Synthesis of Gambanol, *Phomapentenone A and Substituted Cyclopentenones*

Dissertation

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Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Aufnahme in seinen Arbeitskreis, die Überlassung des interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

Für Katharina und meine Familie

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Abbreviations

abs.	absolute
Ac	acetyl
Amphos	bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine
anh.	anhydrous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
^{i}Bu	*iso*-butyl
^{t}Bu	*tert*-butyl
^{s}Bu	*sec*-butyl
bp	boiling point
CN	nitrile
COSY	correlation spectroscopy
CPA	chiral phosphoric acids
Cy	cyclo
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DACH	diaminocyclohexyl
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DMF	*N,N'*-dimethylformamide
DMAP	*N*,*N'*-dimethyl-4-aminopyridine
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
dr	diastereomeric ratio
ee	enatiomeric excess
EtOAc	ethyl acetate
equiv	equivalents
EI	electron impact
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EWG	electron withdrawing group
Hex	hexyl
HMBC	heteronuclear multiple bond correlation
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
LDA	lithium diisopropylamide
LG	leaving group
Me	methyl
min	minute(s)
MHz	megahertz
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PG	protecting group
Ph	phenyl
ppm	part(s) per million
^{i}Pr	*iso*-propyl
R	arbitrary rest
rt	room temperature
rac	racemic
s	second(s)
s.m.	starting material
SPhos	2-Dicyclohexylphosphino-2`,6`-dimethoxybiphenyl
TES	triethylsilyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography

1 Synthesis and Field Bioassays of Gambanol and Derivatives

1.1 Introduction

Volatile organic compounds act as chemical communication between flowering plants and their pollinating insects.[1] In many cases simple and fast characterization of the target molecule *via* NMR spectroscopy is not possible because of insufficient material such as several ortho-(methylthio)phenols[2] in the spider orchid *Caladenia crebra* (Orchidaceae). Instead, a complex synthesis of several potential candidate molecules based on mass spectrometric and/or Fourier transform infrared spectroscopic data was necessary. In other cases such as (*E*,*E*)-α-farnesene-2(3),9(10)-diepoxid[3] in *Evodianthus funifer* (Cyclanthaceae), collection of sufficient material from the desired target molecule was successful, however, purification and fractionation steps were laborious. Furthermore, these steps bear the risk of losing the compound[4] and increase of contaminations[5] due to decomposition or high reactivity of the target molecule.[6]

The working group of Prof. Dr. Stefan Dötterl from the University of Salzburg has developed a simpler protocol *via* high resolution 2D NMR spectroscopy for the identification of volatile compounds avoiding complex purification and fractionation steps. Therefore, it accomplishes direct analysis of crude mixtures containing one or several compounds. *Via* 2D NMR spectroscopy different spin systems coming from multiple compounds can be separated and characterized well in a crude mixture.

This approach was applied by their working group to dynamic headspace scent samples stemming from inflorescences of the aroid *Syngonium hastiferum* (Standley & Williams) for identification and characterization of an unknown floral scent compound that probably acts as an attractant to pollinators such as insects of this plant. The study of pollination biology and pollinator attractants of *Syngonium hastiferum* was conducted in Costa Rica employing multidisciplinary approach combining techniques from ecology, chemical ecology, analytical chemistry and chemical synthesis. It was discovered that this plant is exclusively pollinated by a single, hitherto undescribed mirid bug species (Heteroptera, Miridiae, *Neella* sp. nov.).

The bugs are attracted to flowering individuals of *Syngonium hastiferum* during the morning hours (07:00 – 09:00) of two consecutive days when a strong and pleasant scent is released by the inflorescences. The confirmation for the olfactory stimulation of the pollinators was

obtained by successful attracting numerous individuals of *Neella* sp. nov. to bagged inflorescences that excluded visual but not olfactory cues.

For determination of the scent compounds the dynamic headspace method[5] was employed, trapping the molecules on Tenax TA and Carbotrap B adsorbents followed by thermal desorption–GC/MS. Since no match of the single dominant compound was found in commercially available libraries, sufficient material was collected via dynamic headspace method and eluted with $CDCl_3$ and subjected directly to NMR analysis.

With the integrals in a ^{1}H-NMR spectrum of the scent of *Syngonium hastiferum* it is obvious that the compound **1a** contains two CH-groups and three methyl groups (H5, H7-H8), whereas two groups of latter are in an equivalent environment resulting in a signal with integral of 6 compared to a CH-group (Figure 1). The CH-group (H4) δ^1H at 5.22 ppm (Figure 1) and δ^{13}C at 120 ppm (Figure 3) indicates an involvement in a carbon-carbon double bond.

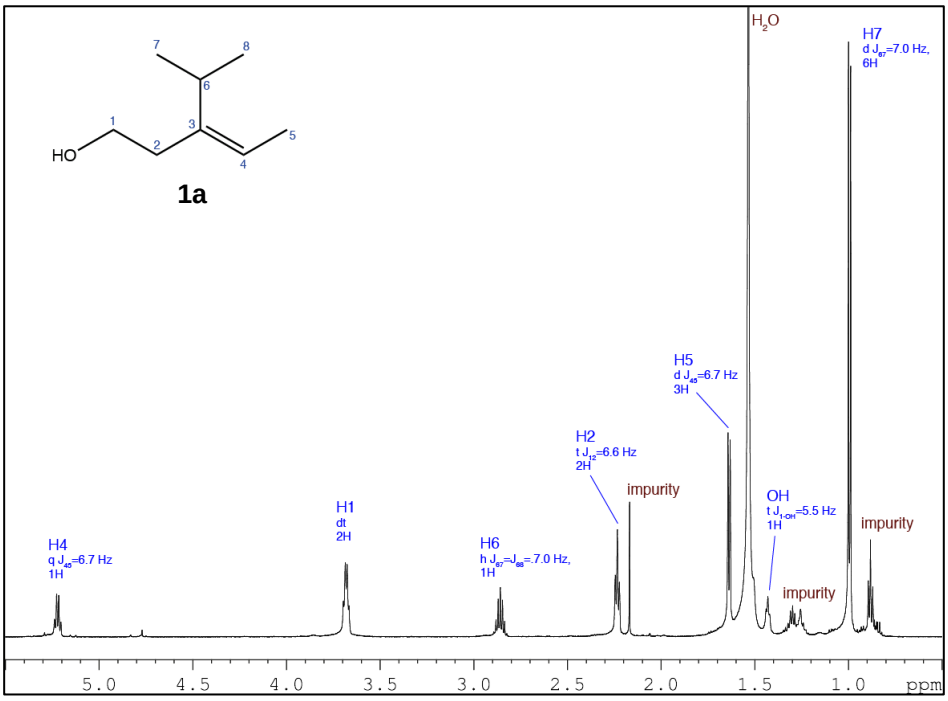


Figure 1. ^{1}H-NMR spectrum of the scent of *Syngonium hastiferum* eluted from the matrix with $CDCl_3$. Figure: Dr. Mario Schubert.

2D ^{1}H-^{1}H TOCSY spectra with different mixing times are shown in Figure 2. Observed short-range ^{1}H-^{1}H correlations are depicted schematically in the form of red arrows on the structure (middle) and selected long-range ^{1}H-^{1}H correlations are indicated by blue arrows (Figure 2a). ^{1}H-^{1}H TOCSY spectrum with 12 ms mixing time (Figure 2b) leads to cross-peaks similar to COSY, but the cross-peaks are fully absorptive. Cross-peaks of CH-group (H4) and methyl

group (H5) indicate a methyl group next to the double bond, the septet signal of CH-group (H6) and the cross-peak with the two methyl groups (H7-8) points to an *iso*-propyl group. Two CH_2-groups and the lacking cross-peak between CH_2-group (H2) and the OH group show a primary alcohol functionality on a C_2-alkyl chain. Cross-peaks of ^1H-^1H TOCSY spectrum with 120 ms mixing time (Figure 2c) provides observation of long-range ^1H-^1H correlations. Interestingly, additional to the cross peaks from the ^1H-^1H TOCSY spectrum with 12 ms mixing time only cross-peaks between each of the CH_2-groups (H1-H2) and the methyl group (H5) were observed.

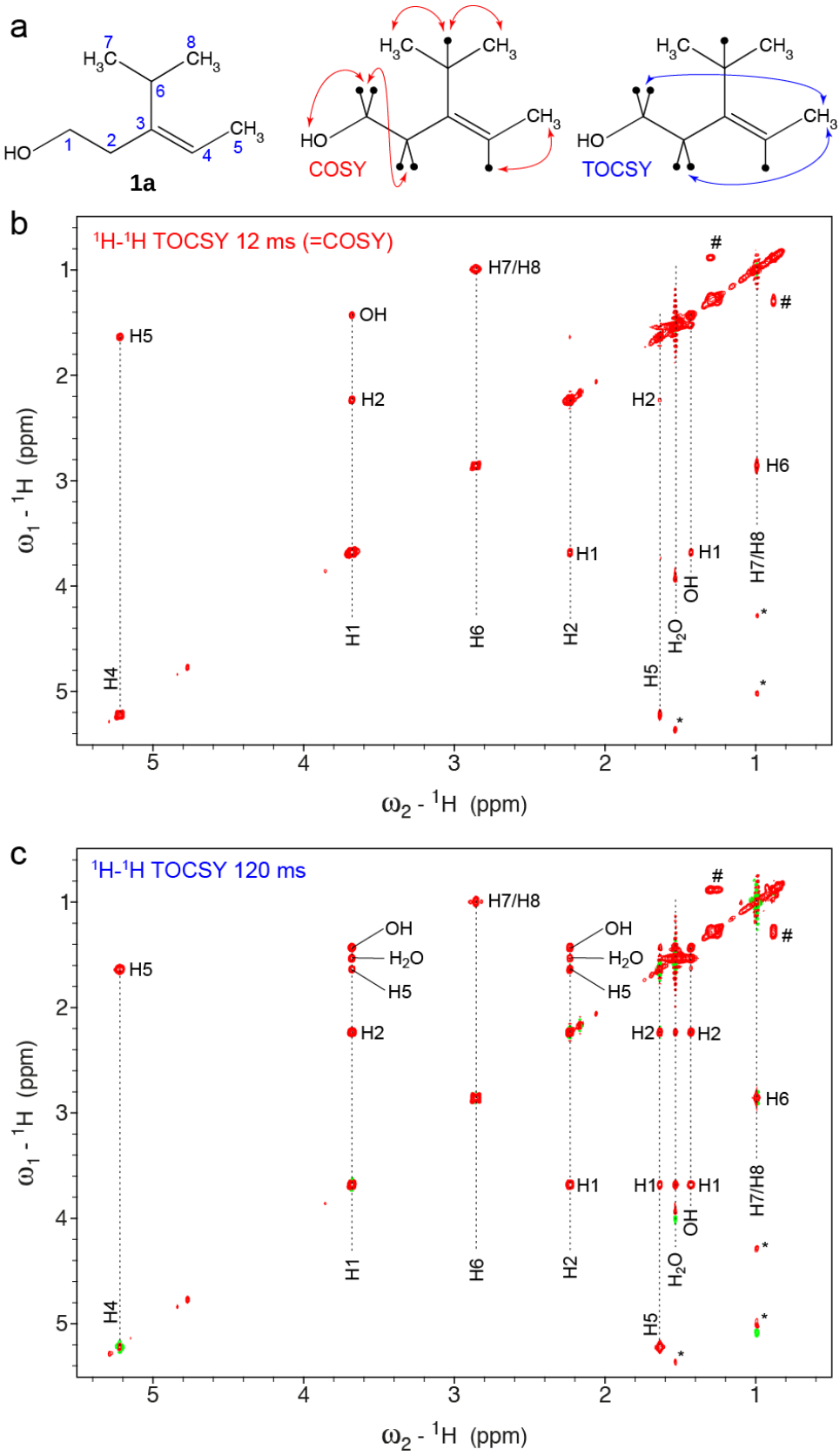


Figure 2. ^{1}H-^{1}H TOCSY spectra of **1a** with different mixing times (#: signals of solvent impurity hexane, *: artefacts in t_1). Figure: Dr. Mario Schubert.

As discussed *vide supra* the CH-group (H4) δ^{1}H at 5.22 ppm (Figure 1) and δ^{13}C at 120 ppm (Figure 3) indicates an involvement in a carbon-carbon double bond. Moreover, the cross-peaks in the ^{1}H-^{13}C HMBC spectrum between the CH-group (H6) from the *iso*-propyl group and the carbons C3-C4 as well as the cross-peaks between the CH_2-group (H2) and the carbons C3-C4 indicate that the *iso*-propyl group and the C_2-alkyl chain are connected to the double bond (Figure 3b).

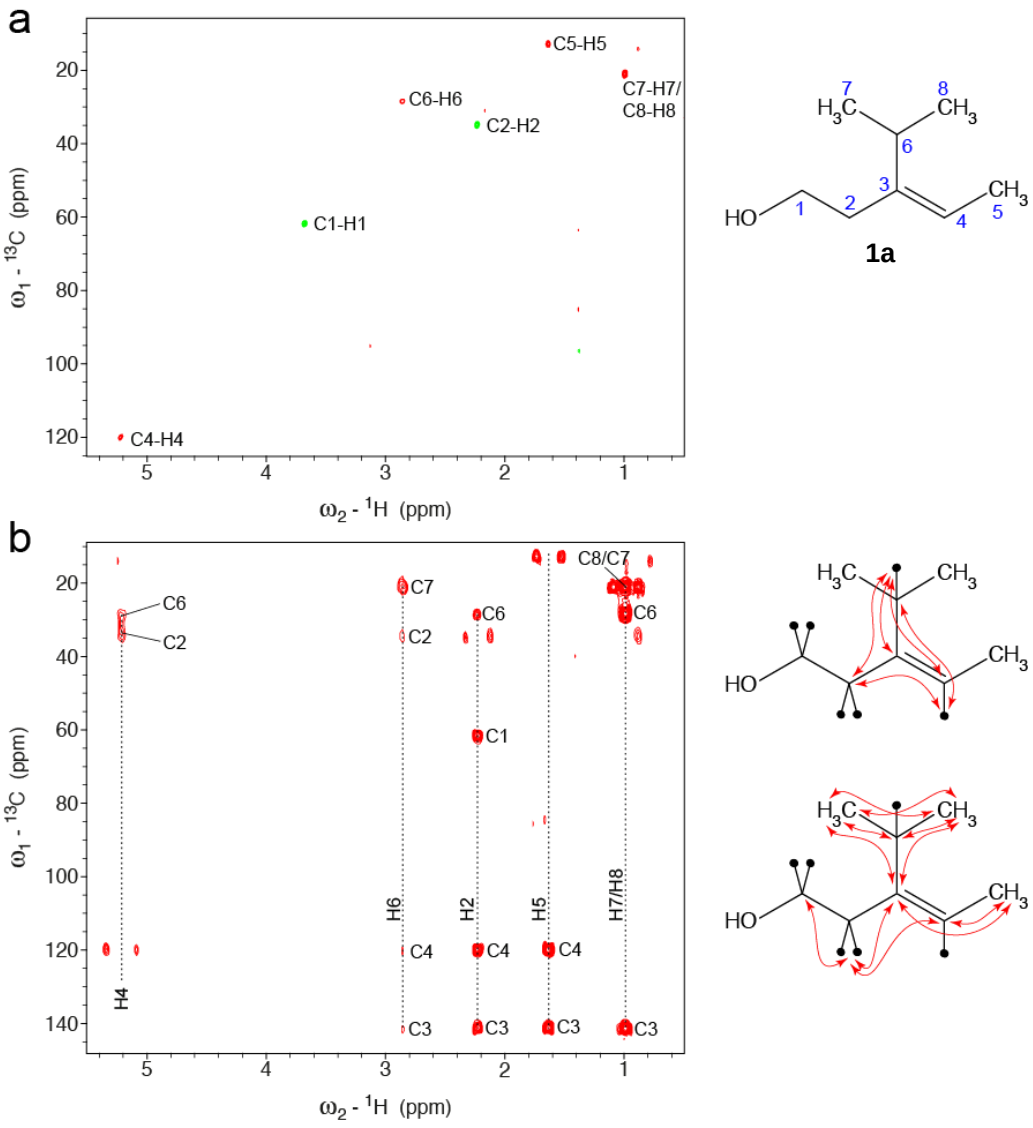


Figure 3. ^{1}H-^{13}C HSQC spectrum (a) and ^{1}H-^{13}C HMBC spectrum (b) of Gambanol (**1a**). Figure: Dr. Mario Schubert.

The cross-peak in the ^{1}H-^{13}C HMBC spectrum between the CH-group (H6) and the carbon C2 as well as the lacking cross peak of the methyl group (H5) with any carbon of the *iso*-propyl group or the C_2-alkyl chain points out a linkage at the same carbon (C3) whereas the methyl

group (H5) is attached to the other remaining carbon (C4) of the double bond (Figure 3b). Taking all these observations into account the chemical structure of the scent compound **1a** is presumed as depicted in Figure 1 - Figure 3. This presumed structure represents a thus far unknown natural product, for which the trivial name “Gambanol” (**1a**) was suggested, in honor of the Tropical Research Station La Gamba.

1.2 Aim of this Work

With the presumed chemical structure of the scent compound in hands, a collaboration between the working group of Dötterl (University of Salzburg) and Reiser (University of Regensburg) was promoted in order to synthesize the target molecule **1a** and compare the analytical data such as NMR and mass spectra with the natural compound derived from the dynamic headspace method.

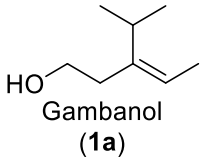


Figure 4. Predicted structure of the single dominant scent compound Gambanol (**1a**).

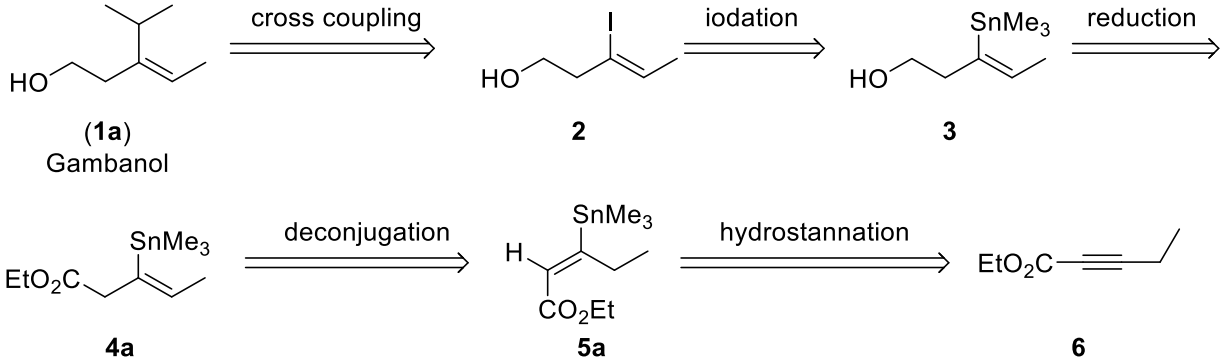
Furthermore, the synthesized compound **1a** should be applied to field bioassays in Costa Rica for verification. In addition, several derivatives of the target molecule Gambanol (**1a**) should be synthesized and tested *via* field bioassays in Costa Rica as well.

1.3 Synthesis of the Scent Compound Gambanol and Derivatives

In respect of the synthesis of the bioactive compound Gambanol (**1a**) two different challenges arise: Gambanol (**1a**) as a floral scent with a molecular mass of 128 g/mol is fairly volatile and therefore requires special care in handling. More particularly, regarding the removal of solvent residues in organic synthesis indicates the utilization of highly volatile solvent such as Et_2O and n-pentane for column chromatography purification.

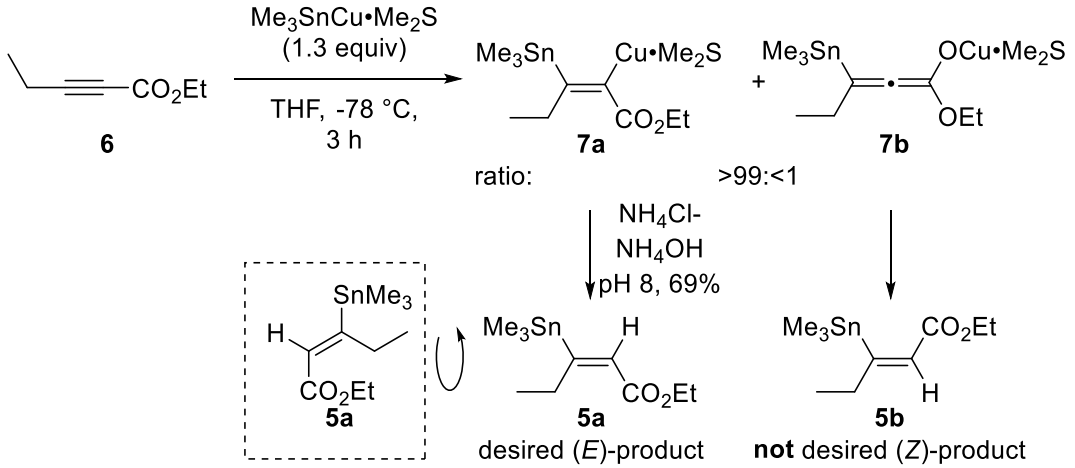
The most important challenge consists in achieving stereocontrol of the quaternary carbon center of Gambanol (**1a**), fortunately, the formation of the suitable precursor **2** with rigorous stereocontrol was reported by Piers [7–9] and coworkers. Aim of the work was to design in the last step of synthesis a suitable cross-coupling reaction with high stereocontrol employing alkyl halide such as isopropyliodide. Since cross-coupling reactions with high stereocontrol

additionally employing free alcohol groups and steric demanding secondary alkyl halides are hardly reported,[10] the outcome of the reaction was not only interesting regarding the natural product but also in terms of the methodology of the cross-coupling reaction.



Scheme 1. Retrosynthesis of Gambanol (**1a**).

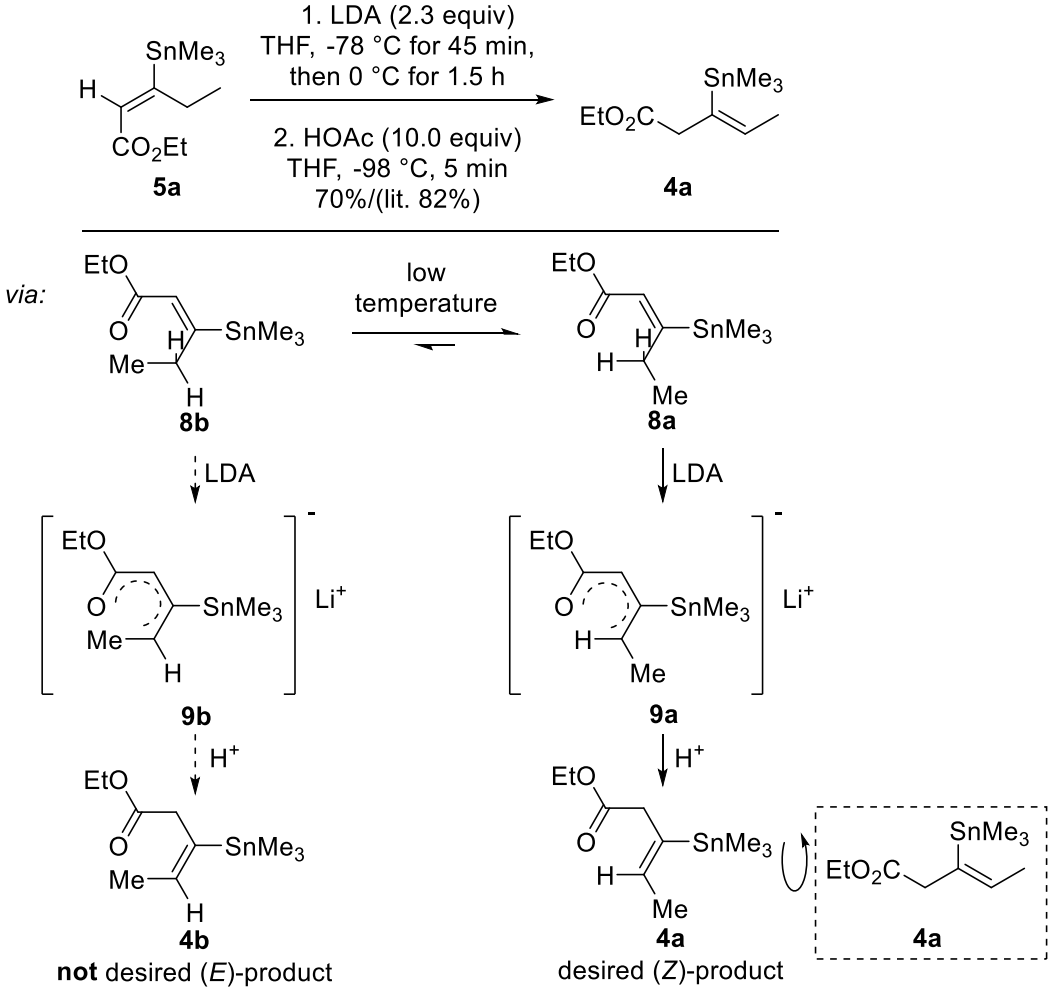
The synthesis of the precursor **2** is based on the hydrostannation of the *α*,*β*-acetylenic ester **6** giving rise to the (*E*)-configurated product **5a** with excellent stereoselectivity due to the use of $Me_3SnCu{\cdot}Me_2S$. Quenching of the intermediate **7a** with NH_4Cl-NH_4OH at ph 8 gave the desired (*E*)-configurated product **5a** in 69% yield. Interestingly, employing $[Me_3SnCuSPh]Li$ as hydrostannation reagent leads to the formation of the (*Z*)-configurated product **5b** *via* rearrangement of the corresponding allenoate **7b**. [7]



Scheme 2. Hydrostannation of *α*,*β*-acetylenic ester **6**.[7]

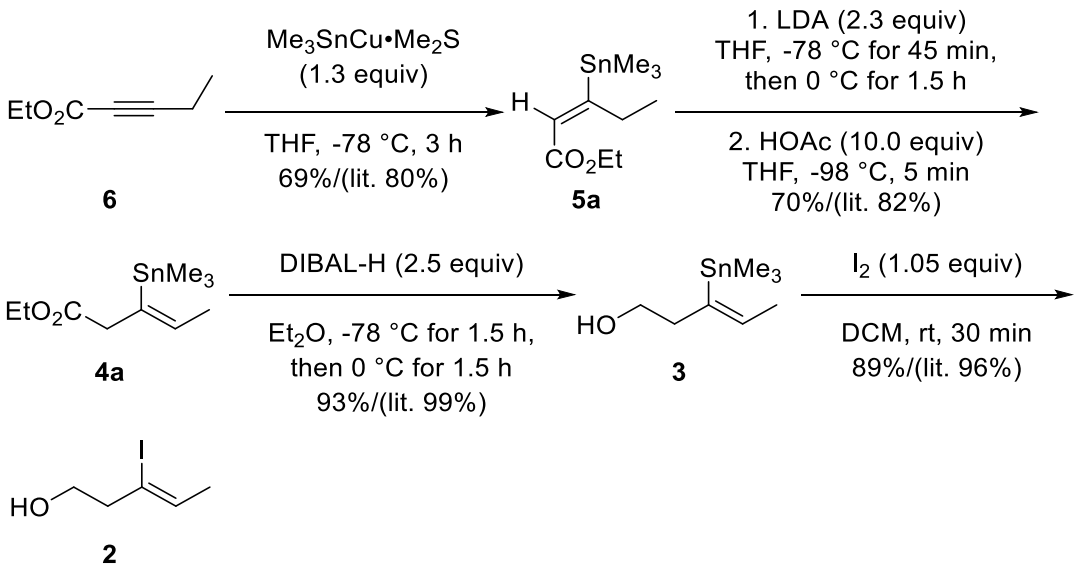
Regarding to the kinetically controlled deprotonation with LDA as strong base at low temperatures the desired (*Z*)-configurated product **4a** was exclusively formed by deconjugation of compound **5a** (Scheme 3). The transition state **9b** derived from conformer **8b** would be destabilized from a notable steric interaction between the methyl and ester group. The steric

interaction of the methyl and the $SnMe_3$ group derived from the transition state **9a** would be considerably smaller owing to the large length of carbon-tin bonds (~0.2 nm).[8]



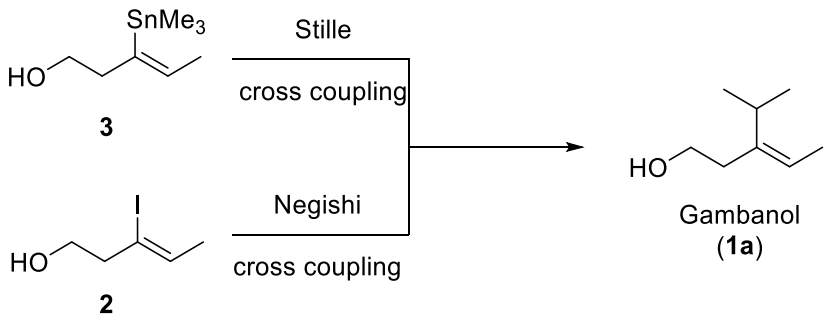
Scheme 3. Deconjugation of α,β-unsaturated ester **5a**.[8]

In the next step of synthesis reduction[9] of the ester **4a** employing DIBAL-H gave compound **3** in very good yield, subsequent iodation[9] of latter gave the final precursor **2** in very good yield as well and is depicted in Scheme 4.



Scheme 4. Synthesis of the precursor **2**.[7–9]

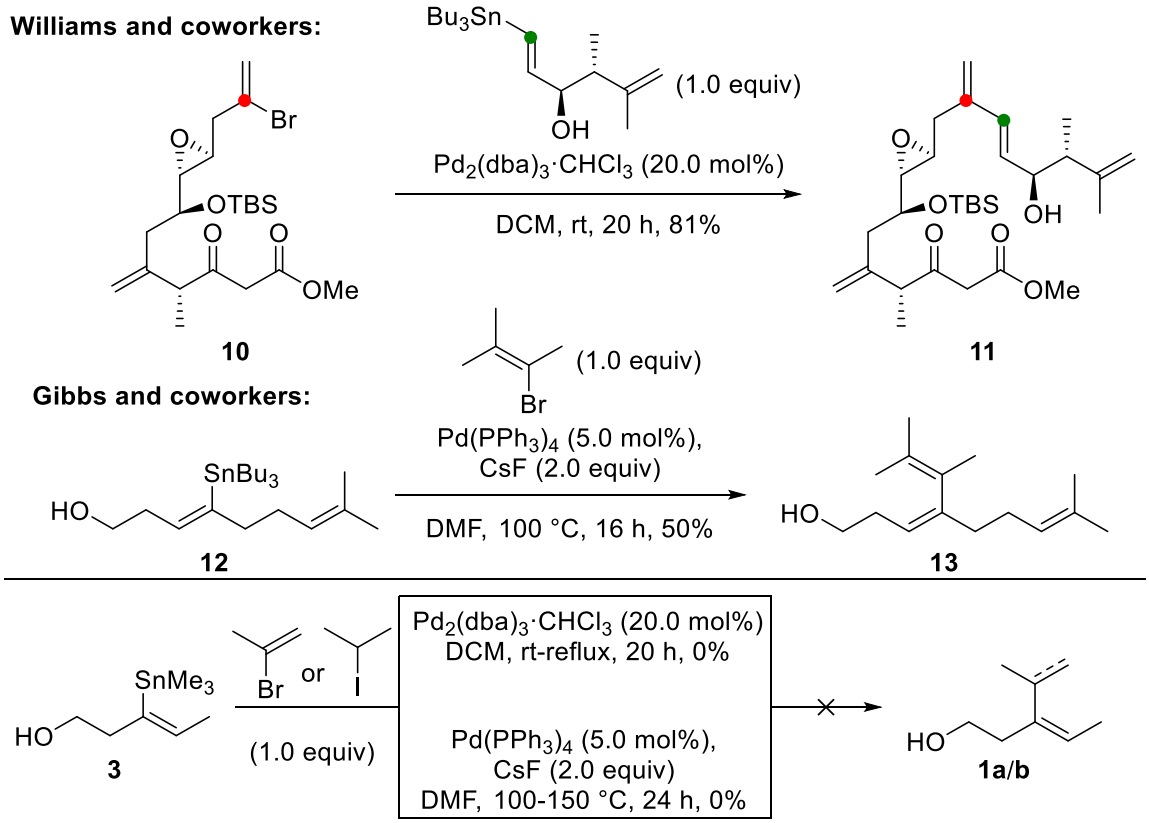
For the synthesis of the target molecule Gambanol (**1a**) two different strategies are arising: subjecting the tin compound **3** and 2-iodopropane to the Stille cross-coupling reaction or carrying out the Negishi cross-coupling reaction employing the precursor **2** and *iso*-propylzinc(II) iodide. Employing the Stille cross-coupling strategy would reduce the overall number of synthesis steps from five to four.



Scheme 5. Different strategies for synthesis of the target molecule Gambanol (**1a**).

Williams[11] and Gibbs[12] were reporting Stille carbon-(sp^2) carbon-(sp^2) cross-coupling reactions of compounds **10**/**12** yielding the desired products **11**/**13** containing free alcohol group employing $Pd_2(dba)_3{\cdot}CHCl_3$ or $Pd(PPh_3)_4$ as catalyst. Unfortunately, carrying out the Stille carbon-(sp^2) carbon-(sp^3) cross-coupling reaction with 2-iodopropane and compound **3** employing the latter reported protocols did not yield to any formation of the product (Scheme 6). Applying higher temperatures did also not influence the outcome of the reaction.

Interestingly, employing more reactive 2-bromoprop-1-ene as sp^2-coupling reagent did also not lead to any product formation of compound **1b**.

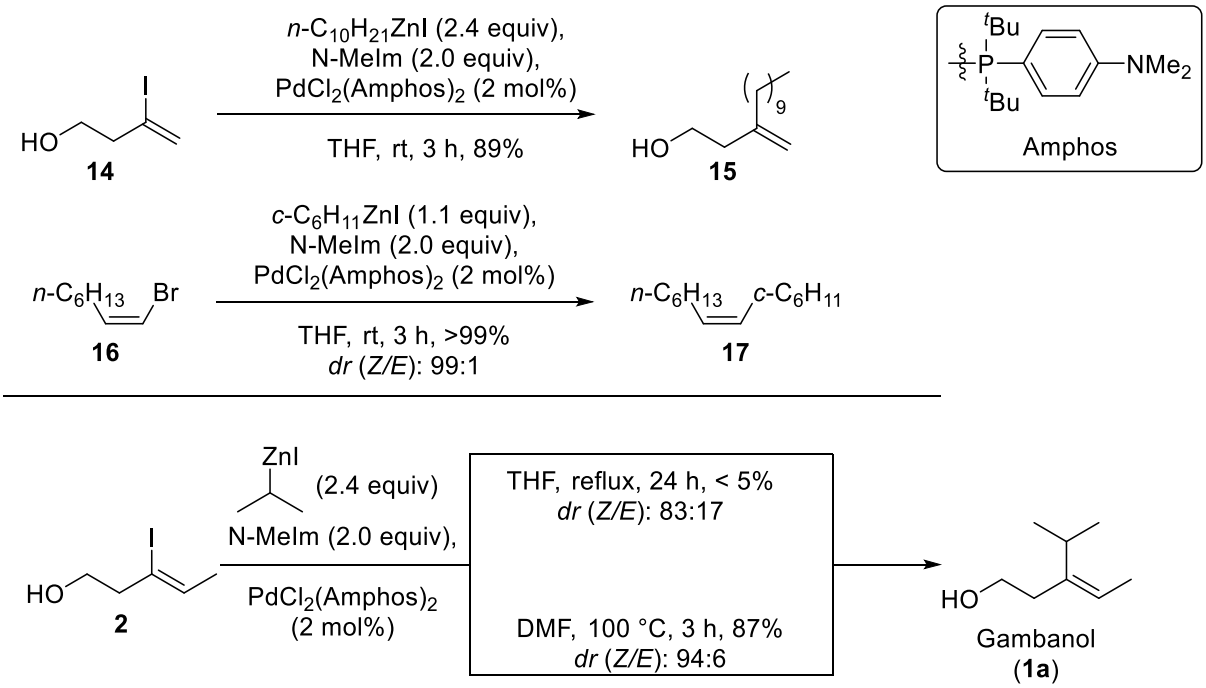


Scheme 6. Stille cross-coupling reactions reported by Williams[11] and Gibbs[12].

Since the synthesis of the target molecule Gambanol (**1a**) *via* Stille cross-coupling was not successful, a different route *via* Negishi cross-coupling reaction was attempted. In 2011, Lipshutz and coworkers[10] reported of struggles of Negishi cross-coupling reactions employing secondary compared to primary alkyl halides caused by the low reactivity of the secondary halides. Use of either $PdCl_2(PPh_3)_2$ or $PdCl_2$(DPEPhos) alone led to only traces of the desired product with secondary zinc iodides whereas the product was easily obtained employing primary zinc iodides. Screening of different Pd-catalysts led to an especially efficient combination of $PdCl_2$(Amphos)$_2$ (2.0 mol%)/*N*-MeIm. (2.0 equiv) converting alkenyl halides and secondary zinc iodides successfully in cross coupled products with complete retention of the configuration. In general, side reactions such as *β*-H elimination or homocoupling *via* ligand scrambling in cross-coupling reactions with alkylzinc halides can be avoided by using bidentate ligands to ensure saturation of the Pd coordination sphere.[13] In the report of Lipshutz it was assumed that the presence of stoichiometric amount of *N*-MeIm provides a coordinating ligand for both stoichiometric zinc and catalytic palladium thus allowing usage of simple Pd catalysts containing monodentate ligand Amphos.

Fortunately, regarding synthesis of Gambanol (**1a**) one successful conversion of compound **14** containing a free alcohol group was reported using 2.4 equiv instead of 1.1 equiv of the primary zinc iodide (Scheme 7). Furthermore, it was reported that secondary cyclohexyl zinc iodide was added to the primary carbon of the alkene **16** giving rise to the product **17** in excellent yield and diastereoselectivity. However, the combination of adding secondary zinc iodide to a secondary carbon of an alkene inhering a free alcohol group in one reaction was not depicted. Carrying out the Negishi cross-coupling reaction with the precursor **2** and *iso*-propyl zinc-(II)-iodide employing the reported conditions of Lipshutz the target molecule Gambanol (**1a**) was formed only in traces under refluxing conditions (Scheme 7), at room temperature no product formation was observed at all.

Negishi[14] reported that the use of polar aprotic solvents such as DMF, is critically important for palladium catalyzed cross-coupling reactions of (*Z*)-3-iodo-2-butenol with organozinc compounds since the use of THF instead of DMF led to dramatically low yields of less than 10%. Inspired by this observation the conditions for the cross-coupling reaction reported by Lipshutz were modified and fortunately, carrying out the reaction in DMF at 100°C led to the formation of the desired target molecule Gambanol (**1a**). In contrast to the reaction in THF the reaction mixture was completely dissolved in DMF due to higher polarity of latter. The advanced solubility and the well-known fact that DMF can act as a ligand in metal complexes[15] could be a possible explanation for the increased yield. Interestingly, the outcome of the diastereomeric ratio of Gambanol was dependent on the solvent in the reaction, employing DMF gave better selectivity compared to THF (*dr* (*Z*/*E*): 94:6 / 83:17).



Scheme 7. Negishi cross-coupling reported by Lipshutz[10] and synthesis of Gambanol (**1a**).

Table 1. Chemical shifts of the inflorescence headspace sample from *Syngonium hastiferum* referenced to TMS, measured in $CDCl_3$ at 298 K at a 600 MHz spectrometer.

position	δ ^{1}H [ppm]	integral, multiplicity	coupling constant [Hz]	δ ^{13}C [ppm]	^{13}C multipli-city	HMBC correlations [ppm]
1	3.68	2H, dt	Overlapped	61.7	CH_2	–
2	2.23	2H, t	6.6	34.9	CH_2	–
3	–	–	–	141.3	C	–
4	5.22	1H, q	6.7	120.0	CH	–
5	1.64	3H, d	6.7	12.8	CH_3	–
6	2.86	1H, sep	7.0	28.5	CH	–
7/8	0.99	6H, d	7.0	20.9	CH_3	–
OH	1.43	1H, t, broad	5.5	–	–	–

Table 2. Chemical shifts of synthesized (*Z*)-3-isopropylpent-3-en-1-ol Gambanol (**1a**) referenced to TMS, measured in $CDCl_3$ at 298 K at a 400 MHz spectrometer.

position	δ ^{1}H [ppm]	integral, multiplicity	coupling constant [Hz]	δ ^{13}C [ppm]	^{13}C multipli-city	HMBC correlations [ppm]
1	3.68	2H, dt	6.6, 5.5	61.8	CH_2	141.2, 34.9
2	2.23	2H, t	6.7	34.9	CH_2	141.2, 119.9, 61.8, 28.4
3	–	–	–	141.2	C	–
4	5.22	1H, q	6.8	119.8	CH	34.9, 28.4, 12.9
5	1.64	3H, d	6.8	13.0	CH_3	141.2, 119.9, 61.8, 34.8, 28.4, 21.0
6	2.86	1H, sep	7.0	28.4	CH	141.2, 119.8, 34.9, 21.0
7/8	1.00	6H, d	7.0	21.0	CH_3	141.2, 28.4, 21.0
OH	1.48	1H, t	5.4	–	–	–

Comparison of the NMR and mass spectra of the natural and synthesized compound Gambanol (**1a**) confirmed the correct prediction of the chemical structure very well, the spectra are in excellent agreement (Table 1, Table 2 and Figure 5).

However, it needs to be noted that the Gambanol compound derived from chemical synthesis in the laboratory comes in a diastereomeric mixture of 94:6. Nevertheless, it is obvious that the compound can be provided cleaner and supplied in greater amounts *via* the synthetic route, furthermore, synthesis was scaled up providing 1 g of the desired scent compound Gambanol (**1a**).

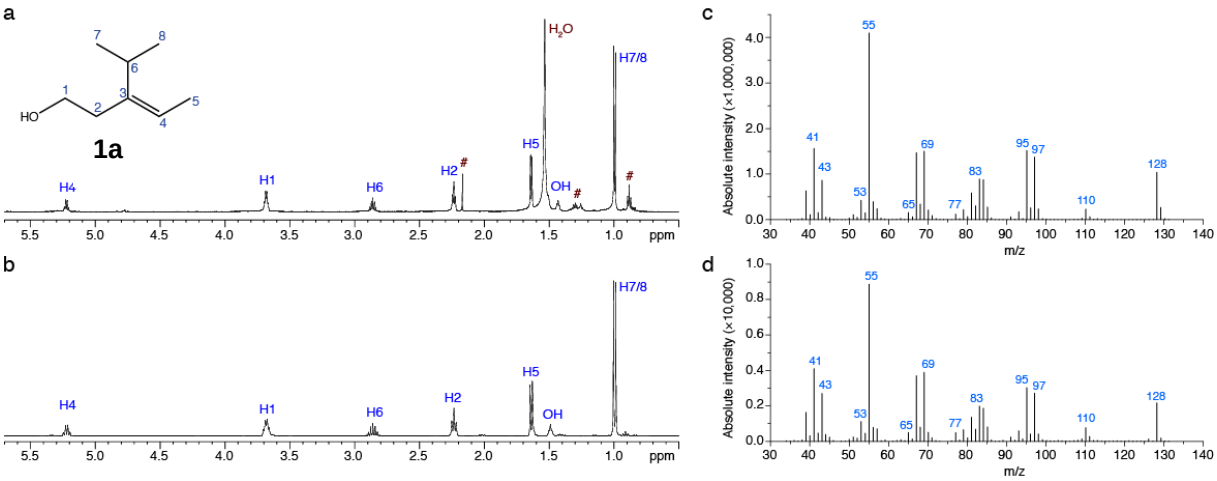
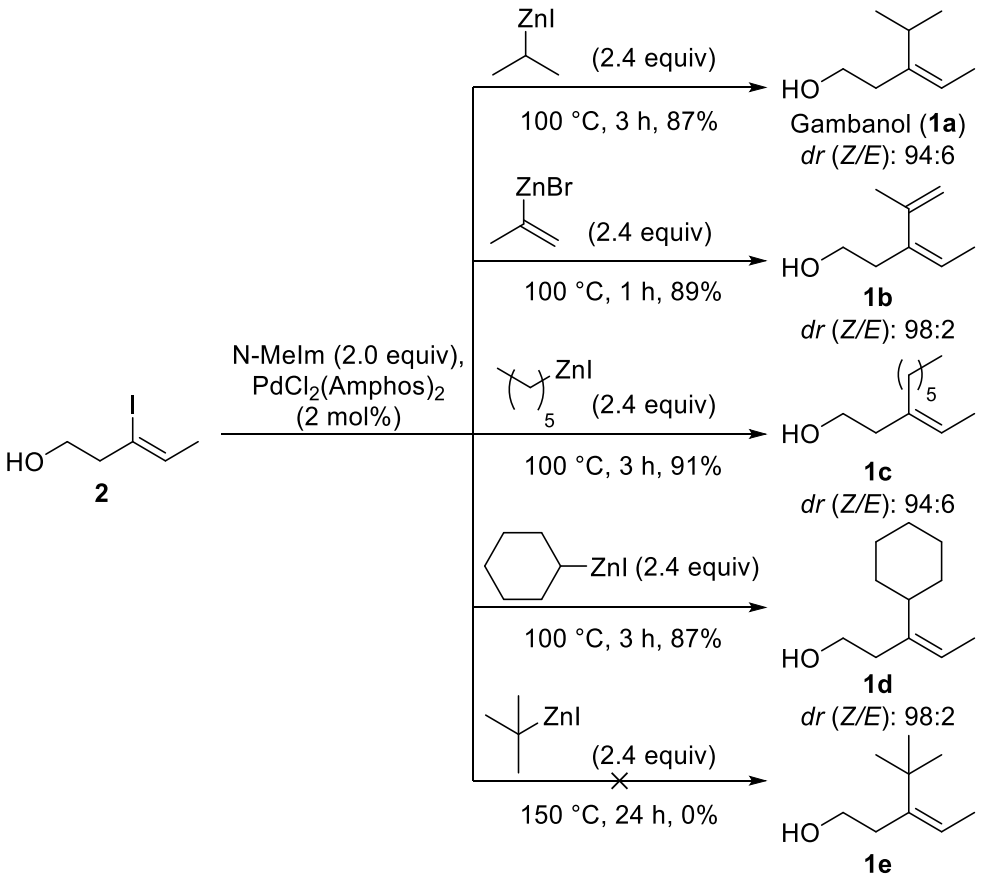


Figure 5. Comparison of NMR and MS spectra between the natural (top) and synthetic compound Gambanol (**1a**) (bottom). Figure: Dr. Mario Schubert.

With the optimized conditions in hands for the cross-coupling reaction, the next goal was the synthesis of various derivatives using different organozinc halides in order to explore the methodology of the reaction as well as the biological attraction of the synthesized compounds to the mirid bug *Neella* sp. nov..

Therefore, cross-coupling reaction was carried out with *iso*-propenyl zinc-(II)-bromide as secondary organozinc halide with sp^2-center. The Gambanol derivative **1b** was obtained in very good yield and even better diastereoselectivity (*dr* (*Z*/*E*): 98:2). The shorter reaction time can be explained due to the higher reactivity of the sp^2-center compared to the sp^3-center from *iso*-propyl zinc-(II)-iodide. Since cross-coupling with less reactive alkyl organozinc compounds is more demanding compared to alkenyl compounds the focus of synthesis was to explore the limitation of reaction regarding the grade of substitution of the sp^3-reaction center.



Scheme 8. Synthesis overview of Gambanol (**1a**) and derivatives.

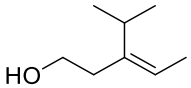
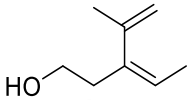
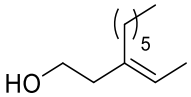
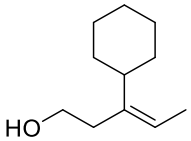
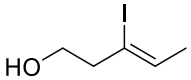
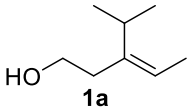
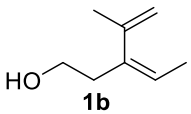
Since the reactivity of the *sp*^{3}-reaction center in this reaction decreases with the grade of substitution and concomitant steric bulkiness, successful synthesis of derivative **1c** in very good yield and selectivity (*dr* (*Z*/*E*): 94:6) utilizing primary zinc iodide was gratifying but not surprising (Scheme 8). Expanding the scope of secondary alkyl iodides, the synthesis of Gambanol derivative **1d** using cyclohexyl iodide was interesting regarding the increasing steric bulkiness compared to isopropyl iodide. Fortunately, the desired product **1d** was achieved in 87% and excellent selectivity in diastereomeric ratio (*dr* (*Z*/*E*): 98:2). Unfortunately, limitation of reaction was outlined employing tertbutyl iodide in the cross-coupling reaction as easiest tertiary alkyl iodide since no formation of product **1e** occurred even under reflux conditions.

1.4 Field Bioassays of Synthesized Gambanol and Derivatives

After successful synthesis of Gambanol (**1a**) and several derivatives **1b**-**d** the compounds were tested in field bioassays in Costa Rica in order to verify the scent compound Gambanol as the attractants for the pollinator *Neella* sp. nov. *in vivo*. Furthermore, testing of the synthesized derivatives should point out the selectivity of attraction level of the pollinators. In general, two-

choice-bioassays were carried out in the field as well as in a 9 x 9 x 3 m fine meshed cage containing several hundred individuals of the pollinators which were collected from fresh inflorescences of *Syngonium hastiferum*. The lures made of paper cones were containing the synthesized substrate **1**-**2** whereas the negative controls were exposed with solvent only. The following tests were carried out by Florian Etl and Prof. Dr. Stefan Dötterl in Costa Rica (Table 3 and Figure 6).

Table 3. Bioassays for synthesized Gambanol (**1a**) and derivatives **1b**-**d**/**2** tested against negative control or each other.

entry	substance	V per test [µL]	number of tests		Number of *Neella* sp. nov.		
			cage	field	cage	field	total
1[a]	 **1a**	100[b]	3	2	255	30	285
2[a]		100	-	3	-	>600	>600
3[a]	 **1b**	20	-	1	-	33	33
4[a]	 **1c**	40	-	1	-	0	0
5[a]	 **1d**	4	2	1	0	0	0
6[a]	 **2**	12	-	1	-	0	0
7[c]	 **1a**	7	-	1	-	41	41
	 **1b**	7				17	17

[a]Scent compound was diluted in Et_2O (100 µL) and offered on a filter paper. Lure and negative control (containing 100 µL Et_2O) were placed 2 m from each other, counting and collecting of the bugs over a time period of 90 min. [b]Scent compound diluted in Et_2O (ratio 1:100). [c]Scent compounds were diluted in Et_2O (100 µL) and offered on different filter papers. Lures were placed 1 m from each other, counting and collecting of the bugs over a time period of 90 min.

For the bioassays the scent compounds were diluted with Et_2O (100 µL) and offered on a filter paper 2 m next to the negative control (100 µL Et_2O only). The lures and the negative controls equipped with a video camera were offered at 7:00 in the morning for 90 min to the mirid bugs *Neella* sp. nov. that were counted and collected afterwards.In general, no bugs were detected on the negative controls. Gratifyingly, the Gambanol (**1a**) turned out to be the attractant for the bug *Neella* sp. nov., indeed, since the cage as well as the field experiments were positive. Overall, 885 individuals of *Neella* sp. nov. were attracted to the lures (255 in cage bioassays and 630 in field bioassays (Table 3 entry 1 and 2); sex ratio determined from a subset of 185 bugs: 50:50). The very similar isopropenyl derivative **1b** showed biological activity against the same mirid bug as well (Table 3 entry 3), however, in a two-choice-field bioassay with Gambanol 128 g/mol it turned out that the alkene derivative **1b** was not as biological active as Gambanol (**1a**) (17 vs. 41 individuals, Table 3, entry 7).

Unfortunately, neither of the other derivatives **1c**-**d** nor the precursor **2** showed any biological activity against *Neella* sp. nov. indicating a high selectivity level of chemical structure for the biological attractants. Furthermore, a second reason for the lack of attraction could be the higher molecular weight compared to Gambanol (**1a**) (128 g/mol) and isopropenyl derivative **1b** (126 g/mol). Since the volatility of organic compounds in similar substance classes decreases with higher molecular mass in general, the alkyl derivatives **1c** (170 g/mol) and **1d** (168 g/mol) as well as the iodide **2** (211 g/mol) do not seem to be suitable for excellent volatile scent compounds.

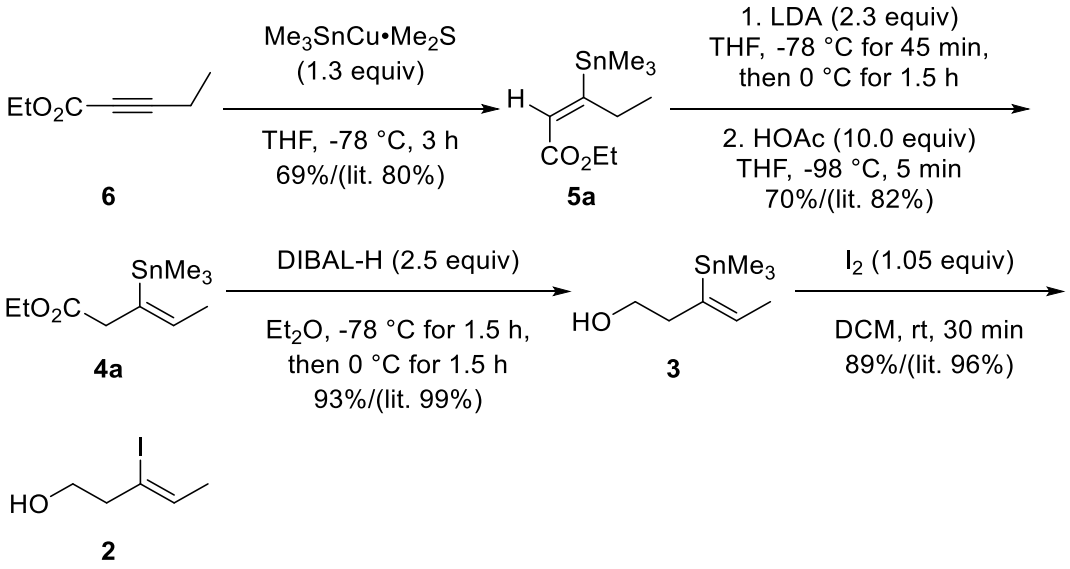
Figure 6. (a) Scented (female) phase of *Syngonium hastiferum*, with hundreds of individuals of the mirid bug species *Neella* sp. nov.. The bugs are covered with pollen grains from male flowers (b) and transfer the pollen to other plant individuals, where they walk on the receptive stigmas of female flowers (c). The same bugs are also attracted to inflorescences which were bagged to exclude visual cues (d), and to a paper cone containing synthetic (*Z*)-3-isopropylpent-3-en-1-ol “Gambanol” (**1a**) (e). Figure and Photographs: Florian Etl.

1.5 Summary

In a collaboration project with the working group of Dötterl (University of Salzburg) a thus far unknown natural product designated as “Gambanol” (**1a**) was determined and therefore synthesized in our working group to verify the predicted structure.

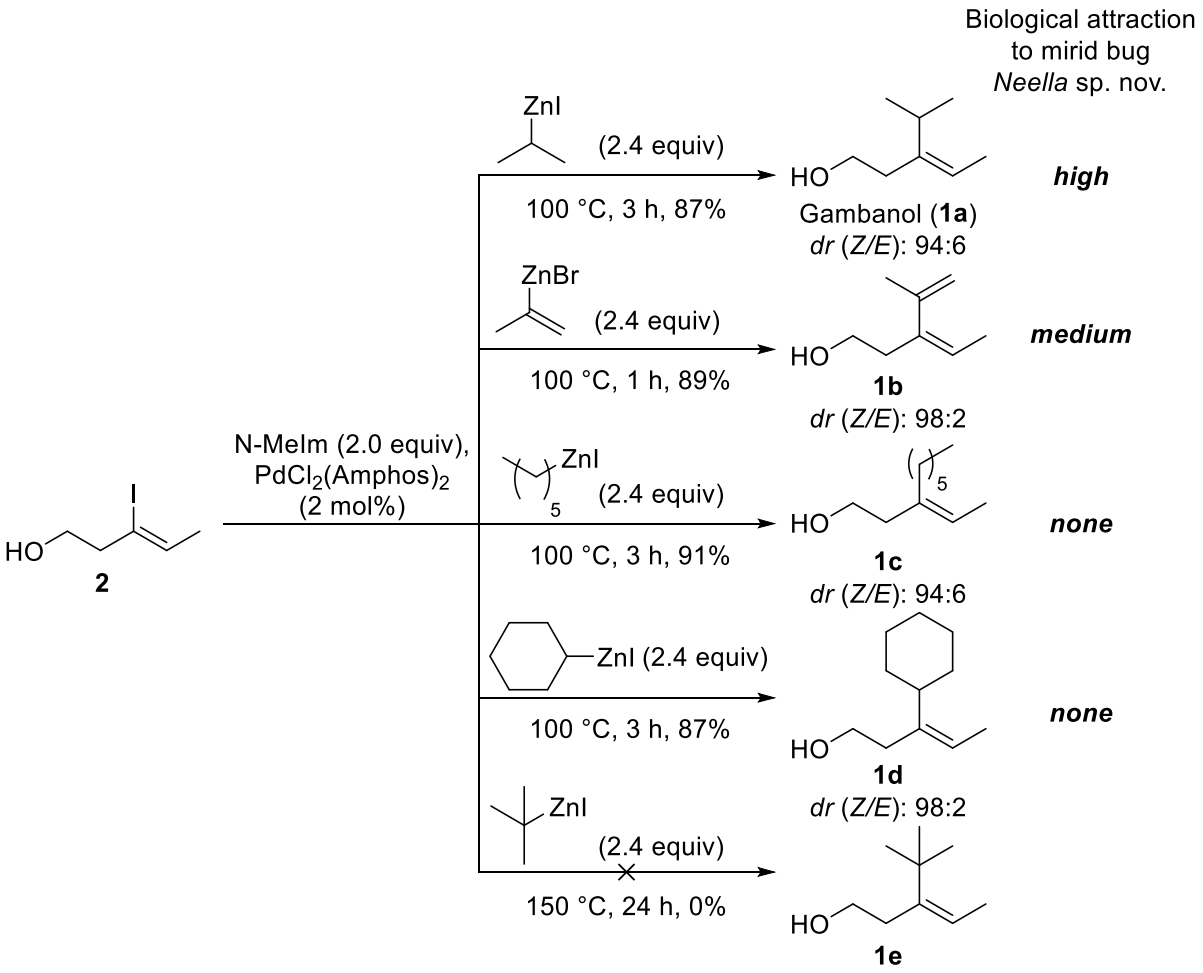
Gratifyingly, the synthesis of the required precursor **2** was well reported in literature starting from commercially available ethyl pent-2-ynoate **6**. Hydrostannation[7] of the alkyne **6** at -78 °C provided the desired (*E*)-configurated product **5a**. Stereoselective deconjugation[8] of latter using LDA as strong base was succeeded by carrying out the reaction at low temperatures

obtaining the desired product **4a**. Reduction of compound **4a** using DIBAL-H gave the alcohol **3** and subsequent iodation resulted in the precursor **2** for the Negishi coupling reaction.[9]



Scheme 9. Synthesis of the precursor **2**. [7–9]

The desired product Gambanol (**1a**) was received in a diastereomeric mixture of 94:6 *via* modification of the protocol reported by Lipshutz[10] and coworkers carrying out the reaction at 100 °C and using DMF as solvent (Scheme 10). Additionally, the isopropenyl derivative **1b** was synthesized as very similar derivative in very good yield and excellent diastereomeric ratio (*dr* (*Z*/*E*): 98:2). The synthesized Gambanol (**1a**) showed high biological attraction to the mirid bug *Neella* sp. nov. in field and cage bioassays carried out in Costa Rica. The similar derivative **1b** turned out to act as attractants as well, however, the activity of the derivative was less compared to the natural compound Gambanol (**1a**) (17 vs. 41 individuals, tested against each other with same amount of both compounds **1b** and Gambanol (**1a**) in a field experiment). For reason of methodology of Negishi cross-coupling reaction the linking of an alkenyl iodide with secondary alkyl halide was fascinating since this target is more demanding compared to coupling with primary alkyl halides, e.g. synthesis of product **1c** with primary hexyl zinc iodide. Fortunately, with the herein reported modification of the protocol of Lipshutz[10] synthesis of product **1d** with secondary cyclohexyl zinc iodide was successful with good yield and stereoselectivity, however, the received compounds **1c**-**d** did not show any biological activity to the mirid bug *Neella* sp. nov. in the bioassays in Cost Rica. Limitation regarding the cross-coupling reaction was shown as linkage of the alkenyl halide with tertiary alkyl iodide did not proceed at all.



Scheme 10. Synthesis and Bioassays of the synthesized target molecule Gambanol (**1a**) and derivatives.

2 Synthesis of Substituted Cyclopentenones

2.1 Introduction

The core structure of cyclopentenones is a very common motif in natural products and pharmaceuticals and therefore a valuable building block for asymmetric synthesis.[16]. The skeleton of the cyclopentenone core structure can be found in various bioactive target molecules, e.g. (3*E*,5*Z*)-misoprostol (**18**)[17], enisoprost (**19**)[18] , *ent*-phytoprostane E_1 (**20**)[19] and PGE_1 methyl ester (**21**)[20] (Figure 7).

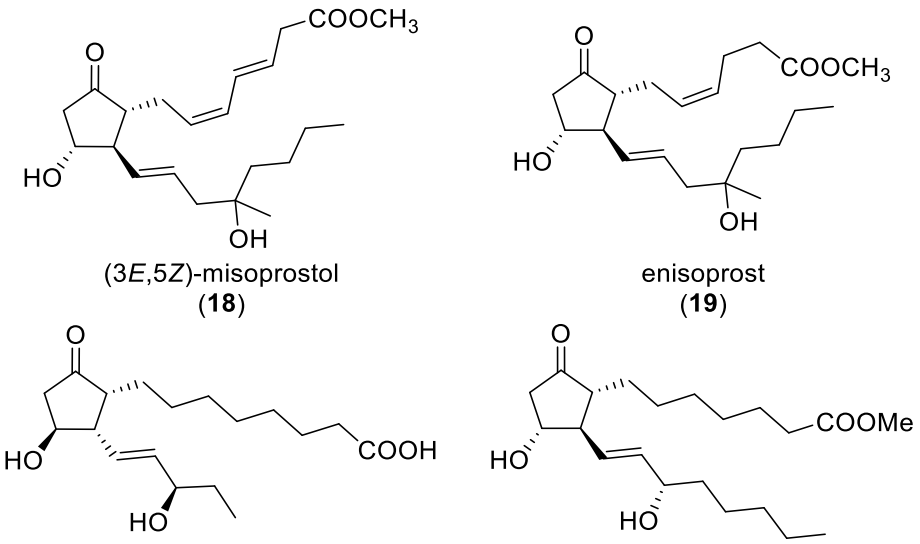
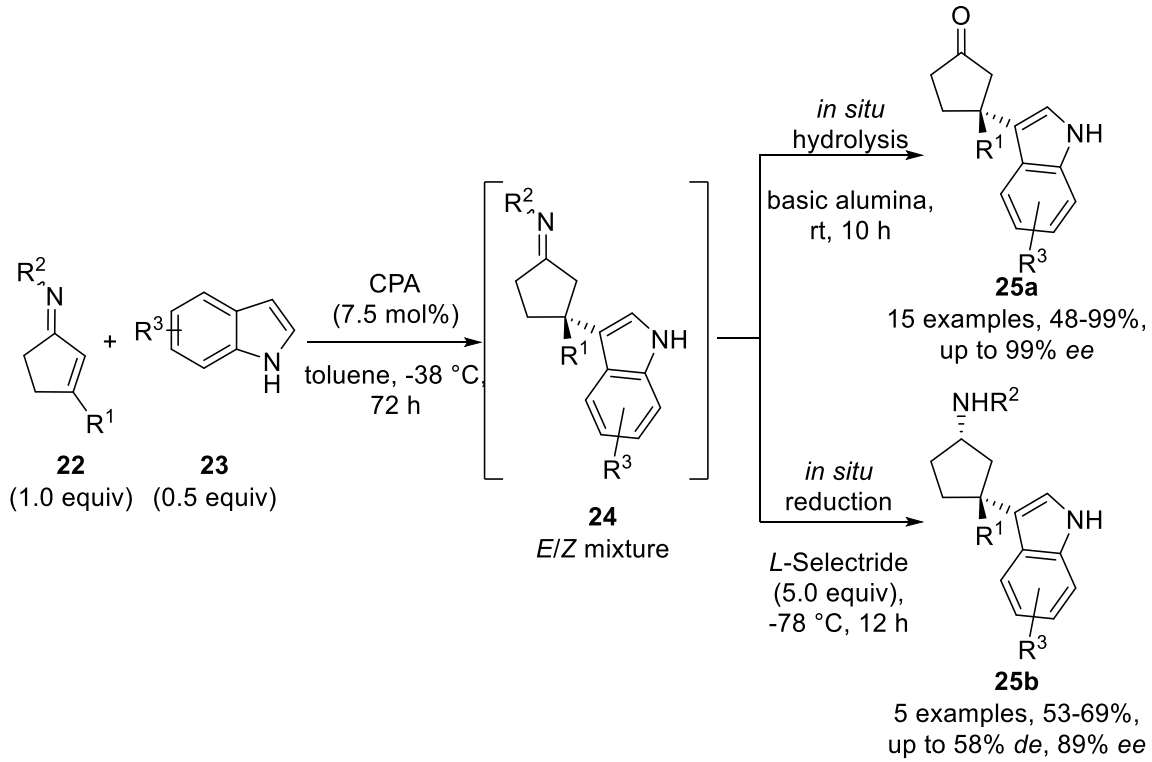


Figure 7. Cyclopentenone as core structure of bioactive compounds and natural products.

Due to the inherent enone system a broad variety of reactions, e.g. 1,2- or 1,4-addition, can be carried out for further transformation of the cyclopentenone synthon. In the last decades a high number of different protocols were reported providing chiral cyclopentenones, thereby two different strategies can be pursued.[21] On the one hand resolution methods give rise to chiral compounds, on the other hand the chirality can be introduced during the generation of the cyclopentenone core structure. In the following, a briefly overview of the recent publications dealing with enantio- or diastereoselective synthesis of cyclopentenones is reported.

In 2019, Yang and coworkers[22] have demonstrated the asymmetric Friedel-Crafts alkylation of indoles **23** with *β*-substituted cyclopentenimines **22** catalyzed by chiral phosphoric acids such as BINOL derivatives (Scheme 11). Depending on the reaction conditions hydrolysis of

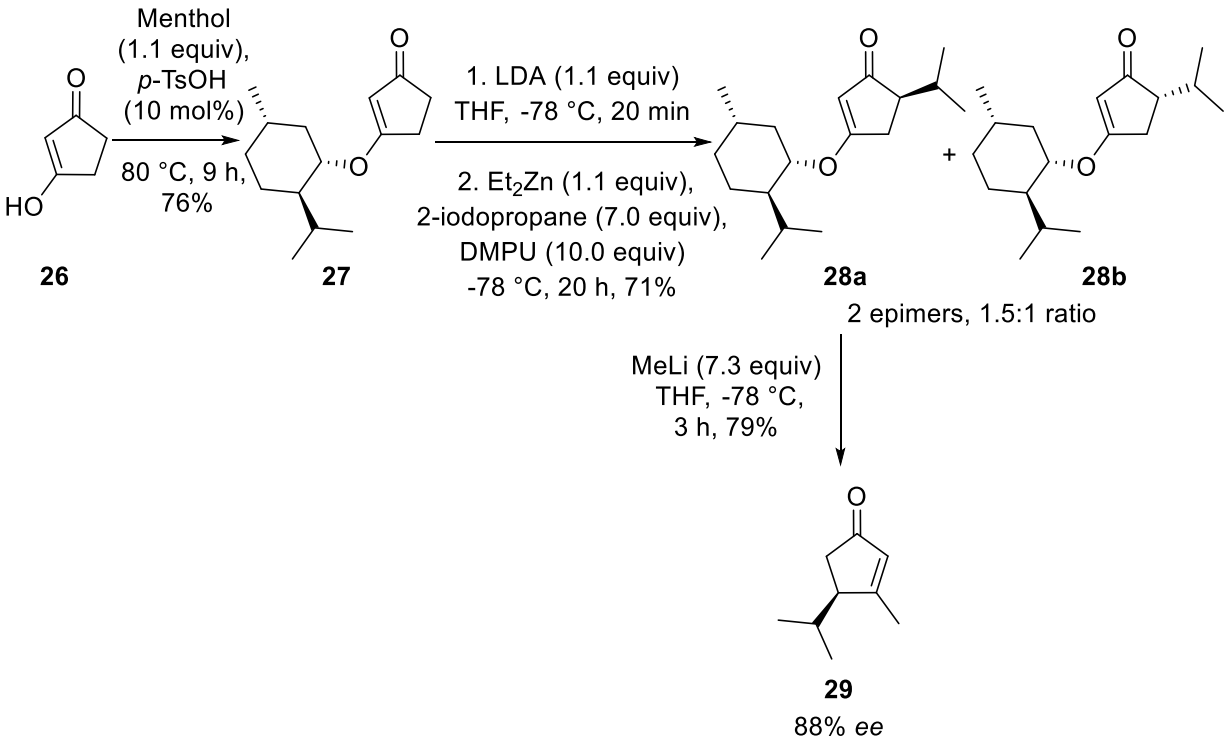
the imine **24** employing basic alumina or reduction with *L*-Selectride led to chiral building blocks, such as *β*-alkyl-*β*-indolyl cyclopentanones **25a** and cyclopentylamides **25b**, in "one-pot aldol reaction".



Scheme 11. Asymmetric Friedel-Crafts alkylation reported by Yang and coworkers[22].

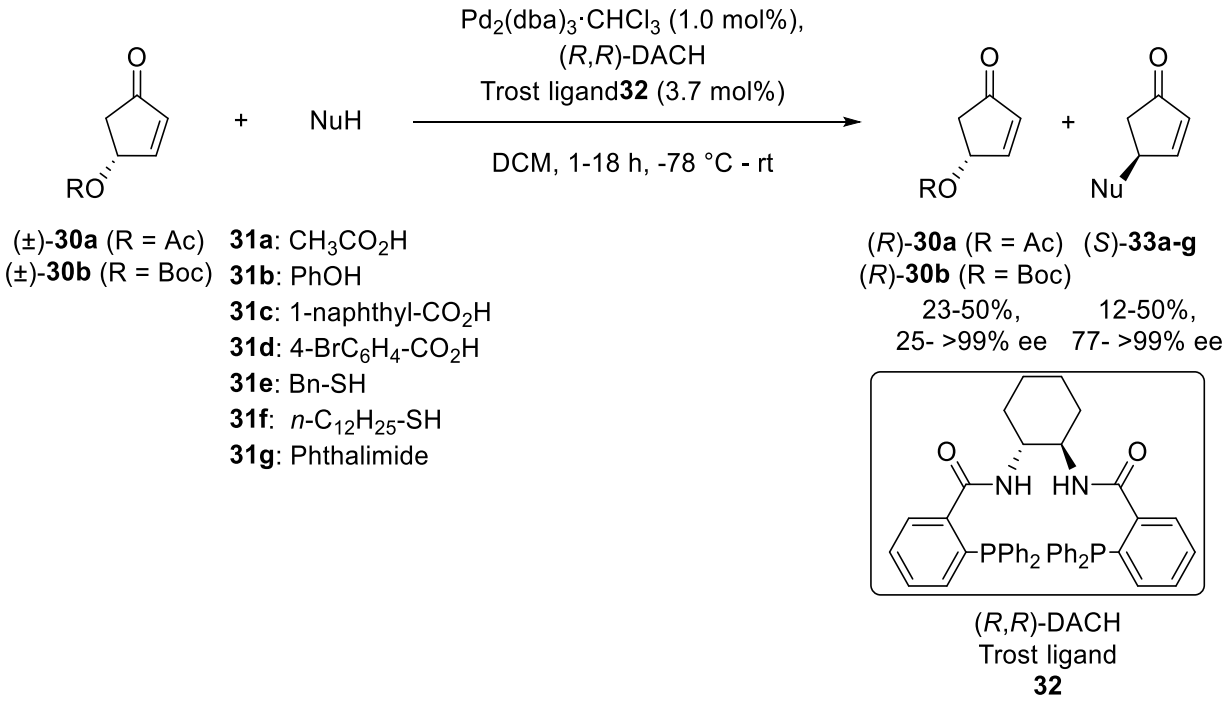
In view of resolution methods two different types have to be differentiated. In the dynamic kinetic resolution both enantiomers are in equilibrium in which ideally only one enantiomer is converted leading to a maximum yield up to 100%. Ward et. al.[23] demonstrated a proline catalyzed aldol reaction *via* dynamic kinetic resolution achieving a high enantioselective reaction. Typically, in a kinetic resolution of racemic mixtures the maximum yield of the desired enantiomer is up to 50% since only one enantiomer is converted.

Iimura and coworkers[24] reported a protocol using Menthol as chiral auxiliary. Condensation of 3-hydroxycyclopent-2-en-1-one (**26**) with menthol followed by *iso*-propylation gave 1.5:1 ratio of separable epimers **28a**-**b**. Subsequent methylation of the major epimer **28a** with MeLi achieved the desired product **29** with very good enantiomeric excess of 88% (Scheme 12).



Scheme 12. Menthol as chiral auxiliary reported by Iimura and coworkers.[24]

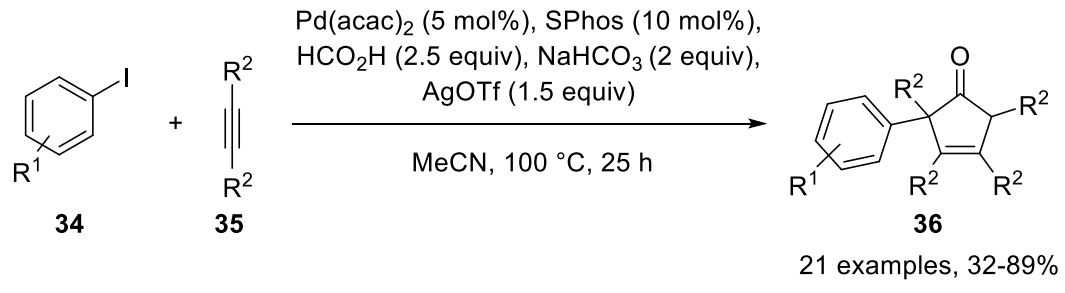
In 2013, Reiser and coworkers[25] described a new protocol for kinetic resolution of cyclopentenones **30** *via* Pd-catalyzed, asymmetric Tsuji-Trost allylation (further information see Chapter 2.4 (Asymmetric Tsuji-Trost Allylation)) giving rise to enantiopure compounds (*R*)-**30** and (*S*)-**33** (Scheme 13). For the kinetic resolution step activation of the hydroxy group was performed *via* Boc-protection.

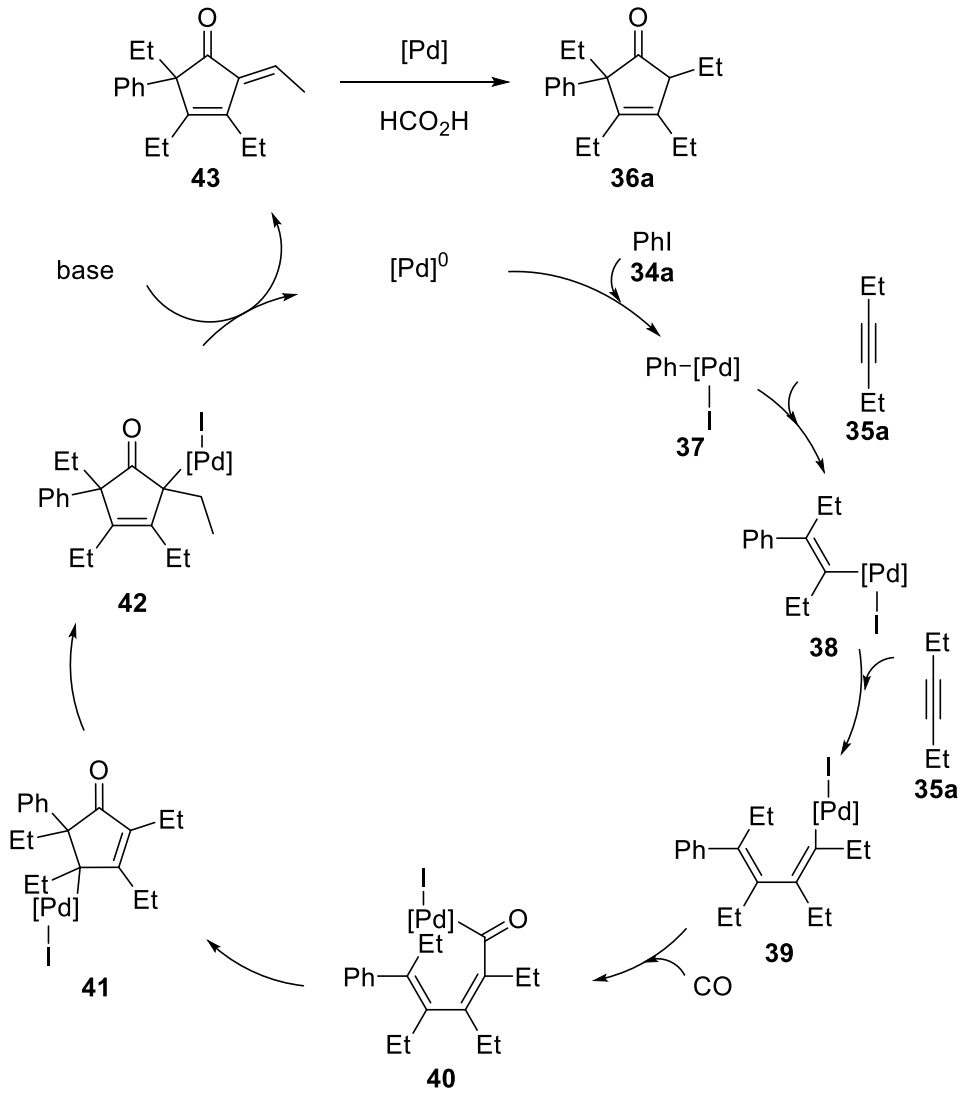


Scheme 13. Asymmetric Tsuji-Trost allylation for kinetic resolution of cyclopentenones demonstrated by Reiser and coworkers.[25]

Beside the kinetic resolution of racemic cyclopentenones stereoinduction can occur during the generation of the cyclopentenone structure. Therefore, Pauson-Khand reaction[26] and Nazarov cyclization[27] are very suitable reaction for asymmetric synthesis of five membered ring systems.

In 2019, Wu and coworkers[28] demonstrated a Pd-catalyzed carbonylative synthesis of substituted cyclopentenones **36** using alkynes **35** and formic acid as [CO]-source (Scheme 14). Although this report does not include the synthesis in an enantioselective fashion, the proposed mechanism is fascinating and depicted in Scheme 14. The mechanism is following the Pauson-Khand reaction pathway originally proposed by Magnus and coworkers[26] in 1985. After oxidative addition of Pd^0 with iodobenzene **34a** the intermediate **37** is generated followed by insertion of alkyne **35a** creating the intermediate **38**. Insertion of a second equivalent of alkyne **35a** produces the complex **39** subsequently followed by insertion of CO generating the acyl Pd-complex **40**. Ring closing step provides complex **41** with Pd in C4-position of the cyclopentenone structure. Finally, reductive elimination of intermediate **42** regenerates Pd^0 source and product **43** that is hydrogenated to the final product **36a** *via* Pd-catalyzed reduction with formic acid as reductant. In summary, formic acid is used as hydrogen source in the last step as well as carbon monoxide source for insertion step.

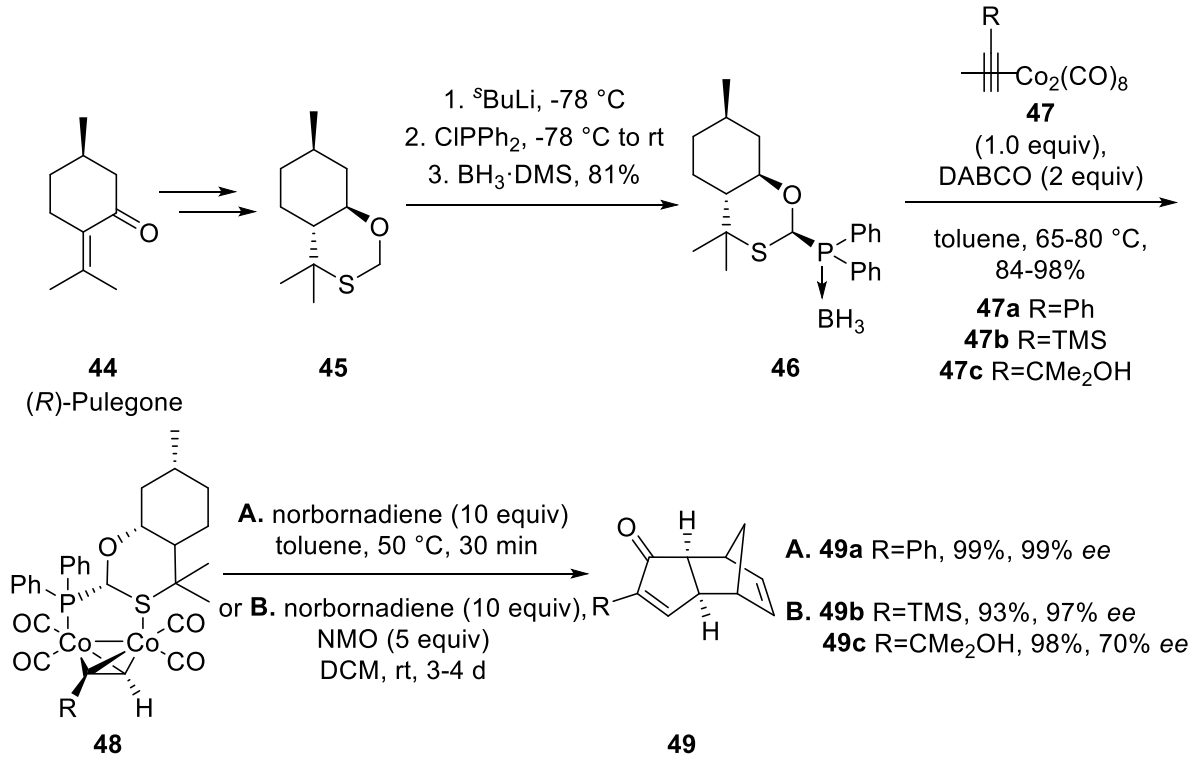




Scheme 14. Pd-catalyzed carbonylative synthesis of substituted cyclopentenones reported by Wu and coworkers.[28]

Verdaguer and coworkers[29] demonstrated an asymmetric intermolecular Pauson-Khand reaction using natural (*R*)-Pulegone **44** as chiral auxiliary that was further transformated[30] into oxathiane **45** (Scheme 15). Latter is deprotonated by ^{s}BuLi, alkylated with chlorodiphenylphosphine and stabilized with BH_3·DMS achieving shelf-stable compound **46**.

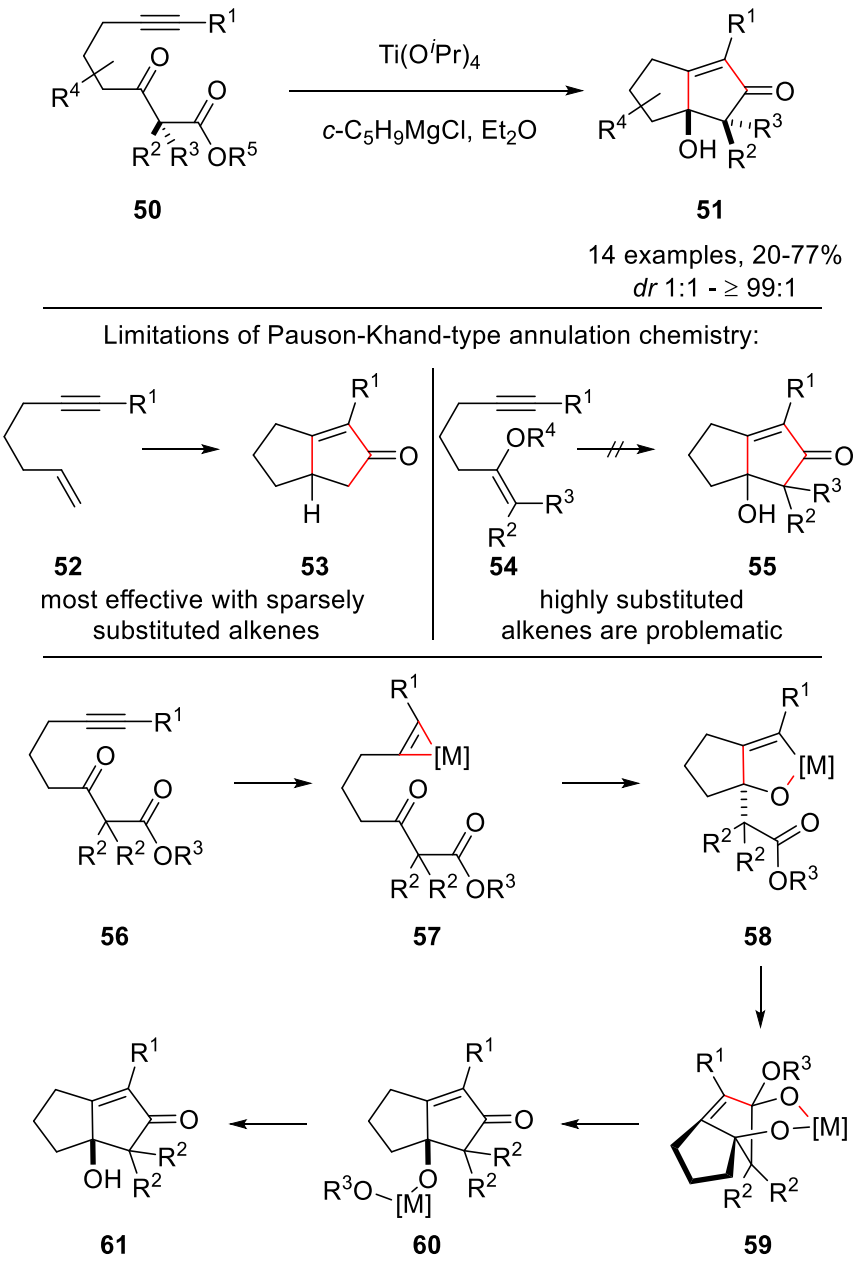
Heating the BH_3 stabilized ligand **46** in toluene with DABCO in presence of dicobalt hexacarbonyl complex **47** derived from terminal alkyne gave rise to chiral complex **48**, the stereochemistry of latter was dependent on the substituent R. Whereas the phenylacetylene complex **47a** led to diastereomeric mixture of compound **48a**, employment of complexes **47b**-**c** led to highly selective formation of phosphines **48b**-**c**. Reacting complex **48a** with norbornadiene, the Pauson-Khand reaction occurred in very stereoselective way achieving the final product **49** in enantiopure fashion under thermal conditions. For complexes **48b**-**c** in presence of *N*-methyl morpholine *N*-oxide (NMO) the products **49b**-**c** could be achieved with better enantioselectivity. The role of NMO is fascinating since the enantioselectivity of the reaction was increased but not the reaction rate. Furthermore, it was observed that in related compounds CO promotes the epimerization of the complex, probably through the intermediacy of nonchelated species. Therefore, it was proposed that N-methyl morpholine N-oxide (NMO) prevents the presence of any free CO in the reaction medium.



Scheme 15. Asymmetric intermolecular Pauson-Khand reaction described by Verdaguer and coworkers.[29]

In 2019, Micalizio and coworkers [31] demonstrated a diastereoselective method for synthesis of fully substituted cyclopentenones **51** *via* intramolecular alkyne-β-keto ester coupling since synthesis of highly substituted alkenes are problematic *via* Pauson-Khand-type annulation (Scheme 16).[32] In the proposed mechanism formation of a metallacyclopropene **57** would

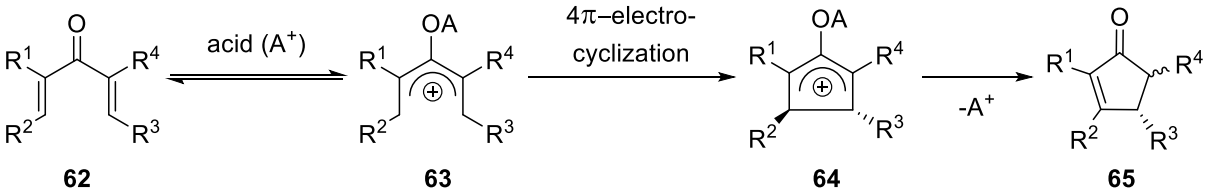
occur followed by intramolecular reaction with the proximal ketone producing the oxametallacyclopentenone **58**. Further it is supposed that formation of the five membered ring leads to a bridged polycyclic metal alkoxide **59**, subsequent rearrangement to the intermediate **60** and hydrolysis of latter give rise to the final product **61**.



Scheme 16. Intramolecular alkyne-β-keto ester coupling reported by Micalizio.[31]

Beside the Pauson-Khand reaction the Nazarov cyclization[27] is very suitable for synthesis of chiral five membered ring systems as well, and inheres the generation of a pentadienyl cation **63** in presence of acids followed by 4π-electrocyclization process leading to the intermediate

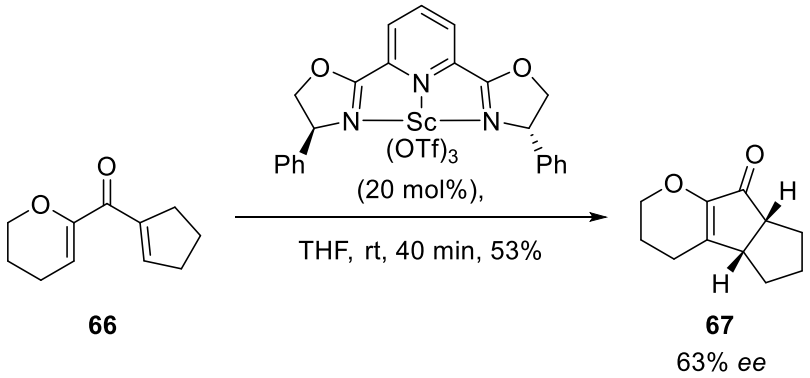
64. Cleavage of the catalyst results in the formation of the final cyclopentenone **65** (Scheme 17, more detailed Nazarov type mechanism is described in Chapter 2.3 (Piancatelli Rearrangement)).



Scheme 17. Nazarov cyclization of dienone **62**. [21]

Unfortunately, the number of publications for asymmetric catalyzed Nazarov cyclization is moderate. Eventually the spatial distance between the carbonyl group connected to the chiral catalyst and the newly generated stereocenters is responsible for the limitations of this synthetic approach. Moreover, the final enantioselectivity of the reaction is decreasing due to potentially racemization of the final cyclopentenone product if the 4π-electrocyclization process is too slow.[21]

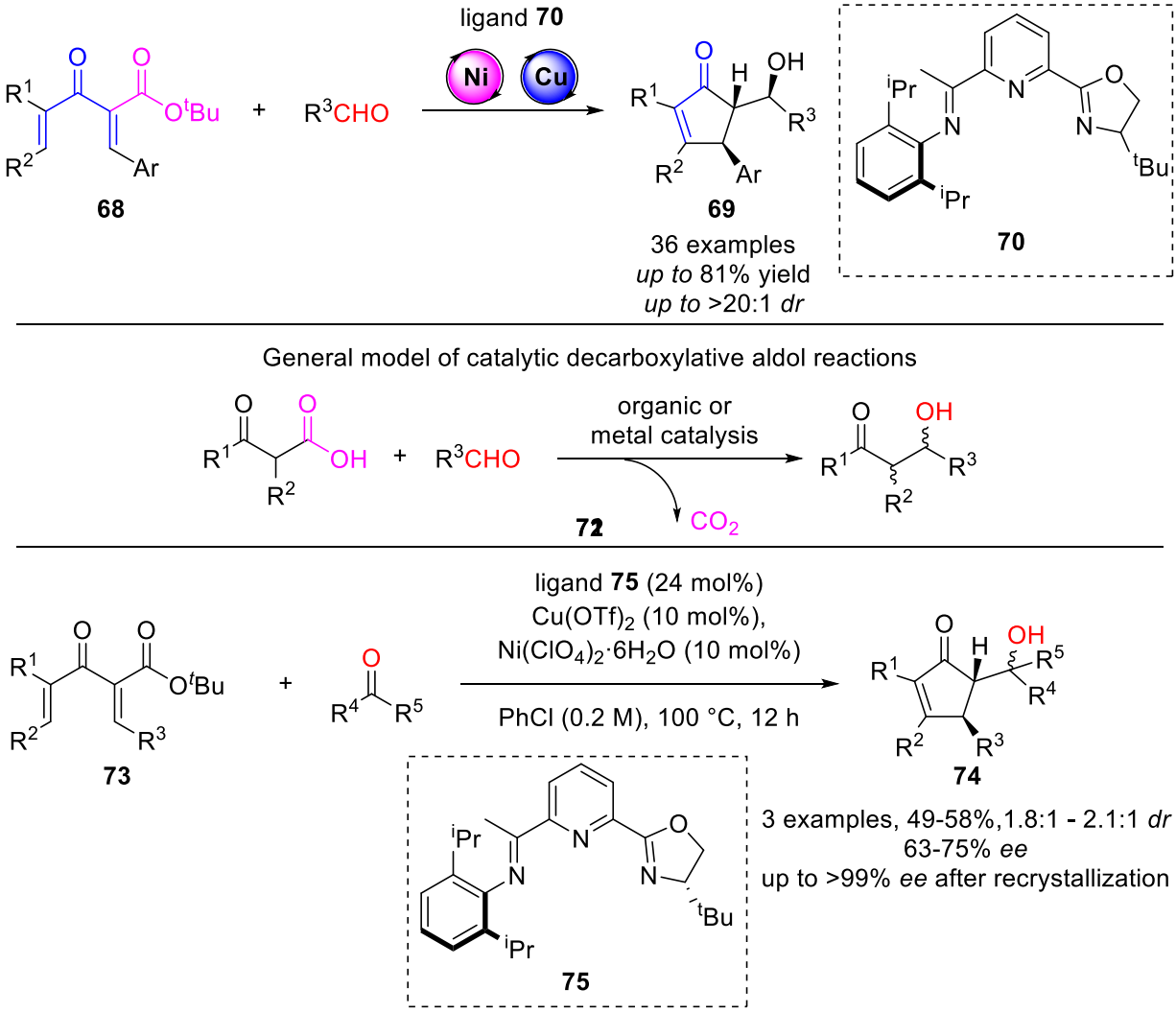
Trauner and coworkers [33] described a Nazarov cyclization promoted by a chiral scandium triflate pyridine-bisoxazoline complex achieving the tricycle **67** in 63% enantiomeric excess (Scheme 18).



Scheme 18. Nazarov reaction promoted by chiral scandium triflate pyridine-bisoxazoline complex reported by Trauner and coworkers.[33]

In 2018, Lu and coworkers[34] developed a Nickel/Copper dual catalysis for sequential Nazarov cyclization and decarboxylative aldol reaction with external aldehyde in one pot fashion. In general, it is well known that *α*-ester divinyl ketones subjected to a Nazarov cyclization can generate cyclopentadienolate intermediates that can be trapped by various electrophiles.[35] Employing oxazoline iminopyridine **70** as ligand in this transformation three new stereocenters were generated with high diastereoselectivites giving rise to the fully substituted

cyclopentenone **69** in good yields. A general model of catalytic decarboxylative aldol reaction using external aldehyde is depicted in Scheme 19. Furthermore, attempt of chiral synthesis was reported using chiral ligand **75**, however, the diastereocontrol of the stereocenter in C1`-position of the products **74** was only moderate with values of 1.8:1 - 2.1:1 *dr*.

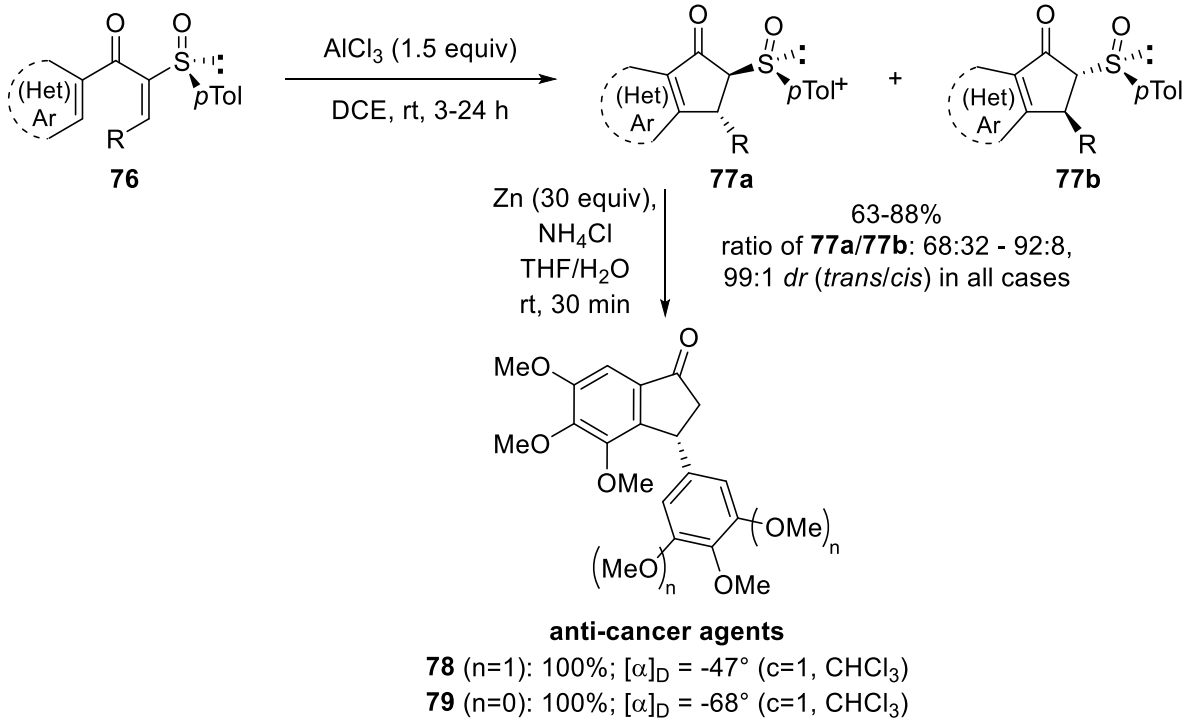


Scheme 19. Nickel/Copper dual catalysis for sequential Nazarov cyclization and decarboxylative aldol reaction developed by Lu and coworkers. [34]

A torquoselective[1] Nazarov cyclization mediated by chiral sulfoxide was reported by Roig and coworkers[37] in 2018 (Scheme 20). The reaction occurred between activated dienones **76** containing an aromatic moiety as an electron-donating group. The chiral sulfoxide act as intramolecular chiral inductor as well as electron-withdrawing group, $AlCl_3$ was employed as

[1] Torquoselectivity: Stereoselectivity observed in electrocyclic reactions, defined as “the preference for inward or outward rotation of substituents in conrotatory or disrotatory electrocyclic reactions." [36].

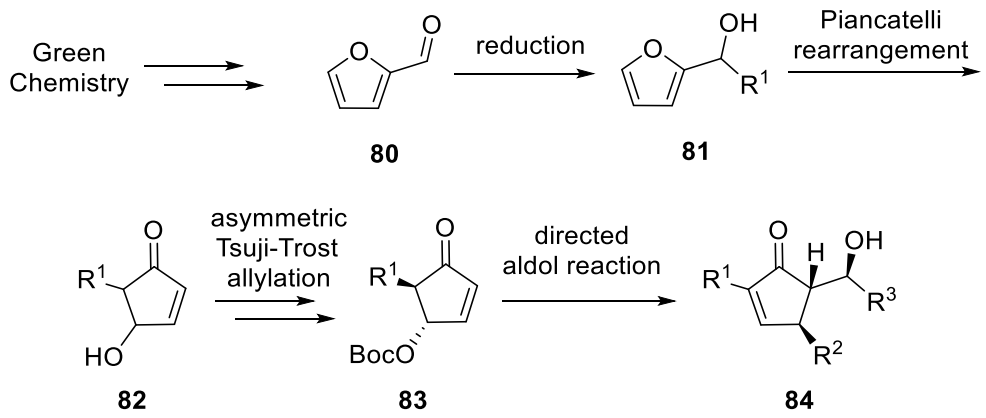
promoter for the reaction. The isomers **77a** and **77b** were achieved in moderate to very good yields in the range of 63-88% as well as very good torquoselectivities up to 92:8, moreover the diastereomeric ratio of 99:1 (*trans*/*cis*) of all obtained compounds was excellent. Fortunately, application of this method was demonstrated by reductive cleavage of the C-S bond of two specified substrates giving rise to two enantiopure anti-cancer agents **78** and **79** in quantitative yield.



Scheme 20. Torquoselective Nazarov cyclization mediated by chiral sulfoxide described by Roig and coworkers.[37]

2.2 Aim of this Work

Starting from furfural **80** that is a suitable outcome of Green Chemistry, investigation on synthesis and reaction methodology of substituted cyclopentenones should be carried out following the work of Ulbrich[38,25] and Arisetti[39] from the working group of Reiser. Key step of the formation of cyclopentenones **82** is the Piancatelli rearrangement followed by activation of the hydroxyl group for the subsequent asymmetric Tsuji-Trost allylation providing enantiomeric substrates **83** (Scheme 21). In the last step of the synthesis directed aldol reaction applying various nucleophiles and electrophiles give rise to 2,4,5-trisubstituted cyclopent-2-en-1-ones **84** with complete stereocontrol of the three new formed stereocenters.

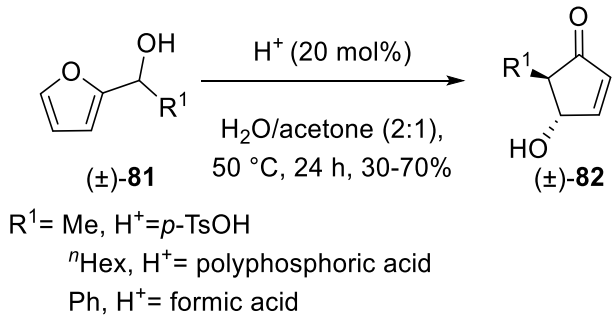


Scheme 21. Aim of the work.

2.3 Piancatelli Rearrangement

2.3.1 Introduction

Acid catalyzed, water mediated rearrangement of 2-furylcarbinols (±)-**81** into 4-hydroxy-5-substituted cyclopent-2-en-1-ones (±)-**82** was discovered by Piancatelli[40] in 1976 stirring the reaction mixture at 50 °C for 24 hours employing a 2:1 mixture of water and acetone.

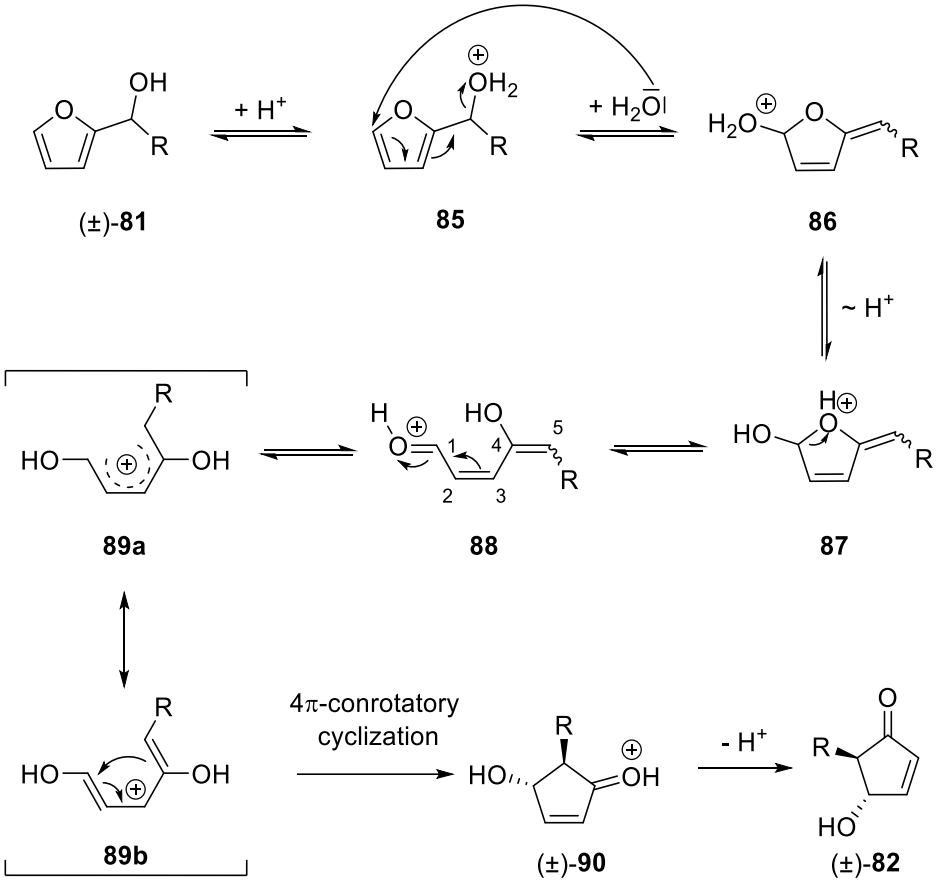


Scheme 22. Rearrangement of 2-furylcarbinols (±)-**81** into 4-hydroxycyclopentenones (±)-**82** discovered by Piancatelli[40].

Piancatelli proposed that the formation of the oxonium ion **86** is driven by nucleophilic attack of water and subsequent dehydration sequence (Scheme 23). Prototropic shift generates intermediate **87** followed by ring opening forming the intermediate **88**. In the next step the 1,4-dihydroxypentadienyl cation **89a/b** is generated undergoing the subsequent “Nazarov” type 4π-conrotatory cyclization leading to *anti*-cyclopentenone **90**. Cleavage of the proton gives rise to the final product (±)-**82**.

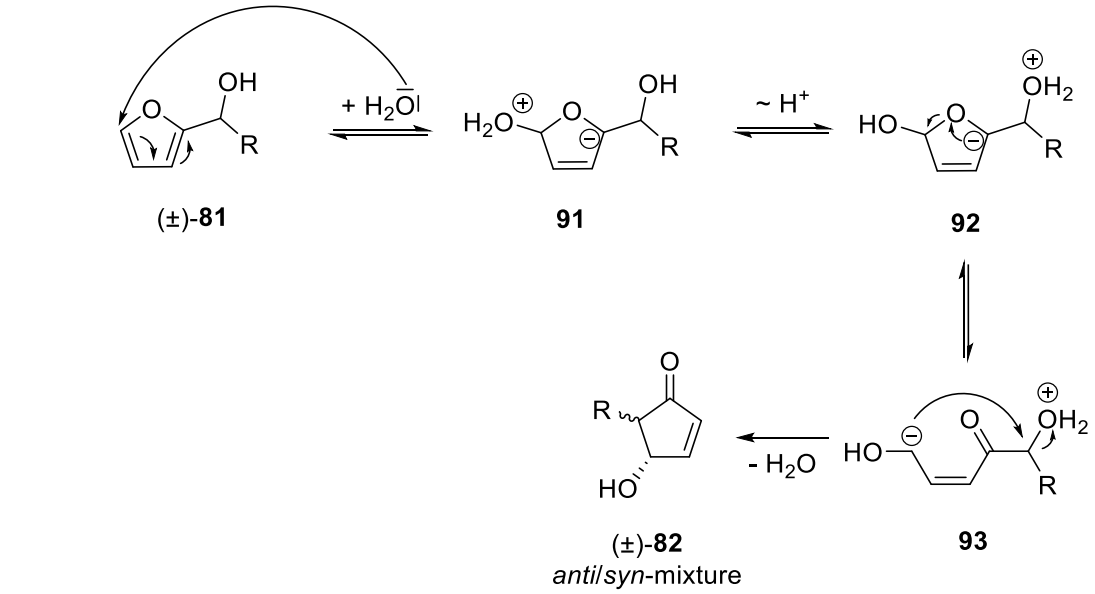
The pericyclic nature of this rearrangement was corroborated by De Lera and coworkers[41] *via* DFT calculations of the isomeric 1,4-dihydroxypentadienyl cation **89a/b**. It was reported that

the high *trans*-stereoselectivity of the intermediate **90** was attributed to the preferred *out-out*-geometry of the hydroxy group and substituent R of the cation **89a**/**b**.



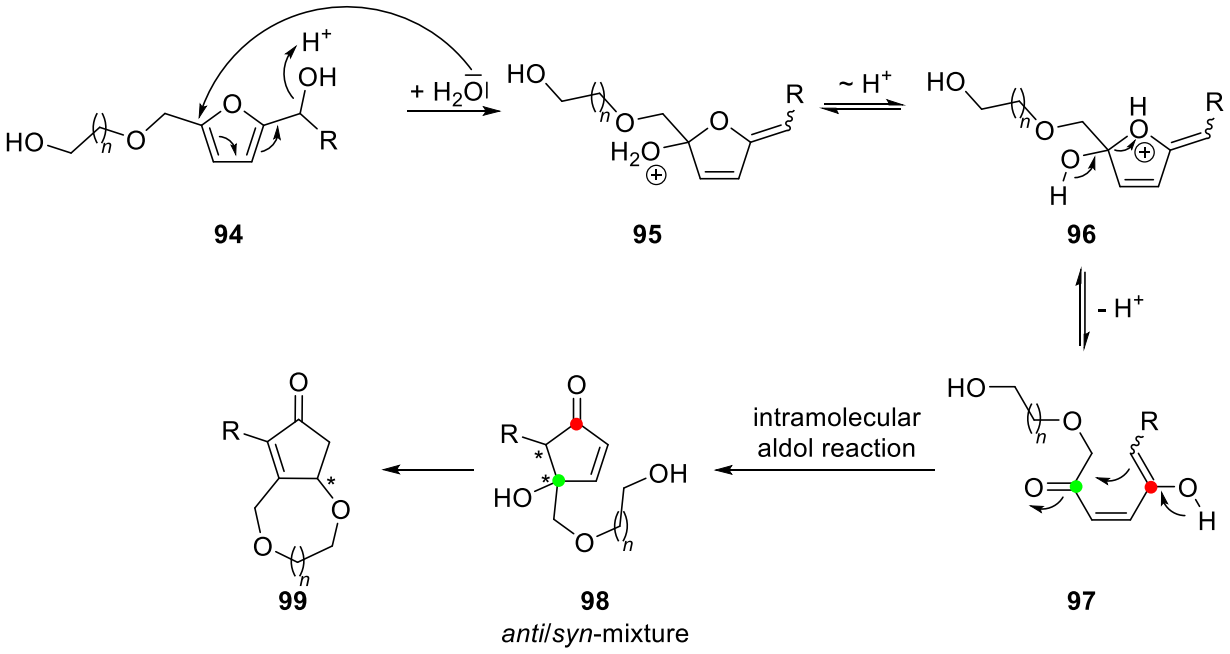
Scheme 23. Rearrangement mechanism proposed by Piancatelli and coworkers[40].

Besides the electrocyclic process two other mechanisms for this rearrangement have been reported in literature. In 2000 D`Auria[42] described a new rearrangement inhering zwitterionic species to explain the formation of the minor *syn*-product received in experiments (Scheme 24). The new mechanism does not involve acid catalyzed rearrangement since the reaction was carried in water without addition of acids. Equal to the mechanism of Piancatelli nucleophilic attack of water in C5-position of furylcarbinol (±)-**81** takes place generating the intermediate **91**, however, no subsequent elimination of the alcohol occurs. Instead of this, prototropic shift takes place forming the zwitterionic species **92**, subsequent ring opening provides directly a reactive carbanion **93** undergoing ring closure and elimination process of water. Following this mechanism mixture of *anti*/*syn*-cyclopentenone **82** is achieved.



Scheme 24. Rearrangement mechanism reported by D`Auria.[42]

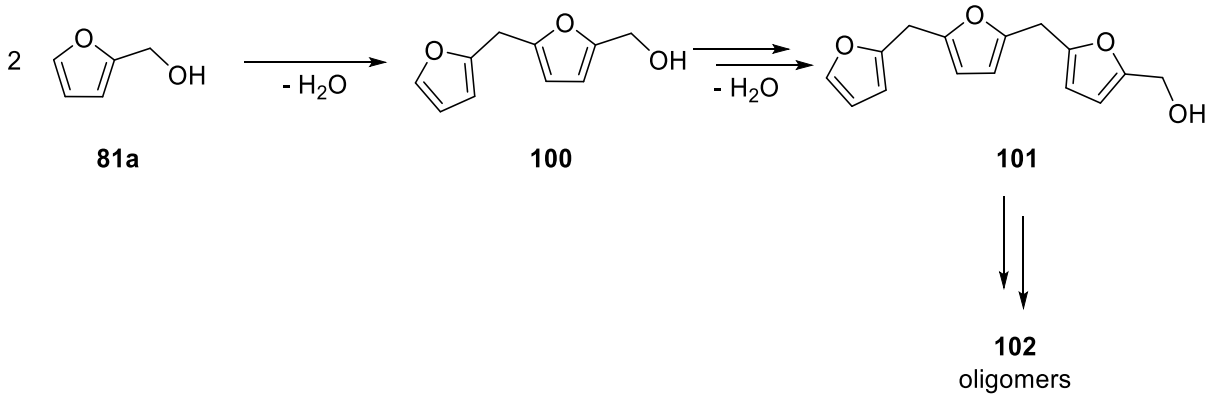
An alternative mechanism was proposed by Yin and coworkers[43] in 2009 involving an intramolecular aldol reaction as ring closing step (Scheme 25). Similar to the mechanism of Piancatelli`s acid catalyzed dehydration process of alcohol and nucleophilic attack of water in C5-position of compound **94** generates *via* prototropic shift the oxoniumion **96**, however, in this mechanism abstraction of proton provides the intermediate **97** inhering a non-protonated ketone.



Scheme 25. Mechanism reported by Yin and coworkers.[43]

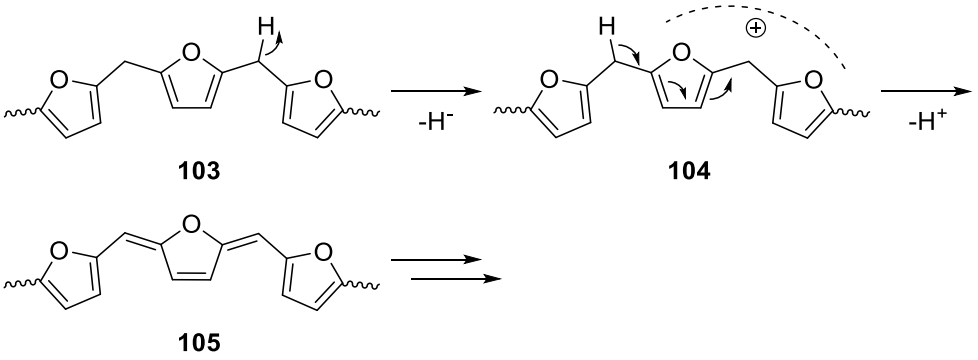
The subsequent intramolecular aldol reaction as key step of the rearrangement explains the formation of the received *anti*/*syn*-mixture of compound **98** as well. Depending on the length of the alkyl chain subsequent formation of bicyclic product **99** was observed *via* oxa-Michael addition.

Various procedures have been published for the Piancatelli rearrangement in the last 40 years conducting reaction times of 22-48 hours with only moderate yields in the range of 40%.[44] Formation of black cross-linked polymeric byproducts is a major issue due to long reaction times, employing high concentration of the furylcarbinols **81** enhances polymerization as well.[38] Polymerization of furfuryl alcohol **81a** occurs *via* alkylation at the C5-position of furfuryl alcohol leading to unconjugated linear oligomers **102** (Scheme 26).[45]



Scheme 26. Formation of linear unconjugated oligomers starting from furfuryl alcohol (**81a**).

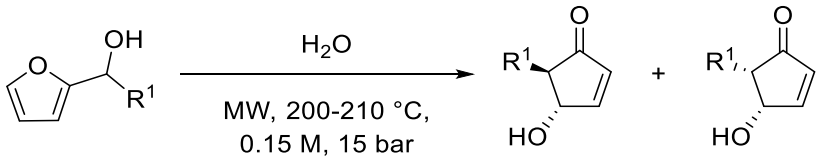
Gandini and coworkers[46] explained the progressive colorization of the reaction solution in the Piancatelli rearrangement *via* H^-/H^+-abstraction cycles. The linear unconjugated oligomers **103** undergo hydride-ion exchanges with the protonated chains of growing species (Scheme 27). Carbenium ion **104** is generated in which the positive charge is located between the methine carbon and the two adjacent furan heterocycles. Abstraction of the proton provides conjugated compound **105**, with each new sequence the degree of conjugation of the oligomer enhances leading to colorization of the polymer.



Scheme 27. Formal H^-/H^+-abstraction cycle leading to conjugated π-system. [45]

In 2010, Reiser and coworkers [38] demonstrated a new efficient method for conversion of substituted furylcarbinols (±)-**81** into cyclopentenones (±)-**82** within several minutes conducting the Piancatelli rearrangement in a microwave reactor (Table 4).

Table 4. Rearrangement of various 2-furylcarbinols (±)-**81** in a microwave reactor.[38]



(±)–**81a**: R^1 = H
(±)–**81b**: R^1 = 2-butenyl
(±)–**81c**: R^1 = Et
(±)–**81d**: R^1 = ^{n}Pent
(±)–**81e** R^1 = ^{n}Dodec

(±)–**82a**: R^1 = H
(±)–**82b**: R^1 = 2-butenyl
(±)–**82c**: R^1 = Et
(±)–**82d**: R^1 = ^{n}Pent
(±)–**82e** R^1 = ^{n}Dodec

entry[a]	R^1	t [min]	yield [%][b]	*dr* (*anti*/*syn*)
1[c]	H (±)-**81a**	4	80	-
2	2-butenyl (±)-**81b**	5	73	12:1
3	Et (±)-**81c**	15	65	7:1
4	^{n}Pent (±)-**81d**	15	54	7:1
5	^{n}Dodec (±)-**81e**	30	0	-

[a]Reaction conditions: 2-furylcarbinol (2.7 mmol) in H_2O (18 mL), microwave irradiation (300 W) under closed vessel conditions (200–210 °C, 15 bar). [b]Isolated yield. [c]Furfuryl alcohol (10.0 mmol) in H_2O (18 mL).

As a result of the very short reaction times the formation of the polymeric byproducts was suppressed resulting in higher yields in the range of 54-80%. In general, high dilution of the starting material (±)-**81** (0.15 M) enhanced the yield as well. Best result was provided by the unsubstituted furylcarbinol (±)-**81a**, elongation of the alkyl chain resulted in lower yields (Table 4, entries 1, 3-4). Employing compound (±)-**81e** with dodecyl substituent no formation of the product was observed at all (Table 4, entry 5). The diastereoselectivity of this

A major drawback of the microwave reactor is the limited volume of the reaction vessel and the necessary of high dilution of the starting material (±)-**81** for good yields. Therefore, a new protocol was described conducting the reaction in a continuous flow system as depicted in Figure 8.

Conversion of furfuryl alcohol **81a** into 4-hydroxycyclopent-2-en-1-one (±)-(**82a**) was carried out on a multigram scale with an average residence time of 53 seconds in the steel tube under subcritical conditions (240 °C, >15 bar). Forming polymers were dissolved employing toluene as cosolvent preventing blockage of the steel tube.

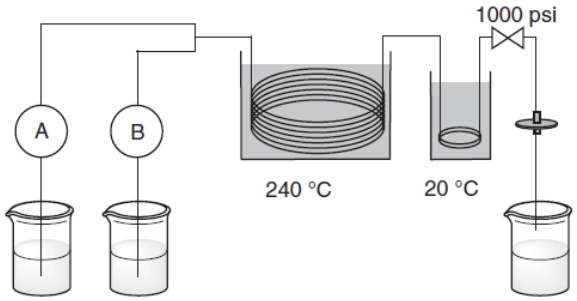


Figure 8. Setup of continuous flow system for Piancatelli rearrangement: **A**: Inlet for furfuryl alcohol (**81a**) in H_2O (c = 0.25 mol/L) adjusted to pH 4 with acetic acid at a flow rate of 1.8 mL/min. **B**: Inlet for toluene at a flow rate of 0.2 mL/min; average residence time in the reactor: 53 s. [38]

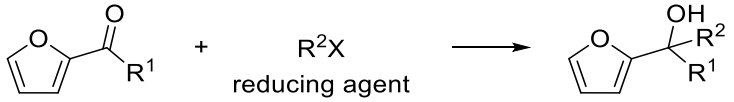
2.3.2 Results and Discussion

In order to perform the microwave induced Piancatelli rearrangement of various furylcarbinols latter were almost exclusively synthesized out of furfural (**80**) which is green outcome from agricultural waste. Merely methyl-furylcarbinol (±)-**81f** was synthesized out of 2-acetyl furan **106** and $NaBH_4$ (Table 5, entry 1) since reduction of furfural with a reducing agent would afford the usage of toxic and highly volatile and cancerogenic iodomethane on gram scale.

Overall, the desired furylcarbinols were obtained in good to excellent yields (65-99% yield), whereby most of the products (*iso*-propyl **81g**, *iso*-butyl **81i**, *n*-hexyl **81k**, phenyl **81l**, *iso*-propenyl **81m** substituted furylcarbinol) were achieved employing furfural and the appropriate

Grignard-reagent (Table 5, entry 2, 4-7). For the *tert*-butyl substituted furylcarbinols **81h** usage of the commercially available ^{t}BuLi-solution as reducing agent was preferred yielding 65% of product **81h**. The nitrile substituted product **81n** was achieved performing the reaction of furfural with KCN in an acid catalyzed reduction employing acetic acid as solvent yielding the product **81n** in almost quantitative yield of 99% (Table 5, entry 8).

Table 5. Synthesis of furylcarbinols as precursor for Piancatelli rearrangement.

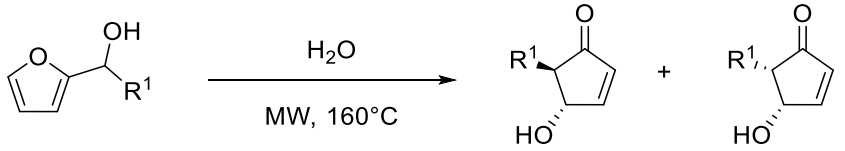


80/**106** (±)-**81**

entry	starting material	R^2X reducing agent	reaction conditions	product	yield [%]
1	R^1=Me acetyl furan **106**	$NaBH_4$ (0.5 equiv)	EtOH, 0 °C, 3 h	(±)-**81f**	81
2	R^1=H furfural (**80**)	^{i}PrMgBr (1.3 equiv)	Et_2O, 0 °C, 15 min	(±)-**81g**	68
3		^{t}BuLi (1.1 equiv)	Et_2O, 0 °C, 10 min	(±)-**81h**	65
4		^{i}BuMgBr (1.3 equiv)	Et_2O, 0 °C, 15 min	(±)-**81i**	80
5		^{n}HexMgBr (1.3 equiv)	Et_2O, 0 °C, 15 min	(±)-**81k**	78
6		PhMgBr (1.3 equiv)	Et_2O, 0 °C, 15 min	(±)-**81l**	69
7		 (1.3 equiv)	Et_2O, 0 °C, 15 min	(±)-**81m**	71
8		KCN (3.0 equiv)	AcOH, 0 °C, 24 h	(±)-**81n**	99

In the next step the Piancatelli rearrangement of the synthesized furylcarbinols (±)-**81** was carried out in a microwave reactor for shorter reaction times and higher yields. The effect of the substitution of the furylcarbinols in combination with different concentrations and different reaction times was explored in view of yield and diastereoselective outcome of the reaction. Therefor two different concentrations (low concentration c = 0.15 M, high concentration c = 0.55 M) of each furylcarbinol were tested performing the microwave induced reaction each for 4 min or 10 min, the results are depicted in Table 6 and Table 7.

Table 6. Piancatelli rearrangement of furylcarbinols (±)-**81** with alkyl-substituents.[a]



(±)-**81** (±)-*anti*-**82** (±)-*syn*-**82**

entry	R	c [mol/L]	t [min]	product	*dr* *(anti/syn)*[b]	yield [%][b]
1[38]	H (±)-**81a**	0.15	4	(±)-**82a**	-	80
2	Me (±)-**81f**	0.15[c]	4	(±)-**82f**	4:1	70
3		0.55[d]	4		8:1	47
4		0.15[c]	10		4:1	66
5		0.55[d]	10		8:1	44/(41)[e]
6	*i*Pr (±)-**81g**	0.15[c]	4	(±)-**82g**	32:1	54
7		0.55[d]	4		58:1	38/(36)[e]
8		0.15[c]	10		25:1	61
9		0.55[d]	10		52:1	37
10	*t*Bu (±)-**81h**	0.15[c]	4	(±)-**82h**	only *anti*	16
11		0.55[d]	4		only *anti*	13
12		0.15[c]	10		only *anti*	31/(28)[e]
13		0.55[d]	10		only *anti*	26
14	*i*Bu (±)-**81i**	0.15[c]	4	(±)-**82i**	8:1	74
15		0.55[d]	4		20:1	57/(54)[e]
16		0.15[c]	10		8:1	43
17		0.55[d]	10		20:1	36
18	*n*Hex (±)-**81k**	0.15[c]	4	(±)-**82k**	5:1	10
19		0.55[d]	4		10:1	9
20		0.15[c]	10		5:1	30
21		0.55[d]	10		10:1	20/(18)[e]

[a]Reaction conditions: microwave irradition (Anton Paar Monowave 300). [b]Determined by crude ^{1}H-NMR spectra with terephtalonitrile as internal standard. [c]Furylcarbinol (0.6 mmol) in 4 mL H_2O. [d]Furylcarbinol (1.1 mmol) in 2 mL H_2O. [e]Isolated yield based on a 10 mmol scale.

The following discussion will focus on the relation between concentration of the starting material and yield as well as diastereoselectivity of the reaction.
In view of the five alkyl substituted methyl, *iso*-propyl, *tert*-butyl, *iso*-butyl and *n*-hexyl products (±)-**82f**-**k** in Table 6 it is obvious that higher concentrations of each of the starting material (±)-**81f**-**k** achieve higher diastereoselectivity (around factor of 2) in the Piancatelli rearrangement in all cases, however, resulting in lower yields as well.

It needs to be mentioned that the solubility of the furylcarbinols (±)-**81** in water is moderate in general and results in a two-phase system. The lower yields caused by employing higher concentration of the furylcarbinols (±)-**81** can be explained by the enhanced polymerization (Scheme 26 and Scheme 27) of the starting material in the larger organic layer that is not soluble in water. This thesis is supported by the fact that in all cases a darker colorized reaction mixture was observed by employing higher concentration compared to lower concentration of the starting material (±)-**81**.
Increasing the size of the unpolar alkyl substitution from C_1-methyl to C_6-hexyl substituents the solubility of the starting material decreases even further, resulting in lower yields (methyl-substituent (±)-**82f**: 70% yield, *n*-hexyl-substituent (±)-**82k**: 10% yield, Table 6, entries 2 and 18) caused by enhanced polymerization in the organic phase.

In view of the very different yield of both C_4-substituted *tert*-butyl and *iso*-butyl products (±)-**82h**-**i** it can been seen that the latter explanation of lower yields caused by increasing the general size of the alkyl substituents is insufficient. The steric bulkiness of the substituent plays a very important role as well and decreases the yield tremendously (*tert*-butyl-substituent (±)-**82h**: 13% yield vs. *iso*-butyl-substituent (±)-**82i** 74% yield, Table 6, entries 10 and 14). Apparently, the reactivity of the substrates in the Piancatelli rearrangement are affected by steric demanding groups.

Longer reaction times influenced the yield of the reaction differently, in case of the methyl and *iso*-propyl substituted cyclopentenones (±)-**82f**-**g** the yields were similar (Table 6, entries 2-9), whereas the yield of the *iso*-butyl substituted product (±)-**82i** decreased strongly (Table 6, entries 14-17). Interestingly, the low yields of the very steric bulky *tert*-butyl substituted and hardly insoluble *n*-hexyl substituted cyclopentenones (±)-**82h** and (±)-**82k** could be raised applying longer reaction times (Table 6, entries 10-13, 18-21).

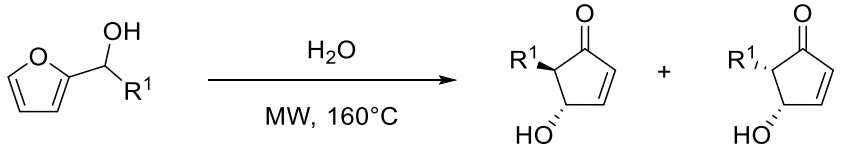
As already mentioned, applying higher concentration of the starting material (±)-**81** the diastereoselectivity of the outcome (±)-**82** of the Piancatelli rearrangement is improved or at

least equal and furthermore independent of the reaction time. The effect of steric bulkiness of the alkyl substituent plays a superior role in view of the diastereoselectivity of the outcome. By increasing the steric demanding group from methyl over *iso*-propyl to *tert*-butyl substituent it is obvious that the *anti*/*syn*-ratio of the products (methyl-substituent (±)-**82f**: *anti*/*syn*-ratio: 4:1, *iso*-propyl-substituent: *anti*/*syn*-ratio (±)-**82g**: 32:1, *tert*-butyl-substituent (±)-**82h**: *anti*/*syn*-ratio: only *anti*-product, Table 6, entries 2, 6 and 10) increases as well. This thesis is furthermore corroborated by the comparison of the outcome of the *iso*-propyl- and *iso*-butyl substituted products (*iso*-propyl-substituent (±)-**82g**: *anti*/*syn*-ratio: 32:1, *iso*-butyl-substituent (±)-**82i**: *anti*/*syn*-ratio: 8:1, Table 6, entries 6 and 14) since the steric demanding branched alkyl chain of *iso*-butyl substituent is in β-position compared to closer α-position in *iso*-propyl-substituent and therefore leading to lower diastereoselectivity.

Interestingly, while the yield of the reaction was dependent from the chain length (solubility) and bulkiness (reactivity) of the substituents of the furylcarbinols, the diastereoselectivity of the reaction is largely independent from the chain length of the substitution comparing the similar *anti*/*syn*-ratios of the methyl- and hexyl substituted products (methyl-substituent: *anti*/*syn*-ratio: 4:1, *n*-hexyl-substituent: *anti*/*syn*-ratio: 5:1, Table 6, entries 2 and 18). The influence of steric bulkiness of the substituents for the diastereoselective outcome of the reaction, however, is tremendous. By increasing the steric bulkiness of the substituent of the cyclopentenone the repulsion of the substituent R with the forming alcohol group is increased and therefore the *anti*-conformation is favored compared to the *syn*-conformation of the cyclopentenone-product (±)-**82**.

Beside the successful conversion of alkyl substituted furylcarbinols (±)-**81f**-**k** (Table 6) into cyclopentenones (±)-**82f**-**k** *via* Piancatelli rearrangement the conversion of arylic and alkenylic furylcarbinols was tested, the results are depicted in Table 7.
The reactivity of the phenyl substituted furylcarbinol (±)-**81l** was higher than the tested alkylic substituted starting materials (±)-**81f**-**k** since the substrate (±)-**81l** was completely converted after a reaction time of 4 min providing yields of 80%. Thus, reactions with running time of 10 min were not carried out. However, the diastereoselectivity of the reactions with the two obligatory concentrations of the phenyl substituted starting material (*anti*/*syn*-ratio: 5:1, Table 7, entries 1-2) was only moderate and identic.

Table 7. Piancatelli rearrangement of various furylcarbinols (±)-**81**.[a]



(±)-**81** (±)-*anti*-**82** (±)-*syn*-**82**

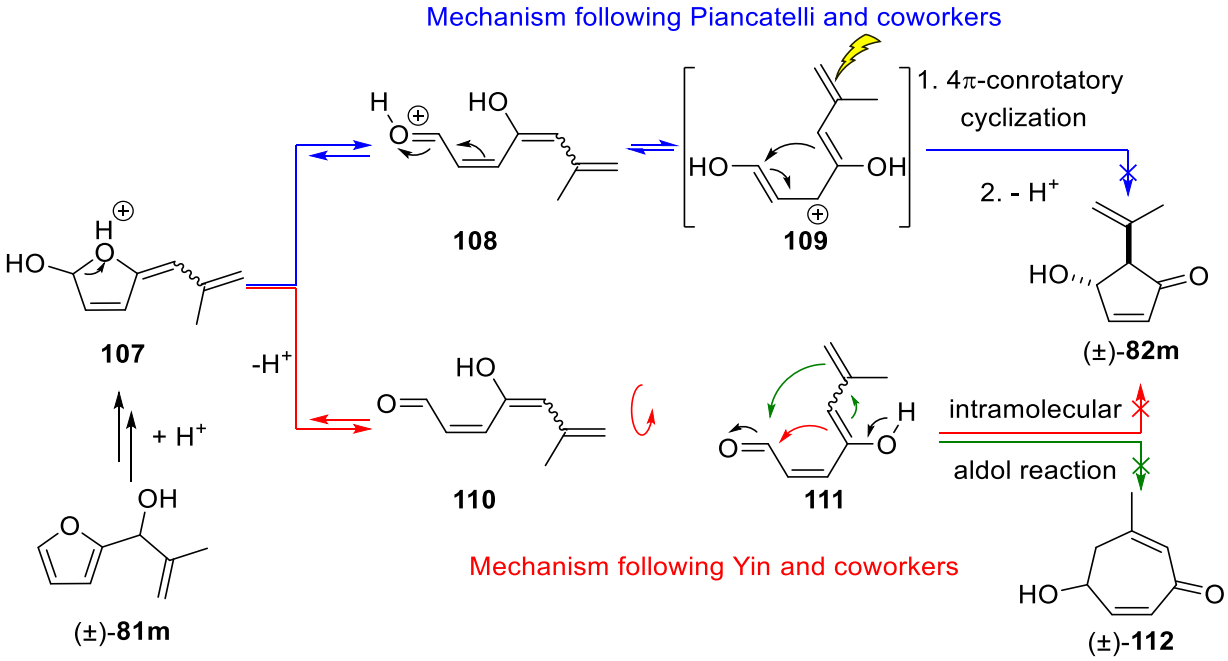
entry	R	c [mol/L]	t [min]	T [°C]	product	*dr* (*anti*/syn)[b]	yield [%][b]
1	Ph (±)-**81l**	0.15[c]	4	160	(±)-**82l**	5:1	82
2		0.55[d]				5:1	80
3		1.0[f]				6:1	83/(79)[e]
4		2.0[g]				6:1	42
5	*iso*-propenyl (±)-**81m**	0.15[c]	4	90	(±)-**82m**	-	no reaction
6				100		-	no reaction
7				110		-	slight. decomp.
8				120		-	decomposition
9	CN (±)-**81n**	0.15[c]	4	90	(±)-**82n**	-	no reaction
10				100		-	no reaction
11				110		-	slight. decomp.
12				120		-	decomposition

[a]Reaction conditions: microwave irradition (Anton Paar Monowave 300). [b]Determined by crude ^{1}H-NMR spectra with terephtalonitrile as internal standard. [c]Furylcarbinol (0.6 mmol) in 4 mL H_2O. [d]Furylcarbinol (1.1 mmol) in 2 mL H_2O. [e]Isolated yield based on a 10 mmol scale. [f]Furylcarbinol (2.0 mmol) in 2 mL H_2O. [g]Furylcarbinol (4.0 mmol) in 2 mL H_2O.

The latter result of equal diastereoselectivity applying different concentrations of starting material is uncommon compared to the results with the alkyl substituted furylcarbinols (±)-**81f-k** in Table 6. Therefore, reactions with higher concentrations (1 M and 2 M) of phenyl substituted starting material (±)-**81l** were carried out to improve the *anti*/*syn*-ratio of the product (±)-**82l** (Table 7, entries 3-4). The optimum of the reaction in view of yield and diastereoselectivity was found out to be employing concentration of 1 M of the starting material, since yield could be raised to 83% and the *anti*/*syn*-ratio of the product (±)-**82l** was increased to 6:1 (Table 7, entry 3). Employing higher concentration of 2 M of the starting material did not

influence the diastereoselective outcome of the reaction but the yield was decreased to 42% caused by polymerization of the starting material since extreme dark solution was observed after the reaction (Table 7, entry 4).

In literature no example of Piancatelli rearrangement of vinyl or *iso*-propenyl substituted furylcarbinols is reported, thus, reaction of latter was tested (Table 7, entries 5-8). Unfortunately, employing short reaction time of 4 min and low concentration (0.15 M) of *iso*-propenyl substituted furylcarbinol (±)-**81m** and screening the reaction temperature from 90-120 °C did not yield to any formation of the product but increasing decomposition of the starting material. In view of the mechanism proposed by Piancatelli the double bond of the *iso*-propenyl substituent enlarges the conjugated π-system of intermediate **109** and therefore disturbs the 4-π-cyclization as depicted in Scheme 28. Following the mechanism proposed by Yin et al. [43] the intramolecular aldol reaction as ring closing step is interfered by the enlarged π-system of intermediate **111** as well. Unfortunately, formation of seven membered ring (±)-**112** was not observed as reaction outcome in the ^{1}H-NMR spectra of the crude reaction mixture.

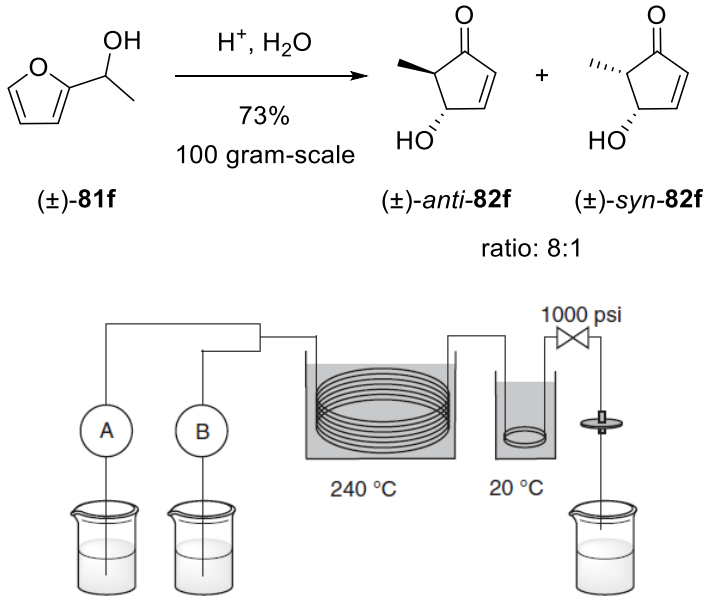


Scheme 28. Reaction mechanism for the *iso*-propenyl substituted furylcarbinols (±)-**81m** following mechanism proposed by Piancatelli et al. [40] and Yin et al. [43].

Testing the nitrile substituted furylcarbinol (±)-**81n** in the microwave reactor for Piancatelli rearrangement did also not provide any product formation but increasing decomposition with higher reaction temperatures (Table 7 entries 9-12). It is assumed that the triple bond of the

nitrile group disturbs the formation of the product similar to the double bond of the *iso*-propenyl substituent by enlarging the π-system.

In view of synthesis of Phomapentenone A (**177**) (see Chapter 3. Synthesis of Phomapentenone A) Piancatelli rearrangement of the methyl substituted furylcarbinol (±)-**81f** as precursor was essential on a multigram scale. Since carrying out the reaction in a microwave reactor batch setup with limited reaction volume would have been laborious a continuous-flow microreactor following the setup described in our working group[38] in 2010 seemed attractive. For this setup two inlets **A** and **B** were implemented in which H_2O adjusted to pH 4 with acetic acid (inlet **A**) and the starting material (±)-**81f** in toluene (inlet **B**) were flowed through with optimized conditions[47] (Scheme 29). Employing toluene as co-solvent suppressed the blockage of the steel tube during the reaction. Fortunately, on a 100 gram scale and with an average residence time of 124 s in the microreactor the cyclopentenone product (±)-**82f** was obtained in *anti*/*syn*-ratio: 8:1 with improved yield of 73% compared to the results of the microwave induced reactions (Table 6, entries 2-5).



Scheme 29. Piancatelli rearrangement of furylcarbinol (±)-**81f** on a multigram scale in a microreactor setup: Flowrate of inlet **A** (H_2O adjusted to pH 4.0 with acetic acid): 3.5 mL/min, lowrate of inlet **B** (2-furylcarbinol (±)-**81f** in toluene (c = 3.4 M)): 0.3 mL/min, average residence time in microreactor: 124s.

2.4 Asymmetric Tsuji-Trost Allylation

2.4.1 Introduction

Synthesis of 4-hydroxycyclopent-2-enones in enantiopure fashion is very attractive since they are core structure of various bioactive molecules and natural products, e.g. prostaglandin derivatives **113**-**116**.[48] The prostaglandin derivatives show a wide variety of effects such as regulation of inflammation[48], hormones[49] and calcium movement[50]. Well known derivatives of prostaglandins are depicted in Figure 9.

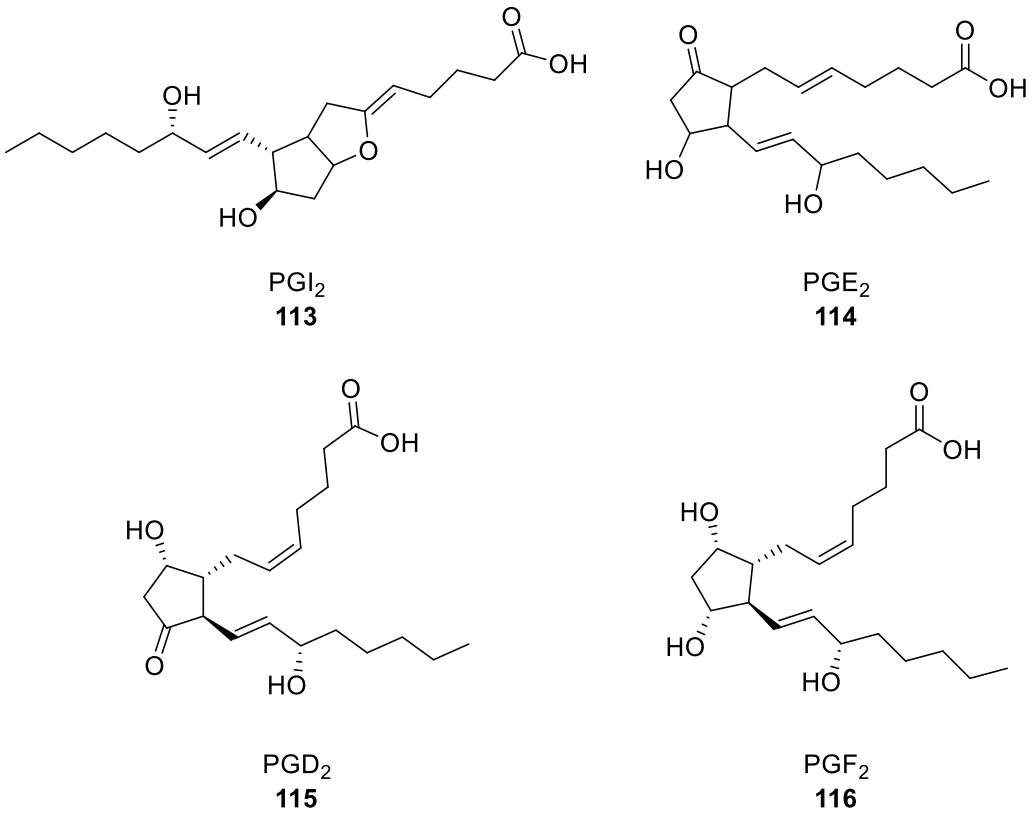
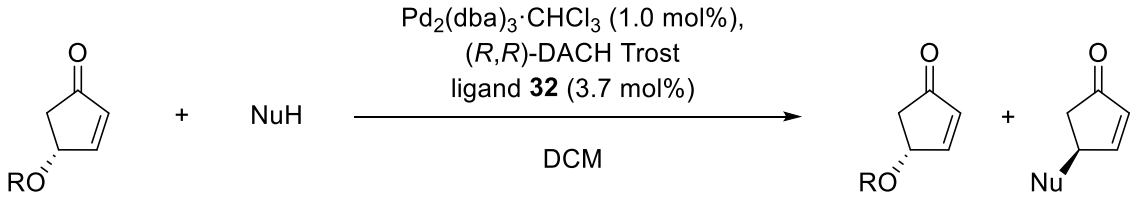


Figure 9. Prostaglandin derivatives.

In literature various synthetic protocols are reported towards enantiopure 4-hydroxycyclopentenones. Enzymatic approach was described *via* penicillin G-acylase [51], esterases [52] or lipases [53]. Hydrogenation reaction of allylic alcohols based on BINAP-Ru(II) catalysis gave also rise to enantiopure 4-hydroxycyclopentenone *via* kinetic resolution. [54]

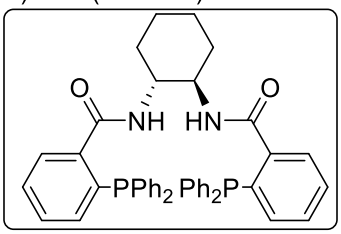
Table 8. Kinetic resolution of cyclopentenones (±)-**30** *via* Tsuji-Trost allylation reported by Reiser and coworkers.[25]



(±)-**30a** (R = Ac)
(±)-**30b** (R = Boc)

31a: CH_3CO_2H
31b: PhOH
31c: 1-naphthyl-CO_2H
31d: 4-BrC_6H_4-CO_2H
31e: Bn-SH
31f: *n*-$C_{12}H_{25}$-SH
31g: Phthalimide

(*R*)-**30a** (R = Ac) (*S*)-**33a-g**
(*R*)-**30b** (R = Boc)



(*R*,*R*)-DACH
Trost ligand **32**

entry[a]	s.m. 30	NuH 31	t [h]	T [°C]	(R)-30		(S)-33		*S*[b]
					yield [%]	*ee* [%]	yield [%]	*ee* [%]	
1	**30a**	**31b**	18	25	23	26	12	91	24
2	**30a**	**31c**	4	0	50	25	30	77	11
3	**30b**	**31a**	1	0	46	96	35	90	31
4	**30b**	**31c**	2	0	34	99	34	93	44
5	**30b**	**31c**	1	0	31	90	46	90	44
6	**30b**	**31c**	4	-20	43	>99	45	>99	501
7	**30b**	**31d**	1	0	44	95	41	91	41
8	**30b**	**31e**	17	-78	33	>99	42	93	56
9	**30b**	**31f**	17	-78	38	92	39	93	50
10	**30b**	**31g**	18	25	31	>99	50	96	194

[a]Reaction conditions: cyclopentenone (±)-**30** (0.5 mmol), nucleophile **31** (0.24 mmol), Pd_2dba_3 (1.2 mol%, 2.3 mol% Pd based on the nucleophile), Tsuji-Trost ligand (*R*,*R*)-**32** (3.7 mol% based on the nucleophile) in DCM (2 mL). Absolute configurations were obtained by comparison of specific rotation values with literature as well as by X-ray crystallography. [b]Selectivity factor *S* described by Kagan. [55,56]

In general, 4-hydroxy-cyclopentenone and its derivatives are suitable for Pd-catalyzed kinetic resolution that is known as Tsuji-Trost allylation.[57] Reiser and coworkers[25] demonstrated a

very efficient method for enantiopure synthesis of 4-oxoprotected cyclopentenones (±)-**30** employing *N*-, *O*- and *S*-nucleophiles with chiral (*R*,*R*)-DACH Trost ligand **32** (Table 8). However, kinetic resolution of acetate derivative (±)-**30a** resulted in low *ee*-values for the recovered starting material compared to the Boc-protected compound (±)-**30b** (Table 8, entries 1,2, and 4). It was proposed that the low selectivity was attributed to the forming allyl acetate moiety that is deactivated by the conjugated carbonyl group.

Fortunately, employing Boc protected cyclopentenone (±)-**30b** gave good enantioselectivities and yields of both recovered starting material (*R*)-**30b** and nucleophile product (*S*)-**33** were provided with various *N*-, *O*- and *S*-nucleophiles. The best result was achieved applying naphthoic acid as nucleophile achieving very good yields and excellent enantioselectivity of recovered starting material as well as the nucleophile product (Table 8 entry 6). *S*- as well as *N*-nucleophiles provided very good results, however, the enantioselectivity for the nucleophile product **33e**-**g** was not excellent with values of 93-96% (Table 8, entries 8-10).

The selectivity factor *S* was defined by Kagan and coworkers [55,56] using the enantiomeric excess "*ee*" of the allylation product as well as the conversion "C" of the reaction as parameters (equation 1).

$$S = \frac{\ln [1 - C(1 + ee)]}{\ln [1 - C(1 - ee)]} \qquad \text{eq.1}$$

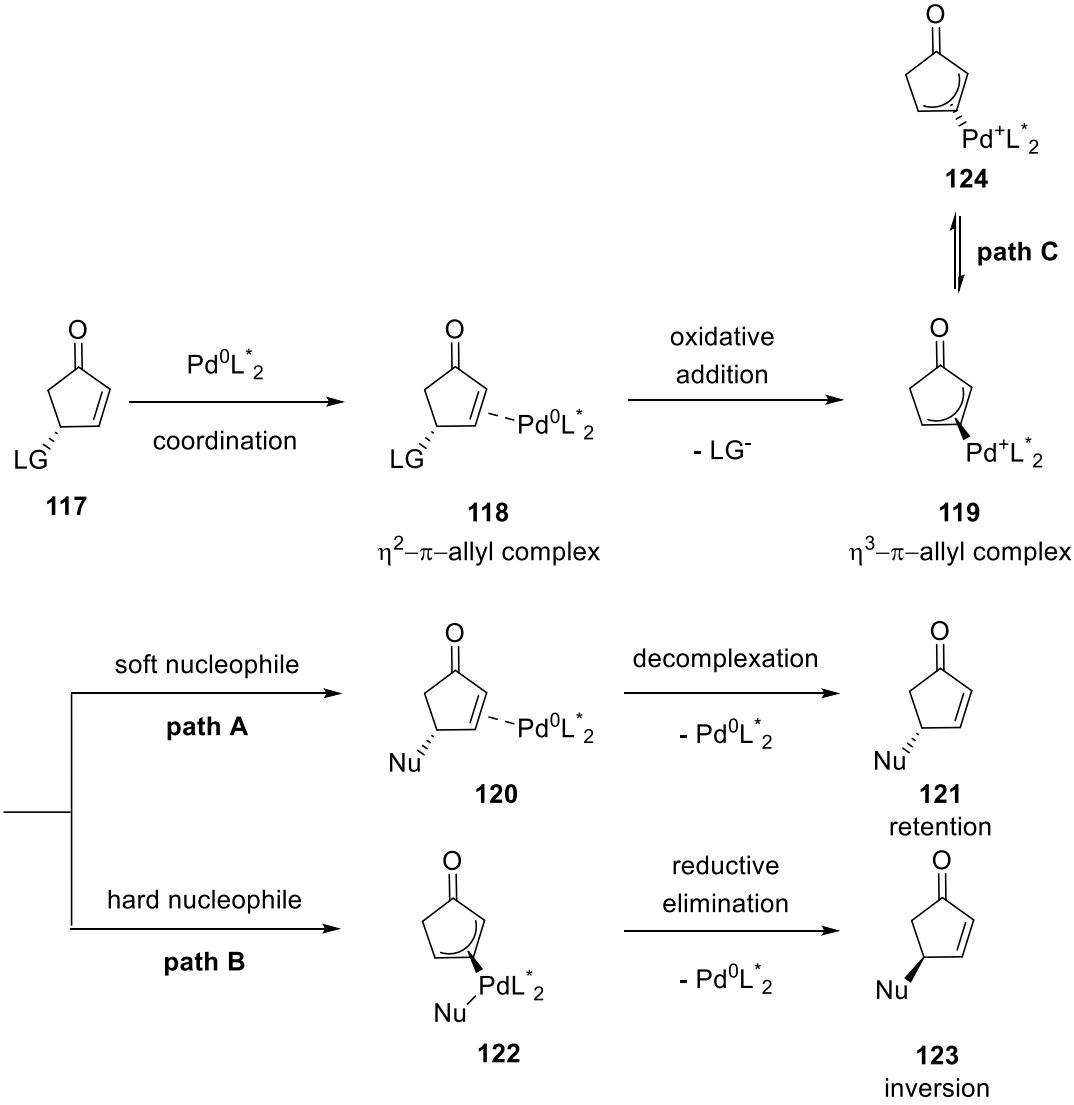
The mechanism of the asymmetric Tsuji-Trost allylation is depicted in Scheme 30. In general, η^2-π-allyl complex **118** is generated *via* coordination of the PdL^*_2-complex to the approaching double bond of the cyclopentenone **117**. In the next step, oxidative addition provides the η^3-π-allyl complex **119** with Pd in *anti*-conformation related to the repulsed LG^- (leaving group). In view of the reaction outcome two different nucleophile products **121** and **123** arise dependent on the nucleophile.

Soft nucleophiles are described as those that derive from conjugate acids with $pK_a < 25$.[57] The attack of these nucleophiles occurs at the soft allylic carbon skeleton of the η^3-π-allyl complex **119** in C4-position since the ketone interferes the nucleophilic attack in C2-position (Scheme 30, **path A**). The nucleophilic attack of the nucleophile takes place in *anti*-conformation related to the Pd-complex leading to intermediate **120**. Finally, the nucleophile product **121** is obtained under retention of the stereocenter in C4-position after decomplexation of the $Pd^0L^*_2$-complex.

Hard nucleophiles are defined as those that derive from conjugate acids with $pK_a > 25$,[57] the nucleophilic attack occur directly at the Pd-metal leading to the Pd-comlex **122** (Scheme 30, **path B**). In the reductive elimination the $Pd^0L^*_2$-complex is regenerated, the bond formation between nucleophile and cyclopentenone takes place in a *syn*-manner related to the Pd-metal.

Therefore, the nucleophile product **123** is received under overall inversion of the stereocenter in C4-position of the ring.

The enantioface exchange of the η³-π-allyl complex **119** leads to low enantioselectivity of the reaction, fortunately, this undesired formation of intermediate **124** can be inhibited by reactive allylic substrates, low Pd^0-concentration and bidentate ligands (Scheme 30, **path C**). [58]

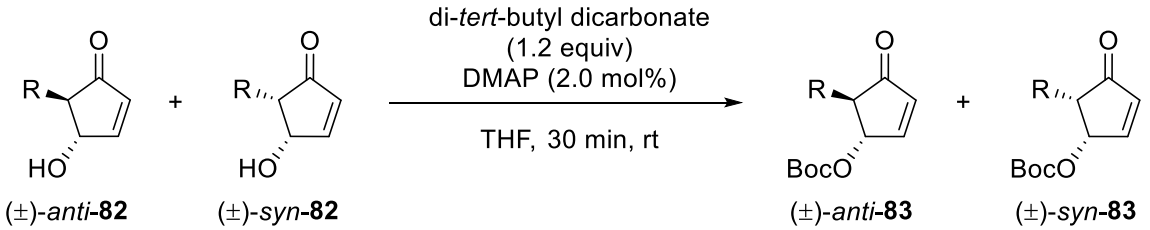


Scheme 30. Mechanism of Tsuji-Trost allylation.

2.4.2 Results and Discussion

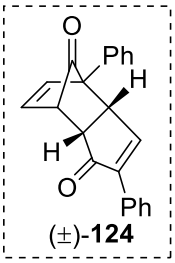
In order to provide enantiopure cyclopentenones the work of Reiser et al.[39,25] was followed developing the Pd-catalyzed Tsuji-Trost allylation of cyclopentenones *via* kinetic resolution. For this it was reported that the hydroxy group needs to be activated, since the kinetic

resolution of 4-*O*Ac protected cyclopentenones was a very sluggish reaction compared to the 4-*O*Boc derivatives, the following activation was carried out *via* Boc-protection (Scheme 31).



(±)-**82a**: R=H
(±)-**82f**: R=Me, *anti*/*syn*: 8:1
(±)-**82g**: R=^{i}Pr, *anti*/*syn*: 58:1
(±)-**82h**: R=^{t}Bu, only *anti*
(±)-**82i**: R=^{i}Bu, *anti*/*syn*: 20:1
(±)-**82k**: R=^{n}Hex, *anti*/*syn*: 10:1
(±)-**82l**: R=Ph, *anti*/*syn*: 6:1

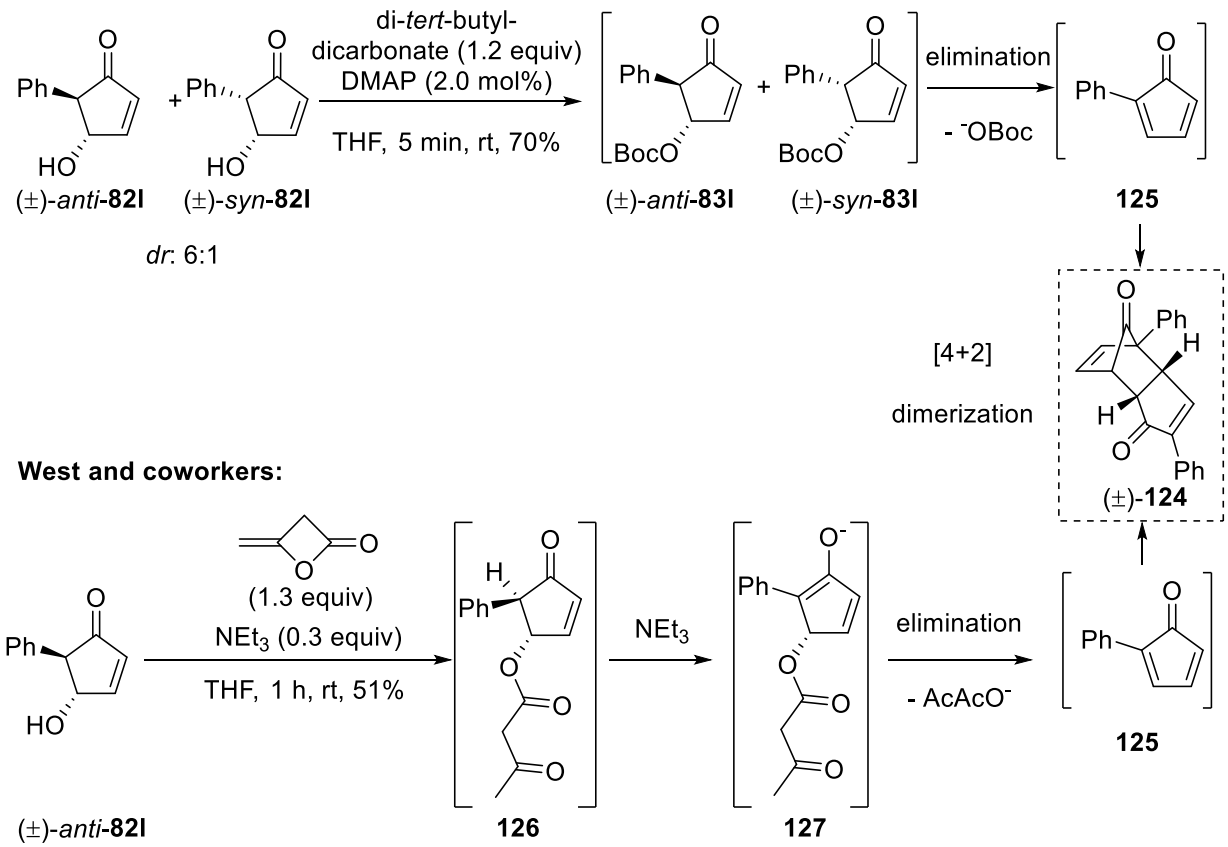
(±)-**83a**: R=H, 80%
(±)-**83f**: R=Me, 80% *anti*/*syn*: 8:1
(±)-**83g**: R=^{i}Pr, 75% only *anti* isolated
(±)-**83h**: R=^{t}Bu, 69 % only *anti* isolated
(±)-**83i**: R=^{i}Bu, 83 % only *anti* isolated
(±)-**83k**: R=^{n}Hex, 65% only *anti* isolated
(±)-**83l**: R=Ph, 0%, (±)-**124**: dimer, 70%



Scheme 31. Activation of the alcohol group *via* Boc-protection.

Fortunately, Boc-protection was successful in almost all the cases except phenyl substituted cyclopentenone (±)-**82l** (discussion *vide infra*). The activated cyclopentenones (±)-**83** were obtained in good yields from 69-83%, the *anti*-and *syn*-configurated methyl derivatives (±)-**83f** could be provided after column chromatography under retention of the ratio. Furthermore, separation of both compounds was possible and necessary for subsequent Tsuji-Trost allylation. In all the other cases no *syn*-compounds were obtained after column chromatography probably due to the lower amount of *syn*-compound and the smaller batch scale compared to the reaction with the methyl derivative (±)-**82f**.

In case of the phenyl substituted furylcarbinol (±)-**82l** no 4-*O*Boc-product formation was observed but fast dimerization in good yield of 70% obtaining the product (±)-**124** (Scheme 32). The formation of latter probably takes place *via* instant elimination of the *O*Boc-moiety subsequently followed by [4+2]-cycloaddition leading to the literature known dimer (±)-**124**. In 1993 West and coworkers[59] reported similar observations adding the lactone diketene to the phenyl substituted starting material (±)-**82l** that was leading to the dimerized product (±)-**124**, as well. Since enolization of the phenyl substituted system is stabilized very well, elimination of the oxo-substituent takes place after activation generating the unstable cyclopentadiene intermediate **125**. Latter undergoes fast [4+2]-cycloaddition providing the stable dimer (±)-**124**.



Scheme 32. [4+2]-Cycloaddition of 4-hydroxy-5-phenyl-cyclopentenone ((±)-**82l**).[59]

With the activated *anti*- and *syn*-cyclopentenones in hands, Pd-catalyzed Tsuji-Trost allylation was carried out employing different nucleophiles. Since lower reaction temperatures achieve better results in yield and enantioselectivity of the reaction,[25] reaction limits were tested by applying the reaction temperature as low as possible. The *anti*- or *syn*-conformation of the recovered starting material as well as of the nucleophile-products in Table 9- Table 11 were determined by 2D-NMR NOESY-spectra (see 5.11 NMR Spectra). In Table 9 *anti*-cyclopentenones were tested using alcohols as nucleophiles for kinetic resolution applying optimized conditions reported by Reiser et al.[39] using *p*-methoxyphenol as the nucleophile.

In view of the experiments carried out with the methyl-derivative (±)-*anti*-**83f** it is obvious, that addition of Cs_2CO_3 leads to worse results in enantioselectivity and yield of both compounds compared to the reported outcome using unsubstituted cyclopentenone (±)-**83a**. The yield of recovered starting material (4*S*,5*R*)-**83f** as well as the product (4*R*,5*S*)-*anti*-**128f** was dropping to the range of 30%, the enantiomeric excess of both was merely in the range of 50%. Therefore, addition of Cs_2CO_3 was renounced in all further Tsuji-Trost reactions (Table 9, entries 1 and 3). Fortunately, in absence of the additive Cs_2CO_3 the outcome of the reaction was strongly improved, the yield of the recovered starting material (4*S*,5*R*)-*anti*-**83f** could be

raised to 43%, the product (4*R*,5*S*)-*anti*-**128f** was achieved in almost quantitative yield of 49%. The enantiopurity of both compounds could be raised as well obtaining *ee*-values in the range of 76-78% (Table 9, entry 4). Carrying out the reaction at room temperature did not influence the results of the reaction (Table 9, entry 5).

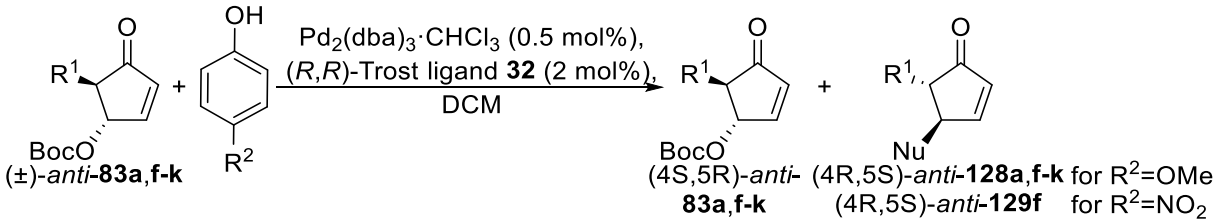
In general, by increasing the nucleophile in a kinetic resolution from 0.5 equivalents to higher amounts, the conversion of the starting material into the product is higher leading to smaller amounts of recovered starting material and higher yields of product instead. Commonly, the *ee*-values of the recovered starting increases whereby the enantiopurity of the product decreases.[60]

However, applying this strategy to the Tsuji-Trost allylation with the methyl substituted cyclopentenone (±)-*anti*-**83f** neither usage of 0.7 equivalents nor 0.9 equivalents of the nucleophile *p*-methoxyphenol could improve the enantiopurity of the recovered starting material (4*S*,5*R*)-*anti*-**83f**. Dropping yields of latter as well as higher yields and lower *ee*-values of the product (4*R*,5*S*)-*anti*-**128f** are in accordance with the previous explanation (Table 9, entries 6-7). Interestingly, the selectivity factor *S* was not influenced by increasing the amount of nucleophile.

Changing the nucleophile from *p*-methoxyphenol to *p*-nitrophenol did not lead to any conversion of the starting material (±)-*anti*-**83f** implicating that the reactivity of the nucleophile is too low caused by the negative mesomeric effect of the nitrogroup compared to the positive mesomeric effect of the methoxy functionality (Table 9, entry 8).

In view of the other alkyl substituted cyclopentenones (±)-*anti*-**83f**-**k** increase of reaction temperature did not influence the outcome strongly, merely the enantiopurity of the *n*-hexyl substituted product (4*R*,5*S*)-*anti*-**128k** was decreased moderately from 82% to 67% enantiomeric excess. Furthermore, increasing the reaction temperature the reaction time was reduced strongly in case of the *iso*-propyl (±)-*anti*-**83g** (60 min → 30 min) and the *iso*-butyl (±)-*anti*-**83i** (90 min → 30 min) substituted cyclopentenones that is in accordance with kinetic resolution. Since the yield of all compounds employing 0.5 equivalents of nucleophile in the absence of the additive Cs_2CO_3 were similar in the range of 43-49%, the enantioselectivity of the reactions will be discussed in particular.

Table 9. Tsuji Trost allylation of cyclopentenones (±)-*anti*-**83** with alcohols as nucleophile.



entry[a]	NuH R^2	NuH [equiv]	R^1	t [h]	T [°C]	Cs_2CO_3 [equiv]	yield of *anti*-83 [%]	*ee* [%][b]	yield of *anti*-128/129 [%]	*ee* [%][b]	*S*[c]
1[39]		0.5	H	3	0	0.3	42	>99	48	92	65
2		0.5		24	-20	0.3	no reaction				
3		0.5		3	0	0.3	30	50	31	53	4
4	OMe	0.5	Me	3	0	-	43	78	49	76	16
5		0.5	**83f**	3	rt	-	44	78	48	76	16
6		0.7		3	0	-	23	78	57	66	14
7		0.9		3	0	-	6	79	73	35	16
8	NO_2	0.5	Me	24	reflux	-	no reaction				
9		0.5		24	-20	-	no reaction				
10		0.5	^{i}Pr	1	0	-	46	97	49	90	53
11		0.5	**83g**	0.5	rt	-	47	97	49	91	61
12		0.5	^{t}Bu	24	reflux	-	no reaction				
13		0.5	**83h**	24	-20	-	no reaction				
14	OMe	0.5	^{i}Bu	1.5	0	-	47	88	47	70	11
15		0.5	**83i**	0.5	rt	-	46	87	48	65	9
16		0.5		24	-20	-	no reaction				
17		0.5	^{n}Hex	3	0	-	44	64	45	82	20
18		0.5	**83k**	3	rt	-	43	69	44	67	9

[a]Reaction conditions: cyclopentenone (±)-*anti*-**83** (1.0 mmol), specified nucleophile NuH, $Pd_2(dba)_3·CHCl_3$ (5.0 µmol, 1.0 mol% based on nucleophile), Trost ligand (*R*,*R*)-**32** (18.5 µmol, 3.7 mol% based on the nucleophile) in DCM (4 mL). [b]Determined by chiral HPLC. [c]Selectivity factor.

Comparing the excellent reaction outcome of the unsubstituted with the alkyl substituted cyclopentenones it is obvious that the results do not clearly follow the trend of enantiopurity improvement by increasing steric bulkiness. As already mentioned, while the outcome of the reaction with the unsubstituted cyclopentenone (±)-**83a** achieves excellent enantiopurity in a range of 92->99% *ee*-value, the enantiopurity of the steric more demanding methyl substituted cyclopentenone declines to *ee*-values in the range of 76-78% (Table 9, entries 1-7). Therefore, it would have been expected that the *ee*-values of both *iso*-propyl-substituted cyclopentenone compounds (4*S*,5*R*)-*anti*-**83g** and (4*R*,5*S*)-*anti*-**128g** decrease even more since the steric bulkiness increases tremendously. Interestingly, the opposite was observed since very good to excellent *ee*-values were obtained with 97% enantiomeric excess of the recovered starting material (4*S*,5*R*)-*anti*-**83g** and at least 90% of the product (4*R*,5*S*)-*anti*-**128g** (Table 9, entries 9-11). Increasing the steric group to *tert*-butyl substituent, no formation of product (4*R*,5*S*)-*anti*-**129f** was observed at all even under reflux conditions (Table 9, entry 12). Apparently, the steric bulkiness of the *tert*-butyl substituent is too high for the allylation. In the Tsuji-Trost allylation *ee*-values of 87-88% of the recovered *iso*-butyl substituted starting material (4*S*,5*R*)-*anti*-**83i** were obtained, whereas the enantiomeric excess of the corresponding nucleophile product (4*R*,5*S*)-*anti*-**128i** was only moderate with values of 65-70%(Table 9, entries 13-15). For the *n*-hexyl substituted recovered starting material (4*S*,5*R*)-*anti*-**83k** only moderate results were achieved in the range of 64-69%. As already mentioned big influence on the enantiomeric excess of the nucleophile product (4*R*,5*S*)-*anti*-**128k** was observed by changing the reaction temperature. Performing the reaction at 0 °C led to an *ee*-value of 82% whereas the value was dropping to 67% when carrying out the reaction at room temperature.

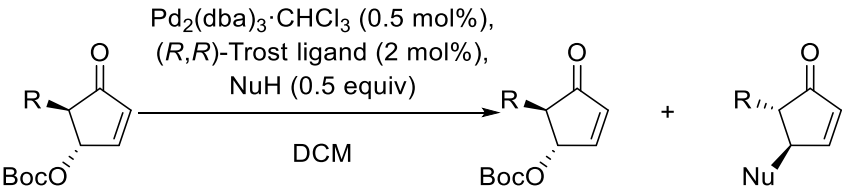
Compared to the increasing diastereoselectivity trend of methyl~hexyl → *iso*-butyl → *iso*-propyl substituted cyclopentenones **82** in the Piancatelli rearrangement the trend of increasing enantiopurity of the compounds **83** is very similar in the Tsuji-Trost allylation. In the Tsuji-Trost reaction best results were achieved employing *iso*-propyl-substituted cyclopentenone **83g** in the range of 90-97% enantiomeric excess followed by *iso*-butyl-cyclopentenone **83i** in the range of 70-88%. *Ee*-values of methyl and *n*-hexyl cyclopentenones (4*S*,5*R*)-*anti*-**83f** and **k** were similar in the range of 64-78%.
Furthermore, in view of the reaction time a very similar trend can been observed, since the reaction time of the methyl (±)-*anti*-**83f** and *n*-hexyl (±)-*anti*-**83k** substituted cyclopentenones are three hours, while full conversion of nucleophile in the reaction for *iso*-propyl (±)-*anti*-**83g** and *iso*-butyl (±)-*anti*-**83i** substituted compounds occurs in only 30 minutes.

However, reasoning the improving enantioselectivity of the reaction by increasing the steric bulkiness of the substituent of the cyclopentenone, the excellent results achieved by the unsubstituted cyclopentenone **83a** can not been explained.

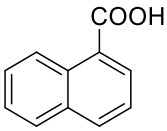
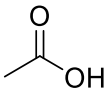
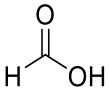
Other nucleophiles were tested in the Tsuji-Trost allylation next and are depicted in Table 10. Changing the nucleophile from *p*-methoxyphenol to naphthoic acid, the same trend of increasing enantiopurity of the compounds, as already discussed before, can been observed. In view of the reported results by Reiser[25] for the unsubstituted 4-oxo-cyclopentenone (±)-**83a** it is obvious that reaction temperature should be applied as low as possible for excellent enantioselectivity of the reaction (Table 10, entries 1-2). Employing same reaction conditions at -20 °C the lowest enantiopurity of recovered starting material (4*S*,5*R*)-*anti*-**83f** (59% *ee*) and product (4*R*,5*S*)-*anti*-**130f** (54% *ee*) is provided by the methyl-derivative (±)-*anti*-**83f** followed by moderate outcome of the *iso*-butyl substituted cyclopentenone with *ee*-values of 72% and 59% for recovered starting material (4*S*,5*R*)-*anti*-**83i** and product (4*R*,5*S*)-*anti*-**130i** (Table 10, entries 4 and 9). Conversion of the *tert*-butyl derivative (±)-*anti*-**83h** was not observed even under reflux conditions, apparently the steric bulkiness of the substituent is too high for the Tsuji-Trost allylation. Again, the reaction of the *iso*-propyl substituted cyclopentenone (±)-*anti*-**83g** achieved the best outcome with *ee*-values of 81%/ 90% and yields of 38%/ 41% of recovered starting material (4*S*,5*R*)-*anti*-**83g** and product (4*R*,5*S*)-*anti*-**130g** (Table 10, entry 6). Compared to the results with *p*-methoxyphenol as nucleophile in Table 9 the yields as well as the enantiopurities of all the substituted cyclopentenones **83a**,**f**-**i** are slightly lower (Table 10, entries 1-9).
The trend of improving enantioselectivity by increasing steric bulkiness of the substituent is independent from the nucleophile, however, the excellent results of the unsubstituted cyclopentenone can not been explained, again.

Interestingly, comparing the results of the methyl-cyclopentenone **83f** using different carboxylic acids such as naphthoic, acetic and formic acid as nucleophile, it can been seen that the *ee*-value 89% of the recovered starting material (4*S*,5*R*)-*anti*-**83f** is much higher employing acetic acid compared to the value of 59% enantiomeric excess using naphthoic acid (Table 10, entries 4 and 11). However, employing the smallest carboxylic acid, formic acid, did not lead to any conversion of the starting material, apparently the acidity of formic acid is too high (Table 10, entry 12).

Table 10. Asymmetric Tsuji Trost allylation of *anti*-cyclopentenones (±)-*anti*-**83** with carboxylic acids as nucleophile.



(±)-*anti*-**83a**,**f-i** (4S,5R)-*anti*-**83a**,**f-i** (4R,5S)-*anti*-**130a**,**f-i** for NuH=naphthoic acid
(4R,5S)-*anti*-**131f** for NuH=acetic acid
(4R,5S)-*anti*-**132f** for NuH=formic acid

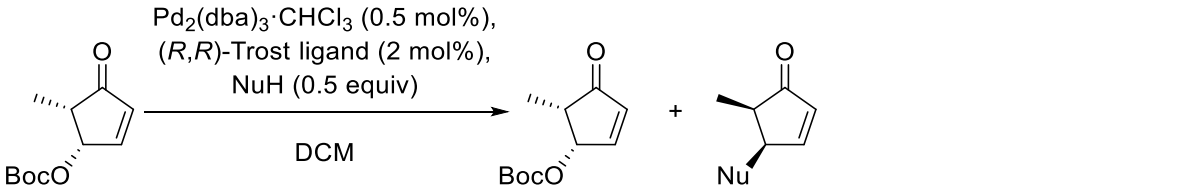
entry[a]	NuH	R	t [h]	T [°C]	yield of *anti*-83 [%]	*ee* [%][b]	yield of *anti*-130-132 [%]	*ee* [%][b]	*S*[c]
1[25]		H	4	-20	43	>99	45	>99	501
2[25]		**83a**	4	0	50	25	30	77	11
3		Me	20	-40	no reaction				
4		**83f**	20	-20	31	59	37	54	5
5		*i*Pr	24	-40	no reaction				
6		**83g**	4	-20	38	81	41	90	36
7		*t*Bu **83h**	24	reflux	no reaction				
8		*i*Bu	24	-40	no reaction				
9		**83i**	24	-20	39	72	40	59	6
10		Me	24	0	no reaction				
11		**83f**	1	25	30	89	37	66	7
12		Me **83f**	24	reflux	no reaction				

[a]Reaction conditions: cyclopentenone (±)-*anti*-**83** (1.0 mmol), specified nucleophile, $Pd_2(dba)_3 \cdot CHCl_3$ (5.0 µmol, 1.0 mol% based on nucleophile), Trost ligand (*R*,*R*)-**32** (18.5 µmol, 3.7 mol% based on the nucleophile) in DCM (4 mL).[b]Determined by chiral HPLC. [c]Selectivity factor.

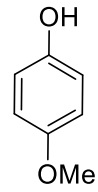
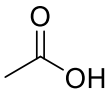
The following experiments were carried out with the *syn*-diastereomer (±)-*syn*-**83f** of the methyl substituted cyclopentenone since this was the only *syn*-diastereomer of all cyclopentenones **83** obtained after column chromatography of the Boc-protection (Table 11). In view of the methodology of the Tsuji-Trost allylation with methyl substituted cyclopentenone (±)-**83f** in *anti*-

and *syn*-conformation the kinetic resolution of both compounds was carried out with acetic acid and *p*-methoxyphenol to test the influence of the nucleophiles as well.

Table 11. Asymmetric Tsuji-Trost allylation of *syn*-cyclopentenone (±)-*syn*-**83f**.



(±)-*syn*-**83f** (4S,5S)-*syn*-**83f** (4R,5R)-*syn*-**128f** for NuH= *p*-methoxyphenol
(4R,5R)-*syn*-**131f** for NuH= acetic acid

entry[a]	NuH	t [h]	T [°C]	yield of *syn*-83f [%]	*ee* [%][b]	yield of *syn*-128f/131f [%]	*ee* [%][b]	*S*[c]
1		24	-20	no reaction				
2		3	0	47	96	47	96	134
3		1	rt	45	>99	48	96	146
4		24	0	no reaction				
5		1	rt	40	>99	39	97	124

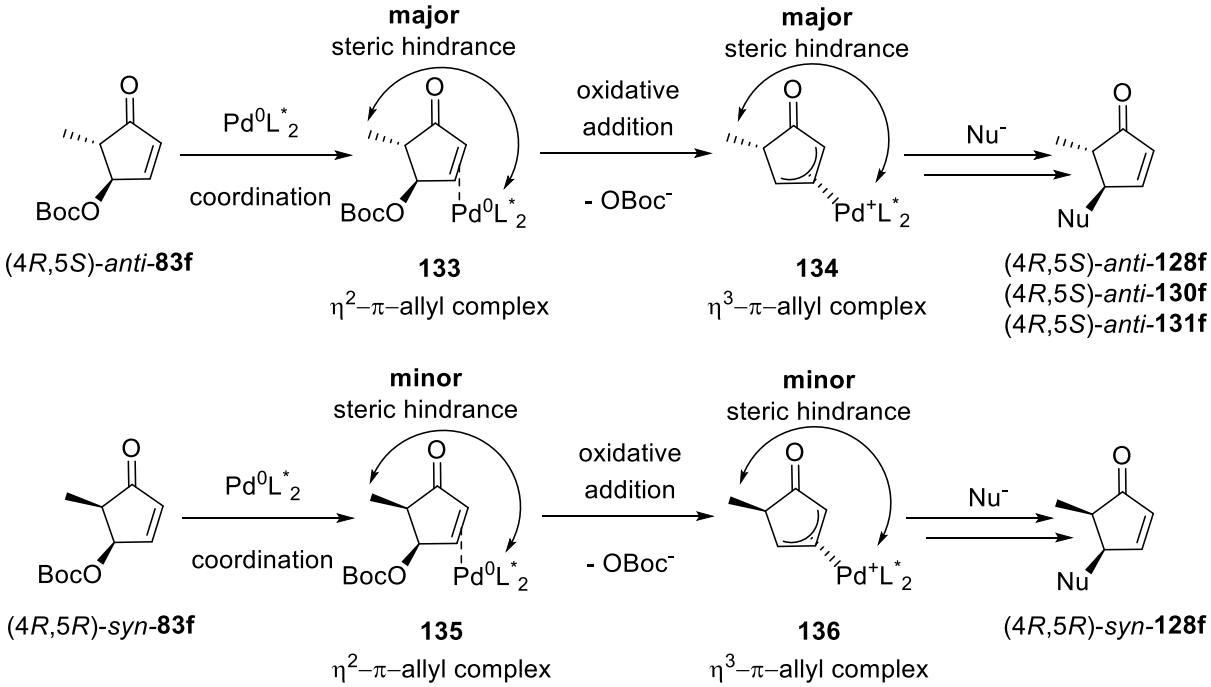
[a]Reaction conditions: cyclopentenone (±)-*syn*-**83f** (1.0 mmol), specified nucleophile, $Pd_2(dba)_3 \cdot CHCl_3$ (5.0 µmol, 1.0 mol% based on nucleophile), Trost ligand (*R*,*R*)-**32** (18.5 µmol, 3.7 mol% based on the nucleophile) in DCM (4 mL). [b]Determined by chiral HPLC. [c]Selectivity factor.

Fortunately, the outcome of all reactions using the *syn*-diastereomer (±)-*syn*-**83f** provided excellent enantioselectivity, interestingly the enantiomeric excess of recovered starting material (4*S*,5*S*)-*syn*-**83f** could be improved from 96% to >99% enantiopurity by raising the reaction temperature from 0 °C to room temperature (Table 10, entries 2-3). The reaction time was reduced from three to one hour that is in accordance to kinetic resolution, however, the enantiopurity of the product (4*R*,5*R*)-*syn*-**128f** was not influenced by change of the reaction temperature (96% *ee* in both cases). Since the yield of nucleophile product (4*R*,5*R*)-*syn*-**128f** as well as the enantiomeric excess were very good in the experiment carried out at room temperature (Table 10, entry 3), the selectivity factor *S* with a value of 146 was excellent compared to the value of 16 deriving from the reaction with the *anti*-diastereomer (4*S*,5*R*)-*anti*-**83f** (Table 9, entry 5). Changing the nucleophile from *p*-methoxyphenol to acetic acid very similar results were achieved since the recovered *syn*-starting material (4*S*,5*S*)-*syn*-**83f** was obtained enantiopure as well, furthermore, the yield of latter was raised from 30% to 40% compared to the reaction with the *anti*-cyclopentenone (4*S*,5*R*)-*anti*-**83f** (Table 9 entry 11 and

Table 10 entry 5). Compared to *anti*-product (4*R*,5*S*)-*anti*-**128f**, especially the enantiopurity of the *syn*-product (4*R*,5*R*)-*syn*-**128f** was improved very well from *ee*-value 66% to 97% while the yield was similar in the range of 40%.

The absolute configuration of the 4-*O*Boc stereocenter of the recovered starting material (4*S*,5*S*)-*syn*-**83f** was proved *via* X-Ray crystallography (see Figure 10) of the aldol product **84** formed in the subsequent aldol reaction assuming nucleophile addition in *anti*-conformation in view of the 4-*O*Boc-moiety (see Chapter 2.5 (One-pot aldol reaction)).

In conclusion, the Tsuji-Trost allylation of *anti*- and *syn*-cyclopentenone (±)-**83f** achieved very different results applying same nucleophiles under identical reaction conditions. Therefore, the configuration of the methyl substituent plays a very important role in the kinetic resolution.

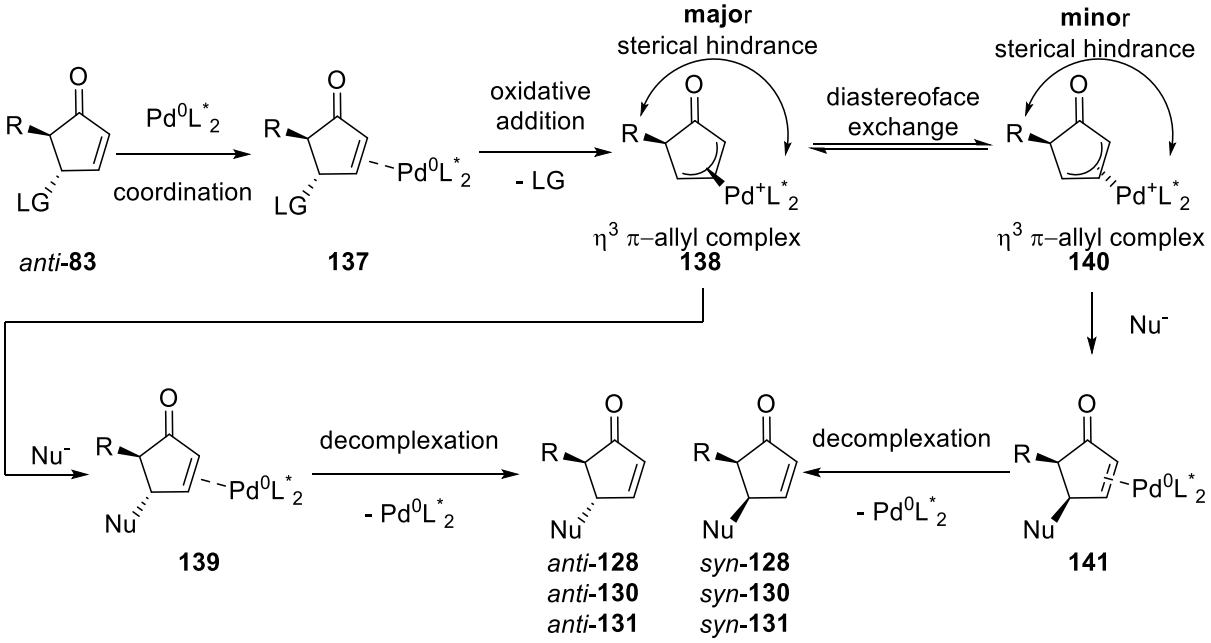


Scheme 33. Mechanism of Tsuji-Trost allylation of *anti*- and *syn*-cyclopentenone **83f**.

Assuming Pd coordinates to the double bond of the cyclopentenones **83f** in *anti*-configuration of the directing *O*Boc moiety, the η^2-π-allyl complex **133**/**135** is formed with Pd below the ring plane in both cases (Scheme 33). In the η^2-**133** as well as in the η^3-π-allyl complex **134** that is formed *via* oxidative addition a major steric hindrance arises between coordinated Pd and the methyl substituent of the *anti*-diastereomer since both are located on the same side of the ring plane. In the case of the *syn*-diastereomer the Pd with its ligands and the methyl substituent from the cyclopentenone are located on different sides of the ring plane in the intermediates

135 and **136** and thus, merely a minor steric hindrance occurs. These favored intermediates deriving from the *syn*-diastereomer could be responsible for the higher enantioselectivity of the allylation with the *syn*-cyclopentenone **83f**.

However, reasoning that major steric hindrance is decreasing the enantioselectivity of the reaction, is not in accordance with the positive trend of enhanced enantioselectivity by increasing the steric bulkiness of the substituent that was discussed for the *anti*-diastereomers. Diastereoface exchange of the coordinated Pd of the intermediate **138** could circumvent steric issues by migration of Pd to the other side of the ring plane forming the more stable complex **140** (Scheme 34). However, although this process is known for ring systems in Tsuji-Trost[57] allylations, this thesis can be excluded since no formation of *syn*-product **83** was observed in any experiment carried out with cyclopentenone (±)-*anti*-**83** as starting material (proven by 2D-NOESY spectra in all cases).



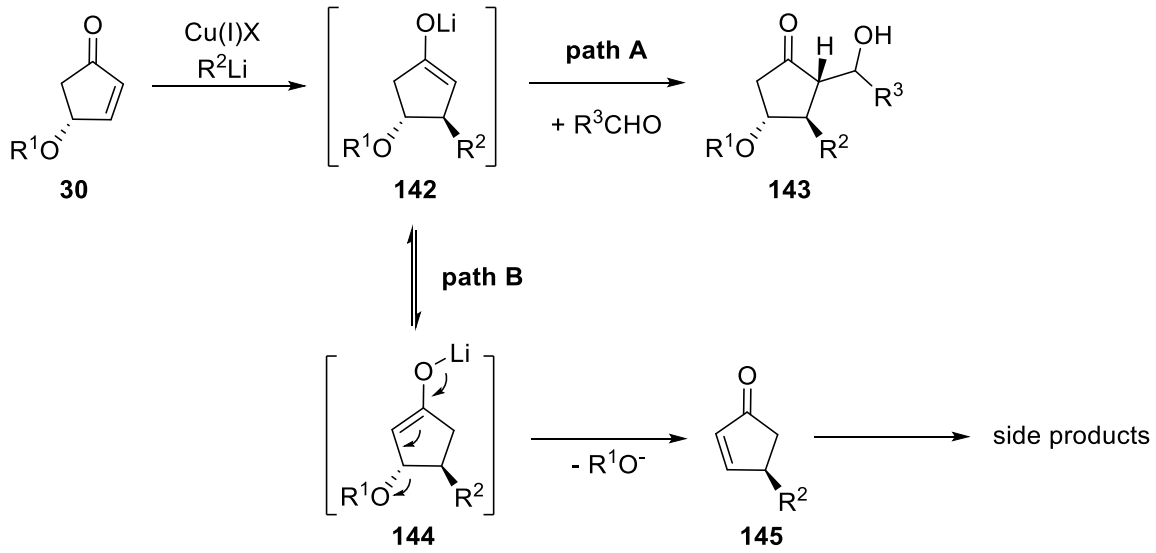
Scheme 34. Mechanism of Tsuji-Trost allylation of *anti*-cyclopentenone **83** undergoing diastereoface exchange.

2.5 One-pot aldol reaction

2.5.1 Introduction

Aldol reactions of *α*,*β*-unsaturated carbonyls with nucleophiles and electrophiles are well known reactions and very suitable for creating a number of stereocenters in one step.[61]

Addition of organometallic compounds such as Grignard reagents or lithiumorganyls R^2Li to *α*,*β*-unsaturated carbonyls **30** in presence of Cu(I)-salts generates lithium enolates **142** that can be trapped with electrophiles, e.g. aldehydes (Scheme 35, **path A**) providing the desired product **143**.[62] This reaction sequence involves some issues presumably attributed to the complex reaction nature of the cascade reaction. Facile migration of the formed double bond of the enolate **142** can lead to an elimination sequence of the 4-*O*-moiety in C4-position of the intermediate **144**, fortunately, this side reaction can be inhibited by employing reactive aldehydes.[63]



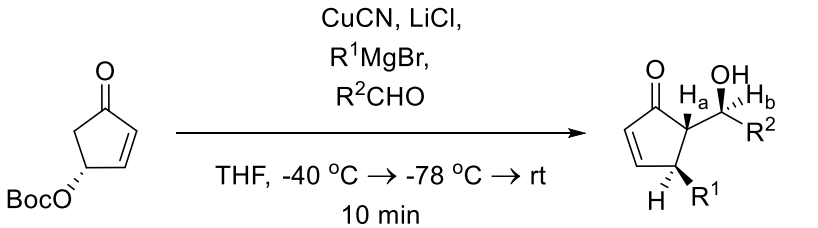
Scheme 35. Side reaction of organocuprates with cyclopentenones.

Toward prostaglandin synthesis Noyori[64–66] examined this aldol reaction employing 4-*O*TBS-protected cyclopentenones receiving no diastereoselectivity of the alcohol stereocenter in C1`-position except in few cases requiring steric demanding aldehydes. In 2015, Reiser et al.[39] described a new diastereoselective protocol. For this transformation 4-*O*Boc protected cyclopentenone (*R*)-**30b** was employed obtaining only one single diastereomer (+)-**146** as product, interestingly, in all cases elimination of the 4-*O*Boc moiety was observed. In the report various alkyl, alkenyl and aryl Grignard reagents as well as aldehydes were successfully converted (Table 12). The relative stereochemistry between H_a and H_b was determined *via* coupling constants of the ^{1}H-NMR spectra according to Kobayashi[67], for *anti*-relation the coupling constant $^3J_{Ha\text{-}Hb}$ is in the range of 6-10 Hz while for *syn*-conformation a value of $^3J_{Ha\text{-}Hb}$ in the range of 3 Hz was reported.

Employing phenyl- and cyclohexylmagnesium bromide the reaction provided very good yields in the range of 70-80% (Table 12), *iso*-propenylmagnesium bromide as Grignard reagent

accomplished good results in the range of 60-70%. With the use of *n*-heptylmagnesium bromide, unfortunately, the yields of the obtained products decreased in all cases to 30-36% yield. Considering the different ranges of yields it is obvious that the reactivity of the Grignard reagent has a strong influence on the reaction. Interestingly, the reaction outcome was hardly affected by the choice of aldehyde in terms of a given Grignard reagent.

Table 12. "One-pot aldol reaction" synthesis reported by Reiser and coworkers.[39]

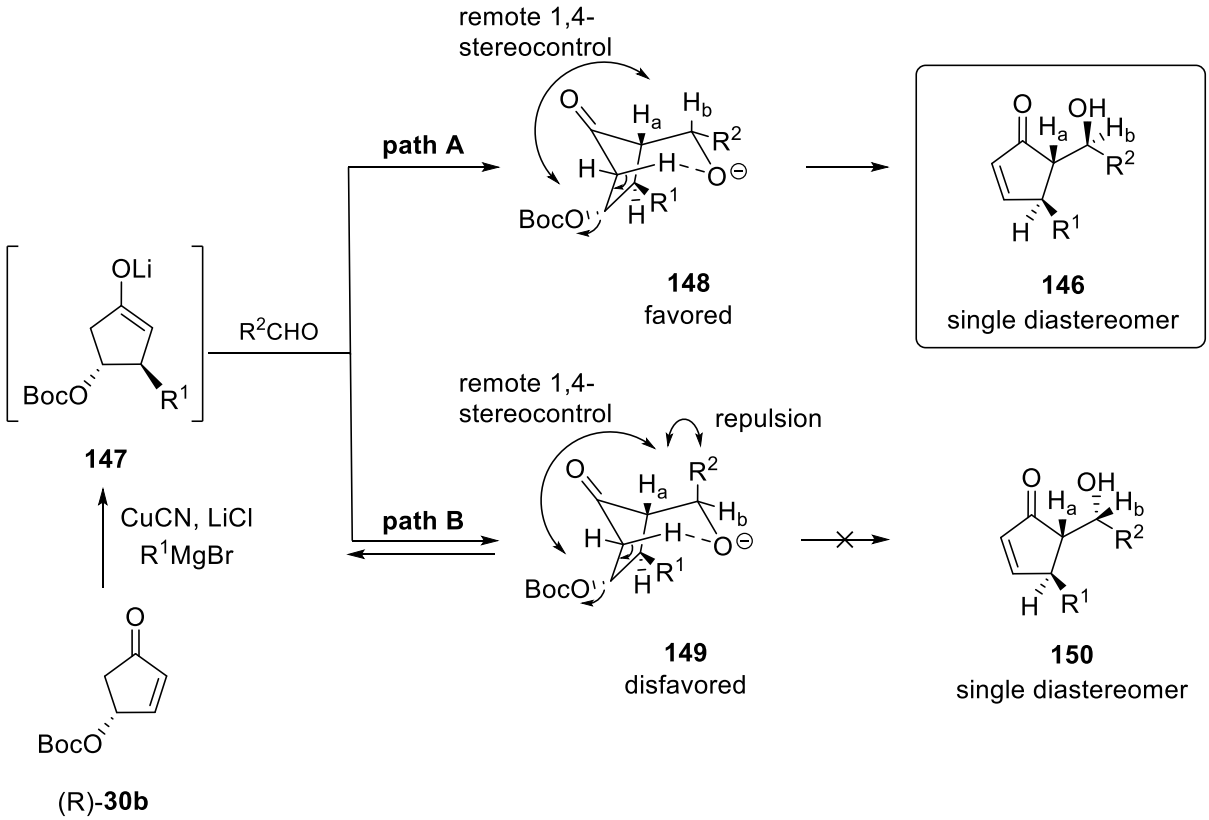


(*R*)-**30b**
>99% ee

(+)-**146**
>99% *de*, >98% ee

R^1MgBr	R^2				
MgBr	**a** (72%)	**b** (68%)	**c** (70%)	**d** (78%)	**e** (72%)
MgBr	**f** (66%)	**g** (66%)	**h** (70%)	**i** (62%)	**j** (59%)
MgBr	**k** (77%)	**l** (70%)	**m** (75%)	**n** (72%)	**o** (74%)
MgBr	**p** (34%)	**q** (32%)	**r** (31%)	**s** (36%)	**t** (30%)

In the report of Reiser and coworkers[39] a mechanism was proposed for this diastereoselective aldol reaction (Scheme 36). After formation of the lithium enolate **147** the addition of the approaching aldehyde can occur in two different pathways (**path A** and **path B**) forming a six membered ring. The intermediate **149** in **path B** is disfavored due to steric repulsion of H_a and the substituent R^2 of the aldehyde in axial position. The conformation of the intermediate **148** is favored followed by elimination of 4-*O*Boc moiety to the final product **146** (**path A**).



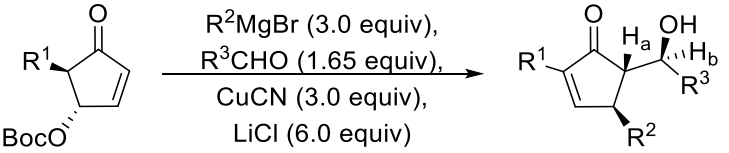
Scheme 36. Proposed mechanism for the stereoinduction in the aldol reaction reported by Reiser and coworkers.[39]

2.5.2 Results and Discussion

Directed aldol reaction is a very powerful synthetic strategy for generating new stereocenters. In terms of the enantioselective aldol reaction of cyclopentenone with organocuprate and aldehyde three new stereogenic centers are provided remote by the 4-*O*-Boc-moiety of the cyclopentenone. In view of the report of aldol reaction employing Boc-protected 4-hydroxycyclopentenones (*R*)-**30b** by Reiser[39] in 2015 the methodology of this reaction was explored applying 5-alkyl-substituted cyclopentenones **83**. Especially the stereocontrol of the forming alcohol in C1`-position of the desired product **84** was examined.

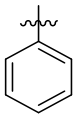
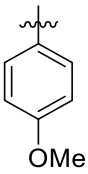
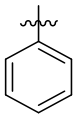
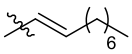
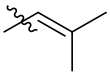
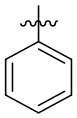
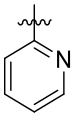
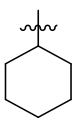
In general, the organocuprate was formed at -40 °C *via* addition of the specified Grignard to a solution of CuCN and LiCl in THF. After cooling the solution to -78 °C, the *anti*-configurated alkyl substituted cyclopentenone **83** was added forming the enolate within several minutes followed by subsequent addition of the aldehyde providing the final product **84** in a “one pot aldol reaction” with a total reaction time of ten minutes. The results of the directed aldol reaction of the alkyl substituted cyclopentenones **83** are depicted in Table 13.

Table 13. Directed aldol reaction of substituted cyclopentenones in a "one-pot aldol reaction".



(*R*)-**30b** R^1=H
(±)-**83** R^1=Me, ^{i}Pr,^{t}Bu,^{n}Hex

(+)-**146** R^1=H
(±)-**84** R^1=Me, ^{i}Pr,^{t}Bu,^{n}Hex

entry	R^1	R^2	R^3	$^3J_{Ha-Hb}$ [Hz]	product	yield [%]
1[39]	H			9.5	(+)-**146d**	78
2	Me			9.6	(±)-**84fa**	75
3	^{i}Pr			9.5	(±)-**84ga**	74
4	^{t}Bu			-	(±)-**84ha**	no reaction
5	^{n}Hex			9.5	(±)-**84ka**	68
6[39]	H			8.6	(+)**146c**	70
7	^{i}Pr			8.6	(±)-**84gb**	70
8	^{t}Bu			-	(±)-**84hb**	no reaction
9	Me			8.9	(±)-**84fb**	62
10	^{n}Hex			8.8	(±)-**84kb**	66
11	H				(±)-**146u**	
12	Me				(±)-**84fc**	
13	^{i}Pr			-	(±)-**84gc**	no reaction
14	^{t}Bu				(±)-**84hc**	
15	^{n}Hex				(±)-**84kc**	
16[39]	H			8.4	(+)**146j**	59
17	Me			6.5	(±)-**84fd**	64
18	^{i}Pr			6.6	(±)-**84gd**	57
19	^{t}Bu			-	(±)-**84hd**	no reaction
20	^{n}Hex			6.5	(±)-**84kd**	56
21[39]	H			7.7	(+)**146k**	77
22	Me			8.0	(±)-**84fe**	43
23	^{i}Pr			8.1	(±)-**84ge**	56
24	^{t}Bu			-	(±)-**84he**	no reaction
25	^{n}Hex			-	(±)-**84ke**	no reaction

[a]Reaction conditions: cyclopentenone (*R*)-**30b**/**83** (0.38 mmol, 1.0 equiv), solvent THF (4 mL).

In general, in all successful reaction experiments elimination of the *O*Boc- moiety was observed, furthermore, the diastereoselectivity of the reaction was excellent since one single diastereomer was received in each reaction. The configuration of the three newly generated stereocenters of enantiomeric product **84fa** was confirmed *via* X-Ray crystallography (Figure 10). Moreover, the configuration of the stereocenter of the formed alcohols is in agreement with the report of Kobayashi[67] in 2002 since the obtained coupling constants $^{3}J_{Ha\text{-}Hb}$ of the products are in the reported range for *anti*-configurated alcohol product. Values of 3 Hz for $^{3}J_{Ha\text{-}Hb}$ coupling constant would point out the corresponding *syn*-isomer, however, this case was not observed.

Compared to the observed reaction trends of the alkyl substituted cyclopentenones **82**-**83** in Piancatelli rearrangement (2.3 Piancatelli Rearrangement) and Tsuji-Trost allylation (2.4 Asymmetric Tsuji-Trost Allylation) no reaction trend in improved selectivity with increasing steric demanding alkyl substituents in C5-position can be observed since all aldol products **84** were obtained as single diastereomers. However, limitation of the reaction scope is given, again, by use of *tert*-butyl substituted cyclopentenone **83h** since no aldol reaction was observed at all. The yield of the reaction is less dependent on the alkyl substituent in C5-position of the cyclopentenone **83** than on the employed nucleophile (organocuprate) and electrophile (aldehyde) since the yields of the alkyl substituted cyclopentenones **84** are similar for each specified nucleophile-electrophile pair (Table 13, entries 1-5, 6-10,16-20) except in the case of cyclohexylcuprate and octanal (Table 13, entries 21-25) that provided very different results.

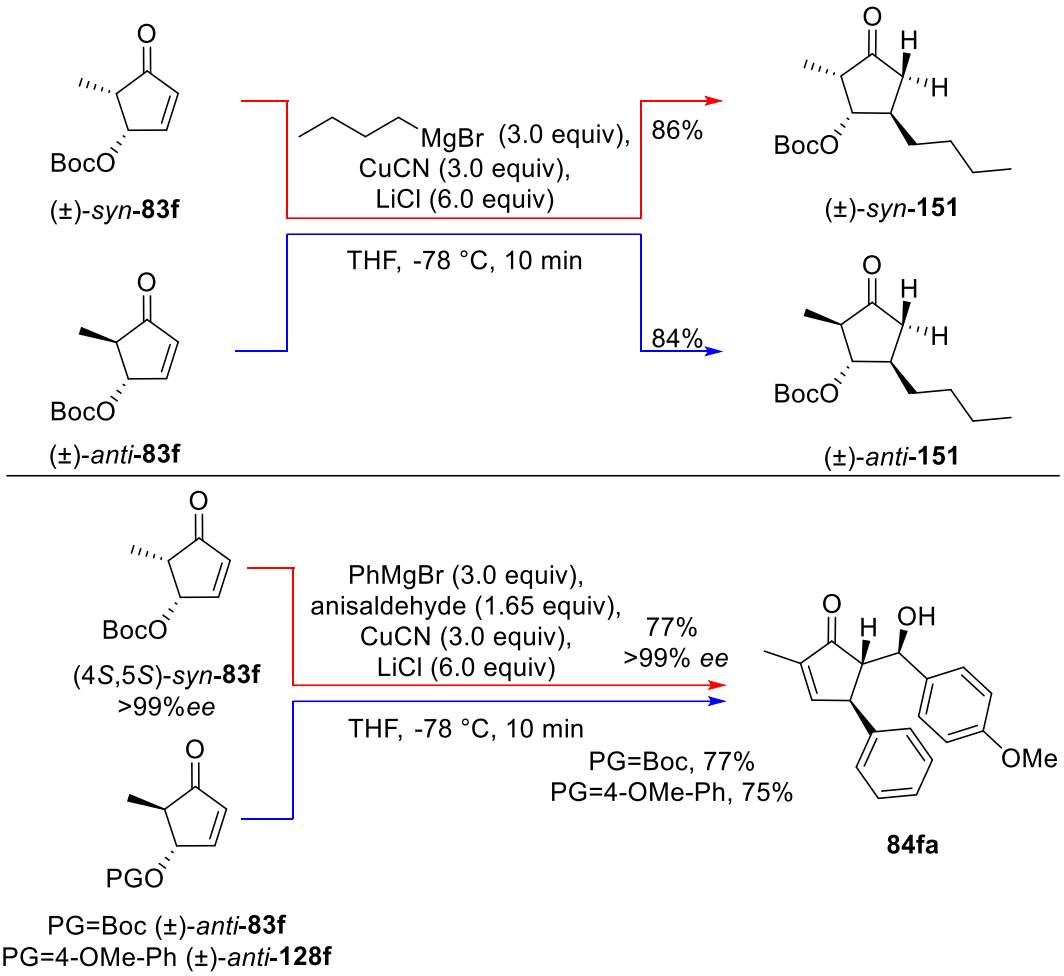
It is obvious that the usage of electron rich aromatic cuprate and anisaldehyde provide best yields of the products (+)-**146d**/ (±)-**84fa**-**ka** in a range of 68-78% compared to the other results in Table 13. As already mentioned, the different alkyl substituents in C5-position of the ring did not influence the yield strongly (Table 13, entries 1-5). Changing the aromatic aldehyde to *α*,*β*-unsaturated Michael acceptors decreased the yield of the products (+)-**146c**/ (±)-**84fb**-**kb** slightly to a range of 62-70%. Fortunately, the chemoselectivity of the aldol reaction was very high since all products were provided with the linkage of the preformed enolate to the hard carbonyl center of the aldehyde (Table 13, entries 6-10). Changing the aldehyde to steric demanding pivalaldehyde no reaction for all tested cyclopentenones occurred at all showing limitation in the scope for aldehydes (Table 13, entries 11-15).

Carrying out the reaction with alkenyl-organocuprate combined with aromatic picolinaldehyde provided moderate yields of the products (+)-**146j**/ (±)-**84fd**-**kd** in the range of 56-64% (Table 13, entries 16-20). Combination of electron poor sp^3 cyclohexyl-cuprate and octanal yielded

worst results of the products (+)-**146k**/ (±)-**84fe**-**ke** in the range of 43-77%, whereby the alkyl substitution in C5-position of the cyclopentenone influenced the yield of the reaction strongly. The outcome of the unsubstituted cyclopentenone (+)-**146k** was high with 77% yield in comparison to the moderate yields of 43%/ 56% for the methyl/ *iso*-propyl substituted cyclopentenones (±)-**84fe**/ (±)-**84ge**. Interestingly, additional to the negative result of the *tert*-butyl-substituted cyclopentenone no reaction was observed as well employing the *n*-hexyl substituted cyclopentenone (±)-**83k**.

In view of the reported results it can be seen that the yield of the reaction is not strongly dependent on the substitution in C5-position of the cyclopentenone but on the nucleophile in most cases. Aryl cuprate as electron rich nucleophile provided best results followed by the alkenyl nucleophile that was giving lower yields although it was combined with the electron rich aromatic picolinaldehyde. Worst results were obtained employing electron poor sp^3 centered cyclohexyl cuprate and therefore these results are in accordance with a new trend of enhanced yield by usage of electron richer nucleophiles.

With the herein reported 4-*O*-Boc-protected cyclopentenones **84** excellent selectivity of the stereocenter in C1`-position is observed, however, in all cases elimination of the 4-*O*Boc-moiety takes place as well. Therefore, mechanistic studies were carried out for a deeper insight for the reaction. Focus of the study was the influence of the *anti*/*syn*-configuration of the alkyl substituent in C5-position as well as the protecting group of the hydroxygroup of the cyclopentenone **83**.
Carrying out the procedure for the “one-pot aldol reaction” without addition of the aldehyde gave interesting outcome **151** of the reaction of both *anti*/*syn*-cyclopentenones **83** in very good yield (Scheme 37). No elimination of the *O*Boc-moiety was observed in both cases, furthermore, no epimerization of the 5-methyl substituted stereocenter of product **151** took place collaborated by NOESY spectra. These experiments prove the fact that the elimination of the *O*Boc-moiety occurs during or after the addition of the aldehyde when carrying out the complete “one-pot aldol reaction” procedure.



Scheme 37. Mechanistic studies towards the “one-pot aldol reaction”.

In the next experiments the influence of the *anti*/*syn*-conformation of the cyclopentenones **83f**/**128f** was examined in view of the reaction outcome. Interestingly, no difference in reaction outcome **84fa** was observed since both 4-*O*Boc protected diastereomers (4*S*,5*S*)-*syn*-**83f** and (±)-*anti*-**83f** gave the same elimination product in same yield under excellent diastereoselectivity since one single diastereomer **84fa** was obtained in both cases. Additionally, the “one-pot aldol reaction“ employing the enantiopure *syn*-cyclopentenone (4*S*,5*S*)-*syn*-**83f** provided the aldol product **84fa** with an enantiomeric excess of >99% as well. Therefore, the “one-pot aldol reaction“ is suitable for enantioselective natural product synthesis (see Chapter 3 Synthesis of Phomapentenone A). Changing the protection group from Boc to 4-methoxyphenol (±)-*anti*-**128f** did also lead to the elimination product as one single diastereomer (±)-**84fa**. In general, the presumed structure of the products **84** in the “one-pot aldol reaction” was proven by X-Ray analysis of compound **84fa** (Figure 10).

Reiser et al.[39] reported low diastereoselectivity (1.5:1 epimers) for the alcohol stereocenter in C1`-position carrying out their protocol for “one-pot aldol reaction“ employing 4-*O*TBS-protected cyclopentenone (±)-**152a**. This observation is in line with the observation of Noyori[64–66], therefore, the elimination step and diastereoselectivity of the stereocenter in C1`-position is dependent on the protection group of the hydroxygroup of the cyclopentenone. Performing the aldol reaction with the *anti*-configurated 5-methyl-4-*O*TBS cyclopentenone (±)-**152b**, a mixture of epimers (±)-**153b** was obtained as well, however, the selectivity of this reaction compared to the unsubstituted cyclopentenone (±)-**153a** was higher since the ratio of the epimers (±)-**153b** was 4:1 compared to the compounds (±)-**153a** (1.5:1 epimers) (Scheme 37). The *anti*-conformation between the methyl group in C5-position and *O*TBS-group in C4-position of the product mixture **153** is proven by NOESY spectra.

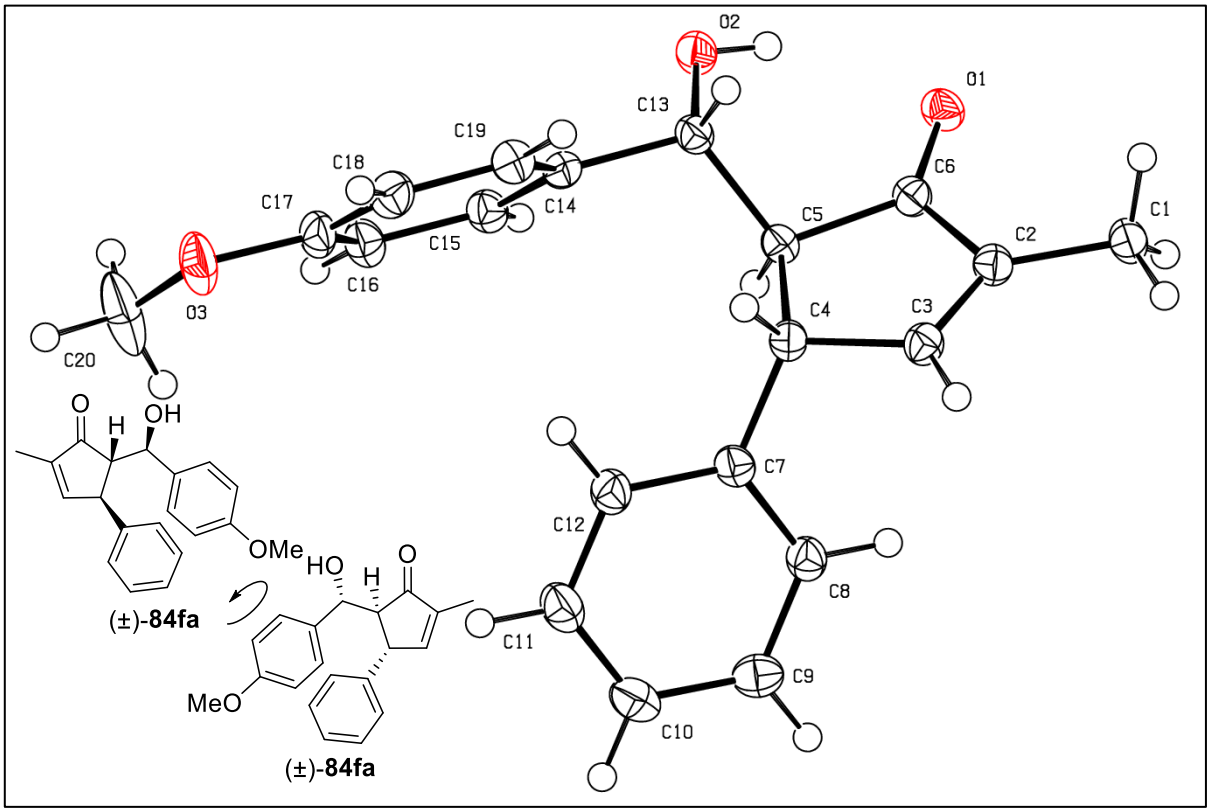
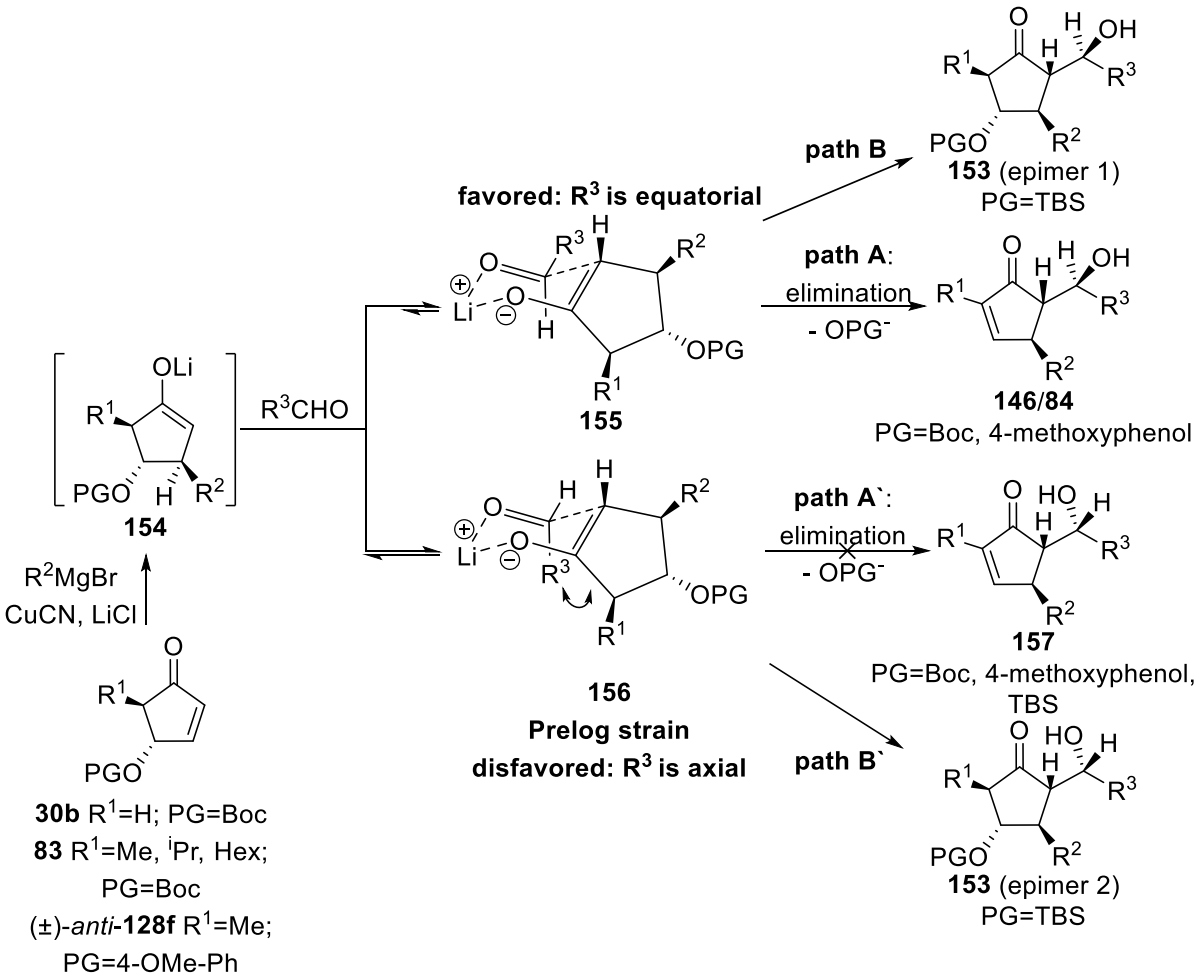


Figure 10. X-Ray structure of cyclopentenone (±)-**84fa**.

Summarizing, the *anti*/*syn*-conformation between 5-alkyl substitution and 4-*O*Boc/methoxyphenol has no influence on the reaction outcome since the same single product was obtained as a single diastereomer, furthermore, the elimination step takes place during or after the addition of the aldehyde. Boc or 4-methoxyphenol as protecting group for the hydroxygroup lead to elimination and excellent diastereoselectivity whereby usage of TBS as protecting group lead to mixture of epimers at the C1`-position.



Scheme 38. Proposed mechanism for “one-pot aldol reaction“ involving Zimmermann-Traxler transition state.

Taking all these facts into account a new mechanism herein is proposed involving the Zimmermann-Traxler model as transition state (Scheme 38).

The nucleophile containing the substituent R^2 attacks as a cuprate to the soft C-C double bond of the enone system of the cyclopentenones **30b**/**83**/**128f** in *anti*-conformation to the steric demanding *O*Boc-moiety. Li-coordinated enolate **154** is generated that is undergoing the Zimmermann Traxler transition state with the approaching aldehyde R^3CHO forming a six membered chair **155**/**156**. In order to avoid steric hindrance, the aldehyde is attached to the cyclopentenone in *anti*-conformation to the substituent R^2. In the chair conformation two possibilities arise for the conformation of the R^3-moiety: equatorial conformation forming the more stable transition state **155** or axial positioning leading to less stable transition state **156** due to 1,3 diaxial Prelog strain[68] in chair conformations.

It is not clear in which step the elimination of the *O*Boc-moiety takes place, however, in view of the mechanistic studies (Scheme 37) it is known that the elimination does not occur before

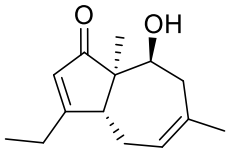
addition of the aldehyde. The conformation of the outcome following the proposed mechanism is in accordance with the outcome of the “one-pot aldol reaction“ proven by X-Ray crystallography in Figure 10.

However, explanation for the observation of excellent diastereoselectivity including elimination step is still not given. Moreover, it is not obvious why Boc and 4-methoxyphenol as protecting group show high diastereoselectivity and elimination process whereas TBS leads to low diastereoselectivity and does not undergo the elimination step. Herein, it is proposed that the stereocontrol at C1`-position is dependent on the leaving group OPG^-. A fast, irreversible elimination of good leaving groups, e.g. $OBoc^-$ and 4-methoxyphenolate, could shift the equilibrium between the two transition states **155** and **156** towards the formation of the more stable intermediate **155** giving rise to the desired products **146**/**83** (**path A**). In case of worse leaving groups as $OTBS^-$, probably an equilibrium of both intermediates **155** and **156** occurs leading to mixture of epimers **153** (**path B** and **path B`**) without elimination process of $OPG^-$ (product **157**, **path A`**).

2.6 Studies Towards Synthesis of Aculene D

2.6.1 Introduction

In view of natural product synthesis and methodology of the reported directed aldol reaction in Chapter 2.5 (One-pot aldol reaction) studies towards synthesis of Aculene D (**158**) seemed attractive.



Aculene D
(**158**)

Figure 11. Chemical structure of Aculene D (**158**) reported by Peterson and coworkers.[69]

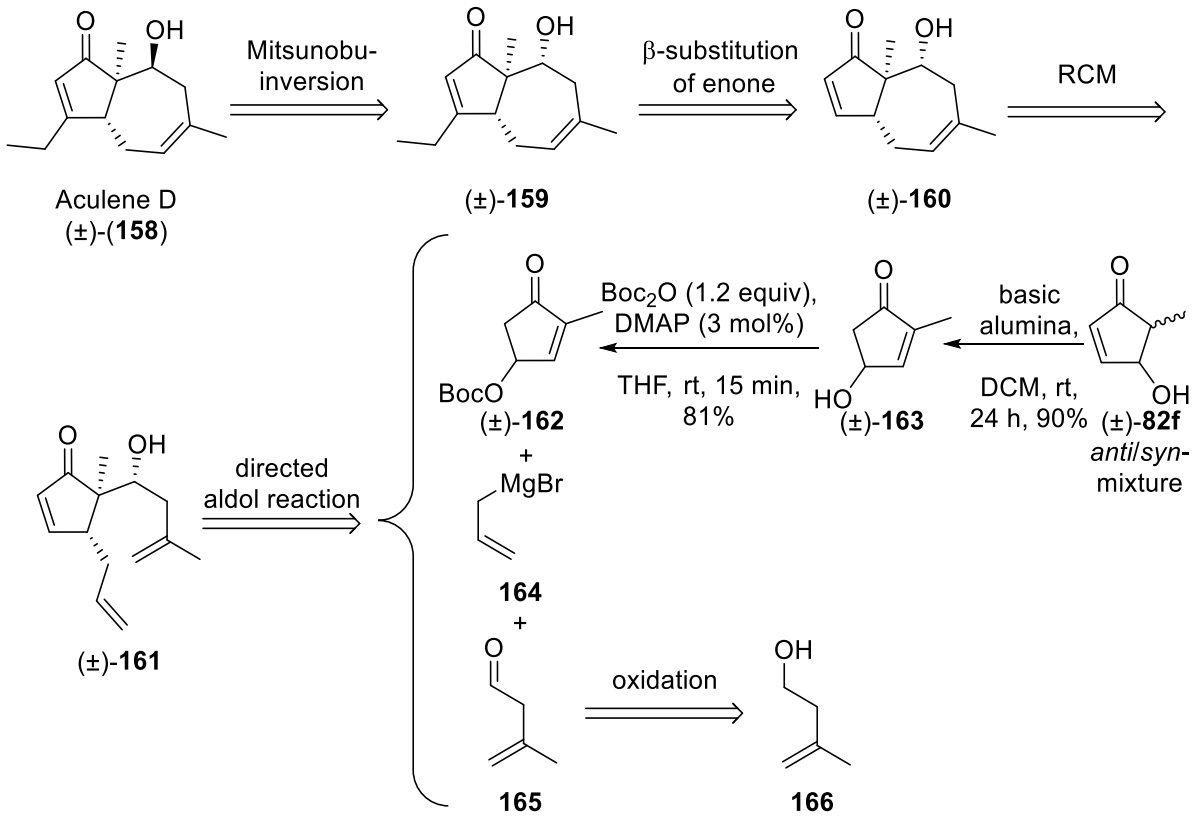
Aculene D (**158**) was discovered in 2014 by Peterson[69] and coworkers, in 2017 Zhao et. al.[70] reported the biological testing and isolation of latter from fermentation broth of *Penicillium* sp. SCS-KFD08 associated with a marine animal *Sipunculus nudus* from the Haikou bay of China.

The compound **158** showed quorum sensing inhibitory effects (MIC[2]: 300 µM) against Chromobacterium violaceum CV026 that is a multi-drug resistant, aquatic bacterium infecting humans and causing abscesses. Quorum sensing inhibitors are supposed to be a further way of bacterial infection inhabitation since they control the production of virulence factors through a population density-dependent manner *via* cell-to-cell communication.[70]

2.6.2 Results and Discussion

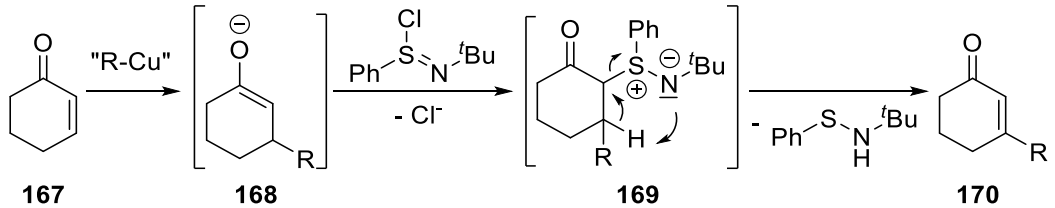
As depicted in Scheme 39, key step of racemic synthesis of compound (±)-**158** is the reported "one-pot aldol reaction" (*vide supra*) employing the 2-substituted cyclopentenone (±)-**162** involving two quaternary carbon centers. The starting material (±)-**162** can be easily provided by literature known rearrangement of diastereomeric mixture of 4-hydroxy-5-methyl-cyclopentenone ((±)-**82f**) into the stable compound (±)-**163** *via* basic alumina. Subsequent Boc-protection of the alcohol (±)-**163** gave the desired compound (±)-**162** in good yield of 81%. The required aldehyde **165** can be generated *via* oxidation of the less expensive alcohol **166**, allylmagnesium bromide **164** is commercially available. For enantiopure synthesis of final product Aculene D (**158**) kinetic resolution of cyclopentenone (±)-**162** would be necessary. However, for the methodology of the extended "one-pot aldol reaction" with quaternary cyclopentenone (±)-**162** racemic starting material was sufficient.
After the key step subsequent ring closing metathesis could form the desired seven membered ring (±)-**160** followed by *β*-substitution of the cyclopentenone ring. Mitsunobu inversion of the alcohol (±)-**159** could provide the final product Aculene D ((±)-**158**) in racemic fashion.

[2] MIC: minimum concentration of compound at which no visible growth of test strain can be observed.



Scheme 39. Retrosynthetic approach to synthesis of Aculene D (±)-(**158**) in racemic fashion.

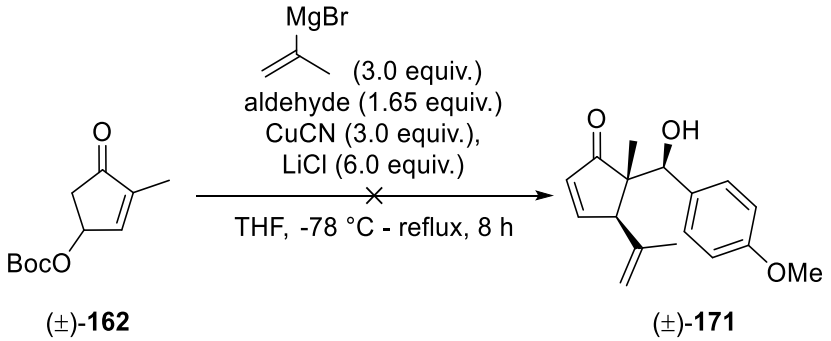
β-Substitution of cyclohexenone and -pentenone systems were successfully described by Matsuo[71] in 2005 and can be used for the synthesis of compound **159** starting from precursor **160** (Scheme 39). Conjugate addition of cyanocuprates to 1,4-Michael systems **167** generates the enolate **168** that is trapped with *N-tert*-butylbenzenesulfinimidoyl chloride (Scheme 40) providing the intermediate **169**. Subsequent elimination of latter achieves the *β*-alkyl substituted enone **170**.



Scheme 40. *β*-Substitution of cyclohexanone **167** employing cuprate and *N-tert*-butylbenzenesulfinimidoyl chloride reported by Matsuo and coworkers[71].

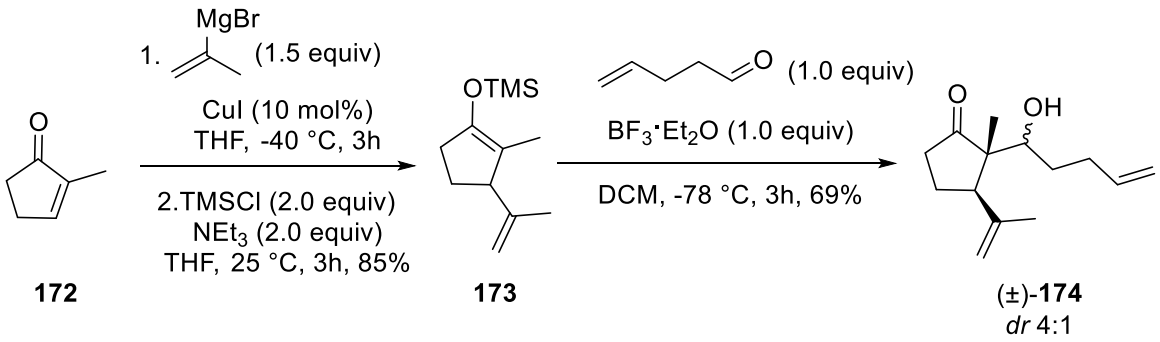
Carrying out the aldol reaction in a “one-pot aldol reaction“ applying the reported procedure in Chapter 2.5 One-pot aldol reaction) did not lead to any product formation, furthermore, the

starting material (±)-**162** was not converted at the low reaction temperature of -78 °C. Therefore, reaction temperature was raised in steps of 20 °C and stirred for each period of one hour with a total reaction time of eight hours. However, the reaction did not provide any product formation even under reflux conditions. This demonstrates that the methyl-substituted enone system from cyclopentenone (±)-**162** is more unreactive or shielded than the unsubstituted 1,4-enone system of the cyclopentenones **83** in Chapter2.5 (One-pot aldol reaction) that were converted in several minutes at the reaction temperature of -78 °C.



Scheme 41. One pot aldol reaction of Boc compound (±)-**162**.

In 2011, Lei and coworkers reported similar struggles when carrying out the aldol reaction of cyclopentenone **172**, therefore a two-step sequence was developed.[72] The 2-methyl substituted cyclopentenone **172** was treated with *iso*-propenyl magnesium bromide and CuI and the formed enolate was trapped successfully with TMSCl providing compound **173**. Mukaiyama aldol reation between the enol ether **173** and pent-4-enal in combination with the Lewis acid $BF_3{\cdot}Et_2O$ gave the desired aldol product **174**, however, the stereocontrol of the formed alcohol in C1`-position was only moderate with a ratio of 4:1.



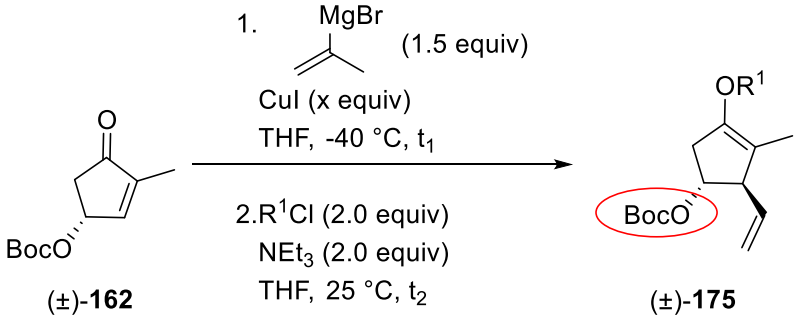
Scheme 42. Mukaiyama aldol reaction reported by Lei and coworkers[72].

Encouraged by these results the aldol reaction with the Boc-protected cyclopentenone (±)-**162** was carried out in a two-step process seeking high stereocontrol of C1`-position remote by the Boc-group similar to the “one-pot aldol reaction” in Chapter2.5 (One-pot aldol reaction).

Using the two-step protocol by Lei and coworkers no enol ether product (±)-**175** was observed but complex reaction mixture (Table 14, entry 1). Interestingly, the sequence of compound addition was different compared to the one-pot protocol for aldol reaction described by Reiser[39]. In the reaction procedure of Lei et al.[72] the cyclopentenone **172** and the CuI were added to the Grignard compound, while the cyclopentenone (*R*)-**30b** was added to a stirred solution of copper salt and Grignard solution according to the procedure of Reiser[39]. Following the sequence of addition reported by Reiser, the desired enol ether product (±)-**175** could at least be obtained after aqueous work up in crude yield of 7% since isolation *via* column chromatography was not possible. Encouraged by this result cuprous iodide was employed in 1.5 equivalents instead of catalytic amount yielding the crude product (±)-**175** in 80% yield (Table 14, entry 3). Gratifyingly, the NMR-spectra of the crude product (±)-**175** were very clean and did not afford further purification.

Raising the amount of CuI to three equivalents did not enhance the yield of the reaction (Table 14, entry 4), therefore optimization of the reaction time was performed. Elongation of the reaction time from three to six hours gave similar reaction outcome (Table 14, entry 5), shorter reaction times of one hour gave good yield of 81% yield (Table 14, entry 6), fortunately. Lowering the reaction time to 30 minutes gave the product (±)-**175** in merely 61% yield (Table 14, entry 7). No product formation was observed but decomposition of the starting material (±)-**162** when changing the trapping agent from TMSCl to TBSCl.

Table 14. 1,4-Michael addition of cyclopentenone (±)-**162** and trapping of the forming enolate.



(±)-**162** (±)-**175**

entry[a]	CuI [equiv]	t_1 [h]	t_2 [h]	R^1Cl	result
1[b]	0.1	3	3		complex reaction mixture
2[c]	0.1	3	3		7% yield of crude product, no isolation *via* column possible
3[c]	1.5	3	3		80% yield of crude product, no isolation *via* column possible
4[c]	3.0	3	3	TMS	79% yield of crude product, no isolation *via* column possible
5[b]	1.5	6	6		78% yield of crude product, no isolation *via* column possible
6[c]	1.5	1	1		81% yield of crude product, no isolation *via* column possible
7[c]	1.5	0.5	0.5		61% yield of crude product, no isolation *via* column possible
8[b]	1.5	1	1	TBS	complex reaction mixture

[a]Reaction conditions: cyclopentenone (±)-**162** (0.5 mmol, 1.0 equiv). [b]Reaction conditions reported by Lei and coworkers[72]: addition of mixture of cyclopentenone and CuI to Grignard reagent. [c]Reaction conditions: addition of cyclopentenone to mixture of Grignard reagent and CuI.

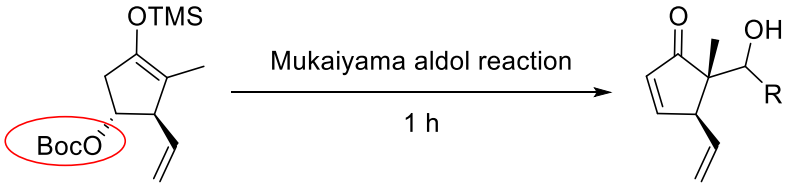
With the enol ether (±)-**175** in hands, the Mukaiyama aldol reaction was explored, however, no formation of product (±)-**176** was achieved at all (Table 15). Applying the reaction conditions from the report of Lei[72] and coworkers, no conversion of the starting material (±)-**175** was observed in DCM at -78 °C with the Lewis acid $BF_3{\cdot}Et_2O$ (Table 15, entry 1). Unfortunately, the decomposition of the starting material (±)-**175** took place by applying higher reaction temperatures (Table 15, entry 2). Changing the aldehyde to the aromatic anisaldehyde similar reaction outcome was obtained since no conversion of the cyclopentenone (±)-**175** occurred at -78 °C. Warming the reaction solution to higher temperatures led to decomposition of

starting material and complex reaction mixture (Table 15, entry 3). Screening of the solvent (THF, MeCN) did also only show decomposition of the starting material (±)-**175** (Table 15, entries 4-5).

In 1974, Mukaiyama[73] reported the successful addition of aldehydes to cyclopent- and cyclohexenol ethers using $TiCl_4$ as Lewis acid, however, employment of latter did not lead to formation of the desired product (±)-**176** (Table 15, entry 6). Changing the solvent from DCM to THF or MeCN did also not provide any product but decomposition of compound (±)-**175** (Table 15, entries 7-8).

Since the Mukaiyama aldol reaction was not successful for the Boc-protected cyclopentenone (±)-**162**, synthesis of Aculene D (**158**) was not further explored.

Table 15. Mukaiyama aldol reaction of the enolate (±)-**175**.



(±)-**175** (±)-**176**

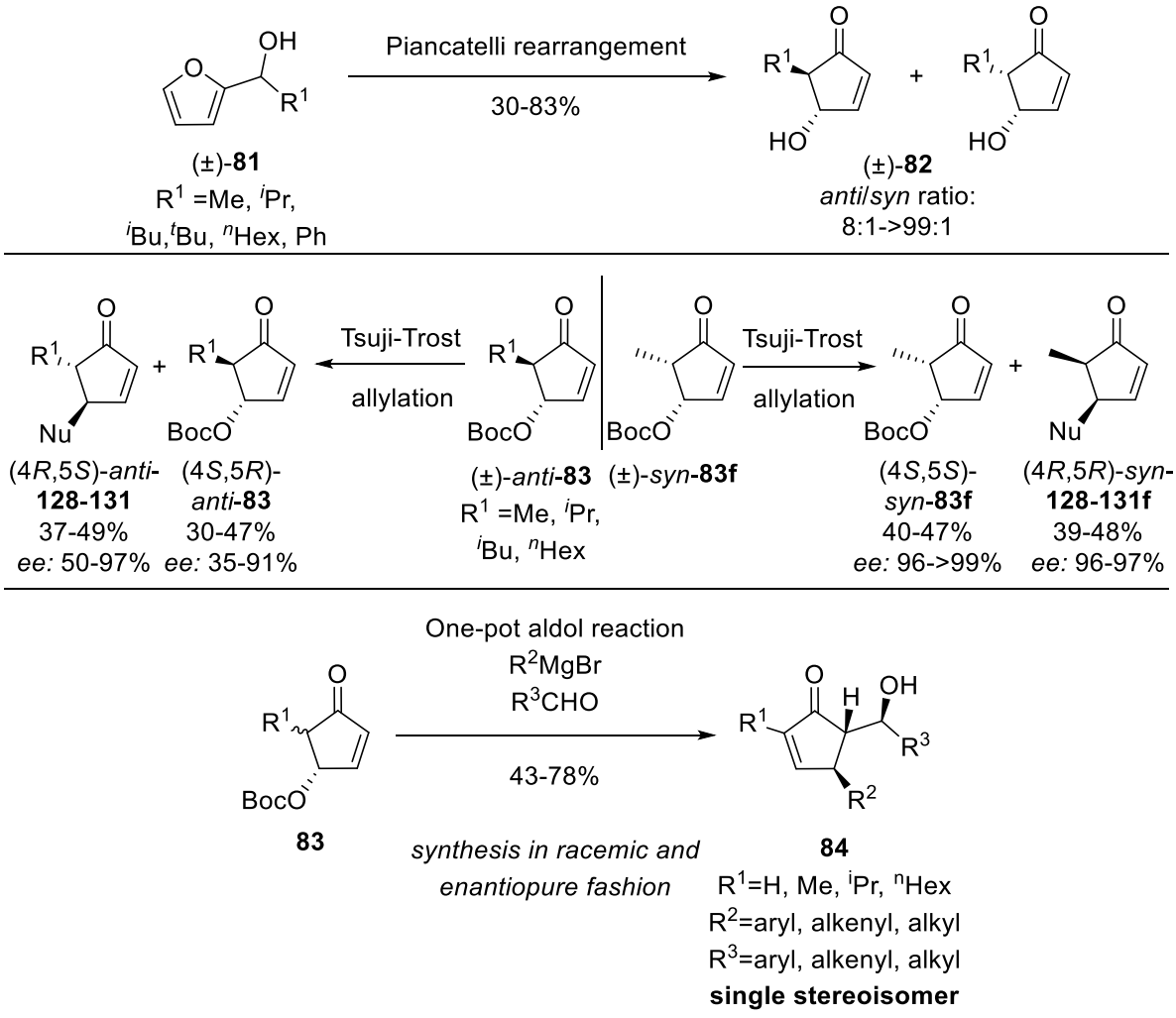
entry	reagent	aldehyde	solvent	T [°C]	result
1[a]	$BF_3{\cdot}Et_2O$ (1.0 equiv)	butanal (1.0 equiv)	DCM	-78 °C	no conversion
2	$BF_3{\cdot}Et_2O$ (1.0 equiv)		DCM	-40 °C – r.t.	decomposition
3	$BF_3{\cdot}Et_2O$ (1.0 equiv)	4-anisaldehyde (1.0 equiv)	DCM	-78 °C – r.t.	decomposition
4	$BF_3{\cdot}Et_2O$ (1.0 equiv)		THF	-78 °C – r.t.	decomposition
5	$BF_3{\cdot}Et_2O$ (1.0 equiv)		MeCN	-78 °C – r.t.	decomposition
6	$TiCl_4$ (1.0 equiv)		DCM	-78 °C – r.t.	decomposition
7	$TiCl_4$ (1.0 equiv)		THF	-78 °C – r.t.	decomposition
8	$TiCl_4$ (1.0 equiv)		MeCN	-78 °C – r.t.	decomposition

[a]Reaction conditions reported by Lei[72] and coworkers.

2.7 Summary

In conclusion, in this chapter three reactions were successfully examined in view of reaction behavior *via* alkyl and aryl substitution. In the Piancatelli rearrangement alkyl and aryl

derivatives (±)-**82** could be obtained in moderate to good yields with good to excellent *anti*/*syn* ratio of the products. Asymmetric Tsuji-Trost allylation of activated cyclopentenones gave interesting results, since reaction with *syn*-cyclopentenone (±)-*syn*-**83f** gave better enantioselectivity compared to the *anti*-cyclopentenone (±)-*anti*-**83f**. In the last reaction, the directed aldol reaction of cyclopentenone **83**, addition of nucleophile and trapping of the forming enolate with aldehyde was performed in moderate to good yields with excellent diastereoselectivity since only one diastereomer (±)-**84** was provided in all cases. Furthermore, this reaction was performed successfully in racemic as well as in enantiopure fashion.

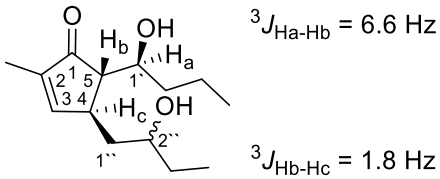


Scheme 43. Summary of results of Piancatelli rearrangement, Tsuji-Trost allylation and "one-pot aldol reaction".

3 Synthesis of Phomapentenone A

3.1 Introduction and Aim of this Work

Based on the successful “one-pot aldol reaction“ with 5-substituted cyclopentenones from Chapter 2.5 (One-pot aldol reaction) an application for natural product synthesis was approached. Phomapentenone A ((–)-**177**) was discovered by Wicklow [74] in 2002 together with Phomadecalin A-D that were showing biological activity against *Bacillus verticillioides* (ATCC 6051) (Figure 12). The compounds were obtained from cultures of *Phoma* sp. (NRRL 25697), a fungal colonist isolated from the stromata of *Hypoxylon* sp.



Phomapentenone A
((–)-**177**)

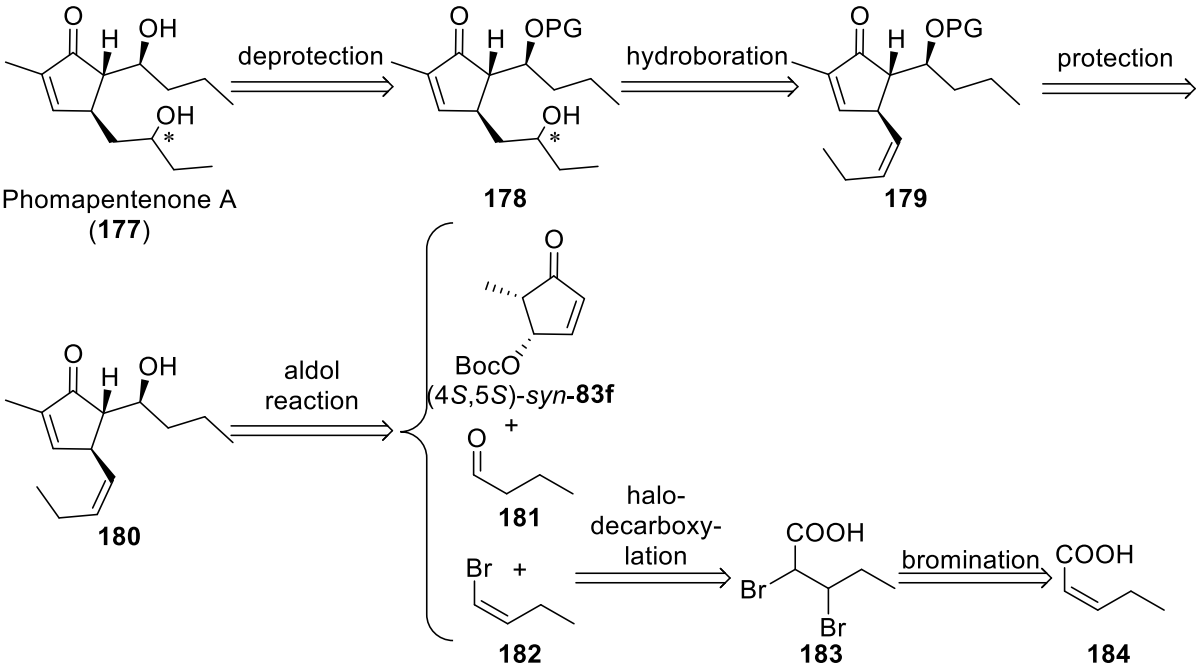
Figure 12. Phomapentenone A ((–)-**177**).

In general, in cyclopentenone rings a vicinal coupling constant $^3J_{H\text{-}H}$ in the range of 5-6 Hz indicates *syn*-conformation, whereas coupling constants about 2 Hz point towards an *anti*-relation.[74] With the reported coupling constants of $^3J_{Hb\text{-}Hc}$ = 1.8 Hz *anti*-relation between H_b and H_c was presumed. According to Kobayashi [67] the coupling constants of $^3J_{Ha\text{-}Hb}$ = 6.6 Hz indicates *anti*-conformation between H_a and H_b. Due to this relative stereochemistry the synthesis of the natural product Phomapentenone A ((–)-**177**) seemed reasonable employing the aldol cascade sequence from Chapter 2.5 (One-pot aldol reaction) starting from 5-methylcyclopentenone **83f**. Furthermore, the stereochemistry of the C2``-center with the alcohol group is not known yet, therefore, synthesis and characterization of latter seemed very attractive.

3.2 Synthesis of the Natural Products

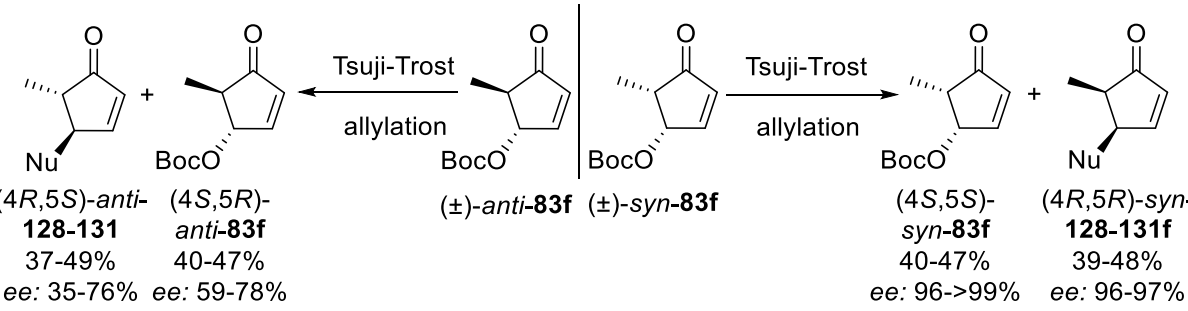
The key step of the synthesis of Phomapentenone A (**177**) is the directed aldol reaction in a “one-pot aldol reaction“ (Scheme 44). Enantiopure starting material (4S,5S)-*syn*-**83f** can be achieved *via* kinetic resolution of cyclopentenones in the Tsuji-Trost allylation described in Chapter 2.4 (Asymmetric Tsuji-Trost Allylation). The required bromo-alkene **182** can be

generated *via* bromination of 2-pentenoic acid **184** and subsequent halo decarboxylation [75] of compound **183**. Protection of the alcohol product **180** provides the starting material **179** for the hydroboration serving as the second key step especially in terms of chemo- and regioselectivity of the reaction. Finally, deprotection of the alcohol **178** gives the final product Phomapentenone A (**177**).



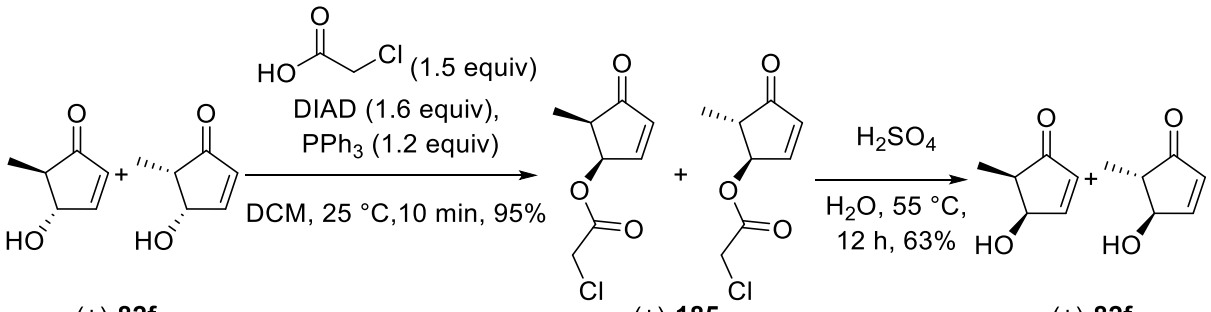
Scheme 44. Retrosynthetic analysis of Phomapentenone A (**177**).

In order to synthesize the enantiopure natural product **177**, the employed cyclopentenone in the “one-pot aldol reaction“ requires ee-values of >99%. This condition is complied with the *syn*-cyclopentenone (4S,5S)-*syn*-**83f** (Scheme 45), however, providing this compound is laborious since the *anti*/*syn*-ratio of the outcome of the Piancatelli rearrangement is 8:1 (see 2.3 Piancatelli Rearrangement).



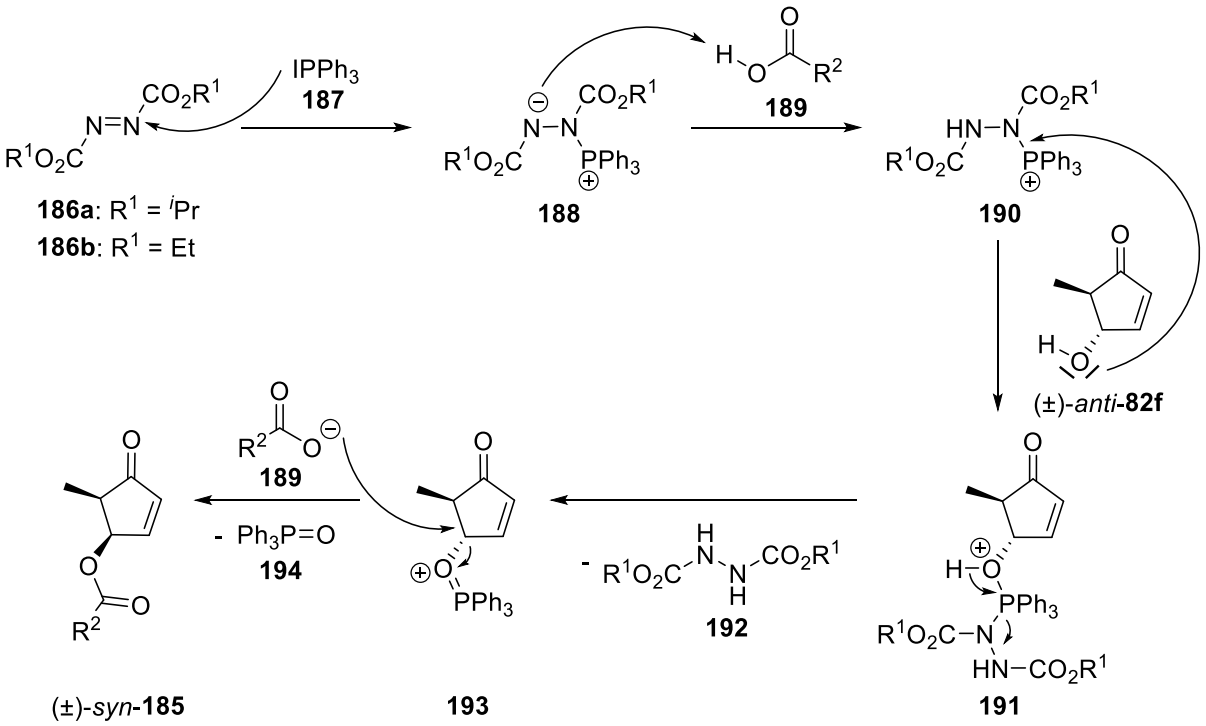
Scheme 45. Comparison of *anti* and *syn*-cyclopentenones **83f** in the asymmetric Tsuji-Trost allylation.

Therefore, Mitsunobu[76] reaction was carried out for inversion of the stereocenter of the alcohol leading to *syn*-cyclopentenone (±)-*syn*-**82f** as major diastereomer. Mitsunobu inversion of the diastereomeric mixture (±)-**82f** with *anti*/*syn*-ratio of 8:1 employing 2-chloroacetic acid gave the desired ester (±)-**185** in 95% yield with *anti*/*syn*-ratio of 1:8, subsequent ester hydrolysis yielded the corresponding hydroxycyclopentenones (±)-**82f** under retention of the stereocenter in 63% (Scheme 46).



Scheme 46. Mitsunobu inversion of cyclopentenones.

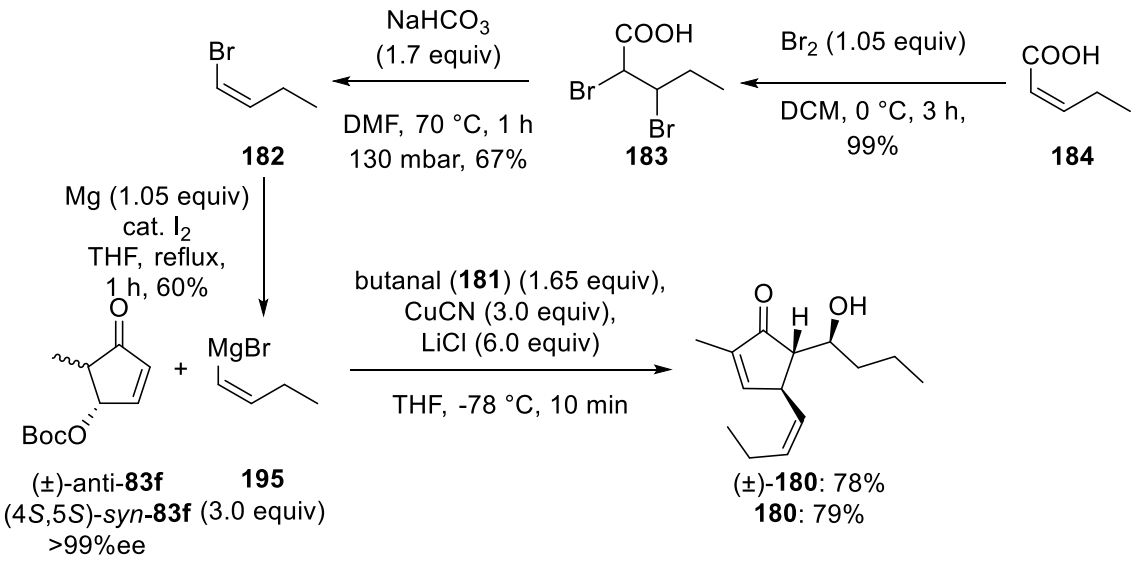
In Scheme 47 the mechanism of the Mitsunobu inversion is depicted. Mitsunobu[76] and coworkers described the reaction of a secondary alcohol which is converted into a good leaving group allowing nucleophilic substitution under inversion of the stereocenter *via* S_N2- reaction. The intermediate **188** is generated by reaction of triphenylphosphine **187** with azodicarboxylate **186** followed by deprotonation of the employed carboxylic acid **189**. Subsequent formation of molecule **191** takes place *via* nucleophilic attack of the alcohol group of the cyclopentenone (±)-**82f** at the phosphonium carboxylate **190**. Cleavage of the hydrazine **192** provides the oxy phosphonium intermediate **193** that is subsequently substituted by the carboxylate **189** under inversion of the stereocenter *via* S_N2- reaction leading to the ester product (±)-**185**.



Scheme 47. Mechanism of the Mitsunobu[76] inversion.

Hence, following this procedure, bromoalkenyl **182** was required for the "one-pot aldol reaction" of cyclopentenone (4S,5S)-*syn*-**83f** and was synthesized starting with commercially available 2-pentenoic acid (**184**) (Scheme 48). Bromination of the latter gave compound **183** in excellent yield and was subjected to a halodecarboxylation[75] reaction. This reaction was carried out at 130 mbar since the product **182** formed during the reaction is volatile and can be isolated easily *via* cooling trap in good yield of 67% yield. Subsequent treatment with iodine in catalytical amount and magnesium gave the desired Grignard reagent **195** in 60% yield determined by titration with salicylaldehyde phenylhydrazone[77].

With the racemic cyclopentenone (±)-*anti*-**83f** and the Grignard reagent **195** in hand the "one-pot aldol reaction" with butanal (**181**) was carried out giving rise to the product (±)-**180** in 78% yield as a single diastereomer, subjecting the enantiopure cyclopentenone (4S,5S)-*syn*-**83f** to the reaction gave similar yield of 79% as single diastereomer **180** as well.

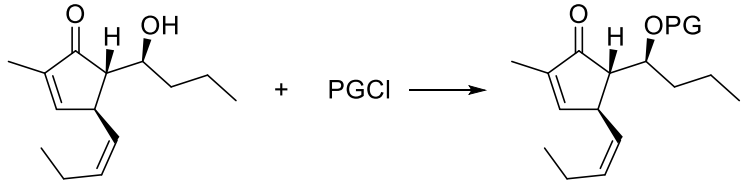


Scheme 48. “One-pot aldol reaction“ for the synthesis of Phomapentenone A.

In view of the hydroboration as the next key step in the reaction plan, protection of the alcohol **180** was required, therefore, different protecting agents were tested (Table 16).

Protection of alcohol (±)-**180** with TBSCl gave the product (±)-**179a** in 81%, however, with a reaction time of 24 hours and the use of 3.0 equivalents of iodine as well as 1-methylimidazole the reaction conditions are not in accordance with the concept of green and sustainable chemistry. Therefore, the reaction was carried out with TESCl giving rise to the product (±)-**179b** with excellent yield of 95% and a reaction time of merely several minutes. Performing the reaction with the enantiopure material **180** gave same results. Changing the protecting agent from silyl to alkyl chloride no reaction occurred, apparently the reactivity of MOMCl is too low for the desired reaction (Table 16, entry 3).

Table 16. Protection of the alcohol group of cyclopentenones (±)-**180**/**180**.



(±)-**180**/ **180** (±)-**179a-b**/ **179b**

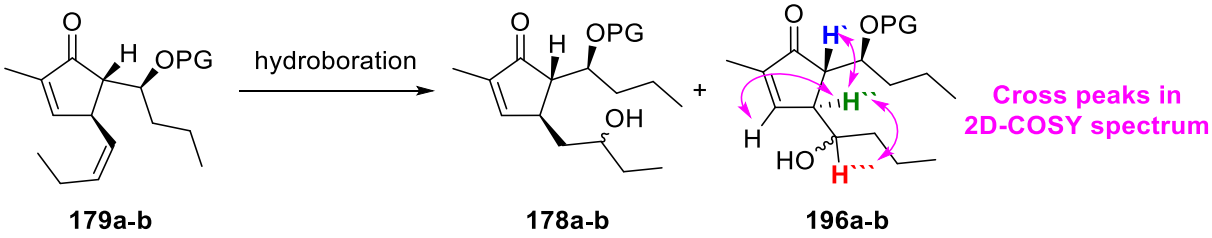
entry	PGCl	reaction conditions	result
1	TBS (1.1 equiv)	1-methylimidazole (3.0 equiv), I_2 (3.0 equiv), THF, reflux, 24 h	(±)-**179a**: 81%
2	TESCl (1.2 equiv)	imidazole (1.2 equiv), DMAP (0.3 equiv), DMF, rt, 5 min	(±)-**179b**: 95%
3			**179b**: 95%
4	MOMCl (1.3 equiv)	DIPEA (1.6 equiv), THF, 50 °C, 24 h	no reaction

Hydroboration as next step of synthesis for Phomapentenone A (**177**) is the most interesting reaction step in view of regio- and diastereoselectivity. Therefore, different hydroboration reagents were tested and depicted in Table 17. In case of the unprotected cyclopentenone (±)-**180** 2.2 equivalents of hydroboration agent were employed because of deprotection of the free alcohol.

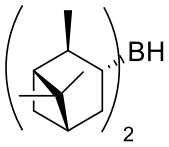
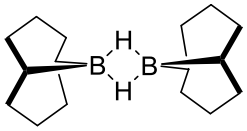
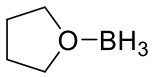
Sterically hindered hydroboration agent (-)-$(Ipc)_2BH$) is provided by treatment of borane with chiral (+)-α-pinene leading to enantioselective reactions in general. However, carrying out the reaction with the cyclopentenones (±)-**179**-**180** with latter hydroboration agent in THF at 0 °C did not lead to any conversion, higher temperatures did also not show any influence (Table 17, entries 1-3). Apparently, the steric hindrance of the hydroboration agent (-)-$(Ipc)_2BH$) is too high for reaction with the employed cyclopentenones.

Employing 9-BBN, derived from 1,5-cyclooctadiene and borane, as agent for hydroboration in THF did not succeed any conversion of the starting materials (±)-**179**-**180**, reaction conditions under reflux did not provide any product formation as well. Apparently, the free double bond in the side chain of the cyclopentenone is sterically more shielded than initially assumed. Persumably, the 1,4-Michael π-system of the cyclopentenone ring interacts with the free double bond leading to a shielding effect. Furthermore, the TBS or TES protecting groups could shield the free double bond as well.

Table 17. Hydroboration of cyclopentenones (±)-**179**-**180**.



179a-b **178a-b** **196a-b**

entry[a]	PG	hydroboration agent	reaction conditions	yield of 178	yield of 196
1[b]	H (±)-**180**	 (-)-(Ipc)$_2$BH (1.1 equiv)	1.THF, 0 °C - reflux, 24 h 2. NaOH, H_2O_2, rt, 1 h		no reaction
2	TBS (±)-**179a**				no reaction
3	TES (±)-**179b**				no reaction
4[b]	H (±)-**180**	 9-BBN (1.1 equiv)			no reaction
5	TBS (±)-**179a**				no reaction
6	TES (±)-**179b**				no reaction
7[b]	H (±)-**180**	 BH_3·THF (1.1 equiv)	1.THF, 0 °C, 1 h 2. NaOH, H_2O_2, rt, 1 h	decomposition	
8	TBS (±)-**179a**			-	one diastereomer (±)-**196a** 63%
9	TES (±)-**179b**			-	one diastereomer (±)-**196b** 65%
10	TES **179b**			-	one diastereomer **196b** 66 %

[a]Reaction conditions: 0.5 mmol alkene, THF (2 mL), NaOH (3 M, 100 µL), H_2O_2 (30 wt-%, 50 µL).

[b]2.2 equiv of hydroboration agent.

Therefore, BH_3·THF was tested as easiest hydroboration agent and gratifyingly, conversion of the alcohol protected starting material (±)-**179a**-**b** was observed leading to formation of the products (±)-**196a**-**b** in 63% (TBS-protected (Table 17, entries 8-9). Employing enantiopure starting material **179b** provided one single product as well. Hydroboration of free alcohol (±)-**180**, however, led to decomposition of the starting material resulting in a complex reaction mixture showing the necessity of protecting group of the alcohol functionality (Table 17, entry 7).

Interestingly, in all cases of alcohol protection only one single product was obtained showing high diastereoselectivity of the reaction. Probably, the selectivity derives from the input of the chiral cyclopentenone moiety shielding one side of the free double bond (Scheme 49).

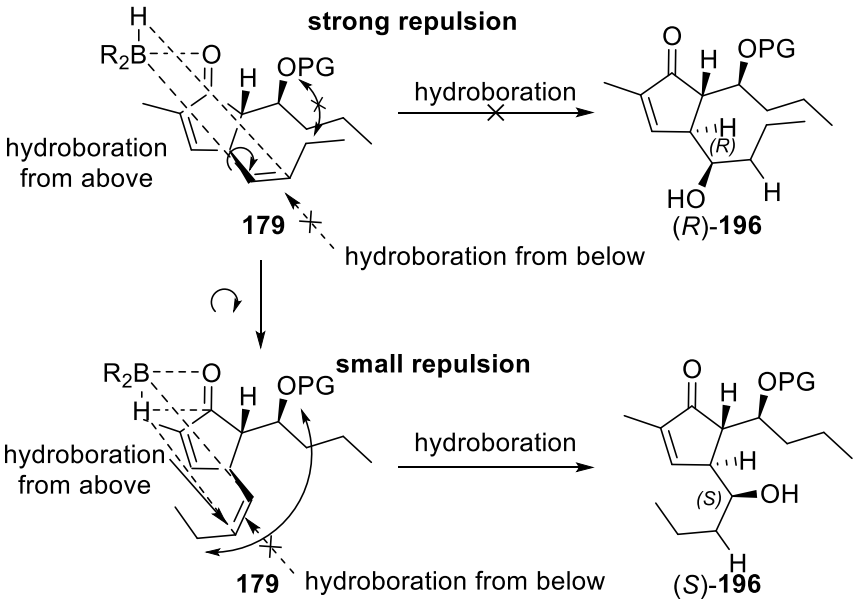
Analyzing the received products *via* 2D-COSY spectrum gave interesting results since the desired and estimated *anti*-Markownikow hydroboration product **178** was not obtained with the formed alcohol in C2``-position.

Instead, the obtained products were characterized as compounds **196a**-**b** with the alcohol group in C1``-position. The regioselectivity of the reaction was proven *via* positive cross peaks of H`` (green) and H``` (red) in 2D-COSY spectra highlighted in the chemical structure of the products **196a**-**b** in Table 17.

Different explanations for the regio- and diastereoselectivity of this reaction are possible. In view of the diastereoselectivity of the reaction one side of the free double needs to be shielded otherwise two epimers would be expected. Therefore, it is assumed that the free rotation of the C-C bond of C3-carbon of cyclopentenone ring and C1``-carbon of the alkenyl sidechain is hindered due to the steric demanding protecting groups TBS or TES. It is suspected that maximum distance between ethyl group from the *cis*-double bond and the protection group of the alcohol is favored for minimum steric repulsion. Furthermore, it is assumed that the hydroboration takes place from above since the cyclopentenone ring with the other side chain including the steric demanding protecting group of the alcohol is blocking the reaction from below.

It is known that boranes interact with enones and can undergo 1,2-and 1,4-addition in 1,4-Michael systems depending on the enone.[78] In view of the regioselectivity of this reaction the approach of the borane to the cyclopentenone molecule could be directed from the interacting enone system in the cyclopentenone ring. This could lead to Markownikow product **196** formation of the free double bond - that is more reactive compared to the enone system- in the side chain of the starting material **179**.

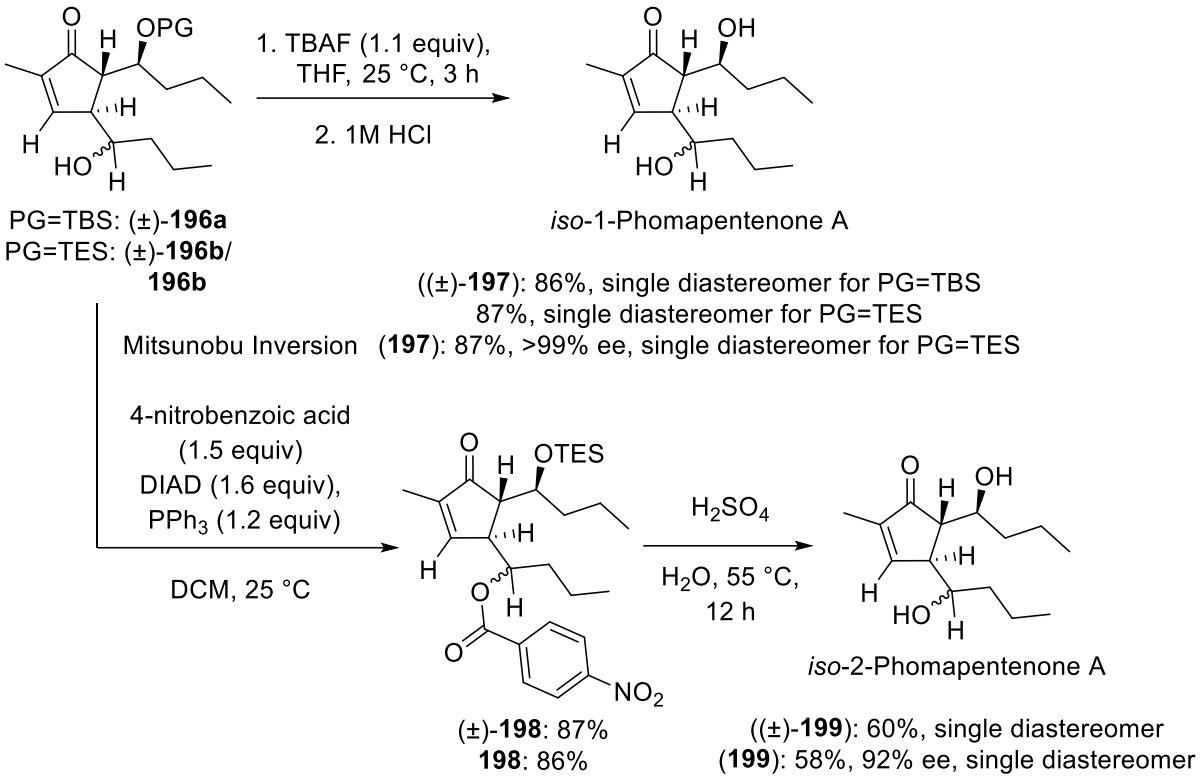
Taking all these assumptions into account diastereo- and regioselective reaction could be given providing the (S)-configurated alcohol (*S*)-**196** in C1``-position.



Scheme 49. Possible explanation for diastereo- and regioselectivity of hydroboration of cyclopentenone **179** due to hindered C-C bond rotation (stereochemistry of (*R*)-**196** and (*S*)-**196** not confirmed).

Since synthesis of Phomapentenone A (**177**) failed due to formation of the alcohol at C1``- instead of C2``-position, next goal was the synthesis and characterization of both epimers called *iso*-Phomapentenone A (**197**) and (**199**) (Scheme 50).

Cleaving the protecting group TBS and TES from the cyclopentenones (±)-**196a**-**b** *via* tetrabutylammonium fluoride gave the exactly same compound called *iso*-1-Phomapentenone (±)-(**197**) in very good yield. Fortunately, the final product **197** could also be provided enantiopure employing enantiomeric cyclopentenone **196b** as starting material.
In order to receive the epimer of *iso*-1-Phomapentenone (±)-(**197**) the Mitsunobu reaction seemed attractive for inversion of the stereocenter employing the TES protected cyclopentenone (±)-**196**. Use of 4-nitrobenzoic acid gave the ester (±)-**198** subsequently hydrolyzed to the desired epimer *iso*-2-Phomapentenone A (±)-(**199**) in moderate yield. The final enantiomeric product **199** was obtained with very good value of 92% enantiomeric excess starting from enantiomeric alcohol **196b** using same strategy of Mitsunobu inversion in very good yield of 86%.



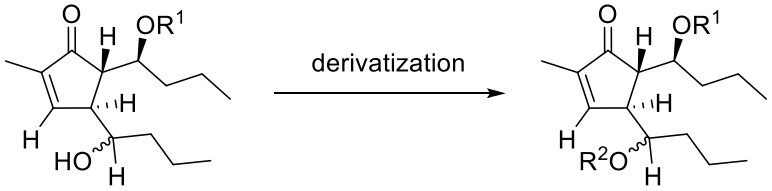
Scheme 50. Synthesis of both epimers of *iso*-Phomapentenone A (**197**) and (**199**).

3.3 Characterization of the Natural Products

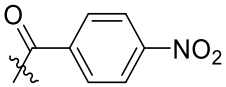
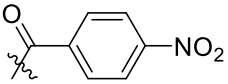
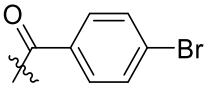
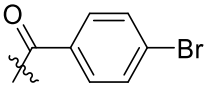
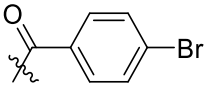
After successful synthesis of the *iso*-Phomapentenones (**197**) and (**199**), characterization of the alcohol stereocenter of both epimers formed in the hydroboration reaction was attractive. Since both compounds were oils, we next aimed for conversion in solid derivatives allowing structural analysis by X-Ray measurement.

Esterification of the *iso*-1-Phomapentenone A (±)-(**197**) with 4-nitrobenzoyl chloride under basic conditions employing stoichiometric amount of triethylamine and catalytic amount of DMAP gave the product (±)-**200** with two ester groups in very good yield of 93%, however, the ester could not be crystallized (Table 18, entry 1). In entry 2 of Table 18 Mitsunobu inversion of TES-protected compound (±)-**196b** carried out at room temperature is depicted and was already reported in Scheme 54. Performing this reaction gave rise to the compound (±)-**198** that inheres TES protected alcohol and 4-nitrobenzoic ester. Unfortunately, this compound is an oil as well and therefore not suitable for X-Ray measurement.

Table 18. Derivatization reactions for X-Ray measurement.



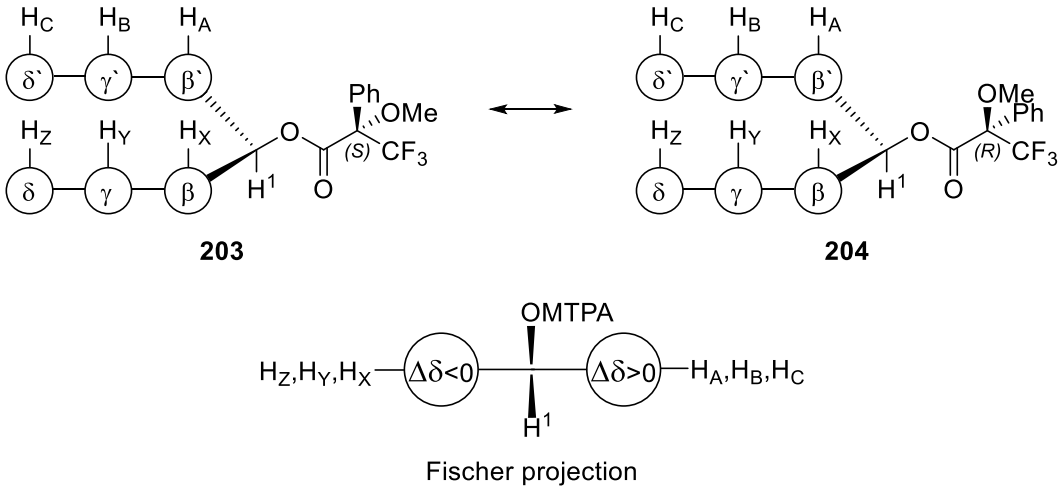
196b, **197** **198**/ **200-202**

entry	substrate	reaction conditions	product	yield [%]
1	R^1=H (±)-**197**	esterification[a]: 4-nitrobenzoyl chloride (2.4 equiv)	(±)-**200** R^1= R^2= 	93, product is oil
2	R^1=TES (±)-**196b**	Mitsunobu inversion[b]: 4-nitrobenzoic acid (1.5 equiv)	(±)-**198** R^1= TES, R^2= 	87, product is oil
3	R^1=H (±)-**197**	esterification[a]: 4-bromobenzoyl chloride (2.4 equiv)	(±)-**201** R^1= R^2= 	no reaction
4	R^1=TES (±)-**196b**	esterification[c]: 4-bromobenzoyl chloride (1.2 equiv)	(±)-**202** R^1= TES, R^2= 	no reaction
5	R^1=TES (±)-**196b**	Mitsunobu inversion[d]: 4-bromobenzoic acid (1.5 equiv)	(±)-**202** R^1= TES, R^2= 	no reaction

[a]esterification: acyl chloride (2.4 equiv), NEt_3 (2.8 equiv), DMAP (1 mol%), DCM, reflux, 24h. [b]Mitsunobu inversion: acid (1.5 equiv), DIAD (1.6 equiv), PPh_3 (1.2 equiv), DCM, rt, 24h. [c]esterification: acyl chloride (1.2 equiv), NEt_3 (1.4 equiv), DMAP (1 mol%), DCM, reflux, 24h. [d]Mitsunobu inversion: acid (1.5 equiv), DIAD (1.6 equiv), PPh_3 (1.2 equiv), DCM, reflux, 24h.

Changing the substituent from nitro group to bromine had a tremendous influence on the esterification of *iso*-1-Phomapentenone A (±)-(**197**) and TES-protected compound (±)-**196b** since no conversion of both starting materials occurred (Table 18, entries 3-4). Interestingly, carrying out the Mitsunobu inversion of TES-protected cyclopentenone (±)-**196b** employing 4-bromobenzoic acid did also not lead to any conversion even under reflux conditions. Apparently, compared to the strong -M-effect of the nitro group, the steric hindrance and the slightly +M-effect of the bromine substituent affects the reactivity strongly and inhibits any conversion of the starting material (±)-**196b**/**197**.

Since derivatization method for X-Ray measurement did not work out, derivatization of compound (±)-**196b** with the Mosher`s acid was tested next. In general, derivatization of secondary alcohols/amines with each (*S*)- and (*R*)-configurated α-methoxy-α-trifluoromethylphenylacetic acid ((MTPA)-Mosher`s acid) in two separated esterification experiments can be used for determination of the absolute stereochemistry of the enantiopure secondary alcohol. An empirical relation between configuration of alcohol stereocenter and ^{1}H-NMR-shifts of each diastereomeric (*S*)- and (*R*)-derivatized Mosher`s ester products **203**/**204** was reported by Mosher[79] et al. in 1969. The slightly different ^{1}H-NMR-shifts of the two diastereomers are given by an “upfield”-shift of the protons caused by the diamagnetic effect of the phenylgroup pointing to the same side of the MTPA-plane that is defined by H^1, the ester group and CF_3-group. In the case of the (*S*)-Mosher ester product **203** H_X, H_Y and H_Z are “upfield”-shifted, for the (*R*)-configurated Mosher ester product **204** H_A, H_B and H_C are affected (Scheme 51).



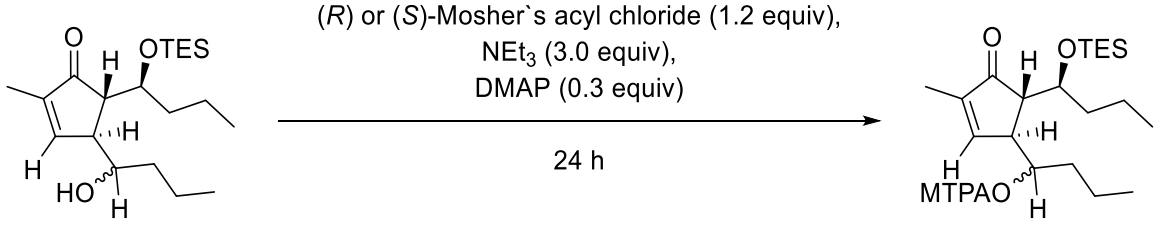
Scheme 51. Determination of the absolute stereochemistry of secondary alcohols *via* using Mosher`s acid *via* ^{1}H-NMR shifts.[80]

$$\Delta\delta = \delta_{(S)-MTPA-ester} - \delta_{(R)-MTPA-ester} \qquad \text{(eq. 2)}$$

Calculating the difference Δδ according to equation 2 the protons with the positive Δδ-values point to the right side of the MTPA plane (Fischer projection Scheme 51), the protons with the negative Δδ-values are analog left sided giving rise to the absolute stereochemistry of the alcohol (Scheme 51).

For higher reactivity of the Mosher acid activation of latter to the acyl chloride is typically carried out.[80] In Table 19 reaction of the two enantiomeric (*R*)- and (*S*)-configurated Mosher`s acyl chlorides with the enantiomeric alcohol **196b** is depicted.

Table 19. Reaction of Mosher`s acyl chloride and enantiomeric cyclopentenone **196b**.



196b (*R*)-**205**/(*S*)-**205**

entry[a]	Mosher`s acyl chloride	solvent	T	result
1		$CDCl_3$		
2		DCM		
3	(*R*)-configurated	THF	rt-reflux	no reaction
4		DMF		
5		MeCN		
6		$CDCl_3$		
7		DCM		
8	(*S*)-configurated	THF	rt-reflux	no reaction
9		DMF		
10		MeCN		

[a]Reaction conditions: alcohol (0.25 mmol, 1.0 equiv), 2 mL solvent.

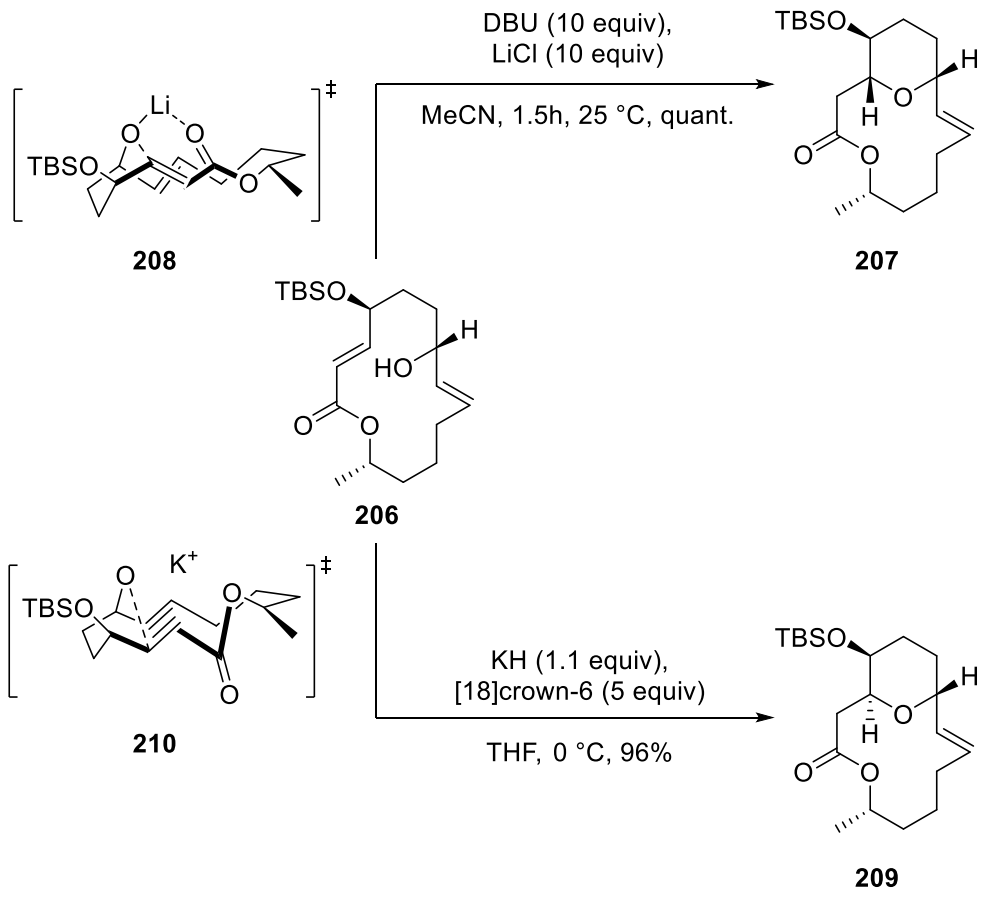
For this reaction the enantiomeric TES protected cyclopentenone **196b** was tested with each (*R*)- and (*S*)-configurated Mosher`s acyl chloride in different solvents at room temperature to provide the products (*R*)-**205** and (*S*)-**205**, however, in all cases no reaction of the starting material occurred. Unfortunately, applying higher reaction temperatures no conversion of the starting material was observed in all cases even under reflux conditions.

Apparently, the reactivity of the Mosher`s acyl chloride for this reaction is not high enough suffering from steric hindrance of the Mosher`s acid moiety. Comparing these results with the derivatization experiments for X-Ray in Table 18 it can be seen that esterification with 4-

nitrobenzoyl chloride containing electron withdrawing group is providing the ester in good yield whereas no reaction is observed with reagents containing electron donating groups and/or steric demanding moieties, e.g. 4-bromobenzoyl chloride (slightly +M-effect) and Mosher`s acyl chloride. Therefore, it seems that the free alcohol group of cyclopentenones **196b** is unreactive and extremely shielded by the cyclopentenone moiety in β-position.

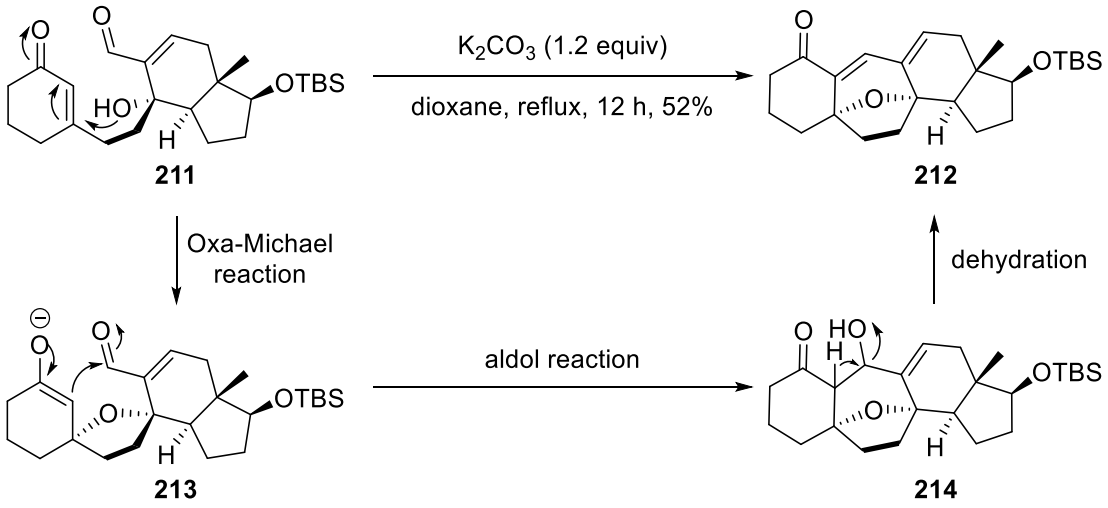
Since solidification *via* derivatization for X-Ray measurement as well as the ^{1}H-NMR determination *via* Mosher`s acid was unsuccessful a new strategy of determination of absolute stereoconfiguration of the *iso*-Phomapentenone A (**197**) and (**199**) was attempted *via* ring closing step. Forming a bicyclic product *via* Oxo-Michael addition of the free alcohol group makes determination possible *via* NOESY spectra. In this reaction typically alcohols activated by base react as nucleophile in a Michael reaction, in case of internal alcohols a new ring system is provided. However, formation of an bicycle containing four membered oxetane and cyclopentenone ring systems *via* oxa-Michael addition is not described in literature,[81] yet, whereas various reports are published dealing with the formation of a five[82] or six[83] membered ring.

Shishido[83] and coworkers demonstrated selective oxa-Michael addition employing different source of base and Lewis acids leading to two epimers **207** and **209** (Scheme 52). Using DBU as base and LiCl as Lewis acid lead to the transition state **208** in that both involved oxygen atoms are located in the coordination sphere of lithium. In case of the employment of KH as base no coordination of the carbonyl oxygen occurs in the transition state **210** leading to the epimer **209**. In both cases a new six membered ring was formed.



Scheme 52. oxa-Michael addition reported by Shishido [83].

Nicolaou and coworkers[82] reported a reaction sequence including oxa-Michael addition, aldol reaction and subsequent dehydration in a one step process using K_2CO_3 as base (Scheme 53).



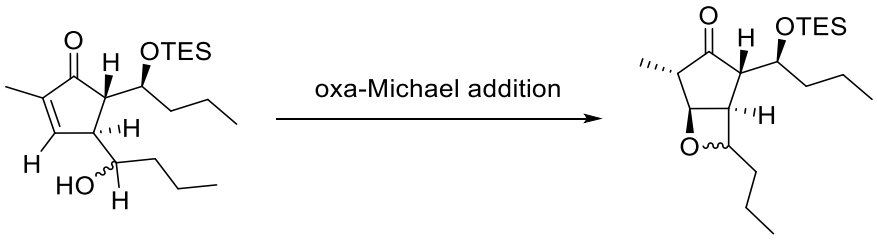
Scheme 53. Oxa-Michael addition reported by Nicolaou[82].

Starting from compound **211** a new five membered ring was generated *via* selective oxa-Michael addition, the forming enolate **213** was trapped with internal aldehyde followed by elimination process of H_2O providing the final product **212** in 52% yield.

In Table 20 the results of ring closing reaction *via* oxa-Michael addition of the cyclopentenone (±)-**196b** are depicted, unfortunately, no positive result can be reported.
In entry 1 of Table 20 the reaction conditions reported by Shishido[83] are carried out using 10 equivalents of DBU and LiCl. However, no conversion of the starting material (±)-**196b** was observed. Leaving out Lewis acid LiCl did also not show any influence (Table 20 entry 2). Solvent and Lewis acid screening with THF and $BF_3{\cdot}Et_2O$ failed as well (Table 20, entries 3-5). Apparently, the combination of DBU, LiCl or $BF_3{\cdot}Et_2O$ is not reactive enough for ring formation of a cyclobutene ring.
Employing the second reported reaction conditions of Shishido[83] with KH as base and [18]crown-6 as additive led to decomposition of the starting material (±)-**196b** at 0 °C (Table 20 entry 6). Therefore, reaction was carried out at lower temperatures, however, no reaction occurred in the range of -78 – -20°C (Table 20 entry 7). In the range of -20 – 0 °C slightly decomposition of the starting material (±)-**196b** was observed. Changing the base from KH to NaH gave very similar results since no reaction occurred at low temperatures, again, slightly decomposition was observed at 0 °C (Table 20 entries 9-10). Changing the solvent from THF to MeCN did also not influence the outcome of the reaction at 0 °C since decomposition of starting material (±)-**196b** was observed (Table 20 entry 11). Apparently, the basicity of NaH and KH are too high since decomposition of the starting material (±)-**196b** was observed at 0 °C.
Following the report of Nicolaou[82], K_2CO_3 was tested next as base in dioxane. Even under reflux conditions no formation of product **215** was observed (Table 20 entry 12). Increasing the amount of base from 1.2 to 5 equivalents did not influence the reaction outcome (Table 20 entry 13). Neither changing the solvent to THF nor employment of additives, eg. [18]crown-6 or LiCl, led to any conversion of the starting material (±)-**196b** (Table 20 entries 14-17).

Apparently, formation of oxetane ring *via* oxa-Michael addition is challenging, since employment of commonly used bases, eg. DBU, KH, K_2CO_3, did not lead to any product formation.
Since all attempts for the characterization of both epimers *iso*-Phomapentenone A (**197**) and (**199**) failed, further investigations were abandoned.

Table 20. Oxa-Michael addition of cyclopentenone (±)-**196b**.



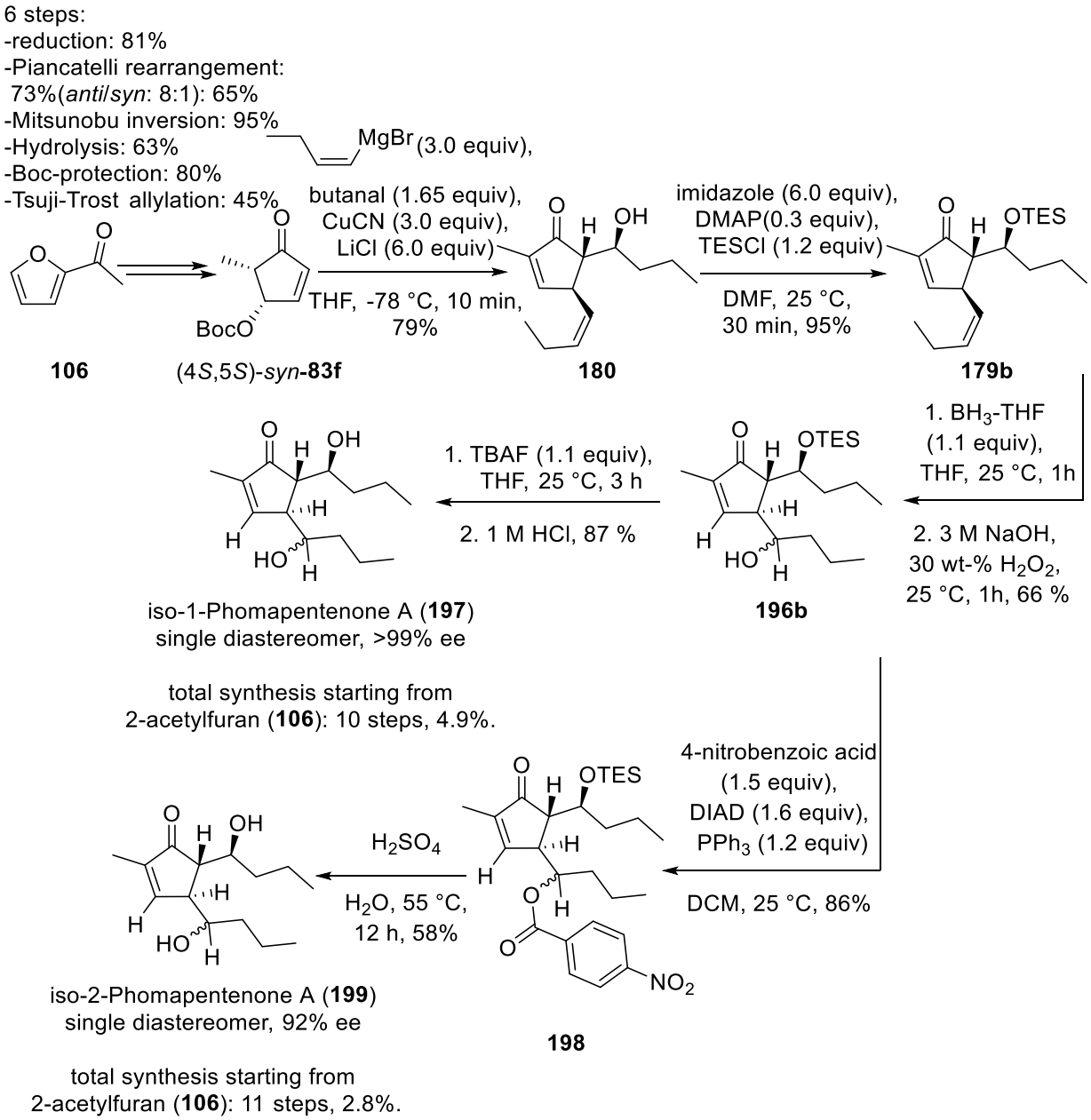
(±)-**196b** **215**

entry[a]	base [equiv]	additive [equiv]	reaction conditions	result
1	DBU (10 equiv)	LiCl (10 equiv)	MeCN, rt-reflux, 24 h	no reaction
2	DBU (10 equiv)	-	MeCN, rt-reflux, 24 h	no reaction
3	DBU (10 equiv)	LiCl (10 equiv)	THF, rt-reflux, 24 h	no reaction
4	DBU (10 equiv)	$BF_3{\cdot}Et_2O$ (10 equiv)	MeCN, rt-reflux, 24 h	no reaction.
5	DBU (10 equiv)	$BF_3{\cdot}Et_2O$ (10 equiv)	THF, rt-reflux, 24 h	no reaction
6	KH (1.1 equiv)	[18]crown-6 (5 equiv)	THF, 0 °C, 2 h	decompos.
7	KH (1.1 equiv)	[18]crown-6 (5 equiv)	THF, -78 – -20 °C, 8 h	no reaction
8	KH (1.1 equiv)	[18]crown-6 (5 equiv)	MeCN, 0 °C, 2 h	decompos.
9	NaH (1.1 equiv)	[18]crown-6 (5 equiv)	THF, 0 °C, 2 h	decompos.
10	NaH (1.1 equiv)	[18]crown-6 (5 equiv)	THF, -78 – -20 °C, 8 h	no reaction
11	NaH (1.1 equiv)	[18]crown-6 (5 equiv)	MeCN, 0 °C, 2 h	decompos.
12	K_2CO_3 (1.2 equiv)	-	dioxane, rt-reflux, 24 h	no reaction
13	K_2CO_3 (5 equiv)	-	dioxane, rt-reflux, 24 h	no reaction
14	K_2CO_3 (1.2 equiv)	[18]crown-6 (5 equiv)	dioxane, rt-reflux, 24 h	no reaction
15	K_2CO_3 (1.2 equiv)	LiCl (10 equiv)	dioxane, rt-reflux, 24 h	no reaction
16	K_2CO_3 (1.2 equiv)	[18]crown-6 (5 equiv)	THF, rt-reflux, 24 h	no reaction
17	K_2CO_3 (1.2 equiv)	LiCl (10 equiv)	THF, rt-reflux, 24 h	no reaction

[a]Reaction conditions: cyclopentenone (±)-**196b** (0.25 mmol, 1.0 equiv), solvent (2 mL).

3.4 Summary

In conclusion, synthesis of the desired natural product Phomapentenone A ((–)-**177**) failed since the regioselectivity of the hydroboration reaction was different than assumed, instead, two new compounds called *iso*-1- and *iso*-2-Phomapentenone A (**197**) and (**199**) were successfully synthesized (Scheme 54).



Scheme 54. Total synthesis of *iso*-1- and *iso*-2-Phomapentenone A (**197**) and (**199**) starting from 2-acetyl furan (**106**).

Synthesis of Phomapentenone A

For the enantioselective synthesis of *iso*-1-compound **197** ten reaction steps were necessary resulting in a total yield of 4.9%. Key steps of synthesis were Piancatelli rearrangement for the formation of the cyclopentenone core structure, Tsuji-Trost allylation provided enantiopure material (4*S*,5*S*)-*syn*-**83f**. “One-pot aldol reaction“ of latter gave the core structure **180** followed by hydroboration reaction, interestingly, employing BH_3·THF as hydroboration agent provided the alcohol **196b** diastereoselectively. Cleavage of the protecting group provided the final product *iso*-2-Phomapentenone (**197**) in enantiopure fashion. The epimer *iso*-2-Phomapentenone (**199**) was provided in a total yield of 2.8% with 92% enantiomeric excess requiring Mitsunobu inversion as an additional reaction step. Fortunately, both epimers (**197**) and (**199**) were each received as single diastereomers.

The absolute determination of the alcohol stereocenter formed in the hydroboration step was attempted *via* derivatization of latter for X-Ray analysis and esterification with Mosher`s acid for ^{1}H-NMR analysis. Oxa-Michael addition of the free alcohol group with the enone system of the cyclopentenone core structure was investigated in order to form a bicyclic product that could be characterized *via* NOESY spectra. Unfortunately, all attempts for characterization of the alcohol stereocenter failed.

4 Summary

4.1 Summary in English

In the first chapter, a new project of natural product synthesis is described in collaboration with Univ.-Prof. Dipl.-Biol. Dr. Stefan Dötterl from University of Salzburg, Austria. A thus far unknown natural product designated as Gambanol (**1a**) was determined as the single dominant scent compound of the flowering plant *Syngonium hastiferum* attracting the mirid bug *Neella* sp. nov. in Costa Rica. *Via* 2D NMR spectroscopy the chemical structure of the scent compound was determined and therefore successfully synthesized in the working group of Reiser. Positive field bioassays in Costa Rica as well as comparison of the analytical data of the natural and synthetic Gambanol (**1a**) verified the predicted structure. Furthermore, three derivatives **1b**-**d** of Gambanol (**1a**) were successfully synthesized for reason of methodology as well as for biological testing. Fortunately, the synthesized Gambanol (**1a**) showed high level of attraction to the mirid bugs, whereas the derivatives **1b**-**d** showed lower or no attraction.

In the second chapter, synthesis of 5-substituted cyclopent-2-en-1-ones **82**-**84** is demonstrated on basis of furfural (**80**) outcoming from “Green Chemistry”. The key step of synthesis was Piancatelli rearrangement for the formation of the cyclopentenone core structure **82**, kinetic resolution of various cyclopentenones **83** was achieved *via* asymmetric Tsuji-Trost allylation. In the subsequent “one pot aldol reaction” of substituted cyclopentenones **83** the reaction was explored in view of diastereoselectivity. Based on nucleophilic addition of Cu(I)-catalyzed Grignard reagents and trapping of the forming enolate with various aldehydes the “one pot aldol reaction” was successfully carried out. Employing alkyl, alkenyl and aryl Grignard reagents as well as aldehydes provided excellent diastereoselectivity resulting in the single diastereomer **84**. Furthermore, a new mechanism was postulated for this aldol reaction based on the Zimmermann-Traxler model. To expand the scope of cyclopentenone substrates further investigations were carried out employing 2-methyl cyclopent-2-en-1-one **162** for the synthesis of Aculene D (**158**) discovered by Peterson[69] in 2014, however, no positive result was obtained.

In the last chapter, synthesis of the natural product Phomapentenone A ((–)-**177**), discovered by Wicklow[74] in 2002, was carried out as application of the “one pot aldol reaction” of cyclopentenones. For introduction of alcohol group in a sidechain of the target molecule **177** hydroboration reaction was performed, unfortunately, the regioselectivity of the reaction was different than assumed. Therefore, two new compounds *iso*-1-Phomapentenone A (**197**) and

iso-2-Phomapentenone A (**199**) were provided selectively in different syntheses instead of Phomapentenone A ((–)-**177**). In order to determine the absolute stereochemistry of the two newly synthesized compounds **197** and **199,** different strategies were examined, e.g. derivatization for X-Ray analysis, esterification with Mosher`s acid for ^{1}H-NMR analysis and formation of a bicyclic product *via* oxa-Michael addition of the free alcohol with the *α,β*-unsaturated enone system of the cyclopentenone. Unfortunately, none of the strategies gave a positive result.

4.2 Summary in German (Zusammenfassung)

Im ersten Kapitel wird in Kollaboration mit Univ.-Prof. Dipl.-Biol. Dr. Stefan Dötterl von der Universität Salzburg (Österreich) ein neues Projekt der Naturstoffsynthese beschrieben. Ein bis dahin unbekannter Naturstoff in Costa Rica, bezeichnet als Gambanol (**1a**), wurde als Hauptbestandteil der Duftstoffe von der Pflanze *Syngonium hastiferum* identifiziert, welcher das Insekt *Neella* sp. Nov anlockt. Mittels 2D-NMR Spektroskopie wurde die Strukturformel des Duftstoffes bestimmt und deshalb erfolgreich in dem Arbeitskreis Reiser synthetisch hergestellt. Positive Feldstudien in Costa Rica als auch ein Vergleich der analytischen Daten des natürlichen und synthetischen Gambanols (**1a**) bewiesen die vermutete chemische Struktur. Hinsichtlich der Methodologie der Reaktion als auch der biologischen Testung wurden weitere Derivate **1b**-**d** des Duftstoffes Gambanol (**1a**) erfolgreich hergestellt und getestet. Erfreulicherweise zeigte das synthetisierte Gambanol (**1a**) einen hohen Grad an biologischer Aktivität gegenüber den Wanzen, wohingegen die Aktivität der Derivate **1b**-**d** leider geringer oder nicht vorhanden waren.

Im zweiten Kapitel wurde die Synthese von 5-substituierten Cyclopent-2-en-1-onen **82**-**84** ausgehend von Furfural (**80**) gezeigt, welches aus der „Grünen Chemie“ gewonnen wird. Für die Bildung des Cyclopentenon Grundkörpers **82** war die Piancatelli Umlagerung ein wichtiger Schlüsselschritt, eine kinetische Racematspaltung diverser Cyclopentenone **83** wurde mittels asymmetrischer Tsuji-Trost Allylierung erreicht. In der darauffolgenden „Ein-Gefäß Aldol Reaktion“ der substituierten Cyclopentenone **83** wurde die Reaktion hinsichtlich ihrer Diastereoselektivität untersucht. Basierend auf der nukleophilen Addition von Cu(I)-katalysierten Grignard-Reagenzien und dem Abfangen des gebildeten Enolats mit diversen Aldehyden wurde die selektive Aldolreaktion erfolgreich demonstriert .In der Reaktion wurden sowohl Alkyl, Alkenyl- und Aryl-Grignard Reagenzien als auch diverse Aldehyde erfolgreich umgesetzt und zeigten exzellente Diastereoselektivität, da lediglich ein einzelnes Diastereomer **84** erhalten wurde. Zudem wurde für diese Aldolreaktion ein neuer

Mechanismus basierend auf dem Zimmermann-Traxler Modell postuliert. Zur Erweiterung dieser diastereoselektiven Reaktion wurde 2-Methyl-cyclopent-2-en-1-one **162** hinsichtlich der Synthese von Aculene D (**158**) verwendet, welches von Peterson[69] 2014 entdeckt wurde, jedoch war die Aldolreaktion nicht erfolgreich.

Im letzten Kapitel wurde eine Anwendung der „Ein-Gefäß Aldol Reaktion“ für Cyclopentenone hinsichtlich der Synthese des Naturstoffs Phomapentenone A ((–)-**177**), entdeckt von Wicklow[74] in 2002, untersucht. Zur Einführung einer Alkoholgruppe in einer Seitenkette des Zielmoleküls **177** wurde eine Hydroborierung durchgeführt, jedoch erfolgte die Regioselektivität der Reaktion anders als ursprünglich angenommen. Daher wurden anstatt Phomapentenone A ((–)-**177**) zwei neue Produkte *Iso*-1-Phomapentenone A (**197**) and *Iso*-2-Phomapentenone A (**199**) in unterschiedlichen Synthesen selektiv erhalten. Zur Bestimmung der absoluten Stereochemie der beiden neuen Substanzen **197** und **199** wurden verschiedene Strategien verfolgt, z.B. Derivatisierung zur X-Ray Analyse von Kristallen, Veresterung mit der Säure nach Mosher zur ^{1}H-NMR-Spektroskopie und die Bildung eines Bizyklus *via* oxa-Michael Addition der freien Alkoholgruppe mit dem *α,β*- ungesättigten Enon des Cyclopentenon-Systems. Allerdings war keine der Strategien erfolgreich.

5 Experimental Part

5.1 General Comments

All commercially available reagents were purchased in high quality and used without further purification unless otherwise stated. All reactions were carried out in oven dried glassware under nitrogen atmosphere unless otherwise stated. DCM and THF were taken from a MBraun MB SPS solvent purification system. Hexanes and EtOAc for chromatographic separations were distilled prior to usage.

^{1}H- and ^{13}C-NMR

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and Bruker Avance 400 (400 MHz for ^{1}H and 101 MHz for ^{13}C). ^{1}H chemical shifts are reported in ppm from internal $CHCl_3$ (7.26 ppm) as standard on the δ scale. Multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, td = triplet of doublet, tdd = triplet of doublet of doublet, dtd = doublet of triplet of doublet and m = multiplet), integration and coupling constant (Hz) of peaks are given in parentheses. ^{13}C chemical shifts are reported in ppm from internal $CHCl_3$ (77.16 ppm) as standard on the δ scale.

Column Chromatography

Column chromatography was performed using Merck silica gel 60 (70-230 mesh ASTM).

HPLC

High performance liquid chromatography was carried out using Varian 920-LC with a photodiode array (PDA) detector. For each compound a specified chiral stationary phase was used (Chiralcel OD-H: 4.6 x 250mm, 10 µm; Chiralcel OJ-H: 4.6 x 250mm, 10 µm; Chiralpak: 4.6 x 250mm, 10 µm).

IR spectroscopy

IR spectroscopy was carried out on an Agilent Technologies Cary 630 FTIR instrument.

Mass spectrometry

High resolution mass spectra (HRMS) were recorded on a Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000 or Agilent Technologies 6540 UHD Accurate-Mass Q-

TOF LC/MS mass spectrometer at the Central Analytical Department (University of Regensburg).

Melting points

Melting points were measured on a SRS MPA 100 OptiMelt instrument. Values thus obtained were not corrected.

Microwave

Microwave reactions were performed in Anton-Paar Monowave 300 microwave using special pressure stable sealed 10 mL or 35 mL *via*ls.

Optical rotation

The optical rotation was determined in an Anton Paar MCP 500 polarimeter at 589 nm wavelength (sodium-d-line).

Thin Layer Chromatography

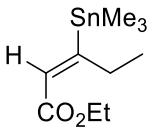
Thin layer chromatography was done on TLC pre-coated aluminium sheets (Merck, silica gel 60 F254, 0.2 mm). Visualization was accomplished with UV light (254 nm) and a vanillin sulfuric acid solution for staining.

X-Ray analysis

X-Ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH).

5.2 Synthesis of Gambanol and Derivatives

Ethyl (*E*)-3-(trimethylstannyl)pent-2-enoate (5a) [7]



The literature known procedure was modified in the following way:

To a solution of naphthalene (416.6 mg, 3.3 mmol, 6.6 mol%) in $THF_{abs.}$ (150 mL) under N_2-atmosphere in a flame dried flask, were added lithium clippings (676.7 mg, 97.6 mmol, 2.0 equiv). The resulting mixture turned dark green and was stirred at room temperature for 1 h. Then tri-*n*-butyltin chloride (13.0 g, 10.8 mL, 65.0 mmol, 1.3 equiv) was added dropwise and the mixture was stirred at room temperature for 3 h and the resulting trimethylstannyl-lithium solution was cooled then to -48 °C. Freshly prepared $CuBr{\cdot}SMe_2$ (13.4 g, 65.0 mmol, 1.3 equiv) was added in one portion to the reaction mixture and was stirred for 10 min at -48 °C to give a dark red solution of the cuprate reagent. The reaction mixture was cooled to -78 °C and ethyl pent-2-ynoate **6** (6.3 g, 6.6 mL, 50 mmol, 1.0 equiv) in THF_{abs} (15 mL) was added. The solution was stirred for 4 h at -78 °C. NH_4Cl-NH_4OH (aq., sat., pH 8, 30 mL) and Et_2O (150 mL) were added, the mixture was allowed to warm to room temperature, and the mixture was stirred until the aqueous phase became deep blue. The organic layer was separated, washed twice with NH_4Cl-$NH_4OH_{aq.}$ (aq., sat., pH 8, 75 mL), dried with $MgSO_4$ and concentrated. The residual oil was purified *via* Kugelrohr distillation (90 °C/0.5 mbar) and the product **5a** was obtained in 69% yield (10.0 g, 34.4 mmol).

Physical state: pale yellow oil.

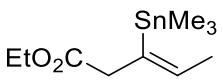
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 5.89 (s, $^3J_{Sn\text{-}H}$ = 74 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.85 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.16 (s, $^2J_{Sn\text{-}H}$ = 54 Hz, 9H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ= 174.6, 164.3, 126.9, 59.7, 28.0, 14.3, 14.2, -9.1.

The analytical data are in agreement with the literature.

Ethyl (*Z*)-3-(trimethylstannyl)pent-3-enoate (4a) [8]



The literature known procedure was modified in the following way:

To a cold (-78 °C), stirred solution of lithium diisopropylamide (LDA) (7.4 g, 69.0 mmol, 2.3 equiv) in $THF_{abs.}$ (150 mL) was added a solution of the ester **5a** (8.7 g, 30.0 mmol, 1.0 equiv) in $THF_{aq.}$ (15 mL). The solution was stirred at -78 °C for 45 min and at 0 °C for 1.5 h. After the solution was cooled to -78 °C, it was transferred *via* cannulation to a vigorously stirred, cold (-98 °C) solution of acetic acid (20 mL) in Et_2O (100 mL). The mixture was warmed to room temperature, and $NaHCO_3$ (aq., sat., 50 mL) and Et_2O (50 mL) were added. The organic phase was separated and the aqueous layer was washed with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried with $MgSO_4$ and the solvent was evaporated. The residual oil was purified *via* Kugelrohr distillation (95 °C/0.5 mbar) and the product **4a** was obtained in 72% yield (6.3 g, 21.7 mmol).

Physical state: pale yellow oil.

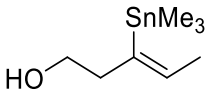
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ 6.14 (qt, *J* = 6.5, 1.3 Hz, $^3J_{Sn-H}$ = 130 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.19 (d, *J* = 1.1 Hz, $^3J_{Sn-H}$ = 52 Hz 2H), 1.75 (dt, *J* = 6.6, 1.0 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.28 – 0.10 (s, $^2J_{Sn-H}$ = 52 Hz, 9H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ= 173.1, 138.5, 137.3, 60.5, 45.1, 19.6, 14.3, -8.3.

The analytical data are in agreement with literature.

(*Z*)-3-(Trimethylstannyl)pent-3-en-1-ol (3) [9]



The literature known procedure was modified in the following way:

To a cold (-78 °C), stirred solution of ester **4a** (5.24 g, 18.0 mmol, 1.0 equiv) in $Et_2O_{abs.}$ (180 mL) was added a solution of diisobutylaluminum hydride (DIBAL-H) (45 mL, 45 mmol, 2.5 equiv) in hexanes and the resulting clear solution was stirred at -78 °C for 1.5 h and at 0 °C for 1.5 h. NH_4Cl-NH_4OH (aq., sat., pH 8, 5 mL) was added and the white slurry was allowed to stir at room temperature for 1 h. $MgSO_4$ (1 g) was added and the slurry was filtered through a column of Celite (10 g).The column was washed with Et_2O (300 mL). The solvent of the combined filtrate was evaporated and the residual oil was purified *via* Kugelrohr distillation (65 °C/0.5 mbar) and the product **3** was obtained in 89% yield (4.0 g, 16.1 mmol).

Physical state: pale yellow oil.

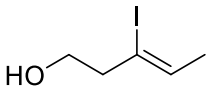
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.18 (q, *J* = 6.5 Hz, $^{3}J_{Sn-H}$ = 137 Hz, 1H), 3.55 (q, *J* = 6.1 Hz, 2H), 2.42 (t, *J* = 6.2 Hz, $^{3}J_{Sn-H}$ = 55 Hz, 2H), 1.76 (dt, *J* = 6.6, 0.9 Hz, 3H), 1.45 – 1.38 (m, 1H), 0.19 (s, $^{2}J_{Sn-H}$ = 137 Hz, 9H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ= 140.8, 138.4, 61.7, 43.1, 19.8, -8.5.

The analytical data are in agreement with literature.

(*Z*)-3-Iodopent-3-en-1-ol (2) [9]



The literature known procedure was modified in the following way:

To a stirred solution of iodine (4.0 g, 15.8 mmol, 1.05 equiv) in $DCM_{abs.}$ (150 mL) at room temperature was added a solution of alcohol **3** (3.7 g, 15.0 mmol, 1.0 equiv) in $DCM_{abs.}$ (15 mL) and the mixture was stirred for 30 min. $Na_2S_2O_3$ (aq., sat., 20 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (4 x 50 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. The residual oil was purified *via* column chromatography (hexanes/Et_2O: 3:1) and subsequent Kugelrohr distillation (60 °C/0.5 mbar) and gave rise to 94% yield (3.0 g, 14.2 mmol) of the product **2**.

Physical state: pale yellow oil.

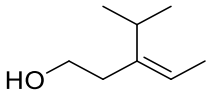
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ= 5.70 (qt, *J* = 6.3, 1.2 Hz, 1H), 3.71 (q, *J* = 5.9 Hz, 2H), 2.68 (tt, *J* = 5.9, 1.2 Hz, 2H), 2.00 (t, *J* = 5.9 Hz, 1H), 1.74 (dt, *J* = 6.3, 1.1 Hz, 3H).

^{13}C-NMR: (75 MHz, $CDCl_3$) δ= 133.0, 105.9, 61.0, 47.9, 22.3.

The analytical data are in agreement with literature.

(*Z*)-3-Isopropylpent-3-en-1-ol (1a)



The 1.0 M organozinc halide solution was prepared as following:

To Zn dust (1.08 g, 16.5 mmol, 1.1 equiv) in $THF_{abs.}$ (15 mL) was added dibromoethane (50 µL) and the suspension was heated until reflux and then cooled down to room temperature. TMSCl (50 µL) was added to the suspension, heated until reflux and cooled down to room temperature again. 2-Iodopropane (2.6 g, 1.5 mL, 15.0 mmol, 1.0 equiv) was added slowly to the suspension under vigorously stirring and the reaction mixture started to boil and was stirred

until the reaction mixture cooled down to room temperature (30 min). The obtained organozinc halide solution was titrated with a solution of iodine in 0.5 M LiCl in THF to receive a 1.0 M solution.

The Negishi coupling reaction[4] was carried out as following with modified conditions:

To $PdCl_2(Amphos)_2$ catalyst (14.2 mg, 20.0 µmol, 2.0 mol%) was added $DMF_{abs.}$ (2 mL) followed by iodide **2** (212.0 mg, 1.0 mmol, 1.0 equiv) and 1-methylimidazole (162.2 mg, 159 µL, 2.0 mmol, 2.0 equiv) under vigorously stirring. The preformed organozinc halide solution (2.4 mL, 2.4 mmol, 2.4 equiv) was added slowly and stirred at room temperature for 30 min. Then the reaction mixture was heated to 100 °C for 3 h until the reaction was complete (checked by TLC). The mixture was cooled down to room temperature and quenched with NH_4Cl (aq., sat., 5 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated. The residual oil was purified *via* column chromatography (*n*-pentane/Et_2O: 2:1) and the product **1a** was received in 87% yield (111.2 mg, 0.87 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

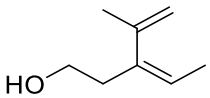
^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 5.22 (q, *J* = 6.8 Hz, 1H), 3.68 (dt, *J* = 6.6, 5.5 Hz, 2H), 2.86 (sep, *J* = 7.0 Hz, 1H), 2.23 (t, *J* = 6.7 Hz, 2H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.48 (t, *J* = 5.4 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 6H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ= 141.2, 119.8, 61.8, 34.9, 28.4, 20.9, 12.8.

IR: (v/cm^{-1}) 3332, 2959, 2870, 1655, 1464, 1383, 1181, 1103, 1028, 962, 883, 824, 746.

HRMS: (EI) exact mass calc. for $C_8H_{16}O$ $[M]^+$: *m/z* 128.1196, found: *m/z* 128.1198.

(*Z*)-3-(prop-1-en-2-yl)pent-3-en-1-ol (1b)



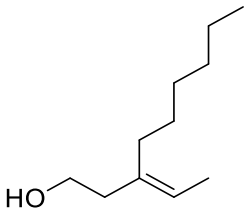
The 1.0 M organozinc halide solution was prepared as following:

To Zn dust (1.08 g, 16.5 mmol, 1.1 equiv) in $THF_{abs.}$ (15 mL) was added dibromoethane (50 µL) and the suspension was heated until reflux and then cooled down to room temperature. TMSCl (50 µL) was added to the suspension, heated until reflux and cooled down to room temperature again. 2-Bromoprop-1-ene (1.81 g, 1.30 mL, 15.0 mmol, 1.0 equiv) was added slowly to the suspension under vigorously stirring and the reaction mixture and was stirred under reflux for 30 min. The obtained organozinc halide solution was titrated with a solution of iodine in 0.5 M LiCl in THF to receive a 1.0 M solution.

The Negishi coupling reaction[4] was carried out as following with modified conditions:
To $PdCl_2(Amphos)_2$ catalyst (14.2 mg, 20.0 µmol, 2.0 mol%) was added $DMF_{abs.}$ (2 mL) followed by iodide **2** (212.0 mg, 1.0 mmol, 1.0 equiv) and 1-methylimidazole (162.2 mg, 159 µL, 2.0 mmol, 2.0 equiv) under vigorously stirring. The preformed organozinc halide solution (2.4 mL, 2.4 mmol, 2.4 equiv) was added slowly and stirred at room temperature for 30 min. Then the reaction mixture was heated to 100 °C for 2 h until the reaction was complete (checked by TLC). The mixture was cooled down to room temperature and quenched with NH_4Cl (aq., sat., 5 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated. The residual oil was purified *via* column chromatography (*n*-pentane/Et_2O: 2:1) and the product **1b** was received in 89% yield (112.0 mg, 0.89 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).
^{1}H-NMR: (300 MHz, $CDCl_3$) δ= ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.35 (qt, *J* = 6.8, 1.3 Hz, 1H), 5.03 (dt, *J* = 2.5, 1.5 Hz, 1H), 4.67 (dt, *J* = 2.3, 1.0 Hz, 1H), 3.68 – 3.56 (m, 2H), 2.41 – 2.29 (m, 2H), 1.79 (s, 3H), 1.65 (dt, *J* = 6.7, 1.1 Hz, 3H).
^{13}C-NMR: (75 MHz, $CDCl_3$) δ=143.3, 139.8, 122.8, 114.3, 60.7, 39.4, 22.1, 14.5.
IR: (v/cm^{-1}) 3324, 3078, 2937, 2877, 1632, 1446, 1371, 1248, 1185, 1151, 965, 894, 827, 678.
HRMS: (EI) exact mass calc. for $C_8H_{14}O$ $[M]^+$: *m/z* 126.1039, found: *m/z* 126.1038.

(*E*)-3-ethylidenenonan-1-ol (1c)

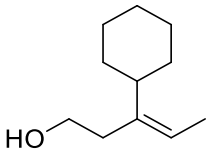


The 1.0 M organozinc halide solution was prepared as following:
To Zn dust (1.08 g, 16.5 mmol, 1.1 equiv) in $THF_{abs.}$ (15 mL) was added dibromoethane (50 µL) and the suspension was heated until reflux and then cooled down to room temperature. TMSCl (50 µL) was added to the suspension, heated until reflux and cooled down to room temperature again. 1-Iodohexane (3.18 g, 2.2 mL, 15.0 mmol, 1.0 equiv) was added slowly to the suspension under vigorously stirring and the reaction mixture was stirred under reflux for 30 min. The obtained organozinc halide solution was titrated with a solution of iodine in 0.5 M LiCl in THF to receive a 1.0 M solution.

The Negishi coupling reaction[4] was carried out as following with modified conditions:
To $PdCl_2(Amphos)_2$ catalyst (14.2 mg, 20.0 µmol, 2.0 mol%) was added $DMF_{abs.}$ (2 mL) followed by iodide **2** (212.0 mg, 1.0 mmol, 1.0 equiv) and 1-methylimidazole (162.2 mg, 159 µL, 2.0 mmol, 2.0 equiv) under vigorously stirring. The preformed organozinc halide solution (2.4 mL, 2.4 mmol, 2.4 equiv) was added slowly and stirred at room temperature for 30 min. Then the reaction mixture was heated to 100 °C for 3 h until the reaction was complete (checked by TLC). The mixture was cooled down to room temperature and quenched with NH_4Cl (aq., sat., 5 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated. The residual oil was purified *via* column chromatography (*n*-pentane/Et_2O: 2:1) and the product **1c** was received in 91% yield (155.0 mg, 0.91 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).
^{1}H-NMR: (400 MHz, $CDCl_3$) δ=5.31 (q, *J* = 6.7 Hz, 1H), 3.64 (q, *J* = 6.1 Hz, 2H), 2.25 (tt, *J* = 6.3, 1.1 Hz, 2H), 2.06 – 1.99 (m, 2H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.43 – 1.24 (m, 10H), 0.94 – 0.79 (m, 3H).
^{13}C-NMR: (101 MHz, $CDCl_3$) δ=136.7, 122.1, 60.6, 40.2, 31.9, 29.6, 29.5, 28.4, 22.8, 14.2, 13.5.
IR: (v/cm^{-1}) 3317, 2926, 2858, 1461, 1379, 1110, 1185, 1039, 868, 820, 723.
HRMS: (EI) exact mass calc. for $C_{11}H_{22}O$ $[M]^+$: *m/z* 170.1665, found: *m/z* 170.1668.

(*Z*)-3-cyclohexylpent-3-en-1-ol (1d)



The 1.0 M organozinc halide solution was prepared as following:
To Zn dust (1.08 g, 16.5 mmol, 1.1 equiv) in $THF_{abs.}$ (15 mL) was added dibromoethane (50 µL) and the suspension was heated until reflux and then cooled down to room temperature. TMSCl (50 µL) was added to the suspension, heated until reflux and cooled down to room temperature again. Iodocyclohexane (3.15 g, 1.9 mL, 15.0 mmol, 1.0 equiv) was added slowly to the suspension under vigorously stirring and the reaction mixture started to boil and was stirred until the reaction mixture cooled down to room temperature (30 min). The obtained

organozinc halide solution was titrated with a solution of iodine in 0.5 M LiCl in THF to receive a 1.0 M solution.

The Negishi coupling reaction[4] was carried out as following with modified conditions:

To $PdCl_2(Amphos)_2$ catalyst (14.2 mg, 20.0 µmol, 2.0 mol%) was added $DMF_{abs.}$ (2 mL) followed by iodide **2** (212.0 mg, 1.0 mmol, 1.0 equiv) and 1-methylimidazole (162.2 mg, 159 µL, 2.0 mmol, 2.0 equiv) under vigorously stirring. The preformed organozinc halide solution (2.4 mL, 2.4 mmol, 2.4 equiv) was added slowly and stirred at room temperature for 30 min. Then the reaction mixture was heated to 100 °C for 3 h until the reaction was complete (checked by TLC). The mixture was cooled down to room temperature and quenched with NH_4Cl (aq., sat., 5 mL) and the organic layer was separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated. The residual oil was purified *via* column chromatography (*n*-pentane/Et_2O: 2:1) and the product **1d** was received in 87% yield (146.0 mg, 0.87 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ=5.22 (q, *J* = 6.7 Hz, 1H), 3.65 (td, *J* = 6.5, 3.3 Hz, 2H), 2.44 (tq, *J* = 8.5, 3.4 Hz, 1H), 2.23 (tt, *J* = 6.7, 1.2 Hz, 2H), 1.82 – 1.44 (m, 10H), 1.32 – 1.26 (m, 3H).

^{13}C-NMR: (101 MHz, $CDCl_3$) δ=140.8, 120.5, 61.7, 39.6, 36.1, 31.2, 26.8, 26.2, 12.9.

IR: (v/cm^{-1}) 3306, 2922, 2851, 1740, 1446, 1375, 1345, 1263, 1207, 1036, 890, 857, 820.

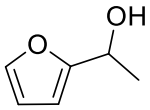
HRMS: (ESI) exact mass calc. for $C_{11}H_{21}O$ $[M+H]^+$: *m/z* 169.1587, found: *m/z* 169.1588.

5.3 Synthesis of Furylcarbinols

General procedure for the synthesis of furylcarbinols with Grignard-reagent

Magnesium (3.16 g, 130 mmol, 1.3 equiv) was suspended in Et_2O (90 mL) and the specified bromide (160 mmol, 1.6 equiv) in Et_2O (45 mL) was added slowly within 15 min under gentle reflux. Then the mixture was refluxed for 1 h. After cooling to 0 °C furfural (8.3 mL, 9.6 g, 100 mmol, 1.0 equiv) in Et_2O (45 mL) was added slowly within 5 min and the mixture was stirred for 10 min. H_2O (50 mL) was added and the organic layer was seperated and the aqueous phase was extracted with Et_2O (2 x 150 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 10:1 – 5:1) to afford the specified product.

(±)-1-(furan-2-yl)ethan-1-ol ((±)-81f) [84]



2-Acetyl furan (**106**) (50.0 g, 454.1 mmol, 1.0 equiv.) was dissolved in ethanol (400 mL), $NaBH_4$ (8.6 g, 227.3 mmol, 0.5 equiv.) was slowly added over a period of 1 h under cooling conditions at 0 C and stirred for 2 h. Acetone (75 mL) was added dropewise over a period of 15 min under cooling conditions and stirred for 30 min. H_2O (200 mL) was added and the solvent was evaporated. The aqueous phase was extracted with EtOAc (5 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was fractional distilled under reduced pressure (bp: 42 °C/4.3 mbar) and gave 2-furylcarbinol (±)-**81f** in 81% yield (41.1 g, 366.5 mmol).

Physical state: pale yellow oil.

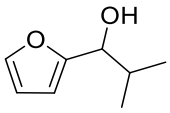
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.36 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21 (m, 1H), 4.93–4.79 (q, *J* = 6.6 Hz, 1H), 2.22 (bs, 1H), 1.53 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 157.6, 141.9, 110.1, 105.1, 63.6, 21.3.

The analytical data are in agreement with literature.

(±)-1-(furan-2-yl)-2-methylpropan-1-ol ((±)-81g) [84]



The compound was prepared according to the general procedure for the synthesis of furylcarbinols with Grignard-reagent with 2-bromopropane (15.0 mL, 19.7 g, 160 mmol, 1.6 equiv) as bromide to obtain the product (±)-**81g** in 68% (9.5 g, 67.8 mmol) yield.

Physical state: pale yellow oil.

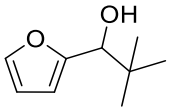
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (dt, *J* = 3.2, 0.7 Hz, 1H), 4.37 (d, *J* = 7.1 Hz, 1H), 2.34 – 1.95 (m, 1H), 1.87 (s, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =156.1, 141.7, 110.0, 106.5, 73.5, 33.4, 18.7, 18.3.

The analytical data are in agreement with literature.

(±)-1-(furan-2-yl)-2,2-dimethylpropan-1-ol ((±)-81h) [84]



A solution of ^{t}BuLi (19.4 mL, 1.7 M, 33.0 mmol, 1.1 equiv) in hexanes was cooled to 0 °C, then furfural (2.5 mL, 2.9 g, 30 mmol, 1.0 equiv) in Et_2O (25 mL) was added slowly within 5 min and the mixture was stirred for 5 min. H_2O (50 mL) was added slowly and the organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 10:1 – 5:1) to afford the product (±)-**81h** in 65% (3.0 g, 19.5 mmol) yield.

Physical state: pale yellow oil.

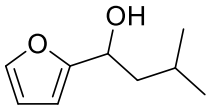
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.22 (dt, *J* = 3.4, 0.6 Hz, 1H), 4.38 (s, 1H), 0.96 (s, 9H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 141.5, 110.1, 107.1, 35.9, 25.9.

The analytical data are in agreement with literature.

(±)-1-(furan-2-yl)-3-methylbutan-1-ol ((±)-81i) [85]



The compound was prepared according to the general procedure for the synthesis of furylcarbinols with Grignard-reagent with 1-bromo-2-methylpropane (17.4 mL, 21.92 g, 160 mmol, 1.6 equiv) as bromide to afford the product (±)-**81i** in 80% (12.4 g, 80.4 mmol) yield.

Physical state: pale yellow oil.

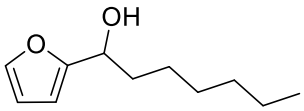
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.37 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 4.74 (dd, *J* = 8.4, 5.3 Hz, 1H), 1.85 (bs, 1H), 1.86 – 1.58 (m, 3H), 0.94 (pdd, *J* = 6.2, 4.3 Hz, 6H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =157.08, 141.89, 110.12, 105.72, 65.98, 44.45, 24.60, 23.04, 22.15.

The analytical data are in agreement with literature.

(±)-1-(furan-2-yl)heptan-1-ol ((±)-81k)



The compound was prepared according to the general procedure for the synthesis of furylcarbinols with Grignard-reagent with 1-bromohexane (22.4 mL, 26.41 g, 160 mmol, 1.6 equiv) as bromide to afford the product (±)-**81k**in 78% (14.2 g, 77.9 mmol) yield.

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

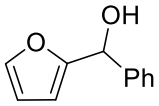
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.34 (d, *J* = 1.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 4.63 (td, *J* = 6.9, 2.9 Hz, 1H), 1.82 (dtd, *J* = 8.5, 6.1, 2.0 Hz, 2H), 1.50 – 1.16 (m, 9H), 0.96 – 0.77 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$): δ = 157.0, 141.8, 110.1, 105.7, 67.7, 35.6, 31.7, 29.1, 25.5, 22.6, 14.1.

IR: (neat, cm^{-1}) 3365, 2926, 2858, 1506, 1465, 1379, 1230, 1178, 1148, 1066, 1006, 917, 887, 805, 731.

HRMS: (EI) exact mass calc. for $C_{11}H_{18}O_2$ $[M]^+$: *m/z* 182.1301, found: *m/z* 182.1299.

(±)-furan-2-yl(phenyl)methanol ((±)-81l) [38]



The compound was prepared according to the general procedure for the synthesis of furylcarbinols with Grignard-reagent with bromobenzene (16.8 mL, 25.1 g, 160 mmol, 1.6 equiv) as bromide to afford the product (±)-**81l** in 69% (12.1 g, 69.4 mmol) yield.

Physical state: pale yellow oil.

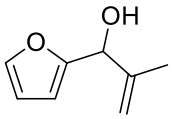
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.45 – 7.33 (m, 5H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.12 (dt, *J* = 3.3, 0.8 Hz, 1H), 5.82 (s, 1H), 2.51 (bs, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =155.9, 142.6, 140.8, 128.5, 128.1, 126.6, 110.3, 107.5, 70.2.

The analytical data are in agreement with literature.

(±)-1-(furan-2-yl)-2-methylprop-2-en-1-ol ((±)-81m) [86]



The compound was prepared according to the general procedure for the synthesis of furylcarbinols with Grignard-reagent with 2-bromoprop-1-ene (14.2 mL, 19.4 g, 160 mmol, 1.6 equiv) as bromide to afford the product (±)-**81m** in 71% (9.8 g, 70.9 mmol) yield.

Physical state: pale yellow oil.

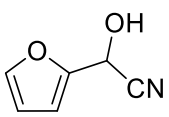
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.34 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.22 (dt, *J* = 3.2, 0.8 Hz, 1H), 5.14 (p, *J* = 1.2 Hz, 1H), 5.11 (d, *J* = 4.7 Hz, 1H), 4.98 (h, *J* = 1.5 Hz, 1H), 2.15 (d, *J* = 4.9 Hz, 1H), 1.69 (t, *J* = 1.1 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =154.8, 144.3, 142.3, 112.1, 110.3, 107.0, 71.5, 18.7.

The analytical data are in agreement with literature.

(±)-2-(furan-2-yl)-2-hydroxyacetonitrile ((±)-81n) [87]



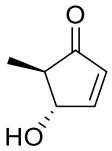
Furfural (384 mg, 4.0 mmol, 1.0 equiv) was dissolved in glacial acetic acid (1.92 g, 32.0 mmol, 8.0 equiv) and cooled to 0 C. Then a solution of KCN (780 mg, 12.0 mmol, 3.0 equiv) in H_2O (2 mL) was added dropwise and the mixture was stirred over night at room temperature. Then H_2O (2 mL) was added, the product was extracted with Et_2O and dried over $MgSO_4$. After filtration and addition of toluene, the solvent was removed. Crude product (±)-**81n** was obtained in 99% yield (490 mg, 3.98 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.61 (dt, *J* = 3.3, 0.8 Hz, 1H), 6.43 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.55 (s, 1H).

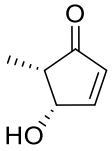
The analytical data are in agreement with literature.

5.4 Piancatelli Rearrangement

(±)-(4*S*,5*R*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-82f) [84]



(±)-(4*S*,5*S*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-82f) [84]



Procedure A: Microwave-Reactor

A 30 mL closed microwave pressure vessel was charged with a solution of 1-(furan-2-yl)ethan-1-ol (±)-**81f** (1.12 g, 10.0 mmol, 1.0 equiv) in H_2O (18 mL, Millipore). The mixture was heated in a microwave reactor for 4 min, reaching a maximum temperature of 160 °C. After the reaction was complete the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 7:1 – 2:1) to afford the cyclopentenones (±)-*anti*-**82f**/(±)-*syn*-**82f** in a 8:1 ratio (^{1}H-NMR) in a combined yield of 44% (493.3 mg, 4.40 mmol).

Procedure B: Microreactor

A solution of 1-(furan-2-yl)ethan-1-ol (±)-**81f** (16.8 g, 0.15 mol, 1.0 equiv) in toluene (total volume 45 mL, flowrate: 0.3 mL/min) was converted with acidulated water (pH 4.0, flowrate: 3.5 mL/min) in a microreactor (stainless steel capillary tube, heated zone: 10 m x 1.0 mm) at 240 °C over a periode of 2.5 h. The solvent was evaporated under reduced pressure and the crude product mixture was purified by fractional distillation under reduced pressure (bp: 58-61 °C/0.1 mbar) to afford the cyclopentenones (±)-*anti*-**82f** /(±)-*syn*-**82f** in a 8:1 ratio (GC-FID) in a combined yield of 73% (12.24 g, 0.11 mol).

Procedure C: Ester Hydrolysis

H_2O (20 mL) was adjusted to pH 3 with H_2SO_4. A diastereomeric mixture of chloroacetic ester (±)-*syn*-**185**/(±)-*anti*-**185** in a ratio of 8:1 (940.0 mg, 5.0 mmol, 1.0 equiv.) were dissolved in the prepared acidulated H_2O. The reaction mixture was stirred for 12 h at 55 °C. The resulting

mixture was neutralized with Na_2CO_3 (150 mg) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 7:1 – 2:1) to afford the cyclopentenones (±)-*anti*-**82f** /(±)-*syn*-**82f** in a 8:1 ratio (^{1}H-NMR) in a combined yield of 63% (353.2 mg, 3.15 mmol).

(±)-(4*S*,5*R*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-**82f**)

Physical state: pale yellow oil.

TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 (dd, *J* = 5.8, 2.1 Hz, 1H), 6.10 (m, 1H), 4.47 (m, 1H), 4.28 – 4.18 (bs, 1H), 2.18 (qd, *J* = 7.5, 2.5 Hz, 1H), 1.13 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 209.1, 162.4, 133.6, 78.1, 50.4, 12.5.

(±)-(4*S*,5*S*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-**82f**)

Physical state: pale yellow oil.

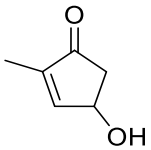
TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.10 (m, 1H), 4.90 (m, 1H), 4.28 – 4.18 (bs, 1H), 2.49 – 2.37 (m, 1H), 1.03 (d, *J* = 7.7 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$): δ = 211.4, 163.0, 133.7, 71.9, 44.7, 10.7.

The analytical data are in agreement with literature.

(±)-4-hydroxy-2-methylcyclopent-2-en-1-one ((±)-163) [88]



The cyclopentenones (±)-*anti*-**82f** /(±)-*syn*-**82f** in a 8:1 ratio (11.21 g, 100 mmol, 1.0 equiv) were dissolved in DCM (75 mL) and basic alumina (50 g) was added. The mixture was stand for 3 d and the product (±)-**163** was eluted with EtOAc (300 mL) from the basic alumina in a yield of 90% (10.1 g, 90.1 mmol).

Physical state: pale yellow oil.

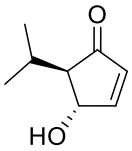
TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.19 (dq, *J* = 2.9, 1.5 Hz, 1H), 4.94 (d, *J* = 5.2 Hz, 1H), 2.81 (dd, *J* = 18.6, 6.0 Hz, 1H), 2.30 (dd, *J* = 18.6, 2.0 Hz, 1H), 1.94 (s, 1H), 1.81 (t, *J* = 1.6 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =206.3, 156.5, 143.8, 68.6, 44.5, 10.0.

The analytical data are in agreement with literature.

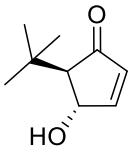
(±)-(4*S*,5*R*)-4-hydroxy-5-isopropylcyclopent-2-en-1-one ((±)-82g) [84]



The compound was prepared according to the procedure A: microwave with 1-(furan-2-yl)-2-methylpropan-1-ol (1.4 g, 10.0 mmol, 1.0 equiv) in H_2O (18 mL) with a reaction time of 4 min to afford the cyclopentenone (±)-**82g** in a yield of 36% (506.9 mg, 3.6 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.17 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.80 (td, *J* = 2.4, 1.3 Hz, 1H), 2.38 – 2.24 (m, 2H), 2.20 (dd, *J* = 4.4, 2.4 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 208.2, 162.2, 134.9, 72.8, 60.8, 27.1, 2.7, 18.2.
The analytical data are in agreement with literature.

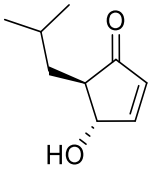
(±)-(4*S*,5*R*)-5-(*tert*-butyl)-4-hydroxycyclopent-2-en-1-one ((±)-82h) [84]



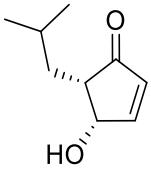
The compound was prepared according to the procedure A: microwave with 1-(furan-2-yl)-2,2-dimethylpropan-1-ol (1.54 g, 10.0 mmol, 1.0 equiv) in H_2O (18 mL) with a reaction time of 10 min afford the cyclopentenone (±)-**82h** in a yield of 28% (433.5 mg, 2.8 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.13 (dd, *J* = 5.8, 1.4 Hz, 1H), 4.81 (td, *J* = 2.4, 1.3 Hz, 1H), 2.01 (d, *J* = 2.6 Hz, 1H), 1.07 (s, 9H).
^{13}C NMR: (75 MHz, $CDCl_3$): δ = 207.4, 160.8, 135.7, 74.2, 64.2, 32.9, 29.9, 28.0.
The analytical data are in agreement with literature.

(±)-(4*S*,5*R*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*anti*-82i)



(±)-(4*S*,5*S*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*syn*-82i)



The compounds were prepared according to the procedure A: microwave with 1-(furan-2-yl)-3-methylbutan-1-ol (1.54 g, 10.0 mmol) in H_2O (18 mL) with a reaction time of 4 min to afford the cyclopentenones (±)-*anti*-**82i**/(±)-*syn*-**82i** in a 20:1 ratio (^{1}H-NMR) in a combined yield of 54% (831.8 mg, 5.4 mmol).

(±)-(4*S*,5*R*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*anti*-**82i**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.48 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.14 (dd, *J* = 5.7, 1.2 Hz, 1H), 4.65 – 4.57 (m, 1H), 3.08 (s, 1H), 2.27 (ddd, *J* = 10.5, 4.7, 2.3 Hz, 1H), 1.87 (dddd, *J* = 13.5, 12.3, 9.1, 6.5 Hz, 1H), 1.64 (dddd, *J* = 13.8, 9.0, 4.7, 1.4 Hz, 1H), 1.27 (ddd, *J* = 14.1, 10.5, 5.3 Hz, 1H), 0.94 (ddd, *J* = 6.7, 3.4, 1.0 Hz, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =209.3, 162.3, 133.8, 53.6, 38.3, 26.4, 23.4, 21.8.

IR: (v/ cm^{-1}) 3407, 2960, 2870, 1692, 1592, 1468, 1409, 1341, 1170, 1099, 1032, 943, 730.

HRMS: (*ESI*): calcd. for $C_{11}H_{16}O_4$ $[M+H]^+$: *m/z* 155.1067, found: *m/z* 155.1067.

(±)-(4*S*,5*S*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*syn*-**82i**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

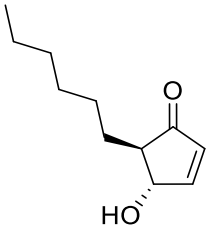
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.55 (dd, *J* = 5.8, 2.6 Hz, 1H), 6.17 (dt, *J* = 5.8, 1.3 Hz, 1H), 4.99 – 4.94 (m, 1H), 2.71 – 2.52 (m, 1H), 2.41 (dt, *J* = 8.8, 6.1 Hz, 1H), 1.91 (d, *J* = 6.5 Hz, 1H), 1.48 – 1.40 (m, 2H), 0.92 – 0.84 (m, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =210.6, 162.3, 134.1, 71.8, 48.0, 34.4, 26.0, 22.9, 22.1.

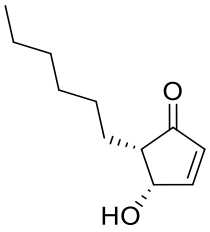
IR: (v/ cm^{-1}) 3407, 2960, 2870, 1692, 1592, 1468, 1409, 1341, 1170, 1099, 1032, 943, 730.

HRMS: (ESI) calcd. for $C_{11}H_{16}O_4$ $[M+H]^+$: *m/z* 155.1067, found: *m/z* 155.1067.

(±)-(4*S*,5*R*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*anti*-82k)



(±)-(4*S*,5*S*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*syn*-82k)



The compounds were prepared according to the procedure A: microwave with 1-(furan-2-yl)heptan-1-ol (1.82 g, 10.0 mmol) in H_2O (18 mL) with a reaction time of 10 min to afford the cyclopentenones (±)-*anti*-**82k**/(±)-*syn*-**82k** in a 10:1 ratio (^{1}H-NMR) in a combined yield of 18% (324.0 mg,1.8 mmol)

(±)-(4*S*,5*R*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*anti*-**82k**)

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.49 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.21 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.73 – 4.65 (m, 1H), 2.27 – 2.17 (m, 1H), 1.89 (d, *J* = 7.1 Hz, 1H), 1.46 – 1.26 (m, 10H), 0.89 (t, *J* = 2.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 208.3, 156.9, 141.9, 110.1, 105.8, 74.2, 67.9, 35.6, 31.7, 29.1, 25.5, 22.6, 14.1.

IR: (neat, cm^{-1}): 3407, 2926, 2858, 1696, 1461, 1341, 1170, 1100, 1044, 798, 723.

HRMS: (EI) exact mass calc. for $C_{11}H_{18}O_2$ $[M]^+$: *m/z* 182.1301, found: *m/z* 182.1297.

(±)-(4*S*,5*S*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*syn*-**82k**)

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

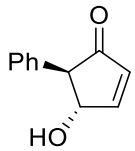
^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.57 (dd, *J* = 5.8, 2.6 Hz, 1H), 6.24 (dd, *J* = 5.8, 1.2 Hz, 1H), 4.97 – 4.91 (m, 1H), 2.27 – 2.17 (m, 1H), 1.89 (d, *J* = 7.1 Hz, 1H), 1.46 – 1.26 (m, 10H), 0.89 (t, *J* = 2.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =208.3, 161.5, 134.4, 110.0, 105.8, 76.8, 67.9, 55.4, 31.6, 29.3, 28.9, 27.3, 14.1.

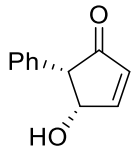
IR: (neat, cm^{-1}) 3407, 2926, 2858, 1696, 1461, 1341, 1170, 1100, 1044, 798, 723.

HRMS: (EI) exact mass calc. for $C_{11}H_{18}O_2$ $[M]^+$: *m/z* 182.1301, found: *m/z* 182.1297.

(±)-(4*S*,5*R*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*anti*-82l) [38]



(±)-(4*S*,5*S*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*syn*-82l) [38]



The compounds were prepared according to the procedure A: microwave with furan-2-yl(phenyl)methanol (1.74 g, 10.0 mmol) in H_2O (10 mL) with a reaction time of 4 min to obtain the cyclopentenones (±)-*anti*-**82l**/(±)-*syn*-**82l** in a 6:1 ratio (^{1}H-NMR) in a combined yield of 79% (1.38 g, 7.9 mmol).

(±)-(4*S*,5*R*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*anti*-**82l**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.10 – 6.97 (m, 2H), 6.21 (dd, *J* = 5.8, 1.5 Hz, 1H), 4.80 (s, 1H), 3.62 – 3.41 (m, 1H), 3.33 (d, *J* = 2.7 Hz, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 206.3, 162.7, 136.8, 134.0, 128.9, 128.4, 127.5, 78.8, 62.0.

(±)-(4*S*,5*S*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*syn*-**82l**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.63 (dd, *J* = 4.8, 2.2 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.10-6.97 (m, 2H), 6.37 (dd, *J* = 5.7, 1.5 Hz, 1H), 3.75 (d, *J* = 5.7Hz, 1H), 3.33 (s, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$): δ = 207.7, 163.7, 135.6, 134.3, 130.1, 128.9, 127.5, 72.1, 57.1.

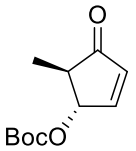
The analytical data are in agreement with literature.

5.5 Activation of the Cyclopentenones *via* Boc-Protection

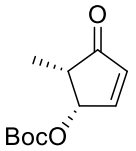
General procedure for the activation of the alcohol *via* Boc-protection

To a solution of the cyclopentenone (25.0 mmol, 1.0 equiv) in $THF_{abs.}$ (25 mL) di-*tert*-butyl dicarbonate (6.5 g, 30.0 mmol, 1.2 equiv.), triethylamine (4.2 mL, 30.0 mmol, 1.2 equiv) and DMAP (50.0 mg, 0.45 mmol, 0.02 equiv.) were added. The reaction mixture was stirred for 30 min, then the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 10:1 → 5:1) to afford the product.

(±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83f)



(±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*syn*-83f)



The compounds were prepared according to the general procedure for the activation of the alcohol *via* Boc protection with 4-hydroxy-5-methylcyclopent-2-enones (±)-*anti*-**82f**/(±)-*syn*-**82f** in a ratio of 8:1 (2.8 g, 25.0 mmol, 1.0 equiv.) to afford (±)-*anti*-**83f** in 73% yield (3.9 g, 18.3 mmol) and (±)-*syn*-**83f** in 9% yield (472.8 mg, 2.2 mmol) (overall yield: 82%).

(±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-**83f**)

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.30 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.32 (m, 1H), 2.43 (qd, *J* = 7.5, 2.5 Hz, 1H), 1.51 (s, 9H), 1.30 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 206.8, 157.2, 152.9, 135.9, 83.2, 81.6, 47.0, 27.7, 13.3.

IR: (v/ cm^{-1}) 2978, 2937, 2877, 1722, 1457, 1394, 1330, 1252, 1159, 1095, 1039, 1002, 957, 909, 853, 793, 827, 729.

HRMS: (ESI) calcd. for $C_{11}H_{16}O_4$ $[M+H]^+$: *m/z* 213.1121, found: *m/z* 213.1118.

(±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*syn*-**83f**)

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

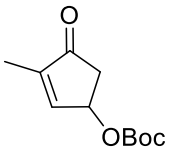
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.32 (dd, *J* = 5.8, 1.5 Hz, 1H), 5.74 (m, 1H), 2.70 (m, 1H), 1.51 (s, 9H), 1.12 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 208.5, 157.9, 153.0, 135.7, 83.0, 75.9, 43.4, 27.7, 10.7.

IR: (v/ cm^{-1}) 2981, 2940, 1722, 1595, 1457, 1394, 1334, 1252, 1159, 1125, 1099, 1036, 950, 894, 853, 816, 749, 697.

HRMS: (ESI) calcd. for $C_{11}H_{16}O_4$ $[M+H]^+$: *m/z* 213.1121, found: *m/z* 213.1122.

(±)-*tert*-butyl (3-methyl-4-oxocyclopent-2-en-1-yl) carbonate ((±)-162)



The compound was prepared according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-2-methylcyclopent-2-en-1-one (±)-**163** (2.8 g, 25.0 mmol, 1.0 equiv.) to afford the product (±)-**162** in 81% yield (4.31 g, 20.3 mmol)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 5:1).

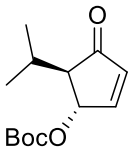
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.16 (dq, *J* = 3.0, 1.5 Hz, 1H), 5.58 – 5.50 (m, 1H), 2.78 (dd, *J* = 18.8, 6.3 Hz, 1H), 2.35 (dd, *J* = 18.8, 2.0 Hz, 1H), 1.76 (t, *J* = 1.6 Hz, 3H), 1.43 (s, 9H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =204.7, 152.9, 152.1, 145.8, 82.9, 72.7, 41.1, 27.7, 10.0.

IR: (v/ cm^{-1}) 2981, 2952, 2922, 2877, 1710, 1442, 1408, 1364, 1326, 1274, 1159, 991, 887, 790.

HRMS: (ESI) calcd. for $C_{11}H_{16}O_4$ $[M+H]^+$: *m/z* 213.1121, found: *m/z* 213.1120.

(±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83g)



The compound was prepared according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-5-isopropylcyclopent-2-en-1-one (±)-*anti*--**82g** (3.50 g, 25.0 mmol, 1.0 equiv.) to afford the product (±)-*anti*-**83g** in 75% yield (4.5 g, 18.7 mmol).

Physical state: white solid.

Melting point: 66 °C.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

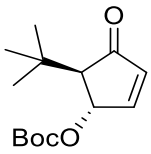
^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.53 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.26 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.59 (td, *J* = 2.4, 1.2 Hz, 1H), 2.39 (dd, *J* = 4.1, 2.5 Hz, 1H), 2.34 – 2.24 (m, 1H), 1.48 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =206.4, 157.8, 152.8, 136.9, 83.1, 76.7, 56.9, 27.7, 27.2, 20.1, 18.1.

IR: (v/ cm^{-1}) 2970, 2873, 1714, 1595, 1461, 1397, 1330, 1252, 1155, 950, 857, 793.

HRMS: (ESI) calcd. for $C_{13}H_{20}O_4$ $[M+H]^+$: *m/z* 241.1434, found: *m/z* 241.1437.

(±)-((4*S*,5*R*)-5-(*tert*-butyl)-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83h)



The compound was prepared according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-5-(*tert*-butyl)-cyclopent-2-en-1-one (±)-*anti*-**82h** (3.86 g, 25.0 mmol, 1.0 equiv.) to afford the product (±)-*anti*-**83h** in 69% yield (4.37 g, 17.2 mmol).

Physical state: white solid.

Melting point: 74 °C.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

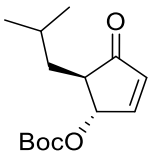
^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.50 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.22 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.62 (td, *J* = 2.5, 1.2 Hz, 1H), 2.26 (d, *J* = 2.7 Hz, 1H), 1.51 (s, 9H), 1.04 (s, 9H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =205.8, 156.7, 152.8, 137.2, 83.1, 77.8, 59.7, 32.7, 27.6.

IR: (v/ cm^{-1}) 2967, 2870, 1736, 1710, 1476, 1394, 1367, 1334, 1278, 1244, 1151, 1092, 1032, 965, 816.

HRMS: (ESI) calcd. for $C_{14}H_{22}O_4$ $[M+H]^+$: *m/z* 255.1591, found: *m/z* 255.1587.

(±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83i)



The compound was prepared according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-5-(iso-butyl)-cyclopent-2-en-1-one (±)-*anti*-**82i**/(±)-*syn*-**82i** in a ratio of 20:1 (3.86 g, 25.0 mmol, 1.0 equiv.) to afford the product (±)-*anti*-**83i** in 83% yield (5.28 g, 20.8 mmol). Isolation of the *syn* product (±)-*syn*-**83i** failed.

Physical state: pale yellow oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

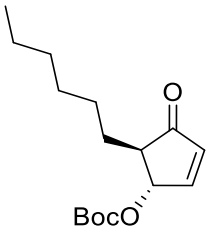
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.48 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.24 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.42 (td, *J* = 2.3, 1.2 Hz, 1H), 2.42 (ddd, *J* = 9.9, 5.1, 2.4 Hz, 1H), 1.81 (ddd, *J* = 12.6, 8.6, 6.3 Hz, 1H), 1.63 (ddd, *J* = 13.8, 8.6, 5.1 Hz, 1H), 1.49 (s, 9H), 1.33 (ddd, *J* = 13.8, 9.9, 5.8 Hz, 1H), 0.89 (d, *J* = 2.4 Hz, 3H), 0.88 (d, *J* = 2.4 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =206.9, 157.2, 152.8, 135.9, 83.0, 80.5, 49.9, 38.1, 27.7, 26.0, 23.0, 21.7.

IR: (v/ cm^{-1}) 2959, 2873, 1722, 1595, 1466, 1371 1330, 1252, 1155, 1099, 1036, 969, 868, 760, 670.

HRMS: (ESI) calcd. for $C_{14}H_{22}O_4$ $[M+H]^+$: *m/z* 255.1591, found: *m/z* 255.1589.

(±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83k)



The compound was prepared according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-5-hexyl-cyclopent-2-en-1-one (±)-*anti*-**82k**/(±)-*syn*-**82k** in a ratio of 10:1 (911.3 mg, 5.0 mmol, 1.0 equiv.) to afford the product (±)-*anti*-**83k** in 65% yield (916.0 g, 3.2 mmol). Isolation of the *syn* product (±)-*syn*-**83k** failed.

Physical state: pale yellow oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

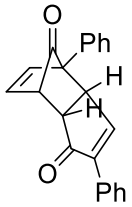
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.53 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.28 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.48 (td, *J* = 2.4, 1.2 Hz, 1H), 2.42 (ddd, *J* = 8.4, 5.0, 2.5 Hz, 1H), 1.83 (ddt, *J* = 14.9, 10.2, 5.0 Hz, 1H), 1.51 (s, 9H), 1.41 – 1.19 (m, 9H), 0.91 – 0.83 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =206.7, 157.4, 152.9, 136.3, 83.1, 79.9, 51.5, 31.6, 29.2, 28.5, 27.7, 26.6, 22.6, 14.0.

IR: (v/ cm^{-1}) 2929, 2858, 1811, 1722, 1595, 1461, 1371, 1330, 1252, 1155, 1103, 961, 857, 790, 723.

HRMS: (ESI) calcd. for $C_{16}H_{26}O_4$ $[M+Na]^+$: *m/z* 305.1723, found: *m/z* 305.1724.

(±)-(3a*R*,4*R*,7*S*,7a*S*)-2,4-diphenyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,8-dione (±)-124



The compound were obtained according to the general procedure for the activation of the alcohol *via* Boc protection with (±)-4-hydroxy-5-phenyl-cyclopent-2-en-1-one (±)-*anti*-**82l**/(±)-*syn*-**82l** in a ratio of 6:1 (1.74 g, 10.0 mmol, 1.0 equiv.) to afford the dimer-product (±)-**124** in 70% yield (2.2 g, 7.0 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.3 (hexanes/ EtOAc 5:1).

^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.71 – 7.64 (m, 2H), 7.61 (d, *J* = 2.9 Hz, 1H), 7.54 – 7.35 (m, 8H), 6.48 (dd, *J* = 6.8, 3.6 Hz, 1H), 6.39 (dd, *J* = 6.9, 1.2 Hz, 1H), 3.83 (dd, *J* = 6.2, 2.9 Hz, 1H), 3.74 (ddd, *J* = 4.9, 3.5, 1.3 Hz, 1H), 3.32 (dd, *J* = 6.1, 5.0 Hz, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =204.1, 199.1, 157.3, 154.7, 151.0, 145.3, 134.2, 133.4, 130.6, 129.2, 128.6, 128.6, 128.0, 127.8, 127.3, 127.1, 61.6, 51.8, 46.3, 44.9, 44.1, 43.6.

IR: (v/ cm^{-1}) 3063, 2959, 1681, 1591, 1490, 1304, 1267, 1129, 980, 931, 879, 775.

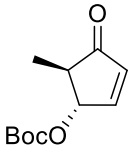
HRMS: (ESI calcd. for $C_{22}H_{16}O_4$ $[M+H]^+$: *m/z* 313.1223, found: *m/z* 313.1226.

5.6 Kinetic Resolution of Substituted Cyclopentenones

General Procedure for the Kinetic Resolution of Substituted Cyclopentenones

4,5-disubstituted cyclopent-2-en-1-one **83** (1.0 mmol, 1.0 equiv) and the nucleophile (0.5 mmol, 0.5 equiv) were dissolved in degassed (three freeze-pump-thaw cycles) $DCM_{abs.}$ (4 mL) at the specified temperature. Separately, a catalyst solution was prepared by stirring $Pd_2(dba)_3 \cdot CHCl_3$ (5.2 mg, 5.0 µmol, 1.0 mol% based on nucleophile) and (*R*,*R*)-Trost ligand **32** (12.8 mg, 18.5 µmol, 3.7 mol% based on nucleophile) in degassed $DCM_{abs.}$ (1 mL) until the initially purple solution turned yellow-brown (1-2 min). Then the catalyst solution was added to the reaction mixture and the resulting solution was stirred until the reaction was complete. The progress of the reaction was monitored by TLC. Upon completion the solvent was evaporated under reduced pressure and the reisolated starting material and the nucleophile product were purified by column chromatography (hexanes:EtOAc : 10:1 – 3:1).

((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83f)

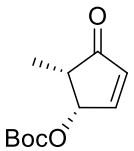


The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and acetic acid as nucleophile (28.6 µL, 0.5 mmol, 0.5 equiv.) to recover the recovered starting material (4*S*,5*R*)-*anti*-**83f** in 30% yield (63.7 mg, 0.30 mmol).

Chiral HPLC: 93% ee (t_R major, minor = 10.2, 8.0 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 99:1, 1.0 mL/min).

$[\alpha]_D^{25}$ = 67.6° (c = 1.0, CH_2Cl_2).

((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*S*)-s*yn*-83f)

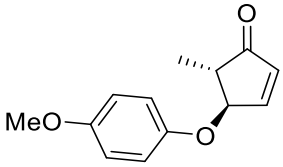


The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy)

cyclopent-2-en-1-one) (±)-*syn*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenol as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the recovered starting material (4*S*,5*S*)-*syn*-**83f** in 45% yield (95.5 mg, 0.45 mmol).

Chiral HPLC: >99% ee (t_R major, minor = 11.3, 14.6 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 99:1, 1.0 mL/min).
$[\alpha]_D^{25}$ = 45.7° (c = 1.0, CH_2Cl_2).

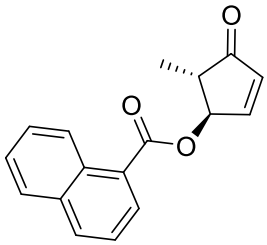
(4*R*,5*S*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128f)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenol as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to afford the product (4*R*,5*S*)-*anti*-**128f** in 49% yield (106.9 mg, 0.49 mmol).

Physical state: yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).
Chiral HPLC: 76% ee (t_R major, minor = 28.7, 17.9 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 65:35, 0.5 mL/min).
$[\alpha]_D^{25}$ = -68.1° (c = 1.0, CH_2Cl_2).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 5.9, 2.1 Hz, 1H), 6.94 – 6.83 (m, 4H), 6.30 (dd, *J* = 5.8, 1.2 Hz, 1H), 4.96 (m, 1H), 3.78 (s, 3H), 2.52 (qd, *J* = 7.5, 2.4 Hz, 1H), 1.27 (d, *J* = 7.5 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 206.3, 157.1, 153.8, 150.4, 134.1, 116.6, 113.8, 83.4, 54.7, 46.7, 12.5.
IR: (v/ cm^{-1}) 2967, 2937, 2036, 1781, 1714, 1591, 1505, 1457, 1353, 1323, 1289, 1211, 1107, 1077, 1032, 995, 902, 820, 767, 741.
HRMS: (ESI) calcd. for $C_{13}H_{14}O_3$ $[M+H]^+$: *m/z* 219.1016, found: *m/z* 219.1019.

(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130f)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and 1-naphthoic acid as nucleophile (86.1 mg, 0.5 mmol, 0.5 equiv.) to afford the product (4*R*,5*S*)-*anti*-**130f** in 37% yield (98.5 mg, 0.37 mmol).

Physical state: colorless oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

Chiral HPLC: 54% ee (t_R major, minor = 12.6, 14.3 min, Phenomenex Lux Cellulose-1 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 95:5, 1.0 mL/min).

$[\alpha]_D^{25}$ = -113.6° (c = 1.0, CH_2Cl_2).

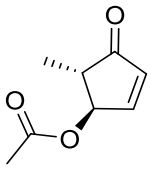
^{1}H NMR: (300 MHz $CDCl_3$): δ = δ 8.95 (m, 1H), 8.21 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.06 (m, 1H), 7.94 – 7.87 (m, 1H), 7.74 – 7.46 (m, 4H), 6.41 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.85 (m, 1H), 2.60 (qd, *J* = 7.6, 2.4 Hz, 1H), 1.42 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 207.2, 166.9, 157.7, 136.1, 134.1, 133.9, 131.4, 130.7, 128.7, 128.1, 126.4, 126.0, 125.6, 124.5, 79.9, 47.3, 13.6.

IR: (v/ cm^{-1}) 3050, 2970, 2937, 1710, 1595, 1509, 1457, 1375, 1326, 1274, 1237, 1192, 1129, 1073, 999, 961, 909, 868, 820.

HRMS: (ESI) calcd. for $C_{17}H_{14}O_3$ $[M+H]^+$: *m/z* 267.1016, found: *m/z* 267.1022.

(4*R*,5*S*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-131f)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and acetic acid as

nucleophile (28.6 µL, 0.5 mmol, 0.5 equiv.) to afford the cyclopentenone (4*R*,5*S*)-*anti*-**131f** in 37% yield (57.0 mg, 0.37 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

Chiral HPLC: 66% ee (t_R major, minor = 29.7, 26.9 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 99:1, 1.0 mL/min).

$[\alpha]_D^{25}$ = -9.0° (c = 1.0, CH_2Cl_2).

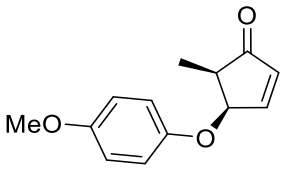
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.47 (m, 1H), 6.29 (m, 1H), 5.47 (m, 1H), 2.34 (m, 1H), 2.09 (s, 3H), 1.26 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 207.1, 170.6, 157.5, 135.8, 79.3, 47.0, 20.9, 13.4.

IR: (v/ cm^{-1}) 2974, 2937, 2837, 1714, 1590, 1457, 1371, 1334, 1223, 1170, 1077, 1021, 980, 910, 820, 678.

HRMS: (ESI) calcd. for $C_8H_{10}O_3$ $[M+H]^+$: *m/z* 155.0700, found: *m/z* 155.0703.

(4*R*,5*R*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*R*)-*syn*-128f)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*syn*-**83f** (212.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenol as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to afford the product (4*R*,5*R*)-*syn*-**128f** in 48% yield (104.8 mg, 0.48 mmol).

Physical state: yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

Chiral HPLC: 96% ee (t_R major, minor = 26.9, 17.7 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 70:30, 0.5 mL/min).

$[\alpha]_D^{25}$ = -19.8° (c = 1.0, CH_2Cl_2).

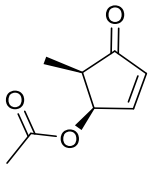
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.91 – 6.83 (m, 4H), 6.31 (dd, *J* = 5.8, 1.5 Hz, 1H), 5.33 (dt, *J* = 6.1, 1.9 Hz, 2H), 3.78 (s, 3H), 2.79 (m, 1H), 1.16 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = δ 209.3, 159.5, 154.4, 152.1, 134.5, 116.1, 114.9, 77.9, 55.7, 44.6, 11.5.

IR: (v/ cm^{-1}) 2982, 2937, 2837, 1714, 1591, 1505, 1453, 1375, 1289, 1215, 1088, 1032, 976, 872, 827, 752.

HRMS: (ESI) calcd. for $C_{13}H_{14}O_3$ $[M+H]^+$: *m/z* 219.1016, found: *m/z* 219.1016.

(4*R*,5*R*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((4*R*,5*R*)-*syn*-131f)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*syn*-**83f** (212.25 mg, 1.0 mmol, 1.0 equiv.) and acetic acid as nucleophile (28.6 µL, 0.5 mmol, 0.5 equiv.) to afford the product (4*R*,5*R*)-*syn*-**131f** in 39% yield (60.1 mg, 0.39 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

Chiral HPLC: 97% ee (t_R major, minor = 31.4, 19.4 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 70:30, 0.5 mL/min).

$[\alpha]_D^{25}$ = -27.8° (c = 1.0, CH_2Cl_2).

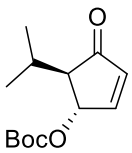
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.32 (dd, *J* = 5.8, 1.4 Hz, 1H), 5.91 (m, 1H), 2.66 (m, 1H), 2.11 (s, 3H), 1.08 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$: δ = 208.7, 170.4, 135.6, 73.5, 43.1, 20.7, 10.8.

IR: (v/ cm^{-1}) 2974, 2937, 2881, 1714, 1590, 1457, 1371, 1226, 1170, 1077, 1021, 980, 910, 820, 775.

HRMS: (ESI) calcd. for $C_8H_{10}O_3$ $[M+H]^+$: *m/z* 155.0703, found: *m/z* 155.0703.

((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83g)

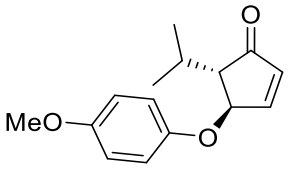


The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (240.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole

as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the starting material (4*S*,5*R*)-*anti*-**83g** in 47% yield (104.4 mg, 0.47 mmol).

Chiral HPLC: 97 % ee (t_R major, minor = 7.2 min, 5.1 min, Chiralpak AS-H 4.6 x 250 mm 10 µm, n-Heptan:^{i}PrOH 95:5, 1.0 mL/min).
$[\alpha]_D^{25}$ = 60.3° (c = 1.0, CH_2Cl_2).

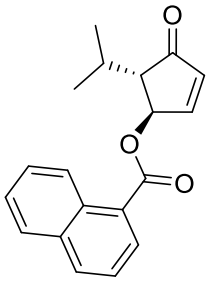
(4R,5S)-5-isopropyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128g)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (240.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the nucleophile product (4*R*,5S)-*anti*-**128g** in 49% yield (120.0 mg, 0.49 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).
Chiral HPLC: 91 % ee (t_R major, minor = 16.0 min, 12.4 min, Chiralpak AS-H 4.6 x 250 mm 10 µm, n-Heptan:^{i}PrOH 95:5, 1.0 mL/min).
$[\alpha]_D^{25}$ = 79.4° (c = 1.0, CH_2Cl_2).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.66 (dd, *J* = 5.9, 2.1 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.90 – 6.83 (m, 2H), 6.28 (dd, *J* = 5.8, 1.1 Hz, 1H), 5.12 (td, *J* = 2.4, 1.1 Hz, 1H), 3.78 (s, 3H), 2.53 (dd, *J* = 4.3, 2.5 Hz, 1H), 2.32 (pd, *J* = 6.9, 4.3 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 207.0, 158.3, 154.9, 151.4, 136.4, 117.9, 114.9, 79.8, 58.1, 55.7, 27.3, 20.6, 18.5.
IR: (v/ cm^{-1}) 2960, 2904, 2878, 2837, 1707, 1592, 1506, 1465, 1364, 1297, 1211, 1088, 1036, 977, 891, 828, 779, 746, 671.
HRMS: (ESI) calcd. for $C_{15}H_{18}O_3$ $[M+H]^+$: *m/z* 246.1250, found: *m/z* 246.1248.

(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isopropylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130g)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (240.3 mg, 1.0 mmol, 1.0 equiv.) and 1-naphthoic acid as nucleophile (86.1 mg, 0.5 mmol, 0.5 equiv.) to recover the nucleophile product (4*R*,5*S*)-*anti*-**130g** in 41% yield (122.0 mg, 0.41 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

Chiral HPLC: 95 % ee (t_R major, minor = 11.4 min, 14.4 min Phenomenex Lux Cellulose-1 4.6 x 250 mm 5 µL, n-Heptan:^{i}PrOH 98:2, 1.0 mL/min).

$[\alpha]_D^{25}$ = 63.2° (c = 1.0, CH_2Cl_2).

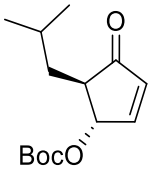
^{1}H NMR: (400 MHz, $CDCl_3$) δ =8.93 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.19 (td, *J* = 7.8, 7.3, 1.3 Hz, 1H), 8.06 (dd, *J* = 8.2, 3.4 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.73 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.65 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.59 – 7.48 (m, 2H), 6.38 (dd, *J* = 5.8, 1.2 Hz, 1H), 6.15 (td, *J* = 2.5, 1.1 Hz, 1H), 2.62 (dd, *J* = 4.3, 2.5 Hz, 1H), 2.43 (pd, *J* = 6.9, 4.2 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =206.7, 166.8, 158.3, 145.0, 137.1, 134.0, 133.9, 131.4, 130.6, 128.7, 128.1, 126.4, 125.5, 124.5, 74.8, 57.2, 27.4, 20.5, 18.2.

IR: (v/ cm^{-1}) 2959, 2873, 1707, 1595, 1509, 1461, 1371, 1237, 1192, 1129, 946, 887, 779, 700.

HRMS: (ESI) calcd. for $C_{15}H_{18}O_3$ $[M+H]^+$: *m/z* 295.1329, found: *m/z* 295.1332.

((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83i)

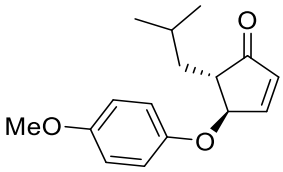


The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy)

cyclopent-2-en-1-one) (±)-*anti*-**83i** (254.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the starting material (4*S*,5*R*)-*anti*-**83i** in 47% yield (119.5 mg, 0.47 mmol).

Chiral HPLC: 88 % ee (t_R major, minor = 7.8 min, 6.0 min, Chiralpak AS-H 4.6 x 250 mm 10 µm,, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).
$[\alpha]_D^{25}$ = 46.5° (c = 1.0, CH_2Cl_2).

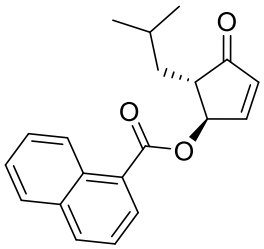
(4*R*,5*S*)-5-isobutyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128i)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83i** (254.3 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the nucleophile product (4*R*,5*S*)-*anti*-**83i** in 48% yield (124.8 mg, 0.48 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).
Chiral HPLC: 70 % ee (t_R major, minor = 19.3 min, 16.3 min, Phenomenex Lux Cellulose-2 4.6 x 250 mm 5 µL, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).
$[\alpha]_D^{25}$ = 95.6° (c = 1.0, CH_2Cl_2).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.64 (dd, *J* = 5.8, 2.0 Hz, 1H), 7.00 – 6.79 (m, 4H), 6.30 (dd, *J* = 5.9, 1.0 Hz, 1H), 5.01 (td, *J* = 2.3, 1.1 Hz, 1H), 3.79 (s, 3H), 2.62 (ddd, *J* = 10.2, 4.6, 2.4 Hz, 1H), 1.85 – 1.67 (m, 2H), 1.35 (ddd, *J* = 13.2, 10.3, 4.8 Hz, 1H), 0.93 (t, *J* = 6.3 Hz, 6H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ =207.6, 157.9, 154.9, 151.5, 135.6, 117.6, 115.0, 83.8, 55.9, 51.1, 38.5, 26.5, 23.4, 21.8.
IR: (v/ cm^{-1}) 3015, 2955, 2870, 2836, 1714, 1591, 1505, 1464, 1356, 1312, 1211, 1095, 954, 857, 827, 745.
HRMS: (EI) calcd. for $C_{16}H_{20}O_3$ $[M]^+$: *m/z* 260.1407, found: *m/z* 260.1404.

(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isobutylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130i)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83i** (254.3 mg, 1.0 mmol, 1.0 equiv.) and 1-naphthoic acid as nucleophile (86.1 mg, 0.5 mmol, 0.5 equiv.) to recover the nucleophile product (4*R*,5*S*)-*anti*-**130i** in 40% yield (123.3 mg, 0.40 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).

Chiral HPLC: 59 % ee (t_R major, minor = 15.0 min, 18.4 min, Phenomenex Lux Cellulose-1 4.6 x 250 mm 5 µL, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).

$[\alpha]_D^{25}$ = 56.1° (c = 1.0, CH_2Cl_2).

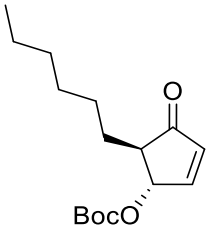
^{1}H NMR: (400 MHz, $CDCl_3$) δ =8.94 (dt, *J* = 8.7, 1.0 Hz, 1H), 8.19 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.99 – 7.85 (m, 1H), 7.71 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.68 – 7.48 (m, 3H), 6.39 (dd, *J* = 5.8, 1.2 Hz, 1H), 5.99 (td, *J* = 2.3, 1.2 Hz, 1H), 2.71 (ddd, *J* = 10.3, 4.8, 2.4 Hz, 1H), 1.93 (dddd, *J* = 13.0, 11.8, 9.1, 6.4 Hz, 1H), 1.79 (ddd, *J* = 13.9, 9.0, 4.8 Hz, 1H), 1.50 (ddd, *J* = 13.8, 10.4, 5.4 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =207.2, 166.8, 157.8, 136.2, 134.1, 133.9, 131.5, 130.6, 128.7, 128.1, 126.4, 126.1, 125.6, 124.5, 78.8, 50.0, 38.3, 26.2, 23.3, 21.7.

IR: (v/ cm^{-1}) 3056, 2955, 2870, 1710, 1595, 1509, 1464, 1386, 1326, 1274, 1237, 1192, 1129, 984, 898, 872, 779.

HRMS: (ESI) calcd. for $C_{20}H_{20}O_3$ $[M+H]^+$: *m/z* 309.1485, found: *m/z* 309.1492.

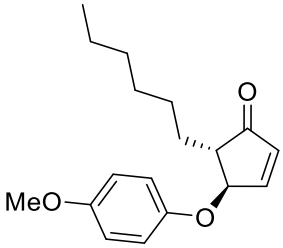
((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83k)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with (±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83k** (282.4 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the starting material (4*S*,5*R*)-*anti*-**83k** in 44% yield (124.0 mg, 0.44 mmol).

Chiral HPLC: 69 % ee (t_R major, minor = 9.4 min, 7.1 min, Chiralpak AS-H 4.6 x 250 mm 10 µm,, n-Heptan:^{i}PrOH 70:30, 0.5 mL/min).
$[\alpha]_D^{25}$ = 70.1° (c = 1.0, CH_2Cl_2).

(4*R*,5*S*)-5-hexyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128k)



The compound was prepared according to the general procedure for kinetic resolution of substituted cyclopentenones with with (±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83k** (282.4 mg, 1.0 mmol, 1.0 equiv.) and 4-methoxyphenole as nucleophile (62.1 mg, 0.5 mmol, 0.5 equiv.) to recover the nucleophile product (4*R*,5*S*)-*anti*-**128k** in 45% yield (129.8 mg, 0.45 mmol).

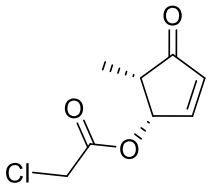
Physical state: pale yellow oil.
TLC: R_f = 0.5 (hexanes/ EtOAc 3:1).
Chiral HPLC: 82 % ee (t_R major, minor = 29.6 min, 20.8 min, Chiralpak AS-H 4.6 x 250 mm 10 µm, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).
$[\alpha]_D^{25}$ = 36.8° (c = 1.0, CH_2Cl_2).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.64 (dd, *J* = 5.9, 2.1 Hz, 1H), 6.97 – 6.80 (m, 4H), 6.30 (dd, *J* = 5.8, 1.1 Hz, 1H), 5.05 (td, *J* = 2.3, 1.1 Hz, 1H), 3.79 (s, 3H), 2.54 (ddd, *J* = 8.6, 4.9, 2.4 Hz, 1H), 1.92 – 1.76 (m, 1H), 1.43 – 1.17 (m, 9H), 0.92 – 0.80 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 207.3, 158.0, 154.9, 151.4, 135.7, 117.8, 114.9, 83.0, 55.7, 52.5, 31.6, 29.2, 28.8, 26.9, 22.6, 14.0.
IR: (v/ cm^{-1}) 2929, 2855, 1714, 1505, 1461, 1358, 1289, 1215, 1095, 1036, 1006, 827, 745.
HRMS: (EI) calcd. for $C_{18}H_{24}O_3$ $[M]^+$: *m/z* 288.1720, found: *m/z* 288.1716.

5.7 Mitsunobu Inversion

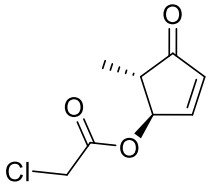
General Procedure for the Mitsunobu Inversion

the specified acid (7.5 mmol, 1.5 equiv.) and triphenylphosphane (1573.5 mg, 6.0 mmol, 1.2 equiv) were dissolved. DIAD (1.58 mL, 8.0 mmol, 1.6 equiv.) was added slowly over a periode of 10 min. The progress of the reaction was monitored by TLC. Afterwards the solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography using an appropriate hexanes:EtOAc mixture.

(±)-(4*S*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-185)



(±)-(4*R*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-185)



To a solution of cyclopent-2-enones (±)-*anti*-**82f**/(±)-*syn*-**82f** in a ratio of 8:1 (560.5 mg, 5.0 mmol, 1.0 equiv.) in $DCM_{abs.}$ (10 mL) 2-chloroacetic acid (0.45 mL, 7.5 mmol, 1.5 equiv.) and triphenylphosphane (1573.5 mg, 6.0 mmol, 1.2 equiv) were dissolved. DIAD (1.58 mL, 8.0 mmol, 1.6 equiv.) was added slowly over a periode of 10 min and stirred for 15 min. Afterwards the solvent was evaporated under reduced pressure and the reaction mixture was purified by column chromatography (hexanes/ EtOAc 10:1 → 5:1). The major product (±)-*syn*-**185** was obtained in 84% yield (492.1 mg, 4.20 mmol) and the minor diastereomer (±)-*anti*-**185** in 9% yield (84.5 mg, 0.45 mmol) (overall yield: 94%).

(±)-(4*S*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-**185**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.32 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.95 (m, 1H), 4.07 (s, 2H), 2.66 (m, 1H), 1.06 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 207.9, 166.9, 157.0, 136.3, 75.2, 42.9, 40.5, 10.7.

IR: (v/ cm^{-1}) 2981, 1759, 1714, 1595, 1457, 1412, 1379, 1334, 1282, 1162, 1080, 961, 924, 875, 820, 782, 734, 693.

HRMS: (ESI) calcd. for $C_8H_9ClO_3$ $[M+H]^+$: *m/z* 189.0313, found: *m/z* 189.0310.

(±)-(4*R*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-**185**)

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.36 (dd, *J* = 5.8, 1.3 Hz, 1H), 5.57 m, 1H), 4.11 (s, 2H), 2.45 – 2.38 (m, 1H), 1.30 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 206.3, 167.1, 156.3, 136.5, 81.0, 46.8, 40.7, 13.4.

IR: (v/ cm^{-1}) 2937, 2874, 1759, 1714, 1595, 1457, 1408, 1379, 1330, 1259, 1162, 1073, 984, 924, 898, 827, 793, 693.

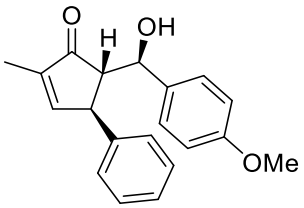
HRMS: (ESI) calcd. for $C_8H_9ClO_3$ $[M+H]^+$: *m/z* 189.0313, found: *m/z* 189.0309.

5.8 One-Pot Aldol Reaction

General Procedure for the "One-Pot Aldol Reaction"

CuCN (102.0 mg, 1.14 mmol, 3.0 equiv.) and anhydrous LiCl (96.6 mg, 2.28 mmol, 6.0 equiv.) were dissolved in THF (4 mL) at 25 °C. The clear solution was cooled to -40 °C followed by dropwise addition of the specified Grignard reagent (1.14 mmol, 3.0 equiv.). The reaction mixture was cooled to –78 °C whereupon a solution of cyclopentenone (0.38 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 4 min followed by addition of the specified aldehyde (0.63 mmol, 1.68 equiv.). The progress of the reaction was monitored by TLC. Upon complete consumption of the starting material (ca. 5 min), the reaction was quenched with NH_4Cl (aq., 5 mL). The reaction mixture was allowed to warm to 25 °C before it was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the reaction mixture was purified by column chromatography using an appropriate hexanes:EtOAc mixture.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fa)



The compound was prepared from (a) 5-methylcyclopent-2-enone (±)-*anti*-**83f**/ (b) 4-methoxyphenol-5-methylcyclopent-2-enone (±)-*anti*-**128f**, phenylmagnesium bromide (0.62 M solution in THF, 1.8 mL, 1.14 mmol, 3.0 equiv.) and 4-methoxybenzaldehyde (77.6 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84fa** was obtained in (a) 77%/ (b) 75% yield (89.7 mg, 0.29 mmol, 86.3 mg, 0.29 mmol).

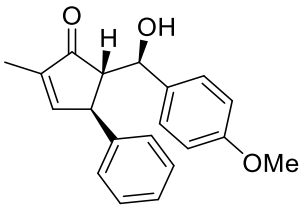
Physical state: white solid.

Melting point: 128 °C.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.23 (m, 1H), 7.20 – 7.15 (m, 2H), 7.15 – 7.05 (m, 3H), 6.83 – 6.76 (m, 2H), 6.54 – 6.47 (m, 2H), 4.70 (d, *J* = 9.5 Hz, 1H), 4.54 (bs, 1H), 3.80 (s, 3H), 3.51 (m, 1H), 2.65 (dd, *J* = 9.6, 2.5 Hz, 1H), 1.90 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 212.8, 161.2, 159.7, 140.9, 133.3, 128.6, 128.4, 127.1, 126.8, 113.8, 75.2, 61.2, 55.4, 48.0, 10.0.
IR: (v/ cm^{-1}) 3403, 3063, 3008, 2959, 2922, 2836, 1673, 1636, 1610, 1513, 1435, 1330, 1244, 1170, 1084, 1032, 916, 864, 834, 812, 760, 697.
HRMS: (ESI) calcd. for $C_{20}H_{20}O_3$ [[M+H]$^+$ - [H_2O]]: *m/z* 307.1329, found: *m/z* 307.1326.

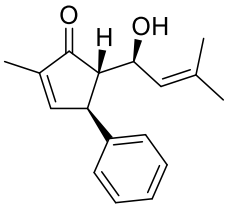
(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((+)-84fa)



The compound was prepared from 5-methylcyclopent-2-enone (4*S*,5*S*)-*syn*-**83f** (>99% *ee*) (80.6 mg, 0.38 mmol), phenylmagnesium bromide (0.62 M solution in THF, 1.8 mL, 1.14 mmol, 3.0 equiv.) and 4-methoxybenzaldehyde (77.6 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product **84fa** was obtained in 77% yield (90.2 mg, 0.29 mmol).

Chiral HPLC: >99% ee (t_R major, minor = 31.5, 27.0 min, Phenomenex Lux Cellulose-1 4.6 x 250 mm 5 µm, heptane:^{i}PrOH 90:10, 0.5 mL/min).
$[\alpha]_D^{25}$ = 231.0° (c = 1.0, CH_2Cl_2).

(±)-(4*R*,5*S*)-5-((*S*)-1-hydroxy-3-methylbut-2-en-1-yl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fb)

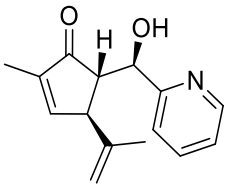


The compound was prepared from 5-methylcyclopent-2-enone (±)-*anti*-**83f** (80.6 mg, 0.38 mmol), phenylmagnesium bromide (0.55 M solution in THF, 2.1 mL, 1.14 mmol, 3.0 equiv.) and 3-methylbut-2-enal (61.5 µL, 0.63 mmol, 1.68 equiv.) according to the general

procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84fb** was isolated in 62% yield (60.4 mg, 0.24 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.34 – 7.28 (m, 2H), 7.26 – 7.22 (m, 2H), 7.06 (m, 1H), 7.04 (m, 1H), 5.11 (m, 1H), 4.56 (t, *J* = 9.1 Hz, 1H), 3.93 (bs, 1H), 3.59 (m, 1H), 2.46 (dd, *J* = 8.9, 2.6 Hz, 1H), 1.88 (dd, *J* = 2.2, 1.4 Hz, 3H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.4 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 212.6, 160.9, 141.5, 141.0, 136.7, 128.8, 127.5, 127.1, 125.5, 69.4, 60.0, 48.3, 25.7, 18.6, 10.0.
IR: (v/ cm^{-1}) 3422, 3063, 3030, 2967, 2914, 1673, 1628, 1599, 1494, 1449, 1420, 1375, 1334, 1293, 1207, 1118, 1073, 1028, 913, 842, 760, 697.
HRMS: (ESI) calcd. for $C_{11}H_{20}O_2$ $[M+H]^+$: *m/z* 257.1536, found: *m/z* 257.1540.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2-methyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84fc)

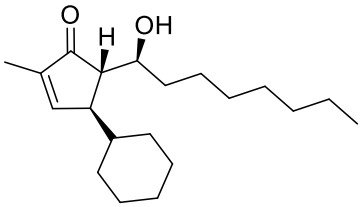


The compound was prepared from 5-methylcyclopent-2-enone (±)-*anti*-**83f** (80.6 mg, 0.38 mmol, 1.0 equiv.), *iso*-propenylmagnesium bromide (0.76 M solution in THF, 1.5 mL, 1.14 mmol, 3.0 equiv.) and picolinaldehyde (60.7 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84fc** was obtained in 64% yield (59.1 mg, 0.24 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.53 (m, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30 (m, 1H), 7.20 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.09 (m, 1H), 5.01 (d, *J* = 6.6 Hz, 1H), 4.65 (m, 1H), 4.51 (m, 1H), 3.37 (m, 1H), 2.71 (dd, *J* = 6.5, 2.4 Hz, 1H), 1.75 (dd, *J* = 2.1, 1.4 Hz, 3H), 1.53 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 210.3, 161.0, 159.4, 148.0, 144.7, 141.2, 136.7, 122.9, 121.3, 112.4, 73.8, 57.0, 48.4, 20.1, 10.0.
IR: (v/ cm^{-1}) 3075, 2974, 2918, 1695, 1591, 1472, 1438, 1379, 1338, 1308, 1222, 1148, 1103, 1047, 995, 894, 834, 775, 749, 701.

HRMS: (ESI) calcd. for $C_{15}H_{17}NO_2$ $[M+H]^+$: *m/z* 244.1330, found: *m/z* 244.1333.

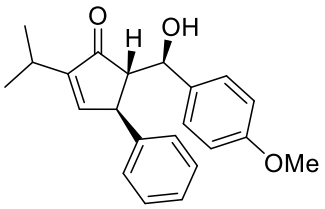
(±)-(4*S*,5*S*)-4-cyclohexyl-5-((*S*)-1-hydroxyoctyl)-2-methylcyclopent-2-en-1-one ((±)-84fd)



The compound was prepared from 5-methylcyclopent-2-enone (±)-*anti*-**83f** (80.6 mg, 0.38 mmol), cyclohexylmagnesium bromide (0.55 M solution in THF, 2.1 mL, 1.14 mmol, 3.0 equiv.) and octanal (99.7 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 10:1 → 5:1) product (±)-**84fd** was obtained in 43% yield (50.2 mg, 0.16 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.31 (m, 1H), 3.59 (m, 1H), 2.42 (m, 1H), 2.16 (dd, *J* = 8.0, 2.1 Hz, 1H), 1.85 – 0.79 (m, 29H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 212.4, 161.1, 140.9, 72.8, 53.8, 48.5, 41.1, 35.7, 31.8, 31.7, 29.6, 29.3, 26.6, 26.4, 26.3, 25.7, 22.6, 14.1, 10.0.
IR: (v/ cm^{-1}) 2974, 2937, 2881, 1714, 1505, 1457, 1371, 1223, 1170, 1077, 1021, 980, 909, 820, 775.
HRMS: (ESI) calcd. for $C_{20}H_{34}O_2$ $[M+H]^+$: *m/z* 307.2632, found: *m/z* 307.2636.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-isopropyl-4-phenylcyclopent-2-en-1-one ((±)-84ga)



The compound was prepared from (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (91.3 mg, 0.38 mmol, 1.0 equiv), phenylmagnesium bromide (0.76 M solution in THF, 1.50 mL, 1.14 mmol, 3.0 equiv.) and 4-methoxybenzaldehyde (77.6 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure

of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) the product (±)-*anti*-**84ga** was obtained in 74% yield (94.6 mg, 0.28 mmol).

Physical state: white solid.

Melting point: 109 °C.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

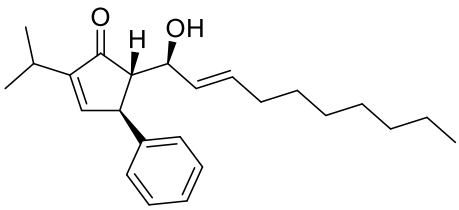
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.21 – 7.15 (m, 3H), 7.10 (qd, *J* = 4.8, 1.5 Hz, 3H), 6.84 – 6.73 (m, 2H), 6.57 – 6.45 (m, 2H), 4.71 (d, *J* = 9.5 Hz, 1H), 4.56 (d, *J* = 1.0 Hz, 1H), 3.79 (s, 3H), 3.50 (q, *J* = 2.3 Hz, 1H), 2.74 (dddd, *J* = 13.8, 6.9, 5.5, 1.4 Hz, 1H), 2.66 (dd, *J* = 9.5, 2.6 Hz, 1H), 1.18 (dd, *J* = 12.2, 6.9 Hz, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =212.2, 159.7, 158.5, 151.3, 141.1, 133.3, 128.6, 128.5, 127.1, 126.8, 113.8, 75.2, 61.9, 55.4, 47.6, 24.7, 21.5, 21.1.

IR: (v/ cm^{-1}) 3451, 2937, 2963, 2877, 1669, 1613, 1513, 1453, 1408, 1330, 1252, 1207, 1170, 1036, 924, 883, 831, 700.

HRMS: (ESI) calcd. for $C_{22}H_{24}O_3$ $[M+H]^+$: *m/z* 337.1798, found: *m/z* 337.1789.

(±)-(4*S*,5*S*)-5-((*S*,*E*)-1-hydroxydec-2-en-1-yl)-2-isopropyl-4-phenylcyclopent-2-en-1-one ((±)-84gb)



The compound was prepared from (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (91.3 mg, 0.38 mmol, 1.0 equiv), phenylmagnesium bromide (0.76 M solution in THF, 1.50 mL, 1.14 mmol, 3.0 equiv.) and decen-2-enal (115.5 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84gb** was isolated in 70% yield (94.7 mg, 0.27 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.33 – 7.24 (m, 3H), 7.19 (dd, *J* = 2.7, 1.2 Hz, 1H), 7.13 – 7.04 (m, 2H), 5.86 – 5.72 (m, 1H), 5.36 (ddt, *J* = 15.3, 7.9, 1.6 Hz, 1H), 4.25 (t, *J* = 8.2 Hz, 1H), 3.89 (s, 1H), 3.70 (q, *J* = 2.4 Hz, 1H), 2.78 – 2.64 (m, 1H), 2.50 (dd, *J* = 8.6, 2.6 Hz, 1H), 2.10 –

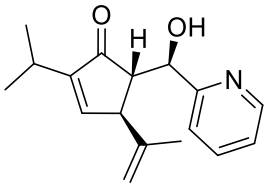
1.95 (m, 2H), 1.31 (dd, *J* = 11.0, 2.2 Hz, 10H), 1.15 (dd, *J* = 9.9, 6.9 Hz, 6H), 0.90 – 0.87 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =211.6, 158.3, 151.3, 141.5, 136.9, 134.7, 129.8, 128.8, 127.7, 127.1, 74.4, 60.3, 47.8, 32.1, 31.8, 29.3, 29.2, 28.9, 27.8, 24.7, 22.7, 21.4, 21.1, 14.1.

IR: (v/ cm^{-1}) 3466, 3030, 2969, 2926, 2855, 1740, 1688, 1625, 1494, 1457, 1371, 1330, 1274, 1162, 1099, 905, 861, 805, 760, 700.

HRMS: (ESI) calcd. for $C_{24}H_{34}O_2$ $[M+Na]^+$: *m/z* 377.2451, found: *m/z* 377.2456.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2-isopropyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84gc)



The compound was prepared from (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (91.3 mg, 0.38 mmol, 1.0 equiv), isopropenylmagnesium bromide (0.50 M solution in THF, 2.28 mL, 1.14 mmol, 3.0 equiv.) and picolinaldehyde (60.7 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84gc** was obtained in 57% yield (59.1 mg, 0.22 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

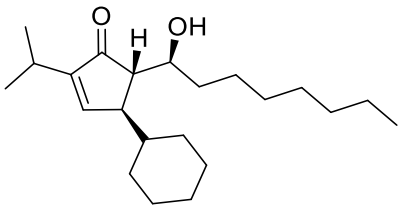
^{1}H NMR: (400 MHz, $CDCl_3$) δ =8.54 (ddd, *J* = 5.0, 1.7, 0.9 Hz, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.21 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.02 (dd, *J* = 2.7, 1.2 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 4.66 (p, *J* = 1.5 Hz, 1H), 4.55 – 4.47 (m, 1H), 3.37 (q, *J* = 2.3 Hz, 1H), 2.72 (dd, *J* = 6.6, 2.4 Hz, 1H), 2.67 – 2.54 (m, 1H), 1.53 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =209.7, 159.3, 158.4, 151.8, 147.8, 144.9, 136.8, 122.9, 121.5, 112.3, 73.8, 57.7, 47.9, 24.6, 21.3, 21.1, 20.1.

IR: (v/ cm^{-1}) 3451, 3078, 2963, 2873, 1736, 1699, 1591, 1468, 1438, 1408, 1371, 1263, 1222, 1155, 1066, 998, 954, 894, 782, 752, 685.

HRMS: (ESI) calcd. for $C_{17}H_{21}NO_2$ $[M+H]^+$: *m/z* 272.1645, found: *m/z* 272.1650.

(±)-(4*S*,5*S*)-4-cyclohexyl-5-((*S*)-1-hydroxyoctyl)-2-isopropylcyclopent-2-en-1-one ((±)-84gd)



The compound was prepared from (±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83g** (91.3 mg, 0.38 mmol, 1.0 equiv), cyclohexylmagnesium bromide (0.60 M solution in THF, 1.90 mL, 1.14 mmol, 3.0 equiv.) and octanal (99.7 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 10:1 → 5:1) product (±)-**84gd** was obtained in 56% yield (70.9 mg, 0.21 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

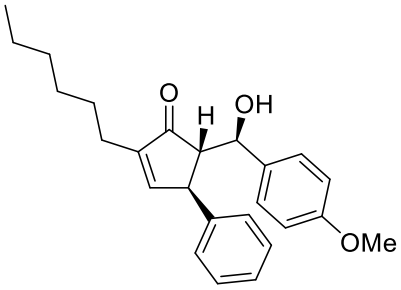
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.23 (dd, *J* = 2.7, 1.2 Hz, 1H), 3.58 (td, *J* = 7.9, 3.6 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.41 (dq, *J* = 4.7, 2.2 Hz, 1H), 2.16 (dd, *J* = 8.1, 2.1 Hz, 1H), 1.83 – 1.47 (m, 12H), 1.36 – 1.23 (m, 11H), 1.09 (d, *J* = 1.0 Hz, 3H), 1.07 (d, *J* = 1.0 Hz, 3H), 0.89 – 0.86 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =211.9, 158.1, 151.5, 72.8, 54.5, 48.1, 41.2, 35.7, 31.8, 31.6, 29.6, 29.5, 29.3, 27.8, 26.6, 26.4, 25.7, 24.6, 22.7, 21.5, 21.1, 14.1.

IR: (v/ cm^{-1}) 3743, 2922, 2855, 1736, 1684, 1625, 1449, 1371, 1330, 1274, 1162, 1099, 1010, 954, 916, 816, 734.

HRMS: (*m*/*z*) calcd. for $C_{22}H_{38}O_2$ $[M+H]^+$: *m/z* 335.2945, found: *m/z* 335.2949.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-hexyl-4-phenylcyclopent-2-en-1-one ((±)-84ka)

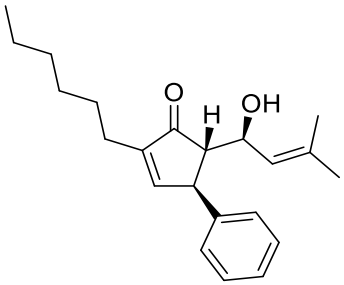


The compound was prepared from (±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83k** (107.3 mg, 0.38 mmol, 1.0 equiv), phenylmagnesium

bromide (0.80 M solution in THF, 1.42 mL, 1.14 mmol, 3.0 equiv.) and 4-methoxybenzaldehyde (77.6 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) the product (±)-**84ka** was obtained in 68% yield (97.8 mg, 0.26 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.22 – 7.16 (m, 3H), 7.14 – 7.05 (m, 3H), 6.87 – 6.75 (m, 2H), 6.51 (dq, *J* = 7.7, 2.4, 1.7 Hz, 2H), 4.70 (d, *J* = 9.5 Hz, 1H), 4.54 (d, *J* = 0.9 Hz, 1H), 3.80 (s, 3H), 3.51 (p, *J* = 2.3 Hz, 1H), 2.66 (dd, *J* = 9.5, 2.6 Hz, 1H), 2.35 – 2.20 (m, 2H), 1.55 – 1.49 (m, 2H), 1.40 – 1.26 (m, 6H), 0.95 – 0.82 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 212.7, 160.4, 159.7, 145.4, 141.0, 133.3, 128.6, 128.4, 127.1, 126.8, 113.8, 75.2, 61.5, 55.4, 48.0, 31.6, 29.0, 27.6, 24.6, 22.6, 14.1
IR: (v/ cm^{-1}) 3463, 2930, 2855, 1685, 1614, 1513, 1454, 1305, 1245, 1174, 1111, 1033, 910, 831, 760, 701.
HRMS: (ESI) calcd. for $C_{25}H_{30}O_3$ $[M+H]^+$: *m/z* 379.2268, found: *m/z* 379.2277.

(±)-(4*R*,5*S*)-5-((*S*)-1-hydroxy-3-methylbut-2-en-1-yl)-2-hexyl-4-phenylcyclopent-2-en-1-one ((±)-84kb)



The compound was prepared from (±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83k** (107.3 mg, 0.38 mmol, 1.0 equiv), phenylmagnesium bromide (0.85 M solution in THF, 1.34 mL, 1.14 mmol, 3.0 equiv.) and 3-methylbut-2-enal (61.5 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84kb** was isolated in 66% yield (81.8 mg, 0.25 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

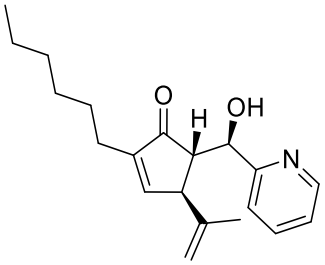
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.28 – 7.20 (m, 3H), 7.17 (dt, *J* = 2.7, 1.3 Hz, 1H), 7.03 – 6.98 (m, 2H), 5.06 (dp, *J* = 9.2, 1.5 Hz, 1H), 4.52 (td, *J* = 9.1, 1.1 Hz, 1H), 3.88 (d, *J* = 1.2 Hz, 1H), 3.55 (p, *J* = 2.3 Hz, 1H), 2.42 (dd, *J* = 8.8, 2.6 Hz, 1H), 2.21 (dddt, *J* = 9.1, 7.0, 4.8, 1.7 Hz, 2H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 4H), 1.53 – 1.46 (m, 2H), 1.31 – 1.24 (m, 6H), 0.87 – 0.83 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =212.5, 160.2, 145.7, 141.8, 136.8, 128.9, 127.7, 127.2, 125.5, 69.5, 60.5, 48.4, 31.7, 29.2, 27.8, 25.9, 24.7, 22.7, 18.8, 14.2

IR: (v/ cm^{-1}) 3466, 3030, 2926, 2859, 1689, 1633, 1495, 1454, 1379, 1338, 1275, 1111, 1029, 910, 842, 760, 731, 701.

HRMS: (ESI) calcd. for $C_{22}H_{30}O_2$ $[M+H]^+$: *m/z* 327.2319, found: *m/z* 327.2320.

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2-hexyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84kc)



The compound was prepared from (±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) (±)-*anti*-**83k** (107.3 mg, 0.38 mmol, 1.0 equiv), isopropenylmagnesium bromide (0.85 M solution in THF, 1.34 mL, 1.14 mmol, 3.0 equiv.) and picolinaldehyde (60.7 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**84kc** was obtained in 56% yield (66.6 mg, 0.21 mmol).

Physical state: pale yellow oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ =8.53 (ddd, *J* = 5.0, 1.7, 1.0 Hz, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.20 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.06 (dt, *J* = 2.7, 1.3 Hz, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 4.66 (t, *J* = 1.5 Hz, 1H), 4.51 (dt, *J* = 1.8, 0.9 Hz, 1H), 3.38 (t, *J* = 2.3 Hz, 1H), 2.72 (dd, *J* = 6.5, 2.4 Hz, 1H), 2.15 (dtd, *J* = 8.6, 4.5, 3.5, 1.8 Hz, 2H), 1.53 (d, *J* = 2.2 Hz, 3H), 1.43 (td, *J* = 11.4, 10.2, 4.1 Hz, 2H), 1.30 – 1.22 (m, 6H), 0.92 – 0.82 (m, 3H).

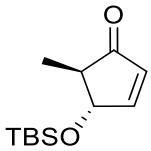
^{13}C NMR: (101 MHz, $CDCl_3$) δ =210.2, 160.4, 159.4, 148.0, 145.8, 144.8, 136.6, 122.8, 121.3, 112.4, 73.9, 57.3, 48.3, 31.5, 28.9, 27.6, 24.5, 22.6, 20.1, 14.1.

IR: (v/ cm^{-1}) 3452, 3079, 2926, 2855, 1741, 1700, 1592, 1439, 1409, 1379, 1312, 1275, 1218, 1152, 1103, 1051, 999, 954, 895, 779, 749.

HRMS: (ESI) calcd. for $C_{20}H_{27}NO_2$ $[M+H]^+$: *m/z* 314.2115, found: *m/z* 314.2119.

5.9 Mechanistic Studies of One-Pot Aldol Reaction

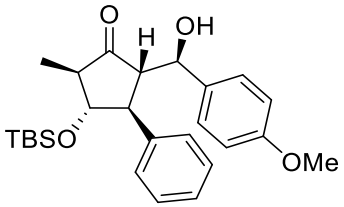
(±)-(4*S*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methylcyclopent-2-en-1-one ((±)-*anti*-152b)[89]



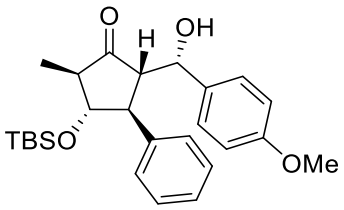
4-Hydroxy-5-methylcyclopent-2-enones (±)-*anti*-**82f**/(±)-*syn*-**82f** in a ratio of 8:1 (112.1 mg, 1.0 mmol, 1.0 equiv.) were dissolved in dry THF (5 mL) and cooled in ice. NEt_3 (271 µL, 1.9 mmol, 1.95 equiv) and DMAP (15.9 mg, 0.13 mmol, 0.13 equiv) were added. A solution of tert-butyldimethylsilyl chloride(TBSCl) (226.1 mg, 1.5 mmol, 1.5 equiv) in dry THF (2 mL) was added dropwise over 20 min under nitrogen atmosphere. The mixture was stirred for 30 min in cold and then allowed to warm to room temperature. After stirring for 2 h, the solvent was removed und der reduced pressure, distilled water (10 mL) was added to the residue, and the product was extracted with ethylacetate (3 × 25 mL). The combined organic layers were dried over anhydrous Mg_2SO_4 and concentrated in vacuum. The resulting mixture was purified *via* column chromatography (hexanes/EtOAc 10:1) to afford the product (±)-*anti*-**152b** in 87% (196.1 mg, 0.87 mmol) yield. Isolation of the *syn* product failed.

Physical state: colourless oil.
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.36 (dd, *J* = 5.8, 2.1 Hz, 1H), 6.15 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.50 (td, *J* = 2.3, 1.3 Hz, 1H), 2.25 (qd, *J* = 7.5, 2.5 Hz, 1H), 1.21 (d, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.13 (d, *J* = 2.4 Hz, 6H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ =208.3, 162.2, 133.4, 79.0, 50.8, 25.9, 18.2, 12.7, -4.4.
The analytical data are in agreement with literature.

(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*R*)-153b)



(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*S*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*S*)-153b)



The compounds were prepared from cyclopentenone (±)-*anti*-**152b** (86.0 mg, 0.38 mmol, 1.0 equiv), phenylmagnesium bromide (0.94 M solution in THF, 1.21 mL, 1.14 mmol, 3.0 equiv.) and anisaldehyde (102 µL, 0.63 mmol, 1.68 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) the products ((±)-(*R*)/(*S*)-**153b** were obtained in a ratio of 4:1 in 76% yield (127.2 mg, 0.29 mmol).

(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*R*)-**153b**)

Physical state: colourless oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.43 – 7.23 (m, 3H), 7.20 – 7.15 (m, 2H), 7.06 – 7.01 (m, 2H), 6.80 – 6.74 (m, 2H), 5.01 (dd, *J* = 6.7, 2.1 Hz, 1H), 3.89 (s, 3H), 3.85 (d, *J* = 2.4 Hz, 1H), 3.04 – 2.94 (m, 2H), 2.56 (dq, *J* = 9.9, 6.9 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 1.4 Hz, 10H), 0.01 (s, 3H), -0.54 (s, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ =218.7, 159.3, 140.5, 132.1, 128.4, 128.3, 128.2, 126.5, 113.5, 82.5, 75.1, 61.6, 55.3, 53.4, 53.3, 25.8, 17.9, 11.8, -4.6, -5.4.
IR: (v/ cm^{-1}) 2955, 2896, 2858, 1733, 1613, 1513, 1461, 1326, 1248, 1174, 1133, 1110, 1036, 909, 857, 775, 726.
HRMS: (ESI) calcd. for $C_{26}H_{36}O_4Si$ $[M+Na]^+$: *m/z* 463.2275, found: *m/z* 463.2283.

(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*S*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*S*)-**153b**)

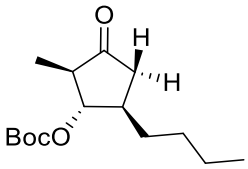
Physical state: colourless oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.47 – 7.27 (m, 7H), 6.94 – 6.90 (m, 2H), 5.08 (dd, *J* = 7.5, 4.4 Hz, 1H), 3.95 (s, 3H), 3.76 (d, *J* = 7.5 Hz, 3H), 3.19 – 3.09 (m, 2H), 2.37 – 2.30 (m, 1H), 1.35 (d, *J* = 5.1 Hz, 3H), 0.90 (s, 9H), 0.00 (s, 3H), -0.51 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 218.3, 159.0, 140.1, 133.3, 128.5, 128.5, 127.4, 127.0, 113.7, 82.4, 72.5, 61.1, 54.3, 51.4, 25.9, 17.9, 11.6, -4.5, -5.3.

IR: (v/ cm^{-1}) 2955, 2896, 2858, 1733, 1613, 1513, 1461, 1326, 1248, 1174, 1133, 1110, 1036, 909, 857, 775, 726.

HRMS: (ESI) calcd. for $C_{26}H_{36}O_4Si$ $[M+Na]^+$: *m/z* 463.2275, found: *m/z* 463.2283.

(±)-tert-butyl ((1*S*,2*R*,5*R*)-5-butyl-2-methyl-3-oxocyclopentyl) carbonate ((±)-*anti*-151)



The compound was prepared from cyclopentenone (±)-*anti*-**83f** (86.7 mg, 0.38 mmol, 1.0 equiv), butylmagnesium bromide (0.80 M solution in THF, 1.42 mL, 1.14 mmol, 3.0 equiv.) and H_2O (5 mL) for subsequent quenching according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) the product (±)-*anti*-**151** was obtained in 84% yield (86.3 mg, 0.32 mmol).

Physical state: colourless oil.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

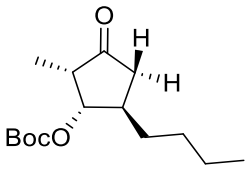
^{1}H NMR: (400 MHz, $CDCl_3$) δ =4.64 (t, *J* = 8.9 Hz, 1H), 2.66 (ddd, *J* = 18.8, 8.5, 2.0 Hz, 1H), 2.36 (dqd, *J* = 9.1, 7.1, 2.0 Hz, 1H), 2.23 (dqd, *J* = 10.8, 8.5, 4.5 Hz, 1H), 1.89 (dd, *J* = 18.8, 10.9 Hz, 1H), 1.66 (s, 1H), 1.51 (s, 9H), 1.37 – 1.25 (m, 5H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =214.6, 153.6, 84.3, 82.7, 50.9, 42.9, 40.5, 32.6, 30.0, 27.9, 22.9, 14.1, 12.1.

IR: (v/ cm^{-1}) 2970, 2929, 1736, 1457, 1394, 1371, 1274, 1151, 1103, 1039, 972, 902, 842, 790, 730.

HRMS: (ESI): calcd. for $C_{15}H_{26}O_4$ $[M+Na]^+$: *m/z* 293.1723, found: *m/z* 293.1725.

(±)-*tert*-butyl ((1*S*,2*S*,5*R*)-5-butyl-2-methyl-3-oxocyclopentyl) carbonate ((±)-*syn*-151)



The compound was prepared from cyclopentenone (±)-*syn*-**83f** (86.7 mg, 0.38 mmol, 1.0 equiv), butylmagnesium bromide (0.80 M solution in THF, 1.42 mL, 1.14 mmol, 3.0 equiv.)

and H_2O (5 mL) for subsequent quenching according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) the product (±)-*syn*-**151** was obtained in 86% yield (88.4 mg, 0.33 mmol).

Physical state: colourless oil.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ =5.02 (dd, *J* = 6.0, 3.1 Hz, 1H), 2.61 – 2.47 (m, 2H), 2.42 – 2.27 (m, 1H), 2.02 (ddt, *J* = 18.8, 4.3, 1.1 Hz, 1H), 1.49 (s, 9H), 1.40 – 1.25 (m, 6H), 1.06 (d, *J* = 7.3 Hz, 3H), 0.93 – 0.88 (m, 3H).

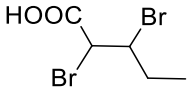
^{13}C NMR: (101 MHz, $CDCl_3$) δ =217.4, 153.3, 82.5, 81.5, 45.8, 41.3, 39.7, 33.2, 30.0, 27.9, 22.8, 14.1, 8.6.

IR: (v/ cm^{-1}) 2959, 2933, 2862, 1736, 1457, 1371, 1274, 1155, 1095, 1039, 998, 939, 913, 853, 793.

HRMS: (ESI) calcd. for $C_{15}H_{26}O_4$ $[M+Na]^+$: *m/z* 293.1723, found: *m/z* 293.1726.

5.10 Synthesis of Phomapentenone A

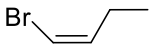
2,3-dibromopentanoic acid (183) [75]



A solution of trans-2-pentenoic acid (**184**) (25 g, 249.8 mmol, 1.0 equiv)in DCM (100 mL) was cooled to 0°C, and bromine (14.1 mL, 274.7 mmol, 1.1 equiv) was added dropwise. The mixture was then stirred for 3h at rt. Then the reaction was quenched by addition of aqueous $Na_2S_20_3$ solution (50 mL). The organic layer was separated, dried with Na_2S0_4 and concentrated under vacuum to yield the product **183** in 99% (64.2 g, 247.0 mmol) yield.

Physical state: pale yellow solid.
TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 9.68 (s, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.40 – 4.30 (m, 1H), 2.31 (dqd, *J* = 14.6, 7.3, 2.6 Hz, 1H), 1.90 (ddd, *J* = 14.8, 7.8, 7.0 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 173.3, 53.5, 46.9, 28.4, 10.7.
Analytical data are in agreement with literature.

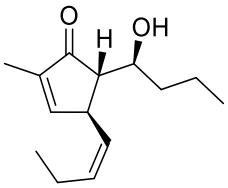
(*Z*)-1-bromobut-1-ene (182) [75]



Dibromopentanoic acid **183** (60.0 g, 230.8 mmol, 1.0 equiv) in DMF (45 mL) was added to a suspension of $NaHCO_3$ (30.0 g, 360 mmol, 1.7 eq.) in DMF (90 mL) within 1 h, which was vigorously stirred at 70°C under vacuum (ca. 140 mbar). Under these conditions, the volatile product distilled off and was collected in a cold trap at -78 °C. The collected material was washed with water (2 mL) and dried over Na_2SO_4 to give product **182** as a colorless liquid in 67% (21 g, 156 mmol) yield.

Physical state: colourless oil.
TLC: R_f = 0.7 (hexanes/ EtOAc 5:1).
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.19 – 5.99 (m, 2H), 2.32 – 2.11 (m, 2H), 1.02 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) 136.5, 107.2, 23.4, 12.8.
Analytical data are in agreement with literature.

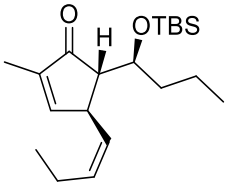
(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-180) / (4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (180)



Preparation of precursor (Z)-but-1-en-1-ylmagnesium bromide (**195**):
In a flame dried 3-neck flask with dropping funnel and reflux condenser Mg (1.46 g, 60.0 mmol, 6.0 equiv), THF (15 mL) and iodine (30 mg) were added and stirred. A mixture of (Z)-1-bromobut-1-ene (**182**) (7.43 g, 55.0 mmol, 5.5 equiv) and THF (40 mL) was filled into to the dropping funnel and 5 mL of the resulting solution was added subsequently. The mixture was stirred smoothly until the reaction started (45 min, exothermic reaction). After the reaction started, the bromide solution was added smoothly over a period of 30 min. After the addition of the bromide the reaction mixture was stirred for further 15 min to obtain the (Z)-but-1-en-1-ylmagnesium bromide (**195**) (0.64 M).
The compound was prepared from 5-methylcyclopent-2-enone (±)-*anti*-**83f** / *syn*-**83f** (2.12 g, 10.0 mmol, 1.0 equiv), (Z)-but-1-en-1-ylmagnesium bromide (**195**) (0.64 M in THF, 46.9 mL, 30.0 mmol, 3.0 equiv). and butanal (1.50 mL, 16.6 mmol, 1.66 equiv.) according to the general procedure of the one pot synthesis. After purification by column chromatography (hexanes/ EtOAc 7:1 → 3:1) product (±)-**180**/ **180** was obtained in 78%/ 79% yield (1.73 g, 7.8 mmol / 1.75 g, 7.9 mmol).

Physical state: pale yellow oil.
TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =6.99 (dq, *J* = 2.9, 1.4 Hz, 1H), 5.46 (dtd, *J* = 10.7, 7.4, 1.0 Hz, 1H), 5.05 (ddt, *J* = 11.4, 10.1, 1.7 Hz, 1H), 4.12 (s, 1H), 3.75 – 3.63 (m, 1H), 3.44 – 3.31 (m, 1H), 2.18 – 2.01 (m, 3H), 1.71 (dd, *J* = 2.2, 1.5 Hz, 4H), 1.51 – 1.38 (m, 4H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ =212.7, 161.0, 140.6, 133.8, 128.4, 71.9, 57.0, 41.1, 37.6, 21.0, 18.2, 14.2, 14.0, 9.9.
IR: (v/ cm^{-1}) 3473, 3004, 2959, 2933, 2873, 1684, 1636, 1461, 1416, 1334, 1226, 1129, 1073, 920, 849, 745.
HRMS: (ESI) calcd. for $C_{14}H_{22}O_2$ $[M+H]^+$: *m/z* 223.1693, found: *m/z* 223.1697.

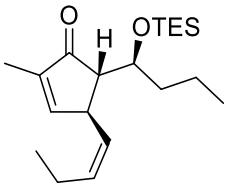
(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methylcyclopent-2-en-1-one ((±)-179a)



The alcohol (±)-**180** (650 mg, 2.9 mmol, 1.0 equiv), 1-methylimidazole (700 µL, 8.8 mmol, 3.0 equiv) and iodine (2.23 g, 8.8 mmol, 3.0 equiv) were dissolved in THF (25 mL) followed by addition of TBSCl (484.7 mg, 3.22 mmol, 1.1 equiv). the reaction was stirred for 24 h under reflux and Et_2O (50 mL) was added. The organic phase was washed with $Na_2S_2O_3$ (2 x 20 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified *via* column chromatography (hexanes/ EtOAc 20:1 → 10:1) to obtain the product (±)-**179a** in 82% (806.9 mg, 2.4 mmol) yield.

Physical state: pale yellow oil.
TLC: R_f = 0.9 (hexanes/ EtOAc 5:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.96 (dq, *J* = 2.8, 1.4 Hz, 1H), 5.39 (dtd, *J* = 10.6, 7.2, 1.1 Hz, 1H), 4.97 (ddt, *J* = 11.0, 9.5, 1.6 Hz, 1H), 4.03 (dt, *J* = 8.0, 4.3 Hz, 1H), 3.77 – 3.59 (m, 1H), 2.32 (dd, *J* = 4.1, 1.9 Hz, 1H), 2.12 (dddd, *J* = 14.6, 12.5, 7.3, 1.6 Hz, 2H), 1.68 (dd, *J* = 2.0, 1.4 Hz, 3H), 1.48 – 1.19 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.84 – 0.77 (m, 12H), -0.01 (d, *J* = 3.5 Hz, 6H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ =209.5, 160.7, 141.1, 133.0, 129.7, 72.5, 58.5, 40.0, 35.5, 25.8, 21.0, 19.5, 18.1, 14.4, 14.2, 10.0, -4.4, -4.5.
IR: (v/ cm^{-1}) 3008, 2959, 2929, 2858, 1703, 1636, 1461, 1379, 1326, 1252, 1066, 1032, 905, 834, 775, 689.
HRMS: (ESI) calcd. for $C_{20}H_{36}O_2Si$ $[M+H]^+$: *m/z* 337.2557, found: *m/z* 337.2550.

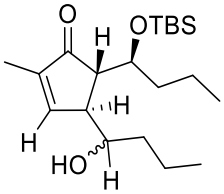
(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-2-methylcyclopent-2-en-1-one ((±)-179b) / (4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-2-methylcyclopent-2-en-1-one (179b)



The alcohol (±)-**180/ 180** (700 mg, 3.2 mmol, 1.0 equiv) was dissolved in DMF (5 mL), then imidazole (261.4 mg, 3.84 mmol, 1.2 equiv), DMAP (115.4 mg, 0.9 mmol, 0.3 equiv) and TESCl (0.63 mL, 3.8 mmol, 1.2 equiv) were added. The reaction was stirred for 5 min and directly purified *via* column chromatography (hexanes/ EtOAc 20:1 → 10:1) to obtain the product (±)-**179b** / **179b** in 95% (1.01 g, 3.0 mmol) yield.

Physical state: colourless oil.
TLC: R_f = 0.9 (hexanes/ EtOAc 5:1).
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.02 (dq, *J* = 2.8, 1.4 Hz, 1H), 5.44 (dtd, *J* = 10.5, 7.2, 1.0 Hz, 1H), 5.12 – 4.96 (m, 1H), 4.11 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.79 – 3.66 (m, 1H), 2.36 (dd, *J* = 4.2, 2.0 Hz, 1H), 2.26 – 2.11 (m, 2H), 1.74 (q, *J* = 2.0 Hz, 3H), 1.56 – 1.20 (m, 6H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.98 – 0.91 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.58 (q, *J* = 7.7 Hz, 6H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ =209.5, 160.7, 141.2, 133.0, 129.7, 72.4, 58.8, 39.9, 35.6, 21.0, 19.6, 14.4, 14.2, 10.0, 6.9, 5.0.
IR: (v/ cm^{-1}): 2959, 2914, 2877, 1740, 1707, 1636, 1461, 1416, 1326, 1237, 1114, 1069, 1006, 969, 857, 779, 723.
HRMS: (ESI) calcd. for $C_{20}H_{36}O_2Si$ $[M+H]^+$: *m/z* 337.2557, found 337.2566.

(±)-(4*S*,5*S*)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)butyl)-4-(1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-196a)



The alkene (±)-**179a** (168.3 mg, 0.5 mmol, 1.0 equiv) was solved in THF (5 mL) and cooled to 0 °C, followed by slow addition of BH_3·THF (550 µL, 1.0 M, 0.55 mmol, 1.1 equiv). The reaction was stirred for 1 h at room temperature followed by subsequent addition of H_2O (0.5 mL), NaOH (0.5 mL, 3.0 M) and H_2O_2 (aq, 30 wt-%, 0.3 mL). The slurry was stirred for 1 h and diluted with DCM (20 mL). The organic phase was washed with H_2O (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude mixture was purified *via* column chromatography (hexanes/ EtOAc 10:1 → 3:1) to obtain the product (±)-**196a** in 63% (111.7 mg, 0.32 mmol) yield.

Physical state: pale yellow oil.
TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

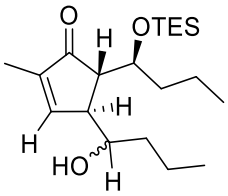
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.21 (dt, *J* = 2.7, 1.5 Hz, 1H), 4.31 (ddd, *J* = 7.7, 5.1, 3.1 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.25 (s, 1H), 2.89 (dq, *J* = 7.6, 2.5 Hz, 1H), 2.48 (t, *J* = 2.9 Hz, 1H), 1.79 (dd, *J* = 2.3, 1.4 Hz, 3H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.54 – 1.40 (m, 3H), 1.33 – 1.28 (m, 1H), 1.18 – 1.06 (m, 1H), 0.98 (t, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.15 (s, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =207.6, 157.1, 142.5, 73.9, 72.3, 58.1, 48.4, 36.9, 26.1, 19.6, 18.6, 18.3, 14.4, 14.3, 10.4, -4.3, -4.3.

IR: (v/ cm^{-1}) 3451, 2963, 2933, 2877, 1736, 1688, 1461, 1371, 1274, 1162, 1073, 1013, 924, 793, 745.

HRMS: (ESI) calcd. for $C_{20}H_{38}O_3Si$ $[M+H]^+$: *m/z* 355.2663, found: *m/z* 355.2662.

(±)-(4*S*,5*S*)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-4-(1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-196b) / (4*S*,5*S*)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-4-(1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (196b)



The alkene (±)-**179b** / **179b** (168.3 mg, 0.5 mmol, 1.0 equiv) was solved in THF (5 mL) and cooled to 0 °C, followed by slow addition of BH_3·THF (550 µL, 1.0 M, 0.55 mmol, 1.1 equiv). The reaction was stirred for 1 h at room temperature followed by subsequent addition of H_2O (0.5 mL), NaOH (0.5 mL, 3.0 M) and H_2O_2 (aq, 30 wt-%, 0.3 mL). The slurry was stirred for 1 h and diluted with DCM (20 mL). The organic phase was washed with H_2O (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude mixture was purified *via* column chromatography (hexanes/ EtOAc 10:1 → 3:1) to obtain the product (±)-**196b** / **196b** in 65% / 66% (115.0 mg, 0.32 mmol/ 117.0 mg, 0.33 mmol) yield.

Physical state: pale yellow oil.

TLC: R_f = 0.4 (hexanes/ EtOAc 3:1).

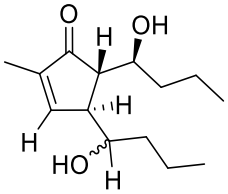
^{1}H NMR: (300 MHz, $CDCl_3$) δ =7.21 (dq, *J* = 2.9, 1.5 Hz, 1H), 4.25 (dt, *J* = 7.9, 4.1 Hz, 1H), 3.79 (tt, *J* = 7.8, 4.0 Hz, 1H), 3.13 (dp, *J* = 4.8, 2.4 Hz, 1H), 2.62 (dd, *J* = 3.7, 2.7 Hz, 1H), 2.53 (d, *J* = 7.7 Hz, 1H), 1.76 (dd, *J* = 2.3, 1.4 Hz, 3H), 1.65 – 1.47 (m, 2H), 1.45 – 1.25 (m, 6H), 1.00 – 0.91 (m, 12H), 0.84 (t, *J* = 7.1 Hz, 3H), 0.70 – 0.60 (m, 6H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ =208.3, 157.3, 142.5, 72.3, 72.1, 54.8, 47.4, 36.6, 36.1, 19.7, 19.6, 14.4, 14.2, 10.4, 7.0, 5.0.

IR: (v/ cm^{-1}) 3350, 2959, 2877, 1736, 1688, 1640, 1461, 1379, 1282, 1237, 1125, 1066, 1013, 902, 842, 730.

HRMS: (ESI) calcd. for $C_{20}H_{38}O_3Si$ $[M+H]^+$: *m/z* 355.2663, found: *m/z* 355.2662.

(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-197) / (4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (197)



To a solution of cyclopentenone (±)-**196a** / (±)-**196b** / **196b** (106.4 mg, 0.3 mmol, 1.0 equiv) in dry THF (5 ml) was added a solution of tetrabutylammonium fluoride (TBAF) (330 µL, 1M in THF, 0.33 mmol, 1.1 equiv) and the reaction mixture was stirred at rt for 3 h After addition of HCl (aq, 2 ml, 1 M), the mixture was extracted with ether (2 x 25 mL) The organic layer was washed with $NaHCO_3$ (aq, sat., 10 mL) and brine (10 mL) and then dried over $MgSO_4$. The solvent was removed under reduce pressure and the residue was purified by column chromatography (PE:EA 5:1 to 1:1) to afford the product (±)-**197** in 86% / 87% / **197** in 87% (61.9 mg, 0.26 mmol / 62.3 mg, 0.26 mmol / 62.1 mg, 0.26 mmol) yield.

Physical state: pale yellow oil.

TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).

Chiral HPLC: >99 % ee (t_R major, minor = 10.0 min, 6.9 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).

$[\alpha]_D^{25}$ = -83.2° (c = 0.07, 4:1 $CHCl_3$/ MeOH).

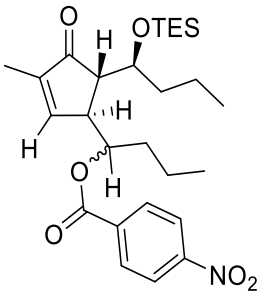
^{1}H NMR: (400 MHz, $CDCl_3$) δ =7.23 (dq, *J* = 2.8, 1.4 Hz, 1H), 3.99 (ddd, *J* = 9.0, 5.8, 2.8 Hz, 1H), 3.54 (ddd, *J* = 8.3, 7.1, 2.3 Hz, 1H), 2.78 (dq, *J* = 7.1, 2.3 Hz, 1H), 2.50 (dd, *J* = 5.8, 2.4 Hz, 1H), 1.79 (dd, *J* = 2.1, 1.4 Hz, 3H), 1.61 – 1.32 (m, 8H), 0.99 – 0.95 (m, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ =209.4, 157.8, 142.7, 73.6, 71.3, 55.2, 48.4, 36.9, 36.2, 19.1, 18.8, 14.1, 14.0, 10.2.

IR: (v/ cm^{-1}) 3436, 2959, 2929, 2873, 2091, 2001, 1692, 1647, 1461, 1379, 1329, 1233, 1069, 1013, 946, 846, 745.

HRMS: (ESI) calcd. for $C_{14}H_{24}O_3$ $[M+H]^+$: *m/z* 241.1798, found: *m/z* 241.1808.

(±)-1-((1*S*,5*S*)-3-methyl-4-oxo-5-((*S*)-1-((triethylsilyl)oxy)butyl)cyclopent-2-en-1-yl)butyl 4-nitrobenzoate ((±)-198) / 1-((1*S*,5*S*)-3-methyl-4-oxo-5-((*S*)-1-((triethylsilyl)oxy)butyl)cyclopent-2-en-1-yl)butyl 4-nitrobenzoate (198)



To a solution of alcohol (±)-**196b / 196b** (88.7 mg, 0.25 mmol, 1.0 equiv.) in $DCM_{abs.}$ (2 mL) 4-nitrobenzoic acid (62.7 mg, 0.38 mmol, 1.5 equiv.) and triphenylphosphane (78.7 mg, 0.3 mmol, 1.2 equiv) were dissolved. DIAD (80.9 mg, 0.4 mmol, 1.6 equiv.) was added slowly over a periode of 10 min. The reaction mixture was stirred for 1 h and the solvent was evaporated under reduced pressure. The reaction mixture was purified by column chromatography (hexanes:EtOAc 7:1) to afford the product (±)-**198** / **198** in 87% / 86% (109.5 mg, 0.22 mmol / 108.1 mg/ 0.21 mmol) yield.

Physical state: pale yellow oil.

TLC: R_f = 0.6 (hexanes/ EtOAc 3:1).

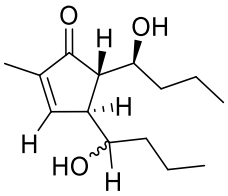
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.34 – 8.28 (m, 2H), 8.25 – 8.19 (m, 2H), 7.23 (dd, *J* = 2.7, 1.5 Hz, 1H), 5.24 (p, *J* = 6.0 Hz, 1H), 4.1 – 4.00 (m, 1H), 2.89 – 2.80 (m, 1H), 2.28 (dd, *J* = 3.6, 2.1 Hz, 1H), 1.93 – 1.74 (m, 4H), 1.71 (t, *J* = 1.7 Hz, 3H), 1.39 – 1.24 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.9 Hz, 9H), 0.58 – 0.53 (m, 3H), 0.53 – 0.48 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 208.3, 164.2, 159.7, 142.0, 130.7, 123.6, 73.1, 58.0, 39.1, 35.9, 27.5, 19.5, 14.2, 10.1, 9.3, 6.9, 5.1.

IR: (v/ cm^{-1}) 3496, 3116, 2933, 2959, 2873, 2363, 1722, 1640, 1605, 1528, 1461, 1408, 1345, 1271, 1170, 1103, 1062, 1013, 961, 872, 838, 782, 719.

HRMS: (ESI) calcd. for $C_{27}H_{41}NO_6Si$ $[M+H]^+$: *m/z* 504.2776, found: *m/z* 504.2782.

(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-199) / (4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (199)



H_2O (4 mL) was adjusted to pH 3 with H_2SO_4. The cyclopentenone ester (±)-**198** / **198** (93.1mg, 0.25 mmol, 1.0 equiv.) was dissolved in the prepared acidulated H_2O. The reaction mixture was stirred for 12 h at 55 °C. The resulting mixture was slowly neutralized with Na_2CO_3 and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc 7:1 – 2:1) to afford the product (±)-**199** / **199** in 60%/ 58% (36.0 mg, 0.15 mmol / 35.0 mg, 0.15 mmol) yield.

Physical state: colourless oil.

TLC: R_f = 0.3 (hexanes/ EtOAc 3:1).

Chiral HPLC: 92 % ee (t_R major, minor = 9.5 min, 6.8 min, Chiralpak AS-H 4.6 x 250 mm 5 µm, n-Heptan:^{i}PrOH 99:1, 1.0 mL/min).

$[\alpha]_D^{25}$ = -88.3° (c = 0.07, 4:1 $CHCl_3$/ MeOH).

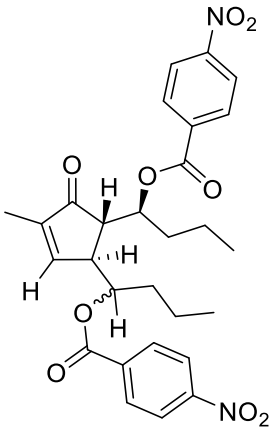
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 2.8, 1.5 Hz, 1H), 3.91 – 3.73 (m, 2H), 2.80 (dq, *J* = 4.5, 2.3 Hz, 1H), 2.49 (dd, *J* = 7.1, 2.4 Hz, 1H), 1.78 (t, *J* = 1.7 Hz, 3H), 1.64 – 1.31 (m, 8H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 211.1, 157.5, 142.9, 72.2, 71.8, 53.1, 48.2, 37.2, 36.9, 19.6, 19.0, 14.1, 10.4.

IR: (v/ cm^{-1}) 3436, 2959, 2929, 1695, 1651, 1461, 1379, 1326, 1237, 1069, 1013, 946, 846, 745.

HRMS: (ESI) calcd. for $C_{14}H_{24}O_3$ $[M+H]^+$: *m/z* 241.1798, found: *m/z* 241.1803.

(±)-(S)-1-((1S,5S)-3-methyl-5-(1-((4-nitrobenzoyl)oxy)butyl)-2-oxocyclopent-3-en-1-yl)butyl 4-nitrobenzoate ((±)-200)



To a solution of alcohol (±)-**199** (60.1 mg, 0.25 mmol, 1.0 equiv), DMAP in cat. amount (1 mg, 1 mol%) and triethylamin (98 µL, 0.7 mmol, 2.8 equiv) in DCM (2 mL) was added a solution of 4-nitrobenzoyl chloride (111 mg, 0.6 mmol, 2.4 equiv) in DCM (2 mL). The reaction mixture was stirred for 24 h under reflux, and the product was purified *via* flash chromatography (hexanes/EtOAc 10:1) to afford the ester (±)-**200** in 93% (125.2 mg, 0.23 mmol) yield.

Physical state: colourless oil.

TLC: R_f = 0.7 (hexanes/ EtOAc 3:1).

^{1}H NMR: (400 MHz, $CDCl_3$) δ =8.29 – 8.18 (m, 4H), 8.09 (t, *J* = 8.6 Hz, 4H), 7.28 (dd, *J* = 2.7, 1.5 Hz, 1H), 5.47 (dt, *J* = 9.0, 4.2 Hz, 1H), 5.31 (dt, *J* = 9.1, 4.5 Hz, 1H), 3.16 (dq, *J* = 4.8, 2.4 Hz, 1H), 2.71 (dd, *J* = 4.2, 2.5 Hz, 1H), 1.93 (dtd, *J* = 14.6, 9.6, 5.6 Hz, 1H), 1.84 (d, *J* = 1.8 Hz, 3H), 1.77 (td, *J* = 9.3, 4.9 Hz, 1H), 1.66 (dddd, *J* = 18.2, 14.2, 7.1, 4.2 Hz, 2H), 1.46 – 1.29 (m, 4H), 0.91 (td, *J* = 7.3, 3.3 Hz, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 206.1, 164.4, 164.4, 154.9, 150.8, 150.7, 143.8, 135.4, 135.1, 130.8, 130.8, 123.8, 123.7, 75.9, 75.7, 50.5, 46.2, 34.4, 33.4, 19.2, 19.2, 13.9, 13.9, 10.5.

IR: (v/ cm^{-1}) 3112, 2959, 2937, 2873, 1722, 1640, 1605, 1528, 1461, 1408, 1345, 1267, 1099, 957, 872, 834. 715.

HRMS: (ESI) calcd. for $C_{28}H_{30}N_2O_9$ $[M+H]^+$: *m/z* 539.2024, found: *m/z* 539.2036.

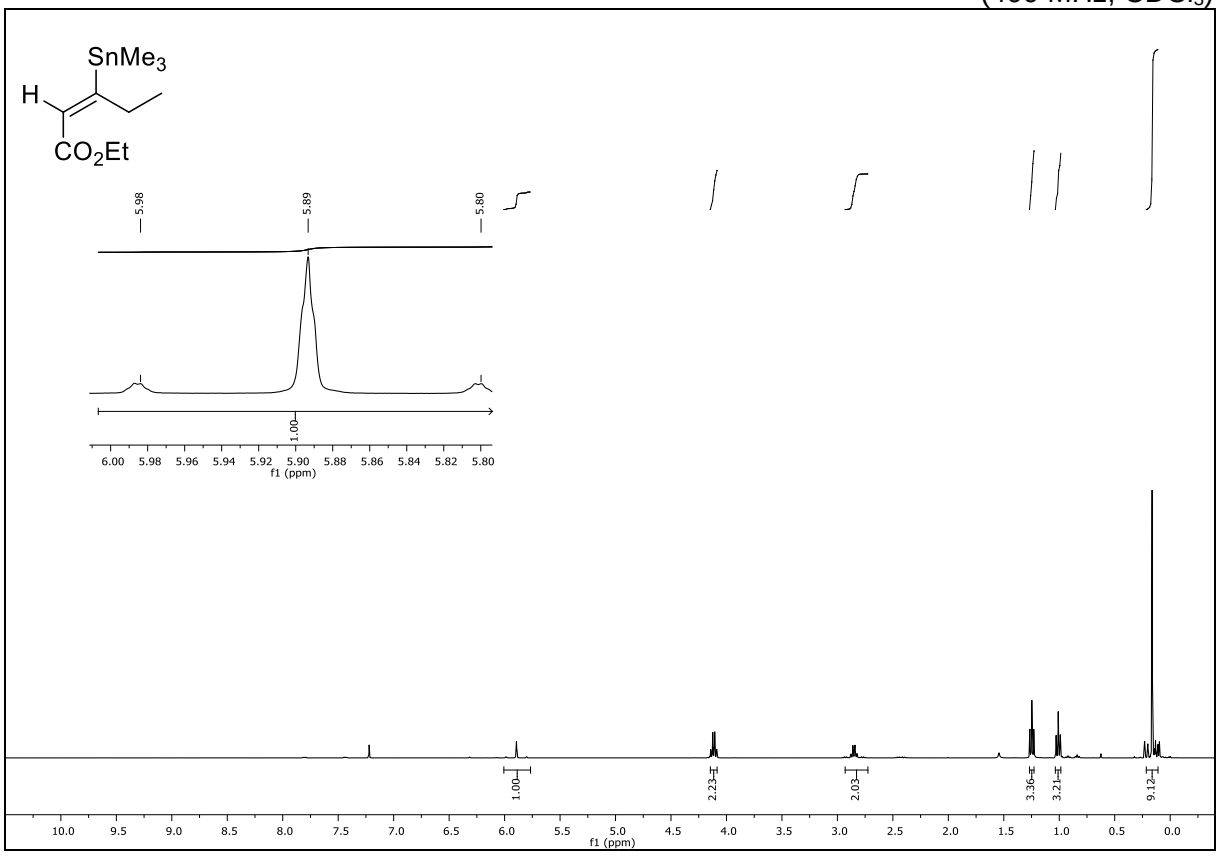
5.11 NMR Spectra

^{1}H-NMR (300 MHz or 400 MHz): -upper image

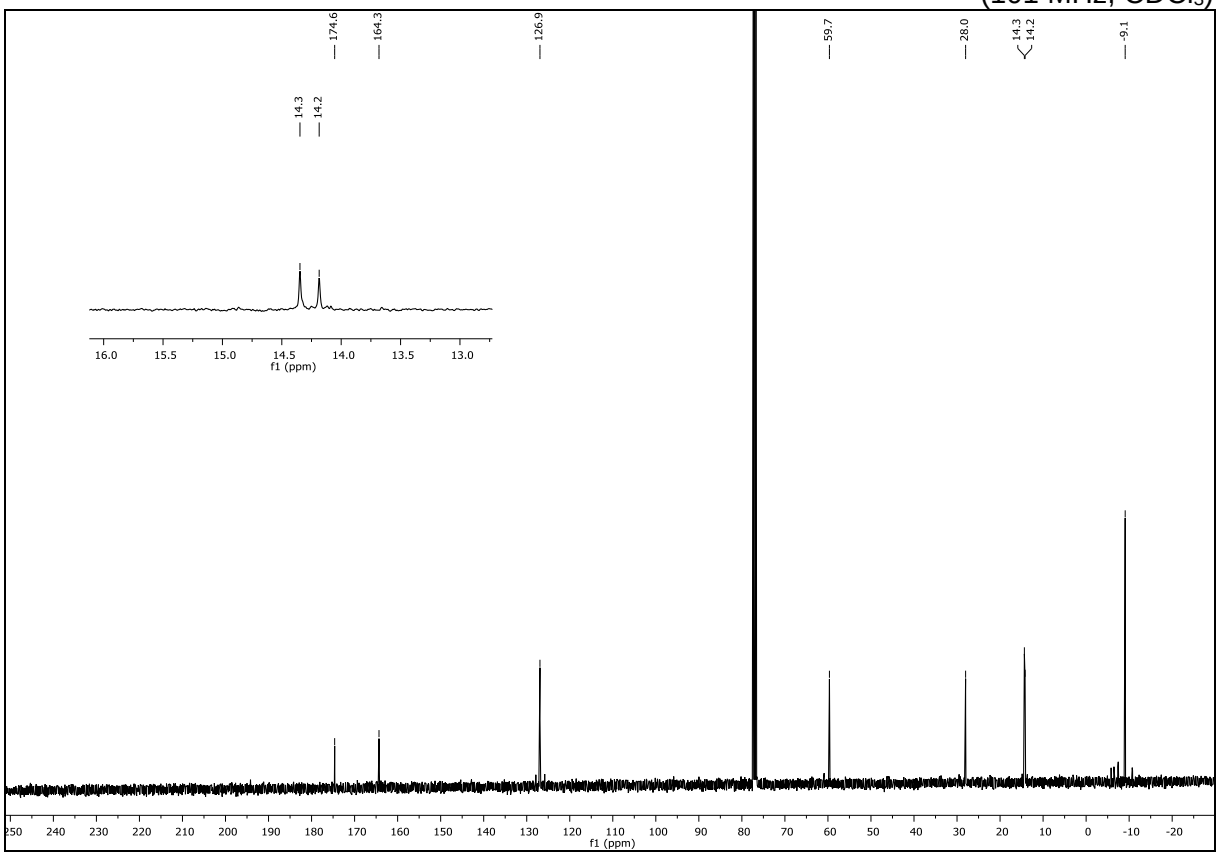
^{13}C-NMR (75 MHz or 101 MHz): -lower image

Ethyl (*E*)-3-(trimethylstannyl)pent-2-enoate (5a)

(400 MHz, $CDCl_3$)

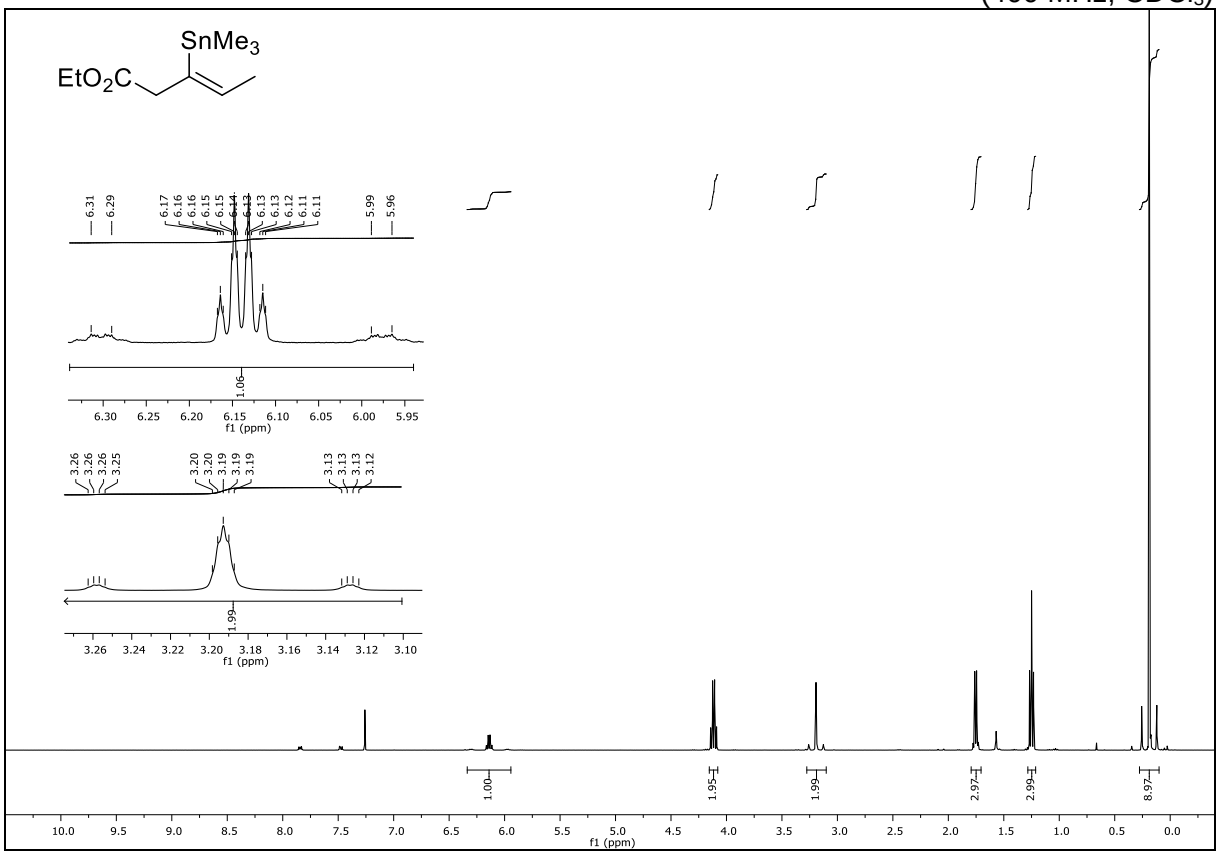


(101 MHz, $CDCl_3$)

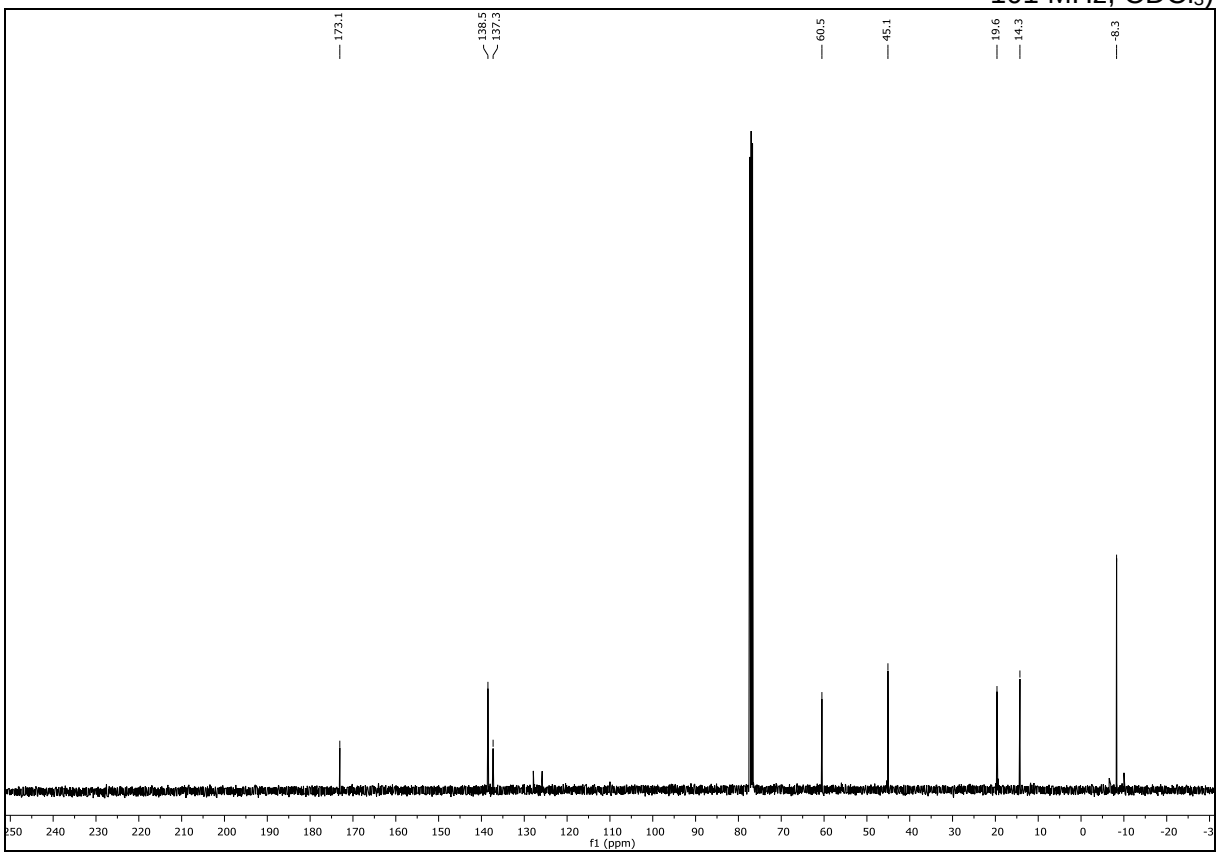


Ethyl (*Z*)-3-(trimethylstannyl)pent-3-enoate (4a)

(400 MHz, $CDCl_3$)

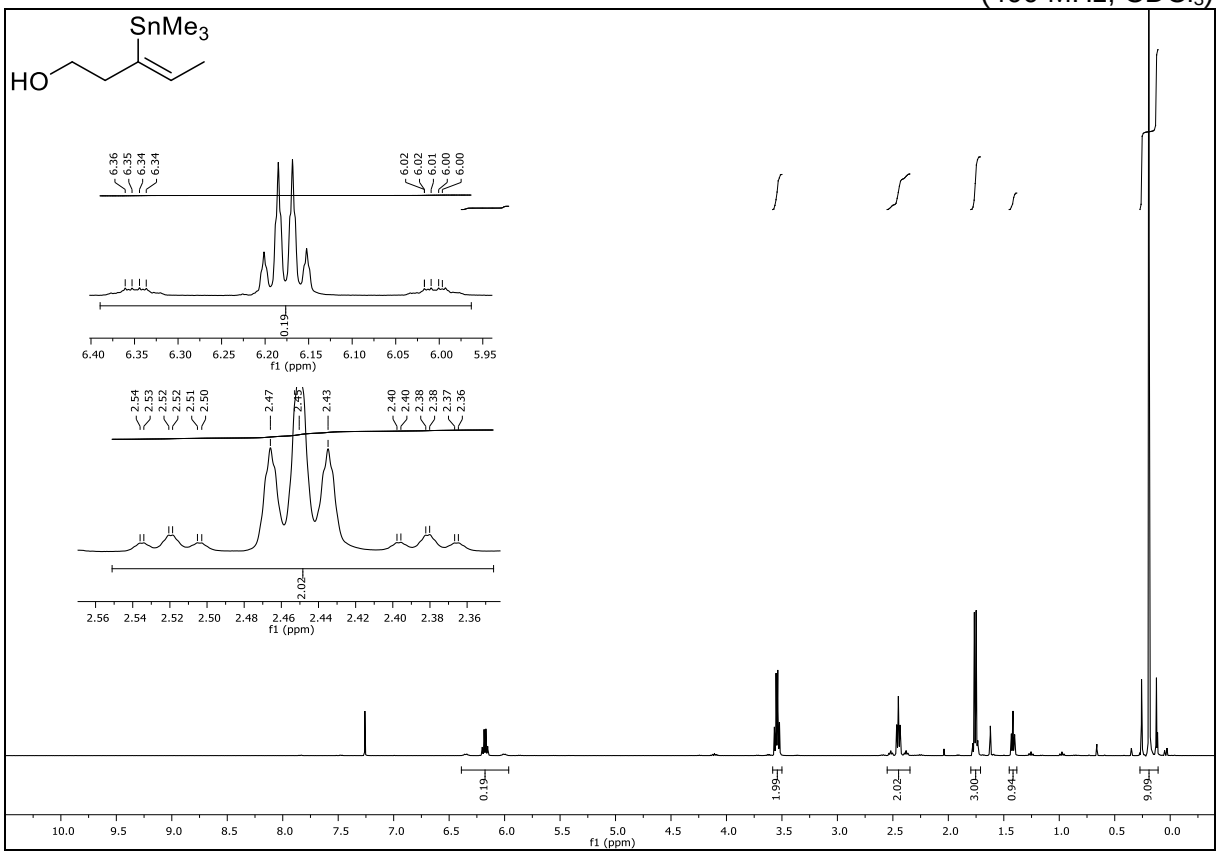


101 MHz, $CDCl_3$)

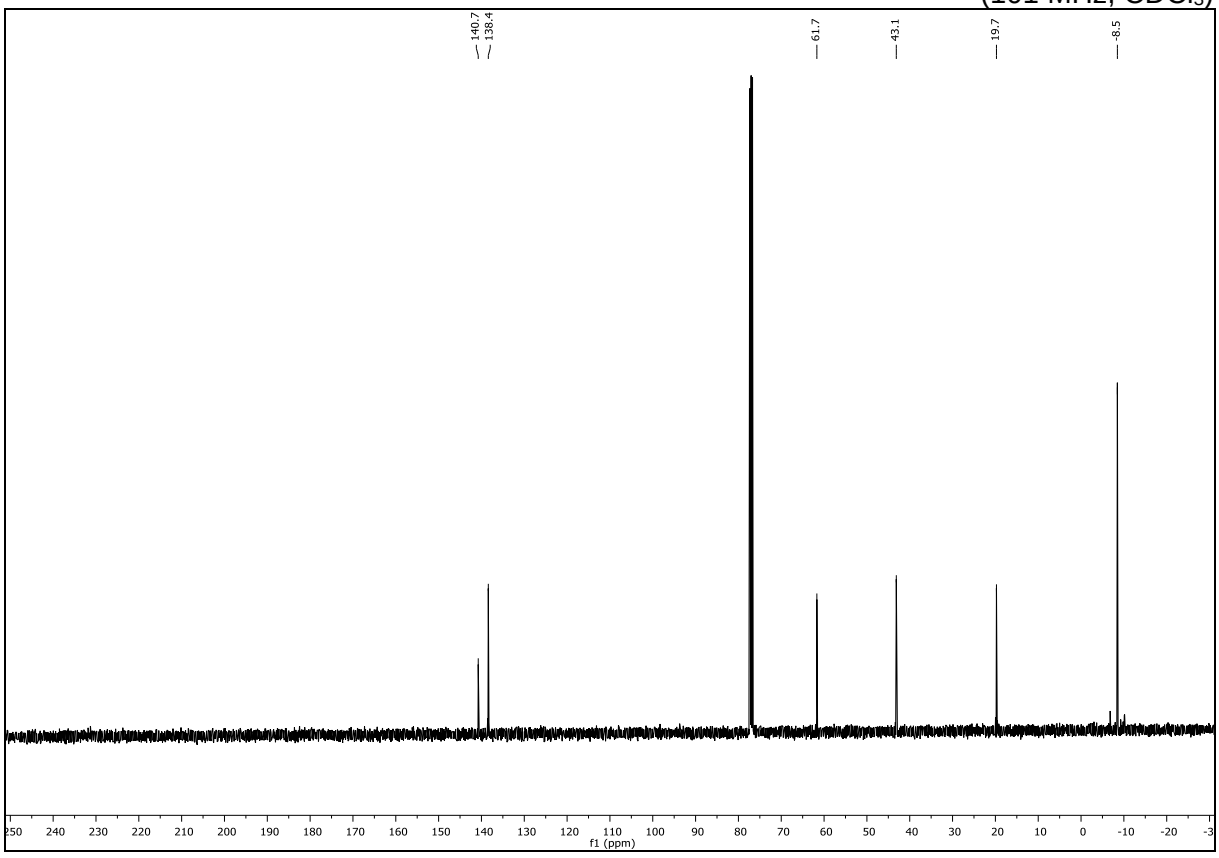


(*Z*)-3-(Trimethylstannyl)pent-3-en-1-ol (3)

(400 MHz, $CDCl_3$)

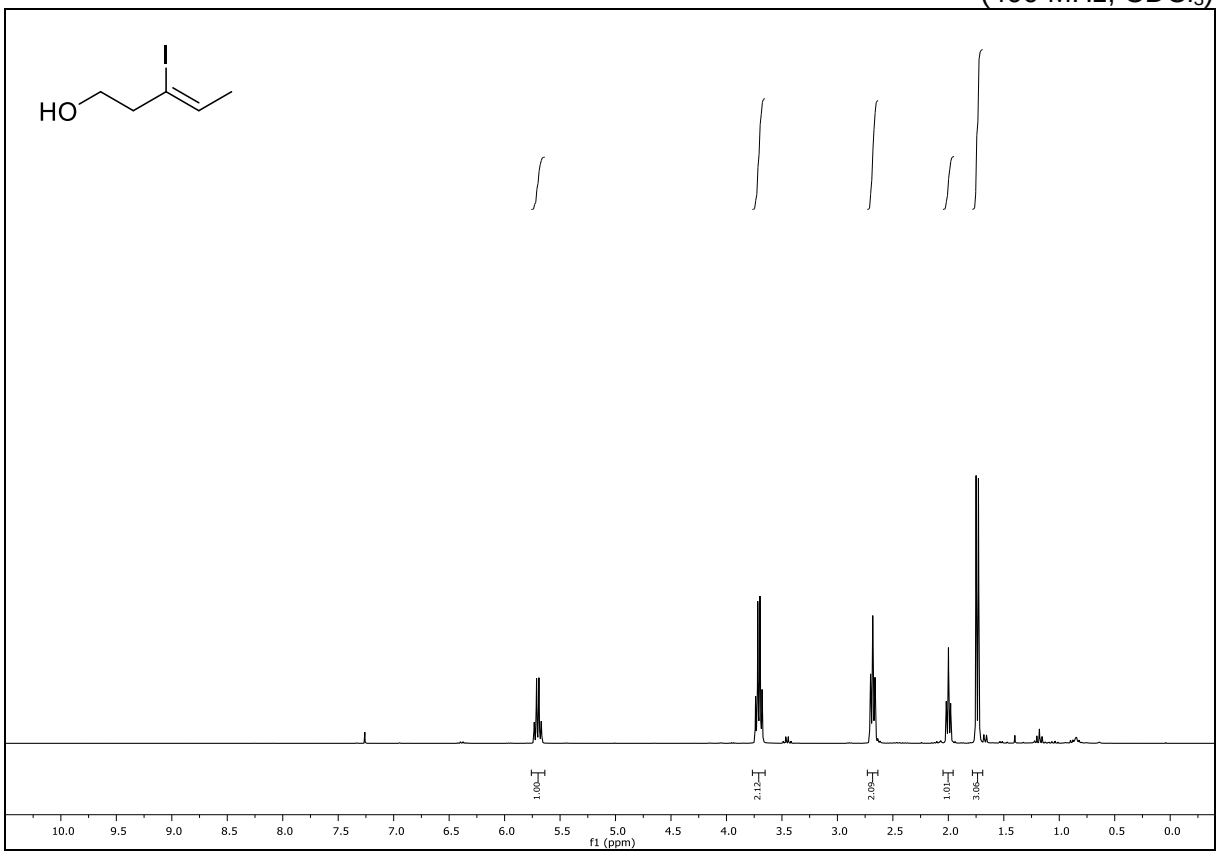


(101 MHz, $CDCl_3$)

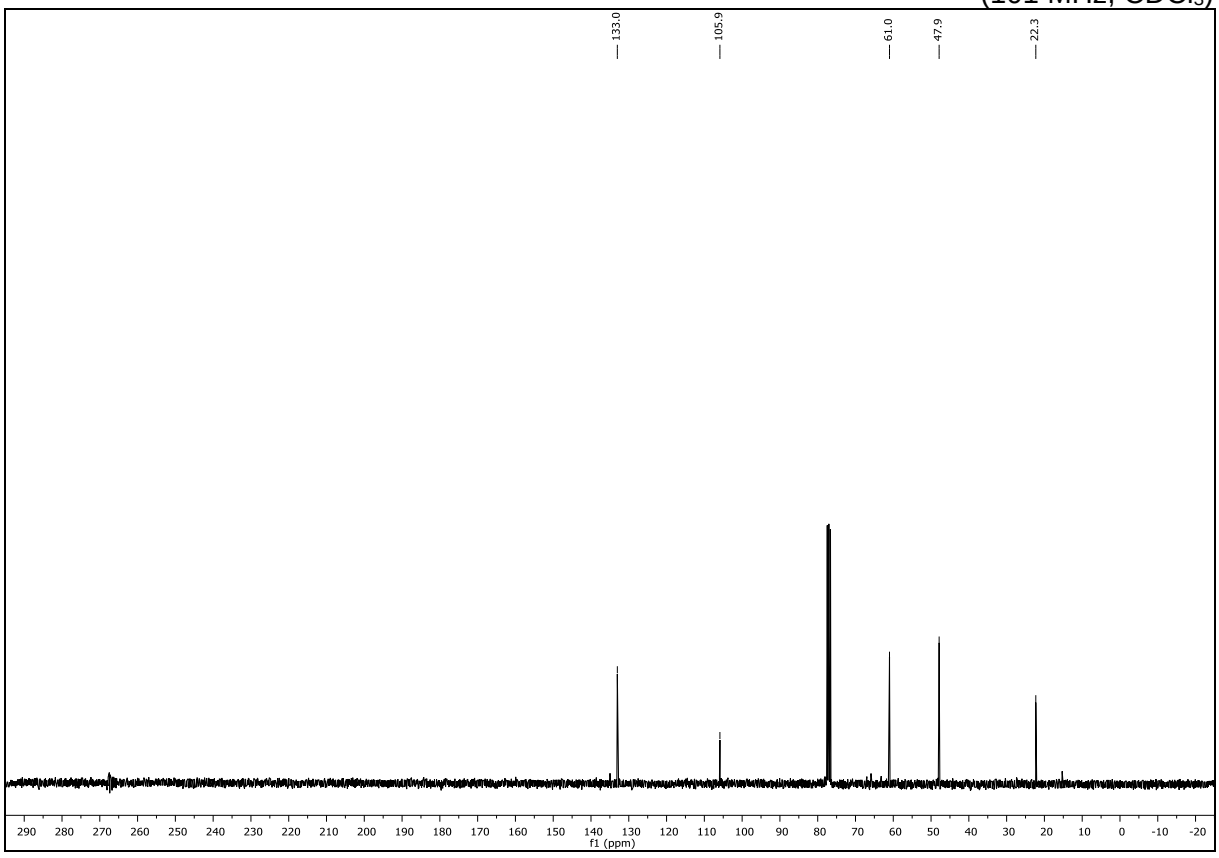


(*Z*)-3-Iodopent-3-en-1-ol (2)

(400 MHz, $CDCl_3$)

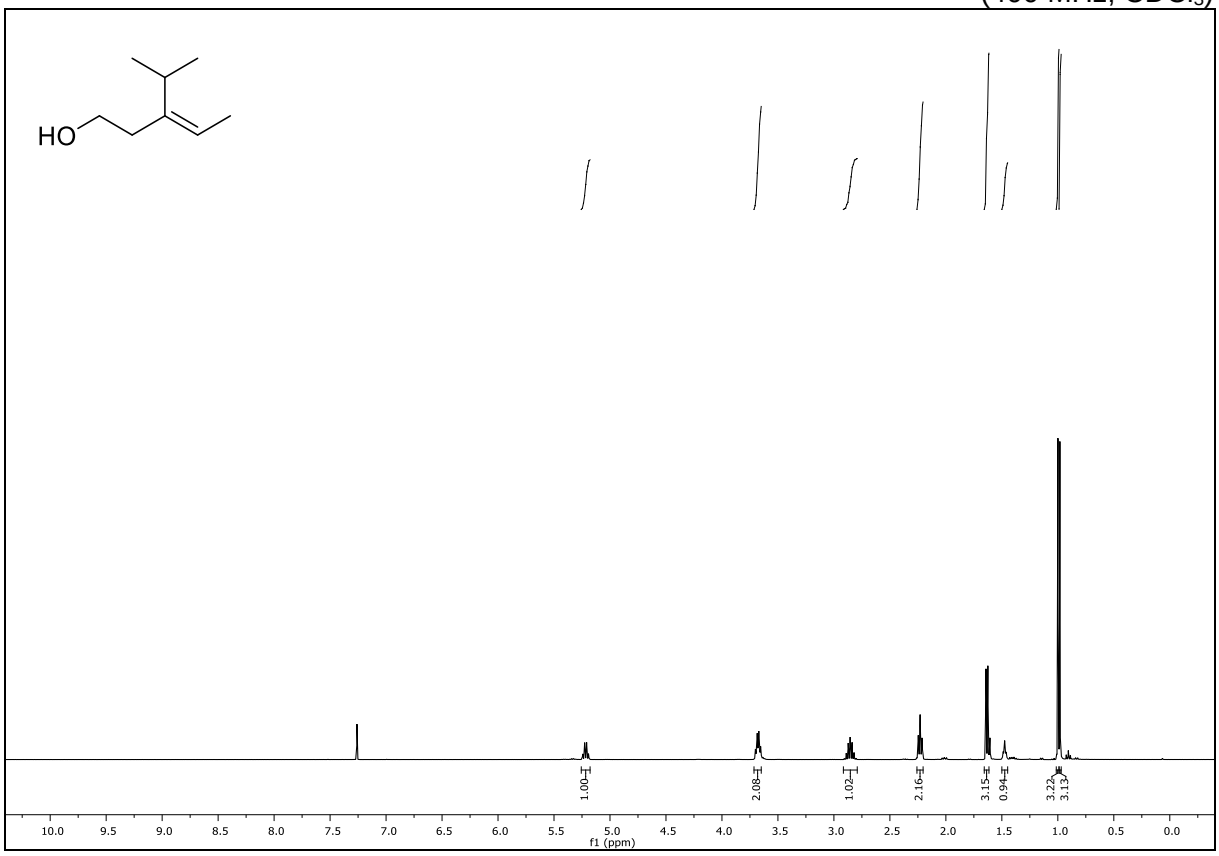


(101 MHz, $CDCl_3$)

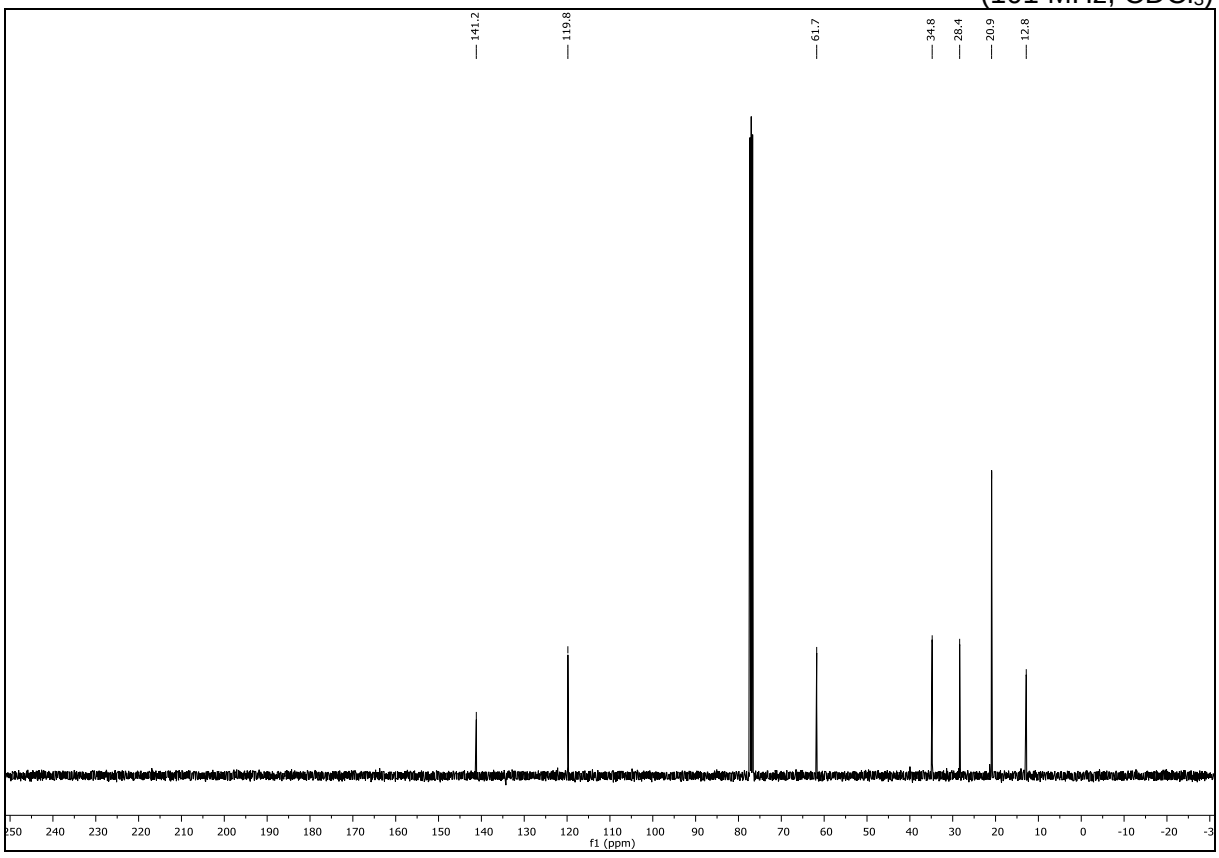


(*Z*)-3-Isopropylpent-3-en-1-ol (1a)

(400 MHz, $CDCl_3$)

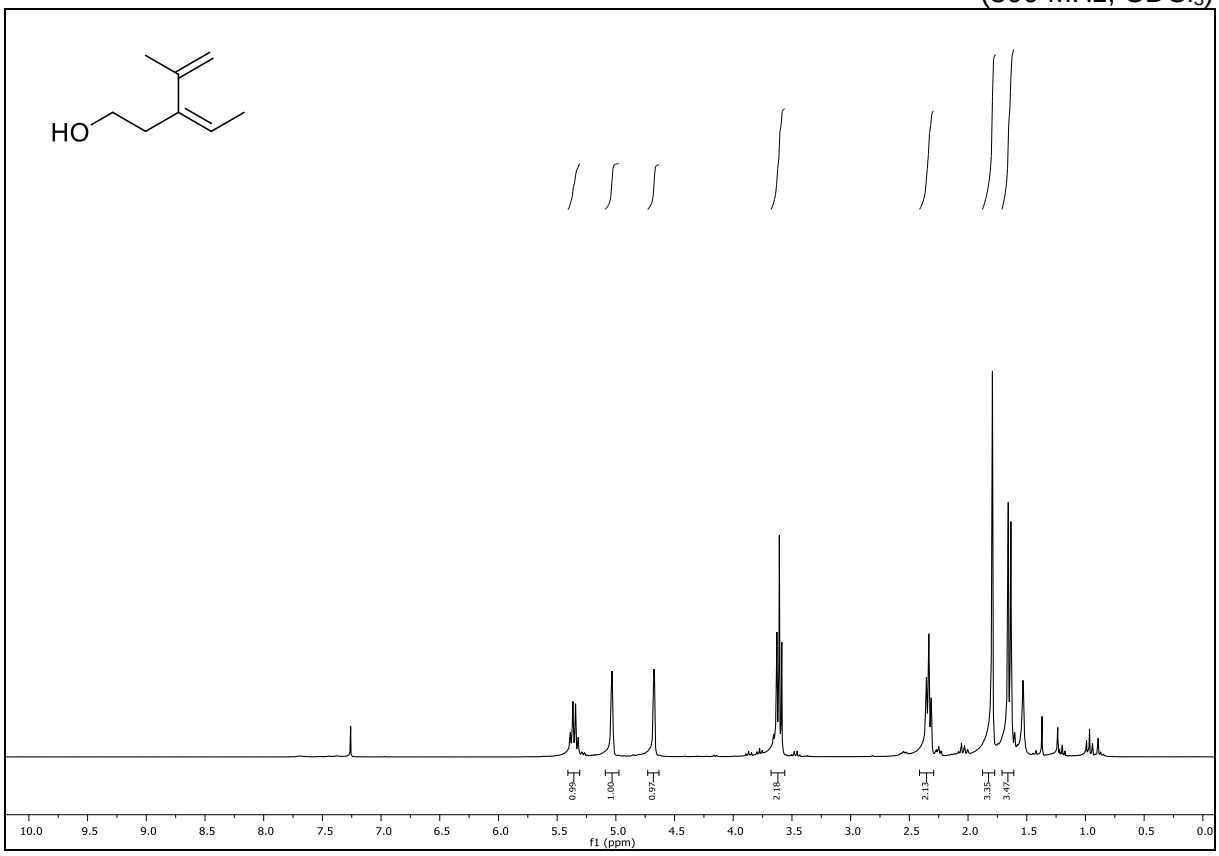


(101 MHz, $CDCl_3$)

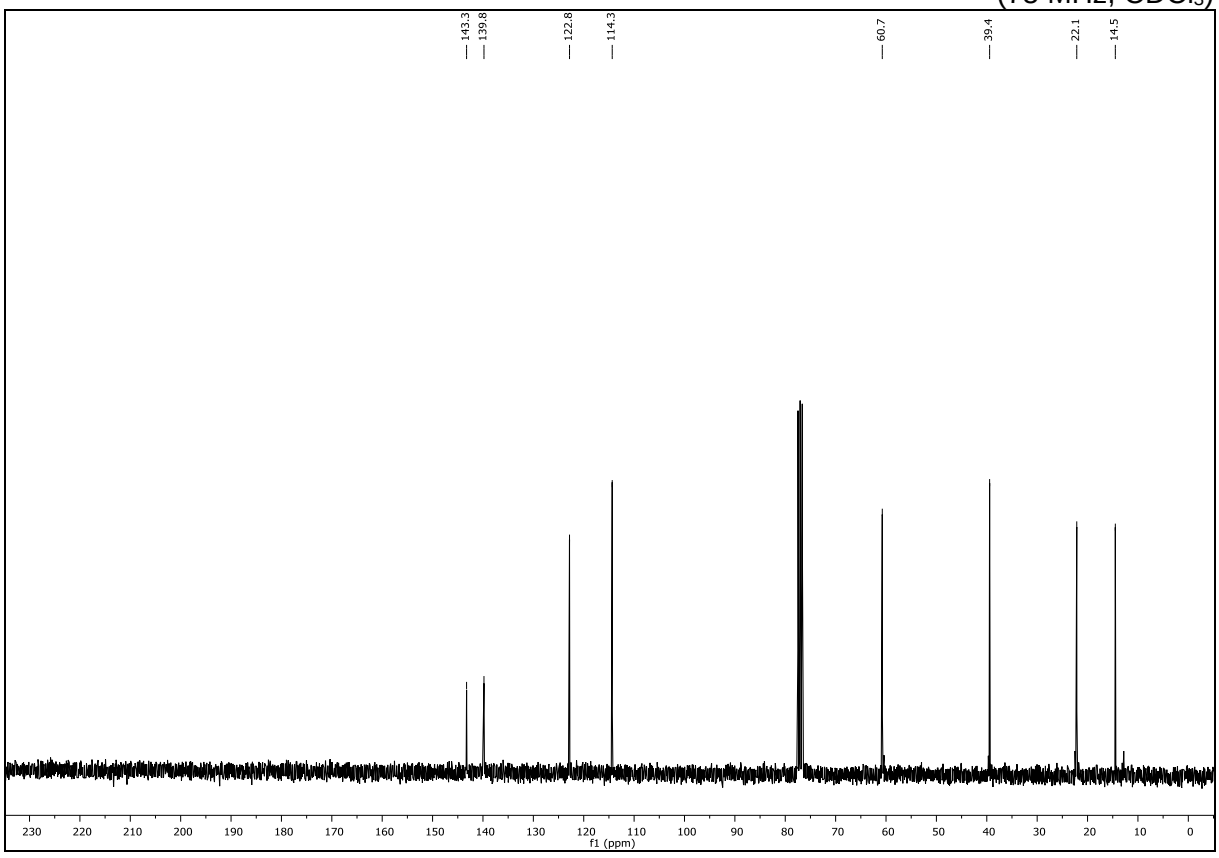


(*Z*)-3-(prop-1-en-2-yl)pent-3-en-1-ol (1b)

(300 MHz, $CDCl_3$)

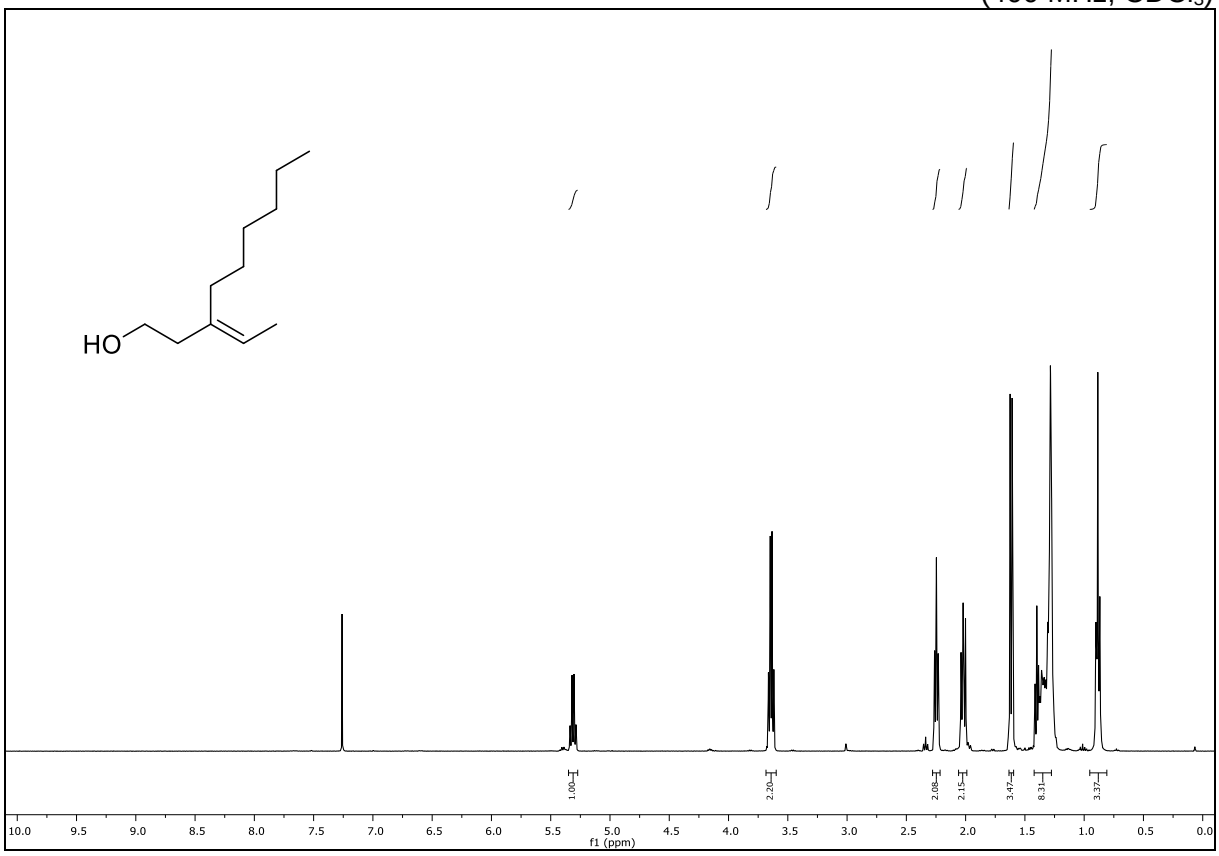


(75 MHz, $CDCl_3$)

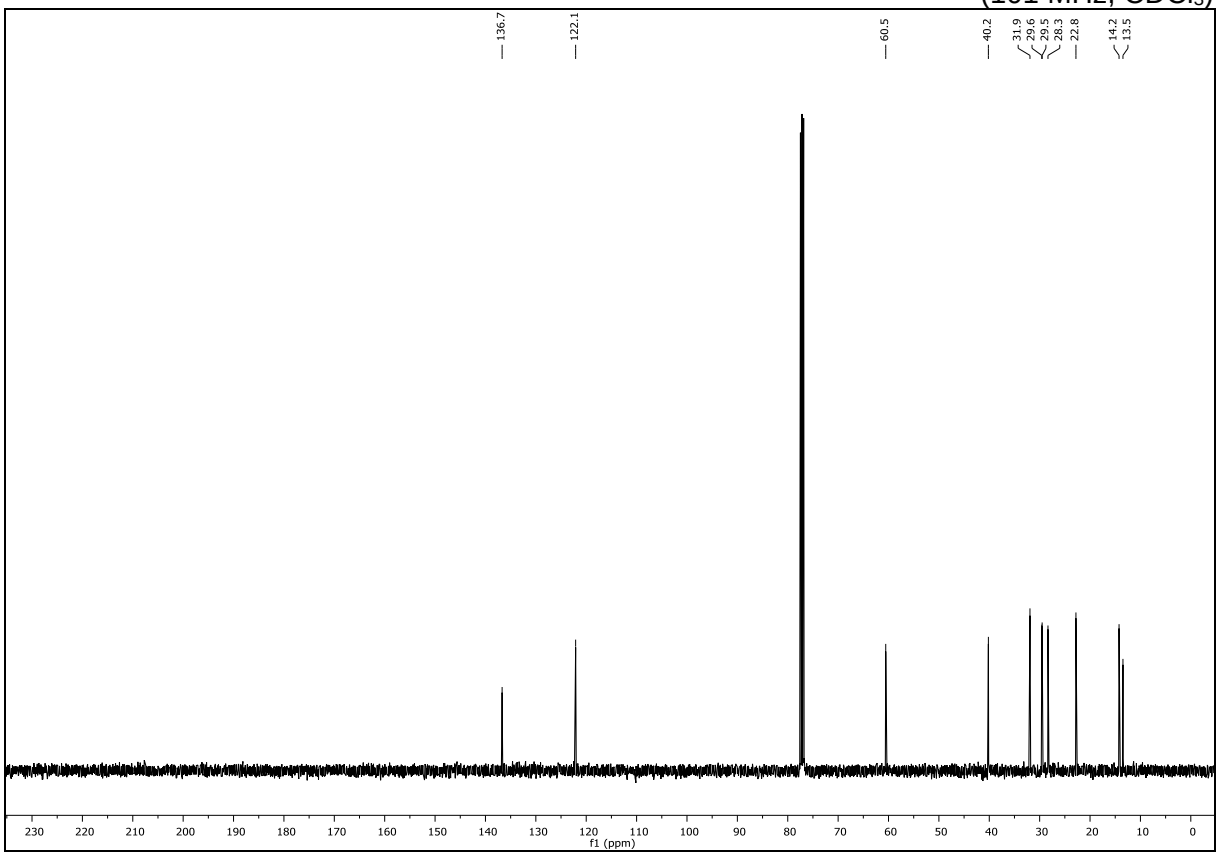


(*E*)-3-ethylidenenonan-1-ol (1c)

(400 MHz, $CDCl_3$)



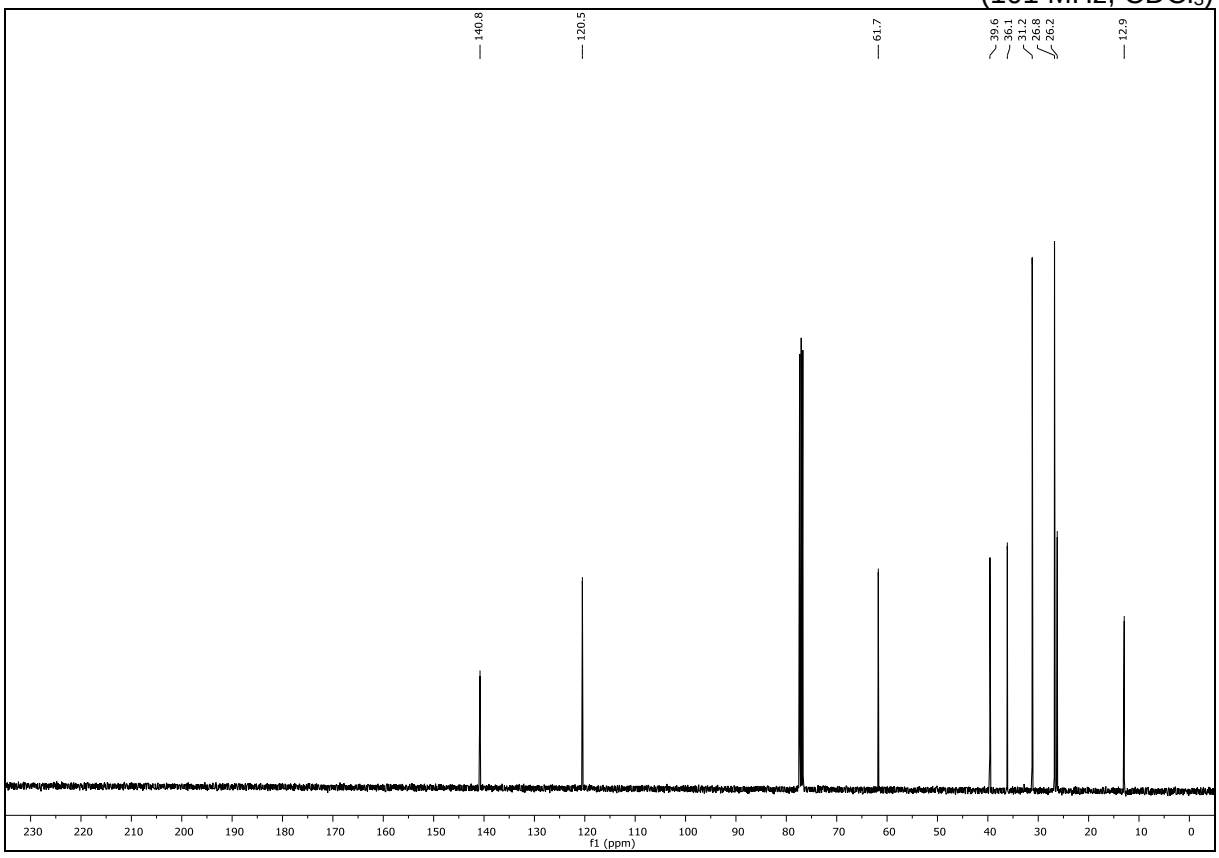
(101 MHz, $CDCl_3$)



(*Z*)-3-cyclohexylpent-3-en-1-ol (1d)

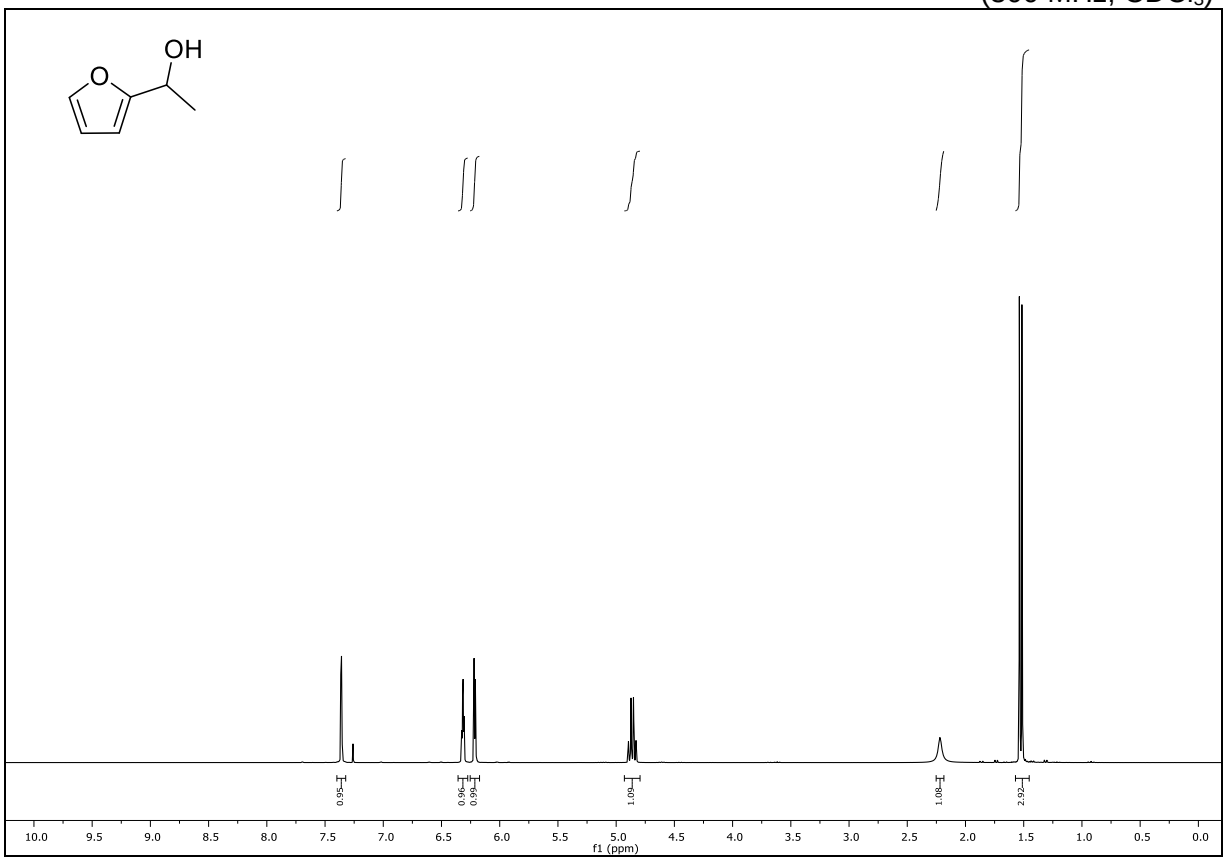
(400 MHz, $CDCl_3$)

(101 MHz, $CDCl_3$)

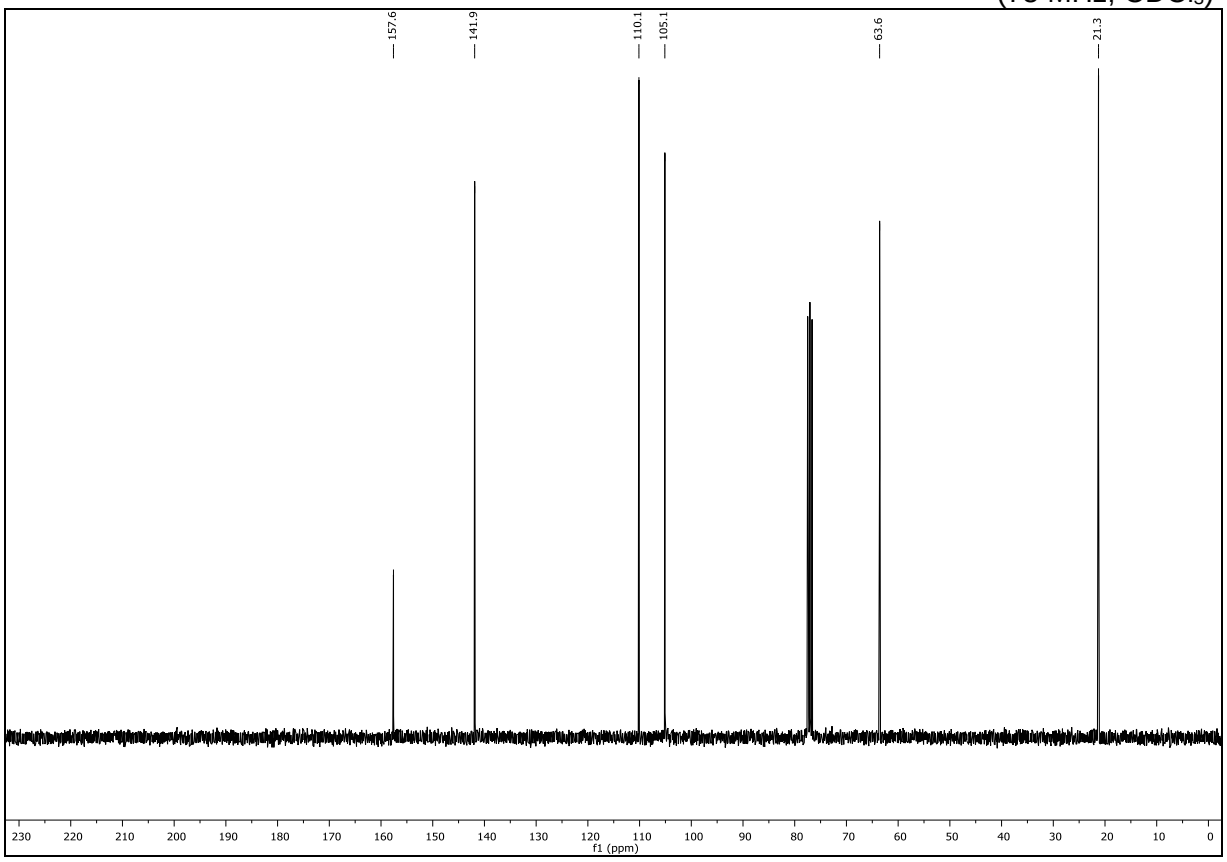


(±)-1-(furan-2-yl)ethan-1-ol ((±)-81f)

(300 MHz, $CDCl_3$)

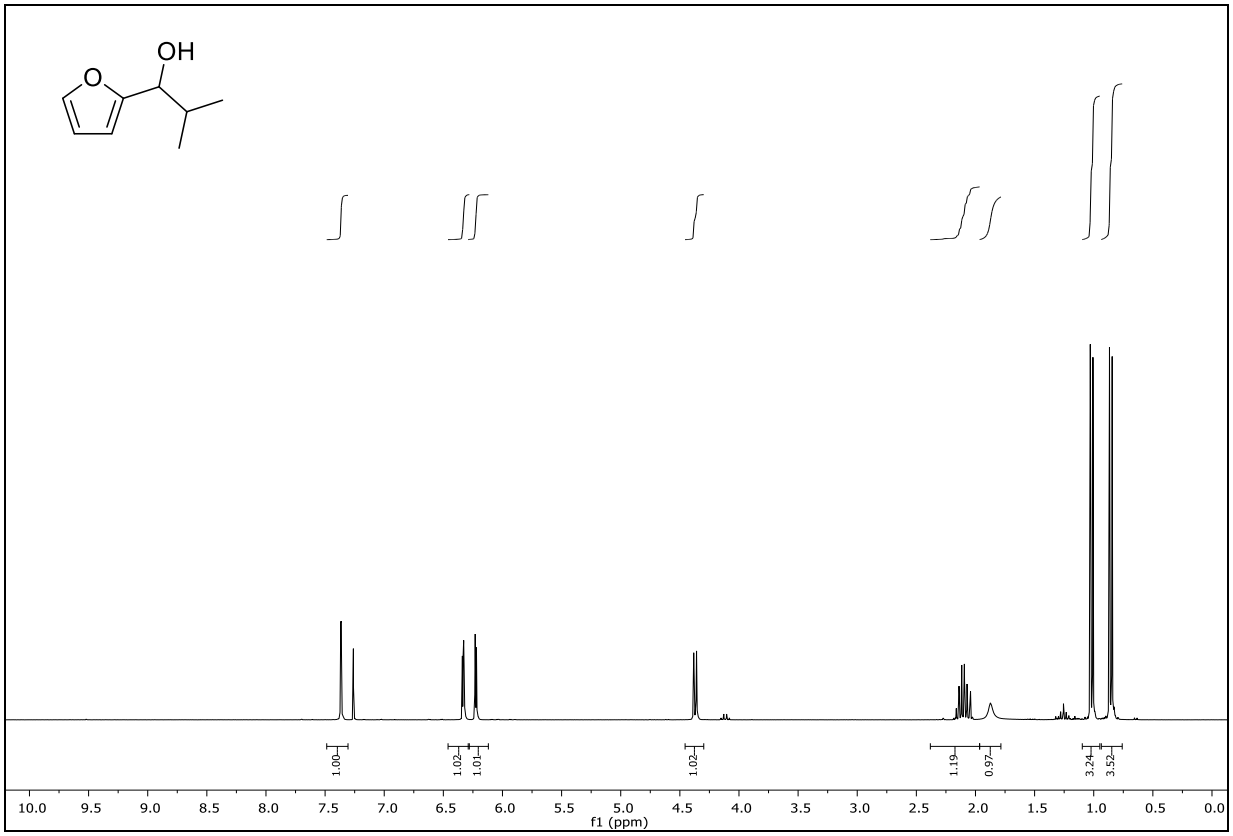


(75 MHz, $CDCl_3$)

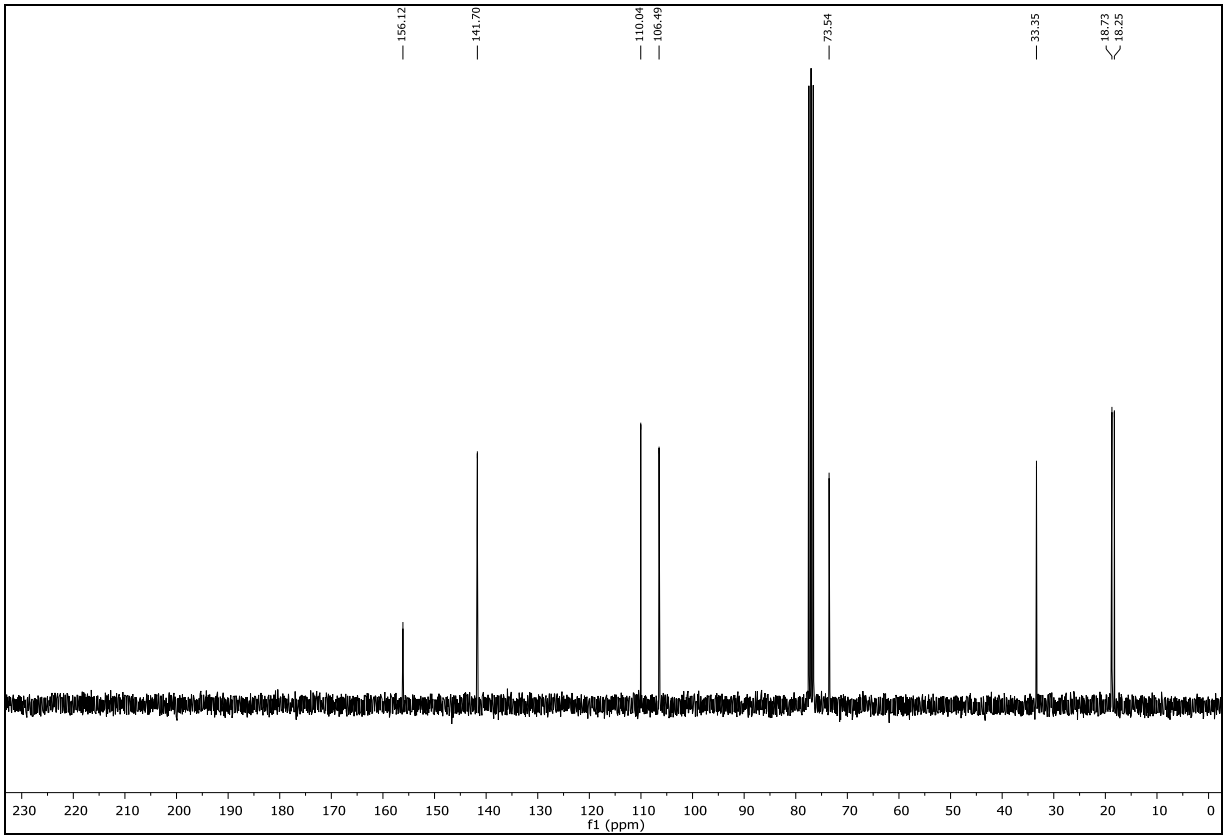


1-(furan-2-yl)-2-methylpropan-1-ol ((±)-81g)

(300 MHz, $CDCl_3$)

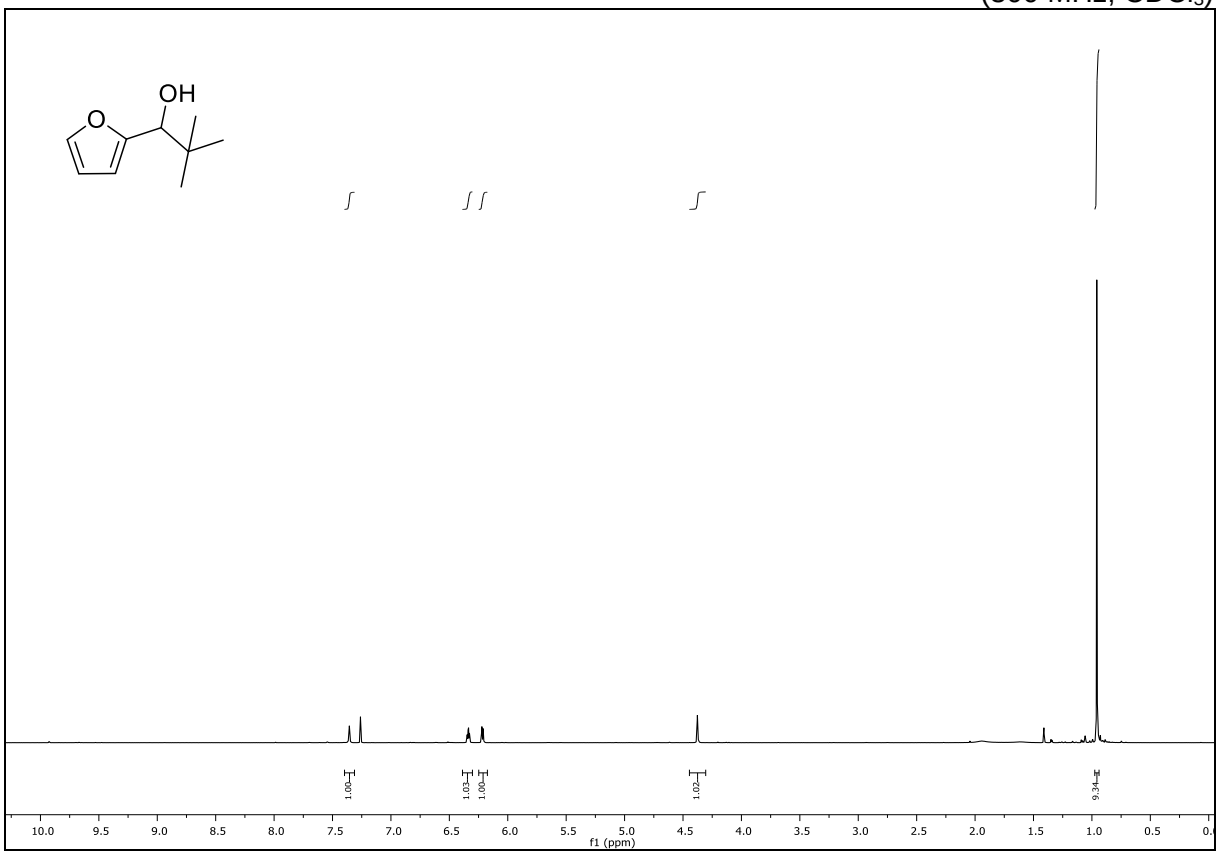


(75 MHz, $CDCl_3$)

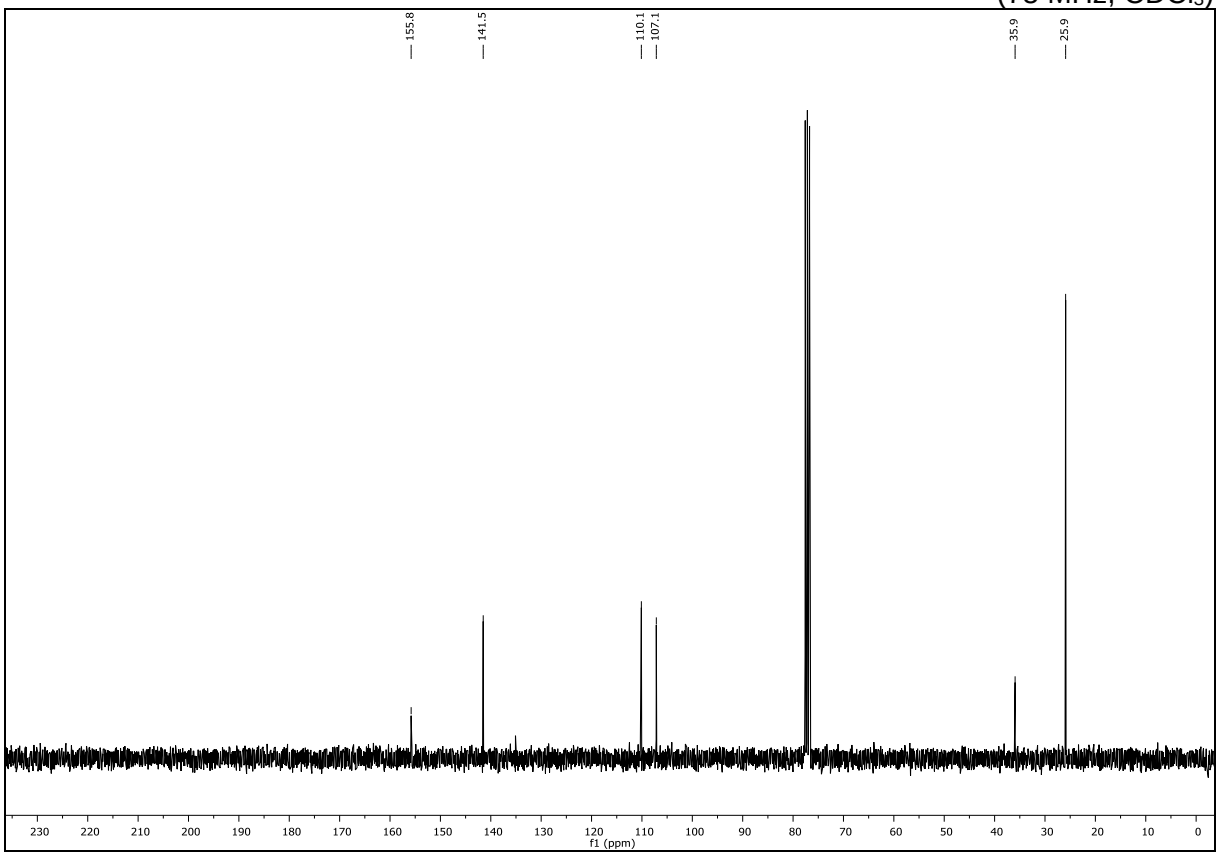


(±)-1-(furan-2-yl)-2,2-dimethylpropan-1-ol ((±)-81h)

(300 MHz, $CDCl_3$)

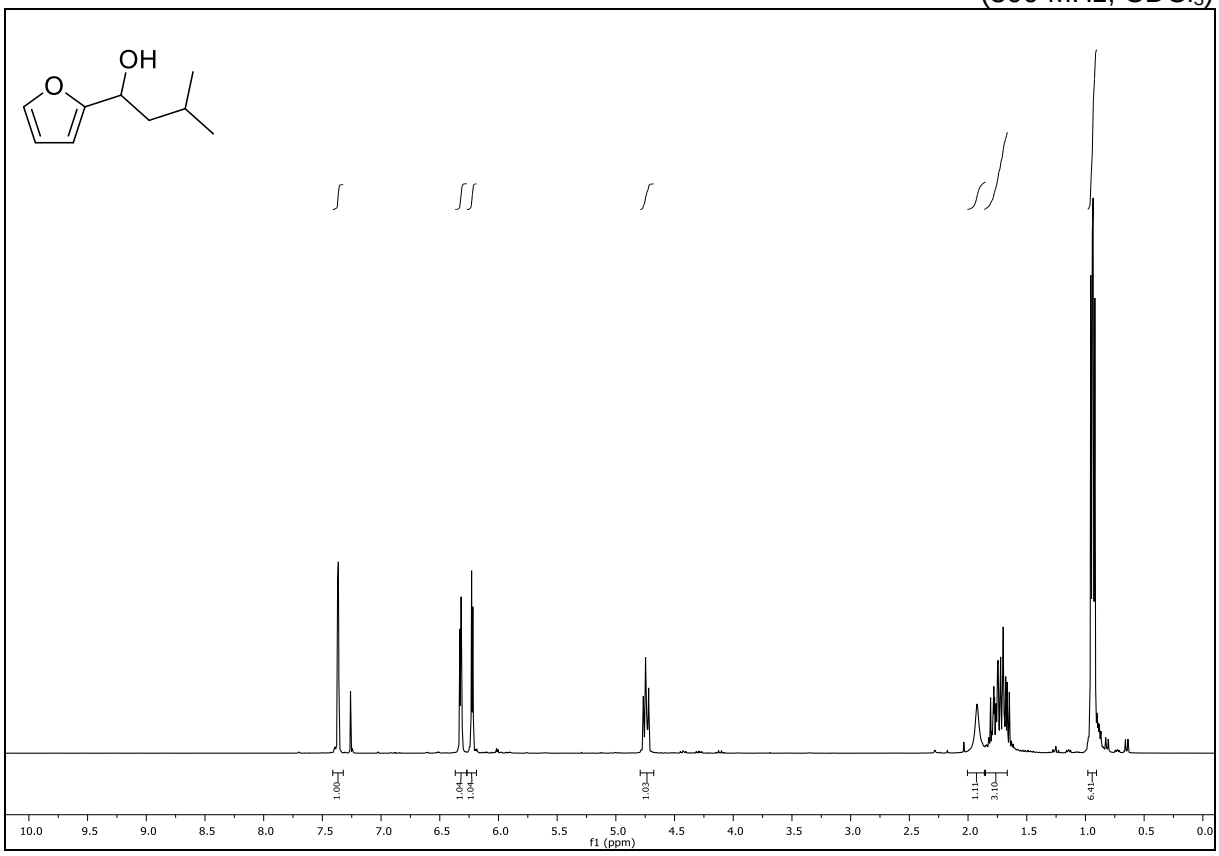


(75 MHz, $CDCl_3$)

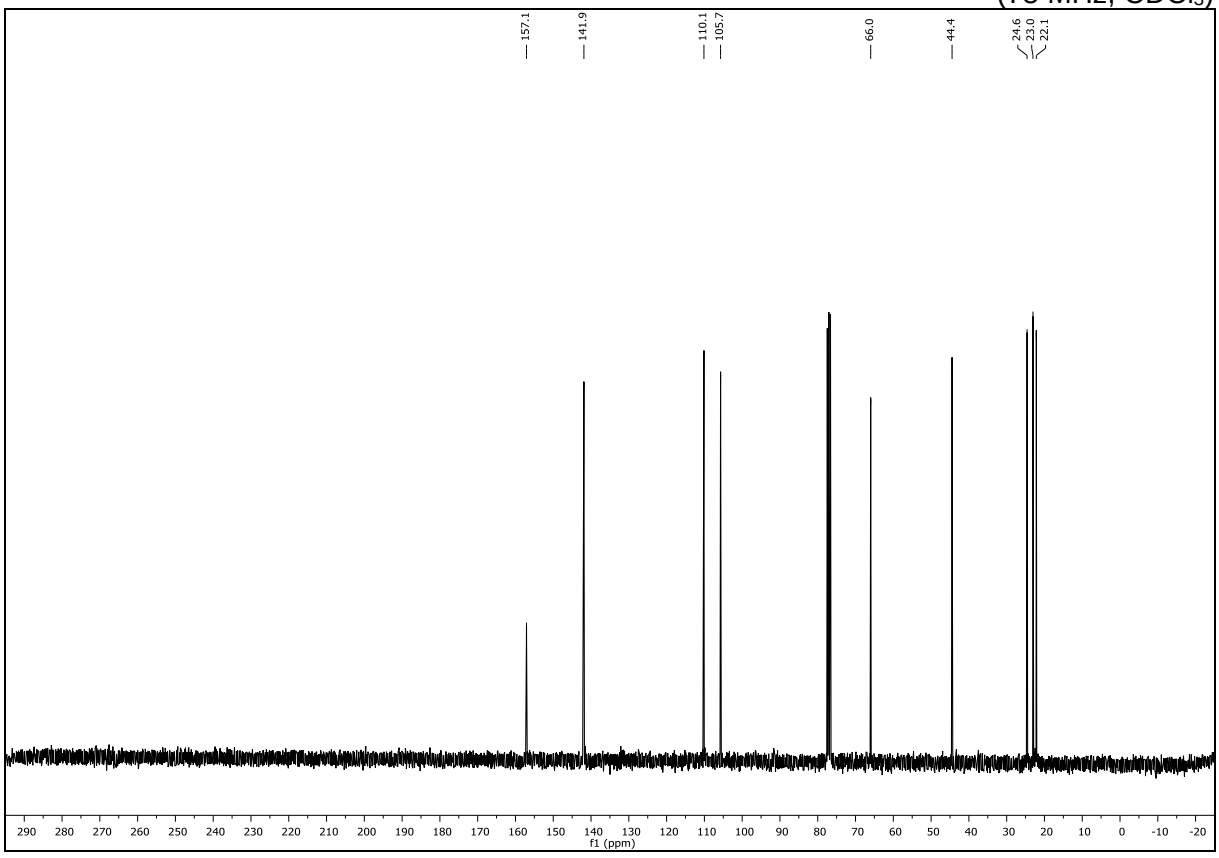


(±)-1-(furan-2-yl)-3-methylbutan-1-ol ((±)-81i)

(300 MHz, $CDCl_3$)

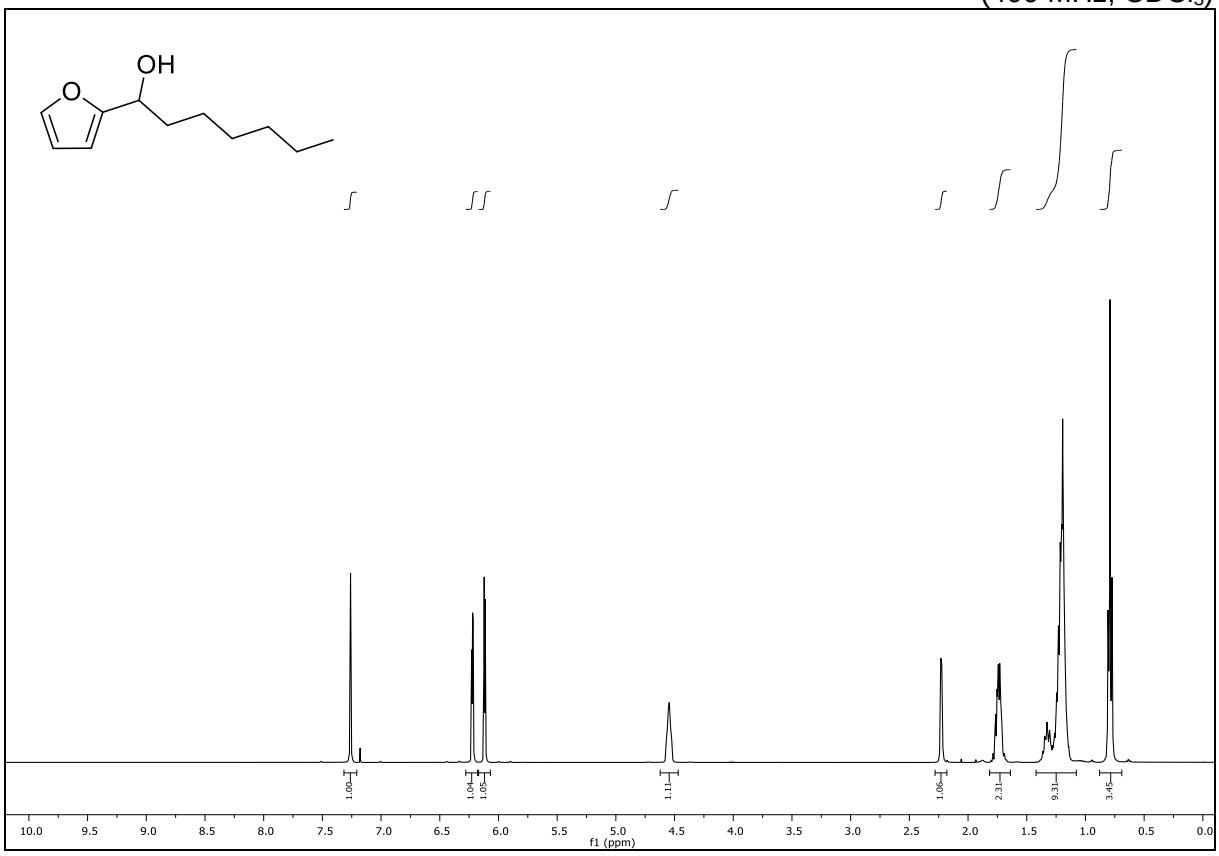


(75 MHz, $CDCl_3$)

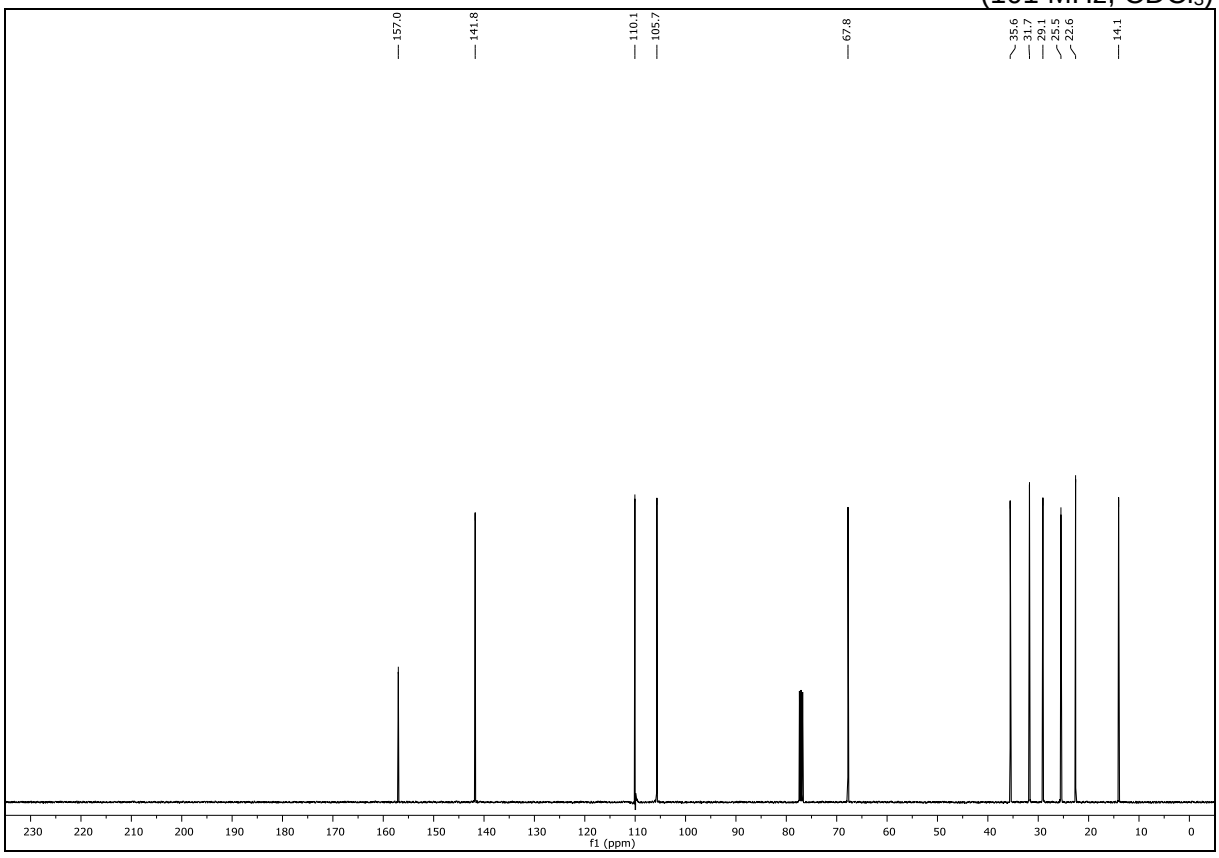


(±)-1-(furan-2-yl)heptan-1-ol ((±)-81k)

(400 MHz, $CDCl_3$)

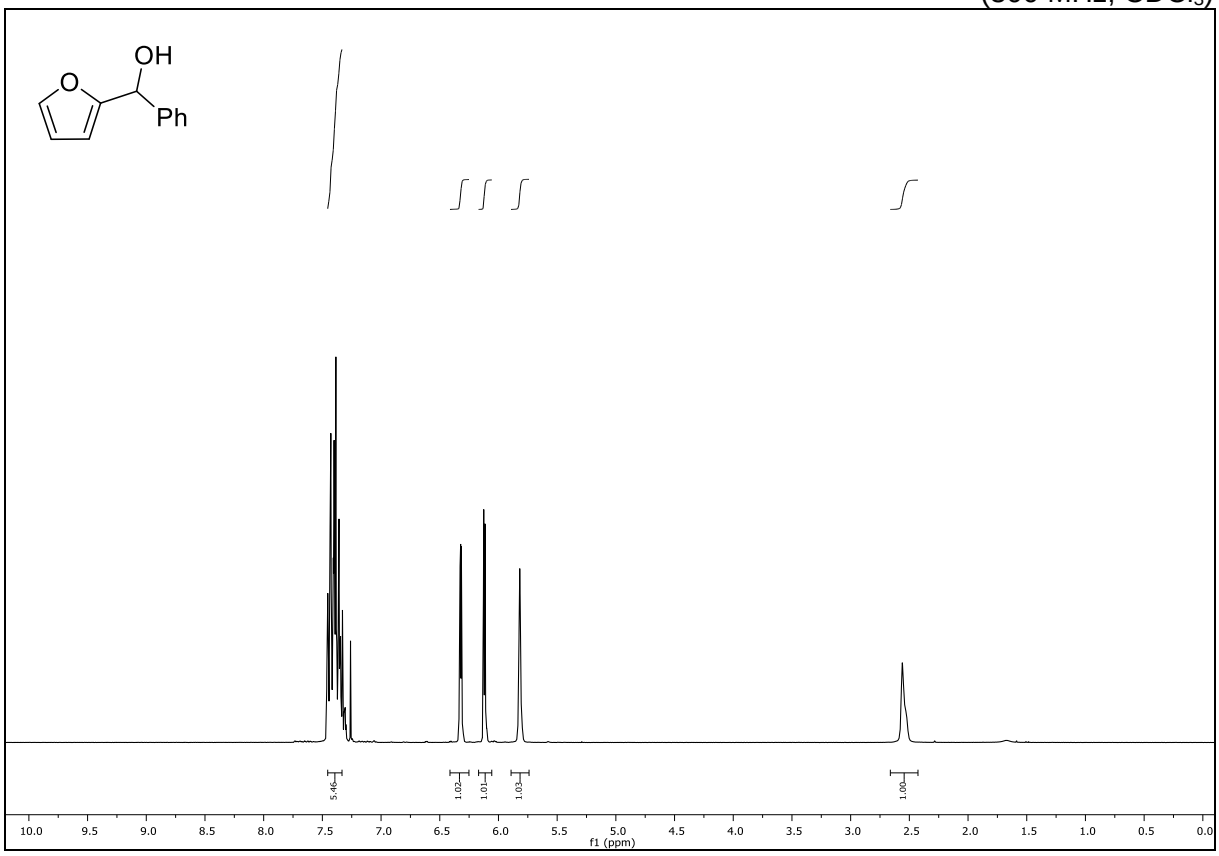


(101 MHz, $CDCl_3$)

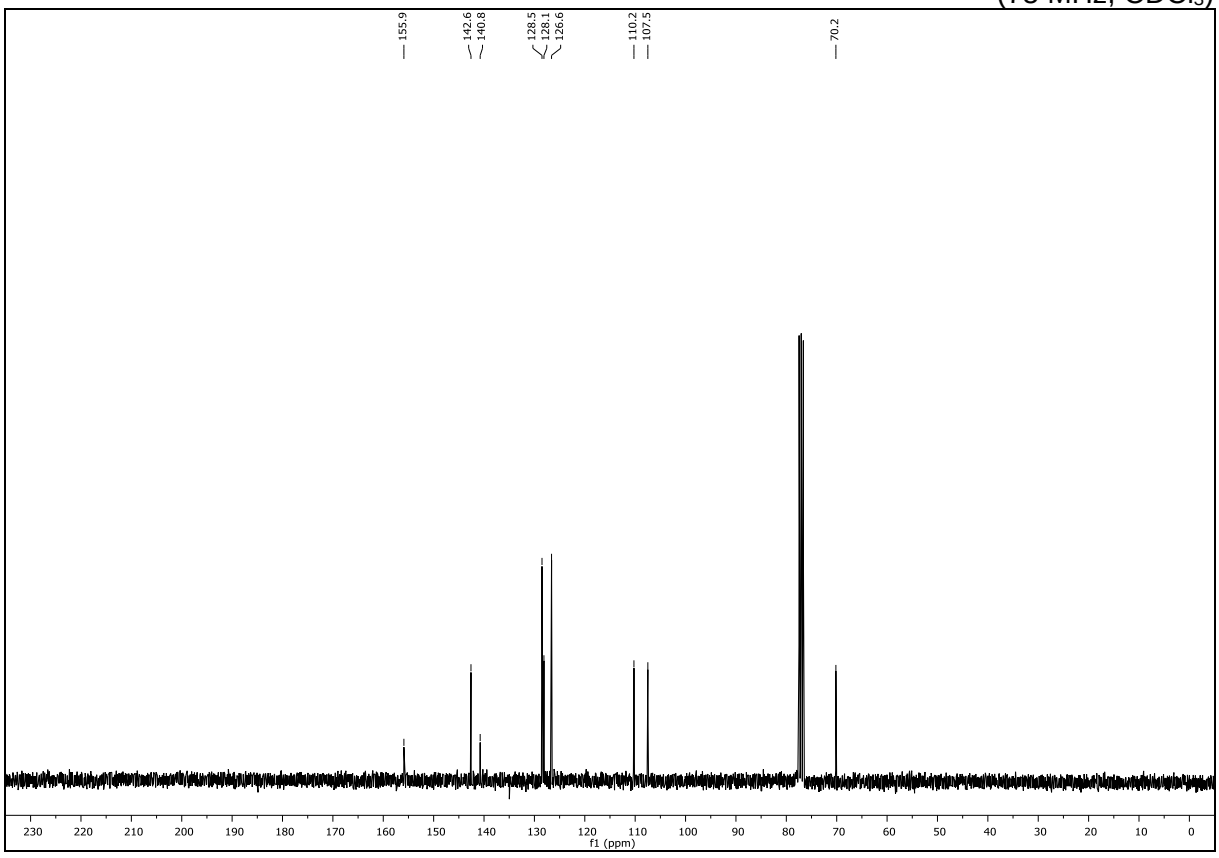


(±)-furan-2-yl(phenyl)methanol ((±)-81l)

(300 MHz, $CDCl_3$)

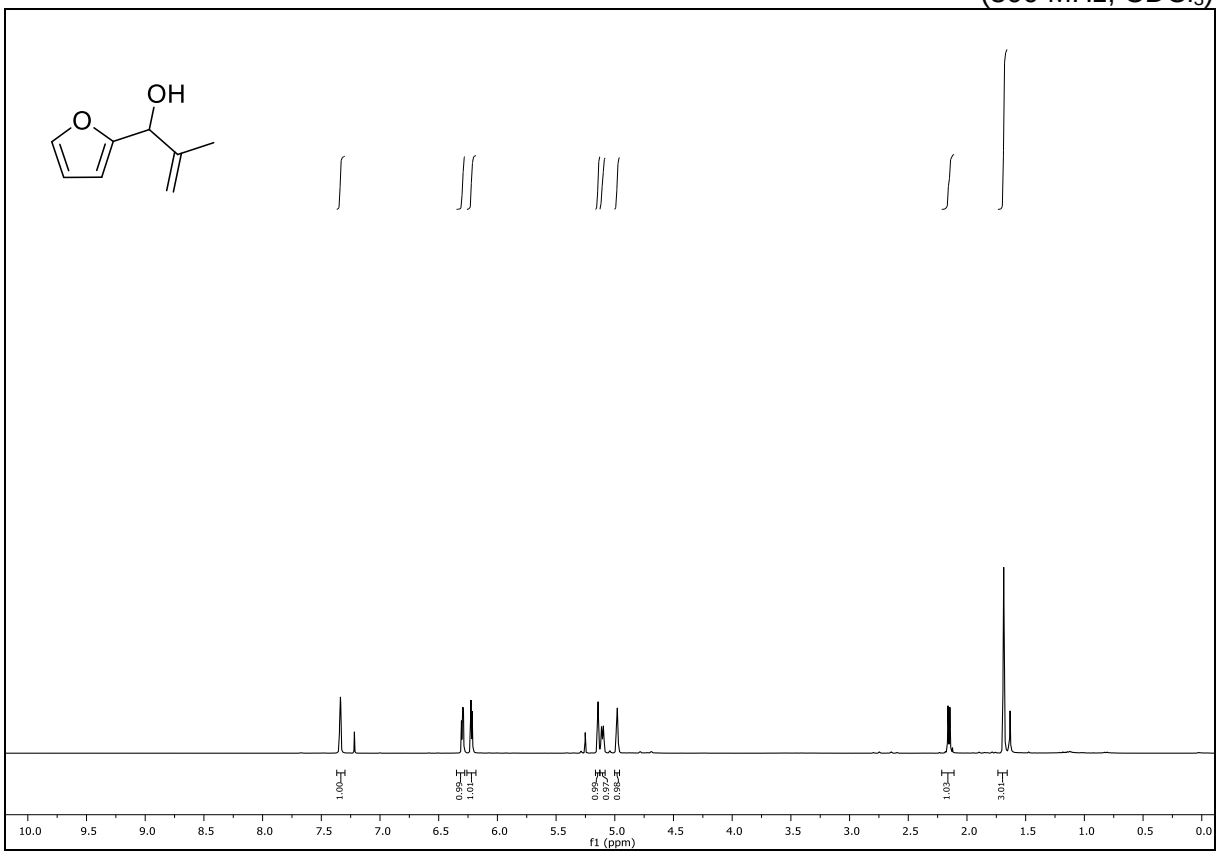


(75 MHz, $CDCl_3$)

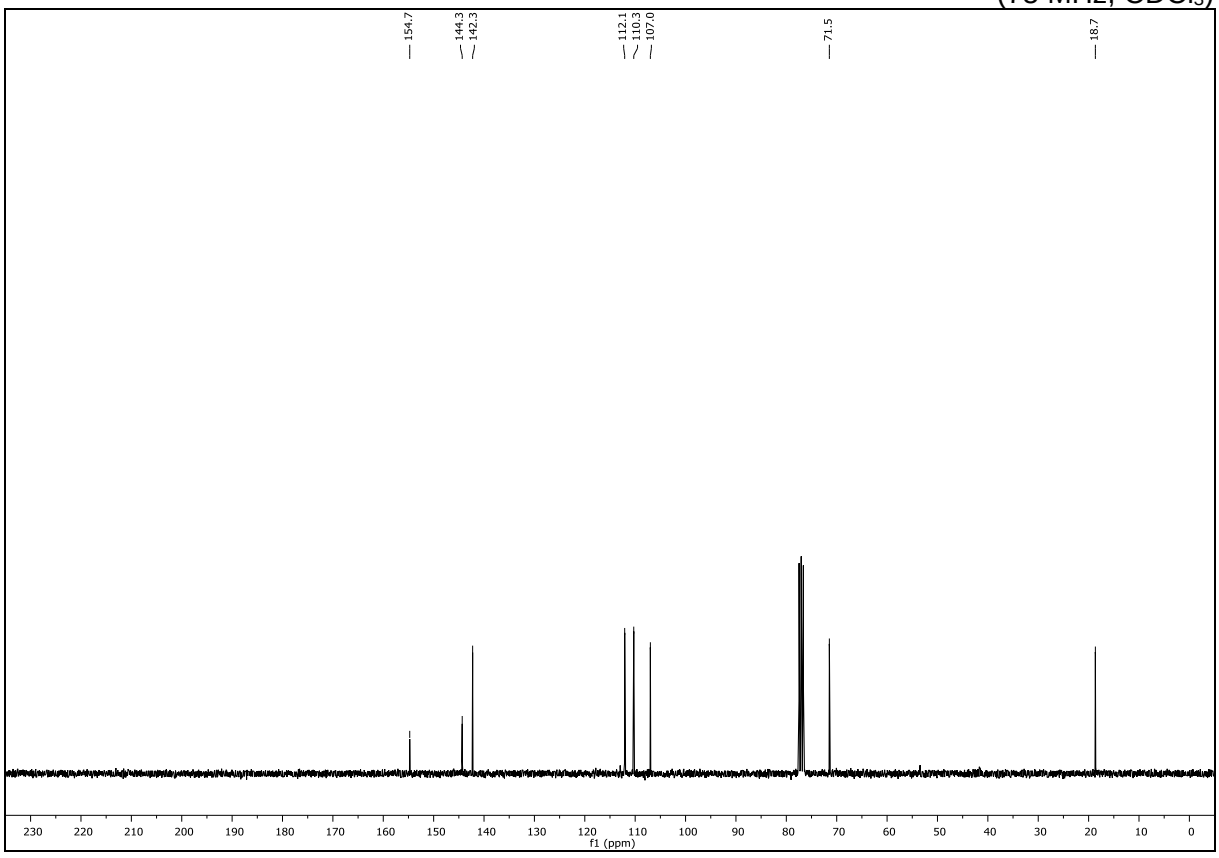


(±)-1-(furan-2-yl)-2-methylprop-2-en-1-ol ((±)-81m)

(300 MHz, $CDCl_3$)

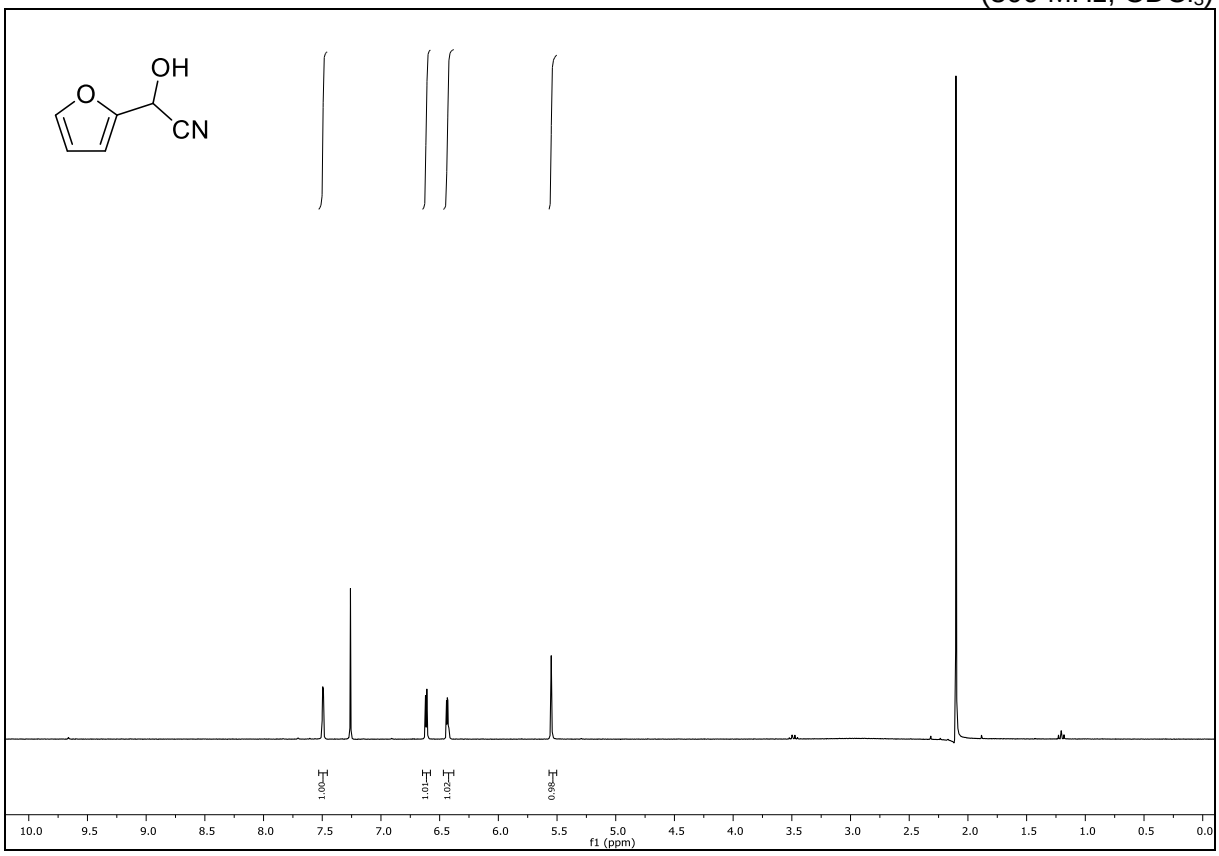


(75 MHz, $CDCl_3$)

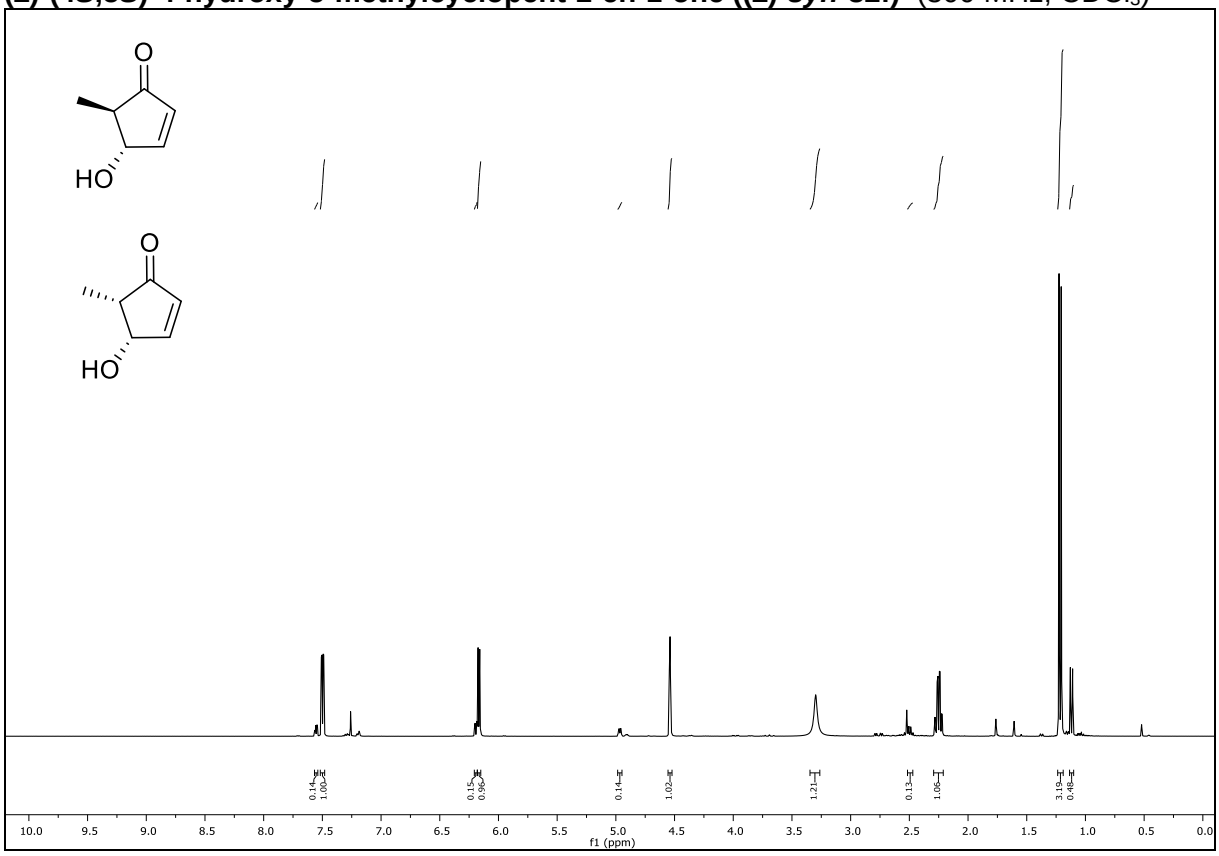


(±)-2-(furan-2-yl)-2-hydroxyacetonitrile ((±)-81n)

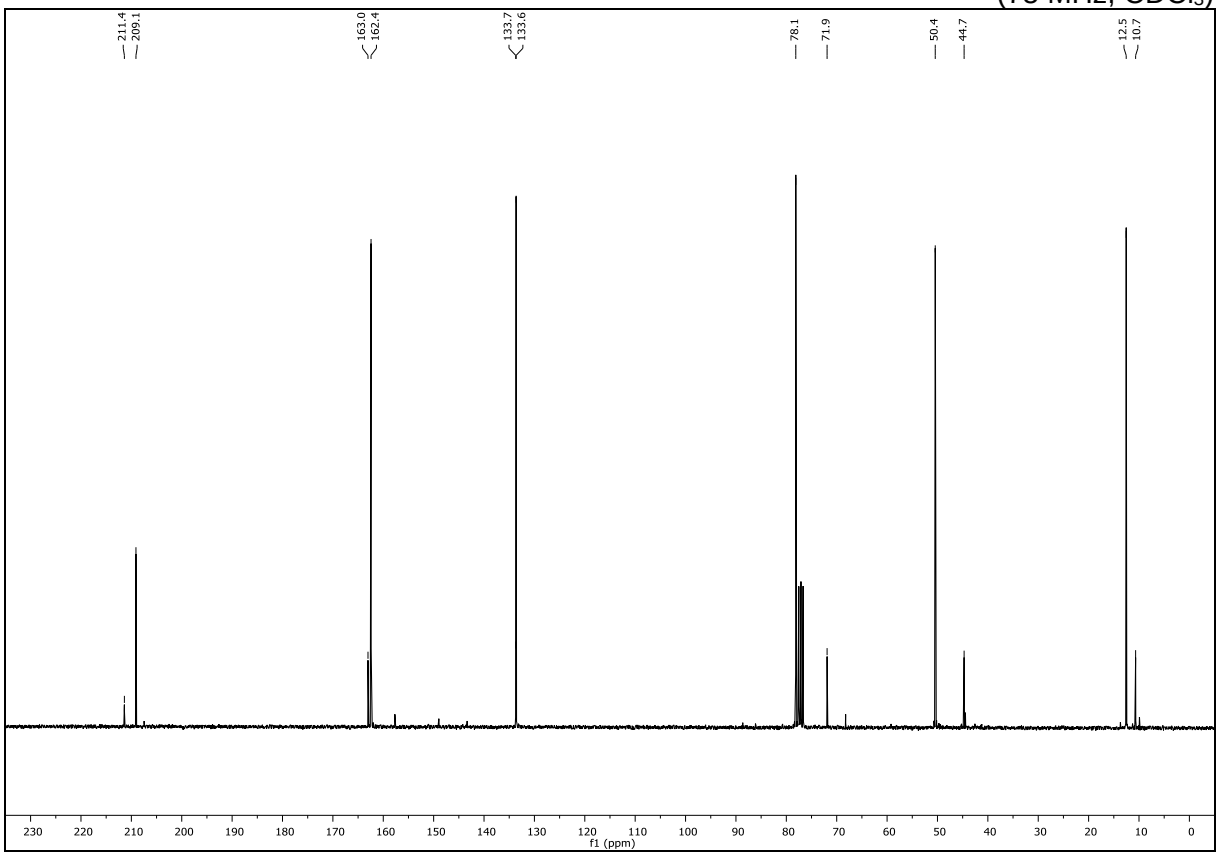
(300 MHz, $CDCl_3$)



(±)-(4*S*,5*R*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-82f)
(±)-(4*S*,5*S*)-4-hydroxy-5-methylcyclopent-2-en-1-one ((±)-s*yn*-82f) (300 MHz, $CDCl_3$)

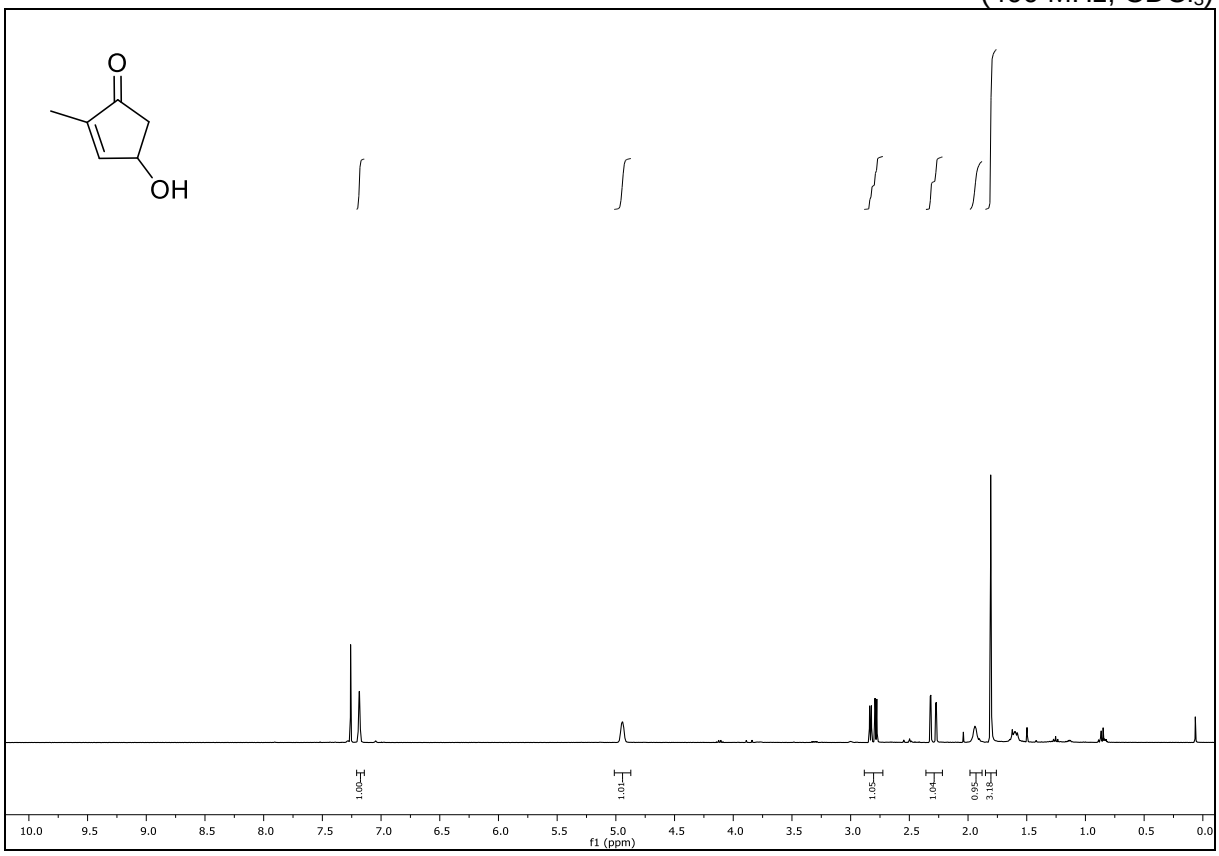


(75 MHz, $CDCl_3$)

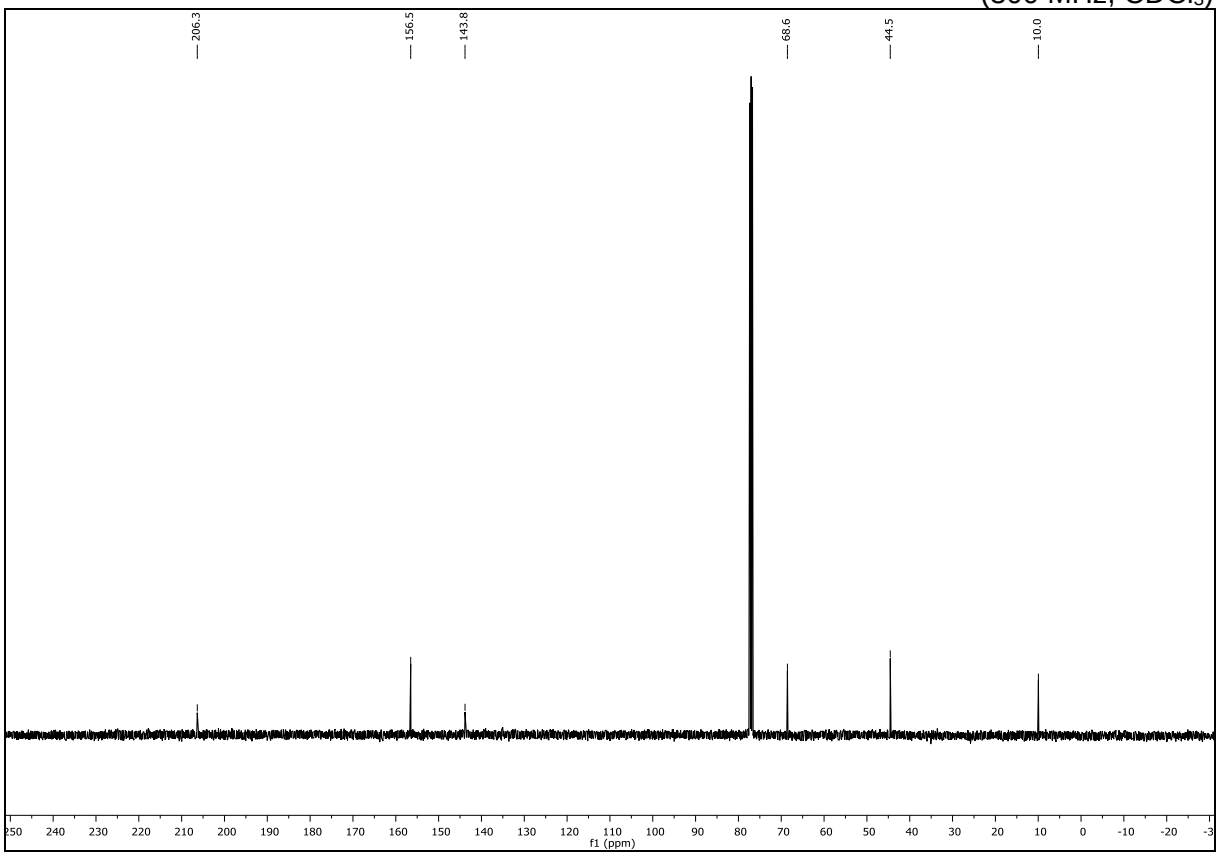


(±)-4-hydroxy-2-methylcyclopent-2-en-1-one ((±)-163)

(400 MHz, $CDCl_3$)

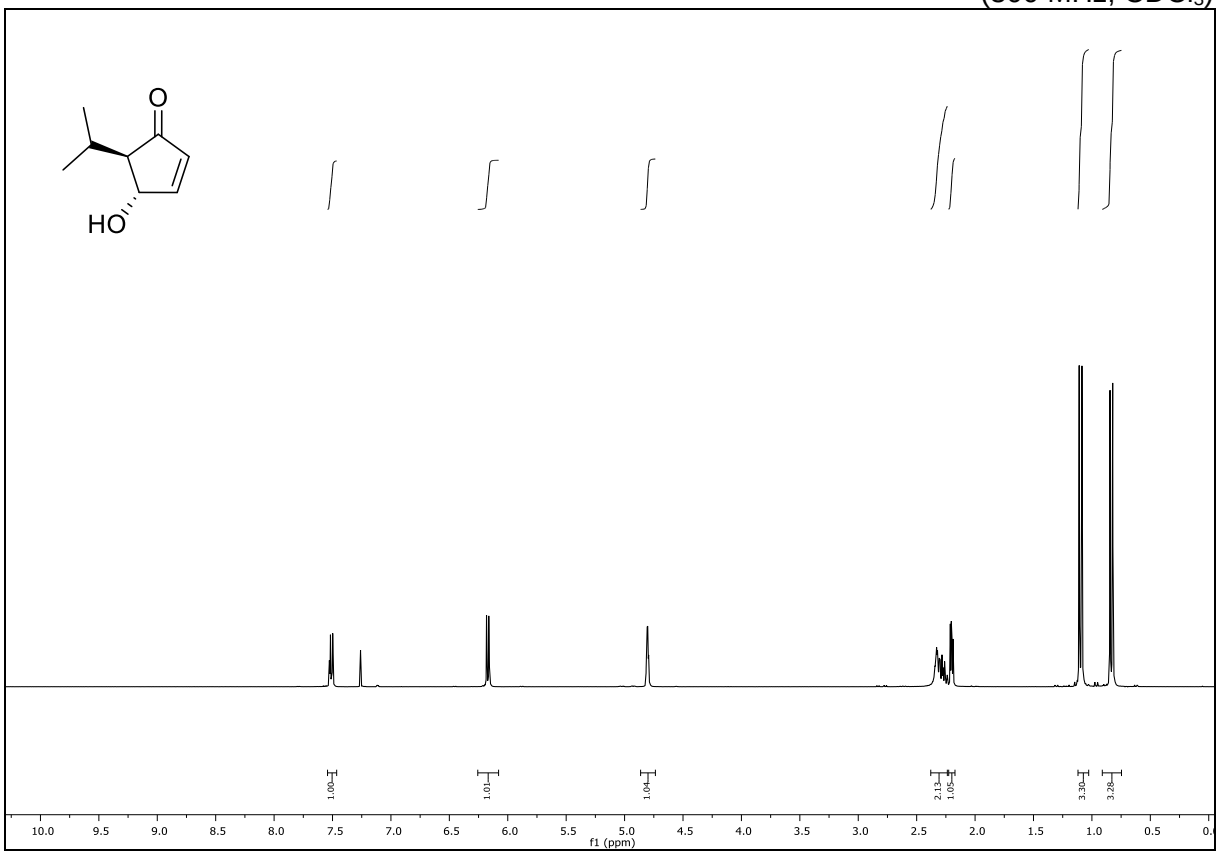


(300 MHz, $CDCl_3$)

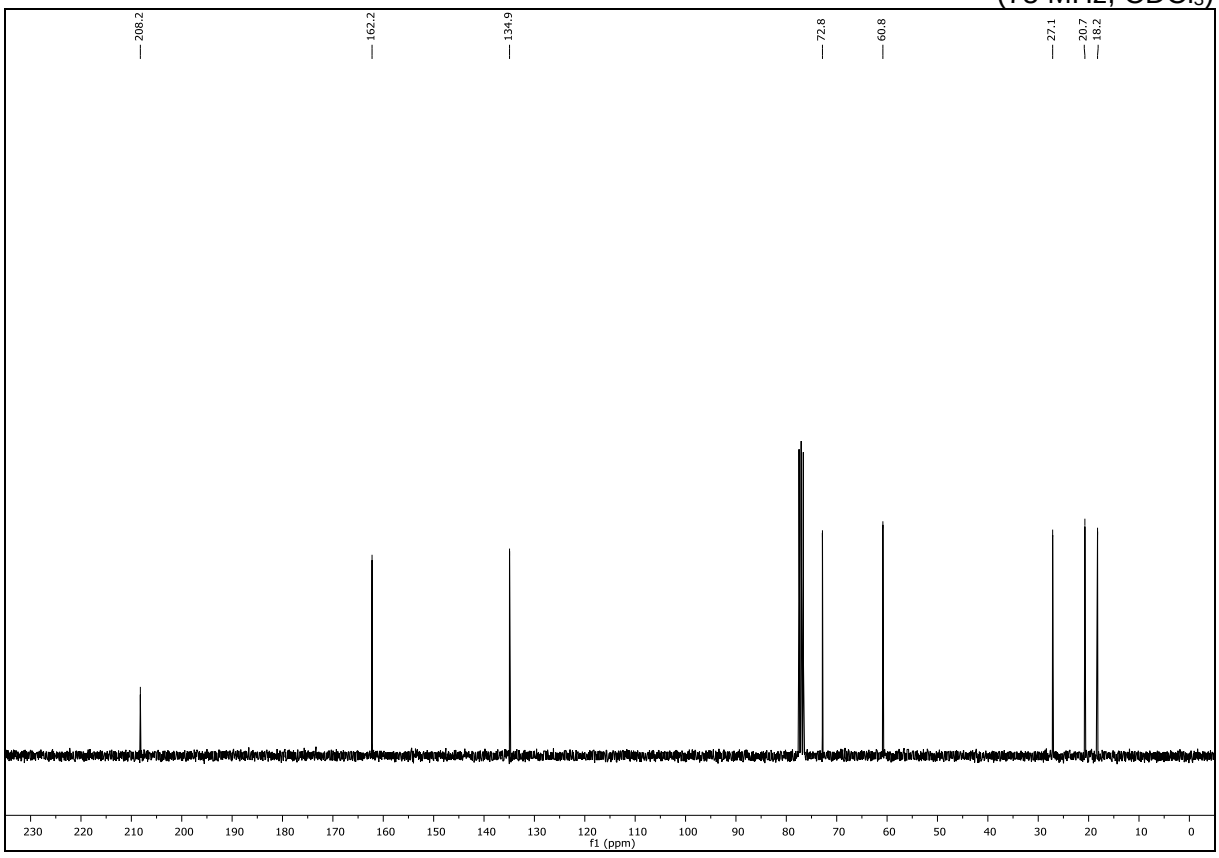


(±)-(4*S*,5*R*)-4-hydroxy-5-isopropylcyclopent-2-en-1-one ((±)-82g)

(300 MHz, $CDCl_3$)

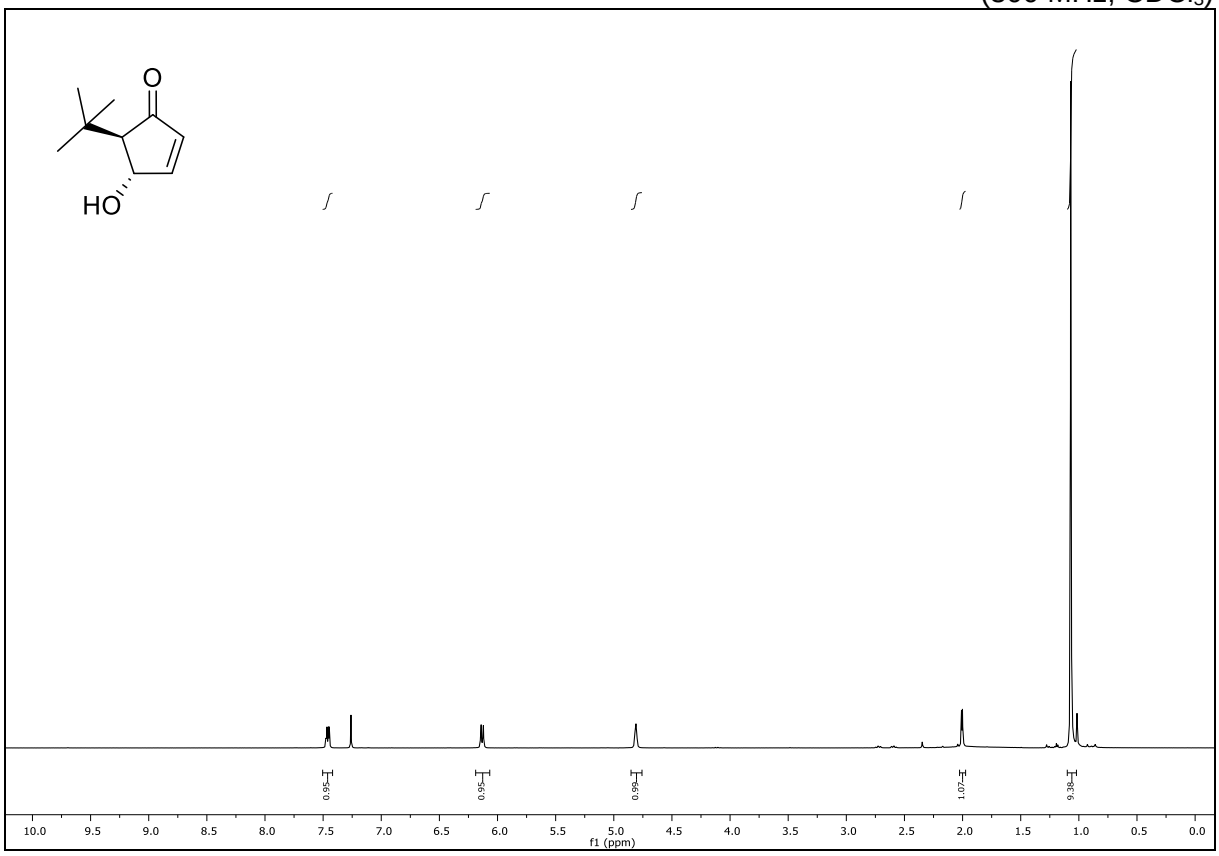


(75 MHz, $CDCl_3$)

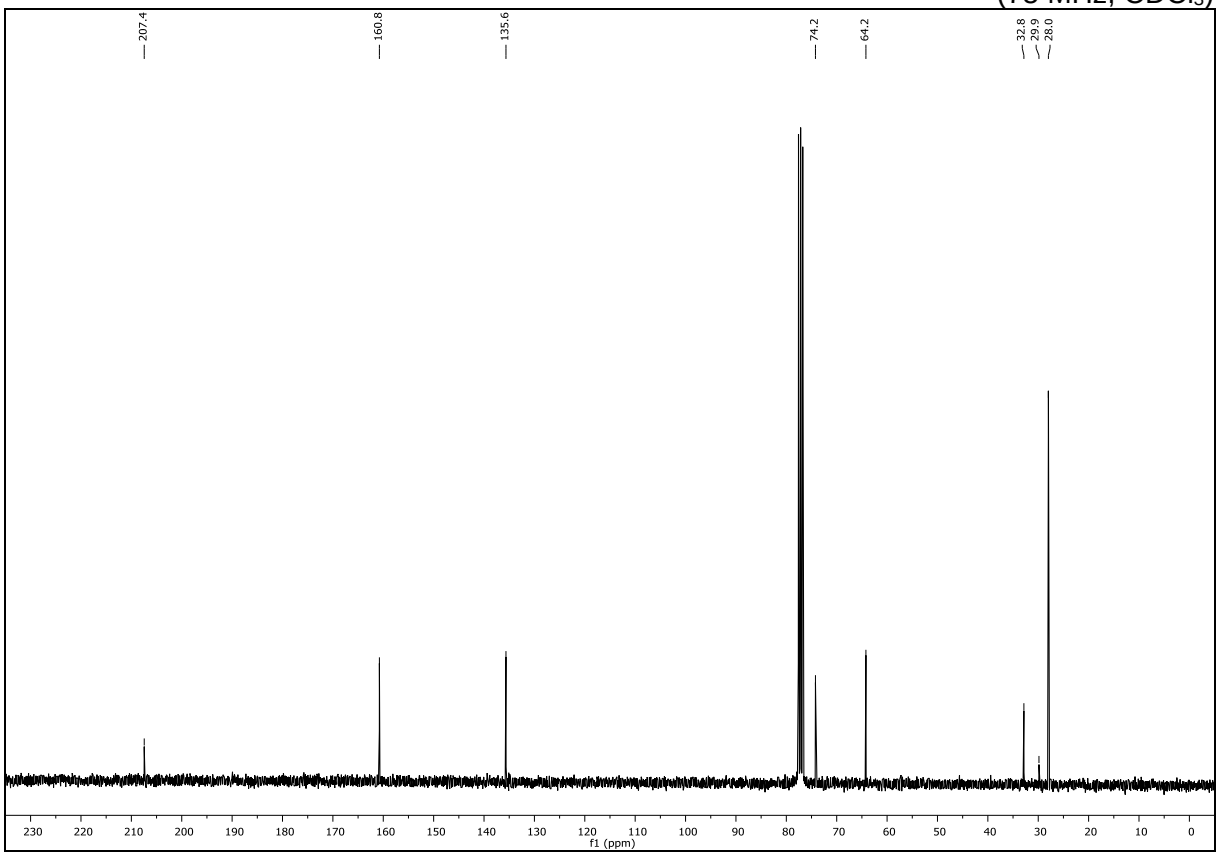


(±)-(4*S*,5*R*)-5-(*tert*-butyl)-4-hydroxycyclopent-2-en-1-one ((±)-82h)

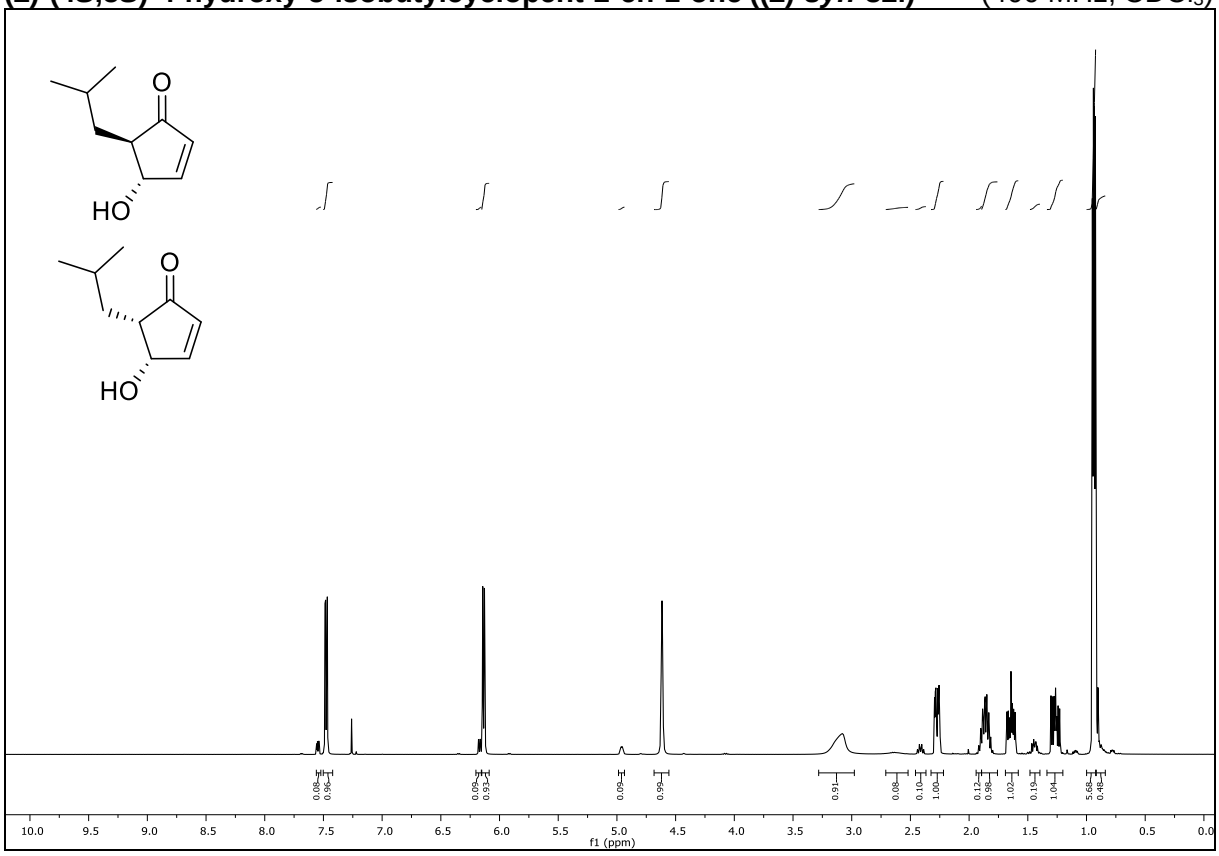
(300 MHz, $CDCl_3$)



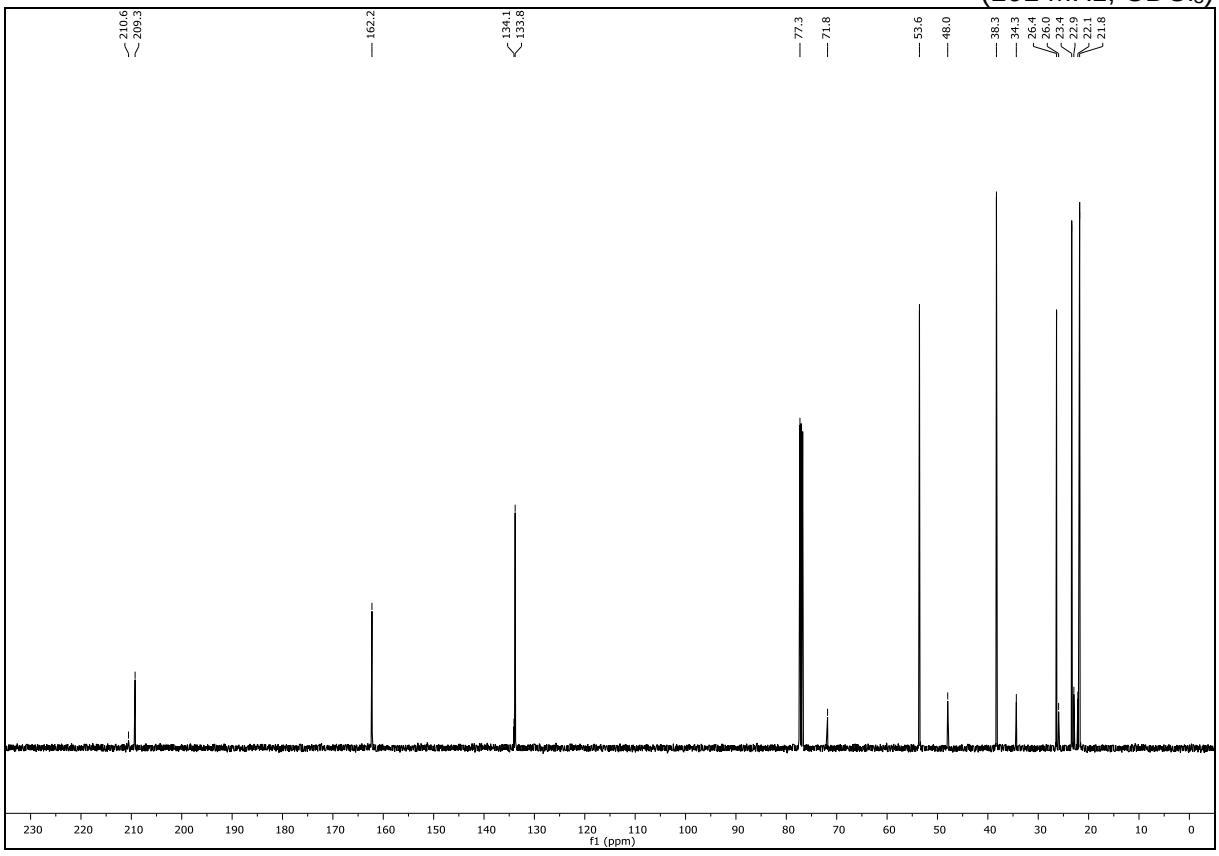
(75 MHz, $CDCl_3$)



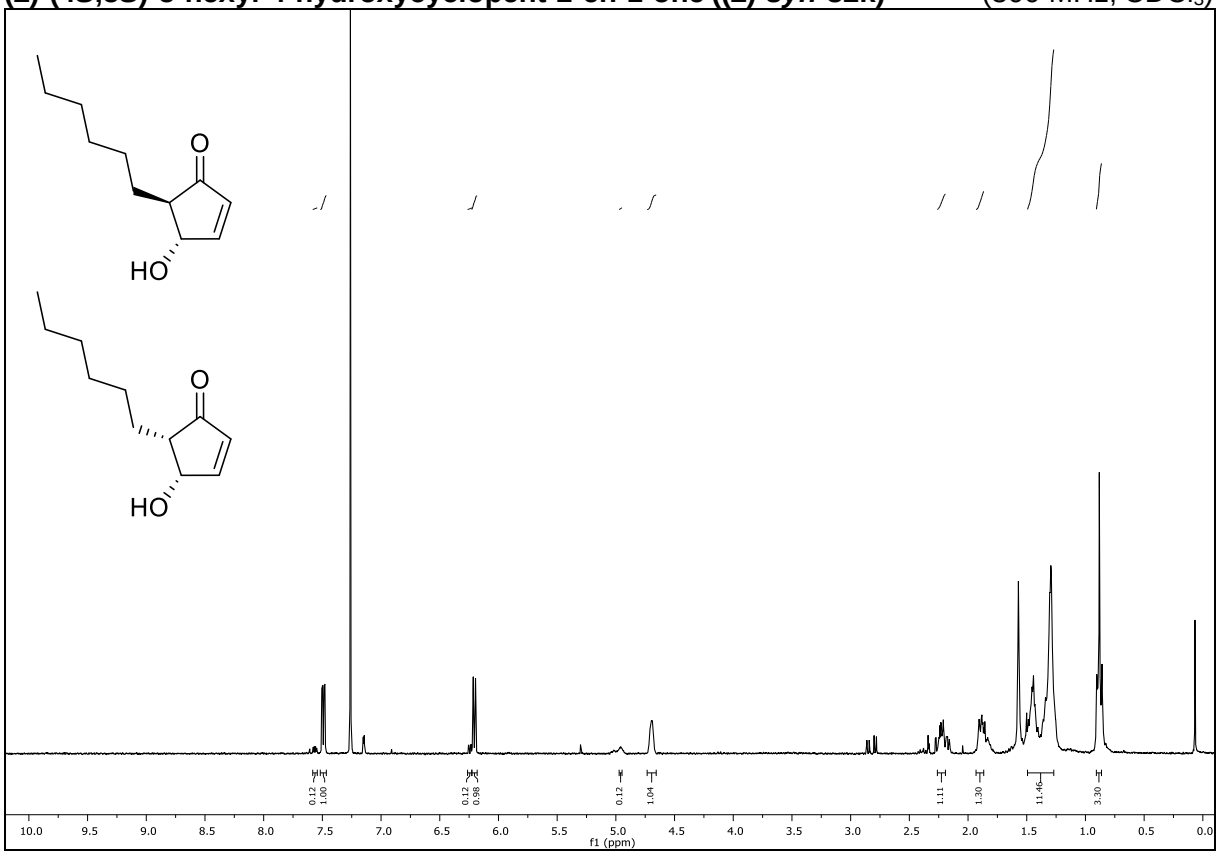
(±)-(4*S*,5*R*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*anti*-82i)
(±)-(4*S*,5*S*)-4-hydroxy-5-isobutylcyclopent-2-en-1-one ((±)-*syn*-82i) (400 MHz, $CDCl_3$)



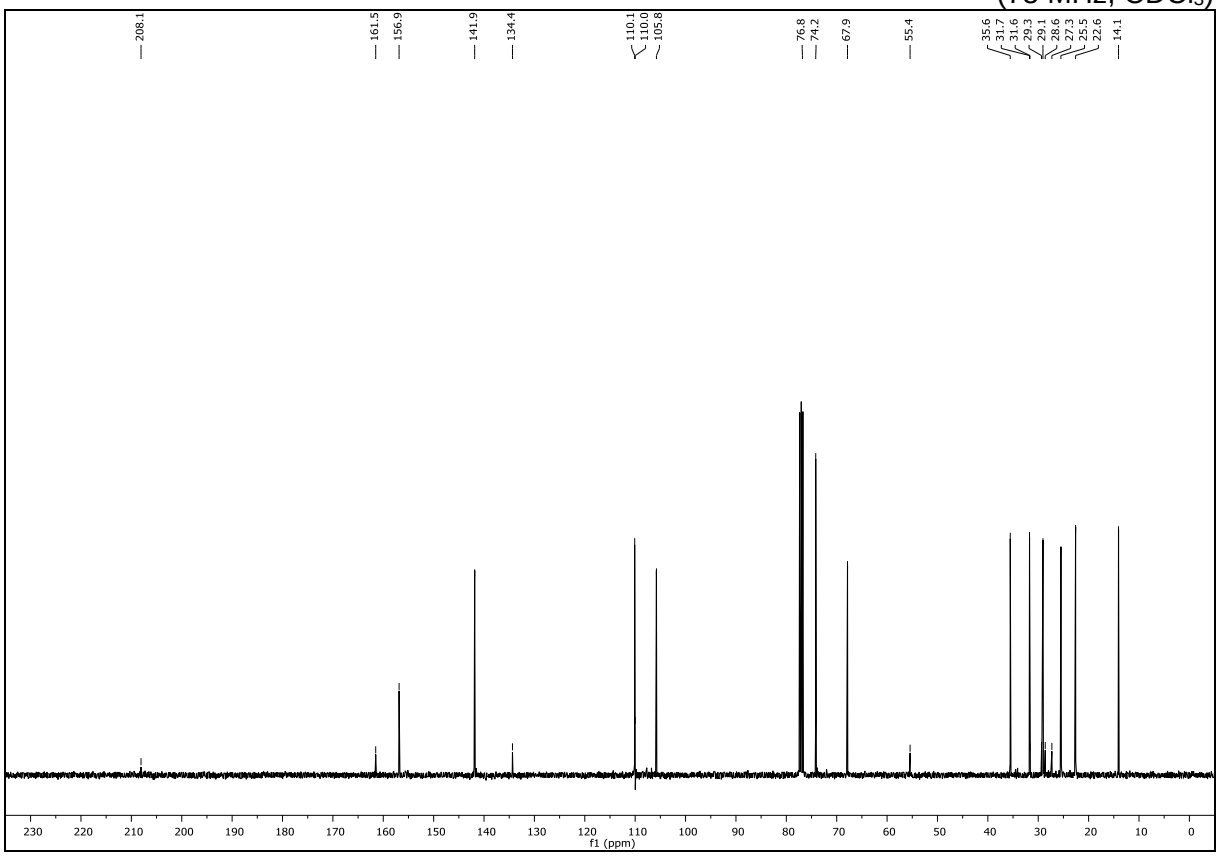
(101 MHz, $CDCl_3$)



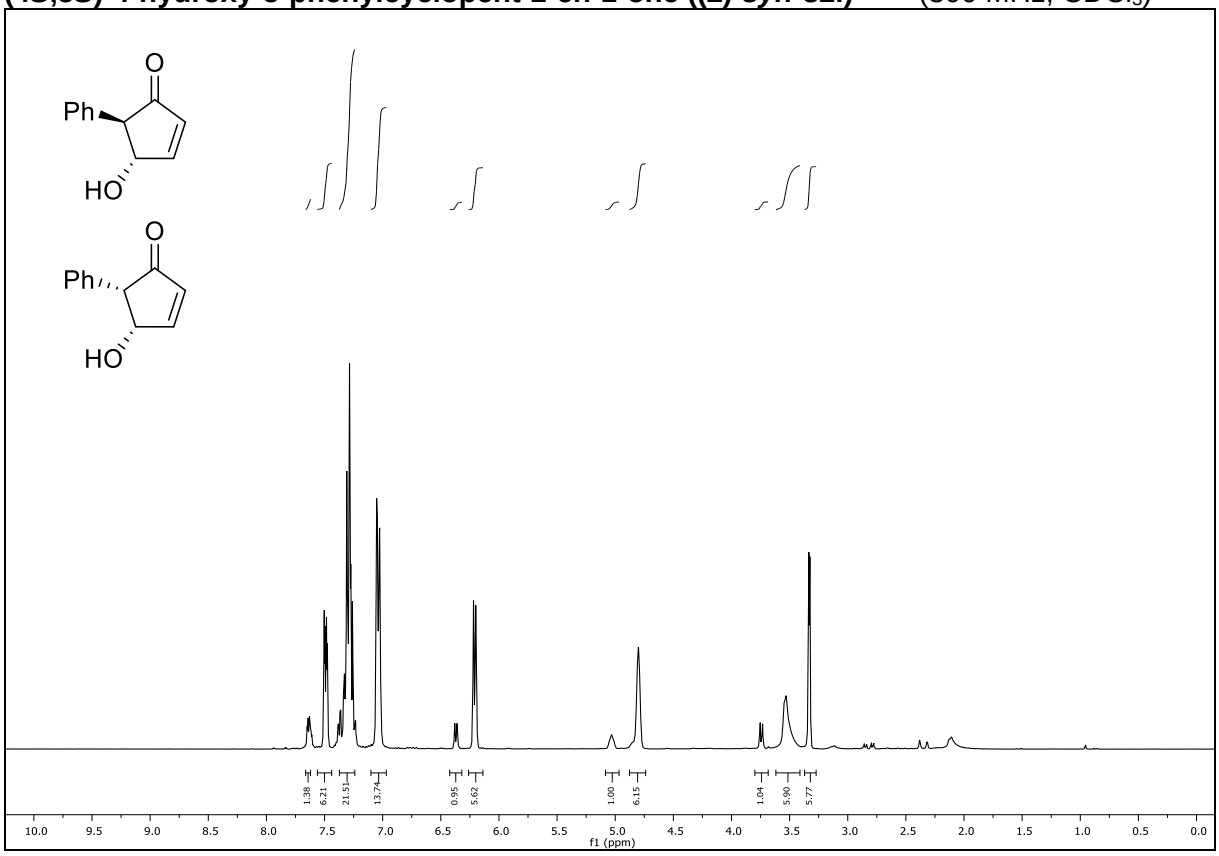
(±)-(4*S*,5*R*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*anti*-82k)
(±)-(4*S*,5*S*)-5-hexyl-4-hydroxycyclopent-2-en-1-one ((±)-*syn*-82k) (300 MHz, $CDCl_3$)



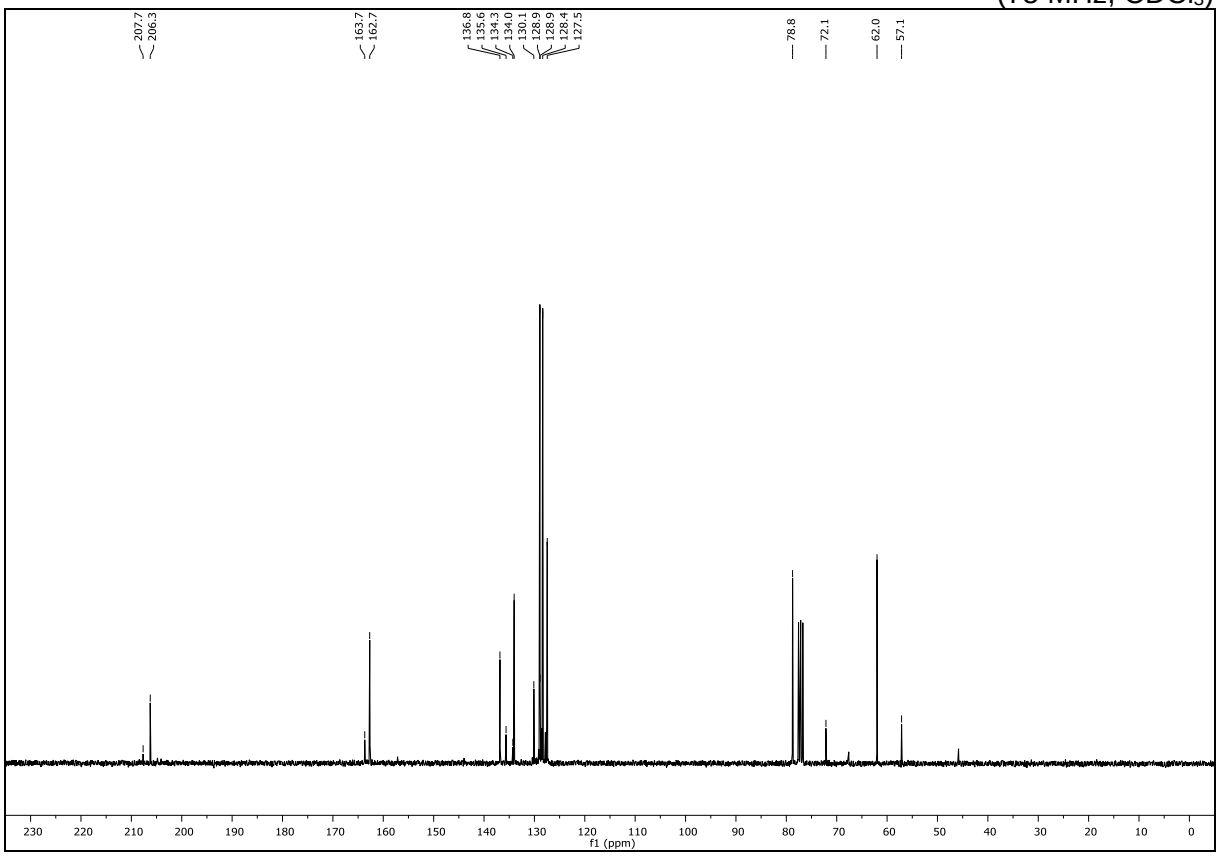
(75 MHz, $CDCl_3$)



(4*S*,5*R*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*anti*-82l)
(4*S*,5*S*)-4-hydroxy-5-phenylcyclopent-2-en-1-one ((±)-*syn*-82l) (300 MHz, $CDCl_3$)

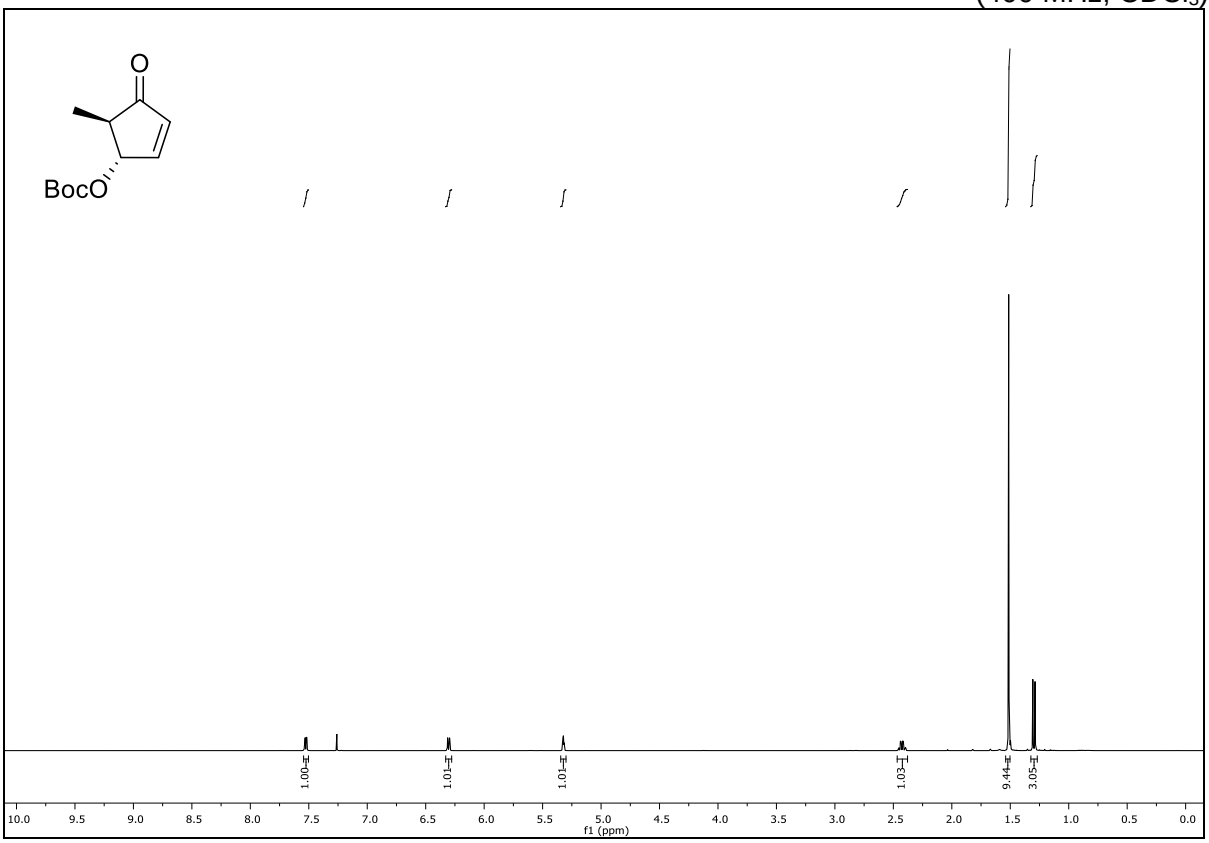


(75 MHz, $CDCl_3$)

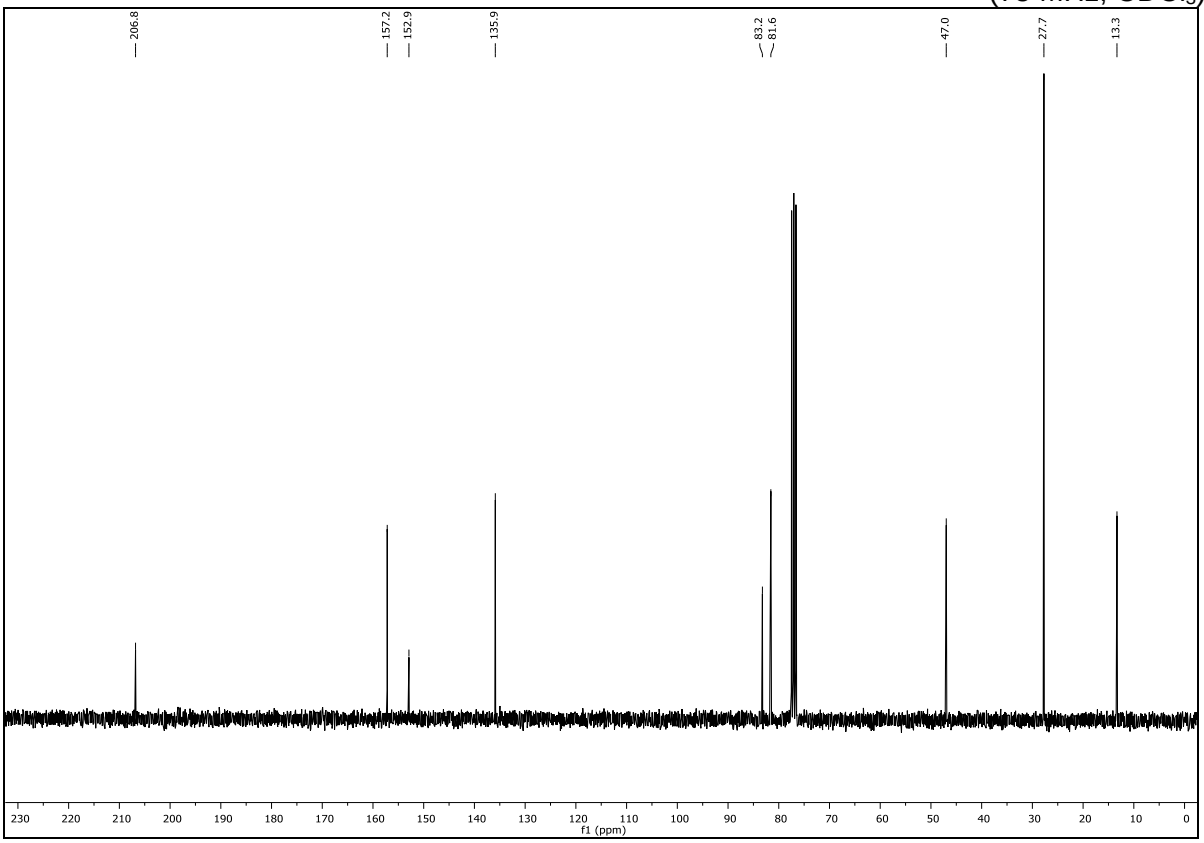


(±)-((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83f)

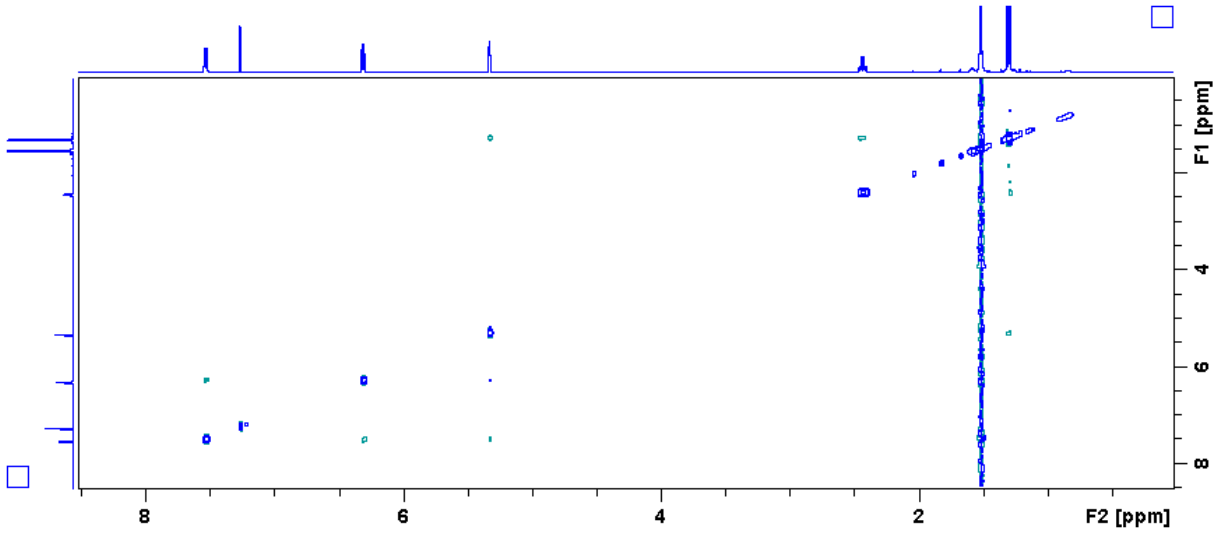
(400 MHz, $CDCl_3$)



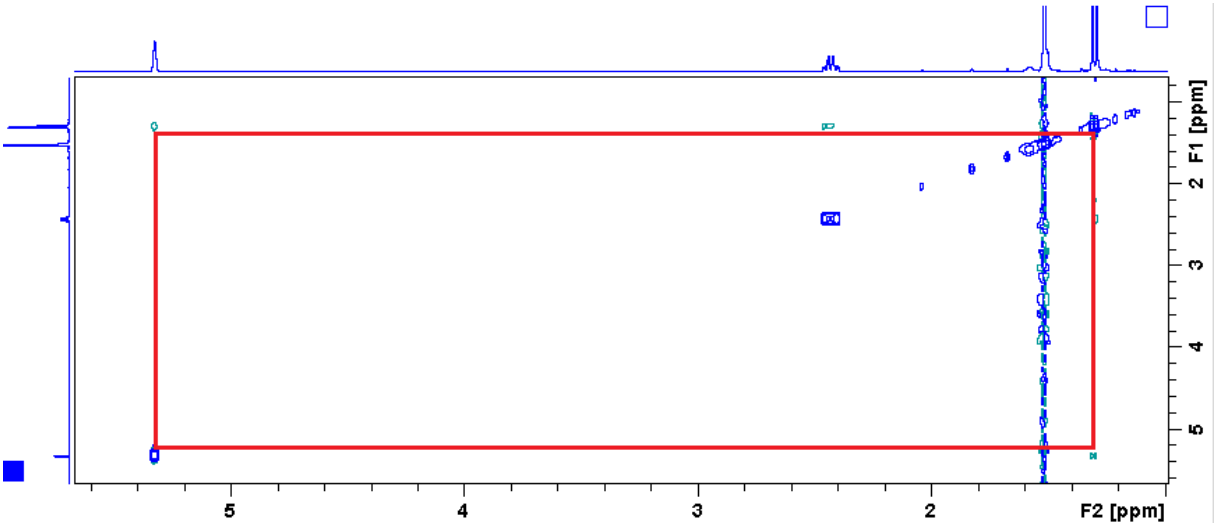
(75 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

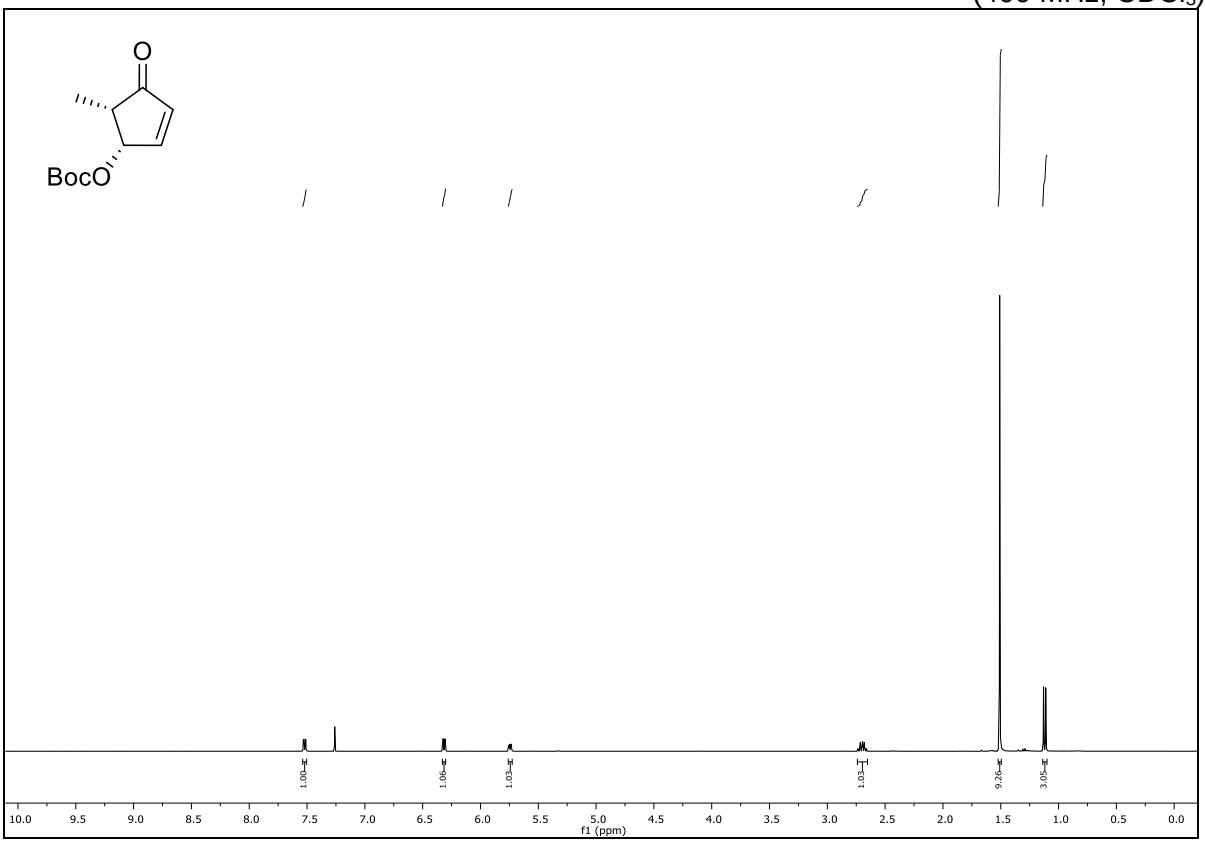


NOESY Zoom In

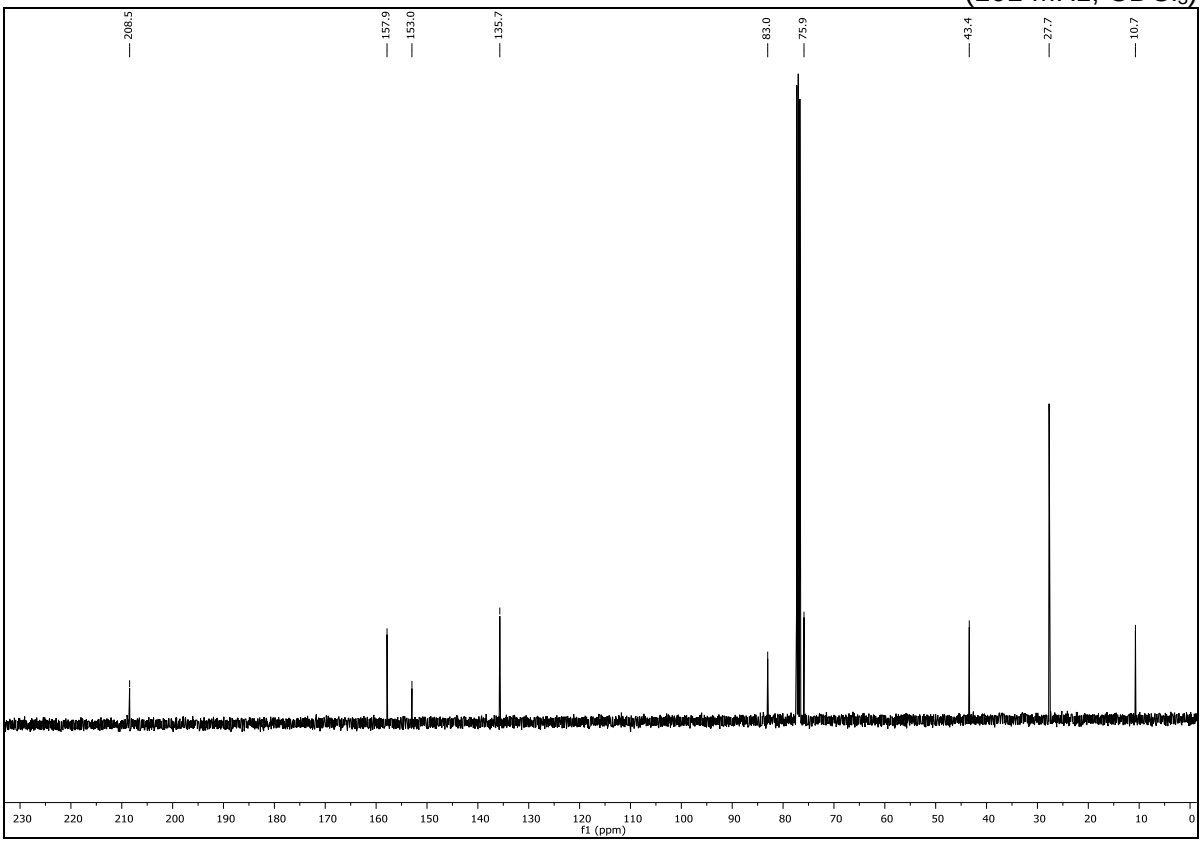


(±)-((4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*syn*-83f)

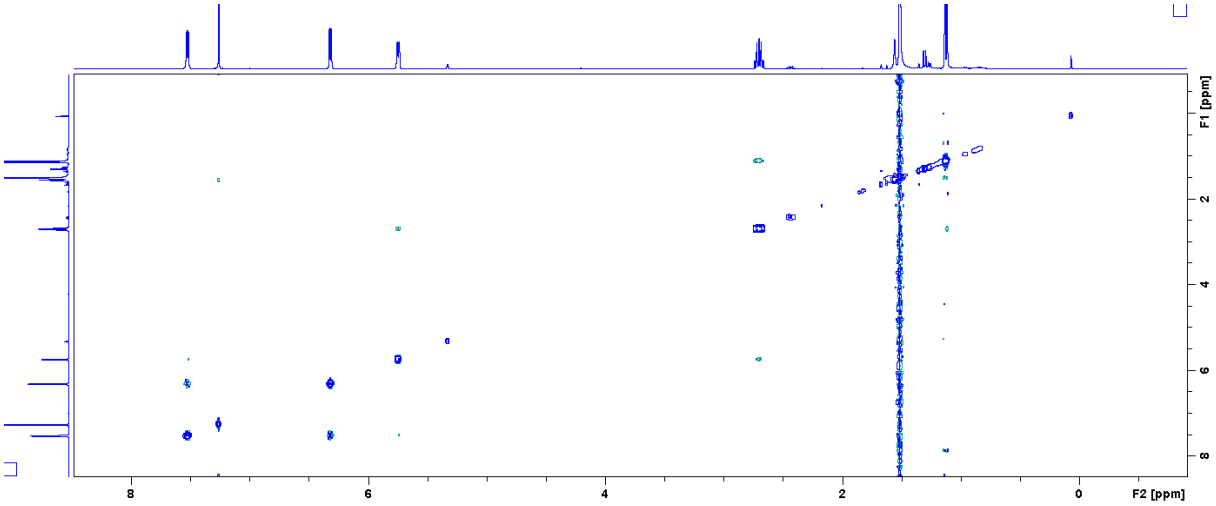
(400 MHz, $CDCl_3$)



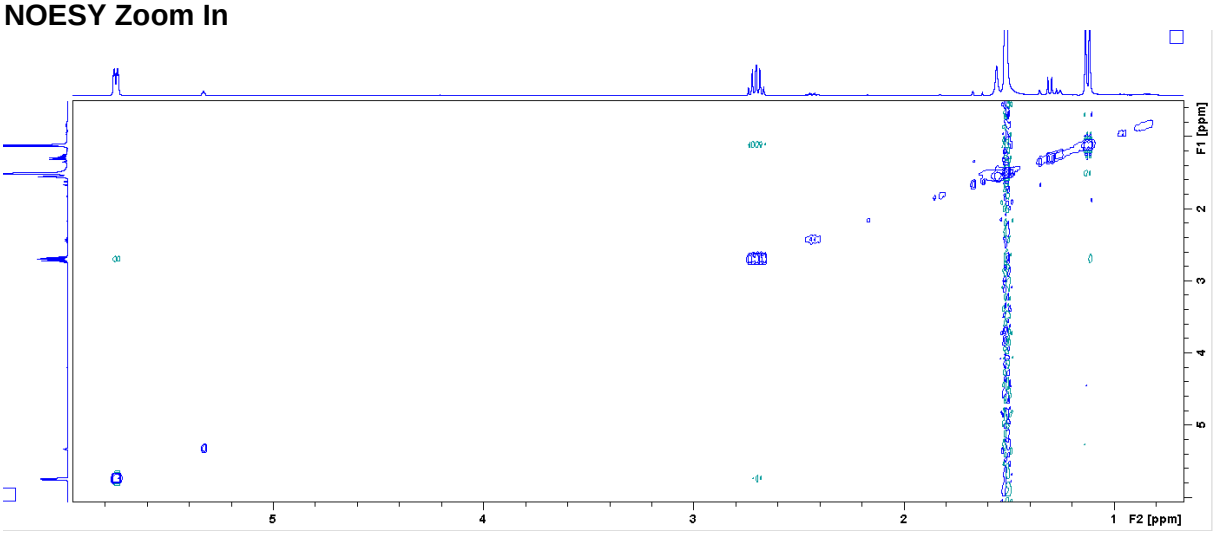
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

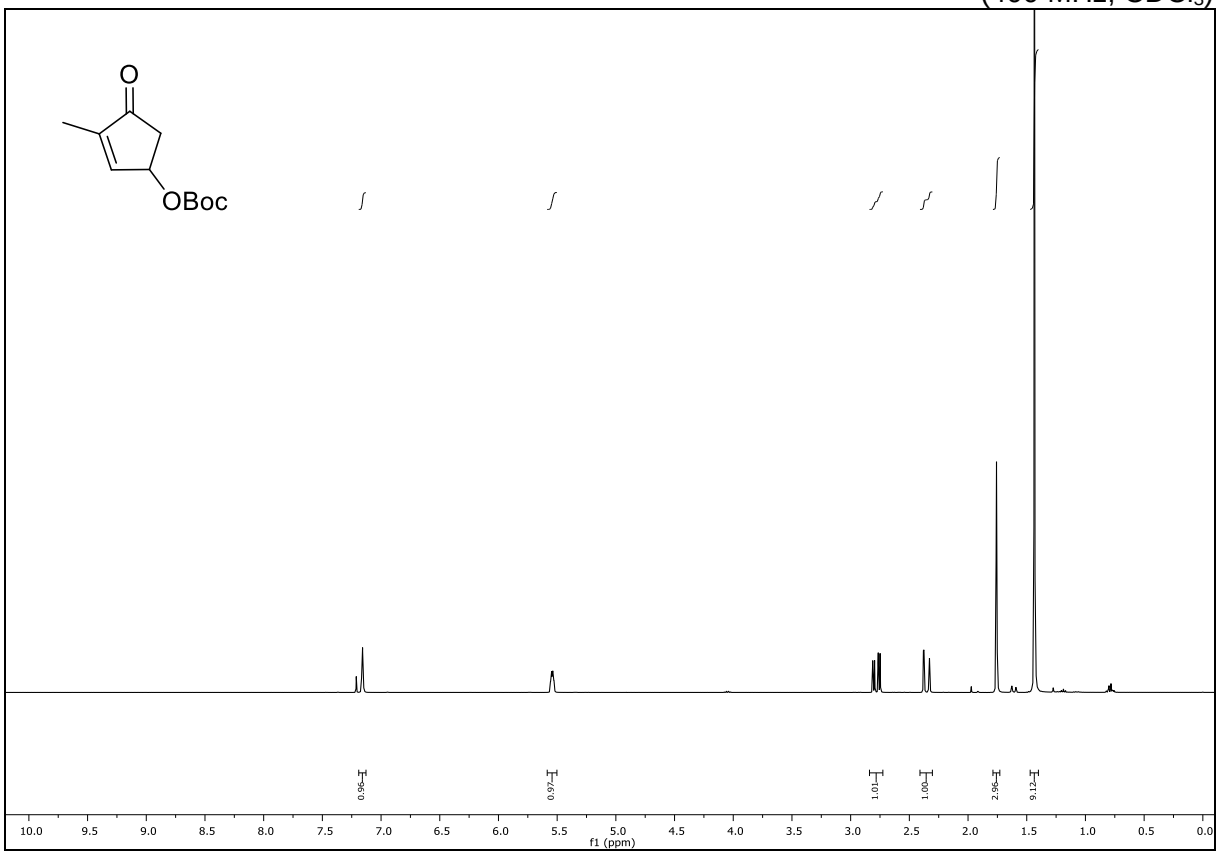


NOESY Zoom In

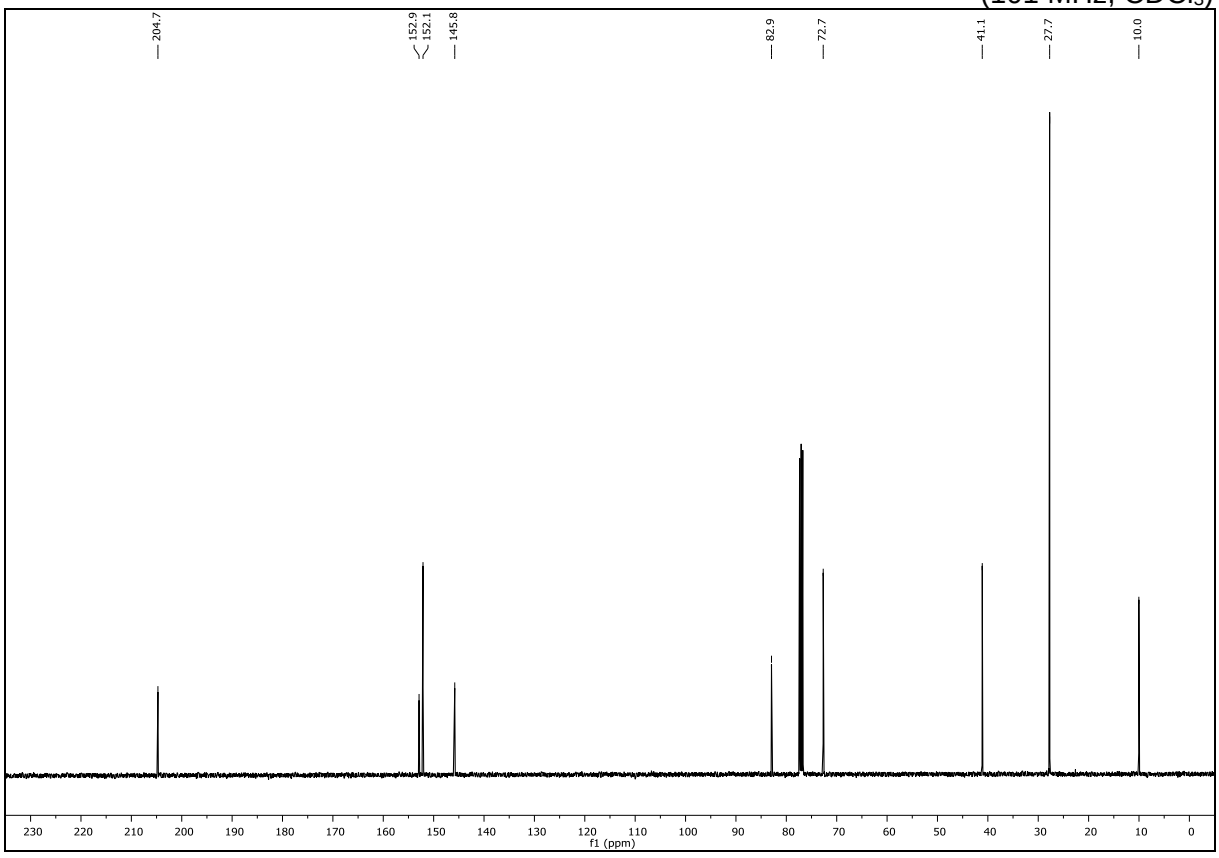


(±)-*tert*-butyl (3-methyl-4-oxocyclopent-2-en-1-yl) carbonate ((±)-162)

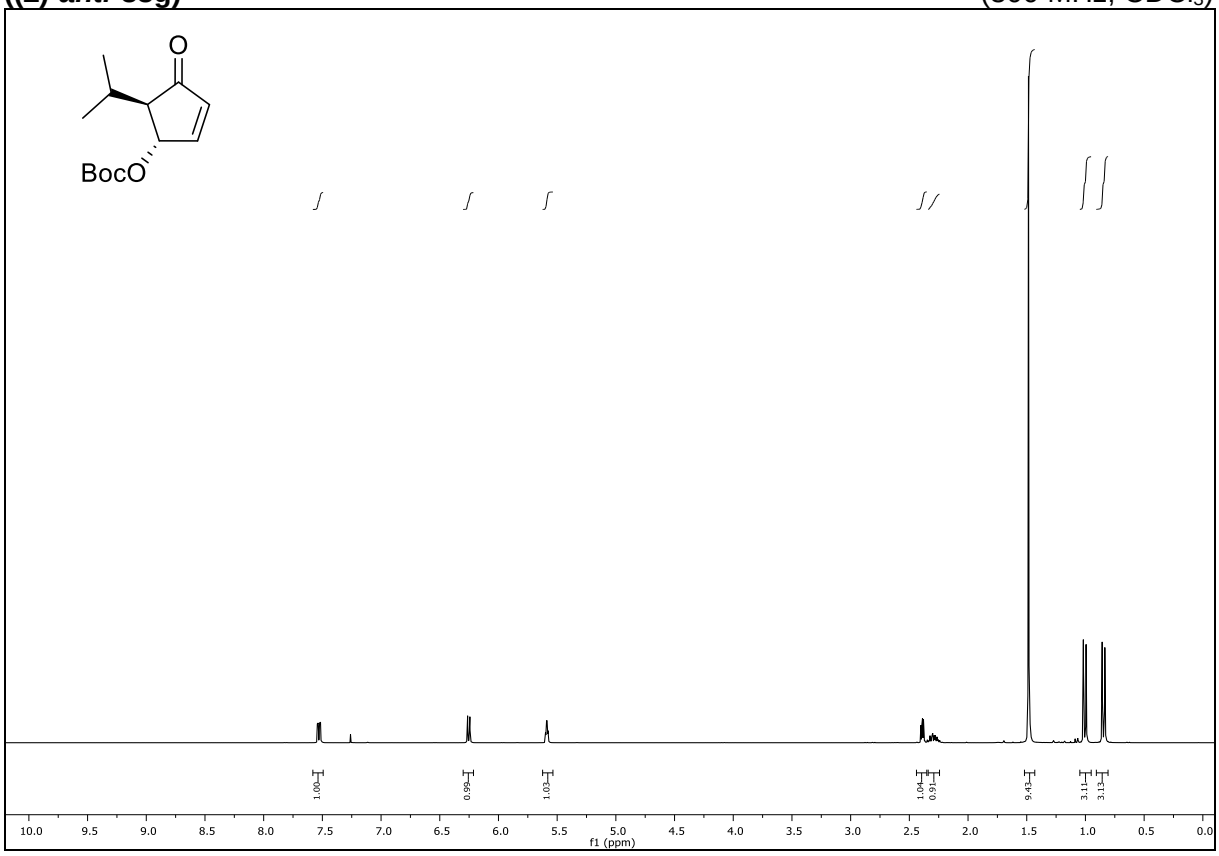
(400 MHz, $CDCl_3$)



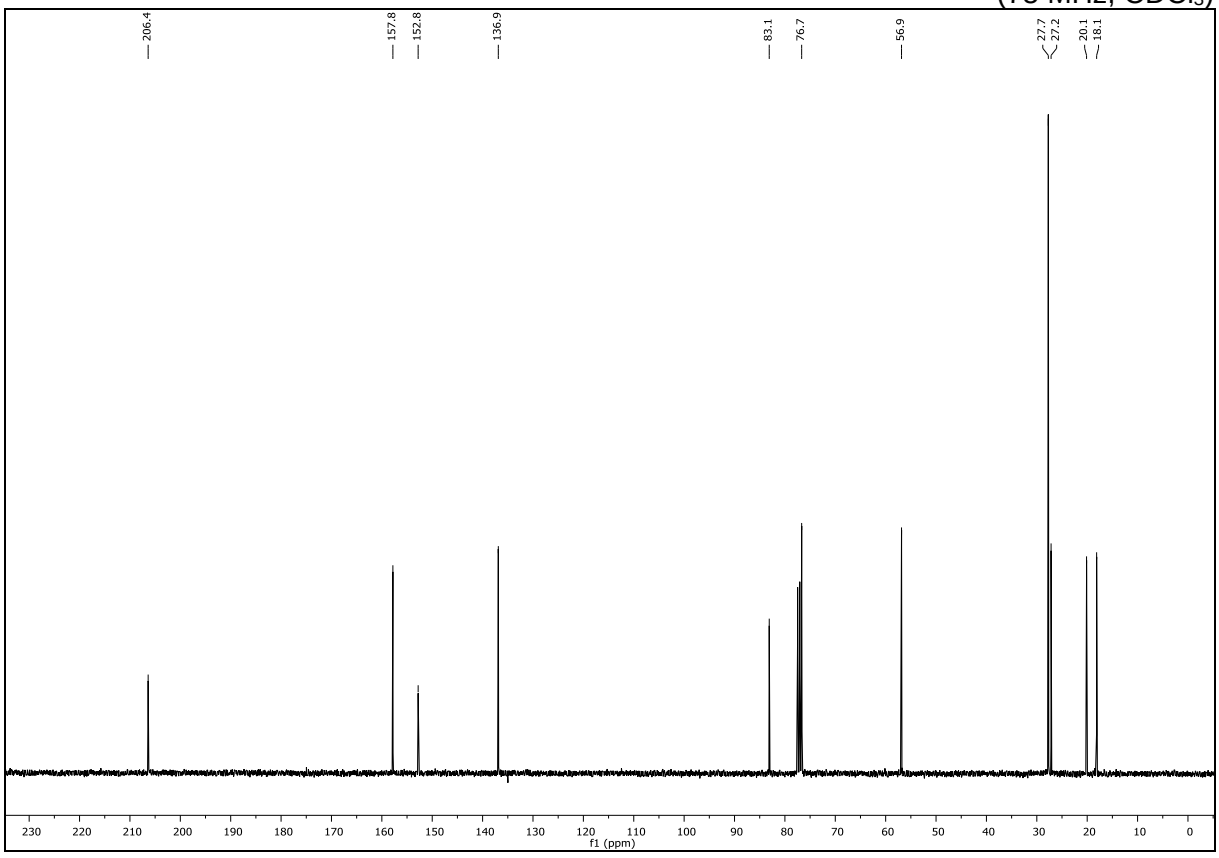
(101 MHz, $CDCl_3$)



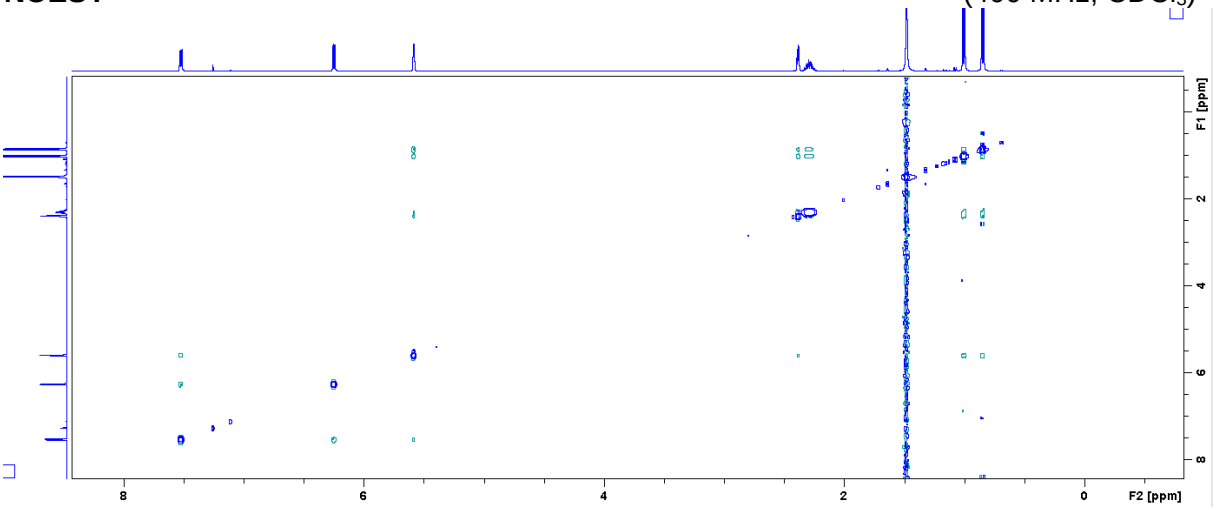
(±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83g) (300 MHz, $CDCl_3$)



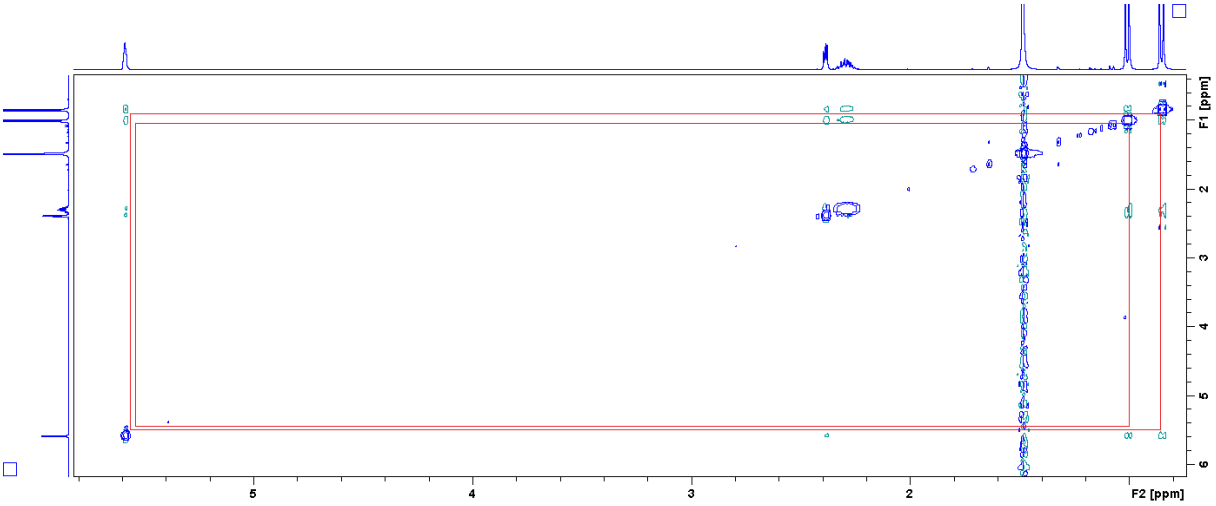
(75 MHz, $CDCl_3$)



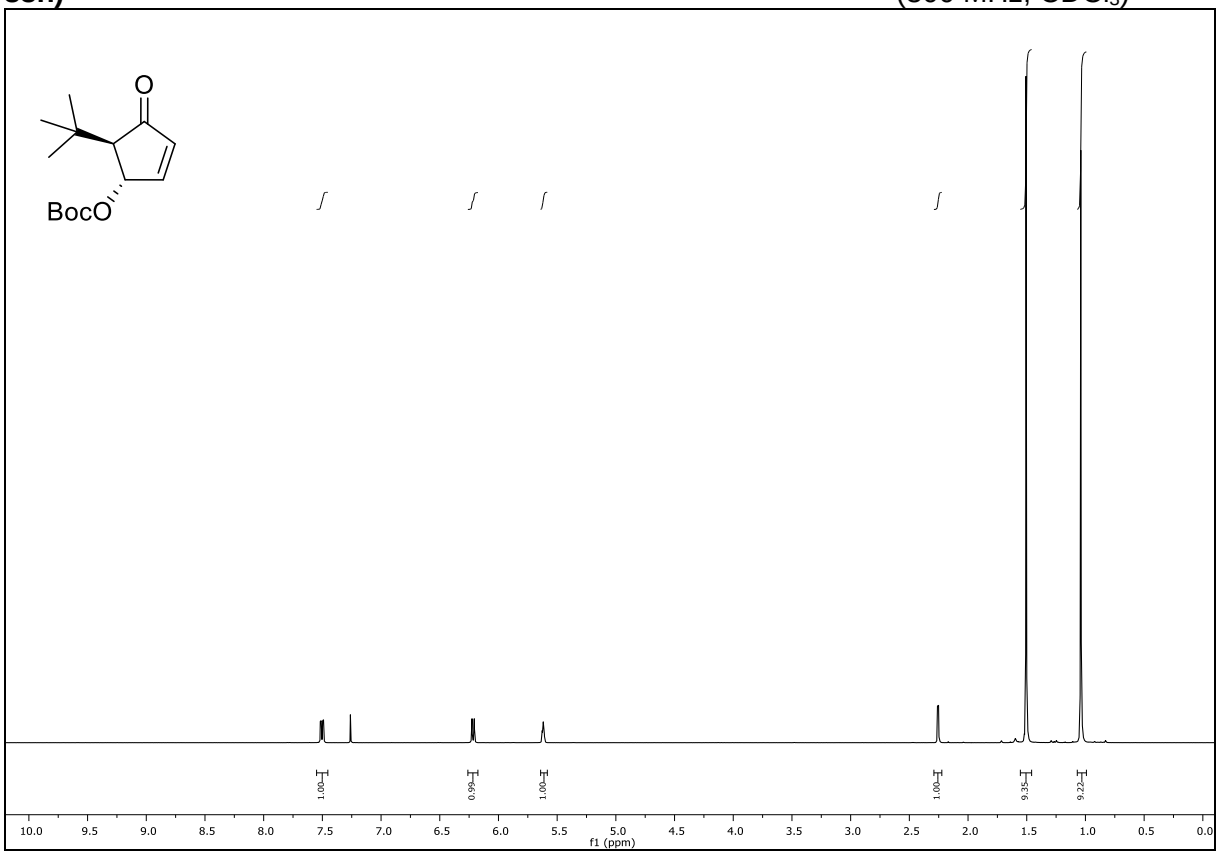
NOESY (400 MHz, $CDCl_3$)



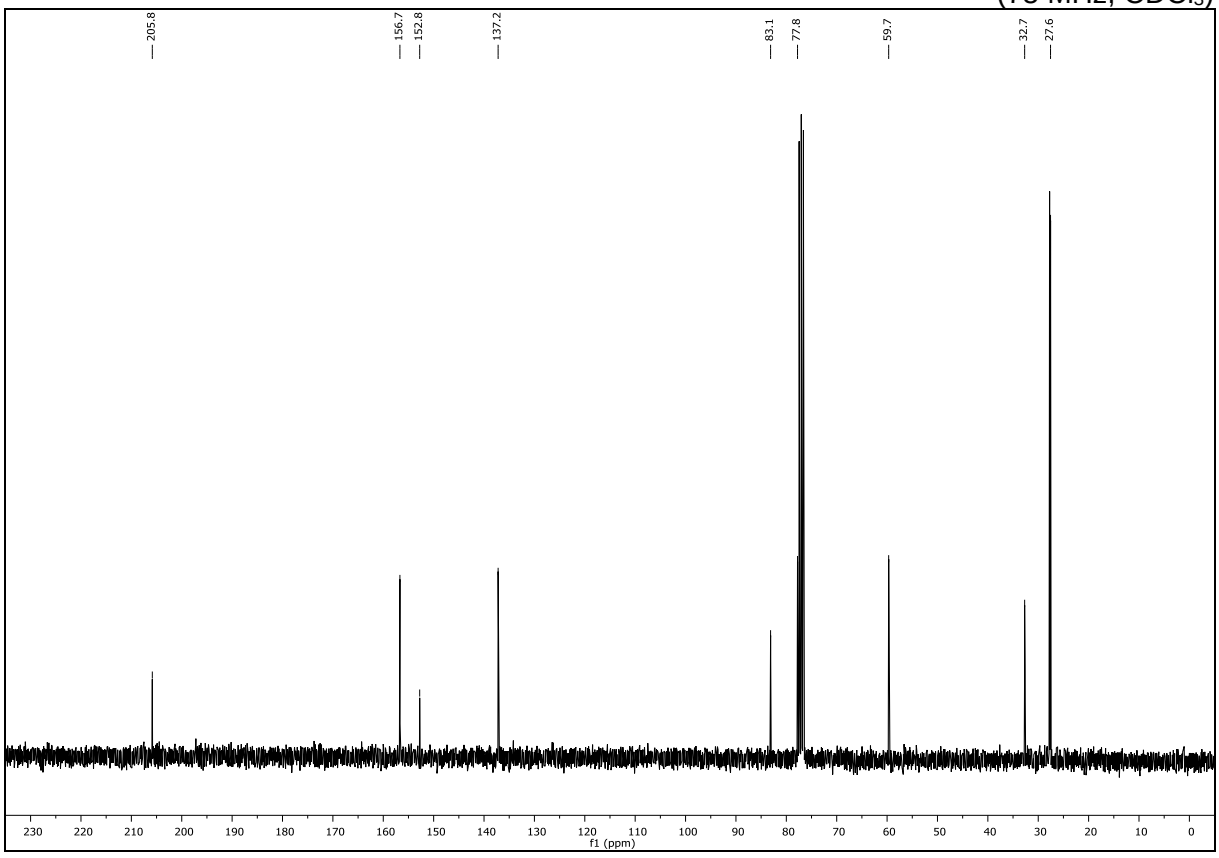
NOESY Zoom In



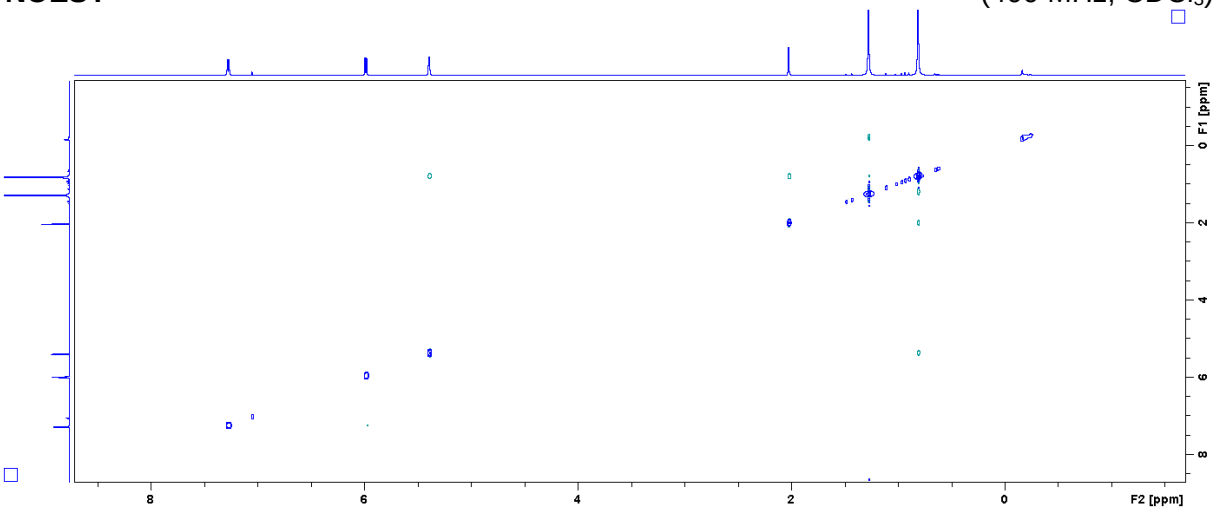
(±)-((4*S*,5*R*)-5-(tert-butyl)-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83h) (300 MHz, $CDCl_3$)



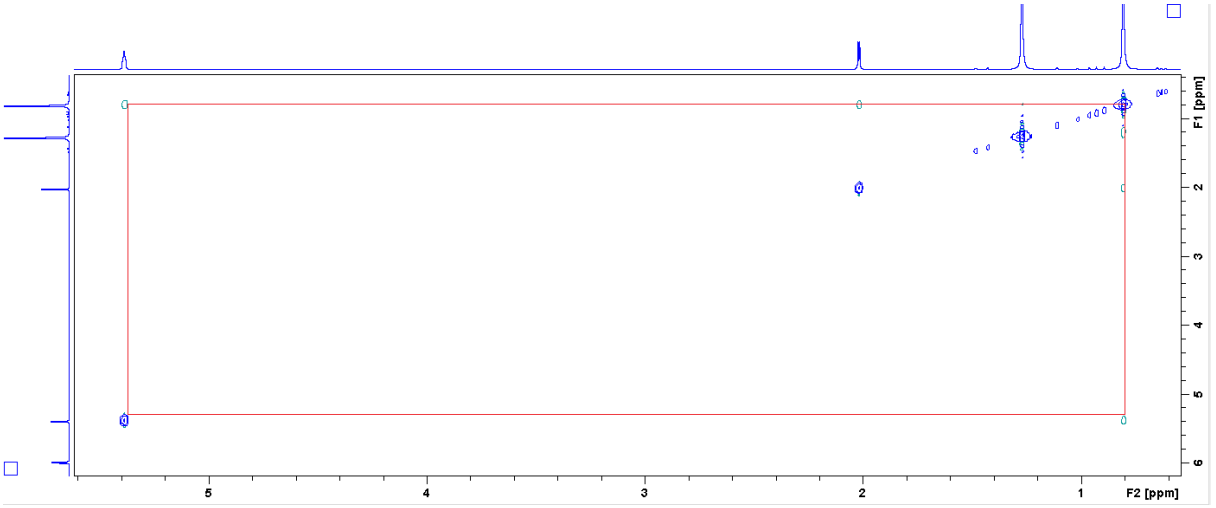
(75 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

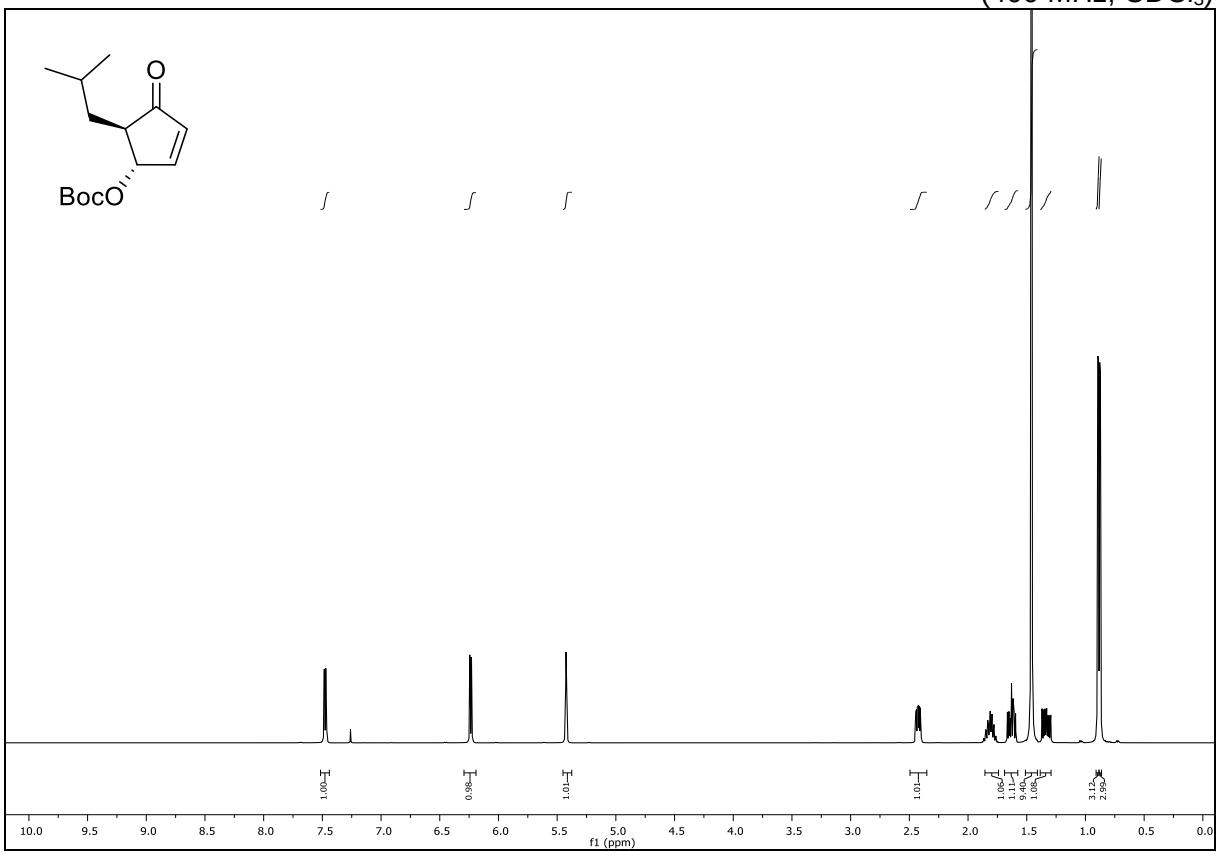


NOESY Zoom In

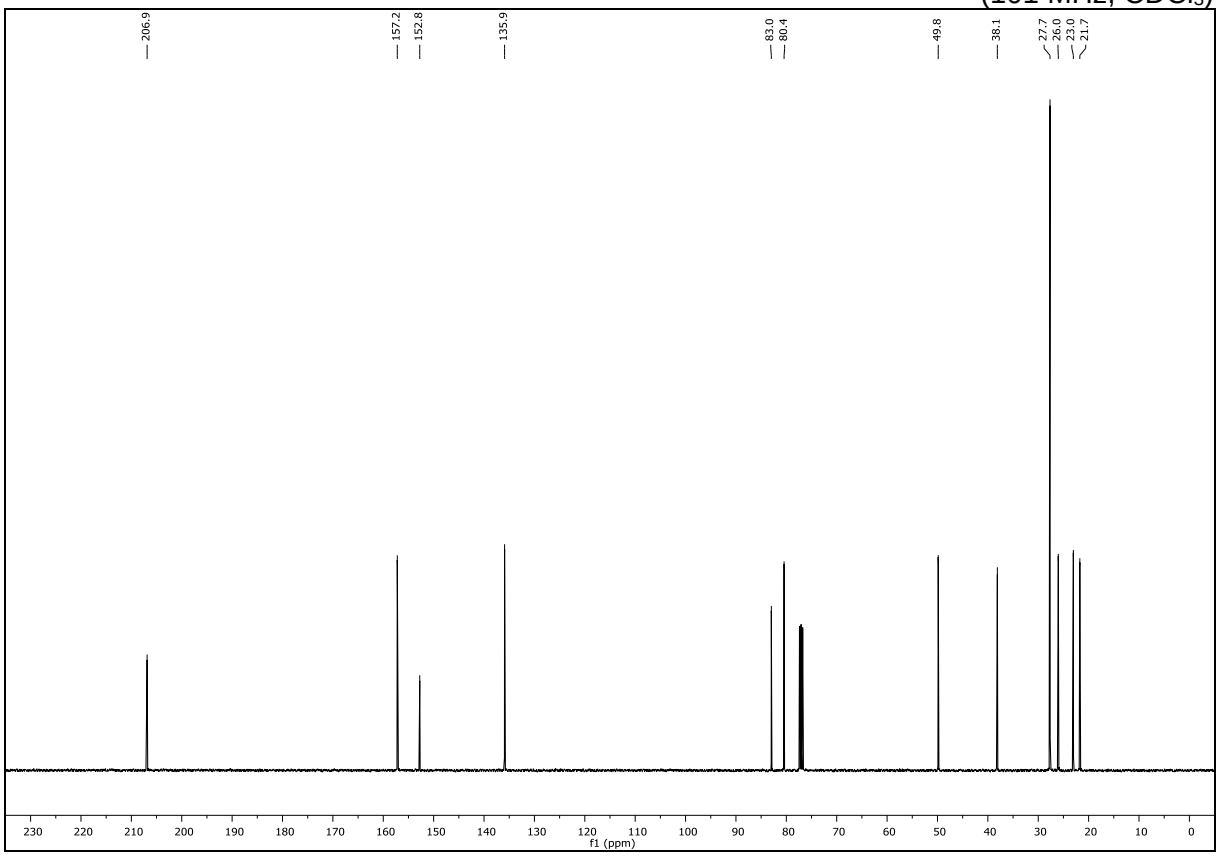


(±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83i)

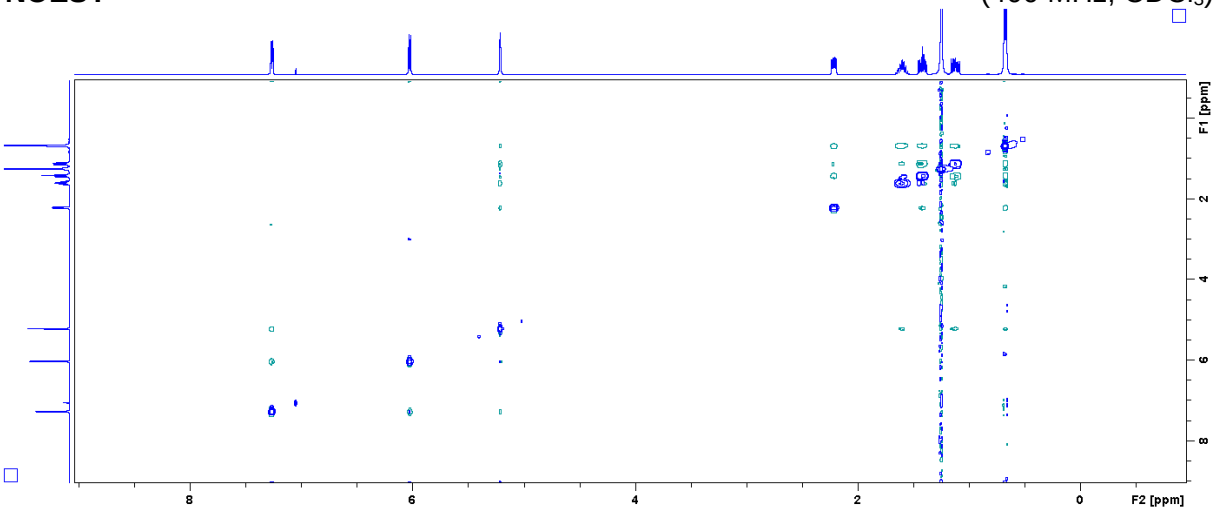
(400 MHz, $CDCl_3$)



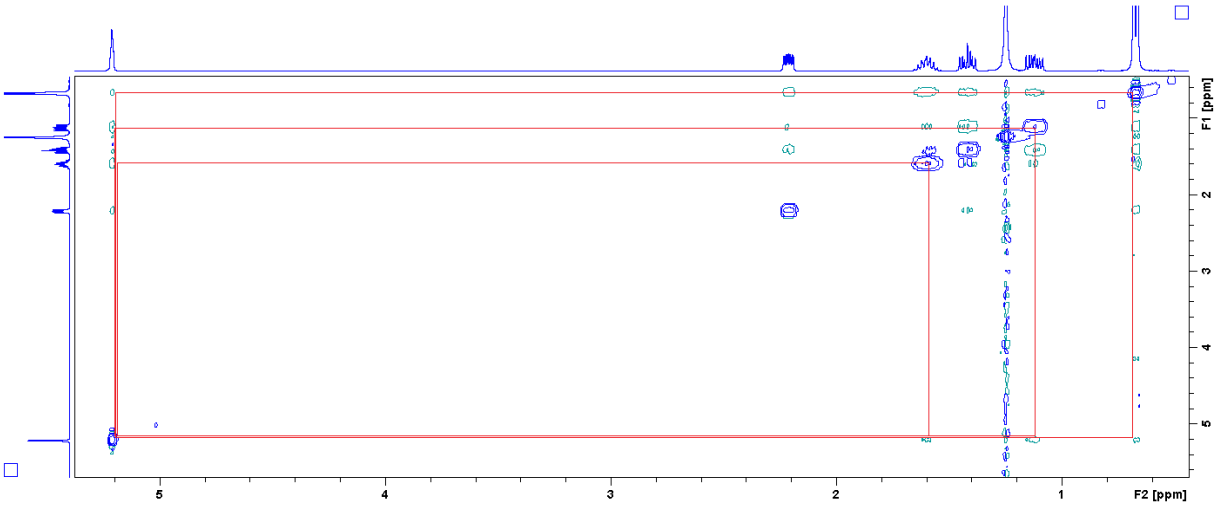
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

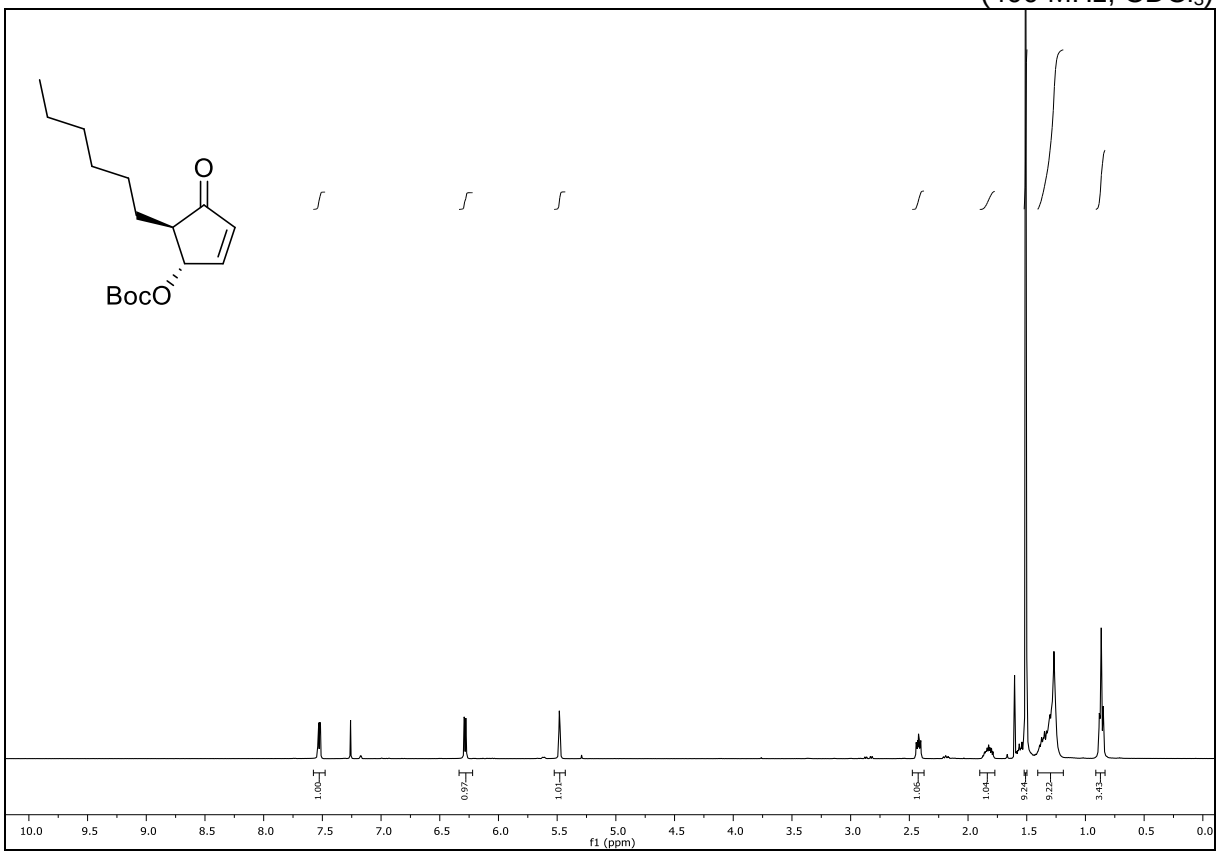


NOESY ZOOM In

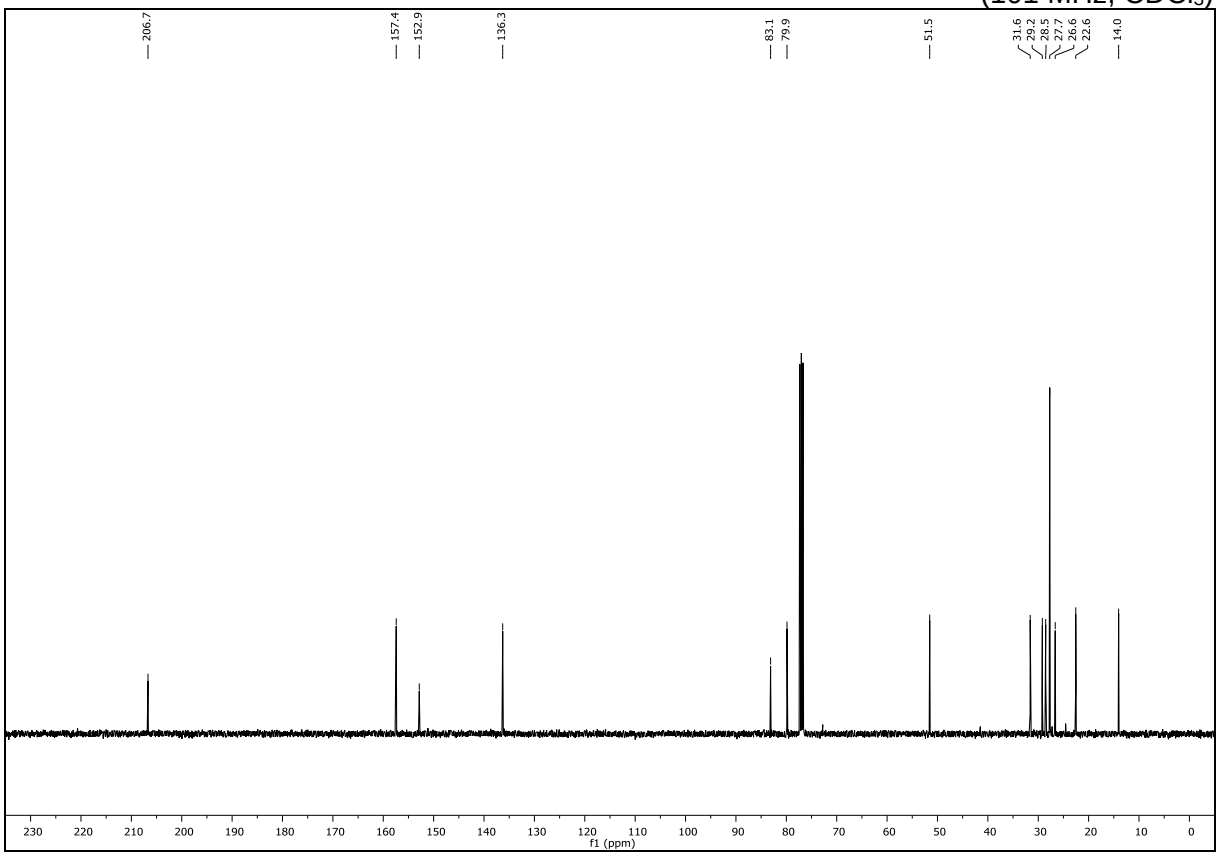


(±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83k)

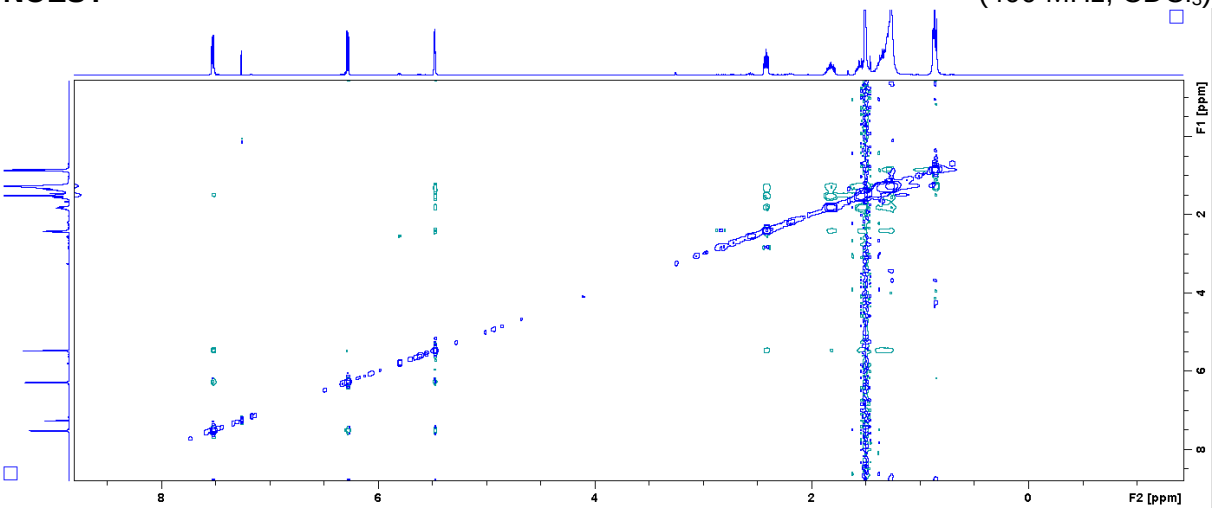
(400 MHz, $CDCl_3$)



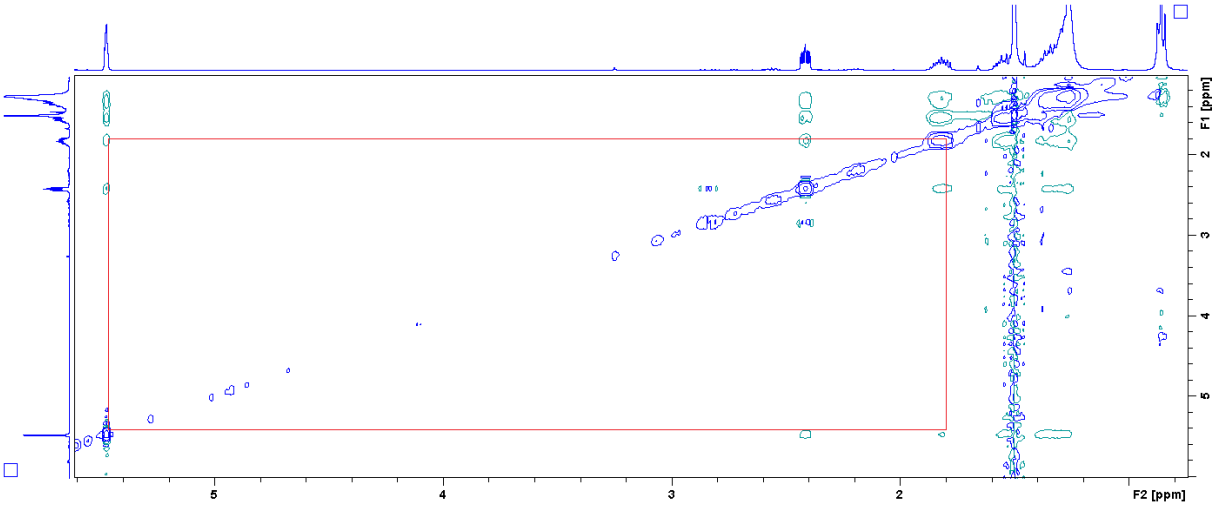
(101 MHz, $CDCl_3$)



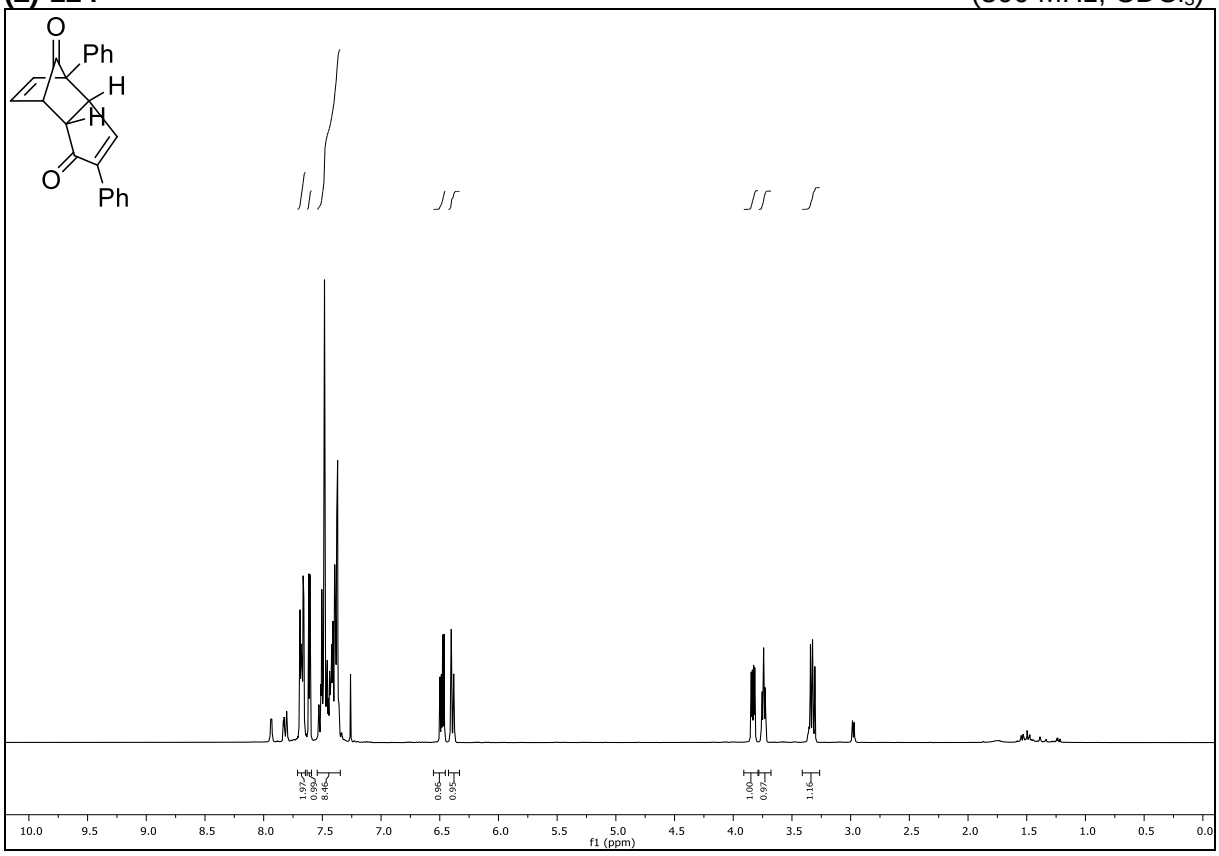
NOESY (400 MHz, $CDCl_3$)



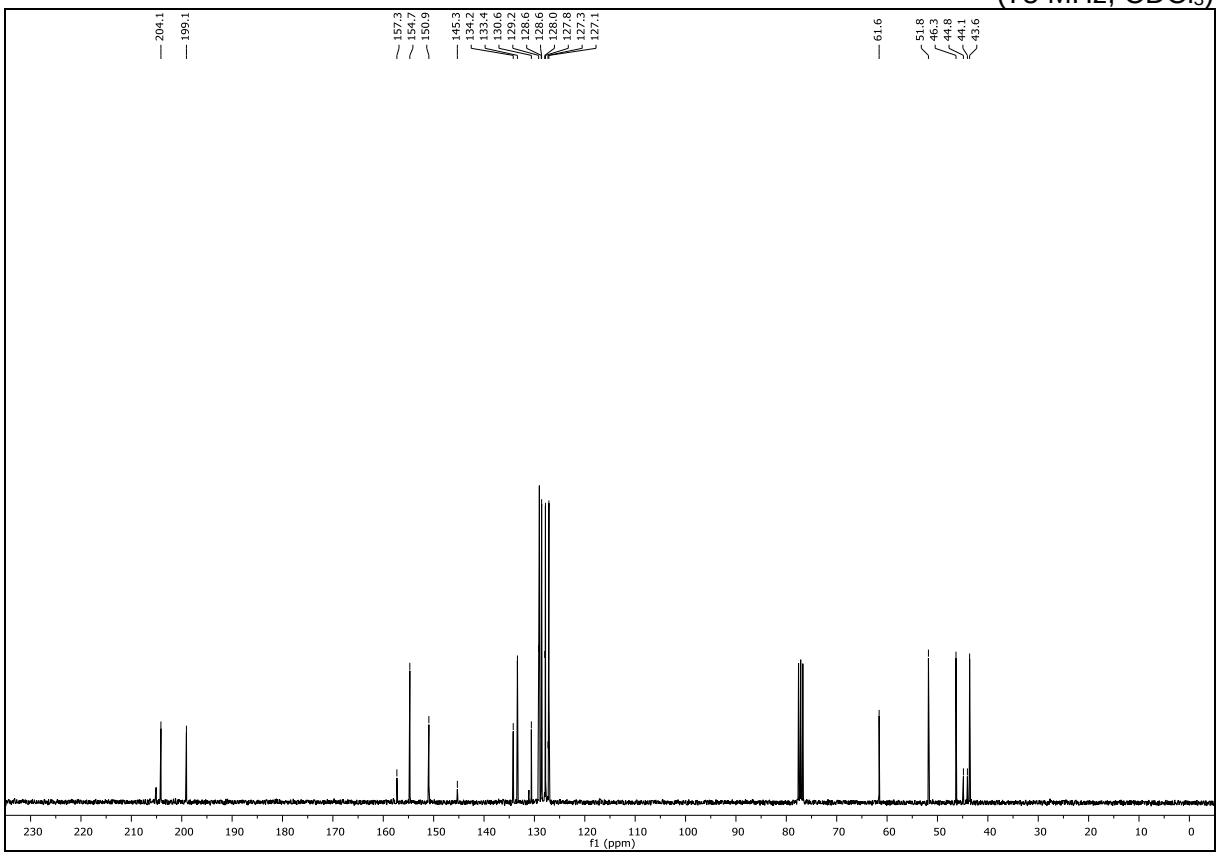
NOESY ZOOM In



(±)-(3a*R*,4*R*,7*S*,7a*S*)-2,4-diphenyl-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,8-dione
(±)-124 (300 MHz, $CDCl_3$)

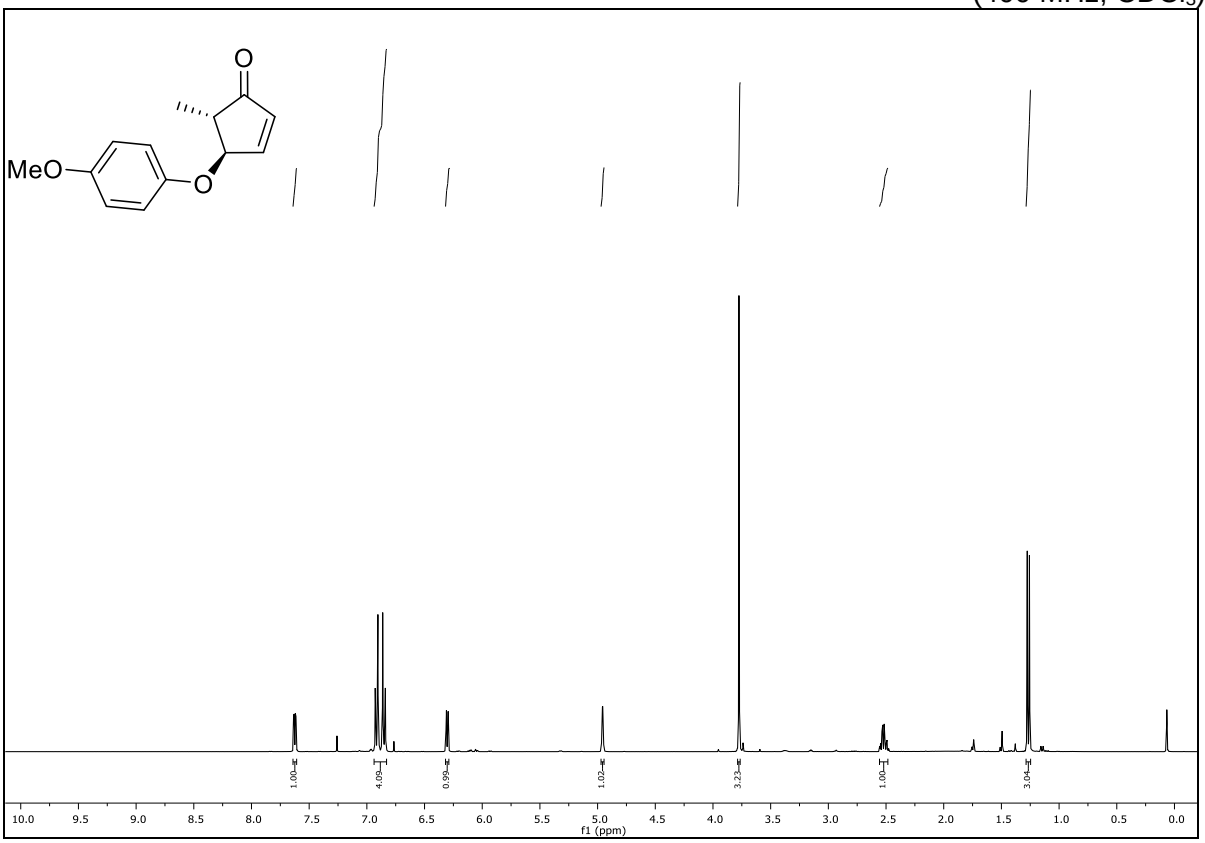


(75 MHz, $CDCl_3$)

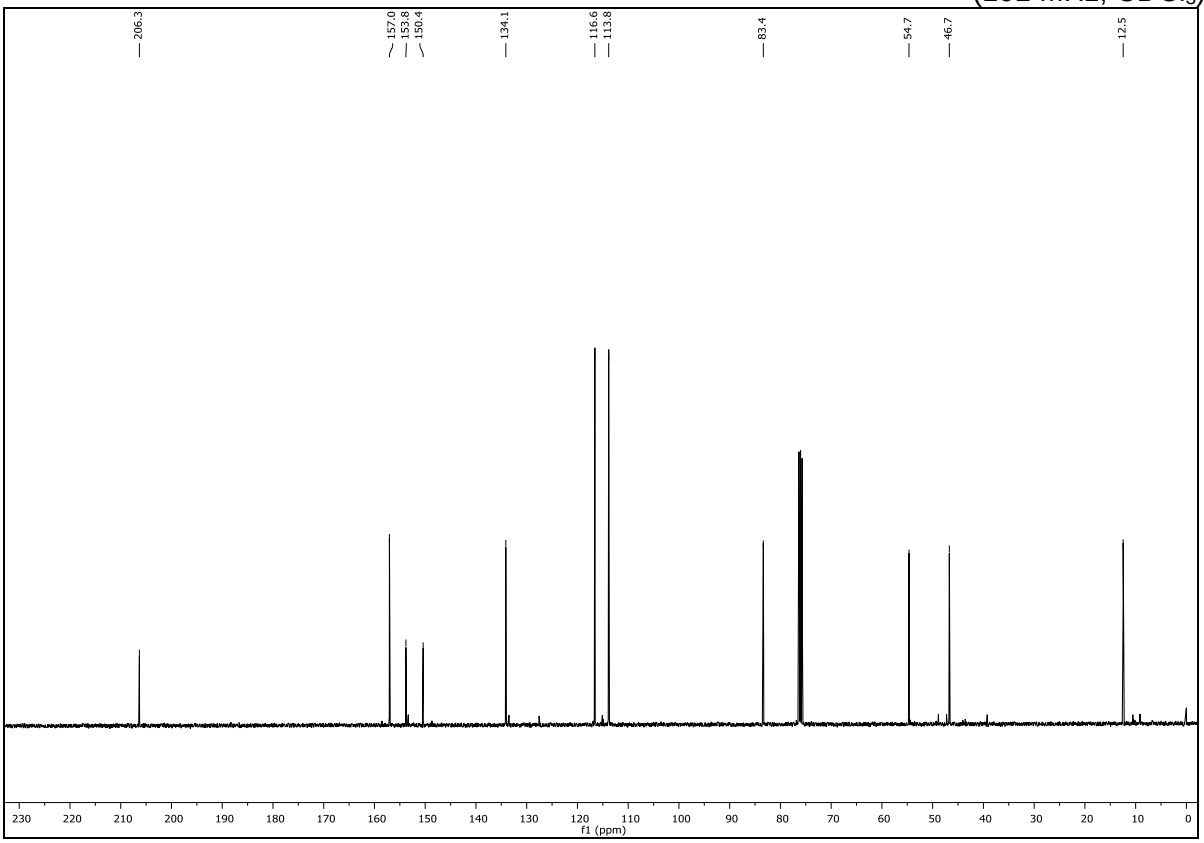


(4*R*,5*S*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128f)

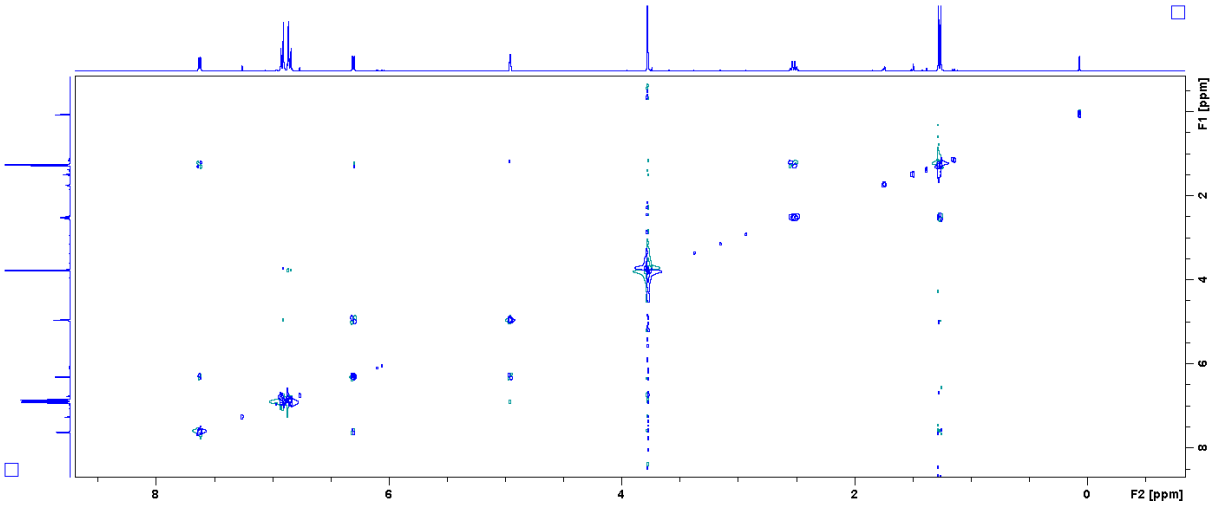
(400 MHz, $CDCl_3$)



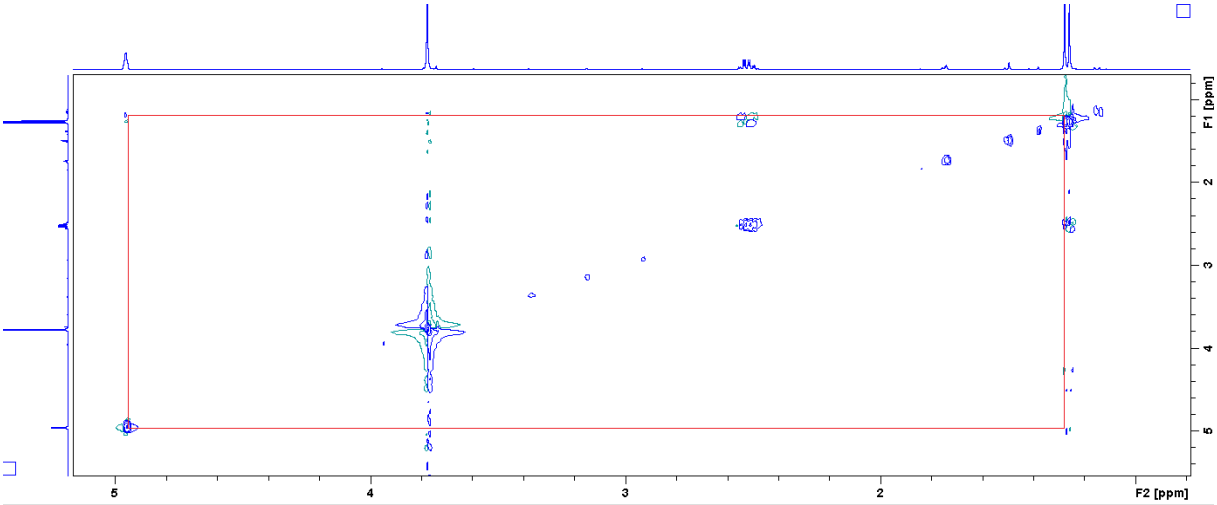
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

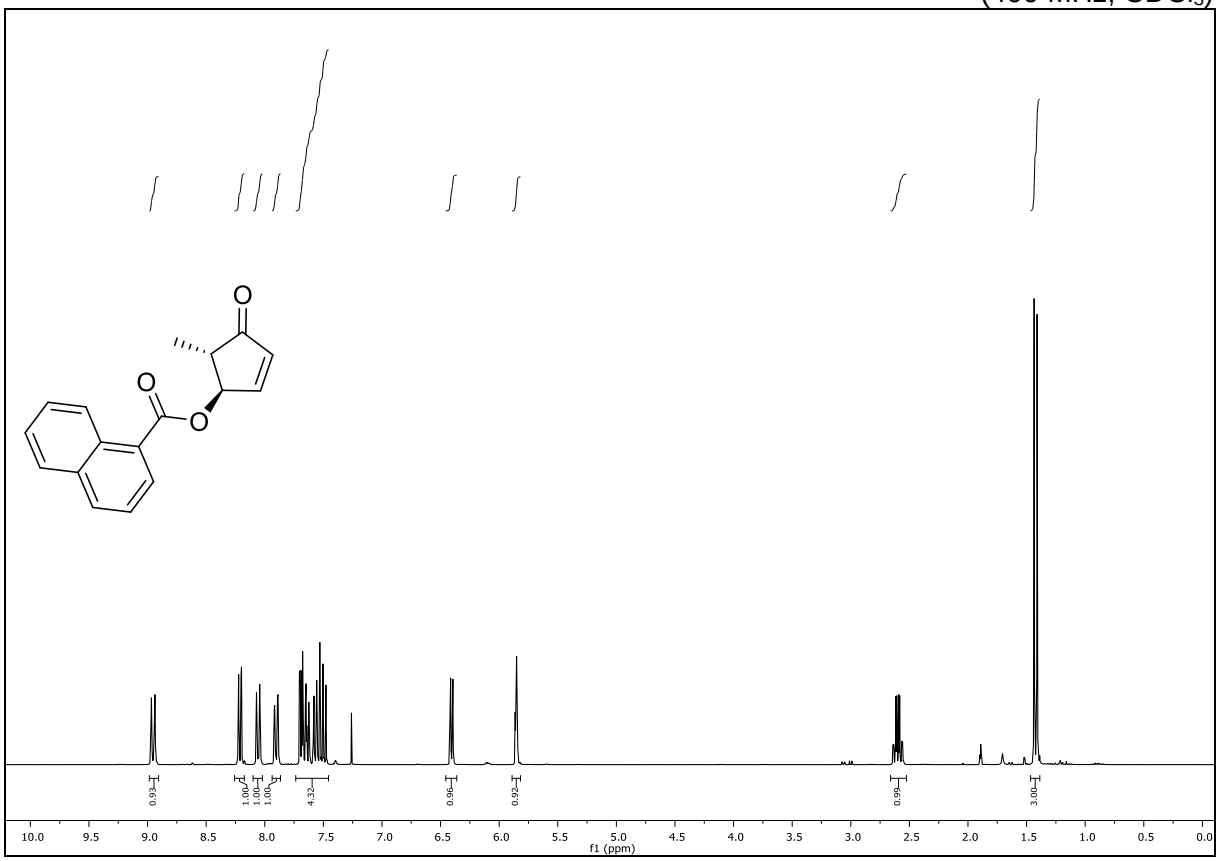


NOESY Zoom In

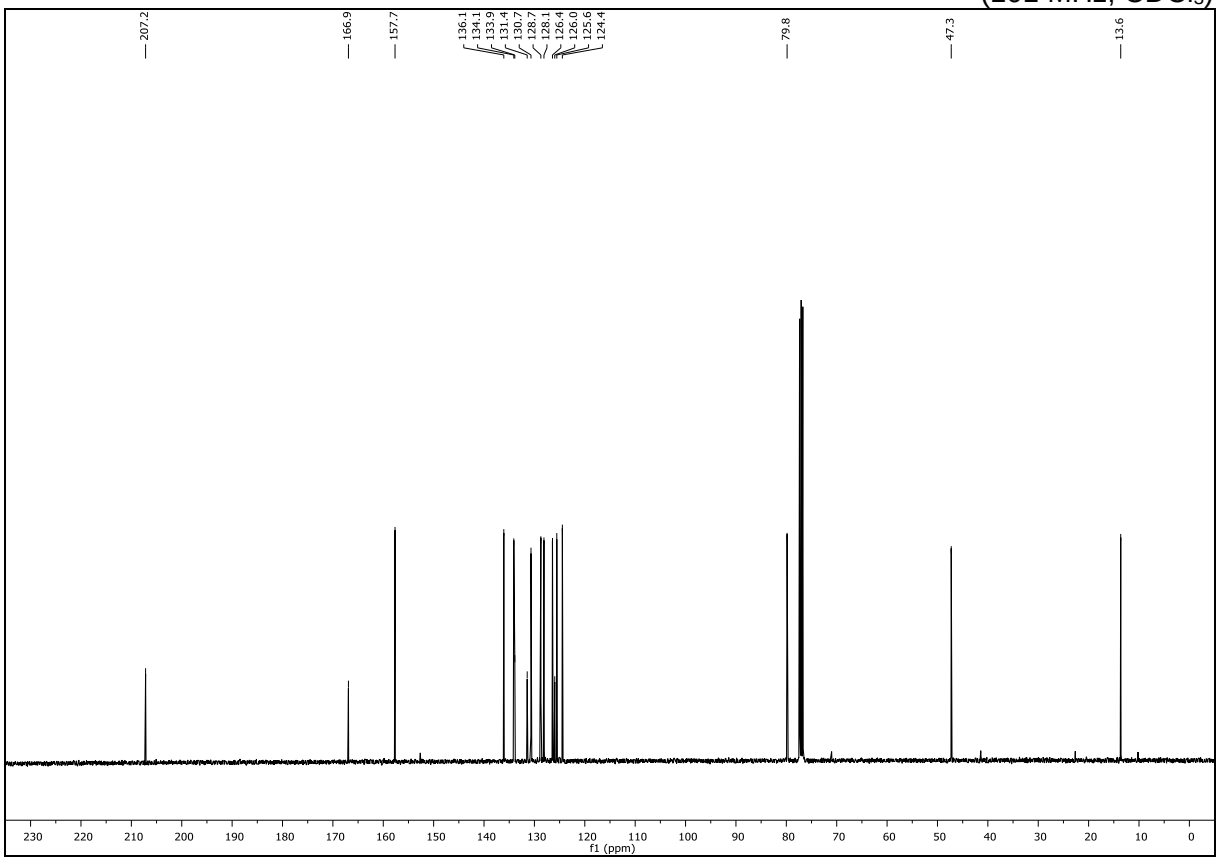


(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130f)

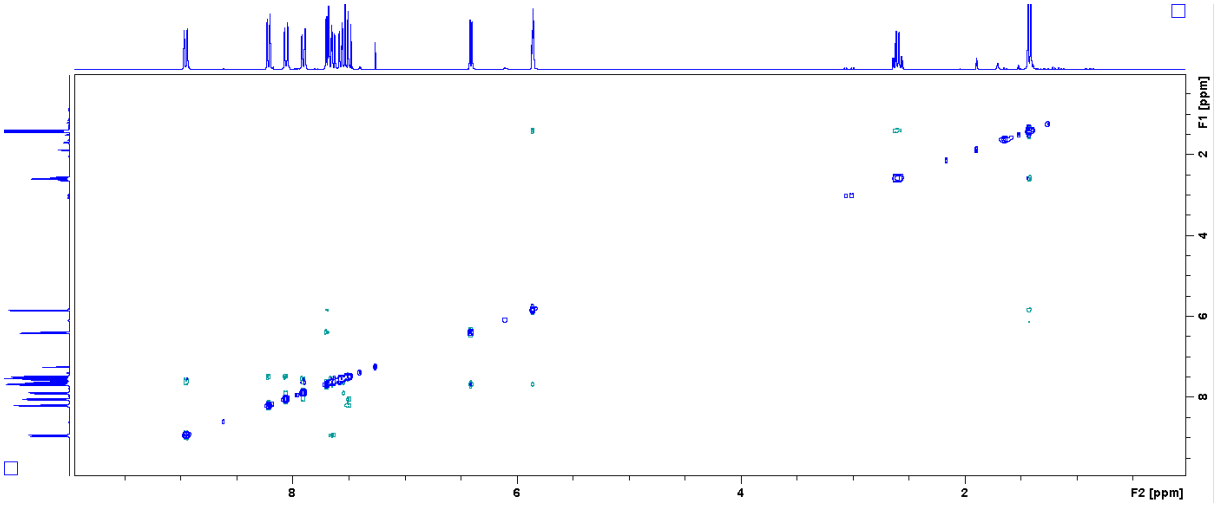
(400 MHz, $CDCl_3$)



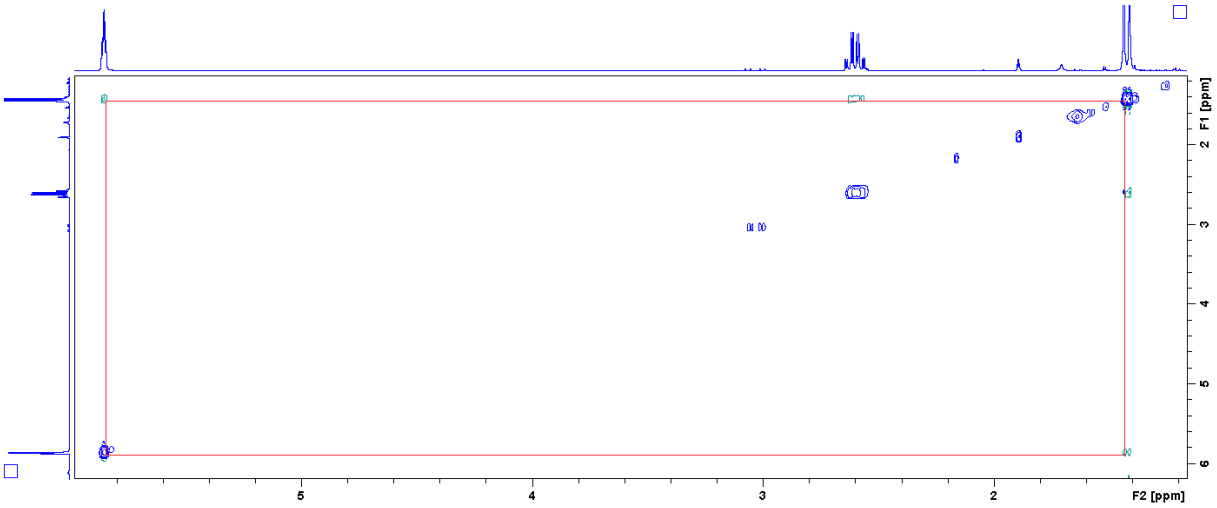
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

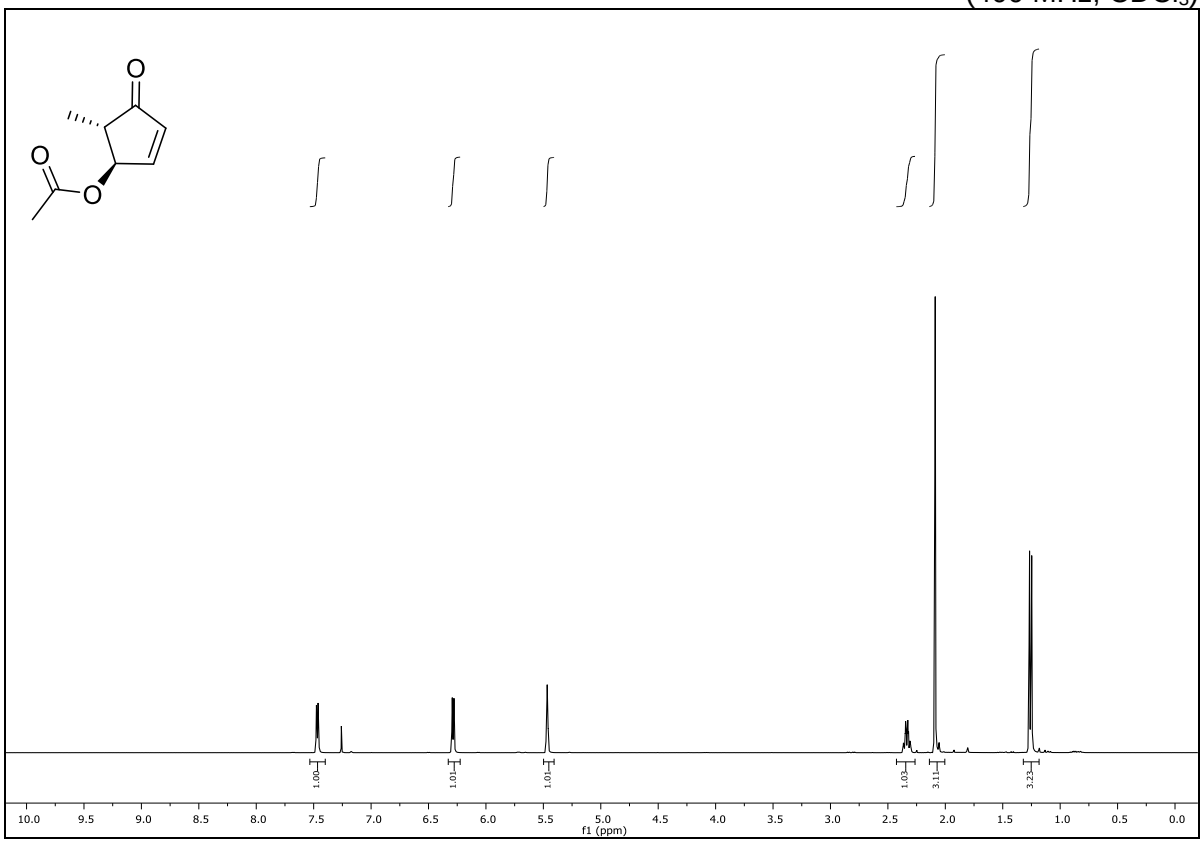


NOESY Zoom In

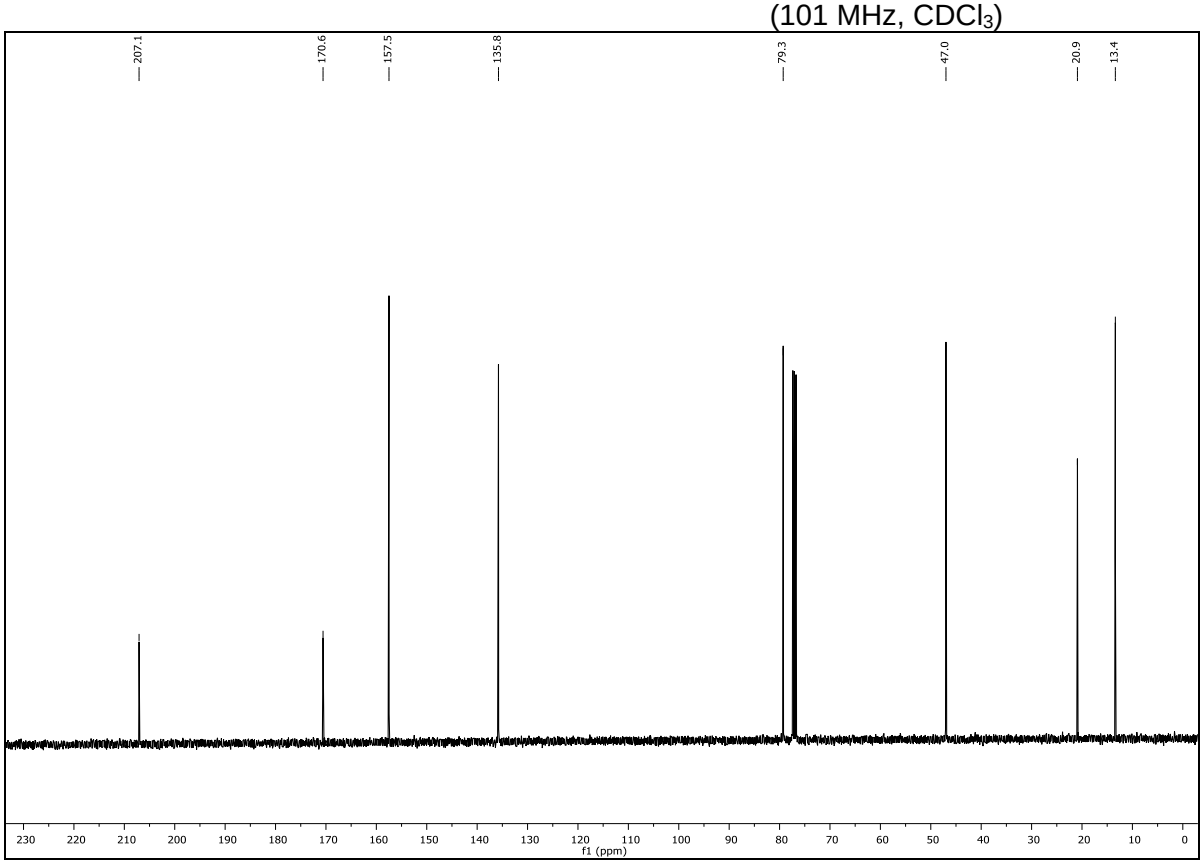


(4*R*,5*S*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-131f)

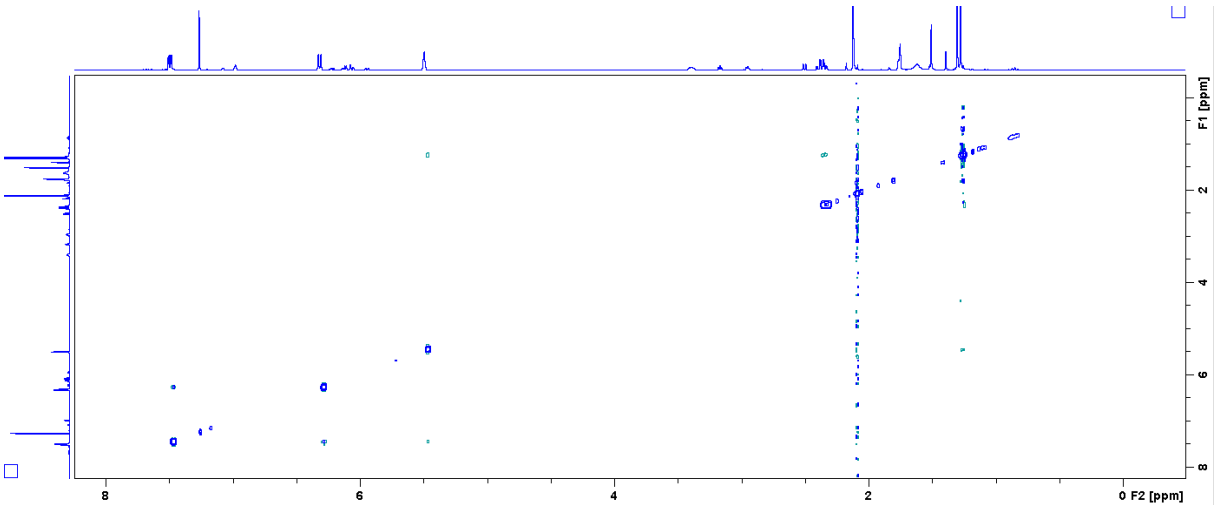
(400 MHz, $CDCl_3$)



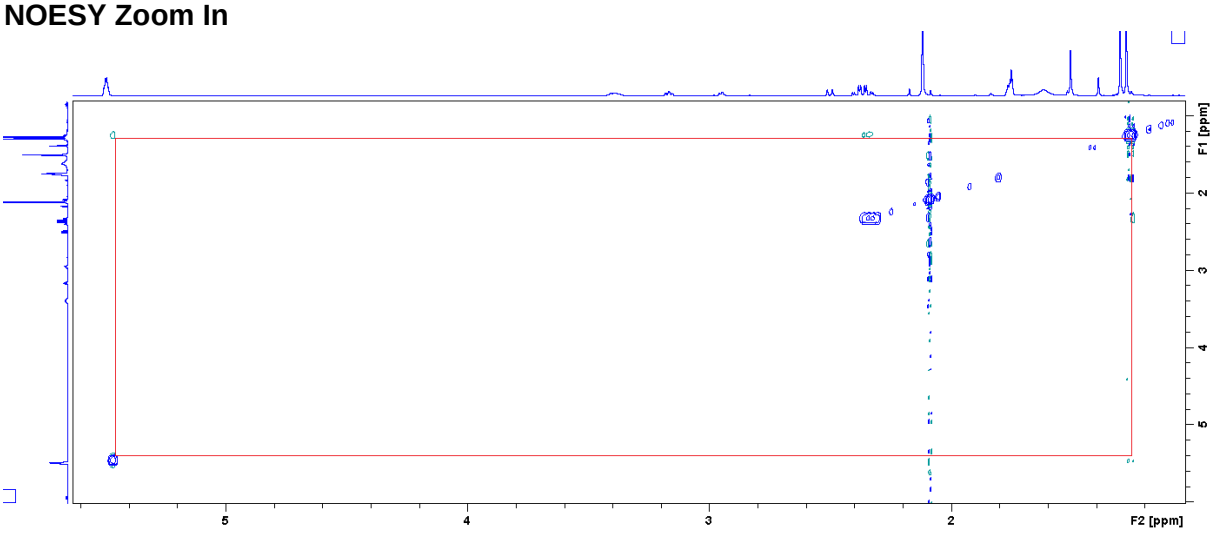
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)



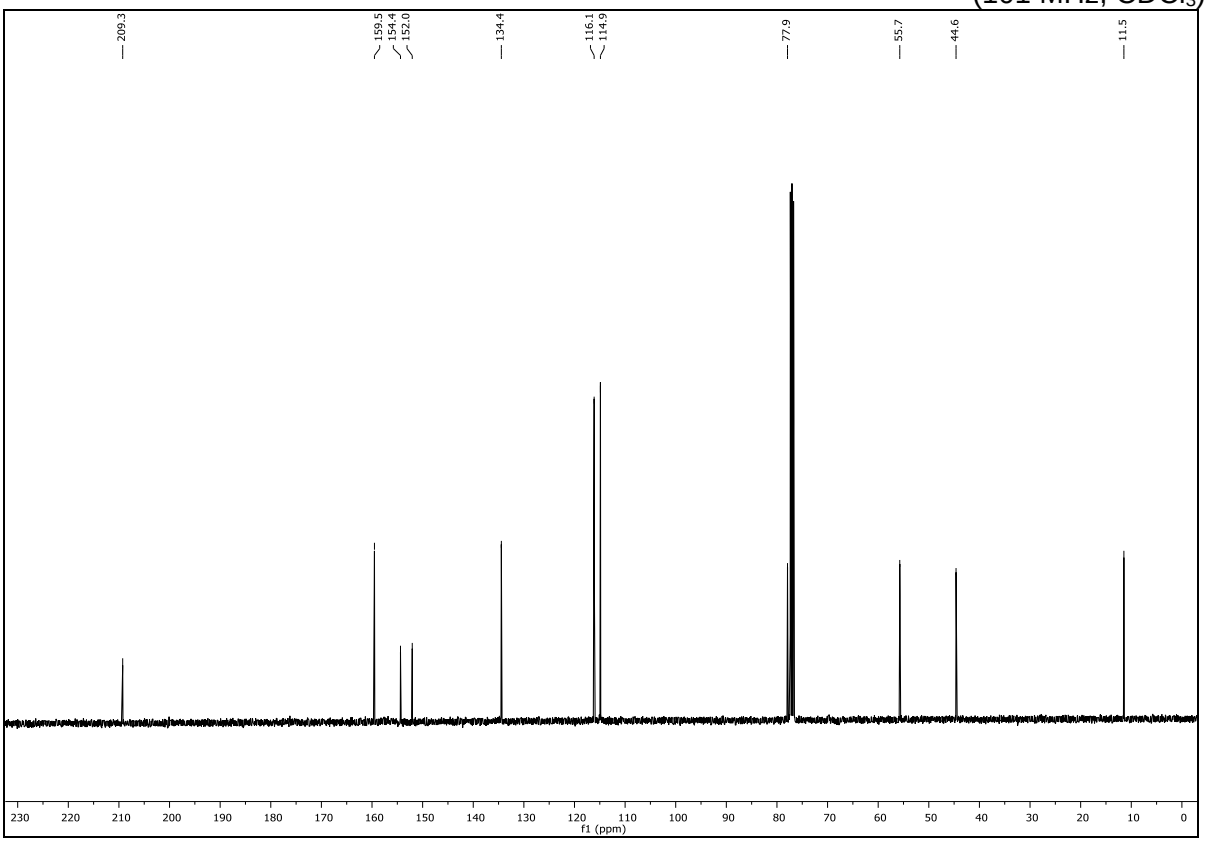
NOESY Zoom In



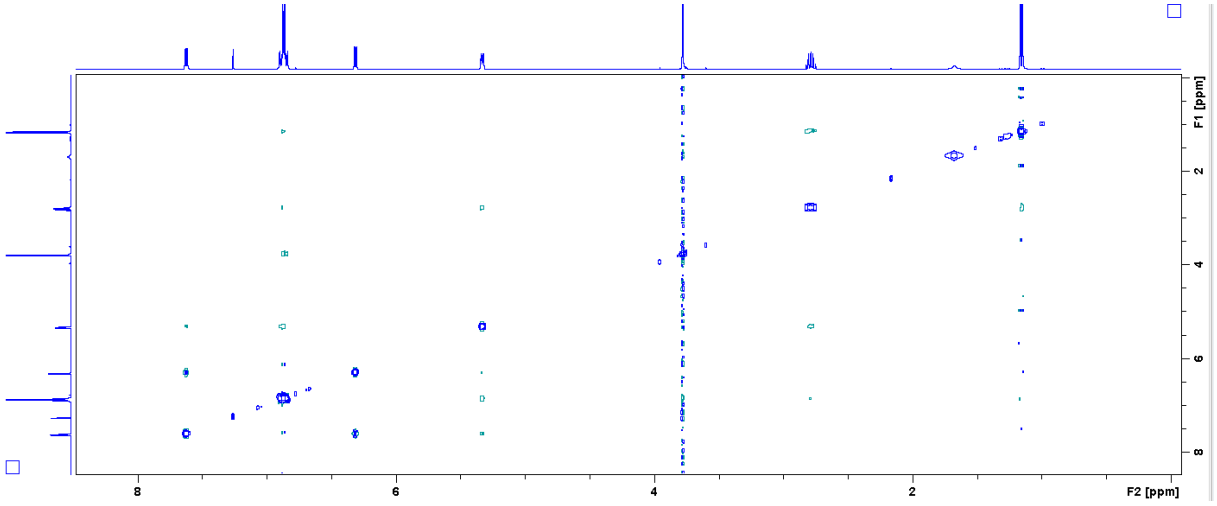
(4*R*,5*R*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((4*R*,5*R*)-*syn*-128f)

400 MHz, $CDCl_3$)

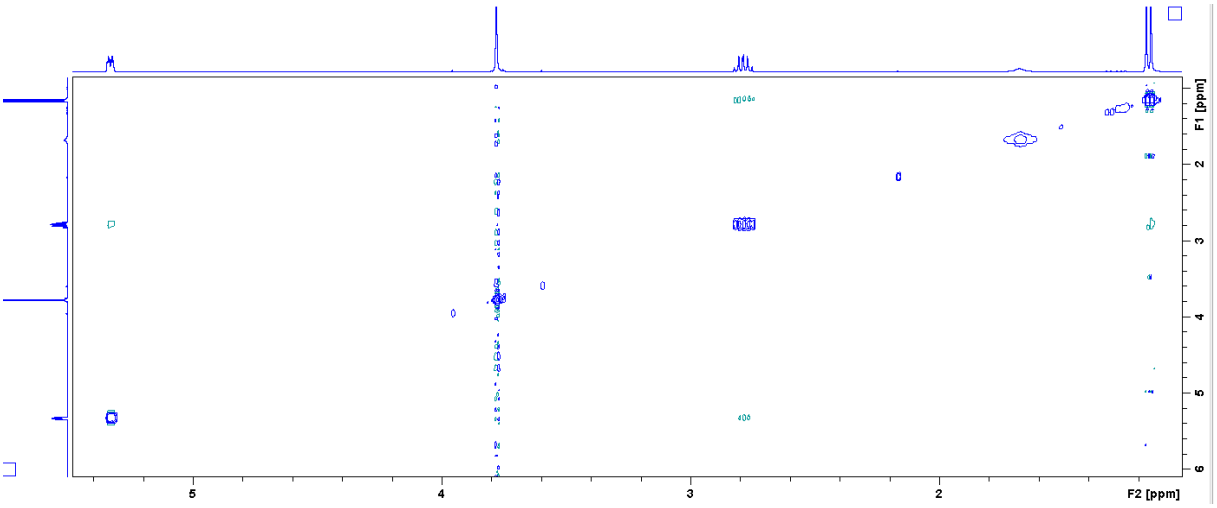
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

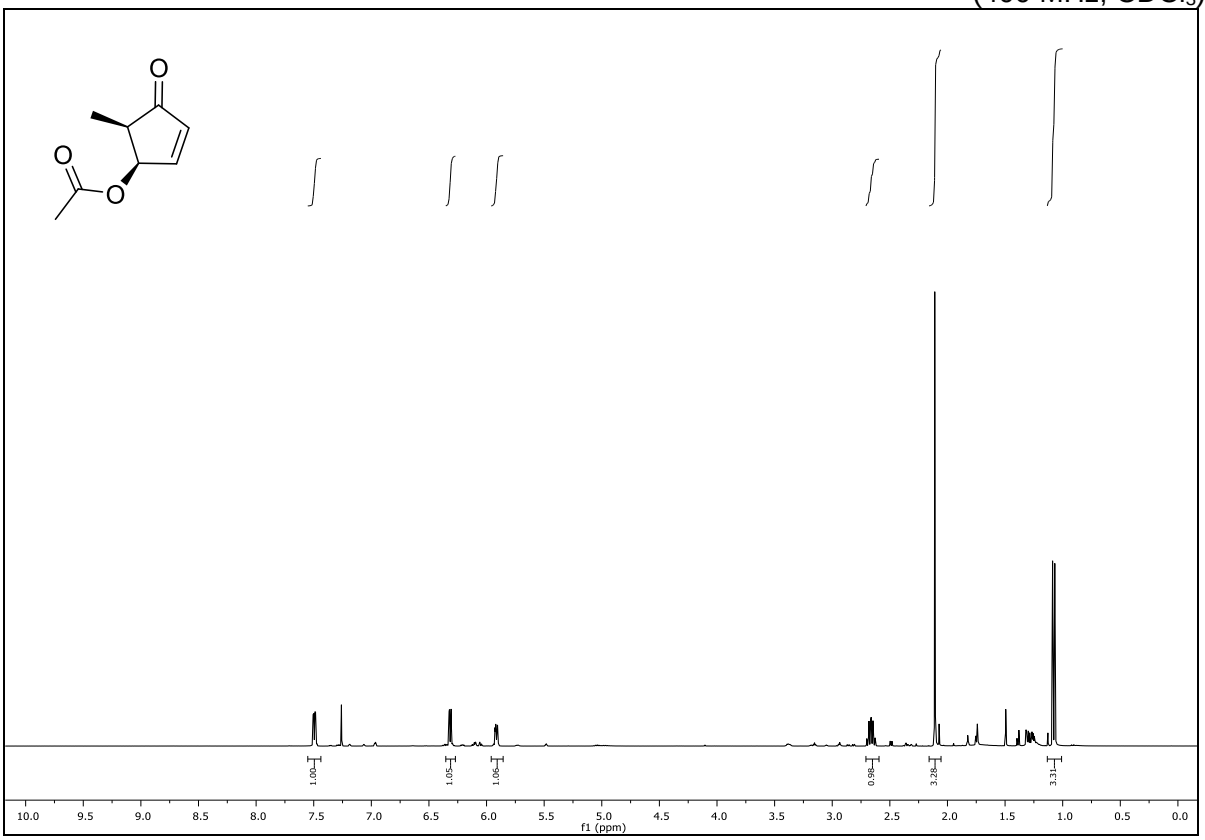


NOESY Zoom In

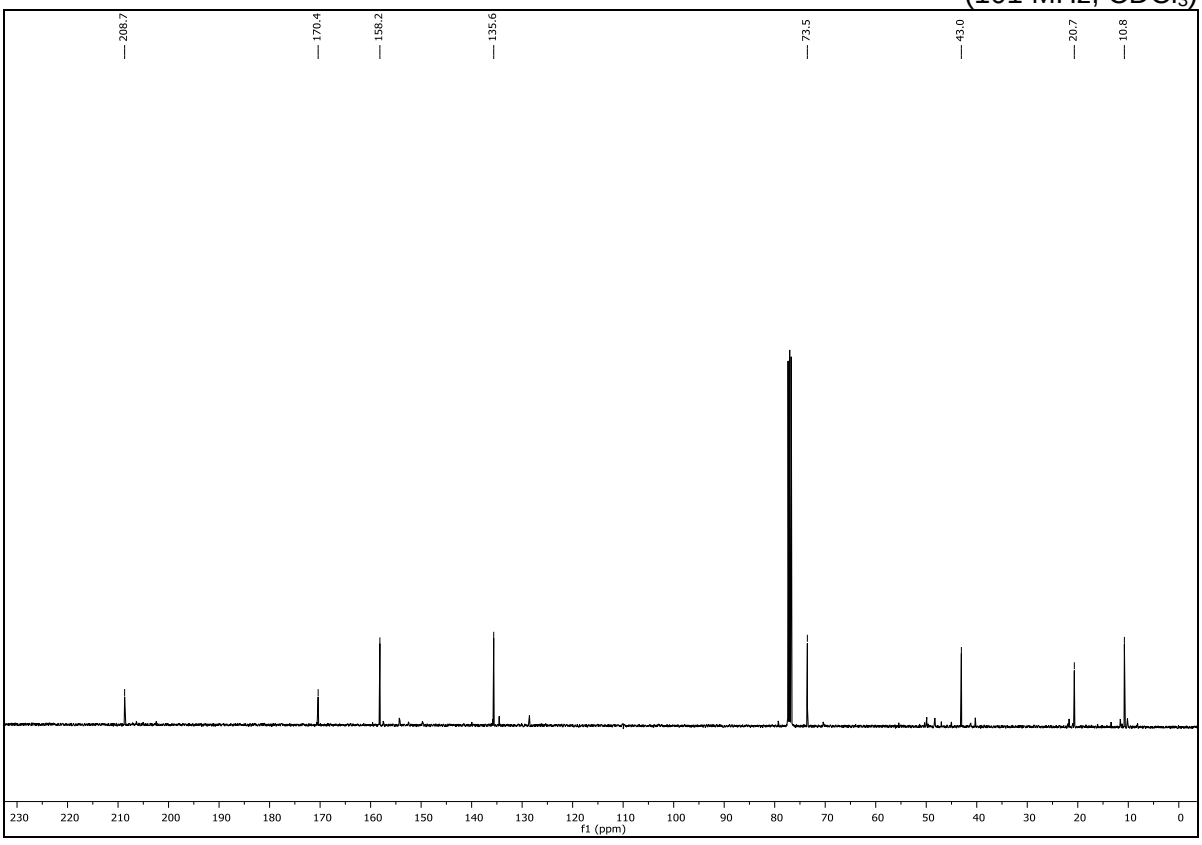


(4*R*,5*R*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((4*R*,5*R*)-*syn*-131f)

(400 MHz, $CDCl_3$)



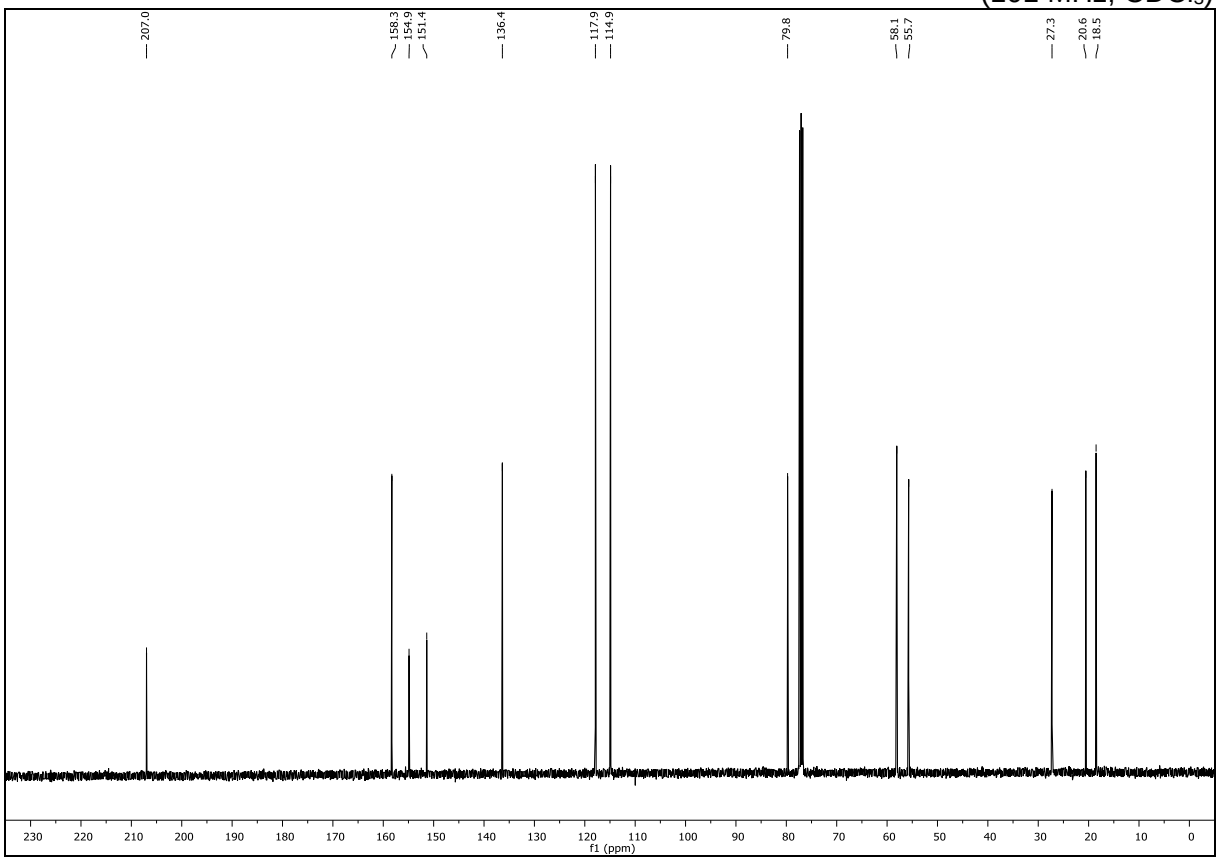
(101 MHz, $CDCl_3$)



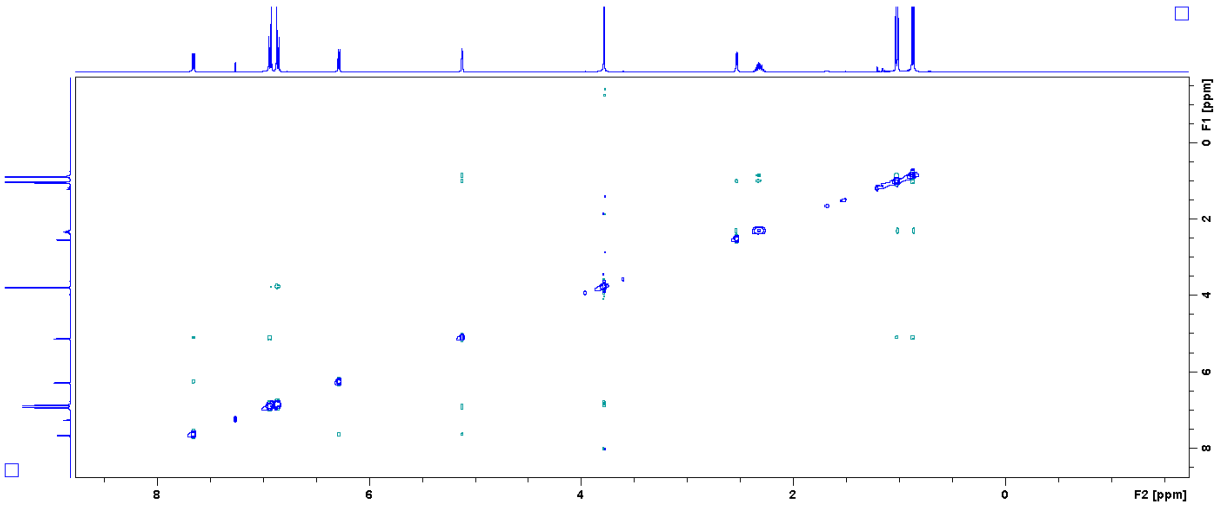
(4*R*,5*S*)-5-isopropyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128g)

(400 MHz, $CDCl_3$)

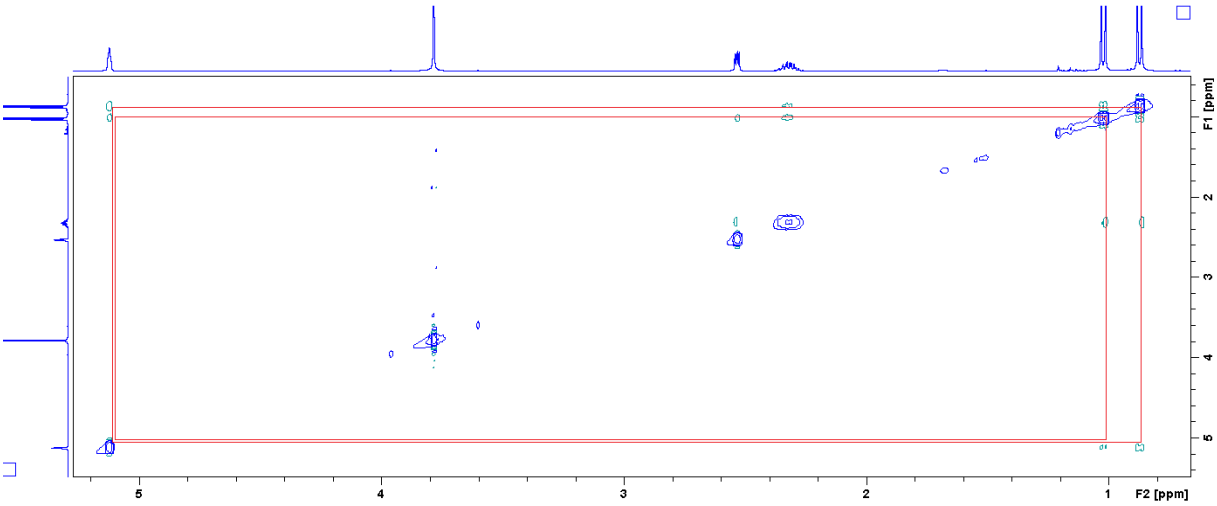
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)



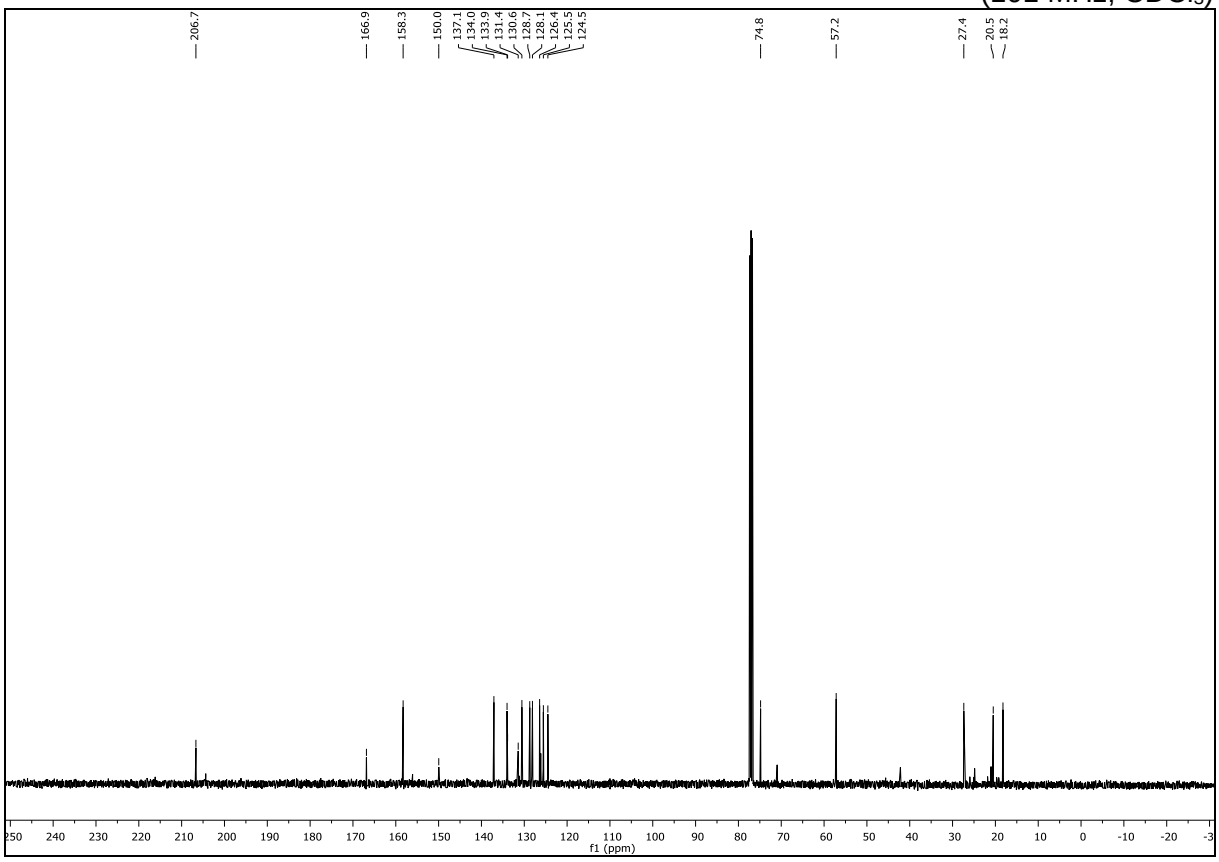
NOESY Zoom In



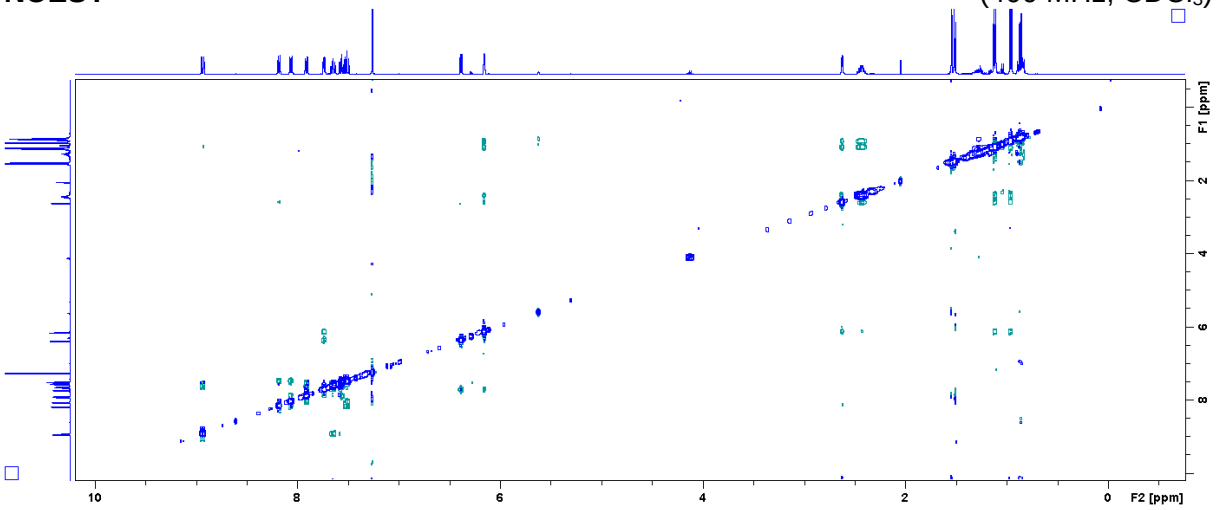
(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isopropylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130g)

(400 MHz, $CDCl_3$)

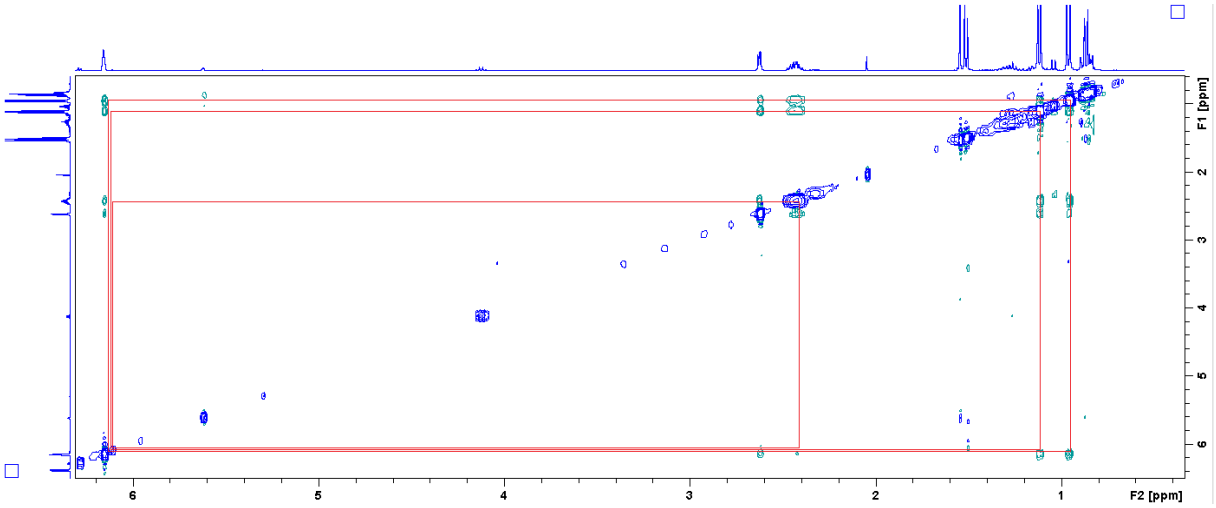
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

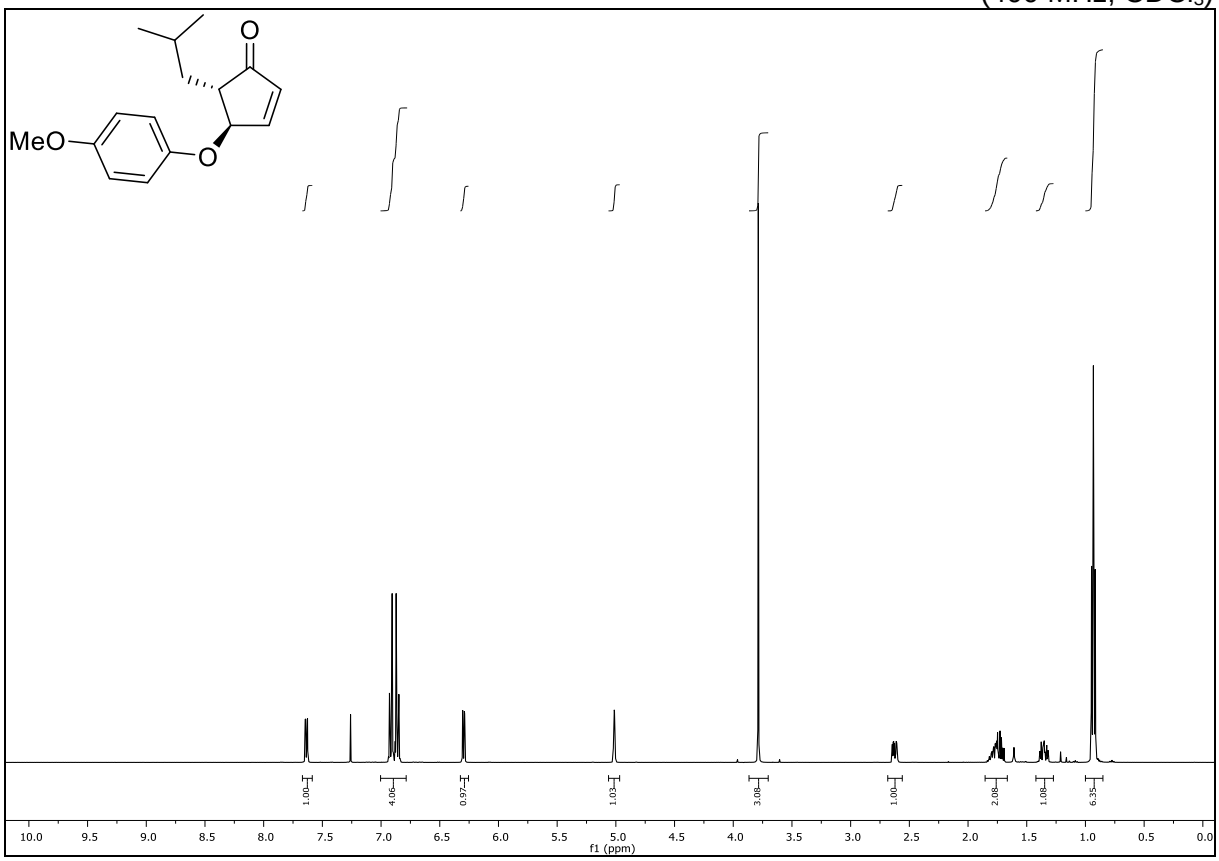


NOESY Zoom In

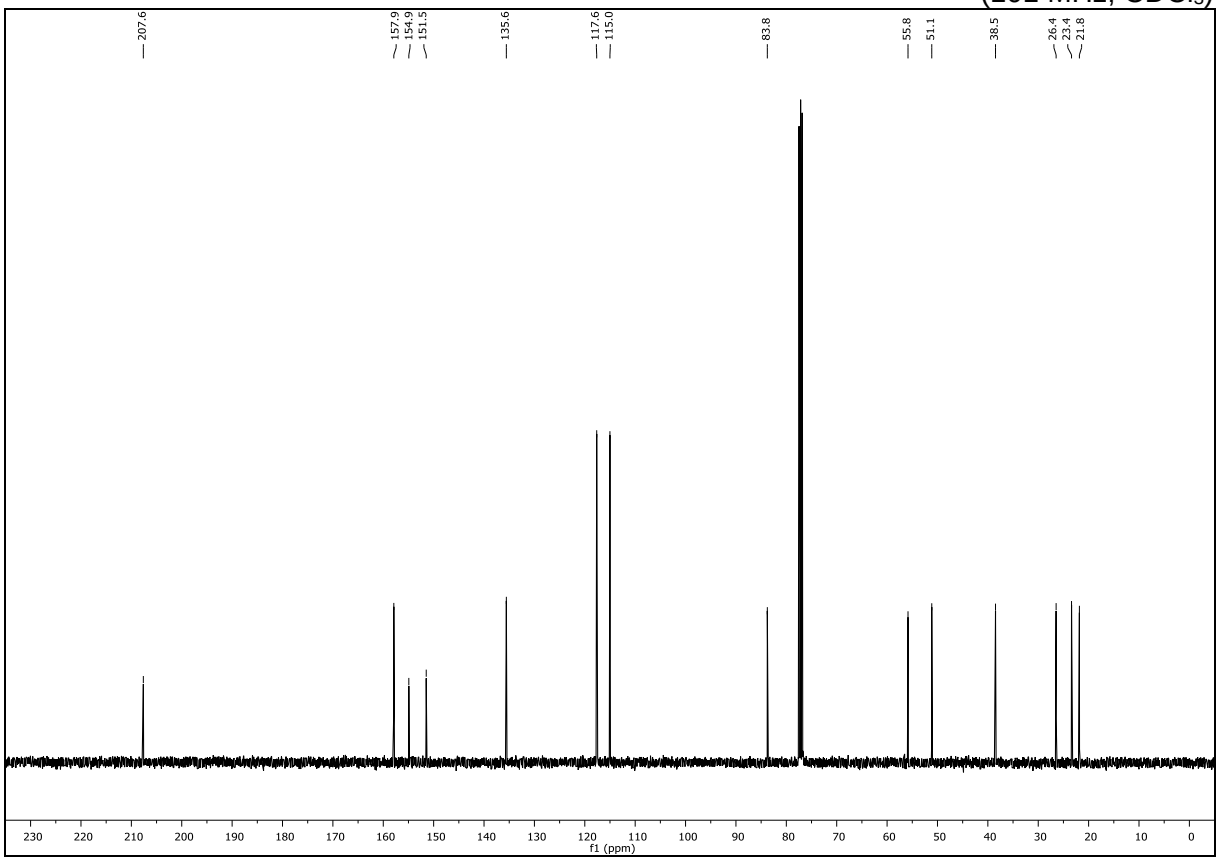


(4*R*,5*S*)-5-isobutyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128i)

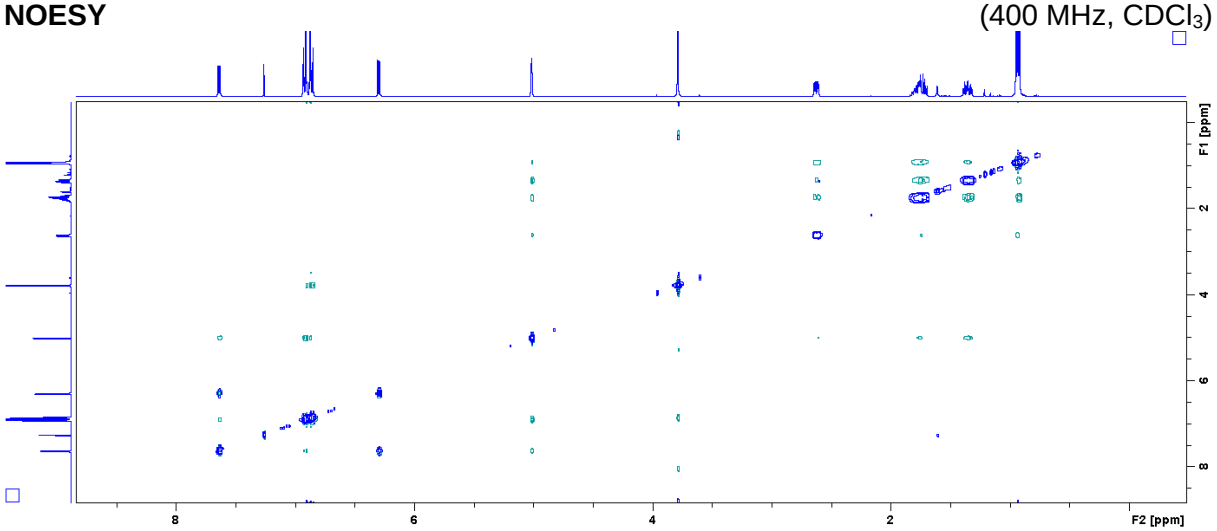
(400 MHz, $CDCl_3$)



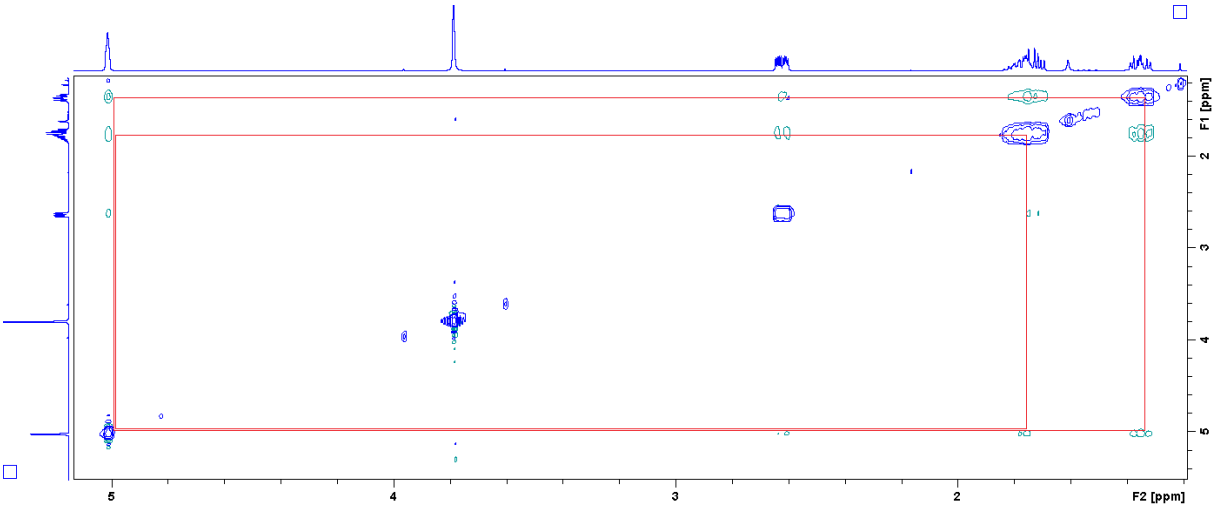
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

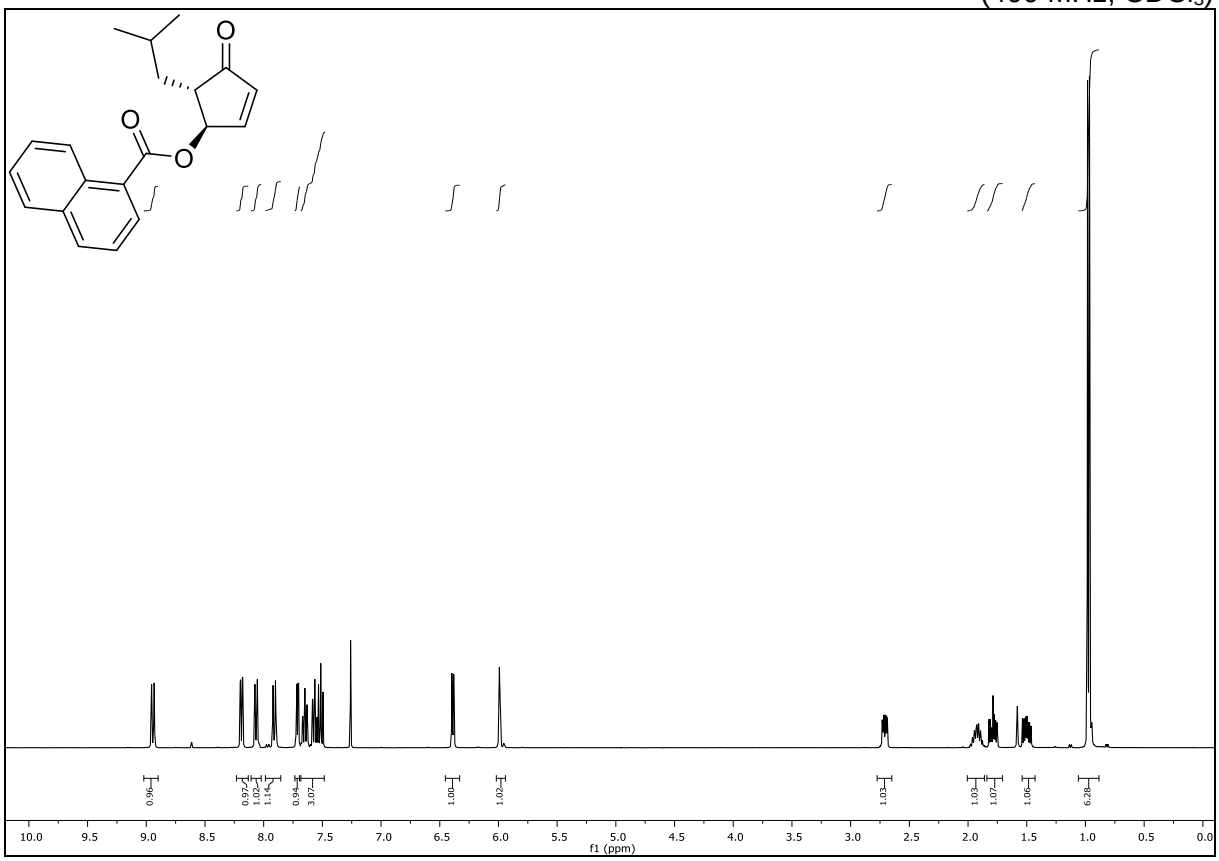


NOESY Zoom In

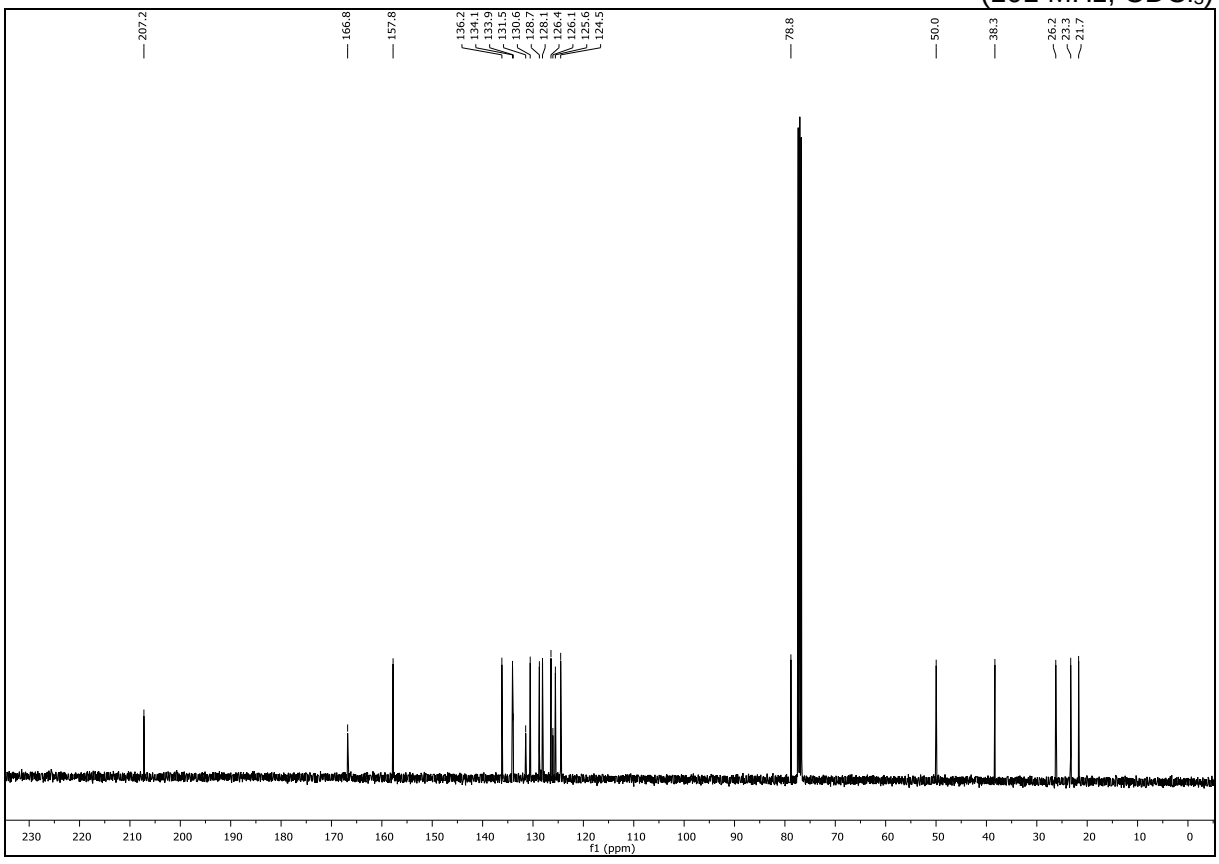


(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isobutylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130i)

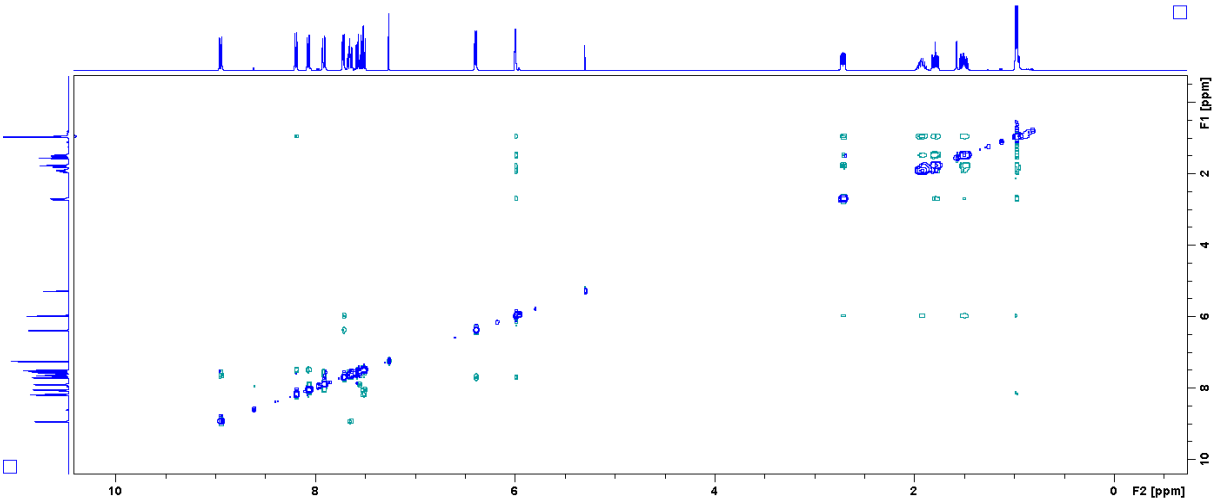
(400 MHz, $CDCl_3$)



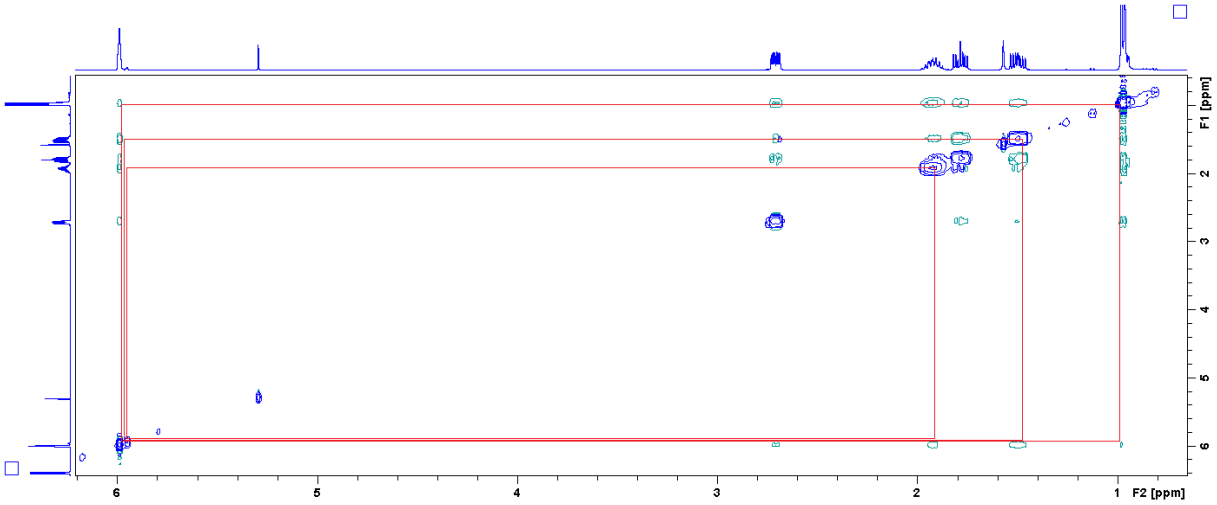
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)



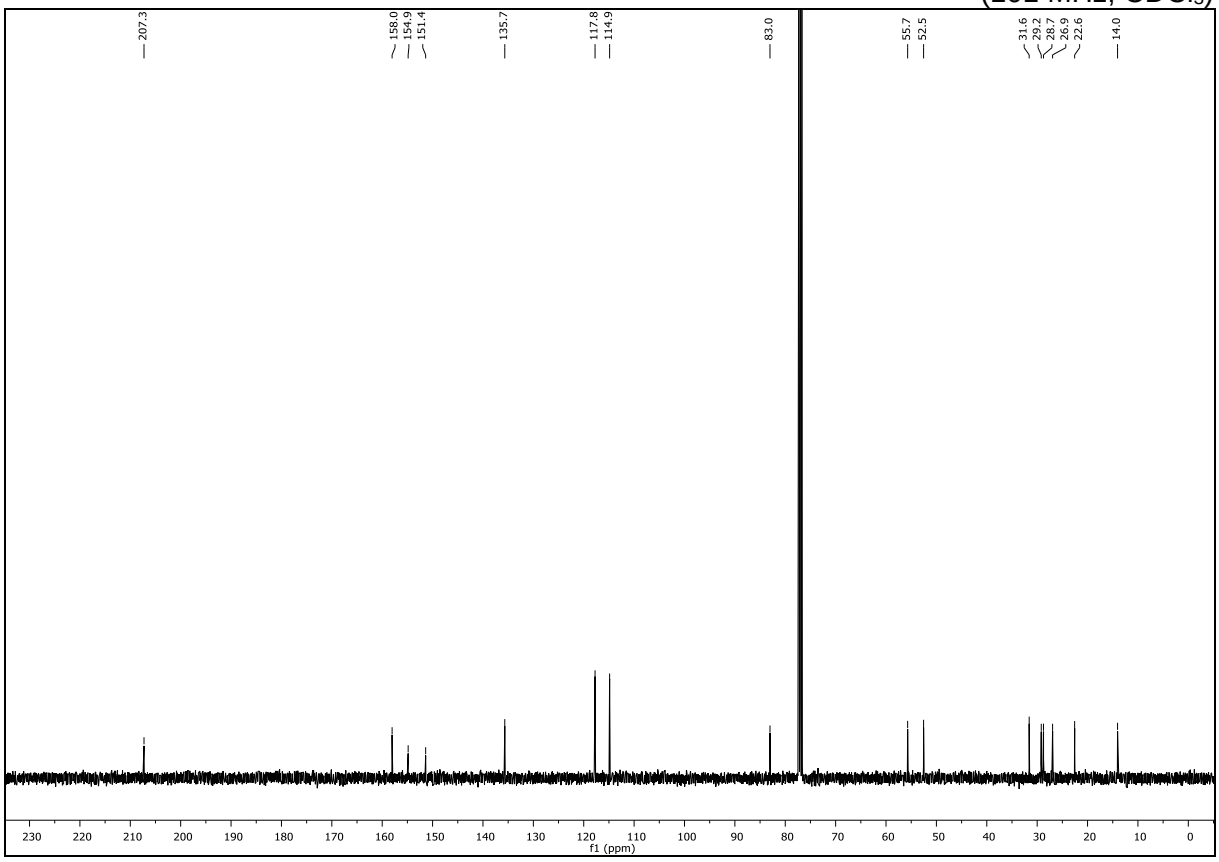
NOESY Zoom In



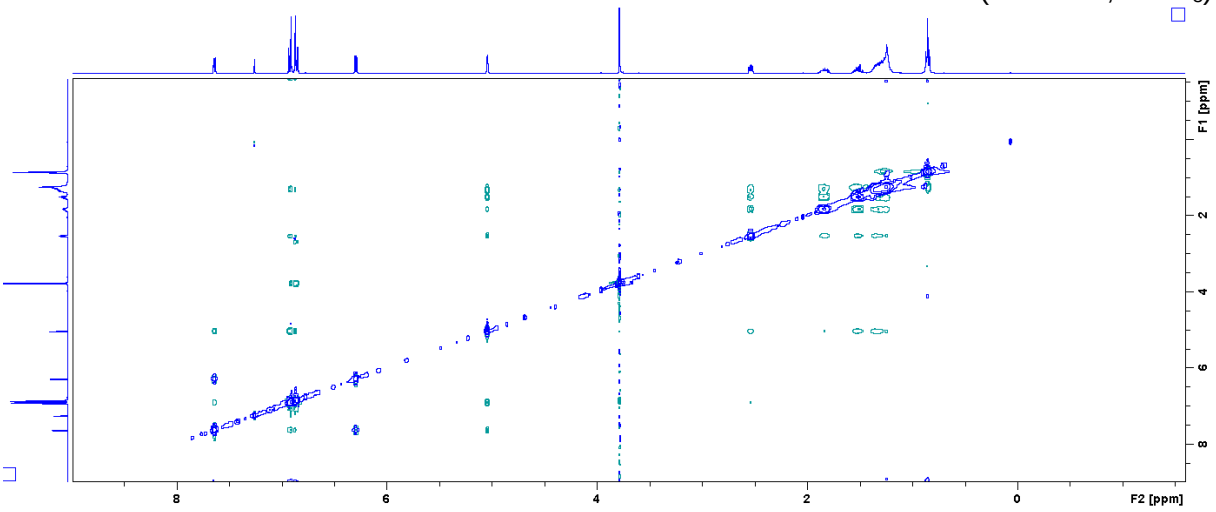
(4*R*,5*S*)-5-hexyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128k)

(400 MHz, $CDCl_3$)

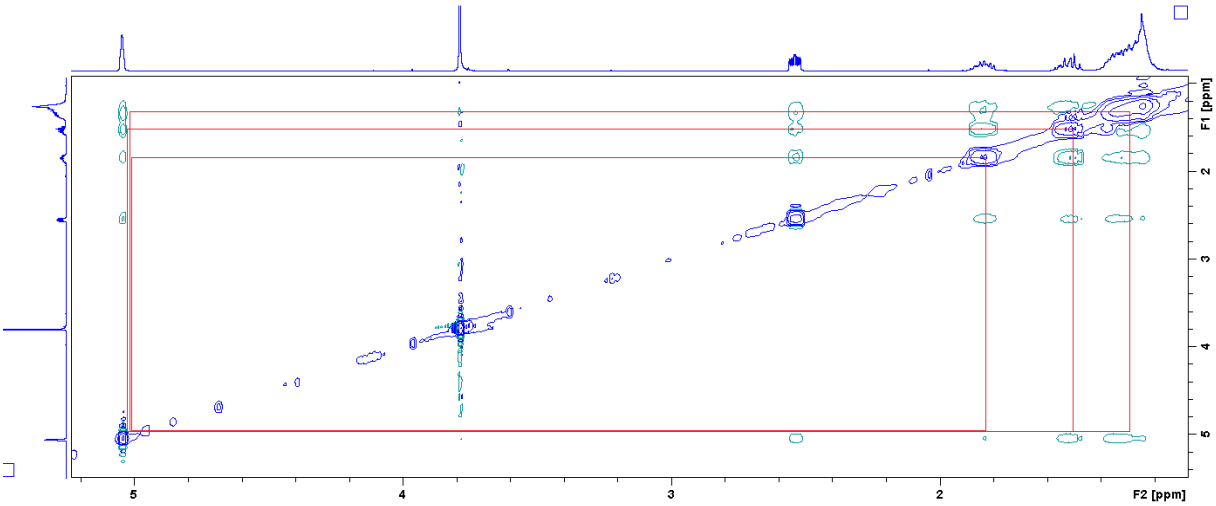
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)



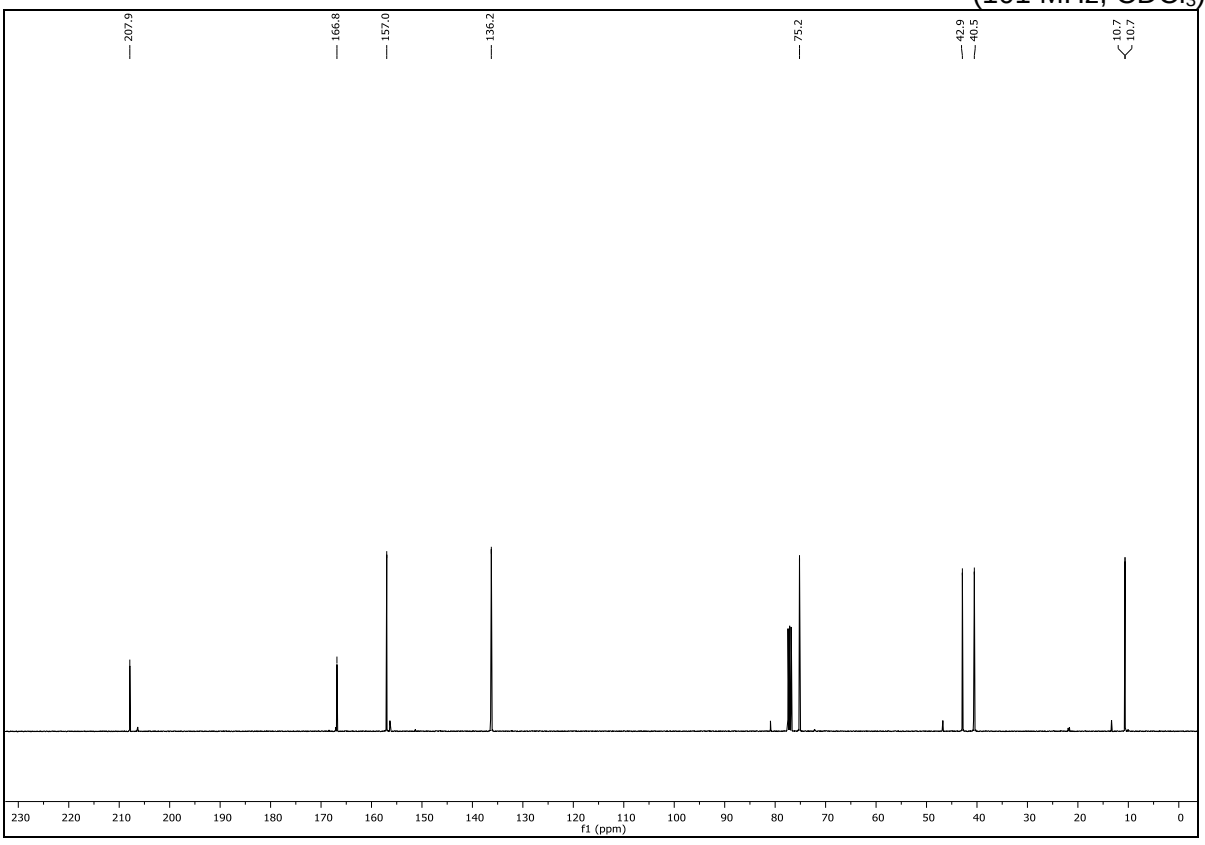
NOESY Zoom In



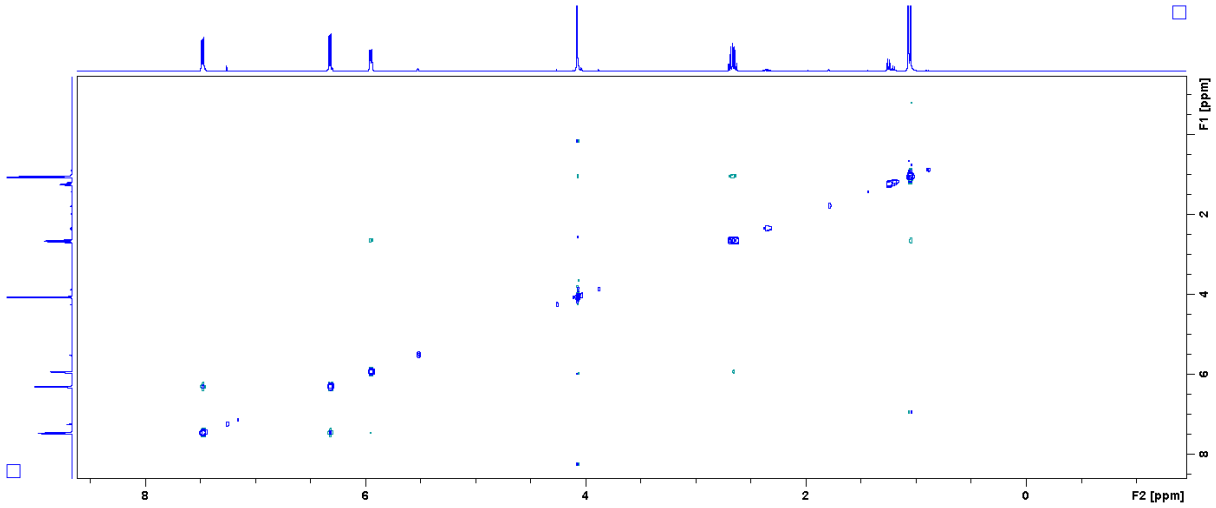
(±)-(4*S*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-185)

(400 MHz, $CDCl_3$)

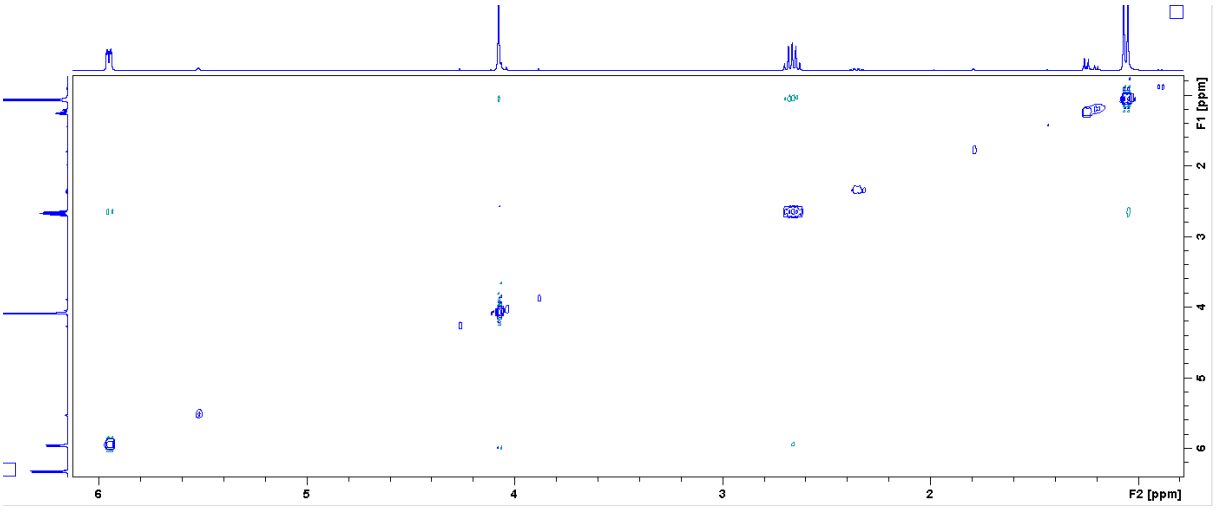
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

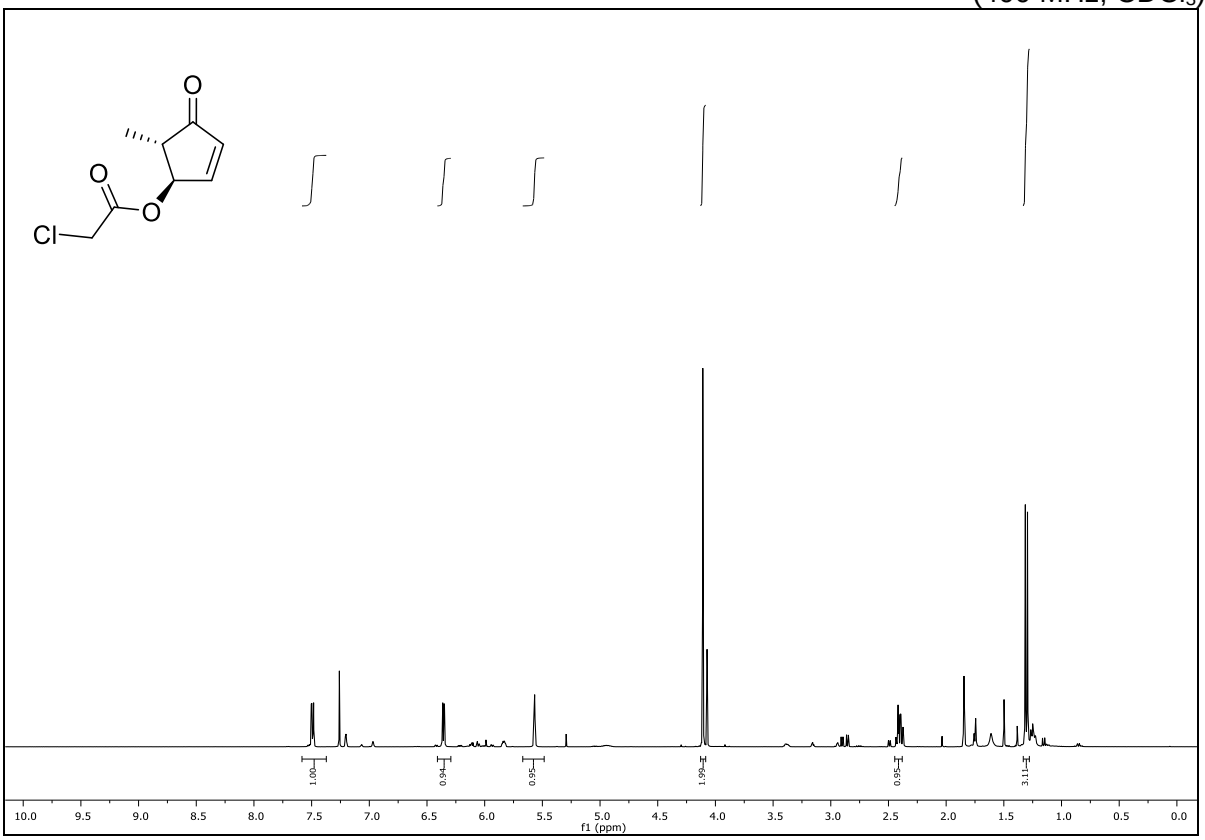


NOESY Zoom In

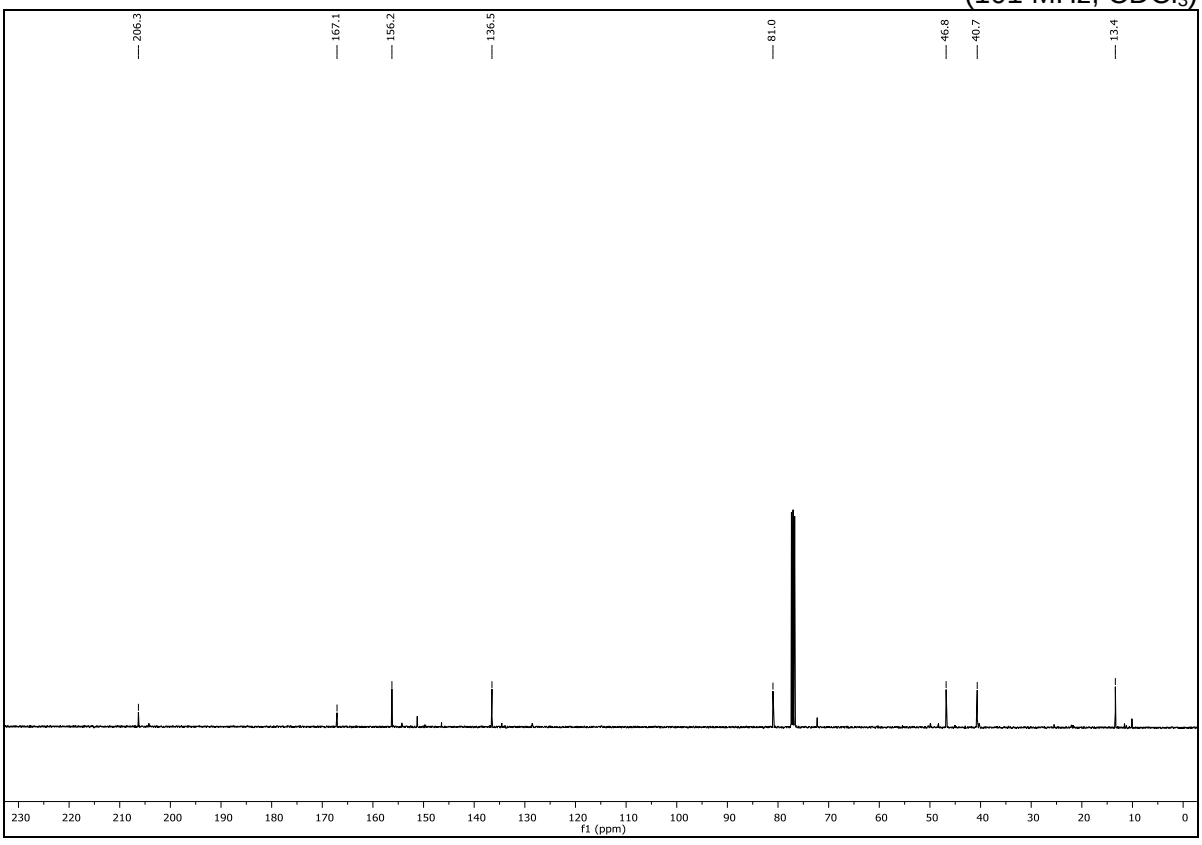


(±)-(4*R*,5*S*)-4-chloroacetoxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-185)

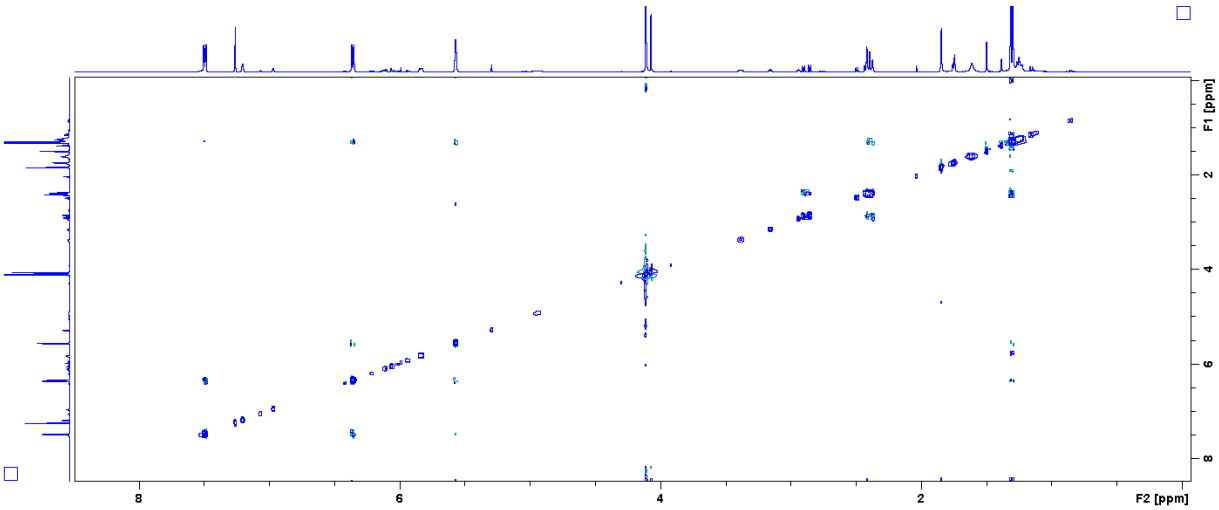
(400 MHz, $CDCl_3$)



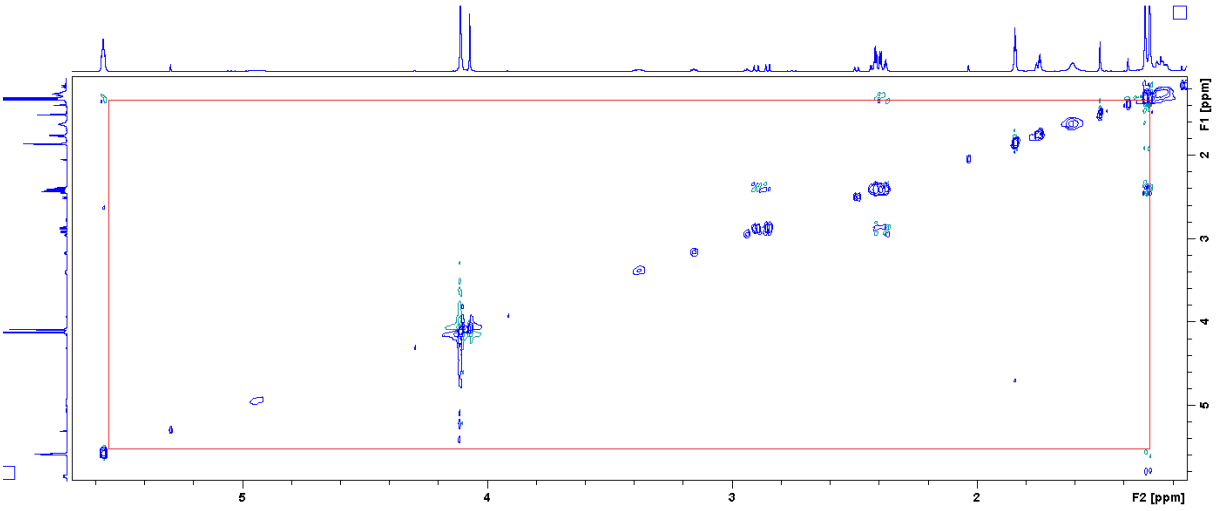
(101 MHz, $CDCl_3$)



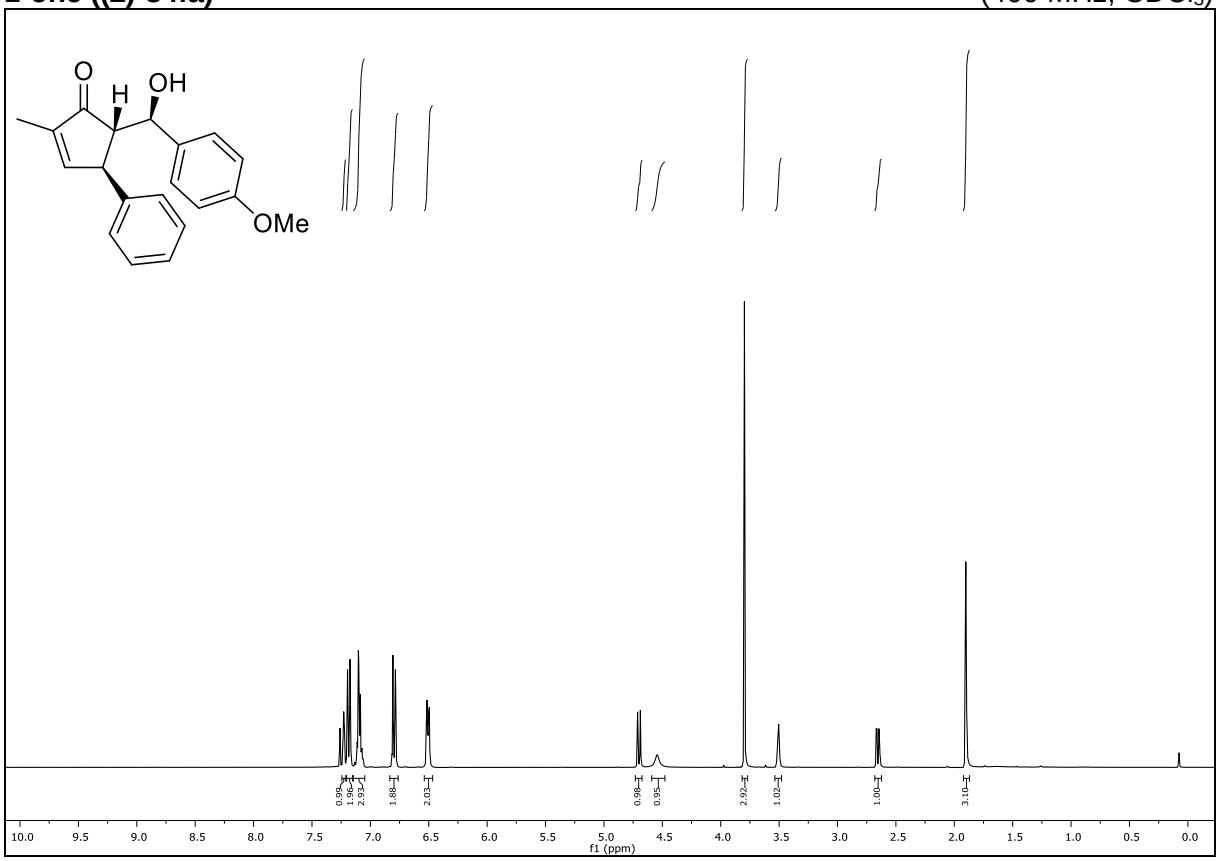
NOESY (400 MHz, $CDCl_3$)



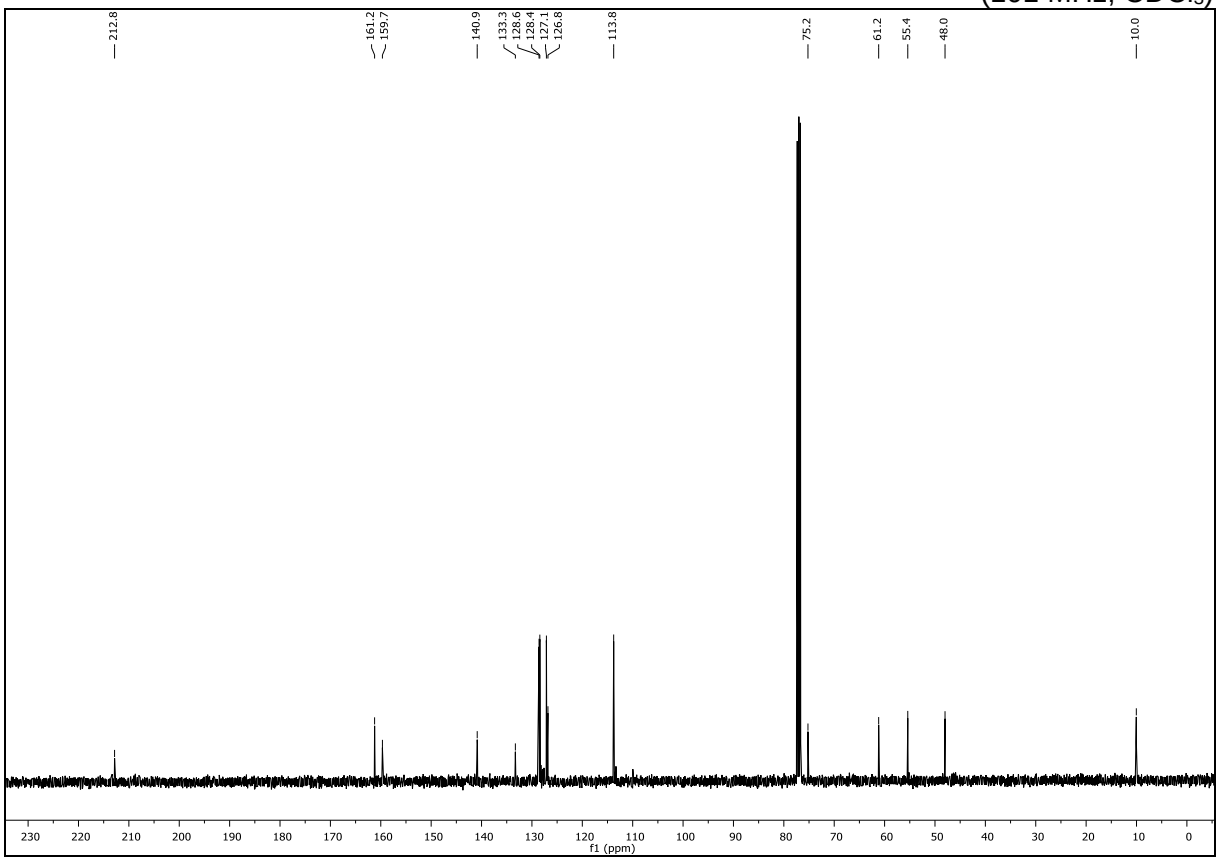
NOESY Zoom In



(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fa) (400 MHz, $CDCl_3$)

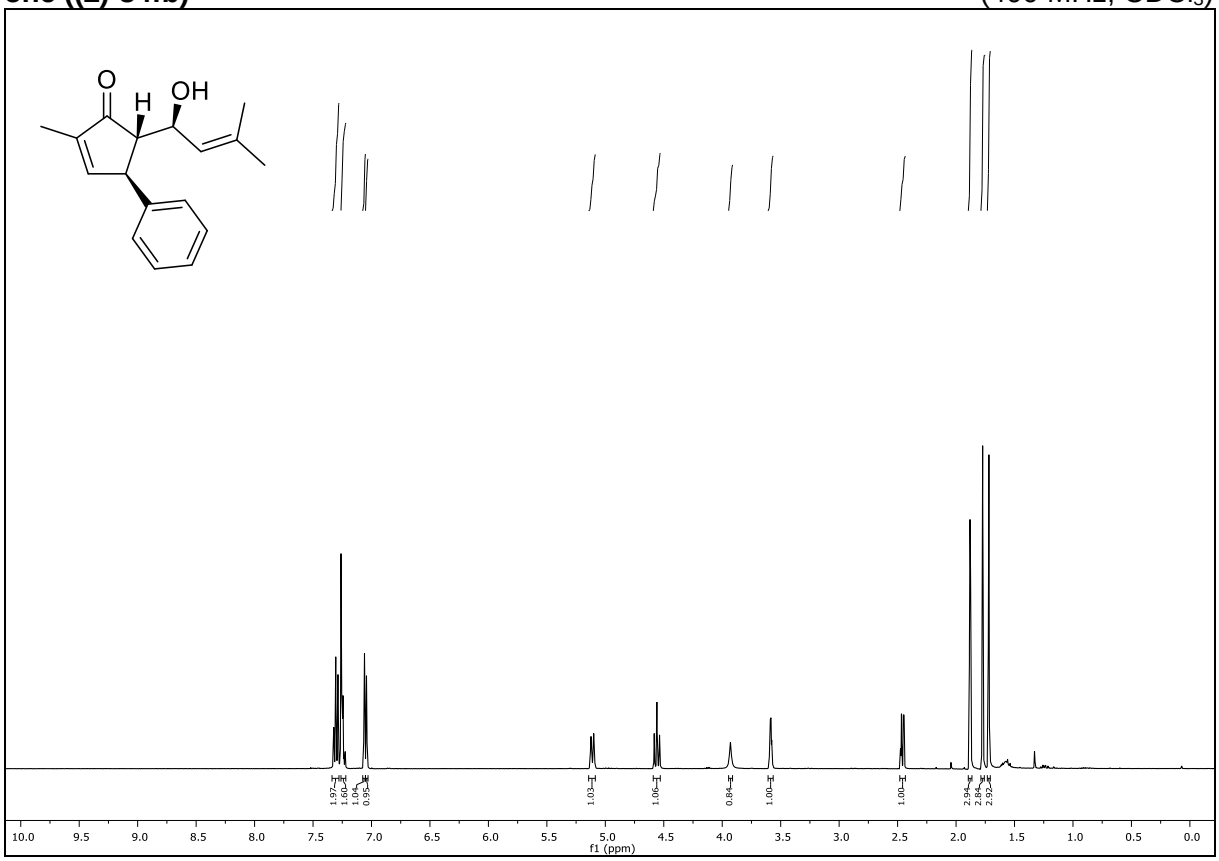


(101 MHz, $CDCl_3$)

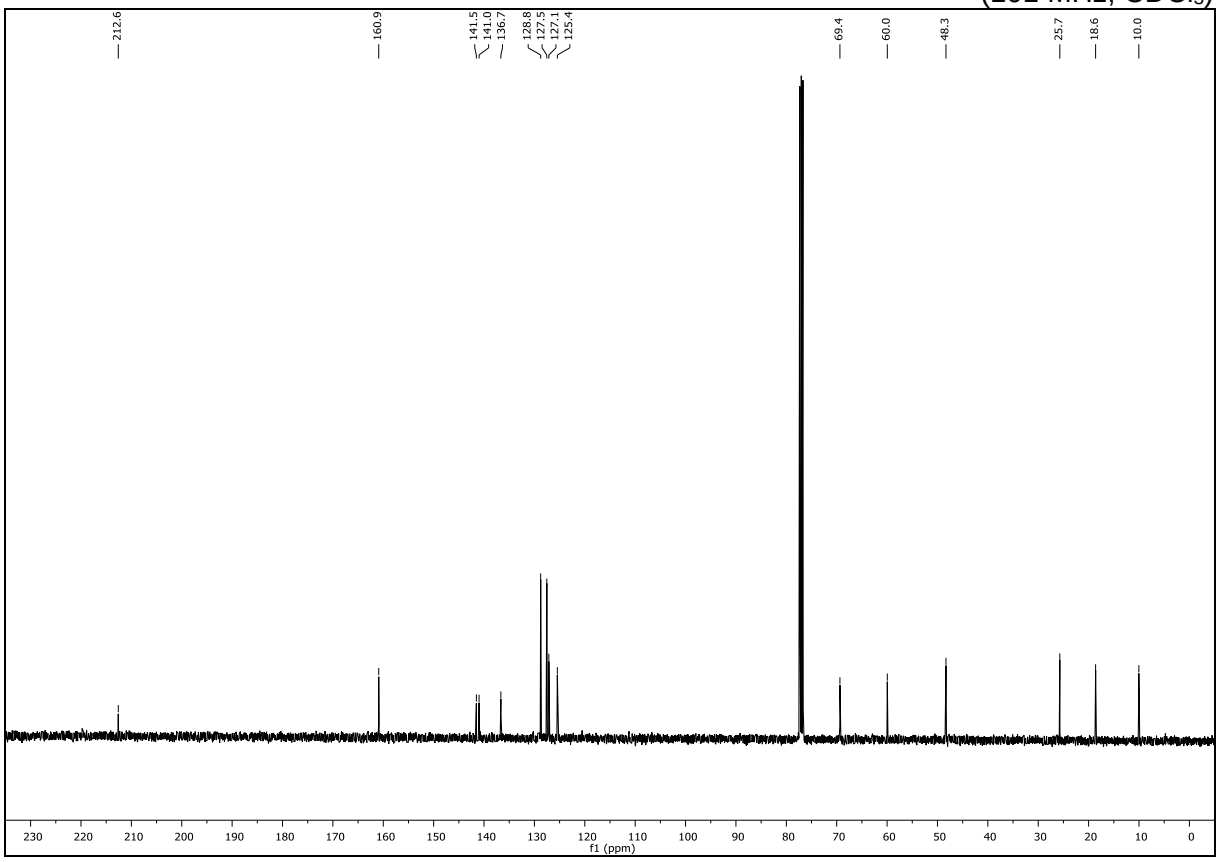


(±)-(4*R*,5*S*)-5-((*S*)-1-hydroxy-3-methylbut-2-en-1-yl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fb)

(400 MHz, $CDCl_3$)

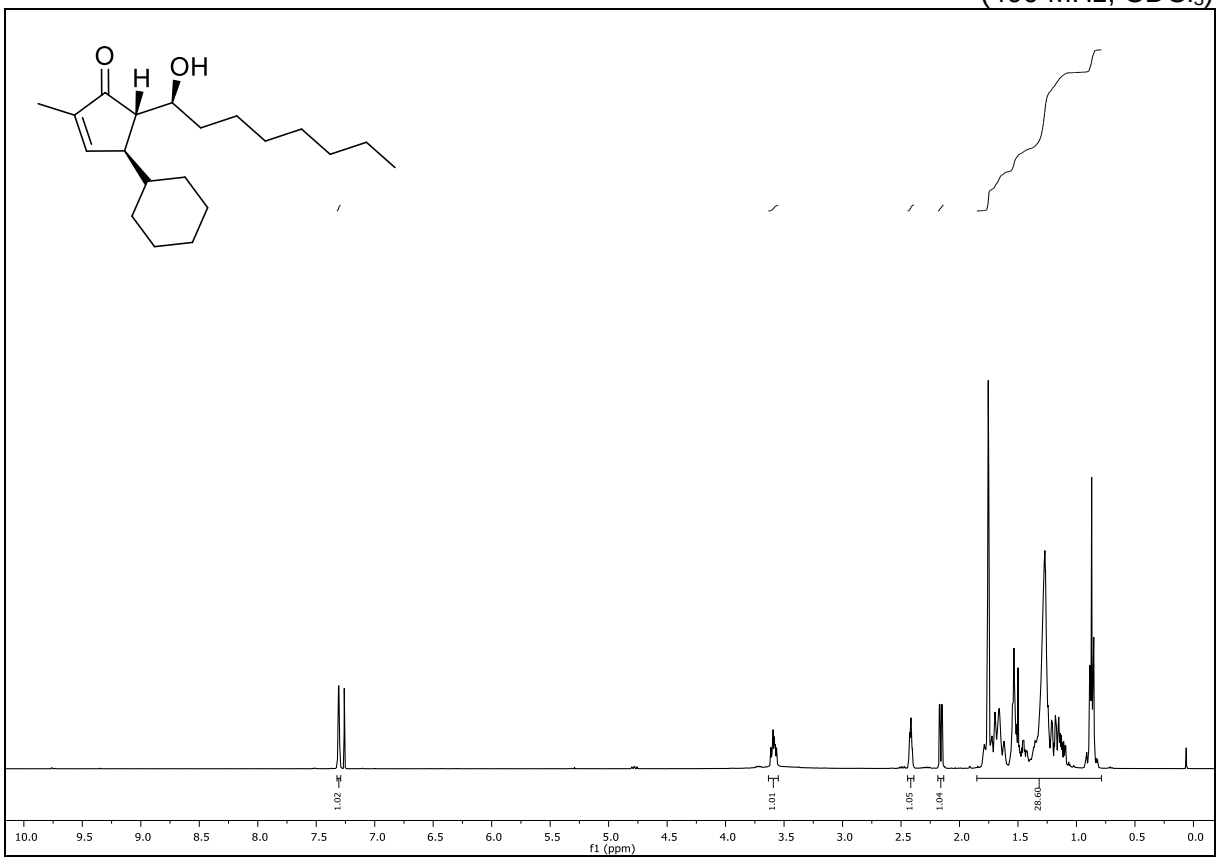


(101 MHz, $CDCl_3$)

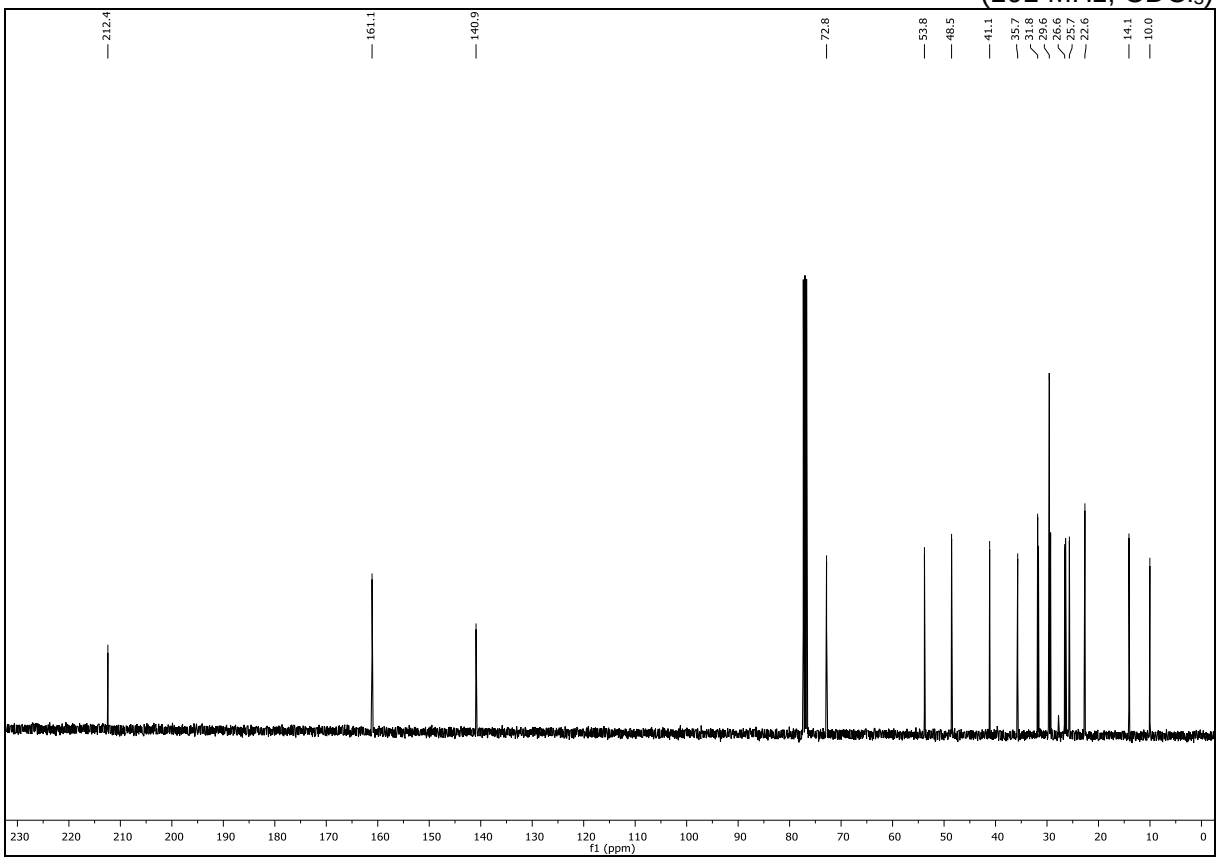


(±)-(4*S*,5*S*)-4-cyclohexyl-5-((*S*)-1-hydroxyoctyl)-2-methylcyclopent-2-en-1-one ((±)-84fc)

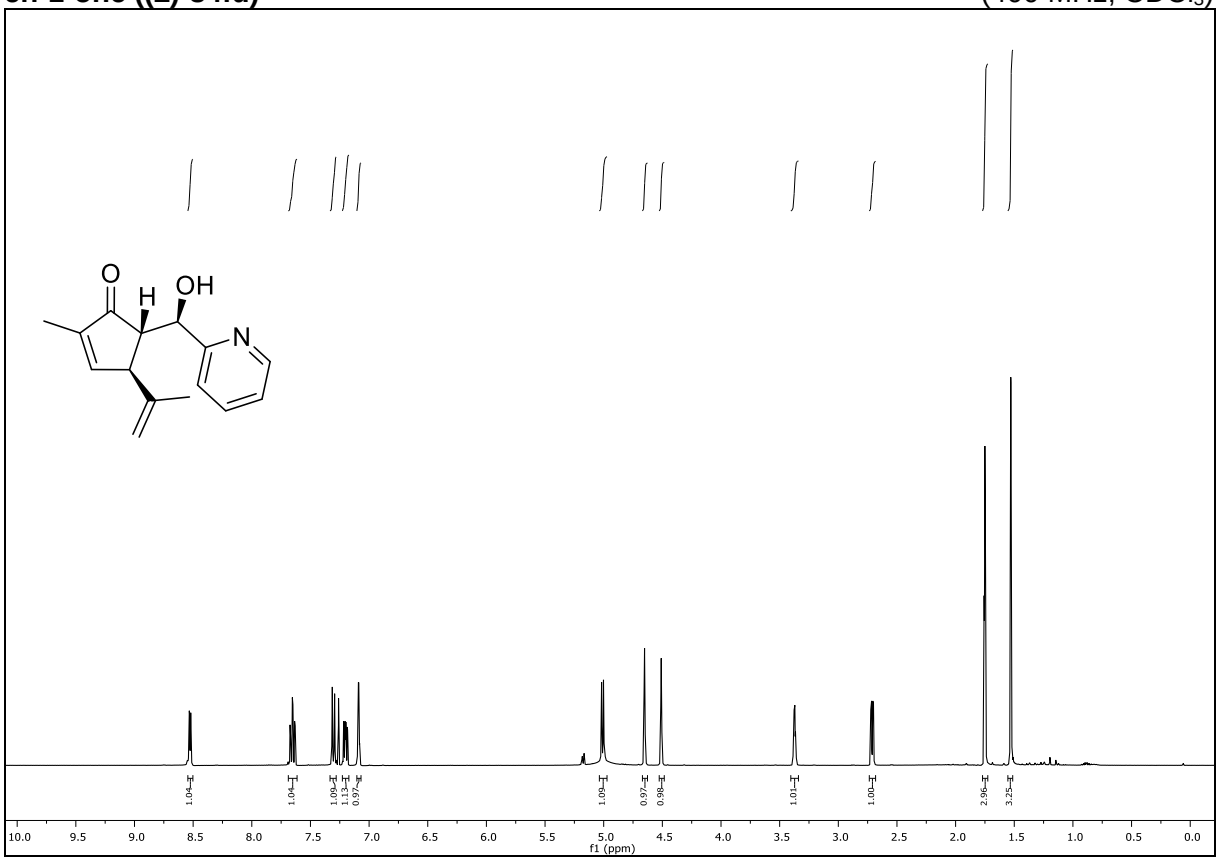
(400 MHz, $CDCl_3$)



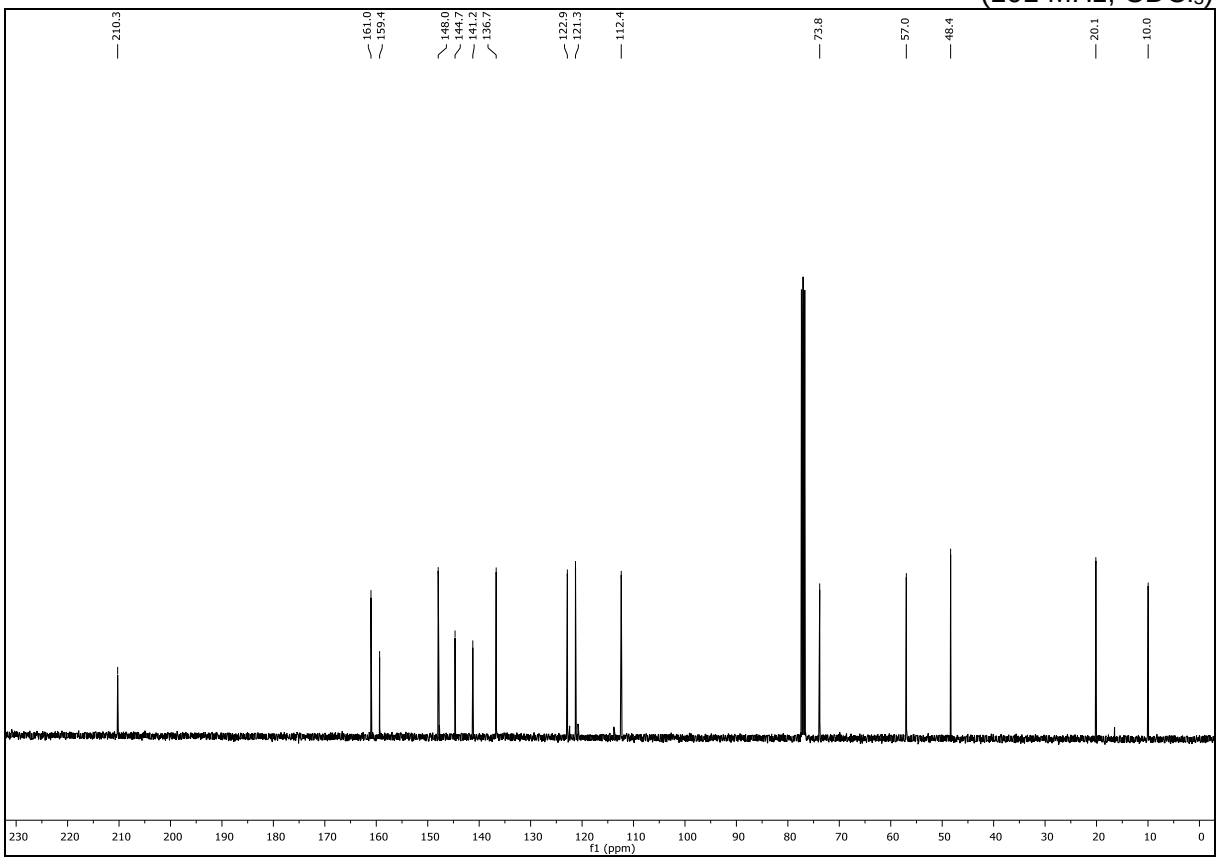
(101 MHz, $CDCl_3$)



(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2-methyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84fd) (400 MHz, $CDCl_3$)

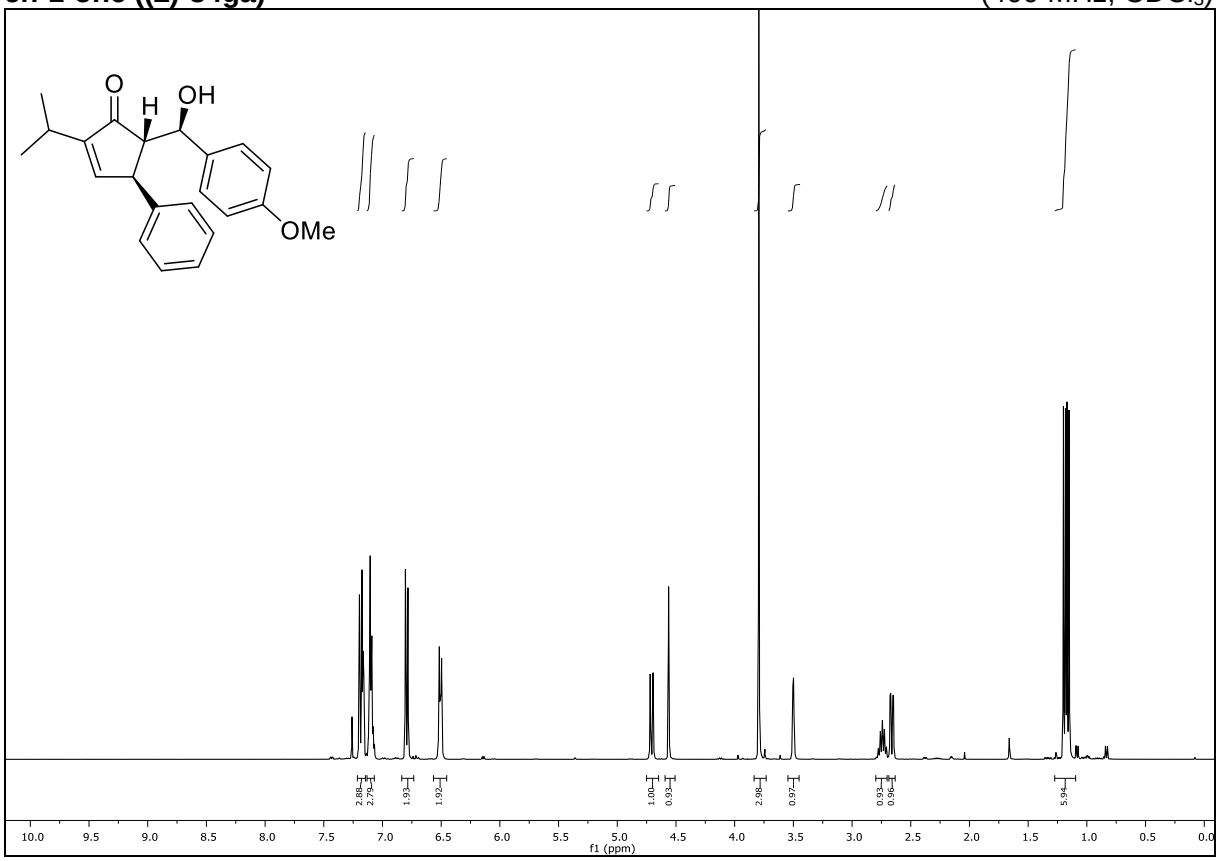


(101 MHz, $CDCl_3$)

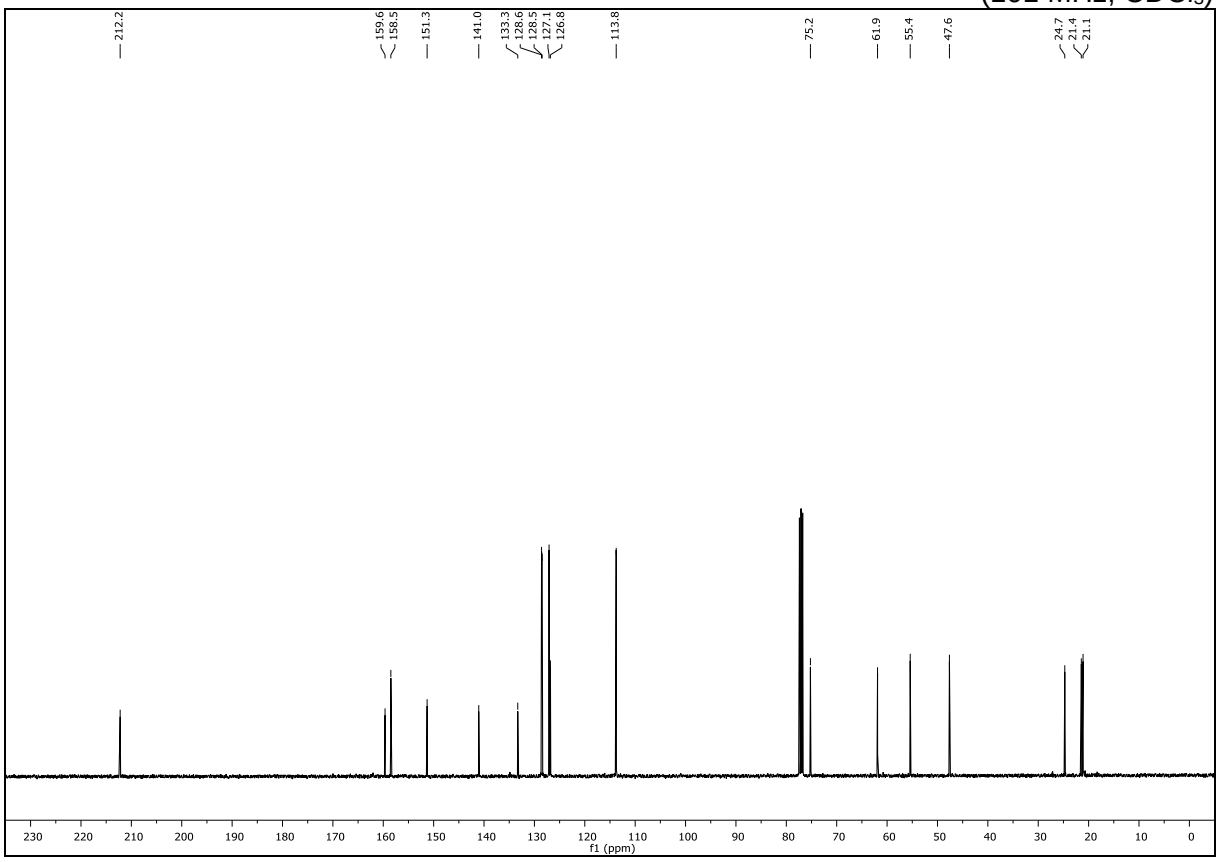


(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-isopropyl-4-phenylcyclopent-2-en-1-one ((±)-84ga)

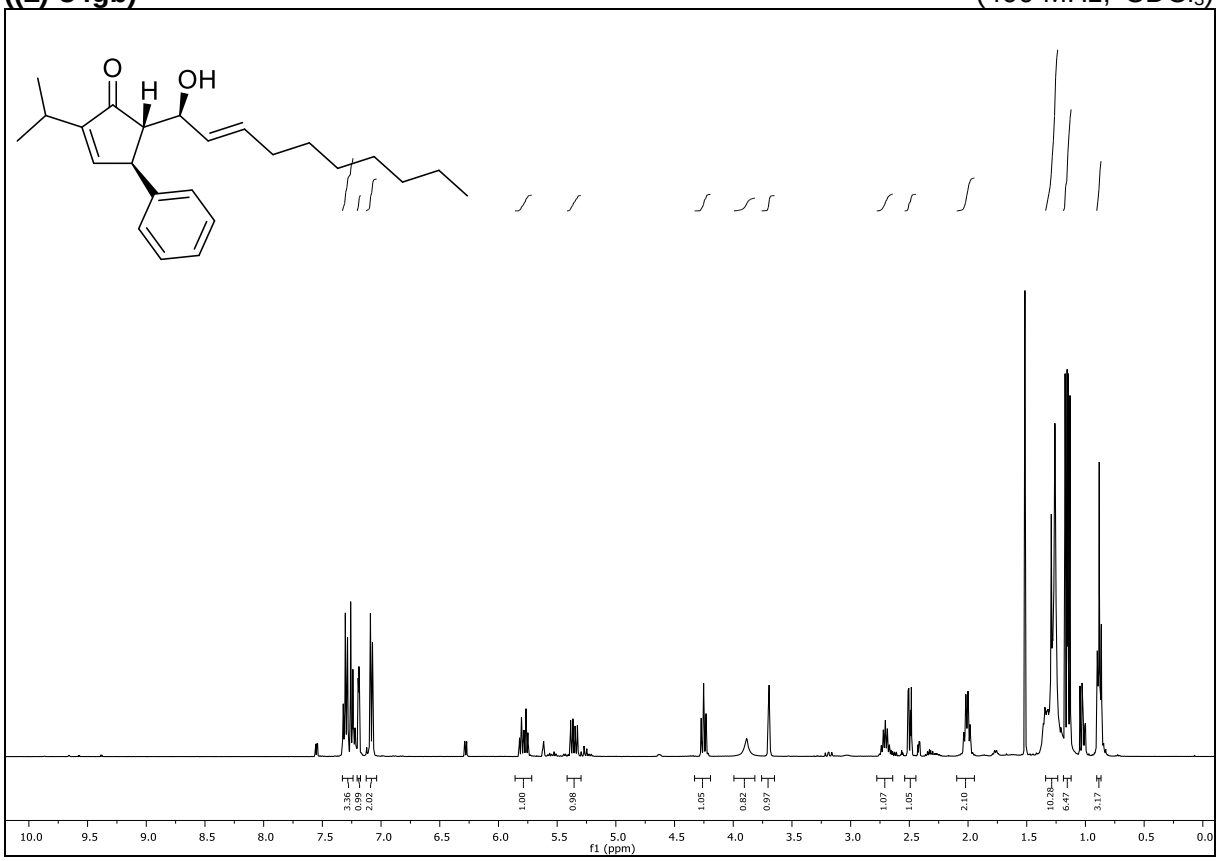
(400 MHz, $CDCl_3$)



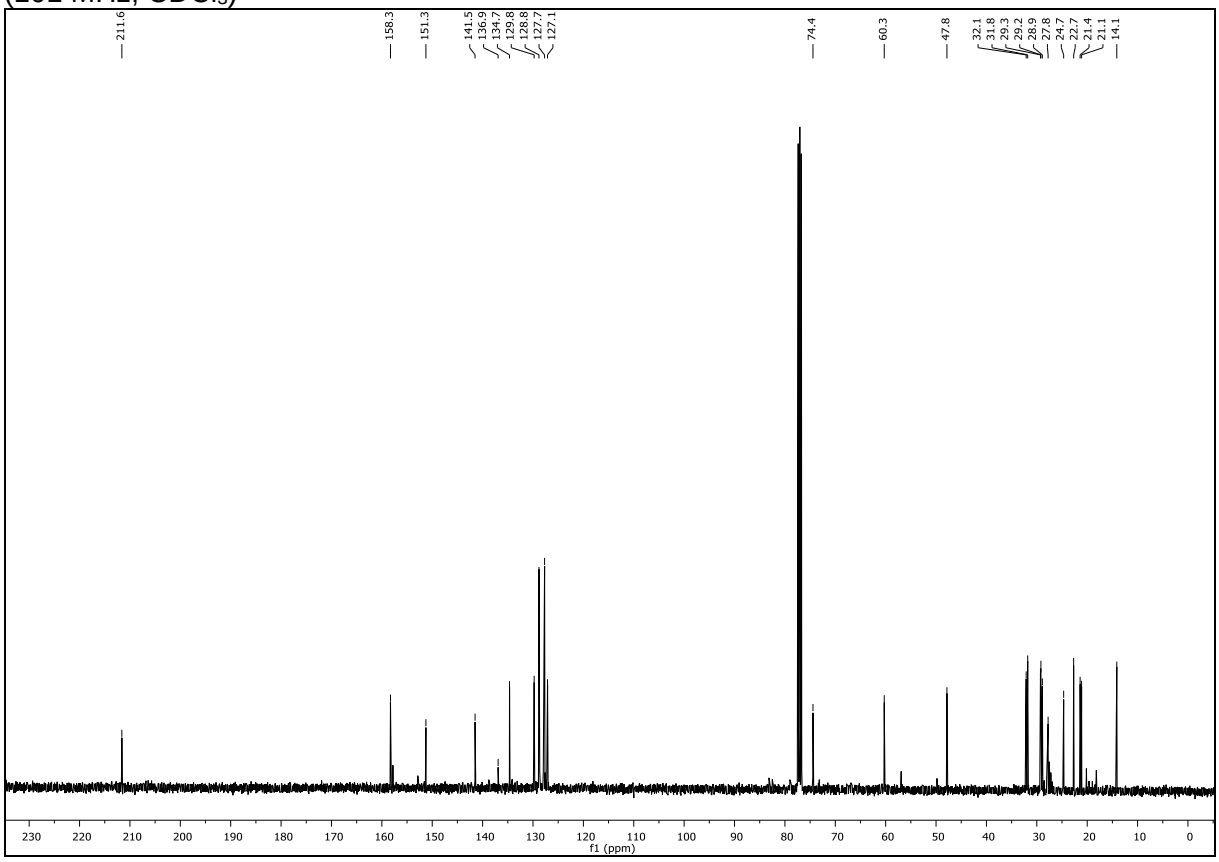
(101 MHz, $CDCl_3$)



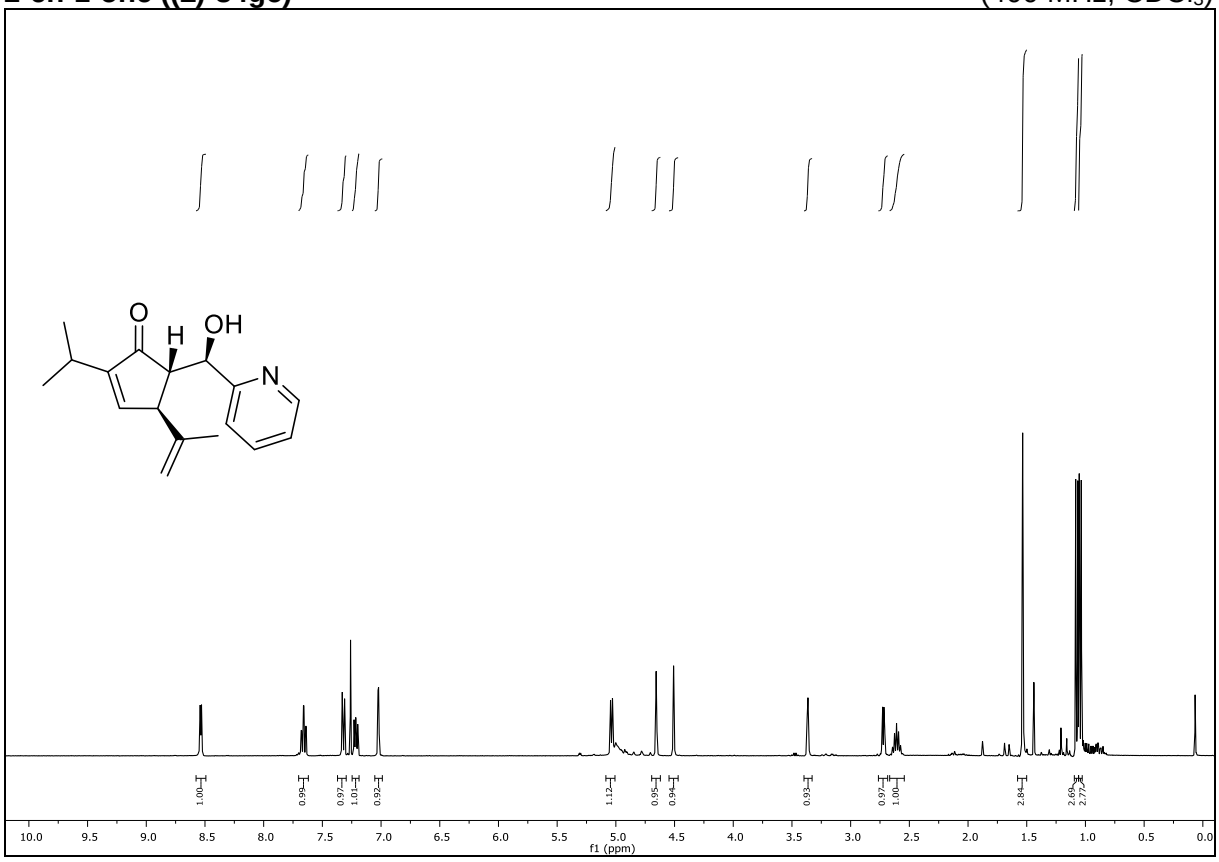
(±)-(4*S*,5*S*)-5-((*S*,*E*)-1-hydroxydec-2-en-1-yl)-2-isopropyl-4-phenylcyclopent-2-en-1-one ((±)-84gb) (400 MHz, $CDCl_3$)



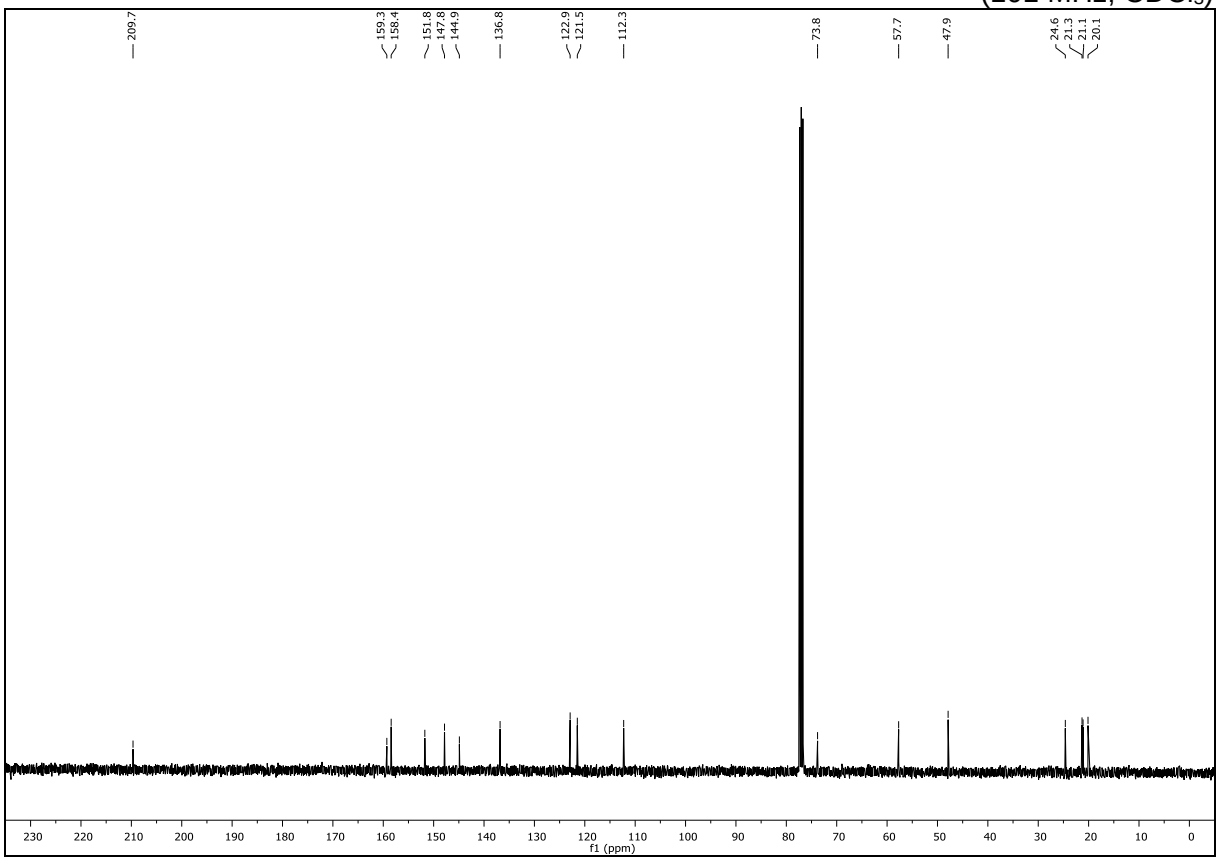
(101 MHz, $CDCl_3$)



(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2isopropyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84gc) (400 MHz, $CDCl_3$)

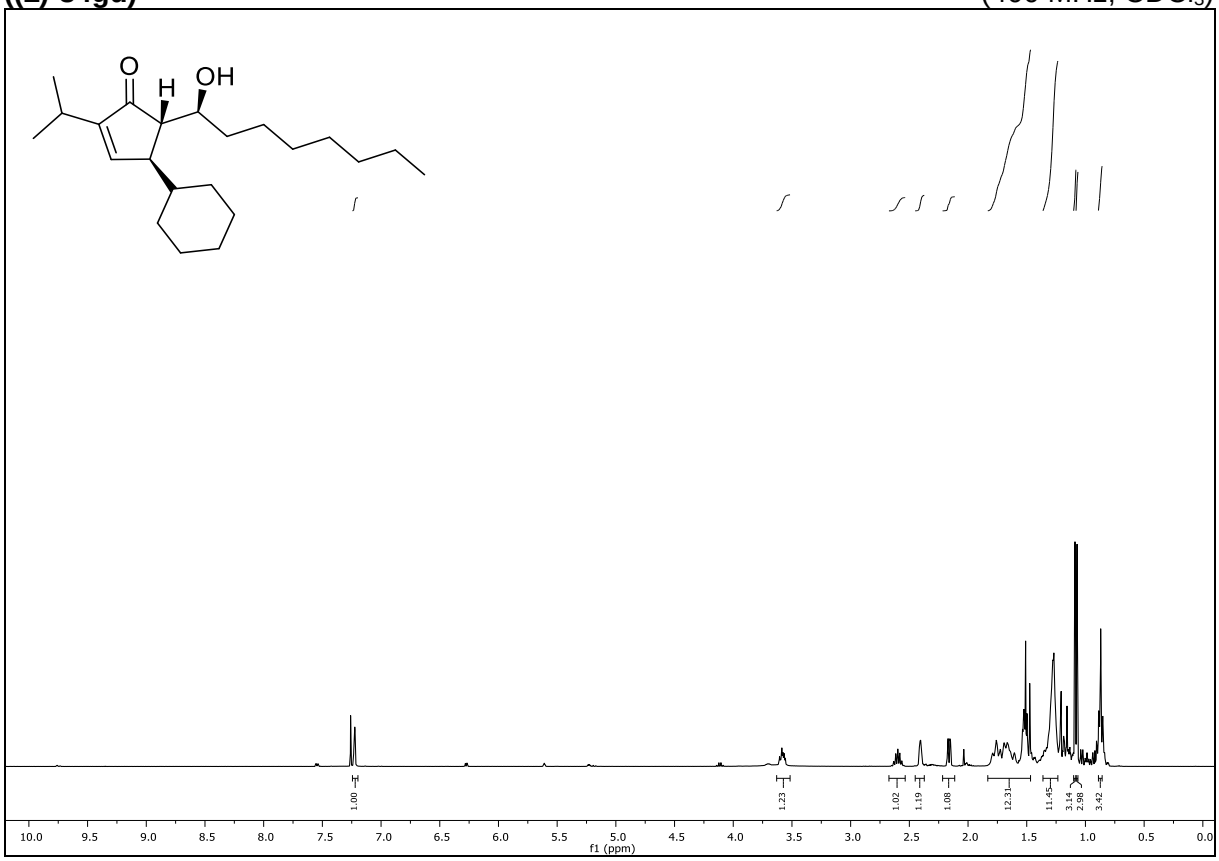


(101 MHz, $CDCl_3$)

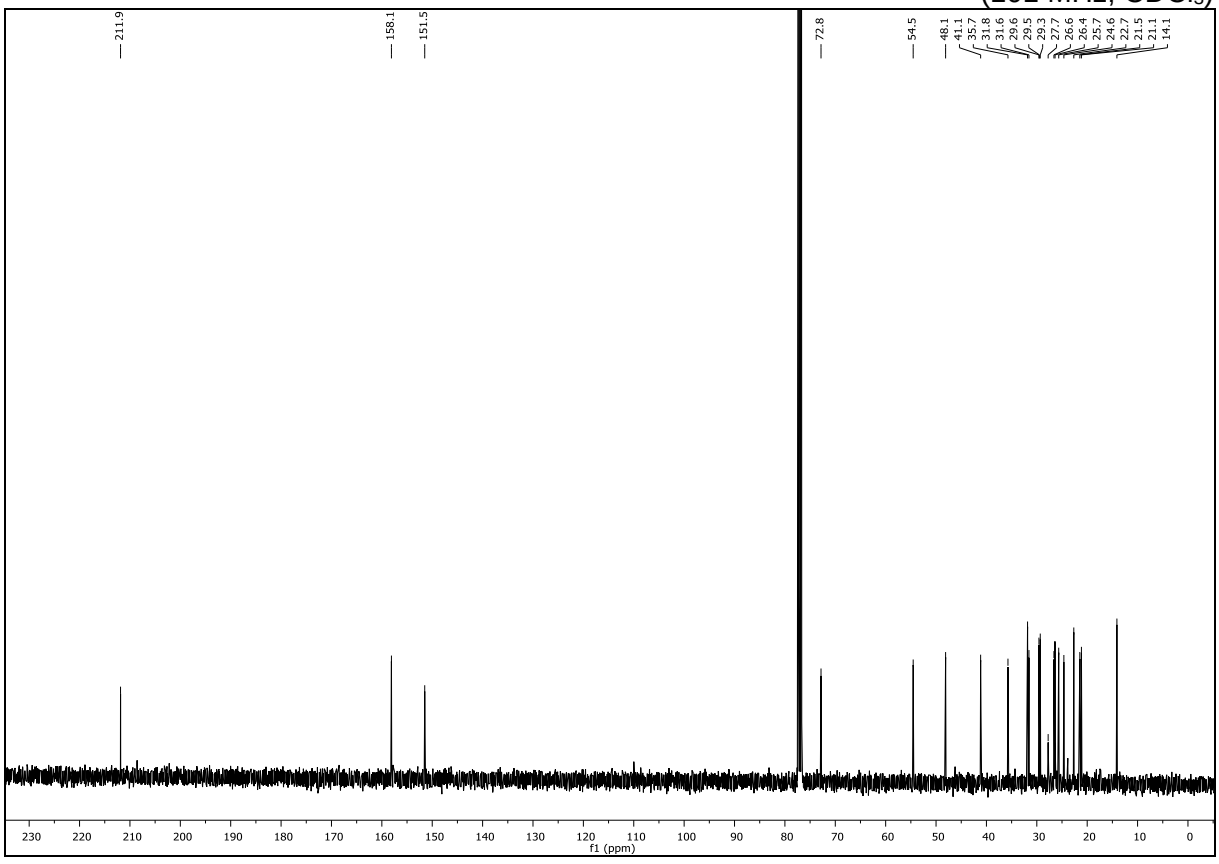


(±)-(4*S*,5*S*)-4-cyclohexyl-5-((*S*)-1-hydroxyoctyl)-2-isopropylcyclopent-2-en-1-one ((±)-84gd)

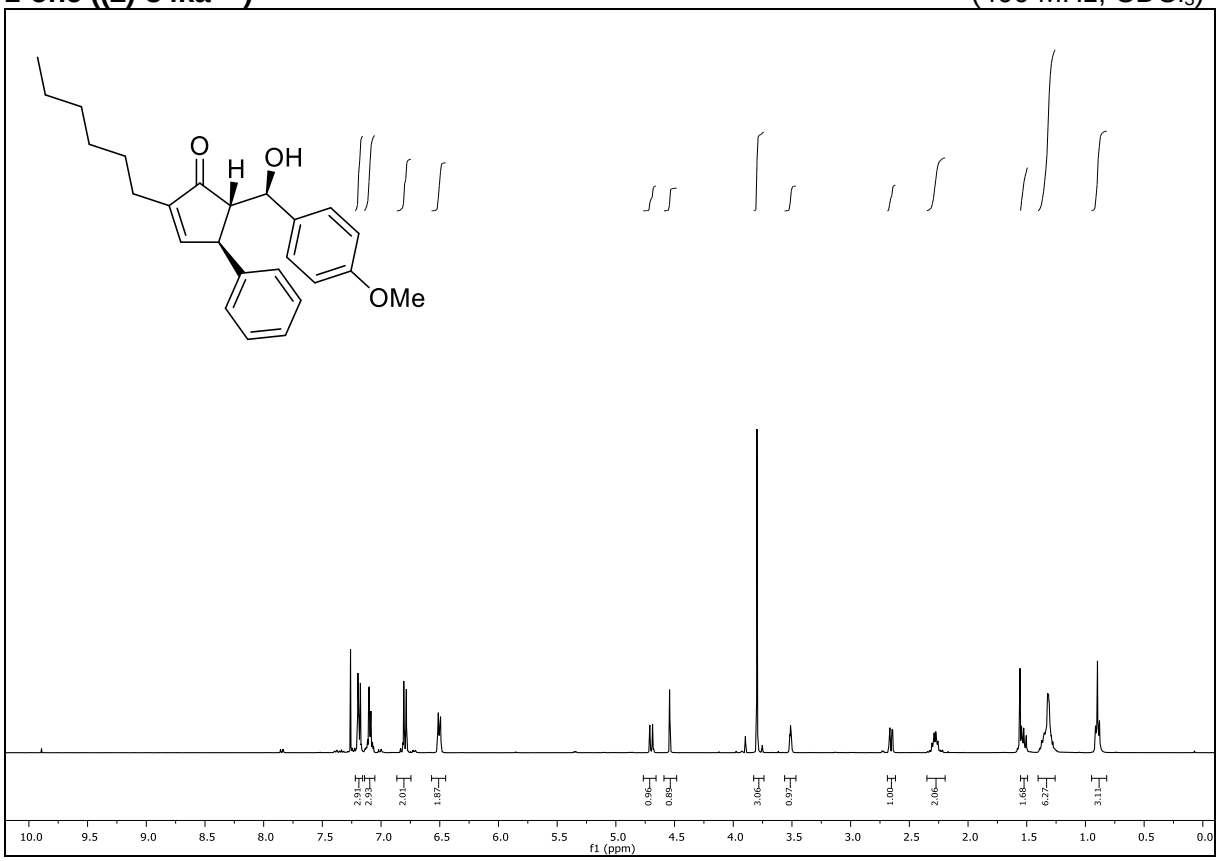
(400 MHz, $CDCl_3$)



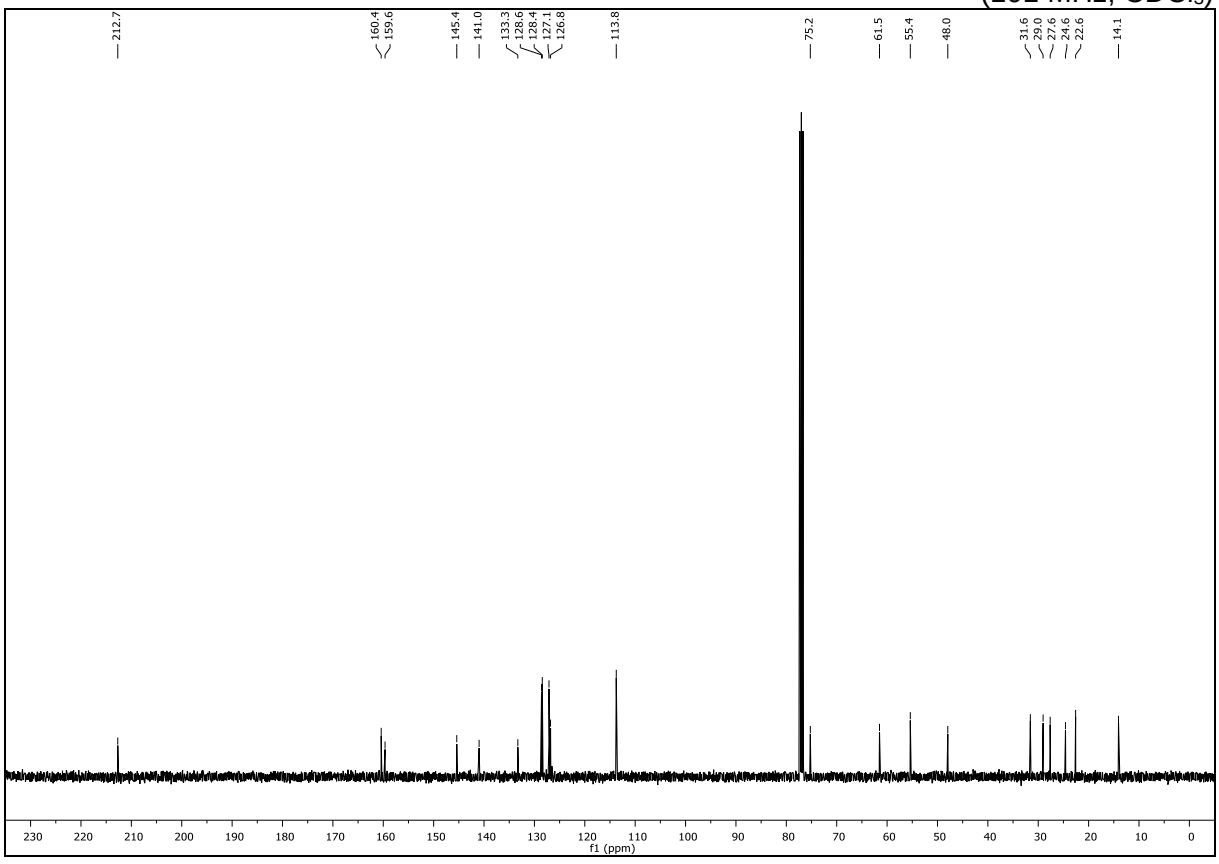
(101 MHz, $CDCl_3$)



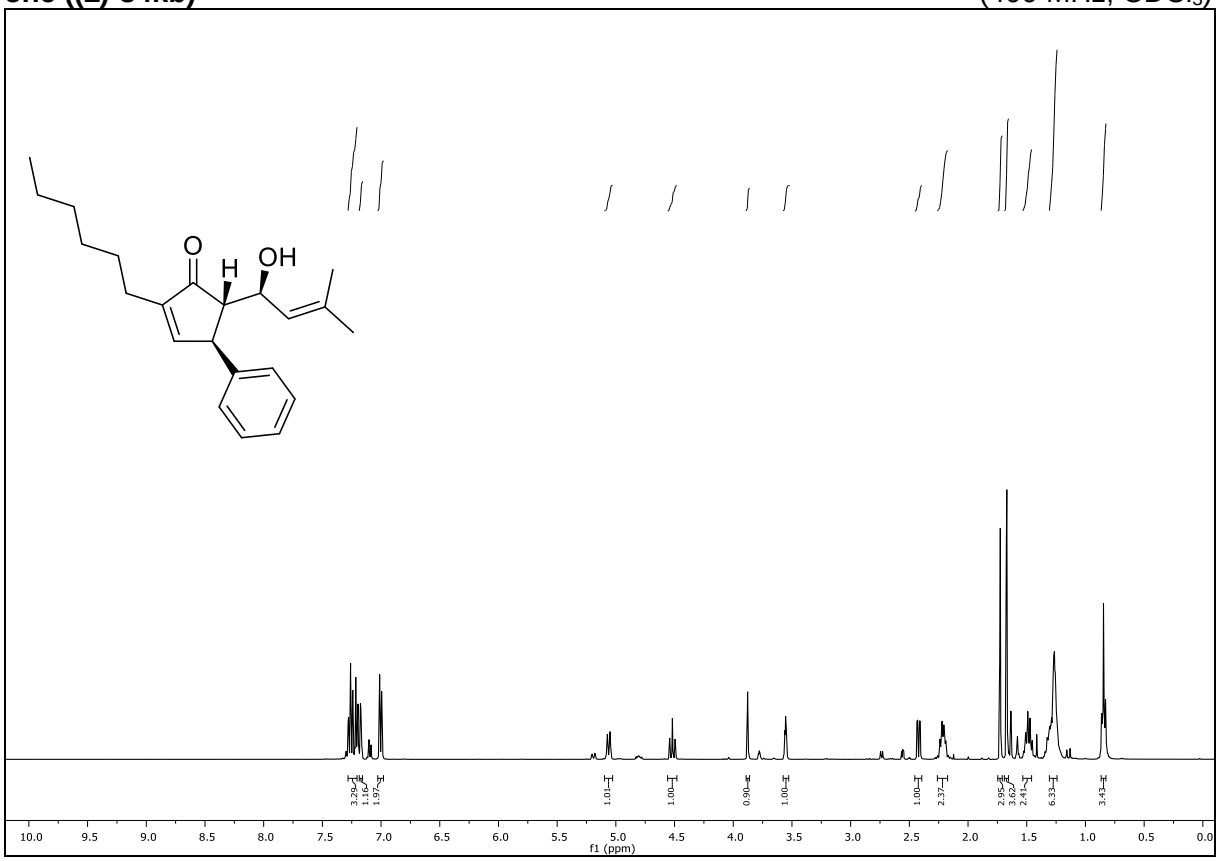
(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-hexyyl-4-phenylcyclopent-2-en-1-one ((±)-84ka) (400 MHz, $CDCl_3$)



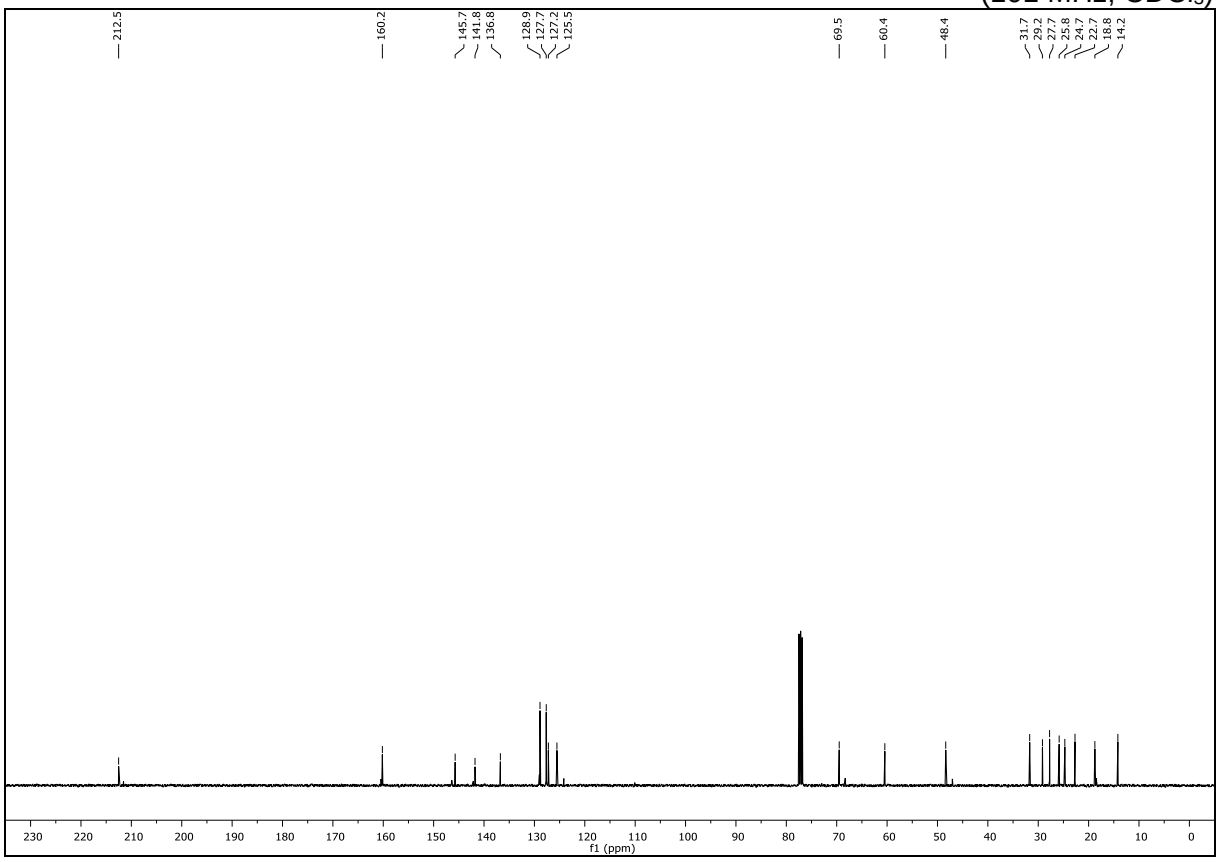
(101 MHz, $CDCl_3$)



(±)-(4*R*,5*S*)-5-((*S*)-1-hydroxy-3-methylbut-2-en-1-yl)-2-hexyl-4-phenylcyclopent-2-en-1-one ((±)-84kb) (400 MHz, $CDCl_3$)

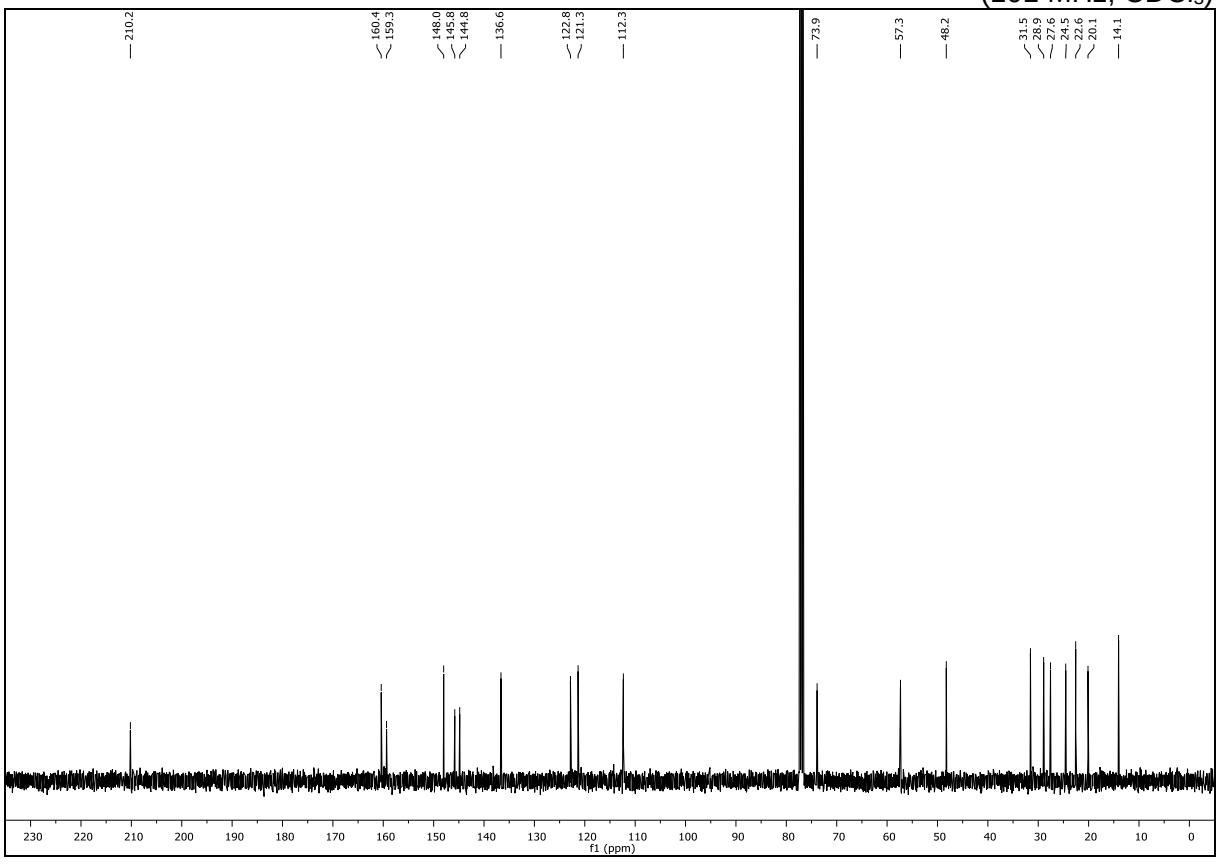


(101 MHz, $CDCl_3$)



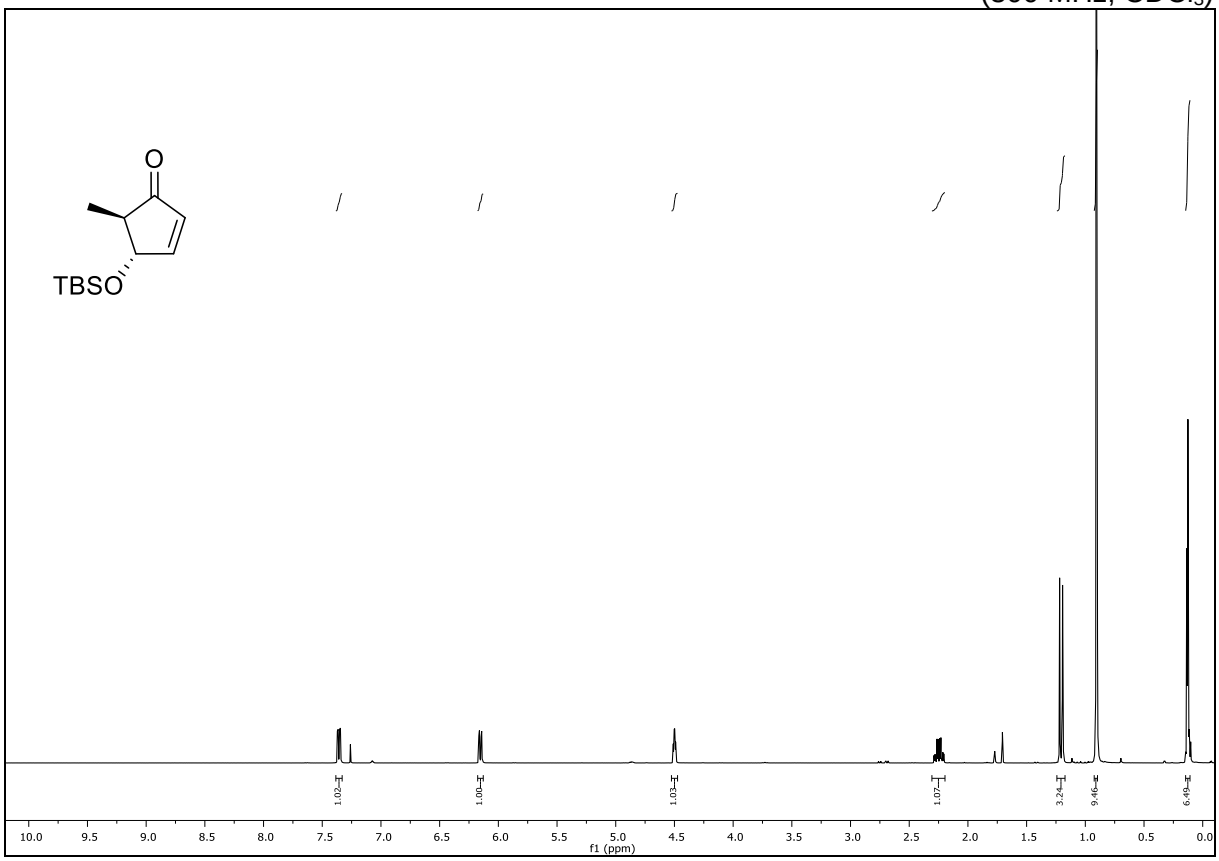
(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(pyridin-2-yl)methyl)-2-hexyl-4-(prop-1-en-2-yl)cyclopent-2-en-1-one ((±)-84kc) (400 MHz, $CDCl_3$)

(101 MHz, $CDCl_3$)

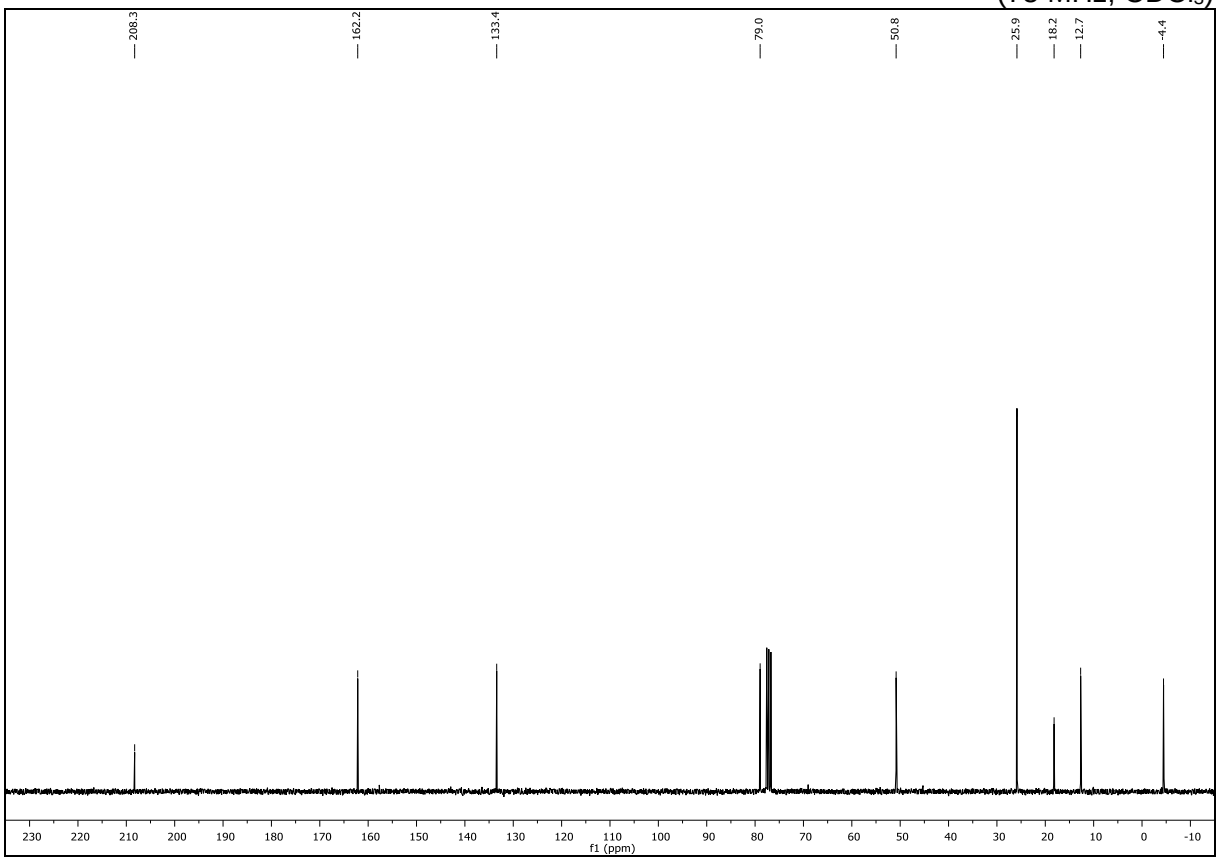


(±)-(4*S*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-methylcyclopent-2-en-1-one ((±)-*anti*-152b)

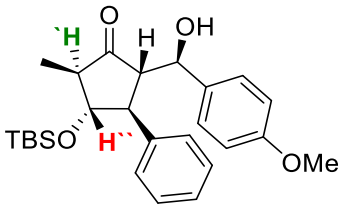
(300 MHz, $CDCl_3$)



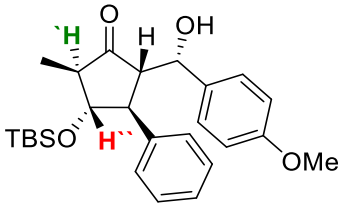
(75 MHz, $CDCl_3$)



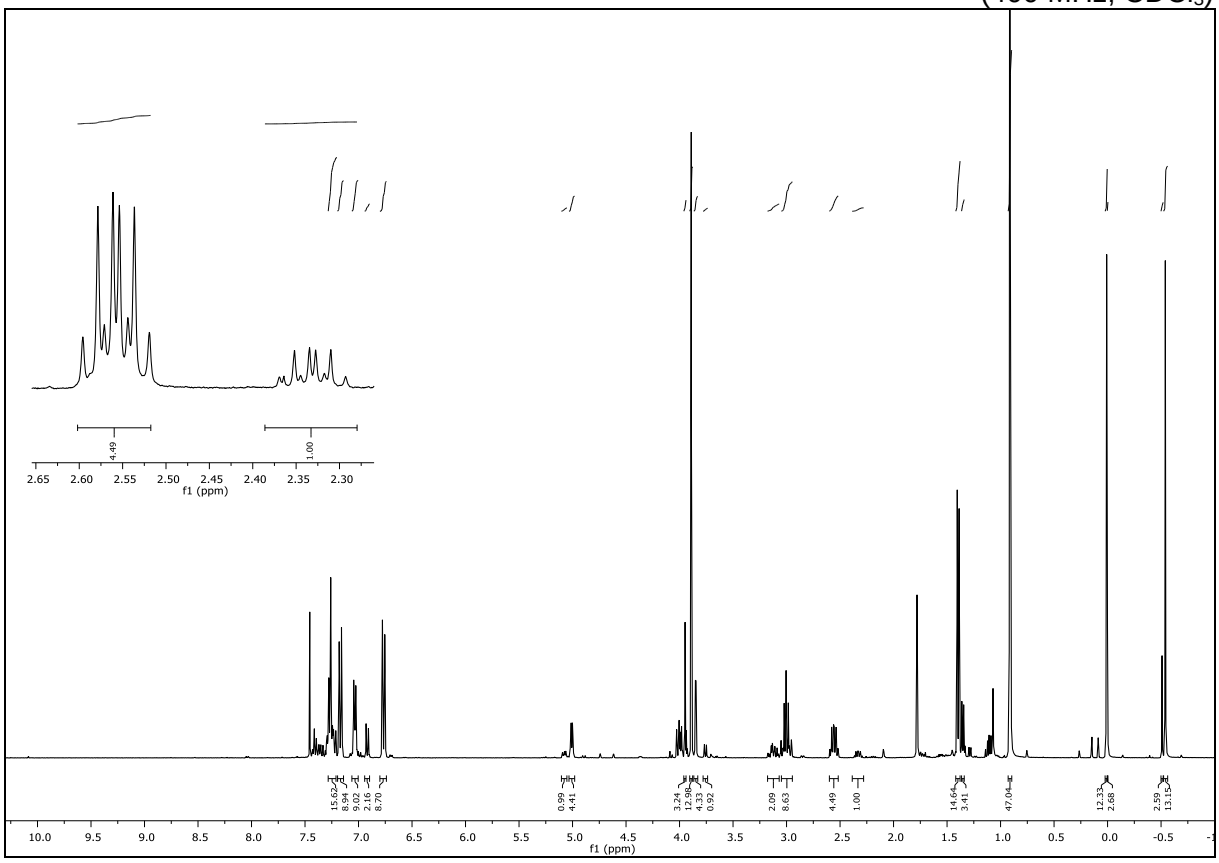
(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*R*)-153b)



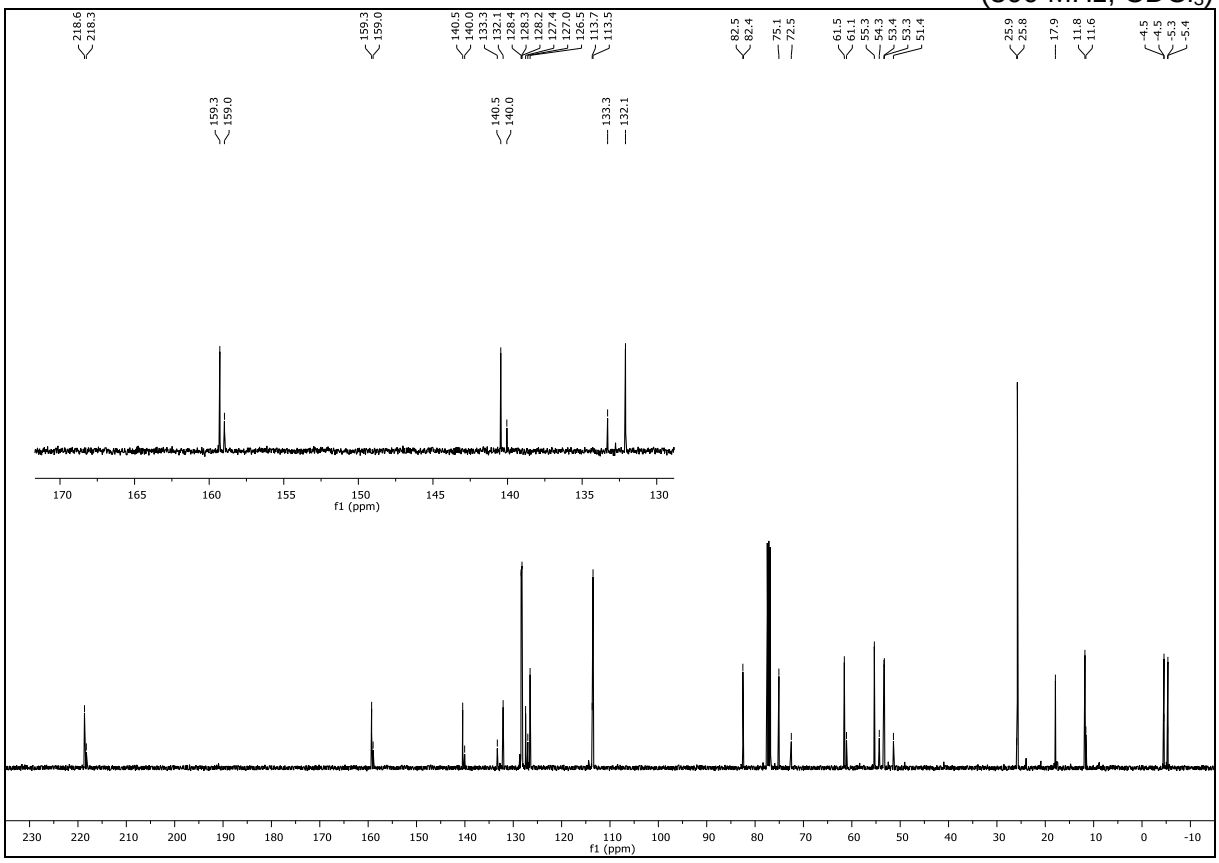
(±)-(2*R*,3*S*,4*S*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*S*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopentan-1-one ((±)-(*S*)-153b)



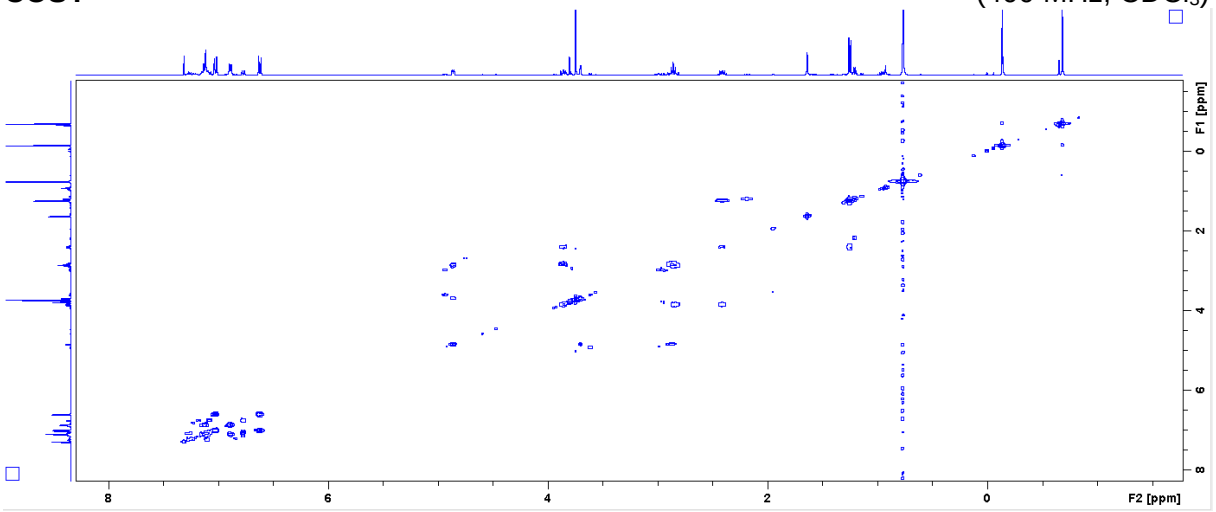
(400 MHz, $CDCl_3$)



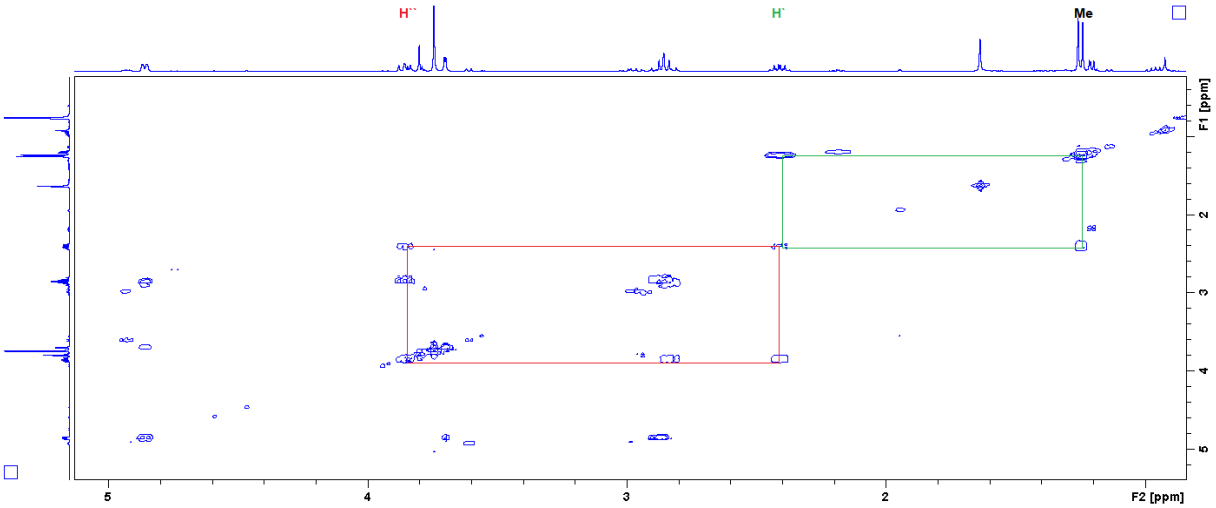
(300 MHz, $CDCl_3$)



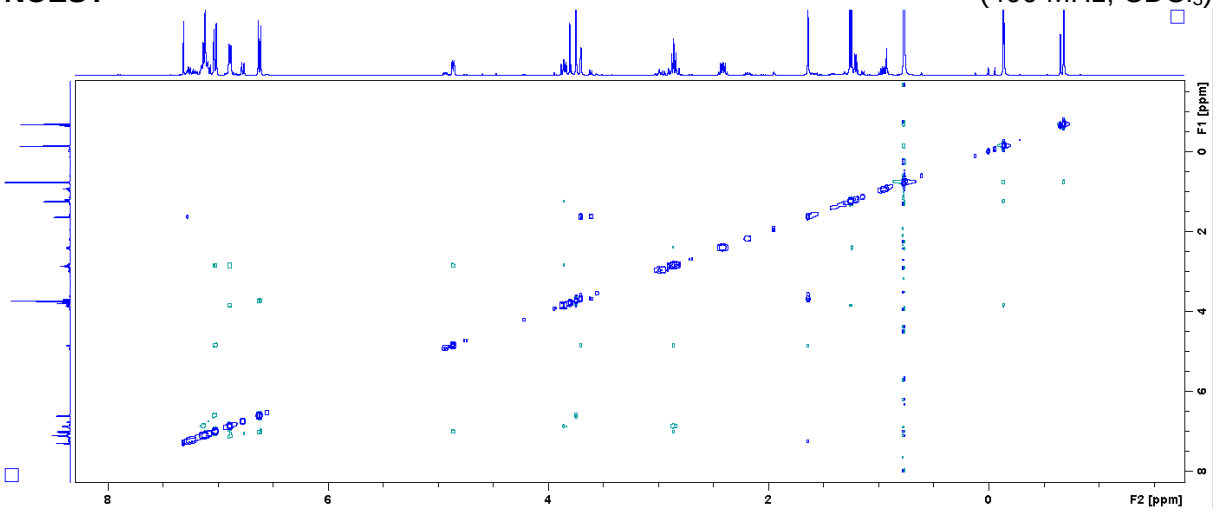
COSY (400 MHz, $CDCl_3$)



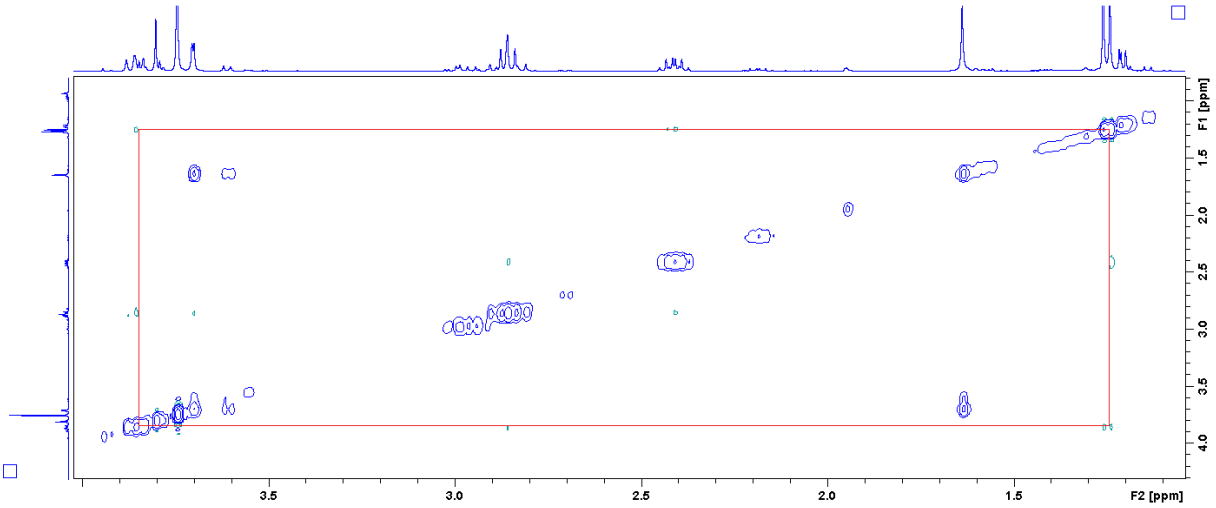
COSY Zoom In



NOESY (400 MHz, $CDCl_3$)

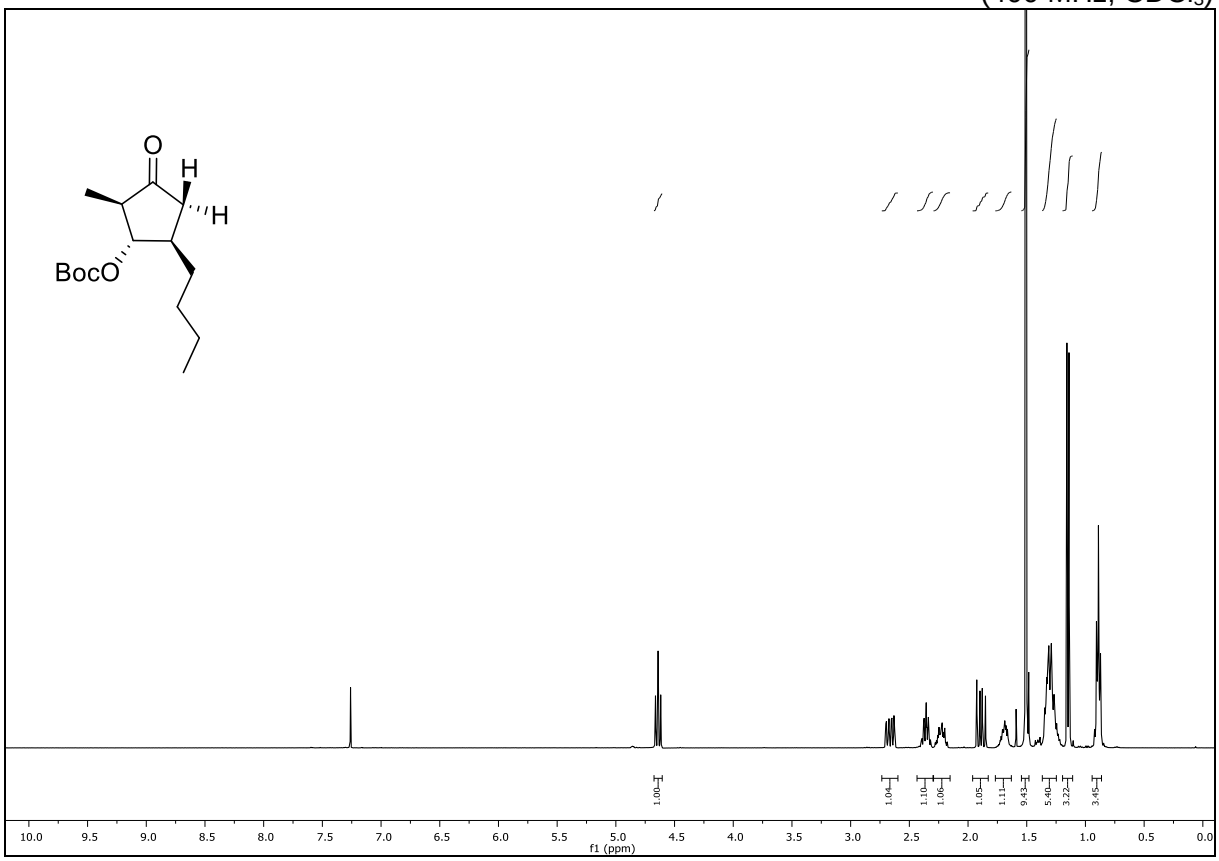


NOESY Zoom In

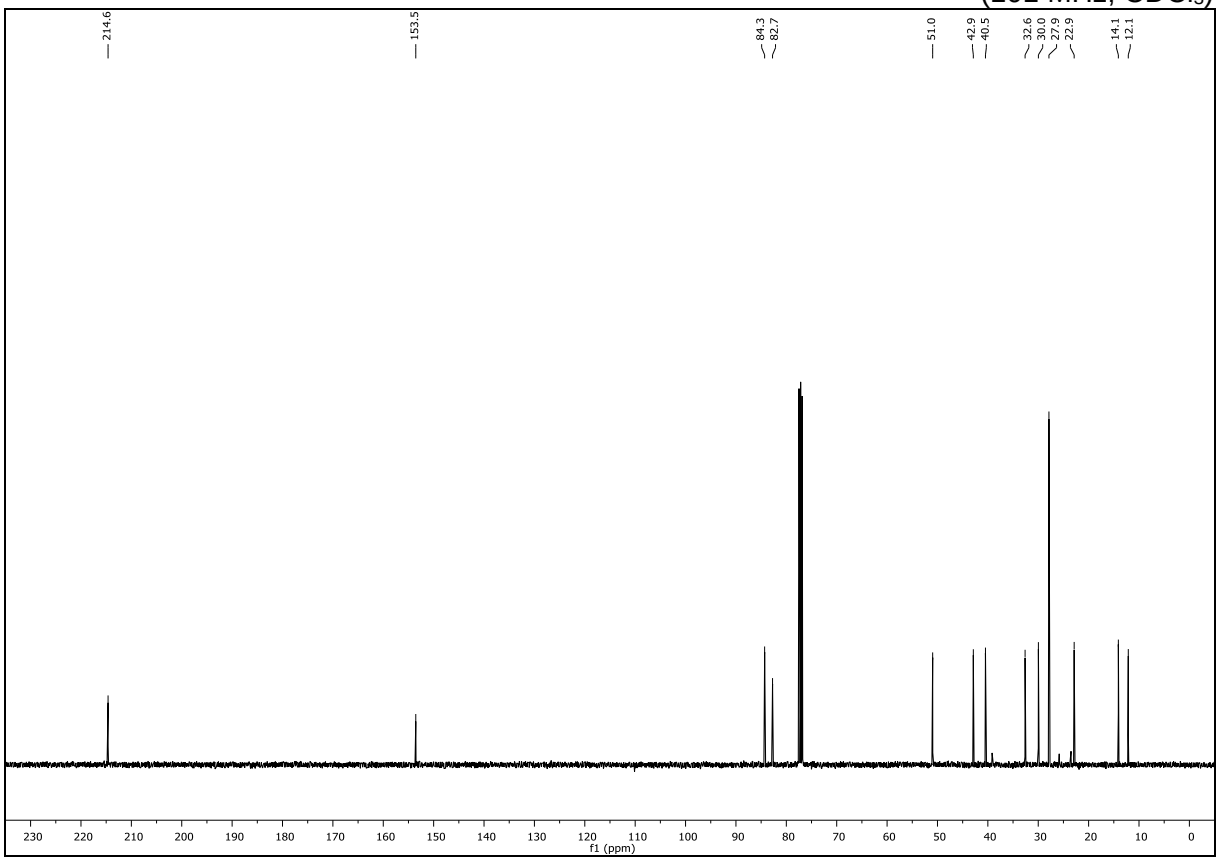


(±)-*tert*-butyl ((1*S*,2*R*,5*R*)-5-butyl-2-methyl-3-oxocyclopentyl) carbonate ((±)-*anti*-151)

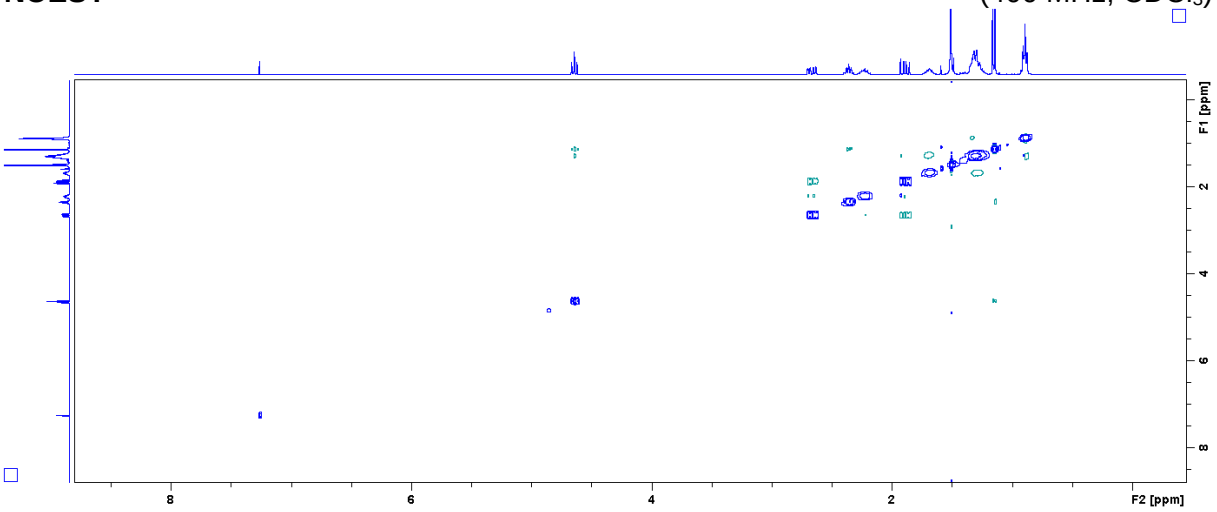
(400 MHz, $CDCl_3$)



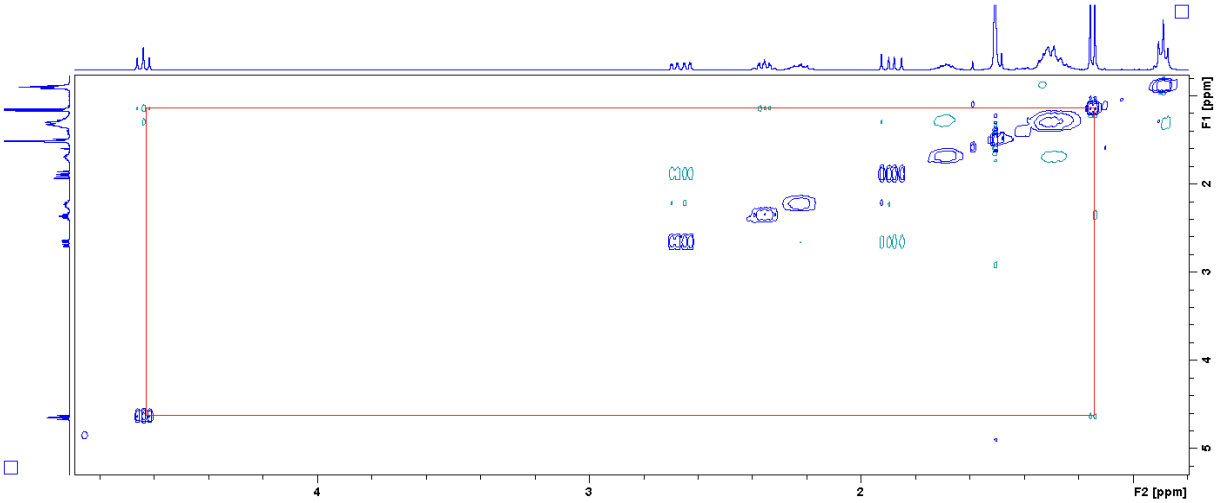
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

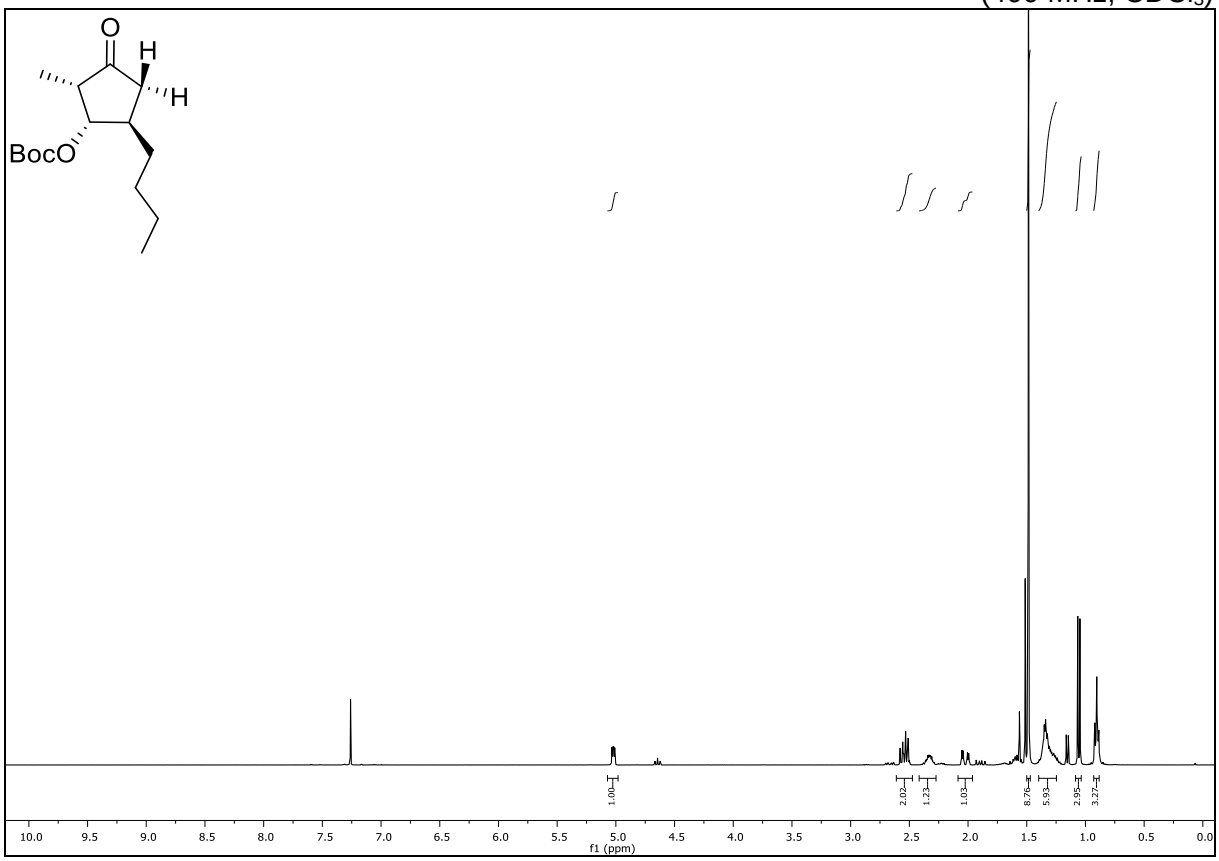


NOESY Zoom In

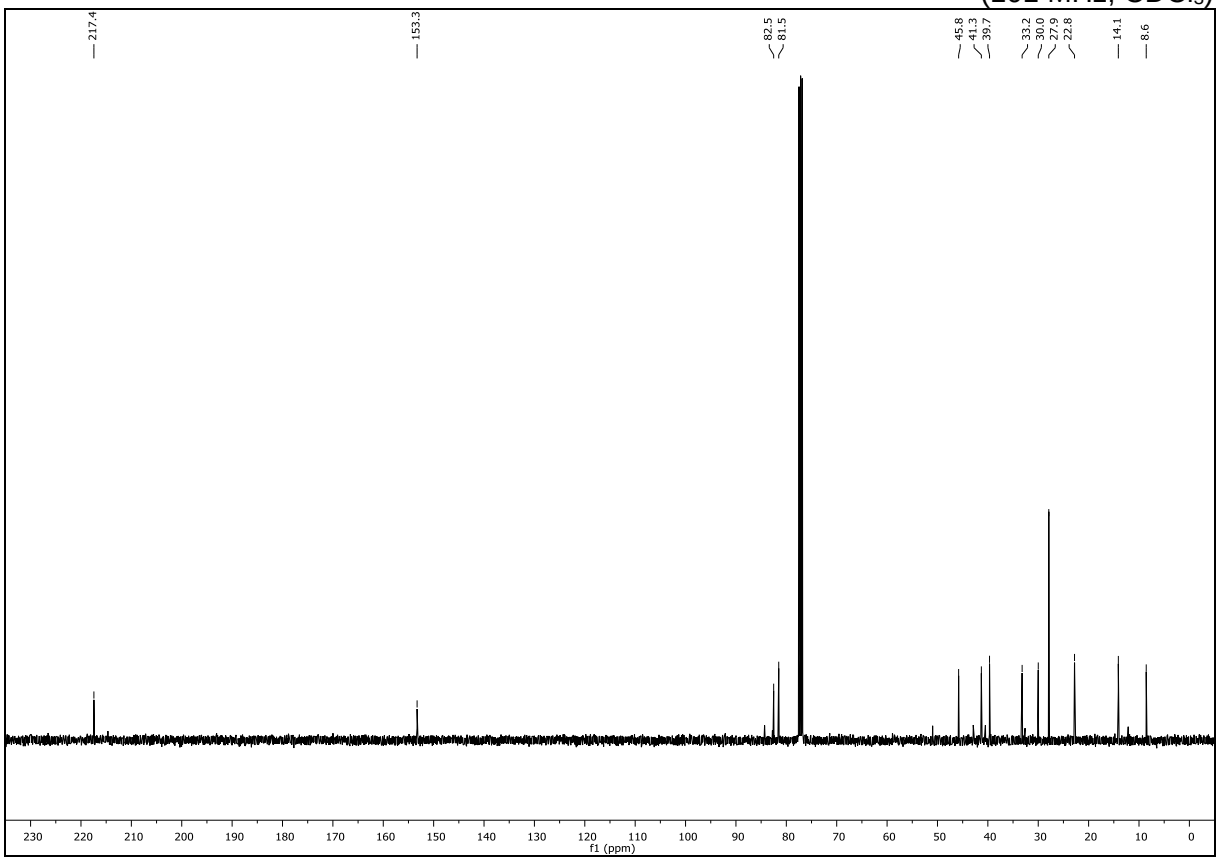


(±)-*tert*-butyl ((1*S*,2*S*,5*R*)-5-butyl-2-methyl-3-oxocyclopentyl) carbonate ((±)-*syn*-151)

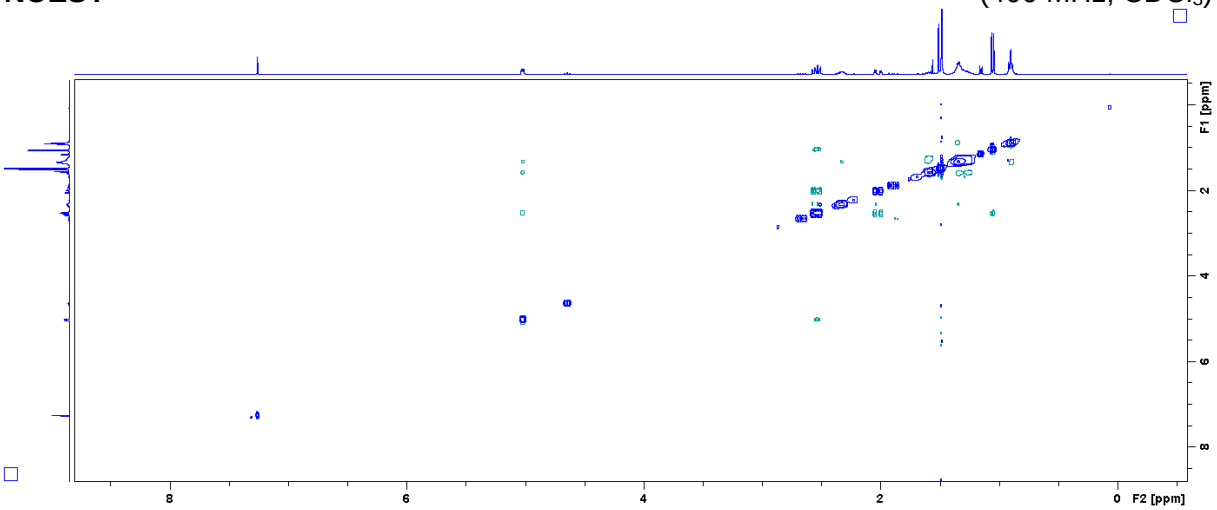
(400 MHz, $CDCl_3$)



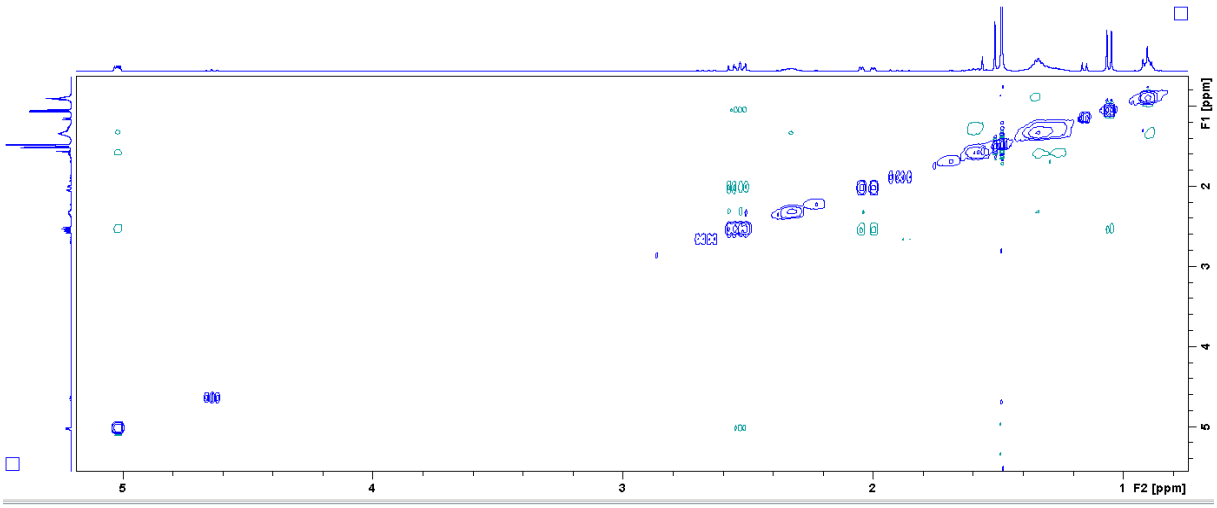
(101 MHz, $CDCl_3$)



NOESY (400 MHz, $CDCl_3$)

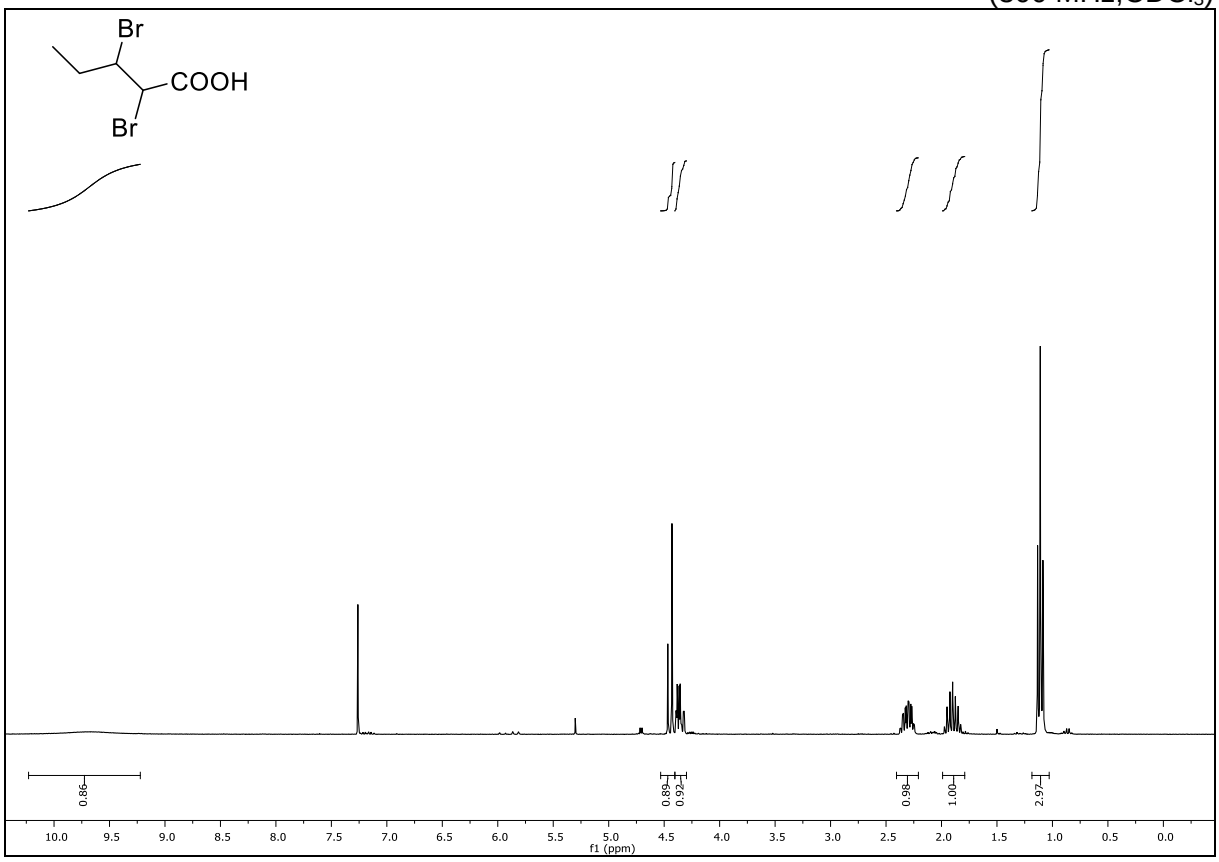


NOESY Zoom In

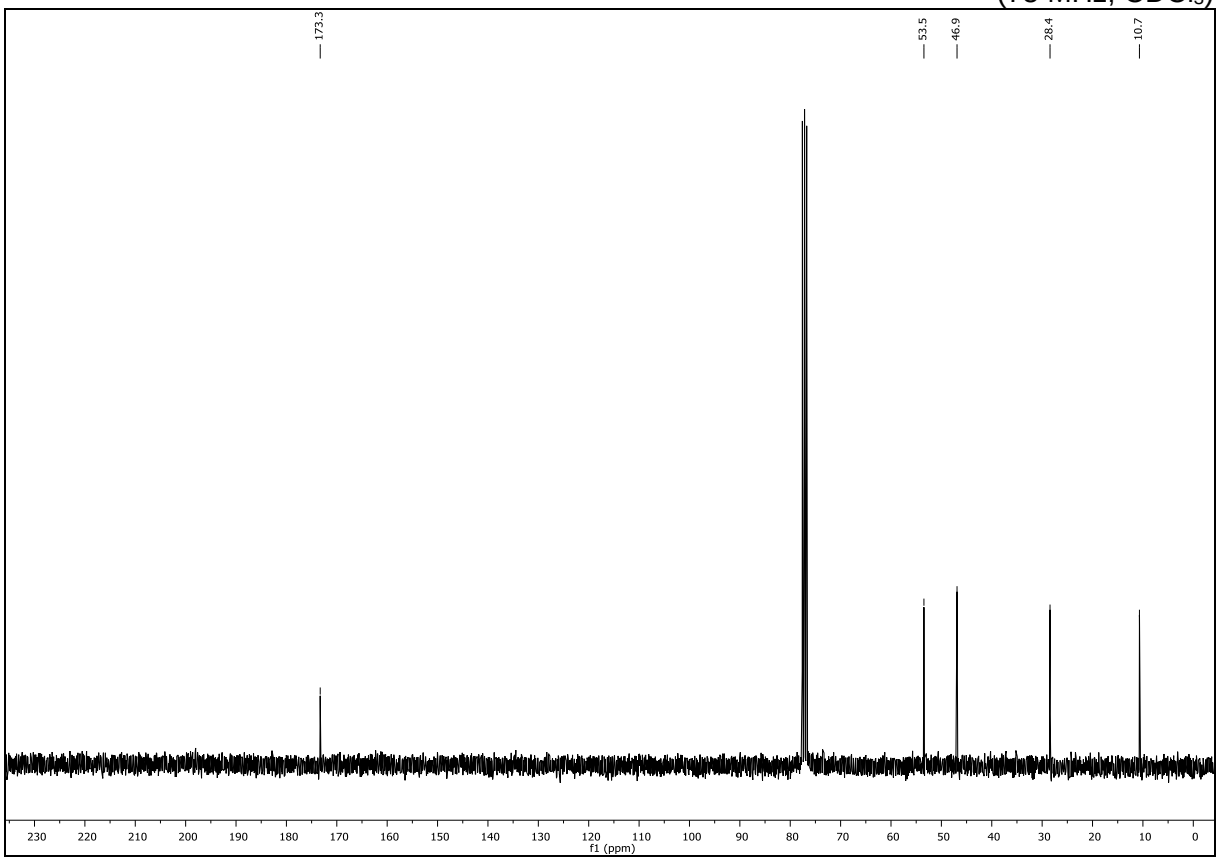


2,3-dibromopentanoic acid (183)

(300 MHz,$CDCl_3$)

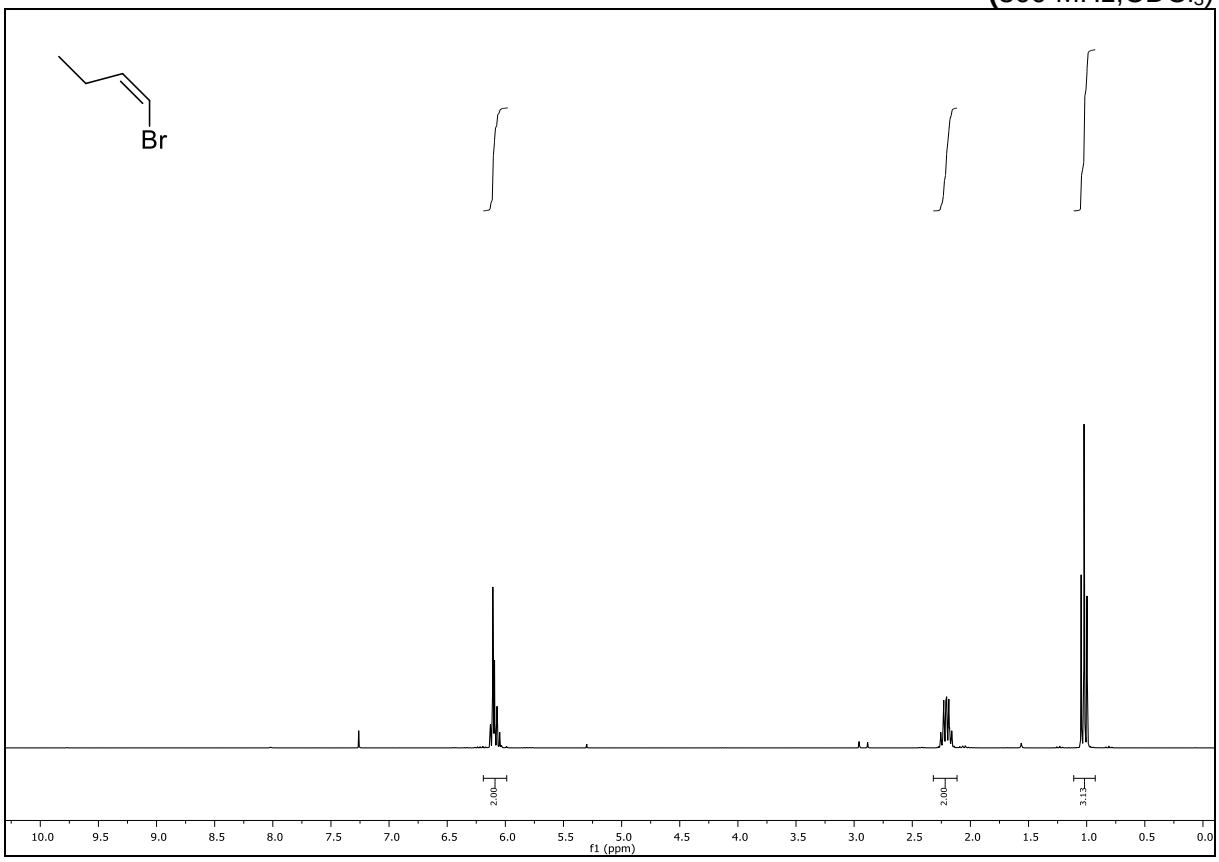


(75 MHz, $CDCl_3$)

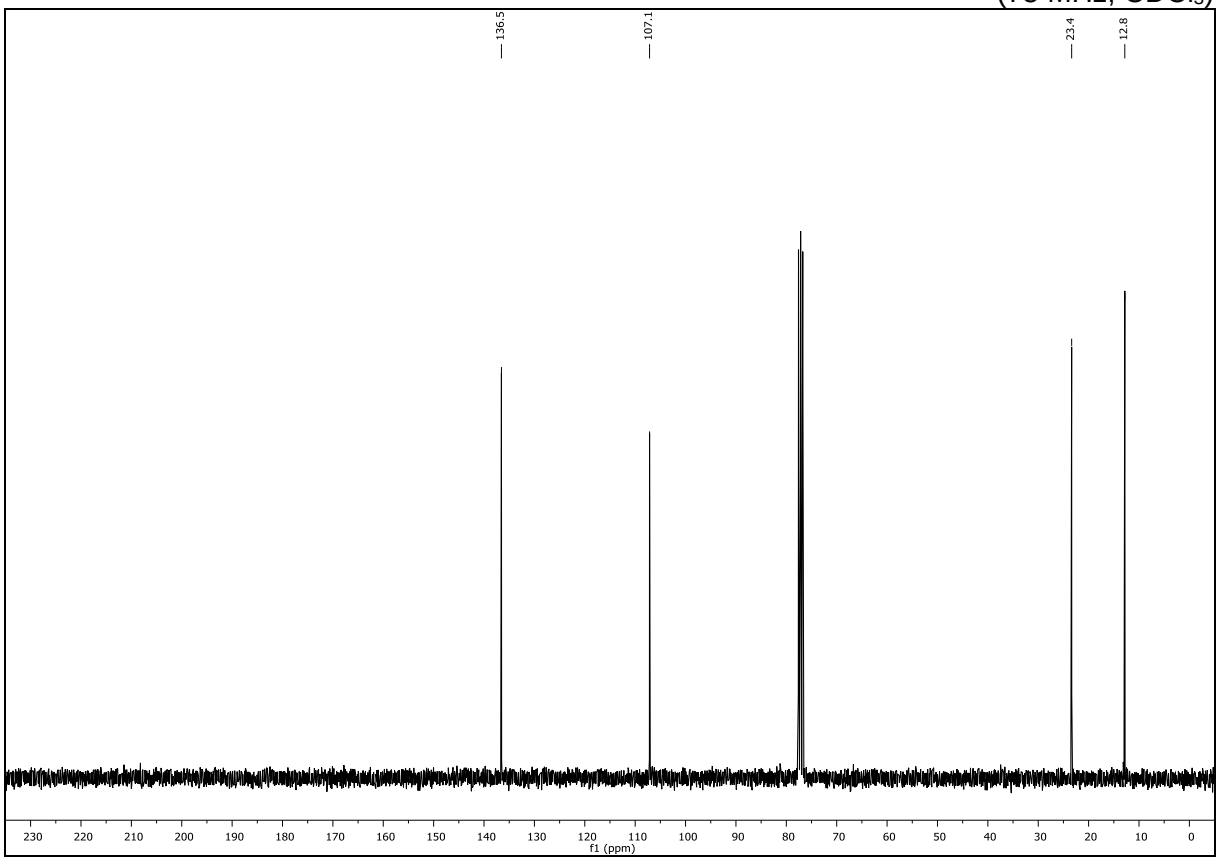


(*Z*)-1-bromobut-1-ene (182)

(300 MHz,$CDCl_3$)

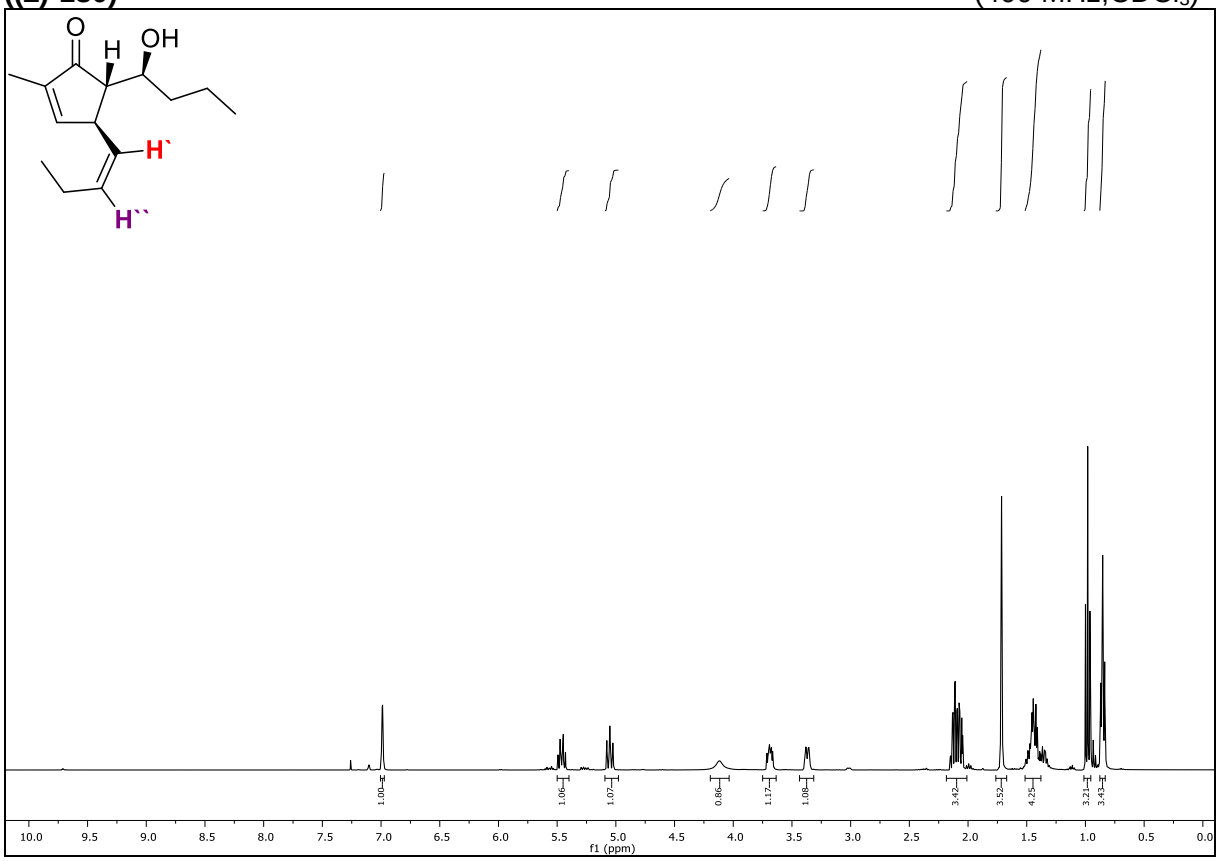


(75 MHz, $CDCl_3$)

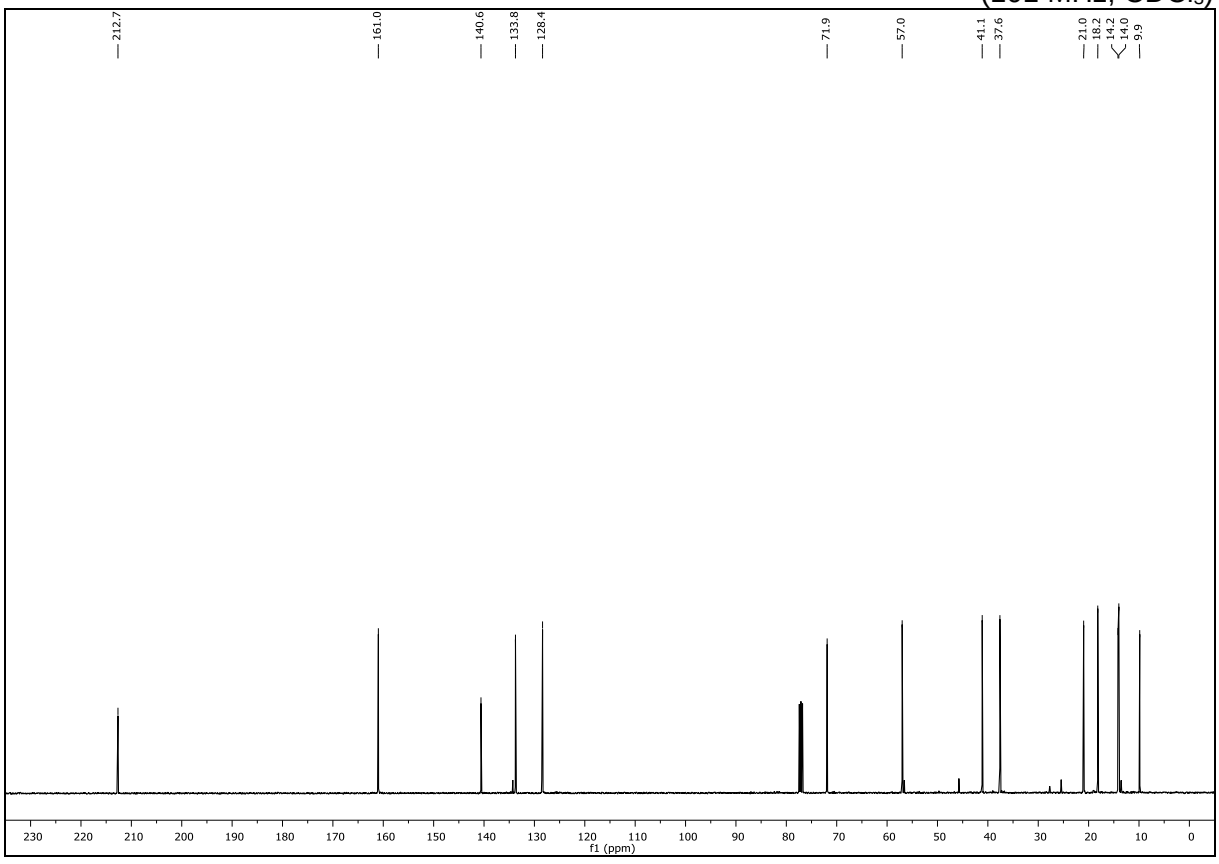


(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-180)

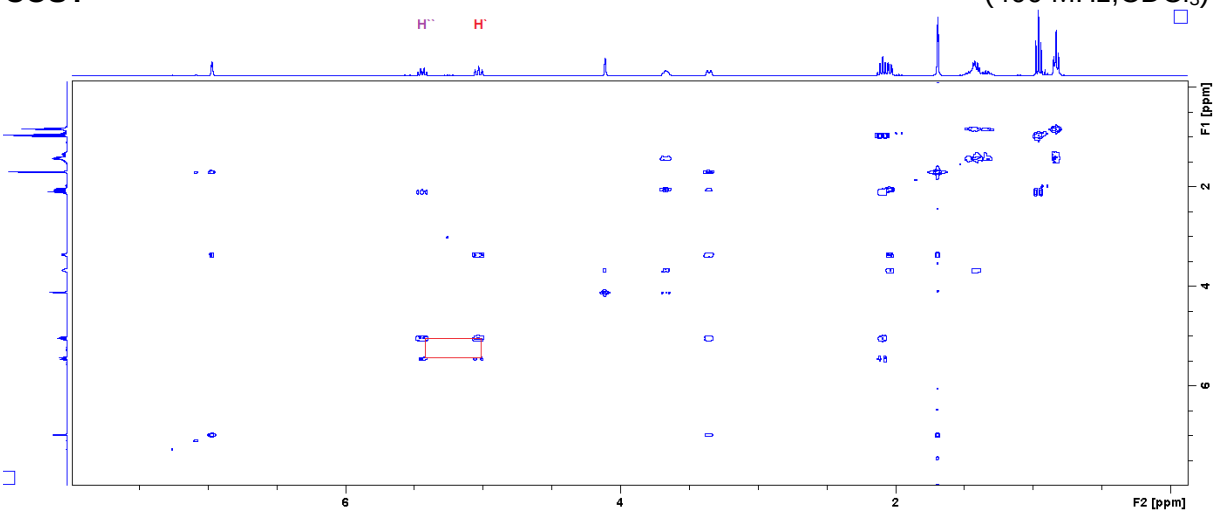
(400 MHz,$CDCl_3$)



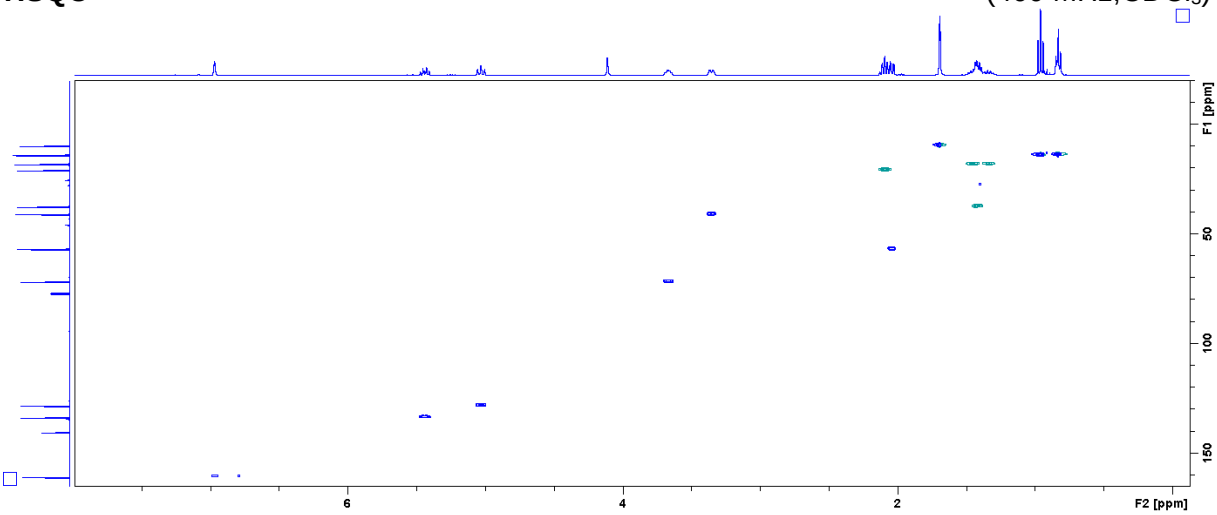
(101 MHz, $CDCl_3$)



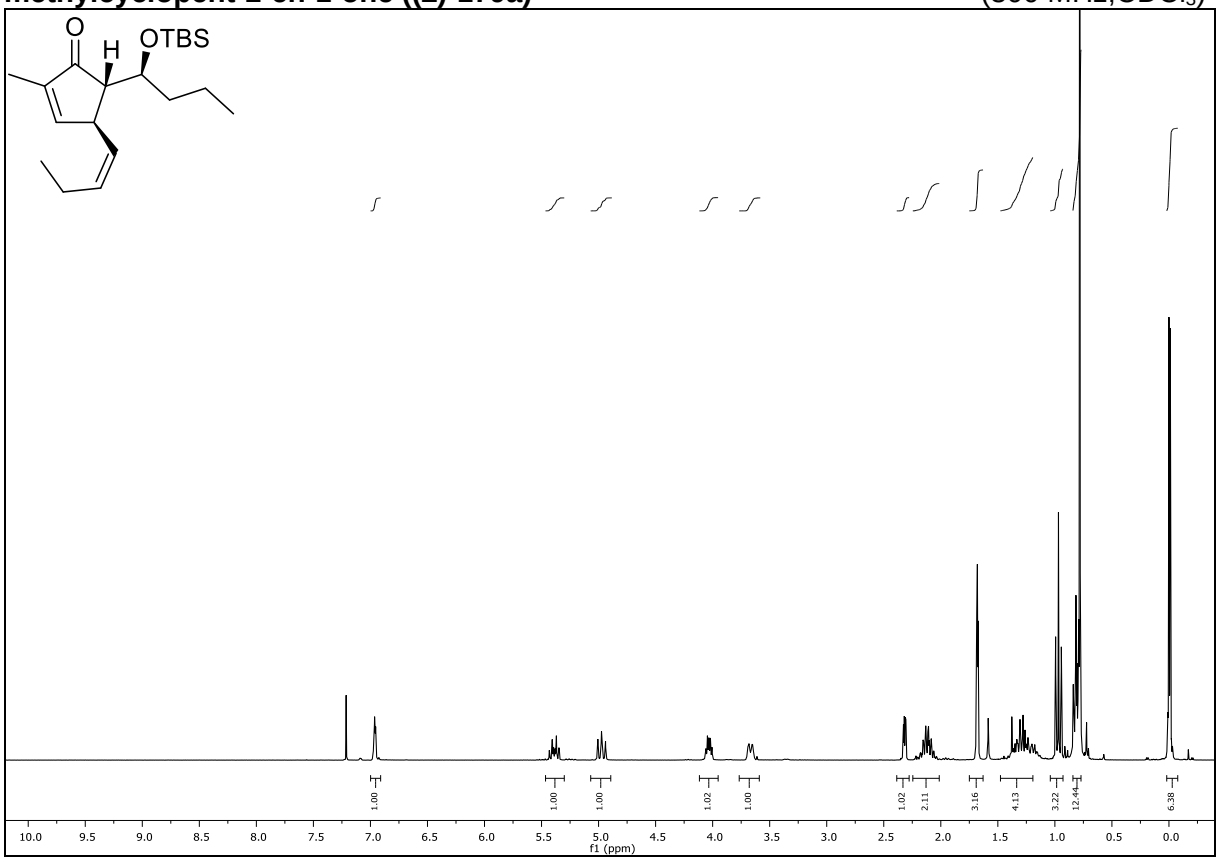
COSY (400 MHz,$CDCl_3$)



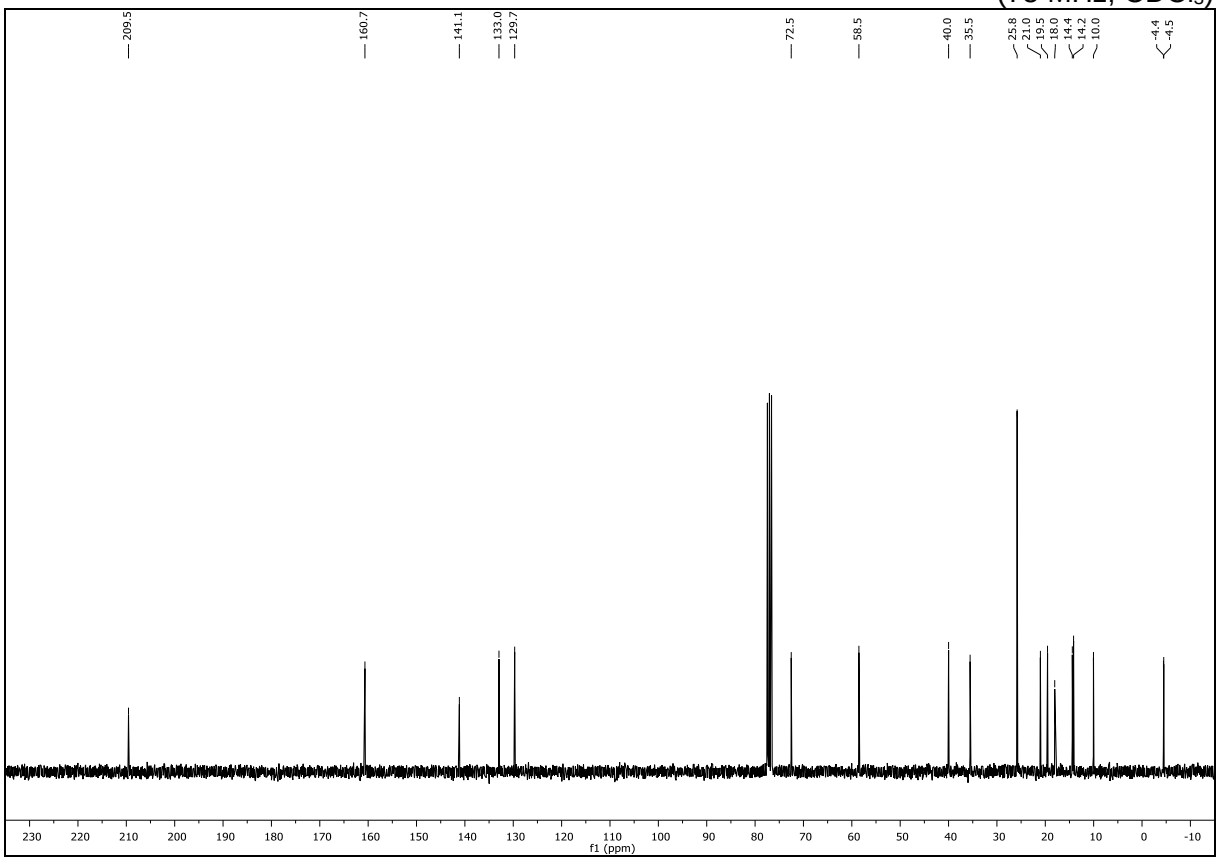
HSQC (400 MHz,$CDCl_3$)



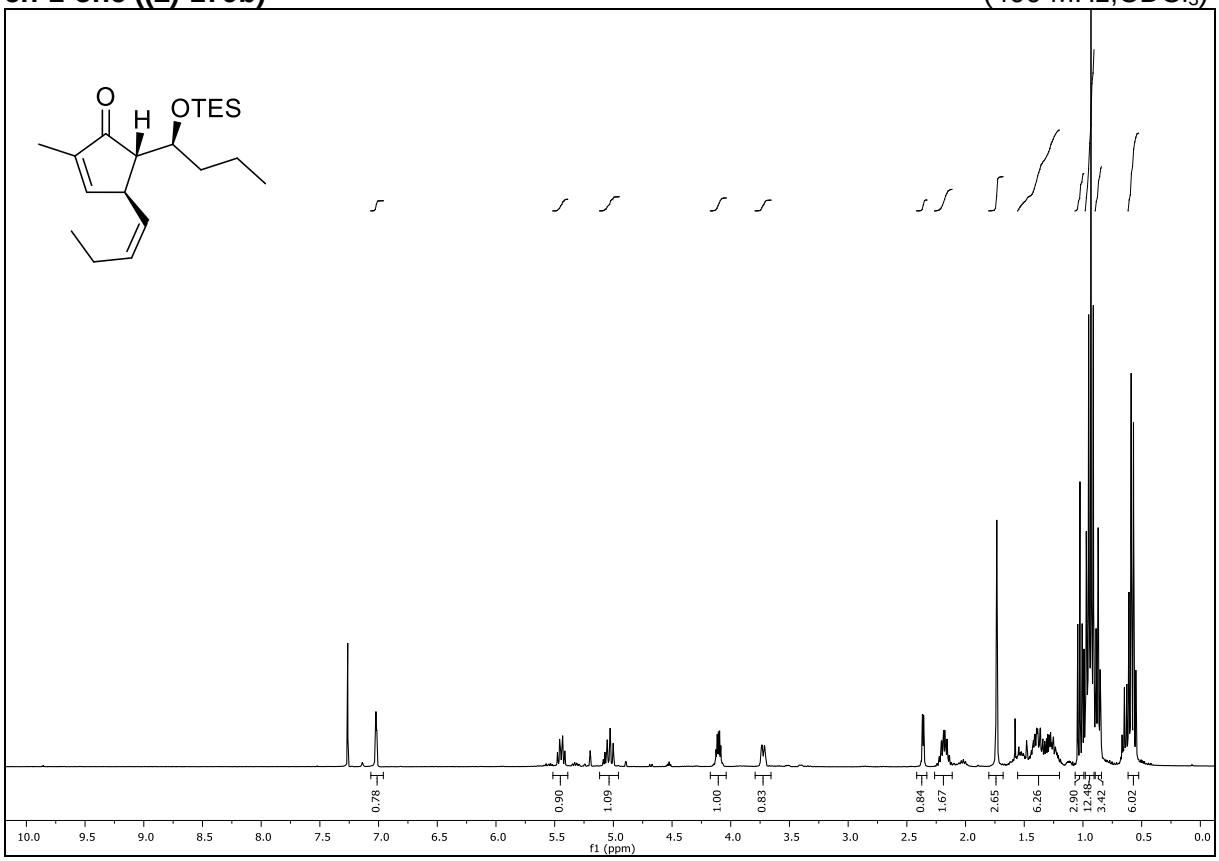
(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methylcyclopent-2-en-1-one ((±)-179a) (300 MHz,$CDCl_3$)



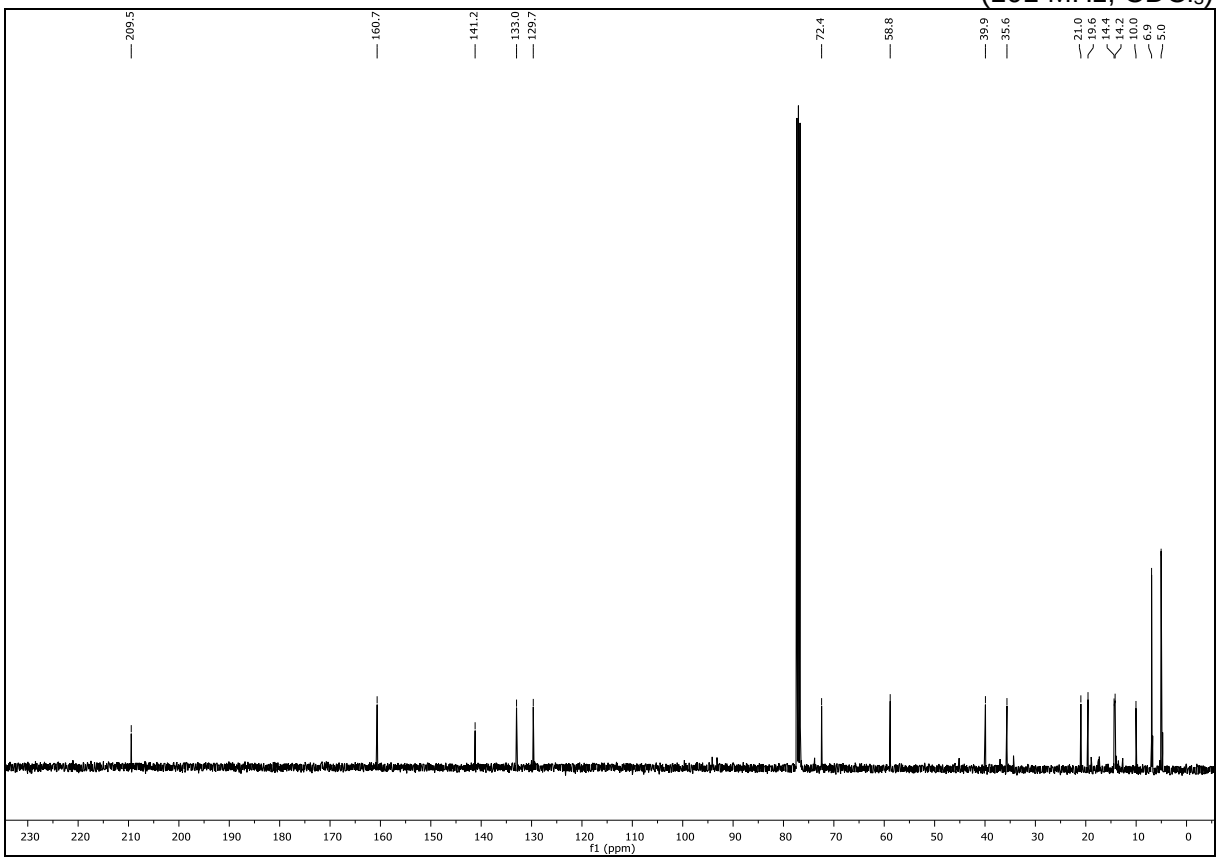
(75 MHz, $CDCl_3$)



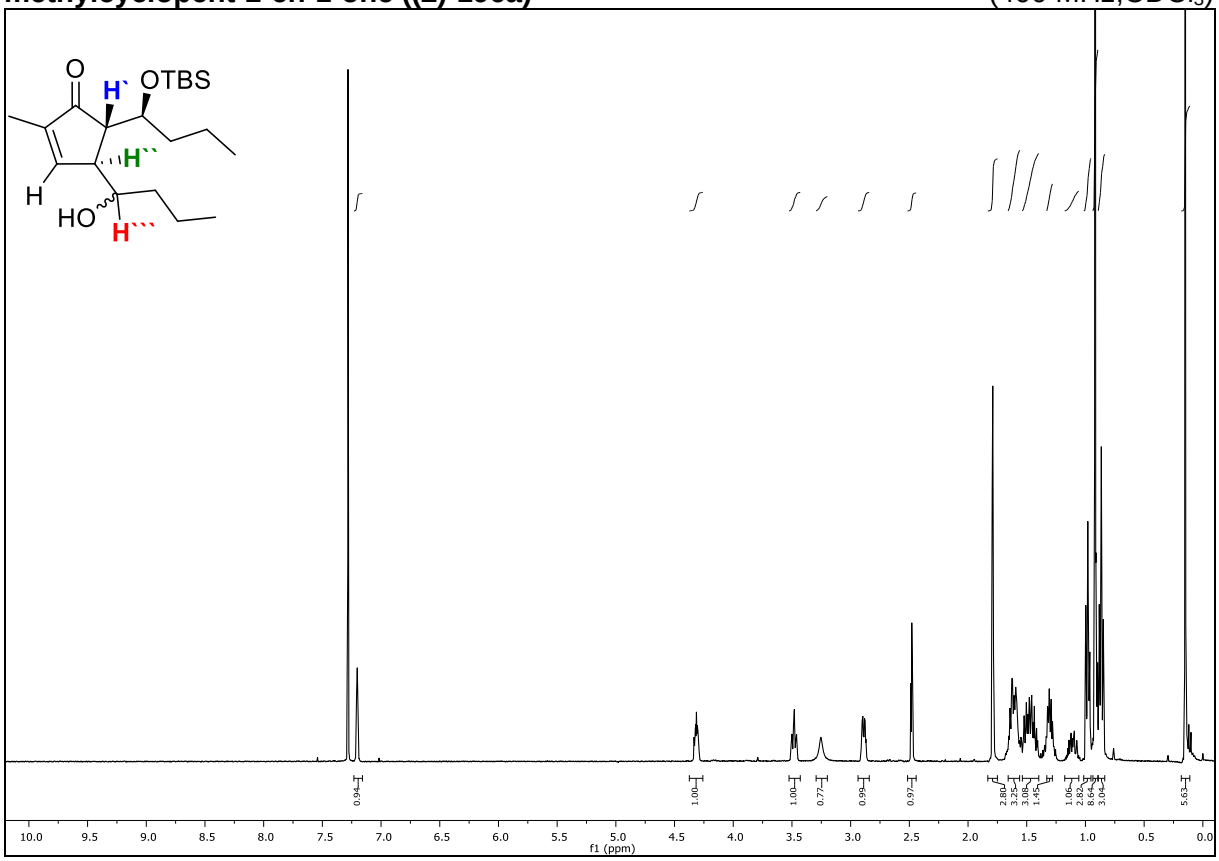
(±)-(4*S*,5*S*)-4-((*Z*)-but-1-en-1-yl)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-2-methylcyclopent-2-en-1-one ((±)-179b) (400 MHz,$CDCl_3$)



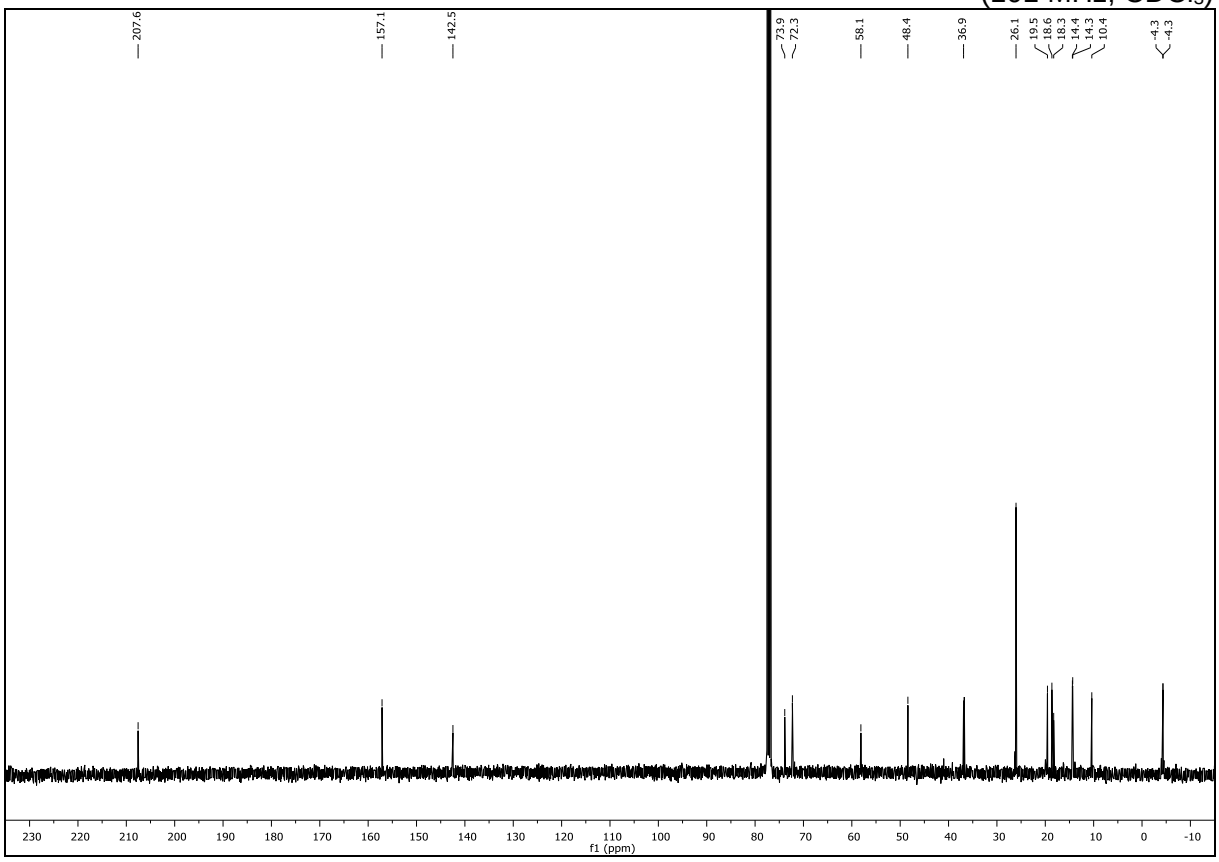
(101 MHz, $CDCl_3$)



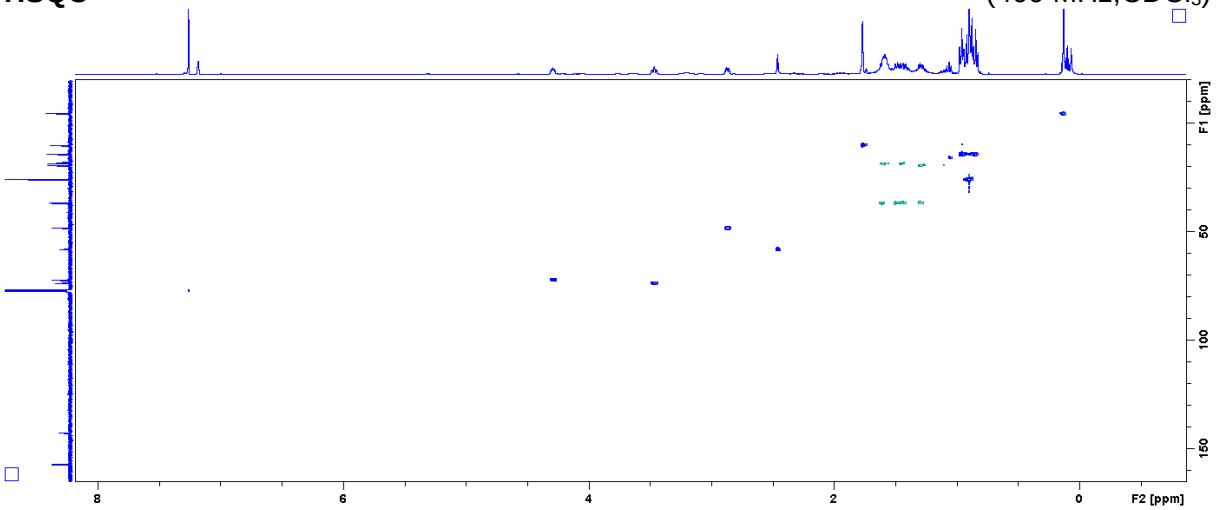
(±)-(4*S*,5*S*)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)butyl)-4-(1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-196a) (400 MHz,$CDCl_3$)



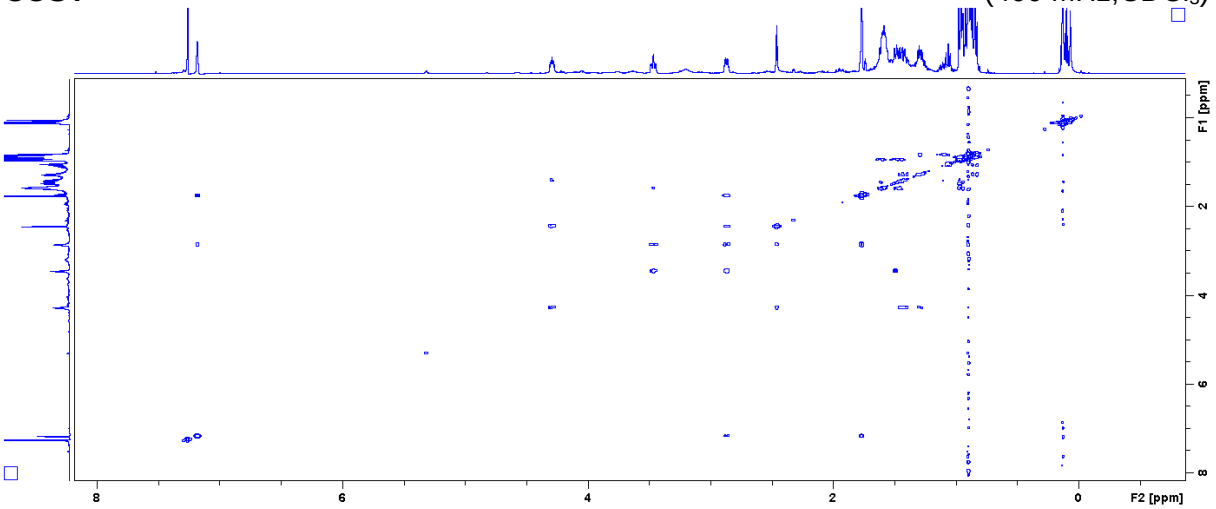
(101 MHz, $CDCl_3$)



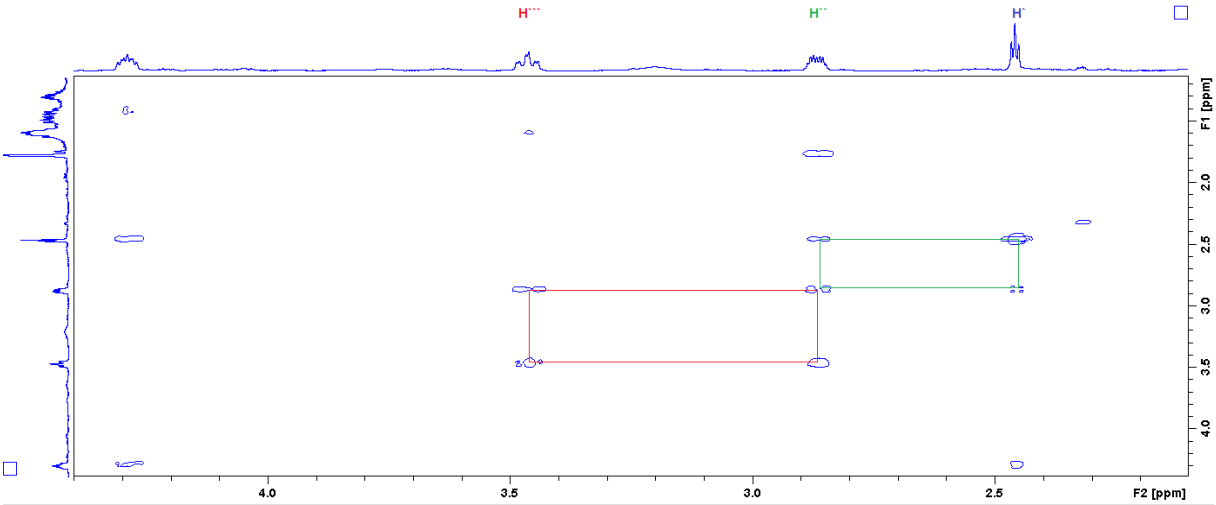
HSQC (400 MHz,$CDCl_3$)



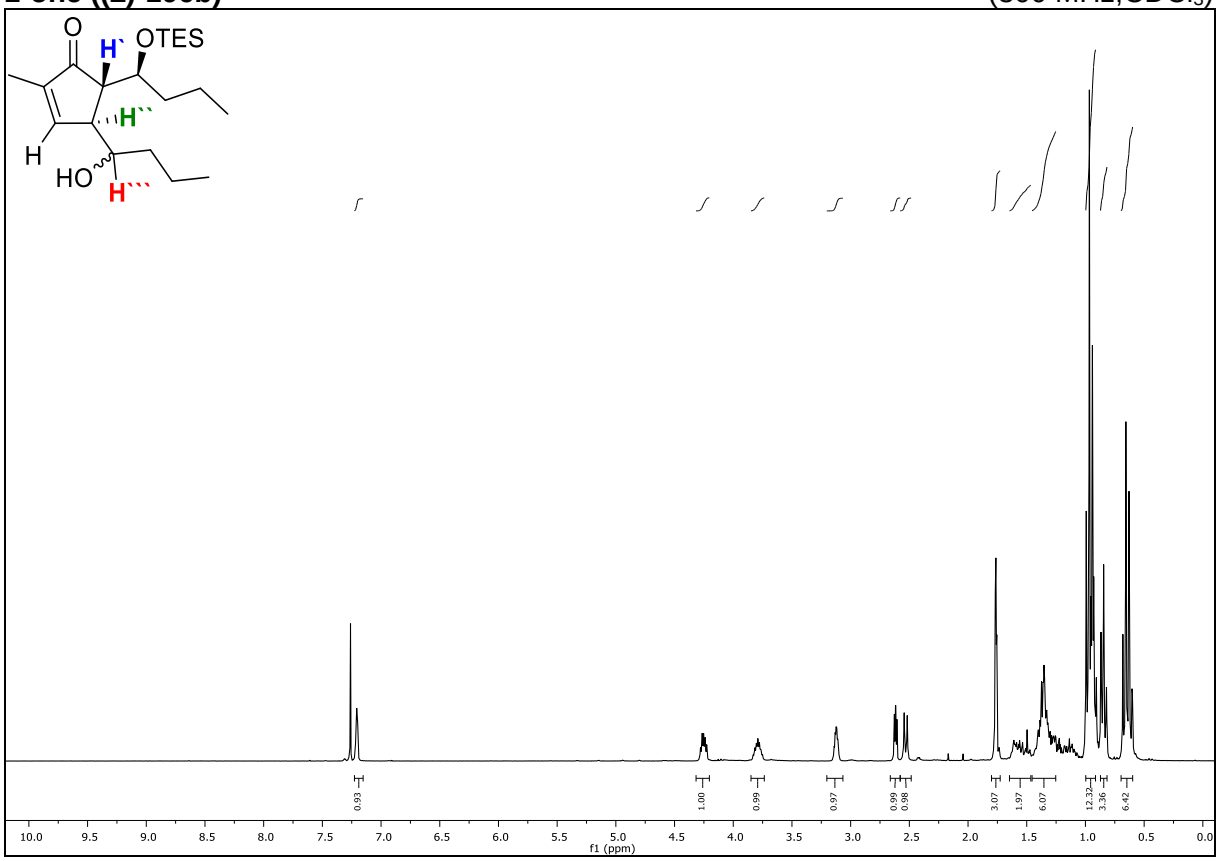
COSY (400 MHz,$CDCl_3$)



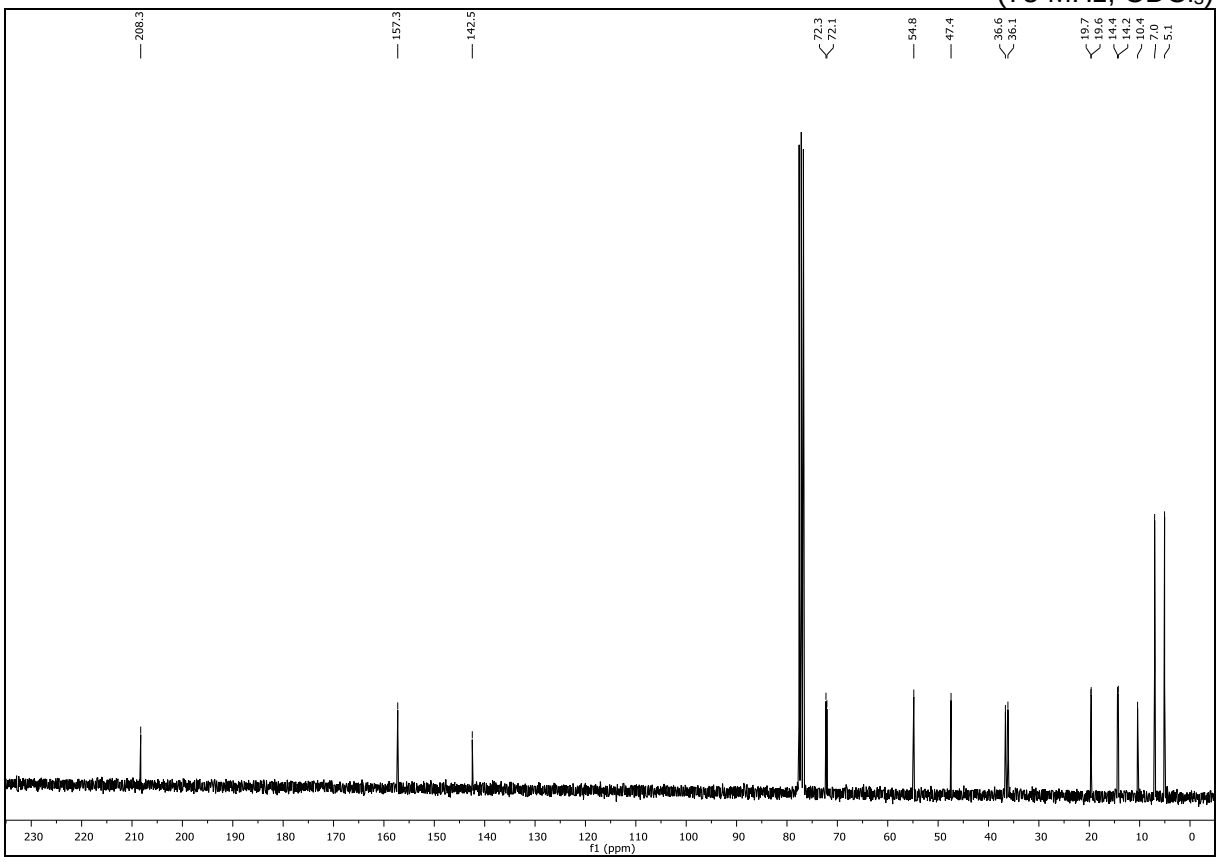
COSY Zoom In



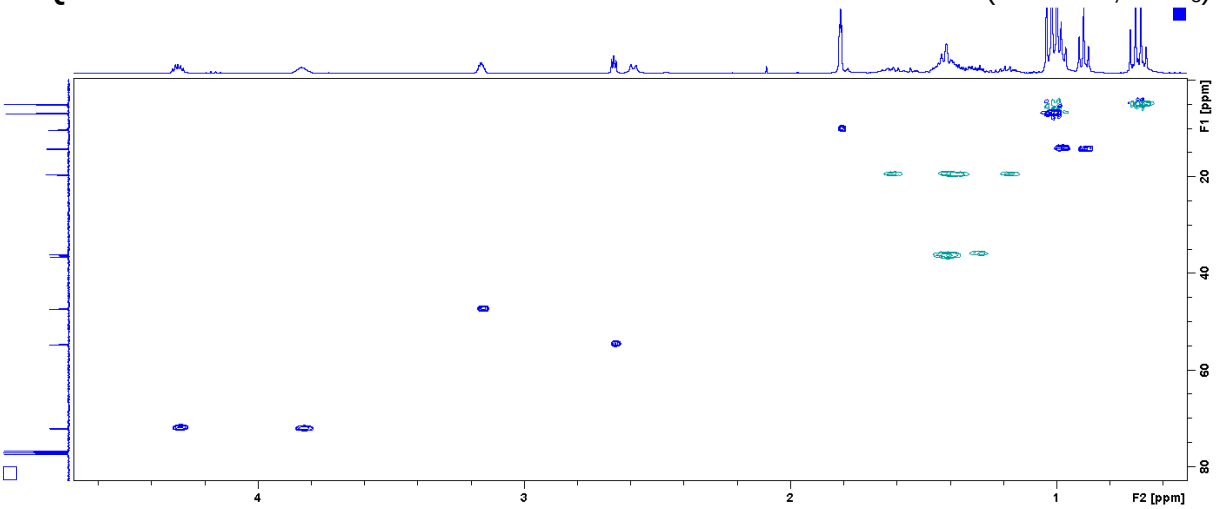
(±)-(4*S*,5*S*)-5-((*S*)-1-((triethylsilyl)oxy)butyl)-4-(1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-196b) (300 MHz,$CDCl_3$)



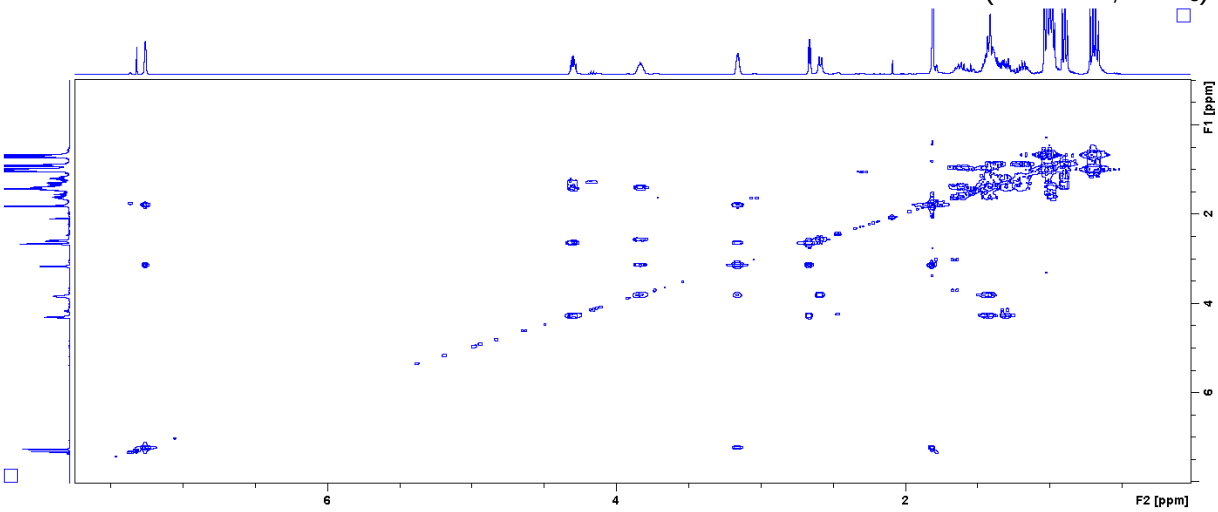
($CDCl_3$, 75 MHz)



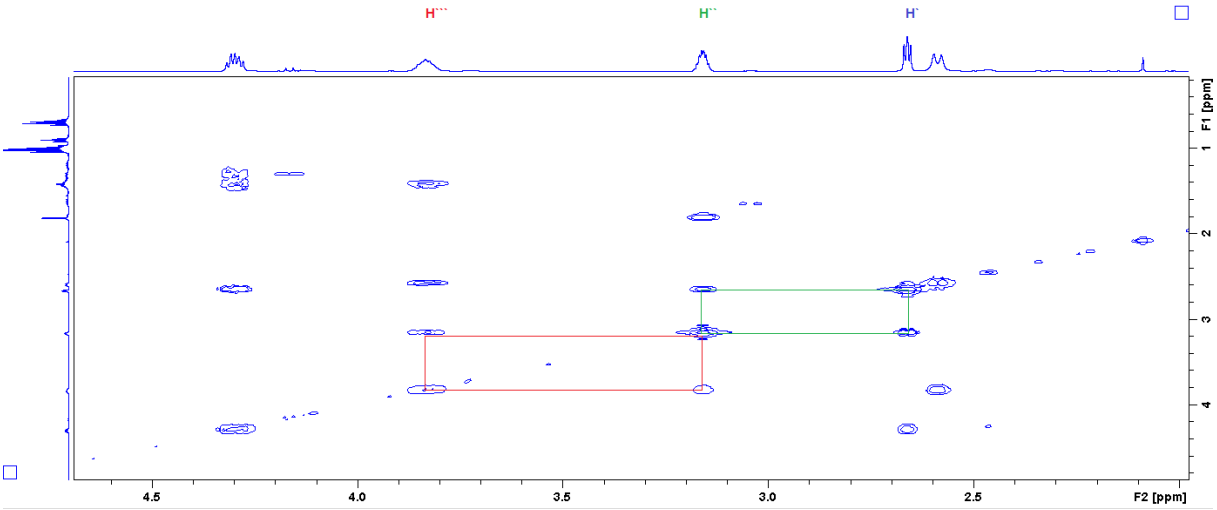
HSQC (400 MHz,$CDCl_3$)



COSY (400 MHz,$CDCl_3$)

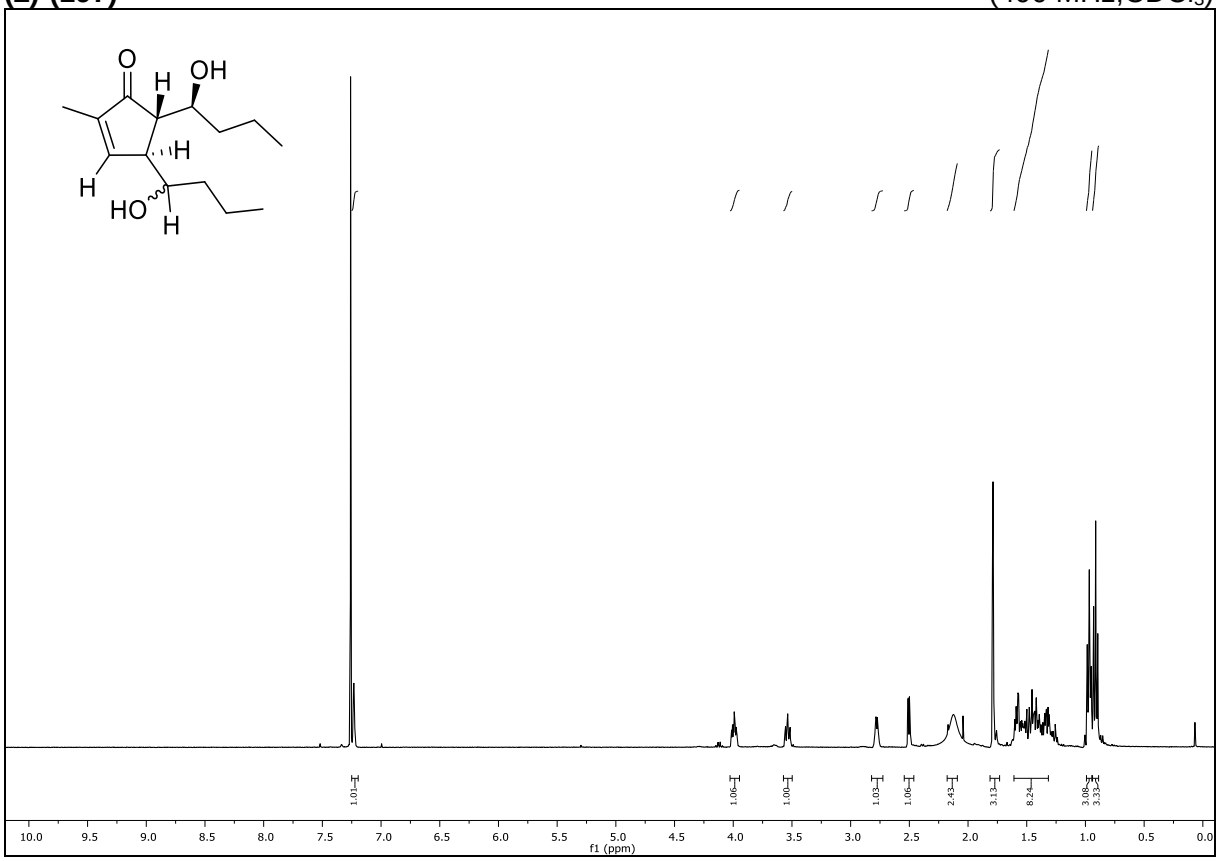


COSY Zoom In

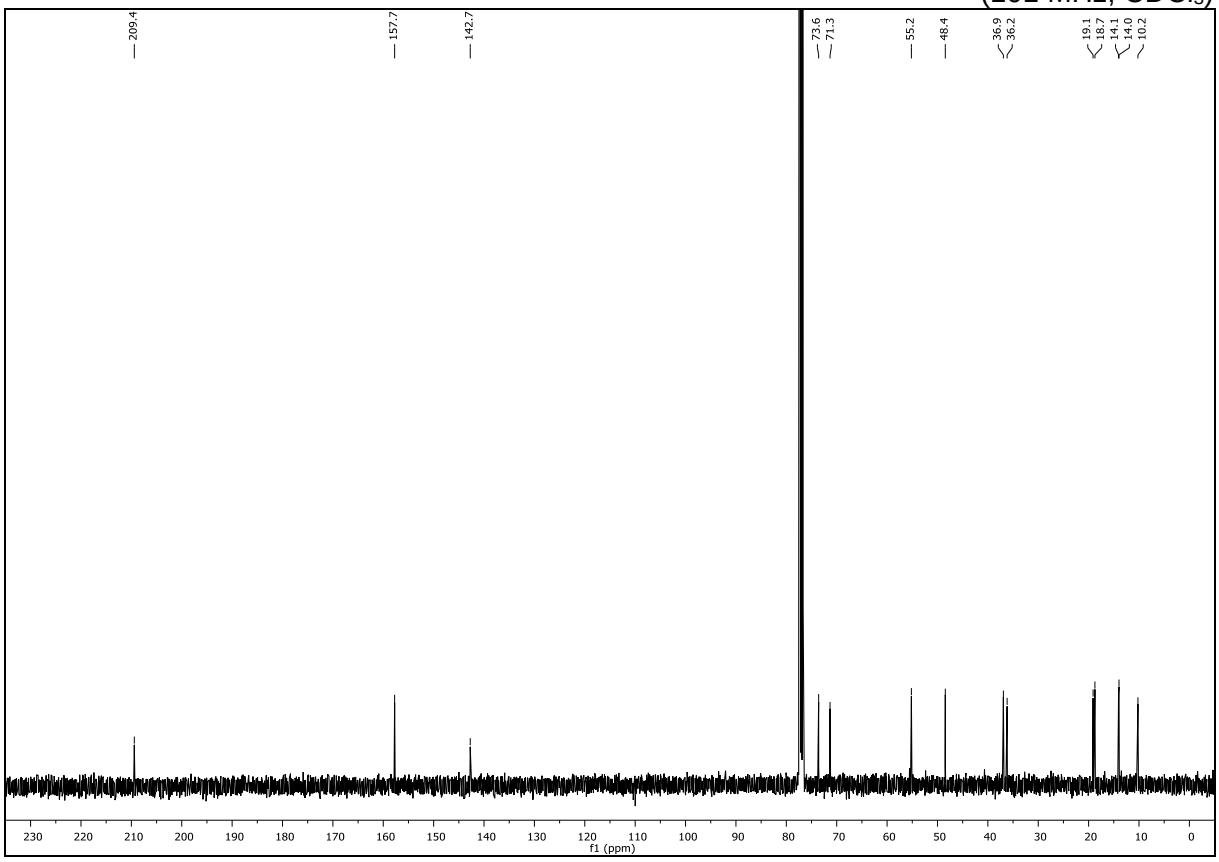


(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (±)-(197)

(400 MHz,$CDCl_3$)

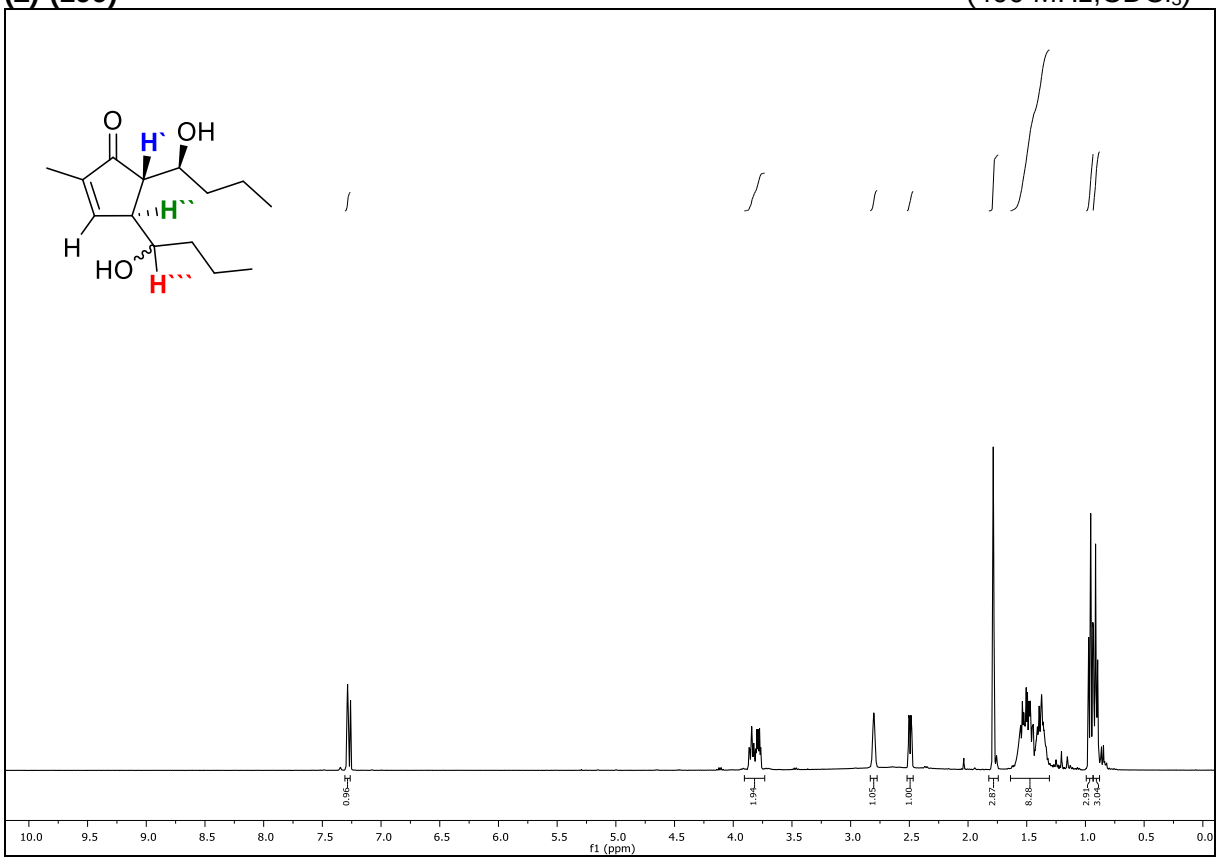


(101 MHz, $CDCl_3$)

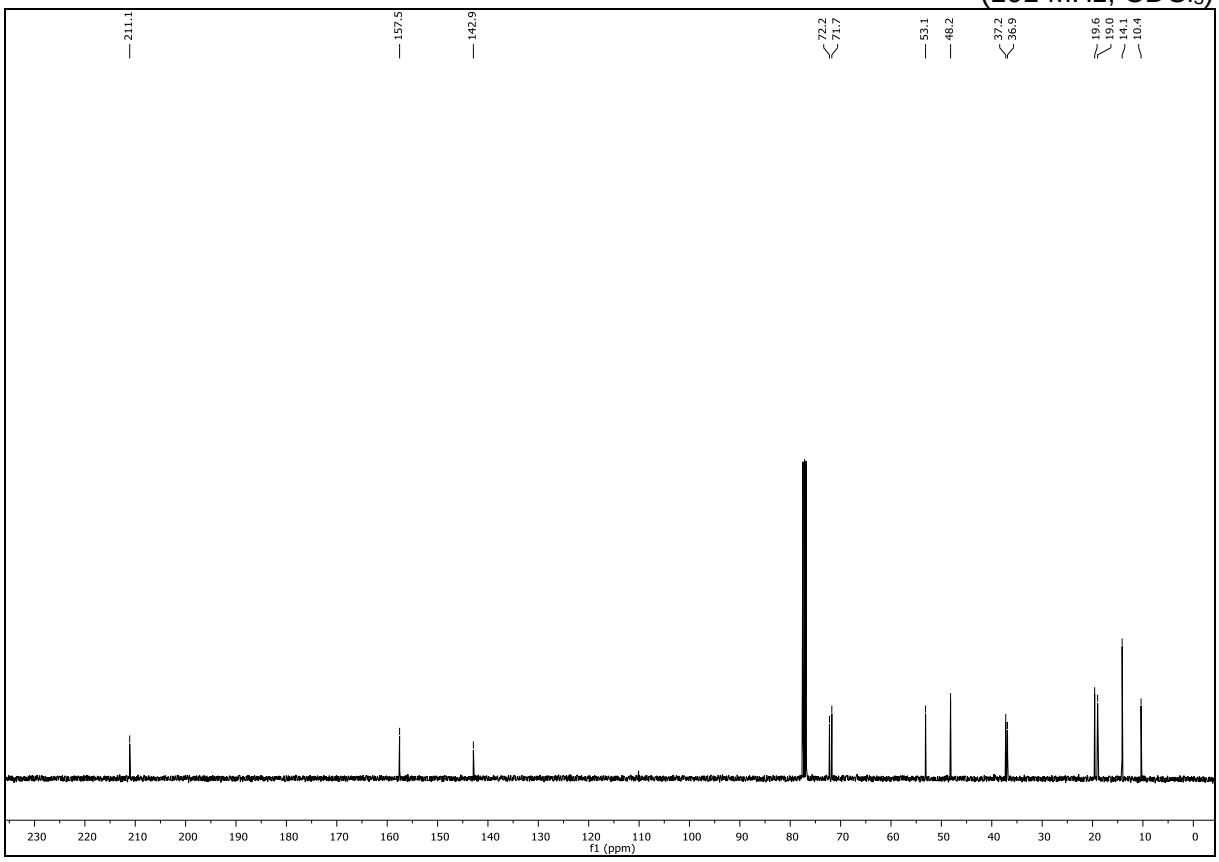


(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (±)-(199)

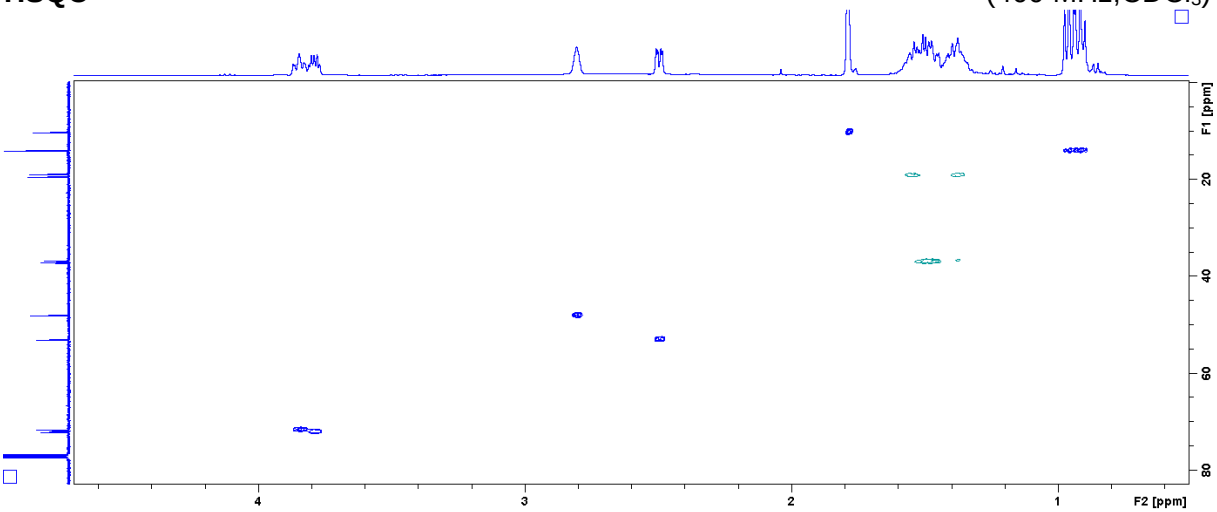
(400 MHz,$CDCl_3$)



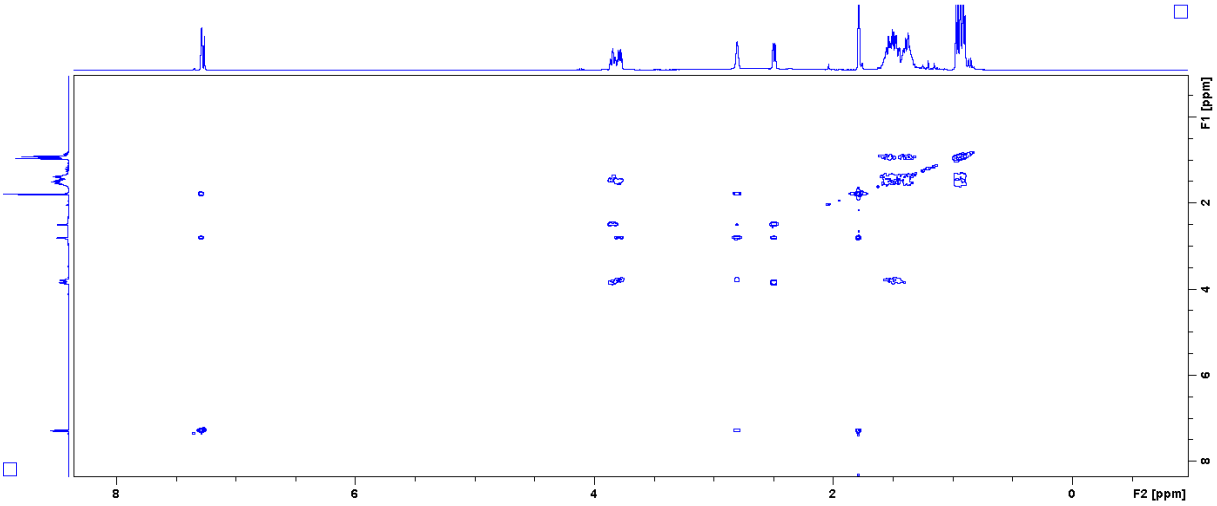
(101 MHz, $CDCl_3$)



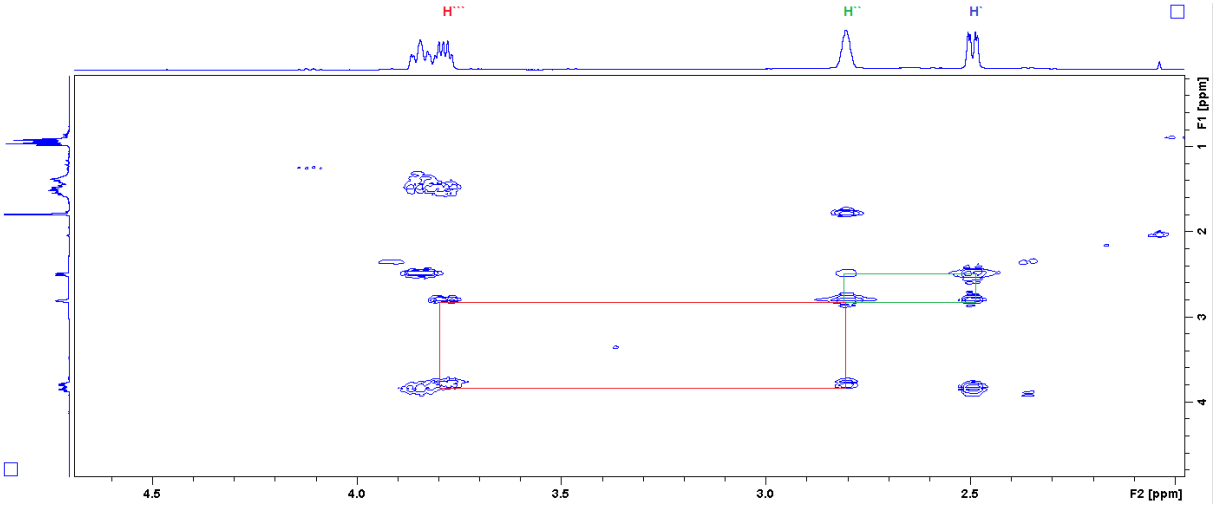
HSQC (400 MHz,$CDCl_3$)



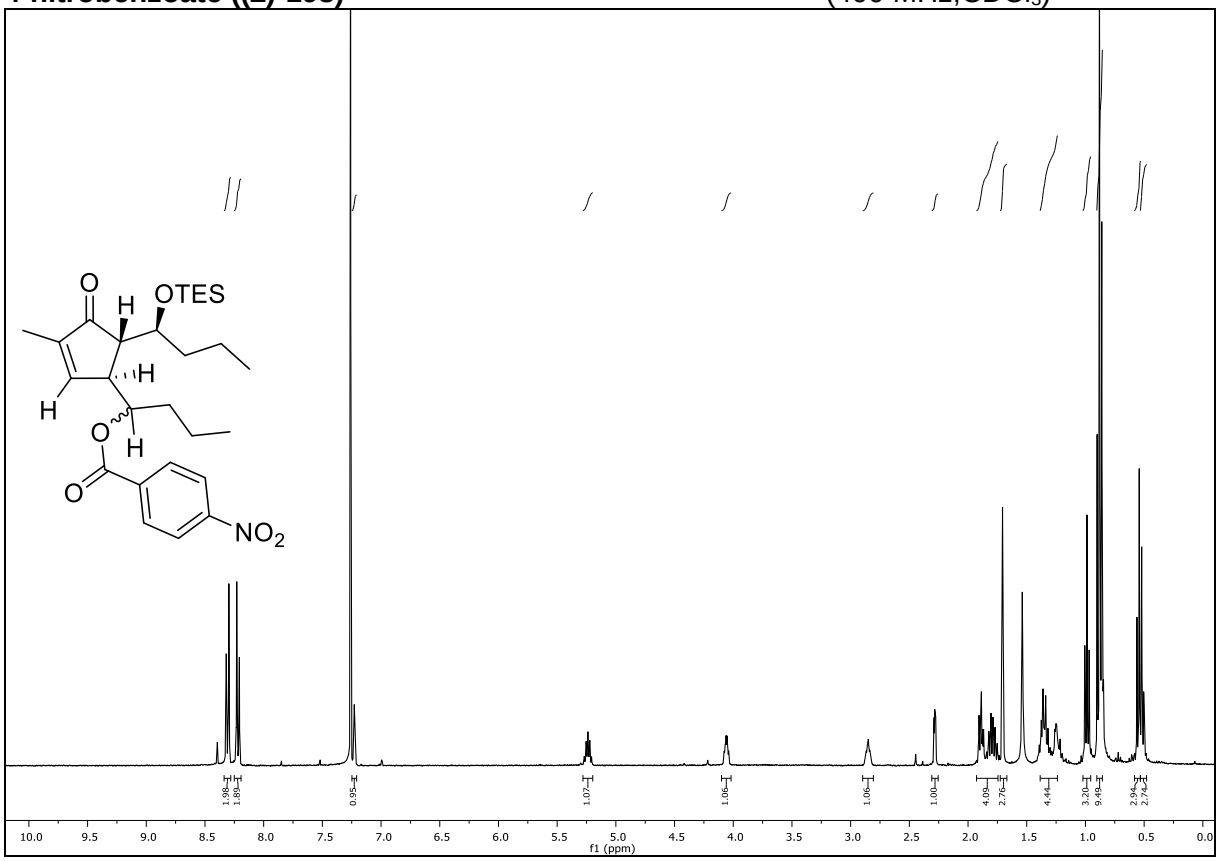
COSY (400 MHz,$CDCl_3$)



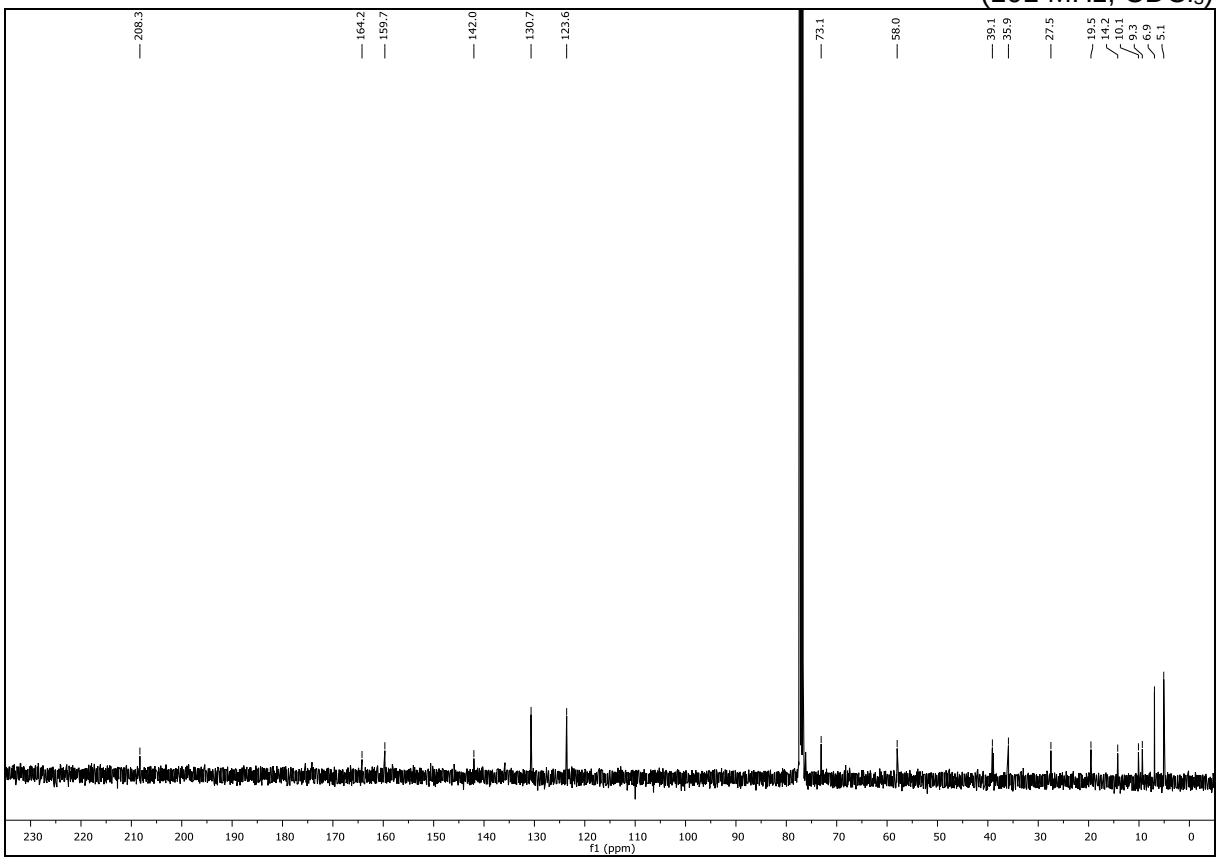
COSY Zoom In



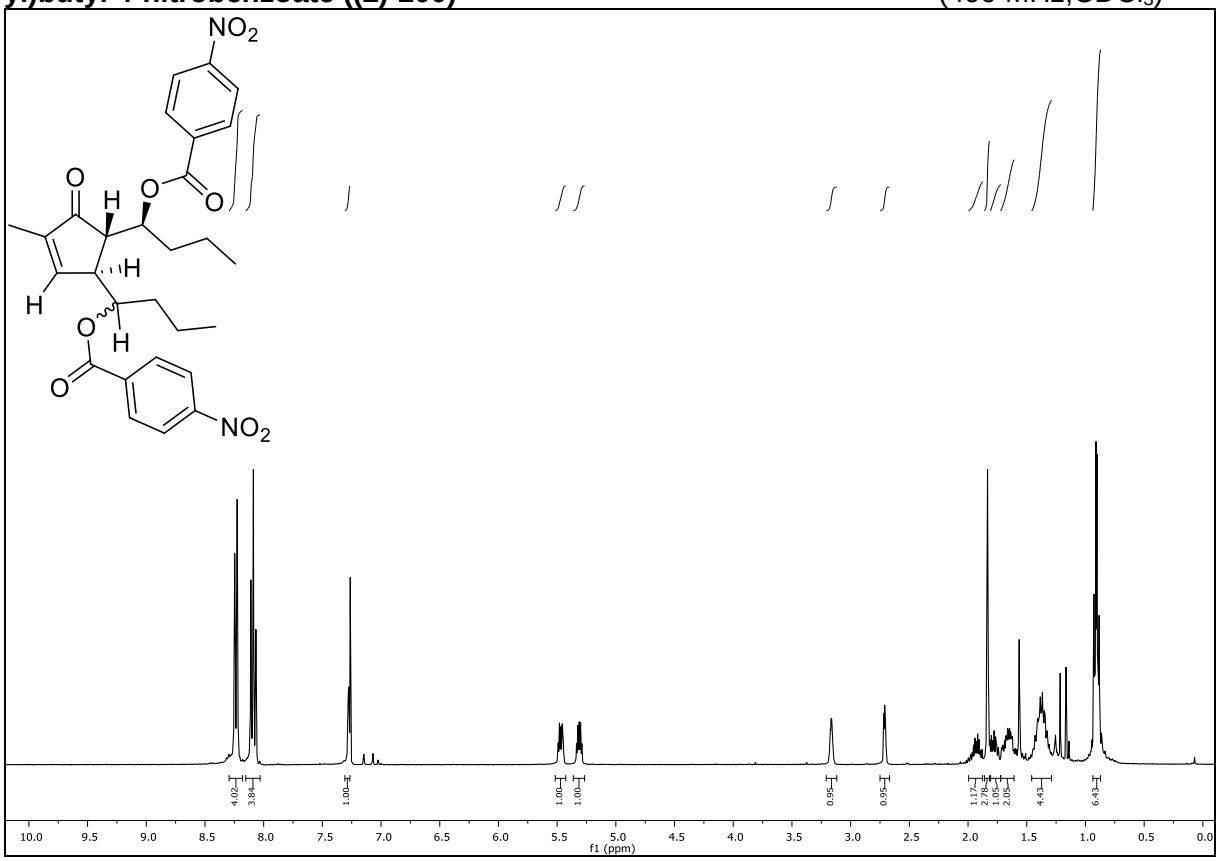
(±)-1-((1*S*,5*S*)-3-methyl-4-oxo-5-((*S*)-1-((triethylsilyl)oxy)butyl)cyclopent-2-en-1-yl)butyl 4-nitrobenzoate ((±)-198) (400 MHz,$CDCl_3$)



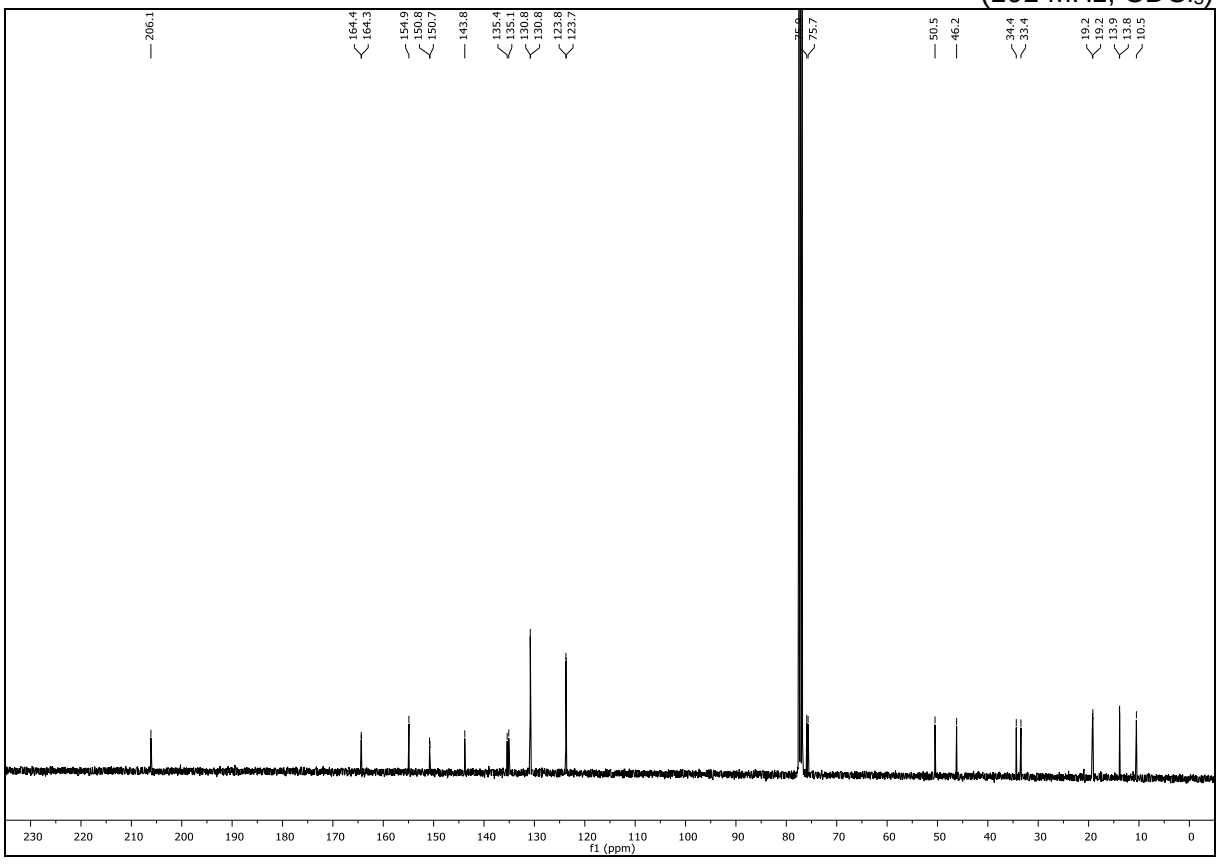
(101 MHz, $CDCl_3$)



(±)-(*S*)-1-((1*S*,5*S*)-3-methyl-5-(1-((4-nitrobenzoyl)oxy)butyl)-2-oxocyclopent-3-en-1-yl)butyl 4-nitrobenzoate ((±)-200) (400 MHz,$CDCl_3$)



(101 MHz, $CDCl_3$)

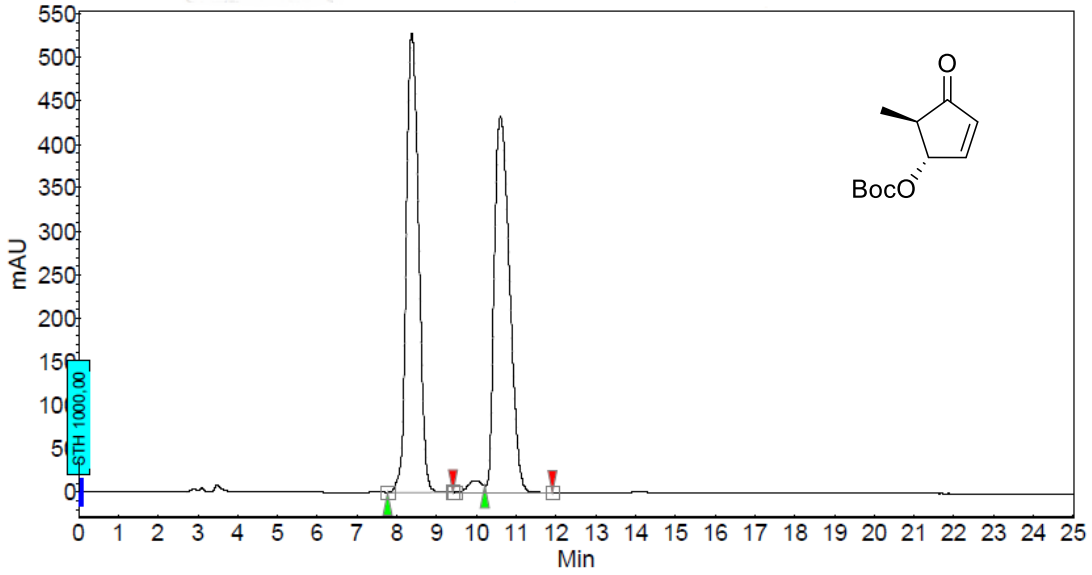


5.12 HPLC Chromatograms

Upper image: chromatogram of racemic compound

Loweer image: chromatogram of enantiomeric compound

((±)-(4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83f)

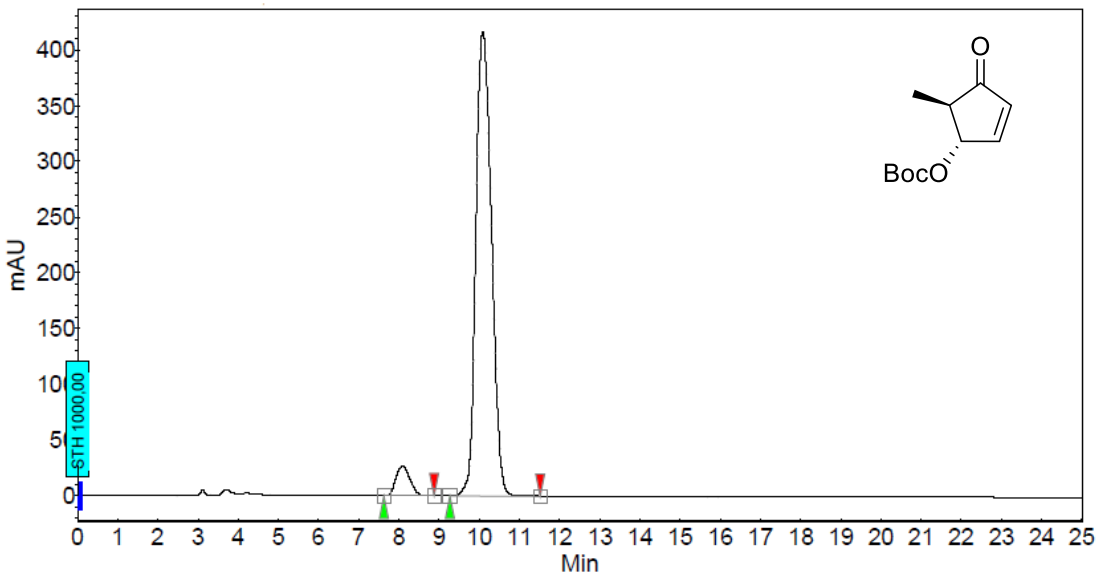


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8,37	49,66	527,4	189,7	49,665
2	UNKNOWN	10,60	50,34	433,4	192,3	50,335
Total			100,00	960,8	382,0	100,000

((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83f)

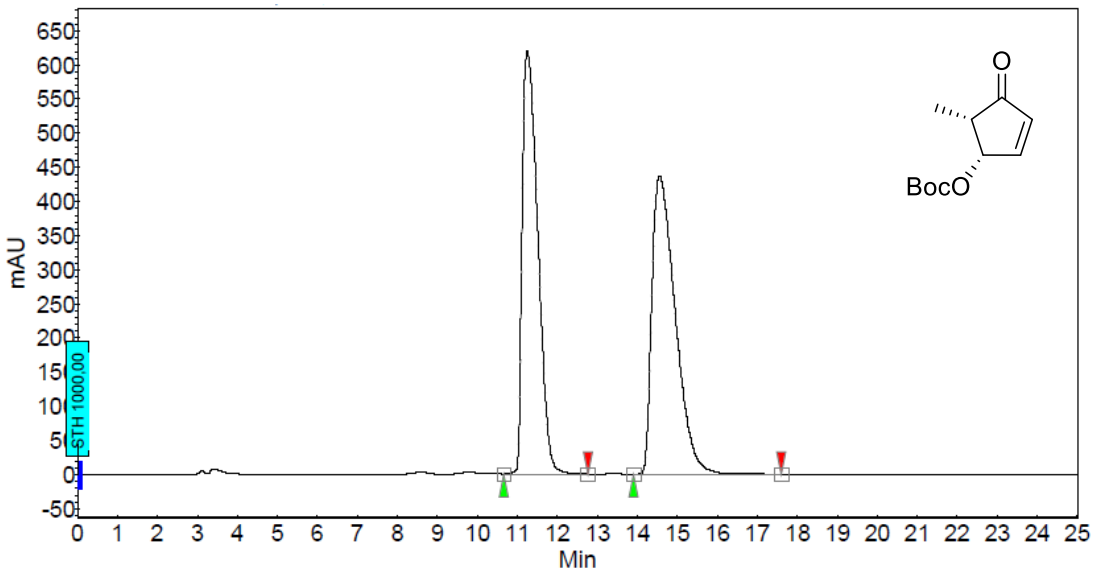
89% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	8,09	5,54	26,6	11,0	5,543
2	UNKNOWN	10,09	94,46	416,3	188,0	94,457
Total			100,00	442,9	199,0	100,000

((±)-(4*S*,5*S*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*syn*-83f)

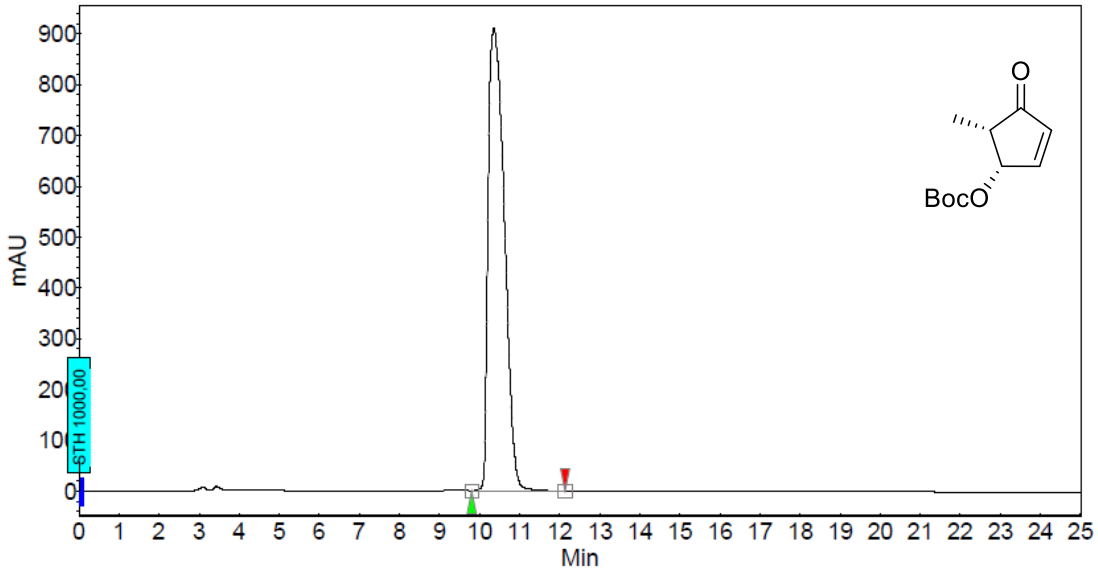


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,25	48,49	620,5	279,6	48,490
2	UNKNOWN	14,56	51,51	437,0	297,0	51,510
Total			100,00	1057,5	576,6	100,000

((4*S*,5*R*)-5-methyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*S*)-*syn*-83f)

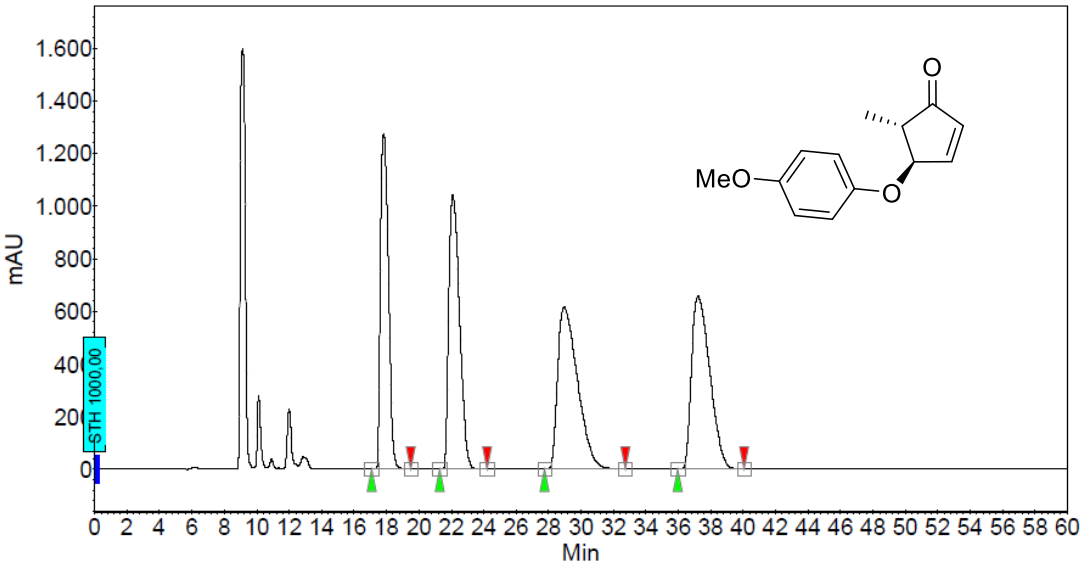
>99% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10,35	100,00	910,7	428,9	100,000
Total			100,00	910,7	428,9	100,000

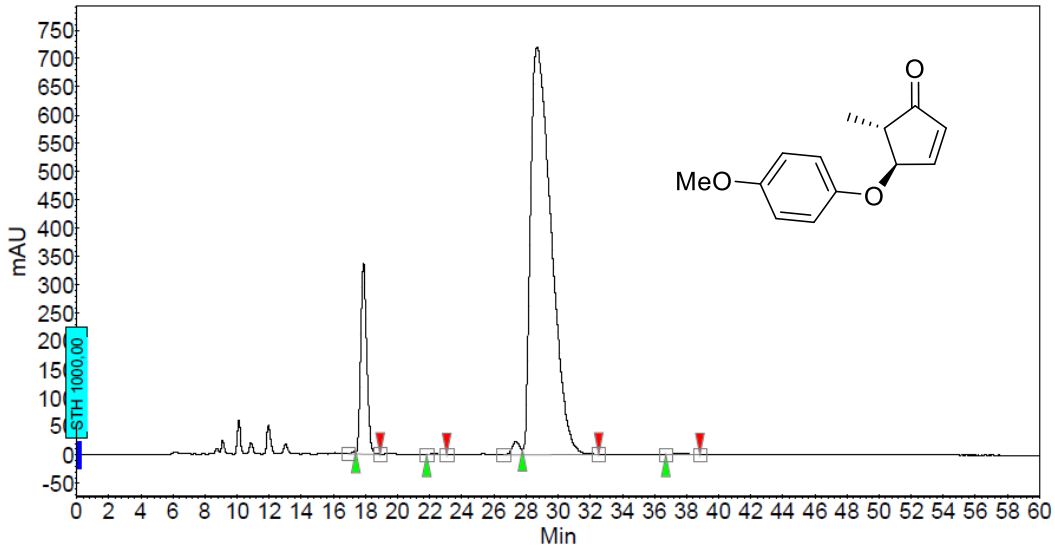
(±)-(4*R*,5*S*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((±)-*anti*-128f)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17,82	22,20	1271,0	724,3	22,198
2	UNKNOWN	22,08	24,63	1042,5	803,6	24,631
3	UNKNOWN	28,96	26,78	615,5	873,7	26,779
4	UNKNOWN	37,22	26,39	657,6	861,1	26,392
Total			100,00	3586,6	3262,7	100,000

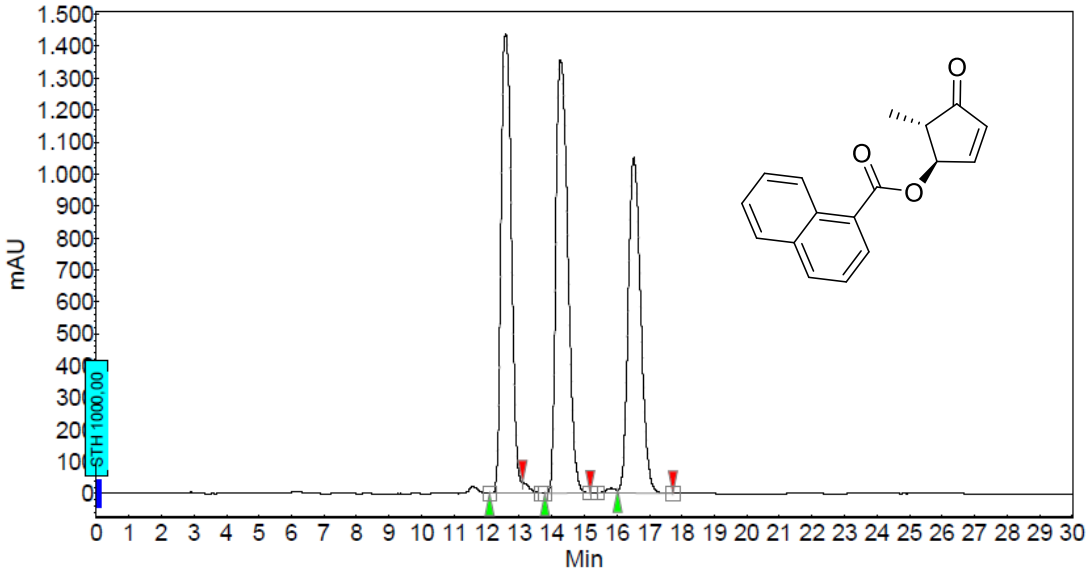
(4*R*,5*S*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one (*anti*-128f) 76% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17,87	11,97	337,2	146,1	11,974
3	UNKNOWN	22,30	0,08	1,8	1,0	0,079
2	UNKNOWN	28,68	87,69	719,8	1069,9	87,693
4	UNKNOWN	37,66	0,25	3,3	3,1	0,254
Total			100,00	1062,1	1220,1	100,000

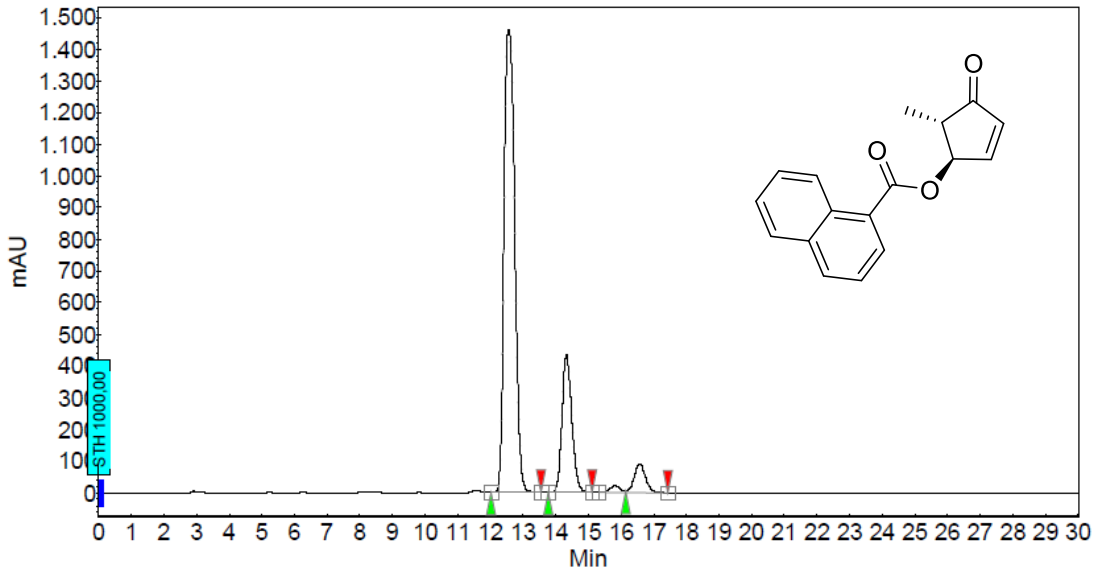
(±)-(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-methylcyclopent-2-en-1-one ((±)-*anti*-130f)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,58	33,64	1436,6	531,2	33,637
3	UNKNOWN	14,27	36,43	1356,9	575,3	36,433
2	UNKNOWN	16,52	29,93	1049,5	472,7	29,931
Total			100,00	3843,0	1579,2	100,000

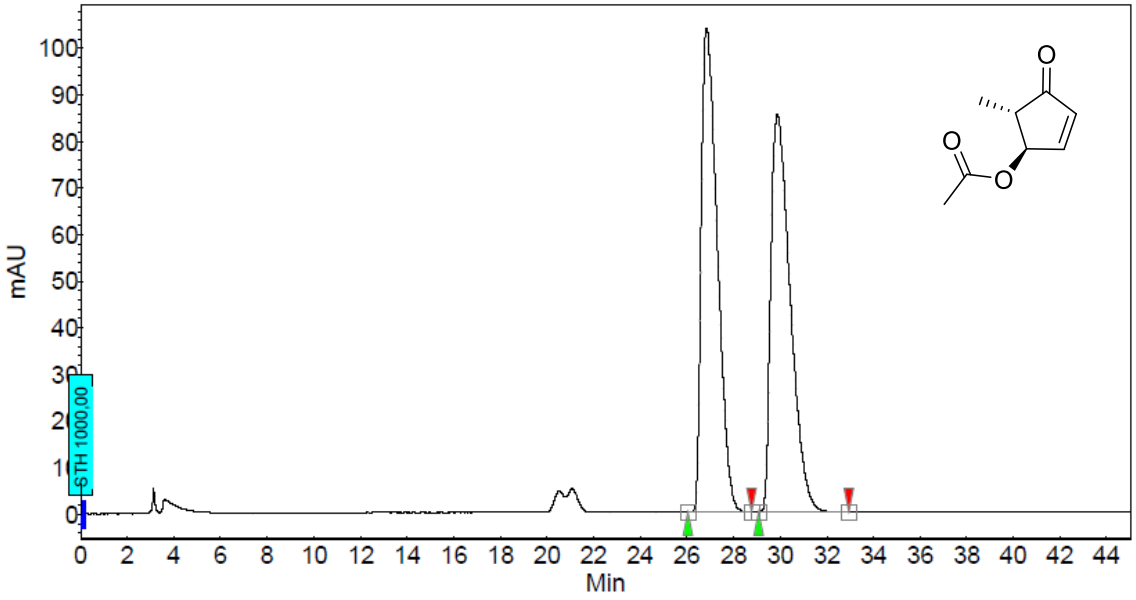
(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-methylcyclopent-2-en-1-one (*anti*-130f) 54% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,56	74,56	1457,9	549,3	74,563
2	UNKNOWN	14,33	20,45	433,8	150,7	20,453
3	UNKNOWN	16,57	4,98	90,9	36,7	4,984
Total			100,00	1982,7	736,8	100,000

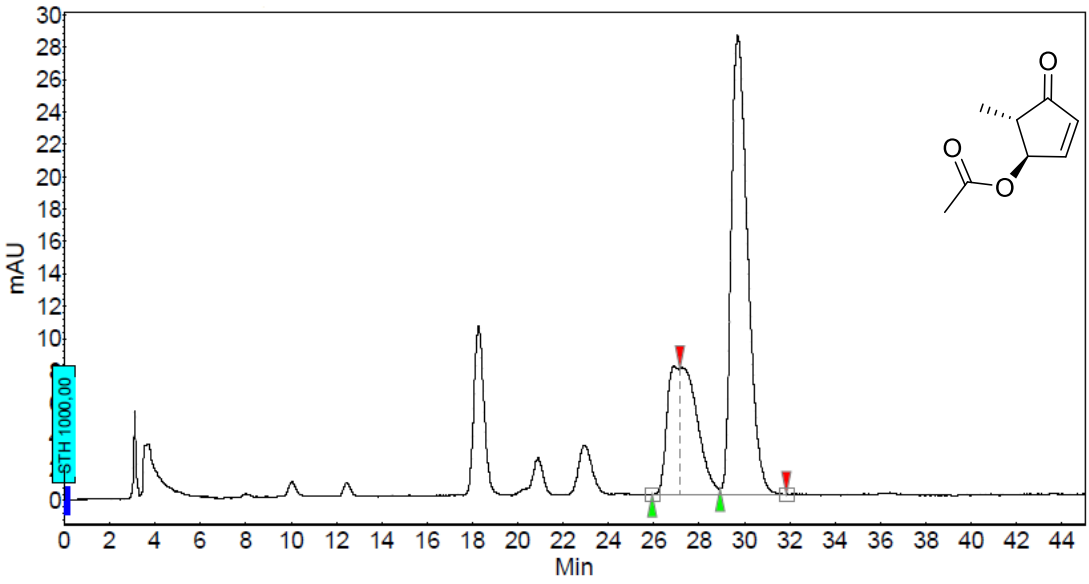
(±)-(4*R*,5*S*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((±)-*anti*-131f)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	26,84	49,93	103,6	82,4	49,929
2	UNKNOWN	29,87	50,07	85,3	82,7	50,071
Total			100,00	188,9	165,1	100,000

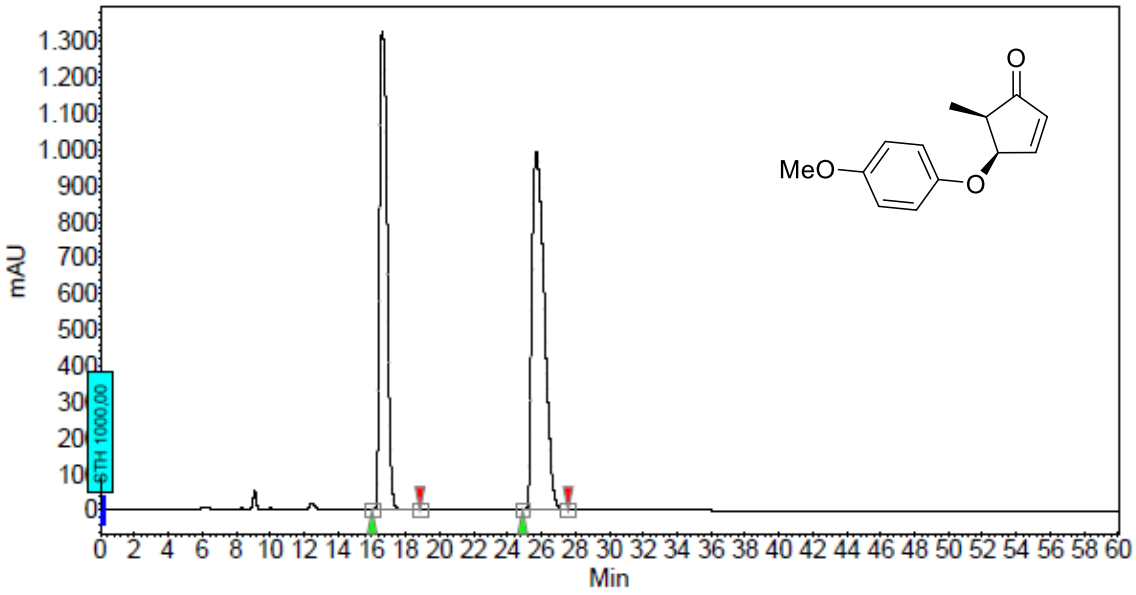
(4*R*,5*S*)-4-acetoxy-5-methylcyclopent-2-en-1-one (*anti*-131f) 66% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	26,87	16,88	7,9	4,8	16,878
2	UNKNOWN	29,70	83,12	28,3	23,9	83,122
Total			100,00	36,2	28,7	100,000

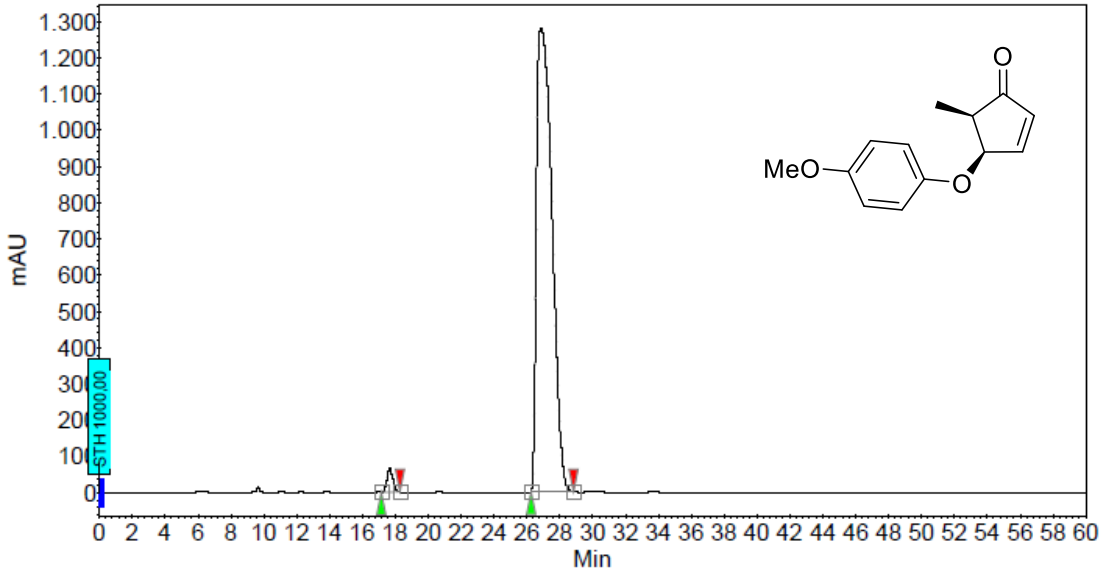
(±)-(4*R*,5*R*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one ((±)-*syn*-128f)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16,63	45,19	1328,4	688,2	45,188
2	UNKNOWN	25,71	54,81	994,0	834,7	54,812
Total			100,00	2322,5	1522,9	100,000

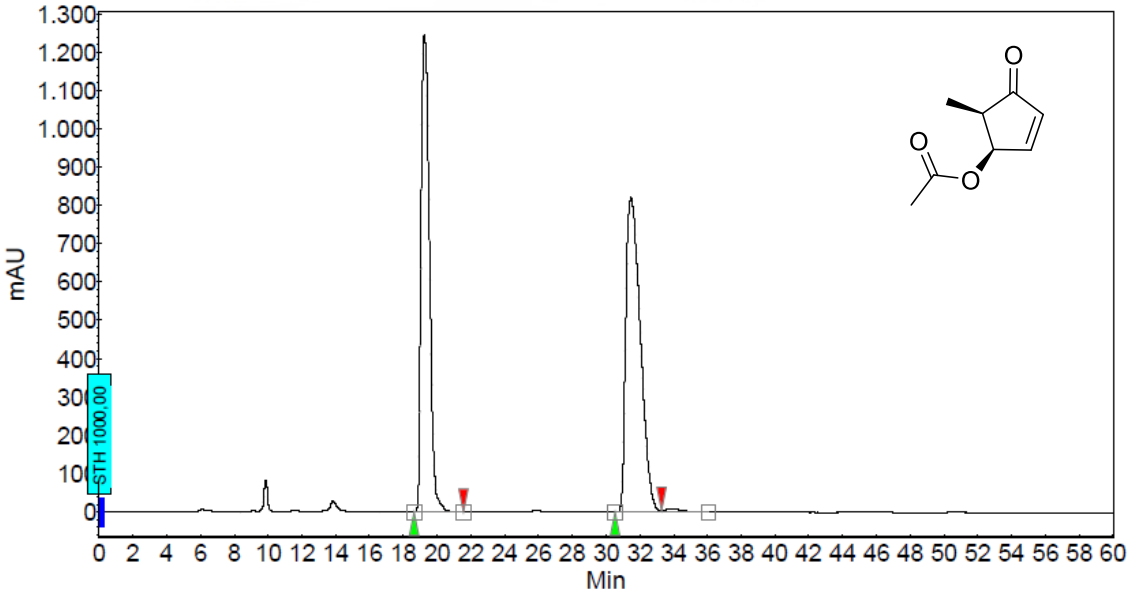
(4*R*,5*R*)-4-(4-methoxyphenoxy)-5-methylcyclopent-2-en-1-one (4*R*,5*R*)-*syn*-128f) 96% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	17,67	1,87	66,3	26,8	1,871
2	UNKNOWN	26,87	98,13	1280,5	1406,1	98,129
Total			100,00	1346,8	1432,9	100,000

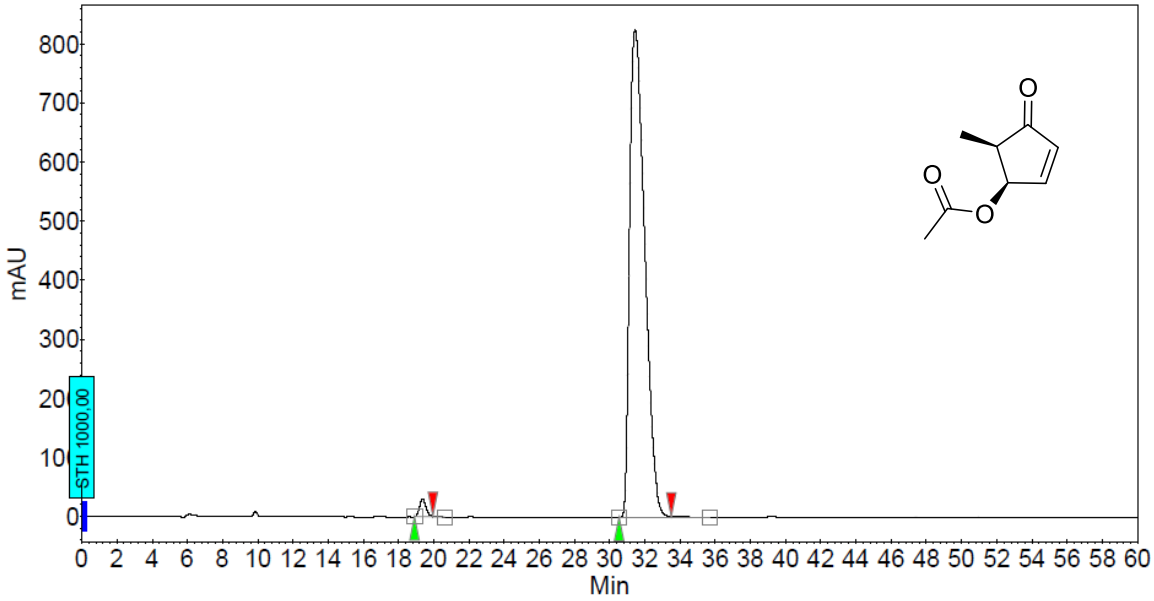
(±)-(4*R*,5*R*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((±)-*syn*-131f)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	19,25	46,63	1243,3	715,5	46,629
2	UNKNOWN	31,47	53,37	821,9	818,9	53,371
Total			100,00	2065,1	1534,5	100,000

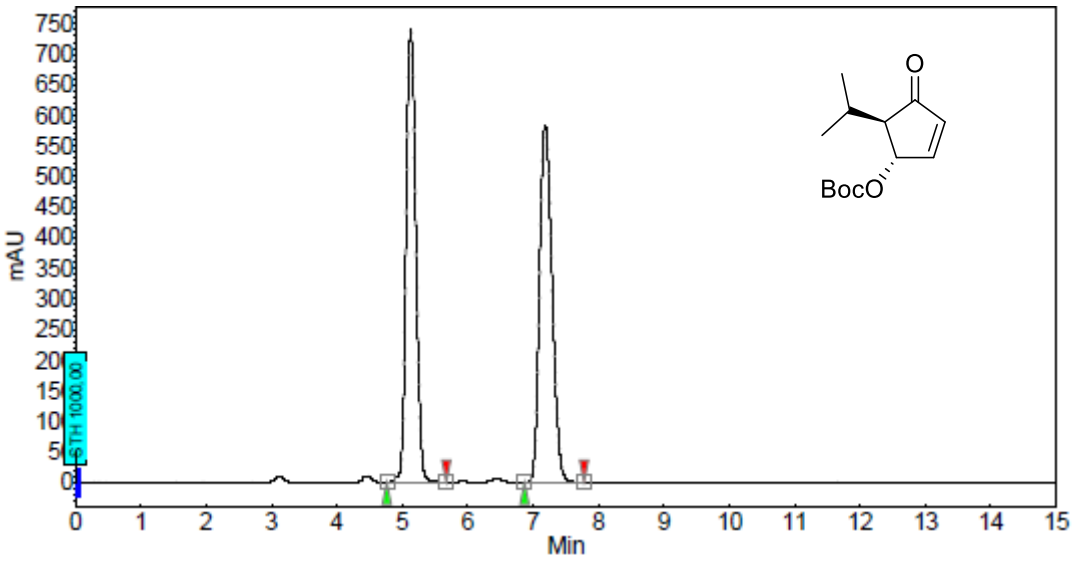
(4*R*,5*R*)-4-acetoxy-5-methylcyclopent-2-en-1-one ((4*R*,5*R*)-*syn*-131f) 97% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	19,37	1,58	30,4	13,2	1,582
1	UNKNOWN	31,44	98,42	824,3	820,8	98,418
Total			100,00	854,7	834,0	100,000

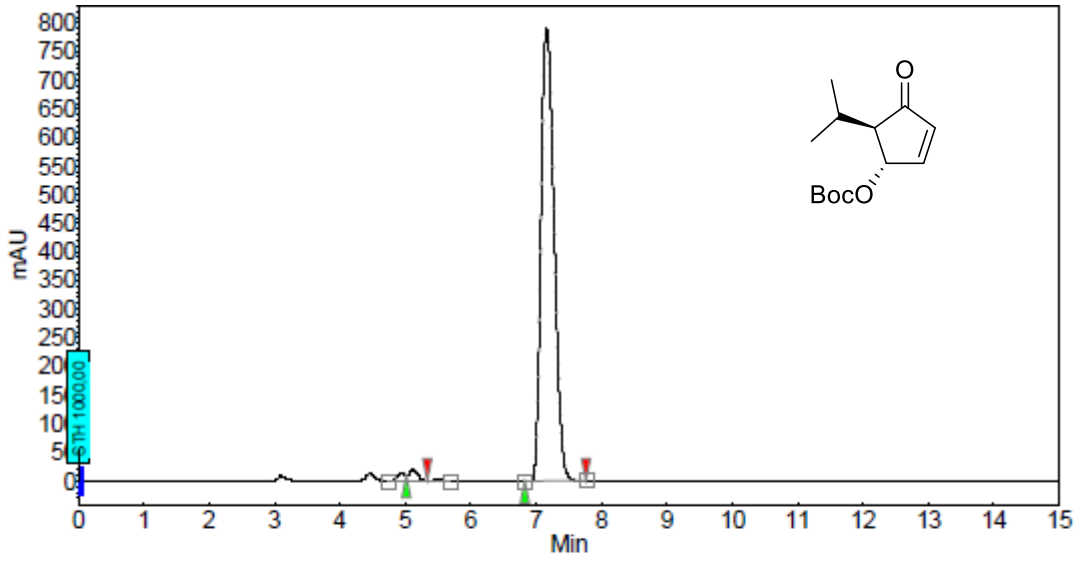
(±)-((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83g)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	5,13	49,53	741,1	127,0	49,534
2	UNKNOWN	7,18	50,47	582,9	129,4	50,466
Total			100,00	1324,0	256,4	100,000

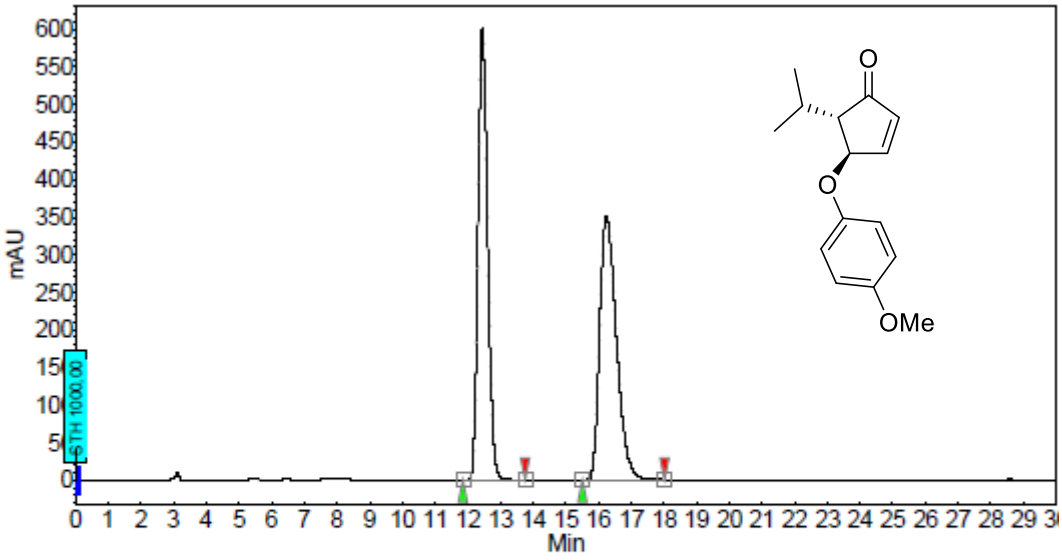
((4*S*,5*R*)-5-isopropyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83g) 97 % ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	5,13	1,73	19,2	3,2	1,729
2	UNKNOWN	7,16	98,27	790,7	182,3	98,271
Total			100,00	809,9	185,5	100,000

(±)-(4*R*,5*S*)-5-isopropyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((±)-*anti*-128g)

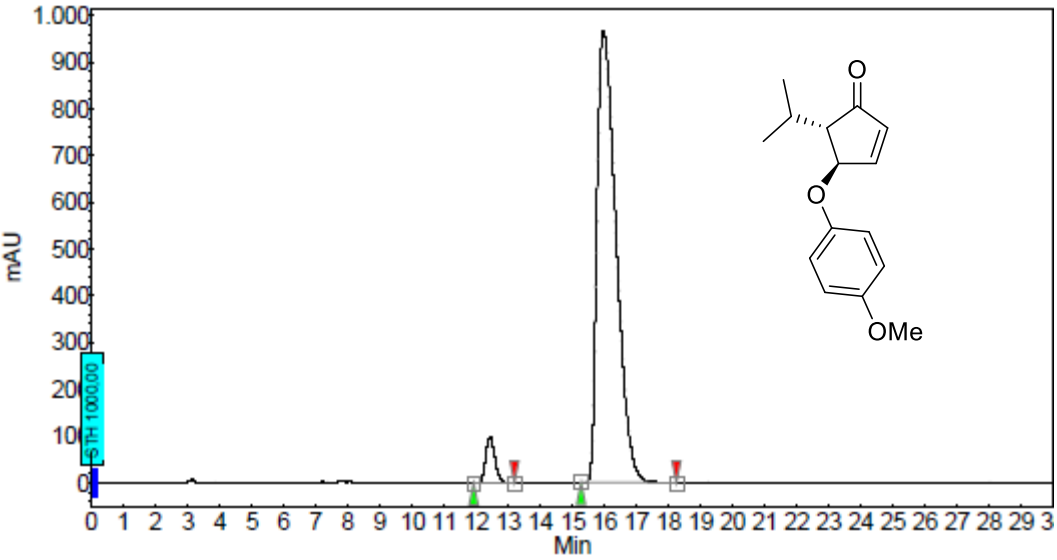


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,44	49,64	601,8	205,6	49,645
2	UNKNOWN	16,24	50,36	350,6	208,6	50,355
Total			100,00	952,3	414,2	100,000

(4*R*,5*S*)-5-isopropyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128g)

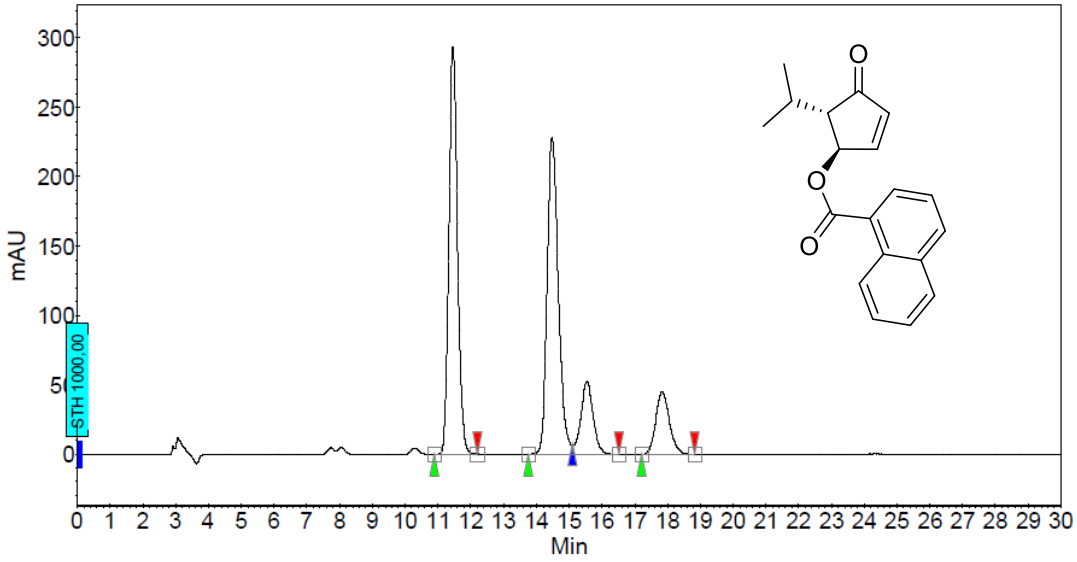
91 % ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,42	4,67	99,5	32,6	4,674
2	UNKNOWN	15,97	95,33	966,4	665,7	95,326
Total			100,00	1065,9	698,3	100,000

(±)-((4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isopropylcyclopent-2-en-1-one ((±)-*anti*-130g)

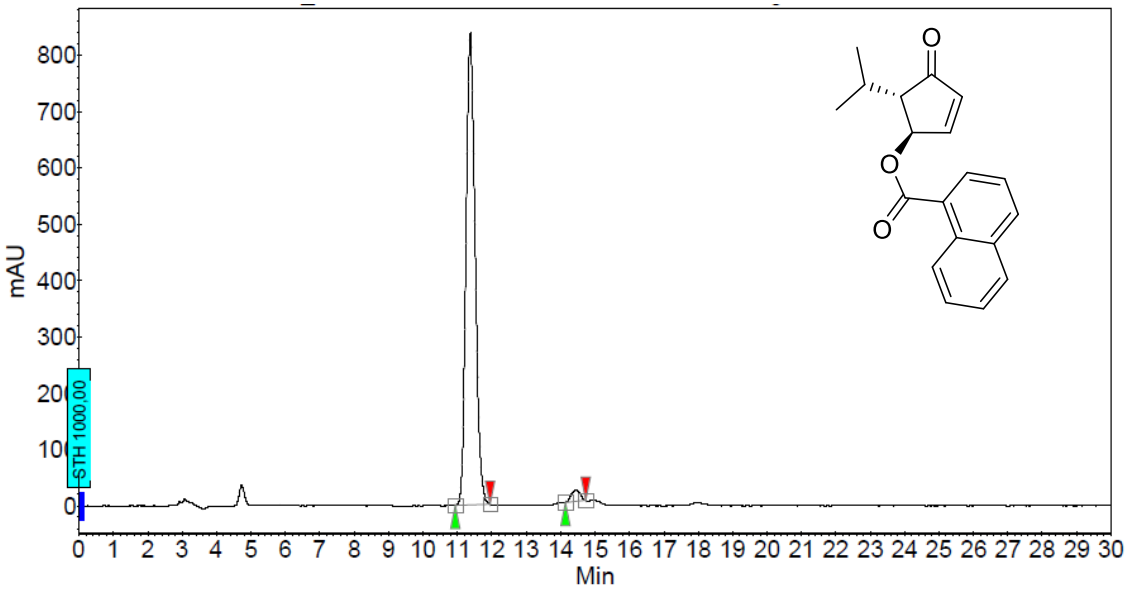


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,46	39,93	293,4	89,5	39,929
2	UNKNOWN	14,48	40,36	228,0	90,4	40,355
4	UNKNOWN	15,54	10,08	52,5	22,6	10,080
3	UNKNOWN	17,83	9,64	45,1	21,6	9,636
Total			100,00	619,0	224,1	100,000

(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isopropylcyclopent-2-en-1-one ((4R,5S)-*anti*-130g)

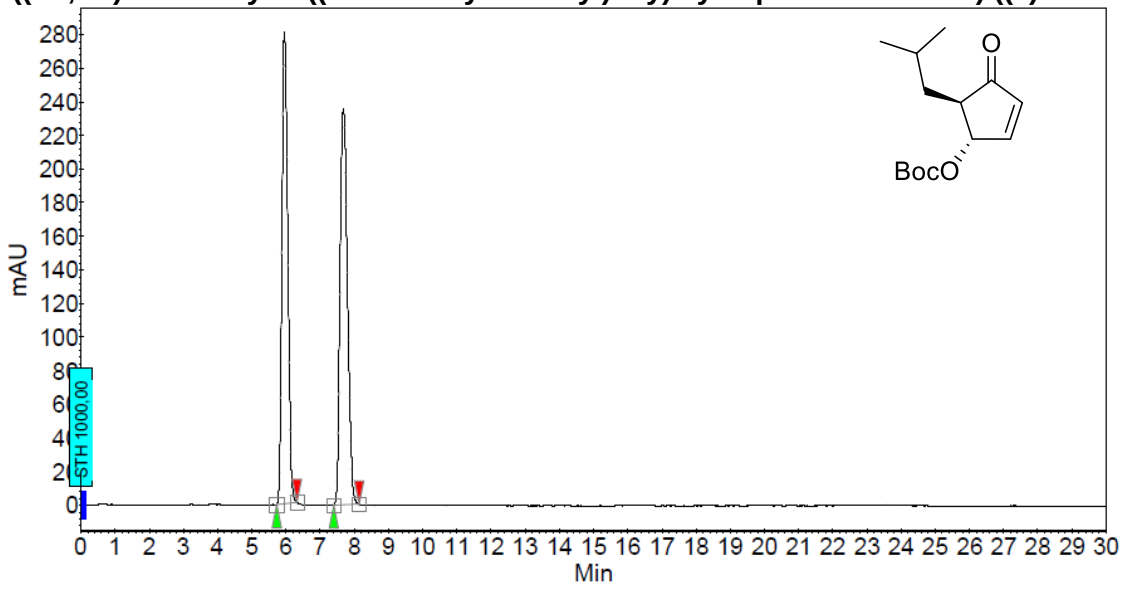
95% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11,37	97,70	838,9	257,4	97,703
2	UNKNOWN	14,44	2,30	20,3	6,1	2,297
Total			100,00	859,1	263,5	100,000

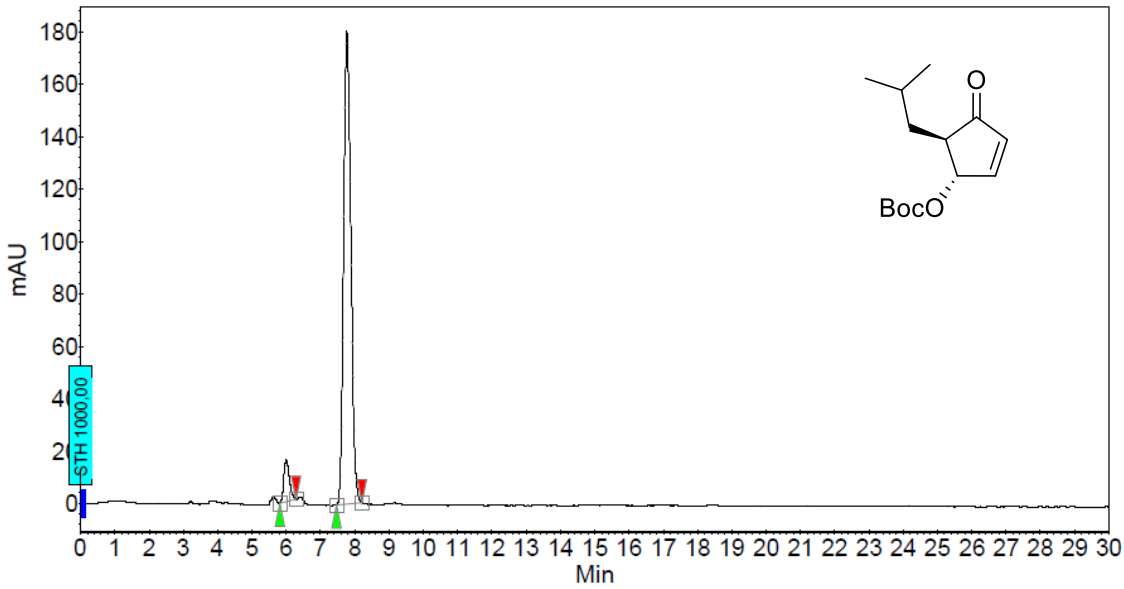
(±)-((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83i)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	5,96	48,51	280,6	55,7	48,509
1	UNKNOWN	7,68	51,49	236,0	59,1	51,491
Total			100,00	516,5	114,8	100,000

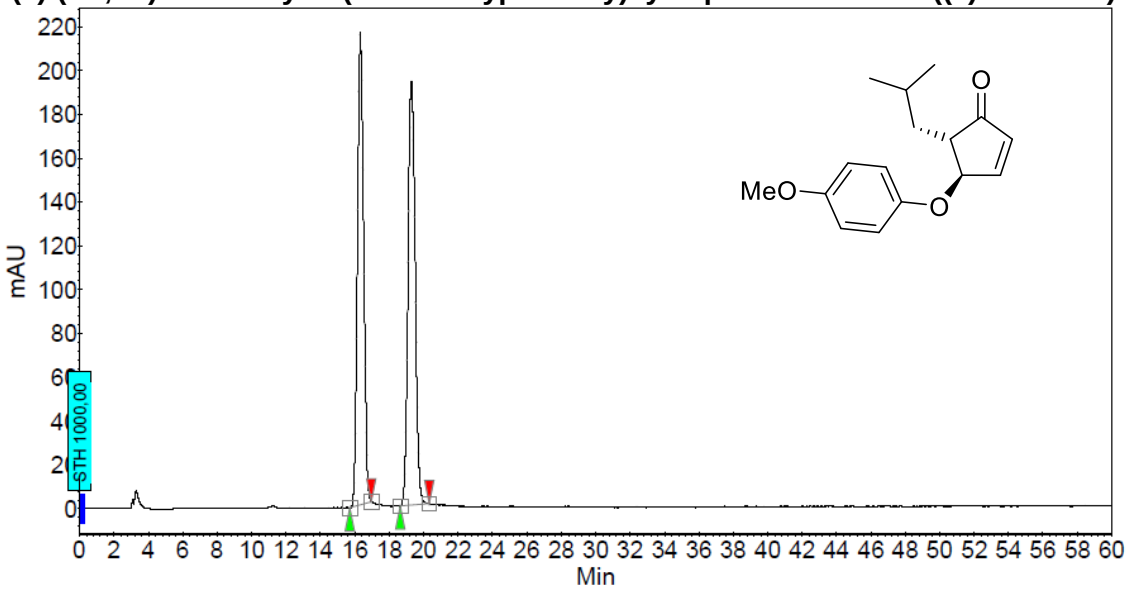
((4*S*,5*R*)-5-isobutyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83i) 88% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,00	6,21	15,9	2,9	6,207
2	UNKNOWN	7,77	93,79	180,4	44,4	93,793
Total			100,00	196,3	47,3	100,000

(±)-(4*R*,5*S*)-5-isobutyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((±)-*anti*-128i)

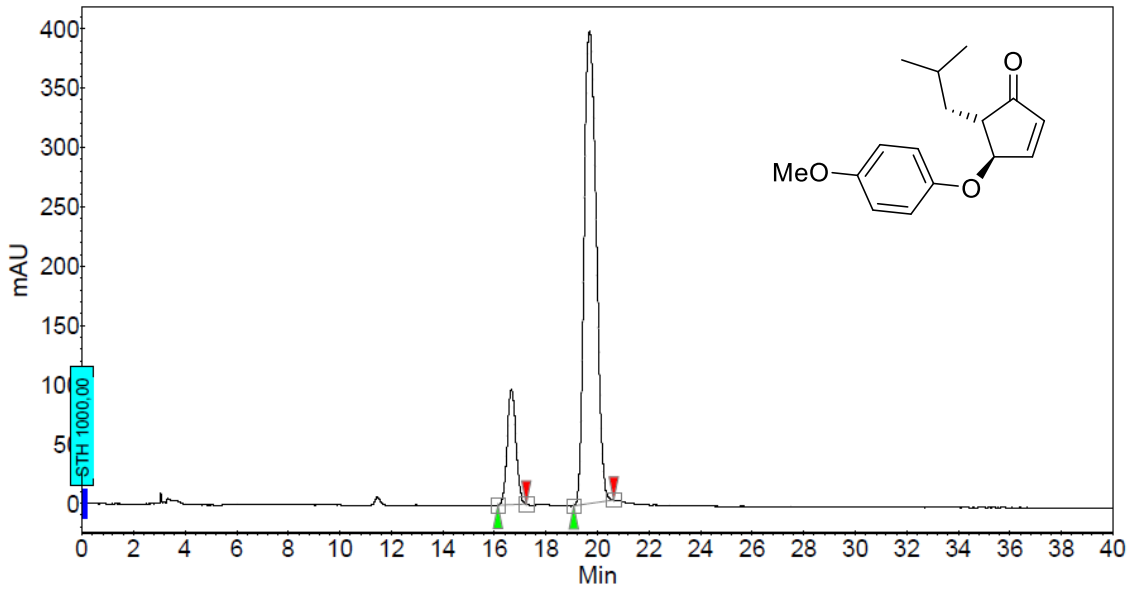


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16,32	49,32	215,6	90,2	49,318
2	UNKNOWN	19,29	50,68	193,8	92,7	50,682
Total			100,00	409,4	182,9	100,000

(4*R*,5*S*)-5-isobutyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128i)

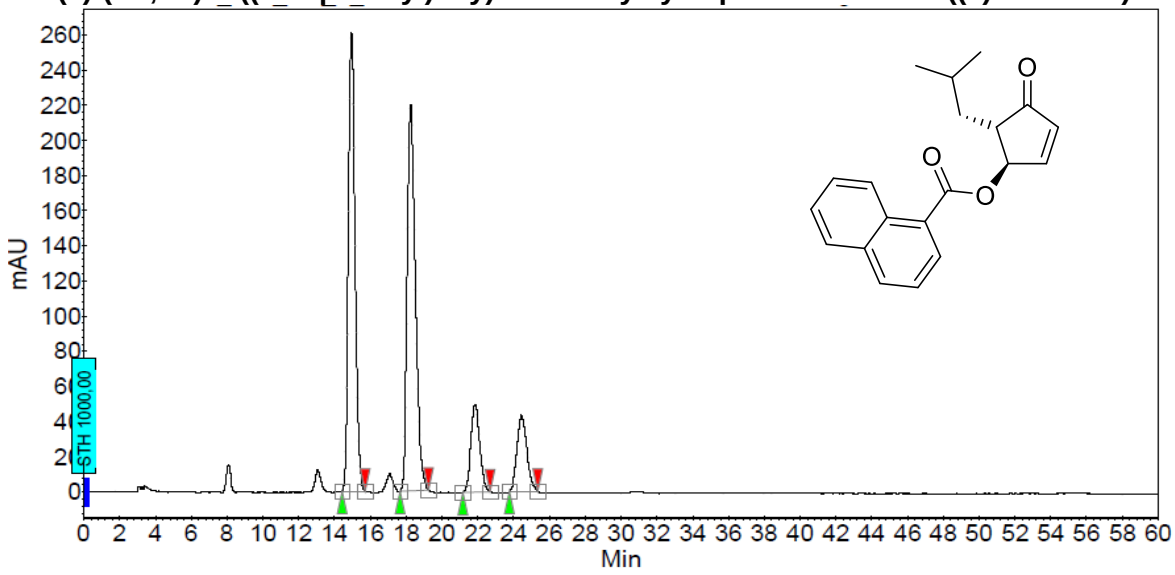
70% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16,66	15,06	97,0	38,3	15,063
2	UNKNOWN	19,68	84,94	397,7	215,9	84,937
Total			100,00	494,8	254,2	100,000

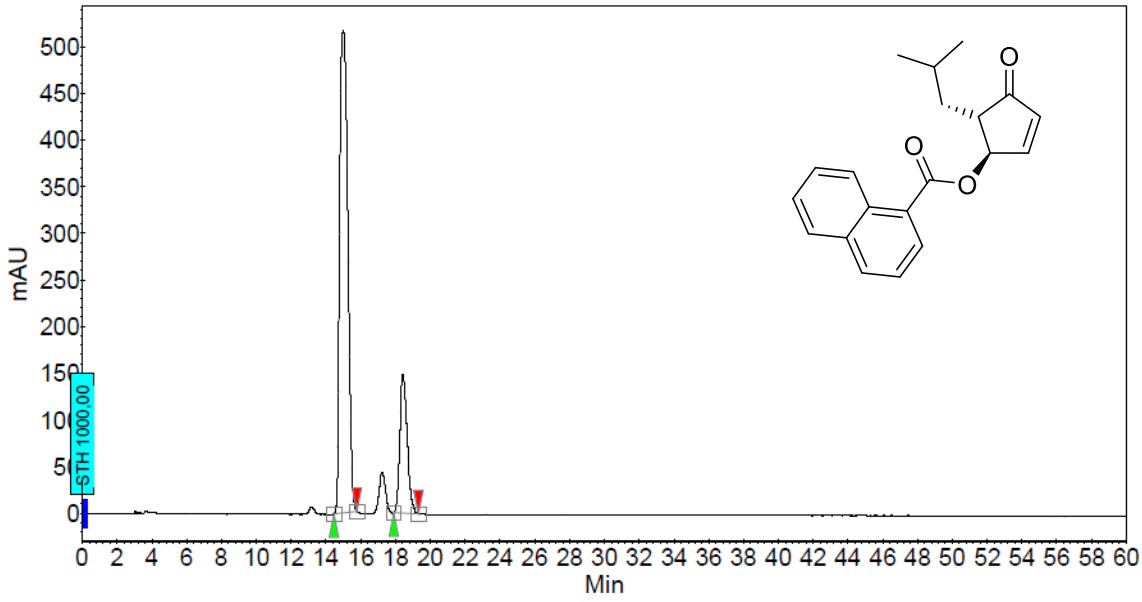
(±)-(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isobutylcyclopent-2-en-1-one ((±)-*anti*-130i)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14,94	39,51	261,0	113,8	39,511
2	UNKNOWN	18,25	40,82	219,9	117,5	40,825
3	UNKNOWN	21,85	10,03	50,0	28,9	10,033
4	UNKNOWN	24,44	9,63	43,4	27,7	9,630
Total			100,00	574,2	287,9	100,000

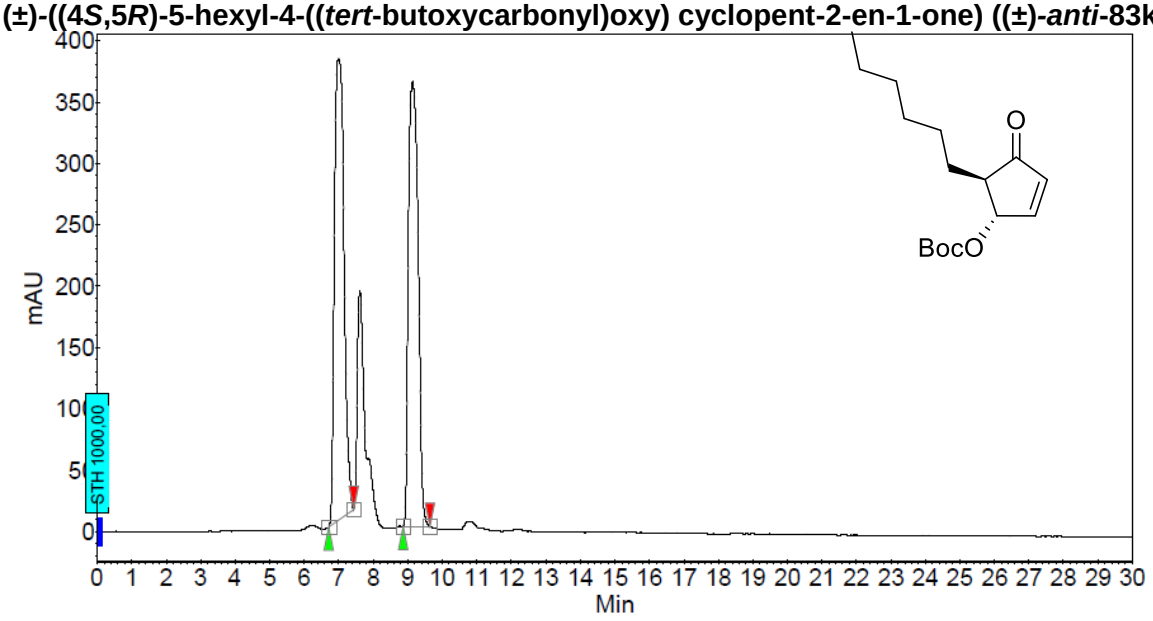
(4*R*,5*S*)-4-((1-naphthoyl)oxy)-5-isobutylcyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-130i) 59% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14,98	79,35	516,8	280,0	79,351
2	UNKNOWN	18,43	20,65	147,9	72,9	20,649
Total			100,00	664,7	352,9	100,000

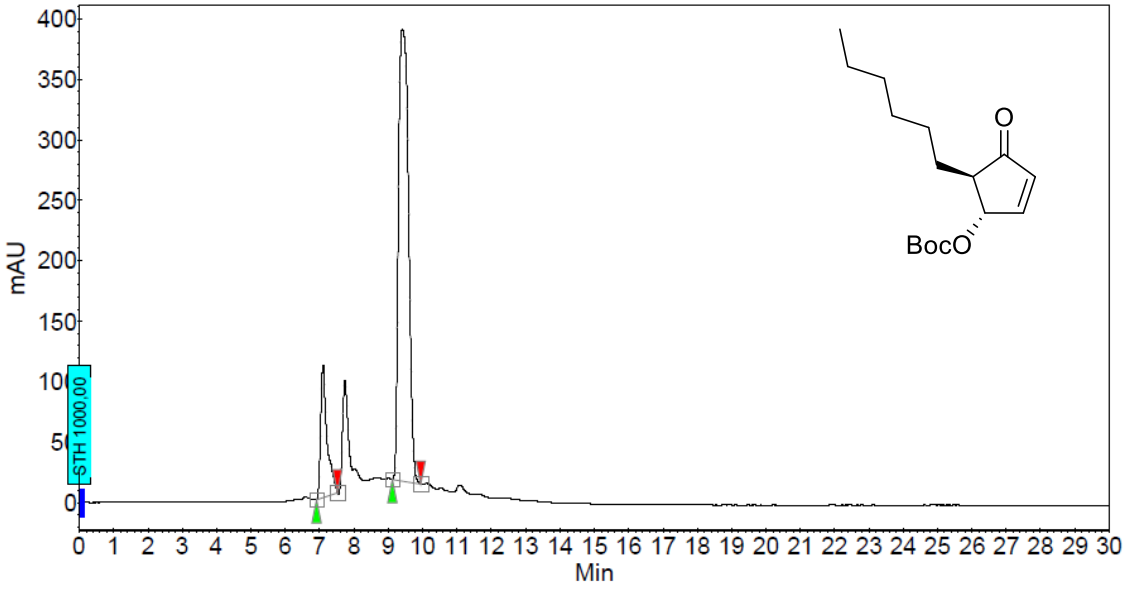
(±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((±)-*anti*-83k)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,99	50,83	376,3	122,1	50,835
2	UNKNOWN	9,13	49,17	362,8	118,1	49,165
Total			100,00	739,1	240,2	100,000

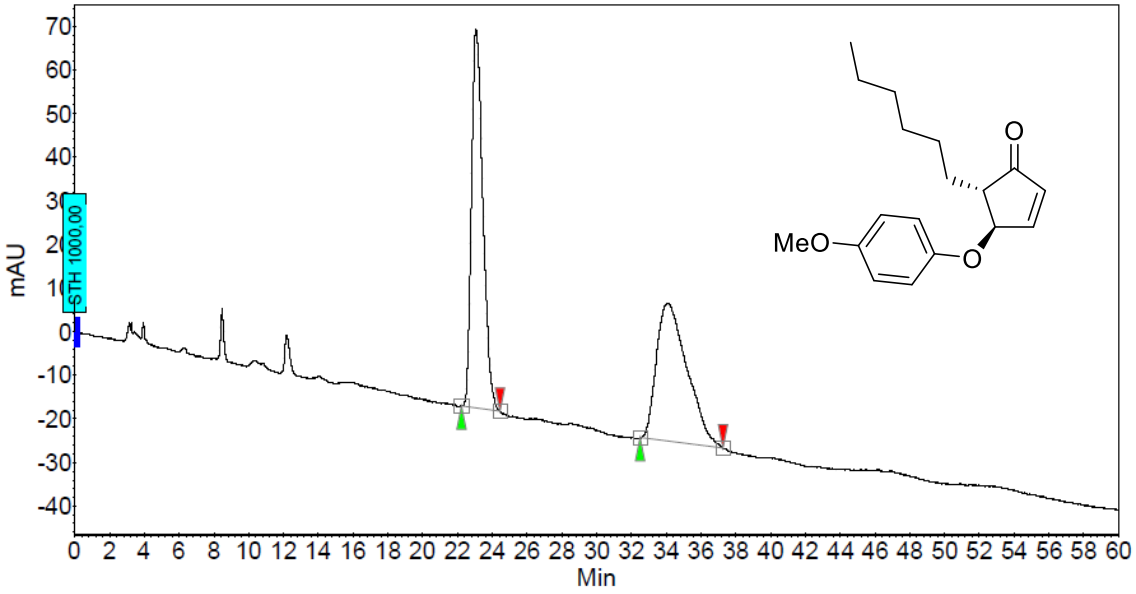
(±)-((4*S*,5*R*)-5-hexyl-4-((*tert*-butoxycarbonyl)oxy) cyclopent-2-en-1-one) ((4*S*,5*R*)-*anti*-83k) 69% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	7,09	15,77	110,0	23,8	15,766
2	UNKNOWN	9,42	84,23	373,7	127,2	84,234
Total			100,00	483,7	151,0	100,000

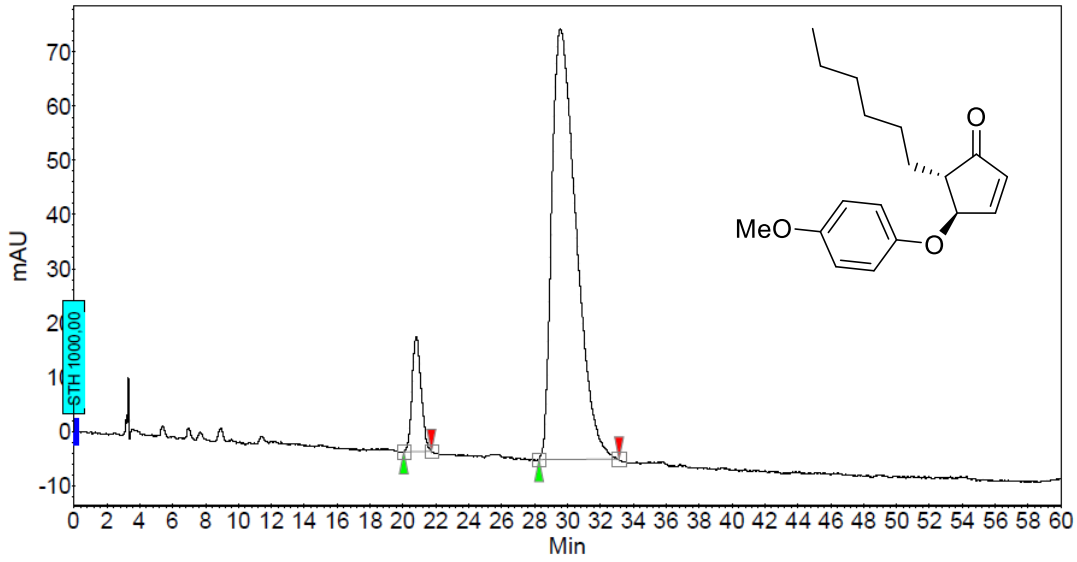
(±)-(4*R*,5*S*)-5-hexyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((±)-*anti*-128k)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,08	50,64	86,7	66,2	50,636
2	UNKNOWN	34,12	49,36	31,6	64,6	49,364
Total			100,00	118,4	130,8	100,000

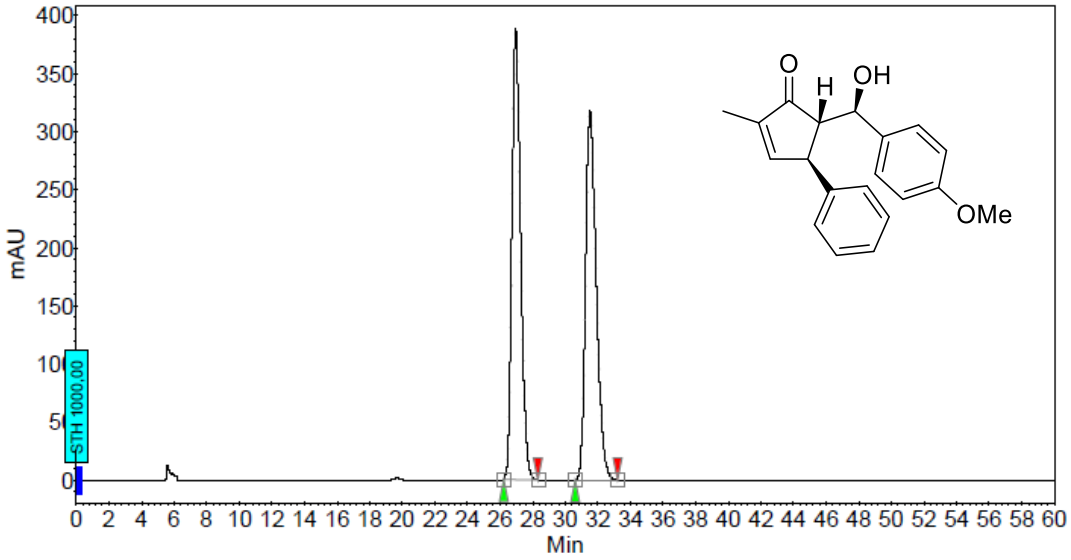
(4*R*,5*S*)-5-hexyl-4-(4-methoxyphenoxy)cyclopent-2-en-1-one ((4*R*,5*S*)-*anti*-128k) 82% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20,82	9,10	21,3	13,6	9,103
2	UNKNOWN	29,57	90,90	79,4	136,1	90,897
Total			100,00	100,7	149,8	100,000

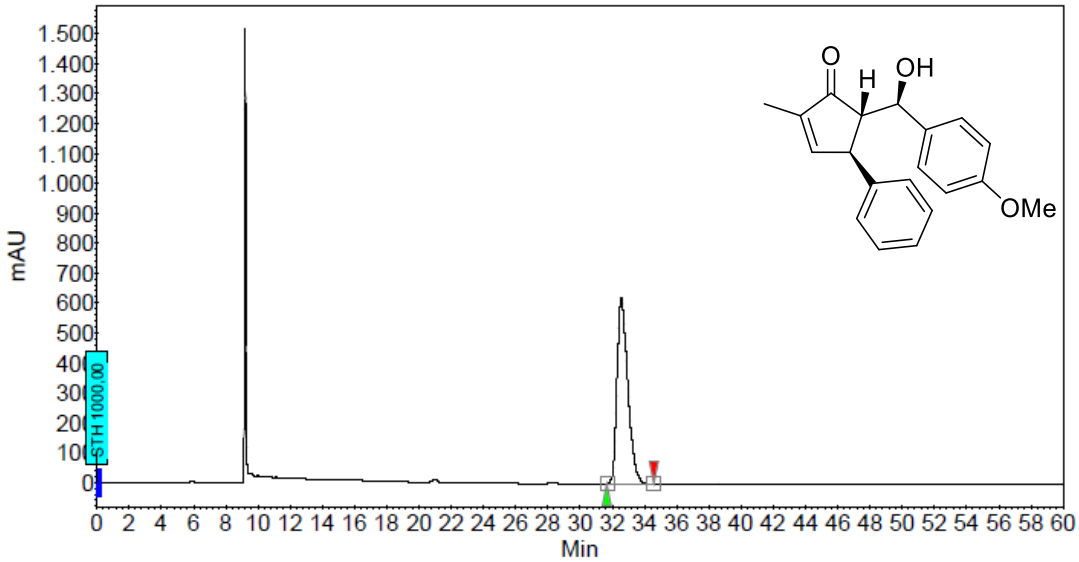
(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fa)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	26,95	49,97	388,3	240,6	49,973
2	UNKNOWN	31,52	50,03	317,3	240,9	50,027
Total			100,00	705,6	481,5	100,000

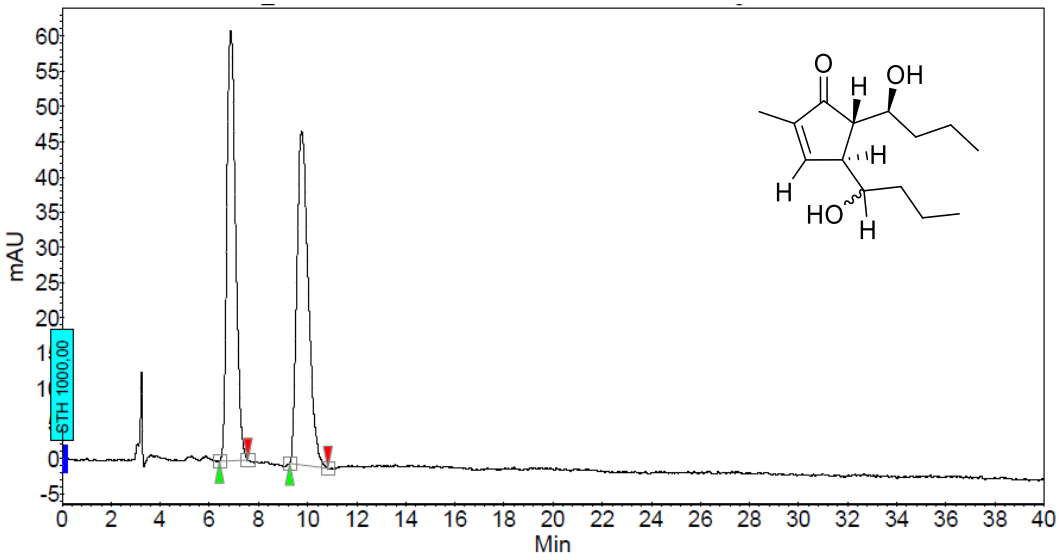
(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((+)-84fa) >99% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	32,57	100,00	622,4	485,9	100,000
Total			100,00	622,4	485,9	100,000

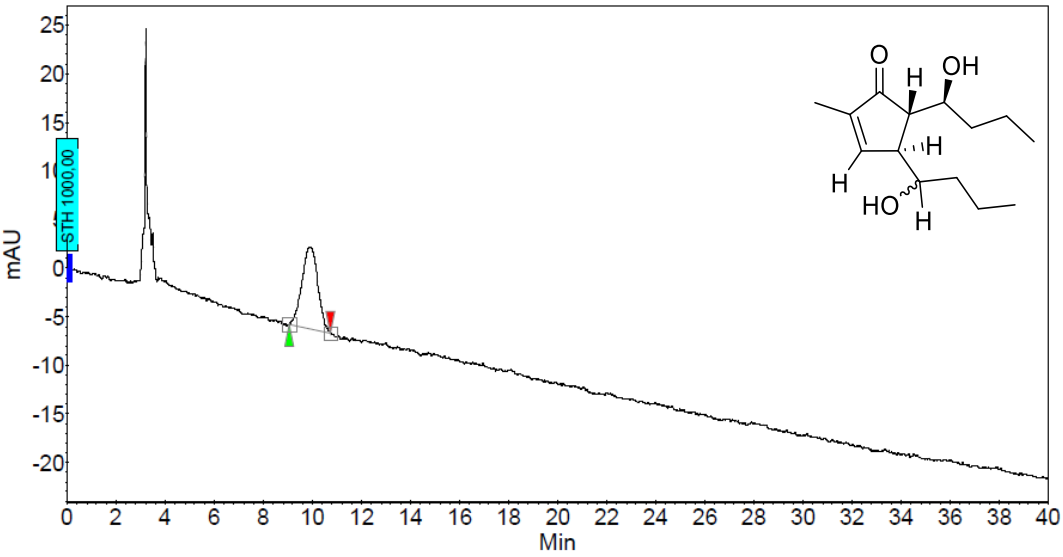
(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-197)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,87	49,64	61,0	25,2	49,642
2	UNKNOWN	9,76	50,36	47,4	25,6	50,358
Total			100,00	108,4	50,8	100,000

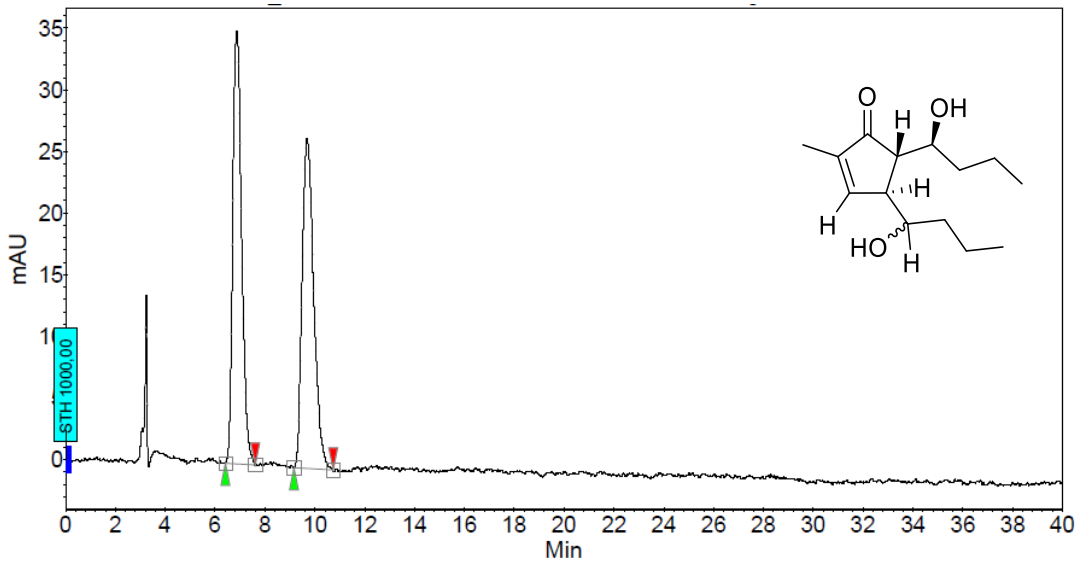
(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (197) >99% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	9,96	100,00	8,5	6,3	100,000
Total			100,00	8,5	6,3	100,000

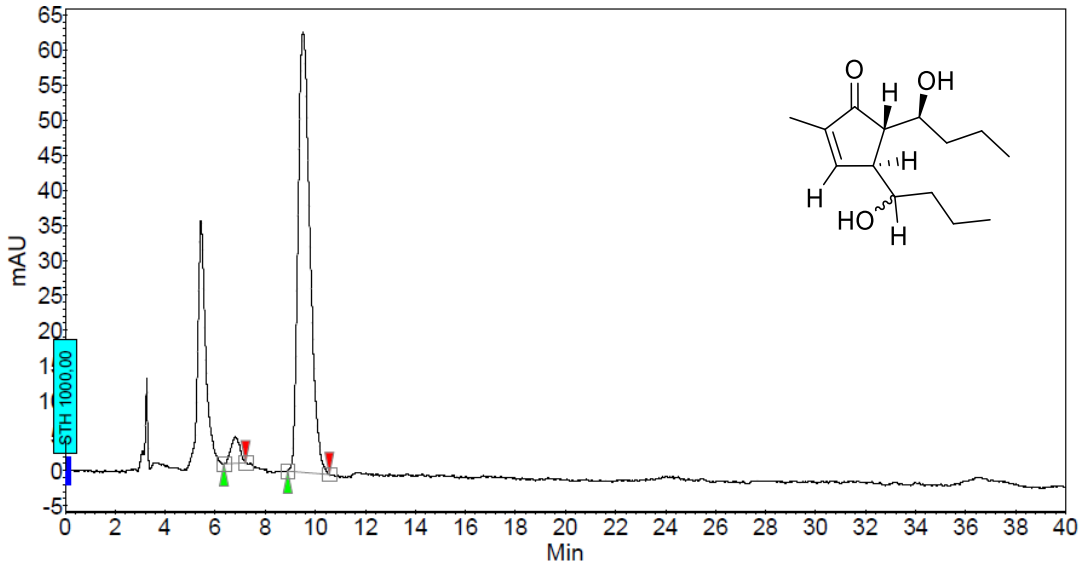
(±)-(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one ((±)-199)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6,86	50,08	35,1	14,5	50,085
2	UNKNOWN	9,69	49,92	26,8	14,5	49,915
Total			100,00	61,9	29,0	100,000

(4*S*,5*S*)-4-(1-hydroxybutyl)-5-((*S*)-1-hydroxybutyl)-2-methylcyclopent-2-en-1-one (199) 92% ee

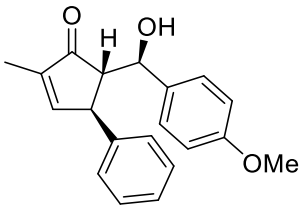


Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	6,79	4,33	3,8	1,6	4,328
1	UNKNOWN	9,51	95,67	62,7	34,6	95,672
Total			100,00	66,6	36,2	100,000

5.13 X-Ray Data

(±)-(4*S*,5*S*)-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-4-phenylcyclopent-2-en-1-one ((±)-84fa)



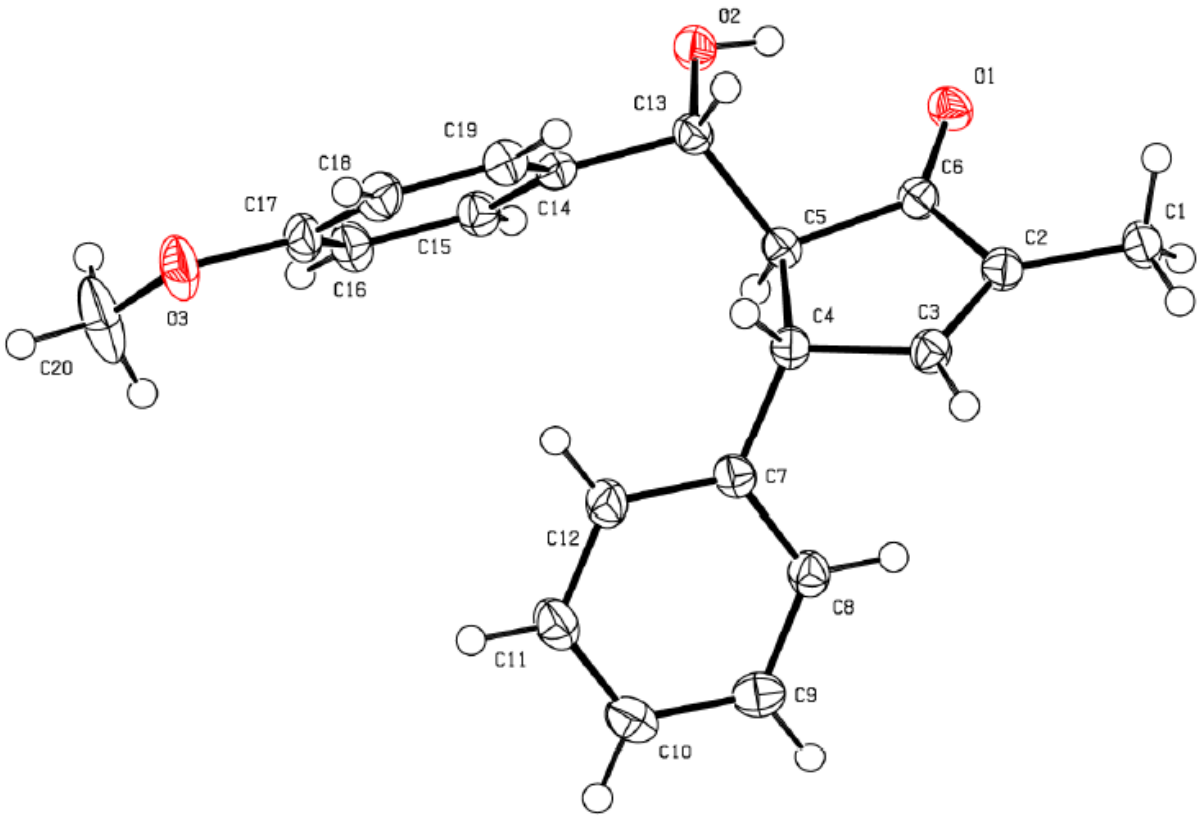


Table 1 Crystal data and structure refinement for cyclopentenone ((±)-84fa).

Empirical formula	$C_{20}H_{20}O_3$
Formula weight	308.36
Temperature/K	123.01(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.95317(9)
b/Å	7.88446(13)
c/Å	34.4065(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1614.96(4)
Z	4
ρ_{calc}g/cm^3	1.268
μ/mm^{-1}	0.674
F(000)	656.0
Crystal size/mm^3	0.159 × 0.099 × 0.074
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.284 to 147.164
Index ranges	-7 ≤ h ≤ 7, -9 ≤ k ≤ 8, -42 ≤ l ≤ 42
Reflections collected	20225
Independent reflections	3239 [R_{int} = 0.0534, R_{sigma} = 0.0251]
Data/restraints/parameters	3239/0/211
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0386, wR_2 = 0.1059
Final R indexes [all data]	R_1 = 0.0406, wR_2 = 0.1079
Largest diff. peak/hole / e Å^{-3}	0.32/-0.23
Flack parameter	-0.19(10)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for cyclopentenone ((±)-84fa). U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	4606(2)	7346.7(19)	4933.8(4)	22.7(3)
O2	5370(3)	9887.1(18)	5464.0(4)	24.3(3)
O3	6022(3)	10896(2)	7270.5(4)	35.6(4)
C6	4556(3)	6422(3)	5219.9(5)	19.3(4)
C12	2897(4)	5682(3)	6559.9(6)	24.2(4)
C15	4090(4)	10095(3)	6267.3(5)	22.0(4)
C17	5870(4)	10349(3)	6891.2(5)	25.1(4)
C16	4068(4)	10713(3)	6647.0(6)	25.2(4)
C19	7675(4)	8799(3)	6377.8(6)	22.8(4)
C3	4960(3)	4048(3)	5591.9(5)	21.0(4)
C13	5909(3)	8497(2)	5715.7(5)	19.3(4)
C9	-690(4)	3605(3)	6357.2(6)	26.1(4)
C7	2769(3)	5043(2)	6180.0(5)	20.2(4)
C2	4928(3)	4581(3)	5221.5(5)	21.0(4)
C10	-536(4)	4249(3)	6732.6(6)	28.6(5)
C14	5884(3)	9144(2)	6128.4(5)	19.8(4)
C18	7655(4)	9390(3)	6757.7(6)	25.9(5)
C8	952(4)	4020(3)	6082.6(5)	22.3(4)
C4	4612(3)	5435(2)	5888.6(5)	19.3(4)
C11	1246(4)	5291(3)	6831.0(6)	28.7(5)
C1	5261(4)	3588(3)	4855.8(5)	23.3(4)
C5	4234(3)	7046(2)	5637.8(5)	18.4(4)
C20	4140(6)	11765(4)	7424.9(7)	52.3(8)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for cyclopentenone ((±)-84fa). The Anisotropic displacement factor exponent takes the form: $-2π^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+…]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	24.2(7)	27.8(7)	16.2(6)	2.5(5)	-2.1(5)	-1.9(6)
O2	35.9(8)	19.2(7)	17.8(6)	2.0(5)	0.4(6)	-0.7(6)
O3	56.7(11)	34.4(9)	15.8(7)	-5.4(6)	-3.8(7)	6.5(8)
C6	16.3(9)	24.2(10)	17.5(8)	-1.2(7)	-1.9(7)	-1.7(8)
C12	31.3(11)	23.1(10)	18.1(9)	0.3(8)	-2.3(8)	-1.1(9)
C15	25.3(9)	21.2(10)	19.6(8)	1.3(7)	-0.1(7)	1.6(9)
C17	39.4(11)	21(1)	15.0(8)	-0.7(7)	-1.5(8)	-1.1(9)
C16	32.9(11)	22.5(10)	20.2(9)	-0.7(7)	2.2(8)	4.9(9)
C19	22(1)	23(1)	23.6(9)	0.1(8)	-0.2(8)	1.3(8)
C3	22.4(9)	18.4(9)	22.2(9)	-1.2(7)	0.6(7)	1.7(8)
C13	22.7(9)	18.3(9)	17.0(8)	0.8(7)	1.8(7)	1.1(8)
C9	24.6(10)	25.3(10)	28.4(10)	5.5(8)	-1.3(8)	-0.5(9)
C7	25.7(9)	17.7(9)	17.2(8)	3.2(7)	-0.5(7)	3.1(8)
C2	18.3(9)	23.4(10)	21.2(9)	-2.8(7)	0.8(7)	-0.7(8)
C10	30.6(11)	30.1(11)	25.2(9)	5.2(8)	6.4(8)	2.4(9)
C14	23.9(9)	16.5(9)	19.1(8)	0.5(7)	0.8(7)	-3.2(8)
C18	29.5(11)	26.5(11)	21.8(9)	1.2(8)	-5.6(8)	-2.4(9)
C8	27.3(10)	21.4(9)	18.4(8)	0.6(7)	-1.8(8)	1.1(8)
C4	23.8(9)	16.9(9)	17.2(8)	0.2(7)	-1.3(7)	1.1(7)
C11	36.3(11)	30.6(11)	19.3(8)	0.2(8)	2.2(8)	2.6(10)
C1	25.7(10)	25.5(10)	18.7(8)	-3.2(7)	1.4(7)	0.4(9)
C5	19.7(8)	19.5(9)	16.0(8)	0.5(7)	0.8(7)	1.2(7)
C20	82(2)	56.4(18)	18.3(9)	-9(1)	-2.2(12)	29.9(17)

Table 4 Bond Lengths for cyclopentenone ((±)-84fa).

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C6	1.225(2)	C19	C18	1.388(3)
O2	C13	1.433(2)	C3	C2	1.342(3)
O3	C17	1.378(2)	C3	C4	1.511(3)
O3	C20	1.416(3)	C13	C14	1.509(2)
C6	C2	1.468(3)	C13	C5	1.541(3)
C6	C5	1.532(2)	C9	C10	1.391(3)
C12	C7	1.403(2)	C9	C8	1.399(3)
C12	C11	1.390(3)	C7	C8	1.390(3)
C15	C16	1.395(3)	C7	C4	1.518(3)
C15	C14	1.390(3)	C2	C1	1.495(2)
C17	C16	1.392(3)	C10	C11	1.384(3)
C17	C18	1.383(3)	C4	C5	1.552(3)
C19	C14	1.396(3)			

Table 5 Bond Angles for cyclopentenone ((±)-84fa).

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C17	O3	C20	117.05(19)	C8	C7	C4	121.42(17)
O1	C6	C2	125.99(18)	C6	C2	C1	122.32(17)
O1	C6	C5	124.46(18)	C3	C2	C6	108.39(17)
C2	C6	C5	109.44(16)	C3	C2	C1	129.27(19)
C11	C12	C7	120.5(2)	C11	C10	C9	119.63(19)
C14	C15	C16	121.20(19)	C15	C14	C19	118.75(18)
O3	C17	C16	123.9(2)	C15	C14	C13	120.92(17)
O3	C17	C18	115.82(19)	C19	C14	C13	120.34(18)
C18	C17	C16	120.30(18)	C17	C18	C19	120.22(19)
C17	C16	C15	119.06(19)	C7	C8	C9	121.12(18)
C18	C19	C14	120.46(19)	C3	C4	C7	113.45(16)
C2	C3	C4	114.37(18)	C3	C4	C5	103.70(14)
O2	C13	C14	107.92(15)	C7	C4	C5	115.41(16)
O2	C13	C5	108.51(15)	C10	C11	C12	120.64(19)
C14	C13	C5	114.08(15)	C6	C5	C13	108.71(15)
C10	C9	C8	119.7(2)	C6	C5	C4	103.95(15)
C12	C7	C4	120.17(18)	C13	C5	C4	114.63(15)
C8	C7	C12	118.39(18)				

Table 6 Torsion Angles for cyclopentenone ((±)-84fa).

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O1	C6	C2	C3	173.88(19)	C2	C3	C4	C7	128.14(18)
O1	C6	C2	C1	-4.6(3)	C2	C3	C4	C5	2.2(2)
O1	C6	C5	C13	-50.2(2)	C10	C9	C8	C7	1.3(3)
O1	C6	C5	C4	-172.75(18)	C14	C15	C16	C17	-0.8(3)
O2	C13	C14	C15	49.0(2)	C14	C19	C18	C17	-0.9(3)
O2	C13	C14	C19	-130.78(19)	C14	C13	C5	C6	-175.77(16)
O2	C13	C5	C6	63.90(19)	C14	C13	C5	C4	-60.0(2)
O2	C13	C5	C4	179.69(15)	C18	C17	C16	C15	0.2(3)
O3	C17	C16	C15	179.9(2)	C18	C19	C14	C15	0.3(3)
O3	C17	C18	C19	-179.10(19)	C18	C19	C14	C13	-179.92(19)
C12	C7	C8	C9	-1.3(3)	C8	C9	C10	C11	-0.2(3)
C12	C7	C4	C3	149.32(18)	C8	C7	C4	C3	-29.1(3)
C12	C7	C4	C5	-91.2(2)	C8	C7	C4	C5	90.3(2)
C16	C15	C14	C19	0.6(3)	C4	C3	C2	C6	0.2(2)
C16	C15	C14	C13	-179.24(18)	C4	C3	C2	C1	178.48(19)
C16	C17	C18	C19	0.7(3)	C4	C7	C8	C9	177.23(18)
C3	C4	C5	C6	-3.45(19)	C11	C12	C7	C8	0.2(3)
C3	C4	C5	C13	-121.97(17)	C11	C12	C7	C4	-178.3(2)
C9	C10	C11	C12	-0.8(3)	C5	C6	C2	C3	-2.6(2)
C7	C12	C11	C10	0.8(3)	C5	C6	C2	C1	178.97(17)
C7	C4	C5	C6	-128.14(16)	C5	C13	C14	C15	-71.6(2)
C7	C4	C5	C13	113.34(18)	C5	C13	C14	C19	108.6(2)
C2	C6	C5	C13	126.30(17)	C20	O3	C17	C16	5.2(3)
C2	C6	C5	C4	3.8(2)	C20	O3	C17	C18	-175.1(2)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for cyclopentenone ((±)-84fa).

Atom	*x*	*y*	*z*	U(eq)
H2	5066	9525	5247	36
H12	4097	6372	6631	29
H15	2882	10323	6104	26
H16	2867	11360	6736	30
H19	8891	8168	6289	27
H3	5179	2918	5660	25
H13	7428	8098	5654	23
H9	-1879	2900	6289	31
H10	-1625	3982	6916	34
H18	8846	9141	6923	31
H8	827	3605	5831	27
H4	6020	5581	6032	23
H11	1340	5734	7081	34
H1A	3969	3718	4691	35
H1B	5458	2411	4919	35
H1C	6570	3997	4723	35
H5	2694	7457	5673	22
H20A	4383	11986	7696	78
H20B	2820	11078	7394	78
H20C	3942	12818	7289	78

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7 Appendix

7.1 Curriculum Vitae

Personal Data

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Education

10/2015 – 09/2019	PhD (Dr. rer. nat.), Organic Chemistry University of Regensburg Dissertation: Synthesis of Gambanol, Phomapentenone A and Substituted Cyclopentenones
10/2013 – 09/2015	Master of Science (M. Sc.), Chemistry University of Regensburg Master thesis: Enantiopure Synthesis of 2,4,5-Trisubstituted Cyclopent-2-en-1-ones
10/2010 – 07/2013	Bachelor of Science (B. Sc.), Chemistry University of Regensburg Bachelor thesis: Magnetische Nanopartikel als wiederverwendbare Trägermaterialien für Katalysatoren
09/2001 – 06/2010	General Qualification for the University Entrance Ludwigsgymnasium Straubing Degree: Allgemeine Hochschulreife

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7.2 Congresses and Scientific Meetings

International

Research Stay Abroad

- Autonomous University of Barcelona (UAB), Spain (11/2015 – 12/2015)

Conferences

- 7. EuCheMS Chemistry Congress in Liverpool, Great Britain (Poster, 09/2018)
- GDCh-Scientific Forum Chemistry in Berlin, Germany (Poster, 09/2017)
- 26. ISHC Congress in Regensburg, Germany (Poster, 09/2017)
- 6. EuCheMS Chemistry Congress in Sevilla, Spain (Poster, 09/2016)

7.3 List of Publications

[1] Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O., "*The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes." ACS Catal.* **2018**, *8*(5), 3950-3956. Impact Factor (2018): 12.221.

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9 Declaration

Herewith I declare that this present PhD thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked clearly, with reference to the literature, license and acknowledgement of collaborative research.

Regensburg, 24.09.2019

Christian Kaiser