Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

Stereochemistry and Biological Activity of Chlorinated Lipids: A Study of Danicalipin A and Selected Diastereomers

*Johannes Boshkow,[†] Stefan Fischer,[†] Adrian M. Bailey, Susanne Wolfrum, and Erick M. Carreira**

Contents

1 General Methods and Materials

Chemicals and Solvents: All chemicals and solvents were purchased from ABCR, ACROS, ALFA-AESAR, APOLLO, J. T. BAKER, COMBI-BLOCKS, FLUKA, FLUOROCHEM, MERCK, TCI, SIGMA-ALDRICH, STREM or LANCASTER and were used as received from the commercial supplier without further purification unless otherwise mentioned. Deuterated solvents for NMR spectroscopy were obtained from ARMAR CHEMICALS, Döttingen, Switzerland. THF, Et_2O, CH_2Cl_2, MeCN, and toluene were dried by passage over two 4" × 36" columns of anhydrous neutral A-2 alumina (MACHEREY & NAGEL; activated over night at 300 °C under a flow of N_2) under an atmosphere of Ar (H_2O content < 30 ppm, KARL–FISCHER titration)[1] or by using an LC TECHNOLOGY SOLUTIONS *SP-1* solvent purification system. MeOH was distilled from magnesium turnings under an atmosphere of dry nitrogen. Pyridine and Et_3N were distilled from KOH under an atmosphere of dry N_2.

General Procedures: All non-aqueous reactions were performed under an inert atmosphere of dry argon or nitrogen in flame dried glassware sealed with a rubber septum unless otherwise noted. Argon was passed over a column of $CaCl_2$ and supplied through a glass manifold. Reactions were stirred magnetically and monitored by thin layer chromatography (TLC). Analytical thin layer chromatography was performed using MERCK Silica Gel F^{254} TLC glass or alumina plates and visualized by ultraviolet light (UV). Additionally, TLC plates were stained with aqueous potassium permanganate ($KMnO_4$) [1.5 g $KMnO_4$, 200 mL H_2O, 10 g K_2CO_3, 2.5 mL 1M NaOH aq.], cerium ammonium molybdate (CAM) [0.5 g $Ce(NH_4)_2(NO_3)_6$, 12 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 235 mL H_2O, 15 mL conc. H_2SO_4] or ethanolic *p*-anisaldehyde [3.7 mL *p*-anisaldehyde, 135 mL EtOH, 5 mL conc. H_2SO_4, 1.5 mL AcOH]. Concentration under reduced pressure (= *in vacuo*) was performed by rotator evaporation at 40 °C at the appropriate pressure unless otherwise noted. Chromatographic purification was performed as flash chromatography[2] on SILACYCLE

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518-1520.
[2] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

SiliaFlash® P60 (230-400 mesh) silica gel at 0.4-0.8 bar over-pressure. Purified compounds were dried further under high vacuum (0.05 to 0.1 torr). Yields refer to the purified compound.

Analytics: Nuclear Magnetic Resonance (NMR): NMR data was recorded on VARIAN *Mercury* (300 MHz), BRUKER *AV* or *DRX* (400 MHz), BRUKER *DRX* or *DRXII* (500 MHz) or BRUKER *AVIII* (600 MHz; cryoprobe) spectrometers. Measurements were carried out at ambient temperature (*ca.* 22 °C). Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.16 ppm, methanol-d4 at 3.31 and 49.0 ppm), unless otherwise noted. The data is reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with broadband ^{1}H-decoupling. Service measurements were performed by the NMR service team of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by Mr. RENÉ ARNOLD, Mr. RAINER FRANKENSTEIN, Mr. STEPHAN BURKHARDT and Mr. PHILIPP ZUMBRUNNEN under the direction of Dr. MARC-OLIVIER EBERT.

Infrared (IR): IR data was recorded on a PERKIN ELMER *Spectrum TWO FT-IR (UATR)* instrument as thin films. Absorptions are given in wavenumbers (cm^{-1}).

High Resolution Mass Spectrometry (HRMS): HRMS analyses were performed as EI measurements on a WATERS MICROMASS *AutoSpec Ultima* instrument at 70 eV or as ESI measurements on a BRUKER DALTONICS *maXis ESI-QTOF* instrument or as ESI/MALDI measurements on a BRUKER DALTONICS *solariX* instrument by the mass spectrometry service of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by Mr. LOUIS BERTSCHI, Mr. OSWALD GRETER and Mr. ROLF HÄFLIGER under direction of Dr. XIANGYANG ZHANG.

Optical Rotations: Optical Rotations were measured on a Jasco *DIP-2000* polarimeter at the sodium D line in 10 cm path length cells with 2 mL of volume, and are reported as $[a]_D^T$ (concentration in g/100 mL, solvent).

2 Analysis of the Spectroscopic Database of Trichlorinated Hexane-1,3-Diols

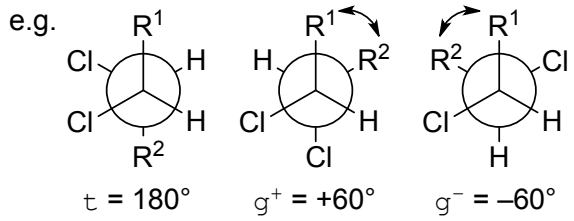
Number of Possible Conformers

$$\frac{a^b \times c^d}{e} = \frac{3^7 \times 2^5}{2} = 34992$$

a: number of staggered conformations per bond
b: number of considered bonds (C10 to C17)
c: number of configurations per stereocenter
d: number of considered stereocenters
e: enantiomers

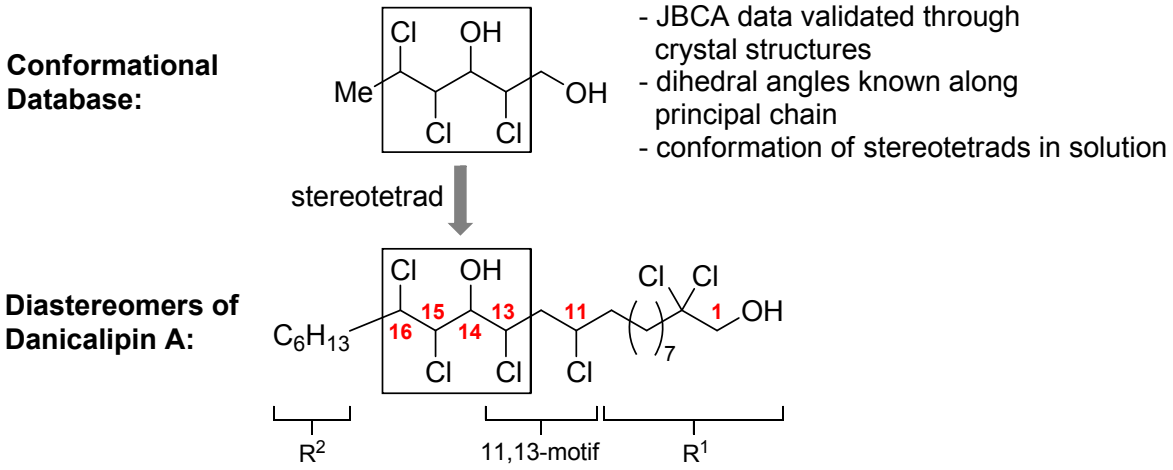
Definition of t, g⁺ and g⁻

For reasons of simplification, the angles in the principle chain (carbon backbone) are considered (t = 180°, g⁺ = +60°, g⁻ = –60°).

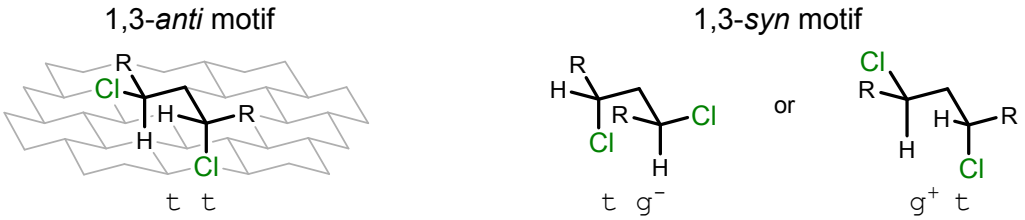


Principle of the Analysis

A conformational database was used to identify interesting danicalipin A diastereomers:[3]



Possible conformations of the 1,3-motif:

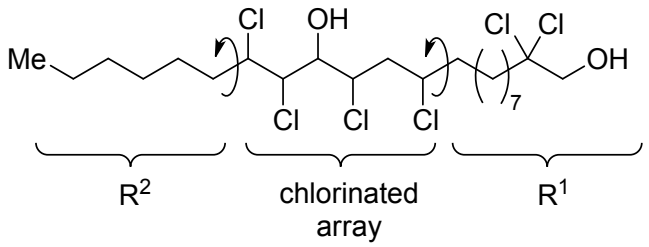


As shown above, a conformational database comprised of defined trichlorinated hexane-1,3-diols was used to predict the conformations of the stereotetrad (C13 to C16) for diastereomeric danicalipin A diols. This analysis was combined with reasonable conformers of the 1,3-motif (`tt` for *anti*, `tg⁻` or `g⁺t` for *syn*).

Despite the proximity to the chlorinated array, rotations around the bonds C10–C11 and C17–C18 cannot be ruled out by the *J*-based configuration analysis and, therefore, were not considered in this preliminary analysis.

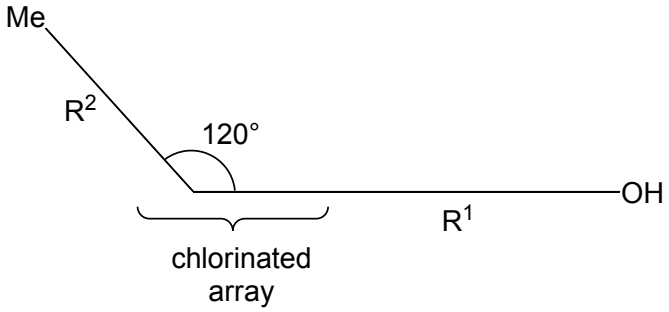
[3] C. Nilewski, R. W. Geisser, M.-O. Ebert, E. M. Carreira, *J. Am. Chem. Soc.* **2009**, *131*, 15866.

Possible rotations around C10–C11 and C17–C18:



The term "overall shape" is defined by the approximate angle between the two alkyl chains (R^1 and R^2), assuming they are completely linear in their ground-state conformation. The results are summarized in Table S1.

Overall shape (R^1 and R^2 are expected to be linear):



Selection Criteria (see Table S1):

- Conformers with angles of 120° (in one plane) were excluded because of their similarity to danicalipin A diol (**4**). This applies to structures 11,16-di-*epi*-danicalipin A (including both possible 11,13-*syn*-motifs), 15-*epi*-danicalipin A, 15,16-di-*epi*-danicalipin A, 11,13,16-tri-*epi*-danicalipin A, and 13,15,16-tri-*epi*-danicalipin A (including both possible 11,13-*syn*-motifs).
- 15,16-di-*epi*-Danicalipin A and 11,15,16-tri-*epi*-danicalipin A diols were excluded. According to Nilewski's database, the stereotetrad (C13 to C16) displays different structures in solution than in solid state – such ambiguities would impede the verification of the conformations.
- 11,15,16-tri-*epi*-Danicalipin A and 13,16-di-*epi*-danicalipin A diols were excluded. The 1,3-*syn* motif (for C12,C13-gauche) does not look favorable in all conformations (*syn*-pentane interaction between Cl ↔ alkyl, alkyl ↔ alkyl).

- Comparison of 11,15,16-tri-*epi*-Danicalipin A, 13,16-di-*epi*-danicalipin A, and 11,15-di-*epi*-danicalipin A diols (for the C12,C13-gauche) reveals that they have a similar overall shape, namely 120° in two planes, probably arising from their g^+tg^+ and g^-tg^- motifs.

  The following differences render 11,15-di-*epi*-danicalipin A diol (**6**) an interesting target: (i) position of both gauche interactions in the middle of the chlorinated array for the potentially more probable conformer (tg^-tg^-t), (ii) the sign of the gauche interactions (g^-) are different from the one in danicalipin A (g^+), (iii) chemically easier to access, (iv) synthetically interesting new all-*syn* motif (question of stability), (v) allows comparison of whether U-shaped or 120° (two planes) is more stable, and (vi) both possible *syn*-motifs would be interesting.
- 11-*epi*-Danicalipin A diol was excluded due to its similarity to danicalipin A diol (**1**) and it bears only one inverted stereocenter (cf. C16-epimer **5**).
- 16-*epi*-danicalipin A diol (**5**) is predicted to be completely linear and it allows direct comparison to the non-chlorinated variant of (+)-danicalipin A (**1**)

Another criterion was the number of gauche interactions in the chlorinated segment, as they correlate with the obtained angles:

- 16-*epi*-danicalipin A diol (**5**): 0 gauche interaction (all-t) (inversion of 1 stereocenter)
- danicalipin A diol (**4**): 1 gauche interaction (g^+)
- 11,15-*di*-epi-danicalipin A diol (**6**): 2 gauche interactions (g^+/g^- or g^-/g^-) (inversion of 2 stereocenters)

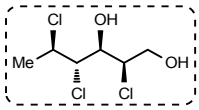
2.1 Overview

Table S1: Overview of conformers for danicalipin A diastereomers.

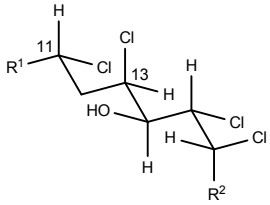
11,13-Motif	Compound (Diols)	Hoffmann Code (C11 → C16)	11,13-*syn* Conformation	Overall Shape
anti	**danicalipin A (4)**	**t t t t g+**		**120°**
syn	11-*epi*-danicalipin A	g+t t t g+	11,12-gauche	120° (two planes)
	11-*epi*-danicalipin A	t g−t t g+	12,13-gauche	U-shaped (same plane)
anti	**16-epi-danicalipin A (5)**	**t t t t t**		**linear**
syn	11,16-di-*epi*-danicalipin A	g+t t t t	11,12-gauche	120°
	11,16-di-*epi*-danicalipin A	t g−t t t	12,13-gauche	120°
anti	15-*epi*-danicalipin A	t t t g−t		120°
syn	**11,15-di-*epi*-danicalipin A**	**g+t t g−t**	**11,12-gauche**	**U-shaped (same plane)**
	11,15-di-*epi*-danicalipin A (6)	**t g−t g−t**	**12,13-gauche**	**120° (two planes)**
anti	15,16-di-*epi*-danicalipin A	t t g+t t		120°
	solid-state	t t t g−g−		90°
syn	11,15,16-tri-*epi*-danicalipin A	g+t g+t t	11,12-gauche	120° (two planes)
		t g−g+t t	12,13-gauche	U-shaped (same plane) *syn*-pentane
		t g+g+t t	12,13-gauche	90° (unlikely)
		g+g+g+t t	both gauche	(unlikely)
	solid-state	g+t t g−g−	11,12-gauche	U-shaped (two planes)
	solid-state	t g−t g−g−	12,13-gauche	U-shaped (two planes)
anti	11,13,16-tri-*epi*-danicalipin A	t t g−t t		120°
syn	13,16-di-*epi*-danicalipin A	g−t g−t t	11,12-gauche	120° (two planes)
	13,16-di-*epi*-danicalipin A	t g+g−t t	12,13-gauche	60° *syn*-pentane
		t g−g−t t	12,13-gauche	90° (unlikely)
		g−g−g−t t	both gauche	(unlikely)
anti	11,13,15,16-tetra-*epi*-danicalipin A	t t t t t		linear
syn	13,15,16-tri-*epi*-danicalipin A	g−t t t t	11,12-gauche	120°
	13,15,16-tri-*epi*-danicalipin A	t g+t t t	12,13-gauche	120°

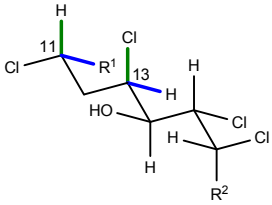
bold: selected
black: 18 low-energy conformers resulting from database and 1,3-motif analyses
grey: potential conformations that lead to unfavorable interactions

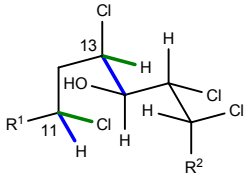
2.1.1 Danicalipin A and 11-*epi*-Danicalipin A Diols



11,13-*anti* **11,13-*syn***







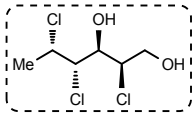
danicalipin A diol (4)
t t t t g$^+$

11-*epi*-danicalipin A diol
g$^+$ t t t g$^+$
(Cl13 ↔ H11)
(R^1 ↔ H13)

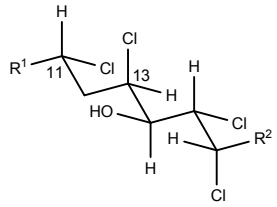
comparable interactions

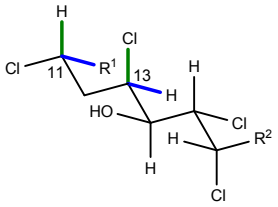
11-*epi*-danicalipin A diol
t g$^-$ t t g$^+$
(Cl11 ↔ H13)
(alkyl ↔ H11)

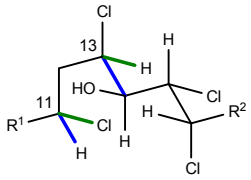
2.1.2 16-*epi*-Danicalipin A and 11,16-Di-*epi*-danicalipin A Diols



11,13-*anti* **11,13-*syn***







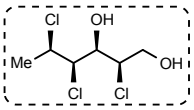
16-*epi*-danicalipin A diol (5)
t t t t t

11,16-di-*epi*-danicalipin A diol
g$^+$ t t t t
(Cl13 ↔ H11)
(R^1 ↔ H13)

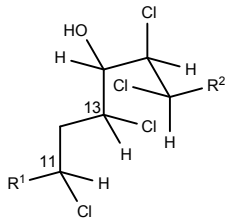
comparable interactions

11,16-di-*epi*-danicalipin A diol
t g$^-$ t t t
(Cl11 ↔ H13)
(alkyl ↔ H11)

2.1.3 15-*epi*-Danicalipin A and 11,15-Di-*epi*-danicalipin A Diols



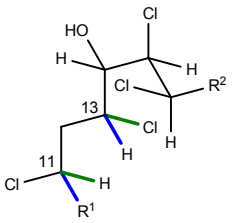
11,13-*anti*



15-*epi*-danicalipin A diol

t t t g⁻ t

11,13-*syn*

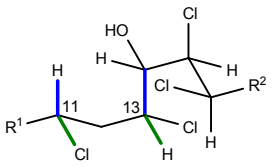


11,15-di-*epi*-danicalipin A diol

g⁺ t t g⁻ t

(Cl13 ↔ H11)

(R^1 ↔ H13)



11,15-di-*epi*-danicalipin A diol (6)

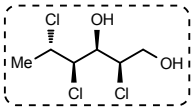
t g⁻ t g⁻ t

(Cl11 ↔ H13)

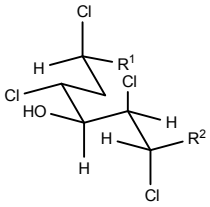
(alkyl ↔ H11)

comparable interactions

2.1.4 15,16-Di-*epi*-danicalipin A and 11,15,16-Tri-*epi*-danicalipin A Diols



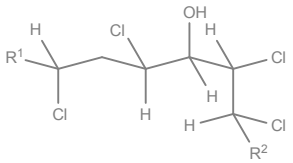
11,13-*anti* (solution-state)



15,16-di-*epi*-danicalipin A diol

t t g^+ t t

11,13-*anti* (solid-state)



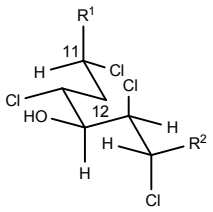
15,16-di-*epi*-danicalipin A diol

t t t g^- g^-

11,13-*syn* (solution-state)

Rotations around stereocenter C12 (rotamers 1, 2, and 3) and minimization of interactions with C11-substituents:

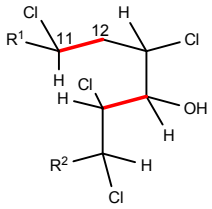
1



11,15,16-tri-*epi*-danicalipin A diol

g⁺ t g⁺ t t

2



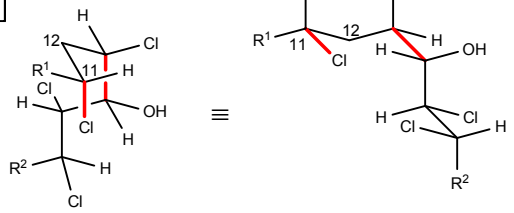
because tg⁻ in **2** leads to an unfavorable *syn*-pentane interaction, rotamer **3** was also modelled

11,15,16-tri-*epi*-danicalipin A diol

t g⁻ g⁺ t t

unfavorable syn-pentane (alkyl ↔ alkyl)

3

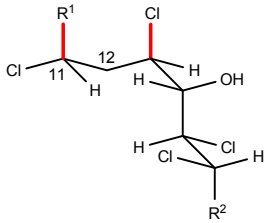


11,15,16-tri-*epi*-danicalipin A diol

t g⁺ g⁺ t t

unfavorable syn-pentane (alkyl ↔ Cl)

rotation around C11 ⟹ minimize unfavorable interaction?



11,15,16-tri-*epi*-danicalipin A diol

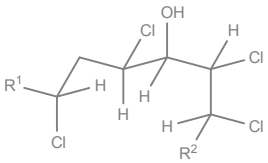
g⁺ g⁺ g⁺ t t

unfavorable syn-pentane (Cl ↔ R¹)

Other possibilities: **g⁺g⁻, g⁻g⁻, g⁻t, g⁻g⁺, tt** ⟹ excluded at the outset of the analysis because of known unfavorable 1,3-motifs

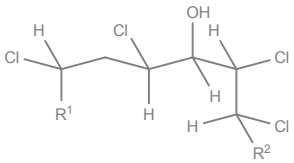
The analysis suggests a clear preference for conformer **1.**

11,13-*syn* (solid-state)



11,15,16-tri-*epi*-danicalipin A diol

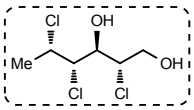
t g⁻ t g⁻ g⁻



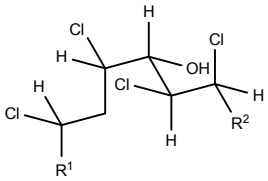
11,15,16-tri-*epi*-danicalipin A diol

g⁺ t t g⁻ g⁻

2.1.5 11,13,16-Tri-*epi*-danicalipin A and 13,16-Di-*epi*-danicalipin A Diols



11,13-*anti*



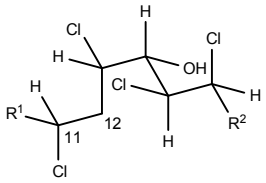
11,13,16-tri-*epi*-danicalipin A diol

t t g⁻ t t

11,13-*syn*

Rotations around stereocenter C12 (rotamers 1,2 and 3) and minimization of interactions with C11-substituents:

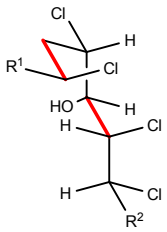
1



13,16-di-*epi*-danicalipin A diol

g⁻ t g⁻ t t

2



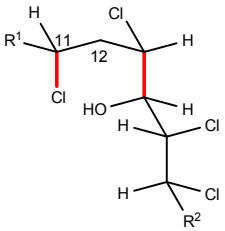
because tg⁺ in **2** leads to an unfavorable *syn*-pentane interaction, rotamer **3** was also modelled

13,16-di-*epi*-danicalipin A diol

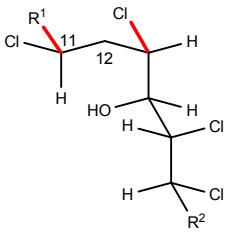
t g⁺ g⁻ t t

unfavorable syn-pentane (alkyl ↔ alkyl)

3



rotation around C11 ⟹ minimize unfavorable interaction?



13,16-di-*epi*-danicalipin A diol

t g⁻ g⁻ t t

unfavorable syn-pentane (Cl ↔ alkyl)

13,16-di-*epi*-danicalipin A diol

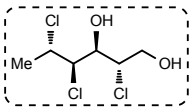
g⁻ g⁻ g⁻ t t

unfavorable syn-pentane (Cl ↔ R¹)

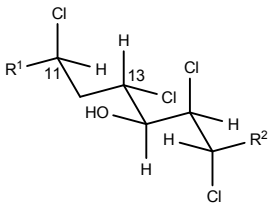
Other possibilities: **g⁺t, g⁺g⁺, g⁺g⁻, g⁻g⁺, tt** ⟹ excluded at the outset of the analysis because of known unfavorable 1,3-motifs

The analysis suggests a clear preference for conformer **1**.

2.1.6 11,13,15,16-Tetra-*epi*-danicalipin A and 13,15,16-Tri-*epi*-danicalipin A Diols



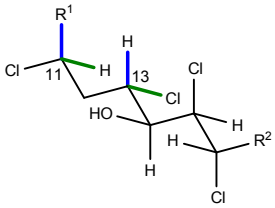
11,13-*anti*



11,13,15,16-tetra-*epi*-danicalipin A diol

t t t t t

11,13-*syn*

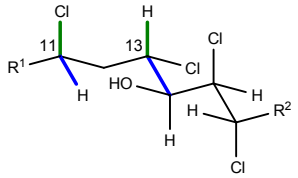


13,15,16-tri-*epi*-danicalipin A diol

g⁻ t t t t

(Cl13 ↔ H11)

(R¹ ↔ H13)



13,15,16-tri-*epi*-danicalipin A diol

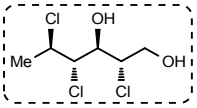
t g⁺ t t t

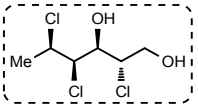
(Cl11 ↔ H13)

(alkyl ↔ H11)

comparable interactions

2.1.7 13-*epi*-Danicalipin A and 13,15-Di-*epi*-danicalipin A Diols





These two diastereomers were not included in the analysis because they showed conformational equilibria in the spectroscopic database.

3 Computational Analysis of 1, 2, 3, 4, 5, and 6

3.1 General Remarks

Conformational Search: All conformational searches were performed using the Monte Carlo Multiple Minimum (MCMM)[4] search protocol as implemented by MacroModel[5] 9.9 with an implicit solvation model in $CHCl_3$ and an OPLS-2005 force field. Conformational spaces were generated employing a Polak-Ribière Conjugate gradient (PRCG) method with a convergence criteria of 0.005 and a maximum of 5000 iterations. All conformations obtained from mixed torsional/low mode sampling (maximum of 5000 steps, 1000 steps per rotable bond) within 2 kcal of the lowest energy conformer were retained to verify sufficient sampling of the conformational space. The results of these conformational searches were manually analyzed. Only conformers without gauche interactions in the C4 to C9 region and C18 to C22 were retained (no experimental evidence can be obtained for these regions and high flexibility is expected), while not omitting any possible conformations in the C11 to C16 region. Duplicated structures were deleted and all retained conformations were considered for further optimization at the DFT level.

DFT calculation: All DFT calculations were performed using the Gaussian 09 program package,[6] and the M06-2X hybrid funtional.[7] All calculations were performed using an SMD solvation model[8] (for **1**, **2**, **3** methanol was used as solvent; for **4**, **5**, **6** chloroform was used). Previously obtained structures were optimized with the Los Alamos National Laboratory 2 double ζ (LANL2DZ) Effective Core Potential and associated basis set[9] augmented with diffuse and polarization functions for Cl (= LANL2DZpd),[10] and a standard 6-31+G**[11] for the remaining elements. Geometry

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[4] G. Chang, W. C. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379.

[5] Macromodel, Version 9.9, Schrödinger, LLC, New York, NY, 2014.

[6] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S.Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[7] Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[8] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.

[9] P. J. Hay and W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270; P. J. Hay and W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 284; P. J. Hay and W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.

[10] C. E. Check, T. O. Faust, J. M. Bailey, B. J. Wright, T. M. Gilbert, L. S. Sunderlin, *J. Phys. Chem. A* **2001**, *105*, 8111.

[11] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724; W. J. Hehre, R. Ditchfield, J. A. Pople, *ibid.* **1972**, *56*, 2257; P. C. Hariharan, J. A. Pople, *Theor. Chem. Acc.* **1973**, *28* 213; P. C. Hariharan, J. A. Pople, *Mol. Phys.* **1974**, *27*, 209; M. S. Gordon, *Chem. Phys. Lett.* **1980**, *76*, 163; M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, D. J. DeFrees, J. A. Pople, M. S. Gordon, *J. Chem. Phys.* **1982**, *77*, 3654; R. C. Binning Jr. and L. A. Curtiss, *J. Comp. Chem.* **1990**, *11*, 1206; J.-P. Blaudeau, M. P. McGrath, L. A. Curtiss, L. Radom, *J. Chem. Phys.* **1997**, *107*, 5016; V. A. Rassolov, J. A. Pople, M. A. Ratner, T. L. Windus, *ibid.* **1998**, *109*, 1223; V. A. Rassolov, M. A. Ratner, J. A. Pople, P. C. Redfern, L. A. Curtiss, *J. Comp. Chem.* **2001**, *22*, 976; G. A. Petersson, A. Bennett, T. G. Tensfeldt, M. A. Al-Laham, W. A. Shirley, J. Mantzaris, *J. Chem. Phys.* **1988**, *89*,

optimizations were carried out without any constraints. All calculations were performed with a quadratically converging self-consistent field[12] with an addional step in case no convergence was met. In case that the structures did not converge, the convergence criterion had to be set to 10^{-7}. Ground state minima were confirmed by frequency calculations, yielding no imaginary frequency unless otherwise noted. Electronic energies obtained, *E*, were converted to relative free energies G^0 at 273.15 K and 1 atm by using zero point energy and thermal energy corrections obtained in the frequency calculation. Optimized geometries for each conformer were then subjected to single point calculations at a M06-2X/6-311++G**/LANL2DZpd(Cl)/SMD(chloroform/methanol) level of theory. The free energy values discussed in the manuscript were derived from the electronic energy values obtained at the M06-2X/6-311++G**/LANL2DZpd(Cl)/SMD(chloroform/methanol)//M06-2X/6-31+G**/LANL2DZpd(Cl)/SMD(chloroform/methanol) level, E_{SP}, according to the following equation: $G^0_{final} = E_{SP} + G^0 - E$. All energies are reported in hartrees/particle, unless otherwise noted. Only conformers with no gauche interactions within the C4 to C9 region and C18 to C22 were considered.

3.2 Overview

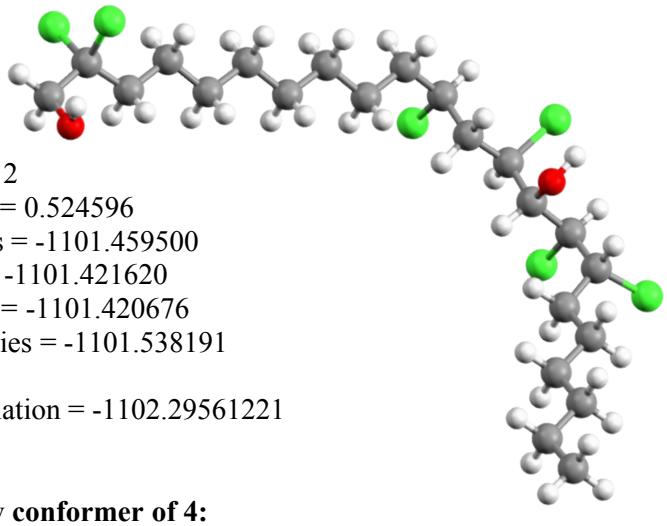
3.2.1 Conformational Analysis of danicalipin A diol (4)

Table S2: Energy differences for different conformers of **4** obtained from DFT calculations.

$\Delta\Delta G^0$ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00	g- t t t t g+ t	g+t
1.12	t t t t t g+ t	g-t
1.58	t t t t t g+ t	g-t
1.93[a)]	t t t t t g+ t	tt
2.49	g+ t t t t g+ t	g-t
2.88	g- t t t t g+ t	tg+
3.03[a,b)]	t t t t t g+ t	tt
3.43	g+ t t t t g+ t	tt

a) additional distortion of dihedral angles leads to different energies;
b) imaginary frequency = 1 (-8.7 cm^{-1}).

2193; G. A. Petersson, M. A. Al-Laham, *ibid.* **1991**, *94*, 6081.
[12] G. B. Bacskay, *Chem. Phys.* **1981**, *61*, 385.



Data from optimization:
Electronic energy = -1102.06278729
Zero-point correction = 0.603287
Thermal correction to Energy = 0.641168
Thermal correction to Enthalpy = 0.642112
Thermal correction to Gibbs Free Energy = 0.524596
Sum of electronic and zero-point Energies = -1101.459500
Sum of electronic and thermal Energies = -1101.421620
Sum of electronic and thermal Enthalpies = -1101.420676
Sum of electronic and thermal Free Energies = -1101.538191

Electronic energy from single point calculation = -1102.29561221

Cartesian coordinates for lowest energy conformer of 4:

C	6.03180400	6.47711100	0.37302600
C	6.61196500	5.19736600	-0.22690400
C	6.68337000	7.73776300	-0.18970300
C	5.97308200	3.92669200	0.32984900
C	6.55838800	2.65211500	-0.27609200
C	5.90464100	1.39285800	0.29019900
C	6.37929200	0.10718500	-0.36781500
C	5.62931000	-1.16611100	0.02753400
Cl	8.15023800	-0.14801700	-0.05916400
Cl	5.71485700	-1.45350100	1.80539400
C	4.14773700	-1.11981500	-0.39792200
O	4.04624100	-0.70448600	-1.74061900
C	3.38628200	-2.42557100	-0.14530600
Cl	4.14038500	-3.75493500	-1.13761400
C	1.91253800	-2.28555500	-0.49599600
C	1.06608400	-3.52830000	-0.26948200
C	-0.37832800	-3.37561500	-0.73108400
Cl	1.10646300	-3.97478700	1.50349700
C	-1.13901300	-2.18219900	-0.15600900
C	-2.62207100	-2.22331000	-0.52247100
C	-3.40609300	-1.03001600	0.01912500
C	-4.89407000	-1.08705500	-0.32182700
C	-5.68110200	0.09625800	0.23716800
C	-7.16844600	0.03564600	-0.11018200
C	-7.92426500	1.22064400	0.48233900
C	-9.41863100	1.28570900	0.20752600
Cl	-9.72408500	1.35182900	-1.57626700
Cl	-10.25679900	-0.16589700	0.86526500
C	-10.09458200	2.50983900	0.84415200
O	-9.52042800	3.71147600	0.40115600
H	4.95060300	6.50597100	0.18415200
H	6.15677800	6.45277300	1.46352100
H	7.69499400	5.17003300	-0.04146300
H	6.48436300	5.21971700	-1.31856600
H	6.25608400	8.64374400	0.25134600
H	6.54646700	7.79780900	-1.27521800
H	7.76062200	7.74440000	0.01034800
H	4.88988800	3.95444400	0.14557600
H	6.10409100	3.90232900	1.42069100

H	7.63834000	2.62510300	-0.08888900
H	6.42393000	2.66973400	-1.36656200
H	4.82146500	1.45756000	0.12164800
H	6.06334100	1.33257400	1.37289600
H	6.30088400	0.19194300	-1.45387000
H	6.12362900	-2.02471500	-0.43387100
H	3.63526200	-0.35557300	0.19797100
H	4.36051600	-1.41425100	-2.32305900
H	3.51184200	-2.74132900	0.89142000
H	1.80997200	-2.00124200	-1.55045300
H	1.51936600	-1.45819000	0.10720400
H	1.51599800	-4.39147400	-0.76286400
H	-0.34581600	-3.29884200	-1.82660200
H	-0.91181600	-4.30398900	-0.49675700
H	-1.03717000	-2.17172600	0.93711500
H	-0.70374700	-1.24508500	-0.52634500
H	-2.72752800	-2.26285000	-1.61590500
H	-3.06139800	-3.15218100	-0.13347800
H	-3.28635600	-0.98460300	1.11074400
H	-2.97744700	-0.10001700	-0.38014100
H	-5.01647000	-1.12205400	-1.41344200
H	-5.31912900	-2.02189500	0.06925500
H	-5.56250700	0.12633400	1.32917200
H	-5.25541400	1.03254900	-0.14949300
H	-7.28775000	0.02763900	-1.20014500
H	-7.59186000	-0.90290700	0.26730200
H	-7.81476300	1.22590000	1.57453500
H	-7.50524200	2.16311000	0.11163000
H	-9.92599100	2.44866900	1.92362600
H	-11.17221800	2.46854400	0.64963400
H	-9.84767200	3.91255000	-0.48661300

3.2.2 Conformational Analysis of 16-*epi*-danicalipin A diol (5)

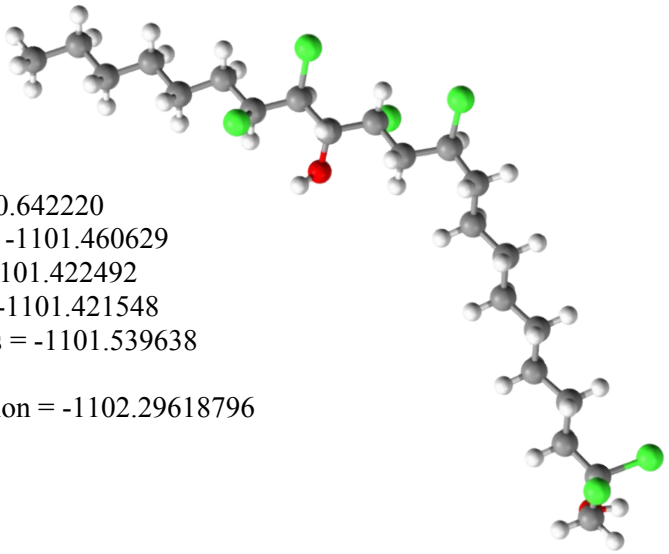
Table S3: Energy differences for different conformers for **5** obtained from DFT calculations.

ΔΔG⁰ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00[a1)]	g+ t t t t t t	g+t
0.31	t t t t t t t	g-t
0.38[a1)]	g+ t t t t t t	g+t
0.45	t t t t t t g+	tt
0.47	g- t t t t t t	g-g-
0.88[a2)]	g- t t t t t t	g-t
0.93[a3)]	t t t t t t t	g+t
0.98[a3)]	t t t t t t t	g+t
1.01[a2)]	g- t t t t t t	g-t
1.45[a2)]	g- t t t t t t	g-t
1.64[a4)]	t t t t t t t	tt
1.67	g- t t t t t t	tt
1.81	g- t t t t t t	tg-
2.18	g- t t t t t g+	tt
2.50	g+ t t t t t t	tt
3.03	t t t t t t t	tg-
3.29[a4)]	t t t t t t t	tt

a) additional distortion of dihedral angles leads to different energies.

Data from optimization:
Electronic energy = -1102.06376784
Zero-point correction = 0.603139
Thermal correction to Energy = 0.641276
Thermal correction to Enthalpy = 0.642112
Thermal correction to Gibbs Free Energy = 0.642220
Sum of electronic and zero-point Energies = -1101.460629
Sum of electronic and thermal Energies = -1101.422492
Sum of electronic and thermal Enthalpies = -1101.421548
Sum of electronic and thermal Free Energies = -1101.539638

Electronic energy from single point calculation = -1102.29618796



Cartesian coordinates for lowest energy conformer of 5:

C	-11.91144300	-2.72431700	-0.05935800
C	-10.43035800	-2.85315100	-0.41139500
C	-9.59355500	-1.67651500	0.08589700
C	-8.11068100	-1.80247400	-0.25972000
C	-7.30721700	-0.60641700	0.24466400
C	-5.83207000	-0.64876400	-0.12650000
C	-5.09530500	0.66449500	0.12077900
C	-12.74166300	-3.90171300	-0.56312300
C	-3.62334900	0.63523500	-0.32345100
Cl	-5.20084100	1.16231400	1.84894500
Cl	-5.00793800	-2.01828100	0.73321000
C	-2.87396600	1.95576100	-0.12915800
C	-1.41122700	1.82932300	-0.52514300
Cl	-3.68243900	3.25014100	-1.12870000
C	-0.57329700	3.08488800	-0.34116100
C	0.86023300	2.93984600	-0.83819000
Cl	-0.56956100	3.55833600	1.42547500
C	1.64404000	1.75765100	-0.27061000
C	3.12197900	1.81907800	-0.65419000
C	3.92313400	0.62201600	-0.14694200
C	5.40945400	0.71040300	-0.48823700
C	6.20691900	-0.49836900	-0.00343700
C	7.70104700	-0.38152200	-0.30467300
C	8.45273000	-1.63764600	0.14236500
C	9.97206800	-1.53082700	0.06612200
Cl	10.67948800	-3.14205300	0.50771400
Cl	10.57509000	-0.33187600	1.26516200
C	10.48555800	-1.15449300	-1.32595400
O	-3.55374200	0.18305000	-1.65695500
O	11.88004800	-1.10472000	-1.43171700
H	-12.30238600	-1.78956900	-0.48231700
H	-12.01578100	-2.63929500	1.03027000
H	-10.03630000	-3.78633600	0.01522600
H	-10.32386700	-2.94139600	-1.50200600
H	-9.98923700	-0.74449300	-0.34186600
H	-9.70316400	-1.58897200	1.17578100
H	-7.99360700	-1.88888700	-1.34882400
H	-7.71197100	-2.72646900	0.17648400
H	-7.40753900	-0.51498500	1.33193700
H	-7.71464400	0.31548500	-0.19397000
H	-5.70964900	-0.87877000	-1.18809700
H	-5.63243500	1.43546300	-0.44166900
H	-12.38386700	-4.84463600	-0.13483100
H	-13.79780900	-3.79331900	-0.29739600
H	-12.67873600	-3.98761600	-1.65369700
H	-3.09362500	-0.10920700	0.28247000
H	-2.96871900	2.29727800	0.90214100
H	-0.99055900	1.01434000	0.07638200
H	-1.33782600	1.53116200	-1.57812100
H	-1.04551400	3.93568200	-0.83537400
H	1.39152000	3.87496700	-0.62637200
H	0.80120000	2.85181600	-1.93176300
H	1.21684600	0.81464500	-0.63516700
H	1.55511500	1.74641200	0.82359300
H	3.55787700	2.74431600	-0.25278600

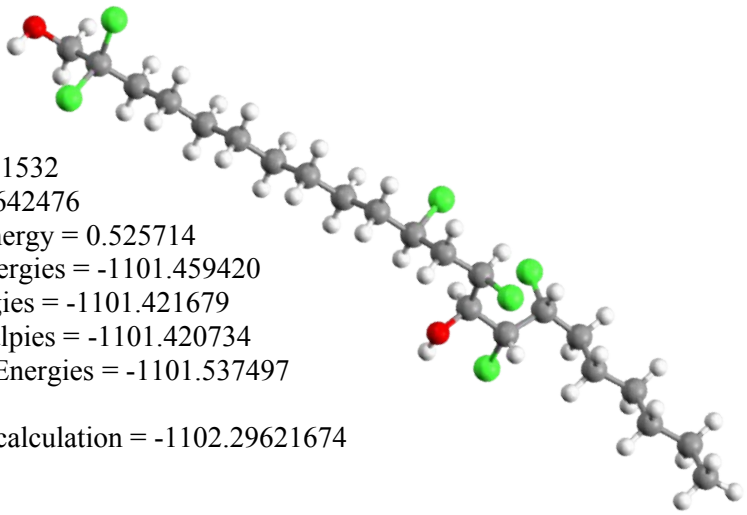
H	3.21329600	1.88065900	-1.74792600
H	3.50637500	-0.30188300	-0.57223600
H	3.80636300	0.54313000	0.94293300
H	5.82895300	1.62370200	-0.04372600
H	5.52745200	0.81118600	-1.57633000
H	5.80866500	-1.40951700	-0.47137200
H	6.06747600	-0.61692800	1.07967500
H	8.10594300	0.50056600	0.20648000
H	7.83917200	-0.22259100	-1.38137700
H	8.16081500	-2.48730000	-0.48619500
H	8.18539000	-1.88965100	1.17426500
H	10.11618700	-0.15219500	-1.55719000
H	10.04159700	-1.86560700	-2.03679100
H	-3.87755500	0.88015400	-2.24920500
H	12.24132000	-1.99878800	-1.35388100

3.2.3 Conformational Analysis of 11,15-di-*epi*-danicalipin A diol (6)

Table S4: Energy differences for different conformers for **6** obtained from DFT calculations.

ΔΔG⁰ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00[a1)]	t t g- t g- t g-	tt
0.07	t t g- t g- t t	g-t
0.29	t t g- t g- t t	g-g-
0.57	t t g- t g- t g-	tg+
0.61	t t g- t g- t t	g+t
1.00[a2,b1)]	t t g- t g- t g-	g-t
1.10[c)]	t t g- t s+ g- t	g+t
1.12	g+ t g- t g- t t	tt
1.35	t t g- t g- t t	tg+
1.69[a3)]	t t g- t g- t t	tt
1.87[a2,b2)]	t t g- t g- t g-	g-t
2.35	g- t g- t g- t g-	tt
2.77	t t g- t g- t t	tg-
2.98[a1,b3)]	t t g- t g- t g-	tt
3.00[a4,b4)]	g- t g- t g- t t	tt
3.01	g+ t g- t g- t t	g-t
3.58[a3)]	t t g- t g- t t	tt
3.63[a4)]	g- t g- t g- t t	tt
4.24	t t g- t g- g- t	g+t
5.18	t t g- t g- g- t	tt

a) additional distortion of dihedral angles leads to different energies; b) imaginary frequency = 1 (1: -34.7 cm^{-1}; 2: -38.7 cm^{-1}; 3: -6.0 cm^{-1}; 4: -21.2 cm^{-1}); c) s-conformation describes an angle that is <60° and closer to a staggered conformation.



Data from optimization:
Electronic energy = -1101.537497
Zero-point correction = 0.603791
Thermal correction to Energy = 0.641532
Thermal correction to Enthalpy = 0.642476
Thermal correction to Gibbs Free Energy = 0.525714
Sum of electronic and zero-point Energies = -1101.459420
Sum of electronic and thermal Energies = -1101.421679
Sum of electronic and thermal Enthalpies = -1101.420734
Sum of electronic and thermal Free Energies = -1101.537497

Electronic energy from single point calculation = -1102.29621674

Cartesian coordinates for lowest energy conformer of 6:

C	12.07151000	-0.07794800	0.48094400
C	10.60594500	0.33997900	0.58868100
C	9.64831200	-0.66964500	-0.04061300
C	8.18239500	-0.25195600	0.07037500
C	7.24937600	-1.27965300	-0.57430900
C	5.81392000	-0.78149800	-0.68620500
C	5.17681900	-0.33881900	0.62443400
C	13.02297100	0.94892300	1.08981000
C	3.70729200	0.10053300	0.54981100
Cl	5.28920000	-1.64785900	1.87243400
Cl	4.79791100	-2.04957200	-1.49352400
C	3.43512800	1.13249600	-0.54327500
C	2.01573800	1.69341400	-0.49083600
Cl	4.58765300	2.53264000	-0.41593400
C	0.91723200	0.63886700	-0.48111700
C	-0.47408500	1.25479400	-0.47915500
Cl	1.10902600	-0.44560600	-1.94077600
C	-1.60515100	0.24489400	-0.29989800
C	-2.98274300	0.90448600	-0.26821700
C	-4.11473800	-0.10437400	-0.07939800
C	-5.50082000	0.53708900	-0.07221200
C	-6.62655700	-0.48091400	0.10314000
C	-8.01268700	0.16280800	0.09584200
C	-9.11389100	-0.88701800	0.21758100
C	-10.54702700	-0.37223300	0.26164400
Cl	-10.78607700	0.67127800	1.72461200
Cl	-10.90818500	0.62271000	-1.19242000
C	-11.55564200	-1.52402600	0.33920500
O	-12.89503000	-1.12146600	0.36647300
O	3.28631900	0.65444300	1.77434600
H	12.20675800	-1.04734400	0.97812300
H	12.32423600	-0.23343200	-0.57610500
H	10.47169100	1.31770800	0.10436800
H	10.34603000	0.47958100	1.64752300
H	9.78218100	-1.64895400	0.43949100
H	9.90704300	-0.80318700	-1.09993400
H	8.04438000	0.72712900	-0.41015100
H	7.92896900	-0.12572300	1.13120000
H	7.26823200	-2.21820400	-0.01007400
H	7.59631100	-1.50308800	-1.58930500
H	5.78480800	0.07869000	-1.36187000
H	5.76741400	0.48844000	1.02579200
H	14.06652500	0.62963600	1.00700900
H	12.92777000	1.91732600	0.58606900
H	12.80418600	1.10477000	2.15206500
H	3.10497500	-0.78150900	0.28703900
H	3.63349200	0.68639600	-1.51930500
H	1.90392500	2.27942100	0.42709200
H	1.87181300	2.36386900	-1.34481000
H	1.02960300	-0.03396900	0.37343700
H	-0.61313900	1.82792300	-1.40478600
H	-0.49488300	1.97365400	0.35143200
H	-1.44510800	-0.31131400	0.63434500
H	-1.57557300	-0.48928000	-1.11417400
H	-3.14141800	1.45620900	-1.20529700

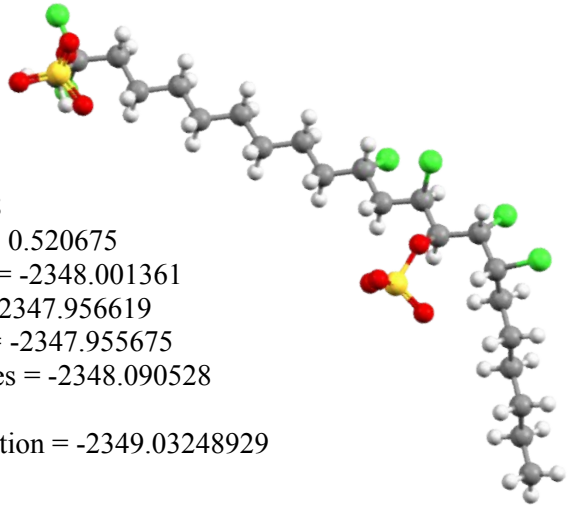
H	-3.01783200	1.64686300	0.54145300
H	-3.96145700	-0.64839000	0.86337500
H	-4.06687500	-0.85374500	-0.88202600
H	-5.65212200	1.08390000	-1.01333900
H	-5.55560200	1.28230300	0.73366700
H	-6.48086000	-1.02580400	1.04620400
H	-6.56670000	-1.22659600	-0.70191500
H	-8.14519400	0.72805000	-0.83361300
H	-8.08873100	0.87990700	0.92210100
H	-8.96551200	-1.47847000	1.12999600
H	-9.06022600	-1.57926400	-0.63260700
H	-11.42160600	-2.13452000	-0.55856500
H	-11.28873700	-2.12689700	1.21747900
H	-13.08224000	-0.68245600	1.20800800
H	3.32139300	-0.02569200	2.46198200

3.2.4 Conformational Analysis of danicalipin A (1)

Table S5: Energy differences for different conformers for **1** obtained from DFT calculations.

ΔΔG⁰ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00	t t t t t g+ t	g+g+
2.02	g+ t t t t g+ t	g+t
2.33	t t t t t g+ t	g-t
2.66[a)]	g- t t t t g+ t	g-t
3.02	g+ t t t t g+ t	g-t
3.17	t t t t t g+ t	g+t
3.18	g- t t t t g+ t	g+t

a) imaginary frequency = 1 (-10.3 cm^{-1}).



Data from optimization:
Electronic energy = -2348.61120273
Zero-point correction = 0.609842
Thermal correction to Energy = 0.654584
Thermal correction to Enthalpy = 0.655528
Thermal correction to Gibbs Free Energy = 0.520675
Sum of electronic and zero-point Energies = -2348.001361
Sum of electronic and thermal Energies = -2347.956619
Sum of electronic and thermal Enthalpies = -2347.955675
Sum of electronic and thermal Free Energies = -2348.090528

Electronic energy from single point calculation = -2349.03248929

Cartesian coordinates for lowest energy conformer of 1:

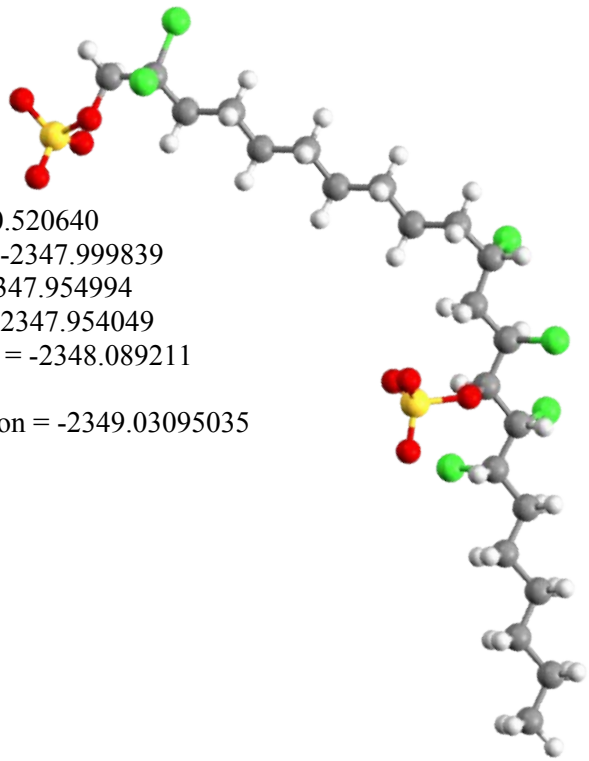
C	-10.97968200	3.38083100	-2.69614600
C	-10.60130600	2.69085200	-1.38673100
C	-12.04688600	4.45576800	-2.50720100
C	-9.51361600	1.63236900	-1.55726200
C	-9.13517800	0.94942800	-0.24442700
C	-8.04646900	-0.10407500	-0.44061700
C	-7.54213000	-0.70128500	0.86361500
C	-6.29217600	-1.57565300	0.78022400
Cl	-8.86706600	-1.68477500	1.64129900
C	-5.00530800	-0.77736400	0.48672000
Cl	-6.50292900	-2.87079900	-0.46080600
C	-3.75900000	-1.64847400	0.30411200
C	-2.50312000	-0.82551200	0.07537700
Cl	-3.53641000	-2.73181100	1.74726700
C	-1.23494200	-1.62135900	-0.19199500
C	-0.03242500	-0.71760900	-0.41286100
Cl	-1.48704500	-2.68650500	-1.66331700
C	1.29022100	-1.45148200	-0.61584700
C	2.48244900	-0.49722700	-0.66005300
C	3.81104200	-1.21514400	-0.88935200
C	5.01022600	-0.26912200	-0.90252800

C	6.34055700	-0.99386700	-1.09584000
C	7.53571200	-0.04109700	-1.10714700
C	8.85219500	-0.81299200	-1.19197600
C	10.08845500	0.06873200	-1.31527600
C	10.18868800	1.17402100	-0.26923300
Cl	10.12597500	0.89063800	-2.91943000
Cl	11.55895000	-0.97630900	-1.19927200
O	10.08615600	0.54403400	1.00446600
S	9.69300100	1.54019900	2.25322100
O	9.74293900	0.61275000	3.38851700
O	10.73187100	2.58272200	2.25529900
O	8.34978500	2.05176000	1.93453600
O	-4.81111500	0.08843200	1.60800500
S	-4.81794200	1.72474900	1.35822200
O	-6.18821200	2.04905000	0.93283300
O	-3.81244900	1.97457100	0.31611600
O	-4.45840100	2.20330300	2.69715400
H	-10.08060700	3.82934000	-3.13913900
H	-11.33731700	2.62836300	-3.41156900
H	-11.49719300	2.22695100	-0.94968000
H	-10.25934200	3.44724900	-0.66592600
H	-12.30290500	4.94055700	-3.45488900
H	-12.96635600	4.02758700	-2.09185300
H	-11.70045700	5.23297600	-1.81666100
H	-8.61888200	2.09964100	-1.99239000
H	-9.85266300	0.87426700	-2.27756800
H	-10.02663700	0.48330600	0.19372700
H	-8.78261400	1.70286100	0.47244900
H	-7.18911500	0.36421900	-0.94047900
H	-8.40520700	-0.90490900	-1.09686700
H	-7.33221900	0.08700700	1.58884300
H	-6.15725500	-2.09798300	1.72903000
H	-5.11077400	-0.19844800	-0.44034500
H	-3.92581000	-2.32746400	-0.53169100
H	-2.69705000	-0.16036100	-0.77468800
H	-2.31348000	-0.19309500	0.95020000
H	-1.03585000	-2.33128000	0.61399200
H	0.03811700	-0.08759200	0.48444700
H	-0.23421000	-0.04821700	-1.25911400
H	1.25356400	-2.02889300	-1.54774800
H	1.43091200	-2.17466000	0.19982200
H	2.32672900	0.24360600	-1.45693800
H	2.53253800	0.06478500	0.28296900
H	3.76878200	-1.76309900	-1.84129400
H	3.95453900	-1.96883700	-0.10211300
H	5.04019400	0.29069100	0.04274300
H	4.88004800	0.47435200	-1.70154400
H	6.31832300	-1.56001300	-2.03720100
H	6.47152400	-1.72914300	-0.28987900
H	7.52118400	0.56206600	-0.19069500
H	7.44391500	0.65120600	-1.95378700
H	8.84246300	-1.50403500	-2.04174300
H	8.98078900	-1.40964000	-0.28243500
H	9.35775900	1.87222100	-0.42003400
H	11.14010800	1.70639200	-0.35936600

3.2.5 Conformational Analysis of 16-*epi*-danicalipin A (2)

Table S6: Energy differences for different conformers for **2** obtained from DFT calculations.

$\Delta\Delta G^0$ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00	g- t t t t t t	g+t
0.92	t t t t t t g+	g+t
1.15	t t t t t t t	g+g+
1.34	t t t t t t t	g-t
4.85	t t t t t g- t	g+t
6.69	t t t t t g- g-	g+t



Data from optimization:
Electronic energy = -2348.60985052
Zero-point correction = 0.610011
Thermal correction to Energy = 0.654857
Thermal correction to Enthalpy = 0.655801
Thermal correction to Gibbs Free Energy = 0.520640
Sum of electronic and zero-point Energies = -2347.999839
Sum of electronic and thermal Energies = -2347.954994
Sum of electronic and thermal Enthalpies = -2347.954049
Sum of electronic and thermal Free Energies = -2348.089211

Electronic energy from single point calculation = -2349.03095035

Cartesian coordinates for lowest energy conformer of 2:

C	-12.17268900	3.67447700	0.02938000
C	-10.65085100	3.60586100	0.14140300
C	-10.08603500	2.22285200	-0.17542900
C	-8.56507100	2.15670100	-0.04922400
C	-8.01895200	0.78037600	-0.42011300
C	-6.51849600	0.63714200	-0.21826500
C	-6.00794200	-0.79177400	-0.37229300
C	-12.72281900	5.06692900	0.32679800
C	-4.50944400	-0.94227100	-0.08492400
Cl	-6.37428600	-1.45074200	-2.01013600
Cl	-5.61959100	1.75696200	-1.33421400
C	-3.93645900	-2.34837200	-0.25308100
C	-2.47052900	-2.39623600	0.14873500
Cl	-4.89866600	-3.54225200	0.72657900
C	-1.78697600	-3.74109000	-0.03122200
C	-0.35796900	-3.76917900	0.49561300
Cl	-1.80571000	-4.20100300	-1.80725700
C	0.57085100	-2.68137900	-0.03944800
C	2.00902100	-2.87683400	0.43793200
C	2.95950500	-1.79408300	-0.06856400
C	4.39725900	-1.99186800	0.40690900
C	5.35228600	-0.91483800	-0.10331600
C	6.78525500	-1.12290400	0.38554100
C	7.71731100	-0.03633400	-0.14087800
C	9.17734600	-0.13815500	0.27548500
Cl	9.89443500	-1.69819400	-0.28018700
Cl	9.32958600	-0.06446700	2.07302500
C	10.05457200	0.95452100	-0.33119200
O	-4.33260700	-0.53425300	1.27056600
S	9.86398900	3.48910400	-0.85453700
O	9.35266800	4.60271700	-0.04843800
O	11.32313000	3.48441300	-1.05505100
O	9.10355500	3.22412500	-2.08755300
O	9.55938500	2.20934900	0.12941000
S	-3.33461600	0.72688200	1.66422500
O	-4.24676900	1.84639400	1.94170500
O	-2.46362200	0.92847800	0.49734300
O	-2.65210500	0.20687700	2.85661500
H	-12.47386500	3.36806500	-0.98130000
H	-12.61784500	2.94714900	0.72098700
H	-10.34943500	3.89862300	1.15745300
H	-10.20477100	4.34387200	-0.54042500
H	-10.37670600	1.93892200	-1.19689100
H	-10.53986700	1.48111200	0.49675900
H	-8.27015300	2.40125400	0.98047500
H	-8.11581400	2.91786200	-0.69897700
H	-8.27562700	0.54028600	-1.45818500
H	-8.48917700	0.01758500	0.21631700
H	-6.23543400	0.96676900	0.78559100
H	-6.57571200	-1.40817700	0.33027900
H	-13.81479500	5.09299500	0.25301200
H	-12.44832100	5.38896600	1.33788300
H	-12.32221000	5.80483900	-0.37754600
H	-3.93961600	-0.29430100	-0.76073600
H	-4.06341300	-2.66624600	-1.28885500

H	-1.95254400	-1.63212600	-0.44307800
H	-2.36757400	-2.12040900	1.20617800
H	-2.36431900	-4.53565600	0.44403100
H	-0.43635300	-3.67958500	1.58792900
H	0.06633700	-4.75901700	0.29096900
H	0.54990800	-2.68342000	-1.13761200
H	0.21709200	-1.69418000	0.28492900
H	2.02844500	-2.89127200	1.53698200
H	2.36986500	-3.86054800	0.10592800
H	2.93849300	-1.77942800	-1.16759200
H	2.59907900	-0.81040600	0.26375800
H	4.41769600	-2.00193500	1.50592700
H	4.75566100	-2.97794100	0.07882500
H	5.33845300	-0.90729500	-1.20204400
H	4.99566500	0.07202700	0.22237400
H	6.79704400	-1.12242000	1.48219600
H	7.13962600	-2.10785300	0.05844300
H	7.71050300	-0.03261500	-1.23861300
H	7.36943700	0.94945600	0.18837000
H	9.97108400	0.88143100	-1.42154500
H	11.09699700	0.82661300	-0.02582100

3.2.5 Conformational Analysis of 11,15-di-*epi*-danicalipin A (3)

The procedure decribed above led to structures which were not in agreement with our NMR data. The data for these structures are described in Table S8. Manual conformational analysis was performed. The conformers of interest were drawn in ChemBio3D and subsequently submitted to calculations on the M06-2X/6-311++G**/LANL2DZpd(Cl)/SMD(methanol)//M06-2X/6-31+G**/LANL2DZpd(Cl)/SMD(methanol) level of theory. The converged structures are presented in Table S7. The lowest-energy structure obtained from this method was 3.15 kcal/mol more stable than the lowest-energy structure in Table S8.

Data from DFT calculations obtained from manual conformational analysis:

Table S7: Structures and energies for **3** obtained from manual conformational analysis and DFT calculations.

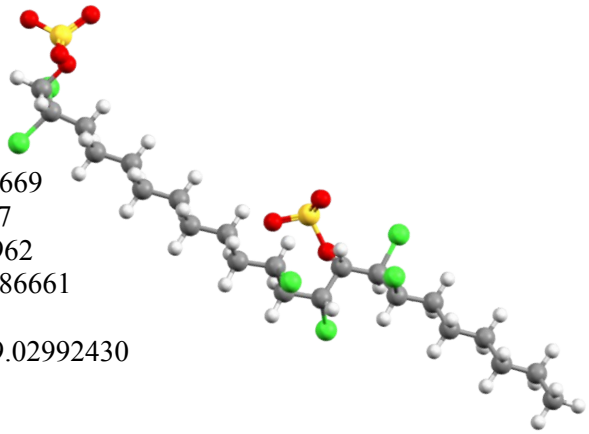
ΔΔG⁰ [kcal/mol]	**conformation C10 to C17**	**C1 to C3**
0.00	t t g- t g- t t	g+ t
0.27[a1)]	t t g- t g- t t	g- t
0.30	g+ t g- t g- t g-	g+ t
0.76	g+ t g- t g- t t	g- t
1.01	g+ t g- t g- t g-	g- t
1.10	g- t g- t g- t g-	g- t
1.22	g- t g- t g- t g-	g+ t
1.67[a2)]	t t g- t g- t g-	g+ t
2.04	g+ t g- t g- t t	g+ t
2.44	g- t g- t g- t t	g+ t
2.72	g- t g- t g- t t	g- t

a) imaginary frequency 1: -19 cm^{-1}, 2: -10 cm^{-1}.

ΔΔG⁰ [kcal/mol]	**conformation C10 to C17**	**C1 to C3**
0.12[b1)]	g+ g+ t t g- t t	g+ t
1.53	g+ g+ t t g- t t	g- t
1.64	t g+ t t g- t t	g+ t
1.98	g+ g+ t t g- t g-	g+ t
2.82	g- g+ t t g- t g-	g- t
3.28[b2)]	t g+ t t g- t g-	g+ t
3.47	t g+ t t g- t t	g- t
3.64	g- g+ t t g- t t	g+ t
3.95	g+ g+ t t g- t g-	g- t
4.12[b3)]	g- g+ t t g- t g-	g+ t
6.19	g- g+ t t g- t t	g- t

b) imaginary frequency 1:-40 cm^{-1}, 2: -20 cm^{-1}, 3: -18 cm^{-1}.

Data from optimization (lowest-energy conformer Table S7):
Electronic energy = -2348.60852270
Zero-point correction = 0.609853
Thermal correction to Energy = 0.654616
Thermal correction to Enthalpy = 0.655560
Thermal correction to Gibbs Free Energy = 0.521862
Sum of electronic and zero-point Energies = -2347.998669
Sum of electronic and thermal Energies = -2347.953907
Sum of electronic and thermal Enthalpies = -2347.952962
Sum of electronic and thermal Free Energies = -2348.086661



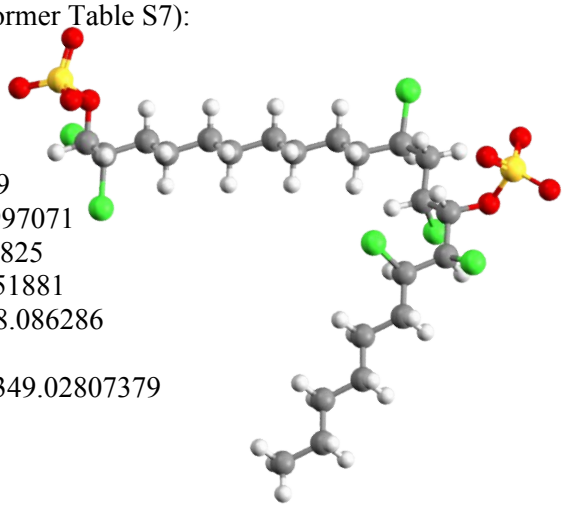
Electronic energy from single point calculation = -2349.02992430

Cartesian coordinates for lowest energy conformer (Table S7) of 3:

C	-12.89344400	2.75258100	-0.25026000
C	-11.42275200	2.65350700	-0.65065500
C	-10.62668000	1.67424100	0.20966400
C	-9.16389100	1.56825700	-0.21733300
C	-8.37088200	0.60645600	0.66394200
C	-6.94502600	0.38353500	0.18281900
C	-6.21651900	-0.75500500	0.88740200
C	-13.67436600	3.73614100	-1.11804300
C	-4.78312700	-1.02076500	0.40775600
Cl	-6.17569600	-0.50116300	2.67367000
Cl	-5.98037500	1.91946400	0.30727100
C	-4.65020800	-1.13091300	-1.11334900
C	-3.26218500	-1.55607900	-1.57928100
Cl	-5.83952300	-2.34637600	-1.76044400
C	-2.13066800	-0.61792200	-1.17926400
C	-0.77844600	-1.13538700	-1.64299400
Cl	-2.44294000	1.04010800	-1.89859000
C	0.40911900	-0.29297700	-1.18618900
C	1.74738000	-0.96908500	-1.47960300
C	2.94475100	-0.10942700	-1.07976700
C	4.28697200	-0.80591100	-1.29527100
C	5.47806100	0.06662600	-0.90497100
C	6.81822100	-0.64999100	-1.06605000
C	7.98082300	0.26668700	-0.69897900
C	9.36663400	-0.36262400	-0.69581000
Cl	9.45177100	-1.68514900	0.53017300
Cl	9.75197800	-1.07247500	-2.30934500
C	10.48200700	0.64095800	-0.41438500
O	10.20109100	1.24074300	0.84658400
O	-4.36474200	-2.23878300	1.01554600
S	-3.00381700	-2.30580800	1.95567100
O	-1.97546800	-2.89381500	1.08168300
O	-2.71485700	-0.91980300	2.35250400
O	-3.43307100	-3.19174900	3.04506000
H	-13.35310000	1.75759200	-0.31811800
H	-12.96154400	3.05647700	0.80272800
H	-10.96219700	3.64975600	-0.58578400
H	-11.35584300	2.34738200	-1.70463100
H	-11.09399500	0.68082700	0.15716100
H	-10.67668200	1.98961200	1.26138400
H	-8.70463100	2.56410200	-0.18166100
H	-9.11189800	1.23018000	-1.26149900
H	-8.85350800	-0.38115300	0.65571600
H	-8.36290000	0.95629100	1.70179200
H	-6.96573200	0.14987100	-0.88554200
H	-6.81355700	-1.65946700	0.74180600
H	-14.72688100	3.78607100	-0.82094500
H	-13.25599700	4.74606800	-1.03950900
H	-13.63880600	3.44183000	-2.17326100
H	-4.14313300	-0.19322200	0.73474700
H	-4.93280100	-0.18072600	-1.57165800
H	-3.03153200	-2.53880900	-1.15426400
H	-3.27534000	-1.65280500	-2.66974100
H	-2.10663000	-0.43538900	-0.10214500
H	-0.78441700	-1.23857900	-2.73581200

H	-0.68527100	-2.14607000	-1.22342000
H	0.32411700	-0.10943300	-0.10570500
H	0.37993200	0.68706700	-1.67844600
H	1.81039200	-1.20587700	-2.55126200
H	1.79253300	-1.92749000	-0.94365200
H	2.85054600	0.16976500	-0.02068500
H	2.92491400	0.82862800	-1.65233100
H	4.38116800	-1.10057000	-2.35011700
H	4.31009600	-1.73466700	-0.70798100
H	5.36463400	0.38834000	0.13953800
H	5.47573100	0.98012100	-1.51570000
H	6.92763500	-0.99360400	-2.10163500
H	6.83025200	-1.54120500	-0.42694400
H	7.82880100	0.68037100	0.30441600
H	8.02743700	1.11433200	-1.39457500
H	11.45262200	0.13546600	-0.39354400
H	10.46736100	1.40034600	-1.20445100
S	11.31867500	2.32293100	1.37841700
O	10.72669800	2.74482300	2.65211900
O	11.36808100	3.36754500	0.34269000
O	12.57066600	1.55881900	1.50476100

Data from optimization (second lowest-energy conformer Table S7):
Electronic energy = -2348.60649509
Zero-point correction = 0.609425
Thermal correction to Energy = 0.653670
Thermal correction to Enthalpy = 0.654614
Thermal correction to Gibbs Free Energy = 0.520209
Sum of electronic and zero-point Energies = -2347.997071
Sum of electronic and thermal Energies = -2347.952825
Sum of electronic and thermal Enthalpies = -2347.951881
Sum of electronic and thermal Free Energies = -2348.086286



Electronic energy from single point calculation = -2349.02807379

Cartesian coordinates for second-lowest energy conformer (Table S7) of 3:

C	-2.67777900	7.96184300	-0.45896800
C	-2.44687900	6.47481100	-0.72130900
C	-3.44302100	5.57520600	0.00652700
C	-3.19398200	4.08807800	-0.23763800
C	-4.20404000	3.21262500	0.49911300
C	-4.00284800	1.72231800	0.26790400
C	-5.16759400	0.85417600	0.72942000
C	-4.97303700	-0.65819100	0.57661500
C	-4.46431800	-1.08834000	-0.79901300
C	-4.33338000	-2.60188300	-0.88939100
C	-3.75320200	-3.08320100	-2.21665000
C	-2.43640100	-2.44346600	-2.63642000
Cl	-5.56974300	-0.47258200	-2.10623800
Cl	-3.54848900	-4.89689000	-2.08488200
Cl	-5.58739800	1.18218900	2.45416100
Cl	-2.45120500	1.17070400	1.04464800
C	-0.05513500	-1.78006600	-2.11067500
C	1.08676200	-1.78596400	-1.09726600
C	2.33154900	-1.05790000	-1.60003800
C	3.47435400	-1.04931200	-0.58753200
C	4.70178700	-0.29477900	-1.09671100
C	5.82282300	-0.29052100	-0.06252000
C	7.07937700	0.48427500	-0.43298000
C	8.13902800	0.48169300	0.66661900
Cl	7.81135300	-0.17820600	-1.94266100
Cl	6.68935200	2.22360800	-0.72067200
C	-1.31239300	-2.48473800	-1.60372000
O	8.46774900	-0.87711200	0.94159900
S	9.88165200	-1.10363200	1.74914300
O	9.85304400	-2.55125600	1.98553100
O	10.93644900	-0.65281100	0.82640500
O	9.76795300	-0.27349000	2.96013800
C	-1.68215400	8.85216700	-1.19749400
O	-6.23177800	-1.27094600	0.83181700
S	-6.41632500	-2.38697300	2.04114900
O	-7.58651100	-1.88203700	2.77113600
O	-5.15787600	-2.37087400	2.80142800
O	-6.66792800	-3.64683600	1.32332400
H	-2.61096900	8.15147300	0.62058500

H	-3.70054500	8.22698700	-0.75828200
H	-2.50650700	6.28403500	-1.80248500
H	-1.42542300	6.20808200	-0.41431800
H	-3.39202700	5.77636700	1.08590100
H	-4.46365000	5.83135800	-0.31085500
H	-3.24625100	3.87689100	-1.31453000
H	-2.17720500	3.83465400	0.08808200
H	-4.17651100	3.42322000	1.57358700
H	-5.21812700	3.44882700	0.14791400
H	-3.86132000	1.54043900	-0.80196200
H	-6.04559200	1.16374900	0.15541500
H	-4.23028200	-1.00465800	1.30364600
H	-3.50180900	-0.60758700	-0.98705300
H	-5.31174600	-3.06272500	-0.72728700
H	-3.67922600	-2.91160900	-0.06451200
H	-4.48844000	-2.96608300	-3.01425600
H	-2.10489300	-2.91704300	-3.56787700
H	-2.66204400	-1.39856800	-2.89420100
H	-0.30499700	-0.74031600	-2.36659000
H	0.28045300	-2.25870900	-3.04150800
H	1.34664800	-2.82429300	-0.84758100
H	0.74431000	-1.31676500	-0.16367300
H	2.06607300	-0.02157000	-1.85285300
H	2.67613300	-1.52761000	-2.53229700
H	3.75464900	-2.08327200	-0.34353600
H	3.12695400	-0.58913000	0.34797000
H	4.41568700	0.73577100	-1.33971500
H	5.05532600	-0.75877200	-2.02548800
H	6.14107600	-1.31737500	0.15206600
H	5.46348700	0.14149000	0.88039600
H	9.02266100	1.03677900	0.33478300
H	7.71399500	0.95054600	1.56060700
H	-1.63346100	-2.00599900	-0.66848000
H	-1.07520500	-3.52791700	-1.35730900
H	-1.86145900	9.91234900	-0.99186700
H	-1.75342300	8.70469400	-2.28117400
H	-0.65327900	8.62186800	-0.89823900

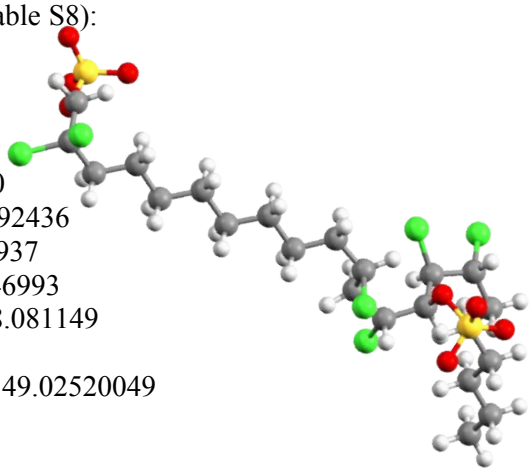
Data from DFT calculations obtained from structures generated by MacroModel:

Table S8: Energy differences for different conformers for **3** obtained from DFT calculations.

$\Delta\Delta G^0$ [kcal/mol]	**conformation C10 to C17**	**conformation C1 to C3**
0.00	g+ t g- g- t g+ g+	g+g+
0.16	t g+ t g- t g+ t	g-t
0.39	t t g- g- t g+ t	g-t
0.41	g- t g- g- t g+ g+	g-t
0.47	t t g- g- t g+ g+	g-t
0.58	t t g- g- t g+ t	g+t
0.65[c)]	t t s+ g- t g+ t	g+t
0.83	g+ t g- g- t g+ g+	g+t
1.16[c)]	t t s+ g- t g+ g+	g-t
1.27	g- t g- g- t g+ g+	g+t
1.31	g- t g- g- t g+ g+	g-g-
1.44	t g+ t g- t g+ g+	g-t
1.48	g+ t s+ g- t g+ g+	g+t
1.62[a1)]	g+ t g- g- t g+ t	g-t
1.64	t t g- t s+ g+ g+	g+t
1.82	t g+ t g- t g+ g+	g+t
1.83	t t s+ g- t g+ g+	g+t
2.19[a2)]	g+ t g- g- t g+ t	g+t
2.62[a2)]	g+ t g- g- t g+ t	g+t
2.98	t t s+ g- t g- t	g-t
3.16[b1)]	g- t g- g- t g+ t	g+t
3.49[a1,b2)]	g+ t g- g- t g+ t	g-t

a) additional distortion of dihedral angles leads to different energies; b) imaginary frequency = 1 (1: -10.4 cm^{-1}; 2: -2.3 cm^{-1}); c) s-conformation describes an angle that is <60° and closer to a staggered conformation.

Data from optimization (lowest-energy conformer Table S8):
Electronic energy = -2348.60330854
Zero-point correction = 0.610872
Thermal correction to Energy = 0.655372
Thermal correction to Enthalpy = 0.656316
Thermal correction to Gibbs Free Energy = 0.522160
Sum of electronic and zero-point Energies = -2347.992436
Sum of electronic and thermal Energies = -2347.947937
Sum of electronic and thermal Enthalpies = -2347.946993
Sum of electronic and thermal Free Energies = -2348.081149



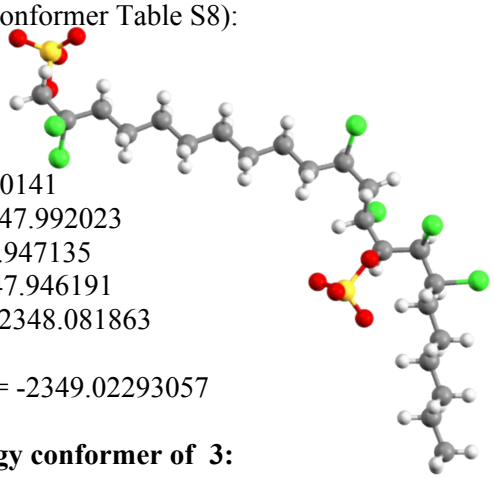
Electronic energy from single point calculation = -2349.02520049

Cartesian coordinates for lowest energy conformer (Table S8) of 3:

C	-10.37425200	3.10878800	2.51476600
C	-9.02506400	3.07362200	1.79923700
C	-8.93755200	1.97411600	0.74354900
C	-7.58320400	1.92329100	0.03794300
C	-7.54613600	0.82007800	-1.01696400
C	-6.27702100	0.73998600	-1.86476100
C	-4.96734800	0.65684300	-1.06952200
C	-10.45842200	4.21603900	3.56179100
C	-4.95314000	-0.54575200	-0.11693700
Cl	-3.57886600	0.55411300	-2.22774300
Cl	-6.21355300	2.20766400	-2.94376800
C	-3.86356500	-0.57848600	0.97303100
C	-2.38737500	-0.52185100	0.59084800
Cl	-4.20045400	0.79973500	2.10841400
C	-1.90493000	-1.67275800	-0.28741900
C	-0.47225800	-1.50223700	-0.77356800
Cl	-2.06949300	-3.24200600	0.64611500
C	0.59153300	-1.27305300	0.29791400
C	1.99114700	-1.21701200	-0.31328800
C	3.09859200	-0.99317300	0.71441400
C	4.48582600	-0.93528700	0.07750800
C	5.61298100	-0.73825300	1.08909800
C	6.98734200	-0.69094000	0.42210300
C	8.10199200	-0.49490800	1.44966900
C	9.50636500	-0.57648800	0.86421300
Cl	10.70143600	-0.15399900	2.15129900
Cl	9.86797700	-2.25592000	0.31417200
C	9.75016900	0.32208500	-0.34369600
O	9.40732900	1.64709200	0.05192900
S	-5.89196700	-2.96670400	-0.53012500
O	-5.34792100	-4.05216800	-1.35180400
O	-7.21430700	-2.47615500	-0.95267800
O	-5.78435100	-3.16396300	0.92410700
O	-4.84622300	-1.74157500	-0.88958500
S	9.17858400	2.70939700	-1.18307800
O	8.96475300	3.96165400	-0.44993200
O	7.99913300	2.21109200	-1.90960700
O	10.41970500	2.65321000	-1.97328500
H	-10.55265600	2.13605900	2.99158600
H	-11.17238800	3.24275600	1.77271100
H	-8.84097500	4.04847700	1.32546300
H	-8.22613400	2.93143700	2.54105900
H	-9.72823600	2.12516300	-0.00466300
H	-9.13506900	1.00103500	1.21489300
H	-6.79792400	1.76016700	0.78828400
H	-7.37892600	2.89466600	-0.43076700
H	-8.38194300	0.94569000	-1.71472200
H	-7.69404700	-0.15821500	-0.54754300
H	-6.33921800	-0.10733900	-2.55166500
H	-4.80677200	1.57493900	-0.49910200
H	-10.32334700	5.20160600	3.10181200
H	-11.42726100	4.21582000	4.07156700
H	-9.68022900	4.09552500	4.32405300
H	-5.90812100	-0.53442600	0.42261900
H	-4.05950700	-1.47846100	1.55943200

H	-2.16021700	0.41609200	0.07382300
H	-1.81462500	-0.52259400	1.52356700
H	-2.56209800	-1.82285500	-1.14097600
H	-0.48727500	-0.64508100	-1.46206100
H	-0.20930000	-2.38085200	-1.37431600
H	0.54957500	-2.08058600	1.04099200
H	0.39421100	-0.33505600	0.83267700
H	2.02600200	-0.41371900	-1.06301400
H	2.18479800	-2.15489600	-0.85280400
H	3.07214400	-1.80149500	1.45902300
H	2.90812900	-0.05795400	1.25973100
H	4.51306700	-0.11841600	-0.65740400
H	4.66453600	-1.86448100	-0.48218900
H	5.59288600	-1.55595200	1.82271700
H	5.44606500	0.19285200	1.64817000
H	7.00647600	0.13117300	-0.30458500
H	7.14907300	-1.62219700	-0.13554100
H	8.02564000	-1.24034600	2.24875400
H	8.00623000	0.49385800	1.91092200
H	10.79770100	0.27251300	-0.65431500
H	9.10503700	-0.01240000	-1.16395800

Data from optimization (second lowest-energy conformer Table S8):
Electronic energy = -2348.60200348
Zero-point correction = 0.609981
Thermal correction to Energy = 0.654869
Thermal correction to Enthalpy = 0.655813
Thermal correction to Gibbs Free Energy = 0.520141
Sum of electronic and zero-point Energies = -2347.992023
Sum of electronic and thermal Energies = -2347.947135
Sum of electronic and thermal Enthalpies = -2347.946191
Sum of electronic and thermal Free Energies = -2348.081863



Electronic energy from single point calculation = -2349.02293057

Cartesian coordinates for second-lowest energy conformer of 3:

C	-9.92402600	5.01891000	-1.69438700
C	-9.91775300	3.70363800	-0.91789300
C	-8.72159800	2.81377700	-1.24928200
C	-8.72352600	1.50097800	-0.46836600
C	-7.54169200	0.61031400	-0.85020500
C	-7.40161600	-0.62826000	0.03222900
C	-6.14930800	-1.46213900	-0.27877000
C	-11.13299500	5.89055600	-1.36380800
C	-4.86442700	-0.67718600	0.01858700
Cl	-6.16583900	-2.99199600	0.68510800
Cl	-8.88168800	-1.65876200	-0.21298500
C	-3.54452100	-1.19972400	-0.57400500
C	-3.09032500	-2.59139100	-0.15789900
Cl	-3.66663100	-1.09243500	-2.38374400
C	-1.63393100	-2.87120300	-0.52767200
C	-0.61810100	-2.03863900	0.23743800
Cl	-1.33685300	-4.64733500	-0.20205300
C	0.83774100	-2.28373100	-0.15367000
C	1.78226800	-1.27664700	0.50024600
C	3.24645500	-1.48719200	0.12001600
C	4.17410100	-0.43927000	0.73210600
C	5.63454300	-0.60783300	0.31876100
C	6.53856100	0.46959400	0.91725100
C	7.97620600	0.32765000	0.42847100
C	8.98061700	1.32725500	0.98353800
Cl	8.46303900	3.01857200	0.61915000
Cl	9.12022800	1.16441800	2.77536500
C	10.39318700	1.12654600	0.43591200
O	10.34562200	1.29699800	-0.97864800
S	-4.49506100	0.94525500	2.03404300
O	-4.31251300	0.66657700	3.46088400
O	-5.74082400	1.65131100	1.69207100
O	-3.30985300	1.48166300	1.34516100
O	-4.69157200	-0.58015100	1.43177600
S	11.13970800	0.16369500	-1.86576900
O	10.87371400	0.62910200	-3.23120100
O	10.50962200	-1.12039800	-1.51662900
O	12.54661400	0.25846900	-1.44040400
H	-9.91034500	4.80159000	-2.77072300
H	-9.00081600	5.57201700	-1.47629800
H	-9.92207700	3.91917500	0.16014300
H	-10.84718500	3.15572400	-1.12970900

H	-7.79122400	3.35975000	-1.03890000
H	-8.72039100	2.59556300	-2.32673200
H	-9.66738800	0.97310900	-0.64751700
H	-8.67503800	1.71502300	0.60871600
H	-6.63398100	1.21273600	-0.75243100
H	-7.61382700	0.29621500	-1.89950500
H	-7.41400700	-0.35882800	1.09181500
H	-6.15936200	-1.76658800	-1.32847800
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H	-11.12024300	6.82828400	-1.92855300
H	-12.06780400	5.37020400	-1.60155800
H	-4.99244900	0.32214300	-0.40691900
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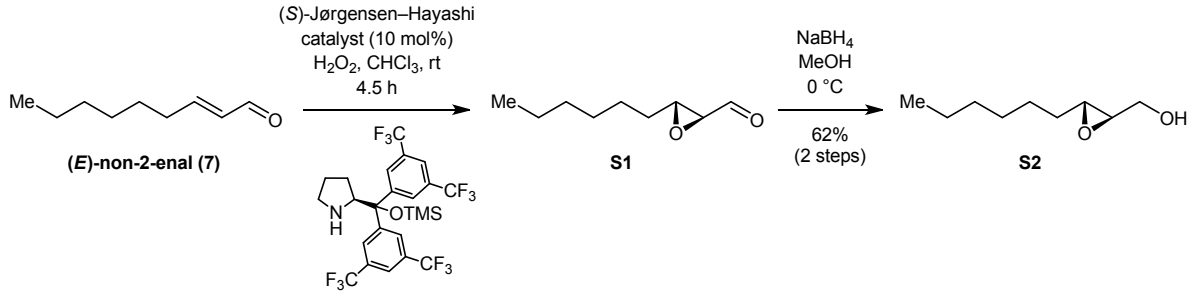
H	-3.20426300	-2.66893200	0.93024200
H	-3.73463500	-3.34441500	-0.61818300
H	-1.48070800	-2.77353700	-1.60560900
H	-0.76206600	-2.19674700	1.31435000
H	-0.85209100	-0.98501600	0.03529800
H	0.93293100	-2.21610400	-1.24657200
H	1.13495700	-3.30096100	0.12890100
H	1.67732100	-1.33570900	1.59281000
H	1.47908400	-0.26000700	0.21289800
H	3.34291400	-1.45832400	-0.97467100
H	3.56711700	-2.49008500	0.43563000
H	4.09828700	-0.48051000	1.82793300
H	3.83091500	0.56138000	0.43344000
H	5.70701700	-0.57335400	-0.77717700
H	5.99247900	-1.59987500	0.62671300
H	6.50529500	0.40690900	2.01190800
H	6.15201400	1.45702100	0.63825800
H	8.01138500	0.42755900	-0.66275200
H	8.36755900	-0.66803200	0.67458900
H	11.08363600	1.85653700	0.86597600
H	10.71279500	0.11292300	0.70134600

4 Syntheses

4.1 Total Synthesis of 16-*epi*-Danicalipin A



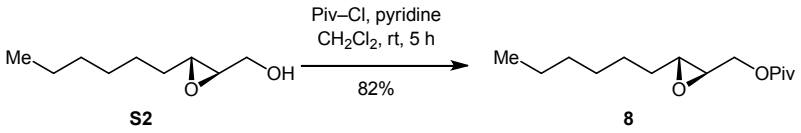
((2*R*,3*R*)-3-Hexyloxiran-2-yl)methanol (S2). To a solution of (*E*)-non-2-enal (**7**) (4.2 g, 5.0 mL, 30 mmol, 1.0 equiv) in $CHCl_3$ (56 mL) was added (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidine (1.8 g, 3.0 mmol, 0.1 equiv) , followed by H_2O_2 (35% in H_2O, 3.2 mL, 36 mmol, 1.2 equiv). The mixture was vigorously stirred for 4.5 h. The mixture was filtered through a plug of silica gel (rinsing with CH_2Cl_2, 2 × 10 mL) and concentrated under reduced pressure (40 °C, 250 mbar). The crude epoxy aldehyde **S1** was directly reduced without purification.

To a solution of the crude epoxy aldehyde **S1** (4.7 g, 30 mmol, 1.0 equiv) in MeOH (150 mL) at 0 °C was added $NaBH_4$ (3.4 g, 90 mmol, 3.0 equiv) portionwise. After 15 min, the reaction mixture was quenched with sat. aq. NH_4Cl solution (50 mL) and extracted with pentane/Et_2O (1:1, 3 × 100 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure (40 °C, 180 mbar). Purification by gradient flash column chromatography (SiO_2, pentane/Et_2O 60:40, then 30:70) afforded the epoxy alcohol **S2** (3.0 g, 19 mmol, 62% over 2 steps, e.r. > 20:1) as a white, amorphous solid.

TLC: R_f = 0.20 (pentane/Et_2O 60:40); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96-3.83 (m, 1H), 3.61 (ddd, J = 12.4, 6.4, 4.4 Hz, 1H), 3.99-2.87 (m, 2H), 1.93 (t, J = 6.2 Hz, 1H), 1.62-1.52 (m, 2H), 1.51-1.20 (m, 8H), 0.94-0.83 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 61.9, 58.6, 56.2, 31.9, 31.7, 29.2, 26.0, 22.7, 14.2; IR (UATR): ν 3265,

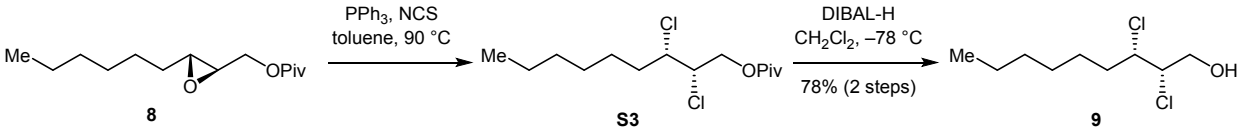
3126, 2954, 2921, 2849, 1460, 1376, 1080, 1044, 1026, 1002, 989, 886, 862, 727, 716 cm^{-1}; Optical Rotation: $[\alpha]_D^{21}$ +37.8 (c = 1.00, $CHCl_3$); Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.46; found C, 67.37; H, 11.64; HRMS (EI): exact mass calculated for $C_9H_{18}O_2^+$ [$(M–OH)^+$] 141.1274; found 141.1274.

The enantiomeric ratio was determined by Mosher ester analysis and compared to the racemic compound.



((2*R*,3*R*)-3-Hexyloxiran-2-yl)methyl pivalate (8). To a solution of **S2** (2.8 g, 18 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) and pyridine (1.9 g, 1.9 mL, 23 mmol, 1.3 equiv) at 0 °C was added Piv–Cl (2.6 g, 2.6 mL, 21 mmol, 1.2 equiv). The reaction was warmed to ambient temperature and was stirred for 5 h. The reaction mixture was diluted with Et_2O (50 mL), washed with sat. aq. NH_4Cl solution (3 × 50 mL) and sat. aq. NaCl solution (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure (40 °C, 250 mbar). Purification by flash column chromatography (SiO_2, pentane/Et_2O 90:10) afforded the product **8** (3.5 g, 14 mmol, 82%) as a colorless oil.

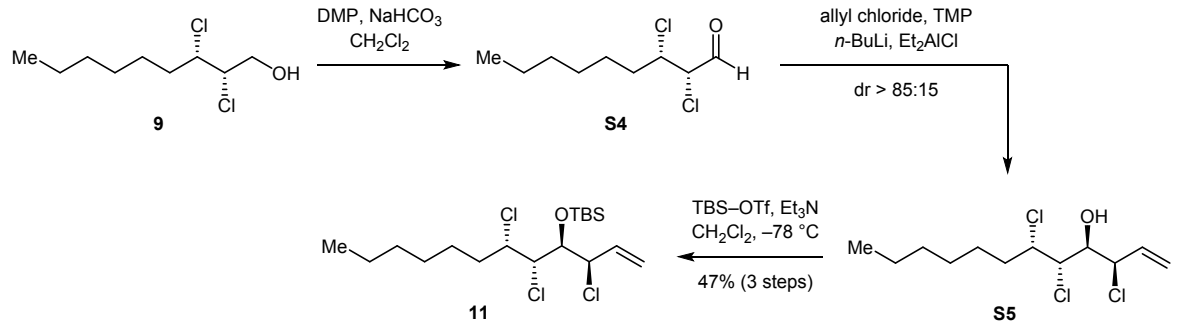
TLC: R_f = 0.50 (pentane/Et_2O 90:10; CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (dd, J = 12.2, 3.4 Hz, 1H), 3.94 (dd, J = 12.2, 6.1 Hz, 1H), 2.95 (ddd, J = 6.1, 3.4, 2.2 Hz, 1H), 2.88-2.79 (m, 1H), 1.63-1.24 (m, 10H), 1.22 (s, 9H), 0.92-0.84 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.5, 64.8, 56.7, 55.6, 39.0, 31.9, 31.7, 29.2, 27.3, 26.0, 22.7, 14.2; IR (UATR): ν 2959, 2930, 2859, 1733, 1481, 1462, 1398, 1367, 1283, 1229, 1152, 1034, 976, 940, 899, 771, 726, 512 cm^{-1}; Optical Rotation: $[\alpha]_D^{24}$ +29.8 (c = 1.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{14}H_{27}O_3^+$ [$(M+H)^+$] 243.1955; found 243.1956.



(2*S*,3*S*)-2,3-Dichlorononan-1-ol (9). To a solution of epoxide **8** (3.5 g, 14 mmol, 1.0 equiv) in toluene (140 mL) was added PPh_3 (15 g, 58 mmol, 4.0 equiv), followed by NCS (7.7 g, 58 mmol, 4.0 equiv) at ambient temperature. The mixture was heated to 90 °C and stirred at that temperature for 3 h. The mixture was cooled to ambient temperature and carefully quenched with sat. aq. $NaHCO_3$ solution (50 mL). After filtration through a plug of Celite eluting with pentane/Et_2O 95:5, the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude **S3**, which was directly deprotected without further purification.

To a stirred solution of the crude **S3** (4.3 g, 14 mmol, 1.0 equiv) in CH_2Cl_2 (110 mL) at –78 °C was added DIBAL-H (1 M in hexane, 36 mL, 36 mmol, 2.5 equiv). After 20 min, the reaction mixture was quenched by addition of sat. aq. NH_4Cl solution (50 mL). The mixture was allowed to reach ambient temperature and was stirred for 30 min at that temperature. Celite was added and the mixture was filtered through a plug of Celite. The organic layer was separated, dried over Na_2SO4_2, filtered and concentrated under reduced pressure (40 °C, 300 mbar). Purification by flash column chromatography (SiO_2, pentane/Et_2O 70:30) afforded the product (**9**) (2.8 g, 11 mmol, 78% over 2 steps) as a colorless oil.

TLC: R_f = 0.21 (hexane/Et_2O 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30-4.14 (m, 2H), 3.98 (dd, J = 11.8, 5.7 Hz, 1H), 3.91 (dd, J = 11.8, 7.0 Hz, 1H), 1.95-1.70 (m, 3H), 1.64-1.51 (m, 1H), 1.49-1.25 (m, 7H), 0.98-0.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 65.6, 64.7, 62.2, 35.4, 31.7, 28.8, 26.7, 22.7, 14.2; IR (UATR): ν 3350, 2955, 2927, 2858, 1465, 1438, 1379, 1340, 1274, 1197, 1121, 1034, 907, 857, 725, 694, 651, 610, 542 cm^{-1}; Optical Rotation: $[\alpha]_D^{21}$ –36.9 (c = 1.00, $CHCl_3$); HRMS (EI): exact mass calculated for $C_9H_{17}ClO^+$ [(M–HCl)$^+$] 176.0968; found 176.0963.



***tert*-Butyldimethyl(((3*R*,4*S*,5*S*,6*S*)-3,5,6-trichlorododec-1-en-4-yl)oxy)silane (11).** To a stirred solution of alcohol **9** (350 mg, 1.6 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added $NaHCO_3$ (420 mg, 5.0 mmol, 3.0 equiv), followed by DMP (1.1 g, 2.5 mmol, 1.5 equiv) at 0 °C. The reaction was stirred for 10 min at 0 °C and then 30 min at ambient temperature. After addition of pentane (2 mL), the mixture was filtered and sat. aq. $NaHCO_3$ (2 mL) was added. The layers were separated. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure (30 °C, 530 mbar). The crude aldehyde **S4** was not purified and directly used for the allylation.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (d, J = 1.3 Hz, 1H), 4.46-4.33 (m, 2H), 1.96-1.82 (m, 2H), 1.60-1.45 (m, 2H), 1.45-1.17 (m, 6H), 0.96-0.80 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.0, 67.1, 60.3, 35.3, 31.7, 28.7, 26.3, 22.7, 14.2.

To a solution of 2,2,6,6-TMP (0.62 mL, 3.6 mmol, 2.2 equiv) in THF (7.4 mL) was added *n*-BuLi (1.65 M in hexane, 2.1 mL, 3.5 mmol, 2.1 equiv) at –78 °C. After 30 min, the solution was added to a stirred solution of allyl chloride (0.28 mL, 3.5 mmol, 2.1 equiv) and Et_2AlCl 1.0 M in hexane, 6.6 mL, 6.6 mmol, 4.0 equiv) in THF (15 mL) at –78 °C and the resulting mixture was stirred for 1 h at –78 °C. A solution of crude aldehyde **S4** (350 mg, 1.6 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 4.5 h. The mixture was quenched with sat. aq. NH_4Cl solution (14 mL) and Rochelle's salt (14 mL) at –78 °C. The mixture was stirred for 15 min at ambient temperature and was then extracted with Et_2O (3 × 35 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (SiO_2,

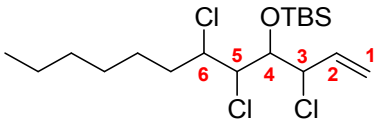
hexane/Et_2O 90:10) afforded an impure sample of the product **S5** (265 mg), which was directly subjected to TBS protection conditions.

TLC: R_f = 0.36 (hexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15-5.99 (m, 1H), 5.55-5.43 (m, 1H), 5.34 (dd, J = 10.2, 0.9 Hz, 1H), 5.10 (dt, J = 7.5, 1.2 Hz, 1H), 4.56 (ddd, J = 9.0, 5.2, 1.5 Hz, 1H), 4.13-3.99 (m, 2H), 2.20 (d, J = 8.3 Hz, 1H), 1.99 (m, 1H), 1.89-1.73 (m, 1H), 1.63-1.21 (m, 8H), 0.94-0.83 (m, 3H).

To a cooled solution of impure alcohol **S5** (265 mg) in CH_2Cl_2 (6.1 mL) was added Et_3N (510 µL, 3.7 mmol, 4.0 equiv), followed by TBS–OTf (740 µL, 3.2 mmol, 3.5 equiv) and the mixture was allowed to reach ambient temperature over 24 h. The mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, pentane) afforded the product **11** (309 mg, 770 µmol, 47% over three steps) as a colorless oil.

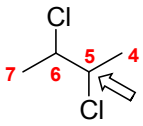
TLC: R_f = 0.50 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (ddd, J = 16.9, 10.2, 7.8 Hz, 1H), 5.39 (dt, J = 16.9, 1.1 Hz, 1H), 5.26 (dt, J = 10.2, 1.1 Hz, 1H), 5.00 (dq, J = 7.8, 1.2 Hz, 1H), 4.37 (ddd, J = 9.1, 5.1, 1.4 Hz, 1H), 4.13 (dd, J = 9.0, 1.3 Hz, 1H), 4.07 (dd, J = 9.0, 1.0 Hz, 1H), 2.00 (ddt, J = 14.2, 9.2, 4.6 Hz, 1H), 1.80 (dddd, J = 14.3, 9.3, 6.0, 5.1 Hz, 1H), 1.60-1.22 (m, 8H), 0.99-0.84 (m, 12H), 0.21 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.3, 118.5, 76.3, 65.6, 64.3, 61.8, 36.6, 31.7, 28.7, 26.6, 26.3 (3C), 22.7, 18.9, 14.2, –3.7, –3.8; IR (UATR): ν 2956, 2929, 2858, 1464, 1257, 1125, 928, 862, 837, 778, 706 cm^{-1}; Optical Rotation: $[\alpha]_D^{23}$ +22.8 (c = 1.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{18}H_{35}AgCl_3OSi^+$ [(M+Ag)$^+$] 507.0568; found 507.0568.

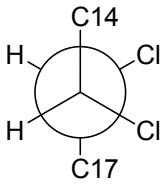
J-Based Configuration Analysis of **11**:



C5-C6 (*syn*)

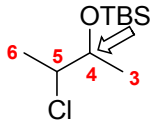
$^{3}J_{H5,H6}$ = 1.4 Hz (S)
$^{3}J_{H5,C7}$ = (1.6 Hz)
$^{3}J_{C4,H6}$ = 1.0 Hz (S)
$^{2}J_{C5,H6}$ = nd
$^{2}J_{C6,H5}$ = (3.2 Hz)

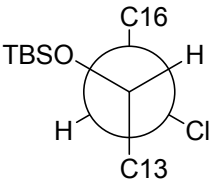




C4-C5 (*anti*)

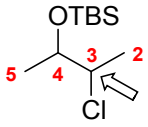
$^{3}J_{H4,H5}$ = 9.0 Hz (L)
$^{3}J_{H4,C6}$ = nd
$^{3}J_{C3,H5}$ = nd
$^{2}J_{C4,H5}$ = –6.5 Hz (L)
$^{2}J_{C5,H4}$ = –5.0 Hz (L)
$NOE_{(H3,H6)}$: not visible

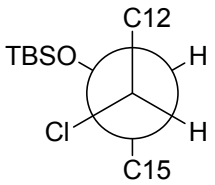


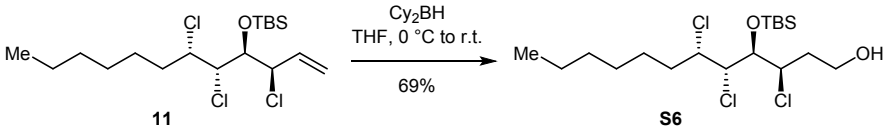


C3-C4 (*syn*)

$^{3}J_{H3,H4}$ = 1.0 Hz (S)
$^{3}J_{H3,C5}$ = 1.3 Hz (S)
$^{3}J_{C2,H4}$ = 2.2 Hz (S)
$^{2}J_{C3,H4}$ = nd
$^{2}J_{C4,H3}$ = nd

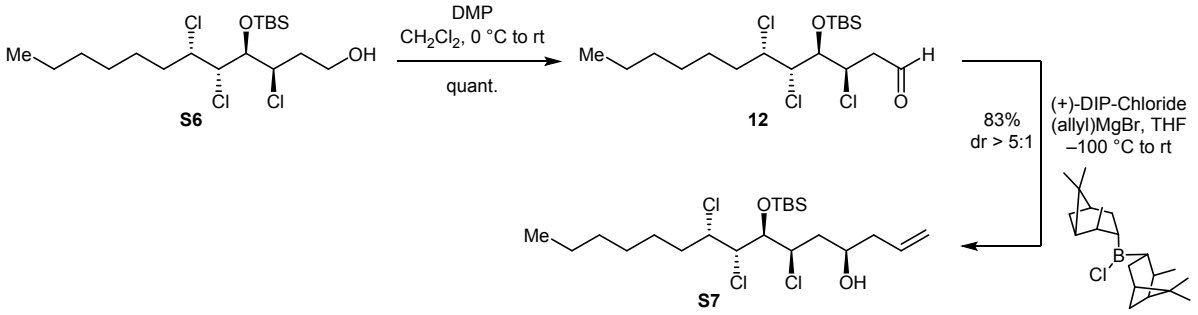






(3*R*,4*S*,5*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3,5,6-trichlorododecan-1-ol (S6). To a solution of Cy_2BH (390 mg, 2.2 mmol, 2.4 equiv) in THF (4.1 mL) at 0 °C was added **11** (370 mg, 920 µmol, 1.0 equiv) in THF (2.0 mL) and the mixture was allowed to reach ambient temperature over 16 h. At 0 °C, H_2O (10 mL) was added, followed by $NaBO_3 \cdot 4H_2O$ (4.2 g, 28 mmol, 30 equiv). The reaction mixture was allowed to reach ambient temperature over 4 h. After filtration through a plug of Celite eluting with EtOAc (40 mL), the organic layer was extracted with EtOAc (3 × 20 mL), washed with sat. aq. NaCl solution (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 80:20) afforded the product (**S6**) (270 mg, 640 µmol, 69%) as a colorless oil.

TLC: R_f = 0.59 (pentane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (ddd, J = 11.1, 3.2, 0.9 Hz, 1H), 4.36 (ddd, J = 9.1, 5.1, 1.4 Hz, 1H), 4.14 (dd, J = 9.0, 1.4 Hz, 1H), 4.01 (dd, J = 9.0, 1.0 Hz, 1H), 3.87 (dd, J = 7.4, 4.4 Hz, 2H), 2.12 (ddt, J = 14.2, 11.1, 4.4 Hz, 1H), 2.02 (ddt, J = 13.7, 9.1, 4.4 Hz, 1H), 1.97-1.87 (m, 1H), 1.85-1.74 (m, 1H), 1.60-1.21 (m, 8H), 0.97-0.85 (m, 12H), 0.24 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 76.2, 65.8, 62.0, 60.7, 59.9, 38.5, 36.6, 31.7, 28.7, 26.6, 26.4 (3C), 22.7, 18.9, 14.2, –3.4, –3.9; IR (UATR): ν 3335, 2956, 2930, 2858, 1464, 1256, 1132, 1058, 835, 777 cm^{-1}; Optical Rotation: $[\alpha]_D^{21}$ +13.5 (c = 1.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{18}H_{38}Cl_3O_2Si^+$ [$(M+H)^+$] 419.1701; found 419.1701.



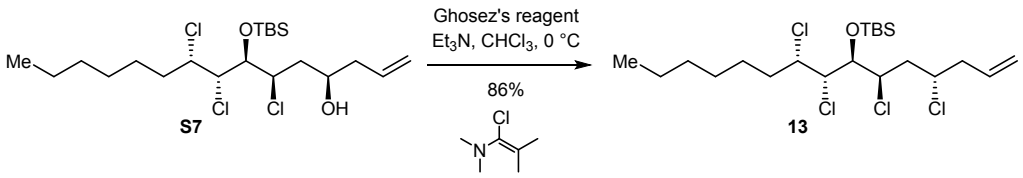
(4*R*,6*R*,7*S*,8*S*,9*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-6,8,9-trichloropentadec-1-en-4-ol (S7). To a solution of **S6** (270 mg, 640 µmol, 1.0 equiv) in CH_2Cl_2 (6.3 mL) at 0 °C was added DMP (320 mg, 760 µmol, 1.2 equiv) and the solution was stirred for 1 h at ambient temperature. Addition of sat. aq. $NaHCO_3$ solution and sat. aq. $Na_2S_2O_3$ solution (1:1, 20 mL), followed by dilution with Et_2O/hexane (1:1, 20 mL). The colorless and clear layers were separated, washed with sat. aq. $Na_2S_2O_3$ solution (20 mL), sat. aq. $NaHCO_3$ solution (20 mL) and sat. aq. NaCl solution (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **12** (270 mg, 640 µmol, quant.) as a colorless oil.

TLC: R_f = 0.23 (hexane/Et_2O 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84-9.70 (m, 1H), 5.11-4.98 (m, 1H), 4.33 (ddd, J = 9.0, 5.1, 1.3 Hz, 1H), 4.12 (dd, J = 9.1, 1.4 Hz, 1H), 4.05 (dd, J = 9.1, 0.9 Hz, 1H), 3.10 (ddd, J = 17.3, 9.9, 2.0 Hz, 1H), 2.76 (ddd, J = 17.4, 4.4, 1.0 Hz, 1H), 2.01 (qd, J = 9.1, 4.6 Hz, 1H), 1.79 (ddd, J = 14.3, 10.2, 4.8 Hz, 1H), 1.45-1.20 (m, 8H), 0.99-0.81 (m, 12H), 0.25 (s, 3H), 0.16 (s, 3H).

A stirred solution of (+)-DIP-Chloride (390 mg, 1.2 mmol, 1.9 equiv) in THF (8.4 mL) was cooled to –78 °C and treated with allylmagnesium bromide (960 µL, 960 µmol, 1.5 equiv). The reaction mixture was stirred for 1 h and was then allowed to reach ambient temperature over 1 h. The reaction mixture was cooled to –100 °C and treated with a solution of crude **12** (270 mg, 640 µmol, 1.0 equiv) in THF (2.1 mL) dropwise. The reaction mixture was stirred for 1 h at –100 °C and then allowed to reach ambient temperature over 16 h. At 0 °C, THF/H_2O (1:1, 16 mL) was added, followed by $NaBO_3 \cdot 4H_2O$ (200 mg, 19 mmol, 30 equiv). The reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 4 h. After filtration through a plug of Celite eluting with EtOAc (50 mL), the organic layer was extracted with EtOAc (3 × 20 mL), washed with sat. aq. NaCl solution (30 mL), dried over Na_2SO_4,

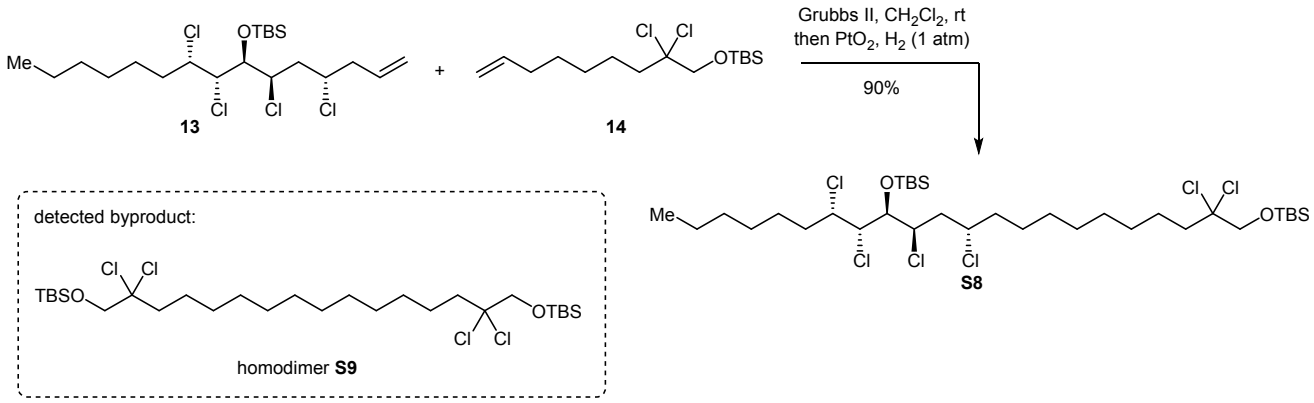
filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, pentane/Et_2O 90:10) afforded the product **S7** (242 mg, 530 µmol, 83%) as a colorless oil.

TLC: R_f = 0.14 (hexane/Et_2O 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90-5.75 (m, 1H), 5.23-5.11 (m, 2H), 4.68 (ddd, J = 9.2, 5.2, 0.9 Hz, 1H), 4.36 (ddd, J = 9.1, 5.0, 1.5 Hz, 1H), 4.12 (dd, J = 9.0, 1.4 Hz, 1H), 4.00 (dd, J = 9.0, 0.9 Hz, 1H), 3.95-3.84 (m, 1H), 2.37 (dddt, J = 13.6, 6.8, 4.3, 1.4 Hz, 1H), 2.27-2.07 (m, 2H), 2.07-1.70 (m, 3H), 1.58-1.21 (m, 8H), 1.00-0.84 (m, 14H), 0.23 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 134.0, 119.1, 75.5, 68.8, 65.7, 62.1, 61.0, 42.2, 41.5, 36.7, 31.7, 28.7, 26.6, 26.4 (3C), 22.7, 19.0, 14.2, –3.4, –3.9; IR (UATR): ν 3402, 2956, 2930, 2858, 1464, 1256, 1135, 837, 778 cm^{-1}; Optical Rotation: $[\alpha]_D^{22}$ +8.9 (c = 2.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{21}H_{42}Cl_3O_2Si^+$ [$(M+H)^+$] 459.2014; found 459.2017.



***tert*-Butyldimethyl(((4*S*,6*R*,7*S*,8*S*,9*S*)-4,6,8,9-tetrachloropentadec-1-en-7-yl)oxy)silane (13).** *Caution: $CHCl_3$ was filtered through a pad of basic alumina prior to the reaction.* To a solution of **S7** (131 mg, 285 µmol, 1.0 equiv) in $CHCl_3$ (1.4 mL) at 0 °C was added 1-chloro-*N*,*N*-2-trimethylprop-1-en-1-amine (Ghosez's reagent) (120 µL, 850 µmol, 3.0 equiv). The mixture was stirred at ambient temperature for 3 h. At 0 °C, Et_3N (160 µL, 1.1 mmol, 4.0 equiv) was added and the mixture was stirred at ambient temperature for 20 min. The reaction mixture was concentrated to half volume under reduced pressure and Celite was added for dry-packing of the column. The suspension was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 95:5) afforded the product (**13**) (120 mg, 250 µmol, 86%) as a colorless oil.

TLC: R_f = 0.80 (hexane/Et_2O 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddt, J = 18.5, 9.5, 6.9 Hz, 1H), 5.21-5.10 (m, 2H), 4.87 (ddd, J = 11.6, 2.1, 1.0 Hz, 1H), 4.39-4.23 (m, 2H), 4.13 (dd, J = 9.0, 1.4 Hz, 1H), 3.99 (dd, J = 9.0, 1.0 Hz, 1H), 2.66-2.50 (m, 2H), 2.34 (ddd, J = 14.7, 11.5, 2.1 Hz, 1H), 2.01 (ddt, J = 14.2, 9.3, 4.6 Hz, 1H), 1.88-1.73 (m, 2H), 1.59-1.20 (m, 8H), 0.99-0.85 (m, 12H), 0.24 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.5, 118.8, 76.2, 65.6, 62.0, 61.5, 59.1, 44.1, 43.3, 36.6, 31.7, 28.7, 26.6, 26.3 (3C), 22.7, 18.9, 14.2, –3.4, –4.0; IR (UATR): ν 2956, 2929, 2858, 1473, 1464, 1256, 1135, 1005, 994, 940, 922, 836, 777, 689 cm^{-1}; Optical Rotation: $[\alpha]_D^{22}$ +28.5 (c = 4.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{21}H_{41}Cl_4OSi^+$ [$(M+H)^+$] 477.1675; found 477.1671.



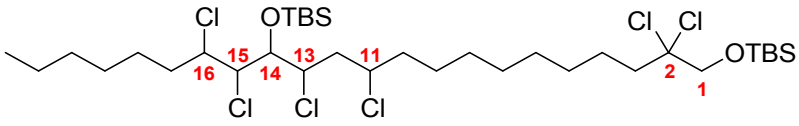
(5*S*,6*R*,8*S*)-6,8,17,17-Tetrachloro-5-((1*S*,2*S*)-1,2-dichlorooctyl)-2,2,3,3,20,20,21,21-octamethyl-4,19-dioxa-3,20-disiladocosane (S8). To a solution of **13** (197 mg, 412 µmol, 1.0 equiv) in degassed CH_2Cl_2 (11 mL) at ambient temperature was added **14**[13] (402 mg, 1.24 mmol, 3.0 equiv) in CH_2Cl_2 (5.5 mL), followed by Grubbs' 2nd generation catalyst (35 mg, 41 µmol, 0.1 equiv). The mixture was heated to 45 °C for 16 h. The reaction was cooled to ambient temperature and PtO_2 (9.4 mg, 41 µmol, 0.1 equiv) was added. The flask was evaquated and refilled with H_2 (1 atm, 5 cycles). The reaction was stirred under an atmosphere of H_2 for 6 h. The reaction mixture was filtered through a pad of silica gel (rinsing with CH_2Cl_2) and the solution was concentrated under reduced pressure. Purification by flash column

[13] A. M. Bailey, S. Wolfrum, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 639.

chromatography (SiO_2, hexane, then hexane/Et_2O 95:5) afforded the product (**S8**) (289 mg, 372 µmol, 90%) as a colorless oil. The homodimer (**S9**) could also be isolated and characterized.

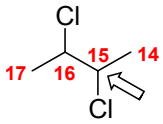
heterodimer (S8): TLC: R_f = 0.26 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 (ddd, J = 11.4, 2.0, 1.0 Hz, 1H), 4.34 (ddd, J = 9.0, 5.0, 1.4 Hz, 1H), 4.20 (dddd, J = 10.4, 7.5, 5.3, 1.9 Hz, 1H), 4.13 (dd, J = 9.0, 1.4 Hz, 1H), 3.99 (dd, J = 9.0, 1.1 Hz, 1H), 3.92 (s, 2H), 2.31 (ddd, J = 14.6, 11.4, 2.1 Hz, 1H), 2.21-2.13 (m, 2H), 2.08-1.94 (m, 1H), 1.87-1.68 (m, 4H), 1.64-1.21 (m, 20H), 0.96-0.87 (m, 21H), 0.24 (s, 3H), 0.16 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 93.6, 76.2, 72.3, 65.6, 62.0, 61.6, 60.7, 44.9, 43.7, 39.1, 36.6, 31.7, 29.43, 29.40, 29.2, 29.1, 28.7, 26.6, 26.5, 26.3 (3C), 25.9 (3C), 24.9, 22.7, 18.9, 18.4, 14.2, –3.4, –3.9, –5.2 (2C); IR (UATR): ν 2954, 2929, 2857, 1464, 1256, 1121, 837, 778 cm^{-1}; Optical Rotation: $[\alpha]_D^{23}$ +14.5 (c = 1.00, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{34}H_{72}Cl_6NO_2Si_2^+$ [$(M+NH_4)^+$] 792.3227; found 792.3218.

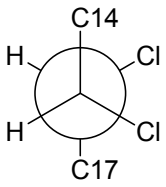
J-Based Configuration Analysis of **S8**:



C15-C16 (*syn*)

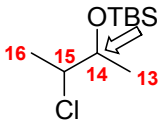
$^{3}J_{H15,H16}$ = 1.4 Hz (S)
$^{3}J_{H15,C17}$ = 1.3 Hz (S)
$^{3}J_{C14,H16}$ = 0.9 Hz (S)
$^{2}J_{C15,H16}$ = nd
$^{2}J_{C16,H15}$ = 3.4 Hz (S)

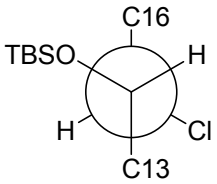




C14-C15 (*anti*)

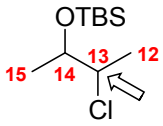
$^{3}J_{H14,H15}$ = 9.0 Hz (L)
$^{3}J_{H14,C16}$ = 2.6 Hz
$^{3}J_{C13,H15}$ = nd
$^{2}J_{C14,H15}$ = –3.6 Hz (L)
$^{2}J_{C15,H14}$ = nd
$NOE_{(H13,H16)}$: not visible

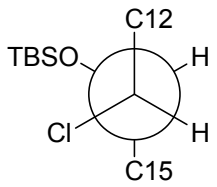




C13-C14 (*syn*)

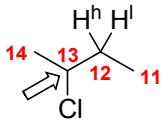
$^{3}J_{H13,H14}$ = 1.0 Hz (S)
$^{3}J_{H13,C15}$ = 1.3 Hz (S)
$^{3}J_{C12,H14}$ = 2.2 Hz (S)
$^{2}J_{C13,H14}$ = nd
$^{2}J_{C14,H13}$ = nd

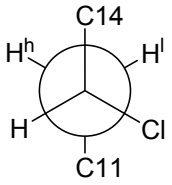




C13-C12 (H_h: higher field, H_l: lower field)

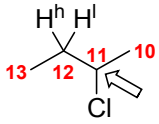
$^3J_{H13,H12l}$ = 11.5 Hz (L)
$^3J_{H13,H12h}$ = 2.1 Hz (S)
$^3J_{H13,C11}$ = 3.6 Hz (S)
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = –7.5 Hz (L)
$^2J_{C13,H12h}$ = 1.2 Hz (S)

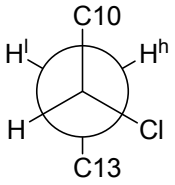




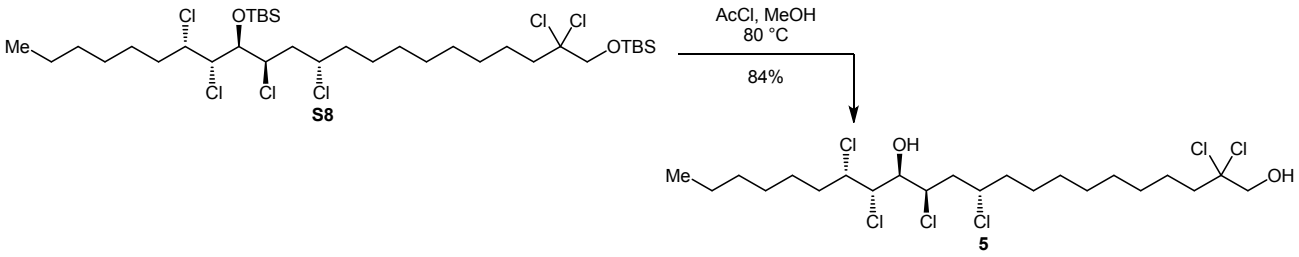
C11-C12 (H_h: higher field, H_l: lower field)

$^3J_{H11,H12l}$ = 2.0 Hz (S)
$^3J_{H11,H12h}$ = 10.3 Hz (L)
$^3J_{H11,C13}$ = 3.1 Hz (S)
$^3J_{C10,H12l}$ = 1.4 Hz (S)
$^3J_{C10,H12h}$ = 1.9 Hz (S)
$^2J_{C11,H12l}$ = nd
$^2J_{C11,H12h}$ = nd





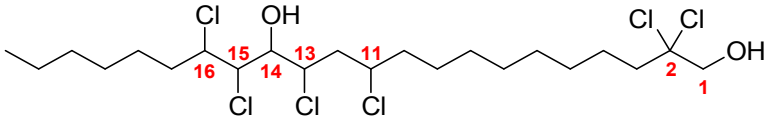
homodimer (S9): TLC: R_f = 0.31 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 4H), 2.23-2.12 (m, 4H), 1.58 (dtd, J = 15.1, 9.1, 8.2, 3.6 Hz, 4H), 1.39-1.21 (m, 16H), 0.91 (s, 18H), 0.11 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 93.7 (2C), 72.3 (2C), 43.7 (2C), 29.7 (2C), 29.6 (2C), 29.5 (2C), 29.2 (2C), 25.9 (6C), 24.9 (2C), 18.4 (2C), –5.2 (4C); IR (UATR): ν 2928, 2856, 1463, 1255, 1153, 1117, 1006, 939, 836, 815, 778, 696, 671 cm^{-1}; HRMS (ESI): exact mass calculated for $C_{28}H_{62}Cl_4NO_2Si_2^+$ [$(M+NH_4)^+$] 640.3068; found 640.3059.



(11*S*,13*R*,14*S*,15*S*,16*S*)-2,2,11,13,15,16-Hexachlorodocosane-1,14-diol (5). To a solution of **S8** (50 mg, 64 μmol, 1.0 equiv) in MeOH (6.4 mL) at ambient temperature was added AcCl (250 mg, 3.2 mmol, 50 equiv) and the mixture was heated to 80 °C for 20 h. The mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 80:20) afforded the product (**5**) (29.5 mg, 54 μmol, 84%) as a colorless oil.

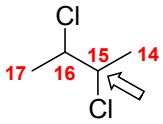
diol (5): TLC: R_f = 0.27 (hexane/EtOAc 80:20, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (ddd, J = 11.2, 2.4, 1.1 Hz, 1H), 4.54 (ddd, J = 9.1, 5.2, 1.7 Hz, 1H), 4.22-4.13 (m, 1H), 4.11 (dd, J = 9.4, 1.7 Hz, 1H), 3.99-3.86 (m, 3H), 2.41-2.26 (m, 2H), 2.25-2.15 (m, 3H), 2.07-1.94 (m, 2H), 1.87-1.73 (m, 3H), 1.70-1.22 (m, 20H), 0.94-0.85 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 94.8, 75.2, 72.3, 64.7, 62.6, 61.9, 60.7, 44.5, 43.7, 38.9, 36.4, 31.7, 29.4, 29.3, 29.1 (2C), 28.9, 26.6, 26.4, 24.9, 22.7, 14.2; IR (UATR): ν 3400, 2928, 2856, 1465, 1379, 1276, 1072, 931, 708, 653, 598 cm^{-1}; Optical Rotation: not measurable; HRMS (MALDI): exact mass calculated for $C_{22}H_{40}Cl_6NaO_2^+$ [(M+Na)$^+$] 569.1052; found 569.1052; HRMS (MALDI): exact mass calculated for $C_{22}H_{40}Cl_6KO_2^+$ [(M+K)$^+$] 585.0791; found 585.0791.

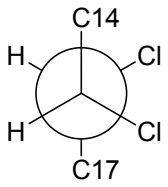
J-Based Configuration Analysis of **5**:



C15-C16 (*syn*)

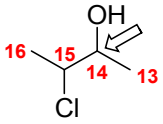
$^{3}J_{H15,H16}$ = 1.7 Hz (S)
$^{3}J_{H15,C17}$ = 1.3 Hz (S)
$^{3}J_{C14,H16}$ = 1.0 Hz (S)
$^{2}J_{C15,H16}$ = 1.7 Hz (S)
$^{2}J_{C16,H15}$ = 3.2 Hz (S)

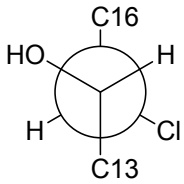




C14-C15 (*anti*)

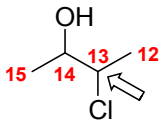
$^{3}J_{H14,H15}$ = 9.4 Hz (L)
$^{3}J_{H14,C16}$ = nd
$^{3}J_{C13,H15}$ = nd
$^{2}J_{C14,H15}$ = –4.1 Hz (L)
$^{2}J_{C15,H14}$ = –4.1 Hz (L)
$NOE_{(H13,H16)}$: not visible

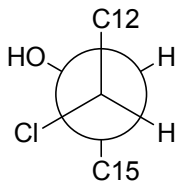




C13-C14 (*not determined, A-1 or B-2*)

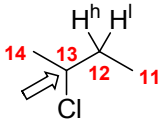
$^{3}J_{H13,H14}$ = 1.2 Hz (S)
$^{3}J_{H13,C15}$ = nd
$^{3}J_{C12,H14}$ = nd
$^{2}J_{C13,H14}$ = nd
$^{2}J_{C14,H13}$ = 0.3 Hz (S)

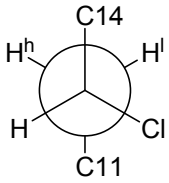




C13-C12 (H_h: higher field, H_l: lower field)

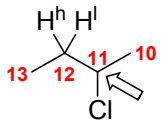
$^{3}J_{H13,H12l}$ = 11.2 Hz (L)
$^{3}J_{H13,H12h}$ = nd (S)
$^{3}J_{H13,C11}$ = 3.4 Hz (S)
$^{3}J_{C14,H12l}$ = nd
$^{3}J_{C14,H12h}$ = nd
$^{2}J_{C13,H12l}$ = –7.6 Hz (L)
$^{2}J_{C13,H12h}$ = 1.2 Hz (S)

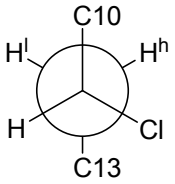


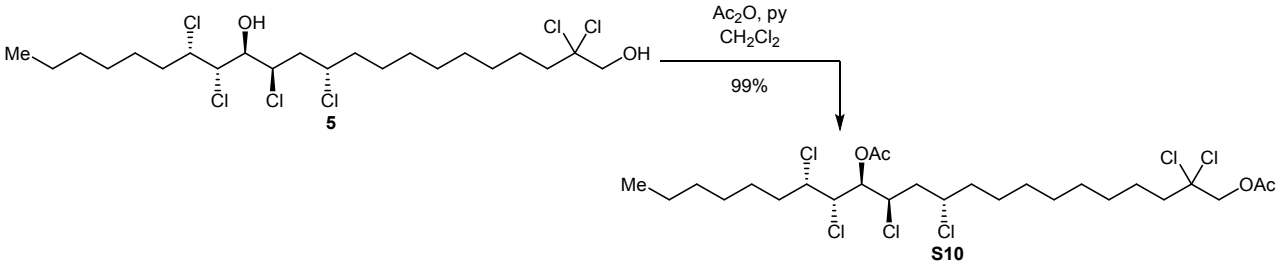


C11-C12 (H_h: higher field, H_l: lower field)

$^3J_{H11,H12l}$ = 2.1 Hz (S)
$^3J_{H11,H12h}$ = nd (L)
$^3J_{H11,C13}$ = 3.0 Hz (S)
$^3J_{C10,H12l}$ = 1.4 Hz (S)
$^3J_{C10,H12h}$ = 2.0 Hz (S)
$^2J_{C11,H12l}$ = 0.8 Hz (S)
$^2J_{C11,H12h}$ = nd





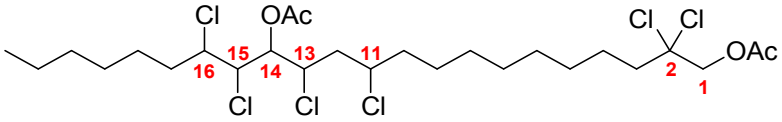


(11*S*,13*R*,14*S*,15*S*,16*S*)-2,2,11,13,15,16-Hexachlorodocosane-1,14-diyl diacetate (S10). To a solution of **5** (6.3 mg, 11 µmol, 1.0 equiv) in CH_2Cl_2 (80 µL) at ambient temperature was added pyridine (4.6 µL, 57 µmol, 5 equiv), Ac_2O (3.3 µL, 34 µmol, 3 equiv) and DMAP (0.3 mg, 2 µmol, 0.2 equiv). The mixture was for 16 h at ambient temperature. The reaction mixture was quenched by addition of sat. aq. NH_4Cl solution (100 µL) and was extracted with CH_2Cl_2 (3 × 1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by preparative thin layer chromatography (SiO_2, hexane/EtOAc 90:10) afforded the product (**S10**) (7.2 mg, 11 µmol, 99%) as a colorless oil.

TLC: R_f = 0.27 (hexane/EtOAc 90:10, CAM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (dd, J = 9.6, 1.4 Hz, 1H), 4.99-4.90 (m, 1H), 4.47 (s, 2H), 4.42 (dd, J = 9.7, 1.8 Hz, 1H), 4.15 (dddd, J = 10.8, 8.2, 4.7, 2.1 Hz, 1H), 4.11 (ddd, J = 8.9, 5.2, 1.8 Hz, 1H), 2.20-2.13 (m, 8H), 2.11-2.05 (m, 1H), 1.97 (dddd, J = 13.9, 10.5, 8.9, 4.7 Hz, 1H), 1.90-1.77 (m, 2H), 1.73 (dddd, J = 14.2, 7.7, 5.7, 2.9 Hz, 2H), 1.67-1.60 (m, 2H), 1.60-1.48 (m, 4H), 1.46-1.22 (m, 14H), 0.96-0.84 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 169.3, 89.9, 75.1, 71.2, 63.0, 60.8, 60.6, 60.2, 44.42, 44.40, 38.8,

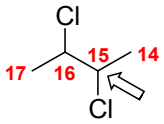
36.4, 31.7, 29.40, 29.37, 29.11, 29.07, 28.9, 26.7, 26.5, 24.9, 22.7, 20.9 (2C), 14.2; IR (UATR): ν 2929, 2857, 1757, 1460, 1373, 1214, 1047, 1026, 933, 705, 656, 610, 505 cm^{-1}; Optical Rotation: $[\alpha]_D^{23}$ +18.9 (c = 0.50, $CHCl_3$); HRMS (ESI): exact mass calculated for $C_{26}H_{48}Cl_6NO_4^+$ $[(M+NH_4)^+]$ 648.1709; found 648.1696.

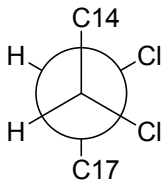
J-Based Configuration Analysis of **S10**:



C15-C16 (*syn*)

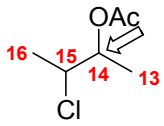
$^{3}J_{H15,H16}$ = 1.8 Hz (S)
$^{3}J_{H15,C17}$ = 1.1 Hz (S)
$^{3}J_{C14,H16}$ = 1.0 Hz (S)
$^{2}J_{C15,H16}$ = nd
$^{2}J_{C16,H15}$ = 2.8 Hz (S)

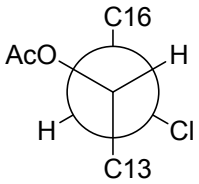




C14-C15 (*anti*)

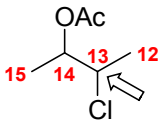
$^{3}J_{H14,H15}$ = 9.7 Hz (L)
$^{3}J_{H14,C16}$ = nd
$^{3}J_{C13,H15}$ = nd
$^{2}J_{C14,H15}$ = –5.2 Hz (L)
$^{2}J_{C15,H14}$ = –5.2 Hz (L)
$NOE_{(H13,H16)}$: not visible

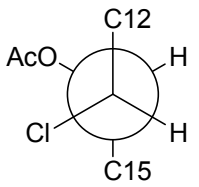




C13-C14 (*syn*)

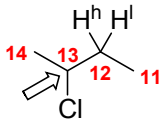
$^{3}J_{H13,H14}$ = 1.4 Hz (S)
$^{3}J_{H13,C15}$ = 0.9 Hz (S)
$^{3}J_{C12,H14}$ = 1.5 Hz (S)
$^{2}J_{C13,H14}$ = nd
$^{2}J_{C14,H13}$ = nd

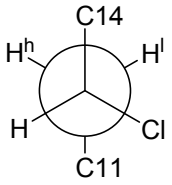




C13-C12 (H_h: higher field, H_l: lower field)

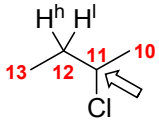
$^3J_{H13,H12l}$ = 2.0 Hz (S)
$^3J_{H13,H12h}$ = 11.4 Hz (L)
$^3J_{H13,C11}$ = 3.4 Hz (S)
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = 1.5 Hz (S)
$^2J_{C13,H12h}$ = –7.7 Hz (L)

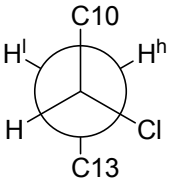


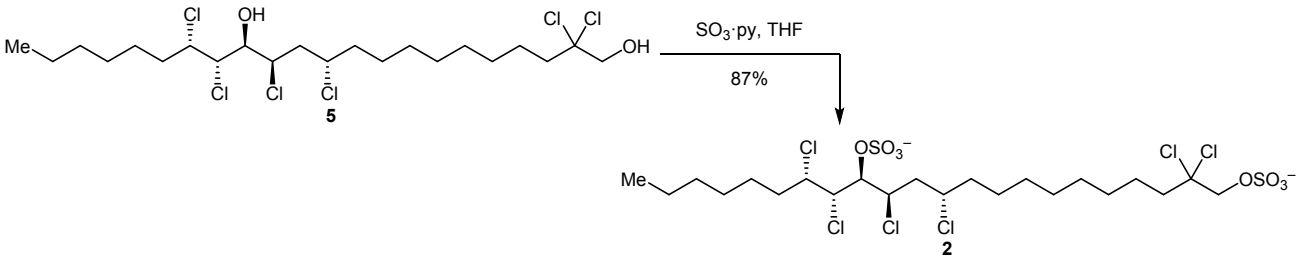


C11-C12 (H_h: higher field, H_l: lower field)

$^3J_{H11,H12l}$ = 10.7 Hz (L)
$^3J_{H11,H12h}$ = 2.1 Hz (S)
$^3J_{H11,C13}$ = 3.1 Hz (S)
$^3J_{C10,H12l}$ = 1.1 Hz (S)
$^3J_{C10,H12h}$ = 1.0 Hz (S)
$^2J_{C11,H12l}$ = nd
$^2J_{C11,H12h}$ = nd







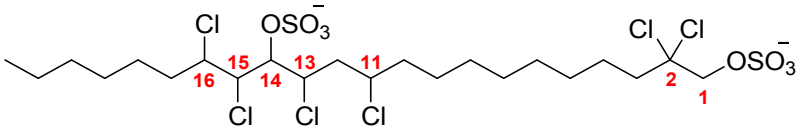
(11*S*,13*R*,14*S*,15*S*,16*S*)-2,2,11,13,15,16-Hexachlorodocosane-1,14-diyl bis(sulfate) disodium salt (2). To a stirred solution of **5** (20 mg, 36 µmol, 1.0 equiv) in THF (290 µL) at ambient temperature was added SO_3·py (24 mg, 150 µmol, 4.1 equiv) and the mixture was stirred for 2.5 h at ambient temperature. Then, sat. aq. $NaHCO_3$ solution (330 µL) was added and the mixture was vigorously stirred for 30 min.[14] After dilution with CH_2Cl_2/MeOH (1:3, 2.5 mL), the mixture was filtered through a short plug of silica gel (rinsing with CH_2Cl_2/MeOH 3:1, 50 mL) and

[14] Since under standard workup conditions (filtration through a plug of Celite eluting with MeOH/CH_2Cl_2), $MeOSO_3H$ was presumably formed, which was not anymore separable from the product, careful quenching of the remaining reagent by sat. aq. $NaHCO_3$ was required.

concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 8:1, 7:1, 6:1, 5:1, 4:1, 3:1) afforded (+)-16-*epi*-danicalipin A (**2**) (23 mg, 32 μmol, 87%) as an amorphous solid. This compound was stable in solution (DMSO) for several months.

TLC: R_f = 0.17 (CH_2Cl_2/MeOH 80:20, CAM); ^{1}H NMR (400 MHz, MeOD): δ 4.91-4.81 (m, 2H), 4.79 (dd, J = 9.5, 1.4 Hz, 1H), 4.32 (s, 2H), 4.30-4.16 (m, 2H), 2.53 (ddd, J = 15.5, 11.4, 2.1 Hz, 1H), 2.31-2.21 (m, 2H), 2.13 (ddd, J = 15.6, 11.2, 2.1 Hz, 1H), 1.96 (dtd, J = 14.2, 9.2, 5.0 Hz, 1H), 1.82 (ddt, J = 10.5, 8.8, 6.3 Hz, 3H), 1.73-1.23 (m, 20H), 0.96-0.86 (m, 3H); ^{13}C NMR (101 MHz, MeOD): δ 91.2, 81.7, 75.5, 65.6, 62.5, 62.3, 62.2, 45.5, 45.1, 39.9, 37.7, 32.8, 30.39, 30.37, 30.1, 30.0, 29.7, 27.6, 27.4, 25.8, 23.6, 14.4; IR (UATR): ν 3469, 2928, 2857, 1618, 1466, 1221, 1083, 1003, 929, 844, 686, 645, 586 cm^{-1}; Optical Rotation: $[\alpha]_D^{23}$ +8.3 (c = 1.00, MeOH); HRMS (ESI): exact mass calculated for $C_{22}H_{44}Cl_6NO_8S_2^+$ [$(M+NH_4)^+$] 724.0634; found 724.0631.

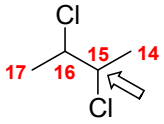
J-Based Configuration Analysis of **2** (spectra measured in acetone-d6):

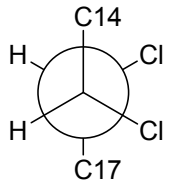


C11, C13 and C16:
- assignment difficult
- overlap of signals

C15-C16

$^3J_{H15,H16}$ = 1.2 Hz (S)
$^3J_{H15,C17}$ = nd
$^3J_{C14,H16}$ = (1.4 Hz, weak)
$^2J_{C15,H16}$ = nd
$^2J_{C16,H15}$ = nd (overlap*)

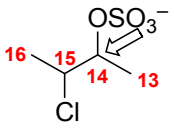


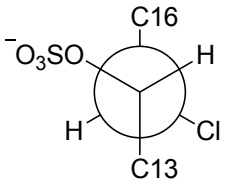


C15-C16 is probably A-1 by comparison with the JBCA of diol **5**, which was used to determine the relative configuration

C14-C15 (*anti*)

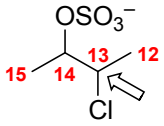
$^3J_{H14,H15}$ = 9.5 Hz
$^3J_{H14,C16}$ = nd
$^3J_{C13,H15}$ = nd (overlap*)
$^2J_{C14,H15}$ = –5.9 Hz
$^2J_{C15,H14}$ = –4.6 Hz
$NOE_{(H13,H16)}$: not visible

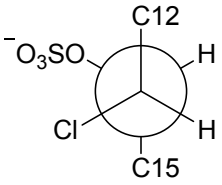




C13-C14

$^3J_{H13,H14}$ = 1.4 Hz (S)
$^3J_{H13,C15}$ = nd (overlap, shoulder)
$^3J_{C12,H14}$ = (1.4 Hz, weak)
$^2J_{C13,H14}$ = nd
$^2J_{C14,H13}$ = nd

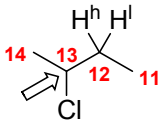


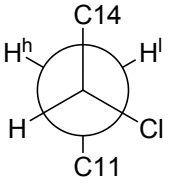


ambiguous, presumably the same as diol **5**

C13-C12 (H_h: higher field, H_l: lower field)

$^3J_{H13,H12l}$ = 11.4 Hz (L, assigned from COSY)
$^3J_{H13,H12h}$ = 2.0 Hz (S, assigned from COSY)
$^3J_{H13,C11}$ = nd
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = overlap$^+$
$^2J_{C13,H12h}$ = overlap$^+$

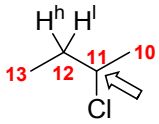


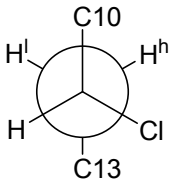


probably C-1, because we know the JBCA of diol **5** and because C12-C11 is D-1

C11-C12 (H_h: higher field, H_l: lower field) (*D-1*)

$^3J_{H11,H12l}$ = 2.2 Hz (S, assigned from COSY)
$^3J_{H11,H12h}$ = 11.3 Hz (L, assigned from COSY)
$^3J_{H11,C13}$ = 2.4 Hz (S)
$^3J_{C10,H12l}$ = 2.2 Hz (S)
$^3J_{C10,H12h}$ = 1.5 Hz (S)
$^2J_{C11,H12l}$ = overlap$^+$
$^2J_{C11,H12h}$ = overlap$^+$

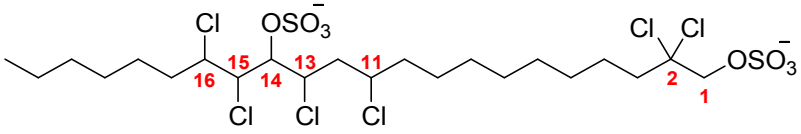




General remarks:

- structure determination is not possible with the JBCA of the sulfate alone
- combining and comparing the analysis of the sulfate **2** with the JBCA of diol **5** leads to a reasonable result
- all sizes of coupling constants are consistant with those observed for diol **5**; these results do not argue against the assumption that diol **5** and disulfate **2** adopt the same conformation in the chlorinated segment

J-Based Configuration Analysis of **2** (spectra measured in DMSO-d6):

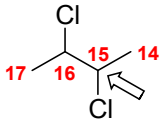


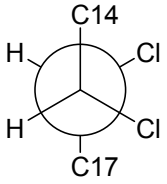
C11, C15:
- cannot be assigned

C3, C12:
- overlap

C15-C16

$^{3}J_{H15,H16}$ = 1.1 Hz (S)
$^{3}J_{H15,C17}$ = nd
$^{3}J_{C14,H16}$ = 1.5 (S)
$^{2}J_{C15,H16}$ = nd
$^{2}J_{C16,H15}$ = nd (overlap*)

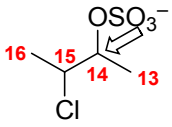


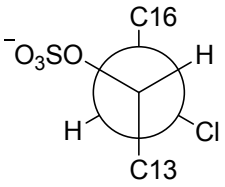


C15-C16 is probably A-1 by comparison with the JBCA of diol **5**, which was used to determine the relative configuration

C14-C15 (*anti*)

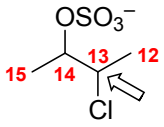
$^{3}J_{H14,H15}$ = 9.4 Hz
$^{3}J_{H14,C16}$ = nd
$^{3}J_{C13,H15}$ = 2.3 Hz (overlap*)
$^{2}J_{C14,H15}$ = –5.6 Hz
$^{2}J_{C15,H14}$ = –4.6 Hz
$NOE_{(H13,H16)}$: not visible

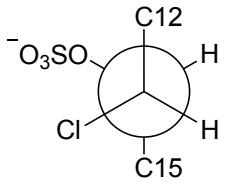




C13-C14

$^{3}J_{H13,H14}$ = 1.7 Hz (S)
$^{3}J_{H13,C15}$ = nd
$^{3}J_{C12,H14}$ = nd
$^{2}J_{C13,H14}$ = nd
$^{2}J_{C14,H13}$ = nd

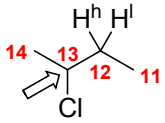


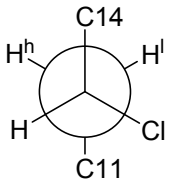


ambiguous, presumably the same as diol **5**

C13-C12 (H_h: higher field, H_l: lower field)

$^3J_{H13,H12l}$ = 11.2 Hz (L, assigned from COSY)
$^3J_{H13,H12h}$ = nd (S, assigned from COSY)
$^3J_{H13,C11}$ = nd (overlap)
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = overlap$^+$
$^2J_{C13,H12h}$ = overlap$^+$

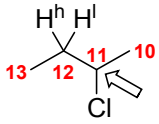


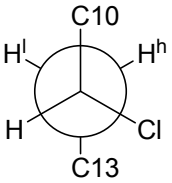


probably C-1, because we know the JBCA of diol **5** and because C12-C11 is D-1

C11-C12 (H_h: higher field, H_l: lower field) (*D-1*)

$^3J_{H11,H12l}$ = 2.2 Hz (S, assigned from COSY)
$^3J_{H11,H12h}$ = nd (L, assigned from COSY)
$^3J_{H11,C13}$ = nd (overlap)
$^3J_{C10,H12l}$ = 0.9 Hz (S)
$^3J_{C10,H12h}$ = 0.7 Hz (S)
$^2J_{C11,H12l}$ = overlap$^+$
$^2J_{C11,H12h}$ = overlap$^+$

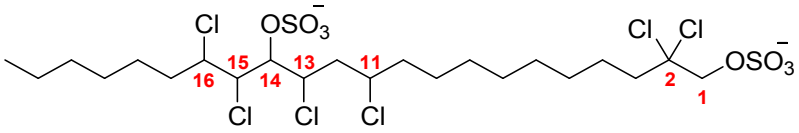




General remarks:

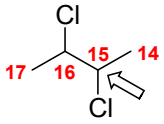
- structure determination is not possible with the JBCA of the sulfate alone
- combining and comparing the analysis of the sulfate **2** with the JBCA of diol **5** leads to a reasonable result
- all sizes of coupling constants are consistant with those observed for diol **5**; these results do not argue against the assumption that diol **5** and disulfate **2** adopt the same conformation in the chlorinated segment

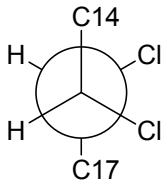
J-Based Configuration Analysis of **2** (spectra measured in methanol-d4):



C15-C16

$^3J_{H15,H16}$ = 1.2 Hz (S)
$^3J_{H15,C17}$ = (1.6 Hz, weak)
$^3J_{C14,H16}$ = 1.3 Hz (S)
$^2J_{C15,H16}$ = nd
$^2J_{C16,H15}$ = nd (overlap*)

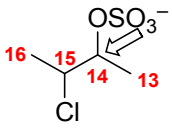


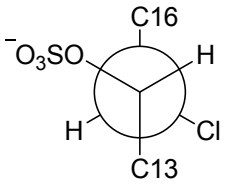


C15-C16 is probably A-1 by comparison with the JBCA of diol **5**, which was used to determine the relative configuration

C14-C15

$^3J_{H14,H15}$ = 9.5 Hz
$^3J_{H14,C16}$ = nd (overlap)
$^3J_{C13,H15}$ = nd (overlap*)
$^2J_{C14,H15}$ = –6.0 Hz
$^2J_{C15,H14}$ = –5.1 Hz
$NOE_{(H13,H16)}$: nd (too close)

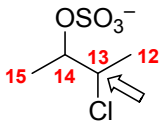


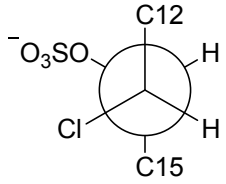


C14-C15 is probably B-3 by comparison with the JBCA of diol **5**

C13-C14

$^3J_{H13,H14}$ = 1.4 Hz (S)
$^3J_{H13,C15}$ = (0.5 Hz, weak)
$^3J_{C12,H14}$ = 1.5 Hz (S)
$^2J_{C13,H14}$ = nd
$^2J_{C14,H13}$ = nd

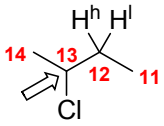


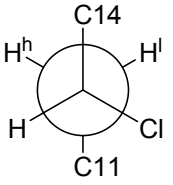


ambiguous, presumably the same as diol **5**

C13-C12 (H_h: higher field, H_l: lower field)

$^3J_{H13,H12l}$ = 11.4 Hz (L, assigned from COSY)
$^3J_{H13,H12h}$ = 2.1 Hz (S, assigned from COSY)
$^3J_{H13,C11}$ = 3.4 Hz (S)
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = overlap$^+$
$^2J_{C13,H12h}$ = overlap$^+$

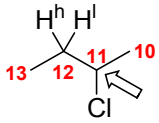


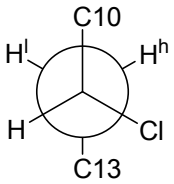


probably C-1, because we know the JBCA of diol **5** and because C12-C11 is D-1

C11-C12 (H_h: higher field, H_l: lower field) (*D-1*)

$^3J_{H11,H12l}$ = 2.1 Hz (S, assigned from COSY)
$^3J_{H11,H12h}$ = 11.2 Hz (L, assigned from COSY)
$^3J_{H11,C13}$ = 3.3 Hz (S)
$^3J_{C10,H12l}$ = 1.4 Hz (S)
$^3J_{C10,H12h}$ = 2.1 Hz (S)
$^2J_{C11,H12l}$ = overlap$^+$
$^2J_{C11,H12h}$ = overlap$^+$

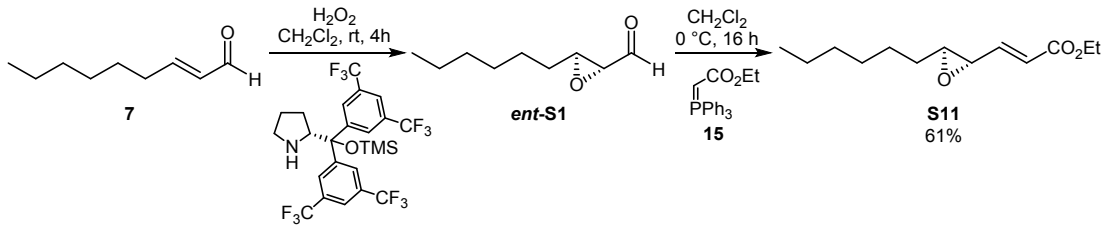




General remarks:

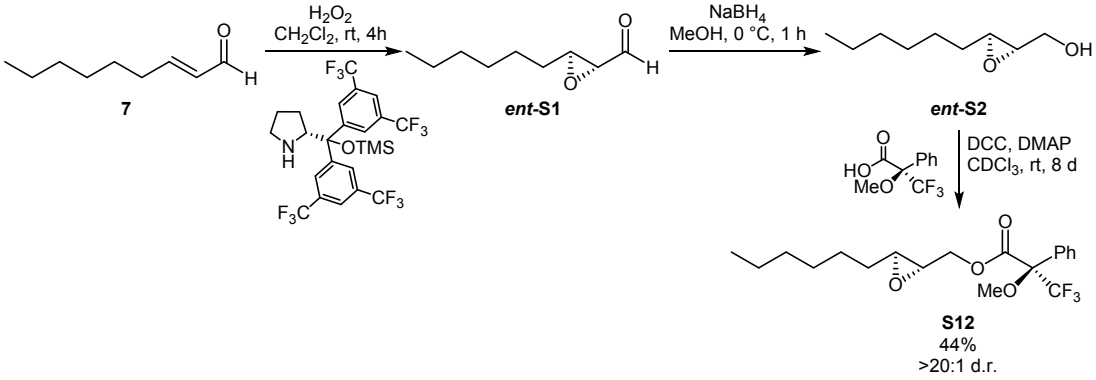
- structure determination is not possible with the JBCA of the sulfate alone
- combining and comparing the analysis of the sulfate **2** with the JBCA of diol **5** leads to a reasonable result
- all sizes of coupling constants are consistant with those observed for diol **5;** these results do not argue against the assumption that diol **5** and disulfate **2** adopt the same conformation in the chlorinated segment

4.2 Total Synthesis of 11,15-di-*epi*-Danicalipin A



(*E*)-ethyl 3-((2*S*,3*S*)-3-hexyloxiran-2-yl)acrylate (S11): To a solution of enal **7** (3.55 mL, 21.4 mmol, 1.00 equiv) in CH_2Cl_2 (42.8 mL) (*R*)-Jørgensen–Hayashi-catalyst (1.28 g, 2.14 mmol, 10.0 mol%). The solution was stirred and aqueous hydrogen peroxide (30%, 2.84 mL, 27.8 mmol, 1.30 equiv) was added. After stirring for 4 hours, the reaction was filtered through a silica gel plug, eluting with CH_2Cl_2. After concentration, the residue was taken up in CH_2Cl_2 (120 mL) and cooled to 0 °C in an ice bath. Ethyl 2-(triphenylphosphoranylidene)acetate (**15**) (7.45 g, 21.4 mmol, 1.00 equiv) was added and the reaction was stirred at 0 °C for 16 hours. After concentration, flash column chromatography (pentane/Et_2O 9:1, SiO_2) gave the desired product **S11** as colorless oil (2.93 g, 13.0 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.12 (d, *J* = 15.7 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.20 (dd, *J* = 7.1, 2.0 Hz, 1H), 2.88 (td, *J* = 5.6, 2.0 Hz, 1H), 1.68 – 1.54 (m, 2H), 1.51 – 1.39 (m, 2H), 1.39 – 1.20 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 145.0, 123.7, 61.7, 60.7, 56.5, 32.1, 31.8, 29.2, 25.9, 22.7, 14.4, 14.2; HRMS (EI): exact mass for $C_{11}H_{17}O_2$ $[M\text{-}C_2H_5O]^+$, calculated 118.1223, found 181.1223; IR (thin film, cm^{-1}): ν 2958, 2930, 2859, 1721, 1567, 1466, 1369, 1344, 1303, 1278, 1259, 1180, 1139, 1039, 977, 853; Optical Rotation: $[\alpha]_D^{23} = -9.5$ (c = 0.57, $CHCl_3$).

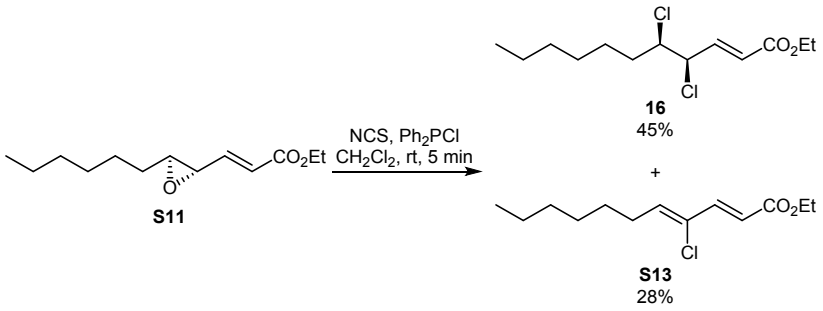


(*R*)-((2*S*,3*S*)-3-hexyloxiran-2-yl)methyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S12): To a solution of enal **7** (0.59 mL, 3.57 mmol, 1.00 equiv) in CH_2Cl_2 (7.1 mL) (*R*)-Jørgensen–Hayashi-catalyst (0.213 g, 0.357 mmol, 10.0 mol%). The solution was stirred and aqueous hydrogen peroxide (30%, 0.473 mL, 4.64 mmol, 1.30 equiv) was added. After stirring for 4 hours, the reaction was filtered through a silica gel plug, eluting with CH_2Cl_2. After concentration, a crude mixture of epoxyaldehyde ***ent*-S1** was obtained (0.629 g).

Of this mixture, an aliquot (34.1 mg, 5.4% of total amount) was dissolved in THF (0.96 mL) and MeOH (0.96 mL) and cooled to 0 °C. Sodium borohydride (10.9 mg, 0.288 mmol, ca. 1.50 equiv) was added and the reaction was stirred at 0 °C for 1 hour. Sat. aq. $NaHCO_3$ was added and the mixture was extracted three times with CH_2Cl_2. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc 3:1, SiO_2) gave alcohol ***ent*-S2** as white solid.

Alcohol ***ent*-S2** was taken up in $CDCl_3$ (1.5 mL) and (*R*)-Mosher-acid (24.8 mg, 0.106 mmol, ca. 0.55 equiv), DCC (21.8 mg, 0.106 mmol, ca. 0.55 equiv), and DMAP (12.9 mg, 0.106 mmol, ca. 0.55 equiv) were added. After stirring overnight, the reaction was concentrated and resuspended in $CDCl_3$ (0.6 mL). After 4 days, the reaction was filtered and concentrated. The residue was taken up in $CDCl_3$ (0.6 mL) and (*R*)-Mosher-acid (24.8 mg, 0.106 mmol, ca. 0.55 equiv), DCC (21.8 mg, 0.106 mmol, ca. 0.55 equiv), and DMAP (12.9 mg, 0.106 mmol, ca. 0.55 equiv) were added. After another 4 days, the reaction was filtered, concentrated and analzed by crude ^{19}F NMR, to show a d.r. of >20:1. Flash column chromatography (pentane/Et_2O 10:1, SiO_2) gave product **S12** as colorless oil (31.8 mg, 0.085 mmol, 44% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.49 (m, 2H), 7.48 – 7.36 (m, 3H), 4.53 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.23 (dd, *J* = 12.0, 6.1 Hz, 1H), 3.57 (d, *J* = 1.2 Hz, 3H), 2.99 (ddd, *J* = 5.9, 3.5, 2.1 Hz, 1H), 2.83 (td, *J* = 5.6, 2.1 Hz, 1H), 1.65 – 1.47 (m, 2H), 1.47 – 1.35 (m, 2H), 1.35 – 1.19 (m, 6H), 0.96 – 0.80 (m, 3H); ^{19}F NMR (377 MHz, $CDCl_3$): δ -71.74; ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 132.2, 129.8, 128.6, 127.4 (app d, J = 1.4 Hz), 123.3 (q, *J* = 288.5 Hz), 84.8 (q, J = 27.9 Hz), 66.4 , 56.9 , 55.7 (app d, J = 1.6 Hz), 54.7, 31.8, 31.6, 29.1, 25.9, 22.7, 14.2; HRMS (EI): exact mass for $C_{19}H_{25}F_3O_4$ $[M]^+$, calculated 174.1705, found 374.1700; IR (thin film, cm^{-1})**:** ν 2931, 1858, 1753, 1452, 1271, 1243, 1169, 1122, 1081, 1022, 765, 719; Optical Rotation: $[\alpha]_D^{25}$ = +22.8 (c = 1.02, $CHCl_3$).



(4*R*,5*R*,*E*)-ethyl 4,5-dichloroundec-2-enoate (16): To a solution of *N*-chlorosuccinimide (2.91 g, 21.8 mmol, 3.50 equiv) in CH_2Cl_2 (75 mL) in a water bath was added chlorodiphenylphosphine (3.45 mL, 18.7 mmol, 3.00 equiv). The water bath was removed and the reaction was stirred for 5 minutes. Epoxide **S11** (1.41 g, 6.23 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) was added rapidly *via* two syringes. After 3 minutes, sat. aq. $NaHCO_3$ was added and the reaction was extracted three times with Et_2O. Combined organic layers were filtered through a silica gel plug, eluting with Et_2O, and finally concentrated. Flash column chromatography (hexanes/Et_2O 100:1, SiO_2) gave dichloride **16** as colorless oil (0.79 g, 2.81 mmol, 45%) and elimination product **S13** (0.43 g, 1.76 mmol, 28%).

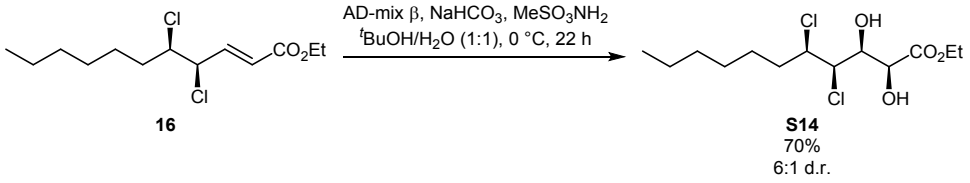
Analytical data for 16:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 15.4, 7.2 Hz, 1H), 6.17 (dd, *J* = 15.4, 1.3 Hz, 1H), 4.73 (ddd, *J* = 7.2, 3.7, 1.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.11 (dt, *J* =

10.1, 3.6 Hz, 1H), 1.99 (dddd, *J* = 13.8, 9.6, 5.7, 3.5 Hz, 1H), 1.79 – 1.64 (m, 1H), 1.47 – 1.19 (m, 11H), 0.91 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 141.7, 125.5, 64.2, 62.7, 61.1, 33.8, 31.7, 29.9, 28.7, 22.7, 14.3, 14.2; HRMS (EI): exact mass for $C_{11}H_{17}Cl_2O$ $[M\text{-}C_2H_5O]^+$, calculated 235.0651, found 235.0651; IR (thin film, cm^{-1}): ν 2928, 2859, 1721, 1661, 1466, 1368, 1309, 1270, 1168, 1039, 976, 864, 768, 726, 661; Optical Rotation: $[\alpha]_D^{24}$ = +53.4 (c = 2.0, $CHCl_3$).

Analytical data for S13:

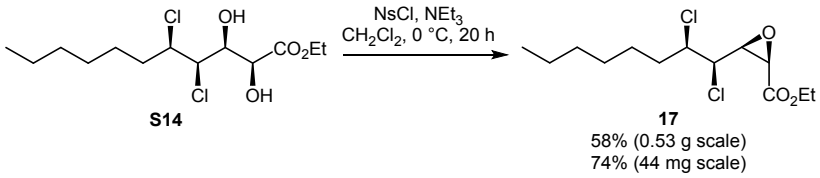
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 14.8, 0.7 Hz, 1H), 6.31 (d, *J* = 14.8 Hz, 1H), 6.13 (t, *J* = 8.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.39 – 2.24 (m, 2H), 1.51 – 1.40 (m, 2H), 1.37 – 1.20 (m, 6H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.97 – 0.80 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 139.7, 135.9, 128.4, 122.2, 60.7, 31.6, 29.1, 28.9, 28.8, 22.5, 14.3, 14.0; HRMS (EI): exact mass for $C_{13}H_{21}ClO_2$ $[M]^+$, calculated 244.1230, found 244.1225; IR (thin film, cm^{-1}): ν 2928, 2858, 1717, 1632, 1465, 1367, 1304, 1265, 1176, 1095, 1036, 964, 869, 728, 691.



(2*S*,3*S*,4*R*,5*R*)-ethyl 4,5-dichloro-2,3-dihydroxyundecanoate (S14): AD-mix β (4.18 g), methanesulfonamide (0.282 g, 2.97 mmol, 1.00 equiv), and sodium bicarbonate (0.748 g, 8.91 mmol, 1.00 equiv) were dissolved in *t*-BuOH (14.9 mL) and water (14.9 mL). After cooling to 0 °C, olefin **16** (0.835 g, 2.97 mmol, 1.00 equiv) was added, rinsing with little *t*-BuOH. After stirring for 22 hours at 0 °C, sodium sulfite (4.49 g, 35.6 mmol, 12.0 equiv) was added and the reaction was allowed to warm to 25 °C. After 1 hour at 25 °C, the mixture was diluted with water and extracted three times with EtOAc. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (pentane/Et_2O 100:1, then toluene/acetone 20:1, SiO_2)[15], gave the product **S14** as pale yellow oil (0.652 g,

2.07 mmol, 70%) as 6:1 mixture of diastereomers (as determined by ^{13}C NMR of the purified product).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.40 – 4.37 (m, 1H), 4.35 – 4.28 (m, 2H), 4.27 (d, *J* = 1.7 Hz, 2H), 4.24 (ddd, *J* = 8.4, 5.4, 1.6 Hz, 1H), 3.20 (d, *J* = 5.7 Hz, 1H), 2.52 (s, 1H), 2.00 – 1.92 (m, 1H), 1.88 (ddt, *J* = 14.1, 10.1, 5.5 Hz, 1H), 1.52 (dddt, *J* = 19.2, 9.9, 7.2, 5.0 Hz, 1H), 1.44 – 1.36 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.36 – 1.28 (m, 6H), 0.91 – 0.85 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 172.3, 74.8, 70.2, 68.3, 62.7, 61.6, 36.8, 31.7, 28.7, 26.4, 22.7, 14.3, 14.2; HRMS (ESI): exact mass for $C_{13}H_{24}Cl_2NaO_4$ $[M+Na]^+$, calculated 337.0944, found 337.0948; IR (thin film, cm^{-1})**:** ν 3461, 2957, 2858, 1740, 1466, 1377, 1277, 1223, 1118, 1064, 1022; Optical Rotation: $[\alpha]_D^{23}$ = +16.3 (c = 0.67, $CHCl_3$).

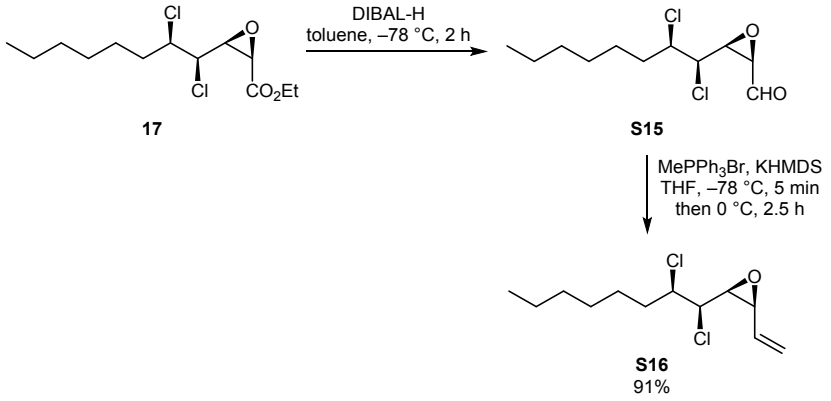


(2*R*,3*S*)-ethyl 3-((1*R*,2*R*)-1,2-dichlorooctyl)oxirane-2-carboxylate (17): To a solution of diol **S14** (0.527 g, 1.67 mmol, 1.00 equiv) in CH_2Cl_2 (16.7 mL) was added triethylamine (0.35 mL, 2.51 mmol, 1.50 equiv). The solution was cooled to 0 °C and after 30 minutes *p*-nitrobenzenesulfonyl chloride (0.389 g, 1.75 mmol, 1.05 equiv) was added. After stirring for 12 hours at 0 °C, triethylamine (0.23 mL, 1.67 mmol, 1.00 equiv) was added and the reaction was stirred for another 8 hours at 0 °C. The reaction was concentrated and the residue applied to a column with hexanes. Flash column chromatography (hexanes/EtOAc 1:0, 100:1, then 50:1, SiO_2) gave epoxide **17** as colorless oil (0.286 g, 0.962 mmol, 58%).

The same procedure on a 44.0 mg scale of diol **S14** produced epoxide **17** in 74% yield.

[15] Upon prolonged reaction times, a significant amount of elimination product was also isolated.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37 – 4.20 (m, 3H), 3.92 (ddd, *J* = 9.3, 4.8, 2.9 Hz, 1H), 3.67 (d, *J* = 4.2 Hz, 1H), 3.57 (dd, *J* = 8.6, 4.3 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.79 (dtd, *J* = 14.2, 9.4, 4.9 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.41 – 1.20 (m, 7H), 0.92 – 0.84 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 167.5, 62.3, 62.3, 61.0, 58.7, 54.4, 34.7, 31.7, 28.6, 26.5, 22.7, 14.3, 14.2; HRMS (ESI): exact mass for $C_{13}H_{22}Cl_2NaO_3$ $[M+Na]^+$, calculated 319.0838, found 319.0839; IR (thin film, cm^{-1}): ν 2957, 2929, 2859, 1748, 1466, 1380, 1202, 1109, 1027, 850, 807, 702; Optical Rotation: $[\alpha]_D^{23}$ = +40.0 (c = 0.33, $CHCl_3$).



17 **S15** **S16** 91%

(2*S*,3*S*)-2-((1*R*,2*R*)-1,2-dichlorooctyl)-3-vinyloxirane (S16): To a solution of ester **17** (0.316 g, 1.06 mmol, 1.00 equiv) in toluene at –78 °C was added DIBAL-H dropwise (1.0 M in CH_2Cl_2, 1.60 mL, 1.60 mmol, 1.50 equiv).After stirring at –78 °C for 2 hours, methanol (1.5 mL) was added and the cooling bath was removed. Then sat. aq. sodium potassium tratrate was added and the mixture was stired vigorously until both phases were clear. The mixture was then poured into water and EtOAc. Phases were separated and the aqueous phase was extracted twice with EtOAc. Combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude aldehyde **S15** was then taken up in THF (8.5 mL) and used in the next reaction as was.

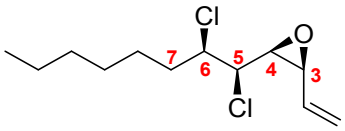
Crude analysis of aldehyde **S15**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 – 9.56 (m, 1H), 4.10 – 4.03 (m, 1H), 3.97 (dt, *J* = 9.8, 3.5 Hz, 1H), 3.72 – 3.63 (m, 2H), 2.12 – 1.97 (m, 1H), 1.85 – 1.69 (m, 1H), 1.64 – 1.45 (m, 1H), 1.29 (m, 7H), 0.93 – 0.86 (m, 3H).

In a separate flask, methyltriphenylphosphonium bromide (0.759 g, 2.13 mmol, 2.00 equiv) was suspended in THF (12.8 mL). After cooling to –78 °C, KHMDS (0.5 M in toluene, 3.20 mL, 1.60 mmol, 1.50 equiv) was added dropwise. The yellow suspension was placed in an ice bath after 5 minutes and stirred for 20 minutes. After cooling back down to –78 °C, the solution of aldehyde **S15** was added dropwise to the reaction (the flask was rinsed with 0.5 mL THF twice). The dark yellow suspension was then placed in an ice bath after 5 minutes and stirred for 2.5 hours. The reaction was then quenched through the addition of sat. aq. NH_4Cl and separated between water and EtOAc. Phases were separated and the aqueous phase extrated three times with pentane. Combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (hexanes/Et_2O gradient 100:1 to 50:1, SiO_2) gave olefin **S16** as colorless oil (0.242 g, 0.963 mmol, 91%).

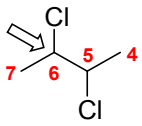
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.74 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H), 5.56 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.43 (ddd, *J* = 10.6, 1.3, 0.9 Hz, 1H), 3.99 (ddd, *J* = 8.8, 5.3, 2.8 Hz, 1H), 3.86 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.66 (ddt, *J* = 6.2, 4.1, 0.9 Hz, 1H), 3.50 (dd, *J* = 8.8, 4.2 Hz, 1H), 1.94 – 1.78 (m, 2H), 1.52 – 1.42 (m, 1H), 1.40 – 1.20 (m, 7H), 0.94 – 0.84 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 130.9, 121.6, 62.9, 62.4, 60.2, 59.0, 35.4, 31.7, 28.7, 26.4, 22.7, 14.2; HRMS (EI): exact mass for $C_{12}H_{20}ClO$ $[M\text{-}Cl]^+$, calculated 215.1197, found 215.1198; IR (thin film, cm^{-1}): ν 2956, 2929, 2859, 1467, 1254, 985, 933, 823, 772, 662; Optical Rotation: $[\alpha]_D^{23}$ = +82.3 (c = 0.55, $CHCl_3$).

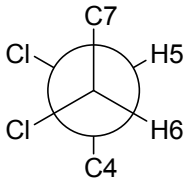
J-Based Configuration Analysis of **S16**:



C5-C6 (A-1, *syn*)

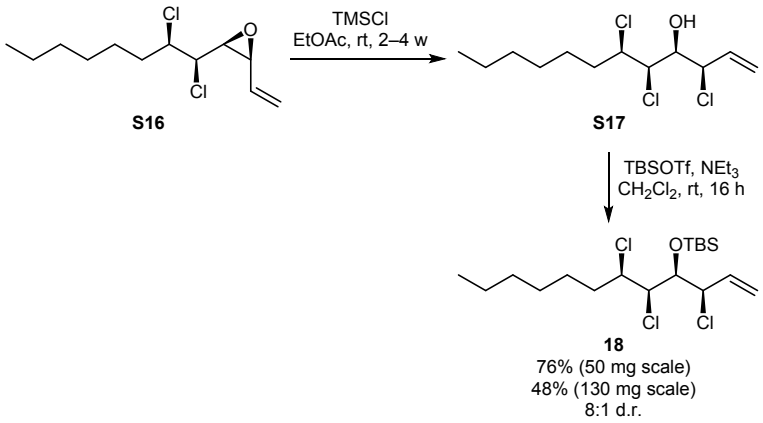
$^{3}J_{H4,H5}$ = 2.8 Hz (S)
$^{3}J_{H4,C6}$ = 2.0 Hz (S)
$^{3}J_{C3,H5}$ = 2.5 Hz (M)
$^{2}J_{C4,H5}$ = –0.9 Hz (S)
$^{2}J_{H4,C5}$ = 1.8 Hz (S)





C3-C4 (*cis* epoxide)

$^{3}J_{H3,H4}$ = 4.1 Hz (L)



***tert*-butyldimethyl(((3*R*,4*S*,5*R*,6*R*)-3,5,6-trichlorododec-1-en-4-yl)oxy)silane (18):** To a solution of epoxide **S16** (50.0 mg, 0.199 mmol, 1.00 equiv) in EtOAc (6.5 mL) at 0 °C was added TMSCl (63.0 µL, 0.498 mmol, 2.50 equiv) in CH_2Cl_2 (184 µL) dropwise. The reaction was allowed to warm to 23 °C and was stirred for 2 weeks. The reaction was quenched with pH7 buffer solution and extracted three times with EtOAc. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give crude alcohol **S17** with a diastereomeric ratio of 8:1 (as determined from crude ^{1}H NMR).

Crude analysis of alcohol **S17**:

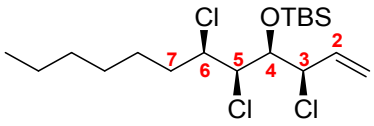
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (ddd, *J* = 17.1, 10.1, 8.4 Hz, 1H), 5.40 (dt, *J* = 16.7, 0.8 Hz, 1H), 5.27 (dt, *J* = 10.3, 0.8 Hz, 1H), 4.54 (dd, *J* = 8.5, 4.8 Hz, 1H), 4.18 – 4.09 (m, 2H), 4.02 (q, *J* = 5.0 Hz, 1H), 2.42 (d, *J* = 4.9 Hz, 1H), 1.99 – 1.72 (m, 2H), 1.41 – 1.14 (m, 8H), 0.89 – 0.72 (m, 3H).

The residue was taken up in CH_2Cl_2 (2.0 mL). Triethylamine (0.111 mL, 0.796 mmol, 4.00 equiv) and TBSOTf (0.137 mL, 0.597 mmol, 3.00 equiv) were added and the reaction was stirred for 16 hours. The solution was then poured into water and extracted three times with CH_2Cl_2. Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (hexanes, SiO_2) gave compound **18** as colorless oil (60.8 mg, 0.151 mmol, 76%).

The same conditions (stirring epoxide opening for 1 month) on a 130 mg scale, gave trichloride **18** in 48% yield.

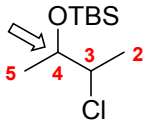
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.00 (ddd, *J* = 16.9, 10.2, 7.7 Hz, 1H), 5.38 (dt, *J* = 17.0, 1.0 Hz, 1H), 5.25 (dt, *J* = 10.2, 0.9 Hz, 1H), 4.61 (ddt, *J* = 7.7, 2.1, 1.0 Hz, 1H), 4.26 (ddd, *J* = 8.1, 5.8, 2.5 Hz, 1H), 4.13 (dd, *J* = 7.0, 2.5 Hz, 1H), 4.10 (dd, *J* = 7.0, 2.2 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.52 – 1.44 (m, 1H), 1.44 – 1.37 (m, 1H), 1.37 – 1.23 (m, 6H), 0.94 (s, 9H), 0.92 – 0.86 (m, 3H), 0.19 (d, *J* = 0.4 Hz, 3H), 0.11 (d, *J* = 0.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 135.8, 118.5, 78.0, 68.1, 63.8, 62.4, 36.8, 31.7, 28.8, 26.3, 26.3, 22.7, 18.8, 14.2, -3.0, -3.3; HRMS (EI): exact mass for $C_{14}H_{26}Cl_3OSi$ $[M\text{-}C_4H_9]^+$, calculated 343.0813, found 343.0813; IR (thin film, cm^{-1}): *ν* 2957, 2929, 2858, 1472, 1464, 1362, 1256, 1134, 991, 929, 861, 838, 805, 778, 707; Optical Rotation: $[\alpha]_D^{23}$ = +30.0 (c = 0.50, $CHCl_3$).

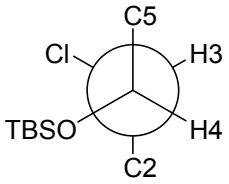
J-Based Configuration Analysis of **18**:



C3-C4 (A-1, *syn*)

$^{3}J_{H3,H4}$ = 2.2 Hz (S)
$^{3}J_{H4,C2}$ = (1.8 Hz)* (S)
$^{3}J_{C5,H3}$ = 1.1 Hz (S)
$^{2}J_{C4,H3}$ = –0.5 Hz (S)
$^{2}J_{C3,H4}$ = (2.5 Hz)* (S)

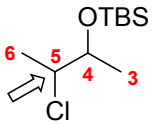


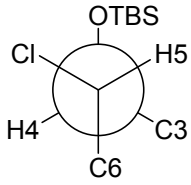


* number in parentheses indicates an inaccurate absolute value

C4-C5 (A-3, *syn*)

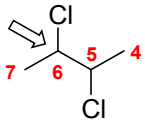
$^{3}J_{H4,H5}$ = 7.0 Hz (L)
$^{3}J_{H5,C3}$ = 1.5 Hz (S)
$^{3}J_{C6,H4}$ = 2.5 Hz (S)
$^{2}J_{C5,H4}$ = –4.8 Hz (L)
$^{2}J_{C4,H5}$ = –5.6 Hz (L)
$NOE_{(H3,H6)}$: visible

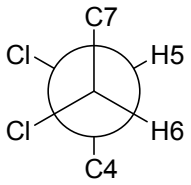


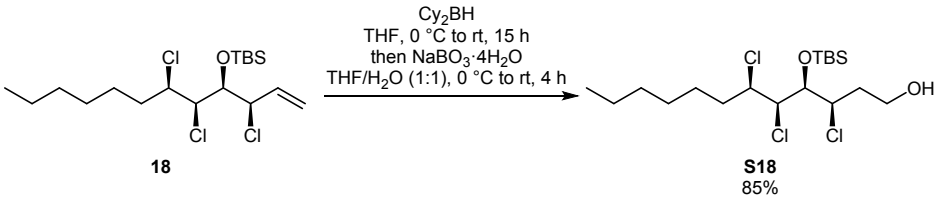


C5-C6 (A-1, *syn*)

$^{3}J_{H5,H6}$ = 2.5 Hz (S)
$^{3}J_{H6,C4}$ = 0.9 Hz (S)
$^{3}J_{C7,H5}$ = 1.2 Hz (S)
$^{2}J_{C6,H5}$ = nd
$^{2}J_{C5,H6}$ = nd (S)

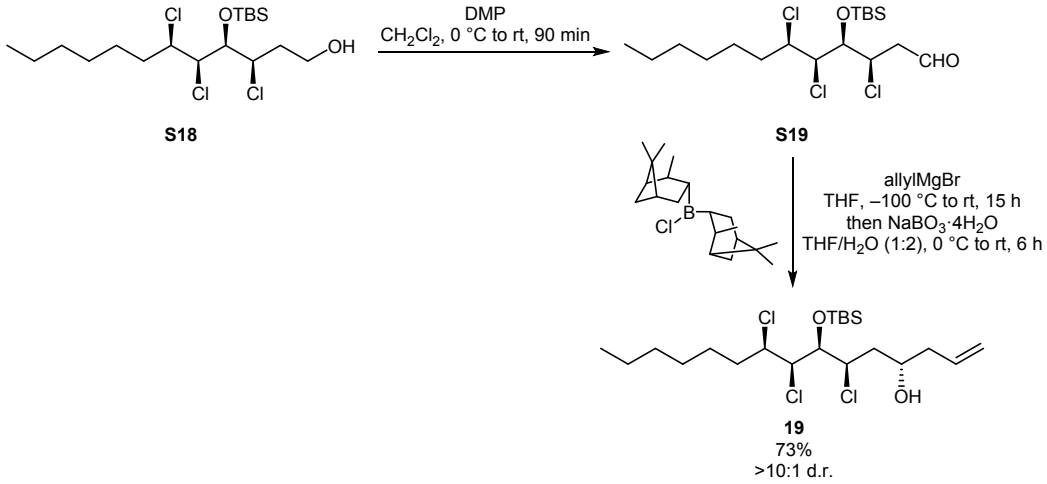






(3*R*,4*S*,5*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3,5,6-trichlorododecan-1-ol (S18): Dicyclohexylborane (111 mg, 0.621 mmol, 2.40 equiv) was suspended in THF (1.5 mL) and cooled to 0 °C. To the suspension was added olefin **18** (104 mg, 0.259 mmol, 1.00 equiv) in THF (0.8 mL), rinsing with THF (2x 0.1 mL). The reaction was allowed to warm to 25 °C during 15 hours. Subsequently it was cooled to 0 °C and water (2.2 mL) was added,followed by $NaBO_3 \cdot 4H_2O$ (1.19 g, 7.76 mmol, 30.0 equiv). Cooling was removed and the reaction was stirred for 4 hours before being separated between water and EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc twice. Combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (hexanes/Et_2O 5:1, SiO_2) gave alcohol **S18** as colorless oil (92.0 mg, 0.219 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (ddd, *J* = 10.0, 3.5, 1.7 Hz, 1H), 4.26 (ddd, *J* = 8.0, 5.9, 2.1 Hz, 1H), 4.21 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.06 (dd, *J* = 7.1, 1.7 Hz, 1H), 3.86 (ddd, *J* = 7.9, 5.2, 3.8 Hz, 2H), 2.08 (ddt, *J* = 14.5, 10.2, 4.4 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.90 (dddd, *J* = 17.6, 9.3, 6.9, 4.4 Hz, 2H), 1.43 (t, *J* = 5.1 Hz, 1H), 1.53 – 1.21 (m, 8H), 0.94 (s, 9H), 0.91 – 0.85 (m, 3H), 0.22 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 77.9, 68.2, 62.3, 59.9, 59.5, 38.4, 37.0, 31.7, 28.8, 26.4, 26.3, 22.7, 18.8, 14.2, -3.0, -3.3; HRMS (ESI): exact mass for $C_{18}H_{37}Cl_3NaO_2Si$ $[M+Na]^+$, calculated 441.1521, found 441.1521; IR (thin film, cm^{-1}): *ν* 3326, 2956, 2929, 2858, 1472, 1254, 1125, 1055, 835, 778, 685, 617; Optical Rotation: $[\alpha]_D^{23}$ = +27.8 (c = 1.0, $CHCl_3$).



(4*S*,6*R*,7*S*,8*R*,9*R*)-7-((*tert*-butyldimethylsilyl)oxy)-6,8,9-trichloropentadec-1-en-4-ol (19): To a solution of alcohol **S18** (92.0 mg, 0.219 mmol, 1.00 equiv) in CH_2Cl_2 (2.2 mL) at 0 °C was added Dess–Martin Periodinane (112 mg, 0.263 mmol, 1.20 equiv). Cooling was removed after 15 minutes and the reaction was stirred for another 75 minutes. Sat. aq. $Na_2S_2O_3$ was added, followed by sat. aq. $NaHCO_3$. The aqueous phase was extracted with Et_2O three times. Combined organic phases were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. Crude aldehyde **S19** was used as is.

Crude analysis of aldehyde **S19**:

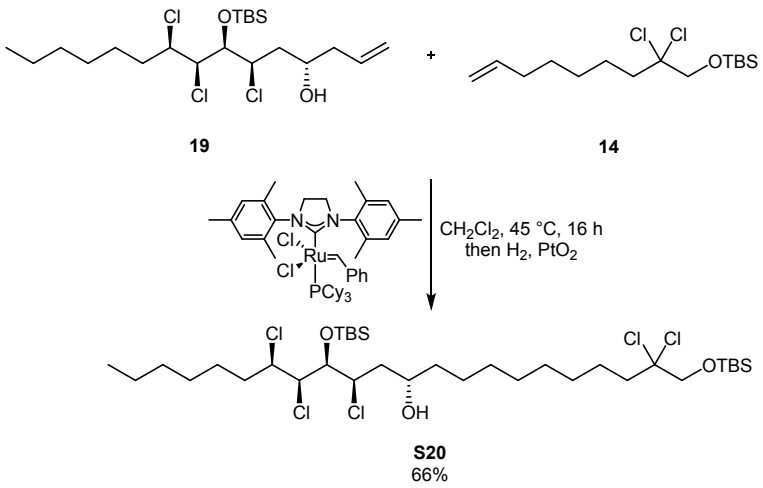
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (d, *J* = 2.1 Hz, 1H), 4.63 (ddd, *J* = 9.3, 4.0, 2.1 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.20 (dd, *J* = 6.8, 2.2 Hz, 1H), 4.12 (dd, *J* = 6.7, 2.0 Hz, 1H), 3.11 (ddd, *J* = 17.9, 9.3, 1.6 Hz, 1H), 2.97 – 2.81 (m, 1H), 1.90 (ddd, *J* = 10.5, 6.1, 2.0 Hz, 2H), 1.49 – 1.19 (m, 8H), 0.95 (s, 9H), 0.89 (td, *J* = 6.8, 6.2, 3.1 Hz, 3H), 0.22 (s, 3H), 0.14 (s, 3H).

To a solution of (–)-DIP-Chloride (140 mg, 0.438 mmol, 2.00 equiv) in THF (3.7 mL) at –78 °C was added allylmagnesium bromide (1.0 M in Et_2O, 0.33 mL, 0.33 mmol, 1.5 equiv) dropwise. After stirring 1 hour at –78 °C and 30 minutes without cooling, the reaction was cooled to –100 °C. Crude aldehyde **S19** in THF (0.7 mL) was added slowly, rinsing with THF (2x 0.1 mL). The reaction was allowed

to warm to 24 °C for 15 hours, before being cooled to 0 °C. Water (8 mL) and $NaBO_3 \cdot 4H_2O$ (1.01 g, 6.57 mmol, 30.0 equiv) was added and the reaction was stirred at 0 °C for 1 hour. After another 5 hours without cooling, the reaction was filtered into water, rinsing with EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc twice. Combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (hexanes/EtOAc 10:1, SiO_2) gave the homoallylic alcohol **19** as colorless oil (73.8 mg, 0.16 mmol, 73% over both steps) in a diastereomeric ratio of >10:1 (as determined from ^{1}H NMR of the purified product).

Employing the same reaction conditions on a 5.0 mg scale, gave product **19** in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dddd, *J* = 16.4, 10.9, 7.8, 6.7 Hz, 1H), 5.19 (s, 1H), 5.17 – 5.11 (m, 1H), 4.49 (dt, *J* = 10.8, 2.0 Hz, 1H), 4.27 (ddd, *J* = 7.9, 6.1, 2.0 Hz, 1H), 4.20 (dd, *J* = 7.3, 2.0 Hz, 1H), 4.03 (dd, *J* = 7.4, 1.6 Hz, 1H), 3.97 (dtt, *J* = 9.5, 4.7, 2.2 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.28 – 2.18 (m, 1H), 2.09 – 1.99 (m, 1H), 1.97 – 1.81 (m, 2H), 1.71 – 1.67 (m, 1H), 1.67 – 1.60 (m, 1H), 1.53 – 1.15 (m, 8H), 0.94 (s, 9H), 0.91 – 0.83 (m, 3H), 0.22 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 134.0, 119.1, 78.4, 68.3, 67.1, 62.1, 60.4, 43.1, 42.6, 37.0, 31.7, 28.8, 26.4, 26.3, 22.7, 18.9, 14.2, -3.0, -3.3; HRMS (EI): exact mass for $C_{21}H_{41}Cl_3O_2Si$ $[M-C_4H_9]^+$, calculated 401.1232, found 401.1232; IR (thin film, cm^{-1}): ν 3362, 2957, 2929, 2858, 1472, 1464, 1255, 1140, 1114, 1071, 995, 919, 836, 778, ; Optical Rotation: $[\alpha]_D^{23} = +35.1$ (c = 0.5, $CHCl_3$).

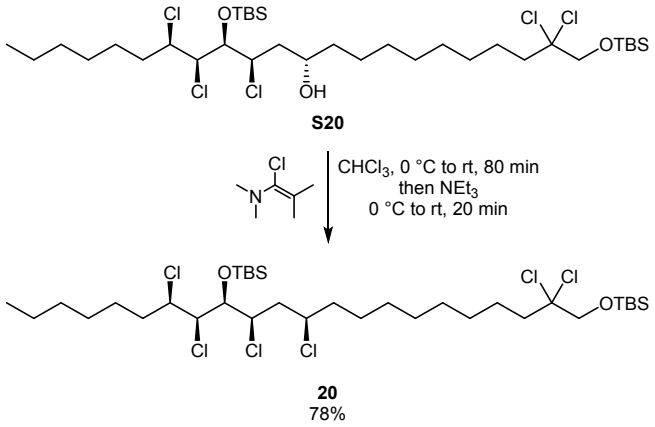


(5*S*,6*R*,8*S*)-6,17,17-trichloro-5-((1*R*,2*R*)-1,2-dichlorooctyl)-2,2,3,3,20,20,21,21-octamethyl-4,19-dioxa-3,20-disiladocosan-8-ol (S20): Homoallylic alcohol **19** (41.0 mg, 89.0 μmol, 1.00 equiv) and olefin **14**[16] (87.0 mg, 0.267 mmol, 3.00 equiv) were dissolved in CH_2Cl_2 (4.5 mL, previously sparged with argon for 20 minutes). Grubbs' 2nd Generation Catalyst (7.6 mg, 8.9 μmol, 10 mol%) was added and the reaction was stirred at 45 °C under argon for 16 hours. The mixture was allowed to cool to 24 °C and PtO_2 (2.0 mg, 8.9 μmol, 10 mol%) was added. The reaction was placed under an atmosphere of hydrogen (5 backfills) and stirred for 6 hours before it was filtered through a plug of silica, eluting with CH_2Cl_2. Solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 30:1, SiO_2) to give alcohol **S20** as colorless oil (44.8 mg, 59.0 μmol, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (dt, *J* = 10.7, 2.0 Hz, 1H), 4.27 (ddd, *J* = 7.9, 6.0, 2.1 Hz, 1H), 4.21 (dd, *J* = 7.4, 2.0 Hz, 1H), 4.02 (dd, *J* = 7.3, 1.6 Hz, 1H), 3.92 (s, 2H), 3.94 – 3.85 (m, 1H), 2.23 – 2.12 (m, 2H), 2.03 (ddd, *J* = 13.5, 10.9, 2.2 Hz, 1H), 1.90 (dddd, *J* = 16.3, 14.0, 8.4, 4.3 Hz, 2H), 1.66 – 1.56 (m, 3H), 1.55 – 1.21 (m, 21H), 0.94 (s, 9H), 0.91 (s, 9H), 0.91 – 0.86 (m, 3H), 0.22 (s, 3H), 0.13 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 93.7, 78.4, 72.3, 68.4, 68.3, 62.2, 60.5, 43.7, 43.5, 38.2, 37.0, 31.7, 29.6, 29.5, 29.4, 29.2, 28.8, 26.4, 26.3, 25.9, 25.7, 24.9, 22.7, 18.9, 18.4, 14.2, -3.0, -3.3, -5.2; HRMS (ESI): exact mass for $C_{34}H_{70}Cl_5O_3Si_2$ $[M+H]^+$, calculated 757.3301, found 757.3198 (high error presumably due to minimal amounts

[16] A. M. Bailey, S. Wolfrum, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 639.

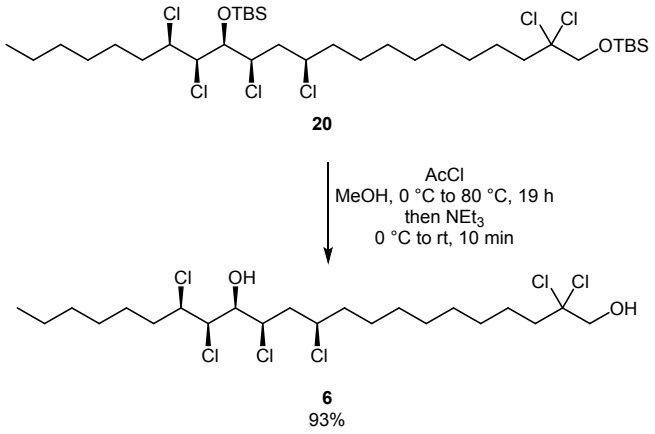
of residual olefin in the sample); IR (thin film, cm^{-1}): ν 3353, 2955, 2929, 2857, 1472, 1463, 1255, 1118, 836, 778, 694; Optical Rotation: $[\alpha]_D^{23} = +17.8$ (c = 1.0, $CHCl_3$).



(5*S*,6*R*,8*R*)-6,8,17,17-tetrachloro-5-((1*R*,2*R*)-1,2-dichlorooctyl)-2,2,3,3,20,20,21,21-octamethyl-4,19-dioxa-3,20-disiladocosane (20): To a solution of alcohol **S20** (44.5 mg, 59.0 μmol, 1.00 equiv) in $CHCl_3$ (1.2 mL, previously filtered through activated basic alumina) at 0 °C was added Ghosez‘ reagent (25 μL, 0.18 mmol, 3.0 equiv). Cooling was removed and the reaction was stirred for 75 minutes. After cooling to 0 °C again, triethylamine (33 μL, 0.23 mmol, 4.0 equiv) were added. Cooling was removed and the reaction was stirred for 20 minutes before celite was added and solvent removed. The solid was applied to a column and purified by repeated column chromatography (hexanes, SiO_2) to give the title compound **20** as colorless oil (35.5 mg, 46.0 μmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (ddd, *J* = 7.7, 6.2, 1.5 Hz, 1H), 4.24 (ddd, *J* = 7.8, 6.0, 2.0 Hz, 1H), 4.15 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.08 (dd, *J* = 7.2, 1.5 Hz, 1H), 4.05 – 3.99 (m, 1H), 3.92 (s, 2H), 2.34 (dt, *J* = 14.9, 7.5 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.20 – 2.12 (m, 2H), 1.99 – 1.83 (m, 2H), 1.76 (m, 1H), 1.72 – 1.65 (m, 1H), 1.65 – 1.55 (m, 3H), 1.52 – 1.19 (m, 17zH), 0.94 (s, 9H), 0.92 (s, 9H), 0.98 – 0.83 (m, 3H), 0.24 (s, 3H), 0.14 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 93.6, 77.1, 72.3, 68.3, 62.0, 59.6, 59.5, 44.0, 43.7, 37.3, 37.0, 31.7, 29.5, 29.4, 29.2, 29.1, 28.8, 26.4, 26.3, 26.1, 25.9, 24.9, 22.7, 18.9, 18.4, 14.2, -2.8, -3.5, -5.2; HRMS (ESI): exact mass for $C_{34}H_{72}Cl_4NO_2Si_2$ $[M+NH_4]^+$, calculated 792.3227, found 792.3219; IR (thin film,

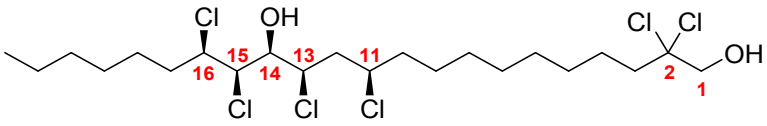
cm^{-1}): ν 2954, 2929, 2857, 1463, 1255, 1120, 837, 778, 696; Optical Rotation: $[\alpha]_D^{23}$ = +13.4 (c = 0.5, $CHCl_3$).



(11*R*,13*R*,14*S*,15*R*,16*R*)-2,2,11,13,15,16-hexachlorodocosane-1,14-diol (6): To a solution of disilylether **20** (7.9 mg, 10.2 μmol, 1.00 equiv) in MeOH (1.0 mL) at 0 °C was added acetyl chloride (36 μL, 0.51 mmol, 50 equiv) and cooling was removed. The reaction was heated at 80 °C for 19 hours before being cooled back to 0 °C. Triethylamine (71 μL, 0.51 mmol, 50 equiv) was added and cooling was removed. After 10 minutes, celite was added and solvent was removed. The solid was purified by flash column chromatography (hexanes/EtOAc gradient from 10:1 to 5:1, SiO_2) to give diol **6** as colorless oil (5.2 mg, 9.5 μmol, 93%).

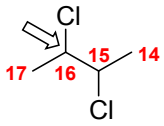
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (ddd, *J* = 8.5, 6.0, 1.9 Hz, 1H), 4.29 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.22 (ddd, *J* = 8.0, 5.9, 2.1 Hz, 1H), 4.12 (ddd, *J* = 7.5, 4.9, 2.1 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.90 (d, *J* = 7.5 Hz, 2H), 2.49 (ddd, *J* = 14.3, 8.6, 4.2 Hz, 1H), 2.45 (dd, *J* = 5.0, 1.1 Hz, 1H), 2.32 (t, *J* = 7.5 Hz, 1H), 2.29 (ddd, *J* = 14.4, 9.7, 5.9 Hz, 1H), 2.24 – 2.19 (m, 2H), 2.03 – 1.84 (m, 2H), 1.82 – 1.69 (m, 2H), 1.68 – 1.60 (m, 3H), 1.56 – 1.17 (m, 17H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 91.3, 81.4, 75.5, 66.4, 63.0, 61.2, 59.5, 45.1, 45.0, 39.0, 37.4, 32.8, 30.4, 30.4, 30.0, 30.0, 29.7, 27.3, 27.0, 25.8, 23.6, 14.4; HRMS (ESI): exact mass for $C_{22}H_{44}Cl_6NO_2$ $[M+NH_4]^+$, calculated 564.1498, found 564.1497; IR (thin film, cm^{-1}): ν 3409, 2928, 2856, 1465, 1378, 1278, 1073, 707, 603; Optical Rotation: $[\alpha]_D^{21}$ = +2.8 (c = 0.25, $CHCl_3$).

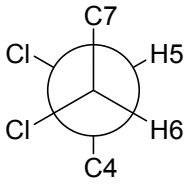
J-Based Configuration Analysis of **6**:



C15-C16 (A-1, *syn*)

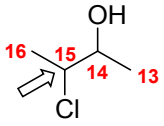
$^{3}J_{H15,H16}$ = 2.1 Hz (S)
$^{3}J_{H16,C14}$ = nd (S)
$^{3}J_{C17,H15}$ = 1.4 Hz (S)
$^{2}J_{C16,H15}$ = 1.9 Hz (S)
$^{2}J_{C15,H16}$ = 2.0 Hz (S)

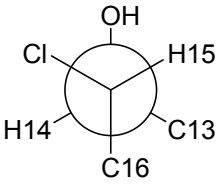




C14-C15 (A-3, *syn*)

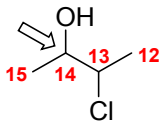
$^{3}J_{H14,H15}$ = 7.0 Hz (L)
$^{3}J_{H15,C13}$ = 1.5 Hz (S)
$^{3}J_{C16,H14}$ = 2.5 Hz (S)
$^{2}J_{C15,H14}$ = –4.8 Hz (L)
$^{2}J_{C14,H15}$ = –5.6 Hz (L)
$NOE_{(H13,H16)}$: visible

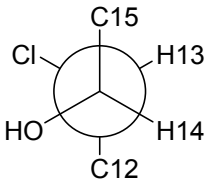




C13-C14 (A-1, *syn*)

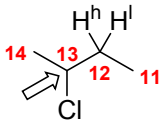
$^{3}J_{H13,H14}$ = 2.0 Hz (S)
$^{3}J_{H14,C12}$ = 0.8 Hz (S)
$^{3}J_{C15,H13}$ = 0.5 Hz (S)
$^{2}J_{C14,H13}$ = nd
$^{2}J_{C13,H14}$ = 2.0 Hz (S)

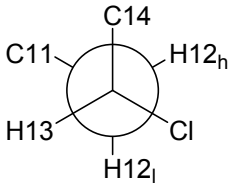




C12-C13 (D-3, H_h: higher field, H_l: lower field)

$^3J_{H13,H12h}$ = 5.9 Hz (M)
$^3J_{H13,H12l}$ = 8.5 Hz (L)
$^3J_{H13,C11}$ = 2.4 Hz (S)
$^3J_{C14,H12h}$ = nd
$^3J_{C14,H12l}$ = nd
$^2J_{C13,H12h}$ = nd (L)*
$^2J_{C13,H12l}$ = nd (S)*

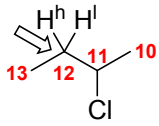


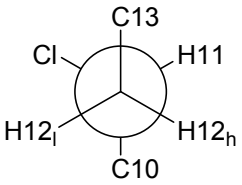


* no absolute value obtained, size derived by comparing intensities in the ps-HMBC

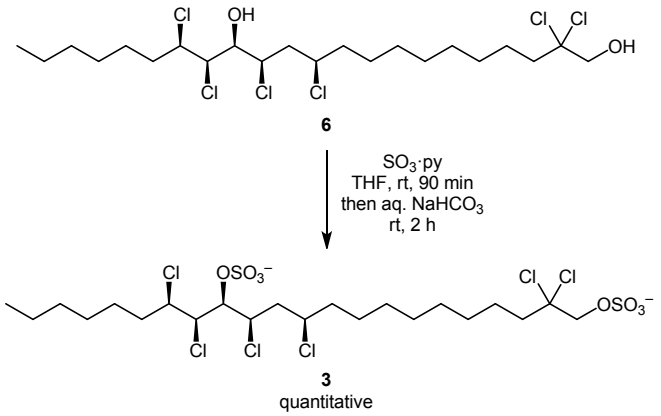
C11-C12 (D-1, H_h: higher field, H_l: lower field)

$^3J_{H12h,H11}$ = 9.7 Hz (L)
$^3J_{H12l,H11}$ = 4.2 Hz (M)
$^3J_{H11,C13}$ = 2.4 Hz (S)
$^3J_{C10,H12h}$ = 3.0 Hz (S)
$^3J_{C10,H12l}$ = 2.0 Hz (S)
$^2J_{C11,H12h}$ = nd (L)*
$^2J_{C11,H12l}$ = nd (S)*





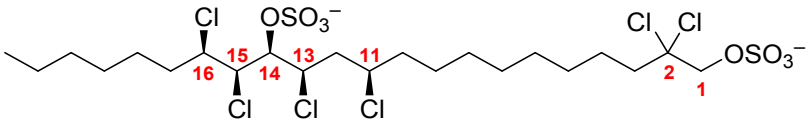
* no value measurable, only possible combination assumed



(11*R*,13*R*,14*S*,15*R*,16*R*)-2,2,11,13,15,16-hexachlorodocosane-1,14-diyl bis(sulfate) disodium salt (3): Diol **6** (9.1 mg, 17 μmol, 1.0 equiv) was dissolved in THF and SO_3·pyridine complex (10.8 mg, 68.0 μmol, 4.1 equiv) was added. After 90 minutes of stirring SO_3·pyrdine complex (5.4 mg, 34 μmol, 2.0 equiv) was added. After another 15 minutes, sat. aq. $NaHCO_3$ was added and the suspension stirred for 2 hours. The mixture was filtered through a silica plug, eluting with CH_2Cl_2/MeOH 3:1. The residue was concentrated and applied to a column. Flash column chromatography (CH_2Cl_2/MeOH gradient from 8:1 to 6:1, SiO_2) gave the title compound **3** as white solid (12.7 mg, 18 μmol, quantitative). This compound was stable in solution (DMSO) for several months.

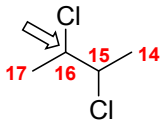
^{1}H NMR (400 MHz, CD_3OD): δ 4.96 (dd, *J* = 7.3, 1.9 Hz, 1H), 4.65 (ddd, *J* = 8.8, 5.5, 1.9 Hz, 1H), 4.42 (dd, *J* = 7.3, 2.6 Hz, 1H), 4.35 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.32 (s, 2H), 4.23 (dtd, *J* = 10.5, 6.3, 5.2, 2.5 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.30 – 2.22 (m, 2H), 2.23 – 2.12 (m, 1H), 2.01 – 1.94 (m, 2H), 1.83 (ddt, *J* = 9.6, 6.1, 3.7 Hz, 1H), 1.66 (m, 3H), 1.60 – 1.20 (m, 18H), 0.92 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD): δ 91.3, 81.3, 75.5, 66.4, 63.0, 61.2, 59.5, 45.1, 45.0, 39.0, 37.4, 32.8, 30.4, 30.4, 30.1, 30.0, 29.7, 27.3, 27.0, 25.8, 23.6, 14.4; HRMS (ESI): exact mass for $C_{22}H_{42}Cl_6NNa_2O_8S_2$ $[M+NH_4]^+$, calculated 724.0634, found 724.0635; IR (thin film, cm^{-1}): ν 3439, 2928, 2857, 1625, 1459, 1227, 1083, 1004, 836, 709; Optical Rotation: $[\alpha]_D^{22}$ = +8.0 (c = 1.0, MeOH).

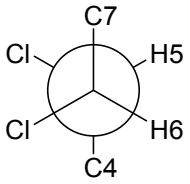
J-Based Configuration Analysis of **3**:



C15-C16 (A-1, *syn*)

$^{3}J_{H15,H16}$ = 2.7 Hz (S)
$^{3}J_{H16,C14}$ = nd (S)*
$^{3}J_{C17,H15}$ = nd (S)*
$^{2}J_{C16,H15}$ = nd
$^{2}J_{C15,H16}$ = nd

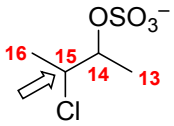


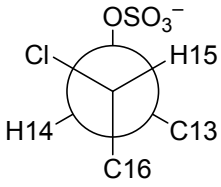


* unreadable but intensity of cross peak points to small coupling constant

C14-C15 (A-3, *syn*)

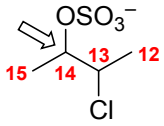
$^{3}J_{H14,H15}$ = 7.3 Hz (L)
$^{3}J_{H15,C13}$ = nd
$^{3}J_{C16,H14}$ = nd
$^{2}J_{C15,H14}$ = –5.0 Hz (L)
$^{2}J_{C14,H15}$ = –5.4 Hz (L)

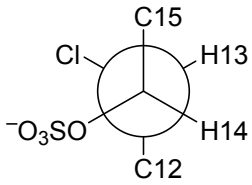




C13-C14 (A-1 or A-2, *syn*)

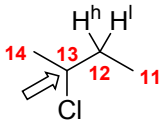
$^{3}J_{H13,H14}$ = 1.9 Hz (S)
$^{3}J_{H14,C12}$ = nd
$^{3}J_{C15,H13}$ = nd
$^{2}J_{C14,H13}$ = nd
$^{2}J_{C13,H14}$ = nd

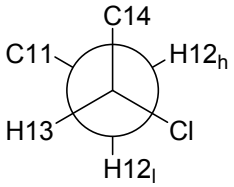




C12-C13 (D-3 + D-1, H_h: higher field, H_l: lower field)

$^3J_{H13,H12h}$ = 5.6 Hz (M)
$^3J_{H13,H12l}$ = 8.7 Hz (L)
$^3J_{H13,C11}$ = (2.0 Hz)* (S)
$^3J_{C14,H12h}$ = nd
$^3J_{C14,H12l}$ = nd
$^2J_{C13,H12h}$ = nd
$^2J_{C13,H12l}$ = (–1.5)* (M)

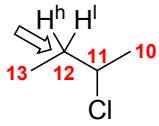


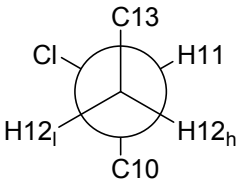


* coupling constants were hard to read from the spectrum, values approximated

C11-C12 (D-1 + D-3, H_h: higher field, H_l: lower field)

$^3J_{H12h,H11}$ = 9.7 Hz (L)
$^3J_{H12l,H11}$ = 4.0 Hz (M)
$^3J_{H11,C13}$ = nd
$^3J_{C10,H12h}$ = nd
$^3J_{C10,H12l}$ = nd
$^2J_{C11,H12h}$ = nd
$^2J_{C11,H12l}$ = nd

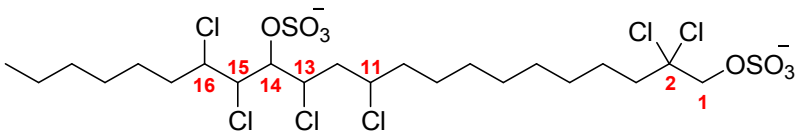




* no value measurable, only possible combination assumed

The coupling constants along both bonds (C11–C12 and C12–C13) are consistent with one conformer dominating (tg$^-$) and a second one contributing less (g$^+$t). Specifically, a coupling constant of 4.0 Hz (or 5.6 Hz) can be explained as a mixture of small and large with the dominant conformation contributing a small coupling constant. Meanwhile a coupling constant of 8.7 Hz (or 9.7 Hz) is explained by the combination of a small and a large coupling constant, with the larger one stemming from the dominant conformation.

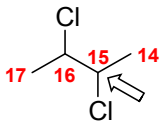
4.3 *J*-Based Configuration Analysis of Danicalipin A

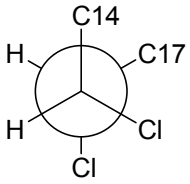


Spectra measured in methanol-d4:

C15-C16

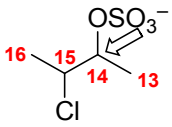
$^{3}J_{H15,H16}$ = 1.9 Hz (S)
$^{3}J_{H15,C17}$ = nd
$^{3}J_{C14,H16}$ = nd
$^{2}J_{C15,H16}$ = (–5.0 Hz)
$^{2}J_{C16,H15}$ = nd

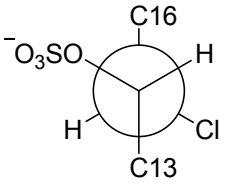




C14-C15 (*anti*)

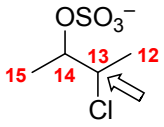
$^{3}J_{H14,H15}$ = 10.2 Hz
$^{3}J_{H14,C16}$ = nd
$^{3}J_{C13,H15}$ = nd
$^{2}J_{C14,H15}$ = –6.1 Hz
$^{2}J_{C15,H14}$ = –7.8 Hz

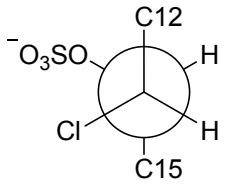




C13-C14

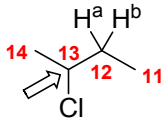
$^{3}J_{H13,H14}$ = 1.5 Hz (S)
$^{3}J_{H13,C15}$ = nd (S)
$^{3}J_{C12,H14}$ = nd
$^{2}J_{C13,H14}$ = nd
$^{2}J_{C14,H13}$ = nd

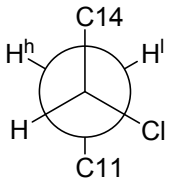




C13-C12 (H_h: higher field, H_l: lower field)

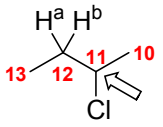
$^3J_{H13,H12l}$ = 11.5 Hz (L)
$^3J_{H13,H12h}$ = 2.1 Hz (S)
$^3J_{H13,C11}$ = nd
$^3J_{C14,H12l}$ = nd
$^3J_{C14,H12h}$ = nd
$^2J_{C13,H12l}$ = nd
$^2J_{C13,H12h}$ = nd

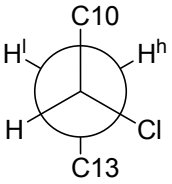




C11-C12 (H_h: higher field, H_l: lower field)

$^3J_{H11,H12l}$ = 2.0 Hz (S)
$^3J_{H11,H12h}$ = 11.2 Hz (L)
$^3J_{H11,C13}$ = 3.4 Hz (S)
$^3J_{C10,H12l}$ = 1.3 Hz (S)
$^3J_{C10,H12h}$ = 1.4 Hz (S)
$^2J_{C11,H12l}$ = nd
$^2J_{C11,H12h}$ = nd





5 Biological Studies

5.1 Experimental Set-up and Reagents for Biological Studies

Solvents, reagents and supplies for biological experiments: All chemicals and solvents were purchased from Sigma Aldrich or Thermo Fisher Scientific. All cell culture material and supplies were purchased from Thermo Fisher Scientific.

Brine Shrimp Assay: The brine shrimp eggs, hatchery, and artemia salt were purchased from a pet store (Qualipet) and were distributed by Hobby. Dry baker's yeast was manufactured and distributed by Patissier and purchased from Migros.

Cell Cytotoxicity and Permeability Testing: The three cell lines were purchased from ATCC®: HT-29 cells (cat. number: HTB-38™), A549 cells (cat. number: CCL-185™), and Hepa 1-6 cells (cat. number: CRL-1830™). (Phenol-red free) DMEM (Dulbecco's modified Eagle's medium), fetal bovine serum (FBS), Penicillin Streptomycin, phosphate buffered saline (PBS; pH = 7.4), 0.25% Trypsin-ethylenediaminetetraacetic acid (Trypsin-EDTA), Hoechst 33342, and Sytox Green dyes were purchased from Fisher Scientific. Black, clear bottom microtiter plates were purchased from Greiner Bio-One International. Tamoxifen, Tergitol (NP40), and HCl were purchased from Sigma Aldrich.

Bacterial Studies: *E. coli* DH5*α* were purchased from Thermo Fisher Scientific. Flat-bottomed, black, 96 well plates were purchased from Nunc.

Microscopy: Brine shrimp naupili were counted using a Zeiss Stemi 2000-C microscope. Fluorescence photographs of cells were taken with an Operetta system and the Harmony software (Perkin Elmer) was used for qualitiv analysis of the pictures. Spectrophotometry and fluorescent quantification of stained bacteria were performed using a Biotek Synergy Mx spectrophotometer.

Software: Brine shrimp and cell viability calculations were performed using Microsoft Excel. All graphs were created using Graph Pad Prism 6.6.

5.2 Brine Shrimp Studies

5.2.1 Brine Shrimp Survival Assay

Sample preparation: Samples were prepared by dissolving 10 mg of **1**, **2** and **3** in 1 mL DMSO yielding a 10 mg/mL stock solution which was then used to prepare the following dilutions: 1:1 with DMSO (5 mg/mL), 1:4 with DMSO (2.5 mg/mL), 1:10 with DMSO (1 mg/mL). The resulting solutions were further diluted with DMSO to the following concentrations: 0.5 mg/ml, 0.25 mg/mL, 0.1 mg/mL and 0.01 mg/mL.

Hatching the brine shrimp: The brine shrimp eggs were hatched using a brine shrimp hatchery; which is a round container that is completely covered except for a hole containing a microsieve in the center. Since the Artemia nauplii are attracted to light, they slowly migrated through a series of baffles toward the center leaving their egg shell behind. This set-up naturally separates the shell from the newly hatched Artemia nauplii. The dish-like device was filled with artificial sea water prepared with artemia salt before *ca.* 0.4g eggs were added to the outer ring of the hatchery. After 48 hours the phototropic nauplii were collected from the microsieve by pipette.

Brine shrimp bioassay: Approximately ten shrimp (9 – 16) were transferred to a 24 well tissue culture plate in 2 mL of artificial sea water. The naupili were counted using a microscope set to 1.25x magnification. 20 µL of the series dilutions of **1**, **2**, and **3** (see above) were added to give final concentrations of 100, 50, 10, 5, 2.5, 1 or 0.1 µg/mL of the respective compound per well. Each condition was tested in triplicate. 20 µL of DMSO was added to three control wells to ascertain that the solvent alone had no toxic effect while three untreated wells served to determine the natural death rate of the shrimp during the time of the treatment. A suspension of dry baker's yeast (22 µL; 3mg/5mL in artificial sea water) was added to each well as food supply. The plates were kept in a room with a normal dark-light cycle and survivors were counted under the microscope after 24 hours.

LC_{50} determination: LC_{50} values were determined from the 24 hour live vs. dead counts by transferring mg to µM concentrations and plotting the ln[concentration in

μM] against the number of live shrimp (see below). Subsequent non-linear curve fitting with Graph Pad Prism 6 yielded the values presented in Table 1.

5.2.2 Results

Blanks						
well	live shrimps (t = 0)	live shrimps (t = 24 h)	alive	average [%]	conditions	s.d.
A1	12	12	100%			
A2	13	13	100%	100%	20 μL DMSO	0.0%
A3	12	12	100%			
A4	11	10	91%			
A5	13	12	92%	90%	blank	7.7%
A6	16	13	81%			
A3*	13	13	100%			

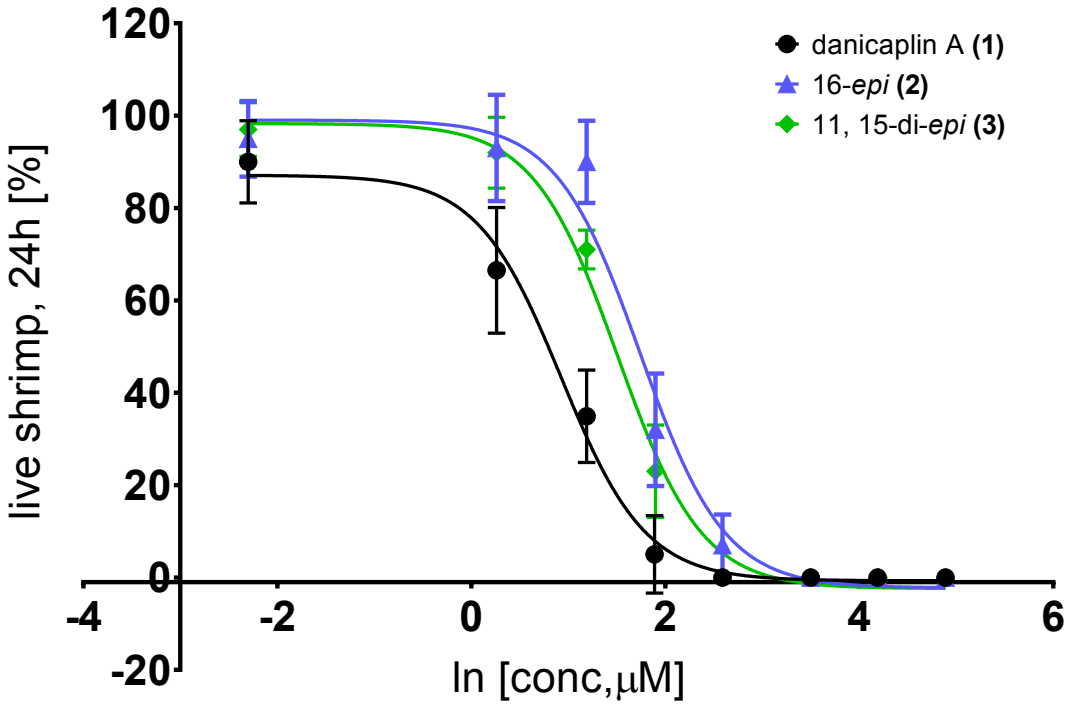
* = data from another well

16-*epi*-Danicalipin A						
well	live shrimps (t = 0)	live shrimps (t = 24 h)	alive	average [%]	final concentration of **2** per well [μM]	s.d.
A1	11	0	0%	0%	133.0	0.0%
A2	13	0	0%			
A4	12	0	0%			
A5	14	0	0%	0%	66.5	0.0%
A6	12	0	0%			
B1	14	0	0%			
B2	9	0	0%	0%	33.0	0.0%
B3	10	0	0%			
B4	14	1	7%			
B5	15	2	13%	7%	13.3	6.7%
B6	10	0	0%			
C1	14	5	36%			
C2	11	2	18%	32%	6.7	12.2%
C3	12	5	42%			
C4	13	11	85%			
C5	13	11	85%	90%	3.3	8.9%
C6	10	10	100%			
D1	10	8	80%			
D2	12	12	100%	93%	1.3	11.5%
D3	10	10	100%			
D4	10	10	100%			
D5	14	12	86%	95%	0.1	8.2%
D6	10	10	100%			

11,15-di-*epi*-Danicalipin A						
well	live shrimps (t = 0)	live shrimps (t = 24 h)	alive	average [%]	final concentration of **3** per well [μM]	s.d.
A1	14	0	0%	0%	133.0	0.0%
A2	14	0	0%			
A4	11	0	0%			
A5	12	0	0%	0%	66.5	0.0%
A6	11	0	0%			
B1	12	0	0%			
B2	11	0	0%	0%	33.0	0.0%
B3	15	0	0%			
B4	15	0	0%			
B5	14	0	0%	0%	13.3	0.0%
B6	15	0	0%			
C1	9	3	33%			
C2	15	2	13%	23%	6.7	10.0%
C3	13	3	23%			
C4	10	7	70%			
C5	12	8	67%	71%	3.3	4.2%
C6	12	9	75%			
D1	9	9	100%			
D2	13	12	92%	92%	1.3	7.7%
D3	13	11	85%			
D4	10	9	90%			
D5	10	10	100%	97%	0.1	5.8%
D6	13	13	100%			

Danicalipin A (Run 1)						
well	live shrimps (t = 0)	live shrimps (t = 24 h)	alive	average [%]	final concentration of **3** per well [μM]	s.d.
A1	10	0	0%			
A2	10	0	0%	0%	133.0	0.0%
A3	11	0	0%			
A4	10	0	0%			
A5	10	0	0%	0%	66.5	0.0%
A6	10	0	0%			
B1	10	0	0%			
B2	10	0	0%	0%	33.0	0.0%
B3	10	0	0%			
B4	10	0	0%			
B5	10	0	0%	0%	13.3	0.0%
B6	10	0	0%			
C1	10	1	10%			
C2	10	2	20%	10%	6.7	10.0%
C3	11	0	0%			
C4	10	2	20%			
C5	10	5	50%	34%	3.3	15.0%
C6	12	4	33%			
D1	10	7	70%			
D2	10	4	40%	63%	1.3	20.8%
D3	10	8	80%			
D4	10	9	90%			
D5	10	8	80%	87%	0.1	5.8%
D6	10	9	90%			

Danicalipin A (Run 2)						
well	live shrimps (t = 0)	live shrimps (t = 24 h)	alive	average [%]	final concentration of **3** per well [μM]	s.d.
A1	10	0	0%			
A2	10	0	0%	0%	133.0	0.0%
A3	11	0	0%			
A4	12	0	0%			
A5	11	0	0%	0%	66.5	0.0%
A6	11	0	0%			
B1	10	0	0%			
B2	11	0	0%	0%	33.0	0.0%
B3	13	0	0%			
B4	10	0	0%			
B5	10	0	0%	0%	13.3	0.0%
B6	10	0	0%			
C1	10	0	0%			
C2	10	0	0%	0%	6.7	0.0%
C3	10	0	0%			
C4	10	3	30%			
C5	11	4	36%	35%	3.3	5.1%
C6	10	4	40%			
D1	13	9	69%			
D2	10	7	70%	70%	1.3	0.4%
D3	10	7	70%			
D4	10	8	80%			
D5	10	10	100%	93%	0.1	11.5%
D6	10	10	100%			



LC-50	µmol/L
danicalipin	2.53
16-epi danicalipin	5.72
11,15 epi danicalipin	4.52

5.3 Cytotoxicity and Permeability Testing in Cell Lines

5.3.1 Procedures

Cell culture: The colorectal adenocarcinoma cell line (HT-29) and the lung carcinoma cell line (A549) from homo sapiens as well as the hepatoma cell line (Hepa 1-6) from mus musculus, were maintained in DMEM containing 10% FBS and 1% Penicillin Streptomycin (growth medium) at 37 °C in a humidified incubator with 5% CO_2. Each cell line was sub-cultured as recommended on the ATCC homepage.

Principle of the cell viability testing: The MTT assay is a colorimetric assay that determines cell viability by measuring NAD(P)H-dependent metabolic activity of cellular oxidoreductases. After entering the cell MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is reduced to insoluble, dark purple formazan crystals. To quantify the formation of formazan spectrophotometrically, the cells are lysed and the crystals solubilized with acidified isopropanol (isopropanol plus 4N HCl (1:100 dilution) and 0.1% Tergitol, NP40 (a commercially available detergent)). As MTT can only be reduced in metabolically active, living cells the assay is a measure of cell viability.

Cell viability analysis: Logarithmically growing cells were washed with PBS, trypsinized with 0.25% Trypsin-EDTA, spun down, resuspended in 10 ml growth medium and counted. HT-29 cells were plated at a density of 5 x 10^4 cells per 96 well while A549 and Hepa 1-6 cells were plated at a density of 2 x 10^4 cells per 96 well in a flat bottom mircotiter plate. For the Hepa 1-6 cells, the plates were collagenized prior to use. After 24h of incubation in standard culture medium at 37°C and 5% CO_2, the cells were treated with final concentrations of 250 µM, 50 µM, 10 µM, 2 µM, 0.4 µM or 80 nM of **1**, **2,** and **3** in phenol red free DMEM supplemented with 1% FBS and 1% Penicillin Streptomycin for 24 hours. Cells left untreated (growth control) or being treated with 1% DMSO (solvent control) served as negative controls whereas 24h treatment with 50 µM Tamoxifen served as positive control. To prepare the compound dilutions stock solutions of **1**, **2,** and **3** at 25 mM, 5 mM, 1 mM, 200 µM, 40 µM and 8 µM were made by a series of 1:5 dilutions in DMSO starting with the 25mM stocks.

These stock solutions were then diluted 1:100 in phenol red medium before they were applied to the cells. Following 24 hour incubation with the compounds, 11 μL of a solution containing 5 mg/mL MTT in PBS was added to each well to reach a final concentration of 0.5 mg/ml. Four hours later, the medium was removed, the cells were lysed and the formazan crystals dissolved in acidified isopropanol. The amount of formazan was quantified by reading the absorbance at 570 nm (test wavelength) and 650 nm (reference wavelength). Cell viability was calculated using Microsoft Excel with the formula: Cell viability (%) = [(OD value of treated wells at 570nm – OD value of treated wells at 650nm) x 100%] / [average of (OD values of untreated wells at 570nm – OD values of untreated wells at 650nm)], where OD is optical density. The average cell viability was determined from an n of 3-11 per condition. Table 1 (in the body of the paper) shows the EC_{50} values that were determined by non-linear regression of graphs plotting the average percent of viable cells over all experiments ± standard deviation versus the dose of the respective compound. The graphs were acquired using Graph Pad Prism 6 (Section 5.3.2). 1-way ANOVA was used for each concentration to determine statistical significance between the compounds for HT-29 cells.

Permeability testing in cell-lines (Sytox/Hoechst): To determine if the compounds **1**, **2**, or **3** alter the integrity of the cellular membrane of mammalian cells, double-staining with Hoechst 33342 (bis-benzimide) trihydrochloride (H-33342) and Sytox green followed by quantification of fluorescent intensity with a confocal microscope (Operetta) was used. H-33342 is a cell-permeant nuclear stain that emits blue fluorescence upon binding to double-stranded DNA. Sytox Green penetrates cells only if they have a compromised membrane. It is an unsymmetrical cyanine dye with three positive charges and a high affinity for nucleic acids. It is important to note that Sytox Green is completely excluded from living cells. After introduction of a foreign agent that compromises the cell membrane, Sytox green will enter the cell, bind DNA, and emit a bright green fluorescence which can be monitored at the fluorescein/Alexa488 wavelengths. Sytox/H-33342 double staining can differentiate cells based on membrane integrity as the nuclei of all cells will be stained blue (H-

33342), but only the nuclei of cells with increased membrane permeability will be stained green (Sytox).

Cells were cultured and plated in a similar manner as described in the cell viability analysis section. For this experiment, 5 x 10^4 HT-29 cells and 2 x 10^4 Hepa 1-6 cells were plated in collagenized, black, clear bottom 96 well mircotiter plates suitable for fluorescent readouts. After 24 hours, the cells were incubated as described above with final concentrations of 50, 25, 10, 5, 2 and 0.4 μM for compounds **1**; **2** and **3** dissolved in phenol red free DMEM supplemented with 10% FBS and 1% Penicillin Streptomycin for an additional 24 hours. These dilutions were selected on the basis of the EC50`s determined in the MTT assay. Cells left untreated (growth control) or being treated with 1% DMSO (solvent control) served as negative controls, whereas 1 hour treatment with 20% ethanol prior to the read-out served as positive control. To determine cell permeability following exposure to various concentrations of **1**, **2,** and **3**, the cells were washed with PBS and incubated with phenol red free DMEM containing 100 nM Sytox Green and 3 μM Hoechst 33342 for 30 min at 37 °C and 5% CO_2. After this incubation, the cells were imaged with an Operetta high-content imaging system at 20x magnification. Fluorescent pictures were taken from 13 fields per 96 well. Adherent cells were identified with the Hoechst channel (Excitation filter: 360-400nm, Emission filter: 410-480 nm) while Sytox green staining was determined using the Alexa488 channel (Excitation filter: 460-490nm, Emission filter: 500-550nm). Each condition was measured in triplicates in at least two independent experiments resulting in 6-12 technical replicates per condition. Compound-induced changes in permeability were determined by qualitative analysis of the pictures. Shown in section 5.3.3 are representative pictures for **1**, **2**, and **3** at concentrations that are considered toxic, concentrations that are borderline non-toxic, and at concentrations that are non-toxic based on the results of the cell viability assay.

Antibacterial Properties and Permeability Testing in Bacteria

Bacteria culture: To determine if compounds **1**, **2**, or **3** alter the integrity of bacterial membranes, we aimed to measure the fluorescence in *Escherichia coli* (*E. coli*) DH5*α* in the presence of these compounds and Hoechst 33342. *E. coli* DH5*α*

were cultured in Luria broth (LB) medium overnight at 37 °C and 300 rpm. These bacteria were then used to inoculate fresh LB medium that was incubated for an additional 5 h at 37 °C. At this point, the optical density of the suspension was adjusted to 0.2 (λ = 600 nm) by adding the appropriate amount of LB. Aliquots of this culture (0.5 mL) were transferred to 1.5 mL Eppendorf tubes with holes punched in the top. Stock solutions of compounds **1**, **2,** and **3** at 50 mM, 25 mM, 5 mM, 1 mM and 200 µM in DMSO were prepared. Small aliquots (2.5 μL) of these stock solutions were added to the bacterial aliquots (0.5 mL; 1:200 dilution) resulting in final concentrations of 250 μM, 125 μM, 25 μM, 5 μM, 1 μM, and 0.2 μM. DMSO (2.5 μL) was added to two tubes as solvent control while four tubes were left untreated. Each condition was set-up in duplicate and the experiment performed at least twice independently. The bacteria were incubated in the presence of the compounds for 1 h at 37 °C and 300 rpm. Following the 1 h incubation, two untreated tubes were incubated at 95°C for 10 min to kill the bacteria (heated/dead bacteria control).

Afterwards two portions (2 x 100 µL) of the 0.5 mL aliquots were transferred to a flat bottom 96 well plate and 11 µL of a solution of 5 mg/mL MTT in PBS (pH = 7.4) was added to reach a final concentration of 0.5 mg/mL. The plates were incubated at 37 °C for 1 h and spun down at 4000 rpm for 5 minutes to form a pellet of bacteria and formazan crystals. After careful removal of the LB medium, the bacteria and formazan crystals were solubilized in acidified isopropanol (see above). The amount of formazan was quantified by reading the absorbance at 570 nm (test wavelength) and 650 nm (reference wavelength) in a spectrophotometer. 25 μL of a 4 μM Hoechst 33342 solution in PBS were mixed with a 225 μL aliquot of the remaining bacterial culture in a second Eppendorf tube. As before, untreated bacteria, DMSO treated, and heat deactivated bacteria were used as controls. The tubes were incubated for 30 min at 37 °C and 300 rpm in an Eppendorf Thermoshaker. Afterwards, the bacteria were pelleted by centrifugation for 5 min at 6000*g* at ambient temperature. The supernatant was removed and the bacterial pellet re-suspended in 250 μL Tris/EDTA buffer (10 mM Tris, 1 mM EDTA, pH = 7.3). Two times 100 μL of this solution were pipetted into a flat-bottom, black 96 well plate. Fluorescence was read from the top of the wells using excitation and emission filters of 355 and 460 nm. Each concentration was set-

up in duplicates and a minimum of two independent experiments were performed yielding a total of at least four technical replicates.

Raw absorbance (MTT) and fluorescence (Hoechst) values were analyzed. For the MTT assay, the viable cells (measured by %) were calculated in Microsoft Excel using the same formula that was used to determine the viability of the cell lines (see above). For the Hoechst measurement, the fold increase of fluorescent intensity was determined by dividing the raw data with the average fluorescent intensity of all the untreated samples. Shown are the mean values for each condition over all experiments (n= 4-6) ± standard deviation. The statistical significance of differences in the accumulation of formazan/Hoechst 33342 was determined using 1-way ANOVA. Heat deactivated/dead bacteria served as negative control for viability in the MTT assay, because they did not form dark purple formazan crystals while solvent and untreated cells were used as positive controls for viable cells. In the Hoechst assay, the DMSO and untreated bacteria did take up minimal amounts of H33342 while the heat deactivated bacteria accumulated high levels of Hoechst due to their highly permeable, punctured membranes. This data is shown in section 5.3.4.

5.3.2 Results from Cell Line Toxicity

LC-50 conc [µM]

plottet: average over all samples, one value per condition

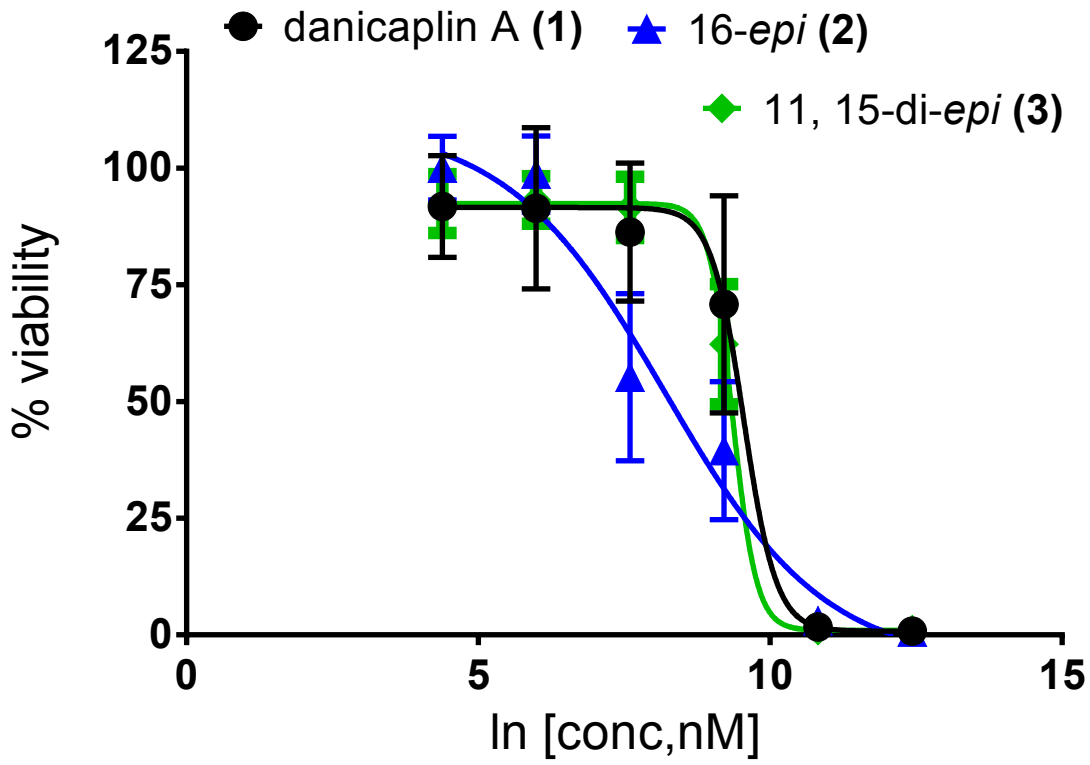
cell line	Danicalipin A	epi 11,15	epi 16
HT29	14.0	3.7	11.6
A549	32.2	36.0	43.5
Hepa	14.7	10.2	13.3

LC-50 conc [µM]

plottet: average calculated from averages of all individual experiments per condition , 3 values per condition

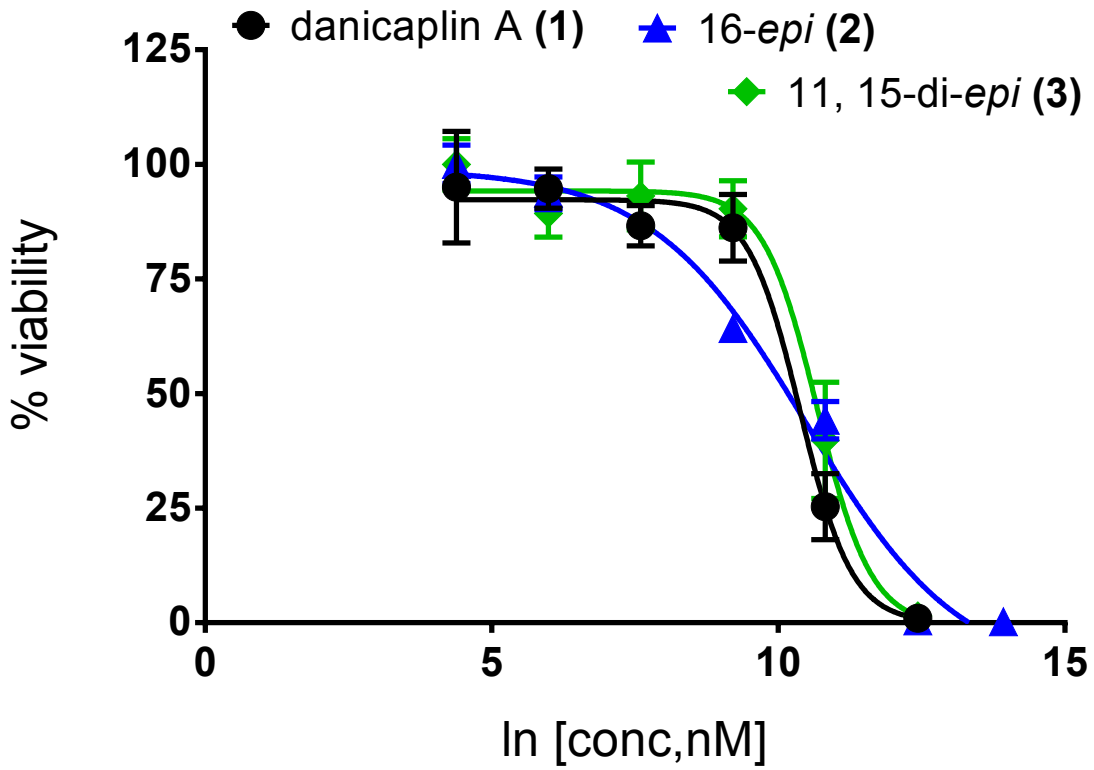
	Danicalipin A		epi 11, 15		epi 16	
cell line	ave	std	ave	std	ave	std
HT29	14.7	0.4	3.7	0.6	10.9	0.1
A549	32.2	0.4	36.0	0.8	42.6	1.3
Hepa	14.7	0.1	10.2	0.1	13.3	0.1

HT-29 Toxicity

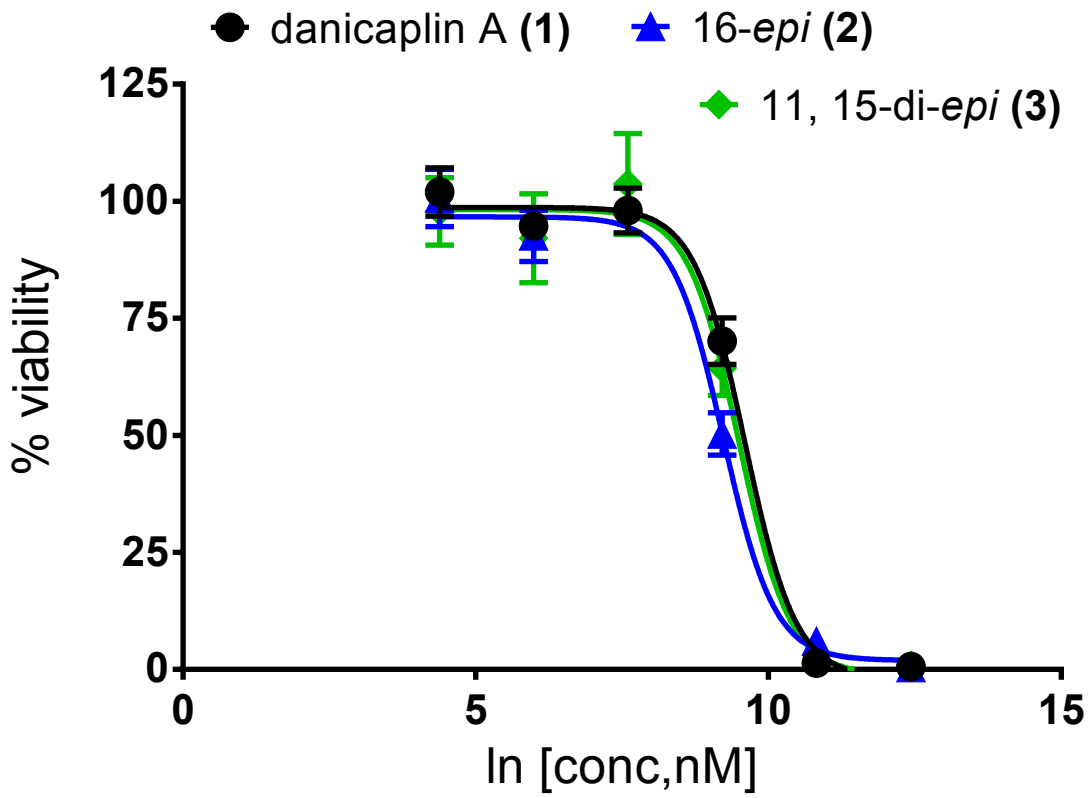


1-way ANOVA adjusted p-value (Tukey Test) concentration	Dani A vs. Epi 11,15		Dani A vs. Epi 16	Epi 11,15 vs. Epi 16	
250 µM	0.8312		0.7785	0.4366	
50 µM	0.3272		0.6433	0.0736	
10 µM	0.0149	*	0.8911	0.0436	*
2 µM	0.0037	**	0.5597	0.0005	***
0.4 µM	0.5382		0.879	0.8233	
80 nM	0.2155		0.7461	0.619	

A549 Toxicity



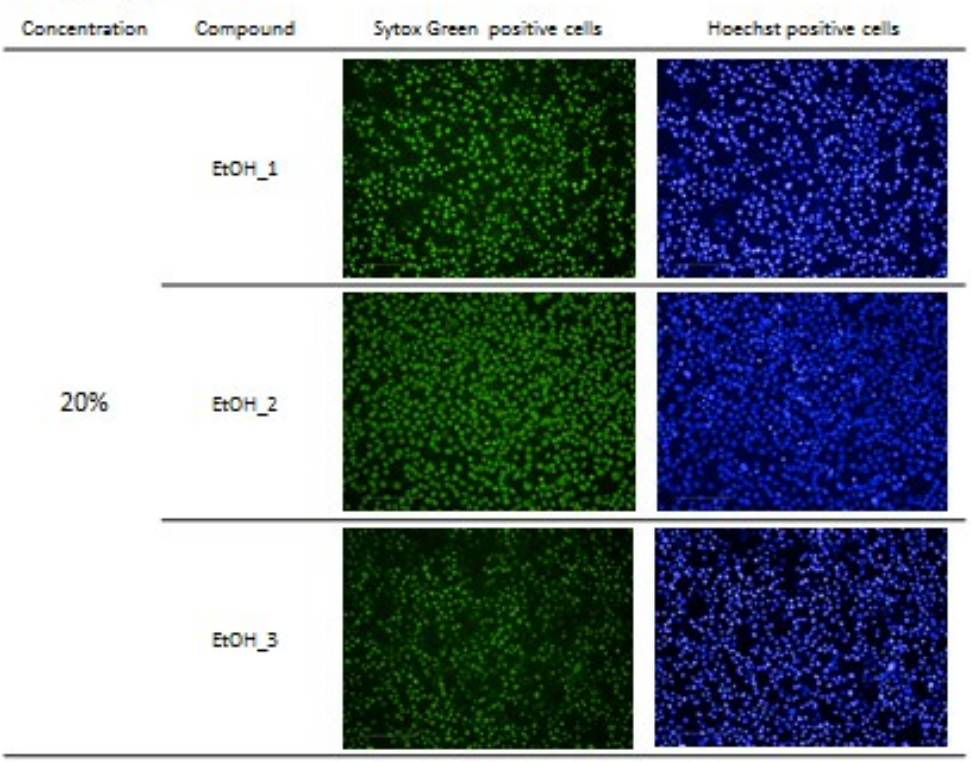
Hepa 1-6 Toxicity



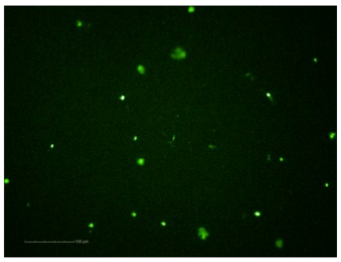
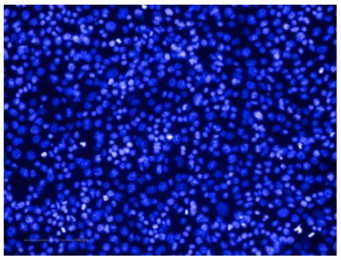
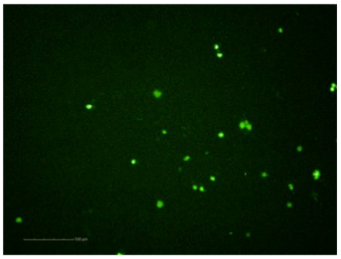
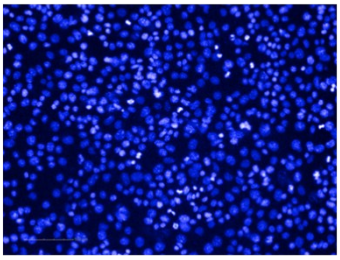
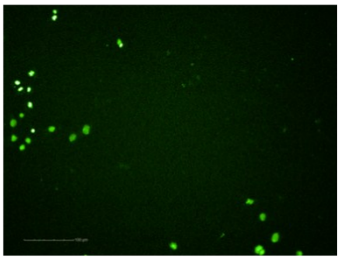
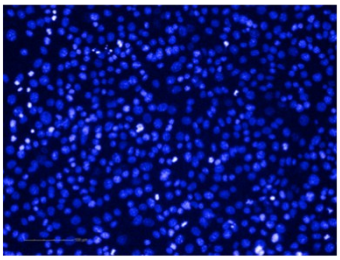
5.3.3 Results from Cell Line Permeability Enhancement

5.3.3.1 Hepa 1-6 Permeability Enhancement

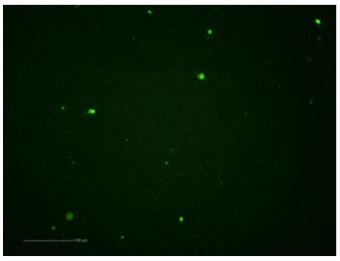
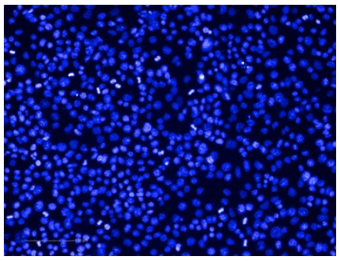
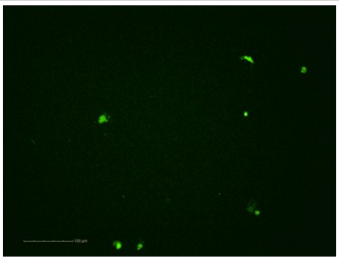
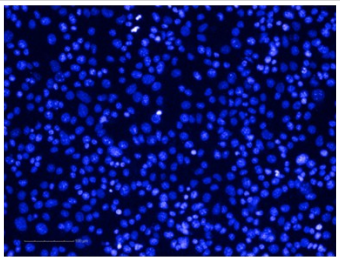
Positive Control

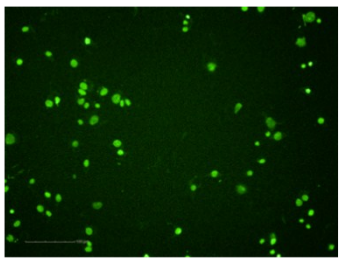
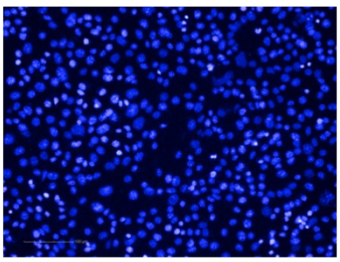
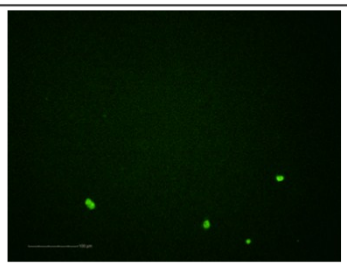
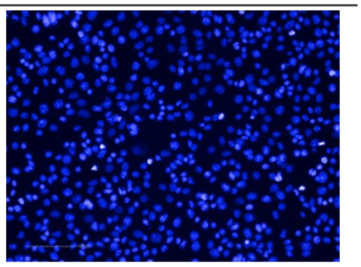
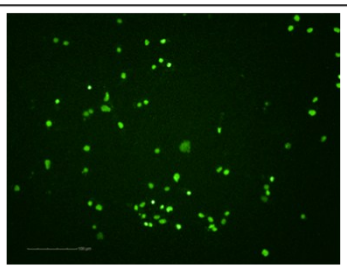
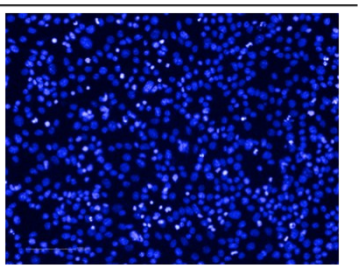


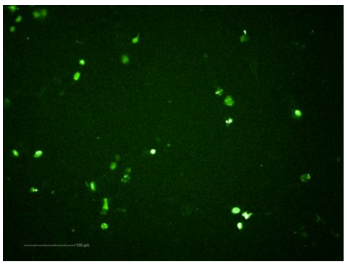
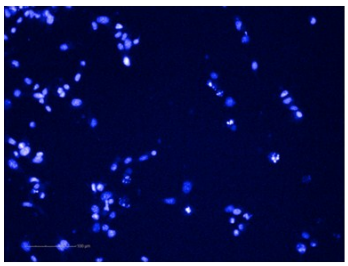
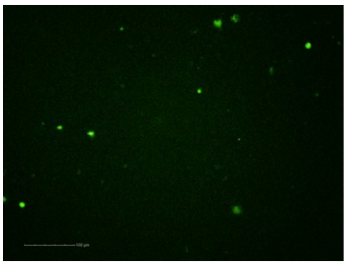
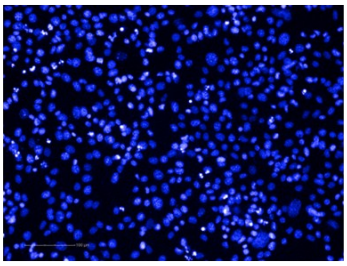
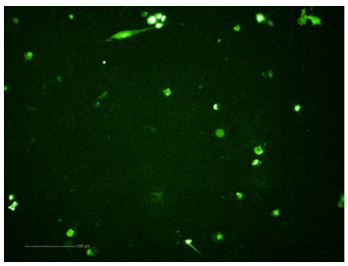
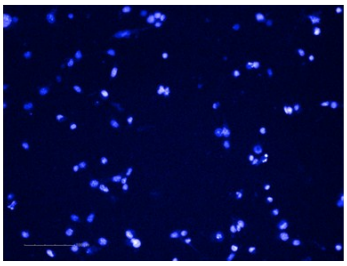
Negative Control

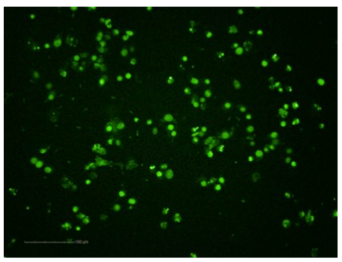
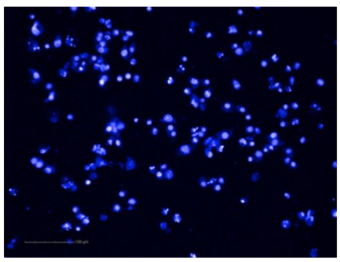
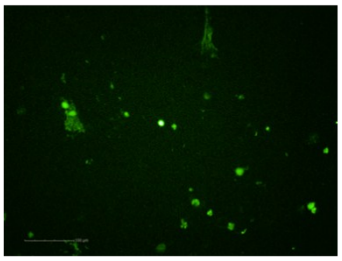
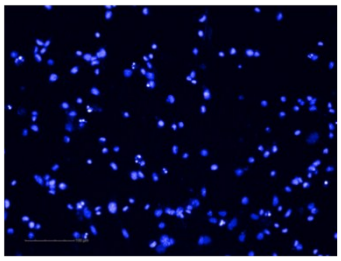
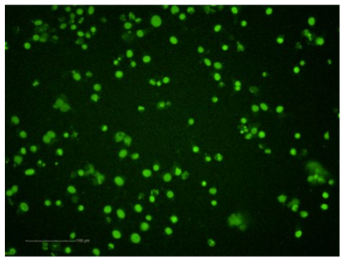
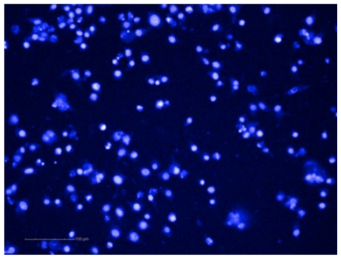
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
1%	DMSO_1		
	DMSO_2		
	DMSO_3		

Serial Dilutions of 1, 2, and 3

Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
2 µM	Danicaplin		
	Epi 16		

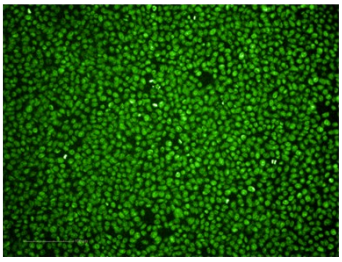
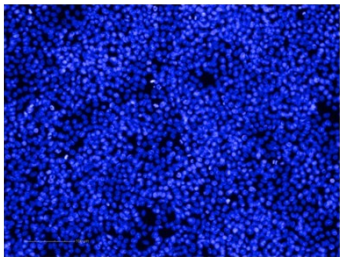
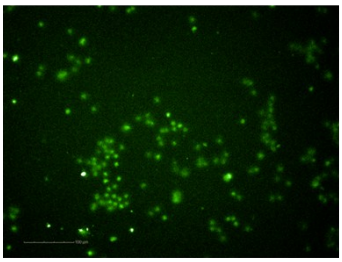
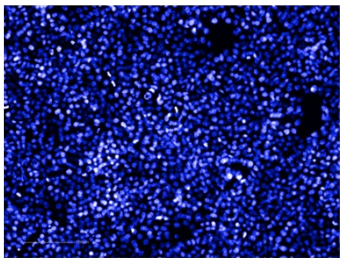
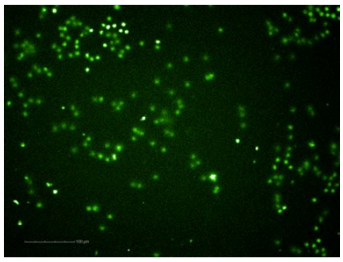
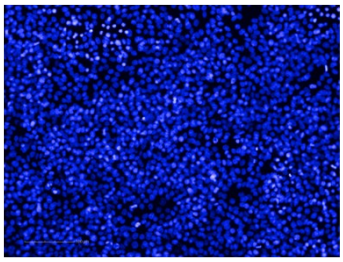
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
5 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
10 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

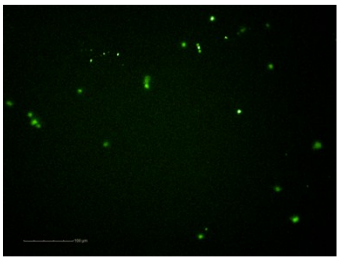
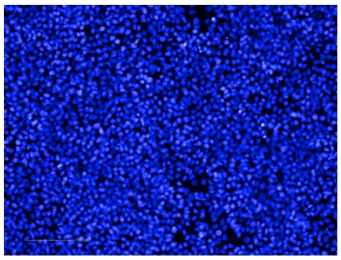
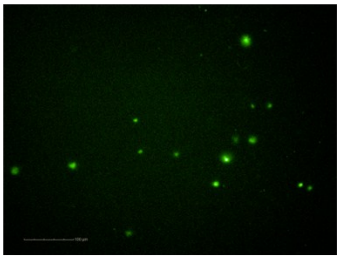
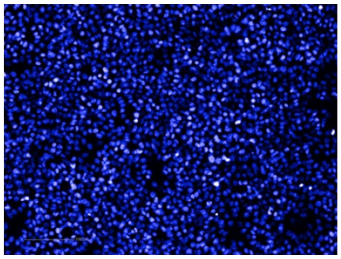
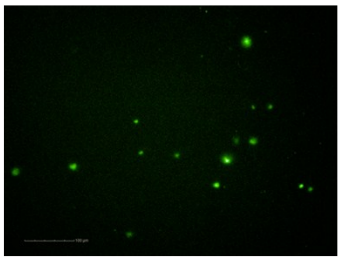
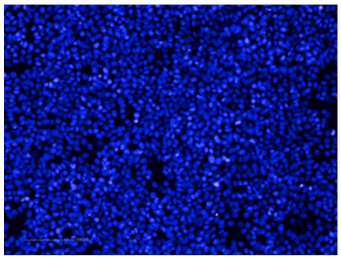
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
25 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

5.3.3.2 HT-29 Permeability Enhancement

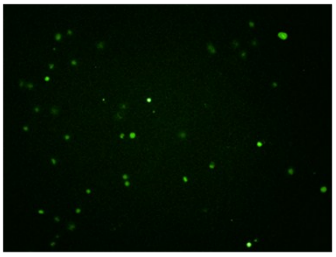
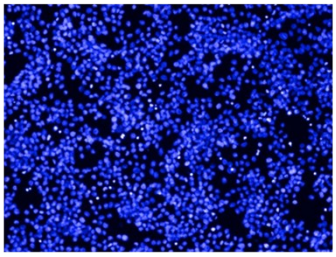
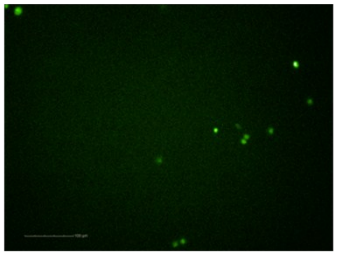
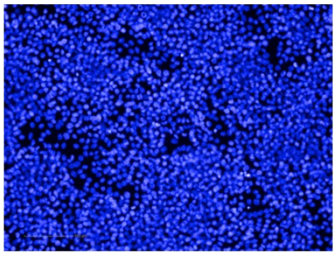
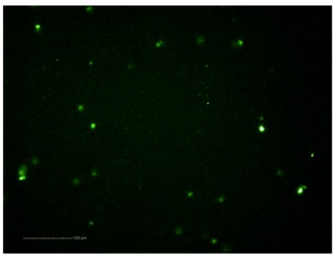
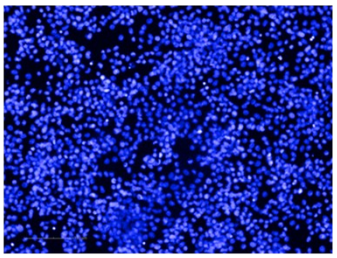
Positive Control

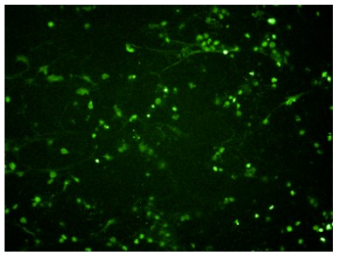
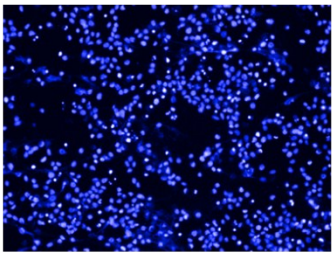
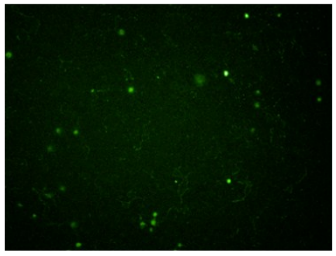
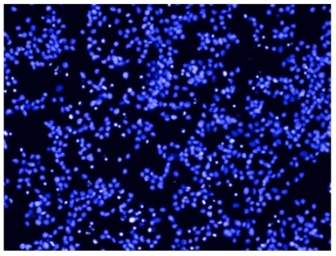
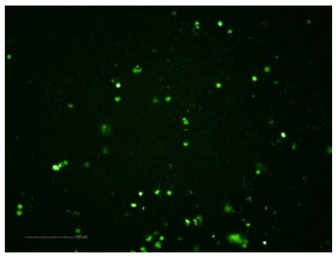
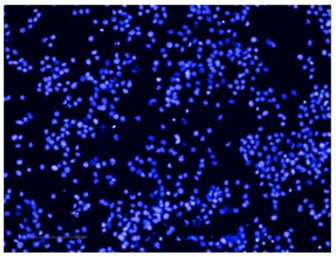
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
	EtOH_1		
20%	EtOH_2		
	EtOH_3		

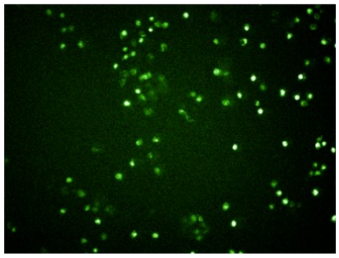
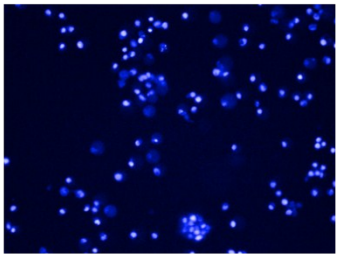
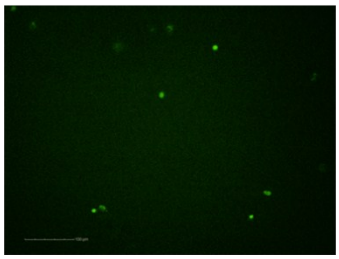
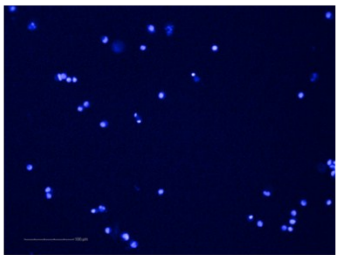
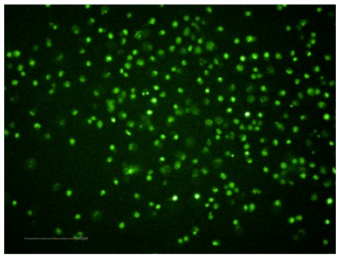
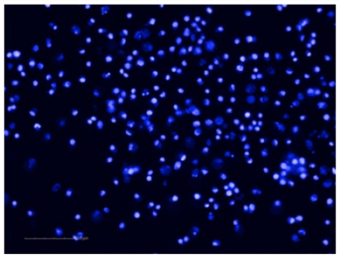
Negative Control

Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
1%	DMSO_1		
	DMSO_2		
	DMSO_3		

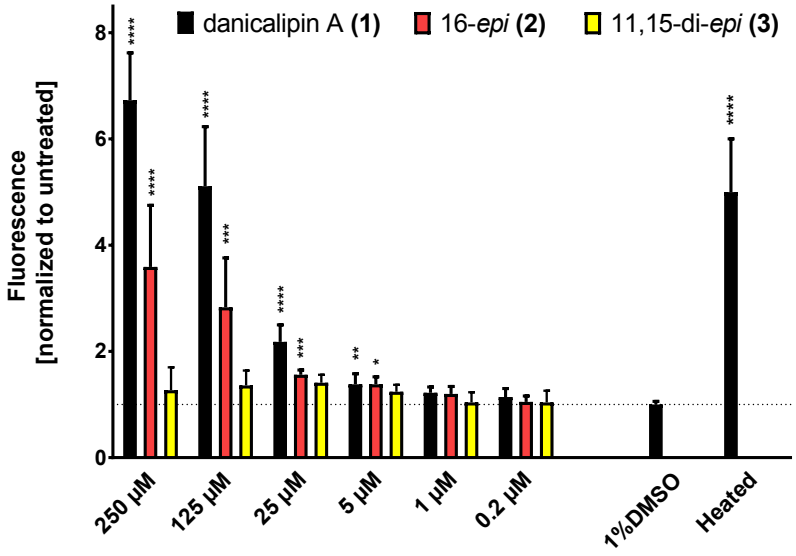
Serial Dilutions of 1, 2, and 3

Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
5 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

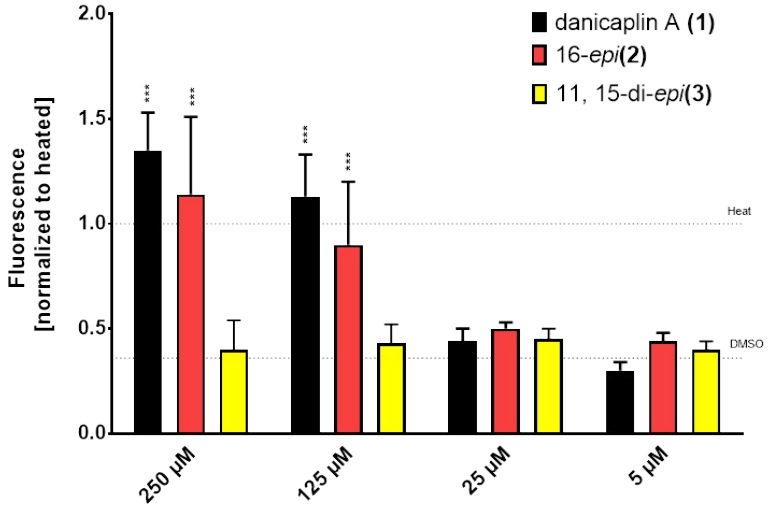
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
10 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

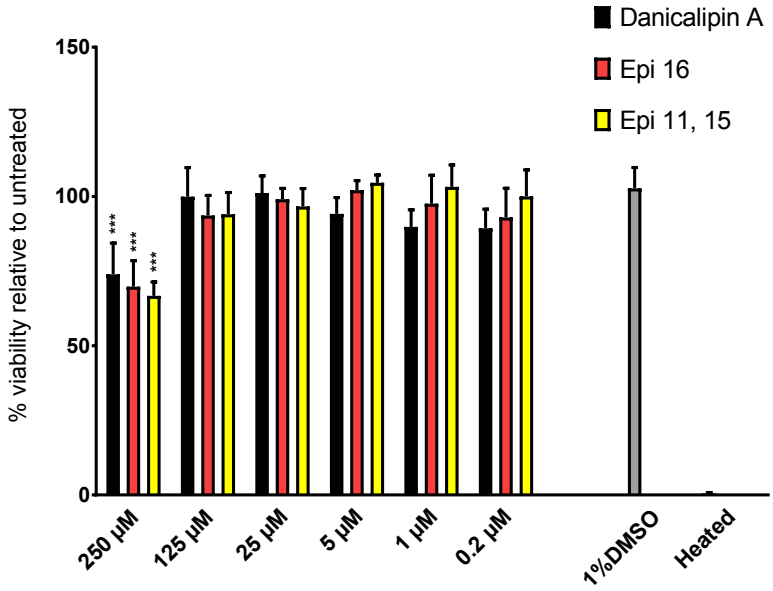
Concentration	Compound	Sytox Green positive cells	Hoechst positive cells
25 µM	Danicaplin		
	Epi 11,15		
	Epi 16		

5.3.4 Results from *E. coli* Permeability Enhancement

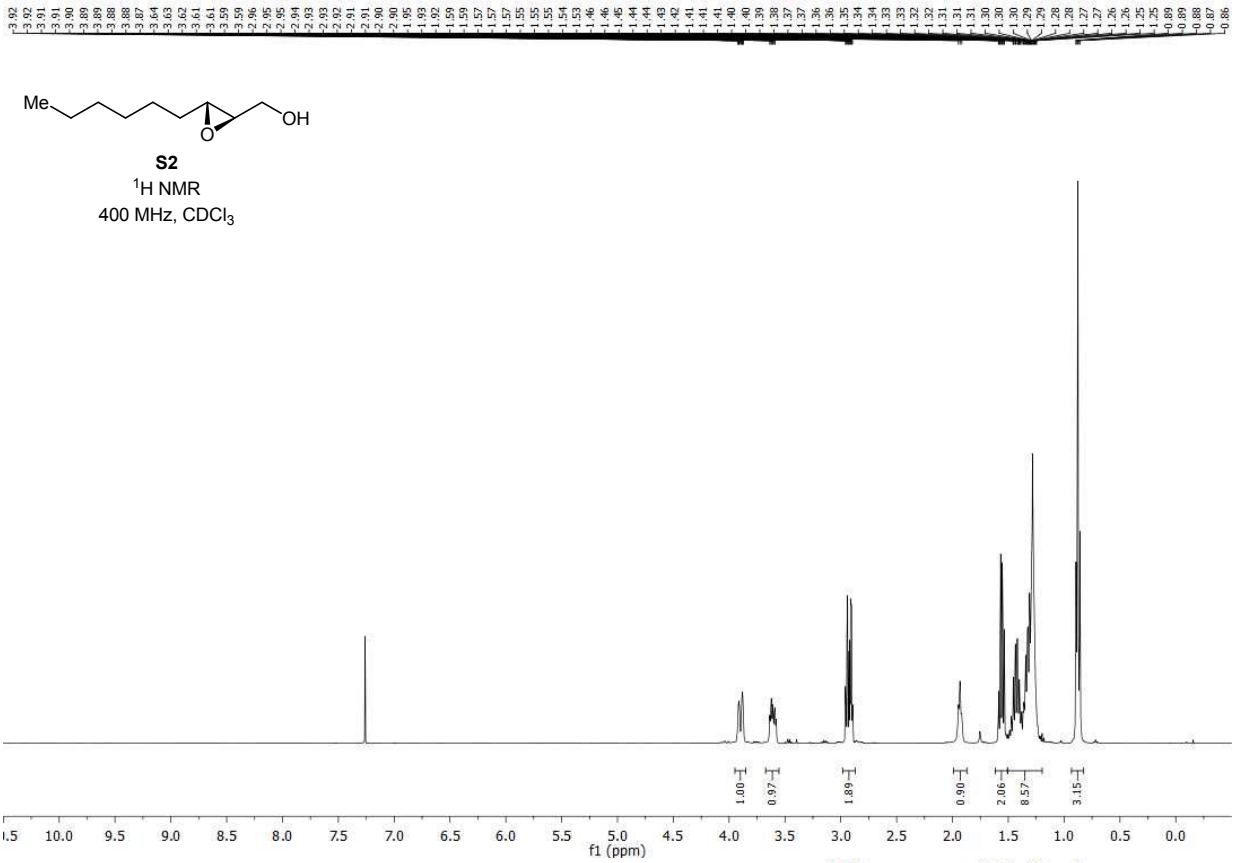


1-way ANOVA							
adjusted p-value (Tukey Test)							
concentration	Dani A vs. DMSO		Epi 16 vs. DMSO		Epi 11,15 vs. DMSO		Heat vs. DMSO
250 µM	0.0001	****	0.0001	****	0.9758	ns	
125 µM	0.0001	****	0.0005	***	0.8989	ns	
25 µM	0.0001	****	0.0009	***	0.0838	ns	
5 µM	0.005	**	0.01	*	0.4127	ns	
1 µM	0.4552	ns	0.7026	ns	0.3668	ns	
0.2 µM	0.9996	ns	0.5692	ns	0.4368	ns	
10 min 95°C							0.0001 ****

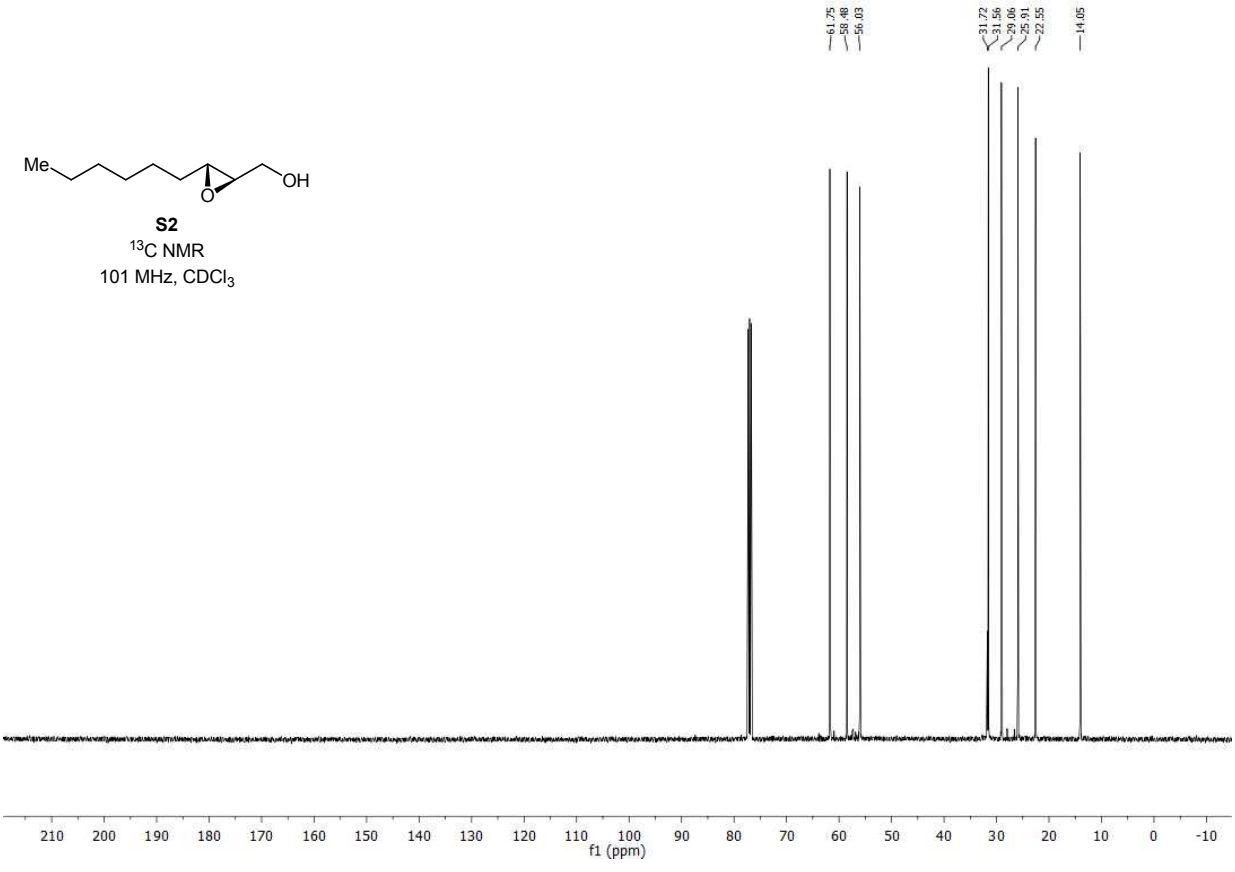



Danicalipin A
Epi 16
Epi 11, 15
% viability relative to untreated
150
100
50
0
***
***
***
250 µM
125 µM
25 µM
5 µM
1 µM
0.2 µM
1%DMSO
Heated

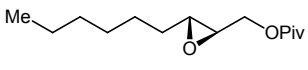
6 Spectra



S2
^{1}H NMR
400 MHz, $CDCl_3$



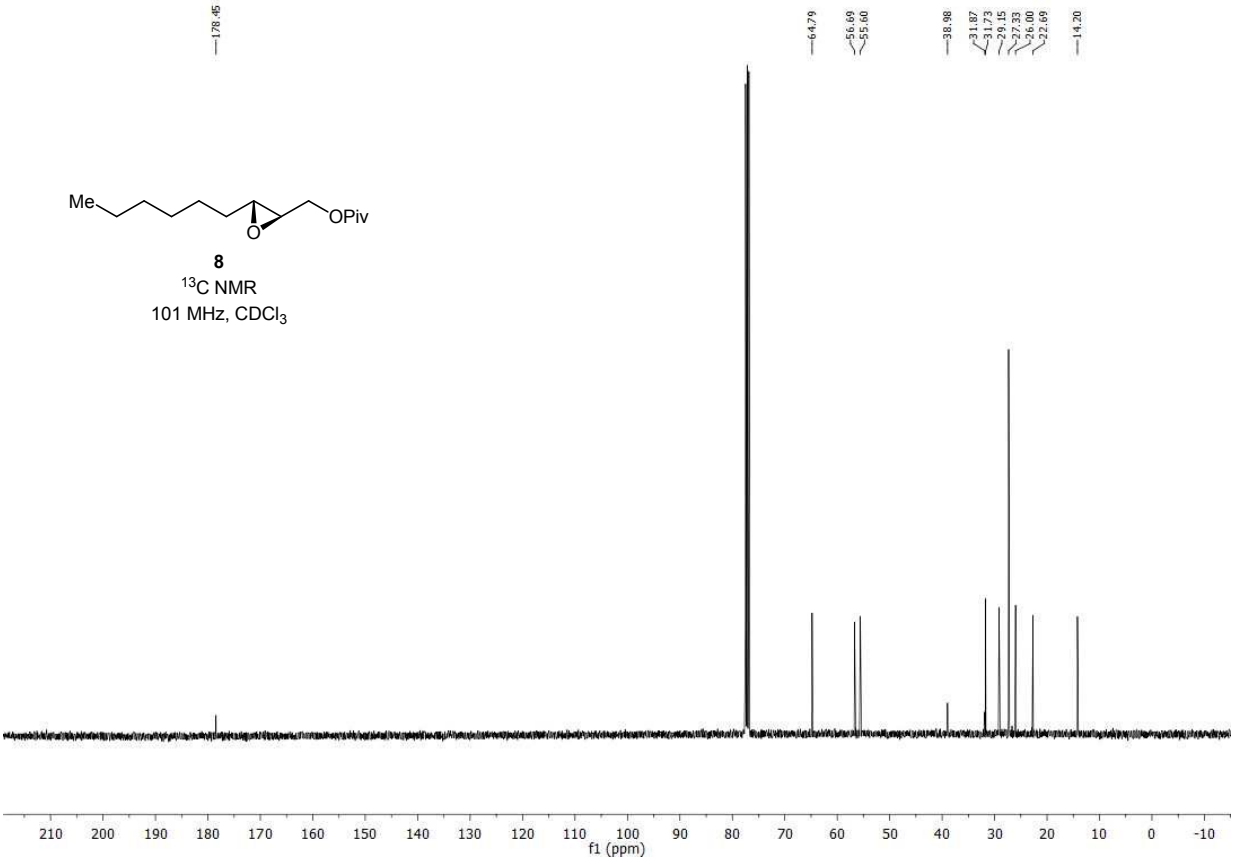
S2
^{13}C NMR
101 MHz, $CDCl_3$



8

^{13}C NMR

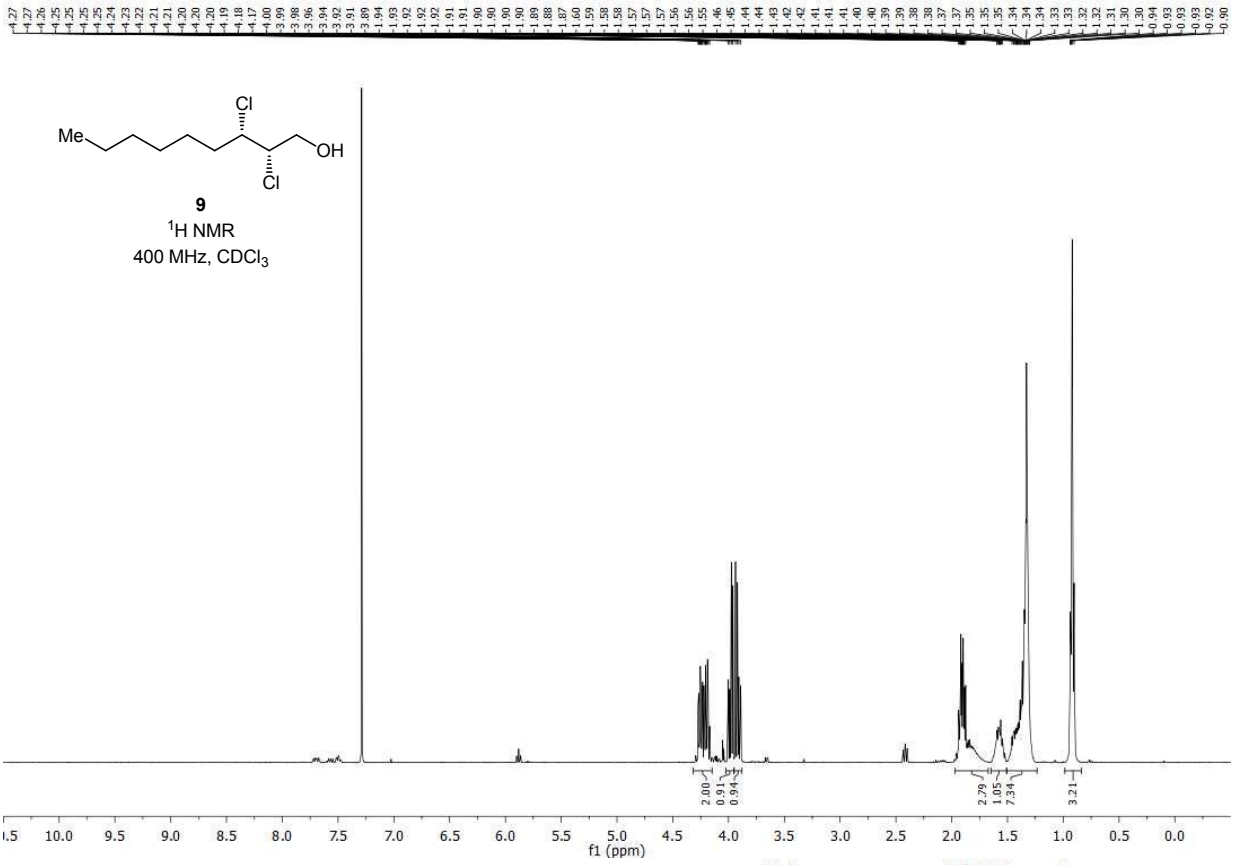
101 MHz, $CDCl_3$

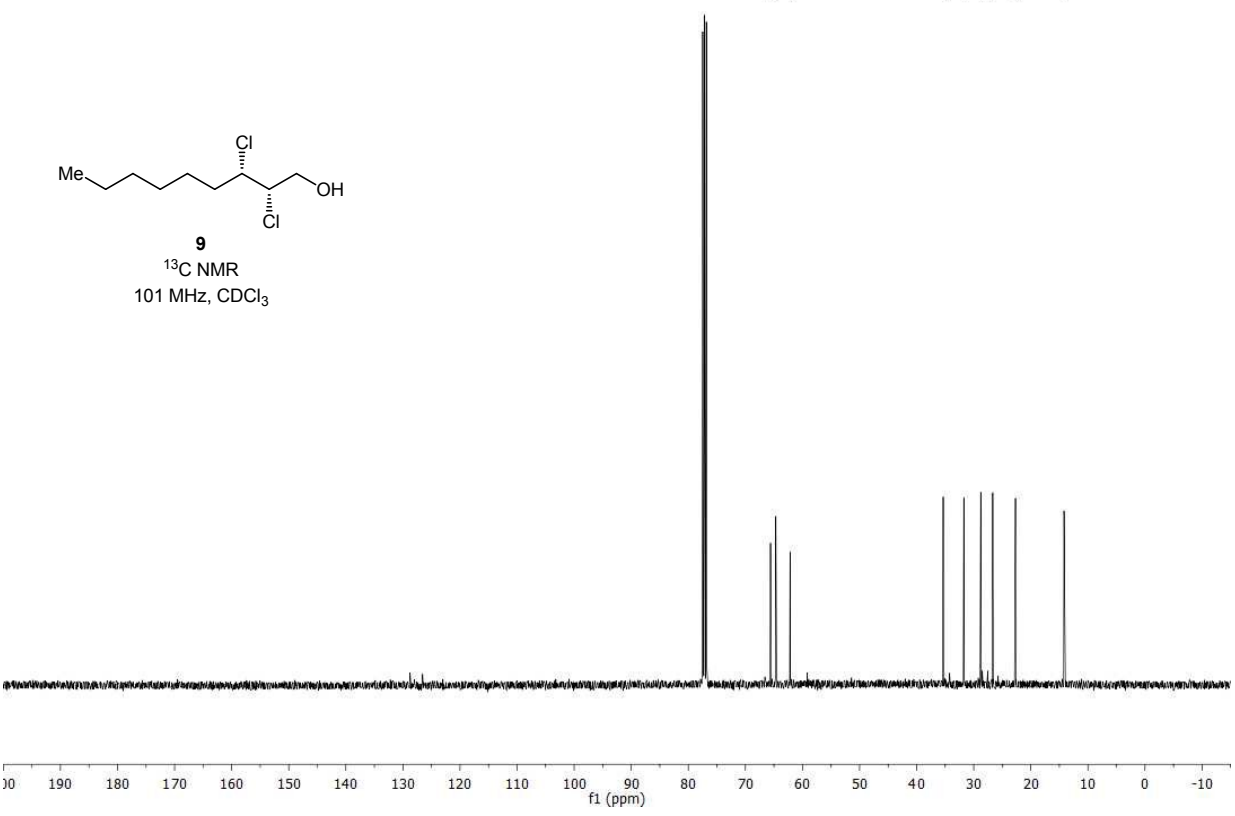


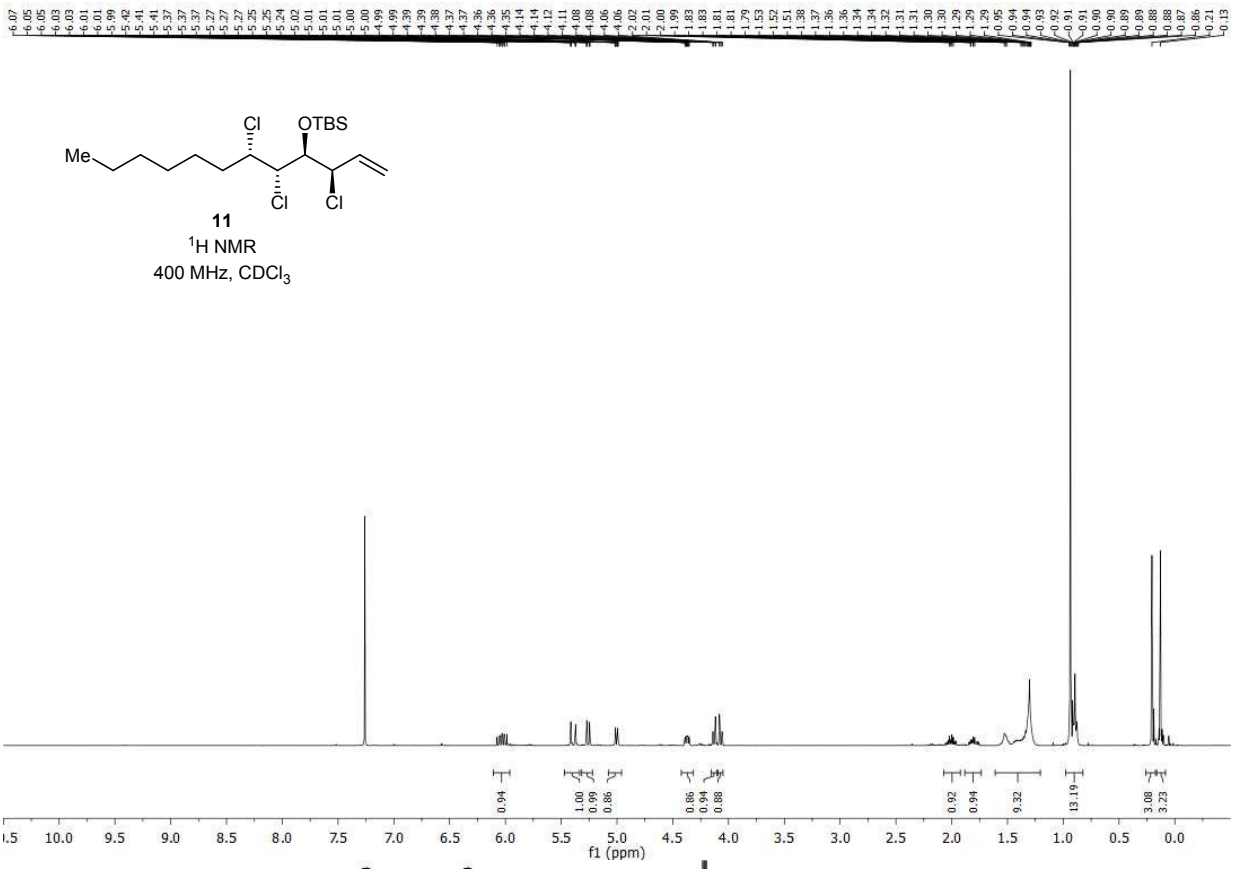
8

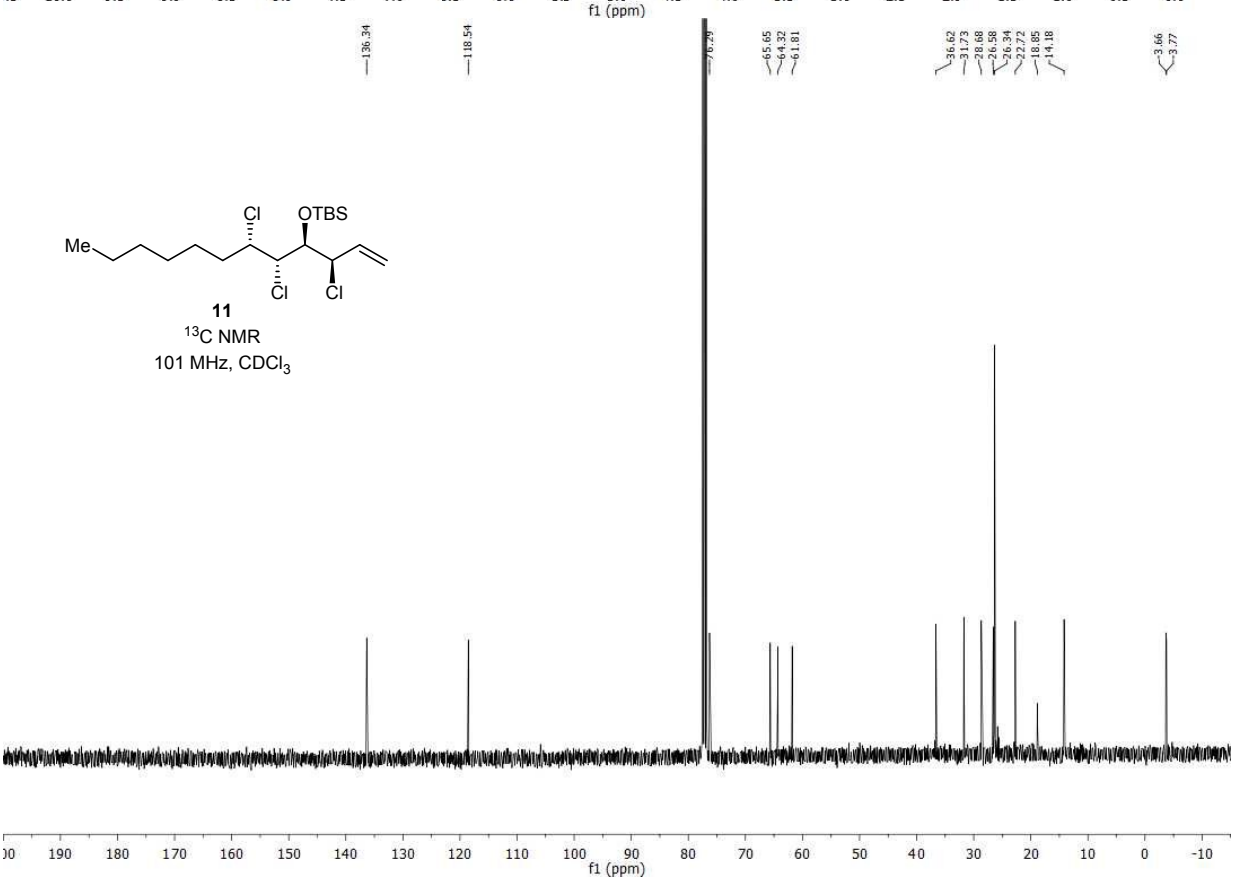
^{13}C NMR

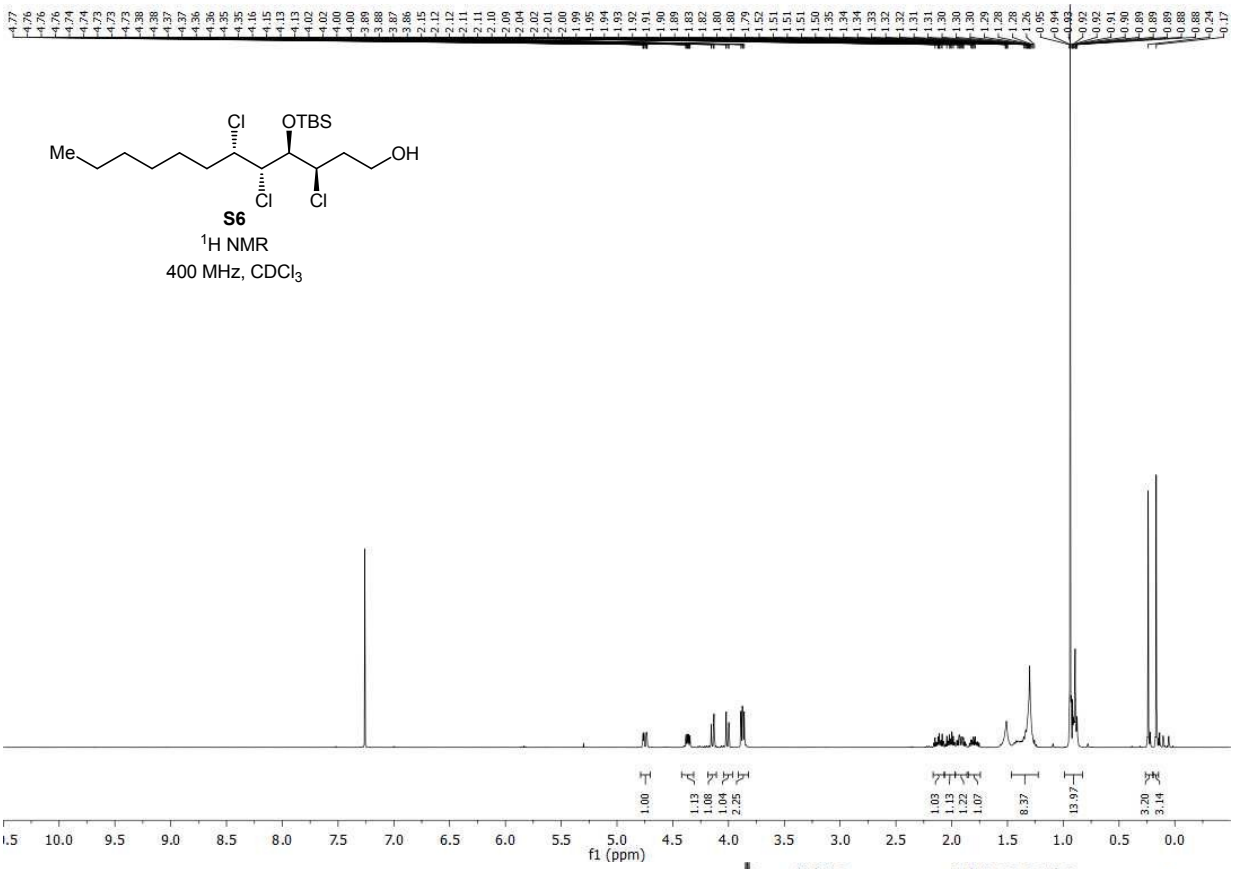
101 MHz, $CDCl_3$

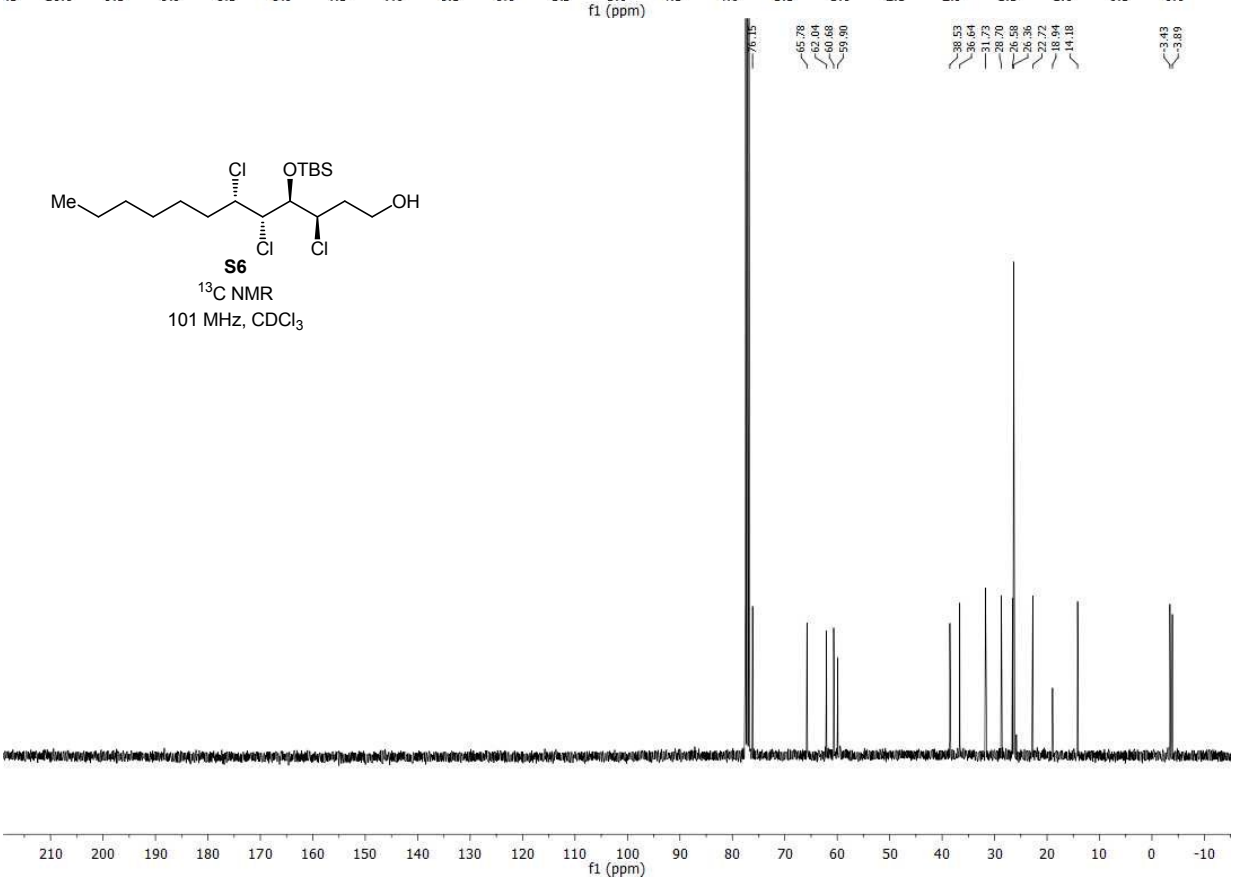

Cl
Me
OH
Cl
9
1H NMR
400 MHz, CDCl3
f1 (ppm)

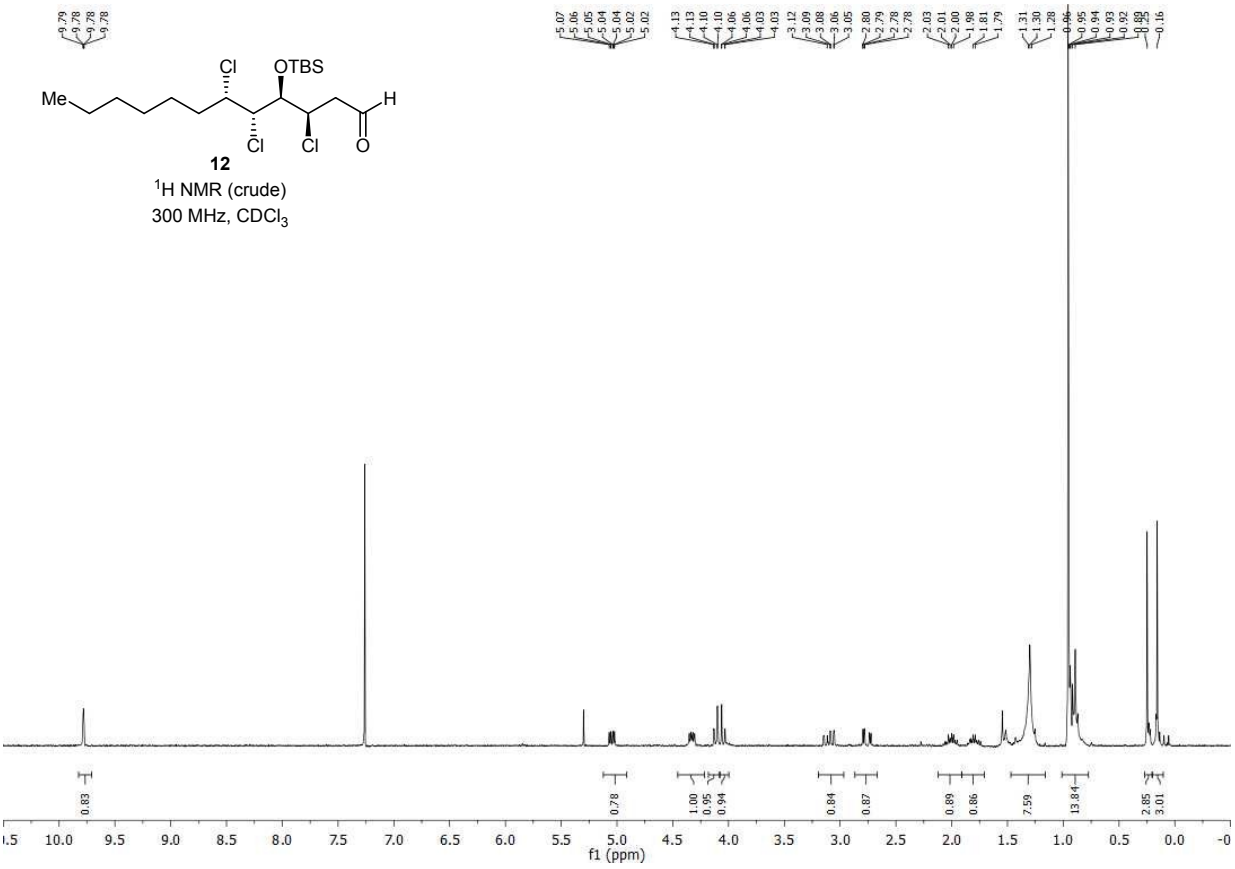

Cl
Me
OH
Cl
9
13C NMR
101 MHz, CDCl3
f1 (ppm)

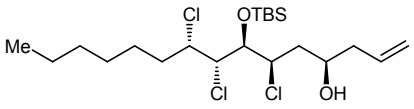

Cl
OTBS
Me
Cl
Cl
11
1H NMR
400 MHz, CDCl3
f1 (ppm)


Cl
OTBS
Me
Cl
Cl
11
13C NMR
101 MHz, CDCl3
f1 (ppm)


Cl
OTBS
Me
OH
Cl
Cl
S6
1H NMR
400 MHz, CDCl3
f1 (ppm)


Cl
OTBS
Me
OH
Cl
Cl
S6
13C NMR
101 MHz, CDCl3
f1 (ppm)

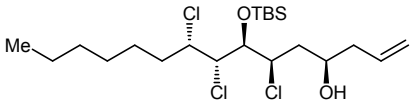

Cl
OTBS
Me
H
Cl
Cl
O
12
1H NMR (crude)
300 MHz, CDCl3
f1 (ppm)



S7

^{1}H NMR

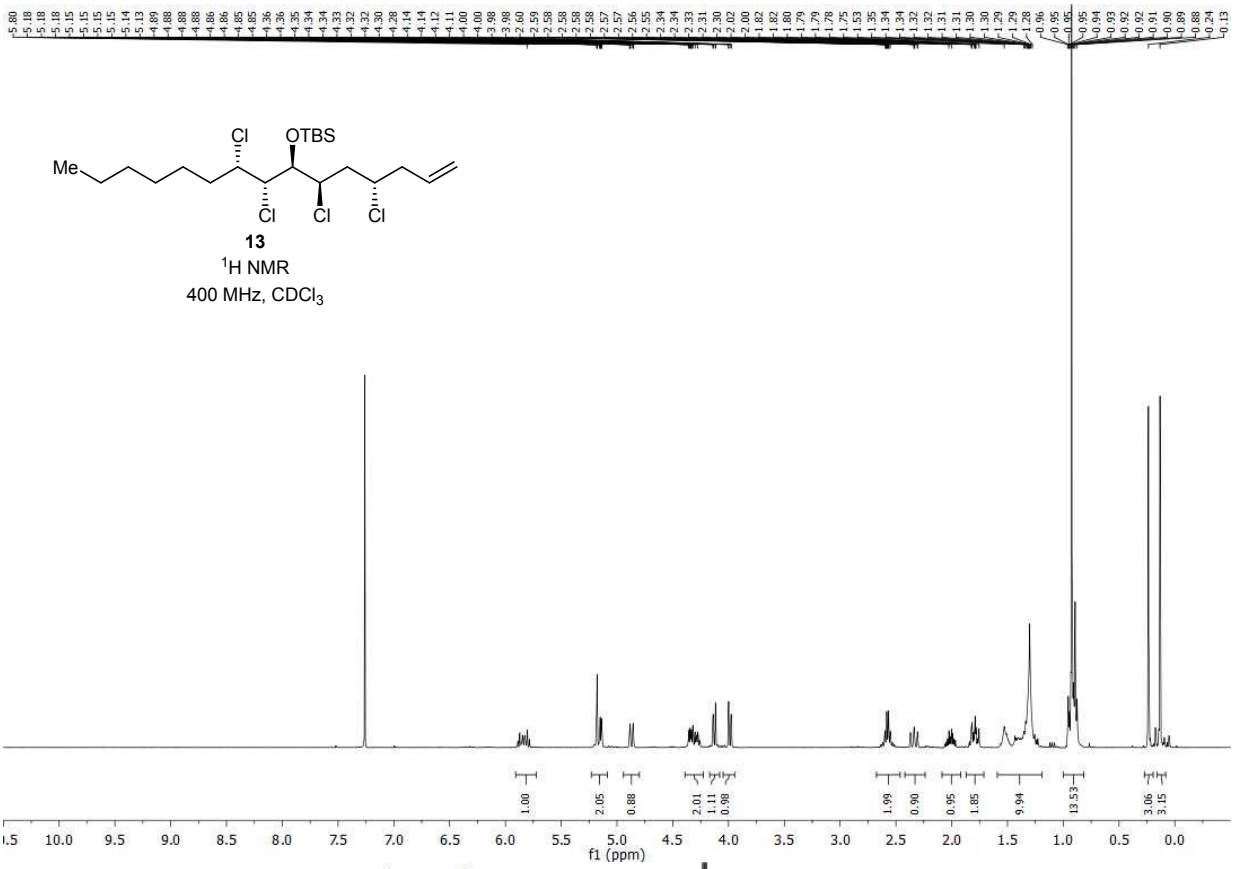
400 MHz, $CDCl_3$

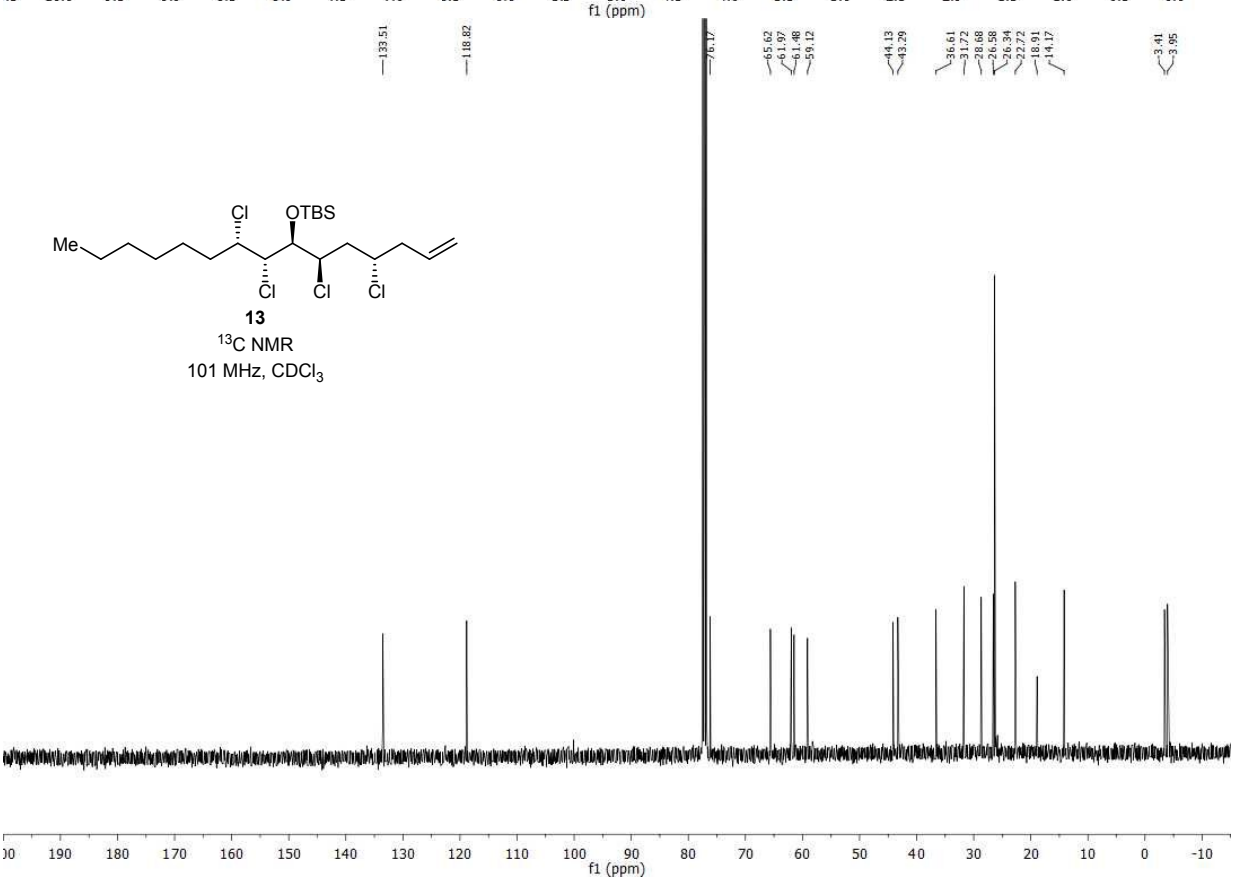


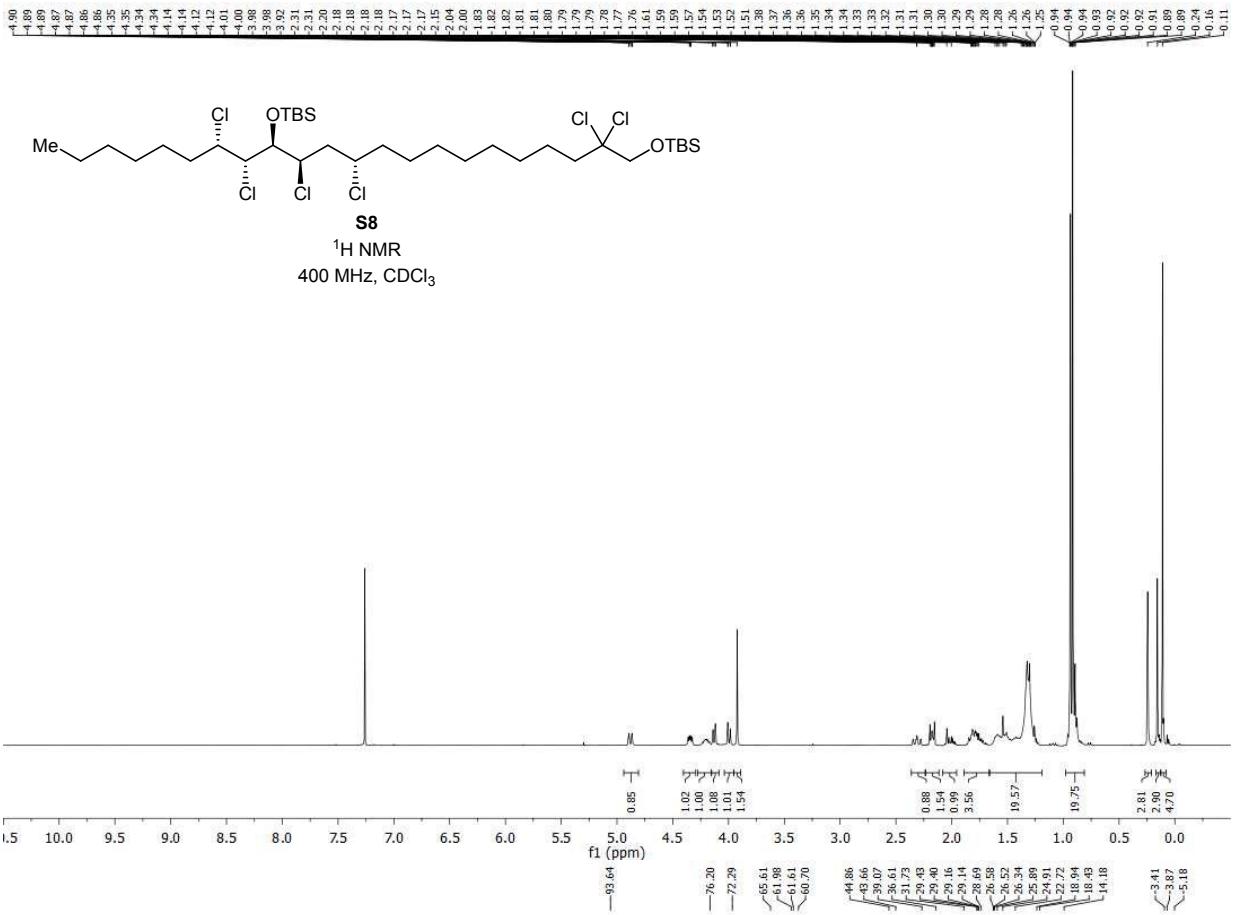
S7

^{13}C NMR

101 MHz, $CDCl_3$


Cl
OTBS
Me
Cl
Cl
Cl
13
1H NMR
400 MHz, CDCl3
f1 (ppm)

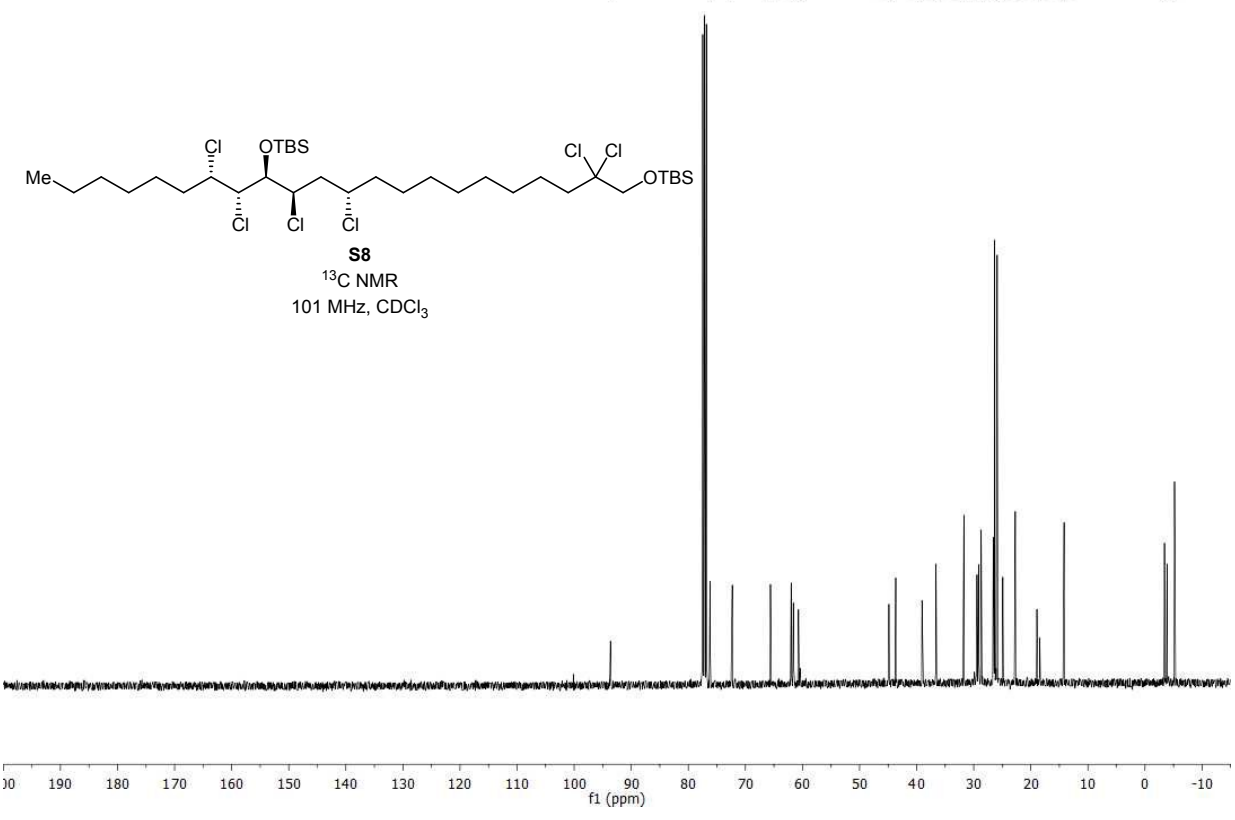

Cl
OTBS
Me
Cl
Cl
Cl
13
13C NMR
101 MHz, CDCl3
f1 (ppm)



S8

^{1}H NMR

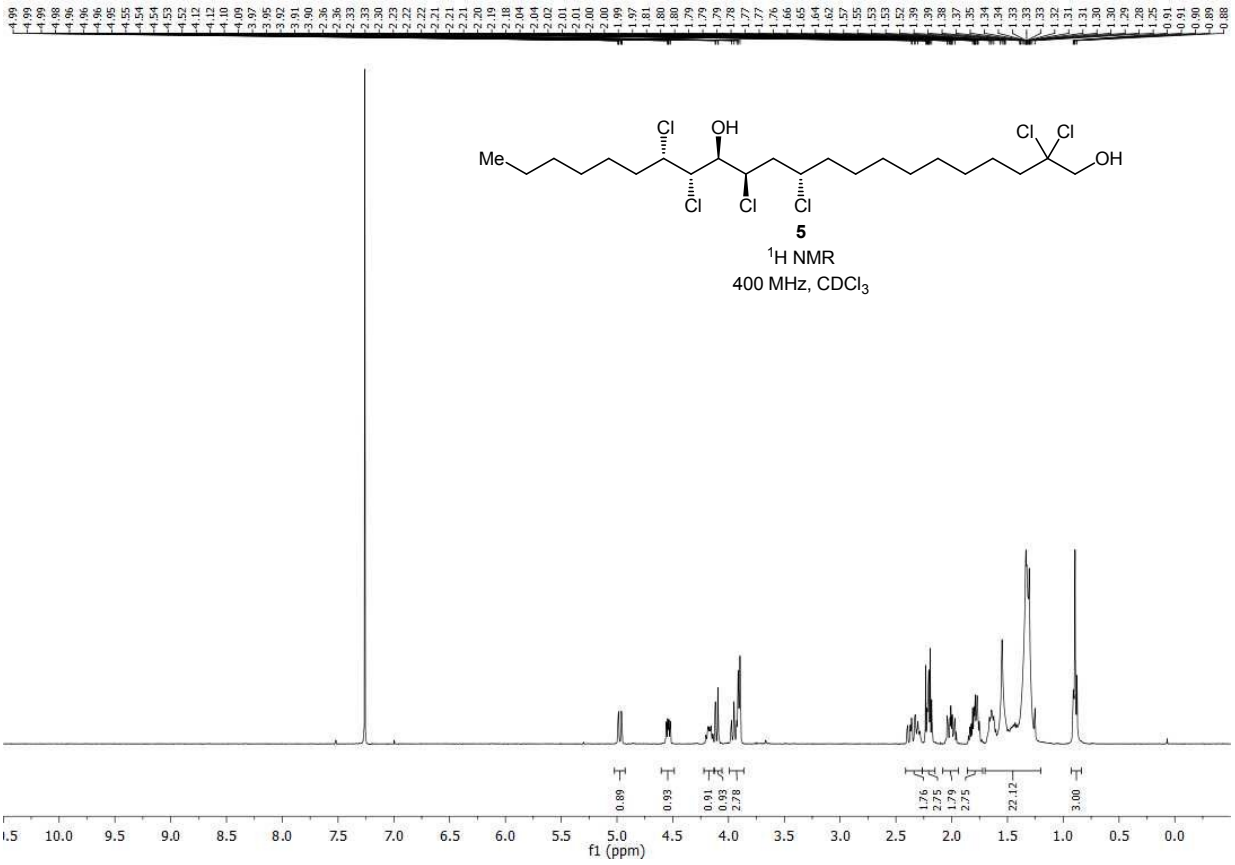
400 MHz, $CDCl_3$

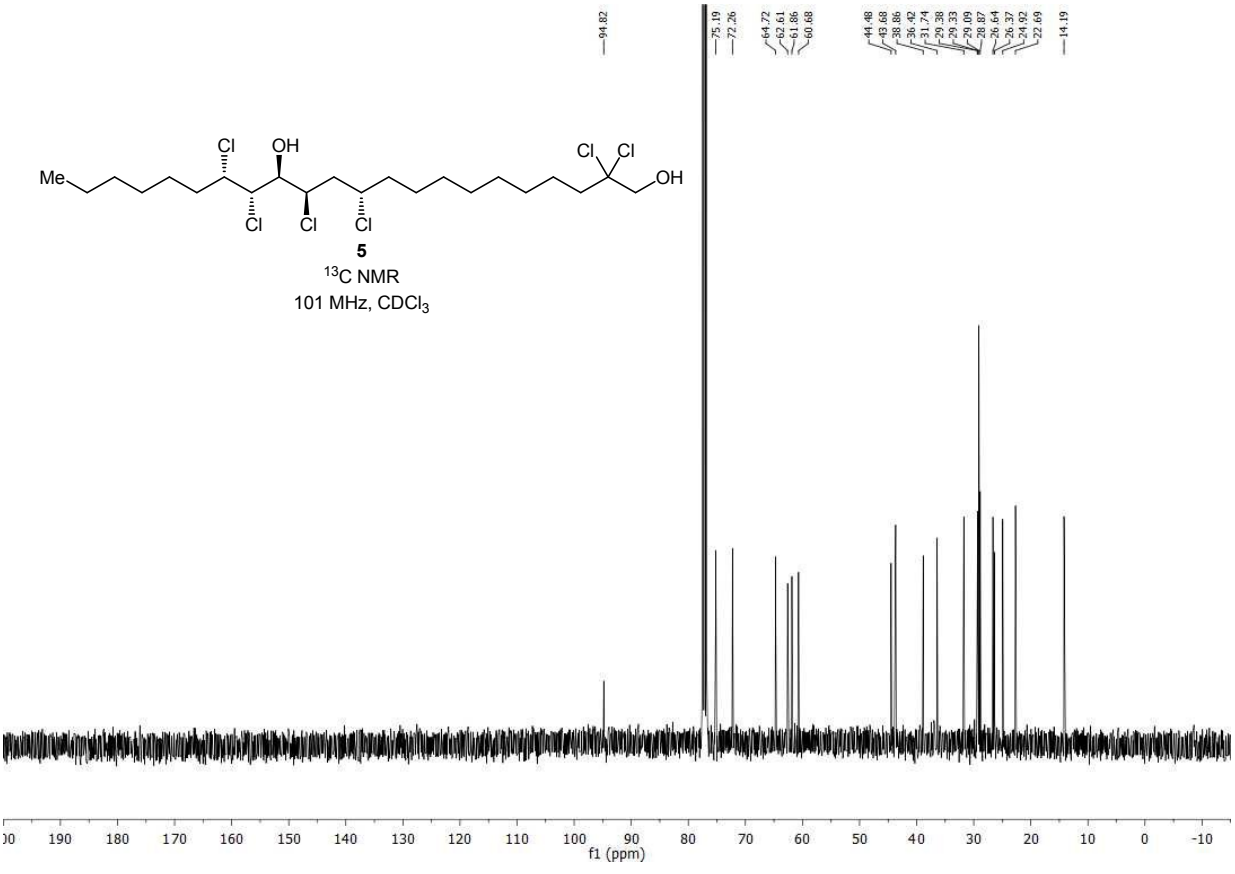


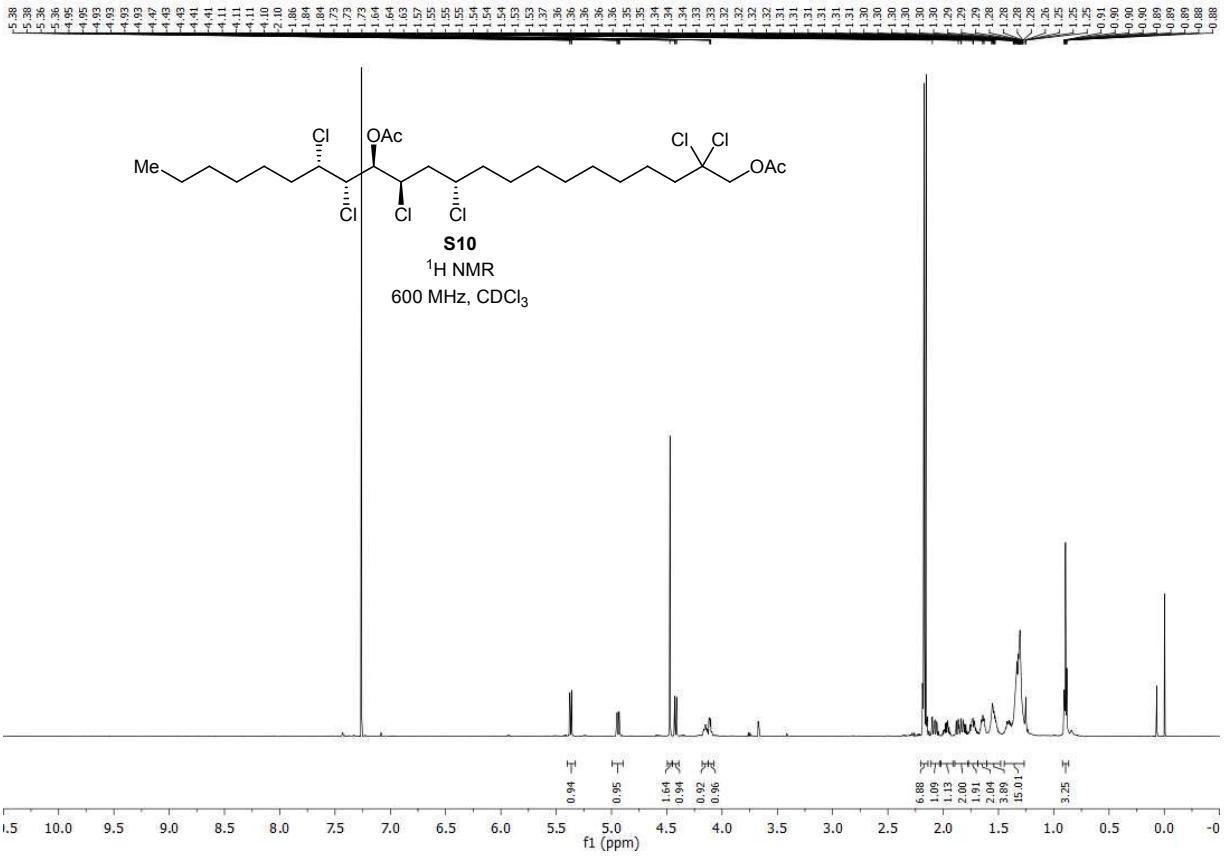
S8

^{13}C NMR

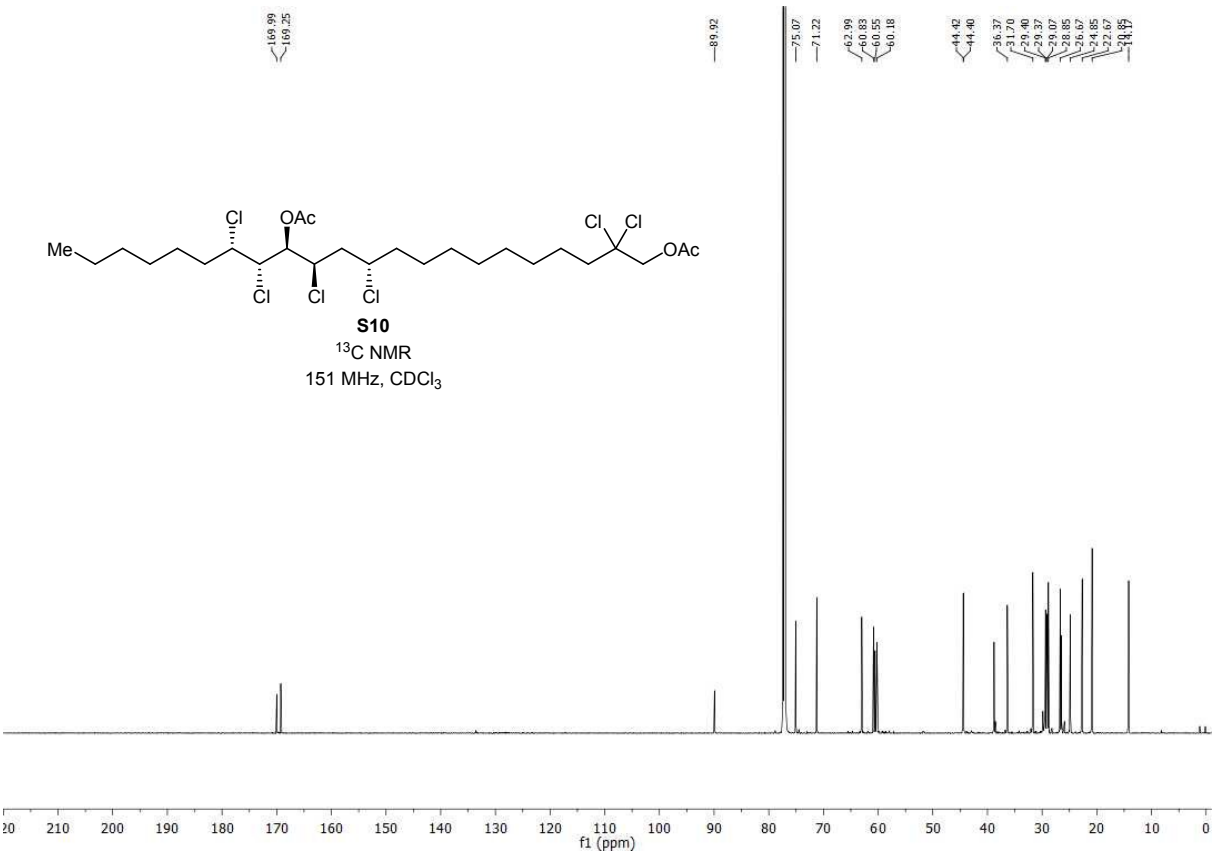
101 MHz, $CDCl_3$


Me
Cl
OH
Cl
Cl
Cl
Cl
Cl
OH
5
1H NMR
400 MHz, CDCl3
f1 (ppm)

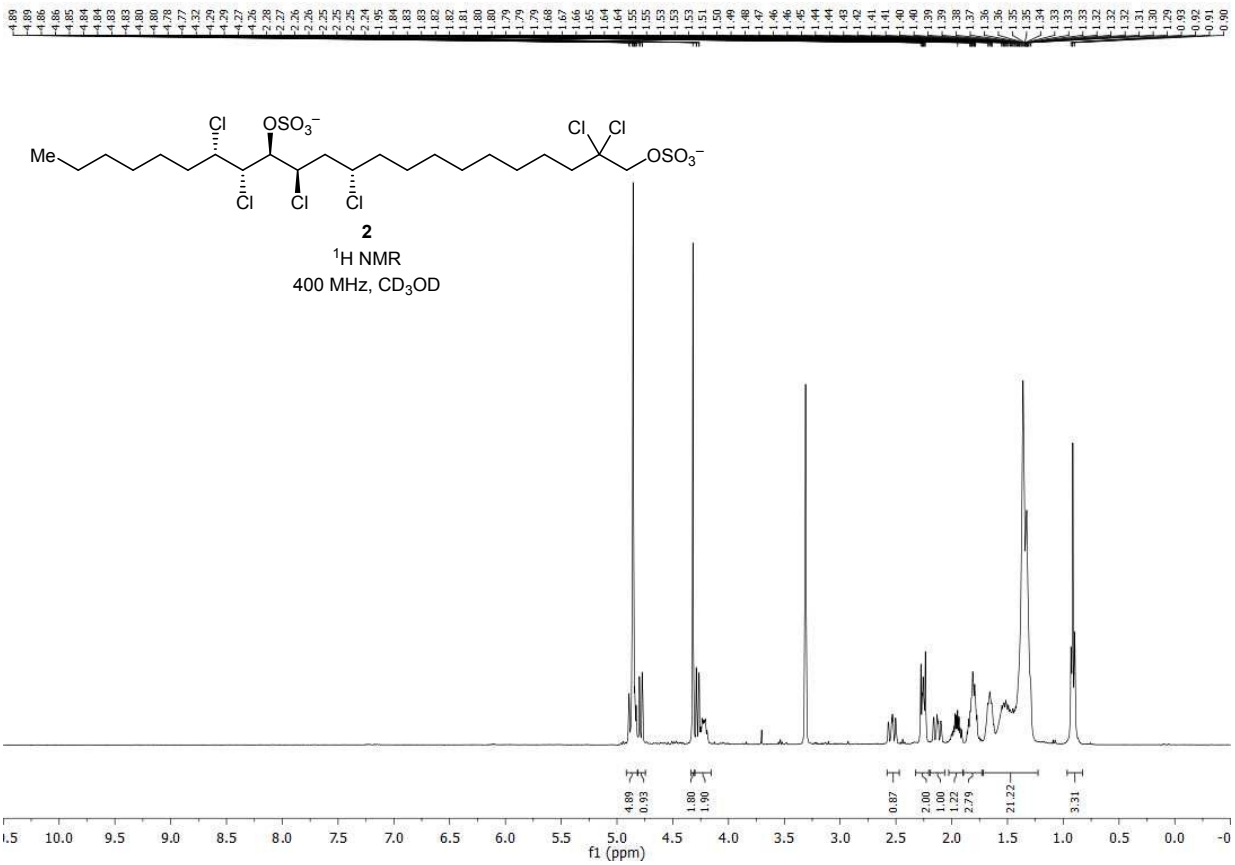

Me
Cl
OH
Cl
Cl
Cl
Cl
Cl
OH
5
13C NMR
101 MHz, CDCl3
f1 (ppm)



S10
^{1}H NMR
600 MHz, $CDCl_3$



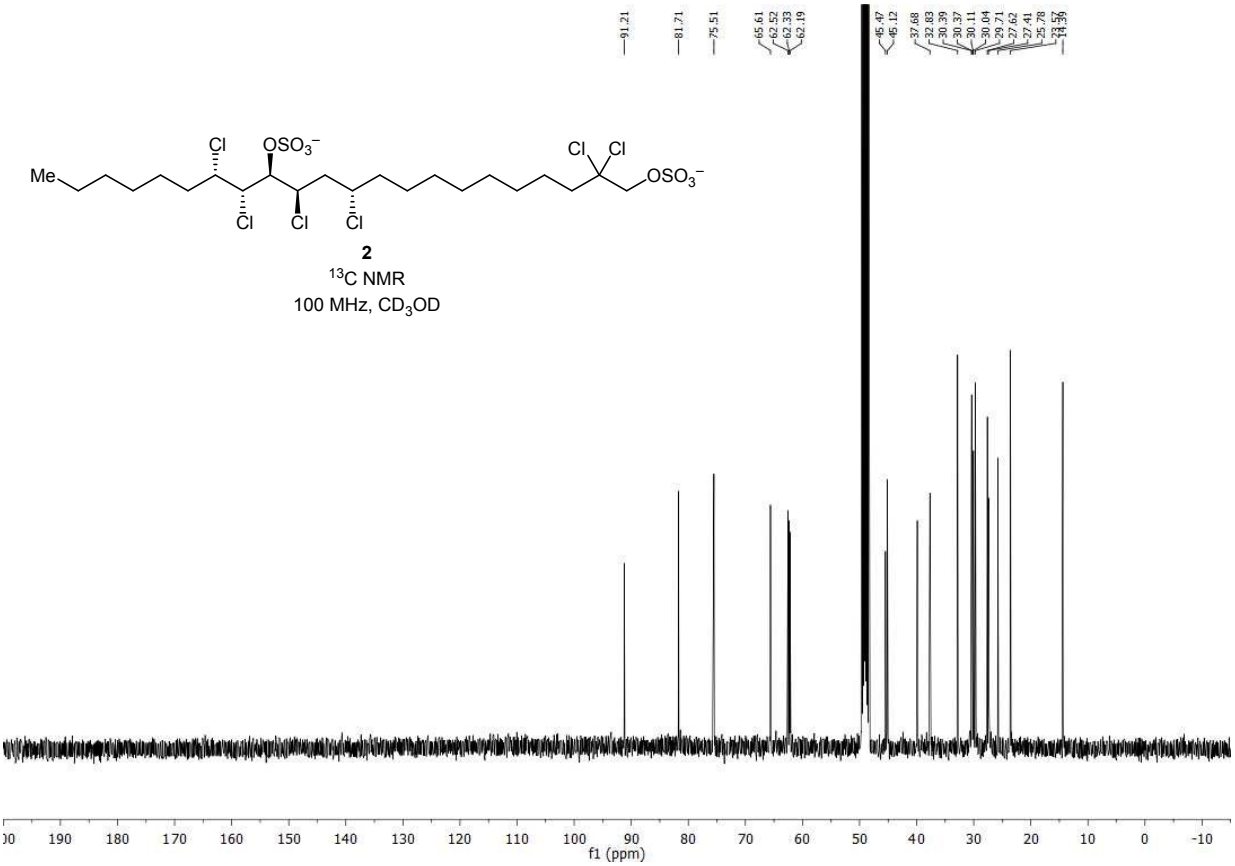
S10
^{13}C NMR
151 MHz, $CDCl_3$



2

^{1}H NMR

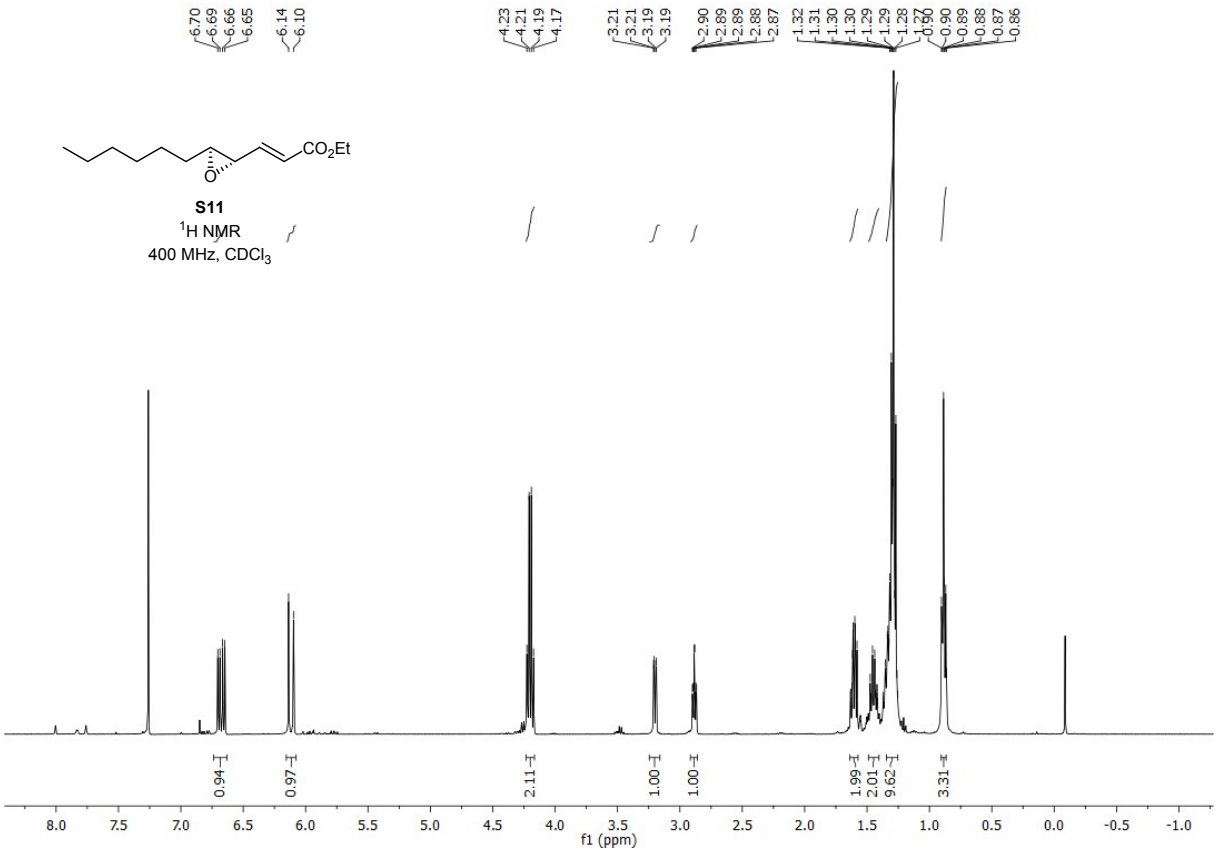
400 MHz, CD_3OD



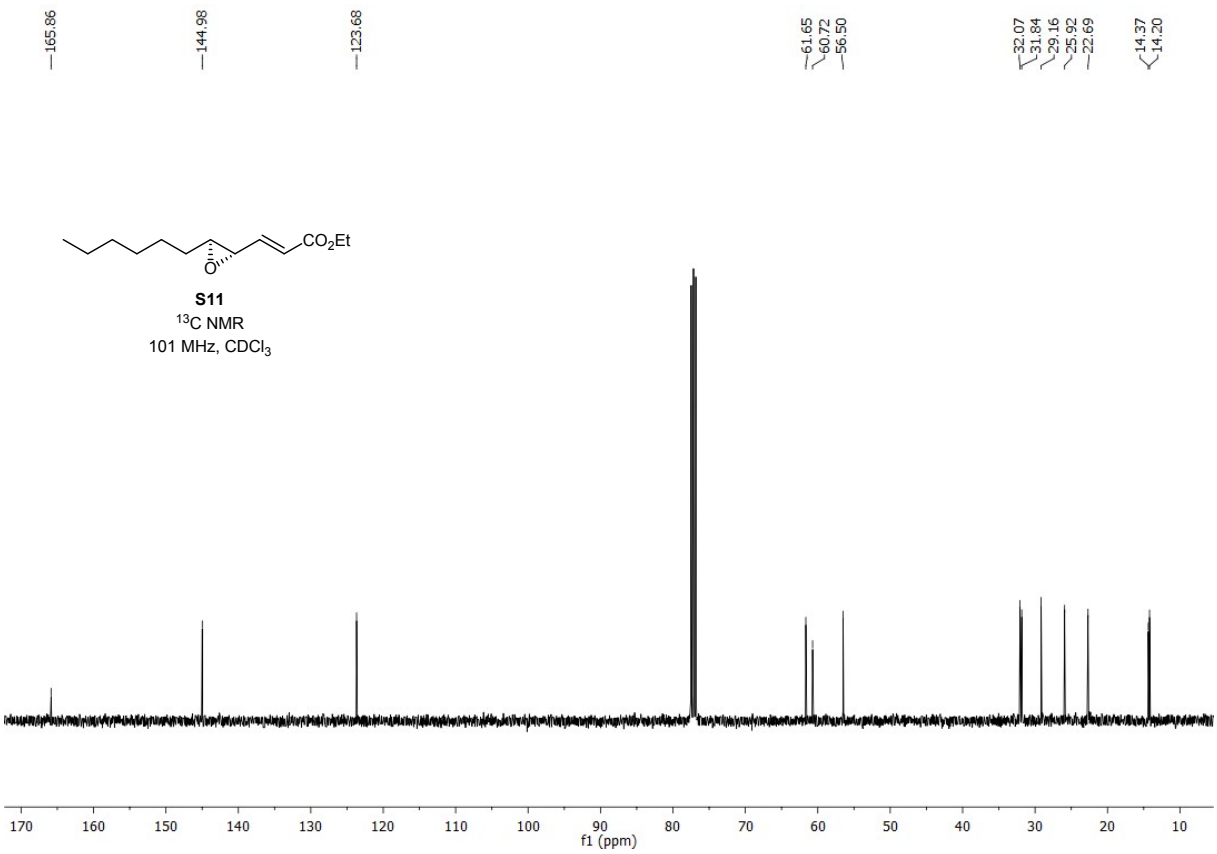
2

^{13}C NMR

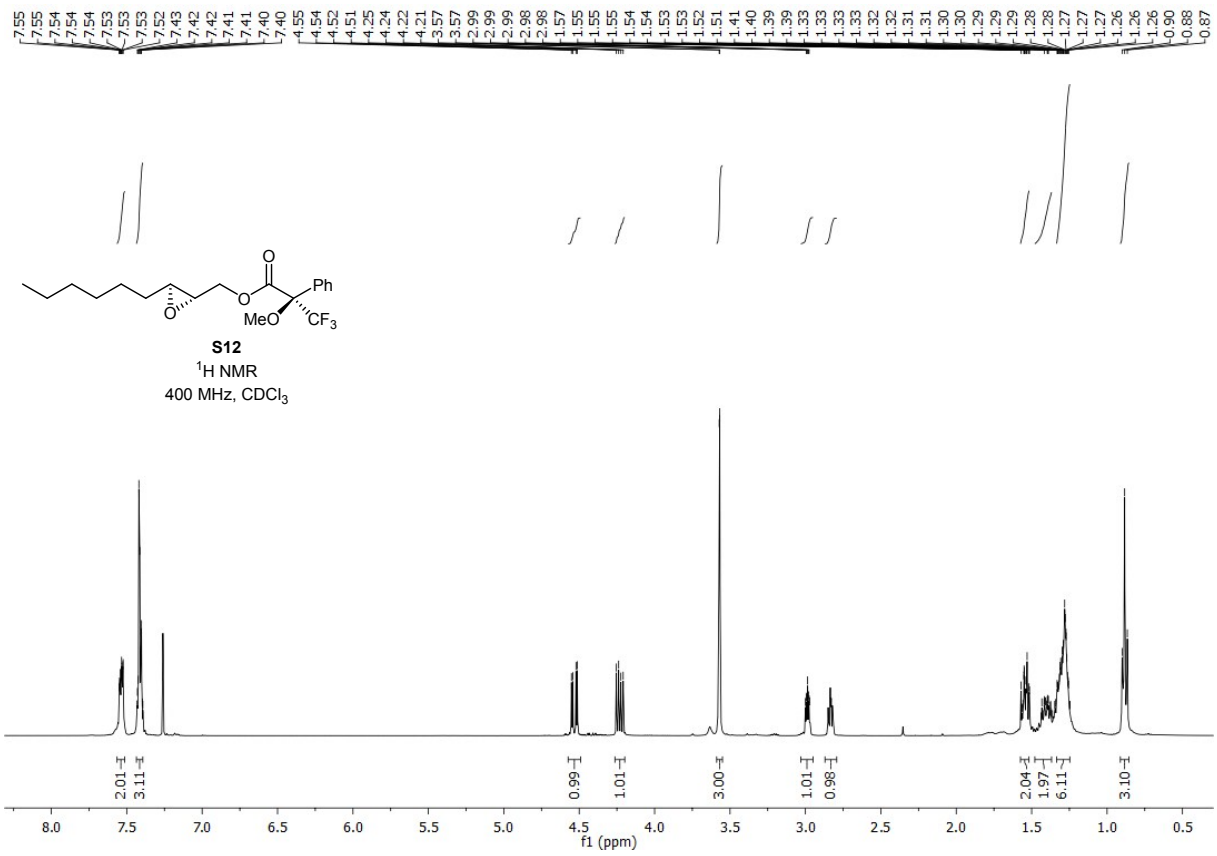
100 MHz, CD_3OD



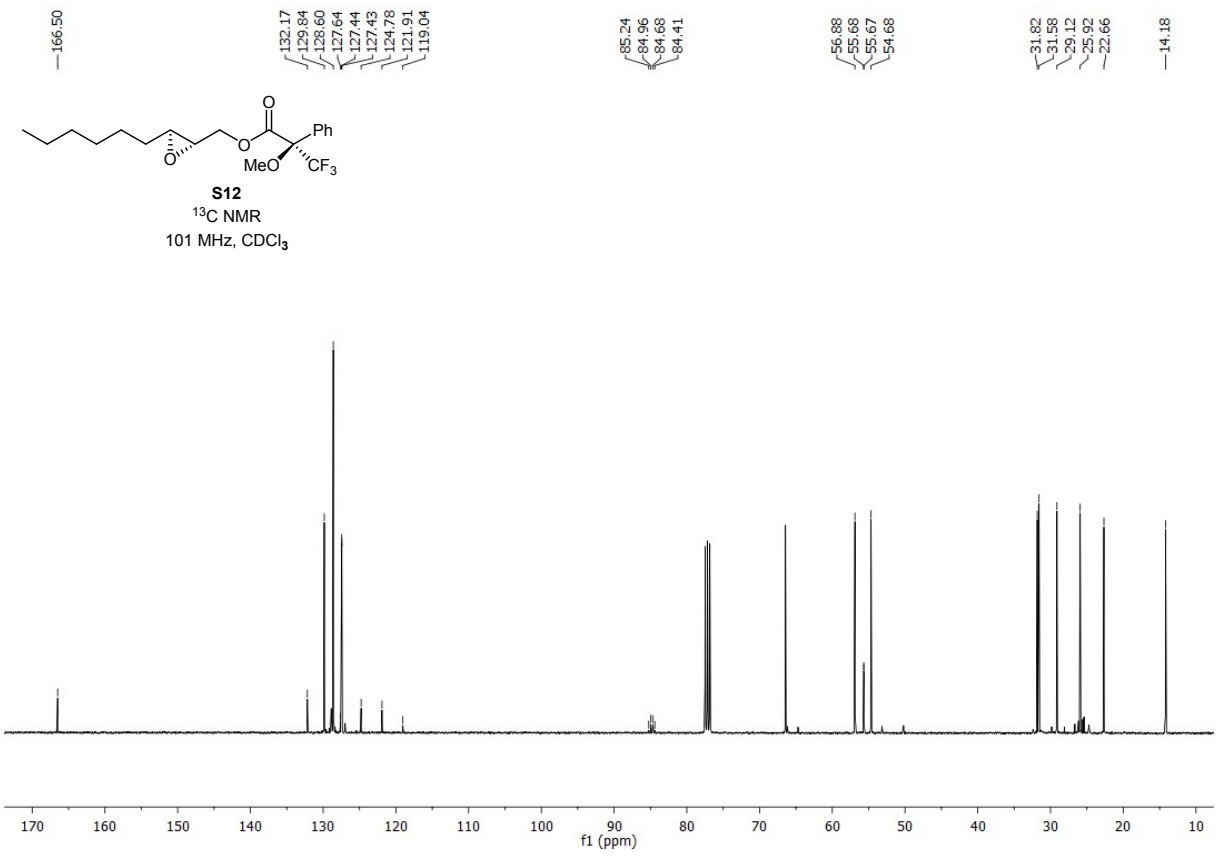
S11
^{1}H NMR
400 MHz, $CDCl_3$



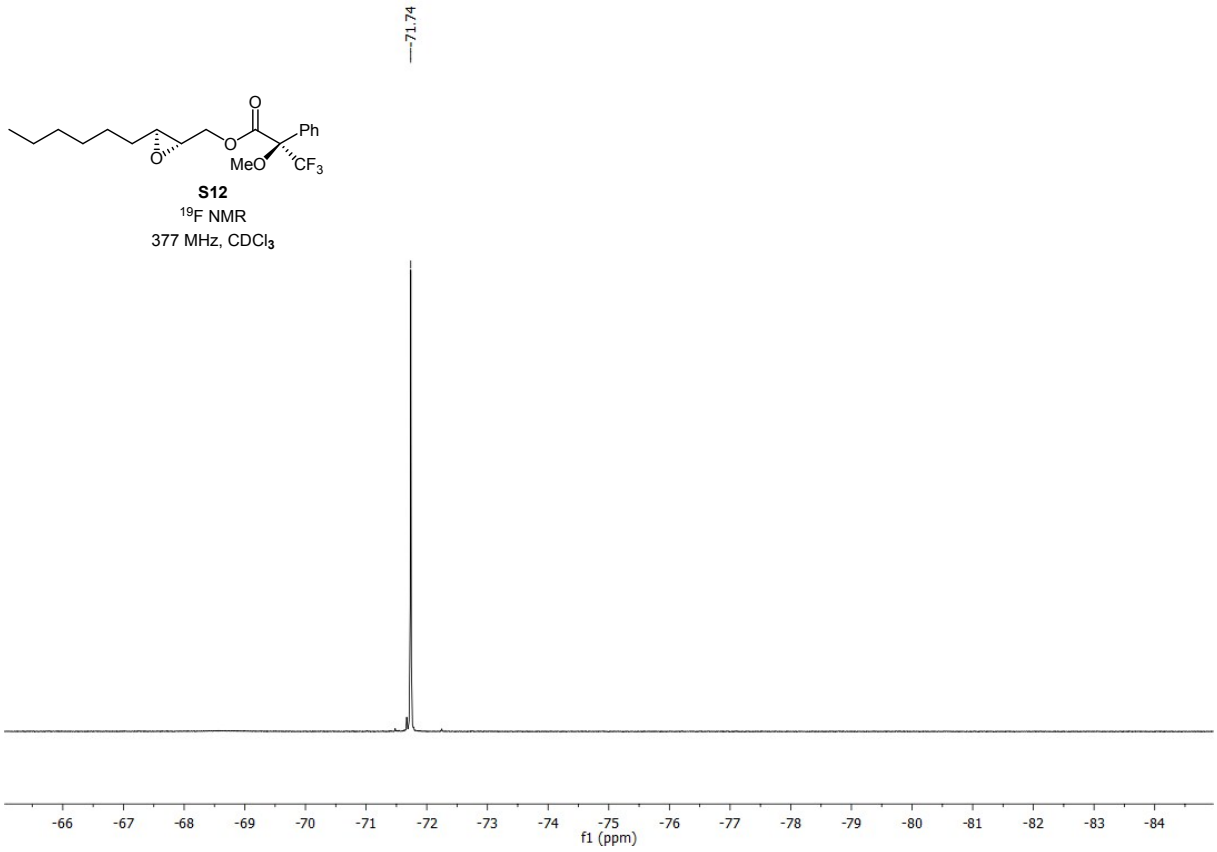
S11
^{13}C NMR
101 MHz, $CDCl_3$



S12
^{1}H NMR
400 MHz, $CDCl_3$



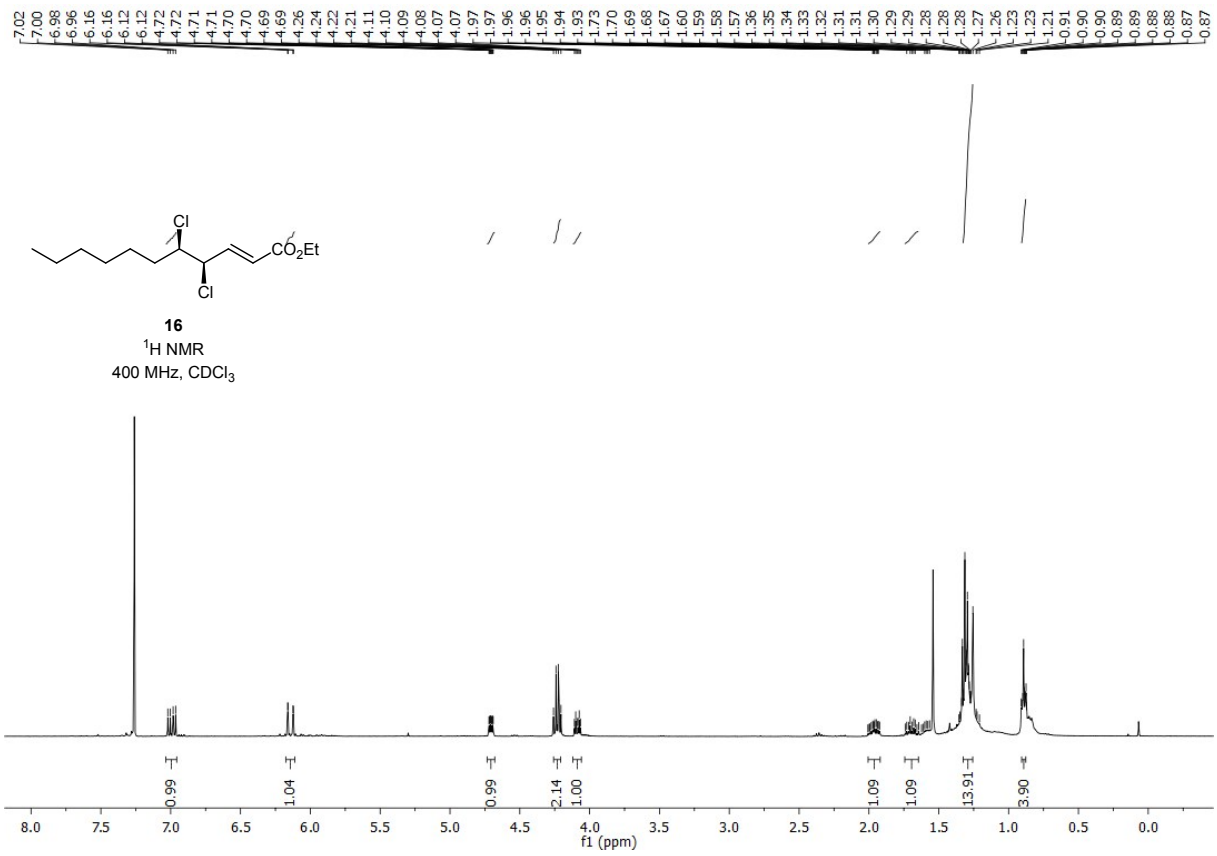
S12
^{13}C NMR
101 MHz, $CDCl_3$



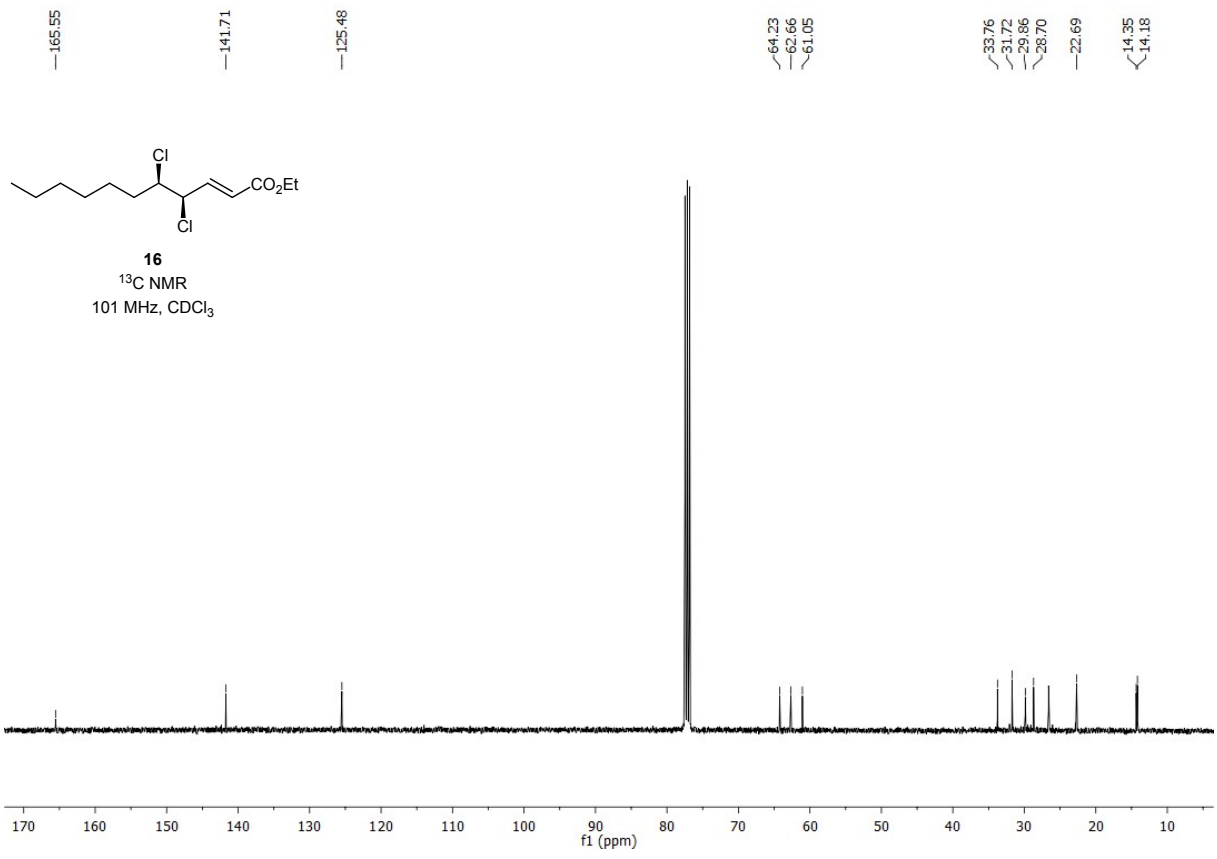
S12

^{19}F NMR

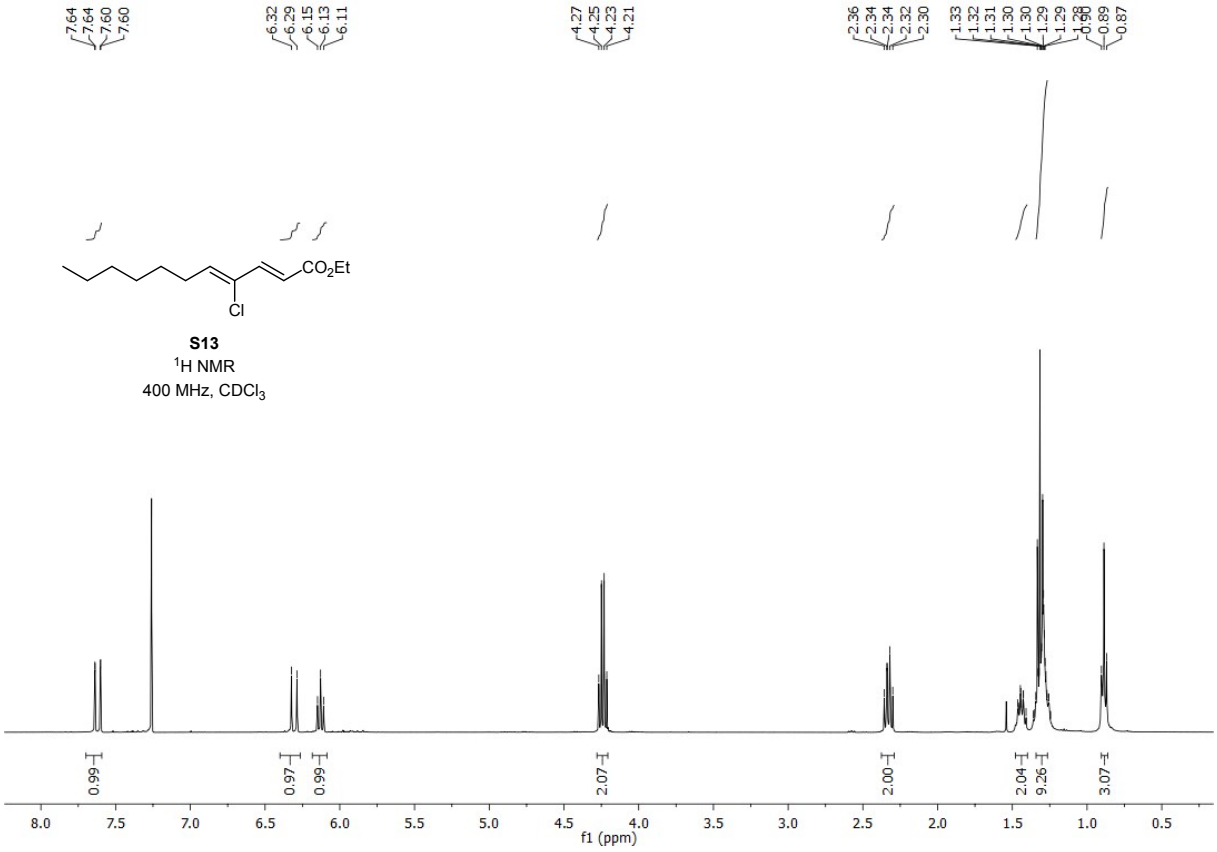
377 MHz, $CDCl_3$



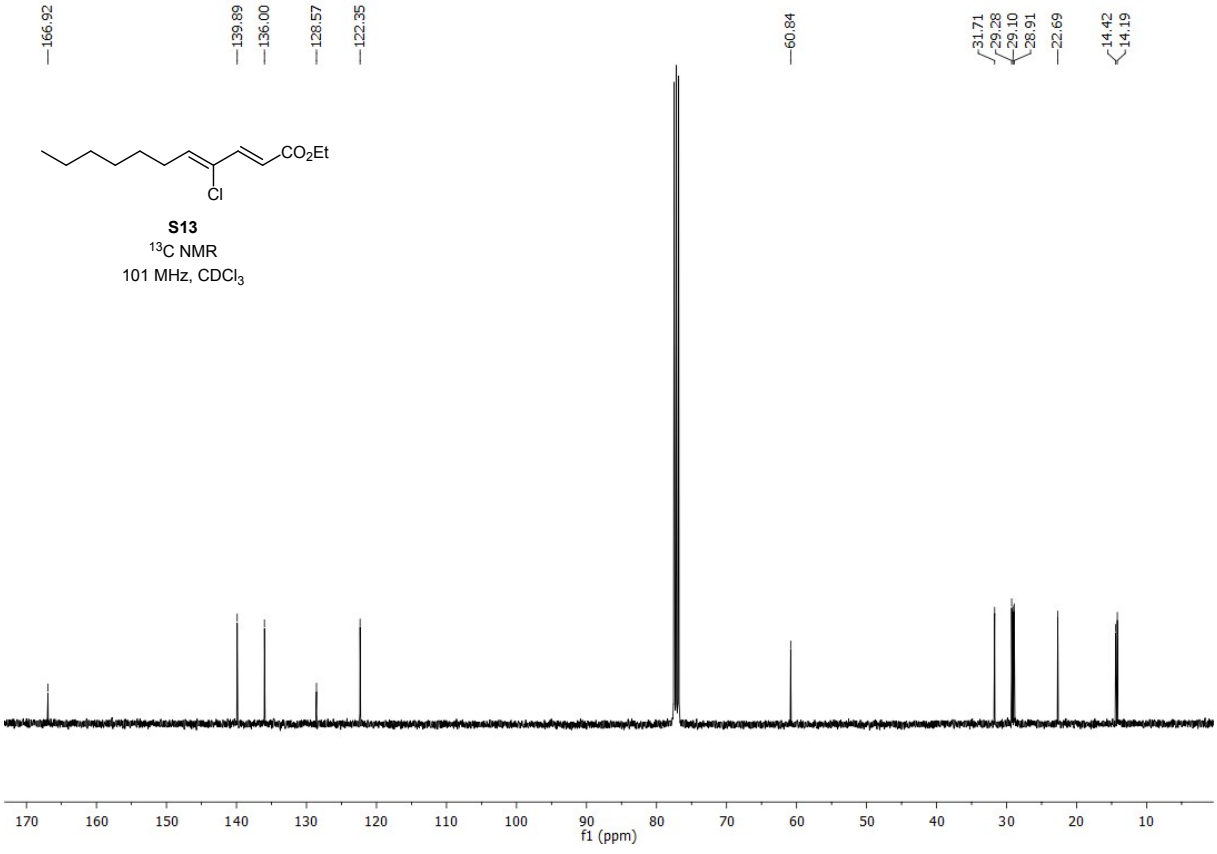
16
^{1}H NMR
400 MHz, $CDCl_3$



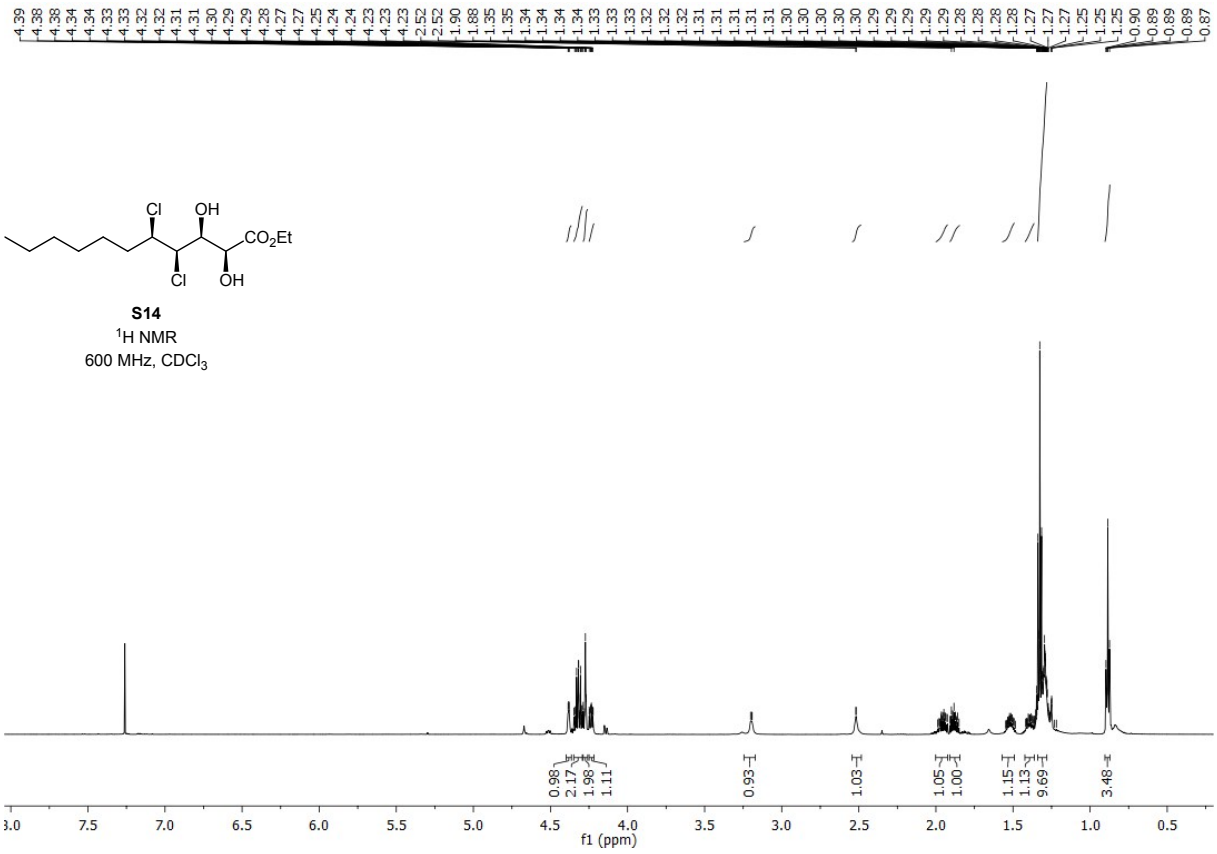
16
^{13}C NMR
101 MHz, $CDCl_3$



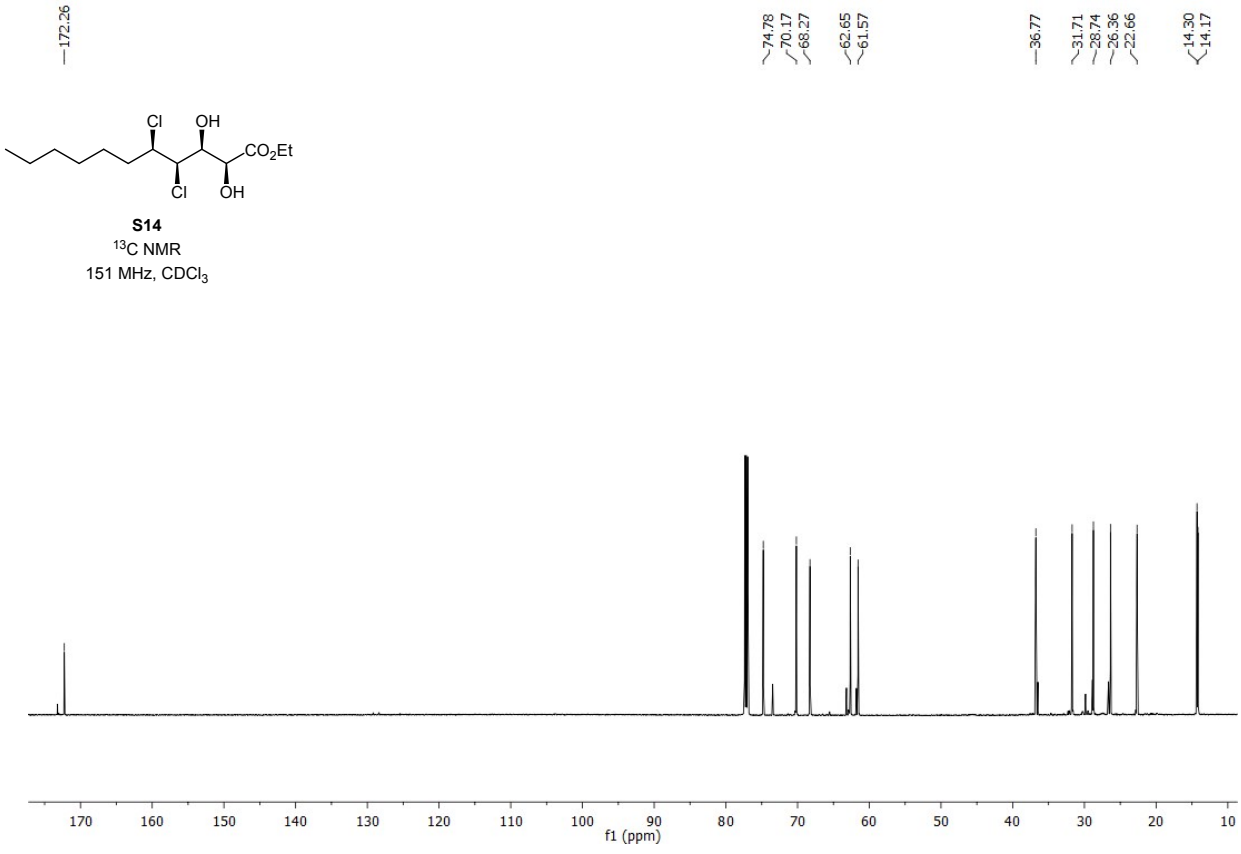
S13
^{1}H NMR
400 MHz, $CDCl_3$



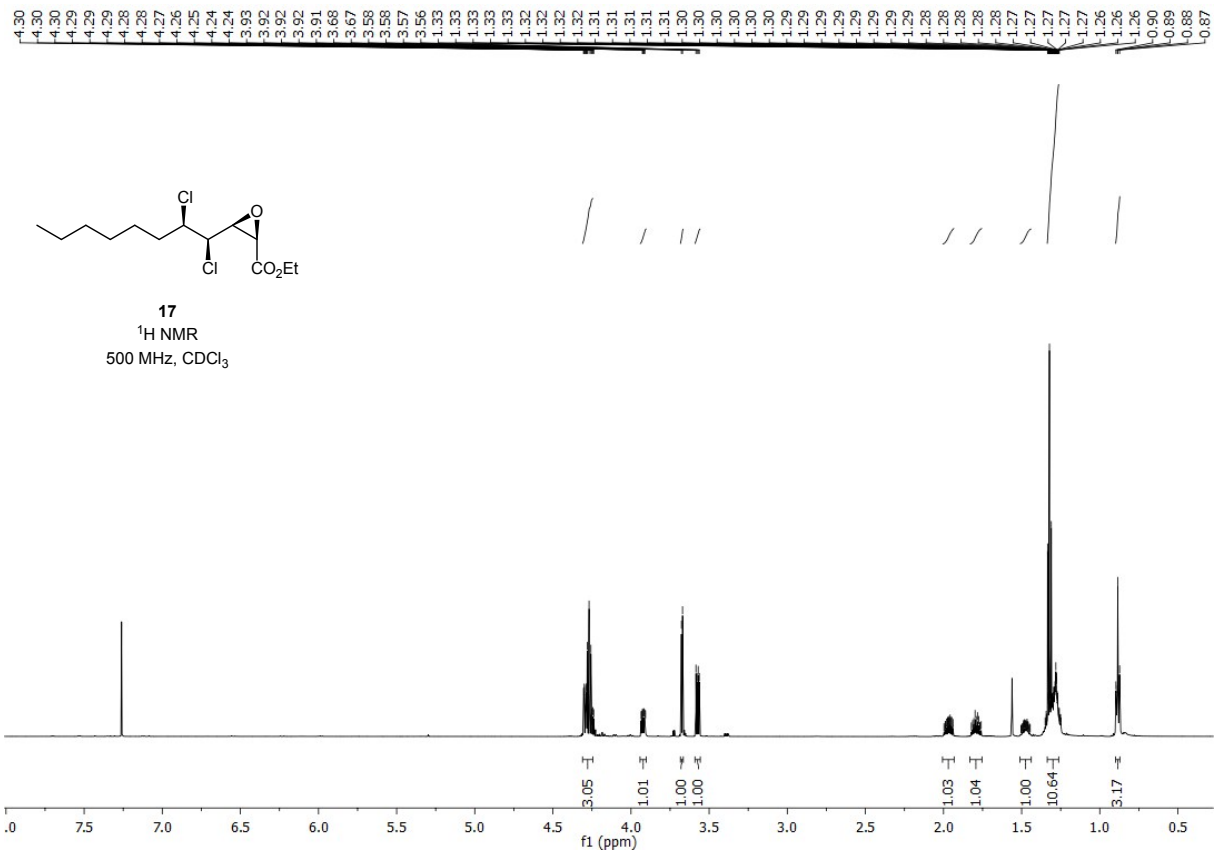
S13
^{13}C NMR
101 MHz, $CDCl_3$



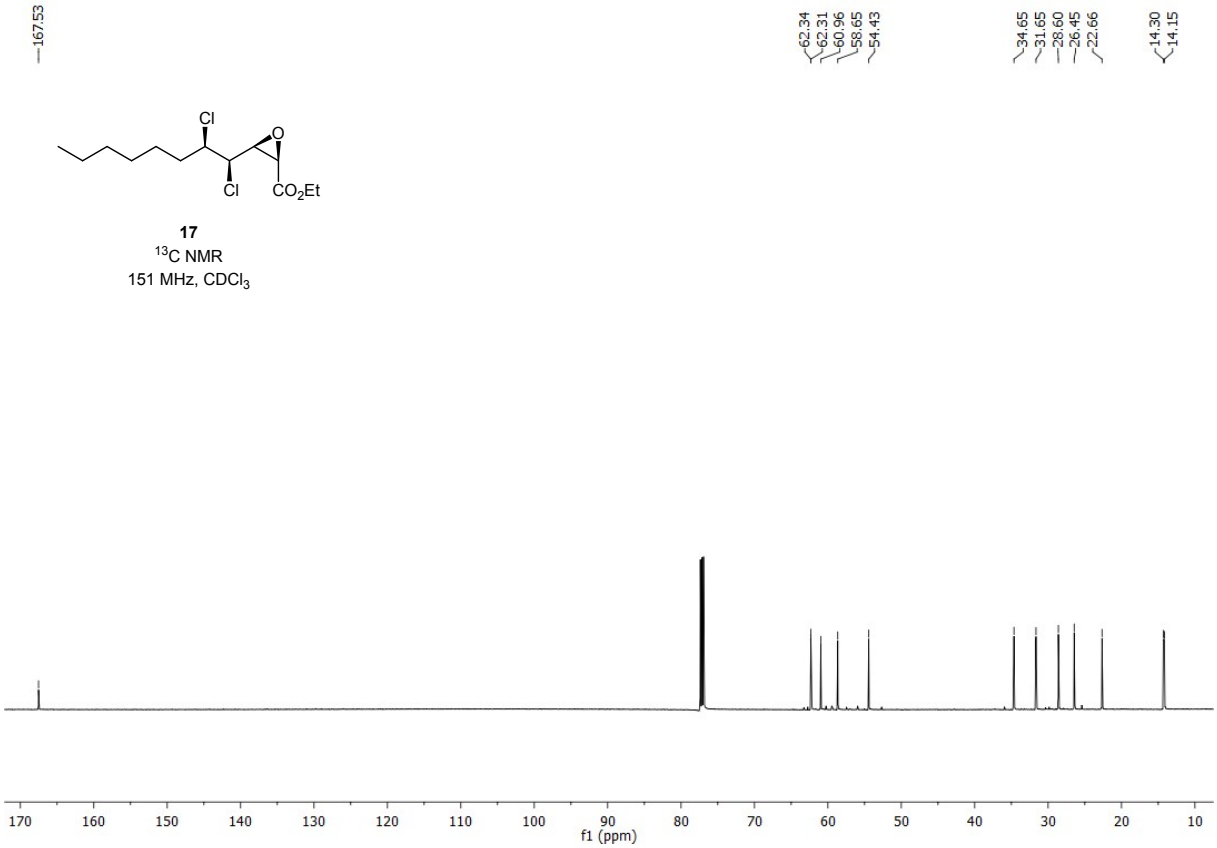
S14
^{1}H NMR
600 MHz, $CDCl_3$



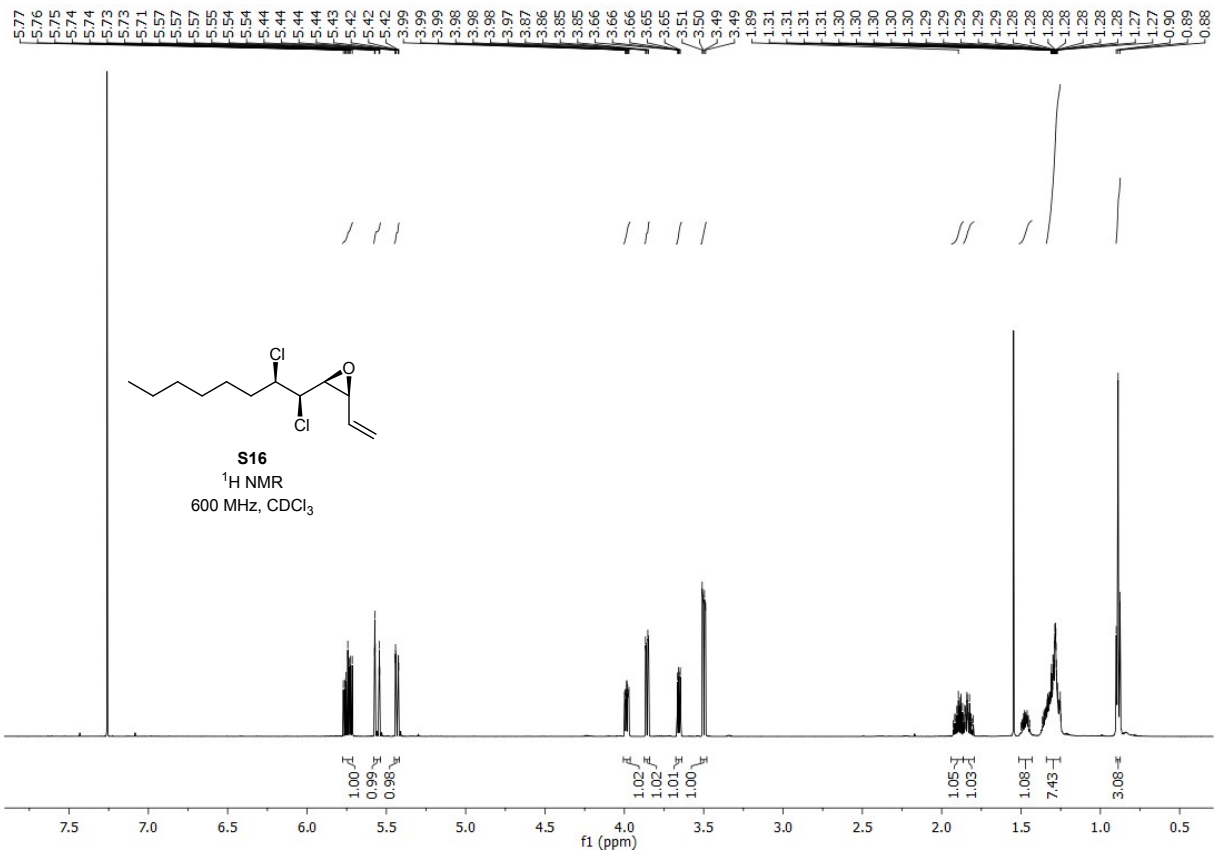
S14
^{13}C NMR
151 MHz, $CDCl_3$



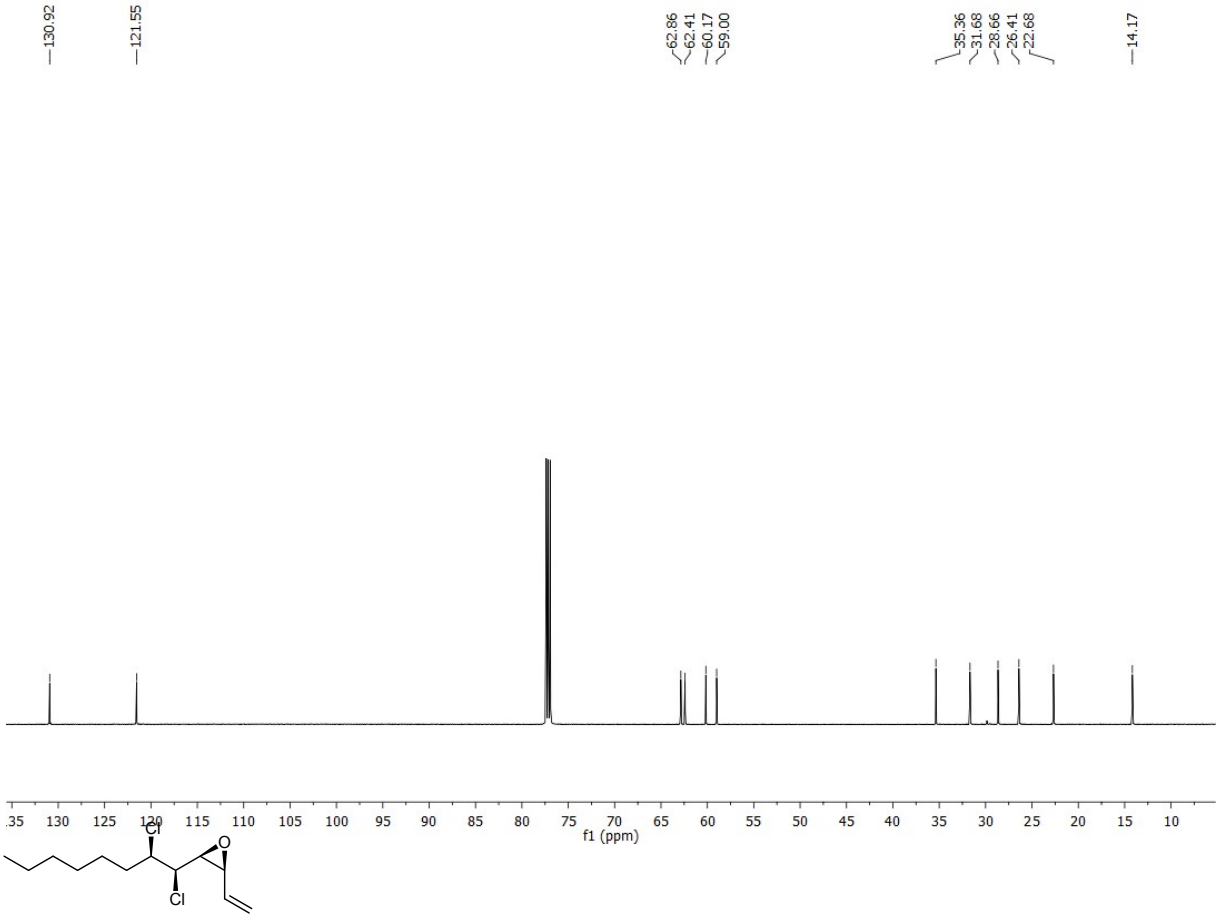
17
^{1}H NMR
500 MHz, $CDCl_3$



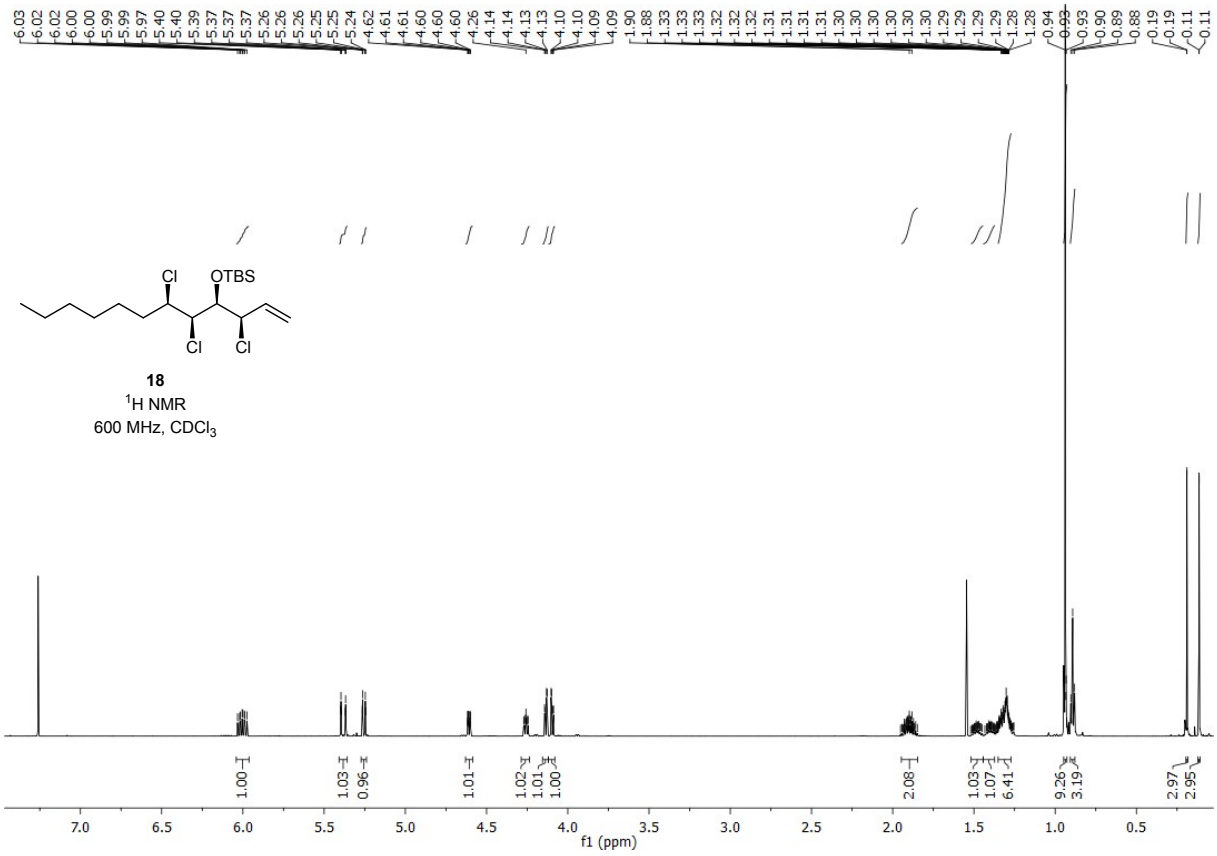
17
^{13}C NMR
151 MHz, $CDCl_3$

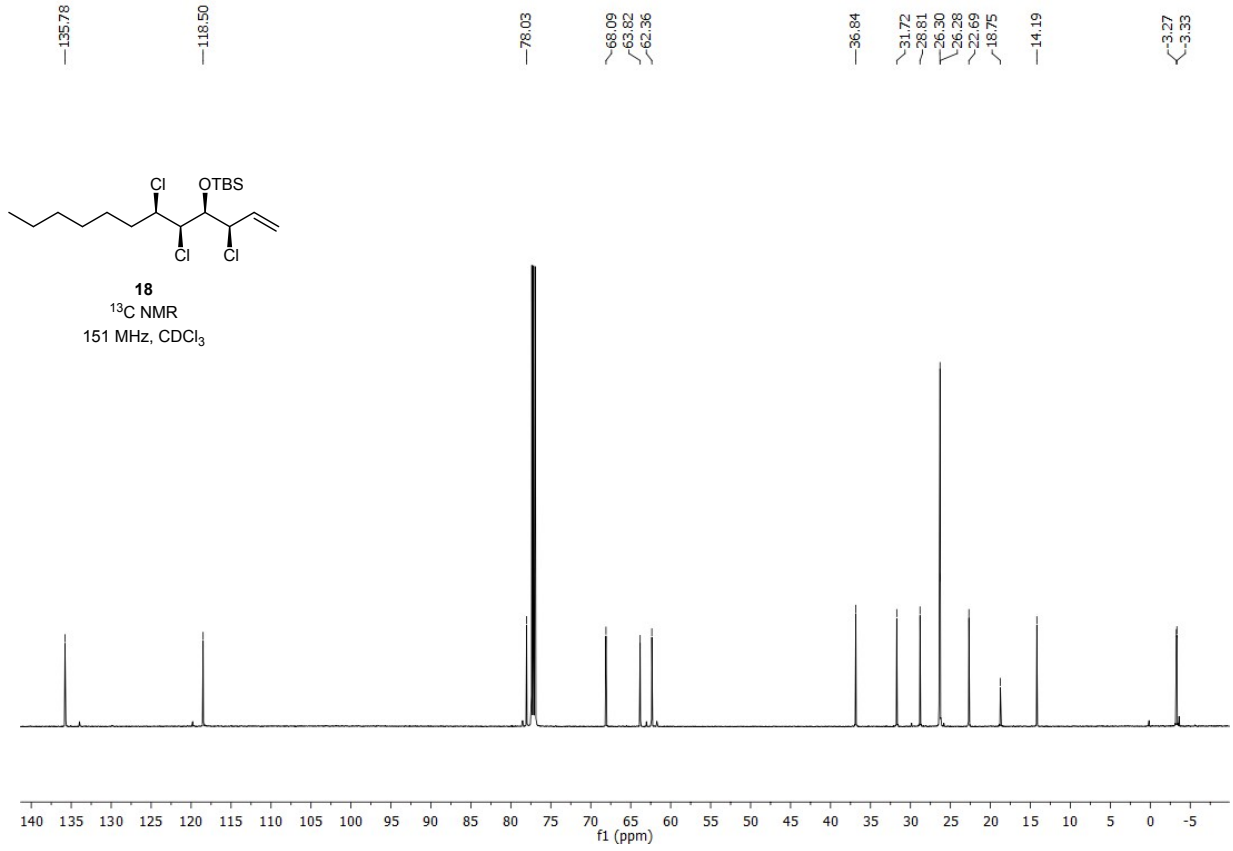


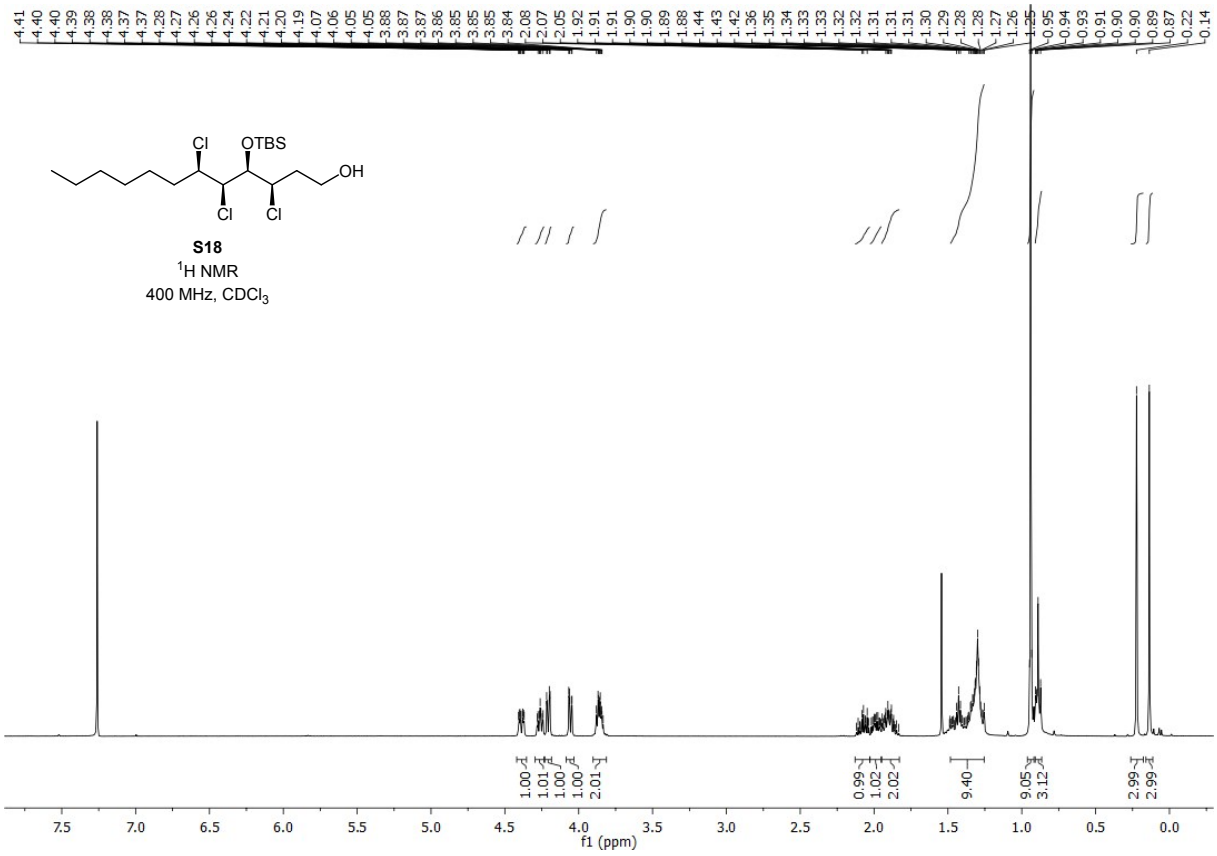
S16
^{1}H NMR
600 MHz, $CDCl_3$

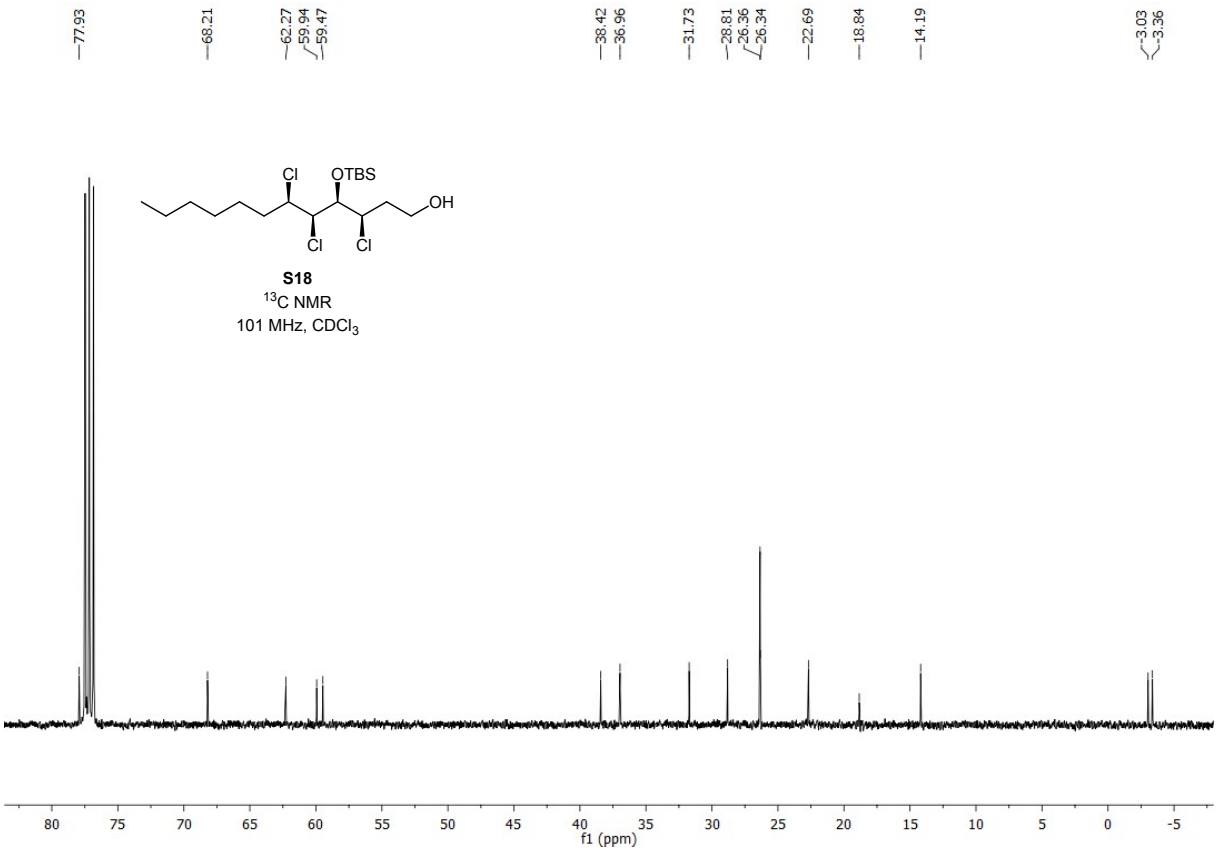


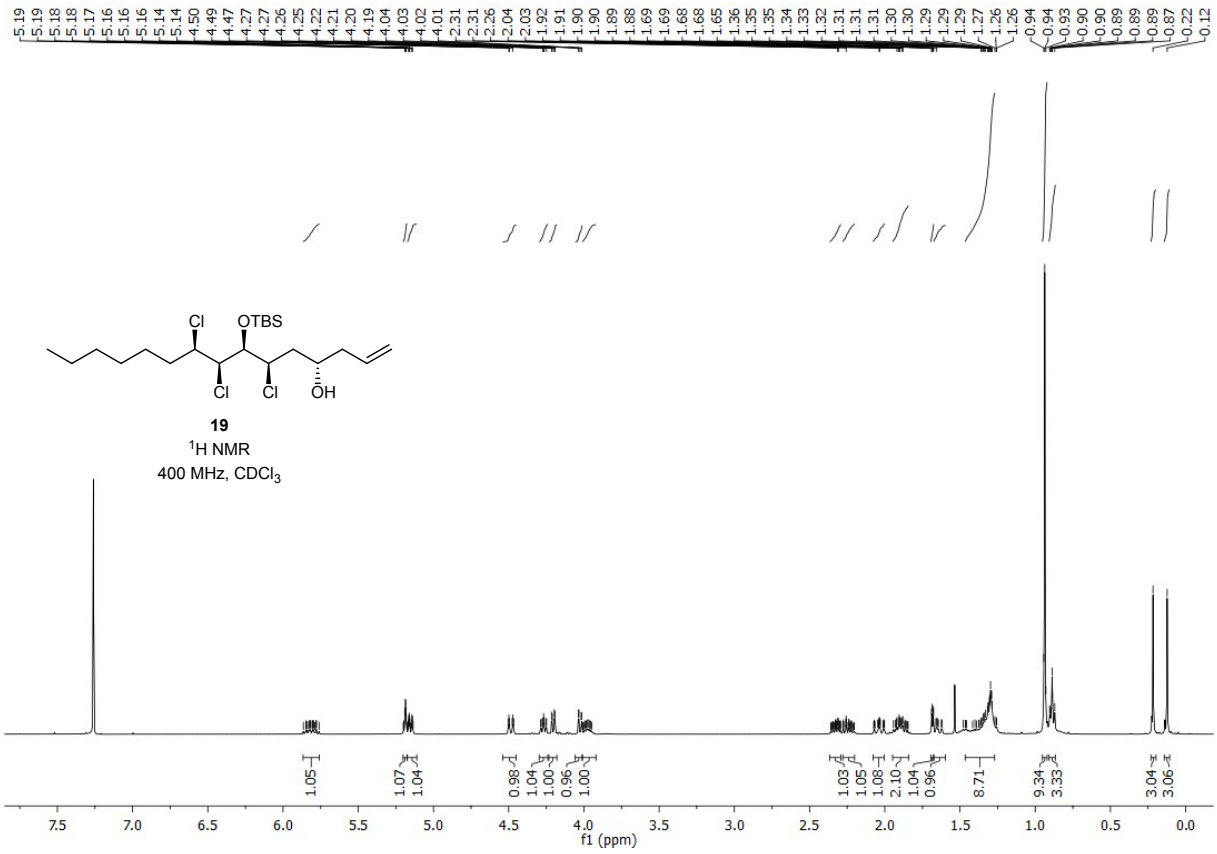
S16
^{13}C NMR
151 MHz, $CDCl_3$

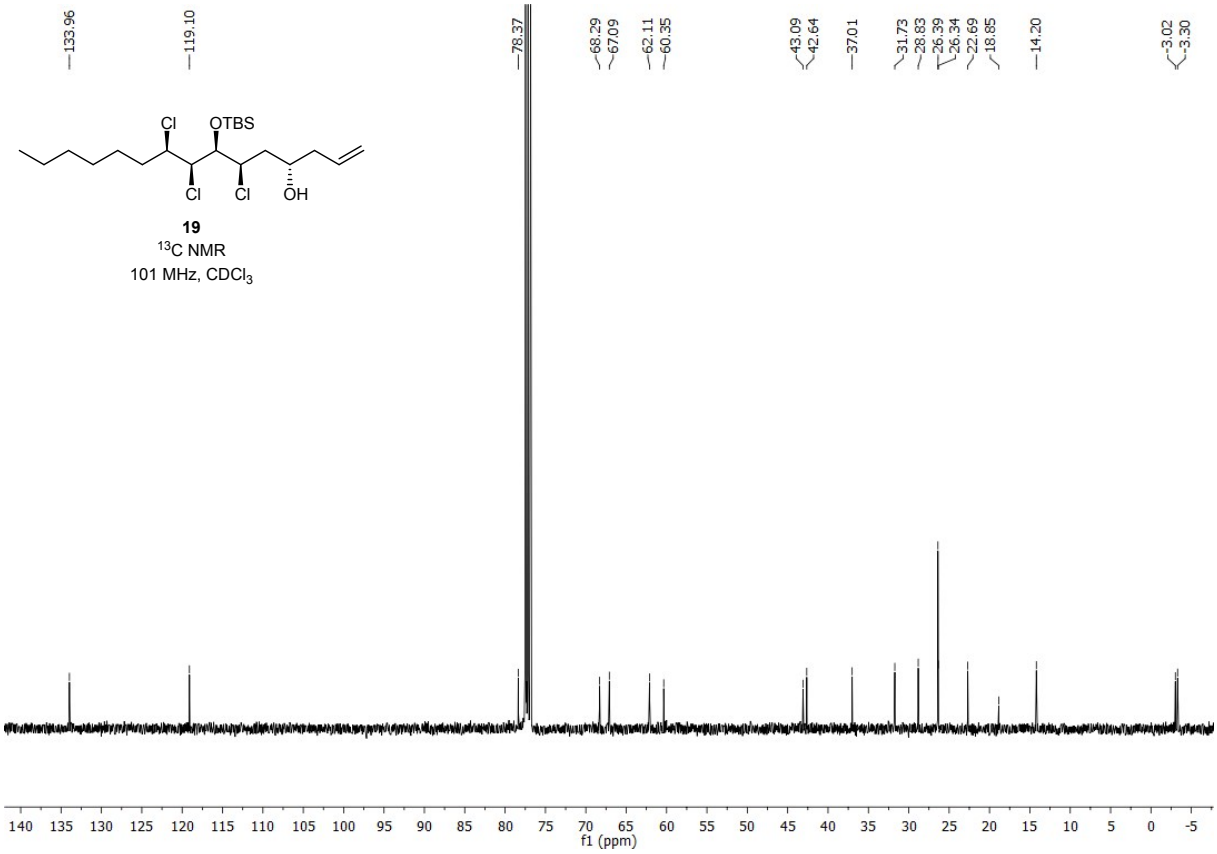

Cl
OTBS
Cl
Cl
18
1H NMR
600 MHz, CDCl3
f1 (ppm)

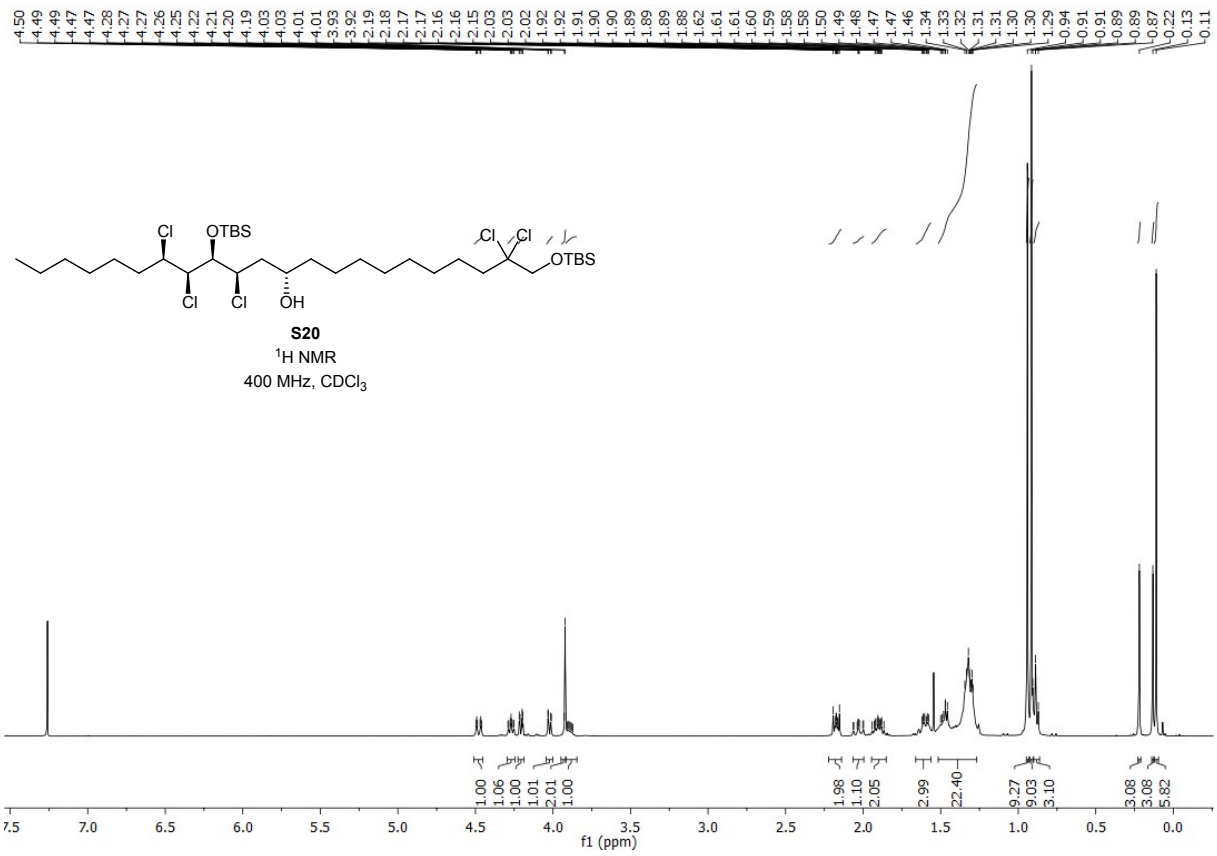

Cl
OTBS
Cl
Cl
18
13C NMR
151 MHz, CDCl3
f1 (ppm)


Cl
OTBS
OH
Cl
Cl
S18
1H NMR
400 MHz, CDCl3
f1 (ppm)

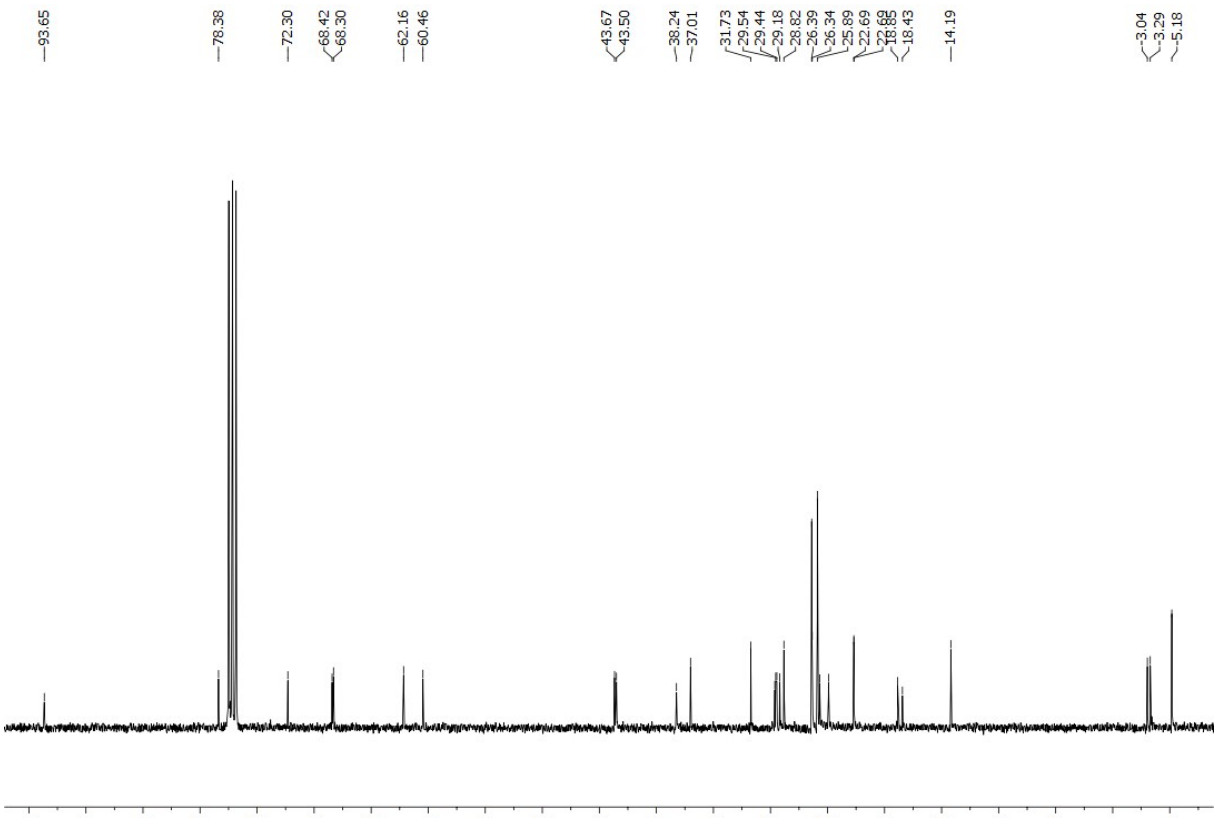

Cl
OTBS
OH
Cl
Cl
S18
13C NMR
101 MHz, CDCl3
f1 (ppm)


Cl
OTBS
Cl
Cl
OH
19
1H NMR
400 MHz, CDCl3
f1 (ppm)

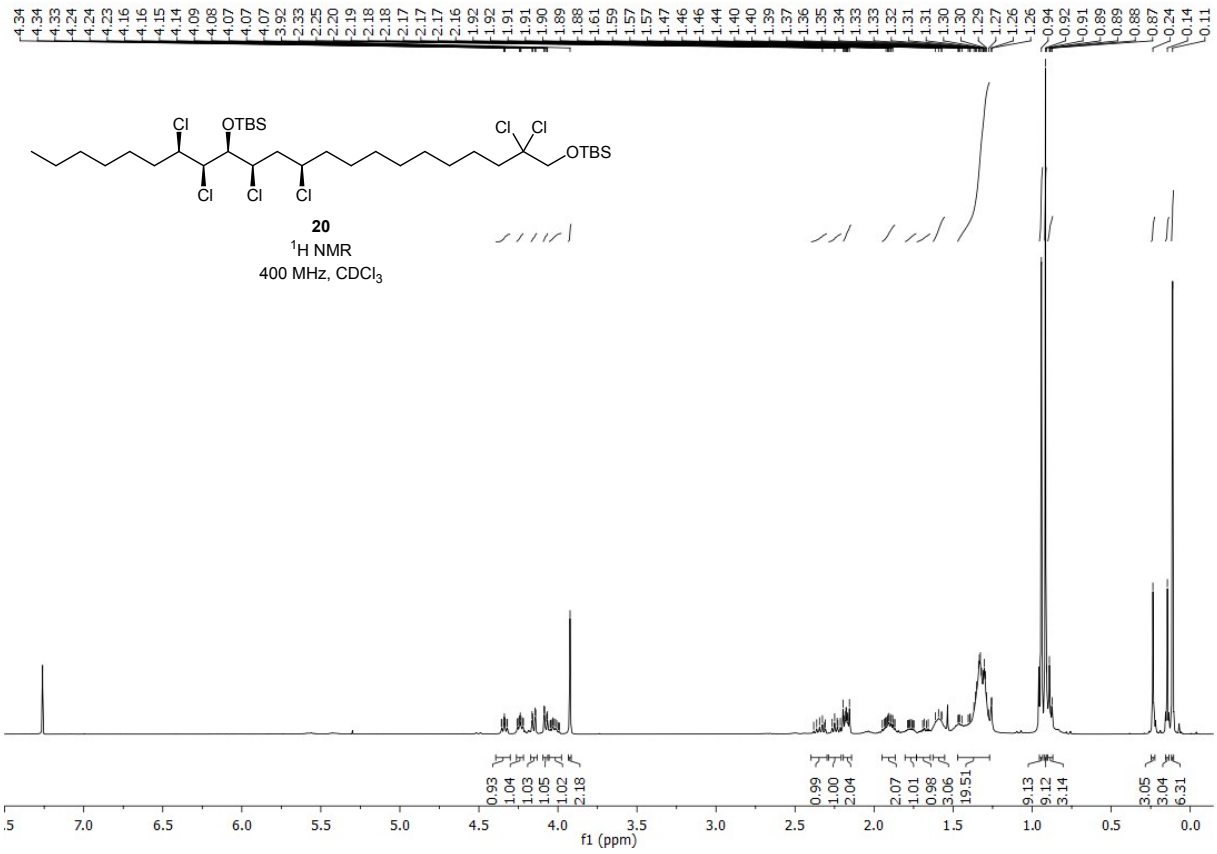

Cl
OTBS
Cl
Cl
OH
19
13C NMR
101 MHz, CDCl3
f1 (ppm)



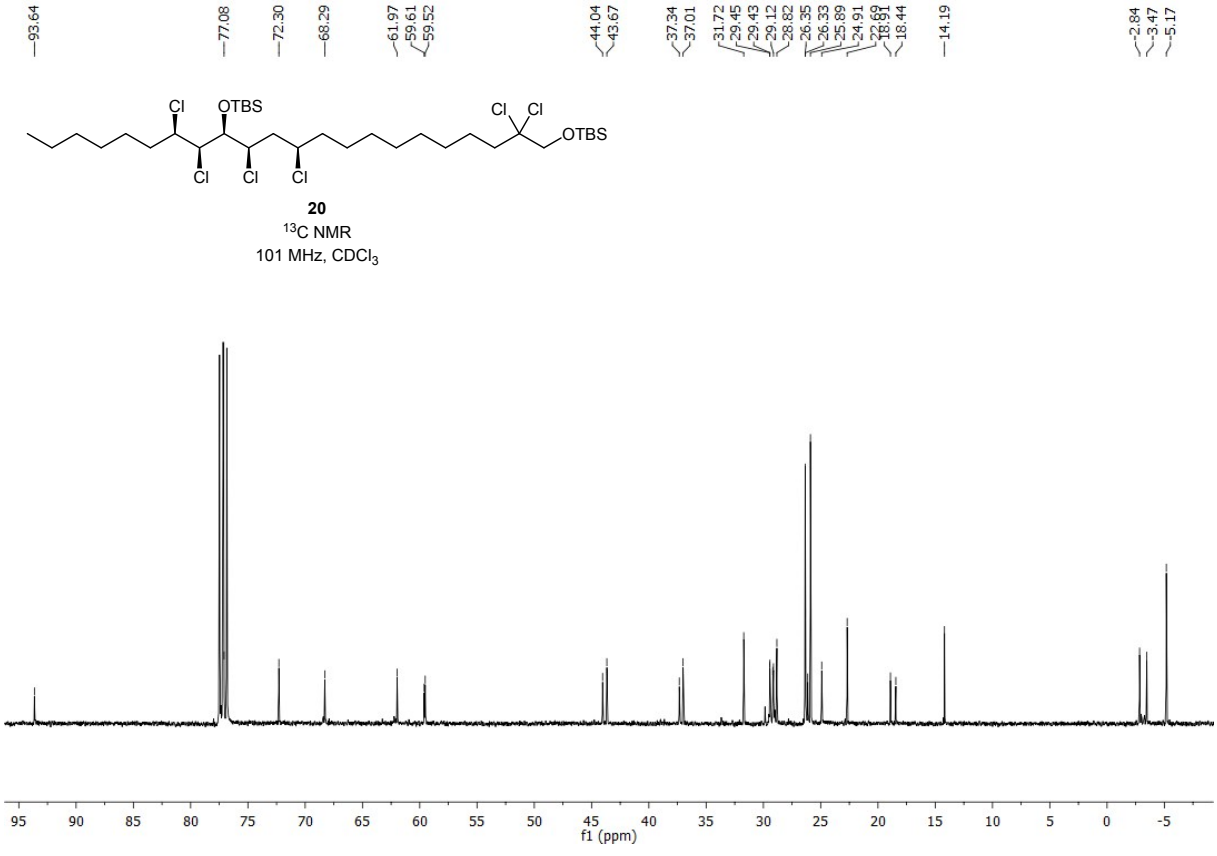
S20
^{1}H NMR
400 MHz, $CDCl_3$



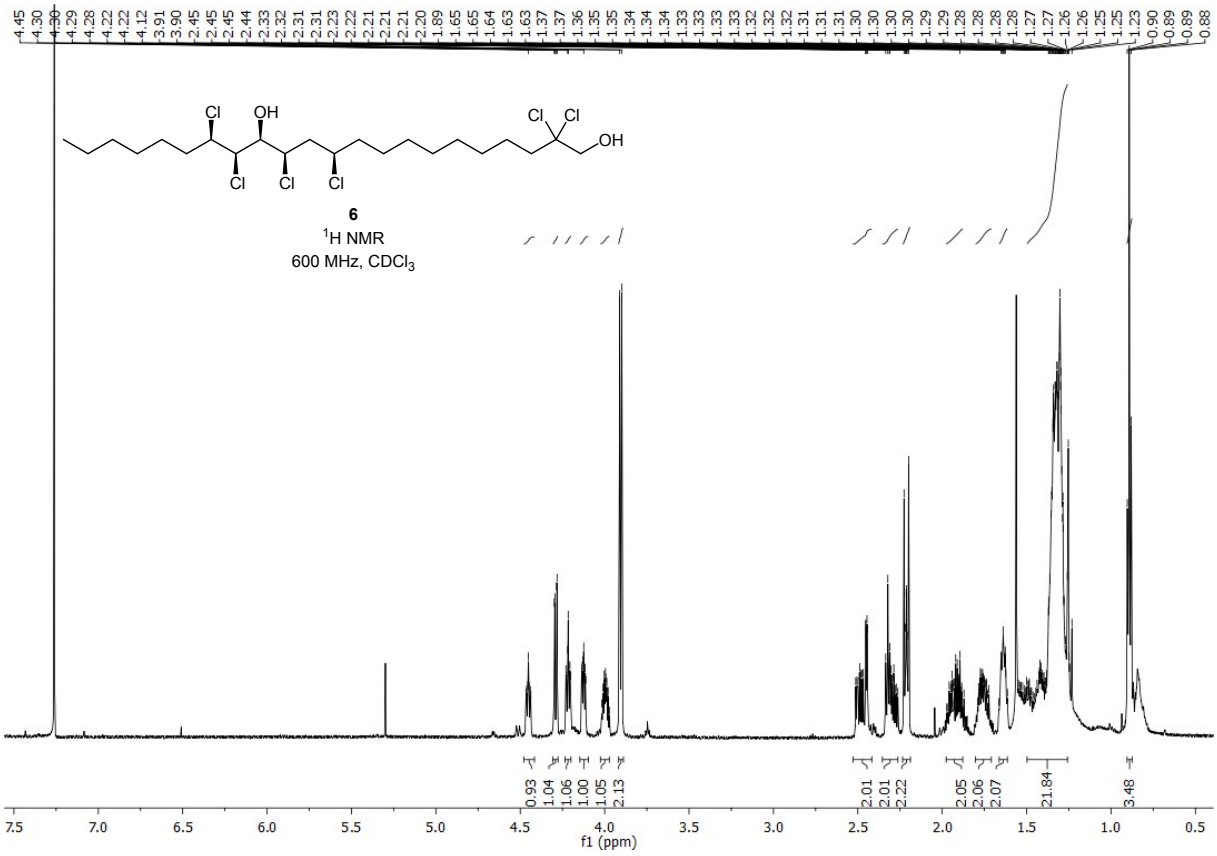
S20
^{13}C NMR
101 MHz, $CDCl_3$

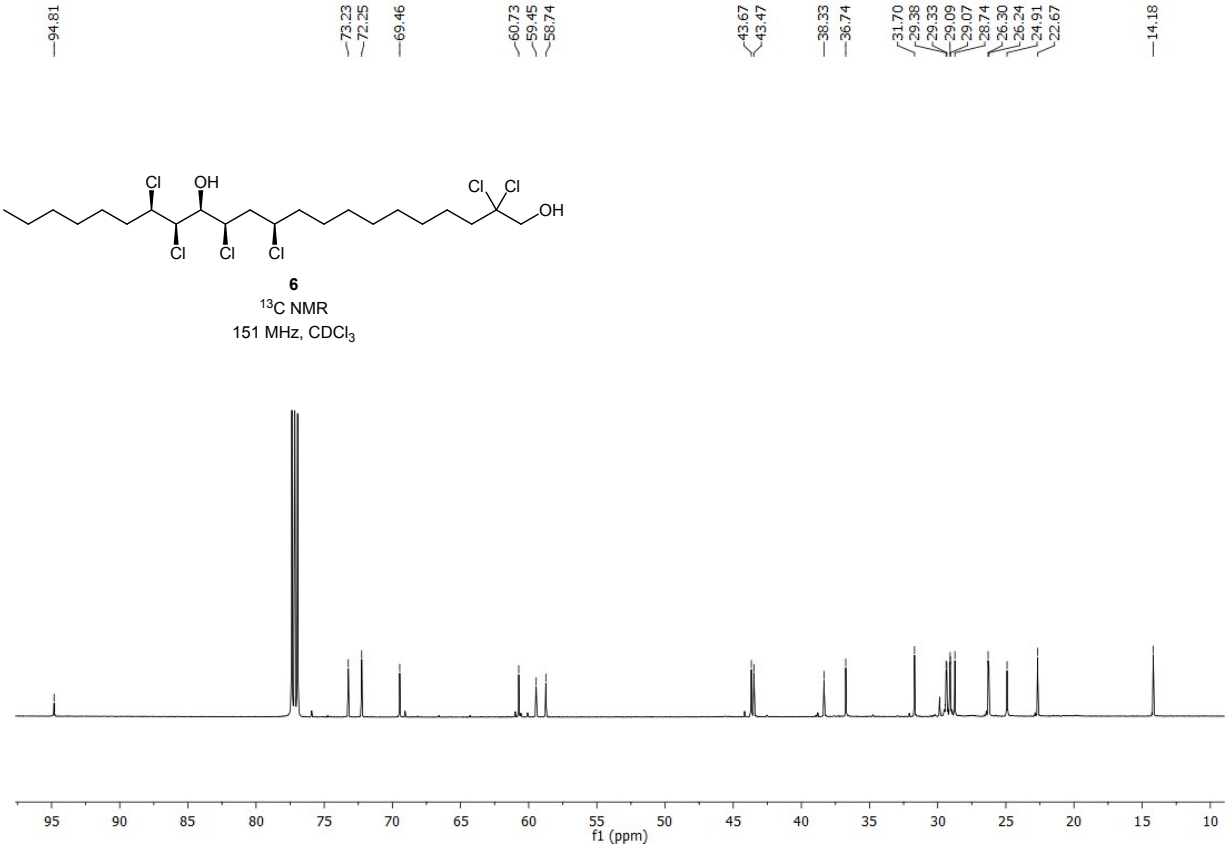


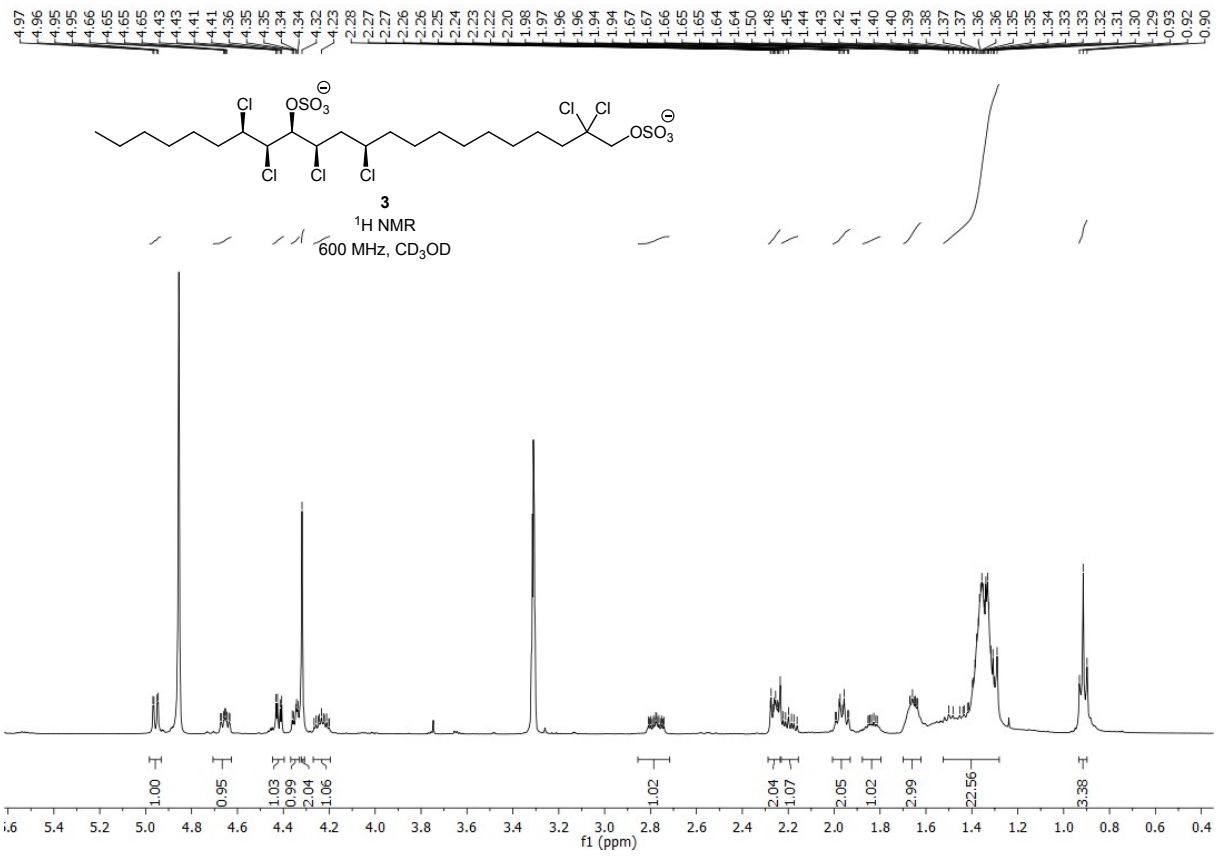
20
^{1}H NMR
400 MHz, $CDCl_3$

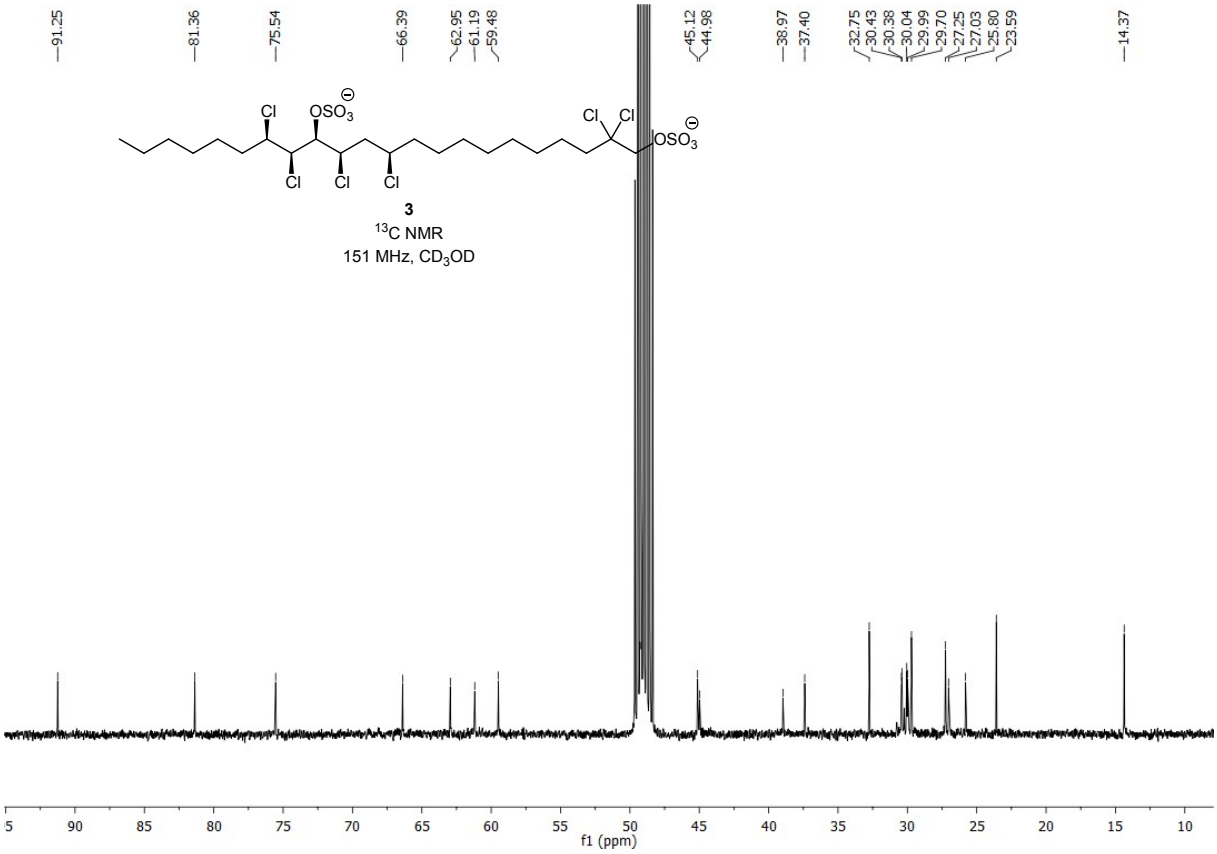


20
^{13}C NMR
101 MHz, $CDCl_3$


Cl
OH
Cl
Cl
Cl
Cl
Cl
OH
6
1H NMR
600 MHz, CDCl3
f1 (ppm)


Cl
OH
Cl
Cl
Cl
Cl
Cl
OH
6
13C NMR
151 MHz, CDCl3
f1 (ppm)


Cl
OSO3
Cl
Cl
Cl
Cl
Cl
OSO3
3
1H NMR
600 MHz, CD3OD
1.00
0.95
1.03
0.99
2.04
1.06
1.02
2.04
1.07
2.05
1.02
2.99
22.56
3.38
f1 (ppm)


91.25
81.36
75.54
66.39
62.95
61.19
59.48
45.12
44.98
38.97
37.40
32.75
30.43
30.38
30.04
29.99
29.70
27.25
27.03
25.80
23.59
14.37
Cl
OSO3
Cl
Cl
Cl
Cl
Cl
OSO3
3
13C NMR
151 MHz, CD3OD
f1 (ppm)