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Cleavage of a C–C bond is a diversifying process in the biogenesis of seco-terpenoids that has produced fascinating molecular structures. Leonuketal is an 8,9-seco-labdane terpenoid with a unique tetracyclic structure, owing to a C–C bond cleavage event in its biosynthesis. We report the first total synthesis of leonuketal, featuring an unusual Shapiro-type reaction as part of an enabling auxiliary ring strategy, and a novel Au-catalysed spirocyclization of a β -keto(enol)lactone.

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Total Synthesis of (±)-Leonuketal

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ABSTRACT: Cleavage of a C–C bond is a diversifying process in the biogenesis of *seco*-terpenoids that has produced fascinating molecular structures. Leonuketal is an 8,9-*seco*-labdane terpenoid with a unique tetracyclic structure, owing to a C–C bond cleavage event in its biosynthesis. We report the first total synthesis of leonuketal, featuring an unusual Shapiro-type reaction as part of an enabling auxiliary ring strategy, and a novel Au-catalysed spirocyclisation of a β -keto(enol)lactone.

Cyclization and oxidation processes are recognized as the principal drivers of complexity generation in the biosynthesis of terpenoid natural products.^{1–9} However, a third mode of complexity generation involving the *cleavage* of a C–C bond is operative in the biogenesis of *seco*-terpenoids (Figure 1A). Such processes lead to increased chemical diversity in a cluster of related secondary metabolites by alteration of the parent carbon skeleton. Moreover, C–C bond cleavage is typically oxidative, and reactions facilitated by the increase in oxidation state—such as ketalisation or aldol processes—lead to further skeletal rearrangement.

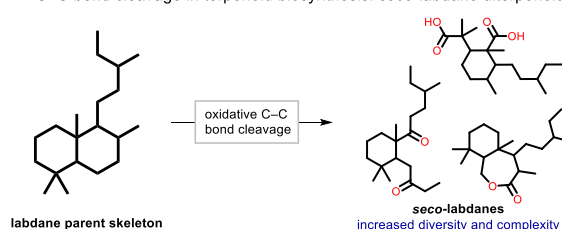
Leonuketal (**1**) is a tetracyclic 8,9-*seco*-labdane terpenoid marked by high stereochemical and architectural complexity—chiefly owing to a C–C bond cleavage event in its biosynthesis (Figure 1B).¹⁰ Peng and co-workers isolated **1** from Chinese liverwort (*Leonurus japonicus*) in 2015 and reported significant vasorelaxant activity (EC₅₀ = 2.32 mM) against KCl-induced contraction of rat aorta.¹⁰ Leonuketal (**1**), and other *seco*-labdanes such as saudin (**2**), pallambin A (**3**), and pallamolide B (**4**), exemplify the structural complexity enabled by biosynthetic C–C bond cleavage (Figure 1B).^{11,12} This characteristic—alongside important bioactivities—has rendered *seco*-labdanes attractive synthetic targets and formidable testing grounds for new methodology.^{13–21} We were prompted to investigate the total synthesis of leonuketal (**1**), a previously unmet goal, because of the challenge presented by its daunting molecular structure.

Previously, we reported the synthesis of the bridged oxabicyclic core of leonuketal (**1**), as lactone **5**, by an efficient Diels-Alder reductive-cyclisation sequence (Figure 1C).²² This strategy relied on a proposed epimerization of the C3 carbon for advancement of **5** to **1**, however, a comprehensive screen of bases failed to identify conditions for the planned transformation.

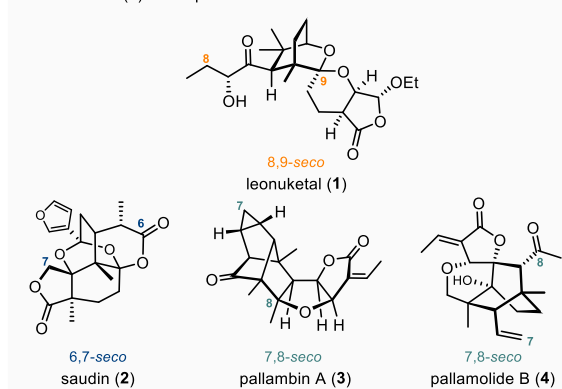
Our revised retrosynthetic strategy was targeted towards late stage spiroketal **7**, which we recognized would provide access to **1** by incorporation of the C3 hydroxybutanone chain and elaboration of the lactone moiety (Figure 1D). We planned to assemble the spirocyclic core of **7** by Au-mediated cyclisation

of alkyne **8**, which could be accessed from halide **9** through appendage of the lactone moiety by alkylation.²³

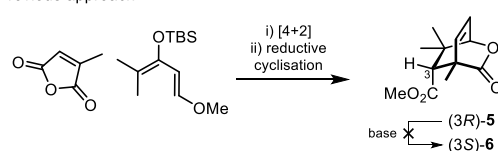
A. C–C bond cleavage in terpenoid biosynthesis: *seco*-labdane diterpenoids



B. Leonuketal (**1**) and representative *seco*-labdanes



C. Previous approach



D. This work

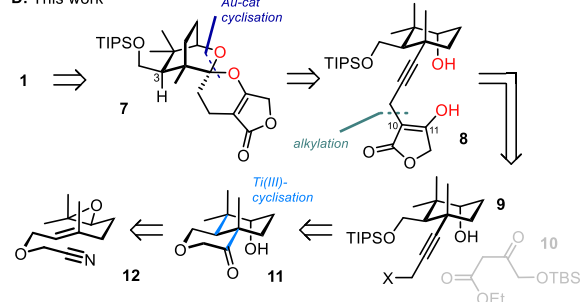
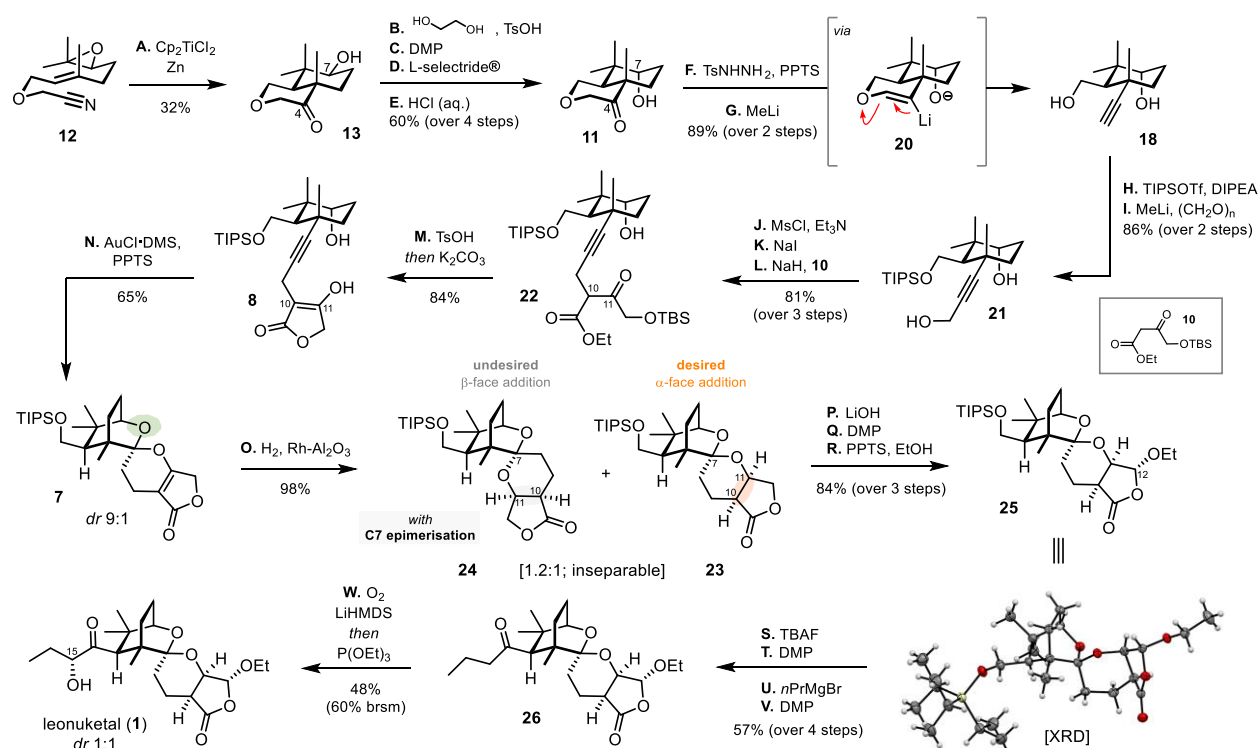


Figure 1. Background and retrosynthetic analysis; NB: numbering in 1B based on parent labdane skeleton.

Scheme 1. Total synthesis of (±)-leonuketal



Reagents and conditions: a) Cp_2TiCl_2 (2.2 eq), Zn (4.6 eq), THF, 60 °C, 1 h then aq. KH_2PO_4 , rt, 30 min, 32%; b) ethylene glycol (15 eq), TsOH (5 mol %), benzene, reflux, 4 h; c) DMP (1.2 eq), pyridine (2.5 eq), CH_2Cl_2 , rt, 1 h, 77% over 2 steps; d) L-Selectride® (2.2 eq), THF, -78 °C to rt, 1.75 h; e) 3 M HCl-THF (1:3, v/v), 40 °C, 16 h, 78% over 2 steps; f) NH_2NHTs (1 eq), PPTS (5 mol%), THF, rt, 16 h; g) MeLi (9 eq), THF-Et₂O (1:1, v/v), 0 °C, 3 h, 89% over 2 steps; h) TIPSOTf (1.2 eq), DIPEA (3 eq), 50 min, 91%; i) paraformaldehyde (12 eq), MeLi (9 eq), Et₂O, -78 °C to 0 °C, 1.5 h, 94%; j) MsCl (1.1 eq), Et₃N (1.5 eq), CH_2Cl_2 , 0 °C, 40 min; k) NaI (2.2 eq), acetone, rt, 16 h; l) **10** (3 eq), NaH (2.9 eq), THF, 0 °C to rt, 16 h, 81% (over 3 steps); m) TsOH (10 mol %), MeOH, rt, 16 h then K_2CO_3 , rt, 4 h, 84%; n) AuCl·DMS (10 mol %), PPTS (1 mol %), rt, 60 h, 65% combined, dr 9:1; o) H_2 (65 psi), Rh- Al_2O_3 , MeOH, rt, 60 h, 98%. 1:1.2 **23-24**; p) 1 N LiOH-THF (1:3, v/v), rt, 16 h; i) DMP (4 eq), CH_2Cl_2 , rt, 30 min; r) PPTS (10 mol %), EtOH, 45 °C, 24 h, 84% over 3 steps; s) TBAF (5 eq), THF, 40 °C, 2 h; t) DMP (4 eq), K_2CO_3 (7 eq), CH_2Cl_2 , rt, 30 min; u) *n*-PrMgBr (1.85 eq), Et₂O, 0 °C, 1 h, v) DMP (4 eq), K_2CO_3 (7 eq), CH_2Cl_2 , rt, 30 min, 57% over 4 steps; w) O_2 , LiHMDS (34 eq), THF, -78 °C, 3.3 h then $\text{P}(\text{OEt})_3$ 0.5 h, 48% combined (60% brsm), dr 1:1.

Efficient synthesis of the alkyne-substituted cyclohexanol ring of **9** posed a challenge. While related cyclohexanols have been assembled from geraniol derivatives, we sought an efficient method to incorporate the requisite alkynyl moiety.^{24–32} To this end, we developed an auxiliary ring strategy wherein bicyclic ketone **11** was used as a synthetic linchpin for the construction of monocyclic alkyne **9** (Figure 1D and Figure 2A). Bicyclic ketone **11** could, in turn, be disconnected to epoxide **12**, a derivative of geraniol, by a Ti(III)-mediated radical cyclisation.

Our synthesis thus began with treatment of epoxide **12** with *in situ* generated Cp_2TiCl_2 , efficiently affording bicyclic ketone **13** after acidic hydrolysis (Scheme 1).^{33–37} This transformation, while proceeding in modest yield (32%), was found to scale up easily (6.5 g), and afforded reliable access to diastereomerically-pure ketone **13**.³⁸ Preliminary investigations revealed that the complementary cyclization employing epoxide **14**—terminating with *intermolecular* addition to acetonitrile—was found to be capricious and low yielding (Figure 2B).³⁹

Next, epimerization of the C7 alcohol of **13** was achieved by an oxidation-reduction sequence, first requiring protection of the C4 ketone. Following ketal protection, the C7 alcohol was oxidized with DMP, then reduced with L-selectride®—affording desired epimer **11** after ketal deprotection. Attempts to effect alcohol epimerization on more advanced intermediates **16** and **17** in exploratory studies, which would have circumvented

the necessary ketone protection-deprotection steps, returned either unreacted starting material or the undesired epimer (Figure 2; see SI for detail).

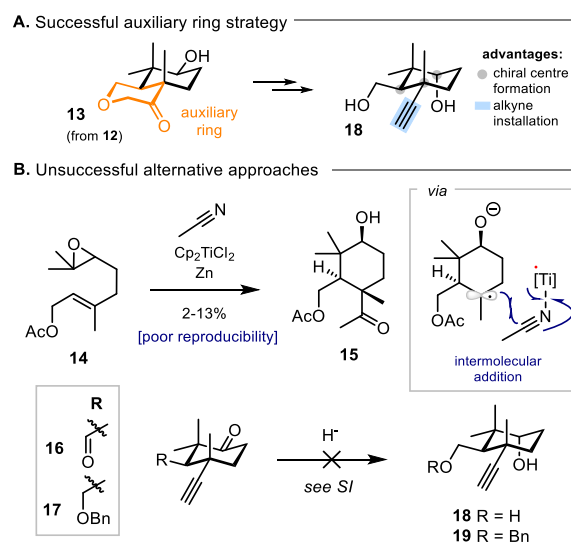


Figure 2. Discussion of the auxiliary ring strategy for synthesis of **20**

Such substrates lacked the rigidifying auxiliary pyran ring of **13**, and as a result, exhibited more conformational freedom. Indeed, the diastereoselectivity observed for formation of **11** may have been enhanced by the rigidity imposed by the auxiliary ring, encouraging equatorial approach of L-selectride® and preventing ring-flipping of the ketone.

With alcohol **11** in hand, attention was turned to cleavage of the auxiliary pyran ring and formation of the requisite alkyne motif. Both transformations were simultaneously achieved by exploitation of an unusual Shapiro-type fragmentation reaction.⁴⁰ To this end, **11** was converted to an intermediate tosyl hydrazone, which was subsequently treated with methyl lithium, resulting in formation of alkyne **18** in 89% yield over two steps.⁴¹ This process likely proceeded *via* generation of vinyl lithium **20**, which subsequently underwent β -elimination. This sequence enabled the synthesis of **18** in 7 steps on gram-scale. Our auxiliary ring strategy parallels the synthesis of *seco*-terpenoids in general, wherein ring-deconstruction is leveraged as an enabling (bio)synthetic tool.

With scalable access to alkyne **18** secured, focus was placed on construction of the caged spiroketal core of leonuketal (**1**). To this end, the iodide derived from **21** was synthesized over 3 steps by hydroxymethylation of **18**, followed by mesylation and iodination. The subsequent alkylation of the iodide required some investigation. Initially, we examined the Frater-Seebach alkylation with β -hydroxyesters, which generally resulted in decomposition of the nucleophile, returning starting material.^{42,43} Next, we examined β -ketoester nucleophiles. Interestingly, cyclic β -ketoesters afforded exclusively *O*-alkylation products, however, acyclic β -ketoesters, such as **10**, proved to be competent *C*-nucleophiles. Accordingly, known β -ketoester **10** was treated with sodium hydride and the iodide derived from **21**, smoothly affording alkyne **22** in 85% yield.

At this juncture, we identified two possible avenues for construction of the spiroketal and the C7, C10, and C11 stereocentres of leonuketal (**1**). Typically, dihydroxy alkynes are employed in Au-catalysed spiroketalizations. However, **22** was a mixture of C10 epimers and reduction of the C11 ketone would likely have afforded four diastereomers. Instead, we elected to explore the Au-catalysed spiroketalization of β -ketoester **22** *without* first reducing the C11 ketone. This transformation of β -ketoesters had not, to the best of our knowledge, been reported previously.

Initial investigations yielded the desired spiroketal product upon treatment of **22** with Au(I)-complexes, however, these results had poor reproducibility and often resulted in decomposition of the substrate. We therefore sought an alternative spiroketal precursor.

TBS deprotection and lactonisation of **22** afforded cyclic β -keto(enol)lactone **8**, as an alternative spiroketalization substrate. To our delight, treatment of **8** with AuCl·DMS and PPTS reliably delivered spiroketal **7** in 65% yield and 9:1 *dr*, thereby demonstrating this previously unexplored class of substrates to be viable Au-catalyzed spiroketalization precursors.

Investigation of **8** as a spiroketalization substrate was prompted by considering the loss of entropy incurred by formation of the rigid caged spirocycle. Straight-chain β -ketoester **22** had greater conformational freedom than the cyclic congener **8**. Hence, the loss of entropy upon forming **7** from **8**, particularly in preventing rotation of the C10-11 bond, would have

been less than for the spiroketalization of straight-chain substrate **22**. This substrate modification proved instrumental to the reliable formation of the caged spiroketal of **1**.

The next challenge in our total synthesis was the diastereoselective reduction of the enol ether of **7**. We posited that hydrogenation at the α -face could be achieved if a haptophilic effect of the posterior spiroketal oxygen (Scheme 1, *green*) directed adsorption of **7** at this face of the molecule.⁴⁴ Rhodium on alumina proved to be a competent catalyst for hydrogenation of **7** at elevated pressure (65 psi), however, no diastereoselectivity was observed regardless of solvent choice.^{45,46} Hence, the desired α -face addition product **23** and diastereomer **24** were obtained as a 1:1.2 mixture, which unfortunately could not be separated. Interestingly, undesired diastereomer **24** corresponds to β -face hydrogenation followed by epimerization of the spiroketal (C7). This result indicated an interplay between the C7, C10, and C11 stereocentres in which the more stable spiroketal epimer was influenced by the C10-11 configuration.

The diastereomeric mixture **23-24** was then advanced to the fully elaborated ketal- γ -lactone portion of leonuketal (**1**). This was achieved by lactone hydrolysis, oxidation of the liberated alcohol, and acid-mediated acetalization to afford **25** as a single C12 epimer in 84% yield over three steps. At this point, the desired diastereomer **25** could be separated from the product derived from **24** (not shown). The securing of **25** completed the unique tetracyclic core of leonuketal (**1**) and all but one chiral centre for the total synthesis. An X-ray structure of **25** allowed us to confirm the stereochemical configuration matched that of leonuketal (**1**).

With **25** in hand, the endgame of our total synthesis could be investigated. Deprotection of **25** proceeded smoothly at slightly elevated temperature, and the free alcohol was oxidized with DMP immediately to prevent possible transketalization. The aldehyde was treated with propylmagnesium bromide, then oxidized directly to afford deoxyleonuketal (**26**) in 57% yield over 4 steps. α -Hydroxylation of the newly formed ketone **26** was the final step in completion of the total synthesis and required some investigation (see Table S4 and S5, SI). Deprotonation of **26** with LiHMDS followed by treatment with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine effected the desired oxidation, but favoured the formation of 15-*epi*-leonuketal (*epi-1*) with a 9:1 *dr*. Surprisingly, the use of Davis' oxaziridine under analogous conditions delivered no detectable amount of **1** or *epi-1* at either full or partial completion of the reaction. Fortunately, bubbling molecular oxygen through a solution of deprotonated **26** delivered leonuketal (**1**), alongside 15-*epi*-leonuketal (*epi-1*), in 48% yield (60% brsm) and 1:1 *dr* after reductive workup. Leonuketal (**1**) was separated from *epi-1* by reverse phase HPLC, and to our delight, the NMR data were in good agreement with the isolation report (Table S6 and S7, SI).

In summary, we report the first total synthesis of complex *seco*-labdane leonuketal (**1**) over 23 steps from **12**. Our strategy featured an unusual Shapiro-type fragmentation as part of an enabling auxiliary ring strategy, as well as a novel Au-catalysed spirocyclization of a β -keto(enol)lactone. This work highlights the role of C–C bond cleavage in the biogenesis of complex terpenoids and demonstrates that the total synthesis of these molecules remains an exciting challenge.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge

Experimental procedures, analytical data (^1H and ^{13}C NMR, MS, IR) for all compounds (PDF)

Crystallographic information for compound **13** (CIF)

Crystallographic information for compound **18** (CIF)

Crystallographic information for compound **25** (CIF)

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Notes

The authors declare no competing financial interest.

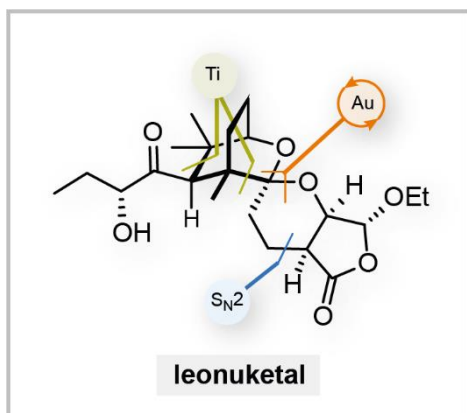
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SUPPORTING INFORMATION

Total Synthesis of (±)-Leonuketal

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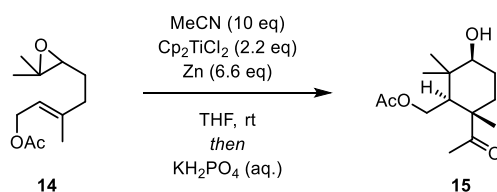
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1. Intermolecular nitrile termination: cyclisation of **14** to afford **15**

The Ti(III)-mediated cyclization of **14** to afford **15**, proceeding with intermolecular addition to acetonitrile, was investigated in early studies.

Initially, a solution of Cp_2TiCl in tetrahydrofuran was added to a solution of epoxide **14** and acetonitrile (10 eq) in tetrahydrofuran at rt, resulting in a complex mixture of products with incomplete conversion (Table S1, entry 1). Dropwise addition of the Cp_2TiCl solution over 10 minutes under otherwise identical conditions also resulted in a complex mixture (entry 2). Decreasing the temperature of the reaction to 0 °C stifled reactivity completely, returning starting material **14** after 6 hours (entry 3). Dropwise addition of the Cp_2TiCl solution over 1 hour lead to the formation of a discernible amount of desired product **15** (13%) after acidic work up with aqueous potassium phosphate, however, conversion was incomplete (entry 4). To increase the conversion and yield of the reaction, both increased equivalents of acetonitrile (50 eq) and Cp_2TiCl (3.3 eq) were trialled, leading unfortunately to decreased yield of the desired product in both cases (5% and 2% respectively, entries 5 & 6). At this juncture, the best conditions (entry 4) were repeated to establish the reproducibility of the results. Unfortunately, the initially observed 13% yield of ketone **15** was not reproduced, and the product was isolated in 2% and 7% yield on first and second repeats with identical scale (0.5 mmol, entries 7 & 8).

Table S1.



entry	deviation from above conditions ^{a,b}	result
1	none	complex mixture w/ 14
2	Cp_2TiCl addition over 10 min	complex mixture w/ 14
3	Cp_2TiCl addition over 10 min, 0 °C	14
4	Cp_2TiCl addition over 1 h	13% w/ 14
5	MeCN (50 eq), Cp_2TiCl addition over 1 h	5%
6	Cp_2TiCl_2 (3.3 eq) addition over 1 h, Zn (9.9 eq)	2%
7	repeat of entry 4	7%
8	repeat of entry 4	2%

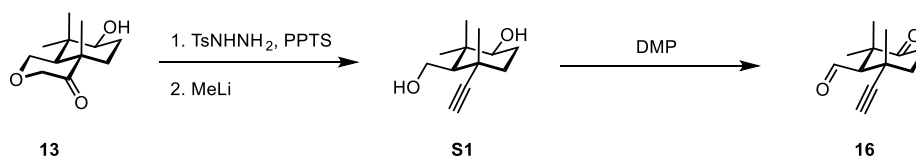
^art unless otherwise specified; ^breaction stirred for 1 hour after addition of Cp_2TiCl solution in THF

Given the low and irreproducible yields of ketone **15** afforded by treatment of epoxide **14** with Cp_2TiCl in presence of acetonitrile, this approach was abandoned.

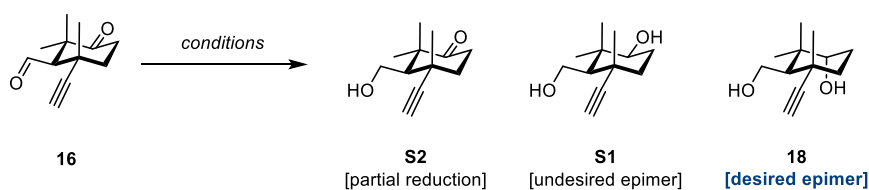
2. Unsuccessful reduction approaches

2.1 Keto aldehyde **16**

A. Synthesis



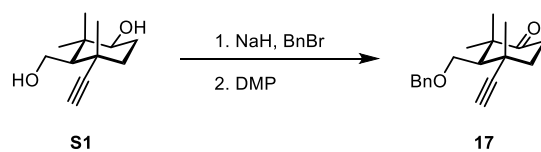
B. Table S2. Attempted stereoselective reduction of **16**



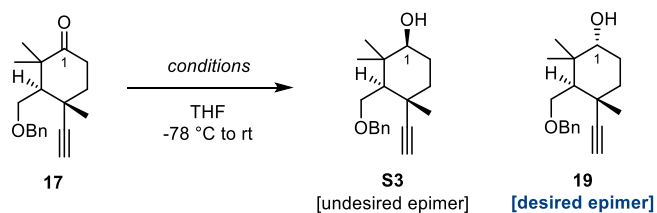
entry	conditions	result
1	L-Selectride®, THF, $-78\text{ }^{\circ}\text{C}$ to rt, 16 h	S2
2	K-Selectride®, THF, $-78\text{ }^{\circ}\text{C}$ to rt, 16 h	S2
3	N-Selectride®, THF, $-78\text{ }^{\circ}\text{C}$ to rt, 16 h	S2
4	Superhydride®, THF, $-78\text{ }^{\circ}\text{C}$ to rt, 1.5 h	S1 83%
5	$\text{Al}(\text{O}i\text{Pr})_3$, $i\text{PrOH}$, reflux, 2 h	decomposition

2.2 Benzyl ether **17**

A. Synthesis



B. Table S3. Attempted stereoselective reduction of **17**



entry	conditions	result
1	L-Selectride®, 16 h	SM
2	K-Selectride®, 16 h	SM
3	N-Selectride®, 16 h	SM
4	Superhydride®, 1.5 h	89% S3 , trace 19 , 8:1 <i>dr</i> ^a

^a ratio by ¹H-NMR

3. Deoxyleonuketal α -hydroxylation optimisation and model studies

Ketone **S4** was used as a model compound for investigating the α -hydroxylation of deoxyleonuketal (**26**) to give leonuketal (**1**). Ketone **S4** was prepared analogously to deoxyleonuketal (**26**).

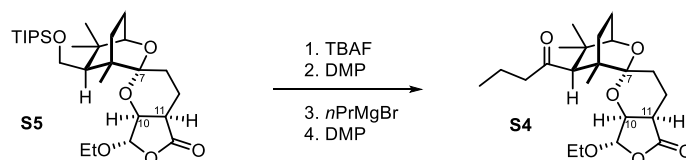
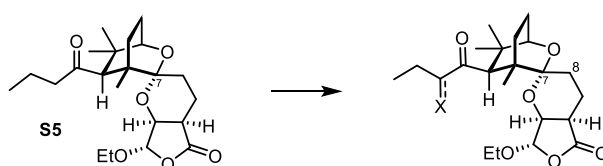


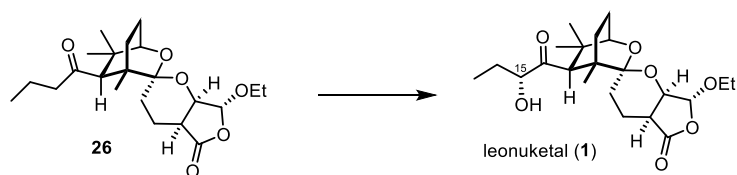
Table S4. α -hydroxylation and bromination studies



entry	conditions	X	result
1	TMSOTf, Et ₃ N, CH ₂ Cl ₂ , 0 °C (<i>then</i> [O])	OH	no formation of TMS enol ether
2	LiHMDS, TMSCl, –78 °C to 0 °C (<i>then</i> [O])	OH	no formation of TMS enol ether
3	CuBr ₂ , THF, rt	Br	C8 bromination
4	benzyltrimethylammonium tribromide, THF, 0 °C to rt	Br	SM
5	NaHMDS, Davis' oxaziridine, THF, –78 °C	OH	Lactone hydroxylation without ketone hydroxylation
6	K ^t OBu, Davis' oxaziridine, DMPU, THF, –78 °C	OH	SM
7	K ^t OBu, Davis' oxaziridine, DMPU, THF, –65 °C	OH	SM
8	tetrabutylammoniumtribromide, THF, 0 °C to rt	Br	SM
9	pyridinium tribromide, THF, rt	Br	trace C8 bromination
10	K ^t OBu, P(OEt) ₃ , O ₂ , THF, 0 °C to rt	OH	decomposition
11	K ^t OBu, P(OEt) ₃ , O ₂ , THF, –78 °C	OH	SM
12	LiHMDS (10 eq), MoOPH (15 eq), THF, –20 °C	OH	SM
13	SeO ₂ , 1,4-dioxane, 100 °C	O	SM
14	SeO ₂ , 1,4-dioxane, 150 °C (sealed tube)	O	SM
15	NaHMDS, P(OEt) ₃ , O ₂ , THF, –78 °C	OH	desired ketone hydroxylation, 1:1 <i>dr</i>

SM – starting material

Table S5. α -hydroxylation of deoxyleonuketal (**26**)



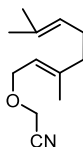
entry	conditions	result
1	NaHMDS (10 eq), (1S)-(+)-(10-camphorsulfonyl)oxaziridine (12 eq), THF, -78 °C	favour <i>epi</i> - 1 , <i>dr</i> 9:1, complete conversion
2	NaHMDS, Davis' oxaziridine, THF, -78 °C	Lactone hydroxylation without ketone hydroxylation
3	NaHMDS, P(OEt) ₃ , O ₂ , THF, -78 °C	C14 ox, <i>dr</i> 1:1, yield ND
4	LiHMDS, P(OEt) ₃ , O ₂ , THF, -78 °C	C14 ox, <i>dr</i> 1:1 to 2:1 in favour of 1 , 48%

4. General Methods

Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Diethyl ether, tetrahydrofuran, dichloromethane, acetonitrile, 1,4-dioxane, dimethylformamide and toluene were dried using an LC Technology Solutions Inc. SP-1 solvent purification system under an atmosphere of dry nitrogen. All reactions were routinely carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using silica plates and compounds were visualised at 254 and/or 360 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on an NMR spectrometer operating at 500, 400 and 300 MHz for ^1H nuclei and 125, 101 and 75 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in CDCl_3/TMS solvent, or the residual, chloroform (δ 7.26 ppm), or DMSO (δ 2.50 ppm) peaks. The ^{13}C NMR values were referenced to the residual acetone, chloroform (δ 77.16 ppm) or DMSO (δ 39.52 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ and assignment. ^1H NMR shift values are reported as chemical shift δ , relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. Assignments are made with the aid of COSY, NOESY, HSQC, and HMBC experiments. All experiments were conducted at 298 K. Conventional NMR tubes (5 mm diameter, Norell) using a sample volume of 500 μL were used. High resolution mass spectra were obtained by electrospray ionisation in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.

5. Experimental Procedures: Total synthesis of leonuketal

Nitrile **S6**

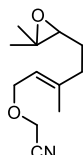


To a stirred suspension of NaH (9.66 g, 60% dispersion in mineral oil, 242 mmol) in THF (200 mL) at rt was added geraniol (23.3 mL, 134 mmol) dropwise. The resulting solution was heated to reflux for 2.5 h, then allowed to cool to rt, and bromoacetonitrile (15.0 mL, 215 mmol) was added by syringe pump over 2.5 h. After stirring at rt for 48 h, NaH (4.50 g, dispersion in mineral oil, 113 mmol) was added and the resulting mixture was stirred for a further 1 h at rt before addition of more bromoacetonitrile (2.67 mL, 38.3 mmol) by syringe pump over 2.5 h. The reaction mixture was allowed to stir for a further 24 h before quenching with MeOH (5 mL). The reaction mixture was filtered through silica. The silica was washed with 1:1 EtOAc-pet. ether (250 mL, v/v) then the filtrate was concentrated in vacuo. The resultant crude oil was purified by short path distillation (1 mbar, 80–110 °C) to give nitrile **S6** (21.9 g, 84%) as a yellow oil.

IR (film) ν_{\max} 2924, 2856, 1739, 1441, 1377, 1078 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 5.33 – 5.26 (m, 1H), 5.10 – 5.04 (m, 1H), 4.21 (s, 2H), 4.15 (dd, $J = 7.1, 0.6$ Hz, 2H), 2.16 – 2.03 (m, 4H), 1.72 (d, $J = 1.3$ Hz, 3H), 1.68 (d, $J = 1.4$ Hz, 3H), 1.60 (d, $J = 0.9$ Hz, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ 143.9 (C), 132.0 (C), 123.7 (CH), 118.4 (CH), 116.3 (C), 67.3 (CH_2), 54.4 (CH_2), 39.7 (CH_2), 26.3 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.5 (CH_3); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 216.1356 calcd for $\text{C}_{12}\text{H}_{19}\text{NNaO}$ 216.1359.

Spectroscopic data were in good agreement with those previously reported.¹

Epoxide **12**

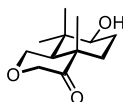


¹ Kropf, C.; Huchel, U.; Bluhm, N.; Bauer, A. Photolabile Fragrance Precursor Compound. WO2016096539 (A1), June 23, 2016.

To a stirred solution of nitrile **S6** (9.80 g, 50.7 mmol) in THF-H₂O (2.0 L, 2:1 v/v) at 0 °C was added NBS (11.4 g, 65.9 mmol) as a solution in THF-H₂O (115 mL, 2:1 v/v) dropwise over 1 h. The reaction mixture was stirred at 0 °C for 1 h before the addition of sat. aq. Na₂S₂O₃ (130 mL). K₂CO₃ (35.3 g, 254 mmol) and MeOH (265 mL) were then added and the resulting mixture was allowed to warm to rt and stir overnight. The majority of organic solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (80 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude oil was then purified by flash chromatography (15-45% EtOAc in pet. ether) to afford the epoxide **12** as a clear oil (7.71 g, 73%).

IR (film) ν_{max} 2961, 1645, 1379, 1088, 882 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.38 – 5.30 (m, 1H), 4.20 (s, 2H), 4.12 (d, J = 7.0 Hz, 2H), 2.67 (dd, J = 6.8, 5.5 Hz, 1H), 2.29 – 2.08 (m, 2H), 1.71 (d, J = 0.7 Hz, 3H), 1.68 – 1.56 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 142.8 (C), 119.0 (CH), 116.3 (C), 67.4 (CH₂), 63.9 (CH), 58.3 (C), 54.7 (CH₂), 36.4 (CH₂), 27.2 (CH₂), 24.9 (CH₃), 18.8 (CH₃), 16.6 (CH₃); **HRMS** (ESI+) [$M + Na$]⁺ 232.1315 calcd for C₁₂H₁₉NNaO₂ 232.1308.

Ketone **13**



A mixture of Cp₂TiCl₂ (17.8 g, 71.4 mmol) and Zn dust (9.34 g, 142 mmol) in rigorously deoxygenated THF (100 mL) was stirred at rt for 15 min.² The resulting green solution was then added dropwise over 1 h *via* syringe pump to a stirred solution of epoxide **12** (6.50 g, 31.1 mmol) in deoxygenated² THF (1.1 L) at 60 °C. After 1 hour, sat. aq. KH₂PO₄ (200 mL) was added and the resulting mixture was stirred at rt for 30 mins. The biphasic mixture was filtered over Celite® and the filtrate was washed with EtOAc (2 × 100 mL). The aqueous phase of the filtered mixture was separated and extracted with Et₂O (2 × 200 mL). The combined organic phases were washed with sat. aq. NaHCO₃ (200 mL), brine (200 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude mixture was purified by flash chromatography (20-50% EtOAc in pet. ether) to give the product as a clear oil (2.11 g, 32%).

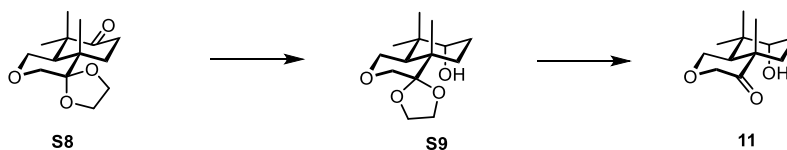
² THF deoxygenated by sparging with nitrogen gas for 2 h at rt

1.74 – 1.52 (m, 3H), 1.42 – 1.36 (m, 1H), 1.19 (s, 3H), 1.04 (s, 3H), 0.79 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 108.9 (C), 78.1 (CH), 66.7 (CH₂), 65.8 (CH₂), 65.5 (CH₂), 63.8 (CH₂), 47.8 (CH), 41.5 (C), 37.3 (C), 28.2 (CH₂), 28.0 (CH₂), 27.0 (CH₃), 16.0 (CH₃), 15.9 (CH₃); **HRMS** (ESI+) [M + Na]⁺ 279.1567 calcd for C₁₄H₂₄NaO₄ 279.1567.

Data for ketone **S8**

IR (film) ν_{\max} 2958, 1703, 1386, 1220, 1159, 1100 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.09 – 3.84 (m, 4H), 3.80 (dd, J = 11.5, 4.0 Hz, 1H), 3.68 (t, J = 11.4 Hz, 1H), 3.57 (d, J = 11.9 Hz, 1H), 3.41 (d, J = 11.8 Hz, 1H), 2.58 (ddd, J = 15.9, 12.2, 6.9 Hz, 1H), 2.45 (ddd, J = 15.9, 6.3, 3.6 Hz, 1H), 2.27 (dd, J = 11.3, 4.0 Hz, 1H), 2.11 (td, J = 12.6, 6.2 Hz, 1H), 1.66 (ddd, J = 13.2, 6.9, 3.7 Hz, 1H), 1.33 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 215.3 (C), 108.4 (C), 66.7 (CH₂), 65.9 (CH₂), 65.5 (CH₂), 64.2 (CH₂), 48.1 (CH), 45.7 (C), 41.0 (C), 34.3 (CH₂), 29.1 (CH₂), 26.4 (CH₃), 21.9 (CH₃), 15.5 (CH₃); **HRMS** (ESI+) [M + Na]⁺ 277.1410 calcd for C₁₄H₂₂NaO₄ 277.1410.

Ketone **11**



To a stirred solution of ketone **S8** (4.36 g, 17.1 mmol) in THF (120 mL) at –78 °C was added L-Selectride® (37.7 mL, 37.7 mmol, 1.0 M in THF) dropwise. The resulting solution was stirred at this temperature for 1 h before allowing to warm to rt and stir for a further 45 min. Sat. aq. NH₄Cl (80 mL) was then added slowly and the aqueous phase of the resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic phases were then washed with brine (100 mL) and concentrated in vacuo.

The crude oil of **S9** was then dissolved in 3 M HCl-THF (150 mL, 3:1, v/v) and the resulting mixture was heated to 40 °C and stirred 16 h, before being allowed to cool to rt. EtOAc (150 mL) was added to the reaction mixture and the organic phase was collected. The aqueous phase was then extracted with EtOAc (2 × 80 mL) and the combined organic phases were washed with brine (100 mL), dried over NaSO₄, and concentrated in vacuo. The resultant crude oil was purified by flash chromatography to give ketone **11** (2.85 g, 78% over two steps) as a clear oil.

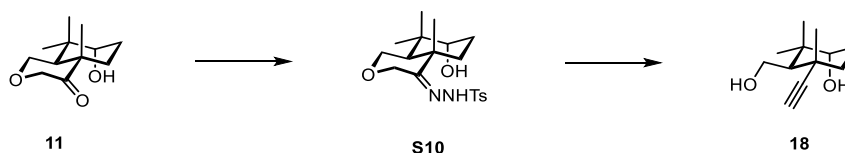
Data for ketal **S9**⁴

IR (film) ν_{\max} 3468, 2874, 1457, 1101, 1082 cm^{-1} ; **¹H NMR** (400 MHz, CDCl_3) δ 4.11 – 3.97 (m, 2H), 3.96 – 3.81 (m, 2H), 3.77 (dd, J = 11.3, 3.7 Hz, 1H), 3.63 (t, J = 11.4 Hz, 1H), 3.56 (d, J = 11.7 Hz, 1H), 3.39 – 3.32 (m, 2H), 2.25 (dd, J = 11.6, 3.7 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.70 – 1.64 (m, 1H), 1.22 (s, 3H), 1.16 – 1.12 (m, 1H) 1.02 (s, 3H), 0.86 (s, 3H); **¹³C NMR** (101 MHz, CDCl_3) δ 108.8 (C), 76.1 (CH), 67.0 (CH_2), 65.8 (CH_2), 65.6 (CH_2), 63.8 (CH_2), 42.4 (CH), 41.6 (C), 36.2 (C), 28.1 (CH_3), 24.9 (CH_2), 22.7 (CH_2), 22.6 (CH_3), 15.8 (CH_3); **HRMS** (ESI+) $[M + \text{Na}]^+$ 279.1566 calcd for $\text{C}_{14}\text{H}_{24}\text{NaO}_4$ 279.1567.

Data for ketone **11**

IR (film) ν_{\max} 3447, 2954, 2871, 1722, 1128, 1066, 923 cm^{-1} ; **¹H NMR** (400 MHz, CDCl_3) δ 4.11 (d, J = 16.8 Hz, 1H), 3.96 (dd, J = 16.5, 13.3 Hz, 3H), 3.44 (t, J = 2.7 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.98 (tdd, J = 14.1, 3.7, 2.3 Hz, 1H), 1.85 (td, J = 13.9, 3.5 Hz, 1H), 1.69 (ddd, J = 14.0, 6.5, 3.3 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.30 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H); **¹³C NMR** (101 MHz, CDCl_3) δ 214.0 (C), 75.2 (CH), 70.3 (CH_2), 63.5 (CH_2), 45.5 (C), 40.1 (CH), 37.5 (CH), 27.3 (CH_2), 25.5 (CH_3), 24.9 (CH_2), 22.3 (CH_3), 17.9 (CH_3); **HRMS** (ESI+) $[M + \text{Na}]^+$ 235.1909 calcd for $\text{C}_{12}\text{H}_{20}\text{NaO}_3$ 235.1905

Alkyne **18**



To a stirred solution of ketone **11** (1.61 g, 7.58 mmol) and *p*-toluenesulfonyl hydrazide (1.41 mg, 7.58 mmol) in THF (15 mL) at rt was added PPTS (95 mg, 0.38 mmol). The resulting solution was allowed to stir at rt for 16 h. The mixture was then diluted in EtOAc (250 mL) and washed with a H_2O (50 mL), then brine (50 mL), then dried over NaSO_4 and concentrated in vacuo. The resultant crude oil was purified by flash

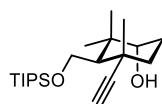
⁴ Analytic sample purified by flash chromatography (65% EtOAc in pet. ether)

chromatography (40% EtOAc in pet. ether) to give the putative *p*-toluenesulfonyl hydrazone **S10** (2.79 g) as a clear oil.⁵

A solution of MeLi (25.4 mL, 66.0 mmol, 2.6 M in dimethoxyethane) was added to Et₂O (50 mL) at 0 °C. To the resulting stirred solution was added dropwise a solution of *p*-toluenesulfonyl hydrazone **S10** (2.79 g, 7.33 mmol) in THF (50 mL) over 10 min. The resulting mixture was stirred at 0 °C for a further 3 h before the addition of sat. aq. NH₄Cl (50 mL). The mixture was then extracted with CH₂Cl₂ (3 × 80 mL) and the combined organic phases were washed with brine (80 mL), dried over Na₂SO₄, and then concentrated in vacuo. The crude oil was then purified by flash chromatography (40% EtOAc in pet. ether) to give alcohol **18** as a clear oil (1.32 g, 89% over two steps).

IR (film) ν_{max} 3397, 3304, 2936, 1457, 1385, 1057, 1021 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.06 – 3.93 (m, 1H), 3.81 (dd, *J* = 11.8, 3.8 Hz, 1H), 3.48 – 3.39 (m, 1H), 2.26 (s, 1H), 2.23 – 2.12 (m, 1H), 1.98 (dd, *J* = 6.0, 3.8 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.66 – 1.56 (m, 2H), 1.30 (s, 3H), 1.14 (s, 3H), 0.89 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 94.5 (C), 75.6 (CH), 68.9 (CH), 62.4 (CH₂), 50.5 (CH), 37.9 (C), 33.8 (CH₂), 33.5 (C), 28.1 (CH₂), 25.1 (CH₃), 23.2 (CH₃), 22.4 (CH₃); **HRMS** (ESI+) [*M* + Na]⁺ 219.1350 calc for C₁₂H₂₀NaO₂ 219.1356; crystals were obtained for XRD analysis by evaporation from diethyl ether, mp 81–83 °C.

Alkyne **S11**



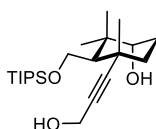
To a stirred solution of diol **18** (325 mg, 1.66 mmol) and DIPEA (0.87 mL, 4.97 mmol) in CH₂Cl₂ (17 mL) at 0 °C was added a solution of TIPSOTf (0.53 mL, 1.97 mmol) in CH₂Cl₂ (4 mL) dropwise over 20 min. The resulting solution was allowed to stir at 0 °C for 30 min then sat. aq. NaHCO₃ (10 mL) was added. The organic phase was then separated, and the aqueous phase was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were then washed with brine (15 mL), dried over Na₂SO₄,

⁵**S10** should be purified quickly to avoid decomposition on silica; unfortunately, purification is necessary for high yield in following step. Attempts to characterise **S10** were prevented by rapid decomposition in CDCl₃.

and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (15% EtOAc in pet. ether) to afford alkyne **S11** (531 mg, 91%).

IR (film) ν_{\max} 3420, 3312, 2943, 2893, 2866, 1463, 1097, 994 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 4.11 (dd, $J = 10.7, 2.5$ Hz, 1H), 4.00 (dd, $J = 10.7, 6.1$ Hz, 1H), 3.50 (s, 1H), 2.15 – 2.03 (m, 2H), 1.87 – 1.76 (m, 2H), 1.71 – 1.57 (m, 2H), 1.25 (s, 3H), 1.19 (s, 3H), 1.10–1.04 (m, 24H); **^{13}C NMR** (101 MHz, CDCl_3) δ 94.5 (C), 76.3 (CH), 67.8 (CH), 62.9 (CH_2), 50.1 (CH), 38.4 (C), 34.6 (CH_2), 34.5 (CH_2), 28.1 (CH_3), 25.6 (CH_2), 24.2 (CH_3), 23.9 (CH_3), 18.3 ($6 \times \text{CH}_3$), 12.1 ($3 \times \text{CH}$); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 375.2686 calc for $\text{C}_{21}\text{H}_{40}\text{NaO}_2\text{Si}$ 375.2690.

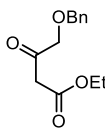
Alcohol **21**



To alkyne **S11** (1.38 g, 3.91 mmol) in Et_2O (30 mL) at -78°C was added MeLi (13.5 mL, 35.2 mmol, 2.6 M in dimethoxyethane) dropwise. The resulting solution was warmed to 0°C and allowed to stir at this temperature for 30 min before cooling to -78°C . Paraformaldehyde (1.41 g, 47.0 mmol) was then added and the resulting suspension was allowed to warm rt and stir for 1 h. Sat. aq. NH_4Cl (15 mL) was then added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were then washed with brine (30 mL), dried over Na_2SO_4 , and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (15–35% EtOAc in pet. ether) to afford alcohol **21** (1.40 g, 94%) as a clear oil.

IR (film) ν_{\max} 3311, 2942, 1461, 1100, 995, 882 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 4.22 (s, 2H), 4.08 (dd, $J = 10.6, 2.4$ Hz, 1H), 3.98 (dd, $J = 10.6, 6.3$ Hz, 1H), 3.50 (s, 1H), 2.09 (td, $J = 12.2, 3.0$ Hz, 1H), 1.86 – 1.75 (m, 2H), 1.69 – 1.55 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.10 – 1.04 (m, 24H); **^{13}C NMR** (101 MHz, CDCl_3) δ 96.3 (C), 77.8 (C), 76.3 (CH), 63.0 (CH_2), 51.7 (CH_2), 50.1 (CH), 38.4 (C), 34.6 (CH_2), 34.5 (CH_2), 28.2 (CH_3), 25.6 (CH_2), 24.1 (CH_3), 23.9 (CH_3), 18.3 ($6 \times \text{CH}_3$), 12.1 ($3 \times \text{CH}$); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 405.2792 calc for $\text{C}_{22}\text{H}_{42}\text{NaO}_3\text{Si}$ 405.2795.

β -Keto ester **S12**

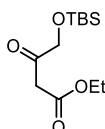


To a stirred suspension of NaH (876 mg, 21.9 mmol, 60% dispersion in mineral oil) in THF (20 mL) at 0 °C was added BnBr (1.14 mL, 11.0 mmol) dropwise. The resulting solution was left to stir for 2 h at 0 °C then ethyl 4-chloroacetoacetate (1.23 mL, 10.0 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stir for 16 h. Sat. aq. NH₄Cl (15 mL) was then added, and the organic phase was separated, then washed with brine (15 mL), dried over Na₂SO₄, and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (40% EtOAc in pet. ether) to afford the β -keto ester **S12** (2.15 g, 84%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.26 (m, 5H), 4.58 (s, 2H), 4.20 – 4.10 (m, 4H), 3.53 (s, 2H), 1.24 (t, J = 7.1 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.8 (C), 167.1 (C), 137.0 (C), 128.6 (2 \times CH), 128.2 (CH), 127.9 (2 \times CH), 74.9 (CH₂), 73.6 (CH₂), 61.5 (CH₂), 46.1 (CH₂), 14.1 (CH₃).

Spectroscopic data were in good agreement with those previously reported.⁶

β -Keto ester **S13**



A suspension of **S12** (1.00 g, 4.23 mmol) and Pd/C (100 mg, 10% w/w) in MeOH (10 mL) was stirred at rt under an atmosphere of H₂ (balloon pressure) for 16 h. The suspension was then filtered over Celite[®] and concentrated in vacuo.

The crude oil was dissolved in CH₂Cl₂ (10 mL), cooled to 0 °C, then imidazole (576 mg, 8.46 mmol) and TBSCl (702 mg, 4.66 mmol) were added. The resultant mixture was allowed to warm to rt and stir for 16 h. CH₂Cl₂ (50 mL) was then added and the mixture was washed with sat. aq. NH₄Cl (2 \times 20 mL), sat. aq. NaHCO₃ (2 \times 20 mL)

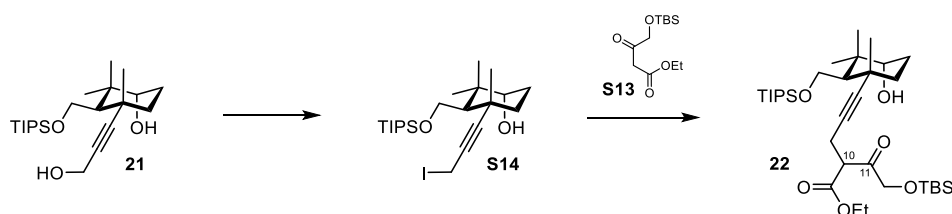
⁶ Fan, W.; Li, W.; Ma, X.; Tao, X.; Li, X.; Yao, Y.; Xie, X.; Zhang, Z. Ru-Catalyzed Asymmetric Hydrogenation of γ -Heteroatom Substituted β -Keto Esters. *J. Org. Chem.* **2011**, 76 (22), 9444–9451. <https://doi.org/10.1021/jo201822k>.

and brine (20 mL), dried over MgSO_4 and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (10% EtOAc in pet. ether) to afford β -keto ester **S13** (931 mg, 84%) as a clear oil.

^1H NMR (400 MHz, CDCl_3) δ 4.22 (s, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.55 (s, 2H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); **^{13}C NMR** (101 MHz, CDCl_3) δ 204.4 (C), 167.4 (C), 69.1 (CH_2), 61.2 (CH_2), 45.5 (CH_2), 25.6 ($3 \times \text{CH}_3$), 18.1 (C), 14.0 (CH_2), – 5.5 ($2 \times \text{CH}_3$).

Spectroscopic data were in good agreement with those previously reported.⁶

β -Keto ester **22**



To alcohol **21** (298 mg, 0.77 mmol) and Et_3N (171 μL , 1.23 mmol) in CH_2Cl_2 (11 mL) at 0 $^\circ\text{C}$ was added a solution of MsCl (65 μL , 0.84 mmol) in CH_2Cl_2 (1.3 mL) dropwise over 10 min. The reaction mixture was allowed to stir at 0 $^\circ\text{C}$ for 30 min, then H_2O (15 mL) was added. The organic phase was then separated, and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were then dried over Na_2SO_4 and concentrated in vacuo.

The crude oil was then dissolved in acetone (11 mL) and NaI (230 mg, 1.53 mmol) was added. The resultant mixture was protected from light and stirred at rt for 16 h. The reaction mixture was then filtered over Celite[®] and the solid residue was washed with Et_2O (2×10 mL). The filtrate was then concentrated in vacuo and purified by flash chromatography (10% EtOAc in pet. ether) to give iodide **S14** (359 mg impure, ~95%) used in the following step immediately to avoid decomposition.

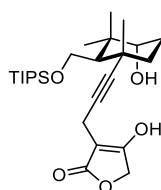
To a suspension of sodium hydride (85 mg, 60% dispersion in mineral oil, 2.11 mmol) in THF (8 mL) at 0 $^\circ\text{C}$ was added β -keto ester **S13** (570 mg, 2.19 mmol) dropwise dissolved in THF (0.8 mL). The resulting suspension was stirred at 0 $^\circ\text{C}$ for 15 min, then at rt for 10 min, then a solution of iodide **S14** (359 mg, 0.73 mmol) in THF (1.7 mL) was added dropwise. The resulting reaction mixture was stirred at rt for 16 h

before being quenched by addition of sat. aq. NH_4Cl (10 mL). The mixture was then extracted with CH_2Cl_2 (3 \times 20 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude residue was purified by flash chromatography (5%-12% EtOAc in pet. ether) to afford β -keto ester **22** (389 mg, 81% over three steps, *dr* 1:1).

IR (film) ν_{max} 2928, 2865, 1724, 1464, 1259, 1096, 780 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 4.32 – 4.27 (m, 2H), 4.14 (m, 2H), 4.03 (dd, J = 10.7, 1.7 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.78 (dd, J = 8.0, 6.9 Hz, 1H), 3.47 (s, 1H), 2.73 – 2.59 (m, 2H), 1.95 (t, J = 11.0 Hz, 1H), 1.75 (tt, J = 11.3, 3.4 Hz, 1H), 1.69 (brs, 1H), 1.64 – 1.57 (m, 1H), 1.57 – 1.46 (m, 1H), 1.25 (dt, J = 7.9, 2.1 Hz, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.06 (t, J = 5.5 Hz, 24H), 0.90 (s, 9H), 0.08 – 0.06 (m, 6H); **^{13}C NMR** (126 MHz, CDCl_3) δ 204.09 (C), 204.07* (C), 168.37 (C), 168.35* (C), 92.5 (C), 76.2 (CH), 75.5 (CH), 69.4 (CH_2), 69.3 (CH_2), 62.9 (CH_2), 61.6 (CH_2), 53.9 (CH), 53.8* (CH), 50.6 (CH), 38.49 (C), 38.46 (CH₃), 34.9 (CH_2), 34.5 (C), 27.8 (CH_2), 25.92 (CH_3), 25.85 (3 \times CH_3), 24.4 (CH_3), 18.4 (C), 18.3 (6 \times CH_3), 17.8 (CH_2), 14.2 (CH_3), 12.4 (3 \times CH_2), -5.46 (CH_3), -5.49 (CH_3); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 647.4130 calc for $\text{C}_{34}\text{H}_{64}\text{NaO}_6\text{Si}_2$ 647.4134.

*denotes signal arising exclusively from one C10 epimer; undesignated signals arise from a mixture of both

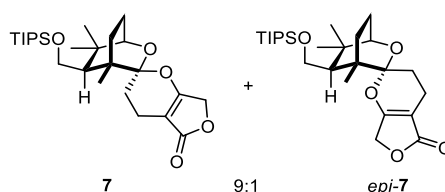
Enol **8**



To TBS ether **22** (190 mg, 0.30 mmol) in MeOH (8 mL) at rt was added TsOH·H₂O (5 mg, 0.03 mmol) as a solution in MeOH (200 μL). The reaction mixture was stirred at rt for 16 h, then K_2CO_3 (126 mg, 0.91 mmol) was added, and the resultant mixture was stirred at rt for a further 4 h. The reaction mixture was diluted with EtOAc (40 mL) and washed with sat. aq. NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (2 \times 30 mL), then the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 , and concentrated in vacuo. The crude oil was purified by flash chromatography (10% MeOH in CH_2Cl_2) to afford enol **8** (120 mg, 85%) as a clear oil.

IR (film) ν_{\max} 2942, 2867, 1739, 1674, 1410, 1102, 1048, 882 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 4.58 (t, $J = 1.7$ Hz, 2H), 4.01 (ddd, $J = 16.6, 10.7, 4.5$ Hz, 2H), 3.49 (brs, 1H), 3.21 – 3.09 (m, 2H), 2.15 (td, $J = 12.8, 3.3$ Hz, 1H), 1.89 – 1.80 (m, 2H), 1.70 – 1.57 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H), 1.07 (d, $J = 4.6$ Hz, 21H), 1.02 (s, 3H); **^{13}C NMR** (126 MHz, CDCl_3) δ 173.5 (C), 172.5 (C), 96.1 (C), 95.9 (C), 76.0 (CH), 73.9 (C), 66.9 (CH₂), 62.9 (CH₂), 49.8 (CH), 38.2 (C), 34.8 (C), 34.5 (CH₂), 28.4 (CH₃), 25.2 (CH₂), 23.7 (CH₃), 23.2 (CH₃), 18.2 (6 \times CH₃), 13.8 (CH₂), 12.1 (3 \times CH); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 487.2856 calc for $\text{C}_{26}\text{H}_{44}\text{NaO}_5\text{Si}$ 487.2850.

Spiroketal **7**

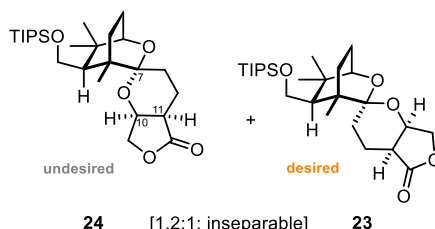


To a solution of $\text{AuCl} \cdot \text{DMS}$ (10 mg, 0.035 mmol) and PPTS (0.9 mg, 0.0035 mmol) in degassed MeOH (18 mL) at rt was added enol **7** (220 mg, 0.35 mmol) as a solution in degassed MeOH (4.5 mL) over 1 h. The resulting mixture was stirred at rt for 60 h, then quenched by addition of Et_3N (0.1 mL), then concentrated in vacuo. The residue was purified by flash chromatography (5% Et_2O in pet. ether) to afford an inseparable mixture of the spiroketal **7** and spiroketal *epi-7* (143 mg, *dr* 9:1 **7** to *epi-7*, 65% combined yield) as a clear oil.

IR (film) ν_{\max} 2931, 2866, 1770, 1680, 1108, 1021, 799 cm^{-1} ; **^1H NMR** (500 MHz, CDCl_3) δ 4.63 – 4.53 (m, 2H), 3.93 – 3.83 (m, 2H), 3.45 – 3.43* (t, $J = 2.5$ Hz, 0.1H), 3.40 (t, $J = 2.6$ Hz, 0.9H), 2.46 – 2.37 (m, 1H), 2.37 – 2.29 (m, 1H), 2.24 – 2.15 (m, 1.1H), 1.96 – 1.82 (m, 2H), 1.70 – 1.63 (m, 1H), 1.62 – 1.45 (m, 2.9H), 1.15 – 1.02 (m, 27H), 0.97* (s, 0.3H), 0.90 (s, 2.7H); **^{13}C NMR** (126 MHz, CDCl_3) δ 173.4 (C), 173.3 (C), 173.2* (C), 173.0* (C), 108.9 (C), 107.8* (C), 100.7 (C), 100.6* (C), 79.6* (CH), 78.8 (CH), 67.0 (CH₂), 66.8* (CH₂), 61.0* (CH₂), 60.7 (CH₂), 48.3 (CH), 44.4* (CH), 38.1 (C), 37.8* (C), 36.6 (C), 35.8* (C), 33.5* (CH₂), 30.6 (CH₃), 30.5* (CH₃), 26.3* (CH₂), 25.2 (CH₂), 23.4 (C), 23.2* (CH₂), 21.9* (CH₂), 21.5 (CH₂), 21.2 (CH₃), 19.7 (CH₃), 19.3* (CH₃), 18.3 (6 \times CH₃), 13.3 (CH₂), 12.0 (3 \times CH); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 487.2837 calc for $\text{C}_{26}\text{H}_{44}\text{NaO}_5\text{Si}$ 487.2850.

*denotes signal arising exclusively from minor diastereomer; undesignated signals are either from the major diastereomer or a mixture of both.

Spiroketal **24**; spiroketal **23**



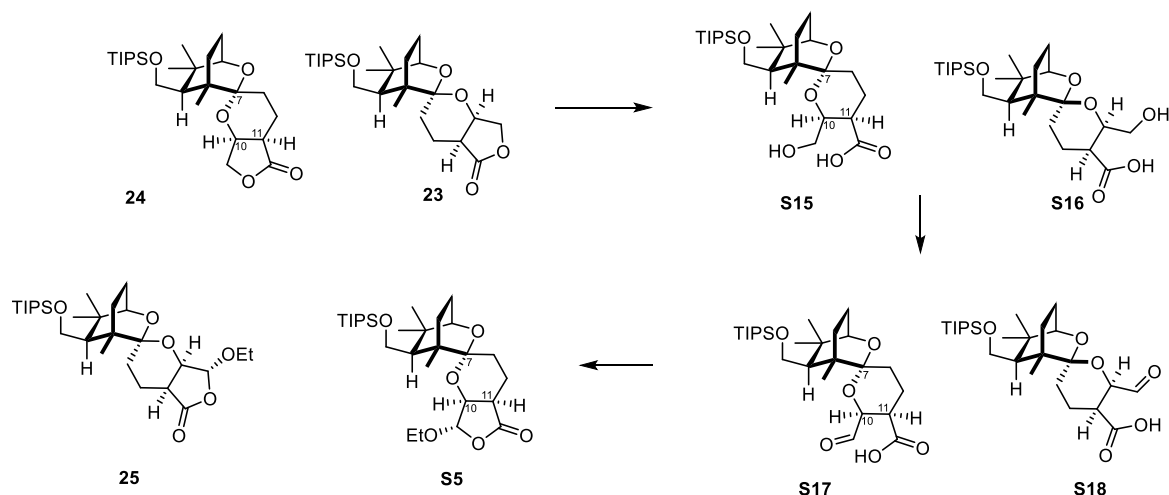
A suspension of **7** (157 mg, 0.022 mmol, mixture of C7 epimers 9:1) and 5% Rh-Al₂O₃ (53 mg, 0.04 mmol, w/w) in MeOH (45 mL) was stirred at rt under an atmosphere of H₂ (65 psi, Parr hydrogenator) for 60 h. The suspension was then filtered and concentrated in vacuo to afford a mixture of spiroketal **23** and spiroketal **24** (154 mg, 1:1.2 **23-24**, 98% combined yield) as a clear oil.

IR (film) ν_{max} 2925, 2858, 1785, 1463, 1261, 1025, 799 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 4.74 (t, J = 3.8 Hz, 1H), 4.29 – 4.18 (m, 2H), 3.80 (ddd, J = 10.2, 7.5, 2.1 Hz, 2H), 3.29 (dd, J = 4.6, 2.4 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.38 – 2.20 (m, 1H), 2.18 – 2.08 (m, 1.5H), 1.85 – 1.76 (m, 1.5H), 1.62 – 1.54 (m, 2.5H), 1.52 – 1.50[†] (m, 0.5H), 1.48 – 1.43 (m, 1H), 1.26 (m, 1H), 1.13 – 1.03 (m, 27H), 1.00 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 177.84^{*} (C), 177.75[†] (C), 101.1^{*} (C), 100.8[†] (C), 78.7[†] (CH), 78.1^{*} (CH), 72.8[†] (CH₂), 72.6^{*} (CH₂), 68.65^{*} (CH), 68.63[†] (CH), 61.3[†] (CH₂), 61.0^{*} (CH₂), 47.3 (CH), 44.2[†] (CH), 39.0^{*} (CH), 38.9[†] (CH), 38.2^{*} (C), 38.0[†] (C), 36.5^{*} (C), 35.8[†] (C), 30.8[†] (C), 30.6^{*} (C), 26.1[†] (CH₂), 25.3^{*} (CH₂), 23.6^{*} (CH₂), 23.5[†] (CH₂), 22.9^{*} (CH₂), 22.7[†] (CH₂), 21.6[†] (CH₃), 21.2^{*} (CH₃), 19.7^{*} (CH₃), 19.4[†] (CH₃), 18.3 (6 × CH₃, SiCH₂CH₃), 16.2^{*} (CH₂), 16.1[†] (CH₂), 12.09[†] (3 × CH), 12.05^{*} (3 × CH); **HRMS** (ESI+) [M + Na]⁺ 489.2990 calc for C₂₆H₄₆NaO₅Si 489.3007.

*denotes signal arising exclusively from minor diastereomer; [†]denotes signal arising exclusively from major diastereomer; undesignated signals arise from a mixture of both.

NB: spiroketal configuration of **24** was assigned based on through-space deshielding of the H-6 resonance (δ 2.18 – 2.08 compared with δ 1.52 – 1.50 in **23**) by the spiroketal oxygen. See HSQC for supporting detail.

Spiroketal **25**; spiroketal **S5**



A solution of **23-24** mixture (96 mg, 0.094 mmol **23**; 0.11 mmol **24**) in 1 M LiOH-THF (1:3, v/v, 10 mL) was stirred at rt for 16 h, then diluted with 1 M HCl (10 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo.

The crude oil was dissolved in CH₂Cl₂ (2 mL), DMP was added (174 mg, 0.41 mmol), and the resulting mixture was stirred at rt. After 30 min 5 % Na₂S₂O₃ (5 mL, w/v) was added, and the reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo.

The crude oil was dissolved in EtOH (15 mL) and PPTS (51 mg, 0.20 mmol) was added. The resulting solution was stirred for 24 h at 45 °C. Sat. aq. NaHCO₃ was then added (40 mL) and the reaction mixture was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried over Na₂SO₄, concentrated in vacuo, and purified by flash chromatography (5-35% Et₂O in pet ether) to afford spiroketal **25** (40 mg, 84% over four steps) and spiroketal **S5** (14 mg, 24% over four steps) as clear oils.

Data for **25**

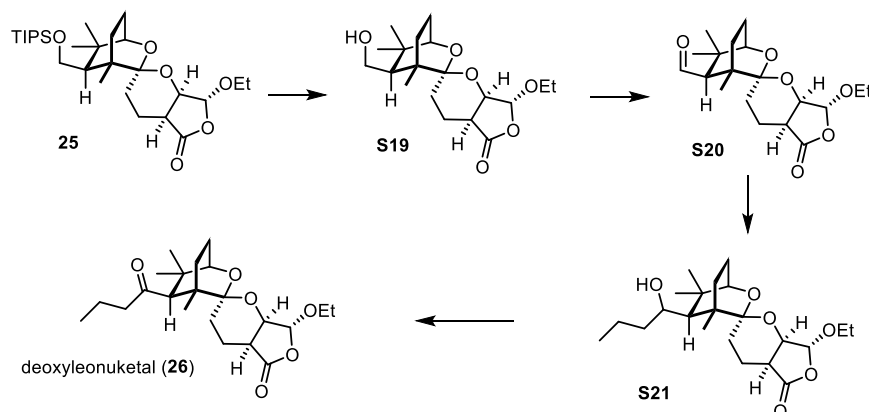
IR (film) ν_{max} 2963, 2924, 2853, 1792, 1465, 1111, 1022 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 5.23 (s, 1H), 4.50 (d, J = 4.4 Hz, 1H), 3.90 – 3.75 (m, 3H), 3.63 (dq, J = 9.5, 7.1 Hz, 2H), 3.30 (t, J = 2.6 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.22 (td, J = 13.6, 6.2, 4.5 Hz, 1H), 2.10 (ddt, J = 9.1, 4.5, 2.1 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.72 (m, 2H), 1.53 – 1.48 (m, 2H), 1.37 (td, J = 13.3, 4.9 Hz, 1H), 1.31 – 1.27 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 6.8 Hz, 24H), 1.00 (s, 3H), 0.76 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃)

δ 177.9 (C), 105.8 (CH), 100.8 (C), 78.0 (CH), 72.3 (CH), 65.2 (CH₂), 60.9 (CH₂), 47.3 (CH), 38.2 (C), 37.2 (CH), 36.5 (C), 30.6 (CH₃), 25.5 (CH₂), 23.5 (CH₂), 21.6 (CH₂), 21.0 (CH₃), 19.7 (CH₃), 18.3 (6 \times CH₃), 15.8 (CH₂), 15.1 (CH₃), 12.0 (3 \times CH); **HRMS** (ESI+) [M + Na]⁺ 533.3258 calc for C₂₈H₅₀NaO₆Si 533.3269; crystals were obtained for XRD analysis by evaporation from petroleum ether, mp 75–78 °C.

Data for **S5**

IR (film) ν_{\max} 3000, 2960, 2923, 2851, 1771, 1375, 1247, 1056 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 5.18 (s, 1H), 4.50 (d, J = 4.3 Hz, 1H), 3.89 – 3.77 (m, 2H), 3.64 (dq, J = 9.5, 7.0 Hz, 1H), 3.29 (t, J = 2.3 Hz, 1H), 2.75 (t, J = 4.3 Hz, 1H), 2.32 – 2.22 (m, 1H), 2.12 (td, J = 11.2, 5.0 Hz, 2H), 1.84 – 1.76 (m, 1H), 1.60 – 1.51 (m, 2H'), 1.47 – 1.42 (m, 1H), 1.23 (s, 3H), 1.19 – 1.11 (m, 5H), 1.10 – 1.03 (m, 21H), 1.00 (s, 3H), 0.80 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 177.9 (C), 105.8 (CH), 100.5 (C), 78.7 (CH), 72.2 (CH), 65.2 (CH₂), 61.4 (CH₂), 44.2 (CH), 38.0 (C), 37.1 (CH), 35.8 (C), 30.9 (CH₃), 26.4 (CH₂), 23.4 (CH₂), 22.7 (CH₂), 21.6 (CH₃), 19.4 (CH₃), 18.3 (6 \times CH₃), 15.7 (CH₂), 15.0 (CH₃), 12.1 (3 \times CH); **HRMS** (ESI+) [M + Na]⁺ 533.3268 calc for C₂₈H₅₀NaO₆Si 533.3269

Deoxyleonuketal (**26**)



To TIPS ether **26** (38.5 mg, 0.075 mmol) in THF (2 mL) at rt was added TBAF (0.38 mL, 0.38 mmol, 1.0 M in THF). The resulting mixture was heated to 40 °C and stirred for 2 hours, before cooling to rt. Sat. aq. NaHCO₃ (10 mL) was then added, and the resulting mixture was extracted with CH₂Cl₂ (3 \times 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo to give the putative alcohol **S19** as a crude oil.

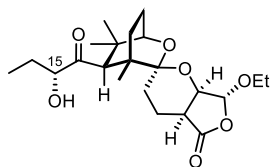
The crude material of **S19** was immediately dissolved in CH₂Cl₂ (2 mL) then K₂CO₃ (72 mg, 0.53 mmol) and DMP (128 mg, 0.30 mmol) were added. The resulting mixture was stirred at rt for 30 min, then quenched by addition of 5% aq. sodium thiosulfate (5 mL, w/w). The resulting mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. The resulting oil was filtered through a short plug of silica eluting with 40% Et₂O in pet. ether, delivering putative aldehyde **S20** (~18 mg, ~0.05 mmol) which was used in the following step immediately.

To the aldehyde **S20** (~18 mg, ~0.05 mmol) in THF (1 mL) at 0 °C was added propylmagnesium bromide (74 µL, 0.093 mmol, 1.25 M in diethyl ether). The resulting solution was stirred for 1 h at 0 °C, then quenched by addition of H₂O (3 mL). The mixture was extracted with Et₂O (3 × 5 mL) and the combined organic phases were dried over Na₂SO₄, then concentrated in vacuo to afford the crude putative alcohol **S21**.

The crude material of **S21** was immediately dissolved in CH₂Cl₂ (1 mL), then K₂CO₃ (50 mg, 0.36 mmol) and DMP (88 mg, 0.21 mmol) were added. The resulting mixture was stirred at rt for 30 min, then quenched by addition of 5% aq. sodium thiosulfate (5 mL, w/w). The resulting mixture was then extracted with CH₂Cl₂ (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude residue was purified by flash chromatography (20% Et₂O in pet ether) to afford deoxyleonuketal (**26**) (15.4 mg, 57% over four steps) as a clear oil.

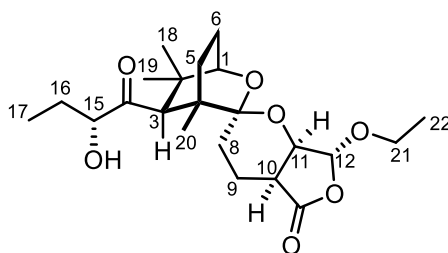
IR (film) ν_{max} 2959, 1788, 1117, 1027, 972, 920 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 5.23 (s, 1H), 4.49 (d, J = 4.4 Hz, 1H), 3.86 (dq, J = 9.5, 7.1 Hz, 1H), 3.63 (dq, J = 9.5, 7.1 Hz, 1H), 3.35 (t, J = 2.7 Hz, 1H), 2.78 – 2.72 (m, 1H), 2.50 (d, J = 2.2 Hz, 1H), 2.38 – 2.31 (m, 3H), 2.27 – 2.18 (m, 1H), 2.13 (dd, J = 9.2, 6.8 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.68 – 1.49 (m, 4H), 1.41 (dd, J = 12.3, 4.4 Hz, 1H), 1.25 – 1.19 (m, 6H), 0.92 (t, J = 7.4 Hz, 3H), 0.83 (s, 3H), 0.75 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 211.0 (C), 177.7 (C), 105.7 (CH), 100.0 (C), 77.9 (CH), 72.4 (CH), 65.3 (CH₂), 56.8 (CH), 50.3 (CH₂), 39.0 (C), 37.1 (CH), 36.2 (C), 30.4 (CH₃), 25.7 (CH₂), 23.5 (CH₂), 22.7 (CH₂), 19.6 (CH₃), 18.8 (CH₂), 16.8 (CH₃), 15.7 (CH₂), 15.0 (CH₃), 13.9 (CH₃); **HRMS** (ESI+) [M + Na]⁺ 417.2251 measured calc for C₂₂H₃₄NaO₆ 417.2248

Leonuketal (**1**)



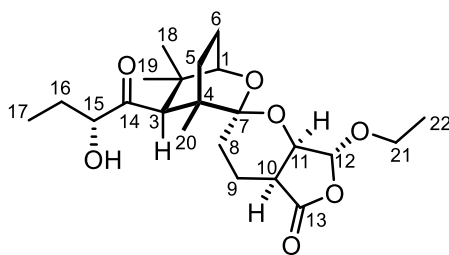
To a stirred solution of deoxyleonuketal (**26**) (2.0 mg, 0.0051 mmol) in THF (0.6 mL) at $-78\text{ }^{\circ}\text{C}$ under argon was added LiHMDS (23 μL , 0.020 mmol, 0.9 M in THF). The resulting solution was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$, then oxygen was bubbled through the solution for 30 min at $-78\text{ }^{\circ}\text{C}$. The reaction vessel headspace was then flushed with argon for 10 min, then another portion of LiHMDS (56 μL , 0.051 mmol, 0.9 M in THF) was added. The resulting solution was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$, then oxygen was bubbled through the solution for 1 h at $-78\text{ }^{\circ}\text{C}$. The reaction vessel headspace was then flushed again with argon for 10 min, and a final portion of LiHMDS (113 μL , 0.101 mmol, 0.9 M in THF) was added. The resulting solution was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$, then oxygen was bubbled through the solution for 1 h at $-78\text{ }^{\circ}\text{C}$. $\text{P}(\text{OEt})_3$ (5 μL , 0.030 mmol) was then added and the reaction was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$, before being quenched by addition of sat. aq. NH_4Cl (2 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O ($3 \times 4\text{ mL}$). The combined organic phases were dried over MgSO_4 and concentrated in vacuo. The crude mixture was then purified by flash chromatography (30% Et_2O in pet. ether) to give recovered deoxyleonuketal (**26**) (0.4 mg), and a mixture of leonuketal **1** and 14-*epi*-leonuketal (*epi*-**1**) (1.0 mg, 48% combined, 60% brsm, 1:1 *dr*). An analytical sample of leonuketal (**1**) was purified by RP-HPLC (Phenomenex Gemini® C18 column, 5 μm , 110 \AA , 250 \times 10 mm) using a gradient of H_2O :MeOH (40 – 100% B over 80 min, 3 mL/min) detecting at 210 nm (t_{R} = 34.4 min).

NB: While the *dr* of the reaction was typically 1:1, we observed a 2:1 *dr* in favour of leonuketal (**1**) at low conversion.

Table S6. Comparison of ^1H -NMR data of natural and synthetic leonuketal (**1**)⁷

H	natural δ_{H} (600 MHz, d_6 -acetone)	synthetic δ_{H} (500 MHz, d_6 -acetone)	$\Delta\delta_{\text{H}}$
1	3.46 (dd, $J = 3.0, 2.4$ Hz)	3.45 (dd, $J = 3.0, 2.4$ Hz)	-0.01
3	2.94 (d, $J = 2.4$ Hz)	2.93 (d, $J = 2.1$ Hz)	-0.1
5a	2.39 (ddd, $J = 13.2, 10.8, 8.4$ Hz)	2.39 (ddd, $J = 12.7, 11.0, 8.4$ Hz)	0
5b	1.56 (dddd, $J = 13.2, 10.8, 2.4, 2.4$ Hz)	1.56 (dddd, $J = 12.7, 11.0, 2.0, 2.0$ Hz)	0
6a	1.87 (m)	1.87 (m)	0
6b	1.81 (m)	1.81 (m)	0
8a	1.79 (ddd, $J = 13.2, 4.8, 2.4$ Hz)	1.79 (m)	0
8b	1.34 (ddd, $J = 13.2, 13.2, 4.8$ Hz)	1.34 (m)	0
9a	2.24 (dddd, $J = 13.8, 13.2, 6.0, 4.8$ Hz)	2.24 (m)	0
9b	2.00 (dddd, $J = 13.8, 4.8, 2.4, 2.4$)	obscured by acetone	-
10	2.78 (ddd, $J = 6.0, 4.2, 2.4$)	obscured by H_2O	-
11	4.48 (d, $J = 4.2$)	4.48 (d, $J = 4.4$)	0
12	5.31 (s)	5.31 (s)	0
15	3.96 (m)	3.97 (m)	+0.01
16a	1.90 (m)	1.89 (m)	-0.1
16b	1.40 (m)	1.40 (m)	0
17	0.98 (t, $J = 7.2$)	0.97 (t, $J = 7.4$)	-0.1
18	0.81 (s)	0.80 (s)	-0.1
19	1.24 (s)	1.24 (s)	0
20	0.75 (s)	0.74 (s)	-0.1
21a	3.81 (dq, $J = 9.6, 7.2$ Hz)	3.81 (dq, $J = 9.4, 7.3$ Hz)	0
21b	3.69 (dq, $J = 9.6, 7.2$ Hz)	3.69 (dq, $J = 9.4, 7.3$ Hz)	0
22	1.20 (t, $J = 7.2$ Hz)	1.20 (t, $J = 7.2$ Hz)	0

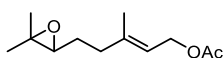
⁷ Xiong, L.; Zhou, Q.-M.; Zou, Y.; Chen, M.-H.; Guo, L.; Hu, G.-Y.; Liu, Z.-H.; Peng, C. Leonuketal, a Spiroketal Diterpenoid from Leonurus Japonicus. *Org. Lett.* **2015**, *17* (24), 6238–6241. <https://doi.org/10.1021/acs.orglett.5b03227>.

Table S7. Comparison of ^1H -NMR data of natural and synthetic leonuketal (**1**)⁷

C	natural	synthetic	$\Delta\delta_{\text{H}}$
	δ_{C} (600 MHz, d_6 -acetone)	δ_{C} (500 MHz, d_6 -acetone)	
1	78.4	78.3	-0.1
2	37.3	37.3	0
3	52.8	52.7	-0.1
4	39.6	39.6	0
5	20.7	20.7	0
6	23.2	23.1	-0.1
7	100.7	100.7	0
8	26.3	26.3	0
9	16.4	16.4	0
10	37.5	37.5	0
11	73.2	73.2	0
12	105.9	105.9	0
13	177.3	177.4	-0.1
14	213.8	213.8	0
15	80.1	80.1	0
16	27.2	27.2	0
17	10.2	10.2	0
18	23.7	23.6	-0.1
19	30.1	obscured by acetone	-
20	19.1	19.1	0
21	65.6	65.6	0
22	15.3	15.3	0

6. Experimental Procedures: Additional compounds

Epoxide **14**

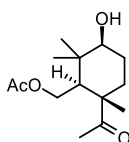


To a stirred solution of geranyl acetate (9.80 g, 50.1 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added *m*-CPBA (11.3 g, 50.3 mmol, 77% w/w). After 1 h, the solution was allowed to warm to rt and 3 M NaOH (25 mL) was added. The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic phases were then washed with brine (2 × 30 mL), dried over MgSO₄, and concentrated in vacuo. The crude oil was purified by flash chromatography (15% EtOAc in pet. ether) to afford the epoxide **14** (7.25 g, 68%) as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 5.39-5.35 (m, 1H), 4.58 (d, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 1H), 2.26-2.10 (m, 2H), 2.04 (s, 3H), 1.71 (s, 3H), 1.70-1.62 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 171.1 (C), 141.3 (C), 118.8 (C), 63.9 (CH), 61.2 (CH), 58.4 (C), 36.1 (CH₂), 27.0 (CH₂), 24.8 (CH₃), 21.0 (CH₃), 18.7 (CH₃), 16.4 (CH₃).

Spectroscopic data were in good agreement with those previously reported.⁸

Ketone **15**



A mixture of Cp₂TiCl₂ (272 mg, 1.1 mmol, 2.2 equiv) and Zn dust (215 mg, 3.3 mmol, 6.6 equiv) in deoxygenated⁹ THF (5 mL) was stirred at rt for 15 min. The resulting green solution was then added dropwise over 1 h *via* syringe pump to a stirred solution of epoxide **14** (110 mg, 0.50 mmol) in deoxygenated THF (5 mL) at rt. After 6 h, the reaction mixture was quenched with sat. aq. KH₂PO₄ solution (10 mL). The mixture was stirred for an additional 30 min then filtered over Celite[®] to remove insoluble titanium salts. The filtrate was then washed with EtOAc (2 × 20 mL) and the combined

⁸ Surendra, K.; Rajendar, G.; Corey, E. J. Useful Catalytic Enantioselective Cationic Double Annulation Reactions Initiated at an Internal π -Bond: Method and Applications. *J. Am. Chem. Soc.* **2014**, 136 (2), 642–645. <https://doi.org/10.1021/ja4125093>

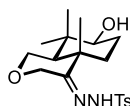
⁹ THF deoxygenated by three freeze-pump-thaw cycles

organic phases were washed with sat. aq. NaHCO₃ (10 mL), brine (10 mL), dried over MgSO₄, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (50% EtOAc in pet. ether) to give ketone **15** as an oil (16 mg, 13%).

IR (film) ν_{\max} 2971, 1739, 1366, 1229, 1217 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.30 (dd, J = 11.5, 4.3 Hz, 1H), 3.99 (dd, J = 11.5, 9.8 Hz, 1H), 3.39 (dd, J = 10.9, 3.7 Hz, 1H), 2.28 (dd, J = 9.8, 4.3 Hz, 1H), 2.17 (s, 3H), 1.95 (s, 3H), 1.75 – 1.57 (m, 3H), 1.50 – 1.44 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 213.3 (C), 170.7 (C), 77.8 (CH), 62.7 (CH₂), 50.7 (C), 47.3 (CH), 38.4 (C), 34.5 (CH₂), 28.6 (CH₃), 26.7 (CH₂), 25.5 (CH₃), 20.9 (CH₃), 17.0 (CH₃), 16.0 (CH₃); **HRMS** (ESI+) [M + Na]⁺ 279.1563 calcd for C₁₄H₂₄NaO₄ 279.1567.

NB: the *dr* could not be determined for the reaction due to inseparable nature of the reaction by-products and the largely unresolved crude ¹H-NMR spectrum.

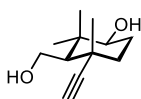
Tosyl hydrazone **S22**



To ketone **13** (345 mg, 1.63 mmol) and *p*-toluenesulfonyl hydrazide (303 mg, 1.63 mmol) in THF (3 mL) at rt was added PPTS (2 mg, 0.08 mmol). The resulting solution was allowed to stir at rt for 16 h. The mixture was then diluted in EtOAc (100 mL) and washed with H₂O (10 mL), then brine (10 mL), dried over MgSO₄, and concentrated *in vacuo* to give tosyl hydrazone **S22** as a white powder (583 mg, 94%).

IR (film) ν_{\max} 2972, 2924, 1739, 1323, 1161, 665 cm⁻¹; **¹H NMR** (400 MHz, DMSO-*d*₆) δ 10.01 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.41 – 7.37 (m, 2H), 4.47 (d, J = 5.1 Hz, 1H), 4.22 (d, J = 15.6 Hz, 1H), 4.05 (d, J = 15.6 Hz, 1H), 3.78 – 2.95 (m, 2H), 2.98 (dt, J = 10.9, 4.8 Hz, 1H), 2.38 (s, 3H), 1.63 – 1.45 (m, 3H), 1.41 – 1.28 (m, 2H), 1.06 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H); **¹³C NMR** (101 MHz, DMSO-*d*₆) δ 165.6 (C), 143.1 (C), 136.0 (C), 129.2 (2 × CH), 127.5 (2 × CH), 76.1 (CH), 62.8 (CH₂), 60.7 (CH₂), 48.5 (CH), 39.6 (C), 37.6 (C), 33.3 (CH₂), 27.4 (CH₃), 26.9 (CH₂), 21.0 (CH₃), 20.3 (CH₃), 15.8 (CH₃); **HRMS** (ESI+) [M + Na]⁺ 403.1653 calcd for C₁₉H₂₈N₂NaO₄S 403.1662.

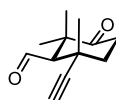
Alkyne **S1**



A solution of MeLi (2.09 mL, 4.18 mmol, 2.0 M in dimethoxyethane) was added to Et₂O (5 mL) at 0 °C. To the resulting stirred solution was added dropwise a suspension of *p*-toluenesulfonyl hydrazone **S22** (256 mg, 0.70 mmol) in THF (5 mL) over 10 min. The resulting mixture was stirred at 0 °C for a further 1.5 h before the addition of H₂O (15 mL). The mixture was then extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic phases were washed with brine (40 mL), dried over Na₂SO₄, and then concentrated in vacuo. The crude oil was then purified by flash chromatography (40% EtOAc in pet. ether) to give alcohol **S1** (128 mg, 94%) as a clear oil.

IR (film) ν_{max} 3290, 2935, 2875, 1738, 1459, 1082, 983 cm⁻¹; **¹H NMR** (400 MHz, DMSO-*d*₆, 70 °C)¹⁰ δ 4.43 (d, *J* = 5.2 Hz, 1H), 4.18 (dd, *J* = 5.7, 3.7 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.70 (dt, *J* = 11.4, 5.8 Hz, 1H), 3.17 – 3.07 (m, 1H), 2.74 (s, 1H), 1.72 (ddd, *J* = 6.7, 5.9, 3.4 Hz, 1H), 1.66 – 1.55 (m, 2H), 1.46 (dddd, *J* = 12.1, 9.9, 7.7, 4.2 Hz, 1H), 1.40 – 1.36 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.87 (s, 3H); **¹³C NMR** (101 MHz, DMSO-*d*₆, 70 °C) δ 94.9 (C), 76.1 (CH), 69.9 (CH), 60.7 (CH₂), 54.6 (CH), 39.5 (CH), 38.0 (CH₂), 34.5 (CH₂), 29.6 (CH₃), 27.3 (CH₃), 23.7 (CH₃), 18.7 (C); **HRMS** (ESI+) [*M* + Na]⁺ 219.1348 calcd for C₁₂H₂₀NaO₂ 219.1356.

Keto aldehyde **16**

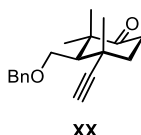


To a solution of alcohol **S1** (85 mg, 0.43 mmol) in CH₂Cl₂ (2.5 mL) at rt was added K₂CO₃ (479 mg, 3.46 mmol) and DMP (643 mg, 1.52 mmol). The reaction mixture was stirred for 1 h before addition of sat. aq. Na₂S₂O₃ (5 mL) and extraction with EtOAc (3 × 5 mL). The combined organic phases were then washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (10% EtOAc in pet. ether) to afford ketone **16** as a clear oil (75 mg, 90%).

¹⁰ ¹H- and ¹³C-NMR displayed poor resolution at room temperature in CDCl₃, possibly due to ring-flipping

IR (film) ν_{\max} 2929, 1737, 1455, 1095, 697 cm^{-1} ; **^1H NMR** (400 MHz, $\text{DMSO}-d_6$, 70 $^\circ\text{C}^\dagger$) δ 7.37 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 11.9 Hz, 1H), 4.02 (dd, J = 5.9, 3.9 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.76 – 3.68 (m, 1H), 3.03 (dd, J = 10.8, 3.7 Hz, 1H), 2.78 (s, 1H), 1.84 (m, 2H), 1.80 – 1.73 (m, 1H), 1.65 (td, J = 13.1, 3.6 Hz, 1H), 1.44 (dd, J = 6.1, 2.8 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 0.93 (s, 3H); **^{13}C NMR** (101 MHz, $\text{DMSO}-d_6$, 70 $^\circ\text{C}^\dagger$) δ 138.9 (C), 127.7 (2 \times CH), 127.0 (2 \times CH), 126.8 (CH), 93.8 (C), 84.8 (CH), 70.5 (CH), 69.2 (CH_2), 59.9 (CH_2), 54.3 (CH), 38.7 (C), 37.7 (CH_2), 33.8 (C), 28.5 (CH_3), 22.1 (CH_3), 21.9 (CH_3), 17.4 (CH_3); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 309.1813 calcd for $\text{C}_{19}\text{H}_{26}\text{NaO}_2$ 309.1816.

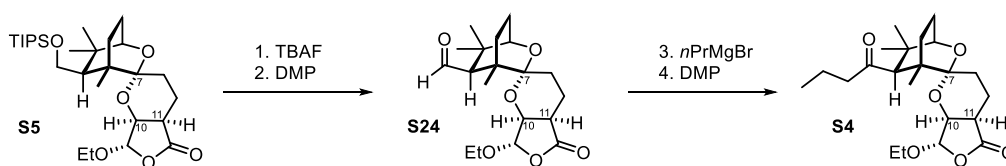
Ketone **17**



To a solution of alcohol **S3** (10 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at rt was added K_2CO_3 (56 mg, 0.41 mmol) and DMP (76 mg, 0.18 mmol). The reaction mixture was stirred for 1 h before addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) and extraction with EtOAc (3 \times 3 mL). The combined organic phases were then washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant crude oil was purified by flash chromatography (5% EtOAc in pet. ether) to afford ketone **17** (10 mg, quant.) as a clear oil.

IR (film) ν_{\max} 2971, 1739, 1366, 1217, 1229 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 7.37 – 7.30 (m, 2H), 7.31 – 7.23 (m, 3H), 4.47 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.69 (d, J = 3.6 Hz, 2H), 2.79 (ddd, J = 15.2, 10.5, 6.1 Hz, 1H), 2.37 (ddd, J = 15.2, 5.8, 5.1 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.23 (s, 1H), 2.07 – 1.99 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 1.17 (s, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ 215.1 (C), 138.2 (C), 128.5 (2 \times CH), 127.7 (CH), 127.6 (2 \times CH), 93.0 (C), 73.3 (CH_2), 69.6 (CH), 68.7 (CH_2), 54.2 (CH), 47.7 (C), 38.0 (CH_2), 34.9 (CH_2), 33.8 (C), 29.2 (CH_3), 26.8 (CH_3), 23.8 (CH_3); **HRMS** (ESI+) $[\text{M} + \text{Na}]^+$ 307.1670 calcd for $\text{C}_{19}\text{H}_{24}\text{NaO}_2$ 307.1679.

Spiroketal **S4**



To TIPS ether **S5** (42 mg, 0.082 mmol) in THF (4 mL) at rt was added TBAF (0.41 mL, 0.41 mmol, 1.0 M in THF). The resulting mixture was heated to 40 °C and stirred for 2 hours, before cooling to rt. Sat. aq. NaHCO₃ (10 mL) was then added, and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo to give the alcohol as a crude oil.

The crude material was immediately dissolved in CH₂Cl₂ (2 mL) then K₂CO₃ (72 mg, 0.53 mmol) and DMP (140 mg, 0.33 mmol) were added. The resulting mixture was stirred at rt for 30 min, then quenched by addition of 5% aq. sodium thiosulfate (5 mL, w/w). The resulting mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. The resulting oil was filtered through a short plug of silica eluting with 40% Et₂O in pet. ether, delivering putative aldehyde **S24** (~16 mg) which was used in the following step immediately.

To the aldehyde **S24** (~16 mg) in THF (1 mL) at 0 °C was added propylmagnesium bromide (51 µL, 0.063 mmol, 1.25 M in diethyl ether). The resulting solution was stirred for 1 h at 0 °C, then quenched by addition of H₂O (3 mL). The mixture was extracted with Et₂O (3 × 5 mL) and the combined organic phases were dried over Na₂SO₄, then concentrated in vacuo to afford the crude alcohol.

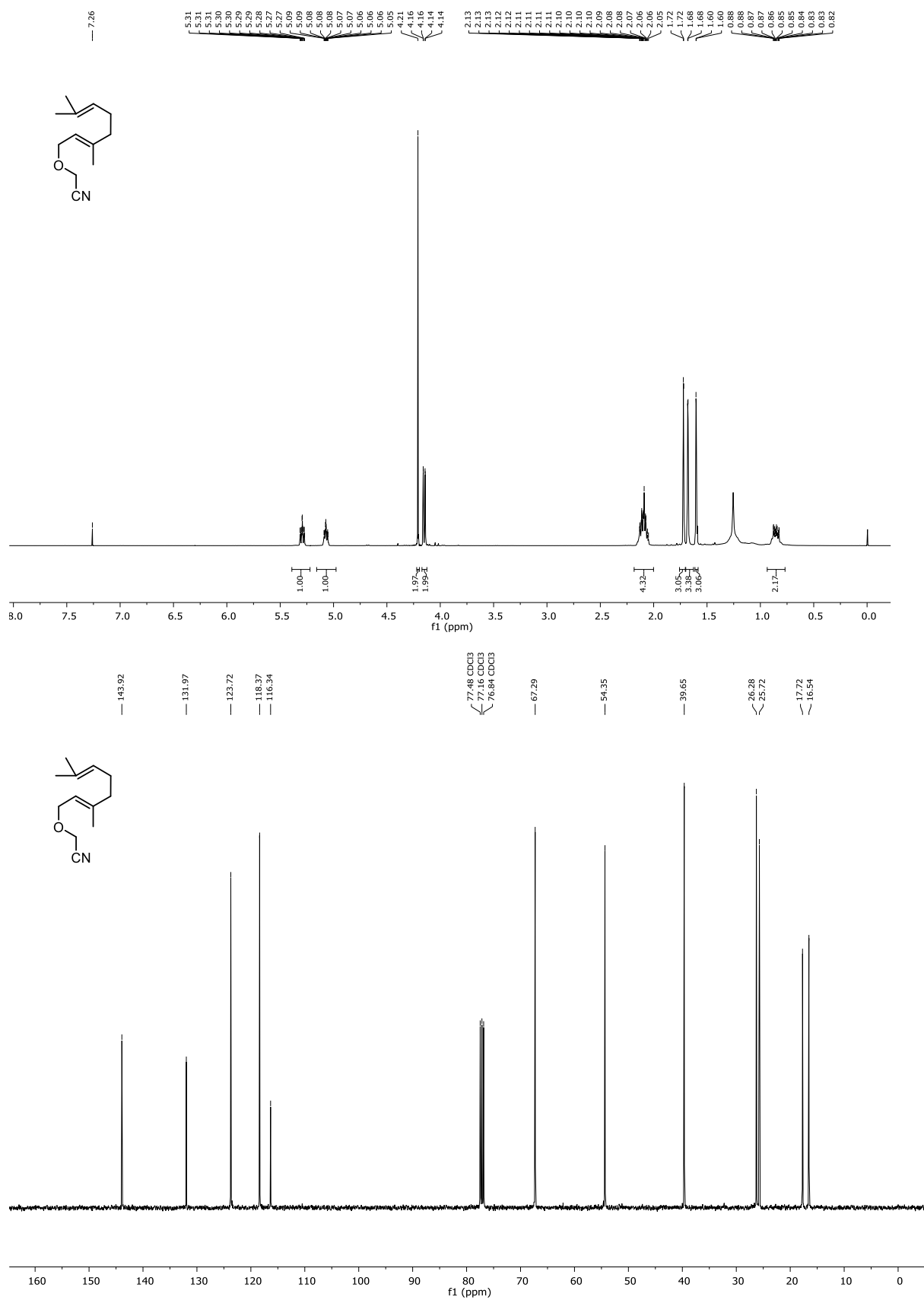
The crude material was immediately dissolved in CH₂Cl₂ (1 mL), then K₂CO₃ (47 mg, 0.34 mmol) and DMP (83 mg, 0.20 mmol) were added. The resulting mixture was stirred at rt for 30 min, then quenched by addition of 5% aq. sodium thiosulfate (5 mL, w/w). The resulting mixture was then extracted with CH₂Cl₂ (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude residue was purified by flash chromatography (20% Et₂O in pet ether) to afford spiroketal (**S4**) (15.4 mg, 44% over four steps) as a clear oil.

IR (film) ν_{max} 2963, 2926, 1261, 1092, 1019 cm⁻¹; **¹H NMR** (500 MHz, CDCl₃) δ 5.25 (s, 1H), 4.51 (d, *J* = 4.3 Hz, 1H), 3.88 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.66 (dq, *J* = 9.5, 7.1

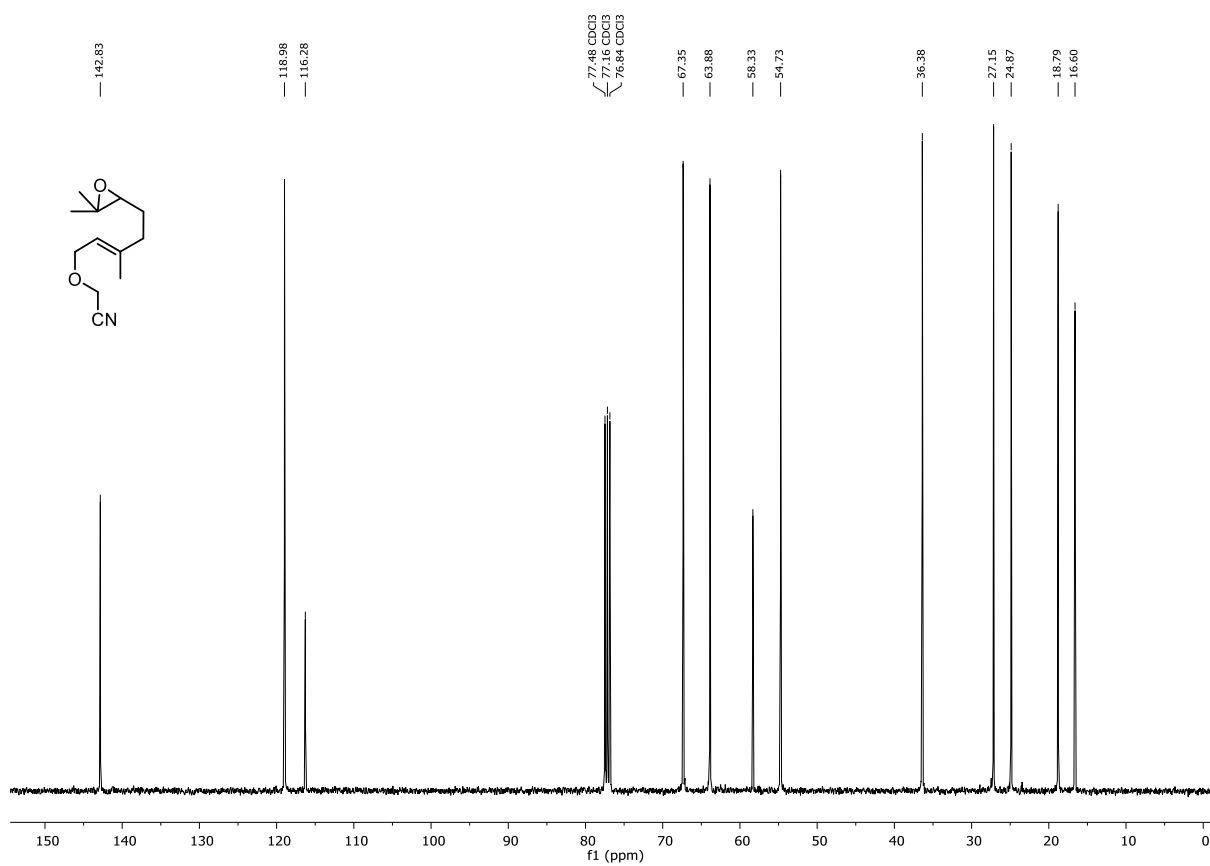
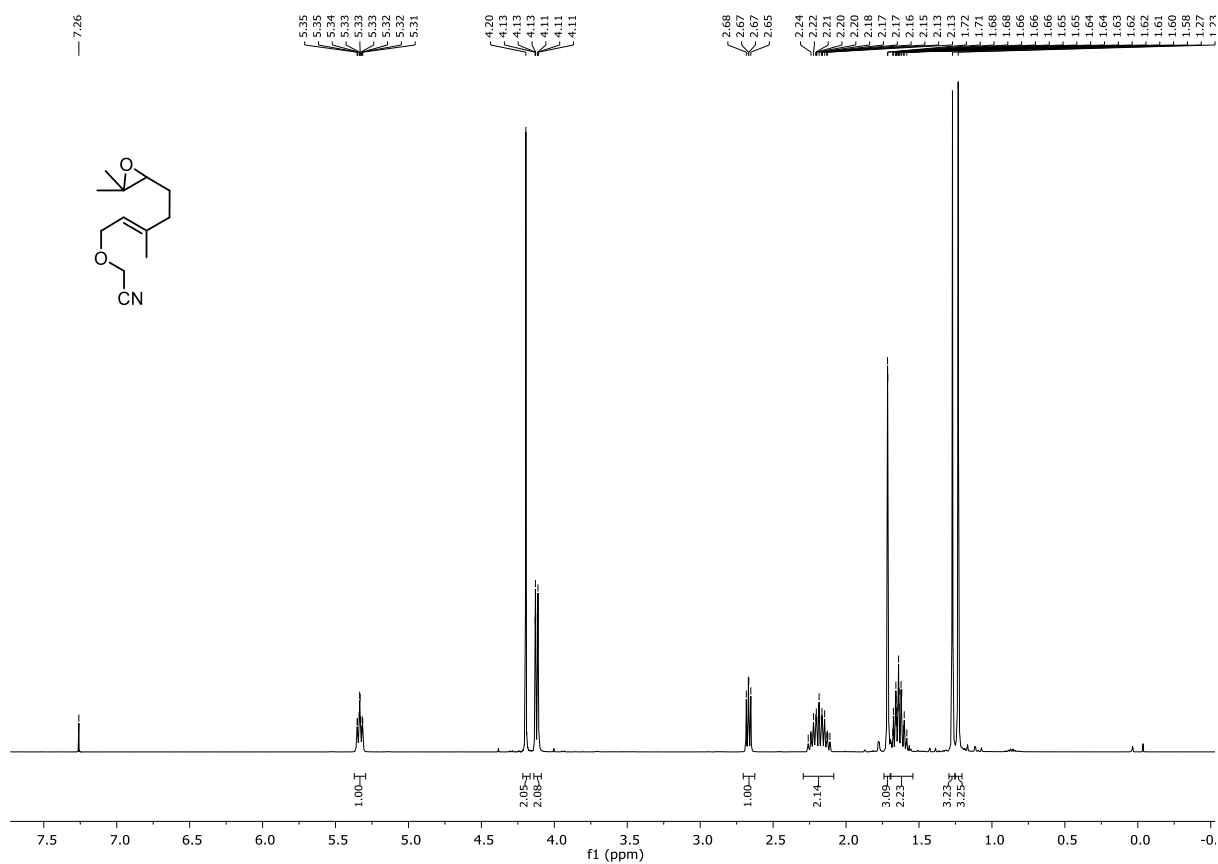
Hz, 1H), 3.35 (dd, J = 3.4, 2.0 Hz, 1H), 3.18 (d, J = 2.2 Hz, 1H), 2.77 (ddd, J = 6.2, 4.3, 1.9 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.37 (t, J = 7.3 Hz, 2H), 2.29 – 2.23 (m, 1H), 2.12 (dd, J = 11.6, 3.3 Hz, 1H), 2.04 (m, 1H), 1.84 (ddd, J = 14.0, 9.3, 2.3 Hz, 1H), 1.61 – 1.56 (m, 2H), 1.53 – 1.48 (m, 2H), 1.28 (s, 3H), 1.24 (d, J = 7.1 Hz, 3H), 1.18 – 1.13 (m, 1H), 0.92 (t, J = 7.4 Hz, 3H), 0.81 (s, 3H), 0.77 (s, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 212.5 (C), 177.6 (C), 105.6 (CH), 100.2 (C), 78.5 (CH), 72.4 (CH), 65.2 (CH₂), 53.7 (CH), 50.5 (CH₂), 38.8 (C), 37.0 (CH), 35.2 (C), 30.7 (CH₃), 26.0 (CH₂), 23.9 (CH₂), 22.7 (CH₂), 20.8 (CH₃), 18.6 (CH₂), 16.7 (CH₃), 15.5 (CH₂), 15.1 (CH₃), 13.9 (CH₃); **HRMS** (ESI+) [M + Na] + 417.2251 calcd for C₂₂H₃₄NaO₆ 417.2248

7. ^1H - and ^{13}C -NMR spectra

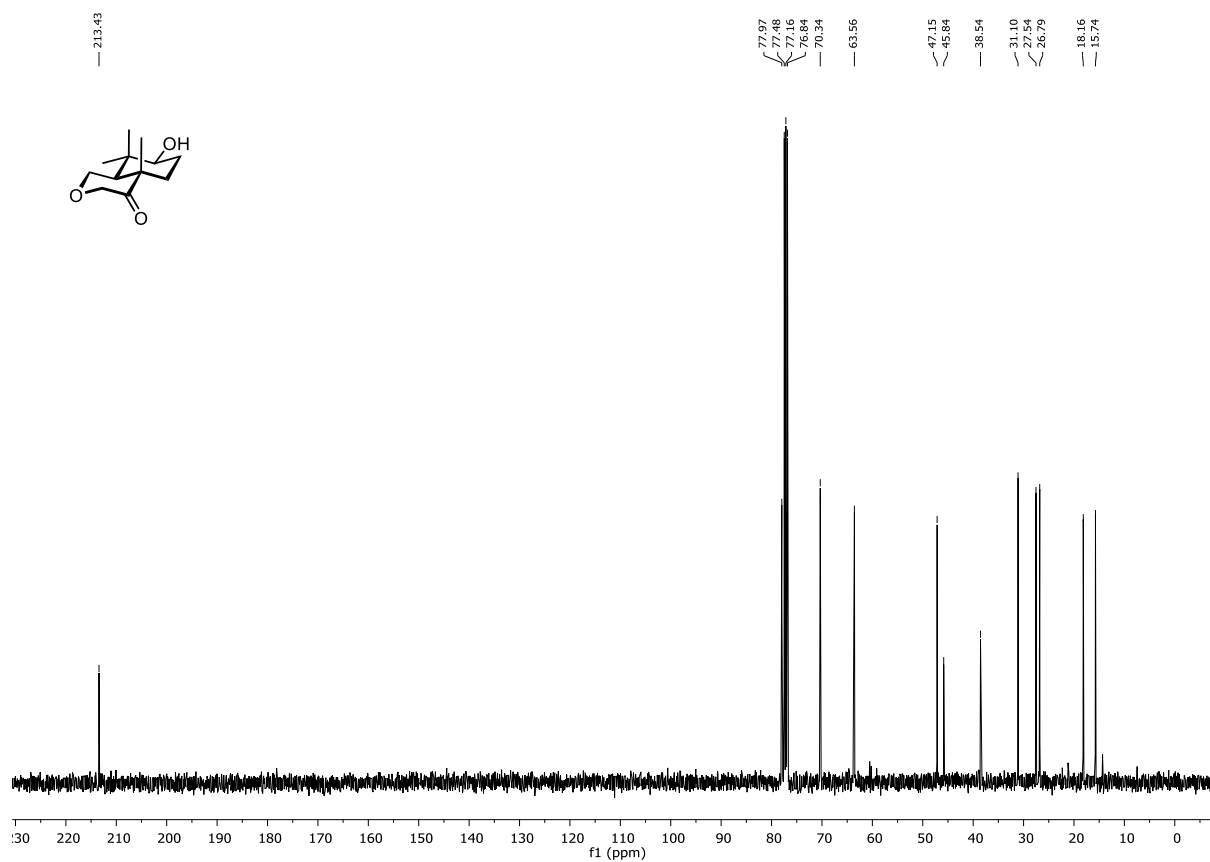
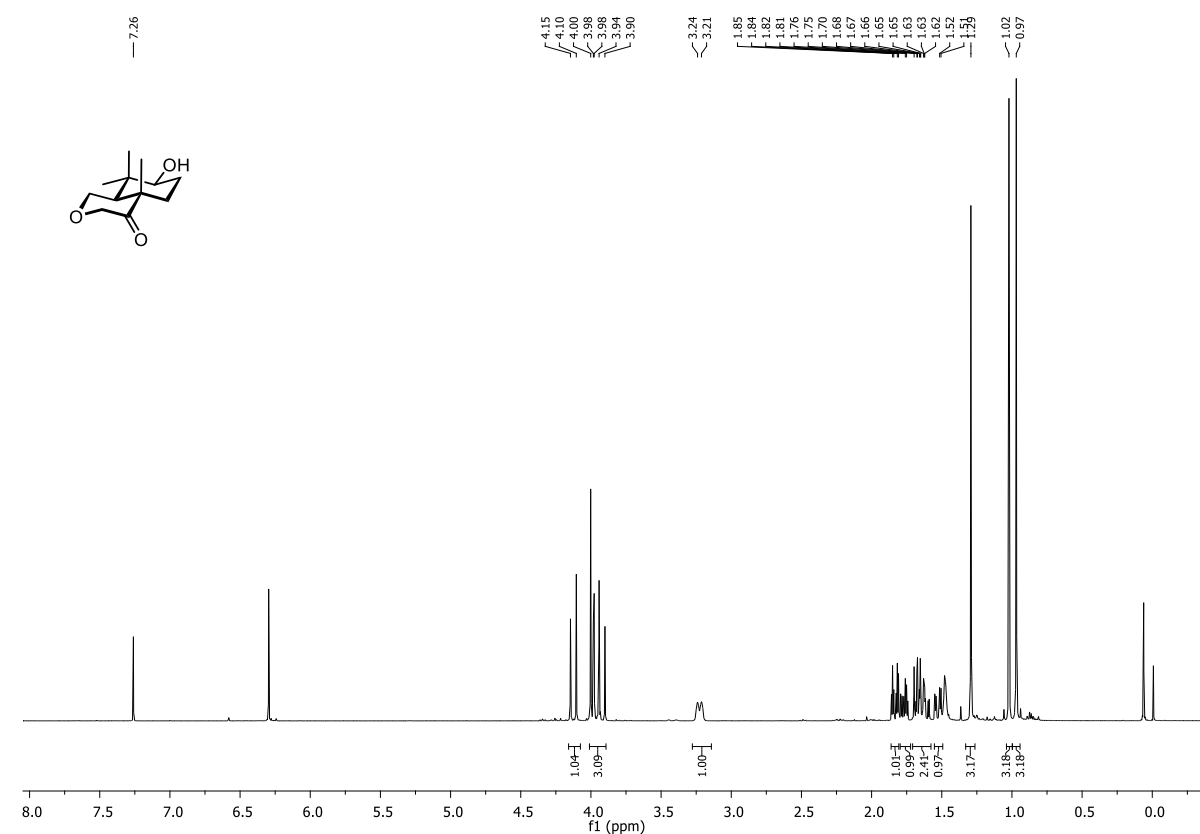
Nitrile **S6**



Epoxide 12

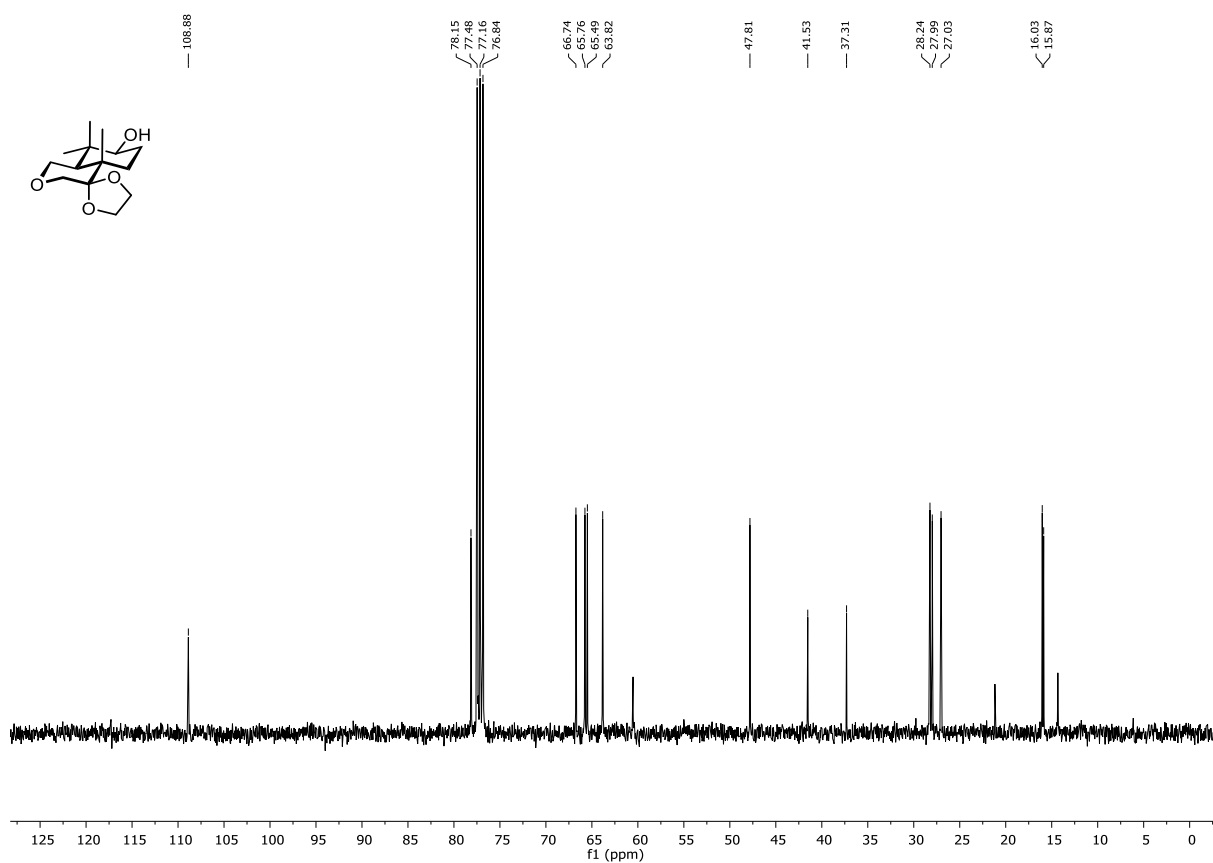


Ketone 13

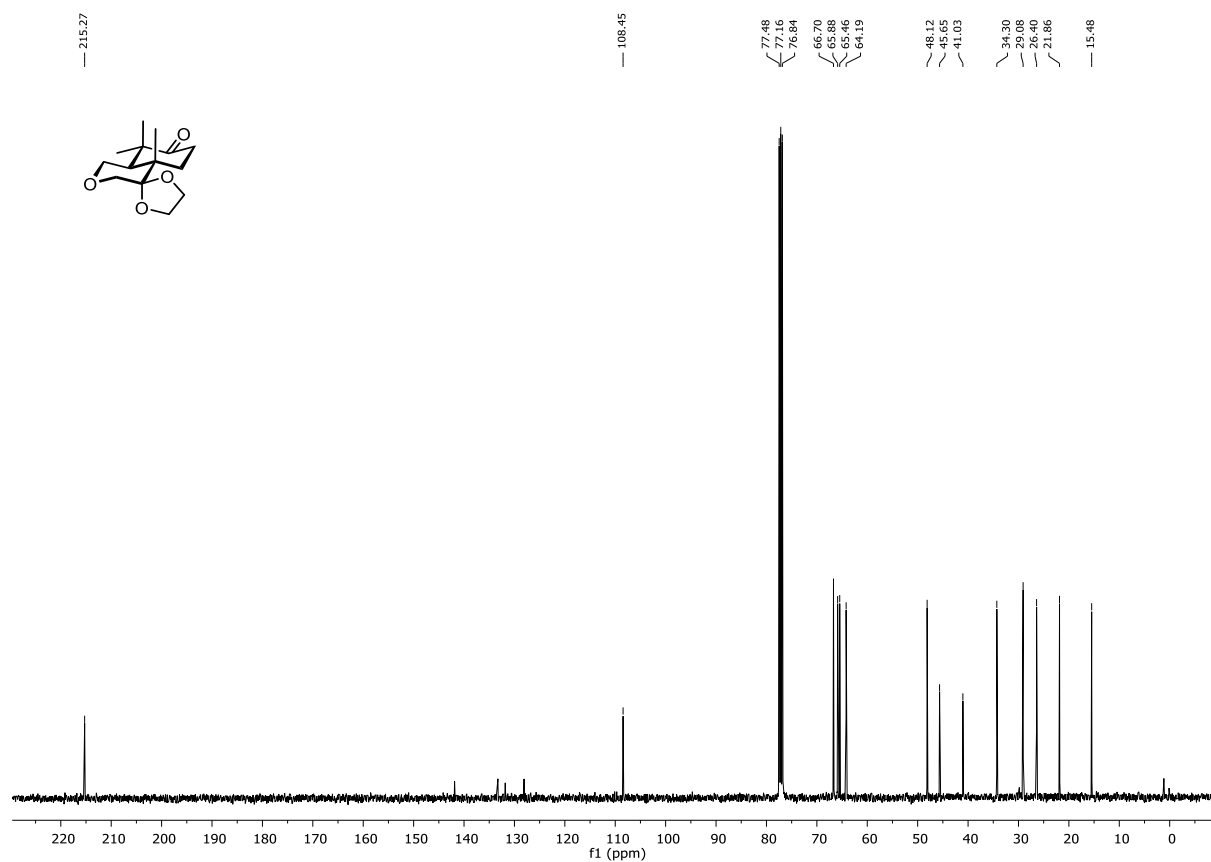
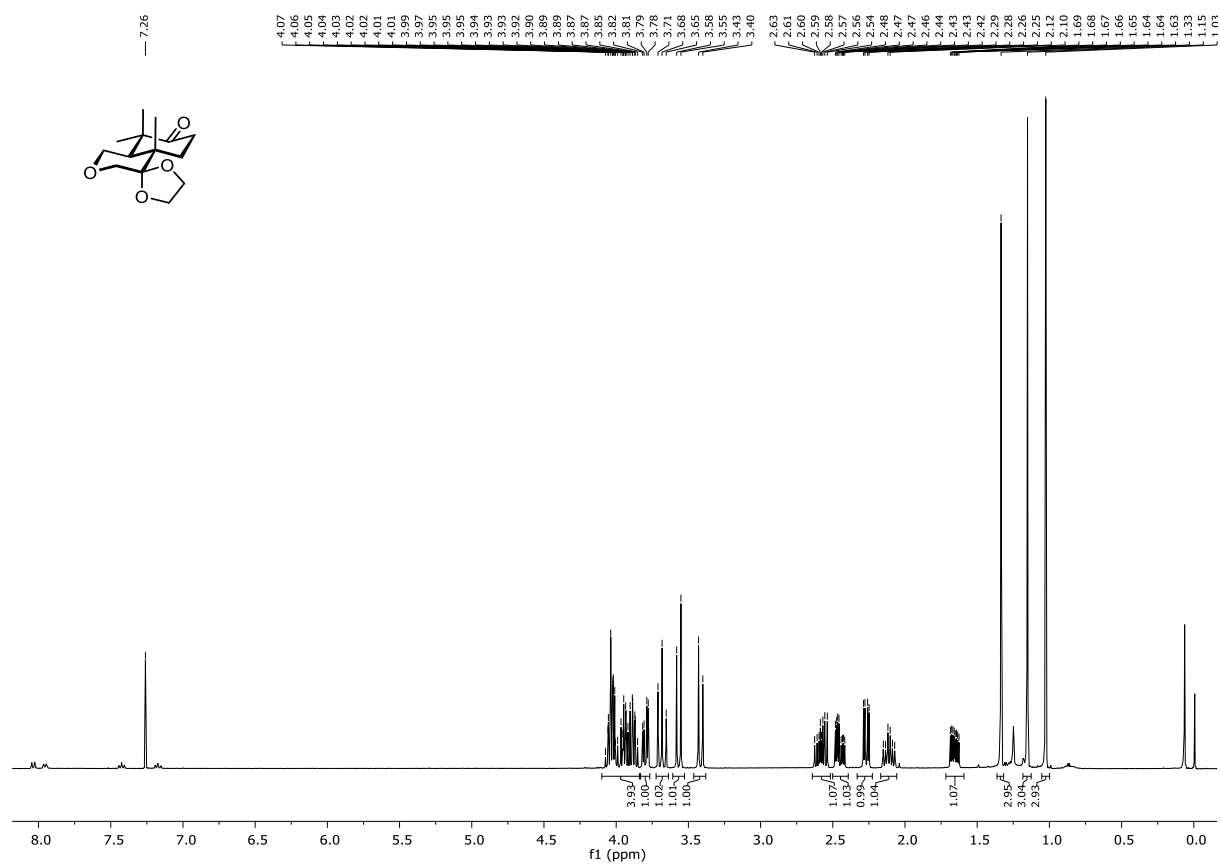


Chemical structure of compound 10a is shown in the top left corner. The ¹H NMR spectrum (CDCl₃) is displayed below the structure, showing peaks from 0.7 to 7.3 ppm. Integration values are provided below the baseline for several peak groups.

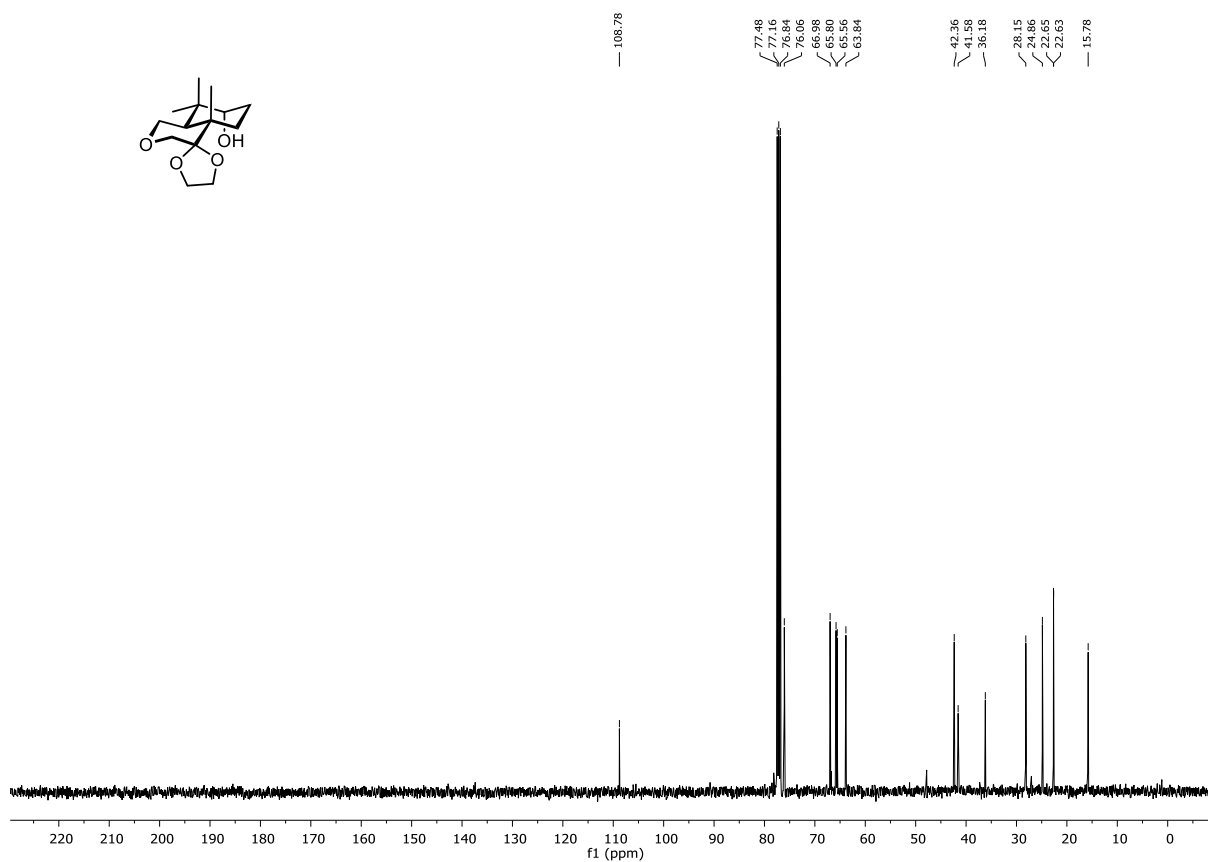
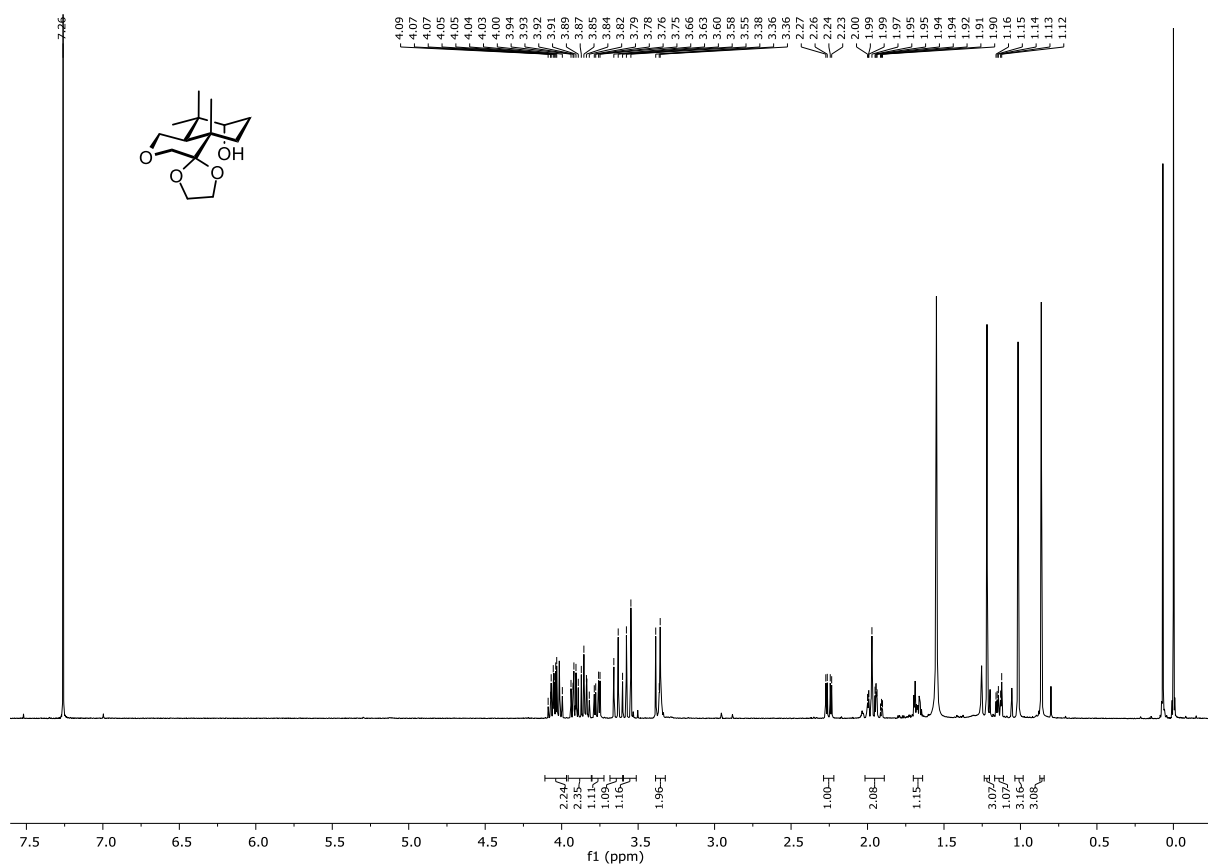
Chemical Shift (ppm)	Integration
~7.2	1.99
~4.0	3.06
~3.5	1.05
~3.4	1.02
~3.3	1.01
~3.2	1.00
~1.9	1.01
~1.7	3.70
~1.6	1.34
~1.4	3.02
~1.3	3.07
~0.8	2.99



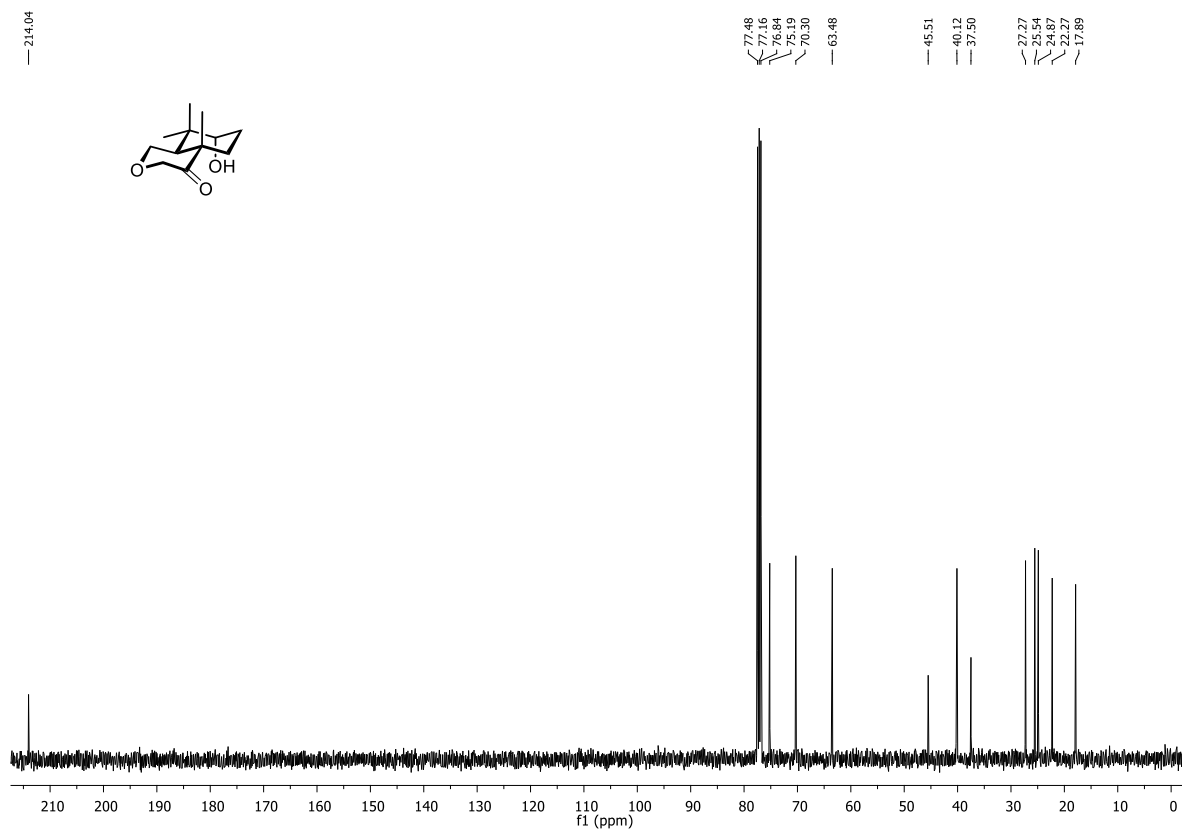
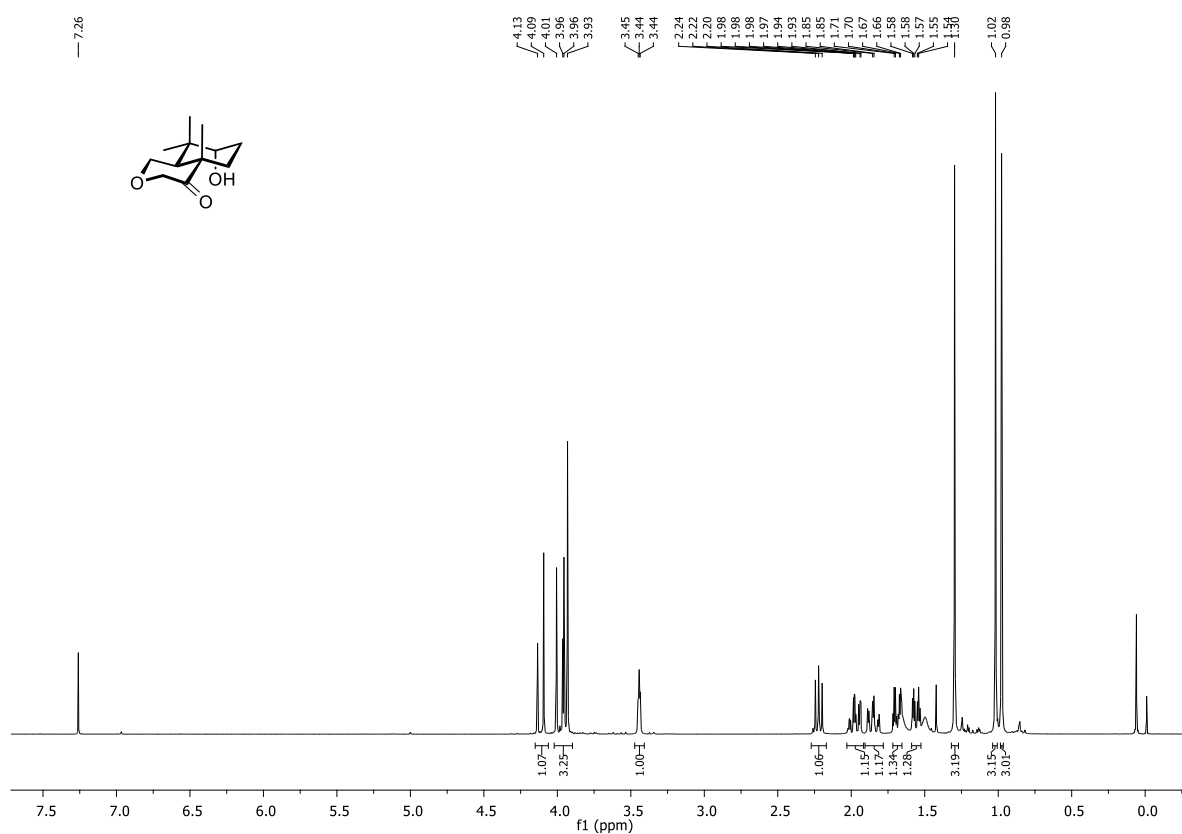
Ketone **S8**



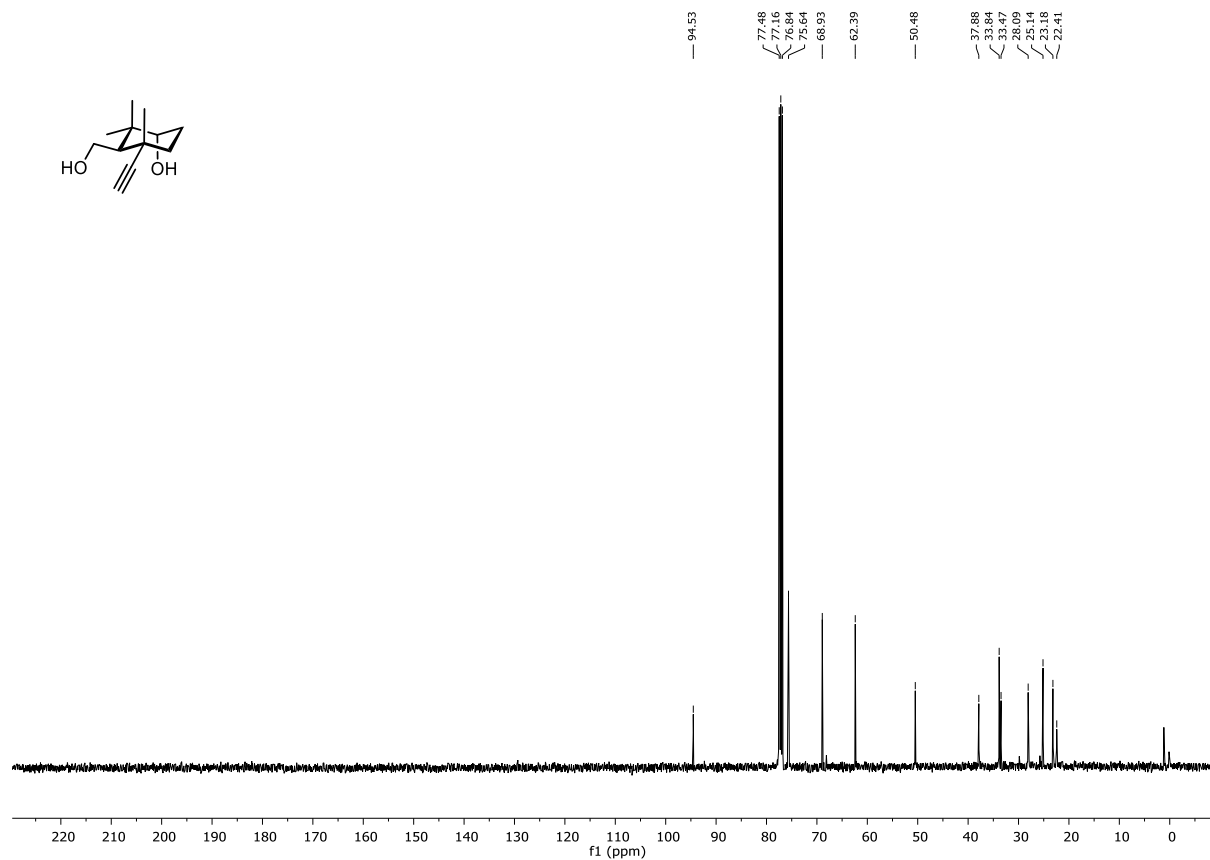
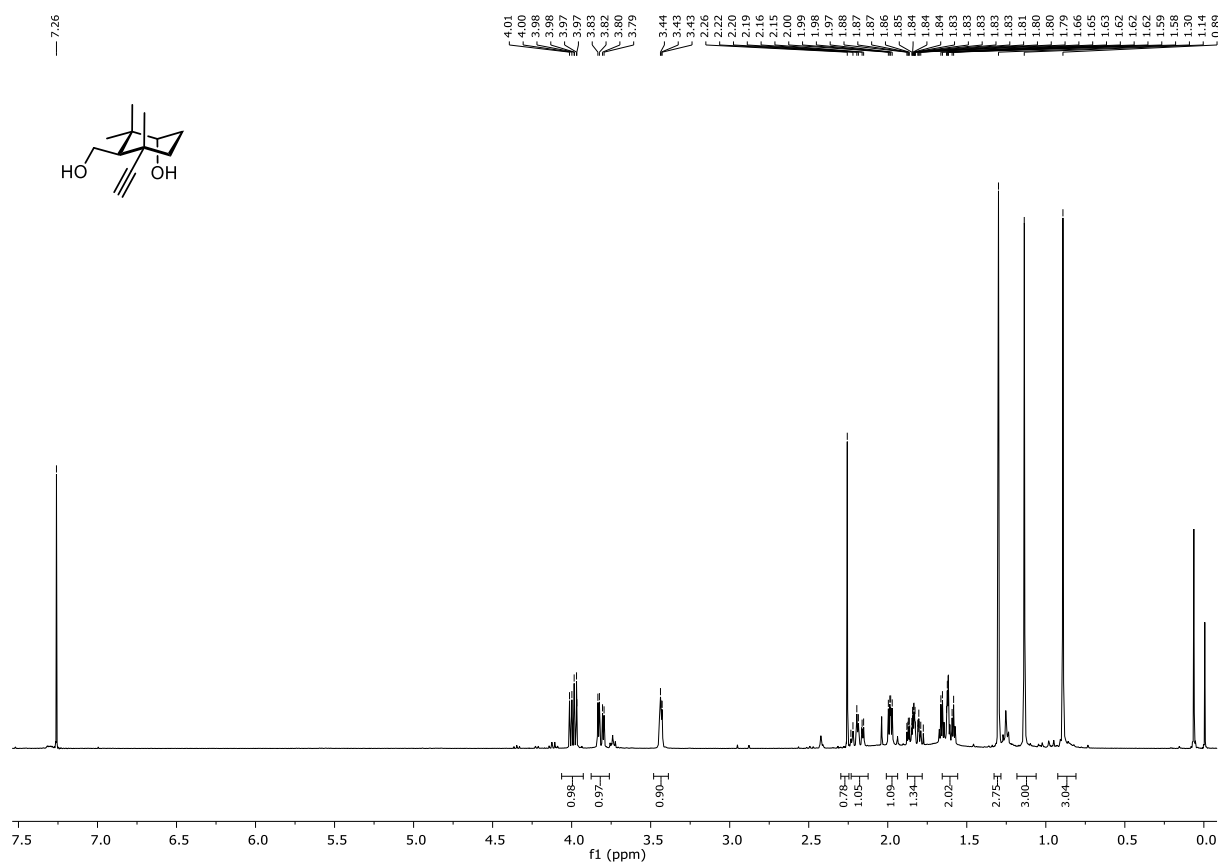
Ketal S9

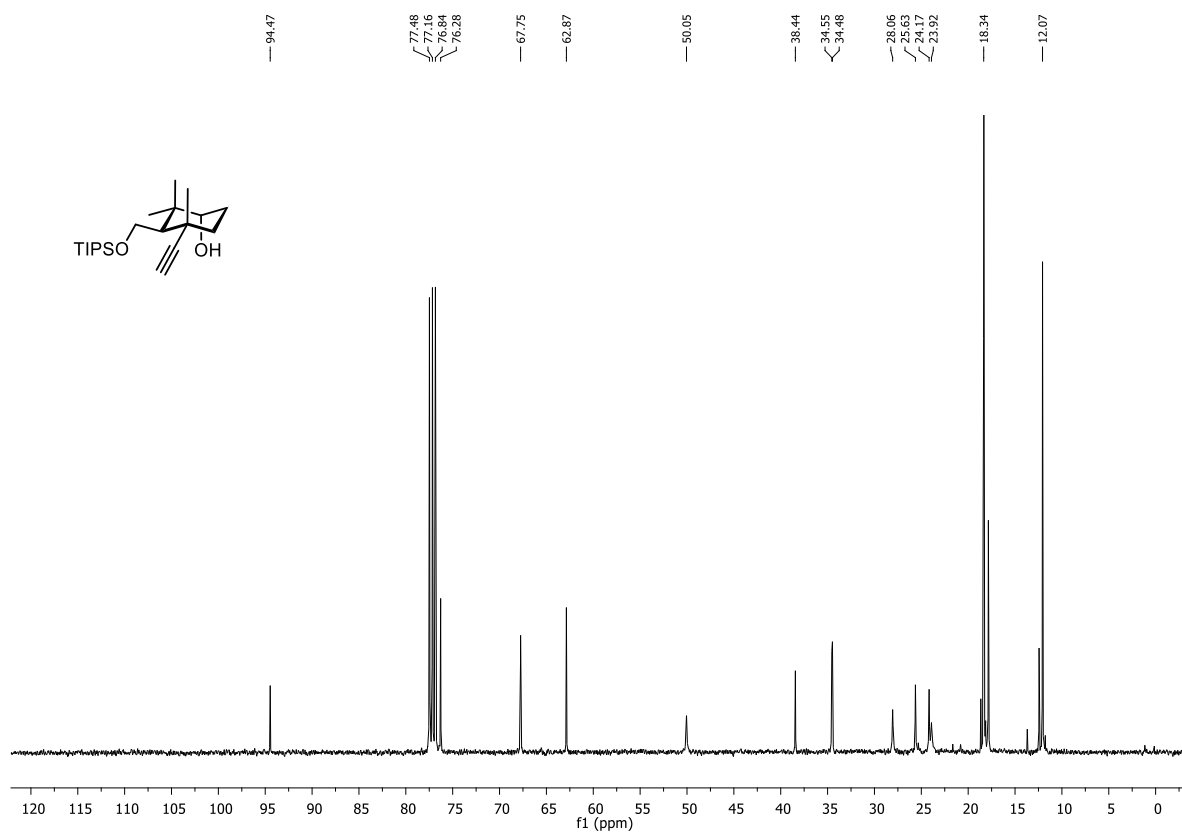
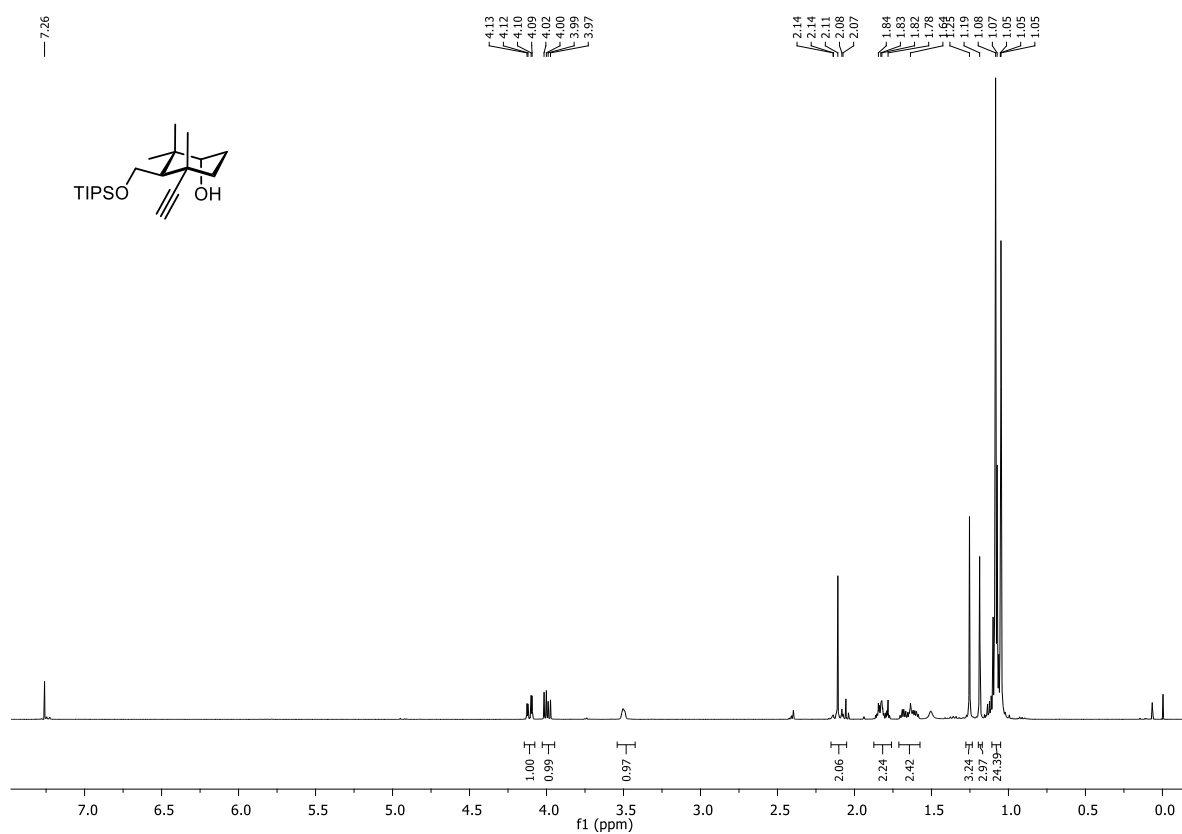


Ketone 11

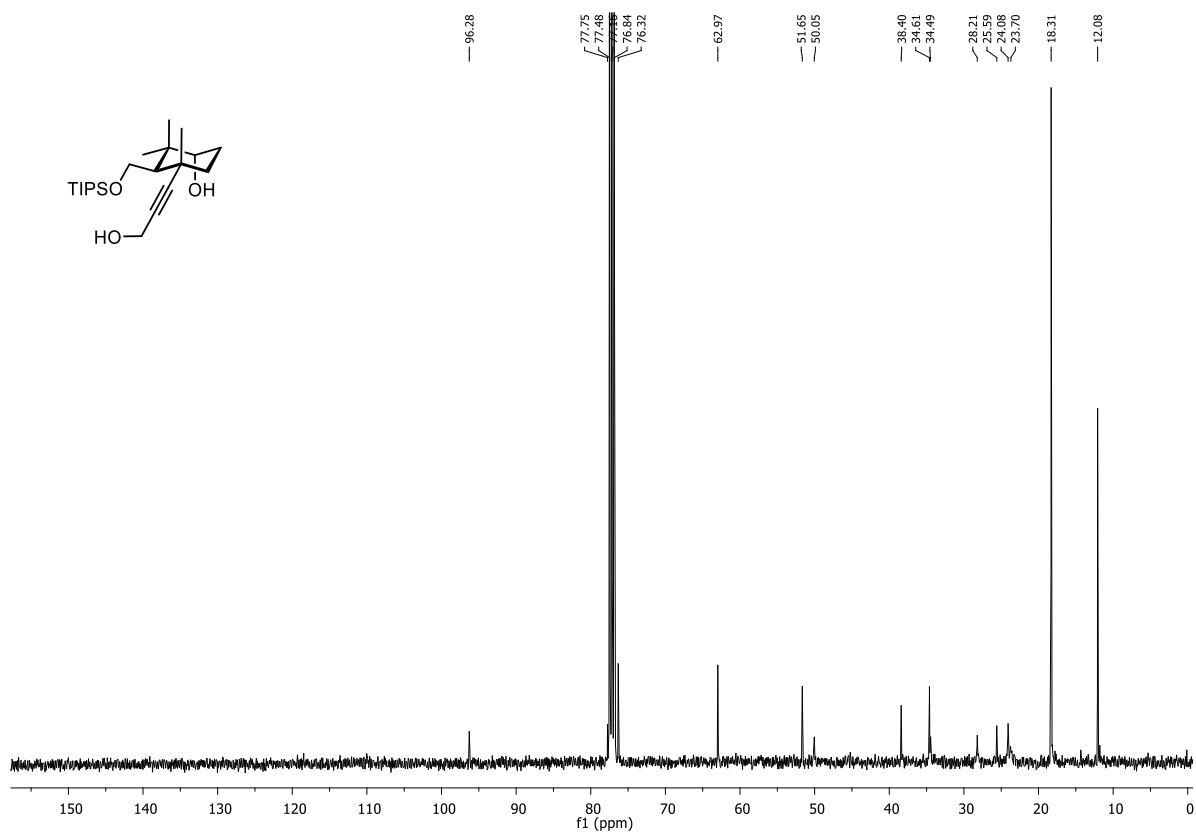
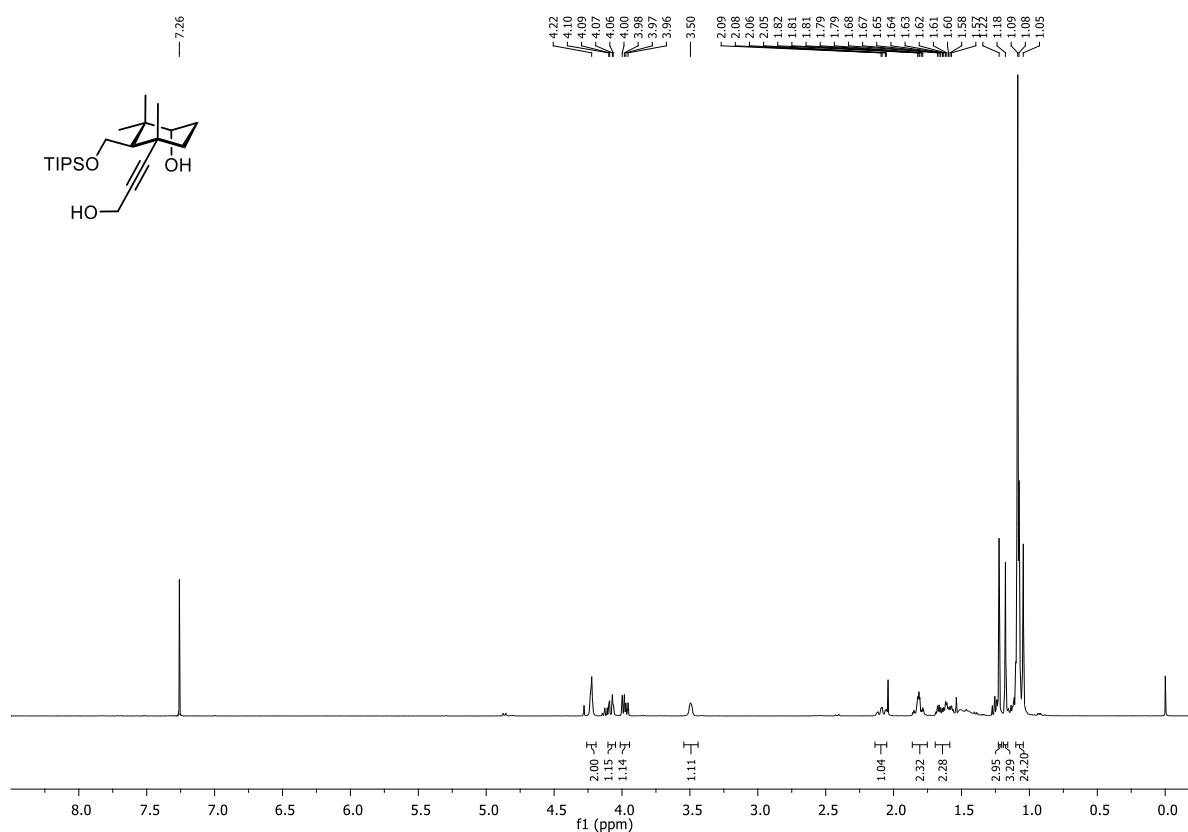


Alkyne 18

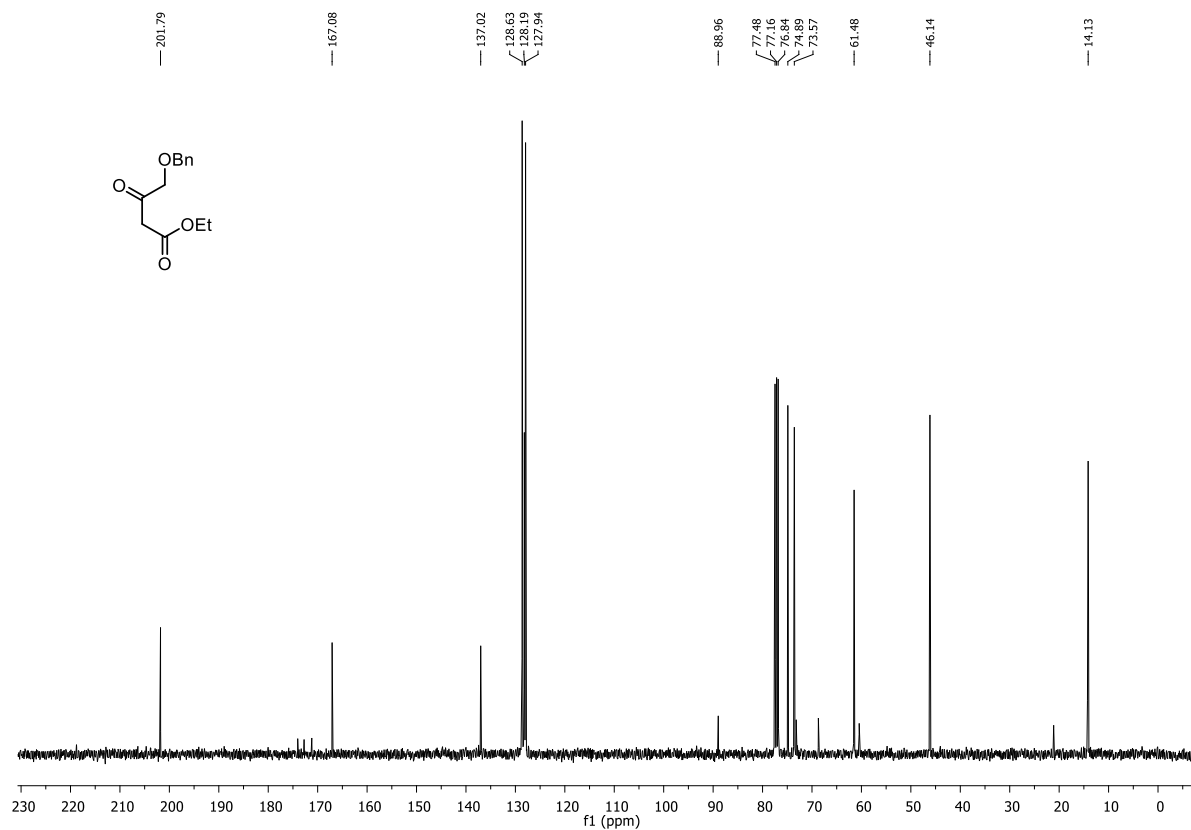
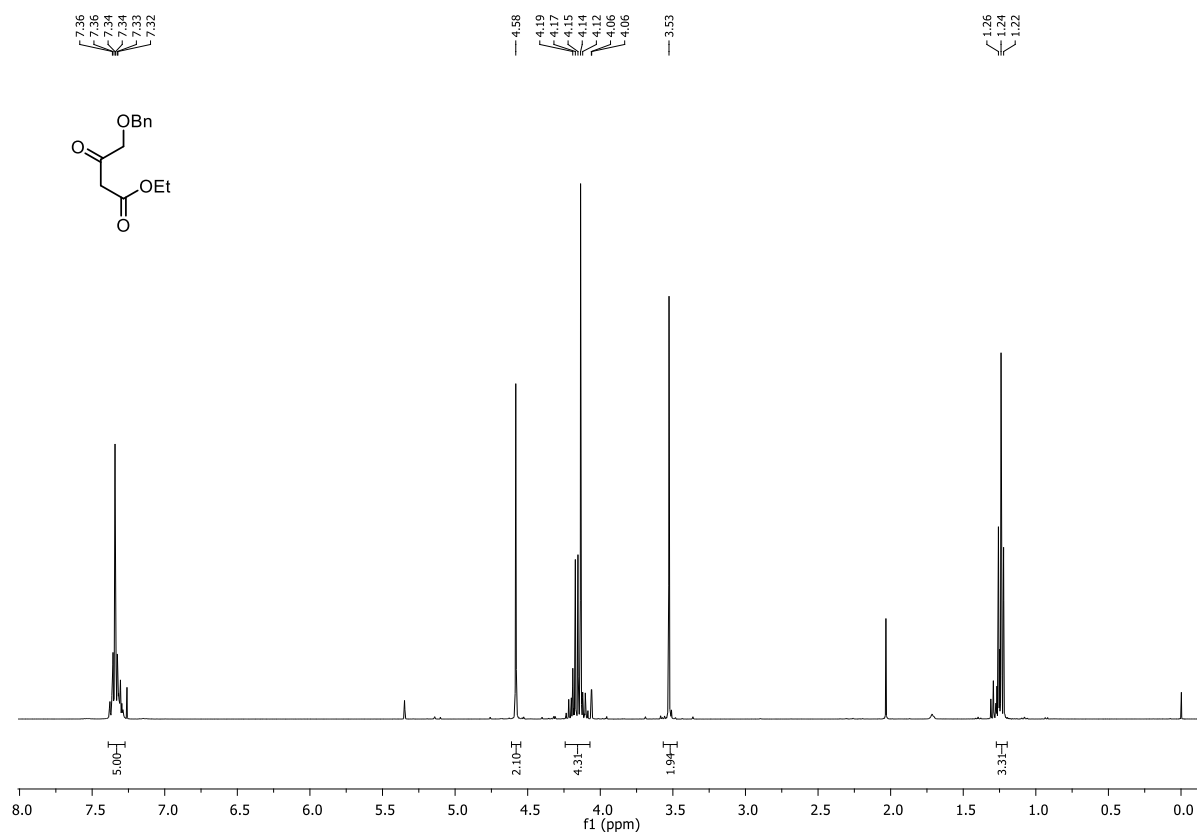


Alkyne **S11**

Alcohol 21

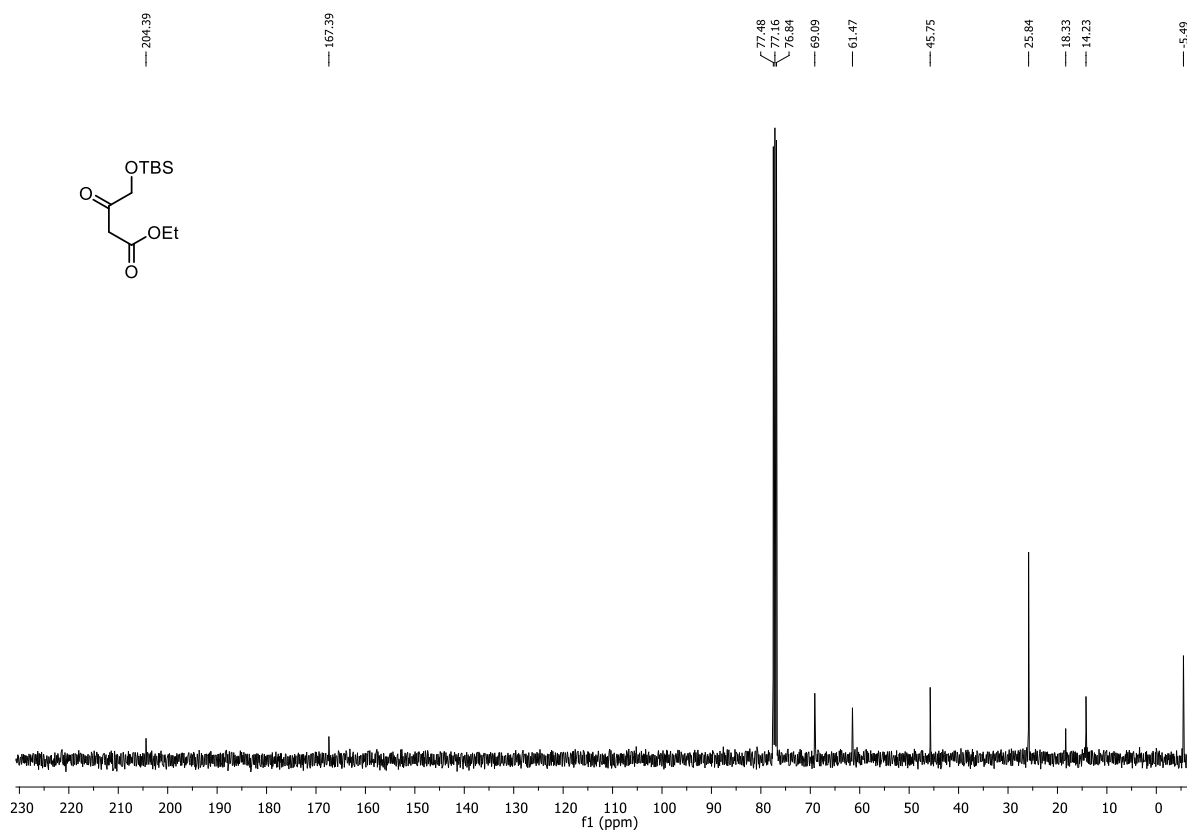
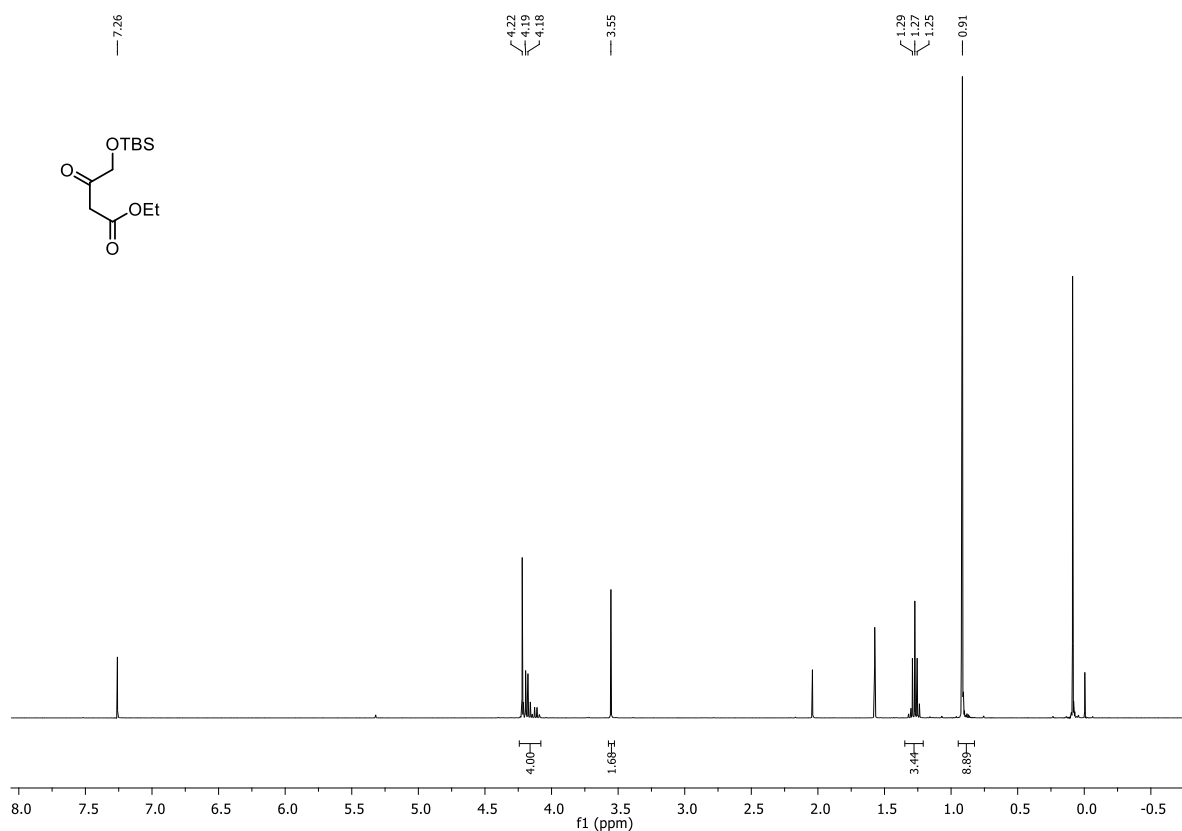


β -keto ester **S12**



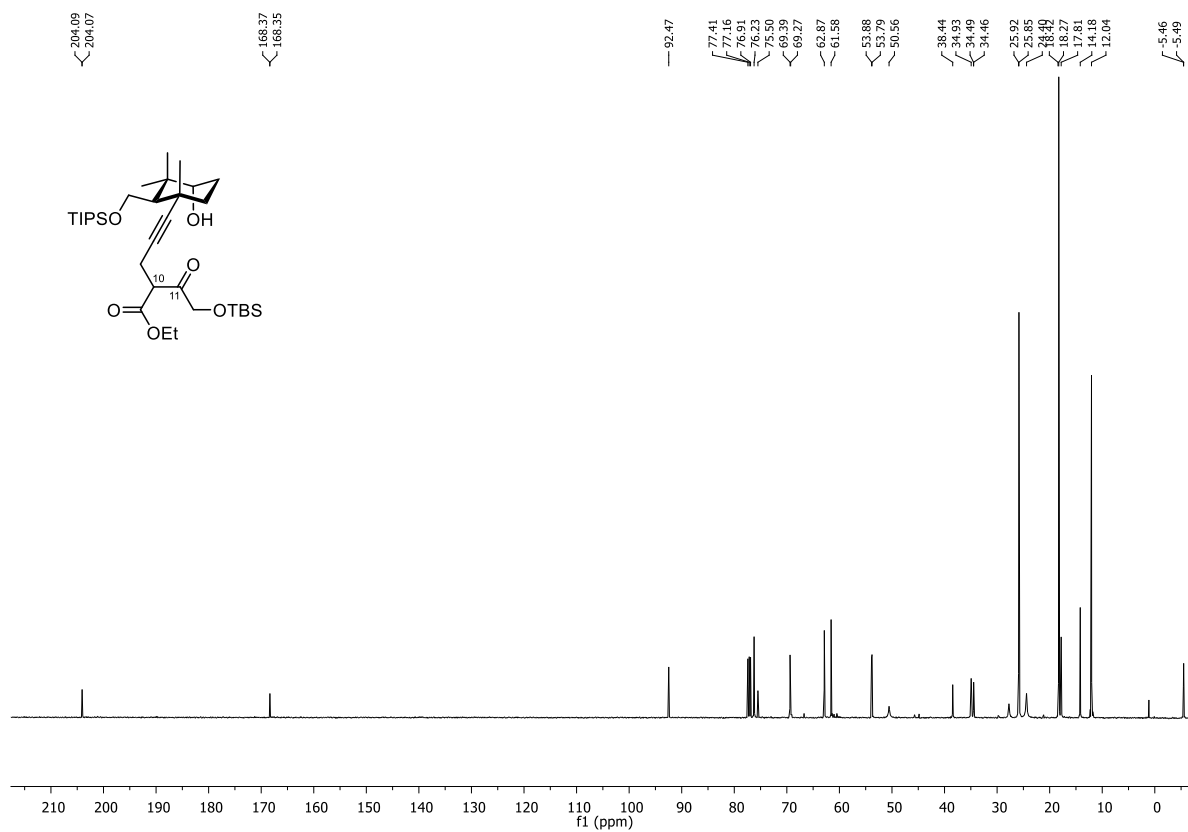
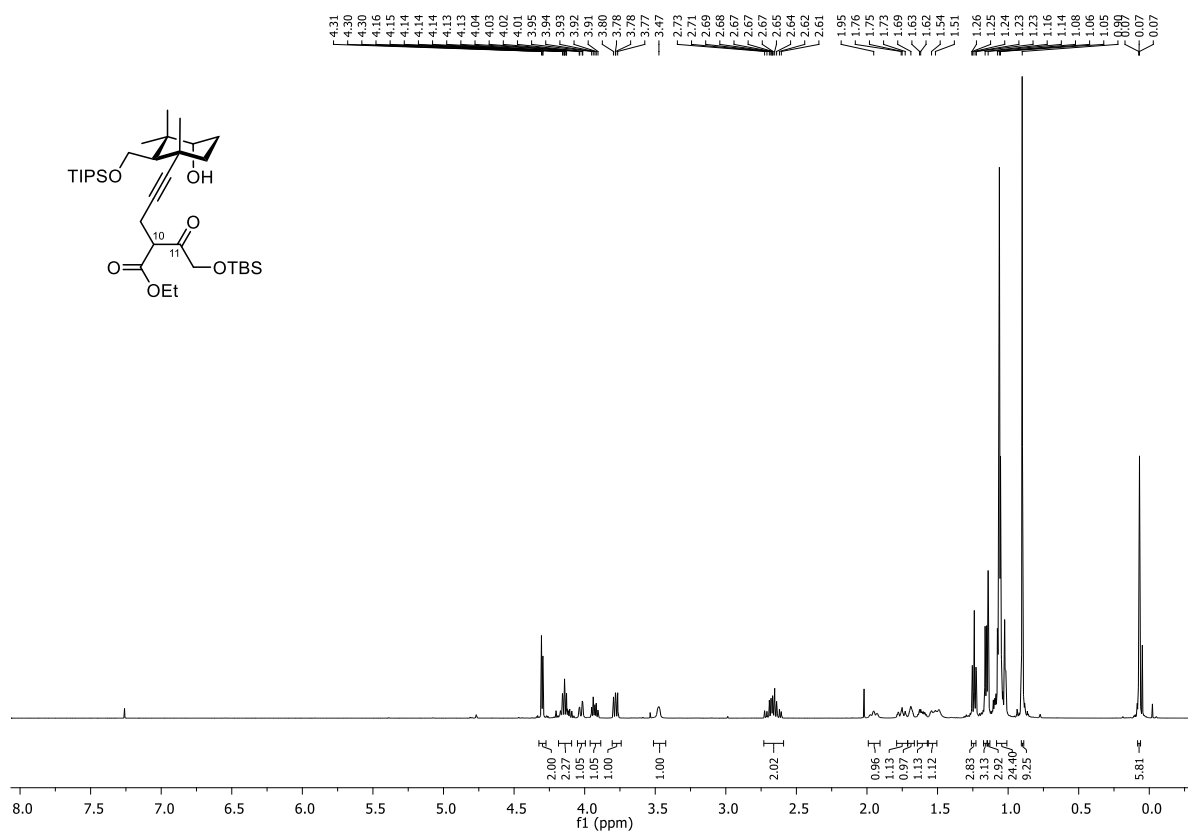
NB: as per Zhang *et al.* peaks associated with the minor enol tautomer are observed⁶

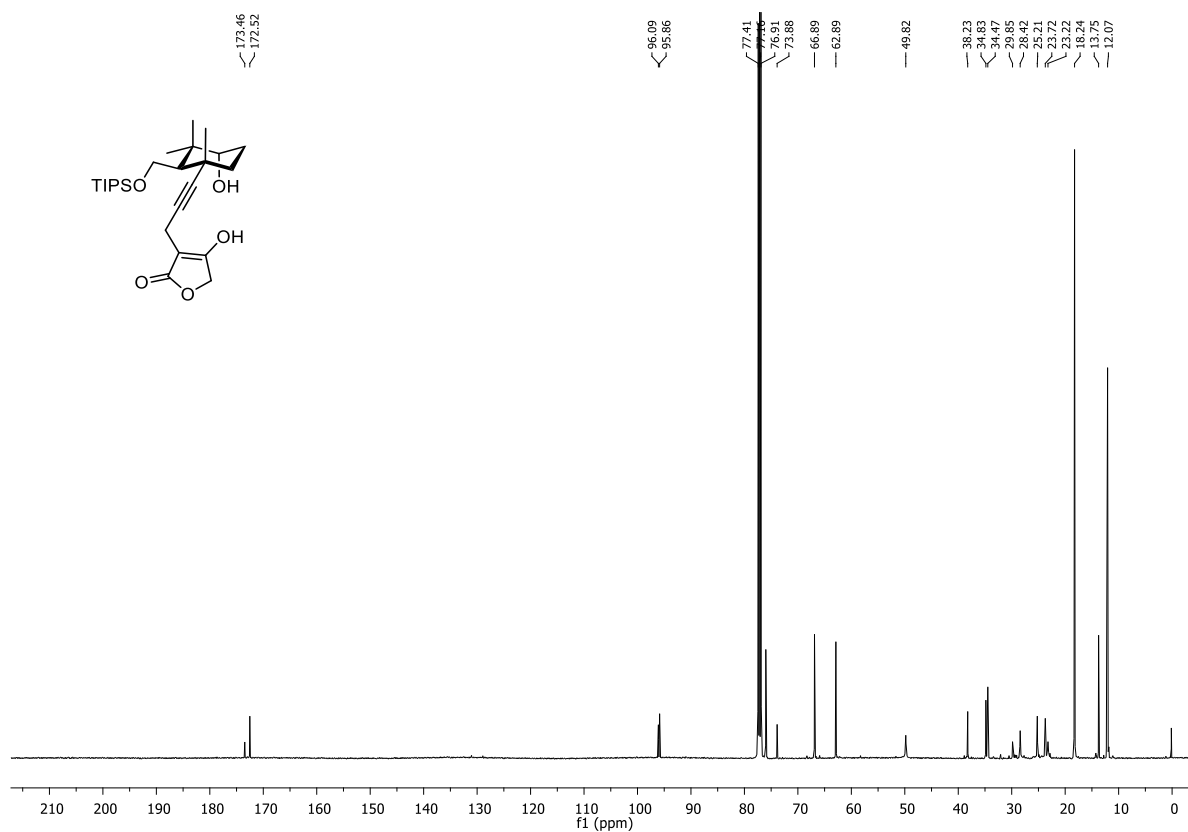
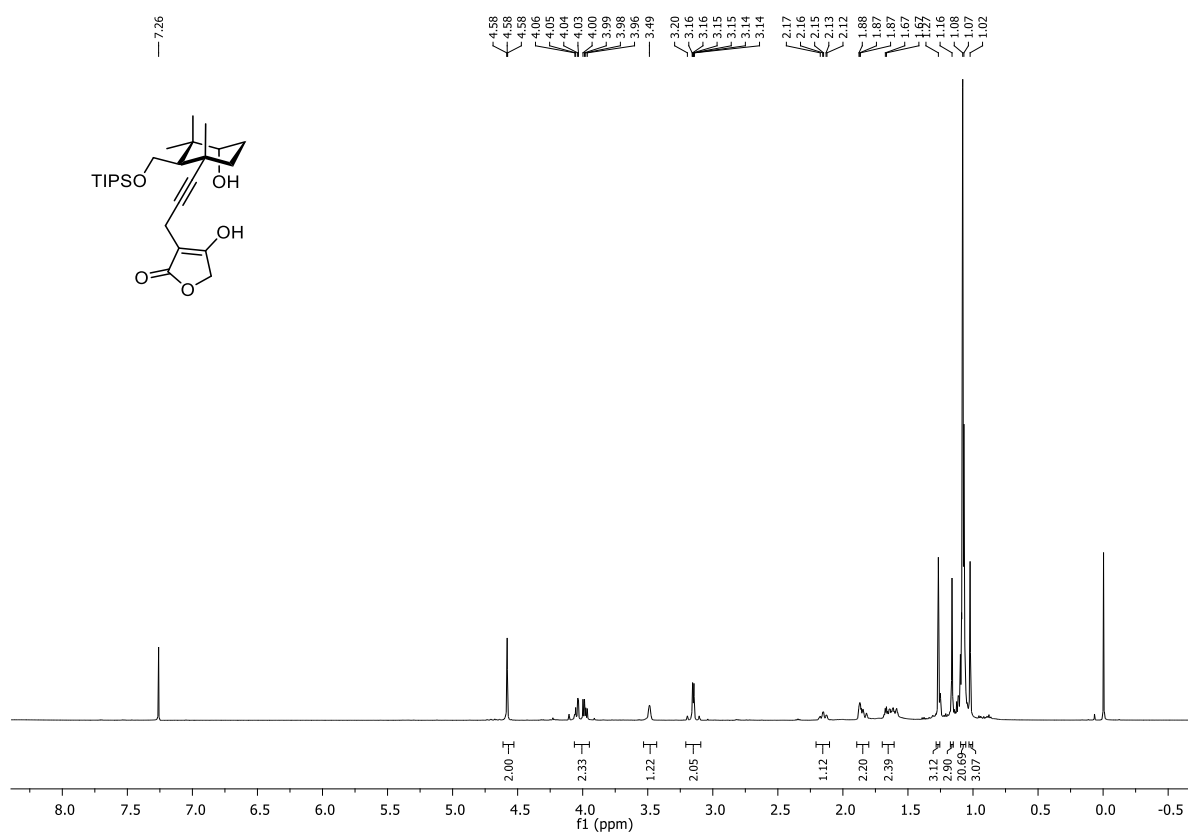
β -keto ester **S13**



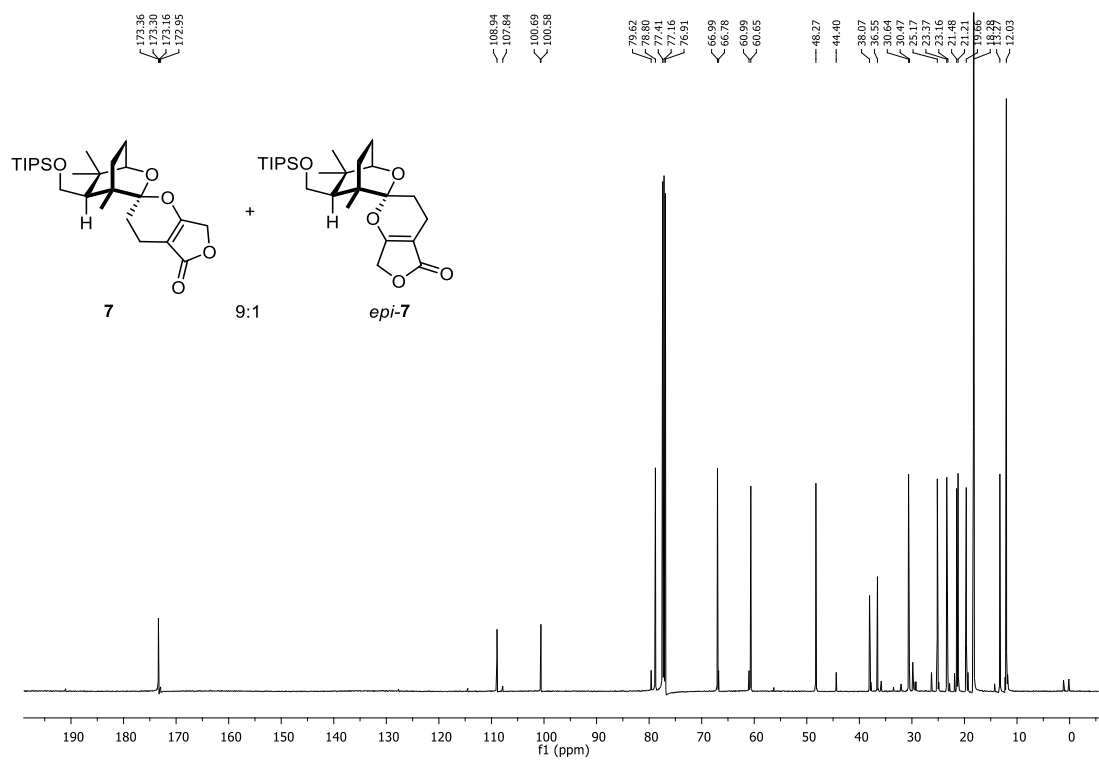
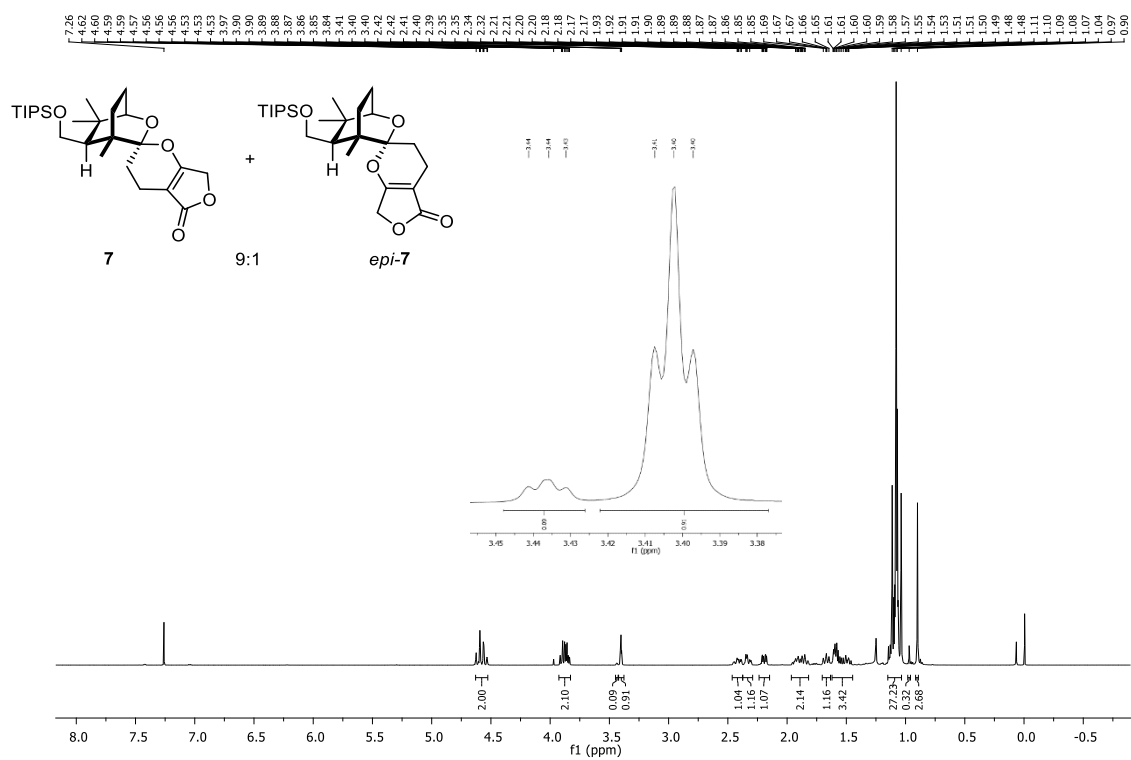
NB: as per Zhang *et al.* peaks associated with the minor enol tautomer are observed⁶

β -Keto ester **22**

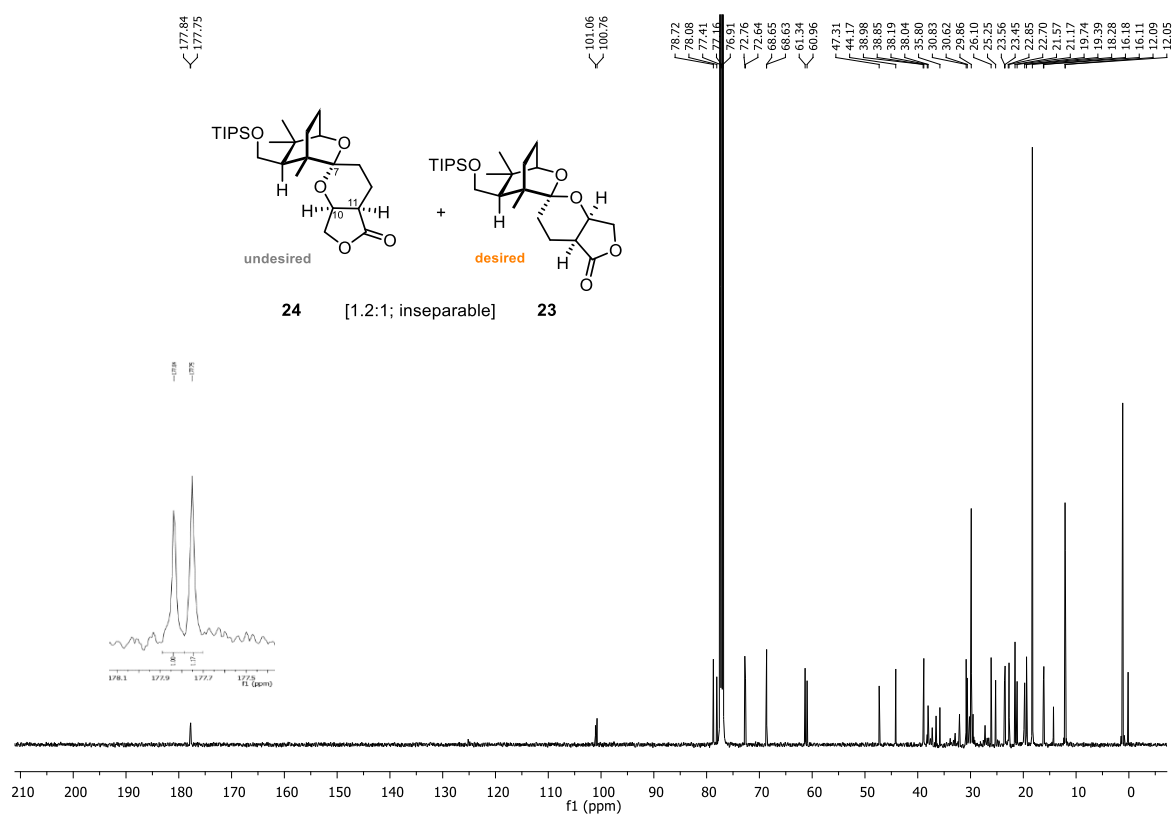
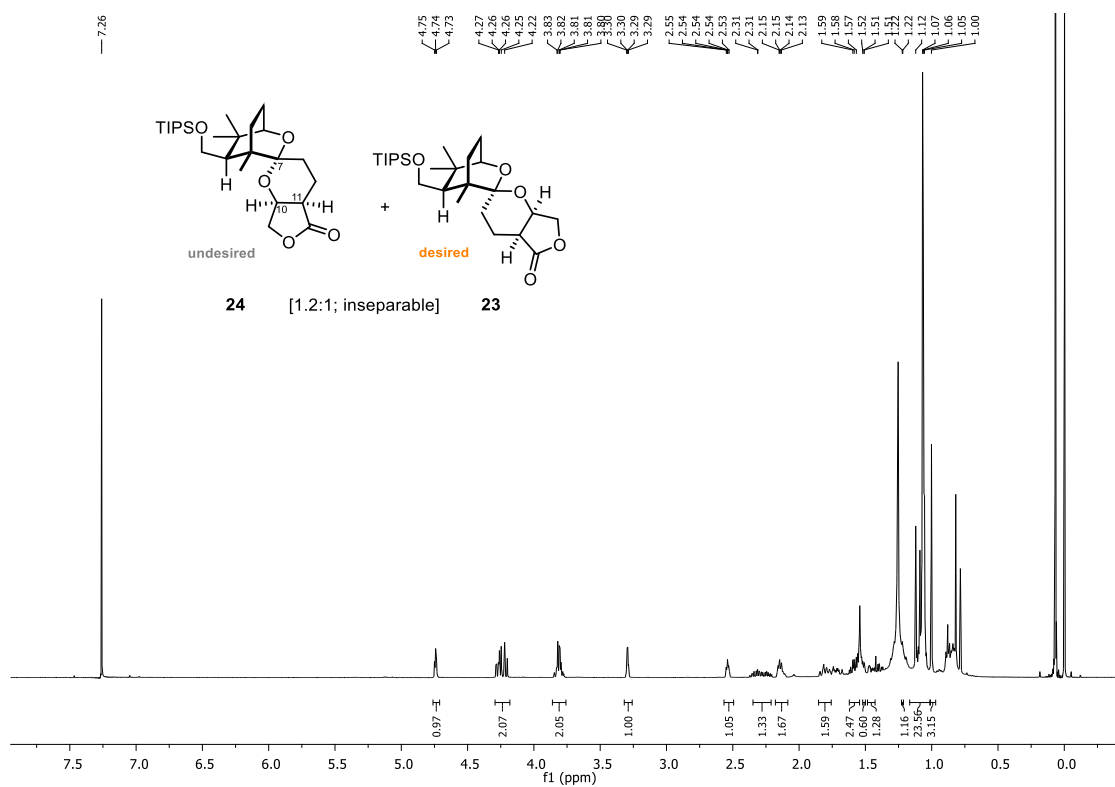


Enol **8**

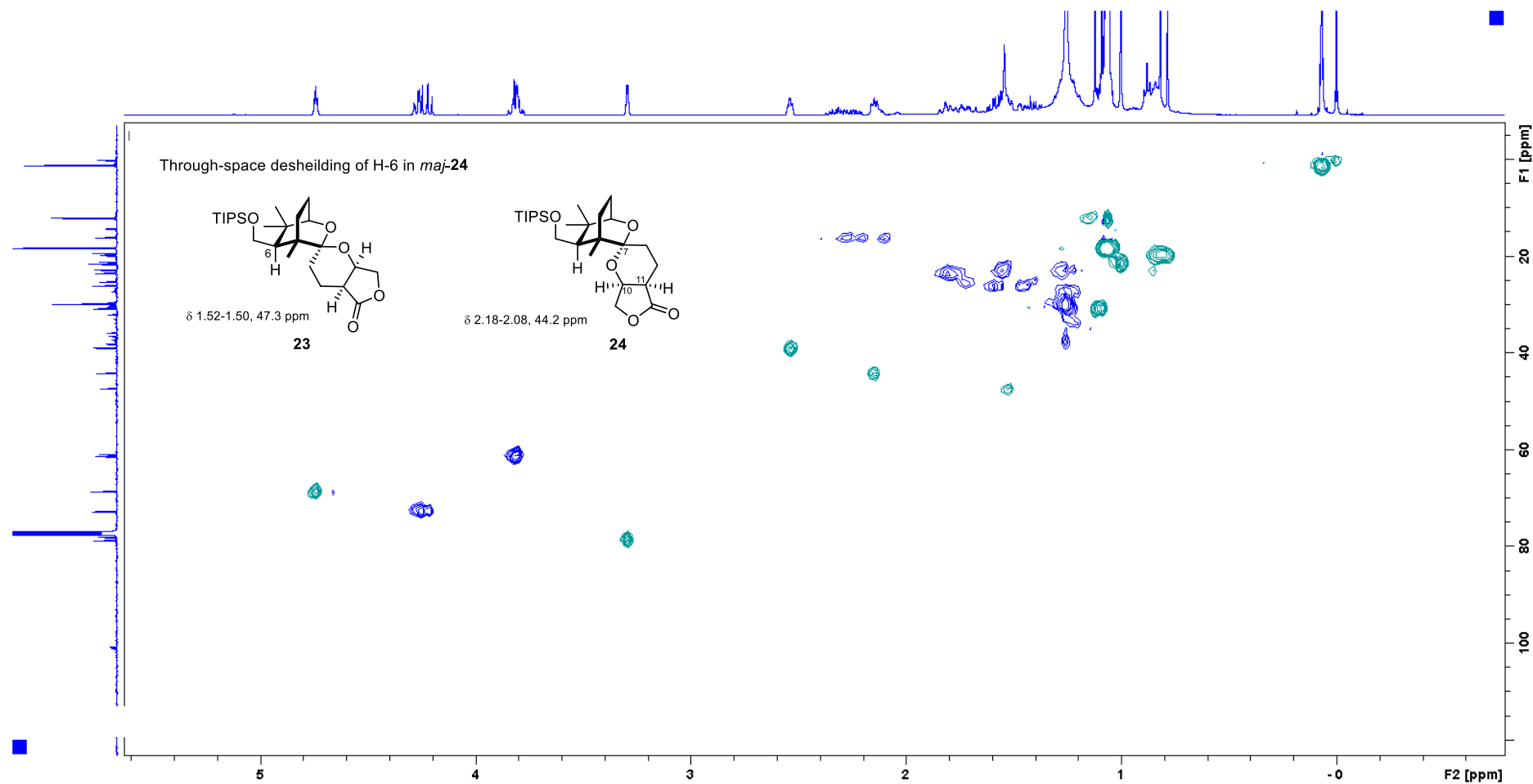
Spiroketal **7** and *epi-7*



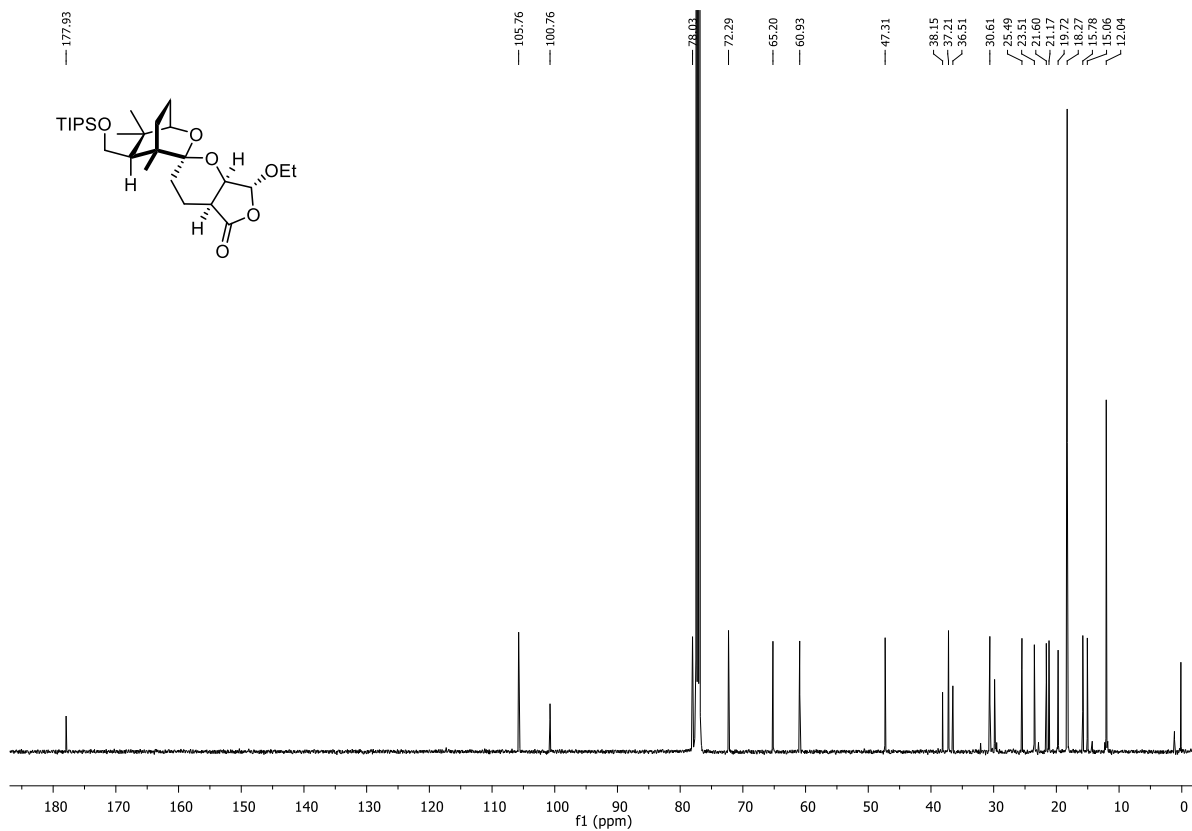
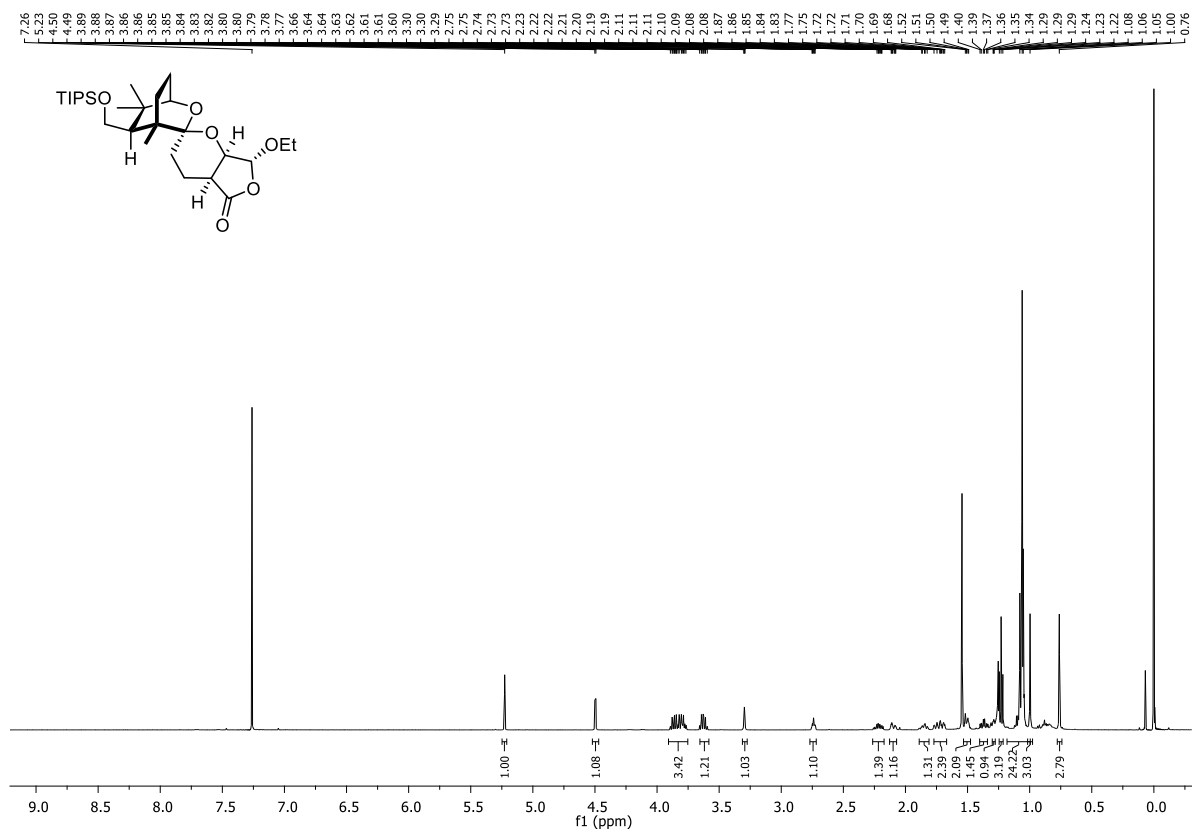
Spiroketal **23**; Spiroketal **24**



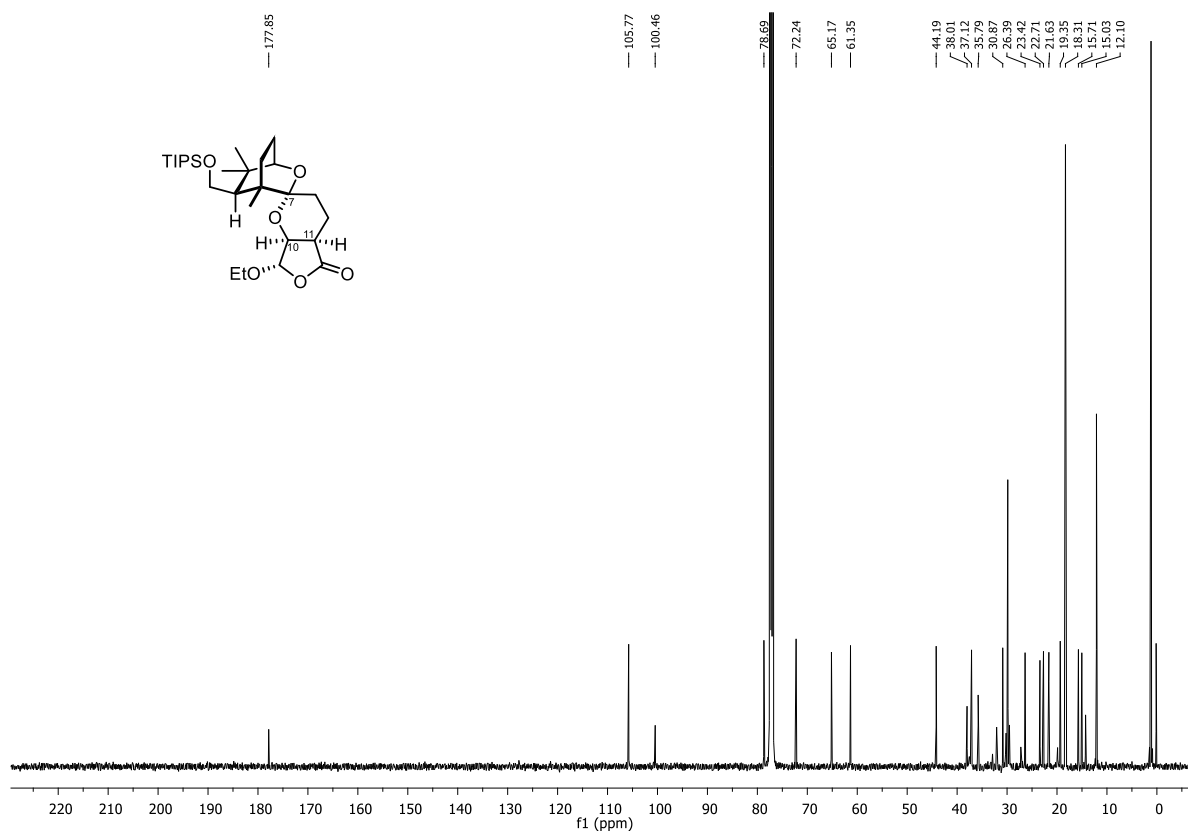
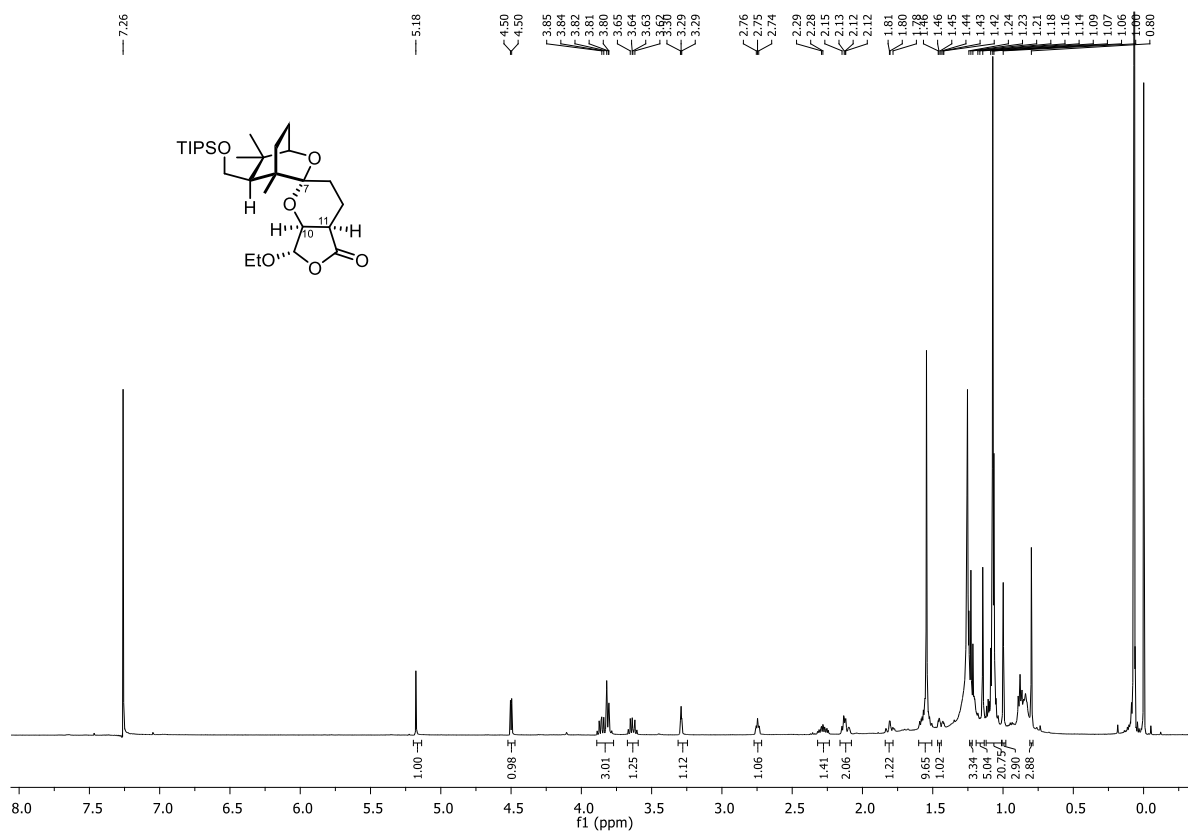
HSQC spectrum **23-24** mixture



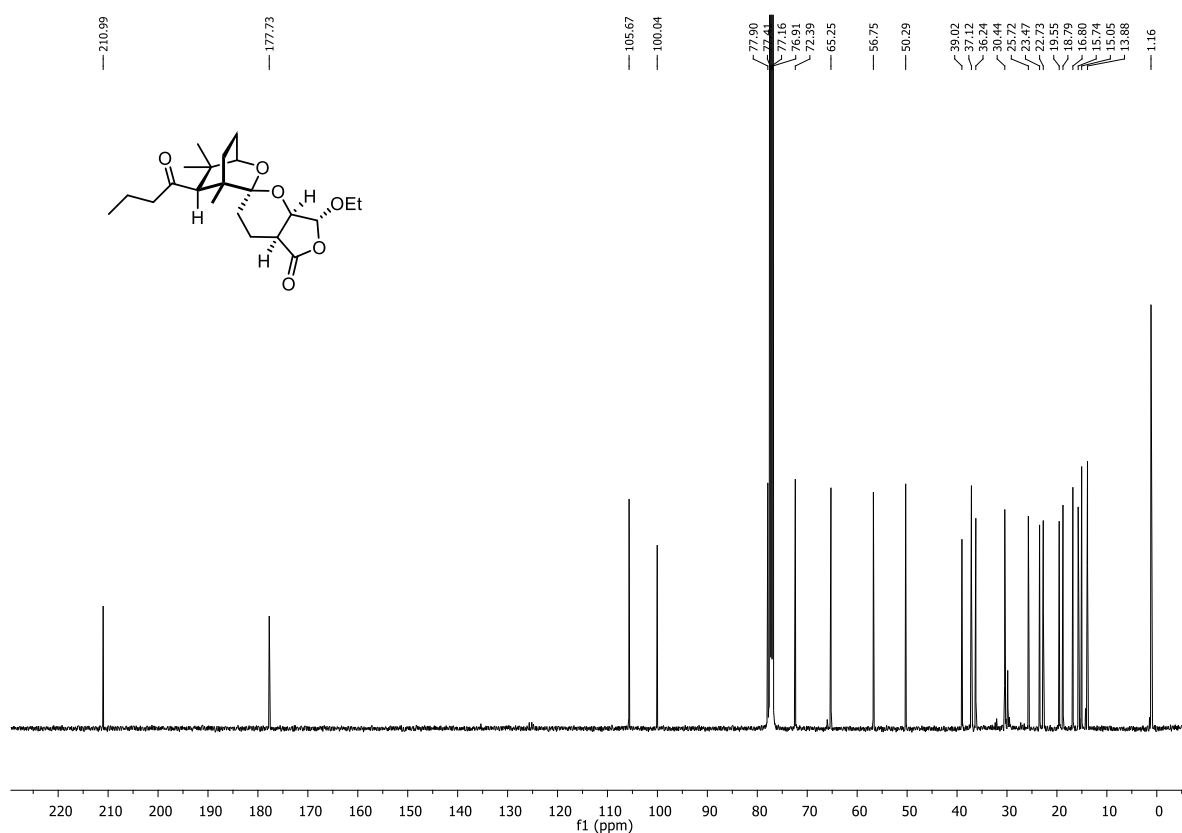
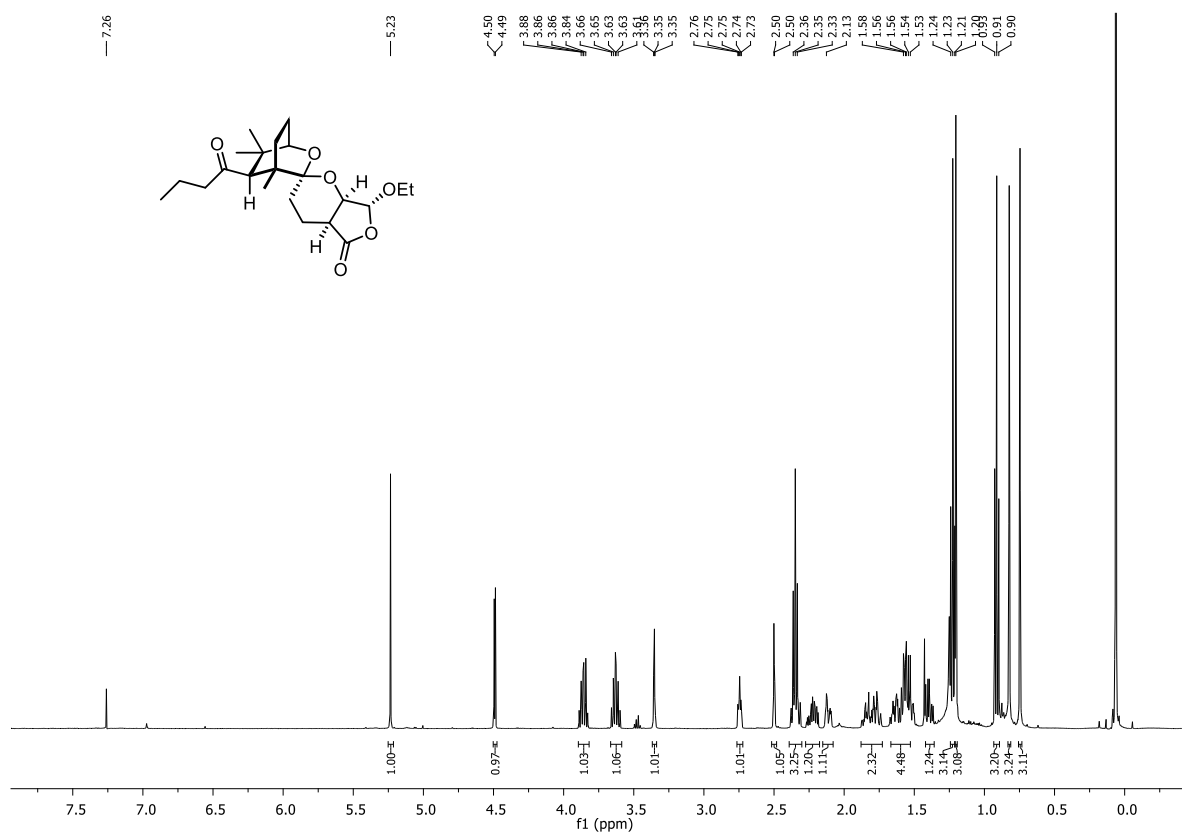
Spiroketal **25**



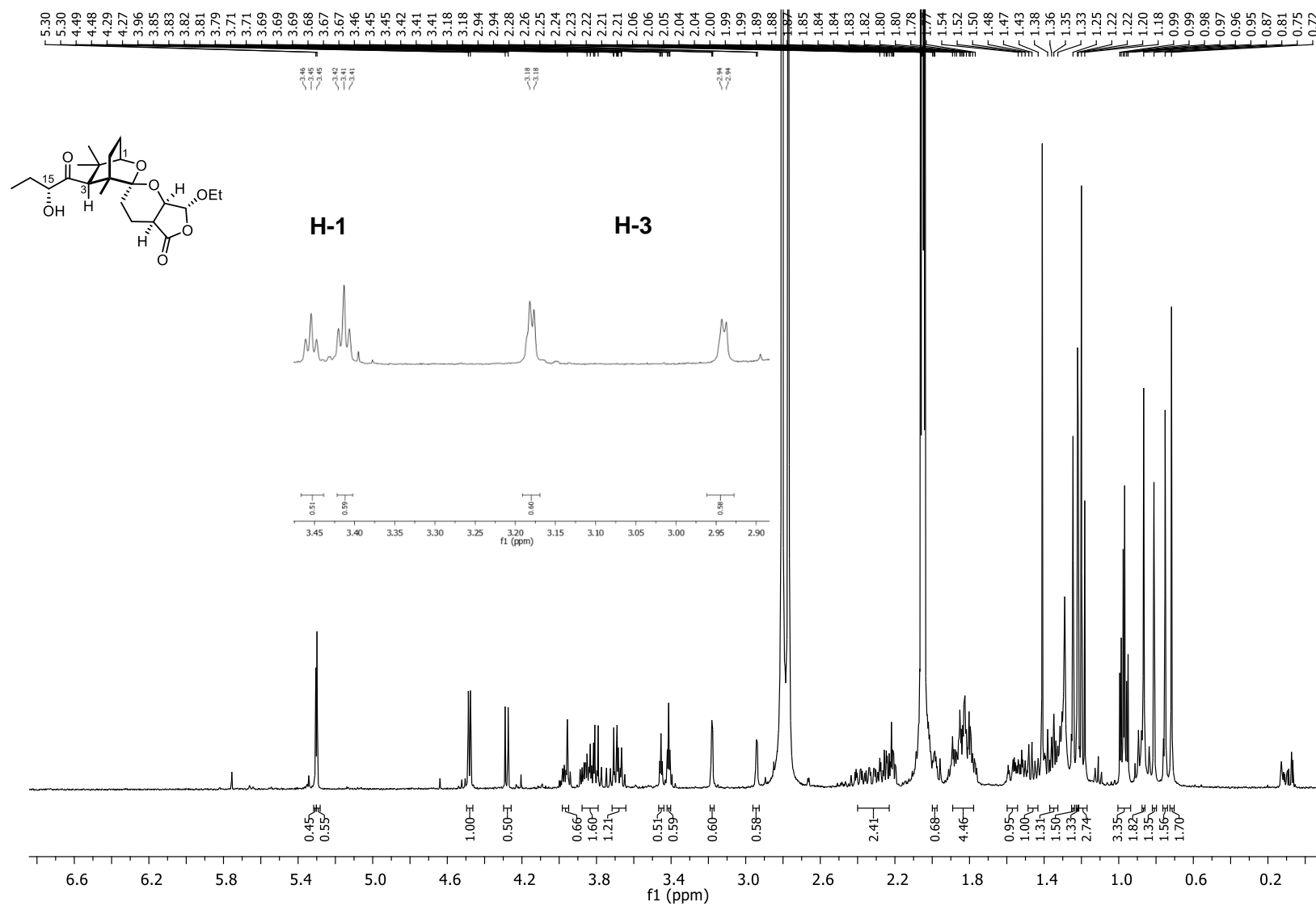
Spiroketal S5



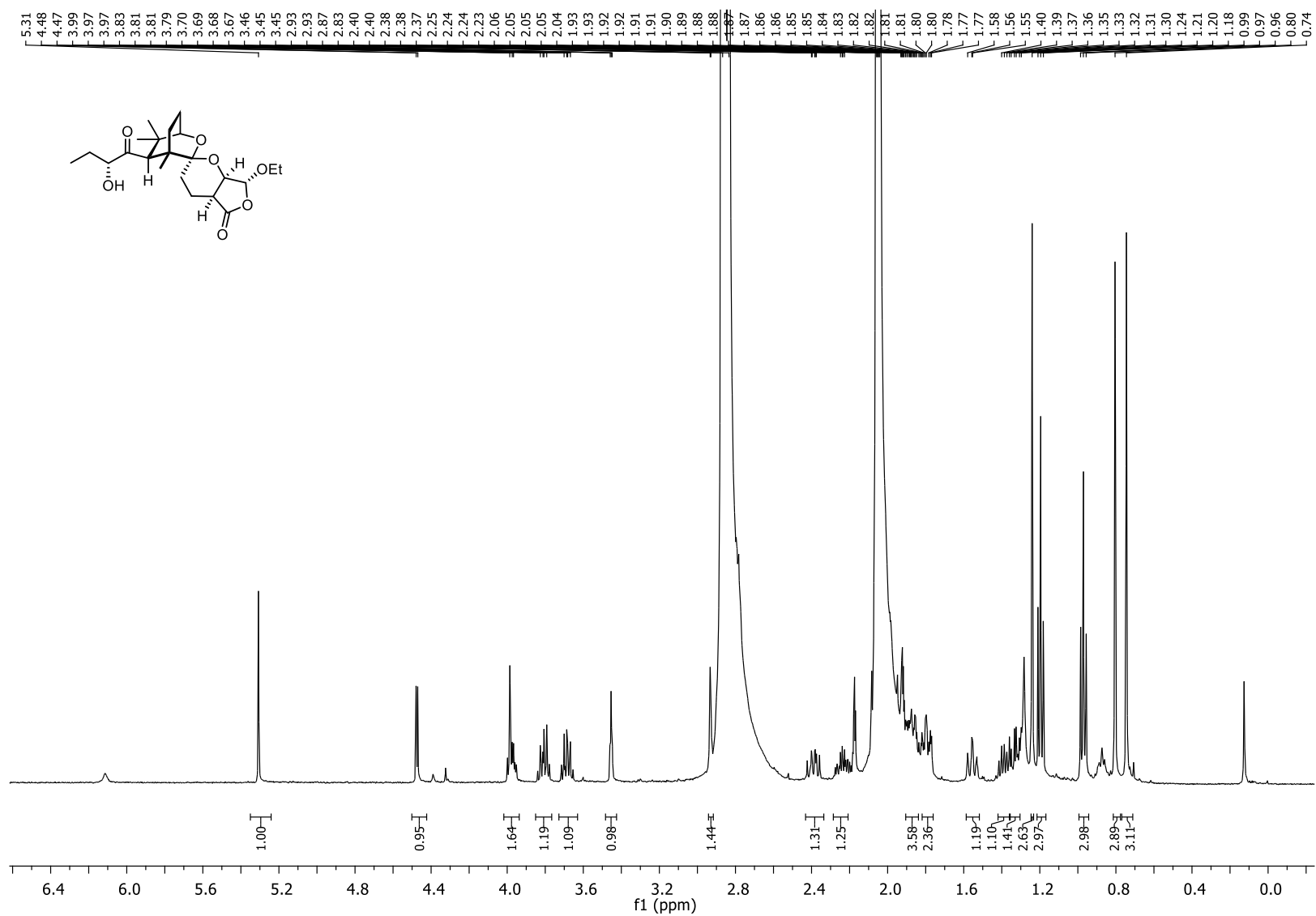
Deoxyleonuketal **26**

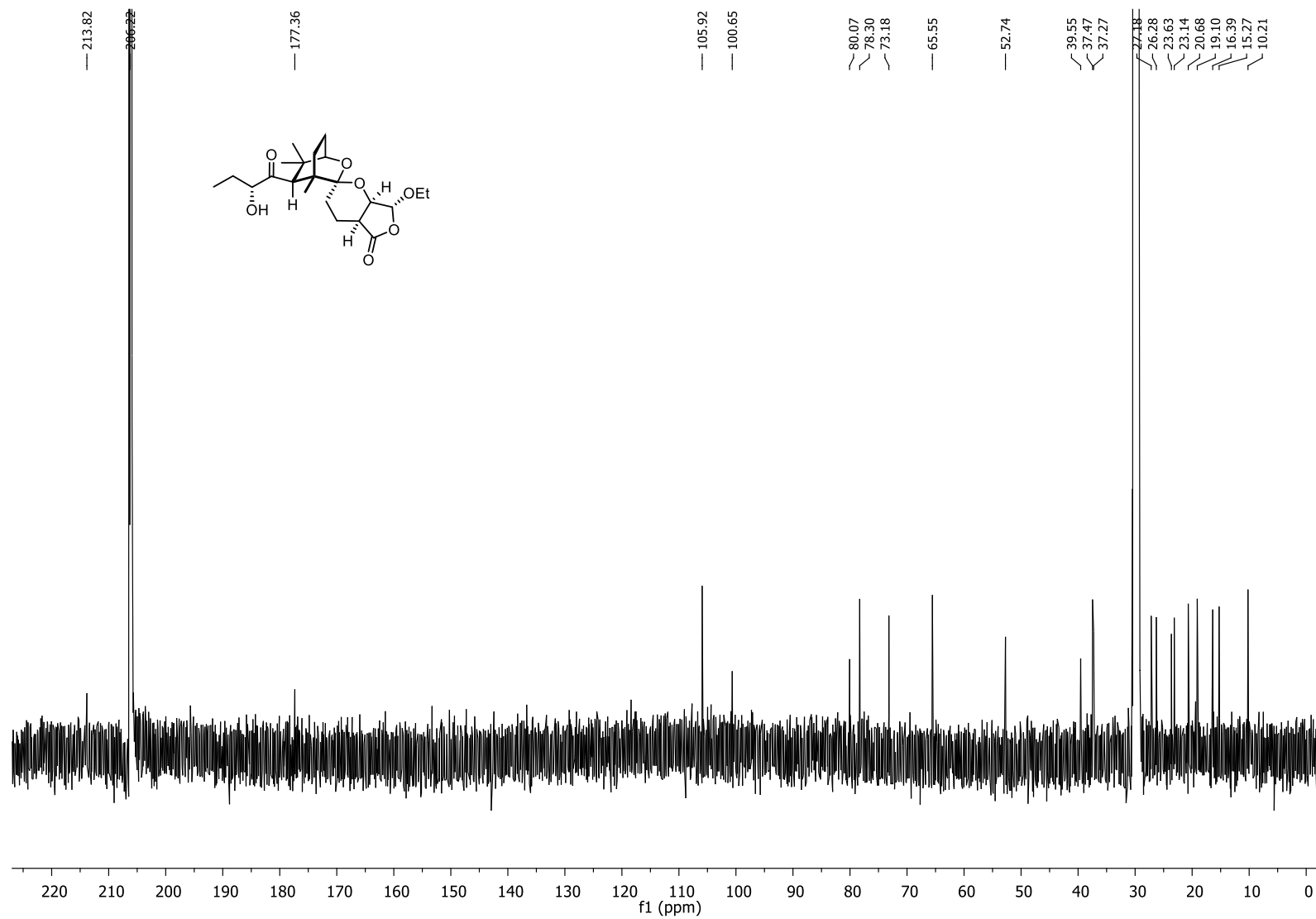


Leonuketal (**1**) epimeric mixture

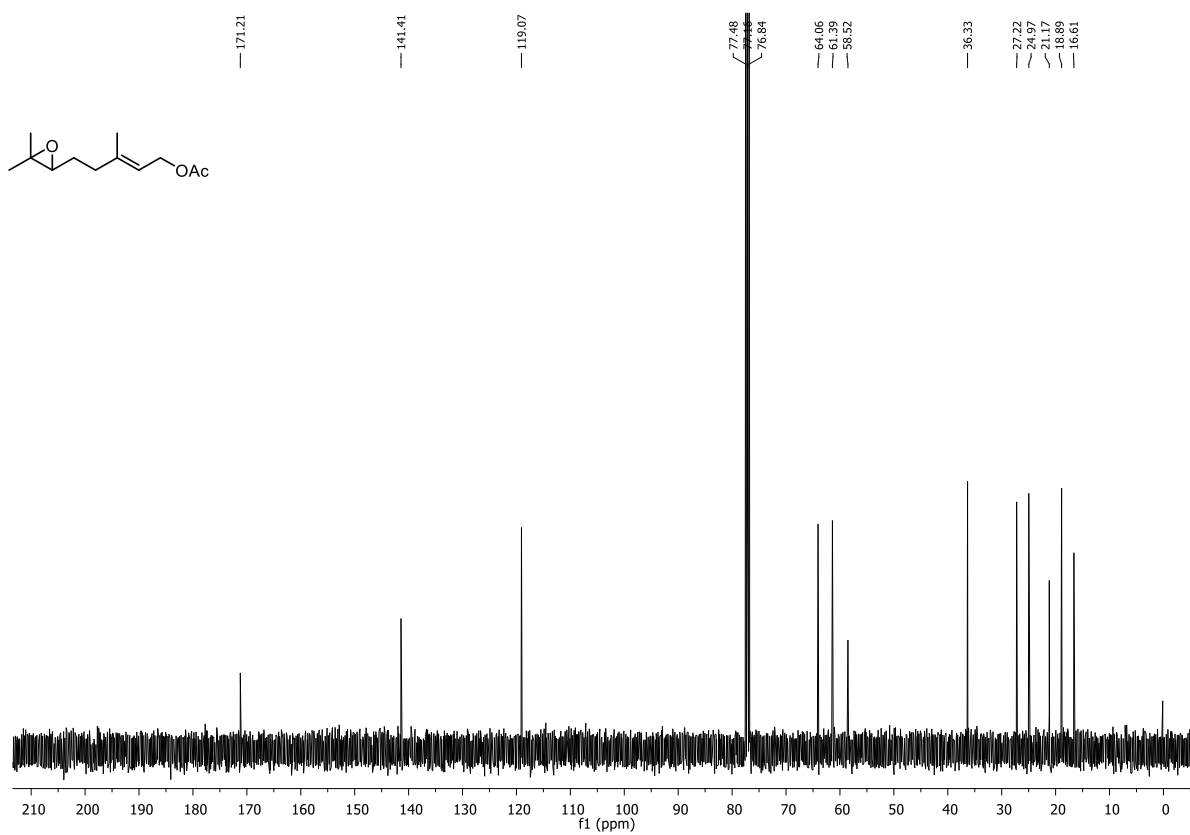
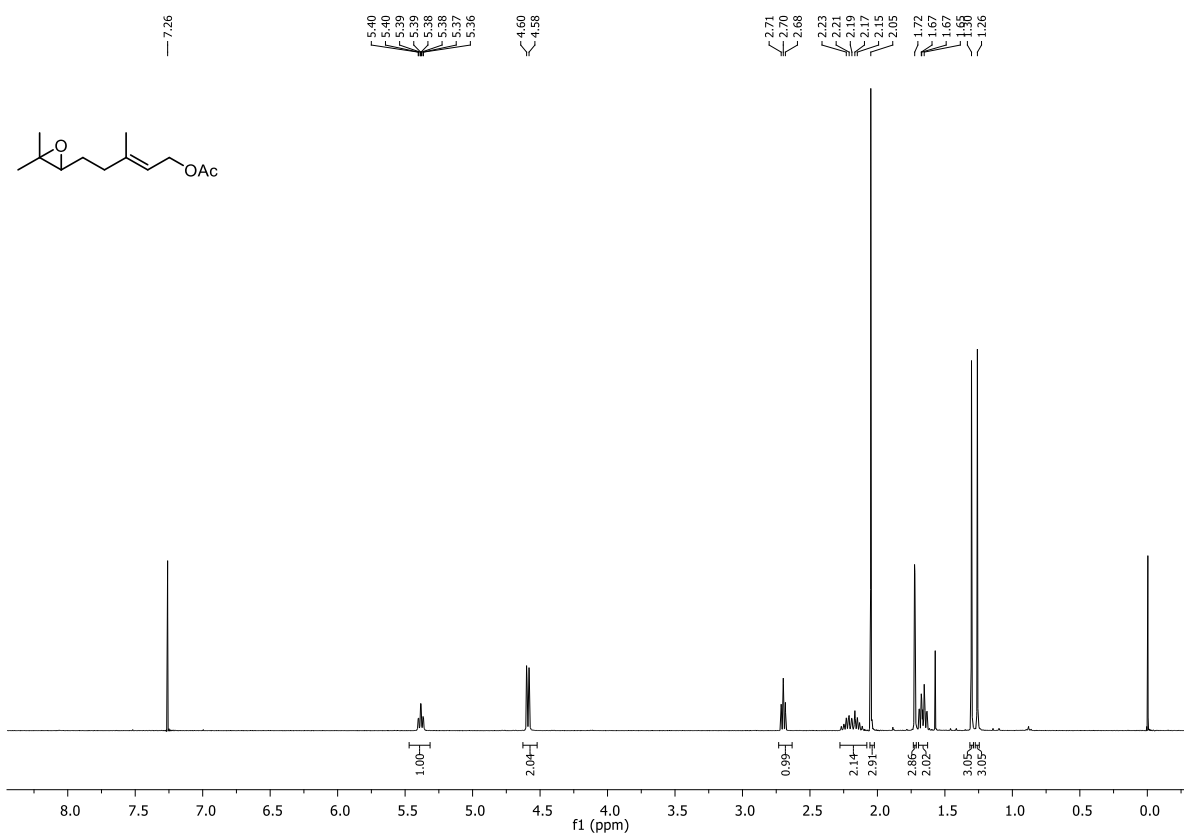


Leonuketal (1) ¹H-NMR

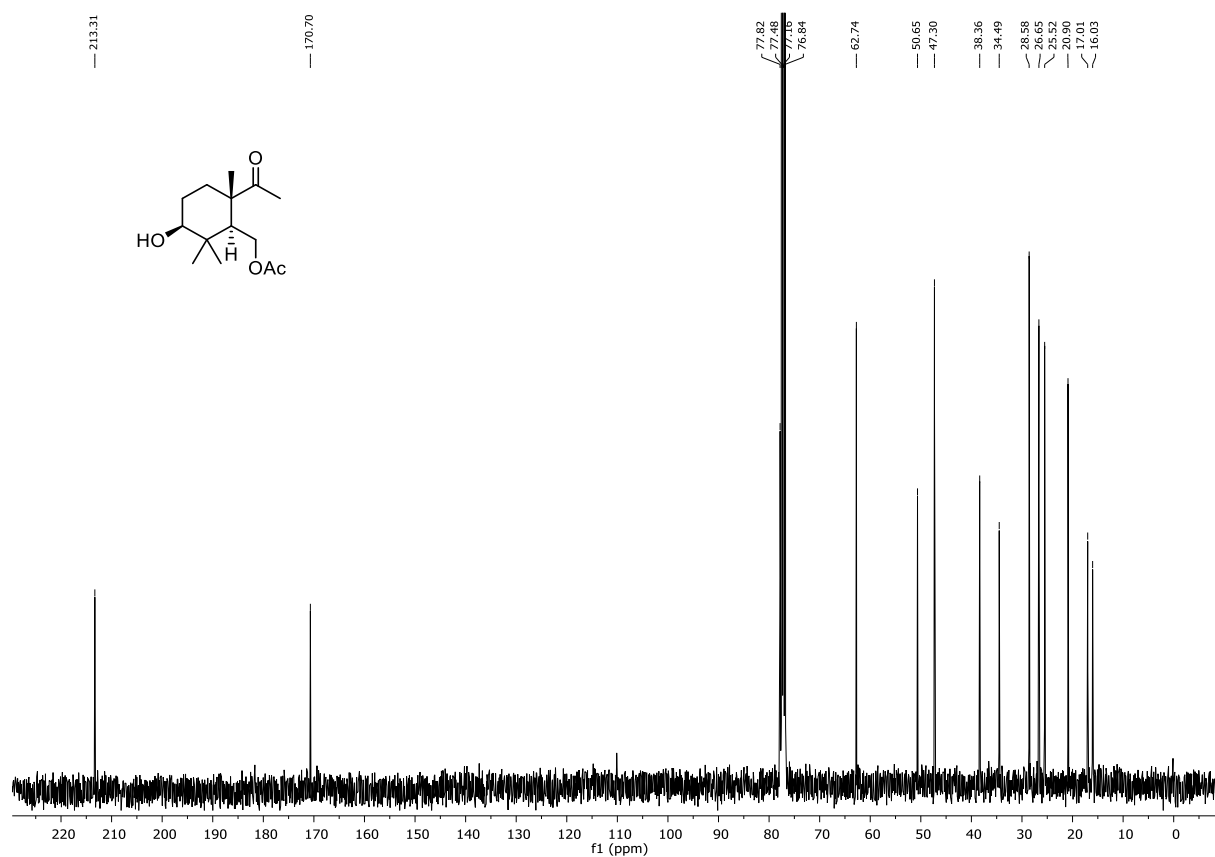
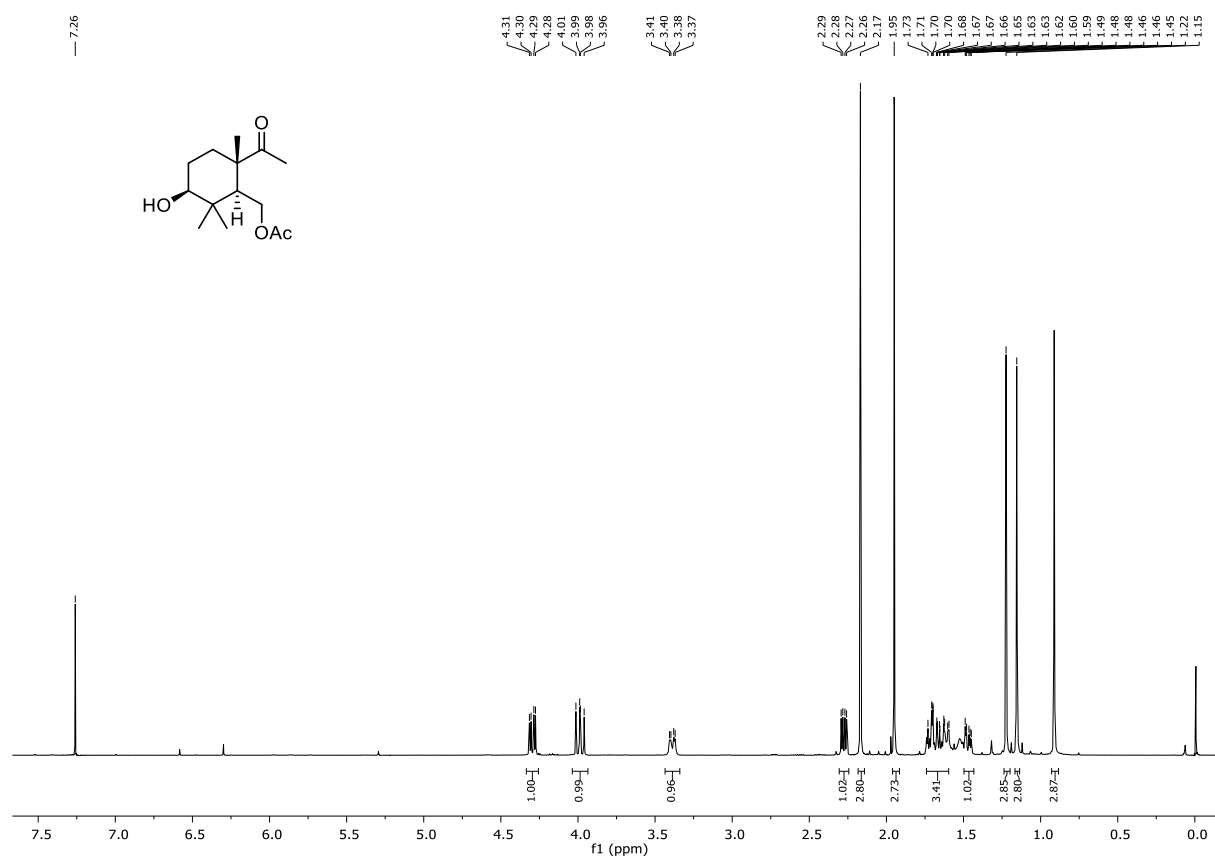




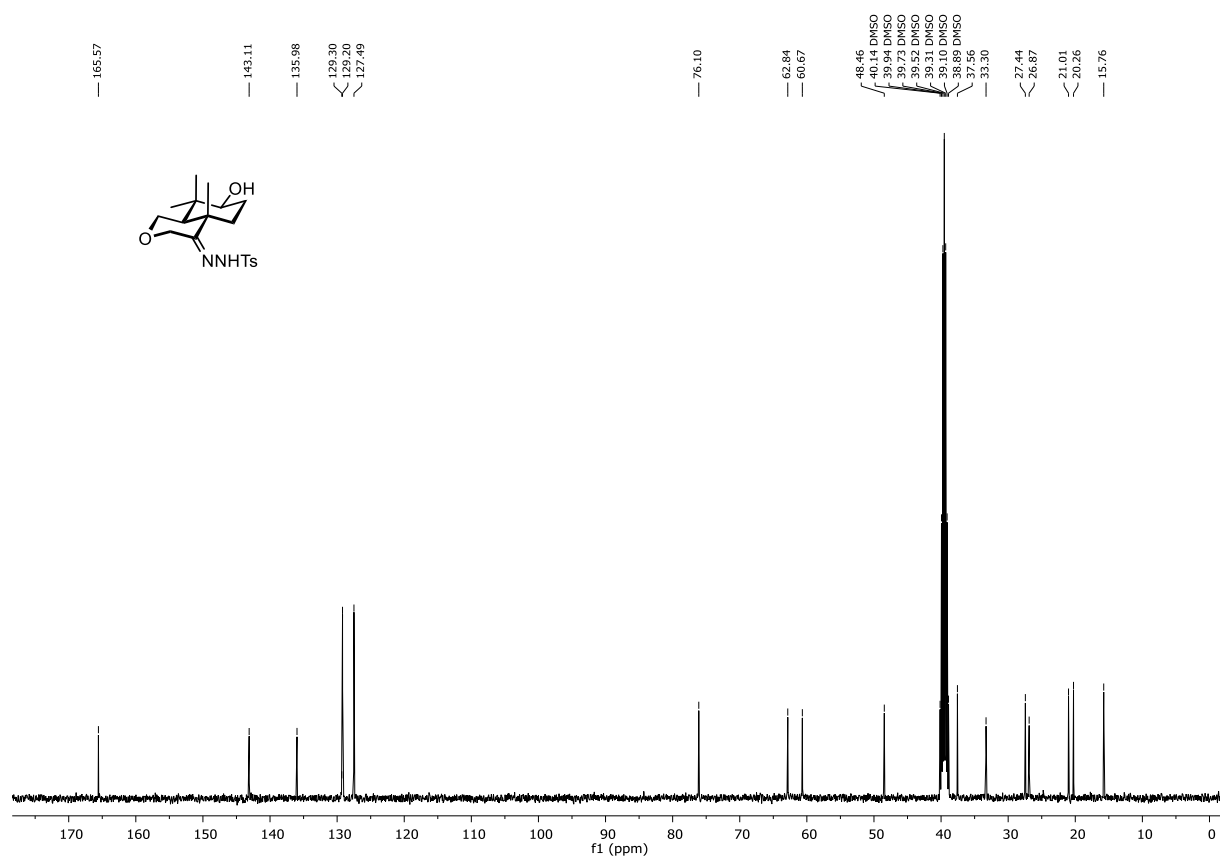
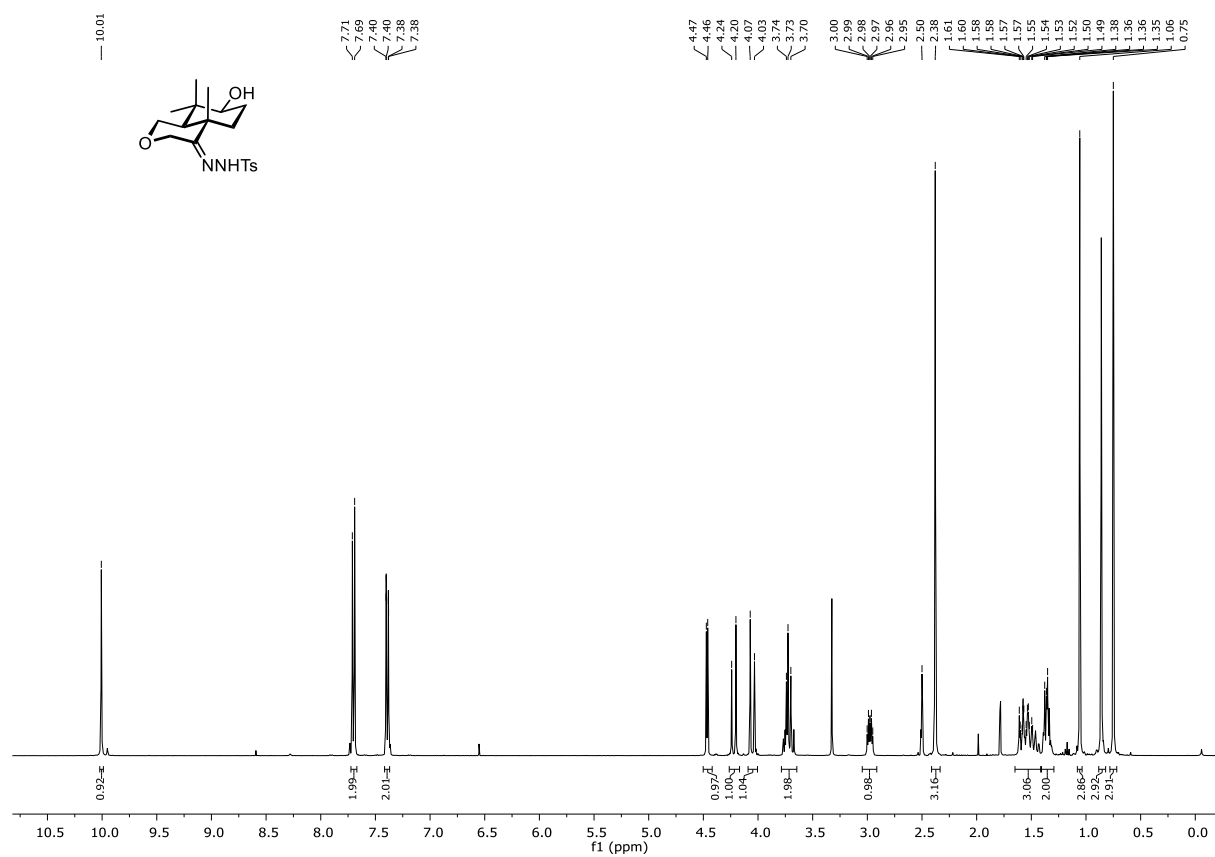
Epoxide 14



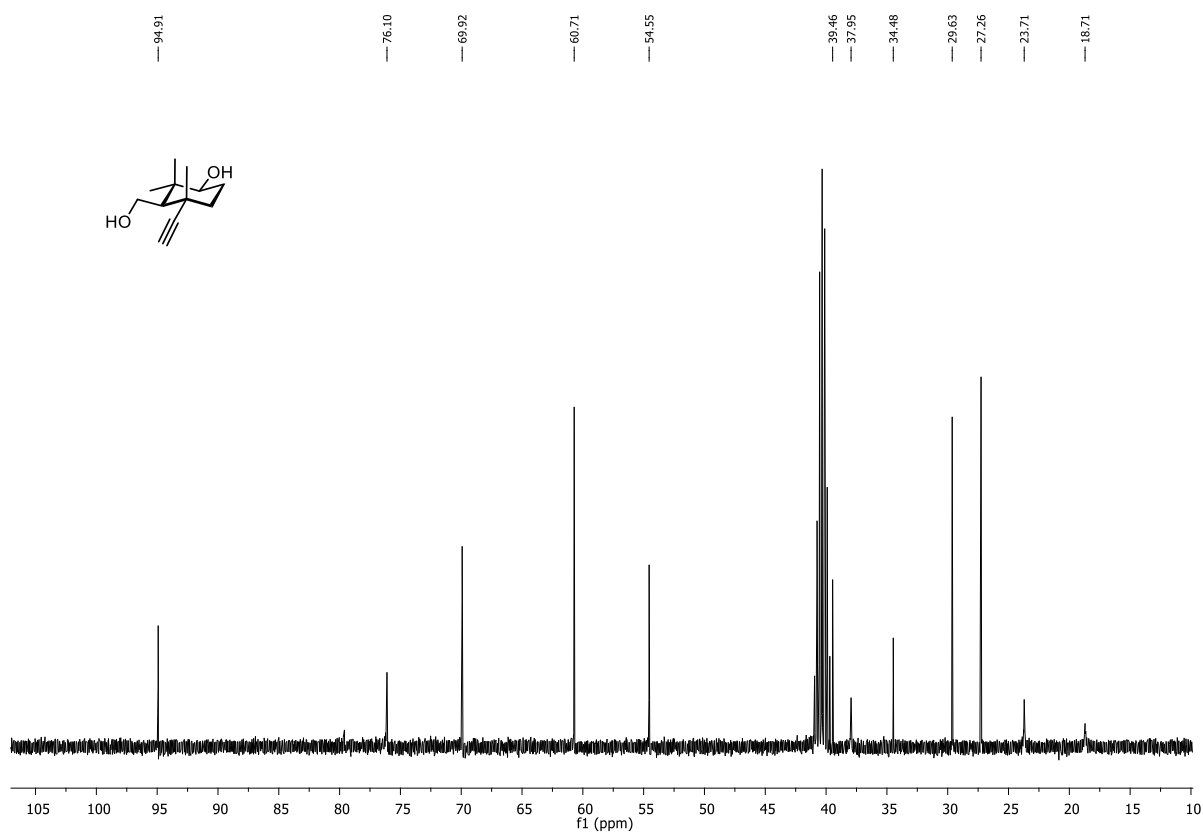
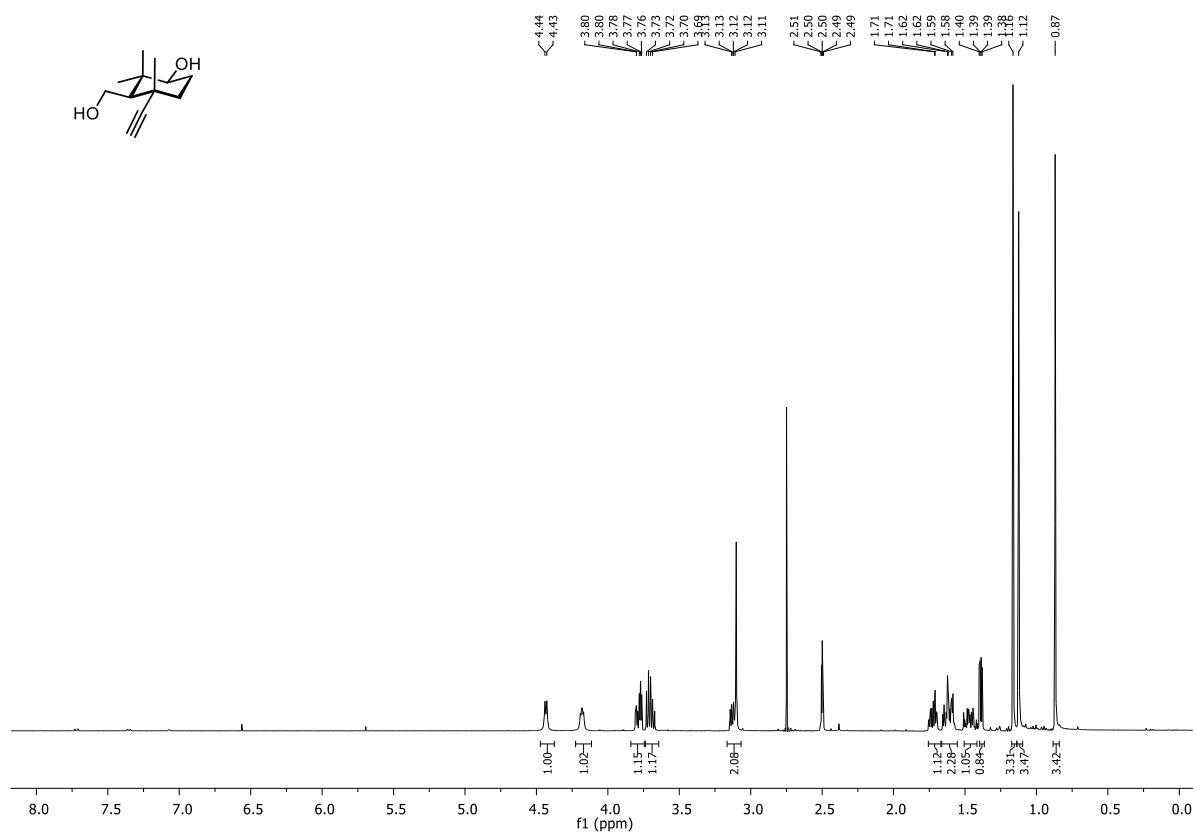
Ketone 15



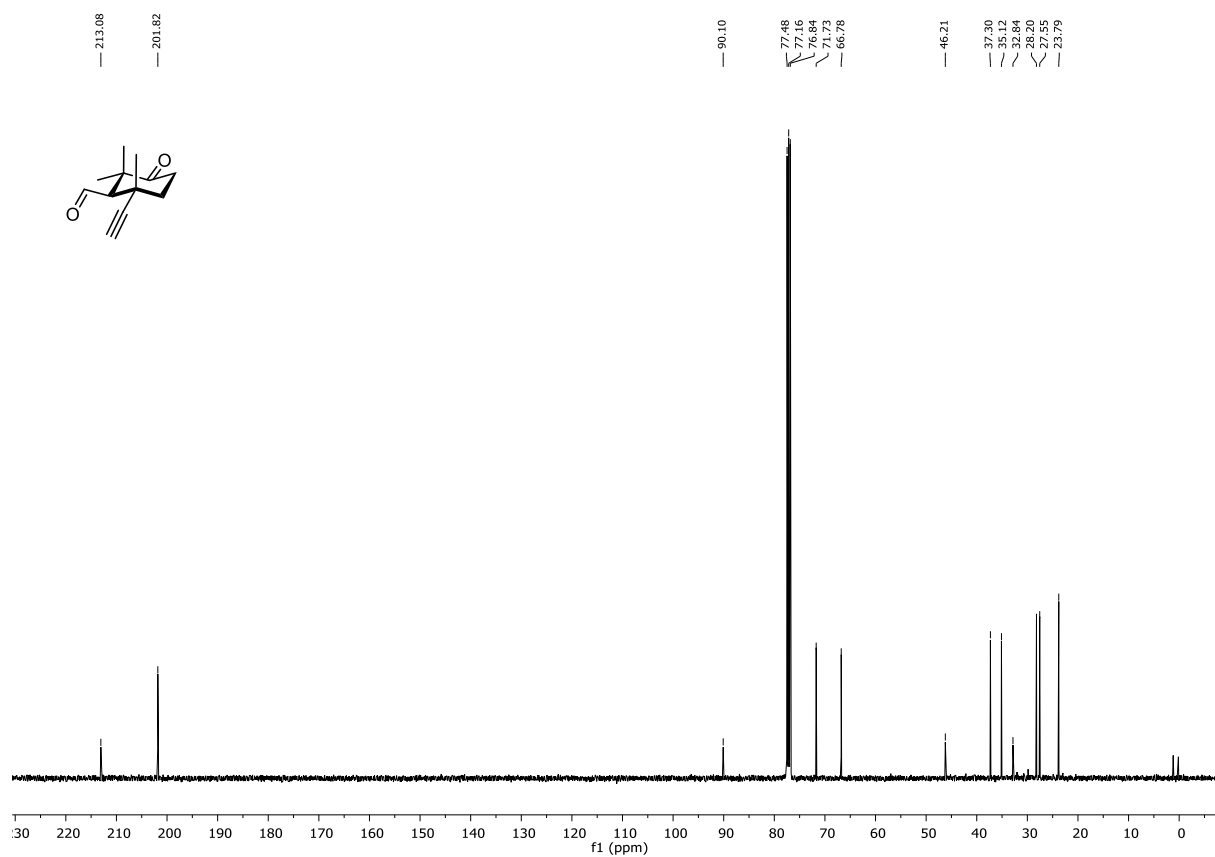
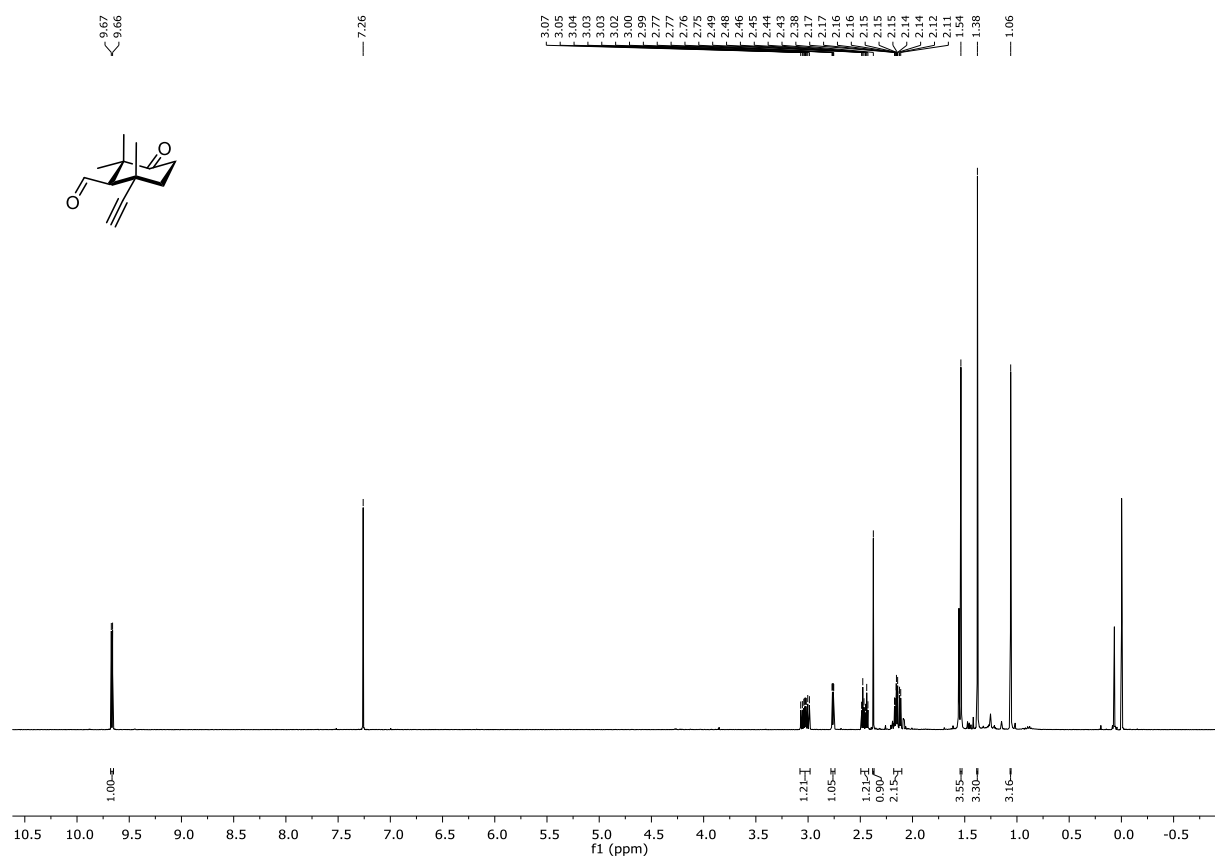
Tosyl hydrazone **S22**



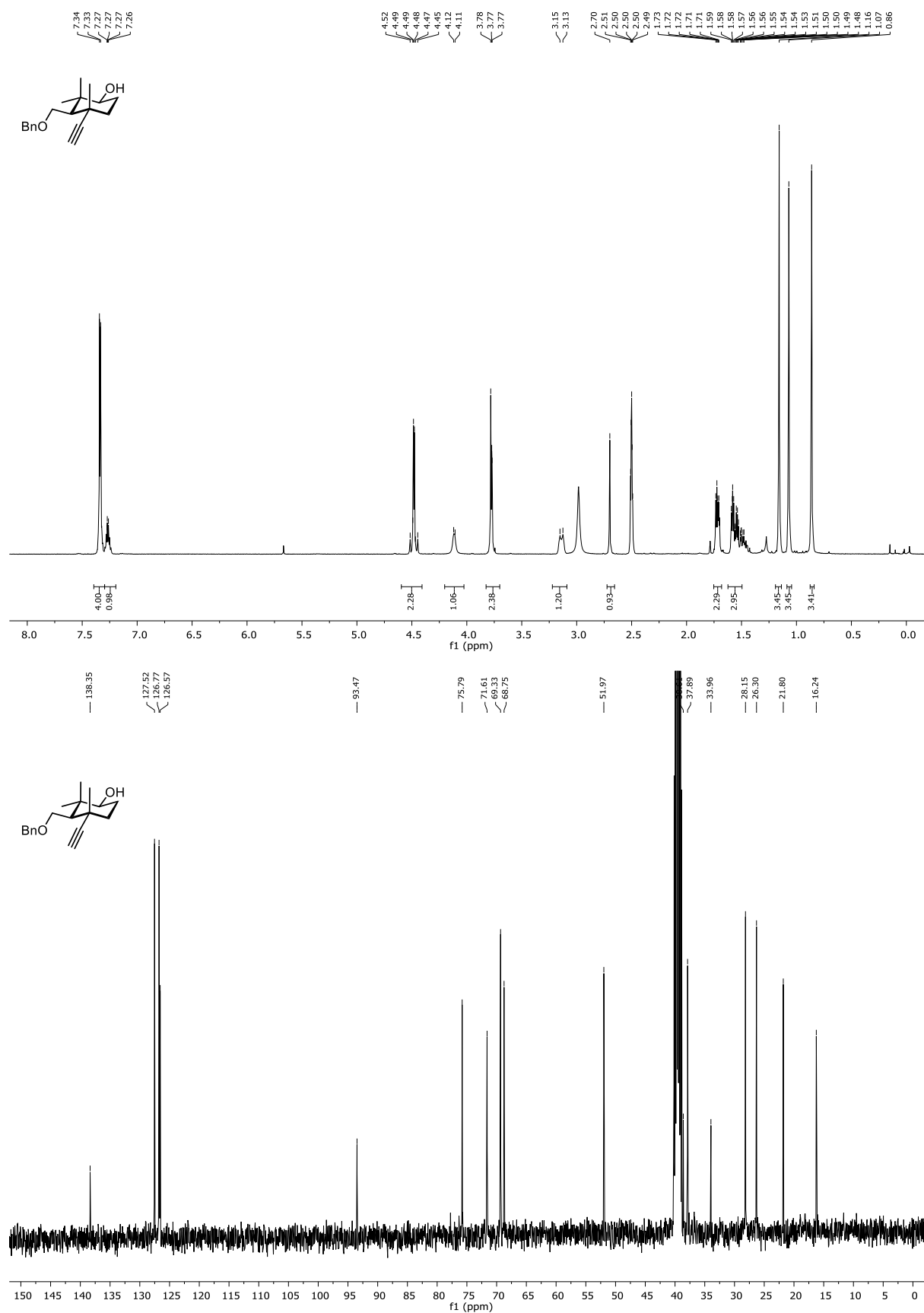
Alkyne S1



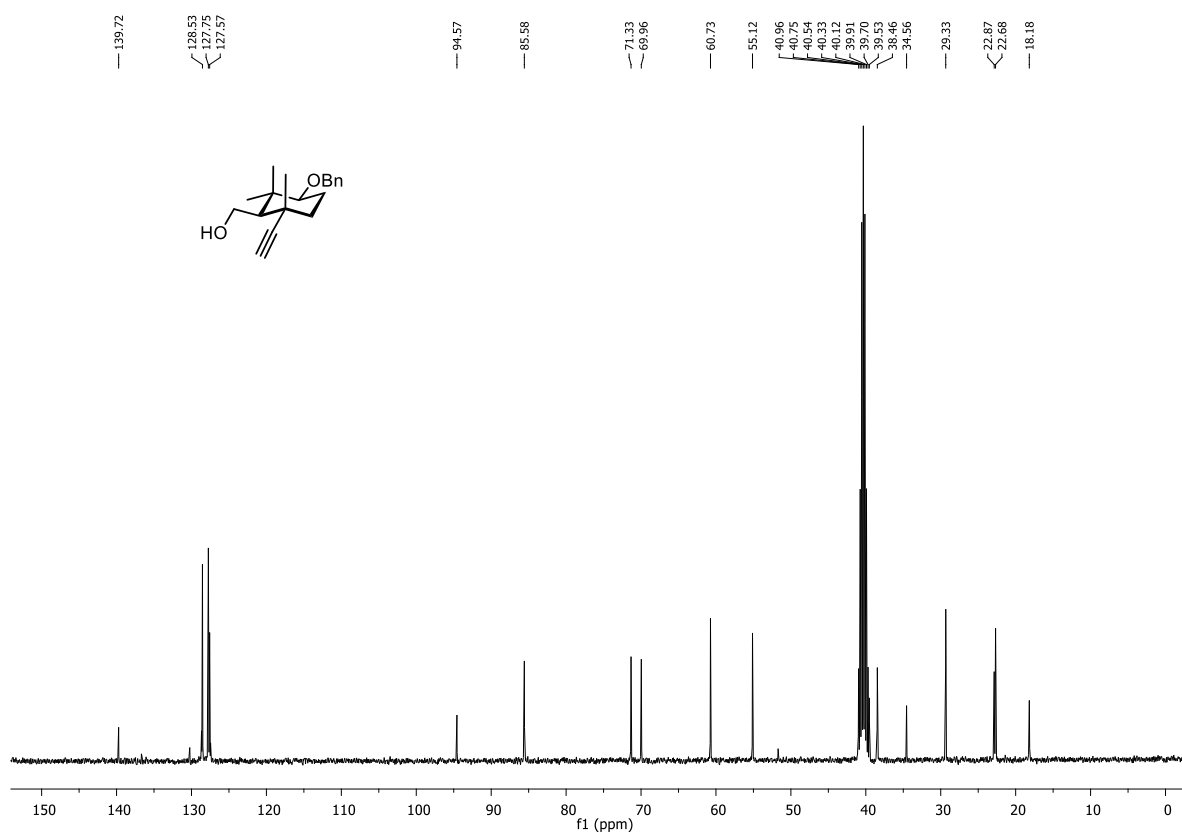
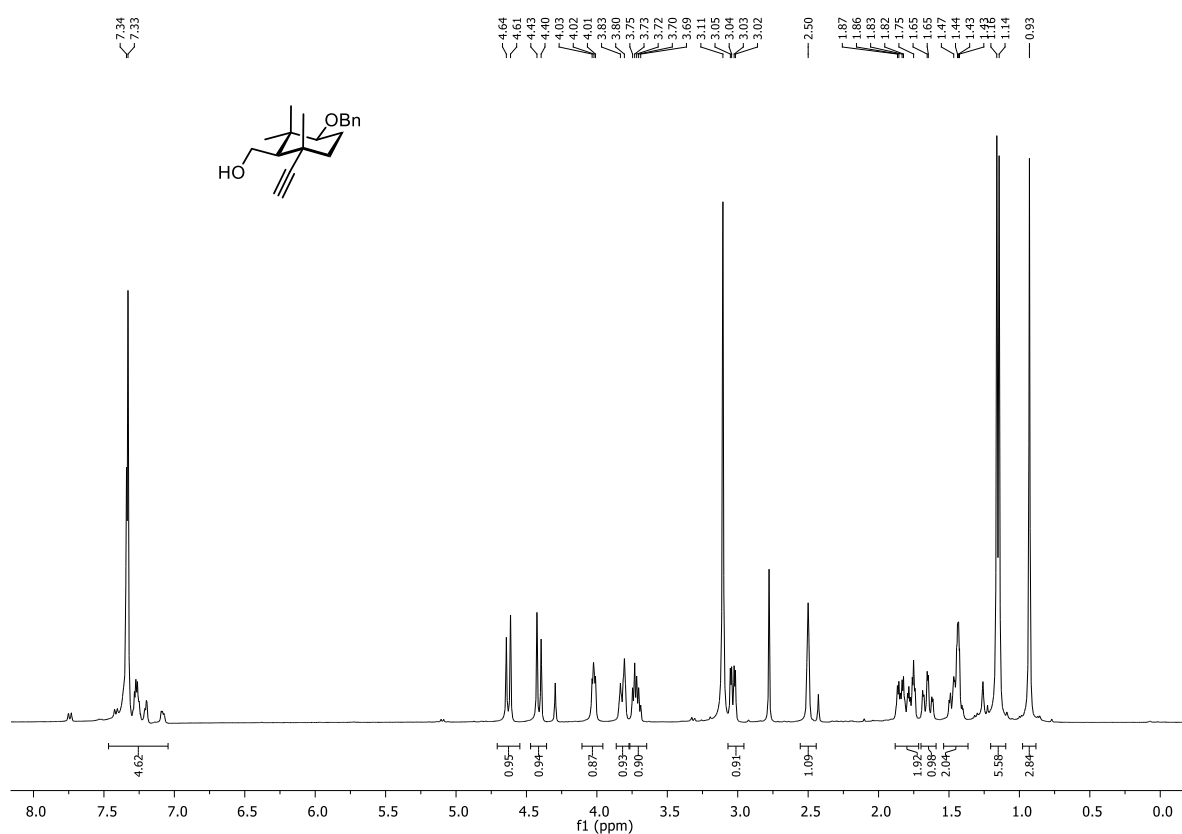
Keto aldehyde **16**



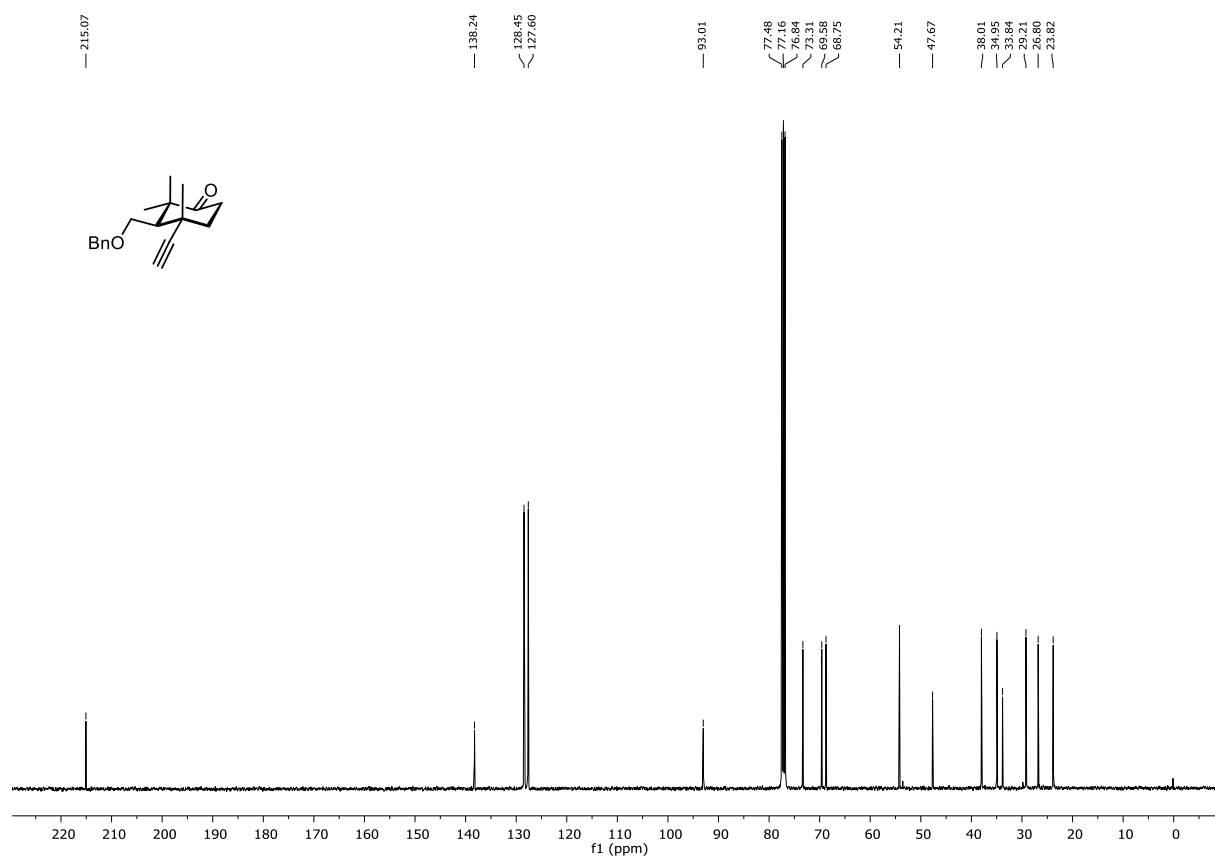
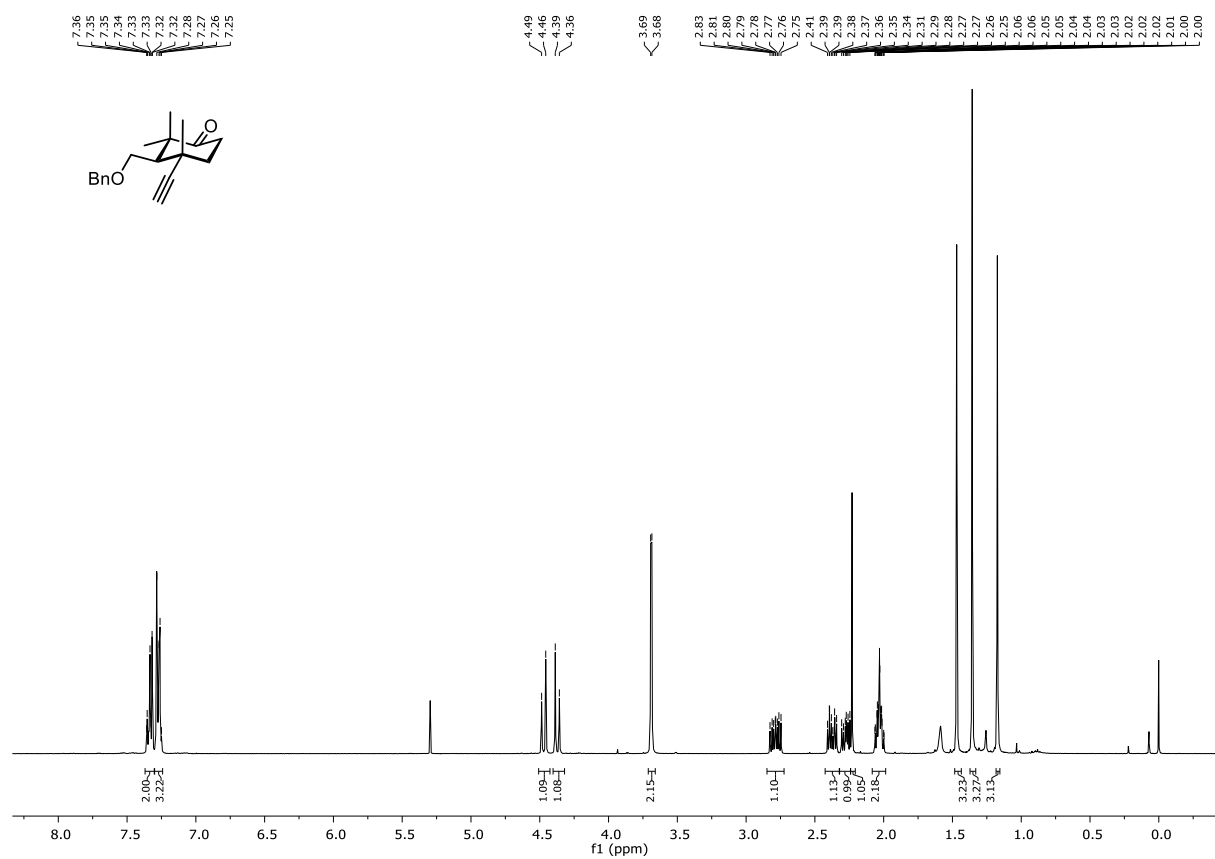
Benzyl ether S3



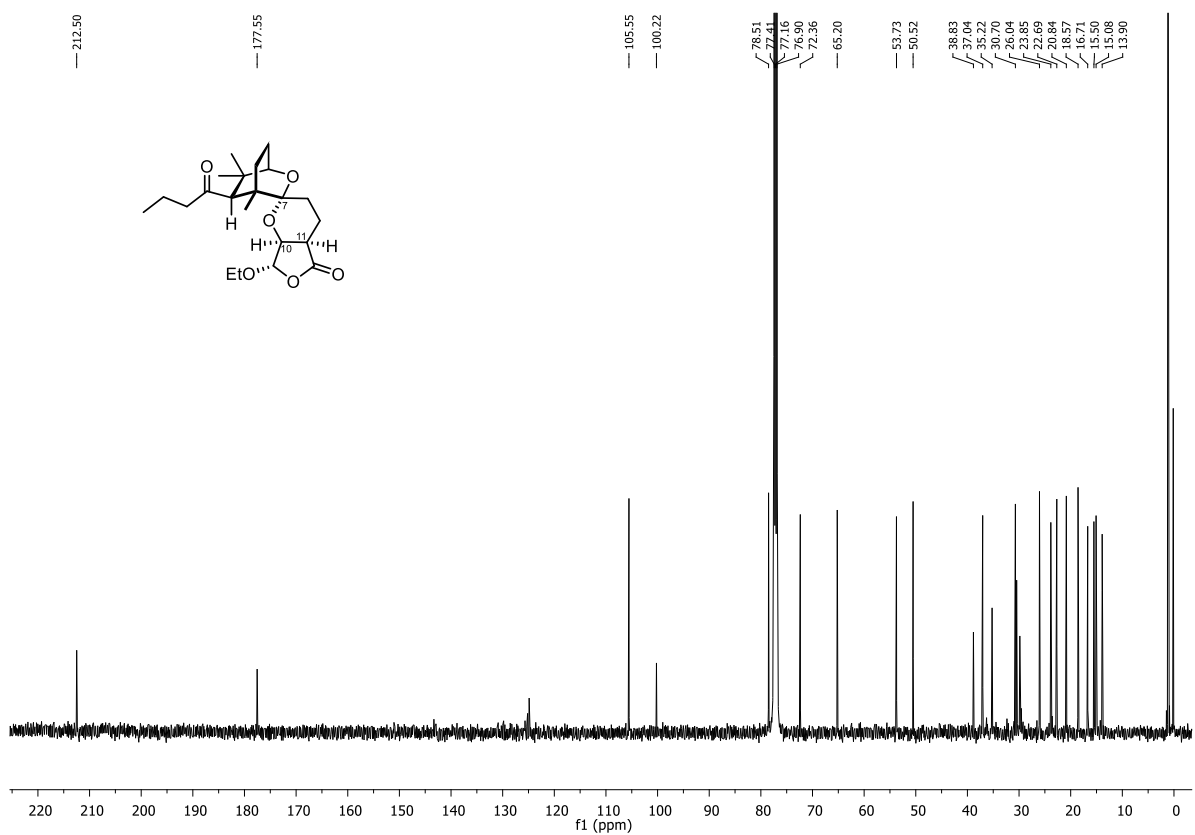
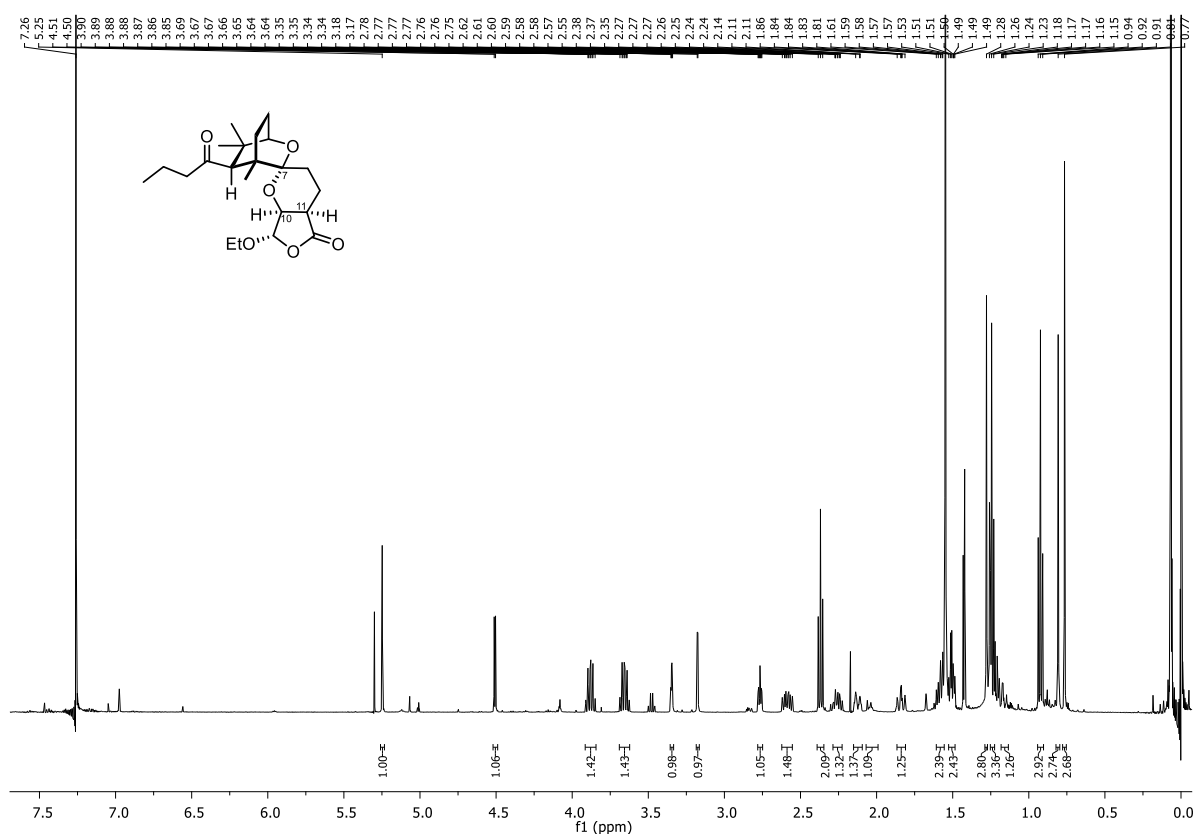
Benzyl ether **S23**



Ketone 17

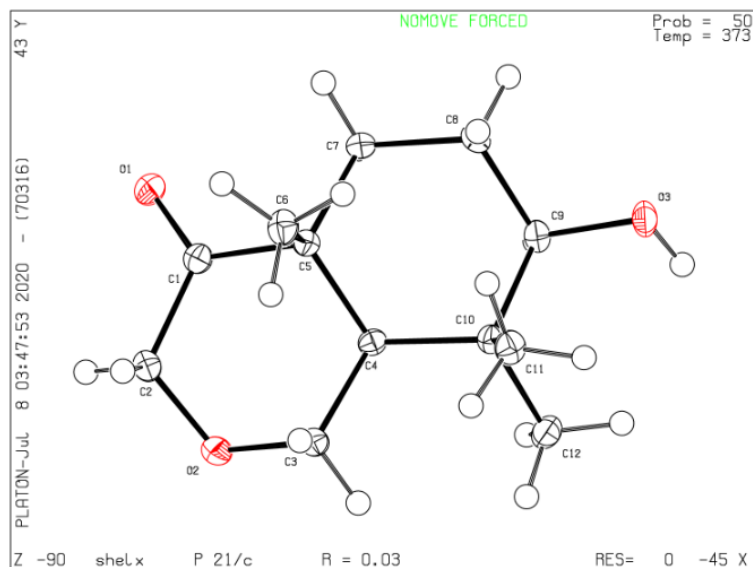


Spiroketal S4



8. Crystallographic data

Ketone 13



Bond precision: C-C = 0.0016 Å Wavelength=1.54184
 Cell: a=11.0620(2) b=7.1209(1) c=14.1569(3)
 alpha=90 beta=102.950(2) gamma=90

Temperature: 373 K

	Calculated	Reported
Volume	1086.80(4)	1086.80(3)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C ₁₂ H ₂₀ O ₃	?
Sum formula	C ₁₂ H ₂₀ O ₃	C ₁₂ H ₂₀ O ₃
Mr	212.28	212.28
Dx, g cm ⁻³	1.297	1.297
Z	4	4
Mu (mm ⁻¹)	0.738	0.738
F ₀₀₀	464.0	464.0
F ₀₀₀ '	465.41	
h,k,lmax	13,8,17	13,8,17
Nref	1987	1984
Tmin,Tmax	0.899,0.929	
Tmin'	0.850	

Correction method= Not given

Data completeness= 0.998

Theta(max)= 68.236

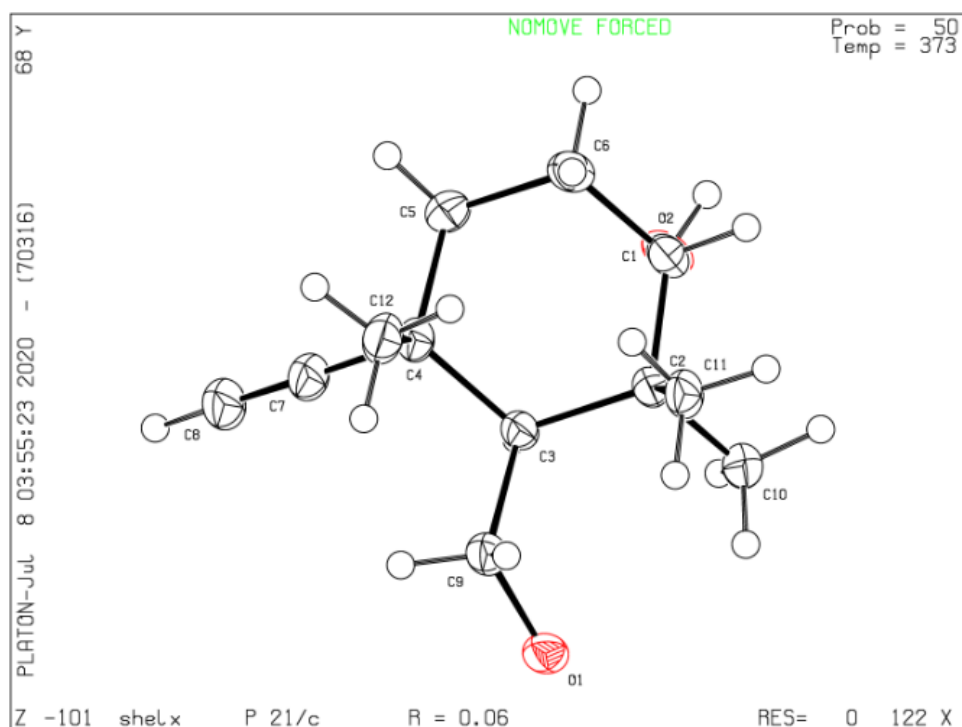
R(reflections)= 0.0327(1794)

wR2(reflections)= 0.0931(1984)

S = 1.073

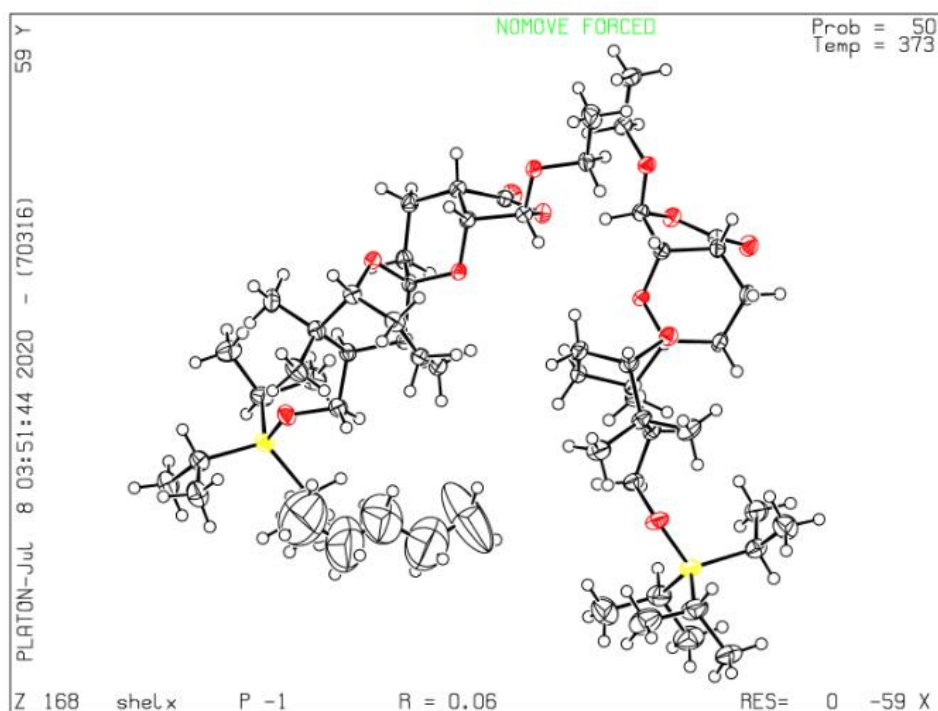
Npar= 140

Alkyne 18



Bond precision:	C-C = 0.0030 Å		Wavelength=1.54184
Cell:	a=10.5524(10)	b=7.6318(6)	c=14.5442(9)
	alpha=90	beta=97.954(7)	gamma=90
Temperature:	373 K		
	Calculated	Reported	
Volume	1160.03(16)	1160.03(16)	
Space group	P 21/c	P 21/c	
Hall group	-P 2ybc	-P 2ybc	
Moiety formula	C12 H20 O2	?	
Sum formula	C12 H20 O2	C12 H20 O2	
Mr	196.28	196.28	
Dx,g cm-3	1.124	1.124	
Z	4	4	
Mu (mm-1)	0.586	0.586	
F000	432.0	432.0	
F000'	433.22		
h,k,lmax	12,9,17	12,9,17	
Nref	2126	2121	
Tmin,Tmax	0.965,0.994		
Tmin'	0.932		
Correction method= Not given			
Data completeness=	0.998	Theta(max)= 68.225	
R(reflections)=	0.0579(1779)	wR2(reflections)= 0.1734(2121)	
S = 1.088	Npar= 136		

Spiroketal 25



Bond precision:	C-C = 0.0038 Å	Wavelength=1.54184	
Cell:	a=8.2254(1)	b=17.1216(1)	c=24.2196(2)
	alpha=75.416(1)	beta=85.608(1)	gamma=89.374(1)
Temperature: 373 K			
	Calculated	Reported	
Volume	3291.18(5)	3291.18(5)	
Space group	P -1	P -1	
Hall group	-P 1	-P 1	
Moiety formula	2(C28 H50 O6 Si), C5 H12	?	
Sum formula	C61 H112 O12 Si2	C61 H112 O12 Si2	
Mr	1093.69	1093.68	
Dx,g cm-3	1.104	1.104	
Z	2	2	
Mu (mm-1)	0.920	0.920	
F000	1204.0	1204.0	
F000'	1208.28		
h,k,lmax	10,21,30	10,21,30	
Nref	13460	13082	
Tmin,Tmax	0.895,0.955		
Tmin'	0.847		
Correction method=	Not given		
Data completeness=	0.972	Theta(max)= 74.398	
R(reflections)=	0.0561(11262)	wR2(reflections)= 0.1650(13082)	
S = 1.049	Npar= 698		

LNK SI ChemRxiv.pdf (5.54 MiB)

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