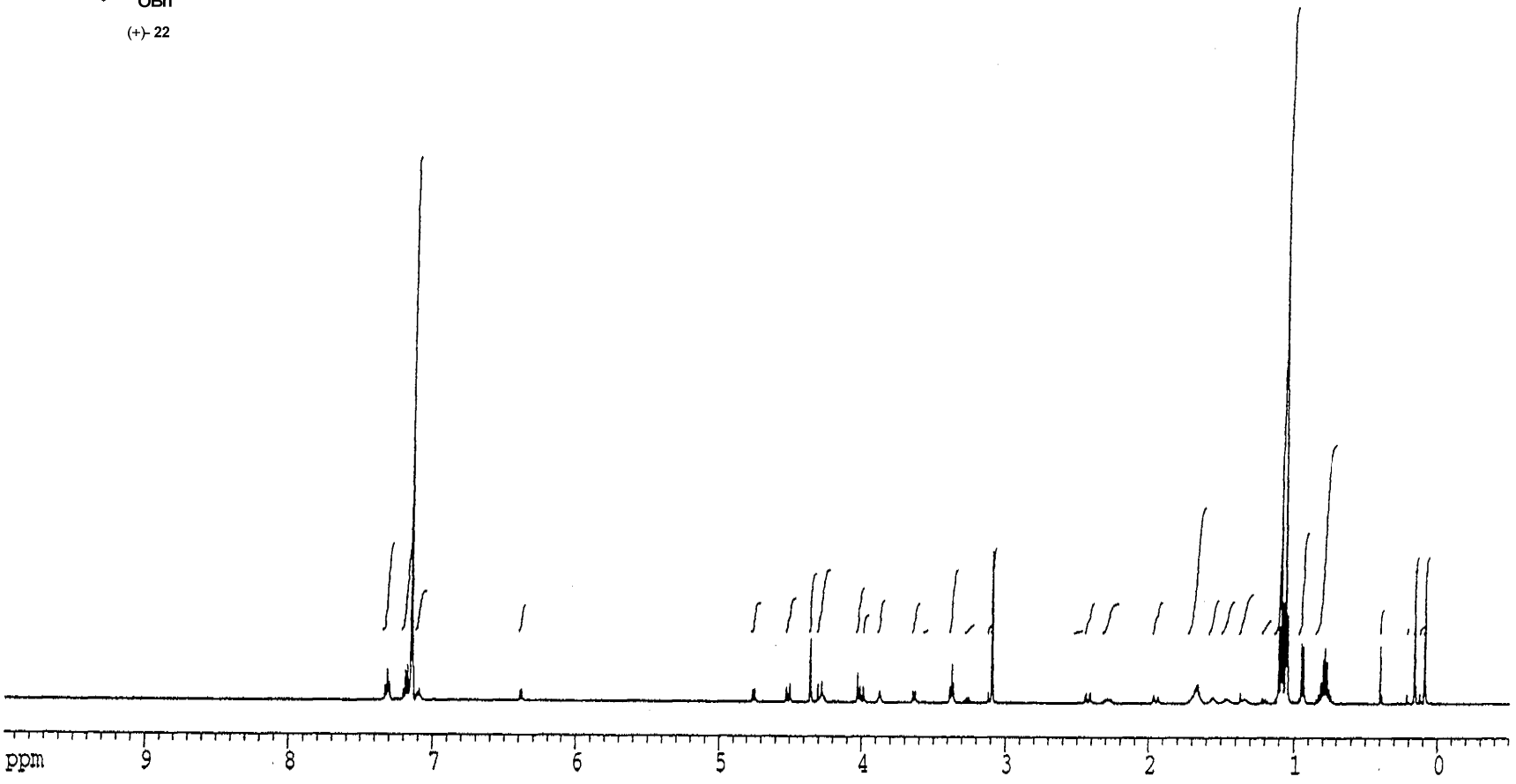
^{1}H NMR spectrum of (+)-Spongistatin 1 in DMSO-D_6

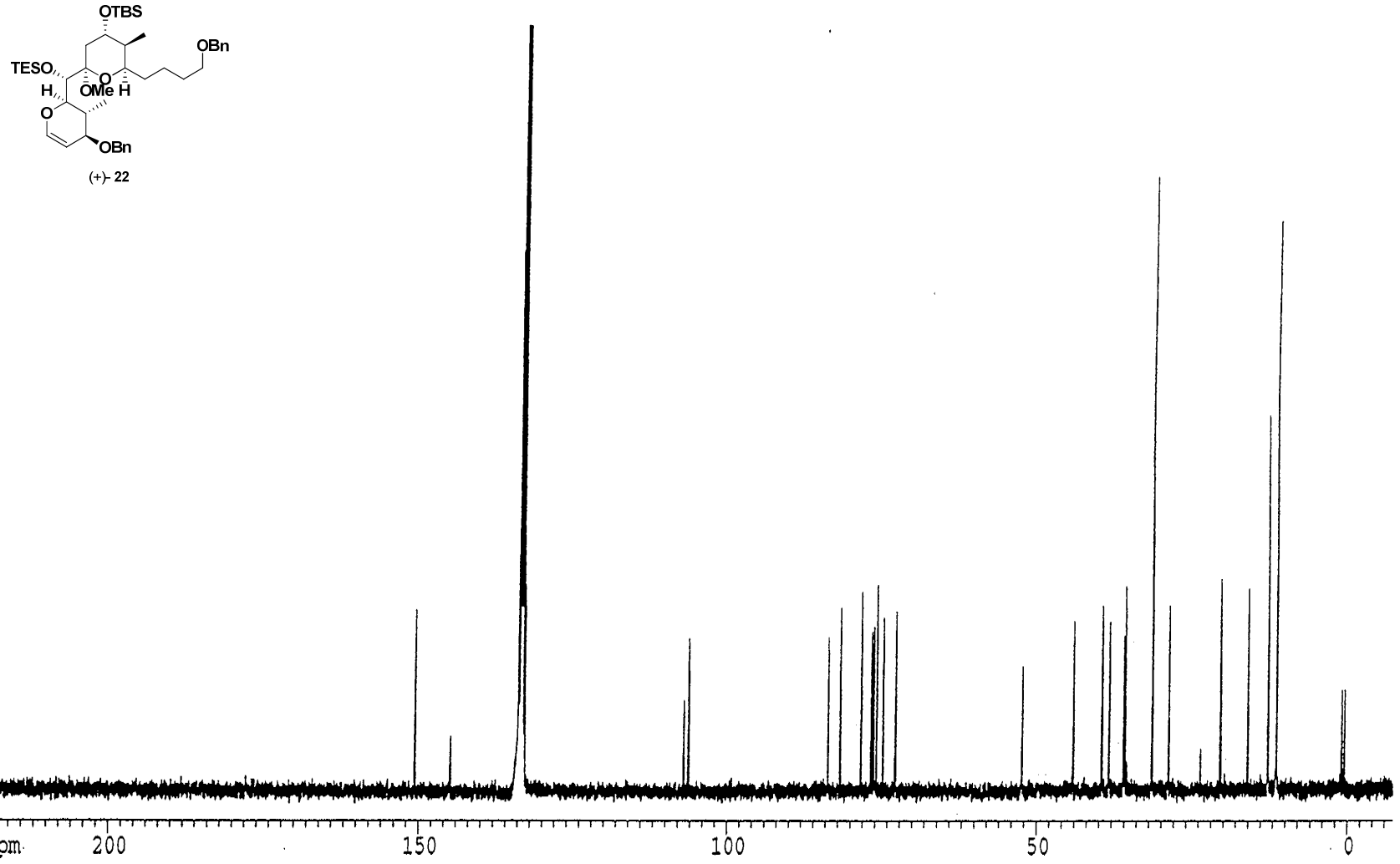


NOESY NMR spectrum of (+)-Spongistatin 1 in DMSO-D_6 (mixing time of 600 ms)



(+)- 22




OTBS
OBn
TESO
O
H
OMe H
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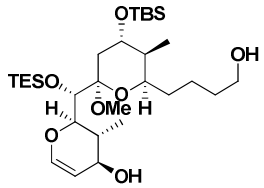
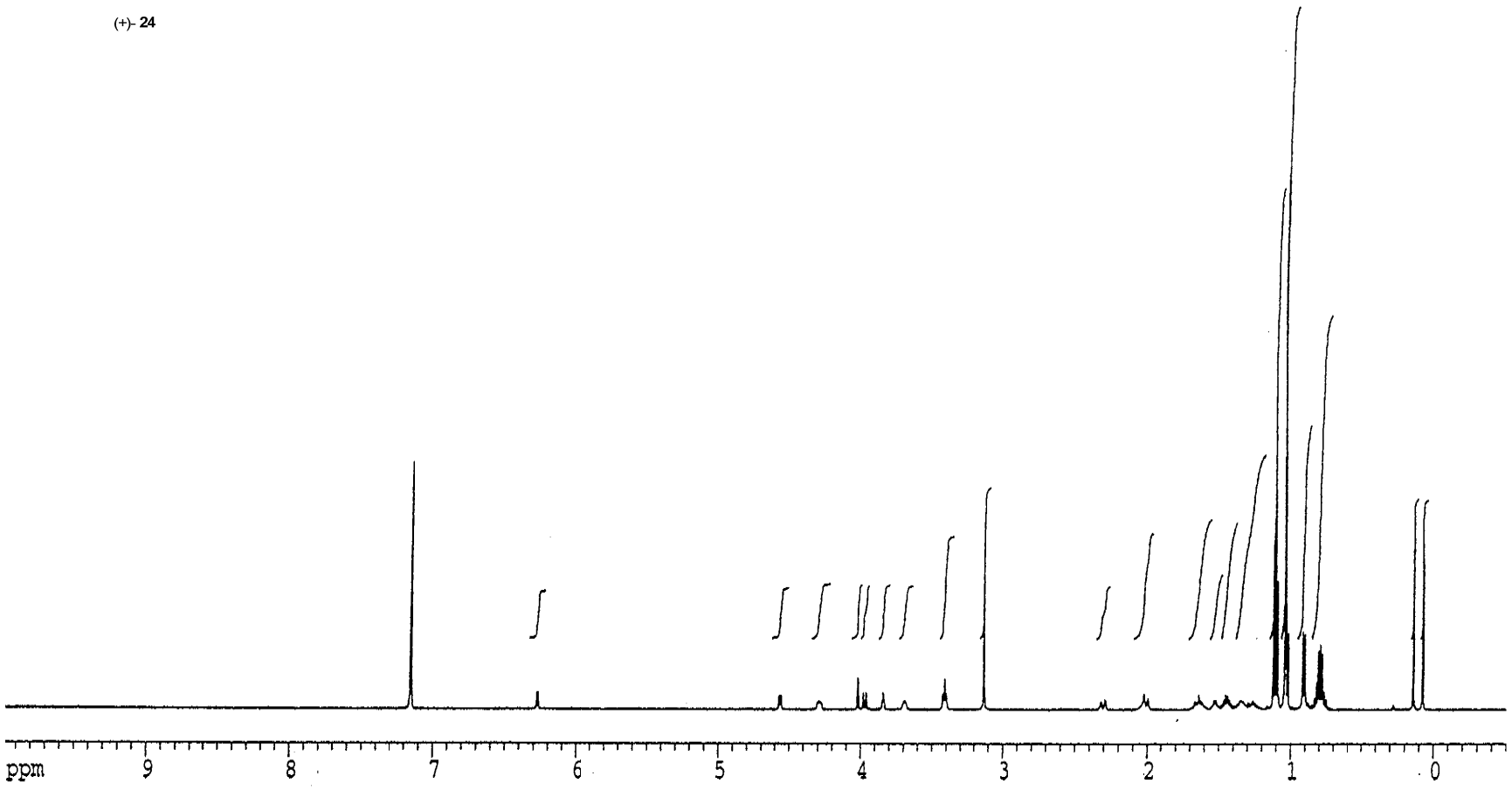
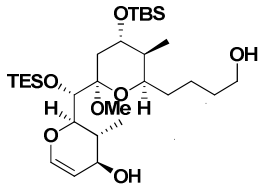
OBn
(+)- 22
ppm
200
150
100
50
0

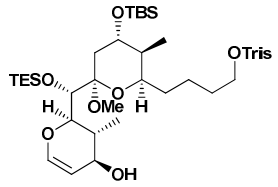


(+)- 24

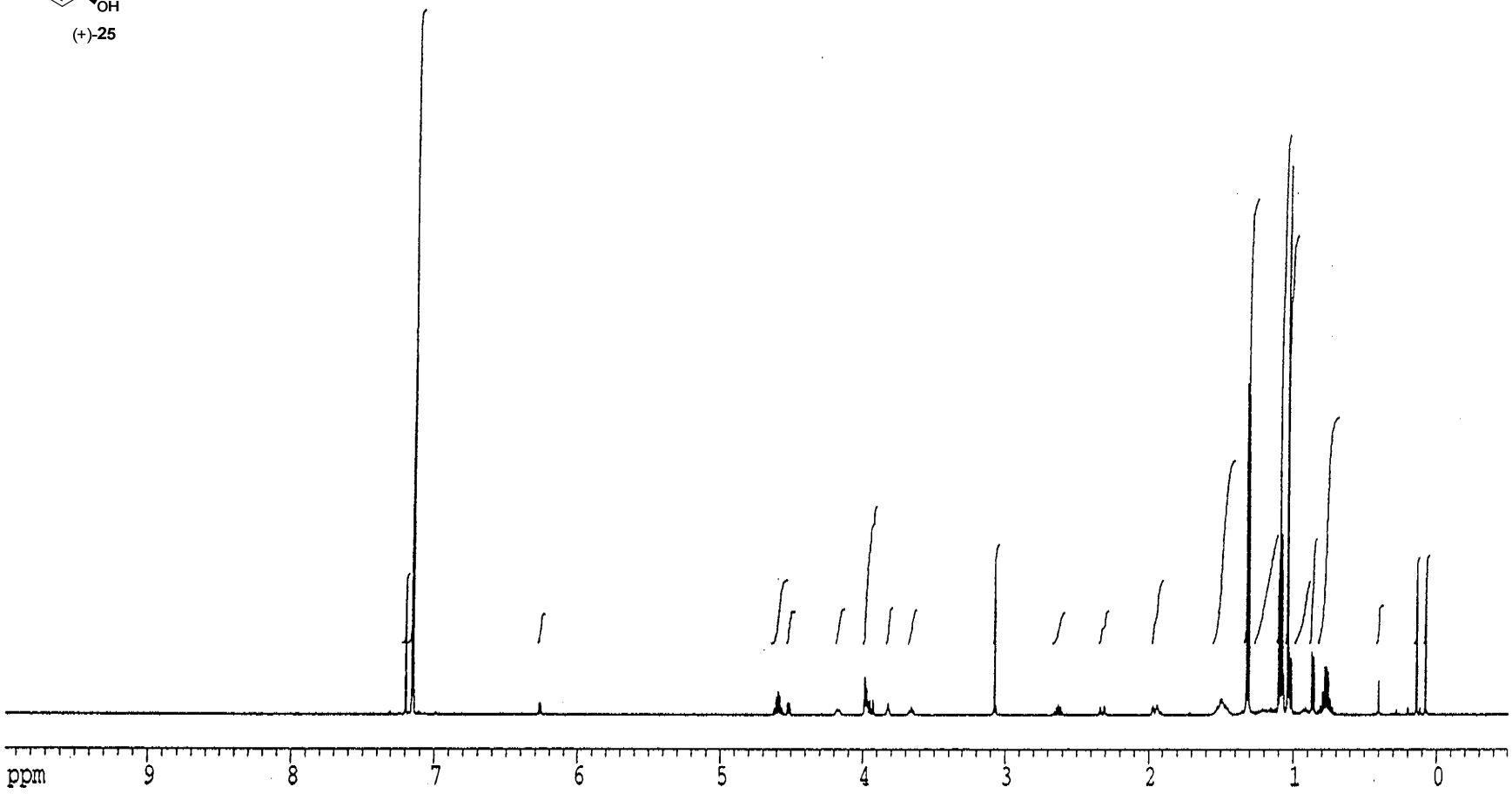


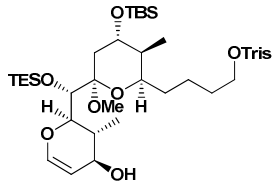


(+)- **24**

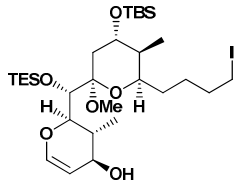


(+)-**25**

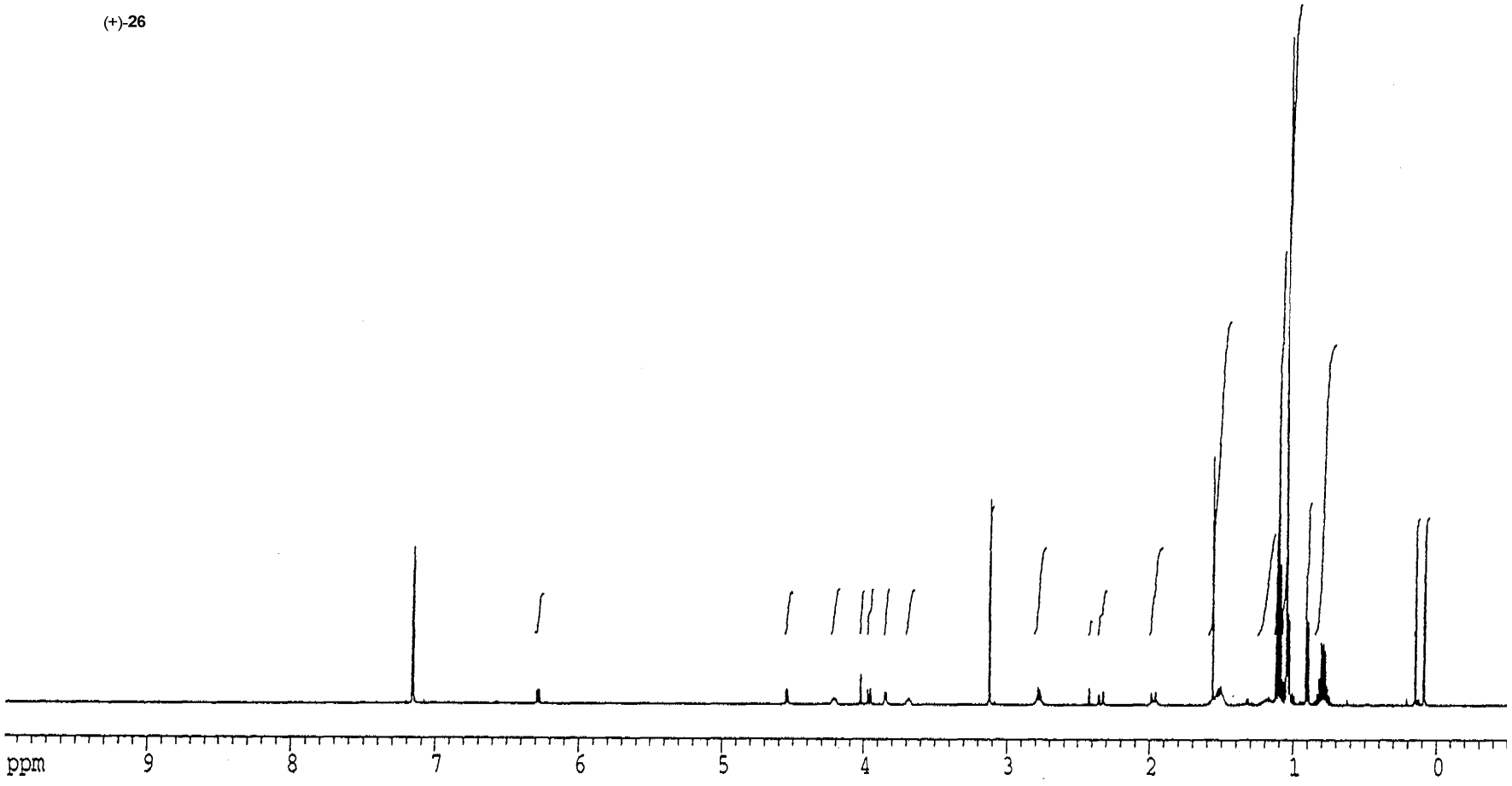


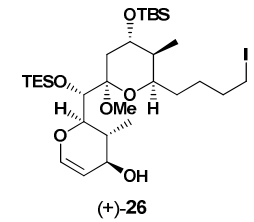


(+)-**25**

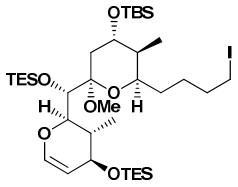


(+)-**26**

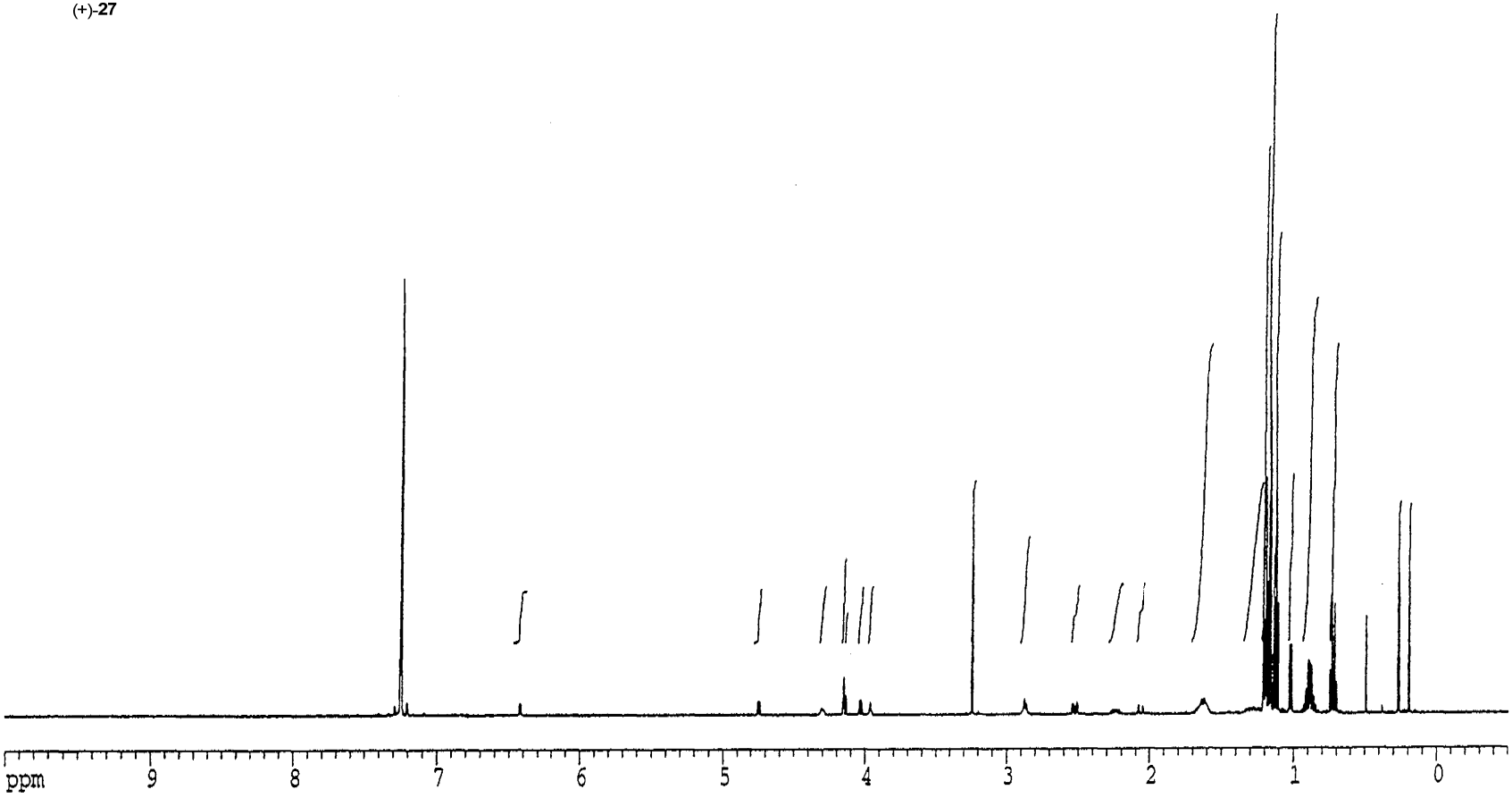


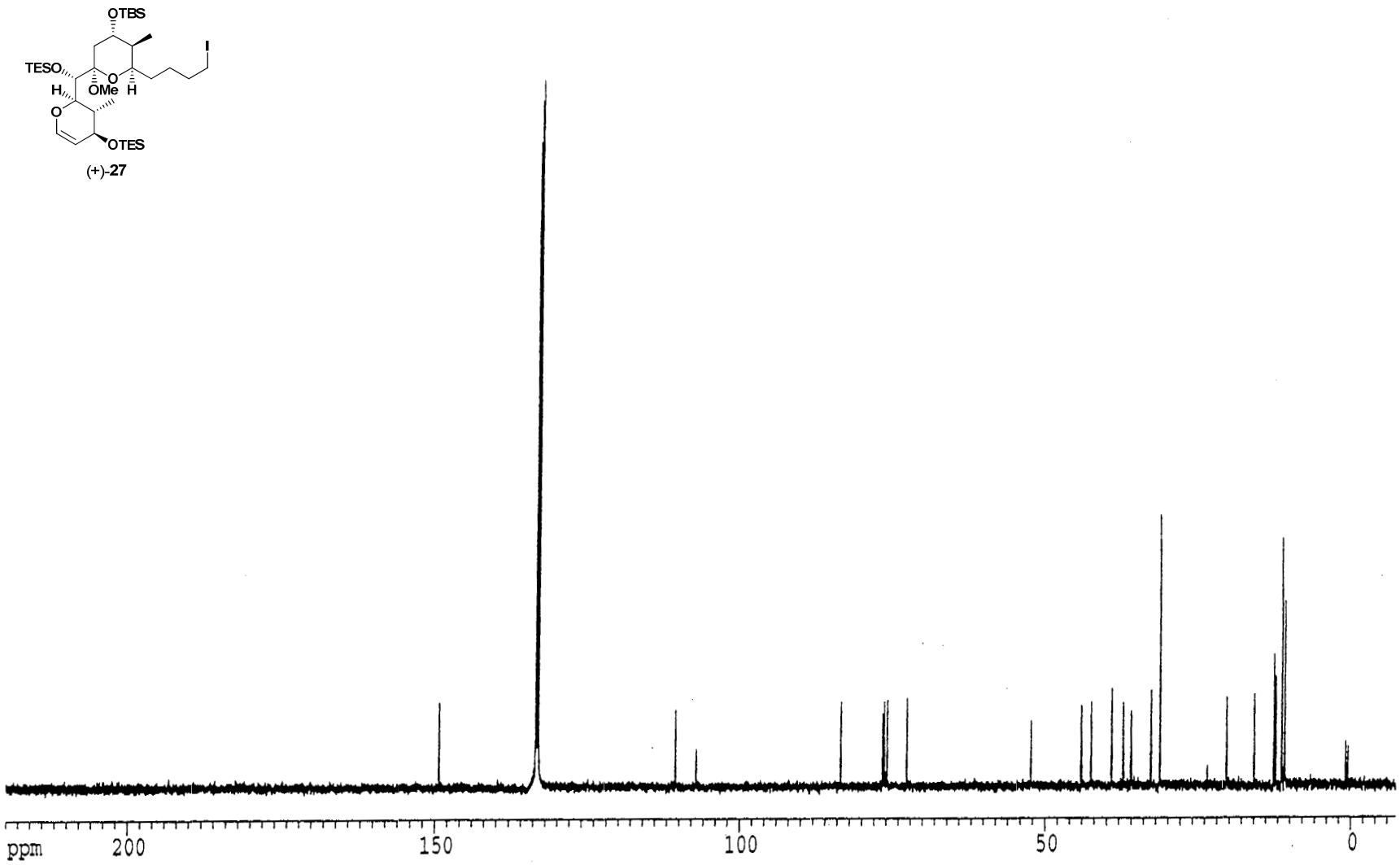


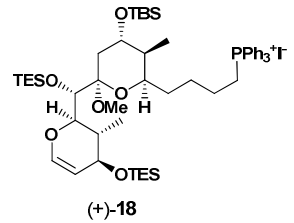
(+)-**26**



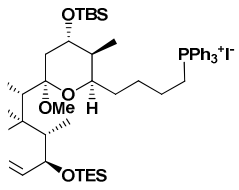
(+)-**27**




OTBS
TESO
H
OMe
H
O
O
OTES
I
(+)-27
ppm
200
150
100
50
0

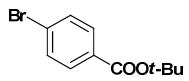


(+)-**18**



(+)-**18**

29



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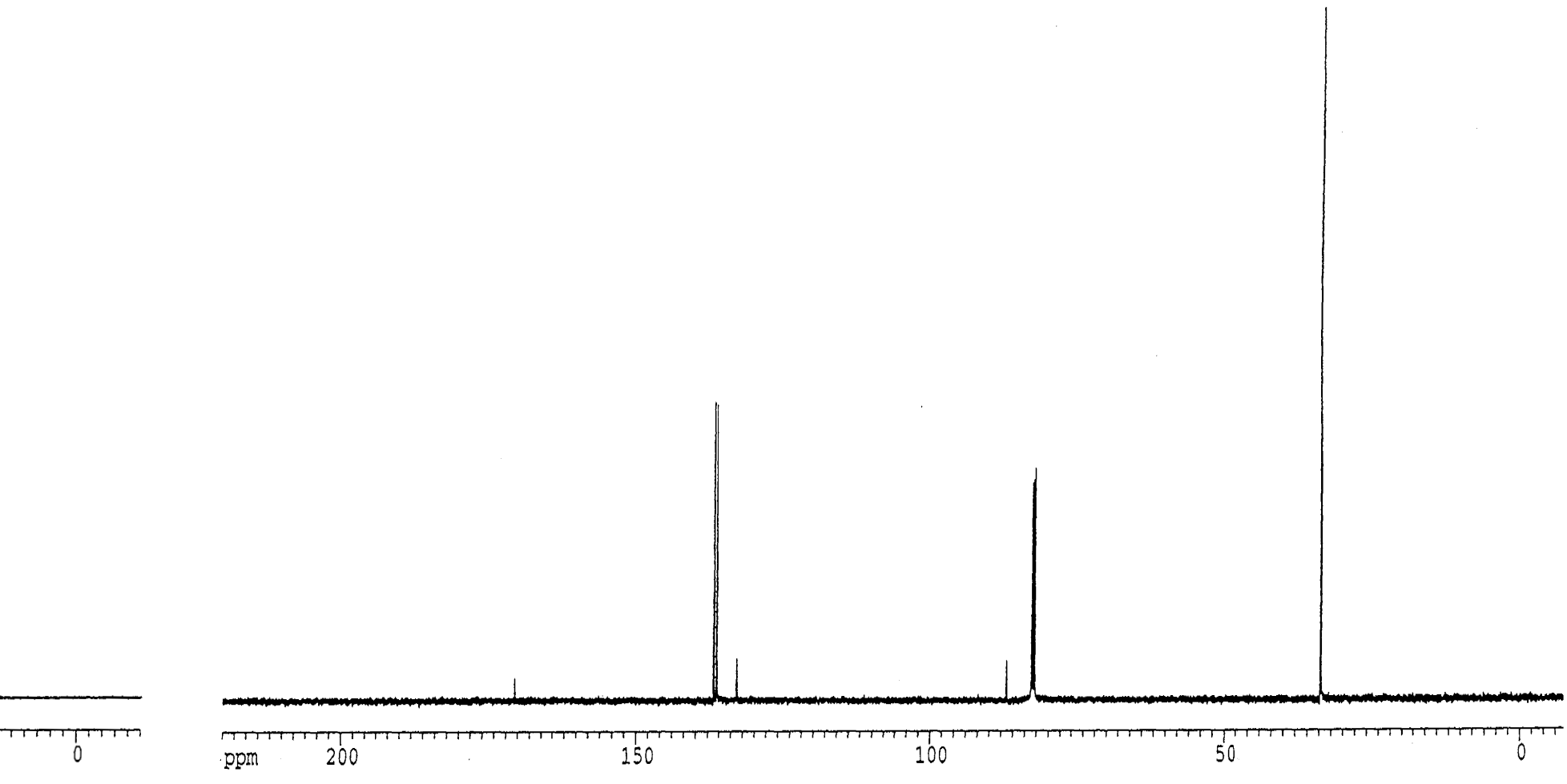

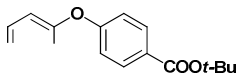

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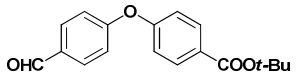
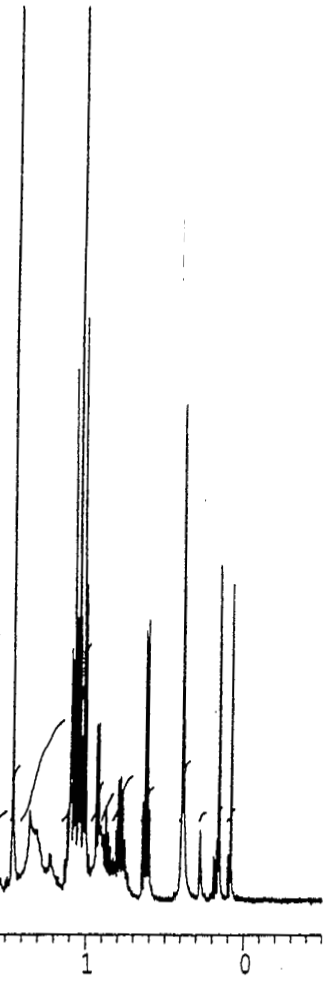
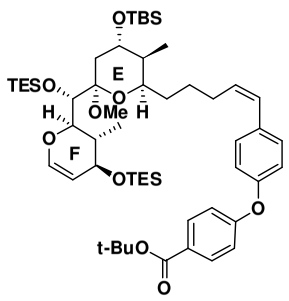
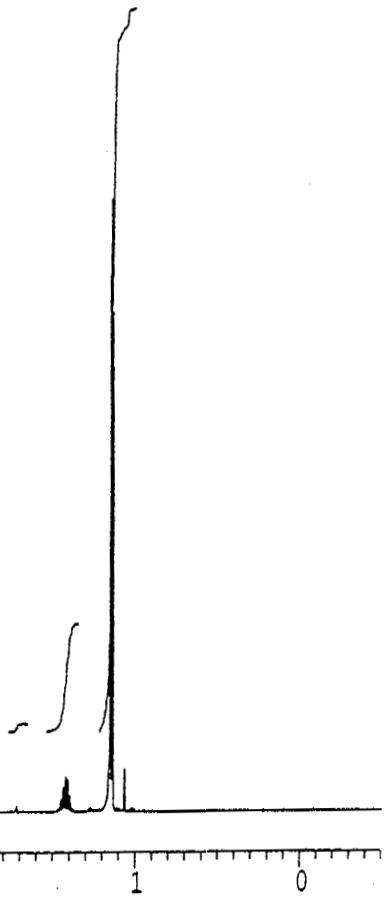


20

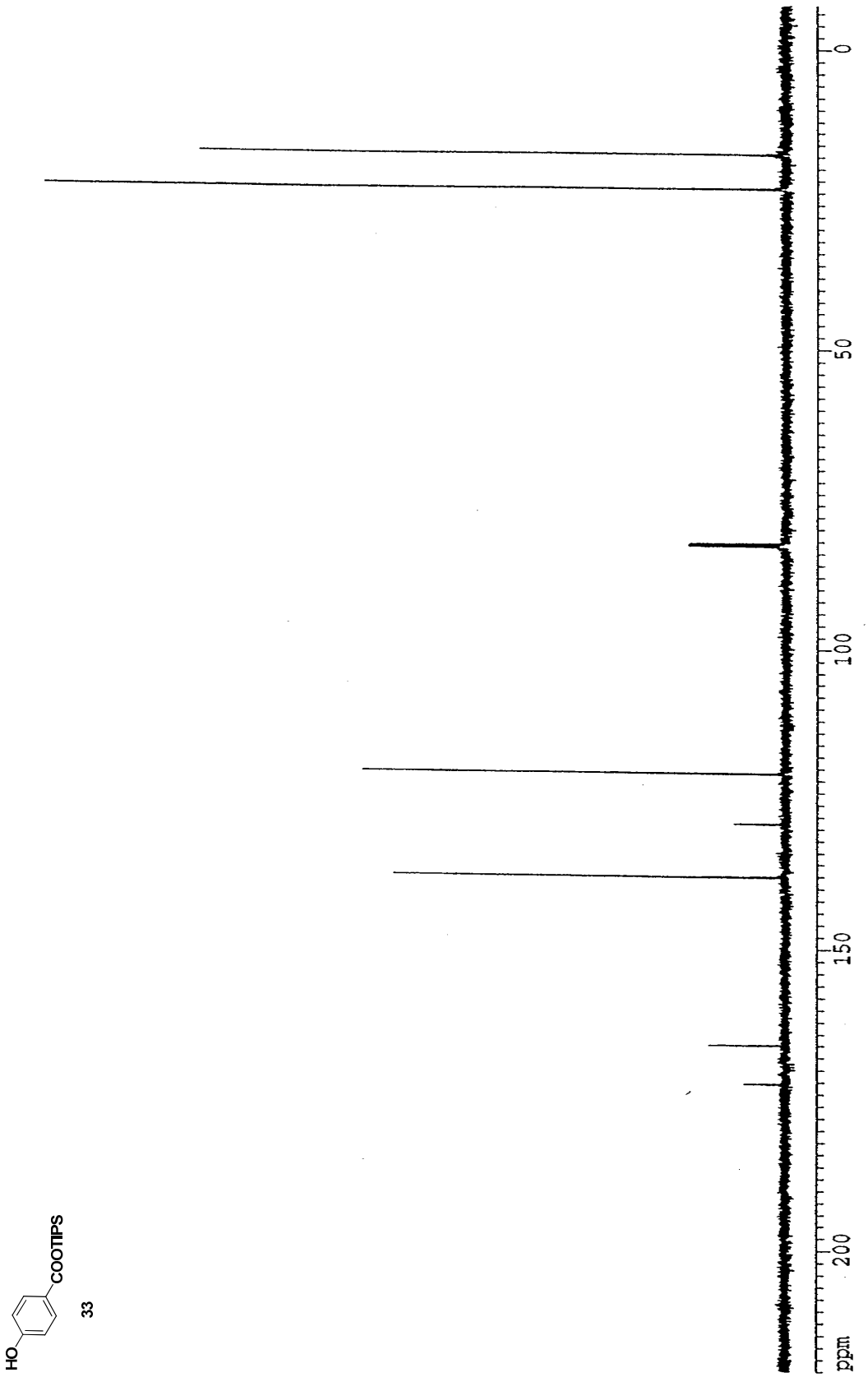


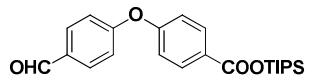


(+)-**30**

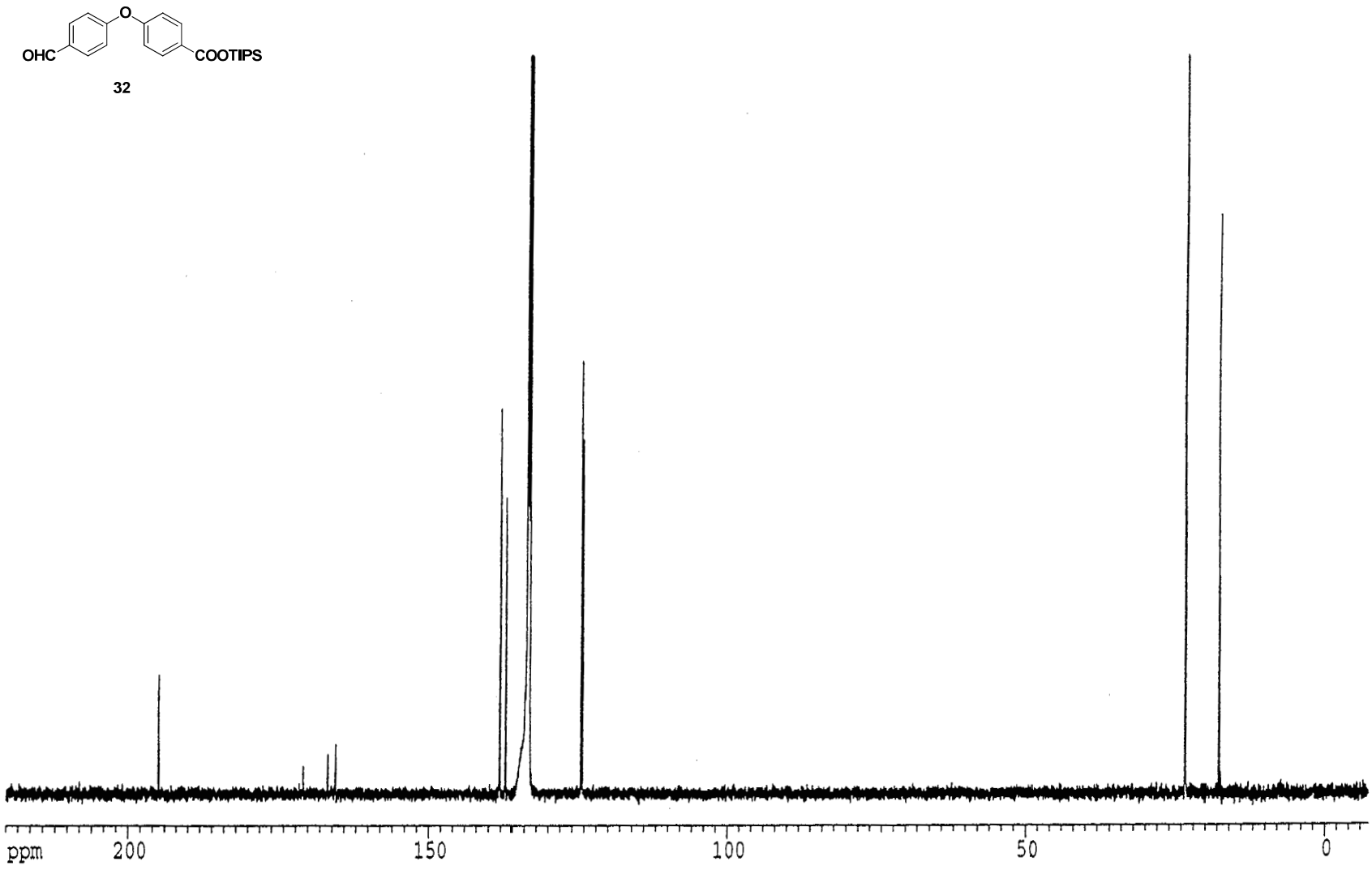


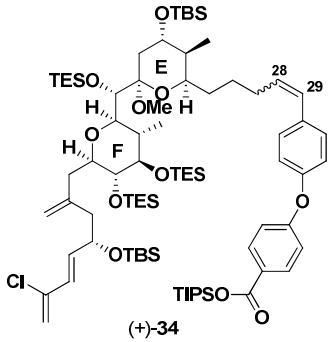
33


HO
COOTIPS
33
0
50
100
150
200
ppm

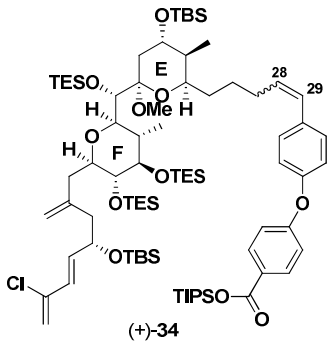


32

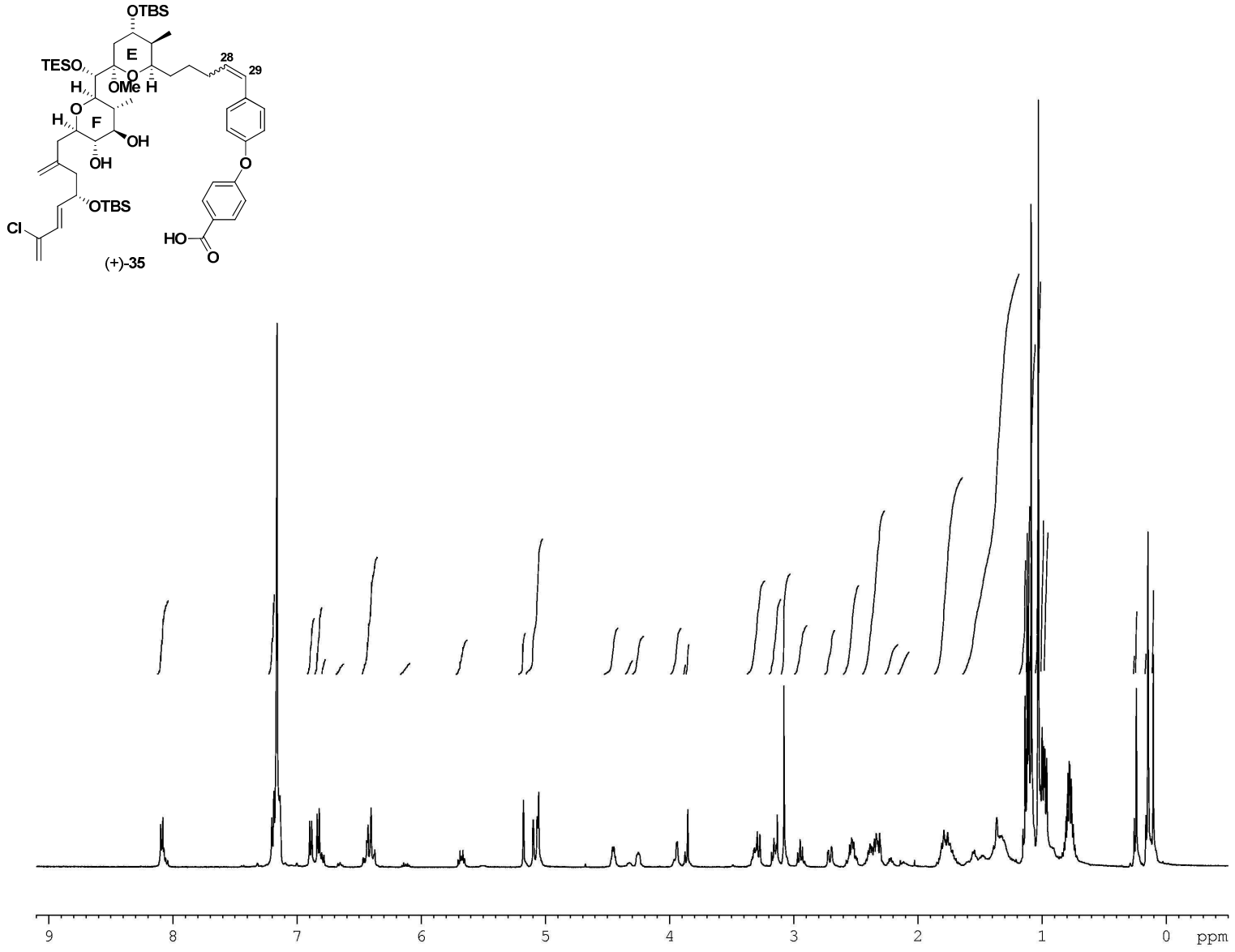

O
OHC
COOTIPS
32
ppm
200
150
100
50
0

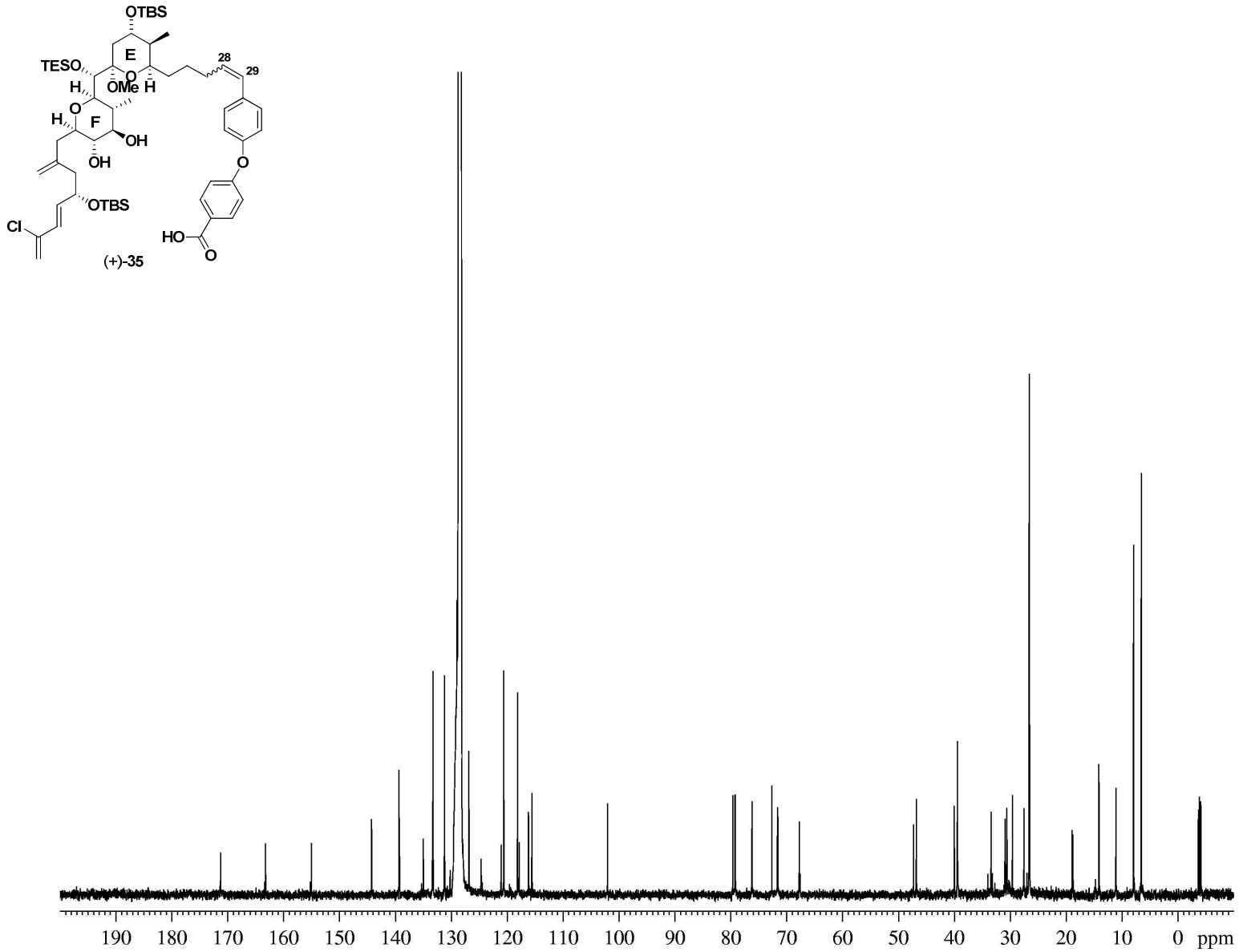

OTBS
E
TESO
28
29
O
H
OMe H
O
H
F
OTES
OTES
O
OTBS
Cl
TIPSO
O
(+)-34

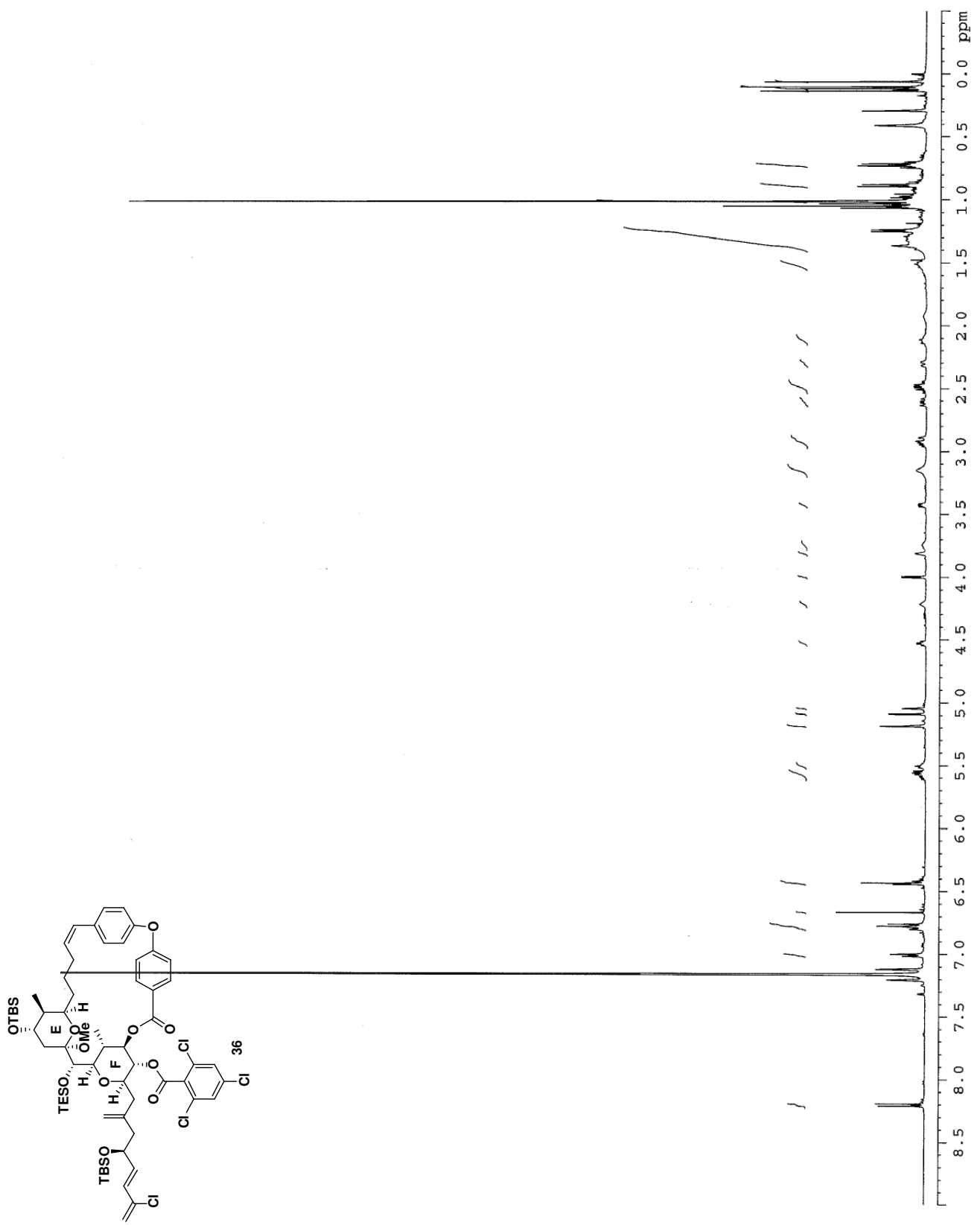
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

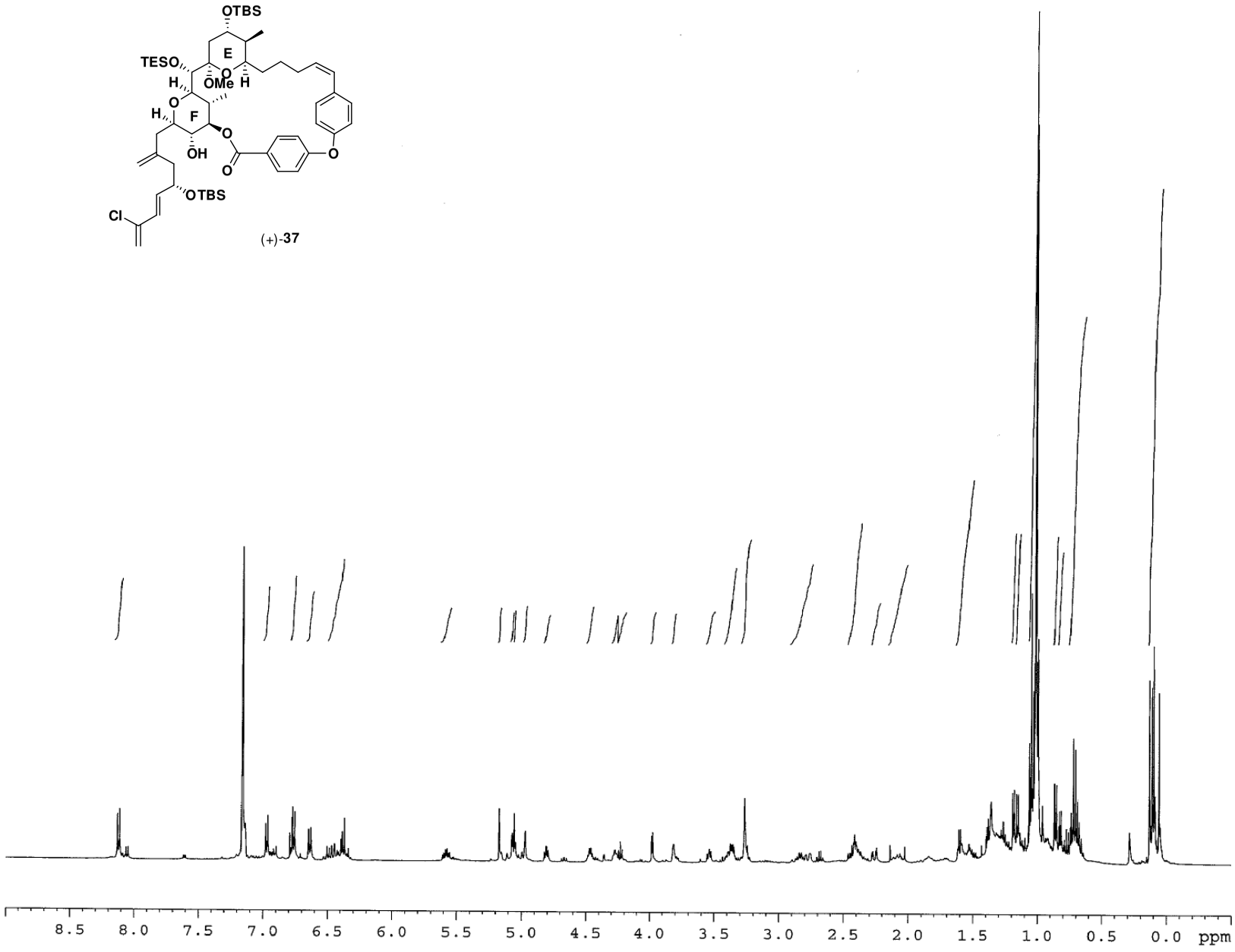

OTBS
E
TESO
28
29
O
H
OMe H
O
H
F
OTES
OTES
O
OTBS
Cl
TIPSO
O
(+)-34

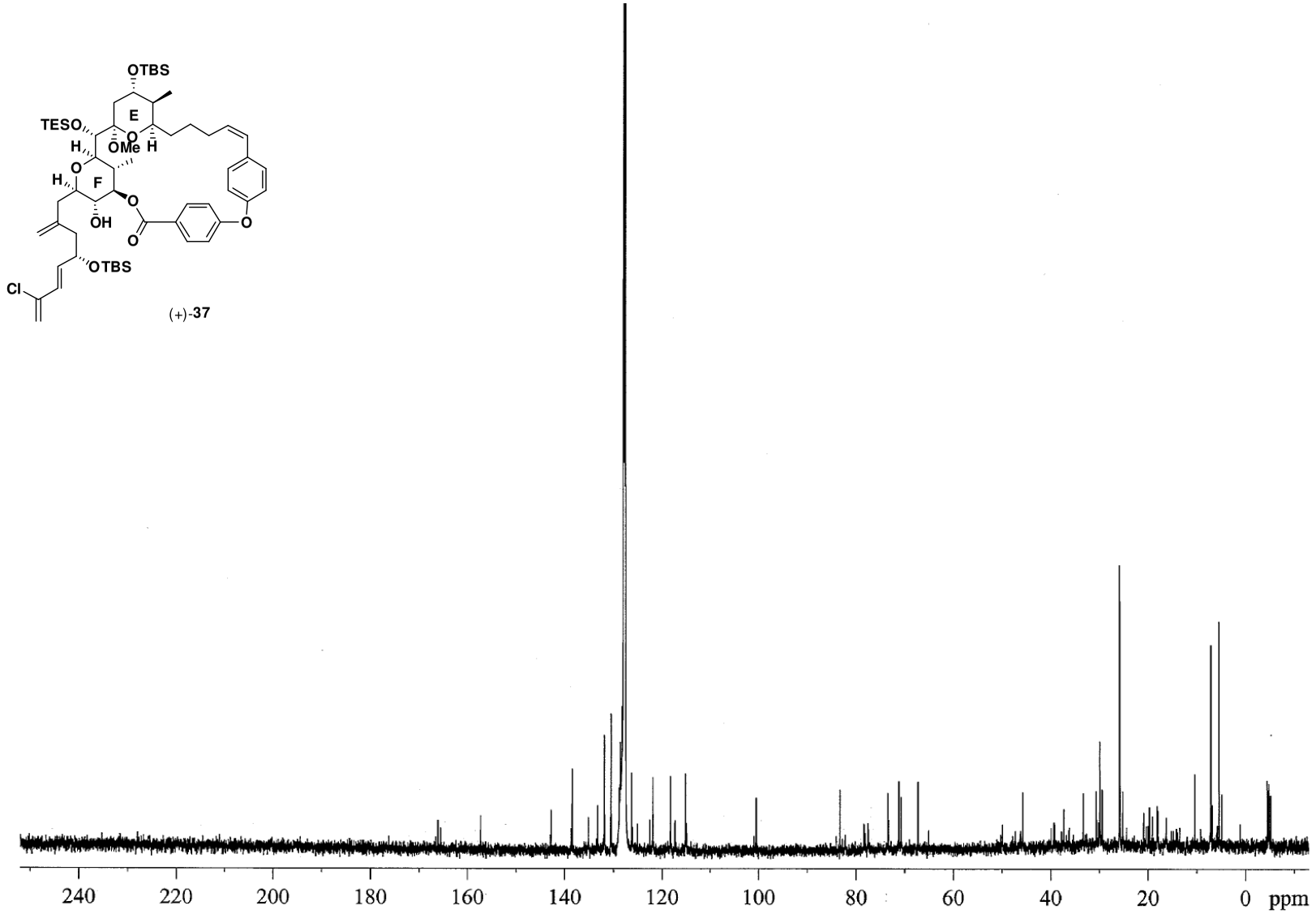
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

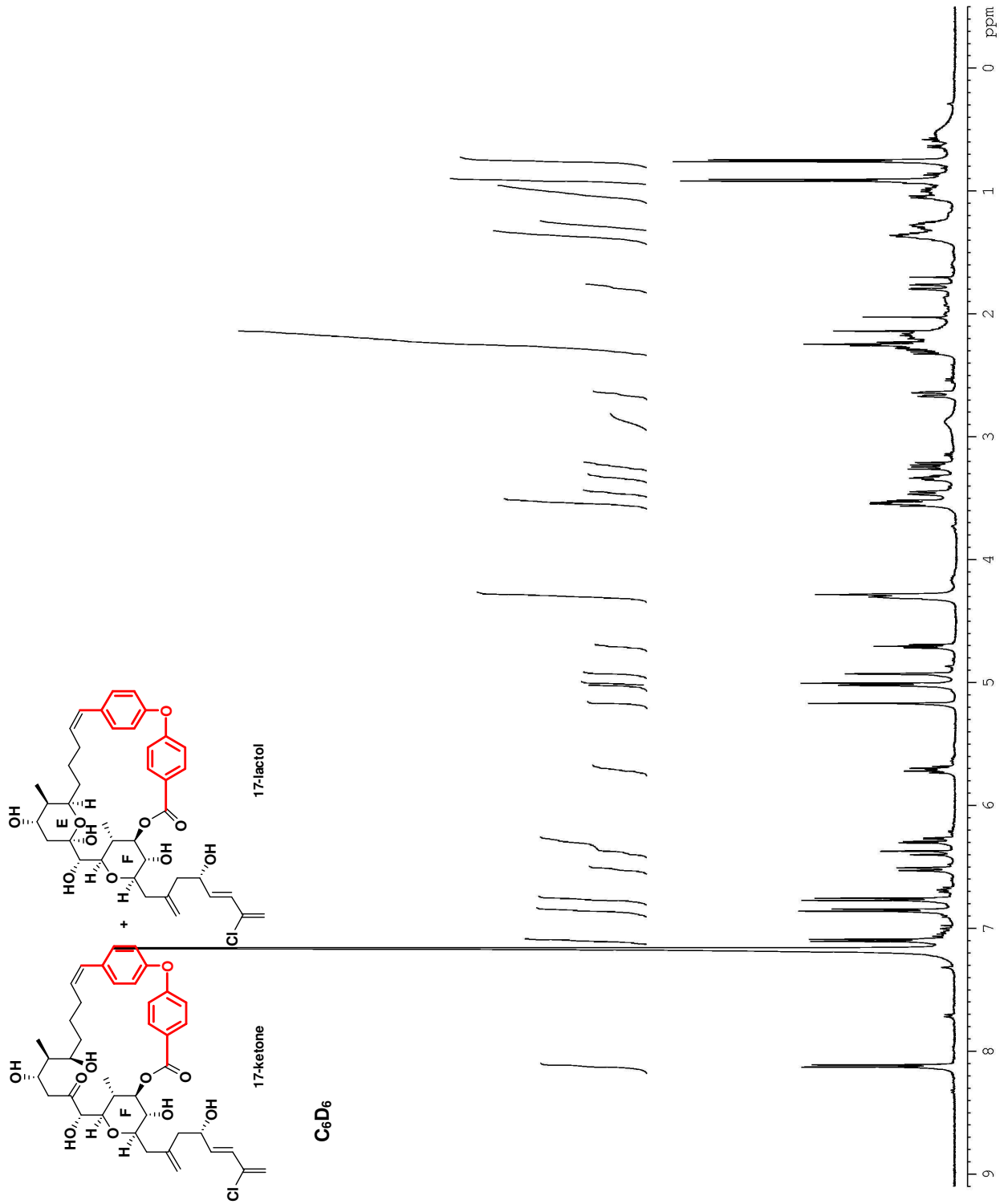

OTBS
E
TESO
28
29
O
H
OMe H
O
H
F
OH
OH
O
OTBS
Cl
HO
O
(+)-35
9
8
7
6
5
4
3
2
1
0
ppm

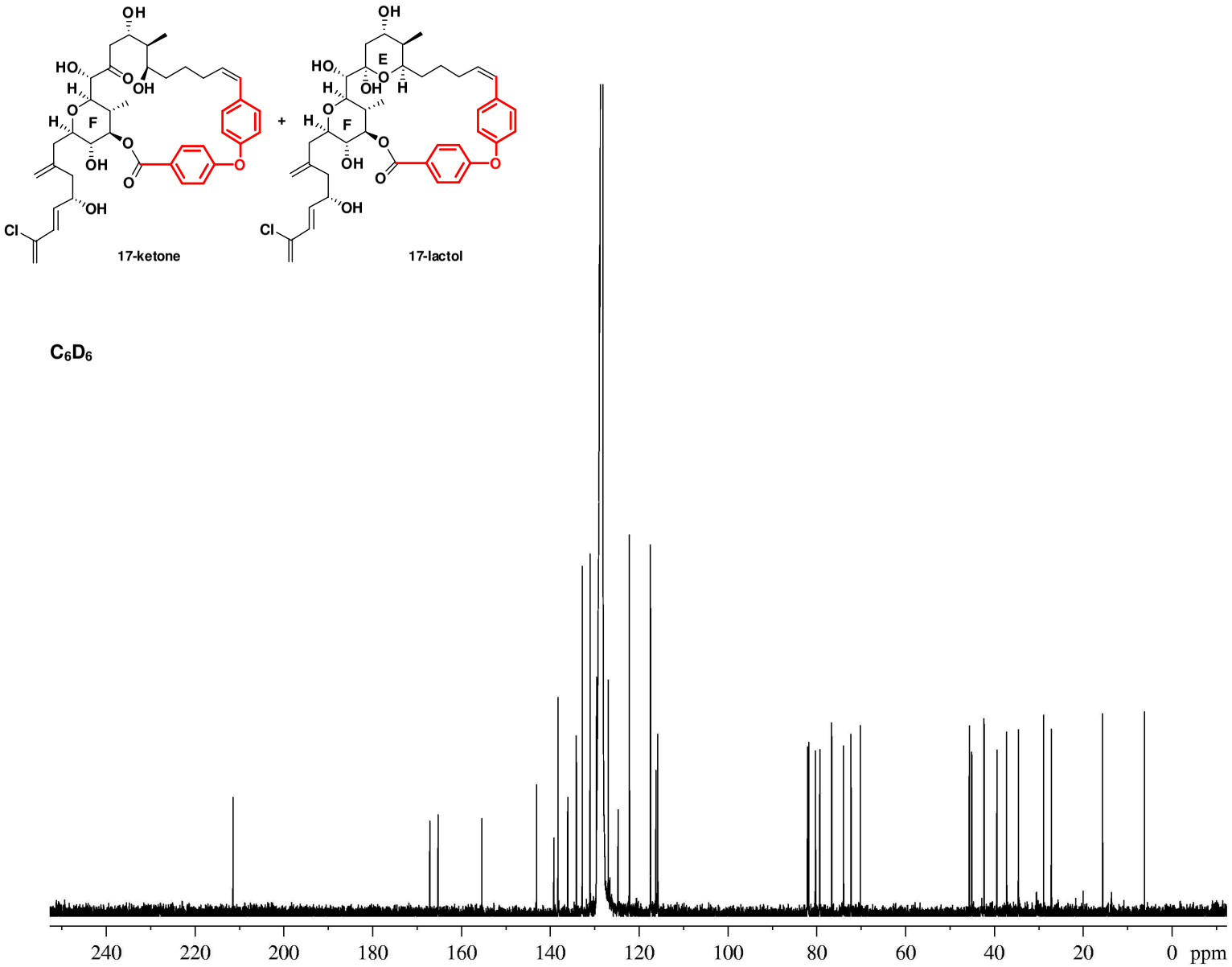

OTBS
E
TESO
28
29
O
H
OMe H
O
H
F
OH
OH
O
OTBS
Cl
HO
O
(+)-35
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

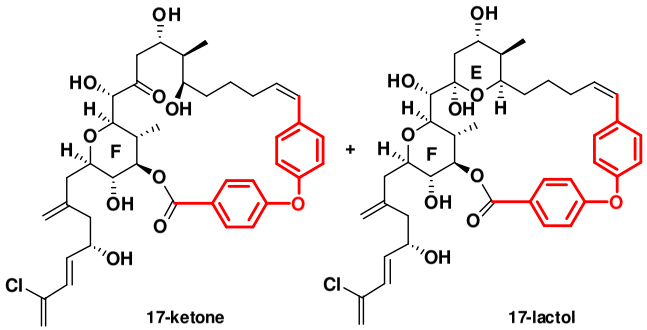

OTBS
E
OMe
H
TESO
H
O
F
H
TBSO
Cl
O
O
O
O
Cl
Cl
Cl
36
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


OTBS
TESO
E
O
H
OMe
H
O
H
F
O
OH
O
O
OTBS
Cl
(+)-37
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
ppm

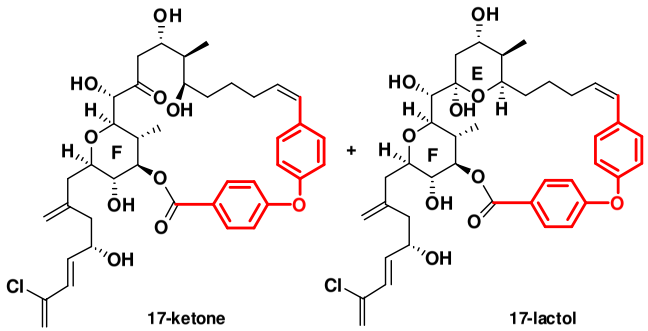

OTBS
TESO
E
H
OMe
H
O
H
F
O
OH
O
O
OTBS
Cl
(+)-37
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm


17-ketone
17-lactol
C6D6
ppm


17-ketone
17-lactol
C6D6
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

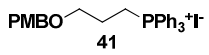


CD_3CN

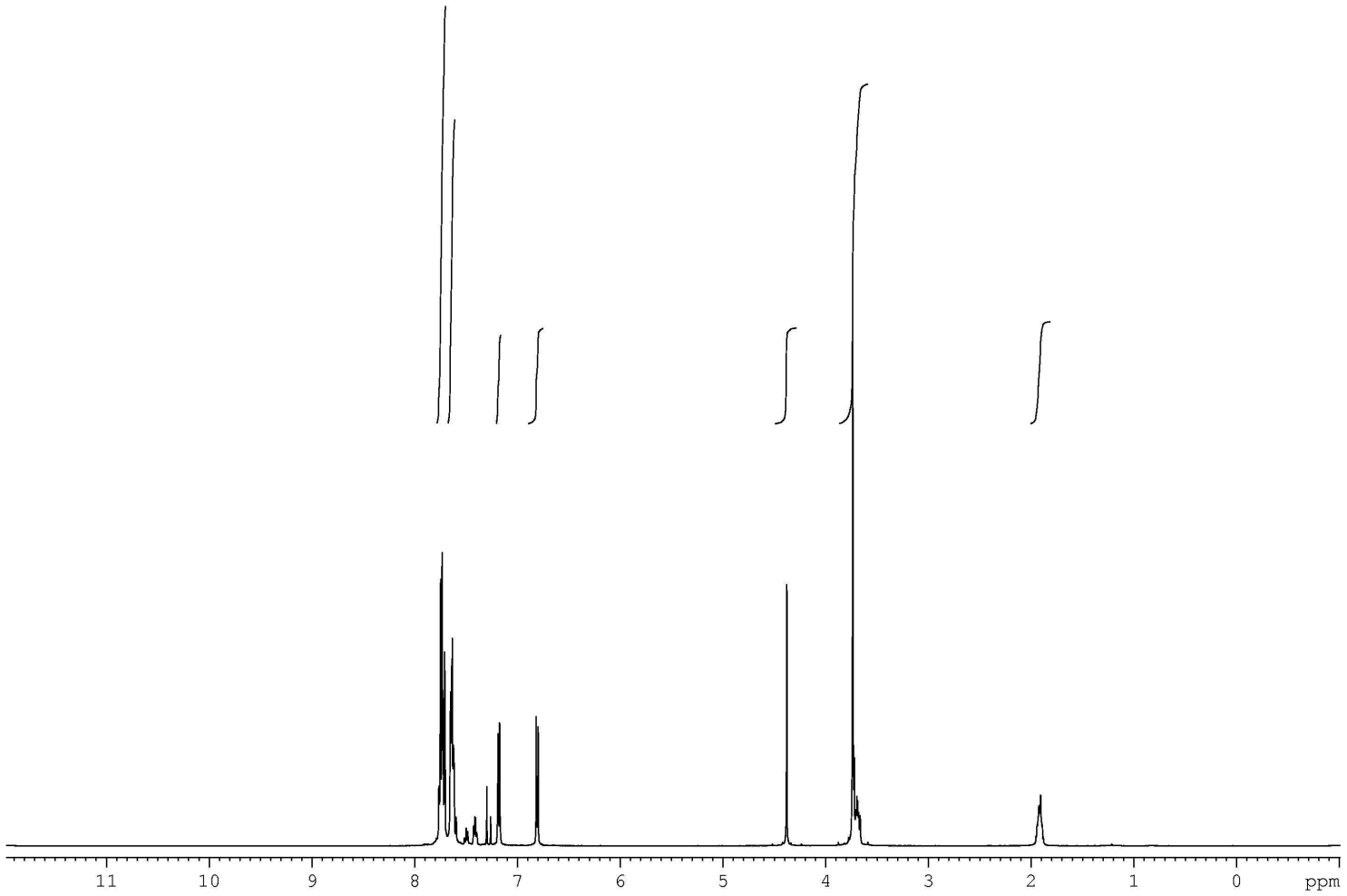

17-ketone
17-lactol

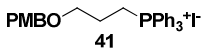
CD_3CN

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

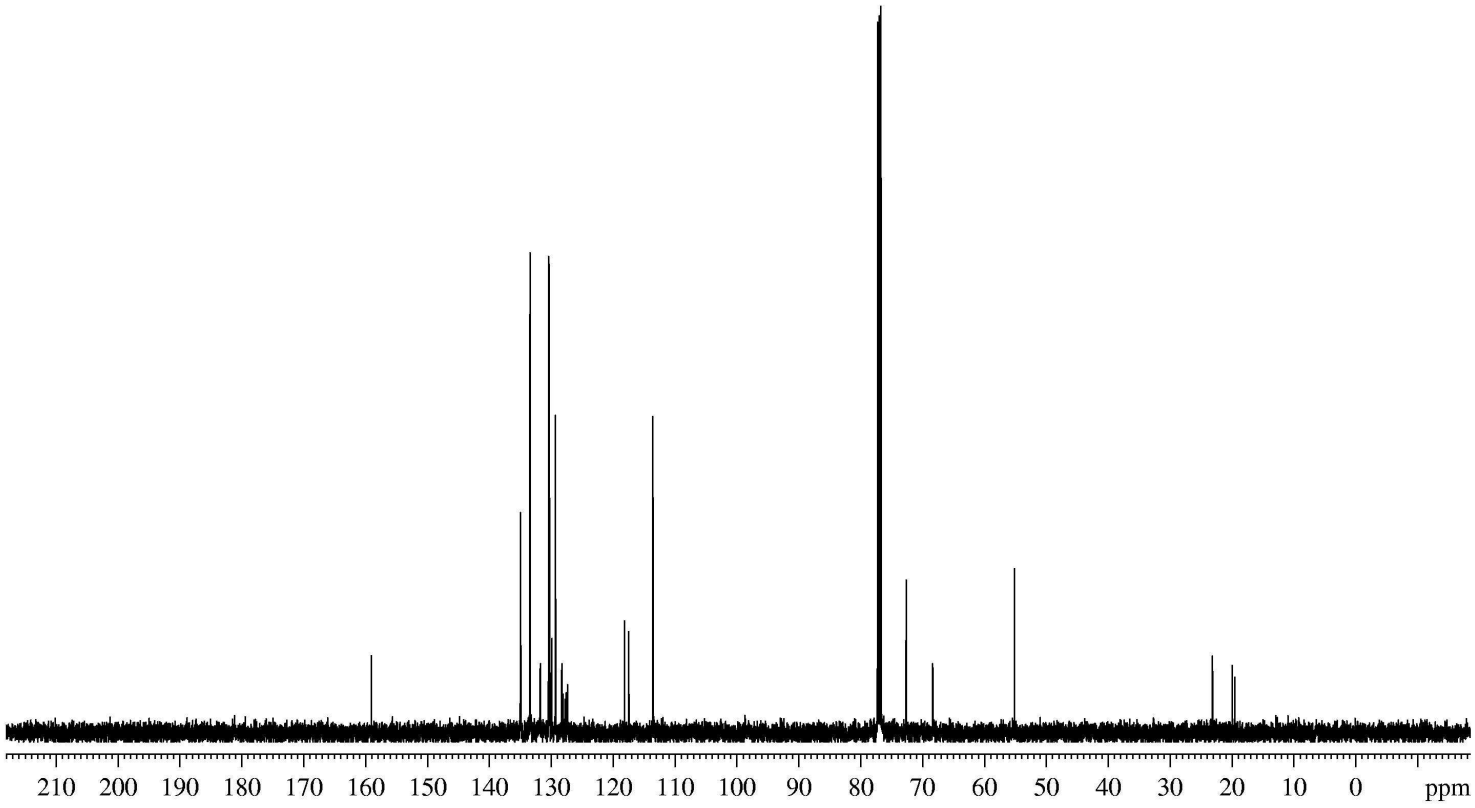


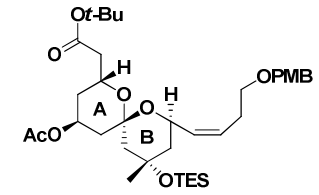
41



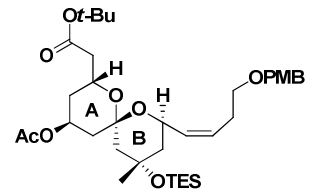

PMBO
PPh3+I-

41

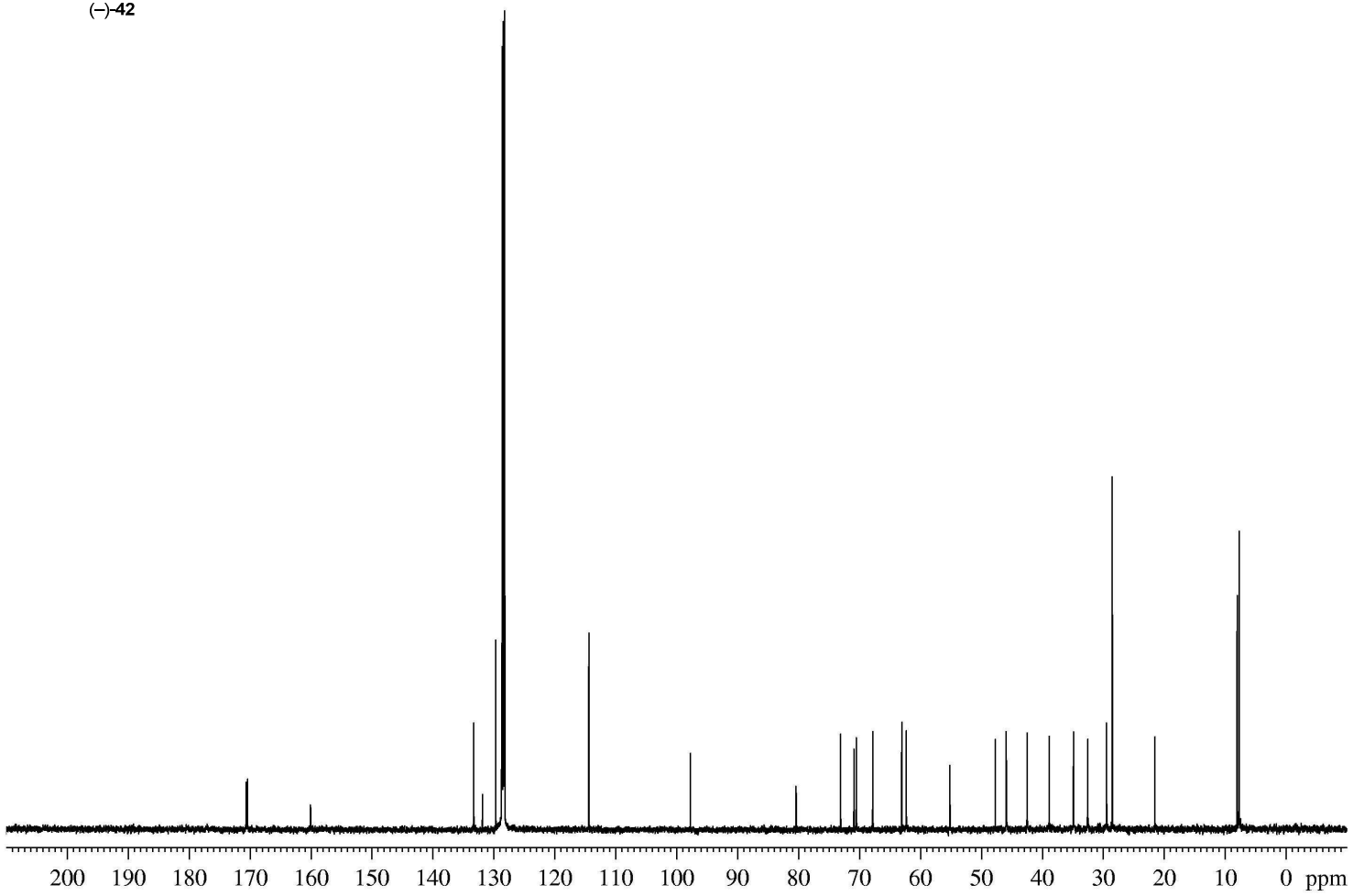

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

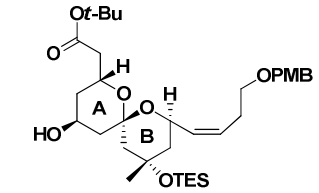


(–)-42

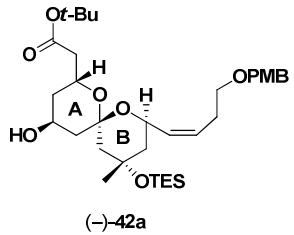

Ot-Bu
O
H
O
H
OPMB
A
O
AcO
B
OTES

(–)-42

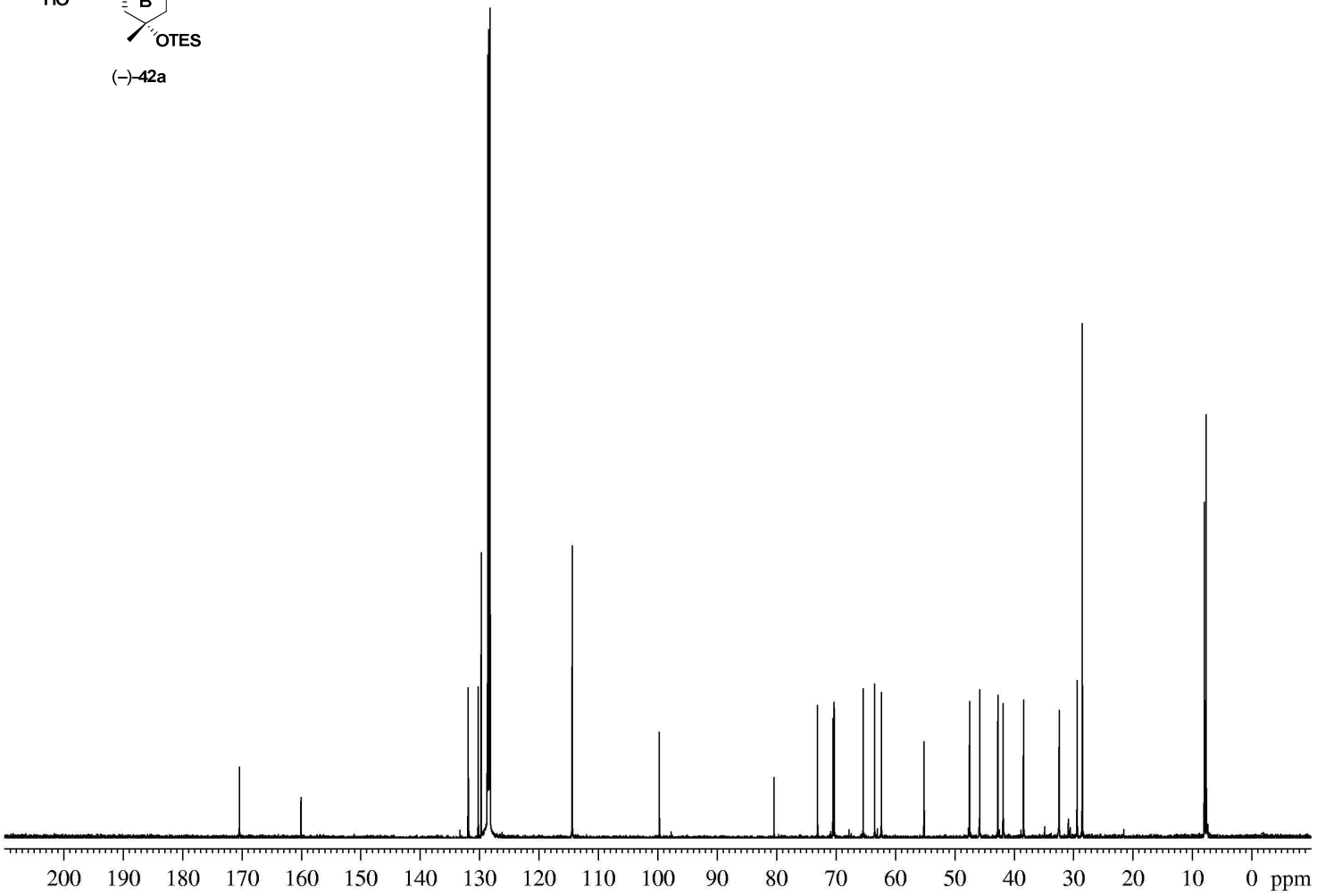

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

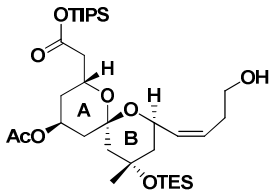


(–)-42a

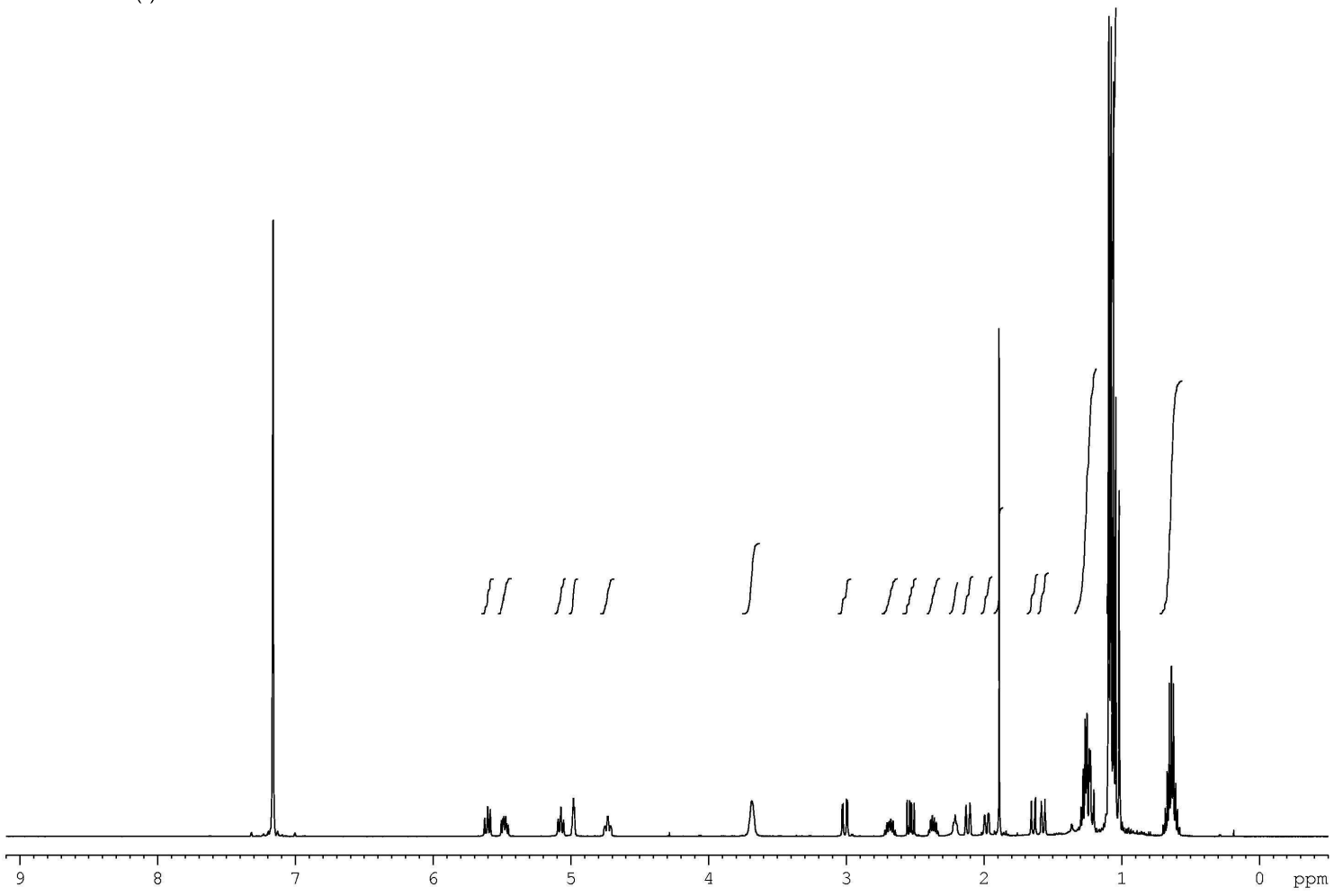

Ot-Bu
O
H
O
A
O
H
OPMB
HO
B
OTES

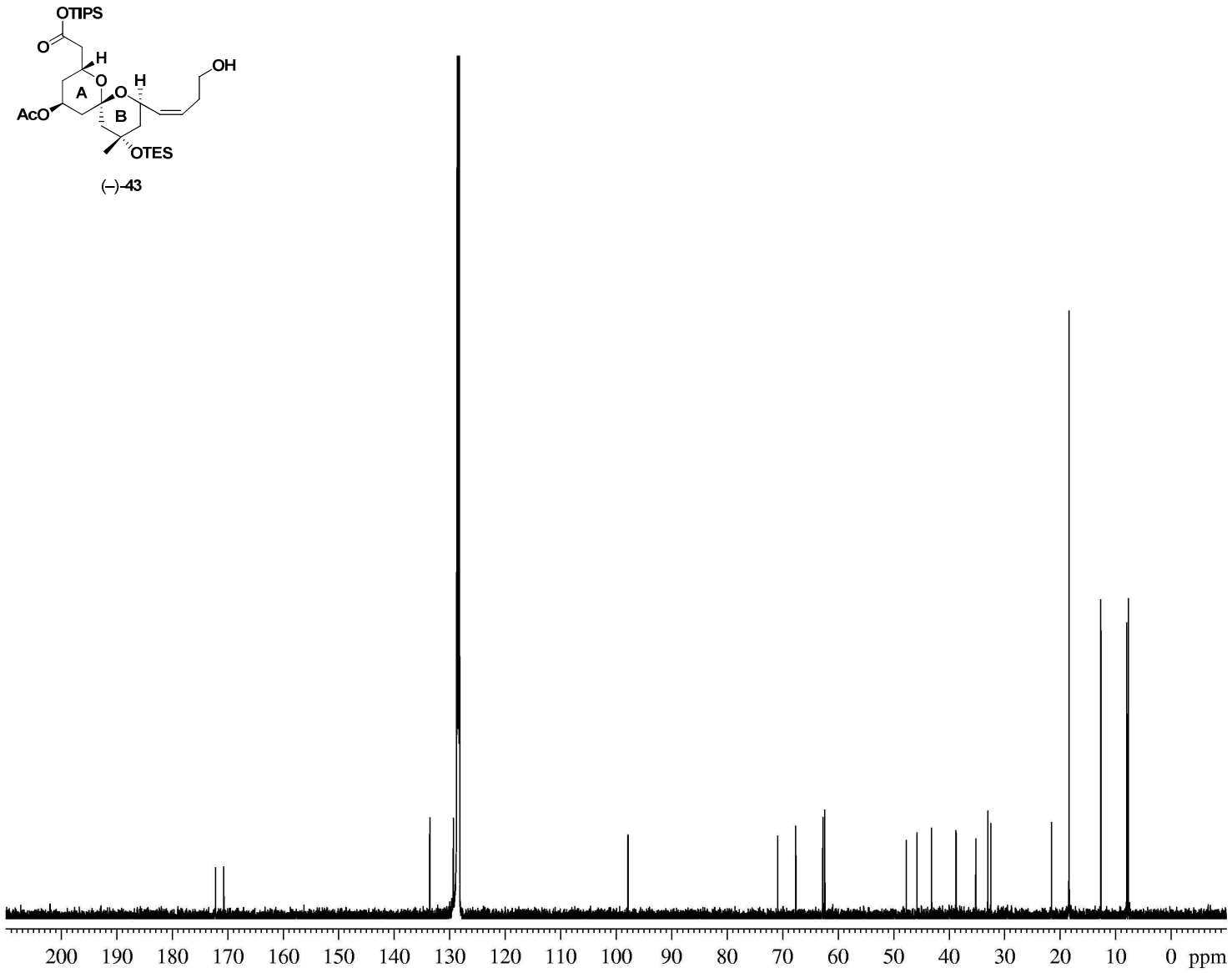
(–)-42a

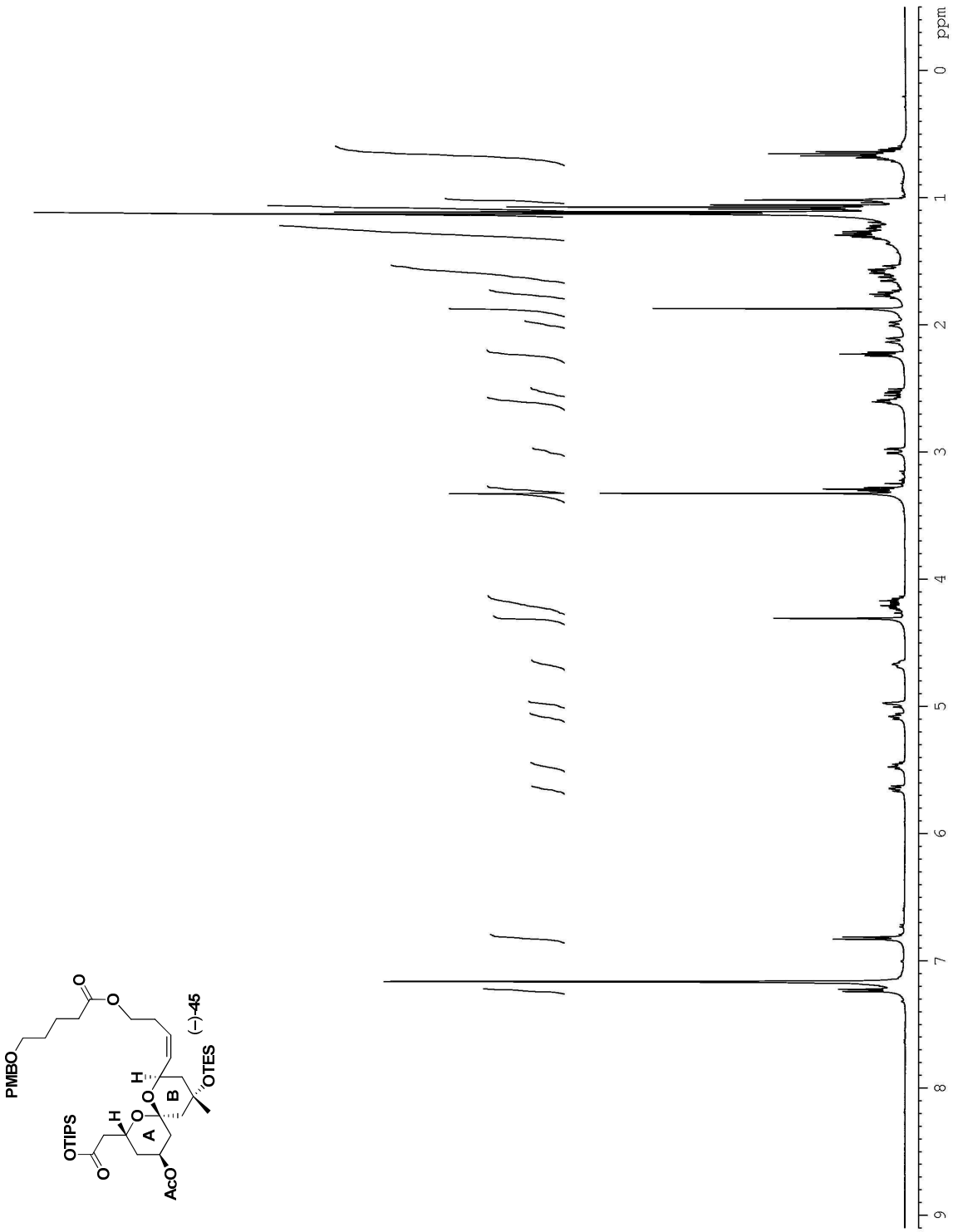

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

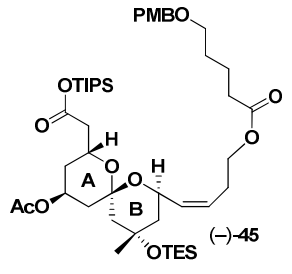


(–)-43

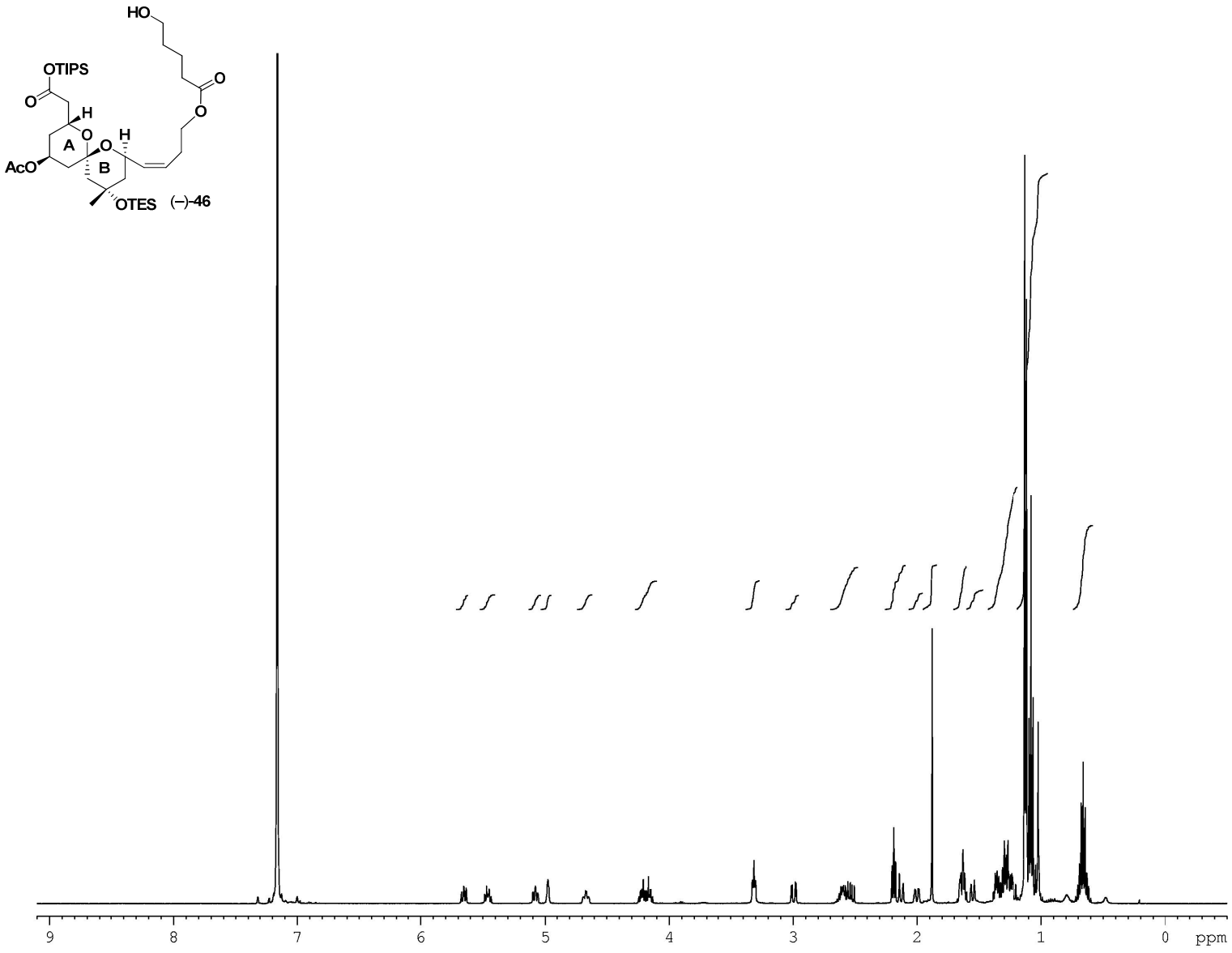


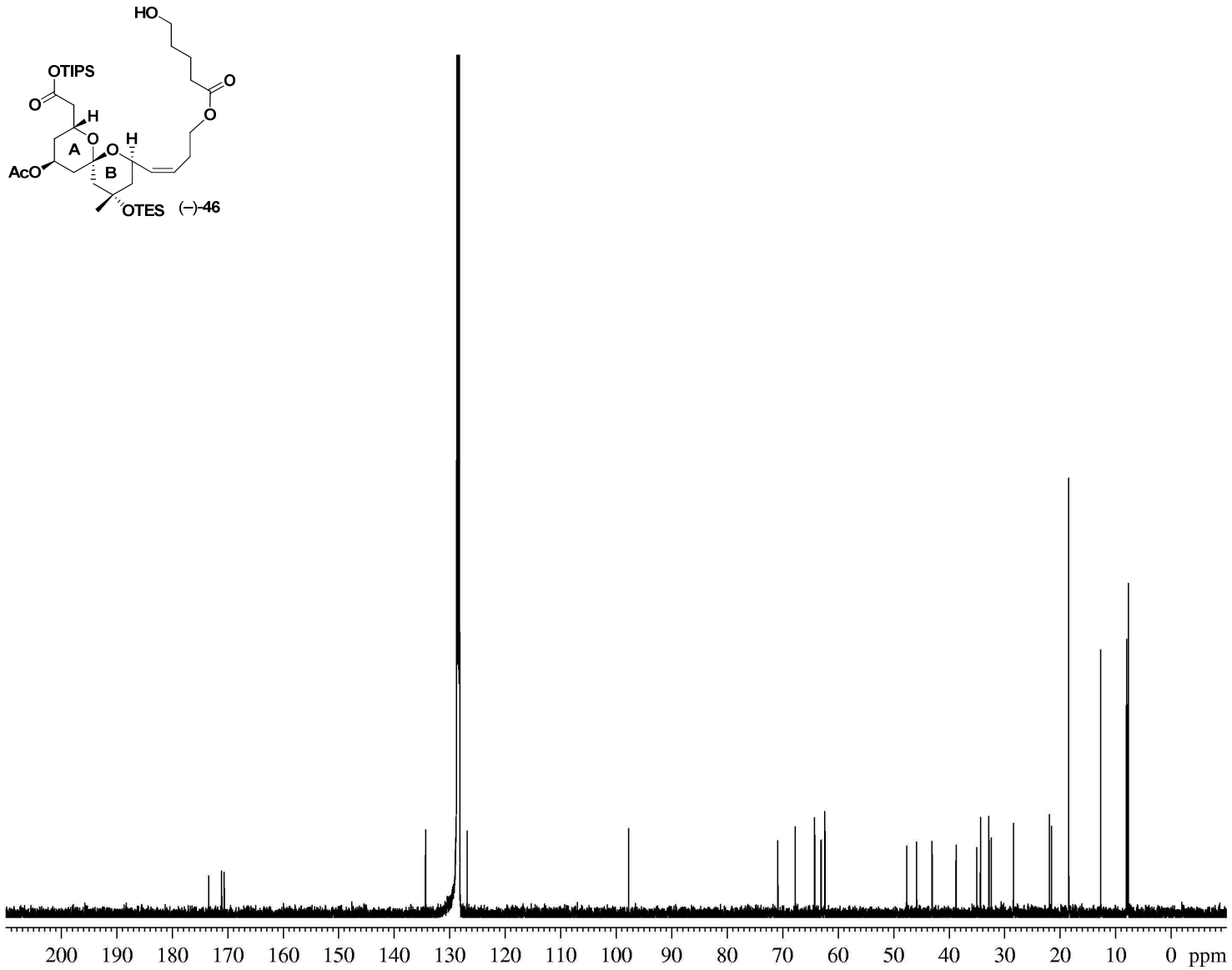

OTIPS
O
H
O
A
O
H
OH
AcO
B
OTES
(–)-43
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

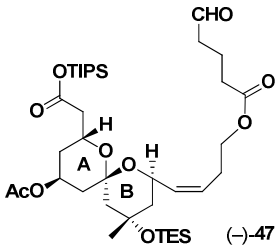

PMBO
OTIPS
AcO
OTES
(–)-45
A
B
H
H
O
O
O
O
O
O
O
O
ppm
0
1
2
3
4
5
6
7
8
9


PMBO
OTIPS
O
O
H
A
O
O
H
AcO
B
OTES
(–)-45

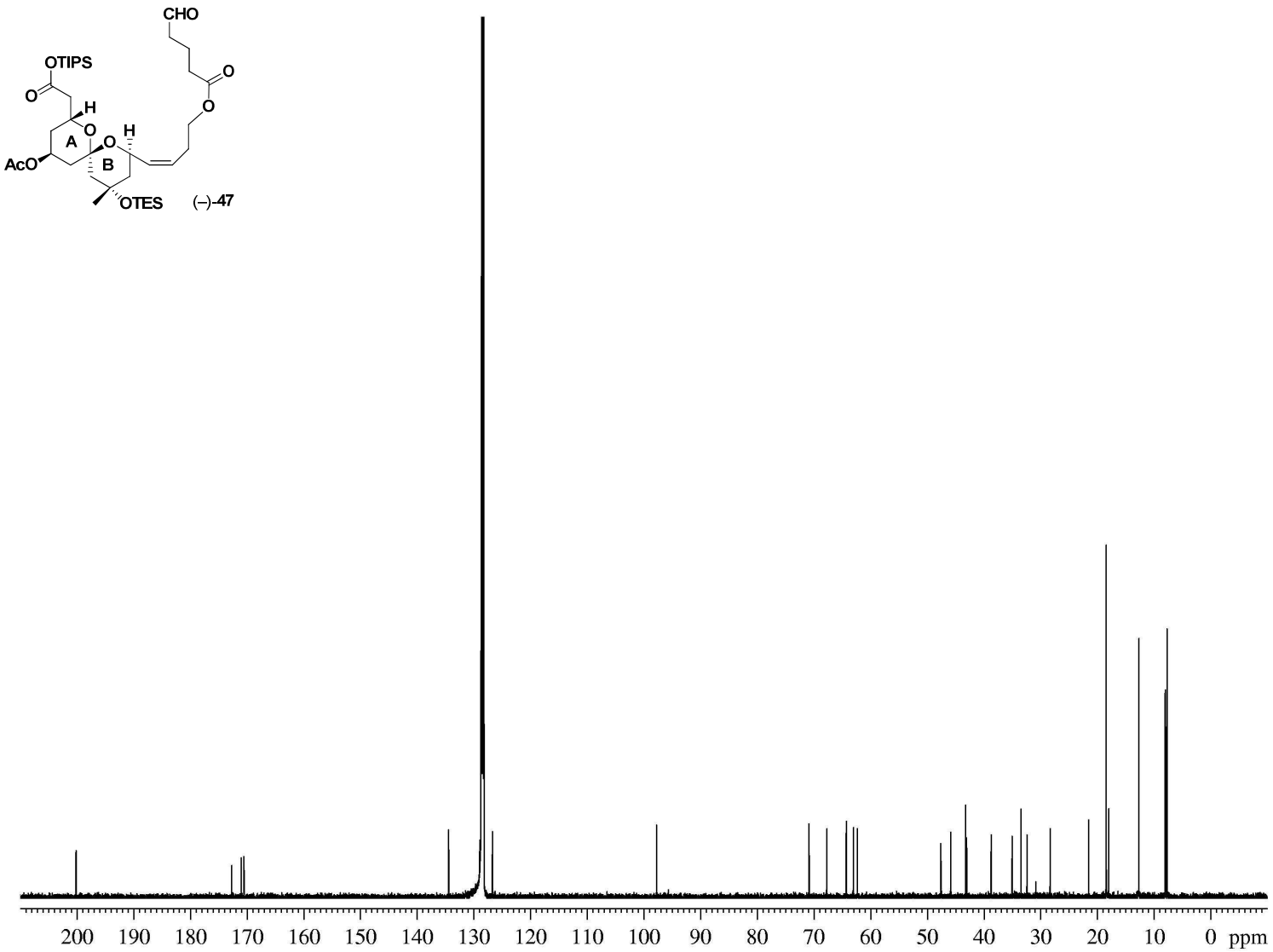
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

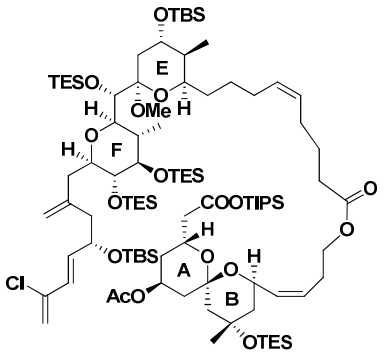

HO
OTIPS
O
O
O
H
A
O
O
H
AcO
B
OTES
(–)-46
9
8
7
6
5
4
3
2
1
0
ppm


HO
OTIPS
O
O
O
H
A
O
O
H
AcO
B
OTES
(−)-46
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



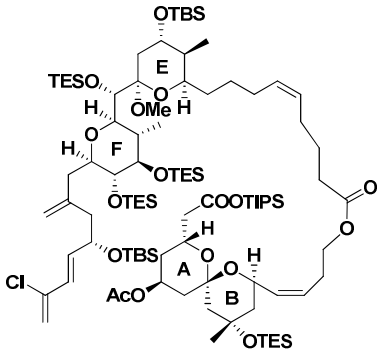
(–)-47


CHO
OTIPS
O
O
O
H
A
O
O
H
AcO
B
OTES
(–)-47
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OTBS
E
TESO
H
O
OMe
H
O
H
F
OTES
OTES
COOTIPS
O
O
H
OTBS
A
O
O
H
Cl
AcO
B
OTES

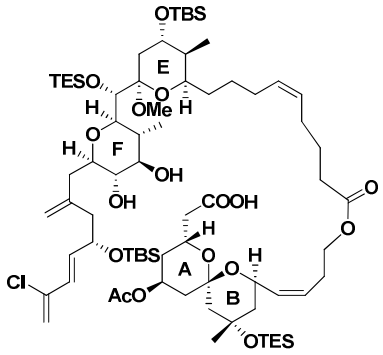
(–)-48

9
8
7
6
5
4
3
2
1
0
ppm


OTBS
E
TESO
H
O
OMe
H
O
H
F
OTES
OTES
COOTIPS
H
O
O
H
OTBS
A
O
Cl
AcO
B
OTES

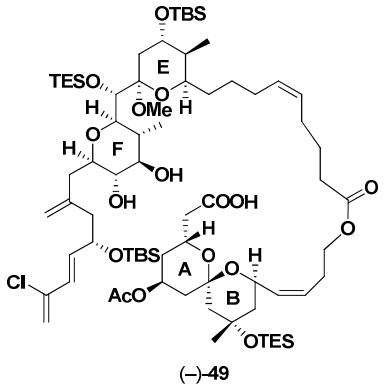
(–)-48

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


OTBS
E
TESO
O
H
OMe
H
O
H
F
OH
OH
COOH
H
O
O
OTBS
A
O
H
Cl
AcO
B
OTES

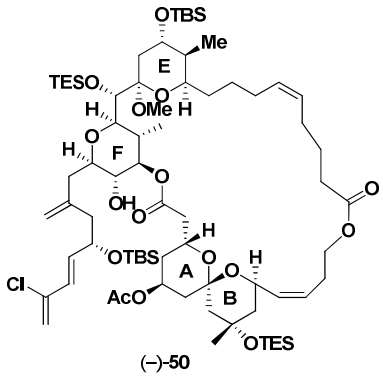
(–)-49

9
8
7
6
5
4
3
2
1
0
ppm


OTBS
E
TESO
H
O
OMe
H
O
H
F
OH
OH
COOH
H
O
O
OTBS
A
O
H
Cl
AcO
B
OTES

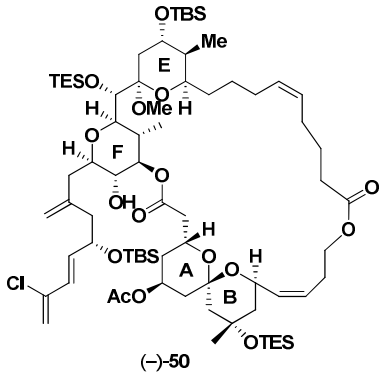
(–)-49

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


OTBS
Me
E
TESO
H
O
OMe H
O
H
F
O
OH
O
O
O
H
OTBS
A
O
O
H
Cl
AcO
B
OTES

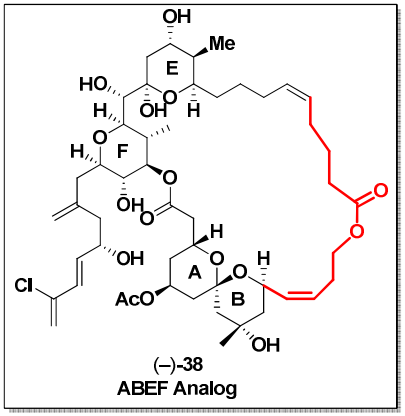
(–)-50

9
8
7
6
5
4
3
2
1
0
ppm


OTBS
Me
E
TESO
H
O
OMe H
O
H
F
O
OH
O
O
O
H
OTBS
A
O
O
H
Cl
AcO
B
OTES

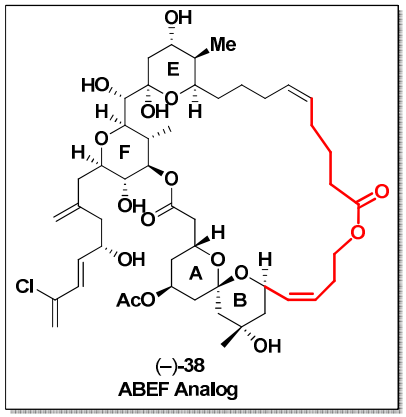
(–)-50

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


OH
Me
E
HO
H
O
H
OH
O
H
F
O
O
OH
O
H
OH
A
O
H
Cl
AcO
O
B
OH
(–)-38
ABEF Analog

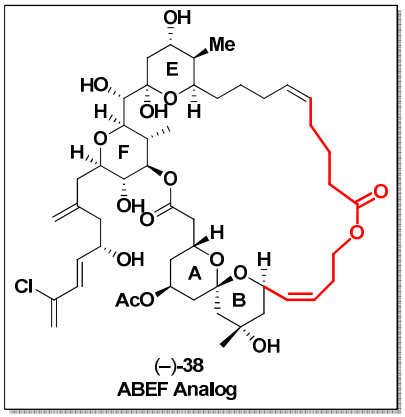
CD_3CN

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
ppm


OH
Me
E
HO
H
O
OH
H
H
O
F
O
OH
O
O
O
H
OH
O
H
A
O
Cl
AcO
B
OH
(–)-38
ABEF Analog

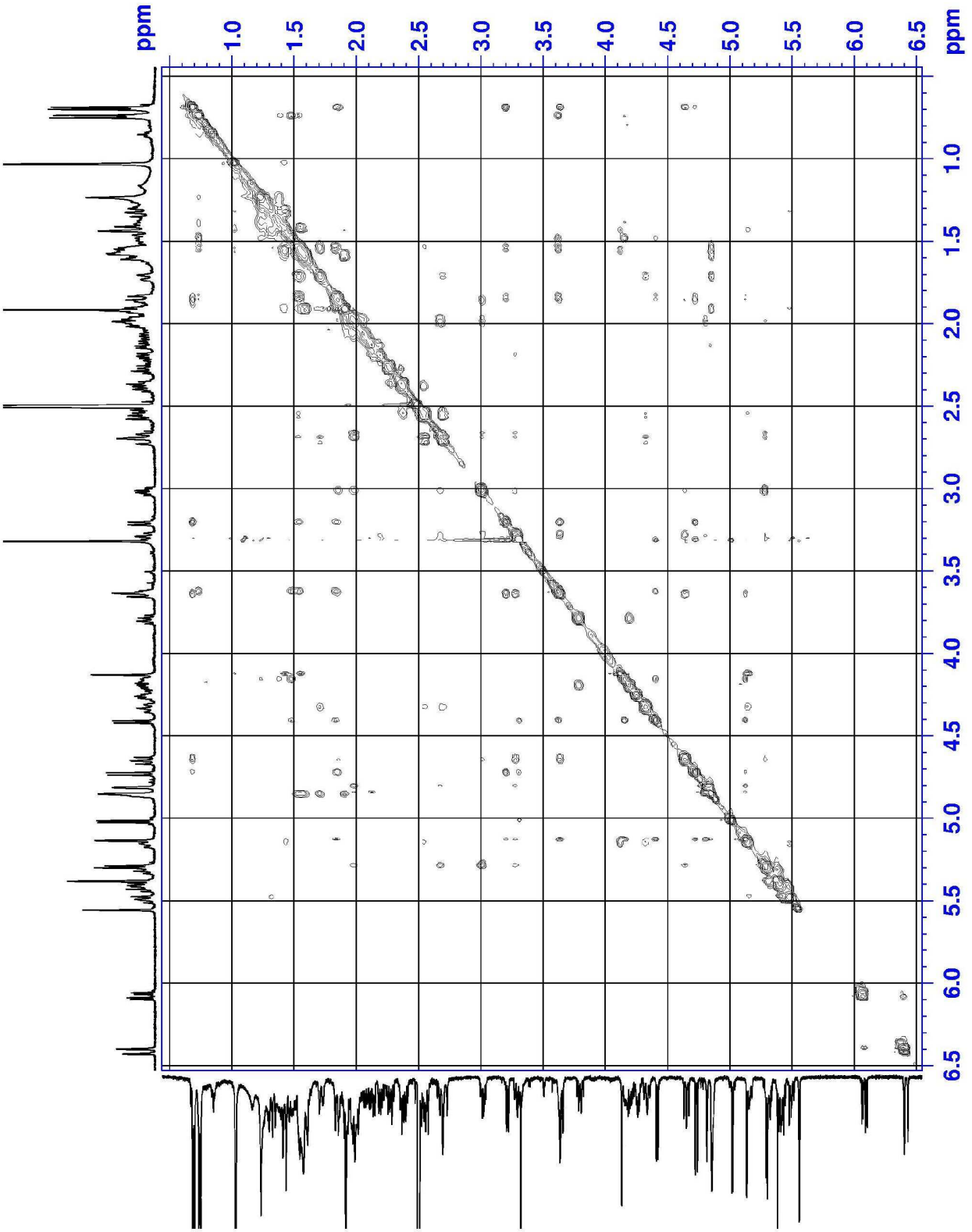
CD_3CN

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


OH
Me
E
HO
H
OH
O
H
O
H
F
O
OH
O
H
OH
O
A
O
H
Cl
AcO
B
OH
O
(–)-38
ABEF Analog

DMSO-*d*$_6$

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
ppm



NOESY NMR spectrum of (–)-**38** in DMSO-D_6 (mixing time of 600 ms)