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Synthesis

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Alexandre Audic, Joëlle Prunet.

Affiliations below.

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Corresponding Author:
Dr. Joëlle Prunet, University of Glasgow, Chemistry, University Avenue, G12 8QQ Glasgow, United Kingdom of Great Britain and Northern Ireland, Joelle.Prunet@glasgow.ac.uk

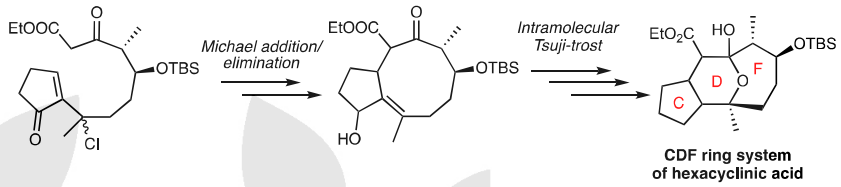
Affiliations:
Alexandre Audic, University of Glasgow, Chemistry, Glasgow, United Kingdom of Great Britain and Northern Ireland
Joëlle Prunet, University of Glasgow, Chemistry, Glasgow, United Kingdom of Great Britain and Northern Ireland

Synthesis of the CDF ring system of hexacyclinic acid

Alexandre Audic[a,1]
Joëlle Prunet*[a]

[a] School of Chemistry, University of Glasgow, Joseph Black Building, Glasgow G12 8QQ, UK.

joelle.prunet@glasgow.ac.uk



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Abstract Diverse approaches to prepare the nine-membered ring precursor of the DEF fragment of hexacyclinic acid are described, culminating in the synthesis of the CDF ring system of this natural product. The key steps are a Michael addition/elimination sequence and an original intramolecular Tsuji-Trost reaction of an enol with an allylic alcohol.

Key words hexacyclinic acid, intramolecular Tsuji-Trost, Crimmins aldol, relay ring-closing metathesis

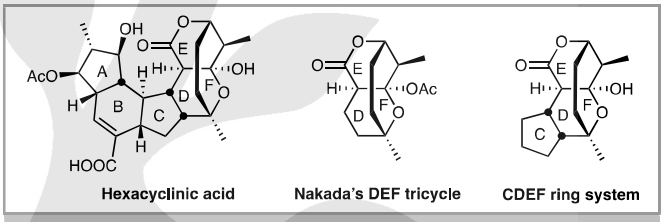
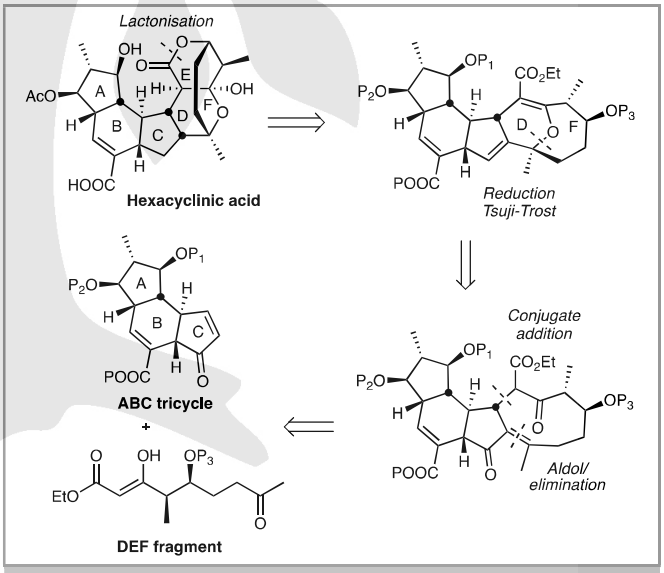


Figure 1 Structures of hexacyclinic acid, Nakada's biologically active DEF tricycle and our target CDEF ring system.

The complex polyketide hexacyclinic acid was isolated by Zeeck *et al.* in 2000 from *Streptomyces cellulosae* (strain S1013).[2] Several NMR experiments and X-ray analysis were needed to determine its structure and the relative configuration of its stereogenic centers. Its absolute configuration was elucidated by use of the Mosher ester method. As indicated by its name, hexacyclinic acid comprises six rings: a 5/6/5 fused ring system (A, B and C) on the left-hand side, connected to a bridged tricyclic system (D, E and F) encompassing a δ-lactone and a cyclic hemiketal on the right-hand side (Figure 1). This natural product exhibits cytotoxic activity against three cancerous cell lines: HM02 (gastric carcinoma), HEPG2 (hepatocellular carcinoma) and MCF7 (breast carcinoma) with GI_{50} values up to 14.0 $\mu molmL^{-1}$. In 2012, Nakada and co-workers synthesized a truncated DEF ring-system analogue of hexacyclinic acid (Figure 1), which was shown to inhibit bipolar spindle formation by disruption of microtubule dynamics, following the same mode of action as paclitaxel.[3]



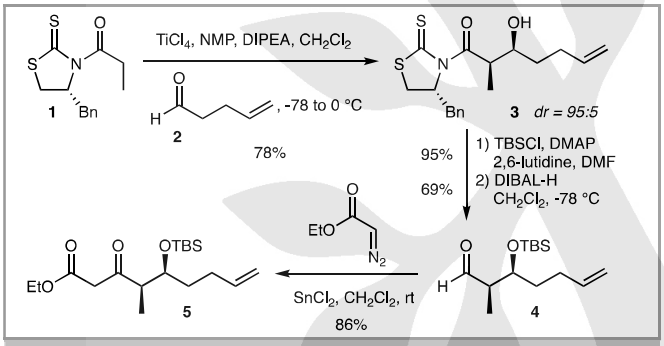
Scheme 1 Retrosynthesis of hexacyclinic acid

No total synthesis of hexacyclinic acid has been reported to date, although the construction of the ABC[4] and DEF[3,5] ring systems have been described by several groups. The retrosynthesis we devised for this compound is shown in Scheme 1. The E ring would be formed by lactonization. The D and F rings would be formed simultaneously by an intramolecular Tsuji-Trost reaction

between a β-keto ester enol nucleophile and an allylic alcohol. The key steps for the assembly of the nine-membered ring precursor of the DEF tricycle are the conjugate addition of the β-keto ester of the DEF fragment onto the enone of the ABC tricycle, followed by an intramolecular aldol/elimination sequence.

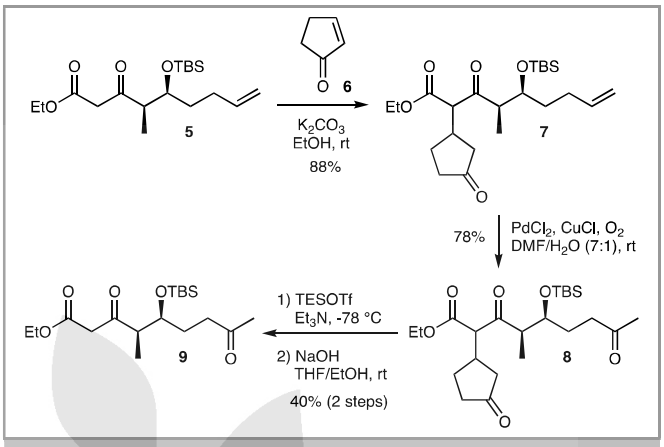
Inspired by the promising activity shown by the DEF truncated analogue reported by Nakada *et al.*,[3] we embarked on the synthesis of a CDEF ring system of hexacyclinic acid (Figure 1). The construction of this compound would serve two purposes: it would pave the way for the preparation of more substituted CDEF truncated analogues of the natural product, which could exhibit stronger activity than Nakada's analogue, and allow the coupling reaction between the ABC tricycle and the DEF fragment to be explored en route to the total synthesis of hexacyclinic acid.

The synthesis of the DEF fragment commenced with a Crimmins aldol reaction between thiazolidinethione **1**[6] and 4-pentenal **2**[7] to furnish compound **3** in good yield and diastereoselectivity[8] (Scheme 2). TBS protection of the alcohol in **3** (the two diastereomers were separated) followed by removal of the chiral auxiliary afforded aldehyde **4**, which was submitted to Roskamp homologation[4f] with ethyl diazoacetate to give the required DEF fragment **5** in good overall yield.



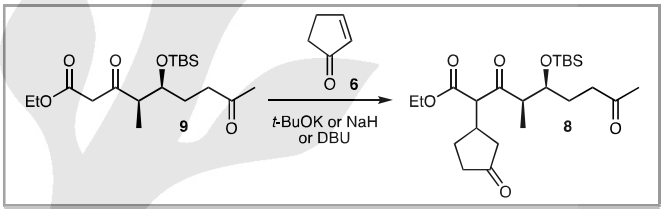
Scheme 2 Synthesis of DEF fragment **5**.

The next step was a Michael addition between β-keto ester **5** and cyclopentenone **6**, which represents the C ring. This reaction proceeded in the presence of potassium carbonate to give compound **7** in 87% yield as a mixture of all four possible diastereomers (Scheme 3). The order of addition of the reagents (the base was added to the mixture of **5** and **6**) was essential for complete conversion of **5**. Subsequent Wacker oxidation led to ketone **8**, and the β-keto ester moiety was protected as the corresponding silyl enol ether. The aldol reaction was conducted under diverse conditions, but without any success. *Inter alia*, sodium hydroxide in THF/EtOH induced a retro-Michael addition and ketone **9** was obtained in 40% yield.



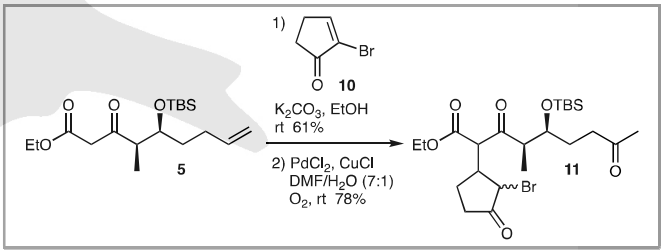
Scheme 3 First attempt at constructing the 9-membered ring by aldol reaction.

We decided to take advantage of the formation of compound **8** and submitted it to various bases (*t*-BuOK, NaH, DBU), in the expectation that a Michael/intramolecular aldol cascade reaction would occur. However, only β-keto ester **8** was obtained (Scheme 4).



Scheme 4 Second attempt at constructing the 9-membered ring by tandem Michael addition/aldol reaction.

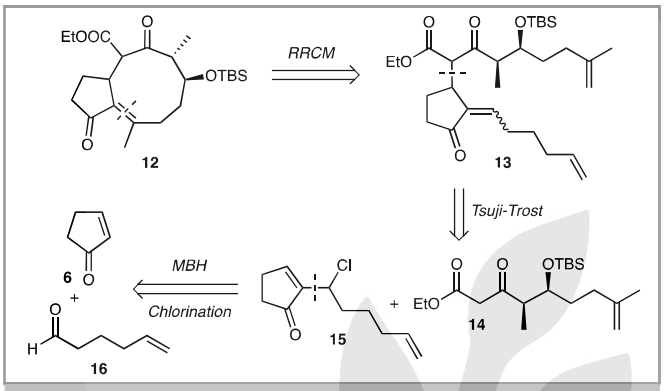
In order to avoid the retro-Michael reaction observed during the attempted aldol reaction under basic conditions, we turned to a Reformatsky reaction, where the enolate of the cyclic ketone would be generated under reducing conditions. Bromoketone **11** was prepared in two steps by Michael addition of β-keto ester **5** onto bromocyclopentenone **10**,[10] followed by Wacker oxidation (Scheme 5). Bromo ketone **11** was added slowly to a solution of samarium diiodide in THF, but unfortunately a mixture of the reduced product **8** and the starting material **11** was obtained instead of the required product. Other conditions ($Zn/CeCl_3 \cdot 7H_20$ and $SnCl_2/LiAlH_4$) only led to the recovery of **11**.



Scheme 5 Construction of the Reformatsky reaction substrate **9**

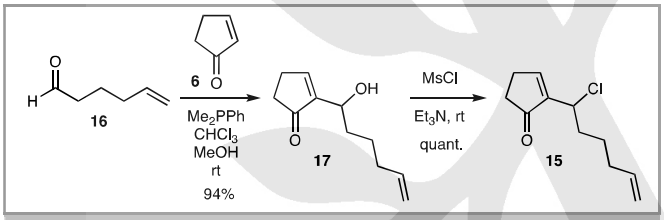
At this point, a new retrosynthesis was envisaged, where the 9-membered ring would be formed by a relay ring-closing metathesis (RRCM) reaction (Scheme 6). The metathesis substrate **13** would be formed by a Tsuji-Trost coupling between β-keto ester **14** and choro enone **15**, which in turn would be

produced by a Morita-Baylis-Hillman (MBH) reaction between cyclopentone **6** and 5-hexenal **16**[9] followed by chlorination.



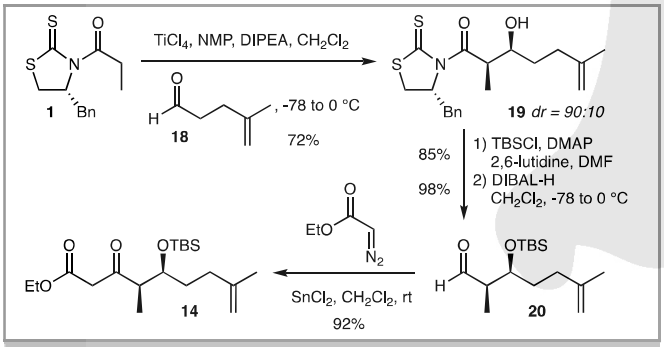
Scheme 6 Retrosynthesis of the 9-membered ring featuring a relay ring-closing metathesis (RRCM) reaction

In the forward direction, MBH reaction of cyclopentenone **6** and 5-hexenal **16** proceeded in 94% yield when using dimethylphenylphosphine as the catalyst[11] (Scheme 7). *β*-Hydroxy enone **17** was then reacted with mesyl chloride and triethylamine to give the unstable *β*-chlorocyclopentenone **15**, which was used in the next step without purification.



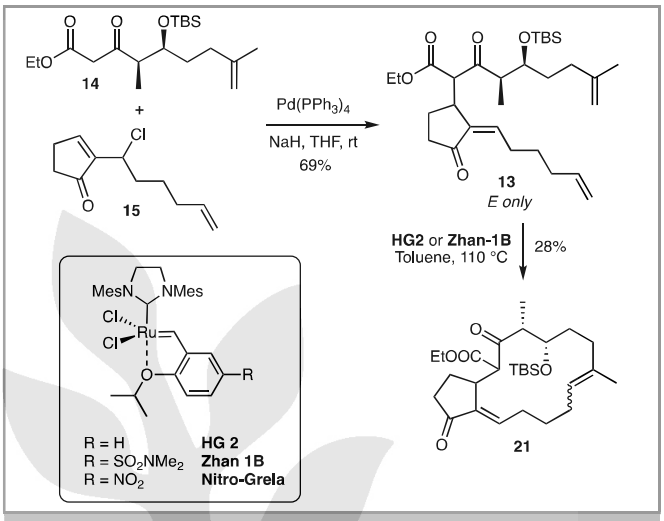
Scheme 7 Synthesis of compound **15**.

β-Keto ester **14** was synthesized in the same fashion as β-keto ester **5**. Crimmins aldol between thiazolidinethione **1**[6] and known aldehyde **18**[5b] furnished compound **19**, which was transformed into aldehyde **20** after TBS protection and DIBAL-H reduction, and subsequent Roskamp homologation completed the synthesis of **14** in good overall yield (Scheme 8).



Scheme 8 Synthesis of compound **14**.

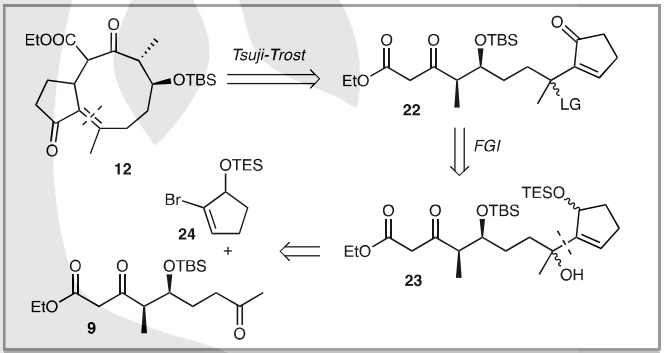
Exposure of β-keto ester **14** and chloro enone **15** to Pd(0) catalysis led to the metathesis precursor **13** in 69% yield as an inseparable mixture of all four diastereomers (Scheme 9). Unfortunately, treatment of triene **13** with either the Hoveyda-Grubbs second-generation complex **HG2** or the more active **Zhan-1B** catalyst only furnished the 14-membered ring **21**, as a 3:1 mixture of *E* and *Z* isomers, resulting from direct RCM rather than relay RCM reaction.



Scheme 9 RRCM attempts for the formation of the 9-membered ring.

Since the electron-deficient enone is not very reactive towards metathesis, compound **13** was reduced to the corresponding allylic alcohol. Treatment of this compound with the Nitro-Grela catalyst resulted in the formation of decomposition products exclusively.

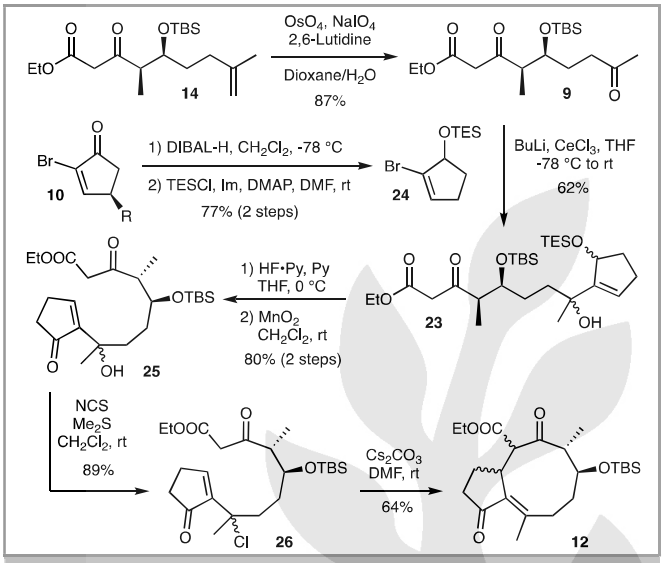
We then decided to use the efficient Tsuji-Trost reaction to form the 9-membered ring from enone **22**[5a] (Scheme 10). β-Keto ester **23** would be obtained by coupling the lithium derivative of protected bromocyclopentenol **24** and the previously obtained retro-Michael product **9** (Scheme 3).



Scheme 10 Retrosynthesis of the 9-membered ring featuring a Tsuji-Trost cyclization.

Compound **9** was prepared in a more straightforward manner by one-pot dihydroxylation/oxidative cleavage of the olefin of β-keto ester **14** (Scheme 11). 2-Bromocyclopentenone (**10**, R = H) was reduced with DIBAL-H and the resulting allylic alcohol was converted into the TES ether **24** in 77% yield for the two steps. With the two fragments in hand, coupling was performed by treating bromide **24** with butyllithium and thoroughly dried cerium trichloride at low temperature, followed by addition of ketone **9** to give tertiary alcohol **23** in 62% yield. It is worth noting that nucleophilic addition to the β-keto ester moiety was not observed, suggesting it is protected as a transient enolate. Cleavage of TES ether in the presence of HF.pyridine with excess

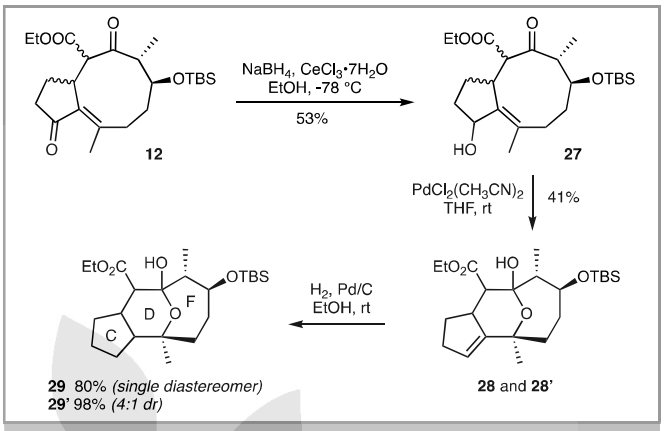
pyridine gave the *bis*-allylic alcohol in 90% yield, which was oxidized with manganese dioxide to enone **25** in good yield for the two steps.



Scheme 11 Synthesis of the 9-membered ring.

Chlorination of the allylic alcohol by reaction with a mixture of dimethyl sulfide and *N*-chlorosuccinimide led to the formation of the desired product **26** in 89% yield (Scheme 11). This unstable product was purified by flash chromatography after neutralisation of the silica gel with triethylamine. Classic Tsuji-Trost conditions with palladium *tetrakis*(triphenylphosphine)palladium(0) and sodium hydride only led to decomposition. Clarke *et al.* have shown that the addition of 1,2-*bis*(diphenylphosphino)ethane (dppe) as a ligand for the Tsuji-Trost reaction greatly improves the yield of nine-membered ring cyclic ketone.[5a] Unfortunately, when product **26** was submitted to Clarke's conditions, only degradation was observed. Addition of Pd(0) being detrimental to our substrate, it was decided to attempt a more classic Michael/elimination cascade. Pleasingly, in the presence of caesium carbonate in dry DMF, the desired nine-membered product **12** was finally obtained as a mixture of all four diastereomers in 64% yield.

Luche reduction of enone **12** furnished allylic alcohol **27** in moderate yield (Scheme 12). There are numerous examples in the literature of metal-assisted heterocyclizations using iron, gold or palladium. When compound **27** was exposed to iron(III) chloride in CH_2Cl_2,[12] traces of an unidentified product were observed. The use of chloro(triphenylphosphine)gold(I) and silver(I) triflate[13] only led to the elimination of the alcohol. Finally, treatment of allylic alcohol **27** with *bis*(acetonitrile)dichloropalladium(II)[14] led to the formation of the bridged hemiketal as a 1:1 separable mixture of 2 diastereomers (**28** and **28'**) in 41% yield. It was not possible to determine the relative configuration of each diastereomer. Hydrogenation of the alkene furnished the CDF tricycles **29** and **29'** in good yields and diasteroeselectivities. Unfortunately, subsequent attempts to form the E-ring lactone failed. TBAF conditions did not cleave the TBS ether, and the conditions employed by Evans *et al.* to form this lactone on the parent compound FR182877 (HF/acetonitrile and TMSOK)[15] also did not furnish the desired product.



Scheme 12 Synthesis of the CDF ring system pf hexacyclinic acid.

In conclusion, various approaches to form the nine-membered ring precursor of the DEF ring system of hexacyclinic acid have been explored, involving an aldol/elimination sequence, a Reformatsky reaction or a relay RCM reaction as the key step, but none of them was successful. A new method was then developed for the assembly of the desired ring, where the cyclization results from a Michael addition/elimination process. The CDF ring system was then constructed by an original intramolecular Tsuji-Trost reaction of an enol and an allylic alcohol. Since the cleavage of the ethyl ester to give the E ring lactone failed, it will be replaced by a *tert*-butyl ester in our future synthetic route; this ester has been shown by Clarke *et al.* to give the E ring lactone under acidic conditions in compounds similar to **29**.[5c] In addition, we will use a chiral C ring precursor such as 2-bromo-4-isopropylcyclopentenone (**10**, R = *i*-Pr, see Scheme 11) instead of 2-bromocyclopentenone (**10**, R = H), to avoid the formation of diastereomeric mixtures of compound **12** and the subsequent products.

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NMR spectra were recorded using a Bruker DPX-400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz) and a Bruker DPX-500 spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both ^{1}H and ^{13}C NMR, with residual solvent peak δ 7.26 being used for calibration of ^{1}H NMR and $CDCl_3$ peak at δ 77.16 for ^{13}C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two dimensional experiments (COSY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. IR spectra were recorded using a Golden Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under FAB, ESI and CI conditions by the University of Glasgow analytical service. Flash chromatography was executed under forced flow conditions, using the indicated solvent system and the EMD Geduran silica gel 60 as solid support. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 covered aluminium sheets, and monitored by UV-light or by staining with a solution of anisaldehyde or $KMnO_4$ mixture. Reactions were collected from an in-house solvent purification system (THF, CH_2Cl_2, Et_2O, CH_3CN, and toluene). Chromatography solvents were HPLC grade solvents, stored in Winchester bottles. All reagents were used directly from supplier, unless prior purification is explicitly stated. Air or moisture sensitive reactions were carried out in pre-dried glassware; either overnight in an oven (125 °C) or by flame drying under vacuum. Argon was used to create an inert atmosphere. Degassing solvent was done using freeze and thaw method.

Procedures

(2*R*,3*S*)-1-((*R*)-4'-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-hept-6-en-1-one 3

To a solution of compound **1** (14.3 g, 53.9 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added titanium tetrachloride (5.94 mL, 53.9 mmol, 1.00 equiv). The mixture was stirred 15 min at 0 °C then diisopropylethylamine (9.40 mL, 53.9 mmol, 1.00 equiv) was added. The reaction was stirred for 1 h then cooled to −78 °C and *N*-methyl-2-pyrrolidinone (5.20 mL, 53.9 mmol, 1.00 equiv) was added. The reaction was stirred for 1 h followed by dropwise addition of compound **2** (4.99 g, 59.3 mmol, 1.10 equiv). The reaction was stirred for 1 h at −78 °C then warmed to RT over 1 h. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (150 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (80:20 PE/EtOAc) to furnish **3** (two diastereomers: 14.7 g, 78%, *dr* = 95:5) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.19 (m, 5H), 5.75 (ddt, *J* = 16.6, 10.1, 6.6 Hz, 1H), 5.28 (ddd, J = 10.5, 7.2, 3.8 Hz, 1H), 4.98 (dq, *J* = 16.6, 1.5 Hz, 1H), 4.98 (ddd, *J* = 10.1, 3.0, 1.1 Hz, 1H), 4.41 (qd, *J* = 6.9, 3.3 Hz, 1H), 3.95 (dq, *J* = 7.5, 3.3 Hz, 1H), 3.33 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.14 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.97 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.83 (d, *J* = 11.5 Hz, 1H), 2.62 (d, *J* = 3.3 Hz, 1H), 2.19–2.12 (m, 1H), 2.08–2.01 (m, 1H), 1.62–1.54 (m, 1H), 1.44–1.37 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.5, 178.5, 138.2, 136.5, 129.6 , 129.1, 127.4, 115.2, 71.8, 68.9, 43.4, 36.9, 33.5 , 32.2 , 30.3 , 10.6.

The spectral data were in accordance with the literature.[8]

(2*R*,3*S*)-3-*(tert*-Butyldimethylsilyloxy)-2-methyl-6-heptenal 4

A solution of aldol **3** (4.89 g, 14.0 mmol) in CH_2Cl_2 (60 mL) was cooled to −78 °C then triethylamine (2.59 mL, 21.0 mmol, 1.50 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.83 mL, 21.0 mmol, 1.50 equiv) were added dropwise to the reaction. The mixture was stirred at −78 °C for 1 h then warmed to 0 °C and stirred for an additional 1 h. The reaction was quenched by addition of water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (97:3 PE/EtOAc) to give TBS-protected aldol (one diastereomer: 6.16 g, 95%) as a yellow oil.

A solution of TBS-protected aldol (6.03 g, 13.0 mmol) in CH_2Cl_2 (120 mL) was cooled to −78 °C and a 1 M solution of diisobutylaluminium hydride in hexanes (26.0 mL, 26.0 mmol, 2.00 equiv) was added dropwise. The mixture was left to stir until the bright yellow colour disappeared, then the reaction was quenched with EtOAc (20 mL) and warmed to RT. The mixture was then diluted with a 10% Rochelle's salt aqueous solution (120 mL) and stirred for 4 h until the organic phase became clear. The mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (90:10 PE/Et_2O) to furnish **4** (one diastereomer: 2.30 g, 69%) as a colorless oil.

$[\alpha]_D^{25}$ −93.3 (*c* = 1.0, $CHCl_3$), literature $[\alpha]_D^{25}$ −98.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (d, *J* = 1.0 Hz, 1H), 5.72 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 4.96 (dq, *J* = 16.9, 1.6 Hz, 1H), 4.98 (dq, *J* = 10.1, 1.6 Hz, 1H), 4.05 (td, *J* = 6.6, 3.6 Hz, 1H), 2.43 (qdd, *J* = 7.0, 3.6, 1.0 Hz, 1H), 2.12–1.94 (m, 2H), 1.62–1.48 (m, 2H,), 1.02 (d, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.4, 138.0, 115.1, 71.7, 51.3, 33.8, 30.1, 25.9, 18.2, 7.9, −4.1, −4.4.

The spectral data were in accordance with the literature.[16]

Ethyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-3-oxonon-8-enoate 5

To a solution of ethyl 2-diazoacetate (0.53 mL, 5.0 mmol, 2.0 equiv) in CH_2Cl_2 (15 mL) was added tin(II) chloride (0.24 g, 1.3 mmol, 0.50 equiv). The reaction was stirred at RT for 5 min then a solution of aldehyde **4** (0.65 g, 2.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture was left to stir at RT for 3 h. The crude mixture was concentrated under vacuum and purified by flash column chromatography (95:5 PE/Et_2O) to yield a 3:1 mixture of keto ester **5** and enol form (one diastereomer: 0.75 g, 86%) as a colorless oil.

$[\alpha]_D^{25}$ −63.0 (*c* = 1.0, $CHCl_3$), literature $[\alpha]_D^{25}$ −187 (*c* = 0.27, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 (ddt, *J* = 17.2, 10.2, 6.5 Hz, 1H), 4.92–4.85 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.82 (dt, *J* = 7.1, 4.1 Hz, 1H), 3.50 (s, 2H), 2.76 (qd, *J* = 7.1, 4.1 Hz, 1H), 1.95 (m, 2H), 1.50 (m, 1H), 1.35 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.4, 167.6, 138.1, 115.0, 73.4, 61.3, 51.8, 49.6, 33.4, 30.0, 26.0, 18.2, 14.3, 11.8, −4.3, −4.3.

The spectral data were in accordance with the literature.[16]

Ethyl (4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3-oxo-2-(3-oxocyclopentyl)non-8-enoate 7

To a solution of **5** (0.51 g, 1.5 mmol, 1.1 equiv) and 2-cyclopentenone **6** (0.11 mL, 1.3 mmol) in ethanol (1 mL) was added potassium carbonate (80 mg, 0.50 mmol, 0.40 equiv). The mixture was left to stir overnight and then was diluted with water (5 mL) and Et_2O (5 mL). The two layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude material was purified by column chromatography (90:10 PE/EtOAc) to furnish the product **7** (four diastereomers, 0.49 g, 88%) as a colorless oil.

Due to the presence of four diastereomers and for purpose of clarity, only the major ones in the ^{1}H NMR are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68–5.56 (m, 1H), 4.89–4.79 (m, 2H), 4.12–4.06 (m, 2H), 3.75 (d, *J* = 7.6 Hz, 1H), 3.64–3.56 (m, 1H), 2.90–2.84 (m, 1H), 2.80–2.64 (m, 2H), 2.43–2.00 (m, 2H), 1.99–1.77 (m, 4H), 1.77–1.61 (m, 1H), 1.50–1.32 (m, 2H), 1.17–1.10 (m, 3H), 1.07–1.04 (m, 3H), 0.82 (s, 9H), 0.05 (s, 3H), −0.02 (s, 3H).

The spectral data were in accordance with the literature.[16]

Ethyl (4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3,8-dioxo-2-(3-oxocyclopentyl) nonanoate 8

Palladium(II) chloride (17 mg, 0.097 mmol, 0.10 equiv) and CuCl (96 mg, 0.97 mmol, 1.0 equiv) was added to a 3:1 mixture of DMF/ water (2.1 mL) and oxygen was bubbled through the solution for 1 h. A solution of **7** (0.41 g, 0.97 mmol) in DMF (0.8 mL) was added and the mixture was stirred overnight under an oxygen atmosphere. The mixture was then diluted with water and extracted with Et_2O (3 x 10 mL) then filtered on celite. The combined organic layers were washed with brine (3 x 10 mL), dried over magnesium sulfate and concentrated under vacuum. The crude material was purified by column chromatography (80:20 PE/EtOAc) to furnish the product **8** (four diastereomers: 0.33 g, 78%) as a colorless oil.

Due to the presence of four diastereomers and for purpose of clarity, only the major ones in the ^{1}H NMR are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12–4.01 (m, 2H), 3.71 (d, *J* = 9.5 Hz, 1H,), 3.66–3.60 (m, 1H), 2.89–2.82 (m, 1H), 2.80–2.64 (m, 2H), 2.43–2.00 (m, 3H), 1.99 (s, 3H), 1.88–1.67 (m, 3H), 1.67–1.52 (m, 1H), 1.51–1.31 (m, 2H), 1.17–1.10 (m, 3H), 1.02–0.91 (m, 3H), 0.79–0.74 (m, 9H), −0.05 (s, 3H), −0.10 (s, 3H).

The spectral data were in accordance with the literature.[16]

Ethyl (4*R*,5*S*)-2-(2'-bromo-3'-oxocyclopentyl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxonon-8-enoate 11

Compound **11** was synthesized according to the procedure for compound **7**.

Yellow oil (eight diastereomers: 671 mg, 60% yield).

IR (thin film) 2955, 2931, 2856, 1755, 1703, 1631, 1462, 1371, 1241, 1224, 1101, 1026 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 5.88–5.70 (m, 1H), 5.09–4.85 (m, 2H), 4.33–4.12 (m, 2H), 4.02–3.93 (m, 1H), 3.92–3.78 (m, 1H), 3.70–3.55 (m, 1H), 2.40–2.20 (m, 2H) 2.19–1.97 (m, 3H), 1.96–1.68 (m, 1H), 1.67–1.41 (m, 1H), 1.37–1.27 (m, 4H), 1.22–1.15 (m, 2H) 1.12 (d, *J* = 6.9 Hz, 3H), 0.93–0.89 (m, 9H), 0.14–0.03 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.3, 173.6, 172.9, 164.8, 139.0, 138.8, 114.8, 114.1, 113.9, 110.1, 109.9, 105.3, 104.8, 86.5, 83.2, 83.0, 82.8, 84, 73.7, 73.3, 73.0, 63.2, 61.9, 61.1, 59.7, 59.4, 53.6, 51.0, 45.6, 43.5, 41.7, 40.9, 37.6, 35.3, 34.9, 34.5, 33.2, 33.1, 29.7, 28.4, 28.2, 27.5, 27.4, 25.7, 25.6, 25.3, 25.1, 24.6, 23.8, 23.5, 20.8, 18.1 17.5, 17.3, 16.0, 15.8, 15.0, 14.5, 14.1, 13.6, −2.8, −5.2.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for 503.1828, found: 503.1832.

2-(1-Hydroxyhex-5-en-1-yl)cyclopent-2-en-1-one 17

2-Cyclopenten-1-one **6** (0.10 mL, 1.2 mmol) and hex-5-en-1-al **16** (0.24 g, 2.4 mmol, 2.0 equiv) were dissolved in a 3:2 mixture of $CHCl_3$/MeOH (2.5 mL). Dimethylphenylphosphine (17 μL, 0.12 mmol, 0.10 equiv) was added dropwise and the reaction was stirred for 2 h at RT. The solvents were concentrated under vacuum and the resulting crude product was purified by flash chromatography (70:30 PE/Et_2O) to furnish product **17** (0.21 g, 94%) as a colorless oil.

^1H NMR ($CDCl_3$, 500 MHz) δ 7.44 (td, *J* = 2.7, 1.1 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.1, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (ddt, *J* = 10.1, 1.7, 1.1 Hz, 1H), 4.48–4.42 (m, 1H), 2.77 (d, *J* = 5.6 Hz, 1H), 2.64–2.59 (m, 2H), 2.47–2.43 (m, 2H), 2.12–2.05 (m, 2H), 1.74–1.65 (m, 2H), 1.62–1.56 (m, 1H), 1.49–1.41 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.2, 157.9, 147.9, 138.7, 114.9, 67.9, 35.5, 35.4, 33.6, 26.8, 24.9.

The spectral data were in accordance with the literature.[17]

2-(1-Chlorohex-5-en-1-yl)cyclopent-2-en-1-one 15

To a solution of **17** (100 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (115 μL, 0.830 mmol, 1.50 equiv) and methanesulfonyl chloride (65 μL, 0.83 mmol, 1.5 equiv). The mixture was stirred at RT for 2 h then was quenched by addition of water (3 mL) and the layers were separated. The organic layer was washed with brine (2 × 5 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give the unstable chlorocyclopentenone **15** (75 mg, 69%) that was used in the next step without further purification.

IR (thin film) 3055, 2932, 2862, 1705, 1643 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz) δ 7.66 (td, *J* = 2.7, 1.1 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 (dt, *J* = 10.2, 1.7 Hz, 1H), 4.68 (ddt, *J* = 7.4, 3.0, 1.3 Hz, 1H), 2.67–2.62 (m, 2H), 2.50–2.47 (m, 2H), 2.15–2.02 (m, 2H), 2.00–1.91 (m, 1H), 1.91–1.83 (m, 1H) 1.65–1.56 (m, 1H), 1.54–1.46 (m, 1H).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for: 199.0884, found: 199.0890.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2,6-dimethylhept-6-en-1-one 19

Compound **19** was synthesized according to the procedure for compound **3**.

Yellow oil (two diastereomers: 4.37 g, 72%, *dr* = 9:1).

IR (thin film): 3464, 2932, 1690, 1257, 1026 cm^{-1}.

^1H NMR δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.31 (m, 2H), 7.32–7.27 (m, 3H), 5.40–5.33 (m, 1H), 4.76–4.71 (m, 2H), 4.55–4.46 (m, 1H), 3.98–3.90 (m, 1H), 3.41 (ddd, *J* = 11.5, 7.1, 1.1 Hz, 1H), 3.22 (dd, *J* = 13.3, 3.9 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.91 (d, *J* = 11.5 Hz, 1H), 2.71 (d, *J* = 3.2 Hz, 1H), 2.24–2.14 (m, 1H), 2.12–2.01 (m, 2H), 1.73 (s, 1H), 1.72–1.64 (m, 1H), 1.60 – 1.49 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.5, 178.5, 145.5, 136.5, 129.8, 129.1, 127.4, 110.5, 72.1, 68.9, 43.4, 37.0, 34.2, 32.3, 32.2, 22.6, 10.7.

HRMS (CI+): *m/z* [M + H]$^+$ calcd for 364.1399, found: 364.1405.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhept-6-enal 20

Compound **20** was synthesized according to the procedure for compound **4**.

Colorless oil (one diastereomer: 3.98 g, 83%).

IR (thin film): 2932, 2855, 1728, 833 cm^{-1}.

$[\alpha]_D^{25}$ −41.5 (*c* = 1.0, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.0 Hz, 1H), 4.74 (s, 1H), 4.69 (s, 1H), 4.13 (td, *J* = 6.5, 3.6 Hz, 1H), 2.49 (qdd, *J* = 7.0, 3.6, 1.0 Hz, 1H), 2.12–2.04 (m, 1H), 2.01–1.93 (m, 1H), 1.74 (s, 2H), 1.72–1.59 (m, 2H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.4, 145.2, 110.4, 71.9, 51.3, 34.0, 32.6, 25.9, 22.6, 18.2, 7.85, -4.1, -4.4

HRMS (ESI): *m/z* [M + H]$^+$ calcd for 293.1907, found: 293.1900.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4,8-dimethyl-3-oxonon-8-enoate 14

Compound **14** was synthesized according to the procedure for compound **5**.

Colorless oil (3:1 mixture of keto ester **14** and enol form, one diastereomer: 4.85 g, 92%).

Keto ester form is described below:

IR (thin film): 3078, 2932, 2862, 1744, 1713, 1643, 833 cm^{-1}.

$[\alpha]_D^{25}$ −38.0 (*c* = 1.0, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (s, 1H), 4.67 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90 (ddd, *J* = 7.2, 5.0, 4.2 Hz, 1H), 3.59 (s, 1H), 3.59 (s, 1H), 2.85 (qd, *J* = 7.0, 4.2 Hz, 1H), 2.13–2.01 (m, 2H), 2.01–1.91 (m, 1H), 1.72 (s, 1H), 1.67–1.58 (m, 2H), 1.52–1.43 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.93–0.89 (m, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.3, 180.8, 167.6, 145.4, 110.3, 76.9, 73.61, 61.3, 51.8, 49.6, 33.9, 32.3, 26.0, 22.7, 18.2, 14.3, 11.7, -4.3, -4.4.

HRMS (CI+): *m/z* [M + H]$^+$ calcd for 357.2456, found: 357.2461.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-2'-(hex-5'-en-1'-ylidene)-3-oxocyclopentyl)-4,8-dimethyl-3-oxonon-8-enoate 13

To a solution of chlorocyclopentenone **15** (254 mg, 1.27 mmol) in THF (5 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (162 mg, 0.14 mmol, 0.11 equiv) and the reaction was stirred for 20 min at RT. In parallel, sodium hydride (59.0 mg, 1.47 mmol, 1.05 equiv) was added to a solution of ketoester **14** (500 mg, 1.40 mmol, 1.10 equiv) in THF (5 mL) and the mixture was stirred for 10 min before dropwise addition to the palladium/chlorocyclopentenone mixture. The reaction was stirred for 5 min then was quenched by addition of a 1 M aqueous solution of hydrochloric acid (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL), the organic phases were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The mixture was purified by flash chromatography (90:10 PE/Et_2O) to yield product **13** (four diastereomers: 458 mg, 69%) as yellow oil.

Due to the presence of 4 diastereomers and for purpose of clarity, only the major ones are described below:

IR (thin film) 2940, 2862, 1736, 1643, 845 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 6.54 (t, *J* = 6.8 Hz, 1H), 5.84–5.71 (m, 1H), 5.05–4.94 (m, 2H), 4.72–4.64 (m, 1H), 4.64 (d, *J* = 1.0 Hz, 1H), 4.18–4.07 (m, 2H), 4.02 (d, *J* = 5.1 Hz, 1H), 3.97–3.90 (m, 1H), 3.73–3.64 (m, 1H), 2.87

(qd, *J* = 7.0, 4.1 Hz, 1H), 2.51–2.38 (m, 1H), 2.33–2.22 (m, 1H), 2.21–2.12 (m, 2H), 2.12–2.02 (m, 3H), 2.02–1.93 (m, 3H), 1.70 (s, 3H), 1.64–1.45 (m, 4H), 1.27–1.19 (m, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.5, 206.3, 168.3, 145.5, 139.0, 138.5, 138.1, 115.4, 110.1, 72.7, 61.6, 60.7, 52.1, 38.1, 35.7, 34.1, 33.4, 33.1, 28.9, 28.0, 26.1, 23.1, 22.7, 18.3, 14.2, 13.1, −4.2, −4.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for: 519.3500, found: 519.3506.

Ethyl (6*R*,7*S*,15*E*)-7-((*tert*-butyldimethylsilyl)oxy)-6,10-dimethyl-1,5-dioxo-2,3,3a,4,5,6,7,8,9,12,13,14-dodecahydro-1H-cyclopenta[14]annulene-4-carboxylate 21

To a degassed solution of Hoveyda-Grubbs catalyst (7.0 mg, 11 μmol, 0.10 equiv) in toluene (1 mL) was added dropwise (over 3 h) a mixture of product **13** (59 mg, 0.11 mmol) in toluene (3 mL) at 110 °C. After addition, the solvent was concentrated under vacuum and the crude was purified by flash chromatography (95:5 PE/Et_2O) to give product **21** (eight diastereomers: 15 mg, 28%, *E*/*Z* = 3:1) as a brown oil.

Mixture of *E* diastereomers is described below:

IR (thin film) 2932, 2855, 1736, 1643, 1713, 833 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.65 (td, *J* = 9.0, 2.3 Hz, 1H,), 5.38 (t, *J* = 7.4 Hz, 1H), 4.23 (ddd, *J* = 8.6, 4.3, 3.0 Hz, 1H), 4.12 (d, *J* = 3.9 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.41–3.35 (m, 1H), 2.83 (qd, *J* = 6.6, 3.0 Hz, 1H), 2.73 (ddd, *J* = 19.1, 10.7, 8.0 Hz, 1H), 2.73–2.69 (m, 1H) 2.36 (ddt, *J* = 13.8, 10.7, 3.2 Hz, 1H), 2.31–2.23 (m, 2H), 2.21–2.16 (m, 2H), 2.12 (ddd, *J* = 14.6, 10.5, 3.9 Hz, 1H), 2.06–1.95 (m, 1H), 1.91–1.82 (m, 2H), 1.74–1.69 (m, 1H), 1.68 (s, 3H), 1.66–1.59 (m, 1H), 1.53–1.47 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), −0.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.2, 205.4, 167.9, 139.1, 137.5, 136.1, 125.6, 70.4, 61.2, 59.4, 49.1, 37.2, 36.9, 35.4, 31.7, 28.9, 28.0, 26.7, 25.9, 19.9, 18.2, 15.5, 14.2, 8.4, −3.5, −4.83.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for: 513.3007, found: 513.2889.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3,8-dioxononanoate 9

To a solution of compound **14** (1.78 g, 5.04 mmol) in a 5:1 mixture of dioxane/water (70 mL) were added 2,6-lutidine (1.18 mL, 10.1 mmol, 2.00 equiv), OsO_4 (2.5wt% in *tert*-butanol, 1.1 mL, 0.10 mmol, 0.020 equiv), and sodium periodate (4.31 g, 20.1 mmol, 4.00 equiv). The reaction was stirred at RT for 4 h. After the reaction was complete, water (80 mL) and CH_2Cl_2 (150 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with brine (250 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (70:30 PE/Et_2O) to afford compound **9** (1.57 g, 87%) as a colorless oil.

IR (thin film): 2932, 1744, 1713, 1636 cm^{-1}.

$[\alpha]_D^{25}$ −44.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, J = 7.2 Hz, 2H), 3.91 (td, *J* = 7.2, 4.7 Hz, 1H), 3.56 (s, 2H), 2.80 (qd, J = 7.0, 4.7 Hz, 1H), 2.55–2.38 (m, 2H), 2.12 (s, 3H), 1.84–1.72 (m, 1H), 1.62–1.50 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 208.2, 205.2, 167.5, 89.8, 72.7, 61.3, 51.9, 49.6, 44.6, 39.3, 30.0, 27.9, 26.0, 18.1, 14.2, 12.3, −4.3, −4.5.

HRMS (CI+): *m/z* [M + H]$^+$ calcd for 381.2068, found: 381.2051.

((2-Bromocyclopent-2-en-1-yl)oxy)triethylsilane 24

A solution of 2-bromocyclopent-2-enone **10** (6.74 g, 41.9 mmol) in CH_2Cl_2 (250 mL) was cooled to −78 °C then a 1 M solution of diisobutylaluminium hydride in heptane (84 mL, 84 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at −78 °C for 1 h then was quenched by addition of a saturated aqueous solution of Rochelle salt (200 mL) and allowed to warm up to RT. The mixture was stirred for 4 h then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL), the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum to furnish the crude allylic alcohol (6.80 g) as a colorless liquid that was used in the next step without further purification.

2-Bromocyclopent-2-en-1-ol (6.80 g, 41.7 mmol) was dissolved in dry DMF (100 mL) then imidazole (8.52 g, 125 mmol, 3.00 equiv) and DMAP (0.51 g, 4.2 mmol, 0.10 equiv) were added. The reaction was cooled to 0 °C then chlorotriethylsilane (10.5 mL, 62.6 mmol, 3.00 equiv) was added dropwise and the reaction was stirred for 5 min. The mixture was warmed to RT and stirred for 1 h. The mixture was then diluted with water (100 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (2 × 300 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (99:1 PE/Et_2O) to give product **24** (8.9 g, 77% over 2 steps) as a yellow oil.

IR (thin film) 2955, 2878, 1096, 1003 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (td, *J* = 2.5, 1.1 Hz, 1H), 4.74–4.69 (m, 1H), 2.51–2.41 (m, 1H), 2.35–2.26 (m, 1H), 2.27–2.17 (m, 1H), 1.82 (ddt, *J* = 12.6, 8.6, 4.4 Hz, 1H), 1.01 (t, *J* = 8.0 Hz, 9H), 0.68 (t, *J* = 8.0 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101MHz) δ 133.7, 125.7, 79.4, 33.4, 30.4, 7.0, 5.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for 299.0437, found: 299.0431.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyl-3-oxo-8-(5'-((triethylsilyl)oxy)cyclopent-1'-en-1'-yl)nonanoate 23

Cerium(III) chloride heptahydrate (1.14 g, 3.06 mmol, 2.20 equiv) was finely grinded then stirred under vacuum (P < 1 mbar) and warmed to 120 °C for 2 h, 140 °C for 2 h and 160 °C for 3 h. Cerium(III) chloride was cooled to RT under inert atmosphere then THF (5 mL) was added and the white suspension was stirred vigorously overnight.

((2-Bromocyclopent-2-en-1-yl)oxy)triethylsilane **24** (775 mg, 2.78 mmol, 2.00 equiv) was dissolved in THF (2 mL), the mixture was cooled to −78 °C and a 2.2 M solution of *n*-BuLi in hexane (1.32 mL, 2.92 mmol, 2.10 equiv) was added. The mixture was stirred for 20 min at −78 °C then was added dropwise to the cerium(III) chloride white suspension at −78 °C.

The red/brown slurry was stirred for 1 h then compound **9** (774 mg, 1.39 mmol) in THF (1 mL) was added dropwise (over 30 min). The mixture was stirred at −78 °C for 4 h then quenched with water (5 mL) and allowed to warm up to RT. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 10 mL), the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (90:10 PE/EtOAc) to yield product **23** (four diastereomers: 478 mg, 62%) as a colorless oil.

Mixture of diastereomers is described below:

IR (thin film): 3495, 2955, 1744, 1713, 1628 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71–5.67 (m, 0.4H), 5.63–5.58 (m, 0.6H), 5.12–5.03 (m, 0.6H), 5.03–4.99 (m, 0.4H), 4.23–4.14 (m, 2H), 4.00–3.85 (m, 1H), 3.63–3.52 (m, 2H), 2.86–2.80 (m, 0.6H), 2.79–2.73 (m, 0.4H), 2.46–2.34 (m, 1H), 2.32–2.22 (m, 1H), 2.23–2.12 (m, 1H), 1.83–1.69 (m, 2H), 1.68–1.57 (m, 2H), 1.54–1.40 (m, 1H), 1.37–1.24 (m, 6H), 1.14–1.04 (m, 3H), 1.04–0.94 (m, 9H), 0.95–0.82 (m, 9H), 0.71–0.63 (m, 6H), 0.12–0.03 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.43, 167.71, 149.24, 126.48, 79.27, 74.31, 72.57, 61.26, 51.76, 49.30, 34.66, 29.47, 28.59, 26.05, 18.19, 14.25, 11.32, 6.97, 5.19, -4.15, -4.43.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for 579.3508, found: 579.3485.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyl-3-oxo-8-(5'-oxocyclopent-1'-en-1'-yl)nonanoate 25

A solution of **23** (384 mg, 0.69 mmol) in THF (3 mL) in a high-density polyethylene vessel was cooled to 0 °C and pyridine (1.12 mL, 13.8 mmol, 20 equiv) was added. The mixture was stirred for 10 min followed by addition of HF.pyridine (0.62 mL, 69 mmol, 10 equiv).

The reaction was stirred at 0 °C for 1 h then was quenched by careful addition of a saturated aqueous solution of sodium bicarbonate (5 mL) and allowed to warm up to RT. The layers were separated and the aqueous layer was extracted with EtOAc (5 x 10 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuum to give the crude diol (275 mg) as a colorless oil. The crude product was used in the next step without further purification.

To a solution of diol (20 mg, 0.045 mmol) in CH_2Cl_2 (1 mL) was added activated manganese(II) oxide (80 mg, 0.90 mmol, 20 equiv) and the reaction was stirred at RT for 3 h. The mixture was filtered through a short pad of celite to furnish product **25** (two diastereomers: 17 mg, 89%, *dr* = 1:1) as a thick colorless oil.

Mixture of diastereomers is described below:

IR (thin film) 2931, 1743, 1690, 1265 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (q, J = 2.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.91–3.84 (m, 1H), 3.56 (s, 1H), 3.55 (s, 1H), 2.86–2.76 (m, 1H), 2.62–2.55 (m, 2H), 2.48–2.43 (m, 2H), 1.88–1.76 (m, 1H), 1.75–1.69 (m, 1H), 1.51–1.45 (m, 1H), 1.44 (s, 3H), 1.44 (s, 3H), 1.34–1.30 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 7.1 Hz, 1.5H), 1.05 (d, J = 7.1 Hz, 1.5H), 0.89 (s, 5H), 0.88 (s, 4H) 0.06 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 205.6, 167.6, 157.8, 149.9, 73.7, 72.2, 61.3, 51.7, 49.5, 37.0, 35.6, 30.5, 28.9, 27.0, 26.2, 26.0, 18.2, 14.3, 12.1, -4.2, -4.4.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 463.2486, found: 463.2465.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-chloro-4-methyl-3-oxo-8-(5'-oxocyclopent-1'-en-1'-yl)nonanoate 26

N-Chlorosuccinimide (54 mg, 0.40 mmol, 3.0 equiv) was dissolved in CH_2Cl_2 (1 mL) at 0 °C and dimethyl sulfide (31 μL, 0.43 mmol, 3.2 equiv) was added dropwise. The white suspension was stirred at 0 °C for an additional 15 min before dropwise addition of compound **25** (59 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL). The reaction was left to stir at 0 °C for 2 h then was quenched by addition of brine (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with brine (3 × 15 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography (40:60:1 PE/Et_2O/Et_3N) to afford chloro product **26** (two diastereomers: 54 mg, 89%, *dr* = 1:1) as a yellow oil.

Mixture of diastereomers is described below:

IR (thin film) 1713, 1705, 910, 734 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (t, *J* = 2.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 1H), 3.92–3.85 (m, 1H) 3.59–3.52 (m, 2H), 2.82–2.73 (m, 1H), 2.62–2.54 (m, 2H), 2.53–2.46 (m, 2H), 2.37–2.11 (m, 1H), 2.10–1.87 (m, 1H), 1.79 (s, 1,5H), 1.78 (s, 1.5H), 1.51–1.31 (m, 2H), 1.29–1.24 (m, 3H), 1.07 (d, *J* = 7.1 Hz, 1.5H), 1.03 (d, *J* = 7.0 Hz, 1.5H), 0.89 (s, 9H), 0.08–0.03 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.62, 205.54, 167.51, 161.74, 148.54, 77.36, 73.15, 71.21, 61.28, 51.61, 49.50, 49.47, 37.55, 36.68, 30.83, 30.04, 26.02, 25.69, 18.19, 14.28, 12.25, -4.20, -4.48.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 481.2147, found: 481.2126.

Ethyl (6*R*,7*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-6,10-dimethyl-1,5-dioxo-1,2,3,3a,4,5,6,7,8,9-decahydrocyclopenta[9]annulene-4-carboxylate 12

Chloro compound **26** (9.5 mg, 0.021 mmol) was dissolved in dry DMF (5 mL) and caesium carbonate (7.0 mg, 0.021 mmol, 1.0 equiv) was added in one portion to the mixture. The reaction was left to stir at RT for 2 h then was diluted with Et_2O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with a saturated aqueous solution of lithium chloride (2 × 15 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (80:20 PE/Et_2O) to afford the nine-membered ring **12** (four diastereomers: 5.6 mg, 64%) as a thick yellow oil.

Mixture of diastereomers is described below:

IR (thin film) 1713, 1705, 910, 734 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 4.27–4.16 (m, 4H), 4.02–3.95 (m, 1H), 3.76–3.69 (m, 2H), 3.64–3.56 (m, 1H), 3.40 (d, *J* = 11.3 Hz, 1H), 3.16 (s, 1H), 2.70 (dq, *J* = 9.4, 7.1 Hz, 1H), 2.40–2.25 (m, 6H), 2.18 (s, 4H), 2.12–1.96 (m, 4H), 1.91 (ddq, *J* = 13.9, 8.1, 3.8 Hz, 2H), 1.76–1.61 (m, 2H), 1.43 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 4H), 1.27–1.23 (m, 5H), 1.11 (d, *J* = 6.8 Hz, 4H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.08–0.04 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.15, 206.09, 168.52, 156.29, 132.30, 73.04, 61.86, 61.19, 52.82, 42.25, 37.19, 37.16, 34.22, 33.99, 33.55, 30.48, 25.96, 25.90, 25.42, 19.69, 19.29, 18.12, 15.25, 14.29, -4.16, -4.46.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 445.2381, found: 445.2361.

Ethyl (6*R*,7*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-6,10-dimethyl-5-oxo-1,2,3,3a,4,5,6,7,8,9-decahydrocyclopenta[9]annulene-4-carboxylate 27

Cyclononane **12** (284 mg, 0.672 mmol) and cerium(III) chloride heptahydrate (661 mg, 1.77 mmol, 2.60 equiv) were dissolved in methanol (15 mL), cooled to −78 °C and stirred for 1 h. Sodium borohydride (27 mg, 0.71 mmol, 1.0 equiv) was then added in small portions. The reaction was left to stir at −78 °C for 2 h. The crude mixture was quenched with a 1 M aqueous solution of hydrochloric acid (15 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purifed by flash chromatography (60:40 PE/Et_2O) to give allylic alcohol **27** (150 mg, 53%) as a thick colorless oil and as an inseparable mixture of 4 diastereomers.

Mixture of diastereomers is described below:

IR (thin film) 3510, 2955, 2932, 2862, 1744, 1706, 1250, 1165, 1080, 1026 cm^{-1}

^1H NMR ($CDCl_3$, 500 MHz) δ ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 – 4.67 (m, 2H), 4.23 – 4.13 (m, 3H), 3.60 (d, *J* = 11.7 Hz, 1H), 3.42 – 3.34 (m, 2H), 2.76 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.19 – 2.08 (m, 1H), 2.08 – 1.98 (m, 1H), 1.92 – 1.84 (m, 1H), 1.82 (s, 3H), 1.81 – 1.72 (m, 3H), 1.43 (s, 7H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 2H), 0.89 (s, 9H), 0.10 – 0.04 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.54, 168.88, 139.77, 139.54, 73.26, 72.82, 72.14, 61.59, 61.14, 53.19, 43.34, 43.13, 34.63, 34.16, 33.78, 30.38, 29.90, 25.94, 19.34, 18.16, 14.30, -4.08, -4.37.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 447.2537, found: 447.2516.

Ethyl (7*S*,8*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-4,8-dimethyl-1,2,4,5,6,7,8,9,10,10a-decahydro-4,9-epoxycyclopenta[9]annulene-10-carboxylate 28 and 28'

To a solution of *bis*(acetonitrile)dichloropalladium(II) (5.5 mg, 0.021 mmol, 0.30 equiv) in THF (0.7 mL) was added dropwise a mixture of allylic alcohol **27** (27 mg, 0.071 mmol) in THF (0.7 mL). The reaction was stirred at RT for 2 h then was filtered through a short pad of celite. The crude was then purified by flash chromatography (80:20 PE/Et_2O) to afford tricycle **28** (5 mg, 19%) as a colorless oil and **28'** (6 mg, 22%) as a colorless oil.

Diastereomer 28:

IR (thin film) 2924, 2855, 1728, 1458, 1259, 1065, 1026, 841 cm^{-1}.

$[\alpha]_D^{25}$ +16.7 (*c* = 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$, 500 MHz) δ 5.37–5.32 (m, 1H), 4.19 (qd, *J* = 7.1, 0.9 Hz, 3H), 3.83 (ddd, *J* = 6.5, 4.7, 1.7 Hz, 1H), 3.59 (s, 1H), 3.29 (d, *J* = 10.3 Hz, 1H), 3.22–3.13 (m, 1H), 2.37–2.22 (m, 3H), 2.06 (m, 2H), 1.93–1.83 (m,

1H), 1.67–1.54 (m, 2H), 1.38 (td, *J* = 9.5, 2.4 Hz, 1H), 1.34 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.26–1.23 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.4, 150.3, 119.8, 98.6, 77.4, 74.9, 72.5, 60.8, 54.4, 48.3, 42.8, 36.5, 32.7, 31.8, 29.7, 29.0, 26.1, 18.3, 14.4, 13.2, -4.7, -4.8.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 447.2537, found: 447.2518.

Diastereomer 28':

$[\alpha]_D^{25}$ −8.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.95–4.91 (m, 1H), 4.15–4.03 (m, 2H), 3.97 (d, *J* = 10.5 Hz, 1H), 3.59 (td, *J* = 10.0, 2.5 Hz, 1H), 3.26–3.15 (m, 1H), 2.51 (dq, *J* = 9.8, 6.9 Hz, 1H), 2.30–2.20 (m, 1H), 2.02–1.87 (m, 2H), 1.87–1.75 (m, 2H), 1.74 (d, *J* = 1.4 Hz, 4H), 1.67 (ddt, *J* = 16.1, 10.1, 3.8 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 4H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), 0.00 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.5, 152.4, 119.2, 98.5, 77.7, 74.3, 61.5, 54.3, 50.8, 44.9, 40.6, 32.9, 31.5, 29.6, 28.4, 26.0, 18.2, 14.7, 14.3, −3.8, −4.3.

Ethyl (7*S*,8*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-4,8-dimethyldodecahydro-4,9-epoxycyclopenta[9]annulene-10-carboxylate 29 and 29'

To a solution of tricycle **28** (5 mg, 0.012 mmol) in ethanol (3 mL) under inert atmosphere was added palladium on carbon. Inert atmosphere was purged, replaced with hydrogen and the reaction was stirred at RT for 2 h. The mixture was filtered through a short pad of Celite® to furnish a separable 4:1 mixture of diastereomers. The crude was then purified by flash chromatography (80:20 PE/Et_2O) to afford saturated tricycle **29** (one diastereomer: 4 mg, 80%) as a white foam.

$[\alpha]_D^{25}$ −6.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) 4.18 (qd, *J* = 7.1, 4.5 Hz, 2H), 3.79–3.71 (m, 2H), 3.41 (s, 1H), 2.55 (tt, *J* = 12.4, 8.0 Hz, 1H), 2.38–2.31 (m, 1H), 2.32–2.25 (m, 1H), 2.08–1.98 (m, 2H), 1.95–1.86 (m, 1H), 1.79–1.67 (m, 2H), 1.51 (dd, *J* = 13.8, 6.5 Hz, 1H), 1.46–1.37 (m, 3H), 1.35–1.28 (m, 1H), 1.28–1.24 (m, 3H), 1.24–1.21 (m, 1H), 1.15–1.05 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.90–0.82 (m, 1H), 0.08 (s, 3H), 0.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.4, 97.3, 74.2, 73.8, 60.8, 50.9, 47.6, 47.5, 35.1, 34.4, 32.1, 30.5, 29.9, 29.5, 28.9, 26.1, 25.8, 21.3, 18.2, 14.4, 12.9, −4.7, −5.1.

Compound **29'** (5 mg) was synthesized according to the procedure for compound **29** (two diastereomers: 5 mg, 98 %, *dr* = 4:1).

IR (thin film) 2924, 2855, 1728, 1458, 1250, 1049, 1026, 841, 772 cm^{-1}.

$[\alpha]_D^{25}$ +18.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24–4.16 (m, 2H), 3.36 (ddd, *J* = 10.8, 9.3, 3.2 Hz, 1H), 2.57 (d, *J* = 12.8 Hz, 1H), 2.49–2.39 (m, 1H), 2.33 (td, *J* = 10.7, 7.7 Hz, 1H), 1.99–1.88 (m, 3H), 1.88–1.82 (m, 1H), 1.77–1.65 (m, 2H), 1.51 (dd, *J* = 7.7, 3.5 Hz, 1H), 1.43 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28–1.19 (m, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.9, 97.2, 77.3, 74.3, 61.3, 54.3, 48.2, 47.5, 37.5, 33.5, 32.7, 32.5, 30.6, 29.7, 28.1, 25.9, 18.1, 14.4, 14.2, −3.8, −4.5.

HRMS (ESI) for *m/z* $[M + H]^+$ calcd for 449.2694, found: 449.2676.

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Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References

(1) New address: A. Audic, Syneos Health, 2500 rue Einstein, Québec, QC, Canada.
(2) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3258.
(3) Kobayakawa, Y.; Mori, Y.; Okajima, H.; Terada, Y.; Nakada, M. *Org. Lett.* **2012**, *14*, 2086.
(4) (a) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889. (b) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485. (c) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221. (d) Clarke, P. A.; Cridland, A. P.; Rolla, G. A.; Iqbal, M.; Bainbridge, N. P.; Whitwood, A. C.; Wilson, C. *J. Org. Chem.* **2009**, *74*, 7812. (e) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985. (f) Toueg, J.; Prunet, J. *Org. Lett.* **2008**, *10*, 45. (g) Audic, A.; Oriez, R.; Prunet, J. *Tetrahedron* **2021**, *79*, 131843.
(5) (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560. (b) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, *61*, 353. (c) Iqbal, M.; Black, R. J. G.; Winn, J.; Reeder, A. T.; Blake, A. J.; Clarke, P. A. *Org. Biomol. Chem.* **2011**, *9*, 5062.
(6) Crimmins, M. T.; Christie, H. M.; Hughes, C. O. *Org. Synth.* **2011**, *88*, 364.
(7) Larsen, M. A.; Hennessy, E. T.; Deem, M. C.; Lam, Y.-h.; Sauri, J.; Sather, A. C. *J. Am. Chem. Soc.* **2020**, *142*, 726.
(8) Crimmins, M. T.; Knight, J. D.; Williams, P. S.; Zhang, Y. *Org. Lett.* **2014**, *16*, 2458.
(9) Liniger, M.; Neuhaus, C.; Hofmann, T.; Fransioli-Ignazio, L.; Jordi, M; Drueckes, P.; Trappe, J.; Fabbro, D.; Altmann, K.-H. *ACS Med. Chem. Lett.* **2011**, *2*, 22.
(10) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088.
(11) Ito, H.; Takenaka, Y.; Fukunishi, S.; Iguchi, K. *Synthesis* **2005**, 3035.
(12) Cornil, J.; Gonnard, L.; Bensoussan, C.; Serra-Muns, A.; Gnamm, C.; Commandeur, C.; Commandeur, M.; Reymond, S.; Guerinot, A.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 761.
(13) Aponick, A.; Li, C. Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669.
(14) Kawai, N.; Lagrange, J.-M.; Uenishi, J. *Eur. J. Org. Chem.* **2007**, 2808.
(15) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531.
(16) Mathieson, M. PhD Thesis, University of Glasgow, **2014**.
(17) Wasnaire, P.; de Merode, T.; Markó, I. E. *Chem. Comm.* **2007**, *99*, 4755.

Supporting information – NMR spectra

Synthesis of the CDF ring system of hexacyclinic acid

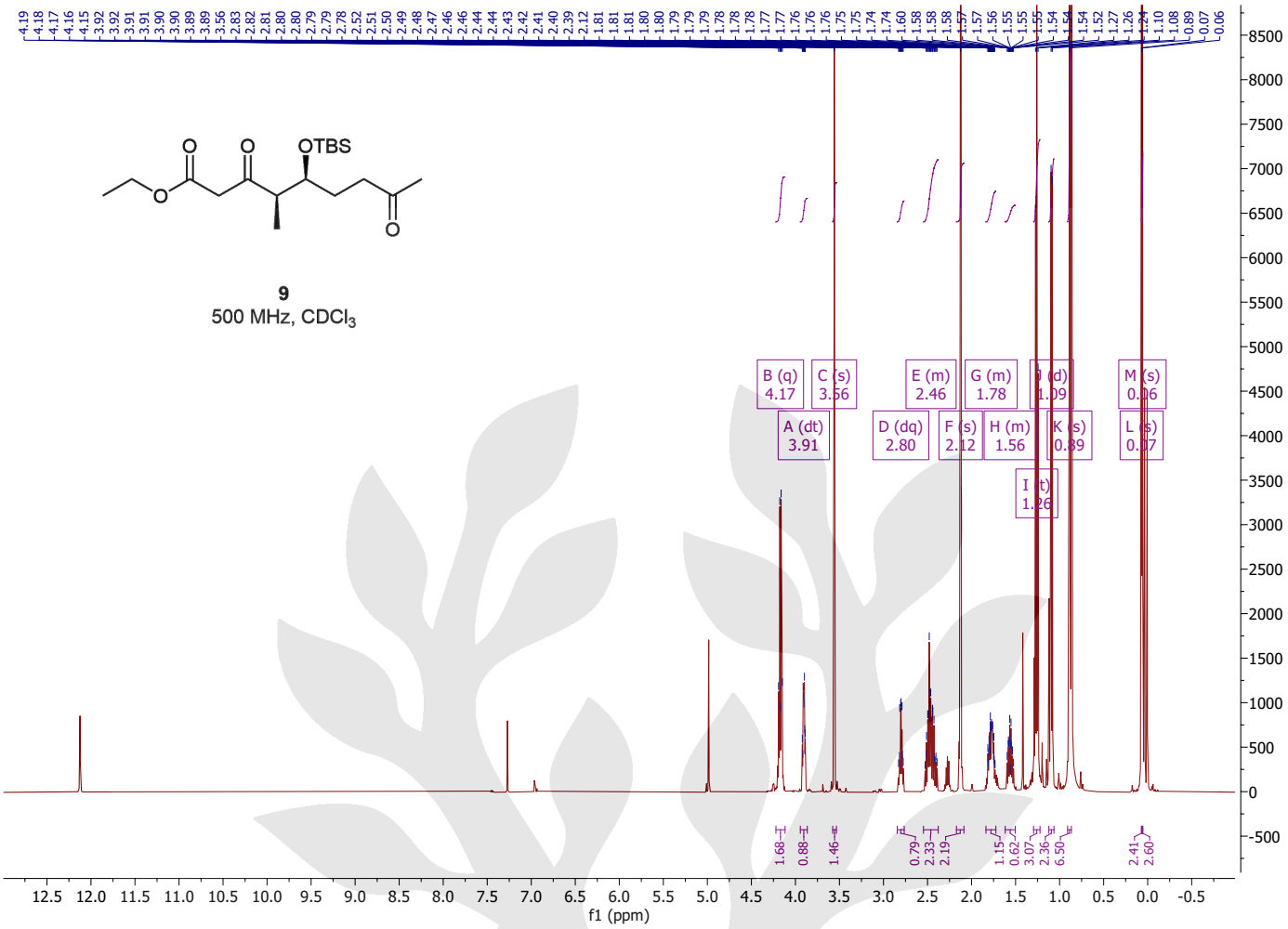
Alexandre Audic,[a,b] *Joëlle Prunet**[a]

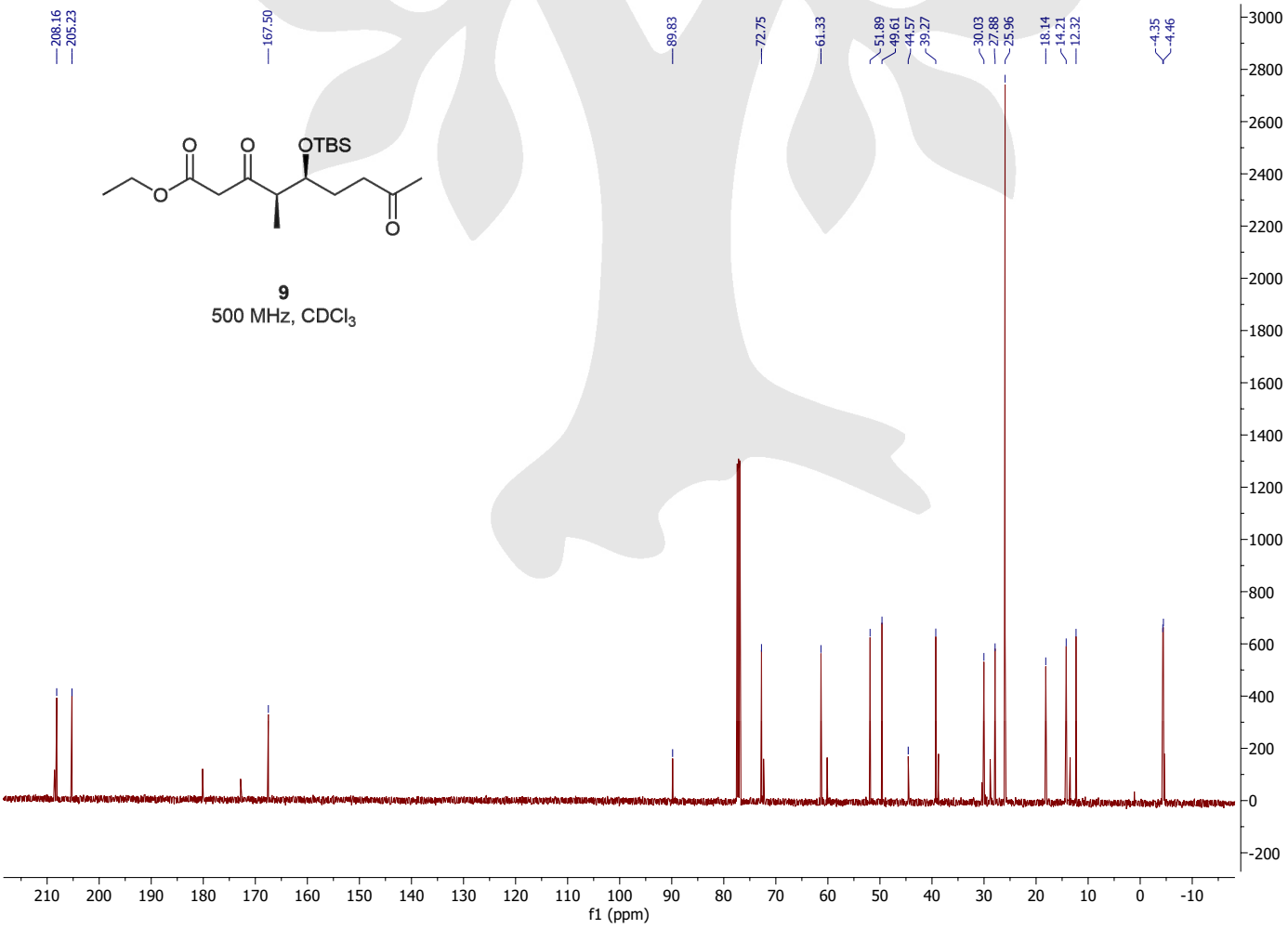
[a] *School of Chemistry, University of Glasgow, Joseph Black Building, Glasgow G12 8QQ, UK.*

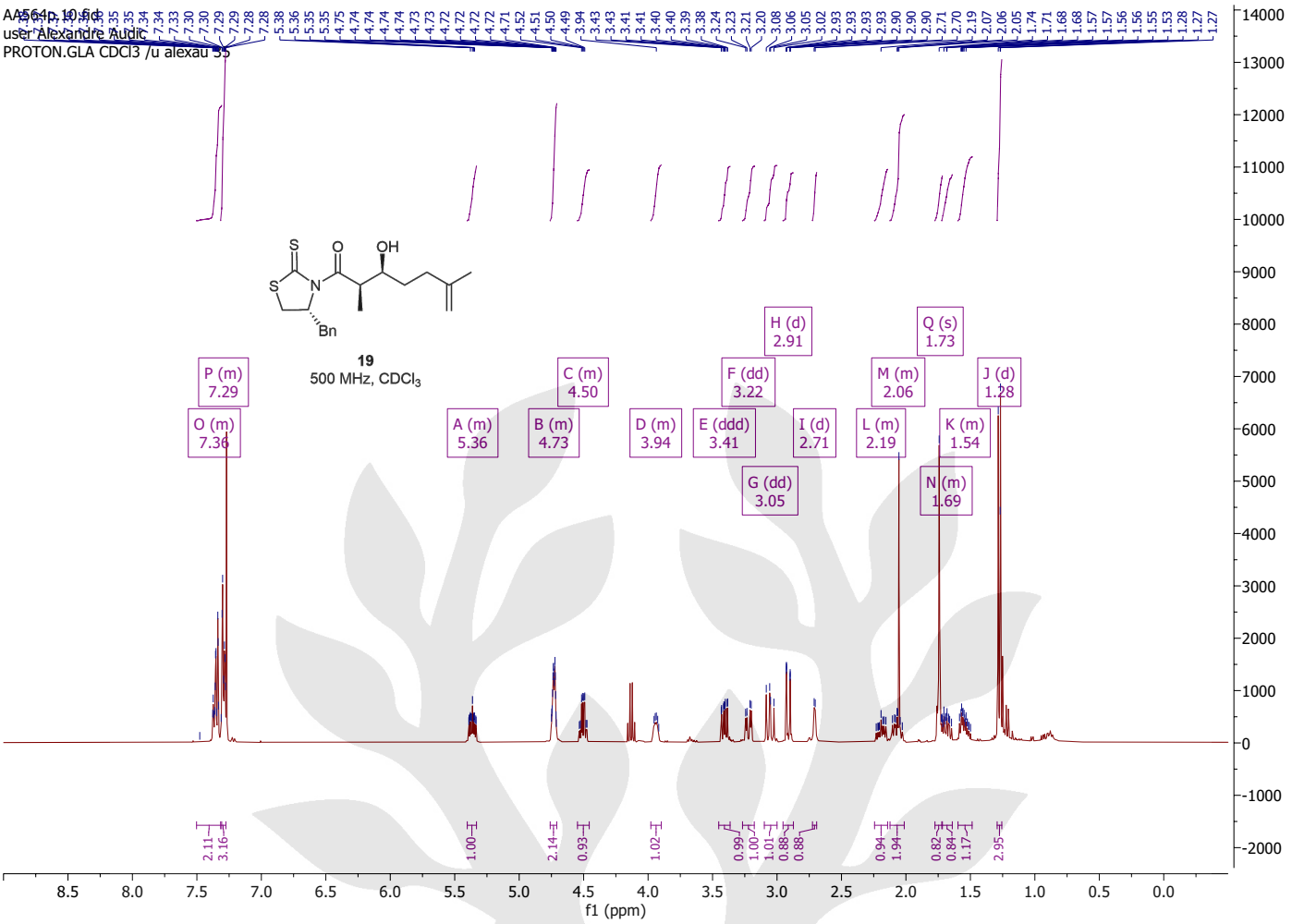
[b] *New address: Syneos Health, 2500 rue Einstein, Québec, QC, Canada.*

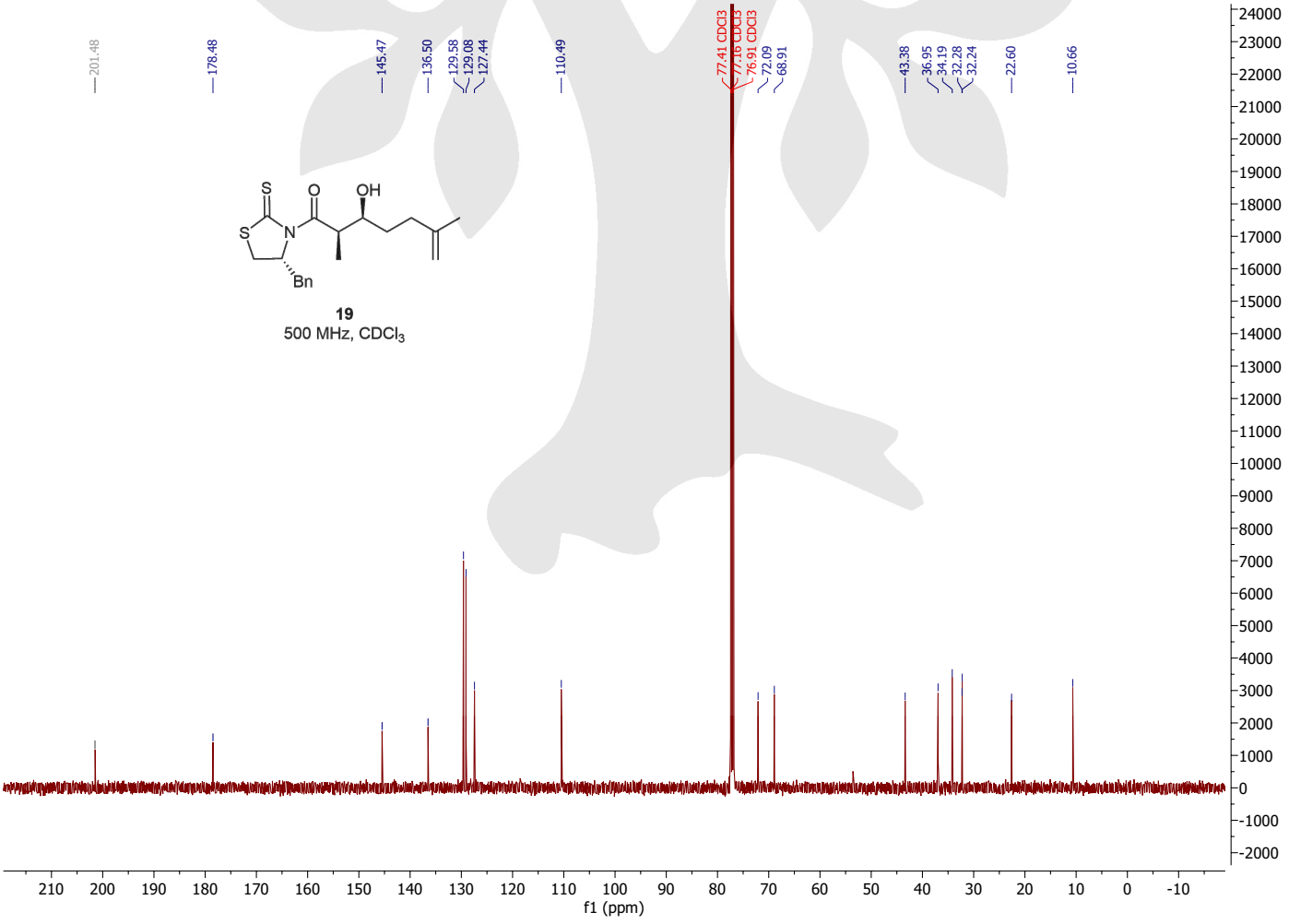
Corresponding author e-mail: joelle.prunet@glasgow.ac.uk

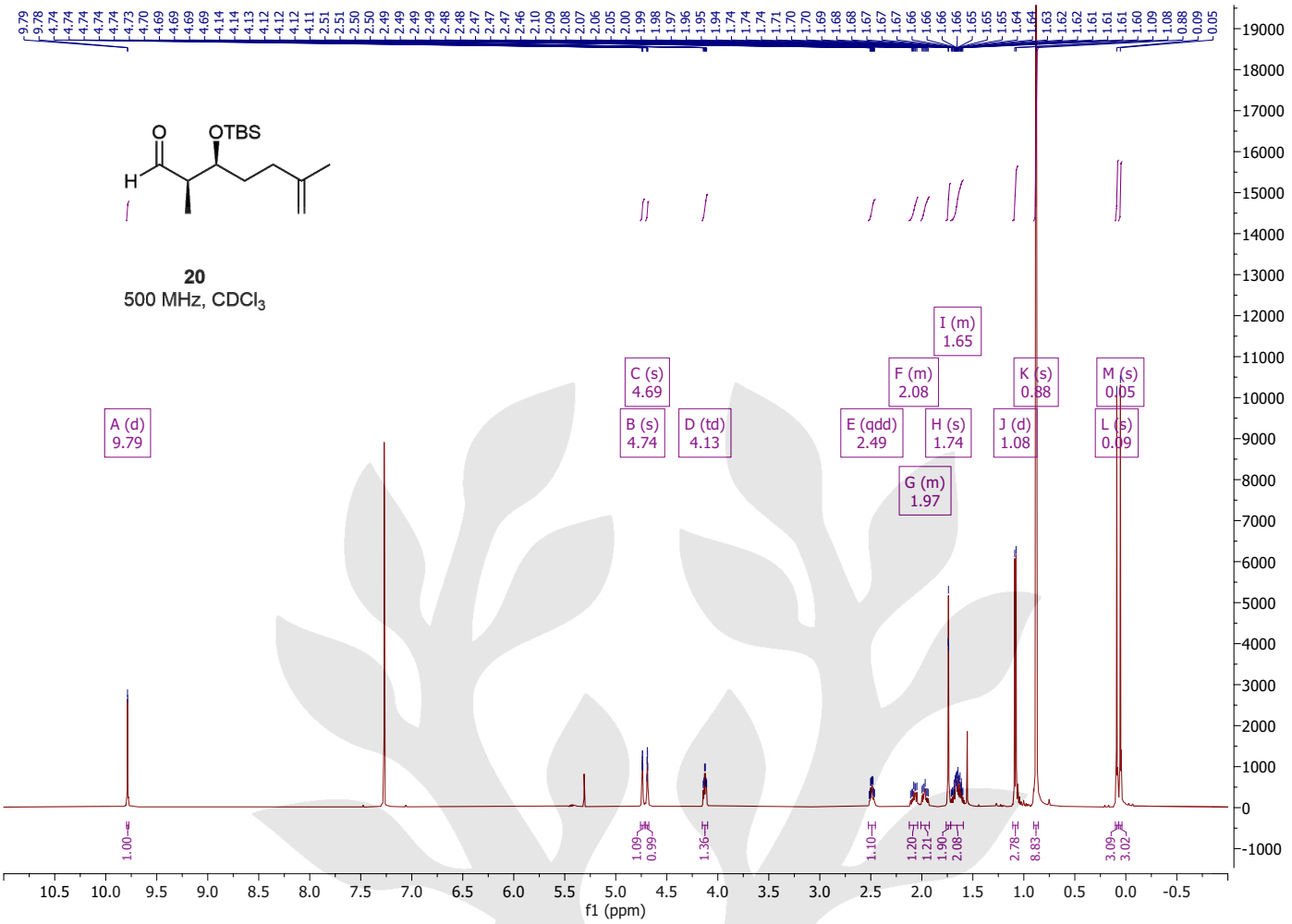
NMR spectra of important products.

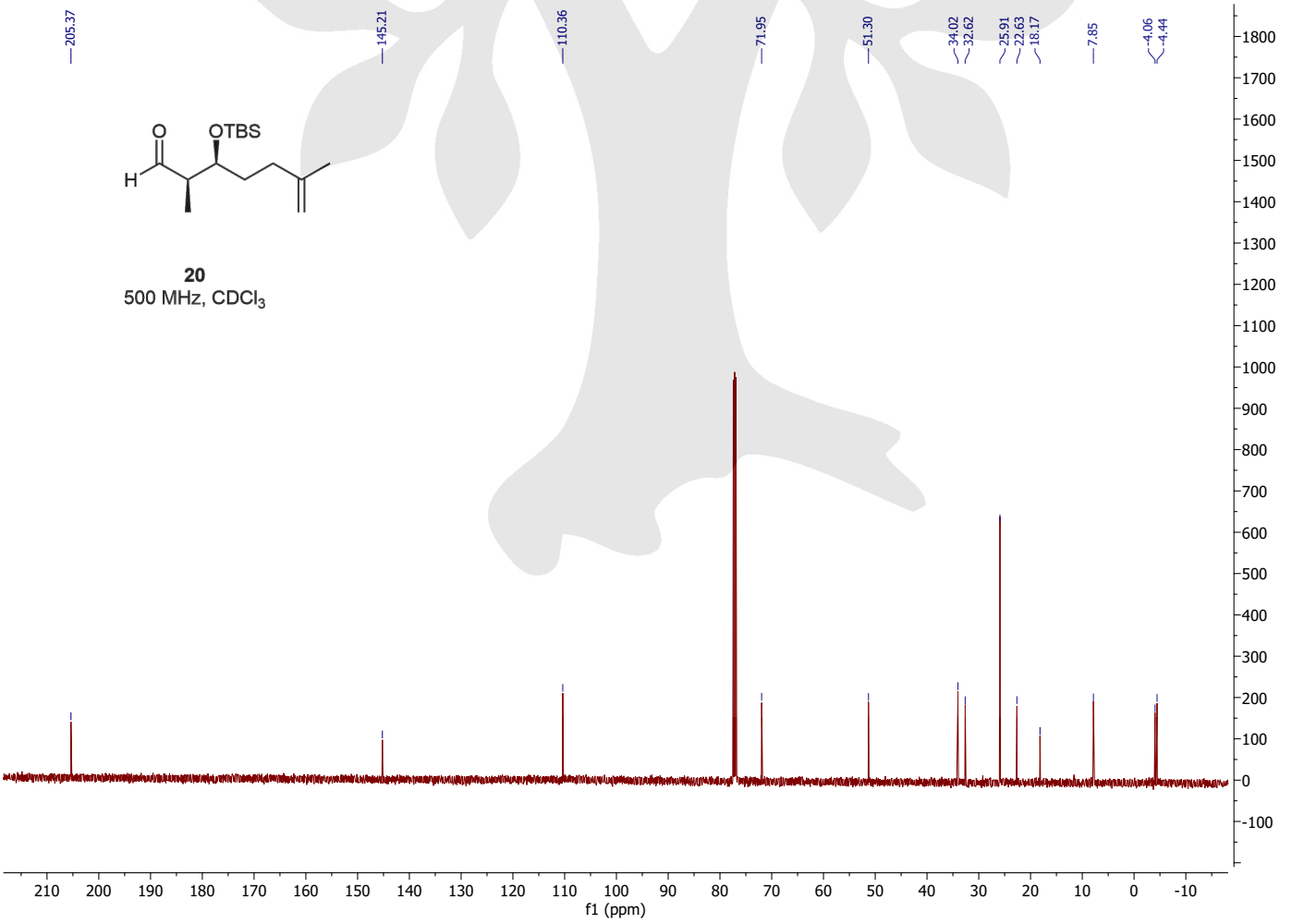


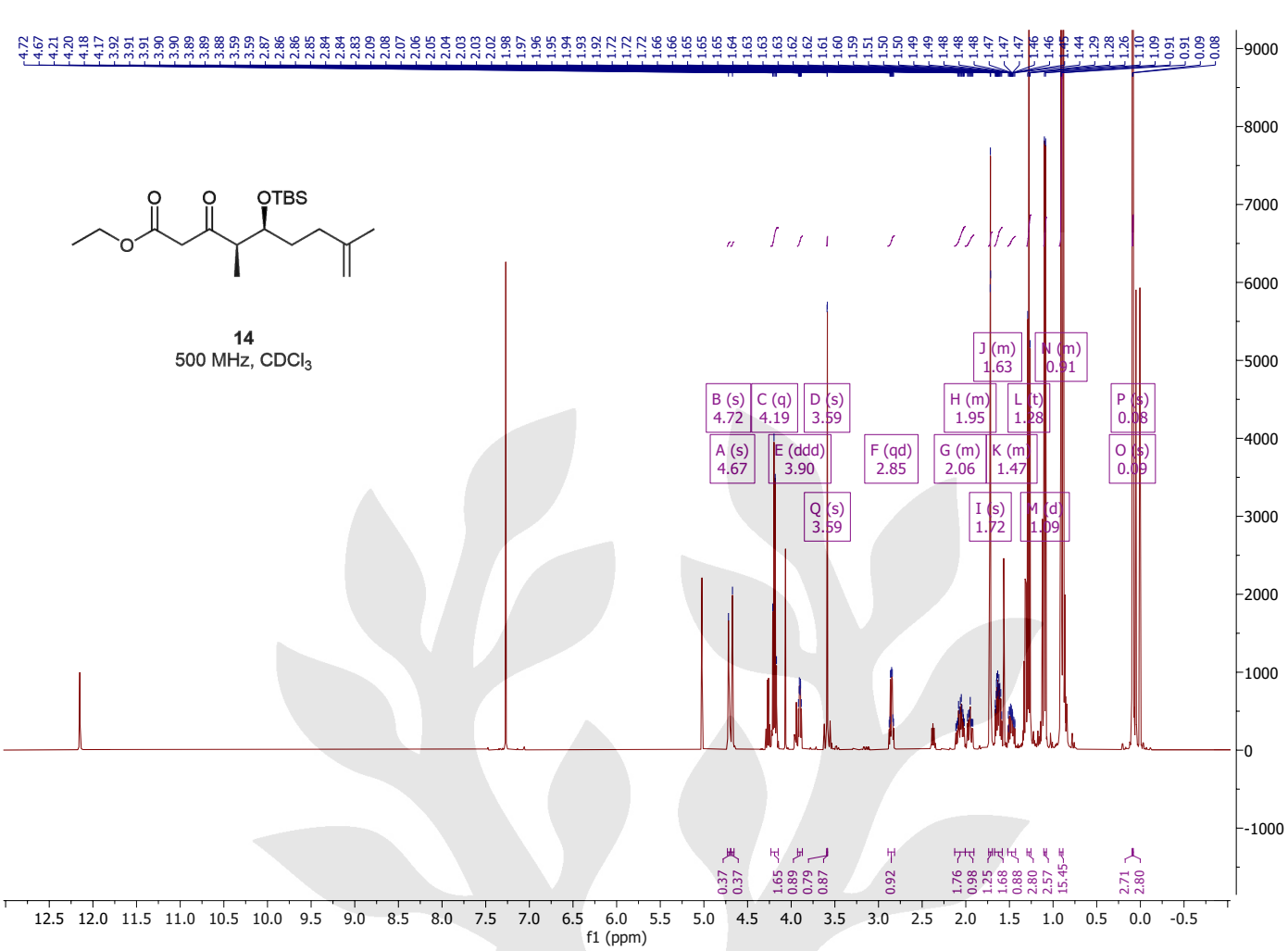


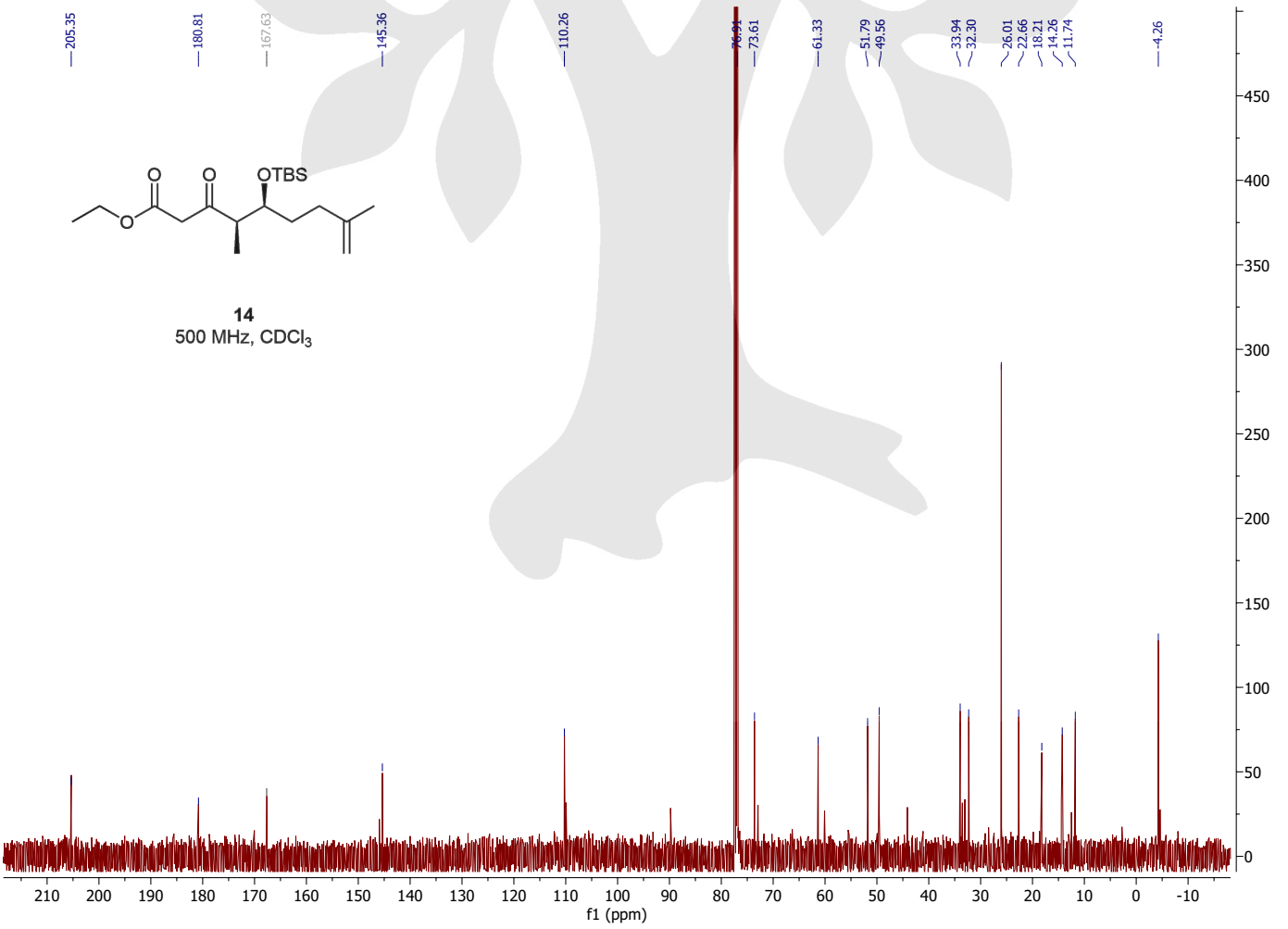


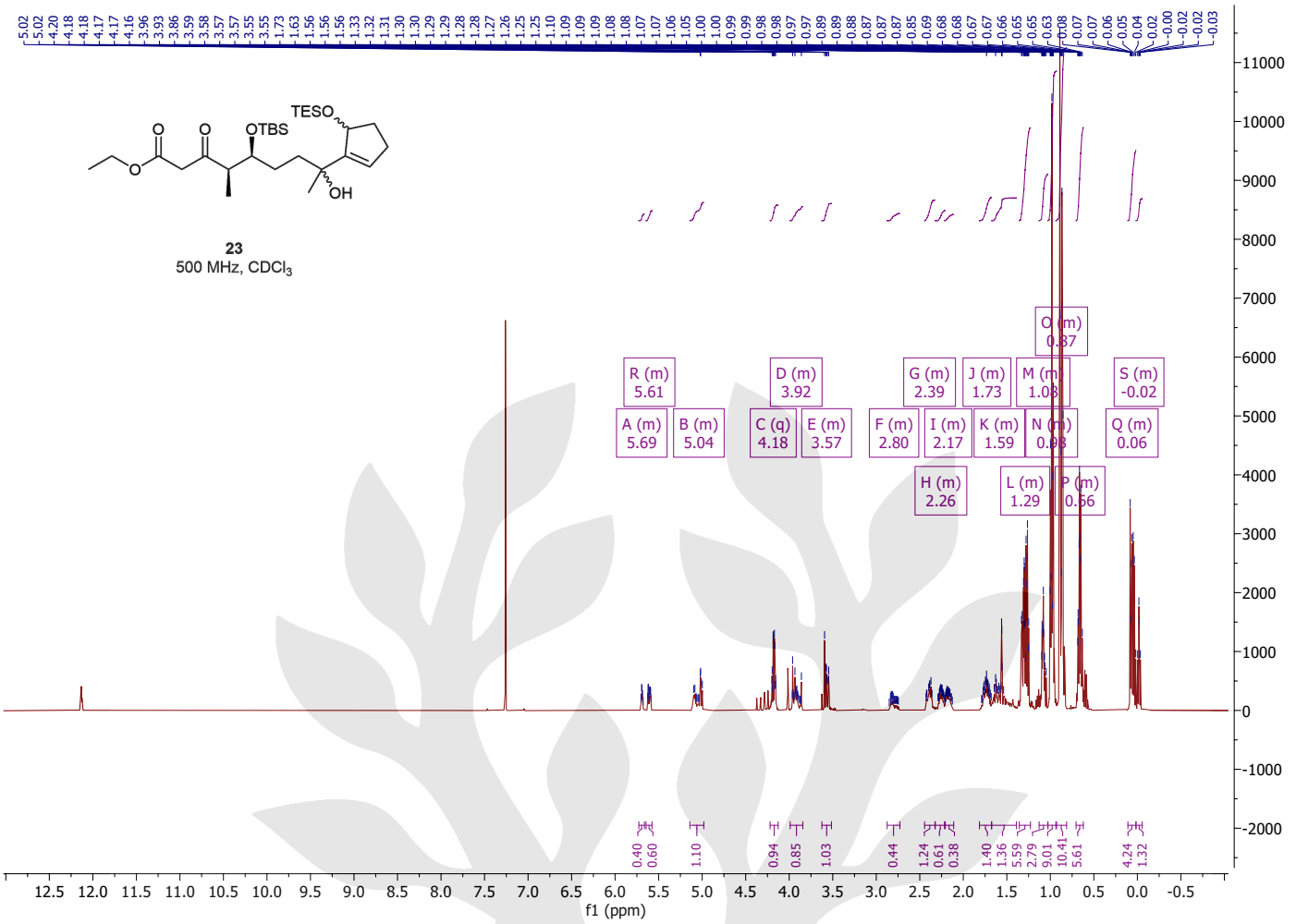


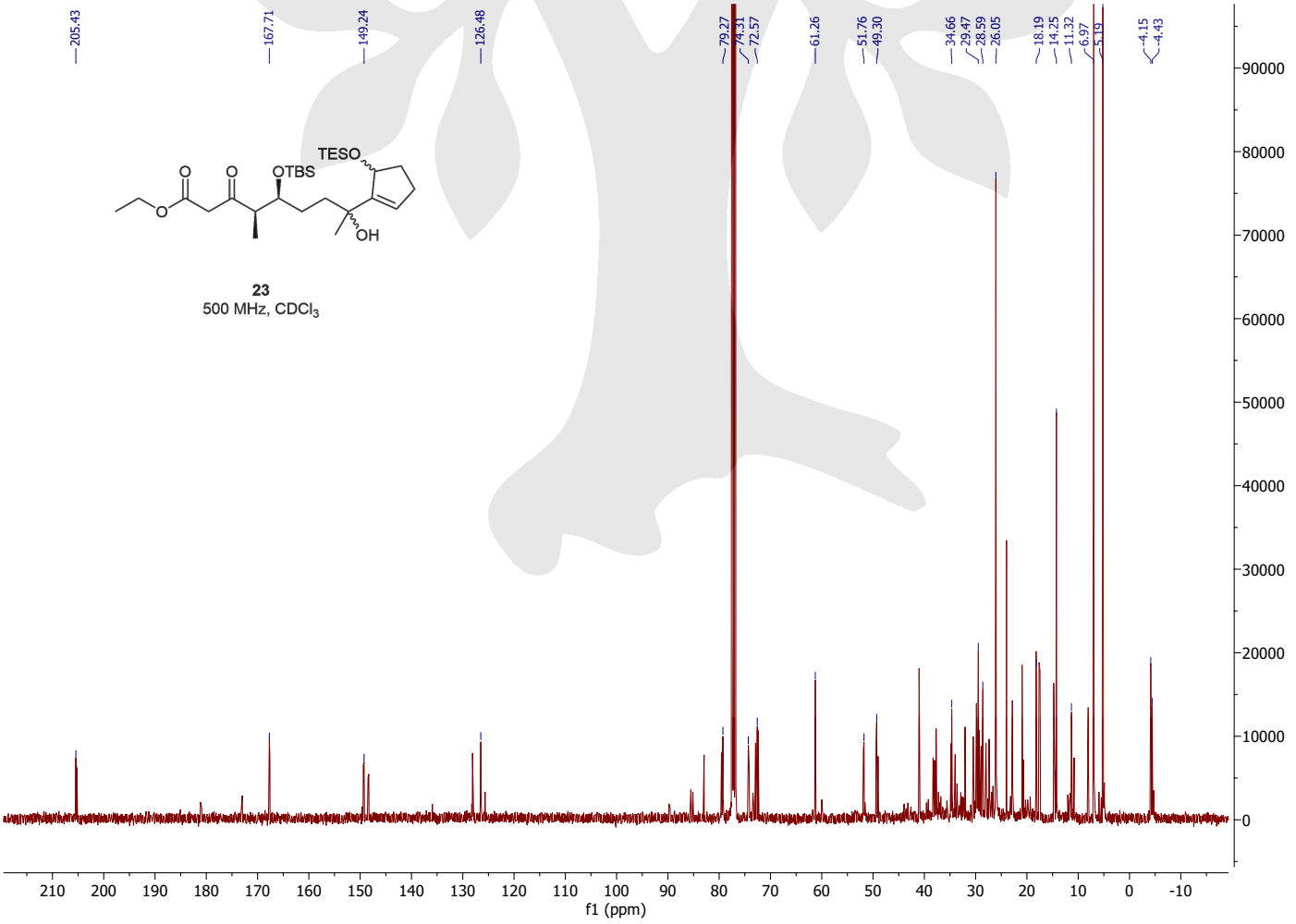


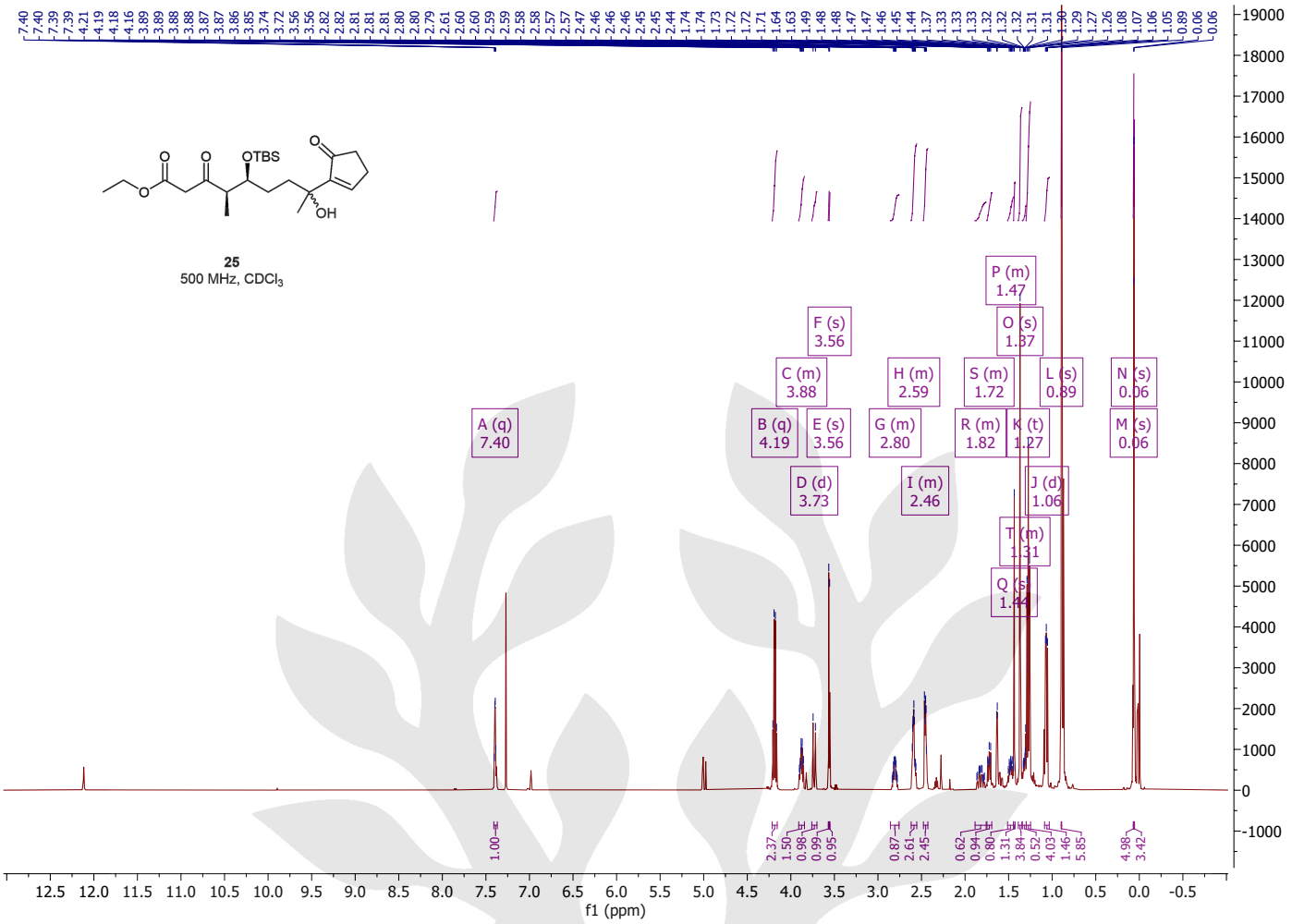


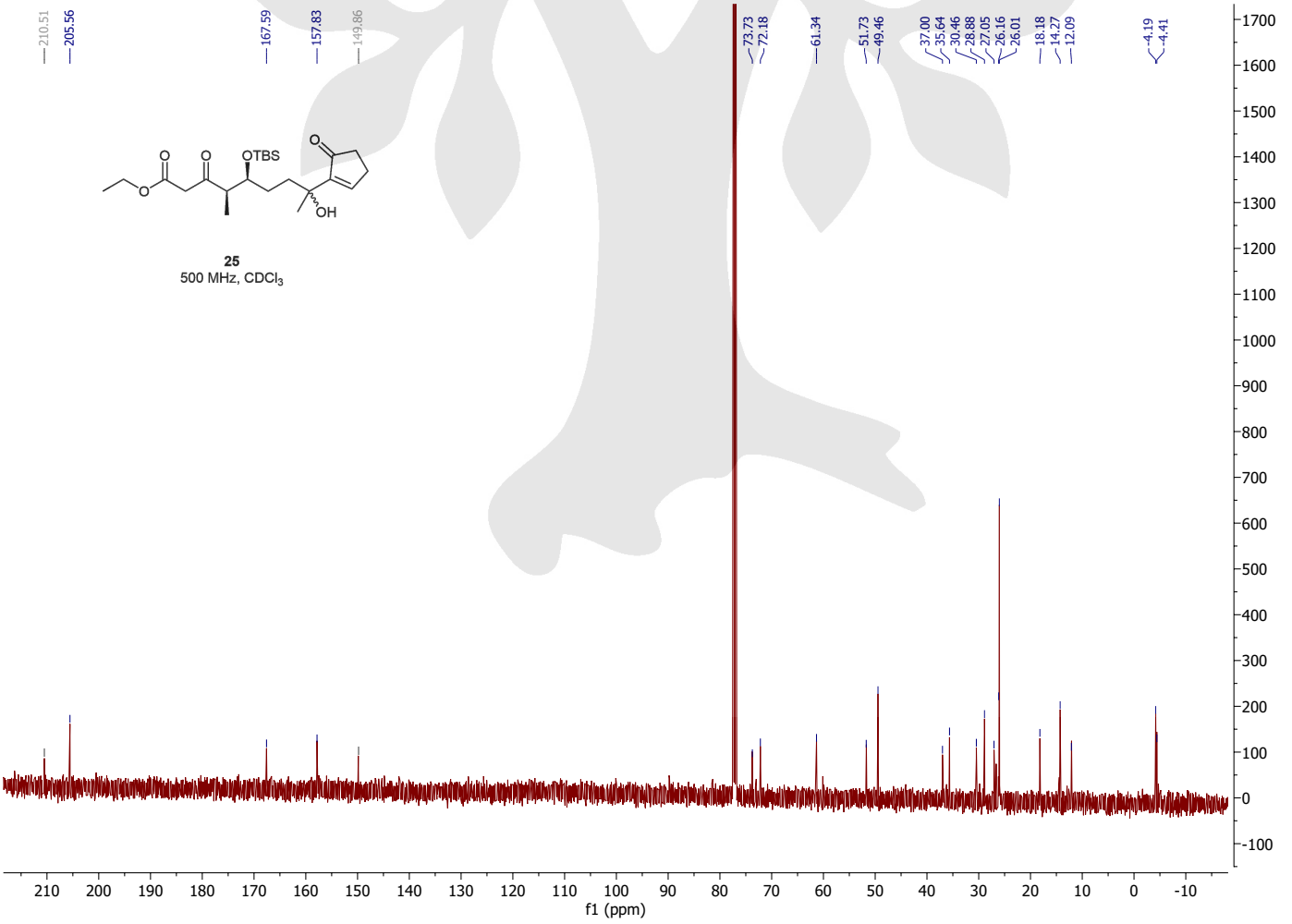


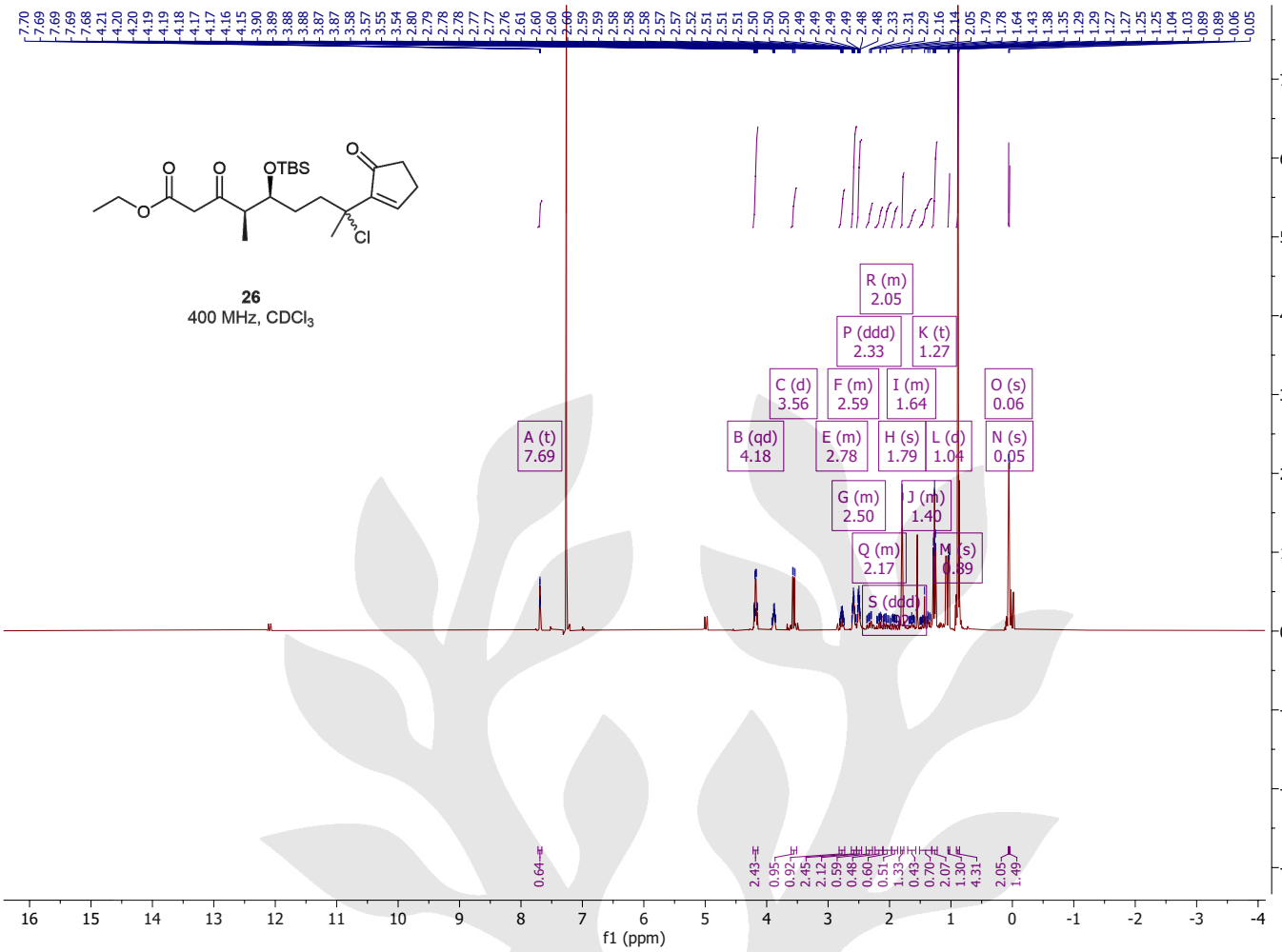


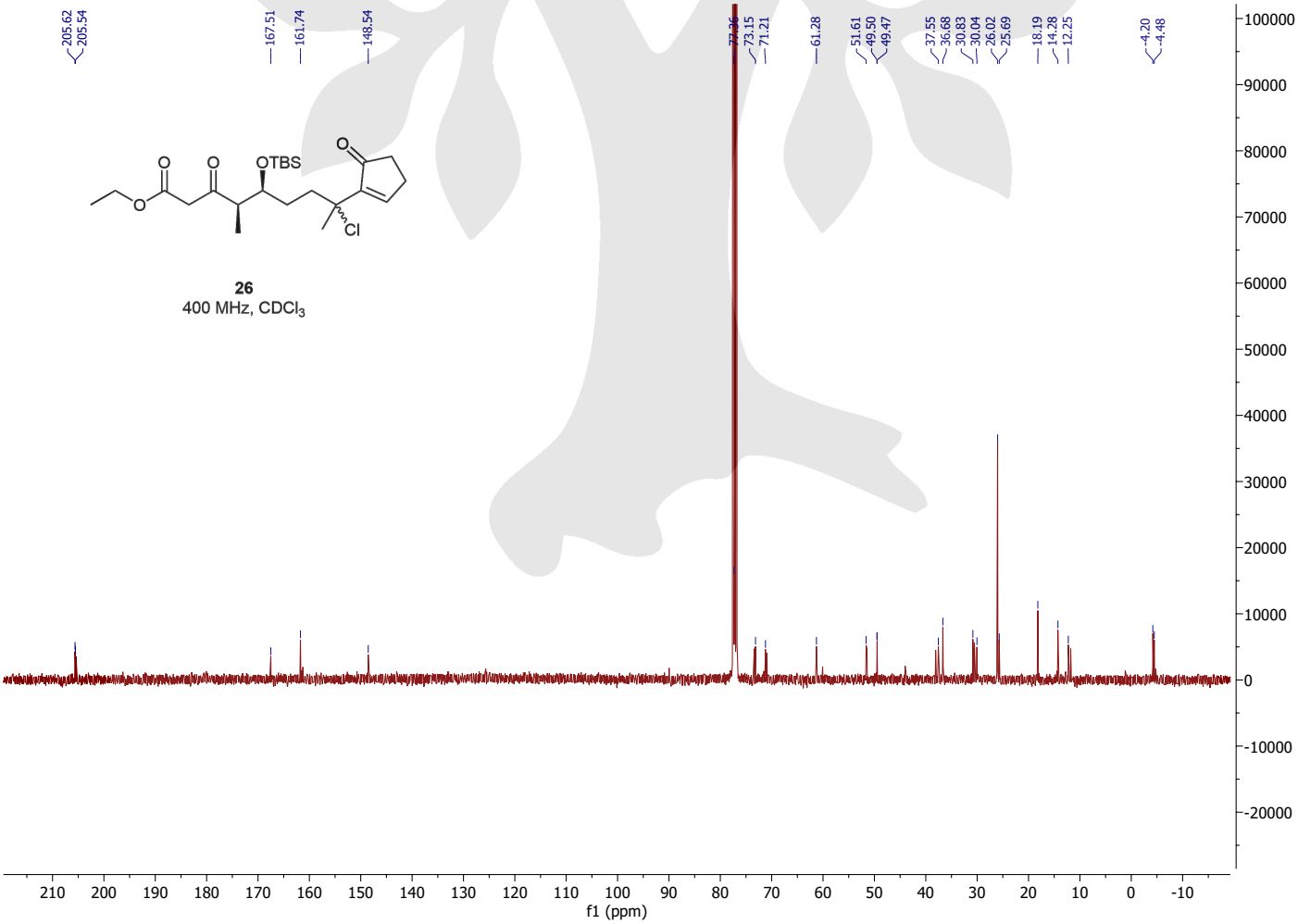


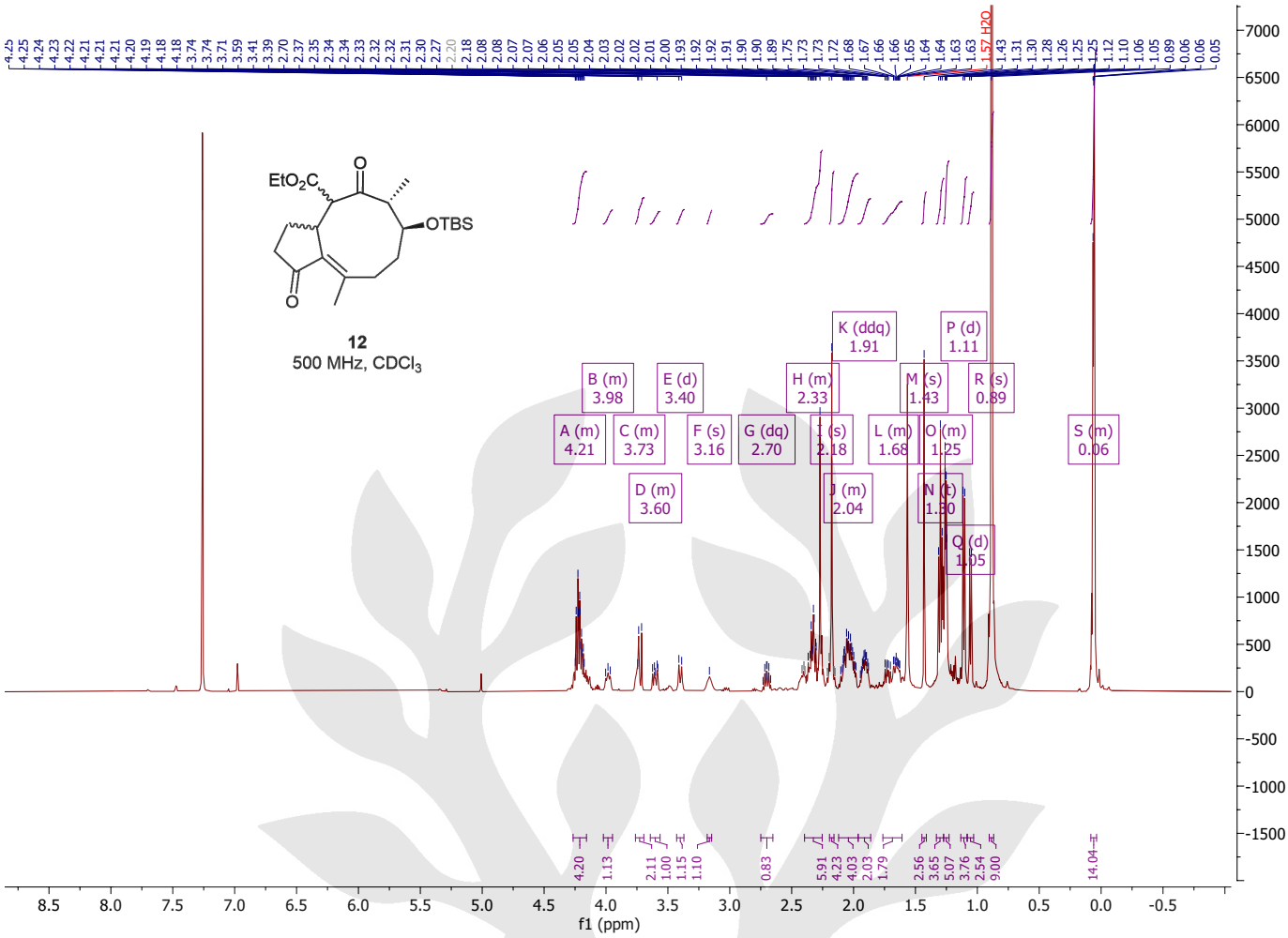


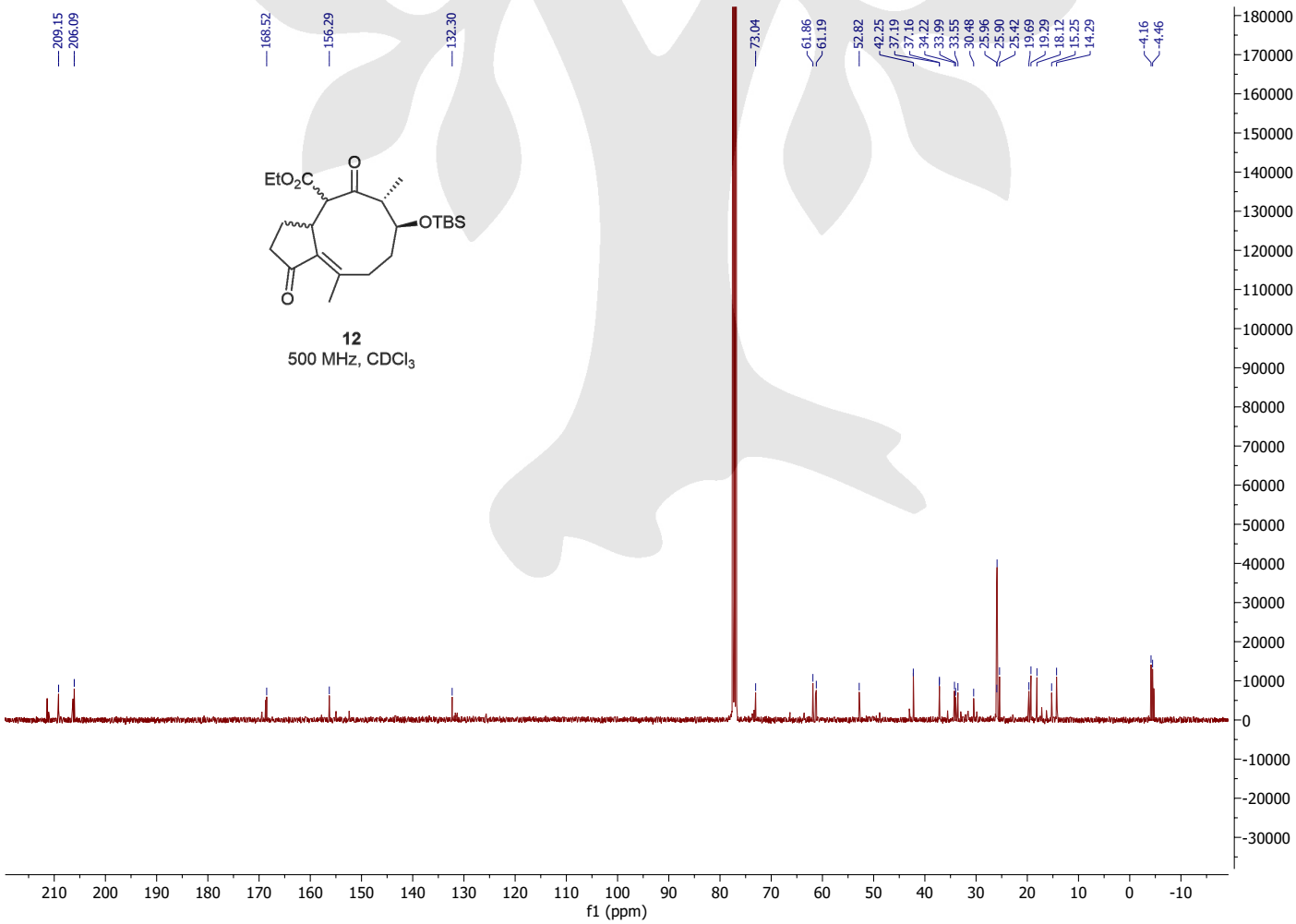


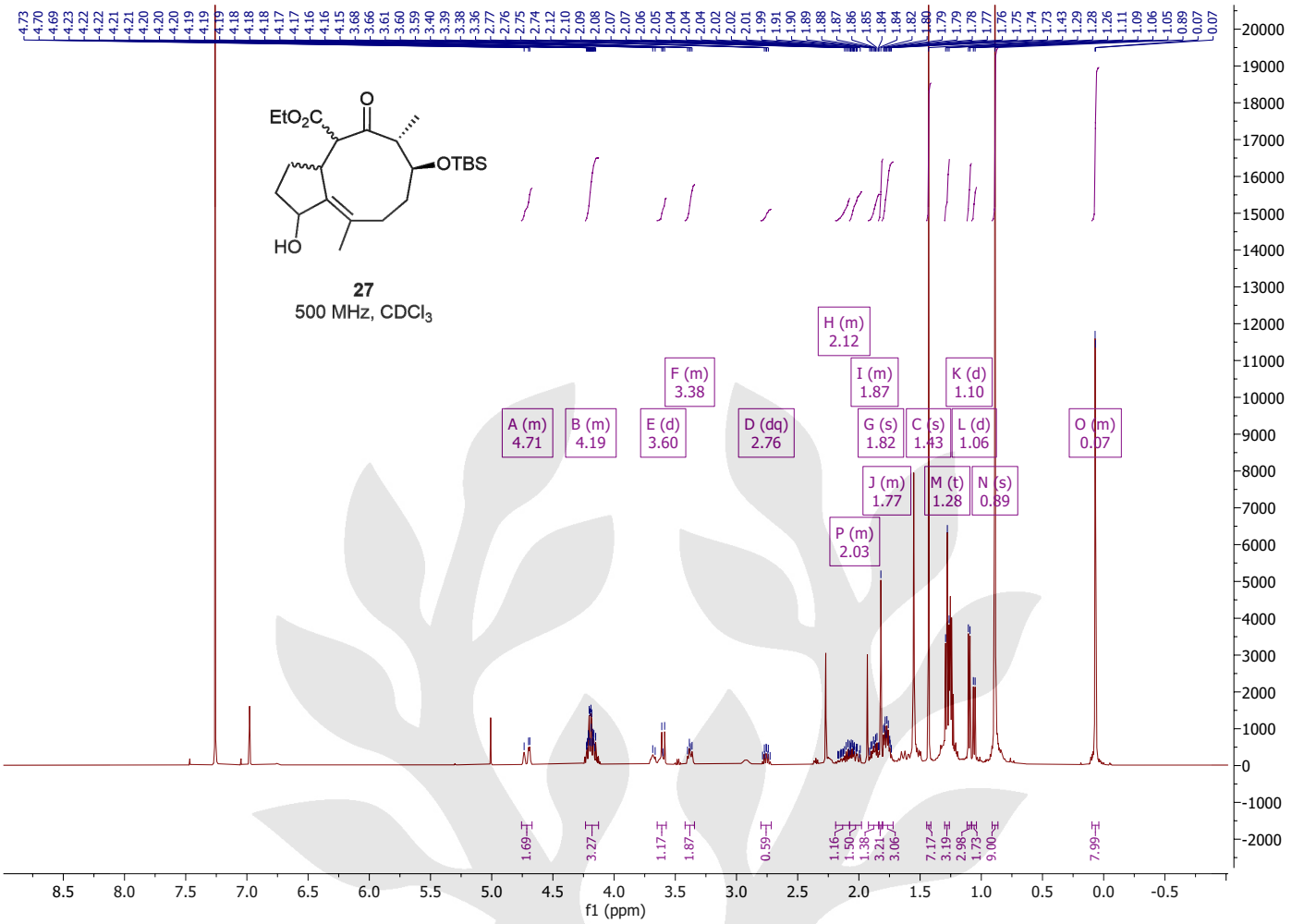


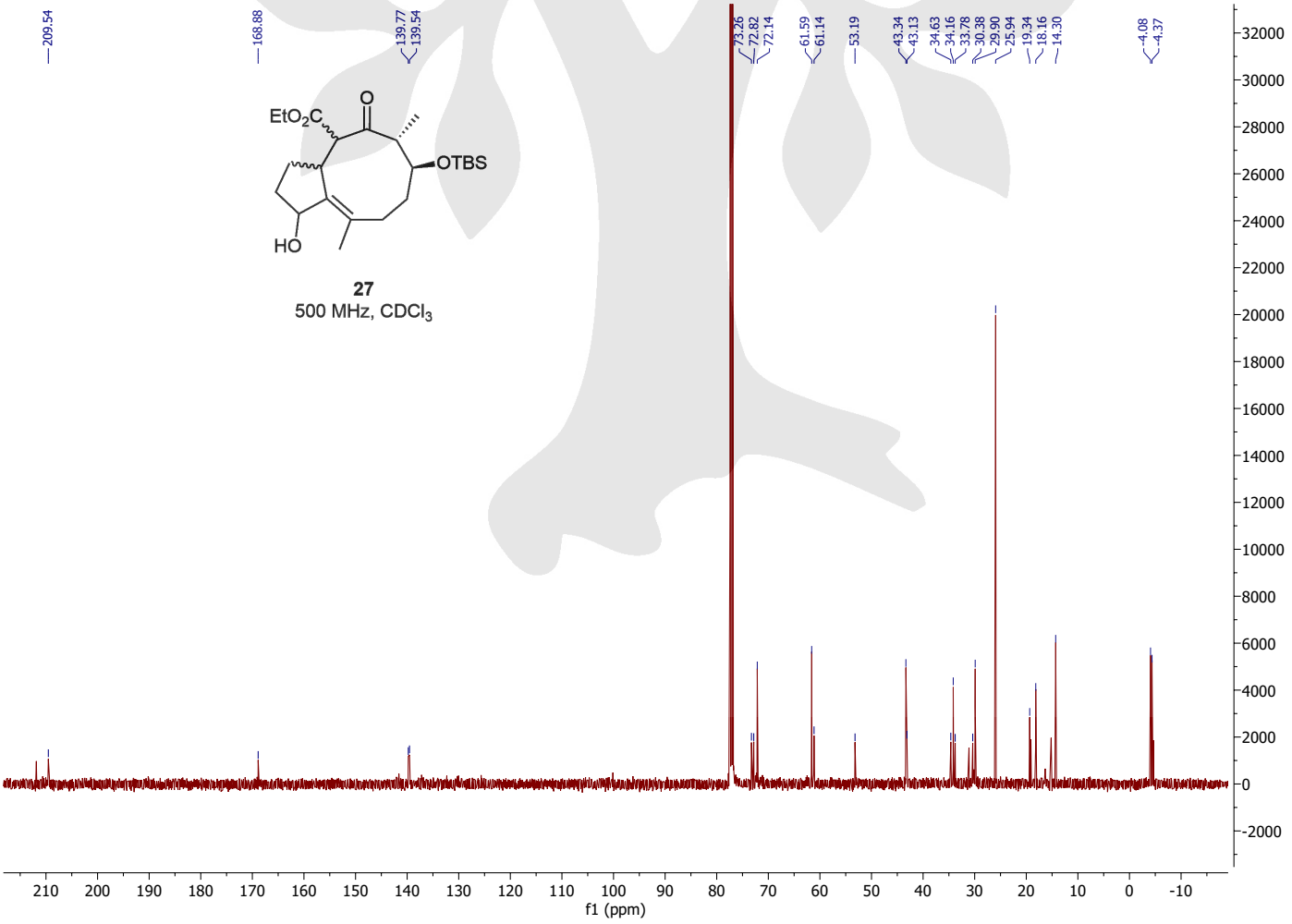


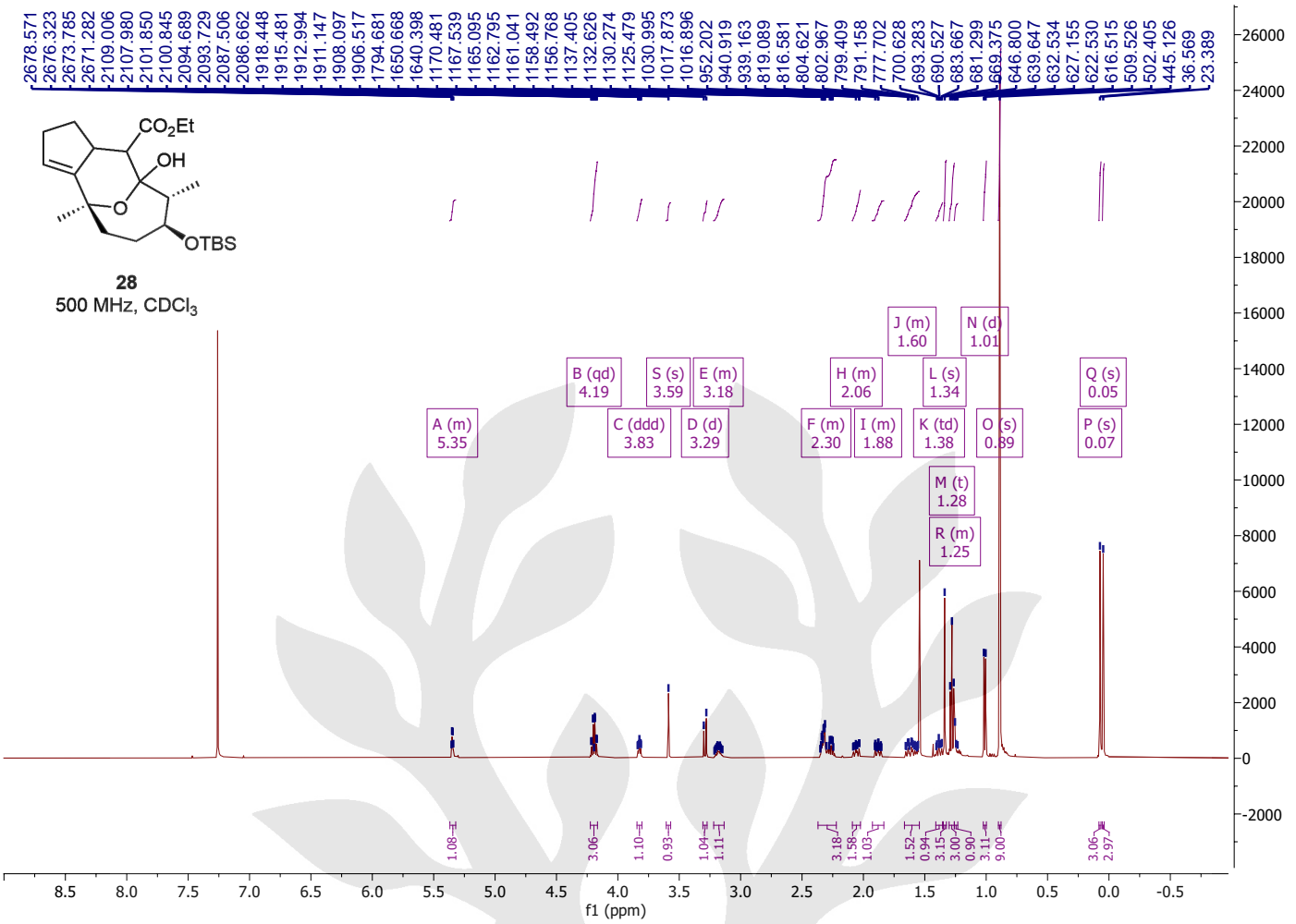


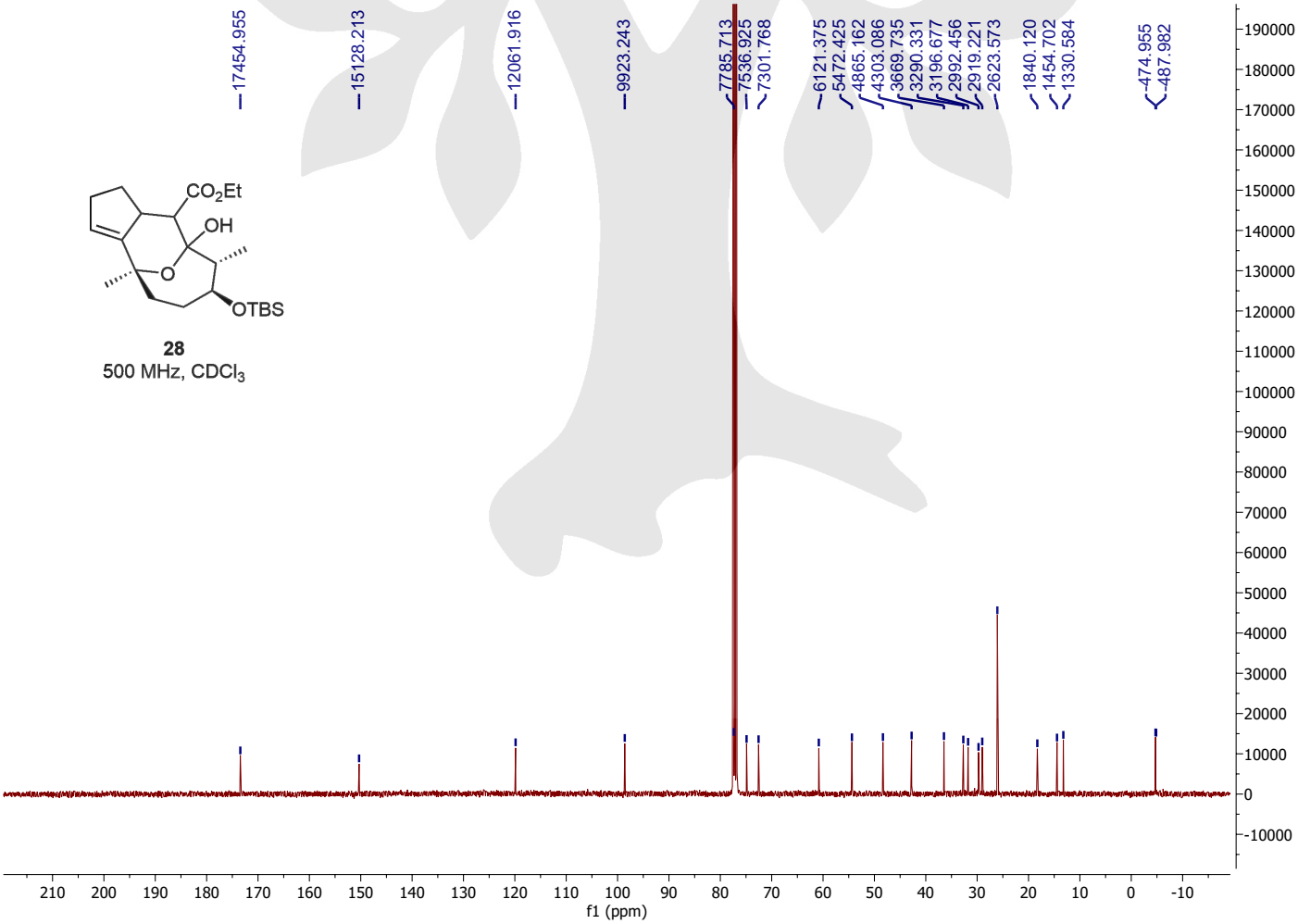


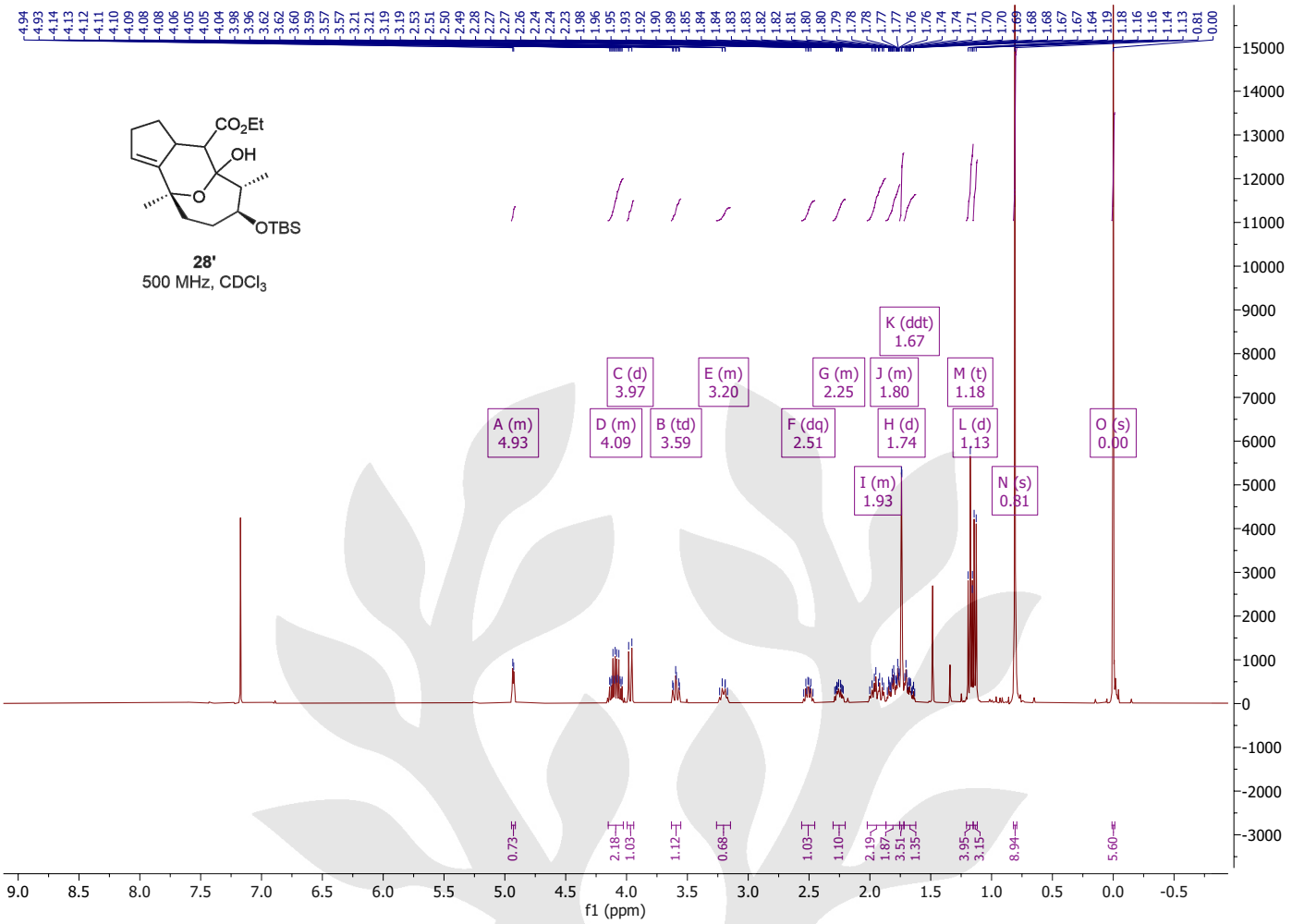


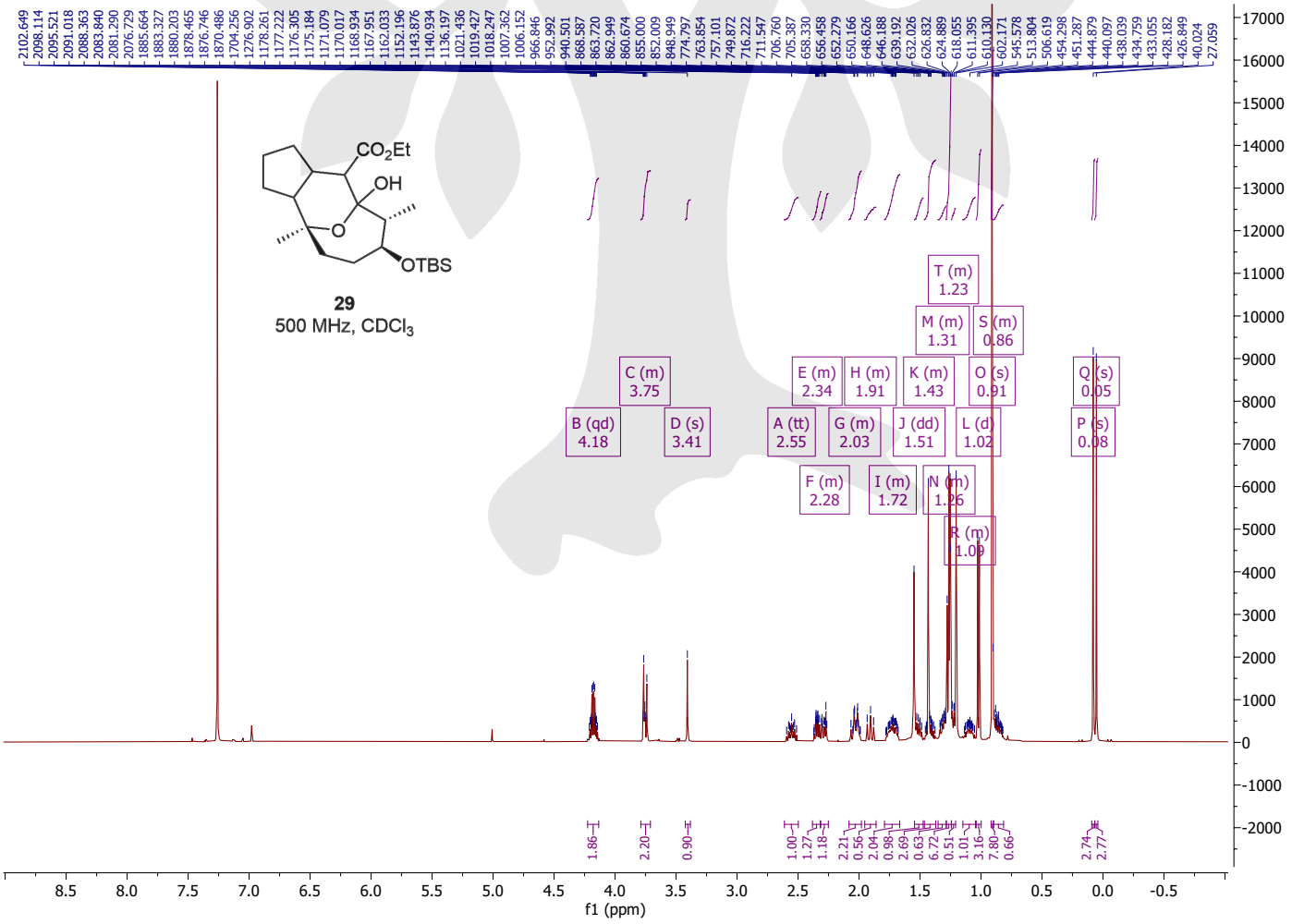


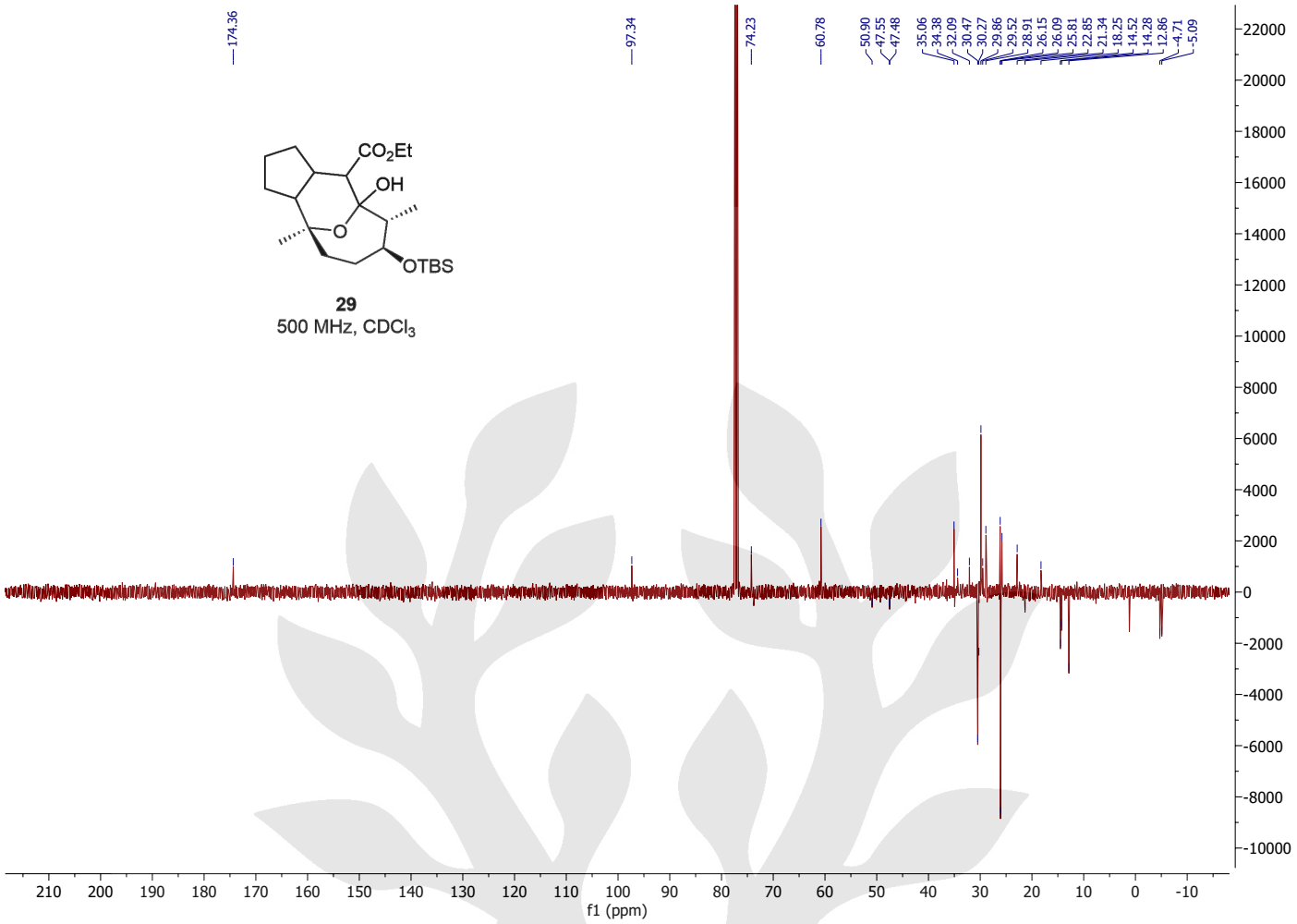












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500 MHz, $CDCl_3$