The Conversion of Furan Derivatives from Renewable Resources into valuable Building Blocks and their Application in Synthetic Chemistry

Dissertation

Zur Erlangung des Doktorgrades

Dr. rer. nat.

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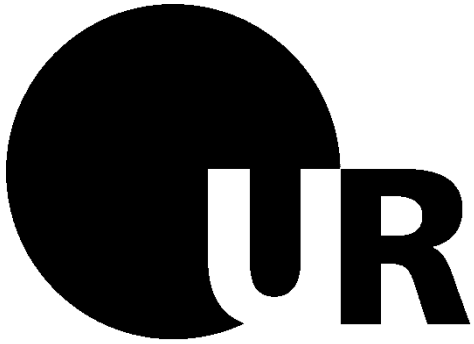

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Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

Meiner Familie

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Abbreviations:

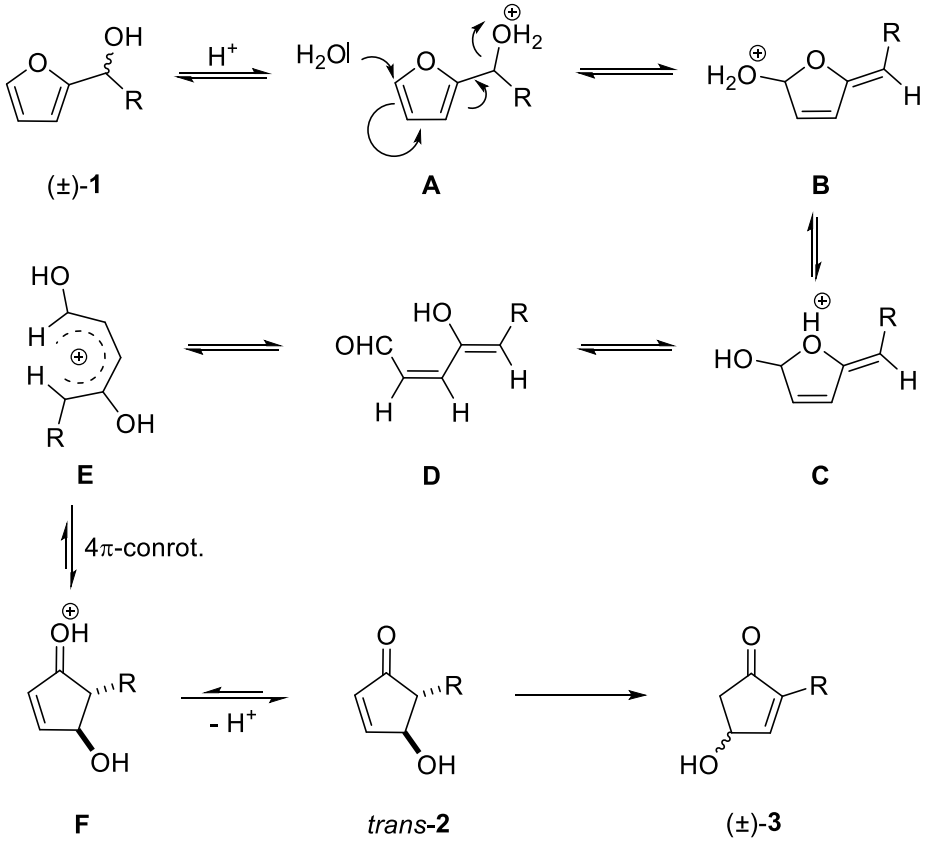
AAA	asymmetric allylic alkylation	Et	ethyl
Ar	aryl	EtOH	ethanol
atm.	atmosphere	g	gram
BHMF	bis(hydroxymethyl)furan	H	hour/hours
Bn	benzyl	HMF	hydroxymethylfurfural
Boc	*tert*-butyloxycarbonyl	HPLC	high performance liquid chromatography
c	concentration	HRMS	high resolution mass spectrometry
calcd	calculated	Hz	Hertz
CI	chemical ionization (MS)	^{i}Pr	*iso*-propyl
d	days	^{i}PrOH	*iso*-propanol
dba	dibenzylideneacetone	IR	infrared spectroscopy
DCC	*N,N'*-dicyclohexylcarbodiimide	L	liter
DCM	dichloromethane	GC	gas chromatography
DEPT	distortionless enhancement polarization transfer	LiHMDS	lithium bis(trimethylsilyl)amide
DFT	density functional theory	ln	logarithmus naturalis
DIAD	diisopropylazodicarboxylate	Me	methyl
DIPEA	N,N-diisopropylethyldiamine	MeCN	acetonitrile
DMAP	dimethylaminopyridin	MeOH	methanol
DMF	dimethylformamide	mg	milligram
DMSO	dimethylsulfoxide	min	minute
DYKAT	dynamic kinetic asymmetric resolution	mmol	millimol
EA	ethyl acetate	mL	milliliter
ee	enantiomeric excess	m.p.	melting point
EI	electron impact	MS	mass spectrometry, molsieve
ent	enantiomer	MW	microwave
eq.	equation	^{n}Bu	*n*-butyl
equiv	equivalent	nd	not determined
ESI	electrospray ionization (MS)	NMM	*N*-methylmorpholine

NMR	nuclear magnetic resonance
Nu	nucleophile
^{n}Pr	*n*-propyl
P	power
PDA	photo diode array
PE	hexanes
Ph	phenyl
ppm	parts per million
psi	pound-force per square inch
PTSA	*para*-toluenesulfonic acid
quant.	quantitative
Q-Tof	quadrupole time-of-flight spectrometer
R	arbitrary rest
rt	room temperature
rac	racemic
O-Ac	acetate
O-Boc	*tert*-butylcarbonate
p	pressure
s	selectivity factor
t	time
T	temperature
TBAF	tetra-*N*-butylammoniumfluoride
TBDMS	*tert*-butyldimethyl silyl
THF	tetrahydrofuran
t_R	retention time
V	volume
W	Watt

A. Introduction

1. The Piancatelli Rearrangement: New Developments and Applications

Since its discovery in 1976[1] the Piancatelli rearrangement has been widely employed in the synthesis of 4-hydroxy-2-cyclopentenones from α-furylcarbinols, and particularly in the last decade several interesting novel developments in this field emerged. This acid catalyzed rearrangement is typically observed in a water containing environment with furfuryl alcohol and derivatives thereof, whereas various substituents can be situated at different positions on the furan ring or at the hydroxymethyl-functionality.[2] The reaction is completely atom economic, as the number of atoms in the molecule involved is being preserved. The products of this type of chemical transformation are substituted 4-hydroxy-2-cyclopentenones, which are highly valuable intermediates in the synthesis of natural products.[3,4] The mechanism proposed by Piancatelli (Scheme 1)[1] commences with the protonation of the α-hydroxymethyl-moiety in (±)**-1**, which leads to the expulsion of water as leaving group. A subsequent nucleophilic attack of another water molecule on the opposite α-position of the furan ring leads to the formation of intermediate **B**.



Scheme 1: Mechanism proposed by Piancatelli *et al.*[1,5]

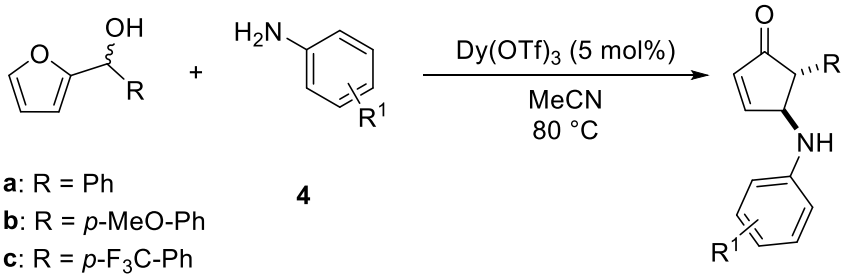
Ring opening and a prototropic shift furnishes the pentadienyl cation **E**, which is believed to undergo a 4-π conrotatory electrocyclic ring-closure similar to a Nazarov-cyclisation.[6] The deprotonation of **F** gives product *trans*-**2** with the substituents showing in most cases a *trans*-configuration on the newly formed carbocyclic scaffold. The mechanism, particularly the ring-closing step, is still under ongoing debate. Mostly an electrocyclic process is favored because of the high diastereoselectivity of the reaction, but also an aldol-type mechanism is proposed. DFT calculations corroborate the electrocyclic nature of ring-closure.[7] Compound *trans*-**2** can be subject of a further isomerization to cyclopentenone (±)-**3**.[5]

The synthesis of 4-hydroxy-2-cyclopentenone derivatives via Piancatelli rearrangement has been reviewed by D'Onofrio in 1994,[2] and since then many publications of diverse developments concerning this reaction and various applications have appeared. This chapter will give an overview about the progress in this field from 1994 up to 2013, which will include new types of the Piancatelli rearrangement like the aza-variant and intramolecular versions. Novel processes to increase the efficiency of the reaction will be elucidated, such as the use of continuous flow systems. Furthermore, new insights about the mechanism and kinetics of the reaction will be explained, and at last also a variety of particular applications will be illustrated.

2. The Aza-Piancatelli Rearrangement

Read de Alaniz *et al.* developed a Lewis acid catalyzed methodology to employ aromatic amines as nucleophiles instead of the conventionally used water (Table 1).[8] This procedure allows the synthesis of exclusively *trans*-substituted 4-amino-5-aryl(alkyl)-2-cyclopentenones **5**. Suitable catalysts for this reaction are Brønsted or Lewis acids, preferably $Dy(OTf)_3$.[9] With furan-2-yl(phenyl)methanol (±)-**1a** as α-furylcarbinol various successful examples are presented by combination with different electron-rich and -deficient aromatic amines as nucleophiles, providing yields between 33–92% (entry 1–11, Table 1). Consistently good results were achieved with diverse substitution patterns on the anilines, including sterically bulky examples bearing 2,4,6-trimethyl substituents (entry 7, Table 1). The only exception made the reaction with 2,6-dimethylanilin, in which the product was obtained in 33% yield because of a competing side-reaction, in which 2,6-dimethylaniline participated in a Friedel-Crafts alkylation with the carbocation formed from starting material (±)-**1a** by loss of water (entry 11, Table 1).

Table 1: $Dy(OTf)_3$ catalyzed aza-Piancatelli rearrangement.[a,8]



(±)-**1a**: R = Ph
(±)-**1b**: R = *p*-MeO-Ph
(±)-**1c**: R = *p*-F_3C-Ph
(±)-**1d**: R = Me
(±)-**1e**: R = ^{i}Pr

4

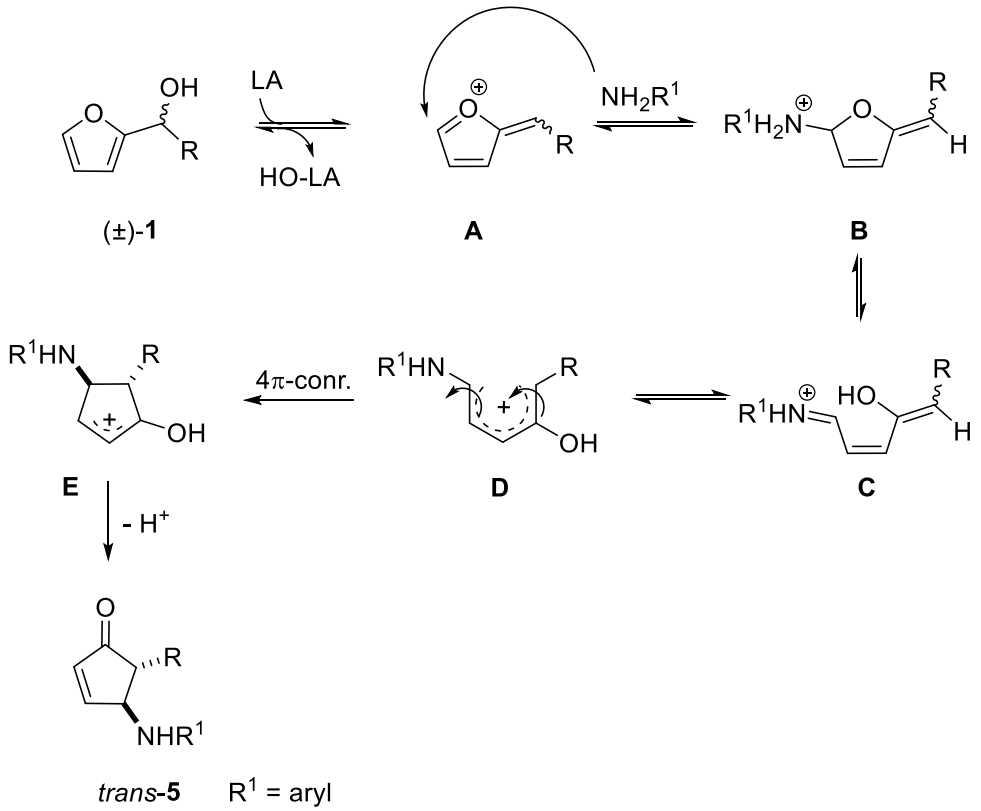
trans-**5**

Entry	1	R^1	t [h]	Yield [%][b]	Entry	1	R^1	t [h]	Yield [%][b]
1	**1a**	*p*-I	0.5	92	12[e]	**1b**	*p*-I	1.5	68
2	**1a**	*p*-MeO_2C	1	86	13[e]	**1b**	*m*-Cl	6.5	82
3[c]	**1a**	*p*-MeO	18	62	14[e]	**1b**	2,4,6-tri-Me	5	89
4	**1a**	3,5-di-Me	3	81	15	**1c**	*p*-I	4.5	83
5[d]	**1a**	3,5-di-F_3C	24	75	16	**1c**	*m*-Cl	2	87
6	**1a**	*m*-Cl	0.33	82	17[f]	**1c**	2,4,6-tri-Me	8	78
7	**1a**	2,4,6-tri-Me	4	91	18	**1d**	*p*-I	2.5	68
8[d]	**1a**	2,4,6-tri-F	3	74	19	**1d**	*m*-Cl	3	10
9	**1a**	H	1.5	86	20	**1d**	2,4,6-tri-Me	3.5	74
10	**1a**	*p*-Me(OH)CH	2	88	21	**1e**	*p*-I	5	73
11	**1a**	2,6-di-Me	3	33	22	**1e**	*m*-Cl	6	52

a) (±)-**1:4** 1:1 equiv. b) isolated yield. c) $Dy(OTf)_3$ (20 mol%). d) (±)-**1:4** 1:3 equiv. e) reaction at rt. f) $Dy(OTf)_3$ (10 mol%).

Moreover, in place of the phenyl substituent in α-position on the furylcarbinols, a *p*-methoxyphenyl, *p*-trifluoromethylphenyl, methyl and an isopropyl group could be used with comparably good results (**1b**–**1e**, entry 12–22, Table 1). In case of the alkyl substituted α-furylcarbinols **1d** and **1e** in combination with an *m*-chloro group on the aniline the yield was decreased by a Friedel-Crafts side reaction (entry 19 and 22, Table 1). Generally, no isomerization to cyclopentenones of type **3** (Scheme 1) was observed, as it was also not the case in the following examples of Lewis acid catalyzed aza-Piancatelli rearrangements.

The mechanism proposed (Scheme 2) is similar to the one suggested by Piancatelli, with the key step involving a 4π-electrocyclisation, though instead of water an amine attacks as nucleophile in α-position of the furan ring. Furthermore, evidence of the formation of the stabilized carbocation **A** (Scheme 2) was found, based on the fact that a Friedel-Crafts alkylation product of **A** and the aniline component could be isolated in certain instances as a by-product (entry 11, 19 and 22, Table 1). In another publication, Yadav *et al.* showed that the same type of transformation (Scheme 2) was achievable by the use of phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) in a similar *trans*-selective manner.[10]



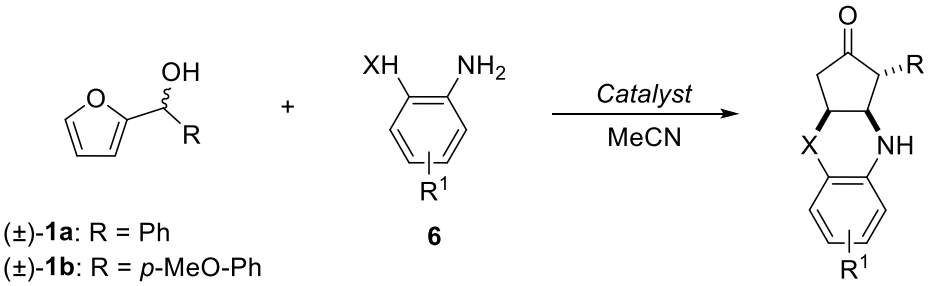
Scheme 2: Aza-Piancatelli mechanism proposed by Read de Alaniz.[13]

A recent publication by Kunwar and co-workers further exploited the idea of an aza-Piancatelli rearrangement by using 2-aminophenols and -thiophenols **6** as nucleophiles, but in their case a subsequent Michael reaction took place to furnish *cis*-fused benzo[1,4]oxazines and -thiazines **7** (Table 2, entry 1–13) with yields of 73–88% as single diastereomers.[11] 10 mol% $In(OTf)_3$ proved to be the most effective catalyst, but also other Lewis acids and even acidic ion exchange resins could be applied. Different aryl-substituted α-furylcarbinols (±)**-1** were employed successfully with various 2-aminophenols or 2-aminothiophenols **6** as the nucleophilic

component. Generally, 2-aminothiophenols gave higher yields in shorter reaction times compared to 2-aminophenols.

At approximately the same time Wang *et al.* published their results of the tandem Piancatelli/Michael reaction, in their case with 5 mol% $La(OTf)_3$ as the preferred catalyst (entry 14–41, Table 2).[12] A comparison of reactions with 2-aminophenol as substrate shows that furan-2-yl(phenyl)methanol (±)-**1a** gave the best results (entry 14, Table 2), whereas substitutions with electron-withdrawing or -donating groups on the phenyl moiety on the α-furylcarbinol decreased the yield significantly (entry 15–17, Table 2). On the contrary, introducing a 3-chloro group on the 2-aminophenol gave favorable results for α-furylcarbinols with a fluoro and trifluoromethyl group on the phenyl substituent (entry 20 and 21, Table 2). Alkyl substituted 2-aminophenols gave generally inferior results (entry 22–29, Table 2), as well as 4-nitro-2-aminophenol which led only to trace amounts of the desired product (entry 30–32, Table 2). A deviation from this trend was observed with the combination of 4-nitro-2-aminophenol and furan-2-yl(4-(trifluoromethyl)phenyl)methanol (±)-**1c** resulting in the exceptionally high yield of 92% (entry 33, Table 2). Furthermore, the applicability of *N*-substituted 1,2-diaminobenzenes as substrates (entry 34–41, Table 2) is presented, though the scope is limited to less electron-deficient aryl substituted α-furylcarbinols (entry 34, 35, 38 and Table 2).

Table 2: Aza-Piancatelli/Michael cascade reaction reported by Kunwar and Wang *et al.*[11,12]



(±)-**1a**: R = Ph
(±)-**1b**: R = *p*-MeO-Ph
(±)-**1c**: R = *p*-F_3C-Ph
(±)-**1f**: R = *p*-F-Ph
(±)-**1g**: R = H
(±)-**1h**: R = Et

6

X = S, O, NR^2

cis,trans-**7**

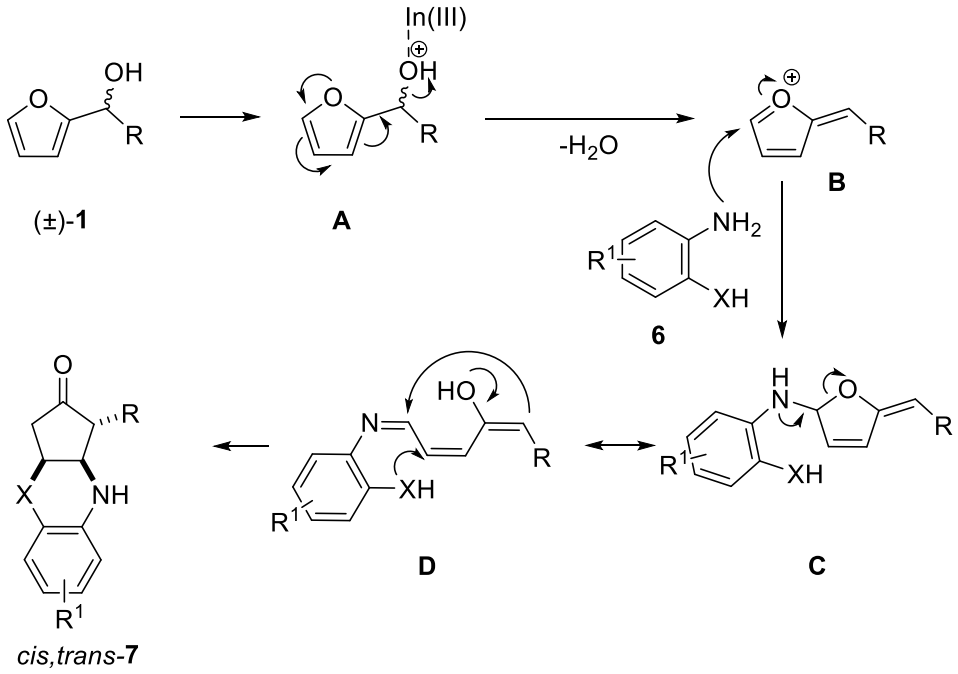
Entry	1	X	R^1	t [h]	Yield [%][a]	Entry	1	X	R^1	t [h]	Yield [%][a]
1[b]	**1a**	S	H	2	86	22[c]	**1a**	O	3-Me	4	48
2[b]	**1a**	O	5-Me	3.5	73	23[c]	**1b**	O	3-Me	4	60

Entry	1	X	R^1	t [h]	Yield [%][a]	Entry	1	X	R^1	t [h]	Yield [%][a]
3[b]	**1a**	O	4-Cl	3.5	78	24[c]	**1f**	O	3-Me	4	48
4[b]	**1a**	S	4-Cl	2.5	85	25[c]	**1c**	O	3-Me	4	trace
5[b]	**1b**	O	H	3	75	26[c]	**1a**	O	3-^{t}Bu	4	53
6[b]	**1b**	S	H	2	87	27[c]	**1b**	O	3-^{t}Bu	4	41
7[b]	**1b**	O	5-Me	2.5	80	28[c]	**1f**	O	3-^{t}Bu	4	74
8[b]	**1b**	O	4-Cl	2.5	82	29[c]	**1c**	O	3-^{t}Bu	4	trace
9[b]	**1b**	S	4-Cl	2.5	88	30[c]	**1a**	O	4-O_2N	4	trace
10[b]	**1f**	O	H	3.5	81	31[c]	**1b**	O	4-O_2N	4	trace
11[b]	**1f**	S	H	2.5	85	32[c]	**1f**	O	4-O_2N	4	trace
12[b]	**1f**	O	3-Me	3.5	78	33[c]	**1c**	O	4-O_2N	4	92
13[b]	**1f**	O	4-Cl	3.5	80	34[c,d]	**1a**	N	H	2	88
14[c]	**1a**	O	H	4	81	35[c,e]	**1a**	N	H	2	83
15[c]	**1b**	O	H	4	46	36[c,f]	**1a**	N	H	2	trace
16[c]	**1f**	O	H	4	46	37[c,d]	**1g**	N	H	2	trace
17[c]	**1c**	O	H	4	10	38[c,d]	**1b**	N	H	2	45
18[c]	**1a**	O	3-Cl	4	66	39[c,d]	**1f**	N	H	2	68
19[c]	**1b**	O	3-Cl	4	51	40[c,d]	**1c**	N	H	2	trace
20[c]	**1f**	O	3-Cl	4	78	41[c,d]	**1h**	N	H	2	trace
21[c]	**1c**	O	3-Cl	4	82						

a) isolated yield. b) ref. 11, $In(OTf)_3$ (10 mol%), reaction at rt, (±)-**1**:**6** 1.2:1 equiv. c) ref. 12, $La(OTf)_3$ (5 mol%), reaction at 80 °C, (±)-**1**:**6** 1.2:1 equiv. d) R^2 = Ts. e) R^2 = Ms. f) R^2 = Ac.

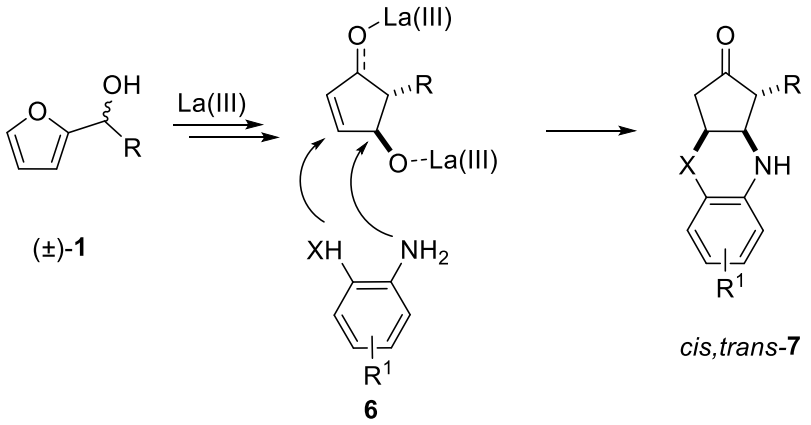
The mechanism Kunwar *et al.* suggest (Scheme 3) starts with the coordination of the Lewis acid to the hydroxy group of the α-furylcarbinol (±)-**1**, which is followed by the formation of the oxocarbenium ion **B**. The amine **6** then attacks at the furan ring in α-position which affords after formation of intermediate **C** the ring-opened species **D**. The ring-closure proceeds through an aldol-type reaction and subsequent 1,4-addition from the other nucleophilic position -XH of

6 to furnish product **7** with a *cis*-fused ring scaffold and the aryl-substituent arranged in a *trans*-position with respect to the heterocycle.



Scheme 3: Mechanism proposed by Kunwar *et al.*[11]

The mechanism proposed by Wang *et al.* (Scheme 4) differs from the one displayed in Scheme 3 by completing first the Piancatelli rearrangement before the nucleophilic amine species **6** does even interact with the α-furylcarbinol. They believe that after the rearrangement a C-N-coupling takes places followed by an intramolecular Michael-addition to give the product *cis,trans*-**7** with the same stereochemical characteristics as described before for the other mechanism (Scheme 3).

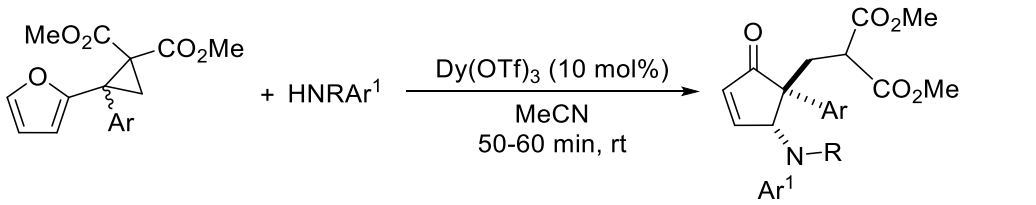


Scheme 4: Mechanism proposed by Wang *et al.*[12]

In 2013 Read de Alaniz *et al.* described an aza-Piancatelli rearrangement initiated by ring opening of donor-acceptor-cyclopropanes (±)-**8** (Table 3).[13] In this type of reaction the Lewis

acid catalyzed opening of the cyclopropyl ring in (±)**-8** leads to the intermediate stabilized cation that undergoes the rearrangement to cyclopentenones **10**. This methodology to synthesize α-quaternary cyclopentenones provides an alternative to the Piancatelli rearrangement of tertiary α-furylcarbinols in which a competitive dehydration pathway decreases the efficiency of the conversion.[14] Among several Lewis acids $Dy(OTf)_3$ was selected to investigate the scope of the reaction, as this catalyst gave superior results with respect to diastereoselectivity and conversion. Various cyclopentenones **10** were obtained with yields ranging from 57–89% and diastereoselectivities from 1:1 to 60:1. Reactions in which the aryl substituent on the cyclopropane was electron-rich (entry 8–10, Table 3) proved to be superior to electron-deficient ones (entry 11-13, Table 3) in terms of diastereoselectivity. Moreover, different primary anilines and also secondary anilines could be employed, showing that electron-withdrawing groups on the aniline had a beneficial effect on the diastereoselectivity (entry 4 and 13, Table 3). In some instances an inverse relationship between selectivity and temperature was observed, i. e. higher reaction temperatures resulted in better selectivities.

Table 3: D-A cyclopropane initiated Piancatelli rearrangement.[13]



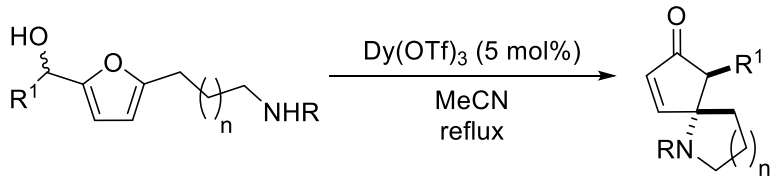
(±)-**8** **9** **10** (major diastereomer)

Entry	Ar	Ar[1]	R	Yield [%][a]	dr[a]	Entry	Ar	Ar[1]	R	Yield [%][a]	dr[a]
1	Ph	*p*-MeO-Ph	H	57	6:1	8	*p*-MeO-Ph	*p*-MeO-Ph	H	87	25:1
2	Ph	Ph	H	89	13:1	9	*p*-MeO-Ph	Ph	H	84	32:1
3	Ph	*p*-Me-Ph	H	80	10:1	10	*p*-MeO-Ph	*p*-F_3C-Ph	H	63	22:1
4	Ph	*p*-F_3C-Ph	H	72	60:1	11	*p*-NC-Ph	*p*-MeO-Ph	H	58	2:1
5	Ph	*p*-I-Ph	H	82	28:1	12	*p*-NC-Ph	Ph	H	76	1:1
6	Ph	*m*-Cl-Ph	H	81	29:1	13	*p*-NC-Ph	*p*-F_3C-Ph	H	65	5:1
7	Ph	Ph	Me	76	57:1						

a) Diastereoselectivity and yield determined by ^{1}H-NMR spectroscopy using dimethyl terephthalate as the internal standard.

An intramolecular modification of the aza-Piancatelli rearrangement has been developed by Read de Alaniz and co-workers.[15] They were able to synthesize azaspirocycles **12** from α-furylcarbinols (±)**-11** that possess an amino group connected by an alkyl chain to the furan ring (Table 4). The proposed mechanism is an intramolecular version of the previously reported one by the same group (Scheme 2) and consistent with the Piancatelli mechanism (Scheme 1). The products **12** were isolated in yields from 37–97% as single diastereomers, in which R^1 and the nitrogen nucleophile are arranged in a *trans*-relation. With substituent R^1 being hydrogen, alkyl or aryl the reaction proceeded smoothly, and moreover different aryl substituents on the amine nucleophile could be employed. The best substitution pattern proved to be an electron-donating group in α-position on the furylcarbinol and an electron-withdrawing group on the nitrogen. This is an observation indicating the electrocyclic nature of the rearrangement, as the related Nazarov reaction also benefits from polarized substrates.[6]

Table 4: Intramolecular aza-Piancatelli rearrangement.[15]



(±)-**11** **12**

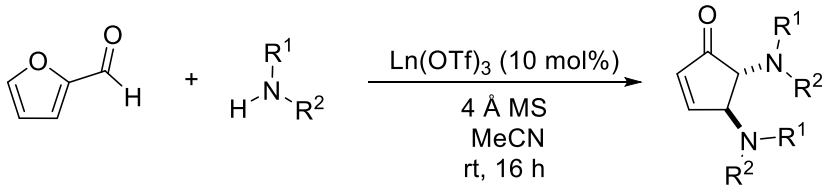
Entry	n	R	R^1	t	Yield [%][a]	Entry	n	R	R^1	t	Yield [%][a]
1	1	Ph	Ph	15 min	96	11	1	Ph	^{n}Bu	15 min	97
2	1	*p*-MeO-Ph	Ph	150 min	74	12	1	*p*-I-Ph	^{n}Bu	15 min	79
3	1	Ph	*p*-O_2N-Ph	5 h	67	13	2	*p*-I-Ph	H	8 h	90
4	1	Ph	*p*-Br-Ph	5 h	84	14	2	Ph	H	48 h	70
5	1	Ph	2,4,6-tri-Me-Ph	2 h	74	15[c]	2	*p*-MeO-Ph	H	72 h	37
6	1	Ph	*p*-MeO-Ph	15 min	81	16	2	*p*-I-Ph	Ph	5 min	69
7	1	Ph	H	15 h	90	17	2	Ph	Ph	1 h	75
8[b]	1	*p*-MeO-Ph	H	48 h	57	18	2	*p*-MeO-Ph	Ph	75 h	74
9	1	Ph	diphenylmethyl	15 h	53	19	2	*p*-I-Ph	^{n}Bu	2 h	65
10	1	Ph	Me	15 min	91	20	2	Ph	^{n}Bu	15 h	54

a) isolated yield. b) $Dy(OTf)_3$ (10 mol%). c) $Dy(OTf)_3$ (20 mol%).

Another variant reported by Batey *et al*. utilizes furfural **13** as starting material instead of α-furylcarbinols. The addition of secondary amines **14** under lanthanide(III) catalysis resulted in

the formation of 4,5-diamino-2-cyclopentenones *trans*-**15** (Table 5).[16] This reaction was first discovered by Lewis and co-workers, but it suffered from low yields and long reaction times, moreover the formation of the thermodynamically stable species similar to (±)-**3** (Scheme 1) posed a serious problem.[17,18] By using Lewis acids as catalysts this could be avoided and the formation of **15** with exclusive *trans*-stereoselectivity was achieved using secondary amines (78–100% yield, entry 1–8, Table 5) and anilines (17–52% yield, entry 10-12, Table 5). Benzylamine was not reactive under the described conditions (entry 9, Table 5).

Table 5: Formation of 4,5-diamino-2-cyclopentenones from furfural.[16]

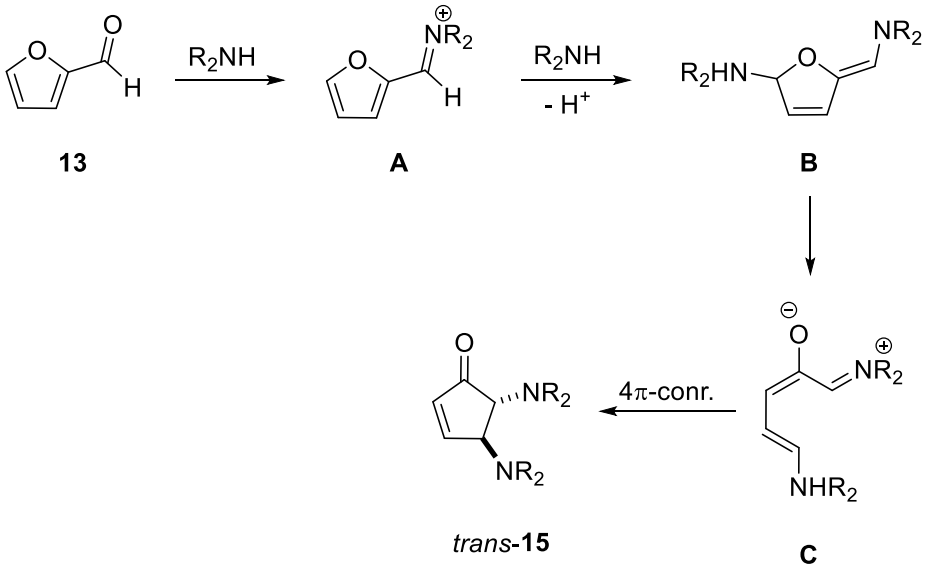


13 **14** *trans*-**15**

Entry	R^1R^2NH	Yield [%][a]	Entry	R^1R^2NH	Yield [%][a]
1	morpholine	quant.	7	1,2,3,4-tetrahydroquinoline	81
2	$(allyl)_2NH$	82	8	indoline	99
3	Bn_2NH	98	9	$BnNH_2$	0
4	(*p*-MeO-Bn)$_2$NH	quant.	10	$PhNH_2$	17
5	1,2,3,4-tetrahydroisoquinoline	92	11	$PhNH_2$	78[b]
6	PhMeNH	78	12	(*o*-MeO-Ph)NH_2	52[b]

a) isolated yields using $Dy(OTf)_3$. b) isolated yields using $Sc(OTf)_3$.

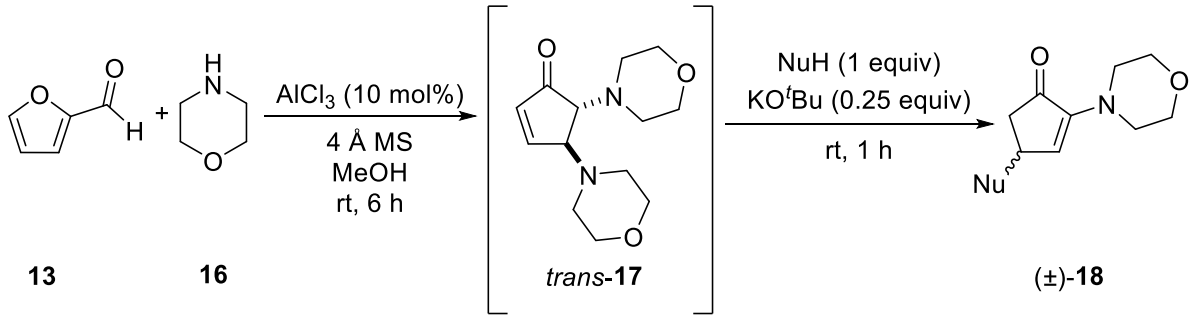
The proposed mechanism (Scheme 5) is similar to the Piancatelli rearrangement with α-furylcarbinols, including the thermal conrotatory 4π-electrocyclisation step and was supported by computational studies (UHF/6-31G**) on the ring closure. The initial condensation of furfural **13** and the amine gives the iminium-ion **A**, on which a second amine molecule as nucleophile can attack at the opposite position of the furan ring. Subsequent ring opening of **B** affords the deprotonated Stenhouse salt **C**, which is then capable of the electrocyclic ring closure providing 4,5-diamino-2-cyclopentenones *trans*-**15**. This strategy was used in a following publication to synthesize the marine sponge pyrrole-2-aminoimidazole alkaloid (±)-agelastatin A.[19]



Scheme 5: Proposed mechanism by Batey and co-workers.[16]

Caddick and co-workers developed this approach further by adding a nucleophile under basic conditions after the formation of the diaminocyclopentenone *trans*-**17** (Table 6).[20] This resulted in a Michael-addition of the nucleophile to *trans*-**17** and ensuing elimination of morpholine **16** gave product (±)-**18**, a process similar to the formation of (±)-**3** from *trans*-**2** (Scheme 1). As nucleophiles NaOMe (entry 1, Table 6), propylamine (entry 15, Table 6), lithium di-*n*-butylcuprate (entry 16, Table 6) and a variety of different thiols (entry 2–14, Table 6) were employed successfully, though a drawback was the competing reaction with morpholine **16** when using other alkoxide nucleophiles and propylamine.

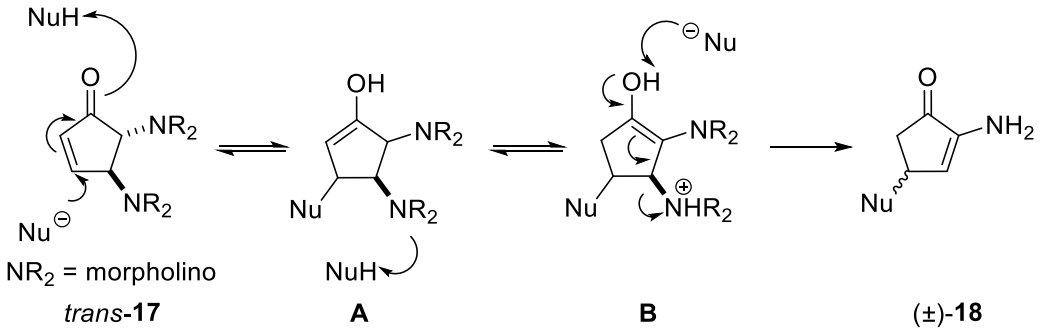
Table 6: Synthesis of 2,4-bifunctionalized cyclopentenones from furfural.[20]



Entry[a]	NuH	Yield [%][b]	Entry[a]	NuH	Yield [%][b]
1	NaOMe	67	9	*m*-MeO-Ph-SH	79
2	Et-SH	73	10	MeO_2C-C_2H_4-SH	74
3	^{i}Pr-SH	77	11[c]	HO_2C-C_2H_4-SH	55
4	cyclohexyl-SH	72	12	HO-C_2H_4-SH	77
5	^{t}Bu-SH	76	13	$(Et)_2N$-C_2H_4-SH	76
6	Ph-SH	71	14	$(MeO)_3Si$-C_3H_6-SH	52
7	Bn-SH	80	15[d]	H_3C-C_2H_4-NH	29
8	trityl-SH	63	16[e]	$LiCu(^{n}Bu)_2$	30

a) morpholine (2 equiv). b) isolated yield. c) KO^{t}Bu (1.25 equiv). d) plus (±)-**18** with Nu = OMe and Nu = morpholine in 21% and 20% yields, respectively. e) work-up of **17** before addition of NuH.

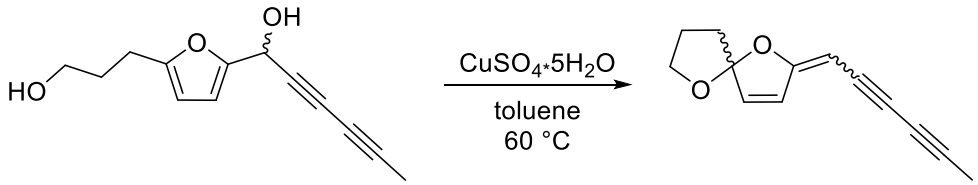
The mechanism (Scheme 6)[17,20,21] for the formation of 2,4-disubstituted cyclopentenones (±)-**18** from 4,5-diamino-2-cyclopentenones *trans*-**17** proceeds via 1,4-addition of the nucleophile to form intermediate **A**, which undergoes successive enolisation to **B**. E1cB-elimination of morpholine **16** furnishes the 2,4-disubstituted product (±)-**18**.



Scheme 6: Proposed mechanism for the formation of 2,4-disubstituted cyclopentenones.[17,20,21]

3. Intramolecular Variants with Alcohols

While working on the total synthesis of the antifeedant component of plants of the tribe *Athemideae* tonghaosu (±)-**20** and derivatives thereof (Scheme 7),[22] Wu *et al.* discovered the rearrangement of the spiroketal enol ethers (±)-**22** (Table 7), which offered in one case access to the natural product chrycorin (±)-**23e**.[23,24] Spiroketal enol ethers (±)-**22** were found to be intermediates in the Piancatelli rearrangement, and the overall process depicted here (Table 7) represents an intramolecular Piancatelli variant with an alcohol as the attacking nucleophile. In contrast to the classical version of the rearrangement, the overall process is a two-step procedure in which the intermediate spiroketal enol ethers (±)-**22** could be isolated.

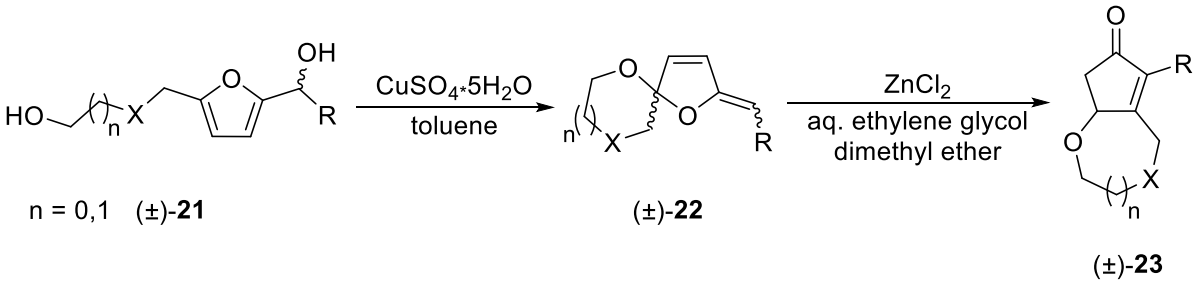


(±)-**19** (±)-**20**

Scheme 7: Synthesis of tonghaosu.[22]

The first step consists of a copper(II) sulfate catalyzed dehydration and spiroketalization of the α-furylcarbinols (±)-**21**, which undergo the rearrangement to 2,3,4-trisubstituted bicyclic cyclopentenones (±)-**23** in aqueous ethylene glycol dimethyl ether with zinc chloride as catalyst. The reaction could be performed with either electron-rich or deficient aryl-substituents with yields ranging from 70–90% for the second step (in case of chrycorin (±)-**23e** in 83%, entry 5, Table 7). The proposed mechanism is in agreement with the one depicted in Scheme 1, including the further isomerization of the product to the thermodynamically more stable (±)-**23**.[23] Later in 2009 the same group published results[24] concluding a different mechanism, in which an intramolecular aldol-like version of the ring-closing step is proposed. Furthermore, in this publication the one-step conversion of different α-furylcarbinols of type (±)-**21** to cyclopentenones (±)-**23** is described by directly applying the aqueous zinc chloride conditions to (±)-**21**.

Table 7: Acid catalyzed rearrangement of spiroketal enol ethers.[23,24]



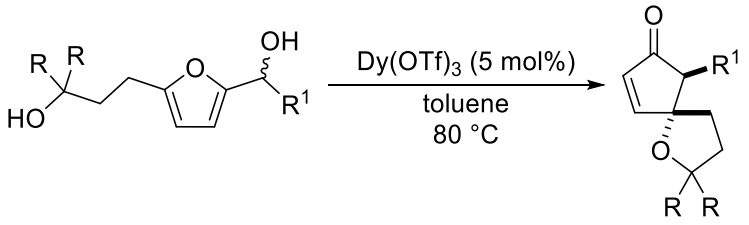
(±)-**23e** chrycorin:
n = 1
R = 1-thiophenyl

Entry	X	R	n	t [h]	Product	Yield [%][a]	Entry	X	R	n	t [h]	Product	Yield [%][a]
1	CH_2	Ph	0	5	**23a**	81	6	CH_2	Ph	1	**6**	**23f**	78
2	CH_2	*p*-Me-Ph	0	4	**23b**	85	7	O	Ph	1	**6**	**23g**	75
3	CH_2	*p*-MeO-Ph	0	3.5	**23c**	90	8	O	*p*-MeO-Ph	1	**5**	**23h**	86
4	CH_2	*p*-O_2N-Ph	0	6	**23d**	75	9	O	*p*-O_2N-Ph	1	**8**	**23i**	70
5	CH_2	thiophene-2-yl	0	4	**23e**	83	10	CH_2	*trans*-styryl	0	**3**	**23j**	84

a) isolated yield.

Read de Alaniz *et al.* observed the same intramolecular rearrangement by using $Dy(OTf)_3$ as catalyst and in addition they were able to avoid the isomerization of the product and achieve the formation of spirocyclic ethers **25** (Table 8).[25] The screening of different catalysts and solvents showed that the resulting product depended on the Lewis acid used in the reaction. When neat PhMe, $CuSO_4 \cdot 5H_2O$ in MeCN or $Dy(OTf)_3$ in MeCN under basic conditions were applied, the spiroketalization product of type (±)-**22** was observed. $ZnCl_2$ in MeCN/H_2O gave the further isomerized species of type (±)-**23**. Only $Dy(OTf)_3$ in PhMe afforded **25** as the single product. A variety of different electron-rich and deficient aryl substituents were tolerated on the hydroxymethyl-functionality on the α-furylcarbinol giving yields between 75–91% (entry 1–9, Table 8). However, alkyl groups in this position proved to be challenging (entry 10 and 12, Table 8), but this could be solved by attaching a dimethyl substituent next to the hydroxy group on the opposite alkyl chain (entry 11 and 13, Table 8).

Table 8: Intramolecular rearrangement of α-furylcarbinols to spirocyclic cyclopentenones.[25]

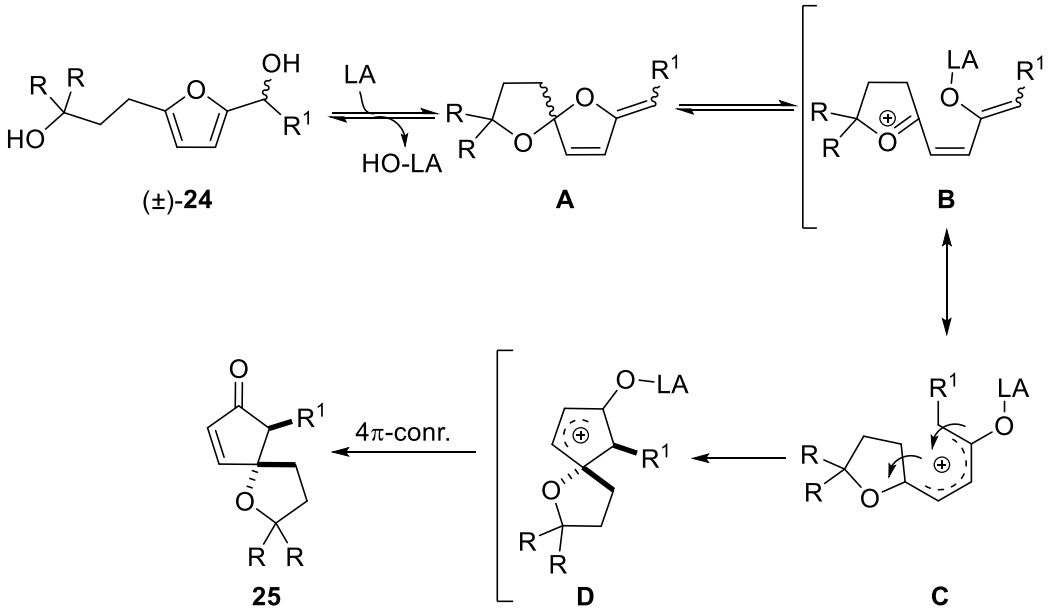


(±)-**24** **25**

Entry	R	R^1	Yield [%][a]	Entry	R	R^1	Yield [%][a]
1	H	Ph	91	8	H	2-naphthalenyl	86
2	H	*p*-MeO-Ph	89	9	Me	Ph	74
3[b]	H	*p*-Br-Ph	83	10	H	^{n}Bu	0
4[b]	H	*p*-F_3C-Ph	88	11	Me	^{n}Bu	98
5[b,c]	H	*p*-O_2N-Ph	75	12	H	^{i}Pr	0
6	H	2,4,6-trimethyl-Ph	78	13	Me	^{i}Pr	25
7	H	1-thiophenyl	90				

a) isolated yield. b) reaction at 100 °C. c) inseparable mixture of diastereomers with 9:1 ratio in this case.

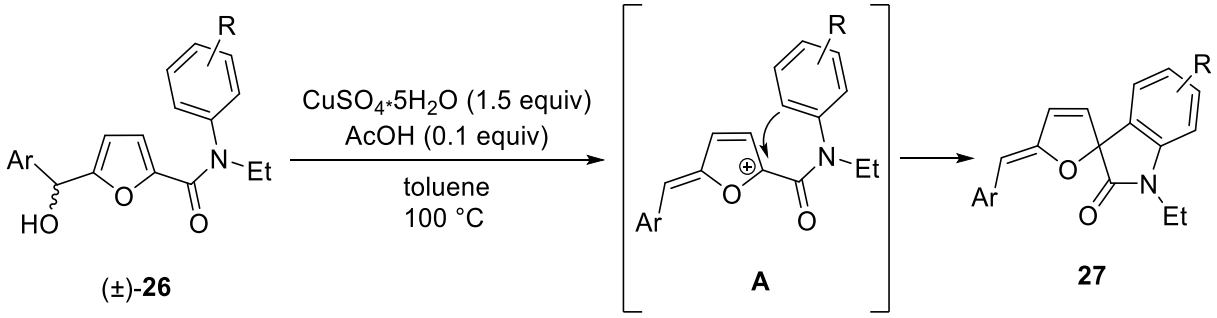
The proposed mechanism is analogous to the aza-version published previously by the same group.[15] The Lewis acid serves two functions in this process, firstly it enhances the leaving group abilities of the α-alcohol functionality in (±)-**24** and secondly it facilitates the ring opening in oxaspirocycles **A** to form the intermediate oxocarbenium ion **B**. The following step proceeds via a 4π-electrocyclic ring closure to give eventually the spirocyclic cyclopentenone **25**.



Scheme 8: Mechanism proposed by Read de Alaniz *et al*.[25]

4. C-Piancatelli Rearrangement

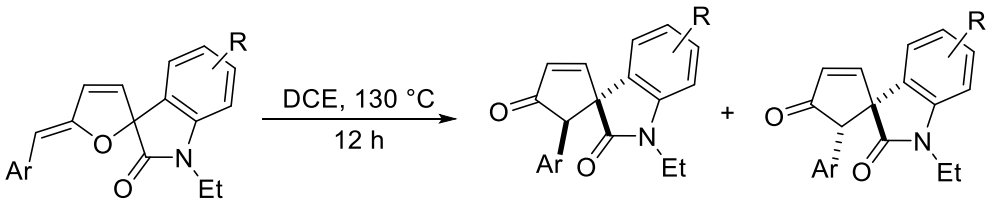
Jiang *et al.* discovered another intramolecular modification of α-furylcarbinol rearrangements to cyclopentenones **28** (Table 9), in which compounds **27** represent intermediates (Scheme **9**).[26,27] The overall transformation is a two-step process and is similar to the intramolecular version with alcohols described in chapter 3 (Scheme 7, Table 7). $CuSO_4 \cdot 5H_2O$ and catalytic amounts of acetic acid proved to be the most effective catalysts for the first step, the formation of spirofurooxindoles **27** (Scheme 9). The scope of the reaction is limited to aromatic rings on the amide with electron-rich substituents, as it participates in an intramolecular Friedel-Crafts reaction with the intermediately formed stabilized cation **A**.



Scheme 9: Trapping of the oxocarbenium intermediate by a Friedel-Crafts reaction.[26]

The second step (Table 9), the ring opening of **27** and closure to form cyclopentenones **28** was found to be most successful by heating **27** in DCE as solvent without the use of any catalyst. For this reaction, yields between 84–94% and diastereoselectivities of 1.2:1 up to >99:1 could be realized. The overall process can be regarded as a C-Piancatelli rearrangement, as the attacking nucleophile on the intermediate oxocarbenium ion is a carbon nucleophile.

Table 9: Rearrangement of spirofurooxindoles into spiropentenoneoxindoles.[27]



27 *cis*-**28** (major) *trans*-**28** (minor)

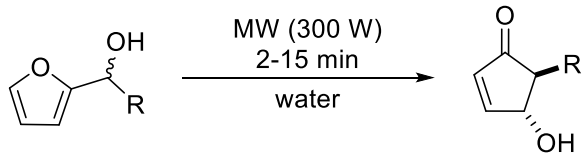
Entry	Ar	R	Yield [%][a]	dr[b]	Entry	Ar	R	Yield [%][a]	dr[b]
1	Ph	3,4,5-tri-MeO	94	4:1	8	*o*-F-Ph	3,4,5-tri-MeO	87	>99:1
2	Ph	3,5-di-MeO	91	5:1	9	*o*-F-Ph	3,5-di-MeO	85	3:2
3	Ph	4,5-di-MeO	89	1.5:1	10	*o*-Cl-Ph	3,4,5-tri-MeO	92	>99:1
4	*p*-Cl-Ph	3,4,5-tri-MeO	93	5.6:1	11	*o*-Cl-Ph	3,5-di-MeO	90	>99:1
5	*p*-Cl-Ph	3,5-di-MeO	90	3:1	12	*o*-Cl-Ph	4,5-di-MeO	89	1.2:1
6	*p*-O_2N-Ph	3,4,5-tri-MeO	86	1.8:1	13	*o*-Me-Ph	3,4,5-tri-MeO	94	>99:1
7	*p*-O_2N-Ph	3,5-di-MeO	84	2.3:1	14	*o*-Me-Ph	3,5-di-MeO	91	5:1

a) isolated yield. b) determined by NMR.

5. Rearrangement in a Continuous Flow Process

A new catalyst-free process to convert furfuryl alcohol **1g** and derivatives thereof in an aqueous solution to 4-hydroxy-2-cyclopentenone (±)**-2a** either in the microwave or a continuous flow system was developed by Reiser *et al.*[28] Different derivatives of furfuryl alcohol featuring an alkyl- or phenyl substituent adjacent to the hydroxyl-functionality could be employed in this reaction with yields ranging from 43–96% (Table 10). Furthermore, very short reaction times of 2–15 min by applying microwave heating could be reached. The selectivities observed fall in a range between 5:1 to 12:1 in favor of the more stable *trans*- to *cis*-diastereomer. A study on the kinetics of the rearrangement of furfuryl alcohol **1g** by Hronec *et al.* confirms the beneficial effects of high temperatures on this reaction.[29]

Table 10: Rearrangement of different α-furylcarbinols in the microwave.[a,28]



(±)-**1g**: R = H
(±)-**1a**: R = Ph
(±)-**1i**: R = 2-butenyl
(±)-**1h**: R = Et
(±)-**1j**: R = pentyl
(±)-**1k**: R = dodecyl

trans-**2**
2a: R = H
2b: R = Ph
2c: R = 2-butenyl
2d: R = Et
2e: R = pentyl
2f: R = dodecyl

Entry	R	c [mol/L]	t [min]	Yield [%][b]	dr (*trans*/*cis*)
1	**1g**	0.25	4	43	-
2	**1a**	0.14	2	96	5:1
3	**1i**	0.15	5	73	12:1
4	**1h**	0.14	15	54	7:1
5	**1j**	0.15	5	65	7:1
6	**1k**	0.15	30	0	-

a) **1** (1.5 mmol) in H_2O (6 mL), microwave irradiation (300 W) under closed vessel conditions (200–210 °C, 15 bar). b) isolated yield.

The application of a continuous flow system for the rearrangement of 4-hydroxy-2-cyclopentenone (±)**-2a** in water under subcritical conditions (240 °C, >15 bar) was achieved with a high throughput and very short reaction time (<1 min, 87% yield), making this process an attractive alternative for the large-scale synthesis of (±)**-2a** compared to conventional batch methods.

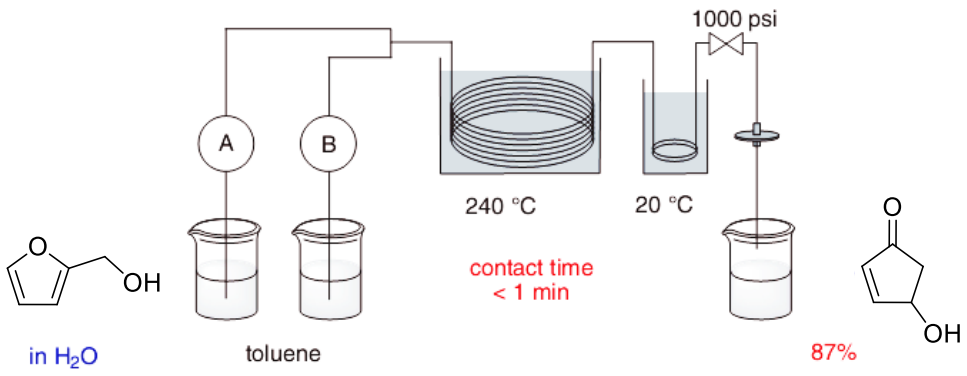
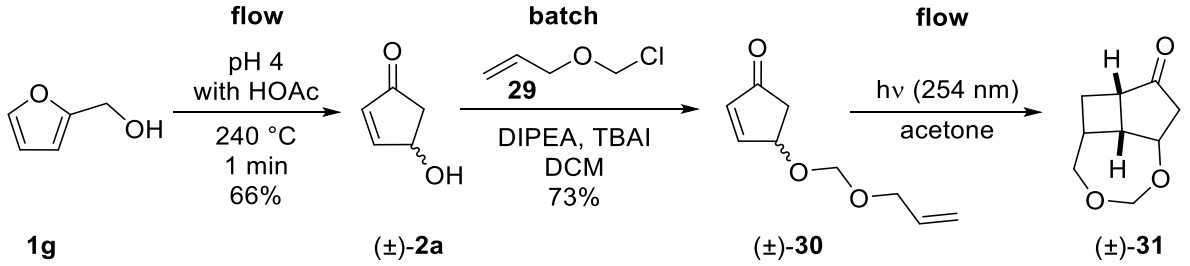


Figure 1: Setup of continuous flow system for rearrangement reaction.[28]

This optimized process was adapted by another group successfully with an additional subsequent photoreaction.[30] The procedure comprises 3 steps in which two of them are conducted in continuous flow systems. At first a slightly modified procedure of the rearrangement of furfuryl alcohol **1g** to 4-hydroxy-2-cyclopentenone (±)**-2a** provided the product in 66% yield on a 100 g scale. The following reaction of (±)**-2a** with 3-chloromethoxy-propene **29** afforded compound (±)**-30**, which is used in the subsequent photochemical process as starting material. The intramolecular [2+2]-cycloaddition leading to product (±)**-31** was again conducted in a flow process, which facilitates the irradiation with 254 nm UV-lamps by providing a high surface area and the exact reaction time by a controllable flow rate.

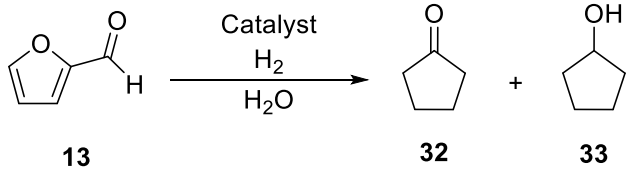


Scheme 10: Rearrangement process with a subsequent photoreaction.[30]

6. Rearrangement and Hydrogenation

In 2012 Hronec *et al.* discovered the formation of cyclopentanone **32** and cyclopentanol **33** as the main products while studying high-pressure hydrogenations of furfural **13** (Table 11).[31] They investigated the performance of Ni, Pt, Pd and Ru catalysts under different hydrogen pressures of 30–80 bar at 140–190 °C (entry 1–5, Table 11). When the hydrogenations were conducted in non-aqueous media, the product range comprised the typically expected compounds from the direct hydrogenation of furfural, like furfuryl alcohol, tetrahydrofurfuryl alcohol, 2-methylfuran and 2-methyltetrahydrofuran. In contrast to this it was observed that reactions carried out in a water containing environment yielded cyclopentanone **32** and cyclopentanol **33** as the main products. Therefore, it can be assumed that after the hydrogenation of the aldehyde functionality of furfural **13** the Piancatelli rearrangement of furfuryl alcohol **1g** took place yielding 4-hydroxy-2-cyclopentenone (±)**-2a**. Thereupon the double bond of the rearranged product 4-hydroxy-2-cyclopentenone (±)**-2a** was hydrogenated and the hydroxy group eliminated. This afforded 2-cyclopentenone which was again hydrogenated leading to cyclopentanone **32** or its reduction product cyclopentanol **33**.

Table 11: Cyclopentanone from furfural.[31,32]



13 **32** **33**

Entry	Catalyst	t	T [°C]	H_2 p [bar]	Conversion [%]	Yield [%] 32	Yield [%] 33
1[a]	5% Pt/C	30 min	160	80	100	77	5
2[a]	5% Pd/C	60 min	160	30	98	67	1
3[a]	5% Ru/C	60 min	175	80	100	57	10
4[a]	CoMnCr	60 min	175	80	100	8	16
5[b]	Raney Ni	60 min	160	30	100	17	40
6[c]	NiCu-50/SBA-15	4 h	160	40	>99	62	3

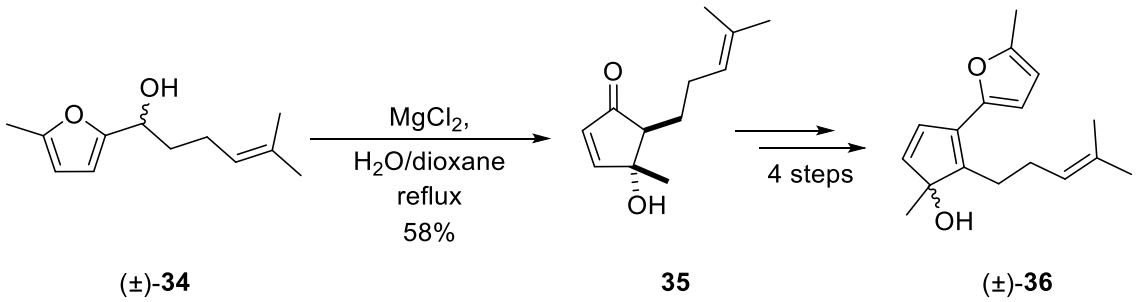
a) **13** (1 g), H_2O (20 mL), catalyst (0.1 g), ref. 31. b) **13** (1 g), H_2O (20 mL), catalyst (0.1 g), ref. 31. c) **13** (10 g), catalyst (0.2 g), ref. 32.

At the same time Xu *et al.* described the identical process using a bimetallic Ni/Cu-catalyst and hydrogen pressures of 40 bar at 160 °C (entry 6, Table 11).[32] In their case also cyclopentanol **33** or cyclopentanone **32** were identified as the main products. Furthermore, the intermediate species cyclopentenone could be isolated by using restricted amounts of hydrogen.

7. Application in Total Synthesis

Because the cyclopentenone scaffold has been recognized as a motif in many natural products, new synthetic procedures providing this structure are highly valuable. The rearrangement of α-furylcarbinols presents a straightforward method for this purpose and is an essential step of many synthetic methodologies. The latest publications concerning this issue are exemplified in the following subsection.

One of the most recent instances was published by Nukada *et al.* who synthesized the core framework 2-homoprenyl-1-methyl-3-(5-methylfuran-2-yl)cyclopenta-2,4-dien-1-ol (±)-**36** of the proposed structure of the brown alga derived natural product sargafuran in 4 steps from intermediate **35**, which was prepared by a Piancatelli rearrangement of α-furylcarbinol (±)-**34** in 58% yield (Scheme 11).[33] The latter was obtained by a Grignard reaction of commercially available 5-methylfurfural and the appropriate alkylbromide.

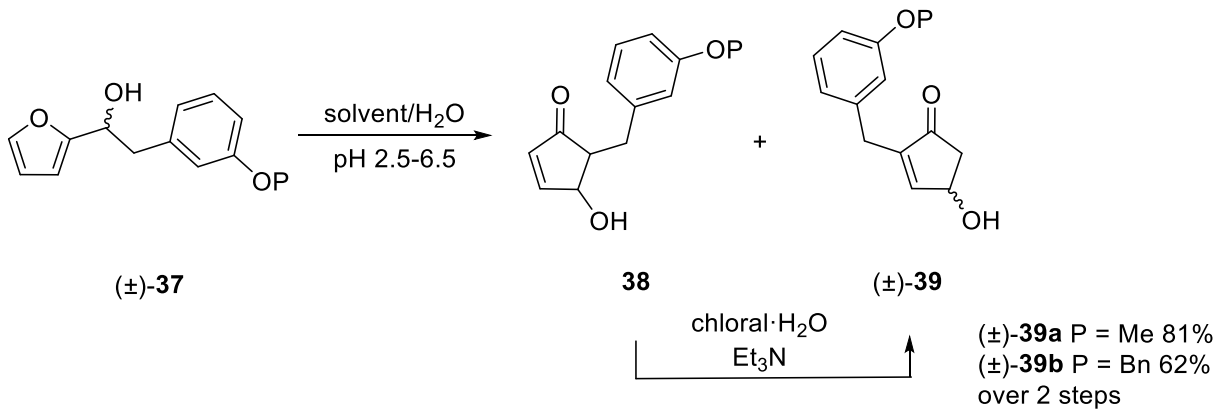


(±)-**34** **35** (±)-**36**

Scheme 11: Synthesis of the core structure of sargafuran.[33]

Another frequently used method is the preparation of racemic or enantiomerically pure TBS-protected 4-hydroxy-2-cylopentenone from **2a** as the starting point for the synthesis of natural products, e.g. (-)-tenuipyrone,[34] (±)-havellockate,[35] and all 15-F_2 isoprostanes.[36] In these examples the rearrangement of furfuryl alcohol **1g** is utilized to allow access to 4-*tert*(butyldimethylsilyloxy)-2-cyclopentenone.

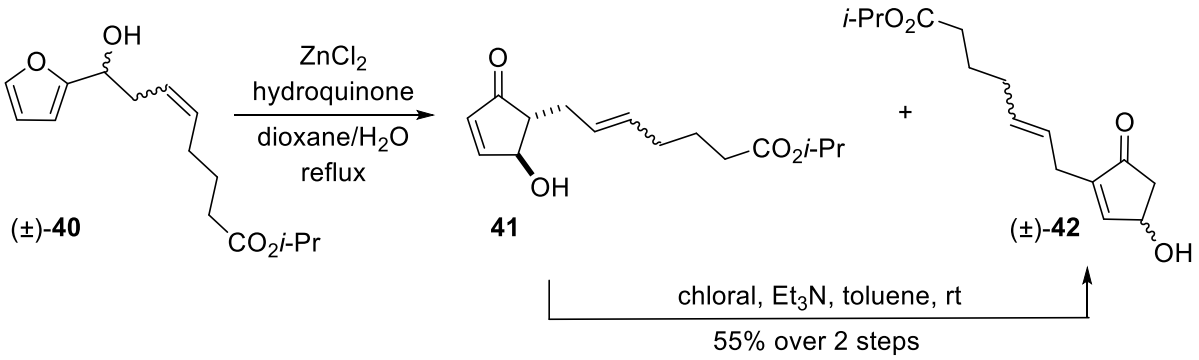
The preparation of prostaglandins and analogues is still in the focus of ongoing research as proven by the following three literature precedents. In the US patent by Yeh *et al.* intermediates (±)-**39** in the synthesis of benzindene prostaglandins were obtained by the rearrangement of α-furylcarbinol (±)-**37** and the further isomerization to the thermodynamically more stable compound (±)-**39** (Scheme 12).[37] P is an acid stable protecting group (e. g. Me, Bn) and the transformation was carried out in an aqueous medium with pH values in the range of 2.5–6.5 and temperatures between 60–200 °C. The isomerization of **38** could be facilitated by the addition of chloral hydrate and triethylamine to give the racemic product (±)-**39** (e. g. 81% for **39a**, 62% for **39b**, Scheme 12). In the following step the synthesis of the enantiomerically pure product from (±)-**39** was achieved by enzymatic kinetic resolution.



(±)-**37** **38** (±)-**39**

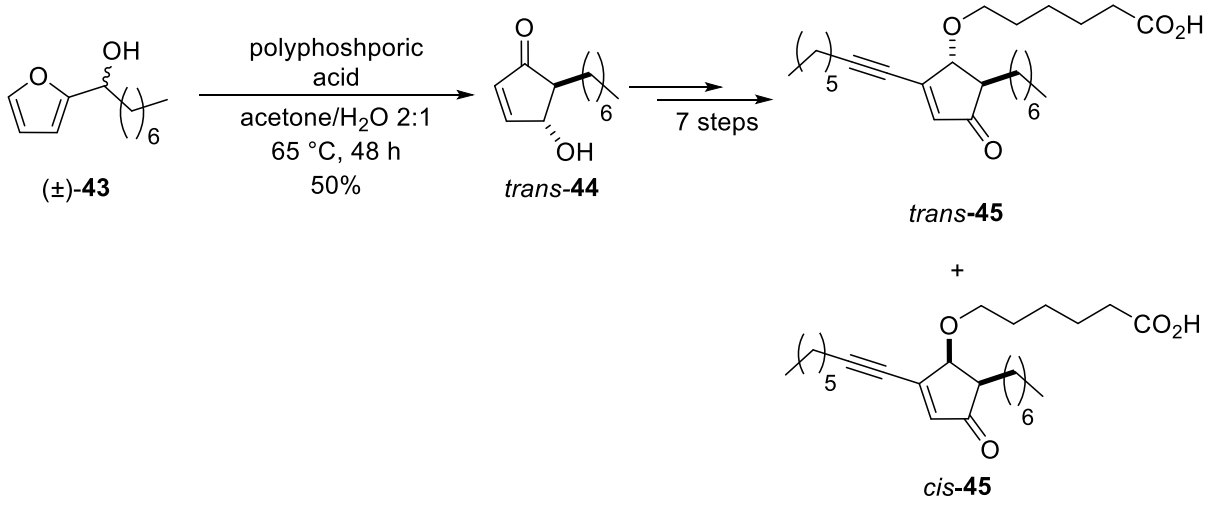
Scheme 12: Process for preparing benzindene prostaglandins.[37]

Qiu and co-workers describe the preparation of cyclopentenones (±)-**42** via Piancatelli rearrangement, which are intermediates for the synthesis of prostaglandin analogues (Scheme 13).[38] The same strategy is pursued by Sung, published in a US patent.[39]



Scheme 13: Intermediate for the synthesis of prostaglandin analogues.[38,39]

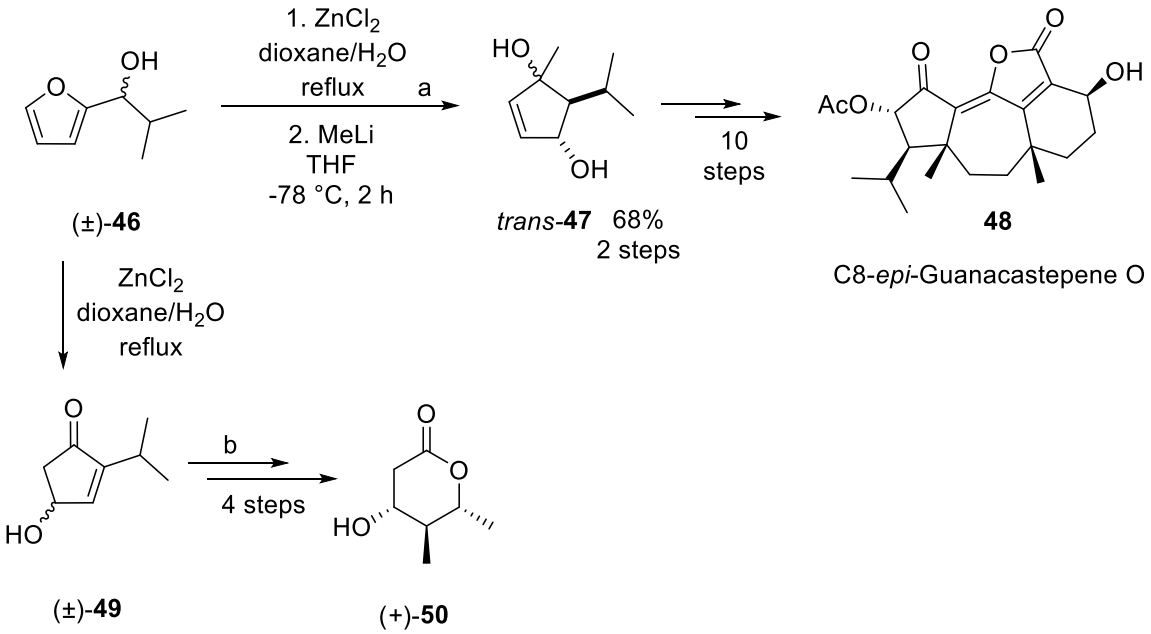
De Lera *et al.* explored the synthesis of potent PPARγ (peroxisome proliferator-activated receptors) agonists with a cyclopentenone core structure.[40,41,42] This has been achieved by the functionalization of 5-heptyl-4-hydroxycyclopentenone *trans*-**44** in 7 steps, which has been synthesized by a Piancatelli rearrangement of (±)-**43** (Scheme 14, a). The rearrangement was carried out at 65 °C for 48 h in the presence of substoichiometric amounts of polyphosphoric acid in a 2:1 acetone/water mixture with 50% yield. The starting material (±)-**43** was obtained by a Grignard reaction of furfural and heptylmagnesium bromide.



Scheme 14: Synthesis of PPAR receptor modulators with cyclopentenone core structure.[40,41,42]

Two other publications from different groups appeared using the same α-furylcarbinol (±)-**46** as starting material for the preparation of natural products **48** and **50**. Firstly, Yang *et al.*

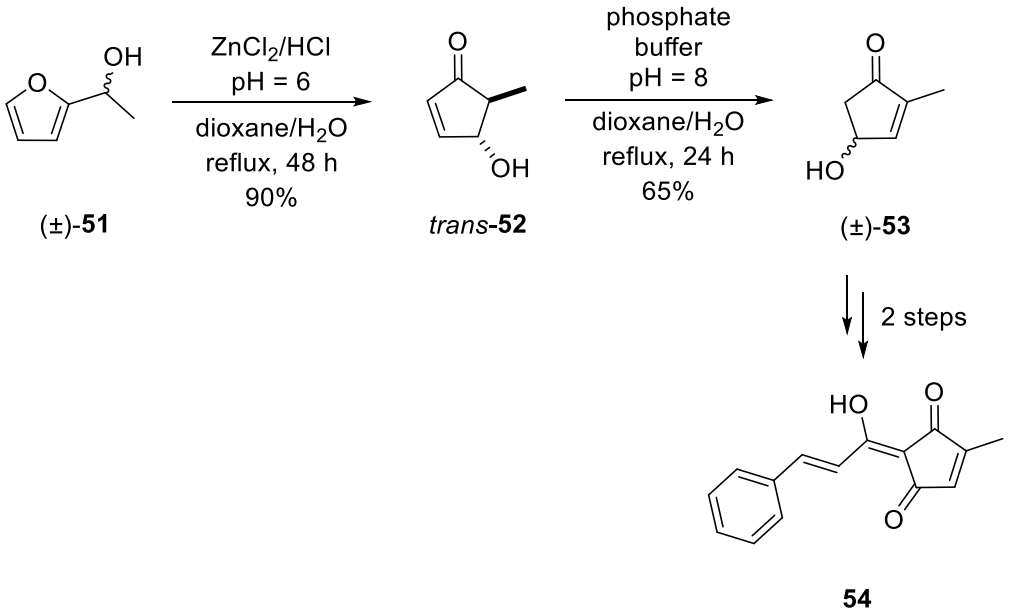
describe the total synthesis of C8-*epi*-guanacastepene O **48** (Scheme 15, a), which has potential anti-bacterial activity.[43] The starting point for the preparation of **48** was the rearrangement of α-furylcarbinol (±)-**46** in a refluxing dioxane/water mixture with $ZnCl_2$ as catalyst, which afforded after methylation cyclopentanol *trans*-**47** in 68% yield.



Scheme 15: Total Synthesis of C8-*epi*-Guanacastepene and (+)-prelactone B.[43,44]

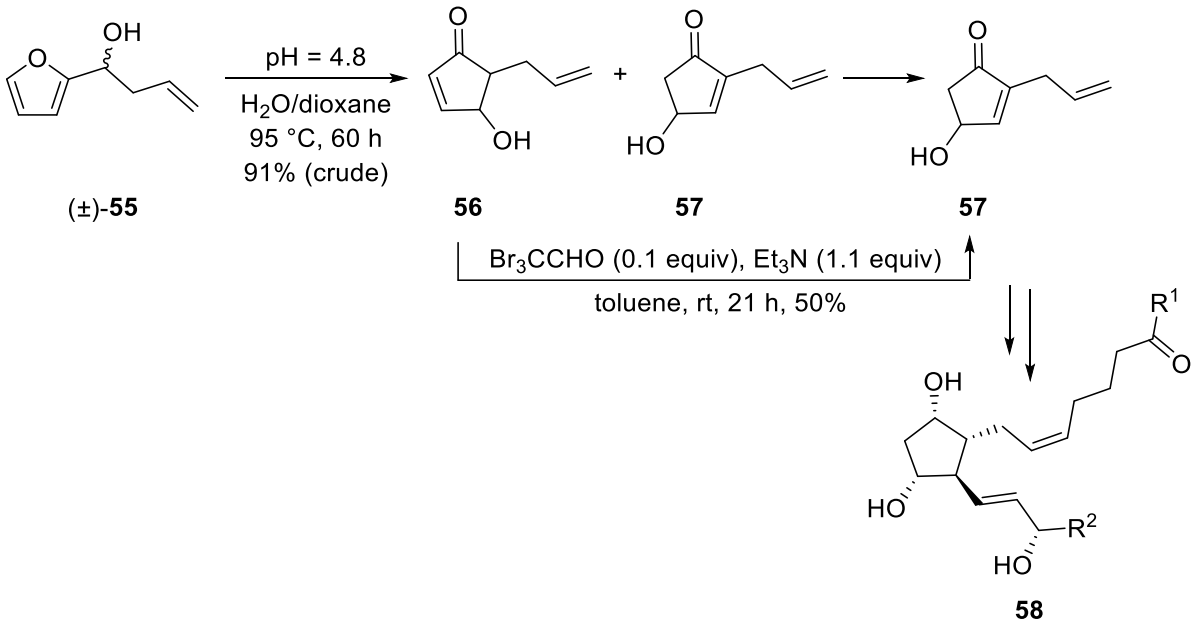
Starting the synthesis from the same compound (±)-**46** Csákÿ *et al.* developed a strategy for the enantioselective synthesis of (+)-prelactone B **50**, isolated from *Streptomyces griseus*, and its C-4 epimer (Scheme 15, b).[44] The rearrangement was conducted under identical conditions as described before (Scheme 15, a, 1). Enzymatic kinetic resolution afforded the enantiomerically pure compound from (+)-**49**, which was then converted to (+)-prelactone B **50** in 4 steps.

Dias and co-workers describe a short synthesis of the new cyclopentene-1,3-dione derivative **54** isolated from *Piper carniconnectivum* (Scheme 16).[45] After reduction of commercially available 2-acetylfuran with $NaBH_4$ yielding α-furylcarbinol (±)-**51**, the latter was heated in a refluxing dioxane/water mixture with $ZnCl_2$ as catalyst at pH 6. This resulted in the rearrangement of (±)-**51** to furnish 5-methyl-4-hydroxy-2-cyclopentenone *trans*-**52**, which underwent a further isomerization under basic conditions to 2-methyl-4-hydroxy-2-cyclopentenone (±)-**53**. Finally this compound could be transformed in 2 steps to the desired natural product **54**.



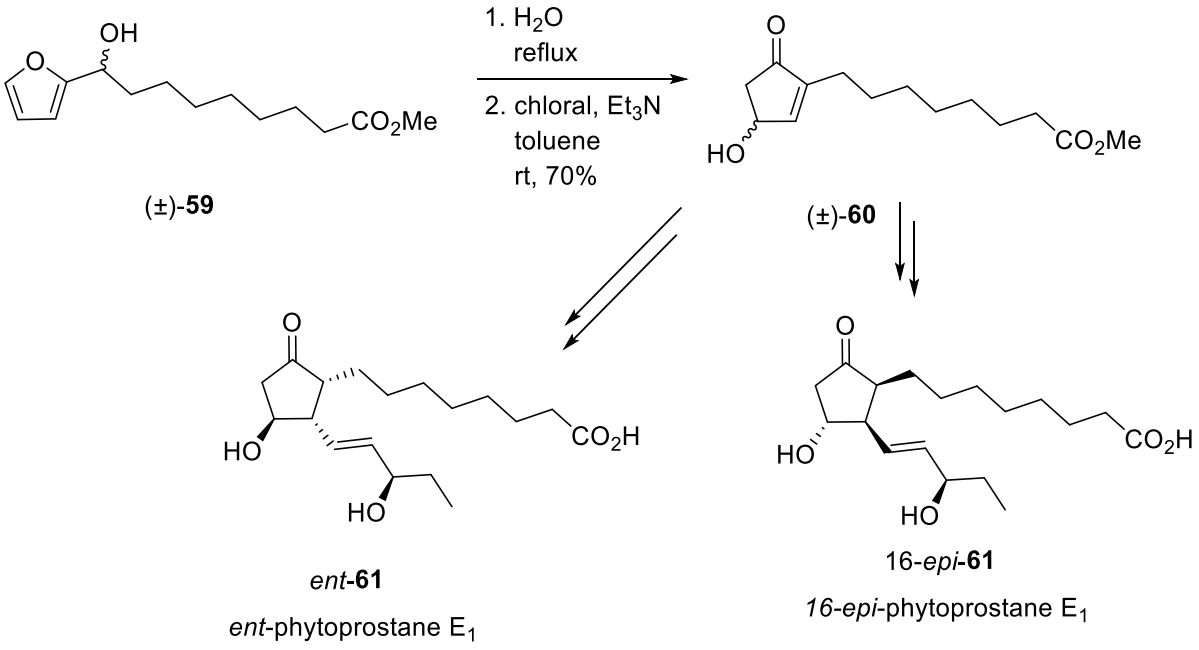
Scheme 16: Synthesis of cyclopentene-1,3-dione derivative isolated from *Piper carniconnectivum*.[45]

The Piancatelli rearrangement of α-furylcarbinol (±)-**55** was exploited by Sharma *et al*. to prepare cyclopentenone **57** for the synthesis of prostaglandins PGF_{α} and analogues **58** (Scheme 17).[46] From a practical point of view, it is worth mentioning that they could perform the rearrangement of (±)-**55** on a 0.5 kg scale.



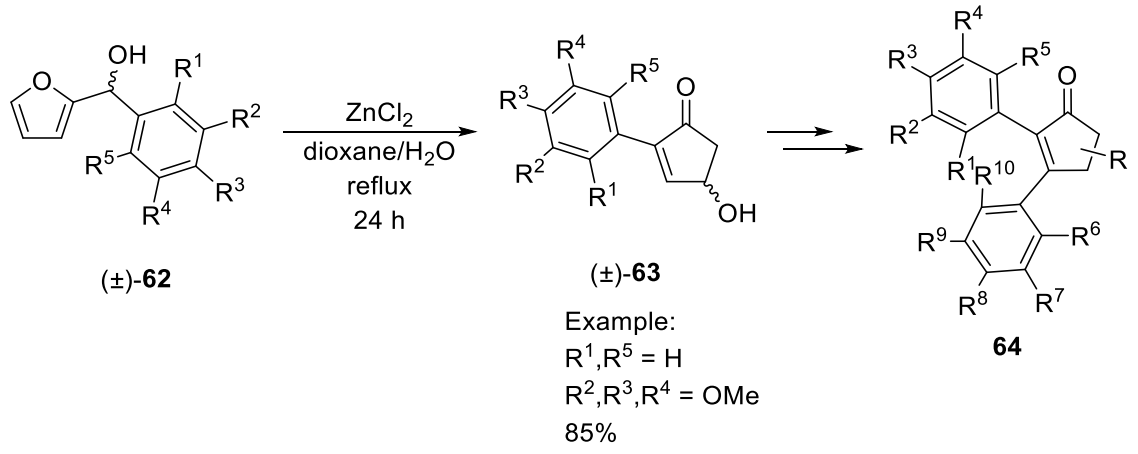
Scheme 17: Prostaglandin synthesis by Sharma *et al*.[46]

Not only for the preparation of prostaglandins, but also in the field of phytoprostane synthesis examples can be found in literature. Spur e*t al.* used the Piancatelli rearrangement for the first total synthesis of two E type I phytoprostanes **61**.[47] They performed the rearrangement of (±)-**59**, which was obtained from furan and commercially available azelaic monomethyl ester and subsequent reduction to the alcohol, in refluxing water. By treatment with catalytic amounts of chloral in the presence of triethylamine the following isomerization to (±)-**60** was achieved in 70% for the two steps. Then cyclopentenone (±)-**60** was transformed either to *ent*-phytoprostane E_1 *ent*-**61** or 16-*epi*-phytoprostane E_1 16-*epi*-**61** in 7 steps, in which the stereochemistry of the hydroxy group at C4 was introduced by enzymatic kinetic resolution.



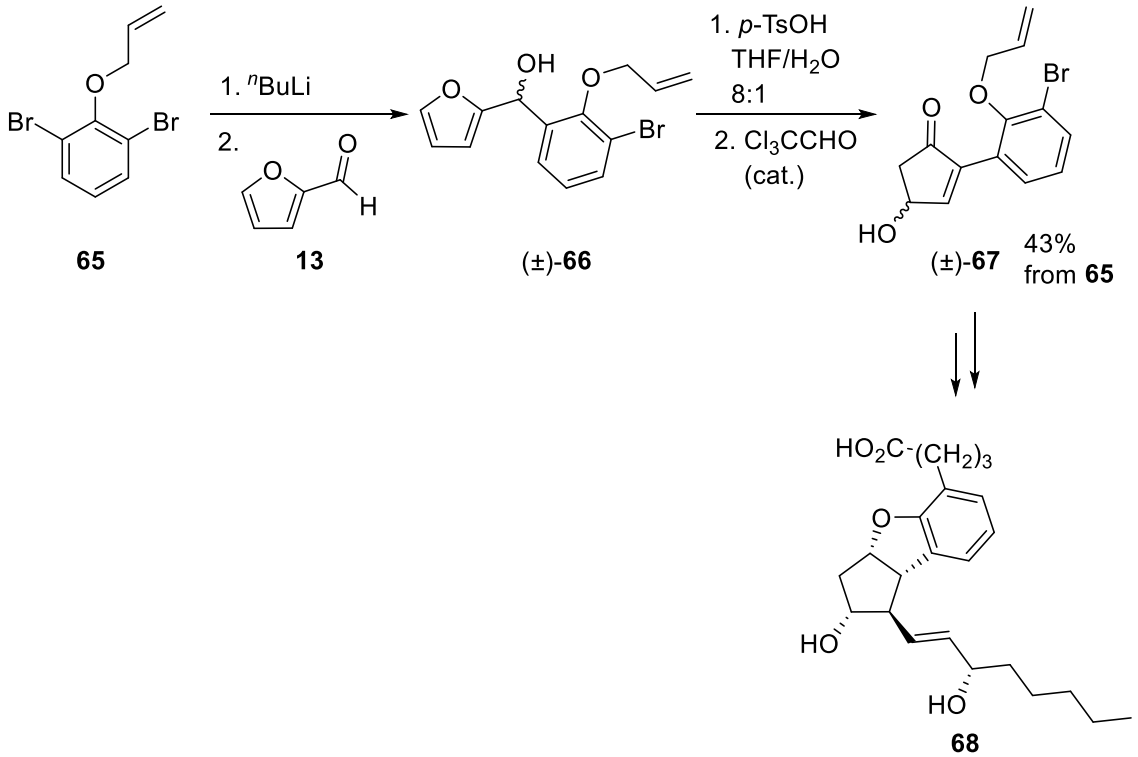
Scheme 18: First total synthesis of two E type I phytoprostanes by Spur *et al*.[47]

Yadav *et al.* used the Piancatelli rearrangement for the synthesis of cyclopentenone derivatives **64** for cancer therapy (Scheme 19).[48] Some compounds of type **64** showed a high activity against human cancer cell lines. The rearrangement of compounds (±)-**62** was conducted with Lewis acids like zinc chloride, though in this case the rearrangement did not stop at the 4,5-disubstiuted cyclopentenones but directly led through isomerization to the more stable 2,4-disubstituted cyclopentenones (±)-**63**.



Scheme 19: Cyclopentenone derivatives for cancer therapy.[48]

Sato *et al.* describe an efficient approach to optically active benzoprostacyclins **68** (prostaglandin I_2 analogue) by a two-component coupling process from cyclopentenone (±)-**67**, which was prepared from α-furylcarbinol (±)-**66** via Piancatelli rearrangement (Scheme 20).[49] The stereochemical information in **68** was introduced by enzymatic kinetic resolution.

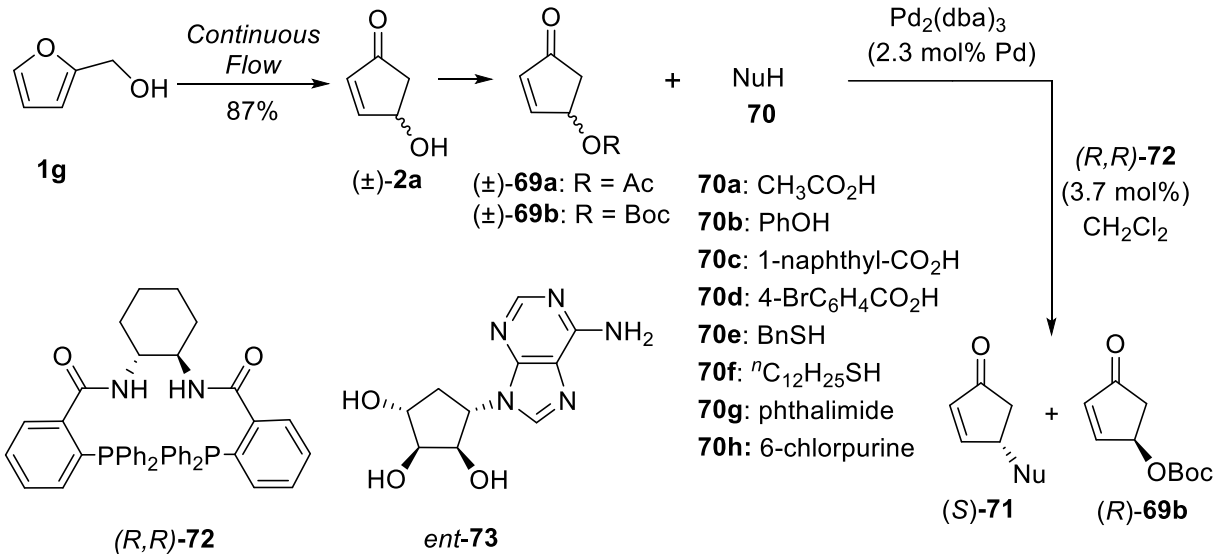


Scheme 20: Approach to optically active benzoprostacyclins.[49]

A novel enantioselective method to synthesize 4-heterosubstituted cyclopentenones and the application of this strategy for the formal synthesis of *ent*-noraristeromycin **74** was developed

by Reiser *et al.* (Table 12).[50] This was achieved by the kinetic resolution of racemic *O*-Ac- or *O*-Boc-substituted cyclopentenones **69a** and **69b** by employing the well-established methodology of nucleophilic allylic substitution, a concept developed by Trost and Tsuji (see chapter 2, main part). The reaction with the Boc-protected cyclopentenone **69b** worked more smoothly than with **69a**, and various N-, O- and S-nucleophiles could be applied. With $Pd_2(dba)_3$ and the Trost ligand (*R*,*R*)-**72** as catalyst remarkably high selectivities with >99% in some cases were reported. Moreover, by using this method a short formal synthesis of *ent*-noraristeromycin **73** was developed (via the product from reaction with **70h**, entry 12, Table 12).

Table 12: Synthesis of 4-heterosubstituted cyclopentenones according to Reiser *et al.*[50]



Entry[a]	69	70	t [h]	T [°C]	Yield [%] 69	ee [%] 69	Yield [%] 71	ee [%] 71	s[b]
1	**69a**	**70b**	18	25	23	26	12	91	24
2	**69a**	**70c**	4	0	50	25	30	77	11
3	**69b**	**70a**	1	0	46	96	35 (**69a**)	90	31
4	**69b**	**70b**	2	0	34	99	34	93	44
5	**69b**	**70c**	1	0	31	90	46	90	44
6	**69b**	**70c**[c]	4	–20	43	>99	45	>99	501
7	**69b**	**70d**	1	0	44	95	41	91	41
8	**69b**	**70e**	17	–78	33	>99	42	93	56
9	**69b**	**70f**	17	–78	38	92	39	93	50
10	**69b**	**70g**	18	rt	31	>99	50[d]	96[d]	194
11	**69b**	**70g**[c]	16	rt	42	>99	48[e]	95[e]	113
12	**69b**	**70h**[c]	24	0	47	>99	46	94	80

a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL); absolute configurations of **71a** and **71d** were obtained by comparison of specific rotation values with literature (see Experimental Part) as well as by X-ray crystallography (**70g**, see Appendix). b) selectivity factor. c) 5 mmol scale, $Pd_2(dba)_3$ (0.5 mol%; 1 mol% of Pd based on the nucleophile), (*R*,*R*)-**72** (2 mol % based on the nucleophile). d) 36%, 99% ee after single recrystallization from ethanol. e) 43%, 97% ee after single recrystallization from ethanol. f) 39%, 98% ee after single recrystallization from PE/EA.

8. Conclusion

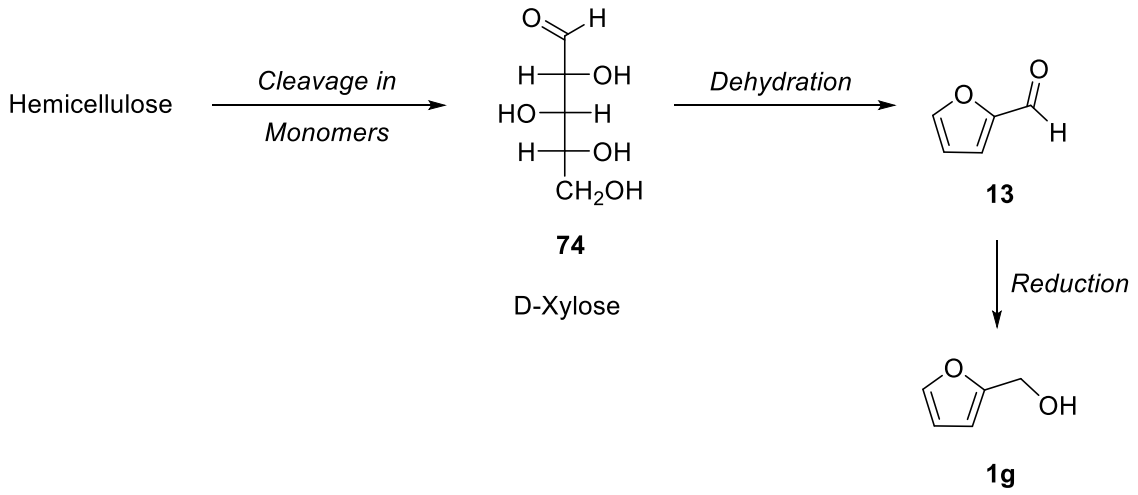
Especially in the last 10 years, the scope of the Piancatelli rearrangement was expanded significantly. The aza- and the C-Piancatelli versions now allow the use of nitrogen and carbon nucleophiles instead of solely water as nucleophile, and moreover intramolecular variants of this reaction have been developed. This gives new perspectives regarding potential future applications, which were until now limited to the classical version. Furthermore, a few technical approaches have been realized, giving the possibility to perform the rearrangement in a continuous flow reactor. This gives now the opportunity for the convenient large-scale production of cyclopentenones. Besides this, a method was developed to synthesize cyclopentanone or cyclopentanol directly from furfuryl alcohol, which is highly valuable in view of the growing interest in using renewable resources. Apart from these new advancements there are frequently appearing publications about applications for the classical Piancatelli rearrangement, proven by the numerous examples in chapter 7. As an outlook, taking the increasing interest in variations of this reaction in the last decade into account, new interesting developments and also applications concerning this issue can be anticipated.

B. Main Part

1. Cycloaddition Approach

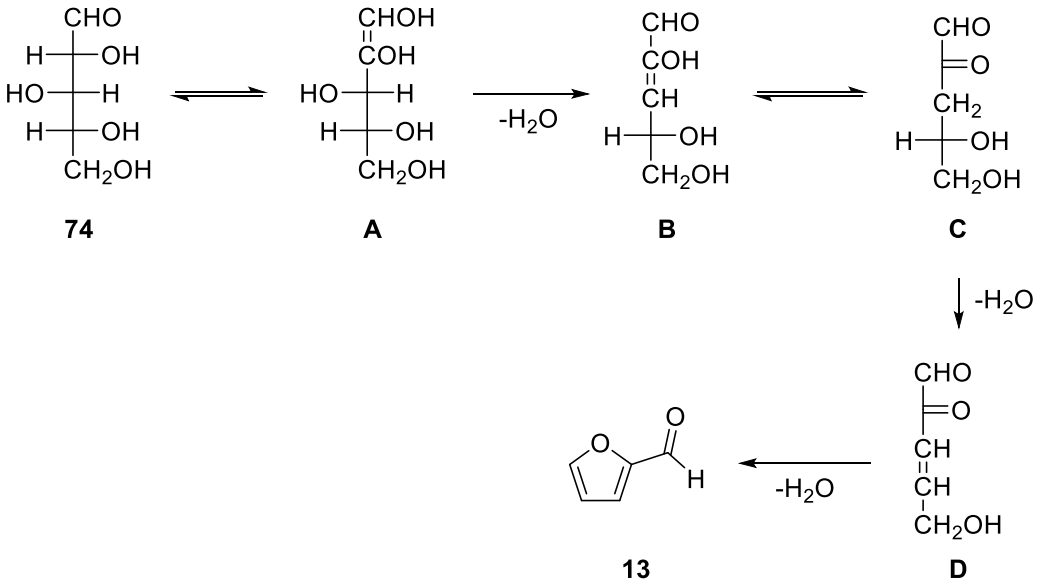
1.1 Introduction

The basic objective of this project was to establish new methods to convert chemicals which are fabricated from a renewable feedstock into valuable building blocks for synthesis in organic chemistry. Ideally, processes in which renewable materials are used for the synthesis of compounds that are otherwise typically produced from fossil resources should be developed. In this respect, an interesting class of compounds are certain furan derivatives that are easily accessible from biomass commodities. Therefore, the main focus of this work will be placed on the investigation of the transformation of these particular furanic compounds. The first chapter starts with exploring the conversion of the heterocyclic compound furfuryl alcohol **1g** to the carbocyclic substance 4-hydroxy-2-cyclopentenone (±)-**2a** which then should be transformed in a subsequent cycloaddition reaction. Furfuryl alcohol **1g** was selected as it is manufactured industrially on a large scale from agricultural residues like bran, bagasse, wheat straw, and wood or paper waste for instance[51,52] and therefore it is inexpensively available in great quantities. These waste products consist principally of cellulose, hemicellulose and lignin. Cellulose is a glucose polymer and hemicellulose a polymer consisting mainly of xylose, a C5-sugar. Hydrolysis of these so-called lignocellulosic materials under acidic conditions results in the cleavage of the polymeric structures to yield the monomeric carbohydrates. In case of the hemicellulosic fraction (Scheme 21) this gives primarily D-xylose **74**, which is then further dehydrated to furfural **13**.[53,54] Reduction affords eventually furfuryl alcohol **1g**.[55]

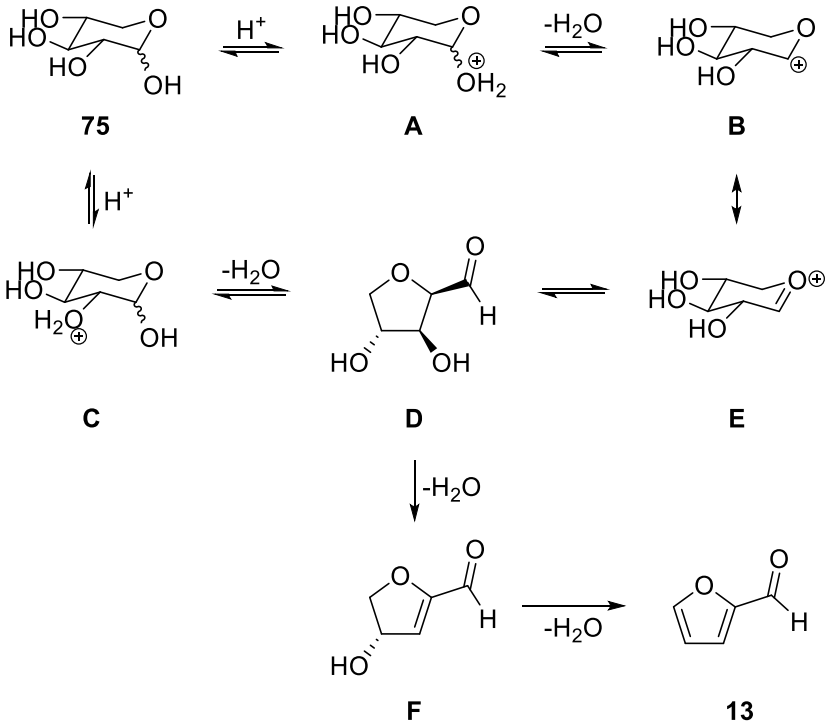


Scheme 21: Process for furfuryl alcohol production.

There exist two mechanisms proposed for the dehydration of pentoses to furfural **13** in literature, an open-chain version and a variant basing on the cyclic form of the carbohydrates (Scheme 22, Scheme 23).[56]



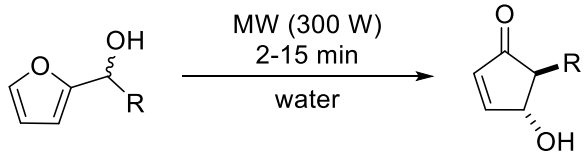
Scheme 22: Open-chain mechanism for dehydration of pentoses to furfural.[56]



Scheme 23: Cyclic-structure mechanism for dehydration of pentoses to furfural.[56]

A procedure to convert furfuryl alcohol **1g** in an aqueous solution to 4-hydroxy-2-cyclopentenone (±)-**2a** in notably high yield and purity either in the microwave or a continuous flow system was developed in our group.[28] There are many other different ways to synthesize racemic cyclopentenones,[57] but this method proved to be especially straightforward and fast. The reason for this are the high temperatures applied, which results in a significant decrease in reaction time (2–15 min for the microwave reactions and even less for the continuous flow system) compared to conventional heating methods. In the microwave reactions also different derivatives of furfuryl alcohol **1g** featuring an alkyl- (**1h**–**1k**) or phenyl (**1a**) substituent adjacent to the hydroxy functionality could be employed with yields ranging from 43–96% and selectivities from a 5:1 to 12:1 ratio of the more stable *trans*- to *cis*-diastereomer (Table 13). A study on the kinetics of the rearrangement of furfuryl alcohol **1g** by Hronec *et al.* confirms the beneficial effects of high temperatures on this reaction.[58]

Table 13: Rearrangement of different α-furylcarbinols in the microwave.[a,28]



(±)-**1g**: R = H
(±)-**1a**: R = Ph
(±)-**1i**: R = 2-butenyl
(±)-**1h**: R = Et
(±)-**1j**: R = pentyl
(±)-**1k**: R = dodecyl

trans-**2**
2a: R = H
2b: R = Ph
2c: R = 2-butenyl
2d: R = Et
2e: R = pentyl
2f: R = dodecyl

Entry	R	c [mol/L]	t [min]	Yield [%][b]	dr (*trans*/*cis*)
1	**1g**	0.25	4	43	-
2	**1a**	0.14	2	96	5:1
3	**1i**	0.15	5	73	12:1
4	**1h**	0.14	15	54	7:1
5	**1j**	0.15	5	65	7:1
6	**1k**	0.15	30	0	-

a) **1** (1.5 mmol) in H_2O (6 mL), microwave irradiation (300 W) under closed vessel conditions (200–210 °C, 15 bar). b) isolated yield.

Detrimental for the application in actual synthesis are the limited reaction volumes the microwave can be operated with (CEM Discover, 10 or 30 mL closed vessels). In combination

with the relatively high dilution of the reaction mixture, which is required for a clean reaction, the quantity of product producible in a given amount of time is restricted.

The employment of a continuous flow system (Figure 2) for the rearrangement of 4-hydroxy-2-cyclopentenone (±)-**2a** could solve this problem by reaching a high throughput and achieving a further enhancement of the yield. Therefore, despite the dilute conditions great quantities of material could be synthesized. Under subcritical conditions (240 °C, >15 bar) 4-hydroxy-2-cyclopentenone (±)-**2a** was produced in an exceptionally short reaction time (<1 min, 87% yield), making this process an attractive alternative for large-scale synthesis compared to conventional batch methods.

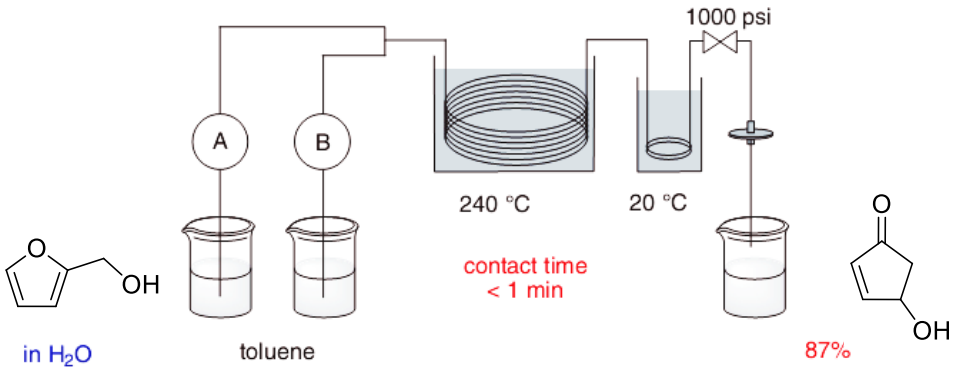
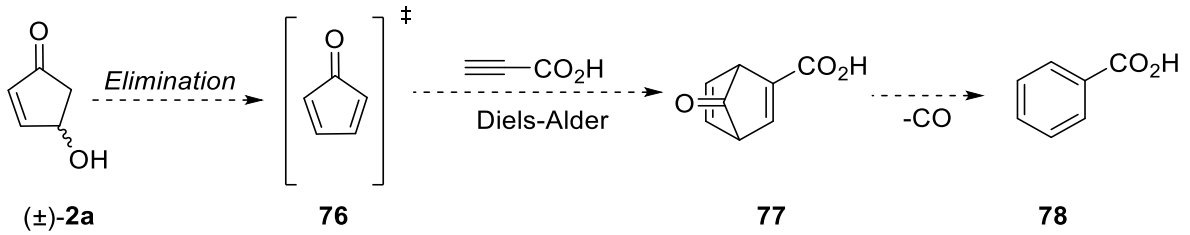


Figure 2: Setup of continuous flow system for rearrangement reaction.[28]

One of the main drawbacks of this method is the fact that the product is obtained as a dilute aqueous solution requiring the complete removal of water in the work-up. 4-Hydroxy-2-cyclopentenone (±)-**2a** is too water-soluble to be extracted with an organic solvent, therefore the water has to be evaporated in an energy-intensive step. Thus, a solution for this issue could be a further transformation of (±)-**2a** directly in the aqueous solution obtained from the continuous flow system. As one of the conceivable possibilities a Diels-Alder reaction was considered, in which the highly reactive cyclopentadienone **76**, generated from (±)-**2a** by elimination of the hydroxy group, reacts with a suitable dienophile (Scheme 24). After decarbonylation this would lead to aromatic compounds, preferably benzoic acid **78**, which could be easily precipitated from an aqueous solution.



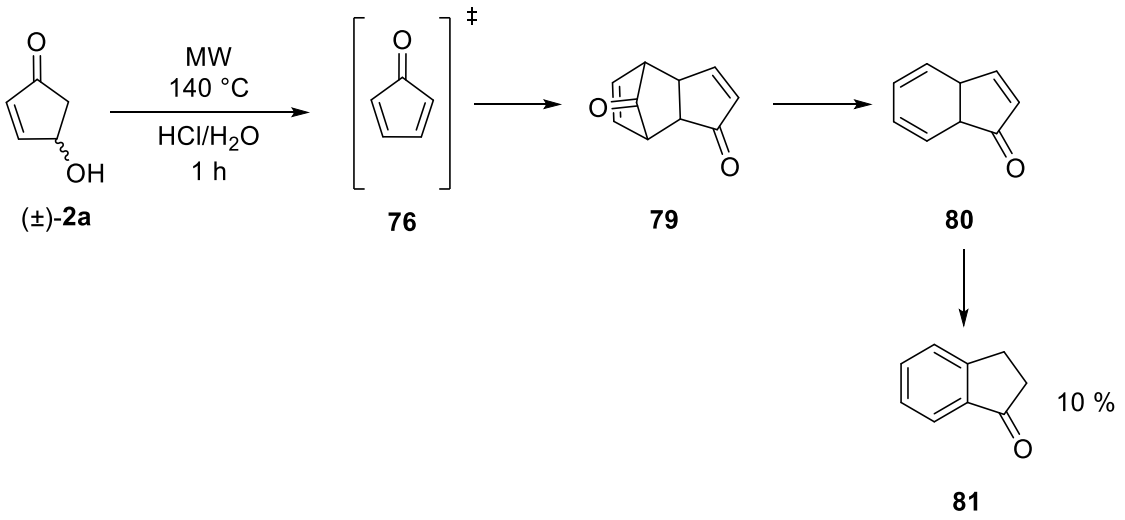
(±)-**2a** **76** **77** **78**

Scheme 24: Hypothetical synthesis of benzoic acid.

The industrial process for the production of benzoic acid **78** is generally predicated on the catalytic oxidation of toluene with molecular oxygen.[59] Toluene, however, emerges from the refinement of crude oil, more precisely from the reforming of naphtha and the distillation of BTX (benzene-toluene-xylene).[60] Consequently, through the envisioned Diels-Alder process benzoic acid **78** could be produced from renewable resources rather than from fossil material.

1.2 Generation of Cyclopentadienone by Pyrolysis

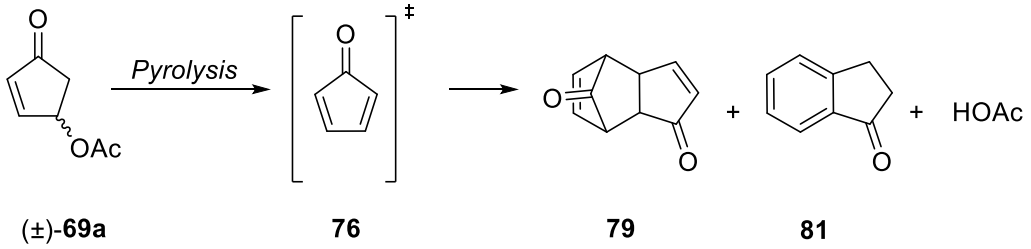
To perform a cycloaddition with a suitable diene and cyclopentadienone **76**, this elusive intermediate first had to be generated from 4-hydroxy-2-cyclopentenone (±)-**2a**. First test reactions were conducted in the microwave to investigate whether this reaction can be accomplished in an aqueous solution (Scheme 25).[61] Evidence of the existence of cyclopentadienone **76** during the reaction was found in the formation of 1-indanone **81** in 10% yield, in which two cyclopentadienone **76** molecules reacted via Diels-Alder reaction and form the dimerization adduct **79**; subsequent decarbonylation[62] and rearomatization[63] afforded the stable 1-indanone **81**.



Scheme 25: Elimination of the hydroxy group in water under microwave irradiation.[61]

Thus the generation of cyclopentadienone **76** in water was demonstrated, but the reaction produced a considerable amount of black tar and therefore could not provide a sufficient amount of the product **81**. A more effective way to generate cyclopentadienone **76** (Table 14) was found in literature[64,65] by pyrolysis of 4-acetoxy-2-cyclopentone (±)-**69a**.

Table 14: Pyrolysis of 4-acetoxy-2-cyclopentenone (±)-**69a**.[64,65]



Conditions	A[a]	B[b]
Vaporization temperature [°C]	–20	N/A
Pyrolysis temperature	850	455
Vacuum [Torr]	10^{-4}	N/A
Conversion	Complete	N/A
Products	**79** + acetic acid	**81** + acetic acid

a) ref 64. b) ref 65.

That idea was leading away from the pursued path of finding reaction conditions in water, but the possibility of trapping **76** via Diels-Alder reactions could be investigated. In Table 14 the conditions for the pyrolysis of 4-acetoxy-2-cyclopentone (±)-**69a** from the two literature examples are described.

First of all a device (Figure 3) to perform a pyrolysis reaction was constructed. Through a pyrolysis oven, heatable to a maximum temperature of 1000 °C, a quartz glass tube was directed on which one end the compound could be evaporated. On the other end of the tube a specifically manufactured cooling trap was installed that could be charged with a cooling mixture of dry ice and acetone achieving a temperature of –78 °C. Vacuum could be applied with a minimum pressure of 0.07 mbar.

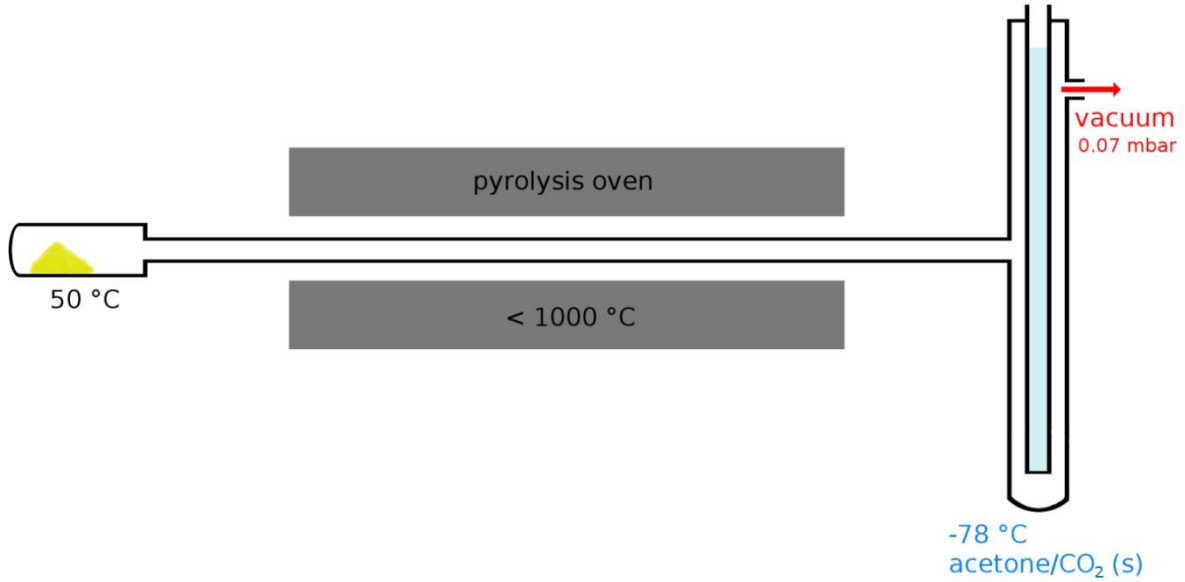


Figure 3: Setup of the pyrolysis device.

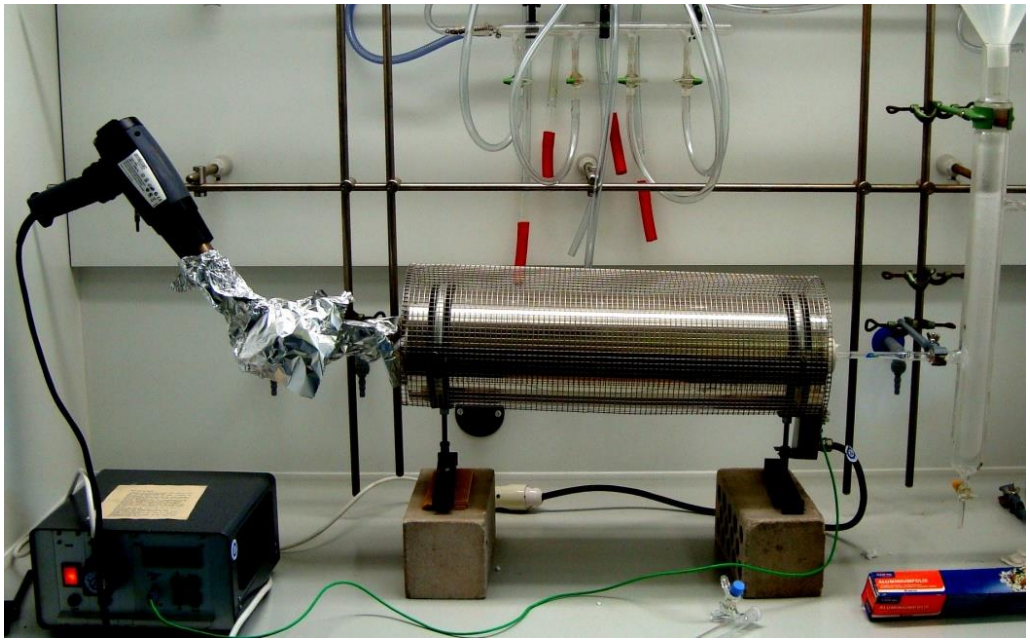


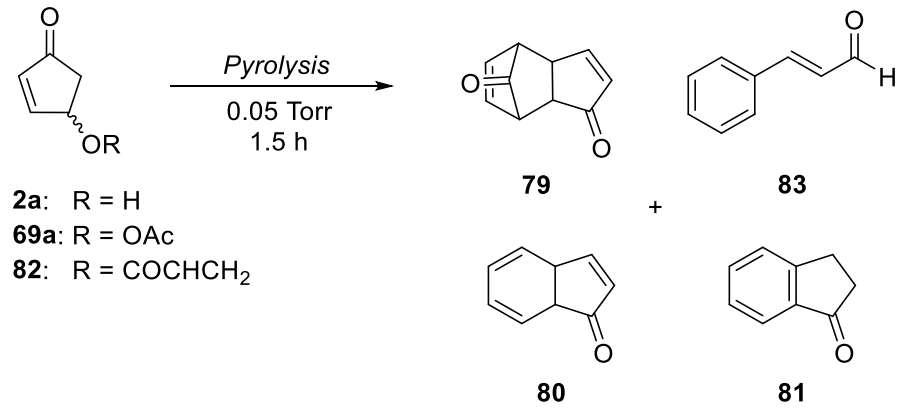
Figure 4: Picture of the pyrolysis device.

Figure 5: Picture of crystals forming on the cooling trap.

4-Acetoxy-2-cyclopentone (±)-**69a**, 4-hydroxy-2-cyclopentenone (±)-**2a**, (±)-4-acryloyloxy-2-cyclopentenone (±)-**82** and the cyclopentadienone dimerization adduct **79** were subjected to pyrolysis at different temperatures (Table 15). The primary objective of these pyrolysis experiments was to generate cyclopentadienone **76** and by addition of a dienophile to accomplish a Diels-Alder reaction in the pyrolysis apparatus resulting in benzoic acid or a derivative thereof. To prevent the dimerization of cyclopentadienone **76** before reaching the cooling trap, its concentration in the pyrolysis tube was kept very low by vaporizing the starting

material steadily at a low rate (1.5 h for approximately 0.5 g of substance). Initially, the behaviour of the pure compounds without the addition of a dienophile under pyrolysis conditions was studied. First 4-acetoxy-2-cyclopentenone (±)-**69a** was examined which eliminated acetic acid smoothly in the pyrolysis device (entry 3–7, Table 15). By observing the dimerization product **79** on the cooling trap, a brief existence of cyclopentadienone **76** can be assumed. At temperatures of less than 500 °C significant amounts of starting material (±)-**69a** were recovered (entry 3 and 4, Table 15). At 600 °C the yield of dimerization product **79** peaked with 76%, but also compounds like **93**, **94** and **83** were observed (entry 5, Table 15). The yield of **79** decreased again with rising temperatures, and increasingly complex mixtures made the isolation of distinct compounds more difficult (entry 6 and 7, Table 15). Literature examples state that by dimerization of cyclopentadienone **76** exclusively the *endo*-isomer of **79** is formed,[66] which was confirmed by comparison with NMR data found in the literature.[67,68]

Table 15: Pyrolysis of different 4-substituted 2-cyclopentenones.[a]

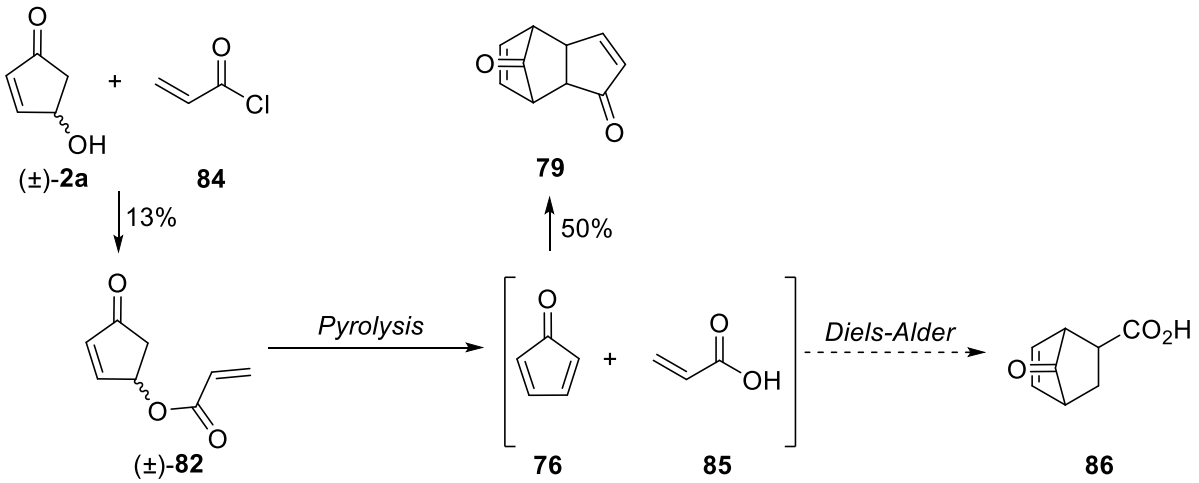


Entry	R	Vaporization T [°C]	Pyrolysis T [°C]	Yield [%][b]
1	H	100	600	**2a**: 40
2	H	100	800	**2a**: 22, **79**: 2
3	$COCH_3$	50	350	**69a**: 91
4	$COCH_3$	50	500	**69a**: 52, **79**: 21
5	$COCH_3$	50	600	**69a**: 2, **79**: 76, **80**: 4, **81**: 2
6	$COCH_3$	50	700	**79**: 43
7	$COCH_3$	50	800	**79**: 15, **83**: 9
8	$COCH=CH_2$	50	600	**79**: 50, **81**: 5
9	**79**	100	600	**80**, **81**, **83**: 30 combined

a) **2a**/**69a**/**82**/**79** (500 mg). b) isolated yield.

Using 4-hydroxy-2-cyclopentenone (±)-**2a** as starting material resulted mainly in the formation of black tar in the pyrolysis tube (entry 1 and 2, Table 15). To confirm the origin of the side products **80**, **81** and **83**, which were assumingly derived from the dimerization product **79**, the latter compound was subjected to pyrolysis resulting in the previously observed side products and some other unidentified compounds (entry 9, Table 15). Generally, the dimerization product **79** and acetic acid condensed mostly at the cooling trap (Figure 5), but some amount of those compounds also accumulated at the end of the pyrolysis tube. Moreover, at temperatures over 600 °C independent of the starting material, increasing amounts of a black precipitate emerged in the pyrolysis tube. In all pyrolysis experiments, 1-indanone **81**, which was the main product in the example published by DePuy,[65] was not observed at all or only in traces.

After confirming the formation of **79**, one major obstacle was the addition of the dienophile to the incoming cyclopentadienone **76** in the pyrolysis tube or the cooling trap. This proved to be technically difficult, therefore, as a solution the covalent binding of the dienophile directly to the cyclopentenone moiety which should be evaporated was considered. By experiencing the high temperatures in the pyrolysis tube, the bond would be cleaved via elimination to generate cyclopentadienone **76** and simultaneously release the dienophile. Therefore, with every cyclopentadienone **76** that occurs one dienophile would be present in its vicinity. Compound (±)-**82**, prepared from 4-hydroxy-2-cyclopentenone (±)-**2a** and acryloyl chloride **84**, could lose acrylic acid **85**, functioning as the dienophile, upon heating (Scheme 26).



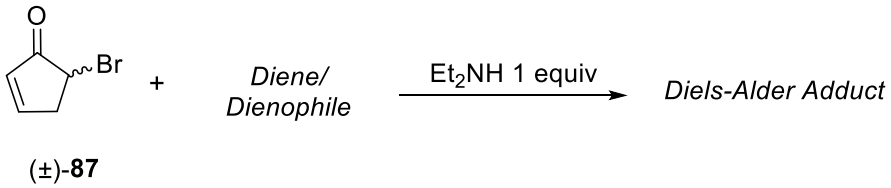
Scheme 26: Attempted Diels-Alder reaction of **76** with covalently bound dienophile.

Unfortunately, by pyrolysing (±)-**82** only the dimerization product **79** and 1-indanone **81** could be observed (entry 8, Table 15). Therefore, another approach to the generation of cyclopentadienone **76** was investigated, which is described in the next chapter that explicates more closely this reaction in solution.

1.3 Diels-Alder Reaction in Solution

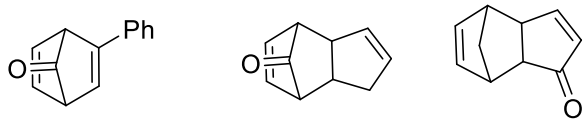
Goliasch *et al.* describe in their paper the generation and reactions of the highly reactive cyclopentadienone **76**.[69] Their experiments are conducted with 5-bromo-2-cyclopentenone (±)-**87** as precursor for the generation of **76**. By treatment of (±)-**87** with diethylamine at –30 °C in Et_2O they observed the cyclopentadienone dimer **79** as the single product, whereas higher temperatures over 20 °C led to more polymerization products and a decline in the yield of **79**. Treatment of (±)-**87** with other bases led to similar results but varying amounts of **79** (influence of base on yield of dimerization product **79**: diethylamine 78%, piperidin 39%, N-methylanillin 18%, pyridine 12%, N-ethyl-cyclohexylamine 4.1%, dimethylamin 0.4%, chinolin and triphenylphosphin did not react). Reaction of 5-bromo-2-cyclopentenone (±)-**87** with diethylamine and a huge excess of phenylacetylene resulted in a minor amount of Diels-Alder adduct (2%). The main product of the reaction was the dimerization product **79**. Diels-Alder reactions with maleic anhydride, cyclohexene, acetylenedicarboxylic dimethylester and tetracyanoethylene failed to yield any Diels-Alder adduct (Table 16). By using diethylamine in cyclopentadiene as solvent at –70 °C and adding 5-bromo-2-cyclopentenone (±)-**87** over 2 h, the Diels-Alder adducts **89** and **90** (Table 16, entry 1) were observed in 15% yield (combined yield, unspecified ratio).

Table 16: Diels-Alder reactions with cyclopentadienone **76**.[69]



(±)-**87**

Observed mixed Diels-Alder adducts:



88 **89** **90**

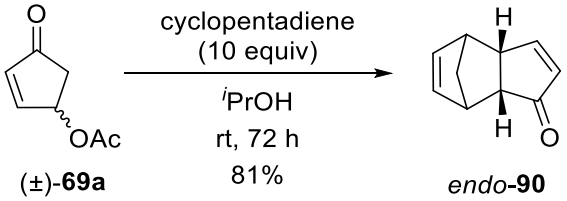
2% 15%[a]

Entry	Dienophile/Diene	Solvent	T [°C]	Result
1	Cyclopentadiene	-	–70	**79**,[a] **89**/**90**: 15%
2	Phenylacetylene	-	–30	**79**: 84%, **88**: 2%
3	Cyclohexene	N/A	N/A	**79**[b]
4	Maleic anhydride	N/A	N/A	**79**[b]
5	Dimethylacetylenedicarboxylate	N/A	N/A	**79**[b]
6	Tetracyanoethylene	N/A	N/A	-

a) ratio not specified. b) yield not specified.

In an own test experiment 4-acetoxy-2-cyclopentenone (±)-**69a** was reacted with 10 equivalents of cyclopentadiene in ^{i}PrOH at rt (Scheme 27). This gave 81% of the Diels-Alder adduct *endo*-**90** (from NMR spectra[70,71] of *endo*- and *exo*-isomer of **90** it can be concluded that only the *endo*-product was formed) which leads to the conclusion that (±)-**69a** reacted as dienophile and the leaving group was expelled later (on the column by purifying the compound, because the crude ^{1}H-NMR did not match the clean spectrum of **90**). Consequently, this could also apply to the literature example (Table 16), and partly not cyclopentadienone **76** reacted as diene, but the starting material (±)-**87** to form adduct **90**. However, the formation of **89** in the literature example[69] can only be explained by a Diels-Alder reaction in which cyclopentadienone **76** acts

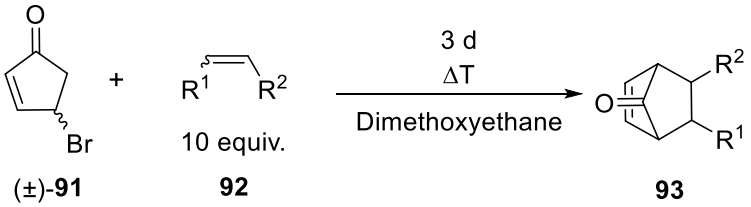
as the diene, but as the ratio of **89**/**90** is not specified a definitive statement about **76** reacting as diene cannot be given.



Scheme 27: Diels-Alder reaction of 4-acetoxy-2-cyclopentenone and cyclopentadiene.

In another publication covering the topic of Diels-Alder reactions with cyclopentadienone **76** Simoni *et al.* showed that with heating of (±)-**91** for 3 days and an excess of dienophile a Diels-Alder reaction took place and the mixed adduct could be obtained in low yield.[72] It has to be emphasized that the key to success as the authors stated was the very slow generation of **76** (over 3 days), to prevent it from reacting with itself to form the dimerization product **79** rather than the mixed adducts.

Table 17: Diels-Alder reaction with cyclopentadienone **76**.[72]

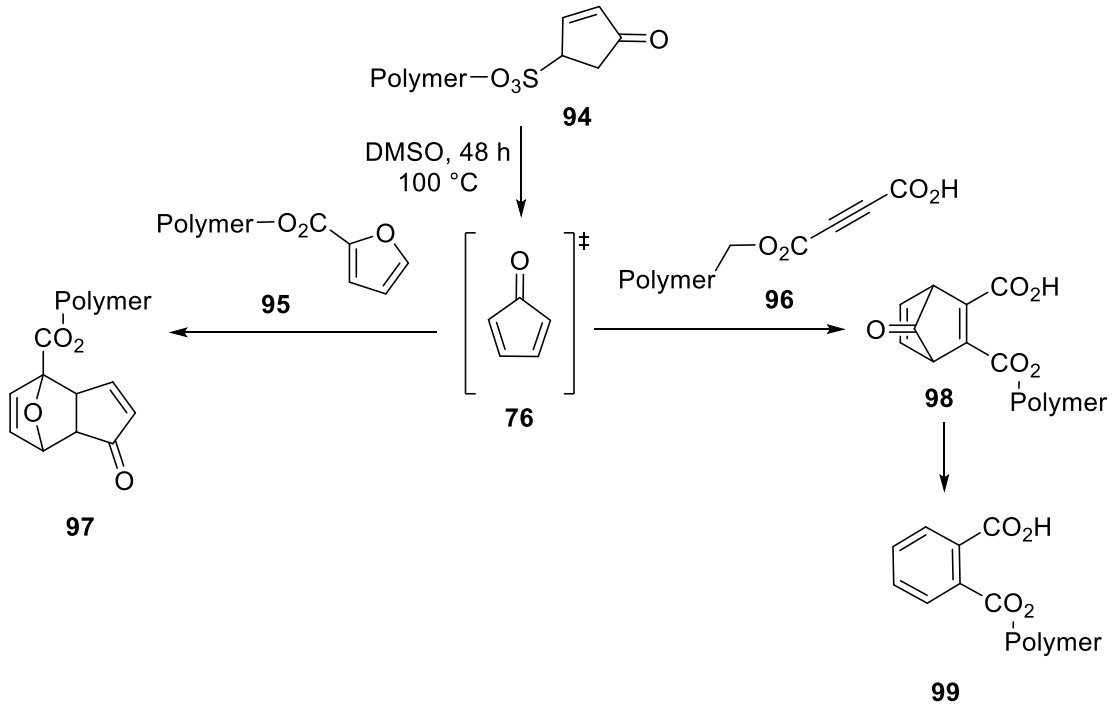


R^1	R^2	Yield [%]
-H	$-CO_2Et$	20
$-CH_3$	$-CO_2Me$	12.5
$-CO_2Me$	$-CO_2Me$	7

Another instance of a successful demonstration of cyclopentadienone **76** acting as diene or dienophile is the three-phase-test (to prove the existence of cyclopentadienone **76**) by Gavina *et al.*[73] They could react polymer-bound dienes **95** or dienophiles **96** with cyclopentadienone **76** being generated from a likewise polymer-bound precursor **94**. Both polymers were separated spatially in a solvent filled confined volume, so that a reaction of the polymer-bound

diene/dienophile with the polymer-bound cyclopentadienone precursor implies a diffusion of cyclopentadienone **76** through the solvent to reach the other reactant. This should prove the intermediate existence of cyclopentadienone **76**. In Table 18 the different trapping resins used for the 3-phase test are described and the yields of the related Diels-Alder adducts are given.

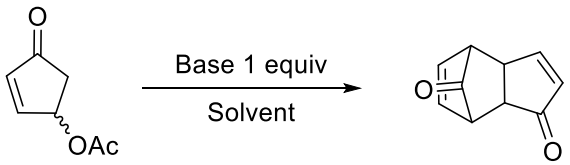
Table 18: Three-phase test by Gavina *et al.*[73]



Entry	Trapping Resin	Yield [%]
1	**P**-CH_2O_2C-C≡C-CO_2H	17
2	**P**-CH_2O_2C-HC=CH-CO_2H	11
3	**P**-CH_2-($NC_4H_2O_2$)	6
4	**P**-CH_2-O_2C-HC=CH-CH_3	51
5	**P**-O_2C-C_6H_4-N=N-$C_6H_2(OH)_2$	21
6	**P**-CH_2O_2C-C_4H_3O	2
7	**P**-CH_2-CO_2-HC=CH-HC=CH_2	72

To perform Diels-Alder attempts in solution, it was ascertained beforehand if the dimerization product **79** could be generated smoothly with satisfactory yields and the most suitable conditions for the elimination reaction were determined. The optimum reaction conditions, reaching a yield of 77%, in which also the reaction time was in an acceptable time range, are displayed in entry 4 (Table 19), using NaOH as a base in ^{i}PrOH. Therefore, these conditions were selected for the attempts of the Diels-Alder reactions. Na_2CO_3 and Cs_2CO_3 could also be employed in this reaction (entry 5 and 6, Table 19). Moreover, it was examined if tertiary amines like Et_3N work as bases, but this proved to be not the case (entry 7 and 8, Table 19).

Table 19: Elimination and dimerization under basic conditions.[a]

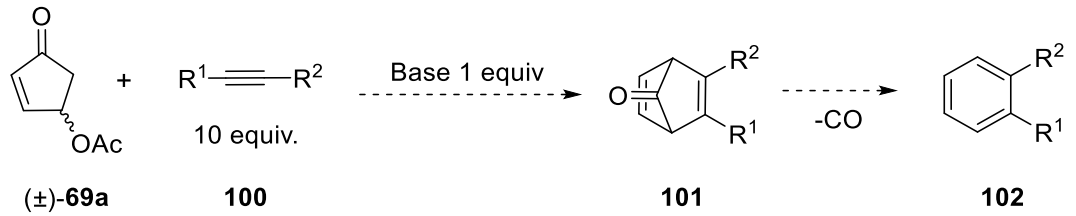


(±)-**69a** **79**

Entry	Base	Solvent	T [°C]	t [h]	Yield [%][b]
1	NaOH	H_2O	65	24	26
2	NaOH	MeOH	65	24	28
2	NaOH	EtOH	65	24	43
3	NaOH	^{i}PrOH	65	24	55
4	NaOH	^{i}PrOH	rt	24	77
5	Na_2CO_3	^{i}PrOH	rt	12 d	86
6	Cs_2CO_3	^{i}PrOH	rt	17	72
7	Et_3N	^{i}PrOH	rt	5 d	0[c]
8	Et_3N	^{i}PrOH	reflux	24	0[c]

a) **69a** (0.7 mmol). b) isolated yield. c) quant. recovery of starting material.

After those preliminary experiments Diels-Alder reactions were explored (Scheme 28, Table 20 and Table 21). To ensure that cyclopentadienone **76** was generated slowly and did not react with itself or the starting material 4-acetoxy-2-cyclopentenone (±)-**69a**, it was added steadily over 24 h in a dilute solution to the diene or dienophile in a basic solution via syringe pump.



Scheme 28: Intended synthesis of aromatic compounds.

As detailed in the literature example[69] mentioned earlier in this chapter, phenylacetylene gave a small amount of Diels-Alder adduct when reacted with 5-bromo-2-cyclopentenone (±)-**100** and a suitable base to provoke the elimination to cyclopentadienone **76**. Therefore, this was considered to be a viable dienophile in the Diels-Alder reaction, hence this and also diphenylacetylene were examined (entry 1 and 2, Table 20). But unfortunately just the dimerization product **79** of cyclopentadienone **76** was observed. Other dienophiles tested were acetylene carboxylic acid or an ester thereof, because these compounds worked in the literature precedents[63,73] already mentioned. This did not lead to the desired product, and again cyclopentadienone dimer **79** and also some of the starting material (±)-**69a** were the only compounds isolated.

Table 20: Different acetylene derivatives as dienophiles.[a]

Entry	R^1	R^2	Solvent	Base	Temperature	Product
1	-Ph	H	^{i}PrOH	NaOH	rt	**79**
2	-Ph	-Ph	^{i}PrOH	NaOH	rt	**79**
3	$-CO_2H$	$-CO_2H$	^{i}PrOH	NaOH	rt	(±)-**69a**
4	$-CO_2Me$	$-CO_2Me$	^{i}PrOH	NaOH	rt	**79**, (±)-**69a**

a) (±)-**69a** (0.7 mmol, added over 24 h in 17 mL ^{i}PrOH via syringe pump), NaOH (1 equiv, 0.7 mmol), **100** (10 equiv, 7 mmol) in 20 mL ^{i}PrOH.

As those attempts failed, other dienophiles and also dienes were investigated. But again no Diels-Alder product could be observed as displayed in Table 21. Therefore, the only successful Diels-Alder reaction so far (Scheme 27) was the reaction of (±)-**69a** and cyclopentadiene as diene without using a base so that cyclopentadiene could react directly with (±)-**69a** to form adduct **90** by eliminating the hydroxy group afterwards.

Table 21: Experiments with other dienes/dienophiles.[a]

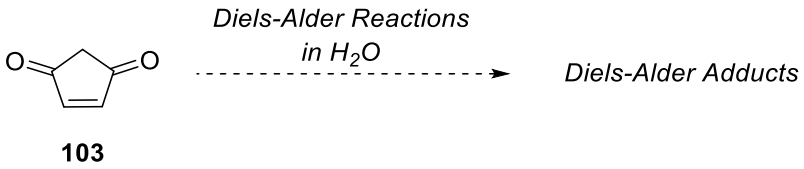
Entry	Diene/Dienophile	Solvent	Base	T [°C]	Result
1	furan	furan/ ^{i}PrOH 20:1	NaOH	rt	**79**
2	maleic anhydride	^{i}PrOH	NaOH	rt	(±)-**69a**
3	maleic anhydride	EtOAc	NaOH[a]	rt	(±)-**69a**
4	maleic anhydride	DCM	NaOH[a]	rt	(±)-**69a**
5	cyclopentadiene	^{i}PrOH	NaOH	rt	**79**
6	ethyl acrylate	^{i}PrOH	NaOH	rt	**79**

a) (±)-**69a** (0.7 mmol, added over 24 h in 17 mL ^{i}PrOH via syringe pump), NaOH (1 equiv, 0.7 mmol), diene/dienophile (10 equiv, 7 mmol) in 20 mL ^{i}PrOH. b) plus methyltrioctylammmoium chloride (1 equiv).

Cyclopentadienone **76** is a remarkably reactive intermediate (it could be observed and spectroscopically analyzed only in a 10 K Argon-matrix)[64] and seems to prefer to react rather with itself in a dimerization reaction than with other dienophiles. This observation is supported by B3LYP/6-31G* calculations that come to the conclusion that the loss of anti-aromaticity of **76** in the transition structure of the cycloaddition of two molecules of **76** is the driving force for the enhanced dimerization preference.[66] Nonetheless, the dimerization product **79**, which can be obtained in reasonable yields from furfuryl alcohol **1g** as a renewable resource, can be used to synthesize 1-indanone **81**,[74] which is itself a valuable compound.

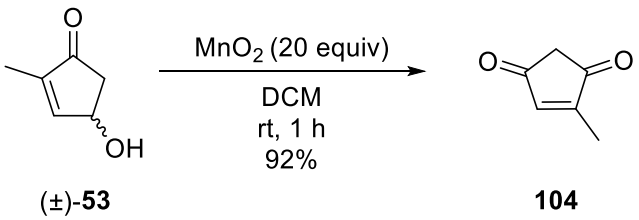
1.4 Oxidation before Cycloaddition

As the approach of employing cyclopentadienone **76** in a Diels-Alder reaction failed, the use of 4-hydroxy-2-cyclopentenone (±)-**2a** directly in a Diels-Alder reaction was considered. But (±)-**2a** itself is a rather unreactive dienophile in Diels-Alder reactions (mostly requiring forcing reaction conditions or the stoichiometric use of Lewis acids),[75] therefore its transformation to dione **103** as a better dienophile was contemplated to solve this problem.



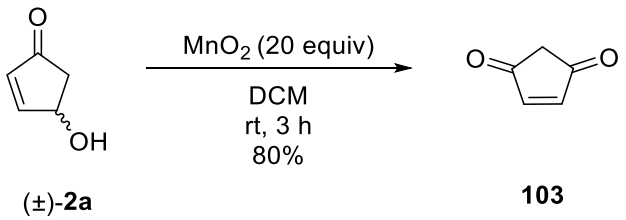
Scheme 29: Diels-Alder reaction with cyclopentenedione.

Since a subsequent process to the rearrangement of furfuryl alcohol **1g** in the continuous flow system (to prevent the energy wasting work-up by converting the product to a less water-soluble compound) was envisioned, the oxidation had to be ultimately conducted in water. Consequently, an oxidation method had to be found that was environmentally benign and that would also work in water before any cycloaddition reactions could be investigated. The oxidation of (±)-**2a** is not known in literature, but oxidations starting from cyclopent-4-ene-1,3-diol to give cyclopentenedione **103** typically are carried out in acidic CrO_3 solutions[76] (Jones-oxidation). As chromium reagents are highly toxic and cancerogenic, a less hazardous alternative had to be developed. Shiota *et al.* reported the oxidation of the allylic alcohol functionality of a similar molecule to (±)-**2a** with MnO_2 as the oxidant (Scheme 30).[77]



Scheme 30: Oxidation of (±)-4-hydroxy-2-methyl-2-cyclopentenone with MnO_2.[77]

The reaction with MnO_2 and 4-hydroxy-2-cyclopentenone (±)-**2a** as substrate gave the enedione **103** in good yields (Scheme 31). Nevertheless, these conditions still did not meet the requirements for a sustainable reaction, as it was carried out in DCM and 20 equiv of MnO_2 were used.



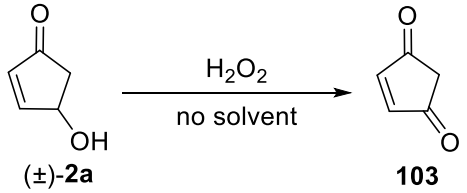
(±)-**2a** **103**

Scheme 31: Oxidation of (±)-4-hydroxy-2-cyclopentenone with MnO_2.

Therefore, catalytic methods employing hydrogen peroxide or oxygen as the oxidant in aqueous medium were investigated.

Initially oxidations with H_2O_2 as the oxidant were tested, as the only byproduct of those reactions is water. Different literature known oxidation methods in aqueous solution were applied to compound (±)-**2a** (Table 22). Sain *et al.* describe the oxidation of various secondary and one allylic secondary alcohol with an aqueous H_2O_2/HBr-solution.[78] Unfortunately, applied on substrate (±)-**2a** this did not lead to any conversion (entry 1, Table 22). Similarly, for the oxidation of secondary and allylic secondary alcohols in water applicable is the method described by Noyori *et al.* with Na_2WO_4 as catalyst.[79] As the recommended 90 °C reaction temperature led to decomposition of the material, the temperature was lowered to 40 °C producing similar results (entry 2 and 3, Table 22). The same reaction at rt did not give any conversion (entry 4, Table 22). Also the use of another tungsten-based catalyst, $Na_9[SbW_9O_{33}]$, which was described in a publication by Manikandan *et al.*,[80] resulted mostly in decomposition (entry 5 and 6, Table 22). Only when the reaction was performed at rt, besides the decomposed material traces of the product **103** have been detected and also 5% of the epoxidation product could be isolated (entry 7, Table 22). Furthermore, a method published by Beller *et al.* was applied, using $Fe(NO_3)_3/KH_2PO_4$ as catalyst system.[81] This resulted again only in the decomposition of the starting material (±)-**2a** (entry 8 and 9, Table 22).

Table 22: Oxidation of (±)-**2a** with H_2O_2.[a]



(±)-**2a** **103**

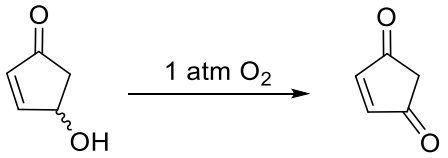
Entry	Catalyst	T [°C]	t	Result
1[b]	HBr	80	3 d	no conversion
2[c]	Na_2WO_4	90	18 h	decomposition
3[c]	Na_2WO_4	40	24 h	decomposition
4[c]	Na_2WO_4	25	18 h	no conversion
5[d]	$Na_9[SbW_9O_{33}]$	80	24 h	decomposition
6[d]	$Na_9[SbW_9O_{33}]$	40	24 h	decomposition
7[d]	$Na_9[SbW_9O_{33}]$	25	5 d	decomposition[e]
8[f]	$Fe(NO_3)_3/KH_2PO_4$	75	5 h	decomposition
9[f]	$Fe(NO_3)_3/KH_2PO_4$	25	24 h	decomposition

a) (±)-**2a** (2 mmol). b) (±)-**2a** (1 mmol), HBr (20 mol%), H_2O_2 30% (2 equiv). c) Na_2WO_4 (0.2 mol%), $(CH_3(n\text{-}C_8H_{17})_3N)Cl$ (0.2 mol%), H_2O_2 30% (l equiv). d) $Na_9[SbW_9O_{33}]$ (0.01 mol%), $(CH_3(n\text{-}C_8H_{17})_3N)Cl$ (0.09 mol%), H_2O_2 30% (5 equiv). d) 5% epoxide (10:1 trans/cis), traces of **116**. f) (±)-**2a** (3 mmol), $Fe(NO_3)_3$ (0.02 mol%), KH_2PO_4 (1 mol%), H_2O_2 30% (1.5 equiv).

Since the oxidations with H_2O_2 were unsuccessful, also oxidations with molecular oxygen were studied (Table 23). Kaneda *et al.* published a method for oxidizing a great variety of different alcohols, including allylic alcohols, with Pd/Hydroxyapatit as the catalyst and O_2 at atmospheric pressure.[82] Applying these conditions to substrate (±)-**2a** led to no conversion (entry 1 and 2, Table 23). The method of Rhee *et al.* for oxidizing benzylic and allylic alcohols[83] resulted only in decomposition (entry 3, Table 23). Also Pt/C, which was used by Matsumura *et al*. in aqueous medium,[84] did not give any conversion of the starting material (entry 4, Table 23). Different ruthenium-based catalyst which were known for their use in oxidations with O_2 were

examined,[85] but again this led not to the desired product **103** (entry 5–8, Table 23). Furthermore, different palladium catalysts were tested unsuccessfully (entry 9–11, Table 23).[86]

Table 23: Oxidation of (±)-**2a** with O_2.[a]

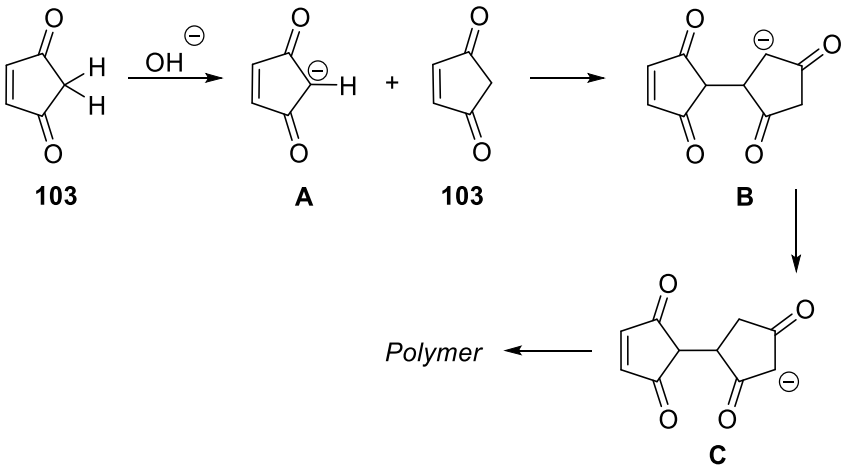


(±)-**2a** **103**

Entry	Catalyst	Solvent	T [°C]	t	Result
1[b]	Pd/Hydroxyapatit	toluene	reflux	3 d	no conversion
2[b]	Pd/Hydroxyapatit	H_2O	reflux	3 d	no conversion
3[c]	Pd/C, $NaBH_4$	H_2O	25	5 d	decomposition
4[d]	Pt/C	H_2O	80	2 d	no conversion
5[e]	$RuCl_3$	H_2O/toluene	80	24 h	decomposition
6[f]	$Ru_2(OAc)_2(CO_3)_2$	H_2O/toluene	80	2 d	decomposition
7[g]	$Ru(PPh_3)_3Cl_2$	DCM	25	5 d	partial decomposition
8[g]	$Ru(PPh_3)_3Cl_2$	H_2O/MeOH	25	5 d	no conversion
9[h]	Pd/C	H_2O	80	5 d	no conversion
10[i]	$PdCl_2$	DCM	25	2 d	no conversion
11[i]	$PdCl_2$	DCM	reflux	2 d	no conversion

a) (±)-**2a** (1 mmol). b) Pd/Hydroxyapatit (0.2 mol%). c) Pd/C 10% (2.5 mol% Pd), $NaBH_4$ (10 mol%). d) (±)-**2a** (0.51 mmol), Pt/C 10% (10 mol% Pt). e) $RuCl_3$ (10 mol%), H_2O/toluene 3:2. f) $Ru(OAc)_4Cl$ (10 mol%), Na_2CO_3 (20 mol%), H_2O/toluene 5:2. g) $RuCl_3 \cdot H_2O$ (10 mol%), PPh_3 (10 mol%), H_2O/MeOH 1:1. h) Pd/C 10% (10 mol% Pd). i) $PdCl_2$ (10 mol%).

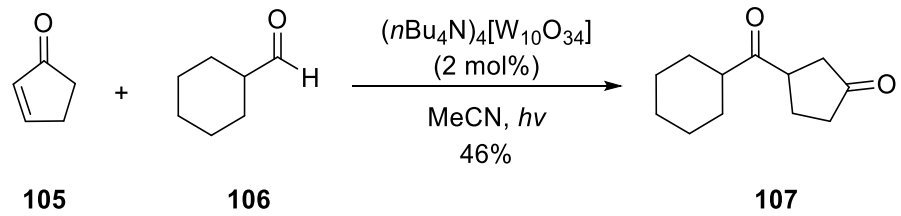
One obstacle was the fact that the addition of any stronger base to 4-hydroxy-2-cyclopentenone (±)-**2a** (only tertiary amines are compatible) led to instantaneous decomposition, therefore basic conditions had to be avoided. Another complication was that according to literature the product of the oxidation **103** itself is not very stable in basic aqueous solution and will decompose eventually (Scheme 32).[87]



Scheme 32: Polymerization of cyclopentenedione.[87]

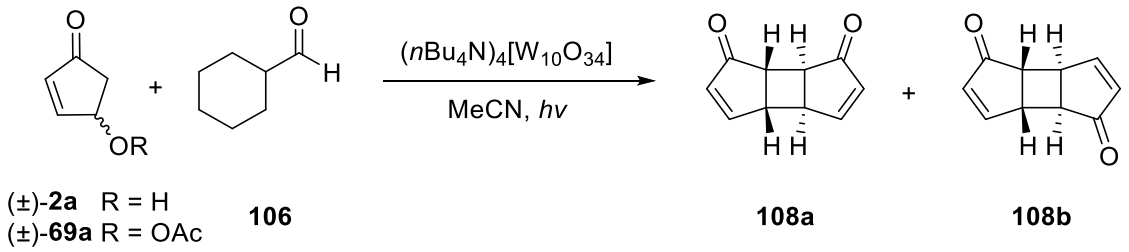
1.5 [2+2]-Cycloaddition

As an alternative strategy for converting 4-hydroxy-2-cyclopentenone (±)-**2a** an acylation of (±)-**2a** as described by Albini *et al.* with cyclopentenone **105** was taken into consideration.[88] Hereby a photochemically generated acyl radical, catalyzed by tetrabutylammonium decatungstate (TBADT), added to an α,β-unsaturated system (Scheme 33). Albini and co-workers irradiated the reaction mixture with six 15 W lamps with an emission centered at 310 nm.



Scheme 33: Photocatalyzed acylation.[88]

The experiments with 4-hydroxy-2-cyclopentenone (±)-**2a** were conducted using conventional UV-lamps normally used for thin layer chromatography (40 W UV-lamp with an emission at 366 nm). Using (±)-**2a** as substrate, besides the recovered starting material (±)-**2a** unfortunately only a complex mixture was obtained (entry 1, Table 24).



(±)-**2a** R = H
(±)-**69a** R = OAc

106 **108a** **108b**

Scheme 34: [2+2]-Cycloaddition products instead of acylation.

Switching the starting material to (±)-**69a** gave not the acylation product but instead the [2+2]-cycloaddition products **108a** and **108b** were isolated (entry 2, Table 24). Without adding the aldehyde this transformation even gave better results with 88% combined yield of cycloaddition products (entry 3, Table 24). Leaving out both the catalyst and the aldehyde, the reaction furnished the cycloaddition products in almost the same quantity (entry 4, Table 24). By comparison of the crude NMR data with the isolated products after column chromatography, it can be concluded that the acetyl group was eliminated during work-up. The two different isomers were identified by comparison with published NMR data.[89,90] Furthermore, the same products were observed by another group, irradiating (±)-**69a** with a high pressure mercury lamp.[91]

Table 24: Reaction conditions for the photoreaction.

Entry	R	Aldehyde [equiv]	Catalyst [mol%]	t [h]	Yield [%][a]
1[b]	H	1.1	2	24	**106**: 36[c]
2[b]	OAc	1.1	2	24	**69a**: 27, **108a**+**108b**: 72[d]
3[b]	OAc	0	2	40	**108a**+**108b**: 88[d]
4[e]	OAc	0	0	48	**108a**+**108b**: 80[d]

a) isolated yield. b) (±)-**2a**/**69a** (0.5 mmol). c) as inseparable mixture with other by-products. d) 1:1 ratio. e) (±)-**69a** (1 mmol).

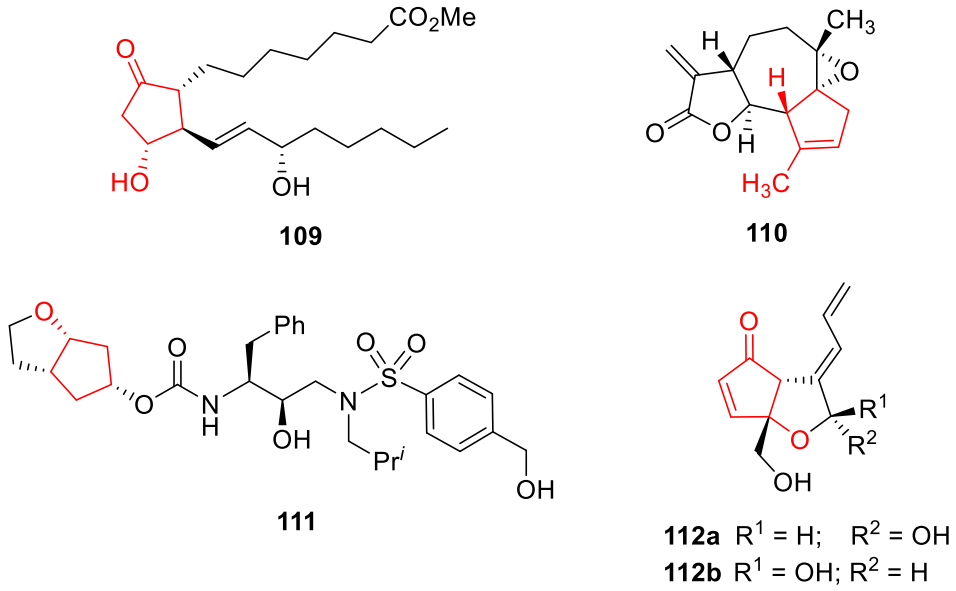
1.6 Conclusion

The main task to produce benzoic acid from 4-hydroxy-2-cyclopentnenone (±)-**2a** by Diels-Alder reactions with cyclopentadienone **76** and a suitable dienophile was not achieved. Instead, the dimerization product **79** was observed. This compound could be synthesized from 4-acetoxy-2-cyclopentenone (±)-**69a** in a facile procedure and with good yields. Oxidations of 4-hydroxy-2-cyclopentenone (±)-**2a** under sustainable conditions were not accomplished, though the oxidation with MnO_2 in DCM was successful.

2. Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones

2.1 Introduction

Enantiomerically pure 4-hydroxy-2-cyclopentenone **2a** and derivatives thereof have served as valuable building blocks in the synthesis of many important organic compounds. It has been used in the synthesis of prostaglandin PGE_1 methyl ester **109**,[92] the farnesyltransferase inhibitor Arglabin™ **110**,[93] the HIV protease inhibitor GRL-06579 **111**[94] and the Didemnenones A **112a** and B **112b**[95] (Scheme 35).

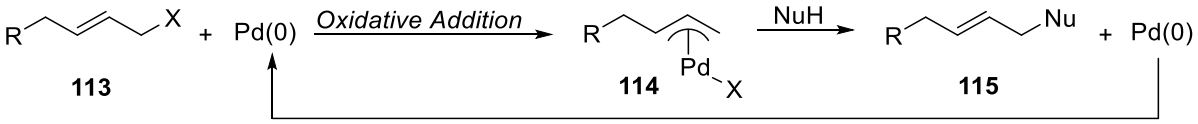


Scheme 35: Natural products and pharmaceuticals from enantiomerically pure 4-hydroxy-2-cyclopentenone **2a**.[92,93,94,95]

Many ways to synthesize enantiopure **2a** and derivatives thereof utilizing the chiral pool,[96] chiral reagents[97] or catalysts[98] have been developed. A majority of these transformations involve selective changing of the oxidation state of the corresponding 1,3-*cis*-diol[99] or 1,3-diketone.[100] The direct deracemization of (±)-**2a** or its *O*-acyl derivative (±)-**69a** was achieved by enzymatic resolution with lipases[101] or penicillin G acylase.[102] Kinetic resolution of (±)-**2a** had also been achieved by catalytic asymmetric isomerization[103] or hydrogenation.[104] A review summarizing the synthesis of both enantiopure and racemic (±)-**2a** as well as its use in synthesis has been published in 2010.[4]

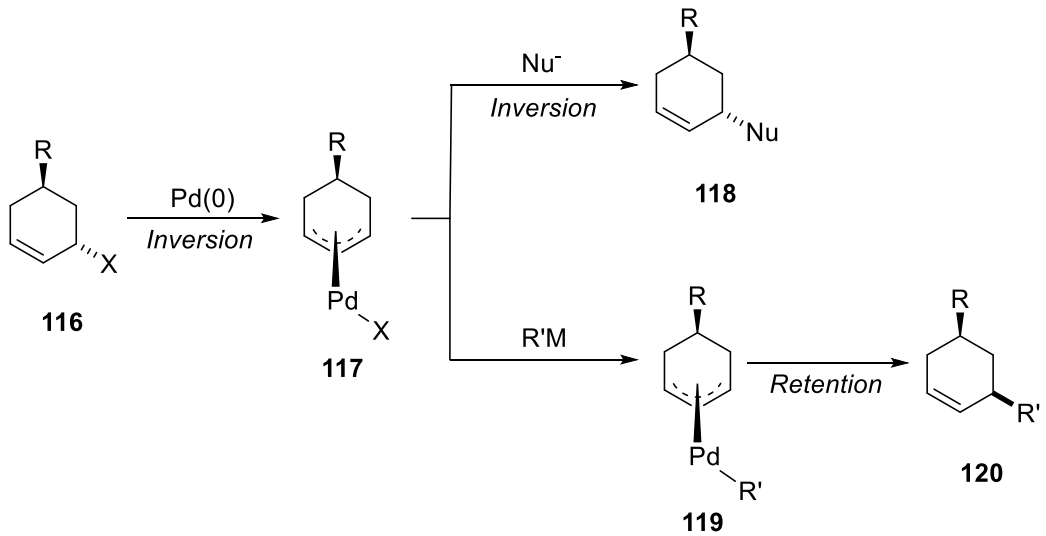
The application of π-allylpalladium chemistry[105,106] for the purpose of synthesizing enantiopure **2a** has not been investigated, despite the remarkable progress that was made in this field since the discovery of the reactivity of π-allylpalladium complexes towards nucleophilic species.[107]

The reaction principle of the palladium-catalyzed allylic substitution, which has been developed in the early 1970s,[108] is outlined in Scheme 36. The allylic compound **113** (e. g. X = -OAc, -OCO_2R, -OCONHR, -epoxide, -OPh, -OH, -$OP(O)(OR)_2$, -Cl, -NO_2, -SO_2R, -NR_2) forms the π-allylpalladium-complex **114** via oxidative addition to a Pd(0)-species. These complexes are electrophilic and are able to react with nucleophiles. After the reaction Pd(0) is regenerated and takes part in the catalytic cycle again.



Scheme 36: Reaction principle of palladium-catalyzed allylic substitution.[105]

The stereochemical outcome of the overall reaction follows the concepts depicted in Scheme 37, which have been investigated thoroughly.[109] The attack of the Pd(0)-species on the allylic compound **116** proceeds by inversion of configuration (*anti*-attack) to form π-allylpalladium-complex **117**. In the next step the direction of the addition of the incoming nucleophile depends on its nature. Soft carbon nucleophiles, N- and O-nucleophiles react by inversion, which leads to an overall retention of configuration (compound **118**). In contrast, organometallic compounds as nucleophiles first add via transmetallation to form complex **119**, and by reductive elimination give product **120** with an overall inversion of configuration.

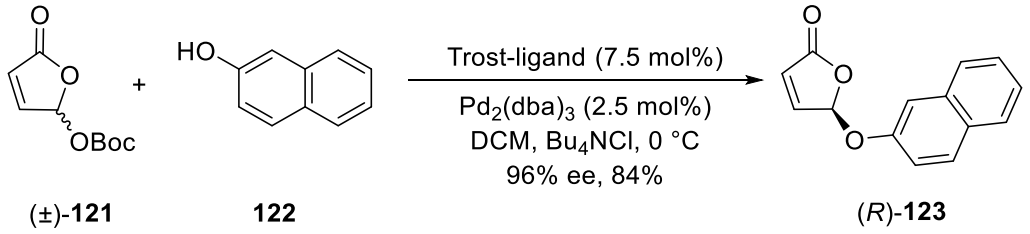


Scheme 37: Stereochemical aspects of palladium-catalyzed allylic substitution.[105]

2.2 Literature Examples of Pd-Catalyzed Allylic Substitution

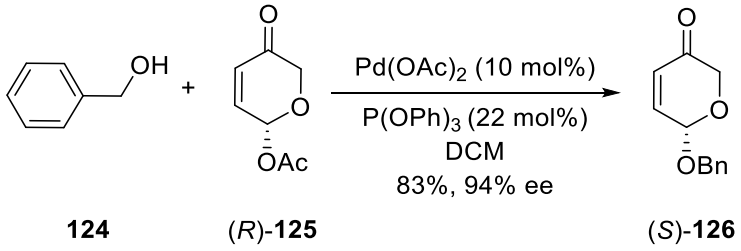
As 4-hydroxy-2-cyclopentenone (±)-**2a** is obtained as a racemic mixture from the continuous flow reactor developed in our group,[28] it would be an interesting perspective if the different enantiomers could be separated by simple kinetic resolution. Asymmetric allylic alkylation reactions with either carbon-nucleophiles (Tsuji-Trost reaction) or heteroatom-nucleophiles are known to provide the means for this purpose,[110] as the compound of interest (±)-**2a** possesses a single stereocenter in allylic position with an alcohol functionality. Moreover, by this methodology various enantiopure 4-substituted cyclopentenones could be obtained, which offers new possibilities for this compound class as building blocks in organic synthesis.

Some examples of compounds exhibiting a γ-hydroxyenone system, similar to 4-hydroxy-2-cyclopentenone (±)-**2a**, that are employed in a Pd-catalyzed allylic substitution with either an *O*-Boc- or *O*-Ac- leaving group can be found in literature (Scheme 38–Scheme 40).



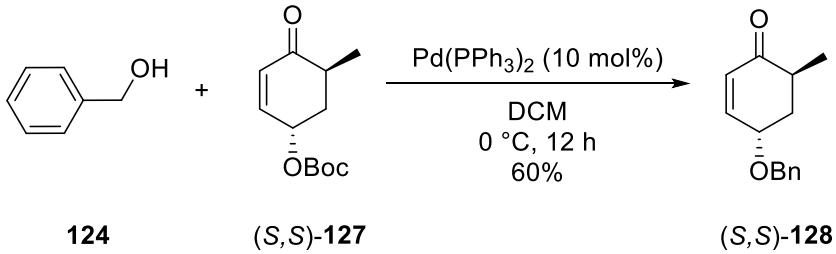
Scheme 38: Dynamic kinetic resolution of the racemic butenolide (±)-**121** and 2-naphthol as nucleophile.[111]

The first example (Scheme 38) describes an asymmetric allylic substitution reaction discovered by Trost *et al*. that leads to a dynamic kinetic resolution with racemic butenolide (±)-**121** and a nucleophile yielding the enantiomerically enriched species (*R*)-**123**.[111] Another study published by Trost explicates the successful use of butenolide (±)-**121** in a kinetic resolution mode and a dynamic kinetic resolution with other phenolic nucleophiles.[112]



Scheme 39: Allylic substitution on enantiomerically pure allylic acetate (*R*)-**125**.[113]

The second example (Scheme 39) is a palladium-catalyzed allylic substitution using enantiomerically pure acetate (*R*)-**125** and the achiral ligand triphenylphosphine oxide.



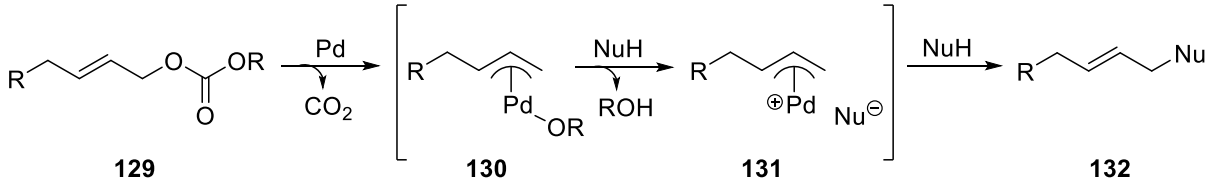
124 (*S,S*)-**127** (*S,S*)-**128**

Scheme 40: Allylic substitution on enantiomerically pure allylic carbonate **127**.[114]

Example three depicts the same reaction principle with the allylic carbonate (*S,S*)-**127** as substrate (Scheme 40). Therefore, in general it should be possible to carry out this type of reaction with substrate (±)-**2a** after protection of the hydroxyfunctionality with either an acetyl or *tert*-butylcarbonate group, as it contains the same γ-hydroxyenone system. Nevertheless, no literature evidence was found applying this reaction on O-protected derivatives of compound (±)-**2a**.

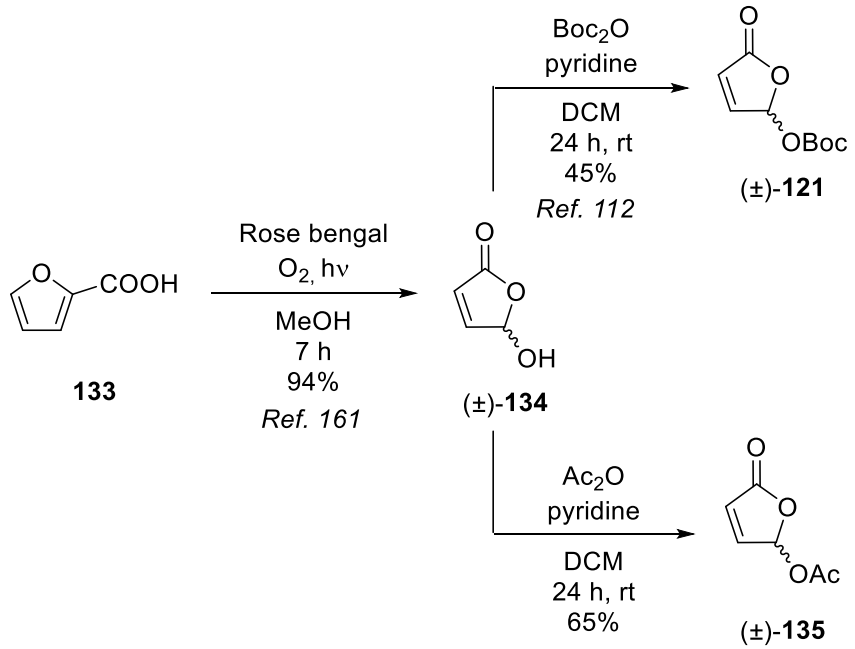
2.3 Kinetic Resolution of 4-Hydroxy-2-Cyclopentenone

For first test experiments the literature known compound butenolide (±)-**121** (Scheme 38) was prepared to investigate if not only the *O*-Boc-leaving group but also the *O*-Ac-leaving group can be used on this system with similar results when subjected to palladium-catalyzed allylic substitution. Both protecting groups display different advantages and detriments. The *O*-Ac-leaving group is environmentally more benign and also less expensive,[115] therefore this one should be preferably used. On the other hand it is a worse leaving group and often requires base for a successful reaction.[105] Moreover, the formation of the π-allylpalladium-complex is reversible. But as allylic acetate (±)-**69a** is a considerably base sensitive compound (chapter 1.3), base free conditions are more desirable. The *O*-Boc-group in an allylic position is among the most reactive functional groups (Scheme 41) for allylic substitution reactions and furthermore these reactions proceed without the need for basic conditions.[105] The oxidative addition of the palladium species to carbonates is accompanied by a decarboxylation leading to the π-allylpalladium alkoxide **130**, which makes the overall process irreversible. The generated alkoxide is basic enough to abstract a proton from the nucleophile to promote the following attack of the nucleophile on the π-allylpalladium complex **131**.



Scheme 41: Behaviour of carbonates in allylic susbtitutions.[105]

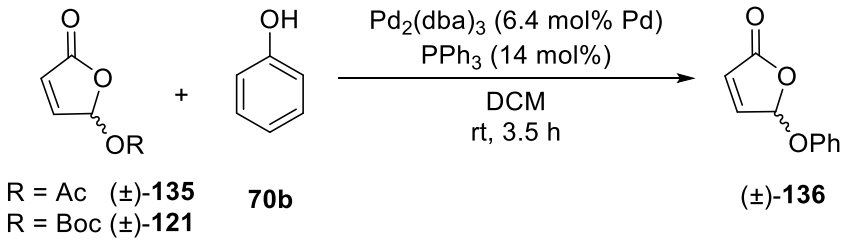
Both butenolides (±)-**135** and (±)-**121** with either an *O*-Ac- and *O*-Boc-leaving group were synthesized from alcohol (±)-**134**. Compound (±)-**134** was prepared by a known procedure[171] from furan-2-carboxylic acid **133** (Scheme 42) by a [4+2]-cycloaddition of singlet oxygen, which could be further transformed by acetylation or Boc-protection into compounds (±)-**135** and (±)-**121**, in case of the latter following a literature known procedure.[112]



Scheme 42: Preparation of butenolides (±)-**121** and (±)-**135**.

Both compounds (±)-**121** and (±)-**135** were used in the palladium catalyzed allylic alkylation with phenol **70b** as nucleophile and the achiral ligand triphenylphosphine to yield the racemic product (±)-**136** (Table 25). Both variants worked almost equally well, giving in case of the Boc-protected substrate product (±)-**136** in quantitative yield and in the other case (±)-**136** in 93% yield. Therefore, presumably both possibilities should be applicable to the allylic system in 4-hydroxy-2-cyclopentenone (±)-**2a**.

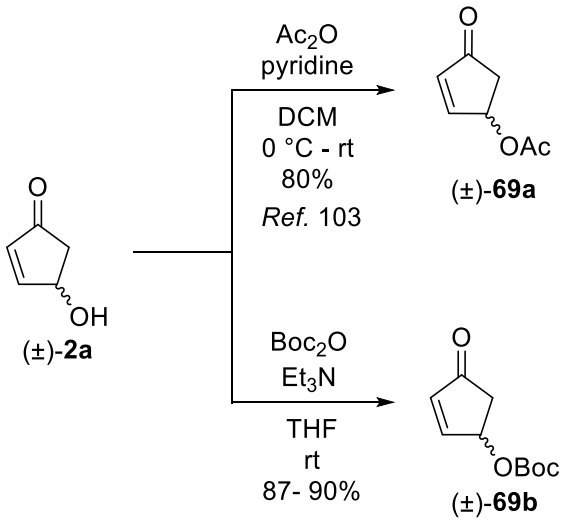
Table 25: Comparison of leaving groups.[a]



Entry	Compound	Yield [%][b]
1	(±)-**121**	quant.
2	(±)-**135**	93

a) (±)-**121**/**135** (0.31 mmol), **70b** (0.46 mmol, 1.5 equiv), $Pd_2(dba)_3$ (3.2 mol%, 6.4 mol% Pd based on the nucleophile), PPh_3 (15 mol% based on the nucleophile) in DCM (10 mL). b) isolated yield.

The synthesis of both the Boc-protected (±)-**69b** and the acylated 4-hydroxy-2-cyclopentenone (±)-**69a** worked smoothly, in case of (±)-**69a**, following a known procedure,[103] in 80% yield and in case of (±)-**69b** in 87–90% yield.

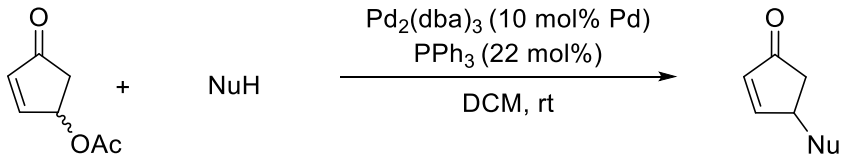


Scheme 43: Synthesis of *O*-Ac- and *O*-Boc-substituted (±)-cyclopentenones.

Initially racemic 4-acetoxy-2-cyclopentenone (±)-**69a** was used as starting material to examine its behaviour in the palladium-catalyzed allylic substitution. As nucleophiles phenol **70b**, *p*-methoxyphenol **70i** or benzyl alcohol **124** were utilized, because phenols and benzyl alcohol have been approved as nucleophiles in this type of reaction (Scheme 38–Scheme

40).[111,112,113,114] For the first test reactions (Table 26) and to produce racemic mixtures for HPLC analysis triphenylphosphine served as ligand for the palladium catalyst whereas in the subsequent experiments on kinetic resolution chiral ligands have been used. The comparison of the solvents diethyl ether, tetrahydrofuran and dichloromethane with the nucleophile phenol **70b** showed that with the first two no product was observed, instead the generation of dimer **79** was detected (entry 1 and 2, Table 26). In dichloromethane the product was formed, although the reactions turned out to be rather sluggish unless a large amount of catalyst and excess of nucleophile were used (entry 3 and 4, Table 26). *p*-Methoxyphenol **70i** could also be employed successfully in this reaction (entry 5, Table 26), whereas benzyl alcohol **124** did not react at all (entry 6, Table 26). The test reactions proved that compound (±)-**69a** could be used in allylic substitution reactions using an achiral ligand, although in most cases the dimerization product of cyclopentadienone **79** was formed to some extent.

Table 26: First test reactions with (±)-4-acetoxy-2-cyclopentenone.[a]



(±)-**69a**

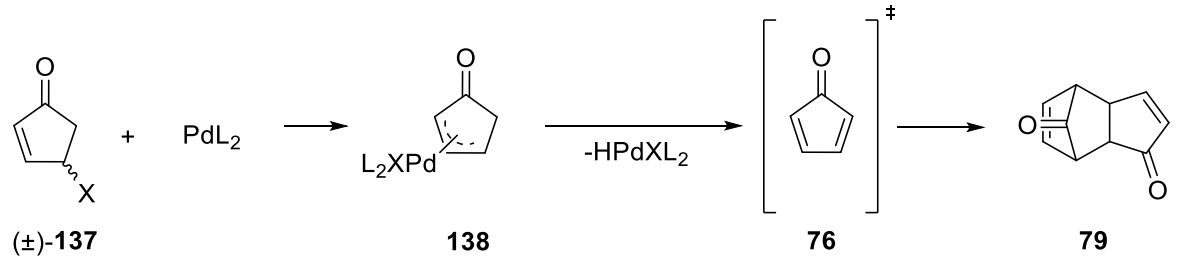
NuH:
1. PhOH **70b**
2. *p*-MeO-PhOH **70i**
3. BnOH **124**

1. **71b**
2. **71i**

Entry	NuH	Nu [equiv]	t [h]	Solvent	Yield [%][b]
1	**70b**	1.5	1.5	Et_2O	0[c]
2	**70b**	1.5	1.5	THF	0[c]
3	**70b**	1.5	24	DCM	**69a**: 24, **79**: 37
4	**70b**	6	1.5	DCM	59[e]
5	**70i**	6.3	1.5	DCM	61
6	**124**	6.3	15	DCM	0[e]

a) (±)-**69a** (0.31 mmol), $Pd_2(dba)_3$ (5 mol%, 10 mol% Pd based on **69a**), PPh_3 (22 mol% based on (±)-**69a**). b) isolated yield. c) only **79** observed. d) conversion incomplete, inseparable impurities. e) 36% **79**.

The generation of **79** as a side-product in many cases can be explained by elimination of $HPdXL_2$ from the π-allylpalladium complex which leads to the transient formation of cyclopentadienone **76** that dimerizes rapidly (Scheme 44). This kind of elimination reaction is known to be a typical side reaction of pathways involving π-allylpalladium complexes and also found its application in the synthesis of dienes.[116]

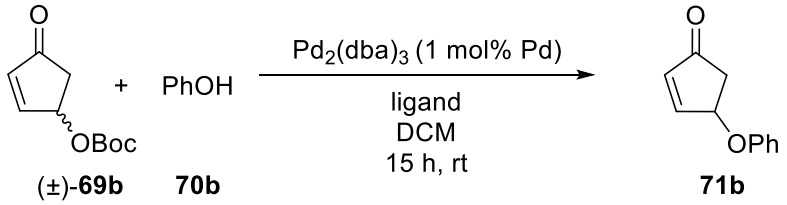


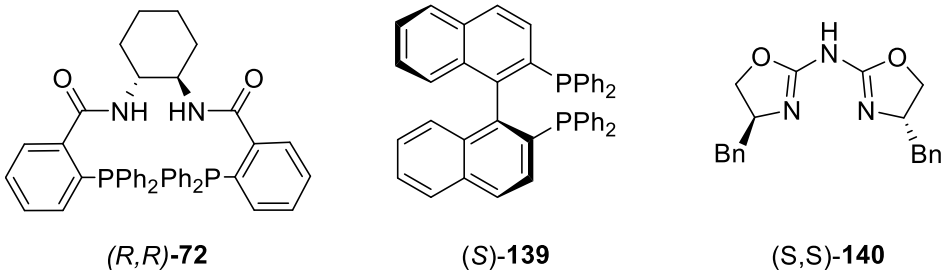
(±)-**137** **138** **76** **79**

Scheme 44: Elimination of $HPdXL_2$ furnishes cyclopentadienone dimer **79.**

The next step included the application of chiral ligands to try the kinetic resolution and optimize the reaction conditions. Some ligands were screened for this reaction (screening by Tirayut Vilaivan, Table 27), and the Trost ligand (*R*,*R*)-**72** proved to be superior for this purpose (entry 2, Table 27). As a benchmark reaction, the substitution with phenol as nucleophile was selected. (*S*)-BINAP **139** and the (*S*,*S*)-Bn-azabox **140** ligands gave no conversion at all when applied in the Pd-catalyzed allylic substitution with phenol (entry 3 and 4, Table 27). In contrast, with the achiral phosphine-ligand PPh_3 the desired product (±)-**71b** could be observed in 30% yield besides the dimerization adduct **79** (entry 1, Table 27).

Table 27: Screening of ligands for allylic alkylation.[a]

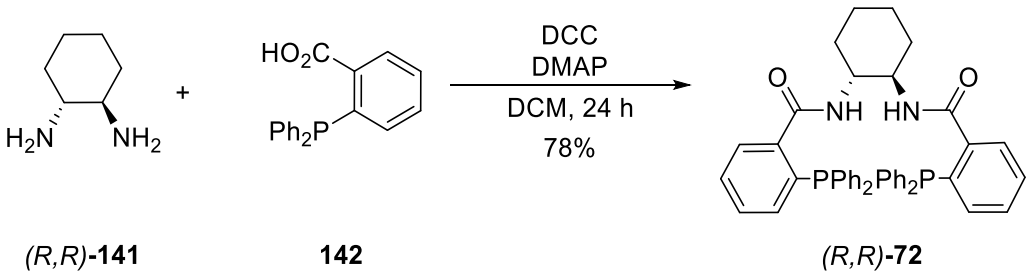




Entry	Ligand	Ligand [mol%]	Yield [%][b]
1	PPh_3	3.5	**71b**: 30, **79**: 47
2	(*R,R*)-**72**	2	**71b**: 63, **79**: 5
3	(*S*)-**139**	2	no reaction
4	(*S,S*)-**140**	2	no reaction

a) (±)-**69** (0.5 mmol), **70b** (0.6 mmol, 1.2 equiv), $Pd_2(dba)_3$, (0.5 mol%, 1 mol% Pd based on the nucleophile), ligand (amount of ligand based on the nucleophile), results by Tirayut Vilaivan. b) isolated yield.

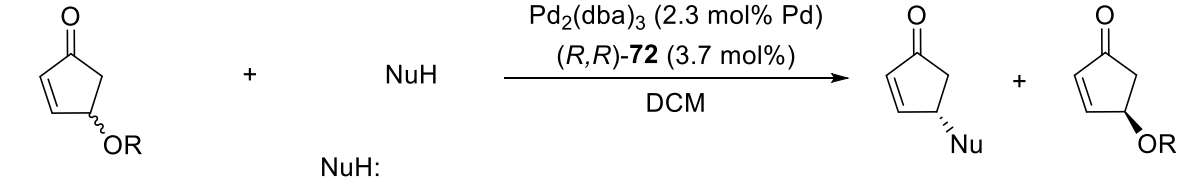
The Trost ligand (*R,R*)-**72** showed the best results among the four ligands screened, consequently it was selected for further investigations. *N,N'*-((*1R,2R*)-cyclohexane-1,2-diyl)bis(2-(diphenylphosphino)benzamide) (*R,R*)-**72**, was prepared according to a known procedure.[117]



Scheme 45: Preparation of (*R,R*)-Trost ligand.[117]

The performance of acetate (±)-**69a** in comparison to *tert*-butylcarbonate (±)-**69b** in the kinetic resolution was evaluated. Generally, the results for (±)-**69a** were only moderate, whereas (±)-**69b** gave excellent values for yields and the enantiomeric excess. In Table 28 the results for (±)-**69a** in the kinetic resolution with different O-nucleophiles are presented. Using phenol **70b** as the nucleophile (entry 2, Table 28) with (±)-**69a** as substrate, the observed yield was low (12%), but nonetheless product (*S*)-**70b** displayed an ee value of 91%. Also only a small amount of the starting material could be recovered. This can be explained by a substantial amount of by-products formed during the reaction, as (±)-**69a** reacts rather sluggish in this kind of transformation and is inclined to form the dimerization adduct of cyclopentadienone **79**.

Table 28: Kinetic resolution with acetate (±)-**69a** and carbonate (±)-**69c**.[a]



Entry	R	NuH	t [h]	T [°C]	Recovered Starting Material		Product		
					Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
1	CO_2Me	**70b**	2	25	-	n.d.	49	0	1
2	Ac	**70b**	18	25	23	26	12	91	24
3	Ac	**70c**	48	25	32	0	32	0	1
4	Ac	**70c**	24	25	33	0	34	0	1
5	Ac	**70c**	4	0	50	25	30	77	11
6	Ac	**70c**	1.5	0	60	25	26	86	18

a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL). b) isolated yield. c) selectivity factor.[118]

The fact that the reaction with (±)-**69a** is slower than with (±)-**69b** can be seen by comparing entry 6 (Table 28) and entry 5 (Table 29) in which both (±)-**69a** and (±)-**69b** react with the nucleophile **70c** at 0° C. With (±)-**69b** the reaction is complete after 1 h, but only 40% of (±)-

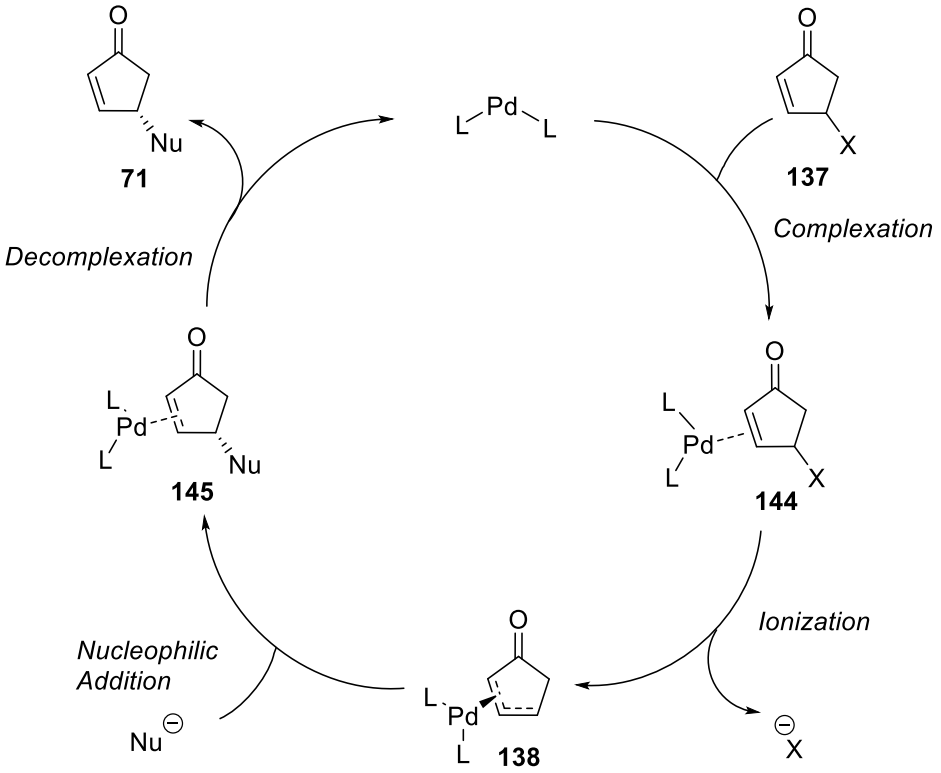
69a is converted after 1.5 h. The replacement of the acetoxy group with the more reactive methylcarbonate moiety as a leaving group yielded the substitution product in almost quantitative yield, but the obtained compound (±)-**70b** was racemic (entry 1, Table 28). As a conclusion, the substrate was presumably too reactive and both enantiomers reacted fast enough to inhibit a successful enantiodiscrimination. When 1-naphtylcarboxylic acid **70c** was used as the nucleophile, the reactions at rt gave full conversion and a yield of about 30% was reached for both 48 h and 24 h (entry 3 and 4, Table 28), but the product (±)-**71c** was obtained as a racemic mixture. Decreasing the reaction temperature to 0 °C within a reaction time of 4 h, complete conversion could still be achieved and an improvement of enantioselectivity to an ee of 77% could be denoted (entry 5, Table 28). An even shorter reaction time of 1.5 h resulted in an incomplete conversion in which 40% of the starting material (±)-**69a** was consumed (entry 6, Table 28). Furthermore, it was observed that at room temperature small amounts of cyclopentadienone dimer **79** were formed, whereas at 0 °C no dimerization product **79** was detected.

The enantiomeric excess was determined by chiral HPLC and the yields in the following tables in this chapter are all isolated yields. The selectivity factor s was calculated by using the equation Kagan *et al.* describe in their publication[118] using both the enantiomeric excess and the conversion of the reaction as variables.

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

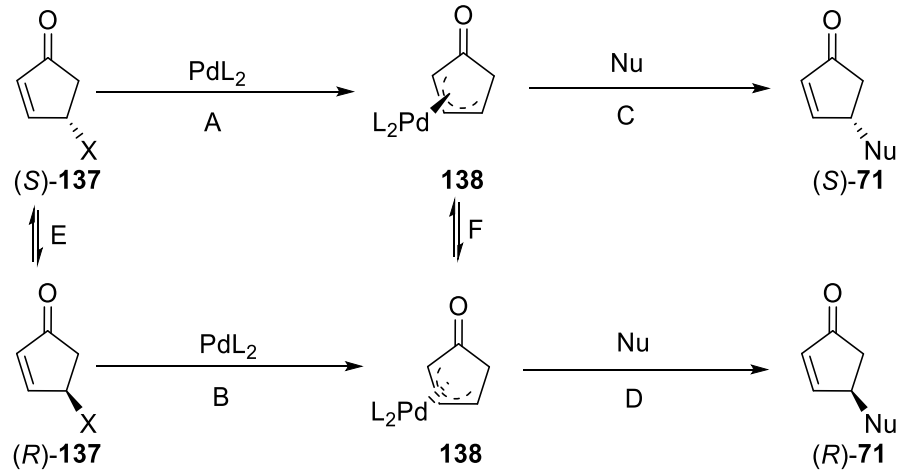
C represents the conversion and ee the enantiomeric excess of the product.

In the following scheme the catalytic cycle of the palladium-catalyzed allylic substitution with 4-substituted cyclopentenones is depicted. In the first step, the palladium complex coordinates to the π-bond in cyclopentenone **137**, which is followed by expulsion of leaving group X^-. After formation of the π-allylpalladium complex **138** a nucleophile can attack, which results in formation of π-complex **145**, which generates after loss of the palladium complex cyclopentenone **71**.



Scheme 46: Catalytic cycle for asymmetric allylic substitutions.[119]

The different reaction pathways concerning this process are outlined in Scheme 47 to explain the occurrence of a kinetic resolution under certain conditions. To allow the kinetic resolution to take place efficiently process E and F should not play a role and process A has to be much faster than process B (or vice versa, Scheme 47). For substrate (±)-**69b** this seems to be the case because after the reaction the remaining substrate can be recovered in excellent yield. This confirms the absence of any racemization of the substrate (path E). In a publication by Trost *et al.*[112] they observed the recovered starting material with low ee values in the kinetic resolution (i. e. racemization of the starting material takes place) and therefore they could perform a dynamic kinetic resolution successfully. In view of those facts the dynamic mode with (±)-**69b** seems not overly promising, but still path F could play a role.

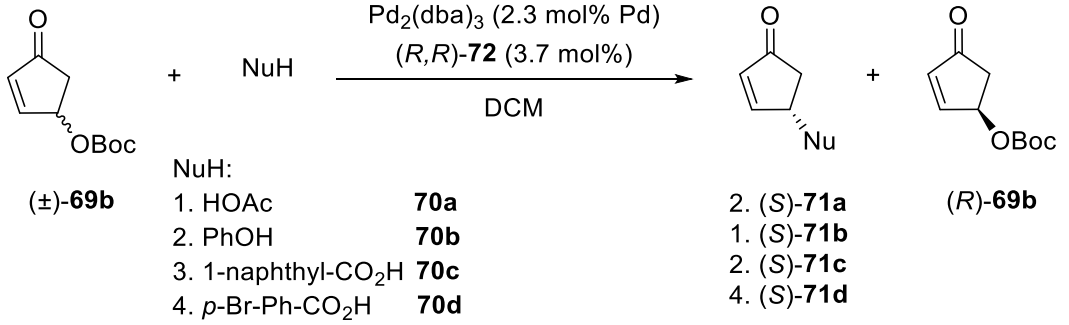


Scheme 47: Reaction pathways of allylic substitution.

The reactions with compound (±)-**69b** as starting material in the kinetic resolution revealed excellent results, using various O-, N- and S- nucleophiles in the reaction. As oxygen-nucleophiles both carboxylic acids and phenols could be employed.

Phenol **70b** as nucleophile afforded moderate yields both for the product (*S*)-**71b** and the recovered starting material (*R*)-**69b**, but the observed enantioselectivity was very high with ee values of 93% and 99%, respectively (entry 2, Table 29). Acetic acid **70a** as nucleophile performed comparable in terms of yield and selectivity, only the yield of the recovered substrate (±)-**69b** was higher (entry 1, Table 29). When 1-naphtylcarboxylic acid **70c** was employed as nucleophile, the same observation as before (entry 3–6, Table 28) with (±)-**69a** as starting material was made, i.e. reactions at rt led to a racemic product. In case of entry 4 (Table 29), the recovered starting material (*R*)-**69b** showed an ee of >99% despite the product was almost racemic. This outcome might be explained by a racemization process of the product (*S*)-**71c** occurring during the reaction at rt. Interestingly, the product (*R*)-**71c** was obtained in 43% ee at rt and a reaction time of 22 h (entry 3, Table 29). Nevertheless, at 0 °C (entry 5, Table 29) both substitution product (*S*)-**71c** and recovered starting material (*R*)-**69b** were obtained in almost quantitative yield and ee values of 90% for both compounds. In an equally successful way, *para*-bromobenzoic acid **70d** could be employed as another carboxylic acid nucleophile (entry 6, Table 29). In summary, for all the O-nucleophiles selectivity factors of 31 for acetic acid and over 40 for the other nucleophiles were calculated. Benzyl alcohol **124** did not show any conversion under the kinetic resolution conditions with (±)-**69b**.

Table 29: Kinetic resolution with O-nucleophiles.[a]

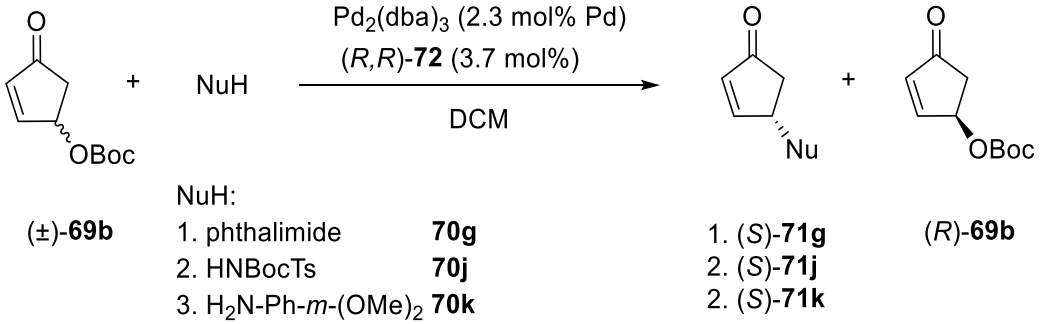


Entry	NuH	t [h]	T [°C]	Recovered Starting Material		Product		
				Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
1[d]	**70a**	1	0	46	96	35	90	31
2	**70b**	2	0	34	99	34	93	44
3	**70c**	22	rt	-	n.d.	33	43[e]	3
4	**70c**	1	rt	21	>99	39	12	1
5	**70c**	1	0	31	90	46	90	44
6[f]	**70d**	1	0	44	95	41[g]	91[g]	41

a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL); results by Tirayut Vilaivan. b) isolated yield. c) selectivity factor.[118] d) absolute configuration of **71a** was obtained by comparison of specific rotation value with literature (see Experimental Part). e) *R*-enantiomer. f) absolute configuration of **71d** was obtained by comparison of specific rotation value with literature (see Experimental Part). g) 34%, 93% ee after single recrystallization from $EtOH/H_2O$.

Displayed in the following scheme and table are the experiments conducted with various N-nucleophiles.

Table 30: Kinetic resolution with N-nucleophiles.[a]



Entry	NuH	t [h]	T [°C]	Recovered Starting Material		Product		
				Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
1[d]	**70g**	18	rt	31	>99	50	96	194
2[d]	**70g**	1	0	44	94	49[e]	96[e]	163
3[d,f]	**70g**	7	0	42	>99	48	96	146
4	**70j**	1	rt	20	>99	43	55	5
5	**70j**	23	0	44	57	39[g]	94[g]	60
6	**70k**	18	rt	39	>99	32	1	1

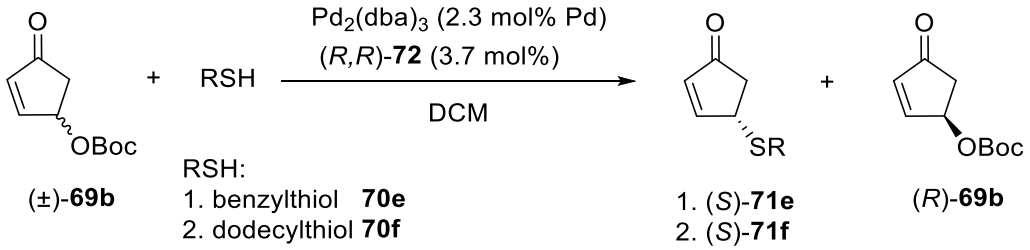
a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL); reactions in this table by Tirayut Vilaivan. b) isolated yield. c) selectivity factor.[118] d) absolute configuration of **70g** was determined by X-ray crystallography (see Figure 6 or Appendix). e) 36%, 99% ee after single recrystallization from EtOH. f) $Pd_2(dba)_3$ (0.575 mol%, 1.15 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (1.85 mol% based on the nucleophile). g) 33%, 95% ee after single recrystallization from EtOH/H_2O.

Here especially phthalimide **70g** has to be pointed out, which showed exceptionally good results with selectivity factors of about 150–200 (entry 1–3, Table 30). Conveniently the reaction at rt also gave a quantitative yield and an ee of 96% concerning product (*S*)-**71g**, although the recovery rate for the starting material (*R*)-**69b** was higher in cases of lower temperature. Moreover, using only half of the catalyst gave the same excellent results. Boc-protected

tosylamine **70j** as nucleophile provided only a moderate selectivity at rt, however, at 0 °C the ee of the product was 94% (entry 4 and 5, Table 30). In contrast when 3,5-dimethoxyaniline **70k** was used, the product (±)-**71k** was obtained as a racemic mixture and in moderate yield (entry 6, Table 30). However, the starting material (*R*)-**69b** was recovered in good yield and an excellent ee of >99%, which indicates a racemization of the product **71k** during the reaction.

The last class of nucleophiles investigated were S-nucleophiles which are described in more detail in the following scheme and table. Both benzylic and aliphatic thiols could be employed in the kinetic resolution. With benzylthiol **175** at 0 °C high yields were obtained but the enantioselectivity for both the product (*S*)-**177** and the recovered starting material (*R*)-**82** was only moderate. By decreasing the temperature to –78 °C the ee values were improved to 99% and 93%, respectively, while still obtaining a high yield. Also dodecylthiol **176** was employed in this reaction successfully with ee values over 90% for both the product (*S*)-**178** and the recovered starting material (*R*)-**82**.

Table 31: Kinetic resolution with S-nucleophiles.[a]



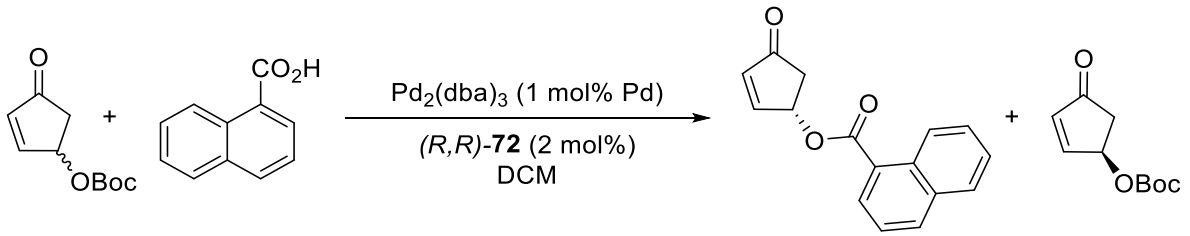
Entry	NuH	t [h]	T [°C]	Recovered Starting Material		Product		
				Yield [%][b]	ee	Yield [%][b]	ee	s[c]
1	**70e**	1	0	49	40	41	81	17
2	**70e**	17	–78	33	>99	42	93	56
3	**70f**	17	–78	38	92	39	93	50

a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL); reactions in this table by Tirayut Vilaivan. b) isolated yield. c) selectivity factor. [118]

2.4 Scale-Up Experiments

To prove the practicability of the kinetic resolution for synthesis, two of the most effective nucleophiles were selected to perform a ten times scaled-up version of this reaction (5 mmol instead of 0.5 mmol of (±)-**69b**). 1-Naphtylcarboxylic acid **70c** and phthalimide **70g** both showed a high selectivity and yield on a small scale, and furthermore afforded nicely crystalline products allowing to improve the enantiomeric excess by recrystallization if necessary. 1-Naphthylcarboxylic acid **70c** was one of the best suited nucleophiles for this reaction (entry 5, Table 29) and the scale-up worked smoothly (Table 32). Here also the tendency was observed that lower temperatures are beneficial for achieving better enantioselectivities and yields. At –20 °C the best results were obtained affording both the *(R)*-enantiomer of 4-BocO-2-cyclopentenone (*R*)-**69b** as recovered starting material and *(S)*-enantiomer of 4-(1-naphtylcarboxylic)-2-cyclopentenone (*S*)-**71c** in almost quantitative yields and ee values over 99% (entry 3, Table 32). In this particular case the remarkably high value of 501 for the selectivity factor was calculated, which can only be achieved by a combination of exceptionally high ee values and excellent yields.

Table 32: Kinetic resolution with 1-naphtylcarboxylic acid **71c** as nucleophile.[a]



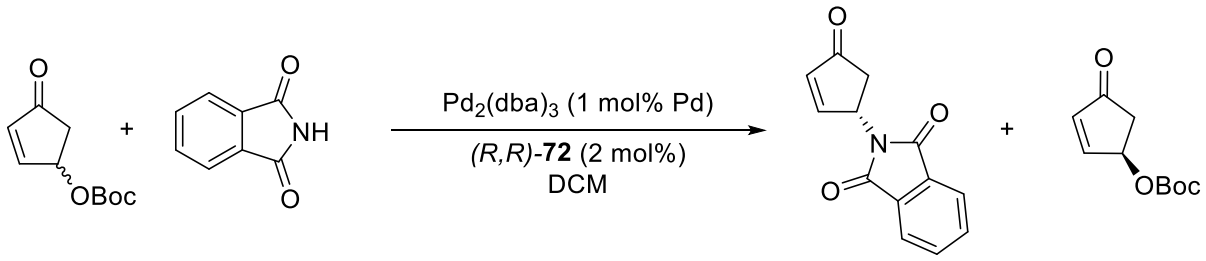
(±)-**69b** **70c** (*S*)-**71c** (*R*)-**69b**

Entry	t [h]	T [°C]	Recovered Starting Material		Product		
			Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
1	1	rt	34	>99	41[d]	48[d]	4
2	1	0	44	>99	49[e]	86[e]	34
3	4	–20	43	>99	45	>99	501

a) (±)-**69b** (5 mmol), **70c** (2.4 mmol), $Pd_2(dba)_3$ (0.5 mol%; 1 mol% of Pd based on the nucleophile), (*R,R*)-**72** (2 mol % based on the nucleophile). b) isolated yield. c) selectivity factor.[118] d) 17%, 57% ee after single recrystallization from EtOH. e) 45%, >99% ee after single recrystallization from EtOH; $[\alpha]^{20}_D$ = +143.7.

The upscaling of the reaction with phthalimide **70g** went smoothly and gave equally good results as on a smaller scale (Table 33). The yields of both recovered starting material (*R*)-**69b** and the product (*S*)-**71g** were almost quantitative and an excellent ee value for (*R*)-**69b** of more than 99% and a good enantioselectivity for (*S*)-**71g** of 95% were observed. The ee of the product (*S*)-**71g** could be improved by recrystallization to 97%.

Table 33: Kinetic resolution with phthalimide **70g** as nucleophile.[a]



(±)-**69b** **70g** (*S*)-**71g** (*R*)-**69b**

t [h]	T [°C]	Recovered Starting Material		Product		
		Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
16	rt	42	> 99	48[d]	95[d]	113

a) (±)-**69b** (5 mmol), **70g** (2.4 mmol), $Pd_2(dba)_3$ (0.5 mol%; 1 mol% of Pd based on the nucleophile), (*R*,*R*)-**72** (2 mol % based on the nucleophile); absolute configurations of **70g** was determined by X-ray crystallography (see Figure 6 or Appendix). b) isolated yield. c) selectivity factor.[118] d) 43%, 97% ee after single recrystallization from ethanol.

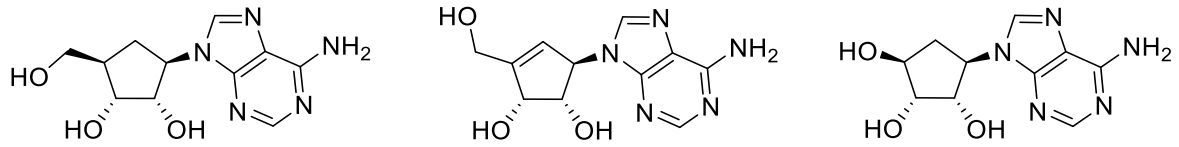
(*S*)-**71g**

Figure 6: Crystal structure of (*S*)-4-phthalimidylcyclopent-2-enone.

The absolute stereochemistry was confirmed by x-ray crystallography to be the (*S*)-enantiomer.

2.5 Application for the Kinetic Resolution

An application for the kinetic resolution was discovered in the field of the synthesis of carbocyclic nucleosides. These compounds are analogous to natural nucleosides with a methylene group replacing the oxygen in the carbohydrate ring. Two prominent representatives of this compound class are aristeromycin **146** and neplanocin A **147** (Scheme 48), two naturally occurring carbocyclic nucleosides. They both exhibit significant antitumor and antiviral activity, which is attributed to their inhibition of the enzyme *S*-adenosyl-L-homocysteine hydrolase.[120] Less cytotoxic than the two latter compounds is the synthetic 5'-noraristeromycin **73**, which also shows antiviral behaviour and was first synthesized in 1992 by Schneller *et al.*[121]

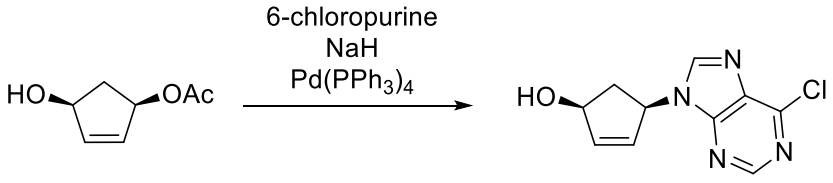


146 **147** **73**

Scheme 48: Aristeromycin **146**, neplanocin A **147** and 5'-noraristeromycin **73**.

Various syntheses of 5'-noraristeromycin **73** commence with the enantiomerically pure starting material (1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl acetate **148** (Scheme 49), or make use of enzymatic resolution methods[122] with *cis*-1,3-acetoxy-2-cyclopentenone to achieve the preparation of enantiopure (1*R*,4*S*)-**148**.[123,124,125]

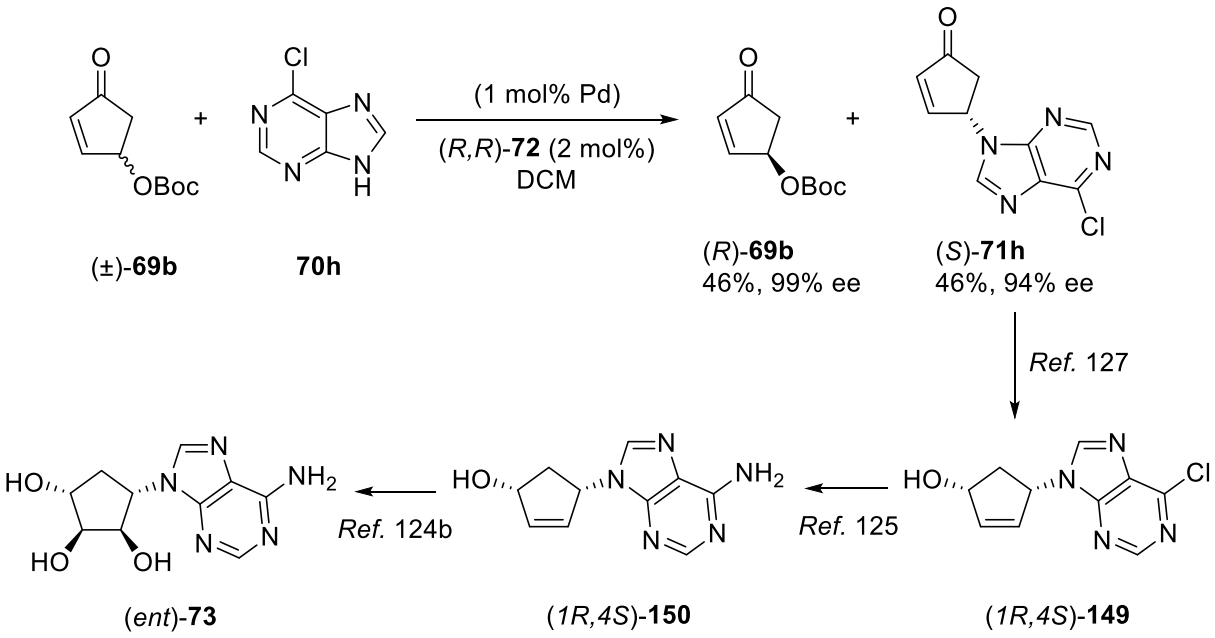
The implementation of palladium-catalyzed allylic substitution to introduce the *N*-heterocycles in the synthesis of carbocyclic nucleosides is well-established (example in Scheme 49),[122,123,124,125,126] but to our knowledge a chiral catalyst was never used to induce enantioselectivity by this method in the molecule.



(*1R,4S*)-**148** (*1S,4R*)-**149**

Scheme 49: Pd-catalyzed allylic substitution with 6-chloropurine.[125]

By applying the method developed for the kinetic resolution of (±)-**69b**, a short formal synthesis of the other enantiomer of 5'-noraristeromycin (*ent*)-**73** was established. Also (*ent*)-**73**, first synthesized by Schneller *et al*.,[124b] shows antiviral activity, in particular it is selectively active against the Hepatitis B virus, in which case **73** was proven to be inactive.[126] On the other hand, **73** shows, contrary to (*ent*)-**73**, significant activity against cytomegalovirus (CMV).[124b] Compound (*ent*)-**73** can be synthesized from intermediate (*S*)-**71h** by literature known protocols, which comprise first the *cis*-selective reduction of the carbonyl-group of (*S*)-**71h** affording alcohol (1*R*,4*S*)-**149**.[127] Aminolysis of the Cl-moiety gives amine (1*R*,4*S*)-**150**,[125] which can be subjected to selective dihydroxylation with osmium tetroxide resulting eventually in the desired product (*ent*)-**73**.[124b]



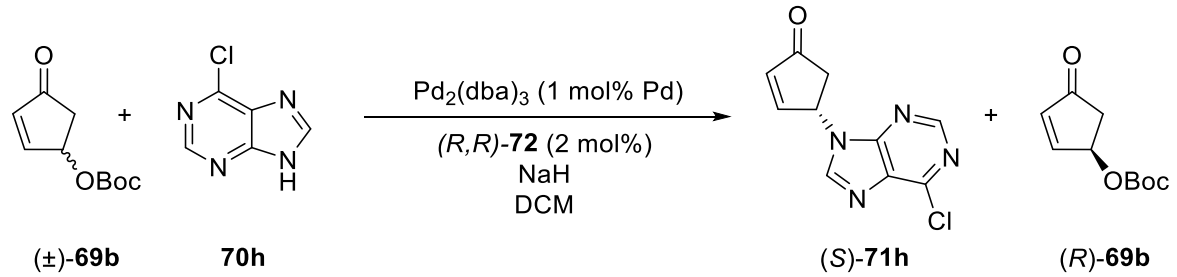
Scheme 50: Formal synthesis of (*ent*)-noraristeromycin *ent*-**73**.

The intermediate compound (*S*)-**71h** can be directly synthesized by kinetic resolution of 4-BocO-2-cyclopentenone (±)-**69b** with the nucleophile 6-chloropurine **70h** (Scheme 50). The great advantage over the other methods is the utilization of the inexpensive and readily available racemic starting material (±)-**2a**, which can be obtained from renewable resources. Furthermore, by switching the stereochemistry of the ligand access to both enantiomers of the product **73** could be enabled theoretically.

The first two entries in Table 34 represent experiments conducted on a small scale with 0.5 mmol of racemic 4-BocO-2-cyclopentenone (±)-**69b** as starting material. As the reaction at rt

only afforded the product (*S*)-**71h** with a moderate ee value of 76% (entry 1, Table 34), the temperature was decreased and at 0 °C appreciable results were obtained giving the product (*S*)-**71h** in 47% yield and 96% ee (entry 2, Table 34). To adapt the method to a synthetically more useful scale, the amount of starting material (±)-**69b** was increased to 5 mmol (entry 3 and 4, Table 34). At 0 °C and 4 h of reaction time the ee of the product (*S*)-**71h** reached 94%, but the recovered starting material (*R*)-**69b** showed only 88% ee.

Table 34: Kinetic resolution with 6-chloropurine **70h** as nucleophile.[a]



(±)-**69b** **70h** (*S*)-**71h** (*R*)-**69b**

Entry	t [h]	T [°C]	NaH	Recovered Starting Material		Product		
				Yield [%][b]	ee [%]	Yield [%][b]	ee [%]	s[c]
1	16	rt	1 equiv	46	>99	40[d]	76[d]	61
2	4	0	1 equiv	47	>99	47	96	80
3[e]	4	0	1 equiv	59	88	39[f]	94[f]	60
4[e]	22	0	1 equiv	46	>99	46[g]	94[g]	80
5	19	rt	-	32	>99	47[h]	89[h]	41
6[e]	19	rt	-	45	96	46[i]	90[i]	44
7[e]	24	0	-	47	98	46[j]	94[j]	80

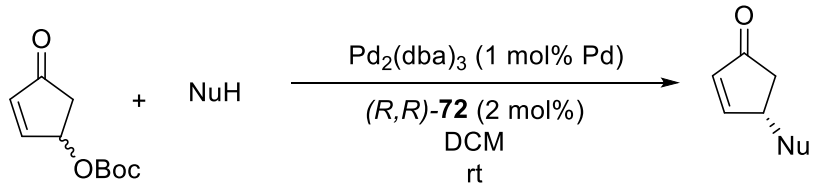
a) (±)-**69** (0.5 mmol), **70** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R*,*R*)-**72** (3.7 mol% based on the nucleophile) in DCM (2 mL). b) isolated yield. c) selectivity factor.[118] d) 7%, 94% ee after single recrystallization from PE/EA. e) 5 mmol scale, $Pd_2(dba)_3$ (0.5 mol%; 1 mol% of Pd based on the nucleophile), (*R*,*R*)-**72** (2 mol % based on the nucleophile). f) 27%, 99% ee after single recrystallization from PE/EA; $[\alpha]^{20}_D$ = -114.5. g) 40%, 98% ee after single recrystallization from PE/EA. h) 32%, 94% ee after single recrystallization from PE/EA. i) 31%, 94% ee after single recrystallization from PE/EA. j) 39%, 98% ee after single recrystallization from PE/EA.

The moderate ee value for (*R*)-**69b** in this case can be attributed to an incomplete conversion of only 41% (entry 3, Table 34). Prolonging the reaction time to 22 h led eventually to a full conversion with 46% yield and 94% ee of the product (*S*)-**71h** (entry 4, Table 34). Additionally, compound (*S*)-**71h** could be recrystallized to improve the ee up to 99%. By examining various literature reactions[122,123,124,125,126] (compare Scheme 49), usually sodium hydride was employed in similar cases, which is the reason for the addition of sodium hydride in the first four reactions described in Table 34. However, because the other nucleophiles previously tested could be consistently used without a base and beyond that by using *O*-Boc as a good leaving group no basic conditions are required in many cases,[105] the kinetic resolution without any additional base and 6-chloropurine **70h** as nucleophile was examined. This attempt proved to be successful and the results were similar compared to the results with sodium hydride (entry 5–7, Table 34). Again the best results were obtained with a reaction scale of 5 mmol at 0 °C and 24 h of reaction time, leading to the product (*S*)-**71h** in 46% yield and 94% ee, which could be recrystallized to increase the ee to 98% (entry 7, Table 34).

2.6 Dynamic Kinetic Asymmetric Transformation (DYKAT)

The concept of dynamic kinetic resolution processes in general has been reviewed[128,129] and it has been shown that resolution resulting in more than 50% of one enantiomer can be achieved by palladium-catalyzed allylic substitution.[111,130,131,132] In this case it was defined as dynamic kinetic asymmetric transformation (DYKAT) by Trost, and depends on the interconversion (process F, Scheme 51) and different reactivity of intermediate diastereomeric species (process C or D faster, Scheme 51). As the dynamic kinetic pathway is superior in efficiency compared to the kinetic one, because the yield of one enantiomer could theoretically reach 100% ee instead of 50%, this approach was also investigated for compound (±)-**69b**. 4-Acetoxy-2-cyclopentenone (±)-**69a** as the substrate did not provide sufficient results referring to yield and enantiomeric excess, therefore only the *O*-Boc-protected derivative (±)-**69b** was tested. The substrate was subjected to similar conditions as for the kinetic resolution, but 1 equivalent of the nucleophile was employed to ensure a possible full conversion of the starting material (±)-**69b**. In none of the cases in Table 35 a dynamic pathway could be observed, which means either the yield stayed under a value of 50% or if higher a poor selectivity could be denoted. Nonetheless, except for HOAc **70a** (entry 5, Table 35) and phthalimide **70g** (entry 8, Table 35) the reactions went to completion, which means the amount of nucleophile applied was consumed after the specified reaction time.

Table 35: Attempted dynamic asymmetric transformation (by Tirayut Vilaivan).[a]



(±)-**69b** **70** (*S*)-**71**

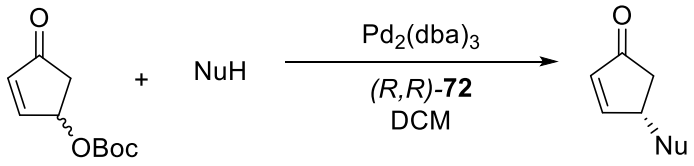
Entry	NuH	t [h]	Yield [%][b]	ee [%]
1	**70b**	19 h	63	25
2	2-Naphth-OH	17 h	68[c]	n.d.
3	2,4-$Cl_2C_6H_3OH$	21 h	31	n.d. ($[\alpha]^{20}_D$ = +6.8)
4	**70a**	3 d	48[d]	69
5	**70a**	3 d	29[e]	n.d. ($[\alpha]^{20}_D$ = –2.8)
6	BzOH	3 h	76	10 ($[\alpha]^{20}_D$ = –10.1)[f]
7	**70c**	16 h	64	11
8	**70g**	18 h	46[g,h]	68

a) (±)-**69b** (0.5 mmol), **70** (0.5 mmol, 1 equiv), $Pd_2(dba)_3$ (0.5 mol%, 1 mol% Pd), (*R*,*R*)-**72** (2 mol%) in DCM (2 mL), reactions in this table by Tirayut Vilaivan. b) isolated yield. c) contains ~10% of inseparable impurities. d) incomplete reaction, the starting material **69b** was recovered in 29% yield, $[\alpha]^{22}_D$ = +85.0 (22 °C, c = 1.60, $CHCl_3$; >99% ee). e) using $[Pd(allyl)Cl]_2$ as the source of Pd(0). f) (*R*)-isomer, lit. $[\alpha]^{22}_D$ of (*S*)-4-benzoyloxy-2-cyclopenten-1-one (99% ee) = –147.9 (c = 0.40, $CHCl_3$).[133] g) incomplete reaction, both **69b** and phthalimide were still present after overnight reaction. h) $[\alpha]^{23}_D$ = –218.8 (c = 0.82, $CHCl_3$) after single recrystallization from EtOH.

By looking more closely at entry 8 (Table 35) the conversion was not complete and only 46% of the product **71g** could be isolated, which is about the value as for the kinetic resolution (the results for the same conditions but half the amount of nucleophile applied are 50% and 96% ee, entry 1, Table 30). Thus the only difference in this case is the amount of nucleophile employed which makes the ee drop from 96% to 68%, which can be explained by a greater availability of nucleophile and consequently a faster reaction and lower enantioselectivity. Nevertheless, most of the other nucleophiles gave complete conversion so this should be possible with phthalimide **70g** as one of the superiorly performing nucleophiles in the kinetic resolution. Moreover, either lower temperatures will possibly improve the enantioselectivity or the successive addition of **70g** to the reaction mixture can prevent a too high concentration of nucleophile. Therefore, this reaction was revised again and initially the feasibility of converting all the starting material (±)-**69b** was examined, which was the case after 3 d of stirring at rt and using 1 equivalent of nucleophile **70g** (entry 1, Table 36). The product (*S*)-**71g** could be isolated in 86% yield with

an ee value of 41%. It contained some impurities which predominantly consisted of the cyclopentadienone dimerization product **79**. After one recrystallization step the clean product (*S*)-**71g** was obtained in 65% yield and 69% ee, which implies that 55% of the *S*-enantiomer was formed. Every value over 50% yield of one enantiomer is an indication of an occurring dynamic pathway of resolution. Using ten times the amount of catalyst (entry 2, Table 36) decreased the reaction time to 2 h and gave the product (*S*)-**71g** in 92% and 34% ee. Also in this case the same impurities have been observed, but to a greater extent, and recrystallization gave the pure product (*S*)-**71g** in 54% yield and 42% ee (38% *S*-enantiomer) which means that no occurrence of a dynamic kinetic resolution could be stated. A problem in this reaction might be the formation of a greater amount of side-product leading to a lower yield of product (*S*)-**71g**. Reduction of the reaction temperature to –15 °C with 0.5 mol% Pd-catalyst and 1 mol% ligand gave after 13 d only about 50% conversion judging from NMR (entry 3, Table 36). No further analysis of this reaction was done, but it is conceivable that the catalyst suffered after the elongated time from a loss in efficiency. By increasing the amount of catalyst by the factor of ten and maintaining the reaction temperature at –15 °C a full conversion could be reached after 13 d (entry 4, Table 36). An annotation has to be made that in this particular case after 12 d an additional equivalent and 0.5 mol% Pd and 1 mol% of ligand were added because the conversion seemed to be not complete and a possibly decomposed catalyst should be replaced. The enantiomeric excess of the reaction was with 90% almost in the range achievable with the kinetic resolution conditions and also the yield proved to be satisfying (84%). The problem with the impurity remained, which was solved by two consecutive recrystallizations (1. 77% yield and 93% ee, 2. 67% and 95% ee). As the reaction went to completion (entry 4, Table 36) after the addition of some more catalyst, because presumably the catalyst was not active any more after prolonged time, it was added stepwise in the next reaction (entry 5, Table 36). The results were almost the same as for the latter reaction except the ee was slightly lower. As the increase of nucleophile **70g** resulted in very low enantiomeric excess (entry 8, Table 36), it was examined if a slower addition of nucleophile **70g** could enhance the ee. A stepwise addition by syringe pump failed because of the poor solubility of phthalimide **70g** in DCM. Therefore, it was added to the reaction mixture by hand in several steps. In the first step slightly less than 0.5 equiv were added which should give the same values as for the kinetic resolution (entry 1, Table 30), and then the rest was given to the solution stepwise.

Table 36: Dynamic kinetic resolution attempts.[a]



(±)-**69b** **70** (*S*)-**71**

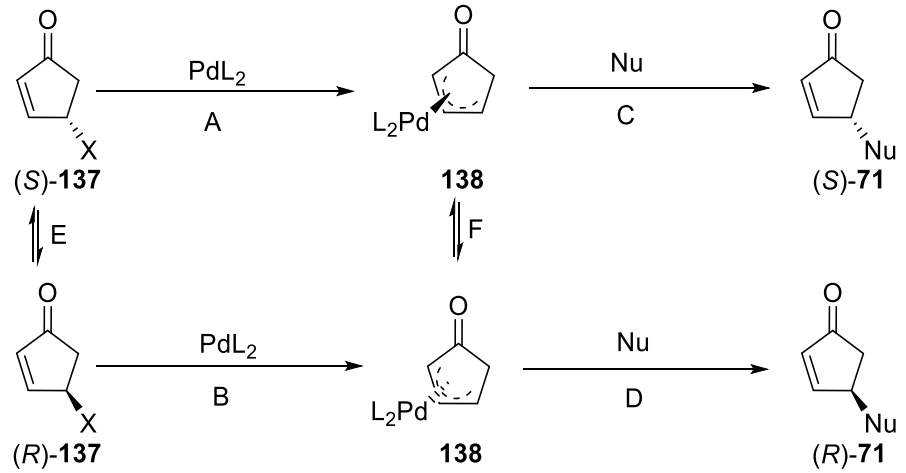
Entry	NuH	$Pd_2(dba)_3$ [mol%]	Ligand [mol%]	t	T [°C]	Yield [%][b]	ee [%]
1	**70g**	0.5	1	4 d	rt	86[c]	41
2	**70g**	5	10	2 h	rt	92[d]	34
3	**70g**	0.5	1	13 d	−15	n.d.	n.d.
4[e]	**70g**	5	10	13 d	−15	84[f]	90
5[g]	**70g**	3x0.5	3x1	12 d	−15	88[h]	74
6[i]	**70g**	0.5	1	5 d	rt	86[j]	52
7[k]	**70g**	0.5	1	7 d	rt	61	57 (*R*)
8	**70b**	2x0.5	2x1	15 d	− 15	72	34
9	**70c**	2x0.5	2x1	10 d	−15	86	3

a) (±)-**69b** (0.5 mmol), **70** (0.5 mmol, 1 equiv), in DCM (2 mL). b) isolated yield. c) some impurities; 65%, 69% ee after single recrystallization from PE/EA. d) some impurities; 54%, 42% ee after single recrystallization from PE/EA. e) additional equiv of nucleophile and 0.5 mol% Pd and 1 mol% ligand added after 12 d. f) some impurities; 77%, 93% ee after single recrystallization from PE/EA, still some impurities; 67%, 95% ee after second recrystallization from PE/EA. g) catalyst added after 7 d and 11 d. h) some impurities; 70%, 82% ee after single recrystallization from PE/EA. i) nucleophile added stepwise. j) some impurities; 73%, 69% ee after single recrystallization from PE/EA. k) (*R*)-**69b** used.

The results are slightly better than for the same reaction in which the nucleophile **70g** was added at once. The clean product (*S*)-**71g** could be isolated after recrystallization with a yield of 62% of the *S*-enantiomer (entry 6, Table 36). Furthermore, when (*R*)-**69b** was employed as the starting material, 61% of the substituted product (*R*)-**71g** could be isolated with an ee value of

57% (entry 7, Table 36). Therefore, it can be concluded that part of the (*R*)-enantiomer can indeed be converted to the (*S*)-enantiomer, assuming that no racemization of the product (*S*)-**71g** took place (unlikely because the product was isolated in the kinetic resolution experiments with excellent ee). Experiments with phenol **70b** as nucleophile showed a low enantioselectivity (entry 8, Table 36) and 1-naphtylcarboxylic acid **70c** gave only a racemic product (entry 9, Table 36), presumably because of racemization of the product **71c**.

A dynamic kinetic process involves racemization of either the starting material (*R*)-**69b** or the π-allylpalladium intermediate. As the recovered starting material always showed an exceptionally high ee value, the assumption can be made that no racemization of the starting material took place (process E, Scheme 51). Racemization of the π-allylpalladium complex has to take place otherwise the enhanced ee could not be explained. If this process was slower than the attack of the nucleophile, the product obtained would be racemic. Therefore, slowing down the rate of the nucleophilic attack is beneficial. In the case of phthalimide the poor solubility of this nucleophile might be advantageous because it dissolved gradually in the course of the reaction and therefore only a low concentration of nucleophile was present in the solution.

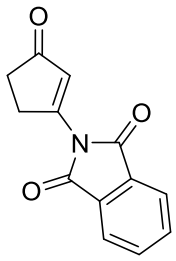


Scheme 51: Reaction pathways of allylic substitution.

That can also explain the low ee in the case of phenol (entry 1, Table 35), because it dissolved immediately in the reaction solution. Moreover, the results show that probably the catalyst decomposes after prolonged reaction times, because when additional catalyst was added after days of no significant conversion, the reaction was completed rapidly.

To see whether the results were influenced by any background reactions, (±)-**82** and the nucleophile were mixed without the addition of any catalyst or ligand (Table 37). A reaction

like a substitution at C4 or a 1,4-addition and elimination is conceivable. In the case of phthalimide **70g**, no reaction was observed even when heated in the microwave at 300 W (entry 1–4, Table 37). The addition of sodium hydride was required to give poor to moderate yields of **71g** (entry 5–7, Table 37), which is compatible with either substitution or an addition/elimination sequence. Furthermore, minor amounts of compound **151** could be isolated, which is only explicable by an addition/elimination mechanism with a subsequent isomerization of the double bond.[134] Also substantial amounts of the cyclopentadienone dimer **79** were isolated.

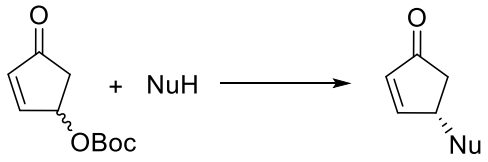


151

Scheme 52: By-product entry 5 Table 37.

1-Naphthylcarboxylic acid **70c** and NaOAc as substrates did not lead to any reaction (entry 11–18, Table 37). The successful reactions of phenol **70b** were again limited to the cases when NaH was employed (entry 21 and 22, Table 37) and were accompanied by **79** in a significant quantity. The only case of an observable reaction of (±)-**69b** without sodium hydride as additive and one of the nucleophiles applied previously in the kinetic resolution was with benzyl thiol **70e** (entry 23, Table 37), though the reaction was rather slow. As a conclusion, a substitution or 1,4-addition as a background reaction under the employed conditions of the dynamic kinetic resolution experiments can be excluded for the nucleophiles tested except for **70e**.

Table 37: Investigation of background reactions.[a]



(±)-**69b** (*S*)-**71**

Entry	NuH	Base[b]	T [°C]	MW P [W][c]	MW p_{max} [bar][c]	t	Yield [%][d]
1	**70g**	-	rt	-	-	5 d	0
2	**70g**	-	reflux	-	-	5 d	0
3	**70g**	-	91	150	5	10 min	0
4	**70g**	-	113	300	9	10 min	0
5	**70g**	NaH	rt	-	-	12 d	21[e]
6	**70g**	NaH	reflux	-	-	12 d	44[f]
7	**70g**	NaH	110	variable	11	1 h	58[g]
8	**70g**	Na_2CO_3	rt	-	-	4 d	0
9	**70g**	Na_2CO_3	reflux	-	-	2 d	0
10	**70g**	Na_2CO_3	109	300	10	10 min	0
11	**70c**	-	rt	-	-	5 d	0
12	**70c**	-	reflux	-	-	5 d	0
13	**70c**	-	94	300	6	10 min	0
14	**70c**	NaH	rt	-	-	5 d	0[h]
15	**70c**	NaH	reflux	-	-	5 d	0
16	NaOAc	-	rt	-	-	5 d	0
17	NaOAc	-	reflux	-	-	22 h	0
18	NaOAc	-	105	300	7	10 min	0
19	**70b**	-	rt	-	-	5 d	0
20	**70b**	-	reflux	-	-	20 h	0
21	**70b**	NaH	rt	-	-	5 d	34[i]
22	**70b**	NaH	rt	-	-	2 d	46[j]
23	**70e**	-	rt	-	-	40 d	32[k]

a) (±)-**69b** (0.25 mmol), **70** (0.25 mmol, 1 equiv), in DCM (2 mL). b) 1 equiv. c) parameters for microwave reaction. d) isolated yield. e) plus 20% of cyclopentadienone dimerization product **79** and 9% **151** and 40% starting material cyclopentenone **69b**. f) plus 30% starting material cyclopentenone (±)-**69b**. g) plus 30% starting material cyclopentenone (±)-**69b**. h) traces of cyclopentadienone dimerization product **79**. i) plus 65% of cyclopentadienone dimerization product **79**, complete conversion. j) plus 35% of cyclopentadienone dimerization product **79**, complete conversion. k) 44% starting material (±)-**69b** recovered.

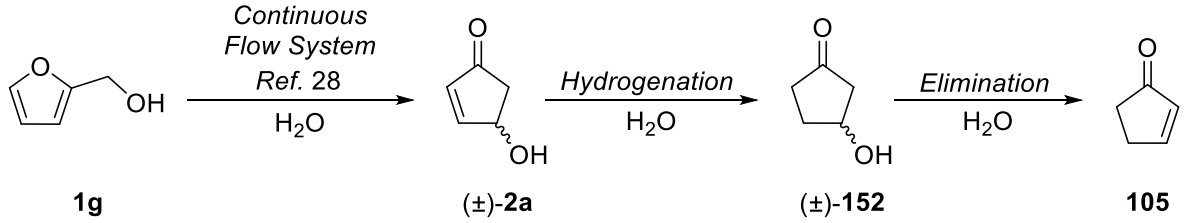
2.7 Conclusion

In summary, a successful kinetic resolution of (±)-**69b** via Pd-catalyzed asymmetric allylic substitution has been demonstrated. Excellent enantioselectivities of both substitution products and recovered starting materials were obtained even at low catalyst loading (1 mol% Pd, 2 mol% ligand). The scope of participating nucleophiles is very broad - phenols, carboxylic acids, thiols and nitrogen-containing heterocycles. This method provides a certainly useful access to an extensive variety of enantiomerically pure 4-substituted-2-cyclopentenone derivatives, particularly because the reaction could be performed on a synthetically useful scale. Additionally, this methodology was applied to achieve a short formal synthesis of (+)-noraristeromycin *ent*-**73**. Moreover, experiments on a conceivable dynamic pathway have been conducted, which came to the conclusion that a dynamic kinetic resolution was possible to a limited extent with phthalimide **70g**. However, this did not prove to be practical in a synthetic perception due to the long reaction times required.

3. Cyclopentenone from Furfuryl Alcohol

3.1 Introduction

Another approach for the conversion of 4-hydroxy-2-cyclopentenone (±)-**2a** into valuable building blocks addresses the problem already mentioned in the first chapter: The continuous flow method for the rearrangement, developed by our group,[28] requires a dilute aqueous solution which causes a highly energy-consuming work-up by evaporating the water from the reaction mixture. Extraction with an organic solvent is no alternative as (±)-**2a** is fairly water-soluble. The challenge was to completely circumvent the evaporation of water by performing a subsequent reaction directly in the aqueous solution obtained from the continuous flow system, to transform 4-hydroxy-2-cyclopentenone (±)-**2a** into another compound that offers a lower water-solubility. Another aspect was to find reaction conditions that could be implemented in a continuous flow-system that follows the initial rearrangement process.



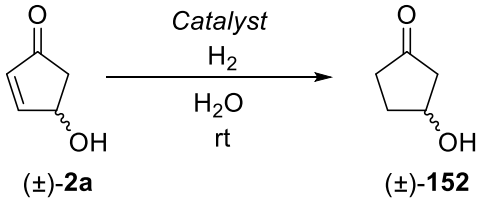
Scheme 53: One-pot reaction sequence to convert furfuryl alcohol **1g** to cyclopentenone **105**.

The transformation into 2-cyclopentenone **105** offers a reasonable solution to this problem, as **105** is less water-soluble than the starting compound (±)-**2a**. Moreover, if all the reactions leading to this compound could be performed in an aqueous environment just with the aid of a catalyst, only water as by-product should be formed and no additional organic waste would be created. Hence the overall process would be obviously valuable in an ecological perception. As described in chapter 1.1, 4-hydroxy-2-cyclopentenone (±)-**2a** was available by the rearrangement in the continuous flow system developed in our group in a concentration of about 25 g/L in water.[28] The next step would consist of hydrogenation of the double bond to yield 3-hydroxycyclopentanone (±)-**152**, which would thereupon afford via elimination of the hydroxy-moiety 2-cyclopentenone **105**. This compound is less water-soluble (but still miscible with water at any ratio)[135] than the starting material (±)-**2a** and can be simply extracted with a low-boiling organic solvent which can be evaporated without using large amounts of energy. Cyclopentenone **105** itself is a valuable building block in chemistry (e.g. for prostaglandins)[136] and is produced on a large scale in industry.

Aim of this project was to use the aqueous solution of 4-hydroxy-2-cyclopentenone (±)-**2a** coming directly from the microreactor system to develop useful conditions to follow-up this process. The catalysts employed in this one–pot reaction sequence had to be suited for the aqueous environment and feasible for the subsequent implementation of this reaction in a continuous flow system. In fact, there is a description of a 2-cyclopentenone **105** multistep synthesis from furfuryl alcohol **1g** in a US patent,[137] and a similar approach was used to find suitable reaction conditions subsequent to the continuous flow rearrangement process and to develop a one-pot-reaction procedure. While working on this project three other publications[31,32] appeared dealing with the synthesis of cyclopentanone **32** and cyclopentanol **33** from furfuryl alcohol **1g** or furfural **13** via a hydrogenation process in a high temperature aqueous solution (>30 bar H_2, >140 °C), wherein 4-hydroxy-2-cyclopentenone (±)-**2a** and 2-cyclopentenone **105** are intermediates. Under the therein described conditions it was not possible to identify 2-cyclopentenone **105** as a product, but instead a high selectivity for cyclopentanone **32** and cyclopentanol **33** was observed.

3.2 Hydrogenation of (±)-4-Hydroxy-2-Cyclopentenone in Water

For the hydrogenation reaction a transition metal catalyst like palladium or platinum was selected. The metal catalysts on solid supports like activated carbon or Al_2O_3 form a heterogeneous system with water that ensures their easy removability afterwards by simple filtration.



(±)-**2a** (±)-**152**

Scheme 54: Hydrogenation of (±)-4-hydroxy-2-cyclpentenone in water.

Hydrogenation of the double bond of (±)-**2a** with hydrogen gas at atmospheric pressure and Pd/C as catalyst proved to be promising. Either in MeOH or in H_2O the product (±)-**152** could be isolated in moderate yields (Table 38). The conversion was always complete concluding from the crude NMR spectra. Cyclopentanone **32** was observed as a by-product but not isolated, causing the drop in yield. As a consequence more favorable reaction conditions were required with a higher selectivity for 2-cyclopentenone **105**.

Table 38: First attempts of hydrogenation (1 atm H_2).[a]

Entry	Catalyst	Solvent	t [h]	Yield [%][b]
1	Pd/C	MeOH	19	36
2	Pd/C	H_2O	18	53

a) (±)-**2a** (10 mmol), Pd/C 10% (0.14 mol% Pd). b) isolated yield.

In the following experiments a study on suitable catalysts, reaction time and hydrogen pressure was performed to identify the optimal conditions for improving the yield of the reaction. The screening of different catalysts was performed in an autoclave with 5 bar hydrogen pressure for 15 min (Table 39, Figure 7). In these experiments the crude reaction mixture produced from the continuous flow reactor was used. A typical reaction consisted of 10 mL of aqueous mixture with a concentration of 25 g/L 4-hydroxy-2-cyclopentenone (±)-**2a** in water. The concentrations of starting material (±)-**2a** and product **152** in the reaction before and after the hydrogenation were determined by GC with 1,4-butanediol as internal standard. In terms of selectivity and conversion the Pd catalysts on activated carbon and alumina performed best with almost complete conversion and a high yield of the hydrogenated hydroxycyclopentanone **152** within the applied reaction time (Table 39, entry 1 and 3). The carbon balance observed is high with about 90% and no occurrence of more than trace amounts of cyclopentanone **32** could be denoted. The remaining loss is attributed to several unidentified side products, presumably from resinification, which becomes more severe at higher temperatures.[31,32]

Table 39: Screening of different catalysts.[a]

Entry	Catalyst	Conversion [%][b]	Yield [%][b]	Selectivity [%]
1	Pd/C 10%	98	84[c]	86
2	Pt/C 10%	73	39[d]	54
3	Pd/Al_2O_3 5%	97	89[c]	92
4	$Pd(OH)_2$/C 10–20%	32	19[c]	59

a) (±)-**2a** (10 mL 25 g/L in H_2O, 2.55 mmol), catalyst (0.15 mol% Pd or Pt), H_2 (5 bar), 15 min, rt. b) determined by GC with internal standard (1,4-butanediol). c) by-product cyclopentanone **32** (traces). d) by-product cyclopentanone **32** (~10%).

$Pd(OH)_2/C$ as catalyst showed a three times lower conversion of the starting material (±)-**2a** as the other palladium catalysts, and moreover, the selectivity was low with various unidentifiable side products (Table 39, entry 4). The platinum on charcoal catalyst performed also unsatisfactory with a slightly higher conversion but very low selectivity caused by the further hydrogenation of the double bond in 2-cyclopentenone **105**, leading in this case to about 10% of cyclopentanone **32** (Table 39, entry 2). **105** was formed by the elimination of the hydroxy group in the product (±)-**152**.

Interestingly, the other publications[31, 32] mentioned that the selectivity for cyclopentanone **32** was very high at the elevated temperatures applied (> 140 °C), and 2-cyclopentenone **105** as product was not observed unless a limited amount of hydrogen was used. It can be concluded that at higher temperatures the elimination of the hydroxy-moiety in 3-hydroxycyclopentanone (±)-**152** took place and that lower reaction temperatures allowed a high selectivity for (±)-**152**.

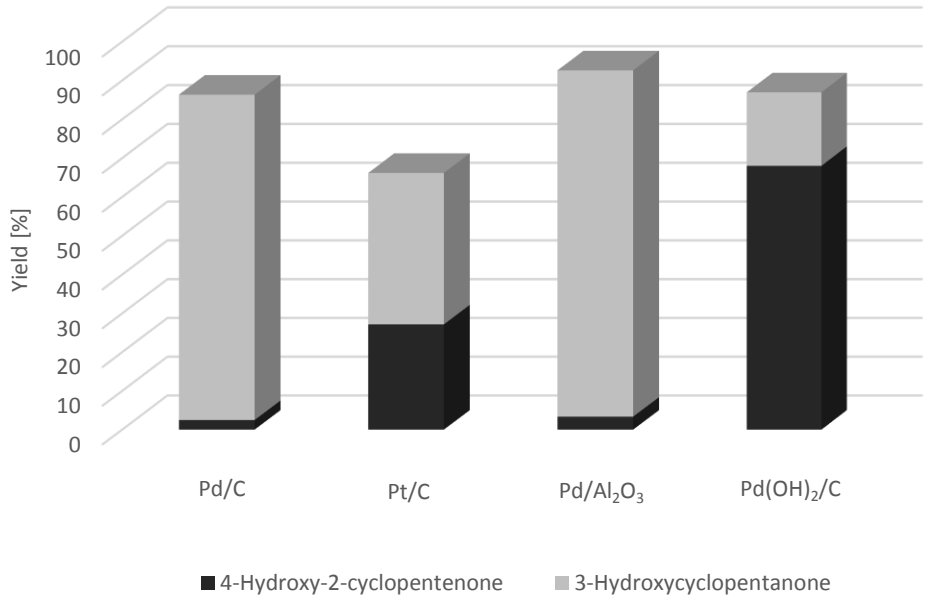


Figure 7: Catalyst screening (Table 39, 5 bar H_2, 15 min, rt, 0.15 mol% catalyst).

As Pd/C proved to be a suitable catalyst for the hydrogenation at room temperature in water, optimization of this reaction system was carried out. The following charts were created using the results gained from experiments with the crude mixture from the continuous flow system. For a typical experiment 10 mL of an aqueous solution with a concentration of approximately 25 g/L 4-hydroxy-2-cyclopentenone (±)-**2a** were applied, and the exact concentration was determined by GC before calculating conversion and yields. 0.15 mol% of palladium on

charcoal was employed with a hydrogen pressure of 5 bar. The yield of the hydrogenation product 3-hydroxy-2-cyclopentanone (±)-**152** was plotted as a function of time.

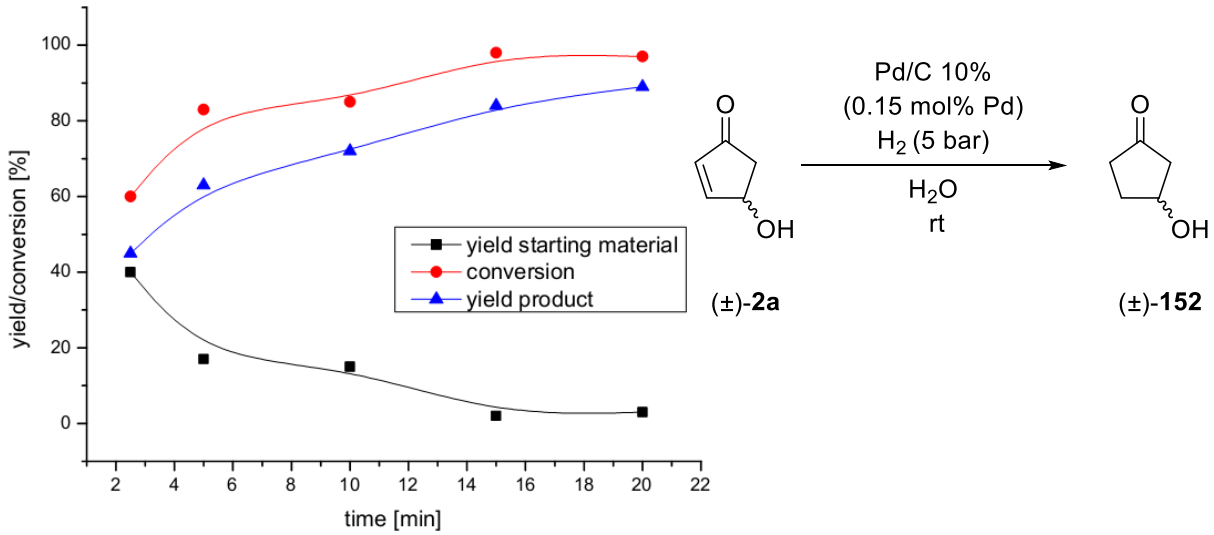


Figure 8: Yield/conversion as a function of time ((±)-**2a** (10 mL 25 g/L in H_2O, 2.55 mmol)).

The conversion was complete under these conditions after 15 minutes and yields of around 80% could be achieved with reaction times of 15–20 minutes. A shorter duration (≤ 10 min) at 5 bar was not sufficient to convert all the starting material. Within the specified reaction times no significant emergence of cyclopentanone **32** was observed. The yield and conversion were determined as before by GC using an internal standard. In the next step the effects of different pressures on yield and conversion were examined. Again the aqueous solution from the continuous flow system was used directly.

With a reaction time of only 2.5 minutes different hydrogen pressures were tested with 0.15 mol% of palladium on charcoal. The yield of 3-hydroxy-2-cyclopentenone (±)-**152** and the conversion of the starting material 4-hydroxy-2-cyclopentenone (±)-**2a** as a function of pressure were plotted. 20 bar of hydrogen pressure sufficed to bring the conversion of the starting material (±)-**2a** to completion within 2.5 min. Yields of about 80-85% could be achieved with 20 and 40 bar pressure. Cyclopentanone **32** as a side product was only observed in trace amounts (< 1%). The catalyst could be simply filtered off after the reaction was finished.

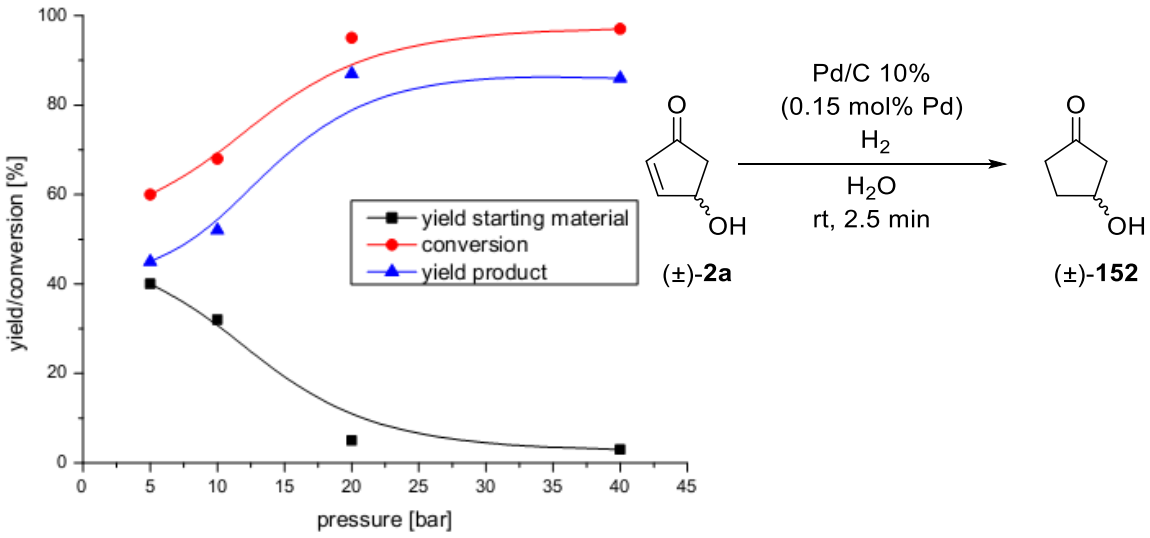


Figure 9: Yield/conversion as a function of pressure ((±)-**2a** (10 mL 25 g/L in H_2O, 2.55 mmol)).

A scale-up of the hydrogenation reaction to a synthetically more valuable dimension of 10 mmol (~ 1g (±)-**2a**) could also be performed in the autoclave (Table 40). Presumably because of a more unfavorable volume to surface ratio in the autoclave (40 mL of reaction mixture), for a full conversion of starting material (±)-**2a** the reaction time had to be increased to 35 min. In the first 15 min only about 50% conversion was observed, in contrast to the 10 mL reaction scale where this time was sufficient for a full conversion. However, after evaporation of the solvent and Kugelrohr distillation the product (±)-**152** could be isolated in 72%.

Table 40: Upscaling of the hydrogenation of (±)-**2a**.[a]

Entry	t [min]	Conversion [%][b]	Yield [%]
1	15	~50	n.d.
2	35	>95	72[c]

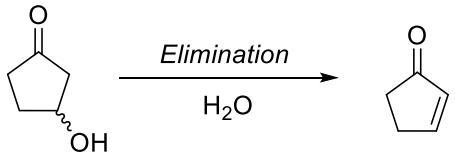
a) (±)-**2a** (40 mL 25 g/L in water, 10 mmol), Pd/C 10% (0.15 mol% Pd), H_2 (5 bar). b) determined approximately by GC without internal standard. c) isolated yield after Kugelrohr distillation.

In comparison with the US patent[137] mentioned above, the hydrogenation was performed in a greatly reduced reaction time (from 3 h described in the patent to minimally 2.5 min) and the reaction can be performed on a synthetically useful scale. Moreover, it can be directly applied

to the solution produced by the continuous flow process developed in our group.[28] An implementation in a subsequent continuous flow system was already successfully tested (Peter Kreitmeier, Reiser group, University of Regensburg) using the commercially available system H-Cube Pro (ThalesNano Nanotechnology Inc.).

3.3 Elimination of the Hydroxy Group

In the publications previously mentioned,[31,32] the elimination of the hydroxy group took already place under the therein described hydrogenation conditions (>30 bar H_2, >140 °C in water), which resulted in cyclopentanone **32** or cyclopentanol **33** as the main products. Therefore, to afford 2-cyclopentenone **105** from alcohol (±)-**152**, the elimination can be carried out conveniently at elevated temperatures without applying hydrogen in water.



(±)-**152** **105**

Scheme 55: Elimination of the hydroxy group of **(±)-152**.

Initially, experiments were carried out using the previously isolated starting material 3-hydroxy-cyclopentanone (±)-**152** (Table 41). An acid catalyst (HCl and in the other instance the acidic ion exchanger Amberlyst XN1010) or no catalyst at all was employed. The acidic ion exchange resin had the advantage of being easily removable and potentially applicable in a continuous flow system. Both catalysts gave the desired product in about 60% yield (entry 1 and 2, Table 41). Even by heating the aqueous solution without any additional catalyst, the hydroxy group could be eliminated, though very slowly.

Table 41: Elimination reactions using conventional heating.[a]

Entry	Catalyst	t	T [°C]	Yield [%][b]
1[c]	HCl	15 min	70	57
2[d]	Amberlyst XN1010	4 h	70	61
3	-	8 h	100	16[e]

a) (±)-**152** (1 mmol), H_2O (4 mL), c = 25 g/L. b) isolated yield. c) pH = 1. d) (±)-**152** (0.4 mmol), Amberlyst XN1010 (20 mg), H_2O (2 mL). e) conversion not complete.

Therefore, the conduction of the elimination reaction in a closed vessel under microwave irradiation was considered, as this allows to heat the solvent over the boiling point at atmospheric pressure. Alcohol (±)-**152** was dissolved at a concentration of 25 g/L in water and then subjected to the conditions described in Table 42.

Table 42: Reaction under microwave irradiation.[a]

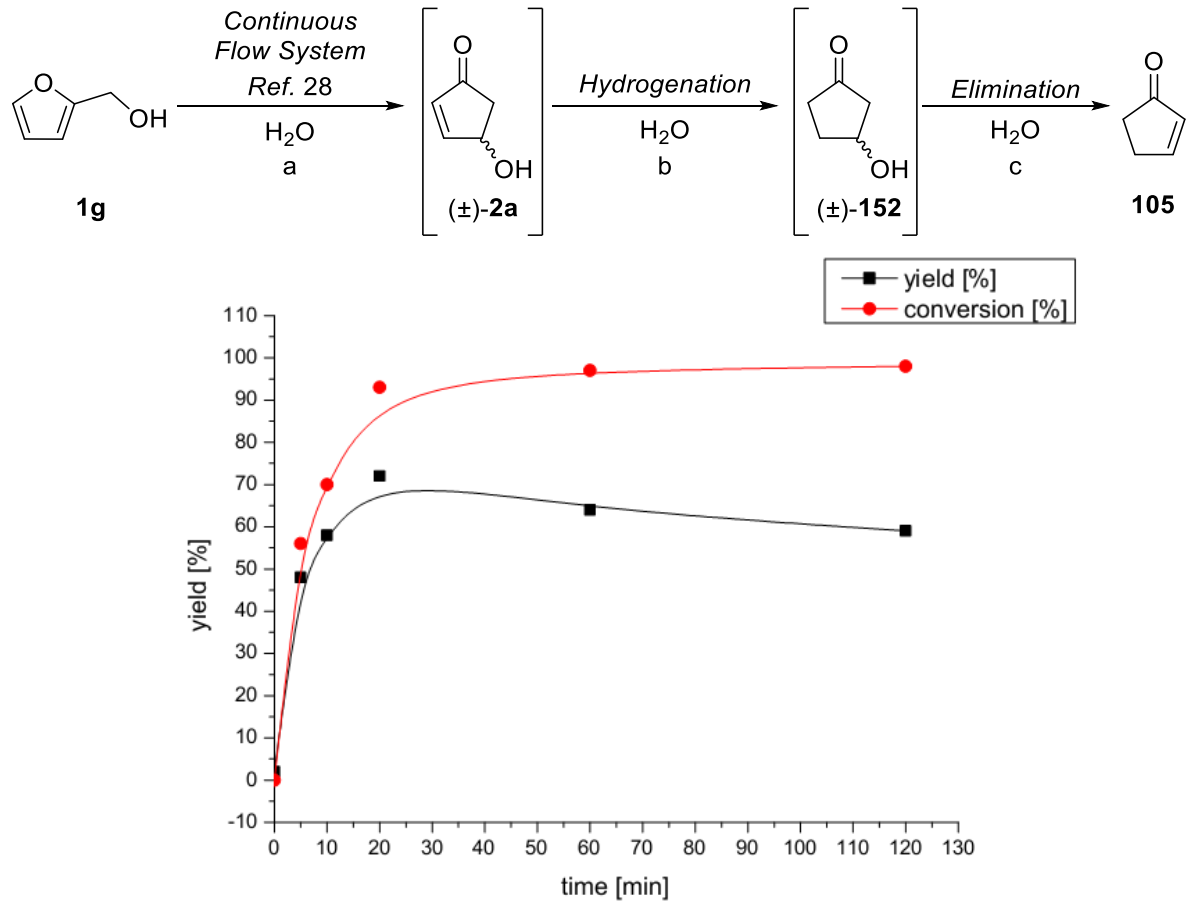
Entry	t [min]	max T [°C]	Yield [%][b]
1	5	180	44
2	2x5	180	77
3	10	180	63
4	15	180	66

a) (±)-**152** (1 mmol), H_2O (4 mL), c = 25 g/L MW: 300 W, closed pressure vessel. b) isolated yield.

To avoid exceeding the pressure limitation of the microwave (CEM Discover), a temperature limit was set at 180 °C at which the power was regulated to maintain the temperature. A reaction time of 5 min did not lead to a full conversion of the starting material (±)-**152** (entry 1, Table 42)**,** but in 10–15 min at 180 °C in the microwave yields up to 77% and full conversion was achieved (entry 2–4, Table 42). No plausible explanation could be given for the discrepancy in yields in entry 2 and 3.

3.4 One-Pot-Procedure Rearrangement/Hydrogenation/Elimination

The previous experiments proved that the hydrogenation step and the elimination step could be performed individually, and moreover the hydrogenation step was successfully combined with the rearrangement in the continuous flow system. The final task in this project comprised the development of a one-step procedure without any additional work-up between the rearrangement, hydrogenation and elimination besides the filtration step to dispose of the catalyst. The concentration of compound (±)-**2a** was measured by GC before the hydrogenation was carried out (Pd/C, 5 bar H_2, 15 min) and the catalyst was filtered off afterwards. The acidic ion-exchange resin Amberlyst XN1010 was added and the solution heated to 90 °C. After the specified periods of time the yield of 2-cyclopentenone **105** was determined via GC.



Conditions: a) **1g** (25 g/L in H_2O), continuous flow system.[50] b) 10 mL, H_2 (5 bar), Pd/C 10% (0.15 mol% Pd), rt, 15 min. c) 4 mL, Amberlyst XN1010 150 mg, 90 °C (yield/conversion determined via GC with internal standard (1,4-butanediol)).

Figure 10: Elimination reaction of one-pot-procedure.

The data is displayed in the graph in Figure 10 as yield of 2-cyclopentenone **105** and the conversion of 3-hydroxycyclopentenone (±)-**152** as a function of time. The yield is based on the starting concentration of 4-hydroxy-2-cyclopentenone (±)-**2a**. Within 20 minutes of reaction time full conversion and a yield of 70% were achieved, whereas longer reaction times decreased the yield of the product **105**.

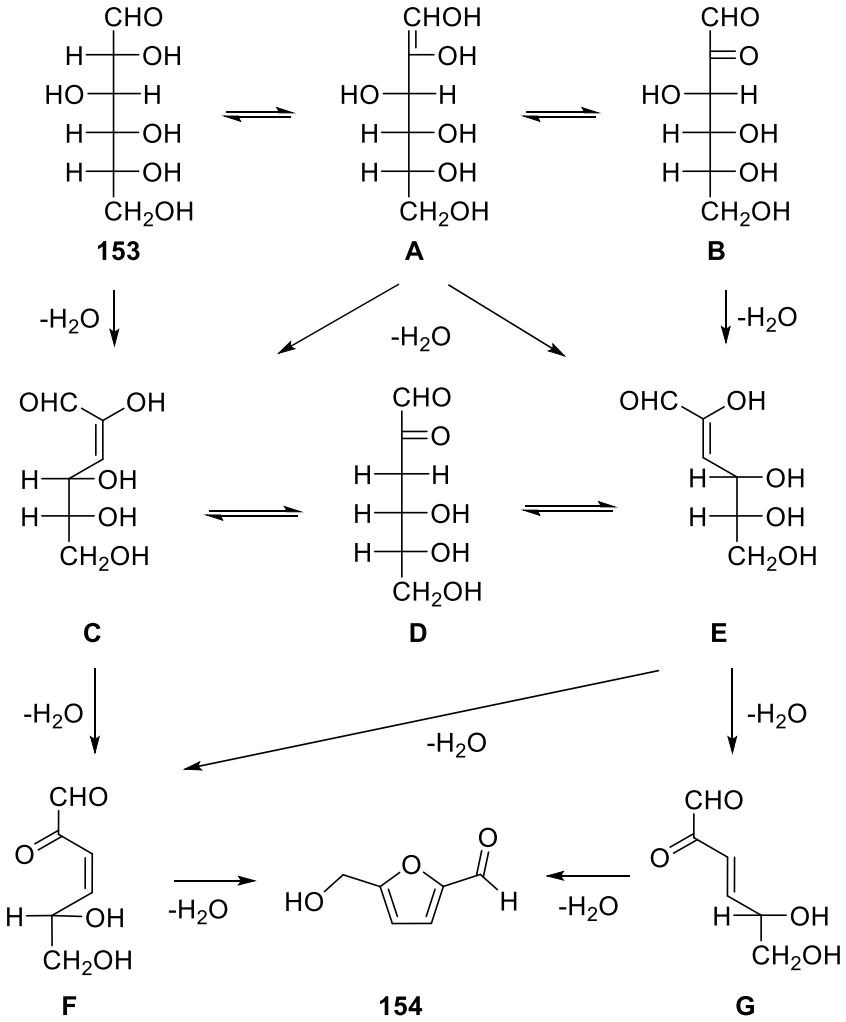
3.5 Conclusion

Reaction conditions were developed to convert 4-hydroxy-2-cyclopentenone (±)-**2a** in the aqueous solution from the continuous flow system into the less water-soluble 2-cyclopentenone **105** in a hydrogenation/elimination sequence. The hydrogenation step was optimized with a Pd/C catalyst to afford (±)-**152** in 80–85% yield. The elimination step could be performed either by conventional heating with an acid catalyst or by heating in a microwave oven to provide the product **105** in up to 77% yield. It was confirmed that all the reactions could be performed in a one-step procedure in direct continuation to the continuous flow process in water leading to an overall yield of 70%. The conditions are suitable for implementation in a subsequent continuous flow process following the rearrangement of **1g** to (±)-**2a**.

4. Investigation of the Piancatelli Rearrangement of HMF/BHMF in the Microwave

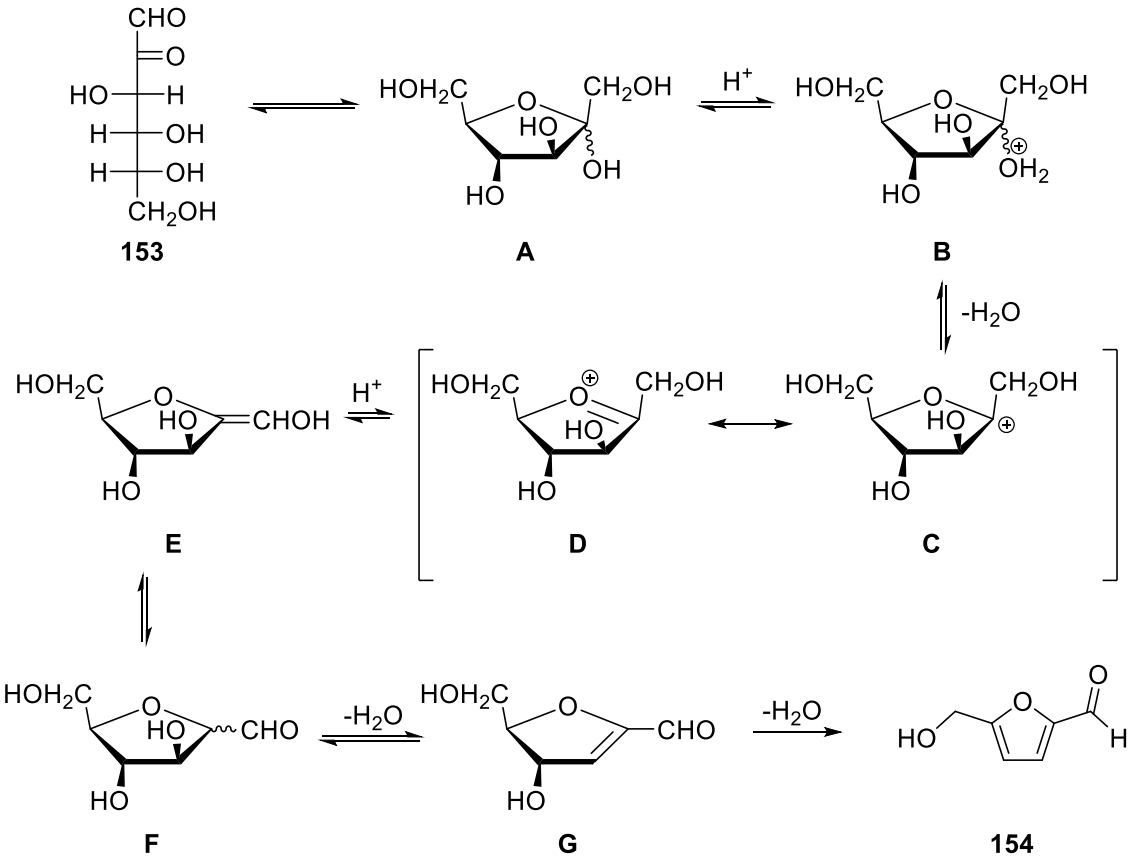
4.1 Introduction

The lignocellulosic feedstock provides also possibilities for the production of other furan derivatives. As furfuryl alcohol **1g** and furfural **13** are synthesized from the hemicellulosic part containing pentoses, 5-hydroxymethylfurfural (HMF) **154** can be accessed by the cellulosic fraction (which consists of the hexose glucose). Acid catalyzed dehydration provides the desired compound **154** starting from various hexoses such as glucose or fructose **153**.[51] Two different mechanisms are proposed in literature describing the conversion of hexoses to HMF **154**.[138] The first one proceeds via an open-chain sequence of dehydrations of the sugar molecule (Scheme 56).



Scheme 56: Open-chain mechanism for HMF **154** generation.[138]

The second mechanism involves the closed-ring structures in the dehydration process (Scheme 57).

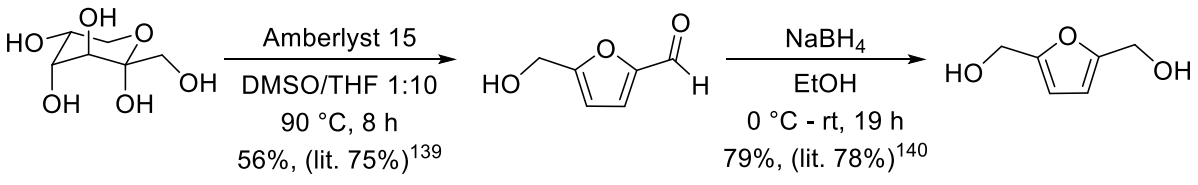


Scheme 57: Closed-ring mechanism for HMF **143** generation.[138]

The reduction of HMF **154** affords bis-(2,4-hydroxymethyl)furan (BHMF) **155**, another interesting furan derivative. In the following chapters, the reactivity of HMF **154** and BHMF **155** in a microwave heated subcritical aqueous medium was explored, paying particular focus on the Piancatelli type rearrangement.

4.2 Synthesis of 5-Hydroxymethylfurfural (HMF) and 2,5-Bis(hydroxymethyl)furan (BHMF)

The two furan derivatives HMF **154** and BHMF **155** were synthesized following literature known methods (Scheme 58).[139,140] Heating *D*-fructose **153** in a DMSO/THF solvent mixture with the acidic ion exchanger Amberlyst 15 afforded HMF **154** in 56% yield following the procedure of Rauchfuss *et al*.[139]



153 **154** **155**

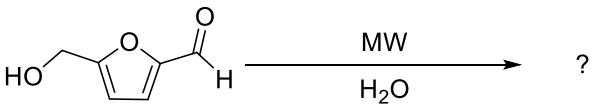
Scheme 58: Synthesis of HMF **154** and BHMF **155**.

Reduction of HMF **154** with $NaBH_4$ provided BHMF **155** in 79% yield as a white solid that could be effectively recrystallized from chloroform.[140]

4.3 HMF under microwave irradiation in subcritical aqueous medium

The concept of microwave-assisted reactions of furan derivatives in water was investigated further to ascertain if similar rearrangement processes as with α-furylcarbinols could be observed with HMF **154** or compounds directly derived from it. Therefore, at first HMF **154** was heated in the microwave in an aqueous medium to temperatures between 133–240 °C (Table 43).

Table 43: HMF **154** in water under different microwave conditions.[a]



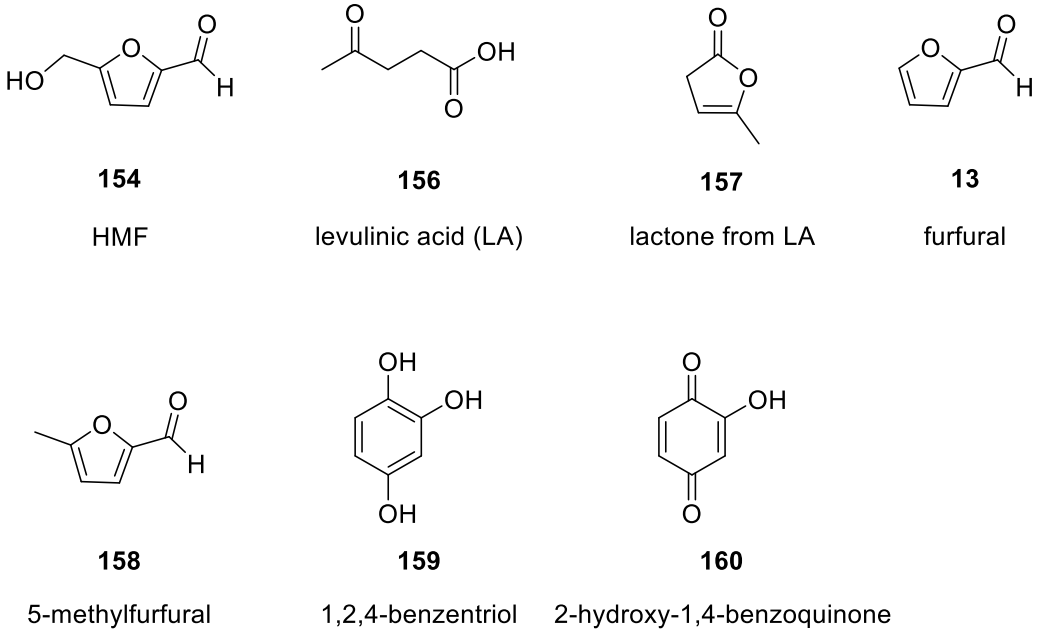
154

Entry	c [g/L]	V [mL]	P [W]	t [min]	T_{max} [°C]	p_{max} [bar]	Yield [%]
1[b]	25	1	300	10	133	3	0
2[b]	25	1	300	30	-	-	0
3[c]	28	1	50–150	10	200	13	0
4[c]	27	1	50–250	10	240	29	0

a) closed pressure vessel. b) CEM Discover, P_{max} = 300 W, pressure limitation 17 bar. c) Anton-Paar Monowave 300, P_{max} = 850 W, pressure limitation 30 bar.

Initially, 1 mL of an aqueous solution with a concentration of 25 g/L HMF **154** was heated in the CEM Discover microwave at 300 W (maximum power) for 10 minutes. Under these conditions the reaction mixture reached a temperature of 133 °C, but no conversion was observed (entry 1, Table 43).Prolonging the reaction time from 10 to 30 minutes did not result in any conversion, although the temperature was presumably higher (entry 2, Table 43, unfortunately the microwave did not record the reaction parameters in this instance). To use more forcing conditions the Anton Paar Monowave 300 microwave was used. It is limited to 30 bar instead of 17 bar as the CEM device, permitting higher reaction temperatures. First HMF **154** was heated up to 200 °C for 10 minutes, then to 240 °C for 10 minutes which seemed to be the maximum which was achievable (entry 3 and 4, Table 43, almost 30 bar pressure were reached under these conditions). However, even despite these high temperatures only starting material **154** could be recovered. The absence of any conversion was confirmed by NMR and by the quantitative reisolation of HMF **154**.

In literature, reactions of HMF **154** in subcritical water at significantly higher temperatures are described where various products were observed (Scheme 59). However, to obtain one of these compounds temperatures over 290 °C were required,[141,142] which is evidently beyond the range of values achievable with the herein described microwave devices.



154 HMF

156 levulinic acid (LA)

157 lactone from LA

13 furfural

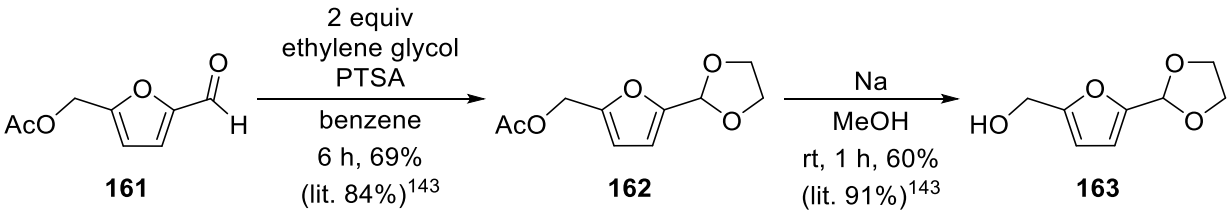
158 5-methylfurfural

159 1,2,4-benzentriol

160 2-hydroxy-1,4-benzoquinone

Scheme 59: Products from reaction of HMF **154** in subcritical water.[141,142]

An explanation for the absent reactivity in the rearrangement reaction can be deduced from contemplating the mechanism, which postulates initially a leaving of the OH-group after its protonation. The electron withdrawing nature of the aldehyde moiety on the other side of the ring might inhibit this type of reaction. To reduce its electron withdrawing effect the protection of the aldehyde moiety of HMF **154** with ethylene glycol to provide the acetal was considered. The acetal was synthesized following a literature known procedure (Scheme 60).[143] Starting from acetylated HMF **161** which was reacted with ethylene glycol using a Dean-Stark apparatus the acetal **162** was obtained, which gave after deacetylation the desired product **163**.

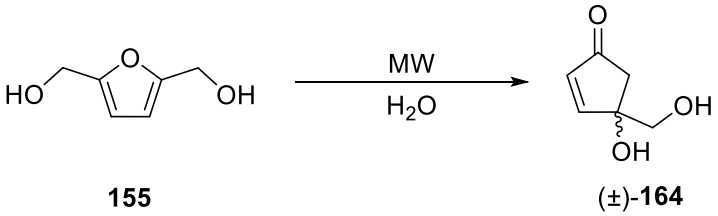


Scheme 60: Synthesis of HMF ethylene acetal.

Compound **163** was subjected to microwave irradiation in an aqueous medium for 10 min at 300 W. However, the acetal was not stable and before losing the hydroxyl-group the aldehyde functionality on the other side of the ring reformed. Consequently, only HMF **154** could be reisolated quantitatively.

4.4 Microwave-assisted Piancatelli Rearrangement of BHMF in subcritical water

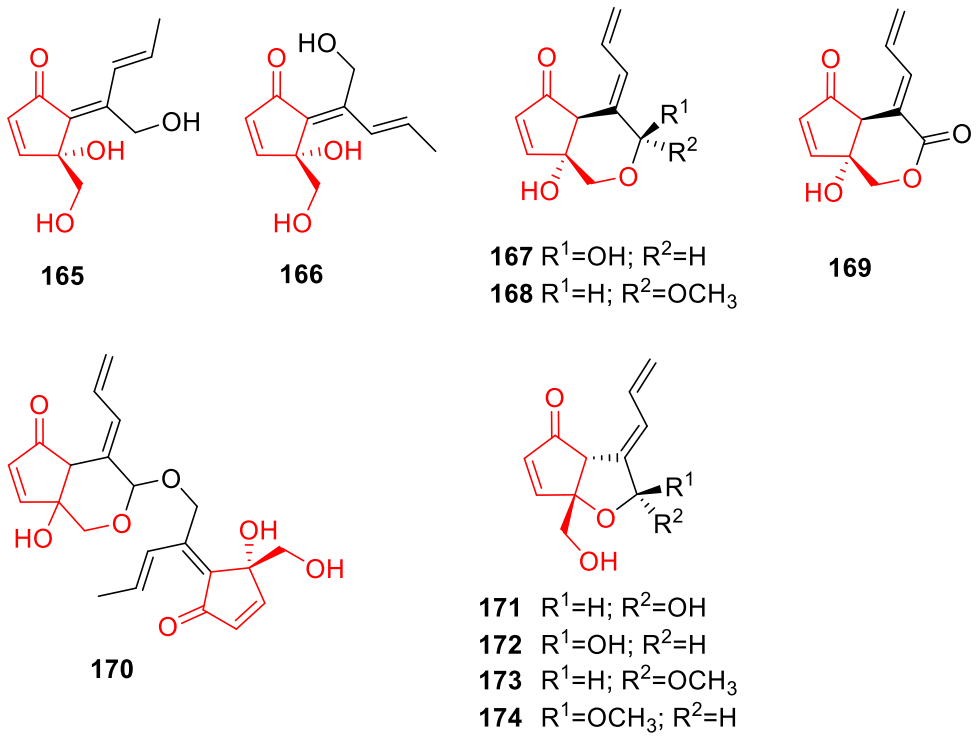
Since HMF **190** reacted rather disappointing in the microwave even under forcing conditions, its reduction product, the bis-alcohol BHMF **155**, was examined. The unreactive behaviour in the rearrangement reaction due to the electron-withdrawing effect of the aldehyde moiety as in HMF **154** should thereby be omitted. In fact, compound **155** exhibits one OH-group on each side of the furan ring which has the potential to be protonated and depart as leaving group to initiate the rearrangement. Interestingly, no literature evidence has been found dealing with the Piancatelli rearrangement of BHMF **155**. In view of the increasing interest in using renewable resources the conversion of BHMF **155** into the substituted cyclopentenone (±)-**164** by this method would be an attractive straightforward procedure.



155 (±)-**164**

Scheme 61: Piancatelli rearrangement of BHMF **155** in water.

Considering the mechanism of the rearrangement (Scheme 62), product (±)-**164** should be expected. This structural motif can be found in different biologically active natural products isolated from marine organisms. In ascidians from the family of the Didemnidae, precisely the species *Lissoclinum* sp. and *Diplosoma* sp., compounds **165–168** in the former and compounds **165**, **166**, **169** and **171–174** in the latter, have been found. Compounds **165** and **166** were significantly cytotoxic against the HCT116, A431 and A549 cancer cell lines, and compounds **167**, **168**, **170**, **171/172** and **174** revealed cytotoxicity against the cell lines HCT116 and A431.[144]



165 **166** **167** R^1=OH; R^2=H
168 R^1=H; R^2=OCH_3 **169**

170

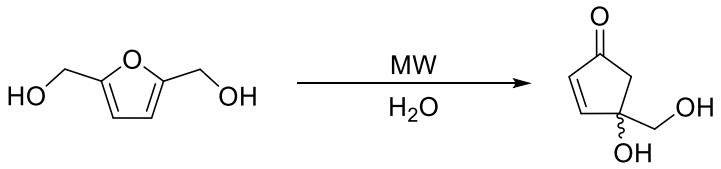
171 R^1=H; R^2=OH
172 R^1=OH; R^2=H
173 R^1=H; R^2=OCH_3
174 R^1=OCH_3; R^2=H

Figure 11: Natural products containing the structural motif of cyclopentenone **164**.[144]

For the rearrangement reaction of BHMF **155**, at first the optimized conditions for this reaction with furfuryl alcohol **1g** in the microwave were applied (Table 13).[28] BHMF **155** at a mass concentration of approximately 25 g/L in water was irradiated in the microwave (CEM

Discover) in a 10 mL closed pressure vessel. The first reaction conducted at 300 W and 5 minutes reaction time reached a maximum temperature of 146 °C, but no conversion of the starting material **155** was observed (entry 1, Table 44). A higher reaction temperature was considered as the rearrangement did not occur as smoothly as with furfuryl alcohol **1g**, which already reacts at temperatures of 100 °C (Table 13).[28] Since 300 W indicates the power limit of the CEM device, longer reaction times had to be applied for reaching higher temperatures to force the rearrangement to occur (temperature increase becomes slower at higher values). This led to a maximum temperature of 195 °C after 23 minutes which was eventually sufficient to allow a reaction to take place (entry 2, Table 44). The resulting complex mixture could not be separated efficiently. Additionally the reaction volume was on a small scale (1 mL), but nevertheless it included the desired product judging from NMR measurements.

Table 44: Conditions for the rearrangement reaction of BHMF **155** in the microwave (CEM).[a]



155 (±)-**164**

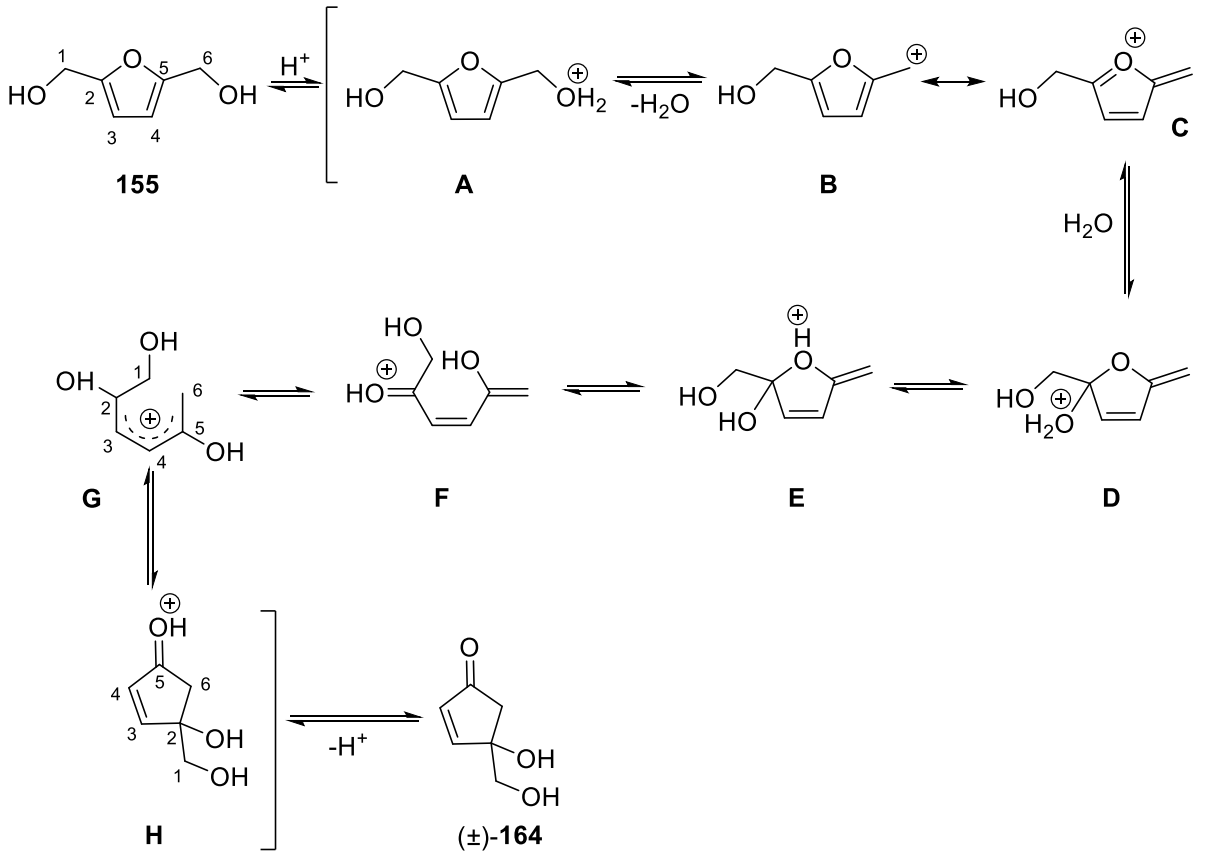
Entry	c [g/L]	V [mL]	Power [W]	T_{max} [°C]	p_{max} [bar]	t [min][b]	Yield [%][c]
1	33	1	300	146	7	5	0
2	25	1	300	195	17	23 (30)	-
3	50	1	300	188	17	14 (20)	59[d]
4	25	10	300	199	18	1.54 (30)	0
5	25	10	variable	185	14	21	60[d]
6	21	10	variable	181	12	12	67
7	25	10	variable	182	12	7	59

a) closed pressure vessel. b) in parentheses: manually adjusted reaction time; outside parentheses: actual reaction time (caused by switching-off due to excessive pressure development). c) isolated yield. d) some impurities.

An enhancement of the concentration to 50 g/L BHMF **155** in water resulted again in a mixture which could not be separated completely due to significant generation of by-products. Nevertheless, the desired product of the reaction could again be observed in the NMR spectra (entry 3, Table 44). To render the separation more facile and to still have the benefit of low concentrations (higher concentrations in this rearrangement reaction ordinarily favor the development of more side products), a larger reaction volume of 10 mL in a 35 mL reaction vessel was chosen (entry 4, Table 44). Applying again 300 W (maximum energy input for this microwave), the reaction stopped automatically after less than 2 minutes because the temperature reached rapidly almost 200 °C and the pressure exceeded the microwave´s pressure limitations (17 bar, CEM discover). Therefore, a temperature limit was set at 180 °C to prevent the pressure to excel the safety value. This approach proved to be successful and the next reaction could be conducted for about 20 min leading to 60% yield of the product (entry 5, Table 44). Unfortunately, the product was still contaminated with several side products that could not be separated. Reduction of reaction time should probably reduce the formation of side products, and this assumption was confirmed as shown in entry 6 and 7 (Table 44), where the clean product (±)-**164** could be isolated in 67% and 59% yield.

There is no literature evidence concerning the particular rearrangement of **155** to (±)-**164**, but a publication describing the hydrogenation of HMF **154** at high temperatures (160 °C, 4 h, 40 bar H_2) in water over a Ni-Cu bimetallic catalyst describes the observation of BHMF **155** as hydrogenation product. Therefore, BHMF **155** was exposed to 160 °C in water for a prolonged time. They could not observe any rearrangement products or hydrogenation products of **155** under the described conditions, thus a temperature over 160 °C is apparently required to achieve this transformation.

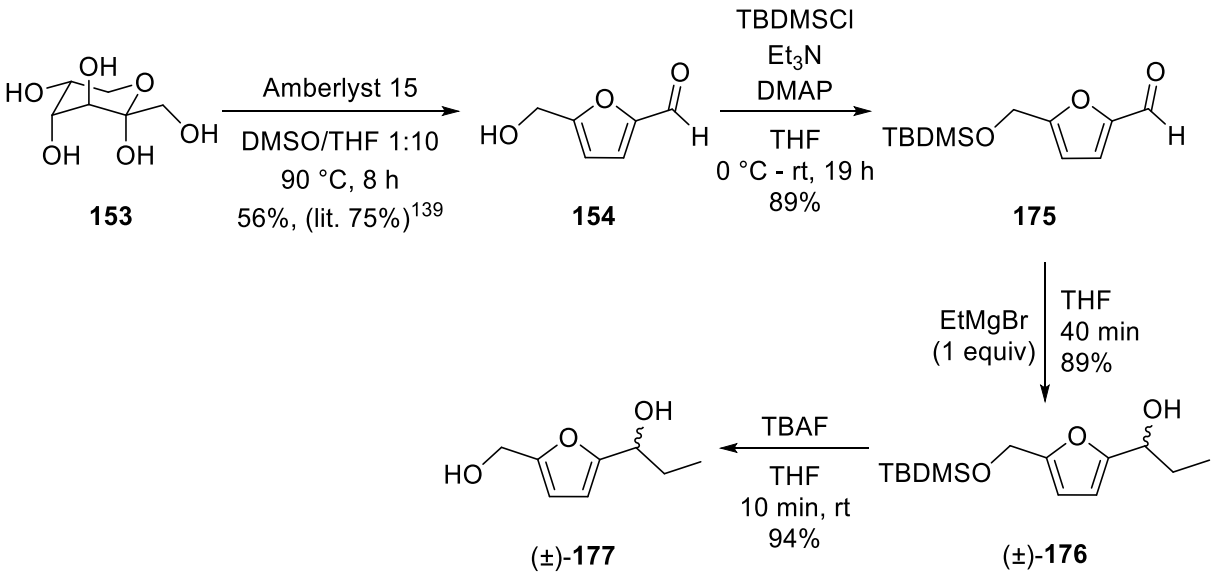
Piancatelli proposed a mechanism for the rearrangement of α-furylcarbinols,[1] and a slightly adapted version concerning the different substitution pattern is proposed in Scheme 62. It shows that protonation of the hydroxy group of α-furylcarbinol **155** leads to the expulsion of a water molecule forming oxocarbenium ion **B/C**. On the other side of the furan ring where the second hydroxymethyl moiety is situated a water molecule can attack as nucleophile. After a prototropic shift and ring opening intermediate **G** undergoes a 4π-conrotatory electrocyclic ring closure which leaves one hydroxy group and the hydroxymethyl moiety on the same carbon atom of the newly formed racemic carbocyclic compound (±)-**164**.



Scheme 62: Mechanism of Piancatelli rearrangement of BHMF.

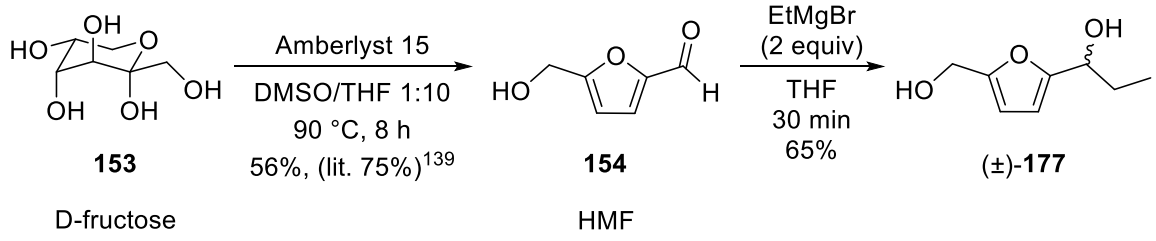
4.5 Synthesis of BHMF Derivative

As the rearrangement of BHMF **155** was successful, another objective was to use a different derivative of BHMF **155** to evaluate its behavior when subjected to similar conditions and to find a conceivable application. A derivative containing an ethyl substituent adjacent to one of the hydroxy functionalities was synthesized (Scheme 63). Starting again from D-fructose **153** HMF **154** was synthesized as before.[139] The free hydroxy group was protected with TBDMSCl to provide **175** in 89% yield. This compound was then subjected to a Grignard reaction with EtMgBr to afford (±)-**176** in 89% yield. Almost quantitative deprotection led to the desired product (±)-**177**.



Scheme 63: Synthesis of BHMF derivative (±)-**177**.

The inefficiency regarding the atom economy of this reaction sequence utilizing the protection/deprotection method with the bulky TBDMS-protecting group could be avoided by using 2 equivalents of EtMgBr without any protection of the hydroxy functionality. This resulted in the desired product (±)-**177** directly from HMF **154** in 65% yield and in 2 steps from D-fructose **153**.



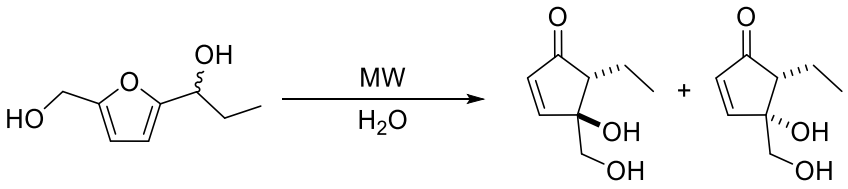
Scheme 64: Alternative route to BHMF derivative (±)-**177**.

4.6 Piancatelli Rearrangement of 1-(5-(Hydroxymethyl)furan-2-yl)propan-1-ol

BHMF derivative (±)-**177** was exposed to a high temperature aqueous environment under microwave irradiation to study its rearrangement. Full conversion was detected with a small scale reaction of 1 mL with 33 g/L concentration of starting material (±)-**177** in water in 30 minutes of reaction time, leading to a maximum temperature of 187 °C (entry 1, Table 45). In the crude NMR spectra a diastereomeric mixture of compound **178** was observed, however, only one diastereomer could be isolated after column chromatography. This may be due to

isomerization on the column at the C5 carbon. The diastereomeric ratio could not be determined because of overlapping signals in the NMR. Increasing the reaction volume to 6 mL with a concentration of 25 g/L led to a lower maximum temperature, but the conversion was still complete after 20 or 30 minutes affording the product in 67% or 74% yield, respectively (entry 2 and entry 3, Table 45).

Table 45: Rearrangement of (±)-**177** in the microwave (CEM, P = 300 W).[a]

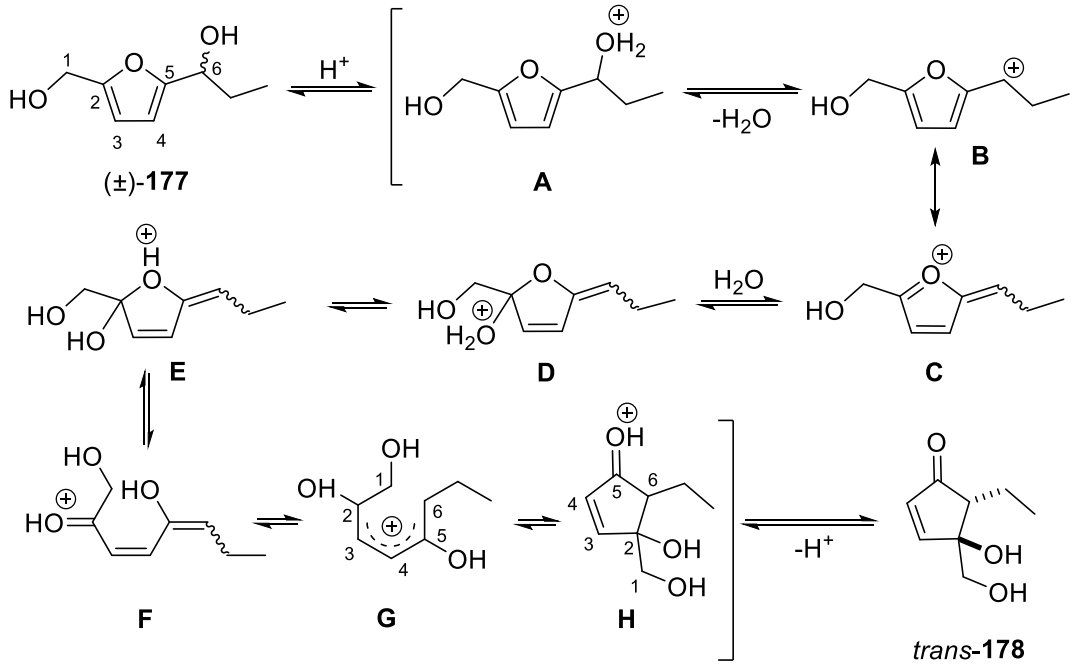


(±)-**177** *trans*-**178** *cis*-**178**

Entry	c [g/L]	V [mL]	max T [°C]	max p [bar]	t [min]	Yield [%][b]
1	33	1	187	13	30	30
2	25	6	133	4	20	67
3	25	6	144	5	30	74

a) closed pressure vessel. b) isolated yield, one diastereomer after column chromatography.

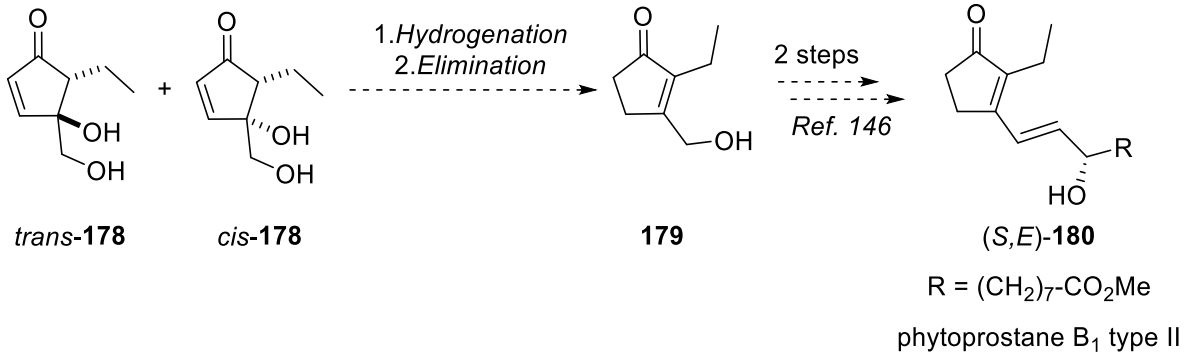
At temperatures exceeding 180 °C a significant loss of material could be stated, observed as a solid black material at the surface of the glass vials used. Concluding from the mechanism (Scheme 65) and observations in other publications, typically the substituent in 5-position and the OH-group formed exclusively a *trans*-relation on the ring (in some cases as the major diastereomer),[145,61] therefore it was assumed that the diastereomer with *trans*-configuration concerning the ethyl- and the hydroxy-moiety was also the major product in this particular case. In own experiments on substituted furfuryl alcohols also the *trans*-isomer was the major product, however, the minor isomer could not be isolated on column chromatography, presumably due to isomerisation.[61]



Scheme 65: Mechanism of Piancatelli rearrangement of BHMF derivative (±)-**177**.

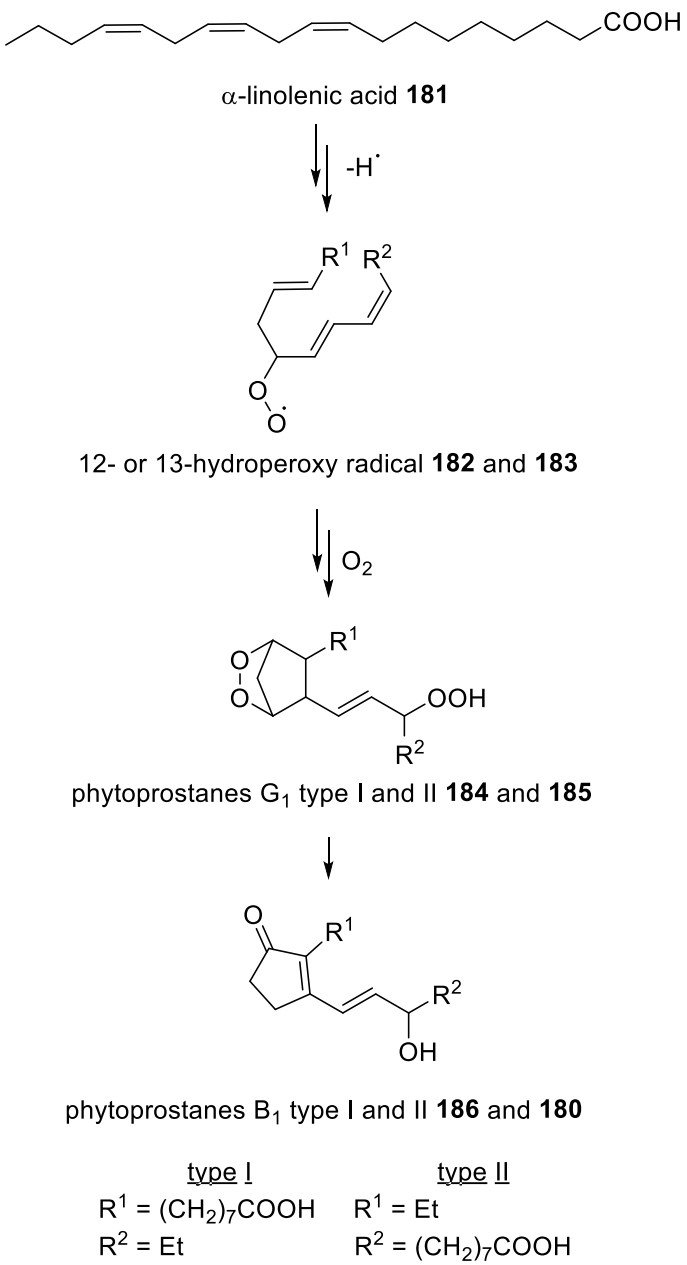
4.7 Formal Synthesis of Phytoprostane B_1 Type II

As application for this reaction a one-pot hydrogenation/elimination sequence in aqueous solution ensuing the rearrangement of (±)-**177** can be utilized to obtain intermediate **179,** which is used in the synthesis of phytoprostane B_1 type II (*S,E*)-**180** (Scheme 66). The obvious advantage of this method is the use of renewable starting materials and a straightforward synthetic procedure. Any difficulties with the separation of diastereomeric mixtures of products in the rearrangement reaction could be omitted by this strategy by simply converting *trans*-**178** and *cis*-**178** into intermediate **179**, which can be further transformed by two literature known steps[146] into PPB_1 type II (*S,E*)-**180**.



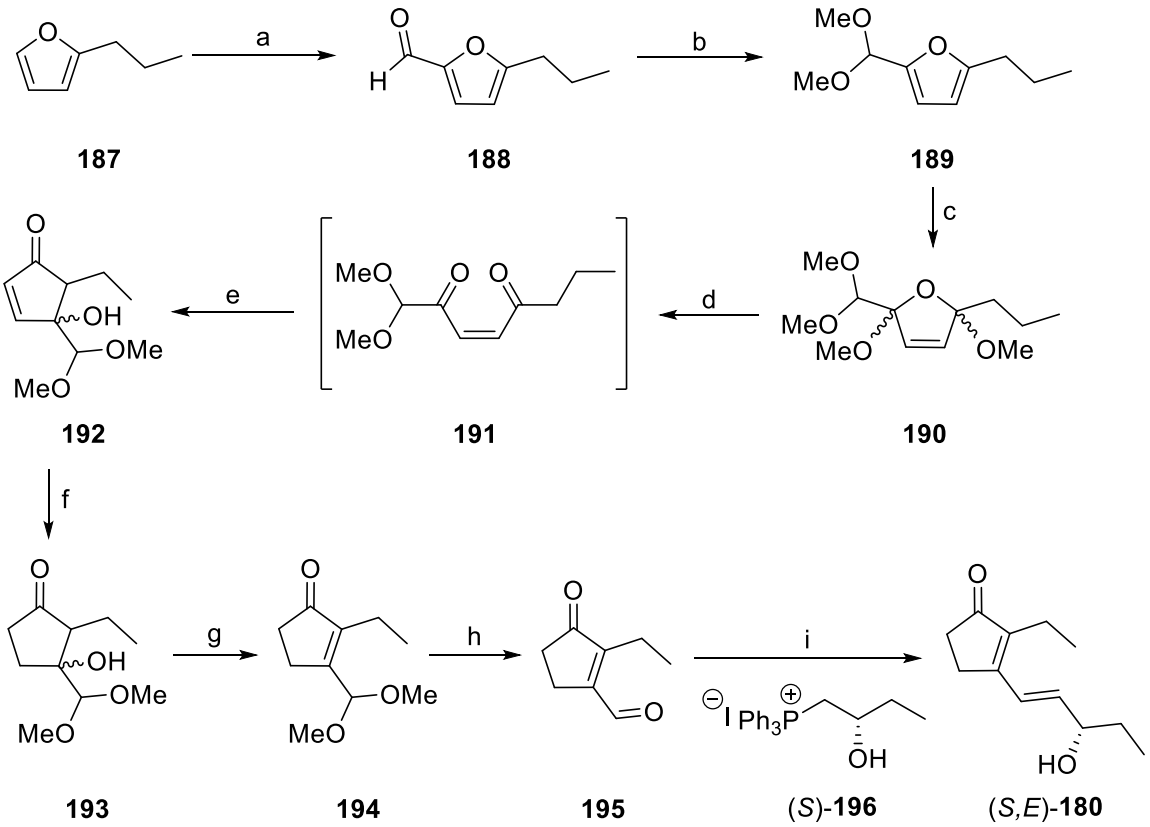
Scheme 66: PPB_1 type II from compound **178** (final 2 steps literature known).[146]

Phytoprostanes[147,148] are like the isoprostanes[149,150,151] a family of compounds known as biomarkers for oxidative stress from the free radical catalyzed peroxidation of polyunsaturated fatty acids (Scheme 67). Unlike the 20 carbon containing isoprostanes which derive from arachidonic acids and occur in mammals, the phytoprostanes are produced from α-linolenic acids in plants and constitute an 18 carbon scaffold. They have presumably a possible function of a plant defense mechanism in response to oxidative stress.[152] PPE_1 and PPF_1 were described by Parchmann and Mueller[147] in 1998 and Imbusch and Mueller[152] in 2000 and the phytoprostanes A_1 and B_1 type I **186** and type II **180** by Mueller in 2003.[150] Zanoni *et al.* reported the first synthesis of phytoprostane A_1[153] and Spur *et al.* published the synthesis of 15-E_2-isoP(PPE_2).[154] Phytoprostanes F_1 were first synthesized by Durand *et al*.[155]



Scheme 67: Phytoprostane pathway from α-linolenic acid.[147]

Up to now 4 methods appeared in literature to synthesize the natural products PPB_1 **186** and **180**. The first synthetic procedure (Scheme 68) appeared in 2005 published by Durand and co-workers, providing both enantiomers of the phytoprostanes B_1 of type I **186** and II **180** in enantiomerically pure form.[156] Type I compound **186** was synthesized starting from furfural **13** in 11 steps and 5.3% overall yield. For PPB_1 type II **180** they used the furan derivative 2-propylfuran **187** which they obtained commercially as starting material, but the synthesis is rather tedious (all in all 9 steps with 8.3% overall yield, Scheme 68).

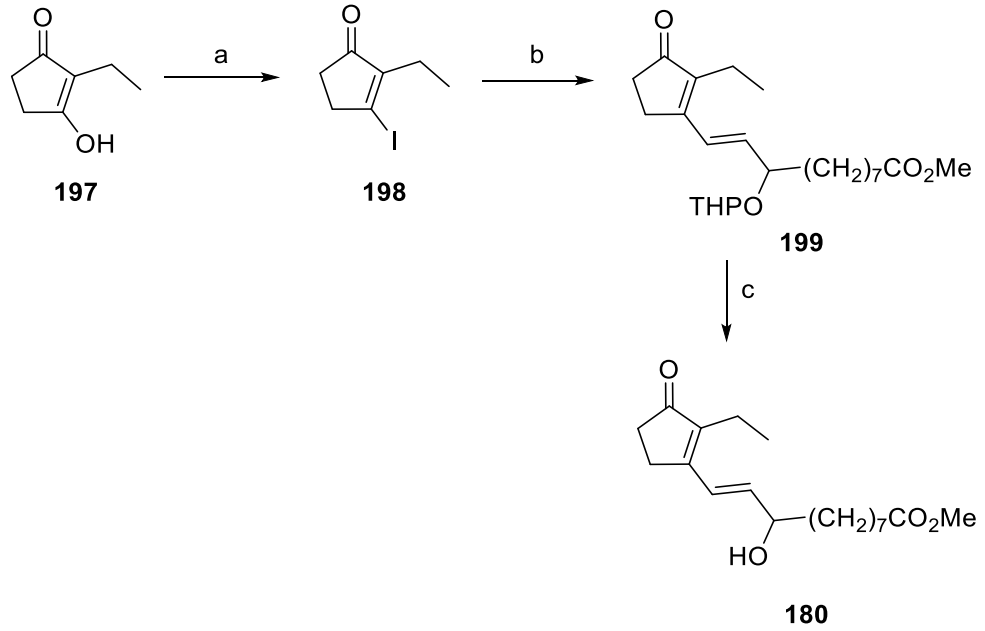


Conditions: a) DMF (1.3 equiv), $POCl_3$ (1.1 equiv), 70 °C, 3 h, 75%. b) $HC(OMe)_3$ (1.6 equiv), *p*-TsOH (0.014 equiv), MeOH, 0 °C – rt, 2 h, 93%. c) Na_2CO_3 (1.5 equiv), Br_2/MeOH (2.25 M, 1.05 equiv), –30 °C, 2 h. d) citric acid (0.1 N), Na_2HPO_4, dioxane, 55 °C, 2 h. e) Na_2HPO_4 (0.2 N), 75 °C, 2 h, 75% after three steps. f) H_2, Pd/C 10% (3% Pd), MeOH, 30 min. g) HCl 3% in MeOH, 20 °C, 3 h, 69% after two steps. h) HCl (1 N), THF, rt, 5 h. i) LiHMDS (1 M in THF, 1.9 equiv), THF, –78 °C, 20 min, 23% after two steps.

Scheme 68: Synthesis of PPB_1 type II according to Durand *et al.*[156]

n-Propylfuran **187** was subjected to a Vilsmeier formylation leading to aldehyde **188**, which was protected subsequently with trimethyl orthoformate under acidic conditions to yield **189**. Oxidation of the furan ring led to bis-acetal **190**, which underwent ring opening under acidic hydrolytic conditions. Ring closure was achieved by treatment with base providing cyclopentenone **192**. Hydrogenation of **192** followed by dehydration and hydrolysis gave aldehyde **195**, which could be coupled with phosphonium salt (*S*)-**196** to yield the desired product (*S*,*E*)-**180**.

In 2006 a protocol for synthesizing phytoprostanes B_1 type I **186** and II **180** was published by Boland *et al.* wherein the very straightforward method provides the products in racemic form.[157] The starting material for the type II synthesis, **197**, was commercially available (Scheme 69).

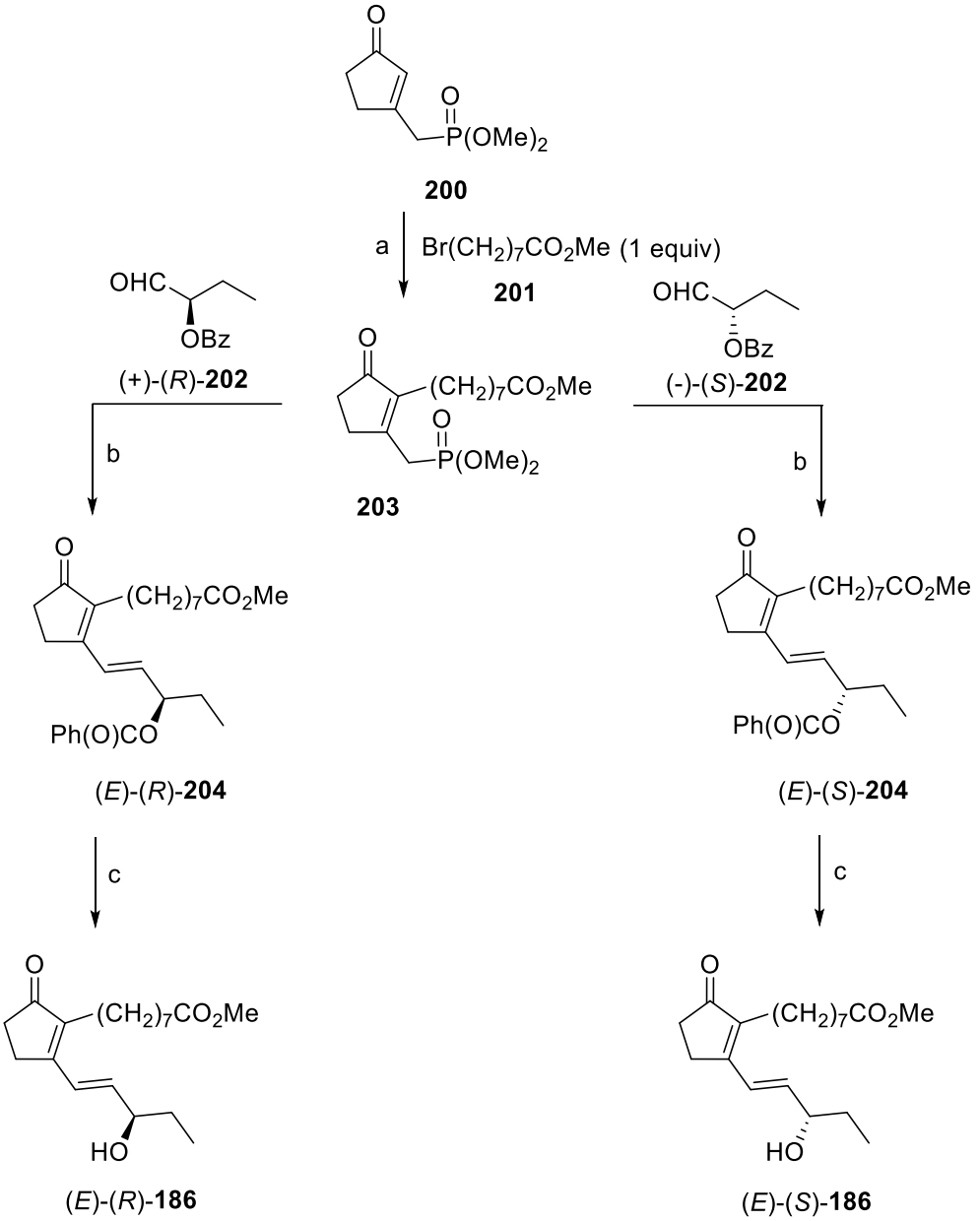


Conditions: a) PPh_3 (1.125 equiv), I_2 (1.125 equiv), Et_3N (1.1 equiv), CH_3CN, 24 h, 77%. b) $CH_2CHCH(OTHP)R_2$ (1.67 equiv), Et_3N (2 equiv), $Pd(OAc)_2 \cdot 2\ PPh_3$, 24 h, 100 °C. c) HOAc/THF/H_2O, 45 °C, 20 h, 69%.

Scheme 69: Synthesis of PPB_1 type II according to Boland *et al*.[157]

The vinyliodine **198** was prepared from vinylalcohol **197** by iodination with I_2 and PPh_3 in acetonitrile. The side chain was introduced by a Heck type alkylation to give **199** which was deprotected to afford the free alcohol **180**.

The third example was published by Mikolajczyk *et al.* and appeared in 2009. It describes the synthesis of phytoprostane B_1 type I **186** in both of its enantiomerically pure forms in 25% overall yield (Scheme 70).[158]



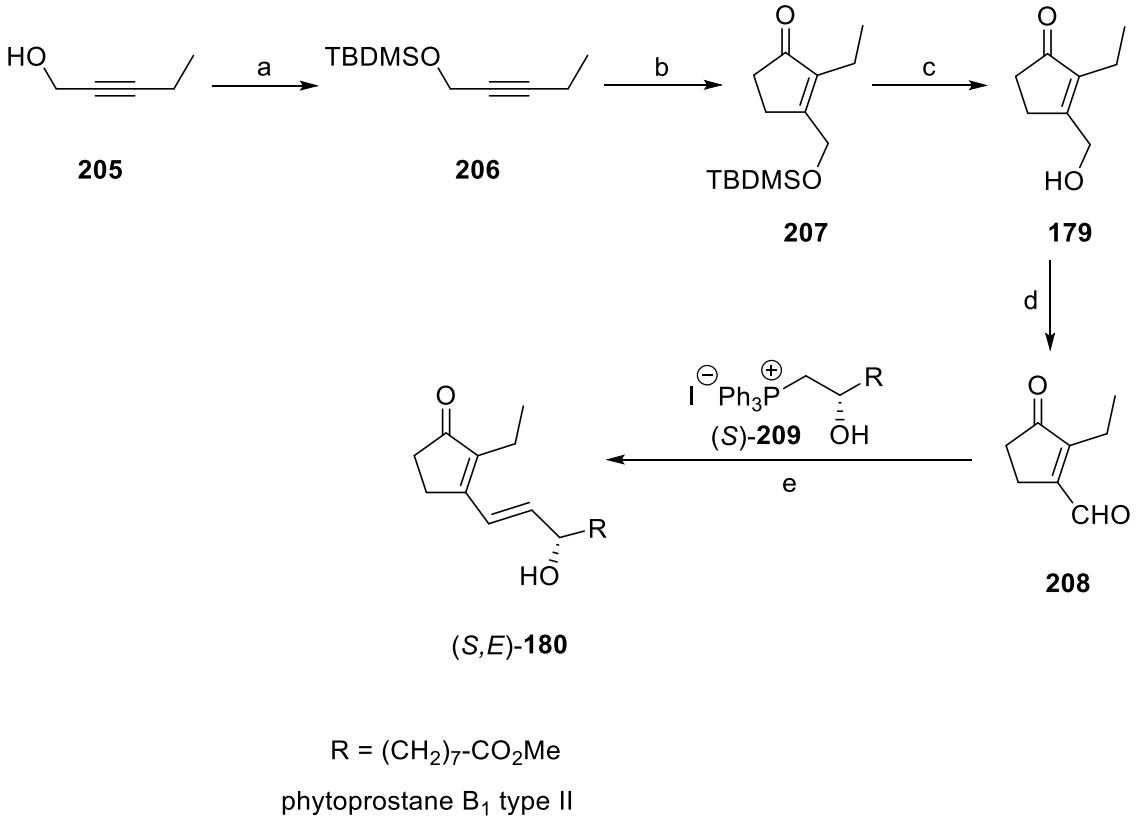
Conditions: a) NaH (1 equiv), DMSO, 45%. b) DBU (2 equiv), $LiClO_4$ (1 equiv), 78%. c) MeOH, K_2CO_3 (1 equiv), 70-75%.

Scheme 70: Synthesis of PPB_1 type I according to Mikolajczyk *et al.*[158]

Alkylation of cyclopentenone **200** with bromide **201** afforded compound **203** which could be further coupled in a Horner reaction with aldehyde **202**. Methanolysis of the ester **204** gave the desired free alcohol **186**.

The fourth and last example describes the synthesis of PGB_1, PPB_1 type I **186** and II **180** and was also published in 2009 by Verdaguer and Riera *et al.* (Scheme 71).[146] In the synthetic procedure intermediate **179** appears which could be obviously synthesized from the

rearrangement product **178** by hydrogenation and elimination which all can be theoretically performed in a one-pot-process in water.



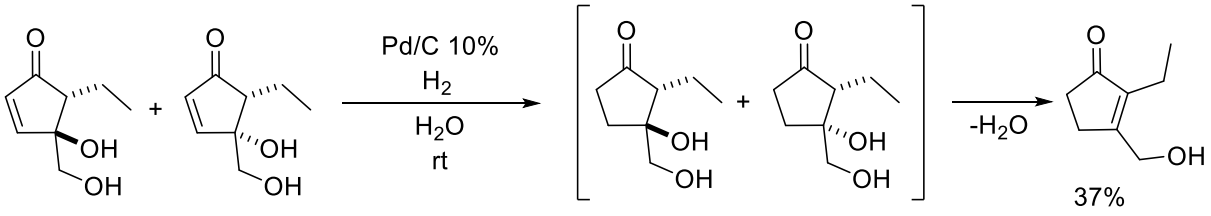
Conditions: a) TBDMSCl, 91%. b) $Co_2(CO)_8$ (1.8 equiv), CH_2CH_2, 6 bar, DCM, 4 Å MS, NMO (6.7 equiv), rt, 67%. c) HF·pyr, 0 °C, quant. d) $(COCl)_2$ (2 equiv), DMSO, Et_3N, DCM, 75%. e) LiHMDS (1.9 equiv), THF, 23%.

Scheme 71: Synthesis of PPB_1 type II according to Verdaguer and Riera *et al.*[146]

In the publication by Verdaguer and Riera (Scheme 71), commercially available pent-2-yn-1-ol **205** was protected as the *tert*-butyldimethylsilyl ether **206**. The key step of the synthesis consisted of a Pauson-Khand reaction to generate the cyclopentenone core structure and providing compound **207** which could be deprotected to free alcohol **179**. Oxidation to the aldehyde **208** and coupling with the phosphonium salt (*S*)-**209** afforded the desired product PPB_1 type II (*S,E*)-**180**. Despite the conciseness of the synthesis the drawback of using stoichiometric amounts of $Co_2(CO)_8$ persists. This disadvantage can be eliminated by preparing intermediate **179** by the previously mentioned synthesis from HMF **154**.

Initially, the hydrogenation of cyclopentenone **178** was examined (Table 46) to find the most suitable reaction conditions for this step. Under high pressure conditions (20 bar H_2, Pd/C) complete conversion of **178** was observed, providing the product **179** in 37% yield. Under these conditions, not cyclopentanone **210** but the product **179** was isolated, hence the elimination of the hydroxy group of intermediate **210** already took place (entry 1, Table 46). To prevent side reactions, like the hydrogenation of the double bond in **179** which could explain the low yield, the reaction was conducted at lower pressures. Hydrogenation at ambient pressure gave full conversion after 24 h, but in this case the elimination of the hydroxy group was not observed as in entry 1. However, intermediates **210** could not be isolated, as on column chromatography partially elimination occurred and a mixture of **210** and **179** was obtained. Therefore, after hydrogenation of **178** the resulting mixture was heated for 2 h in the presence of an acidic ion exchange resin prior to work-up, which proved to be successful and afforded the product **179** in 48% yield (entry 2, Table 46).

Table 46: Hydrogenation of rearrangement products **178**.[a]



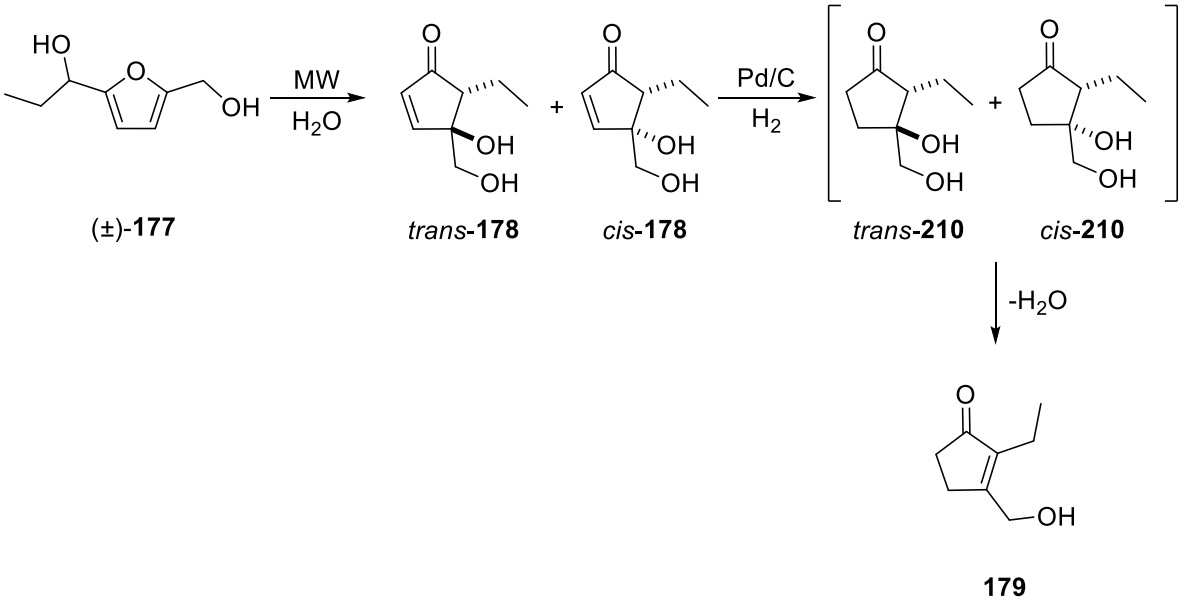
Entry	Pd/C [mol%]	p [bar]	t	Yield [%][b]
1	1	20	15 min	37
2	0.46	1	24 h	48[c]

a) **178** (0.4 mmol), H_2O (5 mL). b) isolated yield**.** c) after hydrogenation refluxed for 2 h with Amberlyst XN1010 (60 mg).

As the hydrogenation step turned out to be successful, the final task comprised the rearrangement/hydrogenation/elimination one-pot sequence. The reaction was performed as before with 25 g/L of α-furylcarbinol (±)-**177** in water, which first was exposed to subcritical conditions under microwave irradiation and then subjected to palladium catalyzed hydrogenation without work-up in between.

The first reaction (entry 1, Table 47) was performed in the Anton-Paar Monowave 300 microwave device, therefore the reaction parameters deviate from the previously reported ones (Table 45). After the rearrangement under microwave irradiation, the resulting solution was subjected hydrogenation conditions at 20 bar, which resulted in 19% of the desired product **179**. As stated before the elimination of the hydroxy moiety under the described conditions could be observed.

Table 47: One-pot rearrangement/hydrogenation/elimination.[a]



Entry	Rearrangement (MW)				Hydrogenation		Yield [%]
	T [°C]	P [W]	p [bar]	t [min]	p [bar]	t [min]	
1[b]	170	variable	10	10	20	15	19[d]
2[c]	137	300	5	20	1	18 h	20[d,e] (31)[f]
3[c,g]	142	300	5	30	1	20	40[d]

a) (±)-**177** (25 g/L in water, 1 mmol), Pd/C 10% (0.43 mol% Pd). c) Anton-Paar Monowave 300. c) CEM Discover. d) isolated yield. e) plus additionally a mixture of product **179** and compound **210** as a diastereomeric mixture. f) heating the rest of the isolated material which is not the product **179** with Amberlyst XN1010 gives additional 11% yield of product **179**. g) before work-up refluxed for 2 h with Amberlyst XN1010.

Considering that the hydrogenation under high pressure afforded very complex mixtures, hydrogenations at atmospheric pressure were examined (entry 2, Table 47). After the rearrangement, this time with the optimized conditions for the CEM device, the reaction mixture was subjected to hydrogenation conditions at atmospheric pressure to provide the

product **179** in 20% yield and additionally an inseparable combination of the product and presumably intermediates **210** as diastereomeric mixture after column chromatography. It can be concluded from those observations that a partial elimination of the hydroxy moiety had occurred, probably during the purification step. Nonetheless, it was considered to increase the yield by subjecting the isolated rest with the mixture of alcohols **210** to conditions promoting the elimination. This was demonstrated by heating the rest of the isolated material with acidic ion exchanger in water, which afforded another 11% of the desired product **179**. Therefore, this step was included in the reaction sequence (entry 3, Table 47), leading to compound **179** with a yield of 40%. Compared to the synthesis of Riera *et al.* (Scheme 71),[146] which afforded 60% of the product **179** in overall yield, the herein described procedure can provide intermediate **179** starting from HMF **154** in 2 steps (26% overall yield). Despite the lower yields, this strategy possesses the advantage of reducing waste by eliminating any protection group chemistry and the usage of stoichiometric amounts of $Co_2(CO)_8$. Moreover, the second step requires solely water as solvent and produces only water as a by-product.

4.8 Conclusion

HMF **154** could not be converted at all under the applied conditions, nevertheless BHMF **155** underwent a Piancatelli rearrangement in water at high temperatures to yield the respective carbocycle (±)-**164** in good yield. The utilized conditions made the use of any additional additives besides water unnecessary. The BHMF derivative 1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol (±)-**177** was employed successfully in the same type of rearrangement and the carbocyclic product **178** could be further exploited to achieve a short and facile formal synthesis of phytoprostane B_1 type I **180**. This was achieved by preparing intermediate **179** from HMF **154** in 2 steps and 26% yield.

5. Tests for Biological Activity

5.1 Compounds

Selected compounds of the 4-substituted cyclopentenone class were tested for their *in vitro* cytotoxic and anti-inflammatory activity (data kindly provided by Hannelore Rücker, group of Dr. Sabine Amslinger, University of Regensburg). Cytotoxicity tests were carried out by using an MTT assay[159] and the anti-inflammatory properties were determined by analyzing the nitrite production in a Griess assay.[160] The compounds (±)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone (±)-**164**, (±)-*tert*-butyl(4-oxocyclopent-2-en-1-yl) carbonate (±)-**69b**, (*S*)-4-oxocyclopent-2-en-1-yl 1-naphthoate (*S*)-**71c**, (±)-methyl(4-oxocyclopent-2-en-1-yl) carbonate (±)-**69c**, (±)-4-((*tert*-butyldimethylsilyl)oxy)-cyclopent-2-enone (±)-**211**, (*S*)-2-(4-oxocyclopent-2-en-1-yl)isoindoline-1,3-dione (*S*)-**71g**, (*S*)-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone (*S*)-**71h** and (±)-4-oxocyclopent-2-en-1-yl acetate (±)-**69a** were investigated.

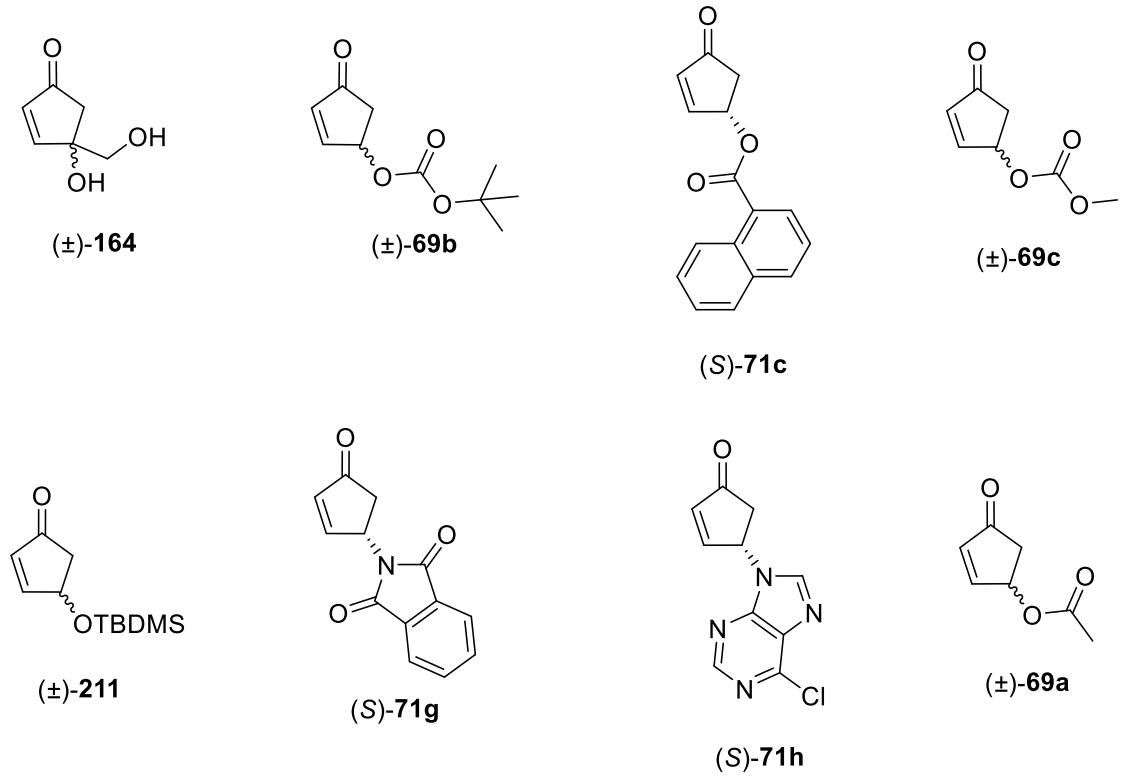


Figure 12: Compounds tested for cytotoxicity and anti-inflammatory activity.

5.2 Cytotoxicity Test

The cytotoxicity of the specified compounds (Figure 12) was determined via MTT assay against the murine macrophage cell line RAW264.7 at the three different concentrations of 100 µM, 10 µM and 1 µM. The MTT assay is a colorimetric method by which the cell viability can be evaluated by determining the mitochondrial function of living cells on the basis of their ability to reduce the yellow dye, tetrazolium salt 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT), into violet formazan by the mitochondrial dehydrogenases. The percentage of living cells can then be deduced by the amount of formazan formation, which can be measured by a spectrophotometer. The cell viability is illustrated by the following diagram (Figure 13) as indicator of the examined compounds' cytotoxicity. In this context a higher cell viability value for the respective substance denotes a lower cytotoxicity.

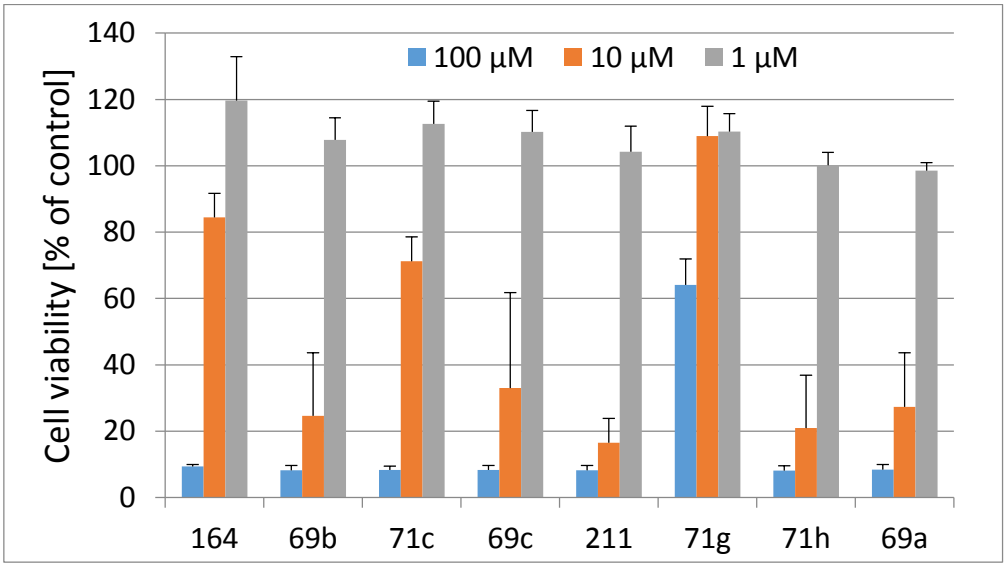


Figure 13: Cytotoxicity tests.

At the highest test concentration of 100 µM, for all compounds except (*S*)-**71g** less than 10% viability of the cells was measured, hence a significant cytotoxicity at this concentration can be asserted. Compound (*S*)-**71g** in contrast showed with slightly more than 60% only a moderate cytotoxicity. The cell viability for the compounds (±)-**69b**, (±)-**69c**, (±)-**211**, (*S*)-**71h** and (±)-**69a** at the medium concentration of 10 µM was still on a considerable low level (20-30%). Compounds (±)-**164** and (*S*)-**71c** showed a moderate viability with about 70-80% and compound (*S*)-**71g** featured no activity at all at this concentration. All examined compounds did not exhibit any cytotoxic activity at the lowest concentration of 1 µM.

Conclusively, the concentration of 1 µM was designated for the measurement of the anti-inflammatory activity in the following test (Griess-assay). As for the activity test a cell viability of 80% is intended, no cytotoxic activity at this concentration should be present and therefore the concentration of 1 µM was suited best.

5.3 Anti-Inflammatory Activity

In order to determine the anti-inflammatory activity of the specified compounds, the inhibition of the pro-inflammatory protein iNOS (inducible NO synthase) was measured by determining the nitrite production in LPS-stimulated RAW264.7 cells. This method works by adding LPS (lipopolysaccharide) to the cell cultures which induces the protein expression of iNOS in RAW cells. NO-synthases catalyze the production of nitric oxide from *L*-arginine, which plays a role in inflammatory processes.[161] Nitrite accumulation in the culture medium was used as an indicator of nitric oxide production in the macrophages. A lower value of nitrite compared to control cells implies a higher iNOS-inhibition and hence a higher anti-inflammatory activity of the compound. To evaluate the nitrite production the Griess assay was employed and the acquired data is displayed in the following diagram (Figure 14).

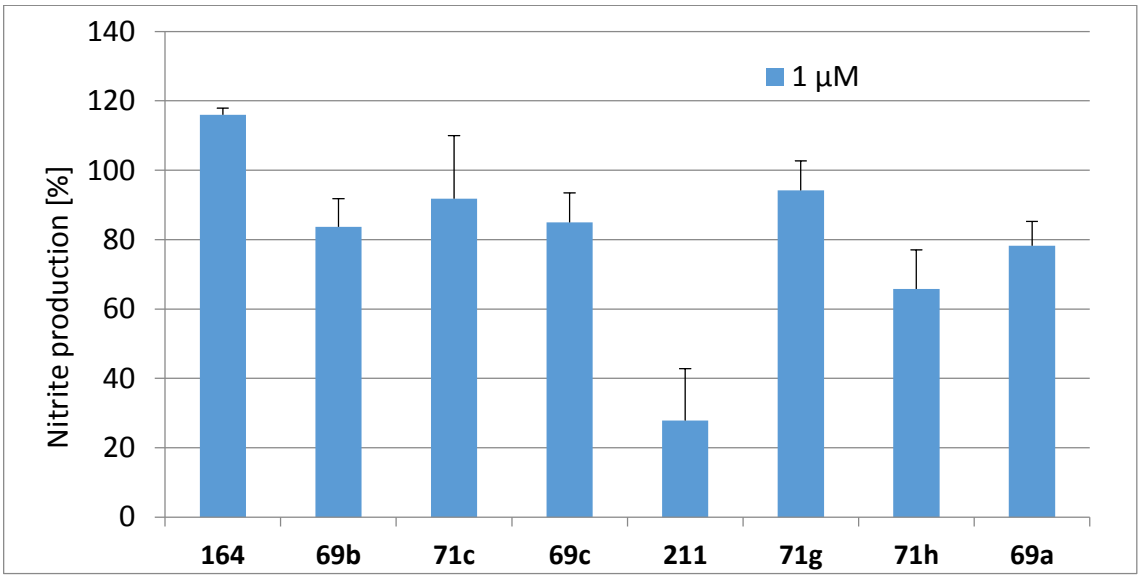


Figure 14: Influence on NO production (Griess assay).

The vast majority of the compounds ((±)-**69b**, (*S*)-**71c**, (±)-**69c**, (*S*)-**71g**, (*S*)-**71h**, (±)- **69a**) showed only moderate to diminutive inhibition of iNOS and therefore a low or no anti-inflammatory activity, deducible from values of about 60% to 90% of the reference. However,

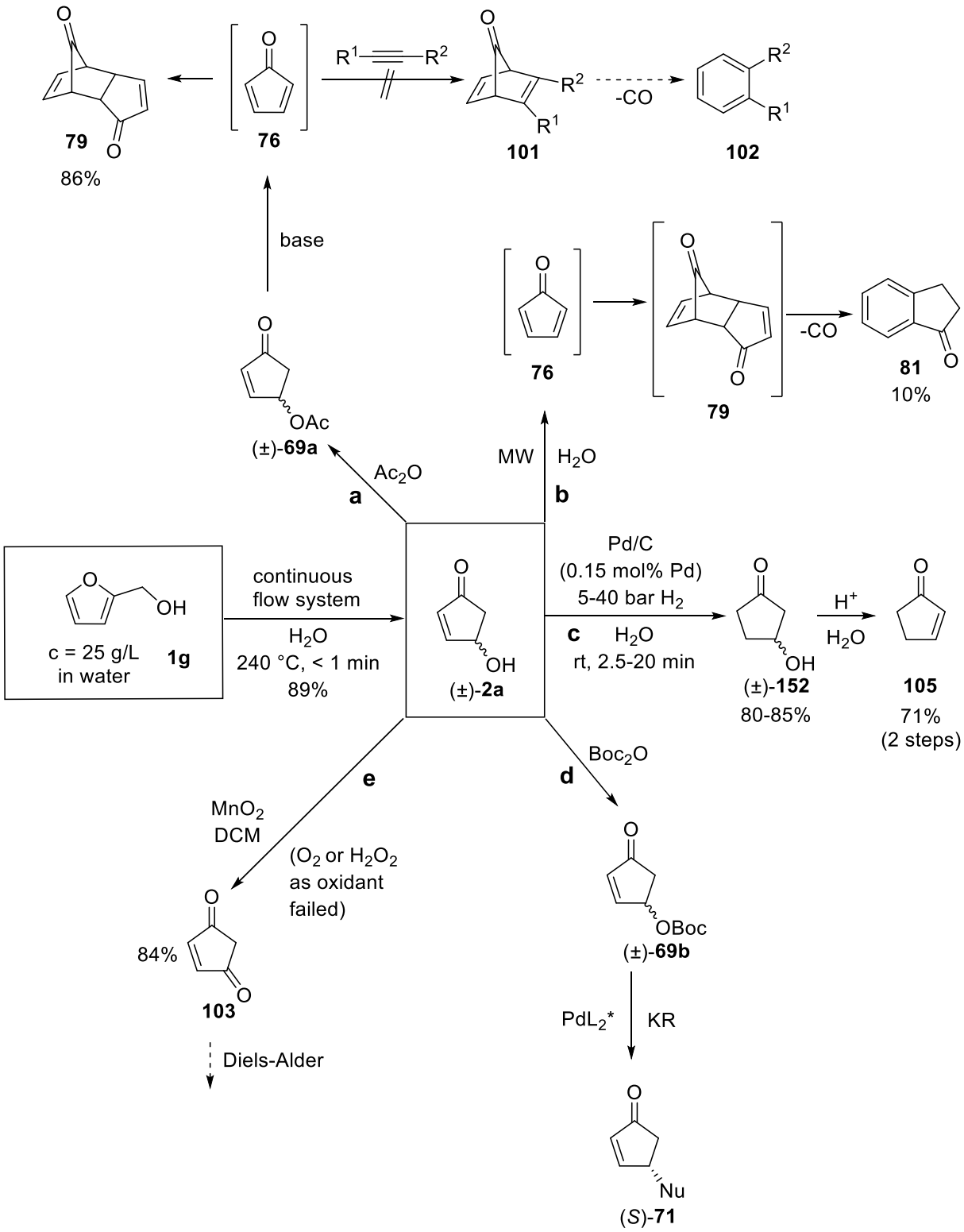
compound (±)-**164** even appears to have a pro-inflammatory activity as the value of 116% suggests. The exception from the mostly moderate active examples made compound (±)-**211**, showing an exceedingly high inhibition of iNOS (28% of the reference NO-production), which means it has a rather high anti-inflammatory activity.

C. Summary

In the first chapter, an application for 4-hydroxy-2-cyclopentenone (±)-**2a** on the basis of cycloaddition reactions was investigated. The main task to produce benzoic acid by Diels-Alder reactions with cyclopentadienone **76** and a suitable dienophile was not accomplished, however, the dimerization product **79** was observed. Adduct **79** could be synthesized from 4-acetoxy-2-cyclopentenone (±)-**69a** in a facile procedure with decent yields (path a/b, Scheme 72). The dimerization adduct **79** can be utilized to prepare another aromatic compound, 1-indanone **81**, by decarbonylation. Oxidations of 4-hydroxy-2-cyclopentenone (±)-**2a** and subsequent Diels-Alder reactions under sustainable conditions were not accomplished, only the oxidation with MnO_2 in DCM was successful (path e, Scheme 72).

In the second chapter, a successful kinetic resolution of protected (±)-**2a** via Pd-catalyzed asymmetric allylic substitution has been demonstrated. Excellent enantioselectivities of both substitution products and recovered starting materials were obtained even at low catalyst loadings (1 mol% Pd, 2 mol% ligand). The scope of participating nucleophiles is very broad - phenols, carboxylic acids, thiols and nitrogen-containing heterocycles could be applied. This method provides a potentially useful access to a variety of optically active 4-substituted-2-cyclopentenone derivatives. Moreover, a short formal synthesis of noraristeromycin ent-**85** via kinetic resolution was developed (path d, Scheme 72).

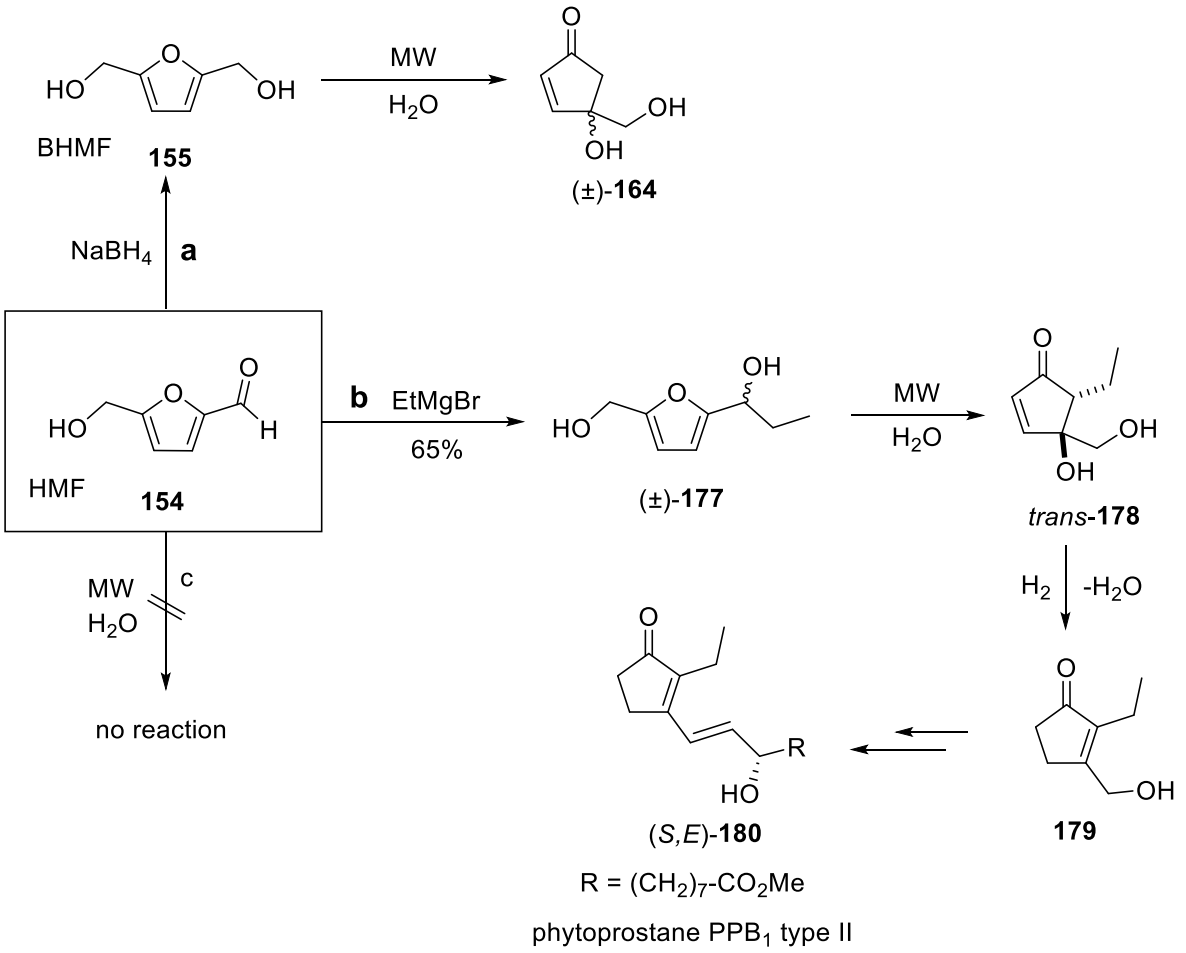
The third chapter explicates the conversion of 4-hydroxy-2-cyclopentenone (±)-**2a**, directly in the aqueous solution obtained from the continuous flow system developed by Reiser *et al.*, into the less water-soluble 2-cyclopentenone **105** via a hydrogenation/elimination sequence. It was confirmed that all the reactions could be performed in a one-pot procedure. The conditions are suitable for implementation in a continuous flow process subsequent to the rearrangement of **1g** to (±)-**2a**, which was already accomplished for the hydrogenation step (path c, Scheme 72).



Scheme 72: Overview of furfuryl alcohol **1g** applications.

The forth chapter covers the Piancatelli rearrangement of BHMF **155**, a derivative thereof and its application in the formal synthesis of a phytoprostane. Whereas HMF **154** could not be converted at all under the applied conditions, BHMF **155** underwent a Piancatelli rearrangement in water at high temperatures to yield the respective carbocycle (±)-**164** in good yield. The

applied conditions made the use of any additives besides water unnecessary. The BHMF derivative 1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol (±)-**177** was employed in the same type of rearrangement successfully and the carbocyclic product **178** was further exploited to achieve a short and facile formal synthesis of the phytoprostane B_1 type I (*S,E*)-**180.**



Scheme 73: Overview HMF **154** applications.

The last chapter contains the testing of several cyclopentenone derivatives on cytotoxicity and anti-inflammatory activity. The test results show that only compound (±)-**211** exhibits a high anti-inflammatory activity, whereas the other compounds showed moderate to low activity.

D. Experimental

1. General comments

All reagents of which the preparation is not described were obtained from commercial suppliers and used without further purification. All reactions were carried out in oven dried glassware under atmospheric conditions unless otherwise stated. DCM and THF were taken from a MBraun MB SPS solvent purification system. In case of the Pd-catalyzed allylic substitutions DCM was degassed by three freeze-pump-thaw cycles. Hexanes and EA for chromatographic separations were distilled prior to usage. Furfuryl alcohol **1g** was distilled and cyclopentadiene cracked prior to its use. Analytical thin layer chromatography was carried out on Merck TLC aluminium sheets silica gel 60 F 254. Visualization was accomplished with UV light (254 nm) and vanillin sulfuric acid solution followed by heating. Column chromatography was performed using Merck silica gel 60 (70-230 mesh ASTM).

^{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). 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, coupling constant (Hz) and assignment of peaks are given in parentheses. ^{13}C chemical shifts are reported in ppm from internal $CHCl_3$ (77 ppm) as standard on the δ scale. The ^{13}C signals were assigned with the help of DEPT 90 and DEPT 135. The assignment of the signals is given in parentheses.

Melting points:

Melting points were measured on a Büchi SMP-20 apparatus in a silicon oil bath or on a SRS MPA 100 OptiMelt. Values thus obtained were not corrected.

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).

IR spectroscopy:

ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System.

Optical rotation:

The optical rotation was determined in a Perkin Elmer 241 polarimeter at 589 nm wavelength (sodium-d-line) in a 1.0 dm measuring cell of ca. 2 mL volume.

HPLC:

High performance liquid chromatography was carried out using Varian 920-LC with PDA and a for each compound specified chiral stationary phase (Phenomenex Lux Cellulose-1, Chiralcel AS-H, Chiralcel OJ-H).

GC:

Gas chromatography was performed on a Fisons GC 8000 with a DBWAX (30 m, 0.25 mm D_i, 0.25 μm film) column with helium at 150 mbar as carrier gas and flame ionization detector.

Microwave:

For the microwave reactions a CEM Discover S-Class or an Anton-Paar Monowave 300 microwave were used with either 10 mL or 35 mL closed vessels.

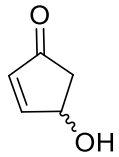
Autoclave:

For hydrogenation reactions a 100 mL stainless steel autoclave with an insertable glass vial, external hydrogen gas tank, manual control of hydrogen-pressure by a valve and integrated magnetic stirring was used.

2. Synthesis of compounds

2.1 Cycloaddition Approach

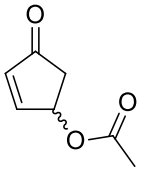
(±)-4-hydroxy-2-cyclopentenone (2a)



The compound was prepared according to a literature protocol.[28,61] The spectroscopic data is in accordance with literature.[162] The data is also related to chapter 2.2 (Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones), chapter 2.3 (Cyclopentenone from Furfuryl Alcohol) and chapter 2.5 (Tests for Biological activity).

Colorless oil. R_f = 0.13 (PE/EA 1:1). GC (DBWAX, 100 °C to 200 °C (10 °C/min), 200 °C (10 min)): t_R = 14.1 min (1,4-butanediol as internal standard, t_R = 10.5 min). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.16 (dd, 1H, *J* = 18.6, 2.1 Hz, CH_2) 2.65 (dd, 1H, *J* = 18.6, 6.0 Hz, CH_2), 4.13 (bs, 1H, OH), 4.94 (m, 1H, C*H*OH), 6.10 (dd, 1H, *J* = 5.6, 1.2 Hz, CH=C*H*-C=O), 7.52 (dd, 1H, *J* = 5.6, 2.3 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 44.2 (CH_2), 70.1 (CHOH), 134.7 (CH=*C*H-C=O), 164.6 (*C*H=CH-C=O), 207.9 (C=O).

(±)-4-acetoxy-2-cyclopentenone (69a)

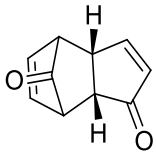


The preparation was carried out according to a literature procedure.[103] The data is also related to chapter 2.2 (Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones) and chapter 2.5 (Tests for Biological activity). (±)-Hydroxy-2-cyclopentenone **2a** (500 mg, 5.1 mmol, 1.0 equiv) was cooled down to 0 °C in 5 mL of dry DCM under N_2. To the cold solution 0.8 mL dry pyridine (786 mg, 10 mmol, 2.0 equiv) was added and the solution was stirred for 10 min. Then 0.72 mL Ac_2O (778 mg, 7.62 mmol, 1.5 equiv) was added dropwise at 0 °C. The resulting

solution was stirred for 15 h at rt. Cold diluted HCl was added to the reaction mixture and the organic layer was washed four times with a 1:4 mixture of brine and dilute HCl solution, followed by washing with cold water, 10% sodium bicarbonate solution and brine. The organic layer was dried over $MgSO_4$ and concentrated under vaccuum. The crude product was subjected to column chromatography (SiO_2, PE/EA 5:1) to afford the pure product in 71% yield (507 mg, 3.62 mmol, lit. 80%).[103] The spectroscopic data is in accordance with literature.[163]

White solid. R_f = 0.70 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.06 (bs, 3H, CH_3), 2.28 (dd, 1H, *J* = 18.7, 2.1 Hz, CH_2), 2.79 (dd, 1H, *J* = 18.7, 6.4 Hz, CH_2), 5.81 (m, 1H, C*H*OH), 6.29 (dt, 1H, *J* = 5.7, 1.4 Hz, CH=C*H*-C=O), 7.53 (dd, 1H, *J* = 5.7, 2.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 41.0 (CH_2), 71.9 (CHOH), 137.0 (CH=*C*H-C=O), 159.0 (*C*H=CH-C=O), 170.4 (O-C=O), 204.9 (*C*=O).

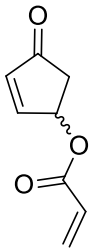
***endo*-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,8-dione (79)**



(±)-4-Acetoxy-2-cyclopentenone **69a** (96 mg, 0.685 mmol, 1.0 equiv) was dissolved in 20 mL of ^{i}PrOH together with NaOH (27 mg, 0.685 mmol, 1.0 equiv). The resulting solution was stirred at rt for 24 h. 75% of the solvent was evaporated and 10 mL of water was added. The aqueous solution was extracted with 20 mL of EA. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was subjected to column chromatography (SiO_2, PE:EA 5:1) to afford the pure product in 77% yield (42 mg, 0.26 mmol). The spectroscopic data is in accordance with literature.[164]

White solid. R_f = 0.33 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.85 (dd, 1H, *J* = 6.0, 5.0, CH), 3.15 (ddt, 1H, *J* = 4.7, 3.6, 1.1, CH), 3.0–3.36 (m, 1H, CH), 3.43–3.5 (m, 1H, CH), 6.11 (ddd, 1H, *J* = 6.8, 3.6, 1.1 Hz, CH=CH), 6.25 (ddd, 1H, *J* = 6.8, 3.5, 1.1 Hz, CH=CH), 6.30 (dd, 1H, *J* = 5.7, 1.6 Hz, CH=C*H*C=O), 7.34 (dd, 1H, *J* = 5.5, 2.5 Hz, C*H*=CHC=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.6 (CH), 43.3 (CH), 49.2 (CH), 50.0 (CH), 129.1 (CH=CH), 129.6 (CH=CH), 141.4 (CH=*C*HC=O), 161.4 (*C*H=C*H*C=O), 199.7 (C=O), 206.6 (CH=CH*C*=O).

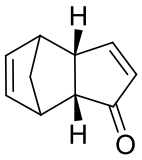
(±)-4-oxocyclopent-2-en-1-yl acrylate (82)



To a solution of (±)-4-hydroxy-2-cyclopentenone **2a** (5 g, 51 mmol, 1.0 equiv) in 80 mL dry DCM under N_2 5 mL of dry pyridine (4.9 g, 62 mmol, 1.2 equiv) was added. At 0 °C 6.8 mL of acryloyl chloride (7.6 g, 84 mmol, 1.6 equiv) was added dropwise. The resulting solution was stirred at rt for 24 h. Then 40 mL of water was added. The organic layer was separated and washed with 40 mL of water and 40 mL of brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. 1663 mg of the crude product was obtained as a yellow oil. Column chromatography (SiO_2, PE/EA 5:1) gave the pure product in 13% yield (991 mg, 6.50 mmol). The ^{1}H-NMR spectrum is not in accordance with the sole literature example,[165] but the herein reported spectra fit the structural features of compound **82** more accurate and the structure was confirmed additionally by ^{13}C-NMR-, DEPT- and HRMS-spectra.

Colorless oil. R_f = 0.71 (PE/EA 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.31 (dd, 1H, *J* = 18.6, 2.2 Hz, CH_2) 2.80 (dd, 1H, *J* = 18.6, 6.4 Hz, CH_2), 5.84 (dd, 1H, *J* = 10.5, 1.3 Hz, C*H*=CH_2), 5.86–5.90 (m, 1H, C*H*OH), 6.07 (dd, 1H, *J* = 17.3, 10.5 Hz, CH=C*H*$_2$), 6.29 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*-C=O), 6.39 (dd, 1H, *J* = 17.3, 1.3 Hz, CH=C*H*$_2$), 7.54 (dd, 1H, *J* = 5.7, 2.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 41.0 (CH_2), 72.0 (CHOH), 127.7 (*C*H=CH_2), 132.0 (CH=*C*H_2), 137.1 (CH=*C*H-C=O), 158.9 (CH=*C*H-C=O), 165.5 (O-C=O), 204.8 (C=O). IR (film): ν (cm^{-1}) = 1720 (C=O), 1633 (C=O), 1407, 1293, 1265, 1180, 1101, 1049, 984, 810. HRMS (EI): m/z calcd for $C_8H_9O_3$: 153.0546 [M+H$^+$]; found: 153.0544.

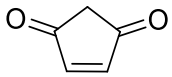
***endo*-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (90)**



(±)-4-Acetoxy-2-cyclopentenone **69a** (100 mg, 0.71 mmol, 1.0 equiv) and cyclopentadiene (472 mg, 7.1 mmol, 0.6 mL, 10.0 equiv) were dissolved in 1 mL of ^{i}PrOH and stirred at rt for 72 h. The solvent was evaporated and column chromatography (SiO_2, PE/EA 5:1) of the crude mixture afforded the clean product as a white solid in 81% yield (84 mg, 0.58 mmol). The spectroscopic data is in accordance with literature.[71]

White solid. R_f = 0.33 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 (dd, 1H, *J* = 8.4, 0.6 Hz, CH_2), 1.74 (d, 1H, *J* = 8.4 Hz, CH_2), 2.78 (t, 1H, *J* = 5.1 Hz, CH), 2.95 (s, 1H, CH), 3.2 (s, 1H, CH), 3.4 (d, 1H, *J* = 2.6 Hz, CH), 5.77 (d, 1H, *J* = 2.9 Hz, CH=C*H*C=O), 5.84–6.02 (m, 2H, CH=CH) 7.37 (dd, 1H, *J* = 5.7, 2.6 Hz, C*H*=CHC=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 44.0 (CH), 45.0 (CH), 48.3 (CH), 50.2 (CH), 52.7 (CH), 132.4 (CH=CH), 132.6 (CH=CH), 137.0 (CH=*C*HC=O), 164.6 (*C*H=C*H*C=O), 210.7 (C=O).

cyclopent-4-ene-1,3-dione (103)



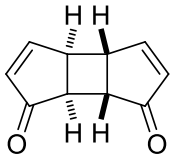
(±)-4-Hydroxy-2-cyclopentenone **2a** (504 mg, 5.14 mmol, 1.0 equiv) and MnO_2 (8.9 g, 102.75 mmol, 20.0 equiv) were stirred in 20 mL DCM at rt for 5 h. The resulting solution was filtered over celite and the solvent was evaporated. The product was obtained as a yellow oil, which solidified in the refrigerator, in 80% yield (393 mg, 4.09 mmol). The spectroscopic data is in accordance with literature.[166]

Yellow solid. R_f = 0.83 (PE/EA 1:2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.88 (s, 2H, CH_2), 7.29 (s, 2H, CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.4 (CH_2), 150.7 (CH), 200.7 (C=O).

(*cis,anti,cis*)-6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,4(3aH,3bH) -dione (108a), (*cis,anti,cis*)-6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,6(3aH, 3bH)-dione (108b)

(±)-4-Acetoxy-2-cyclopentenone **69a** (140 mg, 1.0 mmol, 1.0 equiv) was dissolved in 5 mL MeCN under N_2 in a quartz flask. Then it was irridiated for 48 h with a UV-lamp (366 nm, 40 W, conventionally used for thin layer chromatography). The solvent was evaporated and the crude product (143 mg) was subjected to column chromatography (SiO_2, PE/EA 2:1) to yield **108a** and **108b** in a 1:1 ratio (NMR) in 80% combined yield.

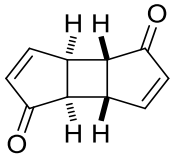
(*cis,anti,cis*)-6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,4(3aH,3bH)-dione **(108a)**



The spectroscopic data is in accordance with literature.[89]

Colorless crystals. R_f = 0.07 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.71 (d, 2H, *J* = 4.3 Hz, CH), 3.15–3.44 (m, 2H, CH), 6.42 (d, 2H, *J* = 5.6 Hz, CH=C*H*-C=O), 7.80 (dd, 2H, *J* = 5.5, 2.8 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 42.9 (CH), 46.5 (CH), 136.6 (CH=*C*H-C=O), 163.4 (*C*H=CH-C=O), 207.5 (C=O).

(*cis,anti,cis*)-6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,6(3aH,3bH)-dione **(108b)**



The spectroscopic data is in accordance with literature.[90]

Colorless crystals. R_f = 0.16 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.78 (dd, 2H, *J* = 4.8, 2.9 Hz, CH), 3.22–3.33 (m, 2H, CH), 6.39 (dd, 2H, *J* = 5.5, 0.9 Hz, CH=C*H*-C=O), 7.89 (dd, *J* = 5.5, 3.3 Hz, 2H, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.9 (CH), 48.2 (CH), 136.0 (CH=*C*H-C=O), 165.0 (*C*H=CH-C=O), 208.1 (C=O).

2.2 Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones

General procedure for Pd-catalyzed kinetic resolution

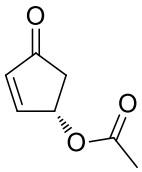
To a solution of (±)-**69b** (0.50 mmol, 1 equiv) and the nucleophile (0.24 mmol, 0.48 equiv) in dry, degassed DCM (2 mL) under N_2 at the specified temperature was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (2.6 mg, 0.0028 mmol, 2.3 mol% Pd based on nucleophile) and (*R,R*)-Trost ligand (6.1 mg, 0.0088 mmol, 3.7 mol% based on nucleophile) in dry, degassed DCM (1 mL) under N_2 until the initially purple solution turned yellow-brown (2–3 min). The progress of the reaction was monitored by TLC. Once the reaction

was complete, the reaction mixture was directly loaded onto a silica gel column and the product was eluted by an appropriate PE:EA mixture.

General procedure for Pd-catalyzed kinetic resolution on larger scale

To a solution of (±)-**69b** (5 mmol, 1 equiv) and the nucleophile (2.4 mmol, 0.48 equiv) in dry, degassed DCM (20 mL) under N_2 at the specified temperature was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 1 mol% Pd based on the nucleophile) and (*R*,*R*)-Trost ligand (33 mg, 0.048 mmol, 2 mol% based on the nucleophile) in dry, degassed DCM (10 mL) under N_2 until the initially purple solution turned yellow-brown (2–3 min). The reaction mixture was monitored by TLC. Once the reaction was complete, the solvent was evaporated and the crude product was purified by column chromatography with PE:EA as eluent mixture.

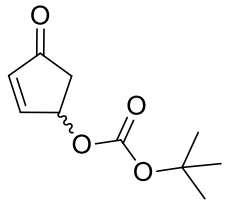
(*S*)-4-acetoxycyclopent-2-enone (69a)



The compound was prepared according to the general procedure for kinetic resolution.

White solid. 90% ee (t_R major, minor = 28.7, 18.1 min, Chiralcel AS-H 4.6×250 mm 10 µm, heptane:^{i}PrOH 90:10, 1.0 mL/min). R_f = 0.22 (PE/EA 8:2). $[\alpha]^{23}_D$= –103.9 (c = 1.22, $CHCl_3$) ($[\alpha]^{20}_D$ of (*S*)-4-acetoxy-2-cyclopenten-1-one = –111 (c = 0.51, $CHCl_3$))[167]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3), 2.32 (dd, 1H, *J* = 18.7, 2.2 Hz, CH_2), 2.83 (dd, 1H, *J* = 18.8, 6.4 Hz, CH_2), 5.85 (dtd, 1H, *J* = 6.1, 2.3, 1.4 Hz, CH-O), 6.33 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*-C=O), 7.57 (dd, 1H, *J* = 5.7, 2.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 41.1 (CH_2), 72.0 (CH-O), 137.1 (CH=*C*H-C=O), 159.0 (*C*H=CH-C=O), 170.5 (Ac C=O), 204.9 (C=O). IR (solid): ν (cm^{-1}) = 2365, 1717 (C=O) 1590, 1404, 1373, 1351, 1231, 1183, 1101, 1030, 985, 905, 794. HRMS (EI): m/z calcd for $C_7H_8O_3$: 140.0473 [$M^{\cdot+}$]; found: 140.0476.

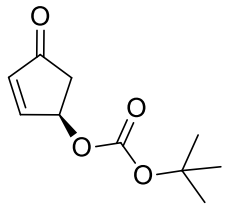
(±)-4-(*tert*-butoxycarbonyloxy)-2-cyclopentenone (69b)



To a solution of (±)-4-hydroxy-2-cyclopentenone **36** (500 mg, 5.0 mmol, 1.0 equiv) and Boc_2O (1.167 g, 6.0 mmol, 1.2 equiv) in 5 mL dry THF 0.84 mL triethylamine (613 mg, 6.0 mmol, 1.2 equiv) and DMAP (10 mg) were added. After stirring at room temperature for 30 min, the solvent was removed and the residue purified by column chromatography to give the product as a white solid in 87% yield (865 mg, 4.36 mmol). The data is also related to chapter 2.5 (Tests for Biological activity).

White solid. M.p. 38–39 °C. R_f = 0.33 (PE/EA 9:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H, CH_3), 2.41 (dd, 1H, *J* = 18.7, 2.3 Hz, CH_2), 2.84 (dd, 1H, *J* = 18.7, 6.4 Hz, CH_2), 5.72 (dtd, 1H, *J* = 6.1, 2.3, 1.3 Hz, CH-O), 6.34 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*-C=O), 7.60 (dd, 1H, *J* = 5.7, 2.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.8 (CH_3), 41.0 (CH_2), 74.2 (CH), 83.3 (Boc-C), 137.2 (CH=*C*H-C=O), 152.7 (Boc-C=O), 158.6 (*C*H=CH-C=O), 204.6 (C=O). IR (solid): ν (cm^{-1}) = 2982, 2929, 1731 (C=O), 1716 (C=O), 1590, 1396, 1371, 1335, 1275, 1256, 1157, 1106, 996, 842, 793. HRMS (EI): m/z calcd for $C_{10}H_{14}O_4$: 198.0892 [$M^{\cdot+}$]; found: 198.0896.

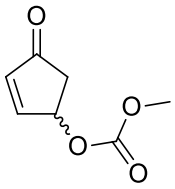
(*R*)-4-(*tert*-butoxycarbonyloxy)-2-cyclopentenone (69b)



The compound was prepared according to the general procedure for kinetic resolution (recovered starting material).

99% ee (t_R major, minor = 12.9, 14.2 min, Chiralcel OJ-H, 4.6 x 250 mm, 10 µm, heptane:^{i}PrOH 99:1, 1.0 mL/min). $[\alpha]^{22}_D$ = +85.0 (c = 1.60, $CHCl_3$).

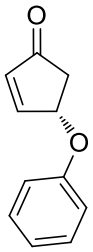
(±)-methyl (4-oxocyclopent-2-en-1-yl) carbonate (69c)



(±)-4-Hydroxy-2-cyclopentenone **2a** (1300 mg, 13 mmmol, 1.0 equiv), 1.3 mL methylchloroformate (1606 mg, 17 mmol, 1.3 equiv), 1.53 mL pyridine (1503 mg, 19 mmol, 1.5 equiv) and DMAP (10 mg, 0.08 mmol, 0.6 mol%) were dissolved in 30 mL of dry DCM under N_2 atmosphere at 0 °C. The resulting solution was stirred at 0 °C for 1 h. Then 30 mL of diluted NH_4Cl-solution was added. The aqueous layer was extracted twice with 20 mL DCM. The organic layers were combined and washed twice with brine (each 20 mL) and dried over $MgSO_4$. The solvent was evaporated and the product subjected to column chromatography (SiO_2, 4:1 PE/EA) to give the pure product as a colorless oil in 57% yield (1153 mg, 7.38 mmol). The data is also related to chapter 2.5 (Tests for Biological activity).

Colorless oil. R_f = 0.56 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 (ddd, 1H, *J* = 18.7, 2.2, 1.5 Hz, CH_2), 2.82 (ddd, 1H, *J* = 18.7, 6.4, 1.4 Hz, CH_2), 3.8 (s, 3H, CH_3), 5.75 (dtt, 1H, *J* = 6.0, 2.3, 1.3 Hz, C*H*-OH), 6.33 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*C=O), 7.57 (ddd, 1H, *J* = 5.7, 2.4, 1.1 Hz, C*H*=CHC=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.8 (CH_3), 55.2 (CH_2), 75.2 (CH-OH), 137.4 (CH=*C*HC=O), 155.1 (OC=O), 158.1 (*C*H=CHC=O), 204.2 (C=O). IR (film): ν (cm^{-1}) = 2692, 1745 (C=O), 1719 (C=O), 1442, 1255, 1182, 993, 789. HRMS (EI): m/z calcd for $C_7H_9O_4$: 157.0495 [M+H^+]; found: 157.0500.

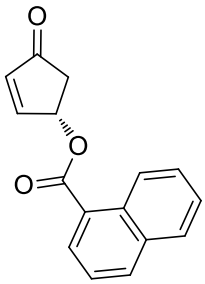
(*S*)-4-phenoxycyclopent-2-enone (71b)



The compound was prepared according to the general procedure for kinetic resolution.

Colorless oil. 93% ee (t_R major, minor = 13.5, 12.4 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:^{i}PrOH 90:10, 1.0 mL/min). R_f = 0.20 (PE/EA 9:1). $[\alpha]^{22}_D$ = –7.2 (c = 1.36, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.47 (dd, 1H, *J* = 18.4, 2.1 Hz, CH_2), 2.90 (dd, 1H, *J* = 18.4, 6.0 Hz, CH_2), 5.47 (dtd, 1H, *J* = 5.8, 2.2, 1.3 Hz, CH-O), 6.38 (dd, 1H, *J* = 5.7, 1.2 Hz, CH=C*H*-C=O), 6.93 (dd, 2H, *J* = 8.7 Hz, Ph *ortho*-CH), 7.01 (t, 1H, *J* = 7.4 Hz, Ph *para*-CH), 7.33 (dd, 2H, *J* = 8.6, 7.5 Hz, Ph *meta* -CH), 7.72 (dd, 1H, *J* = 5.7, 2.3 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.9 (CH_2), 75.1 (CH-O), 115.3 (Ph *ortho*-CH), 121.8 (Ph *para*-CH), 129.8 (Ph *meta*-CH), 136.6 (CH=*C*H-C=O), 157.3 (*C*H=CH-C=O), 159.7 (Ph C), 205.1 (C=O). IR (film): ν (cm^{-1}) = 3063, 2355, 2342, 1720 (C=O), 1597, 1491, 1352, 1227, 1187, 1102, 1035, 787, 754, 692. HRMS (EI): m/z calcd for $C_{11}H_{10}O_2$: 174.0681 [$M^{\cdot+}$]; found: 174.0677.

(*S*)-4-(1-naphthoyl)oxycyclopent-2-enone (71c)

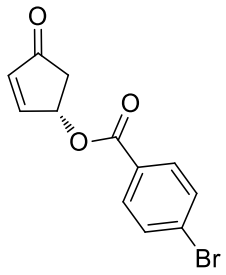


The compound was prepared according to the general procedure for kinetic resolution. The data is also related to chapter 2.5 (Tests for Biological activity).

White solid. M.p. 60-62 °C. 90% ee (t_R major, minor = 16.9, 14.7 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:^{i}PrOH 90:10, 1.0 mL/min). R_f = 0.44 (PE/EA 8:2). $[\alpha]^{22}_D$= –140.8 (c = 1.05, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.56 (dd, 1H, *J* = 18.8, 2.2 Hz, CH_2), 3.01 (dd, 1H, *J* = 18.8, 6.4 Hz, CH_2), 6.20 (tdd, 1H, *J* = 4.6, 3.6, 1.8 Hz, CH-O), 6.42 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*-C=O), 7.47–7.57 (m, 2H, Ar-CH), 7.64 (ddd, 1H, *J* = 8.6, 6.9, 1.5 Hz, Ar-CH), 7.76 (dd, 1H, *J* = 5.7, 2.4 Hz, Ar-CH), 7.90 (dd, 1H, *J* = 8.1, 1.4 Hz, Ar-CH), 8.05 (d, 1H, *J* = 2.0 Hz, Ar-CH), 8.20 (dd, 1H, *J* = 7.3, 1.3 Hz, C*H*=CH-C=O), 8.94 (d, 1H, *J* = 8.8 Hz, Ar-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.3 (CH_2), 72.5 (CH-O), 124.5 (Ar-CH), 125.6 (Ar-CH), 125.9 (Ar-C) , 126.5 (Ar-CH), 128.1 (Ar-CH), 128.8 (Ar-CH), 130.7 (Ar-CH), 131.4 (Ar-C), 133.9 (Ar-C), 134.1 (Ar-CH), 137.3 (CH=*C*H-C=O), 159.1 (*C*H=CH-C=O), 166.8 (Naphthoyl C=O), 205.0 (C=O). IR (solid): ν (cm^{-1}) = 2364, 2342, 1774. 1712

(C=O), 1388, 1364, 1184, 1094, 954, 878, 793, 718. HRMS (EI): m/z calcd for $C_{16}H_{12}O_3$: 252.0786 [$M^{\cdot+}$]; found: 252.0784.

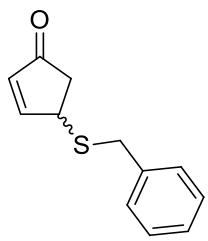
(*S*)-4-(4-bromobenzoyl)oxycyclopent-2-enone (71d) (by Tirayut Vilaivan)



The compound was prepared according to the general procedure for kinetic resolution.

White solid. M.p. 92–93 °C (lit.[168] m.p. 89 °C). 91% ee (t_R major, minor = 13.8, 15.3 min; Phenomenex Lux Cellulose-1 4.6×250 mm 5 µ, heptane:^{i}PrOH 70:30, 0.5 mL/min). R_f = 0.20 (PE/EA 9:1). $[\alpha]^{22}_D$ = –166.0 (*c* = 1.46, $CHCl_3$) {lit.[168] $[\alpha]_D$ = –167.7 (*c* 0.43, $CHCl_3$)}. The spectroscopic data is in accordance with literature.[168] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.48 (dd, 1H, *J* = 2.2, 18.8 Hz, CH_2), 2.95 (dd, 1H, *J* = 6.4, 18.8 Hz, CH_2), 6.10 (dtd, 1H, *J* = 1.2, 2.2, 6.1 Hz, CH-O), 6.41 (dd, 1H, *J* = 1.2, 5.7 Hz, CH=C*H*-C=O), 7.60 (d, 2H, *J* = 8.6 Hz, Ar-CH), 7.68 (dd, 1H, *J* = 2.4, 5.7 Hz, C*H*=CH-C=O), 7.89 (d, 2H, *J* = 8.6 Hz, Ar-CH). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 41.1 (CH_2), 72.7 (CH-O), 128.2 (Ar-C), 128.8 (Ar-C), 131.3 (Ar-CH), 132.0 (Ar- CH), 137.4 (CH=*C*H-C=O), 158.7 (*C*H=CH-C=O), 165.3 (BrBz C=O), 204.7 (C=O). IR (solid): ν (cm^{-1}) = 2362, 1784, 1704, 1590, 1485, 1398, 1266, 1174, 1103, 1012, 849, 756. HRMS (EI): *m/z* calcd for $C_{12}H_9BrO_3$: 279.9733 [$M^{\cdot+}$]; found: 279.9740.

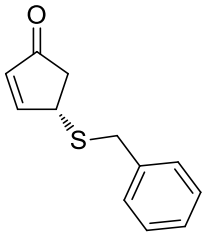
(±)-4-(benzylthio)cyclopent-2-enone (71e)



Tests for background reaction for the kinetic resolution: (±)-4-(*tert*-butoxycarbonyloxy)-2-cyclopentenone **69b** (50 mg, 0.25 mmol, 1.0 equiv) and 29 µL benzyl mercaptane (31 mg, 0.25

mmol, 1.0 equiv) in 2 mL DCM were stirred at rt for 38 d. The solvent was evaporated and the crude reaction mixture subjected to column chromatography (SiO_2, PE/EA 20:1) to provide the product (±)-**71e** in 32% (16 mg, 0.08 mmol) and the recovered starting material (±)-**69b** in 44% (22 mg, 0.11 mmol) yield.

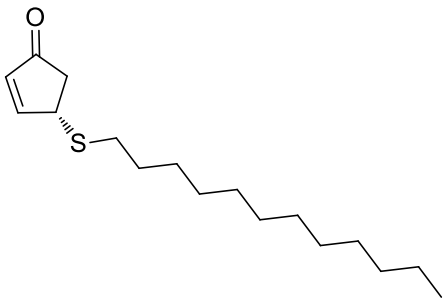
(*S*)-4-(benzylthio)cyclopent-2-enone (71e)



The compound was prepared according to the general procedure for kinetic resolution.

Colorless oil. 93% ee (t_R major, minor = 16.0, 14.8 min, Chiralcel OJ-H 4.6×250 mm 10 µm, heptane:^{i}PrOH 85:15, 1.0 mL/min). The spectoscopic data is in accordance with literature.[169] R_f = 0.15 (PE/EA 9:1). $[\alpha]^{26}_D$ = –163.2 (c = 1.13, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.30 (dd, 1H, *J* = 19.2, 2.1 Hz, CH_2), 2.73 (dd, 1H, *J* = 19.2, 6.5 Hz, CH_2), 3.74–3.84 (m, 2H, $PhCH_2$), 3.91 (tdd, 1H, *J* = 6.5, 2.6, 2.0 Hz, CH-S), 6.19 (dd, 1H, *J* = 5.6, 1.8 Hz, CH=C*H*-C=O), 7.24–7.37 (m, 5H, Ar-CH), 7.46 (dd, 1H, *J* = 5.6, 2.6, Hz, C*H*=CH-C=O). ^{13}C-NMR (101 MHz, $CDCl_3$): δ= 35.7 ($PhCH_2$ S), 42.7 and 43.3 (CH_2 and CH-S), 127.5 (CH=*C*H-C=O), 128.8 and 128.9 (Ar-CH), 134.6 (Ar-CH), 137.6 (Ar-C), 163.4 (*C*H=CH-C=O), 207.3 (C=O). IR (film): ν (cm^{-1}) = 3028, 2917, 2362, 1715 (C=O), 1582, 1494, 1454, 1400, 1340, 1240, 1179, 1096, 1071, 1028, 940, 770, 698. HRMS (EI): m/z calcd for $C_{12}H_{12}OS$: 204.0609 [$M^{\cdot+}$]; found: 204.0606.

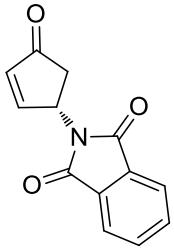
(*S*)-4-(dodecylthio)cyclopent-2-enone (71f) (by Tirayut Vilaivan)



The compound was prepared according to the general procedure for kinetic resolution.

Colorless oil. 93% ee (t_R major, minor = 18.47, 15.60 min; Chiralcel AS-H 4.6×250 mm 10 µ, heptane:^{i}PrOH 85:15, 1.0 mL/min). R_f = 0.18 (PE/EA 9:1). $[\alpha]^{22}_D$ = – 193.8 (*c* = 1.56, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 6.7 Hz, CH_3), 1.25 (m, 16H, 8×CH_2), 1.36 (m, 2H, C*H*$_2$CH$_2$CH$_2$S), 1.58 (m, 2H, CH$_2$C*H*$_2$CH$_2$S), 2.37 (dd, 1H, *J* = 2.1, 19.2 Hz, CH_2-C=O), 2.51 (dd, 2H, *J* = 7.1, 7.7 Hz, CH$_2$CH$_2$C*H*$_2$S), 2.84 (dd, 1H, *J* = 6.6, 19.2 Hz, CH_2-C=O), 4.01 (tdd, 1H, *J* = 2.0, 2.5, 6.5 Hz, CH-S), 6.22 (dd, 1H, *J* = 1.8, 5.6 Hz, CH=C*H*-C=O), 7.57 (dd, 1H, *J* = 2.6, 5.6 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2 (*C*H$_3$CH$_2$), 22.7 (CH$_3$*C*H$_2$), 29.0, 29.2, 29.5, 29.6, 29.7, 29.7 and 29.7 (8×CH_2), 32.0 (CH_2S), 42.8 (*C*H$_2$-C=O), 43.5 (CH-S), 134.3 (CH=*C*H-C=O), 163.9 (*C*H=CH-C=O), 207.6 (C=O). IR (film): ν (cm^{-1}) = 2923 (C-H), 2853, 1720 (C=O), 1717, 1177, 784. HRMS (ESI+): *m/z* calcd for $C_{17}H_{30}OS$: 282.2017 [$M^{\cdot+}$]; found: 282.2021.

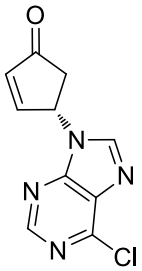
(*S*)-4-phthalimidylcyclopent-2-enone (71g)



The compound was prepared according to the general procedure for kinetic resolution. The data is also related to chapter 2.5 (Tests for Biological activity).

Long white needles. M.p. 156–159 °C. 96% ee (t_R major, minor = 27.2, 30.2 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:^{i}PrOH 90:10, 1.0 mL/min). R_f = 0.15 (PE/EA 8:2). $[\alpha]^{23}_D$ = –230.8 (c = 1.07, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.75 (dd, 1H, *J* = 18.3, 3.5 Hz, CH_2), 2.85 (dd, 1H, *J* = 18.2, 6.8 Hz, CH_2), 5.54 (tdd, 1H, *J* = 6.8, 3.5, 2.3 Hz, CH-N), 6.44 (dd, 1H, *J* = 5.7, 2.2 Hz, CH=C*H*-C=O), 7.52 (dd, 1H, *J* = 5.7, 2.4 Hz, C*H*=CH-C=O), 7.72–7.78 (m, 2H, Ar-CH), 7.82–7.89 (m, 2H, Ar-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 39.6 (CH_2), 49.7 (CH-N), 123.6 (Ar-CH), 131.7 (Ar-C), 134.4 (Ar-CH), 136.2 (CH=*C*H-C=O), 159.6 (*C*H=CH-C=O), 167.6 (Pht C=O), 205.2 (C=O). IR (solid): ν (cm^{-1}) = 2363, 1777, 1700 (C=O), 1593, 1510, 1275, 1240, 1195, 1131, 1015, 780. HRMS (EI): m/z calcd for $C_{13}H_9NO_3$: 227.0582 [$M^{\cdot+}$]; found: 227.0583.

(S)-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone (71h)



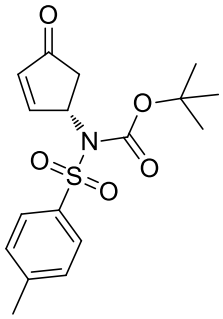
Procedure A (with base): A solution of NaH (60% susp., 96 mg, 2.4 mmol, 0.48 equiv) and 6-chloropurine (371 mg, 2.4 mmol, 0.48 equiv) in dry, degassed dichloromethane (20 mL) under N_2 at rt was stirred for 10 minutes. Then at 0 °C (±)-**69b** (991 mg, 5 mmol, 1 equiv) and the catalyst solution were added, which was separately prepared by stirring $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 0.5 mol% Pd) and (*R*,*R*)-Trost ligand (33 mg, 0.048 mmol, 1 mol% Pd) in dry, degassed dichloromethane (10 mL) under N_2 until the initially purple solution turned yellow-brown (2-3 min). After 22 h stirring at 0 °C 20 mL of water was added. The layers were separated and the aqueous phase was extracted 3 times with 30 mL of DCM. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography with PE:EA (10:1 for recovering starting material and neat EA for product as eluent mixture). The clean product was obtained as a white solid (46% yield, 456 mg, 1.94 mmol) which gave colorless crystals after recrystallization from PE/EA (40% yield, 396 mg, 1.69 mmol).

Procedure B (without base): To a solution of (±)-**69b** (991 mg, 5 mmol, 1 equiv) and 6-chloropurine (371 mg, 2.4 mmol, 0.48 equiv) in dry, degassed dichloromethane (20 mL) under N_2 at 0 °C the catalyst solution was added. It was separately prepared by stirring $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 1 mol% Pd) and the (*R*,*R*)-Trost ligand (33 mg, 0.048 mmol, 2 mol% Pd) in dry, degassed dichloromethane (10 mL) under N_2 until the initially purple solution turned yellow-brown (2-3 min). After 24 h stirring at 0 °C the solvent was evaporated. The crude product was purified by column chromatography with PE:EA (10:1 for recovering starting material and neat EA for product as eluent mixture). The product was obtained as a white solid (46% yield, 536 mg, 2.28 mmol, 94% ee) which gave colorless crystals after recrystallization from PE/EA (39% yield, 463 mg, 1.97 mmol, 98% ee). The spectroscopic data is in accordance with literature.[127] The data is also related to chapter 2.5 (Tests for Biological activity).

Colorless crystals. M.p. 131-133 °C (135.5-136 °C)[127]. 98% ee (t_R major, minor = 24.43, 20.55 min, Chiralcel AS-H 4.6×250 mm 10 µm, heptane:^{i}PrOH 50:50, 0.5 mL/min). R_f = 0.25 (EA).

$[\alpha]^{22}_D$ = –114.5 (c = 0.98, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.69 (dd, 1H, *J* = 18.8, 2.8 Hz, CH_2), 3.18 (dd, 1H, *J* = 18.8, 7.2 Hz, CH_2), 6.01 (ddd, 1H, *J* = 7.2, 4.8, 2.5 Hz, CH-N), 6.65 (dd, 1H, *J* = 5.7, 2.0 Hz, CH=C*H*-C=O), 7.69 (dd, 1H, *J* = 5.7, 2.5 Hz, C*H*=CH-C=O), 8.08 (s, 1H, imidazole CH), 8.76 (s, 1H, pyrimidine CH).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.7 (CH_2), 54.5 (CH-N), 131.9 (NNC=*C*CN), 138.4 (CH=*C*H-C=O), 142.8 (*C*H=CH-C=O), 151.4, 151.6, 152.3 (imidazol CH), 157.0 (pyrimidine CH), 203.5 (C=O). IR (solid): ν (cm^{-1}) = 3070, 2354, 1720 (C=O), 1591, 1560, 1490, 1401, 1336, 1204, 1183, 1148, 951, 912, 857, 792, 636. HRMS (ESI+): m/z calcd for $C_7H_7ClN_4O$: 235.0381 [$M^{\cdot+}$]; found: 235.0384.

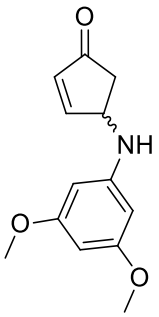
(*S*)-4-(*N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonylamino)cyclopent-2-enone (71j) (by Tirayut Vilaivan)



The compound was prepared according to the general procedure for kinetic resolution.

White solid. M.p. 114–116 °C. 94% ee (t_R major, minor = 13.4, 14.5 min; Phenomenex Lux Cellulose-1 4.6×250 mm 5 µ, heptane:^{i}PrOH 70:30, 0.5 mL/min). R_f = 0.21 (PE/EA 8:2). $[\alpha]^{26}_D$ = –85.0 (*c* = 1.19, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 9H, Boc CH_3), 2.45 (s, 3H, Ts CH_3), 2.60 (dd, 1H, *J* = 3.3, 18.1 Hz, CH_2), 2.82 (dd, 1H, *J* = 7.0, 18.1 Hz, CH_2), 5.79 (tdd, 1H, *J* = 2.5, 3.1, 6.9 Hz, CH-N), 6.25 (dd, 1H, *J* = 2.4, 5.1 Hz, CH=C*H*-C=O), 7.34 (d, 2H, *J* = 8.7 Hz, Ts Ar CH), 7.52 (dd, 1H, *J* = 2.4, 5.7 Hz, C*H*=CH-C=O), 7.79 (d, 2H, *J* = 8.4 Hz, Ts Ar CH). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 21.7 (Ts CH_3), 27.9 (Boc CH_3), 40.5 (CH_2), 56.8 (CH-N), 85.6 (Boc C), 127.9 (Ts Ar CH), 129.6 (Ts Ar CH), 134.5 (CH=*C*H-C=O), 136.8 (Ts Ar C), 144.8 (Ts Ar C), 150.1 (Boc C=O), 161.9 (*C*H=CH-C=O), 205.2 (C=O). IR (solid): ν (cm^{-1}) = 2983, 2942, 2363, 2338, 1713 (C=O), 1596, 1457, 1351, 1284, 1251, 1140, 1089, 1053, 949, 917, 815, 772, 728, 670. HRMS (ESI+): *m/z* calcd for $C_{17}H_{21}NO_5S+H^+$: 352.1213 [M+H]$^+$; found: 352.1213.

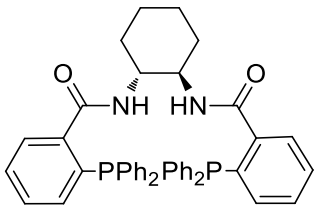
(±)-4-(3,5-dimethoxyphenylamino)cyclopent-2-enone (71k) (by Tirayut Vilaivan)



The compound was prepared according to the general procedure for kinetic resolution.

Light brown oil. 1% ee (t_R = 46.2, 51.9 min; Phenomenex Lux Cellulose-1 4.6×250 mm 5 µ, heptane:^{i}PrOH 70:30, 0.5 mL/min). R_f = 0.10 (PE/EA 8:2). $[\alpha]^{22}_D$ = +1.2 (*c*=1.37, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.20 (dd, 1H, *J* = 2.4, 18.6 Hz, CH_2), 2.89 (dd, 1H, *J* = 6.2, 18.4 Hz, CH_2), 3.75 (s, 6H, 2×CH_3O), 3.81 (br m, 1H, NH), 4.73 (br m, 1H, CH-N), 5.84 (d, 2H, *J* = 2.1 Hz, Ar *ortho*-CH), 5.95 (t, 1H, *J* = 2.1 Hz, Ar *para*-CH), 6.28 (dd, 1H, *J* = 1.7, 5.7 Hz, CH=C*H*-C=O), 7.65 (dd, 1H, *J* = 2.4, 5.7 Hz, C*H*=CH-C=O). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 42.9 (CH_2), 53.9 (CH-N), 55.3 (CH_3O), 90.7 (Ar-C), 92.5 (Ar-CH), 135.5 (CH=*C*H-C=O), 148.3 (Ar-C), 161.9 and 162.2 (Ar-CH and *C*H=CH-C=O), 206.9 (C=O). IR (film): ν (cm^{-1}) = 3372, 2936, 2842, 1783, 1716, 1615, 1598, 1518, 1482, 1458, 1204, 1152, 1069, 812. HRMS (ESI+): *m/z* calcd for $C_{13}H_{14}NO_3$+H^+: 234.1125 $[M+H]^+$; found: 234.1127.

***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-(diphenylphosphino)benzamide) (Trost ligand) (72)**

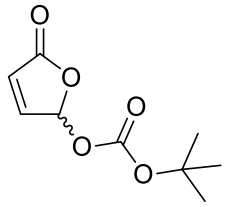


The Trost ligand **72** was prepared according to a known procedure and the spectra are consistent with literature data.[117] (1*R*,2*R*)-cyclohexane-1,2-diamine (400 mg, 3.5 mmol, 1.0 equiv), 2-(diphenylphosphino)benzoic acid (2140 mg, 7 mmol, 2.0 equiv), DCC (1446 mg, 7 mmol, 2.0 equiv) and DMAP (40 mg, 0.32 mmol, 10 mol%) were dissolved under N_2 in 100 mL of dry DCM. The solution was stirred overnight at rt. A white precipitate formed which was filtered

over celite. The solvent was evaporated to give the crude product as a yellow foam. Column chromatography (SiO_2, 5:1 PE/EA) afforded the product as a white solid in 89% yield (2165 mg, 3.13 mmol).

White solid. R_f = 0.41 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.96–1.26 (m, 4H, CH_2), 1.60–166 (m, 2H, CH_2), 1.83–1.87 (m, 2H), 3.76 (m, 2H, CH), 6.31 (m, 2H, NH), 6.90 (m, 2H), 7.18–7.32 (m, 24H, arom.), 7.57 (m, 2H, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 24.6 (CH_2), 32.0 (CH_2), 53.9 (CHN), 127.6 (arom.), 128.4 (arom.), 128.5 (arom.), 128.5 (arom.), 128.6 (arom.), 128.6 (arom.), 128.8 (arom.), 130.2 (arom.), 133.9 (d, *J* = 20.2, arom.), 134.3 (arom.), 136.5 (d, *J* = 21.8, arom.), 137.6 (d, *J* = 4.9 Hz, arom.), 137.8 (d, *J* = 4.9 Hz, arom.), 141.0 (d, *J* = 24.7 Hz, arom.), 169.3 (C=O).

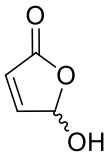
(±)-*tert*-butyl (5-oxo-2,5-dihydrofuran-2-yl) carbonate (121)



(±)-5-hydroxyfuran-2(5H)-one **134** (350 mg, 3.5 mmol, 1.0 equiv) was dissolved in 50 mL dry DCM under N_2 at 0 °C, then 0.57 of mL pyridin (554 mg, 7 mmol, 2.0 equiv) and Boc_2O (1146 mg, 5.25 mmol, 1.5 equiv) were added. The reaction was stirred for 24 h at rt. Water was added and the organic layer was separated, dried over $MgSO_4$ and the solvent evaporated. Column chromatography (SiO_2, PE/EA 20:1) gave the product as white solid in 45% yield (313 mg, 1.56 mmol). The spectroscopic data is in accordance with literature.[170]

White solid. R_f = 0.38 (PE/EA 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9H, CH_3), 6.30 (dd, 1H, *J* = 5.7, 1.2, CH=C*H*-C=O), 6.84 (t, 1H, *J* = 1.3 Hz, C*H*OH), 7.31 (dd, 1H, *J* = 5.7, 1.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.6 (CH_3), 84.8 (CHOH), 95.9 (C), 125.4 (CH=*C*H-C=O), 149.2 (*C*H=CH-C=O), 151.0 (C=O), 169.5 (C=O).

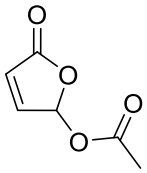
(±)-5-hydroxyfuran-2(5H)-one (134)



Preparation (except for the following reported deviations) and spectra are in accordance with literature.[171] A photoreactor was filled with a solution consisting of furan-1-carboxylic acid **133** (4.0 g, 36 mmol, 1.0 equiv) and Rose Bengal (50 mg, 0.1 mol%) in 110 mL MeOH. O_2 was bubbled through the pink solution for 10 min at rt. As there was no 450 W lamp available which was recommended in the literature example, a 125 W mercury-vapor lamp was used for irradiating the reaction mixture. Over a syringe pump with a flow rate of 1.6 mL/min a solution of 50 mg Rose Bengal in 10 mL MeOH was added, preventing the solution from adopting a brown color. After 7 h the solvent was evaporated. The crude product (3.38 g, 94%) was used without further purification. It could be recrystallized from $CHCl_3$ to give a white solid.

White solid. R_f = 0.39 (PE/EA 1:1). ^{1}H-NMR (300 MHz, acetone-d_6): δ = 6.22 (dd, 1H, *J* = 5.7, 1.1 Hz, CH=C*H*-C=O), 6.26 (bs, 1H, OH), 6.73 (bs, 1H, C*H*OH), 7.45 (d, 1H, *J* = 5.7 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 99.1 (C*H*OH), 124.4 (CH=*C*H-C=O), 152.6 (*C*H=CH-C=O), 172.1 (C=O).

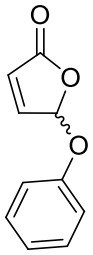
(±)-5-oxo-2,5-dihydrofuran-2-yl acetate (135)



To (±)-5-hydroxyfuran-2(5H)-one **134** (480 mg, 4.8 mmol, 1.0 equiv) and 0.68 mL pyridin (760 mg, 9.6 mmol, 2.0 equiv) in 50 mL dry DCM 0.77 mL of Ac_2O (735 mg, 7.2 mmol, 1.5 equiv) was added dropwise under N_2 at 0 °C. The reaction was stirred for 24 h at rt. Water was added and the organic layer was separated, dried over $MgSO_4$ and the solvent evaporated. Column chromatography (SiO_2, PE/EA 4:1) gave the product as colorless oil in 65% yield (439 mg, 3.1 mmol). The spectroscopic data is in accordance with literature.[172]

Colorless oil. R_f = 0.68 (2:1 PE/EA). ^{1}H-NMR (300 MHz, acetone-d_6): δ = 2.10 (s, 3H, CH_3), 6.25 (dd, 1H, *J* = 5.7, 1.2 Hz, CH=C*H*-C=O), 6.92 (t, 1H, *J* = 1.2 Hz, C*H*OH), 7.29 (dd, 1H, *J* = 5.7, 1.4 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.5 (CH_3), 93.8 (CHOH), 124.9 (CH=*C*H-C=O), 150.2 (*C*H=CH-C=O), 160.1 (C=O), 169.8 (C=O).

(±)-5-phenoxyfuran-2(5H)-one (136)



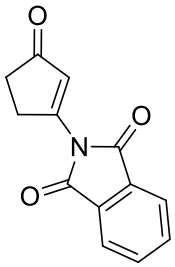
From (±)-**121**: To a solution of (±)-**121** (61 mg, 0.31 mmol, 1.0 equiv) and phenol (43 mg, 0.46 mmol, 1.5 equiv) in dry DCM (2 mL) under N_2 at rt was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 3.2 mol%, 6.4 mol% Pd based on the nucleophile) and PPh_3 (18 mg, 0.067 mmol, 15 mol% based on the nucleophile) in dry DCM (1 mL) under N_2 until the initially purple solution turned yellow-brown (2–3 min). The resulting solution was stirred at rt for 3.5 h. Once the reaction was complete, the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, PE/EA 5:1) to yield the pure compound (±)-**136** in quantitative yield (55 mg, 0.31 mmol).

From (±)-**135**: To a solution of (±)-**135** (44 mg, 0.31 mmol, 1.0 equiv) and phenol (43 mg, 0.46 mmol, 1.5 equiv) in dry DCM (2 mL) under N_2 at rt was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 3.2 mol%, 6.4 mol% Pd based on the nucleophile) and PPh_3 (18 mg, 0.067 mmol, 15 mol% based on the nucleophile) in dry DCM (1 mL) under N_2 until the initially purple solution turned yellow-brown (2–3 min). The resulting solution was stirred at rt for 3.5 h. Once the reaction was complete, the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, PE/EA 5:1) to afford the pure compound (±)-**136** in 93% yield (51 mg, 0.31 mmol). The spectroscopic data is in accordance with literature.[173]

White solid. R_f = 0.25 (PE/EA 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.34 (dd, 1H, *J* = 5.7, 1.3 Hz, CH=C*H*-C=O), 6.43 (t, 1H, *J* = 1.3 Hz, CH-OPh), 7.09–7.18 (m, 3H, arom. *ortho*-, *para*-CH), 7.31–7.43 (m, 3H, 2 arom. *meta*-CH and C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ

= 100.7, 116.9, 125.3 (arom.), 123.8 (arom.), 129.8 (CH=*C*H-C=O), 149.8 (OC=O), 156.3 (*C*H=CH-C=O), 170.9 (C=O).

2-(3-oxocyclopent-1-en-1-yl)isoindoline-1,3-dione (151)

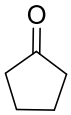


Phthalimide (37 mg, 0.25 mmol, 1 equiv) and NaH (60% susp., 10 mg, 0.25 mmol, 1 equiv) were stirred in 2 mL of dry DCM for 30 min at rt. Then (±)-4-(*tert*-butoxycarbonyloxy)-2-cyclopentenone **69b** (50 mg, 0.25 mmol, 1 equiv) was added and the resulting solution was stirred at rt for 12 d. The solvent was evaporated and the crude mixture was subjected to column chromatography (SiO_2, PE/EA 5:1) to give 21% of (±)-4-phthalimidylcyclopent-2-enone **71g** (12 mg, 0.05 mmol), 20% of *endo*-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,8-dione **79** (4 mg, 0.03 mmol) and 9% of 2-(3-oxocyclopent-1-en-1-yl)isoindoline-1,3-dione **151** (5 mg after one recrystallization from PE/EA, 0.02 mmol).

Colorless crystals. M.p. 130 °C. R_f = 0.76 (2:1 PE/EA). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.53–2.46 (m, 2H, CH_2), 3.39–3.44 (m, 2H, CH_2), 6.90 (t, 1H, *J* = 1.7 Hz, CH), 7.85 (dd, 2H, *J* = 5.5, 3.0 Hz, aryl-H), 7.97 (dd, 2H, *J* = 5.5, 3.0 Hz, aryl-H).^{13}C-NMR (101 MHz, $CDCl_3$): δ = 28.9 (CH_2), 33.2 (CH_2), 119.3 (C=*C*H), 124.4 (aryl-CH), 131.4 (*C*=CH), 135.4 (aryl-CH), 163.2 (aryl-C), 165.8 (N-C=O), 207.7 (C=O). IR (solid): ν (cm^{-1}) = 2983, 2904, 2361, 2338, 1736, 1708, 1393, 1359, 1337, 1243, 1221, 1188, 1055, 716. HRMS (ESI+): m/z calcd for $C_{13}H_{10}NO_3$: 228.0655 [$M+H^+$]; found: 228.0655.

2.3 Cyclopentenone from Furfuryl Alcohol

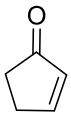
cyclopentanone (32)



By-product of the hydrogenation experiments.

Colorless liquid. R_f = 0.2 (PE/EA 10:1). GC (DBWAX, 100 °C to 200 °C (10 °C/min), 200 °C (10 min)): t_R = 3.0 min (1,4-butanediol as internal standard, t_R = 10.5 min). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.89–1.97 (m, 4H, C*H*$_2$-CH_2-CO), 2.10–2.17 (m, 4H, CH_2-C*H*$_2$-CO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.3 (*C*H_2-CH_2-CO), 38.4 (CH_2-*C*H_2-CO), 220.7 (C=O).

2-cyclopentenone (105)



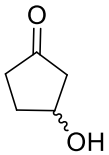
Elimination of hydroxy-moieity from (±)-3-hydroxycyclopentanone **152** with acidic ion-exchanger: (±)-3-hydroxycyclopentanone **152** (40 mg, 0.4 mmol, 1.0 equiv) and 20 mg of Amberlyst XN1010 were dispersed in 1 mL of deionized water (c (**152**) = 40 g/L). The resulting solution was heated to 70 °C for 4 h. After the reaction was complete the aqueous phase was extracted 3 times with 2 mL of DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was carefully evaporated (bp (**105**) = 150 °C). This afforded the pure product in 61% yield (20 mg). The spectroscopic data is in accordance with literature.[174]

Elimination of hydroxy-moiety from (±)-3-hydroxycyclopentanone **152** in the microwave: (±)-3-hydroxycyclopentanone **152** (100 mg, 1 mmol, 1.0 equiv) was dissolved in 4 mL deionized water in a 10 mL closed microwave pressure vessel (c (**152**) = 25 g/L in water). The resulting solution was heated in the microwave at 300 W for 15 min, reaching a maximum temperature of 180 °C. After the reaction was complete the aqueous phase was extracted 3 times with 2 mL of DCM. The organic phase was dried over $MgSO_4$ and the solvent carefully evaporated (bp (**105**) = 150 °C). This afforded the clean product in 66% yield (54 mg). The spectroscopic data is in accordance with literature.[174]

One-pot-procedure from 4-hydroxy-2-cyclopentenone (±)-**2a**: To a 10 mL aqueous solution (c = 25 g/L, concentration determined by GC with 1,4-butanediol as internal standard) of 4-hydroxy-2-cyclopentenone (±)-**2a** (250 mg, 2.5 mmol, 1 equiv, obtained from continuous flow system)[28] Pd/C (10% Pd, 4 mg, 0.4 mg Pd, 0.0038 mmol Pd, 0.15 mol% Pd) was added. The autoclave was sealed and purged with hydrogen to exclude air. The desired hydrogen pressure was applied and the reaction stirred at rt for the appropriate time (chapter 3.4, Figure 10). After the reaction was complete the concentration of product 3-hydroxy-2-cyclopentenone (±)-**152** was determined via GC (1,4-butanediol as internal standard). To perform the subsequent elimination of the hydroxy group the solution obtained from the hydrogenation procedure was heated with 150 mg Amberlyst XN1010 in a closed vessel at 90 °C for 2 h. The concentration of product 2-cyclopentenone **105** was determined via GC (1,4-butanediol as internal standard) in different time intervals.

Colorless liquid. R_f = 0.5 (PE/EA 2:1). GC (DBWAX, 100 °C to 200 °C (10 °C/min), 200 °C (10 min)): t_R = 4.5 min (1,4-butanediol as internal standard, t_R = 10.5 min). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.32–2.37 (m, 2H, CH_2), 2.69 (ddd, 2H, *J* = 7.0, 4.7, 2.3 Hz, CH_2), 6.19 (dt, 1H, *J* = 5.7, 2.2 Hz, CH), 7.72 (dt, 1H, *J* = 5.4, 2.7 Hz, CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 29.0 (*C*H_2-CH_2-CO), 34.0 (CH_2-*C*H_2-CO), 134.5 (CH=*C*H-CO), 165.0 (*C*H=CH-CO), 210.7 (C=O).

(±)-3-hydroxycyclopentanon (152)



At atmospheric pressure: (±)-4-hydroxy-2-cyclopentenone **2a** (981 mg, 10 mmol, 1.0 equiv) and Pd/C (5%, 30 mg, 1.5 mg Pd, 0.014 mmol Pd, 0.14 mol% Pd) were dispersed in 20 mL deionized water. The reaction flask was equipped with a balloon filled with H_2 and the reaction mixture stirred at rt for 18 h. Then the solution was filtered over celite and the solvent was evaporated. The crude product (827 mg) was subjected to column chromatography to afford the clean compound (±)-**152** in 53% yield (532 mg, 5.31 mmol). The NMR data is in accordance with literature example.[175]

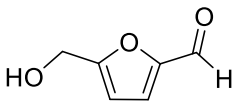
In the autoclave: To a 10 mL aqueous solution (c = 25 g/L, concentration determined by GC with 1,4-butanediol as internal standard) of (±)-4-hydroxy-2-cyclopentenone **2a** (250 mg, 2.5

mmol, 1 equiv, obtained from continuos flow system)[28] Pd/C (10% Pd, 4 mg, 0.4 mg Pd, 0.0038 mmol Pd, 0.15 mol% Pd) was added. The autoclave was sealed and purged with hydrogen to exclude air. Then the desired hydrogen pressure was applied and the reaction was stirred at rt for the appropriate time. After the reaction was complete the pressure was released and a sample was taken from the solution, filtered through a syringe filter to remove Pd/C and analyzed via GC (internal standard 1,4-butanediol).

Colorless oil. R_f = 0.29 (EA/PE 2:1). GC: (DBWAX, 100 °C to 200 °C (10 °C/min), 200 °C (10 min)): t_R = 12.0 min (1,4-butanediol as internal standard, t_R = 10.5 min). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.98–2.51(m, 7H, 2xCH_2 and OH), 4.60 (s, 1H, CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 32.0 (CH_2), 35.6 (CH_2), 47.7 (CH_2), 69.5 (CH), 218.7 (C=O).

2.4 Experiments on the Piancatelli Rearrangement of HMF and BHMF in the Microwave

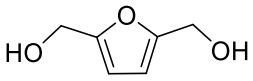
5-hydroxymethylfurfural (HMF) (154)



The compound was prepared as described in literature.[139] *D*-fructose **153** (20 g, 111 mmol, 1.0 equiv) was dissolved in 5.6 mL DMSO and heated to 90 °C. After cooling to rt 60 mL THF and 4.7 g Amberlyst 15 were added. The mixture was stirred at 90 °C for 8 h. The ion exchanger was filtered off. Then the filtrate was treated with 50 mL of water and extracted with diethyl ether. Evaporation of the solvent gave the crude product in 56% (7.871 g, 62 mmol, lit. 75%) yield. The product can be distilled by Kugelrohr distillation at 0.1 Torr and 100 °C providing the product in 43% yield. The spectroscopic data is in accordance with literature.[176]

Yellow solid. R_f = 0.17 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.65 (bs, 1H, OH), 4.71 (s, 2H, CH_2), 6.51 (d, 1H, *J* = 3.5 Hz, C*H*-CCH_2OH), 7.21 (d, 1H, *J* = 3.6 Hz, C*H*-CCHO), 9.57 (s, 1H, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 57.6 (CH_2), 110.0 (*C*H-CCH_2OH), 123.1 (*C*H-CCHO), 152.3 (*C*-CH_2OH), 160.8 (*C*-CHO), 177.8 (CHO).

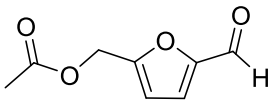
2,5-bis(hydroxymethyl)furan (155)



The compound was prepared as described in literature.[140] 5-Hydroxymethylfurural **154** (1.25 g, 9.9 mmol, 1.0 equiv) was dissolved in 5 mL EtOH and $NaBH_4$ (375 mg, 10 mmol, 1.1 equiv) was added. The reaction mixture was stirred at rt for 19 h. A small amount of water was added and the solvent evaporated. The residue was subjected to column chromatography (SiO_2, $CHCl_3$/2% MeOH) to give the product in 79% (1002 mg, 7.8 mmol) yield. The product can be recrystallized from $CHCl_3$. The spectroscopic data is in accordance with literature.[177]

White solid. R_f = 0.49 (EA/PE 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.04 (bs, 2H, OH), 4.59 (s, 4H, CH_2), 6.24 (s, 2H, CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 57.5 (CH_2), 108.6 (CH), 154.0 (C).

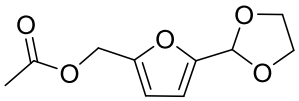
(5-formylfuran-2-yl)methyl acetate (161)



The compound was prepared as described in literature.[143] HMF **154** (201 mg, 1.59 mmol, 1 equiv) was dissolved in 10 mL MeCN under N_2 atmosphere. 0.28 mL Ac_2O (358 mg, 3 mmol, 1.9 equiv) and 0.032 mL pyridine (31 mg, 0.25 equiv) were added. The resulting solution was stirred at rt for 3 h. The solvent was evaporated and the crude product subjected to column chromatography (SiO_2, PE/EA 2:1) to afford the pure product as a yellow oil in 84% yield (225 mg, 1.34 mmol). The spectroscopic data is in accordance with literature.[143]

Yellow oil. R_f = 0.64 (EA/PE 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 6.75 (d, 1H, *J* = 3.6 Hz, C*H*-CCH_2OAc), 7.19 (d, 1H, *J* = 3.6 Hz, C*H*-CCHO), 9.61 (s, 1H, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.7 (CH_3), 57.8 (CH_2), 112.6 (*C*H-CCH_2OH), 121.8 (*C*H-CCHO), 152.8 (*C*-CH_2OH), 155.4 (*C*-CHO), 170.3 (OC=O), 177.8 (HC=O).

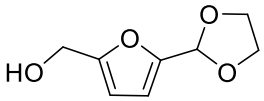
(5-(1,3-dioxolan-2-yl)furan-2-yl)methyl acetate (162)



The compound was prepared as described in literature.[143] (5-formylfuran-2-yl)methyl acetate **161** (529 mg, 3.5 mmol, 1 equiv), 0.39 mL ethylene glycol and a catalytic amount of PTSA were dissolved in 15 mL benzene. The mixture was refluxed in a Dean-Stark-apparatus for 6 h. The organic phase was washed with 10 mL of water, 10 mL of saturated $NaHCO_3$-solution and again 10 mL of water. It was dried over $MgSO_4$ and the solvent evaporated. The product was obtained as a yellow oil in 69% yield (512 mg, 2.41 mmol). The spectroscopic data is in accordance with literature.[143]

Yellow oil. R_f = 0.32 (EA/PE 1:5). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H, CH_3), 4.06 (m, 4H, 2xCH_2), 5.02 (s, 2H, CH_2), 5.89 (s, 1H, OCHO), 6.33 (d, 1H, *J* = 3.3 Hz, furyl-CH), 7.40 (d, 1H, *J* = 3.3 Hz, furyl-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 58.0 (CH_2), 65.2 (2x, CH_2CH_2), 97.6 (CH), 109.6 (furyl-CH), 111.2 (furyl-CH), 150.1 (C), 151.8 (C), 170.6 (OC=O).

(5-(1,3-dioxolan-2-yl)furan-2-yl)methanol (163)

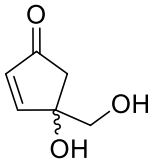


The compound was prepared as described in literature.[143] (5-(1,3-dioxolan-2-yl)furan-2-yl)methyl acetate **162** (434 mg, 2 mmol, 1.0 equiv) was dissolved in 10 mL of MeOH. A small piece of sodium was added and the solution stirred at rt for 1 h. The mixture was neutralized with AcOH and the solvent was evaporated. The residue was dissolved in DCM and filtered. The filtrate was concentrated in vacuum to give 333 mg of the crude product which was purified by column chromatography (SiO_2, PE/EA 2:1, instead of distillation as in the literature example) to give the pure product in 60% yield (201 mg, 1.2 mmol, 91% lit.). The spectroscopic data is in accordance with literature.[143]

Yellow oil. R_f = 0.36 (PE/EA 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 1H, *J* = 19.2 Hz) OH), 3.92–4.18 (m, 4H, 2xCH_2), 4.58 (d, 2H, *J* = 2.9 Hz, CH_2), 5.88 (s, 1H, CH), 6.25 (d, 1H, *J* = 3.2 Hz, furyl-CH), 6.39 (d, 1H, *J* = 3.3 Hz, furyl-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ =

57.5 (CH_2), 65.1 (CH_2CH_2), 97.7 (CH), 108.3 (furyl-CH), 109.7 (furyl-CH), 150.8 (C), 154.9 (C).

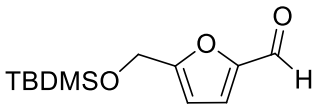
(±)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone (164)



BHMF **155** (216 mg, 1.69 mmol, 1.0 equiv) in 10 mL deionized water (21 g/L) was heated in a 35 mL closed microwave pressure vessel in the microwave at 180 °C for 12 min. The aqueous phase was washed with 6 mL of toluene. The solvent of the aqueous phase was evaporated to give the crude product (179 mg) as a brown oil. Column chromatography (SiO_2, PE/EA 1:1) afforded the clean product (±)-**164** in 67% yield (144 mg, 1.12 mmol). The data is also related to chapter 2.5 (Tests for Biological activity).

Colorless oil. R_f = 0.16 (EA/PE 2:1). ^{1}H-NMR (300 MHz, MeOD): δ = 2.28 (d, 1H, *J* = 18.2 Hz, CH_2), 2.57 (d, 1H, *J* = 18.2 Hz, CH_2), 3.57 (d, 1H, *J* = 11.0 Hz, C*H*$_2$-OH), 3.63 (d, 1H, *J* = 11.0 Hz, C*H*$_2$-OH), 4.87 (s, 2H, OH), 6.17 (d, 1H, *J* = 5.7 Hz, CH), 7.51 (d, 1H, *J* = 5.7 Hz, CH). ^{13}C-NMR (75 MHz, MeOD): δ = 47.1 (CH_2), 67.9 (CH_2-OH), 80.0 (*C*), 135.2 (CH), 166.7 (CH), 209.6 (C=O). IR (film): ν (cm^{-1}) = 3350 (OH), 2928, 2362, 2027, 1707 (C=O), 1589, 1401, 1337, 1270, 1197, 1144, 1066, 1032, 937, 887, 805. HRMS (EI): m/z calcd for $C_6H_8O_3$: 129.0546 $[M+H^{\cdot+}]^+$; found: 129.0546.

5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (175)

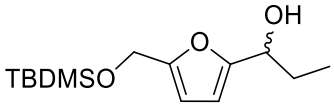


HMF **154** (288 mg, 2.275 mmol, 1.0 equiv), TBSCl (377 mg, 2.5025 mmol, 1.1 equiv), 0.475 mL Et_3N (345 mg, 3.4125 mmol, 1.5 equiv) and 10 mg DMAP were dissolved under N_2 in 10 mL of dry THF. The resulting solution was stirred for 19 h at rt. 10 mL of water was added and the aqueous layer extracted twice with 10 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product (651 mg) was purified by

column chromatography (SiO_2, 20:1 PE/EA) to give compound **175** in 89% yield (486 mg, 2.02 mmol) as a colorless oil. NMR data is in accordance with literature, except for the C-NMR peak at 122.5 which is missing in the literature examples wherein the signal at 109.4 is assigned to both the carbons 3 and 4 of the furan ring. [178,179] This may be due to the fact that this peak exhibits a very small integral and it might have been overlooked. A comparison with the NMR data of HMF **154** and its derivatives indicates that the furyl-carbons in 3 and 4 position show chemical shifts of about 110 respectivly 120 ppm. The electron-withdrawing nature of the aldehyde group shifts the C4 signal more downfield in the NMR.

Colorless oil. R_f = 0.53 (PE/EA 10:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6H, Si-CH_3), 0.87 (s, 9H, CH_3), 4.68 (s, 2H, CH_2), 6.42 (d, 1H, *J* = 3.5 Hz, C*H*-CCH_2OTBS), 7.15 (d, 1H, *J* = 3.6 Hz, C*H*-CCHO), 9.54 (s, 1H, CHO). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = –5.37 (Si-CH_3), 18.3 (*C*(CH_3)$_3$), 25.8 (C(*C*H_3)$_3$), 58.6 (CH_2), 109.4 (*C*H-CCH_2OTBS), 122.5 (*C*H-CCHO), 152.2 (*C*-CH_2OTBS), 161.5 (*C*-CHO), 177.6 (CHO).

(±)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-yl)propan-1-ol (176)

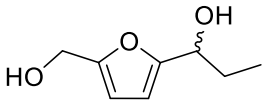


EtBr (668 mg, 6.19 mmol, 0.458 mL, 2.6 equiv) in 5 mL dry THF was added dropwise to a solution of Mg (133 mg, 5.47 mmol, 2.3 equiv) and a small piece of I_2 in 8 mL dry THF under N_2. The solution was heated briefly with a heatgun until the reaction mixture started to boil without external heating. After the boiling stopped the reaction was refluxed another 10 minutes. The solution was cooled down to 0 °C and **175** (300 mg, 2.38 mmol, 1 equiv) in 5 mL dry THF was added dropwise. The solution was stirred for another 30 minutes at rt. 10 mL of water were added. The aqueous phase was seperated and extracted with 3x 20 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product (393 mg) was subjected to column chromatography (SiO_2, PE/EA 5:1), which afforded the pure product (±)-**176** in 65% yield (240 mg, 0.89 mmol).

Colorless liquid. R_f = 0.40 (PE/EA 10:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6H, Si-CH_3), 0.9 (s, 9H, CH_3), 0.95 (t, 3H, *J* = 7.4 Hz, CH_3), 1.87 (m, 2H, C*H*$_2$$CH_3$), 1.96 (bs, 1H, OH), 4.56 (t, 1H, *J* = 6.8 Hz, CH), 4.61 (s, 2H, CH_2), 6.16 (bs, 2H, furyl-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 5.2 (Si-CH_3), 10.0 (CH_2*C*H_3), 18.4 (*C*(CH_3)$_3$), 25.9 (C(*C*H_3)$_3$), 28.6

(CH_2CH_3), 58.2 (CH_2), 69.3 (CH), 106.5 (furyl-CH), 107.8 (furyl-CH), 153.7 (furyl-C), 156.3 (furyl-C). IR (film): ν (cm^{-1}) = 2929, 2859, 1463, 1254, 1077, 833, 776. HRMS (EI): m/z calcd for $C_{14}H_{26}O_3Si$: 271.1724 $[M+H^{\cdot+}]^+$; found: 271.1716.

(±)-1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol (177)

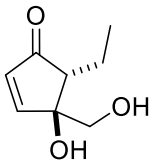


Desilylation of **176**: (±)-1-(5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)propan-1-ol **176** (221 mg, 0.82 mmol, 1 equiv) and TBAF (284 mg, 0.9 mmol, 1.1 equiv) were dissolved in 10 mL THF and the resulting mixture was stirred at rt for 10 min. Then 10 mL of H_2O were added and the aqueous phase was extracted 4 times with 20 mL ethylacetate. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (SiO_2, PE/EA 1:1) of the crude product (206 mg) afforded the pure compound **177** in 94% yield (121 mg, 0.77 mmol).

Direct Grignard reaction with HMF **154**: Mg (133 mg, 5.47 mmol, 2.3 equiv) and a small crystal of I_2 were stirred under N_2 at rt in 8 mL dry THF. 0.458 mL EtBr (668 mg, 6.19 mmol, 2.6 equiv) in 5 mL of dry THF was added dropwise. The solution started to reflux independently after briefly heating the mixture with a heatgun. When the boiling ceased, the solution was refluxed for another 10 min. Then the reaction mixture was cooled down to 0 °C and HMF **154** (300 mg, 2.38, 1 equiv) in 5 mL of dry THF was added dropwise. The solution was stirred at 0 °C for another 30 min and 10 mL of H_2O was added. The aqueous phase was extracted three times with 20 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (SiO_2, PE/EA 5:1) afforded the pure product in 65% yield (240 mg, 1.54 mmol).

Colorless liquid. R_f = 0.20 (PE/EA 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H, *J* = 7.4 Hz, CH_3), 1.85 (qd, 2H, *J* = 7.2, 3.7 Hz, C*H*$_2$-CH_3), 2.34 (bs, 2H, OH), 4.55 (m, 3H, CH_2 + CH), 6.16 (d, 1H, *J* = 3.2 Hz, furyl-CH), 6.21 (d, 1H, *J* = 3.1 Hz, furyl-CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 10.0 (CH_3), 28.4 (CH_2*C*H_3), 57.4 (CH_2), 69.2 (*C*H-OH), 106.7 (fury*l*-*C*H), 108.4 (furyl-CH), 153.4 (C), 156.7 (C). IR (film): ν (cm^{-1}) = 3341 (OH), 2968, 2934, 2876, 1667, 1456, 1188, 1011, 792. HRMS (ESI): m/z calcd for $C_8H_{12}O_3$: 179.0679 $[M+Na^+]$; found: 179.0675.

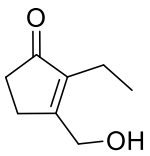
trans-5-ethyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone (178)



(±)-1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol **177** (140 mg, 0.96 mmol, 1 equiv) in 6 mL of deionized water was heated in a 35 mL closed vessel for 30 min at 300 W in the microwave. The temperature reached 144 °C and the pressure 5 bar. After the reaction the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, PE/EA 3:1) to afford the *trans*-diastereomer in 74% yield (103 mg, 0.66 mmol). The other diastereomer was visible in the crude NMR spectra in minor amounts (ratio not determinable due to overlapping signals) but could not be isolated, assumingly by reason of isomerization on C5.

Colorless liquid. R_f = 0.24 (PE/EA 1:2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3H, *J* = 7.4 Hz, CH_3), 1.48 (m, 1H, C*H*$_2$-CH_3), 1.80 (m, 1H, C*H*$_2$-CH_3), 2.37 (dd, 1H, *J* = 8.1, 6.1 Hz, CH), 3.59 (dd, 1H, *J* = 10.6, 5.0 Hz, C*H*$_2$-OH), 3.87 (dd, 1H, *J* = 10.6, 2.7 Hz, C*H*$_2$-OH), 6.24 (d, 1H, *J* = 5.9 Hz, C*H*=CH), 7.52 (d, 1H, *J* = 5.9 Hz, CH=C*H*) . ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_3), 17.6 (*C*H_2*C*H_3), 58.9 (CH), 66.3 (CH_2-OH), 81.3 (C), 133.6 (C=C), 162.4 (C=C), 206.0 (C=O). IR (film): ν (cm^{-1}) = 3403 (OH), 2964, 2938, 2881, 1702 (C=O), 1108,1059. HRMS (ESI): m/z calcd for $C_8H_{13}O_3$: 157.0859 [M+H$^+$]; found: 157.0861.

2-ethyl-3-(hydroxymethyl)cyclopent-2-enone (179)



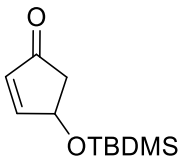
Hydrogenation of **178**: 5-ethyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone **178** (64 mg, 0.41 mmol, 1.0 equiv) and Pd/C 10% (2 mg, 0.2 mg Pd, 0.0019 mmol Pd, 0.46 mol% Pd) in 5 mL water were stirred at rt and 1 atm of H_2 for 24 h. 60 mg of Amberlyst XN1010 was added and the solution refluxed for 2 h. The reaction mixture was decanted and the solvent evaporated. The crude product (54 mg) was purified by column chromatography (SiO_2, PE/EA 2:1) to give compound **179** in 48% yield (28 mg, 0.20 mmol).

One-pot-procedure from **177**: (±)-1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol **177** (143 mg, 0.92 mmol, 1.0 equiv) in 6 mL deionized water (c = 25 g/L) was heated in the microwave (CEM Discover) at 300 W for 30 min. The temperature reached 142 °C and the pressure 5 bar. After adding Pd/C 10% (4 mg, 0.4 mg Pd, 0.0038 mmol, 0.41 mol%), the resulting solution was stirred at rt and 1 atm of H_2 for 20 h. Then 120 mg of Amberlyst XN1010 was added and the solution refluxed for 2 h. The reaction mixture was decanted and the solvent was evaporated. The crude product (125 mg) was purified by column chromatography (SiO_2, PE/EA 2:1) to give compound **179** in 40% yield (47 mg, 0.34 mmol). The spectroscopic data is in accordance with literature.[146]

Colorless oil. R_f = 0.44 (PE/EA 1:2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.6 Hz, 3H, CH_3), 1.71 (bs, 1H, OH), 2.22 (q, J = 7.6 Hz, 1H, C*H*$_2$-CH_3), 2.37-2.43 (m, 2H, CH_2), 2.61-2.68 (m, 2H, CH_2), 4.59 (s, 2H, C*H*$_2$-OH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.3 (CH_3), 16.4 (*C*H_2*C*H_3), 26.8 (CH_2), 34.1 (CH_2), 60.7 (CH_2-OH), 142.0 (C=C), 169.6 (C=C), 209.7 (C=O).

2.5 Tests for Biological Activity

(±)-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-enone (211)



The compound was prepared according to a literature procedure.[180] (±)-4-Hydroxy-2-cyclopentenone **2a** (2370 mg, 24.16 mmol, 1.0 equiv), 5 mL Et_3N (3628 mg, 35.85 mmol, 1.5 equiv) and DMAP (64 mg, 0.52 mmol, 2 mol%) were dissolved in 13 mL dry THF at 0 °C. TBSCl (3651 mg, 24.22 mmol, 1.0 equiv) was added stepwise at 0 °C. The reaction was stirred at rt for 20 h. 26 mL 0.5 M HCl was added and the layers separated. The aqueous layer was extracted 3 x with 15 mL PE. The combined organic layers were washed 2 x with 15 mL 0.5 M HCl, 1 x with 5% $NaHCO_3$-solution and 1 x with 15 mL brine. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude product (yellow oil, 4474 mg) was subjected to column chromatography (SiO_2, PE/EA 20:1, instead of Kugelrohr distillation as described in

the literature procedure) to afford the pure product in 76% yield (3.909 mg, 18.4 mmol, lit. 63%[180]). The spectroscopic data is in accordance with literature.[180]

Colorless solid. R_f = 0.55 (PE/EA 10:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3H, CH_3), 0.10 (s, 3H, CH_3), 0.88 (s, 9H, ^{t}butyl-CH_3), 2.20 (ddd, 1H, *J* = 18.2, 2.2, 0.5 Hz, CH_2), 2.67 (dd, 1H, *J* = 18.2, 6.0 Hz, CH_2), 4.95 (ddd, 1H, *J* = 5.7, 3.4, 2.1 Hz, C*H*-OH), 6.14 (d, 1H, *J* = 5.1 Hz, CH=C*H*-C=O), 7.42 (dd, 1H, *J* = 5.7, 2.3 Hz, C*H*=CH-C=O). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 4.7 (CH_3), 4.8 (CH_3), 18.1 (^{t}butyl-C), 25.7 (3x ^{t}butyl-CH_3), 44.9 (CH_2), 70.8 (CH-OH), 134.4 (CH=*C*H-C=O), 163.8 (*C*H=CH-C=O), 206.4 (C=O).

Biological Tests (performed by Hannelore Rücker, group of Dr. Sabine Amslinger University of Regensburg)

Griess-Assay (Nitrite Assay) and MTT/LPS-Assay (Viability Assay)

Cell culture:

Murine macrophages, RAW264.7 were grown in RPMI supplemented with 10% (v/v) heat inactivated fetal calf serum and 2 mM glutamine. Macrophages were cultured at 37 °C in a humidified air containing 5% CO_2.

Cytotoxicity Test by MTT-Assay:

Cell viability was evaluated by determining mitochondrial function of living cells on the basis of their ability to reduce the yellow dye, tetrazolium salt 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT), into violet formazan by the mitochondrial dehydrogenases. Stock solutions of test compounds were prepared in DMSO (100 mM) and stored at -20 °C. Test concentrations were freshly prepared by diluting the stock solution in culture media and the final concentration of DMSO in the medium was ≤ 0.1%. Cells (5 × 10^3/well) were plated into 96-well plates and allowed to attach for 24 h. Test compounds were added to wells in several concentrations (100/10/1 µM) in presence of LPS (Lipopolysaccharide, 10 ng/ml) and incubated for 20 h. Total assay volume was 100 µl. 10 µL of 4 mg/mL MTT in PBS was added to each well. After 4 h the culture medium was removed and 100 µL of a 10% SDS solution in water was put in each well to solubilize the formazan product. The absorbance was measured at 560 nm in a microplate reader (Multiskan Spectrum, Thermo) after 24 h incubation in the dark at room temperature.

Nitrite Assay

RAW264.7 macrophages (8 x 10^4 cell/well) were plated in 96-well plates, allowed to attach for 24 h and stimulated with test compounds (100/10/1 µM) in the presence of LPS (10 ng/ml) for 24 h. The culture media was then collected (50 µl/well), mixed with an equal volume of Griess reagent (0.1% NED (*N*-(1-Naphthyl)ethylenediamine dihydrochloride), 1% sulfanilamine, 0.35% phosphoric acid in water) and incubated for 15 min at room temperature. The absorbance was measured at 560 nm.

E. Appendix

1. NMR Spectra

^{1}H-NMR (300 MHz or 400 MHz): -upper image

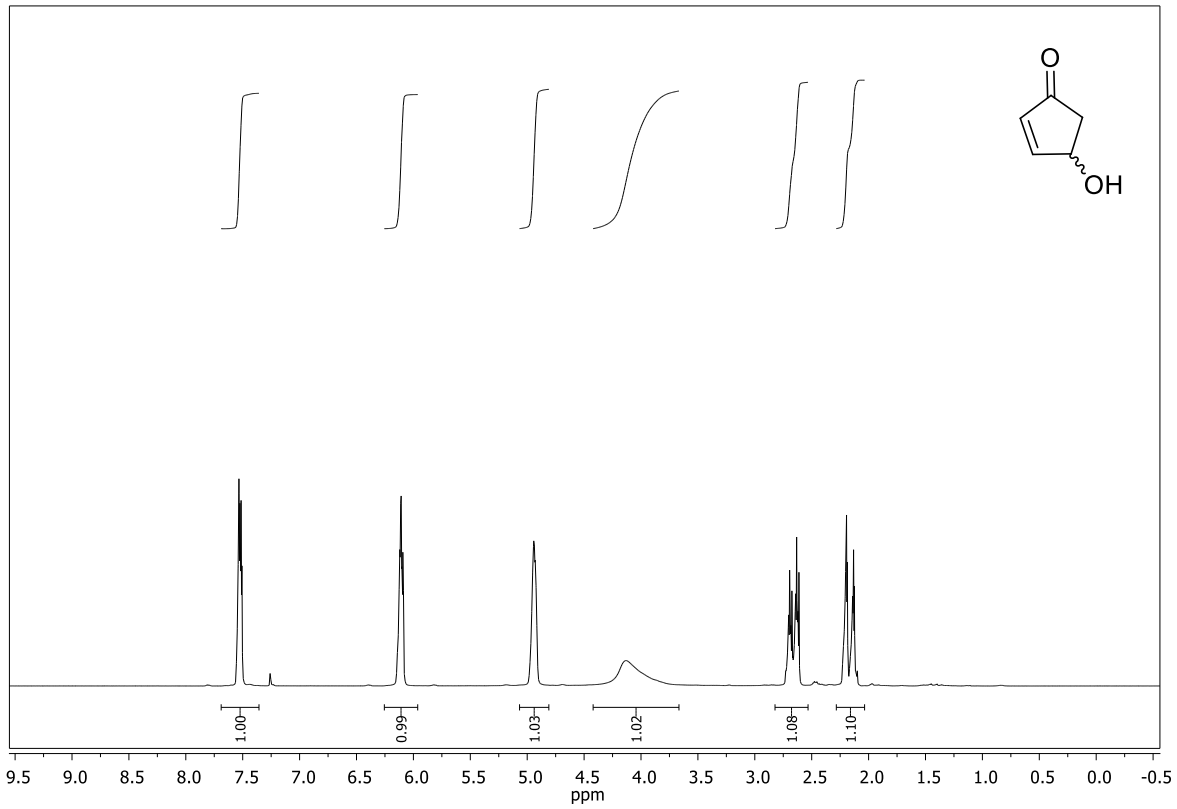
^{13}C-NMR (75 MHz or 101 MHz): -lower image

DEPT-135 (75 MHz or 101 MHz): -upper image

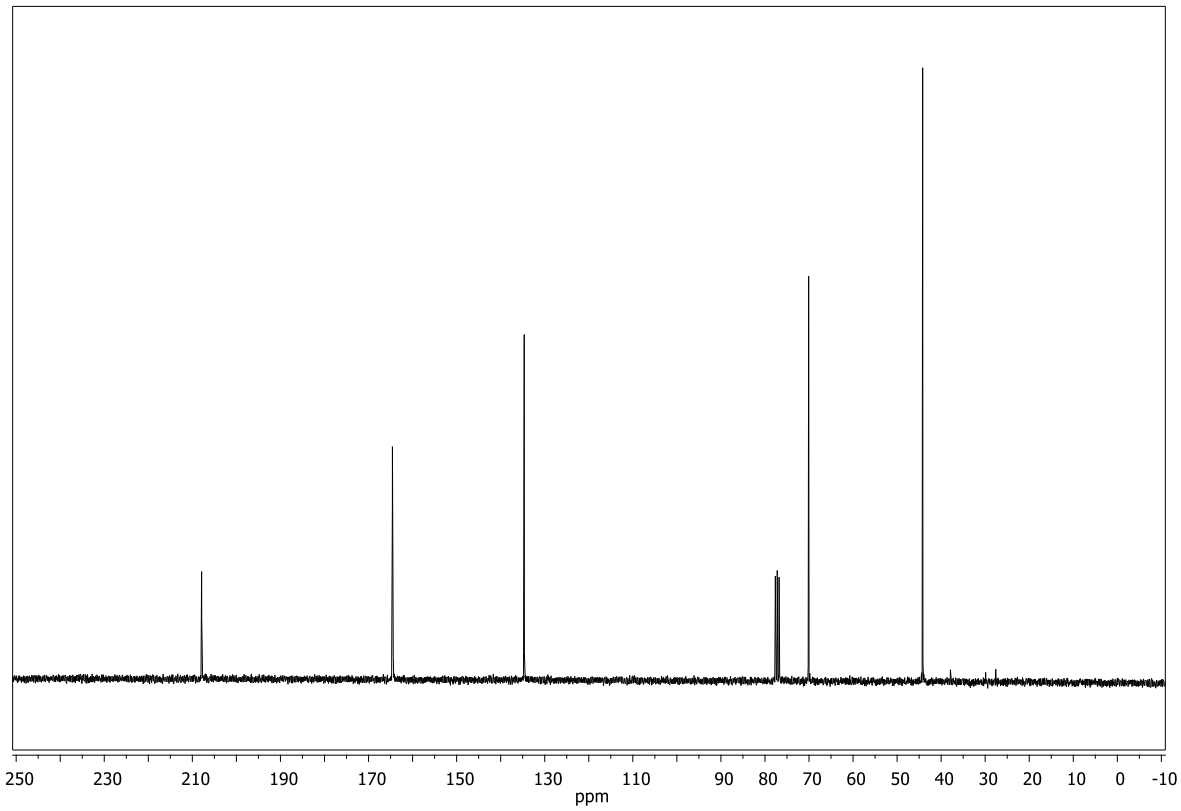
DEPT-90 (75 MHz or 101 MHz): -lower image

Used solvent and frequency are stated at the actual spectra.

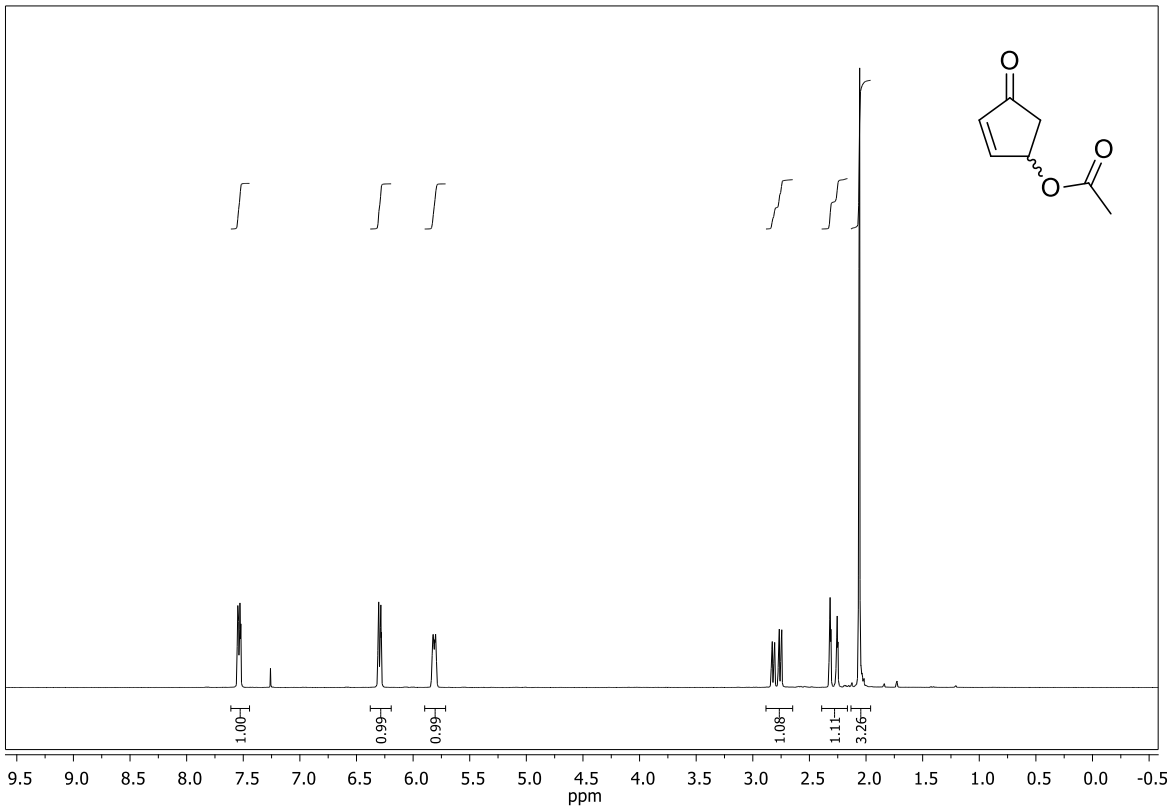
(±)-4-hydroxycyclopent-2-enone (2a) **($CDCl_3$, 300 MHz)**



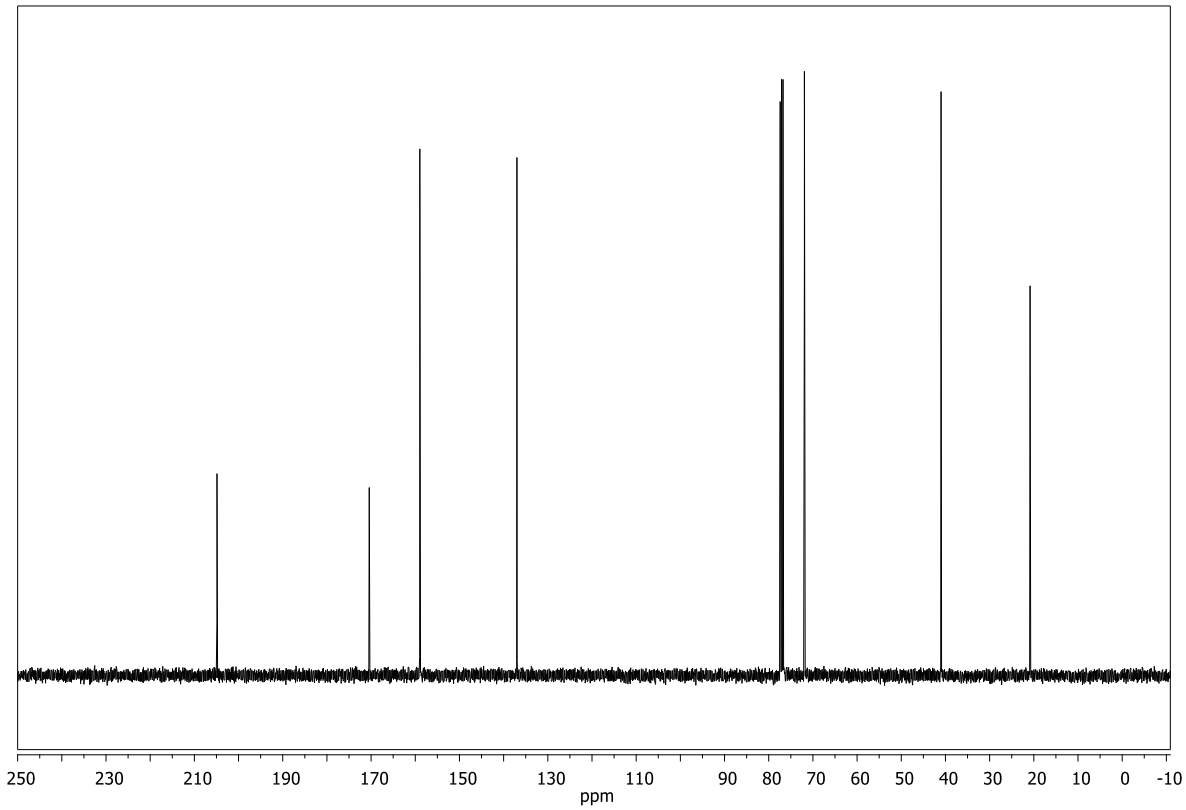
($CDCl_3$, 75 MHz)



(±)-4-acetoxy-2-cyclopentenone (69a) **($CDCl_3$, 300 MHZ)**

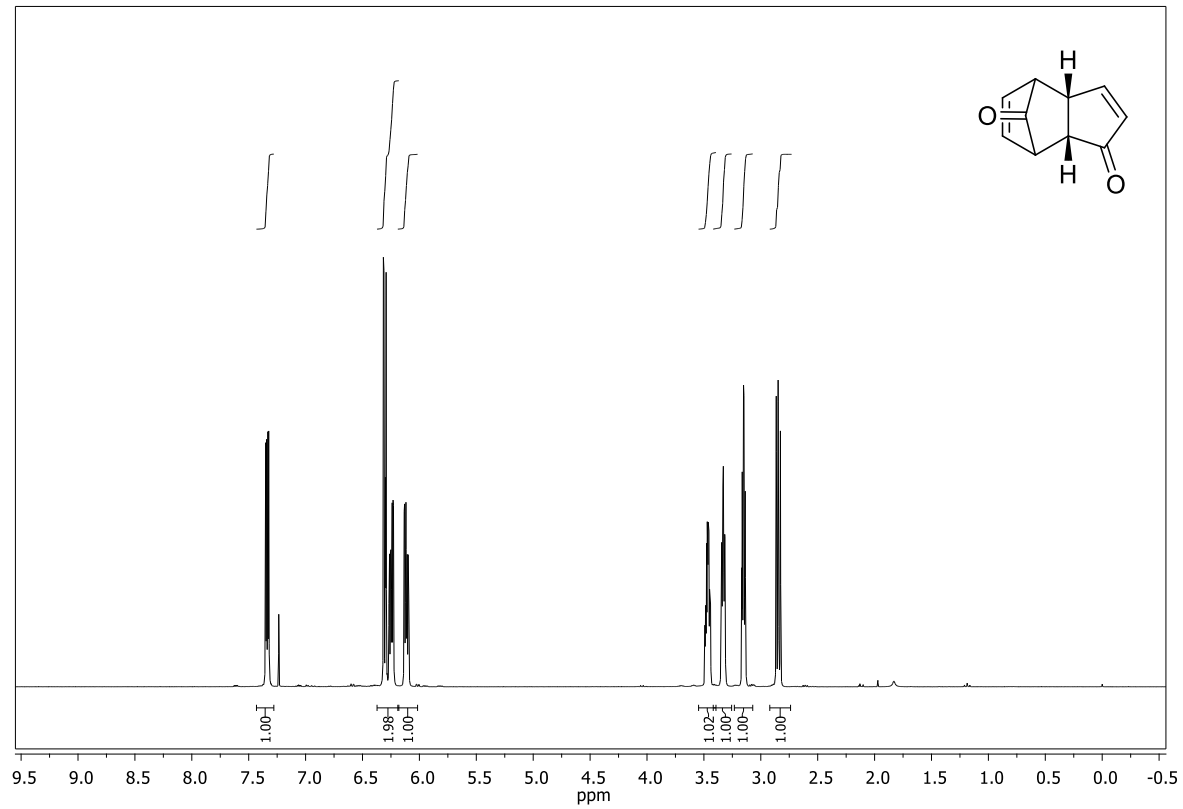


($CDCl_3$, 75 MHz)

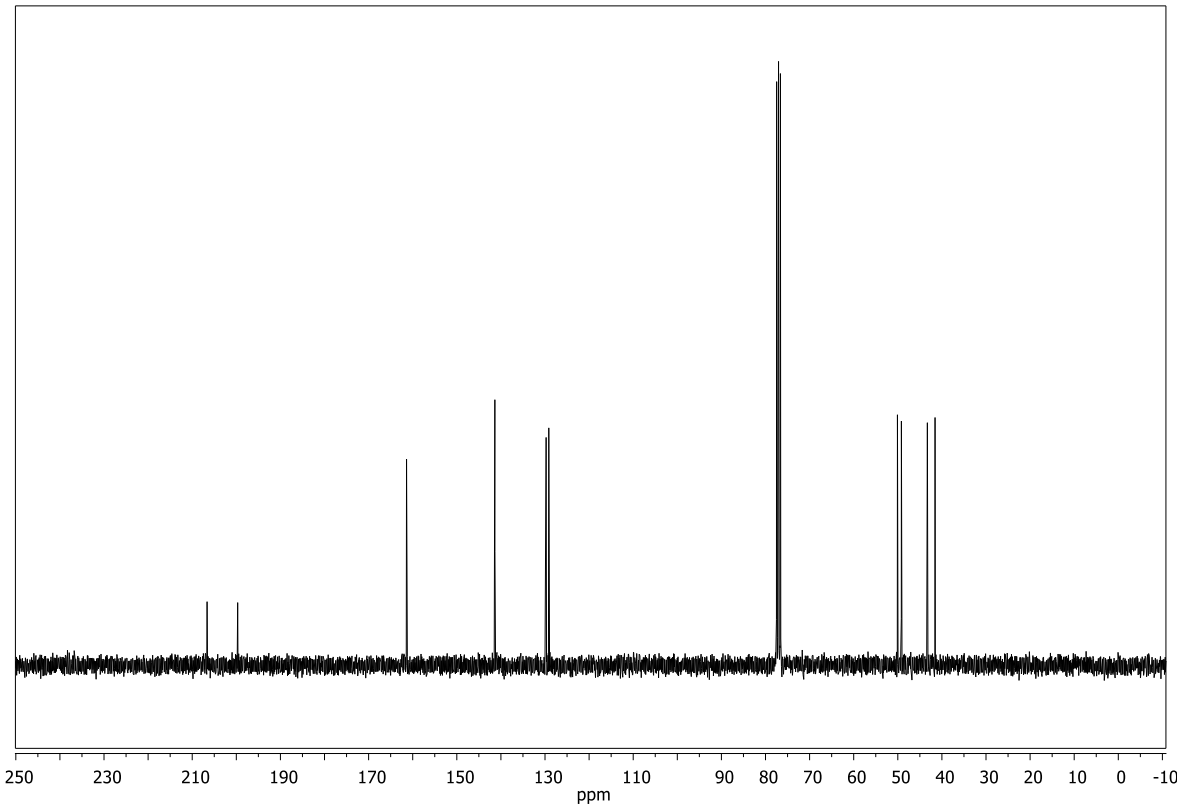


(*endo*)-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene-1,8-dione (79)

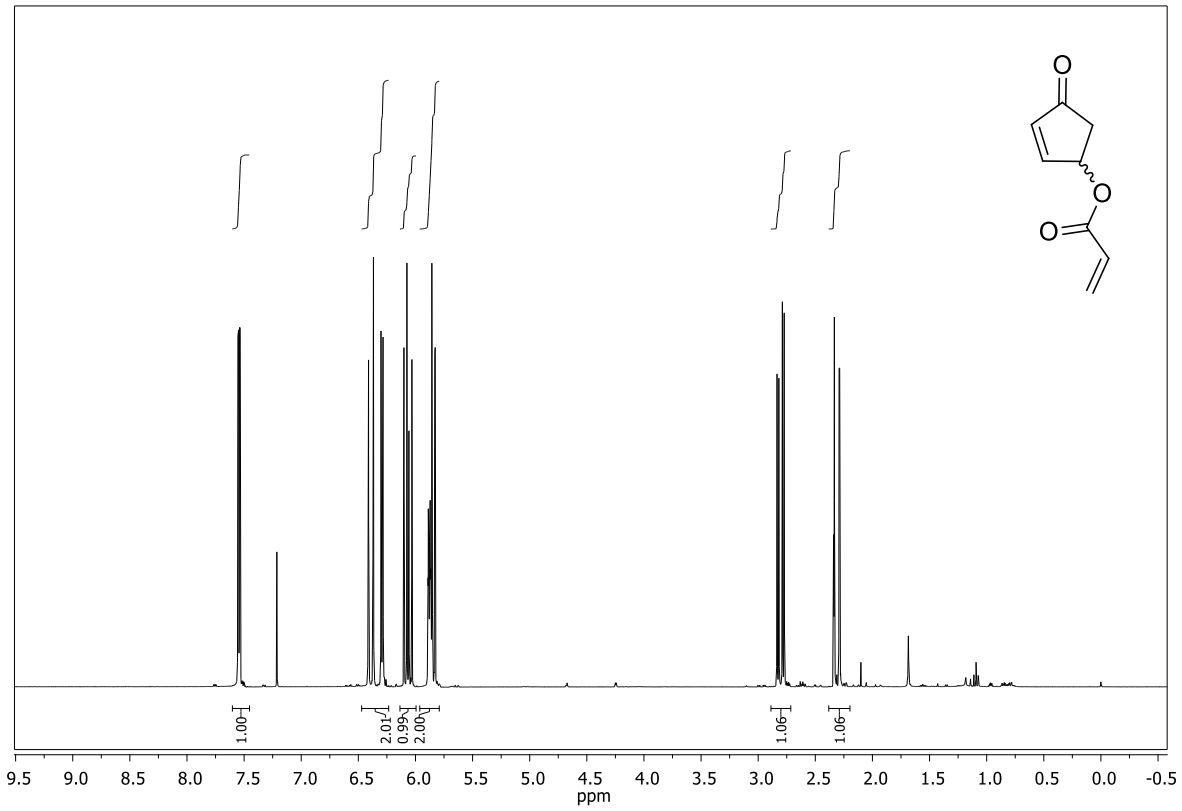
($CDCl_3$, 300 MHz)



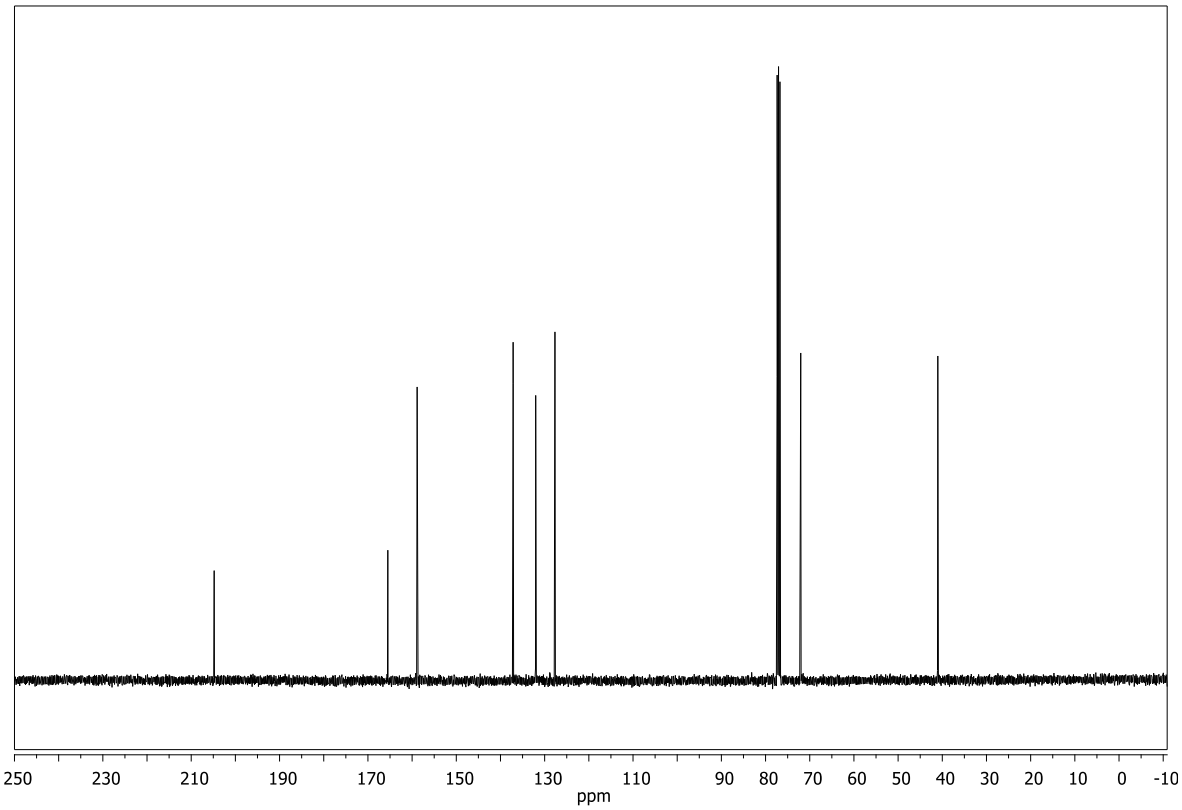
($CDCl_3$, 75 MHz)



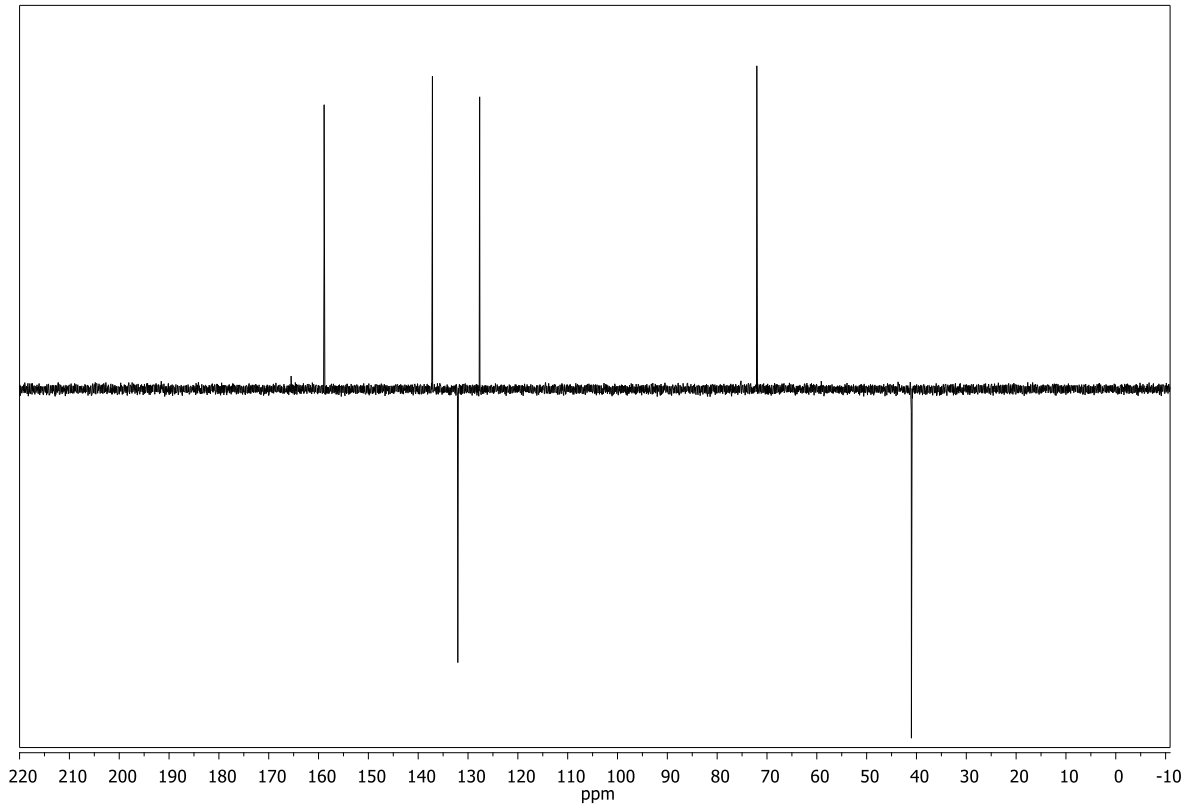
(±)-4-oxocyclopent-2-en-1-yl acrylate (82) **($CDCl_3$, 400 MHz)**



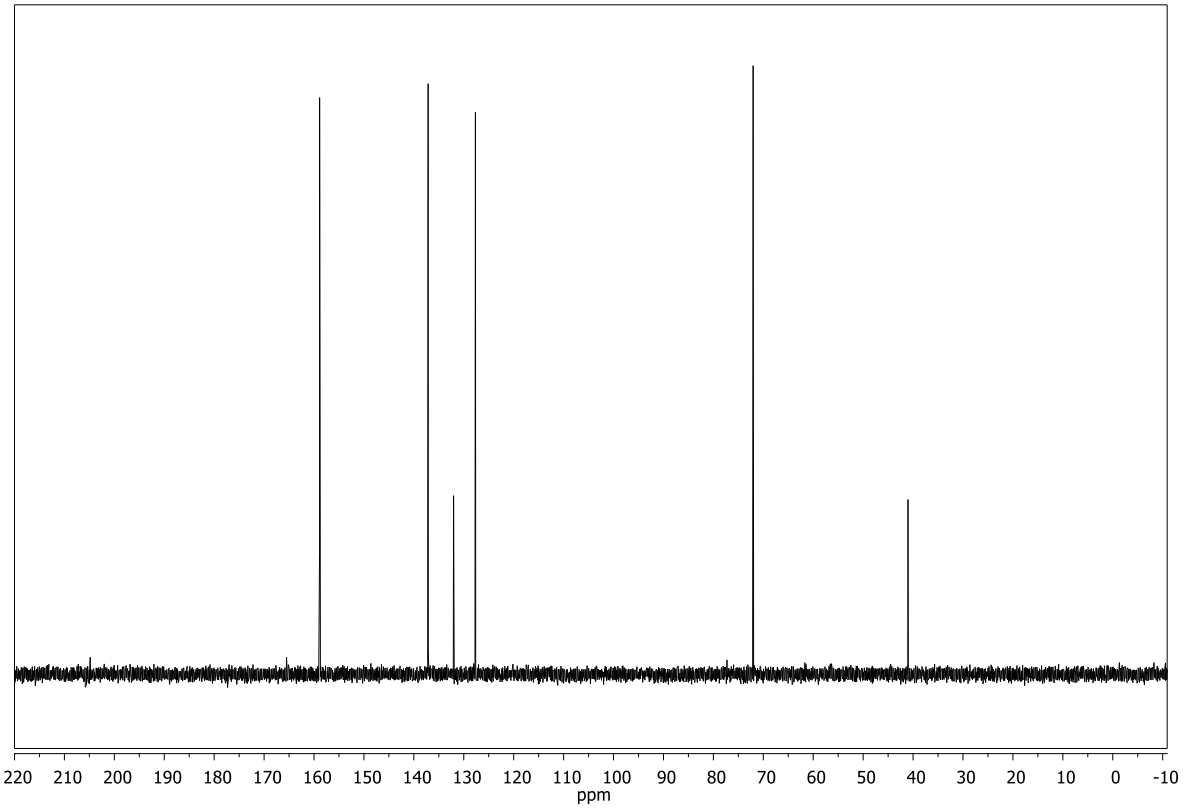
($CDCl_3$, 101 MHz)



($CDCl_3$, 101 MHz)

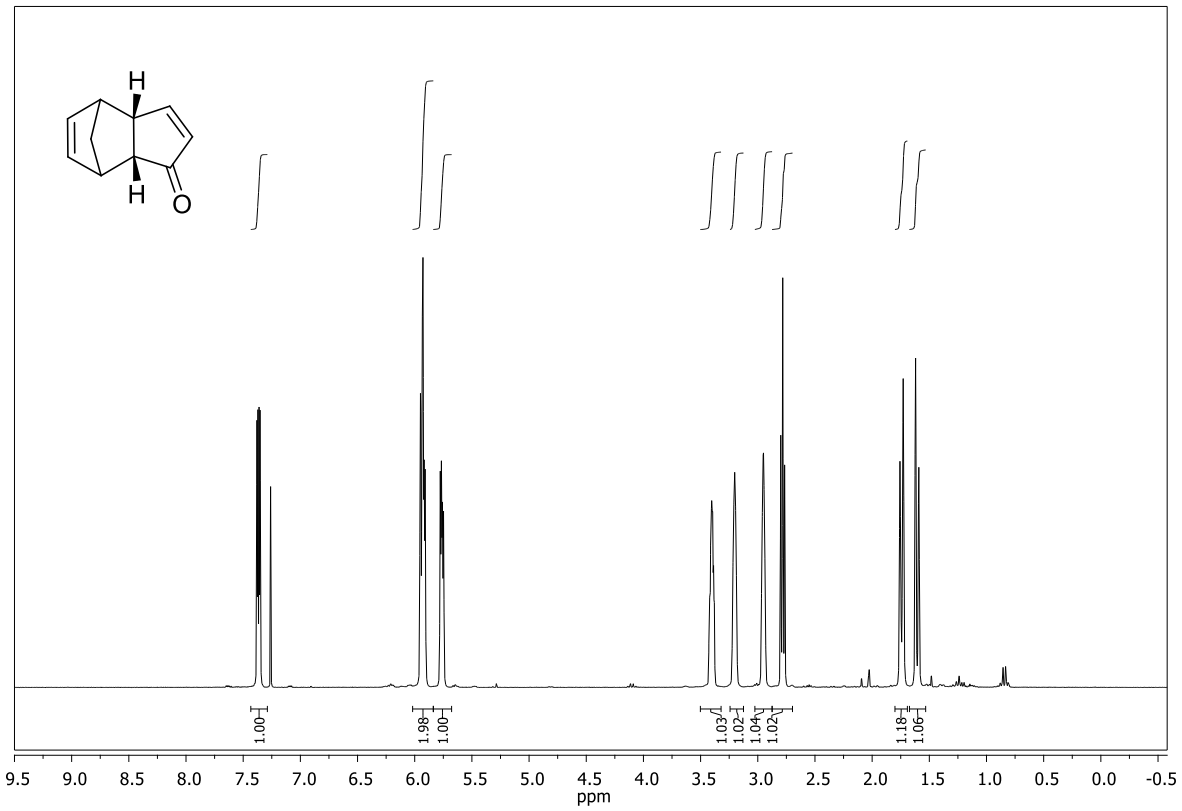


($CDCl_3$, 101 MHz)

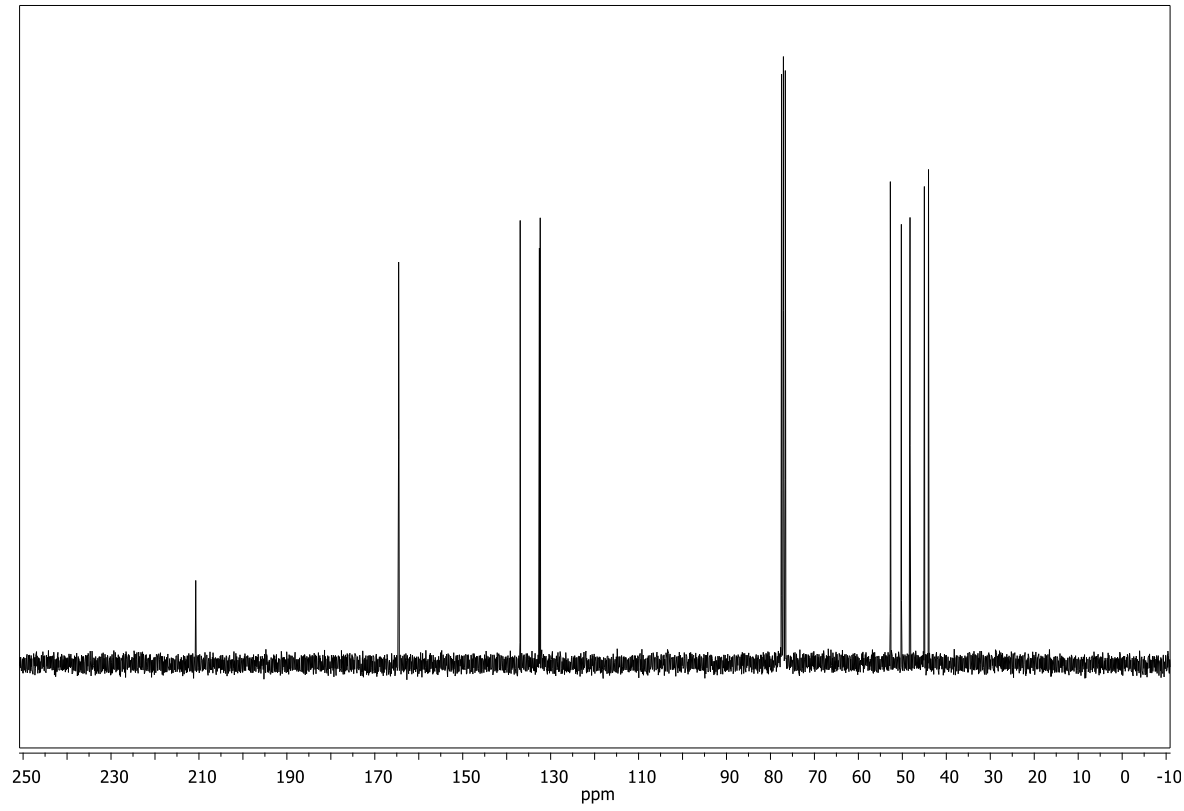


(*endo*)-(3aS,7aR)-3a,4,7,7a-tetrahydro-1H-4,7-methanoinden-1-one (90)

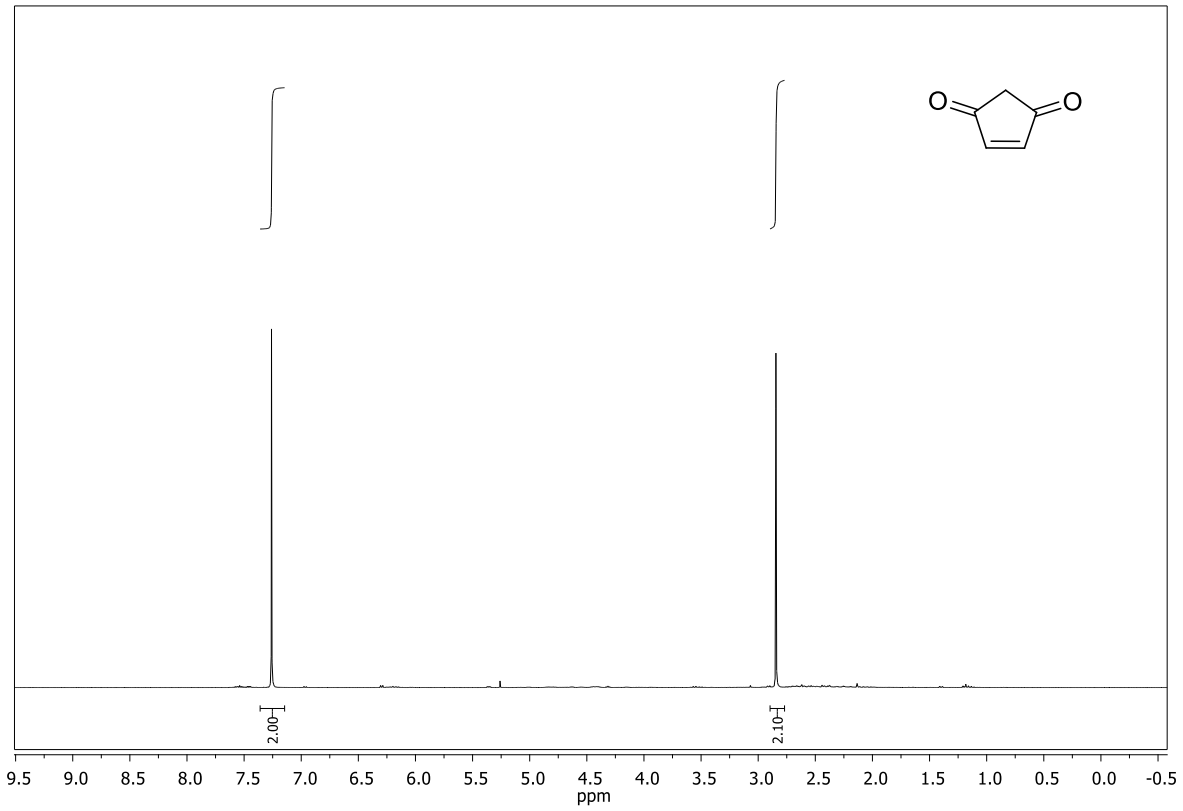
($CDCl_3$, 300 Mhz)



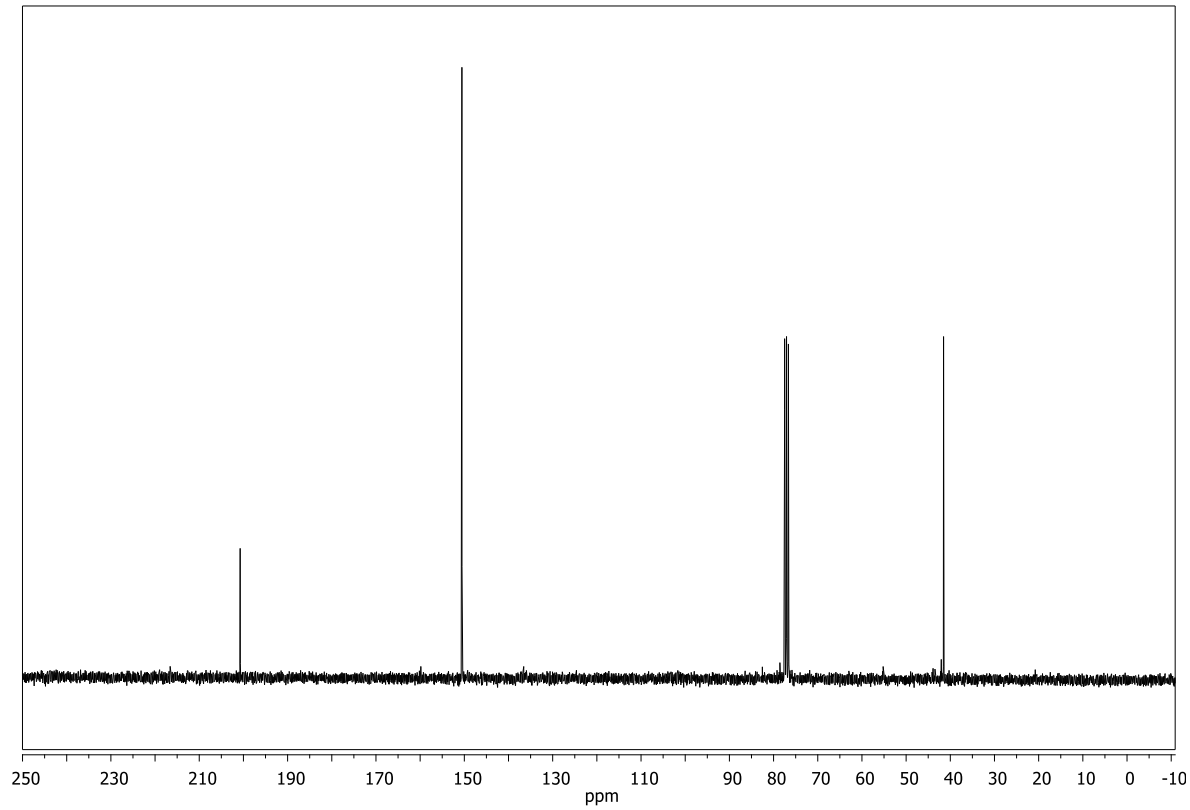
($CDCl_3$, 75 MHz)



cyclopent-4-ene-1,3-dione (103) **($CDCl_3$, 300 MHz)**

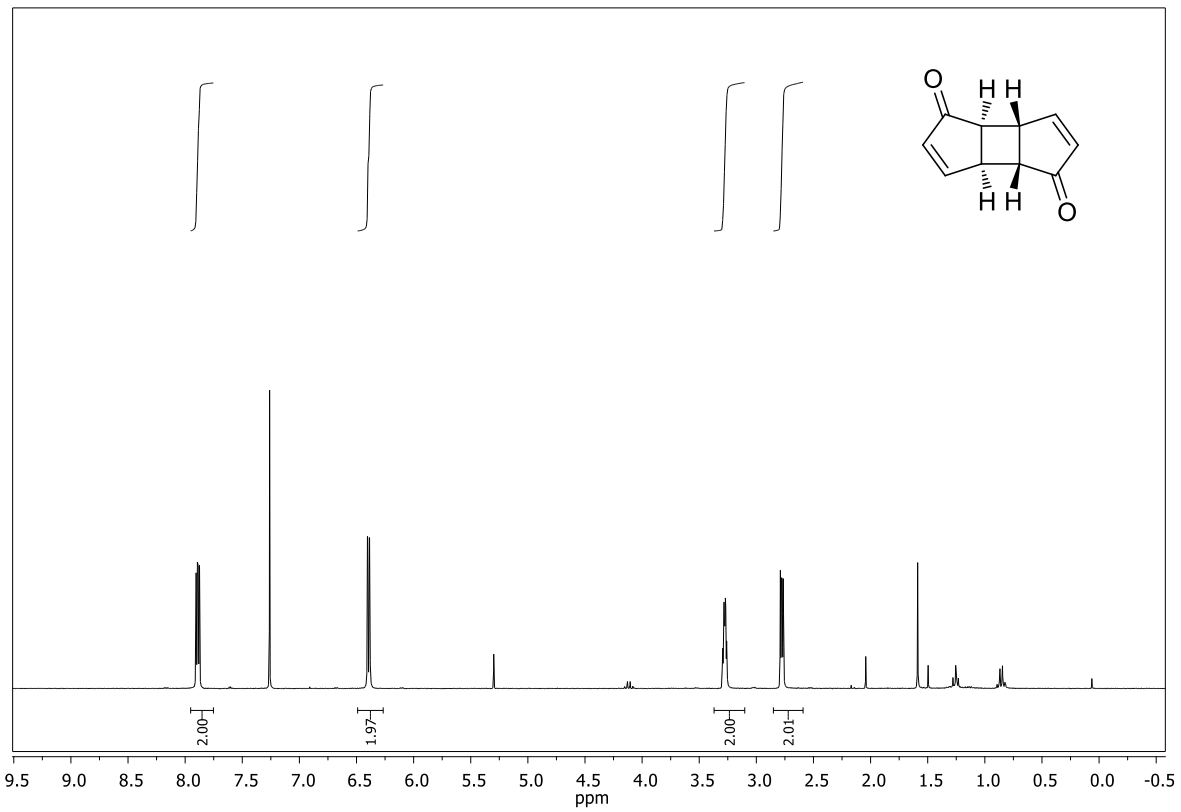


($CDCl_3$, 75 MHz)

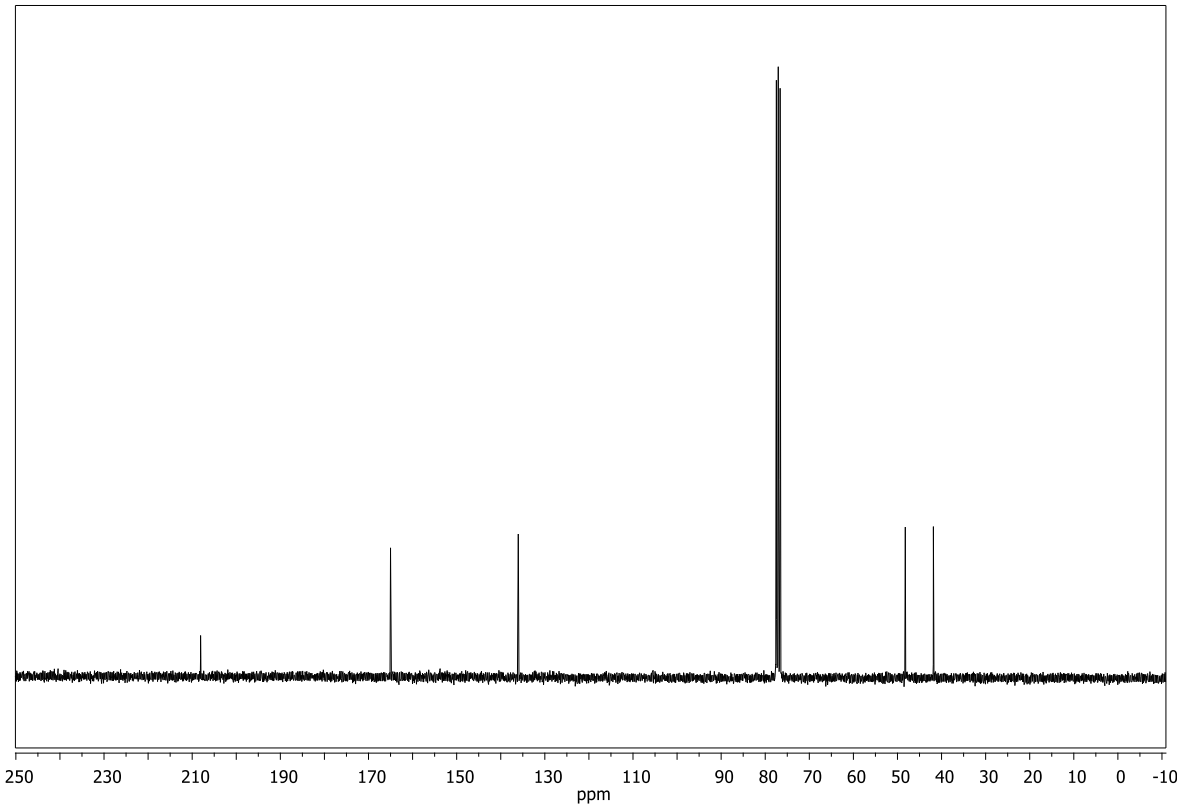


6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,4(3aH,3bH)-dione (108a)

($CDCl_3$, 300 MHz)

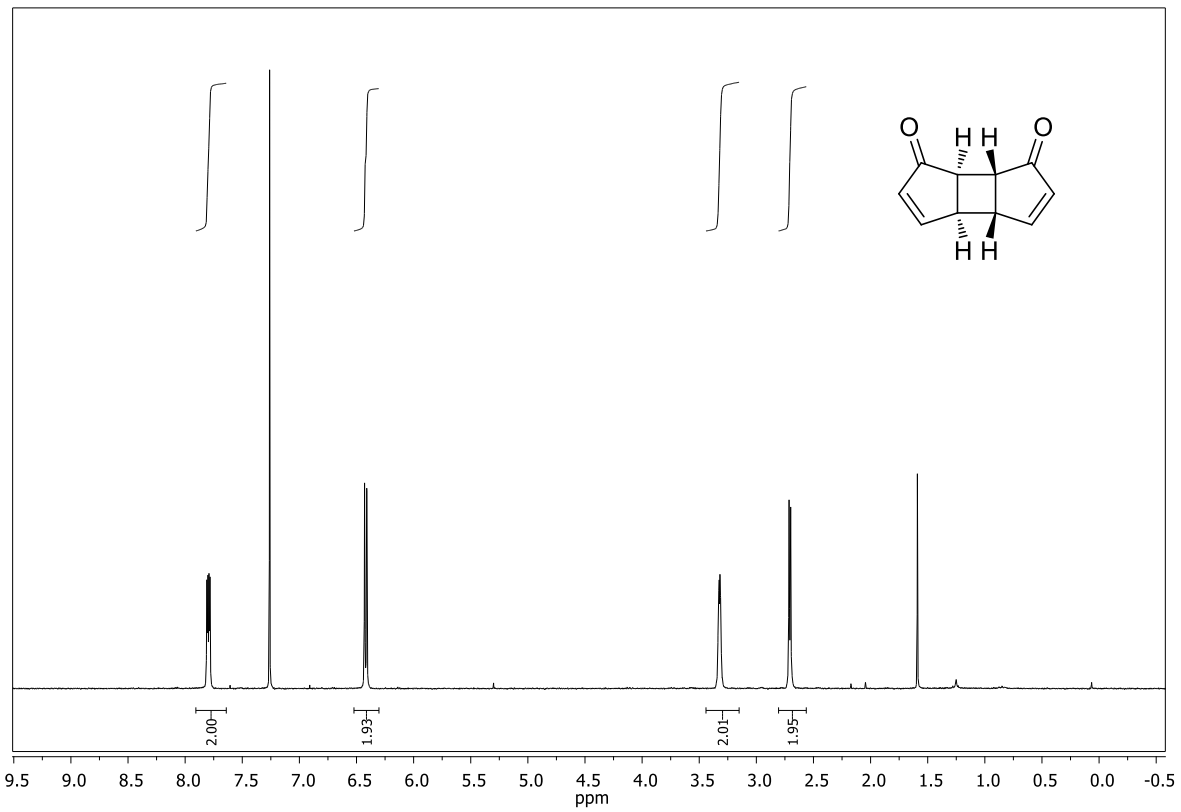


($CDCl_3$, 75 MHz)

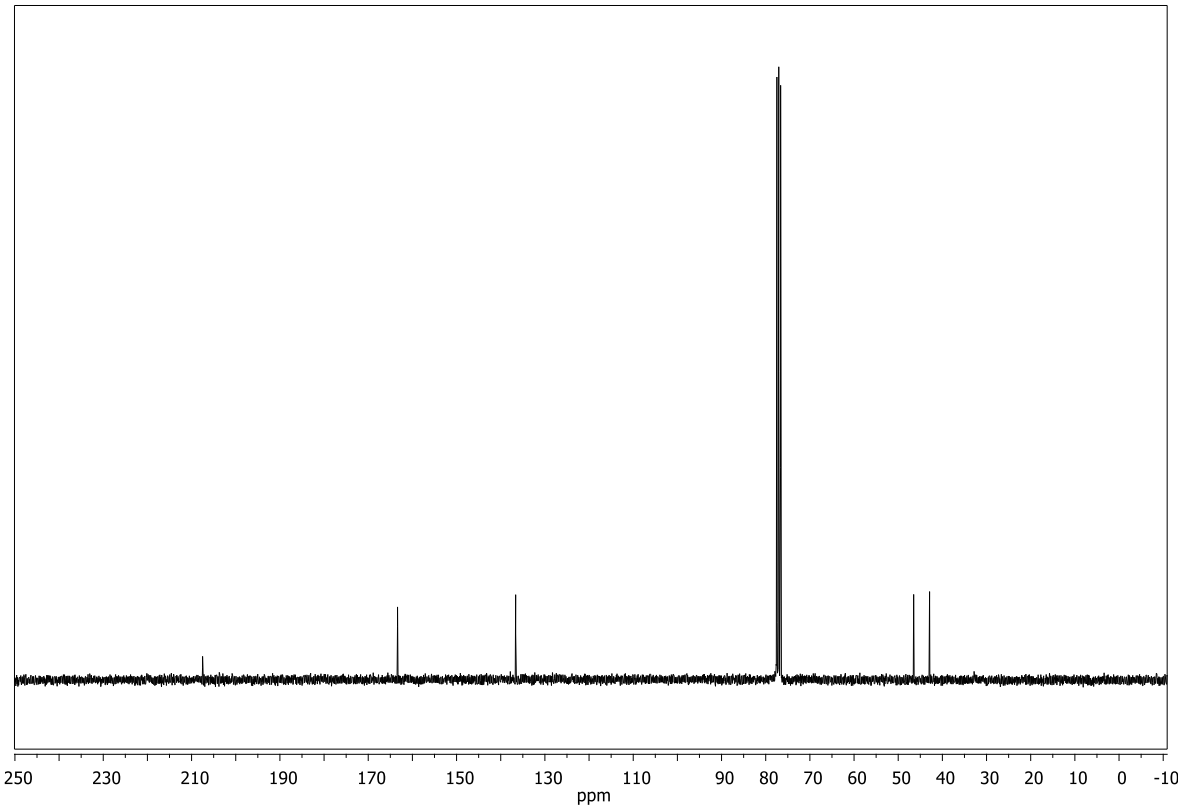


6a,6b-dihydrocyclobuta[1,2:3,4]di[5]annulene-1,6(3aH,3bH)-dione (108b)

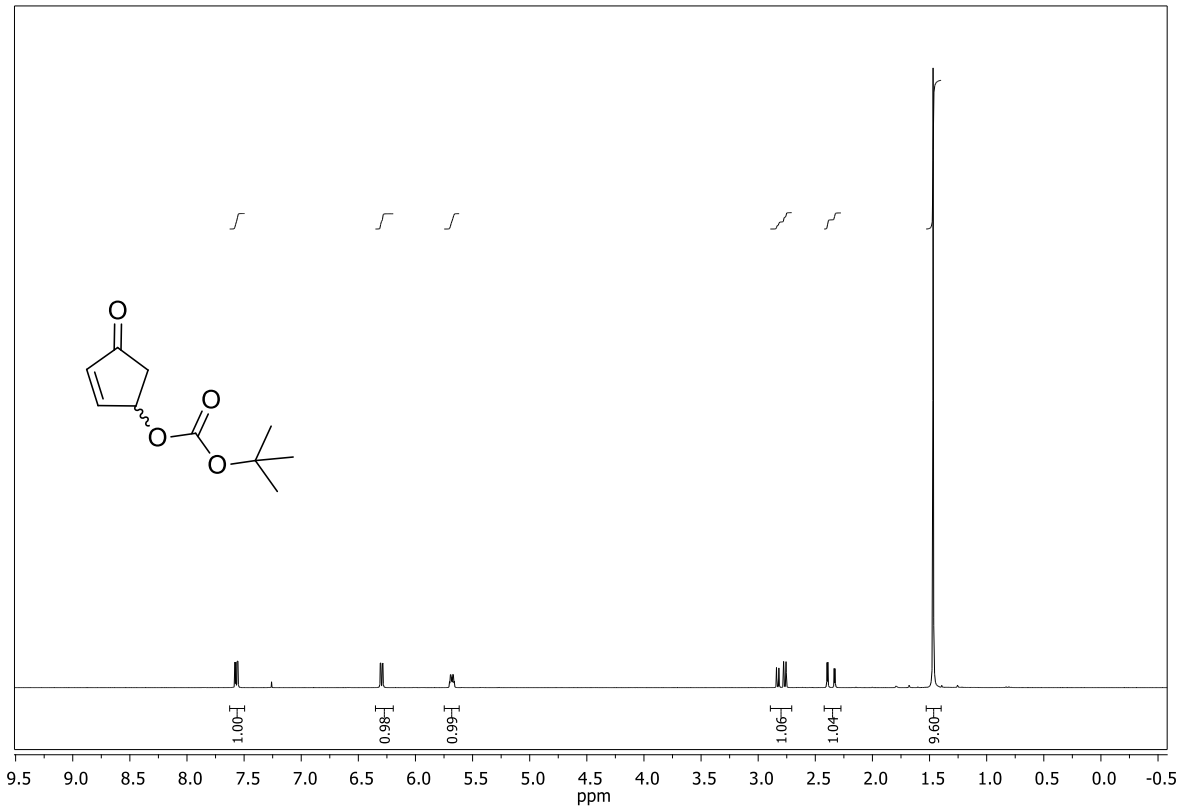
($CDCl_3$, 300 MHz)



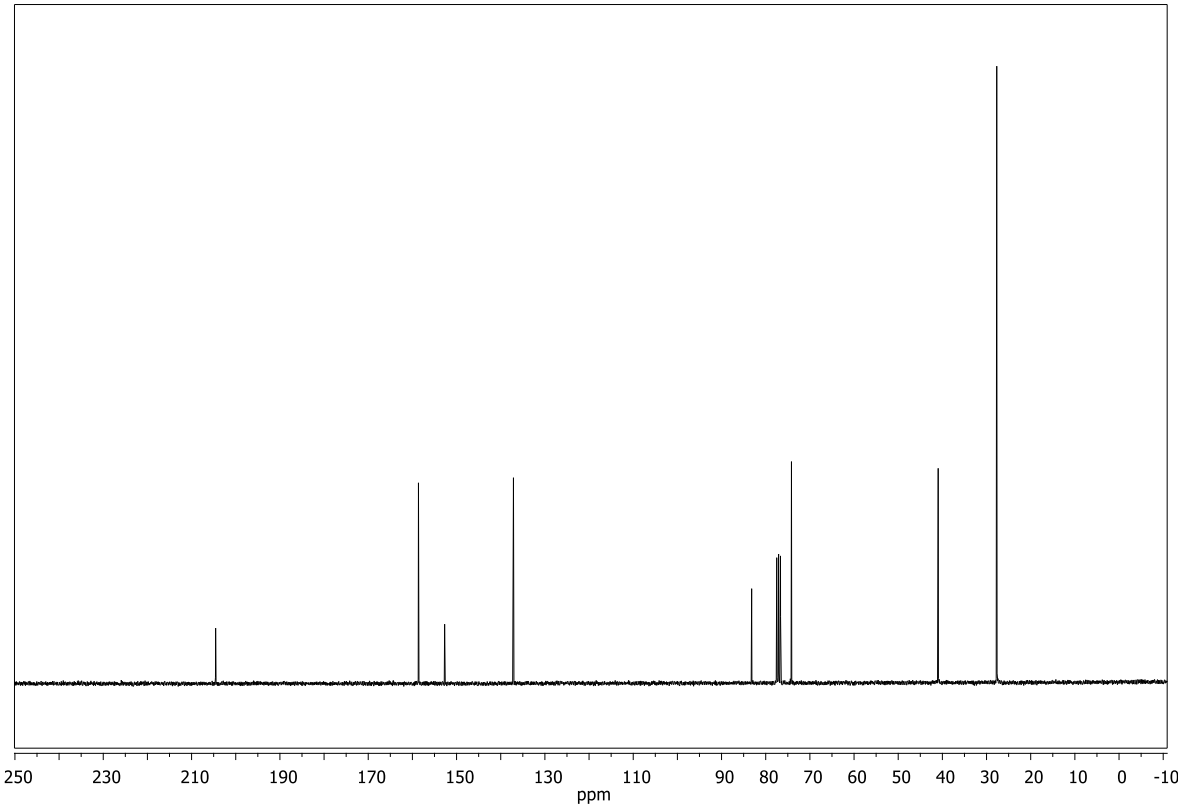
($CDCl_3$, 75 MHz)



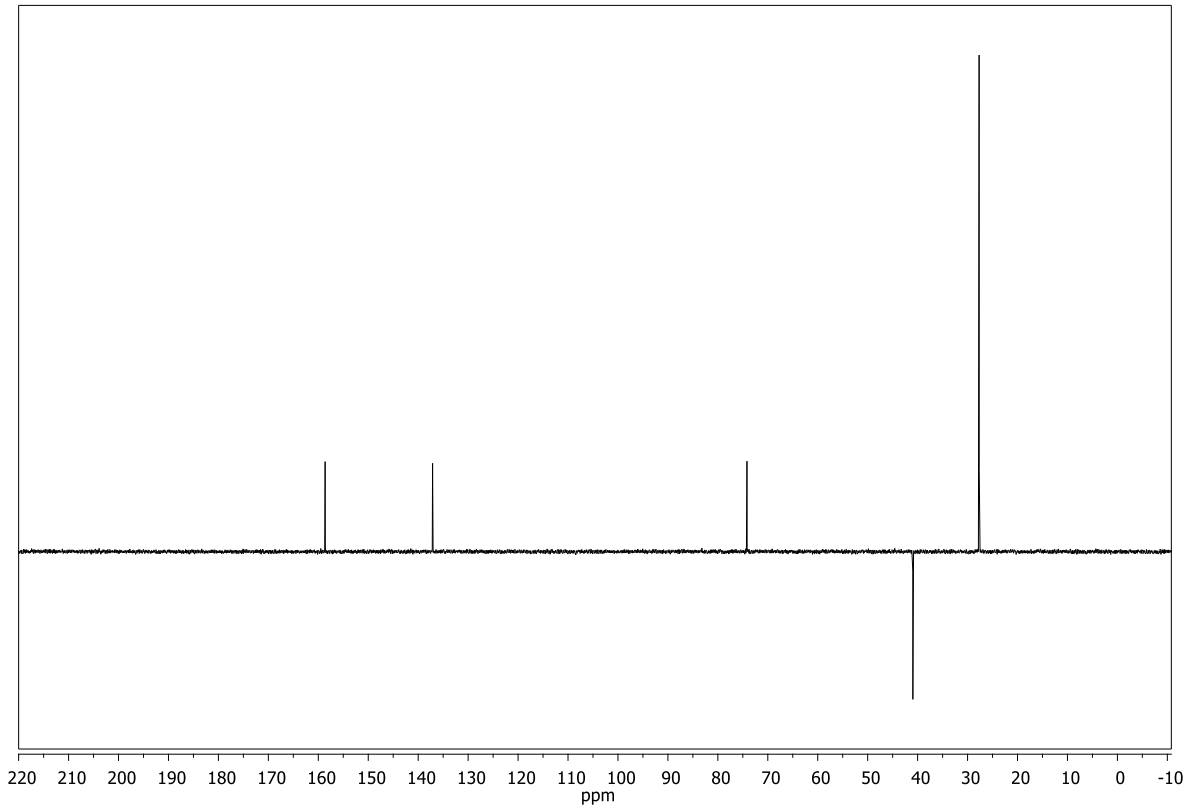
(±)-4-(*tert* -butoxycarbonyloxy)-2-cyclopentenone (69b) **($CDCl_3$, 300 MHz)**



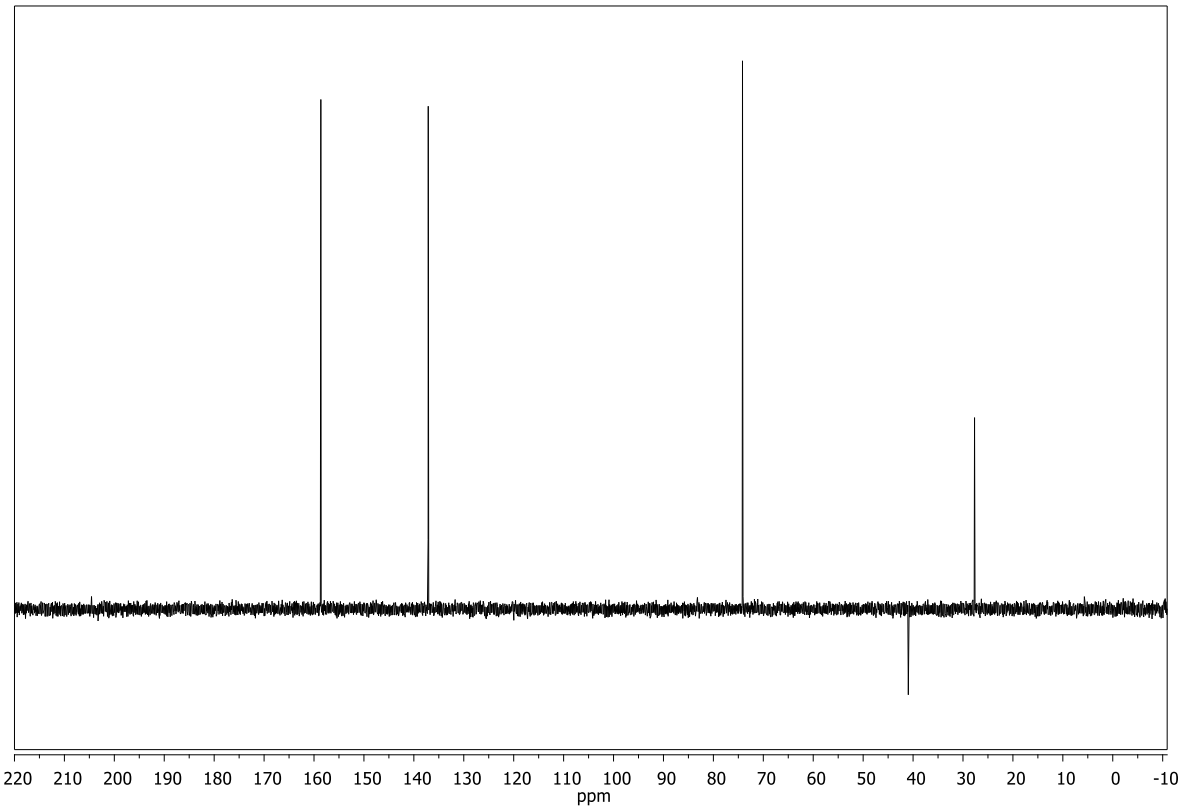
($CDCl_3$, 75 MHz)



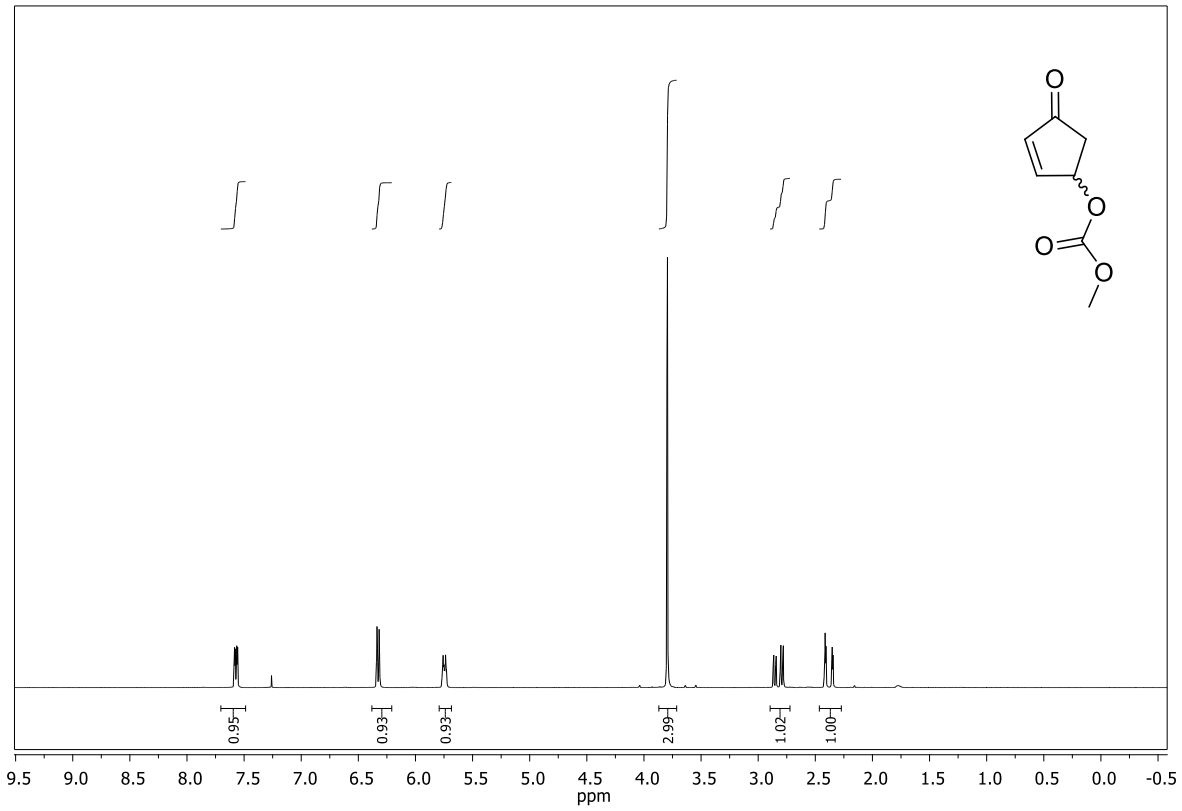
($CDCl_3$, 75 MHz)



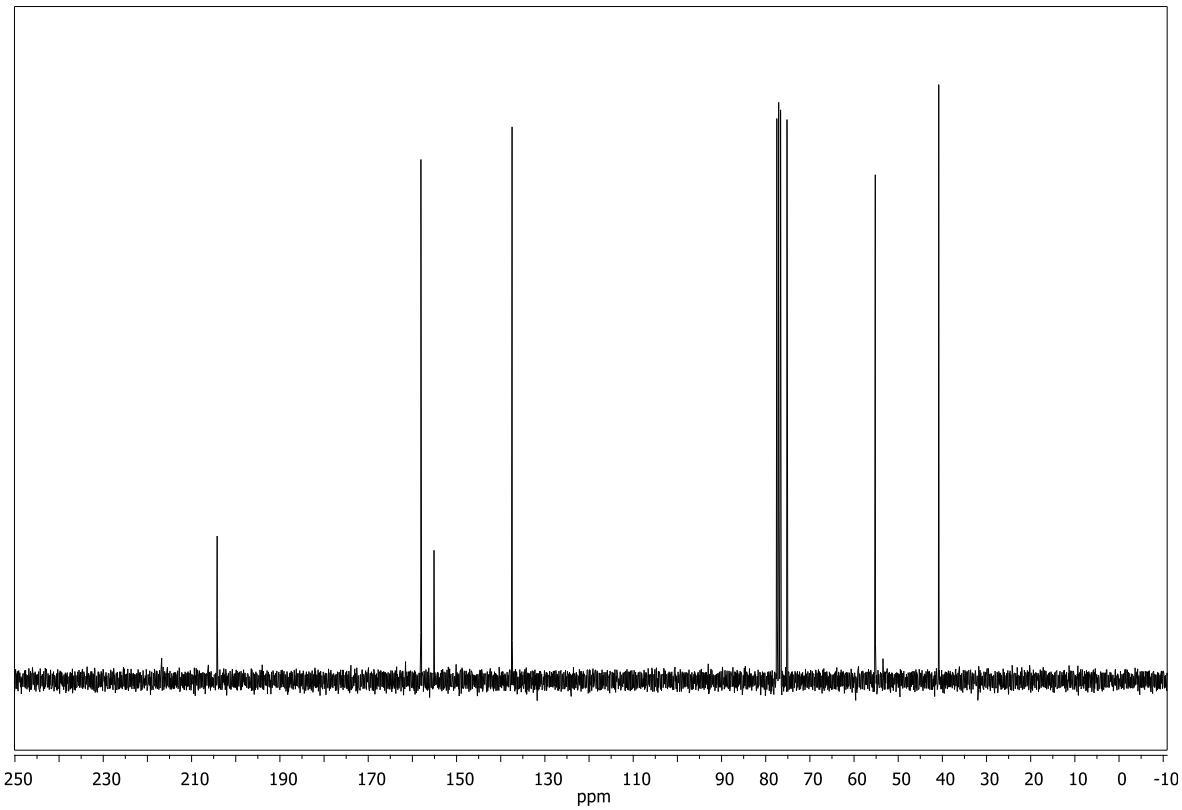
($CDCl_3$, 75 MHz)



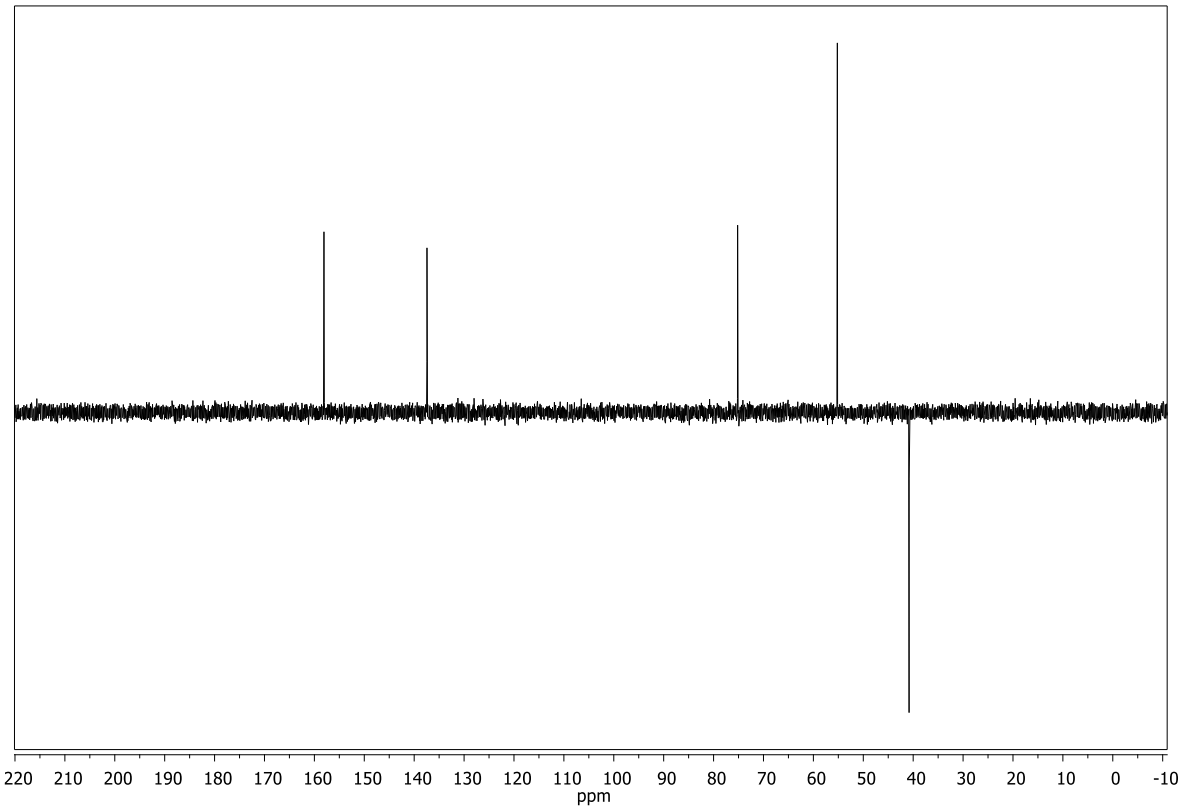
(±)-methyl(4-oxocyclopent-2-en-1-yl)carbonate (69c) **($CDCl_3$, 300 MHz)**



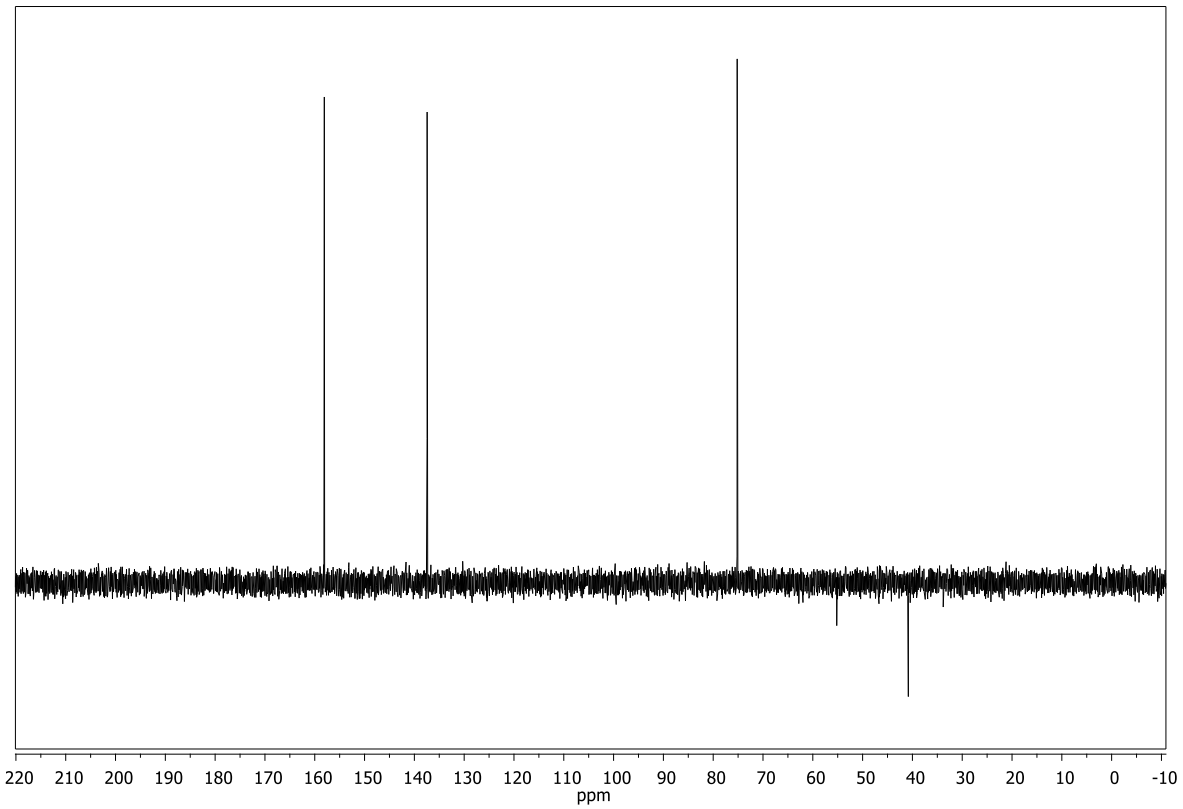
($CDCl_3$, 75 MHz)



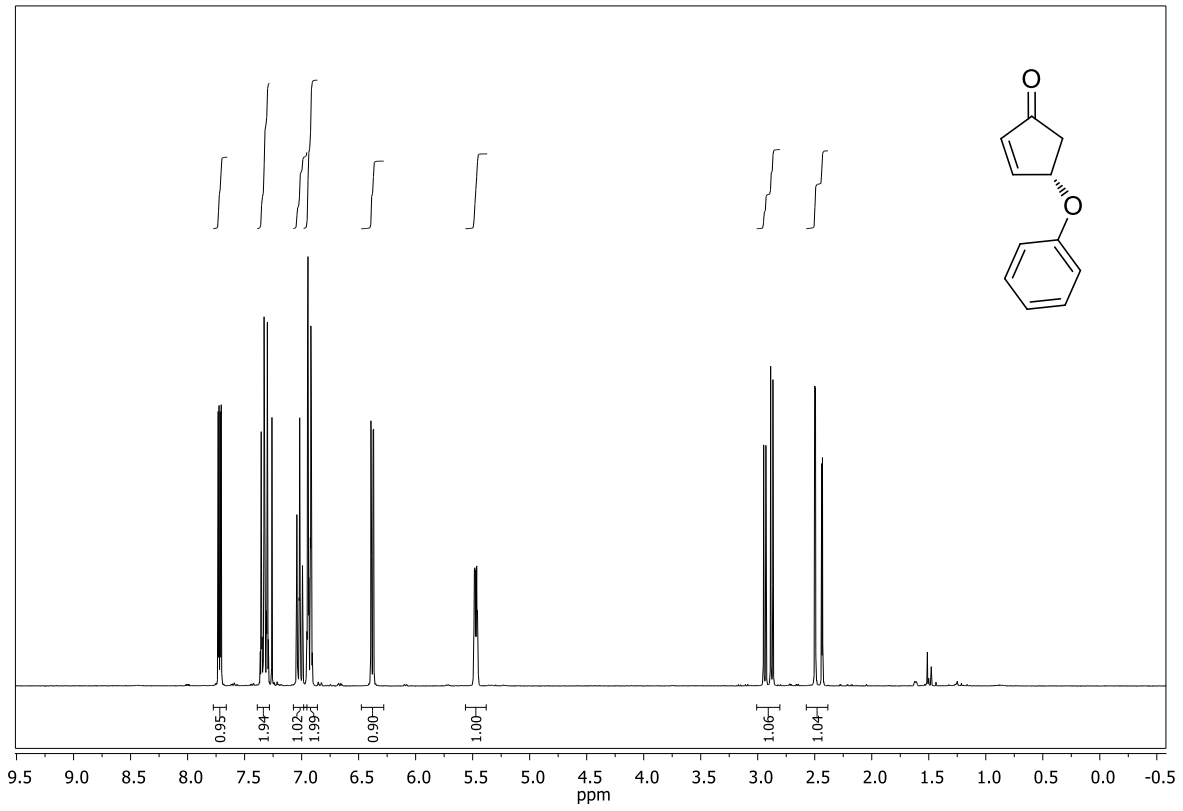
($CDCl_3$, 75 MHz)



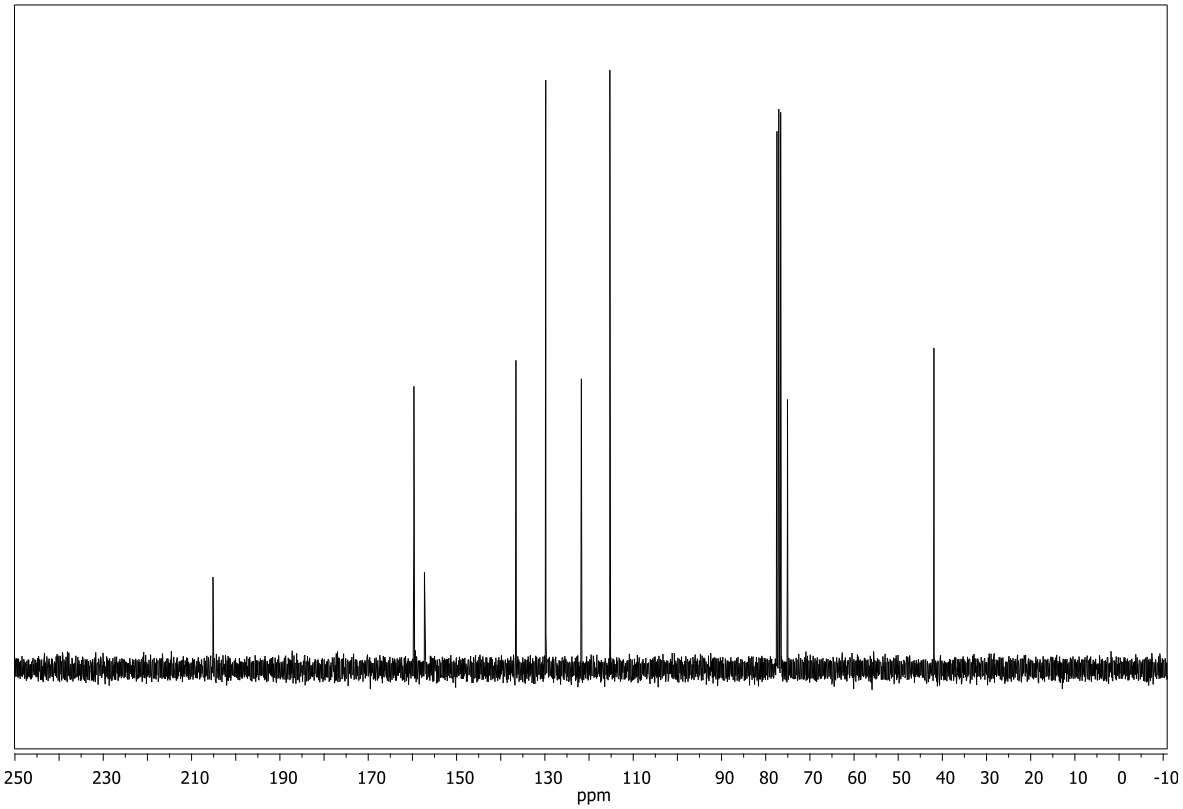
($CDCl_3$, 75 MHz)



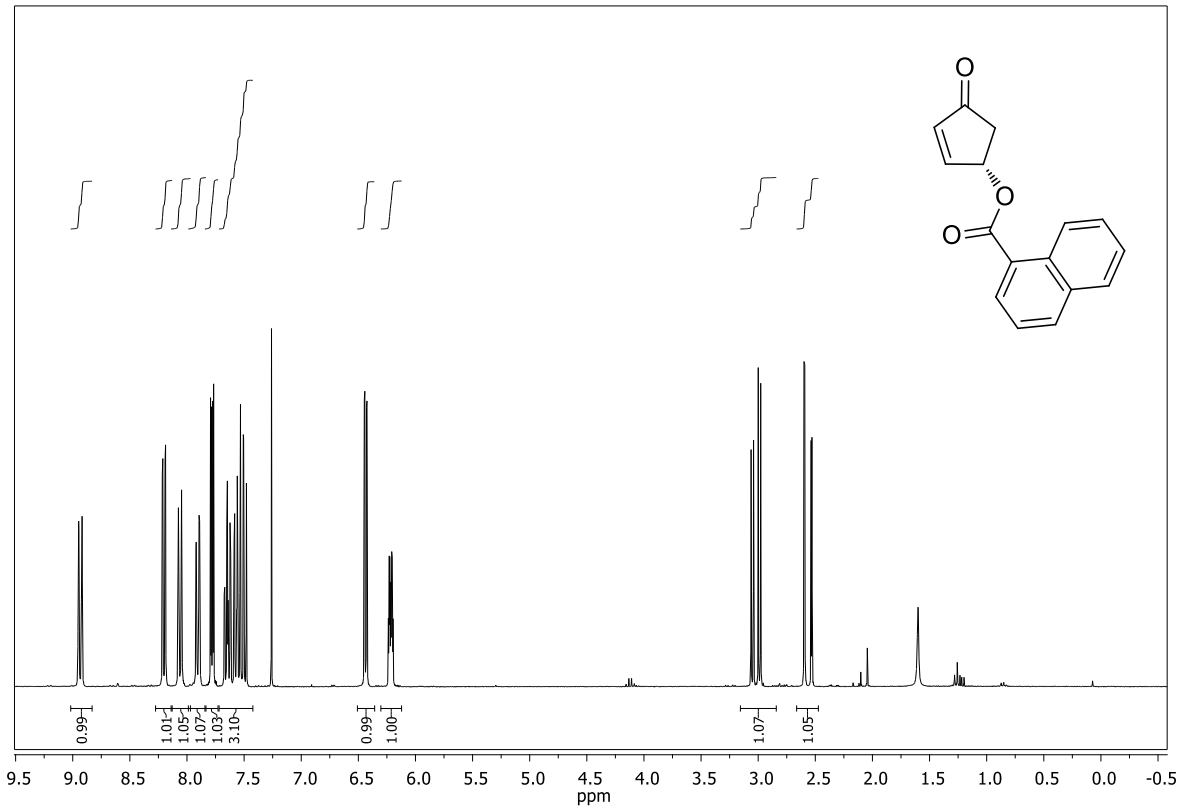
(*S*)-4-phenoxycyclopent-2-enone (71b) **($CDCl_3$, 300 MHz)**



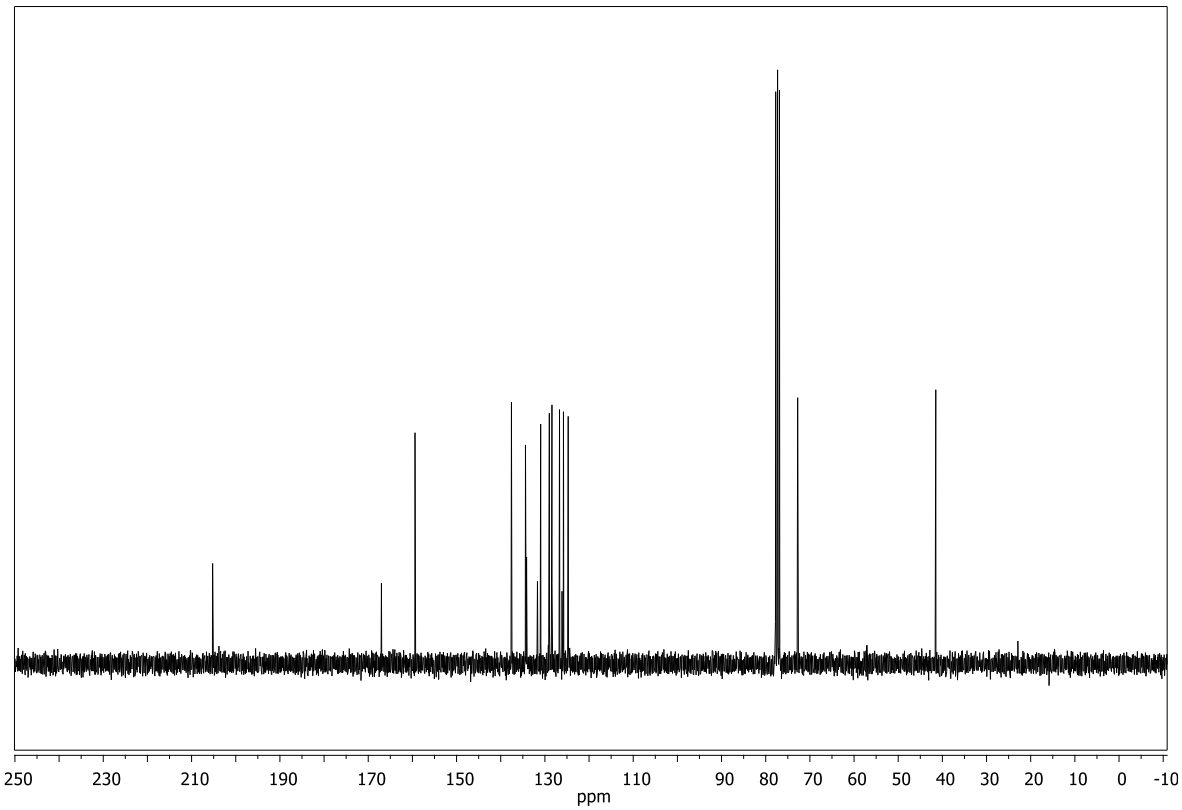
($CDCl_3$, 75 MHz)



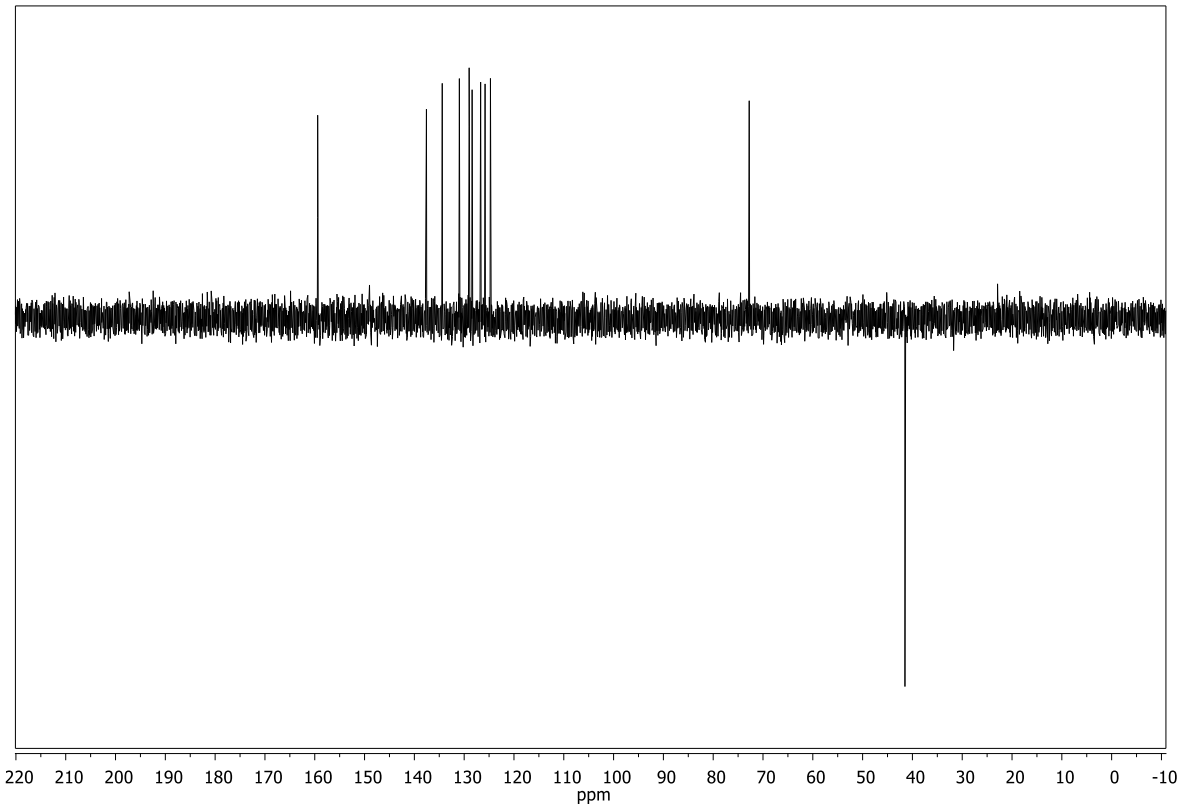
(*S*)-4-(1-naphthoyl)oxycyclopent-2-enone (71c) **($CDCl_3$, 300 MHz)**



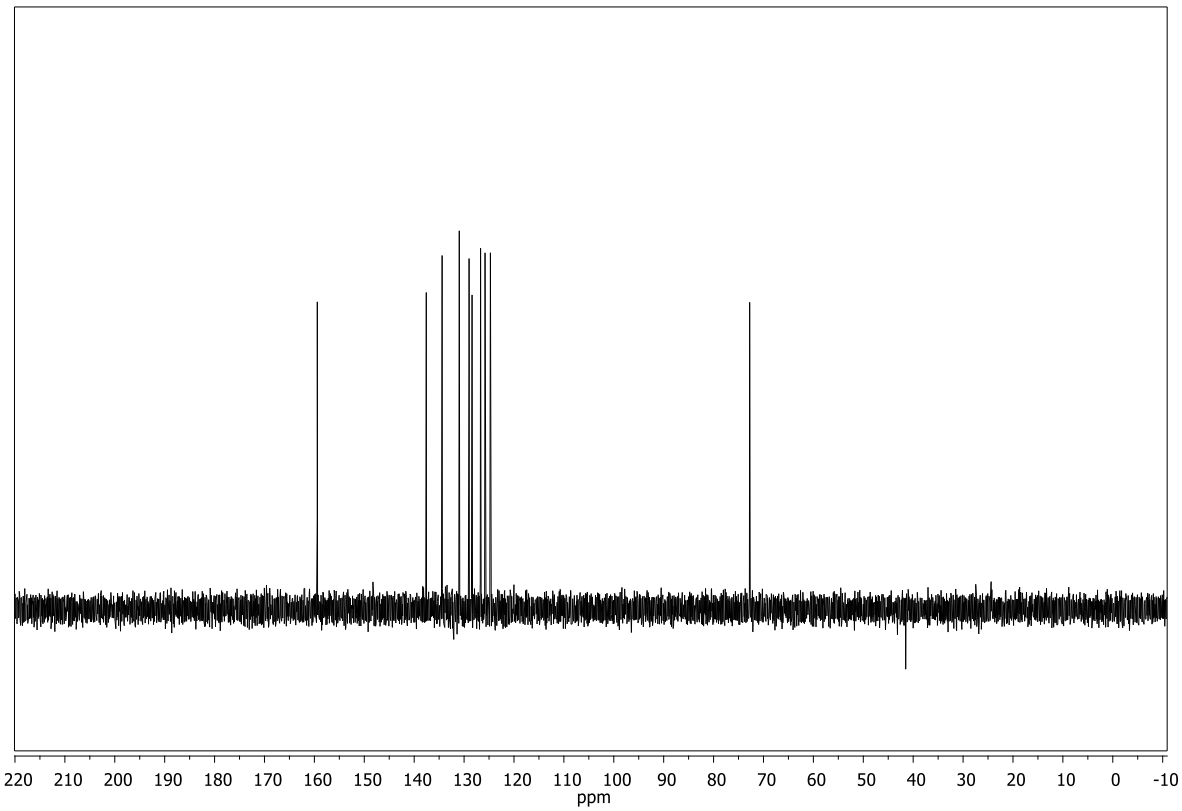
($CDCl_3$, 75 MHz)



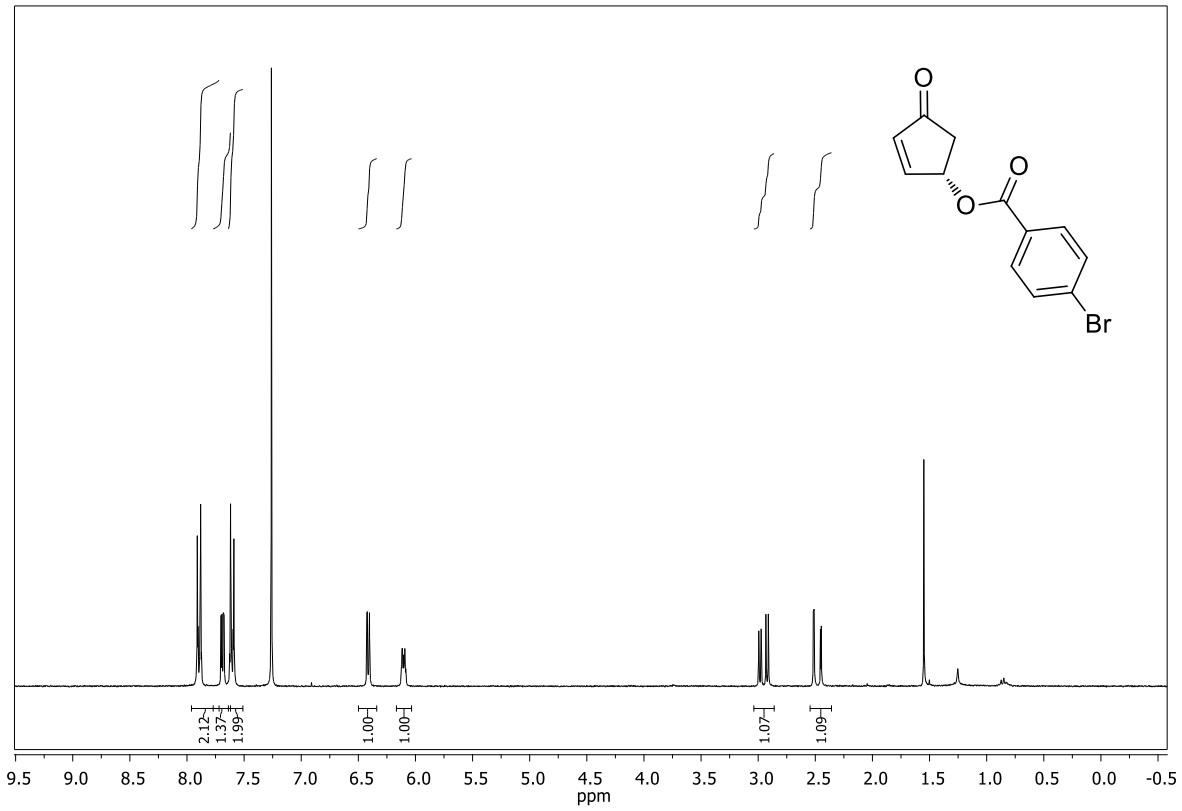
($CDCl_3$, 75 MHz)



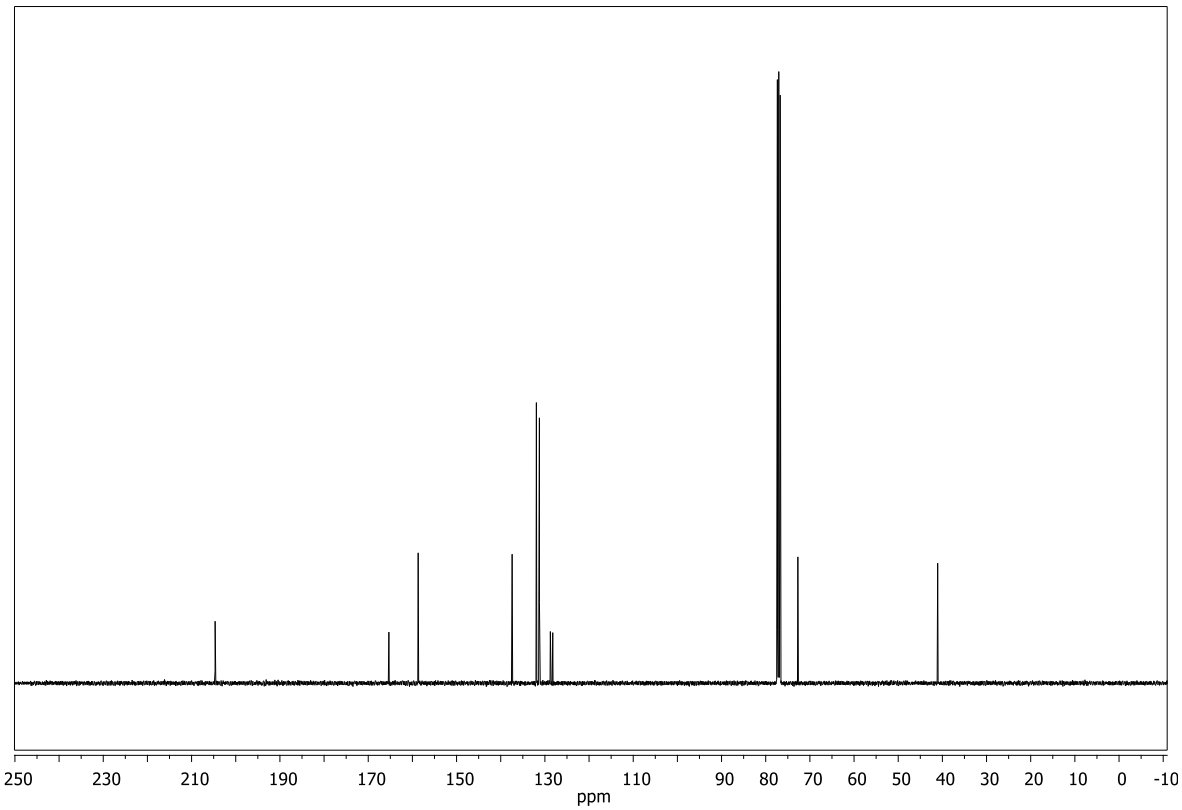
($CDCl_3$, 75 MHz)



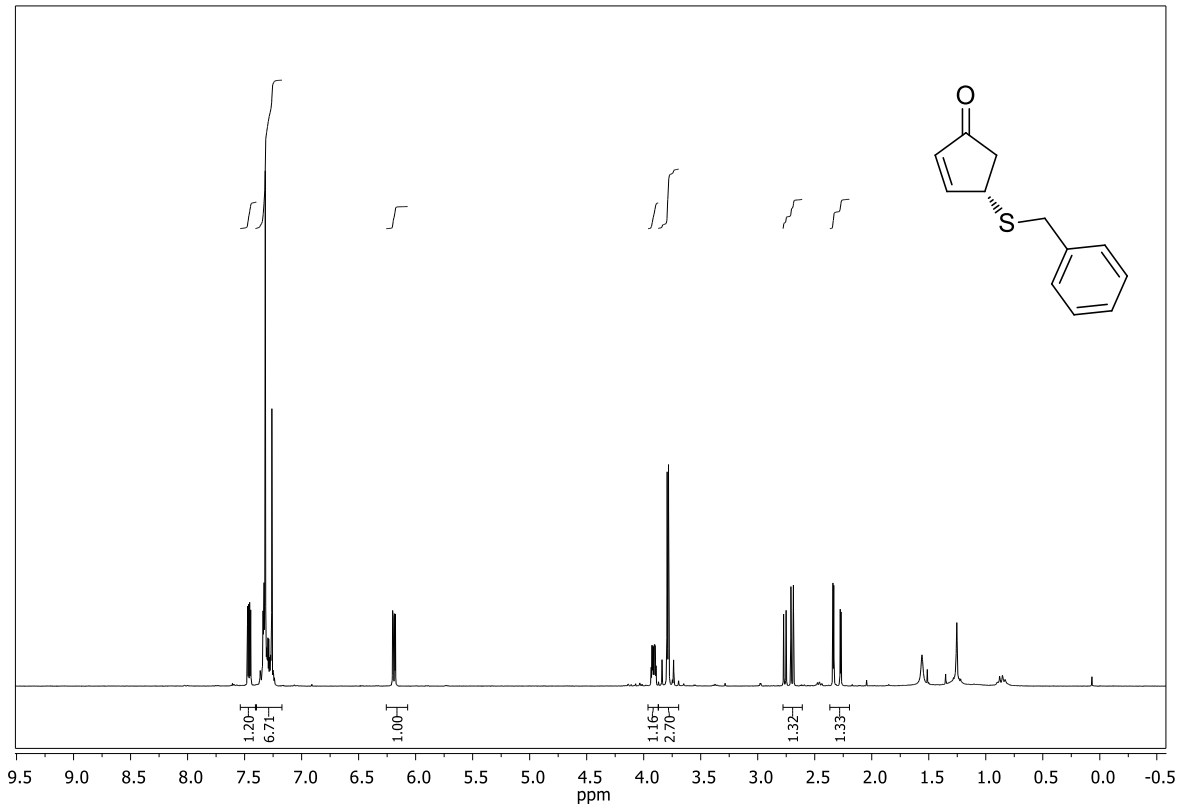
(*S*)-4-(4-bromobenzoyl)oxycyclopent-2-enone (71d) **($CDCl_3$, 300 MHz)**



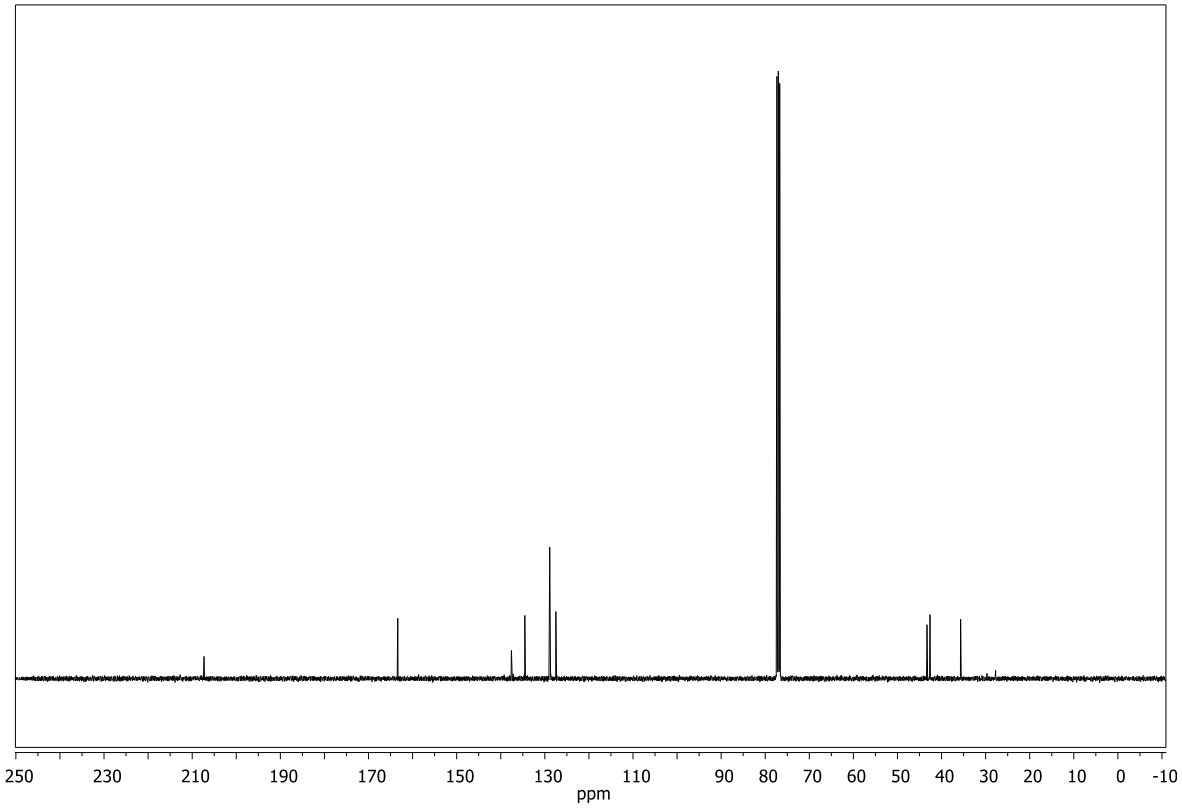
($CDCl_3$, 101 MHz)



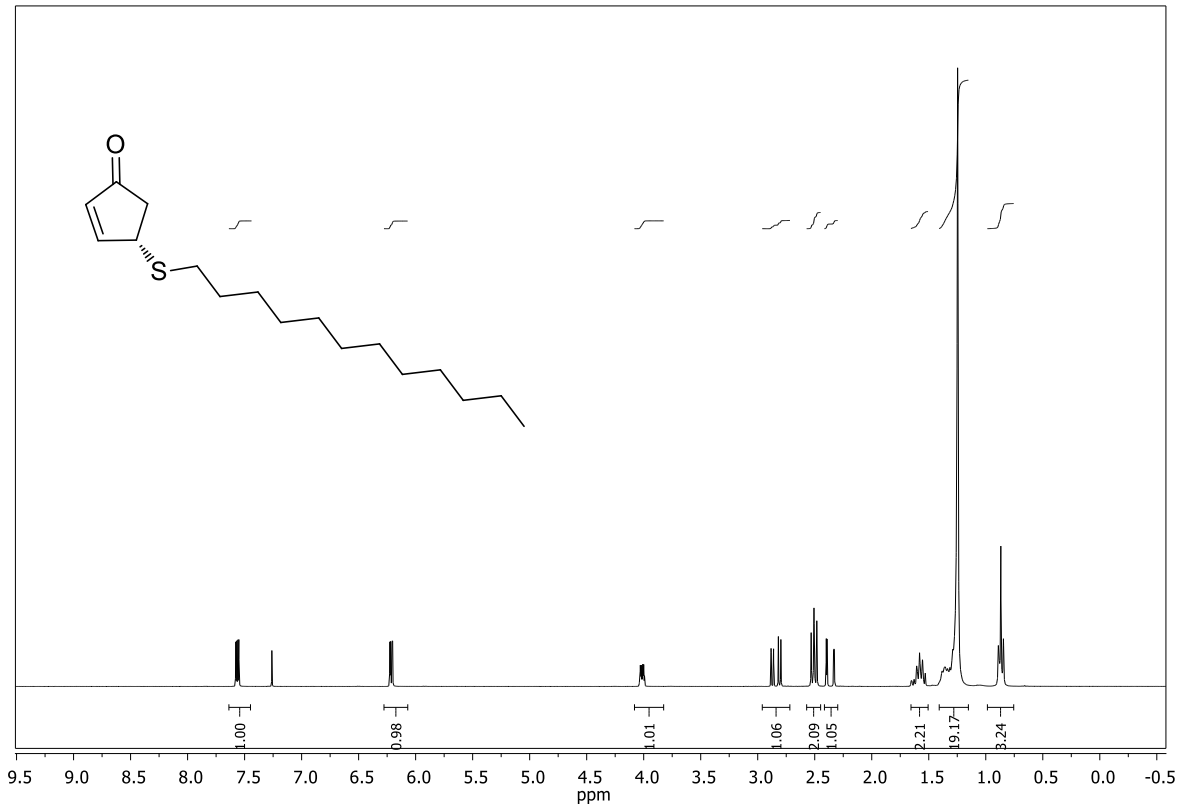
(*S*)-4-(benzylthio)cyclopent-2-enone (71e) **($CDCl_3$, 300 MHz)**



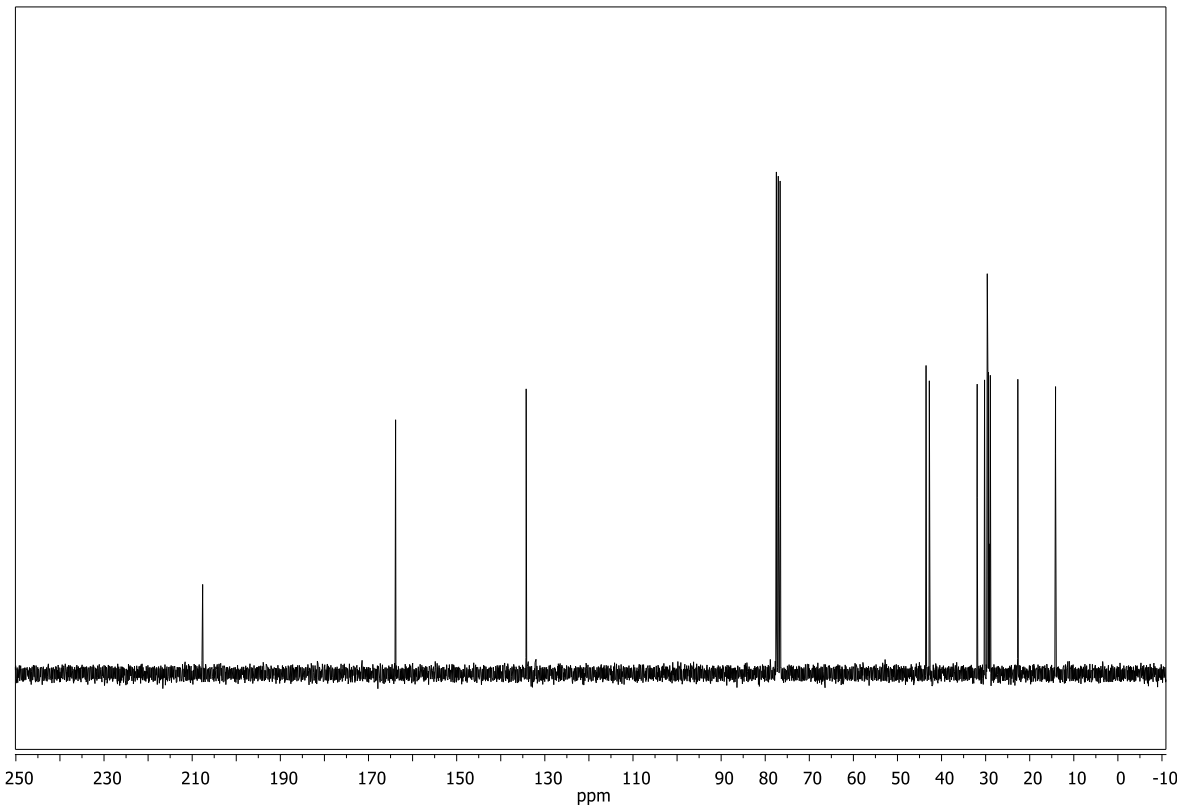
($CDCl_3$, 101 MHz)



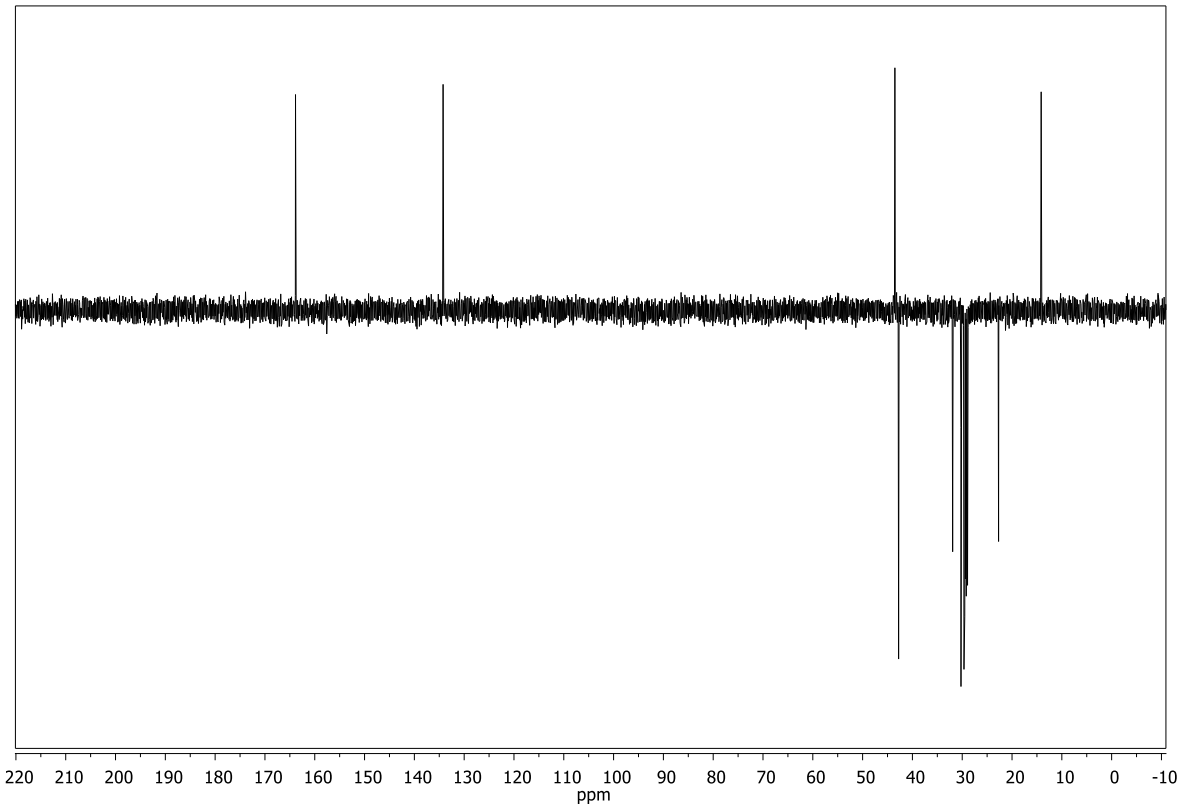
(*S*)-4-(dodecylthio)cyclopent-2-enone (71f) **($CDCl_3$, 300 MHz)**



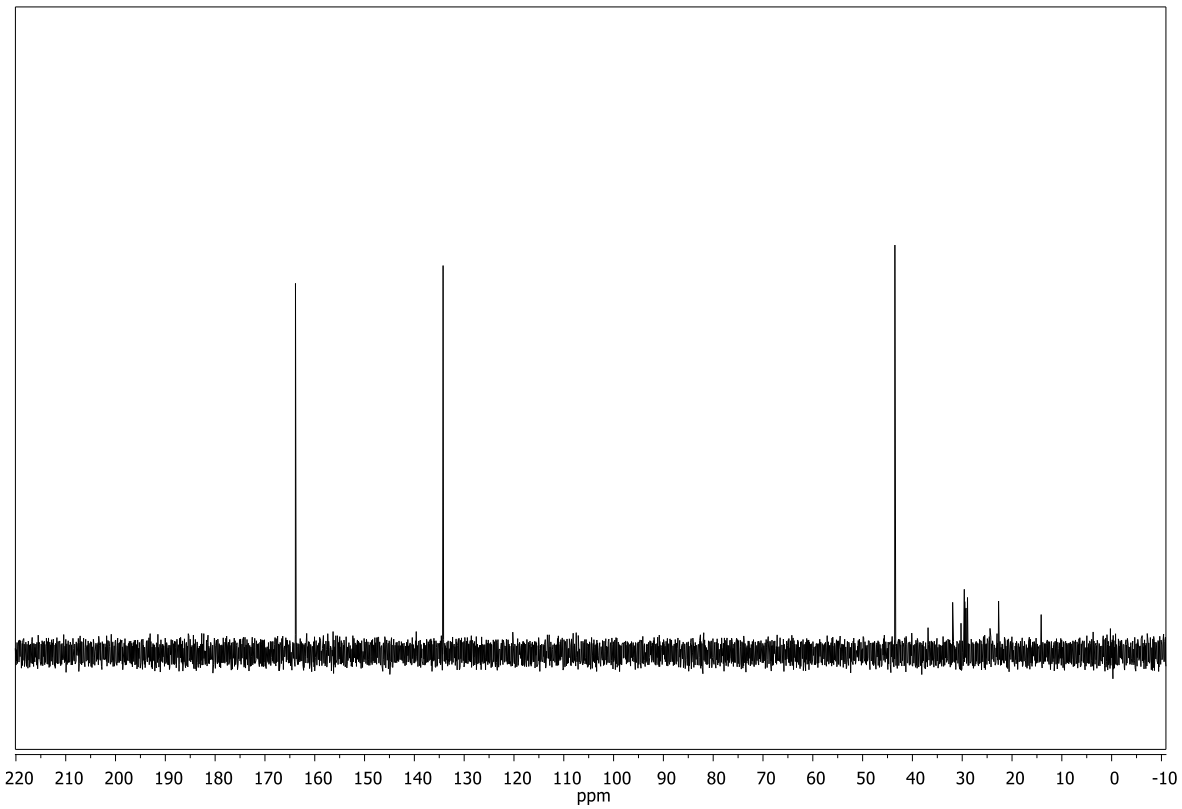
($CDCl_3$, 75 MHz)



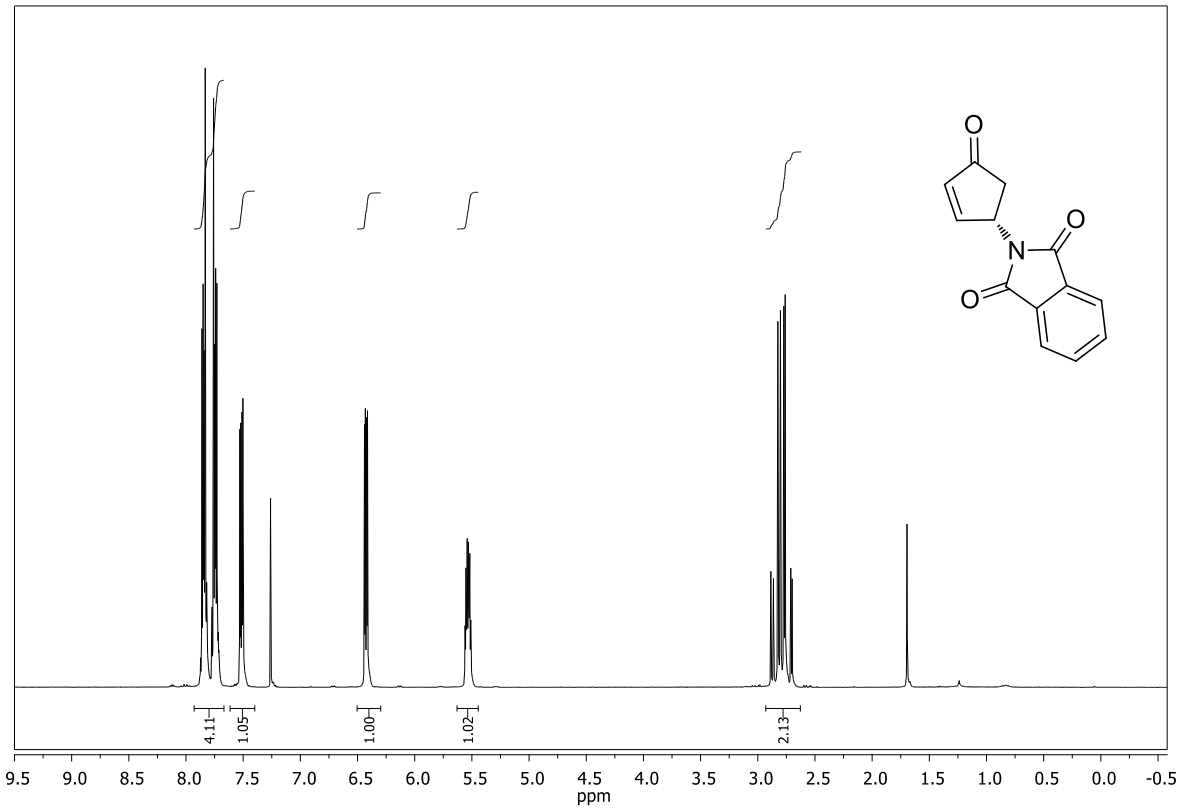
($CDCl_3$, 75 MHz)



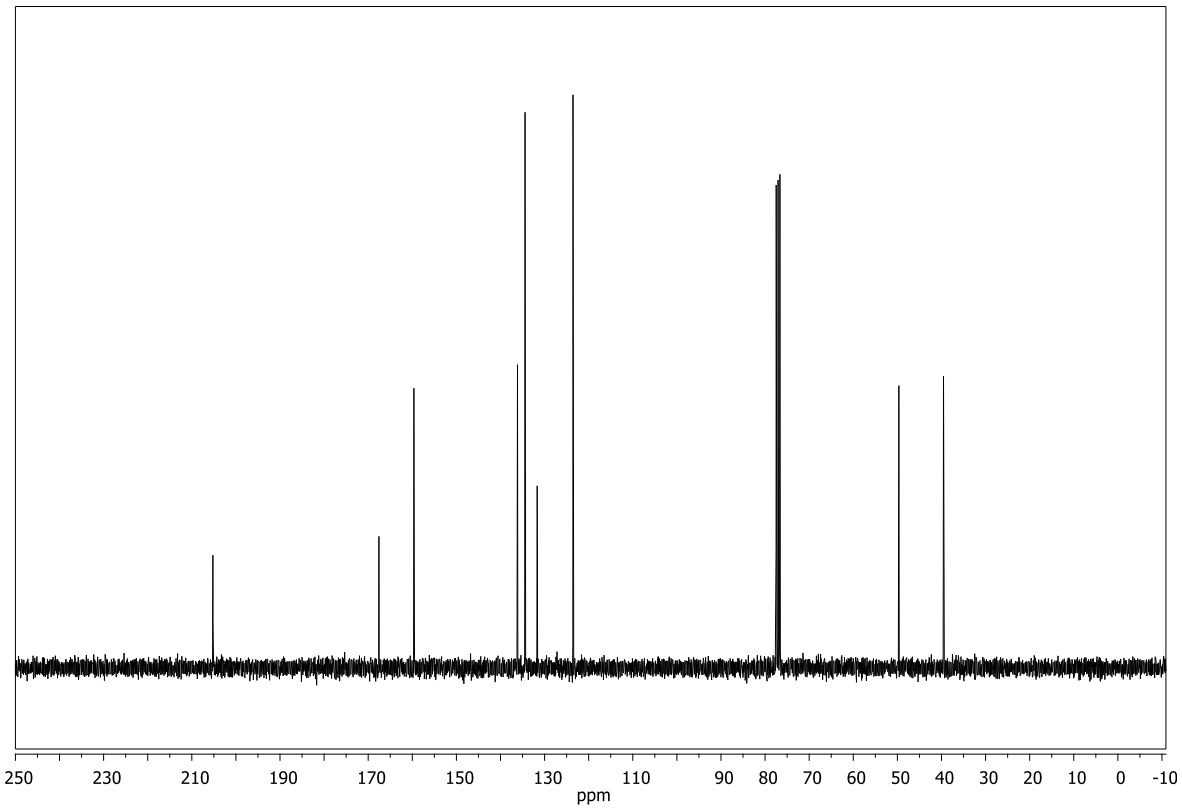
($CDCl_3$, 75 MHz)



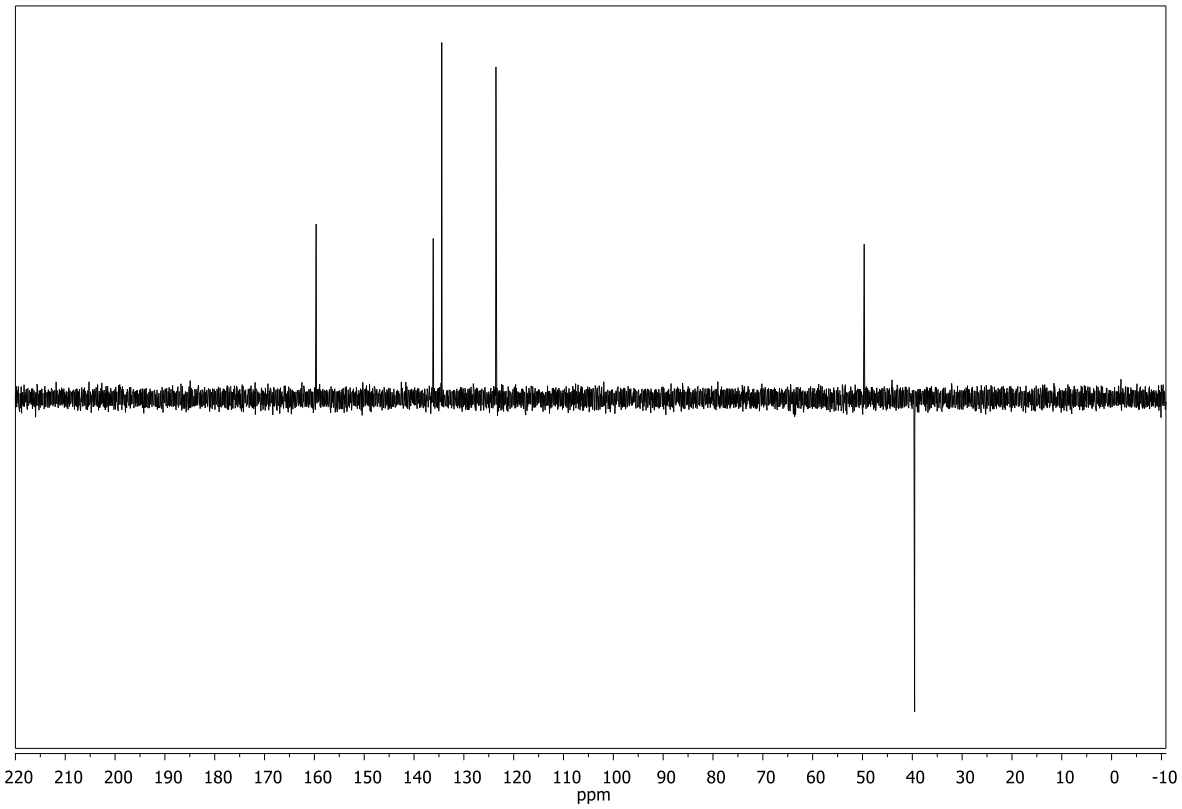
(*S*)-4-phthalimidylcyclopent-2-enone (71g) **($CDCl_3$, 300 MHz)**



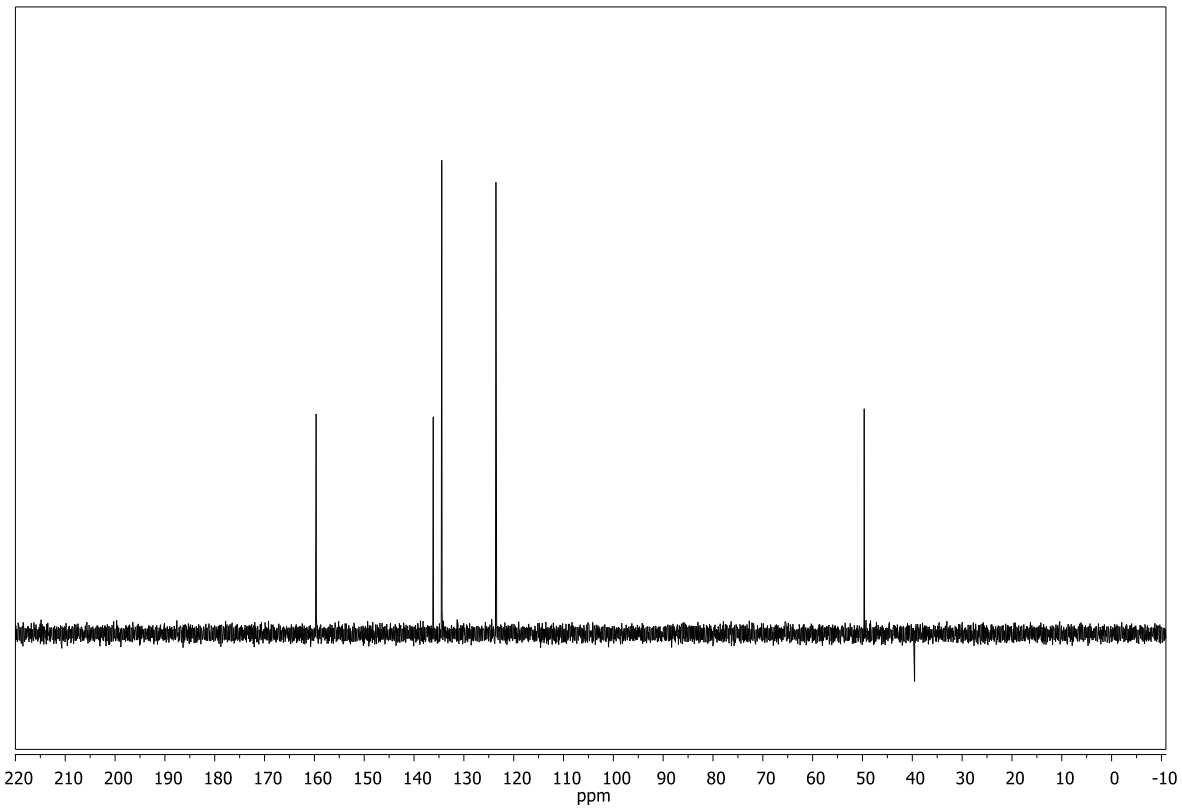
($CDCl_3$, 75 MHz)



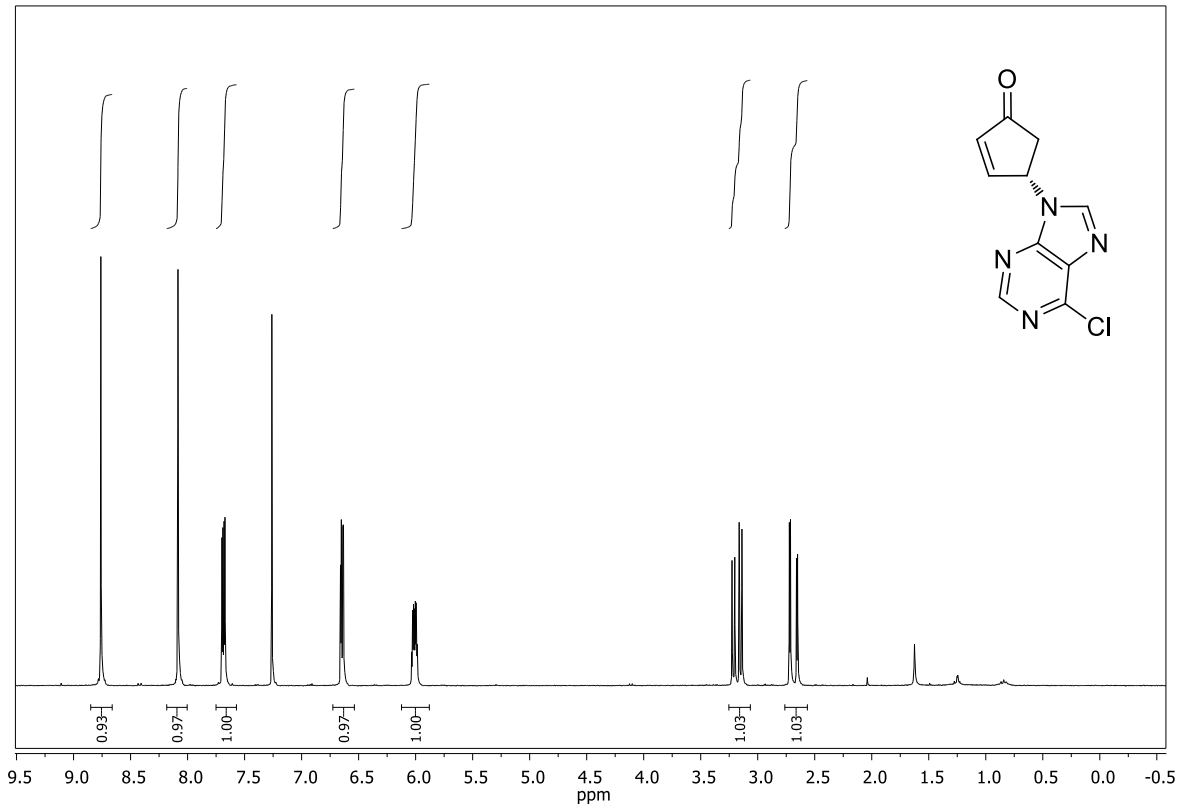
($CDCl_3$, 75 MHz)



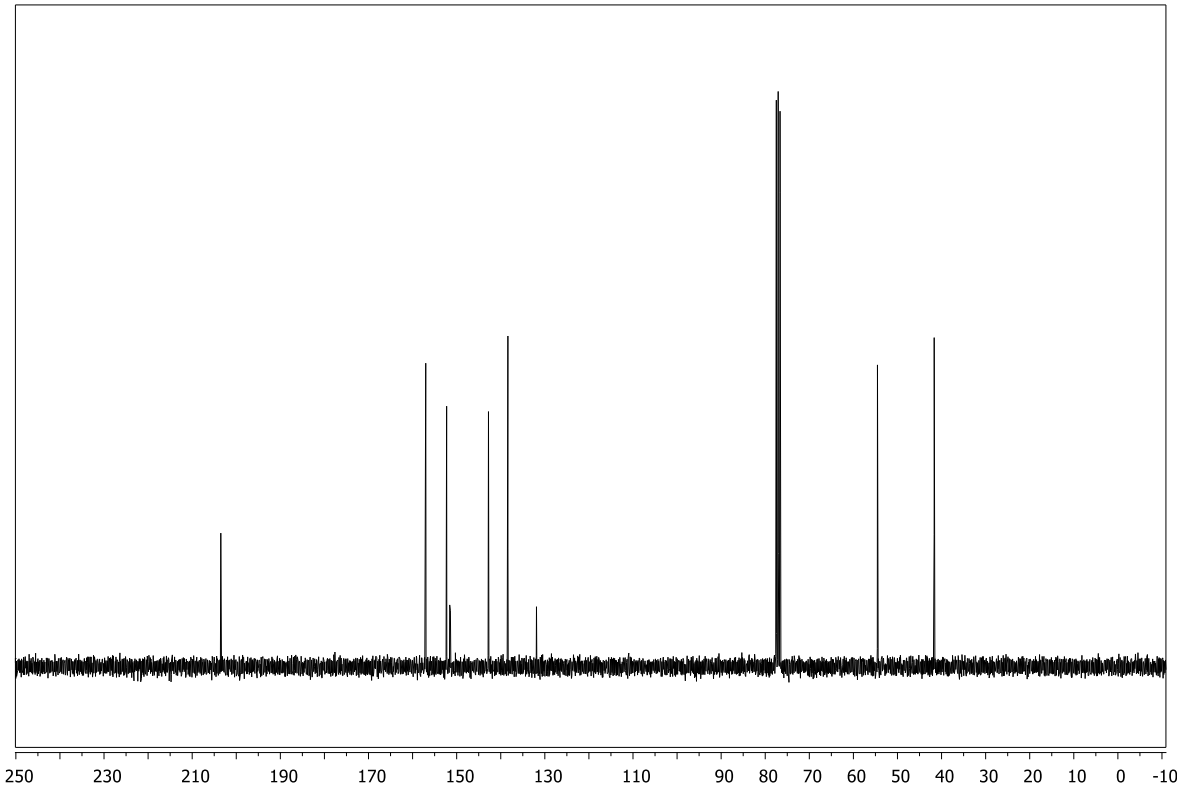
($CDCl_3$, 75 MHz)



(*S*)-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone (71h) **($CDCl_3$, 300 MHz)**

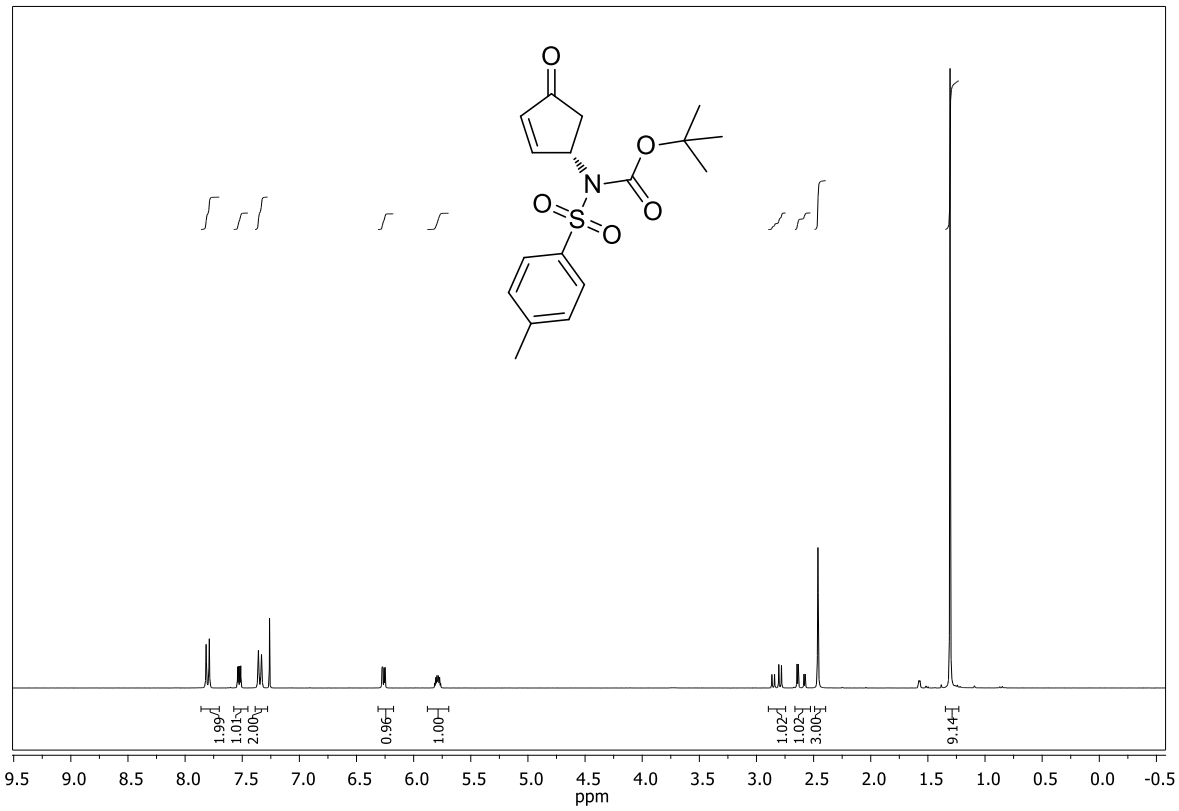


($CDCl_3$, 75 MHz)

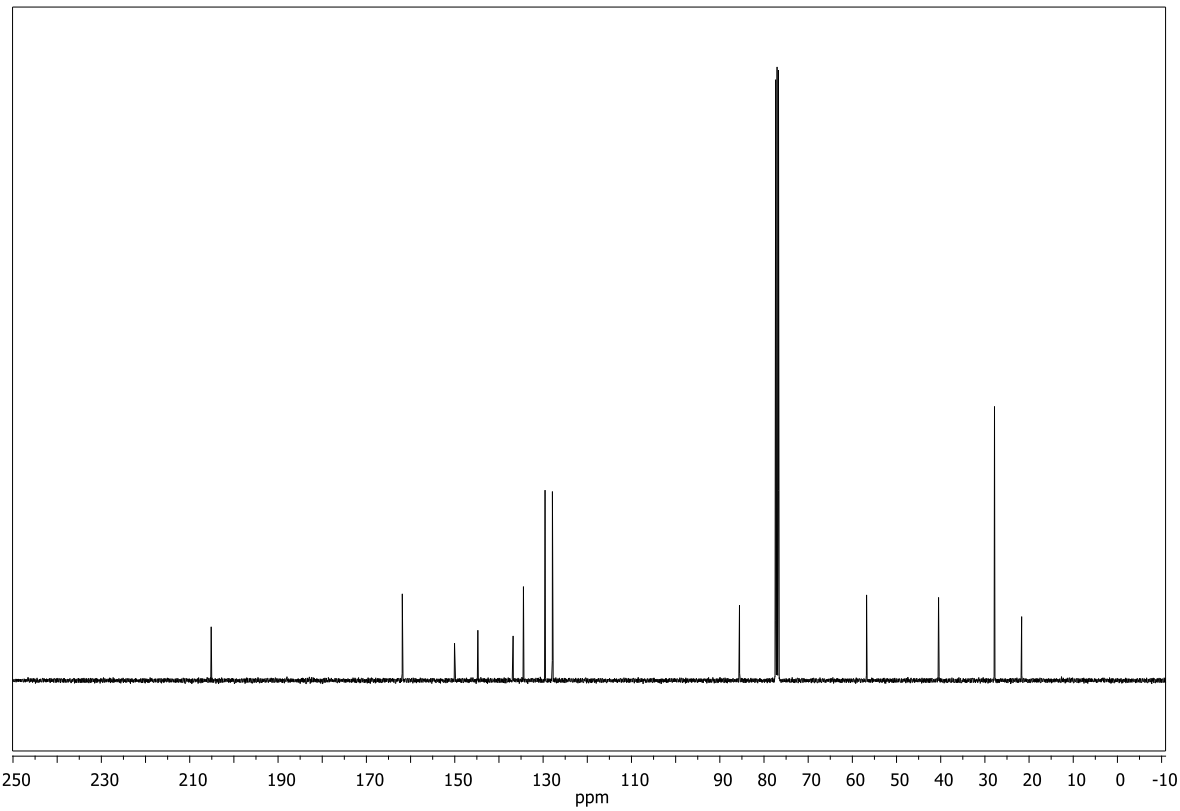


(*S*)-4-(*N*-*tert*-butoxycarbonyl-N-p-toluenesulfonylamino)cyclopent-2-enone (71j)

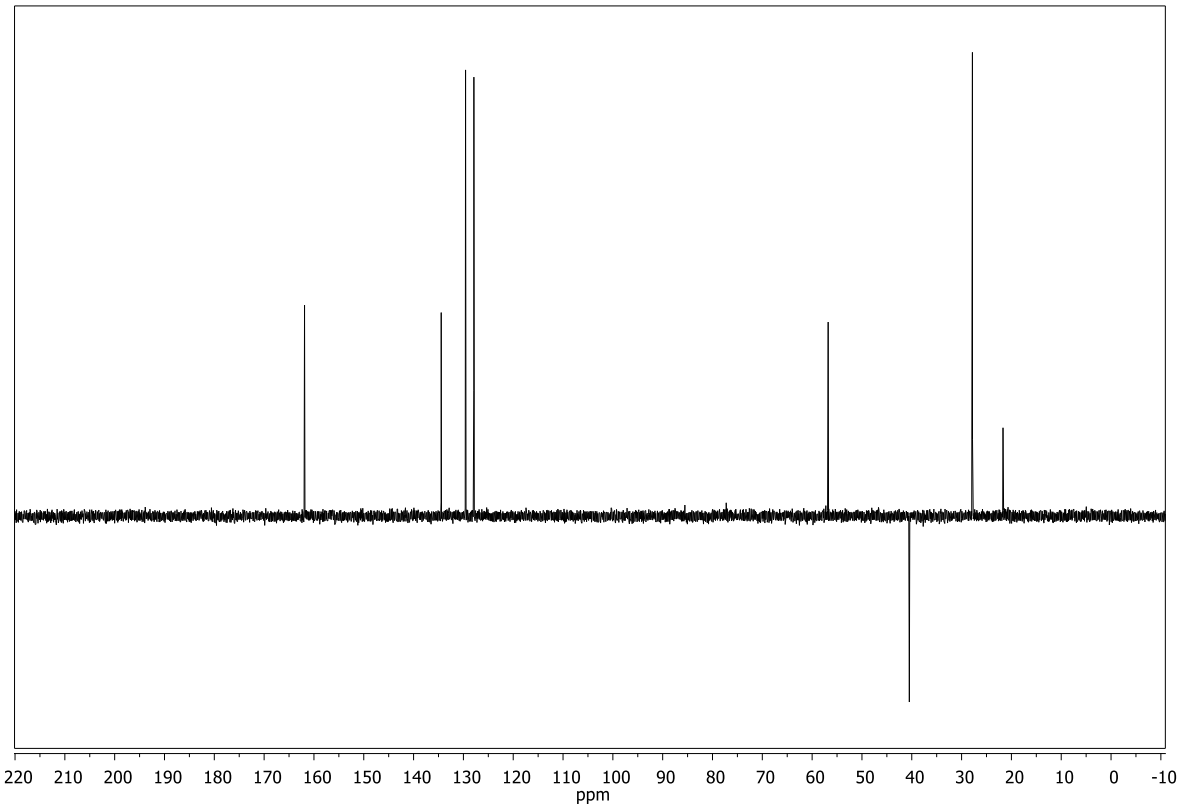
($CDCl_3$, 300 MHz)



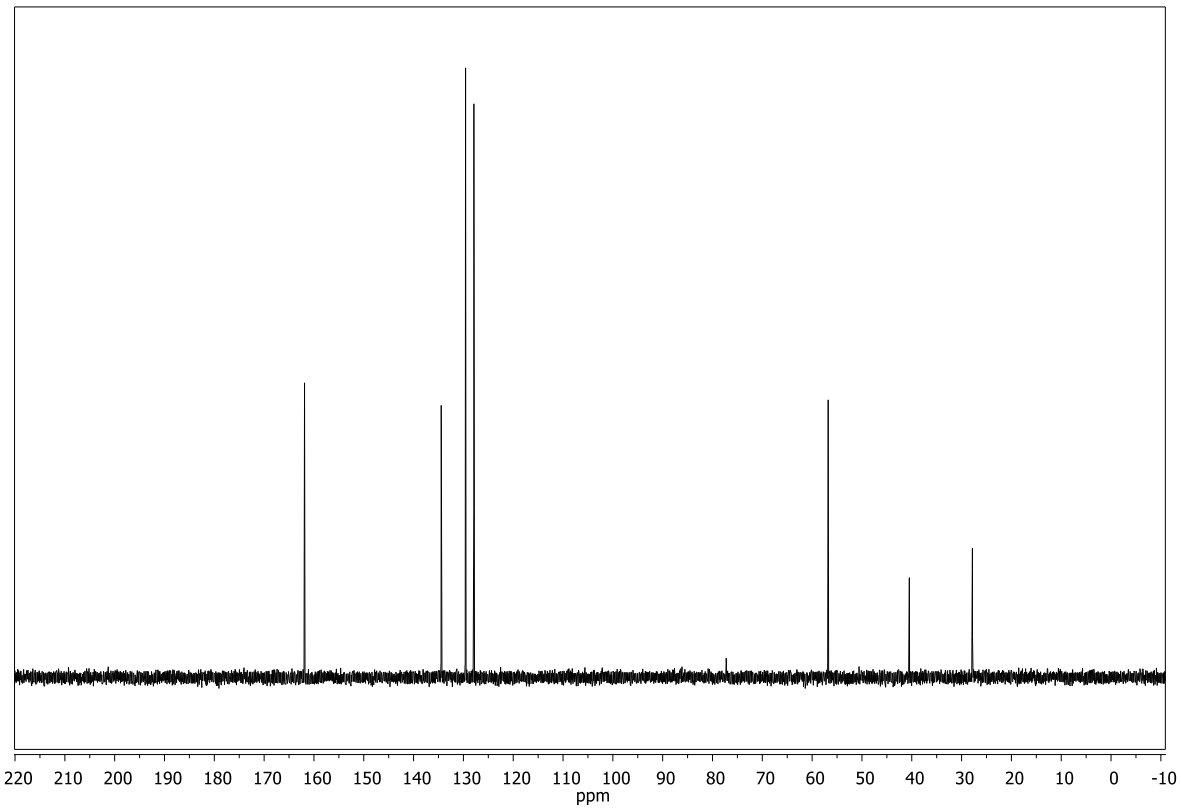
($CDCl_3$, 101 MHz)



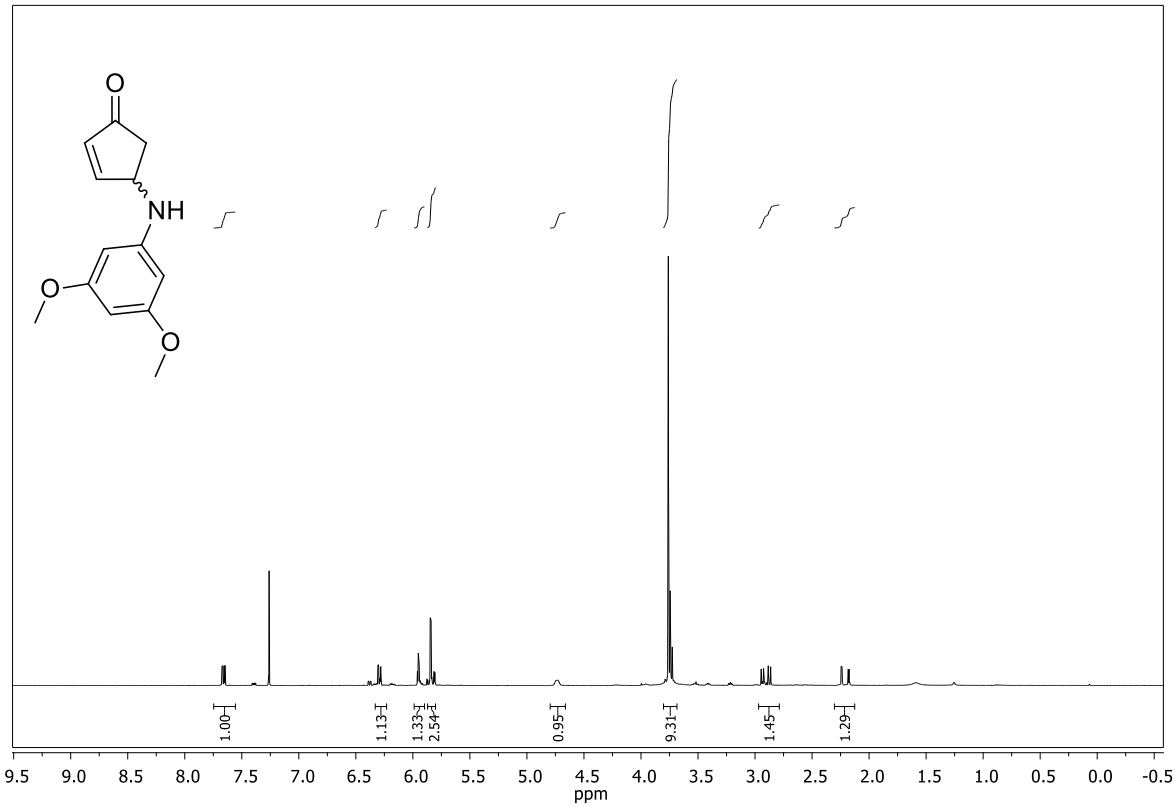
($CDCl_3$, 101 MHz)



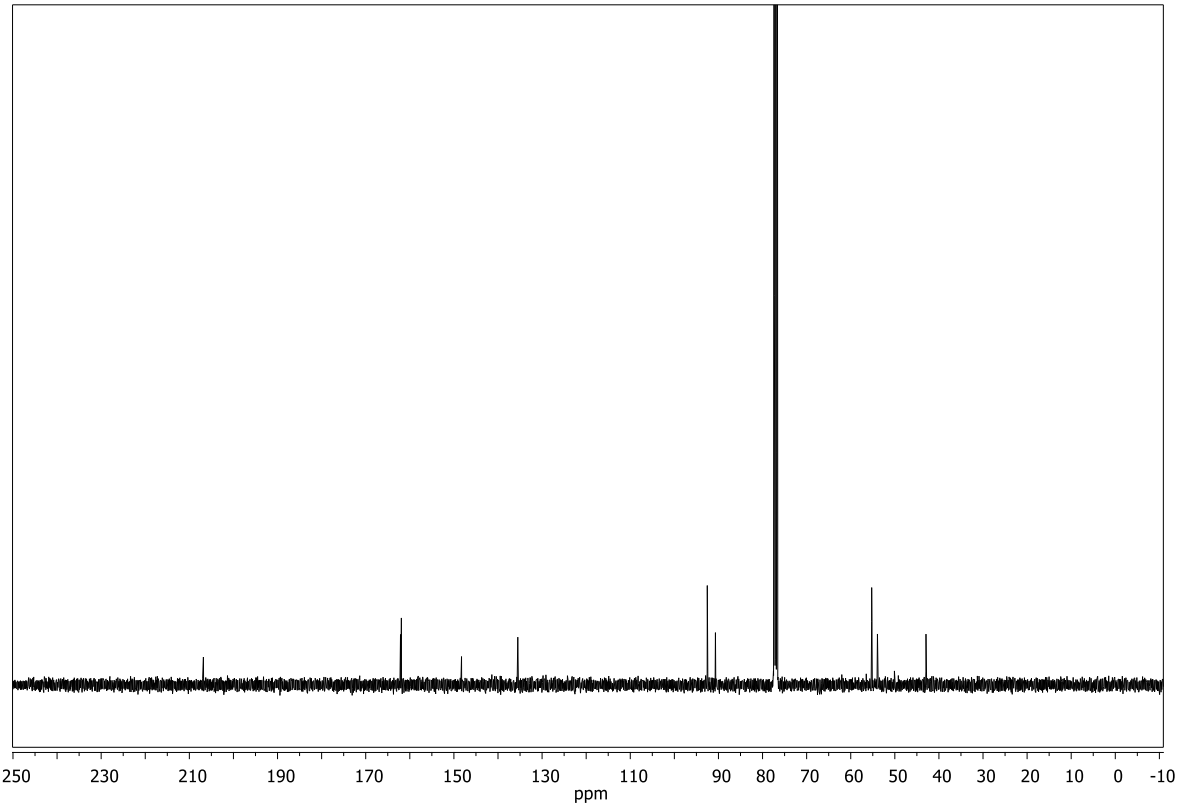
($CDCl_3$, 101 MHz)



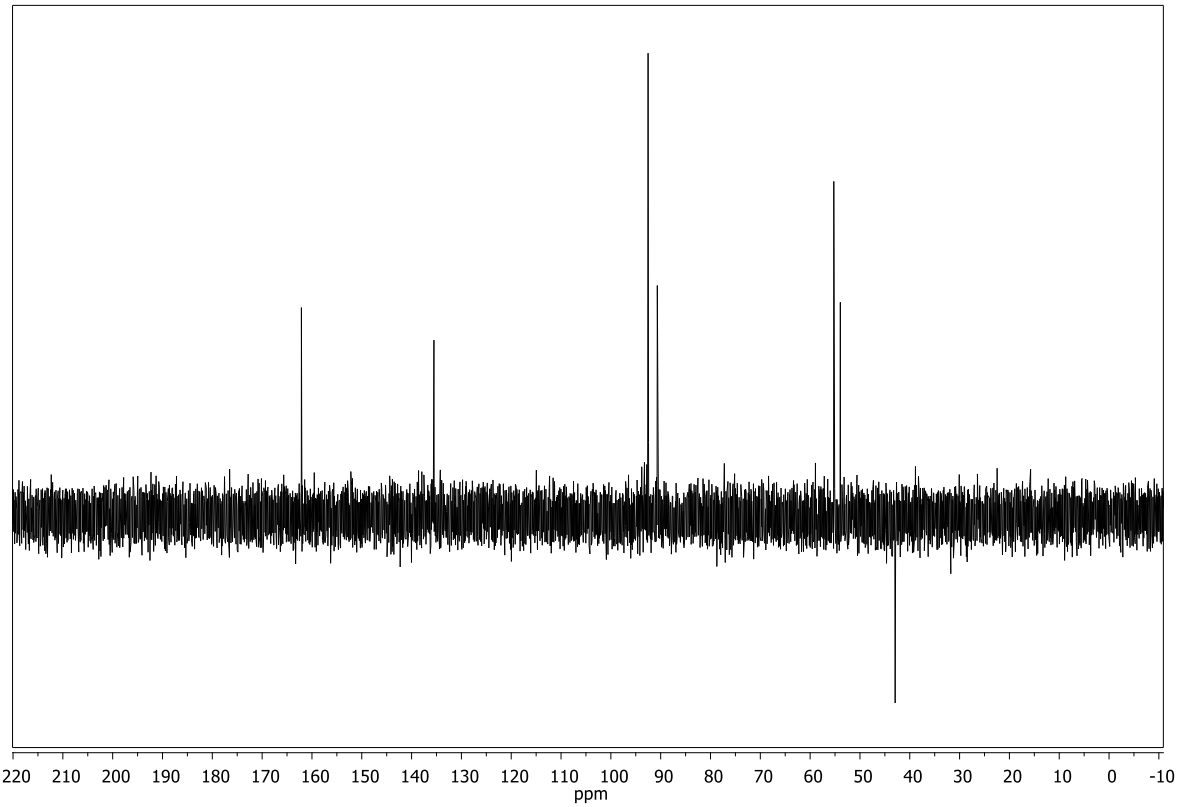
(±)-4-(3,5-dimethoxyphenylamino)cyclopent-2-enone) (71k) **($CDCl_3$, 300 MHz)**



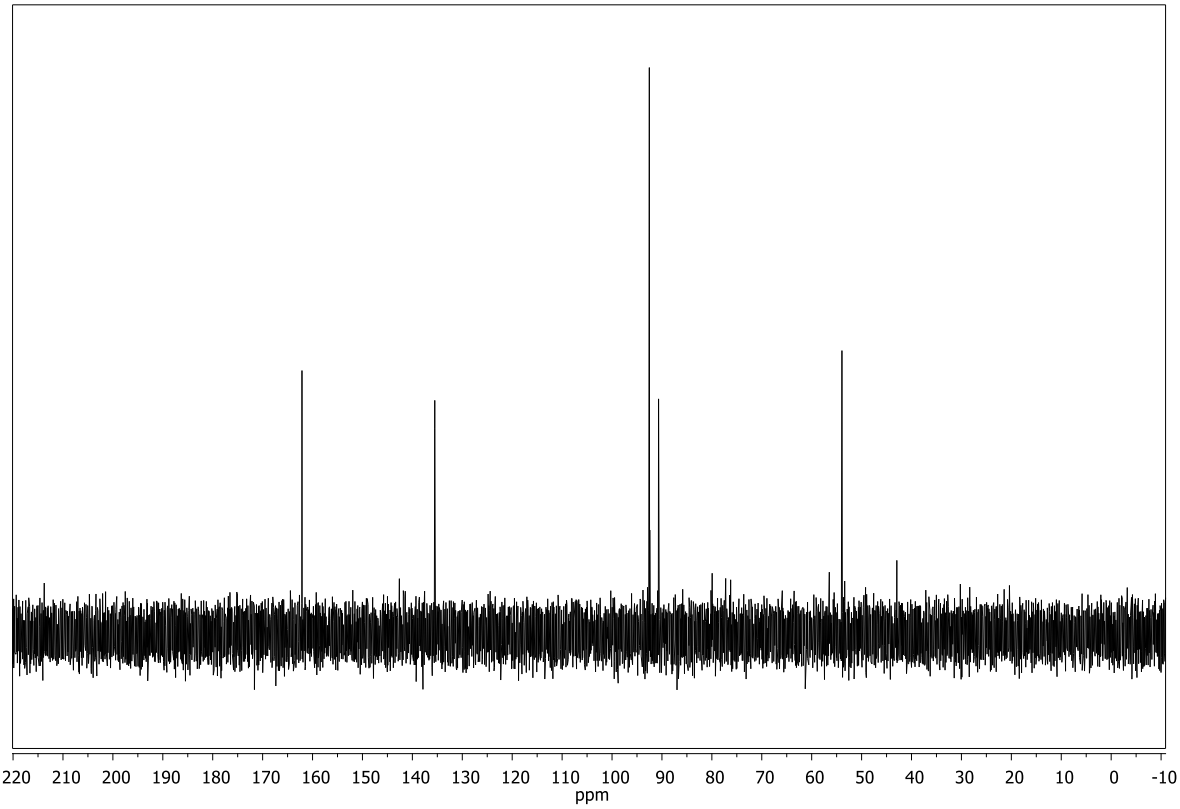
($CDCl_3$, 101 MHz)



($CDCl_3$, 101 MHz)

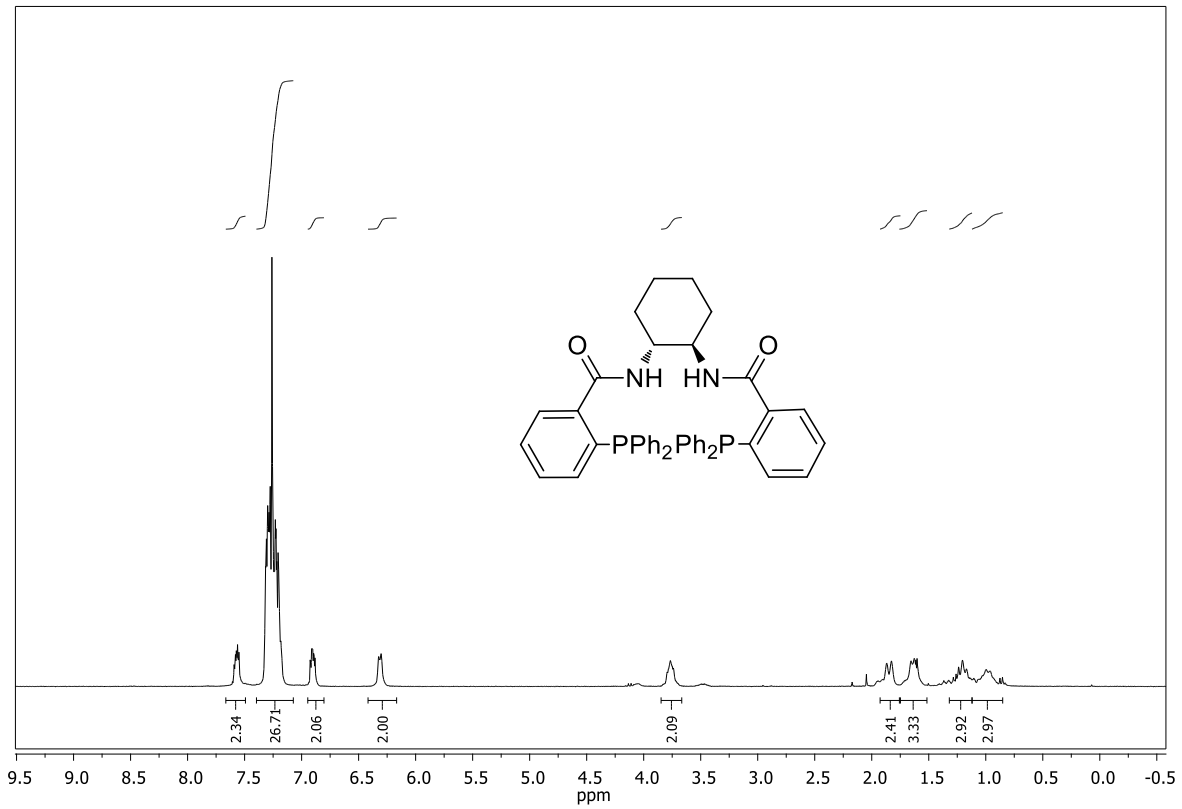


($CDCl_3$, 101 MHz)

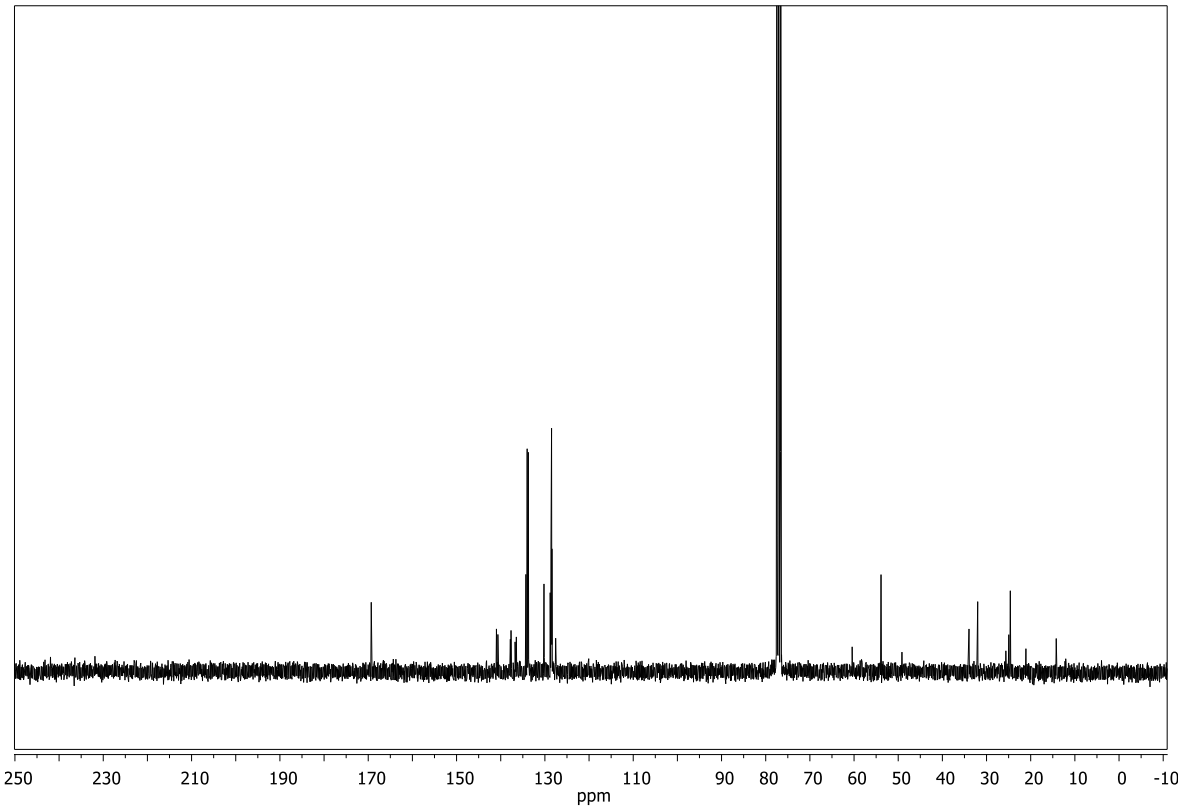


***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-(diphenylphosphino)benzamide) (73)**

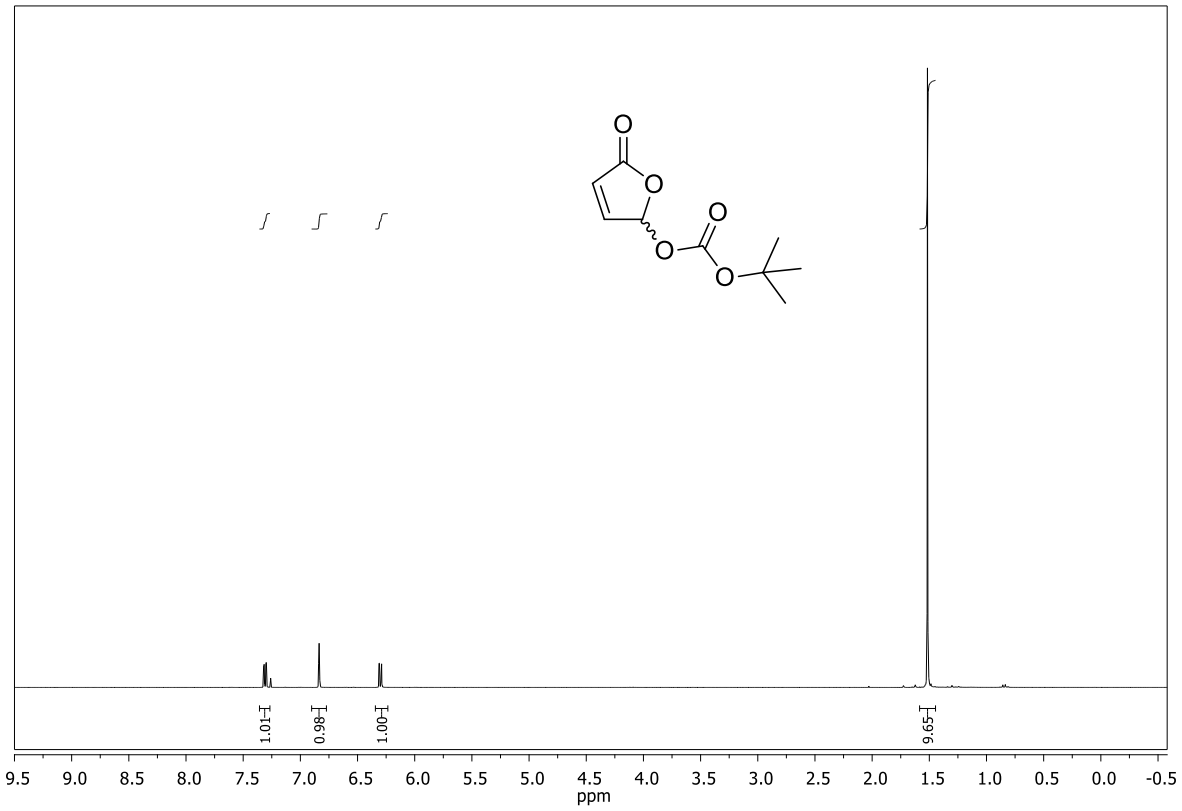
($CDCl_3$, 300 MHz)



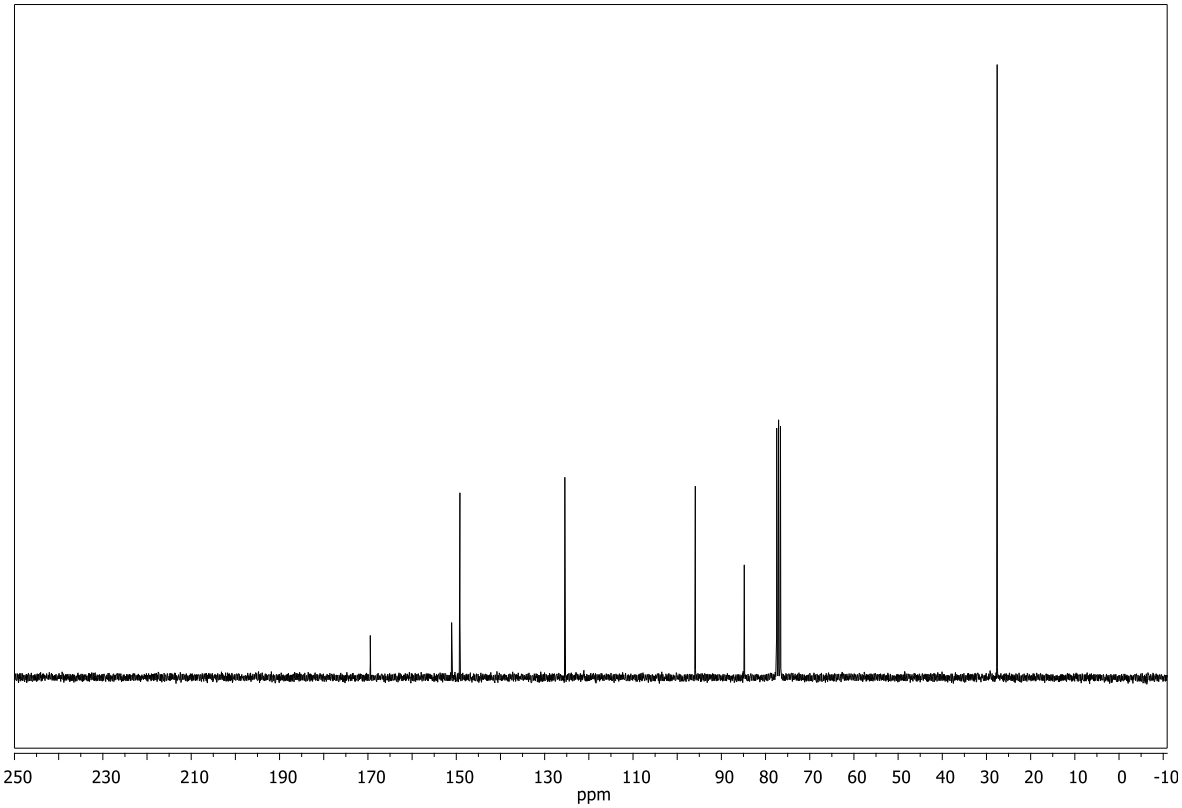
($CDCl_3$, 75 MHz)



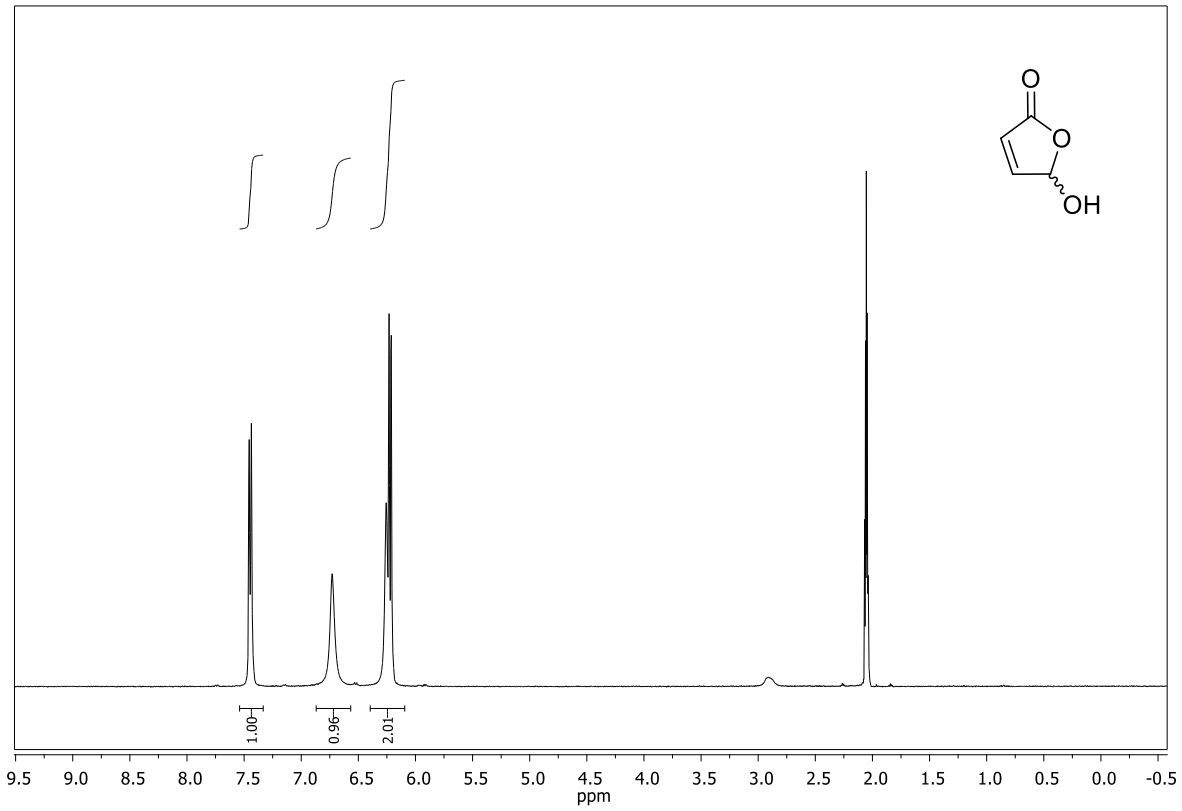
(±)-*tert*-butyl(5-oxo-2,5-dihydrofuran-2-yl)carbonate (121) **($CDCl_3$, 300 MHz)**



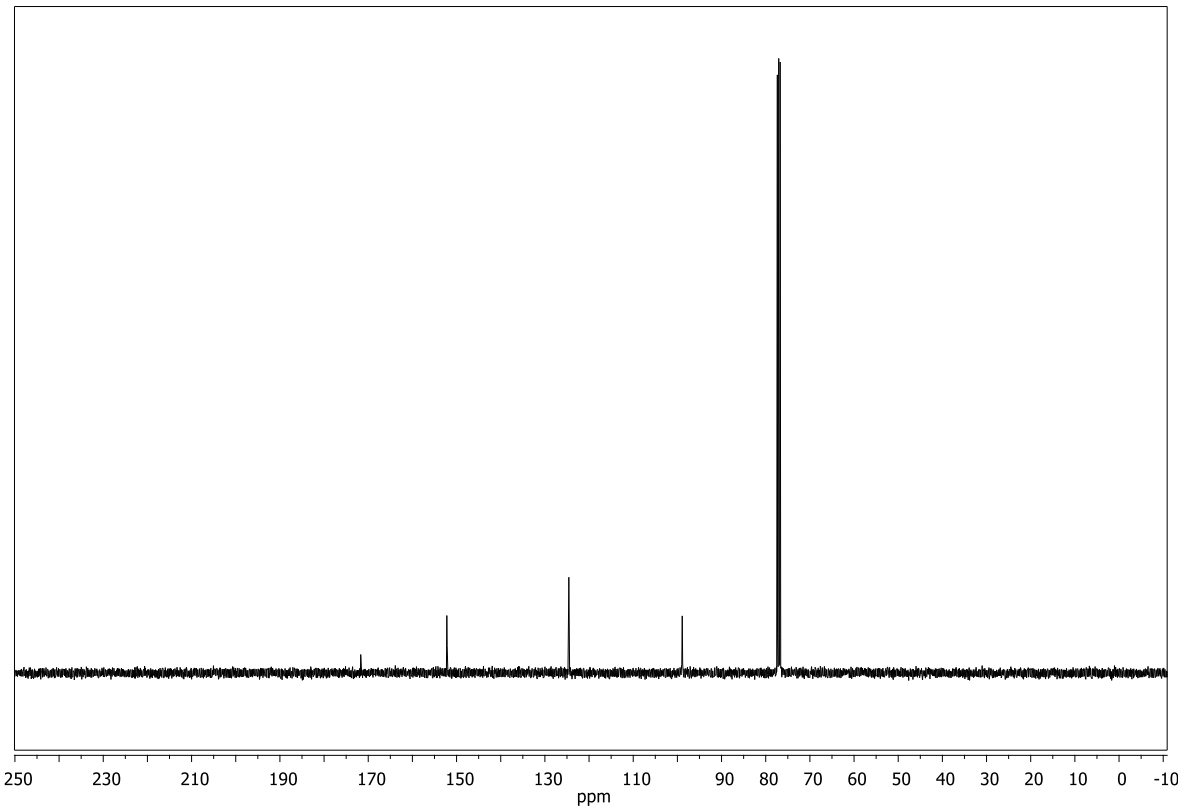
($CDCl_3$, 75 MHz)



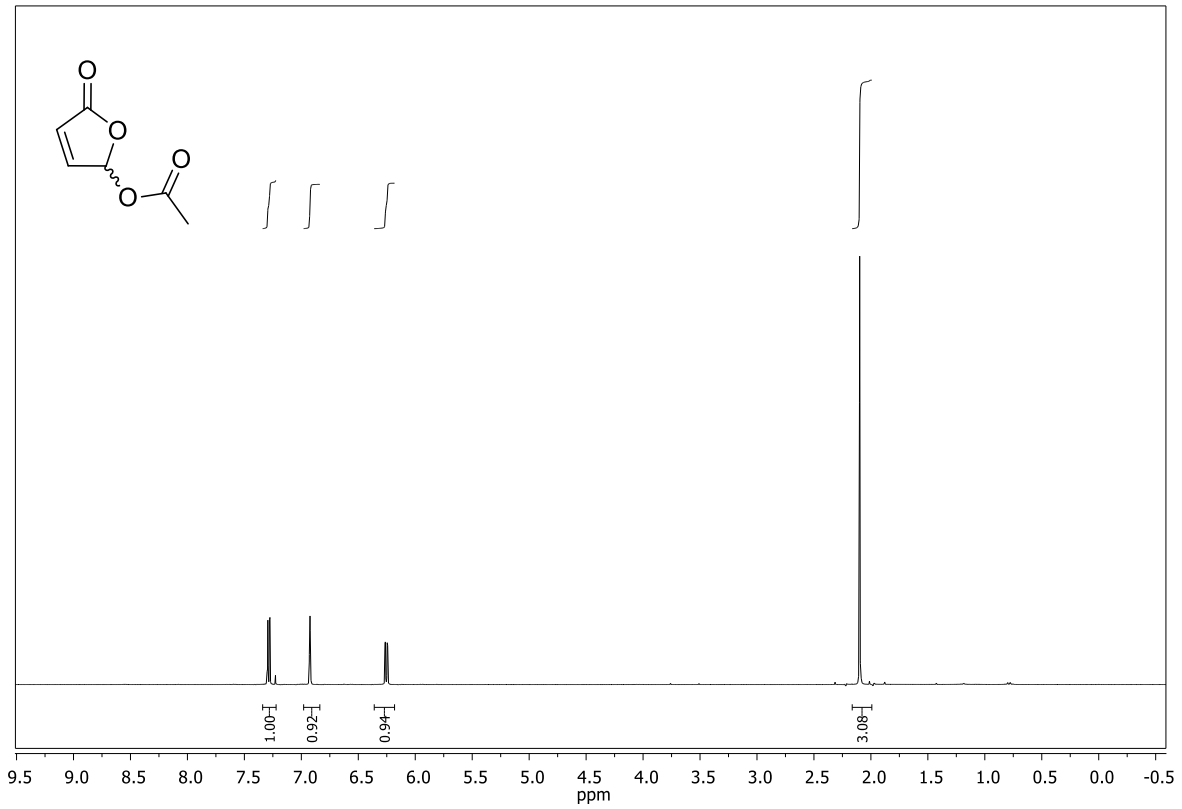
(±)-5-hydroxyfuran-2(5H)-on (134) **(acetone-d_6, 300 MHz)**



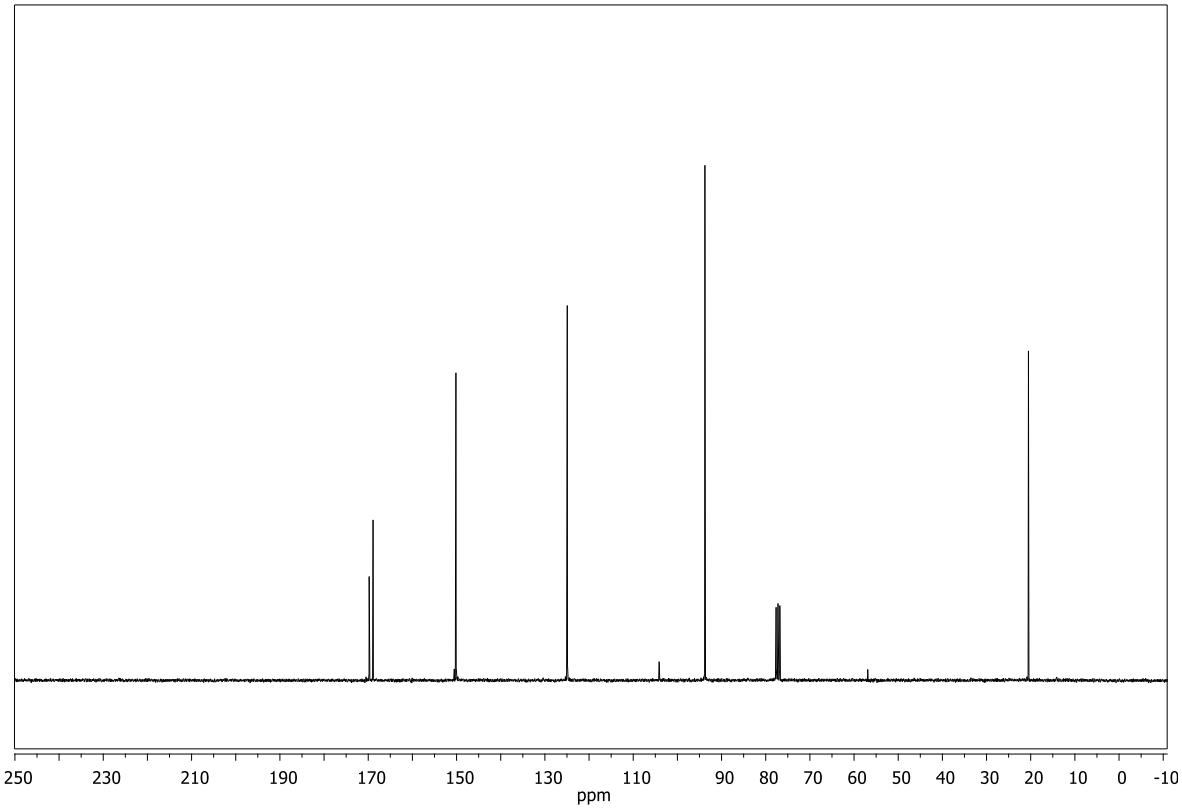
($CDCl_3$, 75 MHz)



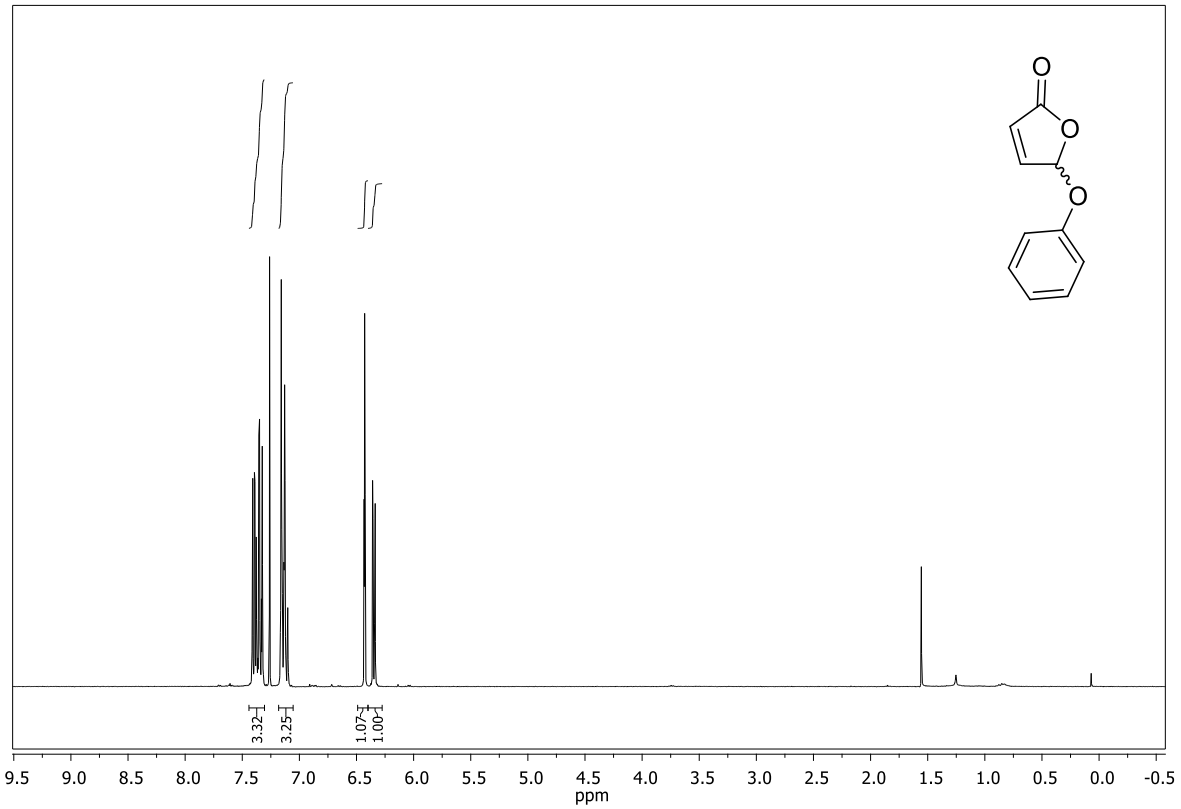
(±)-5-oxo-2,5-dihydrofuran-2-yl acetate (135) **($CDCl_3$, 300 MHz)**



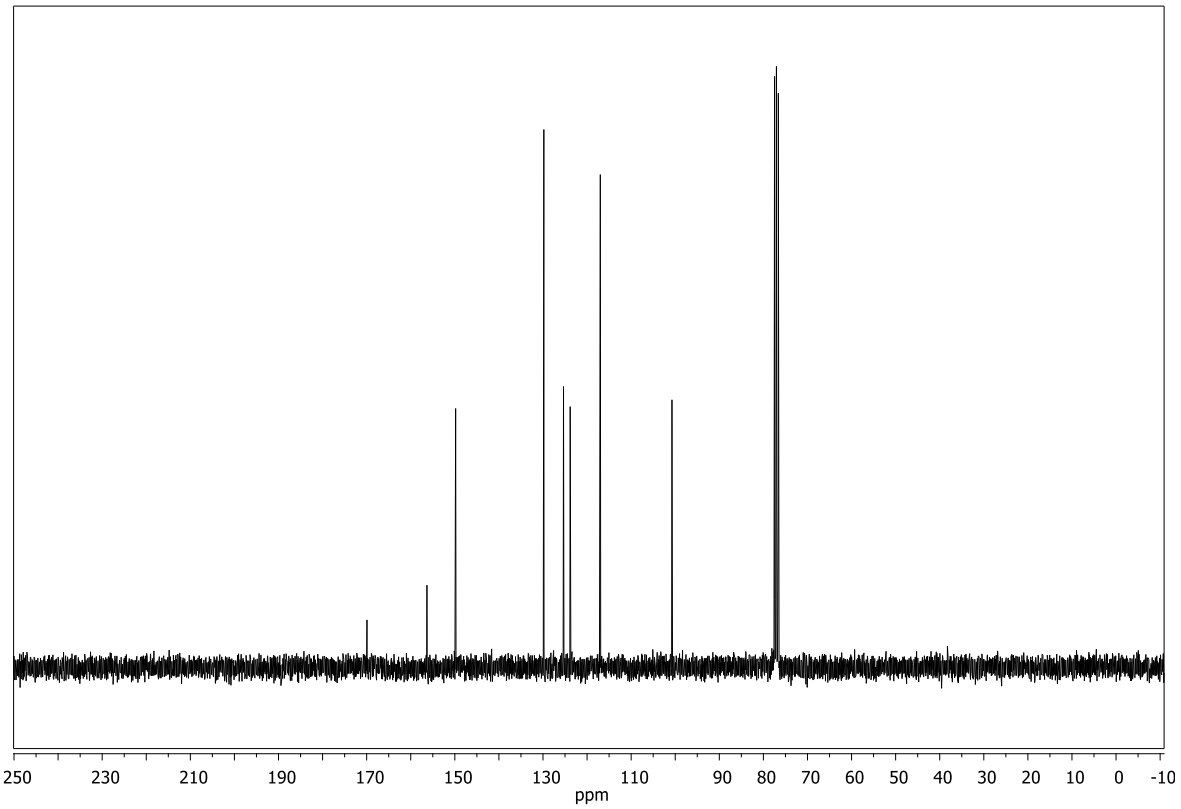
($CDCl_3$, 75 MHz)



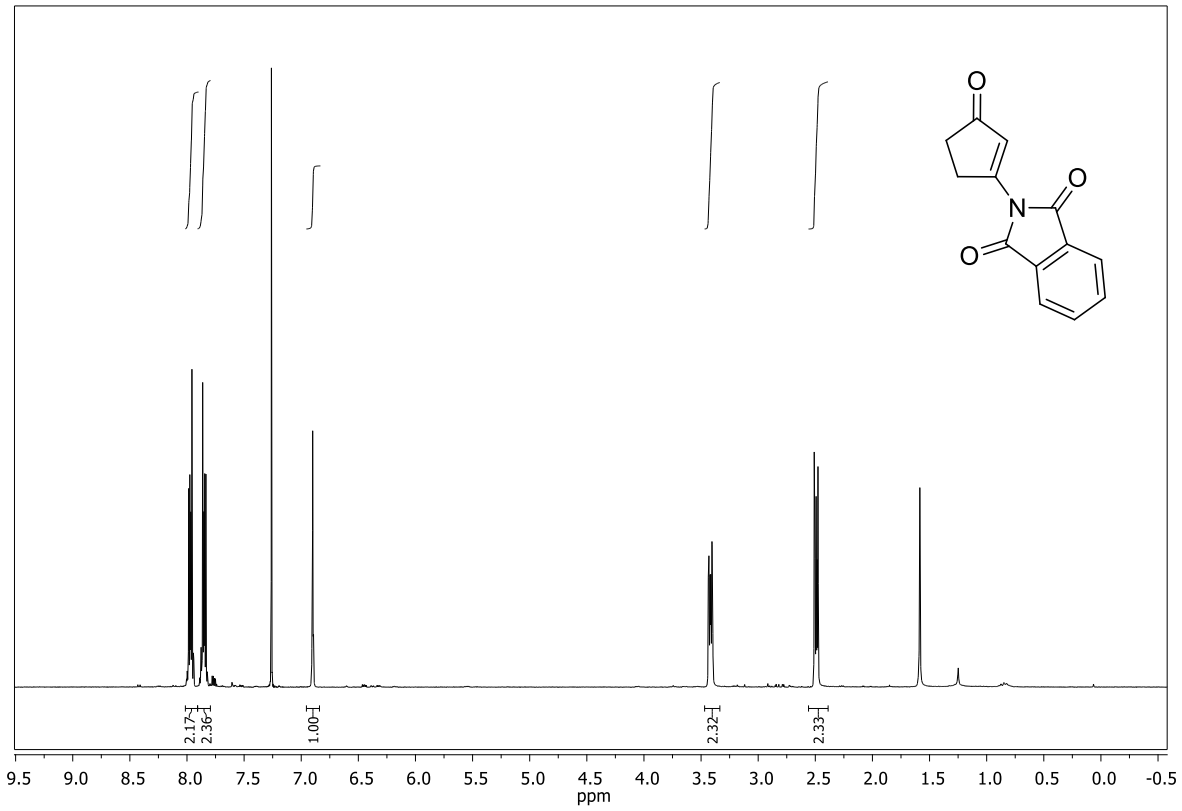
(±)-5-phenoxyfuran-2(5H)-one (136) **($CDCl_3$, 300 MHz)**



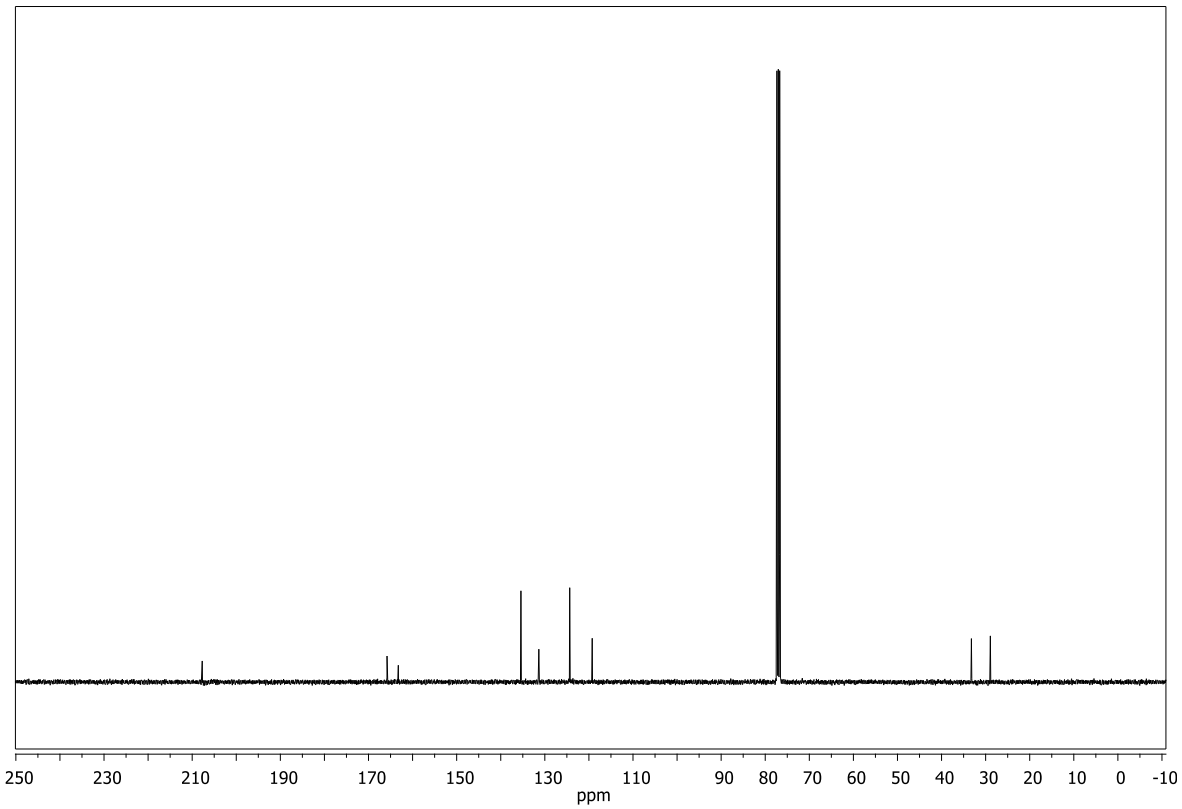
($CDCl_3$, 75 MHz)



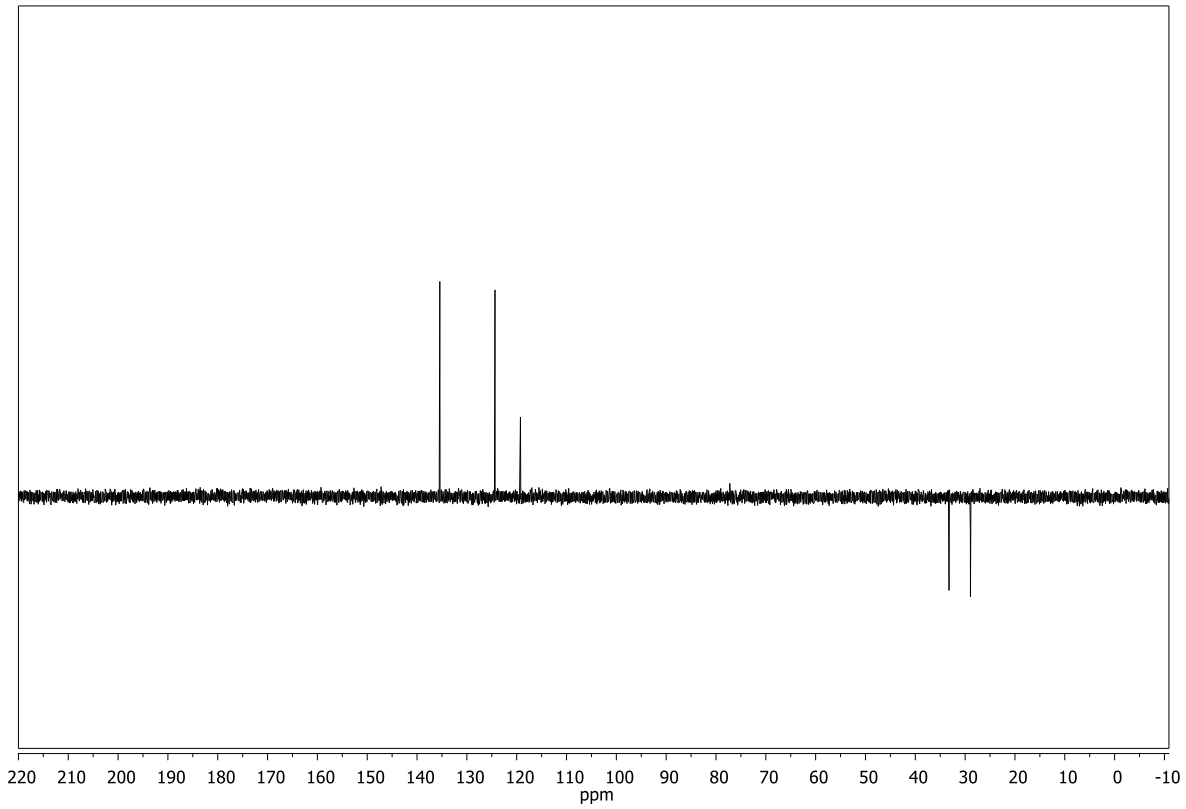
2-(3-oxocyclopent-1-en-1-yl)isoindoline-1,3-dione (151) **($CDCl_3$, 300 MHz)**



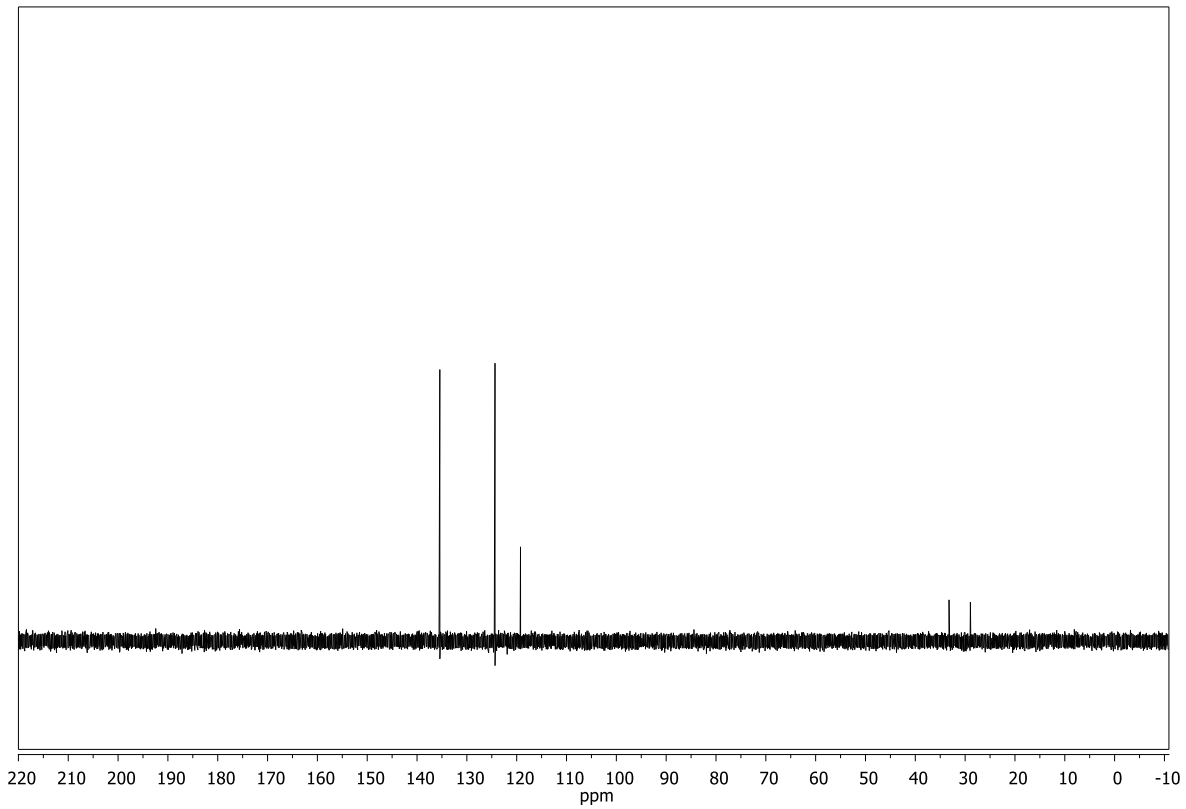
($CDCl_3$, 101 MHz)



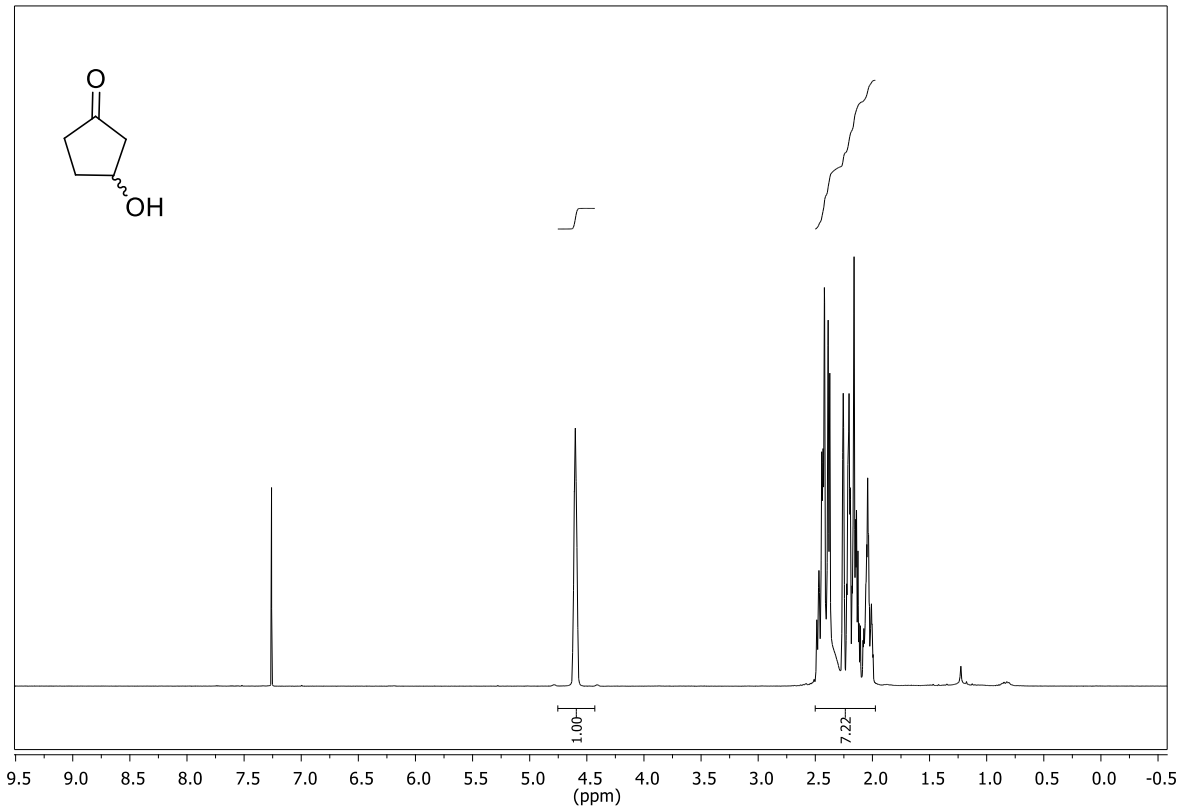
($CDCl_3$, 101 MHz)



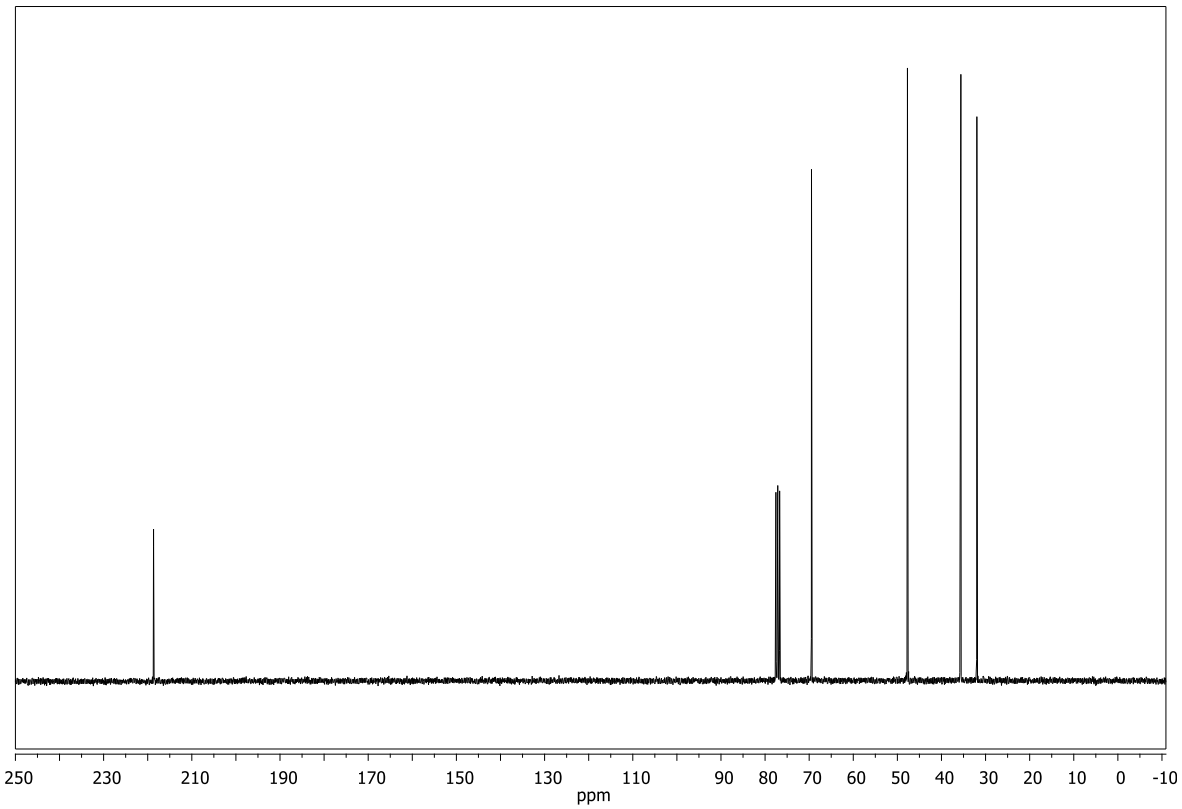
($CDCl_3$, 101 MHz)



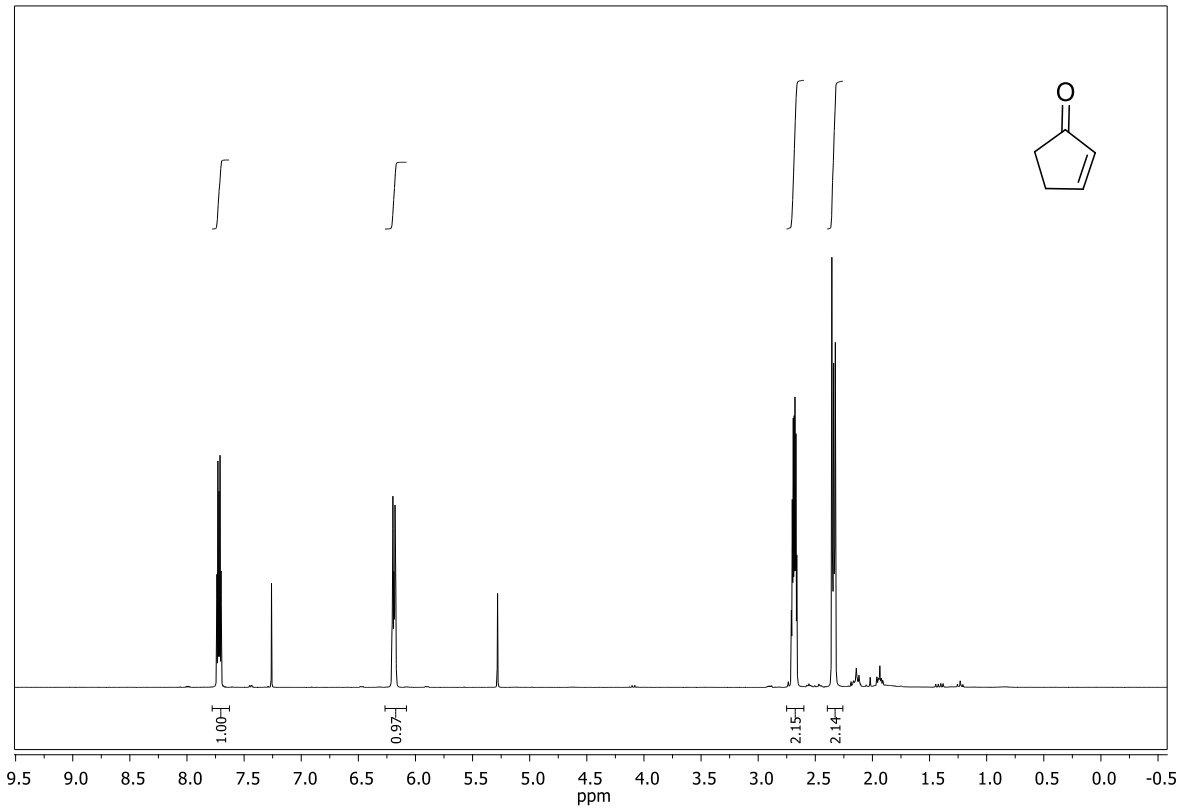
(±)-3-hydroxycyclopentanon (152) **($CDCl_3$, 300 MHz)**



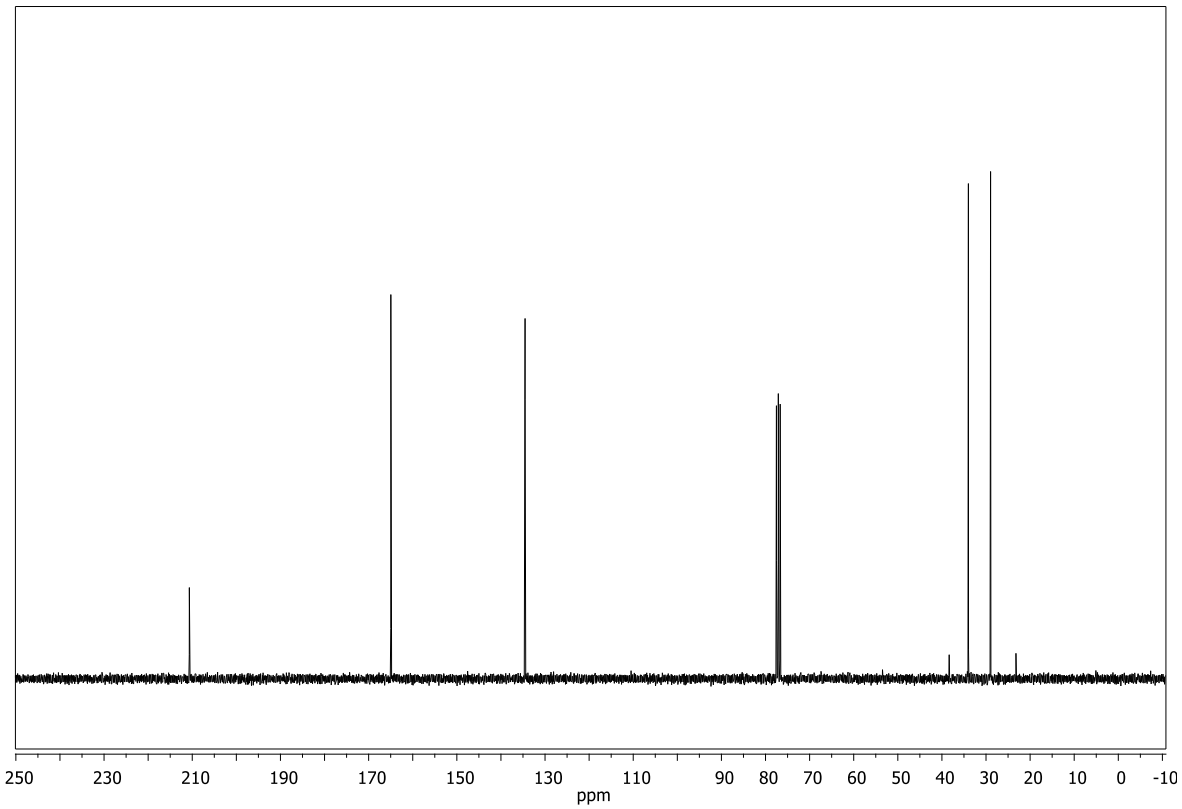
($CDCl_3$, 75 MHz)



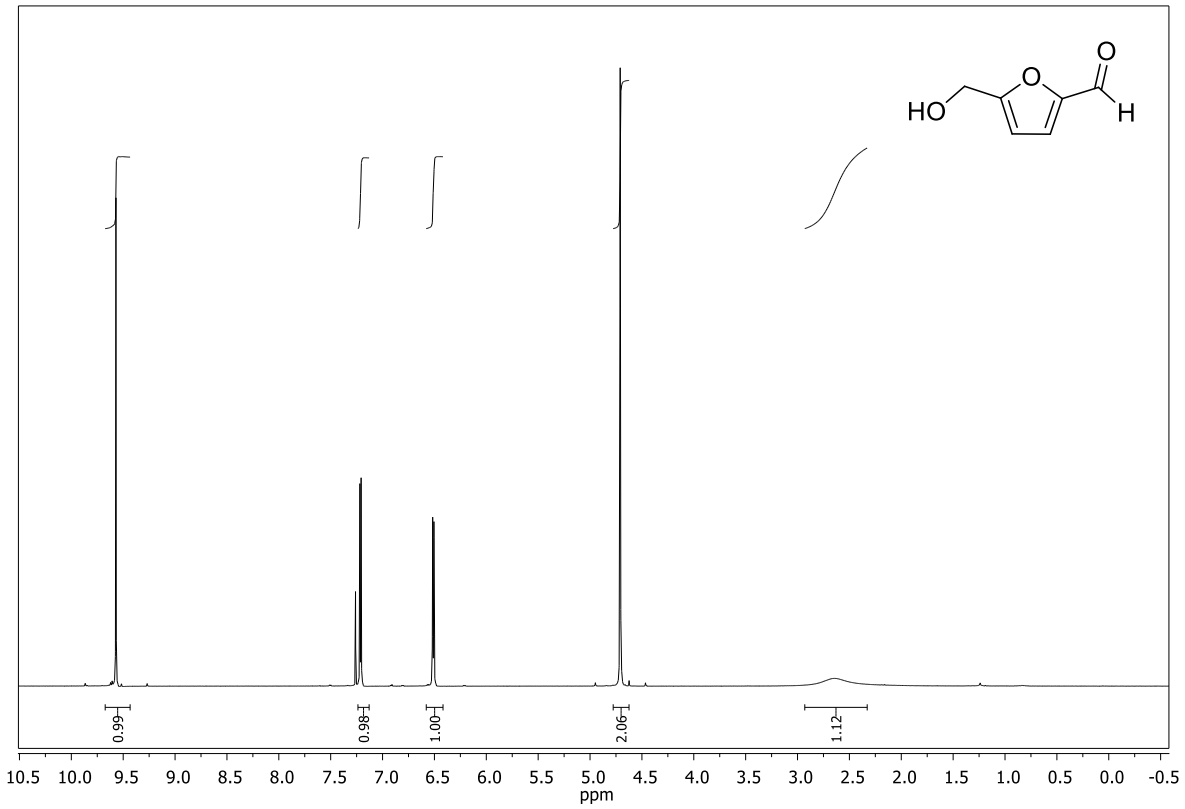
2-cyclopentenone (105) **($CDCl_3$, 300 MHz)**



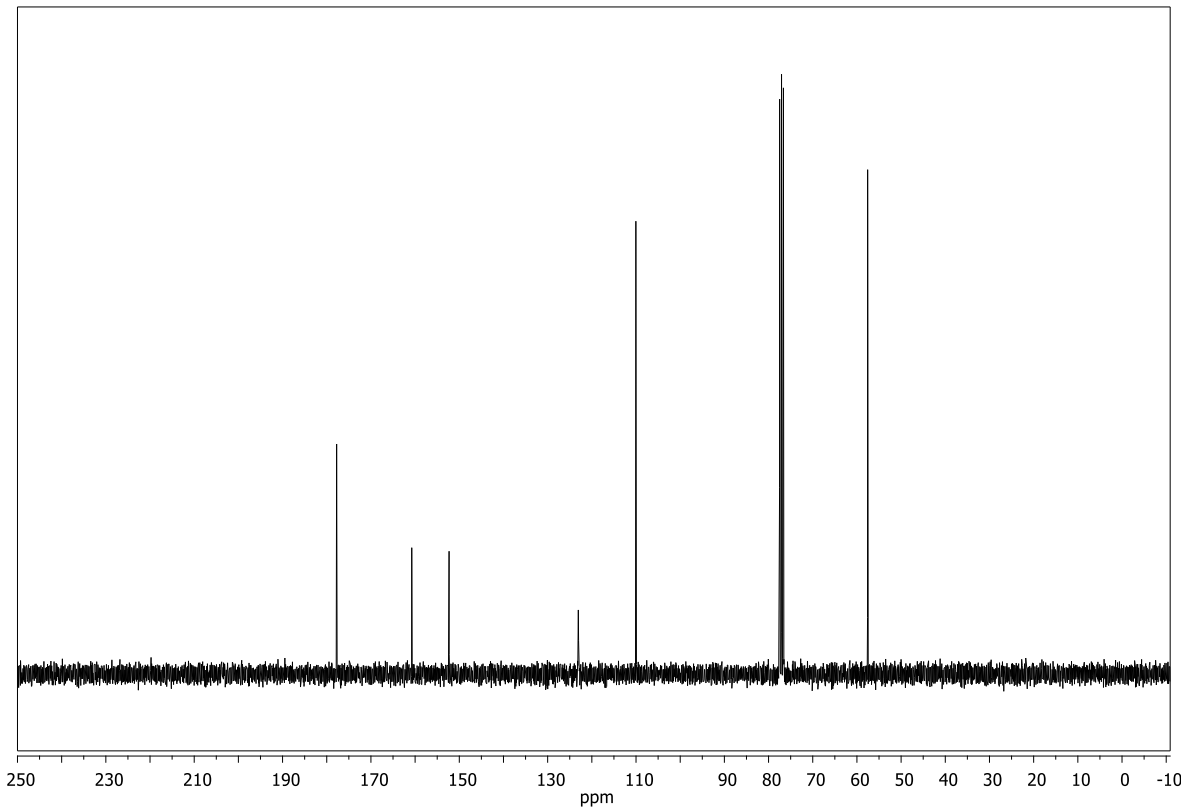
($CDCl_3$, 75 MHz)



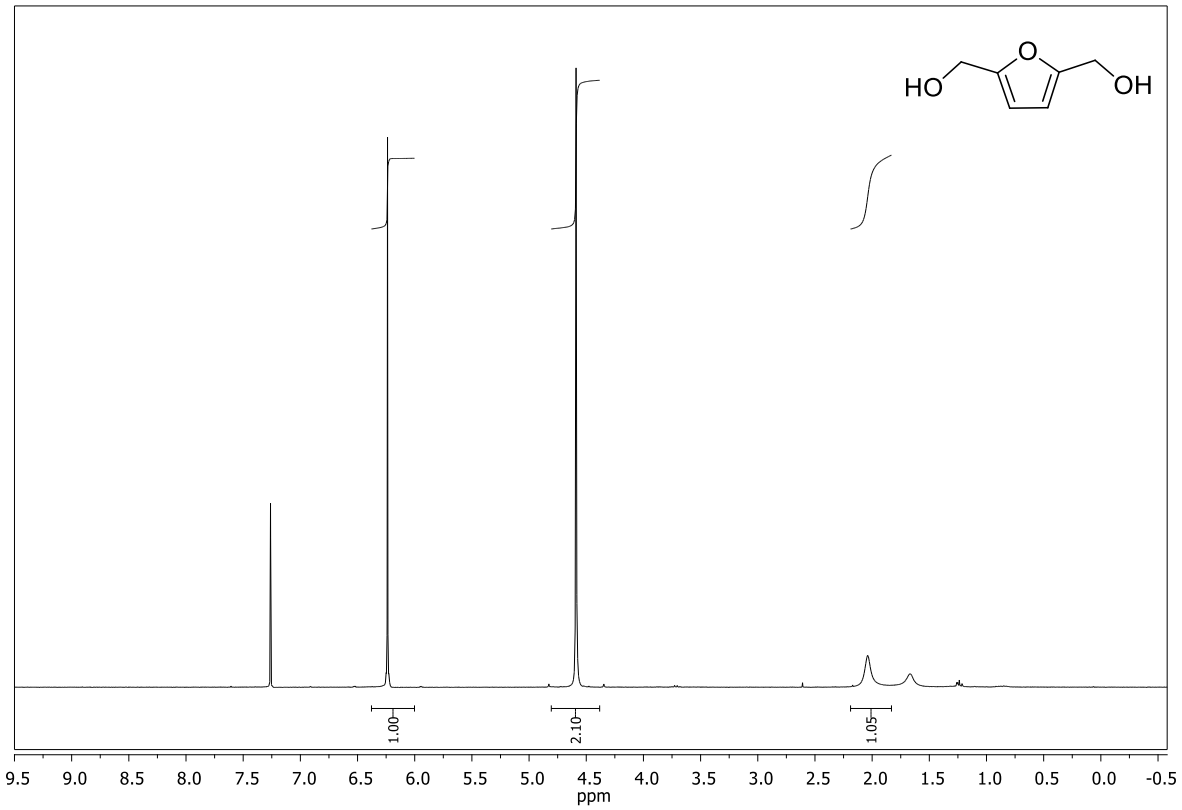
5-hydroxymethylfurfural (HMF) (154) **($CDCl_3$, 300 MHz)**



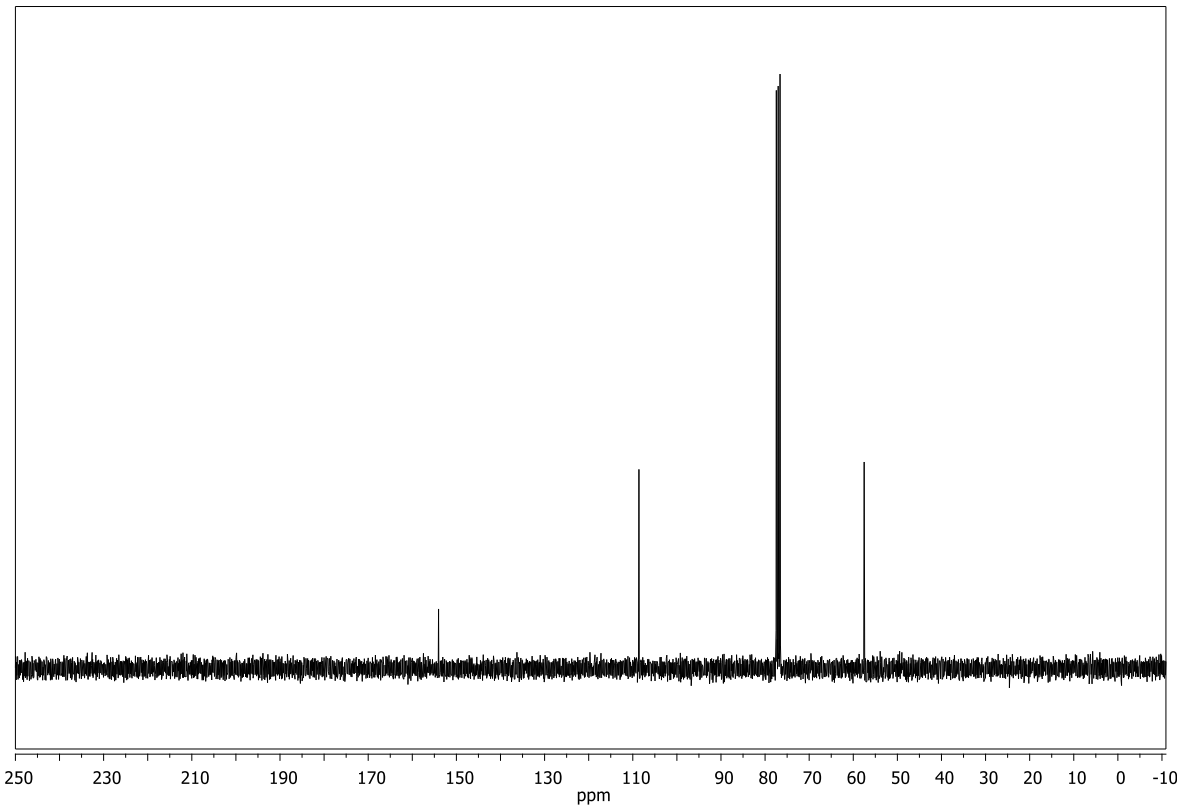
($CDCl_3$, 75 MHz)



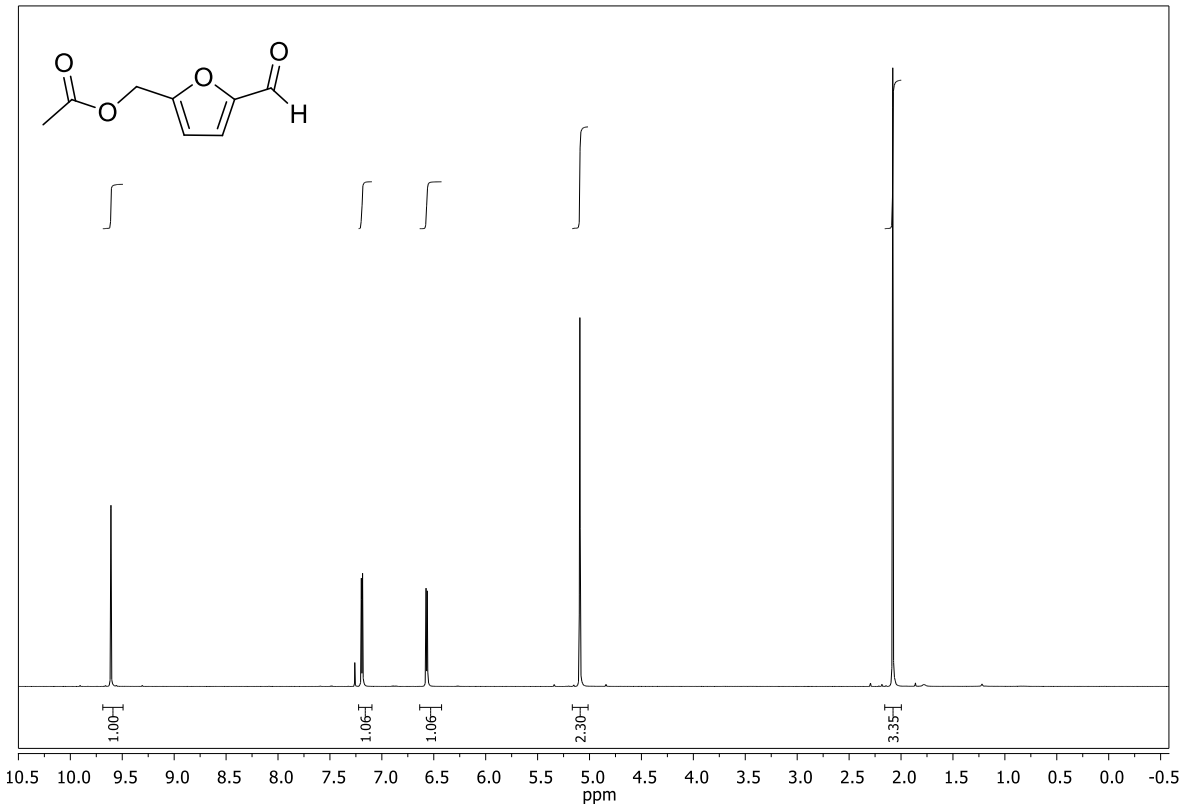
2,5-bis(hydroxymethyl)furan (155) **($CDCl_3$, 300 MHz)**



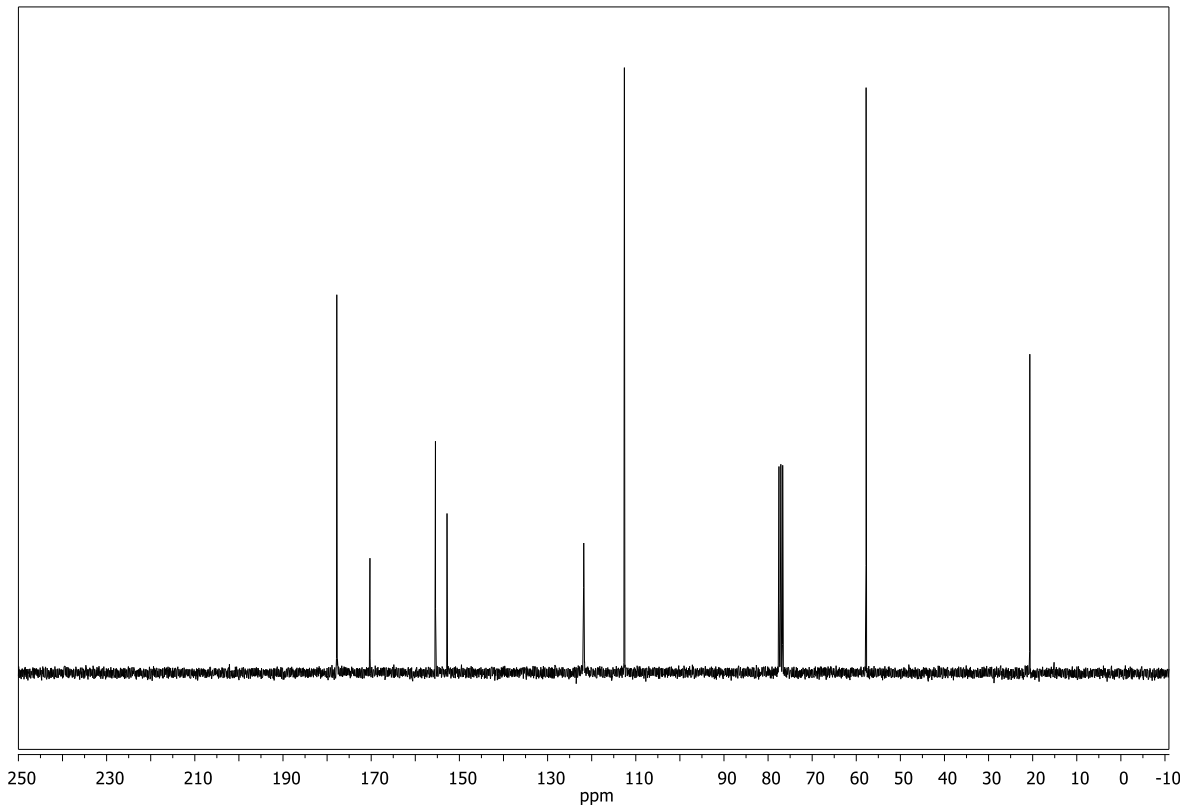
($CDCl_3$, 75 MHz)



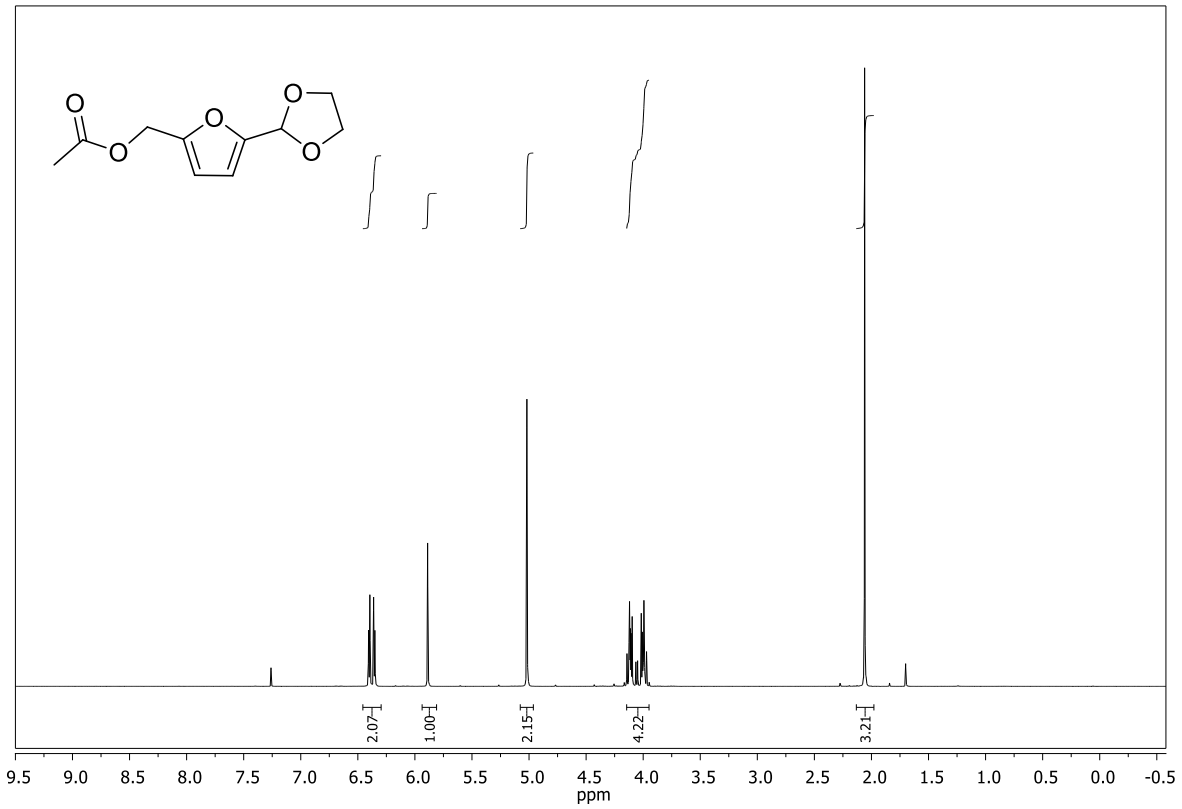
(5-formylfuran-2-yl)methyl acetate (161) **($CDCl_3$, 300 MHz)**



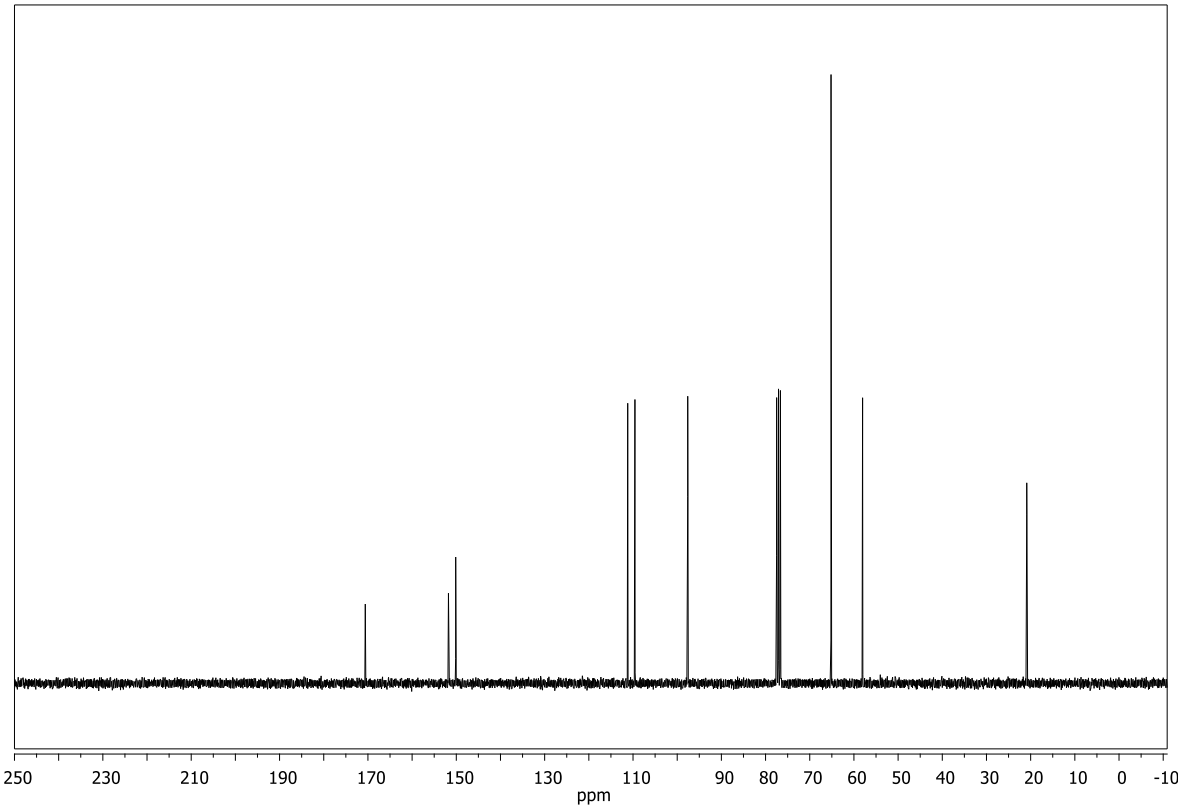
($CDCl_3$, 75 MHz)



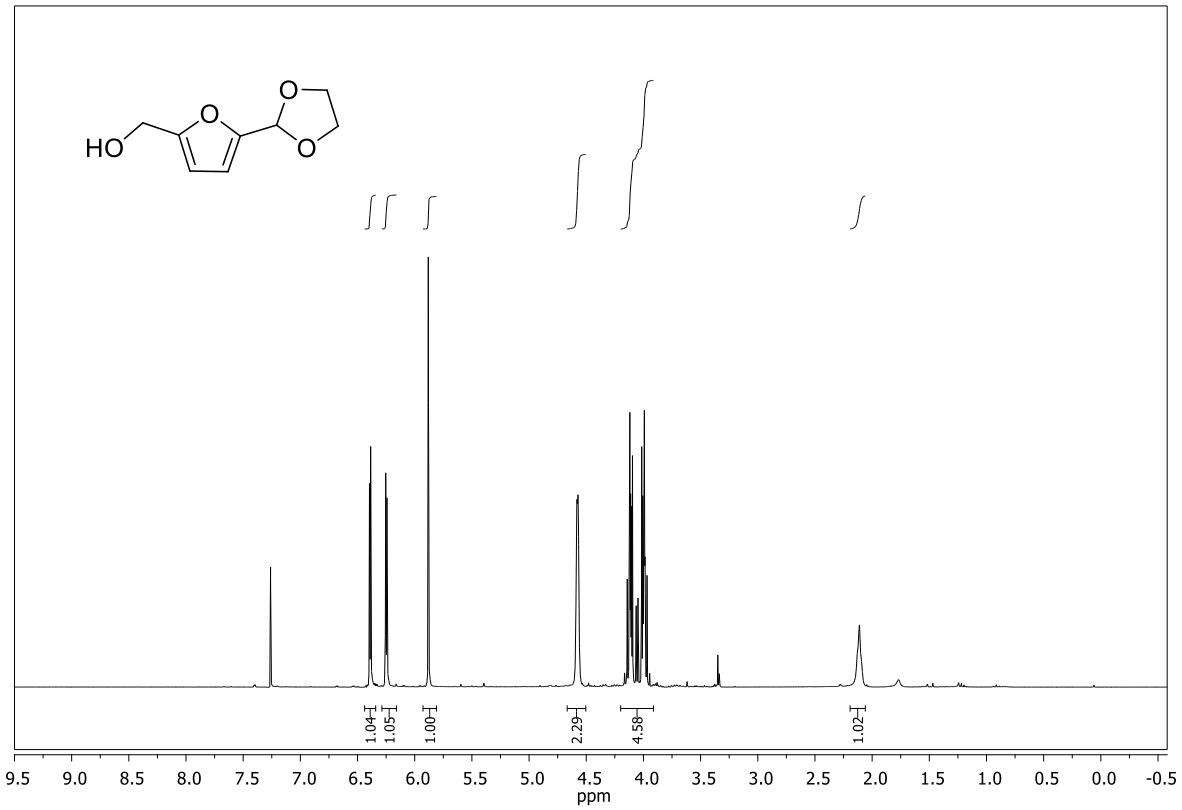
(5-(1,3-dioxolan-2-yl)furan-2-yl)methylacetate (162) **($CDCl_3$, 300 MHz)**



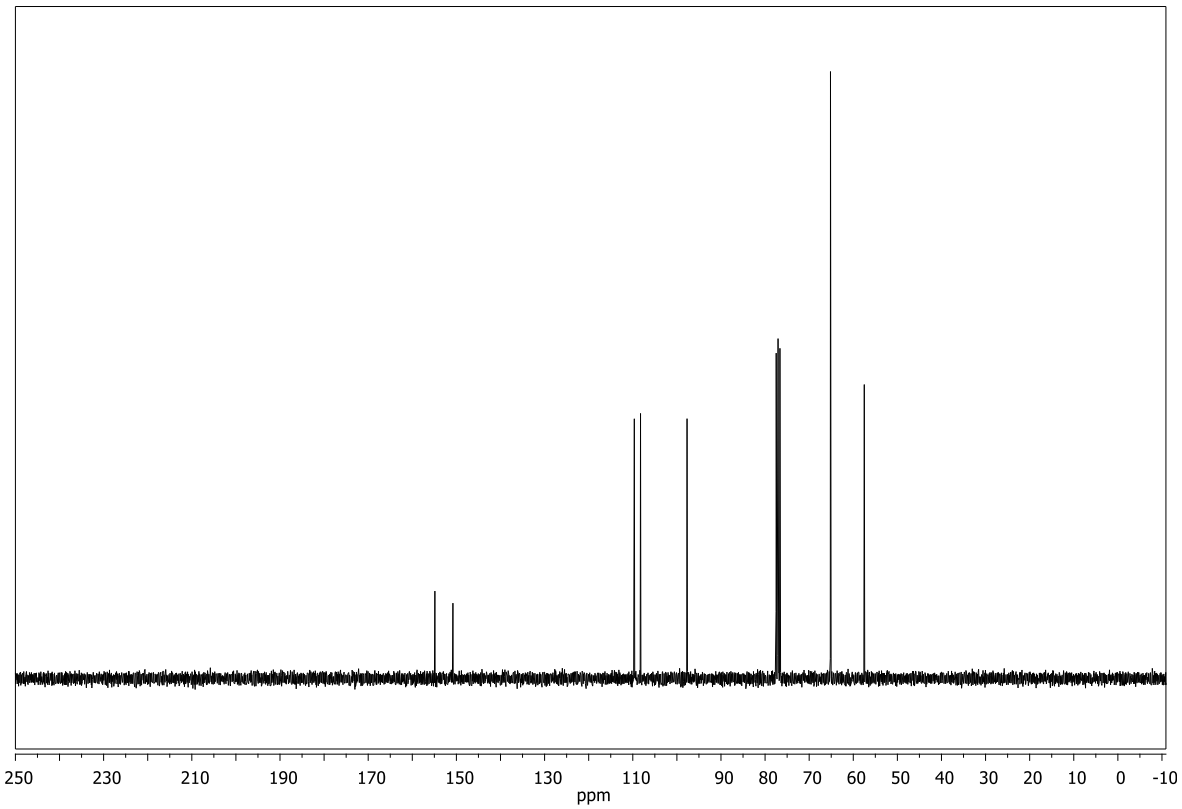
($CDCl_3$, 75 MHz)



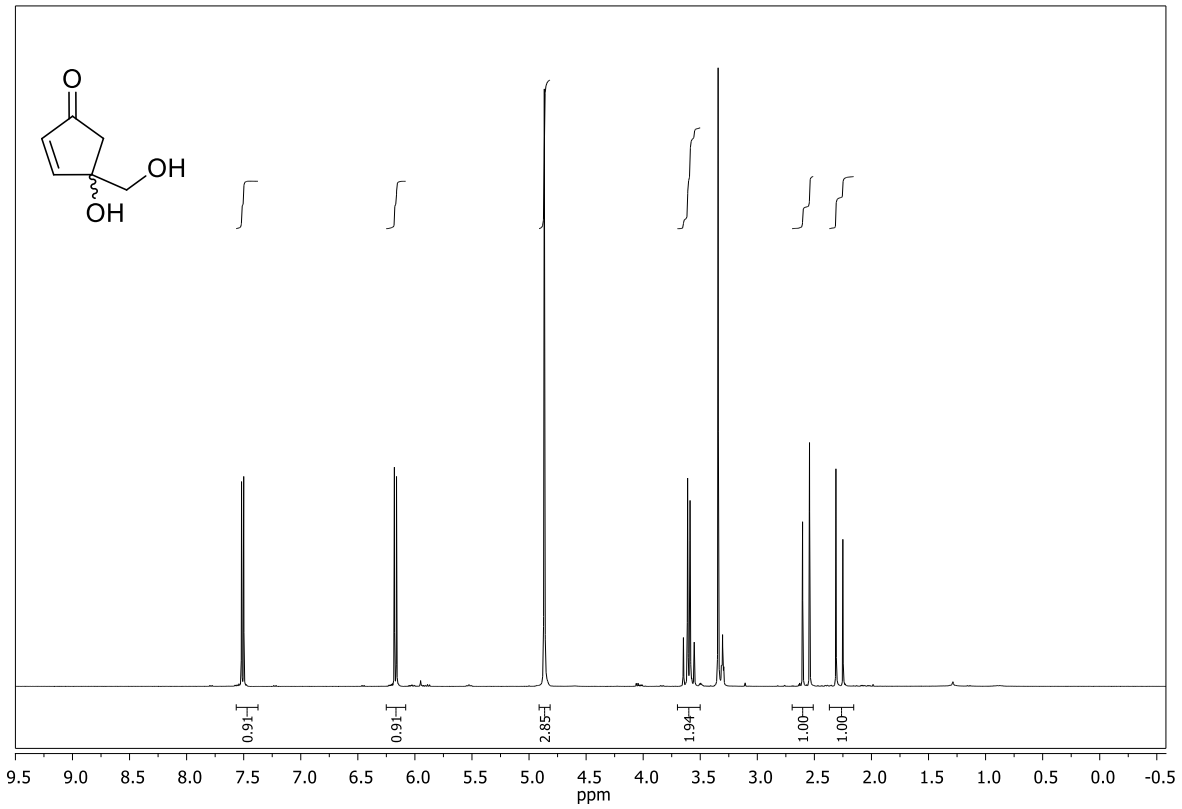
(5-(1,3-dioxolan-2-yl)furan-2-yl)methanol (163) **($CDCl_3$, 300 MHz)**



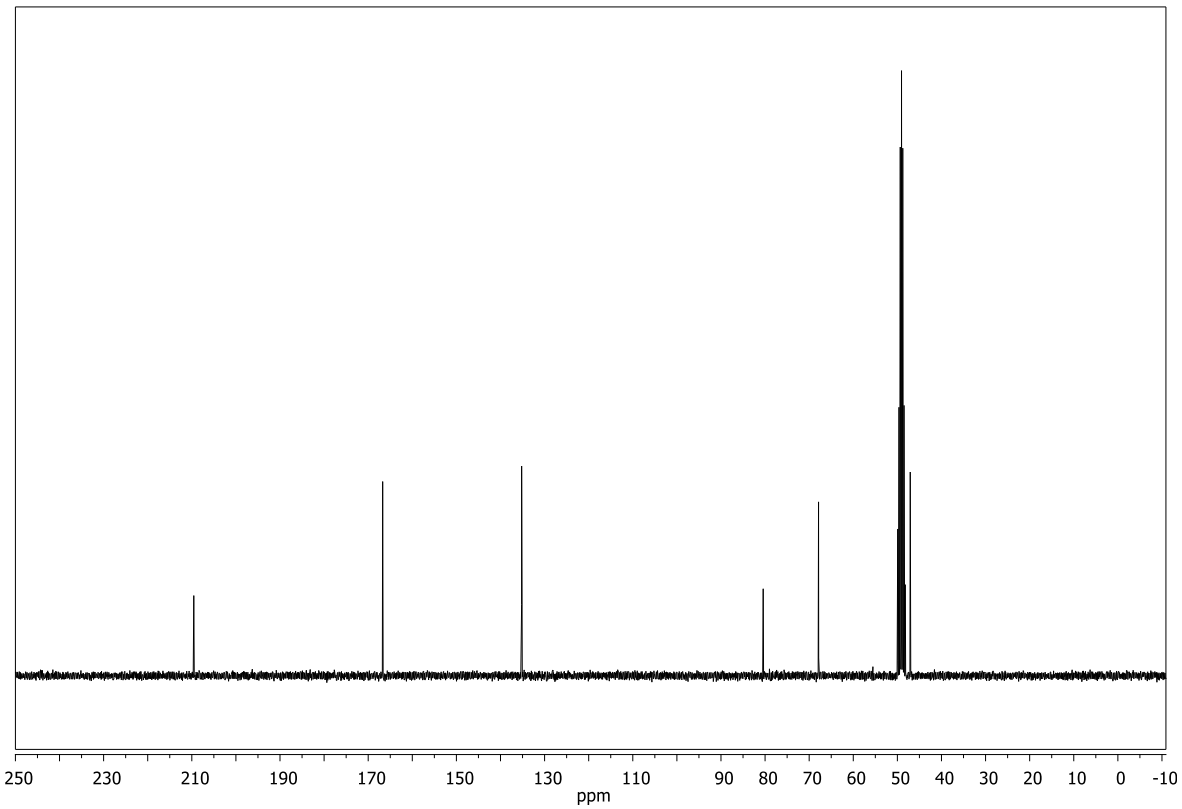
($CDCl_3$, 75 MHz)



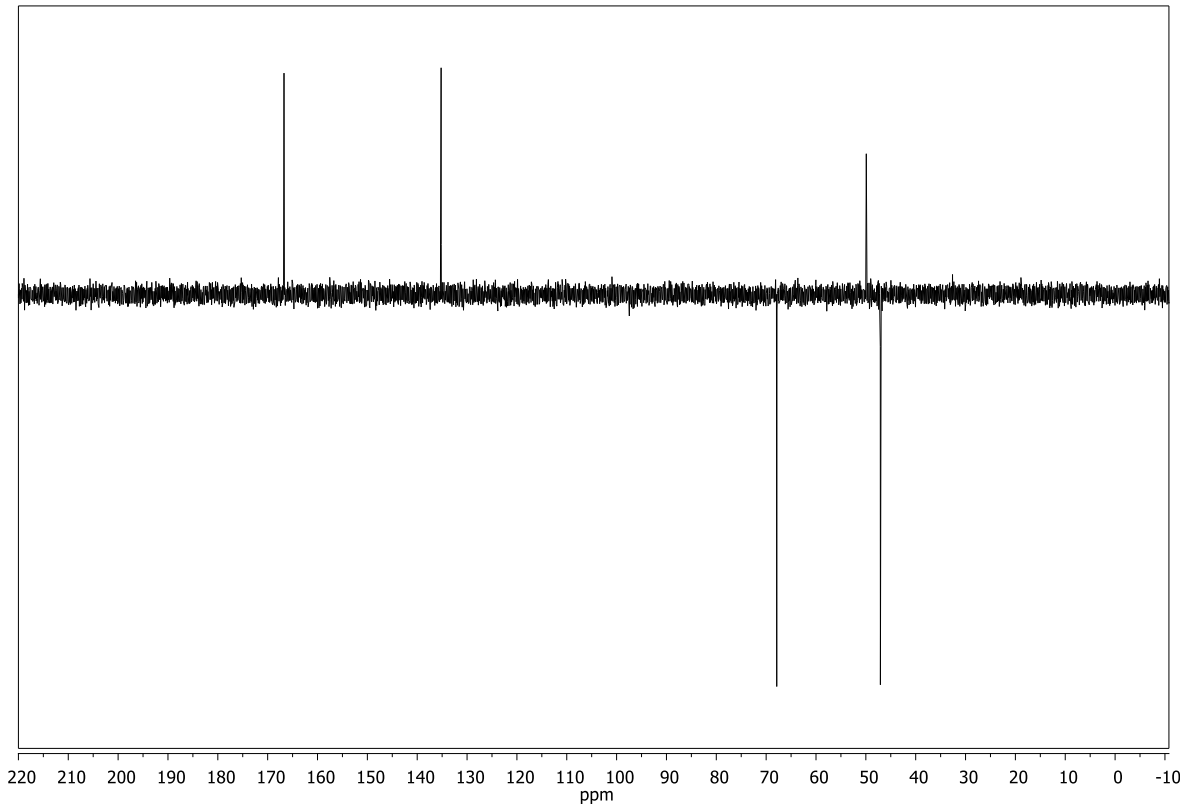
(±)-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone (164) **(MeOD, 300 MHz)**



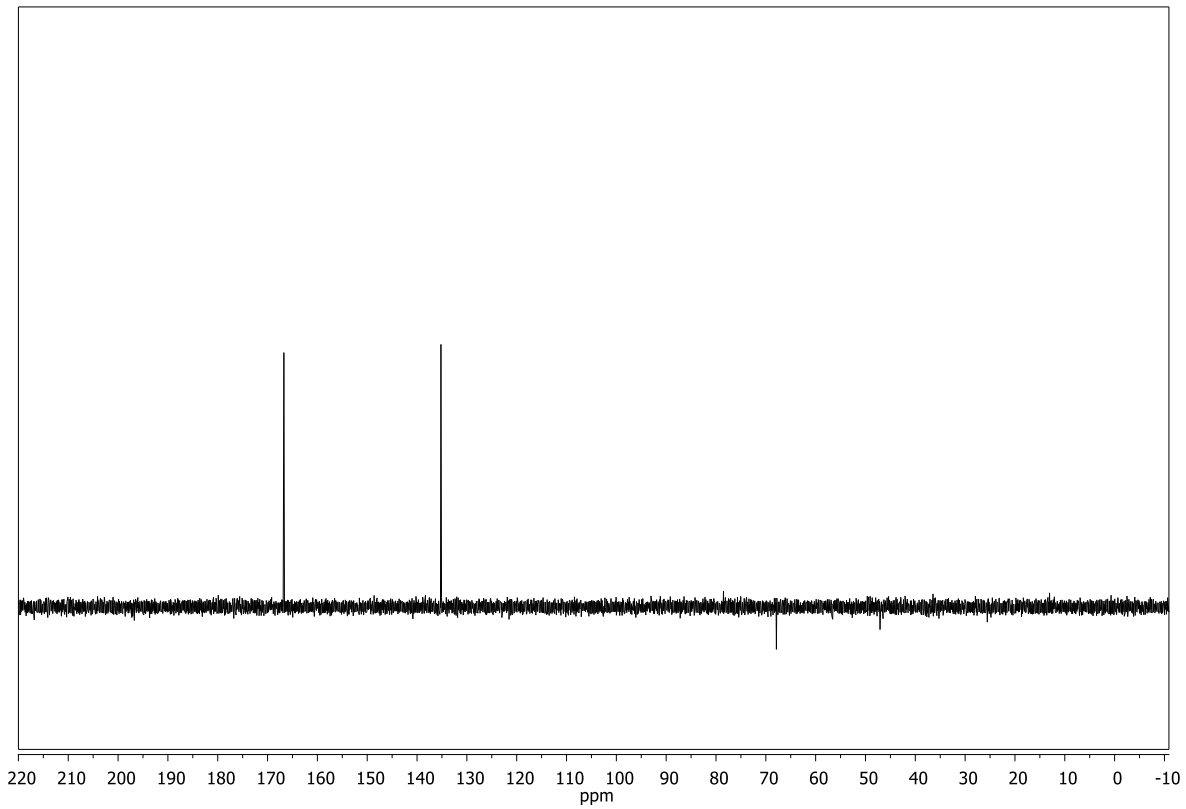
(MeOD, 75 MHz)



(MeOD, 75 MHz)

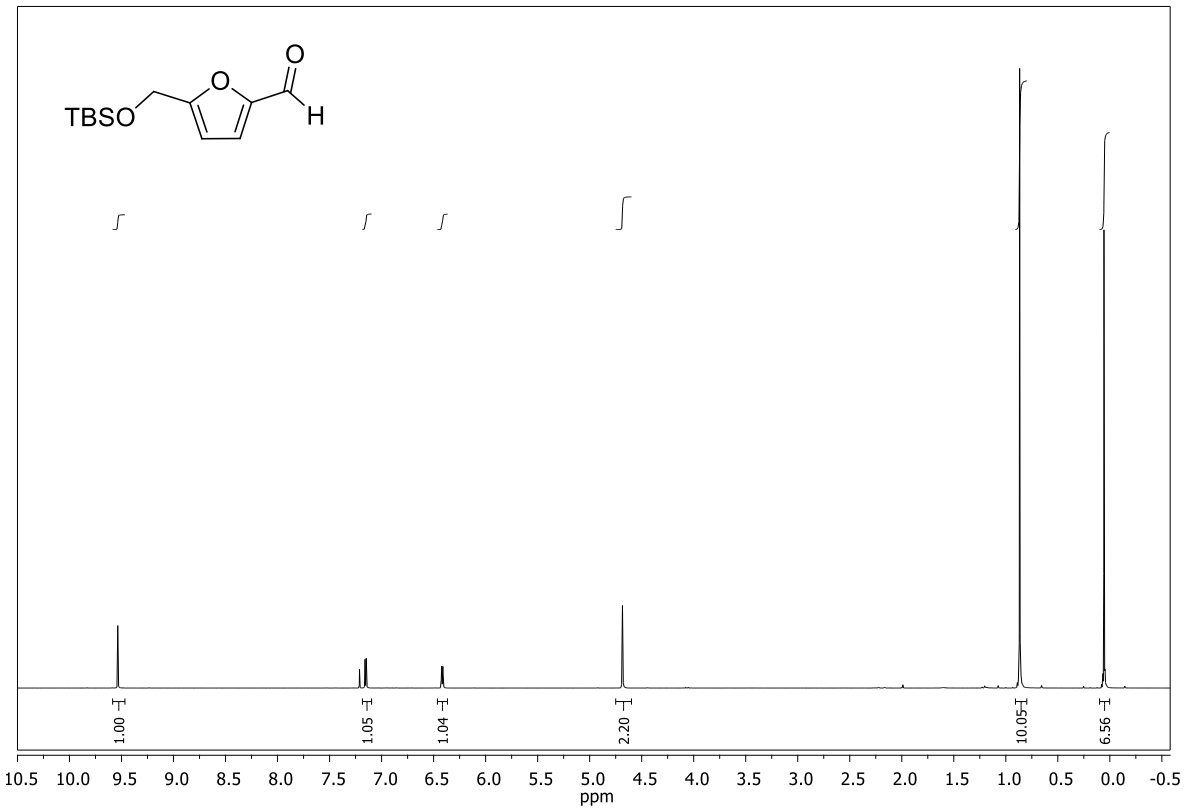


(MeOD, 75 MHz)

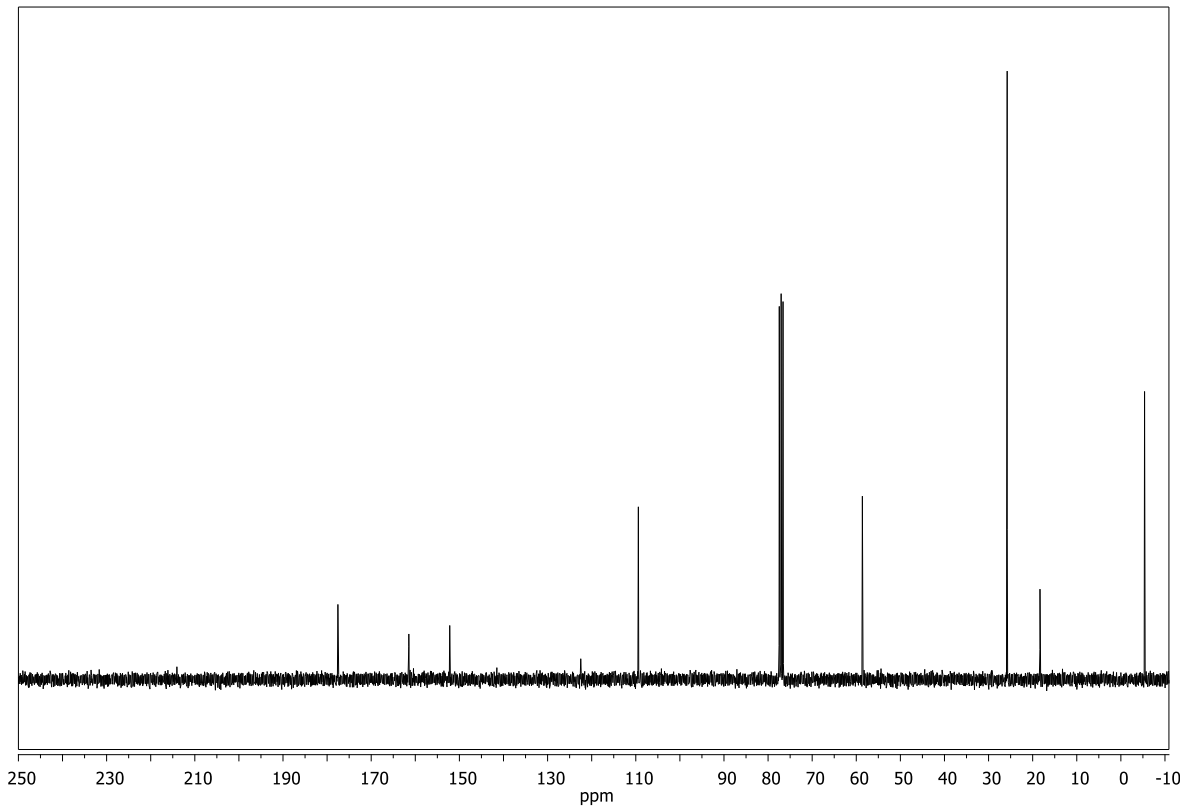


5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (175)

($CDCl_3$, 300 MHz)

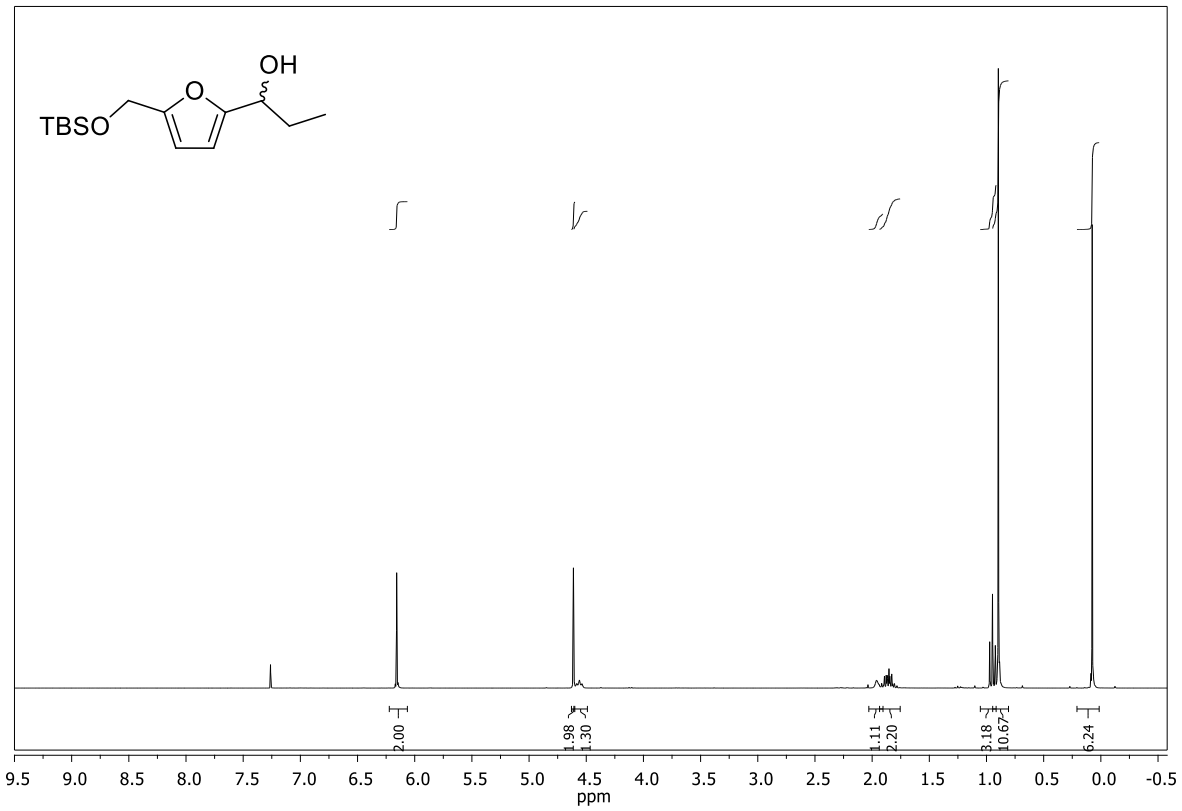


($CDCl_3$, 75 MHz)

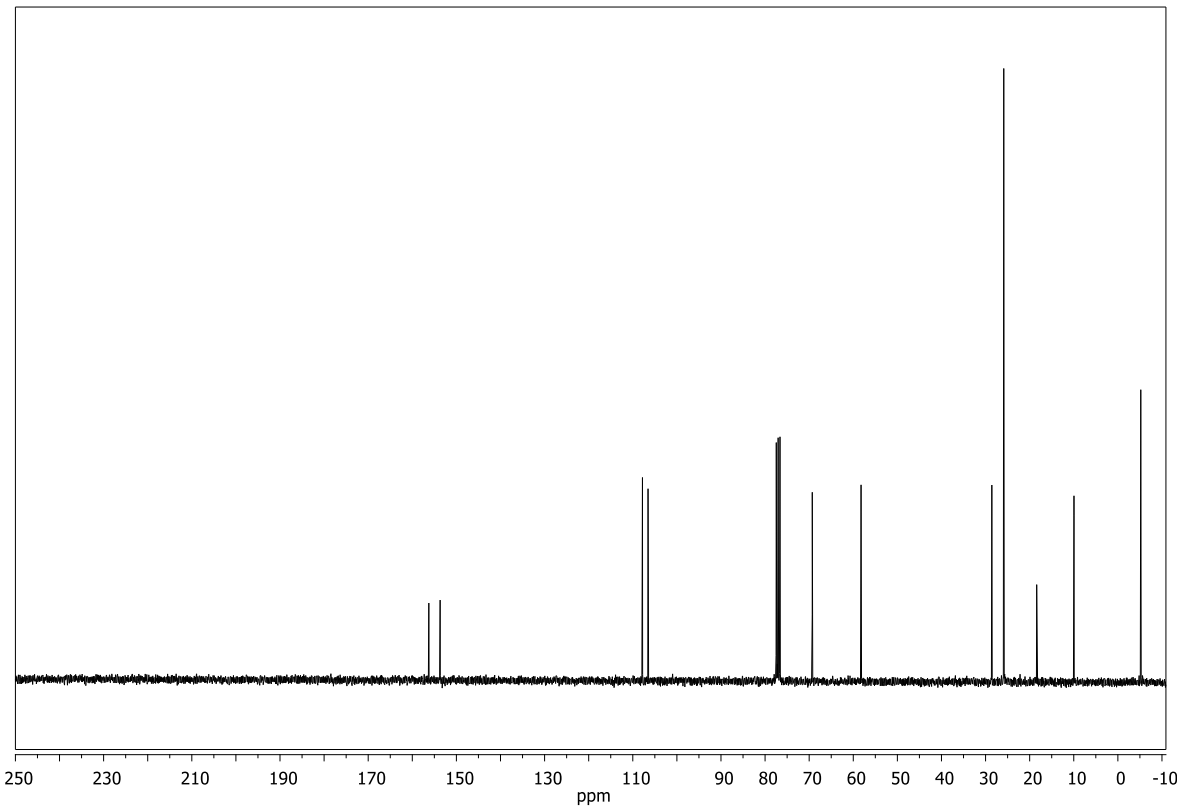


(±)-1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-yl)propan-1-ol (176)

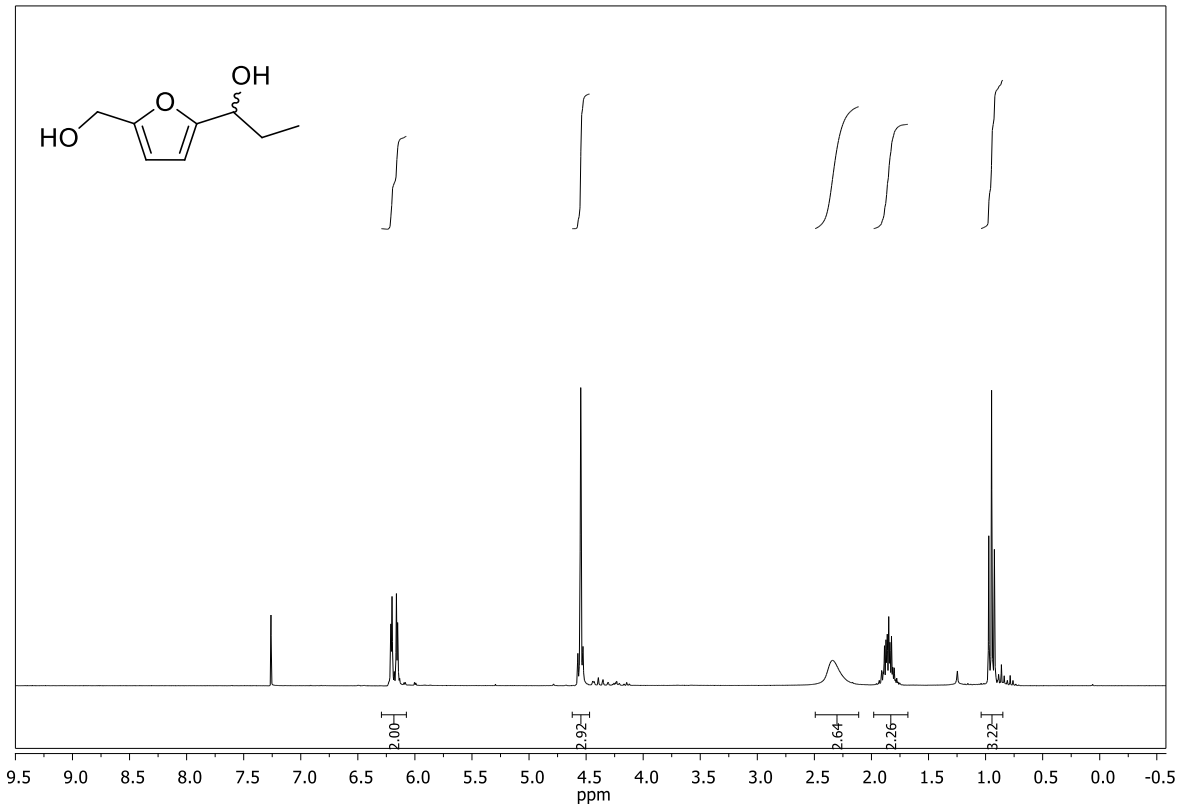
($CDCl_3$, 300 MHz)



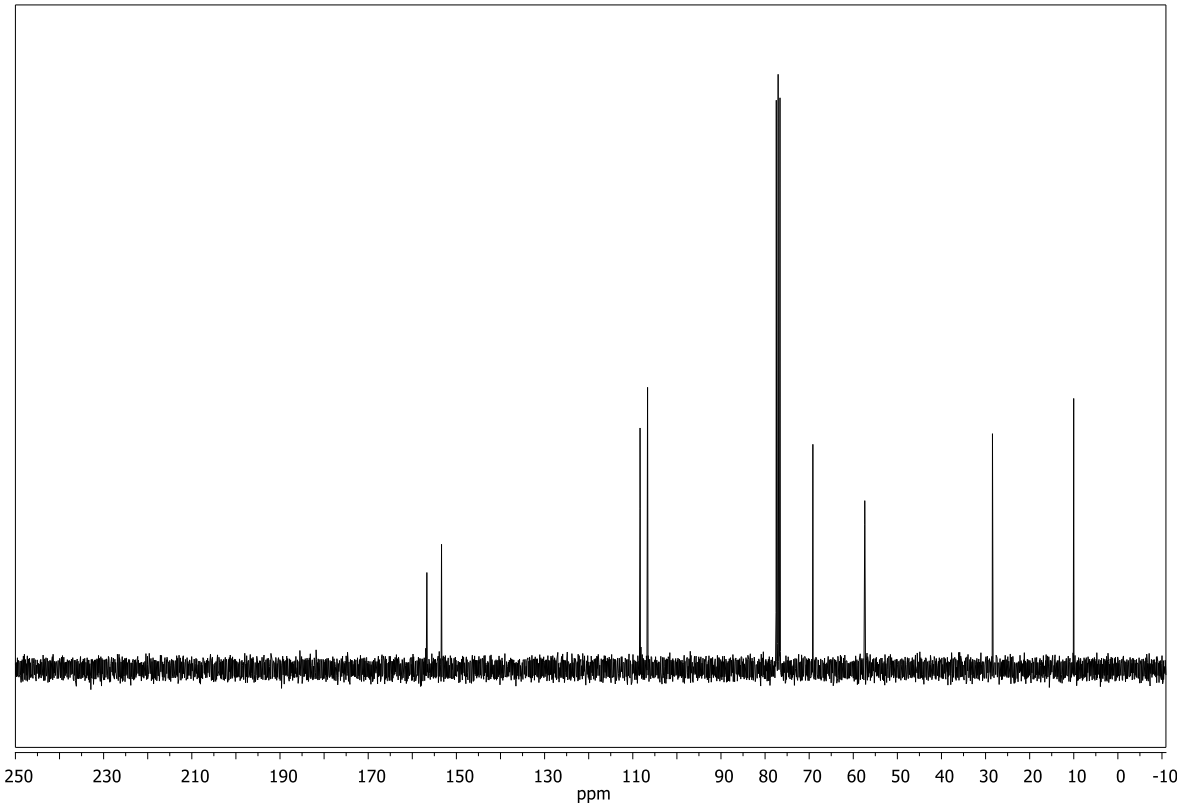
($CDCl_3$, 75 MHz)



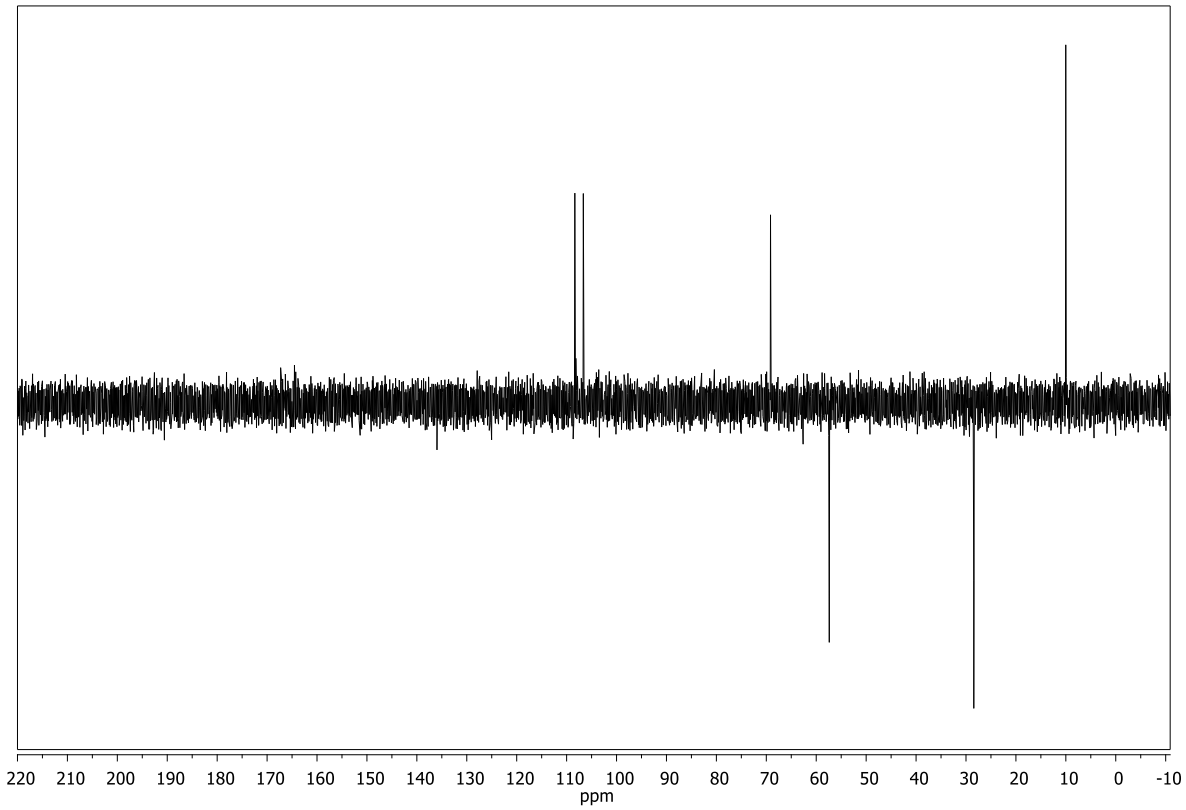
(±)-1-(5-(hydroxymethyl)furan-2-yl)propan-1-ol (177) **($CDCl_3$, 300 MHz)**



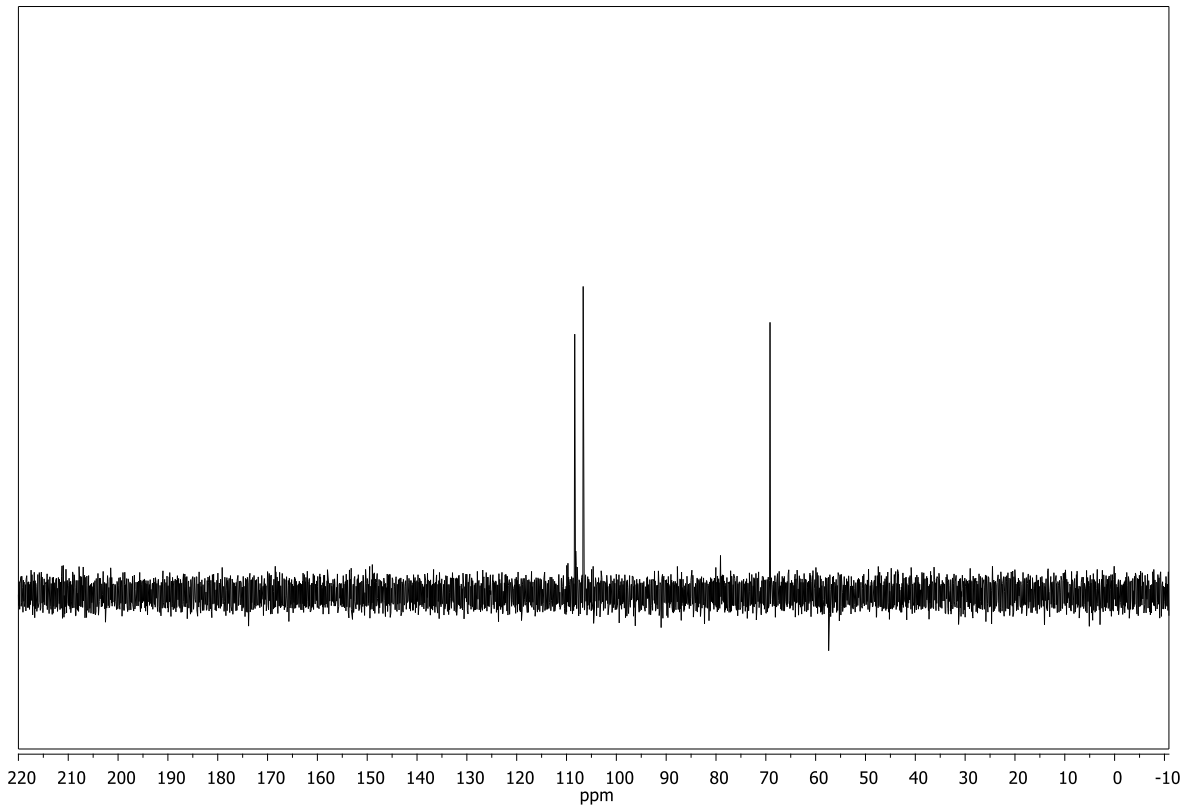
($CDCl_3$, 75 MHz)



($CDCl_3$, 75 MHz)

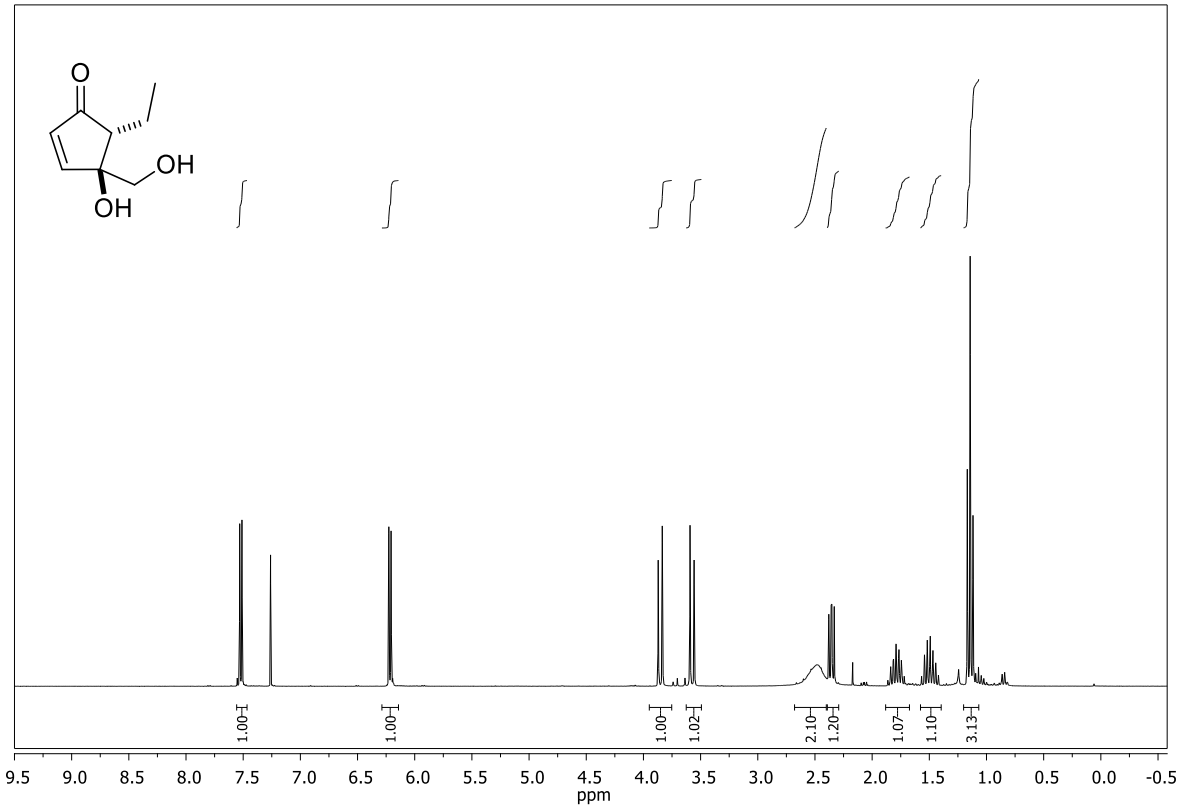


($CDCl_3$, 75 MHz)

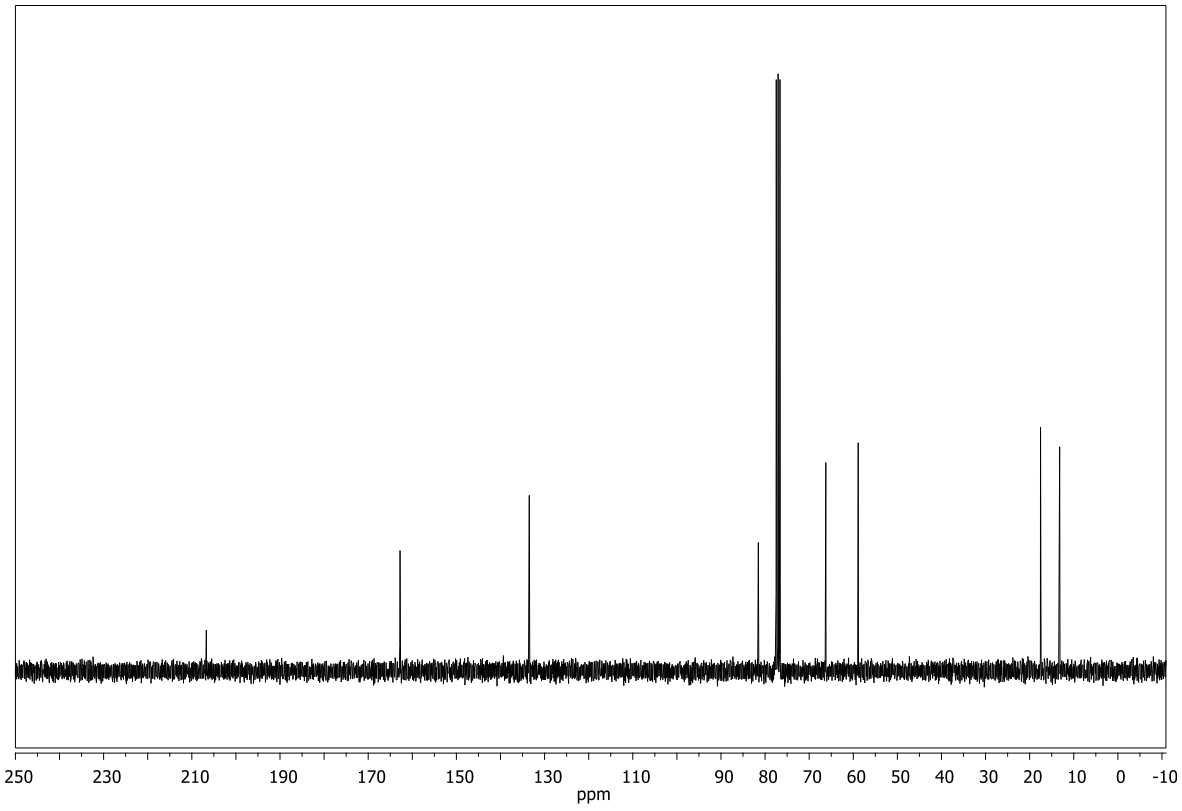


***trans*-5-ethyl-4-hydroxy-4-(hydroxymethyl)cyclopent-2-enone (178)**

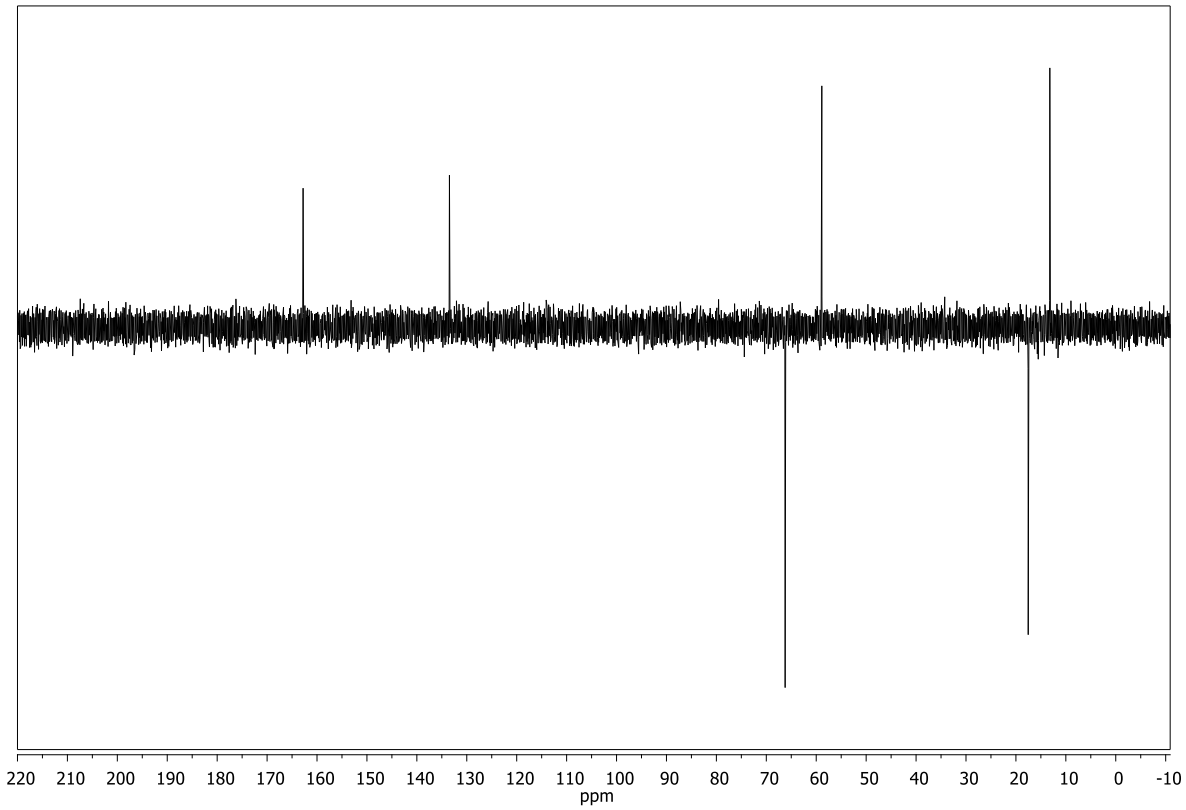
($CDCl_3$, 300 MHz)



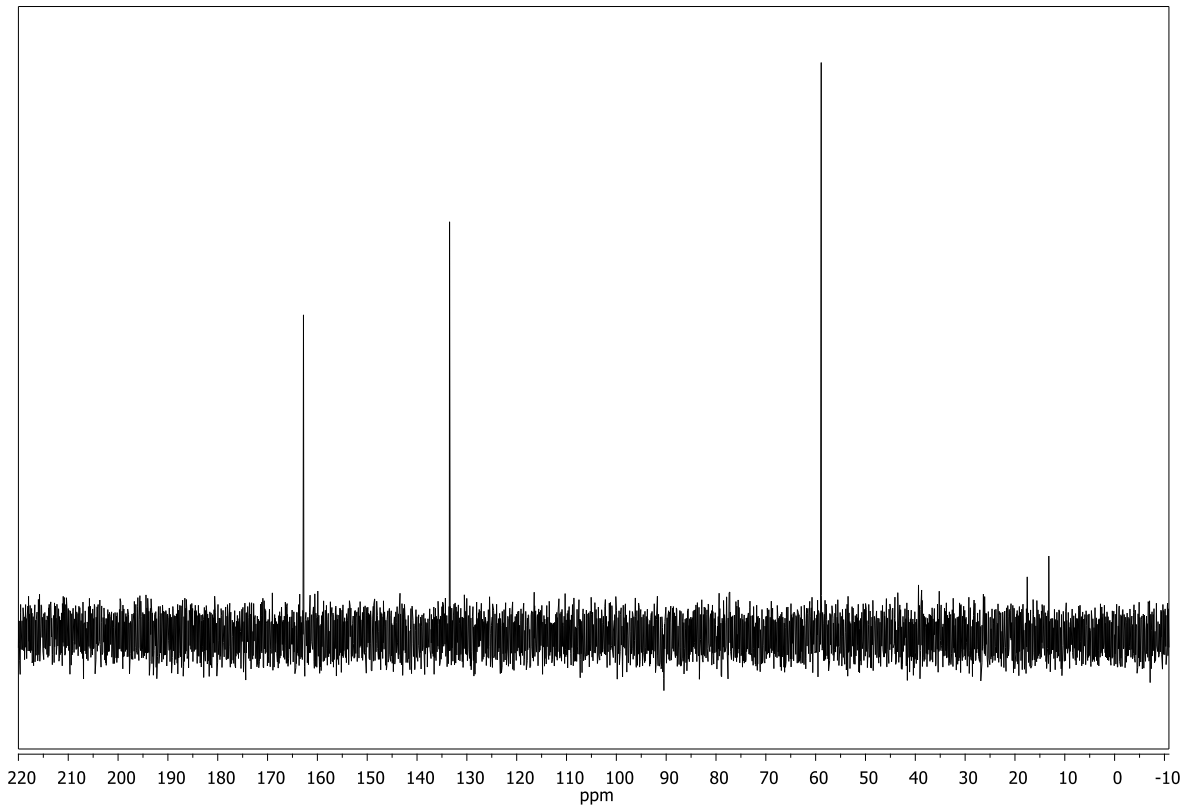
($CDCl_3$, 75 MHz)



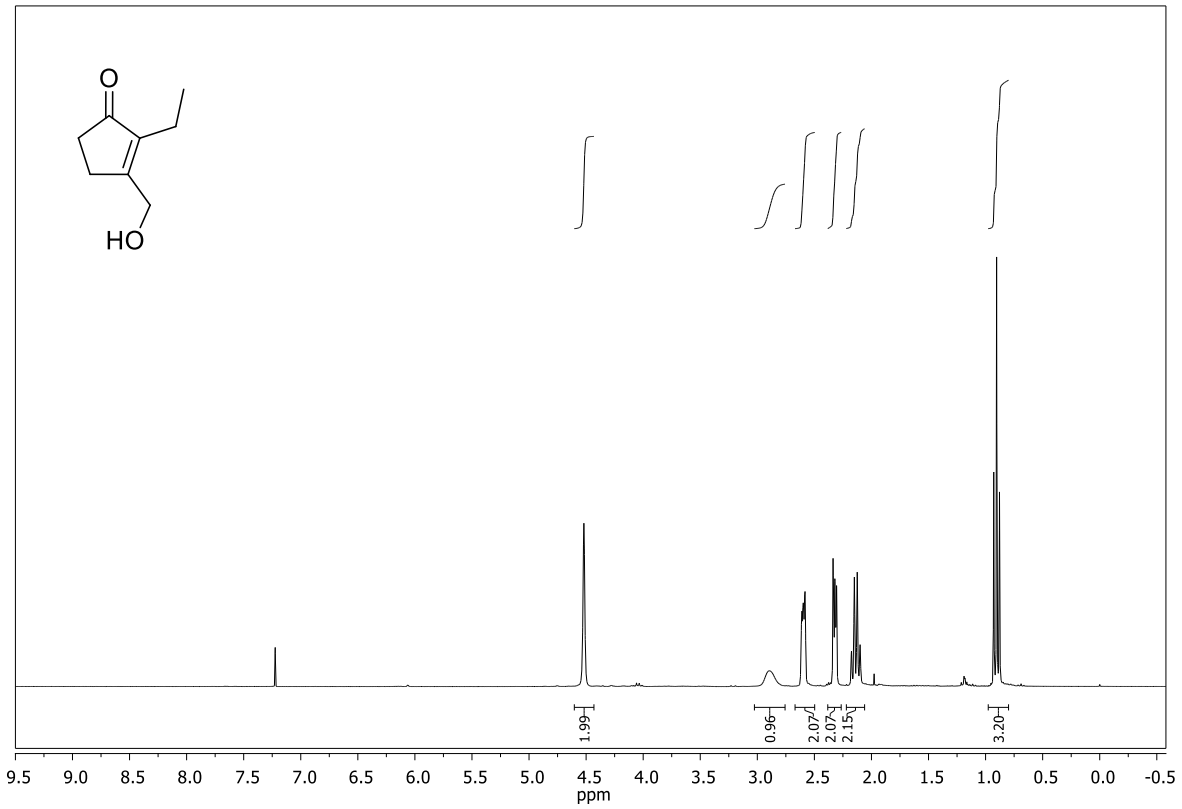
($CDCl_3$, 75 MHz)



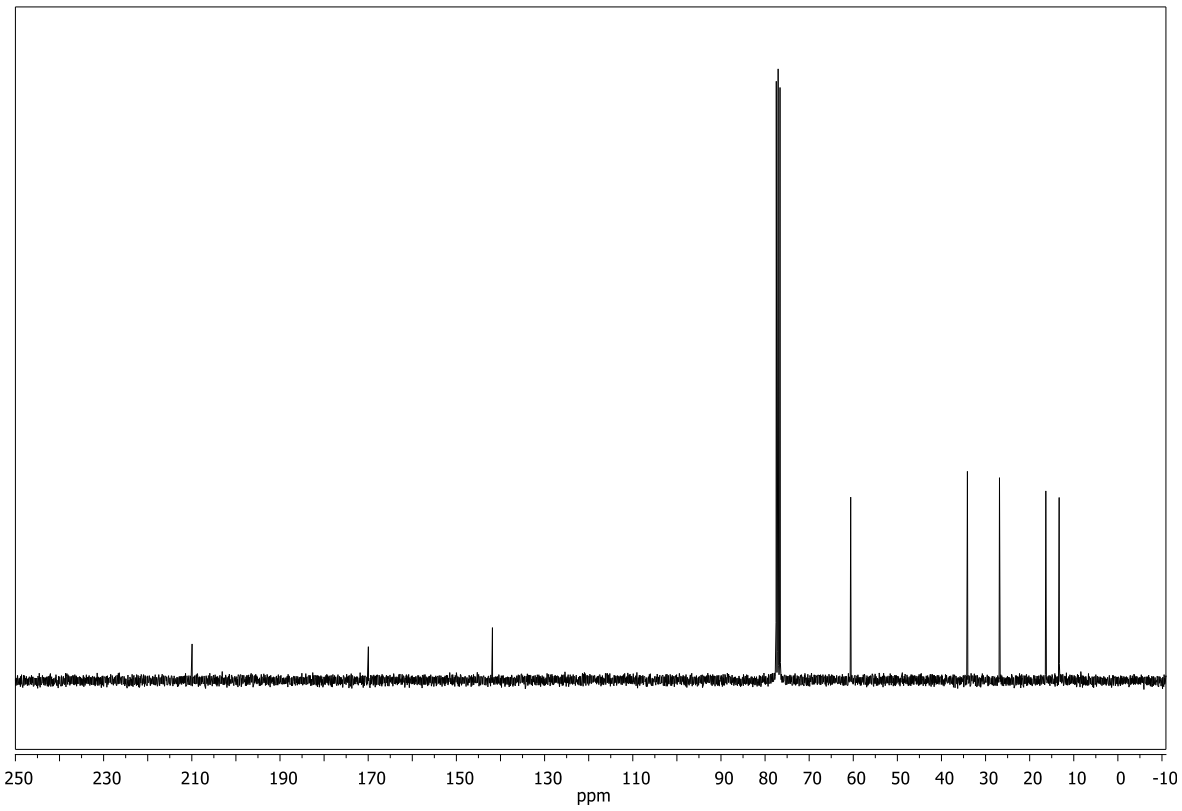
($CDCl_3$, 75 MHz)



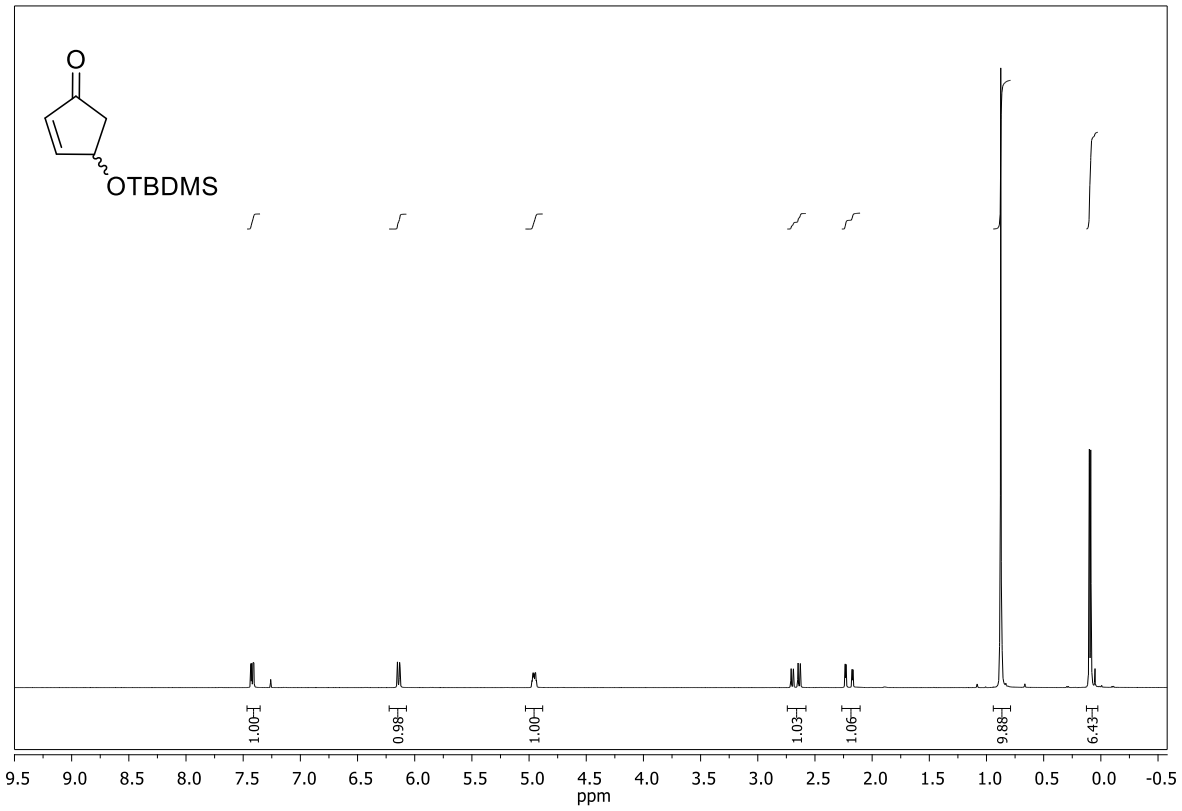
2-ethyl-3-(hydroxymethyl)cyclopent-2-enone (179) **($CDCl_3$, 300 MHz)**



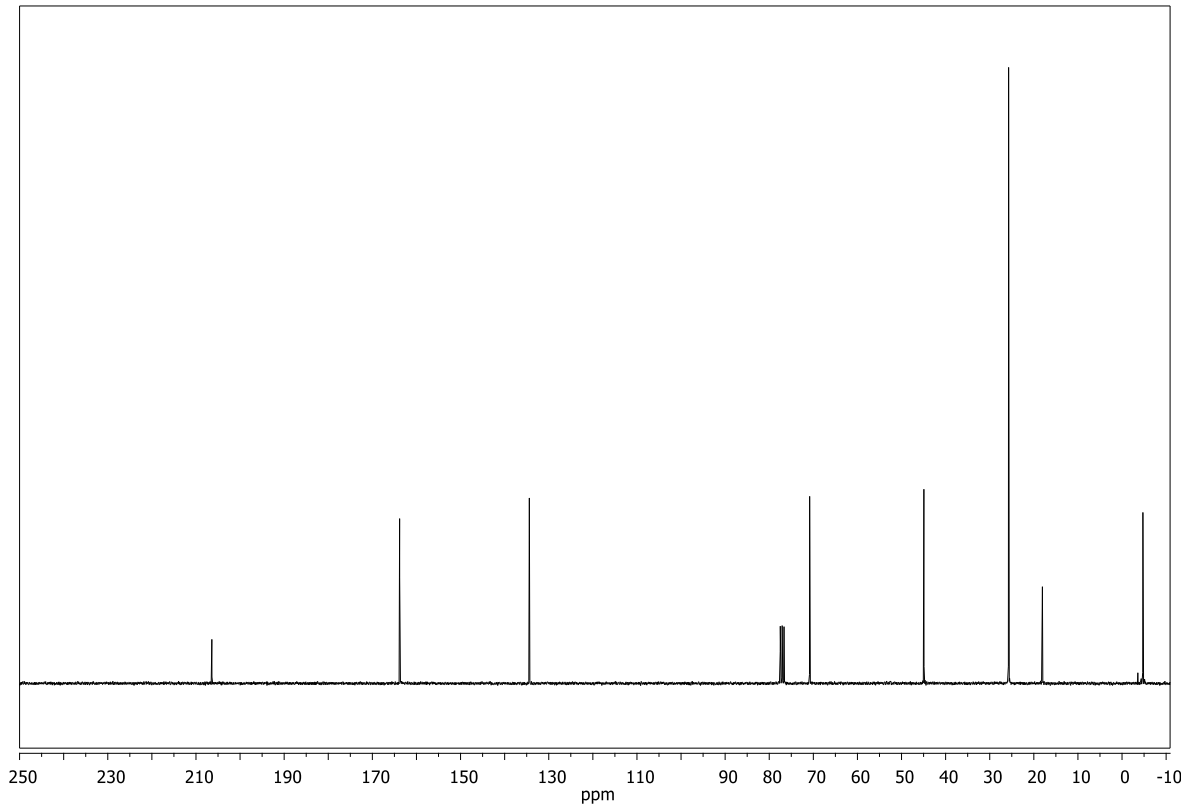
($CDCl_3$, 75 MHz)



(±)-4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-enone) (211) **($CDCl_3$, 300 MHz)**

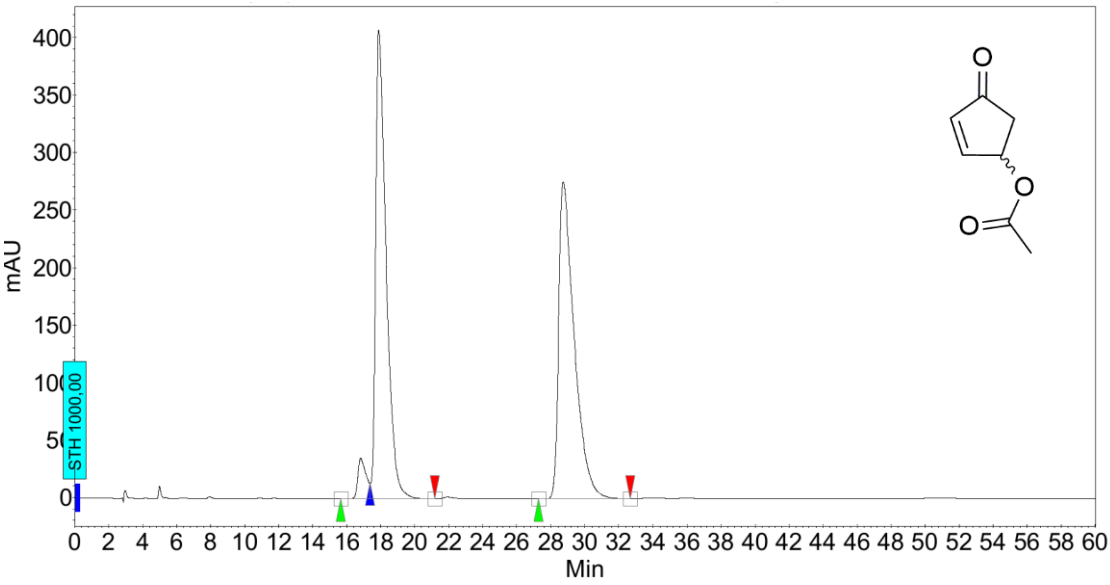


($CDCl_3$, 75 MHz)



2. HPLC Data

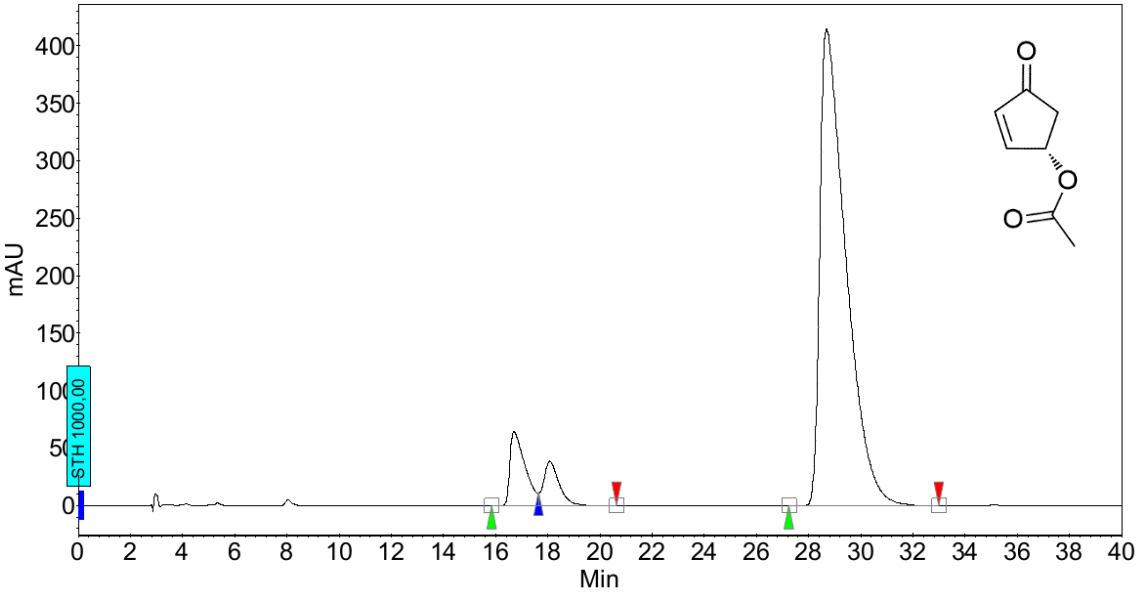
rac-4-acetoxycyclopent-2-enone (69a)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16,81	3,29	35,1	19,9	3,292
3	UNKNOWN	17,88	48,51	407,1	292,6	48,511
2	UNKNOWN	28,73	48,20	275,2	290,7	48,197
Total			100,00	717,4	603,1	100,000

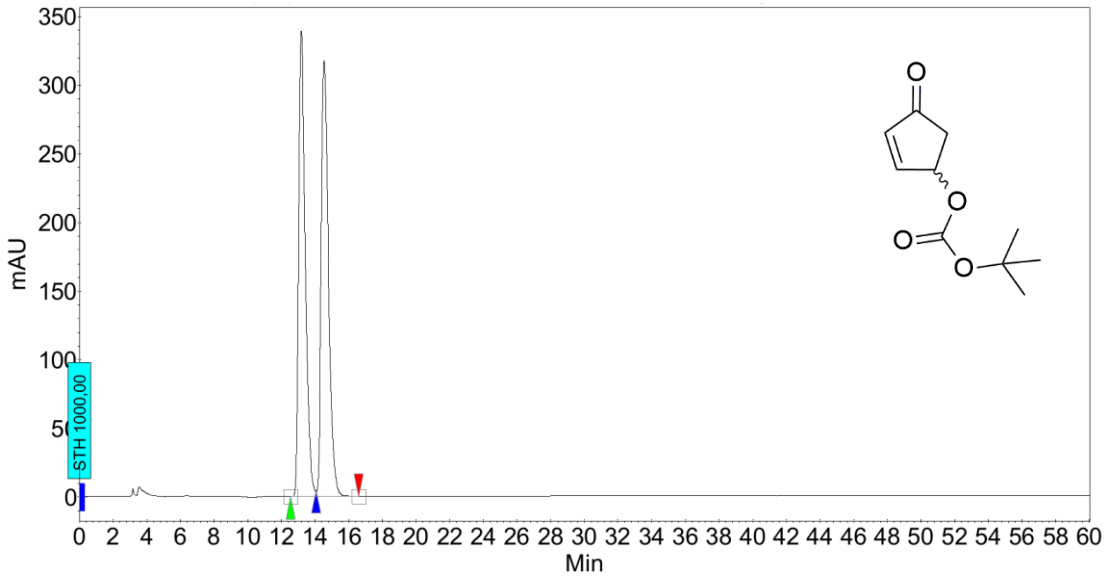
(S)-4-acetoxycyclopent-2-enone (69a) 90% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	16,70	7,91	64,6	43,4	7,910
2	UNKNOWN	18,08	4,82	38,7	26,4	4,816
3	UNKNOWN	28,69	87,27	414,9	478,6	87,274
Total			100,00	518,2	548,4	100,000

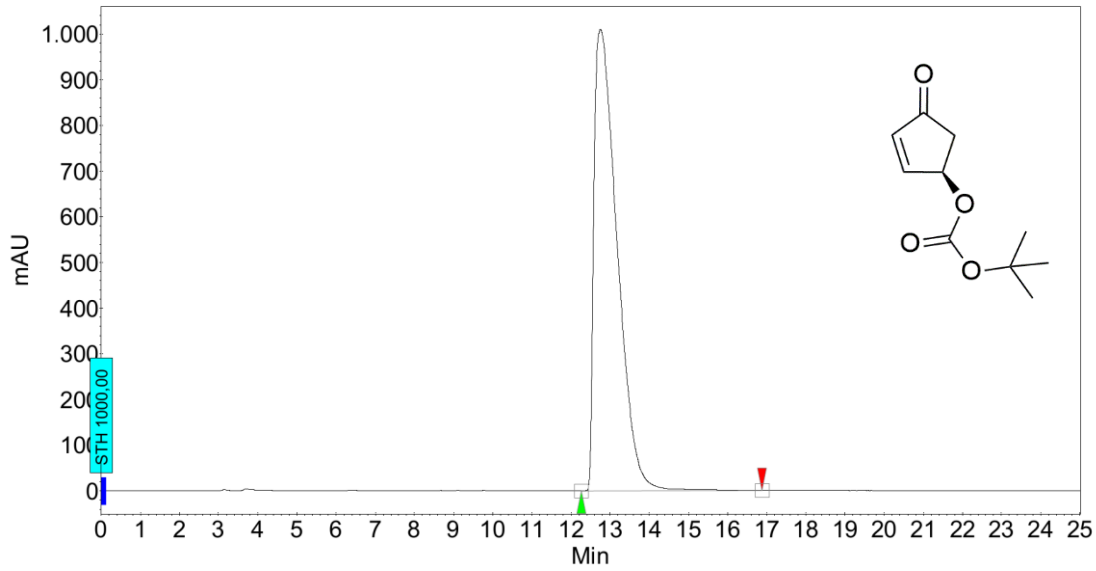
rac-4-(_tert_-butoxycarbonyloxy)-2-cyclopentenone (69b)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,17	49,72	339,4	156,7	49,715
2	UNKNOWN	14,53	50,28	317,7	158,5	50,285
Total			100,00	657,1	315,1	100,000

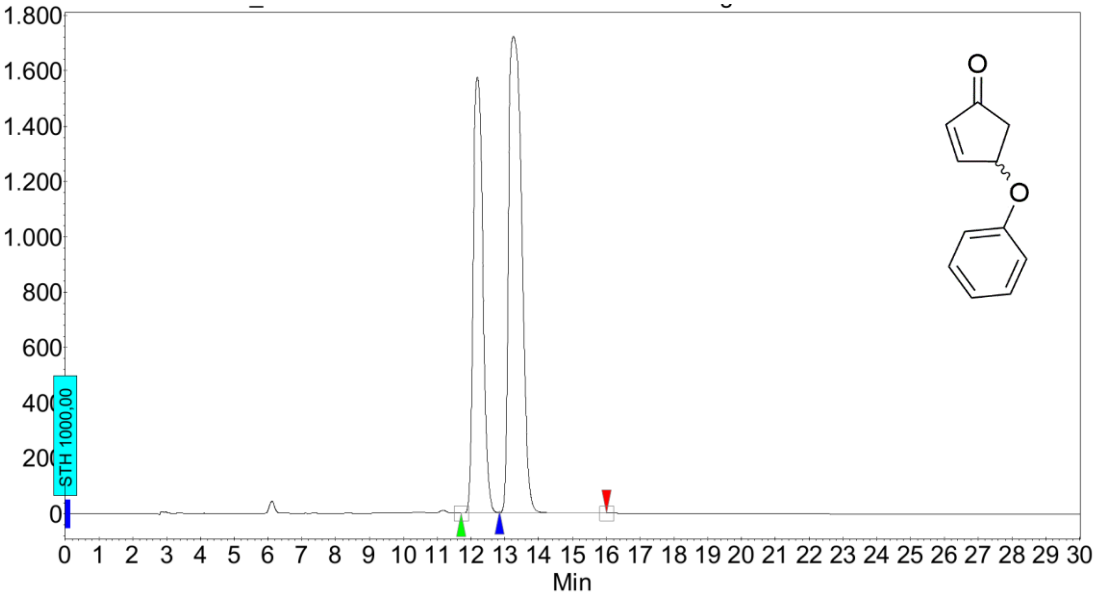
_(R)_-4-(_tert_-butoxycarbonyloxy)-2-cyclopentenone (69b) >99% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,75	100,00	1009,7	690,3	100,000
Total			100,00	1009,7	690,3	100,000

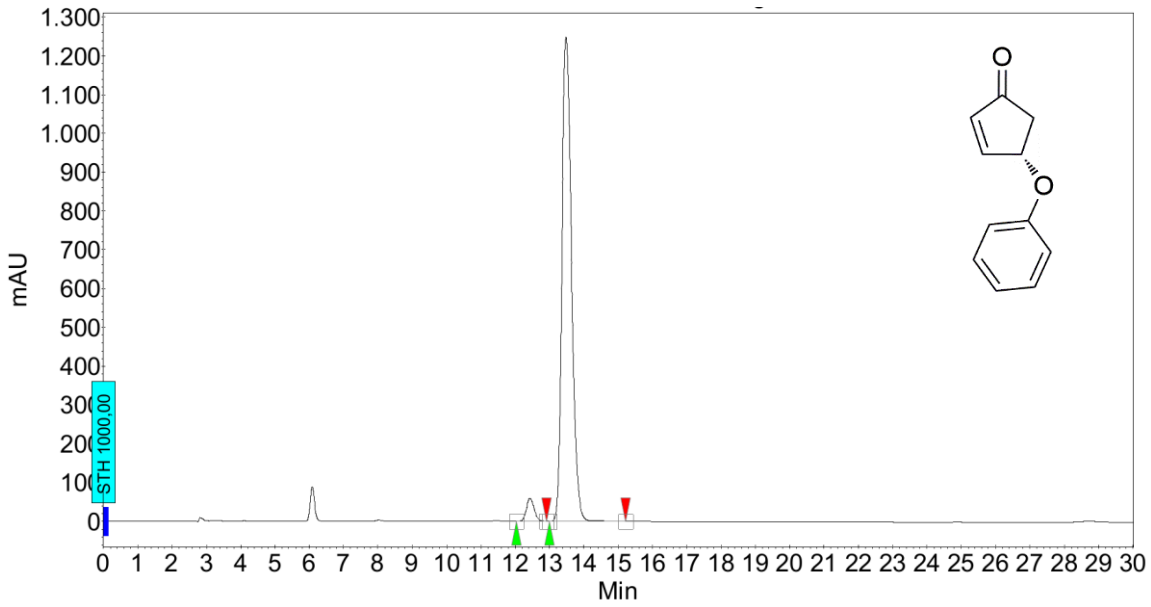
rac-4-phenoxycyclopent-2-enone (71b)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,19	40,23	1577,3	526,2	40,231
2	UNKNOWN	13,26	59,77	1724,0	781,7	59,769
Total			100,00	3301,3	1307,8	100,000

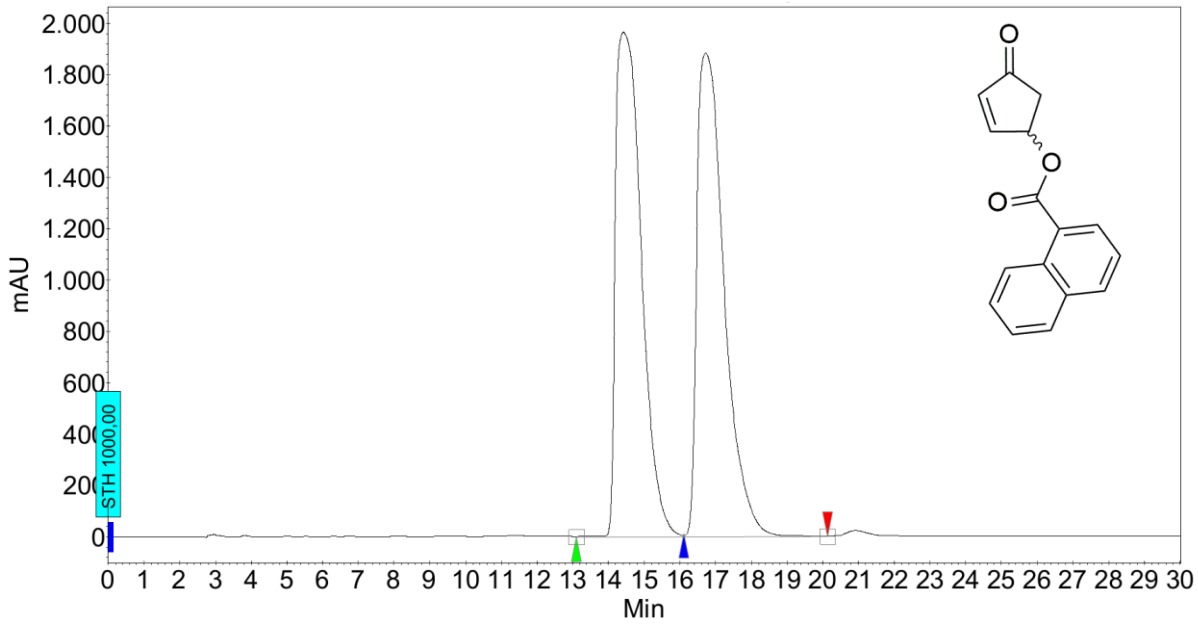
_(S)_-4-phenoxycyclopent-2-enone (71b) 93% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,43	3,76	59,6	15,8	3,762
2	UNKNOWN	13,48	96,24	1248,9	404,5	96,238
Total			100,00	1308,5	420,3	100,000

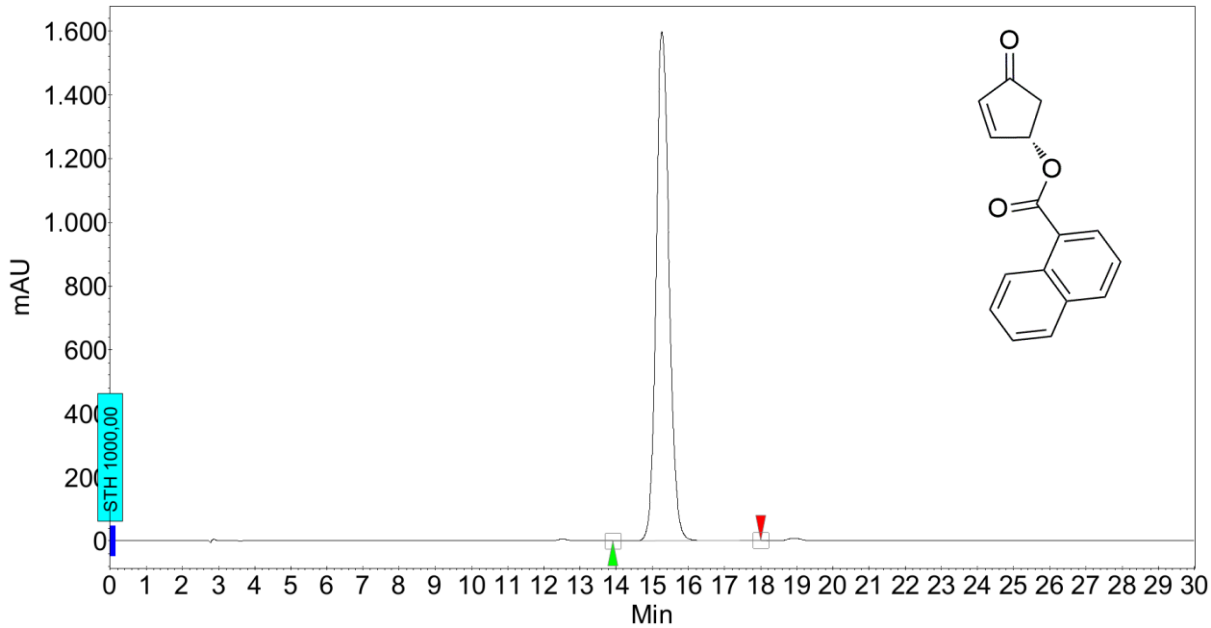
***rac*-4-(1-naphthoyl)oxycyclopent-2-enone (71c)**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14,42	49,68	1964,8	1640,2	49,681
2	UNKNOWN	16,72	50,32	1882,5	1661,3	50,319
Total			100,00	3847,4	3301,5	100,000

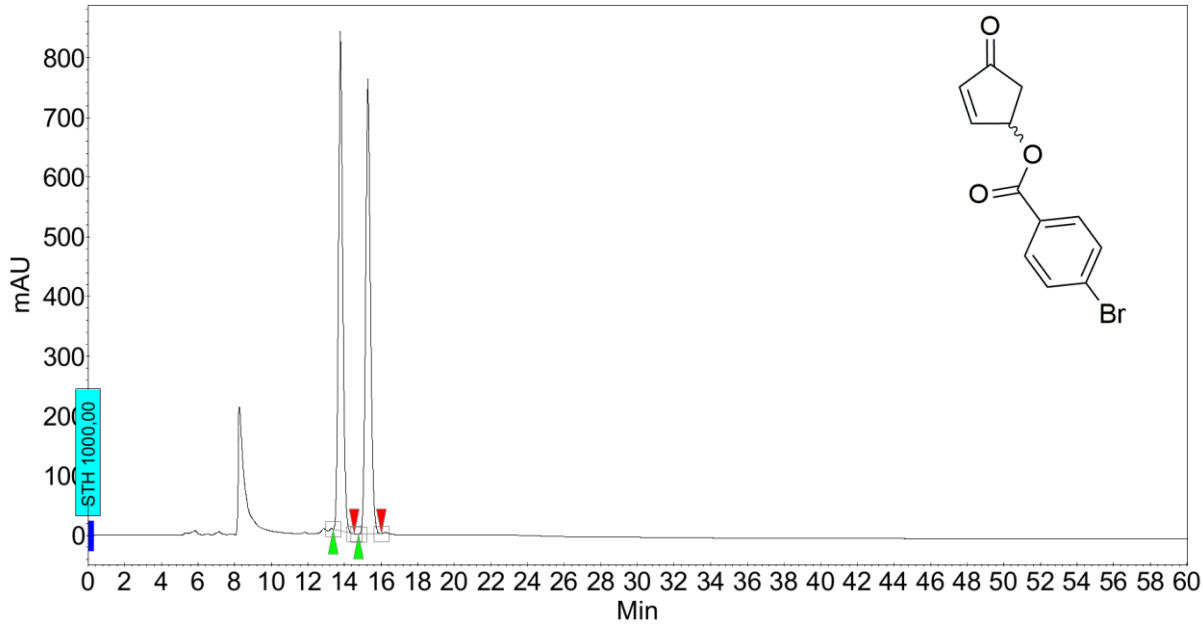
***(S)*-4-(1-naphthoyl)oxycyclopent-2-enone (71c) >99% ee**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15,27	100,00	1596,0	663,7	100,000
Total			100,00	1596,0	663,7	100,000

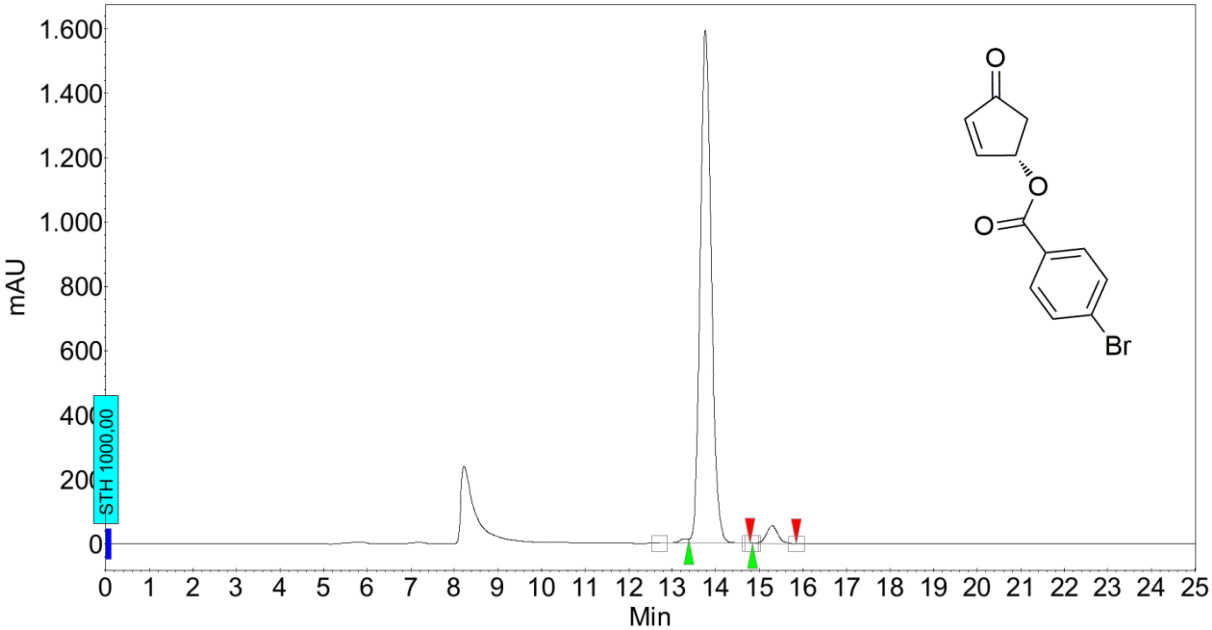
rac-4-(4-bromobenzoyl)oxycyclopent-2-enone (71d)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,78	49,54	838,6	238,6	49,538
2	UNKNOWN	15,28	50,46	763,0	243,1	50,462
Total			100,00	1601,5	481,7	100,000

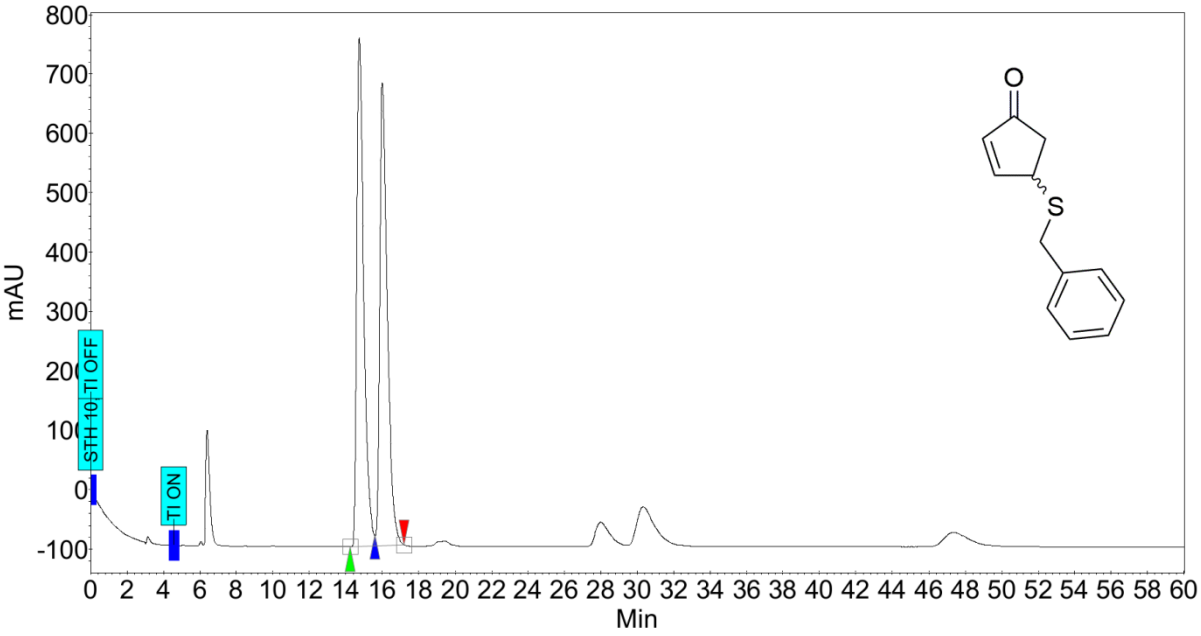
(*S*)-4-(4-bromobenzoyl)oxycyclopent-2-enone (71d) 93% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,76	96,54	1594,0	473,5	96,536
2	UNKNOWN	15,29	3,46	55,3	17,0	3,464
Total			100,00	1649,3	490,5	100,000

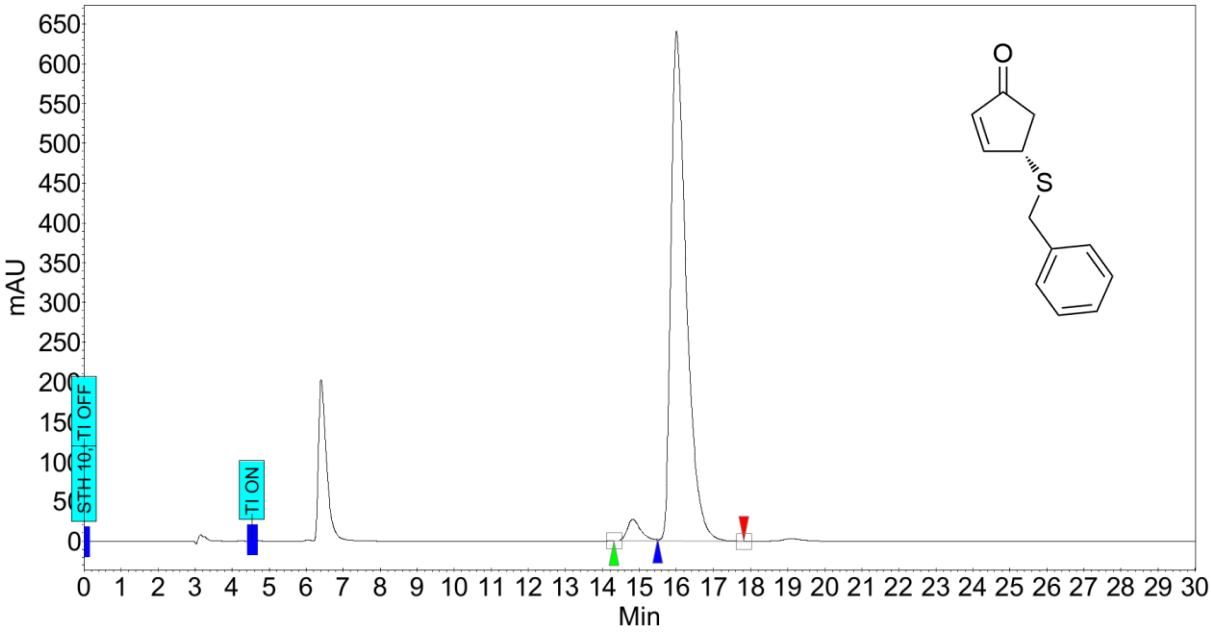
rac-4-(benzylthio)cyclopent-2-enone (71e)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.74	49.93	856.4	377.3	49.926
2	UNKNOWN	16.01	50.07	780.0	378.4	50.074
Total			100.00	1636.5	755.8	100.000

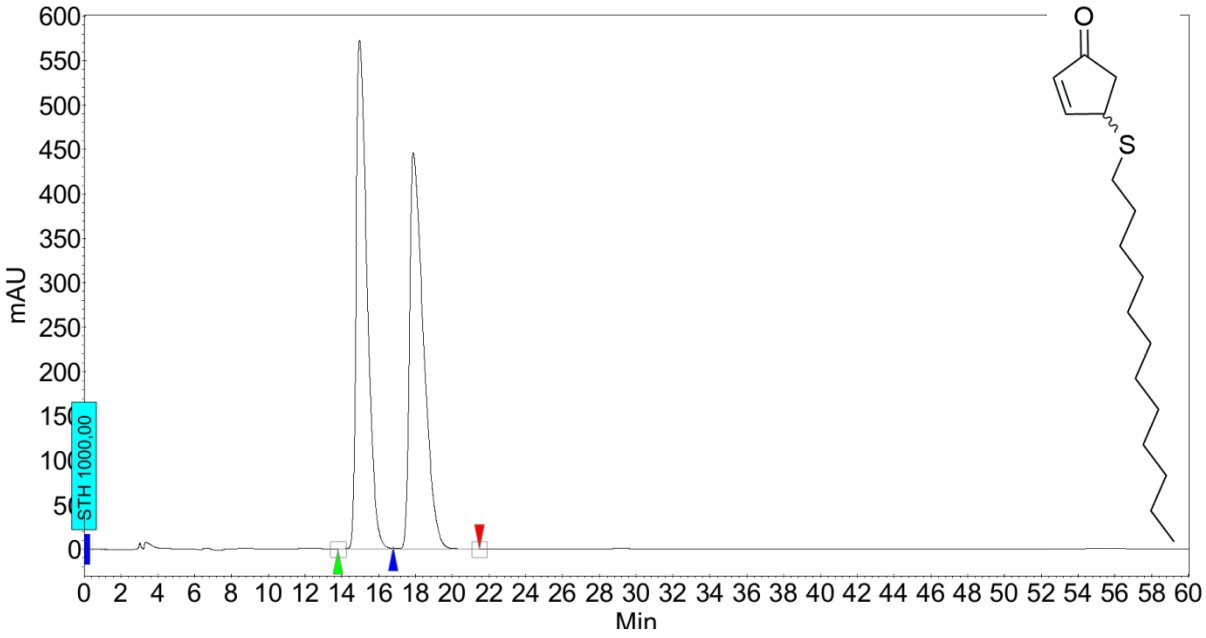
_(S)_-4-(benzylthio)cyclopent-2-enone (71e) 93% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.82	3.59	26.8	11.4	3.587
2	UNKNOWN	16.00	96.41	640.8	307.4	96.413
Total			100.00	667.6	318.8	100.000

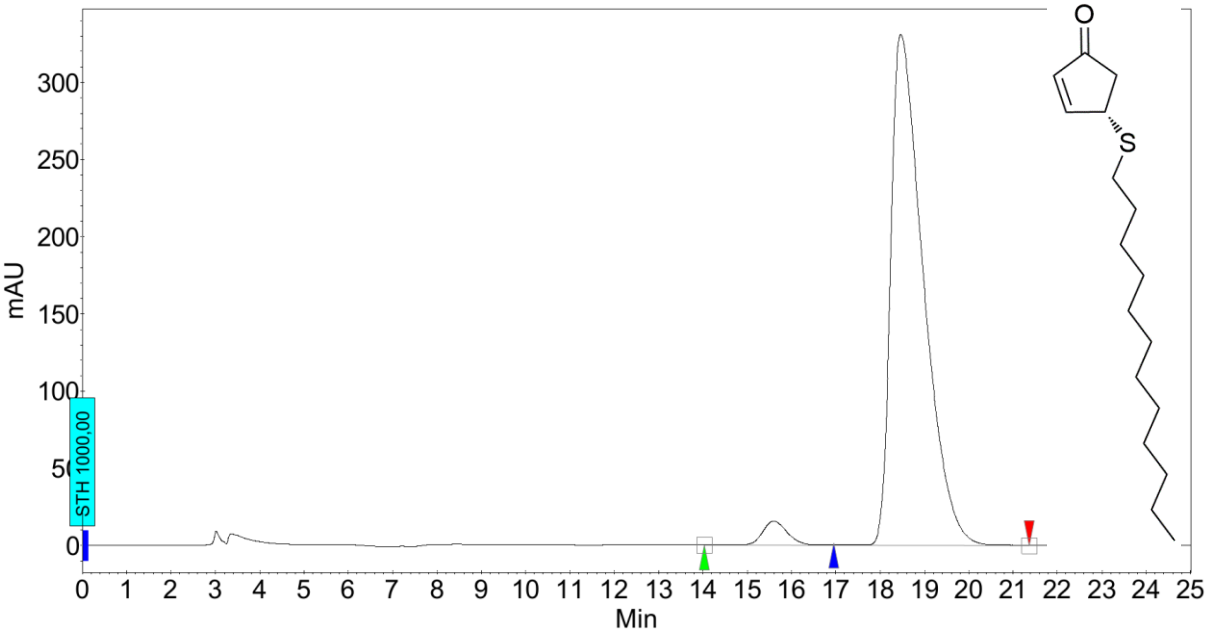
***rac*-4-(dodecylthio)cyclopent-2-enone (71f)**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.96	50.06	572.6	395.4	50.065
2	UNKNOWN	17.89	49.94	446.4	394.3	49.935
Total			100.00	1019.0	789.7	100.000

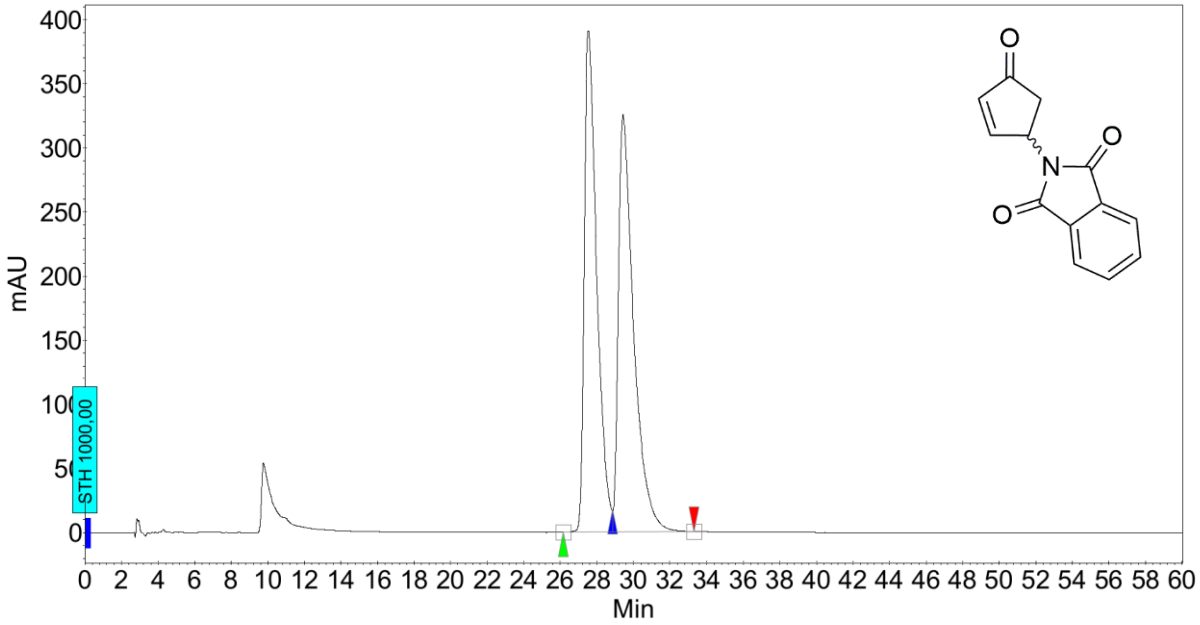
***(S)*-4-(dodecylthio)cyclopent-2-enone (71f) 93% ee**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15.60	3.52	15.6	10.3	3.519
2	UNKNOWN	18.47	96.48	330.9	281.4	96.481
Total			100.00	346.5	291.6	100.000

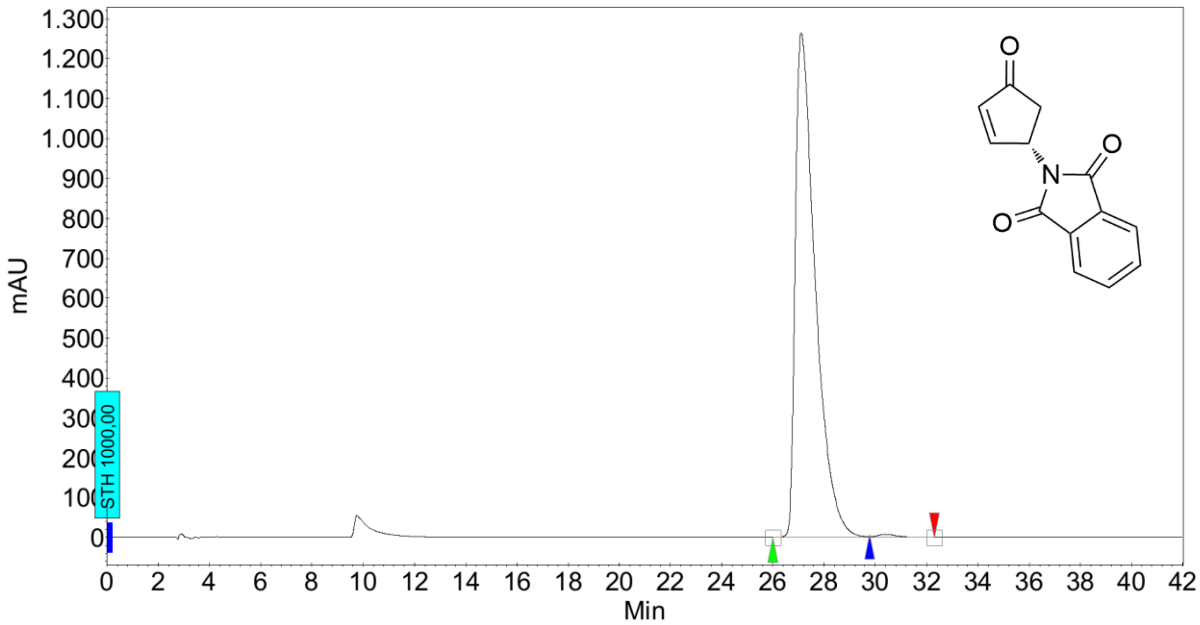
***rac*-4-phthalimidylcyclopent-2-enone (71g)**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27,54	49,48	391,5	309,4	49,484
2	UNKNOWN	29,43	50,52	326,0	315,9	50,516
Total			100,00	717,5	625,3	100,000

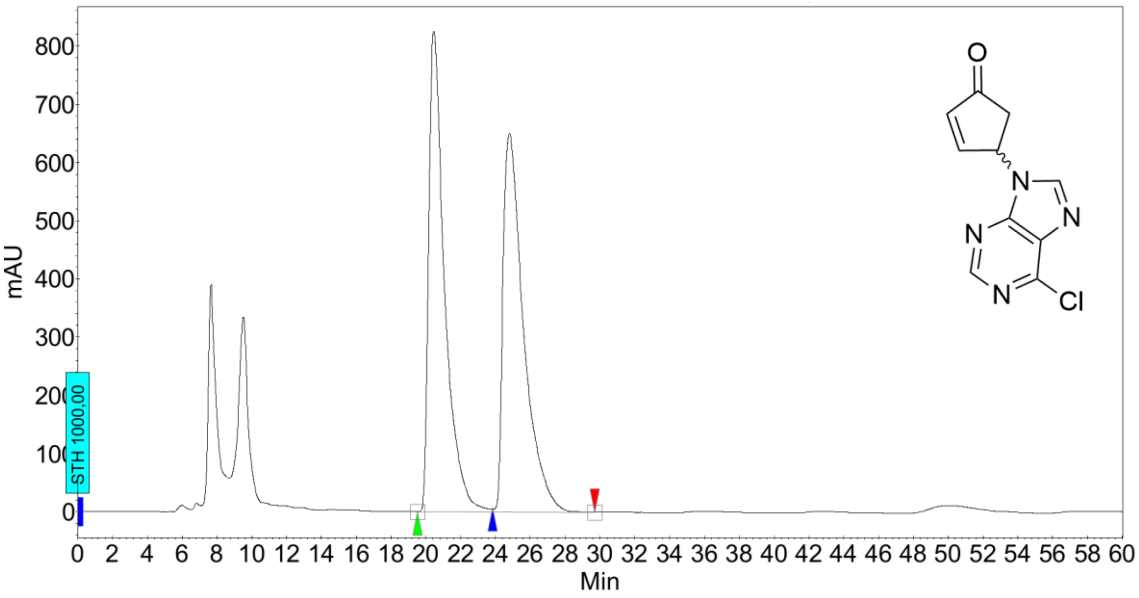
***(S)*-4-phthalimidylcyclopent-2-enone (71g) 99% ee**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27,10	99,30	1265,2	1144,4	99,296
2	UNKNOWN	30,39	0,70	8,0	8,1	0,704
Total			100,00	1273,2	1152,5	100,000

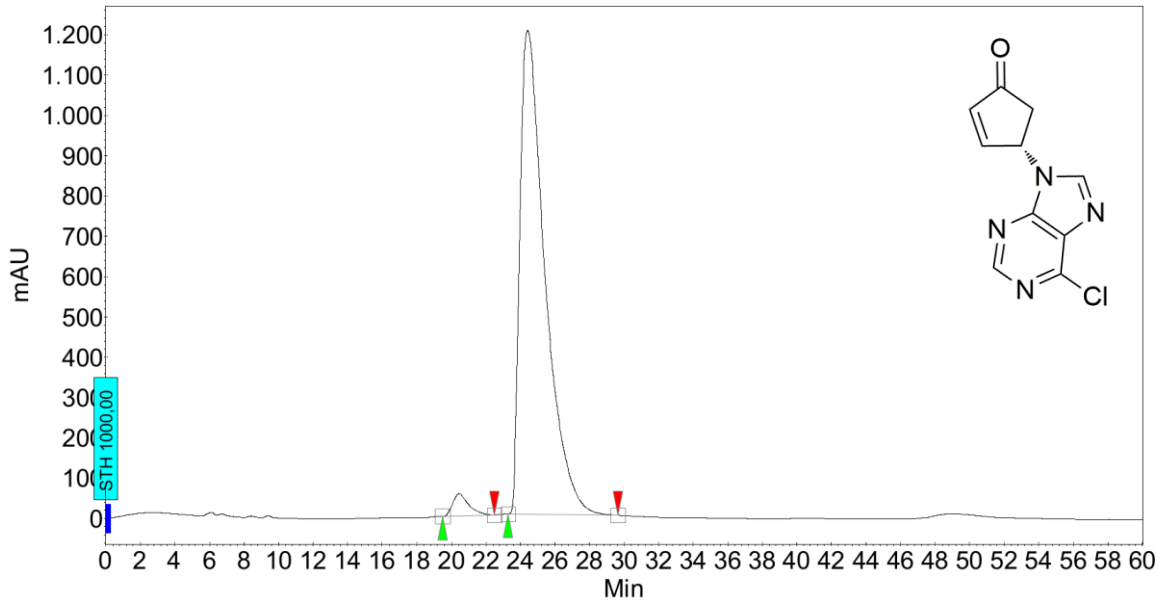
***rac*-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone (71h)**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.46	49.54	826.2	874.2	49.539
2	UNKNOWN	24.80	50.46	650.2	890.5	50.461
Total			100.00	1476.3	1764.7	100.000

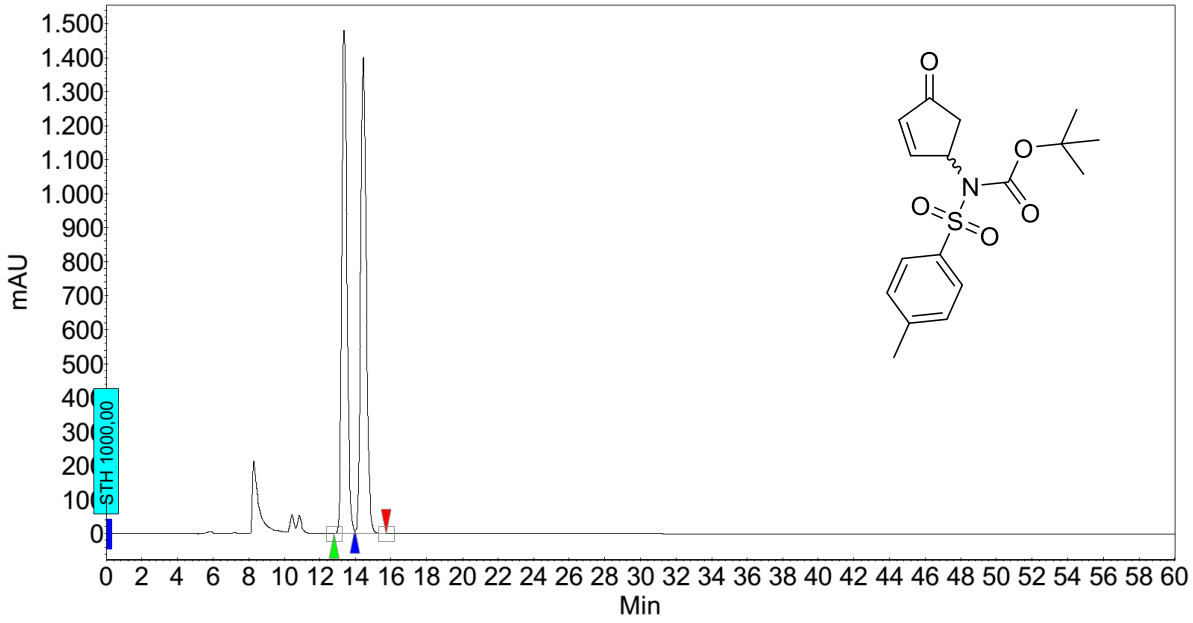
***(S)*-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone (71h) 94% ee**



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.45	2.82	55.0	58.4	2.816
2	UNKNOWN	24.42	97.18	1200.1	2016.6	97.184
Total			100.00	1255.1	2075.0	100.000

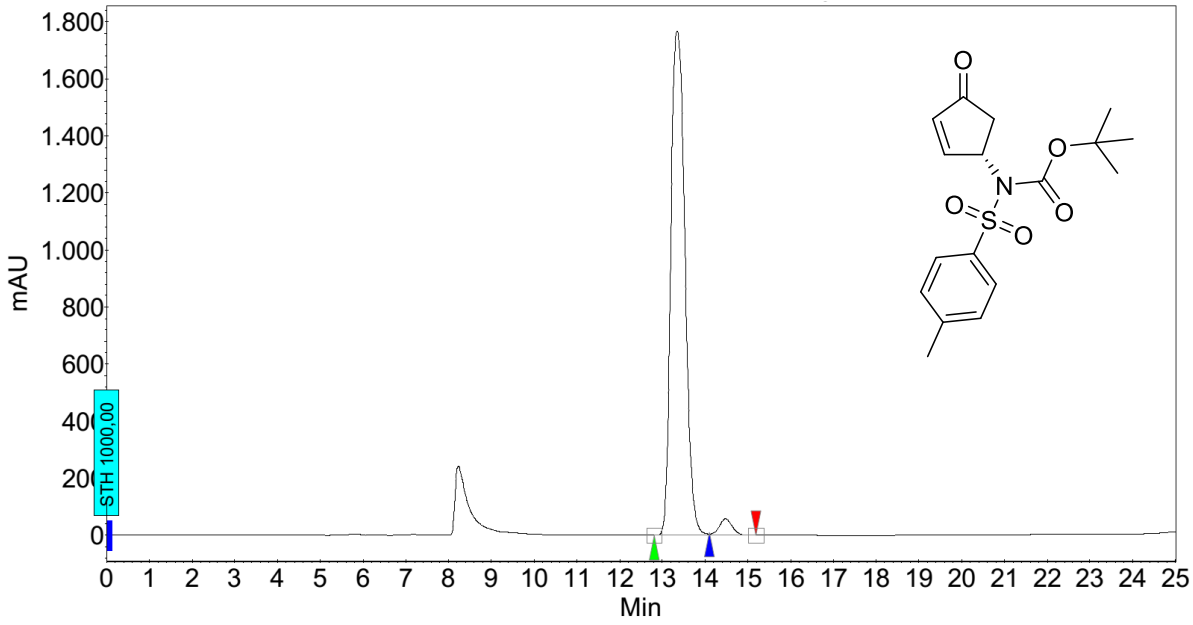
rac-4-(*N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonylamino)cyclopent-2-enone (71j)



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,36	49,58	1478,5	505,5	49,579
2	UNKNOWN	14,43	50,42	1398,9	514,0	50,421
Total			100,00	2877,3	1019,5	100,000

(*S*)-4-(*N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonylamino)cyclopent-2-enone (71j) 94% ee



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,35	97,00	1767,0	674,6	97,004
2	UNKNOWN	14,48	3,00	57,9	20,8	2,996
Total			100,00	1824,9	695,5	100,000

3. Crystallographic Data

(S)-4-Phthalimidylcyclopent-2-enone (71g)

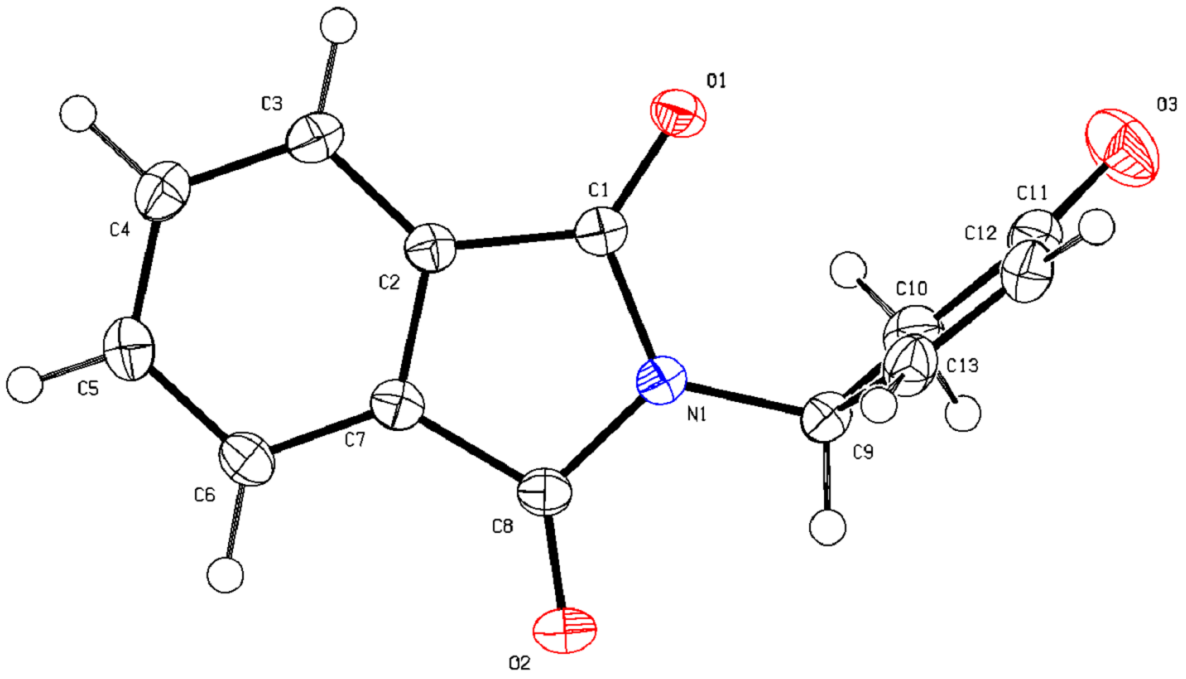


Table 1. Crystal data and structure refinement for **71g**.

Empirical formula	$C_{13}H_9NO_3$	
Formula weight	227.21	
Crystal size	0.28 x 0.10 x 0.09 mm	
Crystal description	rod	
Crystal colour	colourless	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.3790(1) Å	alpha = 90 deg.
	b = 9.7970(1) Å	beta = 90 deg.
	c = 12.8620(2) Å	gamma = 90 deg.
Volume	1055.83(2) $Å^3$	
Z	4	
Calculated density	1.429 Mg/m^3	
Absorption coefficient	0.856 mm^{-1}	
F(000)	472	
Measurement device type	SuperNova, Single source at offset, Atlas	
Measurement method	\w scans	
Temperature	123(1) K	
Wavelength	1.54178 Å	
Monochromator	graphite	
Theta range for data collection	5.68 to 74.93 deg.	
Index ranges	-9<=h<=10, -12<=k<=12, -16<=l<=15	
Reflections collected / unique	9890 / 2156 [R(int) = 0.0282]	

Reflections greater >2\s(i)	2121
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.81056
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	refall
Data / restraints / parameters	2156 / 0 / 190
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0829
R indices (all data)	R1 = 0.0325, wR2 = 0.0837
Absolute structure parameter	-0.09(19)
Largest diff. peak and hole	0.136 and -0.217 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x10^3) for **71g**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8337(1)	2227(1)	7474(1)	22(1)
O(2)	5725(1)	2221(1)	4346(1)	29(1)
O(3)	5970(2)	5349(1)	8759(1)	44(1)
N(1)	6899(1)	2559(1)	5960(1)	20(1)
C(1)	7894(1)	1830(1)	6624(1)	18(1)
C(2)	8225(2)	508(1)	6101(1)	18(1)
C(3)	9145(2)	-593(1)	6411(1)	22(1)
C(4)	9231(2)	-1700(2)	5729(1)	26(1)
C(5)	8404(2)	-1704(2)	4789(1)	26(1)
C(6)	7470(2)	-591(1)	4489(1)	22(1)
C(7)	7413(2)	507(1)	5161(1)	20(1)
C(8)	6557(2)	1824(1)	5053(1)	20(1)
C(9)	6239(2)	3906(1)	6187(1)	23(1)
C(10)	5344(2)	3982(2)	7231(1)	28(1)
C(11)	6242(2)	5047(2)	7859(1)	27(1)
C(12)	7478(2)	5639(2)	7189(1)	28(1)
C(13)	7516(2)	4989(2)	6285(1)	27(1)

Table 3. Bond lengths [Å] and angles [deg] for **71g**.

O(1)-C(1)	1.2175(16)
O(2)-C(8)	1.2096(17)
O(3)-C(11)	1.2167(18)
N(1)-C(1)	1.3913(17)
N(1)-C(8)	1.4004(17)
N(1)-C(9)	1.4607(18)
C(1)-C(2)	1.4851(18)
C(2)-C(3)	1.3842(19)
C(2)-C(7)	1.3880(18)
C(3)-C(4)	1.397(2)
C(4)-C(5)	1.394(2)
C(5)-C(6)	1.396(2)
C(6)-C(7)	1.3811(19)
C(7)-C(8)	1.4829(19)
C(9)-C(10)	1.540(2)
C(9)-C(13)	1.512(2)
C(10)-C(11)	1.519(2)
C(11)-C(12)	1.467(2)
C(12)-C(13)	1.326(2)
C(3)-H(1)	0.989(17)
C(4)-H(2)	0.995(17)
C(5)-H(3)	0.957(18)
C(6)-H(4)	1.021(17)

C(9)-H(5)	0.955(16)
C(10)-H(6)	0.970(19)
C(10)-H(7)	0.99(2)
C(12)-H(8)	0.947(19)
C(13)-H(9)	0.97(2)

C(1)-N(1)-C(8)	111.75(11)
C(1)-N(1)-C(9)	124.62(10)
C(8)-N(1)-C(9)	123.61(11)
O(1)-C(1)-N(1)	124.70(12)
O(1)-C(1)-C(2)	128.93(12)
N(1)-C(1)-C(2)	106.34(10)
C(1)-C(2)-C(3)	130.79(12)
C(1)-C(2)-C(7)	107.69(11)
C(3)-C(2)-C(7)	121.53(12)
C(2)-C(3)-C(4)	116.97(12)
C(3)-C(4)-C(5)	121.42(13)
C(4)-C(5)-C(6)	121.06(13)
C(5)-C(6)-C(7)	117.07(12)
C(2)-C(7)-C(6)	121.94(12)
C(2)-C(7)-C(8)	108.55(11)
C(6)-C(7)-C(8)	129.51(12)
O(2)-C(8)-N(1)	125.37(13)
O(2)-C(8)-C(7)	128.96(13)

N(1)-C(8)-C(7)	105.67(11)
N(1)-C(9)-C(10)	113.71(11)
N(1)-C(9)-C(13)	112.51(12)
C(10)-C(9)-C(13)	103.76(11)
C(9)-C(10)-C(11)	104.80(12)
O(3)-C(11)-C(10)	125.44(14)
O(3)-C(11)-C(12)	126.55(14)
C(10)-C(11)-C(12)	108.01(12)
C(11)-C(12)-C(13)	110.00(14)
C(9)-C(13)-C(12)	113.17(14)
C(2)-C(3)-H(1)	121.6(10)
C(4)-C(3)-H(1)	121.4(10)
C(3)-C(4)-H(2)	118.0(10)
C(5)-C(4)-H(2)	120.6(10)
C(4)-C(5)-H(3)	120.8(11)
C(6)-C(5)-H(3)	118.1(11)
C(5)-C(6)-H(4)	122.4(10)
C(7)-C(6)-H(4)	120.5(10)
N(1)-C(9)-H(5)	103.6(10)
C(10)-C(9)-H(5)	113.6(10)
C(13)-C(9)-H(5)	109.9(10)
C(9)-C(10)-H(6)	113.1(11)
C(9)-C(10)-H(7)	109.9(12)
C(11)-C(10)-H(6)	109.6(11)

C(11)-C(10)-H(7)	110.7(12)
H(6)-C(10)-H(7)	108.7(16)
C(11)-C(12)-H(8)	122.6(11)
C(13)-C(12)-H(8)	127.4(11)
C(9)-C(13)-H(9)	119.8(13)
C(12)-C(13)-H(9)	127.0(13)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **71g**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	23(1)	17(1)	0(1)	-2(1)	-2(1)
O(2)	31(1)	32(1)	24(1)	1(1)	-10(1)	5(1)
O(3)	46(1)	57(1)	30(1)	-13(1)	8(1)	0(1)
N(1)	20(1)	20(1)	20(1)	0(1)	-2(1)	2(1)
C(1)	16(1)	19(1)	19(1)	3(1)	1(1)	-3(1)
C(2)	16(1)	19(1)	20(1)	1(1)	-1(1)	-3(1)
C(3)	20(1)	22(1)	25(1)	4(1)	-2(1)	-1(1)
C(4)	24(1)	21(1)	32(1)	2(1)	-1(1)	1(1)
C(5)	27(1)	21(1)	29(1)	-4(1)	2(1)	-2(1)
C(6)	22(1)	25(1)	21(1)	-2(1)	0(1)	-4(1)
C(7)	18(1)	21(1)	20(1)	1(1)	0(1)	-3(1)
C(8)	18(1)	22(1)	19(1)	1(1)	-1(1)	-1(1)
C(9)	25(1)	21(1)	22(1)	1(1)	-2(1)	5(1)
C(10)	24(1)	32(1)	28(1)	0(1)	3(1)	5(1)
C(11)	28(1)	28(1)	26(1)	-2(1)	-1(1)	8(1)
C(12)	32(1)	20(1)	32(1)	0(1)	-1(1)	3(1)
C(13)	34(1)	21(1)	28(1)	4(1)	4(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **71g**.

	x	y	z	U(eq)
H(1)	9710(20)	-600(17)	7086(13)	21(4)
H(2)	9870(20)	-2507(18)	5946(13)	26(4)
H(3)	8430(20)	-2485(19)	4342(14)	32(5)
H(4)	6850(20)	-574(18)	3806(13)	23(4)
H(5)	5580(20)	4095(18)	5599(12)	21(4)
H(6)	5340(20)	3122(19)	7605(15)	29(4)
H(7)	4230(30)	4270(20)	7114(16)	43(5)
H(8)	8150(20)	6360(20)	7410(14)	38(5)
H(9)	8220(30)	5170(20)	5707(16)	37(5)

Table 6. Torsion angles [deg] for **71g**.

C(8)-N(1)-C(1)-O(1)	-178.14(12)
C(9)-N(1)-C(1)-O(1)	-0.1(2)
C(8)-N(1)-C(1)-C(2)	0.00(14)
C(9)-N(1)-C(1)-C(2)	178.05(11)
C(9)-N(1)-C(8)-C(7)	-177.80(11)
C(1)-N(1)-C(9)-C(10)	-53.58(17)
C(8)-N(1)-C(9)-C(10)	124.25(13)
C(1)-N(1)-C(9)-C(13)	64.01(16)
C(1)-N(1)-C(8)-O(2)	-179.80(13)
C(9)-N(1)-C(8)-O(2)	2.1(2)
C(1)-N(1)-C(8)-C(7)	0.28(14)
C(8)-N(1)-C(9)-C(13)	-118.16(14)
O(1)-C(1)-C(2)-C(3)	-2.3(2)
N(1)-C(1)-C(2)-C(3)	179.70(13)
N(1)-C(1)-C(2)-C(7)	-0.30(14)
O(1)-C(1)-C(2)-C(7)	177.73(13)
C(1)-C(2)-C(3)-C(4)	-179.41(13)
C(7)-C(2)-C(3)-C(4)	0.6(2)
C(1)-C(2)-C(7)-C(6)	-179.58(12)
C(1)-C(2)-C(7)-C(8)	0.47(14)
C(3)-C(2)-C(7)-C(6)	0.4(2)
C(3)-C(2)-C(7)-C(8)	-179.53(12)
C(2)-C(3)-C(4)-C(5)	-1.1(2)

C(3)-C(4)-C(5)-C(6)	0.7(2)
C(4)-C(5)-C(6)-C(7)	0.4(2)
C(5)-C(6)-C(7)-C(8)	179.05(13)
C(5)-C(6)-C(7)-C(2)	-0.9(2)
C(2)-C(7)-C(8)-O(2)	179.62(14)
C(6)-C(7)-C(8)-O(2)	-0.3(2)
C(6)-C(7)-C(8)-N(1)	179.58(13)
C(2)-C(7)-C(8)-N(1)	-0.47(14)
N(1)-C(9)-C(10)-C(11)	119.60(13)
C(13)-C(9)-C(10)-C(11)	-2.95(15)
N(1)-C(9)-C(13)-C(12)	-123.44(14)
C(10)-C(9)-C(13)-C(12)	-0.10(18)
C(9)-C(10)-C(11)-O(3)	-175.17(15)
C(9)-C(10)-C(11)-C(12)	4.89(16)
O(3)-C(11)-C(12)-C(13)	174.86(16)
C(10)-C(11)-C(12)-C(13)	-5.20(18)
C(11)-C(12)-C(13)-C(9)	3.31(19)

Table 7. Hydrogen-bonds for **71g** [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(2)...O(1)#1	0.995(17)	2.541(17)	3.2562(18)	128.6(13)
C(6)-H(4)...O(1)#2	1.021(17)	2.363(17)	3.1218(16)	130.3(13)
C(9)-H(5)...O(2)	0.955(16)	2.446(17)	2.9184(17)	110.4(12)

4. Curriculum Vitae

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Date of birth:	06.07.1983 in Ulm, Germany
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Education:

1.10.2009–30.06.2013	**PhD thesis** at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser "The Conversion of Furan Derivatives from Renewable Resources into valuable Building Blocks and their Application in Synthetic Chemistry"
30.09.2009	**Graduation: Master of Science** in chemistry
1.2009–30.09.2009	**Master thesis** at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser "Konversion von nachwachsenden Rohstoffen in der nachhaltigen Chemie: Mikrowellenunterstützte Umwandlung von Furfurylalkohol"
5.11.2007	**Bachelor of Science** in chemistry
15.10.2004–30.09.2009	**Studies in Chemistry**, University of Regensburg, Germany
2004	**Abitur** (A-levels)
1994–2004	Nikolaus-Kopernikus-Gymnasium, Weißenhorn, Germany (High-school certificate equivalent)
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5. List of Publications

1) **Microwave- or Microreactor-Assisted Conversion of Furfuryl Alcohols into 4-Hydroxy-2-cyclopentenones**

Kathrin Ulbrich, Peter Kreitmeier, Oliver Reiser

Synlett **2010**, 2037–2040.

2) **Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones**

Kathrin Ulbrich, Peter Kreitmeier, Tirayut Vilaivan, Oliver Reiser

J. Org. Chem. **2013**, *78*, 4202–4206.

6. Poster Presentations and Scientific Meetings

1) DBU meeting for Novel Process Windows and KoNaRoM-project, Jena, Germany, 2009

Presentation: *Umwandlung von Biorohstoffen im Mikroreaktor*

2) Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany, 2009.

Poster presentation: *Microwaves and Microreactors in Sustainable Chemistry and Catalysis*

3) Symposium on Flow Chemistry, Cardiff, Great Britain, 2010

4) FeUr, Mini-symposium, Regensburg, Germany, 2012

Poster presentation: *Kinetic resolution of 4-hydroxy-2-cyclopentenone derivatives by Pd-catalyzed allylic alkylation and application in synthesis of carbocyclic nucleosides*

5) 4th EuCheMS Chemistry Congress, Prag, Czech Republic, 2012

Poster presentation: *Kinetic resolution of 4-hydroxy-2-cyclopentenone derivatives by Pd-catalyzed allylic alkylation and application in synthesis of carbocyclic nucleosides*

F. References

[1] Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555–3558.

[2] Review: Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 868–889.

[3] Review: Ellison, R. A. *Synthesis* **1973**, 397–412.

[4] Review on cyclopentenone-synthesis: Roche, S. P.; Aitken, D. J. *Eur. J. Org. Chem.* **2010**, 5339–5358.

[5] Piancatelli, G.; Scettri, A. *Synthesis* **1977**, 116–117.

[6] Reviews on Nazarov-cyclisation: a) Spencer III, W. T.; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, 3621–3633; b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206; c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517; d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606.

[7] Nieto Faza, O.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324–4333.

[8] Veits, G. K.; Wenz, D. R.; Read de Alaniz, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 9484–9487.

[9] Review on Dysprosium-catalysis: Veits, G. K.; Read de Alaniz, J. *Tetrahedron* **2012**, *68*, 2015–2026.

[10] Reddy, B. V. S.; Narasimhulu, G.; Lakshumma, P. S.; Reddy, Y. V.; Yadav, J. S. *Tetrahedron Lett.* **2012**, *53*, 1776–1779.

[11] Reddy, B. V. S.; Reddy, Y. V.; Lakshumma, P. S.; Narasimhulu, G.; Yadav, J. S.; Sridhar, B.; Reddy, P. P.; Kunwar, A. C. *RSC Adv.* **2012**, *2*, 10661–10666.

[12] Liu, J.; Shen, Q.; Yu, J.; Zhu, M.; Han, J.; Wang, L. *Eur. J. Org. Chem.* **2012**, 6933–6939.

[13] Wenz, D. R.; Read de Alaniz, J. *Org. Lett.* **2013**, *15*, 3250–3253.

[14] D'Auria, M.; D'Onofrio, F.; Piancatelli, G.; Scettri, A. *Gazz. Chim. Ital.* **1986**, *116*, 173–175.

[15] Palmer, L. I.; Read de Alaniz, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 7167–7170.

[16] Li, S.-W.; Batey, R. A. *Chem. Commun.* **2007**, 2759–3761.

[17] Review on the chemistry of Stenhouse salts: Lewis, K. G.; Mulquiney, C. E. *Tetrahedron* **1977**, *33*, 463–475.

[18] a) Nicholson, E. S.; Ashworth, B. T. Amine condensate. U.S. Patent 4013720, 1977, Mar 22; b) Lewis, K. G.; Mulquiney, C. E. *Aust. J. Chem.* **1979**, *32*, 1079–1092; c) Hofmann, T. *J. Agric. Food Chem.* **1998**, *46*, 932–940.

[19] Duspara, P. A.; Batey, R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 10862–10866.

[20] Nunes, J. P. M.; Afonso, C. A. M.; Caddick, S. *RSC Adv.* **2013**, *3*, 14975–14978.

[21] West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 2402–2406.

[22] a) Fan, J.-F.; Zhang, Y.-F.; Wu, Y.; Wu, Y.-L. *Chin. J. Chem.* **2001**, *19*, 1254–1258; b) Fan, J.-F.; Yin, B.-L.; Zhang, Y.-F.; Wu, Y.-L.; Wu, Y. *Huaxue Xuebao* **2001**, *59*, 1756–1762; c) Gao, Y.; Wu, W.-L.; Wu, Y.-L.; Ye, B.; Zhou, R. *Tetrahedron* **1998**, *54*, 12523–12538; d) Gao, Y.; Wu, W.-L.; Ye, B.; Zhou, R.; Wu, J.-L. *Tetrahedron Lett.* **1996**, *37*, 893–896; e) Yin, B.-L.; Fan, J.-F.; Gao, Y.; Wu, Y.-L. *Synlett* **2003**, 399–401; f) Chen, L.; Xu, H.-H.; Yin, B.-L.; Xiao, C.; Hu, T.-S.; Wu, Y.-L. *J. Agric. Food Chem.* **2004**, *52*, 6719−6723.

[23] Yin, B.-L.; Wu, Y.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1746–1747.

[24] Yin, B.-L.; Wu, Y.-L.; Lai, J.-Q. *Eur. J. Org. Chem.* **2009**, 2695–2699.

[25] Palmer, L. I.; Read de Alaniz, J. *Org. Lett.* **2013**, *15*, 476–479.

[26] Yin, B.-L.; Lai, J. Q.; Zhang, Z.-R.; Jiang, H.-F. *Adv. Synth. Catal.* **2011**, *353*, 1961–1965.

[27] Yin, B.; Huang, L.; Wang, X.; Liu, J.; Jiang, H. *Adv. Synth. Catal.* **2013**, *355*, 370–376.

[28] Ulbrich, K.; Kreitmeier, P.; Reiser, O. *Synlett* **2010**, 2037–2040.

[29] Hronec, M.; Fulajtárová, K.; Soták, T. *J. Ind. Eng. Chem.* **2013**, in press.

[30] Nettekoven, M.; Püllmann, B.; Martin, R. E.; Wechsler, D. *Tetrahedron Lett.* **2012**, *53*, 1363–1366.

[31] a) Hronec, M.; Fulajtárová, K.; Liptajb, T. *Appl. Catal. A* **2012**, *437–438*, 104–111; b) Hronec, M.; Fulajtárová, K. *Catalysis Commun.* **2012**, *24*, 100–104.

[32] Yang, Y.; Du, Z.; Huang, Y.; Lu, F.; Wang, F.; Gao, J.; Xu, J. *Green Chem.* **2013**, *15*, 1932–1940.

[33] Katsuta, R.; Aoki, K.; Yajima, A.; Nukada, T. *Tetrahedron Lett.* **2013**, *54*, 347–350.

[34] Song, L.; Yao, H.; Zhu, L.; Tong, R. *Org. Lett.* **2013**, *15*, 6–9.

[35] Beingessner, R. L.; Farand, J. A.; Barriault, L. *J. Org. Chem.* **2010**, *75*, 6337–6346.

[36] Schrader, T. O.; Snappe, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998–11000.

[37] Wei, S.-Y.; Chang, W.-C.; Yeh, Y.-C. Processes for preparing cyclopentenones and cyclopentenones for the synthesis of benzindene prostaglandins. US 8350090 B1, Jan 8, 2013.

[38] Henschke, J. P.; Liu, Y.; Huang, X.; Chen, Y.; Meng, D.; Xia, L.; Wei, X.; Xie, A.; Li, D.; Huang, Q.; Sun, T.; Wang, J.; Gu, X.; Huang, X.; Wang, L.; Xiao, J.; Qiu, S. *Org. Process Res. Dev.* **2012**, *16*, 1905−1916.

[39] Henschke, J. P.; Liu, Y.; Chen, Y.-F.; Meng, D.; Sung, T. Process for the Preparation of Prostaglandin Analogues and Intermediates Thereof. US 2009/0259058 A1, Oct 15, 2009.

[40] Otero, M. P.; E Santín, E. P.; Rodríguez-Barrios, F.; Vaz, B.; De Lera, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1883–1886.

[41] De Lera, A. R.; Paz, O. C. M. Nouveaux derives de cyclopent-2-en-1-one, modulateurs des recepteurs ppars et leurs utilization dans des compositions pharmaceutique ou cosmetique. FR2 888 846-A1, Jan 1, 2007.

[42] De Lera, A. R.; Paz, O. C. M. Novel cyclopent-2-en-1-one derivatives which are ppar receptor modulators, and use thereof in pharmaceutical or cosmetic compositions. WO 2007/029121 A2, Mar 15, 2007.

[43] Li, C.-C.; Wang, C.-H.; Liang, B.; Zhang, X.-H.; Deng, L.-J.; Liang, S.; Chen, J.-H.; Wu, Y.-D.; Yang, Z. *J. Org. Chem.* **2006**, *71*, 6892–6897.

[44] Csákÿ, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092–2094.

[45] Dias, L. C.; Shimokomaki, S. B.; Shiota, R. T. *J. Braz. Chem. Soc.* **2005**, *16*, 482–489.

[46] Clissold, D. W.; Craig, S. W.; Gadikota, R. R.; He, M.; Jurayj, J. F.; Kazerani, S.; Rannala, E.; Sharma, P. K. Prostaglandin synthesis. WO 2005/058812 A2, Jun 30, 2005.

[47] Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2003**, *44*, 7411–7415.

[48] Borate, H.; Burman, A.; Chandrasekhar, S.; Desiraju, G.; Gurjar, M.; Jaggi, M.; Kapoor, K.; Mukherjee, R.; Nangia, A.; Sairam, K.; Sarkhel, S.; Singh, A.; Wakharkar, R.; Yadav, J. Cyclopentenone derivatives for cancer therapy. US 2003/0229146 A1, Dec 11, 2003.

[49] Yoshida, Y.; Sato, Y.; Okamoto, S.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1995**, 811–812.

[50] Ulbrich, K.; Kreitmeier, P.; Vilaivan, T.; Reiser, O. *J. Org. Chem.* **2013**, *78*, 4202–4206.

[51] Biorefineries-Industrial Processes and Products; Kamm, B.; Gruber, P.; Kamm, M.; Eds.; Wiley-VCH: Weinheim, 2007.

[52] Zeitsch, K. J. Process and apparatus for the manufacture of furfural. DE 3842825 A1, Jul 20, 1989.

[53] Rodrigues, F.; Guirardello, R. *Chem. Eng. Technol.* **2008**, *31*, 883–892.

[54] Quaker Oats Furfural. GB 203691, Dec 4, 1924.

[55] Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411–2502.

[56] Antal, M. J.; Leesomboon, T.; Mok, W. S.; Richards, G. F. *Carbohydrate Research* **1991**, *217*, 71–85.

[57] a) Barton, D. H. R.; Hulshof, L. A. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1103–1106; b) Corey, E. J.; Mehrotra, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3384–3384; c) Kao, T.-C.; Chuang, G. J.; Liao, C.-C. *Angew. Chem. Int. Ed.* **2008**, *47*, 7325–7327; d) Shono, T.; Matsumura, Y.; Hamaguchi, H.; Nakamura, K. *Chem. Lett.* **1976**, *5*, 1249–1252; e) Mucha, B.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1989**, *30*, 4489–4492; f) Caddick, S.; Khan, S. *J. Chem. Soc., Chem.*

Commun. **1995**, 1971–1972; g) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5465–5468; h) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E. *J. Am. Chem. Soc.* **1993**, *115*, 9351–9352.

[58] Hronec, M.; Fulajtárová, K.; Soták, T. *J. Ind. Eng. Chem.*, in press.

[59] Ilyas, M.; Sadiq, M. *Catal. Lett.* **2009**, *128*, 337–342.

[60] Taskar, U.; Rigs, J. B. *AIChE Journal* **1997**, *43*, 740–753.

[61] Master thesis Kathrin Ulbrich **2009**, University of Regensburg.

[62] Baggiolini, E.; Herzog, E. G.; Iwasaki, S.; Schorta, R.; Schaffner, K. *Helvetica Chimica Acta* **1967**, *50*, 297–306.

[63] Hafner, K.; Goliasch, K. *Chem. Ber.* **1961**, *94*, 2909–2921.

[64] Maier, G.; Franz, L. H.; Hartan, H.-G.; Lanz, K.; Reisenauer, H. P. *Chem. Ber.* **1985**, *118*, 3196–3204.

[65] DePuy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. *J. Org. Chem.* **1964**, *29*, 3503–3507.

[66] Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *J. Org. Chem.* **2003**, *68*, 6035–6038.

[67] Eaton, P. E.; Cerefice, S. A. *Chem. Commun.* **1970**, 1494–1495.

[68] Chaicharoenwimolkul, L.; Munmai, A.; Chairam, S.; Tewasekson, U.; Sapudom, S.; Lakliang, Y.; Somsook, E. *Tetrahedron Lett.* **2008**, *49*, 7299–7302.

[69] Hafner, K.; Goliasch, K. *Chem. Ber.* **1961**, *94*, 2909–2921.

[70] Verdaguer, X.; Lledo, A.; Lopez-Mosquera, C.; Maestro, M. A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 8053–8061.

[71] Shao, C.; Yu, H.-J.; Wu, N.-Y.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.*, **2010**, *12*, 3820–3823.

[72] Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1984**, 1049–1950.

[73] Gavina, F.; Costero, A. M.; Gil, P.; Luis, S. V. *J. Am. Chem. Soc.* **1984**, *106*, 2077–2080.

[74] Harmata, M.; Barnes, C. L.; Brackley, J.; Bohnert, G.; Kirchhoefer, P.; Kuerti, L.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5232–5236.

[75] a) Minuti, L.; Selvaggi, R.; Taticchi, A.; Sandor, P. *Tetrahedron* **1993**, *49*, 1071–1078; b) Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387–395; c) Jacobo, S. H.; Chang, C.-T.; Lee, G.-J.; Lawson, J. A.; Powell, W. S.; Pratico, D.; FitzGerald, G. A.; Rokach, J. *J. Org. Chem.* **2006**, *71*, 1370–1379; d) Minuti, L.; Taticchi, A.; Marrocchi, A.; Broggi, A.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2004**, *15*, 3245–3248; e) Dols, P. P. M. A.; Lacroix, L.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 3739–3742; f) Pudukulathan, Z.; Manna, S.; Hwang, S.-W.; Khanapure, S. P.; Lawson, J. A.;

FitzGerald, G. A.; Rokach, J. *J. Am. Chem. Soc.* **1998**, *120*, 11953–11961; g) Trembleau, L.; Patiny, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 6377–6381; h) Wolter, M.; Borm, C.; Merten, E.; Wartchow, R.; Winterfeldt, E. *Eur. J. Org. Chem.* **2001**, 4051–4060.

[76] a) DePuy, C. H.; Zaweski, E. F. *J. Am. Chem. Soc*. **1959**, *81*, 4920–4924; b) Rasmusson, G. H.; House, H. O.; Zaweski, E. F.; DePuy, C. H. *Org. Synth.* **1962**, *42*, 36–38.

[77] Dias, L. C.; Shimokomaki, S. B.; Shiota, R. T. *J. Braz. Chem. Soc.* **2005**, *16*, 482–489.

[78] Jain, S. L.; Sharma, V. B.; Sain, B. *Tetrahedron* **2006,** *62*, 6841–6847.

[79] Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386–12386.

[80] Ingle, R. H.; Raj, N. K. K.; Manikandan, P. *J. Mol. Catal. A: Chemical* **2007**, *262*, 52–58.

[81] Shi, F.; Tse, M. K.; Li, Z.; Beller, M. *Chem. Eur. J.* **2008**, *14*, 8793–8797.

[82] Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc*. **2004**, *126*, 10657–10666.

[83] An, G.; Lim, M.; Chun, K.-S.; Rhee, H. *Synlett* **2007**, 95–98.

[84] Ng, Y. H.; Ikeda, S.; Harada, T.; Morita, Y.; Matsumura, M. *Chem. Commun.* **2008**, 3181–3183.

[85] Komiya, N.; Nakae, T.; Sato, H.; Naota, T. *Chem. Commun*. **2006**, 4829–4831.

[86] Matsumoto, M.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1981**, 907–908.

[87] Depuy, C. H.; Wells, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 2909–2913.

[88] Eposti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2531–2534.

[89] Klinsmann, U.; Gauthier, J.; Schaffner, K. *Helv. Chim. Acta* **1972**, *55*, 2643–2659.

[90] Eaton, P. *J. Am. Chem. Soc.* **1962**, *84*, 2344–2348.

[91] Schiess, P.; Suter, C. *Synthesis* **1978**, 543–543.

[92] Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244–7254.

[93] Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 6361–6363.

[94] Mihara, H.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2008**, *3*, 359–366.

[95] a) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3497–3505; b) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5912–5914.

[96] a) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett*. **1976**, *10*, 759–762; b) Khanapure, S. P.; Najafi, N.; Manna, S.; Yang, J.-J.; Rokach, J. *J. Org. Chem.* **1995**, *60*, 7548–7551; c) McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett*. **2001**, *42*, 1197–1200; d) Paul, K. G.; Johnson, F.; Favara, D. *J. Am. Chem. Soc.* **1976**, *98*, 1285–1286; e) Gallos, J. K.; Damianou,

K. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 5769–5771; f) Ingate, S. T.; Contelles, J. M. *Org. Prep. Proc. Int.* **1998**, *30*, 121–143.

[97] a) Morita, A.; Kuwahara, S. *Org. Lett.* **2006**, *8*, 1613–1616; b) Rivero, M. R.; de la Rosa, J. K.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992–14993.

[98] a) Dickmeiss, G.; De Sio, V.; Udmark, J.; Poulsen, T. B.; Marcos, V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6650–6653; b) Batsanov, A. S.; Knowles, J. P.; Lightfoot, A. P.; Maw, G.; Thirsk, C. E.; Twiddle, S. J. R.; Whiting, A. *Org. Lett.* **2007**, *9*, 5565–5568.

[99] Sih, C. J. Process for preparing 4-hydroxycyclopent-2-en-1-one. WO 8607611 A1, Dec 31, 1986.

[100] Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.

[101] Ghorpade, S. R.; Bastawade, K. B.; Gokhale, D. V.; Shinde, P. D.; Mahajan, V. A.; Kalkote, U. R.; Ravindranathan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4115–4122.

[102] Kumaraguru, T.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2012**, *23*, 775–779.

[103] Kitamura, M.; Manabe, K.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *40*, 4719–4720.

[104] Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 710–712.

[105] Palladium Reagents and Catalysts - Innovations in Organic Synthesis, Tsuji, J.; Ed.; Wiley, Chichester, UK, 290–422.

[106] General reviews: a) Godleski, S. in Comprehensive Organic Synthesis, Trost, B. M., Ed.; Pergamon Press, Oxford, 1991, vol. 4, 585–661; b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089–1122.

[107] Tsuji, J.; Takahasi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *49*, 4387–4388.

[108] a) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, *11*, 3821–3824; b) Hata, G.; Takahashi, K.; Miyake, A. *Chem. Commun.* **1970**, 1392–1393; c) Hata, G.; Takahashi, K.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230–236.

[109] a) Collins, D. J.; Jackson, W. R.; Timms, R. N. *Tetrahedron Lett.* **1976**, *17*, 495–496; b) Collins, D. J.; Jackson, W. R.; Timms, R. N. *Aust. J. Chem.* **1977**, *30*, 2167–2175; c) Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611–1612; d) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. *J. Am. Chem. Soc.* **1978**, *100*, 3416–3426; e) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435–3443; f) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743; g) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215–3216; h) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem.*

Soc. **1983**, *105*, 7767–7768; i) Hayashi, T.; Konishi, M.; Kumada, M. *Chem. Commun.* **1984**, 107–108; j) Akermark, B.; Bäckvall, J. E.; Löwenborg, A.; Zetterberg, K. *J. Organomet. Chem.* **1979**, *166*, C33–C36; k) Akermark, B; Jutand, A. *J. Organomet. Chem.* **1981**, *217*, C41–C43.

[110] For selected examples of Pd-catalyzed kinetic resolution: a) Mao, B.; Ji, Y.; Fañanás-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 3168–3173; b) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem. Int Ed.* **1998**, *37*, 3118–3121; c) Gais, H. J.; Spalthoff, N.; Jagusch, T.; Frank, M.; Raabe, G. *Tetrahedron Lett.* **2000**, *41*, 3809–3812; d) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 4289–4291; e) Gais, H. J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem. Eur. J.* **2003**, *9*, 4202–4221; f) Lüssem, B. J.; Gais, H. J. *J. Am. Chem. Soc.* **2003**, *125*, 6066–6067; g) Lei, B. L.; Ding, C. H.; Yang, X. F.; Wan, X. L.; Hou, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 18250–18251; h) Rao, R. K.; Sekar, G. *Tetrahedron: Asymmetry* **2011**, *22*, 948–954.

[111] Trost, B. M.; Crawley, M. L. *Chem. Eur. J*. **2004**, *10*, 2237–2252.

[112] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.

[113] Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc*. **2003**, *125*, 8714–8715.

[114] Shan, M.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 2986–2989.

[115] Industrial Organic Chemistry, 5. Ed.; Ape, H. J.; Ed.; Wiley VCH: Weinheim, 2010.

[116] Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E.; Ed.; Wiley & Sons: New York, 2002.

[117] Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9328.

[118] Kagan, H. B.; Fiaud, J.-C. *Top. Stereochem.* **1988**, *18*, 249–330.

[119] Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.

[120] Medicinal Chemistry of Nucleic Acids, First Edition; Zhang, L. H.; Xi, Z.; Chattopadhyaya, J.; Eds.; John Wiley & Sons, Hoboken, 2011.

[121] Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem*. **1992**, *35*, 3372–3377.

[122] Merlo, V.; Reece, F. J.; Roberts, S. M.; Gregson, M.; Storer, R. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1717–1718.

[123] Da Silva, A.; Coimbra, E. S.; Fourrey, J. L.; Machado, A. S.; Robert-Gero, M. *Tetrahedron Lett*. **1993**, *34*, 6745–6748.

[124] a) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267–278;

b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551–554; c) Siddiqi, S. M.; Jacobson, K. A.; Esker, J. L.; Olah, M. E.; Ji, X.-D.; Melman, N.; Tiwari, K. N.; Secrist, J. A., III; Schneller, S. W. *J. Med. Chem.* **1995**, *38*, 1174–1188.

[125] a) Dyatkina, N.; Theil, F.; Janta-Lipinski, M. *Tetrahedron* **1995**, *51*, 761–772; b) Dyatkina, N.; Semizarov, D.; Victorova, L.; Krayevsky, A.; Theil, F.; Janta-Lipinski, M. *Nucleosides Nucleotides* **1995**, *14*, 723–726.

[126] Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095–2099.

[127] Boojamra, C. G.; Parrish, J. P.; Sperandio, D.; Gao, Y.; Petrakovsky, O. V.; Lee, S. K.; Markevitch, D. Y.; Vela, J. E.; Laflamme, G.; Chen, J. M.; Ray, A. S.; Barron, A. C.; Sparacino, M. L.; Desai, M. C.; Kim, C. U.; Cihlar, T.; Mackman, R. L. *Bioorg. Med. Chem.* **2009**, *17*, 1739–1746.

[128] Ward, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.

[129] Steinreiber, J.; Faber, K.; Griengl, H. *Chem. Eur. J.* **2008**, *14*, 8060–8072.

[130] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.***1999**, *121*, 3543–3544.

[131] Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14.

[132] Trost, B. M.; Patterson, D. E.; Hembre, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 10834–10835.

[133] Trost, B. M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, *128*, 2540–2541.

[134] Collins, S.; Hongg, Y.; Kataoka, M.; Nguyen, T. *J. Org. Chem.* **1990**, *55*, 3395–3398.

[135] Wanzlick, H; Gollmer, G.; Milz, H. *Chem. Ber*. **1955**, *88*, 69–73.

[136] Selected examples: a) Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledo, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem.* **2008**, *6*, 4649–4661; b) Furuta, K.; Maeda, M.; Hirata, Y.; Shibata, S.; Kiuchi, K.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5487–5491; c) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110–7123; d) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666–3672; e) Birse, E. F.; Ironside, M. D.; Murray, A. W. *Tetrahedron Lett.* **1995**, *36*, 6309–6312; f) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11689–11702; g) Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Toru, T.; Kurozumi, S. *Tetrahedron* **1987**, *43*, 813–824; h) Bird, C. W.; Butler, H. I.; Caton, M. P. L.; Coffee, E. C. J.; Hardy, C. J.; Hart, T. W.; Mason, H. J. *Tetrahedron Lett.* **1985**, *26*, 4101–4104; i) Luo, F. T.; Negishi, E. *J. Org. Chem.* **1985**, *50*, 4762–4766.

[137] Masayoshi, M. Process for Preparing Oxocyclopentene derivatives. US 4970345, Nov 13, 1990.

[138] Reviews on the two mechanisms: a) Antal, M. J. Jr.; Mok, W. S. L. *Carbohydrate Research* **1990**, *199*, 91–109; b) Newth, F. H. *Adv. Carbohydr. Chem.* **1951**, *6*, 83–106; c) Anet, E. F. L. J. *Adv. Carbohydr. Chem.* **1964**, *19*, 181–218; d) Overend, W. G. The Carbohydrates Vol. 1; Pigman, W.; Horton, D.; Eds.; Academic Press, New York, 1972, 165–194; e) Feather, M. S.; Harris, J. F. *Adv. Carbohydr. Chem. Biochem.* **1973**, *28*, 161–224.

[139] Rauchfuss, B. T.; Thananatthanachon, T. Efficient method for preparing 2,5-dimethylfuran. US 20110263880 A1, Oct 27, 2011.

[140] Goswami, S.; Dey, S.; Jana, S. *Tetrahedron* **2008**, *54*, 6358–6363.

[141] Luijkx, G. C. A.; van Rantwijk, F.; van Bekkum, H. *Carbohydrate Research* **1993**, *242*, 131–139.

[142] Baugh, K. O.; McCarty, P. L. *Biotechnology and Bioengineering* **1988**, *31*, 50–61.

[143] Szechner, B.; Achmatowicz, O. *Collect. Czech. Chem. Commun.* **1992**, *57*, 159–168.

[144] Ogi, T.; Margiastuti, P.; Teruya, T.; Taira, J.; Suenaga, S.; Ueda, K. *Mar. Drugs* **2009**, *7*, 816–832.

[145] D'Auria, M. *Heterocycles* **2000**, *52*, 185–194.

[146] Vásquez-Romero, A.; Cárdenas, L.; Blasi, M.; Verdaguer, X.; Riera, A. *Org. Lett.* **2009**, *11*, 3104–3107.

[147] Parchmann, S.; Mueller, M. J. *J. Biol. Chem*. **1998**, *273*, 32650–32655.

[148] Imbusch, R.; Mueller, M. *J. Plant Physiol*. **2000**, *124*, 1293–12303.

[149] Morrow, J. D.; Hill, K. E.; Burk, R. F.; Nammour, T. M.; Badr, K. F.; Roberts, L. J., II. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9383–9387.

[150] Nourooz-Zadeh, J.; Liu, E. H. C.; Änggard, E. E.; Halliwell, B. *Biochem. Biophys. Res. Commun.* **1998**, *242*, 338–344.

[151] a) Roberts, L. J., II; Montine, T. J.; Markesbery, W. R.; Tapper, A. R.; Hardy, P.; Chemtob, S.; Dettbarn, W. D.; Morrow, J. D. *J. Biol. Chem.* **1998**, *273*, 13605–13612; b) Nourooz-Zadeh, J.; Liu, E. H. C.; Yhlen, B.; Änggard, E. E.; Halliwell, B. *J. Neurochem.* **1999**, *72*, 734–740; c) Roberts, L. J., II; Morrow, J. D. *Free Radical Biol. Med.* **2000**, *28*, 505–513; d) Cracowski, J. L.; Durand, T.; Bessard, G. *Trends Pharmacol. Sci.* **2002**, *23*, 360–366; e) For a general review, see: Durand, T.; Guy, A.; Henry, O.; Roland, A.; Bernad, S.; El Fangour, S.; Vidal, J.-P.; Rossi, J.-C. *Chem. Phys. Lipids* **2004**, *128*, 1–193.

[152] a) Imbusch, R.; Mueller, M. *J. Free Rad. Biol. Med.* **2000**, *28*, 720–726; b) Thoma, I.; Loeffler, C.; Sinha, A. K.; Gupta, M.; Krischke, M.; Steffan, B.; Roitsch, T.; Mueller, M. J. *Plant J.* **2003**, *34*, 363–375; c) Loeffler, C.; Berger, S.; Guy, A.; Durand, T.; Bringmann, G.;

Dreyer, M.; von Rad, U.; Durner, J.; Mueller, M. *J. Plant Physiol.* **2005**, *137*, 328–340.

[153] Zanoni, G.; Porta, A.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 4346–4351.

[154] Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2002**, *43*, 9249–9253.

[155] a) Fangour, S. E.; Guy, A.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *Tetrahedron Lett.* **2003**, *44*, 2105–2108; b) Fangour, S. E.; Guy, A.; Despres, V.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2004**, *69*, 2498–2503.

[156] Fangour, S. E.; Guy, A.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2005**, *70*, 989–997.

[157] Schmidt, A.; Boland, W. *J. Org. Chem.* **2007**, *72*, 1699–1706.

[158] Perlikowska, W.; Mikolajczyk, M. *Synthesis* **2009**, 2715–2718.

[159] Mosmann, T. *J. Immunol. Meth.* **1983**, *65*, 55–63.

[160] Review: Sun, J.; Zhang, X.; Broderick, M.; Fein, H. *Sensors* **2003**, *3*, 276–284.

[161] Review: Aktan, F. *Life Sciences* **2004**, *75*, 639–653.

[162] O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539–545.

[163] Khan, P. M.; Wu, R.; Bisht, K. P. *Tetrahedron* **2007**, *63*, 1116–1126.

[164] Chaicharoenwimolkul, L.; Munmai, A.; Chairam, S.; Tewasekson, U.; Sapudom, S.; Lakliang Y.; Somsook, E. *Tetrahedron Lett.* **2008**, *49*, 7299–7302.

[165] Gaviña, F.; Costero, A. M.; González, A. M.; Luis, S. V. *J. Org. Chem.* **1987**, *52*, 2997–2999.

[166] Shestak, O. P.; Novikov, V. L.; Prokof'eva, N. G.; Chaikina, E. L. *Pharm. Chem. J.* **2000**, *33*, 631–634.

[167] Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 5671–5673.

[168] Iguchi, K.; Kaneta, S.; Tsune, C.; Yamada, Y. *Chem. Pharm. Bull.* **1989**, *37*, 1173–1175.

[169] O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539–545.

[170] Trost, B. M.; Tost, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.

[171] White, J; Carter, P.; Kezar, H. *J. Org. Chem.* **1982**, *47*, 929–932.

[172] Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett*. **2005**, *7*, 4337–4340.

[173] Bajracharya, G. B.; Koranne, P. S.; Nadaf, R. N.; Gabr, R. K. M.; Takenaka, K.; Takizawa, S.; Sasai, H. *Chem. Commun.* **2010**, *46*, 9064–9066.

[174] Das, R.; Chakraborty, D. *Appl. Organometal. Chem.* **2011**, *25*, 437–442.

[175] Kawakami, T.; Shibata, I.; Baba, A. *J. Org. Chem.* **1996**, *61*, 82–87.

[176] Ayer, W. A. *Can. J. Chem.* **1990**, *68*, 2085–2094.

[177] Goswami, S.; Dey, S.; Jana, S. *Tetrahedro*n **2008**, *54*, 6358–6363.

[178] Celanire, S. *Tetrahedron* **2005**, *61*, 3025–3032.

[179] Schinzer, D.; Bourguet, E.; Ducki, S. *Chem. Eur. J.* **2004**, *10*, 3217–3224.

[180] Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857–3858.