Synthesis of a Biomimetic Tetracyclic Precursor of Aspochalasins Allowing a Formal Synthesis of Trichoderone A

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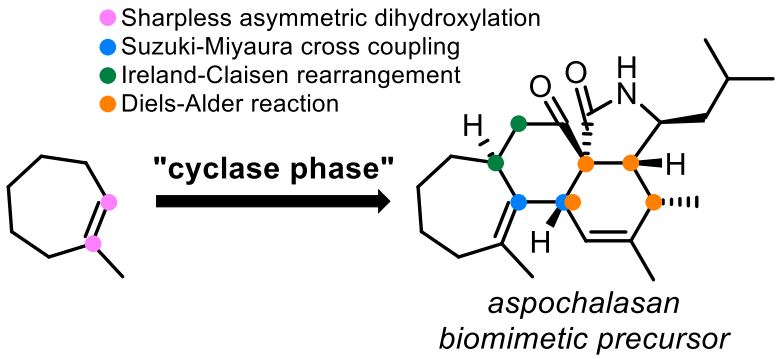
Graphical abstract



Abstract: Aspochalasins are leucine-derived cytochalasins. Their complexity is often associated to a high degree of biosynthetic oxidative transformations that could inspire a two-phase strategy in total synthesis. In that context, we describe the synthesis of a putative biomimetic tetracyclic intermediate. The key constructive steps are an intramolecular Diels-Alder reaction to install the characteristic isoindolone core of cytochalasins, whose branched precursor was obtained from a stereoselective Ireland-Claisen rearrangement made on a highly unsaturated substrate. This work also constitutes a formal synthesis of trichoderone A.

The bio-inspired two-phase synthesis paradigm first relies on the construction of a minimally oxidized natural product skeleton, often referred to as the "cyclase phase".[1] This intermediate is then engaged in a second stage involving functional decorations, also called "oxidation phase" when it comes to selective oxidative functionalization, which aims to produce the final natural products. Highly complex natural products have been achieved by this strategy,[1-9] with the two-phase synthesis of taxol recently achieved by Baran and co-workers standing as a feat in total synthesis.[10] These examples most often concern terpenoids, while biosynthetic oxidative functionalizations are ubiquitous in natural products.

Cytochalasins obey the same two-phase biosynthetic logic.[11,12] A core skeleton is first enzymatically constructed by a hybrid polyketide synthase‑non-ribosomal peptide synthetase (PKS-NRPS) assembly line,[13,14] and then cyclized before additional oxidative functionalizations to deliver the final natural products.[15,16] A two-phase bio-inspired synthetic strategy to synthesize complex cytochalasins or structurally related analogues is thus conceivable if we can efficiently access an appropriate, poorly functionalized precursor.

Owing to their reputed biological activities (*e.g.* as inhibitors of actin polymerization,[17] glucose transporters,[18] or as cytotoxic compounds[19]), cytochalasins have often been the target of total synthesis.[20] More specifically, aspochalasins (*e.g.* **1**)[21] are 11-membered macrocyclic compounds incorporating the typical fused isoindolone heterocycle of cytochalasins (Figure 1). They are biologically derived from l-leucine, as betrayed by the isobutyl substituent. During the biosynthesis, the transannular cyclization of the macrocycle leads to tetracyclic derivatives with a 7/6/6/5 fused system and oxygenated decorations, like aspergillin PZ (**2**)[22] recently synthesized by Trauner though a biomimetic cyclization strategy.[20o] An important array of oxidative functionalizations can be encountered at various positions of this carbocyclic skeleton.[23] Interestingly, oxygen-bridged trichoderone A (**3**)[24] and oxidatively cleaved trichodermone (**4**)[25] could be derived from a common biosynthetic intermediate (**5**) after late-stage oxidative functionalizations (Figure 1), with **5** possibly arising from biosynthetic precursor **6** after transannular cyclization. This retrobiosynthetic hypothesis differs from the previously suggested route that makes aspochalasin D (**1**) a precursor of **3** and **4**, through deoxygenation.[20q,25]

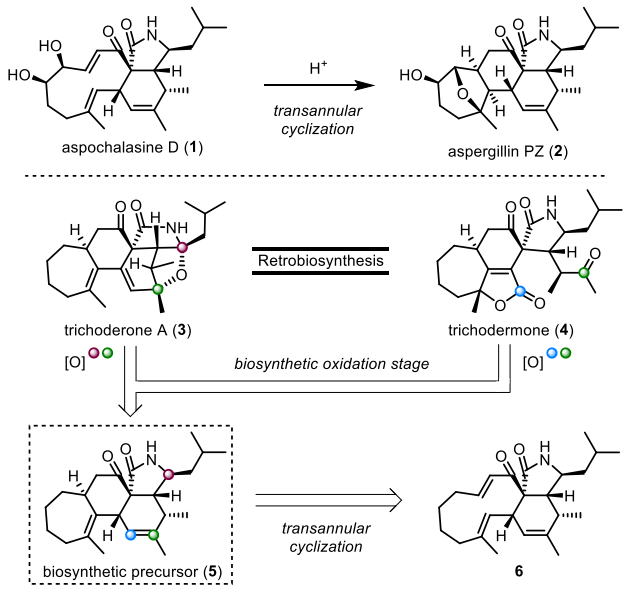
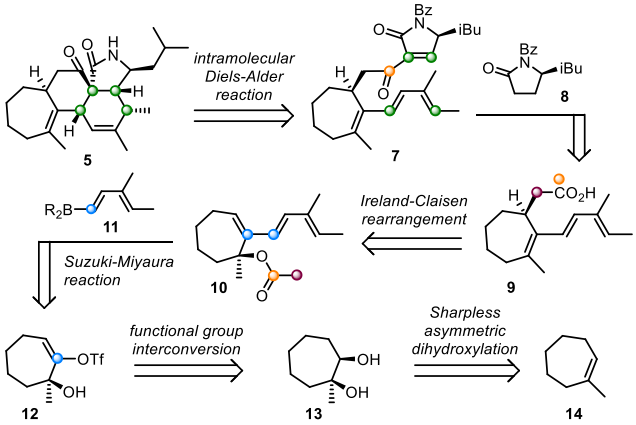


Figure 1. Structure of aspochalasin-related natural products **1**-**4** and retrobiosynthetic analysis of **3** and **4** highlighting precursor **5** for two-phase biomimetic synthesis.

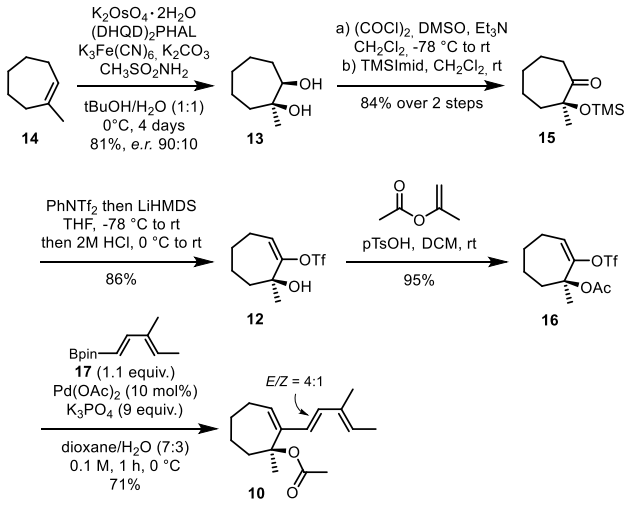
A two-phase biomimetic strategy towards complex aspochalasins and bio-inspired analogues, involving extensive oxidations, could thus be envisaged if precursor **5** can be synthesized, as we report herein. After the recent impressive work of Puno, Deng and co-workers on the divergent synthesis of aspochalasins,[20q] our work also constitutes a formal synthesis of trichoderone A (**3**). Above all, it provides the preliminary "cyclase" phase for future prospects on the second "oxidase" phase towards functionalized derivatives.

Retrosynthetically, compound **5** could be obtained by an intramolecular Diels-Alder reaction (IMDA), expectedly favoring the *endo* cycloadduct. The dienophile in IMDA substrate **7** can be installed in a two-stage manner involving the α-acylation of lactam **8** with carboxylic acid **9** after activation as a mixed anhydride, followed by a selenide-mediated oxidation of the α-position. Lactam **8** is accessible on a decagram scale from l-leucine.[26] Compound **9** could be stereoselectively delivered by an Ireland-Claisen rearrangement[27] of allylic acetate **10**, enabling the transfer of stereochemistry from the chiral acetate.[28] In fact, this allylic acetate is also a sensitive triene and as far as we know, the Ireland-Claisen rearrangement has never been applied to such highly unsaturated substrate. This reaction would however allow an asymmetric access to acid **9**, foreseeing an enantioselective synthesis of acetate precursor **10**. The triene moiety could be installed on enol triflate **12** by a Suzuki-Miyaura sp^2-sp^2 cross-coupling[29] with dienyl boronate **11**. Finally, intermediate **12** could be synthesized from enantioenriched *syn*-diol **13**, which was envisioned to be obtained from 1-methylcycloheptene **14** through a Sharpless asymmetric dihydroxylation.[30] This reaction was expected to provide a reliable entry to secure an asymmetric synthesis of compound **5**.



Scheme 1. Retrosynthetic strategy towards intermediate **5**.

1-Methylcycloheptene **14** was available from a two-step literature sequence starting from commercial cycloheptanone.[31] It was submitted to a Sharpless asymmetric dihydroxylation to access diol **13** (Scheme 2). Since this reaction had not been described on alkene **14**, we relied on ligand guidelines to choose the most appropriate conditions,[32] and on the reported dihydroxylation of 1-methylcyclohexene or 1-phenylcycloheptene using the ligand $(DHQD)_2PHAL$ [dihydroquinidine-1,4-phthalazinediyl diether].[33] In the presence of commercially available AD-mix-β (involving 1 mol% of $(DHQD)_2PHAL$ and 0.4 mol% of K_2OsO_4) combined with 1 equivalent of $CH_3SO_2NH_2$ in a 1:1 mixture of *t*BuOH/H_2O at room temperature, diol **13** was promisingly obtained in 65% yield and an *e.r.* of 84:16 after 3 days,[34] which were improved to 69% and 90:10 at 0°C after 7 days. The anthraquinone ligand $(DHQD)_2AQN$ [dihydroquinidine anthraquinone-1,4-diyl diether], also proposed for trisubstituted olefins, was evaluated giving a better NMR yield (88%) but a lower *e.r.* (86:14). Finally, increasing the loadings of K_2OsO_4 (0.7 mol%) and of $(DHQD)_2PHAL$ (1.75 mol%) resulted in good yields (81%) and *e.r.* (90:10) after 4 days. The reaction was easily reproducible and scalable (5-gram batches).

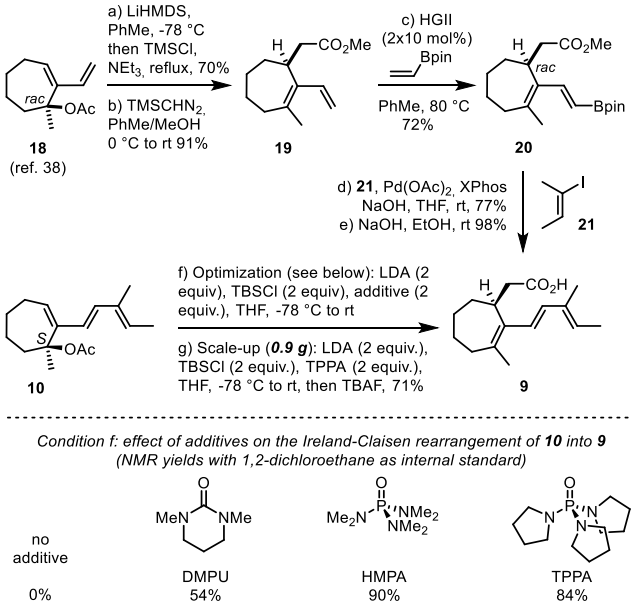


Scheme 2. Synthesis of Ireland-Claisen substrate **10**.

Diol **13** was then engaged in functional group manipulation towards enol triflate **16** (Scheme 2). The oxidation of the secondary alcohol was achieved by a Swern protocol, directly followed by the protection of the tertiary alcohol[35] in presence of 1-(trimethylsilyl)imidazole (TMSImid), affording **15** in 84% yield over two steps (11-gram scale). The enol triflation of **15** was performed by deprotonation with LiHMDS in presence of $PhNTf_2$. The tertiary alcohol was regenerated upon acidic treatment (HCl) at the end of the reaction, giving unprotected enol triflate **12** in 86% (5-gram scale). Significant difficulties were observed with the acetylation of the tertiary alcohol, in view of the Ireland-Claisen rearrangement. The reaction was ineffective in most classical conditions, but finally succeeded in presence of isopropenyl acetate under acid catalysis (*p*TsOH), to give acetate **16** in 95% (1.4 g scale). Unfortunately, these conditions were hardly scalable, the yields dropping gradually from 95% to 52% when scaling-up from 1.4 g to 10 g (this problem was solved by running the reaction in multiple flasks).

Finally, the next step to Ireland-Claisen substrate **10** involved a Suzuki-Miyaura cross coupling between triflate **16** and dienylboronate **17** (easily available from tiglic aldehyde through a boron-Wittig strategy recently reported by Morken[36]). The cross coupling performed well in the presence of $Pd(OAc)_2$ (10 mol%) and K_3PO_4 in a 7:3 dioxane/water mixture at 0 °C without ligand, providing triene **10** in 71% yield after one hour. In fact, the absence of ligand allowed to perform the reaction on a 1.6 g scale, providing **10** as a 4:1 mixture of *E* and *Z* isomers, respectively, supposedly formed through triene isomerization under reaction conditions. The undesired isomer could be separated during the next step. Although electron-rich ligands like PCy_3, $P(2\text{-furyl})_3$ or bis(diphenylphosphino)ferrocene (dppf) allowed the reaction to proceed in good yields (75-80%), these conditions were hardly reproducible when scaling up the reaction.

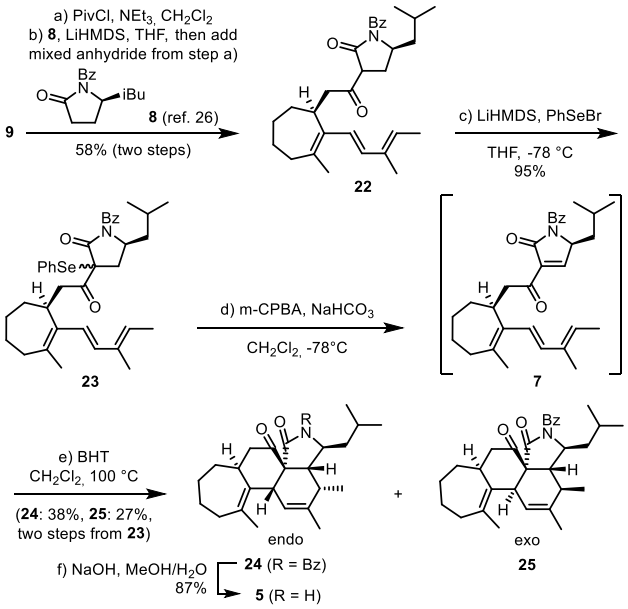
Only a few examples of Ireland-Claisen rearrangements have been performed on branched allylic systems bearing conjugated substituents at position 2, like acetate **10**. In 2006, Diver and co-workers were able to perform tandem enyne metatheses giving products with the branched 2-vinylallylic acetate topology like ours, which were engaged in the Ireland-Claisen rearrangement.[37] We first attempted this rearrangement on simplified substrate **18** previously obtained in a racemic form from enyne metathesis[38] (Scheme 3). Rearranged product **19** was successfully obtained in 70% yield after deprotonation by LiHMDS in toluene, followed by the addition of $TMSCl/Et_3N$ and increasing the temperature to reflux. Diene **19** could also be engaged in additional transformations towards triene **9** (racemic form), through a sequence of cross metathesis with pinacol vinylboronate and a Suzuki-Miyaura cross-coupling with iodoolefin **21** (available from the corresponding bromoolefin by applying Klapars and Buchwald procedure[39]).



Scheme 3. The Ireland-Claisen rearrangement of branched allylic acetates **10** and **18**.

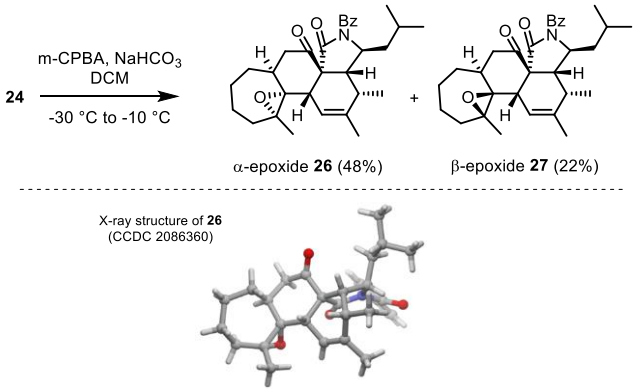
These preliminary results validated our rearrangement strategy, but the conditions were not directly transposable to triene substrate **10**. A screening of new conditions in presence of various bases (LiHMDS, LDA or LiTMP) and silyl reagents (TMSCl or TBSCl) in THF showed that in the absence of any additive, the couple LiTMP/TBSCl was the best to afford partial conversion of starting material **10**, giving 32% of **9**. In fact, the use of an additive was crucial for the success of the reaction in presence of LDA. HMPA and the less toxic TPPA (Scheme 3) were the most effective, furnishing **9** in 90 and 84% yields, respectively. The rearrangement performed well at room temperature in THF. Although the carboxylic acid could be directly obtained on small-scale reactions (0.2 mmol), the same conditions on a larger scale (3.6 mmol) afforded a mixture of the TBS ester and the acid, which needed an additional treatment with TBAF, leading to acid **9** in 71%.

Carboxylic acid **9** was next coupled to γ-lactam **8** (Scheme 4), which is available in 5 steps from *N*-Boc-l-leucine.[26] To do so, **9** was activated as a mixed pivaloyl anhydride and added to deprotonated, benzoyl-protected, γ-lactam **8**, giving α-acyl-γ-lactam **22** in 58% (two steps). These conditions proved superior to the more classical activation of **9** as an acyl imidazole by treatment with carbonyldiimidazole.[20] To install the dienophile, intermediate **22** was converted into selenide **23** in 95% yield by deprotonation in presence of LiHMDS and reaction with PhSeBr. Oxidation and spontaneous elimination in presence of *m*-CPBA and $NaHCO_3$ in CH_2Cl_2 at –78 °C released the IMDA substrate **7**, which was too unstable to be isolated. After reductive and basic treatment of this reaction mixture to eliminate any trace of oxidant and acid, a solution of **7** in CH_2Cl_2 was heated at 100°C in a sealed tube, in presence of BHT as a radical scavenger, to furnish *endo* cycloadduct **24** in 38% yield and *exo* product **25** in 27% yield after purification. It was not possible to improve this reaction, especially by any catalytic process involving a Lewis acid or the Schreiner's catalyst as previously reported for periconiasin derivatives.[19] Finally, the lactam of cycloadduct **24** was deprotected under hydrolytic conditions to achieve the synthesis of biomimetic tetracyclic precusor **5**.



Scheme 4. Final steps towards tetracyclic precursor **5**.

The epoxidation of **24** could selectively be achieved on the cycloheptene ring, furnishing a 2:1 stereoisomeric mixture of separable epoxides **26** (48%) and **27** (22%). Major isomer **26** (α-epoxide) could be crystalized for X-ray analysis (Scheme 5). Above all, based on Puno's and Deng's recent work[20q], this new synthetic strategy provides a formal synthesis of trichoderone A (**3**), which can be formed from **5** upon air oxidation, through allylic peroxidation and oxidative cyclization.



Scheme 5. Epoxidation of **24** furnishing suitable crystals of **26** for X-ray analysis.

In conclusion, we were able to perform the synthesis of a key synthetic precursor (**5**) of tetracyclic aspochalasan natural products and derivatives, the structure of which could be confirmed by X-ray analysis of an epoxide product (**26**). Compound **5** constitutes a good entry to perform the "oxidase" phase in the bio-inspired synthesis of natural products such as trichoderone A (**3**) and trichodermone (**4**). In particular, this work constitutes a formal synthesis of **3**.[20q] Additional oxidations can be envisaged on precursor **5**, either in a total synthesis perspective, or to synthesize a bio-inspired diversity of aspochalasins for biological studies.

Supporting Information

Synthetic procedures and copies of NMR spectra (PDF)

Crystal analysis of **26** (CIF)

CCDC 2086360 (**26**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Supporting Information

Synthesis of a Biomimetic Tetracyclic Precursor of Aspochalasins Allowing a Formal Synthesis of Trichoderone A

Oscar Gayraud, Benjamin Laroche, Nicolas Casaretto, and Bastien Nay

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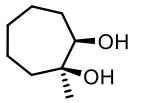
Experimental procedures

General remarks

All reactions were carried out in oven-dried vessels under an atmosphere of argon and in anhydrous solvents unless stated otherwise. Solvents (methylene chloride, diethyl ether and tetrahydrofuran) were purified using a MB-SPS 800 Solvent purification system (MBraun). Analytical thin-layer chromatography (TLC) was carried out using aluminium TLC plates coated with F_{254} silica gel 60 (Merck), which were visualized by exposure to ultraviolet light and/or exposure to a basic solution of potassium permanganate or *p*-anisaldehyde stain followed by heating. Flash chromatography was carried out on silica gel 60 (40-63 μm). Chiral HPLC analyses were performed on a Shimadzu Nexera X2 system equipped with a Prominence diode array detector detector (UV-vis).

Infrared spectra were recorded on a PerkinElmer spectrum two FTIR equipped with a Jasco ATR. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-GCmate II spectrometer (EI+) or on a Bruker tims-TOF mass spectrometer (ESI+), and reported as *m/z*. Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded at 25°C with a Brucker Avance 400 or a Bruker 400 MHz Avance III (^{1}H at 400 MHz, ^{13}C at 100 MHz) or a Bruker 600 MHz Avance III spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz). Chemical shifts in $CDCl_3$ and C_6D_6 solutions are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent (for $CDCl_3$: δ_H = 7.26 and δ_C = 77.0; for C_6D_6: δ_H = 7.16 and δ_C = 128.1). Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectra are reported as follows: chemical shift ppm, referenced to protium (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dq = doublet of quartets, td = triplet of doublets, qq = quartets of quartets, ddd = doublet of doublet of doublets, m = multiplet, integration, and coupling constants (Hz)).

(1*S*,2*R*)-1,2-Dihydroxy-1-methylcycloheptane (13)



13

To a stirred solution of $MeSO_2NH_2$ (4.75 g, 50 mmol, 1 equiv), K_2CO_3 (20.7g,150 mmol, 3 equiv), $K_3Fe(CN)_6$ (49.3 g, 150 mmol, 3 equiv), $(DHQD)_2PHAL$ (681 mg, 0.875 mmol, 0.0175 equiv), $K_2OsO_4.2H_2O$ (129 mg, 0.350 mmol, 0.007 equiv) in 500 mL ^{t}BuOH/H_2O (1:1) was added 1-methylcycloheptene **14** (5.5 g, 50 mmol, 1 equiv, prepared according to Barbier and Hügel[1]) at 0 ° C. The reaction mixture was stirred for 4 days at 0 °C. The reaction was quenched with $Na_2S_2O_3$ (75 g), stirred for 1h at rt. The aqueous layer was extracted with EtOAc (3 x 300 mL). The organic layers were combined, washed with a 1 M solution of NaOH (500 mL), brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography (PE/EA 6:1 to 2:1) to yield 5.92 g (82% yield) of diol **13** with an e.r. of 90:10 (see below), as a colorless oil.

$[\alpha]_D^{25}$ = –4.6 (c 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.44 (br d, 1H), 2.32 (brs, 1H), 2.17 (brs, 1H), 1.89-1.76 (m, 2H), 1.76-1.66 (m, 3H), 1.65-1.56 (m, 2H), 1.50-1.30 (m, 3H), 1.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 78.1, 74.1, 38.6, 31.6, 28.1, 27.8, 23.6, 20.9.

[1] Barbier, M.; Hügel, M. F. *Bull. Soc. Chim. Fr.* **1961**, *28*, 951–954.

IR (ATR) ν cm^{-1}: 3400, 2926, 2859, 1460, 1371, 1261, 1194, 1139, 1096, 1030, 970, 951, 930.

HRMS (EI+) *m/z*: calculated for $C_8H_{16}O_2^{+\cdot}$ [$M^{+\cdot}$]: 144.1145; found: 144.1144.

Measure of the enantiomeric excess of **13**:

Compound **13** was first converted to its 2-*O*-benzoyl ester: To a stirred solution of diol **13** (8 mg, 50 µmol, 1 equiv), DMAP (5 µmol, 0.1 equiv) and NEt_3 (10 µL, 75 µmol, 1.5 equiv) in 500 µL of dry DCM, was added BzCl (9 µL, 75 µmol, 1.5 equiv). After stirring at room temperature overnight, the reaction was quenched with a saturated solution of NH_4Cl (1 mL). The aqueous layer was extracted with DCM (3 x 1 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The ester was passed through a pad of silica (PE/EA 9:1) and analyzed by chiral HPLC, by comparison with retention times (t_R) of a racemic sample prepared from the racemic diol:

HPLC analysis [Nacalai Tesque "COSMOSIL CHiRAL 3B" column: silica gel grafted with cellulose tris(3,5-dimethylphenylcarbamate), particle size 3µm, 4.6 x 250 mm]: elution with MeCN/H_2O = 40/60, 1 mL/min; temperature: 40°C; detection at 230 nm; t_R(minor enantiomer) = 14.5 min, t_R(major enantiomer) = 15.4 min; *e.r.* = 90:10 through peak integration.

(2*S*)-2-Trimethylsilyloxy-2-methylcycloheptan-1-one (15)

To a stirred solution of $(COCl)_2$ (10 mL, 120 mmol, 1.5 equiv) in 100 mL of dry DCM was added a solution of DMSO (17 mL, 240 mmol, 3 equiv) in 100 mL of dry DCM at –78 °C over 1h. After 10 min, a solution of diol **13** (11.5 g, 80 mmol, 1 equiv) in 200 mL of dry DCM was added dropwise over 1 h. The reaction mixture was stirred for 10 min then Et_3N (67 mL, 480 mmol, 6 equiv) was added over 30 min and the solution was allowed to warm up slowly to rt. The reaction was quenched with a saturated solution of NH_4Cl (300 mL). The aqueous layer was extracted with DCM (3 x 400 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo, to furnish ketone intermediate **S1** as a colorless oil whose NMR data were consistent with those reported in the literature.[2] Hydroxyketone **S1** was engaged in next step without additional purification.

Data for hydroxyketone **S1**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 3.84 (s, 1H), 2.75-2.67 (m, 1H), 2.51-2.44 (m, 1H), 2.06-1.98 (m, 1H), 1.98-1.93 (m, 1H), 1.86-1.78 (m, 1H), 1.78-1.70 (m, 1H), 1.68-1.62 (m, 1H), 1.50-1.33 (m, 2H), 1.30 (s, 3H), 1.28-1.17 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm: 216.4, 78.7, 38.5, 37.9, 30.3, 27.2, 27.1, 23.8.

To a stirred solution of hydroxy ketone **S1** (80 mmol, 1 equiv) in 150 mL of DCM was added *N* -trimethylsilylimidazole (17.5 mL, 120 mmol, 1.5 equiv). After stirring at rt overnight, the reaction was quenched with a saturated solution of NH_4Cl (200 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography (PE/Et_2O 98:2 to 95:5) to yield 14.4 g (84% yield over 2 steps) of ketone **15** as a colorless oil.

$[\alpha]_D^{25}$ = +2.8 (c 1.5, $CHCl_3$).

[2] Blackburn, C.; Childs, R. F.; Kennedy, R. A., *Can. J. Chem.* **1983**, *61*, 1981-1986.

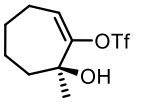
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.78-2.68 (m, 1H), 2.40-2.31 (m, 1H), 1.84-1.77 (m, 1H), 1.76-1.68 (m, 3H), 1.58-1.48 (m, 3H), 1.33 (s, 3H), 1.30-1.22 (m, 1H), 0.12 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.9, 82.3, 40.9, 39.9, 28.9, 26.3, 24.8, 24.7, 2.4.

IR (ATR) ν cm^{-1}: 2931, 2858, 1719, 1453, 1371, 1251, 1203, 1172, 1081.

HRMS (EI+) *m/z*: calculated for $C_{11}H_{22}O_2Si^{+\cdot}$ [$M^{+\cdot}$]: 214.1384; found: 214.1392.

(7*S*)-7-Hydroxy-7-methyl-1-trifluoromethanesulfonyloxycyclohept-1-ene (12)



12

To a stirred solution of ketone **15** (5.2 g, 24 mmol, 1 equiv) and $PhNTf_2$ (12.8 g, 36 mmol, 1.5 equiv) in 200 mL of dry THF was added a 1 M LiHMDS solution in THF (48 mL, 48 mmol, 2 equiv) dropwise over 2h at -78 °C. After stirring at –78 °C for 1h, the reaction mixture was warmed up to rt and stirred overnight. The reaction was quenched with a solution of 2 M HCl (200 mL) at 0 °C and then stirred at rt for 1h. The aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography (PE/EA 98:2 to 95:5) to yield 5.7 g (86% yield) of enol triflate **12** as a yellowish oil.

$[\alpha]_D^{25}$ = +0.9 (c 0.9, $CHCl_3$).

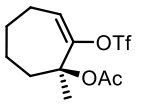
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.86 (t, J = 6.5 Hz, 1H), 2.29-2.11 (m, 2H), 1.94-1.90 (m, 2H), 1.90-1.81 (m, 1H), 1.73-1.62 (m, 3H), 1.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.8, 122.7, 120.0 (q, *J* = 319.5 Hz), 73.7, 39.7, 26.2, 25.6, 23.4, 22.3.

IR (ATR) ν cm^{-1}: 2941, 1411, 1247, 1204, 1143, 1003, 980.

HRMS (EI+) *m/z*: calculated for $C_8H_{10}F_3O_4S^{+\cdot}$ [M-$CH_3^{+\cdot}$] 259.0240 found: 259.0241.

(7*S*)-7-Acetoxy-7-methyl-1-trifluoromethanesulfonyloxycyclohept-1-ene (16)



16

To a stirred solution of enol triflate **12** (1.4 g, 5 mmol, 1 equiv) and isopropenyl acetate (2.8 mL, 25 mmol, 5 equiv) in 50 mL of DCM was added TsOH (125 mg, 0.25 mmol, 0.05 equiv) at rt. After stirring at rt overnight, the reaction was quenched with a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with DCM (3 x 25 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography (PE/EA 98:2 to 95:5) to yield 1.5 g (95% yield) of ester **16** as a colorless oil.

$[\alpha]_D^{25}$ = –10.5 (c 1.1, $CHCl_3$).

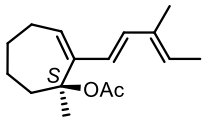
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.97 (dd, *J* = 7.6, 6.2 Hz, 1H), 2.49-2.41 (m, 1H), 2.34-2.24 (m, 1H), 2.21-2.09 (m, 1H), 2.04 (s, 3H), 1.79-1.64 (m, 3H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.8, 151.2, 124.4, 118.5 (q, J = 319.5 Hz), 82.5, 35.0, 25.4, 24.2, 23.5, 23.0, 21.9.

IR (ATR) ν cm^{-1}: 2941, 2865, 1744, 1669, 1413, 1369, 1245, 1209, 1142, 1099, 1050, 1009, 985.

HRMS (EI+) *m/z*: calculated for $C_{10}H_{15}O^{+\cdot}$ [M-OTf$^{+\cdot}$]: 167.1062 found: 167.1067.

(7*S*)-7-Acetoxy-7-methyl-1-[(1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl]cyclohept-1-ene (10), as a 4:1 mixture with the 1*Z* isomer



10

$Pd(OAc)_2$ (113 mg, 0.5 mmol, 0.1 equiv.) was dissolved in 35 mL of dioxane, then 15 mL of a 2 M solution of K_3PO_4 (9.5 g, 45 mmmol, 9 equiv.) in water were added. The solution was cooled down to 4 °C. After 5 min at this temperature, enol triflate **16** (1.58 g, 5 mmol, 1 equiv.) was added, followed by pinacol boronate **17** (1.15 g, 5.5 mmol, 1.1 equiv.). After stirring at 4 °C for 1 h, the reaction was quenched with a saturated solution of NH_4Cl (50 mL). The aqueous layer was extracted with pentane (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via silica gel chromatography (pentane/Et_2O 98:2) to yield 880 mg (71% yield) of triene **10** as a colorless oil.

$[\alpha]_D^{25}$ = +29.1 (c 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.35 (d, *J* = 15.9 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 5.93 (ddd, *J* = 7.9, 5.3, 1.0 Hz, 1H), 5.58-5.50 (m, 1H), 2.75-2.65 (m, 1H), 2.39-2.29 (m, 1H), 2.18-2.10 (m, 1H), 1.97 (s, 3H), 1.88-1.80 (m, 1H), 1.79-1.75 (m, 1H), 1.74 (s, 3H), 1.72 (s, 3H), 1.71-1.65 (m, 2H), 1.62-1.57 (m, 1H), 1.53 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.9, 144.4, 135.0, 133.6, 128.3, 126.5, 126.5, 85.5, 36.6, 27.0, 26.0, 25.9, 23.6, 22.2, 14.1, 12.1.

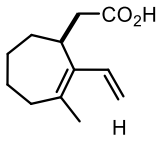
IR (ATR) ν cm^{-1}: 2928, 2858, 1737, 1445, 1367, 1244, 1166, 1144, 1081, 1014, 959.

HRMS (EI+) *m/z*: calculated for $C_{16}H_{24}O_2^{+\cdot}$ [M$^{+\cdot}$]: 248.1771; found: 248.1777.

Control of the enantiomeric ratio:

HPLC analysis [Nacalai Tesque "COSMOSIL CHiRAL 3B" column: silica gel grafted with cellulose tris(3,5-dimethylphenylcarbamate), particle size 3µm, 4.6 x 250 mm]: elution with MeCN/H_2O = 90/10, 0.6 mL/min; temperature: 40°C; detection at 230 nm; t_R(minor enantiomer) = 19.6 min, t_R(major enantiomer) = 20.4 min; *e.r.* = 90:10 through peak integration.

(*rac*)-2-[3-Methyl-2-vinylcyclohept-2-en-1-yl]acetic acid (S2)



S2

To a solution of 1-methyl-2-vinylcyclohept-2-en-1-yl acetate **18**[3] (564 mg, 2.90 mmol) in toluene (10 mL) at –78 °C was added dropwise LiHMDS (1M in THF, 3.48 mL, 3.48 mmol). After stirring at this temperature for 30 min, a solution of freshly distilled TMSCl (0.59 mL, 4.64 mmol) and Et_3N (0.65 mL, 4.64 mmol) in toluene (10 mL) was added dropwise. After stirring for 30 min, the cooling bath was removed and the reaction mixture was stirred at rt for 1h, before being refluxed overnight. After cooling the mixture was poured into an aqueous solution of NaOH (2M, 11 mL, 22 mmol) and stirred for 15 min, followed by dilution with Et2O (10 mL) and extraction with aqueous NaOH (3 x 20 mL, 2M). The combined aqueous phases were acidified to pH 3 with hydrochloric acid (2M) and extracted with Et_2O (3 x 20 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded acid **S2** as a pale yellow oil (335 mg, 59%). The crude material was taken on without further purification.

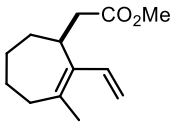
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.59 (1H, dd, *J* = 17.2, 11.1 Hz), 5.20 (1H, d, *J* = 17.2 Hz), 5.00 (1H, d, *J* = 11.1 Hz), 3.23-3.33 (1H, m), 2.49-2.65 (2H, m), 2.31-2.43 (1H, m), 2.04-2.17 (1H, m), 1.83 (3H, s), 1.59-1.79 (5H, m), 1.39-1.51 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.5, 138.6, 136.0, 134.8, 111.6, 36.7, 35.3, 35.1, 29.3, 25.9, 25.0, 22.7.

IR (film on NaCl) ν cm^{-1}: 3055, 2986, 1420, 1265, 895, 737, 706.

HRMS (ESI+) *m/z*: calculated for $C_{12}H_{19}O_2^+$ [MH^+]: 195.1385; found: 195.1383.

(*rac*)-2-[3-Methyl-2-vinylcyclohept-2-en-1-yl]acetic acid, methyl ester (19)



19

To a stirred solution of **S2** (330 mg, 0.31 mmol) in toluene/methanol (3.6:1; 17 mL) at 0 °C was added dropwise $TMSCHN_2$ (2.0 M in Et_2O, 0.94 mL, 1.87 mmol). The cooled bath was removed and the mixture was stirred for 30 min before being concentrated. The crude material was purified by chromatography on silica gel (100:3 cyclohexane/EtOAc) to afford ester **19** as a colorless oil (317 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.57 (1H, dd, *J* = 11.1, 17.2 Hz), 5.19 (1H, d, *J* = 17.2 Hz), 5.00 (1H, d, *J* = 11.1 Hz), 3.66 (3H, s), 3.23-3.32 (1H, m), 2.45-2.61 (2H, m), 2.31-2.44 (1H, m), 2.02-2.14 (1H, m), 1.82 (3H, s), 1.58-1.76 (5H, m), 1.37-1.51 (1H, m).

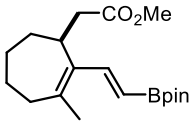
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.6, 138.3, 136.0, 134.9, 111.3, 51.4, 36.5, 35.2, 35.1, 29.4, 25.7, 24.9, 22.6.

IR (film on NaCl) ν cm^{-1}: 3055, 2986, 2928, 1732, 1424, 1265, 895.

HRMS (ESI+) *m/z*: calculated for $C_{13}H_{21}O_2^+$ [MH^+]: 209.1536; found: 209.1539.

(*E*)-2-(3-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohept-2-en-1-yl)acetic acid, methyl ester (20)

[3] Laroche, B.; Detraz, M.; Blond, A.; Dubost, L.; Mailliet, P.; Nay, B. *J. Org. Chem.* **2015**, *80*, 5359–5363.



20

To a flame-dried round bottom flask was added second generation Hoveyda-Grubbs catalyst (84 mg, 0.13 mmol), followed by compound **19** (278 mg, 1.34 mmol) in distilled toluene (13 mL) and pinacol boronate (0.91 mL, 5.35 mmol). The reaction mixture was stirred at 80 °C for 2h, and a second portion of the Hoveyda-Grubbs catalyst was added (84 mg, 0.13 mmol). After 2 extra hours at 80°C and entire consumption of the starting material, the reaction mixture was cooled down to rt and concentrated. The resulting crude material was purified by chromatography on silica gel (100% CH_2Cl_2) to afford pinacol boronate **20** as a pale yellow oil (320 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37 (1H, d, *J* = 18.3 Hz), 5.57 (1H, d, *J* = 18.3 Hz), 3.64 (3H, s), 3.32-3.42 (1H, m), 2.53-2.63 (1H, m), 2.37-2.49 (2H, m), 2.02-2.13 (1H, m), 1.92 (3H, s), 1.54-1.78 (5H, m), 1.34-1.46 (1H, m), 1.27 (12H, s).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm (the carbon bearing boron could not be observed): 173.3, 148.7, 142.8, 135.9, 83.0, 51.4, 36.4, 35.5, 34.6, 29.0, 25.6, 24.8, 24.7, 24.5, 22.9.

IR (film on NaCl) ν cm^{-1}: 3042, 2978, 2928, 2857, 1732, 1615, 1593, 1379, 1371, 1343, 1321, 1146.

HRMS (ESI+) *m/z*: calculated for $C_9H_{32}BO_4^+$ $[MH]^+$: 335.2394; found: 335.2404.

(*E*)-2-Iodobut-2-ene (21)

21

Following Klapars and Buchwald procedure,[4] a Schlenk tube was charged with CuI (95 mg, 0.50 mmol, 5.0 mol%), NaI (2.25 g, 15.0 mmol), evacuated and backfilled with argon. *N,N'*-Dimethylethylenediamine (0.11 mL, 1.00 mmol, 10 mol%), commercial (*E*)-2-bromobut-2-ene (1.01 mL, 10.0 mmol), and *n*-butanol (5 mL) were added under argon. The Schlenk tube was sealed and the reaction mixture was stirred at 120 °C for 24 h. The resulting suspension was allowed to reach room temperature, poured into pentane (50 mL) and washed with a solution of 20% aqueous ammonia (3 mL) in water (50 mL), followed by water (3 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated to ~2 mL volume. The residue was distilled collecting the fraction boiling at 116-122 °C to give 1.155 g (63% yield) of **21** as a colorless liquid. Data were accordance with Shu and Djerassi's previous report.[5]

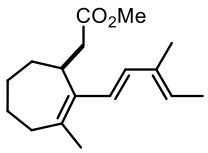
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.21 (1H, qq, *J* = 1.2, 6.9 Hz), 2.36 (3H, pseudo-quint, *J* = 1.2 Hz), 1.61 (3H, dq, *J* = 1.2, 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 135.5, 93.8, 27.0, 16.0,

IR (film on NaCl) ν cm^{-1}: 3036, 2970, 2947, 2916, 2855, 1640, 1597, 1427, 1377, 1115, 1050, 995, 814.

[4] Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.
[5] Shu, A.Y.L.; Djerassi, C. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1291-1305.

2-(3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl)acetic acid, methyl ester (S3)



S3

$Pd(OAc)_2$ (21 mg, 0.093 mmol) and XPhos (89 mg, 0.19 mmol) were added in a round bottom flask under argon, and stirred in dry THF (7 mL) at rt for 30 min (brown solution). Then (*E*)-2-iodobut-2-ene **21** (187 mg, 1.03 mmol) in THF (1 mL), boronate **20** (312 mg, 0.93 mmol) in THF (1 mL) and an aqueous solution of NaOH (2M, 2.3 mL, 4.67 mmol) were added, and the mixture was stirred for 16h at rt in the dark. The reaction was quenched using a saturated solution of NH_4Cl (8 mL), extracted with Et_2O (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by chromatography on silica gel (100:3 cyclohexane/EtOAc) to afford triene **S3** as an orange oil (188 mg, 77%).

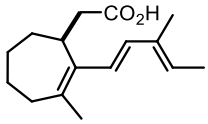
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.34 (1H, d, *J* = 16.0 Hz), 6.28 (1H, d, *J* = 16.0 Hz), 5.59 (1H, q, *J* = 7.0, 14.0 Hz), 3.66 (3H, s), 3.28-3.34 (1H, m), 2.59 (1H, d, *J* = 10.1, 14.9 Hz), 2.50 (1H, dd, *J* = 5.6, 14.9 Hz), 2.36-2.44 (1H, m), 2.09-2.15 (1H, m), 1.86 (3H, s), 1.80 (3H, s), 1.76 (3H, d, *J* = 7.0 Hz), 1.69-1.74 (1H, m), 1.57-1.70 (4H, m, 9-H, 10-Hb), 1.40-1.48 (1H, m).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 173.7, 137.1, 135.2, 134.9, 131.7, 126.3, 125.4, 51.5, 36.8, 36.0, 35.3, 29.6, 26.0, 25.1, 22.8, 14.0, 12.1.

IR (film on NaCl) ν cm^{-1}: 3061, 2988, 2922, 2855, 1738, 1435, 1287, 1265, 1244, 1167, 1138.

HRMS (ESI+) *m/z*: calculated for $C_{17}H_{27}O_2^+$ [MH^+]:263.2006; found: 263.2004.

(*rac*)-2-[3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetic acid (rac-9)



***rac*-9**

An argon-bubbled aqueous solution of NaOH (14.8 M, 1.02 mL, 15.1 mmol) was added to a solution of ester **S3** (198 mg, 0.76 mmol) in EtOH also previously argon-bubbled (8 mL). The reaction mixture was stirred at rt for 7h in the dark before being quenched by an aqueous solution of tartaric acid (0.73M, 20 mL, 14.8 mmol) and extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford ***rac*-9** as an yellowish oil that was used without further purification (180 mg, 96%). Data were

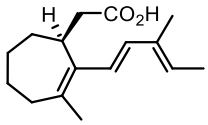
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.33 (d, J = 16.0 Hz, 1H), 6.27 (d, J = 16.0 Hz, 1H), 5.58 (q, J = 14.0, 7.0, 1H), 3.35-3.24 (m, 1H), 2.62 (dd, J = 15.2, 10.4, 1H), 2.51 (dd, J = 15.2, 5.0 Hz, 1H), 2.43-2.31 (m, 1H), 2.16-2.06 (m, 1H), 1.85 (s, 3H), 1.78 (s, 3H), 1.74 (d, J = 7.0 Hz, 3H), 1.72-1.58 (m, 5H), 1.51-1.38 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.7, 137.1, 135.1, 134.7, 131.8, 126.4, 125.2, 36.7, 35.8, 35.2, 29.3, 25.8, 24.9, 22.9, 14.0, 12.1.

IR (ATR) ν cm^{-1}: 3053, 2986, 2924, 2857, 1705, 1441, 1410, 1288, 1265, 741, 704.

HRMS (EI+) *m/z*: calculated for $C_{16}H_{24}O_2^{+\cdot}$ [$M^{+\cdot}$]: 248.1771; found: 248.1772.

2-[(1*S*)-3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetic acid (9)



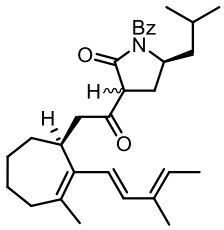
9

To a stirred solution of triene **10** (860 mg, 3.5 mmol, 1 equiv) and TPPA (1.6 mL, 7 mmol, 2 equiv) in 20 mL of dry THF was added a 1M LDA solution in THF/hexane (7 mL, 7 mmol, 2 equiv) dropwise over 20 min at -78 °C. After 1 h, a solution of TBSCl (1.05 g, 7 mmol, 2 equiv) in 7 mL of dry THF was added dropwise over 20 min. After stirring at -78 °C for 1 h, the reaction mixture was warmed up to rt and stirred overnight. The reaction mixture was cooled down to 0 °C and a 1 M solution of TBAF in THF (10.5 mL, 10.5 mmol, 3 equiv) was added. The reaction mixture was warmed up to rt, stirred for 1h and 150 mL of pentane were added. The slurry was filtered and washed with pentane. The precipitate was dissolved with a saturated solution NH_4Cl and extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 617 mg (71% yield) of crude carboxylic acid **9** which was engaged in the next step without additional purification.

Data were consistent with those obtained for **rac-9**.

$[\alpha]_D^{25}$ = +29.1 (c 0.8, $CHCl_3$).

***N*-Benzoyl-5-isobutyl-3-{2-[(1*S*)-3-methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetyl}-2-pyrrolidone (mixture of stereoisomers 22)**



22

To a stirred solution of carboxylic acid **9** (62 mg, 0.25 mmol, 1 equiv) in 2 mL of dry DCM was added Et_3N (70 µL, 0.25 mmol, 1 equiv), followed by a solution of pivaloyl chloride (60 µL, 0.5 mmol, 2 equiv) in 0.5 mL of DCM dropwise at –78 °C. The reaction mixture was then warmed up to 0 °C and stirred in the dark for 30 min before being quenched with 4 mL of cold water. The aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, washed with cold water, cold brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield a yellowish oil. This resulting mixt anhydride was directly engaged in the next step without additional purification. Short description of this intermediate:

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.33 (d, J = 16.1 Hz, 1H), 6.24 (d, J = 16.1 Hz, 1H), 5.56 (q, *J* = 13.1, 6.7 Hz, 1H), 3.38-3.29 (m, 1H), 3.17 (td, *J* = 6.7, 3.4 Hz, 1H), 2.75-2.59 (m, 1H), 2.42-2.33 (m, 1H), 2.16-2.08 (m, 1H), 1.85 (s, 3H), 1.79 (t, *J* = 1.1 Hz, 3H), 1.74 (brs, 3H), 1.78-1.60 (m, 5H), 1.50-1.39 (m, 1H), 1.26 (s, 9H).

To a stirred solution of γ-lactam **8**[6] (120 mg, 0.5 mmol, 2 equiv) in 1 mL of dry THF was added a 1 M solution of LiHMDS in THF (0.5 mL, 0.5 mmol, 2 equiv) dropwise at –78 °C. The reaction mixture was stirred 1 h at this temperature before adding a cold solution of anhydride **32** (0.25 mmol, 1 equiv) in 1 mL of dry THF dropwise. After 5h at –78 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl (4 mL) and then allowed to warmed up to rt. The aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via silica gel chromatography (PE/Et_2O 9:1) to yield 69 mg (58% yield over the 2 steps from **9**) of product **22** (mixture of stereoisomers).

Physical state: yellowish oil.

$[\alpha]_D^{25}$ = +56.2 (c 0.8, $CHCl_3$).

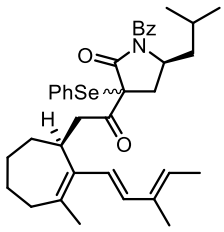
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.65-7.48 (m, 3H), 7.45-7.35 (m, 2H), 6.46-6.06 (m, 2H), 5.65-5.46 (m, 1H), 4.62-4.31 (m, 1H), 3.50-3.22 (m, 1H), 2.60-1.98 (m, 5H), 1.92-1.52 (m, 17H), 1.51-1.27 (m, 3H), 1.04-0.93 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 204.1, 172.6, 170.6, 136.8, 135.4, 135.1, 134.4, 134.4, 132.1, 131.9, 129.1, 127.9, 126.4, 125.6, 56.0, 54.5, 45.5, 43.3, 34.8, 30.1, 29.9, 27.0, 25.8, 25.4, 23.8, 22.8, 21.6, 14.0, 12.6.

IR (ATR) ν cm^{-1}: 3059, 3030, 2957, 2926, 2868, 2855, 1713, 1665, 1632, 1449, 1290, 1281, 1236.

HRMS (ESI+) *m/z*: calculated for $C_{31}H_{42}NO_3^+$ [MH^+]: 476.3159; found: 476.3159.

_N_-Benzoyl-5-isobutyl-3-{2-[(1_S_)-3-methyl-2-((1_E_,3_E_)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetyl}-3-phenylselenyl-2-pyrrolidone (mixture of stereoisomers 23)



23

To a stirred solution of triene **22** (48 mg, 109 µmol, 1 equiv) in 1.5 mL of dry THF was added a 1 M solution of LiHMDS in THF (120 µL, 120 µmol, 1.1 equiv) dropwise at –78 °C. The reaction mixture was stirred 1h at this temperature before adding a cold solution of PhSeBr (36 mg, 150 µmol, 1.4 equiv) in 0.5 mL of dry THF dropwise. After 2h at –78 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl (2 mL) and then allowed to warmed up to rt. The aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography (PE/Et_2O 20:1) to yield 65 mg (95% yield) of selenide **23** as a yellowish oil.

$[\alpha]_D^{25}$ = +109.1 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27-7.68 (m, 10H), 6.42-6.06 (m, 2H), 5.63-5.36 (m, 1H), 4.38-4.06 (m, 1H), 2.55-1.93 (m, 3H), 1.90-1.46 (m, 19H), 1.38-1.08 (m, 3H), 0.96-0.76 (m, 6H).

[6] Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867–12874.

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 201.3, 200.3, 170.9, 137.6, 137.2, 135.3, 134.5, 132.7, 131.4, 130.2, 129.4, 129.3, 128.1, 125.9, 60.7, 54.2, 53.1, 40.5, 35.4, 32.6, 29.7, 25.9, 25.2, 24.8, 23.9, 22.8, 21.2, 14.1, 12.3.

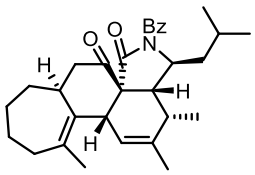
IR (ATR) ν cm^{-1}: 2957, 2924, 2866, 2857, 1724, 1690, 1288, 1273, 1231.

HRMS (ESI+) *m/z*: calculated for $C_{37}H_{46}NO_3Se^+$ [MH^+]: 632.2637; found: 632.2628.

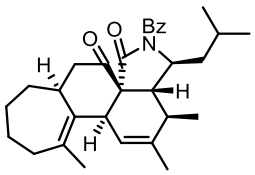
(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13b*R*)-5-Benzoyl-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (*endo* product 24)

and

(3*R*,3a*R*,4*S*,6a*S*,8a*S*,13b*S*)-5-Benzoyl-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (*exo* product 25)



24



25

To a stirred solution of selenide **23** (70 mg, 110 µmol, 1 equiv) in 10 mL of dry DCM was added $NaHCO_3$ (20 mg, 236 µmol, 2.1 equiv) at 0 °C. The reaction mixture was cooled down to –78 °C and a cold solution of *m*-CPBA (50 mg, 220 µmol, 2 equiv) in 1 mL of dry DCM dropwise at –78 °C. After 1h at –78 °C, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (5 mL) and then allowed to warmed up to rt. The organic layer was washed with cold $NaHCO_3$ (5 mL), cold water (5 mL) and cold brine (5 mL), dried over Na_2SO_4, filtered and transferred into a flame-dry sealed tube with a catalytic amount of BHT (0.1 equiv). The resulting solution was heated at 100 °C overnight before being cooled down to rt and concentrated *in vacuo*. The crude product was purified via silica gel chromatography (PE/Et_2O 20:1 to 9:1) to yield 17.7 mg (38% yield) of *endo*-tetracyclic product **24** and 12.5 mg (27% yield) of *exo*-tetracyclic product **25**, both as yellowish resins.

Data for **24**:

$[\alpha]_D^{25}$ = +93 (c 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.50-7.45 (m, 3H), 7.40-7.34 (m, 2H), 5.78 (brs, 1H), 4.33-4.30 (m, 1H), 3.56-3.48 (m, 1H), 3.35 (brs, 1H), 2.75 (dd, *J* = 6.3, 1.8 Hz, 1H), 2.69 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.56-2.44 (m, 1H), 2.30 (dd, *J* = 16.6, 11.3 Hz), 2.20-2.09 (m, 2H), 1.85-1.79 (m, 1H), 1.79 (s, 3H), 1.72-1.67 (m, 2H), 1.65 (s, 3H), 1.64-1.56 (m, 3H), 1.54-1.47 (m, 3H), 1.31 (d, *J* = 7.3 Hz, 3H), 0.99 (d, *J* = 4.5 Hz, 3H), 0.98 (d, *J* = 4.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 208.4, 171.7, 170.5, 137.1, 135.1, 134.8, 133.4, 132.1, 129.8, 128.7, 128.0, 69.6, 54.4, 47.7, 46.0, 44.7, 43.2, 37.3, 35.0, 34.5, 33.7, 27.3, 24.7, 24.4, 24.2, 24.1, 21.9, 19.4, 13.4.

IR (ATR) ν cm^{-1}: 2959, 2928, 2868, 2857, 1736, 1701, 1672, 1653, 1448, 1287, 1221, 1207, 1161, 696, 660.

HRMS (ESI+) *m/z*: calculated for $C_{31}H_{40}NO_3^+$ [MH^+]: 474.3003; found: 474.3022.

Data for **25**:

$[\alpha]_D^{25}$ = +234 (c 0.2, $CHCl_3$).

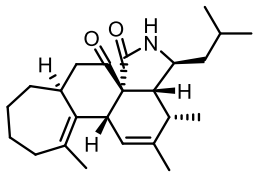
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.77-7.73 (m, 2H), 7.52-7.48 (m, 1H), 7.41-7.37 (m, 2H), 5.48-5.45 (m, 1H), 4.24-4.20 (m, 1H), 3.51-3.47 (m, 1H), 2.92-2.84 (m, 1H), 2.69 (t, *J* = 13.2 Hz, 1H), 2.32 (d, *J* = 4.3 Hz, 1H), 2.31-2.24 (m, 2H), 2.17-2.09 (m, 1H), 2.00-1.84 (m, 2H), 1.80 (s, 3H), 1.78-1.71 (m, 1H), 1.71-1.66 (m, 2H), 1.63 (d, *J* = 1.6 Hz, 3H), 1.62-1.54 (m, 1H), 1.60-1.46 (m, 1H), 1.36-1.28 (m, 1H), 1.20-1.16 (m, 1H), 1.13 (d, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 211.6, 173.4, 171.7, 137.1, 136.6, 134.3, 135.9, 132.8, 129.8, 128.0, 125.3, 60.4, 57.9, 49.5, 45.2, 42.6, 39.4, 38.9, 36.1, 33.1, 31.7, 26.9, 25.1, 24.8, 23.5, 23.0, 21.6, 21.3, 18.5.

IR (KBr pellets) ν cm^{-1}: 2957, 2922, 2851, 1740, 1736, 1701, 1684, 1653, 1448, 1283, 1244, 1201, 1163, 721, 694, 660;

HRMS (ESI+) *m/z*: calculated for $C_{31}H_{40}NO_3^+$ [MH^+]: 474.3003; found: 474.3005.

(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13b*R*)-4-Isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (5)



5

To a stirred solution of tetracyclic cycloadduct **24** (17.7 mg, 37 µmol, 1 equiv) in 0.8 mL of MeOH was added a 14.8 M solution of NaOH in water (10 µL, 150 µmol, 4 equiv) at 0 °C. The reaction mixture was allowed to warm up to rt over 2h. The reaction mixture was quenched with a water (0.5 mL). The aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified via silica gel chromatography (DCM/Et_2O 95:5) to yield 11.8 mg (87% yield) of deprotected cycloadduct **5** as a colorless resin.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.94 (s, 1H), 5.58 (s, 1H), 3.64-3.53 (m, 1H), 3.28 (s, brs), 3.16 (td, *J* = 10.1, 3.5 Hz, 1H), 2.69 (dd, *J* = 5.3, 3.5 Hz, 1H), 2.56 (dd, *J* = 17.3, 5.5 Hz, 1H), 2.42-2.28 (m, 2H), 2.28 (dd, 1H, *J* = 17.3, 12.2 Hz, 1H), 2.19-2.08 (m, 1H), 1.88-1.79 (m, 1H), 1.76 (s, 3H), 1.73 (s, 3H), 1.71-1.41 (m, 6H), 1.36-1.28 (m, 1H), 1.17 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 210.5, 173.3, 136.9, 134.9, 133.6, 128.5, 65.8, 51.2, 51.1, 47.8, 47.2, 41.6, 36.6, 35.7, 34.7, 33.5, 28.2, 24.2, 23.7, 21.5, 20.2, 13.6.

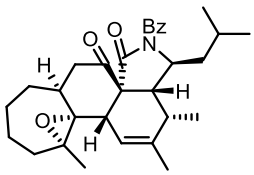
IR (ATR) ν cm^{-1}: 2957, 2922, 2851, 1688, 1653, 1554, 1273, 1264, 745, 696, 664.

HRMS (ESI+) *m/z*: calculated for $C_{24}H_{36}NO_2^+$ [MH^+]: 370.2741; found: 370.2730.

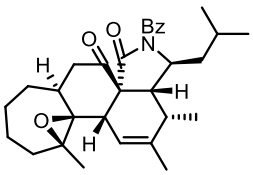
(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13*R*,13a*R*,13b*R*)-5-Benzoyl-13,13a-epoxy-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (26)

and

(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13*S*,13a*S*,13b*R*)-5-Benzoyl-13,13a-epoxy-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (27)



26
Major stereoisomer



27
Minor stereoisomer

To a stirred solution of tetracyclic product **24** (6 mg, 12.7 µmol, 1 equiv) and $NaHCO_3$ (1 mg, 12 µmol, 1 equiv) in 0.3 mL of DCM was added a solution of *m*-CPBA (2.8 mg, 12 µmol, 1 equiv) in 0.1 mL of DCM. The reaction mixture was allowed to warm up to –10 °C during 2h before being quenched with a saturated solution of $Na_2S_2O_3$ (1 mL). The reaction was allowed to warm up to rt and the organic layer was washed with a saturated solution of $NaHCO_3$ (1 mL), brine (1 mL), dried with Na_2SO_4, filtered and con- centrated in vacuo. The crude product was purified via silica gel chromatography (PE/EA 9:1) to yield 3 mg of **26** (48%) and 1.4 mg of **27** (22%), as colorless resins.

Data for **26** (major isomer):

$[\alpha]_D^{25}$ = +3.2 (c 0.53, $CHCl_3$).

7.63-7.58 (m, 2H), 7.09-7.02 (m, 3H), 5.84-5.89 (m, 1H), 4.55-4.50 (m, 1H), 3.96 (dd, *J* = 12.1, 6.8 Hz, 1H), 3.14 (d, *J* = 6.6 Hz, 1H), 2.81-2.76 (m, 1H), 2.31-2.23 (m, 1H, H_{16}), 2.03 (t, *J* = 7.2 Hz 1H), 1.96 (dd, *J* = 12.1, 2.4 Hz, 1H), 1.81-1.59 (m, 4H), 1.58-1.55 (m, 3H), 1.54-1.25 (m, 8H), 1.14 (d, *J* = 0.8 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 9H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm: 204.1, 171.4, 170.0, 137.5, 135.5, 131.9, 129.1, 128.4, 124.9, 71.4, 64.0, 61.2, 54.7, 45.8, 45.0, 44.2, 43.6, 41.4, 38.4, 34.3, 34.0, 29.1, 25.1, 24.1, 23.9, 21.9, 19.4, 18.0, 13.4.

IR (ATR) ν cm^{-1}: 2926, 2854, 1714, 1690, 1452, 1366, 1280, 1212, 1155.

HRMS (ESI+) *m/z*: calculated for $C_{31}H_{40}NO_3^+$ [MH^+]: 490.2952 found: 490.2953.

Data for **27** (minor isomer):

^{1}H NMR (400 MHz, C_6D_6) δ ppm: 7.78-7.81 (m, 2H), 7.04-6.96 (m, 3H), 5.94 (brs, 1H), 4.40-4.36 (m, 1H), 3.15-3.11 (m, 1H), 2.79 (t, *J* = 4.9 Hz, 1H), 2.52-2.44 (m, 2H), 2.36-2.30 (m, 1H), 1.85-1.71 (m, 4H), 1.68-1.51 (m, 5H), 1.57 (brs, 3H), 1.51-1.47 (m, 2H), 1.27-1.21 (m, 1H), 1.24 (s, 3H), 1.00 (d, *J* = 5.9 Hz, 3H), 0.93 (d, *J* = 7.4 Hz, 3H), 0.89 (d, J = 5.9 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm: 208.4, 172.4, 170.8, 138.0, 135.1, 132.6, 130.0, 128.3, 122.9, 66.1, 66.0, 65.2, 56.0, 48.5, 47.5, 46.6, 42.2, 35.8, 35.1, 34.8, 29.7, 29.6, 25.0, 24.0, 23.6, 22.7, 21.3, 20.5, 14.7.

HRMS (ESI+) m/z: calculated for $C_{31}H_{40}NO_3^+$ [MH^+]: 490.2952 found: 490.2953.

X-Ray crystallography of epoxide 26

Suitable single crystals were selected and mounted on a Bruker APEX-II CCD diffractometer. The crystals were kept at 150K during data collection.

Using Olex2,[7] the structure was solved with the SHELXT[8] structure solution program using Intrinsic Phasing and refined with the SHELXL[9] refinement package using Least Squares minimization. The PLATON software[10] was used to treat cases of solvent accessible voids. Pictures of the compound structure were obtained using the MERCURY software. During the refinement steps, all atoms, except hydrogen atoms, were refined anisotropically. The positions of the hydrogen atoms were determined geometrically. The crystal structure of **26** was deposited on the Cambridge Crystallographic Data Centre under CCDC deposition number 2086360.

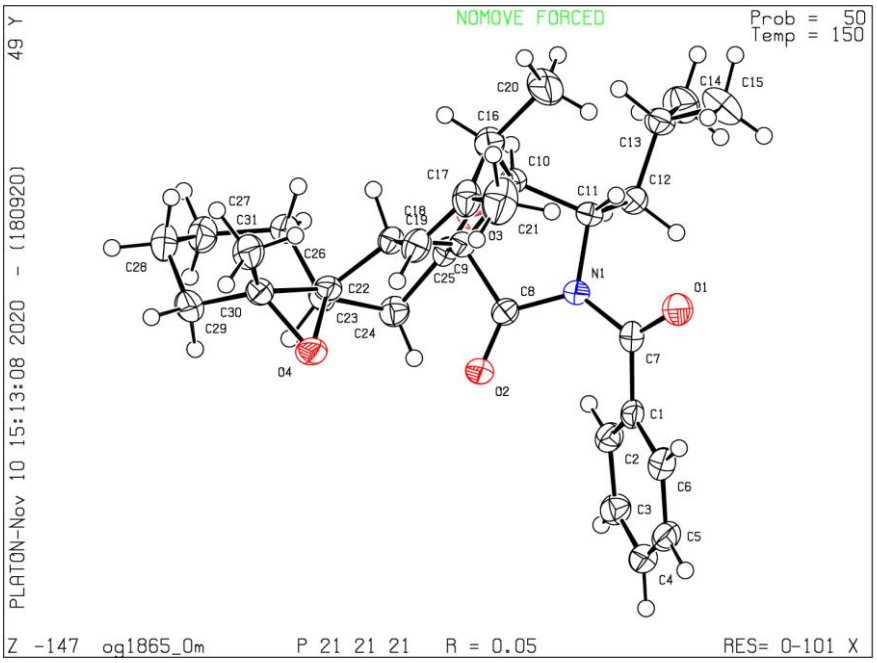


Figure S1. Epsilon plot of compound **26**, atom numbering.

Table 1. Crystal data and structure refinement for **26**.

Identification code	og1865_0m
Empirical formula	$C_{31}H_{39}NO_4$
Formula weight	489.63
Temperature/K	150.01
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.8890(19)
b/Å	10.515(2)

[7] Dolomanov, O.V.; Bourhis, L.J; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339.
[8] Sheldrick, G.M. *Acta Cryst.* **2015**, *A71*, 3.
[9] Sheldrick, G.M. *Acta Cryst.* **2015**, *C71*, 3.
[10] Spek, A. *J. App. Crystallogr.* **2003**, *36*, 7.

c/Å	28.332(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2648.1(10)
Z	4
ρ_{calc}g/cm^3	1.228
μ/mm^{-1}	0.080
F(000)	1056.0
Crystal size/mm^3	0.18 × 0.1 × 0.02
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.802 to 52.04
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 12, -34 ≤ l ≤ 33
Reflections collected	27793
Independent reflections	5191 [R_{int} = 0.0989, R_{sigma} = 0.0732]
Data/restraints/parameters	5191/0/331
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0492, wR_2 = 0.1110
Final R indexes [all data]	R_1 = 0.0765, wR_2 = 0.1253
Largest diff. peak/hole / e Å^{-3}	0.22/-0.29
Flack parameter	-0.4(17)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **26**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
C1	1234(4)	7428(3)	5873.6(11)	26.5(7)
C2	272(4)	6471(3)	5725.8(12)	30.3(8)

C3	-633(4)	6643(3)	5334.1(12)	35.1(8)
C4	-543(4)	7765(3)	5078.9(13)	36.0(9)
C5	407(4)	8726(3)	5220.4(13)	35.3(8)
C6	1283(4)	8568(3)	5620.9(12)	31.9(8)
C7	2134(4)	7320(3)	6312.1(12)	27.3(7)
C8	3216(4)	5197(3)	6144.7(11)	25.5(7)
C9	3860(4)	4108(3)	6442.7(11)	25.0(7)
C10	4029(4)	4689(3)	6941.2(11)	26.8(7)
C11	2941(4)	5832(3)	6949.4(11)	26.0(7)
C12	1456(4)	5559(3)	7204.8(11)	29.7(8)
C13	1619(4)	5467(3)	7745.0(11)	32.6(8)
C14	285(5)	4789(4)	7962.4(14)	47.1(10)
C15	1807(5)	6768(4)	7965.0(14)	50.1(11)
C16	5702(4)	5040(4)	7044.5(12)	39.9(9)
C17	6422(4)	5615(3)	6612.7(13)	38.3(9)
C18	6308(4)	4924(3)	6215.7(13)	33.7(8)
C19	5427(4)	3703(3)	6238.9(12)	27.1(7)
C20	5871(5)	5794(5)	7505.9(14)	60.2(13)
C21	7178(5)	6891(4)	6627.6(18)	57.3(12)
C22	5406(4)	2824(3)	5805.8(11)	27.1(7)
C23	4140(4)	1849(3)	5804.9(12)	29.5(8)
C24	2602(4)	2411(3)	5942.4(12)	31.5(8)
C25	2732(4)	3010(3)	6420.3(12)	28.5(8)
C26	4564(4)	728(3)	6128.9(12)	31.6(8)
C27	5427(5)	-322(3)	5875.3(14)	41.7(9)
C28	6943(5)	43(3)	5668.3(14)	45.2(10)
C29	6917(4)	1162(3)	5324.7(13)	39.3(9)

C30	6825(4)	2442(3)	5569.0(11)	32.3(8)
C31	8350(4)	2929(4)	5717.1(14)	39.7(9)
N1	2640(3)	6098(2)	6445.6(9)	25.5(6)
O1	2399(3)	8217(2)	6566.3(9)	38.4(6)
O2	3233(3)	5244(2)	5716.7(8)	31.1(5)
O3	2026(3)	2649(2)	6763.6(9)	41.2(6)
O4	5813(3)	3374(2)	5355.1(8)	35.9(6)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **26**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	24.0(16)	27.0(17)	28.6(18)	-0.7(15)	4.3(14)	6.2(14)
C2	31.2(19)	26.6(17)	33.2(19)	3.4(15)	1.4(16)	2.9(15)
C3	30.9(19)	37(2)	37(2)	-2.5(16)	-3.8(17)	2.4(16)
C4	36(2)	42(2)	30(2)	0.4(16)	-0.2(17)	11.7(18)
C5	37.1(19)	36(2)	32.9(19)	8.6(16)	5.3(17)	11.6(17)
C6	30.0(19)	27.5(18)	38(2)	3.4(16)	6.2(17)	2.7(15)
C7	26.4(17)	23.4(17)	31.9(18)	-2.0(15)	4.6(15)	2.2(14)
C8	22.3(16)	26.3(16)	27.9(18)	1.2(14)	-1.1(15)	-0.1(14)
C9	24.9(17)	27.8(16)	22.5(16)	0.2(14)	0.2(14)	2.8(13)
C10	25.1(17)	31.8(17)	23.6(17)	0.3(15)	-1.8(14)	3.0(14)
C11	27.7(18)	29.8(17)	20.4(16)	-0.8(14)	-2.3(14)	2.3(14)
C12	24.8(17)	35.4(18)	28.8(18)	-1.9(15)	-1.8(15)	3.5(15)
C13	30.3(18)	43(2)	24.5(17)	1.4(16)	0.7(16)	3.7(17)
C14	43(2)	57(3)	41(2)	4.0(19)	12.0(19)	-2(2)
C15	56(3)	61(3)	33(2)	-10.7(19)	7(2)	-13(2)
C16	32(2)	48(2)	40(2)	-13.1(18)	-12.0(18)	9.4(18)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **26**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C17	27(2)	38(2)	50(2)	-8.7(18)	-0.2(17)	3.0(16)
C18	21.9(17)	35.7(19)	44(2)	0.2(17)	0.8(17)	2.1(15)
C19	22.5(16)	31.1(18)	27.8(18)	0.2(14)	0.1(15)	4.4(14)
C20	43(2)	89(3)	48(3)	-32(2)	-21(2)	15(2)
C21	43(3)	45(2)	84(3)	-17(2)	-7(2)	-2(2)
C22	28.7(17)	30.8(17)	21.8(17)	4.6(13)	2.1(15)	3.9(15)
C23	29.8(18)	31.1(18)	27.7(19)	-6.6(15)	1.0(16)	1.8(15)
C24	25.5(17)	33.8(19)	35(2)	-2.6(16)	-2.9(16)	-0.3(15)
C25	24.5(17)	27.0(17)	34(2)	1.3(15)	0.9(16)	6.0(14)
C26	33.3(19)	31.1(18)	30.3(18)	-0.5(15)	-1.2(16)	1.4(15)
C27	47(2)	31.5(19)	46(2)	-2.7(17)	2(2)	6.2(19)
C28	49(2)	40(2)	47(2)	-5.4(19)	6(2)	16.2(19)
C29	38(2)	50(2)	30.2(19)	-3.6(17)	6.0(18)	9.7(18)
C30	33.0(19)	40(2)	23.9(17)	4.5(16)	5.5(16)	8.8(16)
C31	29.1(19)	49(2)	41(2)	2.5(18)	9.0(18)	4.9(17)
N1	28.4(15)	26.8(14)	21.4(14)	-0.6(11)	-2.6(12)	3.3(12)
O1	49.7(16)	28.7(13)	36.7(14)	-4.2(11)	-4.5(12)	3.6(12)
O2	35.6(13)	35.3(13)	22.5(12)	2.6(10)	1.2(11)	7.2(11)
O3	43.7(15)	40.4(14)	39.5(15)	1.1(12)	16.7(13)	-4.3(13)
O4	36.7(14)	45.2(14)	25.7(12)	10.4(11)	6.0(11)	8.6(12)

Table 4. Bond Lengths for **26**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.386(5)	C13	C15	1.512(5)

Table 4. Bond Lengths for **26**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C6	1.396(5)	C16	C17	1.507(5)
C1	C7	1.482(5)	C16	C20	1.536(5)
C2	C3	1.383(5)	C17	C18	1.343(5)
C3	C4	1.386(5)	C17	C21	1.502(5)
C4	C5	1.376(5)	C18	C19	1.505(5)
C5	C6	1.386(5)	C19	C22	1.536(5)
C7	N1	1.413(4)	C22	C23	1.522(5)
C7	O1	1.210(4)	C22	C30	1.483(5)
C8	C9	1.534(4)	C22	O4	1.448(4)
C8	N1	1.373(4)	C23	C24	1.539(5)
C8	O2	1.214(4)	C23	C26	1.541(5)
C9	C10	1.546(4)	C24	C25	1.498(5)
C9	C19	1.567(4)	C25	O3	1.218(4)
C9	C25	1.530(4)	C26	C27	1.524(5)
C10	C11	1.543(4)	C27	C28	1.520(6)
C10	C16	1.560(5)	C28	C29	1.527(5)
C11	C12	1.532(5)	C29	C30	1.516(5)
C11	N1	1.479(4)	C30	C31	1.508(5)
C12	C13	1.540(5)	C30	O4	1.461(4)
C13	C14	1.514(5)			

Table 5. Bond Angles for **26**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C2	C1	C6	119.2(3)	C18	C17	C21	122.8(4)
C2	C1	C7	122.0(3)	C21	C17	C16	121.7(3)

Table 5. Bond Angles for **26**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C6	C1	C7	118.6(3)	C17	C18	C19	117.7(3)
C3	C2	C1	120.4(3)	C18	C19	C9	104.3(3)
C2	C3	C4	119.8(3)	C18	C19	C22	119.0(3)
C5	C4	C3	120.6(3)	C22	C19	C9	116.5(3)
C4	C5	C6	119.7(3)	C23	C22	C19	114.6(3)
C5	C6	C1	120.3(3)	C30	C22	C19	120.9(3)
N1	C7	C1	117.8(3)	C30	C22	C23	116.5(3)
O1	C7	C1	122.9(3)	O4	C22	C19	117.4(3)
O1	C7	N1	119.2(3)	O4	C22	C23	116.9(3)
N1	C8	C9	108.2(3)	O4	C22	C30	59.8(2)
O2	C8	C9	125.2(3)	C22	C23	C24	113.4(3)
O2	C8	N1	126.6(3)	C22	C23	C26	109.5(3)
C8	C9	C10	104.1(3)	C24	C23	C26	111.1(3)
C8	C9	C19	109.4(3)	C25	C24	C23	108.8(3)
C10	C9	C19	111.0(3)	C24	C25	C9	113.9(3)
C25	C9	C8	107.2(3)	O3	C25	C9	122.7(3)
C25	C9	C10	113.5(3)	O3	C25	C24	123.4(3)
C25	C9	C19	111.3(3)	C27	C26	C23	113.4(3)
C9	C10	C16	110.9(3)	C28	C27	C26	116.4(3)
C11	C10	C9	105.1(3)	C27	C28	C29	115.3(3)
C11	C10	C16	114.2(3)	C30	C29	C28	113.2(3)
C12	C11	C10	113.7(3)	C22	C30	C29	119.5(3)
N1	C11	C10	104.2(3)	C22	C30	C31	123.1(3)
N1	C11	C12	109.6(3)	C31	C30	C29	112.3(3)
C11	C12	C13	113.6(3)	O4	C30	C22	58.9(2)

Table 5. Bond Angles for **26**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C14	C13	C12	111.1(3)	O4	C30	C29	116.0(3)
C15	C13	C12	111.3(3)	O4	C30	C31	116.2(3)
C15	C13	C14	110.2(3)	C7	N1	C11	119.2(3)
C17	C16	C10	110.3(3)	C8	N1	C7	125.4(3)
C17	C16	C20	116.2(3)	C8	N1	C11	113.7(3)
C20	C16	C10	112.1(3)	C22	O4	C30	61.3(2)
C18	C17	C16	115.5(3)				

Table 6. Torsion Angles for **26**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C2	C3	C4	2.1(5)	C19	C9	C10	C11	139.1(3)
C1	C7	N1	C8	41.9(5)	C19	C9	C10	C16	15.1(4)
C1	C7	N1	C11	-154.0(3)	C19	C9	C25	C24	-51.9(4)
C2	C1	C6	C5	-1.6(5)	C19	C9	C25	O3	127.0(3)
C2	C1	C7	N1	32.8(4)	C19	C22	C23	C24	45.2(4)
C2	C1	C7	O1	-144.4(3)	C19	C22	C23	C26	-79.5(3)
C2	C3	C4	C5	-2.0(5)	C19	C22	C30	C29	149.8(3)
C3	C4	C5	C6	0.2(5)	C19	C22	C30	C31	-3.1(5)
C4	C5	C6	C1	1.7(5)	C19	C22	C30	O4	-105.9(3)
C6	C1	C2	C3	-0.3(5)	C19	C22	O4	C30	111.5(3)
C6	C1	C7	N1	-151.8(3)	C20	C16	C17	C18	177.8(3)
C6	C1	C7	O1	31.1(5)	C20	C16	C17	C21	-3.7(5)
C7	C1	C2	C3	175.2(3)	C21	C17	C18	C19	-175.7(3)
C7	C1	C6	C5	-177.2(3)	C22	C23	C24	C25	-57.3(4)
C8	C9	C10	C11	21.5(3)	C22	C23	C26	C27	-89.0(3)

Table 6. Torsion Angles for **26**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C8	C9	C10	C16	-102.5(3)	C23	C22	C30	C29	2.8(4)
C8	C9	C19	C18	53.1(3)	C23	C22	C30	C31	-150.1(3)
C8	C9	C19	C22	-80.3(3)	C23	C22	C30	O4	107.1(3)
C8	C9	C25	C24	67.6(3)	C23	C22	O4	C30	-106.4(3)
C8	C9	C25	O3	-113.5(3)	C23	C24	C25	C9	61.6(4)
C9	C8	N1	C7	170.8(3)	C23	C24	C25	O3	-117.3(4)
C9	C8	N1	C11	6.0(4)	C23	C26	C27	C28	62.2(4)
C9	C10	C11	C12	101.0(3)	C24	C23	C26	C27	145.0(3)
C9	C10	C11	N1	-18.3(3)	C25	C9	C10	C11	-94.7(3)
C9	C10	C16	C17	40.5(4)	C25	C9	C10	C16	141.3(3)
C9	C10	C16	C20	171.7(3)	C25	C9	C19	C18	171.4(3)
C9	C19	C22	C23	-35.8(4)	C25	C9	C19	C22	38.0(4)
C9	C19	C22	C30	176.6(3)	C26	C23	C24	C25	66.6(4)
C9	C19	C22	O4	107.0(3)	C26	C27	C28	C29	-55.8(5)
C10	C9	C19	C18	-61.2(3)	C27	C28	C29	C30	78.3(4)
C10	C9	C19	C22	165.4(3)	C28	C29	C30	C22	-71.0(4)
C10	C9	C25	C24	-177.9(3)	C28	C29	C30	C31	84.6(4)
C10	C9	C25	O3	0.9(4)	C28	C29	C30	O4	-138.4(3)
C10	C11	C12	C13	72.5(4)	C29	C30	O4	C22	110.2(3)
C10	C11	N1	C7	-157.9(3)	C30	C22	C23	C24	-165.7(3)
C10	C11	N1	C8	8.0(4)	C30	C22	C23	C26	69.6(4)
C10	C16	C17	C18	-53.2(4)	C31	C30	O4	C22	-114.5(3)
C10	C16	C17	C21	125.3(4)	N1	C8	C9	C10	-17.3(3)
C11	C10	C16	C17	-78.1(4)	N1	C8	C9	C19	-135.9(3)
C11	C10	C16	C20	53.1(4)	N1	C8	C9	C25	103.3(3)

Table 6. Torsion Angles for **26**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C11	C12	C13	C14	-161.4(3)	N1	C11	C12	C13	-171.4(3)
C11	C12	C13	C15	75.4(4)	O1	C7	N1	C8	-140.8(3)
C12	C11	N1	C7	80.1(4)	O1	C7	N1	C11	23.3(5)
C12	C11	N1	C8	-114.0(3)	O2	C8	C9	C10	162.2(3)
C16	C10	C11	C12	-137.1(3)	O2	C8	C9	C19	43.5(4)
C16	C10	C11	N1	103.6(3)	O2	C8	C9	C25	-77.2(4)
C16	C17	C18	C19	2.8(5)	O2	C8	N1	C7	-8.6(5)
C17	C18	C19	C9	54.1(4)	O2	C8	N1	C11	-173.5(3)
C17	C18	C19	C22	-173.9(3)	O4	C22	C23	C24	-97.9(3)
C18	C19	C22	C23	-162.2(3)	O4	C22	C23	C26	137.4(3)
C18	C19	C22	C30	50.2(4)	O4	C22	C30	C29	-104.3(3)
C18	C19	C22	O4	-19.3(4)	O4	C22	C30	C31	102.8(3)

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **26**.

Atom	*x*	*y*	*z*	U(eq)
H2	234.22	5691.2	5894.72	36
H3	-1314.61	5994.93	5240.19	42
H4	-1141.13	7871.59	4803.93	43
H5	461.8	9493.3	5044.42	42
H6	1919.6	9238.21	5724.02	38
H10	3686.31	4050.57	7179.61	32
H11	3447.48	6581.46	7097.5	31
H12A	1036.52	4748.92	7084.78	36
H12B	729.07	6242.42	7128.77	36
H13	2542.83	4959.36	7815.78	39

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **26**.

Atom	***x***	***y***	***z***	**U(eq)**
H14A	-638.81	5258.3	7889.43	71
H14B	415.99	4743.61	8305.42	71
H14C	214.89	3926.96	7832.97	71
H15A	2666.68	7201.38	7819.73	75
H15B	1983.52	6676.73	8304.7	75
H15C	892.89	7270.22	7912.97	75
H16	6231.42	4213.77	7098.44	48
H18	6767.1	5195.95	5930.29	40
H19	5913.96	3194.64	6494.96	33
H20A	5456.14	6650.05	7463.84	90
H20B	6939.24	5855.77	7588.91	90
H20C	5327.18	5357.66	7759.41	90
H21A	7609.19	7082.5	6317.34	86
H21B	7979.72	6879.19	6864.92	86
H21C	6437.47	7544.87	6710.36	86
H23	4049.4	1510.08	5476.36	35
H24A	2291.04	3056.72	5707.5	38
H24B	1832.3	1730.91	5948.69	38
H26A	5185.19	1050.84	6392.9	38
H26B	3632.97	363.5	6265.11	38
H27A	5585.49	-1029.64	6100.51	50
H27B	4786.41	-650.14	5616.47	50
H28A	7363.23	-706.18	5502.58	54
H28B	7633.88	253.35	5931.01	54
H29A	7837.96	1137.03	5128.57	47

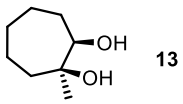
Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **26**.

Atom	***x***	***y***	***z***	**U(eq)**
H29B	6041.42	1068.41	5111.42	47
H31A	8920.95	3184.21	5436.85	59
H31B	8894.24	2255.57	5884.29	59
H31C	8224.1	3663.65	5926.33	59

Copies of NMR spectra

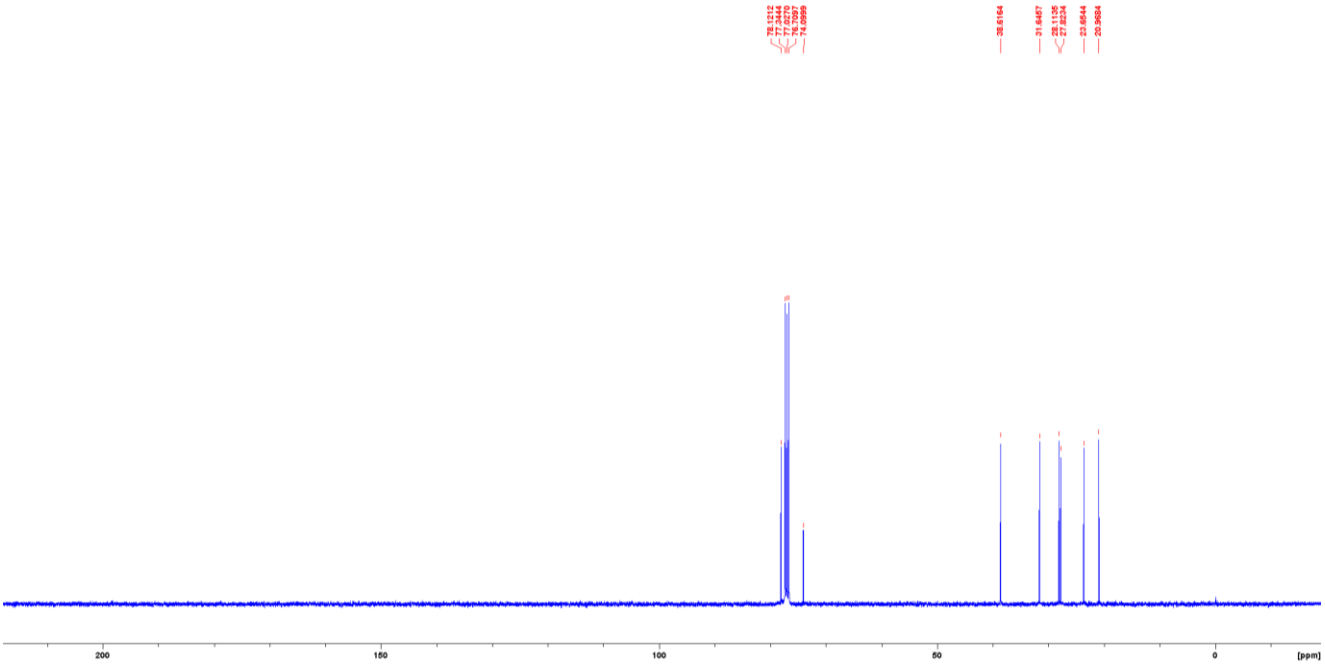
(1S,2R)-1,2-Dihydroxy-1-methylcycloheptane (13)

^{1}H NMR ($CDCl_3$, 400 MHz)



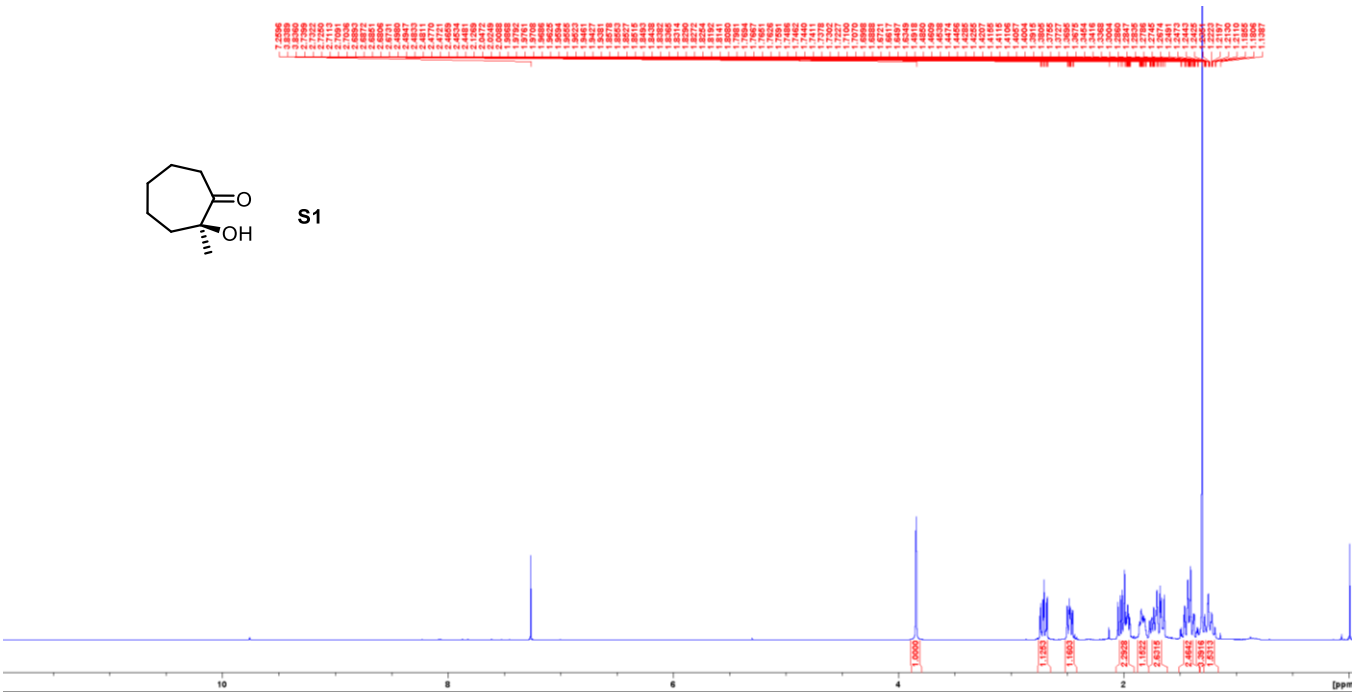
13

^{13}C NMR ($CDCl_3$, 100 MHz)

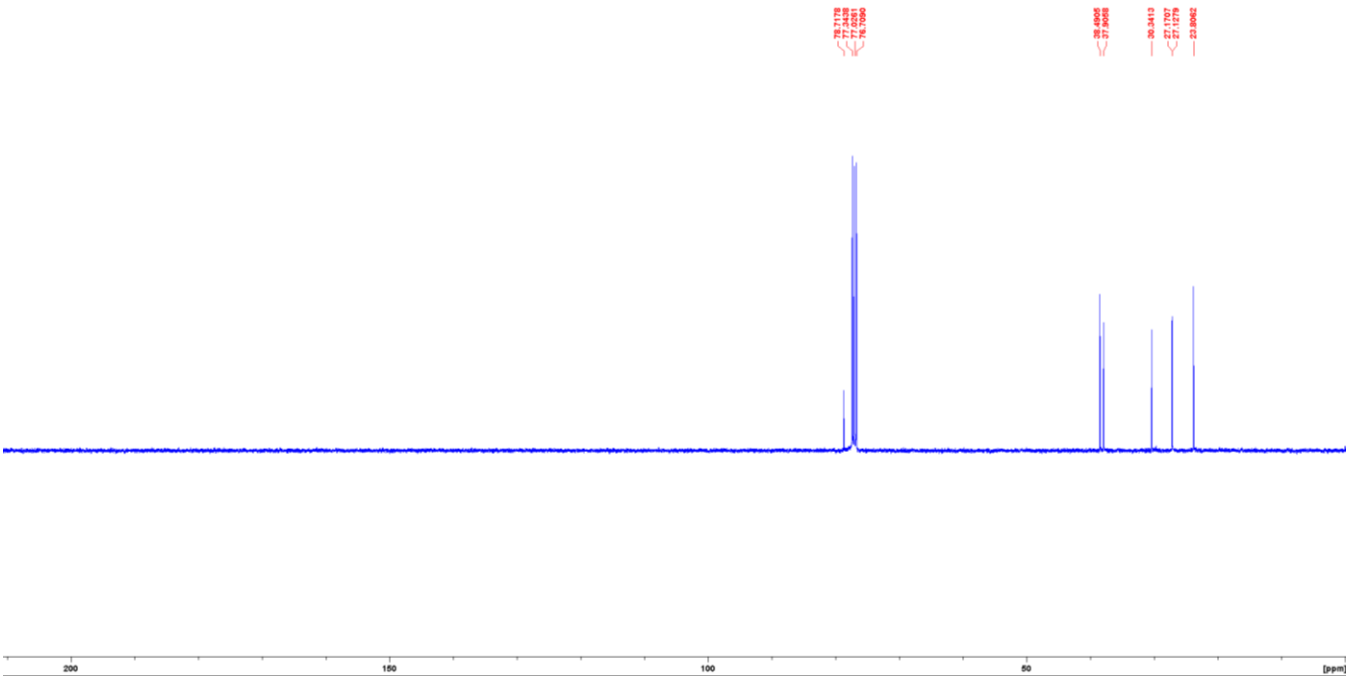


(2*S*)-2-Hydroxy-2-methylcycloheptan-1-one (S1)

^{1}H NMR ($CDCl_3$, 400 MHz)

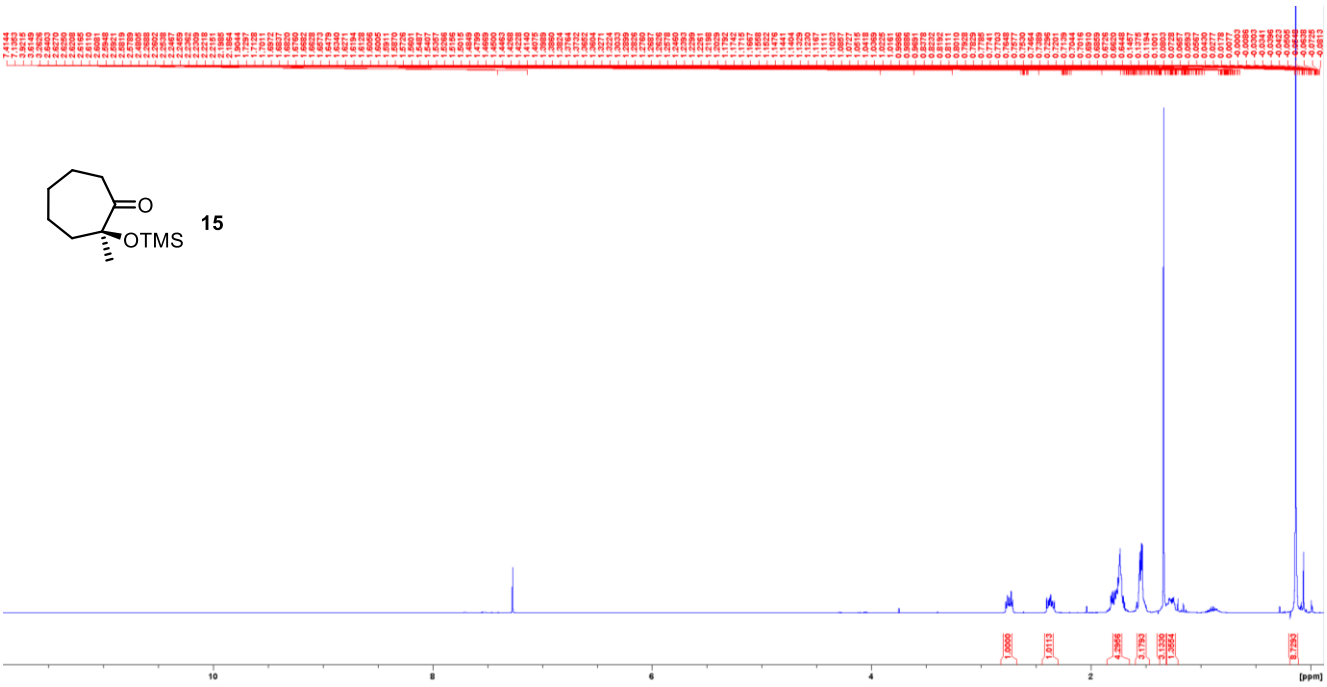


^{13}C NMR ($CDCl_3$, 100 MHz)

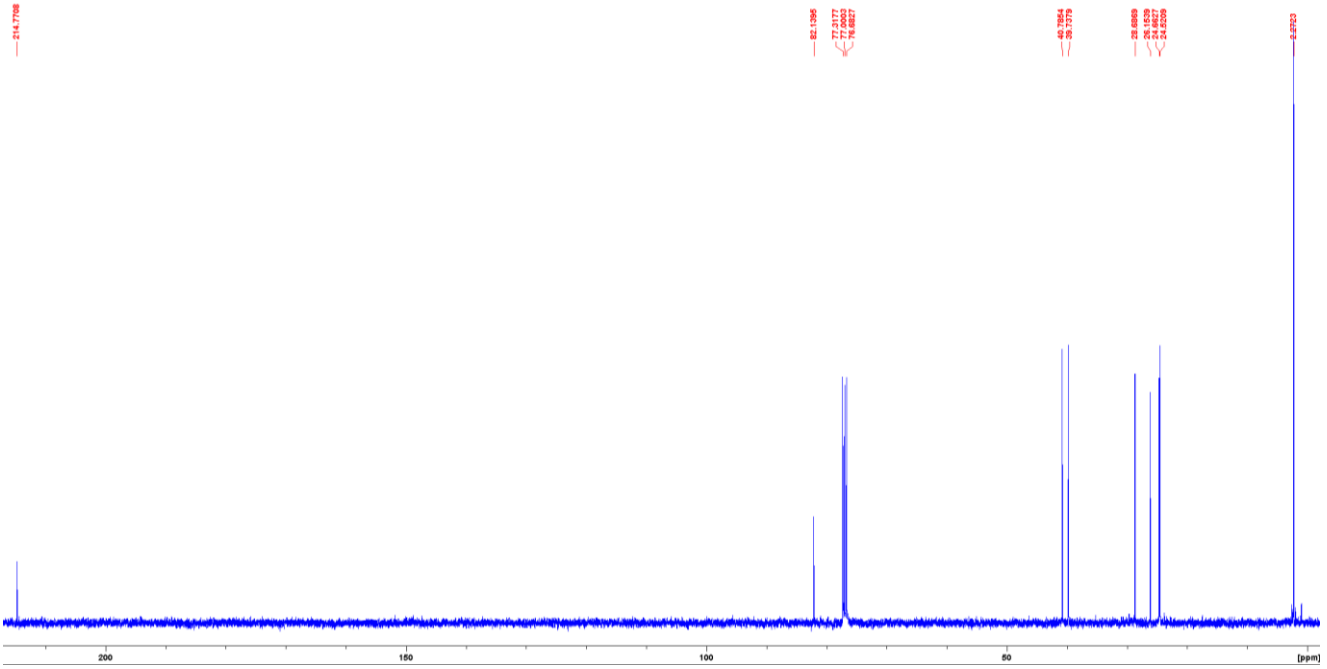


(2*S*)-2-Trimethylsilyloxy-2-methylcycloheptan-1-one (15)

^{1}H NMR ($CDCl_3$, 400 MHz)

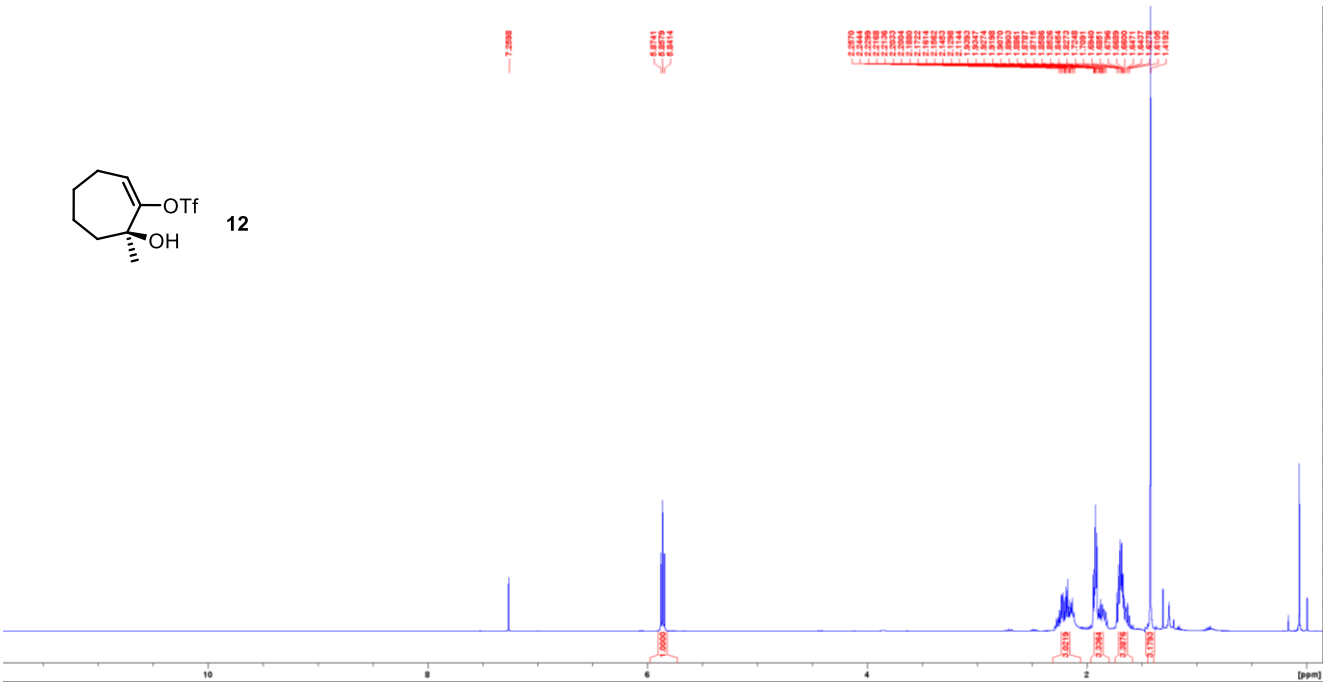


^{13}C NMR ($CDCl_3$, 100 MHz)

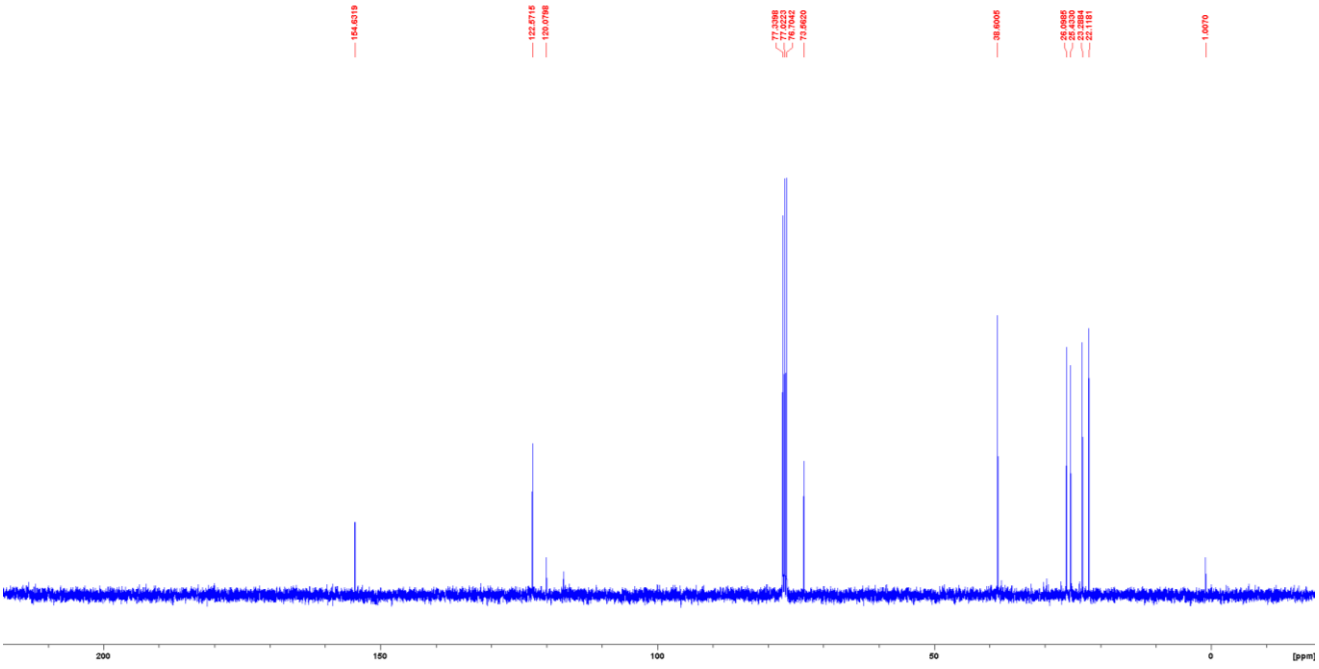


(7*S*)-7-Hydroxy-7-methyl-1-trifluoromethanesulfonyloxycyclohept-1-ene (12)

^{1}H NMR ($CDCl_3$, 400 MHz)

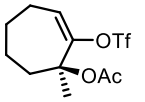


^{13}C NMR ($CDCl_3$, 100 MHz)



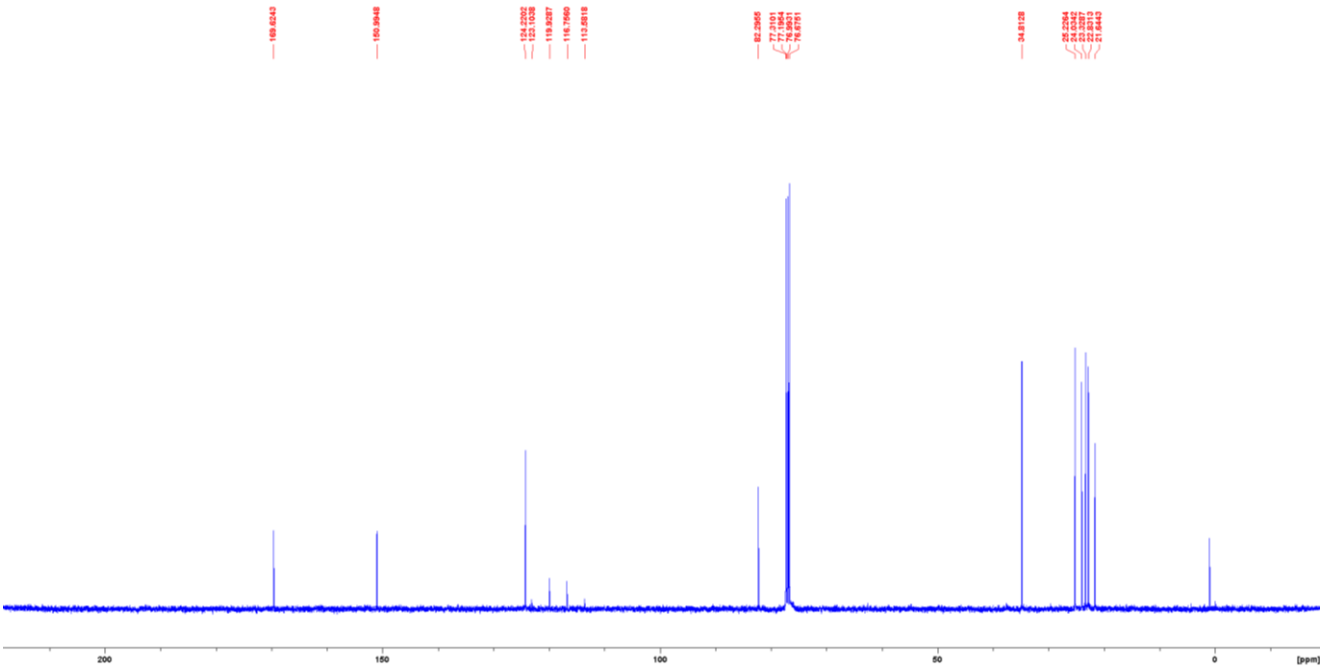
(7*S*)-7-Acetoxy-7-methyl-1-trifluoromethanesulfonyloxycyclohept-1-ene (16)

^{1}H NMR ($CDCl_3$, 400 MHz)



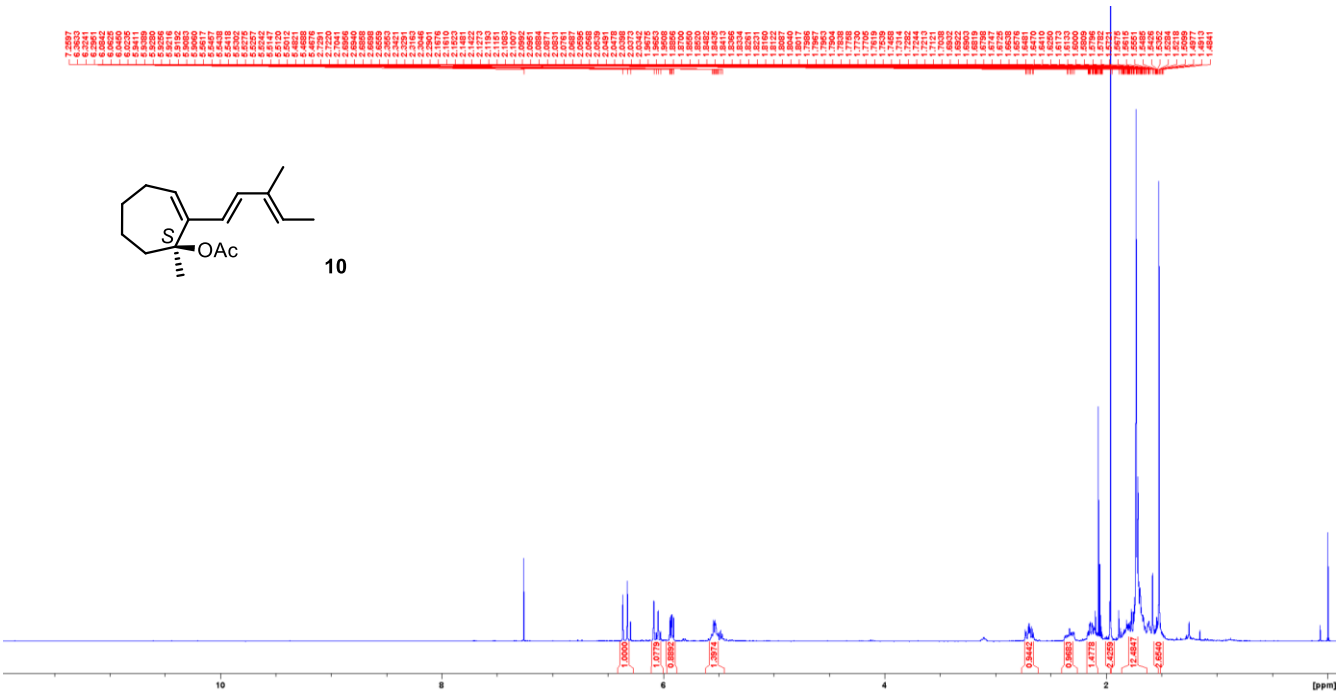
16

^{13}C NMR ($CDCl_3$, 100 MHz)

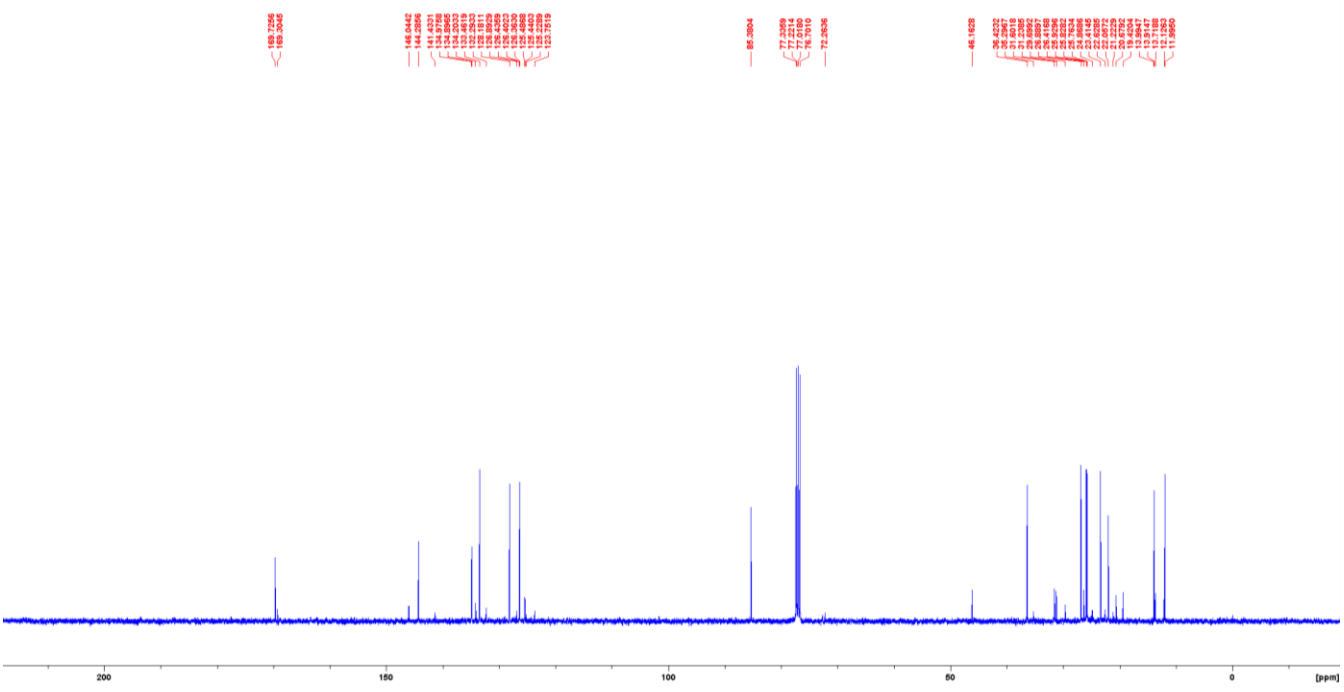


(7*S*)- 7-Acetoxy-7-methyl-1-[(1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl]cyclohept-1-ene (10), as a 4:1 mixture with the 1*Z* isomer

^{1}H NMR ($CDCl_3$, 400 MHz)

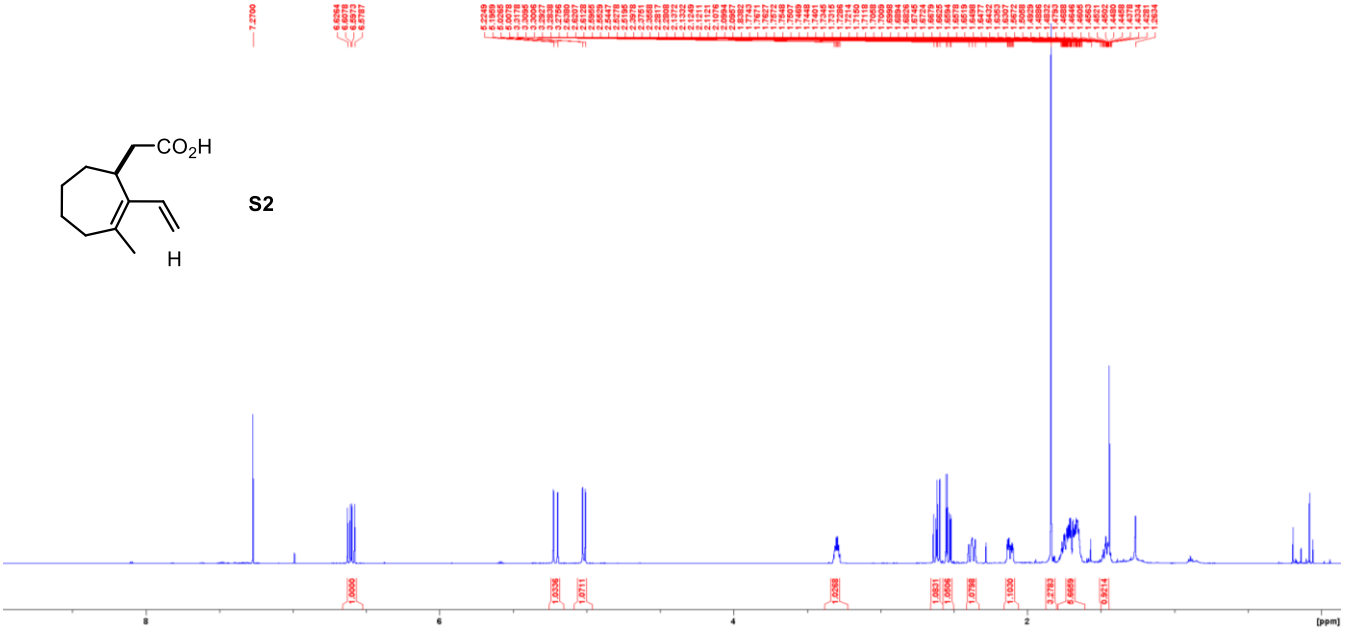


^{13}C NMR ($CDCl_3$, 100 MHz)

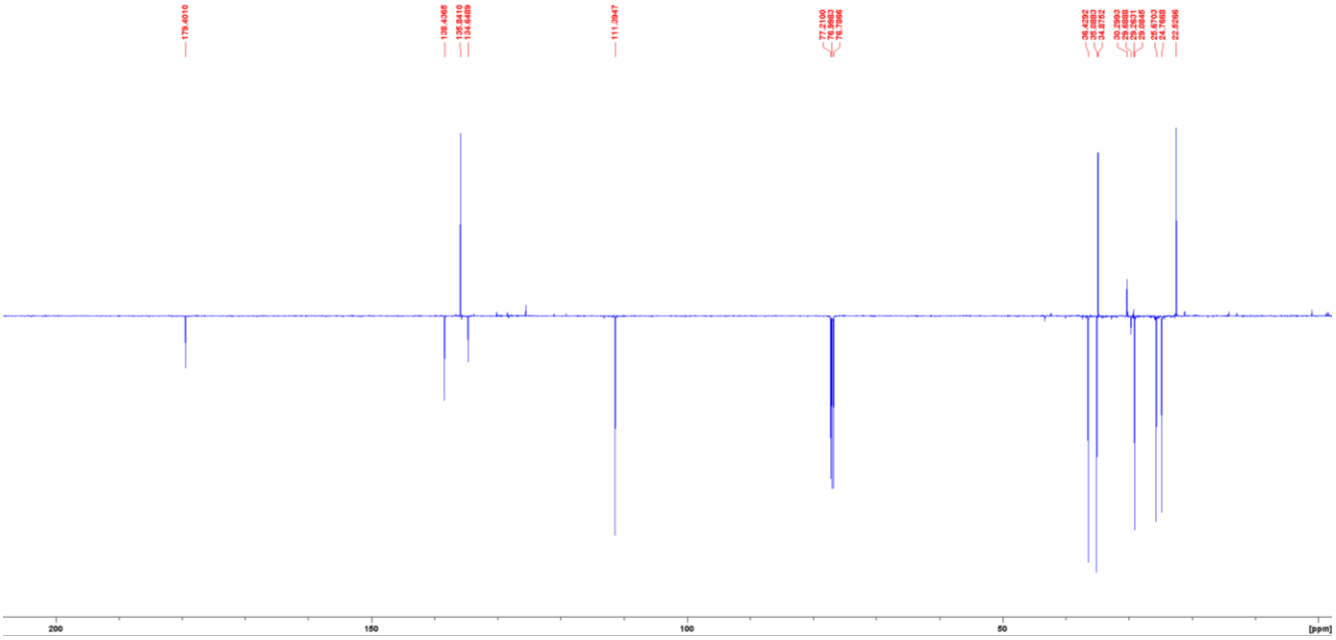


(*rac*)-2-[3-Methyl-2-vinylcyclohept-2-en-1-yl]acetic acid (S2)

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

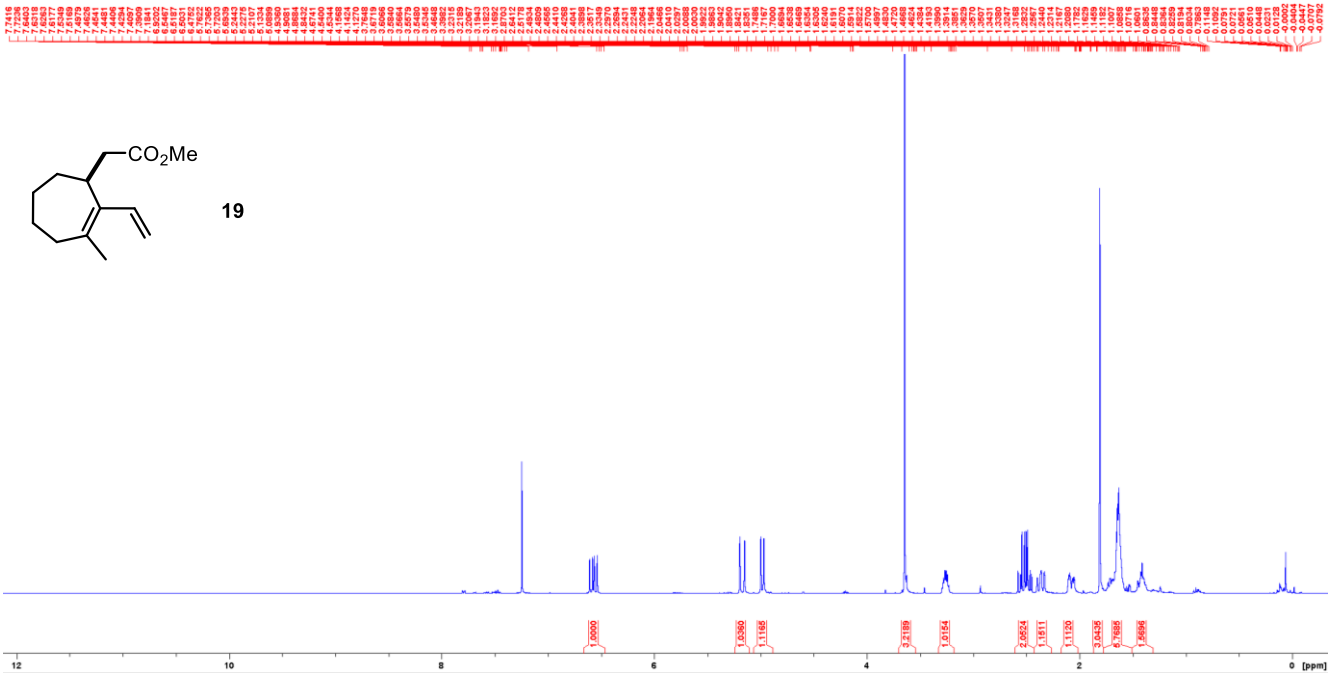


^{13}C NMR ($CDCl_3$, 100 MHz, DEPTQ experiment)

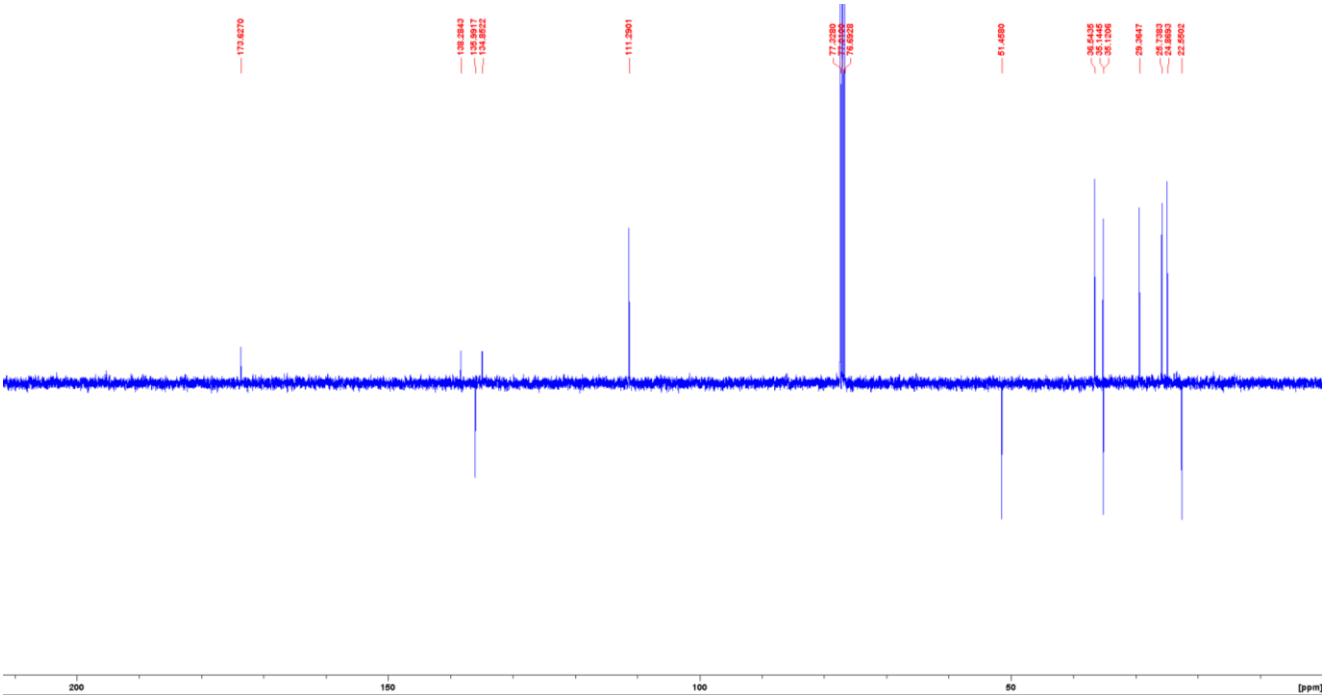


(*rac*)-2-[3-Methyl-2-vinylcyclohept-2-en-1-yl]acetic acid, methyl ester (19)

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

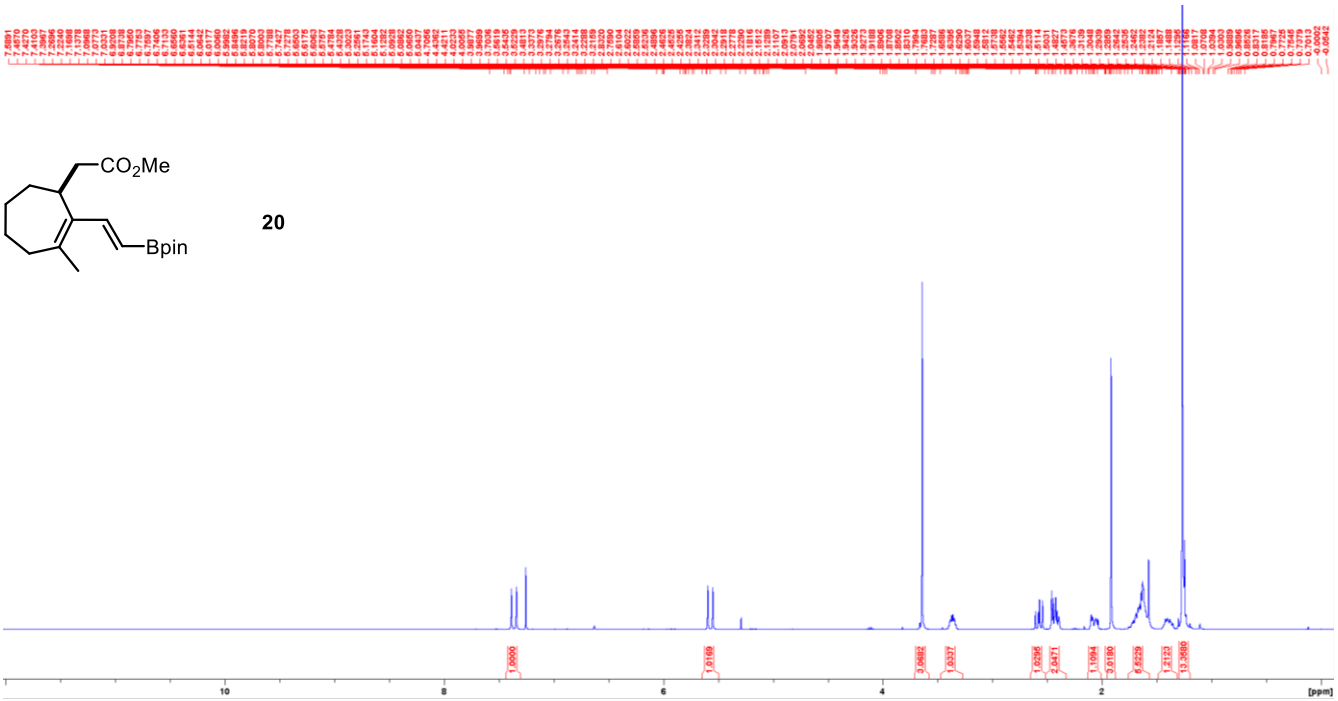


^{13}C NMR ($CDCl_3$, 100 MHz, DEPTQ experiment)

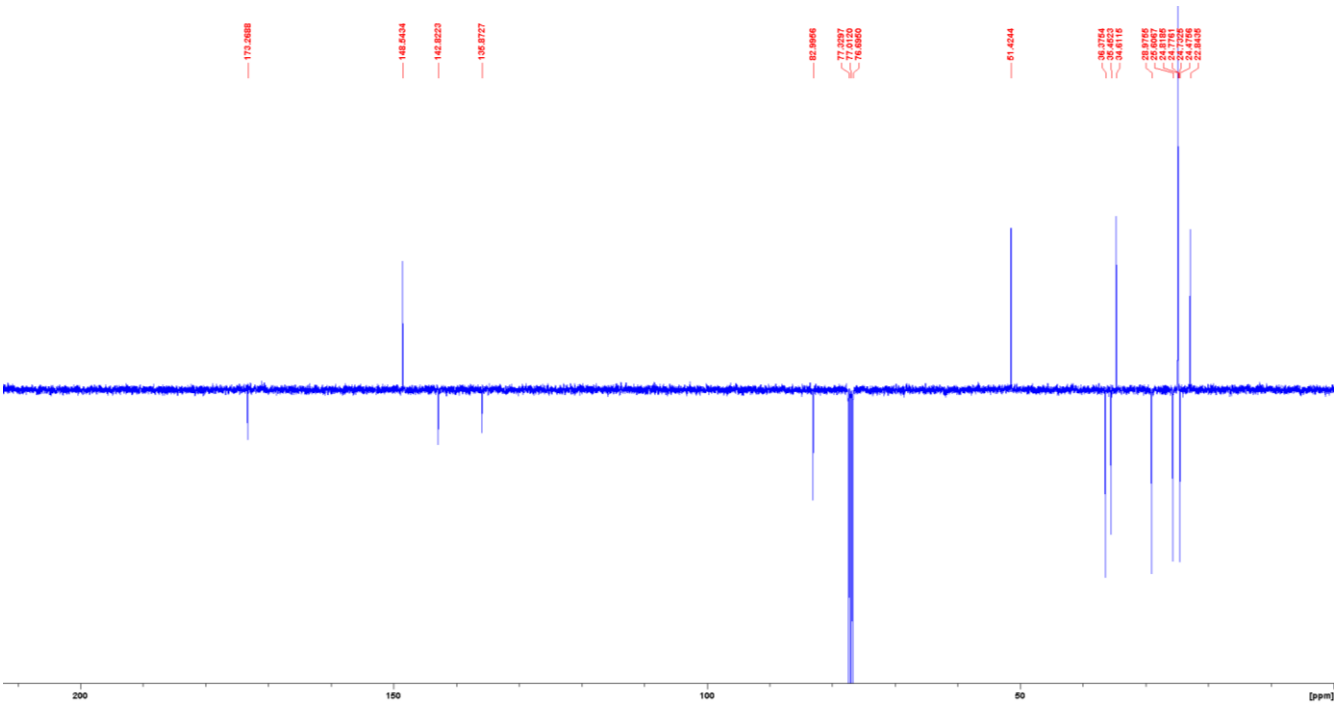


(*E*)-2-(3-Methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohept-2-en-1-yl)acetic acid, methyl ester (20)

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz, DEPTQ experiment)

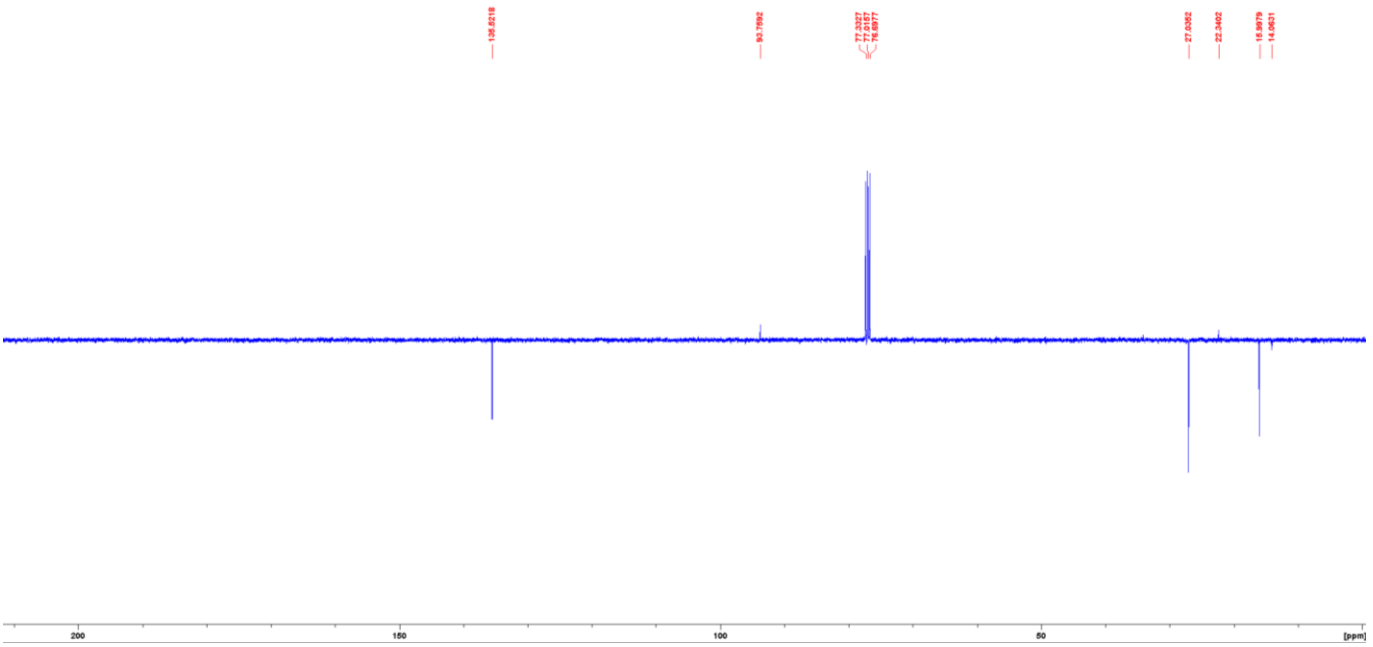


(E)-2-Iodobut-2-ene (21)

^{1}H NMR ($CDCl_3$, 400 MHz)

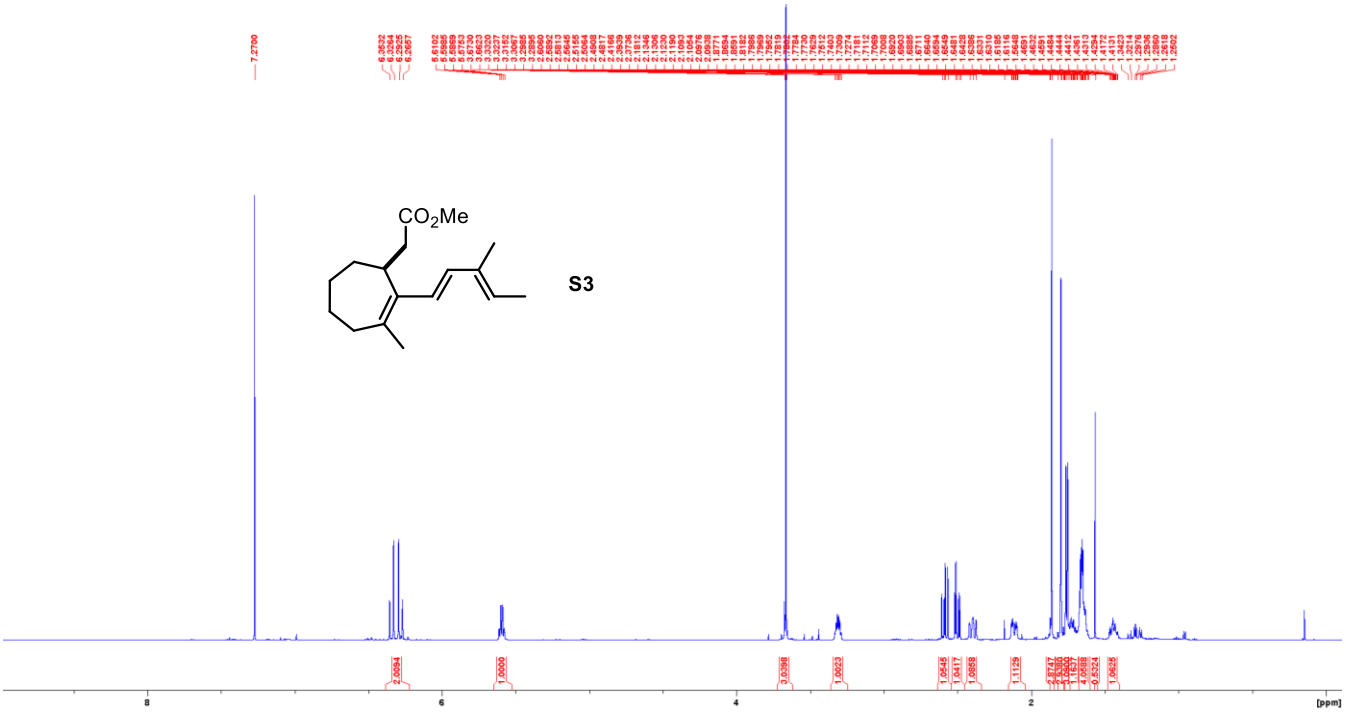
21

^{13}C NMR ($CDCl_3$, 100 MHz, DEPTQ experiment)

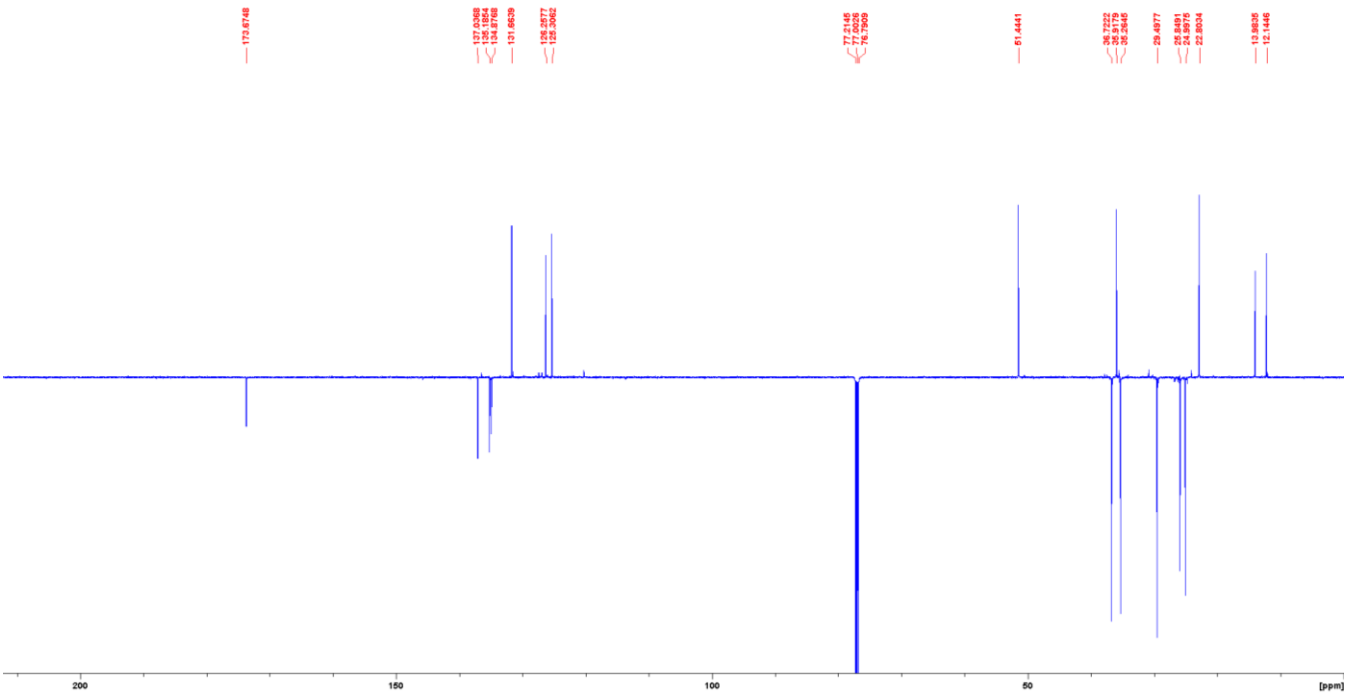


2-(3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl)acetic acid, methyl ester (S3)

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

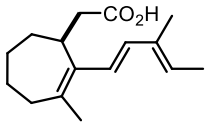


^{13}C NMR ($CDCl_3$, 150 MHz, DEPTQ experiment)



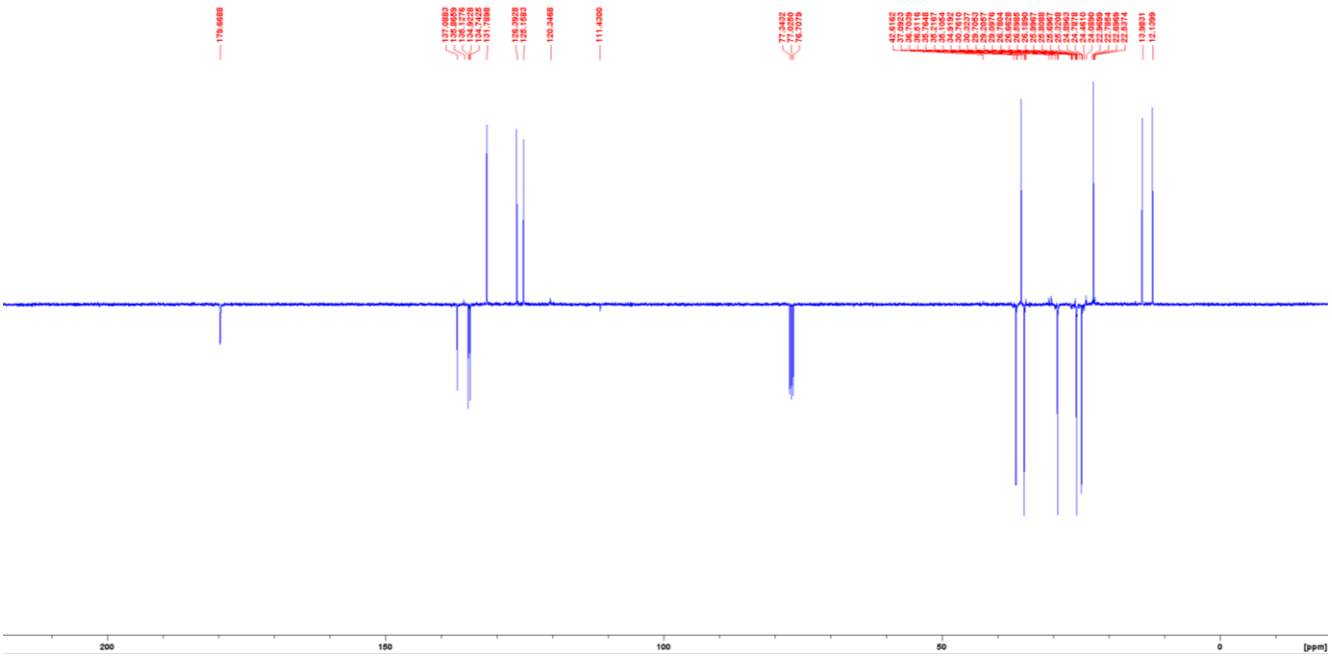
(*rac*)-2-[3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetic acid (*rac*-9)

^{1}H NMR ($CDCl_3$, 400 MHz)



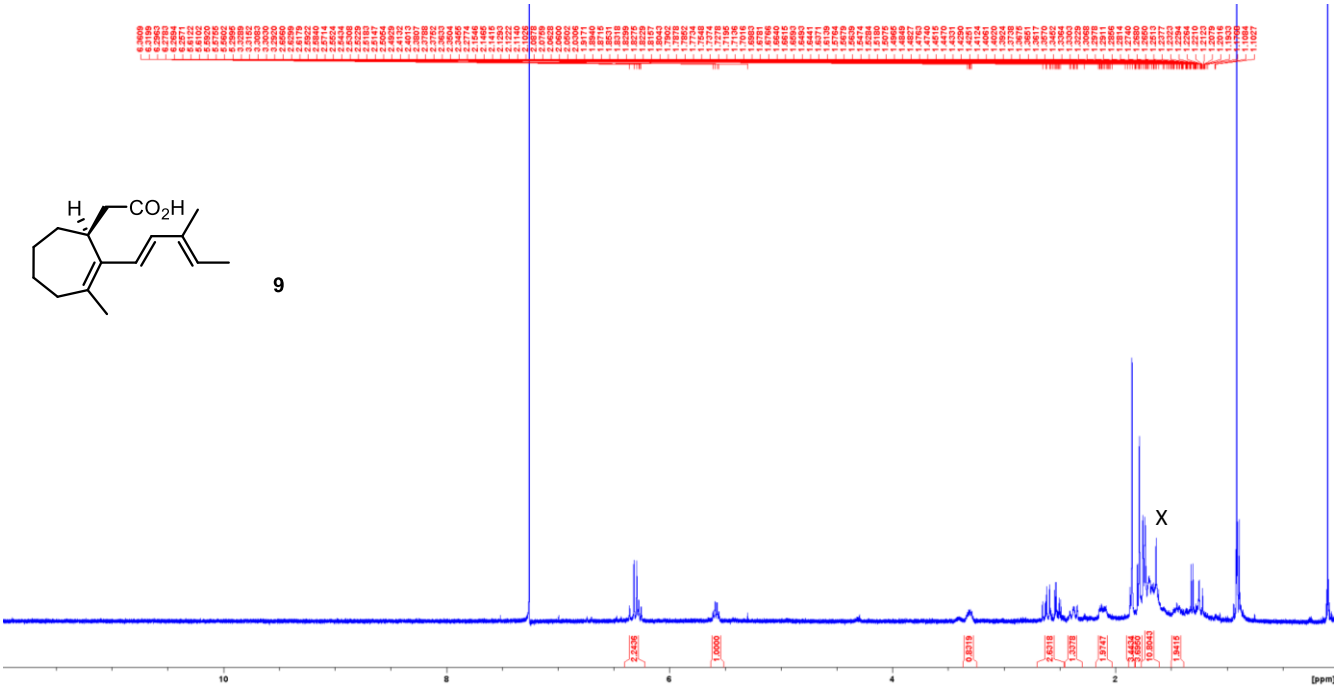
***rac*-9**

^{13}C NMR ($CDCl_3$, 100 MHz, DEPTQ experiment)



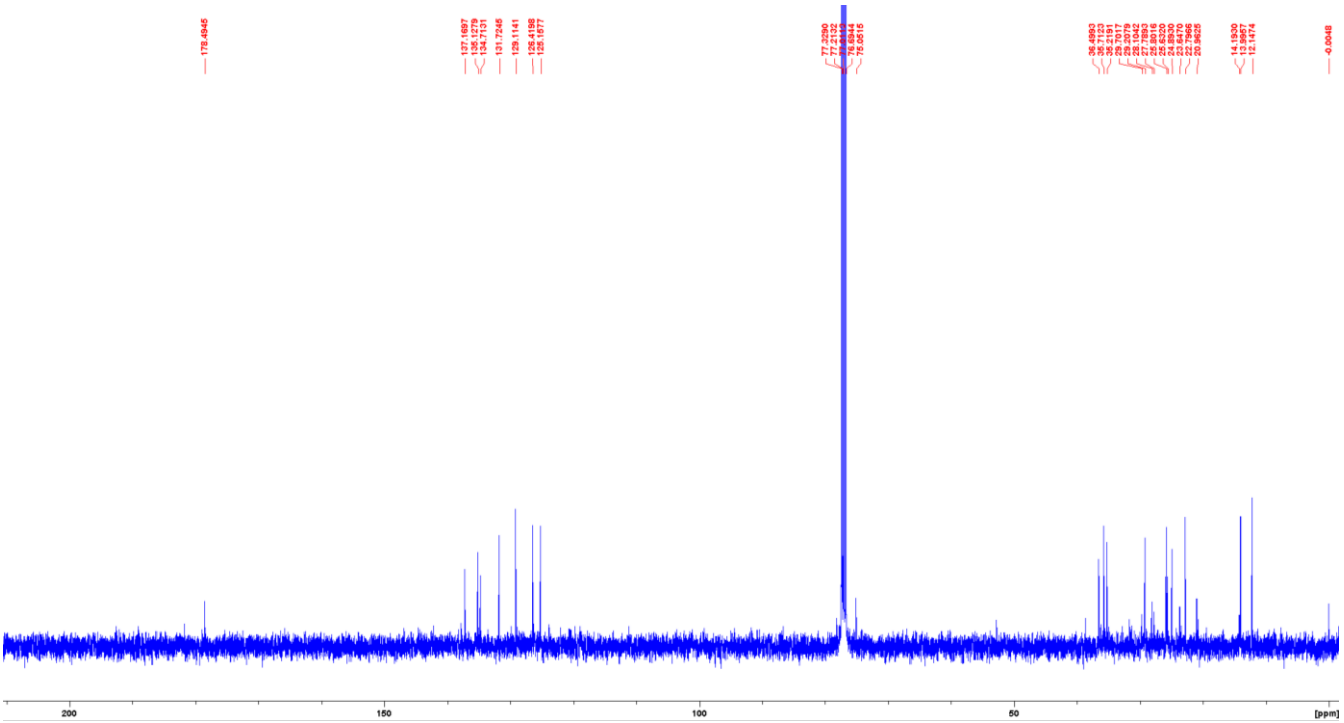
2-[(1*S*)-3-Methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetic acid, crude extract used in the next step (9)

^{1}H NMR ($CDCl_3$, 400 MHz)



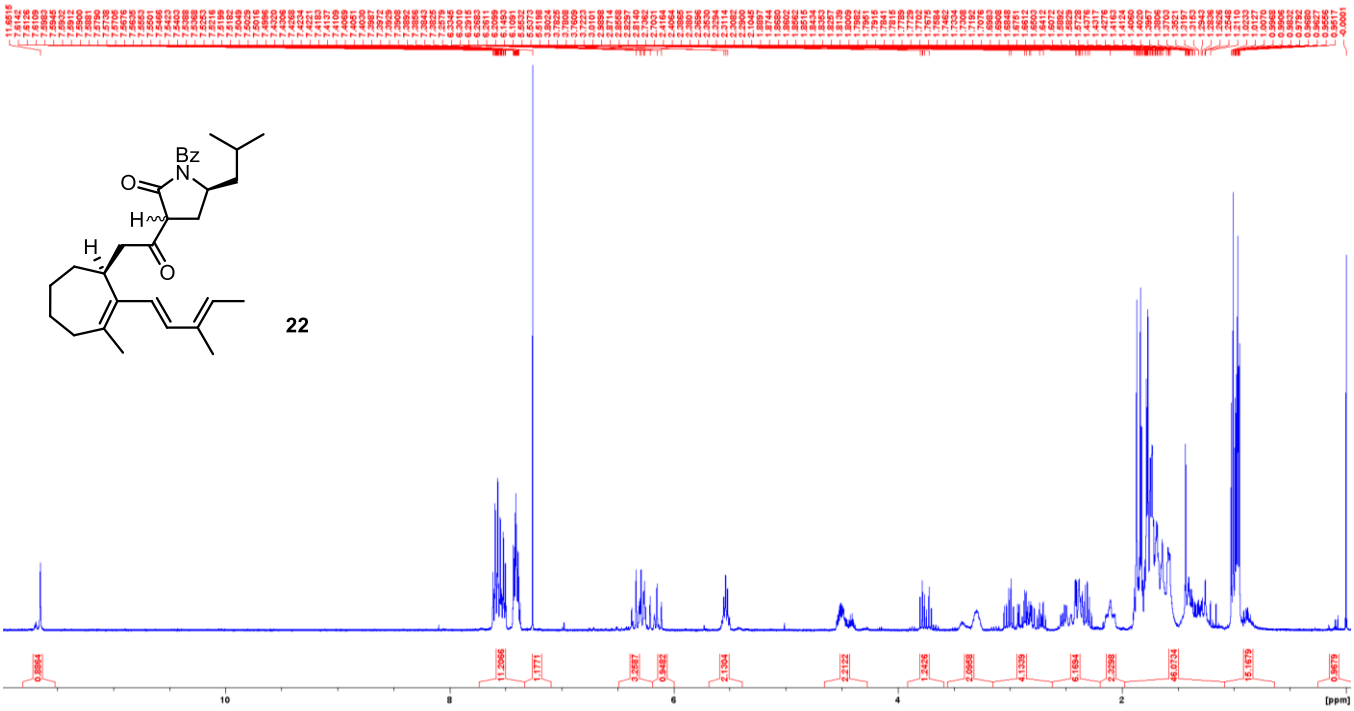
9

^{13}C NMR ($CDCl_3$, 100 MHz)

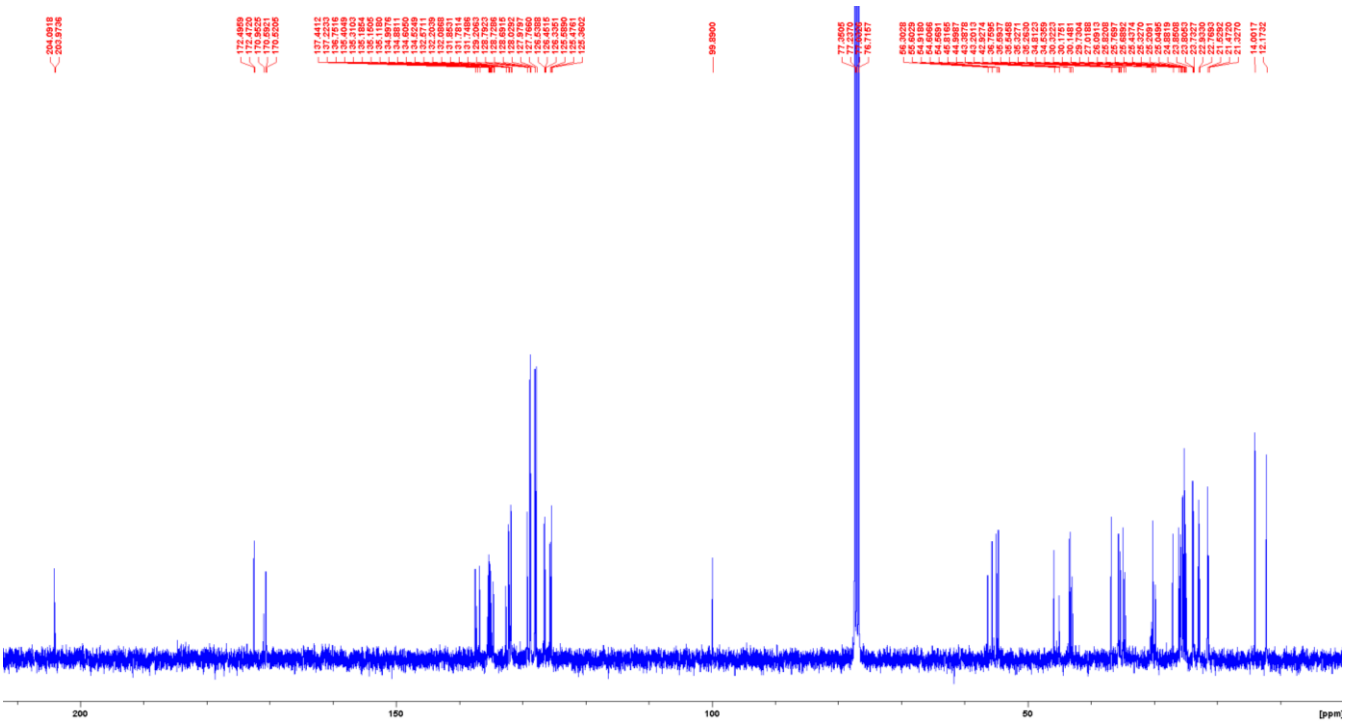


***N*-Benzoyl-5-isobutyl-3-{2-[(1*S*)-3-methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetyl}-2-pyrrolidone, mixture of stereoisomers (22)**

^{1}H NMR ($CDCl_3$, 400 MHz)

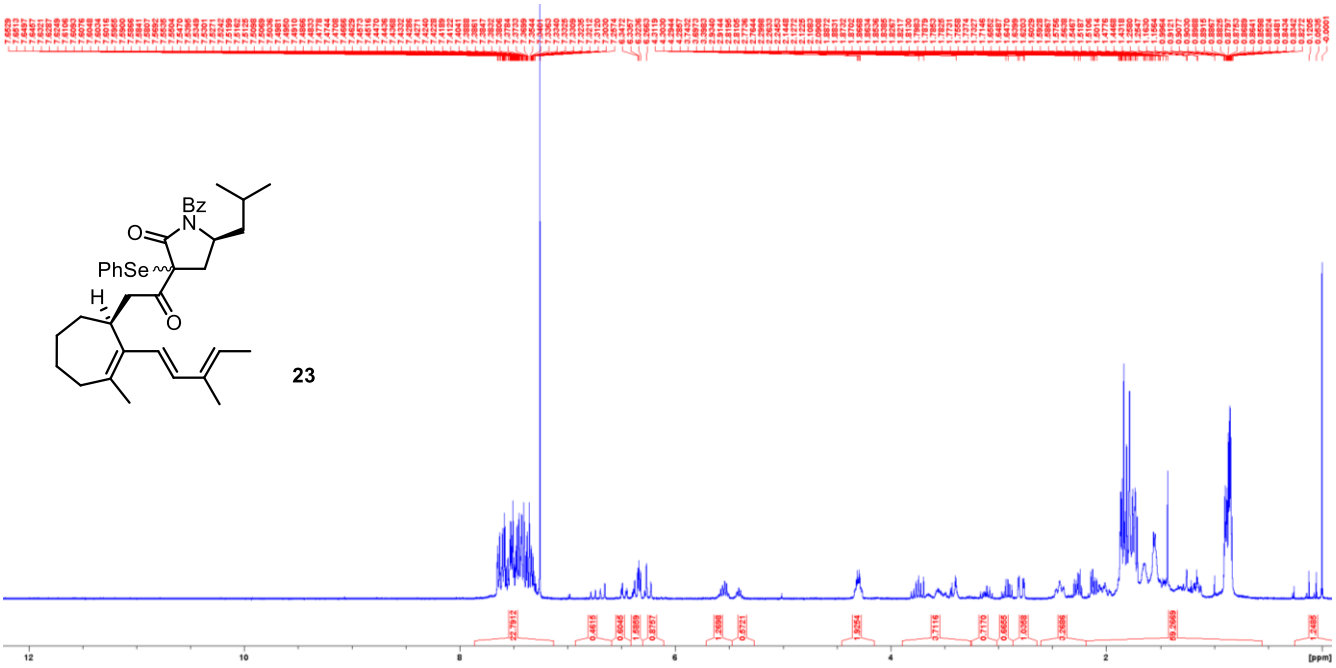


^{13}C NMR ($CDCl_3$, 100 MHz), JMOD

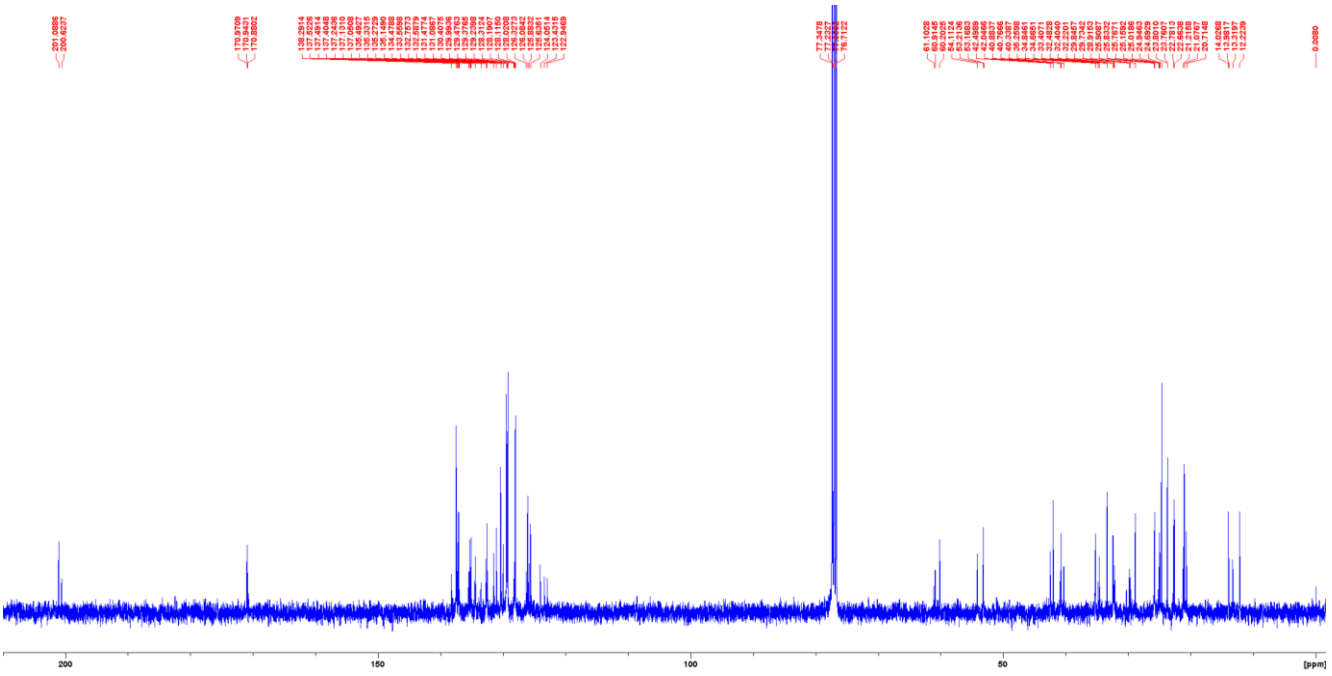


***N*-Benzoyl-5-isobutyl-3-{2-[(1*S*)-3-methyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dien-1-yl)cyclohept-2-en-1-yl]acetyl}-3-phenylselenyl-2-pyrrolidone, mixture of stereoisomers (23)**

^{1}H NMR ($CDCl_3$, 400 MHz)

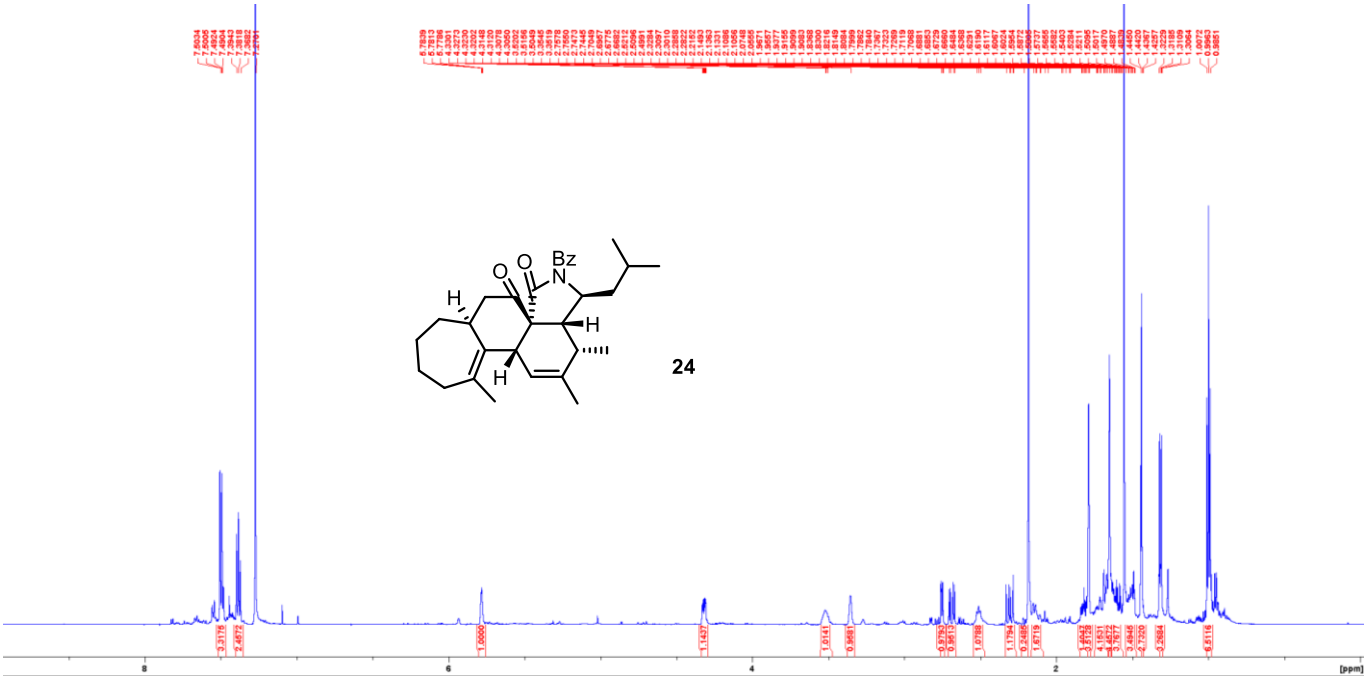


^{13}C NMR ($CDCl_3$, 100 MHz)

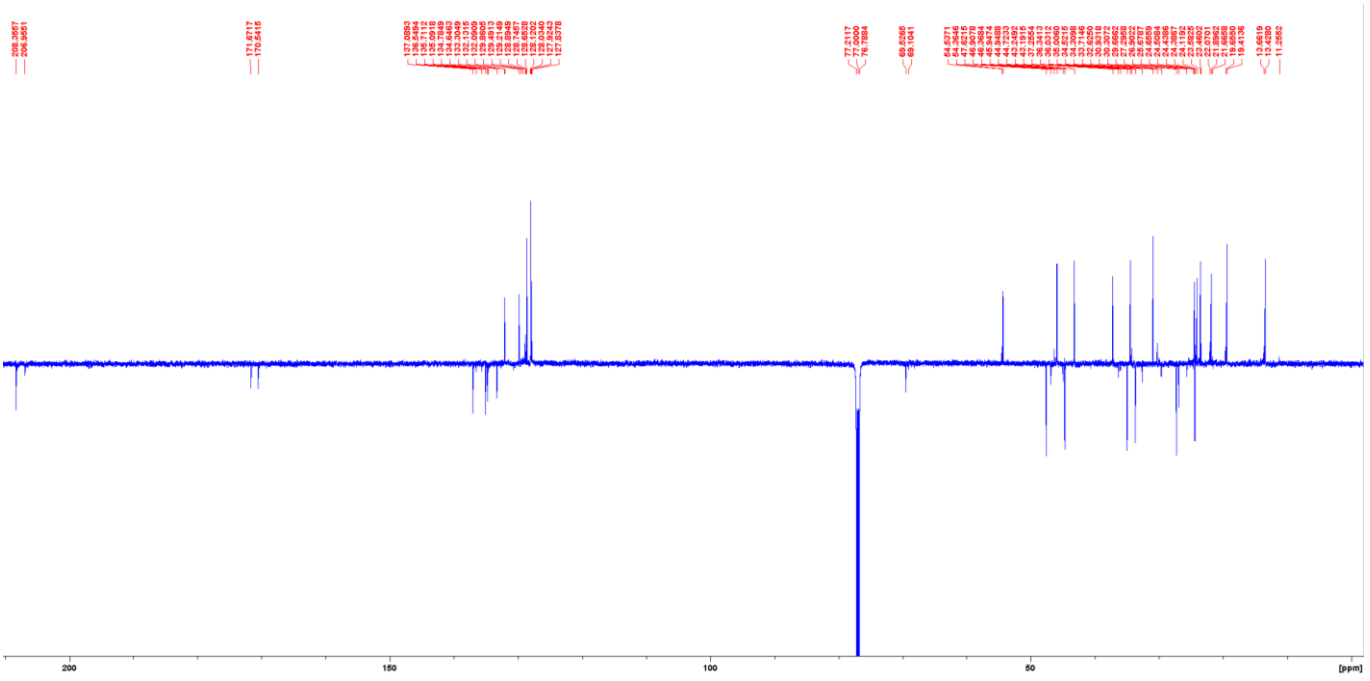


(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13b*R*)-5-Benzoyl-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (*endo* product 24)

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

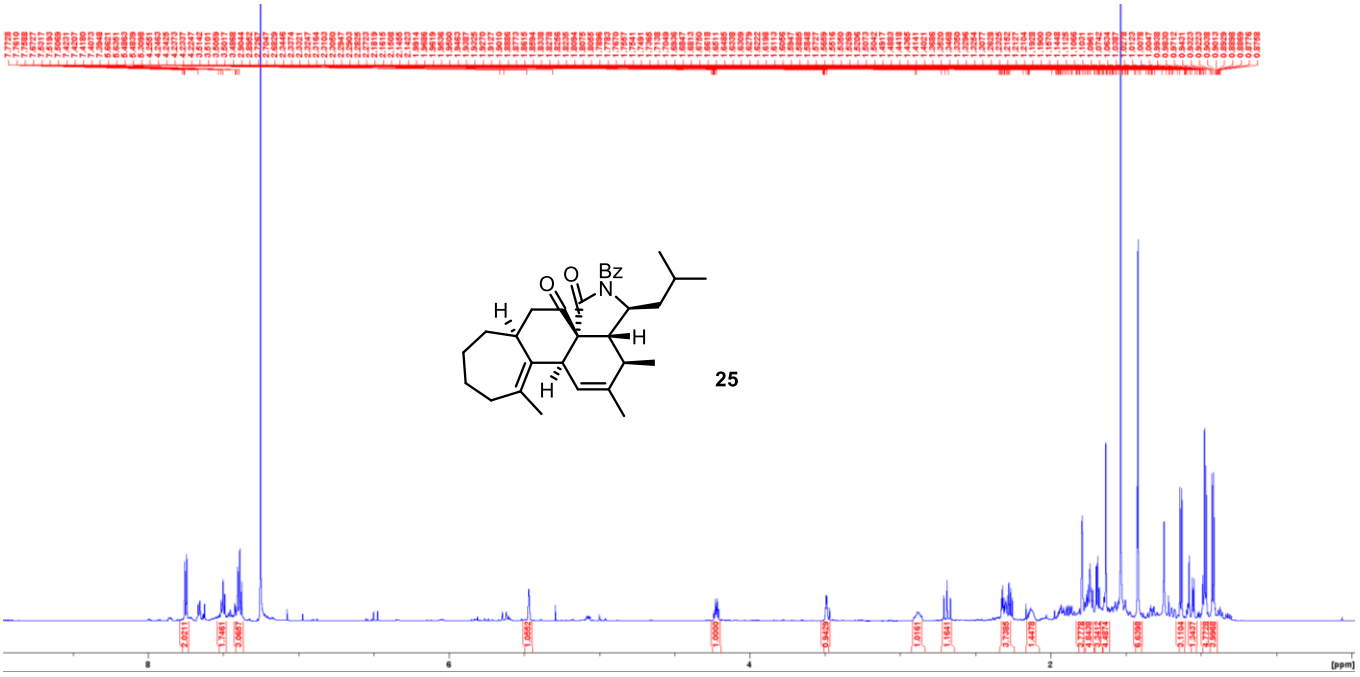


^{13}C NMR ($CDCl_3$, 150 MHz), DEPTQ experiment



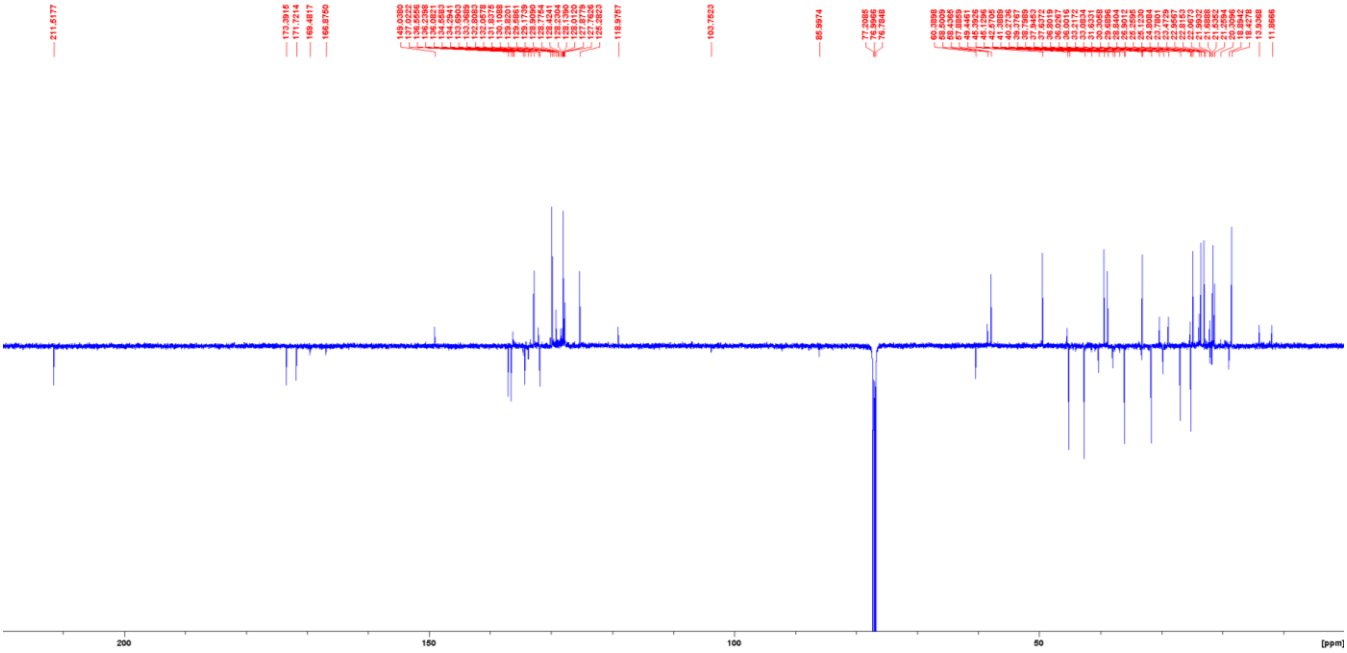
(3*R*,3a*R*,4*S*,6a*S*,8a*S*,13b*S*)-5-benzoyl-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (*exo* product 25)

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



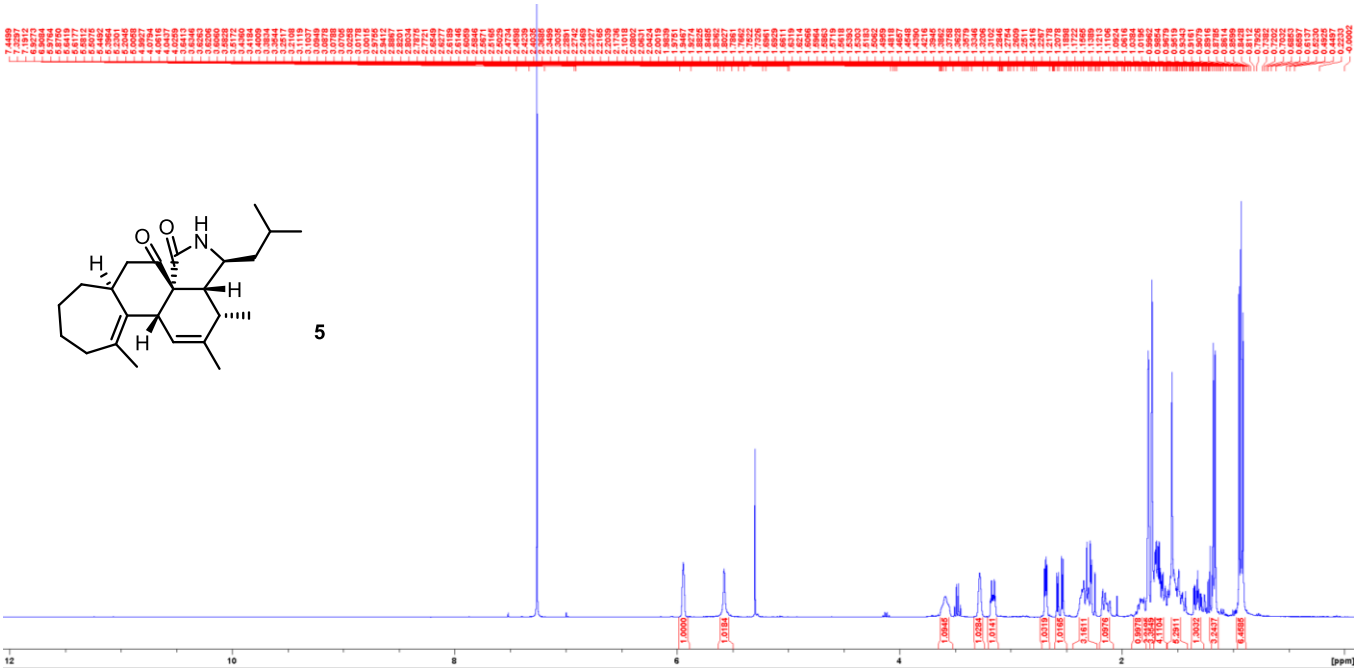
25

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

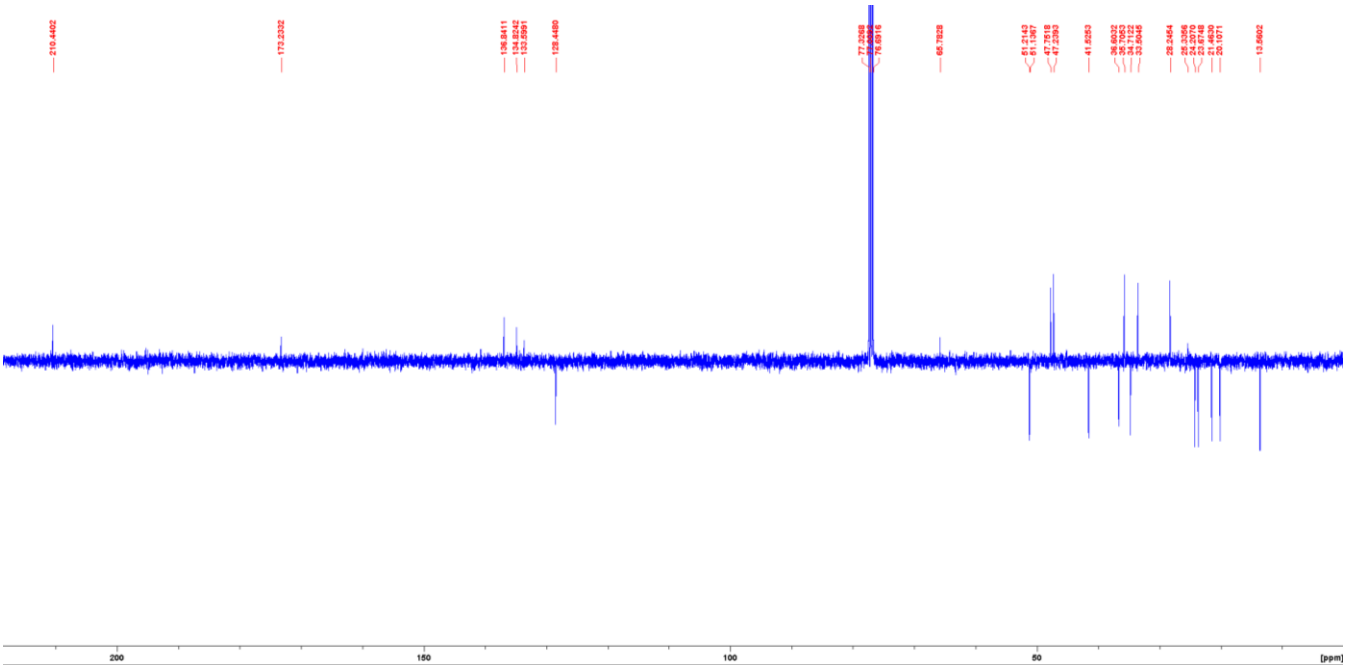


(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13b*R*)-4-Isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3H-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3aH,13bH)-dione (biomimetic precursor 5)

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

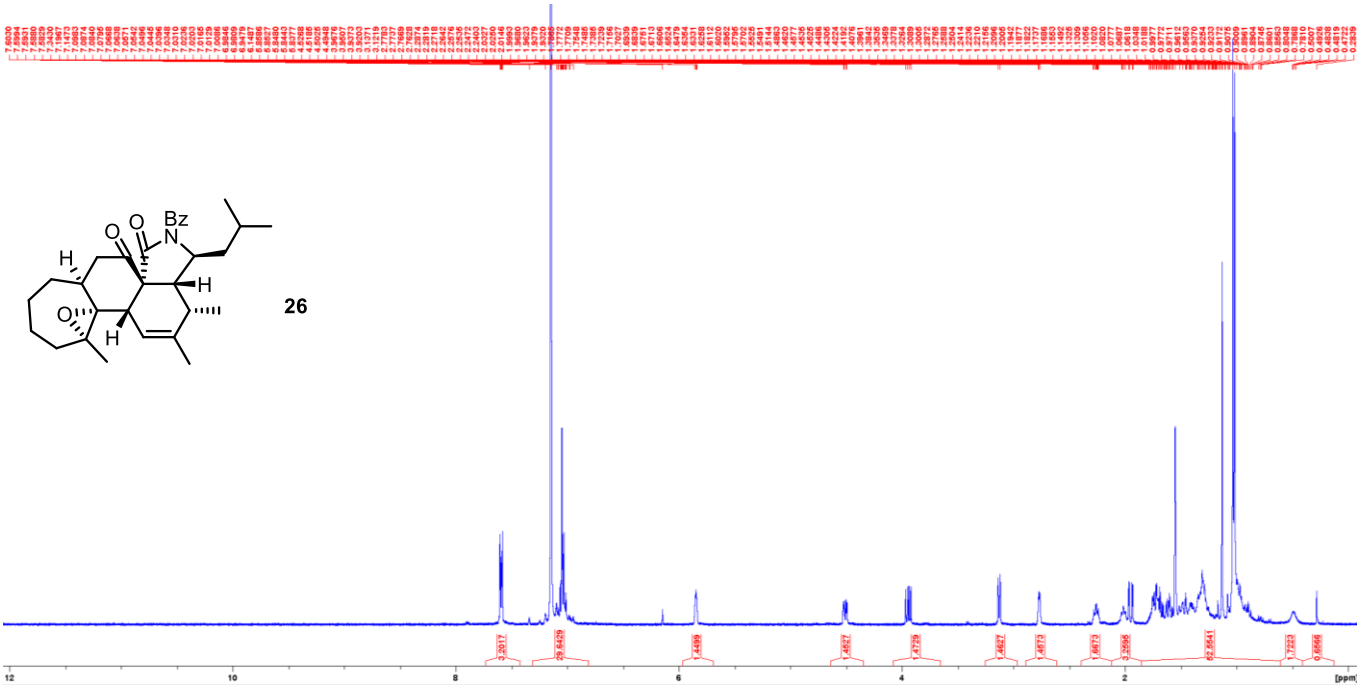


^{13}C NMR ($CDCl_3$, 150 MHz), DEPTQ experiment



(3*S*,3a*R*,4*S*,6a*S*,8a*S*,13*R*,13a*R*,13b*R*)-5-Benzoyl-13,13a-epoxy-4-isobutyl-2,3,13-trimethyl-4,5,8,8a,9,10,11,12-octahydro-3*H*-cyclohepta[3,4]benzo[1,2-d]isoindole-6,7(3a*H*,13b*H*)-dione (26)

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz), DEPTQ experiment