A counterintuitive stereochemical outcome from a chelation-controlled vinylmetal aldehyde addition leads to the configurational reassignment of phormidolide A

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2.1. General Procedures

Unless the reaction contained aqueous reagents or otherwise stated, all reactions were carried out under an atmosphere of argon, using oven dried glassware and standard techniques for handling air sensitive chemicals.

Reagents were purified using standard laboratory procedures; benzene, dichloromethane and dichloroethane were distilled from CaH_2 and stored under argon. THF and Et_2O were distilled from potassium or sodium wire/benzophenone ketyl radical and stored under argon, 2,6-lutidine, DIPEA and Et_3N were distilled from CaH_2 and stored over CaH_2 under argon. Solvents used for extraction and chromatography were distilled. All other chemicals were used as received from the supplier unless otherwise stated. Aqueous solutions of ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$), sodium thiosulfate ($Na_2S_2O_3$), brine (NaCl) and sodium/potassium (Na/K) tartrate were saturated. Buffer solutions were prepared as directed from stock tablets.

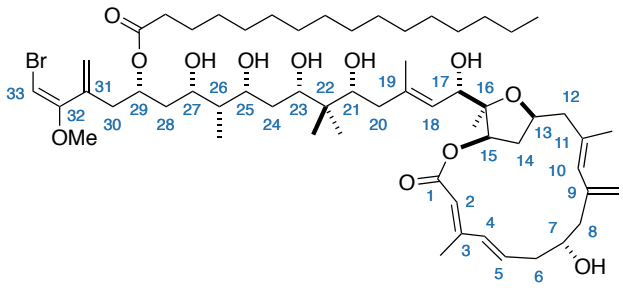
Flash column chromatography was carried out using Kieselgel 60 (230-400 mesh) and a positive solvent pressure. TLC was carried out using Merck Kieselgel 60 F_{254} plates, which were visualised under UV light (254 nm) and stained with potassium permanganate or phosphomolybdic acid/$Ce_2(SO_4)_3$ dips.

NMR spectra were recorded using the following machines: Bruker Avance II (600 MHz), Bruker Avance 500 BB (500 MHz), Avance TCI cryoprobe (500 MHz) and Avance 400 DRX (400 MHz). ^{1}H spectra were recorded at 298 K with an internal deuterium lock for the residual undeuterated solvent: $CDCl_3$ (δ_H = 7.26 ppm). ^{1}H data are presented as: chemical shift (δ / ppm), relative to tetramethylsilane (δ_{TMS} = 0 ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sept = septet, m = multiplet, br = broad, app = apparent, obs = obscured) and coupling constants (*J* in Hz). Unless otherwise indicated, signals are assigned according to the numbering scheme for phormidolide A (*vide infra*). Assignments have been made based on 1D data presented along with 2D spectra and comparison with fully assigned spectra for similar compounds. ^{13}C NMR spectra were recorded at 298 K with broadband proton decoupling and an internal deuterium lock for ^{13}C: $CDCl_3$ (δ_C = 77.0 ppm). Data are listed by chemical shift (δ/ppm) relative to tetramethylsilane (δ_{TMS} = 0 ppm).

Fourier transform IR spectroscopy (FT-IR) was carried out using a Perkin-Elmer Spectrum-One spectrometer and spectra were recorded as a thin film. Wavelengths of maximum absorption (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) and are reported as $[\alpha]_D^{20}$, concentration (*c* in g/100 mL) and solvent used. High resolution mass spectrometry (HRMS) was carried out by the EPSRC National Mass

Spectrometry Facility (Swansea, UK) using electrospray ionisation (ESI). The parent ion $[M+H]^+$, $[M+NH_4]^+$ or $[M+Na]^+$ is quoted. Chiral HPLC was carried out on a Shimadzu XR-LC system, using a Chiralpak® IA column and a solvent system of mixed hexanes and isopropanol.

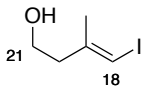
The numbering system used for the carbon skeleton of phormidolide A follows that of Williamson *et al.*[1], with the exception of skeletal substitutions (e.g. hydroxyl, methyl, methoxy and methylene groups), which are denoted by the skeletal carbon to which they are attached. The complete numbering scheme for phormidolide A (**1**) is shown below:



*Numbering scheme for the originally proposed structure of phormidolide A (**1**)*

2.2. Synthesis of the C18-C23 vinyl iodide

Alcohol – 4a

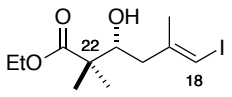


$AlMe_3$ (47.0 mL, 93.9 mmol) was added to a solution of Cp_2ZrCl_2 (1.95 g, 6.67 mmol) in CH_2Cl_2 (90 mL) at –20 °C. The solution was stirred for 10 min at –20 °C, before the addition of water (845 µL, 47.0 mmol). The pale-yellow suspension was stirred for 10 min at –20 °C. A solution of 3-butyn-1-ol (2.12 g, 30.3 mmol) in CH_2Cl_2 (20 mL) was treated with $AlMe_3$ (4.70 ml, 9.39 mmol) and transferred *via* cannula into the reaction. The reaction mixture was stirred for 16 h, with gradual warming to r.t., during which a yellow suspension formed. A solution of I_2 (9.16 g, 36.4 mmol) in Et_2O (200 mL) was transferred *via* cannula to the mixture at –20 °C, resulting in a colour change to vivid yellow, then brown. The reaction mixture was allowed to warm to r.t. and stirred for 2 h. The reaction was quenched by addition of Na/K tartrate (200 mL) and Et_2O (200 mL) and vigorously stirred at r.t. for 1.5 h. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a yellow liquid. Purification by flash column chromatography (Et_2O/PE 30-40: 20% → 30%) afforded the product **4a** as a pale-yellow oil (5.22 g, 26.4 mmol, 87%).

$\mathbf{R_f}$ (Et_2O/PE 30-40: 50%) = 0.54; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.01 (1H, q, J = 1.0 Hz, H18), 3.72 (2H, t, J = 6.3 Hz, H21), 2.48 (2H, t, J = 6.3, H20), 1.87 (3H, s, Me19); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.5, 76.8, 60.1, 42.4, 23.8.

Data in agreement with that presented by Penner[2]

Hydroxyester – 7 and *ent*-7



Dess-Martin Periodinane (2.50 g, 5.89 mmol) was added to a stirred suspension of alcohol **4a** (500 mg, 2.35 mmol) and $NaHCO_3$ (1.50 g, 17.8 mmol) in wet CH_2Cl_2 (25 mL). The reaction mixture was stirred at r.t. until TLC monitoring indicated full consumption of the starting material (*ca.* 1.5 h). The reaction was quenched by the addition of $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ solution (20 mL) and stirred at r.t. for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under

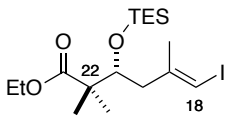
reduced pressure to *ca*. 10 mL. The solution of the crude aldehyde **4** was dried over 4 Å molecular sieves and directly used in the subsequent step without further purification. Aldehyde **4** was both volatile and highly prone to degradation, and an analytically pure sample was not obtained.

$BH_3{\cdot}SMe_2$ (279 μL, 2.95 mmol) was added dropwise to a stirred solution of *N*-tosyl-L-valine[3] (799 mg, 2.95 mmol) in CH_2Cl_2 (7 mL) and THF (1 mL) at 0 °C. The solution was stirred at 0 °C for 1 h before cooling to −78 °C. A combined solution of the crude aldehyde **4** and the silyl ketene acetal **5**[4] (1.11 g, 5.89 mmol, dried over CaH_2) in CH_2Cl_2 (15 mL) was added *via* cannula to the reaction mixture. The reaction mixture was stirred at −78 °C for 3 h before quenching with $NaHCO_3$ solution. Upon warming to r.t., the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 5%) afforded the product **7** as an orange oil (516 mg, 3.95 mmol, 67% over 2 steps, 91% *ee*).

The enantiomeric compound ***ent*-7** was analogously prepared from alcohol **4a** (1.00 g, 4.71 mmol), employing *N*-tosyl-D-valine (1.92 g, 7.07 mmol) as an orange oil (818 mg, 2.51 mmol, 53%)

R_f (EtOAc/PE 40-60: 30%) = 0.57; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.02 (1H, q, *J* = 0.9 Hz, H18), 4.16 (2H, q, *J* = 7.1 Hz, $CH_3\underline{CH_2}O$), 3.81 (1H, ddd, *J* = 10.0, 5.6, 2.5 Hz, H21), 2.39 (1H, d, *J* = 5.6 Hz, OH), 2.33 (1H, br d, *J* = 13.2 Hz, H20a), 2.26 (1H, dd, *J* = 13.9, 10.0 Hz, H20b), 1.90 (3H, d, *J* = 0.9 Hz, Me19), 1.27 (3H, t, *J* = 7.1 Hz, $\underline{CH_3}CH_2O$), 1.20 (3H, s, Me22a), 1.20 (3H, s, Me22b); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 177.1, 145.1, 73.7, 60.8, 46.7, 42.0, 23.9, 21.6, 20.7, 14.2, 14.1; **IR** (thin film): ν_{max} 3526, 2984, 1716, 1469, 1386, 1269, 1134, 1070; $[\alpha]_D^{20}$ +13.9 (**7**, *c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ −12.6 (***ent*-7**, *c* 0.26, $CHCl_3$); **Chiral HPLC** (Chiralpak® IA, *i*PrOH : *n*-hexane: 5%) R_T (major) 10.02 min, R_T (minor) 10.74 min; **HRMS** (ESI^+) calculated for $C_{11}H_{20}O_3I$ $[M+H]^+$ 327.0452, found 327.0451.

TES ether – 7a and *ent*-7a



2,6-Lutidine (128 μL, 1.10 mmol) was added to a stirred solution of hydroxyester **7** (240 mg, 0.736 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was cooled to −78 °C and stirred for 5 min, before the dropwise addition of TESOTf (208 μL, 0.920 mmol). The mixture was stirred at −78 °C for 45 min, before quenching with $NaHCO_3$ solution (10 mL). Upon warming to r.t., the layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with

brine (15 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 10%) afforded the product **7a** as a colourless oil (319 mg, 0.721 mmol, 98%).

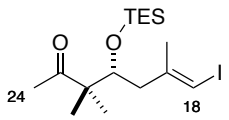
The enantiomeric compound ***ent*-7a** was analogously prepared from hydroxyester ***ent*-7** (818 mg, 2.51 mmol) as a colourless oil (1.01 g, 2.29 mmol, 91%)

R_f (EtOAc/PE 40-60: 30%) = 0.80; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.93 (1H, q, *J* = 1.0 Hz, H18), 4.15-4.08 (3H, m, Me$\underline{CH_2}$O, H21), 2.27 (1H, dd, *J* = 13.7, 7.9 Hz, H20a), 2.21 (1H, dd, *J* = 13.5, 3.4 Hz, H20b), 1.84 (3H, d, *J* = 1.0 Hz, Me19), 1.26 (3H, t, *J* = 7.1 Hz, Me$\underline{CH_2}$), 1.17 (3H, s, Me22a), 1.09 (3H, s, Me22b) 0.94 (9H, t, *J* = 8.0 Hz, Si($CH_2\underline{CH_3}$)$_3$), 0.57 (6H, q, *J* = 8.0 Hz, Si($\underline{CH_2}CH_3$)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 176.7, 144.5, 78.3, 74.3, 60.4, 48.0, 44.6, 23.8, 22.9, 17.8, 14.1, 7.0, 5.4; **IR** (thin film): ν_{max} 2955, 2913, 2877, 1723, 1466, 1384, 1261, 1132, 1095; $[\alpha]_D^{20}$ +3.6 (**7a**, *c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ −3.7 (***ent*-7a**, *c* 0.32, $CHCl_3$); **HRMS** (ESI$^+$) calculated for $C_{17}H_{34}O_3SiI$ $[M+H]^+$ 411.1316, found 411.1311.

Proof of absolute configuration at C21

Attempts at confirming the anticipated configuration[5,6] of hydroxyester **7** from the diastereomeric MTPA esters was inconclusive, yielding inconsistent signs across both sides of the MTPA esters. The absolute configuration at C21 was unambiguously ascertained through the synthesis of the corresponding MTPA esters of ketone **7b**. Experimental procedures for the synthesis of the diastereomeric MTPA esters are outlined below:

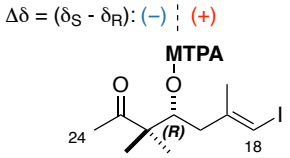
Ketone – 7b



A solution of ester **7a** (42.5 mg, 0.182 mmol) in toluene (0.5 mL) was added *via* cannula to a stirred solution of methylmagnesium bromide (130 μL, 0.886 mmol, 3 M in Et_2O) and triethylamine (255 μL, 1.82 mmol) in toluene (2.5 mL). The mixture was heated to 80 °C and stirred until TLC monitoring indicated complete consumption of the starting material (*ca*. 4 h). The mixture was allowed to cool to r.t. and quenched with NH_4Cl solution (2 mL). The layers were separated, and the aqueous phase extracted with Et_2O (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 4%) afforded the product **7b** as a pale-yellow oil (36.5 mg, 0.168 mmol, 92%).

R_f (EtOAc/PE 40-60: 30%) = 0.78; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.93 (1H, q, *J* = 1.0 Hz, H18), 4.08 (1H, t, *J* = 5.7 Hz, H21), 2.20 (2H, d, *J* = 5.7 Hz, H20), 2.15 (3H, s, H24), 1.84 (3H, d, *J* = 1.0 Hz, Me19), 1.12 (3H, s, Me22a), 1.10 (3H, s, Me22b) 0.94 (9H, t, *J* = 8.0 Hz, $Si(CH_2\underline{CH_3})_3$), 0.57 (6H, q, *J* = 8.0 Hz, $Si(\underline{CH_2}CH_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 213.3, 144.5, 78.4, 74.6, 52.9, 44.4, 27.0, 23.9, 22.2, 19.8, 7.1, 5.4; **IR** (thin film): ν_{max} 2945, 2910, 2876, 1702, 1459, 1353, 1238, 1088, 1004; $[\alpha]_D^{20}$ +16.4 (*c* 0.5, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{16}H_{32}O_2SiI$ $[M+H]^+$ 411.1211, found 411.1206.

Mosher esters – (*R*)-MTPA-7c and (*S*)-MTPA-7c



A solution of TBAF (54 µL, 53.6 µmol, 1 M in THF) was added to a stirred solution of TES ether **7b** (20 mg, 48.7 µmol) in THF (0.5 mL). The pale-yellow solution was stirred for 1 h at r.t. before being quenched with a solution of NH_4Cl (0.5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 1 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude hydroxyketone (11 mg, 38.5 µmol, 79%), which was used directly in subsequent steps without purification.

(R)-Mosher ester **– (*R*)-MTPA-7c**

DCC (54 µL, 54.0 µmol, 1 M in CH_2Cl_2) was added in portion to a stirred solution of crude hydroxyketone (4.0 mg, 13.5 µmol), *(R)*-MTPA (12 mg, 54.0 µmol) and DMAP (one crystal) in CH_2Cl_2 (500 µL). The mixture was stirred for 24 h at r.t., during which the solution became a white suspension. The mixture was filtered through cotton wool and the filtrate reduced to dryness. Purification by flash chromatography (EtOAc/PE 40-60: 10%) afforded the product **(*R*)-7c** as a colourless oil (4.0 mg, 7.80 µmol, 58%).

R_f (EtOAc/PE 40-60: 20%) = 0.48; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48-7.40 (5H, m, Ar<u>H</u>), 5.94 (1H, s, H18), 5.66 (1H, dd, *J* = 9.8, 2.4 Hz, H21), 3.43 (3H, s, OMe), 2.43 (1H, dd, *J* = 14.3, 9.8 Hz, H20a), 2.31 (1H, d br, *J* = 14.3 Hz, H20b), 2.13 (3H, s, H24), 1.93 (3H, s, Me19), 1.17 (3H, s, Me22a), 1.15 (3H, s, Me22b).

(S)-Mosher ester – **(*S*)-MTPA-7c**

DCC (54 μL, 54.0 μmol, 1 M in CH_2Cl_2) was added in portion to a stirred solution of crude hydroxyketone (4.0 mg, 13.5 μmol), *(S)*-MTPA (12 mg, 54.0 μmol) and DMAP (one crystal) in CH_2Cl_2 (500 μL). The mixture was stirred for 24 h at r.t., during which the solution became a white suspension. The mixture was filtered through cotton wool and the filtrate reduced to dryness. Purification by flash chromatography (EtOAc/PE 40-60: 10%) afforded the product (*S*)-**7c** as a colourless oil (4.6 mg, 8.97 μmol, 66%).

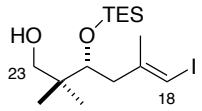
R_f (EtOAc/PE 40-60: 20%) = 0.48; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49-7.41 (5H, m, ArH), 5.95 (1H, s, H18), 5.69 (1H, dd, *J* = 10.1, 2.3 Hz, H21), 3.49 (3H, s, OMe), 2.45 (1H, dd, *J* = 14.4, 10.1 Hz, H20a), 2.30 (1H, br d, *J* = 14.4 Hz, H20b), 2.11 (3H, s, H24), 1.94 (3H, s, Me19), 1.13 (3H, s, Me22a), 1.12 (3H, s, Me22b).

Following the advanced Mosher model described by Hoye *et al.*,[7] the C21 centre arising from the enantioselective Mukaiyama aldol reaction was assigned as 21*R*.

Table S1. Diagnostic ^{1}H NMR signals for the configurational assignment of 21R

Proton	**δH (*S*)-MTPA** (ppm)	**δH (*R*)-MTPA** (ppm)	$\Delta\delta_{S-R}$ (ppm)
H24	2.11	2.13	–0.02
Me22a	1.13	1.17	–0.04
Me22b	1.12	1.15	–0.03
H21	5.69	5.66	+0.03
H20a	2.45	2.43	+0.02
H20b	2.32	2.31	+0.01
Me19	1.94	1.93	+0.01
H18	5.95	5.94	+0.01

Alcohol 7d and *ent*-7d

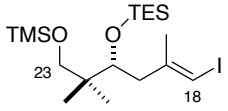


DIBAL (8.31 mL, 8.31 mmol, 1 M solution in hexanes) was added dropwise to a stirred solution of the ester **7a** (1.80 g, 4.16 mmol) in CH_2Cl_2 (42 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min before the addition of an extra aliquot of DIBAL (4.16 mL, 4.16 mmol, 1 M solution in hexanes). The reaction mixture was warmed to –40 °C over 1 h before quenching with the successive addition of MeOH (2 mL) and Na/K tartrate (30 mL). The mixture was allowed to warm to r.t. and stirred for 2 h. The layers were separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 10% → 20%) afforded the product **7d** as a colourless oil (1.31 g, 3.30 mmol, 79%, 90% brsm).

The enantiomeric alcohol ***ent*-7d** was analogously prepared from ester ***ent*-7a** (1.00 g, 2.27 mmol) as a colourless oil (720 mg, 1.82 mmol, 73%).

$\mathbf{R_f}$ (EtOAc/PE 40-60: 30%) = 0.80; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.98 (1H, s, H18), 3.72 (1H, dd, *J* = 8.6, 2.6 Hz, H21), 3.67 (1H, dd, *J* = 10.7, 3.2 Hz, H23a), 3.28 (1H, dd, *J* = 10.7, 7.4 Hz, H23b), 2.66 (1H, dd, *J* = 7.4, 3.4 Hz, OH), 2.48 (1H, dd, *J* = 14.1, 2.6 Hz, H20a), 2.36 (1H, dd, *J* = 14.1, 8.6 Hz, H20b), 1.85 (3H, d, *J* = 0.6 Hz, Me19), 1.04 (3H, s, Me22a), 0.96 (9H, t, *J* = 8.1 Hz, $Si(CH_2\underline{CH_3})_3$), 0.80 (3H, s, Me22b), 0.59, 0.58 (6H, app dq, *J* = 8.0 Hz, $Si(\underline{CH_2}CH_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.8, 78.2, 78.0, 70.0, 43.7, 39.5, 24.0, 23.3, 21.5, 7.1, 5.4; **IR** (thin film): ν_{max} 3477, 2955, 2927, 1459, 1318, 1274, 1090, 1006; $\mathbf{[\alpha]_D^{20}}$ +17.8 (**7d**, *c* 0.15, $CHCl_3$); $\mathbf{[\alpha]_D^{20}}$ –14.7 (***ent*-7d**, *c* 0.30, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{15}H_{31}O_2SiIH$ $[M+H]^+$ 399.1216, found 399.1217.

C18-C23 vinyl iodide 2 and *ent*-2



TMSCl (342 μL, 2.70 mmol) was added to a stirred solution of alcohol **7d** (855 mg, 2.16 mmol), Et_3N (451 μL, 3.24 mmol) and DMAP (26.0 mg, 21.6 μmol) in CH_2Cl_2 (25 mL) at r.t.. The reaction was stirred at r.t. for 1 h before quenching with MeOH (1 mL). The solvent was removed under reduced pressure and the residue resuspended in PE 40-60 before filtering over a pad of silica, eluting with PE 40-60.

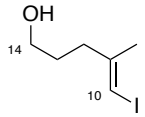
Removal of the solvent under reduced pressure afforded the C18-C23 vinyl iodide **2** as a colourless oil (924 mg, 1.96 mmol, 91%).

The enantiomeric C18-C23 vinyl iodide ***ent*-2** was analogously prepared from alcohol ***ent*-7d** (100 mg, 252 μmol) to afford the product as a colourless oil (89 mg, 189 μmol, 75%).

R_f (EtOAc/PE 40-60: 20%) = 0.66; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.88 (1H, s, H18), 3.77 (1H, dd, *J* = 8.8, 2.4 Hz, H21), 3.34 (1H, d, *J* = 9.6 Hz, H23a), 3.22 (1H, d, *J* = 9.6 Hz, H23b), 2.37 (1H, dd, *J* = 13.6, 2.4 Hz, H20a), 2.24 (1H, dd, *J* = 13.6, 8.8 Hz, H20b), 1.83 (3H, s, Me19), 0.94 (9H, t, *J* = 9.4 Hz, $Si(\underline{CH_2}CH_3)_3$), 0.82 (3H, s, Me22a), 0.79 (3H, s, Me22b), 0.55 (6H, q, *J* = 9.4 Hz, $Si(\underline{CH_2}CH_3)_3$), 0.08 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.8, 74.0, 69.2, 43.4, 40.3, 24.0, 21.1, 20.2, 7.2, 5.5, –0.6; **IR** (thin film): ν_{max} 2877, 2597, 1251, 1092, 1013, 874; $[\alpha]_D^{20}$ +9.6 (**2**, *c* 0.28, $CHCl_3$); $[\alpha]_D^{20}$ –9.0 (***ent*-2**, *c* 0.32, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{18}H_{39}O_2Si_2IH$ $[M+H]^+$ 471.1612, found 471.1615.

2.3. Synthesis of the C10-C17 aldehyde

Vinyl iodide 8a



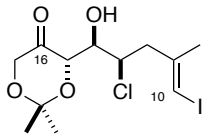
$AlMe_3$ (89 mL, 178 mmol, 2.0 M solution in hexane) was added dropwise to a stirred solution of Cp_2ZrCl_2 (5.20 g, 17.8 mmol) in dichloroethane (200 mL) at –30 °C. The solution was stirred at –30 °C for 5 min before the dropwise addition of H_2O (535 μL, 29.7 mmol) into the reaction mixture. The resultant mixture was allowed to warm to r.t. over 10 min before cooling to –30 °C. A solution of 4-pentyn-1-ol (5.53 ml, 59.4 mmol) in dichloroethane (97 mL) was added dropwise *via* cannula to the reaction mixture at –30 °C. The reaction mixture was allowed to warm to r.t. and stirred at r.t. for 20 h before cooling to– 30°C. A solution of I_2 (30.1 g, 119 mmol) in THF (59 mL) was added dropwise *via* cannula to the reaction mixture. The resulting mixture was stirred at – 30°C for a further 2 h before quenching with Na/K tartrate (200 mL), warming to r.t. and stirred for 16 h at r.t.. The resulting suspension was filtered to remove excess salts and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100mL) and the combined organic phases were washed with brine (300 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column

chromatography (EtOAc/PE 40-60: 30% → 50%) gave the vinyl iodide **8a** as an orange oil (11.7 g, 51.7 mmol, 87%).

R_f (EtOAc/PE 40-60: 50%) = 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.94 (1H, q, *J* = 1.2 Hz, H10), 3.65 (2H, t, *J* = 6.4 Hz, H14), 2.32 (2H, td, *J* = 7.5, 1.1 Hz, H12), 1.87 (3H, d, *J* = 1.2 Hz, Me11), 1.76-1.68 (2H, m, H13).

Data in agreement as presented by Clausen *et al.*[8]

Chlorohydrin 10



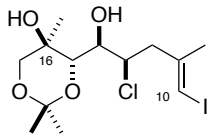
Dess-Martin Periodinane (28.8 g, 68.1 mmol) was added to a stirred suspension of alcohol **8a** (12.8 g, 56.7 mmol), $NaHCO_3$ (14.3 g, 170 mmol) in CH_2Cl_2 (189 mL). The reaction mixture was stirred at r.t. for 1 h before quenching with the addition of $NaHCO_3$ (70 mL), $Na_2S_2O_3$ (70 mL) and H_2O (70 mL). The mixture was stirred for 2 h before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (300 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure to afford the crude aldehyde **9** (12.1 g, 53.9 mmol, 95%), which was used directly in subsequent steps without purification.

NCS (4.31 g, 32.3 mmol) was added to a stirred solution of aldehyde **9** (8.04 g, 35.9 mmol), L-proline (3.72 g, 32.3 mmol) in CH_2Cl_2 (120 mL). The reaction was stirred at r.t. until complete chlorination of the aldehyde was observed by NMR (*ca.* 2 h). At this point, 2,2-dimethyl-1,3-dioxan-5-one (5.62 g, 43.1 mmol) was added and the reaction mixture was stirred at r.t. for 24 h. The reaction was quenched by addition of brine (100 mL) and the layers separated. The organic phase was washed with brine (100 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 10% → 25%) afforded chlorohydrin **10** as a yellow oil (6.57 g, 16.9 mmol, 47%, 98% *ee*) as a separable 5.3 : 1 mixture of diastereomers.

R_f (EtOAc/PE 40-60: 20%) = 0.35; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 6.15 (1H, q, *J* = 1.2 Hz, H10), 4.39 (1H, dd, *J* = 8.9, 1.5 Hz, H15), 4.33–4.26 (2H, m, H13, H17a), 4.08 (1H, d, *J* = 17.6 Hz, H17b), 3.88 (1H, ddd, *J* = 8.9, 3.0, 1.7 Hz, H14), 3.39 (1H, dd, *J* = 3.0, 1.4 Hz, OH), 2.80 (2H, dt, *J* = 7.7, 1.3 Hz, H12), 1.88 (3H, d, *J* = 1.1 Hz, Me11), 1.51 (3H, s, $\underline{Me}_AMe_BCO_2$), 1.43 (s, 3H, $Me_A\underline{Me}_BCO_2$); **^{13}C NMR** (150 MHz,

$CDCl_3$) δ_c 212.4, 143.2, 101.8, 79.5, 72.8, 70.6, 66.5, 58.6, 43.8, 24.0, 23.9, 23.5; **IR** : ν_{max} 3513, 2987, 1738, 1376, 1222, 1086, 863; $[\alpha]_D^{20}$ –68.2 (*c* 1.54, $CHCl_3$); **Chiral HPLC** (Chiralpak® IG, *i*PrOH : *n*-hexane: 1%) R_T (major) 3.47 min, R_T (minor) 2.98 min; **HRMS** (ESI^+) calculated for $C_{12}H_{18}ClIO_4Na$ $[M+Na]^+$ 410.9830, found 410.9841.

Alcohol 11



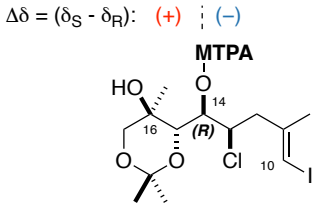
MeMgI (27.6 mL, 82.8 mmol, 3.0 M solution in Et_2O) was added dropwise to a stirred solution of chlorohydrin **9** (9.17 g, 23.6 mmol) in CH_2Cl_2 (79 mL) at –78 °C. The reaction was stirred at –78 °C for 24 h before quenching with HCl (100 mL, 1.0 M solution in H_2O) and warmed to r.t.. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (300 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure to afford the crude alcohol as a 6:1 mixture of diastereomers at C16. Purification by flash column chromatography (EtOAc/PE 40-60: 20% → 30%) afforded alcohol **11** as an off-white solid (4.69 g, 11.6 mmol, 49%) as a single diastereomer.

$\mathbf{R_f}$ (EtOAc/PE 40-60: 30%) = 0.39; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 6.14 (1H, q, *J* = 1.2 Hz, H10), 4.41 (1H, ddd, *J* = 9.0, 6.1, 1.4 Hz, H13), 3.79 (1H, d, *J* = 9.2 Hz, H15), 3.74-3.69 (2H, m, H14, H17a), 3.49 (1H, d, *J* = 11.3 Hz, H17b), 2.76 (1H, ddd, *J* = 14.3, 9.0, 1.0 Hz, H12a), 2.74 (1H, s, OH16), 2.70 (1H, ddd, *J* = 14.3, 6.1, 1.2 Hz, H12b), 2.47 (1H, d, *J* = 8.6 Hz, OH14), 1.89 (3H, d, *J* = 1.1 Hz, Me11), 1.47 (3H, s, $\underline{Me}_AMe_BCO_2$), 1.41 (3H, s, Me16), 1.38 (s, 3H, $Me_A\underline{Me}_BCO_2$).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c 143.2, 99.7, 79.3, 73.6, 72.9, 70.3, 68.2, 60.8, 44.3, 28.9, 23.8, 20.5, 19.2.; **IR** ν_{max} 3397, 3320, 2998, 2876, 1377, 1146, 1080, 1043, 860, 519; $[\alpha]_D^{20}$ –8.7 (*c* 1.3, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{13}H_{22}ClIO_4Na$ $[M+Na]^+$ 427.0149, found 427.0155.

Proof of absolute configuration at C14

The absolute configuration at C14 arising from the L-proline-catalysed aldol reaction was determined by synthesising the diastereomeric Mosher esters **(*R*)**- and **(*S*)-MTPA-11** from alcohol **11**.

Mosher esters – (*R*)-MTPA-11 and (*S*)-MTPA-11



(R)-Mosher ester – **(*R*)-MTPA-11**

A stock solution of DMAP (1.2 mg) in CH_2Cl_2 (1 mL) was separately prepared, of which an aliquot of the DMAP stock solution (250 µL) was used to dissolve alcohol **11** (10.0 mg, 24.7 µmol). DIC (5.7 µL, 37 µmol) and *(R)*-MTPA (8.7 mg, 37 µmol) was added to this solution and the resulting mixture was stirred at r.t. for 24 h, after which product formation was observed by TLC. The solution was diluted with CH_2Cl_2 (1 mL) and quenched with $NaHCO_3$ (1 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL) The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by flash column chromatography (EtOAc/PE 40-60: 10% → 20%) afforded the product **(*R*)-MTPA-11** as a colourless oil (3.4 mg, 5.4 µmol, 23%).

R_f (EtOAc/PE 40-60: 30%) = 0.48; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 7.65 (2H, dd, *J* = 7.1, 2.8 Hz, ArH), 7.47–7.42 (3H, m, ArH), 6.03 (1H, q, *J* = 1.1 Hz, H10), 5.19 (1H, dd, *J* = 9.1, 1.4 Hz, H14), 4.43 (1H, ddd, *J* = 10.4, 4.3, 1.3 Hz, H13), 4.11 (1H, d, *J* = 9.1 Hz, H15), 3.65 (3H, s, OMe), 3.60 (1H, d, *J* = 11.8 Hz, H17a), 3.34 (1H, d, *J* = 11.4 Hz, H17b), 2.60 (1H, m, H12a), 2.40 (1H, ddd, *J* = 14.6, 10.4, 0.8 Hz, H12b), 1.86 (3H, d, J = 1.0 Hz, Me11), 1.46 (3H, s, $\underline{Me}_AMe_BCO_2$), 1.38 (3H, s, $Me_A\underline{Me}_BCO_2$), 1.14 (3H, s, Me16).

(S)-Mosher ester – **(*S*)-MTPA-11**

A stock solution of DMAP (1.2 mg) in CH_2Cl_2 (1 mL) was separately prepared, of which an aliquot of the DMAP stock solution (400 µL) was used to dissolve alcohol **11** (16.0 mg, 39.5 µmol). DIC (122 µL, 0.79 mmol) and *(S)*-MTPA (92.5 mg, 0.40 mmol) was added to this solution and the resulting mixture was stirred at r.t. for 5 h, after which product formation was observed by TLC. The mixture was diluted with CH_2Cl_2 (1 mL) and quenched with $NaHCO_3$ (1 mL) was added. The layers were separated, and the

aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL) The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Purification by flash column chromatography (EtOAc/PE 40-60: 10%) afforded the product **(*S*)-MTPA-11** as a colourless oil (10.5 mg, 17.0 μmol, 43%).

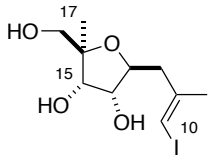
R_f (EtOAc/PE 40-60: 30%) = 0.70; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.69-7.64 (2H, m, ArH), 7.46-7.40 (3H, m, ArH), 5.82 (1H, q, *J* = 1.1 Hz, H10), 5.16 (1H, dd, *J* = 9.2, 1.4 Hz, H14), 4.37 (1H, ddd, *J* = 10.8, 3.9, 1.4 Hz, H13), 4.20 (1H, d, *J* = 9.1 Hz, H15), 3.70 (1H, d, *J* = 11.5 Hz, H17a), 3.47 (3H, s, OMe), 3.45 (1H, d, *J* = 11.5 Hz, H17b), 2.48 (1H, ddd, *J* = 14.7, 4.0, 1.3 Hz, H12a), 2.11 (1H, dd, *J* = 14.5, 10.8 Hz, H12b), 1.80 (3H, d, *J* = 1.1 Hz, Me11), 1.48 (3H, s, $\underline{Me}_AMe_BCO_2$), 1.40 (3H, s, $Me_A\underline{Me}_BCO_2$), 1.29 (3H, s, Me16).

Following the advanced Mosher model described by Hoye *et al.*,[7] the C14 centre arising from the enantioselective L-proline catalysed aldol reaction was assigned as 14*R*.

Table S2. Diagnostic ^{1}H NMR signals for the configurational assignment of 14R

Proton	δ_H **(*S*)-MTPA-11** (ppm)	δ_H **(*R*)-MTPA-11** (ppm)	$\Delta\delta_{S-R}$ (ppm)
Me11	1.80	1.86	-0.06
H12b	2.11	2.40	-0.29
H12a	2.48	2.60	-0.12
H13	4.37	4.43	-0.06
H14	5.16	5.19	-0.03
H15	4.20	4.11	+0.09
Me16	1.29	1.14	+0.15
H17a	3.70	3.60	+0.10
H17b	3.45	3.34	+0.11

Triol 12



Alcohol **11** (1.50 g, 4.57 mmol) was dissolved in MeOH (50 mL) in a pressurised vessel and heated to 120 °C over 15 minutes in a microwave, reaching a pressure of 250 psi. The reaction was maintained at 120 °C at 250 psi for 110 minutes before cooling to r.t.. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (EtOAc: 100%) to afford triol **12** as an off-white solid (1.21 g, 3.66 mmol, 67%).

R_f (CH_2Cl_2/MeOH: 10%) = 0.42; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 6.05 (1H, q, *J* = 1.2 Hz, H10), 4.09 (1H, d, *J* = 6.3 Hz, H15), 3.96 (1H, ddd, *J* = 7.5, 6.1, 5.3 Hz, H13), 3.83 (1H, t, *J* = 6.2 Hz, H14), 3.49 (1H, d, *J* = 11.6 Hz, H17a), 3.44 (1H, d, *J* = 11.6 Hz, H17b), 2.52 (1H, ddd, *J* = 14.5, 5.3, 1.2 Hz, H12a), 2.44 (1H, ddd, *J* = 14.5, 7.5, 1.2 Hz, H12b), 1.90 (3H, d, *J* = 1.1 Hz, Me11), 1.19 (3H, s, Me16). **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c 144.7, 84.8, 79.6, 77.3, 75.4, 72.2, 67.8, 43.3, 24.8, 17.3; **IR** ν_{max} 3301, 2924, 1105, 1045, 1023, 761, 676, 574, 558; **$[\alpha]_D^{20}$** -22.1 (*c* 1.63, MeOH); **HRMS** (ESI^+) calculated for $C_{10}H_{17}IO_4Na$ $[M+Na]^+$ 351.0063, found 351.0078.

The relative configuration in triol **12** was confirmed by observing a NOE enhancement between H13 and Me16, placing H13 and Me16 in a *syn* configuration. Additionally, no NOE enhancements were observed between H13 and H14, as well as H15 and Me16. This support that H13, OH14, OH15 and Me16 are in a *syn* relationship around the THF ring (Figure S1). This result is also supported by NOE data obtained for alcohol **14** (*vide infra*).

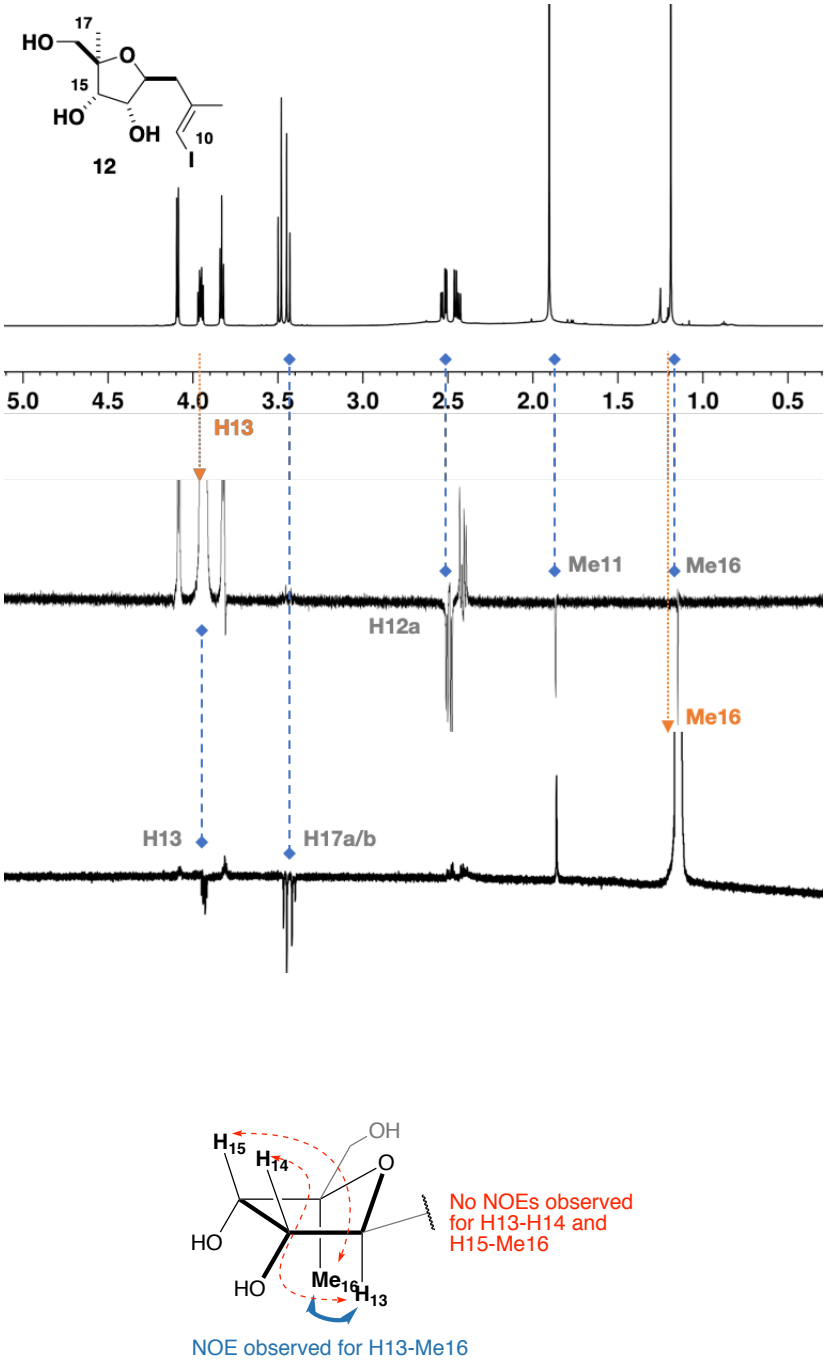
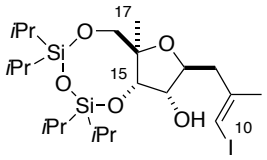


Figure S1. Observed NOE correlations confirming the relative configuration of triol ***12***

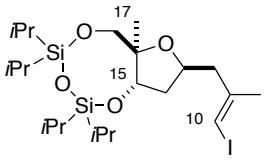
Alcohol 12a



1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (5.07 mL, 15.8 mmol) was added dropwise to a stirred solution of triol **12** (4.33 g, 13.2 mmol) in CH_2Cl_2 (33 mL) and pyridine (11 mL) at 0 °C. The solution was allowed to warm to r.t. and stirred for 48 h at r.t. before quenching with NH_4Cl (50 mL). The layers were separated and the organic phase was washed with NH_4Cl (50 mL). The combined aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 5% → 10%) afforded alcohol **12a** as a yellow oil (6.68 g, 11.7 mmol, 89%).

R_f (EtOAc/PE 40-60: 20%) = 0.72; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 6.02 (1H, q, *J* = 1.2 Hz, H10), 4.13-4.07 (2H, m, H13, H15), 3.80 (1H, dd, *J* = 6.9, 2.9 Hz, H14), 3.66 (2H, d, *J* = 2.3 Hz, H17), 2.86 (1H, s, OH), 2.47-2.39 (2H, m, H12), 1.90 (3H, d, *J* = 1.1 Hz, Me11), 1.24 (3H, s, Me16), 1.12-0.97 (24H, m, *i*PrSi).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c 144.5, 83.1, 81.1, 77.4, 75.0, 74.8, 69.8, 44.0, 25.0, 17.6, 17.7, 17.6, 17.5, 17.4, 17.3, 17.3, 17.2, 17.1, 13.5, 13.0, 13.0, 12.8; **IR** ν_{max} 2944, 2867, 1464, 1113, 1035, 885, 867, 692; **$[\alpha]_D^{20}$** −10.6 (*c* 0.82, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{22}H_{43}IO_5Si_2H$ $[M+H]^+$ 571.1766, found 571.1776.

Siloxane 13



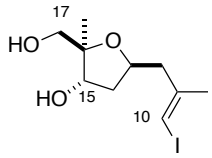
Pyridine (5.28 mL, 65.3 mmol) was added to a solution of alcohol **12a** (7.45 g, 13.1 mmol) in CH_2Cl_2 (43 mL) and the solution was cooled to 0 °C, to which Tf_2O (5.49 mL, 32.7 mmol) was added dropwise to the stirred solution at 0 °C. Upon completion, the stirred solution was allowed to warm to r.t. over 1 h before quenching with $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with brine (150 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude product was filtered over

a plug of silica, eluting with CH_2Cl_2 (90 mL). Owing to the instability of the product, triflate **12b** was used immediately in the subsequent step without further purification.

nBu_4BH_4 (10.1 g, 39.2 mmol) was added to a stirred solution of the crude triflate **12b** (3.21 g, *ca.* 44.5 mmol) in PhMe (43 mL) at r.t.. The mixture was heated to 50 °C and stirred for 1 h before the addition of NH_4Cl (50 mL) and allowing the mixture to cool to r.t.. The layers were separated, and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 2% → 5%) afforded siloxane **13** as a clear oil (5.07 g, 9.14 mmol, 68% over two steps).

R_f (EtOAc/PE 40-60: 10%) = 0.53; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.94 (1H, q, *J* = 1.1 Hz, H10), 4.29 (1H, t, *J* = 8.8 Hz, H15), 4.19 (1H, dddd, *J* = 9.2, 6.9, 5.9, 3.6 Hz, H13), 3.69 (1H, d, *J* = 11.7 Hz, H17a), 3.64 (1H, d, *J* = 11.7 Hz, H17b), 2.43 (1H, ddd, *J* = 14.0, 5.9, 1.2 Hz, H12a), 2.28 (1H, ddd, J = 14.0, 7.0, 1.0 Hz, H12b), 2.13-2.04 (1H, m, H14a), 1.94-1.84 (1H, m, H14b), 1.86 (3H, d, J = 1.1 Hz, Me11), 1.11 (3Hm s, 3H, Me16), 1.13-1.01 (28H, m, *i*PrSi).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ_c 145.0, 83.1, 77.1, 73.0, 72.0, 68.4, 46.8, 37.3, 24.9, 17.7, 17.6, 17.6, 17.6, 17.6, 17.5, 17.4, 17.3, 17.3, 17.2, 16.4, 13.6, 13.2, 12.8, 12.8; **IR** ν_{max} 2943, 2867, 1464, 1105, 1032, 885, 692; $[\alpha]_D^{20}$ −7.2 (*c* 0.93, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{22}H_{43}IO_4Si_2H$ $[M+H]^+$ 555.1817, found 555.1803.

Diol 13a

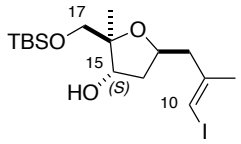


Siloxane **13** (1.16 g, 2.09 mmol) was dissolved in a solution of HCl in MeOH (21 mL, 21.0 mmol, 0.1 M) and stirred at 50 °C for 7 h. The reaction was quenched by the addition of solid $NaHCO_3$ (*ca.* 3 g) and the mixture diluted with CH_2Cl_2 (60 mL). The solids were filtered off, the filtrate collected, and the solvents removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 80%) afforded diol **13a** as clear oil (546 mg, 1.75 mmol, 84%).

R_f (EtOAc)= 0.52; **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H 5.99 (1H, q, *J* = 1.0 Hz, H10), 4.31 (1H, qn, *J* = 6.8 Hz, H13), 4.25 (1Hm, dd, *J* = 6.8, 4.6 Hz, H15), 3.45 (1H, d, *J* = 11.2 Hz, H17a), 3.41 (1H, d, *J* = 11.3 Hz, H17b), 2.46 (1H, dd, *J* = 14.1, 6.8 Hz, H12a), 2.32 (1H, dd, *J* = 14.1, 6.2 Hz, H12b), 2.09-1.96 (3H, m, H14a, OH, OH), 1.89 (1H, dd, *J* = 13.7, 6.5 Hz, H14b), 1.86 (3H, d, *J* = 1.0 Hz, Me11), 1.16 (3H, s, Me16).;

^{13}C NMR (150 MHz, $CDCl_3$) δ_C 144.9, 85.5, 77.2, 74.1, 73.4, 67.8, 46.1, 40.2, 24.6, 17.1.; **IR** ν_{max} 3377, 2933, 1376, 1274, 1044, 769, 669; $[\alpha]_D^{20}$ +6.5 (*c* 1.0, MeOH); **HRMS** (ESI^+) calculated for $C_{10}H_{17}IO_3NH_4$ $[M+NH_4]^+$ 330.0566, found 330.0526.

TBS ether 14



Diol **13**a (707 mg, 2.26 mmol) and imidazole (462 mg, 6.78 mmol) were dissolved in CH_2Cl_2 (23 mL) and cooled to 0 °C. TBSCl (406 mg, 2.71 mmol) was added and the solution was allowed to warm to r.t. over 2 h before quenching with NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine (60 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 10% → 30%) afforded TBS ether **14** as a clear oil (802 mg, 1.88 mmol, 83%).

R_f (EtOAc/PE 40-60: 20%) = 0.53; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.96 (1H, q, *J* = 1.0 Hz, H10), 4.29 (1H, ddd, *J* = 13.0, 7.3, 6.6 Hz, H13), 4.24 (1H, dt, *J* = 6.4, 4.0 Hz, H15), 3.47 (1H, d, *J* = 9.8 Hz, H17a), 3.36 (1H, d, *J* = 9.8 Hz, H17b), 2.48 (1H, dd, *J* = 13.9, 6.4 Hz, H12a), 2.31 (1H, dd, *J* = 13.9, 6.7 Hz, H12b), 1.95* (1H, ddd, *J* = 13.0, 6.5, 4.2 Hz, H14a), 1.92-1.87* (1H, m, H14b), 1.86 (3H, d, *J* = 1.0 Hz, Me11), 1.65 (1H, d, *J* = 4.3 Hz, OH), 1.19 (3H, s, Me16), 0.89 (9H, s, $SiMe_2tBu$), 0.06 (6H, s, $SiMe_2tBu$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.9, 83.4, 79.3, 74.1, 67.9, 46.0, 41.0, 25.7, 24.3, 22.5, 18.0, –5.5, –5.8; **IR** (thin film): ν_{max} 3439, 2928, 2857, 1463, 1258, 1088 779; $[\alpha]_D^{20}$ –1.7 (*c* 0.24, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{16}H_{31}O_3SiIH$ $[M+H]^+$ 427.1165, found 427.1162.

*H14 signals that are particularly characteristic <u>*against*</u> a 15*S* assignment in phormidolide A (H14: 2.33 and 1.57 ppm for H14a and H14b respectively in phormidolide A *vs.* 1.95 and 1.90 ppm for H14a and H14b in **14**). For comparison, H14a and H14b appears at 2.36 and 1.69 ppm in alcohol **15** possessing the 15*R* configuration, which is the configuration reported in phormidolide A (*vide infra*). NOE analysis of alcohol **14**, compared with the reported NOE enhancements observed in phormidolide A also supports our conclusion.

*NOE analysis of TBS ether **14***

1. Correlations were observed in the ^{1}H-^{1}H NOESY spectrum between H15 and H12/H17, showing that H15 lies on the same side as the two alkyl substituents. *This correlation is not seen in alcohol **15** where the C15 configuration is inverted (vide infra).*
2. Correlation was observed between H13 and Me16, positioning the two substituents *syn* to each other
3. No correlations were observed between H15 and Me16, suggesting that H15 and Me16 lie *anti* to each other

These observations suggest that H15 lie *anti* to both H13 and Me16, placing H15 in an *S* configuration (Figure S2). In phormidolide A, NOE enhancements were observed for H15 to H14b and Me16, with H14b correlating to H13. H14a reported no NOE enhancements to any THF signals. These differential results, alongside with chemical shift analysis, confirm that phormidolide does not contain the *S* configuration at C15.

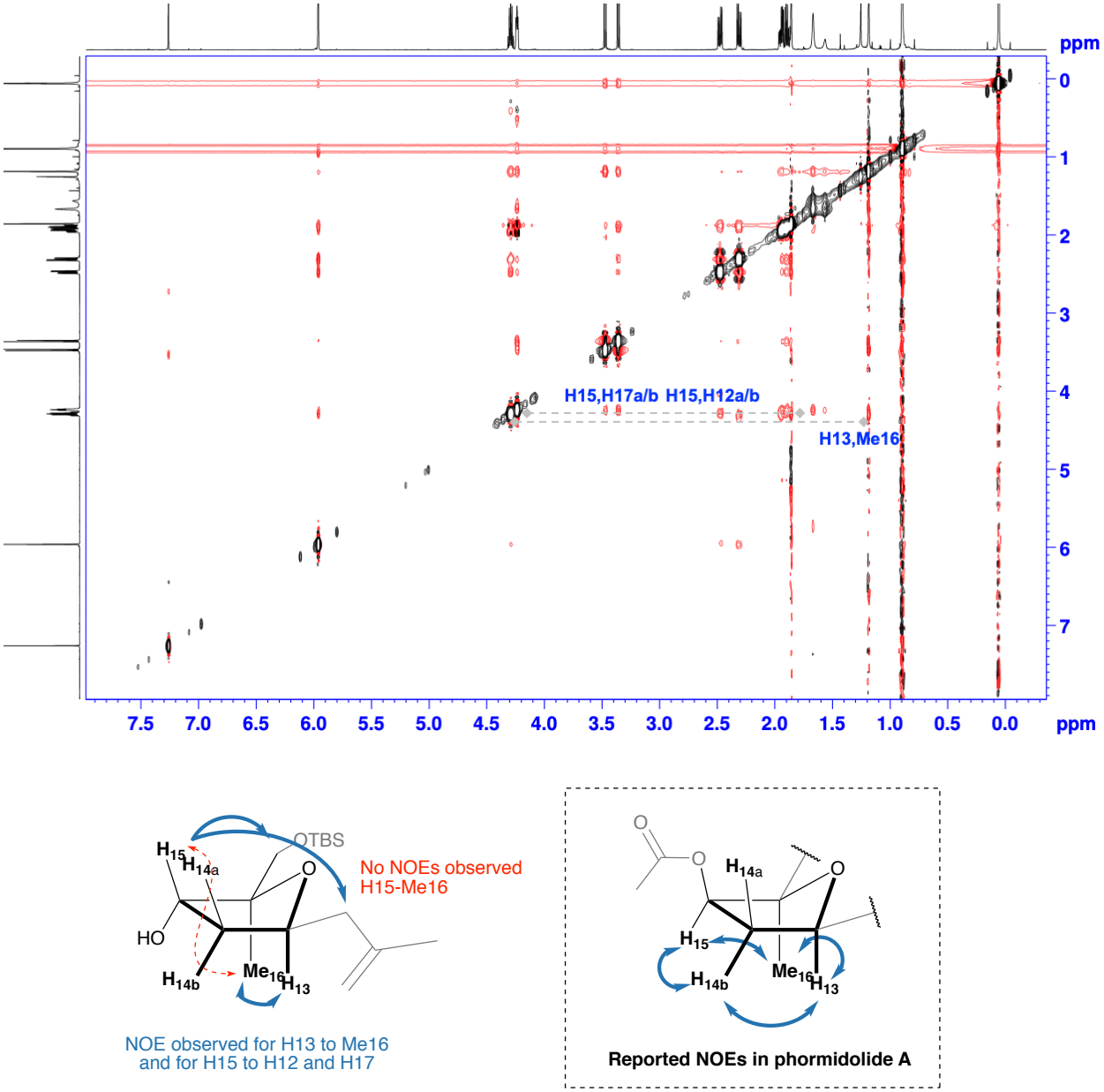
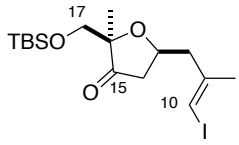


Figure S2. Diagram highlighting the NOE correlations observed for alcohol ***14****. The reported NOE enhancements for phormidolide A is presented alongside for comparison*

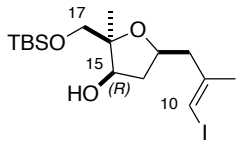
Ketone 14a



Dess-Martin Periodinane (311 mg, 733 μmol) was added to a stirred suspension of alcohol **14** (125 mg, 293 μmol) and $NaHCO_3$ (100 mg, 1.17 mmol) in wet CH_2Cl_2 (4 mL). The reaction mixture was stirred at r.t. until TLC monitoring indicated full consumption of the starting material (*ca.* 30 min). The reaction mixture was quenched by the addition of $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ solution (2 mL) and stirred at r.t. for 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 0% → 5%) afforded the product **14a** as a colourless oil (123 mg, 290 μmol, 99%).

R_f (EtOAc/PE 40-60: 20%) = 0.71; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.03 (1H, q, *J* = 0.9 Hz, H10), 4.33 (1H, app dq, *J* = 10.5, 6.1 Hz, H13), 3.64 (1H, d, *J* = 10.5 Hz, H17a), 3.53 (1H, d, *J* = 10.5 Hz, H17b), 2.71 (1H, dd, *J* = 14.3, 6.1 Hz, H14a), 2.55 (1H, dd, *J* = 14.3, 6.1 Hz, H14b), 2.48 (1H, dd, *J* = 17.4, 5.8 Hz, H12a), 2.19 (1H, dd, *J* = 17.4, 10.5 Hz, H12b), 1.92, (3H, d, *J* = 0.9 Hz, Me11), 1.09 (3H, s, Me16), 0.87 (9H, s, $SiMe_2tBu$), 0.05 (3H, s, $SiMe_2tBu$), 0.02 (3H, s, $SiMe_2tBu$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 216.2, 144.1, 84.8, 77.5, 71.6, 67.3, 45.6, 43.3, 25.9, 24.6, 18.3, 17.7, –5.3, –5.6; **IR** (thin film): ν_{max} 2948, 2867, 1762, 1454, 1253, 1098, 898; **$[\alpha]_D^{20}$** +16.3 (*c* 0.95, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{16}H_{29}O_3SiIH$ $[M+H]^+$ 425.1009, found 425.1006.

Alcohol 15



DIBAL (1.69 mL, 1.69 mmol, 1 M solution in hexanes) was added dropwise to a stirred solution of ketone **14a** (239 mg, 563 μmol) in CH_2Cl_2 (6 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h before quenching with MeOH (500 μL), Na/K tartrate (5 mL) and the stirred mixture allowed to warm to r.t. over 3 h. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure.

Purification by flash column chromatography (EtOAc/PE 40-60: 2%) afforded the product **15** as a colourless oil (238 mg, 559 μmol, 99%) as a single diastereomer.

R_f (EtOAc/PE 40-60: 20%) = 0.53; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.99 (1H, s, H10), 4.14-4.11 (2H, m, H13, H15), 3.76 (1H, d, *J* = 10.3 Hz, H17a), 3.67 (1H, d, *J* = 10.3 Hz, H17b), 3.55 (1H, d, *J* = 6.2 Hz, OH15), 2.59 (1H, dd, *J* = 13.9, 6.8 Hz, H12a), 2.43 (1H, dd, *J* = 13.9, 6.3 Hz, H12b), 2.39-2.32* (1H, m, H14a), 1.88 (3H, s, Me11), 1.70-1.64* (1H, m, H14b), 1.15 (3H, s, Me16), 0.93 (9H, s, $SiMe_2$*t*Bu), 0.13 (3H, s, $SiMe_2$*t*Bu), 0.12 (3H, s, $SiMe_2$*t*Bu); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.9, 83.4, 79.3, 74.1, 67.9, 46.0, 41.0, 25.7, 24.3, 22.5, 18.0, −5.5, −5.8; **IR** (thin film): ν_{max} 3439, 2928, 2857, 1463, 1258, 1088 779; $[\alpha]_D^{20}$ −1.7 (*c* 0.24, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{16}H_{31}O_3SiIH$ $[M+H]^+$ 427.1165, found 427.1162.

*H14 signals that are particularly characteristic *in support* of the reported 15*R* assignment present in phormidolide A (2.33 and 1.57 ppm for H14a and H14b respectively in phormidolide A *vs.* 2.36 and 1.69 ppm for H14a and H14b in **15**). For comparison, H14a and H14b appears at 1.95 and 1.90 ppm in alcohol **14** possessing the 15*S* configuration (*vide supra*). All subsequent intermediates bearing the reported 15*R* configuration contain a signal at *ca.* 2.30- 2.40 ppm, and another at 1.60-1.70 ppm for the diastereotopic protons of H14, which favourably compares with the ones reported for phormidolide A but not with structures bearing the 14*S* configuration.

*NOE analysis for alcohol **15***

1) Correlations were observed between H15 to H14a and Me16, suggesting the three groups are positioned *syn* to each other
2) Correlations were observed between H13 and Me16, suggesting that H13 and Me16 are positioned *syn* to each other. This also means that H15, H14a and H13 are positioned *syn* to each other
3) No correlations were observed for either H13/H15 or Me16 to H14b,

This suggests that the H13 and H15 lies *syn* to H14a and Me16, giving the 15*R* configuration (Figure S3). Notably, the observed correlations are in contrast to the ones observed for alcohol **14** (*vide supra*). The chemical shift values, alongside with NOE enhancements match very favourably to the ones reported in phormidolide A, giving strong evidence that the relative configuration in the THF, especially at C15, is configured correctly as the 15*R* configuration.

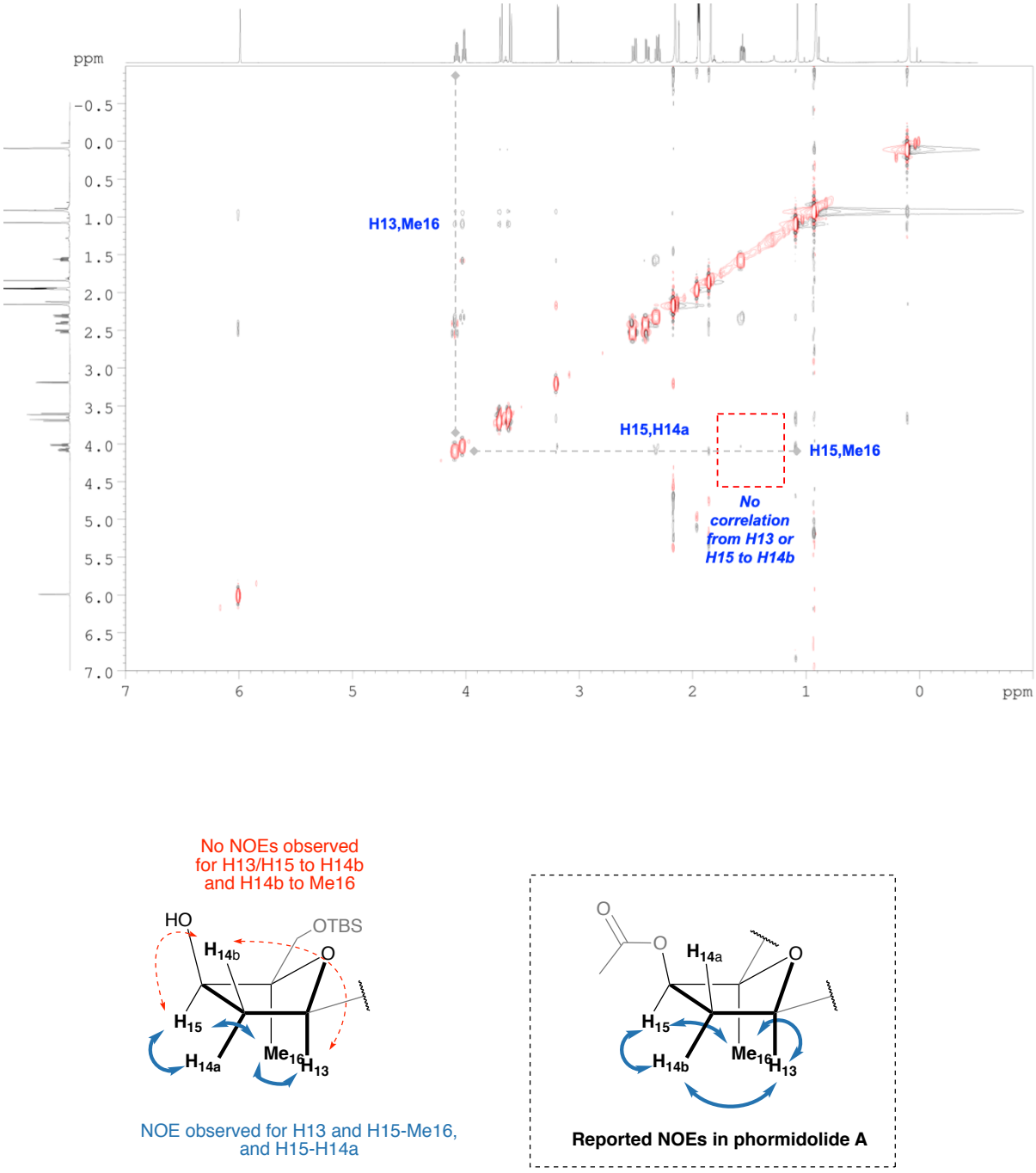
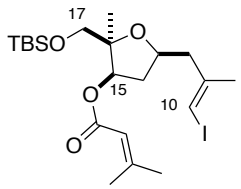


Figure S3. NOE correlations observed for alcohol ***15*** *(spectrum acquired in d_3-MeCN to separate the superimposed H13 and H15) in support of the 15R configuration*

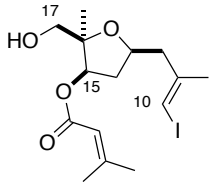
Ester 16



DCC (2.27 mL, 2.27 mmol, 1 M solution in CH_2Cl_2) was added in one portion to a stirred solution of alcohol **15** (160 mg, 378 μmol), dimethylacrylic acid (227 mg, 2.27 mmol), DMAP (277 mg, 2.27 mmol) and DMAP·HCl (359 mg, 2.27 mmol) in CH_2Cl_2 (4 mL) at r.t.. The cloudy white suspension was stirred at r.t. for 24 h before quenching with NH_4Cl (5 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 0% → 5%) afforded the product **16** as a colourless oil (178 mg, 350 μmol, 93%).

R_f (EtOAc/PE 40-60: 20%) = 0.72; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.94 (1H, d, *J* = 1.0 Hz, H10), 5.66 (1H, sept, *J* = 1.2 Hz, =CH), 5.10 (1H, dd, *J* = 6.4, 3.9 Hz, H15), 4.22 (1H, ddt, *J* = 7.5, 6.8, 6.5 Hz, H13), 3.70 (1H, d, *J* = 9.7 Hz, H17a), 3.50 (1H, d, *J* = 9.7 Hz, H17b), 2.56 (1H, dd, *J* = 13.9, 6.8 Hz, H12a), 2.46 (1H, ddd, *J* = 13.8, 7.5, 6.6 Hz, H14a), 2.38 (1H, dd, *J* = 13.9, 6.6 Hz, H12b), 2.17 (3H, d, *J* = 1.7 Hz, =CMe$_a$Me$_b$), 1.91 (3H, d, *J* = 1.2 Hz, =CMe$_a$<u>Me</u>$_b$), 1.85 (3H, d, *J* = 1.0 Hz, Me11), 1.70 (1H, ddd, *J* = 13.9, 6.4, 3.9 Hz, H14b), 1.20 (3H, s, Me16), 0.86 (9H, s, SiMe$_2$*t*Bu), 0.03 (3H, s, SiMe$_2$*t*Bu), 0.01 (3H, s, SiMe$_2$*t*Bu); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 165.7, 157.4, 144.9, 116.0, 84.5, 77.2, 74.5, 66.0, 46.3, 37.6, 27.4, 25.8, 24.5, 21.7, 20.3, 18.2, –5.5, –5.6; **IR** (thin film): ν_{max} 2927, 2853, 1723, 1561, 1444, 1144,1103; **$[\alpha]_D^{20}$** –13.0 (*c* 0.30, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{21}H_{37}O_4SiIH$ $[M+H]^+$ 509.1579, found 509.1572.

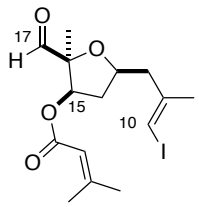
Alcohol 16a



$TsOH{\cdot}H_2O$ (3.5 mg, 20.3 μmol) was added to a stirred solution of TBS ether **16** (103 mg, 203 μmol) in MeOH (1 mL) and CH_2Cl_2 (1 mL) at r.t.. The reaction mixture was stirred for 3 h at r.t., after which it was diluted with CH_2Cl_2 (5 mL) and quenched by the addition of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 20%) afforded the product **16a** as a colourless oil (54.6 mg, 138 μmol, 68%).

R_f (EtOAc/PE 40-60: 20%) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.99 (1H, s, H10), 5.70 (1H, s, =CH), 5.08 (1H, dd, *J* = 6.8, 4.9 Hz, H15), 4.22 (1H, app qn, *J* = 6.8 Hz, H13), 3.57 (1H, dd, *J* = 11.8, 6.3 Hz, H17a), 3.51 (1H, dd, *J* = 11.8, 6.2 Hz, H17b), 2.57 (1H, dd, *J* = 13.9, 6.4 Hz, H12a), 2.52 (1H, ddd, *J* = 13.6, 6.8, 6.8 Hz, H14a), 2.42 (1H, dd, *J* = 13.9, 6.3 Hz, H12b), 2.18 (3H, s, $=CMe_aMe_b$), 1.93 (3H, s, $=CMe_a\underline{Me}_b$), 1.87 (3H, s, Me11), 1.72 (1H, ddd, *J* = 13.5, 7.1, 4.9 Hz, H14b), 1.26 (3H, s, Me16); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.4, 159.1 144.6, 115.3, 84.1, 78.1, 77.2, 74.1, 65.8, 46.0, 37.7, 27.6, 24.5, 21.7, 20.4; **IR** (thin film): ν_{max} 3511, 2919, 1717, 1649, 1377, 1228, 1145, 1008; $[\alpha]_D^{20}$ +2.2 (*c* 0.19, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{15}H_{23}O_4INa$ $[M+Na]^+$ 417.0539, found 417.0535.

C10-C17 Aldehyde 3



Dess-Martin Periodinane (250 mg, 583 μmol) was added to a stirred suspension of alcohol **16a** (46.0 mg, 117 μmol) and $NaHCO_3$ (48 mg, 1.17 mmol) in wet CH_2Cl_2 (2 mL). The reaction mixture was stirred at r.t. for 30 min before quenching by the addition of $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ solution (2 mL) and stirred at r.t. for 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/PE 40-60: 0% → 5%) afforded the product **3** as a colourless oil (30.3 mg, 77.2 μmol, 86% brsm), alongside with 20-30% of the C10 protodeiodinated product that is inseperable at this stage.

R_f (EtOAc/PE 40-60: 20%) = 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.63 (1H, s, H17), 6.03 (1H, q, *J* = 1.1 Hz, H10), 5.59 (1H, s, =CH), 5.19 (1H, dd, *J* = 6.4, 4.1 Hz, H15), 4.41 (1H, dt, *J* = 13.7, 6.6 Hz, H13), 2.70 (1H, dd, *J* = 14.0, 6.7 Hz, H12a), 2.55 (1H, ddd, *J* = 13.7, 7.2, 6.4 Hz, H14a), 2.50 (1H, dd, *J* = 14.0, 6.4 Hz, H12b), 2.15 (3H, d, *J* = 1.3 Hz, =C$\underline{Me}_a$Me$_b$), 1.90 (6H, s, Me11, =CMe$_a$$\underline{Me}_b$), 1.79 (1H, ddd, *J* = 13.7, 6.2, 4.1 Hz, H14b), 1.31 (3H, s, Me16); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 201.0, 165.1, 159.3, 144.4, 114.9, 87.6, 79.7, 77.6, 76.8, 45.9, 37.7, 27.5, 24.4, 20.4, 19.6; **IR** (thin film): ν_{max} 2918, 1738, 1723, 1649, 1443, 1377, 1224, 1138, 1076; $[\alpha]_D^{20}$ –3.4 (*c* 0.29, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{15}H_{21}IO_4Na$ $[M+Na]^+$ 415.0382, found 415.0373.

2.4. Vinylmetal addition and acetonide formation

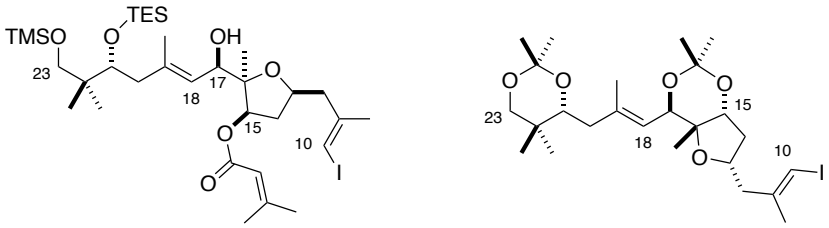
General procedure for the vinylmetal addition of vinyl iodide 2 to aldehyde 3

*t*BuLi (13 eq., molarity in pentane titrated before use) was added dropwise (down the side of the flask) to a stirred solution of vinyl iodide **2** or ***ent*-2** (6.5 eq., dried by azeotroping with PhH and over CaH_2) in Et_2O (0.1 M relative to vinyl iodide) at –78 °C, taking care that the reaction temperature did not exceed –78 °C. The solution was stirred for 30 seconds before the dropwise addition of a freshly prepared solution of $MgBr_2{\cdot}OEt_2$ (19 eq., 0.6 M in Et_2O) into the reaction mixture at –78 °C. The mixture was stirred for 5 min at –78 °C before the dropwise addition of aldehyde **3** (1 eq., dried by azeotroping with PhH × 3) in CH_2Cl_2 (0.1 M relative to aldehyde) *via* cannula (down the side of the flask). The pale-yellow reaction mixture was stirred at –78 °C for 1 h before quenching with NH_4Cl (3 mL) and warmed to r.t.. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (Et_2O/PE 40-60: 0% → 5%) afforded the crude product as a colourless oil as an inseparable mixture of diastereomers, alongside with their C10 protodeiodinated counterparts. The crude product mixture was subjected to the acetonide formation sequence outlined below.

General procedure for the synthesis of diacetonides *anti*-19a, *syn*-19b and 21-*epi*-*anti*-19c

PPTS (one crystal) was added to a stirred solution of *bis*-silyl ethers **17a**, **17b** or **17c** (1 eq.) in CH_2Cl_2 (100 μL) and methanol (100 μL) at r.t.. The reaction mixture was stirred for 16 h at r.t. before quenching with $NaHCO_3$ and diluting with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude triol was dissolved in MeOH (150 μL) and K_2CO_3 (6 mg, *ca*. 10 eq.) was added. The pale-yellow mixture was stirred overnight at r.t. before quenching with NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude tetraol was redissolved in CH_2Cl_2 (100 μL) and 2,2-dimethoxypropane (100 μL) and PPTS (one crystal) was added. The solution was stirred for a further 16 h before quenching with $NaHCO_3$ and diluting with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by preparative thin layer chromatography (EtOAc/PE 40-60: 20%) afforded the diacetonide as a colourless oil.

*Alcohol **17a** and 15,17-anti acetonide anti-**19a***



The addition reaction was performed according to the general procedure described above, using vinyl iodide **2** (42.0 mg, 88.9 μmol), *t*BuLi (120 μL, 185 μmol, 1.5 M in pentane), $MgBr_2{\cdot}OEt_2$ (381 μL, 229 μmol, 0.6 M solution in Et_2O), and aldehyde **3** (4.9 mg, 12.7 μmol) to afford the crude product **17a** (7.2 mg, 9.78 μmol, 77%), a colourless oil as an inseparable 5 : 1 mixture of diastereomers at C17. alongside with the C10 protodeiodinated material.

The crude product was transformed to the corresponding acetonide *anti*-**19a** according to the general procedure described above to afford the pure diacetonide *anti*-**19a** as a colourless oil (1.3 mg, 2.37 mmol, 24% over three steps)

R_f (EtOAc/PE 40-60: 20%) = 0.85; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.97 (1H, q, *J* = 0.9 Hz, H10), 5.19 (1H, dq, *J* = 8.6, 1.0 Hz, H18), 4.40 (1H, d, *J* = 8.6 Hz, H17), 4.21-4.14 (1H, m, H13), 3.94 (1H, dd, *J* = 7.0, 2.1 Hz, H15), 3.64 (1H, dd, *J* = 9.0, 2.7 Hz, H21), 3.61 (1H, d, *J* = 11.4 Hz, H23a), 3.28 (1H, d, *J* = 11.4 Hz, H23b), 2.63 (1H, dd, *J* = 13.9, 7.7 Hz, H12a), 2.48 (1H, dd, *J* = 13.9, 5.5 Hz, H12b), 2.32 (1H, app dt, *J* = 13.9, 7.0 Hz, H14a), 2.11-2.01 (2H, m, H20), 1.85 (3H, d, *J* = 0.9 Hz, Me11), 1.73-1.65 (4H, m, H14b, Me19), 1.39 (3H, s, $\underline{Me}_AMe_BCO(O))^A$, 1.38 (3H, s, $\underline{Me}_AMe_BCO(O))^B$, 1.36 (3H, s, $Me_A\underline{Me}_BCO(O))^B$, 1.34 (3H, s, $Me_A\underline{Me}_BCO(O))^A$, 1.06 (3H, s, Me16), 1.01 (3H, s, Me22a), 0.74 (3H, s, Me22b); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.3, 137.6, 123.0, 100.3^A, 98.6^B, 87.0, 77.7, 76.6, 76.1, 75.5, 72.2, 72.1, 46.4, 39.9, 38.7, 36.7, 32.9, 29.7^B, 25.4^A, 24.2, 23.8^A, 21.8, 18.9^B, 18.5, 18.0, 17.8; **IR** (thin film): ν_{max} 2925, 1460, 1375, 1223, 1100; $[\alpha]_D^{20}$ +19.5 (*c* 0.06, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{25}H_{41}O_5IH$ $[M+H]^+$ 549.2077, found 549.2082.

^{A}Signals attributed to the C15,C17 acetonide ^{B}Signals attributed to the C21,C23 acetonide

The 15,17-*anti* configuration in *anti*-**19a** was confirmed firstly by observing the ^{13}C chemical shifts for the acetonide Me (25.4 and 23.8 ppm) and acetal centre (100.3 ppm), both of which were strongly indicative for the 15,17-*anti* stereochemistry adopted as a result of the twist-boat conformation of the acetonide, placing the two acetonide Me groups in a *pseudo* equivalent chemical environment (Figure S4).[9] This was corroborated by running a series of NOE experiments. Notably:

1) No NOE correlation was observed between Me16 and H17, indicating a *trans* relationship between Me16 and H17
2) H15 show strong NOE enhancements to Me16 and *one* of the acetonide Me, while H17 shows a strong NOE enhancement to the other acetonide Me, indicating that H15 and Me16 sit on one side of the acetonide, while H17 sits on the other. This places H15 and H17 *trans* to each other in this ring, and therefore a 15,17-*anti* relationship exists between them

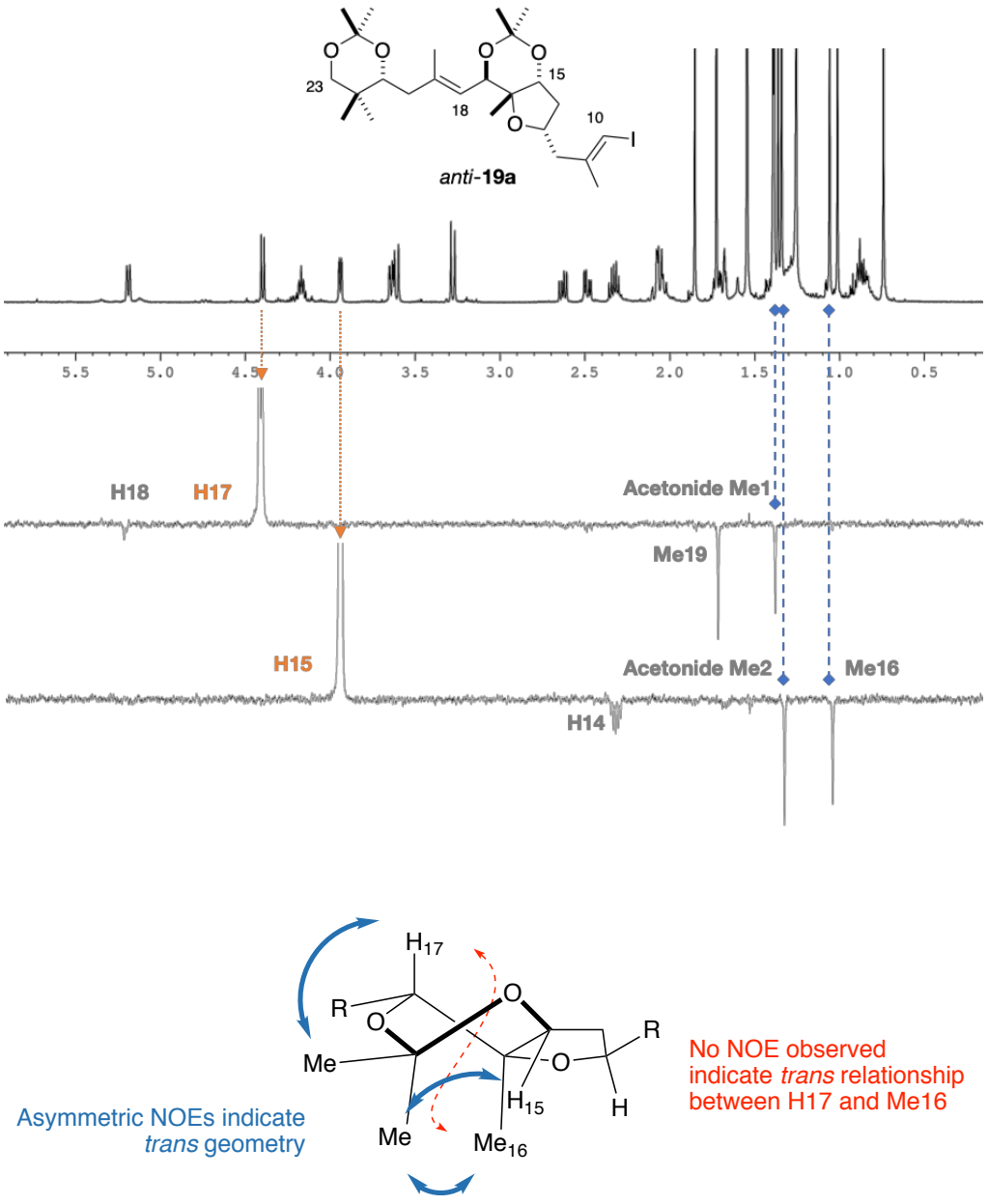
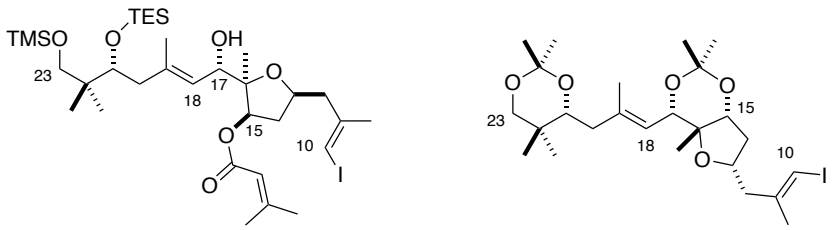


*Figure S4. Observed NOE correlations for anti-**19a**. Irradiated signals are denoted in orange, while observed NOE correlations from the irradiated signals are denoted in grey*

*Alcohol **17b** and 15,17-syn acetonide syn-**19b***



The addition reaction was performed according to the general procedure described above except omitting the addition of $MgBr_2OEt_2$, using vinyl iodide **2** (42.0 mg, 88.9 μmol), *t*BuLi (97 μL, 185 μmol, 1.9 M in pentane), and aldehyde **3** (4.9 mg, 12.7 μmol) to afford the crude product **17b** (3.5 mg, 4.74 μmol, 37%), a colourless oil as an inseperable 4 : 1 mixture of diastereomers at C17, alongside with the C10 protodeiodinated material.

The crude product was transformed to the corresponding acetonide *syn*-**19b** according to the general procedure described above to afford the pure diacetonide as a colourless oil (1.8 mg, 3.28 mmol, 69% over three steps). Owing to competing lithium/iodine exchange at C10 from the formed vinyllithium species in the previous step, the product acetonide contains a 1 : 1 mixture of the C10 protodeiodinated species that was inseparable.

R_f (EtOAc/PE 40-60: 20%) = 0.87; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.98 (1H, s, H10), 5.55 (1H, d, *J* = 8.6 Hz, H18), 4.50 (1H, d, *J* = 8.6 Hz, H17), 4.22-4.19 (1H, m, H13), 4.11 (1H, app d, *J* = 4.5 Hz, H15), 3.81 (1H, dd, *J* = 7.0, 2.2 Hz, H21), 3.66 (1H, d, *J* = 11.6 Hz, H23a), 3.27 (1H, d, *J* = 11.5 Hz, H23b), 2.73 (1H, dd, *J* = 13.5, 7.8 Hz, H12a), 2.44 (1H, dd, *J* = 13.5, 5.8 Hz, H12b), 2.38-2.30 (1H, m, H14a), 2.25 (1H, dd, *J* = 15.5 Hz, 7.0 Hz, H20a), 1.98-1.93 (1H, m, H20b), 1.88 (3H, d, *J* = 1.0 Hz, Me11), 1.76 (3H, s, Me19), 1.74-1.66 (1H, m, H14b), 1.49 (3H, s, $\underline{Me}_AMe_BCO(O))^A$, 1.42 (3H, s, $\underline{Me}_AMe_BCO(O))^A$, 1.42 (3H, s, $\underline{Me}_AMe_BCO(O))^B$, 1.37 (3H, s, $\underline{Me}_AMe_BCO(O))^B$, 1.03 (3H, s, Me22a), 0.93 (3H, s, Me16), 0.74 (3H, s, Me22b); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.6, 140.2, 121.3, 98.5^B, 97.4^A, 78.8, 77.0, 76.9, 75.3, 74.5, 72.3, 69.7, 46.8, 38.5, 36.9, 32.9, 30.0^A, 29.9^B, 24.4, 21.8, 20.6, 19.2^A, 19.0, 18.8^B, 18.1; **IR** (thin film): ν_{max} 2928, 1464, 1377, 1261, 1129, 1098; $[\alpha]_D^{20}$ +17.9 (*c* 0.08, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{25}H_{41}O_5IH$ $[M+H]^+$ 549.2077, found 549.2078.

^{A}Signals attributed to the C15,C17 acetonide ^{B}Signals attributed to the C21,C23 acetonide

The 15,17-*syn* configuration in *syn*-**19b** was confirmed firstly by observing the ^{13}C chemical shifts for the acetonide Me (19.2 and 30.0 ppm) and acetal centre (97.4 ppm), both of which were strongly indicative for the 15,17-*syn* stereochemistry adopted as a result of the chair conformation of the

acetonide, placing the two acetonide Me groups in different chemical environments (Figure S5).[9] This was corroborated by running a series of NOE experiments. Notably, strong NOE enhancements were shown between *one* of the acetonide Me with *all of* H15, Me16 and H17, signifying that all three substituents are sitting on the same side of the ring (the other acetonide Me does not show any NOE enhancements to H15, Me16 or H17). This observation places H15 and H17 *cis* to each other in the ring, and therefore a 15,17-*syn* relationship exists between them

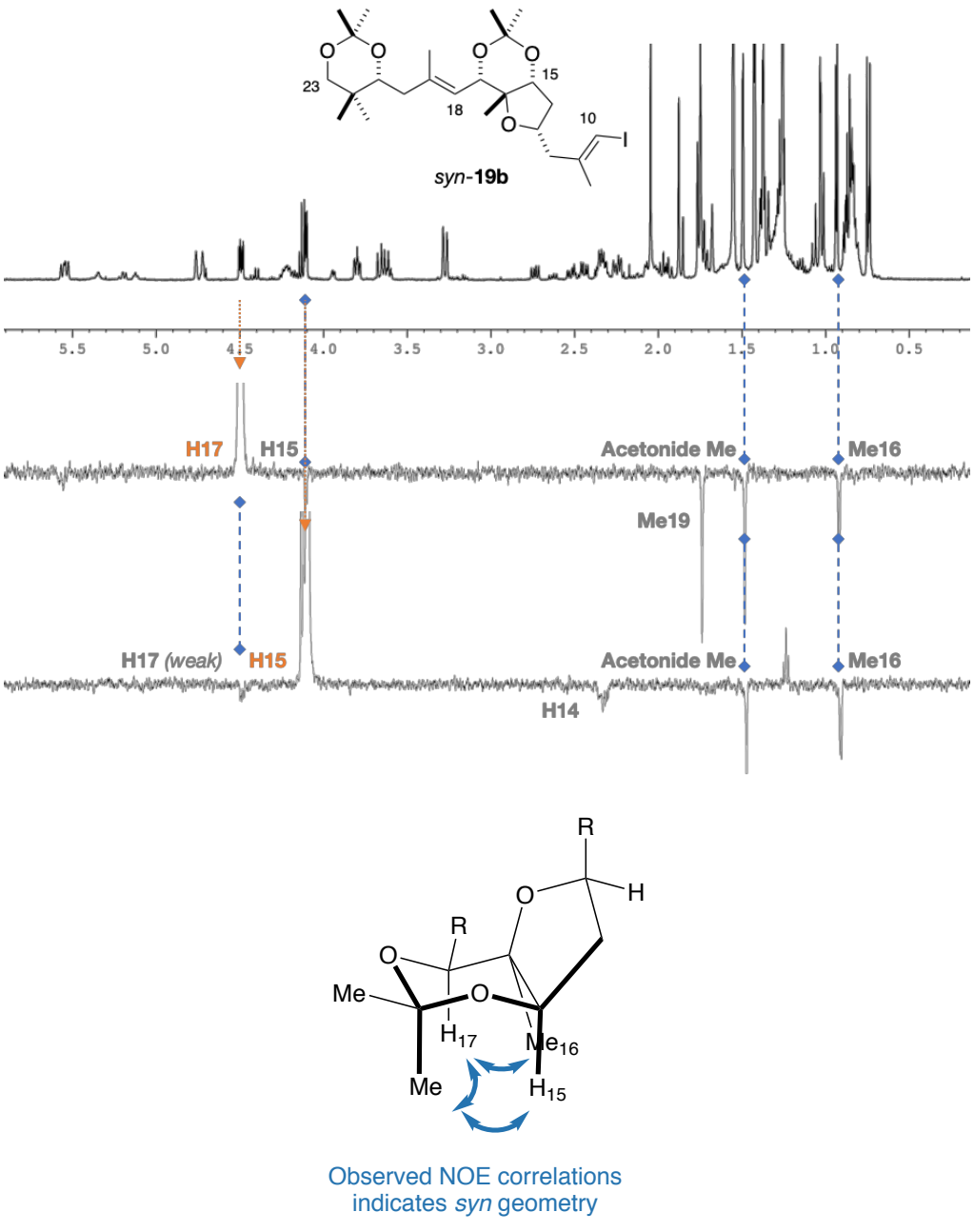
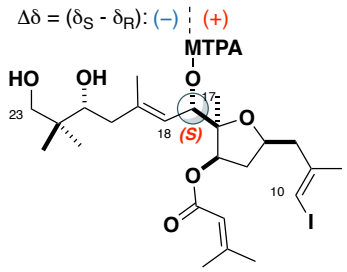


*Figure S5. Observed NOE correlations for syn-**19b**. Irradiated signals are denoted in orange, while observed NOE correlations from the irradiated signals are denoted in grey*

Proof of 17S configuration in 17b



The assigned configuration at C17 was confirmed by forming the diastereomeric MTPA esters of alcohol **17b** described below: DCC (15 µL, 14.9 µmol, 1 M in CH_2Cl_2) was added dropwise to a stirred solution of alcohol **17b** (2.75 mg, 3.73 µmol), (*R*) or (*S*)-MTPA (3.5 mg, 14.9 µmol) and DMAP (one crystal) in CH_2Cl_2 (50 µL). The reaction mixture was stirred at r.t. for 16 h before filtering through a pad of silica[1] The crude product was dissolved in MeOH (25 µL) and CH_2Cl_2 (25 µL) and PPTS (one crystal) was added. The solution was stirred at r.t. for 24 h before quenching with $NaHCO_3$ (one drop), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford the crude (*S*)-MTPA ester diols [(*S*)-MTPA-**17b**, 1.0 mg, 1.30 mmol, 46% over two steps] or crude (*R*)-MTPA ester diols [(*R*)-MTPA-**17b**, 1.0 mg, 1.30 mmol, 46% over two steps] as a colourless oil, which was analysed without further purification.

(*S*)-MTPA-17b

R_f (EtOAc/PE 40-60: 20%) = 0.25; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.81 (1H, d, *J* = 10.0 Hz, H17), 5.79 (1H, s, H10), 5.66 (1H, s, =CH), 5.14 (1H, d, *J* = 10.0 Hz, H18), 5.04 (1H, dd, *J* = 7.0, 5.8 Hz, H15), 4.40 (1H, d, *J* = 10.8 Hz, H23a), 4.18 (1H, m, H13), 4.01 (1H, d, *J* = 10.8 Hz, H23b), 3.48 (1H, m, H21), 2.43 (1H, m, H14a), 2.41 (1H, m, H12a), 2.26 (1H, m, H12b), 2.19 (3H, s, =C$\underline{Me}_a$Me$_b$), 2.11 (1H, m, H20a), 1.94 (1H, m, H20b), 1.93 (3H, s, =CMe$_a$$\underline{Me}_b$), 1.82 (3H, s, Me11), 1.75 (3H, s, Me19), 1.65 (1H, m, H14b), 1.17 (3H, s, Me16), 0.92 (3H, s, Me22a), 0.88 (3H, s, Me22b)

(*R*)-MTPA-17b

R_f (EtOAc/PE 40-60: 20%) = 0.22; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.88 (1H, s, H10), 5.73 (2H, m, =CH, H17), 5.33 (1H, s, H18), 4.95 (1H, dd, *J* = 7.8, 7.0 Hz, H15), 4.29 (1H, d, *J* = 10.4 Hz, H23a), 4.09 (1H, d, *J* = 10.4 Hz, H23b), 4.09 (1H, m, H13), 3.53 (1H, m, H21), 2.51 (1H, m, H12a), 2.32 (1H, m, H12b), 2.21

[1] Analysis of the MTPA esters at this stage gave inconclusive results

(3H, s, =C<u>Me</u>$_a$Me$_b$), 2.17 (1H, m, H20a), 2.13 (1H, m, H14a), 1.98 (3H, s, =CMe$_a$<u>Me</u>$_b$), 1.97 (1H, H20b), 1.81 (3H, s, Me11), 1.76 (3H, s, Me19), 1.14 (3H, s, Me16), 1.10 (1H, m, H14b), 0.92 (3H, s, Me22a), 0.88 (3H, s, Me22b).

Following the advanced Mosher model described by Hoye *et al.*,[7] the C17 stereocentre was assigned as *S* as anticipated from the polar Felkin-Anh controlled addition of the vinyl lithium to aldehyde **3** *via* TS-III in Figure S6.

Table S3. Diagnostic ^{1}H NMR signals for the configurational assignment of 17S

Proton	δ_H (***S***)**-MTPA-17b**	δ_H (***R***)**-MTPA-17b**	$\Delta\delta = \delta_S - \delta_R$
H13	4.18	4.09	+0.09
H14A	2.43	2.13	+0.30
H14B	1.65	1.10	+0.55
H15	5.04	4.95	+0.09
Me16	1.17	1.14	+0.03
H17	5.81	5.73	+0.08
H18	5.14	5.33	-0.19
Me19	1.75	1.76	-0.01
H20A	2.11	2.17	-0.06
H20B	1.94	1.97	-0.03
H21	3.48	3.53	-0.03

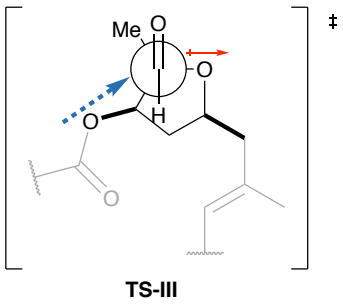
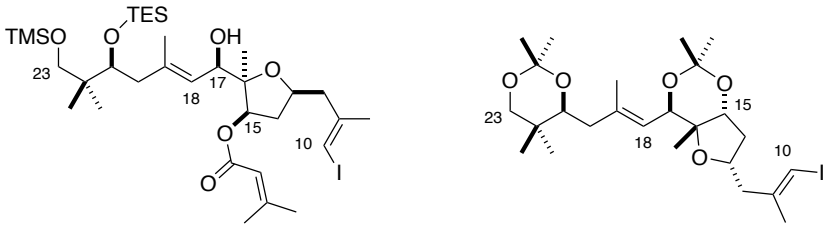


*Figure S6. Stereochemical rationalisation of adduct **17b** via the Polar Felkin-Anh model*

*Alcohol **17c** and 21-epi-anti acetonide 21-epi-anti-**19c***



The addition reaction was performed according to the general procedure described above, using vinyl iodide ***ent*-2** (42.0 mg, 88.9 μmol), *t*BuLi (97 μL, 185 μmol, 1.9 M in pentane), $MgBr_2{\cdot}OEt_2$ (381 μL, 229 μmol, 0.6 M solution in Et_2O), and aldehyde **3** (4.9 mg, 12.7 μmol) to afford the crude product **17c** (5.0 mg, 6.78 μmol, 53%), a colourless oil as an inseparable 5 : 1 mixture of diastereomers at C17, alongside with the C10 protodeiodinated material.

The crude product was transformed to the corresponding acetonide 21-*epi-anti*-**19c** according to the general procedure described above to afford the pure diacetonide 21-*epi-anti*-**19c** as a colourless oil (1.8 mg, 3.28 mmol, 48% over three steps)

R_f (EtOAc/PE 40-60: 20%) = 0.83; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.98 (1H, q, *J* = 0.8 Hz, H10), 5.19 (1H, dq, *J* = 8.6, 1.2 Hz, H18), 4.42 (1H, d, *J* = 8.6 Hz, H17), 4.22-4.16 (1H, m, H13), 3.95 (1H, dd, *J* = 6.9, 1.9 Hz, H15), 3.77 (1H, dd, *J* = 9.2, 2.4 Hz, H21), 3.62 (1H, d, *J* = 11.4 Hz, H23a), 3.27 (1H, d, *J* = 11.4 Hz, H23b), 2.64 (1H, dd, *J* = 13.8, 7.8 Hz, H12a), 2.49 (1H, dd, *J* = 13.9, 6.2 Hz, H12b), 2.33 (1H, app dt, *J* = 14.0, 6.2 Hz, H14a), 2.21-2.18 (1H, m, H20a), 2.03-1.97 (1H, m, H20b), 1.86 (3H, d, *J* = 0.9 Hz, Me11), 1.76 (3H, d, *J* = 1.0 Hz, Me19), 1.75-1.68 (1H, m, H14b), 1.42 (3H, s, $\underline{Me}_AMe_BCO(O))^B$, 1.39 (3H, s, $\underline{Me}_AMe_BCO(O))^A$, 1.38 (3H, s, $Me_A\underline{Me}_BCO(O))^B$, 1.35 (3H, s, $Me_A\underline{Me}_BCO(O))^A$, 1.07 (3H, s, Me16), 1.02 (3H, s, Me22a), 0.73 (3H, s, Me22b); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.3, 138.9, 120.7, 100.4^A, 98.5^B, 86.9, 78.2, 76.9, 76.7, 76.1, 71.9, 71.0, 46.5, 39.4, 36.6, 32.9, 30.9, 29.8^B, 25.3^A, 24.2, 23.6^A, 18.8^B, 18.7, 18.3, 18.1; **IR** (thin film): ν_{max} 2928, 2857, 1465, 1377, 1222, 1090, 1021; $\mathbf{[\alpha]_D^{20}}$ –22.9 (*c* 0.05, $CHCl_3$); **HRMS** (ESI^+) calculated for $C_{25}H_{41}O_5INa$ $[M+Na]^+$ 571.1891, found 571.1885.

^{A}Signals attributed to the C15,C17 acetonide ^{B}Signals attributed to the C21,C23 acetonide

The 15,17-*anti* configuration in *21-epi-anti*-**19c** was confirmed firstly by observing the ^{13}C chemical shifts for the acetonide Me (25.6 and 23.8 ppm) and acetal centre (100.4 ppm), both of which were strongly indicative for the 15,17-*anti* stereochemistry adopted as a result of the twist-boat conformation of the acetonide, placing the two acetonide Me groups in a *pseudo* equivalent chemical environment (Figure S7).[9] This was corroborated by running a series of NOE experiments. Notably:

3) No NOE correlation was observed between Me16 and H17, indicating a *trans* relationship between Me16 and H17

4) H15 show strong NOE enhancements to Me16 and *one* of the acetonide Me, while H17 shows a strong NOE enhancement to the other acetonide Me, indicating that H15 and Me16 sit on one side of the acetonide, while H17 sits on the other. This places H15 and H17 *trans* to each other in this ring, and therefore a 15,17-*anti* relationship exists between them

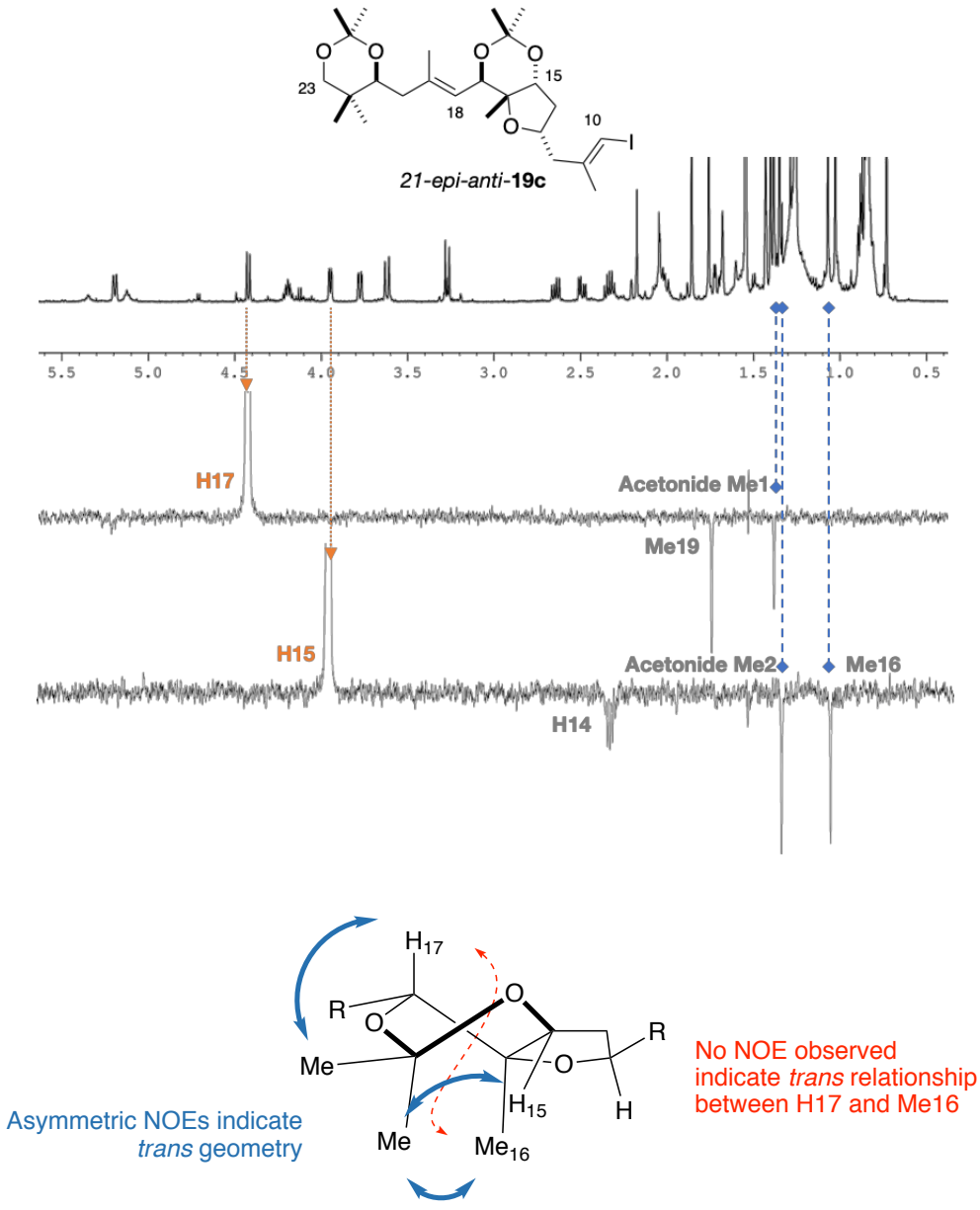


*Figure S7. Observed NOE correlations for 21-epi-anti-**19c**. Irradiated signals are denoted in orange, while observed NOE correlations from the irradiated signals are denoted in grey*

2.5. Discussion on NMR data, comparisons and biogenetic data

2.5.1. Analysis of *J* values and NOE data for the assignment of H17

With contradicting information from our foregoing analysis of the diastereomeric acetonides *vis-à-vis* the data reported for phormidolide A triacetonide, we turned to the reported NOE, $^{3}J_{CH}$ and $^{3}J_{HH}$ to further ascertain the configuration at C17.[1] Reanalysis of the reported NOE enhancements by taking into account all *J* values allowed us to conclude that C17 was misassigned. In particular, the reported conformer, while giving a geometry that takes into account all *J* values, places H18 and Me16 (C37 in isolation paper) too far away to observe a NOE enhancement (Table S4 and Figure S8). The alternative C17 epimer that takes into account all the reported *J* values positions H18 in a proximal geometry to Me16 (C37 in isolation paper), which accounts for the strong NOE correlation observed in the isolation paper. These observations, alongside with the interpretation of the data obtained from comparing *anti*-**19a** and *syn*-**19b** relative to phormidolide triacetonide **18** reinforce the proposed reassignment of C17 from *S* (reported) to *R*.

Table S4: Excerpt of the NOE and ^{3}J data used for the assignment of C17 from the original isolation paper. The key strong NOE enhancement between Me16 (C37 in the original isolation paper) and H18 is highlighted in orange

Atom #	^{13}C (ppm)	^{1}H (ppm)	ROESY	COSY (Hz)	HSQMBC (Hz)
13	76.7	4.48	12b, 14b, Me11, Me16	14a (0.0), 14b (ovlp), 12a (14.0), 12b (5.0)	11 (<0.5), 16 (10.6)
14	34.8	1.57	15	15 (0.0), 13 (0.0)	13 (<0.5), 12 (4.1)
		2.33	13, 15, 2	15 (4.8), 13 (ovlp)	13 (<0.5), 12 (4.5)
15	79.6	5.15	12a, 14a, 17 (st), Me16 (wk), 18 (wk)	14a (0.0), 14b (4.8)	17 (<0.5), Me16 (5.5)
16	86.9	-			
17	69.7	4.70	Me19, 15 (st), Me16 (wk)	18 (9.0)	19 (3.7), 16 (5.6), 15 (5.5), Me16 (5.0)
18	127.0	5.40	**Me16 (st),** 20a, 15 (wk)	17 (9.0)	20 (6.0), 16 (0.8), Me19 (10.0)
19	137.4				
Me16	21.0	1.19	13, 17 (wk), 15, **18 (st)**		

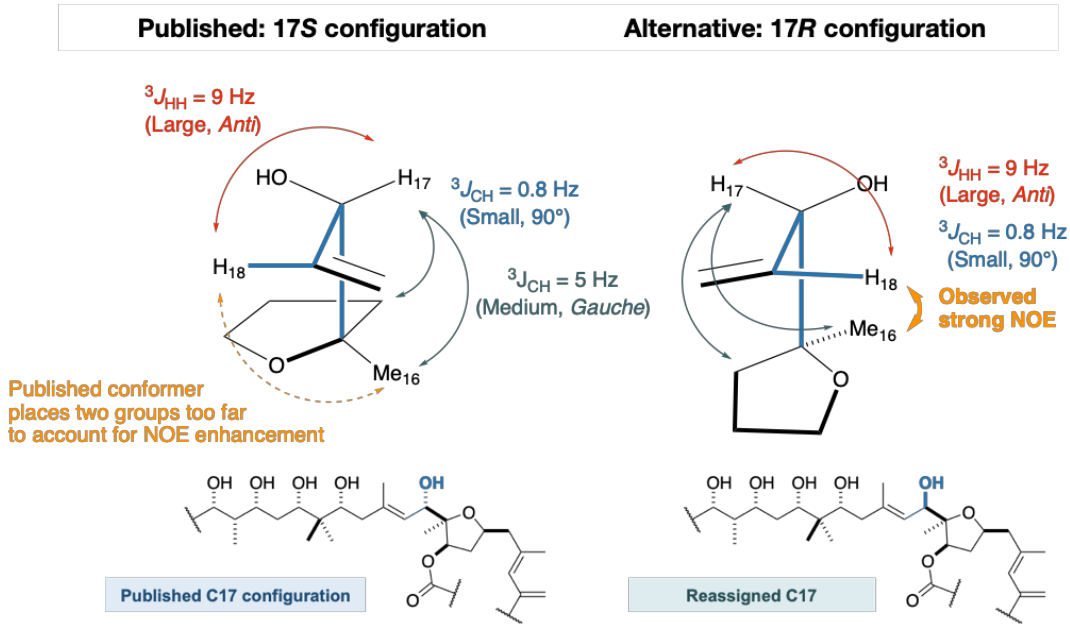


Figure S8: Diagramatic representation of the relevant conformer that enabled the assignment of C17, taking into account all ^3J and NOE data observed for phormidolide A. (Left) The conformer used in the isolation paper to give the originally assigned 17S configuration. (Right) The conformer that gives the 17R configuration taking into account of the strong NOE observed

2.5.2. Rationale for necessitating the reevaluation of C21 relative to C17

In the isolation paper,[1] the stereochemical information at C17 was relayed across the planar sp^2 region (C18-C19) of the natural product. In the absence of a direct long-range correlation (e.g. NOE enhancement or multiple bond *J* values/correlations) between H/C17 and a diastereomeric proton on a sp^3 centre (e.g. H20a or H20b), one cannot definitively conclude that the natural product sits in a particular conformer, as in this instance, rotating the conformer by 180° would have all the *J* values conform but result in the opposite relative configuration of H/C17 relative to H/C21.

There were two instances where this occurred in the assignment of phormidolide A. The first instance relates to the assignment of the THF core relative to H/C7 on the macrolactone. Here, the stereogenic information on H/C7 was relayed across the planar sp^2 C9-C11 diene unit, and onwards onto the H/C13-H/C16 THF moiety. Fortuitously, the alternative conformer (where the entire diene unit is rotated by 180°) would result in a geometry for C1-C7 protruding *away* from the THF that would be unacceptable for ring closure onto H/C15, leaving only one possible conformer for this planar sp^2 region and therefore allowing a conclusive assignment of the THF moiety relative to H/C7 (Table S5 and Figure S9).

Table S5: Excerpt of the NOE and ^{3}J data used for the assignment of C7 and C13 from the original isolation paper. Note that atom number 35 is the exocyclic methylene proton (=CH_2 at C9), and atom 36 is the allylic methyl group appended to C11

Atom #	^{13}C (ppm)	^{1}H (ppm)	ROESY	COSY (Hz)	HSQMBC (Hz)
7	73.1	4.05	6b, 8b, 5, =CH_2 9b	8a (11.5), 8b (2.3), 6a (10.5), 6b (4.0)	9 (<0.5), 9 (<0.5)
8	43.8	2.46	10	7 (11.5)	10 (2.0), =CH_2 9 (3.5), 7 (ovlp), 6 (4.0)
		1.81	7	7 (2.3)	10 (1.4), =CH_2 9 (5.0), 7 (5.9), 6 (4.8)
9	141.5				
10	132.4	5.28	14b, 8a, 4, 2		36 (8.1), 12 (7.1), =CH_2 9 (6.5), 8 (4.7)
11	133.4				
12	48.3	2.33		13 (14.0)	14 (<0.5), 10 (4.8), Me11 (5.5)
		2.58	13, Me11	13 (5.0)	14 (<0.5), 10 (3.0), Me11 (2.8)
13	76.7	4.48	12b, 14b, Me11, Me16	14a (0.0), 14b (ovlp), 12a (14.0), 12b (5.0)	11 (<0.5), 16 (10.6)
=CH_2 9	133.8	4.76	Me3, Me11		10 (5.9), 8 (10.0)
		4.98	7		10 (11.2), 8 (5.9)
Me11	16.8	1.58	13, =CH_2 9a		9, 10, 12

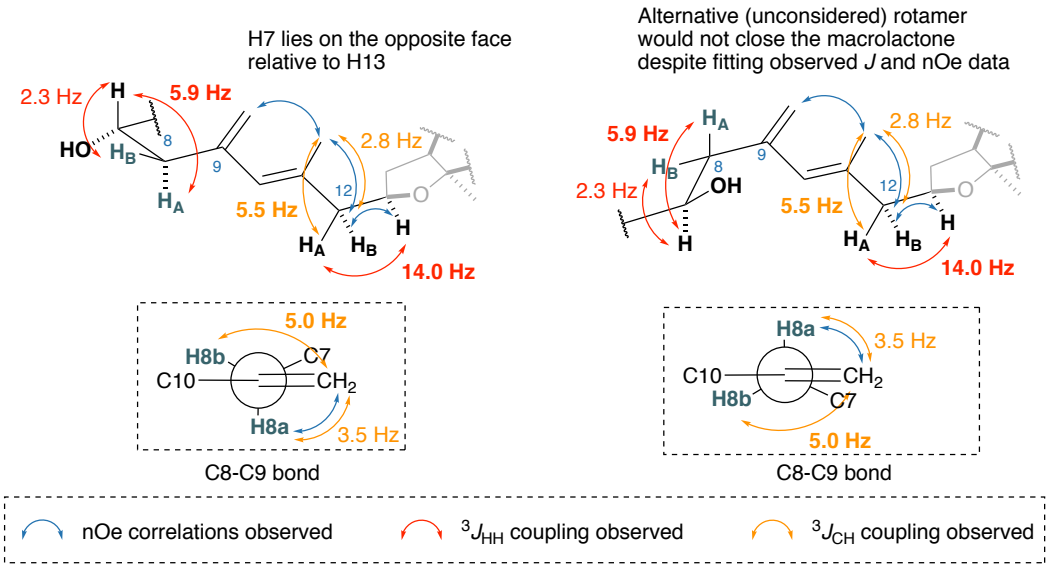


Figure S9: Analysis of the two candidate conformers between H/C7 and H/C13 highlight the alternative (unconsidered) conformer would place the remainder of the chain too far away to enable ring closure, despite fitting all J value and NOE data

The same conclusion cannot be obtained by relaying the stereochemical relationship from H/C17 across the planar sp^2 region (C18-C19) onto H/C21. In this case, the side chain is linear and not constrained geometrically (compared to H/C7 where the macrocycle must close onto H/C15), and so two possible conformers can exist that fits all the observed *J* and NOE values (Table S6, Figure S10). As such, further investigation into the relative configuration between H/C17 and H/C21 was warranted. We optimistically hoped that despite the distal 1,5 nature between the two stereocentres, the conformational

constraints imposed by the acetonides would allow for the facile NMR determination of the correct diastereomer between *anti*-**19a** (possessing the reassigned 17*R* configuration but the reported 21*R* configuration) and 21-*epi*-*anti*-**19c** (possessing the reassigned 17*R* configuration as well as the epimeric 21*S* configuration) (Figure S11)

Table S6: Excerpt of the NOE and ^{3}J data used for the assignment of C17 and C21 from the original isolation paper. Note that atom number 38 is Me19 in our assignment of phormidolide A

Atom #	^{13}C (ppm)	^{1}H (ppm)	ROESY	COSY (Hz)	HSQMBC (Hz)
17	69.7	4.70	Me19 (st), 15 (st), Me16 (wk)	18 (9.0)	19 (3.7), 16 (5.6), 15 (5.5), Me16 (5.0)
18	127.0	5.40	Me16 (st), 20a, 15 (wk)	17 (9.0)	20 (6.0), 16 (0.8), Me19 (10.0)
19	137.4				
20	42.3	2.06	18, Me22a	21 (10.6)	22 (0.4), Me19 (6.3), 18 (6.5), 21 (2.0)
		2.34	21, Me22b, Me19	21 (2.3)	18, 19
21	77.5	3.65	20b, Me19, Me22b, 23	10a (10.6), 20b (2.4)	23 (2.0), Me22a, Me22b, 19 (3.5)
Me19	17.3	1.80	21, 17 (st), 20b		18, 19, 20

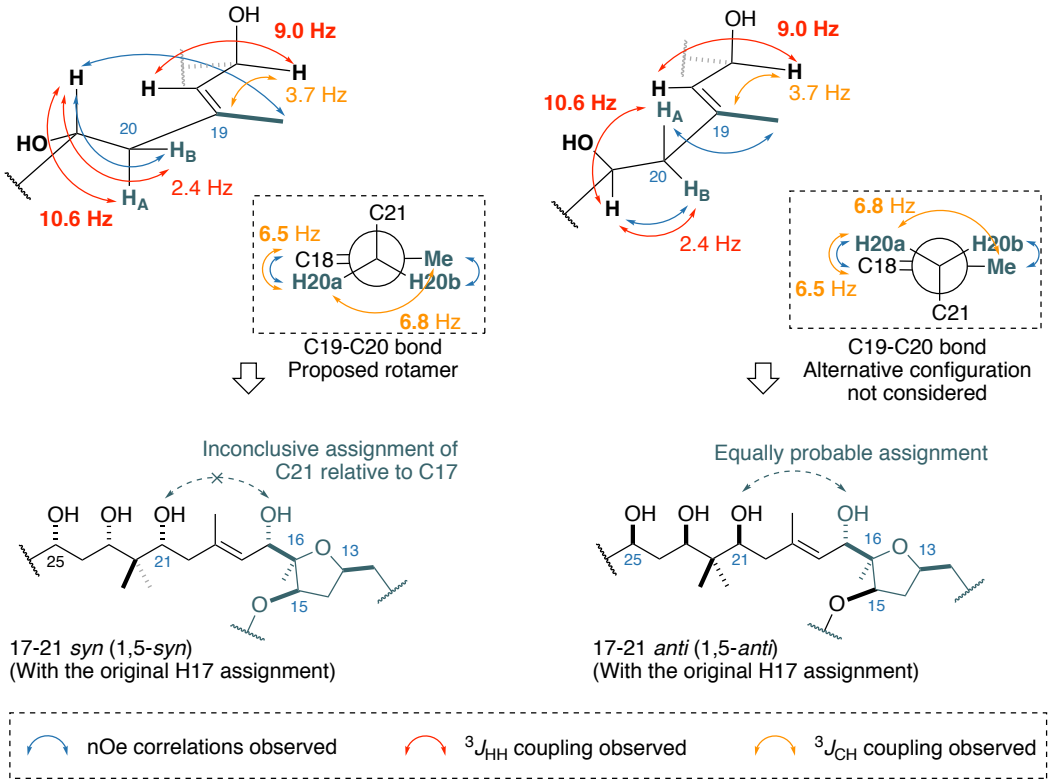


Figure S10: Analysis of the two candidate conformers between H/C17 and H/C21 highlight the equally probable (unconsidered) conformer that conforms to all the J values and NOE correlations observed for phormidolide A

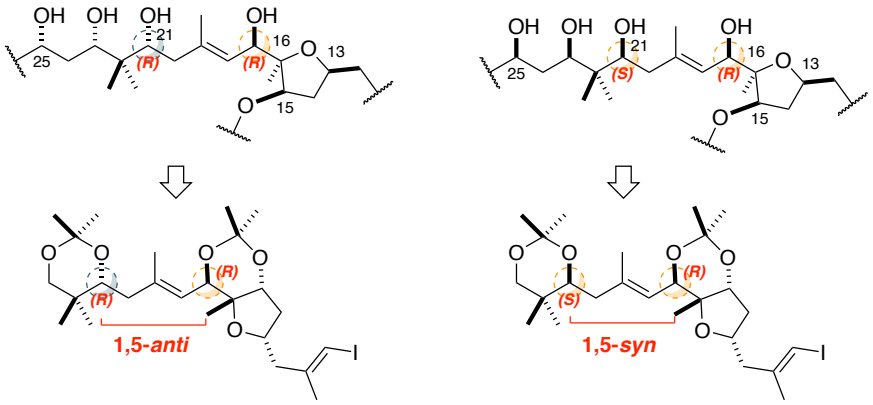


Figure S11: Candidate diastereomers to evaluate the distal 1,5-related stereocentres in the natural product

The remaining *J* based analysis for the side chain from H/C21 to H/C33 was conclusive, especially taking into account the reported preparation of the phormidolide A diacetonide derivative (with the acetonide bridging between OH21 and OH23, and a second acetonide bridging OH25 and OH27). As there exists unambiguous NOE data and *J* values from both the natural product as well as the acetonide derivative to corroborate the all *syn* substitution on the polyol side chain, a reassignment of H/C21 will by extension, result in the analogous reassignment of all remaining stereocentres present on the side chain.

(For a detailed discussion of the assignment of the phormidolide A side chain, please refer to Williamson, R. T.; Boulanger, A.; Vulpanovici, A.; Roberts, M. A.; Gerwick, W. H. *J. Org. Chem.* **2002**, *67* (23), 7927–7936)

2.5.3. NMR comparisons between *anti*-19a, *syn*-19b and 21-*epi*-*anti*-19c with 18

*Table S7: Table of 1H NMR data of phormidolide A triacetonide **18** and diacetonides anti-**19a**, syn-**19b** and 19-epi-anti-**19c***

	Phm A triacetonide ^{1}H (ppm)	*anti*-**19a** ^{1}H	Δ	|Δ|	*syn*-**19b** ^{1}H	Δ	|Δ|	21-*epi*-*anti*-**19c** ^{1}H	Δ	|Δ|
Ac1	1.34	1.34	0.00	0.00	1.49	0.15	0.15	1.35	0.01	0.01
Ac2	1.38	1.39	0.01	0.01	1.38	0.00	0.00	1.39	0.01	0.01
H13*	4.16	4.17	0.01	0.01	4.11	-0.05	0.05	4.19	0.03	0.03
H14A	2.32	2.32	0.00	0.00	2.34	0.02	0.02	2.33	0.01	0.01
H14B	1.75	1.70	-0.05	0.05	1.72	-0.03	0.03	1.71	-0.04	0.04
H15*	3.94	3.94	0.00	0.00	4.21	0.27	0.27	3.95	0.01	0.01
Me16	1.07	1.06	-0.01	0.01	0.93	-0.14	0.14	1.07	0.00	0.00
H17	4.42	4.40	-0.02	0.02	4.50	0.08	0.08	4.42	0.00	0.00
H18	5.18	5.19	0.01	0.01	5.55	0.37	0.37	5.19	0.01	0.01
Me19	1.74	1.72	-0.02	0.02	1.76	0.02	0.02	1.76	0.02	0.02
H20A	2.20	2.09	-0.11	0.11	2.25	0.05	0.05	2.18	-0.02	0.02
H20B	2.03	2.05	0.02	0.02	1.98	-0.05	0.05	2.03	0.00	0.00
H21	3.70	3.64	-0.06	0.06	3.81	0.11	0.11	3.78	0.08	0.08

*Table S8: Table of ^{13}C NMR data of phormidolide A triacetonide **18** and diacetonides anti-**19a**, syn-**19b** and 19-epi-anti-**19c***

	Phm A triacetonide ^{13}C (ppm)	*anti*-**19a** ^{13}C	Δ	|Δ|	*syn*-**19b** ^{13}C	Δ	|Δ|	21-*epi*-*anti*-**19c** ^{13}C	Δ	|Δ|
Ac1	23.7	23.8	0.10	0.10	20.5	-3.2	3.2	23.6	0.1	0.1
Ac2	25.3	25.4	0.10	0.10	30.0	4.7	4.7	25.3	0.0	0.0
C13	76.8	76.6	-0.20	0.20	74.5	-2.3	2.3	76.7	-0.1	0.1
C14	36.7	36.7	0.00	0.00	36.9	0.2	0.2	36.6	-0.1	0.1
C15	78.2	77.7	-0.50	0.50	75.3	-2.9	2.9	78.2	0.0	0.0
C16	87.0	87.0	0.00	0.00	78.8	-8.2	8.2	86.9	-0.1	0.1
Me16	18.4	18.9	0.50	0.50	19.2	0.8	0.8	18.7	0.3	0.3
C17	71.8	73.0	1.20	1.20	70.0	-1.8	1.8	71.9	0.1	0.1
C18	120.3	123.0	2.70	2.70	121.5	1.2	1.2	120.7	0.4	0.4
Me19	18.2	17.8	-0.40	0.40	19.0	0.8	0.8	18.3	0.1	0.1
C20	39.0	40.0	1.00	1.00	38.5	-0.5	0.5	39.4	0.4	0.4
C21	77.6	76.1	-1.50	1.50	76.9	-0.7	0.7	76.1	-1.5	1.5

*In the paper that describes the formation of the phormidolide triacetonide derivative, the ^{1}H values for H13 and H15 were erroneously swapped. A reexamination of their 2D ^{1}H-^{1}H COSY data as well as our NMR data supports this conclusion. Specifically, the signal attributed to δ_H 4.1x ppm couples to δ_H 2.50 and 2.34 ppm (signals that are attributed to H12). This means the signal attributed to 4.1x ppm arises from H13, rather than H15.

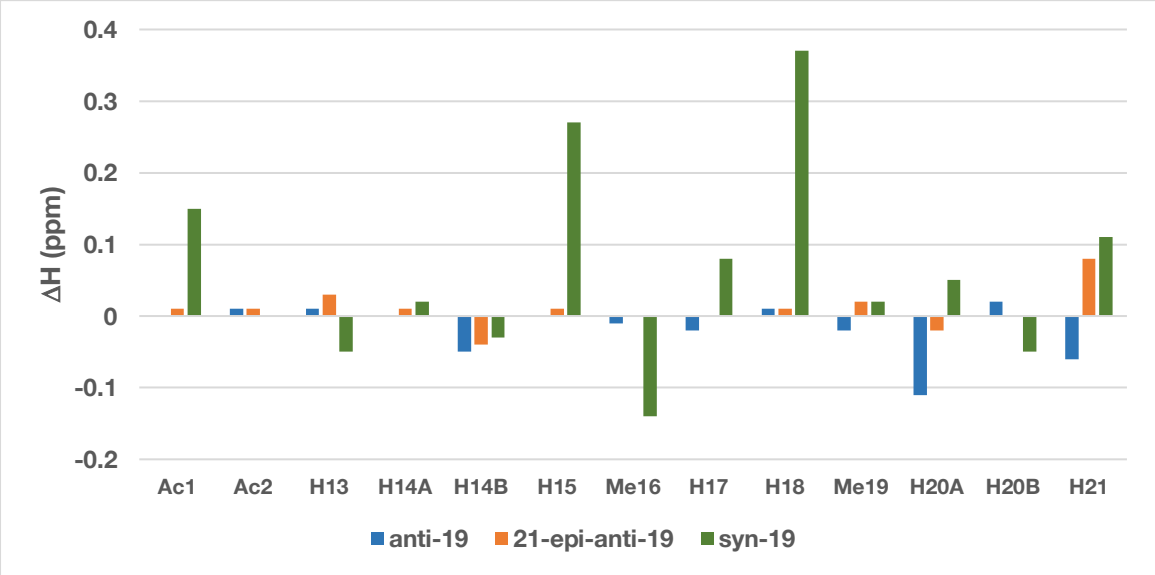


*Figure S12: Bar chart showing ^{1}H NMR shift differences of diacetonides anti-**19a**, syn-**19b** and 19-epi-anti-**19c** between H13-H21 inclusive of acetonide protons.*

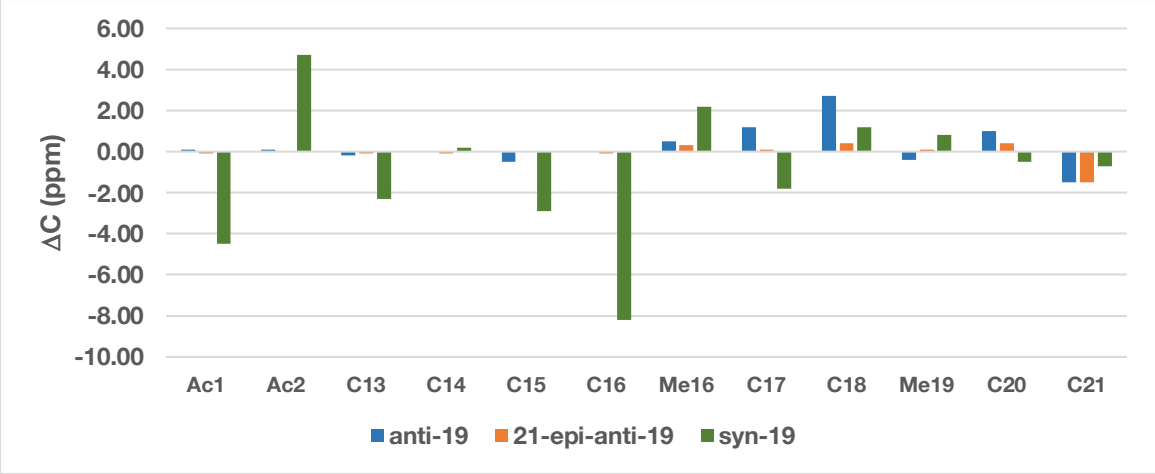


*Figure S13: Bar chart showing ^{13}C NMR shift differences of diacetonides anti-**19a**, syn-**19b** and 19-epi-anti-**19c** between C13-C21 inclusive of acetonide carbons*

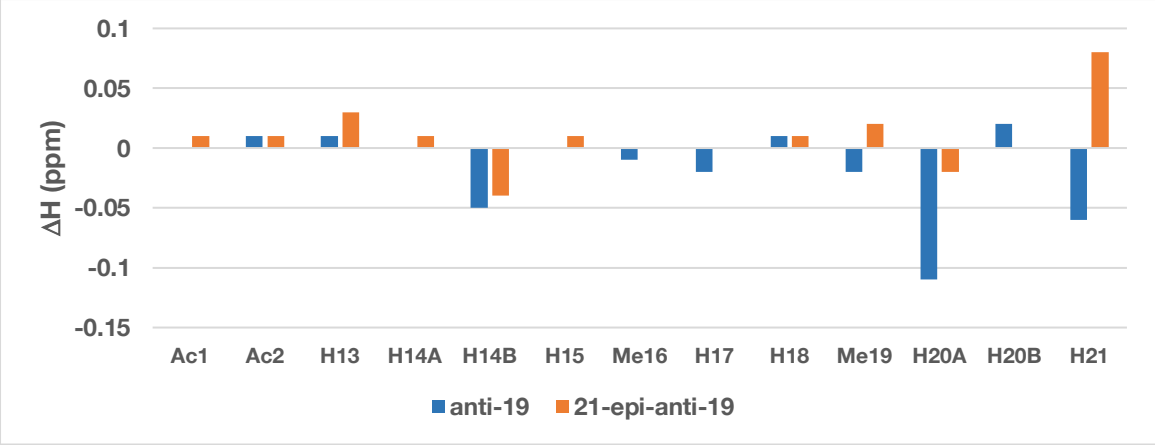


*Figure S14: Bar chart showing ^{1}H NMR shift differences of anti-**19a** and 21-epi-anti-**19c** between H13-H21 inclusive of acetonide protons. The omission of syn-**19** allows a better comparison between which of the two diastereomers is likely to be correct*

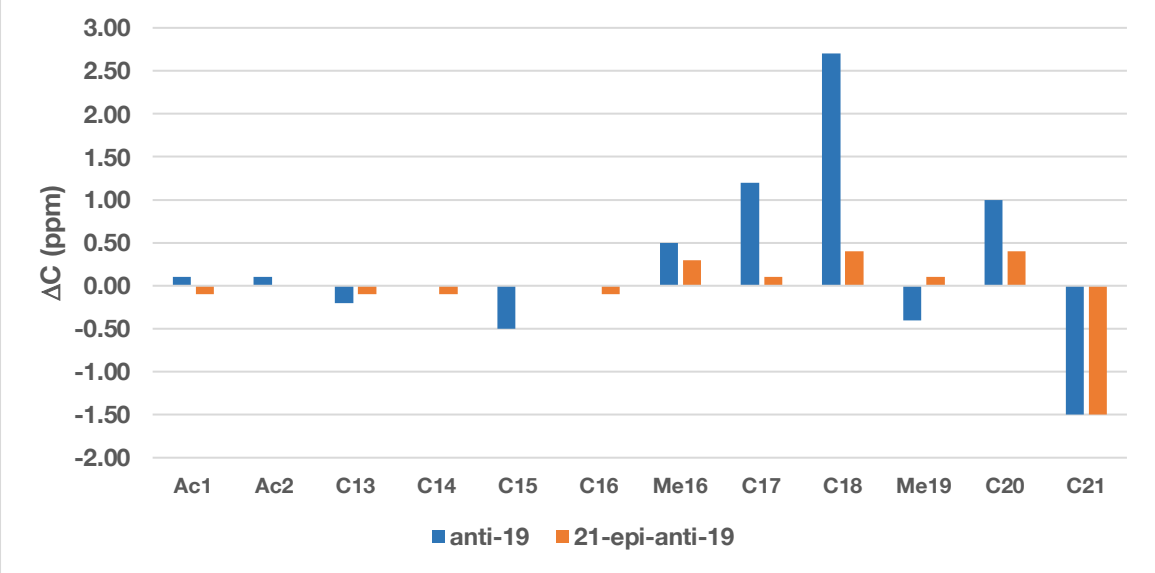


*Figure S15: Bar chart showing ^{13}C NMR shift differences of anti-**19a** and 21-epi-anti-**19c** between C13-C21 inclusive of acetonide protons. The omission of syn-**19b** allows a better comparison between which of the two diastereomers is likely to be correct*

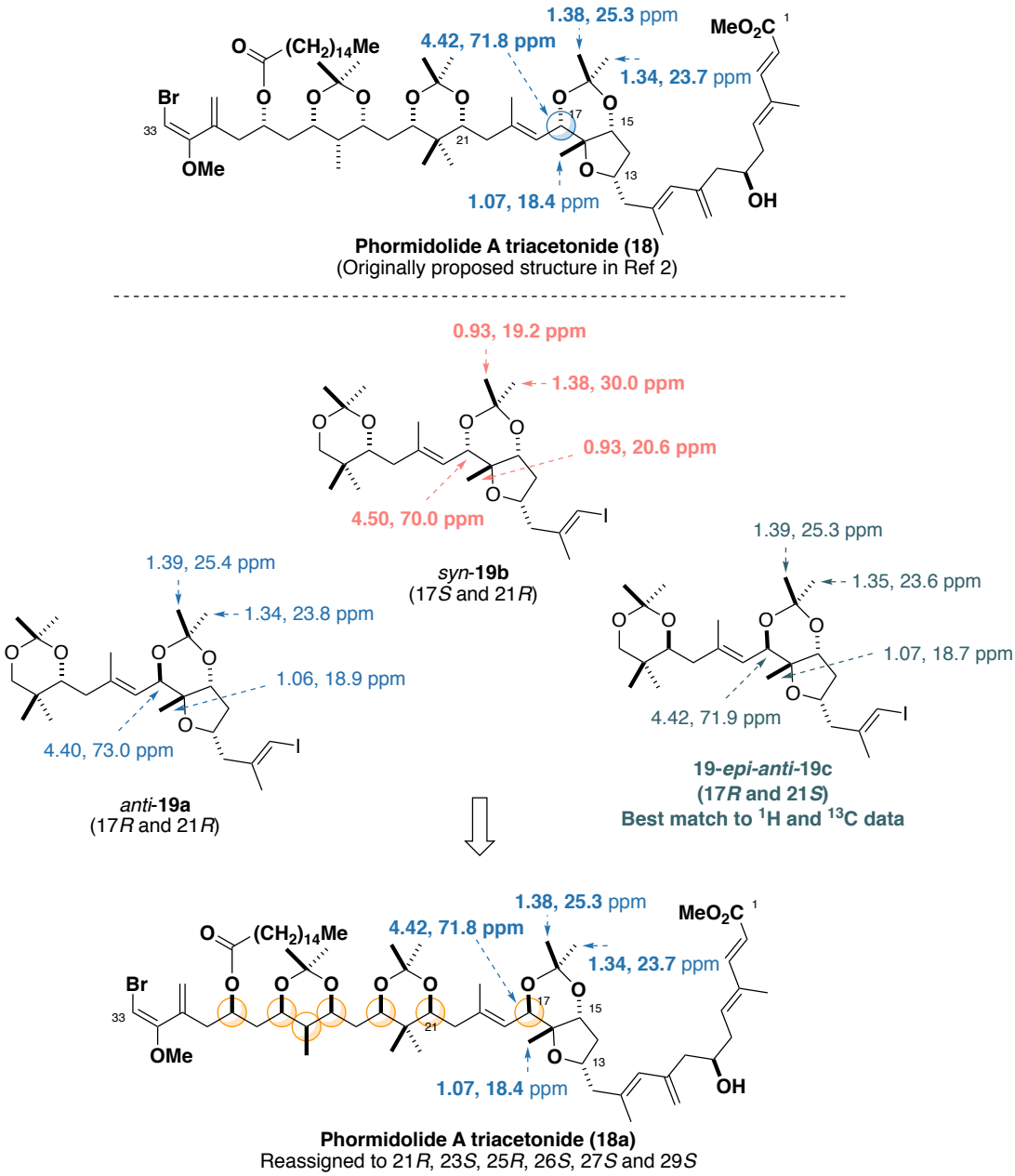


*Figure S16: Summary of diagnostic chemical shifts between phormidolide A triacetonide **18** and diacetonides anti-**19a**, syn-**19b** and 19-epi-anti-**19c***

On comparing NMR shift errors with phormidolide A triacetonide **18**, *syn*-**19b** was immediately eliminated as a possible diastereomer due to the large deviations in the 15,17-acetonide region of the molecule, leaving *anti*-**19a** and 19-*epi*-*anti* **19c** as the remaining candidates (see Figure S12, Figure S13). Of the two remaining diastereomers, ^{13}C NMR correlations were particularly diagnostic for the 17,21-*syn* relationship (leading to the 21*R* configuration), in particular with the large deviations observed in Me16, C17 and C18 (Figure S15). This allowed us to eliminate *anti*-**19a** as a candidate diastereomer, leaving 19-*epi*-*anti*-**19c** as the candidate with the best match for the triacetonide **18**, which is reassigned as **18a** as shown above in Figure S16.

2.5.4. Commentary on ketoreductase domains in the biosynthesis of phormidolide A

In a subsequent account, a comprehensive study[10] on the biosynthesis of phormidolide A was reported. Within the polyketide synthase for phormidolide A, there exists 10 ketoreductase enzymes responsible for catalysing the formation of secondary OH groups from carbonyls, and therefore set the absolute stereochemistry of each carbinol centre OH group present in phormidolide A. Ketoreductases in polyketide synthases are often categorised into one of two types; Type A ketoreductases and type B ketoreductases.[11,12] Type A ketoreductases often contain a W residue near the active site and generally catalyse the formation of L-configured OH groups. Type B ketoreductases often contain a LDD_{1758} motif at the active site and will generally catalyse the formation of D-configured OH groups. In particular, the D_{1758} residue is particularly diagnostic for the generation of D-configured OH groups.

The authors performed a sequence alignment of the 10 ketoreductases present in the phormidolide A polyketide synthase and highlighted that nine of the 10 ketoreductases present contain the D_{1758} motif (but not the LDD triad) (Figure S17A). As all the OHs present in phormidolide A are L configured (rather than the expected D configuration that arises from a type B-like ketoreductase), this prompted in a reevaluation of the absolute configuration of C7 by forming the diastereomeric MTPA esters of the phormidolide A triacetonide derivative, which was reported to corroborate the L configuration at C7 (Figure S17B). As the remaining OHs were all L configured, yet the ketoreductase responsible for the L-OH configuration contained the D_{1758} residue (predictive of a D-OH), they concluded that the presence of the D_{1758} residue was not predictive of D-OH formation and, by extension, reasoned that the remaining D_{1758} containing ketoreductases would also catalyse L-OHs present in phormidolide A.

In light of the ambiguous stereochemical assignment of C21 relative to C17 (see section **2.5.2**), we did not see the analysis of the ketoreductase domains as a conclusive proof for the stereochemistry of phormidolide A, despite several published examples where ketoreductases possessing the D_{1758} residue can go on to catalyse the formation of L-OHs. Our reassignment of the hydroxyl-bearing stereocentres (C17, C21, C23, C25 and C29) leads to reassigning these L-OH configured stereocentres to the corresponding D-OH epimer. Notably, this reassignment is more concordant with the observation that D_{1758} containing/type B-like ketoreductases catalyse the formation of D-OHs (Figure S18), leaving OH7 as the apparent singly anomalous L-OH formed by a D_{1758} containing ketoreductase (rather than *all* the ketoreductases being anomalous).

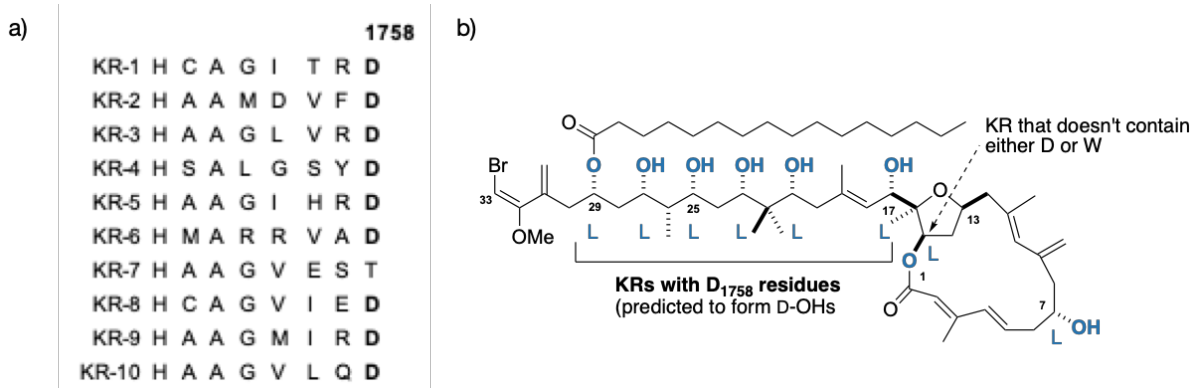


Figure S17: A) Excerpt of sequence alignment data from ref 2, highlighting the conserved D1758 residue that is nominally indicative for D-OH formation B) Structure of phormidolide A highlighting that all OHs in the natural product are L configured. This apparent contradiction was resolved by confirming the absolute stereochemistry at C7 (confirmed L) and extending the logic that the remaining stereocentres could also be L configured.

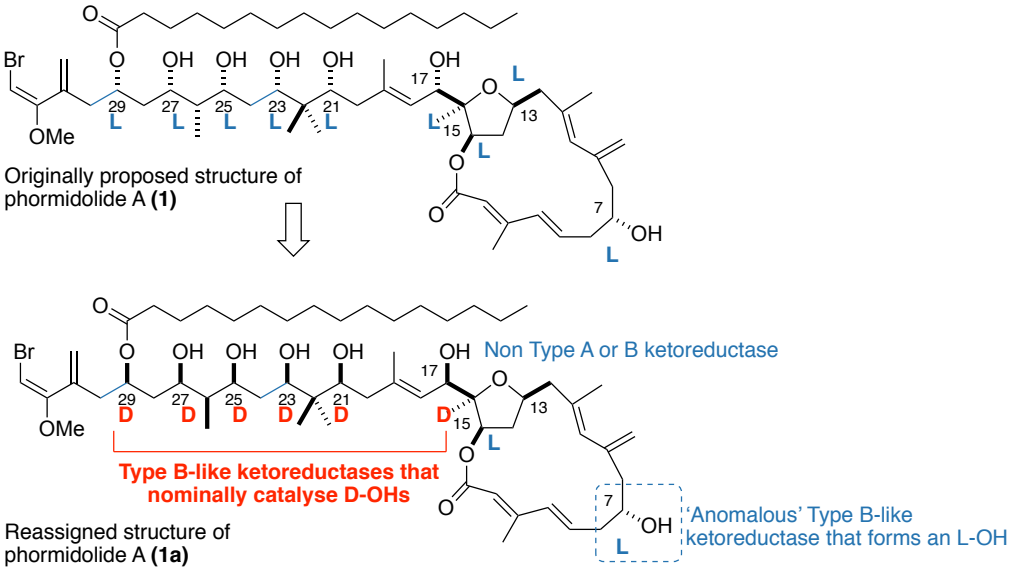


*Figure S18: Reassignment of C17-C29 of phormidolide A from **1** to **1a** allows for greater alignment of the observed stereochemistry of the natural product to the proposed biosynthesis*

In light of our spectroscopic data from the model acetonides, reanalysis of the *J*- and NOE-based configurational analysis as well as the reported genetic data on the biosynthesis of phormidolide A, we believe that this configurational reassignment is fully supported. However, conclusive proof must await the completion of the total synthesis of structure **1a** and comparison with natural phormidolide A.

(For a detailed discussion on the biosynthesis of phormidolide A, please refer to Bertin, M. J.; Vulpanovici, A.; Monroe, E. A.; Korobeynikov, A.; Sherman, D. H.; Gerwick, L.; Gerwick, W. H. *ChemBioChem* **2016**, *17* (2), 164–173)

2.6. References

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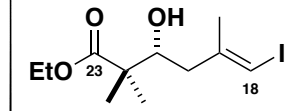
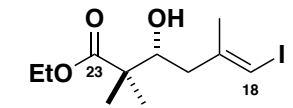
2.7. NMR spectra for all new compounds

See below for ^{1}H and ^{13}C spectra for all new compounds. For *anti*-**19a**, *syn*-**19b** (and Mosher derivatives of **17b**) and 21-*epi*-*anti*-**19c**, ^{1}H-^{1}H COSY spectra are also provided. For *anti*-**19a**, *syn*-**19b** and 21-*epi*-*anti*-**19c**, ^{1}H-^{13}C HSQC (edited) spectra are additionally provided.



7 and *ent-7*

^{1}H NMR ($CDCl_3$, 500 MHz)



7 and *ent-7*

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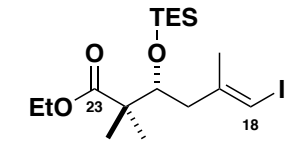
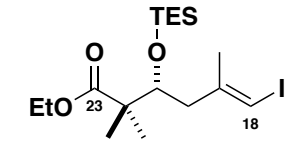


7a and *ent*-7a

^{1}H NMR ($CDCl_3$, 500 MHz)



7a and *ent*-7a

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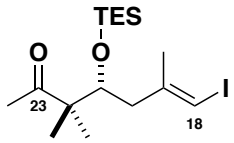
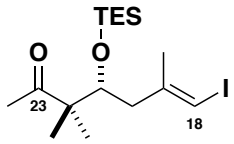


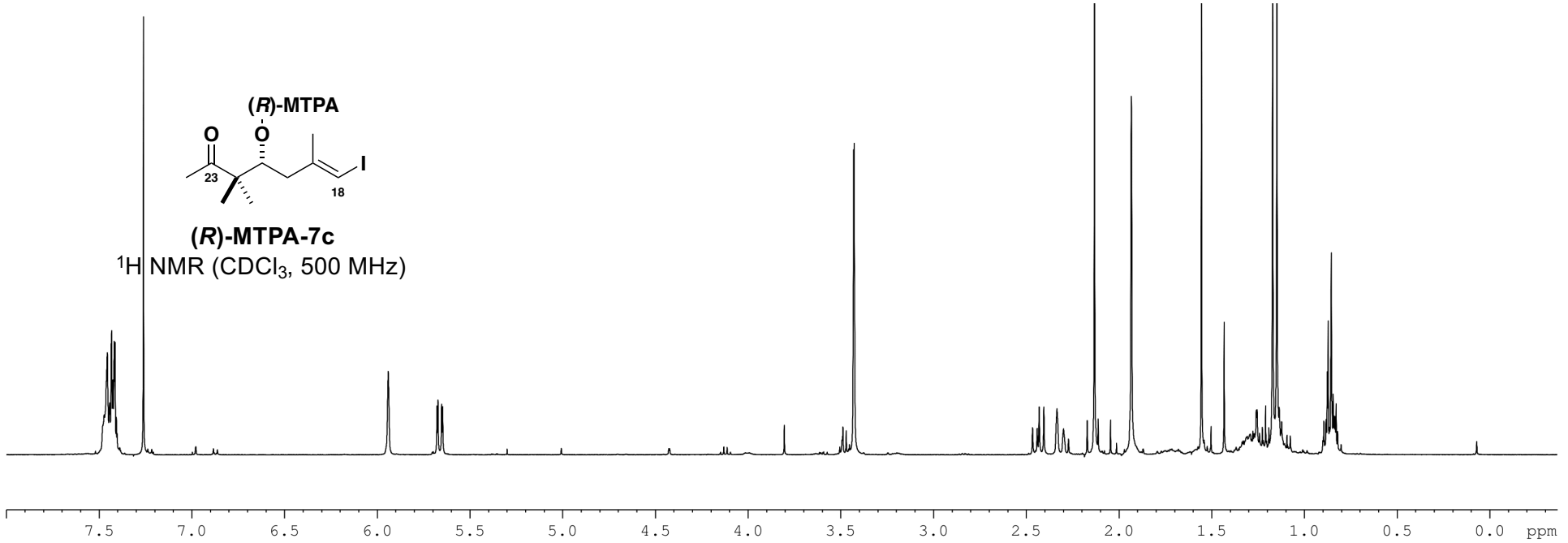
7b

^{1}H NMR ($CDCl_3$, 500 MHz)



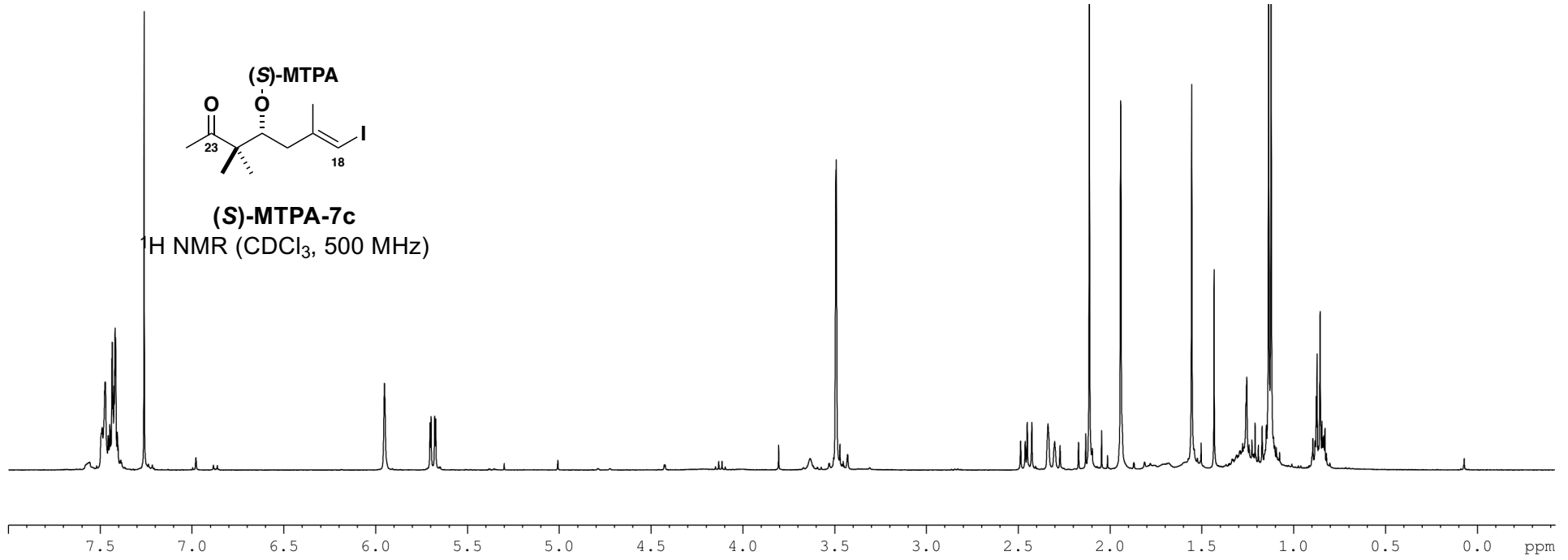
7b

^{13}C NMR ($CDCl_3$, 125 MHz)



(*R*)-MTPA-7c

^{1}H NMR ($CDCl_3$, 500 MHz)



(*S*)-MTPA-7c

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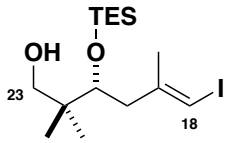

7d and *ent*-7d

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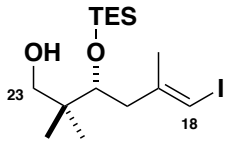

7d and *ent*-7d

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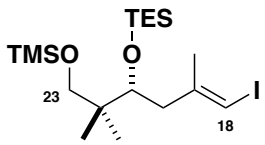
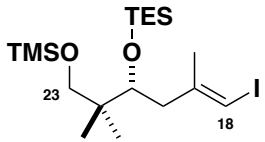


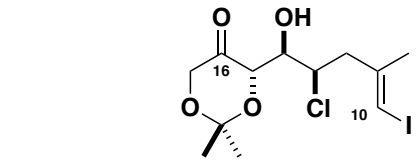
2 and *ent*-2

^{1}H NMR ($CDCl_3$, 500 MHz)



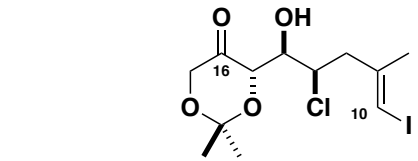
2 and *ent*-2

^{13}C NMR ($CDCl_3$, 125 MHz)



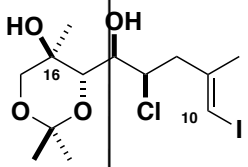
10

^{1}H NMR ($CDCl_3$, 600 MHz)



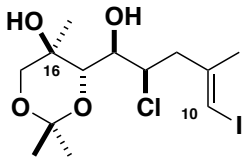
10

^{13}C NMR ($CDCl_3$, 150 MHz)



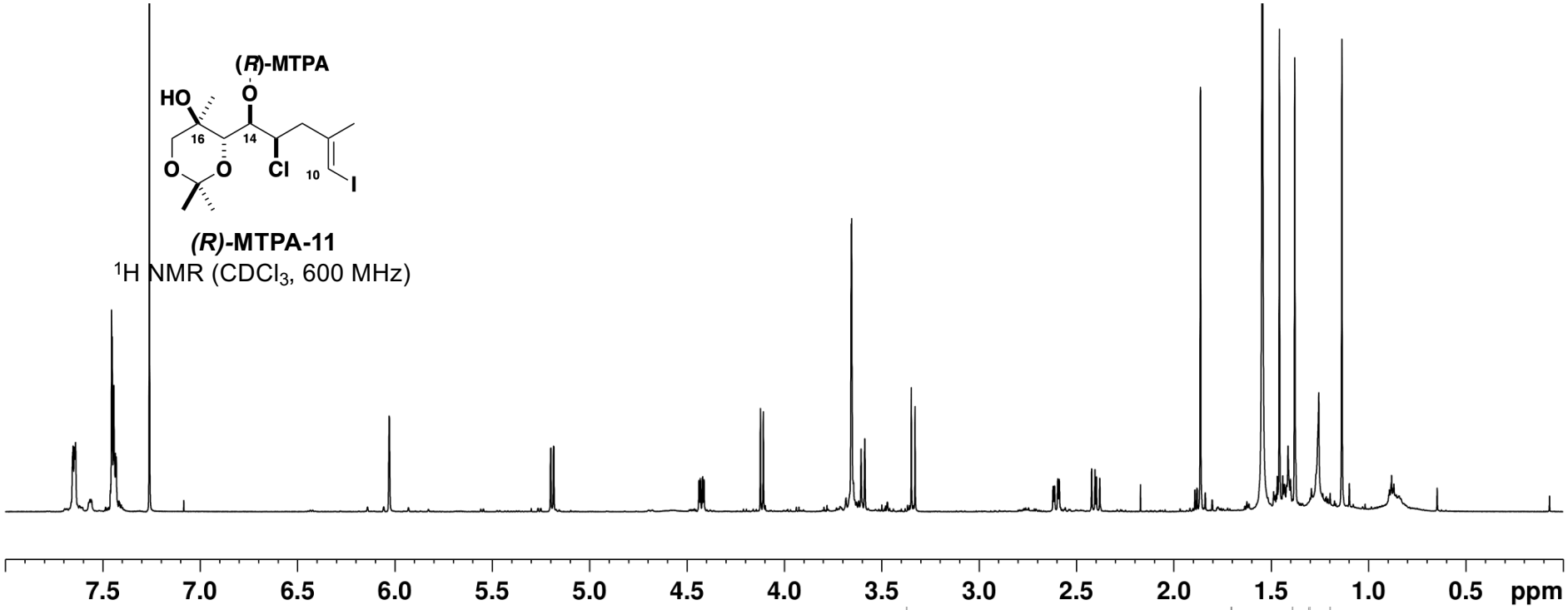
11

^{1}H NMR ($CDCl_3$, 600 MHz)



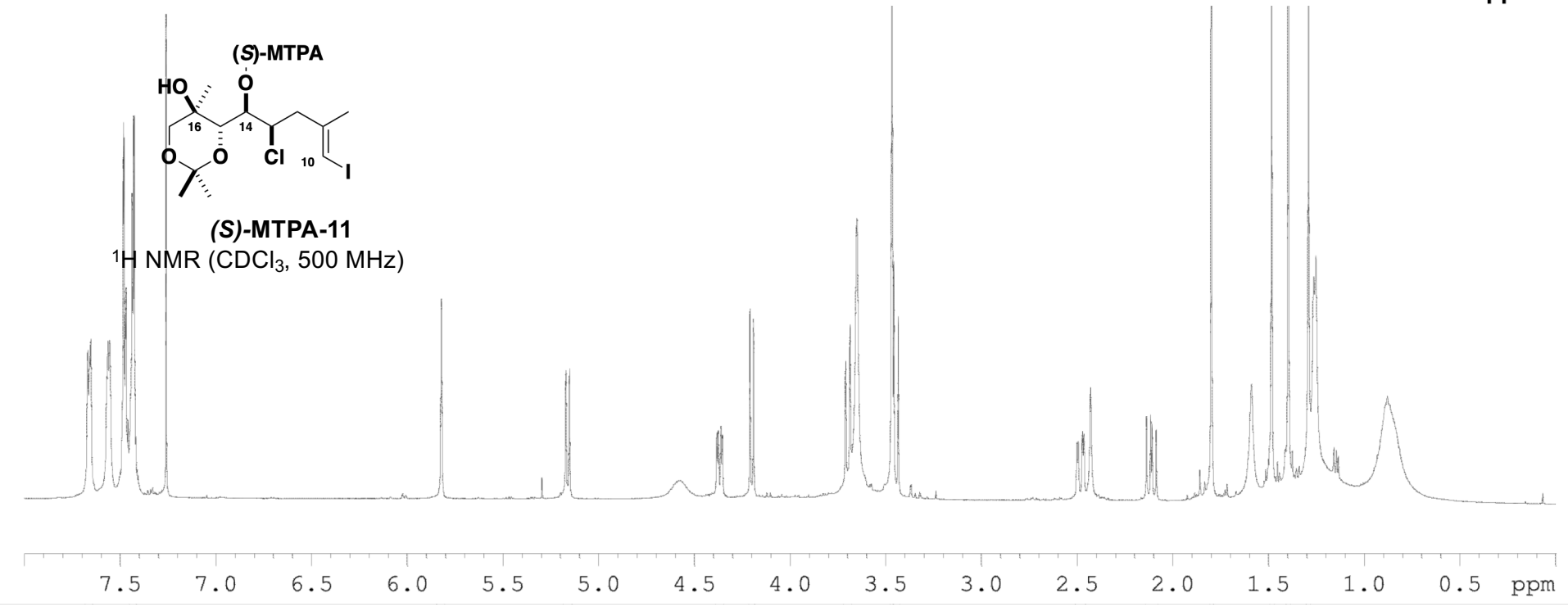
11

^{13}C NMR ($CDCl_3$, 150 MHz)



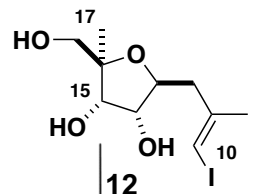
***(R)*-MTPA-11**

^{1}H NMR ($CDCl_3$, 600 MHz)



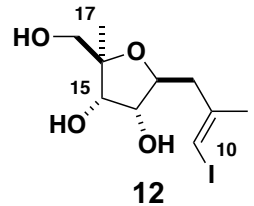
***(S)*-MTPA-11**

^{1}H NMR ($CDCl_3$, 500 MHz)



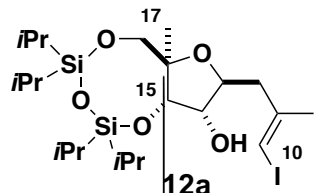
12

^{1}H NMR ($CDCl_3$, 600 MHz)



12

^{13}C NMR ($CDCl_3$, 150 MHz)

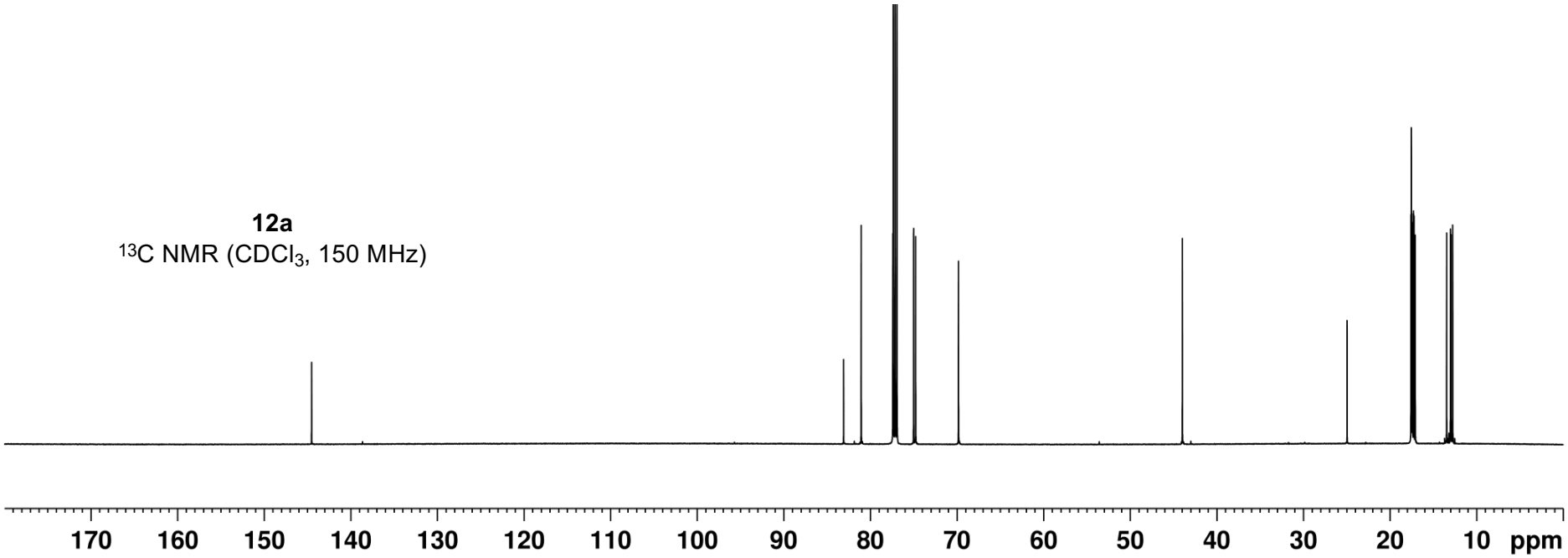


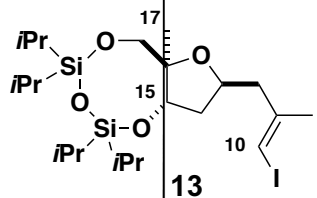
12a

^{1}H NMR ($CDCl_3$, 600 MHz)

12a

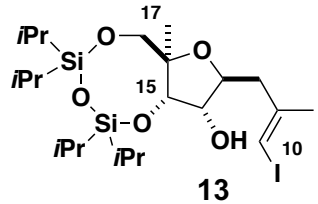
^{13}C NMR ($CDCl_3$, 150 MHz)





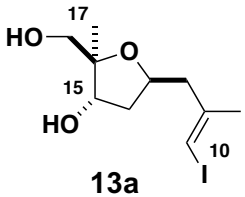
13

^{1}H NMR ($CDCl_3$, 600 MHz)



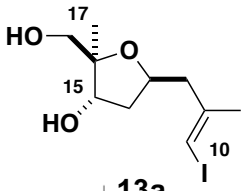
13

^{13}C NMR ($CDCl_3$, 150 MHz)



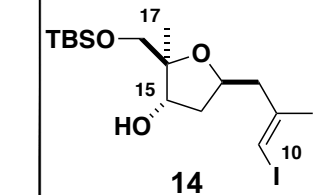
13a

^{1}H NMR ($CDCl_3$, 600 MHz)



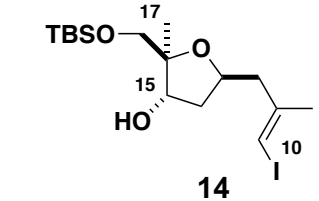
13a

^{13}C NMR ($CDCl_3$, 150 MHz)



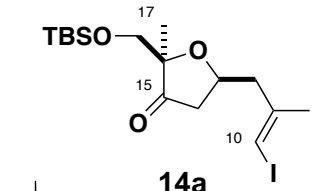
14

^{1}H NMR ($CDCl_3$, 500 MHz)



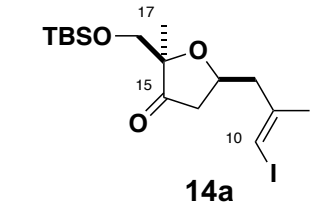
14

^{13}C NMR ($CDCl_3$, 125 MHz)



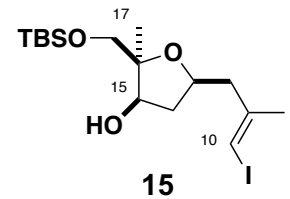
14a

^{1}H NMR ($CDCl_3$, 500 MHz)



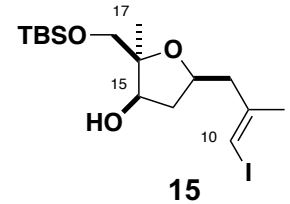
14a

^{13}C NMR ($CDCl_3$, 125 MHz)



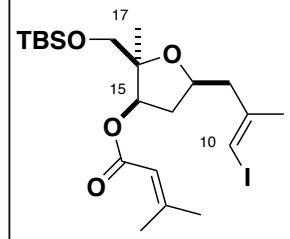
15

^{1}H NMR ($CDCl_3$, 500 MHz)



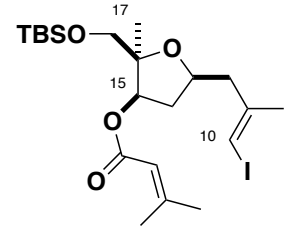
15

^{13}C NMR ($CDCl_3$, 125 MHz)



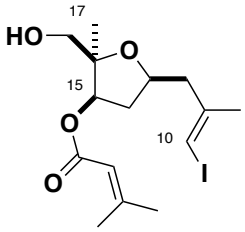
16

^{1}H NMR ($CDCl_3$, 500 MHz)



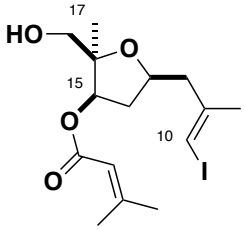
16

^{13}C NMR ($CDCl_3$, 125 MHz)



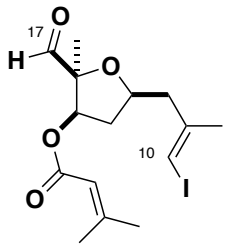
16a

^{1}H NMR ($CDCl_3$, 500 MHz)



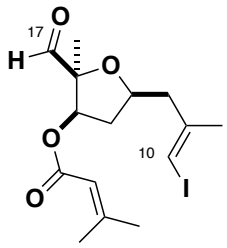
16a

^{13}C NMR ($CDCl_3$, 125 MHz)



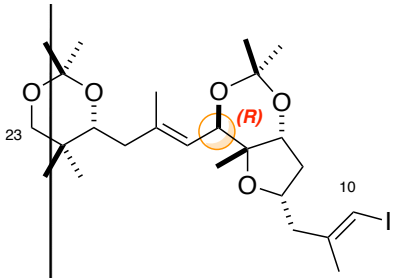
3

^{1}H NMR ($CDCl_3$, 500 MHz)



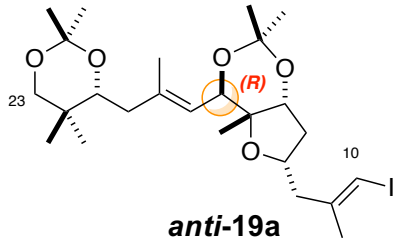
3

^{13}C NMR ($CDCl_3$, 125 MHz)



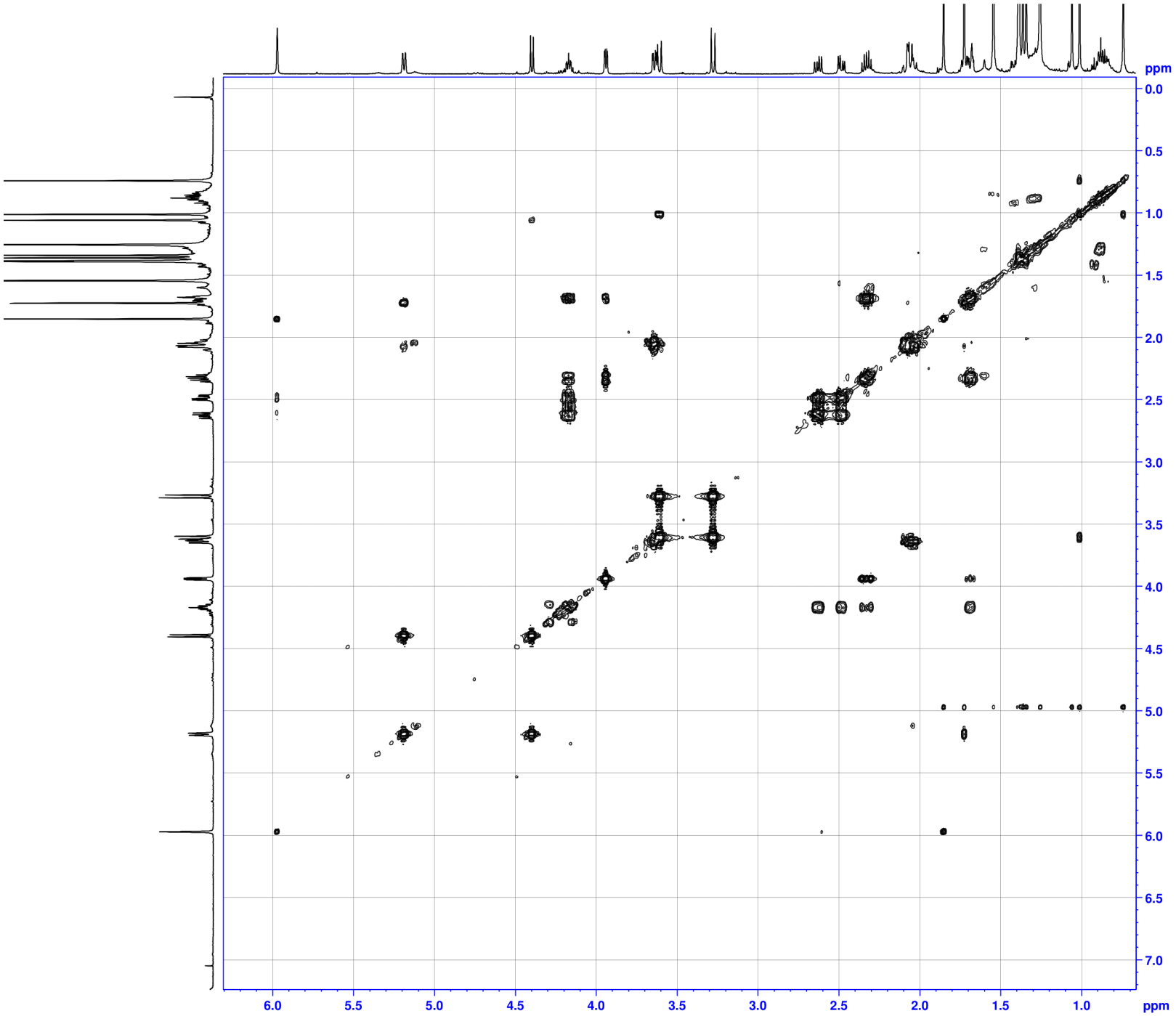
***anti*-19a**

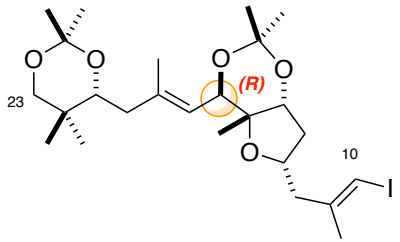
^{1}H NMR ($CDCl_3$, 500 MHz)



***anti*-19a**

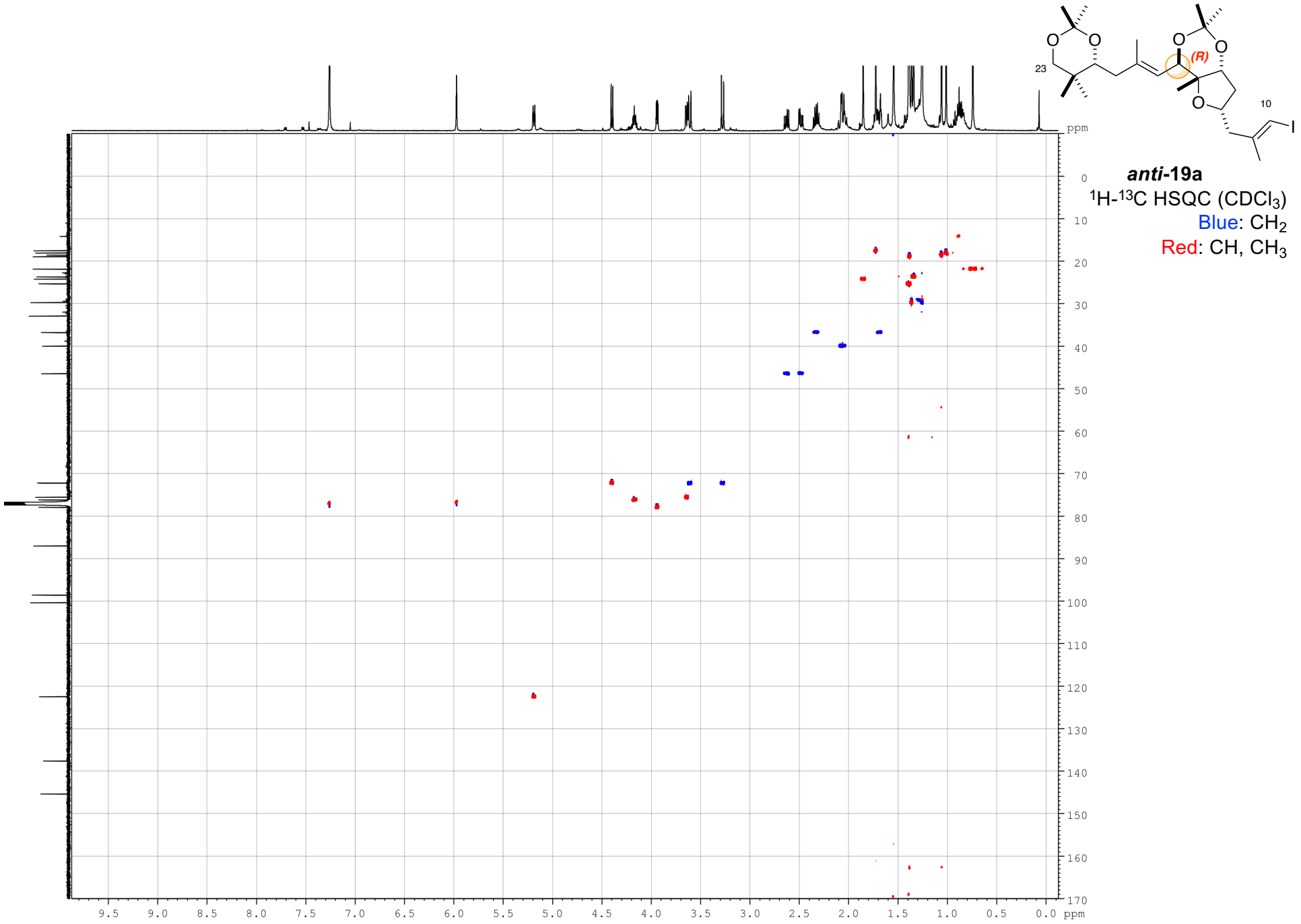
^{13}C NMR ($CDCl_3$, 125 MHz)





***anti*-19a**

^{1}H-^{1}H COSY ($CDCl_3$)

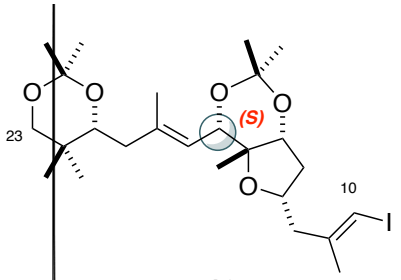


***anti*-19a**

^{1}H-^{13}C HSQC ($CDCl_3$)

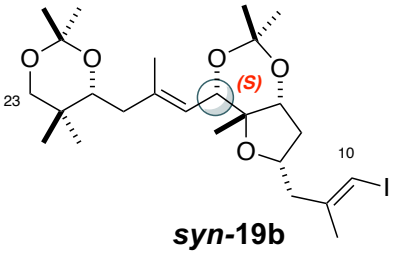
Blue: CH_2

Red: CH, CH_3



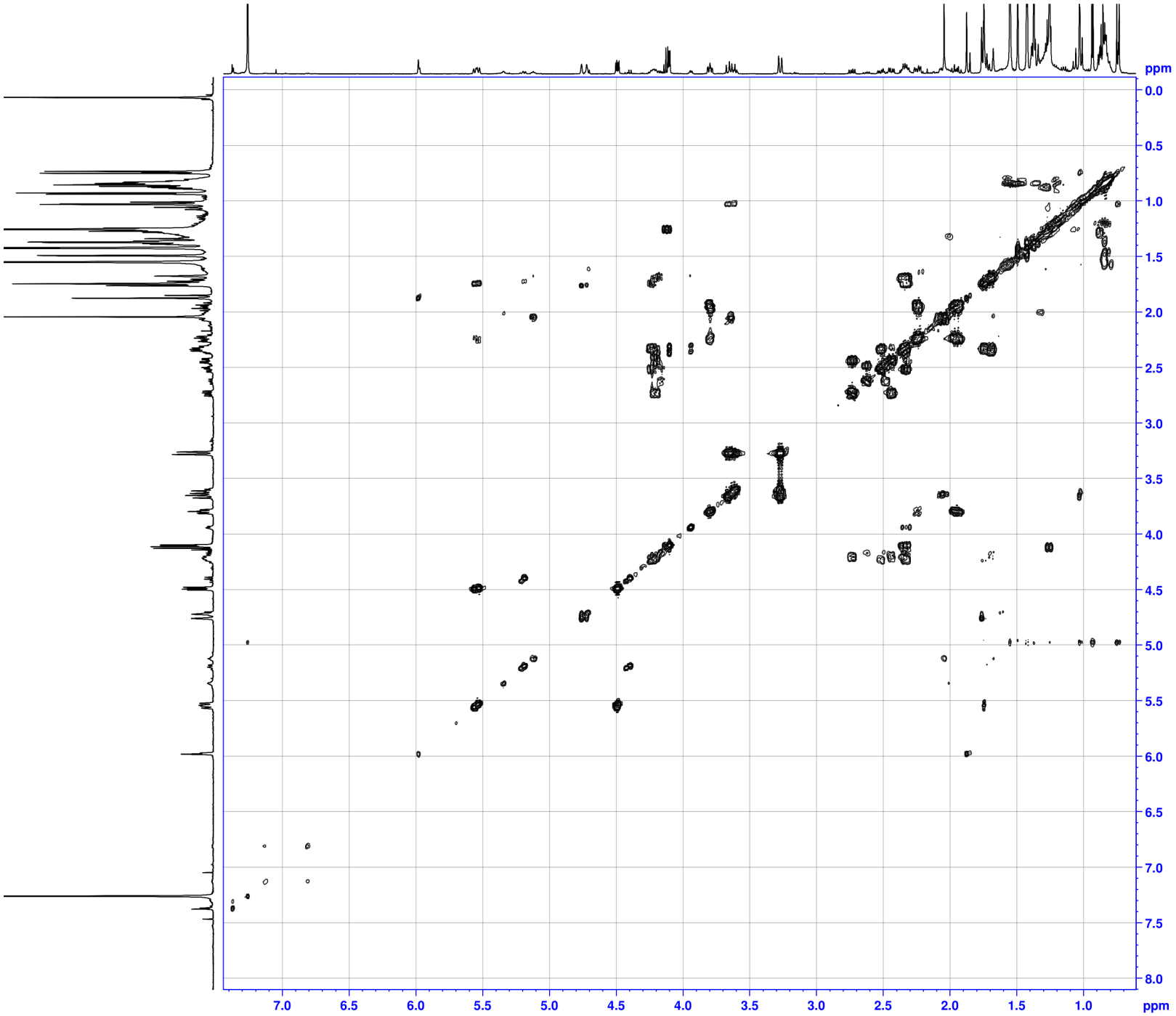
***syn*-19b**

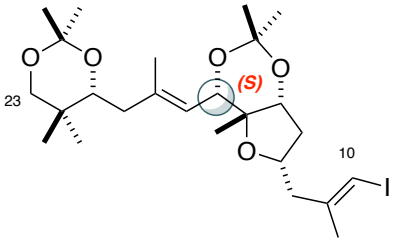
^{1}H NMR ($CDCl_3$, 500 MHz)



***syn*-19b**

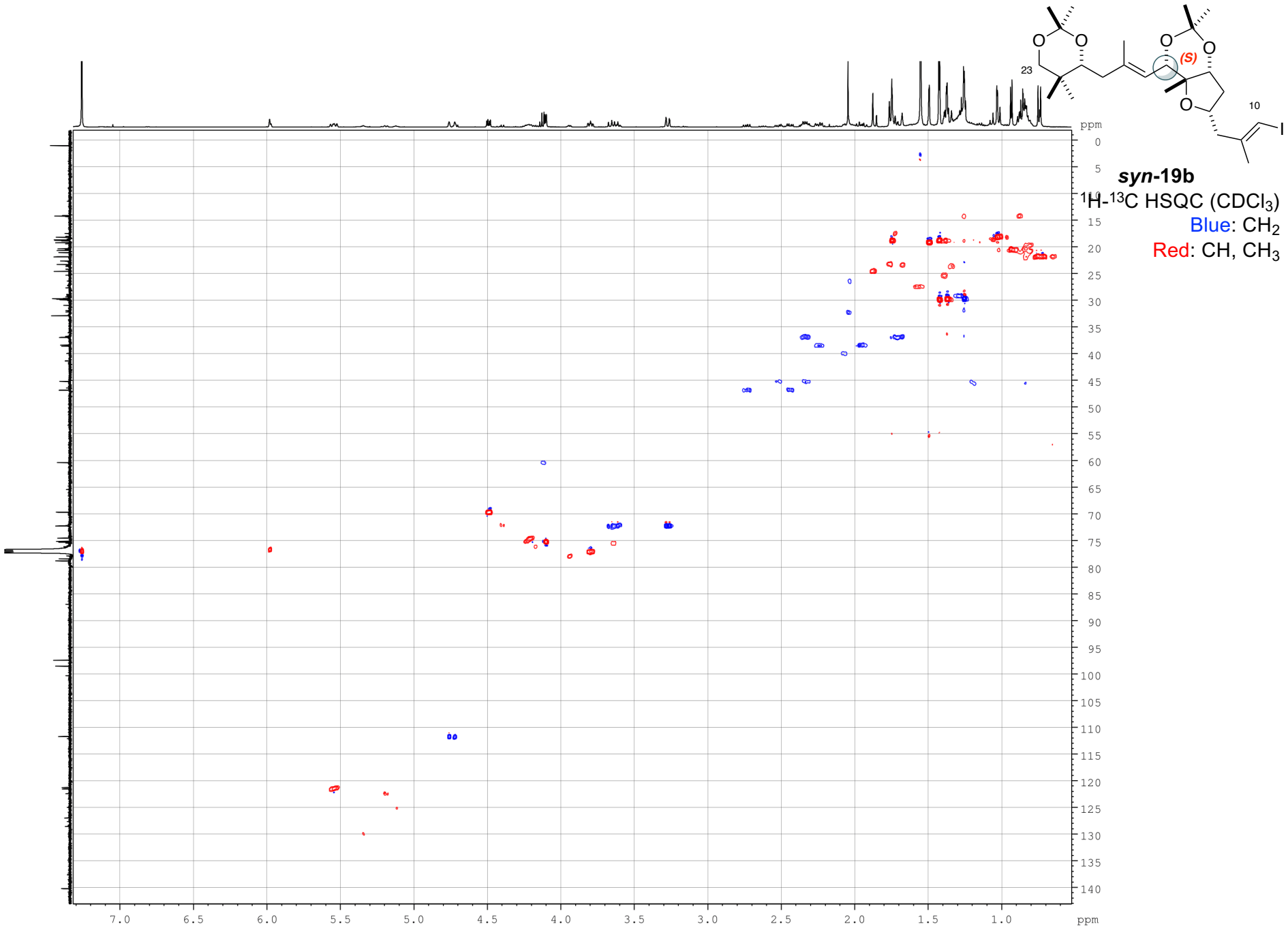
^{13}C NMR ($CDCl_3$, 125 MHz)





***syn*-19b**

^{1}H-^{1}H COSY ($CDCl_3$)

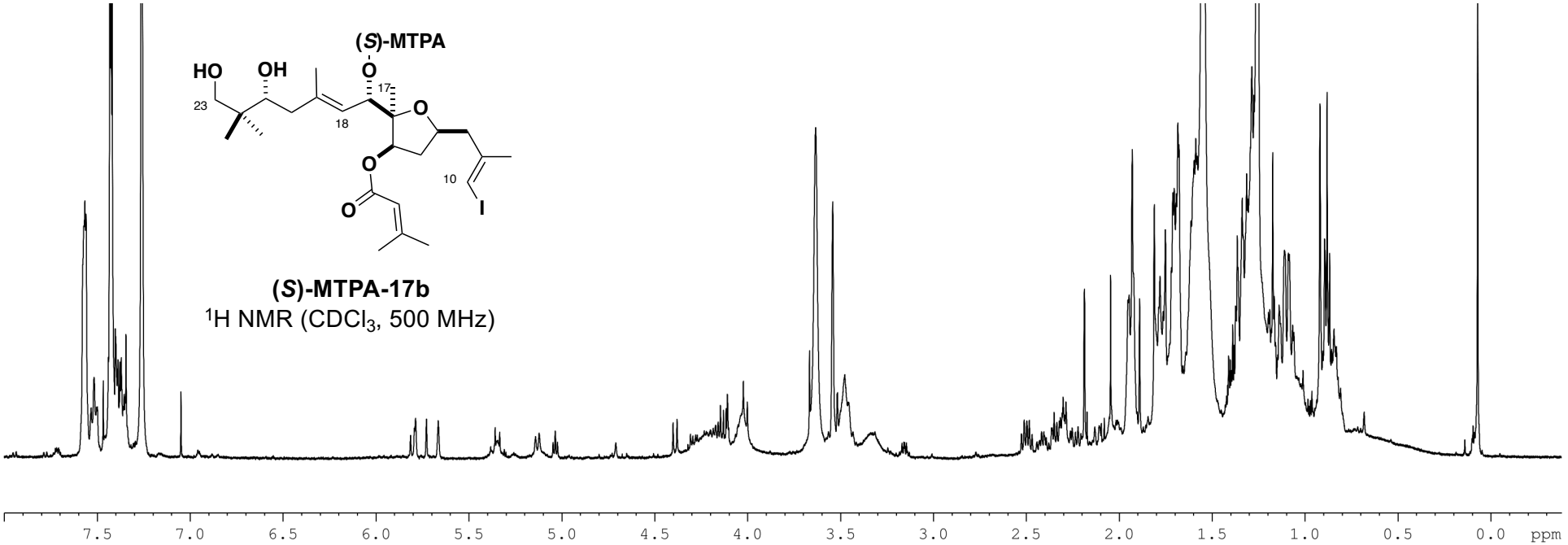


***syn*-19b**

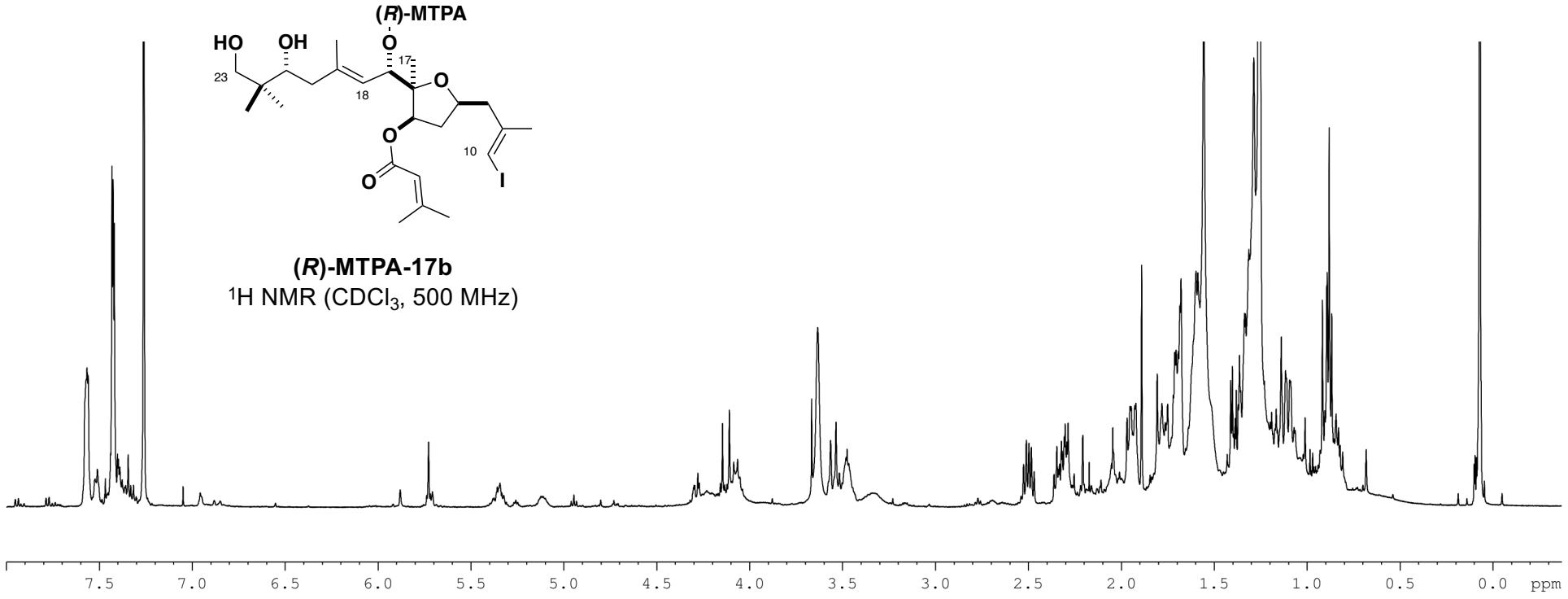
^{1}H-^{13}C HSQC ($CDCl_3$)

Blue: CH_2

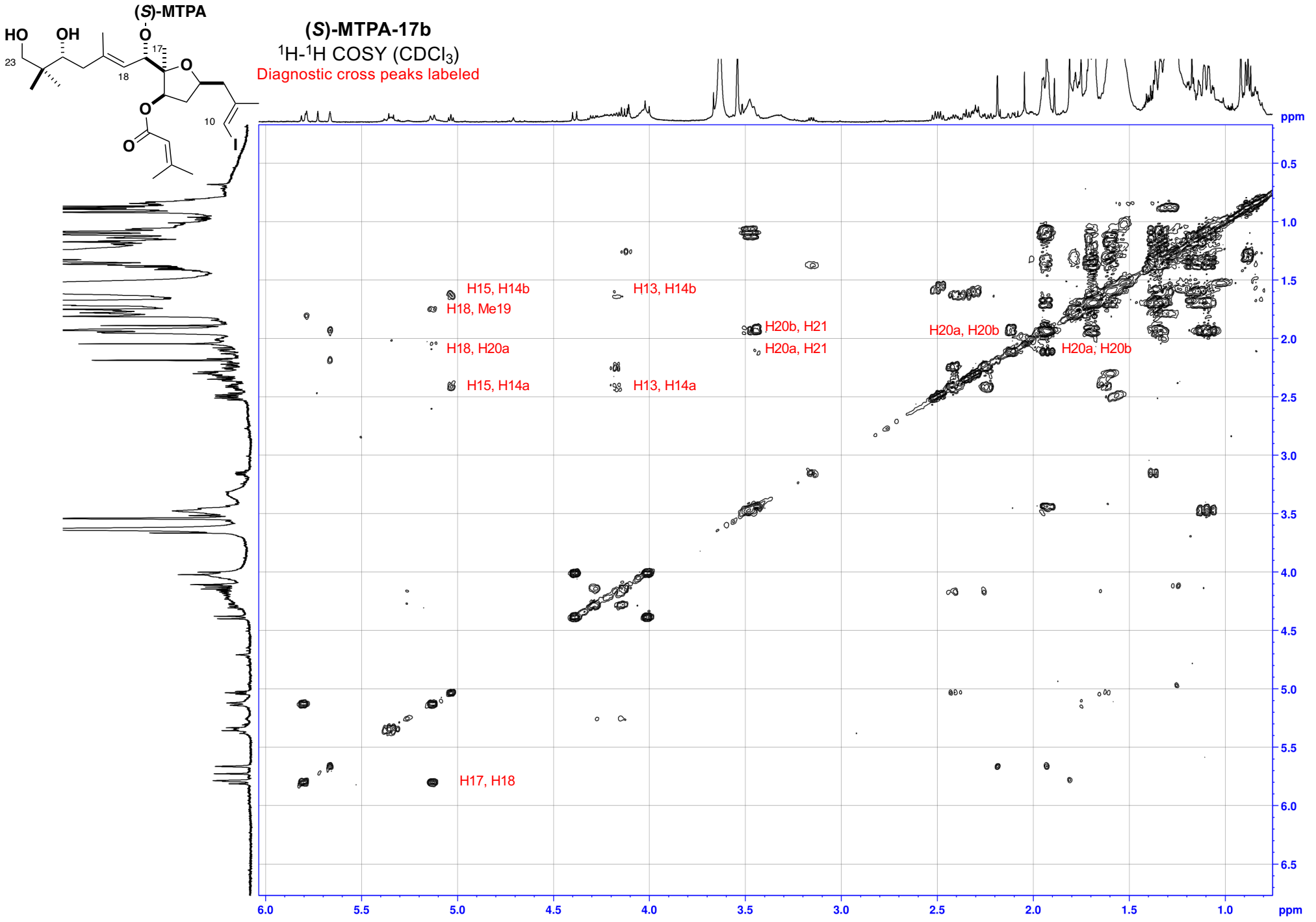
Red: CH, CH_3

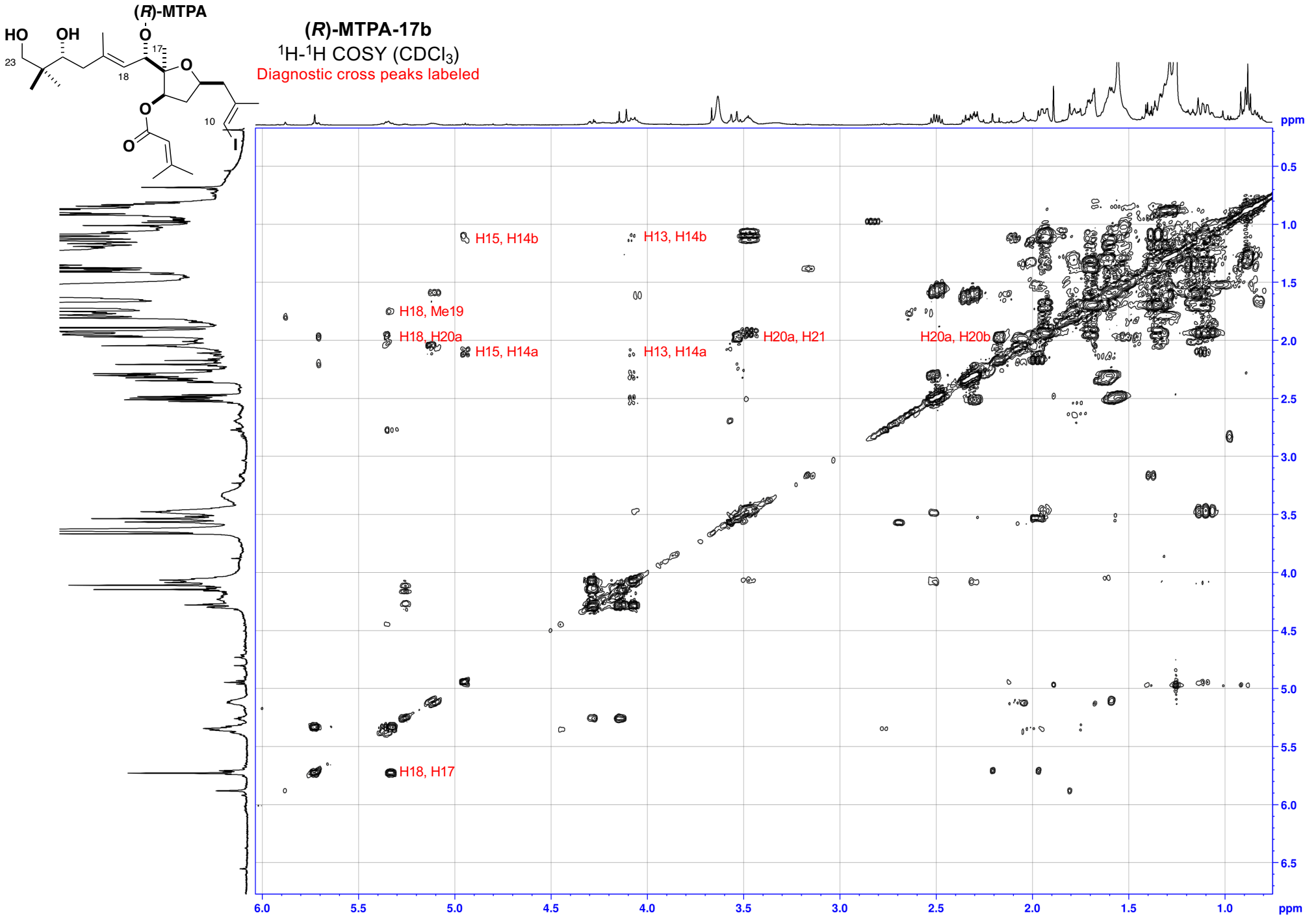


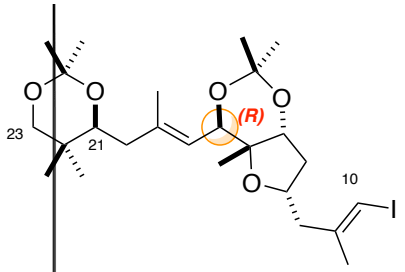
(*S*)-MTPA-17b
^{1}H NMR ($CDCl_3$, 500 MHz)



(*R*)-MTPA-17b
^{1}H NMR ($CDCl_3$, 500 MHz)

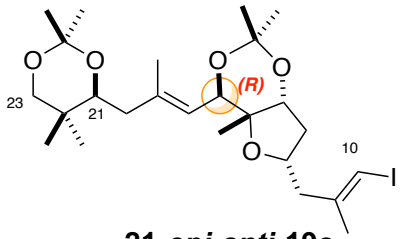

(S)-MTPA
HO
OH
O
17
23
18
O
O
O
10
I
(S)-MTPA-17b
1H-1H COSY (CDCl3)
Diagnostic cross peaks labeled
H15, H14b
H18, Me19
H18, H20a
H15, H14a
H13, H14b
H13, H14a
H20b, H21
H20a, H21
H20a, H20b
H20a, H20b
H17, H18
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


(R)-MTPA
HO
OH
O
17
23
18
O
O
O
10
I
(R)-MTPA-17b
1H-1H COSY (CDCl3)
Diagnostic cross peaks labeled
H15, H14b
H13, H14b
H18, Me19
H18, H20a
H15, H14a
H13, H14a
H20a, H21
H20a, H20b
H18, H17
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



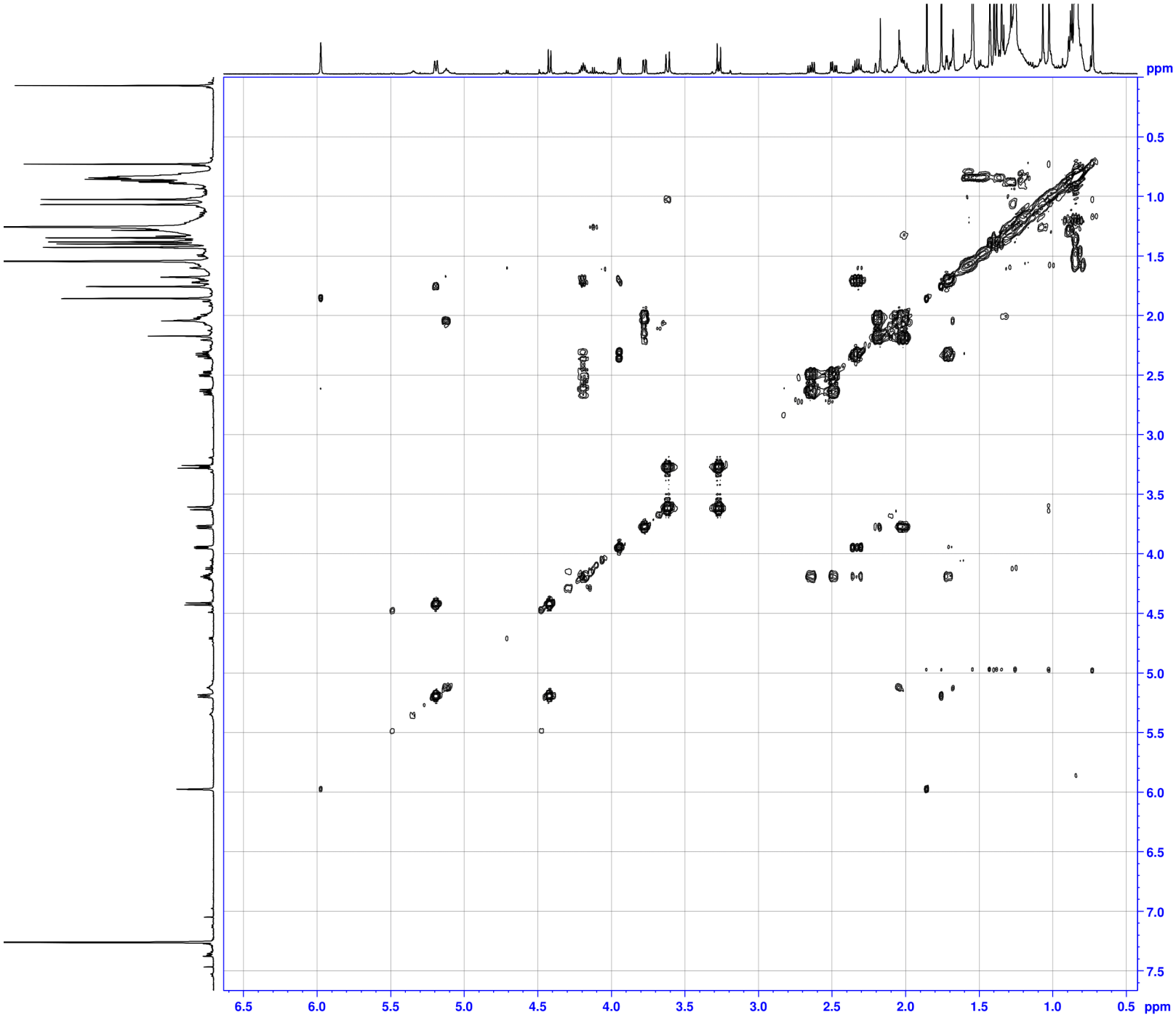
21-*epi-anti*-19c

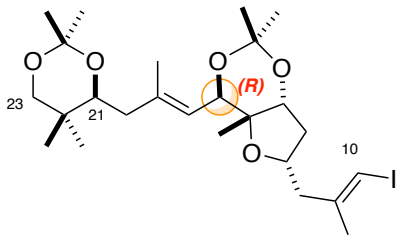
^{1}H NMR ($CDCl_3$, 500 MHz)



21-*epi-anti*-19c

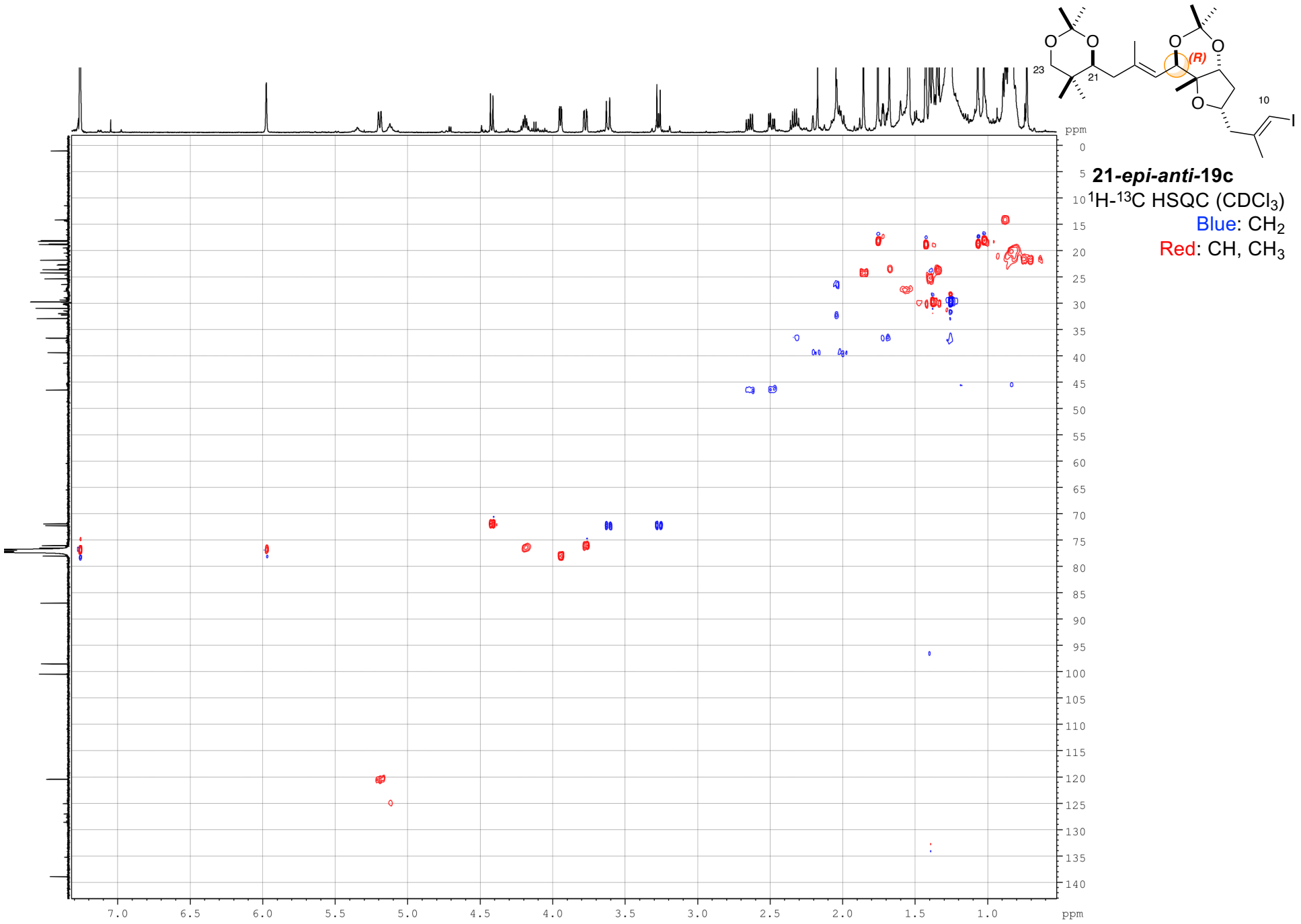
^{13}C NMR ($CDCl_3$, 125 MHz)





21-*epi*-*anti*-19c

^{1}H-^{1}H COSY ($CDCl_3$)



21-*epi*-*anti*-19c

^{1}H-^{13}C HSQC ($CDCl_3$)

Blue: CH_2

Red: CH, CH_3